

Diabetes Care[®]

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Supplement
1

Standards of Care in Diabetes—2023

American Diabetes Association

Standards of Care in Diabetes—2023



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Diabetes Care

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

January 2023 Volume 46, Supplement 1

[T]he simple word *Care* may suffice to express [the journal's] philosophical mission. The new journal is designed to promote better patient care by serving the expanded needs of all health professionals committed to the care of patients with diabetes. As such, the American Diabetes Association views *Diabetes Care* as a reaffirmation of Francis Weld Peabody's contention that "the secret of the care of the patient is in caring for the patient."

—Norbert Freinkel, *Diabetes Care*, January-February 1978

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Diabetes Care is a journal for the health care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes. To achieve these goals, the journal publishes original research on human studies in the following categories: Clinical Care/Education/Nutrition/Psychosocial Research, Epidemiology/Health Services Research, Emerging Technologies and Therapeutics, Pathophysiology/Complications, and Cardiovascular and Metabolic Risk. The journal also publishes ADA statements, consensus reports, clinically relevant review articles, letters to the editor, and health/medical news or points of view. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other health professionals. More information about the journal can be found online at diabetesjournals.org/care.

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Introduction and Methodology: Standards of Care in Diabetes—2023

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Diabetes is a complex, chronic condition requiring continuous medical care with multifactorial risk-reduction strategies beyond glucose management. Ongoing diabetes self-management education and support are critical to empowering people, preventing acute complications, and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.

The American Diabetes Association (ADA) “Standards of Care in Diabetes,” referred to here as the Standards of Care, is intended to provide clinicians, researchers, policy makers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care.

The ADA Professional Practice Committee (PPC) updates the Standards of Care annually and strives to include discussion of emerging clinical considerations in the text, and as evidence evolves, clinical guidance is added to the recommendations in the Standards of Care. The Standards of Care is a “living” document where important updates are published

online should the PPC determine that new evidence or regulatory changes (e.g., drug or technology approvals, label changes) merit immediate inclusion. More information on the “Living Standards” can be found on the ADA professional website DiabetesPro at professional.diabetes.org/content-page/living-standards. The Standards of Care supersedes all previously published ADA position statements—and the recommendations therein—on clinical topics within the purview of the Standards of Care; while still containing valuable analysis, ADA position statements should not be considered the current position of the ADA. The Standards of Care receives annual review and approval by the ADA Board of Directors and is reviewed by ADA staff and clinical leadership. The Standards of Care also undergoes external peer review annually.

SCOPE OF THE GUIDELINES

The recommendations in the Standards of Care include screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health

outcomes of people with diabetes. They also cover the prevention, screening, diagnosis, and management of diabetes-associated complications and comorbidities. The recommendations encompass care throughout the lifespan, for youth (children aged birth to 11 years and adolescents aged 12–17 years), adults (aged 18–64 years), and older adults (aged ≥65 years). The recommendations cover the management of type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and other types of diabetes.

The Standards of Care does not provide comprehensive treatment plans for complications associated with diabetes, such as diabetic retinopathy or diabetic foot ulcers, but offers guidance on how and when to screen for diabetes complications, management of complications in the primary care and diabetes care settings, and referral to specialists as appropriate. Similarly, regarding the psychosocial factors often associated with diabetes and that can affect diabetes care, the Standards of Care provides guidance on how and when to screen, management in the primary care and

The “Standards of Care in Diabetes,” formerly called “Standards of Medical Care in Diabetes,” was originally approved in 1988. Most recent review/revision: December 2022.

Disclosure information for each author is available at <https://doi.org/10.2337/dc23-SDIS>.

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diabetes care settings, and referral but does not provide comprehensive management plans for conditions that require specialized care, such as mental illness.

TARGET AUDIENCE

The target audience for the Standards of Care includes primary care physicians, endocrinologists, nurse practitioners, physician associates/assistants, pharmacists, dietitians, and diabetes care and education specialists. The Standards of Care also provides guidance to specialists caring for people with diabetes and its multitude of complications, such as cardiologists, nephrologists, emergency physicians, internists, pediatricians, psychologists, neurologists, ophthalmologists, and podiatrists. Additionally, these recommendations help payers, policy makers, researchers, research funding organizations, and advocacy groups to align their policies and resources and deliver optimal care for people living with diabetes.

The ADA strives to improve and update the Standards of Care to ensure that clinicians, health plans, and policy makers can continue to rely on it as the most authoritative source for current guidelines for diabetes care. The Standards of Care recommendations are not intended to preclude clinical judgment. They must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, and other patient factors. For more detailed information about the management of diabetes, please refer to *Medical Management of Type 1 Diabetes (1)* and *Medical Management of Type 2 Diabetes (2)*.

METHODOLOGY AND PROCEDURE

The Standards of Care includes discussion of evidence and clinical practice recommendations intended to optimize care for people with diabetes by assisting providers and individuals in making shared decisions about diabetes care. The recommendations are informed by a systematic review of evidence and an assessment of the benefits and risks of alternative care options.

Professional Practice Committee

The PPC of the ADA is responsible for the Standards of Care. The PPC is a multidisciplinary expert committee comprising physicians, nurse practitioners, pharmacists,

diabetes care and education specialists, registered dietitian nutritionists, behavioral health scientists, and others who have expertise in a range of areas including but not limited to adult/pediatric endocrinology, epidemiology, public health, behavioral health, cardiovascular risk management, microvascular complications, nephrology, neurology, ophthalmology, podiatry, clinical pharmacology, preconception and pregnancy care, weight management and diabetes prevention, and use of technology in diabetes management. Appointment to the PPC is based on excellence in clinical practice and research, with attention to appropriate representation of members based on considerations including but not limited to demographic, geographic, work setting, or identity characteristics (e.g., gender, ethnicity, ability level). For the 2023 Standards of Care, as in previous years, two representatives from the American College of Cardiology (ACC) acted as ad hoc PPC members and reviewed and approved Section 10, "Cardiovascular Disease and Risk Management." A PPC chairperson is appointed by the ADA (currently N.A.E.) for a 1-year term and oversees the committee.

Each section of the Standards of Care is reviewed annually and updated with the latest evidence-based recommendations by a PPC member designated as the section lead as well as subcommittee members. The subcommittees perform systematic literature reviews and identify and summarize the scientific evidence. An information specialist with knowledge and experience in literature searching (a librarian) is consulted as necessary. A guideline methodologist (R.R.B. for the 2023 Standards of Care) with expertise and training in evidence-based medicine and guideline development methodology oversees all methodological aspects of the development of the Standards of Care and serves as a statistical analyst.

Disclosure and Duality of Interest Management

All members of the expert panel (the PPC members, ad hoc members, and subject matter experts) and ADA staff are required to comply with the ADA policy on duality of interest, which requires disclosure of any financial, intellectual, or other interests that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the

guideline topic. For transparency, ADA requires full disclosure of all relationships. Full disclosure statements from all committee members are solicited and reviewed during the appointment process. Disclosures are then updated throughout the guideline development process (specifically before the start of every meeting), and disclosure statements are submitted by every Standards of Care author upon submission of the revised Standards of Care section. Members are required to disclose for a time frame that includes 1 year prior to initiation of the committee appointment process until publication of that year's Standards of Care. Potential dualities of interest are evaluated by a designated review group and, if necessary, the Legal Affairs Division of the ADA. The duality of interest assessment is based on the relative weight of the financial relationship (i.e., the monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). In addition, the ADA adheres to Section 7 of the Council for Medical Specialty Societies "Code for Interactions with Companies" (3). The duality of interest review group also ensures the majority of the PPC and the PPC chair are without potential conflict relevant to the subject area. Furthermore, the PPC chair is required to remain unconflicted for 1 year after the publication of the Standards of Care. Members of the committee who disclose a potential duality of interest pertinent to any specific recommendation are prohibited from participating in discussions related to those recommendations. No expert panel members were employees of any pharmaceutical or medical device company during the development of the 2023 Standards of Care. Members of the PPC, their employers, and their disclosed potential dualities of interest are listed in the section "Disclosures: *Standards of Medical Care in Diabetes—2023*." The ADA funds the development of the Standards of Care from general revenue and does not use industry support for this purpose.

Evidence Review

The Standards of Care subcommittee for each section creates an initial list of

relevant clinical questions that is reviewed and discussed by the expert panel. In consultation with a systematic review expert, each subcommittee devises and executes systematic literature searches. For the 2023 Standards of Care, PubMed, Medline, and EMBASE were searched for the time periods of 1 June 2021 to 26 July 2022. Searches are limited to studies published in English. Subcommittee members also manually search journals, reference lists of conference proceedings, and regulatory agency websites. All potentially relevant citations are then subjected to a full-text review. In consultation with the methodologist, the subcommittees prepare the evidence summaries and grading for each section of the Standards of Care. All PPC members discuss and review the evidence summaries and make revisions as appropriate. The final evidence summaries are then deliberated on by the PPC, and the recommendations that will appear in the Standards of Care are drafted.

Grading of Evidence and Recommendation Development

A grading system (Table 1) developed by the ADA and modeled after existing methods is used to clarify and codify the evidence that forms the basis for the recommendations in the Standards of Care. All of the recommendations in the Standards of Care are critical to comprehensive care regardless of rating. ADA recommendations are assigned ratings of **A**, **B**, or **C**, depending on the quality of the evidence in support of the recommendation. Expert opinion **E** is a separate category for recommendations in which there is no evidence from clinical trials, clinical trials may be impractical, or there is conflicting evidence. Recommendations assigned an **E** level of evidence are informed by key opinion leaders in the field of diabetes (members of the PPC) and cover important elements of clinical care. All Standards of Care recommendations receive a rating for the strength of the evidence and not for the strength of the recommendation. Recommendations with **A**-level evidence are based on large, well-designed randomized controlled trials or well-done meta-analyses of randomized controlled trials. Generally, these recommendations have the best chance of improving outcomes when applied to the population for which they are appropriate. Recommendations

Table 1—ADA evidence-grading system for Standards of Care in Diabetes

Level of evidence	Description
A	<p>Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including:</p> <ul style="list-style-type: none"> • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis <p>Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:</p> <ul style="list-style-type: none"> • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	<p>Supportive evidence from well-conducted cohort studies</p> <ul style="list-style-type: none"> • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies <p>Supportive evidence from a well-conducted case-control study</p>
C	<p>Supportive evidence from poorly controlled or uncontrolled studies</p> <ul style="list-style-type: none"> • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports <p>Conflicting evidence with the weight of evidence supporting the recommendation</p>
E	Expert consensus or clinical experience

with lower levels of evidence may be equally important but are not as well supported.

Of course, published evidence is only one component of clinical decision-making. Clinicians care for people, not populations; guidelines must always be interpreted with the individual person in mind. Individual circumstances, such as comorbid and coexisting diseases, age, education, disability, and, above all, the values and preferences of the person with diabetes, must be considered and may lead to different treatment targets and strategies. Furthermore, conventional evidence hierarchies, such as the one adapted by the ADA, may miss nuances important in diabetes care. For example, although there is excellent evidence from clinical trials supporting the importance of achieving multiple risk factor control, the optimal way to achieve this result is less clear. It is difficult to assess each component of such a complex intervention.

In preparation of the 2023 Standards of Care, the expert panel met for a 2-day in-person/virtual meeting in Arlington, Virginia, in July 2022, to present the evidence summaries and to develop the recommendations. All PPC members participate annually in updating the Standards of Care and approve the recommendations therein.

Revision Process

Public comment is particularly important in the development of clinical practice recommendations; it promotes transparency and provides key stakeholders the opportunity to identify and address gaps in care. The ADA holds a year-long public comment period requesting feedback on the Standards of Care. The PPC reviews compiled feedback from the public in preparation for the annual update but considers more pressing updates throughout the year, which may be published as “living” Standards updates. Feedback from the larger clinical community and general public was invaluable for the revision of the Standards of Care—2022. Readers who wish to comment on the 2023 Standards of Care are invited to do so at professional.diabetes.org/SOC.

Feedback for the Standards of Care is also obtained from external peer reviewers. The Standards of Care is reviewed by ADA clinical leadership and scientific and medical staff and is approved by the ADA Board of Directors, which includes health care professionals, scientists, and lay people. The ACC performs an independent external peer review and the ACC Board of Directors provides endorsement of Section 10, “Cardiovascular and Metabolic Risk.” The

ADA adheres to the Council for Medical Specialty Societies "Revised CMSS Principles for Clinical Practice Guideline Development" (4).

ADA STANDARDS, STATEMENTS, REPORTS, AND REVIEWS

The ADA has been actively involved in developing and disseminating diabetes care clinical practice recommendations and related documents for more than 30 years. The ADA Standards of Care is an essential resource for health care professionals caring for people with diabetes. ADA Statements, Consensus Reports, and Scientific Reviews support the recommendations included in the Standards of Care.

Standards of Care

The annual Standards of Care supplement to Diabetes Care contains the official ADA position, is authored by the ADA, and provides all of the ADA's current clinical practice recommendations.

ADA Statement

An ADA statement is an official ADA point of view or belief that does not contain clinical practice recommendations and may be issued on advocacy, policy, economic, or medical issues related to diabetes. ADA statements undergo a formal review process, including a review by the appropriate ADA national committee, ADA clinical leadership, science and health care staff, and the ADA Board of Directors.

Consensus Report

A consensus report on a particular topic contains a comprehensive examination, is authored by an expert panel (i.e., consensus panel), and represents the panel's collective analysis, evaluation, and opinion. The need for a consensus report arises when clinicians, scientists, regulators, and/or policy makers desire guidance and/or clarity on a medical or scientific issue related to diabetes for which the evidence is contradictory, emerging, or incomplete. Consensus reports may also highlight evidence gaps and propose future research areas to address these

gaps. A consensus report is not an ADA position but represents expert opinion only and is produced under the auspices of the ADA by invited experts. A consensus report may be developed after an ADA Clinical Conference or Research Symposium.

Scientific Review

A scientific review is a balanced review and analysis of the literature on a scientific or medical topic related to diabetes. A scientific review is not an ADA position and does not contain clinical practice recommendations but is produced under the auspices of the ADA by invited experts. The scientific review may provide a scientific rationale for clinical practice recommendations in the Standards of Care. The category may also include task force and expert committee reports.

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References

- American Diabetes Association. *Medical Management of Type 1 Diabetes*. 7th ed. Wang CC, Shah AC, Eds. Alexandria, VA, American Diabetes Association, 2017
- American Diabetes Association. *Medical Management of Type 2 Diabetes*. 8th ed. Meneghini L, Ed. Alexandria, VA, American Diabetes Association, 2020
- Council of Medical Specialty Societies. CMSS Code for Interactions with Companies. Accessed 13 October 2022. Available from <https://cmss.org/code-for-interactions-with-companies/>
- Council for Medical Specialty Societies. CMSS Principles for the Development of Specialty Society Clinical Guidelines. Accessed 16 August 2022. Available from <https://cmss.org/wp-content/uploads/2017/11/Revised-CMSS-Principles-for-Clinical-Practice-Guideline-Development.pdf>

Summary of Revisions: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S5–S9 | <https://doi.org/10.2337/dc23-SREV>

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GENERAL CHANGES

The field of diabetes care is rapidly changing as new research, technology, and treatments that can improve the health and well-being of people with diabetes continue to emerge. With annual updates since 1989, the American Diabetes Association (ADA) has long been a leader in producing guidelines that capture the most current state of the field.

The 2023 Standards of Care includes revisions to incorporate person-first and inclusive language. Efforts were made to consistently apply terminology that empowers people with diabetes and recognizes the individual at the center of diabetes care.

Although levels of evidence for several recommendations have been updated, these changes are not outlined below where the clinical recommendation has remained the same. That is, changes in evidence level from, for example, **E** to **C** are not noted below. The 2023 Standards of Care contains, in addition to many minor changes that clarify recommendations or reflect new evidence, more substantive revisions detailed below.

SECTION CHANGES

Section 1. Improving Care and Promoting Health in Populations

(<https://doi.org/10.2337/dc23-S001>)

Recommendation 1.7 was added to address the use of community health workers to support the management of diabetes and cardiovascular risk factors, especially in underserved communities and health care systems.

Additional language and definitions regarding digital health, telehealth, and telemedicine were added, along with the benefits of these modalities of care delivery, including social determinants of health in the telehealth subsection.

The subsection “Access to Care and Quality Improvement” was revised to add language regarding value-based payments to listed quality improvement efforts.

The “Migrant and Seasonal Agricultural Workers” subsection was updated to include more recent data for this population.

More defining terms were added for non-English speakers and diabetes education in the “Language Barriers” subsection.

Section 2. Classification and Diagnosis of Diabetes

(<https://doi.org/10.2337/dc23-S002>)

Recommendation 2.1b was added to the “A1C” subsection to address the utility of point-of-care A1C testing for diabetes screening and diagnosis.

Section 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities

(<https://doi.org/10.2337/dc23-S003>)

Recommendation 3.9 was added to address statin use and the risk of type 2 diabetes, including the recommendation to monitor glucose status regularly and enforce diabetes prevention approaches in individuals at high risk of developing type 2 diabetes who were prescribed statin therapy.

Recommendation 3.10 was added to address the use of pioglitazone for reducing the risk of stroke or myocardial infarction in people with history of stroke and evidence of insulin resistance and prediabetes.

Recommendation 3.12 was added to communicate that pharmacotherapy (e.g., weight management, minimizing the progression of hyperglycemia, cardiovascular risk reduction) may be considered to support person-centered care goals for people at high risk of developing diabetes.

Disclosure information for each author is available at <https://doi.org/10.2337/dc23-SDIS>.

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Recommendation 3.13 was added to state that more intensive preventive approaches should be considered for individuals who are at particularly high risk of progression to diabetes.

Section 4. Comprehensive Medical Evaluation and Assessment of Comorbidities

(<https://doi.org/10.2337/dc23-S004>)

In Recommendation 4.3, language was modified to include evaluation for overall health status and setting of initial goals.

Considerable changes were made in the immunizations subsection to reflect new indications and guidance, particularly for COVID-19 and pneumococcal pneumonia vaccinations, including age-specific recommendations and the bivalent COVID-19 booster.

Table 4.1 was modified to include changes throughout Section 4.

The subsection “Nonalcoholic Fatty Liver Disease” (NAFLD) incorporates more detail regarding its diagnosis and risk stratification in primary care and diabetes clinics, such as using the fibrosis-4 index to assess the risk of liver fibrosis, and includes a fibrosis-4 index risk calculator. It expands on the rationale for fibrosis risk stratification in people with diabetes and when to refer to a gastroenterologist or hepatologist for further workup.

Discussion was added about the management of people with type 2 diabetes who have NAFLD, highlighting lifestyle changes that promote weight loss, the use of obesity pharmacotherapy with emphasis on treatment with glucagon-like peptide 1 (GLP-1) receptor agonists, bariatric surgery, and the role of diabetes medications (e.g., pioglitazone and GLP-1 receptor agonists) to treat people with type 2 diabetes and nonalcoholic fatty liver disease (NASH).

Revisions to Section 4, including the addition of **Fig. 4.2**, are based on the American Gastroenterological Association 2021 “Preparing for the NASH Epidemic: A Call to Action” (reference 64 in this section) and its associated “Clinical Care Pathway for the Risk Stratification and Management of Patients with Nonalcoholic Fatty Liver Disease” (reference 66 in this section), agreed upon by a multidisciplinary task force of experts, including representatives of the ADA. Detailed recommendations from an ADA consensus statement will be published separately in 2023.

Section 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes

(<https://doi.org/10.2337/dc23-S005>)

The title has been changed from “Facilitating Behavior Change and Well-being to Improve Health Outcomes” to be inclusive of strength-based language.

Recommendation 5.8 was added to the “Diabetes Self-Management Education and Support” subsection to address social determinants of health in guiding design and delivery of diabetes self-management education and support (DSMES). Additional information was also added supporting use of telehealth delivery of care and other digital health solutions to deliver DSMES.

Screening for food insecurity by any members of the health care team was added to the nutrition section.

A section on intermittent fasting and time-restricted eating was included in the “Eating Patterns and Meal Planning” subsection.

Emphasis was placed on supporting larger weight losses (up to 15%) based on efficacy and access of newer medications.

Language was added to Recommendation 5.23 about the harms of β -carotene supplementation based on the U.S. Preventative Services Task Force report.

The new subsection “Supporting Positive Health Behaviors” was added, including the addition of Recommendation 5.37, which encourages use of behavioral strategies by members of the diabetes care team, with the goal to support diabetes self-management and engagement in health behaviors to promote optimal diabetes health outcomes.

The “Psychosocial Issues” subsection was renamed “Psychosocial Care” to highlight the recommendations’ emphasis on providing appropriate psychosocial support to people with diabetes as part of or in conjunction with standard diabetes care.

The “Psychosocial Care” subsection includes a new Recommendation 5.55 to screen for sleep health in people with diabetes and make referrals to sleep medicine and/or qualified behavioral health professional as indicated.

Other recommendations in this subsection were revised to specify the roles of diabetes care professionals as well as qualified mental/behavioral health professionals to provide psychosocial care, to specify topics for psychosocial screening,

treatment, and referrals when indicated, and to include caregivers and family members of people with diabetes. Details were added about resources for developing psychosocial screening protocols and about intervention. Across the specific psychosocial domains (e.g., diabetes distress, anxiety), details were added about data supporting intervention and care approaches to support psychosocial and behavioral outcomes in people with diabetes and their family members.

Section 6. Glycemic Targets

(<https://doi.org/10.2337/dc23-S006>)

New language was added to Recommendation 6.5b to outline that for those with frailty or at high risk of hypoglycemia, a target of >50% time in range with <1% time below range is now recommended.

Recommendation 6.9 was added to address the effectiveness of goal setting for glycemic control.

Section 7. Diabetes Technology

(<https://doi.org/10.2337/dc23-S007>)

The importance of “preference” for diabetes devices was added in all recommendations.

Recommendation 7.12 for the use of continuous glucose monitoring (CGM) in adults with diabetes treated with basal insulin was reworded to reflect updated evidence in the literature.

Recommendation 7.15 was modified to state that people with diabetes should have uninterrupted access to their supplies to minimize gaps in CGM use.

Recommendation 7.19 was added to address CGM interfering substances, with evidence level **C**.

A new paragraph addressing substances and factors affecting CGM accuracy was added to the “Continuous Glucose Monitoring Devices” subsection. **Table 7.4** was added to address interfering substances for CGM.

Information was added on all three integrated CGM devices available, and it was specified that although there is more than one CGM system approved by the U.S. Food and Drug Administration (FDA) for use with automated insulin delivery systems, only one system with integrated CGM designation is FDA approved for

use with automated insulin delivery systems.

Literature and information was added on benefits on glycemic outcomes of early initiation of real-time CGM in children and adults and the need to continue CGM use to maximize benefits.

The paragraph on connected pens was updated to include smart pen caps.

References were updated for automated insulin delivery systems to include all the approved systems in the U.S. in 2022.

The text was updated to include do-it-yourself closed loop systems.

The “Inpatient Care” subsection was updated to include updated evidence and a paragraph on the use of CGM in the inpatient setting during the COVID-19 pandemic.

Section 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes

(<https://doi.org/10.2337/dc23-S008>)

Language was amended to reinforce that obesity is a chronic disease.

Recommendation 8.5 was added to reinforce that both small and larger weight losses should be considered as treatment goals on a case-by-case basis. Notably, larger (10% or more) weight loss may have disease-modifying effects, including diabetes remission, and may improve long-term cardiovascular outcomes.

Dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (tirzepatide) was added as a glucose-lowering option with the potential for weight loss.

Section 9. Pharmacologic Approaches to Glycemic Treatment

(<https://doi.org/10.2337/dc23-S009>)

Section 9 was updated to align with the latest consensus report on management of hyperglycemia in type 2 diabetes by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Recommendation 9.4a was added to state that healthy lifestyle behaviors, DSMES, avoidance of clinical inertia, and social determinants of health (SDOH) should be considered in the glucose-lowering management of type 2 diabetes.

Recommendation 9.4b was added to indicate that in adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure,

and/or chronic kidney disease, the treatment plan should include agents that reduce cardiorenal risk.

Recommendation 9.4c was added to address the consideration of pharmacologic approaches that provide the efficacy to achieve treatment goals.

Recommendation 9.4d was added to address weight management as an impactful component of glucose-lowering management in type 2 diabetes.

Information was added to address considerations for a GLP-1 receptor agonist prior to prandial insulin to further address prandial control and to minimize the risks of hypoglycemia and weight gain associated with insulin therapy.

Information was added to address alternative insulin routes.

Table 9.2 and **Fig. 9.3** were updated based on the latest consensus report on management of hyperglycemia in type 2 diabetes by the ADA and the EASD.

Section 10. Cardiovascular Disease and Risk Management

(<https://doi.org/10.2337/dc23-S010>)

Recommendation 10.1 was revised with updated definitions of hypertension. These recommendations align with the current definition of hypertension according to the American College of Cardiology and American Heart Association.

Recommendation 10.4 on blood pressure treatment goals in individuals with diabetes was revised to target a blood pressure of <130/80 mmHg. The discussion of the evidence to support this recommendation was extensively revised. In addition, the recently reported results of the STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) trial were added. Recommendation 10.7 was updated to consider pharmacologic treatment in people with diabetes and a confirmed blood pressure \geq 130/80. **Table 10.1** and **Fig. 10.2** were updated accordingly.

In the subsection “Pregnancy and Antihypertensive Medications,” the results of the CHAP (Chronic Hypertension and Pregnancy) trial were included to further support the current treatment goal recommendations in pregnant individuals with diabetes.

Recommendation 10.20 was revised to recommend the use of high-intensity statin therapy in individuals with diabetes aged 40–75 years at higher risk, including those with one or more

atherosclerotic cardiovascular disease risk factors, to reduce the LDL cholesterol by \geq 50% of baseline and to target an LDL cholesterol goal of <70 mg/dL.

Recommendation 10.21 was added to consider adding treatment with ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy in these individuals.

Recommendations 10.22 and 10.23 were added to recommend continuing statin therapy in adults with diabetes aged >75 years currently receiving statin therapy and to recommend that it may be reasonable to initiate moderate-intensity statin therapy in adults with diabetes aged >75 years, respectively.

Recommendation 10.26 was updated to recommend treatment with high-intensity statin therapy in individuals with diabetes and established atherosclerotic cardiovascular disease to target an LDL cholesterol reduction of \geq 50% from baseline and an LDL cholesterol goal of <55 mg/dL. If this goal is not achieved on maximum tolerated statin therapy, the addition of ezetimibe or a PCSK9 inhibitor is now recommended.

Language regarding evidence in the section “Statin Treatment” was revised to consider the evidence supporting lower LDL cholesterol goals in people with diabetes with and without established cardiovascular disease.

In the subsection “Combination Therapy for LDL Cholesterol Lowering” a paragraph was added to include inclisiran, an siRNA directed against PCSK9, as a new FDA-approved cholesterol-lowering therapy.

Recommendation 10.42b was added to recommend treatment with a sodium–glucose cotransporter 2 inhibitor in individuals with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction to improve symptoms, physical limitations, and quality of life. The discussion of evidence to support this new recommendation was included in the last paragraph of the section “Glucose-Lowering Therapies and Heart Failure.”

Recommendation 10.43 was added to recommend the addition of finerenone in the treatment of individuals with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or angiotensin receptor blocker.

This section is endorsed for the fifth consecutive year by the American College of Cardiology.

Section 11. Chronic Kidney Disease and Risk Management

(<https://doi.org/10.2337/dc23-S011>)

The recommendation order was rearranged to reflect the appropriate order for clinical interventions aimed at preventing and slowing progression of chronic kidney disease.

In Recommendation 11.5a, the levels at which a sodium–glucose cotransporter 2 inhibitor could be initiated were changed. The new levels for initiation are an estimated glomerular filtration rate ≥ 20 mL/min/1.73 m² and urinary albumin ≥ 200 mg/g creatinine.

Recommendation 11.5b also recommends that sodium–glucose cotransporter 2 inhibitor might also be effective in people with urinary albumin of normal to ≥ 200 mg/g creatinine, but this is **B** level at this time, as the study reporting this has not been published.

Mineralocorticoid receptor antagonists are now recommended along with other medications for cardiovascular and kidney protection rather than as alternatives when other treatments have not been effective.

Recommendation 11.8 addressing referral to a nephrologist was expanded to include referrals for continuously increasing urine albumin-to-creatinine ratio and/or for continuously decreasing estimated glomerular filtration rate.

Section 12. Retinopathy, Neuropathy, and Foot Care

(<https://doi.org/10.2337/dc23-S012>)

Language regarding pregnancy as a risk factor for retinopathy in people with preexisting type 1 or type 2 diabetes was revised and updated.

Screening details about autonomic neuropathy were added to Recommendation 12.17.

Language was added to the neuropathy screening subsection to clarify that treatments of other modifiable risk factors (including lipids and blood pressure) can aid in prevention of diabetic peripheral neuropathy progression in type 2 diabetes and may reduce disease progression in type 1 diabetes.

Information was added to the “Diabetic Autonomic Neuropathy” subsection to include criteria for screening for symptoms of autonomic neuropathy.

Additional references were added to support Recommendation 12.18.

Recommendation 12.20 was revised to reflect that gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes and that health care professionals should refer to a neurologist or pain specialist when pain control is not achieved within the scope of practice of the treating physician.

New information was added in the “Neuropathy” subsection, under “Treatment,” to address lipid control and blood pressure control.

The “Neuropathic Pain” subsection includes an expanded discussion of treating neuropathic pain in people with diabetes.

Recommendation 12.25 was added to address screening for peripheral arterial disease.

Recommendation 12.26 was revised to include peripheral arterial disease.

Recommendation 12.27 was edited to signify that not all people who smoke are referred to foot care specialists but that a referral is now recommended for people who smoke and also have other risk factors or symptoms.

Recommendation 12.29 was edited to reflect a change from “severe neuropathy” to “loss of protective sensation,” which is consistent with other recommendations.

Recommendation 12.30 was edited to reflect that topical oxygen therapy is not equivalent to hyperbaric oxygen therapy.

Section 13. Older Adults

(<https://doi.org/10.2337/dc23-S013>)

The language in Recommendation 13.5 was strengthened for older adults with type 1 diabetes to recommend continuous glucose monitoring to reduce hypoglycemia with an evidence grade of **A** based on a 6-month extension of the Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial and observational data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.

Recommendation 13.6 was added to communicate that for older adults with type 2 diabetes on multiple daily doses of insulin, continuous glucose monitoring should be considered to improve glyce-mic outcomes and decrease glucose variability, with an evidence grade of **B** based on results of the DIAMOND (Multiple Daily

Injections and Continuous Glucose Monitoring in Diabetes) trial.

A new Recommendation 13.7 was added: for older adults with type 1 diabetes, consider the use of automated insulin delivery systems (evidence grade **B**) and other advanced insulin delivery devices such as connected pens (evidence grade **E**) should be considered to reduce risk of hypoglycemia, based on individual ability. The addition of this recommendation was based on the results of two small randomized controlled trials (RCTs) in older adults, which demonstrated that hybrid closed-loop advanced insulin delivery improved glucose metrics relative to sensor-augmented pump therapy.

Blood pressure treatment goals in **Table 13.1** were lowered to align with evidence from multiple recent trials.

Recommendation 13.15 was split into two recommendations (now 13.17 and 13.18) to acknowledge the conceptual differences between deintensification of goals (13.17) and simplification of complex regimens (13.18).

In recommendation 13.17, deintensification of treatment goals is now recommended to reduce the risk of hypoglycemia if it can be achieved within the individualized A1C target.

In a new recommendation 13.18, simplification of complex treatment plans (especially insulin) is now recommended to reduce the risk of hypoglycemia and polypharmacy and decrease the burden of the disease if it can be achieved within the individualized A1C target.

Recommendation 13.22 was added to consider use of CGM to assess risk for hypoglycemia in older adults treated with sulfonylureas or insulin, despite the lack of evidence.

Section 14. Children and Adolescents

(<https://doi.org/10.2337/dc23-S014>)

In Recommendations 14.14, 14.106, and 14.107, the language was changed from “assess” to “screen” for consistency with Section 5.

In Recommendations 14.14 and 14.17, text was added for referral to a qualified mental health professional for further assessment and treatment.

More details were added to Recommendation 14.50 on foot examinations for neuropathy.

In Recommendations 14.97 and 14.98, “girls” was changed to “female individuals”

for more consistency in the Standards of Care.

In Recommendation 14.110, “patients” was changed to “adolescents and young adults” for clarity.

In Recommendation 14.111, “pediatric diabetes provider” was changed to “pediatric diabetes care teams” to reflect the team-based nature of diabetes care.

In Recommendation 14.113, “patient” was changed to “young adult” for clarity.

Section 15. Management of Diabetes in Pregnancy

(<https://doi.org/10.2337/dc23-S015>)

Recommendation 15.13 was added to endorse nutrition counseling to improve the quality of carbohydrates and promote a balance of macronutrients including nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish in the eating pattern.

Evidence for preconception counseling was strengthened.

A new study demonstrates that the cost of CGM in pregnancies complicated by type 1 diabetes is offset by improved maternal and neonatal outcomes and provides further support for the use CGM.

Recommendation 15.20 is now a composite recommendation based on two different multicentered RCTs with

different methodologies and different outcomes. Both RCTs support stricter blood pressure targets in pregnancy to improve outcomes. This modification is based on new data from the Chronic Hypertension and Pregnancy (CHAP) trial, which included individuals with preexisting diabetes.

The new Recommendation 15.27 supports breastfeeding to reduce the risk of maternal type 2 diabetes. The benefit of breastfeeding should be considered when choosing whether to breastfeed or formula feed.

New language was added to the text regarding the role of weight/BMI after gestational diabetes mellitus (GDM). Systematic reviews and meta-analyses demonstrate each of the following: weight loss reduces the risk of developing GDM in the subsequent pregnancy, the risk of type 2 diabetes increases by 18% per unit of BMI above the prepregnancy BMI at follow-up, and post-delivery lifestyle interventions are effective in reducing risk of type 2 diabetes. These studies highlight the importance of effective weight management after GDM.

Section 16. Diabetes Care in the Hospital

(<https://doi.org/10.2337/dc23-S016>)

In Recommendation 16.2, additional information was added to support the

use of computerized prescriber order entry (CPOE) to facilitate glycemic management as well as insulin dosing algorithms using machine learning in the future to inform these algorithms.

In Recommendation 16.5, the need for individualization of targets was expanded to include a target range of 100–180 mg/dL (5.6–10.0 mmol/L) for noncritically ill patients with “new” hyperglycemia as well as patients with known diabetes prior to admission.

Recommendation 16.7 was revised to reflect that an insulin regimen with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized patients with adequate nutritional intake.

Use of personal CGM and automated insulin delivery devices that can automatically deliver correction insulin doses and change basal insulin delivery rates in real time should be supported during hospitalization when independent self-management is feasible and proper management supervision is available.

Section 17. Diabetes Advocacy

(<https://doi.org/10.2337/dc23-S017>)

The Diabetes Care and Detention Facilities advocacy statement has been removed from this section pending future updates.

1. Improving Care and Promoting Health in Populations: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S10–S18 | <https://doi.org/10.2337/dc23-S001>

Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, and Robert A. Gabbay, on behalf of the American Diabetes Association

The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

DIABETES AND POPULATION HEALTH

Recommendations

- 1.1 Ensure treatment decisions are timely, rely on evidence-based guidelines, include social community support, and are made collaboratively with patients based on individual preferences, prognoses, comorbidities, and informed financial considerations. **B**
- 1.2 Align approaches to diabetes management with the Chronic Care Model. This model emphasizes person-centered team care, integrated long-term treatment approaches to diabetes and comorbidities, and ongoing collaborative communication and goal setting between all team members. **A**
- 1.3 Care systems should facilitate in-person and virtual team-based care, including those knowledgeable and experienced in diabetes management as part of the team, and utilization of patient registries, decision support tools, and community involvement to meet patient needs. **B**
- 1.4 Assess diabetes health care maintenance (**Table 4.1**) using reliable and relevant data metrics to improve processes of care and health outcomes, with attention to care costs. **B**

Population health is defined as “the health outcomes of a group of individuals, including the distribution of health outcomes within the group”; these outcomes can be measured in terms of health outcomes (mortality, morbidity, health, and functional status), disease burden (incidence and prevalence), and behavioral and metabolic factors (physical activity, nutrition, A1C, etc.) (1). Clinical practice recommendations for health care professionals are tools that can ultimately improve health across populations; however, for optimal outcomes, diabetes care must also be individualized for

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each patient. Thus, efforts to improve population health will require a combination of policy-level, system-level, and patient-level approaches. With such an integrated approach in mind, the American Diabetes Association (ADA) highlights the importance of patient-centered care, defined as care that considers individual patient comorbidities and prognoses; is respectful of and responsive to patient preferences, needs, and values; and ensures that patient values guide all clinical decisions (2). Furthermore, social determinants of health (SDOH)—often out of direct control of the individual and potentially representing lifelong risk—contribute to health care and psychosocial outcomes and must be addressed to improve all health outcomes (3). Clinical practice recommendations, whether based on evidence or expert opinion, are intended to guide an overall approach to care. The science and art of health care come together when the clinician makes treatment decisions for a patient who may not meet the eligibility criteria used in the studies on which guidelines are based. Recognizing that one size does not fit all, the standards presented here provide guidance for when and how to adapt recommendations for an individual. This section provides guidance for health care professionals as well as health systems and policymakers.

Care Delivery Systems

The proportion of people with diabetes who achieve recommended A1C, blood pressure, and LDL cholesterol levels has fluctuated over the years (4). Glycemic management and management of cholesterol through dietary intake remain challenging. In 2013–2016, 64% of adults with diagnosed diabetes met individualized A1C target levels, 70% achieved recommended blood pressure target, 57% met the LDL cholesterol target level, and 85% were nonsmokers (4). However, only 23% met targets for glycemic, blood pressure, and LDL cholesterol measures while also avoiding smoking (4). The mean A1C nationally among people with diabetes increased slightly from 7.3% in 2005–2008 to 7.5% in 2013–2016 based on the National Health and Nutrition Examination Survey (NHANES), with younger adults, women, and non-Hispanic Black individuals less likely to meet treatment targets (4). Certain segments

of the population, such as young adults and individuals with complex comorbidities, financial or other social hardships, and/or limited English proficiency, face particular challenges to goal-based care (5–7). Even after adjusting for these patient factors, the persistent variability in the quality of diabetes care across health care professionals and practice settings indicates that substantial system-level improvements are still needed.

Diabetes poses a significant financial burden to individuals and society. It is estimated that the annual cost of diagnosed diabetes in the U.S. in 2017 was \$327 billion, including \$237 billion in direct health care costs and \$90 billion in reduced productivity. After adjusting for inflation, the economic costs of diabetes increased by 26% from 2012 to 2017 (8). This is attributed to the increased prevalence of diabetes and the increased cost per person with diabetes. Therefore, on going population health strategies are needed to reduce costs and provide optimized care.

Chronic Care Model

Numerous interventions to promote the recommended standards have been implemented. However, a major barrier to optimal care is a delivery system that is often fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the coordinated delivery of chronic care. The Chronic Care Model (CCM) takes these factors into consideration and is an effective framework for improving the quality of diabetes care (9).

Six Core Elements. The CCM includes six core elements to optimize the care of people with chronic disease:

1. Delivery system design (moving from a *reactive* to a *proactive* care delivery system where planned visits are coordinated through a team-based approach)
2. Self-management support
3. Decision support (basing care on evidence-based, effective care guidelines)
4. Clinical information systems (using registries that can provide patient-specific and population-based support to the care team)
5. Community resources and policies (identifying or developing resources to support healthy lifestyles)
6. Health systems (to create a quality-oriented culture)

A 5-year effectiveness study of the CCM in 53,436 people with type 2 diabetes in the primary care setting suggested that the use of this model of care delivery reduced the cumulative incidence of diabetes-related complications and all-cause mortality (10). Patients who were enrolled in the CCM experienced a reduction in cardiovascular disease risk by 56.6%, microvascular complications by 11.9%, and mortality by 66.1% (10). In addition, another study suggested that health care utilization was lower in the CCM group, which resulted in health care savings of \$7,294 per individual over the study period (11).

Redefining the roles of the health care delivery team and empowering patient self-management are fundamental to the successful implementation of the CCM (12). Collaborative, multidisciplinary teams are best suited to provide care for people with chronic conditions such as diabetes and to facilitate patients' self-management (13–15). There are references to guide the implementation of the CCM into diabetes care delivery, including opportunities and challenges (16).

Strategies for System-Level Improvement

Optimal diabetes management requires an organized, systematic approach and the involvement of a coordinated team of dedicated health care professionals working in an environment where patient-centered, high-quality care is a priority (7,16,17). While many diabetes care processes have improved nationally in the past decade, the overall quality of care for people with diabetes remains suboptimal (4). Efforts to increase the quality of diabetes care include providing care that is concordant with evidence-based guidelines (18); expanding the role of teams to implement more intensive disease management strategies (7,19,20); tracking medication-taking behavior at a systems level (21); redesigning the organization of the care process (22); implementing electronic health record tools (23,24); empowering and educating patients (25,26); removing financial barriers and reducing patient out-of-pocket costs for diabetes education, eye exams, diabetes technology, and necessary medications (7); assessing and addressing psychosocial issues (27,28);

and identifying, developing, and engaging community resources and public policies that support healthy lifestyles (29). The National Diabetes Education Program maintains an online resource (cdc.gov/diabetes/professional-info/training.html) to help health care professionals design and implement more effective health care delivery systems for those with diabetes. Given the pluralistic needs of people with diabetes and that the constant challenges they experience vary over the course of disease management (complex insulin treatment plans, new technology, etc.), a diverse team with complementary expertise is consistently recommended (30).

Care Teams

The care team, which centers around the patient, should avoid therapeutic inertia and prioritize timely and appropriate intensification of behavior change (nutrition and physical activity) and/or pharmacologic therapy for patients who have not achieved the recommended metabolic targets (31–33). Strategies shown to improve care team behavior and thereby catalyze reductions in A1C, blood pressure, and/or LDL cholesterol include engaging in explicit and collaborative goal setting with patients (34,35); integrating evidence-based guidelines and clinical information tools into the process of care (18,36,37); identifying and addressing language, numeracy, or cultural barriers to care (37–39); soliciting performance feedback, setting reminders, and providing structured care (e.g., guidelines, formal case management, and patient education resources) (7); and incorporating care management teams including nurses, dietitians, pharmacists, and other health care professionals (19,38). In addition, initiatives such as the Patient-Centered Medical Home can improve health outcomes by fostering comprehensive primary care and offering new opportunities for team-based chronic disease management (39).

Telehealth

Telehealth is a growing field that may increase access to care for people with diabetes. The American Telemedicine Association defines telemedicine as the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. Telehealth includes

a growing variety of applications and services using two-way video, smartphones, wireless tools, and other forms of telecommunications technology (40). Often used interchangeably with telemedicine, telehealth describes a broader range of digital health services in health care delivery (41). This includes synchronous, asynchronous, and remote patient monitoring.

Telehealth should be used complementary to in-person visits to optimize glycemic management in people with unmanaged diabetes (42). Increasingly, evidence suggests that various telehealth modalities may facilitate reducing A1C in people with type 2 diabetes compared with usual care or in addition to usual care (43), and findings suggest that telemedicine is a safe method of delivering type 1 diabetes care to rural patients (44). For rural populations or those with limited physical access to health care, telemedicine has a growing body of evidence for its effectiveness, particularly with regard to glycemic management as measured by A1C (45–47). In addition, evidence supports the effectiveness of telehealth in diabetes, hypertension, and dyslipidemia interventions (48) as well as the telehealth delivery of motivational interviewing (49). Interactive strategies that facilitate communication between health care professionals and patients, including the use of web-based portals or text messaging and those that incorporate medication adjustment, appear more effective. Telehealth and other virtual environments can also be used to offer diabetes self-management education and clinical support and remove geographic and transportation barriers for patients living in underresourced areas or with disabilities (50). Telehealth resources can also have a role in addressing the social determinants of health in young adults with diabetes (51). However, limited data are available on the effectiveness across different populations (52).

Behaviors and Well-being

Successful diabetes care also requires a systematic approach to supporting patients' behavior change efforts. High-quality diabetes self-management education and support (DSMES) has been shown to improve patient self-management, satisfaction, and glucose outcomes. National DSMES standards call for an integrated approach that includes clinical

content and skills, behavioral strategies (goal setting, problem-solving), and engagement with psychosocial concerns. Increasingly, such support is being adapted for online platforms that have the potential to promote patient access to this important resource. These curriculums need to be tailored to the needs of the intended populations, including addressing the "digital divide," i.e., access to the technology required for implementation (53–56).

For more information on DSMES, see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes."

Cost Considerations for Medication-Taking Behaviors

The cost of diabetes medications and devices is an ongoing barrier to achieving glycemic goals. Up to 25% of patients who are prescribed insulin report cost-related insulin underuse (57). Insulin underuse due to cost has also been termed "cost-related medication non-adherence" (here referred to as cost-related barriers to medication use). The cost of insulin has continued to increase in recent years for reasons that are not entirely clear. There are recommendations from the ADA Insulin Access and Affordability Working Group for approaches to this issue from a systems level (58). Recommendations including concepts such as cost-sharing for insured people with diabetes should be based on the lowest price available, the list price for insulins that closely reflects the net price, and health plans that ensure people with diabetes can access insulin without undue administrative burden or excessive cost (58).

The cost of medications (not only insulin) influences prescribing patterns and medication use because of patient burden and lack of secondary payer support (public and private insurance) for effective approved glucose-lowering, cardiovascular disease risk-reducing, and weight management therapeutics. Financial barriers remain a major source of health disparities, and costs should be a focus of treatment goals (59). (See TAILORING TREATMENT FOR SOCIAL CONTEXT and TREATMENT CONSIDERATIONS.) Reduction in cost-related barriers to medication use is associated with better biologic and psychological outcomes, including quality of life.

Access to Care and Quality Improvement

The Affordable Care Act and Medicaid expansion have increased access to care for many individuals with diabetes, emphasizing the protection of people with preexisting conditions, health promotion, and disease prevention (60). In fact, health insurance coverage increased from 84.7% in 2009 to 90.1% in 2016 for adults with diabetes aged 18–64 years. Coverage for those aged ≥ 65 years remained nearly universal (61). Patients who have either private or public insurance coverage are more likely to meet quality indicators for diabetes care (62). As mandated by the Affordable Care Act, the Agency for Healthcare Research and Quality developed a National Quality Strategy based on triple aims that include improving the health of a population, overall quality and patient experience of care, and per capita cost (63,64). As health care systems and practices adapt to the changing landscape of health care, it will be important to integrate traditional disease-specific metrics with measures of patient experience, as well as cost, in assessing the quality of diabetes care (65,66). Information and guidance specific to quality improvement and practice transformation for diabetes care are available from the National Institute of Diabetes and Digestive and Kidney Diseases guidance on diabetes care and quality (67). Using patient registries and electronic health records, health systems can evaluate the quality of diabetes care being delivered and perform intervention cycles as part of quality improvement strategies (68). Improvement of health literacy and numeracy is also a necessary component to improve care (69,70). Critical to these efforts is health professional adherence to clinical practice recommendations (Table 4.1) and the use of accurate, reliable data metrics that include sociodemographic variables to examine health equity within and across populations (71).

In addition to quality improvement efforts, other strategies that simultaneously improve the quality of care and potentially reduce costs are gaining momentum and include reimbursement structures that, in contrast to visit-based billing, reward the provision of appropriate and high-quality care to achieve metabolic goals (72), value-based payments, and incentives that accommodate

personalized care goals (7,73). (Also see COST CONSIDERATIONS FOR MEDICATION-TAKING BEHAVIORS, above, regarding cost-related barriers to medication use.)

TAILORING TREATMENT FOR SOCIAL CONTEXT

Recommendations

- 1.5 Assess food insecurity, housing insecurity/homelessness, financial barriers, and social capital/social community support to inform treatment decisions, with referral to appropriate local community resources. **A**
- 1.6 Provide patients with additional self-management support from lay health coaches, navigators, or community health workers when available. **A**
- 1.7 Consider the involvement of community health workers to support the management of diabetes and cardiovascular risk factors, especially in underserved communities and health care systems. **B**

Health inequities related to diabetes and its complications are well documented, are heavily influenced by SDOH, and have been associated with greater risk for diabetes, higher population prevalence, and poorer diabetes outcomes (74–78). SDOH are defined as the economic, environmental, political, and social conditions in which people live and are responsible for a major part of health inequality worldwide (79). Greater exposure to adverse SDOH over the life course results in worse health (80). The ADA recognizes the association between social and environmental factors and the prevention and treatment of diabetes and has issued a call for research that seeks to understand better how these social determinants influence behaviors and how the relationships between these variables might be modified for the prevention and management of diabetes (81,82). While a comprehensive strategy to reduce diabetes-related health inequities in populations has not been formally studied, general recommendations from other chronic disease management and prevention models can be drawn upon to inform systems-level strategies in diabetes (83). For example, the National Academy of Medicine has published a

framework for educating health care professionals on the importance of SDOH (84). Furthermore, there are resources available for the inclusion of standardized sociodemographic variables in electronic health records to facilitate the measurement of health inequities and the impact of interventions designed to reduce those inequities (65,84,85).

SDOH are not consistently recognized and often go undiscussed in the clinical encounter (77). Among people with chronic illnesses, two-thirds of those who reported not taking medications as prescribed due to cost-related barriers to medication use never shared this with their physician (86). In a study using data from the National Health Interview Survey (NHIS), Patel et al. (77) found that one-half of adults with diabetes reported financial stress and one-fifth reported food insecurity. A recent Canadian study noted an association of one or more adverse SDOH and health care utilization and poor diabetes outcomes in high-risk children with type 1 diabetes (86).

Another population in which such issues must be considered is older adults, where social difficulties may impair quality of life and increase the risk of functional dependency (87) (see Section 13, “Older Adults,” for a detailed discussion of social considerations in older adults). Creating systems-level mechanisms to screen for SDOH may help overcome structural barriers and communication gaps between patients and health care professionals (77,88). In addition, brief, validated screening tools for some SDOH exist and could facilitate discussion around factors that significantly impact treatment during the clinical encounter. Below is a discussion of assessment and treatment considerations in the context of food insecurity, homelessness, limited English proficiency, limited health literacy, and low literacy.

Food Insecurity

Food insecurity is the unreliable availability of nutritious food and the inability to consistently obtain food without resorting to socially unacceptable practices. Over 18% of the U.S. population reported food insecurity between 2005 and 2014 (89). The rate is higher in some racial/ethnic minority groups, including African American and Latino populations, low-income households, and homes

headed by single mothers. The food insecurity rate in individuals with diabetes may be up to 20% (90). Additionally, the risk for type 2 diabetes is increased twofold in those with food insecurity (81) and has been associated with lower engagement in self-care behaviors and medication use, depression, diabetes distress, and worse glycemic management when compared with individuals who are food secure (91–93). Older adults with food insecurity are more likely to have emergency department visits and hospitalizations compared with older adults who do not report food insecurity (94). Risk for food insecurity can be assessed with a validated two-item screening tool (95) that includes the following statements: 1) “Within the past 12 months, we worried whether our food would run out before we got money to buy more” and 2) “Within the past 12 months the food we bought just didn’t last, and we didn’t have money to get more.” An affirmative response to either statement had a sensitivity of 97% and specificity of 83%. Interventions such as food prescription programs are considered promising to address food insecurity by integrating community resources into primary care settings and directly dealing with food deserts in underserved communities (96,97).

Treatment Considerations

In those with diabetes and food insecurity, the priority is mitigating the increased risk for uncontrolled hyperglycemia and severe hypoglycemia. The reasons for the increased risk of hyperglycemia include the steady consumption of inexpensive carbohydrate-rich processed foods, binge eating, financial constraints to filling diabetes medication prescriptions, and anxiety/depression leading to poor diabetes self-care behaviors. Hypoglycemia can occur due to inadequate or erratic carbohydrate consumption following the administration of sulfonylureas or insulin. See **Table 9.2** for drug-specific and patient factors, including cost and risk of hypoglycemia, which may be important considerations for adults with food insecurity and type 2 diabetes. Health care professionals should consider these factors when making treatment decisions for people with food insecurity and seek local resources to help people with diabetes and their family members

obtain nutritious food more regularly (98).

Homelessness and Housing Insecurity

Homelessness/housing insecurity often accompanies many additional barriers to diabetes self-management, including food insecurity, literacy and numeracy deficiencies, lack of insurance, cognitive dysfunction, and mental health issues (99). The prevalence of diabetes in the homeless population is estimated to be around 8% (100). Additionally, people with diabetes who are homeless need secure places to keep their diabetes supplies and refrigerator access to properly store their insulin and take it on a regular schedule. The risk for homelessness can be ascertained using a brief risk assessment tool developed and validated for use among veterans (101). Housing insecurity has also been shown to be directly associated with a person’s ability to maintain their diabetes self-management (102). Given the potential challenges, health care professionals who care for either homeless or housing-insecure individuals should be familiar with resources or have access to social workers who can facilitate stable housing for their patients as a way to improve diabetes care (103).

Migrant and Seasonal Agricultural Workers

Migrant and seasonal agricultural workers may have a higher risk of type 2 diabetes than the overall population. While migrant farmworker-specific data are lacking, most agricultural workers in the U.S. are Latino, a population with a high rate of type 2 diabetes. In addition, living in severe poverty brings with it food insecurity, high chronic stress, and an increased risk of diabetes; there is also an association between the use of certain pesticides and the incidence of diabetes (104).

Data from the Department of Labor indicate that there are 2.5–3 million agricultural workers in the U.S. These agricultural workers travel throughout the country, serving as the backbone for a multibillion-dollar agricultural industry. According to 2021 health center data, 175 health centers across the U.S. reported that they provided health care services to 893,260 adult agricultural patients, and 91,124 had encounters for diabetes (10.2%) (105).

Migrant farmworkers encounter numerous and overlapping barriers to receiving care. Migration, which may occur as frequently as every few weeks for farmworkers, disrupts care. In addition, cultural and linguistic barriers, lack of transportation and money, lack of available work hours, unfamiliarity with new communities, lack of access to resources, and other barriers prevent migrant farmworkers from accessing health care. Without regular care, those with diabetes may suffer severe and often expensive complications that affect quality of life.

Health care professionals should be attuned to all patients’ working and living conditions. For example, if a migrant farmworker with diabetes presents for care, appropriate referrals should be initiated to social workers and community resources, as available, to assist with removing barriers to care.

Language Barriers

Health care professionals who care for non-English speakers should develop or offer educational programs and materials in languages specific to these patients with the specific goals of preventing diabetes and building diabetes awareness in people who cannot easily read or write in English. The National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (National CLAS Standards) provide guidance on how health care professionals can reduce language barriers by improving their cultural competency, addressing health literacy, and ensuring communication with language assistance (106). In addition, the National CLAS Standards website (thinkculturalhealth.hhs.gov) offers several resources and materials that can be used to improve the quality of care delivery to non-English-speaking patients (106).

Health Literacy and Numeracy

Health literacy is defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate decisions (69). Health literacy is strongly associated with patients engaging in complex disease management and self-care (107). Approximately 80 million adults in the U.S. are estimated to have limited or low health literacy (70). Clinicians and

diabetes care and education specialists should ensure they provide easy-to-understand information and reduce unnecessary complexity when developing care plans with patients. Interventions addressing low health literacy in populations with diabetes seem effective in improving diabetes outcomes, including ones focusing primarily on patient education, self-care training, or disease management. Combining easily adapted materials with formal diabetes education demonstrates effectiveness on clinical and behavioral outcomes in populations with low literacy (108). However, evidence supporting these strategies is largely limited to observational studies. More research is needed to investigate the most effective strategies for enhancing both acquisition and retention of diabetes knowledge and examine different media and strategies for delivering interventions to patients (109).

Health numeracy is also essential in diabetes prevention and management. Health numeracy requires primary numeric skills, applied health numeracy, and interpretive health numeracy. An emotional component also affects a person's ability to understand concepts of risk, probability, and communication of scientific evidence (110). People with pre-diabetes or diabetes often need to perform numeric tasks such as interpreting food labels and blood glucose levels to make treatment decisions such as medication dosing. Thus, both health literacy and numeracy are necessary for enabling effective communication between patient and health professional, arriving at a treatment plan, and making diabetes self-management task decisions. If patients appear not to understand concepts associated with treatment decisions, both can be assessed using standardized screening measures (111). Adjunctive education and support may be indicated if limited health literacy and numeracy are barriers to optimal care decisions (27).

Social Capital/Community Support

Social capital, which comprises community and personal network instrumental support, promotes better health, whereas lack of social support is associated with poorer health outcomes in individuals with diabetes (82). Of particular concern are the SDOH, including racism and discrimination, which are likely to

be lifelong (112). These factors are rarely addressed in routine treatment or disease management but may be underlying reasons for lower engagement in self-care behaviors and medication use. Identification or development of community resources to support healthy lifestyles is a core element of the CCM (9), with a particular need to incorporate relevant social support networks. There is currently a paucity of evidence regarding enhancing these resources for those most likely to benefit from such intervention strategies.

Health care community linkages are receiving increasing attention from the American Medical Association, the Agency for Healthcare Research and Quality, and others to promote the translation of clinical recommendations for nutrition and physical activity in real-world settings (113). Community health workers (CHWs) (114), peer supporters (115–117), and lay leaders (118) may assist in the delivery of DSMES services (84,119), particularly in underserved communities. The American Public Health Association defines a CHW as a “frontline public health worker who is a trusted member of and/or has an unusually close understanding of the community served” (120). CHWs can be part of a cost-effective, evidence-based strategy to improve the management of diabetes and cardiovascular risk factors in underserved communities and health care systems (121). The CHW scope of practice in areas such as outreach and communication, advocacy, social support, basic health education, referrals to community clinics, etc., has successfully provided social and primary preventive services to underserved populations in rural and hard-to-reach communities. Even though CHWs' core competencies are not clinical in nature, in some circumstances, clinicians may delegate limited clinical tasks to CHWs. If such is the case, these tasks must always be performed under the direction and supervision of the delegating health professional and following state health care laws and statutes (122,123).

References

- Kindig D, Stoddart G. What is population health? *Am J Public Health* 2003;93:380–383
- Institute of Medicine, Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC National Academies Press 2001

- Haire-Joshu D, Hill-Briggs F. The next generation of diabetes translation: a path to health equity. *Annu Rev Public Health* 2019;40:391–410
- Kazemian P, Shebl FM, McCann N, Walensky RP, Wexler DJ. Evaluation of the cascade of diabetes care in the United States, 2005–2016. *JAMA Intern Med* 2019;179:1376–1385
- Kerr EA, Heisler M, Krein SL, et al. Beyond comorbidity counts: how do comorbidity type and severity influence diabetes patients' treatment priorities and self-management? *J Gen Intern Med* 2007;22:1635–1640
- Fernandez A, Schillinger D, Warton EM, et al. Language barriers, physician-patient language concordance, and glycemic control among insured Latinos with diabetes: the Diabetes Study of Northern California (DISTANCE). *J Gen Intern Med* 2011;26:170–176
- TRIAD Study Group. Health systems, patients factors, and quality of care for diabetes: a synthesis of findings from the TRIAD study. *Diabetes Care* 2010;33:940–947
- American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care* 2018;41:917–928
- Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. *Prev Chronic Dis* 2013;10:E26
- Wan EYF, Fung CSC, Jiao FF, et al. Five-year effectiveness of the multidisciplinary Risk Assessment and Management Programme—Diabetes Mellitus (RAMP-DM) on diabetes-related complications and health service uses—a population-based and propensity-matched cohort study. *Diabetes Care* 2018;41:49–59
- Jiao FF, Fung CSC, Wan EYF, et al. Five-year cost-effectiveness of the Multidisciplinary Risk Assessment and Management Programme—Diabetes Mellitus (RAMP-DM). *Diabetes Care* 2018;41:250–257
- Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. *Health Aff (Millwood)* 2009;28:75–85
- Piatt GA, Anderson RM, Brooks MM, et al. 3-year follow-up of clinical and behavioral improvements following a multifaceted diabetes care intervention: results of a randomized controlled trial. *Diabetes Educ* 2010;36:301–309
- Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010;363:2611–2620
- Parchman ML, Zeber JE, Romero RR, Pugh JA. Risk of coronary artery disease in type 2 diabetes and the delivery of care consistent with the chronic care model in primary care settings: a STARNet study. *Med Care* 2007;45:1129–1134
- Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet* 2012;379:2252–2261
- Schmittiel JA, Gopalan A, Lin MW, Banerjee S, Chau CV, Adams AS. Population health management for diabetes: health care system-level approaches for improving quality and addressing disparities. *Curr Diab Rep* 2017;17:31
- O'Connor PJ, Bodkin NL, Fradkin J, et al. Diabetes performance measures: current status and future directions. *Diabetes Care* 2011;34:1651–1659

19. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. *JAMA* 2013;310:699–705
20. Peikes D, Chen A, Schore J, Brown R. Effects of care coordination on hospitalization, quality of care, and health care expenditures among Medicare beneficiaries: 15 randomized trials. *JAMA* 2009;301:603–618
21. Raebel MA, Schmittiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care* 2013;51(Suppl. 3):S11–S21
22. Feifer C, Nemeth L, Nietert PJ, et al. Different paths to high-quality care: three archetypes of top-performing practice sites. *Ann Fam Med* 2007;5:233–241
23. Reed M, Huang J, Graetz I, et al. Outpatient electronic health records and the clinical care and outcomes of patients with diabetes mellitus. *Ann Intern Med* 2012;157:482–489
24. Cebul RD, Love TE, Jain AK, Hebert CJ. Electronic health records and quality of diabetes care. *N Engl J Med* 2011;365:825–833
25. Battersby M, Von Korff M, Schaefer J, et al. Twelve evidence-based principles for implementing self-management support in primary care. *Jt Comm J Qual Patient Saf* 2010;36:561–570
26. Grant RW, Wald JS, Schnipper JL, et al. Practice-linked online personal health records for type 2 diabetes mellitus: a randomized controlled trial. *Arch Intern Med* 2008;168:1776–1782
27. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2016;39:2126–2140
28. Davis J, Fischl AH, Beck J, et al. 2022. National standards for diabetes self-management education and support. *Sci Diabetes Self Manag Care* 2022;48:44–59
29. Pullen-Smith B, Carter-Edwards L, Leathers KH. Community health ambassadors: a model for engaging community leaders to promote better health in North Carolina. *J Public Health Manag Pract* 2008;14(Suppl.):S73–S81
30. Handlow NE, Nolton B, Winter SE, Wessel CM, Pennock J. 180-LB: Impact of a multidisciplinary diabetes care team in primary care settings on glycemic control (Late-breaking poster presentation) *Diabetes* 2019;68(Suppl. 1). Accessed 11 October 2022. Available from <https://www.healthypeople.gov/2010/hp2020/advisory/Phasel/default.htm>
31. Davidson MB. How our current medical care system fails people with diabetes: lack of timely, appropriate clinical decisions. *Diabetes Care* 2009;32:370–372
32. Selby JV, Uratsu CS, Fireman B, et al. Treatment intensification and risk factor control: toward more clinically relevant quality measures. *Med Care* 2009;47:395–402
33. Raebel MA, Ellis JL, Schroeder EB, et al. Intensification of antihyperglycemic therapy among patients with incident diabetes: a Surveillance Prevention and Management of Diabetes Mellitus (SUPREME-DM) study. *Pharmacoepidemiol Drug Saf* 2014;23:699–710
34. Grant RW, Pabon-Nau L, Ross KM, Youatt EJ, Pandiscio JC, Park ER. Diabetes oral medication initiation and intensification: patient views compared with current treatment guidelines. *Diabetes Educ* 2011;37:78–84
35. Tamhane S, Rodriguez-Gutierrez R, Hargraves I, Montori VM. Shared decision-making in diabetes care. *Curr Diab Rep* 2015;15:112
36. Garg AX, Adhikari NKJ, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* 2005;293:1223–1238
37. Smith SA, Shah ND, Bryant SC, et al.; Evidens Research Group. Chronic care model and shared care in diabetes: randomized trial of an electronic decision support system. *Mayo Clin Proc* 2008;83:747–757
38. Stone RA, Rao RH, Sevick MA, et al. Active care management supported by home telemonitoring in veterans with type 2 diabetes: the DiaTel randomized controlled trial. *Diabetes Care* 2010;33:478–484
39. Bojadzievski T, Gabbay RA. Patient-centered medical home and diabetes. *Diabetes Care* 2011;34:1047–1053
40. Telligen and gpTRAC (Great Plains Telehealth Resource & Assistance Center). Telehealth Start-Up and Resource Guide Version 1.1, October 2014. Accessed 11 October 2022. Available from https://www.healthit.gov/sites/default/files/telehealthguide_final_0.pdf
41. American Medical Association. AMA Telehealth Quick Guide. Accessed 29 August 2022. Available from <https://www.ama-assn.org/practice-management/digital/ama-telehealth-quick-guide>
42. Mullur RS, Hsiao JS, Mueller K. Telemedicine in diabetes care. *Am Fam Physician* 2022;105:281–288
43. Lee SWH, Chan CKY, Chua SS, Chaiyakunapruk N. Comparative effectiveness of telemedicine strategies on type 2 diabetes management: a systematic review and network meta-analysis. *Sci Rep* 2017;7:12680
44. Xu T, Pujara S, Sutton S, Rhee M. Telemedicine in the management of type 1 diabetes. *Prev Chronic Dis* 2018;15:170168
45. Faruque LI, Wiebe N, Ehteshami-Afshar A, et al.; Alberta Kidney Disease Network. Effect of telemedicine on glycated hemoglobin in diabetes: a systematic review and meta-analysis of randomized trials. *CMAJ* 2017;189:E341–E364
46. Marcolino MS, Maia JX, Alkmim MBM, Boersma E, Ribeiro AL. Telemedicine application in the care of diabetes patients: systematic review and meta-analysis. *PLoS One* 2013;8:e79246
47. Heitkemper EM, Mamykina L, Travers J, Smaldone A. Do health information technology self-management interventions improve glycemic control in medically underserved adults with diabetes? A systematic review and meta-analysis. *J Am Med Inform Assoc* 2017;24:1024–1035
48. Timpel P, Oswald S, Schwarz PEH, Harst L. Mapping the evidence on the effectiveness of telemedicine interventions in diabetes, dyslipidemia, and hypertension: an umbrella review of systematic reviews and meta-analyses. *J Med Internet Res* 2020;22:e16791
49. McDaniel CC, Kavookjian J, Whitley HP. Telehealth delivery of motivational interviewing for diabetes management: a systematic review of randomized controlled trials. *Patient Educ Couns* 2022;105:805–820
50. Reagan L, Pereira K, Jefferson V, et al. Diabetes self-management training in a virtual environment. *Diabetes Educ* 2017;43:413–421
51. Garcia JF, Fogel J, Reid M, Bisno DI, Raymond JK. Telehealth for young adults with diabetes: addressing social determinants of health. *Diabetes Spectr* 2021;34:357–362
52. Haynes SC, Kompala T, Neinstein A, Rosenthal J, Crossen S. Disparities in telemedicine use for subspecialty diabetes care during COVID-19 shelter-in-place orders. *J Diabetes Sci Technol* 2021;15:986–992
53. Dack C, Ross J, Stevenson F, et al. A digital self-management intervention for adults with type 2 diabetes: combining theory, data and participatory design to develop HeLP-Diabetes. *Internet Interv* 2019;17:100241
54. Lee MK, Lee DY, Ahn HY, Park CY. A novel user utility score for diabetes management using tailored mobile coaching: secondary analysis of a randomized controlled trial. *JMIR Mhealth Uhealth* 2021;9:e17573
55. Dening J, Islam SMS, George E, Maddison R. Web-based interventions for dietary behavior in adults with type 2 diabetes: systematic review of randomized controlled trials. *J Med Internet Res* 2020;22:e16437
56. Omar MA, Hasan S, Palaia S, Mahameed S. The impact of a self-management educational program coordinated through WhatsApp on diabetes control. *Pharm Pract (Granada)* 2020;18:1841
57. Herkert D, Vijayakumar P, Luo J, et al. Cost-related insulin underuse among patients with diabetes. *JAMA Intern Med* 2019;179:112–114
58. Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Conclusions and recommendations. *Diabetes Care* 2018;41:1299–1311
59. Taylor SI. The high cost of diabetes drugs: disparate impact on the most vulnerable patients. *Diabetes Care* 2020;43:2330–2332
60. Myerson R, Laiteerapong N. The affordable care act and diabetes diagnosis and care: exploring the potential impacts. *Curr Diab Rep* 2016;16:27
61. Casagrande SS, McEwen LN, Herman WH. Changes in health insurance coverage under the affordable care act: a national sample of U.S. adults with diabetes, 2009 and 2016. *Diabetes Care* 2018;41:956–962
62. Doucette ED, Salas J, Scherrer JF. Insurance coverage and diabetes quality indicators among patients in NHANES. *Am J Manag Care* 2016;22:484–490
63. Stiefel M, Nolan K. Measuring the triple aim: a call for action. *Popul Health Manag* 2013;16:219–220
64. Agency for Healthcare Research and Quality. About the National Quality Strategy. Accessed 11 October 2022. Available from <https://www.ahrq.gov/workingforquality/about/index.html>
65. National Quality Forum. National voluntary consensus standards for ambulatory care—measuring healthcare disparities. 2008. Accessed 11 October 2022. Available from https://www.qualityforum.org/Publications/2008/03/National_Voluntary_Consensus_Standards_for_Ambulatory_Care%E2%80%94Measuring_Healthcare_Disparities.aspx
66. Burstin H, Johnson K. Getting to better care and outcomes for diabetes through measurement. Evidence-based diabetes management. *Am J Manag Care* 2016;22(SP4):SP145–SP146
67. National Institute of Diabetes and Digestive and Kidney Diseases. Diabetes and health professionals. Accessed 11 August 2022. Available

- from <https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/diabetes>
68. O'Connor PJ, Sperl-Hillen JM, Fazio CJ, Averbeck BM, Rank BH, Margolis KL. Outpatient diabetes clinical decision support: current status and future directions. *Diabet Med* 2016;33:734–741
 69. Institute of Medicine, Committee on Health Literacy. *Health Literacy: A Prescription to End Confusion*. Nielsen-Bohman L, Panzer AM, Kindig DA, Eds. Washington, DC, National Academies Press, 2004. PMID: 25009856
 70. Schaffler J, Leung K, Tremblay S, et al. The effectiveness of self-management interventions for individuals with low health literacy and/or low income: a descriptive systematic review. *J Gen Intern Med* 2018;33:510–523
 71. Centers for Medicare & Medicaid Services. CMS Framework for Health Equity. Accessed 29 August 2022. Available from <https://www.cms.gov/about-cms/agency-information/omh/health-equity-programs/cms-framework-for-health-equity>
 72. Rosenthal MB, Cutler DM, Feder J. The ACO rules—striking the balance between participation and transformative potential. *N Engl J Med* 2011;365:e6
 73. Washington AE, Lipstein SH. The Patient-Centered Outcomes Research Institute—promoting better information, decisions, and health. *N Engl J Med* 2011;365:e31
 74. Hutchinson RN, Shin S. Systematic review of health disparities for cardiovascular diseases and associated factors among American Indian and Alaska Native populations. *PLoS One* 2014;9:e80973
 75. Borschuk AP, Everhart RS. Health disparities among youth with type 1 diabetes: a systematic review of the current literature. *Fam Syst Health* 2015;33:297–313
 76. Walker RJ, Strom Williams J, Egede LE. Influence of race, ethnicity and social determinants of health on diabetes outcomes. *Am J Med Sci* 2016;351:366–373
 77. Patel MR, Piette JD, Resnicow K, Kowalski-Dobson T, Heisler M. Social determinants of health, cost-related nonadherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health Interview Survey. *Med Care* 2016;54:796–803
 78. Steve SL, Tung EL, Schlichtman JJ, Peek ME. Social disorder in adults with type 2 diabetes: building on race, place, and poverty. *Curr Diab Rep* 2016;16:72
 79. Commission on Social Determinants of Health. Closing the gap in a generation: health equity through action on the social determinants of health. Geneva, World Health Organization, 2008. Accessed 11 October 2022. Available from <https://www.who.int/publications/i/item/WHO-IER-CSDH-08.1>
 80. Dixon B, Peña M-M, Taveras EM. Lifecourse approach to racial/ethnic disparities in childhood obesity. *Adv Nutr* 2012;3:73–82
 81. Hill JO, Galloway JM, Goley A, et al. Scientific statement: socioeconomic determinants of prediabetes and type 2 diabetes. *Diabetes Care* 2013;36:2430–2439
 82. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. *Diabetes Care* 2020;44:258–279
 83. The Secretary's Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2020. Phase I report: recommendations for the framework and format of Healthy People 2020. Accessed 11 October 2022. Available from <https://www.healthypeople.gov/2010/hp2020/advisory/PhaseI/default.htm>
 84. National Academies of Sciences, Engineering, and Medicine. *A Framework for Educating Health Professionals to Address the Social Determinants of Health*. Washington, DC, National Academies Press, 2016
 85. Chin MH, Clarke AR, Nocon RS, et al. A roadmap and best practices for organizations to reduce racial and ethnic disparities in health care. *J Gen Intern Med* 2012;27:992–1000
 86. Hershey JA, Morone J, Lipman TH, Hawkes CP. Social determinants of health, goals and outcomes in high-risk children with type 1 diabetes. *Can J Diabetes* 2021;45:444–450.e1
 87. Laiteerapong N, Karter AJ, Liu JY, et al. Correlates of quality of life in older adults with diabetes: the diabetes & aging study. *Diabetes Care* 2011;34:1749–1753
 88. O'Gurek DT, Henke C. A practical approach to screening for social determinants of health. *Fam Pract Manag* 2018;25:7–12
 89. Walker RJ, Grusnick J, Garacci E, Mendez C, Egede LE. Trends in food insecurity in the USA for individuals with prediabetes, undiagnosed diabetes, and diagnosed diabetes. *J Gen Intern Med* 2019;34:33–35
 90. Berkowitz SA, Karter AJ, Corbie-Smith G, et al. Food insecurity, food “deserts,” and glycemic control in patients with diabetes: a longitudinal analysis. *Diabetes Care* 2018;41:1188–1195
 91. Heerman WJ, Wallston KA, Osborn CY, et al. Food insecurity is associated with diabetes self-care behaviours and glycaemic control. *Diabet Med* 2016;33:844–850
 92. Silverman J, Krieger J, Kiefer M, Hebert P, Robinson J, Nelson K. The relationship between food insecurity and depression, diabetes distress and medication adherence among low-income patients with poorly-controlled diabetes. *J Gen Intern Med* 2015;30:1476–1480
 93. Walker RJ, Garacci E, Ozieh M, Egede LE. Food insecurity and glycemic control in individuals with diagnosed and undiagnosed diabetes in the United States. *Prim Care Diabetes* 2021;15:813–818
 94. Schroeder EB, Zeng C, Sterrett AT, Kimpo TK, Paolino AR, Steiner, JF. The longitudinal relationship between food insecurity in older adults with diabetes and emergency department visits, hospitalizations, hemoglobin A1c, and medication adherence. *J Diabetes Complications* 2019;33:289–295
 95. Hager ER, Quigg AM, Black MM, et al. Development and validity of a 2-item screen to identify families at risk for food insecurity. *Pediatrics* 2010;126:e26–e32
 96. Goddu AP, Roberson TS, Raffel KE, Chin MH, Peek ME. Food Rx: a community-university partnership to prescribe healthy eating on the South Side of Chicago. *J Prev Interv Community* 2015;43:148–162
 97. Feinberg AT, Hess A, Passaretti M, Coolbaugh S, Lee TH. Prescribing food as a specialty drug. *NEJM Catalyst*. 10 April 2018. Accessed 11 October 2022. Available from <https://catalyst.nejm.org/doi/abs/10.1056/CAT.18.0212>
 98. Seligman HK, Schillinger D. Hunger and socioeconomic disparities in chronic disease. *N Engl J Med* 2010;363:6–9
 99. White BM, Logan A, Magwood GS. Access to diabetes care for populations experiencing homelessness: an integrated review. *Curr Diab Rep* 2016;16:112
 100. Bernstein RS, Meurer LN, Plumb EJ, Jackson JL. Diabetes and hypertension prevalence in homeless adults in the United States: a systematic review and meta-analysis. *Am J Public Health* 2015;105:e46–e60
 101. Montgomery AE, Fargo JD, Kane V, Culhane DP. Development and validation of an instrument to assess imminent risk of homelessness among veterans. *Public Health Rep* 2014;129:428–436
 102. Stahre M, VanEenwyk J, Siegel P, Njai R. Housing Insecurity and the association with health outcomes and unhealthy behaviors, Washington State, 2011. *Prev Chronic Dis* 2015;12:E109
 103. Baxter AJ, Tweed EJ, Katikireddi SV, Thomson H. Effects of Housing First approaches on health and well-being of adults who are homeless or at risk of homelessness: systematic review and meta-analysis of randomised controlled trials. *J Epidemiol Community Health* 2019;73:379–387
 104. Evangelou E, Ntritsos G, Chondrogiorgi M, et al. Exposure to pesticides and diabetes: a systematic review and meta-analysis. *Environ Int* 2016;91:60–68
 105. Health Resources & Services Administration. 2021 Special Populations Funded Programs. Accessed 5 October 2022. Available from <https://data.hrsa.gov/tools/data-reporting/special-populations>
 106. U.S. Department of Health & Human Services. National Standards for Culturally and Linguistically Appropriate Services (CLAS) in Health and Health Care. Accessed 11 October 2022. Available from <https://www.thinkculturalhealth.hhs.gov/assets/pdfs/enhancednationalclasstandards.pdf>
 107. Aaby A, Friis K, Christensen B, Rowlands G, Maingal HT. Health literacy is associated with health behaviour and self-reported health: a large population-based study in individuals with cardiovascular disease. *Eur J Prev Cardiol* 2017;24:1880–1888
 108. White RO, Eden S, Wallston KA, et al. Health communication, self-care, and treatment satisfaction among low-income diabetes patients in a public health setting. *Patient Educ Couns* 2015;98:144–149
 109. Schillinger D, Piette J, Grumbach K, et al. Closing the loop: physician communication with diabetic patients who have low health literacy. *Arch Intern Med* 2003;163:83–90
 110. Schapira MM, Fletcher KE, Gilligan MA, et al. A framework for health numeracy: how patients use quantitative skills in health care. *J Health Commun* 2008;13:501–517
 111. Carpenter CR, Kaphingst KA, Goodman MS, Lin MJ, Melson AT, Griffey RT. Feasibility and diagnostic accuracy of brief health literacy and numeracy screening instruments in an urban emergency department. *Acad Emerg Med* 2014;21:137–146
 112. Williams DR, Lawrence JA, Davis BA. Racism and health: evidence and needed research. *Annu Rev Public Health* 2019;40:105–125
 113. Agency for Healthcare Research and Quality. Clinical-community linkages. Content last reviewed December 2016. Accessed 11 October 2022. Available from <https://www.ahrq.gov/professionals/>

prevention-chronic-care/improve/community/index.html

114. Egbujie BA, Delobelle PA, Levitt N, Puoane T, Sanders D, van Wyk B. Role of community health workers in type 2 diabetes mellitus self-management: a scoping review. *PLoS One* 2018;13:e0198424
115. Heisler M, Vijan S, Makki F, Piette JD. Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. *Ann Intern Med* 2010;153:507–515
116. Long JA, Jahnle EC, Richardson DM, Loewenstein G, Volpp KG. Peer mentoring and financial incentives to improve glucose control in African American veterans: a randomized trial. *Ann Intern Med* 2012;156:416–424
117. Fisher EB, Boothroyd RI, Elstad EA, et al. Peer support of complex health behaviors in prevention and disease management with special reference to diabetes: systematic reviews. *Clin Diabetes Endocrinol* 2017;3:4
118. Foster G, Taylor SJ, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst Rev* 2007(4): CD005108
119. Piatt GA, Rodgers EA, Xue L, Zgibor JC. Integration and utilization of peer leaders for diabetes self-management support: results from Project SEED (Support, Education, and Evaluation in Diabetes). *Diabetes Educ* 2018;44:373–382
120. Rosenthal EL, Rush CH, Allen CG. Understanding scope and competencies: a contemporary look at the United States community health worker field: progress report of the Community Health Worker (CHW) Core Consensus (C3) Project: Building National Consensus on CHW Core Roles, Skills, and Qualities. CHW Central, 2016. Available from <https://files.ctctcdn.com/a907c850501/1c1289f0-88cc-49c3-a238-66def942c147.pdf>
121. Guide to Community Preventive Services. Community health workers help patients manage diabetes. Updated 2018. Accessed 11 October 2022. Available from <https://www.thecommunityguide.org/content/community-health-workers-help-patients-manage-diabetes>
122. The Network for Public Health Law. Legal considerations for community health workers and their employers. Accessed 11 October 2022. Available from <https://www.networkforphl.org/wp-content/uploads/2020/01/Legal-Considerations-Community-Health-Workers.pdf>
123. Cuellar AE, Calonge BN. The Community Preventive Services Task Force: 25 years of effectiveness, economics, and equity. *Am J Prev Med* 2022;62:e371–e373

2. Classification and Diagnosis of Diabetes: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a non-autoimmune progressive loss of adequate β -cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

This section reviews most common forms of diabetes but is not comprehensive. For additional information, see the American Diabetes Association (ADA) position statement “Diagnosis and Classification of Diabetes Mellitus” (1).

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both age groups. Children with type 1 diabetes often present with the hallmark symptoms of polyuria/polydipsia, and

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approximately half present with diabetic ketoacidosis (DKA) (2–4). The onset of type 1 diabetes may be more variable in adults; they may not present with the classic symptoms seen in children and may experience temporary remission from the need for insulin (5–7). The features most useful in discrimination of type 1 diabetes include younger age at diagnosis (<35 years) with lower BMI (<25 kg/m²), unintentional weight loss, ketoacidosis, and glucose >360 mg/dL (20 mmol/L) at presentation (8). Occasionally, people with type 2 diabetes may present with DKA (9,10), particularly members of ethnic and racial minorities (11). It is important for the health care professional to realize that classification of diabetes type is not always straightforward at presentation and that misdiagnosis is common (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes, individuals with maturity-onset diabetes of the young [MODY] misdiagnosed as having type 1 diabetes). Although difficulties in distinguishing diabetes type may occur in all age groups at onset, the diagnosis becomes more obvious over time in people with β -cell deficiency as the degree of β -cell deficiency becomes clear.

In both type 1 and type 2 diabetes, various genetic and environmental factors can result in the progressive loss of β -cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, people with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will be informed by better characterization of the many paths to β -cell demise or dysfunction (12). Across the globe, many groups are working on

combining clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes that are currently clustered into the type 1 diabetes versus type 2 diabetes nomenclature with the goal of optimizing personalized treatment approaches. Many of these studies show great promise and may soon be incorporated into the diabetes classification system (13).

Characterization of the underlying pathophysiology is more precisely developed in type 1 diabetes than in type 2 diabetes. It is now clear from prospective studies that the persistent presence of two or more islet autoantibodies is a near-certain predictor of clinical diabetes (14). The rate of progression is dependent on the age at first detection of autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels rise well before the clinical onset of diabetes, making diagnosis feasible well before the onset of DKA. Three distinct stages of type 1 diabetes can be identified (Table 2.1) and serve as a framework for research and regulatory decision-making (12,15). There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or type 1 diabetes. The clinical priority with detection of LADA is awareness that slow autoimmune β -cell destruction can occur in adults leading to a long duration of marginal insulin secretory capacity. For the purpose of this classification, all forms of diabetes mediated by autoimmune β -cell destruction are included under the rubric of type 1 diabetes. Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness of a population of adults likely to have

progressive autoimmune β -cell destruction (16), thus accelerating insulin initiation prior to deterioration of glucose management or development of DKA (6,17).

The paths to β -cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β -cell insulin secretion, frequently in the setting of insulin resistance, appears to be the common denominator. Type 2 diabetes is associated with insulin secretory defects related to genetics, inflammation, and metabolic stress. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β -cell dysfunction (12,13,18–20).

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT) or A1C criteria (21) (Table 2.2).

Generally, FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic screening. It should be noted that detection rates of different screening tests vary in both populations and individuals. Moreover, the efficacy of interventions for primary prevention of type 2 diabetes has mainly been demonstrated among individuals who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria (22,23).

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes (Table 2.2 and Table 2.5) (24). Diabetes may be identified anywhere along the spectrum of clinical

Table 2.1—Staging of type 1 diabetes (12,16)

	Stage 1	Stage 2	Stage 3
Characteristics	<ul style="list-style-type: none"> • Autoimmunity • Normoglycemia • Presymptomatic 	<ul style="list-style-type: none"> • Autoimmunity • Dysglycemia • Presymptomatic 	<ul style="list-style-type: none"> • Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	<ul style="list-style-type: none"> • Multiple islet autoantibodies • No IGT or IFG 	<ul style="list-style-type: none"> • Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or \geq10% increase in A1C 	<ul style="list-style-type: none"> • Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

Table 2.2—Criteria for the diagnosis of diabetes

FPG \geq 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG \geq 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

A1C \geq 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose \geq 200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

scenarios—in seemingly low-risk individuals who happen to have glucose testing, in individuals screened based on diabetes risk assessment, and in symptomatic patients. For additional details on the evidence used to establish the criteria for the diagnosis of diabetes, prediabetes, and abnormal glucose tolerance (IFG, IGT), see the ADA position statement “Diagnosis and Classification of Diabetes Mellitus” (1) and other reports (21,25,26).

Fasting and 2-Hour Plasma Glucose

The FPG and 2-h PG may be used to diagnose diabetes (Table 2.2). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes (27). In people in whom there is discordance between A1C values and glucose values, FPG and 2-h PG are more accurate (28).

A1C

Recommendations

- 2.1a** To avoid misdiagnosis or missed diagnosis, the A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay. **B**
- 2.1b** Point-of-care A1C testing for diabetes screening and diagnosis should be restricted to U.S.

Food and Drug Administration–approved devices at laboratories proficient in performing testing of moderate complexity or higher by trained personnel. **B**

- 2.2** Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1C assay interference and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes. **B**
- 2.3** In conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes. **B**
- 2.4** Adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to oral glucose tolerance testing as a screen for diabetes. **A**

The A1C test should be performed using a method that is certified by the NGSP (ngsp.org) and standardized or traceable to the Diabetes Control and

Complications Trial (DCCT) reference assay. Point-of-care A1C assays may be NGSP certified and cleared by the U.S. Food and Drug Administration (FDA) for use in monitoring glycemic control in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)-regulated and CLIA-waived settings. FDA-approved point-of-care A1C testing can be used in laboratories or sites that are CLIA certified, are inspected, and meet the CLIA quality standards. These standards include specified personnel requirements (including documented annual competency assessments) and participation three times per year in an approved proficiency testing program (29–32). As discussed in Section 6, “Glycemic Targets,” point-of-care A1C assays may be more generally applied for assessment of glycemic stability in the clinic.

A1C has several advantages compared with FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and fewer day-to-day perturbations during stress, changes in nutrition, or illness. However, these advantages may be offset by the lower sensitivity of A1C at the designated cut point, greater cost, limited availability of A1C testing in certain regions of the developing world, and the imperfect correlation between A1C and average glucose in certain individuals. The A1C test, with a diagnostic threshold of \geq 6.5% (48 mmol/mol), diagnoses only 30% of the diabetes cases identified collectively using A1C, FPG, or 2-h PG, according to National Health and Nutrition Examination Survey (NHANES) data (33). Despite these limitations with A1C, in 2009, the International Expert Committee added A1C to the diagnostic criteria with the goal of increased screening (21).

When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia, such as hemodialysis, pregnancy, HIV treatment (34,35), age, race/ethnicity, genetic background, and anemia/hemoglobinopathies. (See OTHER CONDITIONS ALTERING THE RELATIONSHIP OF A1C AND GLYCEMIA below for more information.)

Age

The epidemiologic studies that formed the basis for recommending A1C to

diagnose diabetes included only adult populations (33). However, recent ADA clinical guidance concluded that A1C, FPG, or 2-h PG could be used to test for prediabetes or type 2 diabetes in children and adolescents (see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS below for additional information) (36).

Race/Ethnicity/Hemoglobinopathies

Hemoglobin variants can interfere with the measurement of A1C, although most assays in use in the U.S. are unaffected by the most common variants. Marked discrepancies between measured A1C and plasma glucose levels should prompt consideration that the A1C assay may not be reliable for that individual. For individuals with a hemoglobin variant but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from hemoglobin variants should be used. An updated list of A1C assays with interferences is available at ngsp.org/interf.asp.

African American individuals heterozygous for the common hemoglobin variant HbS may have, for any given level of mean glycemia, lower A1C by about 0.3% compared with those without the trait (37). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African American individuals, was associated with a decrease in A1C of about 0.8% in homozygous men and 0.7% in homozygous women compared with those without the variant (38). For example, in Tanzania, where there is a high likelihood of hemoglobinopathies in people with HIV, A1C may be lower than expected based on glucose, limiting its usefulness for screening (39).

Even in the absence of hemoglobin variants, A1C levels may vary with race/ethnicity independently of glycemia (40–42). For example, African American individuals may have higher A1C levels than non-Hispanic White individuals with similar fasting and post-glucose load glucose levels (43). Though conflicting data exist, African American individuals may also have higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (44,45). Similarly, A1C levels may be higher for a given mean glucose concentration when

measured with continuous glucose monitoring (46). A recent report in Afro-Caribbean people demonstrated a lower A1C than predicted by glucose levels (47). Despite these and other reported differences, the association of A1C with risk for complications appears to be similar in African American and non-Hispanic White populations (42,48). In the Taiwanese population, age and sex have been reported to be associated with increased A1C in men (49); the clinical implications of this finding are unclear at this time.

Other Conditions Altering the Relationship of A1C and Glycemia

In conditions associated with increased red blood cell turnover, such as sickle cell disease, pregnancy (second and third trimesters), glucose-6-phosphate dehydrogenase deficiency (50,51), hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes (52). A1C is less reliable than blood glucose measurement in other conditions such as the postpartum state (53–55), HIV treated with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) (34), and iron-deficient anemia (56).

Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dL [11.1 mmol/L]), diagnosis requires two abnormal screening test results, either from the same sample (57) or in two separate test samples. If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold when analyzed from the same sample or in two different test samples, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of the possibility of A1C assay interference. The diagnosis is made

on the basis of the confirmatory screening test. For example, if a patient meets the diabetes criterion of the A1C (two results $\geq 6.5\%$ [48 mmol/mol]) but not FPG (<126 mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Each of the screening tests has preanalytic and analytic variability, so it is possible that a test yielding an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is likely for FPG and 2-h PG if the glucose samples remain at room temperature and are not centrifuged promptly. Because of the potential for preanalytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If patients have test results near the margins of the diagnostic threshold, the health care professional should discuss signs and symptoms with the patient and repeat the test in 3–6 months.

People should consume a mixed diet with at least 150 g of carbohydrates on the 3 days prior to oral glucose tolerance testing (58–60). Fasting and carbohydrate restriction can falsely elevate glucose level with an oral glucose challenge.

Diagnosis

In a patient with classic symptoms, measurement of plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose ≥ 200 mg/dL [11.1 mmol/L]). In these cases, knowing the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Some health care professionals may also want to know the A1C to determine the chronicity of the hyperglycemia. The criteria to diagnose diabetes are listed in **Table 2.2**.

TYPE 1 DIABETES

Recommendations

2.5 Screening for presymptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2, or zinc transporter 8 is currently recommended in the setting of a research study or

can be considered an option for first-degree family members of a proband with type 1 diabetes. **B**

- 2.6** Development of and persistence of multiple islet autoantibodies is a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial or screening for stage 2 type 1 diabetes. **B**

Immune-Mediated Diabetes

This form, previously called “insulin-dependent diabetes” or “juvenile-onset diabetes,” accounts for 5–10% of diabetes and is due to cell-mediated autoimmune destruction of the pancreatic β -cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to GAD (glutamic acid decarboxylase, GAD65), insulin, the tyrosine phosphatases islet antigen 2 (IA-2) and IA-2 β , and zinc transporter 8. Numerous clinical studies are being conducted to test various methods of preventing type 1 diabetes in those with evidence of islet autoimmunity (trialnet.org/our-research/prevention-studies) (14,17,61–64). Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoimmune markers. The disease has strong HLA associations, with linkage to the *DQB1* and *DRB1* haplotypes, and genetic screening has been used in some research studies to identify high-risk populations. Specific alleles in these genes can be either predisposing or protective (**Table 2.1**).

The rate of β -cell destruction is quite variable, being rapid in some individuals (particularly but not exclusively in infants and children) and slow in others (mainly but not exclusively adults) (65,66). Children and adolescents often present with DKA as the first manifestation of the disease, and the rates in the U.S. have increased dramatically over the past 20 years (2–4). Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or DKA with infection or other stress. Adults may retain sufficient β -cell function to prevent DKA for many years; such individuals may have remission or decreased insulin needs for months or years and eventually become

dependent on insulin for survival and are at risk for DKA (5–7,67,68). At this later stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes is the most common form of diabetes in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of β -cells has multiple genetic factors and is also related to environmental factors that are still poorly defined. Although individuals do not typically have obesity when they present with type 1 diabetes, obesity is increasingly common in the general population; as such, obesity should not preclude testing for type 1 diabetes. People with type 1 diabetes are also prone to other autoimmune disorders such as Hashimoto thyroiditis, Graves disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see Section 4, “Comprehensive Medical Evaluation and Assessment of Comorbidities”). Type 1 diabetes can be associated with monogenic polyglandular autoimmune syndromes, including immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, which is an early-onset systemic autoimmune, genetic disorder caused by mutation of the forkhead box protein 3 (*FOXP3*) gene, and another caused by the autoimmune regulator (*AIRE*) gene mutation (69,70). As indicated by the names, these disorders are associated with other autoimmune and rheumatological diseases.

Introduction of immunotherapy, specifically checkpoint inhibitors, for cancer treatment has led to unexpected adverse events, including immune system activation precipitating autoimmune disease. Fulminant onset of type 1 diabetes can develop, with DKA and low or undetectable levels of C-peptide as a marker of endogenous β -cell function (71,72). Fewer than half of these patients have autoantibodies that are seen in type 1 diabetes, supporting alternate pathobiology. This immune-related adverse event occurs in just under 1% of checkpoint inhibitor-treated patients but most commonly occurs with agents that block the programmed cell death protein 1/programmed cell death ligand 1 pathway alone or in combination with other

checkpoint inhibitors (73). To date, the majority of immune checkpoint inhibitor-related cases of type 1 diabetes occur in people with high-risk HLA-DR4 (present in 76% of patients), whereas other high-risk HLA alleles are not more common than those in the general population (73). To date, risk cannot be predicted by family history or autoantibodies, so all health care professionals administering these medications should be mindful of this adverse effect and educate patients appropriately.

Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. These individuals have permanent insulinopenia and are prone to DKA but have no evidence of β -cell autoimmunity. However, only a minority of people with type 1 diabetes fall into this category. Individuals with autoantibody-negative type 1 diabetes of African or Asian ancestry may suffer from episodic DKA and exhibit varying degrees of insulin deficiency between episodes (possibly ketosis-prone diabetes) (74). This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected individuals may be intermittent. Future research is needed to determine the cause of β -cell destruction in this rare clinical scenario.

Screening for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes are increasing (75). People with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and 40–60% are diagnosed with life-threatening DKA (2–4). Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes (15) or in children from the general population (76,77) can effectively identify those who will develop type 1 diabetes. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (14). These findings are highly significant because while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were

recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both “sporadic” and familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases (63,78,79). In The Environmental Determinants of Diabetes in the Young (TEDDY) study, type 1 diabetes developed in 21% of 363 subjects with at least one autoantibody at 3 years of age (80). Such testing, coupled with education about diabetes symptoms and close follow-up, has been shown to enable earlier diagnosis and prevent DKA (81,82).

While widespread clinical screening of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions, several innovative research screening programs are available in Europe (e.g., Fr1da, gppad.org) and the U.S. (trialnet.org, askhealth.org). Participation should be encouraged to accelerate development of evidence-based clinical guidelines for the general population and relatives of those with type 1 diabetes. Individuals who test positive should be counseled about the risk of developing diabetes, diabetes symptoms, and DKA prevention. Numerous clinical studies are being conducted to test various methods of preventing and treating stage 2 type 1 diabetes in those with evidence of autoimmunity with promising results (see clinicaltrials.gov and trialnet.org). Delay of overt diabetes development in stage 2 type 1 diabetes with the anti-CD3 antibody teplizumab in relatives at risk for type 1 diabetes was reported in 2019, with an extension of the randomized controlled trial in 2021 (83,84). Based on these data, this agent has been submitted to the FDA for the indication of delay or prevention of clinical type 1 diabetes in at-risk individuals. Neither this agent nor others in this category are currently available for clinical use.

PREDIABETES AND TYPE 2 DIABETES

Recommendations

2.7 Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated risk calculator should be done in asymptomatic adults. **B**

- 2.8** Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian American individuals) who have one or more risk factors (Table 2.3). **B**
- 2.9** For all people, screening should begin at age 35 years. **B**
- 2.10** If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (i.e., weight gain). **C**
- 2.11** To screen for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are each appropriate (Table 2.2 and Table 2.5). **B**
- 2.12** When using oral glucose tolerance testing as a screen for diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. **A**
- 2.13** In people with prediabetes and type 2 diabetes, identify and treat cardiovascular disease risk factors. **A**

- 2.14** Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥ 85 th percentile) or obesity (BMI ≥ 95 th percentile) and who have one or more risk factors for diabetes. (See Table 2.4 for evidence grading of risk factors.) **B**
- 2.15** People with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually. **E**

Prediabetes

“Prediabetes” is the term used for individuals whose glucose levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism (48,85). People with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol)

Table 2.3—Criteria for screening for diabetes or prediabetes in asymptomatic adults

- Testing should be considered in adults with overweight or obesity (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian American individuals) who have one or more of the following risk factors:
 - First-degree relative with diabetes
 - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
 - History of CVD
 - Hypertension ($\geq 140/90$ mmHg or on therapy for hypertension)
 - HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L)
 - Individuals with polycystic ovary syndrome
 - Physical inactivity
 - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- People with prediabetes (A1C $\geq 5.7\%$ [39 mmol/mol], IGT, or IFG) should be tested yearly.
- People who were diagnosed with GDM should have lifelong testing at least every 3 years.
- For all other people, testing should begin at age 35 years.
- If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
- People with HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥ 85 th percentile) or obesity (≥ 95 th percentile) **A** and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation **A**
- Family history of type 2 diabetes in first- or second-degree relative **A**
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) **A**
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) **B**

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

(**Table 2.5**). Prediabetes should not be viewed as a clinical entity in its own right but rather as a risk factor for progression to diabetes and cardiovascular disease (CVD). Criteria for screening for diabetes or prediabetes in asymptomatic adults are outlined in **Table 2.3**. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors.

Diagnosis

IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (82,83) and IGT as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) (25). It should be noted that the World Health Organization and numerous other diabetes organizations define the IFG lower limit at 110 mg/dL (6.1 mmol/L).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes as

defined by A1C criteria demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with A1C between 5.5% and 6.0% (between 37 and 42 mmol/mol) had a substantially increased risk of diabetes (5-year incidence from 9% to 25%). Those with an A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25% and 50% and a relative risk 20 times higher compared with A1C of 5.0% (31 mmol/mol) (86). In a community-based study of African American and non-Hispanic White adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (87). Other analyses suggest that A1C of 5.7% (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (88), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (89).

Table 2.5—Criteria defining prediabetes*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)

OR

2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

OR

A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Hence, it is reasonable to consider an A1C range of 5.7–6.4% (39–47 mmol/mol) as identifying individuals with prediabetes. Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4% (39–47 mmol/mol) should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities”). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (86). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C $> 6.0\%$ [42 mmol/mol]).

Table 2.5 summarizes the categories of prediabetes, and **Table 2.3** outlines the criteria for screening for prediabetes. The ADA Diabetes Risk Test is an additional option for assessment to determine the appropriateness of screening for diabetes or prediabetes in asymptomatic adults (**Fig. 2.1**) (diabetes.org/socrisktest). For additional background regarding risk factors and screening for prediabetes, see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN ASYMPTOMATIC ADULTS and also SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS below. For details regarding individuals with prediabetes most likely to benefit from a formal behavioral or lifestyle intervention, see Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities.”

Type 2 Diabetes

Type 2 diabetes, previously referred to as “non-insulin-dependent diabetes” or “adult-onset diabetes,” accounts for 90–95% of all diabetes. This form encompasses individuals who have relative (rather than absolute) insulin deficiency and have peripheral insulin resistance. At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive.

There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction of β -cells does not occur, and patients do not have any of the other known causes of diabetes. Most, but not all, people with type 2 diabetes have



Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you?

- Less than 40 years (0 points)
- 40–49 years (1 point)
- 50–59 years (2 points)
- 60 years or older (3 points)

2. Are you a man or a woman?

- Man (1 point)
- Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?

- Yes (1 point)
- No (0 points)

4. Do you have a mother, father, sister or brother with diabetes?

- Yes (1 point)
- No (0 points)

5. Have you ever been diagnosed with high blood pressure?

- Yes (1 point)
- No (0 points)

6. Are you physically active?

- Yes (0 points)
- No (1 point)

7. What is your weight category?

See chart at right.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

ADD UP YOUR SCORE.

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Learn more at diabetes.org/risktest | 1-800-DIABETES (800-342-2383)

Diabetes Risk Test | American Diabetes Association®

Figure 2.1—ADA risk test (diabetes.org/socrisktest).

overweight or obesity. Excess weight itself causes some degree of insulin resistance. Individuals who do not have obesity or overweight by traditional weight criteria may have an increased

percentage of body fat distributed predominantly in the abdominal region.

DKA seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the stress of another

illness such as infection or myocardial infarction or with the use of certain drugs (e.g., corticosteroids, atypical antipsychotics, and sodium–glucose cotransporter 2 inhibitors) (90,91). Type 2 diabetes frequently goes

undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms caused by hyperglycemia, such as dehydration or unintentional weight loss. Nevertheless, even undiagnosed people with diabetes are at increased risk of developing macrovascular and microvascular complications.

People with type 2 diabetes may have insulin levels that appear normal or elevated, yet the failure to normalize blood glucose reflects a relative defect in glucose-stimulated insulin secretion. Thus, insulin secretion is defective in these individuals and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, physical activity, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Recent interventions with intensive diet and exercise or surgical weight loss have led to diabetes remission (92–98) (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”).

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity (99,100). It occurs more frequently in individuals with prior gestational diabetes mellitus (GDM) or polycystic ovary syndrome. It is also more common in people with hypertension or dyslipidemia and in certain racial/ethnic subgroups (African American, Native American, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition or family history in first-degree relatives (more so than type 1 diabetes). However, the genetics of type 2 diabetes are poorly understood and under intense investigation in this era of precision medicine (18). In adults without traditional risk factors for type 2 diabetes and/or of younger age, consider islet autoantibody testing (e.g., GAD65 autoantibodies) to exclude the diagnosis of type 1 diabetes (8).

Screening and Testing for Prediabetes and Type 2 Diabetes in Asymptomatic Adults

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (Table 2.3) or with an assessment tool, such as the ADA risk test (Fig. 2.1) (online at diabetes.org/socrisktest), is recommended to

guide health care professionals on whether performing a diagnostic test (Table 2.2) is appropriate. Prediabetes and type 2 diabetes meet criteria for conditions in which early detection via screening is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical disease are readily available (101). The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes. It is important to individualize risk/benefit of formal intervention for people with prediabetes and consider patient-centered goals. Risk models have explored the benefit, in general finding higher benefit of intervention in those at highest risk (102) (see Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities”) and reduce the risk of diabetes complications (103) (see Section 10, “Cardiovascular Disease and Risk Management,” Section 11, “Chronic Kidney Disease and Risk Management,” and Section 12, “Retinopathy, Neuropathy, and Foot Care”). In the most recent National Institutes of Health (NIH) Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes (104) resulted in lower rates of developing retinopathy and nephropathy (105). Similar impact on diabetes complications was reported with screening, diagnosis, and comprehensive risk factor management in the U.K. Clinical Practice Research Datalink database (103). In that report, progression from prediabetes to diabetes augmented risk of complications.

Approximately one-quarter of people with diabetes in the U.S. and nearly half of Asian and Hispanic American people with diabetes are undiagnosed (106,107). Although screening of asymptomatic individuals to identify those with prediabetes or diabetes might seem reasonable, rigorous clinical trials to prove the effectiveness of such screening have not been conducted and are unlikely to occur. Clinical conditions, such as hypertension, hypertensive pregnancy, and obesity, enhance risk (108). Based on a population estimate, diabetes in people of childbearing age is underdiagnosed

(109). Employing a probabilistic model, Peterson et al. (110) demonstrated cost and health benefits of preconception screening.

A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care (111). General practice patients between the ages of 40 and 69 years were screened for diabetes and randomly assigned by practice to intensive treatment of multiple risk factors or routine diabetes care. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment compared with routine care, but the incidence of first CVD events or mortality was not significantly different between the groups (26). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors’ ability to determine whether screening and early treatment improved outcomes compared with no screening and later treatment after clinical diagnoses. Computer simulation modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of hyperglycemia and cardiovascular risk factors in type 2 diabetes (112); moreover, screening, beginning at age 30 or 45 years and independent of risk factors, may be cost-effective (<\$11,000 per quality-adjusted life year gained—2010 modeling data) (113). Cost-effectiveness of screening has been reinforced in cohort studies (114,115).

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic individuals include the following.

Age

Age is a major risk factor for diabetes. Testing should begin at no later than age 35 years for all people (116). Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

BMI and Ethnicity

In general, BMI ≥ 25 kg/m² is a risk factor for diabetes. However, data suggest that the BMI cut point should be lower for the Asian American population (117,118). The BMI cut points fall consistently between 23 and 24 kg/m²

(sensitivity of 80%) for nearly all Asian American subgroups (with levels slightly lower for Japanese American individuals). This makes a rounded cut point of 23 kg/m² practical. An argument can be made to push the BMI cut point to lower than 23 kg/m² in favor of increased sensitivity; however, this would lead to an unacceptably low specificity (13.1%). Data from the World Health Organization also suggest that a BMI of ≥ 23 kg/m² should be used to define increased risk in Asian American individuals (119). The finding that one-third to one-half of diabetes in Asian American people is undiagnosed suggests that testing is not occurring at lower BMI thresholds (99,120).

Evidence also suggests that other populations may benefit from lower BMI cut points. For example, in a large multiethnic cohort study, for an equivalent incidence rate of diabetes, a BMI of 30 kg/m² in non-Hispanic White individuals was equivalent to a BMI of 26 kg/m² in African American individuals (121).

Medications

Certain medications, such as glucocorticoids, thiazide diuretics, some HIV medications (34), and atypical antipsychotics (92), are known to increase the risk of diabetes and should be considered when deciding whether to screen.

HIV

Individuals with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies; a screening protocol is therefore recommended (122). The A1C test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring (35). In those with prediabetes, weight loss through healthy nutrition and physical activity may reduce the progression toward diabetes. Among people with HIV and diabetes, preventive health care using an approach used in people without HIV is critical to reduce the risks of microvascular and macrovascular complications. Diabetes risk is increased with certain PIs and NRTIs. New-onset diabetes is estimated to occur in more than 5% of individuals infected with HIV on PIs, whereas more than 15% may have prediabetes (123).

PIs are associated with insulin resistance and may also lead to apoptosis of

pancreatic β -cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance. For people with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available (124). Before making ARV substitutions, carefully consider the possible effect on HIV virological control and the potential adverse effects of new ARV agents. In some cases, antihyperglycemic agents may still be necessary.

Testing Interval

The appropriate interval between screening tests is not known (125). The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced, and individuals with false-negative tests will be retested before substantial time elapses and complications develop (125). In especially high-risk individuals, particularly with weight gain, shorter intervals between screening may be useful.

Community Screening

Ideally, screening should be carried out within a health care setting because of the need for follow-up and treatment. Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. However, in specific situations where an adequate referral system is established beforehand for positive tests, community screening may be considered. Community screening may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed (126).

Screening in Dental Practices

Because periodontal disease is associated with diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (127–129), with one study estimating that 30% of patients ≥ 30 years of age seen in general dental practices had dysglycemia (129,130). A similar study in 1,150 dental patients >40 years old in India reported 20.69%

and 14.60% meeting criteria for prediabetes and diabetes, respectively, using random blood glucose. Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting.

Screening and Testing for Prediabetes and Type 2 Diabetes in Children and Adolescents

In the last decade, the incidence and prevalence of type 2 diabetes in children and adolescents has increased dramatically, especially in racial and ethnic minority populations (75). See **Table 2.4** for recommendations on risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (36). See **Table 2.2** and **Table 2.5** for the criteria for the diagnosis of diabetes and prediabetes, respectively, that apply to children, adolescents, and adults. See Section 14, “Children and Adolescents,” for additional information on type 2 diabetes in children and adolescents.

Some studies question the validity of A1C in the pediatric population, especially among certain ethnicities, and suggest OGTT or FPG as more suitable diagnostic tests (131). However, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (132). The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes, and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C and the criteria in **Table 2.2** for diagnosis of type 2 diabetes in this cohort to decrease barriers to screening (133,134).

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

2.16 Annual screening for cystic fibrosis–related diabetes with an oral glucose tolerance test should begin by age 10 years in all people with cystic fibrosis

not previously diagnosed with cystic fibrosis–related diabetes. **B**

- 2.17** A1C is not recommended as a screening test for cystic fibrosis–related diabetes. **B**
- 2.18** People with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. **A**
- 2.19** Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended. **E**

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults (135). Diabetes in this population, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β -cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD. Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. OGTT is the recommended screening test; however, recent publications suggest that an A1C cut point threshold of 5.5% (5.8% in a second study) would detect more than 90% of cases and reduce patient screening burden (136,137). Ongoing studies are underway to validate this approach, and A1C is not recommended for screening (138). Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening (136,137). The Cystic Fibrosis Foundation Patient Registry (139) evaluated 3,553 people with cystic fibrosis and diagnosed 445 (13%) with CFRD. Early diagnosis and treatment of CFRD was

associated with preservation of lung function. The European Cystic Fibrosis Society Patient Registry reported an increase in CFRD with age (increased 10% per decade), genotype, decreased lung function, and female sex (140,141). Continuous glucose monitoring or HOMA of β -cell function (142) may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking these results to long-term outcomes is lacking, and these tests are not recommended for screening outside of the research setting (143).

CFRD mortality has significantly decreased over time, and the gap in mortality between people with cystic fibrosis with and without diabetes has considerably narrowed (144). There are limited clinical trial data on therapy for CFRD. The largest study compared three regimens: premeal insulin aspart, repaglinide, or oral placebo in people with cystic fibrosis and diabetes or abnormal glucose tolerance. Participants all had weight loss in the year preceding treatment; however, in the insulin-treated group, this pattern was reversed, and participants gained 0.39 (\pm 0.21) BMI units ($P = 0.02$). The repaglinide-treated group had initial weight gain, but it was not sustained by 6 months. The placebo group continued to lose weight (144). Insulin remains the most widely used therapy for CFRD (145). The primary rationale for the use of insulin in people with CFRD is to induce an anabolic state while promoting macronutrient retention and weight gain.

Additional resources for the clinical management of CFRD can be found in the position statement “Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes: A Position Statement of the American Diabetes Association and a Clinical Practice Guideline of the Cystic Fibrosis Foundation, Endorsed by the Pediatric Endocrine Society” (146) and in the International Society for Pediatric and Adolescent Diabetes 2018 clinical practice consensus guidelines (135).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

- 2.20** After organ transplantation, screening for hyperglycemia should be done. A formal diagnosis of posttransplantation

diabetes mellitus is best made once the individual is stable on an immunosuppressive regimen and in the absence of an acute infection. **B**

- 2.21** The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. **B**
- 2.22** Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. **E**

Several terms are used in the literature to describe the presence of diabetes following organ transplantation (147). “New-onset diabetes after transplantation” (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes people with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (148). Another term, “posttransplantation diabetes mellitus” (PTDM) (148,149), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset.

Hyperglycemia is very common during the early posttransplant period, with ~90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (148–151). In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge (151,152). Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM, and the role of the diabetes care health care professional is to treat hyperglycemia appropriately regardless of the type of immunosuppression (148). Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, etc.) as well as transplant-specific factors, such as use of immunosuppressant agents (153–155). Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the patient is stable on maintenance immunosuppression and

in the absence of acute infection (151–153,156). In a recent study of 152 heart transplant recipients, 38% had PTDM at 1 year. Risk factors for PTDM included elevated BMI, discharge from the hospital on insulin, and glucose values in the 24 h prior to hospital discharge (157). In an Iranian cohort, 19% had PTDM after heart and lung transplant (158). The OGTT is considered the gold-standard test for the diagnosis of PTDM (1 year posttransplant) (148, 149,159,160). Pretransplant elevation in hs-CRP was associated with PTDM in the setting of renal transplant (161,162). However, screening people with fasting glucose and/or A1C can identify high-risk individuals requiring further assessment and may reduce the number of overall OGTTs required.

Few randomized controlled studies have reported on the short- and long-term use of antihyperglycemic agents in the setting of PTDM (153,163,164). Most studies have reported that transplant patients with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (151,153,165). Insulin therapy is the agent of choice for the management of hyperglycemia, PTDM, and pre-existing diabetes and diabetes in the hospital setting. After discharge, people with preexisting diabetes could go back on their pretransplant regimen if they were in good control before transplantation. Those with previously poor glycemic stability or with persistent hyperglycemia should continue insulin with frequent home glucose monitoring to determine when insulin dose reductions may be needed and when it may be appropriate to switch to noninsulin agents.

No studies to date have established which noninsulin agents are safest or most efficacious in PTDM. The choice of agent is usually made based on the side effect profile of the medication and possible interactions with the patient's immunosuppression regimen (153). Drug dose adjustments may be required because of decreases in the glomerular filtration rate, a relatively common complication in transplant patients. A small short-term pilot study reported that metformin was safe to use in renal transplant recipients (166), but its safety has not been determined in other types of organ transplant. Thiazolidinediones have been used successfully in

people with liver and kidney transplants, but side effects include fluid retention, heart failure, and osteopenia (167,168). Dipeptidyl peptidase 4 inhibitors do not interact with immunosuppressant drugs and have demonstrated safety in small clinical trials (169,170). Well-designed intervention trials examining the efficacy and safety of these and other antihyperglycemic agents in people with PTDM are needed.

MONOGENIC DIABETES SYNDROMES

Recommendations

- 2.23** Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. **A**
- 2.24** Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and who often have a family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. **A**
- 2.25** In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Monogenic defects that cause β -cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of people with diabetes (<5%). **Table 2.6** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (171).

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed “neonatal” or “congenital” diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (8,172–175). Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before

6 months of age. Neonatal diabetes can either be transient or permanent. Transient diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin. Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (*KCNJ11*) and SUR1 subunit (*ABCC8*) of the β -cell K_{ATP} channel. A recent report details a de novo mutation in *EIF2B1* affecting eIF2 signaling associated with permanent neonatal diabetes and hepatic dysfunction, similar to Wolcott-Rallison syndrome but with few severe comorbidities (176). The recent ADA-European Association for the Study of Diabetes type 1 diabetes consensus report recommends that regardless of current age, individuals diagnosed under 6 months of age should have genetic testing (8). Correct diagnosis has critical implications because 30–50% of people with K_{ATP} -related neonatal diabetes will exhibit improved blood glucose levels when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, and while intensive insulin management is currently the preferred treatment strategy, there are important genetic counseling considerations, as most of the mutations that cause diabetes are dominantly inherited.

Maturity-Onset Diabetes of the Young

MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 13 genes on different chromosomes identified to date (177). The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

For individuals with MODY, the treatment implications are considerable and warrant genetic testing (178,179). Clinically, people with GCK-MODY exhibit mild, stable fasting hyperglycemia and do not require antihyperglycemic therapy except commonly during pregnancy.

Table 2.6—Most common causes of monogenic diabetes (171)

	Gene	Inheritance	Clinical features
MODY	<i>HNF1A</i>	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	<i>HNF4A</i>	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	<i>HNF1B</i>	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
	<i>GCK</i>	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically, does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
Neonatal diabetes	<i>KCNJ11</i>	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	<i>INS</i>	AD	Permanent: IUGR; insulin requiring
	<i>ABCC8</i>	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (<i>PLAGL1</i> , <i>HYMA1</i>)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	<i>GATA6</i>	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	<i>EIF2AK3</i>	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	<i>EIF2B1</i> <i>FOXP3</i>	AD X-linked	Permanent diabetes: can be associated with fluctuating liver function (172) Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

Individuals with HNF1A- or HNF4A-MODY usually respond well to low doses of sulfonylureas, which are considered first-line therapy; in some instances, insulin will be required over time. Mutations or deletions in *HNF1B* are associated with renal cysts and uterine malformations (renal cysts and diabetes [RCAD] syndrome). Other extremely rare forms of MODY have been reported to involve other transcription factor genes, including *PDX1* (*IPF1*) and *NEUROD1*.

Diagnosis of Monogenic Diabetes

A diagnosis of one of the three most common forms of MODY, including HNF1A-MODY, GCK-MODY, and HNF4A-MODY, allows for more cost-effective therapy (no therapy for GCK-MODY; sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members. Genetic screening is increasingly available and cost-effective (176,178).

A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members

with diabetes not characteristic of type 1 or type 2 diabetes, although admittedly, “atypical diabetes” is becoming increasingly difficult to precisely define in the absence of a definitive set of tests for either type of diabetes (173–175, 178–184). In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in people with monogenic diabetes has been reported (185). Individuals in whom monogenic diabetes is suspected should be referred to a specialist for further evaluation if available, and consultation can be obtained from several centers. Readily available commercial genetic testing following the criteria listed below now enables a cost-effective (186), often cost-saving, genetic diagnosis that is increasingly supported by health insurance. A biomarker screening pathway, such as the combination of urinary C-peptide/creatinine ratio and antibody screening, may aid in determining who should get genetic testing for MODY (187). It is critical to correctly diagnose one of the monogenic forms of diabetes because these individuals may

be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment plans and delays in diagnosing other family members (188). The correct diagnosis is especially critical for those with GCK-MODY mutations, where multiple studies have shown that no complications ensue in the absence of glucose-lowering therapy (189). The risks of microvascular and macrovascular complications with HNF1A- and HNF4A-MODY are similar to those observed in people with type 1 and type 2 diabetes (190,191). Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis and addressing comprehensive cardiovascular risk.

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly *INS* and *ABCC8* mutations) (172,192)

- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

PANCREATIC DIABETES OR DIABETES IN THE CONTEXT OF DISEASE OF THE EXOCRINE PANCREAS

Pancreatic diabetes includes both structural and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction and is commonly misdiagnosed as type 2 diabetes. Hyperglycemia due to general pancreatic dysfunction has been called “type 3c diabetes,” and, more recently, diabetes in the context of disease of the exocrine pancreas has been termed pancreoprivic diabetes (1). The diverse set of etiologies includes pancreatitis (acute and chronic), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed elsewhere in this chapter), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders (193), and idiopathic forms (1); as such, pancreatic diabetes is the preferred umbrella terminology.

Pancreatitis, even a single bout, can lead to postpancreatitis diabetes mellitus (PPDM). Both acute and chronic pancreatitis can lead to PPDM, and the risk is highest with recurrent bouts. A distinguishing feature is concurrent pancreatic exocrine insufficiency (according to the monoclonal fecal elastase 1 test or direct function tests), pathological pancreatic imaging (endoscopic ultrasound, MRI, computed tomography), and absence of type 1 diabetes-associated autoimmunity (194–199). There is loss of both insulin and glucagon secretion and often higher-than-expected insulin requirements. Risk for microvascular complications appears to be similar to that of other forms of diabetes. In the context of pancreatectomy, islet autotransplantation can be done to retain insulin secretion (200,201). In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirements (202).

GESTATIONAL DIABETES MELLITUS

Recommendations

- 2.26a** In individuals who are planning pregnancy, screen those with risk factors **B** and consider testing all individuals of childbearing potential for undiagnosed diabetes. **E**
- 2.26b** Before 15 weeks of gestation, test individuals with risk factors **B** and consider testing all individuals **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria if not screened preconception.
- 2.26c** Individuals of childbearing potential identified as having diabetes should be treated as such. **A**
- 2.26d** Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus diagnosis. **B** Treatment may provide some benefit. **E**
- 2.26e** Screen for early abnormal glucose metabolism using fasting glucose of 110–125 mg/dL (6.1 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). **B**
- 2.27** Screen for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant individuals not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. **A**
- 2.28** Screen individuals with gestational diabetes mellitus for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**
- 2.29** Individuals with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**
- 2.30** Individuals with a history of gestational diabetes mellitus

found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

Definition

For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy (86), regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has serious limitations (203). First, the best available evidence reveals that many cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant individuals of reproductive age. It is the severity of hyperglycemia that is clinically important with regard to both short- and long-term maternal and fetal risks.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in people of reproductive age, with an increase in the number of pregnant individuals with undiagnosed type 2 diabetes in early pregnancy (204–206). Ideally, undiagnosed diabetes should be identified preconception in individuals with risk factors or in high-risk populations (207–212), as the preconception care of people with preexisting diabetes results in lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age birth weight, and neonatal intensive care unit admission (213). If individuals are not screened prior to pregnancy, universal early screening at <15 weeks of gestation for undiagnosed diabetes may be considered over selective screening (Table 2.3), particularly in populations with high prevalence of risk factors and undiagnosed diabetes in people of childbearing age. Strong racial and ethnic disparities exist in the prevalence of undiagnosed diabetes. Therefore, early screening provides an initial step to identify these health disparities so that they can begin to be addressed (209–212). Standard diagnostic criteria for identifying undiagnosed diabetes in early pregnancy are the same as those used in the nonpregnant population (Table 2.2). Individuals found to have

diabetes by the standard diagnostic criteria used outside of pregnancy should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly.

Early abnormal glucose metabolism, defined as fasting glucose threshold of 110 mg/dL (6.1 mmol/L) or an A1C of 5.9% (39 mmol/mol), may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes (preeclampsia, macrosomia, shoulder dystocia, perinatal death), are more likely to need insulin treatment, and are at high risk of a later GDM diagnosis (214–220). An A1C threshold of 5.7% has not been shown to be associated with adverse perinatal outcomes (221,222).

If early screening is negative, individuals should be rescreened for GDM between 24 and 28 weeks of gestation (see Section 15, “Management of Diabetes in Pregnancy”). The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT, as well as the GDM screening and diagnostic criteria used in the two-step approach, were not derived from data in the first half of pregnancy and should not be used for early screening (223). To date, most randomized controlled trials of treatment of early abnormal glucose metabolism have been underpowered for outcomes. Therefore, the benefits of treatment for early abnormal glucose metabolism remain uncertain. Nutrition counseling and periodic “block” testing of glucose levels weekly to identify individuals with high glucose levels are suggested. Testing frequency may proceed to daily, and treatment may be intensified, if the fasting glucose is predominantly >110 mg/dL prior to 18 weeks of gestation.

Both the fasting glucose and A1C are low-cost tests. An advantage of the A1C is its convenience, as it can be added to the prenatal laboratories and does not require an early-morning fasting appointment. Disadvantages include inaccuracies in the presence of increased red blood cell turnover and hemoglobinopathies (usually reads lower) and higher values with anemia and reduced red blood cell turnover (224). A1C is not reliable to screen for GDM or for preexisting diabetes at 15 weeks of

gestation or later. See Recommendation 2.3 above.

GDM is often indicative of underlying β -cell dysfunction (225), which confers marked increased risk for later development of diabetes, generally but not always type 2 diabetes, in the mother after delivery (226,227). As effective prevention interventions are available (228,229), individuals diagnosed with GDM should receive lifelong screening for prediabetes to allow interventions to reduce diabetes risk and for type 2 diabetes to allow treatment at the earliest possible time (230).

Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (231), a large-scale multinational cohort study completed by more than 23,000 pregnant individuals, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM.

GDM diagnosis (**Table 2.7**) can be accomplished with either of two strategies:

1. The “one-step” 75-g OGTT derived from the IADPSG criteria, or
2. The older “two-step” approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive based on the work of Carpenter-Coustan’s interpretation of the older O’Sullivan and Mahan (232) criteria.

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk, leading some experts to debate, and disagree on, optimal strategies for the diagnosis of GDM.

One-Step Strategy

The IADPSG defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h PG values during a 75-g OGTT in individuals at 24–28 weeks of gestation who participated in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG levels of the study population. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value,

Table 2.7—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥ 130 , 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [251]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test. *American College of Obstetricians and Gynecologists notes that one elevated value can be used for diagnosis (247).

not two, became sufficient to make the diagnosis (233). Many regional studies have investigated the impact of adopting the IADPSG criteria on prevalence and have seen a roughly one- to threefold increase (234). The anticipated increase in the incidence of GDM could have a substantial impact on costs and medical infrastructure needs and has the potential to “medicalize” pregnancies previously categorized as normal. A recent follow-up study of individuals participating in a blinded study of pregnancy OGTTs found that 11 years after their pregnancies, individuals who would have been diagnosed with GDM by the one-step approach, as compared with those without, were at 3.4-fold higher risk of developing prediabetes and type 2 diabetes and had children with a higher risk of obesity and increased body fat, suggesting that the larger group of individuals identified by the one-step approach would benefit from the increased screening for diabetes and prediabetes that would accompany a history of GDM (235,236). The ADA recommends the IADPSG diagnostic criteria with the intent of optimizing gestational outcomes because these criteria are the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

The expected benefits of using IADPSG criteria to the offspring are inferred from intervention trials that focused on individuals with lower levels of hyperglycemia than identified using older GDM diagnostic criteria. Those trials found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (237,238). It is important to note that 80–90% of participants being treated for mild GDM in these two randomized controlled trials could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped the thresholds recommended by the IADPSG, and in one trial (238), the 2-h PG threshold (140 mg/dL [7.8 mmol/L]) was lower than the cutoff recommended by the IADPSG (153 mg/dL [8.5 mmol/L]).

No randomized controlled trials of treating versus not treating GDM diagnosed by the IADPSG criteria but not the Carpenter-Coustan criteria have been published to date. However, a recent randomized trial of testing for GDM at 24–28 weeks of gestation by the

one-step method using IADPSG criteria versus the two-step method using a 1-h 50-g glucose loading test (GLT) and, if positive, a 3-h OGTT by Carpenter-Coustan criteria identified twice as many individuals with GDM using the one-step method compared with the two-step method. Despite treating more individuals for GDM using the one-step method, there was no difference in pregnancy and perinatal complications (239). However, concerns have been raised about sample size estimates and unanticipated suboptimal engagement with the protocol with regard to screening and treatment. For example, in the two-step group, 165 participants who did not get counted as having GDM were treated for isolated elevated fasting glucose >95 mg/dL (240). The high prevalence of prediabetes in people of childbearing age may support the more inclusive IADPSG criteria. NHANES data demonstrate a 21.5% prevalence of prediabetes in people of reproductive age 20–44 years, which is comparable to or higher than the prevalence of GDM diagnosed by the one-step method (241).

The one-step method identifies the long-term risks of maternal prediabetes and diabetes and offspring abnormal glucose metabolism and adiposity. Post hoc GDM in individuals diagnosed by the one-step method in the HAPO cohort was associated with higher prevalence of IGT; higher 30-min, 1-h, and 2-h glucoses during the OGTT; and reduced insulin sensitivity and oral disposition index in their offspring at 10–14 years of age compared with offspring of mothers without GDM. Associations of mother’s fasting, 1-h, and 2-h values on the 75-g OGTT were continuous with a comprehensive panel of offspring metabolic outcomes (236,242). In addition, HAPO Follow-up Study (HAPO FUS) data demonstrate that neonatal adiposity and fetal hyperinsulinemia (cord C-peptide), both higher across the continuum of maternal hyperglycemia, are mediators of childhood body fat (243).

Data are lacking on how the treatment of mother’s hyperglycemia in pregnancy affects her offspring’s risk for obesity, diabetes, and other metabolic disorders. Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of individuals with GDM diagnosed by the one-step strategy (244,245).

Two-Step Strategy

In 2013, the NIH convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (246). The 15-member panel had representatives from obstetrics and gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended a two-step approach to screening that used a 1-h 50-g GLT followed by a 3-h 100-g OGTT for those who screened positive. The American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (247). Updated from 2014, a 2021 U.S. Preventive Services Task Force systematic review continues to conclude that one-step versus two-step screening is associated with increased likelihood of GDM (11.5% vs. 4.9%) but without improved health outcomes. It reports that the oral glucose challenge test using 140 or 135 mg/dL thresholds had sensitivities of 82% and 93% and specificities of 82% and 79%, respectively, against Carpenter-Coustan criteria. Fasting plasma glucose cutoffs of 85 mg/dL or 90 mg/dL had sensitivities of 88% and 81% and specificities of 73% and 82%, respectively, against Carpenter-Coustan criteria (248). The use of A1C at 24–28 weeks of gestation as a screening test for GDM does not function as well as the GLT (249).

Key factors cited by the NIH panel in their decision-making process were the lack of clinical trial data demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large group of individuals with GDM, including medicalization of pregnancy with increased health care utilization and costs. Moreover, screening with a 50-g GLT does not require fasting and therefore is easier to accomplish for many individuals. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (250), and shoulder dystocia without increasing small-for-gestational-age births. ACOG currently supports the two-step approach but notes that one elevated value, as opposed to two, may be used for the diagnosis of GDM (247). If this approach is implemented, the incidence of GDM by the two-step strategy will likely increase markedly. ACOG recommends

either of two sets of diagnostic thresholds for the 3-h 100-g OGTT—Carpenter-Coustan or National Diabetes Data Group (251,252). Each is based on different mathematical conversions of the original recommended thresholds by O’Sullivan and Mahan (232), which used whole blood and nonenzymatic methods for glucose determination. A secondary analysis of data from a randomized clinical trial of identification and treatment of mild GDM (253) demonstrated that treatment was similarly beneficial in people meeting only the lower thresholds per Carpenter-Coustan (251) and in those meeting only the higher thresholds per National Diabetes Data Group (252). If the two-step approach is used, it would appear advantageous to use the Carpenter-Coustan lower diagnostic thresholds, as shown in step 2 in **Table 2.7**.

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. A systematic review of economic evaluations of GDM screening found that the one-step method identified more cases of GDM and was more likely to be cost-effective than the two-step method (254). The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

The IADPSG criteria (“one-step strategy”) have been adopted internationally as the preferred approach. Data comparing population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (239,255–257). In addition, pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have outcomes comparable to pregnancies with diagnosed GDM by the more stringent two-step criteria (258,259). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently underway.

References

- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014;37(Suppl. 1):S81–S90
- Rewers A, Dong F, Slover RH, Klingensmith GJ, Rewers M. Incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado youth, 1998–2012. *JAMA* 2015;313:1570–1572
- Alonso GT, Coakley A, Pyle L, Manseau K, Thomas S, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado children, 2010–2017. *Diabetes Care* 2020;43:117–121
- Jensen ET, Stafford JM, Saydah S, et al. Increase in prevalence of diabetic ketoacidosis at diagnosis among youth with type 1 diabetes: the SEARCH for Diabetes in Youth Study. *Diabetes Care* 2021;44:1573–1578
- Humphreys A, Bravis V, Kaur A, et al. Individual and diabetes presentation characteristics associated with partial remission status in children and adults evaluated up to 12 months following diagnosis of type 1 diabetes: an ADDRESS-2 (After Diagnosis Diabetes Research Support System-2) study analysis. *Diabetes Res Clin Pract* 2019;155:107789
- Thomas NJ, Lynam AL, Hill AV, et al. Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. *Diabetologia* 2019;62:1167–1172
- Hope SV, Wienand-Barnett S, Shepherd M, et al. Practical Classification Guidelines for Diabetes in patients treated with insulin: a cross-sectional study of the accuracy of diabetes diagnosis. *Br J Gen Pract* 2016;66:e315–e322
- Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2021;44:2589–2625
- Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998–2013: a retrospective cohort study. *Diabetes Care* 2018;41:1870–1877
- Lawrence JM, Slezak JM, Quesenberry C, et al. Incidence and predictors of type 1 diabetes among younger adults aged 20–45 years: the Diabetes in Young Adults (DiYA) study. *Diabetes Res Clin Pract* 2021;171:108624
- Newton CA, Raskin P. Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus: clinical and biochemical differences. *Arch Intern Med* 2004;164:1925–1931
- Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. *Diabetes* 2017;66:241–255
- Lynam AL, Dennis JM, Owen KR, et al. Logistic regression has similar performance to optimised machine learning algorithms in a clinical setting: application to the discrimination between type 1 and type 2 diabetes in young adults. *Diagn Progn Res* 2020;4:6
- Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA* 2013;309:2473–2479
- Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care* 2015;38:1964–1974
- Zhu Y, Qian L, Liu Q, et al. Glutamic acid decarboxylase autoantibody detection by electrochemiluminescence assay identifies latent autoimmune diabetes in adults with poor islet function. *Diabetes Metab J* 2020;44:260–266
- Lynam A, McDonald T, Hill A, et al. Development and validation of multivariable clinical diagnostic models to identify type 1 diabetes requiring rapid insulin therapy in adults aged 18–50 years. *BMJ Open* 2019;9:e031586
- Chung WK, Erion K, Florez JC, et al. Precision medicine in diabetes: a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2020;43:1617–1635
- Gale EA. Declassifying diabetes. *Diabetologia* 2006;49:1989–1995
- Schwartz SS, Epstein S, Corkey BE, Grant SFA, Gavin JR 3rd, Aguilar RB. The time is right for a new classification system for diabetes: rationale and implications of the β -cell-centric classification schema. *Diabetes Care* 2016;39:179–186
- International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327–1334
- Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
- Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343–1350
- Chadha C, Pittas AG, Lary CW, et al.; D2d Research Group. Reproducibility of a prediabetes classification in a contemporary population. *Metabol Open* 2020;6:100031
- Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183–1197
- Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003;26(Suppl. 1):S5–S20
- Meijnikman AS, De Block CEM, Dirinck E, et al. Not performing an OGTT results in significant underdiagnosis of (pre)diabetes in a high risk adult Caucasian population. *Int J Obes* 2017;41:1615–1620
- Gonzalez A, Deng Y, Lane AN, et al. Impact of mismatches in HbA_{1c} vs glucose values on the diagnostic classification of diabetes and prediabetes. *Diabet Med* 2020;37:689–696
- Lenters-Westra E, Slingerland RJ. Six of eight hemoglobin A1c point-of-care instruments do not meet the general accepted analytical performance criteria. *Clin Chem* 2010;56:44–52
- Hirst JA, McLellan JH, Price CP, et al. Performance of point-of-care HbA_{1c} test devices: implications for use in clinical practice—a systematic review and meta-analysis. *Clin Chem Lab Med* 2017;55:167–180

31. Nathan DM, Griffin A, Perez FM, Basque E, Do L, Steiner B. Accuracy of a point-of-care hemoglobinA1c assay. *J Diabetes Sci Technol* 2019;13:1149–1153
32. Centers for Medicare & Medicaid Services. CLIA Brochures. Accessed 26 August 2022. Available from https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_Brochures
33. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. *Diabetes Care* 2010;33:562–568
34. Eckhardt BJ, Holzman RS, Kwan CK, Baghdadi J, Aberg JA. Glycated hemoglobin A_{1c} as screening for diabetes mellitus in HIV-infected individuals. *AIDS Patient Care STDS* 2012;26:197–201
35. Kim PS, Woods C, Georgoff P, et al. A1C underestimates glycemia in HIV infection. *Diabetes Care* 2009;32:1591–1593
36. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. *Diabetes Care* 2018;41:2648–2668
37. Lacy ME, Wellenius GA, Sumner AE, Correa A, Carnethon MR, Liem RI, et al. Association of sickle cell trait with hemoglobin A1c in African Americans. *JAMA*. 2017 07;317(5):507–515.
38. Wheeler E, Leong A, Liu CT, et al.; EPIC-CVD Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study. Impact of common genetic determinants of hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. *PLoS Med* 2017;14:e1002383
39. Kweka B, Lyimo E, Jeremiah K, et al. Influence of hemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency on diagnosis of diabetes by HbA1c among Tanzanian adults with and without HIV: A cross-sectional study. *PLoS One* 2020;15:e0244782
40. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. *Ann Intern Med* 2010;152:770–777
41. Kumar PR, Bhansali A, Ravikiran M, et al. Utility of glycated hemoglobin in diagnosing type 2 diabetes mellitus: a community-based study. *J Clin Endocrinol Metab* 2010;95:2832–2835
42. Herman WH. Are there clinical implications of racial differences in HbA1c? Yes, to not consider can do great harm! *Diabetes Care* 2016;39:1458–1461
43. Herman WH, Ma Y, Uwaifo G, et al.; Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. *Diabetes Care* 2007;30:2453–2457
44. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Racial differences in glycemic markers: a cross-sectional analysis of community-based data. *Ann Intern Med* 2011;154:303–309
45. Herman WH, Dungan KM, Wolfenbutter BHR, et al. Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. *J Clin Endocrinol Metab* 2009;94:1689–1694
46. Bergenstal RM, Gal RL, Connor CG, et al.; T1D Exchange Racial Differences Study Group. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. *Ann Intern Med* 2017;167:95–102
47. Khosla L, Bhat S, Fullington LA, Horlyck-Romanovsky MF. HbA_{1c} performance in African descent populations in the United States with normal glucose tolerance, prediabetes, or diabetes: a scoping review. *Prev Chronic Dis* 2021;18:E22
48. Selvin E. Are there clinical implications of racial differences in HbA1c? A difference, to be a difference, must make a difference. *Diabetes Care* 2016;39:1462–1467
49. Huang SH, Huang PJ, Li JY, Su YD, Lu CC, Shih CL. Hemoglobin A1c levels associated with age and gender in Taiwanese adults without prior diagnosis with diabetes. *Int J Environ Res Public Health* 2021;18:3390
50. Paterson AD. HbA1c for type 2 diabetes diagnosis in Africans and African Americans: personalized medicine NOW! *PLoS Med* 2017;14:e1002384
51. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 2008;371:64–74
52. Picón MJ, Murri M, Muñoz A, Fernández-García JC, Gomez-Huelgas R, Tinahones FJ. Hemoglobin A1c versus oral glucose tolerance test in postpartum diabetes screening. *Diabetes Care* 2012;35:1648–1653
53. Göbl CS, Bozkurt L, Yarragudi R, Tura A, Pacini G, Kautzky-Willer A. Is early postpartum HbA1c an appropriate risk predictor after pregnancy with gestational diabetes mellitus? *Acta Diabetol* 2014;51:715–722
54. Megia A, Näf S, Herranz L, et al. The usefulness of HbA1c in postpartum reclassification of gestational diabetes. *BJOG* 2012;119:891–894
55. Welsh KJ, Kirkman MS, Sacks DB. Role of glycated proteins in the diagnosis and management of diabetes: research gaps and future directions. *Diabetes Care* 2016;39:1299–1306
56. Kim C, Bullard KM, Herman WH, Beckles GL. Association between iron deficiency and A1C levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999–2006. *Diabetes Care* 2010;33:780–785
57. Selvin E, Wang D, Matsushita K, Grams ME, Coresh J. Prognostic implications of single-sample confirmatory testing for undiagnosed diabetes: a prospective cohort study. *Ann Intern Med* 2018;169:156–164.
58. Klein KR, Walker CP, McFerren AL, Huffman H, Frohlich F, Buse JB. Carbohydrate intake prior to oral glucose tolerance testing. *J Endocr Soc* 2021;5:bvab049
59. CoNN JW. Interpretation of the glucose tolerance test. The necessity of a standard preparatory diet. *Am J Med Sci* 1940;199:555–564
60. Wilkerson HL, Butler FK, Francis JO. The effect of prior carbohydrate intake on the oral glucose tolerance test. *Diabetes* 1960;9:386–391
61. Ziegler AG; BABYDIAB-BABYDIET Study Group. Age-related islet autoantibody incidence in offspring of patients with type 1 diabetes. *Diabetologia* 2012;55:1937–1943
62. Parikka V, Näntö-Salonen K, Saarinen M, et al. Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in children at genetic risk. *Diabetologia* 2012;55:1926–1936
63. Steck AK, Vehik K, Bonifacio E, et al.; TEDDY Study Group. Predictors of Progression From the Appearance of Islet Autoantibodies to Early Childhood Diabetes: The Environmental Determinants of Diabetes in the Young (TEDDY). *Diabetes Care* 2015;38:808–813
64. McKeigue PM, Spiliopoulou A, McGurnaghan S, Colombo M, Blackburn L, McDonald TJ, et al. Persistent C-peptide secretion in type 1 diabetes and its relationship to the genetic architecture of diabetes. *BMC Med* 2019;17:165
65. Bogun MM, Bundy BN, Golland RS, Greenbaum CJ. C-peptide levels in subjects followed longitudinally before and after type 1 diabetes diagnosis in TrialNet. *Diabetes Care* 2020;43:1836–1842
66. Greenbaum CJ, Beam CA, Boulware D, et al.; Type 1 Diabetes TrialNet Study Group. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. *Diabetes* 2012;61:2066–2073
67. Mishra R, Hodge KM, Cousminer DL, Leslie RD, Grant SFA. A global perspective of latent autoimmune diabetes in adults. *Trends Endocrinol Metab* 2018;29:638–650
68. Buzzetti R, Zampetti S, Maddaloni E. Adult-onset autoimmune diabetes: current knowledge and implications for management. *Nat Rev Endocrinol* 2017;13:674–686
69. Ben-Skowronek I. IPEX syndrome: genetics and treatment options. *Genes (Basel)* 2021;12:323
70. Frommer L, Kahaly GJ. Autoimmune polyendocrinopathy. *J Clin Endocrinol Metab* 2019;104:4769–4782
71. Smith CJ, Almodallal Y, Jatou A. Rare adverse events with programmed death-1 and programmed death-1 ligand inhibitors: justification and rationale for a systematic review. *Curr Oncol Rep* 2021;23:86
72. Zhao Z, Wang X, Bao XQ, Ning J, Shang M, Zhang D. Autoimmune polyendocrine syndrome induced by immune checkpoint inhibitors: a systematic review. *Cancer Immunol Immunother* 2021;70:1527–1540
73. Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes* 2018;67:1471–1480
74. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. *Endocr Rev* 2008;29:292–302
75. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 2014;311:1778–1786
76. McQueen RB, Geno Rasmussen C, Waugh K, et al. Cost and cost-effectiveness of large-scale screening for type 1 diabetes in Colorado. *Diabetes Care* 2020;43:1496–1503
77. Ziegler AG, Kick K, Bonifacio E, et al.; Fr1da Study Group. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. *JAMA* 2020;323:339–351
78. Sosenko JM, Skyler JS, Palmer JP, et al.; Type 1 Diabetes TrialNet Study Group; Diabetes Prevention Trial-Type 1 Study Group. The prediction of type 1 diabetes by multiple autoantibody levels and their incorporation into an autoantibody risk score in relatives of type 1 diabetic patients. *Diabetes Care* 2013;36:2615–2620
79. Orban T, Sosenko JM, Cuthbertson D, et al.; Diabetes Prevention Trial-Type 1 Study Group. Pancreatic islet autoantibodies as predictors of

- type 1 diabetes in the Diabetes Prevention Trial-Type 1. *Diabetes Care* 2009;32:2269–2274
80. Jacobsen LM, Larsson HE, Tamura RN, et al.; TEDDY Study Group. Predicting progression to type 1 diabetes from ages 3 to 6 in islet autoantibody positive TEDDY children. *Pediatr Diabetes* 2019;20:263–270
81. Barker JM, Goehrig SH, Barriga K, et al.; DAISY study. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care* 2004;27:1399–1404
82. Elding Larsson H, Vehik K, Gesualdo P, et al.; TEDDY Study Group. Children followed in the TEDDY study are diagnosed with type 1 diabetes at an early stage of disease. *Pediatr Diabetes* 2014;15:118–126
83. Herold KC, Bundy BN, Long SA, et al.; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med* 2019;381:603–613
84. Sims EK, Bundy BN, Stier K, et al.; Type 1 Diabetes TrialNet Study Group. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci Transl Med* 2021;13:eabc8980
85. Selvin E, Rawlings AM, Bergenstal RM, Coresh J, Brancati FL. No racial differences in the association of glycosylated hemoglobin with kidney disease and cardiovascular outcomes. *Diabetes Care* 2013;36:2995–3001
86. Zhang X, Gregg EW, Williamson DF, et al. A1C level and future risk of diabetes: a systematic review. *Diabetes Care* 2010;33:1665–1673
87. Selvin E, Steffes MW, Zhu H, et al. Glycosylated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010;362:800–811
88. Ackermann RT, Cheng YJ, Williamson DF, Gregg EW. Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c National Health and Nutrition Examination Survey 2005–2006. *Am J Prev Med* 2011;40:11–17
89. Diabetes Prevention Program Research Group. HbA1c as a predictor of diabetes and as an outcome in the diabetes prevention program: a randomized clinical trial. *Diabetes Care* 2015;38:51–58
90. Umpierrez G, Korytkowski M. Diabetic emergencies—ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nat Rev Endocrinol* 2016;12:222–232
91. Fadini GP, Bonora BM, Avogaro A. SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System. *Diabetologia* 2017;60:1385–1389
92. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391:541–551
93. Taheri S, Zaghoul H, Chagoury O, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADeM-I): an open-label, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol* 2020;8:477–489
94. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;7:344–355
95. Roth AE, Thornley CJ, Blackstone RP. Outcomes in bariatric and metabolic surgery: an updated 5-year review. *Curr Obes Rep* 2020;9:380–389
96. Conte C, Lapeyre-Mestre M, Hanaire H, Ritz P. Diabetes remission and relapse after bariatric surgery: a nationwide population-based study. *Obes Surg* 2020;30:4810–4820
97. Yoshino M, Kayser BD, Yoshino J, Stein RI, Reeds D, Eagon JC, et al. Effects of diet versus gastric bypass on metabolic function in diabetes. *N Engl J Med*. 2020 20;383(8):721–32.
98. Cresci B, Cosentino C, Monami M, Mannucci E. Metabolic surgery for the treatment of type 2 diabetes: a network meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2020;22:1378–1387
99. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020: Estimates of Diabetes and Its Burden in the United States. Accessed 14 October 2022. Available from <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>
100. International Diabetes Federation. IDF Diabetes Atlas, 10th edition. Brussels, Belgium, International Diabetes Federation, 2021. Accessed 29 March 2022. Available from <https://www.diabetesatlas.org/atlas/tenth-edition/>
101. Bardenheier BH, Wu WC, Zullo AR, Gravenstein S, Gregg EW. Progression to diabetes by baseline glycemic status among middle-aged and older adults in the United States, 2006–2014. *Diabetes Res Clin Pract* 2021;174:108726
102. Sussman JB, Kent DM, Nelson JP, Hayward RA. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. *BMJ* 2015;350:h454
103. Palladino R, Tabak AG, Khunti K, et al. Association between pre-diabetes and microvascular and macrovascular disease in newly diagnosed type 2 diabetes. *BMJ Open Diabetes Res Care* 2020;8:e001061
104. Perreault L, Pan Q, Aroda VR, et al.; Diabetes Prevention Program Research Group. Exploring residual risk for diabetes and microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). *Diabet Med* 2017;34:1747–1755
105. Nathan DM, Bennett PH, Crandall JP, et al.; Research Group. Does diabetes prevention translate into reduced long-term vascular complications of diabetes? *Diabetologia* 2019;62:1319–1328
106. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011;34(Suppl. 1):S62–S69
107. Genuth S, Alberti KGMM, Bennett P, et al.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–3167
108. Lin C-H, Wei J-N, Fan K-C, et al. Different cutoffs of hypertension, risk of incident diabetes and progression of insulin resistance: a prospective cohort study. *J Formos Med Assoc* 2022;121:193–201
109. Wei Y, Xu Q, Yang H, et al. Preconception diabetes mellitus and adverse pregnancy outcomes in over 6.4 million women: a population-based cohort study in China. *PLoS Med* 2019;16:e1002926
110. Peterson C, Grosse SD, Li R, et al. Preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the United States. *Am J Obstet Gynecol* 2015;212:74.e1–74.e9
111. Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet* 2011;378:156–167
112. Herman WH, Ye W, Griffin SJ, et al. Early detection and treatment of type 2 diabetes reduce cardiovascular morbidity and mortality: a simulation of the results of the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Europe). *Diabetes Care* 2015;38:1449–1455
113. Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet* 2010;375:1365–1374
114. Zhou X, Siegel KR, Ng BP, et al. Cost-effectiveness of diabetes prevention interventions targeting high-risk individuals and whole populations: a systematic review. *Diabetes Care* 2020;43:1593–1616
115. Chatterjee R, Narayan KMV, Lipscomb J, et al. Screening for diabetes and prediabetes should be cost-saving in patients at high risk. *Diabetes Care* 2013;36:1981–1987
116. Chung S, Azar KMJ, Baek M, Lauderdale DS, Palaniappan LP. Reconsidering the age thresholds for type II diabetes screening in the U.S. *Am J Prev Med* 2014;47:375–381
117. Araneta MRG, Kanaya A, Fujimoto W, et al. Optimum BMI cut points to screen Asian Americans for type 2 diabetes. *Diabetes Care* 2015;38:814–820
118. Hsu WC, Araneta MRG, Kanaya AM, Chiang JL, Fujimoto W. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care* 2015;38:150–158
119. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157–163
120. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. *JAMA* 2015;314:1021–1029
121. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care* 2011;34:1741–1748
122. Schambelan M, Benson CA, Carr A, et al.; International AIDS Society-USA. Management of metabolic complications associated with anti-retroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr* 2002;31:257–275
123. Monroe AK, Glesby MJ, Brown TT. Diagnosing and managing diabetes in HIV-infected patients: current concepts. *Clin Infect Dis* 2015;60:453–462
124. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis* 2006;43:645–653
125. Johnson SL, Tabaei BP, Herman WH. The efficacy and cost of alternative strategies for systematic screening for type 2 diabetes in the

- U.S. population 45-74 years of age. *Diabetes Care* 2005;28:307-311
126. Tabaei BP, Burke R, Constance A, et al. Community-based screening for diabetes in Michigan. *Diabetes Care* 2003;26:668-670
 127. Lalla E, Kunzel C, Burkett S, Cheng B, Lamster IB. Identification of unrecognized diabetes and pre-diabetes in a dental setting. *J Dent Res* 2011;90:855-860
 128. Lalla E, Cheng B, Kunzel C, Burkett S, Lamster IB. Dental findings and identification of undiagnosed hyperglycemia. *J Dent Res* 2013;92:888-892
 129. Herman WH, Taylor GW, Jacobson JJ, Burke R, Brown MB. Screening for prediabetes and type 2 diabetes in dental offices. *J Public Health Dent* 2015;75:175-182
 130. Jadhav AN, Tarte PR, Puri SK. Dental clinic: potential source of high-risk screening for prediabetes and type 2 diabetes. *Indian J Dent Res* 2019;30:851-854
 131. Buse JB, Kaufman FR, Linder B, Hirst K, El Ghormli L; HEALTHY Study Group. Diabetes screening with hemoglobin A(1c) versus fasting plasma glucose in a multiethnic middle-school cohort. *Diabetes Care* 2013;36:429-435
 132. Kapadia C; Drugs and Therapeutics Committee of the Pediatric Endocrine Society. Hemoglobin A1c measurement for the diagnosis of Type 2 diabetes in children. *Int J Pediatr Endocrinol* 2012;2012:31
 133. Kester LM, Hey H, Hannon TS. Using hemoglobin A1c for prediabetes and diabetes diagnosis in adolescents: can adult recommendations be upheld for pediatric use? *J Adolesc Health* 2012;50:321-323
 134. Wu EL, Kazzi NG, Lee JM. Cost-effectiveness of screening strategies for identifying pediatric diabetes mellitus and dysglycemia. *JAMA Pediatr* 2013;167:32-39
 135. Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD clinical practice consensus guidelines 2018: management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes* 2018;19(Suppl. 27):64-74
 136. Gilmour JA. Response to the letter to the editor from Dr. Boudreau et al., "Validation of a Stepwise Approach Using Glycated Hemoglobin Levels to Reduce the Number of Required Oral Glucose Tolerance Tests to Screen for Cystic Fibrosis-Related Diabetes in Adults". *Can J Diabetes* 2019;43:163
 137. Gilmour JA, Sykes J, Etchells E, Tullis E. Cystic fibrosis-related diabetes screening in adults: a gap analysis and evaluation of accuracy of glycated hemoglobin levels. *Can J Diabetes* 2019; 43:13-18
 138. Darukhanavala A, Van Dessel F, Ho J, Hansen M, Kremer T, Alfego D. Use of hemoglobin A1c to identify dysglycemia in cystic fibrosis. *PLoS One* 2021;16:e0250036
 139. Franck Thompson E, Watson D, Benoit CM, Landvik S, McNamara J. The association of pediatric cystic fibrosis-related diabetes screening on clinical outcomes by center: a CF patient registry study. *J Cyst Fibros* 2020;19:316-320
 140. Olesen HV, Drevinek P, Gulmans VA, et al.; ECFSPR Steering Group. Cystic fibrosis related diabetes in Europe: prevalence, risk factors and outcome. *J Cyst Fibros* 2020;19:321-327
 141. Prentice BJ, Chelliah A, Ooi CY, et al. Peak OGTT glucose is associated with lower lung function in young children with cystic fibrosis. *J Cyst Fibros* 2020;19:305-309
 142. Mainguy C, Bellon G, Delaup V, et al. Sensitivity and specificity of different methods for cystic fibrosis-related diabetes screening: is the oral glucose tolerance test still the standard? *J Pediatr Endocrinol Metab* 2017;30:27-35
 143. Ode KL, Moran A. New insights into cystic fibrosis-related diabetes in children. *Lancet Diabetes Endocrinol* 2013;1:52-58
 144. Moran A, Pekow P, Grover P, et al. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. *Diabetes Care* 2009;32:1783-1788
 145. Onady GM, Stolfi A. Insulin and oral agents for managing cystic fibrosis-related diabetes. *Cochrane Database Syst Rev* 2016;4:CD004730
 146. Moran A, Brunzell C, Cohen RC, et al.; CFRD Guidelines Committee. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care* 2010;33:2697-2708
 147. Shivaswamy V, Boerner B, Larsen J. Post-transplant diabetes mellitus: causes, treatment, and impact on outcomes. *Endocr Rev* 2016;37:37-61
 148. Sharif A, Hecking M, de Vries APJ, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant* 2014;14:1992-2000
 149. Hecking M, Werzowa J, Haidinger M, et al.; European-New-Onset Diabetes After Transplantation Working Group. Novel views on new-onset diabetes after transplantation: development, prevention and treatment. *Nephrol Dial Transplant* 2013;28:550-566
 150. Ramirez SC, Maaske J, Kim Y, et al. The association between glycemic control and clinical outcomes after kidney transplantation. *Endocr Pract* 2014;20:894-900
 151. Thomas MC, Moran J, Mathew TH, Russ GR, Rao MM. Early peri-operative hyperglycaemia and renal allograft rejection in patients without diabetes. *BMC Nephrol* 2000;1:1
 152. Chakkerla HA, Weil EJ, Castro J, et al. Hyperglycemia during the immediate period after kidney transplantation. *Clin J Am Soc Nephrol* 2009;4:853-859
 153. Wallia A, Illuri V, Molitch ME. Diabetes care after transplant: definitions, risk factors, and clinical management. *Med Clin North Am* 2016; 100:535-550
 154. Kim HD, Chang JY, Chung BH, et al. Effect of everolimus with low-dose tacrolimus on development of new-onset diabetes after transplantation and allograft function in kidney transplantation: a multicenter, open-label, randomized trial. *Ann Transplant* 2021;26:e927984
 155. Cheng CY, Chen CH, Wu MF, et al. Risk factors in and long-term survival of patients with post-transplantation diabetes mellitus: a retrospective cohort study. *Int J Environ Res Public Health* 2020;17:E4581
 156. Gulsoy Kirnap N, Bozkus Y, Haberal M. Analysis of risk factors for posttransplant diabetes mellitus after kidney transplantation: single-center experience. *Exp Clin Transplant* 2020;18(Suppl. 1): 36-40
 157. Munshi VN, Saghaian S, Cook CB, Eric Steidley D, Hardaway B, Chakkerla HA. Incidence, risk factors, and trends for postheart transplantation diabetes mellitus. *Am J Cardiol* 2020; 125:436-440
 158. Kgosidialwa O, Blake K, O'Connell O, Egan J, O'Neill J, Hatunic M. Post-transplant diabetes mellitus associated with heart and lung transplant. *Ir J Med Sci* 2020;189:185-189
 159. Sharif A, Moore RH, Baboolal K. The use of oral glucose tolerance tests to risk stratify for new-onset diabetes after transplantation: an underdiagnosed phenomenon. *Transplantation* 2006;82:1667-1672
 160. Hecking M, Kainz A, Werzowa J, et al. Glucose metabolism after renal transplantation. *Diabetes Care* 2013;36:2763-2771
 161. Pham Vu T, Nguyen Thi Thuy D, Truong Quy K, et al. Serum hs-CRP measured prior transplantation predicts of new-onset diabetes after transplantation in renal transplant recipients. *Transpl Immunol* 2021;66:101392
 162. Grundman JB, Wolfsdorf JI, Marks BE. Post-transplantation diabetes mellitus in pediatric patients. *Horm Res Paediatr* 2020;93:510-518
 163. Galindo RJ, Fried M, Breen T, Tamler R. Hyperglycemia management in patients with post-transplantation diabetes. *Endocr Pract* 2016;22: 454-465
 164. Jenssen T, Hartmann A. Emerging treatments for post-transplantation diabetes mellitus. *Nat Rev Nephrol* 2015;11:465-477
 165. Thomas MC, Mathew TH, Russ GR, Rao MM, Moran J. Early peri-operative glycaemic control and allograft rejection in patients with diabetes mellitus: a pilot study. *Transplantation* 2001;72:1321-1324
 166. Kurian B, Joshi R, Helmuth A. Effectiveness and long-term safety of thiazolidinediones and metformin in renal transplant recipients. *Endocr Pract* 2008;14:979-984
 167. Budde K, Neumayer HH, Fritsche L, Sulowicz W, Stompör T, Eckland D. The pharmacokinetics of pioglitazone in patients with impaired renal function. *Br J Clin Pharmacol* 2003;55:368-374
 168. Luther P, Baldwin D Jr. Pioglitazone in the management of diabetes mellitus after transplantation. *Am J Transplant* 2004;4:2135-2138
 169. Strøm Halden TA, Åsberg A, Vik K, Hartmann A, Jenssen T. Short-term efficacy and safety of sitagliptin treatment in long-term stable renal recipients with new-onset diabetes after transplantation. *Nephrol Dial Transplant* 2014;29: 926-933
 170. Lane JT, Odegaard DE, Haire CE, Collier DS, Wrenshall LE, Stevens RB. Sitagliptin therapy in kidney transplant recipients with new-onset diabetes after transplantation. *Transplantation* 2011;92:e56-e57
 171. Carmody D, Støy J, Greeley SAW, Bell GI, Philipson LH. Chapter 2—A clinical guide to monogenic diabetes. In *Genetic Diagnosis of Endocrine Disorders*. 2nd ed. Weiss RE, Refetoff S, Eds. Academic Press, 2016, pp. 21-30
 172. De Franco E, Flanagan SE, Houghton JAL, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet* 2015;386: 957-963

173. Sanyoura M, Letourneau L, Knight Johnson AE, et al. GCK-MODY in the US Monogenic Diabetes Registry: description of 27 unpublished variants. *Diabetes Res Clin Pract* 2019;151:231–236
174. Carmody D, Naylor RN, Bell CD, et al. GCK-MODY in the US National Monogenic Diabetes Registry: frequently misdiagnosed and unnecessarily treated. *Acta Diabetol* 2016;53:703–708
175. Timsit J, Saint-Martin C, Dubois-Laforgue D, Bellanné-Chantelot C. Searching for maturity-onset diabetes of the young (MODY): when and what for? *Can J Diabetes* 2016;40:455–461
176. De Franco E, Caswell R, Johnson MB, et al. De novo mutations in *EIF2B1* affecting eIF2 signaling cause neonatal/early-onset diabetes and transient hepatic dysfunction. *Diabetes* 2020;69:477–483
177. Valkovicova T, Skopkova M, Stanik J, Gasperikova D. Novel insights into genetics and clinics of the HNF1A-MODY. *Endocr Regul* 2019;53:110–134
178. Awa WL, Schober E, Wiegand S, et al. Reclassification of diabetes type in pediatric patients initially classified as type 2 diabetes mellitus: 15 years follow-up using routine data from the German/Austrian DPV database. *Diabetes Res Clin Pract* 2011;94:463–467
179. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia* 2010;53:2504–2508
180. Shepherd M, Shields B, Hammersley S, et al.; UNITED Team. Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. *Diabetes Care* 2016;39:1879–1888
181. SEARCH Study Group. SEARCH for Diabetes in Youth: a multicenter study of the prevalence, incidence and classification of diabetes mellitus in youth. *Control Clin Trials* 2004;25:458–471
182. Pihoker C, Gilliam LK, Ellard S, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. *J Clin Endocrinol Metab* 2013;98:4055–4062
183. Draznin B (Ed.). *Atypical Diabetes: Pathophysiology, Clinical Presentations, and Treatment Options*. Arlington, VA, American Diabetes Association, 2018
184. Exeter Diabetes. MODY Probability Calculator. Accessed 14 October 2022. Available from <https://www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator>
185. Urbanová J, Rypáčková B, Procházková Z, et al. Positivity for islet cell autoantibodies in patients with monogenic diabetes is associated with later diabetes onset and higher HbA1c level. *Diabet Med* 2014;31:466–471
186. Naylor RN, John PM, Winn AN, et al. Cost-effectiveness of MODY genetic testing: translating genomic advances into practical health applications. *Diabetes Care* 2014;37:202–209
187. Shields BM, Shepherd M, Hudson M, et al.; UNITED study team. Population-based assessment of a biomarker-based screening pathway to aid diagnosis of monogenic diabetes in young-onset patients. *Diabetes Care* 2017;40:1017–1025
188. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2009;10(Suppl. 12):33–42
189. Rubio-Cabezas O, Hattersley AT, Njolstad PR, et al.; International Society for Pediatric and Adolescent Diabetes. ISPAD clinical practice consensus guidelines 2014. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2014;15(Suppl. 20):47–64
190. Steele AM, Shields BM, Shepherd M, Ellard S, Hattersley AT, Pearson ER. Increased all-cause and cardiovascular mortality in monogenic diabetes as a result of mutations in the HNF1A gene. *Diabet Med* 2010;27:157–161
191. Anök A, Çatlö G, Abacı A, Böber E. Maturity-onset diabetes of the young (MODY): an update. *J Pediatr Endocrinol Metab* 2015;28:251–263
192. Greeley SAW, Naylor RN, Philipson LH, Bell GI. Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment. *Curr Diab Rep* 2011;11:519–532
193. Le Bodic L, Bignon JD, Raguénès O, et al. The hereditary pancreatitis gene maps to long arm of chromosome 7. *Hum Mol Genet* 1996;5:549–554
194. Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? *Diabetes Care* 2008;31(Suppl. 2):S165–S169
195. Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (type 3c): a retrospective cohort study. *Diabetes Care* 2017;40:1486–1493
196. Duggan SN, Ewald N, Kelleher L, Griffin O, Gibney J, Conlon KC. The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. *Eur J Clin Nutr* 2017;71:3–8
197. Makuc J. Management of pancreatogenic diabetes: challenges and solutions. *Diabetes Metab Syndr Obes* 2016;9:311–315
198. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. *Diabetes* 2017;66:1103–1110
199. Petrov MS, Basina M. Diagnosis of endocrine disease: diagnosing and classifying diabetes in diseases of the exocrine pancreas. *Eur J Endocrinol* 2021;184:R151–R163
200. Bellin MD, Gelrud A, Arreaza-Rubin G, et al. Total pancreatectomy with islet autotransplantation: summary of an NIDDK workshop. *Ann Surg* 2015;261:21–29
201. Anazawa T, Okajima H, Masui T, Uemoto S. Current state and future evolution of pancreatic islet transplantation. *Ann Gastroenterol Surg* 2018;3:34–42
202. Quartuccio M, Hall E, Singh V, et al. Glycemic predictors of insulin independence after total pancreatectomy with islet autotransplantation. *J Clin Endocrinol Metab* 2017;102:801–809
203. Huvinen E, Koivusalo SB, Meinilä J, Valkama A, Tiitinen A, Rönö K, et al. Effects of a lifestyle intervention during pregnancy and first postpartum year: findings from the RADIEL study. *J Clin Endocrinol Metab* 2018;103:1669–1677
204. Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996–2010. *Diabetes Care* 2014;37:1590–1596
205. Peng TY, Ehrlich SF, Crites Y, et al. Trends and racial and ethnic disparities in the prevalence of pregestational type 1 and type 2 diabetes in Northern California: 1996–2014. *Am J Obstet Gynecol* 2017;216:177.e1–177.e8
206. Jovanović L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N. Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. *Diabetes Metab Res Rev* 2015;31:707–716
207. Poltavskiy E, Kim DJ, Bang H. Comparison of screening scores for diabetes and prediabetes. *Diabetes Res Clin Pract* 2016;118:146–153
208. Mission JF, Catov J, Deihl TE, Feghali M, Scifres C. Early pregnancy diabetes screening and diagnosis: prevalence, rates of abnormal test results, and associated factors. *Obstet Gynecol* 2017;130:1136–1142
209. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018;138:271–281
210. Britton LE, Hussey JM, Crandell JL, Berry DC, Brooks JL, Bryant AG. Racial/ethnic disparities in diabetes diagnosis and glycemic control among women of reproductive age. *J Womens Health (Larchmt)* 2018;27:1271–1277
211. Robbins C, Boulet SL, Morgan I, et al. Disparities in preconception health indicators—Behavioral Risk Factor Surveillance System, 2013–2015, and Pregnancy Risk Assessment Monitoring System, 2013–2014. *MMWR Surveill Summ* 2018;67:1–16
212. Yuen L, Wong VW, Simmons D. Ethnic disparities in gestational diabetes. *Curr Diab Rep* 2018;18:68
213. Wahabi HA, Fayed A, Esmaeil S, et al. Systematic review and meta-analysis of the effectiveness of pre-pregnancy care for women with diabetes for improving maternal and perinatal outcomes. *PLoS One* 2020;15:e0237571
214. Zhu WW, Yang HX, Wei YM, et al. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. *Diabetes Care* 2013;36:586–590
215. Hughes RCE, Moore MP, Gullam JE, Mohamed K, Rowan J. An early pregnancy HbA1c $\geq 5.9\%$ (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care* 2014;37:2953–2959
216. Mañé L, Flores-Le Roux JA, Gómez N, et al. Association of first-trimester HbA1c levels with adverse pregnancy outcomes in different ethnic groups. *Diabetes Res Clin Pract* 2019;150:202–210
217. Boe B, Barbour LA, Allshouse AA, Heyborne KD. Universal early pregnancy glycosylated hemoglobin A1c as an adjunct to Carpenter-Coustan screening: an observational cohort study. *Am J Obstet Gynecol MFM* 2019;1:24–32
218. Immanuel J, Simmons D. Screening and treatment for early-onset gestational diabetes mellitus: a systematic review and meta-analysis. *Curr Diab Rep* 2017;17:115
219. Yefet E, Jeda E, Tzur A, Nachum Z. Markers for undiagnosed type 2 diabetes mellitus during pregnancy—a population-based retrospective cohort study. *J Diabetes* 2020;12:205–214
220. Kattini R, Hummelen R, Kelly L. Early gestational diabetes mellitus screening with

- glycated hemoglobin: a systematic review. *J Obstet Gynaecol Can* 2020;42:1379–1384
221. Chen L, Pocobelli G, Yu O, et al. Early pregnancy hemoglobin A1c and pregnancy outcomes: a population-based study. *Am J Perinatol* 2019;36:1045–1053
222. Osmundson SS, Zhao BS, Kunz L, et al. First trimester hemoglobin A1c prediction of gestational diabetes. *Am J Perinatol* 2016;33:977–982
223. McIntyre HD, Sacks DA, Barbour LA, et al. Issues with the diagnosis and classification of hyperglycemia in early pregnancy. *Diabetes Care* 2016;39:53–54
224. Cavagnoli G, Pimentel AL, Freitas PAC, Gross JL, Camargo JL. Factors affecting A1C in non-diabetic individuals: review and meta-analysis. *Clin Chim Acta* 2015;445:107–114
225. Buchanan TA, Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? *Diabetes Care* 2007;30(Suppl. 2):S105–S111
226. Noctor E, Crowe C, Carmody LA, et al.; ATLANTIC-DIP investigators. Abnormal glucose tolerance post-gestational diabetes mellitus as defined by the International Association of Diabetes and Pregnancy Study Groups criteria. *Eur J Endocrinol* 2016;175:287–297
227. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2002;25:1862–1868
228. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774–4779
229. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. *J Clin Endocrinol Metab* 2015;100:1646–1653
230. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. *Am J Obstet Gynecol* 2017;216:340–351
231. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002
232. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 1964;13:278–285
233. Sacks DA, Hadden DR, Maresh M, et al.; HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care* 2012;35:526–528
234. Brown FM, Wyckoff J. Application of one-step IADPSG versus two-step diagnostic criteria for gestational diabetes in the real world: impact on health services, clinical care, and outcomes. *Curr Diab Rep* 2017;17:85
235. Lowe WL Jr, Scholtens DM, Lowe LP, et al.; HAPO Follow-up Study Cooperative Research Group. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. *JAMA* 2018;320:1005–1016
236. Lowe WL Jr, Scholtens DM, Kuang A, et al.; HAPO Follow-up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. *Diabetes Care* 2019;42:372–380
237. Landon MB, Spong CY, Thom E, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;361:1339–1348
238. Crowther CA, Hillier JE, Moss JR, McPhee AJ, Jeffries WS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477–2486
239. Hillier TA, Pedula KL, Ogasawara KK, et al. A pragmatic, randomized clinical trial of gestational diabetes screening. *N Engl J Med* 2021;384:895–904
240. Coustan DR, Dyer AR, Metzger BE. One-step or 2-step testing for gestational diabetes: which is better? *Am J Obstet Gynecol* 2021;225:634–644
241. Cowie CC, Casagrande SS, Menke A, et al., Eds. *Diabetes in America*. 3rd ed. National Institute of Diabetes and Digestive and Kidney Diseases, 2018. Accessed 3 March 2022. Available from <https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/diabetes-in-america-3rd-edition>
242. Scholtens DM, Kuang A, Lowe LP, et al.; HAPO Follow-up Study Cooperative Research Group; HAPO Follow-Up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal glycemia and childhood glucose metabolism. *Diabetes Care* 2019;42:381–392
243. Josefson JL, Scholtens DM, Kuang A, et al.; HAPO Follow-up Study Cooperative Research Group. Newborn adiposity and cord blood C-peptide as mediators of the maternal metabolic environment and childhood adiposity. *Diabetes Care* 2021;44:1194–1202
244. Tam WH, Ma RCW, Ozaki R, et al. In utero exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. *Diabetes Care* 2017;40:679–686
245. Landon MB, Rice MM, Varner MW, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network. Mild gestational diabetes mellitus and long-term child health. *Diabetes Care* 2015;38:445–452
246. Vandorsten JP, Dodson WC, Espeland MA, et al. NIH consensus development conference: diagnosing gestational diabetes mellitus. *NIH Consens State Sci Statements* 2013;29:1–31
247. Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 190: gestational diabetes mellitus. *Obstet Gynecol* 2018;131:e49–e64
248. Pillay J, Donovan L, Guitard S, et al. Screening for Gestational Diabetes Mellitus: A Systematic Review to Update the 2014 U.S. Preventive Services Task Force Recommendation. Rockville, MD, Agency for Healthcare Research and Quality (U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews), 2021. Accessed 8 September 2022. Available from <http://www.ncbi.nlm.nih.gov/books/NBK573100/>
249. Khalafallah A, Phuah E, Al-Barazan AM, et al. Glycosylated haemoglobin for screening and diagnosis of gestational diabetes mellitus. *BMJ Open* 2016;6:e011059
250. Horvath K, Koch K, Jaitler K, Matyas E, Bender R, Bastian H, et al. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. *BMJ* 2010;340:c1395
251. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol* 1982;144:768–773
252. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;28:1039–1057
253. Harper LM, Mele L, Landon MB, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Carpenter-Coustan compared with national diabetes data group criteria for diagnosing gestational diabetes. *Obstet Gynecol* 2016;127:893–898
254. Mo X, Gai Tobe R, Takahashi Y, et al. Economic evaluations of gestational diabetes mellitus screening: a systematic review. *J Epidemiol* 2021;31:220–230
255. Wei Y, Yang H, Zhu W, et al. International Association of Diabetes and Pregnancy Study Group criteria is suitable for gestational diabetes mellitus diagnosis: further evidence from China. *Chin Med J (Engl)* 2014;127:3553–3556
256. Feldman RK, Tieu RS, Yasumura L. Gestational diabetes screening: the International Association of the Diabetes and Pregnancy Study Groups compared with Carpenter-Coustan Screening. *Obstet Gynecol* 2016;127:10–17
257. Saccone G, Khalifeh A, Al-Kouatly HB, Sendek K, Berghella V. Screening for gestational diabetes mellitus: one step versus two step approach. A meta-analysis of randomized trials. *J Matern Fetal Neonatal Med* 2020;33:1616–1624
258. Ethridge JK Jr, Catalano PM, Waters TP. Perinatal outcomes associated with the diagnosis of gestational diabetes made by the international association of the diabetes and pregnancy study groups criteria. *Obstet Gynecol* 2014;124:571–578
259. Mayo K, Melamed N, Vandenberghe H, Berger H. The impact of adoption of the international association of diabetes in pregnancy study group criteria for the screening and diagnosis of gestational diabetes. *Am J Obstet Gynecol* 2015;212:224.e1–224.e9

3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For guidelines related to screening for increased risk for type 2 diabetes (prediabetes), please refer to Section 2, “Classification and Diagnosis of Diabetes.” For guidelines related to screening, diagnosis, and management of type 2 diabetes in youth, please refer to Section 14, “Children and Adolescents.”

Recommendation

3.1 Monitor for the development of type 2 diabetes in those with prediabetes at least annually; modify based on individual risk/benefit assessment. **E**

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (Table 2.3) or with an assessment tool, such as the American Diabetes Association risk test (Fig. 2.1), is recommended to guide health care professionals on whether performing a diagnostic test for prediabetes (Table 2.5) and previously undiagnosed type 2 diabetes (Table 2.2) is appropriate (see Section 2, “Classification and Diagnosis of Diabetes”). Testing high-risk adults for prediabetes is warranted because the laboratory assessment is safe and reasonable in cost, substantial time exists before the development of type 2 diabetes and its complications during which one can intervene, and there is an effective means of preventing or delaying type 2 diabetes in those determined to have prediabetes with an A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance, or impaired fasting glucose. The utility of A1C screening for prediabetes and diabetes may be limited in the presence of hemoglobinopathies and conditions that affect red blood cell turnover. See Section 2, “Classification and Diagnosis of Diabetes,” and Section 6, “Glycemic Targets,” for additional details on the appropriate use and limitations of A1C testing.

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LIFESTYLE BEHAVIOR CHANGE FOR DIABETES PREVENTION

Recommendations

- 3.2** Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥ 150 min/week of moderate-intensity physical activity. **A**
- 3.3** A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. **B**
- 3.4** Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. **A** Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed.
- 3.5** Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

The Diabetes Prevention Program

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial (1), the Finnish Diabetes Prevention Study (DPS) (2), and the Da Qing Diabetes Prevention Study (Da Qing study) (3), demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic markers (such as blood pressure, lipids, and inflammation) (4). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial (1). The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression

to type 2 diabetes: 39% reduction at 30 years in the Da Qing study (5), 43% reduction at 7 years in the Finnish DPS (2), and 34% reduction at 10 years (6) and 27% reduction at 15 years (7) in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min moderate-intensity physical activity per week, such as brisk walking. The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals (8). Although weight loss was the most important factor in reducing the risk of incident diabetes, it was also found that achieving the target behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44% (9).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes. Participants were encouraged to achieve the $\geq 7\%$ weight loss during the first 6 months of the intervention. Further analysis suggests maximal prevention of diabetes with at least 7–10% weight loss (9). The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the dietary intervention was on reducing total fat rather than calories. After several weeks, the concept of calorie balance and the need to restrict calories and fat was introduced (8).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (8).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for the tailoring of interventions to reflect the diversity of the population (8).

The DPP intervention was administered as a structured core curriculum followed by a flexible maintenance program of individual counseling, group sessions, motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program. It included sessions on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors, and guidance on managing psychological, social, and motivational challenges. Further details are available regarding the core curriculum sessions (8).

Nutrition

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total dietary fat and calories (1,8,9). However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals (10). Based on other intervention trials, a variety of eating patterns characterized by the totality of food and beverages habitually consumed (10,11) may also be appropriate for individuals with prediabetes (10), including Mediterranean-style and low-carbohydrate eating plans (12–15). Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes (16–19). Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes (18,20–22). As is

the case for those with diabetes, individualized medical nutrition therapy (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes,” for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (23).

Physical Activity

Just as 150 min/week of moderate-intensity physical activity, such as brisk walking, showed beneficial effects in those with prediabetes (1), moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (24,25). Based on these findings, health care professionals are encouraged to promote a DPP-style program, including a focus on physical activity, to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training (8,26,27). Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels (28,29). The preventive effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM) (30).

Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention

Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes among those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payers ensued (31–35). Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (36–40).

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities (cdc.gov/diabetes/prevention/index.htm). This online resource includes

locations of CDC-recognized diabetes prevention lifestyle change programs (cdc.gov/diabetes/prevention/find-a-program.html). To be eligible for this program, individuals must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing, a previous diagnosis of GDM, or a positive risk test (cdc.gov/prediabetes/takethetest/). During the first 4 years of implementation of the CDC’s National DPP, 35.5% achieved the 5% weight loss goal (41). The CDC has also developed the Diabetes Prevention Impact Tool Kit (nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP lifestyle change program (42). In an effort to expand preventive services using a cost-effective model, the Centers for Medicare & Medicaid Services expanded Medicare reimbursement coverage for the National DPP lifestyle intervention to organizations recognized by the CDC that become Medicare suppliers for this service (innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program). The locations of Medicare DPPs are available online at innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program/mdpp-map. To qualify for Medicare coverage, individuals must have BMI >25 kg/m² (or BMI >23 kg/m² if self-identified as Asian) and laboratory testing consistent with prediabetes in the last year. Medicaid coverage of the DPP lifestyle intervention is also expanding on a state-by-state basis.

While CDC-recognized behavioral counseling programs, including Medicare DPP services, have met minimum quality standards and are reimbursed by many payers, lower retention rates have been reported for younger adults and racial/ethnic minority populations (43). Therefore, other programs and modalities of behavioral counseling for diabetes prevention may also be appropriate and efficacious based on individual preferences and availability. The use of community health workers to support DPP efforts has been shown to be effective and cost-effective (44,45) (see Section 1, “Improving Care and Promoting Health in Populations,” for more information). The use of community health workers may facilitate the adoption of behavior changes for diabetes prevention while bridging barriers related to social determinants of health. However, coverage

by third-party payers remains problematic. Counseling by a registered dietitian nutritionist (RDN) has been shown to help individuals with prediabetes improve eating habits, increase physical activity, and achieve 7–10% weight loss (10,46–48). Individualized medical nutrition therapy (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes,” for more detailed information) is also effective in improving glycemia in individuals diagnosed with prediabetes (23,46). Furthermore, trials involving medical nutrition therapy for adults with prediabetes found significant reductions in weight, waist circumference, and glycemia. Individuals with prediabetes can benefit from referral to an RDN for individualized medical nutrition therapy upon diagnosis and at regular intervals throughout their treatment plan (47,49). Other health care professionals, such as pharmacists and diabetes care and education specialists, may be considered for diabetes prevention efforts (50,51).

Technology-assisted programs may effectively deliver the DPP program (52–57). Such technology-assisted programs may deliver content through smartphones, web-based applications, and telehealth and may be an acceptable and efficacious option to bridge barriers, particularly for low-income individuals and people residing in rural locations; however, not all programs are effective in helping people reach targets for diabetes prevention (52,58–60). The CDC Diabetes Prevention Recognition Program (DPRP) (cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based programs; such programs must use an approved curriculum, include interaction with a coach, and attain the DPP outcomes of participation, physical activity reporting, and weight loss. Therefore, health care professionals should consider referring adults with prediabetes to certified technology-assisted DPP programs based on their preferences.

PHARMACOLOGIC INTERVENTIONS

Recommendations

3.6 Metformin therapy for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the Diabetes Prevention

Program, especially those aged 25–59 years with BMI ≥ 35 kg/m², higher fasting plasma glucose (e.g., ≥ 110 mg/dL), and higher A1C (e.g., $\geq 6.0\%$), and in individuals with prior gestational diabetes mellitus. **A**

3.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. **B**

Because weight loss through behavior changes in diet and physical activity alone can be difficult to maintain long term (6), people at high risk of diabetes may benefit from support and additional pharmacotherapeutic options, if needed. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α -glucosidase inhibitors, glucagon-like peptide 1 receptor agonists (liraglutide, semaglutide), thiazolidinediones, testosterone (61), and insulin have been shown to lower the incidence of diabetes in specific populations (62–67), whereas diabetes prevention was not seen with nateglinide (68).

In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years (9). In postpartum individuals with GDM, the risk of type 2 diabetes increased by 18% for every 1 unit BMI above the preconception baseline (69). Several medications evaluated for weight loss (e.g., orlistat, phentermine topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of diabetes to various degrees in those with prediabetes (67, 70–72).

Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan but no efficacy in preventing diabetes with ramipril or anti-inflammatory drugs (73–76). Although the Vitamin D and Type 2 Diabetes (D2d) prospective randomized controlled trial showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk (77), post hoc

analyses and meta-analyses suggest a potential benefit in specific populations (77–80). Further research is needed to define characteristics and clinical indicators where vitamin D supplementation may be of benefit (61).

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for a specific indication of type 2 diabetes prevention. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost, side effects, and efficacy considerations. Metformin has the longest history of safety data as a pharmacologic therapy for diabetes prevention (81).

Metformin was overall less effective than lifestyle modification in the DPP, though group differences declined over time in the DPP0S (7), and metformin may be cost-saving over a 10-year period (33). In the DPP, metformin was as effective as lifestyle modification in participants with BMI ≥ 35 kg/m² and in younger participants aged 25–44 years (1). In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (82). Both interventions remained highly effective during a 10-year follow-up period (83). By the time of the 15-year follow-up (DPP0S), exploratory analyses demonstrated that participants with a higher baseline fasting glucose (≥ 110 mg/dL vs. 95–109 mg/dL), those with a higher A1C (6.0–6.4% vs. $< 6.0\%$), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that benefitted the most from metformin (84). In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; of note, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP (85). Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., those with a history of GDM or those with BMI ≥ 35 kg/m²). Consider periodic monitoring of vitamin B12 levels in those taking metformin chronically to check for possible deficiency (86,87) (see Section 9, “Pharmacologic Approaches to Glycemic Treatment,” for more details). While there is not a universally accepted recommended periodicity of monitoring, it is

notable that the lowering effect of metformin on vitamin B12 increases with time (88), with a significantly higher risk for vitamin B12 deficiency (< 150 pmol/L) noted at 4.3 years in the HOME (Hyperinsulinaemia: the Outcome of its Metabolic Effects) study (88) and significantly greater risk of low B12 levels (≤ 203 pg/mL) at 5 years in the DPP (87). It has been suggested that a person who has been on metformin for more than 4 years or is at risk for vitamin B12 deficiency should be monitored for vitamin B12 deficiency annually (89).

PREVENTION OF VASCULAR DISEASE AND MORTALITY

Recommendations

3.8 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**

3.9 Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be discontinued. **B**

3.10 In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fracture. **A** Lower doses may mitigate the risk of adverse effects. **C**

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia (90), and are at increased risk for cardiovascular disease (91,92). If indicated, evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes (93–95), a time when individuals should

be monitored for diabetes development and receive concurrent evidence-based lifestyle behavior change for diabetes prevention described in this section. See Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes,” for more detailed information. The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors (96,97). In longer-term follow-up, lifestyle interventions for diabetes prevention also prevented the development of microvascular complications among women enrolled in the DPPOS and in the study population enrolled in the China Da Qing Diabetes Prevention Outcome Study (7,98). The lifestyle intervention in the latter study was also efficacious in preventing cardiovascular disease and mortality at 23 and 30 years of follow-up (3,5). Treatment goals and therapies for hypertension and dyslipidemia in the primary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular diseases risk factors (99). Statins have been associated with a modestly increased risk of diabetes (100–104). In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled hazard ratio [95% CI] for incident diabetes 1.36 [1.17–1.58]) (102). In studies of primary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes (105,106), suggesting a favorable benefit-to-harm balance with statin therapy. Hence, discontinuation of statins is not recommended in this population due to concerns of diabetes risk.

Cardiovascular outcome trials in people without diabetes also inform risk reduction potential in people without diabetes at increased cardiometabolic risk (see Section 10, “Cardiovascular Disease and Risk Management,” for more details). The IRIS (Insulin Resistance Intervention after Stroke) trial was a dedicated study of people with a recent (<6 months) stroke or transient ischemic attack, without diabetes but with insulin resistance, as defined by a HOMA of insulin resistance index of ≥ 3.0 , evaluating pioglitazone

(target dose of 45 mg daily) compared with placebo. At 4.8 years, the risk of stroke or myocardial infarction, as well as the risk of diabetes, was lower within the pioglitazone group than with placebo, though risks of weight gain, edema, and fracture were higher in the pioglitazone treatment group (107–109). Lower doses may mitigate the adverse effects, though further study is needed to confirm the benefit at lower doses (110).

PERSON-CENTERED CARE GOALS

Recommendations

- 3.11** In adults with overweight/obesity at high risk of type 2 diabetes, care goals should include weight loss or prevention of weight gain, minimizing the progression of hyperglycemia, and attention to cardiovascular risk and associated comorbidities. **B**
- 3.12** Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, cardiovascular risk reduction) may be considered to support person-centered care goals. **B**
- 3.13** More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥ 35 kg/m², those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, A1C $\geq 6.0\%$), and individuals with a history of gestational diabetes mellitus. **A**

Individualized risk/benefit should be considered in screening, intervention, and monitoring to prevent or delay type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications (111,112). In the DPP, which enrolled high-risk individuals with impaired glucose tolerance, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo arm was 11.0 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 28.9% (1).

Characteristics of individuals in the DPP/DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases/100 person-years) included BMI ≥ 35 kg/m², those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, and A1C $\geq 6.0\%$), and individuals with a history of gestational diabetes (1,82,83). In contrast, in the community-based Atherosclerosis Risk in Communities (ARIC) study, observational follow-up of older adults (mean age 75 years) with laboratory evidence of prediabetes (based on A1C 5.7–6.4% and/or fasting glucose 100–125 mg/dL), but not meeting specific BMI criteria, found much lower progression to diabetes over 6 years: 9% of those with A1C-defined prediabetes, 8% with impaired fasting glucose (112).

Thus, it is important to individualize the risk/benefit of intervention and consider person-centered goals. Risk models have explored risk-based benefit, generally finding higher benefit of the intervention in those at highest risk (9). Diabetes prevention and observational studies highlight key principles that may guide person-centered goals. In the DPP, which enrolled a high-risk population meeting criteria for overweight/obesity, weight loss was an important mediator of diabetes prevention or delay, with greater metabolic benefit generally seen with greater weight loss (9,113). In the DPP/DPPOS, progression to diabetes, duration of diabetes, and mean level of glycemia were important determinants of the development of microvascular complications (7). Furthermore, the ability to achieve normal glucose regulation, even once, during the DPP was associated with a lower risk of diabetes and lower risk of microvascular complications (114). Observational follow-up of the Da Qing study also showed that regression from impaired glucose tolerance to normal glucose tolerance or remaining with impaired glucose tolerance rather than progressing to type 2 diabetes at the end of the 6-year intervention trial resulted in significantly lower risk of cardiovascular disease and microvascular disease over 30 years (115). Prediabetes is associated with increased cardiovascular disease and mortality (92), emphasizing the importance of attending to cardiovascular risk in this population.

Pharmacotherapy for weight management (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes,” for more details), minimizing the progression of hyperglycemia (see Section 9, “Pharmacologic Approaches to Glycemic Treatment,” for more details), and cardiovascular risk reduction (see Section 10, “Cardiovascular Disease and Risk Management,” for more details) are important tools that can be considered to support individualized person-centered goals, with more intensive preventive approaches considered in individuals at high risk of progression.

References

- Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
- Lindström J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006;368:1673–1679
- Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol* 2014;2:474–480
- Nathan DM, Bennett PH, Crandall JP, et al.; DPP Research Group. Does diabetes prevention translate into reduced long-term vascular complications of diabetes? *Diabetologia* 2019;62:1319–1328
- Gong Q, Zhang P, Wang J, et al.; Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019;7:452–461
- Knowler WC, Fowler SE, Hamman RF, et al.; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374:1677–1686
- Diabetes Prevention Program Research Group; Nathan DM, Barrett-Connor E, Crandall JP, et al. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications: the DPP Outcomes Study. *Lancet Diabetes Endocrinol* 2015;3:866–875
- Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care* 2002;25:2165–2171
- Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006;29:2102–2107
- Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care* 2019;42:731–754
- Department of Health and Human Services and Department of Agriculture. Dietary Guidelines for Americans 2015–2020, Eighth Edition. Accessed 12 October 2022. Available from <https://www.health.gov/dietaryguidelines/2015/guidelines>
- Salas-Salvadó J, Guasch-Ferré M, Lee C-H, Estruch R, Clish CB, Ros E. Protective effects of the Mediterranean diet on type 2 diabetes and metabolic syndrome. *J Nutr* 2016;146:9205–9275
- Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on health outcomes of a Mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. *Ann Intern Med* 2016;165:491–500
- Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;378:e34
- Stentz FB, Brewer A, Wan J, et al. Remission of pre-diabetes to normal glucose tolerance in obese adults with high protein versus high carbohydrate diet: randomized control trial. *BMJ Open Diabetes Res Care* 2016;4:e000258
- Chiu THT, Pan W-H, Lin M-N, Lin C-L. Vegetarian diet, change in dietary patterns, and diabetes risk: a prospective study. *Nutr Diabetes* 2018;8:12
- Lee Y, Park K. Adherence to a vegetarian diet and diabetes risk: a systematic review and meta-analysis of observational studies. *Nutrients* 2017;9:E603
- Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA Intern Med* 2019;179:1335–1344
- Esposito K, Chiodini P, Maiorino MI, Bellastella G, Panagiotakos D, Giugliano D. Which diet for prevention of type 2 diabetes? A meta-analysis of prospective studies. *Endocrine* 2014;47:107–116
- Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *Lancet* 2014;383:1999–2007
- Jacobs S, Harmon BE, Boushey CJ, et al. A priori-defined diet quality indexes and risk of type 2 diabetes: the Multiethnic Cohort. *Diabetologia* 2015;58:98–112
- Chiuvè SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr* 2012;142:1009–1018
- Parker AR, Byham-Gray L, Denmark R, Winkle PJ. The effect of medical nutrition therapy by a registered dietitian nutritionist in patients with prediabetes participating in a randomized controlled clinical research trial. *J Acad Nutr Diet* 2014;114:1739–1748
- Fedewa MV, Gist NH, Evans EM, Dishman RK. Exercise and insulin resistance in youth: a meta-analysis. *Pediatrics* 2014;133:e163–e174
- Davis CL, Pollock NK, Waller JL, et al. Exercise dose and diabetes risk in overweight and obese children: a randomized controlled trial. *JAMA* 2012;308:1103–1112
- Sigal RJ, Alberga AS, Goldfield GS, et al. Effects of aerobic training, resistance training, or both on percentage body fat and cardiometabolic risk markers in obese adolescents: the Healthy Eating Aerobic and Resistance Training in Youth randomized clinical trial. *JAMA Pediatr* 2014;168:1006–1014
- Dai X, Zhai L, Chen Q, et al. Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes: a randomized control trial. *Diabetes Metab Res Rev* 2019;35:e3143
- Thorpe AA, Kingwell BA, Sethi P, Hammond L, Owen N, Dunstan DW. Alternating bouts of sitting and standing attenuate postprandial glucose responses. *Med Sci Sports Exerc* 2014;46:2053–2061
- Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time: beneficial associations with metabolic risk. *Diabetes Care* 2008;31:661–666
- Russo LM, Nobles C, Ertel KA, Chasan-Taber L, Whitcomb BW. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. *Obstet Gynecol* 2015;125:576–582
- Herman WH, Hoeger TJ, Brandle M, et al.; Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 2005;142:323–332
- Chen F, Su W, Becker SH, et al. Clinical and economic impact of a digital, remotely-delivered intensive behavioral counseling program on Medicare beneficiaries at risk for diabetes and cardiovascular disease. *PLoS One* 2016;11:e0163627
- Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care* 2012;35:723–730
- Alva ML, Hoeger TJ, Jeyaraman R, Amico P, Rojas-Smith L. Impact of the YMCA of the USA Diabetes Prevention Program on Medicare spending and utilization. *Health Aff (Millwood)* 2017;36:417–424
- Zhou X, Siegel KR, Ng BP, et al. Cost-effectiveness of diabetes prevention interventions targeting high-risk individuals and whole populations: a systematic review. *Diabetes Care* 2020;43:1593–1616
- Ackermann RT, Finch EA, Brizendine E, Zhou H, Marrero DG. Translating the Diabetes Prevention Program into the community. The DEPLOY Pilot Study. *Am J Prev Med* 2008;35:357–363
- Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. *Ann Intern Med* 2015;163:437–451
- Li R, Qu S, Zhang P, et al. Economic evaluation of combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. *Ann Intern Med* 2015;163:452–460
- Gilmer T, O'Connor PJ, Schiff JS, et al. Cost-effectiveness of a community-based Diabetes Prevention Program with participation incentives for Medicaid beneficiaries. *Health Serv Res* 2018;53:4704–4724
- Ackermann RT, Kang R, Cooper AJ, et al. Effect on health care expenditures during nationwide

implementation of the Diabetes Prevention Program as a health insurance benefit. *Diabetes Care* 2019;42:1776–1783

41. Ely EK, Gruss SM, Luman ET, et al. A national effort to prevent type 2 diabetes: participant-level evaluation of CDC's National Diabetes Prevention Program. *Diabetes Care* 2017;40:1331–1341
42. Lanza A, Soler R, Smith B, Hoerger T, Neuwahl S, Zhang P. The Diabetes Prevention Impact Tool Kit: an online tool kit to assess the cost-effectiveness of preventing type 2 diabetes. *J Public Health Manag Pract* 2019;25:E1–E5
43. Cannon MJ, Masalovich S, Ng BP, et al. Retention among participants in the National Diabetes Prevention Program lifestyle change program, 2012–2017. *Diabetes Care* 2020;43:2042–2049
44. The Community Guide. Diabetes Prevention: Interventions Engaging Community Health Workers, 2016. Accessed 12 October 2022. Available from <https://www.thecommunityguide.org/findings/diabetes-prevention-interventions-engaging-community-health-workers>
45. Jacob V, Chattopadhyay SK, Hopkins DP, et al. Economics of community health workers for chronic disease: findings from Community Guide systematic reviews. *Am J Prev Med* 2019;56:e95–e106
46. Raynor HA, Davidson PG, Burns H, et al. Medical nutrition therapy and weight loss questions for the Evidence Analysis Library prevention of type 2 diabetes project: systematic reviews. *J Acad Nutr Diet* 2017;117:1578–1611
47. Sun Y, You W, Almeida F, Estabrooks P, Davy B. The effectiveness and cost of lifestyle interventions including nutrition education for diabetes prevention: a systematic review and meta-analysis. *J Acad Nutr Diet* 2017;117:404–421.e36
48. Briggs Early K, Stanley K. Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. *J Acad Nutr Diet* 2018;118:343–353
49. Powers MA, Bardsley JK, Cypress M, et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. *Diabetes Care* 2020;43:1636–1649
50. Hudspeth BD. Power of prevention: the pharmacist's role in prediabetes management. *Diabetes Spectr* 2018;31:320–323
51. Butcher MK, Vanderwood KK, Hall TO, Gohdes D, Helgerson SD, Harwell TS. Capacity of diabetes education programs to provide both diabetes self-management education and to implement diabetes prevention services. *J Public Health Manag Pract* 2011;17:242–247
52. Grock S, Ku J-H, Kim J, Moin T. A review of technology-assisted interventions for diabetes prevention. *Curr Diab Rep* 2017;17:107
53. Sepah SC, Jiang L, Peters AL. Translating the Diabetes Prevention Program into an online social network: validation against CDC standards. *Diabetes Educ* 2014;40:435–443
54. Bian RR, Piatt GA, Sen A, et al. The effect of technology-mediated diabetes prevention interventions on weight: a meta-analysis. *J Med Internet Res* 2017;19:e76
55. Sepah SC, Jiang L, Peters AL. Long-term outcomes of a web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. *J Med Internet Res* 2015;17:e92
56. Moin T, Damschroder LJ, AuYoung M, et al. Results from a trial of an online Diabetes Prevention Program intervention. *Am J Prev Med* 2018;55:583–591
57. Michaelides A, Major J, Pienkosz E Jr, Wood M, Kim Y, Toro-Ramos T. Usefulness of a novel mobile Diabetes Prevention Program delivery platform with human coaching: 65-week observational follow-up. *JMIR Mhealth Uhealth* 2018;6:e93
58. Kim SE, Castro Sweet CM, Cho E, Tsai J, Cousineau MR. Evaluation of a digital diabetes prevention program adapted for low-income patients, 2016–2018. *Prev Chronic Dis* 2019;16:E155
59. Vadheim LM, Patch K, Brokaw SM, et al. Telehealth delivery of the Diabetes Prevention Program to rural communities. *Transl Behav Med* 2017;7:286–291
60. Fischer HH, Durfee MJ, Raghunath SG, Ritchie ND. Short message service text message support for weight loss in patients with prediabetes: pragmatic trial. *JMIR Diabetes* 2019;4:e12985
61. Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. *Lancet Diabetes Endocrinol* 2021;9:32–45
62. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319–328
63. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011;364:1104–1115
64. Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–1105
65. le Roux CW, Astrup A, Fujioka K, et al.; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017;389:1399–1409
66. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072–2077
67. Wilding JPH, Batterham RL, Calanna S, et al.; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384:989–1002
68. Holman RR, Haffner SM, McMurray JJ, et al.; NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010;362:1463–1476
69. Dennison RA, Chen ES, Green ME, et al. The absolute and relative risk of type 2 diabetes after gestational diabetes: a systematic review and meta-analysis of 129 studies. *Diabetes Res Clin Pract* 2021;171:108625
70. Torgerson JS, Hauptman J, Boldrin MN, Sjörström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27:155–161
71. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care* 2014;37:912–921
72. Jastreboff AM, Aronne LJ, Ahmad NN, et al.; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;387:205–216
73. McMurray JJ, Holman RR, Haffner SM, et al.; NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010;362:1477–1490
74. Bosch J, Yusuf S, Gerstein HC, et al.; DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006;355:1551–1562
75. Everett BM, Donath MY, Pradhan AD, Thuren T, Pais P, Nicolau JC, et al. Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. *J Am Coll Cardiol* 2018;71:2392–2401.
76. Ray KK, Colhoun HM, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;7:618–628
77. Pittas AG, Dawson-Hughes B, Sheehan P, et al.; D2d Research Group. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med* 2019;381:520–530
78. Dawson-Hughes B, Staten MA, Knowler WC, et al.; D2d Research Group. Intratrial exposure to vitamin D and new-onset diabetes among adults with prediabetes: a secondary analysis from the vitamin D and type 2 diabetes (D2d) study. *Diabetes Care* 2020;43:2916–2922
79. Zhang Y, Tan H, Tang J, et al. Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes: a systematic review and meta-analysis. *Diabetes Care* 2020;43:1650–1658
80. Barbarawi M, Zayed Y, Barbarawi O, Bala A, Alabdouh A, Gakhal I, et al. Effect of vitamin D supplementation on the incidence of diabetes mellitus. *J Clin Endocrinol Metab* 2020;105:dga335.
81. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2012;35:731–737
82. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774–4779

83. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. *J Clin Endocrinol Metab* 2015;100:1646–1653
84. Diabetes Prevention Program Research Group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2019;42:601–608
85. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006;49:289–297
86. Griffin SJ, Bethel MA, Holman RR, et al. Metformin in non-diabetic hyperglycaemia: the GLINT feasibility RCT. *Health Technol Assess* 2018;22:1–64
87. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab* 2016;101:1754–1761
88. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ* 2010;340:c2181
89. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020;98(4S):S1–S115
90. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988–2014. *Lancet Diabetes Endocrinol* 2018;6:392–403
91. Pan Y, Chen W, Wang Y. Prediabetes and outcome of ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2019;28:683–692
92. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ* 2016;355:i5953
93. Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. *Ann Intern Med* 2010;152:10–17
94. Oba S, Noda M, Waki K, et al.; Japan Public Health Center-Based Prospective Study Group. Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study. *PLoS One* 2012;7:e17061
95. Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, et al. Smoking cessation, weight change, type 2 diabetes, and mortality. *N Engl J Med* 2018;379:623–632
96. Orchard TJ, Temprosa M, Barrett-Connor E, et al.; Diabetes Prevention Program Outcomes Study Research Group. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. *Diabet Med* 2013;30:46–55
97. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, et al.; PREDIMED-Plus investigators. Effect of a lifestyle intervention program with energy-restricted mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus Trial. *Diabetes Care* 2019;42:777–788
98. Gong Q, Gregg EW, Wang J, et al. Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. *Diabetologia* 2011;54:300–307
99. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596–e646
100. Thakker D, Nair S, Pagada A, Jamdade V, Malik A. Statin use and the risk of developing diabetes: a network meta-analysis. *Pharmacoepidemiol Drug Saf* 2016;25:1131–1149
101. Macedo AF, Douglas I, Smeeth L, Forbes H, Ebrahim S. Statins and the risk of type 2 diabetes mellitus: cohort study using the UK Clinical Practice Research Datalink. *BMC Cardiovasc Disord* 2014;14:85
102. Crandall JP, Mather K, Rajpathak SN, et al. Statin use and risk of developing diabetes: results from the Diabetes Prevention Program. *BMJ Open Diabetes Res Care* 2017;5:e000438
103. Preiss D, Seshasai SRK, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305:2556–2564
104. Mansi IA, Chansard M, Lingvay I, Zhang S, Halm EA, Alvarez CA. Association of statin therapy initiation with diabetes progression: a retrospective matched-cohort study. *JAMA Intern Med* 2021;181:1562–1574
105. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012;380:565–571
106. Cai T, Abel L, Langford O, et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. *BMJ* 2021;374:n1537
107. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016;374:1321–1331
108. Inzucchi SE, Viscoli CM, Young LH, et al.; IRIS Trial Investigators. Pioglitazone prevents diabetes in patients with insulin resistance and cerebrovascular disease. *Diabetes Care* 2016;39:1684–1692
109. Spence JD, Viscoli CM, Inzucchi SE, et al.; IRIS Investigators. Pioglitazone therapy in patients with stroke and prediabetes: a post hoc analysis of the IRIS randomized clinical trial. *JAMA Neurol* 2019;76:526–535
110. Spence JD, Viscoli C, Kernan WN, et al. Efficacy of lower doses of pioglitazone after stroke or transient ischaemic attack in patients with insulin resistance. *Diabetes Obes Metab* 2022;24:1150–1158
111. Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-onset type 2 diabetes consensus report: current status, challenges, and priorities. *Diabetes Care* 2016;39:1635–1642
112. Rooney MR, Rawlings AM, Pankow JS, et al. Risk of progression to diabetes among older adults with prediabetes. *JAMA Intern Med* 2021;181:511–519
113. Lachin JM, Christophi CA, Edelstein SL, et al.; DPP Research Group. Factors associated with diabetes onset during metformin versus placebo therapy in the diabetes prevention program. *Diabetes* 2007;56:1153–1159
114. Perreault L, Pan Q, Schroeder EB, et al.; Diabetes Prevention Program Research Group. Regression from prediabetes to normal glucose regulation and prevalence of microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). *Diabetes Care* 2019;42:1809–1815
115. Chen Y, Zhang P, Wang J, et al. Associations of progression to diabetes and regression to normal glucose tolerance with development of cardiovascular and microvascular disease among people with impaired glucose tolerance: a secondary analysis of the 30 year Da Qing Diabetes Prevention Outcome Study. *Diabetologia* 2021;64:1279–1287

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PERSON-CENTERED COLLABORATIVE CARE

Recommendations

- 4.1 A person-centered communication style that uses person-centered, culturally sensitive, and strength-based language and active listening; elicits individual preferences and beliefs; and assesses literacy, numeracy, and potential barriers to care should be used to optimize health outcomes and health-related quality of life. **B**
- 4.2 People with diabetes can benefit from a coordinated multidisciplinary team that may include and is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. **E**

A successful medical evaluation depends on beneficial interactions between the person with diabetes and the care team. The Chronic Care Model (1–3) (see Section 1, “Improving Care and Promoting Health in Populations”) is a person-centered approach to care that requires a close working relationship between the person with diabetes and clinicians involved in treatment planning. People with diabetes should receive health care from a coordinated interdisciplinary team that may include but is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. Individuals with diabetes must assume an active role in their care. Based on the preferences of the

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person with diabetes, the family or support group and health care team together formulate the management plan, which includes lifestyle management (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”).

The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life (Fig. 4.1). Treatment goals and plans should be created with people with diabetes based on their individual preferences, values, and goals. This individualized management plan should take into account the person’s age, cognitive abilities, school/work schedule and conditions, health beliefs, support systems, eating patterns, physical activity, social situation, financial concerns, cultural factors, literacy and numeracy (mathematical literacy), diabetes history (duration, complications, current use of medications), comorbidities, disabilities, health priorities, other medical conditions, preferences for care, and life expectancy. Various strategies and tech-

niques should be used to support the person’s self-management efforts, including providing education on problem-solving skills for all aspects of diabetes management.

Health care professional communication with people with diabetes and families should acknowledge that multiple factors impact glycemic management but also emphasize that collaboratively developed treatment plans and a healthy lifestyle can significantly improve disease outcomes and well-being (4–8). Thus, the goal of communication between health care professionals and people with diabetes is to establish a collaborative relationship and to assess and address self-management barriers without blaming people with diabetes for “noncompliance” or “nonadherence” when the outcomes of self-management are not optimal (9). The familiar terms “noncompliance” and “nonadherence” denote a passive, obedient role for a person with diabetes in “following doctor’s orders” that is at odds with the active role people with

diabetes take in directing the day-to-day decision-making, planning, monitoring, evaluation, and problem-solving involved in diabetes self-management. Using a nonjudgmental approach that normalizes periodic lapses in management may help minimize the person’s resistance to reporting problems with self-management. Empathizing and using active listening techniques, such as open-ended questions, reflective statements, and summarizing what the person said, can help facilitate communication. Perceptions of people with diabetes about their own ability, or self-efficacy, to self-manage diabetes constitute one important psychosocial factor related to improved diabetes self-management and treatment outcomes in diabetes (10–12) and should be a target of ongoing assessment, education, and treatment planning.

Language has a strong impact on perceptions and behavior. The use of empowering language in diabetes care and education can help to inform and motivate people, yet language that shames

DECISION CYCLE FOR PERSON-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES

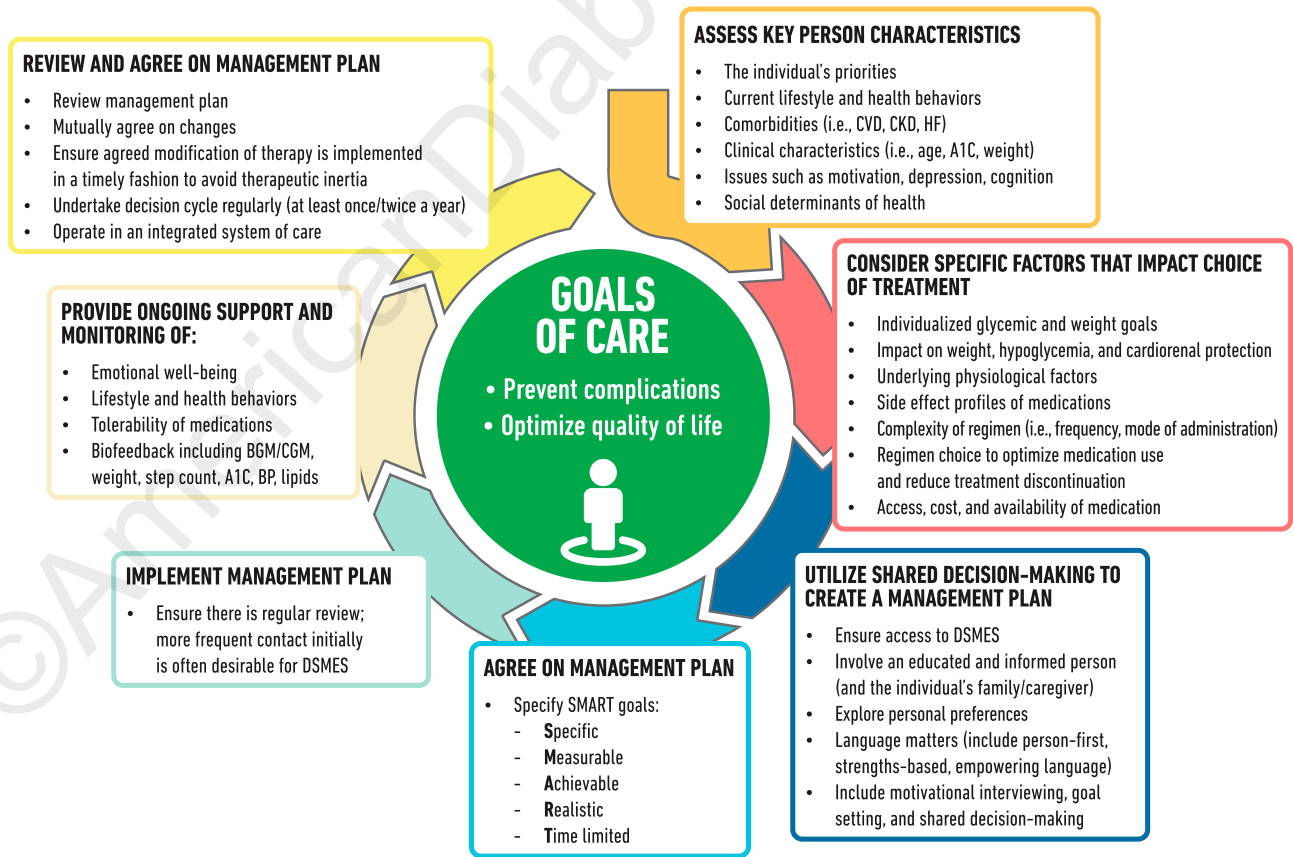


Figure 4.1—Decision cycle for person-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (211). BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, atherosclerotic cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure.

and judges may undermine this effort. The American Diabetes Association (ADA) and the Association of Diabetes Care & Education Specialists (formerly called the American Association of Diabetes Educators) joint consensus report, “The Use of Language in Diabetes Care and Education,” provides the authors’ expert opinion regarding the use of language by health care professionals when speaking or writing about diabetes for people with diabetes or for professional audiences (13). Although further research is needed to address the impact of language on diabetes outcomes, the report includes five key consensus recommendations for language use:

- Use language that is neutral, non-judgmental, and based on facts, actions, or physiology/biology.
- Use language free from stigma.
- Use language that is strength based, respectful, and inclusive and that imparts hope.
- Use language that fosters collaboration between people with diabetes and health care professionals.
- Use language that is person centered (e.g., “person with diabetes” is preferred over “diabetic”).

COMPREHENSIVE MEDICAL EVALUATION

Recommendations

4.3 A complete medical evaluation should be performed at the initial visit to:

- Confirm the diagnosis and classify diabetes. **A**
- Evaluate for diabetes complications, potential comorbid conditions, and overall health status. **A**
- Review previous treatment and risk factor management in people with established diabetes. **A**
- Begin engagement with the person with diabetes in the formulation of a care management plan including initial goals of care. **A**
- Develop a plan for continuing care. **A**

4.4 A follow-up visit should include most components of the initial

comprehensive medical evaluation (**Table 4.1**). **A**

4.5 Ongoing management should be guided by the assessment of overall health status, diabetes complications, cardiovascular risk, hypoglycemia risk, and shared decision-making to set therapeutic goals. **B**

The comprehensive medical evaluation includes the initial and follow-up evaluations, assessment of complications, psychosocial assessment, management of comorbid conditions, overall health status, and engagement of the person with diabetes throughout the process. While a comprehensive list is provided in **Table 4.1**, in clinical practice the health care professional may need to prioritize the components of the medical evaluation given the available resources and time. The goal is to provide the health care team information so it can optimally support people with diabetes. In addition to the medical history, physical examination, and laboratory tests, health care professionals should assess diabetes self-management behaviors, nutrition, social determinants of health, and psychosocial health (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”) and give guidance on routine immunizations. The assessment of sleep pattern and duration should be considered; a meta-analysis found that poor sleep quality, short sleep, and long sleep were associated with higher A1C in people with type 2 diabetes (14). Interval follow-up visits should occur at least every 3–6 months individualized to the person and then at least annually.

Lifestyle management and psychosocial care are the cornerstones of diabetes management. People with diabetes should be referred for diabetes self-management education and support, medical nutrition therapy, and assessment of psychosocial/emotional health concerns if indicated. People with diabetes should receive recommended preventive care services (e.g., immunizations, cancer screening); smoking cessation counseling; and ophthalmological, dental, and podiatric referrals, as needed.

The assessment of risk of acute and chronic diabetes complications and

treatment planning are key components of initial and follow-up visits (**Table 4.2**). The risk of atherosclerotic cardiovascular disease and heart failure (see Section 10, “Cardiovascular Disease and Risk Management”), chronic kidney disease staging (see Section 11, “Chronic Kidney Disease and Risk Management”), presence of retinopathy (see Section 12, “Retinopathy, Neuropathy, and Foot Care”), and risk of treatment-associated hypoglycemia (**Table 4.3**) should be used to individualize targets for glycemia (see Section 6, “Glycemic Targets”), blood pressure, and lipids and to select specific glucose-lowering medication (see Section 9, “Pharmacologic Approaches to Glycemic Treatment”), antihypertension medication, and statin treatment intensity.

Additional referrals should be arranged as necessary (**Table 4.4**). Clinicians should ensure that people with diabetes are appropriately screened for complications and comorbidities. Discussing and implementing an approach to glycemic management with the person is a part, not the sole goal, of the clinical encounter.

IMMUNIZATIONS

Recommendation

4.6 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.5** for highly recommended vaccinations for adults with diabetes). **A**

The importance of routine vaccinations for people living with diabetes has been elevated by the coronavirus disease 2019 (COVID-19) pandemic. Preventing avoidable infections not only directly prevents morbidity but also reduces hospitalizations, which may additionally reduce risk of acquiring infections such as COVID-19. Children and adults with diabetes should receive vaccinations according to age-appropriate recommendations (15,16). The Centers for Disease Control and Prevention (CDC) provides vaccination schedules specifically for children, adolescents, and adults with diabetes (cdc.gov/vaccines/). The CDC Advisory Committee on Immunization Practices (ACIP) makes recommendations based on its own review and rating of the evidence, provided in **Table 4.5** for selected vaccinations. The ACIP evidence

Table 4.1 - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	Diabetes history			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment plans and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Common comorbidities (e.g., obesity, OSA, NAFLD)	✓		
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Macrovascular and microvascular complications	✓		✓
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		✓
▪ Last dental visit	✓		✓	
▪ Last dilated eye exam			✓	
▪ Visits to specialists			✓	
Interval history				
▪ Changes in medical/family history since last visit		✓	✓	
BEHAVIORAL FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Assess familiarity with carbohydrate counting (e.g., type 1 diabetes, type 2 diabetes treated with MDI)	✓		✓
	▪ Physical activity and sleep behaviors	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication plan	✓	✓	✓
	▪ Medication-taking behavior	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use, connected pen and glucose data	✓	✓	✓
SOCIAL LIFE ASSESSMENT	Social network			
	▪ Identify existing social supports	✓		✓
	▪ Identify surrogate decision maker, advanced care plan	✓		✓
	▪ Identify social determinants of health (e.g., food security, housing stability & homelessness, transportation access, financial security, community safety)	✓		✓

Continued on p. S53

Table 4.1 (cont.) - Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses—refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
	▪ Screen for depression, anxiety, and disordered eating	✓		✓
	▪ Consider assessment for cognitive performance*	✓		✓
▪ Consider assessment for functional performance*	✓		✓	
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides [#]	✓		✓ [^]
	• Liver function tests [#]	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate ⁺	✓		✓
	• Thyroid-stimulating hormone in people with type 1 diabetes [#]	✓		✓
	• Vitamin B12 if on metformin	✓		✓
	• Serum potassium levels in people with diabetes on ACE inhibitors, ARBs, or diuretics ⁺	✓		✓

ABI, ankle-brachial pressure index; ARBs, angiotensin receptor blockers; CGM, continuous glucose monitors; MDI, multiple daily injections; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; PAD, peripheral arterial disease.

*At 65 years of age or older.

+May be needed more frequently in people with diabetes with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see **Table 11.1**).

#May also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications).

[^]In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be less frequent.

**Should be performed at every visit in people with diabetes with sensory loss, previous foot ulcers, or amputations.

review has evolved over time with the adoption of Grading of Recommendations Assessment, Development and Evaluation (GRADE) in 2010 and then the Evidence to Decision or Evidence to Recommendation frameworks in 2018 (17). Here we discuss the particular importance of specific vaccines.

Influenza

Influenza is a common, preventable infectious disease associated with high mortality

and morbidity in vulnerable populations, including youth, older adults, and people with chronic diseases. Influenza vaccination in people with diabetes has been found to significantly reduce influenza and diabetes-related hospital admissions (18). In people with diabetes and cardiovascular disease, influenza vaccine has been associated with lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (19). Given the benefits of the annual

influenza vaccination, it is recommended for all individuals ≥6 months of age who do not have a contraindication. Influenza vaccination is critically important as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses will both be active in the U.S. during the 2022–2023 season (20). The live attenuated influenza vaccine, which is delivered by nasal spray, is an option for people who are age 2 years through age 49 years and who are

Table 4.2—Assessment and treatment plan*

Assessing risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (see **Table 4.3**)
- Assessment for retinopathy
- Assessment for neuropathy

Goal setting

- Set A1C/blood glucose/time-in-range target
- If hypertension is present, establish blood pressure target
- Diabetes self-management goals

Therapeutic treatment plans

- Lifestyle management
- Pharmacologic therapy: glucose lowering
- Pharmacologic therapy: cardiovascular and renal disease risk factors
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education and medical specialists (as needed)

ASCVD, atherosclerotic cardiovascular disease. *Assessment and treatment planning are essential components of initial and all follow-up visits.

not pregnant, but people with chronic conditions such as diabetes are cautioned against taking the live attenuated influenza vaccine and are instead recommended to receive the inactive or recombinant influenza vaccination. For individuals ≥ 65 years of age, there may be additional benefit from the high-dose quadrivalent inactivated influenza vaccine (20).

Pneumococcal Pneumonia

Like influenza, pneumococcal pneumonia is a common, preventable disease. People with diabetes are at increased risk for the bacteremic form of pneumococcal infection and have been reported to have a high risk of nosocomial bacteremia, with a mortality rate as high as 50% (21). There are two types of vaccines available in the U.S., pneumococcal conjugate

vaccines (PCV13, PCV15, and PCV20) and pneumococcal polysaccharide vaccine (PPSV23), with distinct schedules for children and adults.

It is recommended that all children receive a four-dose series of PCV13 or PCV15 by 15 months of age. For children with diabetes who have incomplete series by ages 2–5 years, the CDC recommends a catch-up schedule to ensure that these children have four doses. Children with diabetes between 6 and 18 years of age are also advised to receive one dose of PPSV23, preferably after receipt of PCV13.

Adults aged ≥ 65 years whose vaccine status is unknown or who have not received pneumococcal vaccine should receive one dose of PCV15 or PCV20. If PCV15 is used, it should be followed by PPSV23.

Adults aged 19–64 years with certain underlying risk factors or other medical conditions whose vaccine status is unknown or who have not received pneumococcal vaccine should receive one dose of PCV15 or PCV20. As for adults aged ≥ 65 years, if PCV15 is used, it should be followed by PPSV23.

The recommended interval between PCV15 and PPSV23 is ≥ 1 year. If PPSV23 is the only dose received, PCV15 or PCV20 may be given ≥ 1 year later.

For adults with immunocompromising conditions, cochlear implant, or cerebrospinal fluid leak, a minimum interval of 8 weeks can be considered for dosing of PCV15 and PPSV23 when PCV15 has been used.

Adults who received PCV13 should follow the previously recommended PPSV23 series. Adults who received only PPSV23 may receive a PCV15 or PCV20 ≥ 1 year after their last dose.

Hepatitis B

Compared with the general population, people with type 1 or type 2 diabetes have higher rates of hepatitis B. This may be due to contact with infected blood or through improper equipment use (glucose monitoring devices or infected needles). Because of the higher likelihood of transmission, hepatitis B vaccine is recommended for adults with diabetes aged < 60 years. For adults aged ≥ 60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician

Table 4.3—Assessment of hypoglycemia risk

Factors that increase risk of treatment-associated hypoglycemia

- Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)
- Impaired kidney or hepatic function
- Longer duration of diabetes
- Frailty and older age
- Cognitive impairment
- Impaired counterregulatory response, hypoglycemia unawareness
- Physical or intellectual disability that may impair behavioral response to hypoglycemia
- Alcohol use
- Polypharmacy (especially ACE inhibitors, angiotensin receptor blockers, nonselective β -blockers)
- History of severe hypoglycemic event

In addition to individual risk factors, consider use of comprehensive risk prediction models (198).

See references 199–203.

Table 4.4—Referrals for initial care management

- Eye care professional for annual dilated eye exam
- Family planning for individuals of childbearing potential
- Registered dietitian nutritionist for medical nutrition therapy
- Diabetes self-management education and support
- Dentist for comprehensive dental and periodontal examination
- Mental health professional, if indicated
- Audiology, if indicated
- Social worker/community resources, if indicated

Table 4.5—Highly recommended immunizations for adults with diabetes (Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention)

Vaccination	Age-group recommendations	Frequency	GRADE evidence type*	Reference
Hepatitis B	<60 years of age; ≥60 years of age discuss with health care professionals	Two- or three-dose series	2	Centers for Disease Control and Prevention, Use of Hepatitis B Vaccination for Adults With Diabetes Mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP) (204)
Human papilloma virus (HPV)	≤26 years of age; 27–45 years of age may also be vaccinated against HPV after a discussion with health care professionals	Three doses over 6 months	2 for female individuals, 3 for male individuals	Meites et al., Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices (205)
Influenza	All people with diabetes advised not to receive live attenuated influenza vaccine	Annual	—	Demicheli et al., Vaccines for Preventing Influenza in the Elderly (206)
Pneumonia (PPSV23 [Pneumovax])	19–64 years of age, vaccinate with Pneumovax	One dose is recommended for those that previously received PCV13. If PCV15 used, follow with PPSV23 ≥1 year later. PPSV23 is not indicated after PCV20. Adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose.	2	Centers for Disease Control and Prevention, Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) (207)
	≥65 years of age	One dose is recommended for those that previously received PCV13. If PCV15 was used, follow with PPSV23 ≥1 year later. PPSV23 is not indicated after PCV20. Adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose.	2	Falkenhorst et al., Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) Against Pneumococcal Disease in the Elderly: Systematic Review and Meta-analysis (208)
PCV20 or PCV15	Adults 19–64 years of age, with an immunocompromising condition (e.g., chronic renal failure), cochlear implant, or cerebrospinal fluid leak	One dose of PCV15 or PCV20 is recommended by the CDC.	3	Kobayashi et al., Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2022 (22)
	19–64 years of age, immunocompetent	For those who have never received any pneumococcal vaccine, the CDC recommends one dose of PCV15 or PCV20.		
	≥65 years of age, immunocompetent, have shared decision-making discussion with health care professionals	One dose of PCV15 or PCV20. PPSV23 may be given ≥8 weeks after PCV15. PPSV23 is not indicated after PCV20.		
Tetanus, diphtheria, pertussis (TDAP)	All adults; pregnant individuals should have an extra dose	Booster every 10 years	2 for effectiveness, 3 for safety	Havers et al., Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2019 (209)
Zoster	≥50 years of age	Two-dose Shingrix, even if previously vaccinated	1	Dooling et al., Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines (210)

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV 20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. *Evidence type: 1, randomized controlled trials (RCTs) or overwhelming evidence from observational studies; 2, RCTs with important limitations or exceptionally strong evidence from observational studies; 3, observational studies or RCTs with notable limitations; 4, clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations. For a comprehensive list, refer to the Centers for Disease Control and Prevention (CDC) at cdc.gov/vaccines/.

based on the person's likelihood of acquiring hepatitis B infection.

COVID-19

As of September 2022, the COVID-19 vaccines are recommended for all adults and some children, including people with diabetes, under approval from the U.S. Food and Drug Administration (FDA) (24). The bivalent booster protecting against the omicron variant and original strain has now replaced the monovalent booster for many.

For people 6 months to 17 years of age, most can receive the monovalent Moderna vaccine doses 1 and 2 at least 4–8 weeks apart. For those who are moderately or severely immunocompromised, doses 1 and 2 and doses 2 and 3 should be at least 4 weeks apart.

For the Pfizer-BioNTech monovalent vaccine for most people aged 6 months to 4 years, doses 1 and 2 should be at least 3–8 weeks apart and doses 2 and 3 at least 8 weeks apart. For those aged 6 months to 4 years who are moderately or severely compromised, doses 1 and 2 should be at least 4 weeks apart and doses 2 and 3 at least 4 weeks apart. For most people aged 5–11 years, doses 1 and 2 should be at least 3–8 weeks apart and doses 2 and 3 at least 5 months apart. For those who are moderately or severely immunocompromised, doses 1 and 2 should be at least 3 weeks apart and doses 2 and 3 should be at least 8 weeks apart. For most people aged 12–17 years, doses 1 and 2 should be at least 3–8 weeks apart. For those who are moderately to severely immunocompromised, doses 1 and 2 should be at least 3 weeks apart and doses 2 and 3 should be at least 4 weeks apart.

For the Novavax vaccine, for most people over 12 years of age, doses 1 and 2 should be at least 3–8 weeks apart. For those who are moderately to severely immunocompromised, doses 1 and 2 should be at least 3 weeks apart. For most people aged ≥ 18 years receiving the Moderna vaccine, doses 1 and 2 should be at least 4–8 weeks apart. For those who are moderately or severely compromised, doses 1 and 2 should be at least 4 weeks apart and doses 2 and 3 at least 4 weeks apart. For most people receiving the Pfizer-BioNTech vaccine, doses 1 and 2 should be at least 3–8 weeks apart. For those who are moderately or severely

compromised, doses 1 and 2 should be at least 3 weeks apart and doses 2 and 3 at least 4 weeks apart.

For most people aged ≥ 18 years receiving Novavax vaccine, doses 1 and 2 should be at least 3–8 weeks apart. For those who are moderately to severely compromised, doses 1 and 2 should be at least 3 weeks apart. The Janssen monovalent vaccine is currently authorized for use in certain limited situations due to safety considerations.

For most people 12–17 years of age who received the Moderna vaccine, the Pfizer-BioNTech bivalent booster may be given at least 8 weeks from doses 2 and 3. For those moderately or severely compromised, doses 3 and 4 should be at least 8 weeks apart.

For most people aged 12–17 years who received the Pfizer-BioNTech vaccine, the Pfizer-BioNTech bivalent booster may be given at least 8 weeks from doses 2 and 3. For those moderately or severely compromised, doses 3 and 4 should be at least 8 weeks apart.

For most people aged ≥ 12 years receiving the Novavax vaccine, the Pfizer-BioNTech bivalent booster may be given as doses 2 and 3 at least 8 weeks apart. For those moderately to severely immunocompromised, doses 2 and 3 should be given at least 8 weeks apart.

Those ≥ 18 years of age receiving the Moderna vaccine may be given the Moderna bivalent booster 8 weeks after their last dose. Those ≥ 18 years of age receiving the Pfizer-BioNTech vaccine may receive the Pfizer-BioNTech bivalent booster 8 weeks after their last dose. Those receiving the Janssen vaccine may receive the Moderna or Pfizer-BioNTech bivalent booster 8 weeks after their last dose. Those receiving the Novavax vaccine aged ≥ 12 years may receive either the Moderna or Pfizer-BioNTech bivalent booster 8 weeks after their last dose.

ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and people with diabetes need to be aware of common comorbidities that affect people with diabetes and that may complicate management (25–29). Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes. This section

discusses many of the common comorbidities observed in people with diabetes but is not necessarily inclusive of all the conditions that have been reported.

Autoimmune Diseases

Recommendations

- 4.7** People with type 1 diabetes should be screened for autoimmune thyroid disease soon after diagnosis and periodically thereafter. **B**
- 4.8** Adults with type 1 diabetes should be screened for celiac disease in the presence of gastrointestinal symptoms, signs, laboratory manifestations, or clinical suspicion suggestive of celiac disease. **B**

People with type 1 diabetes are at increased risk for other autoimmune diseases, with thyroid disease, celiac disease, and pernicious anemia (vitamin B12 deficiency) being among the most common (30). Other associated conditions include autoimmune hepatitis, primary adrenal insufficiency (Addison disease), collagen vascular diseases, and myasthenia gravis (31–34). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic disorders or polyglandular autoimmune syndromes (35). Given the high prevalence, nonspecific symptoms, and insidious onset of primary hypothyroidism, routine screening for thyroid dysfunction is recommended for all people with type 1 diabetes. Screening for celiac disease should be considered in adults with diabetes with suggestive symptoms (e.g., diarrhea, malabsorption, abdominal pain) or signs (e.g., osteoporosis, vitamin deficiencies, iron deficiency anemia) (36,37). Measurement of vitamin B12 levels should be considered for people with type 1 diabetes and peripheral neuropathy or unexplained anemia.

Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (38). The association may result from shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (39), such as underlying disease physiology

or diabetes treatments, although evidence for these links is scarce. People with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings and to reduce their modifiable cancer risk factors (obesity, physical inactivity, and smoking). New onset of atypical diabetes (lean body habitus, negative family history) in a middle-aged or older person may precede the diagnosis of pancreatic adenocarcinoma (40). However, in the absence of other symptoms (e.g., weight loss, abdominal pain), routine screening of all such individuals is not currently recommended.

Cognitive Impairment/Dementia

Recommendation

4.9 In the presence of cognitive impairment, diabetes treatment plans should be simplified as much as possible and tailored to minimize the risk of hypoglycemia. **B**

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia (41,42). A recent meta-analysis of prospective observational studies in people with diabetes showed 73% increased risk of all types of dementia, 56% increased risk of Alzheimer dementia, and 127% increased risk of vascular dementia compared with individuals without diabetes (43). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia. In a 15-year prospective study of community-dwelling people >60 years of age, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer dementia, and vascular dementia compared with rates in those with normal glucose tolerance (44). See Section 13, "Older Adults," for a more detailed discussion regarding screening for cognitive impairment.

Hyperglycemia

In those with type 2 diabetes, the degree and duration of hyperglycemia are related to dementia. More rapid cognitive decline is associated with both increased A1C and longer duration of

diabetes (43). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found that each 1% higher A1C level was associated with lower cognitive function in individuals with type 2 diabetes (45). However, the ACCORD study found no difference in cognitive outcomes in participants randomly assigned to intensive and standard glycemic management, supporting the recommendation that intensive glucose management should not be advised for the improvement of cognitive function in individuals with type 2 diabetes (46).

Hypoglycemia

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe hypoglycemia. In a long-term study of older people with type 2 diabetes, individuals with one or more recorded episodes of severe hypoglycemia had a stepwise increase in risk of dementia (47). Likewise, the ACCORD trial found that as cognitive function decreased, the risk of severe hypoglycemia increased (48). This has also been demonstrated in people with type 1 diabetes. Tailoring glycemic therapy may help to prevent hypoglycemia in individuals with cognitive dysfunction (49). See Section 13, "Older Adults," for more detailed discussion of hypoglycemia in older people with type 1 and type 2 diabetes.

Nutrition

In one study, following the Mediterranean diet correlated with improved cognitive function (50). However, a Cochrane review found insufficient evidence to recommend any specific dietary change for the prevention or treatment of cognitive dysfunction (51).

Statins

A systematic review has reported that data do not support an adverse effect of statins on cognition (52). The FDA post-marketing surveillance databases have also revealed a low reporting rate for cognitive function–related adverse events, including cognitive dysfunction or dementia, with statin therapy, similar to rates seen with other commonly prescribed cardiovascular medications (52). Therefore, fear of cognitive decline should not be a barrier to statin use in

people with diabetes and a high risk for cardiovascular disease.

Nonalcoholic Fatty Liver Disease

Recommendation

4.10 People with type 2 diabetes or prediabetes with cardiometabolic risk factors, who have either elevated liver enzymes (ALT) or fatty liver on imaging or ultrasound, should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

Screening

Nonalcoholic fatty liver disease (NAFLD) is the term used to identify the broad spectrum of the disease ranging from nonalcoholic fatty liver with macrovesicular hepatic steatosis only (or with mild inflammation) to steatohepatitis (nonalcoholic steatohepatitis [NASH]) to cirrhosis. This is in the absence of ongoing or recent consumption of significant amounts of alcohol (defined as ingestion of >21 standard drinks per week in men and >14 standard drinks per week in women over a 2-year period preceding evaluation) or the presence of other secondary causes of fatty liver disease. Diabetes is a major risk factor for developing NASH and for disease progression and worse liver outcomes (53). Recent studies in adults in the U.S. estimate that NAFLD is prevalent in >70% of people with type 2 diabetes (54–56). This is consistent with studies from many other countries (57). NASH is defined histologically as having $\geq 5\%$ hepatic steatosis and associated with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis (58). Steatohepatitis is estimated to affect more than half of people with type 2 diabetes with NAFLD (59), and it appears to be a driver for the development of fibrosis. Fibrosis stages are classified histologically as the following: F0, no fibrosis; F1, mild; F2, moderate (significant); F3, severe (advanced); and F4, cirrhosis. In the U.S., between 12% and 20% of people with type 2 diabetes have clinically significant fibrosis ($\geq F2$) (54,55,59), similar to that observed worldwide (53,57). NASH is a leading cause of hepatocellular carcinoma (HCC) (60,61) and of liver transplantation in the U.S.,

with transplant waiting lists being over-represented by people with type 2 diabetes (62). Still, clinicians underestimate its prevalence and do not consistently implement appropriate screening strategies, thus missing the diagnosis of NAFLD in high-risk groups, such as those having obesity or type 2 diabetes. This pattern of underdiagnosis is compounded by sparse referral to specialists and inadequate prescription of medications with proven efficacy in NASH (63,64).

The goal of screening is not to identify steatosis per se (being already highly prevalent in this population) but rather to use it to identify those on a disease path of future cirrhosis. This risk is higher in people who have obesity and cardiometabolic risk factors or insulin resistance, are >50 years of age, and/or have persistently elevated plasma aminotransferases (AST and/or ALT >30 units/L for more >6 months) (65,66). Some genetic variants that alter hepatocyte triglyceride metabolism may also increase the risk of NASH progression and cirrhosis (67,68), amplifying the impact of obesity, but the role of genetic testing in clinical practice remains to be established.

Individuals with clinically significant fibrosis ($\geq F2$), especially those with type 2 diabetes, have a greater risk of cirrhosis with liver decompensation, HCC, liver transplantation, and all-cause mortality (69–72). Excess mortality associated with NAFLD is attributable not only to cirrhosis and HCC but also to extrahepatic cancer (61), type 2 diabetes (73), and cardiovascular disease (74,75). Their estimated relative impact depends on length of follow-up and population studied, among other factors. Emerging evidence suggests that NAFLD increases the risk of chronic kidney disease, particularly when liver fibrosis is present (76,77), although the association of NAFLD with diabetic retinopathy is less clear (78). Therefore, early diagnosis is essential to prevent future cirrhosis.

A recent meta-analysis reported a prevalence of NAFLD of 22% in people with type 1 diabetes (79). This risk may be linked to the fact that about one-third in the U.S. have obesity (80). However, there was a large variability across studies, and most measured liver fat by ultrasound. In one of the few studies using the gold-standard MRI technique to quantitate liver fat, the prevalence of steatosis in a population with type 1 diabetes with

low prevalence of obesity was only 8.8% compared with 68% in people with type 2 diabetes (81). The prevalence of fibrosis was not established. Therefore, screening for fibrosis in people with type 1 diabetes should only be considered in the presence of additional risk factors for NAFLD, such as obesity, incidental hepatic steatosis on imaging, or elevated plasma aminotransferases.

There is consensus that the fibrosis-4 index (FIB-4) is the most cost-effective strategy for the initial screening of people with prediabetes and cardiometabolic risk factors or type 2 diabetes in the primary care and diabetes clinical setting (58,64–66,82–84). See the proposed diagnostic algorithm by an expert group that included ADA representatives in **Fig. 4.2** (64). A screening strategy based on elevated plasma aminotransferases >40 units/L would miss most individuals with NASH in these settings, as clinically significant fibrosis ($\geq F2$) is frequently observed with plasma aminotransferases below the commonly used cutoff of 40 units/L (54–56,59, 85,86). The American College of Gastroenterology considers the upper limit of normal ALT levels to be 29–33 units/L for male individuals and 19–25 units/L for female individuals (87), as higher levels are associated with increased liver-related mortality, even in the absence

of identifiable risk factors. The FIB-4 estimates the risk of hepatic cirrhosis and is calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count (mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). A value of <1.3 is considered lower risk, while >2.67 is considered as having a high probability of advanced fibrosis (F3–F4). It also predicts changes over time in hepatic fibrosis (88,89) and allows risk stratification of individuals in terms of future liver-related morbidity and mortality (90,91). FIB-4 has an area under the receiver–operating characteristic curve of only 0.78–0.80 (89,92–95); thus, a confirmatory test is often needed. It has a reasonable specificity and negative predictive value to rule out advanced fibrosis but lacks adequate sensitivity and positive predictive value to establish presence of advanced fibrosis in many cases, which is the reason why people with diabetes often fall in the “indeterminate risk” group for establishing the advanced fibrosis (or intermediate) group (between 1.3 and 2.67). However, its low cost, simplicity, and good specificity make it the initial test of choice (**Fig. 4.2**). Performance is better in a population with higher prevalence of significant fibrosis (i.e., hepatology clinics) compared with primary care settings. FIB-4 has not been

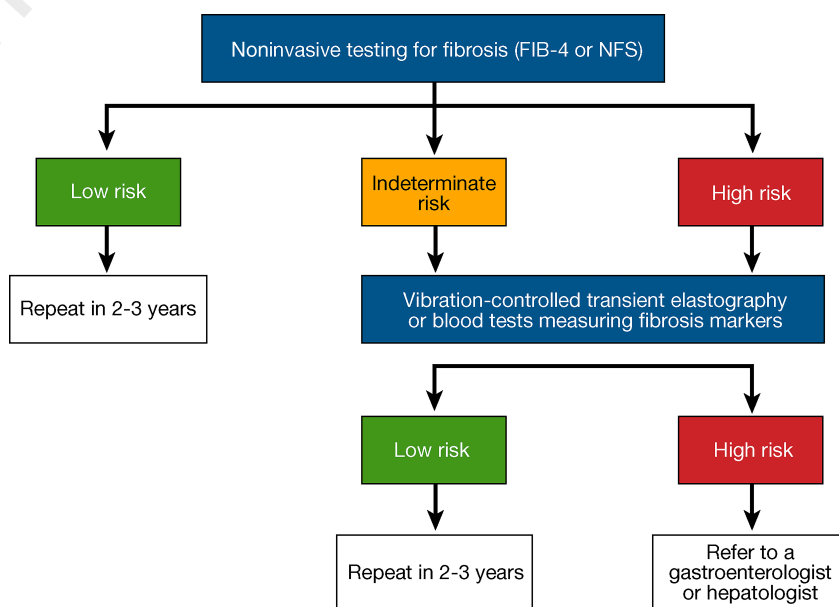


Figure 4.2—A proposed algorithm for risk stratification in individuals with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). NFS, NAFLD fibrosis score created by a group of experts that included American Diabetes Association representatives. Reprinted from Kanwal et al. (64).

well validated in pediatric populations and does not perform as well in those aged <35 years. In people with diabetes ≥ 65 years of age, higher cutoffs for FIB-4 have been recommended (1.9–2.0 rather than >1.3) (96,97).

In people with an indeterminate or high FIB-4, additional risk stratification is required with a liver stiffness measurement (LSM) by transient elastography (Fig. 4.2) or, if unavailable, by commercial blood fibrosis biomarkers such as the Enhanced Liver Fibrosis (ELF) test (98) or others. Use of a second non-proprietary diagnostic panel is not recommended (i.e., NAFLD fibrosis score, others), as they generally do not perform better than FIB-4 (56,92). Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in NAFLD (58,65,99). An LSM value of <8.0 kPa has a good negative predictive value to exclude advanced fibrosis ($\geq F3$ – $F4$) (100–102) and indicates low risk for clinically significant fibrosis. Such individuals with diabetes can be followed in nonspecialty clinics with repeat surveillance testing every ≥ 2 years. If the LSM is >12 kPa, the risk for advanced fibrosis is high and people with diabetes should be referred to the hepatologist (100). FIB-4 followed by LSM helps stratify people with diabetes by risk level and minimize referrals to the specialist (91,94,99,103,104) (Fig. 4.2).

Specialists may order additional tests for fibrosis risk stratification (64–66,84,99), with magnetic resonance elastography having the best overall performance (particularly for early fibrosis stages). Finally, liver biopsy remains the gold standard for the diagnosis of NASH, and its indication is reserved to the discretion of the specialist within a multidisciplinary team approach.

The American Gastroenterological Association convened an international conference, including representatives of the ADA, to review and discuss published literature on the burden, screening, risk stratification, diagnosis, and management of individuals with NAFLD (64). See Fig. 4.2, which is reproduced from this special report (64). A Clinical Care Pathway summarized the diagnosis and management of NAFLD in a subsequent publication (66). Consensus is emerging to start screening with FIB-4 followed by

LSM and/or patented biomarkers for the noninvasive fibrosis risk stratification of individuals with NAFLD in primary care and diabetes clinics (58,64–66,82–84).

After initial risk stratification (i.e., FIB-4, LSM, and/or patented biomarkers), people with diabetes at indeterminate or high risk of fibrosis should be referred, based on practice setting, to a gastroenterologist or hepatologist for further workup within the framework of a multidisciplinary team (64,105,106).

Management

While steatohepatitis and cirrhosis occur in lean people with diabetes and are believed to be linked to genetic predisposition, insulin resistance, and environmental factors (107–109), there is ample evidence to implicate excess adiposity in people with overweight and obesity in the pathogenesis of the disease (110,111). Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis (112). Therefore, clinicians should recommend lifestyle changes in people with overweight or obesity and NAFLD. A minimum weight loss goal of 5%, preferably $\geq 10\%$ (113,114), is needed to improve liver histology, with fibrosis requiring the larger weight reduction to change (114–116). Individualized, structured weight loss and exercise programs offer greater benefit than standard counseling in people with NAFLD (107,117).

Dietary recommendations to induce an energy deficit are not different than those for people with diabetes with obesity without NAFLD and should include a reduction of macronutrient content, limiting saturated fat, starch, and added sugar, with adoption of healthier eating patterns. The Mediterranean diet has the best evidence for improving liver and cardiometabolic health (58,65,82,83,117–121). Both aerobic and resistance training improve NAFLD in proportion to treatment engagement and intensity of the program (122–124).

Obesity pharmacotherapy may assist with weight loss in the context of lifestyle modification if not achieved by lifestyle modification alone.

Bariatric surgery improves NASH and cardiometabolic health, altering the natural history of the disease (125). Meta-analyses report that 70–80% of people have improvement in hepatic steatosis,

50–75% in inflammation and hepatocyte ballooning (necrosis), and 30–40% in fibrosis (126,127). It may also reduce the risk of HCC (127). Bariatric surgery should be used with caution in individuals with compensated cirrhosis, but in experienced hands the risk of hepatic decompensation is similar to that for those with less advanced liver disease. Because of the paucity of safety and outcome data, bariatric surgery is not recommended in individuals with decompensated cirrhosis who also have a much higher risk of postoperative liver-related complications (encephalopathy, variceal bleeding, or ascites) (58,65,66).

At present, there are no FDA-approved drugs for the treatment of NASH. Therefore, treatment for people with type 2 diabetes and NASH is centered on the dual purpose of treating hyperglycemia and obesity, especially if clinically significant fibrosis ($\geq F2$) is present. The rationale for the treatment of people with type 2 diabetes is based on their high prevalence of NASH with significant fibrosis (10–15% of people with type 2 diabetes) (54,55,57), their higher risk of disease progression and liver-related mortality (53,72,128), and the lack of pharmacological treatments once cirrhosis is established (129). Therefore, early diagnosis and treatment of NAFLD offers the best opportunity for cirrhosis prevention. Pioglitazone and some glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been shown to be effective to treat steatohepatitis (64,65,130–132) and may slow fibrosis progression (133–135) and decrease cardiovascular disease (65,131), which is the number one cause of death in people with type 2 diabetes and NAFLD (74).

Pioglitazone improves glucose and lipid metabolism and reverses steatohepatitis in people with prediabetes, type 2 diabetes (136,137), or even without diabetes (138–140). Fibrosis also improved in some trials (137,139). A meta-analysis (133) concluded that pioglitazone treatment results in resolution of NASH and may improve fibrosis. Pioglitazone may halt the accelerated pace of fibrosis progression observed in people with type 2 diabetes (134) and is overall cost-effective for the treatment of NASH (141,142). Vitamin E may be beneficial for the treatment of NASH in people without diabetes (138). However, in people with type 2 diabetes,

treatment in a small randomized controlled trial (RCT) was largely negative as monotherapy (134), and when added to pioglitazone, it did not seem to enhance pioglitazone's efficacy, as reported in an earlier trial in this population (137). Pioglitazone causes dose-dependent weight gain (15 mg/day, mean of 1–2%; 45 mg/day, 3–5%), increases fracture risk, may promote heart failure if used in individuals with preexisting congestive heart failure, and may increase the risk of bladder cancer, although this remains controversial (64,65,131, 132).

GLP-1 RAs are effective in inducing weight loss and ameliorating elevated plasma aminotransferases and steatosis (130). However, there are only two RCTs in biopsy-proven individuals with NASH. A small RCT reported that liraglutide improved some features of NASH and, of particular relevance, delayed the progression of fibrosis (143). More recently, once-daily subcutaneous semaglutide in 320 people with biopsy-proven NASH (62% having type 2 diabetes) reported resolution of steatohepatitis in 59% at the higher dose (equivalent to 2.4 mg/week semaglutide) compared with 17% in the placebo group ($P < 0.001$) (135). Cumulatively, semaglutide did not significantly affect the stage of liver fibrosis in this group of people (70% of whom had F2 or F3 at baseline), but it significantly slowed over 72 weeks the progression of liver fibrosis (4.9% with the GLP-1 RA at the highest dose compared with 18.8% on placebo). Tirzepatide (144), sodium–glucose cotransporter inhibitors (145–147), and insulin (132) reduce hepatic steatosis, but their effects on steatohepatitis remain unknown.

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for cardiovascular disease, are significantly higher (4- to 10-fold) with obesity, especially with central obesity (148). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep-disordered breathing may be as high as 58% (149,150). In participants with obesity enrolled in the Action for Health in Diabetes (Look AHEAD) trial, it exceeded 80% (151). Individuals with symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, witnessed apnea)

should be considered for screening (152). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure management. The evidence for a treatment effect on glycemic control is mixed (153).

Periodontal Disease

Periodontal disease is more severe, and may be more prevalent, in people with diabetes than in those without and has been associated with higher A1C levels (154–156). Longitudinal studies suggest that people with periodontal disease have higher rates of incident diabetes. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (29,157). In an RCT, intensive periodontal treatment was associated with better glycemic outcomes (A1C 8.3% vs. 7.8% in control subjects and the intensive-treatment group, respectively) and reduction in inflammatory markers after 12 months of follow-up (158).

DIABETES AND COVID-19

Recommendations

- 4.11** Health care professionals should help people with diabetes aim to achieve individualized targeted glycemic control to reduce the risk of macrovascular and microvascular risk as well as reduce the risk of COVID-19 and its complications. **B**
- 4.12** As we move into the recovery phase, diabetes health care services and practitioners should address the impact of the pandemic in higher-risk groups, including ethnic minority, deprived, and older populations. **B**
- 4.13** People who have been infected with SARS-CoV-2 should be followed up in the longer term to assess for complications and symptoms of long COVID. **E**
- 4.14** People with new-onset diabetes need to be followed up regularly in routine clinical practice to determine if diabetes is transient. **B**
- 4.15** Health care professionals need to carefully monitor people with diabetes for diabetic ketoacidosis

during the COVID-19 pandemic. **C**

- 4.16** People with diabetes and their families/caregivers should be monitored for psychological well-being and offered support or referrals as needed, including mental/behavioral health care, self-management education and support, and resources to address related risk factors. **E**
- 4.17** Health care systems need to ensure that the vulnerable populations are not disproportionately disadvantaged by use of technological methods of consultations. **E**
- 4.18** There is no clear indication to change prescribing of glucose-lowering therapies in people with diabetes infected by the SARS-CoV-2 virus. **B**
- 4.19** People with diabetes should be prioritized and offered SARS-CoV-2 vaccines. **B**

SARS-CoV-2, the virus that causes the clinical disease COVID-19, was first reported in December 2019 in China and has disproportionately impacted certain groups, including men, older people, ethnic minority populations, and people with certain chronic conditions, including diabetes, cardiovascular disease, kidney disease, and certain respiratory diseases. COVID-19 has now been recognized as a complex multisystem disease including widespread insulin resistance, endothelial dysfunction, hematological disorders, and hyperimmune responses (159). There is now evidence of not only direct but also indirect adverse effects of COVID-19 in people with diabetes. Many people with multiple long-term conditions have diabetes, which has also been associated with worse outcomes in people with COVID-19 (160). The association with BMI and COVID-19 mortality is U-shaped in both type 1 and type 2 diabetes (161).

COVID-19 has disproportionately affected certain groups, such as older people and those from some ethnic populations who are known to have high prevalence of chronic conditions such as diabetes, cardiovascular disease, kidney disease, and certain respiratory diseases (162). People with chronic

conditions have experienced some of the worst COVID-19 outcomes, including hospital admission and mortality (163). In people with diabetes, higher blood glucose levels both prior to and during COVID-19 admission have been associated with poor outcomes, including mortality (164). Type 1 diabetes has been associated with higher risk of COVID-19 mortality than type 2 diabetes (165). One whole-population-level study of over 61 million people in England in the first wave of the pandemic reported that after adjustment for age, sex, ethnicity, deprivation, and geographical region, the odds ratios for in-hospital COVID-19–related deaths were 3.51 (95% CI 3.16–3.90) in people with type 1 diabetes and 2.03 (1.97–2.09) in people with type 2 diabetes compared with the general population (166). There were also excess deaths in the first wave by 59.1% in people with type 1 diabetes and 64.3% in people with type 2 diabetes compared with death rates in the same time period for the previous 3 years (161). The largest study of people with diabetes to date, using whole-population data from England with over 3 million people, reported a higher association for mortality in people with type 1 diabetes than type 2 diabetes (161). Male sex, older age, renal impairment, non-White ethnicity, socioeconomic deprivation, and previous stroke and heart failure were associated with increased COVID-19–related mortality in both type 1 and type 2 diabetes (161).

Much of the evidence for recommendations is from a recent systematic review that was commissioned by the World Health Organization on the latest research evidence on the impact of COVID-19 on people with diabetes (165). Data were summarized from 112 systematic reviews that were narratively synthesized. The review reported that there are no appropriate data to determine whether diabetes is a risk factor for acquiring SARS-CoV-2 infection. Diabetes is a risk factor for severe disease and death from COVID-19.

Reasons for the higher rates of COVID-19 and severity in minority ethnic groups are complex and could be due to higher prevalence of comorbid conditions (e.g., diabetes), differences in exposure risk (e.g., overcrowded living conditions, essential worker jobs), and access to

treatment (e.g., health insurance status, specialist services, and medications), which all relate to long-standing structural inequities that vary by ethnicity (167).

There is now overwhelming evidence that approximately 30–40% of people who are infected with COVID-19 get persistent and sometimes relapsing and remitting symptoms 4 weeks after infection, which has been termed post-acute sequelae of COVID-19, post-COVID-19 condition, post-acute COVID-19 syndrome, or long COVID (168,169). Currently, data on long COVID specifically in people with diabetes are lacking, and people who have been infected with SARS-CoV-2 should be followed up in the longer term.

There have also been recent reports of development of new-onset diabetes in people who have had COVID-19. There are conflicting reports of new-onset diabetes, with publications from a number of countries. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known but may include previously undiagnosed diabetes presenting early or later in the disease trajectory, stress hyperglycemia, steroid-induced hyperglycemia, and possibly direct or indirect effects of SARS-CoV-2 on the β -cell (170). Whether new-onset diabetes is likely to remain permanent or is more aggressive is not known, and it will be important for health care professionals to monitor these people in the longer term. One large U.S. retrospective study of over 27 million people reported that COVID-19 was associated with significantly increased risk of new-onset type 1 diabetes and a disproportionately higher risk in ethnic minority people (171). Another recent cross-sectional population–based Canadian study observed a slightly higher but nonsignificant increase in diabetes incidence in children during the pandemic, suggesting this resulted from delays in diagnosis early during the pandemic with a catch-up effect (172). Whether COVID-19 leads to new-onset diabetes is not known.

There have been several publications on the risk of diabetic ketoacidosis (DKA) during the pandemic. A German diabetes prospective study using registry data of children and adolescents found an increase in type 1 diabetes in the first 3 months of the first wave, and the frequency of DKA at presentation was significantly higher than those for 2019

(44.7% vs. 24.5%, adjusted risk ratio 1.84) and 2018 (vs. 24.1%, adjusted risk ratio 1.85) as well as the proportion with severe DKA (173). A larger study using national data in England during the first two waves found that rates of DKA were higher than those for preceding years across all pandemic periods studied (174). The study reported lower DKA hospital admissions in people with type 1 diabetes but higher rates of DKA in people with type 2 diabetes and those newly diagnosed with diabetes.

There is also evidence of adverse effects of COVID-19 on mental health (175) and health-promoting lifestyles during the pandemic. Some small studies in people with diabetes have reported longer-term psychological impact of SARS-CoV-2 infection in people with diabetes, including fatigue and risk of suicide (176). Longitudinal follow-up of the Look AHEAD study of older adults with type 2 diabetes reported a 1.6-fold higher prevalence for depressive symptoms and 1.8-fold higher prevalence for loneliness during the pandemic compared with prepandemic levels (177). Furthermore, people with diabetes remain fearful of attending face-to-face contact due to the possible threat from mutant strains of coronavirus (178). Negative emotions due to the pandemic, including lockdowns, have been associated with reduced motivation, physical inactivity, and sedentary behavior (179). Higher levels of pandemic-related distress have been linked to higher A1C (180). Greater pandemic-related life disruptions have been related to higher distress in parents of youth with diabetes, which may have impacted families from racial and ethnic minority groups to a greater degree than non-Hispanic White families (181). On the other hand, for some youth with type 1 diabetes, increased time at home during the early phases of the COVID-19 pandemic provided opportunities for enhanced family support for diabetes self-management and reduced diabetes-related distress (182).

Recurrent lockdowns and other public health measures due to the pandemic have restricted access to routine diabetes care and have affected self-management, care-seeking behavior, and access to medications (183). This has resulted in compromised routine care and management of risk factors (184,185). There have been reductions in diagnosis of

type 2 diabetes and reductions in new prescriptions of metformin during the pandemic (186). Due to unemployment or lost income during the pandemic, people living with diabetes have experienced financial hardships that may have reduced their affordability for medications in countries where costs for medications are out of pocket (184). Many individuals with diabetes have avoided or delayed seeking medical attention for routine non-COVID-19–related problems due to fear of infection and/or to reduce strain on health care services (187). Disruptions in care delivery and completion of care processes have been associated with an increased risk of non-COVID-19–related deaths in people with diabetes (188).

Direct contact will still be necessary if blood tests or physical examinations are required. However, it will be important to ensure that disparities are not widened for vulnerable groups such as the elderly and socioeconomically challenged and ethnic minority groups due to access to literacy.

As we recover from the pandemic, it is essential that we prioritize the highest-risk groups for their routine review and assessment as well as management of their mental/behavioral health and risk factors. Diabetes professional bodies in some countries have published guidance on risk stratification and who to prioritize for diabetes review (189,190). Factors to consider for prioritization should include demographics, socioeconomic status, education levels, established complications, comorbidities, and modifiable risk factors, which are associated with high risk of progression of diabetes-related complications.

In many countries, health care professionals have reduced face-to-face contact and adapted technological methods of delivering routine diabetes care. One small RCT in adults with type 2 diabetes with follow-up to 16 weeks showed that remote consultations during the pandemic reduced the prevalence of mental health- and diabetes-related emotional distress (191). The number of face-to-face appointments is now increasing, and hybrid models with both virtual and face-to-face consultations are likely to remain (192). Technological interventions such as telehealth in people with diabetes may be a solution to improve care and clinical outcomes (193). However,

such technological interventions may further widen disparities in vulnerable populations such as the elderly, ethnic minority groups, frail populations, and those from deprived communities (194).

Several pharmacoepidemiological studies have examined the association between glucose-lowering medications and risk of COVID-19 and have reported conflicting findings, although most studies showed a lower risk of mortality with metformin and a higher risk in people on insulin. However, the absolute differences in the risks have been small, and these findings could be due to confounding by indication (195). The gold standard for assessing the effects of therapies is by RCT, and only one RCT, the Dapagliflozin in Patients with Cardio-metabolic Risk Factors Hospitalized with COVID-19 (DARE-19), a double-blind, placebo-controlled RCT in people with and without type 2 diabetes with at least one cardiovascular risk factor, has been reported (196). In this study, dapagliflozin was well tolerated and resulted in fewer events of organ dysfunction, but results were not statistically significant for the dual primary outcome of prevention (time to new or worsening organ dysfunction or death) and the hierarchical composite outcome of recovery by 30 days.

Great progress has been made globally to develop vaccines against SARS-CoV-2, and RCT data and real-world data show that vaccines have led to reduced infections, transmission, hospitalization, and mortality. It is therefore important that people with diabetes have regular SARS-CoV-2 vaccines (see IMMUNIZATIONS, above, for detailed information on COVID-19 vaccines).

It is unclear currently how often people with diabetes will require booster vaccines. Though limited data are available on COVID-19 vaccination attitudes or uptake in people with diabetes in the U.S. (197), diabetes health care professionals may be in a position to address questions and concerns among people with diabetes and encourage vaccination.

References

1. Stelfox M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. *Prev Chronic Dis* 2013;10:E26
2. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the chronic care model in the new millennium. *Health Aff (Millwood)* 2009;28:75–85

3. Gabbay RA, Bailit MH, Mauger DT, Wagner EH, Siminerio L. Multipayer patient-centered medical home implementation guided by the chronic care model. *Jt Comm J Qual Patient Saf* 2011;37:265–273
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
5. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
6. Lachin JM, Genuth S, Nathan DM, Zinman B; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial—revisited. *Diabetes* 2008;57:995–1001
7. White NH, Cleary PA, Dahms W, Goldstein D, Malone J; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 2001;139:804–812
8. Rodriguez K, Ryan D, Dickinson JK, Phan V. Improving quality outcomes: the value of diabetes care and education specialists. *Clin Diabetes* 2022; 40:356–365
9. Anderson RM, Funnell MM. Compliance and adherence are dysfunctional concepts in diabetes care. *Diabetes Educ* 2000;26:597–604
10. Sarkar U, Fisher L, Schillinger D. Is self-efficacy associated with diabetes self-management across race/ethnicity and health literacy? *Diabetes Care* 2006;29:823–829
11. King DK, Glasgow RE, Toobert DJ, et al. Self-efficacy, problem solving, and social-environmental support are associated with diabetes self-management behaviors. *Diabetes Care* 2010;33: 751–753
12. Nouwen A, Urquhart Law G, Hussain S, McGovern S, Napier H. Comparison of the role of self-efficacy and illness representations in relation to dietary self-care and diabetes distress in adolescents with type 1 diabetes. *Psychol Health* 2009;24:1071–1084
13. Dickinson JK, Guzman SJ, Maryniuk MD, et al. The use of language in diabetes care and education. *Diabetes Care* 2017;40:1790–1799
14. Lee SWH, Ng KY, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Sleep Med Rev* 2017;31:91–101
15. Robinson CL, Bernstein I, Poehling K, Romero JR, Szilagyi P. Advisory Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger—United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:130–132
16. Freedman MS, Hunter P, Ault K, Kroger A. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older—United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:133–135
17. Lee G, Carr W, ACIP Evidence-Based Recommendations Work Group. Updated framework for development of evidence-based recommenda-

- tions by the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2018;67:1271–1272
18. Goeijenbier M, van Sloten TT, Slobbe L, et al. Benefits of flu vaccination for persons with diabetes mellitus: a review. *Vaccine* 2017;35:5095–5101
 19. Yedlapati SH, Khan SU, Talluri S, et al. Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc* 2021;10:e019636
 20. Grohskopf LA, Alyanak E, Broder KR, Blanton LH, Fry AM, Jernigan DB, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2020–21 influenza season. *MMWR Recomm Rep* 2020;69:1–24
 21. Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care* 2000;23:95–108
 22. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:109–117
 23. Ahmed SS, Pondo T, Xing W, et al. Early impact of 13-valent pneumococcal conjugate vaccine use on invasive pneumococcal disease among adults with and without underlying medical conditions—United States. *Clin Infect Dis* 2020;70:2484–2492
 24. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines, 2022. Accessed 7 October 2022. Available from <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>
 25. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. *Diabetes Care* 2006;29:2415–2419
 26. Grant RW, Ashburner JM, Hong CS, Chang Y, Barry MJ, Atlas SJ. Defining patient complexity from the primary care physician's perspective: a cohort study. *Ann Intern Med* 2011;155:797–804
 27. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition—multimorbidity. *JAMA* 2012;307:2493–2494
 28. Sudore RL, Karter AJ, Huang ES, et al. Symptom burden of adults with type 2 diabetes across the disease course: diabetes & aging study. *J Gen Intern Med* 2012;27:1674–1681
 29. Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *J Periodontol* 2013;84(Suppl.):S135–S152
 30. Nederstigt C, Uitbeijerse BS, Janssen LGM, Corssmit EPM, de Koning EJP, Dekkers OM. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. *Eur J Endocrinol* 2019;180:135–144
 31. De Block CE, De Leeuw IH, Van Gaal LF. High prevalence of manifestations of gastric autoimmunity in parietal cell antibody-positive type 1 (insulin-dependent) diabetic patients. The Belgian Diabetes Registry. *J Clin Endocrinol Metab* 1999;84:4062–4067
 32. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 2011;34:1211–1213
 33. Hughes JW, Riddlesworth TD, DiMeglio LA, Miller KM, Rickels MR, McGill JB. Autoimmune diseases in children and adults with type 1 diabetes from the T1D Exchange clinic registry. *J Clin Endocrinol Metab* 2016;101:4931–4937
 34. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. *Autoimmun Rev* 2016;15:644–648
 35. Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. *N Engl J Med* 2004;350:2068–2079
 36. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108:656–676
 37. Husby S, Murray JA, Katzka DA. AGA clinical practice update on diagnosis and monitoring of celiac disease-changing utility of serology and histologic measures: expert review. *Gastroenterology* 2019;156:885–889
 38. Suh S, Kim KW. Diabetes and cancer: is diabetes causally related to cancer? *Diabetes Metab J* 2011;35:193–198
 39. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *CA Cancer J Clin* 2010;60:207–221
 40. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas* 2013;42:198–201
 41. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. *Diabetologia* 2005;48:2460–2469
 42. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006;5:64–74
 43. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. *J Diabetes Investig* 2013;4:640–650
 44. Ohara T, Doi Y, Ninomiya T, et al. Glucose tolerance status and risk of dementia in the community: the Hisayama study. *Neurology* 2011;77:1126–1134
 45. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al.; Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) Investigators. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial. *Diabetes Care* 2009;32:221–226
 46. Launer LJ, Miller ME, Williamson JD, et al.; ACCORD MIND investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol* 2011;10:969–977
 47. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301:1565–1572
 48. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care* 2012;35:787–793
 49. Lacy ME, Gilsanz P, Eng C, Beer MS, Karter AJ, Whitmer RA. Severe hypoglycemia and cognitive function in older adults with type 1 diabetes: the Study of Longevity in Diabetes (SOLID). *Diabetes Care* 2020;43:541–548
 50. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. *Arch Neurol* 2009;66:216–225
 51. Ooi CP, Loke SC, Yassin F, Hamid TA. Carbohydrates for improving the cognitive performance of independent-living older adults with normal cognition or mild cognitive impairment. *Cochrane Database Syst Rev* 2011;4:CD007220
 52. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013;159:688–697
 53. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019;71:793–801
 54. Lomonaco R, Godínez Leiva E, Bril F, et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening. *Diabetes Care* 2021;44:399–406
 55. Ciardullo S, Monti T, Perseghin G. High prevalence of advanced liver fibrosis assessed by transient elastography among U.S. adults with type 2 diabetes. *Diabetes Care* 2021;44:519–525
 56. Barb D, Repetto EM, Stokes ME, Shankar SS, Cusi K. Type 2 diabetes mellitus increases the risk of hepatic fibrosis in individuals with obesity and nonalcoholic fatty liver disease. *Obesity (Silver Spring)* 2021;29:1950–1960
 57. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. *Lancet Diabetes Endocrinol* 2022;10:284–296
 58. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328–357
 59. Harrison SA, Gawrieh S, Roberts K, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. *J Hepatol* 2021;75:284–291
 60. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. *Hepatology* 2020;72:1605–1616
 61. Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. *Gut* 2021;70:1375–1382
 62. Burra P, Becchetti C, Germani G. NAFLD and liver transplantation: disease burden, current management and future challenges. *JHEP Rep* 2020;2:100192
 63. Younossi ZM, Ong JP, Takahashi H, et al.; Global Nonalcoholic Steatohepatitis Council. A global survey of physicians knowledge about nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2022;20:e1456–e1468
 64. Kanwal F, Shubrook JH, Younossi Z, et al. Preparing for the NASH epidemic: a call to action. *Diabetes Care* 2021;44:2162–2172
 65. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022;28:528–562
 66. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and manage-

- ment of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2021;161:1657–1669
67. Gellert-Kristensen H, Richardson TG, Davey Smith G, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. Combined effect of PNPLA3, TM6SF2, and HSD17B13 variants on risk of cirrhosis and hepatocellular carcinoma in the general population. *Hepatology* 2020;72:845–856
68. Stender S, Kozlitina J, Nordestgaard BG, Tybjaerg-Hansen A, Hobbs HH, Cohen JC. Adiposity amplifies the genetic risk of fatty liver disease conferred by multiple loci. *Nat Genet* 2017;49:842–847
69. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015;149:389–97.e10
70. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015;61:1547–1554
71. Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology* 2020;158:1611–1625.e12
72. Sanyal AJ, Van Natta ML, Clark J, et al.; NASH Clinical Research Network (CRN). Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med* 2021;385:1559–1569
73. Mantovani A, Byrne CD, Bonora E, Targher G. Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. *Diabetes Care* 2018;41:372–382
74. Duell PB, Welty FK, Miller M, et al.; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifestyle and Cardio-metabolic Health; and Council on Peripheral Vascular Disease. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol* 2022;42:e168–e185
75. Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6:903–913
76. Ciardullo S, Ballabeni C, Trevisan R, Perseghin G. Liver stiffness, albuminuria and chronic kidney disease in patients with NAFLD: a systematic review and meta-analysis. *Biomolecules* 2022;12:105
77. Musso G, Gambino R, Tabibian JH, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014;11:e1001680
78. Song D, Li C, Wang Z, Zhao Y, Shen B, Zhao W. Association of non-alcoholic fatty liver disease with diabetic retinopathy in type 2 diabetic patients: a meta-analysis of observational studies. *J Diabetes Investig* 2021;12:1471–1479
79. de Vries M, Westerink J, Kaasjager KHAH, de Valk HW. Prevalence of nonalcoholic fatty liver disease (NAFLD) in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2020;105:dga575
80. Corbin KD, Driscoll KA, Pratley RE, Smith SR, Maahs DM; Advancing Care for Type 1 Diabetes and Obesity Network (ACT1ON). Obesity in type 1 diabetes: pathophysiology, clinical impact, and mechanisms. *Endocr Rev* 2018;39:629–663
81. Cusi K, Sanyal AJ, Zhang S, et al. Non-alcoholic fatty liver disease (NAFLD) prevalence and its metabolic associations in patients with type 1 diabetes and type 2 diabetes. *Diabetes Obes Metab* 2017;19:1630–1634
82. Arab JP, Dirchwolf M, Álvares-da-Silva MR, et al. Latin American Association for the Study of the Liver (ALEH) practice guidance for the diagnosis and treatment of non-alcoholic fatty liver disease. *Ann Hepatol* 2020;19:674–690
83. Eslam M, Sarin SK, Wong VW, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. *Hepatol Int* 2020;14:889–919
84. European Association for the Study of the Liver. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis—2021 update. *J Hepatol* 2021;75:659–689
85. Portillo-Sanchez P, Bril F, Maximos M, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. *J Clin Endocrinol Metab* 2015;100:2231–2238
86. Maximos M, Bril F, Portillo Sanchez, et al. The role of liver fat and insulin resistance as determinants of plasma aminotransferase elevation in nonalcoholic fatty liver disease. *Hepatology* 2014;61:153–160
87. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *J Am Coll Gastroenterol* 2017;112:18–35
88. Younossi ZM, Anstee QM, Wai-Sun Wong V, et al. The association of histologic and noninvasive tests with adverse clinical and patient-reported outcomes in patients with advanced fibrosis due to nonalcoholic steatohepatitis. *Gastroenterology* 2021;160:1608–1619.e13
89. Siddiqui MS, Yamada G, Vuppalanchi R, et al.; NASH Clinical Research Network. Diagnostic accuracy of noninvasive fibrosis models to detect change in fibrosis stage. *Clin Gastroenterol Hepatol* 2019;17:1877–1885.e5
90. Unalp-Arida A, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. *Hepatology* 2017;66:84–95
91. Lee J, Vali Y, Boursier J, et al. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: a systematic review. *Liver Int* 2021;41:261–270
92. Qadri S, Ahlholm N, Lønsmann I, et al. Obesity modifies the performance of fibrosis biomarkers in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab* 2022;107:e2008–e2020
93. Bril F, McPhaul MJ, Caulfield MP, et al. Performance of plasma biomarkers and diagnostic panels for nonalcoholic steatohepatitis and advanced fibrosis in patients with type 2 diabetes. *Diabetes Care* 2020;43:290–297
94. Anstee QM, Lawitz EJ, Alkhoury N, et al. Noninvasive tests accurately identify advanced fibrosis due to NASH: baseline data from the STELLAR trials. *Hepatology* 2019;70:1521–1530
95. Singh A, Gosai F, Siddiqui MT, et al. Accuracy of noninvasive fibrosis scores to detect advanced fibrosis in patients with type-2 diabetes with biopsy-proven nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2020;54:891–897
96. McPherson S, Hardy T, Dufour JF, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. *Am J Gastroenterol* 2017;112:740–751
97. Ishiba H, Sumida Y, Tanaka S, et al.; Japan Study Group of Non-Alcoholic Fatty Liver Disease (JSG-NAFLD). The novel cutoff points for the FIB4 index categorized by age increase the diagnostic accuracy in NAFLD: a multi-center study. *J Gastroenterol* 2018;53:1216–1224
98. Vali Y, Lee J, Boursier J, et al.; LITMUS Systematic Review Team. Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: a systematic review and meta-analysis. *J Hepatol* 2020;73:252–262
99. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology* 2019;156:1264–1281.e4
100. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology* 2019;156:1717–1730
101. Mózes FE, Lee JA, Selvaraj EA, et al.; LITMUS Investigators. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. *Gut* 2022;71:1006–1019
102. Elhence A, Anand A, Biswas S, et al. Compensated advanced chronic liver disease in nonalcoholic fatty liver disease: two-step strategy is better than Baveno criteria. *Dig Dis Sci* 2022
103. Chan WK, Treeprasertsuk S, Goh GBB, et al. Optimizing use of nonalcoholic fatty liver disease fibrosis score, fibrosis-4 score, and liver stiffness measurement to identify patients with advanced fibrosis. *Clin Gastroenterol Hepatol* 2019;17:2570–2580.e37
104. Petta S, Wai-Sun Wong V, Bugianesi E, et al. Impact of obesity and alanine aminotransferase levels on the diagnostic accuracy for advanced liver fibrosis of noninvasive tools in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol* 2019;114:916–928
105. Lazarus JV, Anstee QM, Hagström H, et al. Defining comprehensive models of care for NAFLD. *Nat Rev Gastroenterol Hepatol* 2021;18:717–729
106. Wong VW, Zelber-Sagi S, Cusi K, et al. Management of NAFLD in primary care settings. *Liver Int* 2022;42:2377–2389
107. Long MT, Noureddin M, Lim JK. AGA clinical practice update: diagnosis and management of nonalcoholic fatty liver disease in lean individuals: expert review. *Gastroenterology* 2022;163:764–774.e1
108. Cusi K. Nonalcoholic steatohepatitis in nonobese patients: not so different after all. *Hepatology* 2017;65:4–7
109. Younes R, Bugianesi E. NASH in lean individuals. *Semin Liver Dis* 2019;39:86–95
110. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of non-alcoholic fatty liver disease. *Cell* 2021;184:2537–2564
111. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. *Gastroenterology* 2012;142:711–725.e6
112. Schuppan D, Surabattula R, Wang XY. Determinants of fibrosis progression and regression in NASH. *J Hepatol* 2018;68:238–250

113. Akbulut UE, Isik IA, Atalay A, et al. The effect of a Mediterranean diet vs. a low-fat diet on non-alcoholic fatty liver disease in children: a randomized trial. *Int J Food Sci Nutr* 2022;73:357–366
114. Koutoukidis DA, Koshiaris C, Henry JA, et al. The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Metabolism* 2021;115:154455
115. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010;51:121–129
116. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology* 2015;149:367–78.e5; quiz e14–e15
117. Gepner Y, Shelef I, Komy O, et al. The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. *J Hepatol* 2019;71:379–388
118. Kawaguchi T, Charlton M, Kawaguchi A, et al. Effects of Mediterranean diet in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression analysis of randomized controlled trials. *Semin Liver Dis* 2021;41:225–234
119. Younossi ZM, Corey KE, Lim JK. AGA clinical practice update on lifestyle modification using diet and exercise to achieve weight loss in the management of nonalcoholic fatty liver disease: expert review. *Gastroenterology* 2021;160:912–918
120. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388–1402
121. Plauth M, Bernal W, Dasarathy S, et al. ESPEN guideline on clinical nutrition in liver disease. *Clin Nutr* 2019;38:485–521
122. Orzi LA, Gariani K, Oldani G, Delaune V, Morel P, Toso C. Exercise-based interventions for nonalcoholic fatty liver disease: a meta-analysis and meta-regression. *Clin Gastroenterol Hepatol* 2016;14:1398–1411
123. Hashida R, Kawaguchi T, Bekki M, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: a systematic review. *J Hepatol* 2017;66:142–152
124. Sargeant JA, Gray LJ, Bodicoat DH, et al. The effect of exercise training on intrahepatic triglyceride and hepatic insulin sensitivity: a systematic review and meta-analysis. *Obes Rev* 2018;19:1446–1459
125. Aminian A, Al-Kurd A, Wilson R, et al. Association of bariatric surgery with major adverse liver and cardiovascular outcomes in patients with biopsy-proven nonalcoholic steatohepatitis. *JAMA* 2021;326:2031–2042
126. Fakhry TK, Mhaskar R, Schwitalla T, Muradova E, Gonzalvo JP, Murr MM. Bariatric surgery improves nonalcoholic fatty liver disease: a contemporary systematic review and meta-analysis. *Surg Obes Relat Dis* 2019;15:502–511
127. Ramai D, Singh J, Lester J, et al. Systematic review with meta-analysis: bariatric surgery reduces the incidence of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2021;53:977–984
128. Kanwal F, Kramer JR, Li L, et al. Effect of metabolic traits on the risk of cirrhosis and hepatocellular cancer in nonalcoholic fatty liver disease. *Hepatology* 2020;71:808–819
129. Younossi Z, Stepanova M, Sanyal AJ, et al. The conundrum of cryptogenic cirrhosis: Adverse outcomes without treatment options. *J Hepatol* 2018;69:1365–1370
130. Patel Chavez C, Cusi K, Kadiyala S. The emerging role of glucagon-like peptide-1 receptor agonists for the management of NAFLD. *J Clin Endocrinol Metab* 2022;107:29–38
131. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. *JHEP Rep* 2019;1:312–328
132. Budd J, Cusi K. Role of agents for the treatment of diabetes in the management of nonalcoholic fatty liver disease. *Curr Diab Rep* 2020;20:59
133. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. *JAMA Intern Med* 2017;177:633–640
134. Bril F, Kalavalapalli S, Clark VC, et al. Response to pioglitazone in patients with nonalcoholic steatohepatitis with vs without type 2 diabetes. *Clin Gastroenterol Hepatol* 2018;16:558–566.e2
135. Newsome PN, Buchholtz K, Cusi K, et al.; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021;384:1113–1124
136. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;355:2297–2307
137. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with non-alcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165:305–315
138. Sanyal AJ, Chalasani N, Kowdley KV, et al.; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;362:1675–1685
139. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008;135:1176–1184
140. Huang JF, Dai CY, Huang CF, et al. First-in-Asian double-blind randomized trial to assess the efficacy and safety of insulin sensitizer in non-alcoholic steatohepatitis patients. *Hepatol Int* 2021;15:1136–1147
141. Nouredin M, Jones C, Alkhoury N, Gomez EV, Dieterich DT; NASHNET. Screening for non-alcoholic fatty liver disease in persons with type 2 diabetes in the United States is cost-effective: a comprehensive cost-utility analysis. *Gastroenterology* 2020;159:1985–1987.e4
142. Mahady SE, Wong G, Craig JC, George J. Pioglitazone and vitamin E for nonalcoholic steatohepatitis: a cost utility analysis. *Hepatology* 2012;56:2172–2179
143. Armstrong MJ, Gaunt P, Aithal GP, et al.; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387:679–690
144. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol* 2022;10:393–406
145. Cusi K, Bril F, Barb D, et al. Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. *Diabetes Obes Metab* 2019;21:812–821
146. Kahl S, Gancheva S, Straßburger K, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: a randomized, double-blind, phase 4, placebo-controlled trial. *Diabetes Care* 2020;43:298–305
147. Latva-Rasku A, Honka MJ, Kullberg J, et al. The SGLT2 inhibitor dapagliflozin reduces liver fat but does not affect tissue insulin sensitivity: a randomized, double-blind, placebo-controlled study with 8-week treatment in type 2 diabetes patients. *Diabetes Care* 2019;42:931–937
148. Li C, Ford ES, Zhao G, Croft JB, Balluz LS, Mokdad AH. Prevalence of self-reported clinically diagnosed sleep apnea according to obesity status in men and women: National Health and Nutrition Examination Survey, 2005–2006. *Prev Med* 2010;51:18–23
149. West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 2006;61:945–950
150. Resnick HE, Redline S, Shahar E, et al.; Sleep Heart Health Study. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diabetes Care* 2003;26:702–709
151. Foster GD, Sanders MH, Millman R, et al.; Sleep AHEAD Research Group. Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care* 2009;32:1017–1019
152. Bibbins-Domingo K, Grossman DC, Curry SJ, et al.; US Preventive Services Task Force. Screening for obstructive sleep apnea in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2017;317:407–414
153. Shaw JE, Punjabi NM, Wilding JP, Alberti KGMM; International Diabetes Federation Taskforce on Epidemiology and Prevention. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. *Diabetes Res Clin Pract* 2008;81:2–12
154. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. *J Diabetes Complications* 2006;20:59–68
155. Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: a two-way relationship. *Br Dent J* 2014;217:433–437
156. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA, Genco RJ. Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009–2014. *J Am Dent Assoc* 2018;149:576–588.e6
157. Simpson TC, Weldon JC, Worthington HV, et al. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. *Cochrane Database Syst Rev* 2015 (11):CD004714
158. D’Aiuto F, Gkraniias N, Bhowruth D, et al.; TASTE Group. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *Lancet Diabetes Endocrinol* 2018;6:954–965

159. Roberts CM, Levi M, McKee M, Schilling R, Lim WS, Grocott MPW. COVID-19: a complex multi-system disorder. *Br J Anaesth* 2020;125:238–242
160. Chudasama YV, Zaccardi F, Gillies CL, et al. Patterns of multimorbidity and risk of severe SARS-CoV-2 infection: an observational study in the U.K. *BMC Infect Dis* 2021;21:908
161. Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020;8:823–833
162. Martin CA, Jenkins DR, Minhas JS, et al.; Leicester COVID-19 consortium. Socio-demographic heterogeneity in the prevalence of COVID-19 during lockdown is associated with ethnicity and household size: results from an observational cohort study. *EClinicalMedicine* 2020;25:100466
163. Singh AK, Gillies CL, Singh R, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: a systematic review and meta-analysis. *Diabetes Obes Metab* 2020;22:1915–1924
164. Hartmann-Boyce J, Morris E, Goyder C, et al. Diabetes and COVID-19: risks, management, and learnings from other national disasters. *Diabetes Care* 2020;43:1695–1703
165. Hartmann-Boyce J, Rees K, Perring JC, et al. Risks of and from SARS-CoV-2 infection and COVID-19 in people with diabetes: a systematic review of reviews. *Diabetes Care* 2021;44:2790–2811
166. Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020;8:813–822
167. Khunti K, Feldman EL, Laiteerapong N, Parker W, Routen A, Peek M. The impact of the COVID-19 pandemic on ethnic minority groups with diabetes. *Diabetes Care*. 9 August 2022 [Epub ahead of print]. DOI: 10.2337/dc21-2495
168. Chen C, Hauptert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post COVID-19 condition or long COVID: a meta-analysis and systematic review. *J Infect Dis* 2022;226:1593–1607
169. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med* 2021;27:601–615
170. Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, hyperglycemia, and new-onset diabetes. *Diabetes Care* 2021;44:2645–2655
171. Qeadan F, Tingey B, Egbert J, et al. The associations between COVID-19 diagnosis, type 1 diabetes, and the risk of diabetic ketoacidosis: a nationwide cohort from the US using the Cerner Real-World Data. *PLoS One* 2022;17:e0266809
172. Shulman R, Cohen E, Stukel TA, Diong C, Guttman A. Examination of trends in diabetes incidence among children during the COVID-19 pandemic in Ontario, Canada, from March 2020 to September 2021. *JAMA Netw Open* 2022;5:e2223394
173. Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. *JAMA* 2020;324:801–804
174. Misra S, Barron E, Vamos E, et al. Temporal trends in emergency admissions for diabetic ketoacidosis in people with diabetes in England before and during the COVID-19 pandemic: a population-based study. *Lancet Diabetes Endocrinol* 2021;9:671–680
175. Violant-Holz V, Gallego-Jiménez MG, González-González CS, et al. Psychological health and physical activity levels during the COVID-19 pandemic: a systematic review. *Int J Environ Res Public Health* 2020;17:E9419
176. Alessi J, Scherer GDLG, Erthal IN, et al. One in ten patients with diabetes have suicidal thoughts after 1 year of the COVID-19 pandemic: we need to talk about diabetes and mental health not only during Suicide Prevention Awareness Month. *Acta Diabetol* 2022;59:143–145
177. Chao AM, Wadden TA, Clark JM, et al. Changes in the prevalence of symptoms of depression, loneliness, and insomnia in U.S. older adults with type 2 diabetes during the COVID-19 pandemic: the Look AHEAD Study. *Diabetes Care* 2022;45:74–82
178. Caballero AE, Ceriello A, Misra A, et al. COVID-19 in people living with diabetes: an international consensus. *J Diabetes Complications* 2020;34:107671
179. Stockwell S, Trott M, Tully M, et al. Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: a systematic review. *BMJ Open Sport Exerc Med* 2021;7:e000960
180. O'Donnell MB, Hilliard ME, Cao VT, et al. "It just kind of feels like a different world now:" stress and resilience for adolescents with type 1 diabetes in the era of COVID-19. *Front Clin Diabetes Healthcare*. Accessed 7 October 2022. Available from <https://www.frontiersin.org/articles/10.3389/fcdhc.2022.835739>
181. Wang CH, Hilliard ME, Carreon SA, et al. Predictors of mood, diabetes-specific and COVID-19-specific experiences among parents of early school-age children with type 1 diabetes during initial months of the COVID-19 pandemic. *Pediatr Diabetes* 2021;22:1071–1080
182. Ferguson K, Moore H, Kaidbey JH, et al. Impacts of the COVID-19 pandemic on pediatric type 1 diabetes management: a qualitative study. *Sci Diabetes Self Manag Care*. 24 September 2022. DOI: 10.1177/26350106221125701
183. Mohseni M, Ahmadi S, Azami-Aghdash S, et al. Challenges of routine diabetes care during COVID-19 era: a systematic search and narrative review. *Prim Care Diabetes* 2021;15:918–922
184. Ratzki-Leewing AA, Ryan BL, Buchenberger JD, Dickens JW, Black JE, Harris SB. COVID-19 hinterland: surveilling the self-reported impacts of the pandemic on diabetes management in the USA (cross-sectional results of the INPHORM study). *BMJ Open* 2021;11:e049782
185. Seidu S, Hambling C, Holmes P, et al.; PCDS Research Group. The impact of the COVID pandemic on primary care diabetes services in the UK: a cross-sectional national survey of views of health professionals delivering diabetes care. *Prim Care Diabetes* 2022;16:257–263
186. Carr MJ, Wright AK, Leelarathna L, et al. Impact of COVID-19 restrictions on diabetes health checks and prescribing for people with type 2 diabetes: a UK-wide cohort study involving 618 161 people in primary care. *BMJ Qual Saf* 2022;31:503–514
187. Vamos EP, Khunti K. Indirect effects of the COVID-19 pandemic on people with type 2 diabetes: time to urgently move into a recovery phase. *BMJ Qual Saf* 2022;31:483–485
188. Valabhji J, Barron E, Gorton T, et al. Associations between reductions in routine care delivery and non-COVID-19-related mortality in people with diabetes in England during the COVID-19 pandemic: a population-based parallel cohort study. *Lancet Diabetes Endocrinol* 2022;10:561–570
189. DiabetesontheNet. How to undertake a remote diabetes review. Accessed 29 August 2022. Available from <https://diabetesonthenet.com/diabetes-primary-care/how-undertake-remote-diabetes-review/>
190. Nagi D, Wilmot E, Owen K, et al. ABCD position statement on risk stratification of adult patients with diabetes during COVID-19 pandemic. *British Journal of Diabetes*. 2021;21:123–131
191. Alessi J, de Oliveira GB, Franco DW, et al. Telehealth strategy to mitigate the negative psychological impact of the COVID-19 pandemic on type 2 diabetes: a randomized controlled trial. *Acta Diabetol* 2021;58:899–909
192. Kilvert A, Wilmot EG, Davies M, Fox C. Virtual consultations: are we missing anything? *Pract Diabetes* 2020;37:143–146
193. Phillip M, Bergenstal RM, Close KL, et al. The digital/virtual diabetes clinic: the future is now—recommendations from an international panel on diabetes digital technologies introduction. *Diabetes Technol Ther* 2021;23:146–154
194. O'Connor S, Hanlon P, O'Donnell CA, Garcia S, Glanville J, Mair FS. Understanding factors affecting patient and public engagement and recruitment to digital health interventions: a systematic review of qualitative studies. *BMC Med Inform Decis Mak* 2016;16:120
195. Khunti K, Knighton P, Zaccardi F, et al. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol* 2021;9:293–303
196. Kosiborod MN, Esterline R, Furtado RHM, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2021;9:586–594
197. Czeisler MÉ, Barrett CE, Siegel KR, et al. Health care access and use among adults with diabetes during the COVID-19 pandemic - United States, February-March 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1597–1602
198. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. *JAMA Intern Med* 2017;177:1461–1470
199. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med* 2014;174:1116–1124
200. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 1997;157:1681–1686
201. Abdelhafiz AH, Rodríguez-Mañas L, Morley JE, Sinclair AJ. Hypoglycemia in older people—a less well recognized risk factor for frailty. *Aging Dis* 2015;6:156–167
202. Yun JS, Ko SH, Ko SH, et al. Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. *Diabetes Care* 2013;36:1283–1289
203. Chelliah A, Burge MR. Hypoglycaemia in elderly patients with diabetes mellitus: causes and strategies for prevention. *Drugs Aging* 2004; 21:511–530

204. Centers for Disease Control and Prevention (CDC). Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2011;60:1709–1711
205. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2019;68:698–702
206. Demicheli V, Jefferson T, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2018;2:CD004876
207. Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR Morb Mortal Wkly Rep* 2010;59:1102–1106.
208. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. *PLoS One* 2017; 12:e0169368
209. Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2019. *MMWR Morb Mortal Wkly Rep* 2020;69:77–83
210. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep* 2018;67:103–108
211. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022;45:2753–2786

5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Building positive health behaviors and maintaining psychological well-being are foundational for achieving diabetes treatment goals and maximizing quality of life (1,2). Essential to achieving these goals are diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), routine physical activity, tobacco cessation counseling when needed, health behavior counseling, and psychosocial care. Following an initial comprehensive medical evaluation (see Section 4, “Comprehensive Medical Evaluation and Assessment of Comorbidities”), people with diabetes and health care professionals are encouraged to engage in person-centered collaborative care (3–6), which is guided by shared decision-making in treatment plan selection; facilitation of obtaining medical, behavioral, psychosocial, and technology resources as needed; and shared monitoring of agreed-upon treatment plans and behavioral goals (7,8). Reevaluation during routine care should include assessment of medical, behavioral, and mental health outcomes, especially during times of change in health and well-being.

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendations

- 5.1 All people with diabetes should participate in diabetes self-management education and support to facilitate the knowledge, decision-making, and skills mastery for diabetes self-care. **A**
- 5.2 There are four critical times to evaluate the need for diabetes self-management education and support to promote skills acquisition to aid treatment plan implementation, medical nutrition therapy, and well-being: at diagnosis, annually

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and/or when not meeting treatment targets, when complicating factors develop (medical, physical, psychosocial), and when transitions in life and care occur. **E**

- 5.3 Clinical outcomes, health status, and well-being are key goals of diabetes self-management education and support that should be measured as part of routine care. **C**
- 5.4 Diabetes self-management education and support should be person-centered, may be offered in group or individual settings, and should be communicated with the entire diabetes care team. **A**
- 5.5 Digital coaching and digital self-management interventions can be effective methods to deliver diabetes self-management education and support. **B**
- 5.6 Reimbursement by third-party payers is recommended **C** because diabetes self-management education and support can improve outcomes and reduce costs. **B**
- 5.7 Identify and address barriers to diabetes self-management education and support that exist at the health system, payer, health care professional, and individual levels. **E**
- 5.8 Include social determinants of health of the target population in guiding design and delivery of diabetes self-management education and support **C** with the ultimate goal of health equity across all populations.
- 5.9 Consider addressing barriers to diabetes self-management education and support access through telehealth delivery of care **B** and other digital health solutions. **C**

The overall objectives of diabetes self-management education and support (DSMES) are to support informed decision-making, self-care behaviors, problem-solving, and active collaboration with the health care team to improve clinical outcomes, health status, and well-being in a cost-effective manner (2). DSMES services facilitate the knowledge, decision-making, and skills mastery necessary for optimal diabetes self-care and incorporate the

needs, goals, and life experiences of the person with diabetes. Health care professionals are encouraged to consider the burden of treatment (9) and the person's level of confidence and self-efficacy for management behaviors as well as the level of social and family support when providing DSMES. An individual's engagement in self-management behaviors and the effects on clinical outcomes, health status, and quality of life, as well as the psychosocial factors impacting the person's ability to self-manage, should be monitored as part of routine clinical care. A randomized controlled trial (RCT) testing a decision-making education and skill-building program (10) showed that addressing these targets improved health outcomes in a population in need of health care resources. Furthermore, following a DSMES curriculum improves quality of care (11).

Additionally, in response to the growing body of evidence that associates potentially judgmental words with increased feelings of shame and guilt, health care professionals are encouraged to consider the impact that language has on building therapeutic relationships and to choose positive, strength-based words and phrases that put people first (4,12). Please see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for more on use of language.

In accordance with the national standards for DSMES (13), all people with diabetes should participate in DSMES as it helps people with diabetes to identify and implement effective self-management strategies and cope with diabetes (2). Ongoing DSMES helps people with diabetes to maintain effective self-management throughout the life course as they encounter new challenges and as advances in treatment become available (14).

There are four critical time points when the need for DSMES should be evaluated by the health care professional and/or multidisciplinary team, with referrals made as needed (2):

1. At diagnosis
2. Annually and/or when not meeting treatment targets
3. When complicating factors (health conditions, physical limitations, emotional factors, or basic living needs) develop that influence self-management

4. When transitions in life and care occur

DSMES focuses on empowering individuals with diabetes by providing people with diabetes the tools to make informed self-management decisions (15). DSMES should be person-centered. This is an approach that places the person with diabetes and their family and/or support system at the center of the care model, working in collaboration with health care professionals. Person-centered care is respectful of and responsive to individual preferences, needs, and values. It ensures that the values of the person with diabetes guide all decision-making (16).

Evidence for the Benefits

DSMES is associated with improved diabetes knowledge and self-care behaviors (17), lower A1C (17–21), lower self-reported weight (22), improved quality of life (19,23,24), reduced all-cause mortality risk (25), positive coping behaviors (5,26), and reduced health care costs (27–29). DSMES is associated with an increased use of primary care and preventive services (27,30,31) and less frequent use of acute care and inpatient hospital services (22). People with diabetes who participate in DSMES are more likely to follow best practice treatment recommendations, particularly those with Medicare, and have lower Medicare and insurance claim costs (28,31). Better outcomes were reported for DSMES interventions that were more than 10 h over the course of 6–12 months (20), included ongoing support (14,32), were culturally (33–35) and age appropriate (36,37), were tailored to individual needs and preferences, addressed psychosocial issues, and incorporated behavioral strategies (15,26,38,39). Individual and group approaches are effective (40–42), with a slight benefit realized by those who engage in both (20). Strong evidence now exists on the benefits of virtual, telehealth, or internet-based DSMES services for diabetes prevention and management in a wide variety of populations (43–54).

Technologies such as mobile apps, simulation tools, digital coaching, and digital self-management interventions can also be used to deliver DSMES (55–60). These methods provide comparable or even improved outcomes compared with traditional in-person care (61). Greater A1C reductions are demonstrated with

increased patient engagement (62), although data from trials are considerably heterogeneous.

Technology-enabled diabetes self-management solutions improve A1C most effectively when there is two-way communication between the person with diabetes and the health care team, individualized feedback, use of person-generated health data, and education (46). Continuous glucose monitoring, when combined with individualized diabetes education or behavioral interventions, has demonstrated greater improvement on glycemic and psychosocial outcomes compared with continuous glucose monitoring alone (63,64). Incorporating a systematic approach for technology assessment, adoption, and integration into the care plan may help ensure equity in access and standardized application of technology-enabled solutions (8, 30,65–67).

Research supports diabetes care and education specialists (DCES), including nurses, registered dietitian nutritionists (RDNs), and pharmacists as providers of DSMES who may also tailor curriculum to the person's needs (68–70). Many other health disciplines can also become DCES. Members of the DSMES team should have specialized clinical knowledge in diabetes and behavior change principles. In addition, a DCES needs to be knowledgeable about technology-enabled services and may serve as a technology champion within their practice (65). Certification as a DCES (cbdce.org/) and/or board certification in advanced diabetes management (diabeteseducator.org/education/certification/bc_adm) demonstrates an individual's specialized training in and understanding of diabetes management and support (43), and engagement with qualified professionals has been shown to improve disease-related outcomes. Additionally, there is growing evidence for the role of community health workers (71,72), as well as peer (71–76) and lay leaders (77), in providing ongoing support.

Given individual needs and access to resources, a variety of culturally adapted DSMES programs need to be offered in a variety of settings. The use of technology to facilitate access to DSMES services, support self-management decisions, and decrease therapeutic inertia suggests that these approaches need broader adoption (78). Additionally, it is important

to include social determinants of health (SDOH) of the target population in guiding design and delivery of DSMES. The DSMES team should take into account demographic characteristics such as race, ethnic/cultural background, sex/gender, age, geographic location, technology access, education, literacy, and numeracy (43,79).

Despite the benefits of DSMES, reports indicate that only 5–7% of individuals eligible for DSMES through Medicare or a private insurance plan actually receive it (80,81). Barriers to DSMES exist at the health system, payer, health care professional, and individual levels. This low participation may be due to lack of referral or other identified barriers, such as logistical issues (accessibility, timing, costs) and the lack of a perceived benefit (81). Health system, programmatic, and payer barriers include lack of administrative leadership support, limited numbers of DSMES professionals, not having referral to DSMES services effectively embedded in the health system service structure, and limited reimbursement rates (82). Thus, in addition to educating referring health care professionals about the benefits of DSMES and the critical times to refer, efforts need to be made to identify and address all of the various potential barriers (2). Support from institutional leadership is foundational for the success of DSMES services. Expert stakeholders should also support DSMES by providing input and advocacy (43). Alternative and innovative models of DSMES delivery (56) need to be explored and evaluated, including the integration of technology-enabled diabetes and cardiometabolic health services (8,65). Barriers to equitable access to DSMES may be addressed through telehealth delivery of care and other digital health solutions (43).

Reimbursement

Medicare reimburses DSMES when that service meets the national standards (2,43) and is recognized by the American Diabetes Association (ADA) through the Education Recognition Program (professional.diabetes.org/diabetes-education) or Association of Diabetes Care & Education Specialists (diabeteseducator.org/practice/diabetes-education-accreditation-program). DSMES is also covered by most health insurance plans. Ongoing support has been shown

to be instrumental for improving outcomes when it is implemented after the completion of education services. DSMES is frequently reimbursed when performed in person. However, although DSMES can also be provided via phone calls and telehealth, these remote versions may not always be reimbursed (13). Medicare reimburses remote physiologic monitoring for glucose and other cardiometabolic data if certain conditions are met (83).

Changes in reimbursement policies that increase DSMES access and utilization will result in a positive impact to beneficiaries' clinical outcomes, quality of life, health care utilization, and costs (13,84–86). During the time of the coronavirus disease 2019 (COVID-19) pandemic, reimbursement policies were revised ([professional.diabetes.org/content-page/dsmes-and-mnt-during-covid-19-national-pandemic](https://diabetes.org/content-page/dsmes-and-mnt-during-covid-19-national-pandemic)), and these changes may provide a new reimbursement paradigm for future provision of DSMES through telehealth channels.

MEDICAL NUTRITION THERAPY

Please refer to the ADA consensus report “Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report” for more information on nutrition therapy (70). Despite agreement in nutrition recommendations from large scientific bodies, including the American Heart Association, American College of Lifestyle Medicine, and the U.S. Dietary Guidelines (87–93), confusion and controversy remain. For many individuals with diabetes, the most challenging part of the treatment plan is determining what to eat. There is not a “one-size-fits-all” eating pattern for individuals with diabetes, and meal planning should be individualized. Nutrition therapy plays an integral role in overall diabetes management, and each person with diabetes should be actively engaged in education, self-management, and treatment planning with the health care team, including the collaborative development of an individualized eating plan (70,94). All health care professionals should refer people with diabetes for individualized MNT provided by an RDN who is knowledgeable and skilled in providing diabetes-specific MNT (21,95,96) at diagnosis and as needed throughout the life span, similar to DSMES. MNT delivered by an RDN is associated with A1C absolute decreases of 1.0–1.9% for people

with type 1 diabetes (97) and 0.3–2.0% for people with type 2 diabetes (97). See **Table 5.1** for specific nutrition recommendations. Because of the progressive nature of type 2 diabetes, behavior modification alone may not be adequate to maintain euglycemia over time. However, after medication is initiated, nutrition therapy continues to be an important component, and RDNs providing MNT in diabetes care should assess and monitor medication changes in relation to the nutrition care plan (70,94).

Goals of Nutrition Therapy for Adults With Diabetes

1. To promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, to improve overall health and:
 - achieve and maintain body weight goals
 - attain individualized glycemic, blood pressure, and lipid goals
 - delay or prevent the complications of diabetes
2. To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes, and existing barriers to change
3. To maintain the pleasure of eating by providing nonjudgmental messages about food choices while limiting food choices only when indicated by scientific evidence
4. To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods

Weight Management

Management and reduction of weight is important for people with type 1 diabetes, type 2 diabetes, or prediabetes with overweight or obesity. To support weight loss and improve A1C, cardiovascular disease (CVD) risk factors, and well-being in adults with overweight/obesity and prediabetes or diabetes, MNT and DSMES services should include an individualized eating plan in a format that results in an energy deficit in combination with enhanced physical activity (70). Lifestyle intervention programs should be intensive and have frequent follow-up to achieve significant reductions in excess body

weight and improve clinical indicators. There is strong and consistent evidence that modest, sustained weight loss can delay the progression from prediabetes to type 2 diabetes (97–99) (see Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities”) and is beneficial for the management of type 2 diabetes (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”).

In prediabetes, the weight loss goal is 7–10% for preventing progression to type 2 diabetes (100). In conjunction with support for healthy lifestyle behaviors, medication-assisted weight loss can be considered for people at risk for type 2 diabetes when needed to achieve and sustain 7–10% weight loss (101,102) (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”). People with prediabetes at a healthy weight should also be considered for behavioral interventions to help establish routine aerobic and resistance exercise (100,103,104) as well as to establish healthy eating patterns. Services delivered by practitioners familiar with diabetes and its management, such as an RDN, have been found to be effective (95).

For many individuals with overweight and obesity with type 2 diabetes, 5% weight loss is needed to achieve beneficial outcomes in glycemic control, lipids, and blood pressure (105). It should be noted, however, that the clinical benefits of weight loss are progressive, and more intensive weight loss goals (i.e., 15%) may be appropriate to maximize benefit depending on need, feasibility, and safety (106,107). Long-term durability of weight loss remains a challenge; however, newer medications (beyond metabolic surgery) may have potential for sustainability, impact on cardiovascular outcomes, and weight reduction beyond 10–15% (108–111).

In select individuals with type 2 diabetes, an overall healthy eating plan that results in energy deficit in conjunction with weight loss medications and/or metabolic surgery should be considered to help achieve weight loss and maintenance goals, lower A1C, and reduce CVD risk (101,112,113). Overweight and obesity are also increasingly prevalent in people with type 1 diabetes and present clinical challenges regarding diabetes treatment and CVD risk factors (114,115). Sustaining weight loss can be challenging

(105,116) but has long-term benefits; maintaining weight loss for 5 years is associated with sustained improvements in A1C and lipid levels (117). MNT guidance from an RDN with expertise in diabetes and weight management throughout the course of a structured weight loss plan is strongly recommended.

Along with routine medical management visits, people with diabetes and prediabetes should be screened during DSMES and MNT encounters for a history of dieting and past or current disordered eating behaviors. Nutrition therapy should be individualized to help address maladaptive eating behavior (e.g., purging) or compensatory changes in medical treatment plan (e.g., overtreatment of hypoglycemic episodes, reduction in medication dosing to reduce hunger) (70) (see DISORDERED EATING BEHAVIOR, below). Disordered eating, eating disorders, and/or disrupted eating can increase challenges for weight and diabetes management. For example, caloric restriction may be essential for glycemic management and weight maintenance, but rigid meal plans may be contraindicated for individuals who are at increased risk of clinically significant maladaptive eating behaviors (118). If eating disorders are identified during screening with diabetes-specific questionnaires, individuals should be referred to a qualified mental health professional (1).

Studies have demonstrated that a variety of eating plans, varying in macronutrient composition, can be used effectively and safely in the short term (1–2 years) to achieve weight loss in people with diabetes. These plans include structured low-calorie meal plans with meal replacements (106,117,119), a Mediterranean eating pattern (120), and low-carbohydrate meal plans with additional support (121,122). However, no single approach has been proven to be consistently superior (70,123–125), and more data are needed to identify and validate those meal plans that are optimal with respect to long-term outcomes and acceptability. The importance of providing guidance on an individualized meal plan containing nutrient-dense foods, such as vegetables, fruits, legumes, dairy, lean sources of protein (including plant-based sources as well as lean meats, fish, and poultry), nuts, seeds, and whole grains, cannot be overemphasized (124), as well as guidance on achieving the

Table 5.1—Medical nutrition therapy recommendations

	Recommendations
Effectiveness of nutrition therapy	<p>5.10 An individualized medical nutrition therapy program as needed to achieve treatment goals, provided by a registered dietitian nutritionist, preferably one who has comprehensive knowledge and experience in diabetes care, is recommended for all people with type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus. A</p> <p>5.11 Because diabetes medical nutrition therapy can result in cost savings B and improved cardiometabolic outcomes A, medical nutrition therapy should be adequately reimbursed by insurance and other payers. E</p>
Energy balance	<p>5.12 For all people with overweight or obesity, behavioral modification to achieve and maintain a minimum weight loss of 5% is recommended. A</p>
Eating patterns and macronutrient distribution	<p>5.13 There is no ideal macronutrient pattern for people with diabetes; meal plans should be individualized while keeping nutrient quality, total calorie, and metabolic goals in mind. E</p> <p>5.14 A variety of eating patterns can be considered for the management of type 2 diabetes and to prevent diabetes in individuals with prediabetes. B</p> <p>5.15 Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied to a variety of eating patterns that meet individual needs and preferences. B</p>
Carbohydrates	<p>5.16 Carbohydrate intake should emphasize nutrient-dense carbohydrate sources that are high in fiber (at least 14 g fiber per 1,000 kcal) and minimally processed. Eating plans should emphasize nonstarchy vegetables, fruits, legumes, and whole grains, as well as dairy products, with minimal added sugars. B</p> <p>5.17 People with diabetes and those at risk are advised to replace sugar-sweetened beverages (including fruit juices) with water or low calorie, no calorie beverages as much as possible to manage glycemia and reduce risk for cardiometabolic disease B and minimize consumption of foods with added sugar that have the capacity to displace healthier, more nutrient-dense food choices. A</p> <p>5.18 When using a flexible insulin therapy program, education on the glycemic impact of carbohydrate A, fat, and protein B should be tailored to an individual's needs and preferences and used to optimize mealtime insulin dosing.</p> <p>5.19 When using fixed insulin doses, individuals should be provided with education about consistent patterns of carbohydrate intake with respect to time and amount while considering the insulin action time, as it can result in improved glycemia and reduce the risk for hypoglycemia. B</p>
Protein	<p>5.20 In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations. Therefore, carbohydrate sources high in protein should be avoided when trying to treat or prevent hypoglycemia. B</p>
Dietary fat	<p>5.21 An eating plan emphasizing elements of a Mediterranean eating pattern rich in monounsaturated and polyunsaturated fats may be considered to improve glucose metabolism and lower cardiovascular disease risk. B</p> <p>5.22 Eating foods rich in long-chain n-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA), is recommended to prevent or treat cardiovascular disease. B</p>
Micronutrients and herbal supplements	<p>5.23 There is no clear evidence that dietary supplementation with vitamins, minerals (such as chromium and vitamin D), herbs, or spices (such as cinnamon or aloe vera) can improve outcomes in people with diabetes who do not have underlying deficiencies, and they are not generally recommended for glycemic control. C There may be evidence of harm for certain individuals with β carotene supplementation. B</p>
Alcohol	<p>5.24 Adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for adult women and no more than two drinks per day for adult men). C</p> <p>5.25 Educating people with diabetes about the signs, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially when using insulin or insulin secretagogues, is recommended. The importance of glucose monitoring after drinking alcoholic beverages to reduce hypoglycemia risk should be emphasized. B</p>
Sodium	<p>5.26 Sodium consumption should be limited to <2,300 mg/day. B</p>
Nonnutritive sweeteners	<p>5.27 The use of nonnutritive sweeteners as a replacement for sugar-sweetened products may reduce overall calorie and carbohydrate intake as long as there is not a compensatory increase in energy intake from other sources. There is evidence that low- and no-calorie sweetened beverages are a viable alternative to water. B</p>

desired energy deficit (126–129). Any approach to meal planning should be individualized, considering the health status, personal preferences, and ability of the person with diabetes to sustain the recommendations in the plan.

Eating Patterns and Meal Planning

Evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for people with diabetes. Therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals. Dietary guidance should emphasize the importance of a healthy dietary pattern as a whole rather than focusing on individual nutrients, foods, or food groups, given that individuals rarely eat foods in isolation. Personal preferences (e.g., tradition, culture, religion, health beliefs and goals, economics), as well as metabolic goals, need to be considered when working with individuals to determine the best eating pattern (70,97,130). Members of the health care team should complement MNT by providing evidence-based guidance that helps people with diabetes make healthy food choices that meet their individualized needs and improve overall health. A variety of eating patterns are acceptable for the management of diabetes (70,97,131,132). Health care professionals should focus on the core dimensions common among the patterns: 1) emphasize nonstarchy vegetables, 2) minimize added sugars and refined grains, and 3) choose whole foods over highly processed foods to the extent possible (70). An individualized eating pattern also considers the individual's health status, food and numeracy skills, resources, food preferences, health goals, and food access. Any member of the health care team can screen for food insecurity using The Hunger Vital Sign. Households are considered at risk if they answer either or both of the following statements as "often true" or "sometimes true" (compared with "never true") (133):

- "Within the past 12 months, we worried whether our food would run out before we got money to buy more."
- "Within the past 12 months, the food we bought just didn't last, and we didn't have money to get more."

Referral to an RDN is essential to assess the overall nutrition status of, and to work collaboratively with, the person with diabetes to create a personalized meal plan that coordinates and aligns with the overall treatment plan, including physical activity and medication use. The Mediterranean (130,134–136), low-carbohydrate (137–139), and vegetarian or plant-based (135,136,140,141) eating patterns are all examples of healthful eating patterns that have shown positive results in research for individuals with type 2 diabetes, but individualized meal planning should focus on personal preferences, needs, and goals. There is currently inadequate research in type 1 diabetes to support one eating pattern over another. Moreover, there is a paucity of evidence and agreement as it relates to nutrition management among children and adolescents with type 1 diabetes. There remains a significant gap in the literature as it relates to the efficacy and long-term management implications of nutrition interventions for young children with type 1 diabetes (142).

For individuals with type 2 diabetes not meeting glycemic targets or for whom reducing glucose-lowering drugs is a priority, reducing overall carbohydrate intake with a low- or very-low-carbohydrate eating pattern is a viable option (137–139). As research studies on low-carbohydrate eating plans generally indicate challenges with long-term sustainability (143), it is important to reassess and individualize meal plan guidance regularly for those interested in this approach. In response to questions regarding implementation of low-carbohydrate and very-low-carbohydrate eating patterns, the ADA has developed a guide for health care professionals that may assist in the practical implementation of these eating patterns (144). Most individuals with diabetes report a moderate intake of carbohydrates (44–46% of total calories) (97,144). Efforts to modify habitual eating patterns are often unsuccessful in the long term; people generally go back to their usual macronutrient distribution (97). Thus, the recommended approach is to individualize meal plans with a macronutrient distribution that is more consistent with personal preference and usual intake to increase the likelihood for long-term maintenance.

An RCT found that two meal-planning approaches (diabetes plate method and

carbohydrate counting) were effective in helping achieve improved A1C (145). The diabetes plate method is a commonly used visual approach for providing basic meal planning guidance. This simple graphic (featuring a 9-inch plate) shows how to portion foods (1/2 of the plate for nonstarchy vegetables, 1/4 of the plate for protein, and 1/4 of the plate for carbohydrates). Carbohydrate counting is a more advanced skill that helps plan for and track how much carbohydrate is consumed at meals and snacks. Meal planning approaches should be customized to the individual, including their numeracy (145) and food literacy level. Food literacy generally describes proficiency in food-related knowledge and skills that ultimately impact health, although specific definitions vary across initiatives (146,147).

There has been an increased interest in time-restricted eating and intermittent fasting as strategies for weight management. Intermittent fasting is an umbrella term which includes three main forms of restricted eating: alternate-day fasting (energy restriction of 500–600 calories on alternate days), the 5:2 diet (energy restriction of 500–600 calories on consecutive or nonconsecutive days) with usual intake the other five, and time-restricted eating (daily calorie restriction based on window of time of 8–15 h). Each produces mild to moderate weight loss (3–8% loss from baseline) over short durations (8–12 weeks) with no significant differences in weight loss when compared with continuous calorie restriction (148–151). A few studies have extended up to 52 weeks and show similar findings (152–155). Time-restricted eating (shortening the eating window) is generally easier to follow compared with alternate-day fasting or the 5:2 plan, largely due to ease, no need to count calories, sustainability, and feasibility. This may have implications as people with diabetes are looking for practical eating management tools.

Carbohydrates

Studies examining the ideal amount of carbohydrate intake for people with diabetes are inconclusive, although monitoring carbohydrate intake and considering the blood glucose response to dietary carbohydrate are key for improving postprandial glucose management

(156,157). The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, often with varying definitions of low- and high-glycemic-index foods (158,159). The glycemic index ranks carbohydrate foods on their postprandial glycemic response, and glycemic load takes into account both the glycemic index of foods and the amount of carbohydrate eaten. Studies have found mixed results regarding the effect of glycemic index and glycemic load on fasting glucose levels and A1C, with one systematic review finding no significant impact on A1C (160) while others demonstrated A1C reductions of 0.15% (158) to 0.5% (161,162).

Reducing overall carbohydrate intake for individuals with diabetes has demonstrated evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences (70). For people with type 2 diabetes, low-carbohydrate and very-low-carbohydrate eating patterns in particular have been found to reduce A1C and the need for antihyperglycemic medications (70,130,143,163–165). Systematic reviews and meta-analyses of RCTs found carbohydrate-restricted eating patterns, particularly those considered low carbohydrate (<26% total energy), were effective in reducing A1C in the short term (<6 months), with less difference in eating patterns beyond 1 year (125,126, 137,138,164). Questions still remain about the optimal degree of carbohydrate restriction and the long-term effects of those meal patterns on cardiovascular disease. A systematic review and meta-analysis of RCTs investigating the dose-dependent effect of carbohydrate restriction on metabolic control found each 10% decrease in carbohydrate intake had reductions in levels of A1C, fasting plasma glucose, body weight, lipids, and systolic blood pressure at 6 months, but favorable effects diminished and were not maintained at follow-up or at greater than 12 months. This systematic review highlights the metabolic complexity of response to dietary intervention in type 2 diabetes as well as the need to better understand longer-term sustainability and results (166). Part of the challenge in interpreting low-carbohydrate research has been due to the wide range of definitions for a low-carbohydrate eating plan (139,161). Weight reduction was also a goal in many low-carbohydrate

studies, which further complicates evaluating the distinct contribution of the eating pattern (47,121,125,167).

The quality of carbohydrate and/or what is absent from the diet may contribute to confounding results. However, when core dimensions of the comparative diets are similar, there is little difference in outcome measures. When Gardner et al. (168) tested a low-carbohydrate ketogenic diet and a low-carbohydrate Mediterranean diet, in a randomized crossover design, metabolic improvements were seen in both diets without significant differences between them. Each of the interventions avoided added sugars and refined grains and included nonstarchy vegetables. Legumes, fruits, and whole intact grains were included in the Mediterranean but not in the ketogenic diet. The improvements (fasting glucose, insulin, HDL cholesterol, and A1C) were likely due to the nutritional quality of both interventions. However, the ketogenic plan led to a greater decrease in triglycerides (168) but also a greater increase in LDL cholesterol.

As studies on low-carbohydrate eating plans generally indicate challenges with long-term sustainability (143), it is important to reassess and individualize meal plan guidance regularly for those interested in this approach. Health care professionals should maintain consistent medical oversight and recognize that insulin and other diabetes medications may need to be adjusted to prevent hypoglycemia, and blood pressure will need to be monitored. In addition, very-low-carbohydrate eating plans are not currently recommended for individuals who are pregnant or lactating, children, people who have renal disease, or people with or at risk for disordered eating, and these plans should be used with caution in those taking sodium-glucose cotransporter 2 inhibitors because of the potential risk of ketoacidosis (169,170).

Regardless of amount of carbohydrate in the meal plan, focus should be placed on high-quality, nutrient-dense carbohydrate sources that are high in fiber and minimally processed. The addition of dietary fiber modulates composition of gut microbiota and increases gut microbial diversity. Although there is still much to be elucidated with the gut microbiome and chronic disease, higher-fiber diets are advantageous (171). Both children and adults with diabetes are encouraged to

minimize intake of refined carbohydrates with added sugars, fat, and sodium and instead focus on carbohydrates from vegetables, legumes, fruits, dairy (milk and yogurt), and whole grains. People with diabetes and those at risk for diabetes are encouraged to consume a minimum of 14 g of fiber/1,000 kcal, with at least half of grain consumption being whole, intact grains, according to the Dietary Guidelines for Americans (172). Regular intake of sufficient dietary fiber is associated with lower all-cause mortality in people with diabetes (173,174), and prospective cohort studies have found dietary fiber intake is inversely associated with risk of type 2 diabetes (175–177). The consumption of sugar-sweetened beverages and processed food products with large amounts of refined grains and added sugars is strongly discouraged (172,178,179), as these have the capacity to displace healthier, more nutrient-dense food choices.

Individuals with type 1 or type 2 diabetes taking insulin at mealtime should be offered intensive and ongoing education on the need to couple insulin administration with carbohydrate intake. For people whose meal schedule or carbohydrate consumption is variable, regular education to increase understanding of the relationship between carbohydrate intake and insulin needs is important. In addition, education on using insulin-to-carbohydrate ratios for meal planning can assist individuals with effectively modifying insulin dosing from meal to meal to improve glycemic management (97,156,180–183). Studies have shown that dietary fat and protein can impact early and delayed postprandial glycemia (184–187), and it appears to have a dose-dependent response (188–191). Results from high-fat, high-protein meal studies highlight the need for additional insulin to cover these meals; however, more studies are needed to determine the optimal insulin dose and delivery strategy. The results from these studies also point to individual differences in postprandial glycemic response; therefore, a cautious approach to increasing insulin doses for high-fat and/or high-protein mixed meals is recommended to address delayed hyperglycemia that may occur 3 h or more after eating (70). If using an insulin pump, a split bolus feature (part of the bolus delivered immediately, the remainder over a programmed duration of time) may provide

better insulin coverage for high-fat and/or high-protein mixed meals (185,192).

The effectiveness of insulin dosing decisions should be confirmed with a structured approach to blood glucose monitoring or continuous glucose monitoring to evaluate individual responses and guide insulin dose adjustments. Checking glucose 3 h after eating may help to determine if additional insulin adjustments are required (i.e., increasing or stopping bolus) (185,192,193). Refining insulin doses to account for high-fat and/or -protein meals requires determination of anticipated nutrient intake to calculate the mealtime dose. Food literacy, numeracy, interest, and capability should be evaluated (70). For individuals on a fixed daily insulin schedule, meal planning should emphasize a relatively fixed carbohydrate consumption pattern with respect to both time and amount while considering insulin action. Attention to resultant hunger and satiety cues will also help with nutrient modifications throughout the day (70,194).

Protein

There is no evidence that adjusting the daily level of protein intake (typically 1–1.5 g/kg body wt/day or 15–20% total calories) will improve health, and research is inconclusive regarding the ideal amount of dietary protein to optimize either glycemic management or CVD risk (159,195). Therefore, protein intake goals should be individualized based on current eating patterns. Some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety (196).

Historically, low-protein eating plans were advised for individuals with diabetic kidney disease (DKD) (with albuminuria and/or reduced estimated glomerular filtration rate); however, current evidence does not suggest that people with DKD need to restrict protein to less than the generally recommended protein intake (70). Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the rate at which glomerular filtration rate declines and may increase risk for malnutrition (197,198).

In individuals with type 2 diabetes, protein intake may enhance or increase the insulin response to dietary carbohydrates (199). Therefore, use of carbohydrate sources high in protein (e.g., nuts) to treat or prevent hypoglycemia should be avoided due to the potential concurrent rise in endogenous insulin. Health care professionals should counsel patients to treat hypoglycemia with pure glucose (i.e., glucose tablets) or carbohydrate-containing foods at the hypoglycemia alert value of <70 mg/dL. See Section 6, “Glycemic Targets,” for more information.

Fats

Evidence suggests that there is not an ideal percentage of calories from fat for people with or at risk for diabetes and that macronutrient distribution should be individualized according to the patient’s eating patterns, preferences, and metabolic goals (70). The type of fats consumed is more important than total amount of fat when looking at metabolic goals and CVD risk, and it is recommended that the percentage of total calories from saturated fats should be limited (120,172,200–202). Multiple RCTs including people with type 2 diabetes have reported that a Mediterranean eating pattern (120,203–208) can improve both glycemic management and blood lipids. The Mediterranean eating pattern is based on the traditional eating habits in the countries bordering the Mediterranean Sea. Although eating styles vary, they share a number of common features, including consumption of fresh fruits and vegetables, whole grains, beans, and nuts/seeds; olive oil as the primary fat source; low to moderate amounts of fish, eggs, and poultry; and limited added sugars, sugary beverages, sodium, highly processed foods, refined carbohydrates, saturated fats, and fatty or processed meats.

Evidence does not conclusively support recommending n-3 (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) supplements for all people with diabetes for the prevention or treatment of cardiovascular events (70,209,210). In individuals with type 2 diabetes, two systematic reviews with n-3 and n-6 fatty acids concluded that the dietary supplements did not improve glycemic management (159,211). In the ASCEND trial (A Study of Cardiovascular Events in Diabetes), when

compared with placebo, supplementation with n-3 fatty acids at the dose of 1 g/day did not lead to cardiovascular benefit in people with diabetes without evidence of CVD (212). However, results from the Reduction of Cardiovascular Events With Icosapent Ethyl—Intervention Trial (REDUCE-IT) found that supplementation with 4 g/day of pure EPA significantly lowered the risk of adverse cardiovascular events. This trial of 8,179 participants, in which over 50% had diabetes, found a 5% absolute reduction in cardiovascular events for individuals with established atherosclerotic CVD taking a preexisting statin with residual hypertriglyceridemia (135–499 mg/dL) (213). See Section 10, “Cardiovascular Disease and Risk Management,” for more information. People with diabetes should be advised to follow the guidelines for the general population for the recommended intakes of saturated fat, dietary cholesterol, and *trans* fat (172). *Trans* fats should be avoided. In addition, as saturated fats are progressively decreased in the diet, they should be replaced with unsaturated fats and not with refined carbohydrates (207).

Sodium

As for the general population, people with diabetes are advised to limit their sodium consumption to <2,300 mg/day (70). Restriction to <1,500 mg, even for those with hypertension, is generally not recommended (214–216). Sodium recommendations should take into account palatability, availability, affordability, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate diet (217).

Micronutrients and Supplements

There continues to be no clear evidence of benefit from herbal or nonherbal (i.e., vitamin or mineral) supplementation for people with diabetes without underlying deficiencies (70). Metformin is associated with vitamin B12 deficiency per a report from the Diabetes Prevention Program Outcomes Study (DPPOS), suggesting that periodic testing of vitamin B12 levels should be considered in people taking metformin, particularly in those with anemia or peripheral neuropathy (218). Routine supplementation with antioxidants, such as vitamins E and C, is not advised due to lack of evidence of efficacy and

concern related to long-term safety. Based on the recent U.S. Preventative Services Task Force statement, the harms of β -carotene outweigh the benefits for the prevention of CVD or cancer. β -Carotene was significantly associated with increased lung cancer and cardiovascular mortality risk (219).

In addition, there is insufficient evidence to support the routine use of herbal supplements and micronutrients, such as cinnamon (220), curcumin, vitamin D (221), aloe vera, or chromium, to improve glycemia in people with diabetes (70,222).

Although the Vitamin D and Type 2 Diabetes Study (D2d) prospective RCT showed no significant benefit of vitamin D versus placebo on the progression to type 2 diabetes in individuals at high risk (223), post hoc analyses and meta-analyses suggest a potential benefit in specific populations (223–226). Further research is needed to define individual characteristics and clinical indicators where vitamin D supplementation may be of benefit.

For special populations, including pregnant or lactating individuals, older adults, vegetarians, and people following very-low-calorie or low-carbohydrate diets, a multivitamin may be necessary.

Alcohol

Moderate alcohol intake does not have major detrimental effects on long-term blood glucose management in people with diabetes. Risks associated with alcohol consumption include hypoglycemia and/or delayed hypoglycemia (particularly for those using insulin or insulin secretagogue therapies), weight gain, and hyperglycemia (for those consuming excessive amounts) (70,222). People with diabetes should be educated about these risks and encouraged to monitor glucose frequently after drinking alcohol to minimize such risks. People with diabetes can follow the same guidelines as those without diabetes. For women, no more than one drink per day, and for men, no more than two drinks per day is recommended (one drink is equal to a 12-oz beer, a 5-oz glass of wine, or 1.5 oz of distilled spirits).

Nonnutritive Sweeteners

The U.S. Food and Drug Administration has approved many nonnutritive sweeteners for consumption by the general

public, including people with diabetes (70,227). For some people with diabetes who are accustomed to regularly consuming sugar-sweetened products, nonnutritive sweeteners (containing few or no calories) may be an acceptable substitute for nutritive sweeteners (those containing calories, such as sugar, honey, and agave syrup) when consumed in moderation (228,229). Nonnutritive sweeteners do not appear to have a significant effect on glycemic management (97,230,231), and they can reduce overall calorie and carbohydrate intake (97,228) as long as individuals are not compensating with additional calories from other food sources (70,232). There is mixed evidence from systematic reviews and meta-analyses for nonnutritive sweetener use with regard to weight management, with some finding benefit in weight loss (233–235) while other research suggests an association with weight gain (236,237). This may be explained by reverse causality and residual confounding variables (237). The addition of nonnutritive sweeteners to diets poses no benefit for weight loss or reduced weight gain without energy restriction (238). In a recent systematic review and meta-analysis using low-calorie and no-calorie sweetened beverages as an intended substitute for sugar-sweetened beverages, a small improvement in body weight and cardiometabolic risk factors was seen without evidence of harm and had a direction of benefit similar to that seen with water. Health care professionals should continue to recommend water, but people with overweight or obesity and diabetes may also have a variety of no-calorie or low-calorie sweetened products so that they do not feel deprived (239).

PHYSICAL ACTIVITY

Recommendations

- 5.28** Children and adolescents with type 1 diabetes **C** or type 2 diabetes or prediabetes **B** should engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week.
- 5.29** Most adults with type 1 diabetes **C** and type 2 diabetes **B** should engage in 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread

over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.

- 5.30** Adults with type 1 diabetes **C** and type 2 diabetes **B** should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.
- 5.31** All adults, and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior. **B** Prolonged sitting should be interrupted every 30 min for blood glucose benefits. **C**
- 5.32** Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance. **C**
- 5.33** Evaluate baseline physical activity and sedentary time. Promote increase in nonsedentary activities above baseline for sedentary individuals with type 1 diabetes **E** and type 2 diabetes. **B** Examples include walking, yoga, housework, gardening, swimming, and dancing.

Physical activity is a general term that includes all movement that increases energy use and is an important part of the diabetes management plan. Exercise is a more specific form of physical activity that is structured and designed to improve physical fitness. Both physical activity and exercise are important. Exercise has been shown to improve blood glucose levels, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being (240). Physical activity is as important for those with type 1 diabetes as it is for the general population, but its specific role in the prevention of diabetes complications and the management of blood glucose is not as clear as it is for those with type 2 diabetes. Many individuals with type 2 diabetes do not meet the recommended exercise level per week (150 min).

Objective measurement by accelerometer in 871 individuals with type 2 diabetes showed that 44.2%, 42.6%, and 65.1% of White, African American, and Hispanic individuals, respectively, met the recommended threshold of exercise (241). An RCT in 1,366 individuals with prediabetes combined a physical activity intervention with text messaging and telephone support, which showed improvement in daily step count at 12 months compared with the control group. Unfortunately, this was not sustained at 48 months (242). Another RCT, including 324 individuals with prediabetes, showed increased physical activity at 8 weeks with supportive text messages, but by 12 weeks there was no difference between groups (243). It is important for diabetes care management teams to understand the difficulty that many people have reaching recommended treatment targets and to identify individualized approaches to improve goal achievement, which may need to change over time.

Moderate to high volumes of aerobic activity are associated with substantially lower cardiovascular and overall mortality risks in both type 1 and type 2 diabetes (244). A prospective observational study of adults with type 1 diabetes suggested that higher amounts of physical activity led to reduced cardiovascular mortality after a mean follow-up time of 11.4 years for people with and without chronic kidney disease (245). Additionally, structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even without a significant change in BMI (246). There are also considerable data for the health benefits (e.g., increased cardiovascular fitness, greater muscle strength, improved insulin sensitivity) of regular exercise for those with type 1 diabetes (247). Exercise training in type 1 diabetes may also improve several important markers such as triglyceride level, LDL cholesterol, waist circumference, and body mass (248). In adults with type 2 diabetes, higher levels of exercise intensity are associated with greater improvements in A1C and in cardiorespiratory fitness (249); sustained improvements in cardiorespiratory fitness and weight loss have also been associated with a lower risk of heart failure (250). Other benefits include slowing the decline in mobility among overweight people

with diabetes (251). The ADA position statement "Physical Activity/Exercise and Diabetes" reviews the evidence for the benefits of exercise in people with type 1 and type 2 diabetes and offers specific recommendations (252). Increased physical activity (soccer training) has also been shown to be beneficial for improving overall fitness in Latino men with obesity, demonstrating feasible methods to increase physical activity in an often hard-to-engage population (253). Physical activity and exercise should be recommended and prescribed to all individuals who are at risk for or with diabetes as part of management of glycemia and overall health. Specific recommendations and precautions will vary by the type of diabetes, age, activity, and presence of diabetes-related health complications. Recommendations should be tailored to meet the specific needs of each individual (252).

Exercise and Children

All children, including children with diabetes or prediabetes, should be encouraged to engage in regular physical activity. Children should engage in at least 60 min of moderate to vigorous aerobic activity every day, with muscle- and bone-strengthening activities at least 3 days per week (254). In general, youth with type 1 diabetes benefit from being physically active, and an active lifestyle should be recommended to all (255). Youth with type 1 diabetes who engage in more physical activity may have better health outcomes and health-related quality of life (256,257). See Section 14, "Children and Adolescents," for details.

Frequency and Type of Physical Activity

People with diabetes should perform aerobic and resistance exercise regularly (209). Aerobic activity bouts should ideally last at least 10 min, with the goal of ~30 min/day or more most days of the week for adults with type 2 diabetes. Daily exercise, or at least not allowing more than 2 days to elapse between exercise sessions, is recommended to decrease insulin resistance, regardless of diabetes type (258,259). A study in adults with type 1 diabetes found a dose-response inverse relationship between self-reported bouts of physical activity per week and A1C, BMI, hypertension, dyslipidemia, and diabetes-related complications such as hypoglycemia, diabetic

ketoacidosis, retinopathy, and microalbuminuria (260). Over time, activities should progress in intensity, frequency, and/or duration to at least 150 min/week of moderate-intensity exercise. Adults able to run at 6 miles/h (9.7 km/h) for at least 25 min can benefit sufficiently from shorter-intensity activity (75 min/week) (252). Many adults, including most with type 2 diabetes, may be unable or unwilling to participate in such intense exercise and should engage in moderate exercise for the recommended duration. Adults with diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days (261). Although heavier resistance training with free weights and weight machines may improve glycemic control and strength (262), resistance training of any intensity is recommended to improve strength, balance, and the ability to engage in activities of daily living throughout the life span. Health care professionals should help people with diabetes set stepwise goals toward meeting the recommended exercise targets. As individuals intensify their exercise program, medical monitoring may be indicated to ensure safety and evaluate the effects on glucose management. (See PHYSICAL ACTIVITY AND GLYCEMIC CONTROL, below.)

Evidence supports that all individuals, including those with diabetes, should be encouraged to reduce the amount of time spent being sedentary—waking behaviors with low energy expenditure (e.g., working at a computer, watching television)—by breaking up bouts of sedentary activity (>30 min) by briefly standing, walking, or performing other light physical activities (263,264). Participating in leisure-time activity and avoiding extended sedentary periods may help prevent type 2 diabetes for those at risk (265,266) and may also aid in glycemic management for those with diabetes.

A systematic review and meta-analysis found higher frequency of regular leisure-time physical activity was more effective in reducing A1C levels (267). A wide range of activities, including yoga, tai chi, and other types, can have significant impacts on A1C, flexibility, muscle strength, and balance (240,268–270). Flexibility and balance exercises may be particularly important in older adults with diabetes to maintain range of motion, strength, and balance (252) (Fig. 5.1).

Physical Activity and Glycemic Management

Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes (252) and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (271). If not contraindicated, people with type 2 diabetes should be encouraged to do at least two weekly sessions of resistance exercise (exercise with free weights or weight machines), with each session consisting of at least one set (group of consecutive repetitive exercise motions) of five or more different resistance exercises involving the large muscle groups (272).

For people with type 1 diabetes, although exercise, in general, is associated with improvement in disease status, care needs to be taken in titrating exercise with respect to glycemic management. Each individual with type 1 diabetes has a variable glycemic response to exercise. This variability should be taken into consideration when recommending the type and duration of exercise for a given individual (247).

Individuals of childbearing potential with preexisting diabetes, particularly type 2 diabetes, and those at risk for or presenting with gestational diabetes mellitus should be advised to engage in regular moderate physical activity prior to and during their pregnancies as tolerated (252).

Pre-exercise Evaluation

As discussed more fully in Section 10, "Cardiovascular Disease and Risk Management," the best protocol for assessing asymptomatic people with diabetes for coronary artery disease remains unclear. The ADA consensus report "Screening for Coronary Artery Disease in Patients With Diabetes" (273) concluded that routine testing is not recommended. However, health care professionals should perform a careful history, assess cardiovascular risk factors, and be aware of the atypical presentation of coronary artery disease, such as recent reported or tested decrease in exercise tolerance in people with diabetes. Certainly, those with high risk should be encouraged to start with short periods of low-intensity exercise and slowly increase the intensity and duration as tolerated. Health care professionals should assess for conditions that might contraindicate certain types of exercise or predispose to

injury, such as uncontrolled hypertension, untreated proliferative retinopathy, autonomic neuropathy, peripheral neuropathy, and a history of foot ulcers or Charcot foot. Age and previous physical activity level should be considered when customizing the exercise plan to the individual's needs. Those with complications may need a more thorough evaluation prior to starting an exercise program (247).

Hypoglycemia

In individuals taking insulin and/or insulin secretagogues, physical activity may cause hypoglycemia if the medication dose or carbohydrate consumption is not adjusted for the exercise bout and postbout impact on glucose. Individuals on these therapies may need to ingest some added carbohydrate if pre-exercise glucose levels are <90 mg/dL (5.0 mmol/L), depending on whether they are able to lower insulin doses during the workout (such as with an insulin pump or reduced pre-exercise insulin dosage), the time of day exercise is done, and the intensity and duration of the activity (247). In some people with diabetes, hypoglycemia after exercise may occur and last for several hours due to increased insulin sensitivity. Hypoglycemia is less common in those who are not treated with insulin or insulin secretagogues, and no routine preventive measures for hypoglycemia are usually advised in these cases. Intense activities may actually raise blood glucose levels instead of lowering them, especially if pre-exercise glucose levels are elevated (247). Because of the variation in glycemic response to exercise bouts, people with diabetes need to be educated to check blood glucose levels before and after periods of exercise and about the potential prolonged effects (depending on intensity and duration).

Exercise in the Presence of Microvascular Complications

See Section 11, "Chronic Kidney Disease and Risk Management," and Section 12, "Retinopathy, Neuropathy, and Foot Care," for more information on these long-term complications.

Retinopathy

If proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy is present, then vigorous-intensity aerobic or resistance exercise may be

contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (274). Consultation with an ophthalmologist prior to engaging in an intense exercise plan may be appropriate.

Peripheral Neuropathy

Decreased pain sensation and a higher pain threshold in the extremities can result in an increased risk of skin breakdown, infection, and Charcot joint destruction with some forms of exercise. Therefore, a thorough assessment should be done to ensure that neuropathy does not alter kinesthetic or proprioceptive sensation during physical activity, particularly in those with more severe neuropathy. Studies have shown that moderate-intensity walking may not lead to an increased risk of foot ulcers or reulceration in those with peripheral neuropathy who use proper footwear (275). In addition, 150 min/week of moderate exercise was reported to improve outcomes in people with prediabetic neuropathy (276). All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non-weight-bearing activities.

Autonomic Neuropathy

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and greater susceptibility to hypoglycemia (277). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (278). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Diabetic Kidney Disease

Physical activity can acutely increase urinary albumin excretion. However, there is no evidence that vigorous-intensity exercise accelerates the rate of progression of DKD, and there appears to be no need for specific exercise restrictions for people with DKD in general (274).

SMOKING CESSATION: TOBACCO AND E-CIGARETTES

Recommendations

- 5.34** Advise all individuals not to use cigarettes and other tobacco products or e-cigarettes. **A**
- 5.35** After identification of tobacco or e-cigarette use, include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. **A**
- 5.36** Address smoking cessation as part of diabetes education programs for those in need. **B**

Results from epidemiologic, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and health risks (279). Data show tobacco use is higher among adults with chronic conditions (280) as well as in adolescents and young adults with diabetes (281). People with diabetes who smoke (and people with diabetes exposed to second-hand smoke) have a heightened risk of CVD, premature death, microvascular complications, and worse glycemic outcomes when compared with those who do not smoke (282–284). Smoking may have a role in the development of type 2 diabetes (285–287).

The routine and thorough assessment of tobacco use is essential to prevent smoking or encourage cessation. Numerous large RCTs have demonstrated the efficacy and cost-effectiveness of brief counseling in smoking cessation, including the use of telephone quit lines, in reducing tobacco use. Pharmacologic therapy to assist with smoking cessation in people with diabetes has been shown to be effective (288), and for people who are motivated to quit, the addition of pharmacologic therapy to counseling is more effective than either treatment alone (289). Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse (290). Although some people may gain weight in the period shortly after smoking cessation (291), recent research has demonstrated that this weight gain does not diminish the substantial CVD benefit realized from smoking cessation (292). One study in people who smoke who had newly diagnosed type 2 diabetes found that smoking cessation

was associated with amelioration of metabolic parameters and reduced blood pressure and albuminuria at 1 year (293).

In recent years, e-cigarettes have gained public awareness and popularity because of perceptions that e-cigarette use is less harmful than regular cigarette smoking (294,295). However, in light of recent Centers for Disease Control and Prevention evidence (296) of deaths related to e-cigarette use, no individuals should be advised to use e-cigarettes, either as a way to stop smoking tobacco or as a recreational drug.

Diabetes education programs offer potential to systematically reach and engage individuals with diabetes in smoking cessation efforts. A cluster randomized trial found statistically significant increases in quit rates and long-term abstinence rates (>6 months) when smoking cessation interventions were offered through diabetes education clinics, regardless of motivation to quit at baseline (297).

SUPPORTING POSITIVE HEALTH BEHAVIORS

Recommendation

- 5.37** Behavioral strategies should be used to support diabetes self-management and engagement in health behaviors (e.g., taking medications, using diabetes technologies, physical activity, healthy eating) to promote optimal diabetes health outcomes. **A**

Given associations with glycemic outcomes and risk for future complications (298,299), it is important for diabetes care professionals to support people with diabetes to engage in health-promoting behaviors (preventive, treatment, and maintenance), including blood glucose monitoring, taking insulin and medications, using diabetes technologies, engaging in physical activity, and making nutritional changes. Evidence supports using a variety of behavioral strategies and multicomponent interventions to help people with diabetes and their caregivers or family members develop health behavior routines and overcome barriers to self-management behaviors (300–302). Behavioral strategies with empirical support include motivational interviewing (303–305), patient activation (306), goal setting and action

planning (305,307–309), problem-solving (308,310), tracking or self-monitoring health behaviors with or without feedback from a health care professional (305,307–309), and facilitating opportunities for social support (305,308,309). Multicomponent intervention packages have the highest efficacy for behavioral and glycemic outcomes (300,309,311). For youth with diabetes, family-based behavioral intervention packages and multisystem interventions that facilitate health behavior change demonstrate benefit for increasing management behaviors and improving glycemic outcomes (301). Health behavior change strategies may be delivered by mental health professionals, DCES, or other trained health care professionals (307,312–314) or qualified community health workers (307,308). These approaches may be delivered via digital health tools (309,313,315).

PSYCHOSOCIAL CARE

Recommendations

- 5.38** Psychosocial care should be provided to all people with diabetes, with the goal of optimizing health-related quality of life and health outcomes. Such care should be integrated with routine medical care and delivered by trained health care professionals using a collaborative, person-centered, culturally informed approach. **A** When indicated and available, qualified mental health professionals should provide additional targeted mental health care. **B**
- 5.39** Diabetes care teams should implement psychosocial screening protocols that may include but are not limited to attitudes about diabetes, expectations for treatment and outcomes, general and diabetes-related mood, stress and/or quality of life, available resources (financial, social, family, and emotional), and/or psychiatric history. Screening should occur at periodic intervals and when there is a change in disease, treatment, or life circumstances. **C**
- 5.40** When indicated, refer to mental health professionals or other trained health care professionals for further assessment and

treatment for symptoms of diabetes distress, depression, suicidality, anxiety, treatment-related fear of hypoglycemia, disordered eating, and/or cognitive capacities. Such specialized psychosocial care should use age-appropriate standardized and validated tools and treatment approaches. **B**

- 5.41** Consider screening older adults (aged ≥ 65 years) with diabetes for cognitive impairment, frailty, and depressive symptoms. Monitoring of cognitive capacity, i.e., the ability to actively engage in decision-making regarding treatment plan behaviors, is advised. **B**

Please refer to the ADA position statement “Psychosocial Care for People With Diabetes” for a list of assessment tools and additional details (1) and the ADA Mental Health Toolkit for assessment questionnaires and surveys (professional. diabetes.org/mental-health-toolkit).

Complex environmental, social, family, behavioral, and emotional factors, known as psychosocial factors, influence living with diabetes, both type 1 and type 2, and achieving optimal health outcomes and psychological well-being. Thus, individuals with diabetes and their families are challenged with complex, multifaceted issues when integrating diabetes care into daily life (183). Clinically significant mental health diagnoses are considerably more prevalent in people with diabetes than in those without (316,317). Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual’s (43,318–322) or family’s (321) ability to carry out diabetes care tasks and, therefore, potentially compromise health status. Therefore, psychological symptoms, both clinical and subclinical, must be addressed. In addition to impacting a person’s ability to carry out self-management and the association of mental health diagnosis with poorer short-term glycemic stability, symptoms of emotional distress are associated with mortality risk (316,323).

There are opportunities for diabetes health care professionals to routinely monitor and screen psychosocial status in a timely and efficient manner for

referral to appropriate services (324,325). Various health care professionals working with people with diabetes may contribute to psychosocial care in different ways based on training, experience, need, and availability (313,326,327). Ideally, qualified mental health professionals with specialized training and experience in diabetes should be integrated with or provide collaborative care as part of diabetes care teams (328–331), or referrals for in-depth assessment and treatment for psychosocial concerns should be made to such mental health professionals when indicated (314,332,333). A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C (standardized mean difference -0.29%) and mental health outcomes (334). There was a limited association between the effects on A1C and mental health, and no intervention characteristics predicted benefit on both outcomes. However, cost analyses have shown that behavioral health interventions are both effective and cost-efficient approaches to the prevention of diabetes (335).

Screening

Health care teams should develop and implement psychosocial screening protocols to ensure routine monitoring of psychosocial well-being and concerns among people with diabetes, following published guidance and recommendations (336–340). Topics to screen for may include, but are not limited to, attitudes about diabetes, expectations for treatment and outcomes (especially related to starting a new treatment or technology), general and diabetes-related mood, stress, and/or quality of life (e.g., diabetes distress, depressive symptoms, anxiety symptoms, and/or fear of hypoglycemia), available resources (financial, social, family, and emotional), and/or psychiatric history. A list of age-appropriate screening and evaluation measures is provided in the ADA position statement “Psychosocial Care for People with Diabetes” (1). Key opportunities for psychosocial screening occur at diabetes diagnosis, during regularly scheduled management visits, during hospitalizations, with new onset of complications, during significant transitions in care such as from pediatric to adult care teams (341), at the time of medical treatment changes, or when

problems with achieving A1C goals, quality of life, or self-management are identified. People with diabetes are likely to exhibit psychological vulnerability at diagnosis, when their medical status changes (e.g., end of the honeymoon period), when the need for intensified treatment is evident, and when complications are discovered. Significant changes in life circumstances and SDOH are known to considerably affect a person’s ability to self-manage their condition. Thus, screening for SDOH (e.g., loss of employment, birth of a child, or other family-based stresses) should also be incorporated into routine care (342). In circumstances where individuals other than the person with diabetes are significantly involved in diabetes management (e.g., caregivers or family members), these issues should be monitored and treated by appropriate professionals (341,343,344).

Standardized, validated, age-appropriate tools for psychosocial monitoring and screening can also be used (1). Health care professionals may also use informal verbal inquires, for example, by asking whether there have been persistent changes in mood during the past 2 weeks or since the individual’s last appointment and whether the person can identify a triggering event or change in circumstances. Diabetes care professionals should also ask whether there are new or different barriers to treatment and self-management, such as feeling overwhelmed or stressed by having diabetes (see *DIABETES DISTRESS*, below), changes in finances, or competing medical demands (e.g., the diagnosis of a comorbid condition).

Psychological Assessment and Treatment

When psychosocial concerns are identified, referral to a qualified behavioral and/or mental health professional, ideally one specializing in diabetes, should be made for comprehensive evaluation, diagnosis, and treatment (313,314,332,333). Indications for referral may include positive screening for overall stress related to work-life balance, diabetes distress, diabetes management difficulties, depression, anxiety, disordered eating, and cognitive dysfunction (see **Table 5.2** for a complete list). It is preferable to incorporate psychosocial assessment and treatment into routine care rather than waiting for a specific problem or deterioration in metabolic or psychological status to occur (38,321).

Table 5.2—Situations that warrant referral of a person with diabetes to a qualified behavioral or mental health professional for evaluation and treatment

- A positive screen on a validated screening tool for depressive symptoms, diabetes distress, anxiety, fear of hypoglycemia, or cognitive impairment
- The presence of symptoms or suspicions of disordered eating behavior, an eating disorder, or disrupted patterns of eating
- Intentional omission of insulin or oral medication to cause weight loss is identified
- A serious mental illness is suspected
- In youth and families with behavioral self-care difficulties, repeated hospitalizations for diabetic ketoacidosis, failure to achieve expected developmental milestones, or significant distress
- Declining or impaired ability to perform diabetes self-care behaviors
- Before undergoing bariatric or metabolic surgery and after surgery, if assessment reveals an ongoing need for adjustment support

Health care professionals should identify behavioral and mental health professionals, knowledgeable about diabetes treatment and the psychosocial aspects of diabetes, to whom they can refer patients. The ADA provides a list of mental health professionals who have specialized expertise or who have received education about psychosocial and behavioral issues related to diabetes in the ADA Mental Health Professional Directory Listing (professional.diabetes.org/mhp_listing). Ideally, mental health professionals should be embedded in diabetes care settings. In recognition of limited behavioral health resources and to optimize availability, other health care professionals who have been trained in behavioral and mental health interventions may also provide this specialized psychosocial care (326,329,345,346). Although some health care professionals may not feel qualified to treat psychological problems (347), optimizing the relationship between a person with diabetes and health care professional may increase the likelihood of the individual accepting referral for other services. Collaborative care interventions and a team approach have demonstrated efficacy in diabetes self-management, outcomes of depression, and psychosocial functioning (5,6).

Evidence supports interventions for people with diabetes and psychosocial concerns, including issues that affect mental and behavioral health. Successful therapeutic approaches include cognitive behavioral (330,332,348,349) and mindfulness-based therapies (346,350,351). See the sections below for details about interventions for specific psychological concerns. Behavioral interventions may also be indicated in a preventive

manner even in the absence of positive psychosocial screeners, such as resilience-promoting interventions to prevent diabetes distress in adolescence (352,353) and behavioral family interventions to promote collaborative family diabetes management in early adolescence (354,355) or to support adjustment to a new treatment plan or technology (64). Psychosocial interventions can be delivered via digital health platforms (356). Group-based or shared diabetes appointments that address both medical and psychosocial issues relevant to living with diabetes are a promising model to consider (327,357).

Although efficacy has been demonstrated with psychosocial interventions, there has been varying success regarding sustained increases in engagement in health behaviors and improved glycemic outcomes associated with behavioral and mental health issues. Thus, health care professionals should systematically monitor these outcomes following implementation of current evidence-based psychosocial treatments to determine ongoing needs.

Diabetes Distress

Recommendation

5.42 Routinely monitor people with diabetes, caregivers, and family members for diabetes distress, particularly when treatment targets are not met and/or at the onset of diabetes complications. Refer to a qualified mental health professional or other trained health care professional for further assessment and treatment if indicated. **B**

Diabetes distress is very common (321, 358–360). While it shares some features with depression, diabetes distress is distinct and has unique relationships with glycemic and other outcomes (359,361). Diabetes distress refers to significant negative psychological reactions related to emotional burdens and worries specific to an individual's experience in having to manage a severe, complicated, and demanding chronic condition such as diabetes (358,359,362). The constant behavioral demands of diabetes self-management (medication dosing, frequency, and titration; monitoring of glucose, food intake, eating patterns, and physical activity) and the potential or actuality of disease progression are directly associated with reports of diabetes distress (358). The prevalence of diabetes distress is reported to be 18–45%, with an incidence of 38–48% over 18 months in people with type 2 diabetes (362). In the second Diabetes Attitudes, Wishes, and Needs (DAWN2) study, significant diabetes distress was reported by 45% of the participants, but only 24% reported that their health care teams asked them how diabetes affected their lives (321). Similar rates have been identified among adolescents with type 1 diabetes (360) and in parents of youth with type 1 diabetes. High levels of diabetes distress significantly impact medication-taking behaviors and are linked to higher A1C, lower self-efficacy, and less optimal eating and exercise behaviors (5,358,362). Diabetes distress is also associated with symptoms of anxiety, depression, and reduced health-related quality of life (363).

Diabetes distress should be routinely monitored (364) using diabetes-specific validated measures (1). If diabetes

distress is identified, it should be acknowledged and addressed. If indicated, the person should be referred for follow-up care (333). This may include specific diabetes education to address areas of diabetes self-care causing distress and impacting clinical management and/or behavioral intervention from a qualified mental health professional, ideally with expertise in diabetes, or from another trained health care professional. Several educational and behavioral intervention strategies have demonstrated benefits for diabetes distress and, to a lesser degree, glycemic outcomes, including education, psychological therapies such as cognitive behavioral therapy and mindfulness-based therapies, and health behavior change approaches such as motivational interviewing (348,349,365,366). Data support diabetes distress interventions delivered using technology (356). DSMES has been shown to reduce diabetes distress (5) and may also benefit A1C when combined with peer support (367). It may be helpful to provide counseling regarding expected diabetes-related versus generalized psychological distress, both at diagnosis and when disease state or treatment changes occur (368). A multi-site RCT with adults with type 1 diabetes and elevated diabetes distress and A1C demonstrated large improvements in diabetes distress and small reductions in A1C through two 3-month intervention approaches: a diabetes education intervention with goal setting and a psychological intervention that included emotion regulation skills, motivational interviewing, and goal setting (369). Among adults with type 2 diabetes in the Veterans Affairs system, an RCT demonstrated benefits of integrating a single session of mindfulness intervention into DSMES, followed by a booster session and mobile app-based home practice over 24 weeks, with the strongest effects on diabetes distress (370). An RCT of cognitive behavioral therapy demonstrated positive benefits for diabetes distress, A1C, and depressive symptoms for up to 1 year among adults with type 2 diabetes and elevated symptoms of distress or depression (371). An RCT among people with type 1 and type 2 diabetes found mindful self-compassion training increased self-compassion, reduced depression and diabetes distress, and improved A1C (372). An RCT of a resilience-focused cognitive behavioral and social problem-solving intervention

compared with diabetes education (353) in teens with type 1 diabetes showed that diabetes distress and depressive symptoms were significantly reduced for up to 3 years post-intervention, though neither A1C nor self-management behaviors improved over time. These recent studies support that a combination of educational, behavioral, and psychological intervention approaches is needed to address distress, depression, and A1C.

As with treatment of other diabetes-associated behavioral and psychosocial factors affecting disease outcomes, there is little outcome data on long-term systematic treatment of diabetes distress integrated into routine care. As the diabetes disease course and its management are fluid, it can be expected that related distress may fluctuate and may need different methods of remediation at different points in the life course and as disease progression occurs.

Anxiety

Recommendations

- 5.43** Consider screening people with diabetes for anxiety symptoms or diabetes-related worries. Health care professionals can discuss diabetes-related worries and may refer to a qualified mental health professional for further assessment and treatment if anxiety symptoms indicate interference with diabetes self-management behaviors or quality of life. **B**
- 5.44** Refer people with hypoglycemia unawareness, which can co-occur with fear of hypoglycemia, to a trained professional to receive evidence-based intervention to help re-establish awareness of symptoms of hypoglycemia and reduce fear of hypoglycemia. **A**

Anxiety symptoms and diagnosable disorders (e.g., generalized anxiety disorder, body dysmorphic disorder, obsessive compulsive disorder, specific phobias, and posttraumatic stress disorder) are common in people with diabetes (373). The Behavioral Risk Factor Surveillance System estimated the lifetime prevalence of generalized anxiety disorder to be 19.5% in people with either type 1 or type 2 diabetes (374). A common

diabetes-specific concern is fears related to hypoglycemia (375,376), which may explain avoidance of behaviors associated with lowering glucose, such as increasing insulin doses or frequency of monitoring. Other common sources of diabetes-related anxiety include not meeting blood glucose targets (373), insulin injections or infusion (377), and onset of complications (1). People with diabetes who exhibit excessive diabetes self-management behaviors well beyond what is prescribed or needed to achieve glycemic targets may be experiencing symptoms of obsessive-compulsive disorder (378). General anxiety is a predictor of injection-related anxiety and is associated with fear of hypoglycemia (376,379).

Psychological and behavioral care can be helpful to address symptoms of anxiety in people with diabetes. Among adults with type 2 diabetes and elevated depressive symptoms, an RCT of collaborative care demonstrated benefits on anxiety symptoms for up to 1 year (380). Fear of hypoglycemia and hypoglycemia unawareness often co-occur, so interventions aimed at treating one often benefit both (381). If fear of hypoglycemia is identified and a person does not have symptoms of hypoglycemia, a structured program of blood glucose awareness training delivered in routine clinical practice can improve A1C, reduce the rate of severe hypoglycemia, and restore hypoglycemia awareness (382,383). If not available within the practice setting, a structured program targeting both fear of hypoglycemia and unawareness should be sought out and implemented by a qualified behavioral practitioner (381,383–385). An RCT comparing blood glucose awareness training with a cognitively focused psychoeducation program in adults with type 1 diabetes and impaired awareness of hypoglycemia that has been treatment resistant suggested that both approaches were beneficial for reducing hypoglycemia (386). Thus, specialized behavioral intervention from a trained health care professional is needed to treat hypoglycemia-related anxiety and unawareness.

Depression

Recommendations

- 5.45** Consider at least annual screening of depressive symptoms in

all people with diabetes, especially those with a self-reported history of depression. Use age-appropriate, validated depression screening measures, recognizing that further evaluation will be necessary for individuals who have a positive screen. **B**

5.46 Beginning at diagnosis of complications or when there are significant changes in medical status, consider assessment for depression. **B**

5.47 Refer to qualified mental health professionals or other trained health care professionals with experience using evidence-based treatment approaches for depression in conjunction with collaborative care with the diabetes treatment team. **A**

History of depression, current depression, and antidepressant medication use are risk factors for the development of type 2 diabetes, especially if the individual has other risk factors such as obesity and family history of type 2 diabetes (387–389). Elevated depressive symptoms and depressive disorders affect one in four people with type 1 or type 2 diabetes (320). Thus, routine screening for depressive symptoms is indicated in this high-risk population, including people with type 1 or type 2 diabetes, gestational diabetes mellitus, and postpartum diabetes. Regardless of diabetes type, women have significantly higher rates of depression than men (390).

Routine monitoring with age-appropriate validated measures (1) can help to identify if referral is warranted (333,339). Multisite studies have demonstrated feasibility of implementing depressive symptom screening protocols in diabetes clinics and published practical guides for implementation (336–339,391). Adults with a history of depressive symptoms need ongoing monitoring of depression recurrence within the context of routine care (387). Integrating mental and physical health care can improve outcomes. When a person with diabetes is receiving psychological therapy, the mental/behavioral health professional should be incorporated into or collaborate with the diabetes treatment team (392). As with DSMES, person-centered collaborative care approaches

have been shown to improve both depression and medical outcomes (392). Depressive symptoms may also be a manifestation of reduced quality of life secondary to disease burden (also see *DIABETES DISTRESS*, above) and resultant changes in resource allocation impacting the person and their family. When depressive symptoms are identified, it is important to query origins, both diabetes-specific and due to other life circumstances (363,393).

Trials have shown consistent evidence of improvements in depressive symptoms and variable benefits for A1C when depression is simultaneously treated (331,392,394), whether through pharmacological treatment, group therapy, psychotherapy, or collaborative care (328,348,349,395,396). Psychological interventions targeting depressive symptoms have shown efficacy when delivered via digital technologies (397). Physical activity interventions also demonstrate benefits for depressive symptoms and A1C (398). It is important to note that medical treatment plan should also be monitored in response to reduction in depressive symptoms. People may agree to or adopt previously refused treatment strategies (improving ability to follow recommended treatment behaviors), which may include increased physical activity and intensification of treatment plan behaviors and monitoring, resulting in changed glucose profiles.

Disordered Eating Behavior

Recommendations

5.48 Consider screening for disordered or disrupted eating using validated screening measures when hyperglycemia and weight loss are unexplained based on self-reported behaviors related to medication dosing, meal plan, and physical activity. In addition, a review of the medical treatment plan is recommended to identify potential treatment-related effects on hunger/caloric intake. **B**

5.49 Consider reevaluating the treatment plan of people with diabetes who present with symptoms of disordered eating behavior, an eating disorder, or disrupted patterns of eating, in consultation with a qualified professional as available. Key qualifications include familiarity with the diabetes

disease physiology, treatments for diabetes and disordered eating behaviors, and weight-related and psychological risk factors for disordered eating behaviors. **B**

Estimated prevalence of disordered eating behavior and diagnosable eating disorders in people with diabetes varies (399–401). For people with type 1 diabetes, insulin omission causing glycosuria in order to lose weight is the most commonly reported disordered eating behavior (402,403); in people with type 2 diabetes, bingeing (excessive food intake with an accompanying sense of loss of control) is most commonly reported. For people with type 2 diabetes treated with insulin, intentional omission is also frequently reported (404). People with diabetes and diagnosable eating disorders have high rates of comorbid psychiatric disorders (405). People with type 1 diabetes and eating disorders have high rates of diabetes distress and fear of hypoglycemia (406).

Diabetes care professionals should monitor for disordered eating behaviors using validated measures (407). When evaluating symptoms of disordered or disrupted eating (when the individual exhibits eating behaviors that appear maladaptive but are not volitional, such as bingeing caused by loss of satiety cues), etiology and motivation for the behavior should be evaluated (401,408). Mixed intervention results point to the need for treatment of eating disorders and disordered eating behavior in the context of the disease and its treatment. Given the complexities of treating disordered eating behaviors and disrupted eating patterns in people with diabetes, it is recommended that multidisciplinary care teams include or collaborate with a health professional trained to identify and treat eating behaviors with expertise in disordered eating and diabetes (409). Key qualifications for such professionals include familiarity with the diabetes disease physiology, weight-related and psychological risk factors for disordered eating behaviors, and treatments for diabetes and disordered eating behaviors. More rigorous methods to identify underlying mechanisms of action that drive change in eating and treatment behaviors, as well as associated mental distress, are

needed (410). Health care teams may consider the appropriateness of technology use among people with diabetes and disordered eating behaviors, although more research on the risks and benefits is needed (411). Caution should be taken in labeling individuals with diabetes as having a diagnosable psychiatric disorder, i.e., an eating disorder, when disordered or disrupted eating patterns are found to be associated with the disease and its treatment. In other words, patterns of maladaptive food intake that appear to have a psychological origin may be driven by physiologic disruption in hunger and satiety cues, metabolic perturbations, and/or secondary distress because of the individual's inability to control their hunger and satiety (401,408).

The use of incretin therapies may have potential implications and relevance for the treatment of disrupted or disordered eating (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"). These medications promote substantial weight loss and maintenance of lost weight beyond conventional nutrition therapies (412), which may improve quality of life. Incretin therapies work in the appetite and reward circuitries to modulate food intake and energy balance, reducing uncontrollable hunger, overeating, and bulimic symptoms (413), although mechanisms are not completely understood. Health care professionals may see expanded use of these medications as data become available (401). This therapy has the potential to improve psychosocial outcomes and control overeating behaviors in people with diabetes, which may ultimately benefit engagement with medical nutrition therapy recommendations (414). More research is needed about adjunctive use of incretins and other medications affecting physiologically based eating behavior in people with diabetes.

Serious Mental Illness

Recommendations

5.50 Provide an increased level of support for people with diabetes and serious mental illness through enhanced monitoring of and assistance with diabetes self-management behaviors. **B**

5.51 In people who are prescribed atypical antipsychotic medications, screen for prediabetes and diabetes 4 months after medication initiation and sooner if clinically indicated, at least annually. **B**

5.52 If a second-generation antipsychotic medication is prescribed for adolescents or adults with diabetes, changes in weight, glycemia, and cholesterol levels should be carefully monitored, and the treatment plan should be reassessed accordingly. **C**

Studies of individuals with serious mental illness, particularly schizophrenia and other thought disorders, show significantly increased rates of type 2 diabetes (415). People with schizophrenia should be monitored for type 2 diabetes because of the known comorbidity. Disordered thinking and judgment can be expected to make it difficult to engage in behavior that reduces risk factors for type 2 diabetes, such as restrained eating for weight management. Further, people with serious mental health disorders and diabetes frequently experience moderate psychological distress, suggesting pervasive intrusion of mental health issues into daily functioning (416).

Coordinated management of diabetes or prediabetes and serious mental illness is recommended to achieve diabetes treatment targets. The diabetes care team, in collaboration with other care professionals, should work to provide an enhanced level of care and self-management support for people with diabetes and serious mental illness based on individual capacity and needs. Such care may include remote monitoring, facilitating health care aides, and providing diabetes training for family members, community support personnel, and other caregivers. Qualitative research suggests that educational and behavioral intervention may provide benefit via group support, accountability, and assistance with applying diabetes knowledge (417). In addition, those taking second-generation (atypical) antipsychotics, such as olanzapine, require greater monitoring because of an increase in risk of type 2 diabetes associated with this medication (418–420). Because of this increased risk, people should be screened for prediabetes or diabetes 4 months after medication initiation and at least annually thereafter.

Serious mental illness is often associated with the inability to evaluate and utilize information to make judgments about treatment options. When a person has an established diagnosis of a mental illness that impacts judgment, activities of daily living, and ability to establish a collaborative relationship with care professionals, it is wise to include a nonmedical caretaker in decision-making regarding the medical treatment plan. This person can help improve the patient's ability to follow the agreed-upon treatment plan through both monitoring and caretaking functions (421).

Cognitive Capacity/Impairment

Recommendations

5.53 Cognitive capacity should be monitored throughout the life span for all individuals with diabetes, particularly in those who have documented cognitive disabilities, those who experience severe hypoglycemia, very young children, and older adults. **B**

5.54 If cognitive capacity changes or appears to be suboptimal for patient decision-making and/or behavioral self-management, referral for a formal assessment should be considered. **E**

Cognitive capacity is generally defined as attention, memory, logic and reasoning, and auditory and visual processing, all of which are involved in diabetes self-management behavior (422). Having diabetes over decades—type 1 and type 2—has been shown to be associated with cognitive decline (423–425). Declines have been shown to impact executive function and information processing speed; they are not consistent between people, and evidence is lacking regarding a known course of decline (426). Diagnosis of dementia is also more prevalent among people with diabetes, both type 1 and type 2 (427). Thus, monitoring of cognitive capacity of individuals is recommended, particularly regarding their ability to self-monitor and make judgments about their symptoms, physical status, and needed alterations to their self-management behaviors, all of which are mediated by executive function (427). As with other disorders affecting mental capacity (e.g., major psychiatric disorders), the key issue is

IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIORS FOR TYPE 2 DIABETES

SITTING/BREAKING UP PROLONGED SITTING

Limit sitting. Breaking up prolonged sitting (every 30 min) with short regular bouts of slow walking/simple resistance exercises can improve glucose metabolism.



STEPPING

- An increase of only 500 steps/day is associated with 2-9% decreased risk of cardiovascular morbidity and all-cause mortality.
- A 5- to 6-min brisk-intensity walk per day equates to ~4 years' greater life expectancy.



SLEEP

Aim for consistent, uninterrupted sleep, even on weekends.



Quantity - Long (>8 h) and short (<6 h) sleep durations negatively impact A1C.



Quality - Irregular sleep results in poorer glycemic levels, likely influenced by the increased prevalence of insomnia, obstructive sleep apnea, and restless leg syndrome in people with type 2 diabetes.



Chronotype - Evening chronotypes (i.e., night owl: go to bed late and get up late) may be more susceptible to inactivity and poorer glycemic levels vs. morning chronotypes (i.e., early bird: go to bed early and get up early).

SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)

- Encourage ≥150 min/week of moderate-intensity physical activity (i.e., uses large muscle groups, rhythmic in nature) OR ≥75 min/week vigorous-intensity activity spread over ≥3 days/week, with no more than 2 consecutive days of inactivity. Supplement with two to three resistance, flexibility, and/or balance sessions.
- As little as 30 min/week of moderate-intensity physical activity improves metabolic profiles.



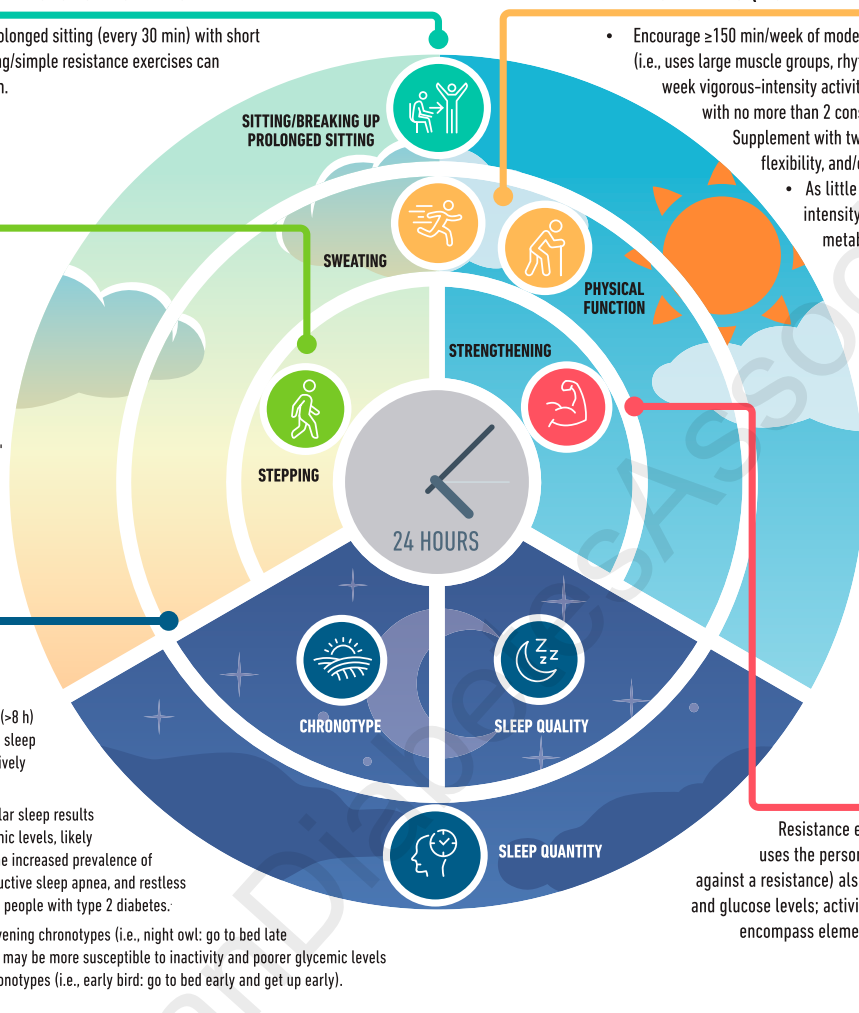
Physical function/frailty/sarcopenia

- The frailty phenotype in type 2 diabetes is unique, often encompassing obesity alongside physical frailty, at an earlier age. The ability of people with type 2 diabetes to undertake simple functional exercises in middle age is similar to that in those over a decade older.



STRENGTHENING

Resistance exercise (i.e., any activity that uses the person's own body weight or works against a resistance) also improves insulin sensitivity and glucose levels; activities like tai chi and yoga also encompass elements of flexibility and balance.



	Glucose/insulin	Blood pressure	A1C	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ Higher levels/improvement (physical function, quality of life); ↓ Lower levels/improvement (glucose/insulin, blood pressure, A1C, lipids, depression); ? no data available; ↑ Green arrows = strong evidence; ↑ Yellow arrows = medium-strength evidence; ↑ Red arrows = limited evidence.

Figure 5.1—Importance of 24-h physical behaviors for type 2 diabetes. Reprinted from Davies et al. (88).

whether the person can collaborate with the care team to achieve optimal metabolic outcomes and prevent complications, both short and long term (416).

When this ability is shown to be altered, declining, or absent, a lay care professional should be introduced into the care team who serves in the capacities of

day-to-day monitoring as well as a liaison with the rest of the care team (1). Cognitive capacity also contributes to ability to benefit from diabetes education and

may indicate the need for alternative teaching approaches as well as remote monitoring. Youth will need second-party monitoring (e.g., parents and adult caregivers) until they are developmentally able to evaluate necessary information for self-management decisions and to inform resultant behavior changes.

Episodes of severe hypoglycemia are independently associated with decline, as well as the more immediate symptoms of mental confusion (428). Early-onset type 1 diabetes has been shown to be associated with potential deficits in intellectual abilities, especially in the context of repeated episodes of severe hypoglycemia (429). (See Section 14, “Children and Adolescents,” for information on early-onset diabetes and cognitive abilities and the effects of severe hypoglycemia on children’s cognitive and academic performance.) Thus, for myriad reasons, cognitive capacity should be assessed during routine care to ascertain the person’s ability to maintain and adjust self-management behaviors, such as dosing of medications, remediation approaches to glycemic excursions, etc., and to determine whether to enlist a caregiver in monitoring and decision-making regarding management behaviors. If cognitive capacity to carry out self-maintenance behaviors is questioned, an age-appropriate test of cognitive capacity is recommended (1). Cognitive capacity should be evaluated in the context of the person’s age, for example, in very young children who are not expected to manage their disease independently and in older adults who may need active monitoring of treatment plan behaviors.

Sleep Health

Recommendation

5.55 Consider screening for sleep health in people with diabetes, including symptoms of sleep disorders, disruptions to sleep due to diabetes symptoms or management needs, and worries about sleep. Refer to sleep medicine and/or a qualified behavioral health professional as indicated. **B**

The associations between sleep problems and diabetes are complex: sleep disorders are a risk factor for developing

type 2 diabetes (430,431) and possibly gestational diabetes mellitus (432,433). Moreover, sleep disturbances are associated with less engagement in diabetes self-management and may interfere with the achievement of glycemic targets among people with type 1 and type 2 diabetes (434–439). Disrupted sleep and sleep disorders, including obstructive sleep apnea (440), insomnia, and sleep disturbances (435), are common among people with diabetes. In type 1 diabetes, estimates of poor sleep range from 30% to 50% (441), and estimates of moderate to severe obstructive sleep apnea are >50% (436). In type 2 diabetes, 24–86% of people are estimated to have obstructive sleep apnea (442), 39% to have insomnia, and 8–45% to have restless leg syndrome (439). Risk of hypoglycemia poses specific challenges for sleep in people with type 1 diabetes and may require targeted assessment and treatment approaches (443). People with diabetes and their family members also describe diabetes management needs interfering with sleep and experiencing worries about poor sleep; technology has been described as both a help and challenge in relation to sleep (444). Cognitive behavioral therapy shows benefits for sleep in people with diabetes (348), including cognitive behavioral therapy for insomnia, which demonstrates improvements in sleep outcomes and possible small improvements in A1C and fasting glucose (445). There is also evidence that sleep extension and pharmacological treatments for sleep can improve sleep outcomes and possibly insulin resistance (443,445). Thus, referral to sleep specialists to address the medical and behavioral aspects of sleep is recommended, ideally in collaboration with the diabetes care professional (Fig. 5.1).

References

1. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2016;39:2126–2140
2. Powers MA, Bardsley JK, Cypress M, et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. *Diabetes Care* 2020;43:1636–1649

3. Rutten GEHM, Alzaid A. Person-centred type 2 diabetes care: time for a paradigm shift. *Lancet Diabetes Endocrinol* 2018;6:264–266
4. Dickinson JK, Guzman SJ, Maryniuk MD, et al. The use of language in diabetes care and education. *Diabetes Care* 2017;40:1790–1799
5. Fisher L, Hessler D, Glasgow RE, et al. REDEEM: a pragmatic trial to reduce diabetes distress. *Diabetes Care* 2013;36:2551–2558
6. Huang Y, Wei X, Wu T, Chen R, Guo A. Collaborative care for patients with depression and diabetes mellitus: a systematic review and meta-analysis. *BMC Psychiatry* 2013;13:260
7. Hill-Briggs F. Problem solving in diabetes self-management: a model of chronic illness self-management behavior. *Ann Behav Med* 2003;25:182–193
8. Greenwood DA, Howell F, Scher L, et al. A framework for optimizing technology-enabled diabetes and cardiometabolic care and education: the role of the diabetes care and education specialist. *Diabetes Educ* 2020;46:315–322
9. Tran VT, Barnes C, Montori VM, Falissard B, Ravaud P. Taxonomy of the burden of treatment: a multi-country web-based qualitative study of patients with chronic conditions. *BMC Med* 2015;13:115
10. Fitzpatrick SL, Golden SH, Stewart K, et al. Effect of DECIDE (Decision-making Education for Choices In Diabetes Everyday) program delivery modalities on clinical and behavioral outcomes in urban African Americans with type 2 diabetes: a randomized trial. *Diabetes Care* 2016;39:2149–2157
11. Brunisholz KD, Briot P, Hamilton S, et al. Diabetes self-management education improves quality of care and clinical outcomes determined by a diabetes bundle measure. *J Multidiscip Healthc* 2014;7:533–542
12. Dickinson JK, Maryniuk MD. Building therapeutic relationships: choosing words that put people first. *Clin Diabetes* 2017;35:51–54
13. Davis J, Fischl AH, Beck J, et al. 2022 National standards for diabetes self-management education and support. *Sci Diabetes Self Manag Care* 2022;48:44–59
14. Tang TS, Funnell MM, Brown MB, Kurlander JE. Self-management support in “real-world” settings: an empowerment-based intervention. *Patient Educ Couns* 2010;79:178–184
15. Marrero DG, Ard J, Delamater AM, et al. Twenty-first century behavioral medicine: a context for empowering clinicians and patients with diabetes: a consensus report. *Diabetes Care* 2013;36:463–470
16. Rutten GEHM, Van Vugt H, de Koning E. Person-centered diabetes care and patient activation in people with type 2 diabetes. *BMJ Open Diabetes Res Care* 2020;8:e001926
17. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. *Diabetes Care* 2002;25:1159–1171
18. Frosch DL, Uy V, Ochoa S, Mangione CM. Evaluation of a behavior support intervention for patients with poorly controlled diabetes. *Arch Intern Med* 2011;171:2011–2017
19. Cooke D, Bond R, Lawton J, et al.; U.K. NIHR DAFNE Study Group. Structured type 1 diabetes education delivered within routine care: impact

- on glycemic control and diabetes-specific quality of life. *Diabetes Care* 2013;36:270–272
20. Chvala CA, Sherr D, Lipman RD. Diabetes self-management education for adults with type 2 diabetes mellitus: a systematic review of the effect on glycemic control. *Patient Educ Couns* 2016;99:926–943
 21. Marincic PZ, Salazar MV, Hardin A, et al. Diabetes self-management education and medical nutrition therapy: a multisite study documenting the efficacy of registered dietitian nutritionist interventions in the management of glycemic control and diabetic dyslipidemia through retrospective chart review. *J Acad Nutr Diet* 2019;119:449–463
 22. Steinsbekk A, Rygg LØ, Lisulo M, Rise MB, Fretheim A. Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis. *BMC Health Serv Res* 2012;12:213
 23. Cochran J, Conn VS. Meta-analysis of quality of life outcomes following diabetes self-management training. *Diabetes Educ* 2008;34:815–823
 24. Davidson P, LaManna J, Davis J, et al. The effects of diabetes self-management education on quality of life for persons with type 1 diabetes: a systematic review of randomized controlled trials. *Sci Diabetes Self Manag Care* 2022;48:111–135
 25. He X, Li J, Wang B, et al. Diabetes self-management education reduces risk of all-cause mortality in type 2 diabetes patients: a systematic review and meta-analysis. *Endocrine* 2017;55:712–731
 26. Thorpe CT, Fahey LE, Johnson H, Deshpande M, Thorpe JM, Fisher EB. Facilitating healthy coping in patients with diabetes: a systematic review. *Diabetes Educ* 2013;39:33–52
 27. Robbins JM, Thatcher GE, Webb DA, Valdmanis VG. Nutritionist visits, diabetes classes, and hospitalization rates and charges: the Urban Diabetes Study. *Diabetes Care* 2008;31:655–660
 28. Duncan I, Ahmed T, Li QE, et al. Assessing the value of the diabetes educator. *Diabetes Educ* 2011;37:638–657
 29. Strawbridge LM, Lloyd JT, Meadow A, Riley GF, Howell BL. One-year outcomes of diabetes self-management training among medicare beneficiaries newly diagnosed with diabetes. *Med Care* 2017;55:391–397
 30. Johnson TM, Murray MR, Huang Y. Associations between self-management education and comprehensive diabetes clinical care. *Diabetes Spectr* 2010;23:41–46
 31. Duncan I, Birkmeyer C, Coughlin S, Li QE, Sherr D, Boren S. Assessing the value of diabetes education. *Diabetes Educ* 2009;35:752–760
 32. Piatt GA, Anderson RM, Brooks MM, et al. 3-year follow-up of clinical and behavioral improvements following a multifaceted diabetes care intervention: results of a randomized controlled trial. *Diabetes Educ* 2010;36:301–309
 33. Dallosso H, Mandalia P, Gray LJ, et al. The effectiveness of a structured group education programme for people with established type 2 diabetes in a multi-ethnic population in primary care: a cluster randomised trial. *Nutr Metab Cardiovasc Dis* 2022;32:1549–1559
 34. Glazier RH, Bajcar J, Kennie NR, Willson K. A systematic review of interventions to improve diabetes care in socially disadvantaged populations. *Diabetes Care* 2006;29:1675–1688
 35. Hawthorne K, Robles Y, Cannings-John R, Edwards AGK. Culturally appropriate health education for type 2 diabetes mellitus in ethnic minority groups. *Cochrane Database Syst Rev* 1996;3:CD006424
 36. Chodosh J, Morton SC, Mojica W, et al. Meta-analysis: chronic disease self-management programs for older adults. *Ann Intern Med* 2005;143:427–438
 37. Sarkisian CA, Brown AF, Norris KC, Wintz RL, Mangione CM. A systematic review of diabetes self-care interventions for older, African American, or Latino adults. *Diabetes Educ* 2003;29:467–479
 38. Peyrot M, Rubin RR. Behavioral and psychosocial interventions in diabetes: a conceptual review. *Diabetes Care* 2007;30:2433–2440
 39. Naik AD, Palmer N, Petersen NJ, et al. Comparative effectiveness of goal setting in diabetes mellitus group clinics: randomized clinical trial. *Arch Intern Med* 2011;171:453–459
 40. Mannucci E, Giaccari A, Gallo M, et al. Self-management in patients with type 2 diabetes: group-based versus individual education. A systematic review with meta-analysis of randomized trials. *Nutr Metab Cardiovasc Dis* 2021
 41. Duke SAS, Colagiuri S, Colagiuri R. Individual patient education for people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2009;2009:CD005268
 42. Odgers-Jewell K, Ball LE, Kelly JT, Isenring EA, Reidlinger DP, Thomas R. Effectiveness of group-based self-management education for individuals with type 2 diabetes: a systematic review with meta-analyses and meta-regression. *Diabet Med* 2017;34:1027–1039
 43. Davis J, Fischl AH, Beck J, et al. 2022 National standards for diabetes self-management education and support. *Diabetes Care* 2022;45:484–494
 44. Pereira K, Phillips B, Johnson C, Vorderstrasse A. Internet delivered diabetes self-management education: a review. *Diabetes Technol Ther* 2015;17:55–63
 45. Sepah SC, Jiang L, Peters AL. Long-term outcomes of a web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. *J Med Internet Res* 2015;17:e92
 46. Greenwood DA, Gee PM, Fatkin KJ, Peeples M. A systematic review of reviews evaluating technology-enabled diabetes self-management education and support. *J Diabetes Sci Technol* 2017;11:1015–1027
 47. Athinarayanan SJ, Adams RN, Hallberg SJ, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. *Front Endocrinol (Lausanne)* 2019;10:348
 48. Kumar S, Moseson H, Uppal J, Juusola JL. A diabetes mobile app with in-app coaching from a certified diabetes educator reduces A1C for individuals with type 2 diabetes. *Diabetes Educ* 2018;44:226–236
 49. Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Ther* 2018;9:583–612
 50. Xu T, Pujara S, Sutton S, Rhee M. Telemedicine in the management of type 1 diabetes. *Prev Chronic Dis* 2018;5:E13
 51. Denning J, Islam SMS, George E, Maddison R. Web-based interventions for dietary behavior in adults with type 2 diabetes: systematic review of randomized controlled trials. *J Med Internet Res* 2020;22:e16437
 52. Anderson A, O'Connell SS, Thomas C, Chimmanamada R. Telehealth interventions to improve diabetes management among Black and Hispanic patients: a systematic review and meta-analysis. *J Racial Ethn Health Disparities* 2022;9:2375–2386
 53. Sherifali D, Brozic A, Agema P, et al. Effect of diabetes health coaching on glycemic control and quality of life in adults living with type 2 diabetes: a community-based, randomized, controlled trial. *Can J Diabetes* 2021;45:594–600
 54. von Storch K, Graaf E, Wunderlich M, Rietz C, Polidori MC, Woopen C. Telemedicine-assisted self-management program for type 2 diabetes patients. *Diabetes Technol Ther* 2019;21:514–521
 55. Omar MA, Hasan S, Palaian S, Mahameed S. The impact of a self-management educational program coordinated through WhatsApp on diabetes control. *Pharm Pract (Granada)* 2020;18:1841
 56. Liang K, Xie Q, Nie J, Deng J. Study on the effect of education for insulin injection in diabetic patients with new simulation tools. *Medicine (Baltimore)* 2021;100:e25424
 57. Sahin C, Courtney KL, Naylor PJ, E Rhodes R. Tailored mobile text messaging interventions targeting type 2 diabetes self-management: a systematic review and a meta-analysis. *Digit Health* 2019;5:2055207619845279
 58. Leong CM, Lee TI, Chien YM, Kuo LN, Kuo YF, Chen HY. Social media-delivered patient education to enhance self-management and attitudes of patients with type 2 diabetes during the COVID-19 pandemic: randomized controlled trial. *J Med Internet Res* 2022;24:e31449
 59. Xia SF, Maitiniyazi G, Chen Y, et al. Web-based TangPlan and WeChat combination to support self-management for patients with type 2 diabetes: randomized controlled trial. *JMIR Mhealth Uhealth* 2022;10:e30571
 60. Jiang Y, Ramachandran HJ, Teo JYC, et al. Effectiveness of a nurse-led smartphone-based self-management programme for people with poorly controlled type 2 diabetes: a randomized controlled trial. *J Adv Nurs* 2022;78:1154–1165
 61. Gershkowitz BD, Hillert CJ, Crotty BH. Digital coaching strategies to facilitate behavioral change in type 2 diabetes: a systematic review. *J Clin Endocrinol Metab* 2021;106:e1513–e1520
 62. Lee MK, Lee DY, Ahn HY, Park CY. A novel user utility score for diabetes management using tailored mobile coaching: secondary analysis of a randomized controlled trial. *JMIR Mhealth Uhealth* 2021;9:e17573
 63. Yoo JH, Kim G, Lee HJ, Sim KH, Jin SM, Kim JH. Effect of structured individualized education on continuous glucose monitoring use in poorly controlled patients with type 1 diabetes: a randomized controlled trial. *Diabetes Res Clin Pract* 2022;184:109209
 64. Strategies to Enhance New CGM Use in Early Childhood (SENCE) Study Group. A randomized clinical trial assessing continuous glucose monitoring (CGM) use with standardized education with or without a family behavioral intervention compared with fingerstick blood glucose moni-

- toring in very young children with type 1 diabetes. *Diabetes Care* 2021;44:464–472
65. Isaacs D, Cox C, Schwab K, et al. Technology integration: the role of the diabetes care and education specialist in practice. *Diabetes Educ* 2020;46:323–334
66. Scalzo P. From the Association of Diabetes Care & Education Specialists: the role of the diabetes care and education specialist as a champion of technology integration. *Sci Diabetes Self Manag Care* 2021;47:120–123
67. Greenwood DA, Litchman ML, Isaacs D, et al. A new taxonomy for technology-enabled diabetes self-management interventions: results of an umbrella review. *J Diabetes Sci Technol* 2021;16:812–824
68. van Eikenhorst L, Taxis K, van Dijk L, de Gier H. Pharmacist-led self-management interventions to improve diabetes outcomes. A systematic literature review and meta-analysis. *Front Pharmacol* 2017;8:891
69. Tshiananga JKT, Kocher S, Weber C, Erny-Albrecht K, Berndt K, Neeser K. The effect of nurse-led diabetes self-management education on glycosylated hemoglobin and cardiovascular risk factors: a meta-analysis. *Diabetes Educ* 2012;38:108–123
70. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care* 2019;42:731–754
71. Shah M, Kaselitz E, Heisler M. The role of community health workers in diabetes: update on current literature. *Curr Diab Rep* 2013;13:163–171
72. Spencer MS, Kieffer EC, Sinco B, et al. Outcomes at 18 months from a community health worker and peer leader diabetes self-management program for Latino adults. *Diabetes Care* 2018;41:1414–1422
73. Heisler M, Vijan S, Makki F, Piette JD. Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. *Ann Intern Med* 2010;153:507–515
74. Long JA, Jahnle EC, Richardson DM, Loewenstein G, Volpp KG. Peer mentoring and financial incentives to improve glucose control in African American veterans: a randomized trial. *Ann Intern Med* 2012;156:416–424
75. Fisher EB, Boothroyd RI, Elstad EA, et al. Peer support of complex health behaviors in prevention and disease management with special reference to diabetes: systematic reviews. *Clin Diabetes Endocrinol* 2017;3:4
76. Litchman ML, Oser TK, Hodgson L, et al. In-person and technology-mediated peer support in diabetes care: a systematic review of reviews and gap analysis. *Diabetes Educ* 2020;46:230–241
77. Foster G, Taylor SJ, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst Rev* 2007:CD005108
78. Powell RE, Zaccardi F, Beebe C, et al. Strategies for overcoming therapeutic inertia in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2021;23:2137–2154
79. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. *Diabetes Care* 2020;43:200053
80. Strawbridge LM, Lloyd JT, Meadow A, Riley GF, Howell BL. Use of Medicare's diabetes self-management training benefit. *Health Educ Behav* 2015;42:530–538
81. Horigan G, Davies M, Findlay-White F, Chaney D, Coates V. Reasons why patients referred to diabetes education programmes choose not to attend: a systematic review. *Diabet Med* 2016
82. Carey ME, Agarwal S, Horne R, Davies M, Slevin M, Coates V. Exploring organizational support for the provision of structured self-management education for people with type 2 diabetes: findings from a qualitative study. *Diabet Med* 2019;36:761–770
83. Department of Health and Human Services. Telehealth.HHS.gov. Telehealth and remote patient monitoring. Accessed 6 October 2022. Available from: <https://telehealth.hhs.gov/providers/preparing-patients-for-telehealth/telehealth-and-remote-patient-monitoring/>
84. Center For Health Law and Policy Innovation. Reconsidering cost-sharing for diabetes self-management education: recommendations for policy reform. Accessed 19 October 2022. Available from <https://chlp.org/wp-content/uploads/2015/07/6.11.15-Reconsidering-Cost-Sharing-for-DSME-cover.jpg>
85. Turner RM, Ma Q, Lorig K, Greenberg J, DeVries AR. Evaluation of a diabetes self-management program: claims analysis on comorbid illnesses, health care utilization, and cost. *J Med Internet Res* 2018 20:e207
86. Centers for Medicare & Medicaid Services. COVID-19 Frequently Asked Questions (FAQs) on Medicare Fee-for-Service (FFS) Billing. 19 October 2022. Available from <https://www.cms.gov/files/document/03092020-covid-19-faqs-508.pdf>
87. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2021;44:2589–2625
88. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022;45:2753–2786
89. English LK, Ard JD, Bailey RL, et al. Evaluation of dietary patterns and all-cause mortality: a systematic review. *JAMA Netw Open* 2021;4:e2122277
90. Dietary Guidelines for America Committee. Scientific report of the 2020 Dietary Guidelines Advisory Committee: advisory report to the Secretary of Agriculture and the Secretary of Health and Human Services. Washington, DC, Agricultural Research Service, 2020. Available from <https://doi.org/10.52570/DGAC2020>
91. Lichtenstein AH, Appel LJ, Vadiveloo M, et al. 2021 Dietary guidance to improve cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 2021;144:e472–e487
92. Rosenfeld RM, Kelly JH, Agarwal M, et al. Dietary interventions to treat type 2 diabetes in adults with a goal of remission: an expert consensus statement from the American College of Lifestyle Medicine. *Am J Lifestyle Med* 2022;16:342–362
93. Joseph JJ, Deedwania P, Acharya T, et al.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; and Council on Hypertension. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the American Heart Association. *Circulation* 2022;145:e722–e759
94. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669–2701
95. Briggs Early K, Stanley K. Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. *J Acad Nutr Diet* 2018;18:343–353
96. Dobrow L, Estrada I, Burkholder-Cooley N, Miklavcic J. Potential effectiveness of registered dietitian nutritionists in healthy behavior interventions for managing type 2 diabetes in older adults: a systematic review. *Front Nutr* 2022;8:737410
97. Franz MJ, MacLeod J, Evert A, et al. Academy of Nutrition and Dietetics Nutrition practice guideline for type 1 and type 2 diabetes in adults: systematic review of evidence for medical nutrition therapy effectiveness and recommendations for integration into the nutrition care process. *J Acad Nutr Diet* 2017;17:1659–1679
98. Mudaliar U, Zabetian A, Goodman M, et al. Cardiometabolic risk factor changes observed in diabetes prevention programs in US settings: a systematic review and meta-analysis. *PLoS Med* 2016;13:e1002095
99. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the community preventive services task force combined diet and physical activity promotion programs to prevent diabetes. *Ann Intern Med* 2015;163:437–451
100. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006;29:2102–2107
101. Garvey WT, Ryan DH, Bohannon NJV, et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. *Diabetes Care* 2014;37:3309–3316
102. Kahan S, Fujioka K. Obesity pharmacotherapy in patients with type 2 diabetes. *Diabetes Spectr* 2017;30:250–257
103. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. *Diabetes Care* 2007;30:744–752
104. Duncan GE, Perri MG, Theraque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care* 2003;26:557–562
105. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. *J Acad Nutr Diet* 2015;15:1447–1463

106. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DIRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391:541–551
107. Wing RR, Lang W, Wadden TA, et al.; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011;34:1481–1486
108. Look AHEAD Research Group. Does lifestyle intervention improve health of adults with overweight/obesity and type 2 diabetes? Findings from the Look AHEAD randomized trial. *Obesity (Silver Spring)* 2021;29:1246–1258
109. Garvey WT. Long-term health benefits of intensive lifestyle intervention in the Look AHEAD study. *Obesity (Silver Spring)* 2021;29:1242–1243
110. Davies M, Færch L, Jeppesen OK, et al.; STEP 2 Study Group. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397:971–984
111. Jastreboff AM, Aronne LJ, Ahmad NN, et al.; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;387:205–216
112. Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014;311:2297–2304
113. Cefalu WT, Leiter LA, de Bruin TWA, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. *Diabetes Care* 2015;38:1218–1227
114. Prinz N, Schwandt A, Becker M, et al. Trajectories of body mass index from childhood to young adulthood among patients with type 1 diabetes—a longitudinal group-based modeling approach based on the DPV Registry. *J Pediatr* 2018;201:78–85.e4
115. Lipman TH, Levitt Katz LE, Ratcliffe SJ, et al. Increasing incidence of type 1 diabetes in youth: twenty years of the Philadelphia Pediatric Diabetes Registry. *Diabetes Care* 2013;36:1597–1603
116. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* 2011;365:1597–1604
117. Hamdy O, Mottalib A, Morsi A, et al. Long-term effect of intensive lifestyle intervention on cardiovascular risk factors in patients with diabetes in real-world clinical practice: a 5-year longitudinal study. *BMJ Open Diabetes Res Care* 2017;5:e000259
118. Nip ASY, Reboussin BA, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. Disordered eating behaviors in youth and young adults with type 1 or type 2 diabetes receiving insulin therapy: the SEARCH for Diabetes in Youth Study. *Diabetes Care* 2019;42:859–866
119. Mottalib A, Salsberg V, Mohd-Yusof BN, et al. Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. *Nutr J* 2018;17:42
120. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;378:e34
121. Saslow LR, Daubenmier JJ, Moskowitz JT, et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. *Nutr Diabetes* 2017;7:304
122. Yancy WS, Crowley MJ, Dar MS, et al. Comparison of group medical visits combined with intensive weight management vs group medical visits alone for glycemia in patients with type 2 diabetes: a noninferiority randomized clinical trial. *JAMA Intern Med* 2019
123. Emadian A, Andrews RC, England CY, Wallace V, Thompson JL. The effect of macronutrients on glycaemic control: a systematic review of dietary randomised controlled trials in overweight and obese adults with type 2 diabetes in which there was no difference in weight loss between treatment groups. *Br J Nutr* 2015;114:1656–1666
124. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *JAMA* 2018;319:667–679
125. Korsmo-Haugen HK, Brurberg KG, Mann J, Aas AM. Carbohydrate quantity in the dietary management of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2019;21:15–27
126. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859–873
127. de Souza RJ, Bray GA, Carey VJ, et al. Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. *Am J Clin Nutr* 2012;95:614–625
128. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA* 2014;312:923–933
129. Fox CS, Golden SH, Anderson C, et al.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research; American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2015;38:1777–1803
130. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. *Eur J Epidemiol* 2018;33:157–170
131. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 2017;105:1462–1473
132. Benson G, Hayes J. An update on the Mediterranean, vegetarian, and DASH eating patterns in people with type 2 diabetes. *Diabetes Spectr* 2020;33:125–132
133. Hager ER, Quigg AM, Black MM, et al. Development and validity of a 2-item screen to identify families at risk for food insecurity. *Pediatrics* 2010;126:e26–e32
134. Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med* 2009;151:306–314
135. de Carvalho GB, Dias-Vasconcelos NL, Santos RKF, Brandão-Lima PN, da Silva DG, Pires LV. Effect of different dietary patterns on glycemic control in individuals with type 2 diabetes mellitus: a systematic review. *Crit Rev Food Sci Nutr* 2020;60:1999–2010
136. Papamichou D, Panagiotakos DB, Itsiopoulos C. Dietary patterns and management of type 2 diabetes: a systematic review of randomised clinical trials. *Nutr Metab Cardiovasc Dis* 2019;29:531–543
137. Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2018;139:239–252
138. van Zuuren EJ, Fedorowicz Z, Kuijpers T, Pijl H. Effects of low-carbohydrate- compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments. *Am J Clin Nutr* 2018;108:300–331
139. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. *BMJ Open Diabetes Res Care* 2017;5:e000354
140. Rinaldi S, Campbell EE, Fournier J, O'Connor C, Madill J. A comprehensive review of the literature supporting recommendations from the Canadian Diabetes Association for the use of a plant-based diet for management of type 2 diabetes. *Can J Diabetes* 2016;40:471–477
141. Pawlak R. Vegetarian diets in the prevention and management of diabetes and its complications. *Diabetes Spectr* 2017;30:82–88
142. Handu D, Piotrowski M. Nutrition interventions in pediatric patients with type 1 diabetes: an evidence analysis center scoping review. *J Acad Nutr Diet* 2021;122:424–431
143. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. *J Clin Lipidol* 2019;13:689–711.e1
144. Siverhus K. Low carbohydrate and very low carbohydrate eating patterns in adults with diabetes: a guide for health care providers. Arlington, VA, American Diabetes Association. Accessed 9 September 2022. Available from <https://shopdiabetes.org/products/low-carbohydrate-and-very-low-carbohydrate-eating-patterns>

- in-adults-with-diabetes-a-guide-for-health-care-providers
145. Bowen ME, Cavanaugh KL, Wolff K, et al. The diabetes nutrition education study randomized controlled trial: a comparative effectiveness study of approaches to nutrition in diabetes self-management education. *Patient Educ Couns* 2016; 99:1368–1376
146. Truman E, Lane D, Elliott C. Defining food literacy: a scoping review. *Appetite* 2017;116: 365–371
147. Food Literacy Center. What is food literacy? Accessed 31 August 2021. Available from <https://www.foodliteracycenter.org/about>
148. Jamshed H, Steger FL, Bryan DR, et al. Effectiveness of early time-restricted eating for weight loss, fat loss, and cardiometabolic health in adults with obesity: a randomized clinical trial. *JAMA Intern Med* 2022;182:953–962
149. Lowe DA, Wu N, Rohdin-Bibby L, et al. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: the TREAT randomized clinical trial. *JAMA Intern Med* 2020;180:1491–1499
150. Gabel K, Hoddy KK, Haggerty N, et al. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: a pilot study. *Nutr Healthy Aging* 2018;4:345–353
151. Chow LS, Manoogian ENC, Alvear A, et al. Time-restricted eating effects on body composition and metabolic measures in humans who are overweight: a feasibility study. *Obesity (Silver Spring)* 2020;28:860–869
152. Liu D, Huang Y, Huang C, et al. Calorie restriction with or without time-restricted eating in weight loss. *N Engl J Med* 2022;386:1495–1504
153. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med* 2017; 177:930–938
154. Carter S, Clifton PM, Keogh JB. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized noninferiority trial. *JAMA Netw Open* 2018;1:e180756
155. Overland J, Toth K, Gibson AA, et al. The safety and efficacy of weight loss via intermittent fasting or standard daily energy restriction in adults with type 1 diabetes and overweight or obesity: A pilot study. *Obes Med* 2018;12:13–17
156. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomized controlled trial. *BMJ* 2002;325:746
157. Delahanty LM, Nathan DM, Lachin JM, et al.; Diabetes Control and Complications Trial/ Epidemiology of Diabetes. Association of diet with glycated hemoglobin during intensive treatment of type 1 diabetes in the Diabetes Control and Complications Trial. *Am J Clin Nutr* 2009;89:518–524
158. Zafar MI, Mills KE, Zheng J, Regmi A, Hu SQ, Gou L, et al. Low-glycemic index diets as an intervention for diabetes: a systematic review and meta-analysis. *Am J Clin Nutr* 2019;110: 891–902
159. Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. *Diabetes Care* 2012;35:434–445
160. Vega-López S, Venn BJ, Slavin JL. Relevance of the glycemic index and glycemic load for body weight, diabetes, and cardiovascular disease. *Nutrients* 2018;10:E1361
161. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. *Cochrane Database Syst Rev* 2009;2009:CD006296
162. Chiavaroli L, Lee D, Ahmed A, Cheung A, Khan TA, Blanco S, et al. Effect of low glycaemic index or load dietary patterns on glycaemic control and cardiometabolic risk factors in diabetes: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2021;374: n1651
163. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract* 2017;131:124–131
164. Goldenberg JZ, Day A, Brinkworth GD, et al. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. *BMJ* 2021;372:m4743
165. Lennerz BS, Koutnik AP, Azova S, Wolfsdorf JI, Ludwig DS. Carbohydrate restriction for diabetes: rediscovering centuries-old wisdom. *J Clin Invest* 2021;131:142246
166. Jayedi A, Zeraattalab-Motlagh S, Jabbarzadeh B, et al. Dose-dependent effect of carbohydrate restriction for type 2 diabetes management: a systematic review and dose-response meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2022;116:40–56
167. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. *Am J Clin Nutr* 2015;102: 780–790
168. Gardner CD, Landry MJ, Perelman D, et al. Effect of a ketogenic diet versus mediterranean diet on HbA1c in individuals with prediabetes and type 2 diabetes mellitus: the interventional keto-med randomized crossover trial. *Am J Clin Nutr* 2022;116:640–652
169. U.S. Food and Drug Administration. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Silver Spring, MD, U.S. Food and Drug Administration. Accessed 30 August 2022. Available from <https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sgl2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious>
170. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. *Diabetes Metab Res Rev* 2017;33:10.1002/dmrr.2924
171. Cronin P, Joyce SA, O'Toole PW, O'Connor EM. Dietary fibre modulates the gut microbiota. *Nutrients* 2021;13:1655
172. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary guidelines for Americans 2020–2025. 9th Edition, December 2020. Accessed 19 October 2022. Available from https://www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf
173. He M, van Dam RM, Rimm E, Hu FB, Qi L. Whole-grain, cereal fiber, bran, and germ intake and the risks of all-cause and cardiovascular disease-specific mortality among women with type 2 diabetes mellitus. *Circulation* 2010;121: 2162–2168
174. Burger KNJ, Beulens JWJ, van der Schouw YT, et al. Dietary fiber, carbohydrate quality and quantity, and mortality risk of individuals with diabetes mellitus. *PLoS One* 2012;7:e43127
175. Partula V, Deschasaux M, Druesne-Pecollo N, Latino-Martel P, Desmetz E, Chazelas E, et al. Associations between consumption of dietary fibers and the risk of cardiovascular diseases, cancers, type 2 diabetes, and mortality in the prospective NutriNet-Santé cohort. *Am J Clin Nutr* 2020;112:195–207
176. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet* 2019;393:434–445
177. Hu Y, Ding M, Sampson L, et al. Intake of whole grain foods and risk of type 2 diabetes: results from three prospective cohort studies. *BMJ* 2020;370:m2206
178. Nansel TR, Lipsky LM, Liu A. Greater diet quality is associated with more optimal glycemic control in a longitudinal study of youth with type 1 diabetes. *Am J Clin Nutr* 2016;104:81–87
179. Katz ML, Mehta S, Nansel T, Quinn H, Lipsky LM, Laffel LMB. Associations of nutrient intake with glycemic control in youth with type 1 diabetes: differences by insulin regimen. *Diabetes Technol Ther* 2014;16:512–518
180. Rossi MCE, Nicolucci A, Di Bartolo P, et al. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. *Diabetes Care* 2010;33:109–115
181. Laurenzi A, Bolla AM, Panigoni G, et al. Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GIOCAR). *Diabetes Care* 2011;34:823–827
182. Sämann A, Mühlhauser I, Bender R, Kloos Ch, Müller UA. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. *Diabetologia* 2005;48: 1965–1970
183. Bell KJ, Barclay AW, Petocz P, Colagiuri S, Brand-Miller JC. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2014;2:133–140
184. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care* 2015;38: 1008–1015
185. Bell KJ, Toschi E, Steil GM, Wolpert HA. Optimized mealtime insulin dosing for fat and protein in type 1 diabetes: application of a model-based approach to derive insulin doses for

- open-loop diabetes management. *Diabetes Care* 2016;39:1631–1634
186. Smart CEM, Evans M, O'Connell SM, et al. Both dietary protein and fat increase postprandial glucose excursions in children with type 1 diabetes, and the effect is additive. *Diabetes Care* 2013;36:3897–3902
187. Smith TA, Smart CE, Howley PP, Lopez PE, King BR. For a high fat, high protein breakfast, preprandial administration of 125% of the insulin dose improves postprandial glycaemic excursions in people with type 1 diabetes using multiple daily injections: a cross-over trial. *Diabet Med* 2021;38:e14512
188. Paterson MA, Smart CEM, Lopez PE, et al. Increasing the protein quantity in a meal results in dose-dependent effects on postprandial glucose levels in individuals with type 1 diabetes mellitus. *Diabet Med* 2017;34:851–854
189. O'Connell SM, O'Toole N, Cronin C, et al. Is the glycaemic response from fat in meals dose dependent in children and adolescents with T1DM on intensive insulin therapy? ESPE Abstracts 89 FC3.4, 2018. Accessed 19 October 2022. Available from <https://abstracts.eurosp.org/hrp/0089/hrp0089fc3.4>
190. Bell KJ, Fio CZ, Twigg S, et al. Amount and type of dietary fat, postprandial glycemia, and insulin requirements in type 1 diabetes: a randomized within-subject trial. *Diabetes Care* 2020;43:59–66
191. Furthner D, Lukas A, Schneider AM, et al. The role of protein and fat intake on insulin therapy in glycaemic control of paediatric type 1 diabetes: a systematic review and research gaps. *Nutrients* 2021;13:3558
192. Metwally M, Cheung TO, Smith R, Bell KJ. Insulin pump dosing strategies for meals varying in fat, protein or glycaemic index or grazing-style meals in type 1 diabetes: a systematic review. *Diabetes Res Clin Pract* 2021;172:108516
193. Campbell MD, Walker M, King D, et al. Carbohydrate counting at meal time followed by a small secondary postprandial bolus injection at 3 hours prevents late hyperglycemia, without hypoglycemia, after a high-carbohydrate, high-fat meal in type 1 diabetes. *Diabetes Care* 2016;39:e141–e142
194. Angelopoulos T, Kokkinos A, Liaskos C, et al. The effect of slow spaced eating on hunger and satiety in overweight and obese patients with type 2 diabetes mellitus. *BMJ Open Diabetes Res Care* 2014;2:e000013
195. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care* 2014;37:2864–2883
196. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *Lancet* 2014;383:1999–2007
197. Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2008;88:660–666
198. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. *Cochrane Database Syst Rev* 2007;4:CD002181
199. Layman DK, Clifton P, Gannon MC, Krauss RM, Nuttall FQ. Protein in optimal health: heart disease and type 2 diabetes. *Am J Clin Nutr* 2008;87:1571S–1575S
200. Ros E. Dietary cis-monounsaturated fatty acids and metabolic control in type 2 diabetes. *Am J Clin Nutr* 2003;78(Suppl.):617S–625S
201. Forouhi NG, Imamura F, Sharp SJ, et al. Association of plasma phospholipid n-3 and n-6 polyunsaturated fatty acids with type 2 diabetes: the EPIC-InterAct case-cohort study. *PLoS Med* 2016;13:e1002094
202. Wang DD, Li Y, Chiuve SE, et al. Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern Med* 2016;176:1134–1145
203. Brehm BJ, Lattin BL, Summer SS, et al. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. *Diabetes Care* 2009;32:215–220
204. Shai I, Schwarzfuchs D, Henkin Y, et al.; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–241
205. Brunerova L, Smejkalova V, Potockova J, Anzel M. A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and type 2 diabetic patients. *Diabet Med* 2007;24:533–540
206. Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on health outcomes of a Mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. *Ann Intern Med* 2016;165:491–500
207. Sacks FM, Lichtenstein AH, Wu JHY, et al.; American Heart Association. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation* 2017;136:e1–e23
208. Jacobson TA, Maki KC, Orringer CE, et al.; NLA Expert Panel. National lipid association recommendations for patient-centered management of dyslipidemia: part 2. *J Clin Lipid* 2015;9:S1–S122.e1
209. Holman RR, Paul S, Farmer A, Tucker L, Stratton IM; Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes Study Group. Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes (AFORRD): a randomised controlled trial. *Diabetologia* 2009;52:50–59
210. Bosch J, Gerstein HC, Dagenais GR, et al.; ORIGIN Trial Investigators. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012;367:309–318
211. Brown TJ, Brainard J, Song F, Wang X, Abdelhamid A, Hooper L, et al. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2019;366:14697
212. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med* 2018;379:1540–1550
213. Bhatt DL, Steg PG, Miller M, et al.; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;380:11–22
214. Thomas MC, Moran J, Forsblom C, et al.; FinnDiane Study Group. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care* 2011;34:861–866
215. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care* 2011;34:703–709
216. Lennon SL, DellaValle DM, Rodder SG, et al. 2015 Evidence analysis library evidence-based nutrition practice guideline for the management of hypertension in adults. *J Acad Nutr Diet* 2017;117:1445–1458.e17
217. Mailliot M, Drewnowski A. A conflict between nutritionally adequate diets and meeting the 2010 dietary guidelines for sodium. *Am J Prev Med* 2012;42:174–179
218. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab* 2016;101:1754–1761
219. Mangione CM, Barry MJ, Nicholson WK, et al.; US Preventive Services Task Force. Vitamin, mineral, and multivitamin supplementation to prevent cardiovascular disease and cancer: US Preventive Services Task Force recommendation statement. *JAMA* 2022;327:2326–2333
220. Allen RW, Schwartzman E, Baker WL, Coleman CI, Phung OJ. Cinnamon use in type 2 diabetes: an updated systematic review and meta-analysis. *Ann Fam Med* 2013;11:452–459
221. Mitri J, Pittas AG. Vitamin D and diabetes. *Endocrinol Metab Clin North Am* 2014;43:205–232
222. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation* 2016;133:187–225
223. Pittas AG, Dawson-Hughes B, Sheehan P, et al.; D2d Research Group. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med* 2019;381:520–530
224. Dawson-Hughes B, Staten MA, Knowler WC, et al.; D2d Research Group. Intratrial exposure to vitamin D and new-onset diabetes among adults with prediabetes: a secondary analysis from the Vitamin D and Type 2 Diabetes (D2d) study. *Diabetes Care* 2020;43:2916–2922
225. Zhang Y, Tan H, Tang J, et al. Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes: a systematic review and meta-analysis. *Diabetes Care* 2020;43:1650–1658
226. Barbarawi M, Zayed Y, Barbarawi O, et al. Effect of vitamin D supplementation on the incidence of diabetes mellitus. *J Clin Endocrinol Metab* 2020;105:dga335
227. National Agricultural Library, U.S. Department of Agriculture. Nutritive and nonnutritive sweetener resources. Accessed 19 October 2022. Available from <https://www.nal.usda.gov/human-nutrition-and-food-safety/food-composition/sweeteners>
228. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596–e646
229. Johnson RK, Lichtenstein AH, Anderson CAM, et al.; American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Quality of Care and Outcomes Research; Stroke Council. Low-calorie sweetened

- beverages and cardiometabolic health: a science advisory from the American Heart Association. *Circulation* 2018;138:e126–e140
230. Grotz VL, Pi-Sunyer X, Porte D Jr, Roberts A, Richard Trout J. A 12-week randomized clinical trial investigating the potential for sucralose to affect glucose homeostasis. *Regul Toxicol Pharmacol* 2017;88:22–33
231. Lohner S, Kuellenberg de Gaudry D, Toews I, Ferenci T, Meerpohl JJ. Non-nutritive sweeteners for diabetes mellitus. *Cochrane Database Syst Rev* 2020;5:CD012885
232. Sylvestry AC, Chandran A, Talegawkar SA, Welsh JA, Drews K, El Ghormli L. Consumption of beverages containing low-calorie sweeteners, diet, and cardiometabolic health in youth with type 2 diabetes. *J Acad Nutr Diet* 2020;120:1348–1358.e6
233. Miller PE, Perez V. Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies. *Am J Clin Nutr* 2014;100:765–777
234. Rogers PJ, Hogenkamp PS, de Graaf C, et al. Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies. *Int J Obes* 2016;40:381–394
235. Laviada-Molina H, Molina-Segui F, Pérez-Gaxiola G, et al. Effects of nonnutritive sweeteners on body weight and BMI in diverse clinical contexts: systematic review and meta-analysis. *Obes Rev* 2020;21:e13020
236. Azad MB, Abou-Setta AM, Chauhan BF, et al. Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. *CMAJ* 2017;189:E929–E939
237. Lee JJ, Khan TA, McGlynn N, et al. Relation of change or substitution of low- and no-calorie sweetened beverages with cardiometabolic outcomes: a systematic review and meta-analysis of prospective cohort studies. *Diabetes Care* 2022;45:1917–1930
238. Mattes RD, Popkin BM. Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. *Am J Clin Nutr* 2009;89:1–14
239. McGlynn ND, Khan TA, Wang L, et al. Association of low- and no-calorie sweetened beverages as a replacement for sugar-sweetened beverages with body weight and cardiometabolic risk: a systematic review and meta-analysis. *JAMA Netw Open* 2022;5:e222092
240. 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC, U.S. Department of Health and Human Services, 2018
241. Bazargan-Hejazi S, Arroyo JS, Hsia S, Brojeni NR, Pan D. A racial comparison of differences between self-reported and objectively measured physical activity among US adults with diabetes. *Ethn Dis* 2017;27:403–410
242. Khunti K, Griffin S, Brennan A, et al. Behavioural interventions to promote physical activity in a multiethnic population at high risk of diabetes: PROPELS three-arm RCT. *Health Technol Assess* 2021;25:1–190
243. Bootwong P, Intarut N. The effects of text messages for promoting physical activities in prediabetes: a randomized controlled trial. *Telemed J E Health* 2022;28:896–903
244. Sluik D, Buijse B, Muckelbauer R, et al. Physical activity and mortality in individuals with diabetes mellitus: a prospective study and meta-analysis. *Arch Intern Med* 2012;172:1285–1295
245. Tikkanen-Dolenc H, Wadén J, Forsblom C, et al.; FinnDiane Study Group. Physical activity reduces risk of premature mortality in patients with type 1 diabetes with and without kidney disease. *Diabetes Care* 2017;40:1727–1732
246. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001;286:1218–1227
247. Peters AL, Laffel L (Eds.). American Diabetes Association/JDRF Type 1 Diabetes Sourcebook. Alexandria, VA, American Diabetes Association, 2013
248. Ostman C, Jewiss D, King N, Smart NA. Clinical outcomes to exercise training in type 1 diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2018;139:380–391
249. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia* 2003;46:1071–1081
250. Pandey A, Patel KV, Bahnson JL, et al.; Look AHEAD Research Group. Association of intensive lifestyle intervention, fitness, and body mass index with risk of heart failure in overweight or obese adults with type 2 diabetes mellitus: an analysis from the Look AHEAD Trial. *Circulation* 2020;141:1295–1306
251. Rejeski WJ, Ip EH, Bertoni AG, et al.; Look AHEAD Research Group. Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med* 2012;366:1209–1217
252. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2016;39:2065–2079
253. Frediani JK, Bienvenida AF, Li J, Higgins MK, Lobelo F. Physical fitness and activity changes after a 24-week soccer-based adaptation of the U.S diabetes prevention program intervention in Hispanic men. *Prog Cardiovasc Dis* 2020;63:775–785
254. Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. *Int J Behav Nutr Phys Act* 2010;7:40
255. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol* 2017;5:377–390
256. Anderson BJ, Laffel LM, Domenger C, et al. Factors associated with diabetes-specific health-related quality of life in youth with type 1 diabetes: the Global TEENs Study. *Diabetes Care* 2017;40:1002–1009
257. Adolfsson P, Riddell MC, Taplin CE, et al. ISPAD Clinical Practice Consensus Guidelines 2018: exercise in children and adolescents with diabetes. *Pediatr Diabetes* 2018;19(Suppl. 27):205–226
258. Jelleyman C, Yates T, O'Donovan G, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. *Obes Rev* 2015;16:942–961
259. Little JP, Gillen JB, Percival ME, et al. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J Appl Physiol* 2011;111:1554–1560
260. Bohn B, Herbst A, Pfeifer M, et al.; DPV Initiative. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: a cross-sectional multicenter study of 18,028 patients. *Diabetes Care* 2015;38:1536–1543
261. U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd ed. Accessed 19 October 2022. Available from https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf
262. Willey KA, Singh MAF. Battling insulin resistance in elderly obese people with type 2 diabetes: bring on the heavy weights. *Diabetes Care* 2003;26:1580–1588
263. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc* 2009;41:998–1005
264. Dempsey PC, Larsen RN, Sethi P, et al. Benefits for type 2 diabetes of interrupting prolonged sitting with brief bouts of light walking or simple resistance activities. *Diabetes Care* 2016;39:964–972
265. Wang Y, Lee DC, Brellenthin AG, et al. Leisure-time running reduces the risk of incident type 2 diabetes. *Am J Med* 2019;132:1225–1232
266. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013;159:543–551
267. Pai LW, Li TC, Hwu YJ, Chang SC, Chen LL, Chang PY. The effectiveness of regular leisure-time physical activities on long-term glycemic control in people with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2016;113:77–85
268. Cui J, Yan JH, Yan LM, Pan L, Le JJ, Guo YZ. Effects of yoga in adults with type 2 diabetes mellitus: a meta-analysis. *J Diabetes Investig* 2017;8:201–209
269. Lee MS, Jun JH, Lim HJ, Lim HS. A systematic review and meta-analysis of tai chi for treating type 2 diabetes. *Maturitas* 2015;80:14–23
270. Rees JL, Johnson ST, Boulé NG. Aquatic exercise for adults with type 2 diabetes: a meta-analysis. *Acta Diabetol* 2017;54:895–904
271. Church TS, Blair SN, Cocroham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2010;304:2253–2262
272. Kanaley JA, Colberg SR, Corcoran MH, et al. Exercise/physical activity in individuals with type 2 diabetes: a consensus statement from the American College of Sports Medicine. *Med Sci Sports Exerc* 2022;54:353–368
273. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO; ADA. Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 2007;30:2729–2736
274. Colberg SR. Exercise and Diabetes: A Clinician's Guide to Prescribing Physical Activity. 1st ed. Alexandria, VA, American Diabetes Association, 2013

275. Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. *Med Sci Sports Exerc* 2003;35:1093–1099
276. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care* 2006;29:1294–1299
277. Spallone V, Ziegler D, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011;27:639–653
278. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010;33:1578–1584
279. Suarez L, Barrett-Connor E. Interaction between cigarette smoking and diabetes mellitus in the prediction of death attributed to cardiovascular disease. *Am J Epidemiol* 1984;120:670–675
280. Stanton CA, Keith DR, Gaalema DE, et al. Trends in tobacco use among US adults with chronic health conditions: National Survey on Drug Use and Health 2005–2013. *Prev Med* 2016;92:160–168
281. Bae J. Differences in cigarette use behaviors by age at the time of diagnosis with diabetes from young adulthood to adulthood: results from the National Longitudinal Study of Adolescent Health. *J Prev Med Public Health* 2013;46:249–260
282. Śliwińska-Mossoń M, Milnerowicz H. The impact of smoking on the development of diabetes and its complications. *Diab Vasc Dis Res* 2017;14:265–276
283. Kar D, Gillies C, Zaccardi F, Webb D, Seidu S, Tesfaye S, et al. Relationship of cardiometabolic parameters in non-smokers, current smokers, and quitters in diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2016;15:158
284. Pan A, Wang Y, Talaai M, Hu FB. Relation of smoking with total mortality and cardiovascular events among patients with diabetes mellitus: a meta-analysis and systematic review. *Circulation* 2015;132:1795–1804
285. Jankowich M, Choudhary G, Taveira TH, Wu WC. Age-, race-, and gender-specific prevalence of diabetes among smokers. *Diabetes Res Clin Pract* 2011;93:e101–e105
286. Akter S, Goto A, Mizoue T. Smoking and the risk of type 2 diabetes in Japan: a systematic review and meta-analysis. *J Epidemiol* 2017;27:553–561
287. Liu X, Bragg F, Yang L, et al.; China Kadoorie Biobank Collaborative Group. Smoking and smoking cessation in relation to risk of diabetes in Chinese men and women: a 9-year prospective study of 0.5 million people. *Lancet Public Health* 2018;3:e167–e176
288. Tonstad S, Lawrence D. Varenicline in smokers with diabetes: a pooled analysis of 15 randomized, placebo-controlled studies of varenicline. *J Diabetes Investig* 2017;8:93–100
289. West R. Tobacco smoking: health impact, prevalence, correlates and interventions. *Psychol Health* 2017;32:1018–1036
290. Ranney L, Melvin C, Lux L, McClain E, Lohr KN. Systematic review: smoking cessation intervention strategies for adults and adults in special populations. *Ann Intern Med* 2006;145:845–856
291. Tian J, Venn A, Otahal P, Gall S. The association between quitting smoking and weight gain: a systematic review and meta-analysis of prospective cohort studies. *Obes Rev* 2015;16:883–901
292. Clair C, Rigotti NA, Porneala B, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. *JAMA* 2013;309:1014–1021
293. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. *Metabolism* 2011;60:1456–1464
294. Huerta TR, Walker DM, Mullen D, Johnson TJ, Ford EW. Trends in E-cigarette awareness and perceived harmfulness in the U.S. *Am J Prev Med* 2017;52:339–346
295. Pericot-Valverde I, Gaalema DE, Priest JS, Higgins ST. E-cigarette awareness, perceived harmfulness, and ever use among U.S. adults. *Prev Med* 2017;104:92–99
296. Centers for Disease Control and Prevention. Smoking & tobacco use: outbreak of lung injury associated with e-cigarette use, or vaping, products. Accessed 19 October 2022. Available from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
297. Reid RD, Malcolm J, Wooding E, et al. Prospective, cluster-randomized trial to implement the Ottawa model for smoking cessation in diabetes education programs in Ontario, Canada. *Diabetes Care* 2018;41:406–412
298. Hood KK, Peterson CM, Rohan JM, Drotar D. Association between adherence and glycemic control in pediatric type 1 diabetes: a meta-analysis. *Pediatrics* 2009;124:e1171–e1179
299. Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther* 2011;33:74–109
300. Hood KK, Rohan JM, Peterson CM, Drotar D. Interventions with adherence-promoting components in pediatric type 1 diabetes: meta-analysis of their impact on glycemic control. *Diabetes Care* 2010;33:1658–1664
301. Hilliard ME, Powell PW, Anderson BJ. Evidence-based behavioral interventions to promote diabetes management in children, adolescents, and families. *Am Psychol* 2016;71:590–601
302. Hood KK, Hilliard M, Piatt G, Levers-Landis CE. Effective strategies for encouraging behavior change in people with diabetes. *Diabetes Manag (Lond)* 2015;5:499–510
303. Berhe KK, Gebru HB, Kahsay HB. Effect of motivational interviewing intervention on HgbA1C and depression in people with type 2 diabetes mellitus (systematic review and meta-analysis). *PLoS One* 2020;15:e0240839
304. Powell PW, Hilliard ME, Anderson BJ. Motivational interviewing to promote adherence behaviors in pediatric type 1 diabetes. *Curr Diab Rep* 2014;14:531
305. Liang W, Lo SHS, Tola YO, Chow KM. The effectiveness of self-management programmes for people with type 2 diabetes receiving insulin injection: a systematic review and meta-analysis. *Int J Clin Pract* 2021;75:e14636
306. Almutairi N, Hosseinzadeh H, Gopaldasani V. The effectiveness of patient activation intervention on type 2 diabetes mellitus glycemic control and self-management behaviors: a systematic review of RCTs. *Prim Care Diabetes* 2020;14:12–20
307. Rosales CB, Denman CA, Bell ML, et al. Meta Salud Diabetes for cardiovascular disease prevention in Mexico: a cluster-randomized behavioural clinical trial. *Int J Epidemiol* 2021;50:1272–1282
308. Gray KE, Hoerster KD, Taylor L, Krieger J, Nelson KM. Improvements in physical activity and some dietary behaviors in a community health worker-led diabetes self-management intervention for adults with low incomes: results from a randomized controlled trial. *Transl Behav Med* 2021;11:2144–2154
309. Van Rhoon L, Byrne M, Morrissey E, Murphy J, McSharry J. A systematic review of the behaviour change techniques and digital features in technology-driven type 2 diabetes prevention interventions. *Digit Health* 2020;6:2055207620914427
310. Fitzpatrick SL, Schumann KP, Hill-Briggs F. Problem solving interventions for diabetes self-management and control: a systematic review of the literature. *Diabetes Res Clin Pract* 2013;100:145–161
311. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. *Diabetes Care* 2012;35:2681–2689
312. Nicolucci A, Haxhi J, D'Errico V, et al.; Italian Diabetes and Exercise Study 2 (IDES_2) Investigators. Effect of a behavioural intervention for adoption and maintenance of a physically active lifestyle on psychological well-being and quality of life in patients with type 2 diabetes: the IDES_2 randomized clinical trial. *Sports Med* 2022;52:643–654
313. Crowley MJ, Tarkington PE, Bosworth HB, et al. Effect of a comprehensive telehealth intervention vs telemonitoring and care coordination in patients with persistently poor type 2 diabetes control: a randomized clinical trial. *JAMA Intern Med* 2022;182:943–952
314. Kichler JC, Harris MA, Weissberg-Benchell J. Contemporary roles of the pediatric psychologist in diabetes care. *Curr Diabetes Rev* 2015;11:210–221
315. Harris MA, Freeman KA, Duke DC. Seeing is believing: using skype to improve diabetes outcomes in youth. *Diabetes Care* 2015;38:1427–1434
316. Naicker K, Johnson JA, Skogen JC, et al. Type 2 diabetes and comorbid symptoms of depression and anxiety: longitudinal associations with mortality risk. *Diabetes Care* 2017;40:352–358
317. de Groot M, Golden SH, Wagner J. Psychological conditions in adults with diabetes. *Am Psychol* 2016;71:552–562
318. Anderson RJ, Grigsby AB, Freedland KE, et al. Anxiety and poor glycemic control: a meta-analytic review of the literature. *Int J Psychiatry Med* 2002;32:235–247
319. Delahanty LM, Grant RW, Wittenberg E, et al. Association of diabetes-related emotional distress with diabetes treatment in primary care patients with type 2 diabetes. *Diabet Med* 2007;24:48–54
320. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid de-

- pression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069–1078
321. Nicolucci A, Kovacs Burns K, Holt RIG, et al.; DAWN2 Study Group. Diabetes Attitudes, Wishes and Needs second study (DAWN2): cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes. *Diabet Med* 2013;30:767–777
322. Ducat L, Philipson LH, Anderson BJ. The mental health comorbidities of diabetes. *JAMA* 2014;312:691–692
323. Guerrero Fernández de Alba I, Gimeno-Miguel A, Poblador-Plou B, et al. Association between mental health comorbidity and health outcomes in type 2 diabetes mellitus patients. *Sci Rep* 2020;10:19583
324. Gonzalvo JD, Hamm J, Eaves S, et al. A practical approach to mental health for the diabetes educator. *AADE Pract* 2019;7:29–44
325. Robinson DJ, Coons M, Haensel H, Vallis M; Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes and mental health. *Can J Diabetes* 2018;42(Suppl. 1):S130–S141
326. Cho MK, Kim MY. Self-management nursing intervention for controlling glucose among diabetes: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2021;18:12750
327. Majidi S, Reid MW, Fogel J, et al. Psychosocial outcomes in young adolescents with type 1 diabetes participating in shared medical appointments. *Pediatr Diabetes* 2021;22:787–795
328. Diaz Bustamante L, Ghattas KN, Ilyas S, Al-Refai R, Maharjan R, Khan S. Does treatment for depression with collaborative care improve the glycemic levels in diabetic patients with depression? A systematic review. *Cureus* 2020;12:e10551
329. Phillips S, Culpepper J, Welch M, et al. A multidisciplinary diabetes clinic improves clinical and behavioral outcomes in a primary care setting. *J Am Board Fam Med* 2021;34:579–589
330. Xu C, Dong Z, Zhang P, et al. Effect of group cognitive behavioural therapy on psychological stress and blood glucose in people with type 2 diabetes mellitus: a community-based cluster randomized controlled trial in China. *Diabet Med* 2021;38:e14491
331. Ali MK, Chwastiak L, Poongothai S, et al.; INDEPENDENT Study Group. Effect of a collaborative care model on depressive symptoms and glycated hemoglobin, blood pressure, and serum cholesterol among patients with depression and diabetes in India: the INDEPENDENT randomized clinical trial. *JAMA* 2020;324:651–662
332. Rechenberg K, Koerner R. Cognitive behavioral therapy in adolescents with type 1 diabetes: an integrative review. *J Pediatr Nurs* 2021;60:190–197
333. McMorrow R, Hunter B, Hendrieckx C, et al. Effect of routinely assessing and addressing depression and diabetes distress on clinical outcomes among adults with type 2 diabetes: a systematic review. *BMJ Open* 2022;12:e054650
334. Harkness E, Macdonald W, Valderas J, Coventry P, Gask L, Bower P. Identifying psychosocial interventions that improve both physical and mental health in patients with diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33:926–930
335. Radcliff TA, Côté MJ, Whittington MD, et al. Cost-effectiveness of three doses of a behavioral intervention to prevent or delay type 2 diabetes in rural areas. *J Acad Nutr Diet* 2020;120:1163–1171
336. T1D Exchange. Depression screening change package. Accessed 10 September 2022. Available from <https://t1dexchange.org/depression-screening-change-package/>
337. Mulvaney SA, Mara CA, Kichler JC, et al. A retrospective multisite examination of depression screening practices, scores, and correlates in pediatric diabetes care. *Transl Behav Med* 2021;11:122–131
338. Monaghan M, Mara CA, Kichler JC, et al. Multisite examination of depression screening scores and correlates among adolescents and young adults with type 2 diabetes. *Can J Diabetes* 2021;45:411–416
339. Watson SE, Spurling SE, Fieldhouse AM, Montgomery VL, Wintergerst KA. Depression and anxiety screening in adolescents with diabetes. *Clin Pediatr (Phila)* 2020;59:445–449
340. Brodar KE, Davis EM, Lynn C, et al. Comprehensive psychosocial screening in a pediatric diabetes clinic. *Pediatr Diabetes* 2021;22:656–666
341. Weissberg-Benchell J, Shapiro JB. A review of interventions aimed at facilitating successful transition planning and transfer to adult care among youth with chronic illness. *Pediatr Ann* 2017;46:e182–e187
342. O'Gurek DT, Henke C. A practical approach to screening for social determinants of health. *Fam Pract Manag* 2018;25:7–12
343. Zhang H, Zhang Q, Luo D, et al. The effect of family-based intervention for adults with diabetes on HbA1c and other health-related outcomes: systematic review and meta-analysis. *J Clin Nurs* 2022;31:1488–1501
344. McBroom LA, Enriquez M. Review of family-centered interventions to enhance the health outcomes of children with type 1 diabetes. *Diabetes Educ* 2009;35:428–438
345. Oyediji AD, Ullah I, Weich S, Bentall R, Booth A. Effectiveness of non-specialist delivered psychological interventions on glycemic control and mental health problems in individuals with type 2 diabetes: a systematic review and meta-analysis. *Int J Ment Health Syst* 2022;16:9
346. Chen SM, Lin HS, Atherton JJ, MacIsaac RJ, Wu CJ. Effect of a mindfulness programme for long-term care residents with type 2 diabetes: a cluster randomised controlled trial measuring outcomes of glycaemic control, relocation stress and depression. *Int J Older People Nurs* 2020;15:e12312
347. Beverly EA, Hultgren BA, Brooks KM, Ritholz MD, Abrahamson MJ, Weinger K. Understanding physicians' challenges when treating type 2 diabetic patients' social and emotional difficulties: a qualitative study. *Diabetes Care* 2011;34:1086–1088
348. Li Y, Storch EA, Ferguson S, Li L, Buys N, Sun J. The efficacy of cognitive behavioral therapy-based intervention on patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2022;189:109965
349. Vlachou E, Ntikoudi A, Owens DA, Nikolakopoulou M, Chalimourdas T, Cauli O. Effectiveness of cognitive behavioral therapy-based interventions on psychological symptoms in adults with type 2 diabetes mellitus: an update review of randomized controlled trials. *J Diabetes Complications* 2022;36:108185
350. Nikkiah Ravari O, Mousavi SZ, Babak A. Evaluation of the effects of 12 weeks mindfulness-based stress reduction on glycemic control and mental health indices in women with diabetes mellitus type 2. *Adv Biomed Res* 2020;9:61
351. Ni YX, Ma L, Li JP. Effects of mindfulness-based intervention on glycemic control and psychological outcomes in people with diabetes: a systematic review and meta-analysis. *J Diabetes Investig* 2021;12:1092–1103
352. Hood KK, Iturralde E, Rausch J, Weissberg-Benchell J. Preventing diabetes distress in adolescents with type 1 diabetes: results 1 year after participation in the STEPS Program. *Diabetes Care* 2018;41:1623–1630
353. Weissberg-Benchell J, Shapiro JB, Bryant FB, Hood KK. Supporting Teen Problem-Solving (STEPS) 3 year outcomes: preventing diabetes-specific emotional distress and depressive symptoms in adolescents with type 1 diabetes. *J Consult Clin Psychol* 2020;88:1019–1031
354. Laffel LMB, Vangness L, Connell A, Goebel-Fabbri A, Butler D, Anderson BJ. Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes. *J Pediatr* 2003;142:409–416
355. Wysocki T, Harris MA, Buckloh LM, et al. Effects of behavioral family systems therapy for diabetes on adolescents' family relationships, treatment adherence, and metabolic control. *J Pediatr Psychol* 2006;31:928–938
356. Yap JM, Tantonio N, Wu VX, Klainin-Yobas P. Effectiveness of technology-based psychosocial interventions on diabetes distress and health-relevant outcomes among type 2 diabetes mellitus: a systematic review and meta-analysis. *J Telemed Telecare* 26 November 2021 [Epub ahead of print]. DOI: 10.1177/1357633X211058329
357. Bisno DI, Reid MW, Fogel JL, Pyatak EA, Majidi S, Raymond JK. Virtual Group Appointments Reduce Distress and Improve Care Management in Young Adults with Type 1 Diabetes. *J Diabetes Sci Technol* 2021;30:19322968211035768
358. Fisher L, Hessler DM, Polonsky WH, Mullan J. When is diabetes distress clinically meaningful? Establishing cut points for the Diabetes Distress Scale. *Diabetes Care* 2012;35:259–264
359. Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with glycemic control among patients with type 2 diabetes. *Diabetes Care* 2010;33:1034–1036
360. Hagger V, Hendrieckx C, Sturt J, Skinner TC, Speight J. Diabetes distress among adolescents with type 1 diabetes: a systematic review. *Curr Diab Rep* 2016;16:9
361. Wasserman RM, Eshtehardi SS, Anderson BJ, Weissberg-Benchell JA, Hilliard ME. Profiles of depressive symptoms and diabetes distress in preadolescents with type 1 diabetes. *Can J Diabetes* 2021;45:436–443
362. Aikens JE. Prospective associations between emotional distress and poor outcomes in type 2 diabetes. *Diabetes Care* 2012;35:2472–2478
363. Liu X, Haagsma J, Sijbrands E, et al. Anxiety and depression in diabetes care: longitudinal associations with health-related quality of life. *Sci Rep* 2020;10:8307
364. Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. *Lancet Diabetes Endocrinol* 2015;3:450–460

365. Sturt J, Dennick K, Hessler D, Hunter BM, Oliver J, Fisher L. Effective interventions for reducing diabetes distress: systematic review and meta-analysis. *International Diabetes Nursing* 2015;12:40–55
366. Ngan HY, Chong YY, Chien WT. Effects of mindfulness- and acceptance-based interventions on diabetes distress and glycaemic level in people with type 2 diabetes: systematic review and meta-analysis. *Diabet Med* 2021;38:e14525
367. Presley C, Agne A, Shelton T, Oster R, Cherrington A. Mobile-enhanced peer support for African Americans with type 2 diabetes: a randomized controlled trial. *J Gen Intern Med* 2020;35:2889–2896
368. Fisher L, Skaff MM, Mullan JT, et al. Clinical depression versus distress among patients with type 2 diabetes: not just a question of semantics. *Diabetes Care* 2007;30:542–548
369. Fisher L, Hessler D, Polonsky WH, et al. T1-REDEEM: a randomized controlled trial to reduce diabetes distress among adults with type 1 diabetes. *Diabetes Care* 2018;41:1862–1869
370. DiNardo MM, Greco C, Phares AD, et al. Effects of an integrated mindfulness intervention for veterans with diabetes distress: a randomized controlled trial. *BMJ Open Diabetes Res Care* 2022;10:e002631
371. Lutes LD, Cummings DM, Littlewood K, et al. A tailored cognitive-behavioural intervention produces comparable reductions in regimen-related distress in adults with type 2 diabetes regardless of insulin use: 12-month outcomes from the COMRADE trial. *Can J Diabetes* 2020;44:530–536
372. Friis AM, Johnson MH, Cutfield RG, Consedine NS. Kindness matters: a randomized controlled trial of a mindful self-compassion intervention improves depression, distress, and HbA1c among patients with diabetes. *Diabetes Care* 2016;39:1963–1971
373. Smith KJ, Béland M, Clyde M, et al. Association of diabetes with anxiety: a systematic review and meta-analysis. *J Psychosom Res* 2013;74:89–99
374. Li C, Barker L, Ford ES, Zhang X, Strine TW, Mokdad AH. Diabetes and anxiety in US adults: findings from the 2006 Behavioral Risk Factor Surveillance System. *Diabet Med* 2008;25:878–881
375. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. *Diabetes Care* 1987;10:617–621
376. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. *Patient Educ Couns* 2007;68:10–15
377. Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. *Diabetes Res Clin Pract* 1999;46:239–246
378. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA, American Psychiatric Association, 2013
379. Mitsonis C, Dimopoulos N, Psarra V. P01-138 Clinical implications of anxiety in diabetes: a critical review of the evidence base. *Eur Psychiatry* 2009;24:S526
380. Kemp CG, Johnson LCM, Sagar R, et al. Effect of a collaborative care model on anxiety symptoms among patients with depression and diabetes in India: the INDEPENDENT randomized clinical trial. *Gen Hosp Psychiatry* 2022;74:39–45
381. Yeoh E, Choudhary P, Nwokolo M, Ayis S, Amiel SA. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2015;38:1592–1609
382. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care* 2001;24:637–642
383. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. *Diabetes Care* 2011;34:801–806
384. Cox DJ, Kovatchev B, Koev D, et al. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. *Int J Behav Med* 2004;11:212–218
385. Lamounier RN, Geloneze B, Leite SO, et al.; HAT Brazil study group. Hypoglycemia incidence and awareness among insulin-treated patients with diabetes: the HAT study in Brazil. *Diabetol Metab Syndr* 2018;10:83
386. Amiel SA, Potts L, Goldsmith K, et al. A parallel randomised controlled trial of the Hypoglycaemia Awareness Restoration Programme for adults with type 1 diabetes and problematic hypoglycaemia despite optimised self-care (HARPOdoc). *Nat Commun* 2022;13:2229
387. Lustman PJ, Griffith LS, Clouse RE. Depression in adults with diabetes. Results of 5-yr follow-up study. *Diabetes Care* 1988;11:605–612
388. de Groot M, Crick KA, Long M, Saha C, Shubrook JH. Lifetime duration of depressive disorders in patients with type 2 diabetes. *Diabetes Care* 2016;39:2174–2181
389. Rubin RR, Ma Y, Marrero DG, et al.; Diabetes Prevention Program Research Group. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. *Diabetes Care* 2008;31:420–426
390. Clouse RE, Lustman PJ, Freedland KE, Griffith LS, McGill JB, Carney RM. Depression and coronary heart disease in women with diabetes. *Psychosom Med* 2003;65:376–383
391. Vassilopoulos A, Nicholl M, Wolf RM, Slifer KJ, Cirincione L. Discrepancies in assessing symptoms of depression in adolescents with diabetes using the patient health questionnaire and semi-structured interviews. *Diabetes Spectr* 2020;33:339–346
392. Katon WJ, Von Korff M, Lin EHB, et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. *Arch Gen Psychiatry* 2004;61:1042–1049
393. Cannon A, Handelsman Y, Heile M, Shannon M. Burden of illness in type 2 diabetes mellitus. *J Manag Care Spec Pharm* 2018;24(Suppl.):S5–S13
394. Atlantis E, Fahey P, Foster J. Collaborative care for comorbid depression and diabetes: a systematic review and meta-analysis. *BMJ Open* 2014;4:e004706
395. van der Feltz-Cornelis C, Allen SF, Holt RIG, Roberts R, Nouwen A, Sartorius N. Treatment for comorbid depressive disorder or subthreshold depression in diabetes mellitus: systematic review and meta-analysis. *Brain Behav* 2021;11:e01981
396. Lu X, Yang D, Liang J, et al. Effectiveness of intervention program on the change of glycaemic control in diabetes with depression patients: a meta-analysis of randomized controlled studies. *Prim Care Diabetes* 2021;15:428–434
397. Varela-Moreno E, Carreira Soler M, Guzmán-Parra J, Jódar-Sánchez F, Mayoral-Cleries F, Anarte-Ortiz MT. Effectiveness of eHealth-based psychological interventions for depression treatment in patients with type 1 or type 2 diabetes mellitus: a systematic review. *Front Psychol* 2022;12:746217
398. Mohammad Rahimi GR, Aminzadeh R, Azimkhani A, Saatchian V. The effect of exercise interventions to improve psychosocial aspects and glycemic control in type 2 diabetic patients: a systematic review and meta-analysis of randomized controlled trials. *Biol Res Nurs* 2022;24:10–23
399. Pinhas-Hamiel O, Hamiel U, Levy-Shraga Y. Eating disorders in adolescents with type 1 diabetes: challenges in diagnosis and treatment. *World J Diabetes* 2015;6:517–526
400. Papelbaum M, Appolinário JC, Moreira R de O, Ellinger VCM, Kupfer R, Coutinho WF. Prevalence of eating disorders and psychiatric comorbidity in a clinical sample of type 2 diabetes mellitus patients. *Rev Bras Psiquiatr* 2005;27:135–138
401. Young-Hyman DL, Davis CL. Disordered eating behavior in individuals with diabetes: importance of context, evaluation, and classification. *Diabetes Care* 2010;33:683–689
402. Pinhas-Hamiel O, Hamiel U, Greenfield Y, et al. Detecting intentional insulin omission for weight loss in girls with type 1 diabetes mellitus. *Int J Eat Disord* 2013;46:819–825
403. Goebel-Fabbri AE, Fikkan J, Franko DL, Pearson K, Anderson BJ, Weinger K. Insulin restriction and associated morbidity and mortality in women with type 1 diabetes. *Diabetes Care* 2008;31:415–419
404. Weinger K, Beverly EA. Barriers to achieving glycemic targets: who omits insulin and why? *Diabetes Care* 2010;33:450–452
405. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry* 2007;61:348–358
406. Martyn-Nemeth P, Quinn L, Hacker E, Park H, Kujath AS. Diabetes distress may adversely affect the eating styles of women with type 1 diabetes. *Acta Diabetol* 2014;51:683–686
407. Pursey KM, Hart M, Jenkins L, McEvoy M, Smart CE. Screening and identification of disordered eating in people with type 1 diabetes: a systematic review. *J Diabetes Complications* 2020;34:107522
408. Peterson CM, Fischer S, Young-Hyman D. Topical review: a comprehensive risk model for disordered eating in youth with type 1 diabetes. *J Pediatr Psychol* 2015;40:385–390
409. Zaremba N, Watson A, Kan C, et al. Multidisciplinary healthcare teams' challenges and strategies in supporting people with type 1 diabetes to recover from disordered eating. *Diabet Med* 2020;37:1992–2000
410. Banting R, Randle-Phillips C. A systematic review of psychological interventions for comorbid type 1 diabetes mellitus and eating disorders. *Diabetes Manag (Lond)* 2018;8:1–18

411. Priesterroth L, Grammes J, Clauter M, Kubiak T. Diabetes technologies in people with type 1 diabetes mellitus and disordered eating: A systematic review on continuous subcutaneous insulin infusion, continuous glucose monitoring and automated insulin delivery. *Diabet Med* 2021;38:e14581
412. Hansson L, Zanchetti A, Carruthers SG, et al.; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755–1762
413. van Bloemendaal L, IJzerman RG, Ten Kulve JS, et al. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. *Diabetes* 2014;63:4186–4196
414. Devarajoo C, Chinna K. Depression, distress and self-efficacy: the impact on diabetes self-care practices. *PLoS One* 2017;12:e0175096
415. Suvisaari J, Perälä J, Saarni SI, et al. Type 2 diabetes among persons with schizophrenia and other psychotic disorders in a general population survey. *Eur Arch Psychiatry Clin Neurosci* 2008; 258:129–136
416. Mulligan K, McBain H, Lamontagne-Godwin F, et al. Barriers to effective diabetes management—a survey of people with severe mental illness. *BMC Psychiatry* 2018;18:165
417. Schnitzer K, Cather C, Zvonar V, et al. Patient experience and predictors of improvement in a group behavioral and educational intervention for individuals with diabetes and serious mental illness: mixed methods case study. *J Particip Med* 2021;13:e21934
418. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002;325:243
419. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27:596–601
420. Holt RIG. Association between antipsychotic medication use and diabetes. *Curr Diab Rep* 2019;19:96–96
421. Kruse J, Schmitz N; German National Health Interview and Examination Survey. On the association between diabetes and mental disorders in a community sample: results from the German National Health Interview and Examination Survey. *Diabetes Care* 2003; 26:1841–1846
422. Biessels GJ, Whitmer RA. Cognitive dysfunction in diabetes: how to implement emerging guidelines. *Diabetologia* 2020;63:3–9
423. Brands AMA, Biessels GJ, de Haan EHF, Kappelle LJ, Kessels RPC. The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care* 2005;28:726–735
424. Carmichael OT, Neiberg RH, Dutton GR, et al. Long-term change in physiological markers and cognitive performance in type 2 diabetes: the Look AHEAD Study. *J Clin Endocrinol Metab* 2020;105:dga591
425. Avila JC, Mejia-Arangom S, Jupiter D, Downer B, Wong R. The effect of diabetes on the cognitive trajectory of older adults in Mexico and the United States. *J Gerontol B Psychol Sci Soc Sci* 2021;76:e153–e164
426. Munshi MN. Cognitive dysfunction in older adults with diabetes: what a clinician needs to know. *Diabetes Care* 2017;40:461–467
427. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol* 2018;14: 591–604
428. Feinkohl I, Aung PP, Keller M, et al.; Edinburgh Type 2 Diabetes Study (ET2DS) Investigators. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Diabetes Care* 2014;37:507–515
429. Strudwick SK, Carne C, Gardiner J, Foster JK, Davis EA, Jones TW. Cognitive functioning in children with early onset type 1 diabetes and severe hypoglycemia. *J Pediatr* 2005;147: 680–685
430. Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis. *Sleep Med Rev* 2016;30:11–24
431. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33:414–420
432. Zhu B, Shi C, Park CG, Reutrakul S. Sleep quality and gestational diabetes in pregnant women: a systematic review and meta-analysis. *Sleep Med* 2020;67:47–55
433. Zhang X, Zhang R, Cheng L, et al. The effect of sleep impairment on gestational diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Sleep Med* 2020;74:267–277
434. Lee SWH, Ng KY, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Sleep Med Rev* 2017;31:91–101
435. Barone MTU, Menna-Barreto L. Diabetes and sleep: a complex cause-and-effect relationship. *Diabetes Res Clin Pract* 2011;91:129–137
436. Reutrakul S, Thakkinstian A, Anothaisintawee T, et al. Sleep characteristics in type 1 diabetes and associations with glycemic control: systematic review and meta-analysis. *Sleep Med* 2016;23: 26–45
437. Ji X, Wang Y, Saylor J. Sleep and type 1 diabetes mellitus management among children, adolescents, and emerging young adults: a systematic review. *J Pediatr Nurs* 2021;61:245–253
438. Perez KM, Hamburger ER, Lyttle M, et al. Sleep in type 1 diabetes: implications for glycemic control and diabetes management. *Curr Diab Rep* 2018;18:5
439. Schipper SBJ, Van Veen MM, Elders PJM, et al. Sleep disorders in people with type 2 diabetes and associated health outcomes: a review of the literature. *Diabetologia* 2021;64:2367–2377
440. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. *Chest* 2017;152:1070–1086
441. Denic-Roberts H, Costacou T, Orchard TJ. Subjective sleep disturbances and glycemic control in adults with long-standing type 1 diabetes: The Pittsburgh's Epidemiology of Diabetes Complications study. *Diabetes Res Clin Pract* 2016;119:1–12
442. Ogilvie RP, Patel SR. The epidemiology of sleep and diabetes. *Curr Diab Rep* 2018;18:82
443. Tan X, van Egmond L, Chapman CD, Cedernaes J, Benedict C. Aiding sleep in type 2 diabetes: therapeutic considerations. *Lancet Diabetes Endocrinol* 2018;6:60–68
444. Carreon SA, Cao VT, Anderson BJ, Thompson DI, Marrero DG, Hilliard ME. 'I don't sleep through the night': qualitative study of sleep in type 1 diabetes. *Diabet Med* 2022;39:e14763
445. Kothari V, Cardona Z, Chirakalwasan N, Anothaisintawee T, Reutrakul S. Sleep interventions and glucose metabolism: systematic review and meta-analysis. *Sleep Med* 2021;78:24–35

6. Glycemic Targets: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

ASSESSMENT OF GLYCEMIC CONTROL

Glycemic control is assessed by the A1C measurement, continuous glucose monitoring (CGM) using time in range (TIR) and/or glucose management indicator (GMI), and blood glucose monitoring (BGM). A1C is the metric used to date in clinical trials demonstrating the benefits of improved glycemic control. Individual glucose monitoring (discussed in detail in Section 7, “Diabetes Technology”) is a useful tool for diabetes self-management, which includes meals, physical activity, and medication adjustment, particularly in individuals taking insulin. CGM serves an increasingly important role in the management of the effectiveness and safety of treatment in many people with type 1 diabetes and in selected people with type 2 diabetes. Individuals on a variety of insulin treatment plans can benefit from CGM with improved glucose control, decreased hypoglycemia, and enhanced self-efficacy (Section 7, “Diabetes Technology”) (1).

Glycemic Assessment

Recommendations

- 6.1 Assess glycemic status (A1C or other glycemic measurement such as time in range or glucose management indicator) *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**
- 6.2 Assess glycemic status at least quarterly and as needed in patients whose therapy has recently changed and/or who are not meeting glycemic goals. **E**

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A1C reflects average glycemia over approximately 3 months. The performance of the test is generally excellent for National Glycohemoglobin Standardization Program

(NGSP)-certified assays (ngsp.org). The test is the primary tool for assessing glycemic control and has a strong predictive value for diabetes complications (2–4). Thus, A1C testing should be performed routinely in all people with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained. A 14-day CGM assessment of TIR and GMI can serve as a surrogate for A1C for use in clinical management (5–9). The frequency of A1C testing should depend on the clinical situation, the treatment plan, and the clinician's judgment. The use of point-of-care A1C testing or CGM-derived TIR and GMI may provide an opportunity for more timely treatment changes during encounters between patients and health care professionals. People with type 2 diabetes with stable glycemia well within target may do well with A1C testing or other glucose assessment only twice per year. Unstable or intensively managed patients or people not at goal with treatment adjustments may require testing more frequently (every 3 months with interim assessments as needed for safety) (10). CGM parameters can be tracked in the clinic or via telehealth to optimize diabetes management.

A1C Limitations

The A1C test is an indirect measure of average glycemia and, as such, is subject to limitations. As with any laboratory test, there is variability in the measurement of A1C. Although A1C variability is lower on an intraindividual basis than that of blood glucose measurements, clinicians should exercise judgment when using A1C as the sole basis for assessing glycemic control, particularly if the result is close to the threshold that might prompt a change in medication therapy. For example, conditions that affect red blood cell turnover (hemolytic and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, and pregnancy) may result in discrepancies between the A1C result and the patient's true mean glycemia (11). Hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's CGM or BGM levels. However,

most assays in use in the U.S. are accurate in individuals who are heterozygous for the most common variants (ngsp.org/interf.asp). Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol are available, but their translation into average glucose levels and their prognostic significance are not as clear as for A1C and CGM. Though some variability in the relationship between average glucose levels and A1C exists among different individuals, in general the association between mean glucose and A1C within an individual correlates over time (12).

A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from BGM/CGM and A1C. Discordant results between BGM/CGM and A1C can be the result of the conditions outlined above or glycemic variability, with BGM missing the extremes.

Correlation Between BGM and A1C

Table 6.1 shows the correlation between A1C levels and mean glucose levels based on the international A1C-Derived Average Glucose (ADAG) study, which assessed the correlation between A1C and frequent BGM and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes (13), and an empirical study of the average blood glucose levels at premeal, postmeal, and bedtime associated with specified A1C levels using data from the ADAG trial (14). The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation ($r = 0.92$) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in **Table 6.1** are based on ~2,700 readings per A1C measurement in the ADAG trial. In a report, mean glucose measured with CGM versus central laboratory-measured A1C in 387 participants in three randomized trials demonstrated that A1C may underestimate or overestimate mean glucose in individuals (12). Thus, as suggested, a patient's BGM or CGM profile

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (13,14). Adapted from Nathan et al. (13).

has considerable potential for optimizing their glycemic management (13).

A1C Differences in Ethnic Populations and Children

In the ADAG study, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although the study was underpowered to detect a difference and there was a trend toward a difference between the African and African American and the non-Hispanic White cohorts, with higher A1C values observed in the African and African American cohorts compared with non-Hispanic White cohorts for a given mean glucose. Other studies have also demonstrated higher A1C levels in African American participants than in White participants at a given mean glucose concentration (15,16). In contrast, a recent report in Afro-Caribbean individuals found lower A1C relative to glucose values (17). Taken together, A1C and glucose parameters are essential for the optimal assessment of glycemic status.

A1C assays are available that do not demonstrate a statistically significant difference in individuals with hemoglobin variants. Other assays have statistically significant interference, but the difference is not clinically significant. Use of an assay with such statistically significant interference may explain a report that

Table 6.2—Standardized CGM metrics for clinical care

1. Number of days CGM device is worn (recommend 14 days)	
2. Percentage of time CGM device is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. Glucose management indicator	
5. Glycemic variability (%CV) target $\leq 36\%$ *	
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Some studies suggest that lower %CV targets ($<33\%$) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (35).

for any level of mean glycemia, African American individuals heterozygous for the common hemoglobin variant HbS had lower A1C by about 0.3 percentage points when compared with those without the trait (18,19). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African American individuals, was associated with a decrease in A1C of about 0.8% in hemizygous men and 0.7% in homozygous women compared with those without the trait (20).

A small study comparing A1C to CGM data in children with type 1 diabetes found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation ($r = 0.7$) was significantly lower than that in the ADAG trial (21). Whether there are clinically meaningful differences in how A1C relates to average glucose in children or in different ethnicities is an area for further study (15,22,23). Until further evidence is available, it seems prudent to establish A1C goals in these populations with consideration of individualized CGM, BGM, and A1C results. Limitations in perfect alignment between glycemic measurements do not interfere with the usefulness of BGM/CGM for insulin dose adjustments.

Glucose Assessment by Continuous Glucose Monitoring

Recommendations

6.3 Standardized, single-page glucose reports from continuous glucose monitoring (CGM) devices with

visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices. **E**

6.4 Time in range is associated with the risk of microvascular complications and can be used for assessment of glycemic control. Additionally, time below range and time above range are useful parameters for the evaluation of the treatment plan (**Table 6.2**). **C**

CGM is rapidly improving diabetes management. As stated in the recommendations, time in range (TIR) is a useful metric of glycemic control and glucose patterns, and it correlates well with A1C in most studies (24–29). New data support the premise that increased TIR correlates with the risk of complications. The studies supporting this assertion are reviewed in more detail in Section 7, “Diabetes Technology”; they include cross-sectional data and cohort studies (30–32) demonstrating TIR as an acceptable end point for clinical trials moving forward and that it can be used for assessment of glycemic control. Additionally, time below range (<70 and <54 mg/dL [3.9 and 3.0 mmol/L]) and time above range (>180 mg/dL [10.0 mmol/L]) are useful parameters for insulin dose adjustments and reevaluation of the treatment plan.

For many people with diabetes, glucose monitoring is key for achieving

glycemic targets. Major clinical trials of insulin-treated patients have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications (33). BGM is thus an integral component of effective therapy of patients taking insulin. In recent years, CGM has become a standard method for glucose monitoring for most adults with type 1 diabetes (34). Both approaches to glucose monitoring allow patients to evaluate individual responses to therapy and assess whether glycemic targets are being safely achieved. The international consensus on TIR provides guidance on standardized CGM metrics (**Table 6.2**) and considerations for clinical interpretation and care (35). To make these metrics more actionable, standardized reports with visual cues, such as the ambulatory glucose profile (**Fig 6.1**), are recommended (35) and may help the patient and the health care professional better interpret the data to guide treatment decisions (24,27). BGM and CGM can be useful to guide medical nutrition therapy and physical activity, prevent hypoglycemia, and aid medication management. While A1C is currently the primary measure to guide glucose management and a valuable risk marker for developing diabetes complications, the CGM metrics TIR (with time below range and time above range) and GMI provide the insights for a more personalized diabetes management plan. The incorporation of these metrics into clinical practice is in evolution, and remote access to these data can be critical for telehealth. A rapid optimization and harmonization of CGM terminology and remote access is occurring to meet patient and health care professional needs (36–38). The patient’s specific needs and goals should dictate BGM frequency and timing and consideration of CGM use. Please refer to Section 7, “Diabetes Technology,” for a more complete discussion of the use of BGM and CGM.

With the advent of new technology, CGM has evolved rapidly in both accuracy and affordability. As such, many patients have these data available to assist with self-management and their health care professionals’ assessment of glycemic status. Reports can be generated from CGM that will allow the health care professional and person with diabetes to determine TIR, calculate GMI, and

AGP Report: Continuous Glucose Monitoring

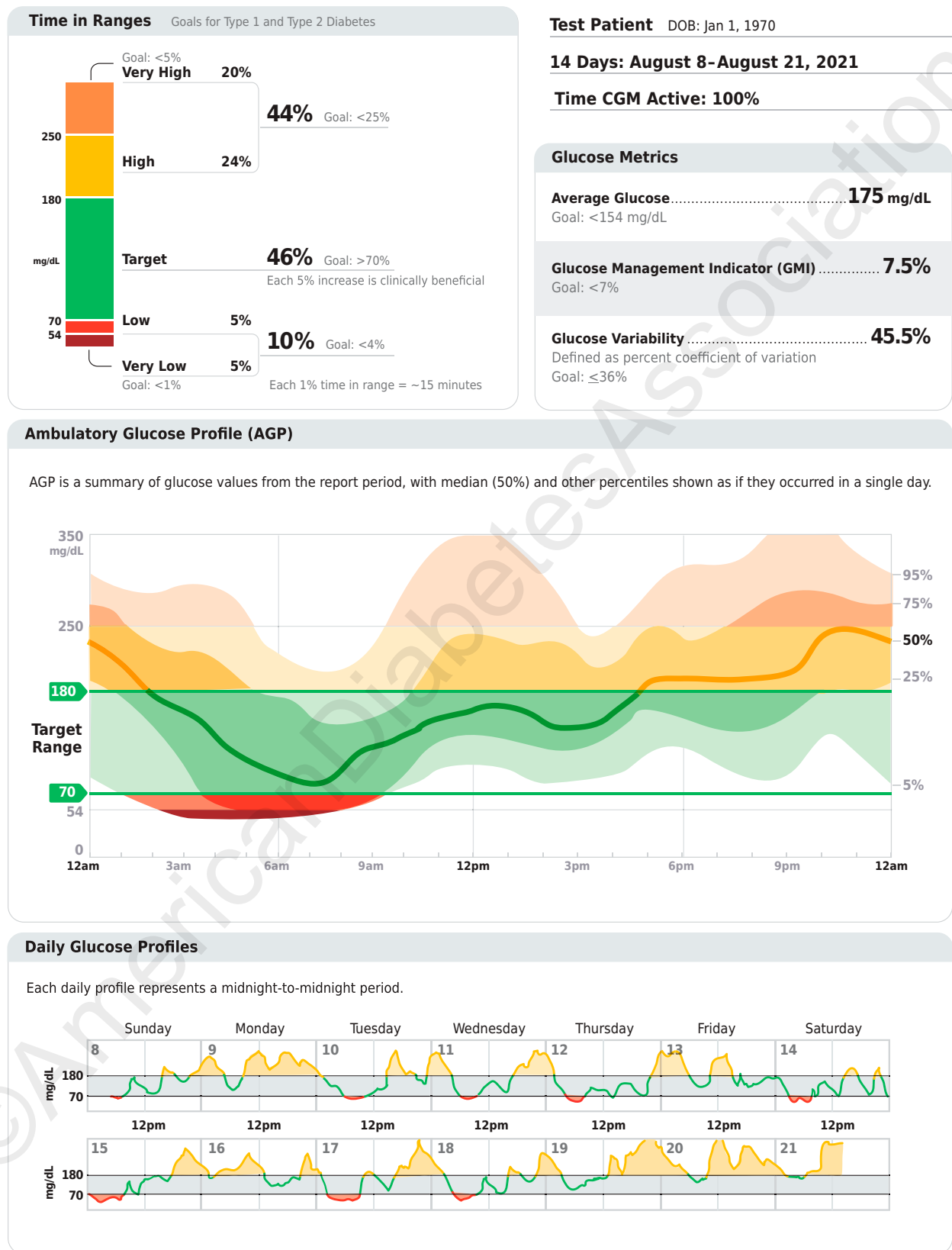


Figure 6.1—Key points included in standard ambulatory glucose profile (AGP) report. Reprinted from Holt et al. (34).

assess hypoglycemia, hyperglycemia, and glycemic variability. As discussed in a recent consensus document, a report formatted as shown in **Fig. 6.1** can be generated (35). Published data from two retrospective studies suggest a strong correlation between TIR and A1C, with a goal of 70% TIR aligning with an A1C of ~7% (8,26). Note the goals of therapy next to each metric in **Fig. 6.1** (e.g., low, <4%; very low, <1%) as values to guide changes in therapy.

GLYCEMIC GOALS

For glycemic goals in older adults, please refer to Section 13, "Older Adults." For glycemic goals in children, please refer to Section 14, "Children and Adolescents." For glycemic goals during pregnancy, please refer to Section 15, "Management of Diabetes in Pregnancy." Overall, regardless of the population being served, it is critical for the glycemic targets to be woven into the overall person-centered strategy. For example, in a very young child, safety and simplicity may outweigh the need for glycemic stability in the short run. Simplification may decrease parental anxiety and build trust and confidence, which could support further strengthening of glycemic targets and self-efficacy. In healthy older adults, there is no empiric need to loosen control; however, less stringent A1C goals may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits (39,40).

However, the health care professional needs to work with an individual and should consider adjusting targets for simplifying the treatment plan if this change is needed to improve safety and medication-taking behavior. Setting goals by face-to-face or remote consultations has been shown to be more effective than usual care for glycemic control in type 2 diabetes for fasting plasma glucose and glycated hemoglobin (41).

Recommendations

- 6.5a** An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. **A**
- 6.5b** If using ambulatory glucose profile/glucose management indicator to assess glycemia, a

parallel goal for many nonpregnant adults is time in range of >70% with time below range <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% time in range with <1% time below range is recommended. (See **Fig. 6.1** and **Table 6.2.**) **B**

- 6.6** On the basis of health care professional judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **B**
- 6.7** Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. Health care professionals should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. **B**
- 6.8** Reassess glycemic targets based on the individualized criteria in **Fig. 6.2.** **E**
- 6.9** Setting a glycemic goal during consultations is likely to improve patient outcomes. **E**

A1C and Microvascular Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The Diabetes Control and Complications Trial (DCCT) (33), a prospective randomized controlled trial of intensive (mean A1C about 7% [53 mmol/mol]) versus standard (mean A1C about 9% [75 mmol/mol]) glycemic control in people with type 1 diabetes, showed definitively that better glycemic control is associated with 50–76% reductions in rates of development and progression of microvascular (retinopathy, neuropathy, and diabetic kidney disease) complications. Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (42,43) demonstrated persistence of these microvascular benefits over two decades despite the fact that the

glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (44) and UK Prospective Diabetes Study (UKPDS) (45,46) confirmed that intensive glycemic control significantly decreased rates of microvascular complications in people with short-duration type 2 diabetes. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (47).

Therefore, achieving A1C targets of <7% (53 mmol/mol) has been shown to reduce microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease (2,48). Findings from the DCCT (33) and UKPDS (49) studies demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair/good control. These analyses also suggest that further lowering of A1C from 7 to 6% (53 mmol/mol to 42 mmol/mol) is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. The implication of these findings is that there is no need to deintensify therapy for an individual with an A1C between 6 and 7% in the setting of low hypoglycemia risk with a long life expectancy. There are now newer agents that do not cause hypoglycemia, making it possible to maintain glucose control without the risk of hypoglycemia (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Given the substantially increased risk of hypoglycemia in type 1 diabetes and with polypharmacy in type 2 diabetes, the risks of lower glycemic targets may outweigh the potential benefits on microvascular complications. Three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to test the effects of near normalization of blood glucose on cardiovascular outcomes in individuals with long-standing type 2 diabetes and either known cardiovascular disease (CVD) or high cardiovascular

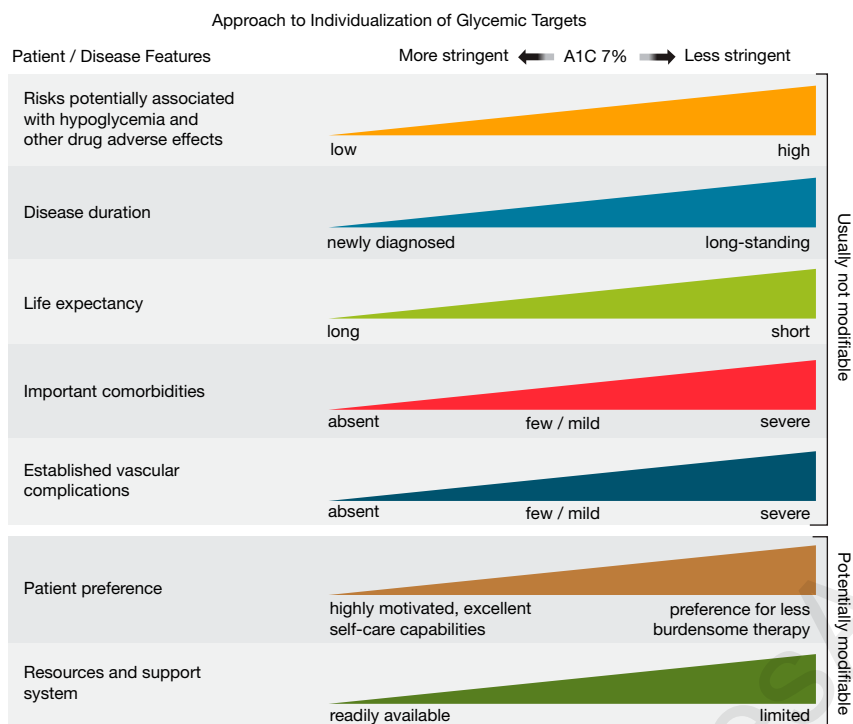


Figure 6.2—Patient and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (71).

risk. These trials showed that lower A1C levels were associated with reduced onset or progression of some microvascular complications (50–52).

The concerning mortality findings in the ACCORD trial discussed below and the relatively intense efforts required to achieve near euglycemia should also be considered when setting glycemic targets for individuals with long-standing diabetes, such as those populations studied in ACCORD, ADVANCE, and VADT. Findings from these studies suggest caution is needed in treating diabetes to near-normal A1C goals in people with long-standing type 2 diabetes with or at significant risk of CVD.

These landmark studies need to be considered with an important caveat; glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors were not approved at the time of these trials. As such, these agents with established cardiovascular and renal benefits appear to be safe and beneficial in this group of individuals at high risk for cardiorenal complications. Randomized clinical trials examining these agents for cardiovascular safety were not designed to test

higher versus lower A1C; therefore, beyond post hoc analysis of these trials, we do not have evidence that it is the glucose lowering by these agents that confers the CVD and renal benefit (53). As such, based on clinician judgment and patient preferences, select patients, especially those with little comorbidity and a long life expectancy, may benefit from adopting more intensive glycemic targets if they can achieve them safely and without hypoglycemia or significant therapeutic burden.

A1C and Cardiovascular Disease Outcomes

Cardiovascular Disease and Type 1 Diabetes CVD is a more common cause of death than microvascular complications in populations with diabetes. There is evidence for a cardiovascular benefit of intensive glycemic control after long-term follow-up of cohorts treated early in the course of type 1 diabetes. In the DCCT, there was a trend toward lower risk of CVD events with intensive control. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk

of nonfatal myocardial infarction (MI), stroke, or cardiovascular death compared with those previously randomized to the standard arm (54). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (55) and to be associated with a modest reduction in all-cause mortality (56).

Cardiovascular Disease and Type 2 Diabetes

In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. In addition, data from the Swedish National Diabetes Registry (56) and the Joint Asia Diabetes Evaluation (JADE) demonstrate greater proportions of people with diabetes being diagnosed at <40 years of age and a demonstrably increased burden of heart disease and years of life lost in people diagnosed at a younger age (57–60). Thus, to prevent both microvascular and macrovascular complications of diabetes, there is a major call to overcome therapeutic inertia and treat to target for an individual patient (60,61). During the UKPDS, there was a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance ($P = 0.052$), and there was no suggestion of benefit on other CVD outcomes (e.g., stroke). Similar to the DCCT/EDIC, after 10 years of observational follow-up, those originally randomized to intensive glycemic control had significant long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy) and in all-cause mortality (13% and 27%, respectively) (47).

ACCORD, ADVANCE, and VADT suggested no significant reduction in CVD outcomes with intensive glycemic control in participants followed for shorter durations (3.5–5.6 years) and who had more advanced type 2 diabetes and CVD risk than the UKPDS participants. All three trials were conducted in relatively older participants with a longer known duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. The target A1C among intensive-control participants was <6% (42 mmol/mol) in ACCORD, <6.5% (48 mmol/mol) in ADVANCE,

and a 1.5% reduction in A1C compared with control participants in VADT, with achieved A1C of 6.4% vs. 7.5% (46 mmol/mol vs. 58 mmol/mol) in ACCORD, 6.5% vs. 7.3% (48 mmol/mol vs. 56 mmol/mol) in ADVANCE, and 6.9% vs. 8.4% (52 mmol/mol vs. 68 mmol/mol) in VADT. Details of these studies are reviewed extensively in the joint ADA position statement “Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials” (61).

The glycemic control comparison in ACCORD was halted early due to an increased mortality rate in the intensive compared with the standard treatment arm (1.41% vs. 1.14% per year; hazard ratio 1.22 [95% CI 1.01–1.46]), with a similar increase in cardiovascular deaths. Analysis of the ACCORD data did not identify a clear explanation for the excess mortality in the intensive treatment arm (62).

Longer-term follow-up has shown no evidence of cardiovascular benefit, or harm, in the ADVANCE trial (63). The end-stage renal disease rate was lower in the intensive treatment group over follow-up. However, 10-year follow-up of the VADT cohort (64) did demonstrate a reduction in the risk of cardiovascular events (52.7 [control group] vs. 44.1 [intervention group] events per 1,000 person-years) with no benefit in cardiovascular or overall mortality. Heterogeneity of mortality effects across studies was noted, which may reflect differences in glycemic targets, therapeutic approaches, and, importantly, population characteristics (65).

Mortality findings in ACCORD (62) and subgroup analyses of VADT (66) suggest that the potential risks of intensive glycemic control may outweigh its benefits in higher-risk individuals. In all three trials, severe hypoglycemia was significantly more likely in participants who were randomly assigned to the intensive glycemic control arm. Individuals with a long duration of diabetes, a known history of hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets (67,68).

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events

and mortality (69). Therefore, health care professionals should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in people in whom such targets cannot be safely and reasonably achieved. As discussed in Section 9, “Pharmacologic Approaches to Glycemic Treatment,” addition of specific SGLT2 inhibitors or GLP-1 receptor agonists that have demonstrated CVD benefit is recommended in patients with established CVD, chronic kidney disease, and heart failure. As outlined in more detail in Section 9, “Pharmacologic Approaches to Glycemic Treatment,” and Section 10, “Cardiovascular Disease and Risk Management,” the cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered (70):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C target.

Setting and Modifying A1C Goals

Numerous factors must be considered when setting glycemic targets. The ADA proposes general targets appropriate for many people but emphasizes the importance of individualization based on key patient characteristics. Glycemic targets must be individualized in the context of shared decision-making to address individual needs and preferences and consider characteristics that influence risks and benefits of therapy; this approach may optimize engagement and self-efficacy.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. This figure is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision-making (71) and

engage people with type 1 and type 2 diabetes in shared decision-making. More aggressive targets may be recommended if they can be achieved safely and with an acceptable burden of therapy and if life expectancy is sufficient to reap the benefits of stringent targets. Less stringent targets (A1C up to 8% [64 mmol/mol]) may be recommended if the patient’s life expectancy is such that the benefits of an intensive goal may not be realized, or if the risks and burdens outweigh the potential benefits. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment plans, including setting higher glycemic goals.

Diabetes is a chronic disease that progresses over decades. Thus, a goal that might be appropriate for an individual early in the course of their diabetes may change over time. Newly diagnosed patients and/or those without comorbidities that limit life expectancy may benefit from intensive control proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS demonstrated metabolic memory, or a legacy effect, in which a finite period of intensive control yielded benefits that extended for decades after that control ended. Thus, a finite period of intensive control to near-normal A1C may yield enduring benefits even if control is subsequently deintensified as patient characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby decreasing the potential to reap benefits from intensive control. Also, with longer disease duration, diabetes may become more difficult to control, with increasing risks and burdens of therapy. Thus, A1C targets should be reevaluated over time to balance the risks and benefits as patient factors change.

Recommended glycemic targets for many nonpregnant adults are shown in **Table 6.3**. The recommendations include blood glucose levels that appear to correlate with achievement of an A1C of <7% (53 mmol/mol). Pregnancy recommendations are discussed in more detail in Section 15, “Management of Diabetes in Pregnancy.”

The issue of preprandial versus postprandial BGM targets is complex (72,73). Elevated postchallenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiologic studies, whereas intervention trials have not

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and Fig. 6.1. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per Fig. 6.2). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

shown postprandial glucose to be a cardiovascular risk factor independent of A1C. In people with diabetes, surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia. It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being greater at A1C levels that are closer to 7% (53 mmol/mol). However, outcome studies have shown A1C to be the primary predictor of complications, and landmark trials of glycemic control such as the DCCT and UKPDS relied overwhelmingly on preprandial BGM. Additionally, a randomized controlled trial in patients with known CVD found no CVD benefit of insulin treatment plans targeting postprandial glucose compared with those targeting preprandial glucose (73). Therefore, it is reasonable to check postprandial glucose in individuals who have premeal glucose values within target but A1C values above target. In addition, when intensifying insulin therapy, measuring postprandial plasma glucose 1–2 h after the start of a meal (using BGM or CGM) and using treatments aimed at reducing postprandial plasma glucose values to <180 mg/dL (10.0 mmol/L) may help to lower A1C.

An analysis of data from 470 participants in the ADAG study (237 with type 1 diabetes and 147 with type 2 diabetes) found that the glucose ranges highlighted in Table 6.1 are adequate to meet targets and decrease hypoglycemia (14). These findings support that premeal glucose targets may be relaxed without undermining overall glycemic control as measured by A1C. These data prompted the revision in the ADA-recommended premeal glucose target

to 80–130 mg/dL (4.4–7.2 mmol/L) but did not affect the definition of hypoglycemia.

HYPOGLYCEMIA

Recommendations

- 6.10** Occurrence and risk for hypoglycemia should be reviewed at every encounter and investigated as indicated. Awareness of hypoglycemia should be considered using validated tools. **C**
- 6.11** Glucose (approximately 15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if blood glucose monitoring (BGM) shows continued hypoglycemia, the treatment should be repeated. Once the BGM or glucose pattern is trending up, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **B**
- 6.12** Glucagon should be prescribed for all individuals at increased risk of level 2 or 3 hypoglycemia, so that it is available should it be needed. Caregivers, school personnel, or family members providing support to these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals. **E**
- 6.13** Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger

hypoglycemia avoidance education and reevaluation and adjustment of the treatment plan to decrease hypoglycemia. **E**

- 6.14** Insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**
- 6.15** Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if impaired or declining cognition is found. **B**

Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations regarding the classification of hypoglycemia are outlined in Table 6.4 (74–83). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but \geq 54 mg/dL (3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for neuroendocrine responses to falling glucose in people without diabetes. Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level <70 mg/dL (3.9 mmol/L) is considered clinically important (independent of the severity of acute hypoglycemic symptoms). Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If a patient has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have hypoglycemia unawareness (discussed further below). This clinical scenario warrants investigation and review of the treatment plan (75,79). Use Clarke score, Gold score, or Pedersen-Bjergaard score to assess impaired awareness (76). Lastly, level 3 hypoglycemia is defined as a severe

Table 6.4—Classification of hypoglycemia

Glycemic criteria/description	
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and \geq 54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

Reprinted from Agiostratidou et al. (74).

event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, and hunger. Hypoglycemia may be inconvenient or frightening to people with diabetes. Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. Hypoglycemia is reversed by administration of rapid-acting glucose or glucagon. Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury. Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with medical treatment plan adjustment, behavioral intervention, and, in some cases, use of technology to assist with hypoglycemia prevention and identification (76,79–82). A large cohort study suggested that among older adults with type 2 diabetes, a history of level 3 hypoglycemia was associated with greater risk of dementia (84). Conversely, in a substudy of the ACCORD trial, cognitive impairment at baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of level 3 hypoglycemia (85). Evidence from DCCT/EDIC, which involved adolescents and younger adults with type 1 diabetes, found no association between frequency of level 3 hypoglycemia and cognitive decline (86).

Studies of rates of level 3 hypoglycemia that rely on claims data for hospitalization, emergency department visits, and ambulance use substantially underestimate rates of level 3 hypoglycemia (87) yet reveal a high burden of hypoglycemia in adults over 60 years of age in the community (88). African American individuals are at substantially

increased risk of level 3 hypoglycemia (88,89). In addition to age and race, other important risk factors found in a community-based epidemiologic cohort of older adults with type 2 diabetes include insulin use, poor or moderate versus good glycemic control, albuminuria, and poor cognitive function (88). Level 3 hypoglycemia was associated with mortality in participants in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward. An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial (90). An association between self-reported level 3 hypoglycemia and 5-year mortality has also been reported in clinical practice (91). Glucose variability is also associated with an increased risk for hypoglycemia (92).

Young children with type 1 diabetes and the elderly, including those with type 1 and type 2 diabetes (84,93), are noted as particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glucose targets, patient education, nutrition intervention (e.g., bedtime snack to prevent overnight hypoglycemia when specifically needed to treat low blood glucose), physical activity management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes (94). CGM with automated low glucose suspend and hybrid closed-loop systems have been shown to be effective in reducing hypoglycemia in type 1 diabetes (95). For people with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, human islet transplantation may be an option, but the approach remains experimental (96,97).

In 2015, the ADA changed its preprandial glycemic target from 70–130 mg/dL (3.9–7.2 mmol/L) to 80–130 mg/dL (4.4–7.2 mmol/L). This change reflects the results of the ADAG study, which demonstrated that higher glycemic targets corresponded to A1C goals (14). An additional goal of raising the lower range of the glycemic target was to limit overtreatment and provide a safety margin in patients titrating glucose-lowering drugs such as insulin to glycemic targets.

Hypoglycemia Treatment

Health care professionals should continue to counsel patients to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less. This should be reviewed at each patient visit. Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods (98–100). The acute glycemic response correlates better with the glucose content of food than with the carbohydrate content of food. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. In type 2 diabetes, ingested protein may increase insulin response without increasing plasma glucose concentrations (101). Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery. Once the glucose returns to normal, the individual should be counseled to eat a meal or snack to prevent recurrent hypoglycemia.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, childcare professionals, correctional institution staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. An individual does not need to be a health care professional to safely

administer glucagon. In addition to traditional glucagon injection powder that requires reconstitution prior to injection, intranasal glucagon and ready-to-inject glucagon preparations for subcutaneous injection are available and may be beneficial in view of safety, efficacy, and ease of use. Care should be taken to ensure that glucagon products are not expired (102).

Hypoglycemia Prevention

Hypoglycemia prevention is a critical component of diabetes management. BGM and, for some individuals, CGM are essential tools to assess therapy and detect incipient hypoglycemia. People with diabetes should understand situations that increase their risk of hypoglycemia, such as when fasting for laboratory tests or procedures, when meals are delayed, during and after the consumption of alcohol, during and after intense physical activity, and during sleep. Hypoglycemia may increase the risk of harm to self or others, such as when driving. Teaching people with diabetes to balance insulin use and carbohydrate intake and physical activity are necessary, but these strategies are not always sufficient for prevention (77, 103–105). Formal training programs to increase awareness of hypoglycemia and to develop strategies to decrease hypoglycemia have been developed, including the Blood Glucose Awareness Training Program, Dose Adjusted for Normal Eating (DAFNE), and DAFNE-plus. Conversely, some individuals with type 1 diabetes or type 2 diabetes and hypoglycemia who have a fear of hyperglycemia are resistant to relaxation of glycemic targets (74–83). Regardless of the factors contributing to hypoglycemia and hypoglycemia unawareness, this represents an urgent medical issue requiring intervention.

In type 1 diabetes and severely insulin-deficient type 2 diabetes, hypoglycemia unawareness (or hypoglycemia-associated autonomic failure) can severely compromise stringent diabetes control and quality of life. This syndrome is characterized by deficient counterregulatory hormone release, especially in older adults, and a diminished autonomic response, which are both risk factors for and caused by hypoglycemia. A corollary to this “vicious cycle” is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counterregulation and hypoglycemia awareness in many people with

diabetes (106). Hence, individuals with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic targets and availability of glucagon (107). Any person with recurrent hypoglycemia or hypoglycemia unawareness should have their glucose management treatment plan adjusted.

Use of CGM Technology in Hypoglycemia Prevention

With the advent of sensor-augmented CGM and CGM-assisted pump therapy, there has been a promise of alarm-based prevention of hypoglycemia (108,109). To date, there have been a number of randomized controlled trials in adults with type 1 diabetes and studies in adults and children with type 1 diabetes using real-time CGM (see Section 7, “Diabetes Technology”). These studies had differing A1C at entry and differing primary end points and thus must be interpreted carefully. Real-time CGM studies can be divided into studies with elevated A1C with the primary end point of A1C reduction and studies with A1C near target with the primary end point of reduction in hypoglycemia (98, 109–124). In people with type 1 and type 2 diabetes with A1C above target, CGM improved A1C between 0.3 and 0.6%. For studies targeting hypoglycemia, most studies demonstrated a significant reduction in time spent between 54 and 70 mg/dL. A report in people with type 1 diabetes over the age of 60 years revealed a small but statistically significant decrease in hypoglycemia (125). No study to date has reported a decrease in level 3 hypoglycemia. In a single study using intermittently scanned CGM, adults with type 1 diabetes with A1C near goal and impaired awareness of hypoglycemia demonstrated no change in A1C and decreased level 2 hypoglycemia (115). For people with type 2 diabetes, studies examining the impact of CGM on hypoglycemic events are limited; a recent meta-analysis does not reflect a significant impact on hypoglycemic events in type 2 diabetes (126), whereas improvements in A1C were observed in most studies (126–132). Overall, real-time CGM appears to be a useful tool for decreasing time spent in a hypoglycemic range in people with impaired awareness. For people with type 2 diabetes, other strategies to assist them with

insulin dosing can improve A1C with minimal hypoglycemia (133,134).

INTERCURRENT ILLNESS

For further information on management of individuals with hyperglycemia in the hospital, see Section 16, “Diabetes Care in the Hospital.”

Stressful events (e.g., illness, trauma, surgery) may worsen glycemic control and precipitate diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar state, life-threatening conditions that require immediate medical care to prevent complications and death. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose; ketosis-prone patients also require urine or blood ketone monitoring. If accompanied by ketosis, vomiting, or alteration in the level of consciousness, marked hyperglycemia requires temporary adjustment of the treatment plan and immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or medical nutrition therapy alone may require insulin. Adequate fluid and caloric intake must be ensured. Infection or dehydration are more likely to necessitate hospitalization of individuals with diabetes versus those without diabetes.

A clinician with expertise in diabetes management should treat the hospitalized patient. For further information on the management of diabetic ketoacidosis and the nonketotic hyperglycemic hyperosmolar state, please refer to the ADA consensus report “Hyperglycemic Crises in Adult Patients With Diabetes” (134).

References

1. Deshmukh H, Wilmot EG, Gregory R, et al. Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the Association of British Clinical Diabetologists (ABCD) nationwide audit. *Diabetes Care* 2020;43:2153–2160
2. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging Study). *Diabetes Care* 2019;42:416–426
3. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–412
4. Little RR, Rohlfing CL; National Glycohemoglobin Standardization Program (NGSP) Steering Committee. Status of hemoglobin A1c measurement and goals

- for improvement: from chaos to order for improving diabetes care. *Clin Chem* 2011;57:205–214
5. Valenzano M, Cibirano Bertolotti I, Valenzano A, Grassi G. Time in range-A1c hemoglobin relationship in continuous glucose monitoring of type 1 diabetes: a real-world study. *BMJ Open Diabetes Res Care* 2021;9:e001045
 6. Fabris C, Heinemann L, Beck R, Cobelli C, Kovatchev B. Estimation of hemoglobin A1c from continuous glucose monitoring data in individuals with type 1 diabetes: is time in range all we need? *Diabetes Technol Ther* 2020;22:501–508
 7. Ranjan AG, Rosenlund SV, Hansen TW, Rossing P, Andersen S, Nørgaard K. Improved time in range over 1 year is associated with reduced albuminuria in individuals with sensor-augmented insulin pump-treated type 1 diabetes. *Diabetes Care* 2020;43:2882–2885
 8. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. *J Diabetes Sci Technol* 2019;13:614–626
 9. Šoupal J, Petruželková L, Grunberger G, et al. Glycemic outcomes in adults with T1D are impacted more by continuous glucose monitoring than by insulin delivery method: 3 years of follow-up from the COMISAIR study. *Diabetes Care* 2020;43:37–43
 10. Jovanović L, Savas H, Mehta M, Trujillo A, Pettitt DJ. Frequent monitoring of A1C during pregnancy as a treatment tool to guide therapy. *Diabetes Care* 2011;34:53–54
 11. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020;98(4S):S1–S115
 12. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA_{1c} alone to assess glycemic control can be misleading. *Diabetes Care* 2017;40:994–999
 13. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. *Diabetes Care* 2008;31:1473–1478
 14. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA_{1c} goals. *Diabetes Care* 2014;37:1048–1051
 15. Selvin E. Are there clinical implications of racial differences in HbA_{1c}? A difference, to be a difference, must make a difference. *Diabetes Care* 2016;39:1462–1467
 16. Bergenstal RM, Gal RL, Connor CG, et al.; T1D Exchange Racial Differences Study Group. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. *Ann Intern Med* 2017;167:95–102
 17. Khosla L, Bhat S, Fullington LA, Horlyck-Romanovsky MF. HbA_{1c} performance in african descent populations in the United States with normal glucose tolerance, prediabetes, or diabetes: a scoping review. *Prev Chronic Dis* 2021;18:E22
 18. Lacy ME, Wellenius GA, Sumner AE, Correa A, Carnethon MR, Liem RI, et al. Association of sickle cell trait with hemoglobin A1c in African Americans. *JAMA* 2017;317:507–515.
 19. Rohlfing C, Hanson S, Little RR. Measurement of hemoglobin A1c in patients with sickle cell trait. *JAMA* 2017;317:2237.
 20. Wheeler E, Leong A, Liu CT, et al.; EPIC-CVD Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study. Impact of common genetic determinants of hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. *PLoS Med* 2017;14:e1002383
 21. Diabetes Research in Children Network (DirecNet) Study Group. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by high-frequency glucose determinations by sensors. *Diabetes Care* 2008;31:381–385
 22. Buse JB, Kaufman FR, Linder B, Hirst K, El Ghormli L; HEALTHY Study Group. Diabetes screening with hemoglobin A(1c) versus fasting plasma glucose in a multiethnic middle-school cohort. *Diabetes Care* 2013;36:429–435
 23. Kamps JL, Hempe JM, Chalew SA. Racial disparity in A1C independent of mean blood glucose in children with type 1 diabetes. *Diabetes Care* 2010;33:1025–1027
 24. Advani A. Positioning time in range in diabetes management. *Diabetologia* 2020;63:242–252
 25. Avari P, Uduku C, George D, Herrero P, Reddy M, Oliver N. Differences for percentage times in glycemic range between continuous glucose monitoring and capillary blood glucose monitoring in adults with type 1 diabetes: analysis of the REPLACE-BG dataset. *Diabetes Technol Ther* 2020;22:222–227
 26. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technol Ther* 2019;21:81–85
 27. Kröger J, Reichel A, Siegmund T, Ziegler R. Clinical recommendations for the use of the ambulatory glucose profile in diabetes care. *J Diabetes Sci Technol* 2020;14:586–594
 28. Livingstone R, Boyle JG, Petrie JR. How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes? *Diabet Med* 2020;37:513–521
 29. Messer LH, Berget C, Vigers T, et al. Real world hybrid closed-loop discontinuation: Predictors and perceptions of youth discontinuing the 670G system in the first 6 months. *Pediatr Diabetes* 2020;21:319–327
 30. Mayeda L, Katz R, Ahmad I, et al. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. *BMJ Open Diabetes Res Care* 2020;8:e000991
 31. Yoo JH, Choi MS, Ahn J, et al. Association between continuous glucose monitoring-derived time in range, other core metrics, and albuminuria in type 2 diabetes. *Diabetes Technol Ther* 2020;22:768–776
 32. Lu J, Ma X, Shen Y, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes Technol Ther* 2020;22:72–78
 33. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
 34. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A Consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2021;44:2589–2625
 35. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. *Diabetes Care* 2019;42:1593–1603
 36. Tcherro H, Kangambega P, Briatte C, Brunet-Houdard S, Retali GR, Rusch E. Clinical effectiveness of telemedicine in diabetes mellitus: a meta-analysis of 42 randomized controlled trials. *Telemed J E Health* 2019;25:569–583
 37. Salabelle C, Ly Sall K, Eroukhanoff J, et al. COVID-19 pandemic lockdown in young people with type 1 diabetes: positive results of an unprecedented challenge for patients through telemedicine and change in use of continuous glucose monitoring. *Prim Care Diabetes* 2021;15:884–886
 38. Prabh Navis J, Leelarathna L, Mubita W, et al. Impact of COVID-19 lockdown on flash and real-time glucose sensor users with type 1 diabetes in England. *Acta Diabetol* 2021;58:231–237
 39. Seidu S, Kunutsor SK, Topsever P, Hambling CE, Cos FX, Khunti K. Deintensification in older patients with type 2 diabetes: a systematic review of approaches, rates and outcomes. *Diabetes Obes Metab* 2019;21:1668–1679
 40. Khunti K, Davies MJ. Clinical inertia—time to reappraise the terminology? *Prim Care Diabetes* 2017;11:105–106
 41. Whitehead L, Glass C, Coppell K. The effectiveness of goal setting on glycaemic control for people with type 2 diabetes and prediabetes: a systematic review and meta-analysis. *J Adv Nurs* 2022;78:1212–1227
 42. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group; Lachin JM, White NH, Hainsworth DP, et al. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. *Diabetes* 2015;64:631–642
 43. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group; Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000;342:381–389
 44. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103–117
 45. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–865
 46. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
 47. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589

48. Lind M, Pivodic A, Svensson AM, Ólafsdóttir AF, Wedel H, Ludvigsson J. HbA_{1c} level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. *BMJ* 2019;366:14894
49. Adler AI, Stratton IM, Neil HAW, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000;321:412–419
50. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139
51. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
52. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
53. Buse JB, Bain SC, Mann JFE, et al.; LEADER Trial Investigators. Cardiovascular risk reduction with liraglutide: an exploratory mediation analysis of the LEADER trial. *Diabetes Care* 2020;43:1546–1552
54. Nathan DM, Cleary PA, Backlund JYC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653
55. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). *Arch Intern Med* 2009;169:1307–1316
56. Emerging Risk Factors Collaboration; Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA* 2015;314:52–60
57. Yeung RO, Zhang Y, Luk A, et al. Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. *Lancet Diabetes Endocrinol* 2014;2:935–943
58. Sattar N, Rawshani A, Franzén S, et al. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation* 2019;139:2228–2237
59. Zabala A, Darsalia V, Holzmann MJ, et al. Risk of first stroke in people with type 2 diabetes and its relation to glycaemic control: a nationwide observational study. *Diabetes Obes Metab* 2020;22:182–190
60. Zoungas S, Woodward M, Li Q, et al.; ADVANCE Collaborative group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia* 2014;57:2465–2474
61. Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;32:187–192
62. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–2559
63. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392–1406
64. Hayward RA, Reaven PD, Wiitala WL, et al.; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;372:2197–2206
65. Turnbull FM, Abraira C, Anderson RJ, et al.; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288–2298
66. Duckworth WC, Abraira C, Moritz TE, et al.; Investigators of the VADT. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. *J Diabetes Complications* 2011;25:355–361
67. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. *JAMA Intern Med* 2015;175:356–362
68. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. *JAMA Intern Med* 2014;174:1227–1234
69. Lee AK, Warren B, Lee CJ, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. *Diabetes Care* 2018;41:104–111
70. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669–2701
71. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38:140–149
72. American Diabetes Association. Postprandial blood glucose. *Diabetes Care* 2001;24:775–778
73. Raz I, Wilson PWF, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. *Diabetes Care* 2009;32:381–386
74. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA_{1c} for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care* 2017;40:1622–1630
75. Polonsky WH, Fortmann AL, Price D, Fisher L. "Hyperglycemia aversiveness": investigating an overlooked problem among adults with type 1 diabetes. *J Diabetes Complications* 2021;35:107925
76. Ghandi K, Pieri B, Dornhorst A, Hussain S. A comparison of validated methods used to assess impaired awareness of hypoglycaemia in type 1 diabetes: an observational study. *Diabetes Ther* 2021;12:441–451
77. Li P, Geng Z, Ladage VP, Wu J, Lorincz I, Doshi JA. Early hypoglycaemia and adherence after basal insulin initiation in a nationally representative sample of Medicare beneficiaries with type 2 diabetes. *Diabetes Obes Metab* 2019;21:2486–2495
78. Hendrieckx C, Ivory N, Singh H, Frier BM, Speight J. Impact of severe hypoglycaemia on psychological outcomes in adults with type 2 diabetes: a systematic review. *Diabet Med* 2019;36:1082–1091
79. Amiel SA, Potts L, Goldsmith K, et al. A parallel randomised controlled trial of the Hypoglycaemia Awareness Restoration Programme for adults with type 1 diabetes and problematic hypoglycaemia despite optimised self-care (HARPro). *Nat Commun* 2022;13:2229
80. Khunti K, Alsifri S, Aronson R, et al. Impact of hypoglycaemia on patient-reported outcomes from a global, 24-country study of 27,585 people with type 1 and insulin-treated type 2 diabetes. *Diabetes Res Clin Pract* 2017;130:121–129
81. Choudhary P, Amiel SA. Hypoglycaemia in type 1 diabetes: technological treatments, their limitations and the place of psychology. *Diabetologia* 2018;61:761–769
82. Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. *Diabetes Care* 2012;35:1638–1642
83. Yang W, Ma J, Yuan G, et al. Determining the optimal fasting glucose target for patients with type 2 diabetes: results of the multicentre, open-label, randomized-controlled FPG GOAL trial. *Diabetes Obes Metab* 2019;21:1973–1977
84. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301:1565–1572
85. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care* 2012;35:787–793
86. Jacobson AM, Musen G, Ryan CM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 2007;356:1842–1852
87. Karter AJ, Moffet HH, Liu JY, Lipska KJ. Surveillance of hypoglycemia—limitations of emergency department and hospital utilization data. *JAMA Intern Med* 2018;178:987–988
88. Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. risk factors for severe hypoglycemia in

- black and white adults with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 2017;40:1661–1667
89. Karter AJ, Lipska KJ, O'Connor PJ, et al.; SUPREME-DM Study Group. High rates of severe hypoglycemia among African American patients with diabetes: the surveillance, prevention, and Management of Diabetes Mellitus (SUPREME-DM) network. *J Diabetes Complications* 2017;31:869–873
90. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410–1418
91. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 2012;35:1897–1901
92. Cahn A, Zuker I, Eilenberg R, et al. Machine learning based study of longitudinal HbA1c trends and their association with all-cause mortality: analyses from a national diabetes registry. *Diabetes Metab Res Rev* 2022;38:e3485
93. DuBose SN, Weinstock RS, Beck RW, et al. Hypoglycemia in older adults with type 1 diabetes. *Diabetes Technol Ther* 2016;18:765–771
94. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384–1395
95. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232
96. Hering BJ, Clarke WR, Bridges ND, et al.; Clinical Islet Transplantation Consortium. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. *Diabetes Care* 2016;39:1230–1240
97. Harlan DM. Islet transplantation for hypoglycemia unawareness/severe hypoglycemia: caveat emptor. *Diabetes Care* 2016;39:1072–1074
98. McTavish L, Wiltshire E. Effective treatment of hypoglycemia in children with type 1 diabetes: a randomized controlled clinical trial. *Pediatr Diabetes* 2011;12(4pt2):381–387
99. McTavish L, Corley B, Weatherall M, Wiltshire E, Krebs JD. Weight-based carbohydrate treatment of hypoglycaemia in people with type 1 diabetes using insulin pump therapy: a randomized crossover clinical trial. *Diabet Med* 2018;35:339–346
100. Georgakopoulos K, Katsilambros N, Fragaki M, et al. Recovery from insulin-induced hypoglycemia after saccharose or glucose administration. *Clin Physiol Biochem* 1990;8:267–272
101. Layman DK, Clifton P, Gannon MC, Krauss RM, Nuttall FQ. Protein in optimal health: heart disease and type 2 diabetes. *Am J Clin Nutr* 2008;87:1571S–1575S
102. Pontiroli AE, Ceriani V. Intranasal glucagon for hypoglycaemia in diabetic patients. An old dream is becoming reality? *Diabetes Obes Metab* 2018;20:1812–1816
103. Stanton-Fay SH, Hamilton K, Chadwick PM, et al.; DAFNEplus study group. The DAFNEplus programme for sustained type 1 diabetes self management: intervention development using the Behaviour Change Wheel. *Diabet Med* 2021;38:e14548
104. Farrell CM, McCrimmon RJ. Clinical approaches to treat impaired awareness of hypoglycaemia. *Ther Adv Endocrinol Metab* 2021;12:20420188211000248
105. Cox DJ, Gonder-Frederick L, Julian DM, Clarke W. Long-term follow-up evaluation of blood glucose awareness training. *Diabetes Care* 1994;17:1–5
106. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;350:2272–2279
107. Mitchell BD, He X, Sturdy IM, Cagle AP, Settles JA. Glucagon prescription patterns in patients with either type 1 or 2 diabetes with newly prescribed insulin. *Endocr Pract* 2016;22:123–135
108. Hermanns N, Heinemann L, Freckmann G, Waldenmaier D, Ehrmann D. Impact of CGM on the management of hypoglycemia problems: overview and secondary analysis of the HypoDE study. *J Diabetes Sci Technol* 2019;13:636–644
109. Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, et al. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *Lancet* 2018;391:1367–1377
110. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* 2017;317:371–378
111. Sequeira PA, Montoya L, Ruelas V, et al. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. *Diabetes Technol Ther* 2013;15:855–858
112. Tuminia A, Crimi S, Sciacca L, et al. Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial. *Diabetes Metab Res Rev* 2015;31:61–68
113. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016;388:2254–2263
114. Hermanns N, Schumann B, Kulzer B, Haak T. The impact of continuous glucose monitoring on low interstitial glucose values and low blood glucose values assessed by point-of-care blood glucose meters: results of a crossover trial. *J Diabetes Sci Technol* 2014;8:516–522
115. Reddy M, Jugnee N, El Laboudi A, Spanudakis E, Anantharaja S, Oliver N. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia. *Diabet Med* 2018;35:483–490
116. Riddlesworth T, Price D, Cohen N, Beck RW. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. *Diabetes Ther* 2017;8:947–951
117. van Beers CAJ, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. *Lancet Diabetes Endocrinol* 2016;4:893–902
118. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012;55:3155–3162
119. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 2006;29:2730–2732
120. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476
121. O'Connell MA, Donath S, O'Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. *Diabetologia* 2009;52:1250–1257
122. Beck RW, Hirsch IB, Laffel L, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383
123. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011;34:795–800
124. Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics* 2003;111:933–938
125. Pratley RE, Kanapka LG, Rickels MR, Ahmann A, Aleppo G, Beck R, et al. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. *JAMA* 2020;323:2397–2406
126. Dicembrini I, Mannucci E, Monami M, Pala L. Impact of technology on glycemic control in type 2 diabetes: a meta-analysis of randomized trials on continuous glucose monitoring and continuous subcutaneous insulin infusion. *Diabetes Obes Metab* 2019;21:2619–2625
127. Beck RW, Riddlesworth TD, Ruedy K, et al.; DIAMOND Study Group. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. *Ann Intern Med* 2017;167:365–374
128. Ehrhardt NM, Chellappa M, Walker MS, Fonda SJ, Vigersky RA. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. *J Diabetes Sci Technol* 2011;5:668–675
129. Haak T, Hanair H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther* 2017;8:55–73
130. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. *Diabetes Res Clin Pract* 2008;82:73–79
131. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose

sensor: a randomized controlled trial. *Diabetes Care* 2006;29:44–50

132. New JP, Ajjan R, Pfeiffer AFH, Freckmann G. Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose

Level Awareness in Diabetes Study (GLADIS). *Diabet Med* 2015;32:609–617

133. Bergenstal RM, Johnson M, Passi R, et al. Automated insulin dosing guidance to optimise insulin management in patients with type 2

diabetes: a multicentre, randomised controlled trial. *Lancet* 2019;393:1138–1148

134. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335–1343

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7. Diabetes Technology: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes technology is the term used to describe the hardware, devices, and software that people with diabetes use to assist with self-management, ranging from lifestyle modifications to glucose monitoring and therapy adjustments. Historically, diabetes technology has been divided into two main categories: insulin administered by syringe, pen, or pump (also called continuous subcutaneous insulin infusion), and glucose as assessed by blood glucose monitoring (BGM) or continuous glucose monitoring (CGM). Diabetes technology has expanded to include automated insulin delivery (AID) systems, where CGM-informed algorithms modulate insulin delivery, as well as diabetes self-management support software serving as medical devices. Diabetes technology, when coupled with education, follow-up, and support, can improve the lives and health of people with diabetes; however, the complexity and rapid evolution of the diabetes technology landscape can also be a barrier to implementation for both people with diabetes and the health care team.

GENERAL DEVICE PRINCIPLES

Recommendations

- 7.1** The type(s) and selection of devices should be individualized based on a person’s specific needs, preferences, and skill level. In the setting of an individual whose diabetes is partially or wholly managed by someone else (e.g., a young child or a person with cognitive impairment or dexterity, psychosocial, and/or physical limitations), the caregiver’s skills and preferences are integral to the decision-making process. **E**
- 7.2** When prescribing a device, ensure that people with diabetes/caregivers receive initial and ongoing education and training, either in-person or remotely, and ongoing evaluation of technique, results, and their ability to utilize data, including uploading/sharing data (if applicable), to monitor and adjust therapy. **C**

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- 7.3** People with diabetes who have been using continuous glucose monitoring, continuous subcutaneous insulin infusion, and/or automated insulin delivery for diabetes management should have continued access across third-party payers, regardless of age or A1C levels. **E**
- 7.4** Students should be supported at school in the use of diabetes technology, such as continuous glucose monitoring systems, continuous subcutaneous insulin infusion, connected insulin pens, and automated insulin delivery systems, as prescribed by their health care team. **E**
- 7.5** Initiation of continuous glucose monitoring, continuous subcutaneous insulin infusion, and/or automated insulin delivery early in the treatment of diabetes can be beneficial depending on a person's/caregiver's needs and preferences. **C**

Technology is rapidly changing, but there is no “one-size-fits-all” approach to technology use in people with diabetes. Insurance coverage can lag behind device availability, patient interest in devices and willingness for adoption can vary, and health care teams may have challenges keeping up with newly released technology. An American Diabetes Association resource, which can be accessed at consumerguide.diabetes.org, can help health care professionals and people with diabetes make decisions as to the initial choice of devices. Other sources, including health care professionals and device manufacturers, can help people troubleshoot when difficulties arise.

Education and Training

In general, no device used in diabetes management works optimally without education, training, and ongoing support. There are multiple resources for online tutorials and training videos as well as written material on the use of devices. People with diabetes vary in comfort level with technology, and some prefer in-person training and support. Those with more education regarding device use have better outcomes (1,2); therefore, the need for additional education should be periodically

assessed, particularly if outcomes are not being met.

Use in Schools

Instructions for device use should be outlined in the student's diabetes medical management plan (DMMP). A backup plan should be included in the DMMP for potential device failure (e.g., BGM, CGM, and/or insulin delivery devices). School nurses and designees should complete training to stay up to date on diabetes technologies prescribed for use in the school setting. Updated resources to support diabetes care at school, including training materials and a DMMP template, can be found online at diabetes.org/safeatschool.

Initiation of Device Use

The use of CGM devices should be considered from the outset of the diagnosis of diabetes that requires insulin management (3,4). This allows for close tracking of glucose levels with adjustments of insulin dosing and lifestyle modifications and removes the burden of frequent BGM. In addition, early CGM initiation after diagnosis of type 1 diabetes in youth has been shown to decrease A1C and is associated with high parental satisfaction and reliance on this technology for diabetes management (5,6). In appropriate individuals, early use of AID systems or insulin pumps may be considered. Interruption of access to CGM is associated with a worsening of outcomes (7,8); therefore, it is important for individuals on CGM to have consistent access to devices.

BLOOD GLUCOSE MONITORING

Recommendations

- 7.6** People with diabetes should be provided with blood glucose monitoring devices as indicated by their circumstances, preferences, and treatment. People using continuous glucose monitoring devices must also have access to blood glucose monitoring at all times. **A**
- 7.7** People who are on insulin using blood glucose monitoring should be encouraged to check their blood glucose levels when appropriate based on their insulin therapy. This may include checking when fasting, prior to meals and

snacks, after meals, at bedtime, prior to exercise, when hypoglycemia is suspected, after treating low blood glucose levels until they are normoglycemic, when hyperglycemia is suspected, and prior to and while performing critical tasks such as driving. **B**

- 7.8** Health care professionals should be aware of the differences in accuracy among blood glucose meters—only meters approved by the U.S. Food and Drug Administration (or comparable regulatory agencies for other geographical locations) with proven accuracy should be used, with unexpired strips purchased from a pharmacy or licensed distributor. **E**
- 7.9** Although blood glucose monitoring in individuals on noninsulin therapies has not consistently shown clinically significant reductions in A1C, it may be helpful when altering nutrition plan, physical activity, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program. **E**
- 7.10** Health care professionals should be aware of medications and other factors, such as high-dose vitamin C and hypoxemia, that can interfere with glucose meter accuracy and provide clinical management as indicated. **E**

Major clinical trials of insulin-treated people with diabetes have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic management on diabetes complications (9). BGM is thus an integral component of effective therapy of individuals taking insulin. In recent years, CGM has emerged as a method for the assessment of glucose levels (discussed below). Glucose monitoring allows people with diabetes to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. Integrating results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, or adjusting medications (particularly

prandial insulin doses). The specific needs and goals of the person with diabetes should dictate BGM frequency and timing or the consideration of CGM use. As recommended by the device manufacturers and the U.S. Food and Drug Administration (FDA), people with diabetes using CGM must have access to BGM for multiple reasons, including whenever there is suspicion that the CGM is inaccurate, while waiting for warm-up, for calibration (some sensors) or if a warning message appears, and in any clinical setting where glucose levels are changing rapidly (>2 mg/dL/min), which could cause a discrepancy between CGM and blood glucose.

Meter Standards

Glucose meters meeting FDA guidance for meter accuracy provide the most reliable data for diabetes management. There are several current standards for the accuracy of blood glucose meters, but the two most used are those of the International Organization for Standardization (ISO) (ISO 15197:2013) and the FDA. The current ISO and FDA standards are compared in **Table 7.1**. In Europe, currently marketed meters must meet current ISO standards. In the U.S., currently marketed meters must meet the standard under which they were approved, which may not be the current standard. Moreover, the monitoring of current accuracy post-marketing is left to the manufacturer and not routinely checked by an independent source.

People with diabetes assume their glucose meter is accurate because it is FDA cleared, but that may not be the case. There is substantial variation in the accuracy of widely used BGM systems (10,11). The Diabetes Technology Society Blood Glucose Monitoring System

Surveillance Program provides information on the performance of devices used for BGM (diabetestechology.org/surveillance/). In one analysis, 6 of the top 18 glucose meters met the accuracy standard (12). In a subsequent analysis with updated glucose meters, 14 of 18 glucose meters met the minimum accuracy requirements (13). There are single-meter studies in which benefits have been found with individual meter systems, but few studies have compared meters head-to-head. Certain meter system characteristics, such as the use of lancing devices that are less painful (14) and the ability to reapply blood to a strip with an insufficient initial sample, may also be beneficial to people with diabetes (15) and may make BGM less burdensome to perform.

Counterfeit Strips

People with diabetes should be advised against purchasing or reselling preowned or secondhand test strips, as these may give incorrect results. Only unopened and unexpired vials of glucose test strips should be used to ensure BGM accuracy.

Optimizing Blood Glucose Monitoring Device Use

Optimal use of BGM devices requires proper review and interpretation of data by both the person with diabetes and the health care professional to ensure that data are used in an effective and timely manner. In people with type 1 diabetes, there is a correlation between greater BGM frequency and lower A1C (16). Among those who check their blood glucose at least once daily, many report taking no action when results are high or low (17). Some meters now provide advice to the user in real time when monitoring glucose levels (18), whereas others can be used as a part of integrated health

platforms (19). People with diabetes should be taught how to use BGM data to adjust food intake, physical activity, or pharmacologic therapy to achieve specific goals. The ongoing need for and frequency of BGM should be reevaluated at each routine visit to ensure its effective use (17,20,21).

People With Diabetes on Intensive Insulin Therapies

BGM is especially important for people with diabetes treated with insulin to monitor for and prevent hypoglycemia and hyperglycemia. Most individuals on intensive insulin therapies (multiple daily injections [MDI] or insulin pump therapy) should be encouraged to assess glucose levels using BGM (and/or CGM) prior to meals and snacks, at bedtime, occasionally postprandially, prior to physical activity, when they suspect hypoglycemia or hyperglycemia, after treating hypoglycemia until they are normoglycemic, and prior to and while performing critical tasks such as driving. For many individuals using BGM, this requires checking up to 6–10 times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjusting for multiple confounders, increased daily frequency of BGM was significantly associated with lower A1C (-0.2% per additional check per day) and with fewer acute complications (22).

People With Diabetes Using Basal Insulin and/or Oral Agents and Noninsulin Injectables

The evidence is insufficient regarding when to prescribe BGM and how often monitoring is needed for insulin-treated people with diabetes who do not use intensive insulin therapy, such as those

Table 7.1—Comparison of ISO 15197:2013 and FDA blood glucose meter accuracy standards

Setting	FDA (248,254)	ISO 15197:2013 (255)
Home use	95% within 15% for all BG in the usable BG range† 99% within 20% for all BG in the usable BG range†	95% within 15% for BG ≥ 100 mg/dL 95% within 15 mg/dL for BG < 100 mg/dL
Hospital use	95% within 12% for BG ≥ 75 mg/dL 95% within 12 mg/dL for BG < 75 mg/dL 98% within 15% for BG ≥ 75 mg/dL 98% within 15 mg/dL for BG < 75 mg/dL	99% in A or B region of consensus error grid‡

BG, blood glucose; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization. To convert mg/dL to mmol/L, see endmemo.com/medical/unitconvert/Glucose.php. †The range of blood glucose values for which the meter has been proven accurate and will provide readings (other than low, high, or error). ‡Values outside of the “clinically acceptable” A and B regions are considered “outlier” readings and may be dangerous to use for therapeutic decisions (256).

with type 2 diabetes taking basal insulin with or without oral agents and/or non-insulin injectables. However, for those taking basal insulin, assessing fasting glucose with BGM to inform dose adjustments to achieve blood glucose targets results in lower A1C (23,24).

In people with type 2 diabetes not taking insulin, routine glucose monitoring may be of limited additional clinical benefit. By itself, even when combined with education, it has shown limited improvement in outcomes (25–28). However, for some individuals, glucose monitoring can provide insight into the impact of nutrition, physical activity, and medication management on glucose levels. Glucose monitoring may also be useful in assessing hypoglycemia, glucose levels during intercurrent illness, or discrepancies between measured A1C and glucose levels when there is concern an A1C result may not be reliable in specific individuals. It may be useful when coupled with a treatment adjustment program. In a year-long study of insulin-naïve people with diabetes with suboptimal initial glycemic outcomes, a group trained in structured BGM (a paper tool was used at least quarterly to collect and interpret seven-point BGM profiles taken on 3 consecutive days) reduced their A1C by 0.3% more than the control group (29). A trial of once-daily BGM that included enhanced feedback from people with diabetes through messaging found no clinically or statistically significant change in A1C at 1 year (28). Meta-analyses have suggested that BGM can reduce A1C by 0.25–0.3% at 6 months (30–32), but the effect was attenuated at 12 months in one analysis (30). Reductions in A1C were greater (–0.3%) in trials where structured BGM data were used to adjust medications, but A1C was not changed significantly without such structured diabetes therapy adjustment (32). A key consideration is that performing BGM alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management plans.

Glucose Meter Inaccuracy

Although many meters function well under various circumstances, health care professionals and people with diabetes must be aware of factors impairing meter accuracy. A meter reading that seems discordant with the clinical picture needs to be retested or tested in a laboratory. Health

care professionals in intensive care unit settings need to be particularly aware of the potential for abnormal meter readings during critical illness, and laboratory-based values should be used if there is any doubt.

Some meters give error messages if meter readings are likely to be false (33).

Oxygen. Currently available glucose monitors utilize an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase (34). Glucose oxidase monitors are sensitive to the oxygen available and should only be used with capillary blood in people with normal oxygen saturation. Higher oxygen tensions (i.e., arterial blood or oxygen therapy) may result in false low glucose readings, and low oxygen tensions (i.e., high altitude, hypoxia, or venous blood readings) may lead to false high glucose readings. Glucose dehydrogenase-based monitors are not sensitive to oxygen.

Temperature. Because the reaction is sensitive to temperature, all monitors have an acceptable temperature range (34). Most will show an error if the temperature is unacceptable, but a few will provide a reading and a message indicating that the value may be incorrect. Humidity and altitude may also alter glucose readings.

Interfering Substances. There are a few physiologic and pharmacologic factors that interfere with glucose readings. Most interfere only with glucose oxidase systems (34). They are listed in **Table 7.2**.

CONTINUOUS GLUCOSE MONITORING DEVICES

Recommendations

7.11 Real-time continuous glucose monitoring **A** or intermittently scanned continuous glucose monitoring **B** should be offered for diabetes management in adults with diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

Table 7.2—Interfering substances for glucose meter readings

Glucose oxidase monitors

Uric acid
Galactose
Xylose
Acetaminophen
L-DOPA

Ascorbic acid

Glucose dehydrogenase monitors

Icodextrin (used in peritoneal dialysis)

See **Table 7.3** for definitions of types of continuous glucose monitoring devices.

7.12 Real-time continuous glucose monitoring **A** or intermittently scanned continuous glucose monitoring **C** should be offered for diabetes management in adults with diabetes on basal insulin who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.13 Real-time continuous glucose monitoring **B** or intermittently scanned continuous glucose monitoring **E** should be offered for diabetes management in youth with type 1 diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs.

7.14 Real-time continuous glucose monitoring or intermittently scanned continuous glucose monitoring should be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs. **E**

- 7.15** In people with diabetes on multiple daily injections or continuous subcutaneous insulin infusion, real-time continuous glucose monitoring devices should be used as close to daily as possible for maximal benefit. **A** Intermittently scanned continuous glucose monitoring devices should be scanned frequently, at a minimum once every 8 h. **A** People with diabetes should have uninterrupted access to their supplies to minimize gaps in continuous glucose monitoring. **A**
- 7.16** When used as an adjunct to pre- and postprandial blood glucose monitoring, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. **B**
- 7.17** Periodic use of real-time or intermittently scanned continuous glucose monitoring or use of professional continuous glucose monitoring can be helpful for diabetes management in circumstances where continuous use of continuous glucose monitoring is not appropriate, desired, or available. **C**
- 7.18** Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in successful use of devices. **E**
- 7.19** Continuous glucose monitoring device users should be educated on potential interfering substances and other factors that may affect accuracy. **C**

CGM measures interstitial glucose (which correlates well with plasma glucose, although at times, it can lag if glucose

levels are rising or falling rapidly). There are two basic types of CGM devices: those that are owned by the user, unblinded, and intended for frequent/continuous use, including real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), and professional CGM devices that are owned and applied in the clinic, which provide data that are blinded or unblinded for a discrete period of time. The types of sensors currently available are either disposable (rtCGM and isCGM) or implantable (rtCGM). **Table 7.3** provides the definitions for the types of CGM devices. For people with type 1 diabetes using CGM, frequency of sensor use was an important predictor of A1C lowering for all age-groups (35,36). The frequency of scanning with isCGM devices was also correlated with improved outcomes (37–40).

Some real-time systems require calibration by the user, which varies in frequency depending on the device. Additionally, some CGM systems are called “adjunctive,” meaning the user should perform BGM for making treatment decisions such as dosing insulin or treating hypoglycemia. Devices that do not have this requirement outside of certain clinical situations (see BLOOD GLUCOSE MONITORING above) are called “nonadjunctive” (41–43).

One specific isCGM device (FreeStyle Libre 2 [no generic form available]) and two specific rtCGM devices (Dexcom G6 [no generic form available] and FreeStyle Libre 3 [no generic form available]) have been designated as integrated CGM (iCGM) devices (44). This is a higher standard set by the FDA so that these devices can be integrated with other digitally connected devices. Presently, although the Medtronic Guardian 3 rtCGM (no generic available) is FDA approved for use with the 670/770G AID systems, Dexcom G6 rtCGM is the only system

with iCGM designation and FDA approval for use with AID systems.

Benefits of Continuous Glucose Monitoring

Data From Randomized Controlled Trials

Multiple randomized controlled trials (RCTs) have been performed using rtCGM devices, and the results have largely been positive in terms of reducing A1C levels and/or episodes of hypoglycemia as long as participants regularly wore the devices (35,36,45–67). The initial studies were primarily done in adults and youth with type 1 diabetes on insulin pump therapy and/or MDI (35,36,45–48,51–61). The primary outcome was met and showed benefit in adults of all ages (35,45,46,51,52,54, 56,57,68–71) including seniors (53,72,73). Data in children are less consistent; however, rtCGM in young children with type 1 diabetes reduced hypoglycemia; in addition, behavioral support in parents of young children with diabetes using rtCGM showed the benefits of reducing hypoglycemia concerns and diabetes distress (35,60,74). Similarly, A1C reduction was seen in adolescents and young adults with type 1 diabetes using rtCGM (59). RCT data on rtCGM use in individuals with type 2 diabetes on MDI (63), mixed therapies (64,65), and basal insulin (66,75) have consistently shown reductions in A1C but not a reduction in rates of hypoglycemia. The improvements in type 2 diabetes have largely occurred without changes in insulin doses or other diabetes medications. CGM discontinuation in individuals with type 2 diabetes on basal insulin caused partial reversal of A1C reduction and time in range (TIR) improvements, suggesting that continued CGM use achieves the greatest benefits (8).

RCT data for isCGM is more limited. One study was performed in adults with

Table 7.3—Continuous glucose monitoring devices

Type of CGM	Description
rtCGM	CGM systems that measure and display glucose levels continuously
isCGM with and without alarms	CGM systems that measure glucose levels continuously but require scanning for visualization and storage of glucose values
Professional CGM	CGM devices that are placed on the person with diabetes in the health care professional's office (or with remote instruction) and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. Unlike rtCGM and isCGM devices, these devices are clinic-based and not owned by the person with diabetes.

CGM, continuous glucose monitoring; isCGM, intermittently scanned CGM; rtCGM, real-time CGM.

type 1 diabetes and met its primary outcome of a reduction in rates of hypoglycemia (49). In adults with type 2 diabetes on insulin, two studies were done; one study did not meet its primary end point of A1C reduction (76) but achieved a secondary end point of a reduction in hypoglycemia, and the other study met its primary end point of an improvement in Diabetes Treatment Satisfaction Questionnaire score as well as a secondary end point of A1C reduction (77). In a study of individuals with type 1 or type 2 diabetes taking insulin, the primary outcome of a reduction in severe hypoglycemia was not met (78). One study in youth with type 1 diabetes did not show a reduction in A1C (79); however, the device was well received and was associated with an increased frequency of testing and improved diabetes treatment satisfaction (79). A recent randomized trial of adults with type 1 diabetes showed that the use of iCGM with optional alerts and alarms resulted in reduction of A1C compared with BGM use (80).

Observational and Real-World Studies

iCGM has been widely available in many countries for people with diabetes, and this allows for the collection of large amounts of data across groups of people with diabetes. In adults with diabetes, these data include results from observational studies, retrospective studies, and analyses of registry and population data (81,82). In individuals with type 1 diabetes wearing iCGM devices, most (40,81,83), but not all (84), studies have shown improvement in A1C levels. Reductions in acute diabetes complications, such as diabetic ketoacidosis (DKA), episodes of severe hypoglycemia or diabetes-related coma, and hospitalizations for hypoglycemia and hyperglycemia, have been observed (40,84,85). Some retrospective/observational data have shown an improvement in A1C levels for adults with type 2 diabetes on MDI (86), basal insulin (87), and basal insulin or noninsulin therapies (88). In a retrospective study of adults with type 2 diabetes taking insulin, a reduction in acute diabetes-related events and all-cause hospitalizations was seen (89). Results of self-reported outcomes varied, but where measured, people with diabetes had an increase in treatment satisfaction when comparing iCGM with BGM.

In an observational study in youth with type 1 diabetes, a slight increase in A1C and weight was seen, but the device was associated with a high user satisfaction rate (82).

Retrospective data from rtCGM use in a Veterans Affairs population (90) with type 1 and type 2 diabetes treated with insulin showed that the use of rtCGM significantly lowered A1C and reduced rates of emergency department visits or hospitalizations for hypoglycemia but did not significantly lower overall rates of emergency department visits, hospitalizations, or hyperglycemia.

Real-time Continuous Glucose Monitoring Compared With Intermittently Scanned Continuous Glucose Monitoring

In adults with type 1 diabetes, three RCTs have been done comparing iCGM and rtCGM (91–93). In two of the studies, the primary outcome was a reduction in time spent in hypoglycemia, and rtCGM showed benefit compared with iCGM (91,92). In the other study, the primary outcome was improved TIR, and rtCGM also showed benefit compared with iCGM (93). A retrospective analysis also showed improvement in TIR, comparing rtCGM with iCGM (94).

Data Analysis

The abundance of data provided by CGM offers opportunities to analyze data for people with diabetes more granularly than previously possible, providing additional information to aid in achieving glycemic targets. A variety of metrics have been proposed (95) and are discussed in Section 6, “Glycemic Targets.” CGM is essential for creating an ambulatory glucose profile and providing data on TIR, percentage of time spent above and below range, and glycemic variability (96).

Real-time Continuous Glucose Monitoring Device Use in Pregnancy

One well-designed RCT showed a reduction in A1C levels in adult women with type 1 diabetes on MDI or insulin pump therapy who were pregnant and using rtCGM in addition to standard care, including optimization of pre- and postprandial glucose targets (97). This study demonstrated the value of rtCGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C without an increase in hypoglycemia and reductions in large-for-gestational-age

births, length of stay, and neonatal hypoglycemia (97). An observational cohort study that evaluated the glycemic variables reported using rtCGM and iCGM found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes (98). Use of the rtCGM-reported mean glucose is superior to use of glucose management indicator (GMI) and other calculations to estimate A1C given the changes to A1C that occur in pregnancy (99). Two studies employing intermittent use of rtCGM showed no difference in neonatal outcomes in women with type 1 diabetes (100) or gestational diabetes mellitus (101).

Use of Professional and Intermittent Continuous Glucose Monitoring

Professional CGM devices, which provide retrospective data, either blinded or unblinded, for analysis, can be used to identify patterns of hypoglycemia and hyperglycemia (102,103). Professional CGM can be helpful to evaluate individuals when either rtCGM or iCGM is not available to the individual or they prefer a blinded analysis or a shorter experience with unblinded data. It can be particularly useful to evaluate periods of hypoglycemia in individuals on agents that can cause hypoglycemia in order to make medication dose adjustments. It can also be useful to evaluate individuals for periods of hyperglycemia.

Some data have shown the benefit of intermittent use of CGM (rtCGM or iCGM) in individuals with type 2 diabetes on noninsulin and/or basal insulin therapies (64,104). In these RCTs, people with type 2 diabetes not on intensive insulin therapy used CGM intermittently compared with those randomized to BGM. Both early (64) and late improvements in A1C were found (64,104).

Use of professional or intermittent CGM should always be coupled with analysis and interpretation for people with diabetes, along with education as needed to adjust medication and change lifestyle behaviors (105–107).

Side Effects of Continuous Glucose Monitoring Devices

Contact dermatitis (both irritant and allergic) has been reported with all devices that attach to the skin (108–110). In

Table 7.4—Continuous glucose monitoring devices interfering substances

Medication	Systems affected	Effect
Acetaminophen >4 g/day Any dose	Dexcom G6 Medtronic Guardian	Higher sensor readings than actual glucose Higher sensor readings than actual glucose
Alcohol	Medtronic Guardian	Sensor readings may be higher than actual glucose
Ascorbic acid (vitamin C), >500 mg/day	FreeStyle Libre	Higher sensor readings than actual glucose
Hydroxyurea	Dexcom G6, Medtronic Guardian	Higher sensor readings than actual glucose
Mannitol	Senseonics Eversense	Sensor bias within therapeutic concentration ranges
Tetracycline	Senseonics Eversense	Sensor bias within therapeutic concentration ranges

some cases, this has been linked to the presence of isobornyl acrylate, a skin sensitizer that can cause an additional spreading allergic reaction (111–113). Patch testing can sometimes identify the cause of contact dermatitis (114). Identifying and eliminating tape allergens is important to ensure the comfortable use of devices and promote self-care (115–118). In some instances, using an implanted sensor can help avoid skin reactions in those sensitive to tape (119,120).

Substances and Factors Affecting

Continuous Glucose Monitoring Accuracy

Sensor interference due to several medications/substances is a known potential source of CGM measurement errors (Table 7.4). While several of these substances have been reported in the various CGM brands' user manuals, additional interferences have been discovered after the market release of these products. Hydroxyurea, used for myeloproliferative disorders and hematologic conditions, is one of the most recently identified interfering substances that cause a temporary increase in sensor glucose values discrepant from actual glucose values (121–126). Therefore, it is crucial to routinely review the medication list of the person with diabetes to identify possible interfering substances and advise them accordingly on the need to use additional BGM if sensor values are unreliable due to these substances.

INSULIN DELIVERY

Insulin Syringes and Pens

Recommendations

7.20 For people with insulin-requiring diabetes on multiple daily injections, insulin pens are preferred in most cases. Still, insulin

syringes may be used for insulin delivery considering individual and caregiver preference, insulin type, dosing therapy, cost, and self-management capabilities. **C**

7.21 Insulin pens or insulin injection aids should be considered for people with dexterity issues or vision impairment to facilitate the accurate dosing and administration of insulin. **C**

7.22 Connected insulin pens can be helpful for diabetes management and may be used in people with diabetes using injectable therapy. **E**

7.23 U.S. Food and Drug Administration–approved insulin dose calculators/decision support systems may be helpful for titrating insulin doses. **C**

Injecting insulin with a syringe or pen (127–143) is the insulin delivery method used by most people with diabetes (134,144), although inhaled insulin is also available. Others use insulin pumps or AID devices (see INSULIN PUMPS AND AUTOMATED INSULIN DELIVERY SYSTEMS). For people with diabetes who use insulin, insulin syringes and pens are both able to deliver insulin safely and effectively for the achievement of glycemic targets. Individual preferences, cost, insulin type, dosing therapy, and self-management capabilities should be considered when choosing among delivery systems. Trials with insulin pens generally show equivalence or small improvements in glycemic outcomes compared with using a vial and syringe. Many individuals with diabetes prefer using a pen due to its simplicity and convenience. It is important to note that while many insulin types are

available for purchase as either pens or vials, others may be available in only one form or the other, and there may be significant cost differences between pens and vials (see Table 9.4 for a list of insulin product costs with dosage forms). Insulin pens may allow people with vision impairment or dexterity issues to dose insulin accurately (145–147), and insulin injection aids are also available to help with these issues. (For a helpful list of injection aids, see consumerguide.diabetes.org/collections/injection-aids). Inhaled insulin can be useful in people who have an aversion to injection.

The most common syringe sizes are 1 mL, 0.5 mL, and 0.3 mL, allowing doses of up to 100 units, 50 units, and 30 units of U-100 insulin, respectively. In a few parts of the world, insulin syringes still have U-80 and U-40 markings for older insulin concentrations and veterinary insulin, and U-500 syringes are available for the use of U-500 insulin. Syringes are generally used once but may be reused by the same individual in resource-limited settings with appropriate storage and cleansing (147).

Insulin pens offer added convenience by combining the vial and syringe into a single device. Insulin pens, allowing push-button injections, come as disposable pens with prefilled cartridges or reusable pens with replaceable insulin cartridges. Pens vary with respect to dosing increment and minimal dose, ranging from half-unit doses to 2-unit dose increments. U-500 pens come in 5-unit dose increments. Some reusable pens include a memory function, which can recall dose amounts and timing. Connected insulin pens are insulin pens with the capacity to record and/or transmit insulin dose data. Insulin pen caps are also available and are placed on existing insulin

pens and assist with calculating insulin doses. Some connected insulin pens and pen caps can be programmed to calculate insulin doses and provide downloadable data reports. These pens and pen caps are useful to people with diabetes for real-time insulin dosing and allow clinicians to retrospectively review the insulin delivery times and in some cases doses and glucose data in order to make informed insulin dose adjustments (148).

Needle thickness (gauge) and length are other considerations. Needle gauges range from 22 to 34, with a higher gauge indicating a thinner needle. A thicker needle can give a dose of insulin more quickly, while a thinner needle may cause less pain. Needle length ranges from 4 to 12.7 mm, with some evidence suggesting shorter needles (4–5 mm) lower the risk of intramuscular injection and possibly the development of lipohypertrophy. When reused, needles may be duller and, thus, injection more painful. Proper insulin injection technique is a requisite for receiving the full dose of insulin with each injection. Concerns with technique and use of the proper technique are outlined in Section 9, “Pharmacologic Approaches to Glycemic Treatment.”

Bolus calculators have been developed to aid dosing decisions (149–154). These systems are subject to FDA approval to ensure safety and efficacy in terms of algorithms used and subsequent dosing recommendations. People interested in using these systems should be encouraged to use those that are FDA approved. Health care professional input and education can be helpful for setting the initial dosing calculations with ongoing follow-up for adjustments as needed.

Insulin Pumps and Automated Insulin Delivery Systems

Recommendations

7.24 Automated insulin delivery systems should be offered for diabetes management to youth and adults with type 1 diabetes **A** and other types of insulin-deficient diabetes **E** who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual’s circumstances, preferences, and needs.

7.25 Insulin pump therapy alone with or without sensor-augmented pump low glucose suspend feature and/or automated insulin delivery systems should be offered for diabetes management to youth and adults on multiple daily injections with type 1 diabetes **A** or other types of insulin-deficient diabetes **E** who are capable of using the device safely (either by themselves or with a caregiver) and are not able to use or do not choose an automated insulin delivery system. The choice of device should be made based on the individual’s circumstances, preferences, and needs. **A**

7.26 Insulin pump therapy can be offered for diabetes management to youth and adults on multiple daily injections with type 2 diabetes who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual’s circumstances, preferences, and needs. **A**

7.27 Individuals with diabetes who have been using continuous subcutaneous insulin infusion should have continued access across third-party payers. **E**

Insulin Pumps

Insulin pumps have been available in the U.S. for over 40 years. These devices deliver rapid-acting insulin throughout the day to help manage blood glucose levels. Most insulin pumps use tubing to deliver insulin through a cannula, while a few attach directly to the skin without tubing. AID systems, which can adjust insulin delivery rates based on current sensor glucose values, are preferred over nonautomated pumps and MDI in people with type 1 diabetes.

Most studies comparing MDI with insulin pump therapy have been relatively small and of short duration. However, a systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C (–0.30% [95% CI –0.58 to –0.02]) and for reducing severe hypoglycemia rates in children

and adults (155). There is no consensus to guide choosing which form of insulin administration is best for a given individual, and research to guide this decision-making process is needed (155). Thus, the choice of MDI or an insulin pump is often based upon the characteristics of the person with diabetes and which method is most likely to benefit them. DiabetesWise (DiabetesWise.org) and the PANTHER Program (pantherprogram.org) have helpful websites to assist health care professionals and people with diabetes in choosing diabetes devices based on their individual needs and the features of the devices. Newer systems, such as sensor-augmented pumps and AID systems, are discussed below.

Adoption of pump therapy in the U.S. shows geographical variations, which may be related to health care professional preference or center characteristics (157,158) and socioeconomic status, as pump therapy is more common in individuals of higher socioeconomic status as reflected by race/ethnicity, private health insurance, family income, and education (157,158). Given the additional barriers to optimal diabetes care observed in disadvantaged groups (159), addressing the differences in access to insulin pumps and other diabetes technology may contribute to fewer health disparities.

Pump therapy can be successfully started at the time of diagnosis (160,161). Practical aspects of pump therapy initiation include assessment of readiness of the person with diabetes and their family, if applicable (although there is no consensus on which factors to consider in adults [162] or children and adolescents with diabetes), selection of pump type and initial pump settings, individual/family education on potential pump complications (e.g., DKA with infusion set failure), transition from MDI, and introduction of advanced pump settings (e.g., temporary basal rates, extended/square/dual wave bolus).

Older individuals with type 1 diabetes benefit from ongoing insulin pump therapy. There are no data to suggest that measurement of C-peptide levels or antibodies predicts success with insulin pump therapy (163,164). Additionally, the frequency of follow-up does not influence outcomes. Access to insulin pump therapy, including AID systems, should be allowed or continued in older adults as it is in younger people.

Complications of the pump can be caused by issues with infusion sets (dislodgement, occlusion), which place individuals at risk for ketosis and DKA and thus must be recognized and managed early (165). Other pump skin issues included lipohypertrophy or, less frequently, lipatrophy (166,167) and pump site infection (168). Discontinuation of pump therapy is relatively uncommon today; the frequency has decreased over the past few decades, and its causes have changed (168,169). Current reasons for attrition are problems with cost or wearability, dislike for the pump, suboptimal glycemic outcomes, or mood disorders (e.g., anxiety or depression) (170).

Insulin Pumps in Youth

The safety of insulin pumps in youth has been established for over 15 years (171). Studying the effectiveness of insulin pump therapy in lowering A1C has been challenging because of the potential selection bias of observational studies. Participants on insulin pump therapy may have a higher socioeconomic status that may facilitate better glycemic outcomes (172) versus MDI. In addition, the fast pace of development of new insulins and technologies quickly renders comparisons obsolete. However, RCTs comparing insulin pumps and MDI with rapid-acting insulin analogs demonstrate a modest improvement in A1C in participants on insulin pump therapy (173,174). Observational studies, registry data, and meta-analysis have also suggested an improvement in glycemic outcomes in participants on insulin pump therapy (175–177). Although hypoglycemia was a major adverse effect of intensified insulin therapy in the Diabetes Control and Complications Trial (DCCT) (178), data suggest that insulin pumps may reduce the rates of severe hypoglycemia compared with MDI (177,179–181).

There is also evidence that insulin pump therapy may reduce DKA risk (177,182) and diabetes complications, particularly retinopathy and peripheral neuropathy in youth, compared with MDI (162). In addition, treatment satisfaction and quality-of-life measures improved on insulin pump therapy compared with MDI (183,184). Therefore, insulin pumps can be used safely and effectively in youth with type 1 diabetes to assist with achieving targeted glycemic outcomes while reducing the risk of hypoglycemia and DKA, improving

quality of life, and preventing long-term complications. Based on shared decision-making by people with diabetes and health care professionals, insulin pumps may be considered in all children and adolescents with type 1 diabetes. In particular, pump therapy may be the preferred mode of insulin delivery for children under 7 years of age (185). Because of a paucity of data in adolescents and youth with type 2 diabetes, there is insufficient evidence to make recommendations.

Common barriers to pump therapy adoption in children and adolescents are concerns regarding the physical interference of the device, discomfort with the idea of having a device on the body, therapeutic effectiveness, and financial burden (175,186).

Sensor-Augmented Pumps

Sensor-augmented pumps that suspend insulin when glucose is low or are predicted to go low within the next 30 min have been approved by the FDA. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial of 247 people with type 1 diabetes showed that sensor-augmented insulin pump therapy with a low glucose suspend function significantly reduced nocturnal hypoglycemia over 3 months without increasing A1C levels (55). In a different sensor-augmented pump, predictive low glucose suspend reduced time spent with glucose <70 mg/dL from 3.6% at baseline to 2.6% (3.2% with sensor-augmented pump therapy without predictive low glucose suspend) without rebound hyperglycemia during a 6-week randomized crossover trial (187). These devices may offer the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia. Additional studies have been performed in adults and children, showing the benefits of this technology (188–190).

Automated Insulin Delivery Systems

AID systems increase and decrease insulin delivery based on sensor-derived glucose levels to mimic physiologic insulin delivery. These systems consist of three components: an insulin pump, a continuous glucose monitoring system, and an algorithm that calculates insulin delivery. All AID systems on the market today adjust basal delivery in real time, and some deliver correction doses automatically. While insulin delivery in closed-loop

systems eventually may be truly automated, currently used hybrid closed-loop systems require the manual entry of carbohydrates consumed to calculate prandial doses, and adjustments for physical activity must be announced. Multiple studies using various systems with varying algorithms, pumps, and sensors have been performed in adults and children (191–200). Evidence suggests AID systems may reduce A1C levels and improve TIR (201–205). They may also lower the risk of exercise-related hypoglycemia (206) and may have psychosocial benefits (207–210). The use of AID systems depends on the preference of the person with diabetes and the selection of individuals (and/or caregivers) who are capable of safely and effectively using the devices.

Insulin Pumps in People With Type 2 and Other Types of Diabetes

Traditional insulin pumps can be considered for the treatment of people with type 2 diabetes who are on MDI as well as those who have other types of diabetes resulting in insulin deficiency, for instance, those who have had a pancreatectomy and/or individuals with cystic fibrosis (211–215). Similar to data on insulin pump use in people with type 1 diabetes, reductions in A1C levels are not consistently seen in individuals with type 2 diabetes when compared with MDI, although this has been seen in some studies (213,216). Use of insulin pumps in insulin-requiring people with any type of diabetes may improve patient satisfaction and simplify therapy (164,211).

For people with diabetes judged to be clinically insulin deficient who are treated with an intensive insulin therapy, the presence or absence of measurable C-peptide levels does not correlate with response to therapy (164). Alternative pump options in people with type 2 diabetes may include disposable patch-like devices, which provide either a continuous subcutaneous infusion of rapid-acting insulin (basal) with bolus insulin in 2-unit increments at the press of a button or bolus insulin only delivered in 2-unit increments used in conjunction with basal insulin injections (212,214,217,218). Use of an insulin pump as a means of insulin delivery is an individual choice for people with diabetes and should be considered an option in those who are capable of safely using the device.

Do-It-Yourself Closed-Loop Systems

Recommendation

7.28 Individuals with diabetes may be using systems not approved by the U.S. Food and Drug Administration, such as do-it-yourself closed-loop systems and others; health care professionals cannot prescribe these systems but should assist in diabetes management to ensure the safety of people with diabetes. **E**

Some people with type 1 diabetes have been using “do-it-yourself” (DIY) systems that combine an insulin pump and an rtCGM with a controller and an algorithm designed to automate insulin delivery (219–223). These systems are not approved by the FDA, although efforts are underway to obtain regulatory approval for some of them. The information on how to set up and manage these systems is freely available on the internet, and there are internet groups where people inform each other as to how to set up and use them. Although health care professionals cannot prescribe these systems, it is crucial to keep people with diabetes safe if they are using these methods for automated insulin delivery. Part of this entails ensuring people have a backup plan in case of pump failure. Additionally, in most DIY systems, insulin doses are adjusted based on the pump settings for basal rates, carbohydrate ratios, correction doses, and insulin activity. Therefore, these settings can be evaluated and modified based on the individual’s insulin requirements.

Digital Health Technology

Recommendation

7.29 Systems that combine technology and online coaching can be beneficial in treating prediabetes and diabetes for some individuals. **B**

Increasingly, people are turning to the internet for advice, coaching, connection, and health care. Diabetes, partly because it is both common and numeric, lends itself to the development of apps and online programs. Recommendations for developing and implementing a digital

diabetes clinic have been published (224). The FDA approves and monitors clinically validated, digital, and usually online health technologies intended to treat a medical or psychological condition; these are known as digital therapeutics or “digiceuticals” ([fda.gov/medical-devices/digital-health-center-excellence/device-software-functions-including-mobile-medical-applications](https://www.fda.gov/medical-devices/digital-health-center-excellence/device-software-functions-including-mobile-medical-applications)) (225). Other applications, such as those that assist in displaying or storing data, encourage a healthy lifestyle or provide limited clinical data support. Therefore, it is possible to find apps that have been fully reviewed and approved by the FDA and others designed and promoted by people with relatively little skill or knowledge in the clinical treatment of diabetes. There is insufficient data to provide recommendations for specific apps for diabetes management, education, and support in the absence of RCTs and validations of apps unless they are FDA cleared.

An area of particular importance is that of online privacy and security. Established cloud-based data aggregator programs, such as Tidepool, Glooko, and others, have been developed with appropriate data security features and are compliant with the U.S. Health Insurance Portability and Accountability Act of 1996. These programs can help monitor people with diabetes and provide access to their health care team (226). Consumers should read the policy regarding data privacy and sharing before entering data into an application and learn how they can control the way their data will be used (some programs offer the ability to share more or less information, such as being part of a registry or data repository or not).

Many online programs offer lifestyle counseling to aid with weight loss and increase physical activity (227). Many include a health coach and can create small groups of similar participants on social networks. Some programs aim to treat prediabetes and prevent progression to diabetes, often following the model of the Diabetes Prevention Program (228,229). Others assist in improving diabetes outcomes by remotely monitoring clinical data (for instance, wireless monitoring of glucose levels, weight, or blood pressure) and providing feedback and coaching (230–235). There are text messaging approaches that tie into a variety of different types of lifestyle and treatment

programs, which vary in terms of their effectiveness (236,237). There are limited RCT data for many of these interventions, and long-term follow-up is lacking. However, for an individual with diabetes, opting into one of these programs can be helpful in providing support and, for many, is an attractive option.

Inpatient Care

Recommendation

7.30 People with diabetes who are competent to safely use diabetes devices such as insulin pumps and continuous glucose monitoring systems should be supported to continue using them in an inpatient setting or during outpatient procedures, once competency is established and proper supervision is available. **E**

Individuals who are comfortable using their diabetes devices, such as insulin pumps and CGM, should be allowed to use them in an inpatient setting if they are well enough to take care of the devices and have brought the necessary supplies (238–242). People with diabetes who are familiar with treating their own glucose levels can often adjust insulin doses more knowledgeably than inpatient staff who do not personally know the individual or their management style. However, this should occur based on the hospital’s policies for diabetes management and use of diabetes technology, and there should be supervision to ensure that the individual is achieving and maintaining glycemic targets during acute illness in a hospitalized setting where factors such as infection, certain medications, immobility, changes in nutrition, and other factors can impact insulin sensitivity and the insulin response.

With the advent of the coronavirus disease 2019 pandemic, the FDA exercised enforcement discretion by allowing CGM device use temporarily in the hospital for patient monitoring (243). This approach has been used to reduce the use of personal protective equipment and more closely monitor patients so that health care personnel do not have to go into a patient room solely to measure a glucose level (244–246). Studies

are underway to assess the effectiveness of this approach, which may ultimately lead to the approved use of CGM for monitoring hospitalized individuals (247–253).

When used in the setting of a clinical trial or when clinical circumstances (such as during a shortage of personal protective equipment) require it, CGM can be used to manage hospitalized individuals in conjunction with BGM. Point-of-care BGM remains the approved method for glucose monitoring in hospitals, especially for dosing insulin and treating hypoglycemia. For more information, see Section 16, “Diabetes Care in the Hospital.”

The Future

The pace of development in diabetes technology is extremely rapid. New approaches and tools are available each year. It is hard for research to keep up with these advances because newer versions of the devices and digital solutions are already on the market when a study is completed. The most important component in all of these systems is the person with diabetes. Technology selection must be appropriate for the individual. Simply having a device or application does not change outcomes unless the human being engages with it to create positive health benefits. This underscores the need for the health care team to assist people with diabetes in device and program selection and to support its use through ongoing education and training. Expectations must be tempered by reality—we do not yet have technology that completely eliminates the self-care tasks necessary for managing diabetes, but the tools described in this section can make it easier to manage.

References

1. Broos B, Charleer S, Bolsens N, et al. Diabetes knowledge and metabolic control in type 1 diabetes starting with continuous glucose monitoring: FUTURE-PEAK. *J Clin Endocrinol Metab* 2021;106:e3037–e3048
2. Yoo JH, Kim G, Lee HJ, Sim KH, Jin SM, Kim JH. Effect of structured individualized education on continuous glucose monitoring use in poorly controlled patients with type 1 diabetes: a randomized controlled trial. *Diabetes Res Clin Pract* 2022;184:109209
3. Champakanath A, Akturk HK, Alonso GT, Snell-Bergeon JK, Shah VN. Continuous glucose monitoring initiation within first year of type 1 diabetes diagnosis is associated with improved

glycemic outcomes: 7-year follow-up study. *Diabetes Care* 2022;45:750–753

4. Patton SR, Noser AE, Youngkin EM, Majidi S, Clements MA. Early initiation of diabetes devices relates to improved glycemic control in children with recent-onset type 1 diabetes mellitus. *Diabetes Technol Ther* 2019;21:379–384
5. Prahalad P, Ding VY, Zaharieva DP, et al. Teamwork, targets, technology, and tight control in newly diagnosed type 1 diabetes: the Pilot 4T study. *J Clin Endocrinol Metab* 2022;107:998–1008
6. Tanenbaum ML, Zaharieva DP, Addala A, et al. ‘I was ready for it at the beginning’: parent experiences with early introduction of continuous glucose monitoring following their child’s type 1 diabetes diagnosis. *Diabet Med* 2021;38:e14567
7. Addala A, Maahs DM, Scheinker D, Chertow S, Leverenz B, Prahalad P. Uninterrupted continuous glucose monitoring access is associated with a decrease in HbA1c in youth with type 1 diabetes and public insurance. *Pediatr Diabetes* 2020;21:1301–1309
8. Aleppo G, Beck RW, Bailey R, et al.; MOBILE Study Group; Type 2 Diabetes Basal Insulin Users: The Mobile Study (MOBILE) Study Group. The effect of discontinuing continuous glucose monitoring in adults with type 2 diabetes treated with basal insulin. *Diabetes Care* 2021;44:2729–2737
9. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
10. King F, Ahn D, Hsiao V, Porco T, Klonoff DC. A review of blood glucose monitor accuracy. *Diabetes Technol Ther* 2018;20:843–856
11. Brazg RL, Klaff LJ, Parkin CG. Performance variability of seven commonly used self-monitoring of blood glucose systems: clinical considerations for patients and providers. *J Diabetes Sci Technol* 2013;7:144–152
12. Klonoff DC, Parkes JL, Kovatchev BP, et al. Investigation of the accuracy of 18 marketed blood glucose monitors. *Diabetes Care* 2018;41:1681–1688
13. Pleus S, Baumstark A, Jendrike N, et al. System accuracy evaluation of 18 CE-marked current-generation blood glucose monitoring systems based on EN ISO 15197:2015. *BMJ Open Diabetes Res Care* 2020;8:e001067
14. Grady M, Lamps G, Shemain A, Cameron H, Murray L. Clinical evaluation of a new, lower pain, one touch lancing device for people with diabetes: virtually pain-free testing and improved comfort compared to current lancing systems. *J Diabetes Sci Technol* 2019;15:53–59
15. Harrison B, Brown D. Accuracy of a blood glucose monitoring system that recognizes insufficient sample blood volume and allows application of more blood to the same test strip. *Expert Rev Med Devices* 2020;17:75–82
16. Miller KM, Beck RW, Bergenstal RM, et al.; T1D Exchange Clinic Network. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care* 2013;36:2009–2014
17. Grant RW, Huang ES, Wexler DJ, et al. Patients who self-monitor blood glucose and their

unused testing results. *Am J Manag Care* 2015;21:e119–e129

18. Katz LB, Stewart L, Guthrie B, Cameron H. Patient satisfaction with a new, high accuracy blood glucose meter that provides personalized guidance, insight, and encouragement. *J Diabetes Sci Technol* 2020;14:318–323
19. Shaw RJ, Yang Q, Barnes A, et al. Self-monitoring diabetes with multiple mobile health devices. *J Am Med Inform Assoc* 2020;27:667–676
20. Gellad WF, Zhao X, Thorpe CT, Mor MK, Good CB, Fine MJ. Dual use of Department of Veterans Affairs and Medicare benefits and use of test strips in veterans with type 2 diabetes mellitus. *JAMA Intern Med* 2015;175:26–34
21. Endocrine Society and Choosing Wisely. Five things physicians and patients should question. Accessed 17 October 2022. Available from <https://www.choosingwisely.org/societies/endocrine-society/>
22. Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J; DPV-Wiss-Initiative. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2011;12:11–17
23. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008;51:408–416
24. Garber AJ. Treat-to-target trials: uses, interpretation and review of concepts. *Diabetes Obes Metab* 2014;16:193–205
25. Farmer A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ* 2007;335:132
26. O’Kane MJ, Bunting B, Copeland M; ESMON study group. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. *BMJ* 2008;336:1174–1177
27. Simon J, Gray A, Clarke P, Wade A, Neil A; Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. *BMJ* 2008;336:1177–1180
28. Young LA, Buse JB, Weaver MA, et al.; Monitor Trial Group. Glucose self-monitoring in non-insulin-treated patients with type 2 diabetes in primary care settings: a randomized trial. *JAMA Intern Med* 2017;177:920–929
29. Polonsky WH, Fisher L, Schikman CH, et al. Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the Structured Testing Program study. *Diabetes Care* 2011;34:262–267
30. Malanda UL, Welschen LMC, Riphagen II, Dekker JM, Nijpels G, Bot SDM. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. *Cochrane Database Syst Rev* 2012;1:CD005060
31. Willett LR. ACP Journal Club. Meta-analysis: self-monitoring in non-insulin-treated type 2 diabetes improved HbA1c by 0.25%. *Ann Intern Med* 2012;156:JC6–JC12

32. Mannucci E, Antenore A, Giorgino F, Scavini M. Effects of structured versus unstructured self-monitoring of blood glucose on glucose control in patients with non-insulin-treated type 2 diabetes: a meta-analysis of randomized controlled trials. *J Diabetes Sci Technol* 2018;12:183–189
33. Sai S, Urata M, Ogawa I. Evaluation of linearity and interference effect on SMBG and POCT devices, showing drastic high values, low values, or error messages. *J Diabetes Sci Technol* 2019;13:734–743
34. Ginsberg BH. Factors affecting blood glucose monitoring: sources of errors in measurement. *J Diabetes Sci Technol* 2009;3:903–913
35. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476
36. Tumminia A, Crimi S, Sciacca L, et al. Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial. *Diabetes Metab Res Rev* 2015;31:61–68
37. Hansen KW, Bibby BM. The frequency of intermittently scanned glucose and diurnal variation of glycemic metrics. *J Diabetes Sci Technol* 2022;16:1461–1465
38. Urakami T, Yoshida K, Kuwabara R, et al. Frequent scanning using flash glucose monitoring contributes to better glycemic control in children and adolescents with type 1 diabetes. *J Diabetes Investig* 2022;13:185–190
39. Lameijer A, Lommerde N, Dunn TC, et al. Flash Glucose Monitoring in the Netherlands: Increased monitoring frequency is associated with improvement of glycemic parameters. *Diabetes Res Clin Pract* 2021;177:108897
40. Hohendorff J, Gumprecht J, Mysliwicz M, Zozulinska-Ziolkiewicz D, Malecki MT. Intermittently scanned continuous glucose monitoring data of polish patients from real-life conditions: more scanning and better glycemic control compared to worldwide data. *Diabetes Technol Ther* 2021;23:577–585
41. Aleppo G, Ruedy KJ, Riddlesworth TD, et al.; REPLACE-BG Study Group. REPLACE-BG: a randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. *Diabetes Care* 2017;40:538–545
42. U.S. Food and Drug Administration. –FDA News Release: FDA expands indication for continuous glucose monitoring system, first to replace fingerstick testing for diabetes treatment decisions, 2016. Accessed 17 October 2022. Available from <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534056.htm>
43. U.S. Food and Drug Administration. –FDA News Release: FDA approves first continuous glucose monitoring system for adults not requiring blood sample calibration, 2017. Accessed 17 October 2022. Available from <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577890.htm>
44. U.S. Food and Drug Administration. Product classification [database]. Accessed 17 October 2022. Available from <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/classification.cfm>
45. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* 2017;317:371–378
46. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. *JAMA* 2017;317:379–387
47. Riddlesworth T, Price D, Cohen N, Beck RW. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. *Diabetes Ther* 2017;8:947–951
48. Sequeira PA, Montoya L, Ruelas V, et al. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. *Diabetes Technol Ther* 2013;15:855–858
49. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016;388:2254–2263
50. Hermanns N, Schumann B, Kulzer B, Haak T. The impact of continuous glucose monitoring on low interstitial glucose values and low blood glucose values assessed by point-of-care blood glucose meters: results of a crossover trial. *J Diabetes Sci Technol* 2014;8:516–522
51. van Beers CAJ, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. *Lancet Diabetes Endocrinol* 2016;4:893–902
52. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012;55:3155–3162
53. Pratley RE, Kanapka LG, Rickels MR, et al.; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study Group. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. *JAMA* 2020;323:2397–2406
54. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 2006;29:2730–2732
55. O’Connell MA, Donath S, O’Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. *Diabetologia* 2009;52:1250–1257
56. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011;34:795–800
57. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *Lancet* 2018;391:1367–1377
58. Beck RW, Hirsch IB, Laffel L, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383
59. Laffel LM, Kanapka LG, Beck RW, et al.; CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group; CDE10. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: a randomized clinical trial. *JAMA* 2020;323:2388–2396
60. Strategies to Enhance New CGM Use in Early Childhood (SENCE) Study Group. A randomized clinical trial assessing continuous glucose monitoring (CGM) use with standardized education with or without a family behavioral intervention compared with fingerstick blood glucose monitoring in very young children with type 1 diabetes. *Diabetes Care* 2021;44:464–472
61. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care* 2006;29:44–50
62. New JP, Aijan R, Pfeiffer AFH, Freckmann G. Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). *Diabet Med* 2015;32:609–617
63. Beck RW, Riddlesworth TD, Ruedy K, et al.; DIAMOND Study Group. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. *Ann Intern Med* 2017;167:365–374
64. Ehrhardt NM, Chellappa M, Walker MS, Fonda SJ, Vigersky RA. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. *J Diabetes Sci Technol* 2011;5:668–675
65. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. *Diabetes Res Clin Pract* 2008;82:73–79
66. Martens T, Beck RW, Bailey R, et al.; MOBILE Study Group. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: a randomized clinical trial. *JAMA* 2021;325:2262–2272
67. Gubitosi-Klug RA, Braffett BH, Bebu I, et al. Continuous glucose monitoring in adults with type 1 diabetes with 35 years duration from the DCCT/EDIC study. *Diabetes Care* 2022;45:659–665
68. Teo E, Hassan N, Tam W, Koh S. Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis. *Diabetologia* 2022;65:604–619
69. Garg SK, Liljenquist D, Bode B, et al. Evaluation of Accuracy and Safety of the Next-Generation Up to 180-Day Long-Term Implantable Eversense Continuous Glucose Monitoring System: The PROMISE Study. *Diabetes Technol Ther* 2022;24:84–92
70. Garg SK, Kipnes M, Castorino K, et al. Accuracy and safety of Dexcom G7 continuous glucose monitoring in adults with diabetes. *Diabetes Technol Ther* 2022;24:373–380
71. Laffel LM, Bailey TS, Christiansen MP, Reid JL, Beck SE. Accuracy of a seventh-generation continuous glucose monitoring system in children and adolescents with type 1 diabetes. *J Diabetes*

- Sci Technol. 25 April 2022 [Epub ahead of print]. DOI: 10.1177/19322968221091816
72. Miller KM, Kanapka LG, Rickels MR, et al. Benefit of continuous glucose monitoring in reducing hypoglycemia is sustained through 12 months of use among older adults with type 1 diabetes. *Diabetes Technol Ther* 2022;24:424–434
73. Bao S, Bailey R, Calhoun P, Beck RW. Effectiveness of continuous glucose monitoring in older adults with type 2 diabetes treated with basal insulin. *Diabetes Technol Ther* 2022;24:299–306
74. Van Name MA, Kanapka LG, DiMeglio LA, et al. Long-term continuous glucose monitor use in very young children with type 1 diabetes: one-year results from the SENCE study. *J Diabetes Sci Technol*. 26 March 2022 [Epub ahead of print]. DOI: 10.1177/19322968221084667
75. Price DA, Deng Q, Kipnes M, Beck SE. Episodic real-time CGM use in adults with type 2 diabetes: results of a pilot randomized controlled trial. *Diabetes Ther* 2021;12:2089–2099
76. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther* 2017;8:55–73
77. Yaron M, Roitman E, Aharon-Hananel G, et al. Effect of flash glucose monitoring technology on glycemic control and treatment satisfaction in patients with type 2 diabetes. *Diabetes Care* 2019;42:1178–1184
78. Davis TME, Dwyer P, England M, Fegan PG, Davis WA. Efficacy of intermittently scanned continuous glucose monitoring in the prevention of recurrent severe hypoglycemia. *Diabetes Technol Ther* 2020;22:367–373
79. Boucher SE, Gray AR, Wiltshire EJ, et al. Effect of 6 months of flash glucose monitoring in youth with type 1 diabetes and high-risk glycemic control: a randomized controlled trial. *Diabetes Care* 2020;43:2388–2395
80. Leelarathna L, Evans ML, Neupane S; FLASH-UK Trial Study Group. Intermittently scanned continuous glucose monitoring for type 1 diabetes. *N Engl J Med* 2022;387:1477–1487
81. Deshmukh H, Wilmot EG, Gregory R, et al. Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the Association of British Clinical Diabetologists (ABCD) nationwide audit. *Diabetes Care* 2020;43:2153–2160
82. Charleer S, Gillard P, Vandoorne E, Cammaerts K, Mathieu C, Casteels K. Intermittently scanned continuous glucose monitoring is associated with high satisfaction but increased HbA_{1c} and weight in well-controlled youth with type 1 diabetes. *Pediatr Diabetes* 2020;21:1465–1474
83. Al Hayek A, Al Dawish M, El Jammal M. The impact of flash glucose monitoring on markers of glycaemic control and patient satisfaction in type 2 diabetes. *Cureus* 2021;13:e16007
84. Nathanson D, Svensson AM, Miftaraj M, Franzén S, Bolinder J, Eeg-Olofsson K. Effect of flash glucose monitoring in adults with type 1 diabetes: a nationwide, longitudinal observational study of 14,372 flash users compared with 7691 glucose sensor naive controls. *Diabetologia* 2021;64:1595–1603
85. Roussel R, Riveline JP, Vicaute E, et al. Important drop in rate of acute diabetes complications in people with type 1 or type 2 diabetes after initiation of flash glucose monitoring in France: the RELIEF study. *Diabetes Care* 2021;44:1368–1376
86. Wright EE Jr, Kerr MSD, Reyes IJ, Nabutovsky Y, Miller E. Use of flash continuous glucose monitoring is associated with A1C reduction in people with type 2 diabetes treated with basal insulin or noninsulin therapy. *Diabetes Spectr* 2021;34:184–189
87. Charleer S, De Block C, Van Huffel L, et al. Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): a prospective observational real-world cohort study. *Diabetes Care* 2020;43:389–397
88. Elliott T, Beca S, Beharry R, Tsoukas MA, Zarruk A, Abitbol A. The impact of flash glucose monitoring on glycated hemoglobin in type 2 diabetes managed with basal insulin in Canada: a retrospective real-world chart review study. *Diab Vasc Dis Res* 2021;18:14791641211021374
89. Tyndall V, Stimson RH, Zammit NN, et al. Marked improvement in HbA_{1c} following commencement of flash glucose monitoring in people with type 1 diabetes. *Diabetologia* 2019;62:1349–1356
90. Karter AJ, Parker MM, Moffet HH, Gilliam LK, Dlott R. Association of real-time continuous glucose monitoring with glycemic control and acute metabolic events among patients with insulin-treated diabetes. *JAMA* 2021;325:2273–2284
91. Reddy M, Jugnee N, El Laboudi A, Spanudakis E, Anantharaja S, Oliver N. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with type 1 diabetes and impaired awareness of hypoglycaemia. *Diabet Med* 2018;35:483–490
92. Hásková A, Radovnická L, Petruželková L, et al. Real-time CGM is superior to flash glucose monitoring for glucose control in type 1 diabetes: the CORRIDA randomized controlled trial. *Diabetes Care* 2020;43:2744–2750
93. Visser MM, Charleer S, Fieuws S, et al. Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. *Lancet* 2021;397:2275–2283
94. Sandig D, Grimsman J, Reinauer C, et al. Continuous glucose monitoring in adults with type 1 diabetes: real-world data from the German/Austrian Prospective Diabetes Follow-Up Registry. *Diabetes Technol Ther* 2020;22:602–612
95. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017;40:1631–1640
96. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019;42:1593–1603
97. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPT): a multicentre international randomised controlled trial. *Lancet* 2017;390:2347–2359
98. Kristensen K, Ögge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. *Diabetologia* 2019;62:1143–1153
99. Law GR, Gilthorpe MS, Secher AL, et al. Translating HbA_{1c} measurements into estimated average glucose values in pregnant women with diabetes. *Diabetologia* 2017;60:618–624
100. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. *Diabetes Care* 2013;36:1877–1883
101. Wei Q, Sun Z, Yang Y, Yu H, Ding H, Wang S. Effect of a CGMS and SMBG on maternal and neonatal outcomes in gestational diabetes mellitus: a randomized controlled trial. *Sci Rep* 2016;6:19920
102. Ajjan RA, Jackson N, Thomson SA. Reduction in HbA_{1c} using professional flash glucose monitoring in insulin-treated type 2 diabetes patients managed in primary and secondary care settings: a pilot, multicentre, randomised controlled trial. *Diab Vasc Dis Res* 2019;16:385–395
103. Ribeiro RT, Andrade R, Nascimento do Ó D, Lopes AF, Raposo JF. Impact of blinded retrospective continuous glucose monitoring on clinical decision making and glycemic control in persons with type 2 diabetes on insulin therapy. *Nutr Metab Cardiovasc Dis* 2021;31:1267–1275
104. Wada E, Onoue T, Kobayashi T, et al. Flash glucose monitoring helps achieve better glycemic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial. *BMJ Open Diabetes Res Care* 2020;8:e001115
105. Fantasia KL, Stockman MC, Ju Z, et al. Professional continuous glucose monitoring and endocrinology eConsult for adults with type 2 diabetes in primary care: results of a clinical pilot program. *J Clin Transl Endocrinol* 2021;24:100254
106. Simonson GD, Bergenstal RM, Johnson ML, Davidson JL, Martens TW. Effect of professional CGM (pCGM) on glucose management in type 2 diabetes patients in primary care. *J Diabetes Sci Technol* 2021;15:539–545
107. Ulrich H, Bowen M. The clinical utility of professional continuous glucose monitoring by pharmacists for patients with type 2 diabetes. *J Am Pharm Assoc* (2003) 2021;S1544-3191:00195-3
108. Pleus S, Ulbrich S, Zschornack E, Kamann S, Haug C, Freckmann G. Documentation of skin-related issues associated with continuous glucose monitoring use in the scientific literature. *Diabetes Technol Ther* 2019;21:538–545
109. Herman A, de Montjoye L, Baeck M. Adverse cutaneous reaction to diabetic glucose sensors and insulin pumps: irritant contact dermatitis or allergic contact dermatitis? *Contact Dermat* 2020;83:25–30
110. Rigo RS, Levin LE, Belsito DV, Garzon MC, Gandica R, Williams KM. Cutaneous reactions to continuous glucose monitoring and continuous subcutaneous insulin infusion devices in type 1 diabetes mellitus. *J Diabetes Sci Technol* 2021;15:786–791
111. Kamann S, Aerts O, Heinemann L. Further evidence of severe allergic contact dermatitis from isobornyl acrylate while using a continuous glucose monitoring system. *J Diabetes Sci Technol* 2018;12:630–633
112. Aerts O, Herman A, Bruze M, Goossens A, Mowitz M. FreeStyle Libre: contact irritation versus contact allergy. *Lancet* 2017;390:1644

113. Herman A, Aerts O, Baeck M, et al. Allergic contact dermatitis caused by isobornyl acrylate in Freestyle Libre, a newly introduced glucose sensor. *Contact Dermat* 2017;77:367–373
114. Hyry HSI, Liippo JP, Virtanen HM. Allergic contact dermatitis caused by glucose sensors in type 1 diabetes patients. *Contact Dermat* 2019;81:161–166
115. Asarani NAM, Reynolds AN, Boucher SE, de Bock M, Wheeler BJ. Cutaneous complications with continuous or flash glucose monitoring use: systematic review of trials and observational studies. *J Diabetes Sci Technol* 2020;14:328–337
116. Lombardo F, Salzano G, Crisafulli G, et al. Allergic contact dermatitis in pediatric patients with type 1 diabetes: an emerging issue. *Diabetes Res Clin Pract* 2020;162:108089
117. Ooppel E, Kamann S, Heinemann L, Reichl FX, Högg C. The implanted glucose monitoring system Eversense: an alternative for diabetes patients with isobornyl acrylate allergy. *Contact Dermat* 2020;82:101–104
118. Freckmann G, Buck S, Waldenmaier D, et al. Skin reaction report form: development and design of a standardized report form for skin reactions due to medical devices for diabetes management. *J Diabetes Sci Technol* 2021;15:801–806
119. Deiss D, Irace C, Carlson G, Tweden KS, Kaufman FR. Real-World Safety of an Implantable Continuous Glucose Sensor Over Multiple Cycles of Use: A Post-Market Registry Study. *Diabetes Technol Ther* 2020;22:48–52
120. Sanchez P, Ghosh-Dastidar S, Tweden KS, Kaufman FR. Real-world data from the first U.S. commercial users of an implantable continuous glucose sensor. *Diabetes Technol Ther* 2019;21:677–681
121. Heinemann L. Interferences with CGM systems: practical relevance? *J Diabetes Sci Technol* 2022;16:271–274
122. Tellez SE, Hornung LN, Courter JD, et al. Inaccurate glucose sensor values after hydroxyurea administration. *Diabetes Technol Ther* 2021;23:443–451
123. Szmilowicz ED, Aleppo G. Interferent effect of hydroxyurea on continuous glucose monitoring. *Diabetes Care* 2021;44:e89–e90
124. Pfützner A, Jensch H, Cardinal C, Srikanthamoorthy G, Riehn E, Thomé N. Laboratory protocol and pilot results for dynamic interference testing of continuous glucose monitoring sensors. *J Diabetes Sci Technol*. 13 May 2022 [Epub ahead of print]. DOI: 10.1177/19322968221095573
125. Lorenz C, Sandoval W, Mortellaro M. Interference assessment of various endogenous and exogenous substances on the performance of the everSense long-term implantable continuous glucose monitoring system. *Diabetes Technol Ther* 2018;20:344–352
126. Denham D. Effect of repeated doses of acetaminophen on a continuous glucose monitoring system with permselective membrane. *J Diabetes Sci Technol* 2021;15:517–518
127. Piras de Oliveira C, Mitchell BD, Fan L, et al. Patient perspectives on the use of half-unit insulin pens by people with type 1 diabetes: a cross-sectional observational study. *Curr Med Res Opin* 2021;37:45–51
128. Machry RV, Cipriani GF, Pedrosa HU, et al. Pens versus syringes to deliver insulin among elderly patients with type 2 diabetes: a randomized controlled clinical trial. *Diabetol Metab Syndr* 2021;13:64
129. Ignaut DA, Schwartz SL, Sarwat S, Murphy HL. Comparative device assessments: Humalog KwikPen compared with vial and syringe and FlexPen. *Diabetes Educ* 2009;35:789–798
130. Korytkowski M, Bell D, Jacobsen C, FlexPen Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther* 2003;25:2836–2848
131. Asche CV, Shane-McWhorter L, Raparla S. Health economics and compliance of vials/syringes versus pen devices: a review of the evidence. *Diabetes Technol Ther* 2010;12(Suppl. 1):S101–S108
132. Singh R, Samuel C, Jacob JJ. A Comparison of insulin pen devices and disposable plastic syringes - simplicity, safety, convenience and cost differences. *Eur Endocrinol* 2018;14:47–51
133. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. *Mayo Clin Proc* 2016;91:1231–1255
134. Lasalvia P, Barahona-Correa JE, Romero-Alvernia DM, et al. Pen devices for insulin self-administration compared with needle and vial: systematic review of the literature and meta-analysis. *J Diabetes Sci Technol* 2016;10:959–966
135. Slabaugh SL, Bouchard JR, Li Y, Baltz JC, Meah YA, Moretz DC. Characteristics relating to adherence and persistence to basal insulin regimens among elderly insulin-naïve patients with type 2 diabetes: pre-filled pens versus vials/syringes. *Adv Ther* 2015;32:1206–1221
136. Chandran A, Bonafede MK, Nigam S, Saltiel-Berzin R, Hirsch LJ, Lahue BJ. Adherence to insulin pen therapy is associated with reduction in healthcare costs among patients with type 2 diabetes mellitus. *Am Health Drug Benefits* 2015;8:148–158
137. Pawaskar MD, Camacho FT, Anderson RT, Cobden D, Joshi AV, Balkrishnan R. Health care costs and medication adherence associated with initiation of insulin pen therapy in Medicaid-enrolled patients with type 2 diabetes: a retrospective database analysis. *Clin Ther* 2007;29:1294–1305
138. Seggelke SA, Hawkins RM, Gibbs J, Rasouli N, Wang CCL, Draznin B. Effect of glargine insulin delivery method (pen device versus vial/syringe) on glycemic control and patient preferences in patients with type 1 and type 2 diabetes. *Endocr Pract* 2014;20:536–539
139. Ahmann A, Szeinbach SL, Gill J, Traylor L, Garg SK. Comparing patient preferences and healthcare provider recommendations with the pen versus vial-and-syringe insulin delivery in patients with type 2 diabetes. *Diabetes Technol Ther* 2014;16:76–83
140. Asche CV, Luo W, Aagren M. Differences in rates of hypoglycemia and health care costs in patients treated with insulin aspart in pens versus vials. *Curr Med Res Opin* 2013;29:1287–1296
141. Eby EL, Boye KS, Lage MJ. The association between use of mealtime insulin pens versus vials and healthcare charges and resource utilization in patients with type 2 diabetes: a retrospective cohort study. *J Med Econ* 2013;16:1231–1237
142. Anderson BJ, Redondo MJ. What can we learn from patient-reported outcomes of insulin pen devices? *J Diabetes Sci Technol* 2011;5:1563–1571
143. Luijff YM, DeVries JH. Dosing accuracy of insulin pens versus conventional syringes and vials. *Diabetes Technol Ther* 2010;12(Suppl. 1):S73–S77
144. Hanas R, de Beaufort C, Hoey H, Anderson B. Insulin delivery by injection in children and adolescents with diabetes. *Pediatr Diabetes* 2011;12:518–526
145. Pfützner A, Schipper C, Niemeier M, et al. Comparison of patient preference for two insulin injection pen devices in relation to patient dexterity skills. *J Diabetes Sci Technol* 2012;6:910–916
146. Reinauer KM, Joksich G, Renn W, Eggstein M. Insulin pens in elderly diabetic patients. *Diabetes Care* 1990;13:1136–1137
147. Thomas DR, Fischer RG, Nicholas WC, Beghe C, Hatten KW, Thomas JN. Disposable insulin syringe reuse and aseptic practices in diabetic patients. *J Gen Intern Med* 1989;4:97–100
148. Arab JP, Dirchwolf M, Álvares-da-Silva MR, et al. Latin American Association for the Study of the Liver (ALEH) practice guidance for the diagnosis and treatment of non-alcoholic fatty liver disease. *Ann Hepatol* 2020;19:674–690
149. Bailey TS, Stone JY. A novel pen-based Bluetooth-enabled insulin delivery system with insulin dose tracking and advice. *Expert Opin Drug Deliv* 2017;14:697–703
150. Eiland L, McLarney M, Thangavelu T, Drincic A. App-based insulin calculators: current and future state. *Curr Diab Rep* 2018;18:123
151. Huckvale K, Adomaviciute S, Prieto JT, Leow MKS, Car J. Smartphone apps for calculating insulin dose: a systematic assessment. *BMC Med* 2015;13:106
152. Breton MD, Patek SD, Lv D, et al. Continuous glucose monitoring and insulin informed advisory system with automated titration and dosing of insulin reduces glucose variability in type 1 diabetes mellitus. *Diabetes Technol Ther* 2018;20:531–540
153. Bergenstal RM, Johnson M, Passi R, et al. Automated insulin dosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre, randomised controlled trial. *Lancet* 2019;393:1138–1148
154. Schneider JE, Parikh A, Stojanovic I. Impact of a novel insulin management service on non-insulin pharmaceutical expenses. *J Health Econ Outcomes Res* 2018;6:53–62
155. Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med* 2012;157:336–347
156. Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. *J Diabetes Sci Technol* 2013;7:1567–1574
157. Lin MH, Connor CG, Ruedy KJ, et al.; Pediatric Diabetes Consortium. Race, socioeconomic status, and treatment center are associated with insulin pump therapy in youth in the first year following diagnosis of type 1 diabetes. *Diabetes Technol Ther* 2013;15:929–934
158. Willi SM, Miller KM, DiMeglio LA, et al.; T1D Exchange Clinic Network. Racial-ethnic disparities in management and outcomes among children with type 1 diabetes. *Pediatrics* 2015;135:424–434
159. Redondo MJ, Libman I, Cheng P, et al.; Pediatric Diabetes Consortium. Racial/ethnic minority youth with recent-onset type 1 diabetes

have poor prognostic factors. *Diabetes Care* 2018;41:1017–1024

160. Ramchandani N, Ten S, Anhalt H, et al. Insulin pump therapy from the time of diagnosis of type 1 diabetes. *Diabetes Technol Ther* 2006;8:663–670

161. Berghaeuser MA, Kapellen T, Heidtmann B, Haberland H, Klinkert C; German working group for insulin pump treatment in paediatric patients. Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of type 1 diabetes mellitus. A multicenter analysis of 104 patients from 63 centres in Germany and Austria. *Pediatr Diabetes* 2008;9:590–595

162. Peters AL, Ahmann AJ, Battelino T, et al. Diabetes technology-continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2016;101:3922–3937

163. Gill M, Chhabra H, Shah M, Zhu C, Grunberger G. C-peptide and beta-cell auto-antibody testing prior to initiating continuous subcutaneous insulin infusion pump therapy did not improve utilization or medical costs among older adults with diabetes mellitus. *Endocr Pract* 2018;24:634–645

164. Vigersky RA, Huang S, Cordero TL, et al.; Opt2mise Study Group. Improved HbA1C, total daily insulin dose, and treatment satisfaction with insulin pump therapy compared to multiple daily insulin injections in patients with type 2 diabetes irrespective of baseline C-peptide levels. *Endocr Pract* 2018;24:446–452

165. Wheeler BJ, Heels K, Donaghue KC, Reith DM, Ambler GR. Insulin pump-associated adverse events in children and adolescents—a prospective study. *Diabetes Technol Ther* 2014;16:558–562

166. Kordonouri O, Lauterborn R, Deiss D. Lipohypertrophy in young patients with type 1 diabetes. *Diabetes Care* 2002;25:634–634

167. Kordonouri O, Hartmann R, Remus K, Bläsing S, Sadeghian E, Danne T. Benefit of supplementary fat plus protein counting as compared with conventional carbohydrate counting for insulin bolus calculation in children with pump therapy. *Pediatr Diabetes* 2012;13:540–544

168. Guinn TS, Bailey GJ, Mecklenburg RS. Factors related to discontinuation of continuous subcutaneous insulin-infusion therapy. *Diabetes Care* 1988;11:46–51

169. Wong JC, Boyle C, DiMeglio LA, et al.; T1D Exchange Clinic Network. Evaluation of pump discontinuation and associated factors in the T1D Exchange clinic registry. *J Diabetes Sci Technol* 2017;11:224–232

170. Wong JC, Dolan LM, Yang TT, Hood KK. Insulin pump use and glycemic control in adolescents with type 1 diabetes: predictors of change in method of insulin delivery across two years. *Pediatr Diabetes* 2015;16:592–599

171. Plotnick LP, Clark LM, Brancati FL, Erlinger T. Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. *Diabetes Care* 2003;26:1142–1146

172. Redondo MJ, Connor CG, Ruedy KJ, et al.; Pediatric Diabetes Consortium. Pediatric Diabetes Consortium Type 1 Diabetes New Onset (NeOn) study: factors associated with HbA1c levels one year after diagnosis. *Pediatr Diabetes* 2014;15:294–302

173. Doyle EA, Weinzimer SA, Steffen AT, Ahern JAH, Vincent M, Tamborlane WVA. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 2004;27:1554–1558

174. Alemzadeh R, Ellis JN, Holzum MK, Parton EA, Wyatt DT. Beneficial effects of continuous subcutaneous insulin infusion and flexible multiple daily insulin regimen using insulin glargine in type 1 diabetes. *Pediatrics* 2004;114:e91–e95

175. Sherr JL, Hermann JM, Campbell F, et al.; T1D Exchange Clinic Network, the DPV Initiative, and the National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health registries. Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. *Diabetologia* 2016;59:87–91

176. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 2008;51:941–951

177. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. *JAMA* 2017;318:1358–1366

178. The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *Am J Med* 1991;90:450–459

179. Haynes A, Hermann JM, Miller KM, et al.; T1D Exchange, WACDD and DPV registries. Severe hypoglycemia rates are not associated with HbA1c: a cross-sectional analysis of 3 contemporary pediatric diabetes registry databases. *Pediatr Diabetes* 2017;18:643–650

180. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 2008;25:765–774

181. Birkebaek NH, Drivvoll AK, Aakeson K, et al. Incidence of severe hypoglycemia in children with type 1 diabetes in the Nordic countries in the period 2008–2012: association with hemoglobin A_{1c} and treatment modality. *BMJ Open Diabetes Res Care* 2017;5:e000377

182. Maahs DM, Hermann JM, Holman N, et al.; National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health, the DPV Initiative, and the T1D Exchange Clinic Network. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. *Diabetes Care* 2015;38:1876–1882

183. Weintrob N, Benzaquen H, Galatzer A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. *Pediatrics* 2003;112:559–564

184. Opipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M, Foster C. Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. *Pediatr Diabetes* 2007;8:377–383

185. Sundberg F, Barnard K, Cato A, et al. ISPAD Guidelines. Managing diabetes in preschool children. *Pediatr Diabetes* 2017;18:499–517

186. Commissariat PV, Boyle CT, Miller KM, et al. Insulin pump use in young children with type 1 diabetes: sociodemographic factors and parent-reported barriers. *Diabetes Technol Ther* 2017;19:363–369

187. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. *Diabetes Care* 2018;41:2155–2161

188. Wood MA, Shulman DI, Forlenza GP, et al. In-clinic evaluation of the MiniMed 670G system “suspend before low” feature in children with type 1 diabetes. *Diabetes Technol Ther* 2018;20:731–737

189. Beato-Víbora PI, Quirós-López C, Lázaro-Martín L, et al. Impact of sensor-augmented pump therapy with predictive low-glucose suspend function on glycemic control and patient satisfaction in adults and children with type 1 diabetes. *Diabetes Technol Ther* 2018;20:738–743

190. Brown SA, Beck RW, Raghinaru D, et al.; iDCL Trial Research Group. Glycemic outcomes of use of CLC versus PLGS in type 1 diabetes: a randomized controlled trial. *Diabetes Care* 2020;43:1822–1828

191. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA* 2016;316:1407–1408

192. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2017;19:155–163

193. Tauschmann M, Thabit H, Bally L, et al.; APCam11 Consortium. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. *Lancet* 2018;392:1321–1329

194. Ekhlaspour L, Forlenza GP, Chernavsky D, et al. Closed loop control in adolescents and children during winter sports: use of the Tandem Control-IQ AP system. *Pediatr Diabetes* 2019;20:759–768

195. Buckingham BA, Christiansen MP, Forlenza GP, et al. Performance of the Omnipod personalized model predictive control algorithm with meal bolus challenges in adults with type 1 diabetes. *Diabetes Technol Ther* 2018;20:585–595

196. Renard E, Tubiana-Rufi N, Bonnemaison-Gilbert E, et al. Closed-loop driven by control-to-range algorithm outperforms threshold-low-glucose-suspend insulin delivery on glucose control albeit not on nocturnal hypoglycaemia in prepubertal patients with type 1 diabetes in a supervised hotel setting. *Diabetes Obes Metab* 2019;21:183–187

197. Forlenza GP, Ekhlaspour L, Breton M, et al. Successful at-home use of the Tandem Control-IQ artificial pancreas system in young children during a randomized controlled trial. *Diabetes Technol Ther* 2019;21:159–169

198. Anderson SM, Buckingham BA, Breton MD, et al. Hybrid closed-loop control is safe and effective for people with type 1 diabetes who are at moderate to high risk for hypoglycemia. *Diabetes Technol Ther* 2019;21:356–363

199. Forlenza GP, Pinhas-Hamiel O, Liljenquist DR, et al. Safety evaluation of the MiniMed 670G system in children 7-13 years of age with type 1 diabetes. *Diabetes Technol Ther* 2019;21:11-19
200. Karageorgiou V, Papaioannou TG, Bellos I, et al. Effectiveness of artificial pancreas in the non-adult population: a systematic review and network meta-analysis. *Metabolism* 2019;90:20-30
201. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med* 2019;381:1707-1717
202. Kaur H, Schneider N, Pyle L, Campbell K, Akturk HK, Shah VN. Efficacy of hybrid closed-loop system in adults with type 1 diabetes and gastroparesis. *Diabetes Technol Ther* 2019;21:736-739
203. Sherr JL, Buckingham BA, Forlenza GP, et al. Safety and performance of the Omnipod hybrid closed-loop system in adults, adolescents, and children with type 1 diabetes over 5 days under free-living conditions. *Diabetes Technol Ther* 2020;22:174-184
204. Lal RA, Basina M, Maahs DM, Hood K, Buckingham B, Wilson DM. One Year Clinical Experience of the First Commercial Hybrid Closed-Loop System. *Diabetes Care* 2019;42:2190-2196
205. Kovatchev B, Anderson SM, Raghinaru D, et al.; iDCL Study Group. Randomized controlled trial of mobile closed-loop control. *Diabetes Care* 2020;43:607-615
206. Sherr JL, Cengiz E, Palerm CC, et al. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. *Diabetes Care* 2013;36:2909-2914
207. Troncone A, Bonfanti R, Iafusco D, et al. Evaluating the experience of children with type 1 diabetes and their parents taking part in an artificial pancreas clinical trial over multiple days in a diabetes camp setting. *Diabetes Care* 2016;39:2158-2164
208. Barnard KD, Wysocki T, Allen JM, et al. Closing the loop overnight at home setting: psychosocial impact for adolescents with type 1 diabetes and their parents. *BMJ Open Diabetes Res Care* 2014;2:e000025
209. Weissberg-Benchell J, Hessler D, Polonsky WH, Fisher L. Psychosocial impact of the bionic pancreas during summer camp. *J Diabetes Sci Technol* 2016;10:840-844
210. Carlson AL, Sherr JL, Shulman DI, et al. Safety and glycemic outcomes during the MiniMed advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2022;24:178-189
211. Grunberger G, Sze D, Ermakova A, Sieradzian R, Oliveria T, Miller EM. Treatment intensification with insulin pumps and other technologies in patients with type 2 diabetes: results of a physician survey in the United States. *Clin Diabetes* 2020;38:47-55
212. Grunberger G, Rosenfeld CR, Bode BW, et al. Effectiveness of V-Go for patients with type 2 diabetes in a real-world setting: a prospective observational study. *Drugs Real World Outcomes* 2020;7:31-40
213. Layne JE, Parkin CG, Zisser H. Efficacy of a tubeless patch pump in patients with type 2 diabetes previously treated with multiple daily injections. *J Diabetes Sci Technol* 2017;11:178-179
214. Raval AD, Nguyen MH, Zhou S, Grabner M, Barron J, Quimbo R. Effect of V-Go versus multiple daily injections on glycemic control, insulin use, and diabetes medication costs among individuals with type 2 diabetes mellitus. *J Manag Care Spec Pharm* 2019;25:1111-1123
215. Leahy JLL, Aleppo G, Fonseca VA, et al. Optimizing postprandial glucose management in adults with insulin-requiring diabetes: report and recommendations. *J Endocr Soc* 2019;3:1942-1957
216. Reznik Y, Cohen O, Aronson R, et al.; Opt2mise Study Group. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (Opt2mise): a randomised open-label controlled trial. *Lancet* 2014;384:1265-1272
217. Winter A, Lintner M, Knezevich E. V-Go insulin delivery system versus multiple daily insulin injections for patients with uncontrolled type 2 diabetes mellitus. *J Diabetes Sci Technol* 2015;9:1111-1116
218. Bergenstal RM, Peyrot M, Dreon DM, et al.; Calibra Study Group. Implementation of basal-bolus therapy in type 2 diabetes: a randomized controlled trial comparing bolus insulin delivery using an insulin patch with an insulin pen. *Diabetes Technol Ther* 2019;21:273-285
219. Lewis D. History and perspective on DIY closed looping. *J Diabetes Sci Technol* 2019;13:790-793
220. Hng TM, Burren D. Appearance of do-it-yourself closed-loop systems to manage type 1 diabetes. *Intern Med J* 2018;48:1400-1404
221. Petruzelkova L, Soupal J, Plasova V, et al. Excellent glycemic control maintained by open-source hybrid closed-loop AndroidAPS during and after sustained physical activity. *Diabetes Technol Ther* 2018;20:744-750
222. Kesavadev J, Srinivasan S, Saboo B, Krishna B M, Krishnan G. The do-it-yourself artificial pancreas: a comprehensive review. *Diabetes Ther* 2020;11:1217-1235
223. Braune K, Lal RA, Petruzelková L, et al.; OPEN International Healthcare Professional Network and OPEN Legal Advisory Group. Open-source automated insulin delivery: international consensus statement and practical guidance for health-care professionals. *Lancet Diabetes Endocrinol* 2022;10:58-74
224. Phillip M, Bergenstal RM, Close KL, et al. The digital/virtual diabetes clinic: the future is now—recommendations from an international panel on diabetes digital technologies introduction. *Diabetes Technol Ther* 2021;23:146-154
225. Fleming GA, Petrie JR, Bergenstal RM, Holl RW, Peters AL, Heinemann L. Diabetes digital app technology: benefits, challenges, and recommendations. a consensus report by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) Diabetes Technology Working Group. *Diabetes Care* 2020;43:250-260
226. Wong JC, Izadi Z, Schroeder S, et al. A pilot study of use of a software platform for the collection, integration, and visualization of diabetes device data by health care providers in a multidisciplinary pediatric setting. *Diabetes Technol Ther* 2018;20:806-816
227. Chao DY, Lin TM, Ma WY. Enhanced self-efficacy and behavioral changes among patients with diabetes: cloud-based mobile health platform and mobile app service. *JMIR Diabetes* 2019;4:e11017
228. Sepah SC, Jiang L, Peters AL. Translating the Diabetes Prevention Program into an online social network: validation against CDC standards. *Diabetes Educ* 2014;40:435-443
229. Kaufman N, Ferrin C, Sugrue D. Using digital health technology to prevent and treat diabetes. *Diabetes Technol Ther* 2019;21(S1):S79-S94
230. Öberg U, Isaksson U, Jutterström L, Orre CJ, Hörnsten Å. Perceptions of persons with type 2 diabetes treated in Swedish primary health care: qualitative study on using ehealth services for self-management support. *JMIR Diabetes* 2018;3:e7
231. Bollyky JB, Bravata D, Yang J, Williamson M, Schneider J. Remote lifestyle coaching plus a connected glucose meter with certified diabetes educator support improves glucose and weight loss for people with type 2 diabetes. *J Diabetes Res* 2018;2018:3961730
232. Wilhide Ili CC, Peebles MM, Anthony Kouyaté RC. Evidence-based mHealth chronic disease mobile app intervention design: development of a framework. *JMIR Res Protoc* 2016;5:e25
233. Dixon RF, Zisser H, Layne JE, et al. A virtual type 2 diabetes clinic using continuous glucose monitoring and endocrinology visits. *J Diabetes Sci Technol* 2019;14:908-911
234. Yang Y, Lee EY, Kim H-S, Lee S-H, Yoon K-H, Cho J-H. Effect of a mobile phone-based glucose-monitoring and feedback system for type 2 diabetes management in multiple primary care clinic settings: cluster randomized controlled trial. *JMIR Mhealth Uhealth* 2020;8:e16266
235. Levine BJ, Close KL, Gabbay RA. Reviewing U.S. connected diabetes care: the newest member of the team. *Diabetes Technol Ther* 2020;22:1-9
236. McGill DE, Volkening LK, Butler DA, Wasserman RM, Anderson BJ, Laffel LM. Text-message responsiveness to blood glucose monitoring reminders is associated with HbA_{1c} benefit in teenagers with type 1 diabetes. *Diabet Med* 2019;36:600-605
237. Shen Y, Wang F, Zhang X, et al. Effectiveness of internet-based interventions on glycemic control in patients with type 2 diabetes: meta-analysis of randomized controlled trials. *J Med Internet Res* 2018;20:e172
238. Stone MP, Agrawal P, Chen X, et al. Retrospective analysis of 3-month real-world glucose data after the MiniMed 670G system commercial launch. *Diabetes Technol Ther* 2018;20:689-692
239. Umpierrez GE, Klonoff DC. Diabetes technology update: use of insulin pumps and continuous glucose monitoring in the hospital. *Diabetes Care* 2018;41:1579-1589
240. Yeh T, Yeung M, Mendelsohn Curanaj FA. Managing patients with insulin pumps and continuous glucose monitors in the hospital: to wear or not to wear. *Curr Diab Rep* 2021;21:7
241. Galindo RJ, Umpierrez GE, Rushakoff RJ, et al. Continuous glucose monitors and automated insulin dosing systems in the hospital consensus guideline. *J Diabetes Sci Technol* 2020;14:1035-1064
242. Houlden RL, Moore S. In-hospital management of adults using insulin pump therapy. *Can J Diabetes* 2014;38:126-133

243. U.S. Food and Drug Administration. Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Revised), 2020. Accessed 17 October 2022. Available from <https://www.fda.gov/media/136290/download>
244. Davis GM, Faulds E, Walker T, et al. Remote continuous glucose monitoring with a computerized insulin infusion protocol for critically ill patients in a COVID-19 medical ICU: proof of concept. *Diabetes Care* 2021;44:1055–1058
245. Sadhu AR, Serrano IA, Xu J, et al. Continuous glucose monitoring in critically ill patients with COVID-19: results of an emergent pilot study. *J Diabetes Sci Technol* 2020;14:1065–1073
246. Agarwal S, Mathew J, Davis GM, et al. Continuous glucose monitoring in the intensive care unit during the COVID-19 pandemic. *Diabetes Care* 2021;44:847–849
247. Ushigome E, Yamazaki M, Hamaguchi M, et al. Usefulness and safety of remote continuous glucose monitoring for a severe COVID-19 patient with diabetes. *Diabetes Technol Ther* 2020
248. Galindo RJ, Aleppo G, Klonoff DC, et al. Implementation of continuous glucose monitoring in the hospital: emergent considerations for remote glucose monitoring during the COVID-19 pandemic. *J Diabetes Sci Technol* 2020;14:822–832
249. Korytkowski MT, Muniyappa R, Antinori-Lent K, et al. Management of hyperglycemia in hospitalized adult patients in non-critical care settings: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2022;107:2101–2128
250. Longo RR, Elias H, Khan M, Seley JJ. Use and accuracy of inpatient CGM during the COVID-19 pandemic: an observational study of general medicine and ICU patients. *J Diabetes Sci Technol* 2022;16:1136–1143
251. Davis GM, Spanakis EK, Migdal AL, et al. Accuracy of Dexcom G6 continuous glucose monitoring in non-critically ill hospitalized patients with diabetes. *Diabetes Care* 2021;44:1641–1646
252. Baker M, Musselman ME, Rogers R, Hellman R. Practical implementation of remote continuous glucose monitoring in hospitalized patients with diabetes. *Am J Health Syst Pharm* 2022;79:452–458
253. Wright JJ, Williams AJ, Friedman SB, et al. Accuracy of continuous glucose monitors for inpatient diabetes management. *J Diabetes Sci Technol*. 7 February 2022 [Epub ahead of print]. DOI: 10.1177/19322968221076562
254. U.S. Food and Drug Administration. Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use. Guidance for Industry and Food and Drug Administration Staff, September 2020. Accessed 17 October 2022. Available from <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/self-monitoring-blood-glucose-test-systems-over-counter-use>
255. U.S. Food and Drug Administration. Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use: Guidance for Industry and Food and Drug Administration Staff, September 2020. Accessed 18 October 2021. Available from <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/blood-glucose-monitoring-test-systems-prescription-point-care-use>
256. Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care* 2000;23:1143–1148

8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Obesity is a chronic and often progressive disease with numerous medical, physical, and psychosocial complications, including a substantially increased risk for type 2 diabetes (1). There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type 2 diabetes (2–6) and is highly beneficial in treating type 2 diabetes (7–18). In people with type 2 diabetes and overweight or obesity, modest weight loss improves glycemia and reduces the need for glucose-lowering medications (7–9), and larger weight loss substantially reduces A1C and fasting glucose and has been shown to promote sustained diabetes remission through at least 2 years (11,19–23). Several modalities, including intensive behavioral counseling, obesity pharmacotherapy, and bariatric surgery, may aid in achieving and maintaining meaningful weight loss and reducing obesity-associated health risks. Metabolic surgery strongly improves glycemia and often leads to remission of diabetes, improved quality of life, improved cardiovascular outcomes, and reduced mortality. The importance of addressing obesity is further heightened by numerous studies showing that both obesity and diabetes increase the risk for more severe coronavirus disease 2019 (COVID-19) infections (24–27). This section aims to provide evidence-based recommendations for obesity management, including behavioral, pharmacologic, and surgical interventions, in people with type 2 diabetes and in those at risk. This section focuses on obesity management in adults; further discussion on obesity in older individuals and children can be found in Section 13, “Older Adults,” and Section 14, “Children and Adolescents,” respectively.

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ASSESSMENT

Recommendations

- 8.1** Use person-centered, nonjudgmental language that fosters collaboration between individuals and health care professionals, including person-first language (e.g., “person with obesity” rather than “obese person”). **E**
- 8.2** Measure height and weight and calculate BMI at annual visits or more frequently. Assess weight trajectory to inform treatment considerations. **E**
- 8.3** Based on clinical considerations, such as the presence of comorbid heart failure or significant unexplained weight gain or loss, weight may need to be monitored and evaluated more frequently. **B** If deterioration of medical status is associated with significant weight gain or loss, inpatient evaluation should be considered, especially focused on associations between medication use, food intake, and glycemic status. **E**
- 8.4** Accommodations should be made to provide privacy during weighing. **E**
- 8.5** Individuals with diabetes and overweight or obesity may benefit from modest or larger magnitudes of weight loss. Relatively small weight loss (approximately 3–7% of baseline weight) improves glycemia and other intermediate cardiovascular risk factors. **A** Larger, sustained weight losses (>10%) usually confer greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality. **B**

A person-centered communication style that uses inclusive and nonjudgmental language and active listening to elicit individual preferences and beliefs and assesses potential barriers to care should be used to optimize health outcomes and health-related quality of life. Use person-first language (e.g., “person with obesity” rather than “obese person”) to avoid defining people by their condition (28–30).

Height and weight should be measured to calculate BMI annually or more frequently when appropriate (20). BMI, calculated as weight in kilograms divided by the square of height in meters (kg/m^2), is calculated automatically by most electronic medical records. Use BMI to document weight status (overweight: BMI 25–29.9 kg/m^2 ; obesity class I: BMI 30–34.9 kg/m^2 ; obesity class II: BMI 35–39.9 kg/m^2 ; obesity class III: BMI ≥ 40 kg/m^2) but note that misclassification can occur, particularly in very muscular or frail individuals. In some groups, notably Asian and Asian American populations, the BMI cut points to define overweight and obesity are lower than those in other populations due to differences in body composition and cardiometabolic risk (Table 8.1) (30,31). Clinical considerations, such as the presence of comorbid heart failure or unexplained weight change, may warrant more frequent weight measurement and evaluation (32,33). If weighing is questioned or refused, the practitioner should be mindful of possible prior stigmatizing experiences and query for concerns, and the value of weight monitoring should be explained as a part of the medical evaluation process that helps to inform treatment decisions (34,35). Accommodations should be made to ensure privacy during weighing, particularly for those individuals who report or exhibit a high level of weight-related distress or dissatisfaction. Scales should be situated in a private area or room. Weight should be measured and reported nonjudgmentally. Care should be taken to regard a person’s weight (and weight changes) and BMI as sensitive health information. In addition to weight and BMI, assessment of weight distribution (including propensity for central/visceral adipose deposition) and weight gain pattern and trajectory can further inform risk stratification and treatment options (36).

Health care professionals should advise individuals with overweight or obesity and those with increasing weight trajectories that, in general, higher BMIs increase the risk of diabetes, cardiovascular disease, and all-cause mortality, as well as other adverse health and quality of life outcomes. Health care professionals should assess readiness to engage in behavioral changes for weight loss and jointly determine behavioral and weight loss goals and individualized intervention strategies (37). Strategies may include nutrition changes, physical activity, behavioral

counseling, pharmacologic therapy, medical devices, and metabolic surgery (Table 8.1). The latter three strategies may be considered for carefully selected individuals as adjuncts to nutrition changes, physical activity, and behavioral counseling.

Among people with type 2 diabetes and overweight or obesity who have inadequate glycemic, blood pressure, and lipid control and/or other obesity-related medical conditions, modest and sustained weight loss improves glycemia, blood pressure, and lipids and may reduce the need for medications (7–9,38). Greater weight loss may produce even greater benefits (21,22).

As little as 3–7% weight loss reduces the risk for diabetes in people at risk and improves glycemia in those with diabetes (2,7,8,39,40). Given the challenge of losing weight and maintaining weight loss, aiming for relatively small and attainable weight loss is often an effective clinical strategy, particularly for individuals who feel overwhelmed by larger weight loss targets. Nevertheless, mounting data from intensive nutrition and behavioral change interventions, pharmacotherapy, and bariatric surgery have shown that more substantial weight loss usually confers still greater benefits on glycemia and possibly disease remission as well as other cardiometabolic and quality-of-life outcomes (6,21–23,41–50).

With the increasing availability of more effective obesity treatments, individuals with diabetes and overweight or obesity should be informed of the potential benefits of both modest and more substantial weight loss and guided in the range of available treatment options, as discussed in the sections below. Shared decision-making should be used when counseling on behavioral changes, intervention choices, and weight management goals.

NUTRITION, PHYSICAL ACTIVITY, AND BEHAVIORAL THERAPY

Recommendations

- 8.6** Nutrition, physical activity, and behavioral therapy to achieve and maintain $\geq 5\%$ weight loss are recommended for most people with type 2 diabetes and overweight or obesity. Additional weight loss usually results in further improvements in the management of diabetes and cardiovascular risk. **B**

Table 8.1—Treatment options for overweight and obesity in type 2 diabetes

Treatment	BMI category (kg/m ²)		
	25.0–26.9 (or 23.0–24.9*)	27.0–29.9 (or 25.0–27.4*)	≥30.0 (or ≥27.5*)
Nutrition, physical activity, and behavioral counseling	†	†	†
Pharmacotherapy		†	†
Metabolic surgery			†

*Recommended cut points for Asian American individuals (expert opinion). †Treatment may be indicated for select motivated individuals.

- 8.7** Such interventions should include a high frequency of counseling (≥16 sessions in 6 months) and focus on nutrition changes, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit. **A**
- 8.8** An individual’s preferences, motivation, and life circumstances should be considered, along with medical status, when weight loss interventions are recommended. **C**
- 8.9** Behavioral changes that create an energy deficit, regardless of macronutrient composition, will result in weight loss. Nutrition recommendations should be individualized to the person’s preferences and nutritional needs. **A**
- 8.10** Evaluate systemic, structural, and socioeconomic factors that may impact nutrition patterns and food choices, such as food insecurity and hunger, access to healthful food options, cultural circumstances, and social determinants of health. **C**
- 8.11** For those who achieve weight loss goals, long-term (≥1 year) weight maintenance programs are recommended when available. Such programs should, at minimum, provide monthly contact and support, recommend ongoing monitoring of body weight (weekly or more frequently) and other self-monitoring strategies, and encourage regular physical activity (200–300 min/week). **A**
- 8.12** Short-term nutrition intervention using structured, very-low-calorie meals (800–1,000 kcal/day) may be prescribed for carefully selected individuals by trained

practitioners in medical settings with close monitoring. Long-term, comprehensive weight maintenance strategies and counseling should be integrated to maintain weight loss. **B**

8.13 There is no clear evidence that nutrition supplements are effective for weight loss. **A**

For a more detailed discussion of lifestyle management approaches and recommendations, see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes.” For a detailed discussion of nutrition interventions, please also refer to “Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report” (127).

Look AHEAD Trial

Although the Action for Health in Diabetes (Look AHEAD) trial did not show that the intensive lifestyle intervention reduced cardiovascular events in adults with type 2 diabetes and overweight or obesity (39), it did confirm the feasibility of achieving and maintaining long-term weight loss in people with type 2 diabetes. In the intensive lifestyle intervention group, mean weight loss was 4.7% at 8 years (40). Approximately 50% of intensive lifestyle intervention participants lost and maintained ≥5% of their initial body weight, and 27% lost and maintained ≥10% of their initial body weight at 8 years (40). Participants assigned to the intensive lifestyle group required fewer glucose-, blood pressure-, and lipid-lowering medications than those randomly assigned to standard care. Secondary analyses of the Look AHEAD trial and other large cardiovascular outcome studies document additional weight loss benefits in people with type 2 diabetes, including improved mobility, physical and

sexual function, and health-related quality of life (32). Moreover, several subgroups had improved cardiovascular outcomes, including those who achieved >10% weight loss (41) and those with moderately or poorly managed diabetes (A1C >6.8%) at baseline (42).

Behavioral Interventions

Significant weight loss can be attained with lifestyle programs that achieve a 500–750 kcal/day energy deficit, which in most cases is approximately 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men, adjusted for the individual’s baseline body weight. Clinical benefits typically begin upon achieving 3–5% weight loss (20,51), and the benefits of weight loss are progressive; more intensive weight loss goals (>5%, >7%, >15%, etc.) may be pursued if needed to achieve further health improvements and/or if the individual is more motivated and more intensive goals can be feasibly and safely attained.

Nutrition interventions may differ by macronutrient goals and food choices as long as they create the necessary energy deficit to promote weight loss (20,52–54). Using meal replacement plans prescribed by trained practitioners, with close monitoring, can be beneficial. Within the intensive lifestyle intervention group of the Look AHEAD trial, for example, the use of a partial meal replacement plan was associated with improvements in nutrition quality and weight loss (51). The nutrition choice should be based on the individual’s health status and preferences, including a determination of food availability and other cultural circumstances that could affect nutrition patterns (55).

Intensive behavioral interventions should include ≥16 sessions during the initial 6 months and focus on nutrition changes, physical activity, and behavioral strategies to achieve an ~500–750 kcal/day energy deficit. Interventions should be provided

by trained interventionists in either individual or group sessions (51). Assessing an individual's motivation level, life circumstances, and willingness to implement behavioral changes to achieve weight loss should be considered along with medical status when weight loss interventions are recommended and initiated (37,56).

People with type 2 diabetes and overweight or obesity who have lost weight should be offered long-term (≥ 1 year) comprehensive weight loss maintenance programs that provide at least monthly contact with trained interventionists and focus on ongoing monitoring of body weight (weekly or more frequently) and/or other self-monitoring strategies such as tracking intake, steps, etc.; continued focus on nutrition and behavioral changes; and participation in high levels of physical activity (200–300 min/week) (57). Some commercial and proprietary weight loss programs have shown promising weight loss results. However, most lack evidence of effectiveness, many do not satisfy guideline recommendations, and some promote unscientific and possibly dangerous practices (58,59).

When provided by trained practitioners in medical settings with ongoing monitoring, short-term (generally up to 3 months) intensive nutrition intervention may be prescribed for carefully selected individuals, such as those requiring weight loss before surgery and those needing greater weight loss and glycemic improvements. When integrated with behavioral support and counseling, structured very-low-calorie meals, typically 800–1,000 kcal/day, utilizing high-protein foods and meal replacement products, may increase the pace and/or magnitude of initial weight loss and glycemic improvements compared with standard behavioral interventions (21,22). As weight regain is common, such interventions should include long-term, comprehensive weight maintenance strategies and counseling to maintain weight loss and behavioral changes (60,61).

Despite widespread marketing and orbitant claims, there is no clear evidence that nutrition supplements (such as herbs and botanicals, high-dose vitamins and minerals, amino acids, enzymes, antioxidants, etc.) are effective for obesity management or weight loss (62–64). Several large systematic reviews show that most trials evaluating nutrition supplements for weight loss are of low quality and at high risk for bias. High-quality published studies show

little or no weight loss benefits. In contrast, vitamin/mineral (e.g., iron, vitamin B12, vitamin D) supplementation may be indicated in cases of documented deficiency, and protein supplements may be indicated as adjuncts to medically supervised weight loss therapies.

Health disparities adversely affect people who have systematically experienced greater obstacles to health based on their race or ethnicity, socioeconomic status, gender, disability, or other factors. Overwhelming research shows that these disparities may significantly affect health outcomes, including increasing the risk for obesity, diabetes, and diabetes-related complications. Health care professionals should evaluate systemic, structural, and socioeconomic factors that may impact food choices, access to healthful foods, and nutrition patterns; behavioral patterns, such as neighborhood safety and availability of safe outdoor spaces for physical activity; environmental exposures; access to health care; social contexts; and, ultimately, diabetes risk and outcomes. For a detailed discussion of social determinants of health, refer to “Social Determinants of Health: A Scientific Review” (65).

PHARMACOTHERAPY

Recommendations

- 8.14** When choosing glucose-lowering medications for people with type 2 diabetes and overweight or obesity, consider the medication's effect on weight. **B**
- 8.15** Whenever possible, minimize medications for comorbid conditions that are associated with weight gain. **E**
- 8.16** Obesity pharmacotherapy is effective as an adjunct to nutrition, physical activity, and behavioral counseling for selected people with type 2 diabetes and BMI ≥ 27 kg/m². Potential benefits and risks must be considered. **A**
- 8.17** If obesity pharmacotherapy is effective (typically defined as $\geq 5\%$ weight loss after 3 months' use), further weight loss is likely with continued use. When early response is insufficient (typically $< 5\%$ weight loss after 3 months' use) or if there are significant safety or tolerability issues, consider

discontinuation of the medication and evaluate alternative medications or treatment approaches. **A**

Glucose-Lowering Therapy

A meta-analysis of 227 randomized controlled trials of glucose-lowering treatments in type 2 diabetes found that A1C changes were not associated with baseline BMI, indicating that people with obesity can benefit from the same types of treatments for diabetes as normal-weight individuals (66). As numerous effective medications are available when considering medication plans, health care professionals should consider each medication's effect on weight. Agents associated with varying degrees of weight loss include metformin, α -glucosidase inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, dual glucagon-like peptide 1/glucose–dependent insulinotropic polypeptide receptor agonist (tirzepatide), and amylin mimetics. Dipeptidyl peptidase 4 inhibitors are weight neutral. In contrast, insulin secretagogues, thiazolidinediones, and insulin are often associated with weight gain (see Section 9, “Pharmacologic Approaches to Glycemic Treatment”).

Concomitant Medications

Health care professionals should carefully review the patient's concomitant medications and, whenever possible, minimize or provide alternatives for medications that promote weight gain. Examples of medications associated with weight gain include antipsychotics (e.g., clozapine, olanzapine, risperidone), some antidepressants (e.g., tricyclic antidepressants, some selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), glucocorticoids, injectable progestins, some anticonvulsants (e.g., gabapentin, pregabalin), and possibly sedating antihistamines and anticholinergics (67).

Approved Obesity Pharmacotherapy Options

The U.S. Food and Drug Administration (FDA) has approved medications for both short-term and long-term weight management as adjuncts to nutrition, physical activity and behavioral therapy. Nearly all

FDA-approved obesity medications have been shown to improve glycemia in people with type 2 diabetes and delay progression to type 2 diabetes in at-risk individuals (23). Phentermine and other older adrenergic agents are indicated for short-term (≤ 12 weeks) treatment (68). Five medications are FDA approved for long-term use (> 12 weeks) in adults with BMI ≥ 27 kg/m² with one or more obesity-associated comorbid conditions (e.g., type 2 diabetes, hypertension, and/or dyslipidemia) who are motivated to lose weight (23). (Refer to Section 14, “Children and Adolescents,” for medications approved for adolescents with obesity.) Medications approved by the FDA for the treatment of obesity, summarized in **Table 8.2**, include orlistat, phentermine/topiramate ER, naltrexone/bupropion ER, liraglutide 3 mg, and semaglutide 2.4 mg. (In addition, setmelanotide, a melanocortin 4 receptor agonist, is approved for use in cases of rare genetic mutations resulting in severe hyperphagia and extreme obesity, such as leptin receptor deficiency and proopiomelanocortin deficiency.) In principle, medications help improve adherence to nutrition recommendations, in most cases by modulating appetite or satiety. Health care professionals should be knowledgeable about the product label and balance the potential benefits of successful weight loss against the potential risks of the medication for each individual. These medications are contraindicated in individuals who are pregnant or actively trying to conceive and not recommended for use in women who are nursing. Individuals of reproductive potential should receive counseling regarding the use of reliable methods of contraception. Of note, while weight loss medications are often used in people with type 1 diabetes, clinical trial data in this population are limited.

Assessing Efficacy and Safety

Upon initiating weight loss medication, assess efficacy and safety at least monthly for the first 3 months and at least quarterly thereafter. Modeling from published clinical trials consistently shows that early responders have improved long-term outcomes (69–71). Unless clinical circumstances (such as poor tolerability) or other considerations (such as financial expense or individual preference) suggest otherwise, those who achieve sufficient early weight loss upon starting a chronic weight loss medication (typically defined as $> 5\%$ weight loss after 3 months' use) should

continue the medication. When early use appears ineffective (typically $< 5\%$ weight loss after 3 months' use), it is unlikely that continued use will improve weight outcomes; as such, it should be recommended to discontinue the medication and consider other treatment options.

MEDICAL DEVICES FOR WEIGHT LOSS

While gastric banding devices have fallen out of favor in recent years, since 2015, several minimally invasive medical devices have been approved by the FDA for short-term weight loss, including implanted gastric balloons, a vagus nerve stimulator, and gastric aspiration therapy (72). Given the current high cost, limited insurance coverage, and paucity of data in people with diabetes, medical devices for weight loss are rarely utilized at this time, and it remains to be seen how they may be used in the future (73).

An oral hydrogel (Plenity) has recently been approved for long-term use in those with BMI > 25 kg/m² to simulate the space-occupying effect of implantable gastric balloons. Taken with water 30 min before meals, the hydrogel expands to fill a portion of the stomach volume to help decrease food intake during meals. Though average weight loss is relatively small (2–3% greater than placebo), the subgroup of participants with prediabetes or diabetes at baseline had improved weight loss outcomes (8.1% weight loss) compared with the overall treatment (6.4% weight loss) and placebo (4.4% weight loss) groups (74).

METABOLIC SURGERY

Recommendations

- 8.18** Metabolic surgery should be a recommended option to treat type 2 diabetes in screened surgical candidates with BMI ≥ 40 kg/m² (BMI ≥ 37.5 kg/m² in Asian American individuals) and in adults with BMI 35.0–39.9 kg/m² (32.5–37.4 kg/m² in Asian American individuals) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. **A**
- 8.19** Metabolic surgery may be considered as an option to treat type 2 diabetes in adults

with BMI 30.0–34.9 kg/m² (27.5–32.4 kg/m² in Asian American individuals) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. **A**

- 8.20** Metabolic surgery should be performed in high-volume centers with multidisciplinary teams knowledgeable about and experienced in managing obesity, diabetes, and gastrointestinal surgery. **E**
- 8.21** People being considered for metabolic surgery should be evaluated for comorbid psychological conditions and social and situational circumstances that have the potential to interfere with surgery outcomes. **B**
- 8.22** People who undergo metabolic surgery should receive long-term medical and behavioral support and routine micronutrient, nutritional, and metabolic status monitoring. **B**
- 8.23** If postbariatric hypoglycemia is suspected, clinical evaluation should exclude other potential disorders contributing to hypoglycemia, and management includes education, medical nutrition therapy with a dietitian experienced in postbariatric hypoglycemia, and medication treatment, as needed. **A** Continuous glucose monitoring should be considered as an important adjunct to improve safety by alerting individuals to hypoglycemia, especially for those with severe hypoglycemia or hypoglycemia unawareness. **E**
- 8.24** People who undergo metabolic surgery should routinely be evaluated to assess the need for ongoing mental health services to help with the adjustment to medical and psychosocial changes after surgery. **C**

Surgical procedures for obesity treatment—often referred to interchangeably as bariatric surgery, weight loss surgery, metabolic surgery, or metabolic/bariatric surgery—can promote significant and durable weight loss and improve type 2

Table 8.2—Medications approved by the FDA for the treatment of overweight or obesity in adults

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (128)	National Average Drug Acquisition Cost (30-day supply) (129)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (130–134)	Possible safety concerns/considerations (130–134)
				Treatment arms	Weight loss (% loss from baseline)		
Short-term treatment (≤12 weeks)							
Sympathomimetic amine anorectic							
Phentermine (135)	8–37.5 mg q.d.*	\$5–\$56 (37.5 mg dose)	\$2–\$3 (37.5 mg dose)	15 mg q.d.† 7.5 mg q.d.† PBO	6.1 5.5 1.2	Dry mouth, insomnia, dizziness, irritability, increased blood pressure, elevated heart rate	<ul style="list-style-type: none"> Contraindicated for use in combination with monoamine oxidase inhibitors
Long-term treatment (>12 weeks)							
Lipase inhibitor							
Orlistat (4)	60 mg t.i.d. (OTC) 120 mg t.i.d. (Rx)	\$41–\$82 \$781–\$904	NA \$722	120 mg t.i.d.‡ PBO	9.6 5.6	Abdominal pain, flatulence, fecal urgency	<ul style="list-style-type: none"> Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants, etc.) Rare cases of severe liver injury reported Cholelithiasis Nephrolithiasis
Sympathomimetic amine anorectic/antiepileptic combination							
Phentermine/topiramate ER (45)	7.5 mg/46 mg q.d.S 7.5 mg/46 mg q.d.∥	\$223 (7.5 mg/46 mg dose)	\$179 (7.5 mg/46 mg dose)	15 mg/92 mg q.d.∥ 7.5 mg/46 mg q.d.∥ PBO	9.8 7.8 1.2	Constipation, paresthesia, insomnia, nasopharyngitis, xerostomia, increased blood pressure	<ul style="list-style-type: none"> Contraindicated for use in combination with monoamine oxidase inhibitors Birth defects Cognitive impairment Acute angle-closure glaucoma Contraindicated in people with unmanaged hypertension and/or seizure disorders Contraindicated for use with chronic opioid therapy Acute angle-closure glaucoma
Opioid antagonist/antidepressant combination							
Naltrexone/bupropion ER (16)	16 mg/180 mg b.i.d.	\$750	\$599	16 mg/180 mg b.i.d. PBO	5.0 1.8	Constipation, nausea, headache, xerostomia, insomnia, elevated heart rate and blood pressure	<ul style="list-style-type: none"> Contraindicated for use with chronic opioid therapy Acute angle-closure glaucoma <p>Black box warning:</p> <ul style="list-style-type: none"> Risk of suicidal behavior/ideation in people younger than 24 years old who have depression

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Table 8.2—Continued

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (128)	National Average Drug Acquisition Cost (30-day supply) (129)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (130–134)	Possible safety concerns/ considerations (130–134)
				Treatment arms	Weight loss (% loss from baseline)		
Glucagon-like peptide 1 receptor agonist Liraglutide (17)**	3 mg q.d.	\$1,619	\$1,295	3.0 mg q.d. 1.8 mg q.d. PBO	6.0 4.7 2.0	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate, hypoglycemia	<ul style="list-style-type: none"> Pancreatitis has been reported in clinical trials, but causality has not been established. Discontinue if pancreatitis is suspected. Use caution in people with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury. May cause cholelithiasis and gallstone-related complications. <p>Black box warning:</p> <ul style="list-style-type: none"> Risk of thyroid C-cell tumors in rodents; human relevance not determined
Semaglutide (46,47)	2.4 mg once weekly	\$1,619	\$1,295	2.4 mg weekly PBO	9.6 3.4	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate, hypoglycemia	<ul style="list-style-type: none"> Pancreatitis has been reported in clinical trials, but causality has not been established. Discontinue if pancreatitis is suspected. May cause cholelithiasis and gallstone-related complications. <p>Black box warning:</p> <ul style="list-style-type: none"> Risk of thyroid C-cell tumors in rodents; human relevance not determined

All medications are contraindicated in individuals who are or may become pregnant. Individuals of reproductive potential must be counseled regarding the use of reliable methods of contraception. Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. b.i.d., twice daily; ER, extended release; OTC, over the counter; NA, data not available; PBO, placebo; q.d., daily; Rx, prescription; t.i.d., three times daily. *Use lowest effective dose; maximum appropriate dose is 37.5 mg. †Duration of treatment was 28 weeks in a general adult population with obesity. ‡Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. §Maximum dose, depending on response, is 15 mg/92 mg q.d. ||Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance. **Agent has demonstrated cardiovascular safety in a dedicated cardiovascular outcome trial (47).

diabetes. Given the magnitude and rapidity of improvement of hyperglycemia and glucose homeostasis, these procedures have been suggested as treatments for type 2 diabetes even in the absence of severe obesity and will be referred to here as “metabolic surgery.”

A substantial body of evidence, including data from numerous large cohort studies and randomized controlled (non-blinded) clinical trials, demonstrates that metabolic surgery achieves superior glycemic control and reduction of cardiovascular risk in people with type 2 diabetes and obesity compared with nonsurgical intervention (18). In addition to improving glycemia, metabolic surgery reduces the incidence of microvascular disease (75), improves quality of life (43,76,77), decreases cancer risk, and improves cardiovascular disease risk factors and long-term cardiovascular events (78–89). Cohort studies that match surgical and nonsurgical subjects strongly suggest that metabolic surgery reduces all-cause mortality (90,91).

The overwhelming majority of procedures in the U.S. are vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB). Both procedures result in an anatomically smaller stomach pouch and often robust changes in enteroendocrine hormones. In VSG, ~80% of the stomach is removed, leaving behind a long, thin sleeve-shaped pouch. RYGB creates a much smaller stomach pouch (roughly the size of a walnut), which is then attached to the distal small intestine, thereby bypassing the duodenum and jejunum (Fig. 8.1).

Several organizations recommend lowering the BMI criteria for metabolic surgery to 30 kg/m² (27.5 kg/m² for Asian American individuals) for people with type 2 diabetes who have not achieved sufficient weight loss and improved comorbidities (including hyperglycemia) with reasonable nonsurgical treatments. Studies have documented diabetes remission after 1–5 years in 30–63% of patients with RYGB (18,93).

Most notably, the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, which randomized 150 participants with unmanaged diabetes to receive either metabolic surgery or medical treatment, found that 29% of those treated with RYGB and 23% treated with VSG achieved A1C of 6.0% or lower after 5 years (43). Available data suggest an erosion of

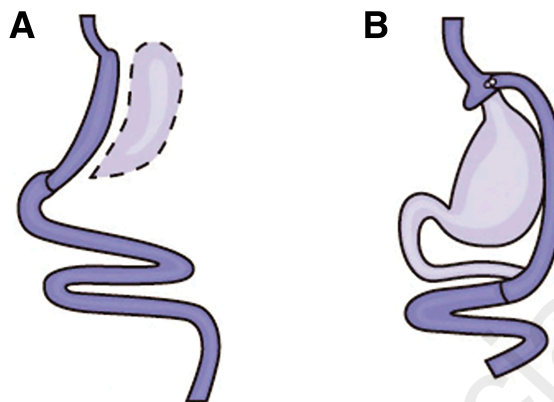


Figure 8.1—A: Vertical sleeve gastrectomy. B: Roux-en-Y gastric bypass surgery. Images reprinted from National Institute of Diabetes and Digestive and Kidney Diseases (92).

diabetes remission over time (44); at least 35–50% of patients who initially achieve remission of diabetes eventually experience recurrence. Still, the median disease-free period among such individuals following RYGB is 8.3 years (94,95), and the majority of those who undergo surgery maintain substantial improvement of glycemia from baseline for at least 5–15 years (43,76,79,80,95–98).

Exceedingly few presurgical predictors of success have been identified, but younger age, shorter duration of diabetes (e.g., <8 years) (70), and lesser severity of diabetes (better glycemic control, non-use of insulin) are associated with higher rates of diabetes remission (43,79,97,99). Greater baseline visceral fat area may also predict improved postoperative outcomes, especially among Asian American people with type 2 diabetes (100).

Although surgery has been shown to improve the metabolic profiles of people with type 1 diabetes, larger and longer-term studies are needed to determine the role of metabolic surgery in such individuals (101).

Whereas metabolic surgery has greater initial costs than nonsurgical obesity treatments, retrospective analyses and modeling studies suggest that surgery may be cost-effective or even cost-saving for individuals with type 2 diabetes. However, these results largely depend on assumptions about the long-term effectiveness and safety of the procedures (102,103).

Potential Risks and Complications

The safety of metabolic surgery has improved significantly with continued refinement of minimally invasive (laparoscopic)

approaches, enhanced training and credentialing, and involvement of multidisciplinary teams. Perioperative mortality rates are typically 0.1–0.5%, similar to those of common abdominal procedures such as cholecystectomy or hysterectomy (104–108). Major complications occur in 2–6% of those undergoing metabolic surgery, which compares favorably with the rates for other commonly performed elective operations (108). Postsurgical recovery times and morbidity have also dramatically declined. Minor complications and need for operative reoperation occur in up to 15% (104–113). Empirical data suggest that the proficiency of the operating surgeon and surgical team is an important factor in determining mortality, complications, reoperations, and readmissions (114). Accordingly, metabolic surgery should be performed in high-volume centers with multidisciplinary teams experienced in managing diabetes, obesity, and gastrointestinal surgery.

Beyond the perioperative period, longer-term risks include vitamin and mineral deficiencies, anemia, osteoporosis, dumping syndrome, and severe hypoglycemia (115). Nutritional and micronutrient deficiencies and related complications occur with a variable frequency depending on the type of procedure and require routine monitoring of micronutrient and nutritional status and lifelong vitamin/nutritional supplementation (115). Dumping syndrome usually occurs shortly (10–30 min) after a meal and may present with diarrhea, nausea, vomiting, palpitations, and fatigue; hypoglycemia is usually not present at the time of symptoms but, in some cases, may develop several hours later.

Postbariatric hypoglycemia (PBH) can occur with RYGB, VSG, and other gastrointestinal procedures and may severely impact quality of life (116–118). PBH is driven in part by altered gastric emptying of ingested nutrients, leading to rapid intestinal glucose absorption and excessive postprandial secretion of glucagon-like peptide 1 and other gastrointestinal peptides. As a result, overstimulation of insulin release and a sharp drop in plasma glucose occur, most commonly 1–3 h after a high-carbohydrate meal. Symptoms range from sweating, tremor, tachycardia, and increased hunger to impaired cognition, loss of consciousness, and seizures. In contrast to dumping syndrome, which often occurs soon after surgery and improves over time, PBH typically presents >1 year post-surgery. Diagnosis is primarily made by a thorough history, detailed records of food intake, physical activity, and symptom patterns, and exclusion of other potential causes (e.g., malnutrition, side effects of medications or supplements, dumping syndrome, and insulinoma). Initial management includes education to facilitate reduced intake of rapidly digested carbohydrates while ensuring adequate intake of protein and healthy fats, and vitamin/nutrient supplements. When available, patients should be offered medical nutrition therapy with a dietitian experienced in PBH and the use of continuous glucose monitoring (ideally real-time continuous glucose monitoring, which can detect dropping glucose levels before severe hypoglycemia occurs), especially for those with hypoglycemia unawareness. Medication treatment, if needed, is primarily aimed at slowing carbohydrate absorption (e.g., acarbose) or reducing glucagon-like peptide 1 and insulin secretion (e.g., diazoxide, octreotide) (119).

People who undergo metabolic surgery may also be at increased risk for substance abuse, worsening or new-onset depression and/or anxiety disorders, and suicidal ideation (115,120–125). Candidates for metabolic surgery should be assessed by a mental health professional with expertise in obesity management prior to consideration for surgery (126). Surgery should be postponed in individuals with alcohol or substance use disorders, severe depression, suicidal ideation, or other significant

mental health conditions until these conditions have been sufficiently addressed. Individuals with preoperative or new-onset psychopathology should be assessed regularly following surgery to optimize mental health and postsurgical outcomes.

References

- Narayan KVM, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the U.S. *Diabetes Care* 2007;30:1562–1566
- Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
- Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care* 2014;37:912–921
- Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27:155–161
- le Roux CW, Astrup A, Fujioka K, et al.; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017;389:1399–1409
- Booth H, Khan O, Prevost T, et al. Incidence of type 2 diabetes after bariatric surgery: population-based matched cohort study. *Lancet Diabetes Endocrinol* 2014;2:963–968
- UKPDS Group. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. *Metabolism* 1990;39:905–912
- Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord* 1992;16:397–415
- Pastors JG, Warshaw H, Daly A, Franz M, Kulkarni K. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care* 2002;25:608–613
- Lim EL, Hollingsworth KG, Arribas BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011;54:2506–2514
- Jackness C, Karmally W, Febres G, et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and β -cell function in type 2 diabetic patients. *Diabetes* 2013;62:3027–3032
- Rothberg AE, McEwen LN, Kraftson AT, Fowler CE, Herman WH. Very-low-energy diet for type 2 diabetes: an underutilized therapy? *J Diabetes Complications* 2014;28:506–510
- Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care* 1998;21:1288–1294
- Garvey WT, Ryan DH, Bohannon NJV, et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. *Diabetes Care* 2014;37:3309–3316
- O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012;20:1426–1436
- Hollander P, Gupta AK, Plodkowski R, et al.; COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* 2013;36:4022–4029
- Davies MJ, Bergenstal R, Bode B, et al.; NN8022-1922 Study Group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA* 2015;314:687–699
- Rubino F, Nathan DM, Eckel RH, et al.; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by International Diabetes Organizations. *Obes Surg* 2017;27:2–21
- Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. *Diabetes Care* 2016;39:808–815
- Jensen MD, Ryan DH, Apovian CM, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol* 2014;63(25 Pt B):2985–3023
- Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DIRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391:541–551
- Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DIRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;7:344–355
- Kahan S, Fujioka K. Obesity pharmacotherapy in patients with type 2 diabetes. *Diabetes Spectr* 2017;30:250–257
- Cao P, Song Y, Zhuang Z, et al. Obesity and COVID-19 in adult patients with diabetes. *Diabetes* 2021;70:1061–1069
- Richardson S, Hirsch JS, Narasimhan M, et al.; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;323:2052–2059
- Chu Y, Yang J, Shi J, Zhang P, Wang X. Obesity is associated with increased severity of disease in COVID-19 pneumonia: a systematic review and meta-analysis. *Eur J Med Res* 2020;25:64
- Popkin BM, Du S, Green WD, et al. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. *Obes Rev* 2020;21:e13128
- AMA Manual of Style Committee. *AMA Manual of Style: A Guide for Authors and Editors*. 11th ed. New York, Oxford University Press, 2020

29. American Medical Association. Person-First Language for Obesity H-440.821. Accessed 12 October 2022. Available from <https://policysearch.ama-assn.org/policyfinder/detail/obesity?uri=%2FAMADoc%2FHOD.xml-H-440.821.xml>
30. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157–163
31. Araneta MRG, Kanaya A, Hsu WC, et al. Optimum BMI cutpoints to screen Asian Americans for type 2 diabetes. *Diabetes Care* 2015;38:814–820
32. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;70:776–803
33. Bosch X, Monclús E, Escoda O, et al. Unintentional weight loss: clinical characteristics and outcomes in a prospective cohort of 2677 patients. *PLoS One* 2017;12:e0175125
34. Wilding JPH. The importance of weight management in type 2 diabetes mellitus. *Int J Clin Pract* 2014;68:682–691
35. Van Gaal L, Scheen A. Weight management in type 2 diabetes: current and emerging approaches to treatment. *Diabetes Care* 2015;38:1161–1172
36. Kushner RF, Batsis JA, Butsch WS, et al. Weight history in clinical practice: the state of the science and future directions. *Obesity (Silver Spring)* 2020;28:9–17
37. Warren J, Smalley B, Barefoot N. Higher motivation for weight loss in African American than Caucasian rural patients with hypertension and/or diabetes. *Ethn Dis* 2016;26:77–84
38. Rothberg AE, McEwen LN, Kraftson AT, et al. Impact of weight loss on waist circumference and the components of the metabolic syndrome. *BMJ Open Diabetes Res Care* 2017;5:e000341
39. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–154
40. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity (Silver Spring)* 2014;22:5–13
41. Gregg EW, Jakicic JM, Blackburn G, et al.; Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomized clinical trial. *Lancet Diabetes Endocrinol* 2016;4:913–921
42. Baum A, Scarpa J, Bruzelius E, Tamler R, Basu S, Faghmous J. Targeting weight loss interventions to reduce cardiovascular complications of type 2 diabetes: a machine learning-based post-hoc analysis of heterogeneous treatment effects in the Look AHEAD trial. *Lancet Diabetes Endocrinol* 2017;5:808–815
43. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N Engl J Med* 2017;376:641–651
44. Ikramuddin S, Korner J, Lee WJ, et al. Durability of addition of Roux-en-Y gastric bypass to lifestyle intervention and medical management in achieving primary treatment goals for uncontrolled type 2 diabetes in mild to moderate obesity: a randomized control trial. *Diabetes Care* 2016;39:1510–1518
45. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:1341–1352
46. Davies M, Færch L, Jeppesen OK, et al.; STEP 2 Study Group. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397:971–984
47. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–322
48. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–154
49. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* 2021;398:143–155
50. Frías JP, Davies MJ, Rosenstock J, et al.; SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503–515
51. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. *J Acad Nutr Diet* 2015;115:1447–1463
52. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859–873
53. de Souza RJ, Bray GA, Carey VJ, et al. Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. *Am J Clin Nutr* 2012;95:614–625
54. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA* 2014;312:923–933
55. Leung CW, Epel ES, Ritchie LD, Crawford PB, Laraia BA. Food insecurity is inversely associated with diet quality of lower-income adults. *J Acad Nutr Diet* 2014;114:1943–53.e2
56. Kahan S, Manson JE. Obesity treatment, beyond the guidelines: practical suggestions for clinical practice. *JAMA* 2019;321:1349–1350
57. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW; American College of Sports Medicine. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc* 2009;41:459–471
58. Gudzone KA, Doshi RS, Mehta AK, et al. Efficacy of commercial weight-loss programs: an updated systematic review. *Ann Intern Med* 2015;162:501–512
59. Bloom B, Mehta AK, Clark JM, Gudzone KA. Guideline-concordant weight-loss programs in an urban area are uncommon and difficult to identify through the internet. *Obesity (Silver Spring)* 2016;24:583–588
60. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring)* 2006;14:1283–1293
61. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2014;99:14–23
62. Batsis JA, Apolzan JW, Bagley PJ, et al. A systematic review of dietary supplements and alternative therapies for weight loss. *Obesity (Silver Spring)* 2021;29:1102–1113
63. Bessell E, Maunder A, Lauche R, Adams J, Sainsbury A, Fuller NR. Efficacy of dietary supplements containing isolated organic compounds for weight loss: a systematic review and meta-analysis of randomised placebo-controlled trials. *Int J Obes* 2021;45:1631–1643
64. Maunder A, Bessell E, Lauche R, Adams J, Sainsbury A, Fuller NR. Effectiveness of herbal medicines for weight loss: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2020;22:891–903
65. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. *Diabetes Care* 2020;44:258–279
66. Cai X, Yang W, Gao X, Zhou L, Han X, Ji L. Baseline body mass index and the efficacy of hypoglycemic treatment in type 2 diabetes: a meta-analysis. *PLoS One* 2016;11:e0166625
67. Domecq JP, Prutsky G, Leppin A, et al. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015;100:363–370
68. Drugs.com. Phentermine [FDA prescribing information]. Accessed 17 October 2022. Available from <https://www.drugs.com/pro/phentermine.html>
69. Apovian CM, Aronne LJ, Bessesen DH, et al.; Endocrine Society. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2015;100:342–362
70. Fujioka K, O'Neil PM, Davies M, et al. Early weight loss with liraglutide 3.0 mg predicts 1-year weight loss and is associated with improvements in clinical markers. *Obesity (Silver Spring)* 2016;24:2278–2288
71. Fujioka K, Plodkowski R, O'Neil PM, Gilder K, Walsh B, Greenway FL. The relationship between early weight loss and weight loss at 1 year with naltrexone ER/bupropion ER combination therapy. *Int J Obes* 2016;40:1369–1375
72. Sullivan S. Endoscopic medical devices for primary obesity treatment in patients with diabetes. *Diabetes Spectr* 2017;30:258–264
73. Kahan S, Saunders KH, Kaplan LM. Combining obesity pharmacotherapy with endoscopic bariatric and metabolic therapies. *Techniques and Innovations in Gastrointestinal Endoscopy* 2020;22:154–158
74. Greenway FL, Aronne LJ, Raben A, et al. A randomized, double-blind, placebo-controlled study of Gelesis100: a novel nonsystemic oral hydrogel for weight loss. *Obesity (Silver Spring)* 2019;27:205–216
75. O'Brien R, Johnson E, Haneuse S, et al. Microvascular outcomes in patients with diabetes

- after bariatric surgery versus usual care: a matched cohort study. *Ann Intern Med* 2018;169:300–310
76. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2015;386:964–973
77. Halperin F, Ding SA, Simonson DC, et al. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. *JAMA Surg* 2014;149:716–726
78. Sjöström L, Lindroos AK, Peltonen M, et al.; Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683–2693
79. Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014;311:2297–2304
80. Adams TD, Davidson LE, Litwin SE, et al. Health benefits of gastric bypass surgery after 6 years. *JAMA* 2012;308:1122–1131
81. Sjöström L, Narbro K, Sjöström CD, et al.; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357:741–752
82. Sjöström L, Gummesson A, Sjöström CD, et al.; Swedish Obese Subjects Study. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol* 2009;10:653–662
83. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *JAMA* 2012;307:56–65
84. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;357:753–761
85. Arterburn DE, Olsen MK, Smith VA, et al. Association between bariatric surgery and long-term survival. *JAMA* 2015;313:62–70
86. Adams TD, Arterburn DE, Nathan DM, Eckel RH. Clinical outcomes of metabolic surgery: microvascular and macrovascular complications. *Diabetes Care* 2016;39:912–923
87. Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The long-term effects of bariatric surgery on type 2 diabetes remission, microvascular and macrovascular complications, and mortality: a systematic review and meta-analysis. *Obes Surg* 2017;27:2724–2732
88. Fisher DP, Johnson E, Haneuse S, et al. Association between bariatric surgery and macrovascular disease outcomes in patients with type 2 diabetes and severe obesity. *JAMA* 2018;320:1570–1582
89. Billeter AT, Scheurlen KM, Probst P, et al. Meta-analysis of metabolic surgery versus medical treatment for microvascular complications in patients with type 2 diabetes mellitus. *Br J Surg* 2018;105:168–181
90. Aminian A, Zajick A, Arterburn DE, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. *JAMA* 2019;322:1271–1282
91. Syn NL, Cummings DE, Wang LZ, et al. Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174,772 participants. *Lancet* 2021;397:1830–1841
92. National Institute of Diabetes and Digestive and Kidney Diseases. Diabetes for Health Professionals. Accessed 17 October 2022. Available from <https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/diabetes>
93. Isaman DJM, Rothberg AE, Herman WH. Reconciliation of type 2 diabetes remission rates in studies of Roux-en-Y gastric bypass. *Diabetes Care* 2016;39:2247–2253
94. Sjöholm K, Pajunen P, Jacobson P, et al. Incidence and remission of type 2 diabetes in relation to degree of obesity at baseline and 2 year weight change: the Swedish Obese Subjects (SOS) study. *Diabetologia* 2015;58:1448–1453
95. Arterburn DE, Bogart A, Sherwood NE, et al. A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. *Obes Surg* 2013;23:93–102
96. Cohen RV, Pinheiro JC, Schiavon CA, Salles JE, Wajchenberg BL, Cummings DE. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. *Diabetes Care* 2012;35:1420–1428
97. Brethauer SA, Aminian A, Romero-Talamás H, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. *Ann Surg* 2013;258:628–636; discussion 636–637
98. Hsu CC, Almulaifi A, Chen JC, et al. Effect of bariatric surgery vs medical treatment on type 2 diabetes in patients with body mass index lower than 35: five-year outcomes. *JAMA Surg* 2015;150:1117–1124
99. Hariri K, Guevara D, Jayaram A, Kini SU, Herron DM, Fernandez-Ranvier G. Preoperative insulin therapy as a marker for type 2 diabetes remission in obese patients after bariatric surgery. *Surg Obes Relat Dis* 2018;14:332–337
100. Yu H, Di J, Bao Y, et al. Visceral fat area as a new predictor of short-term diabetes remission after Roux-en-Y gastric bypass surgery in Chinese patients with a body mass index less than 35 kg/m². *Surg Obes Relat Dis* 2015;11:6–11
101. Kirwan JP, Aminian A, Kashyap SR, Burguera B, Brethauer SA, Schauer PR. Bariatric surgery in obese patients with type 1 diabetes. *Diabetes Care* 2016;39:941–948
102. Rubin JK, Hinrichs-Krapels S, Hesketh R, Martin A, Herman WH, Rubino F. Identifying barriers to appropriate use of metabolic/bariatric surgery for type 2 diabetes treatment: policy lab results. *Diabetes Care* 2016;39:954–963
103. Fouse T, Schauer P. The socioeconomic impact of morbid obesity and factors affecting access to obesity surgery. *Surg Clin North Am* 2016;96:669–679
104. Flum DR, Belle SH, King WC, et al.; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med* 2009;361:445–454
105. Courcoulas AP, Christian NJ, Belle SH, et al.; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. *JAMA* 2013;310:2416–2425
106. Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. *BMJ* 2014;349:g3961
107. Young MT, Gebhart A, Phelan MJ, Nguyen NT. Use and outcomes of laparoscopic sleeve gastrectomy vs laparoscopic gastric bypass: analysis of the American College of Surgeons NSQIP. *J Am Coll Surg* 2015;220:880–885
108. Aminian A, Brethauer SA, Kirwan JP, Kashyap SR, Burguera B, Schauer PR. How safe is metabolic/diabetes surgery? *Diabetes Obes Metab* 2015;17:198–201
109. Birkmeyer NJO, Dimick JB, Share D, et al.; Michigan Bariatric Surgery Collaborative. Hospital complication rates with bariatric surgery in Michigan. *JAMA* 2010;304:435–442
110. Altieri MS, Yang J, Telem DA, et al. Lap band outcomes from 19,221 patients across centers and over a decade within the state of New York. *Surg Endosc* 2016;30:1725–1732
111. Hutter MM, Schirmer BD, Jones DB, et al. First report from the American College of Surgeons Bariatric Surgery Center Network: laparoscopic sleeve gastrectomy has morbidity and effectiveness positioned between the band and the bypass. *Ann Surg* 2011;254:410–420; discussion 420–422
112. Nguyen NT, Slone JA, Nguyen XMT, Hartman JS, Hoyt DB. A prospective randomized trial of laparoscopic gastric bypass versus laparoscopic adjustable gastric banding for the treatment of morbid obesity: outcomes, quality of life, and costs. *Ann Surg* 2009;250:631–641
113. Courcoulas AP, King WC, Belle SH, et al. Seven-year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) study. *JAMA Surg* 2018;153:427–434
114. Birkmeyer JD, Finks JF, O'Reilly A, et al.; Michigan Bariatric Surgery Collaborative. Surgical skill and complication rates after bariatric surgery. *N Engl J Med* 2013;369:1434–1442
115. Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures—2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists—executive summary. *Endocr Pract* 2019;25:1346–1359
116. Service FJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N Engl J Med* 2005;353:249–254
117. Sheehan A, Patti ME. Hypoglycemia after upper gastrointestinal surgery: clinical approach to assessment, diagnosis, and treatment. *Diabetes Metab Syndr Obes* 2020;13:4469–4482
118. Lee D, Dreyfuss JM, Sheehan A, Puleio A, Mulla CM, Patti ME. Glycemic patterns are distinct in post-bariatric hypoglycemia after gastric bypass (PBH-RYGB). *J Clin Endocrinol Metab* 2021;106:2291–2303
119. Salehi M, Vella A, McLaughlin T, Patti ME. Hypoglycemia after gastric bypass surgery: current concepts and controversies. *J Clin Endocrinol Metab* 2018;103:2815–2826
120. Conason A, Teixeira J, Hsu CH, Puma L, Knafo D, Geliebter A. Substance use following bariatric weight loss surgery. *JAMA Surg* 2013;148:145–150
121. Bhatti JA, Nathens AB, Thiruchelvam D, Grantcharov T, Goldstein BI, Redelmeier DA. Self-harm

- emergencies after bariatric surgery: a population-based cohort study. *JAMA Surg* 2016;151:226–232
122. Peterhänsel C, Petroff D, Klinitzke G, Kersting A, Wagner B. Risk of completed suicide after bariatric surgery: a systematic review. *Obes Rev* 2013;14:369–382
123. Jakobsen GS, Småtuen MC, Sandbu R, et al. Association of bariatric surgery vs medical obesity treatment with long-term medical complications and obesity-related comorbidities. *JAMA* 2018;319:291–301
124. King WC, Chen JY, Mitchell JE, et al. Prevalence of alcohol use disorders before and after bariatric surgery. *JAMA* 2012;307:2516–2525
125. Young-Hyman D, Peyrot M. *Psychosocial Care for People with Diabetes*. 1st ed. Alexandria, VA, American Diabetes Association, 2012
126. Greenberg I, Sogg S, M Perna F. Behavioral and psychological care in weight loss surgery: best practice update. *Obesity* (Silver Spring) 2009; 17:880–884
127. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care* 2019;42:731–754
128. IBM. Micromedex Red Book. Accessed 9 November 2022. Available from <https://www.ibm.com/products/micromedex-red-book>
129. Data.Medicaid.gov. NADAC (National Average Drug Acquisition Cost). Accessed 4 October 2022. Available from <https://data.medicaid.gov/dataset/dfa2ab14-06c2-457a-9e36-5cb6d80f8d93>
130. U.S. National Library of Medicine. Phentermine–phentermine hydrochloride capsule. Accessed 17 October 2022. Available from <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=737eef3b-9a6b-4ab3-a25c-49d84d2a0197>
131. Nalpropion Pharmaceuticals. Contrave (naltrexone HCl/bupropion HCl) extended-release tablets. Accessed 17 October 2022. Available at <https://contrave.com>
132. CHEPLAPHARM and H2-Pharma. Xenical (orlistat). Accessed 17 October 2022. Available from <https://xenical.com>
133. Vivus. Qsymia (phentermine and topiramate extended-release) capsules. Accessed 17 October 2022. Available from <https://qsymia.com>
134. Novo Nordisk. Saxenda (liraglutide injection 3 mg). Accessed 17 October 2022. Available from <https://www.saxenda.com>
135. Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity* (Silver Spring) 2013;21:2163–2171

9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

- 9.1 Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**
- 9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**
- 9.3 Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. **B**

Insulin Therapy

Because the hallmark of type 1 diabetes is absent or near-absent β -cell function, insulin treatment is essential for individuals with type 1 diabetes. In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily injections for the six or seven decades after the discovery of insulin. However, over the past three decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3).

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The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive control (7%) led to ~50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 patient-years of therapy). Follow-up of subjects from the DCCT more than 10 years after the active treatment component of the study demonstrated fewer macrovascular as well as fewer microvascular complications in the group that received intensive treatment (2,4).

Insulin replacement regimens typically consist of basal insulin, mealtime insulin, and correction insulin (5). Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump. Basal insulin analogs have longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A1C compared with human insulins (6–8). More recently, two injectable insulin formulations with enhanced rapid-action profiles have been introduced. Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA and may cause less hypoglycemia and weight gain (9) (see also subsection ALTERNATIVE INSULIN ROUTES IN PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES), and faster-acting insulin aspart and insulin lispro-aabc may reduce prandial excursions better than RAA (10–12). In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes (13,14). Despite the advantages of insulin analogs in individuals with type 1 diabetes, for some individuals the expense and/or intensity of treatment required for their use is prohibitive. There are multiple approaches to insulin treatment, and the central precept in the management of type 1 diabetes is that some form of insulin be given in a planned regimen tailored

to the individual to keep them safe and out of diabetic ketoacidosis and to avoid significant hypoglycemia, with every effort made to reach the individual's glycemic targets.

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. However, a systematic review and meta-analysis concluded that CSII via pump therapy has modest advantages for lowering A1C (-0.30% [95% CI -0.58 to -0.02]) and for reducing severe hypoglycemia rates in children and adults (15). However, there is no consensus to guide the choice of injection or pump therapy in a given individual, and research to guide this decision-making is needed (16). The arrival of continuous glucose monitors (CGM) to clinical practice has proven beneficial in people using insulin therapy. Its use is now considered standard of care for most people with type 1 diabetes (5) (see Section 7, "Diabetes Technology"). Reduction of nocturnal hypoglycemia in individuals with type 1 diabetes using insulin pumps with CGM is improved by automatic suspension of insulin delivery at a preset glucose level (16–18). When choosing among insulin delivery systems, individual preferences, cost, insulin type and dosing regimen, and self-management capabilities should be considered (see Section 7, "Diabetes Technology").

The U.S. Food and Drug Administration (FDA) has now approved multiple hybrid closed-loop pump systems (also called automated insulin delivery [AID] systems). The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (19,20), and evidence suggests that a closed-loop system is superior to sensor-augmented pump therapy for glycemic control and reduction of hypoglycemia over 3 months of comparison in children and adults with type 1 diabetes (21). In the International Diabetes Closed Loop (iDCL) trial, a 6-month trial in people with type 1 diabetes at least 14 years of age, the use of a closed-loop system was associated with a greater percentage of time spent in the target glycemic range, reduced mean glucose and A1C levels, and a lower percentage of time spent in hypoglycemia compared with use of a sensor-augmented pump (22).

Intensive insulin management using a version of CSII and continuous glucose

monitoring should be considered in most individuals with type 1 diabetes. AID systems may be considered in individuals with type 1 diabetes who are capable of using the device safely (either by themselves or with a caregiver) in order to improve time in range and reduce A1C and hypoglycemia (22). See Section 7, "Diabetes Technology," for a full discussion of insulin delivery devices.

In general, individuals with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial, but this is dependent on a number of factors, including whether the individual consumes lower or higher carbohydrate meals. Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts are required during puberty, pregnancy, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in individuals with type 1 diabetes who are metabolically stable, with half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption (23); this guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (24).

Typical multidose regimens for individuals with type 1 diabetes combine premeal use of shorter-acting insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best controlled by a well-timed injection of prandial insulin. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation (regular, RAA, inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demands for glucose. To approach this variability in people using insulin treatment, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education on how to

adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be offered to most individuals (25,26). For individuals in whom carbohydrate counting is effective, estimates of the fat and protein content of meals can be incorporated into their prandial dosing for added benefit (27) (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”).

The 2021 ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of type 1 diabetes in adults summarizes different insulin regimens and glucose monitoring strategies in individuals with type 1 diabetes (Fig. 9.1 and Table 9.1) (5).

Insulin Injection Technique

Ensuring that individuals and/or caregivers understand correct insulin injection technique is important to optimize glucose control and insulin use safety. Thus, it is important that insulin be delivered into the proper tissue in the correct way. Recommendations have been published elsewhere outlining best practices for insulin injection (28). Proper insulin injection technique includes injecting into appropriate body areas, injection site rotation, appropriate care of injection sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery.

Exogenously delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared with longer needles, including a study performed in adults with obesity (29).

Injection site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to

the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection site rotation and how to recognize and avoid areas of lipohypertrophy. As noted in Table 4.1, examination of insulin injection sites for the presence of lipohypertrophy, as well as assessment of injection device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral glucose-lowering drugs have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β -cell peptide amylin and is approved for use in adults with type 1 diabetes. Clinical trials have demonstrated a modest reduction in A1C (0.3–0.4%) and modest weight loss (~1 kg) with pramlintide (30–33). Similarly, results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes caused small reductions in body weight and lipid levels but did not improve A1C (34,35). The largest clinical trials of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in type 1 diabetes have been conducted with liraglutide 1.8 mg daily, showing modest A1C reductions (~0.4%), decreases in weight (~5 kg), and reductions in insulin doses (36,37). Similarly, sodium–glucose cotransporter 2 (SGLT2) inhibitors have been studied in clinical trials in people with type 1 diabetes, showing improvements in A1C, reduced body weight, and improved blood pressure (38–40); however, SGLT2 inhibitor use in type 1 diabetes is associated with an increased rate of diabetic ketoacidosis. The risks and benefits of adjunctive agents continue to be evaluated, with consensus statements providing guidance on patient selection and precautions (41).

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (42).

The 2021 ADA/EASD consensus report on the management of type 1 diabetes in adults offers a simplified overview of indications for β -cell replacement therapy in people with type 1 diabetes (Fig. 9.2) (5).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

- 9.4a** Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. **A**
- 9.4b** In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk (Fig. 9.3 and Table 9.2). **A**
- 9.4c** Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy (Fig. 9.3 and Table 9.2). **A**
- 9.4d** Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering

Representative relative attributes of insulin delivery approaches in people with type 1 diabetes¹

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less-preferred, alternative injected insulin regimens			
MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+

Continuous insulin infusion regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
Hybrid closed-loop technology	+++++	+++++	+++++
Insulin pump with threshold/predictive low-glucose suspend	++++	++++	++++
Insulin pump therapy without automation	+++	+++	++++

Figure 9.1—Choices of insulin regimens in people with type 1 diabetes. Continuous glucose monitoring improves outcomes with injected or infused insulin and is superior to blood glucose monitoring. Inhaled insulin may be used in place of injectable prandial insulin in the U.S. ¹The number of plus signs (+) is an estimate of relative association of the regimen with increased flexibility, lower risk of hypoglycemia, and higher costs between the considered regimens. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Reprinted from Holt et al. (5).

treatment regimen should consider approaches that support weight management goals (Fig. 9.3 and Table 9.2). **A**

- 9.5 Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. **A**
- 9.6 Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. **A**
- 9.7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. **E**
- 9.8 A person-centered approach should guide the choice of pharmacologic agents. Consider the

effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences (Fig. 9.3 and Table 9.2). **E**

- 9.9 Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (Fig. 9.3, Table 9.2, Table 10.3B, and Table 10.3C) is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors (Fig. 9.3) (see Section 10, “Cardiovascular Disease and Risk Management,”

for details on cardiovascular risk reduction recommendations). **A**

- 9.10 In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**
- 9.11 If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. **A**
- 9.12 Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. **A**
- 9.13 Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (Fig. 4.1 and Table 9.2). **E**
- 9.14 Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or postprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. **E**

The ADA/EASD consensus report “Management of Hyperglycemia in Type 2 Diabetes, 2022” (43–45) recommends a holistic, multifactorial person-centered approach accounting for the lifelong nature of type 2 diabetes. Person-specific factors that affect choice of treatment include individualized glycemic and weight goals, impact on weight, hypoglycemia and cardiorenal protection (see Section 10, “Cardiovascular Disease and Risk Management,” and Section 11 “Chronic Kidney Disease and Risk Management”), underlying physiologic factors, side effect profiles of medications, complexity of regimen, regimen choice to optimize medication use and reduce treatment discontinuation, and access, cost, and availability of medication. Lifestyle

Table 9.1—Examples of subcutaneous insulin regimens

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Regimens that more closely mimic normal insulin secretion				
Insulin pump therapy (hybrid closed-loop, low-glucose suspend, CGM-augmented open-loop, BGM-augmented open-loop)	Basal delivery of URAA or RAA; generally 40–60% of TDD. Mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with pre-meal insulin ~15 min before eating.	Can adjust basal rates for varying insulin sensitivity by time of day, for exercise and for sick days. Flexibility in meal timing and content. Pump can deliver insulin in increments of fractions of units. Potential for integration with CGM for low-glucose suspend or hybrid closed-loop. TIR % highest and TBR % lowest with: hybrid closed-loop > low-glucose suspend > CGM-augmented open-loop > BGM-augmented open-loop.	Most expensive regimen. Must continuously wear one or more devices. Risk of rapid development of ketosis or DKA with interruption of insulin delivery. Potential reactions to adhesives and site infections. Most technically complex approach (harder for people with lower numeracy or literacy skills).	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. Basal rates: adjust based on overnight, fasting or daytime glucose outside of activity of URAA/RAA bolus.
MDI: LAA + flexible doses of URAA or RAA at meals	LAA once daily (insulin detemir or insulin glargine may require twice-daily dosing); generally 50% of TDD. Mealtime and correction: URAA or RAA based on ICR and/or ISF and target glucose.	Can use pens for all components. Flexibility in meal timing and content. Insulin analogs cause less hypoglycemia than human insulins.	At least four daily injections. Most costly insulins. Smallest increment of insulin is 1 unit (0.5 unit with some pens). LAAs may not cover strong dawn phenomenon (rise in glucose in early morning hours) as well as pump therapy.	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. LAA: based on overnight or fasting glucose or daytime glucose outside of activity time course, or URAA or RAA injections.
MDI regimens with less flexibility				
Four injections daily with fixed doses of N and RAA	Pre-breakfast: RAA ~20% of TDD. Pre-lunch: RAA ~10% of TDD. Pre-dinner: RAA ~10% of TDD. Bedtime: N ~50% of TDD.	May be feasible if unable to carbohydrate count. All meals have RAA coverage. N is less expensive than LAAs.	Shorter duration RAA may lead to basal deficit during day; may need twice-daily N. Greater risk of nocturnal hypoglycemia with N. Requires relatively consistent mealtimes and carbohydrate intake.	Pre-breakfast RAA: based on BGM after breakfast or before lunch. Pre-lunch RAA: based on BGM after lunch or before dinner. Pre-dinner RAA: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.

Continued on p. S145

Table 9.1—Continued

Regimen	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Four injections daily with fixed doses of N and R	Pre-breakfast: R ~20% of TDD. Pre-lunch: R ~10% of TDD. Pre-dinner: R ~10% of TDD. Bedtime: N ~50% of TDD.	May be feasible if unable to carbohydrate count. R can be dosed based on ICR and correction. All meals have R coverage. Least expensive insulins.	Greater risk of nocturnal hypoglycemia with N. Greater risk of delayed post-meal hypoglycemia with R. Requires relatively consistent mealtimes and carbohydrate intake. R must be injected at least 30 min before meal for better effect.	Pre-breakfast R: based on BGM after breakfast or before lunch. Pre-lunch R: based on BGM after lunch or before dinner. Pre-dinner R: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.
Regimens with fewer daily injections				
Three injections daily: N+R or N+RAA	Pre-breakfast: ~40% N + ~15% R or RAA. Pre-dinner: ~15% R or RAA. Bedtime: 30% N.	Morning insulins can be mixed in one syringe. May be appropriate for those who cannot take injection in middle of day. Morning N covers lunch to some extent. Same advantages of RAAs over R. Least (N+R) or less expensive insulins than MDI with analogs.	Greater risk of nocturnal hypoglycemia with N than LAAs. Greater risk of delayed post-meal hypoglycemia with R than RAAs. Requires relatively consistent mealtimes and carbohydrate intake. Coverage of post-lunch glucose often suboptimal. R must be injected at least 30 min before meal for better effect.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Pre-dinner R: based on bedtime BGM. Pre-dinner RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.
Twice-daily “split-mixed”: N+R or N+RAA	Pre-breakfast: ~40% N + ~15% R or RAA. Pre-dinner: ~30% N + ~15% R or RAA.	Least number of injections for people with strong preference for this. Insulins can be mixed in one syringe. Least (N+R) or less (N+RAA) expensive insulins vs analogs. Eliminates need for doses during the day.	Risk of hypoglycemia in afternoon or middle of night from N. Fixed mealtimes and meal content. Coverage of post-lunch glucose often suboptimal. Difficult to reach targets for blood glucose without hypoglycemia.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Evening R: based on bedtime BGM. Evening RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.

BGM, blood glucose monitoring; CGM, continuous glucose monitoring; ICR, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor; LAA, long-acting analog; MDI, multiple daily injections; N, NPH insulin; R, short-acting (regular) insulin; RAA, rapid-acting analog; TDD, total daily insulin dose; URAA, ultra-rapid-acting analog. Reprinted from Holt et al. (5).

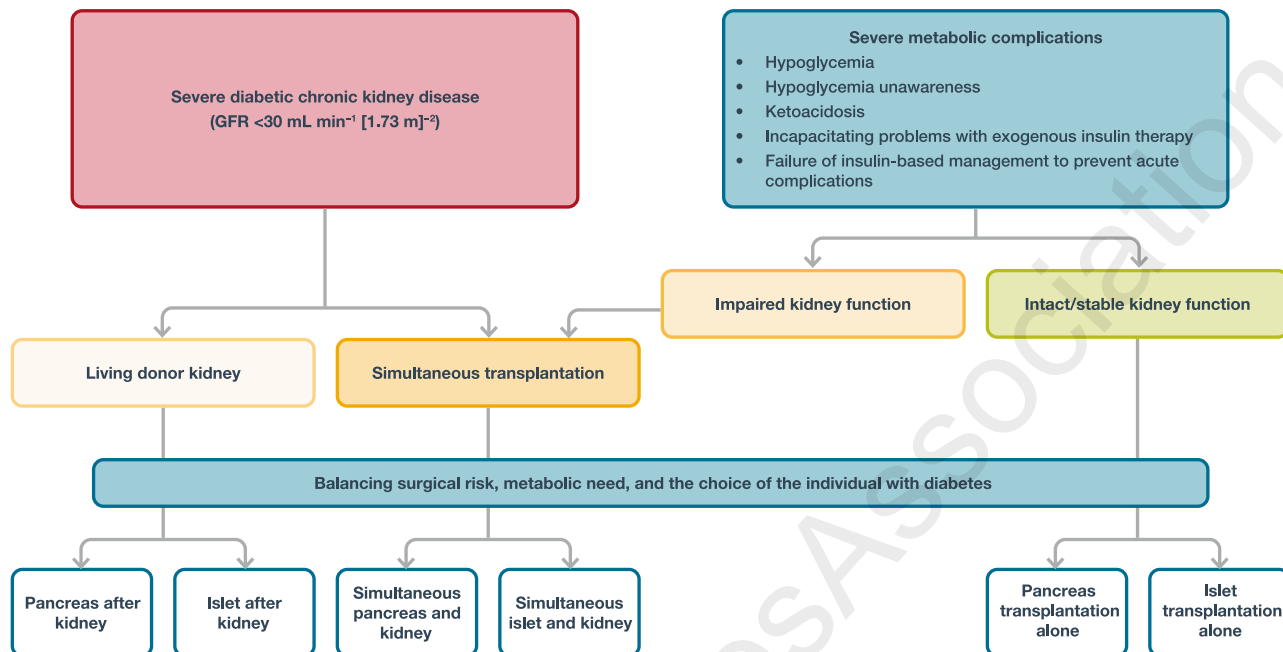
Simplified overview of indications for β -cell replacement therapy in people with type 1 diabetes

Figure 9.2—Simplified overview of indications for β -cell replacement therapy in people with type 1 diabetes. The two main forms of β -cell replacement therapy are whole-pancreas transplantation or islet cell transplantation. β -Cell replacement therapy can be combined with kidney transplantation if the individual has end-stage renal disease, which may be performed simultaneously or after kidney transplantation. All decisions about transplantation must balance the surgical risk, metabolic need, and the choice of the individual with diabetes. GFR, glomerular filtration rate. Reprinted from Holt et al. (5).

modifications and health behaviors that improve health (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”) should be emphasized along with any pharmacologic therapy. Section 13, “Older Adults,” and Section 14, “Children and Adolescents,” have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10, “Cardiovascular Disease and Risk Management,” and Section 11, “Chronic Kidney Disease and Risk Management,” have recommendations for the use of glucose-lowering drugs in the management of cardiovascular and renal disease, respectively.

Choice of Glucose-Lowering Therapy

Healthy lifestyle behaviors, diabetes self-management, education, and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Pharmacotherapy should be started at the time type 2 diabetes is diagnosed unless there are contraindications. Pharma-

cologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals (45). In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD), the treatment regimen should include agents that reduce cardiovascular risk (see Fig. 9.3, Table 9.2, Section 10, “Cardiovascular Disease and Risk Management,” and Section 11, “Chronic Kidney Disease and Risk Management”). Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, specified as metformin or agent(s), including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals (Fig. 9.3 and Table 9.2). In general, higher-efficacy approaches have greater likelihood of achieving glycemic goals, with the following considered to have very high efficacy for glucose lowering: the GLP-1 RAs dulaglutide (high dose) and semaglutide, the gastric inhibitory peptide (GIP) and GLP-1 RA tirzepatide, insulin, combination oral therapy, and combination injectable therapy.

Weight management is an impactful component of glucose-lowering management in type 2 diabetes (45,46). The glucose-lowering treatment regimen should consider approaches that support weight management goals, with very high efficacy for weight loss seen with semaglutide and tirzepatide (Fig. 9.3 and Table 9.2) (45).

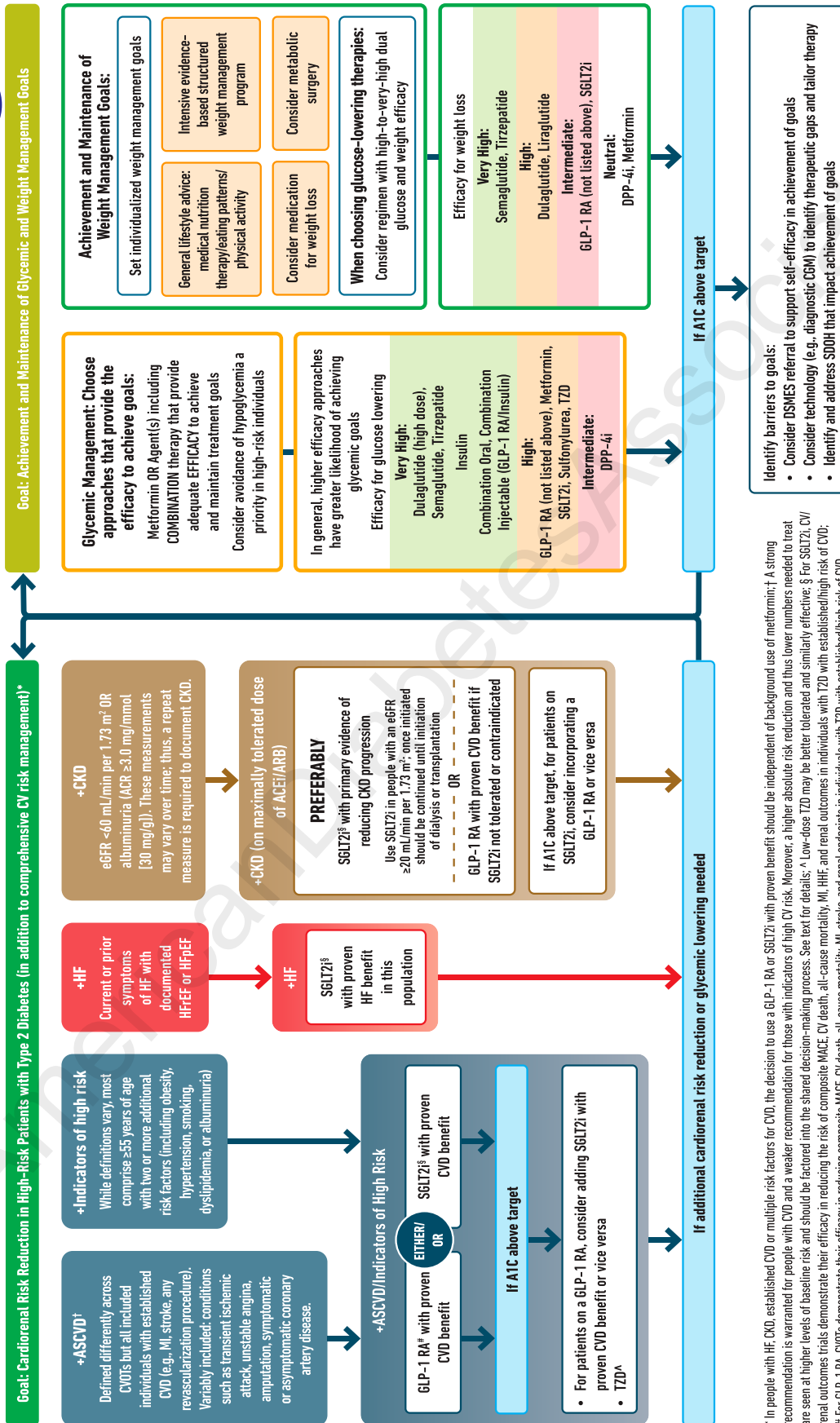
Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (47). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality (48).

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration. The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND RECALIBRATE THERAPY EVERY 3-4 MONTHS



* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin.† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.‡ Low-dose TZD may be better tolerated and similarly effective. § For SGLT2i, renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVDs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, M, stroke, and renal outcomes in individuals with T2D with established/high risk of CVD.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TZD, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

Table 9.2—Medications for lowering glucose, summary of characteristics

	Efficacy ¹	Hypoglycemia	Weight change ²	CV effects		Progression of DKD	Renal effects		Oral/SQ	Cost	Clinical considerations
				Effect on MACE	HF		Dosing/risk considerations [*]				
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	<ul style="list-style-type: none"> Contra-indicated with eGFR <30 mL/min per 1.73 m² 	Oral	Low	<ul style="list-style-type: none"> GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food Potential for vitamin B12 deficiency; monitor at regular intervals 	
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	<ul style="list-style-type: none"> See labels for renal dose considerations of individual agents Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR 	Oral	High	<ul style="list-style-type: none"> DKA risk, rare in T2DM; discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk Increased risk of genital mycotic infections Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports; institute prompt treatment if suspected Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable 	
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	<ul style="list-style-type: none"> See labels for renal dose considerations of individual agents No dose adjustment for dulaglutide, liraglutide, semaglutide Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions 	SQ, oral (semaglutide)	High	<ul style="list-style-type: none"> Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected 	
GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	<ul style="list-style-type: none"> See label for renal dose considerations No dose adjustment Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions 	SQ	High	<ul style="list-style-type: none"> Risk of thyroid C-cell tumors in rodents; human relevance not determined Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected 	
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	<ul style="list-style-type: none"> Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment No dose adjustment required for linagliptin 	Oral	High	<ul style="list-style-type: none"> Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected Discontinue if pancreatitis is suspected Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected Joint pain Bullous pemphigoid (postmarketing); discontinue if suspected 	
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	<ul style="list-style-type: none"> No dose adjustment required Generally not recommended in renal impairment due to potential for fluid retention 	Oral	Low	<ul style="list-style-type: none"> Congestive HF (pioglitazone, rosiglitazone) Fluid retention (edema; heart failure) Benefit in NASH Risk of bone fractures Weight gain; consider lower doses to mitigate weight gain and edema 	
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral	<ul style="list-style-type: none"> Glyburide: generally not recommended in chronic kidney disease Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia Lower insulin doses required with a decrease in eGFR; titrate per clinical response 	Oral	Low	<ul style="list-style-type: none"> FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) Use with caution in persons at risk for hypoglycemia 	
Insulin	High to very high	Yes	Gain	Neutral	Neutral	Neutral	<ul style="list-style-type: none"> Injection site reactions Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs 	SQ, inhaled SQ	Low (SQ) High	<ul style="list-style-type: none"> Injection site reactions Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs 	

CV, cardiovascular; CVOT, cardiovascular outcomes trial; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; NASH, nonalcoholic steatohepatitis; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes mellitus. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. ¹Tsapas et al. (62). ²Tsapas et al. (114). Reprinted from Davies et al. (45).

safely used in people with reduced estimated glomerular filtration rates (eGFR); the FDA has revised the label for metformin to reflect its safety in people with $eGFR \geq 30$ mL/min/1.73 m² (49). A randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (50). This is compatible with a report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (51) (see Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities”).

When A1C is $\geq 1.5\%$ (12.5 mmol/mol) above the glycemic target (see Section 6, “Glycemic Targets,” for appropriate targets), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their target A1C level (45,52) (Fig. 9.3 and Table 9.2). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels ≥ 300 mg/dL (16.7 mmol/L) or A1C $> 10\%$ (86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss) (Fig. 9.4). As glucose toxicity resolves, simplifying the regimen and/or changing to noninsulin agents is often possible. However, there is evidence that people with uncontrolled hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea (53).

Combination Therapy

Because type 2 diabetes is a progressive disease in many individuals, maintenance of glycemic targets often requires combination therapy. Traditional recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and reduce potential side effects and expense (54). However, there are data to support initial combination therapy for more rapid attainment of glycemic goals (55,56) and later combination therapy for longer

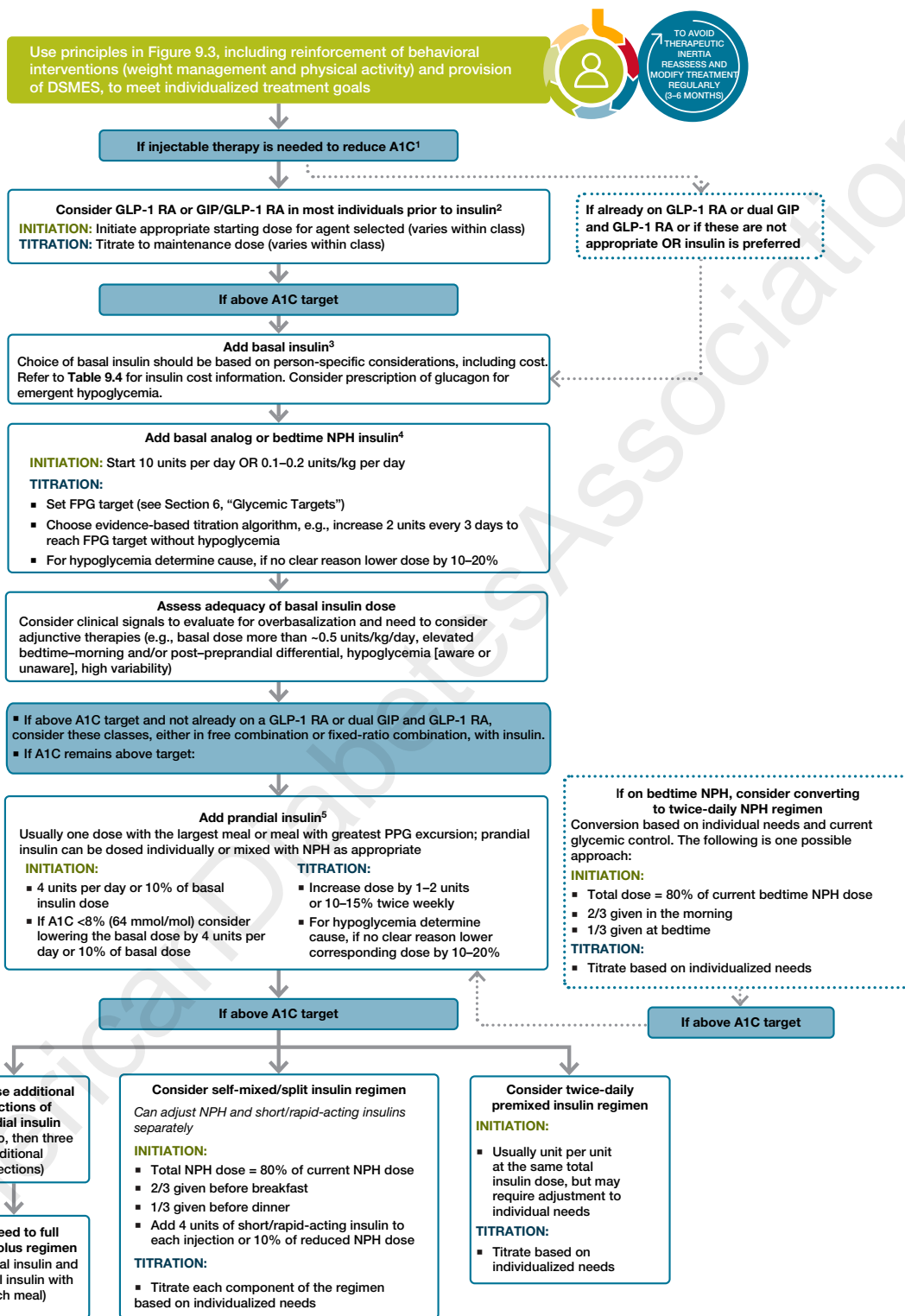
durability of glycemic effect (57). The VERIFY (Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes) trial demonstrated that initial combination therapy is superior to sequential addition of medications for extending primary and secondary failure (58). In the VERIFY trial, participants receiving the initial combination of metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin had a slower decline of glycemic control compared with metformin alone and with vildagliptin added sequentially to metformin. These results have not been generalized to oral agents other than vildagliptin, but they suggest that more intensive early treatment has some benefits and should be considered through a shared decision-making process, as appropriate. Initial combination therapy should be considered in people presenting with A1C levels 1.5–2.0% above target. Finally, incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular/renal risk reduction (e.g., GLP-1 RAs, SGLT2 inhibitors) may allow for weaning of the current regimen, particularly of agents that may increase the risk of hypoglycemia. Thus, treatment intensification may not necessarily follow a pure sequential addition of therapy but instead reflect a tailoring of the regimen in alignment with person-centered treatment goals (Fig. 9.3).

Recommendations for treatment intensification for people not meeting treatment goals should not be delayed. Shared decision-making is important in discussions regarding treatment intensification. The choice of medication added to initial therapy is based on the clinical characteristics of the individual and their preferences. Important clinical characteristics include the presence of established ASCVD or indicators of high ASCVD risk, HF, CKD, obesity, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, and risk for specific adverse drug effects, as well as safety, tolerability, and cost. Results from comparative effectiveness meta-analyses suggest that each new class of noninsulin agents added to initial therapy with metformin generally lowers A1C approximately 0.7–1.0% (59,60) (Fig. 9.3 and Table 9.2).

For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated CVD benefit (see Table 9.2, Table 10.3B,

Table 10.3C, and Section 10, “Cardiovascular Disease and Risk Management”) is recommended as part of the glucose-lowering regimen independent of A1C, independent of metformin use and in consideration of person-specific factors (Fig. 9.3). For people without established ASCVD, indicators of high ASCVD risk, HF, or CKD, medication choice is guided by efficacy in support of individualized glycemic and weight management goals, avoidance of side effects (particularly hypoglycemia and weight gain), cost/access, and individual preferences (61). A systematic review and network meta-analysis suggests greatest reductions in A1C level with insulin regimens and specific GLP-1 RAs added to metformin-based background therapy (62). In all cases, treatment regimens need to be continuously reviewed for efficacy, side effects, and burden (Table 9.2). In some instances, the individual will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, intolerable side effects, expense, or a change in glycemic goals (e.g., in response to development of comorbidities or changes in treatment goals). Section 13, “Older Adults,” has a full discussion of treatment considerations in older adults, in whom changes of glycemic goals and de-escalation of therapy are common.

The need for the greater potency of injectable medications is common, particularly in people with a longer duration of diabetes. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent regimens is a well-established approach that is effective for many individuals. In addition, evidence supports the utility of GLP-1 RAs in people not at glycemic goal. While most GLP-1 RAs are injectable, an oral formulation of semaglutide is commercially available (63). In trials comparing the addition of an injectable GLP-1 RA or insulin in people needing further glucose lowering, glycemic efficacy of injectable GLP-1 RA was similar or greater than that of basal insulin (64–70). GLP-1 RAs in these trials had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support GLP-1 RAs as the preferred option for individuals requiring the potency of an injectable therapy for glucose control (Fig. 9.4). In individuals



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider individual preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For people on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an A.M. dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

Figure 9.4—Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (43).

who are intensified to insulin therapy, combination therapy with a GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effect, as well as weight and hypoglycemia benefit, than treatment intensification with insulin alone (45). However, cost and tolerability issues are important considerations in GLP-1 RA use.

Costs for diabetes medications have increased dramatically over the past two decades, and an increasing proportion is now passed on to patients and their families (71). **Table 9.3** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (72) and National Average Drug Acquisition Costs (NADAC) (73), separate measures to allow for a comparison of drug prices, but do not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by the patient. Medication costs can be a major source of stress for people with diabetes and contribute to worse medication-taking behavior (74); cost-reducing strategies may improve medication-taking behavior in some cases (75).

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in adults with type 2 diabetes treated with an SGLT2 inhibitor or GLP-1 RA; see Section 10, "Cardiovascular Disease and Risk Management" for details. Participants enrolled in many of the cardiovascular outcomes trials had A1C $\geq 6.5\%$, with more than 70% taking metformin at baseline, with analyses indicating benefit with or without metformin (45). Thus, a practical extension of these results to clinical practice is to use these medications preferentially in people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk. For these individuals, incorporating one of the SGLT2 inhibitors and/or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (see **Fig. 9.3**, **Table 9.2**, and Section 10, "Cardiovascular Disease and Risk Management"). Emerging data suggest that use of both classes of drugs will provide additional cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 RA may be considered to

provide the complementary outcomes benefits associated with these classes of medication (76). In cardiovascular outcomes trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, and dulaglutide all had beneficial effects on indices of CKD, while dedicated renal outcomes studies have demonstrated benefit of specific SGLT2 inhibitors. See Section 11, "Chronic Kidney Disease and Risk Management," for discussion of how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See the section INSULIN INJECTION TECHNIQUE, above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients, and clinicians should avoid using insulin as a threat or describing it as a sign of personal failure or punishment. Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of other agents should be emphasized. Educating and involving patients in insulin management is beneficial. For example, instruction of individuals with type 2 diabetes initiating insulin in self-titration of insulin doses based on glucose monitoring improves glycemic control (77). Comprehensive education regarding blood glucose monitoring, nutrition, and the avoidance and appropriate treatment of hypoglycemia are critically important in any individual using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin treatment and can be added to metformin and other noninsulin injectables. Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (78,79). Control of fasting glucose can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal

analogs (U-100 glargine or detemir) have been demonstrated to reduce the risk of symptomatic and nocturnal hypoglycemia compared with NPH insulin (80–85), although these advantages are modest and may not persist (86). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in combination with oral agents (87–93). Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose greater than ~ 0.5 units/kg, high bedtime–morning or postprandial glucose differential (e.g., bedtime–morning glucose differential ≥ 50 mg/dL), hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy (94).

The cost of insulin has been rising steadily over the past two decades, at a pace severalfold that of other medical expenditures (95). This expense contributes significant burden to patients as insulin has become a growing "out-of-pocket" cost for people with diabetes, and direct patient costs contribute to decrease in medication-taking behavior (95). Therefore, consideration of cost is an important component of effective management. For many individuals with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns), human insulin (NPH and regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use (96). Human regular insulin, NPH, and 70/30 NPH/regular products can be purchased for considerably less than the AWP and NADAC prices listed in **Table 9.4** at select pharmacies. Additionally, approval of follow-on biologics for insulin glargine, the first interchangeable insulin glargine product, and generic versions of analog insulins may expand cost-effective options.

Prandial Insulin

Many individuals with type 2 diabetes require doses of insulin before meals, in addition to basal insulin, to reach glycemic targets. If the individual is not already being treated with a GLP-1 RA, a GLP-1 RA (either in free combination or fixed-ratio combination) should be considered prior to prandial insulin to further

Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/ product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	850 mg (IR)	\$106 (\$5, \$189)	\$2	2,550 mg
		1,000 mg (IR)	\$87 (\$3, \$144)	\$2	2,000 mg
		1,000 mg (ER)	\$242 (\$242, \$7,214)	\$32 (\$32, \$160)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	\$74 (\$71, \$198)	\$3	8 mg
		10 mg (IR)	\$70 (\$67, \$91)	\$6	40 mg
	• Glipizide	10 mg (XL/ER)	\$48 (\$46, \$48)	\$11	20 mg
		• Glyburide	6 mg (micronized)	\$52 (\$48, \$71)	\$12
		5 mg	\$79 (\$63, \$93)	\$9	20 mg
Thiazolidinedione	• Pioglitazone	45 mg	\$345 (\$7, \$349)	\$4	45 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	\$106 (\$104, \$106)	\$29	300 mg
	• Miglitol	100 mg	\$241 (\$241, \$346)	NA	300 mg
Meglitinides	• Nateglinide	120 mg	\$155	\$27	360 mg
	• Repaglinide	2 mg	\$878 (\$58, \$897)	\$31	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	\$234	\$154	25 mg
	• Saxagliptin	5 mg	\$565	\$452	5 mg
	• Linagliptin	5 mg	\$606	\$485	5 mg
	• Sitagliptin	100 mg	\$626	\$500	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	\$390	\$312	15 mg
	• Dapagliflozin	10 mg	\$659	\$527	10 mg
	• Canagliflozin	300 mg	\$684	\$548	300 mg
	• Empagliflozin	25 mg	\$685	\$547	25 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	\$936	\$726	2 mg**
	• Exenatide	10 µg pen	\$961	\$770	20 µg
	• Dulaglutide	4.5 mg mL pen	\$1,064	\$852	4.5 mg**
	• Semaglutide	1 mg pen	\$1,070	\$858	2 mg**
		14 mg (tablet)	\$1,070	\$858	14 mg
	• Liraglutide	1.8 mg pen	\$1,278	\$1,022	1.8 mg
• Lixisenatide	20 µg pen	\$814	NA	20 µg	
GLP-1/GIP dual agonist	• Tirzepatide	15 mg pen	\$1,169	\$935	15 mg**
Bile acid sequestrant	• Colesevelam	625 mg tabs	\$711 (\$674, \$712)	\$83	3.75 g
		3.75 g suspension	\$674 (\$673, \$675)	\$177	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	\$1,118	\$899	4.8 mg
Amylin mimetic	• Pramlintide	120 µg pen	\$2,783	NA	120 µg/injection††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium-glucose cotransporter 2. †Calculated for 30-day supply (AWP [72] or NADAC [73] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP and NADAC calculated based on 120 µg three times daily.

address prandial control and to minimize the risks of hypoglycemia and weight gain associated with insulin therapy (45). For individuals who advance to prandial insulin, a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy. The prandial insulin regimen can then be intensified based on individual needs (Fig. 9.4). Individuals with type 2 diabetes are generally more insulin resistant than those

with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia (97). Titration can be based on home glucose monitoring or A1C. With significant additions to the prandial insulin dose, particularly with the evening meal, consideration should be given to decreasing basal insulin. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported important differences in A1C or hypoglycemia (98,99).

Concentrated Insulins

Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. U-500 regular insulin has distinct pharmacokinetics with delayed onset and longer duration of action, has characteristics more like an intermediate-acting (NPH) insulin, and can be used as two or three daily injections (100). U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100

Table 9.4—Median cost of insulin products in the U.S. calculated as AWP (72) and NADAC (73) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Lispro follow-on product	U-100 vial	\$118 (\$118, \$157)	\$94
		U-100 prefilled pen	\$151	\$121
	• Lispro	U-100 vial	\$99†	\$79†
		U-100 cartridge	\$408	\$326
		U-100 prefilled pen	\$127†	\$102†
		U-200 prefilled pen	\$424	\$339
	• Lispro-aabc	U-100 vial	\$330	\$261
		U-100 prefilled pen	\$424	\$339
		U-200 prefilled pen	\$424	NA
	• Glulisine	U-100 vial	\$341	\$272
		U-100 prefilled pen	\$439	\$351
	• Aspart	U-100 vial	\$174†	\$140†
		U-100 cartridge	\$215†	\$172†
		U-100 prefilled pen	\$224†	\$180†
	• Aspart (“faster acting product”)	U-100 vial	\$347	\$277
U-100 cartridge		\$430	\$344	
U-100 prefilled pen		\$447	\$357	
Inhalation cartridges		\$1,418	NA	
Short-acting	• Human regular	U-100 vial	\$165††	\$132††
		U-100 prefilled pen	\$208	\$166
Intermediate-acting	• Human NPH	U-100 vial	\$165††	\$132††
		U-100 prefilled pen	\$208	\$168
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	\$178	\$142
		U-500 prefilled pen	\$230	\$184
Long-acting	• Glargine follow-on products	U-100 prefilled pen	\$261 (\$118, \$323)	\$209 (\$209, \$258)
		U-100 vial	\$118 (\$118, \$323)	\$95
	• Glargine	U-100 vial; U-100 prefilled pen	\$136†	\$109†
		U-300 prefilled pen	\$346	\$277
	• Detemir	U-100 vial; U-100 prefilled pen	\$370	\$296
		U-100 vial; U-100 prefilled pen; U-200 prefilled pen	\$407	\$326
	Premixed insulin products	• NPH/regular 70/30	U-100 vial	\$165††
U-100 prefilled pen			\$208	\$167
• Lispro 50/50		U-100 vial	\$342	\$274
		U-100 prefilled pen	\$424	\$339
• Lispro 75/25		U-100 vial	\$342	\$273
		U-100 prefilled pen	\$127†	\$103†
• Aspart 70/30		U-100 vial	\$180†	\$146†
		U-100 prefilled pen	\$224†	\$178†
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 µg prefilled pen	\$646	\$517
	• Degludec/Liraglutide	100/3.6 µg prefilled pen	\$944	\$760

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in Table 9.3. †Generic prices used when available. ††AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately \$25/vial; median listed alone when only one product and/or price.

formulations, respectively, and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action than U-100 glargine but modestly lower efficacy per unit administered (101,102). The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL), and insulin lispro-aabc (U-200). These concentrated preparations may be more convenient and comfortable for individuals to inject and may improve treatment plan engagement in those with insulin resistance

who require large doses of insulin. While U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors.

Alternative Insulin Routes

Insulins with different routes of administration (inhaled, bolus-only insulin delivery patch pump) are also available (45). Inhaled insulin is available as a rapid-acting insulin; studies in individuals with type 1 diabetes suggest rapid

pharmacokinetics (8). Studies comparing inhaled insulin with injectable insulin have demonstrated its faster onset and shorter duration compared with rapid-acting insulin lispro as well as clinically meaningful A1C reductions and weight reductions compared with insulin aspart over 24 weeks (103–105). Use of inhaled insulin may result in a decline in lung function (reduced forced expiratory volume in 1 s [FEV₁]). Inhaled insulin is contraindicated in individuals with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not

recommended in individuals who smoke or who recently stopped smoking. All individuals require spirometry (FEV₁) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day with indications of need for other therapy) and A1C remains above target, consider advancing to combination injectable therapy (Fig. 9.4). This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of insulin. The combination of basal insulin and GLP-1 RA has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens (106–111). The DUAL VIII (Durability of Insulin Degludec Plus Liraglutide Versus Insulin Glargine U100 as Initial Injectable Therapy in Type 2 Diabetes) randomized controlled trial demonstrated greater durability of glycemic treatment effect with the combination GLP-1 RA–insulin therapy compared with addition of basal insulin alone (57). In select individuals, complex insulin regimens can also be simplified with combination GLP-1 RA–insulin therapy in type 2 diabetes (112). Two different once-daily, fixed dual combination products containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide (IGlarLixi) and insulin degludec plus liraglutide (IDegLira).

Intensification of insulin treatment can be done by adding doses of prandial insulin to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a regimen with multiple prandial doses if necessary (113). Alternatively, in an individual on basal insulin in whom additional prandial coverage is desired, the regimen can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal-prandial regimens offer greater flexibility for individuals who eat on irregular schedules. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (70/30) formulations, are less costly alternatives to insulin analogs. Figure 9.4 outlines these

options as well as recommendations for further intensification, if needed, to achieve glycemic goals. When initiating combination injectable therapy, metformin therapy should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued. In individuals with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once a basal-bolus insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (also known as pattern control or pattern management). As people with type 2 diabetes get older, it may become necessary to simplify complex insulin regimens because of a decline in self-management ability (see Section 13, “Older Adults”).

References

1. Cleary PA, Orchard TJ, Genuth S, et al.; DCCT/EDIC Research Group. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes* 2006;55:3556–3565
2. Nathan DM, Cleary PA, Backlund JYC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653
3. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. *Diabetes Care* 2016;39:1378–1383
4. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002;287:2563–2569
5. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2021;44:2589–2625
6. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ* 2014;349:g5459

7. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to neutral protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. *Diabet Med* 2008;25:442–449
8. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003;289:2254–2264
9. Bode BW, McGill JB, Lorber DL, Gross JL, Chang PC; Affinity 1 Study Group. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. *Diabetes Care* 2015;38:2266–2273
10. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). *Diabetes Care* 2017;40:943–950
11. Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: Results from the 26-week PRONTO-T1D study. *Diabetes Obes Metab* 2020;22:1799–1807
12. Blevins T, Zhang Q, Frias JP, Jinnouchi H; PRONTO-T2D Investigators. Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. *Diabetes Care* 2020;43:2991–2998
13. Lane W, Bailey TS, Gerety G, et al.; Group Information; SWITCH 1. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. *JAMA* 2017;318:33–44
14. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). *Diabetes Care* 2015;38:2217–2225
15. Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med* 2012;157:336–347
16. Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. *J Diabetes Sci Technol* 2013;7:1567–1574
17. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232
18. Buckingham BA, Raghinaru D, Cameron F, et al.; In Home Closed Loop Study Group. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. *Diabetes Care* 2015;38:1197–1204
19. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA* 2016;316:1407–1408
20. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2017;19:155–163
21. Tauschmann M, Thabit H, Bally L, et al.; APCam11 Consortium. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a

- multicentre, 12-week randomised trial. *Lancet* 2018;392:1321–1329
22. Brown SA, Kovatchev BP, Raghinaru D, et al.; IDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med* 2019;381:1707–1717
23. Peters AL, Laffel L (Eds.). *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook*. Alexandria, VA, American Diabetes Association, 2013
24. Chiang JL, Kirkman MS, Laffel LMB; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care* 2014;37:2034–2054
25. Bell KJ, Barclay AW, Petocz P, Colagiuri S, Brand-Miller JC. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2014;2:133–140
26. Vaz EC, Porfírio GJM, Nunes HRC, Nunes-Nogueira VDS. Effectiveness and safety of carbohydrate counting in the management of adult patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *Arch Endocrinol Metab* 2018;62:337–345
27. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care* 2015;38:1008–1015
28. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. *Mayo Clin Proc* 2016;91:1231–1255
29. Bergenstal RM, Strock ES, Peremislov D, Gibney MA, Parvu V, Hirsch LJ. Safety and efficacy of insulin therapy delivered via a 4mm pen needle in obese patients with diabetes. *Mayo Clin Proc* 2015;90:329–338
30. Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care* 2002;25:724–730
31. Ratner RE, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol Ther* 2002;4:51–61
32. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 2003;26:784–790
33. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004;21:1204–1212
34. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J. Effect of metformin on glycaemic control in patients with type 1 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Metab Res Rev* 2018;34:e2983
35. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017;5:597–609
36. Mathieu C, Zinman B, Hemmingsson JU, et al.; ADJUNCT ONE Investigators. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. *Diabetes Care* 2016;39:1702–1710
37. Ahrén B, Hirsch IB, Pieber TR, et al.; ADJUNCT TWO Investigators. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. *Diabetes Care* 2016;39:1693–1701
38. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;5:864–876
39. Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. *Diabetes Care* 2018;41:2560–2569
40. Snaith JR, Holmes-Walker DJ, Greenfield JR. Reducing type 1 diabetes mortality: role for adjunctive therapies? *Trends Endocrinol Metab* 2020;31:150–164
41. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. *Diabetes Care* 2019;42:1147–1154
42. Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. *BMJ* 2017;357:j1321. Accessed 18 October 2022. Available from <https://www.bmj.com/content/357/bmj.j1321>
43. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669–2701
44. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2020;43:487–493
45. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022;45:2753–2786
46. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet* 2022;399:394–405
47. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589
48. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2016;164:740–751
49. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Accessed 18 October 2022. Available from www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain-patients-reduced-kidney-function
50. Out M, Kooy A, Leher P, Schalkwijk CA, Stehouwer CDA. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: post hoc analysis of a randomized controlled 4.3-year trial. *J Diabetes Complications* 2018;32:171–178
51. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab* 2016;101:1754–1761
52. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. *Int J Clin Pract* 2012;66:446–456
53. Babu A, Mehta A, Guerrero P, et al. Safe and simple emergency department discharge therapy for patients with type 2 diabetes mellitus and severe hyperglycemia. *Endocr Pract* 2009;15:696–704
54. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. *Diabetes Care* 2016;39(Suppl. 2):S137–S145
55. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab* 2015;17:268–275
56. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes Obes Metab* 2014;16:410–417
57. Aroda VR, González-Galvez G, Grøn R, et al. Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;7:596–605
58. Matthews DR, Paldanius PM, Proot P, Chiang Y, Stumvoll M; VERIFY study group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet* 2019;394:1519–1529
59. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann Intern Med* 2011;154:602–613
60. Maloney A, Rosenstock J, Fonseca V. A model-based meta-analysis of 24 antihyperglycemic drugs for type 2 diabetes: comparison of treatment effects at therapeutic doses. *Clin Pharmacol Ther* 2019;105:1213–1223
61. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. *JAMA Intern Med* 2014;174:1227–1234
62. Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review

- and network meta-analysis. *Ann Intern Med* 2020;173:278–286
63. Pratley R, Amod A, Hoff ST, et al.; PIONEER 4 investigators. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet* 2019;394:39–50
64. Singh S, Wright EE Jr, Kwan AYM, et al. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab* 2017;19:228–238
65. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. *Diabetes Metab Syndr Obes* 2017;10:123–139
66. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. *Diabetes Obes Metab* 2017;19:216–227
67. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtnr V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care* 2015;38:2241–2249
68. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naïve patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol* 2017;5:355–366
69. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. *Diabetes Care* 2013;36:1368–1376
70. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet* 2010;375:2234–2243
71. Riddle MC, Herman WH. The cost of diabetes care—an elephant in the room. *Diabetes Care* 2018;41:929–932
72. IBM. Micromedex Red Book. Accessed 9 November 2022. Available from <https://www.ibm.com/products/micromedex-red-book>
73. Data.Medicare.gov. NADAC (National Average Drug Acquisition Cost). Accessed 23 October 2022. Available from <https://data.medicare.gov/dataset/dfa2ab14-06c2-457a-9e36-5cb6d80f8d93>
74. Kang H, Lobo JM, Kim S, Sohn MW. Cost-related medication non-adherence among U.S. adults with diabetes. *Diabetes Res Clin Pract* 2018;143:24–33
75. Patel MR, Piette JD, Resnicow K, Kowalski-Dobson T, Heisler M. Social determinants of health, cost-related nonadherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health interview survey. *Med Care* 2016;54:796–803
76. Gerstein HC, Sattar N, Rosenstock J, et al.; AMPITUDE-O Trial Investigators. Cardiovascular and renal outcomes with epeglenatide in type 2 diabetes. *N Engl J Med* 2021;385:896–907
77. Blonde L, Merilainen M, Karwe V; TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets—the TITRATE study. *Diabetes Obes Metab* 2009;11:623–631
78. Porcellati F, Lucidi P, Cioli P, et al. Pharmacokinetics and pharmacodynamics of insulin glargine given in the evening as compared with in the morning in type 2 diabetes. *Diabetes Care* 2015;38:503–512
79. Wang Z, Hedrington MS, Gogitidze Joy N, et al. Dose-response effects of insulin glargine in type 2 diabetes. *Diabetes Care* 2010;33:1555–1560
80. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ* 2009;180:385–397
81. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007 2:CD005613
82. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2008;81:184–189
83. Owens DR, Traylor L, Mullins P, Landgraf W. Patient-level meta-analysis of efficacy and hypoglycaemia in people with type 2 diabetes initiating insulin glargine 100U/mL or neutral protamine Hagedorn insulin analysed according to concomitant oral antidiabetes therapy. *Diabetes Res Clin Pract* 2017;124(Suppl. C):57–65
84. Riddle MC, Rosenstock J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080–3086
85. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care* 2006;29:1269–1274
86. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006;49:442–451
87. Bolli GB, Riddle MC, Bergenstal RM, et al.; on behalf of the EDITION 3 Study Investigators. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab* 2015;17:386–394
88. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). *Diabetes Obes Metab* 2016;18:366–374
89. Yki-Järvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. *Diabetes Obes Metab* 2015;17:1142–1149
90. Marso SP, McGuire DK, Zinman B, et al.; DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 2017;377:723–732
91. Rodbard HW, Cariou B, Zinman B, et al.; BEGIN Once Long Trial Investigators. Comparison of insulin degludec with insulin glargine in insulin-naïve subjects with type 2 diabetes: a 2-year randomized, treat-to-target trial. *Diabet Med* 2013;30:1298–1304
92. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine u100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA* 2017;318:45–56
93. Zinman B, Philis-Tsimikas A, Cariou B, et al.; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care* 2012;35:2464–2471
94. Cowart K. Overbasalization: addressing hesitancy in treatment intensification beyond basal insulin. *Clin Diabetes* 2020;38:304–310
95. Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Conclusions and recommendations. *Diabetes Care* 2018;41:1299–1311
96. Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of initiation of basal insulin analogs vs neutral protamine hagedorn insulin with hypoglycemia-related emergency department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. *JAMA* 2018;320:53–62
97. McCall AL. Insulin therapy and hypoglycemia. *Endocrinol Metab Clin North Am* 2012;41:57–87
98. Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. *Diabetes Obes Metab* 2009;11:53–59
99. Heller S, Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. *J Diabetes* 2013;5:482–491
100. Wysham C, Hood RC, Warren ML, Wang T, Morwick TM, Jackson JA. Effect of total daily dose on efficacy, dosing, and safety of 2 dose titration regimens of human regular U500 insulin in severely insulin-resistant patients with type 2 diabetes. *Endocr Pract* 2016;22:653–665
101. Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes Obes Metab* 2015;17:835–842
102. Yki-Järvinen H, Bergenstal R, Ziemer M, et al.; EDITION 2 Study Investigators. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care* 2014;37:3235–3243
103. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily

- injections: the STAT study. *Diabetes Technol Ther* 2018;20:639–647
104. Hoogwerf BJ, Pantalone KM, Basina M, Jones MC, Grant M, Kendall DM. Results of a 24-week trial of technosphere insulin versus insulin aspart in type 2 diabetes. *Endocr Pract* 2021;27:38–43
105. Grant M, Heise T, Baughman R. Comparison of pharmacokinetics and pharmacodynamics of inhaled technosphere insulin and subcutaneous insulin lispro in the treatment of type 1 diabetes mellitus. *Clin Pharmacokinet* 2022;61:413–422
106. Diamant M, Nauck MA, Shaginian R, et al.; 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care* 2014; 37:2763–2773
107. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet* 2014;384:2228–2234
108. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care* 2017;40:614–624
109. Aroda VR, Rosenstock J, Wysham C, et al.; LixiLan-L Trial Investigators. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care* 2016; 39:1972–1980
110. Lingvay I, Pérez Manghi F, García-Hernández P, et al.; DUAL V Investigators. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized clinical trial. *JAMA* 2016;315:898–907
111. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. *JAMA* 2022;327:534–545
112. Taybani Z, Bótyik B, Katkó M, Gyimesi A, Várkonyi T. Simplifying complex insulin regimens while preserving good glycemic control in type 2 diabetes. *Diabetes Ther* 2019;10:1869–1878
113. Rodbard HW, Visco VE, Andersen H, Hiert LC, Shu DHW. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial. *Lancet Diabetes Endocrinol* 2014;2: 30–37
114. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetes Obes Metab* 2021;23: 2116–2124

10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, “Children and Adolescents.”

Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and results in an estimated \$37.3 billion in cardiovascular-related spending per year associated with diabetes (1). Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors are addressed simultaneously. Under the current paradigm of aggressive risk factor modification in people with diabetes, there is evidence that measures of 10-year CHD risk among U.S. adults with diabetes have improved significantly over the past decade (2) and that ASCVD morbidity and mortality have decreased (3,4).

Heart failure is another major cause of morbidity and mortality from cardiovascular disease. Recent studies have found that rates of incident heart failure hospitalization (adjusted for age and sex) were twofold higher in people with diabetes compared with those without (5,6). People with diabetes may have heart failure with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). Hypertension is often a precursor of heart failure of either type, and ASCVD can coexist with either type (7), whereas prior myocardial infarction (MI) is often a major factor in HFpEF. Rates of heart failure hospitalization have been improved in recent trials including people with type 2 diabetes, most of whom also had ASCVD, with sodium–glucose cotransporter 2 (SGLT2) inhibitors (8–11).

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A recent meta-analysis indicated that SGLT2 inhibitors reduce the risk of heart failure hospitalization, cardiovascular mortality, and all-cause mortality in people with (secondary prevention) and without (primary prevention) cardiovascular disease (12).

For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all people with diabetes. These risk factors include duration of diabetes, obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease (CKD), and the presence of albuminuria. Modifiable abnormal risk factors should be treated as described in these guidelines. Notably, the majority of evidence supporting interventions to reduce cardiovascular risk in diabetes comes from trials of people with type 2 diabetes. No randomized trials have been specifically designed to assess the impact of cardiovascular risk reduction strategies in people with type 1 diabetes. Therefore, the recommendations for cardiovascular risk factor modification for people with type 1 diabetes are extrapolated from data obtained in people with type 2 diabetes

and are similar to those for people with type 2 diabetes.

As depicted in **Fig. 10.1**, a comprehensive approach to the reduction in risk of diabetes-related complications is recommended. Therapy that includes multiple, concurrent evidence-based approaches to care will provide complementary reduction in the risks of microvascular, kidney, neurologic, and cardiovascular complications. Management of glycemia, blood pressure, and lipids and the incorporation of specific therapies with cardiovascular and kidney outcomes benefit (as individually appropriate) are considered fundamental elements of global risk reduction in diabetes.

THE RISK CALCULATOR

The American College of Cardiology/American Heart Association ASCVD risk calculator (Risk Estimator Plus) is generally a useful tool to estimate 10-year risk of a first ASCVD event (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus). The calculator includes diabetes as a risk factor, since diabetes itself confers increased risk for ASCVD, although it should be acknowledged that these risk calculators do not account for the duration of diabetes or the presence of diabetes complications,

such as albuminuria. Although some variability in calibration exists in various subgroups, including by sex, race, and diabetes, the overall risk prediction does not differ in those with or without diabetes (13–16), validating the use of risk calculators in people with diabetes. The 10-year risk of a first ASCVD event should be assessed to better stratify ASCVD risk and help guide therapy, as described below.

Recently, risk scores and other cardiovascular biomarkers have been developed for risk stratification of secondary prevention patients (i.e., those who are already high risk because they have ASCVD) but are not yet in widespread use (17,18). With newer, more expensive lipid-lowering therapies now available, use of these risk assessments may help target these new therapies to “higher risk” ASCVD patients in the future.

HYPERTENSION/BLOOD PRESSURE CONTROL

Hypertension is defined as a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 80 mmHg (19). This is in agreement with the definition of hypertension by the American College of Cardiology and American Heart Association (19). Hypertension is common among people with either type 1 or type 2 diabetes. Hypertension is a major risk factor for both ASCVD and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the American Diabetes Association position statement “Diabetes and Hypertension” for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (20) and recent updated hypertension guideline recommendations (19,21,22).

Screening and Diagnosis

Recommendations

10.1 Blood pressure should be measured at every routine clinical visit. When possible, individuals found to have elevated blood pressure (systolic blood pressure 120–129 mmHg and diastolic < 80 mmHg) should have blood pressure confirmed using multiple readings, including measurements

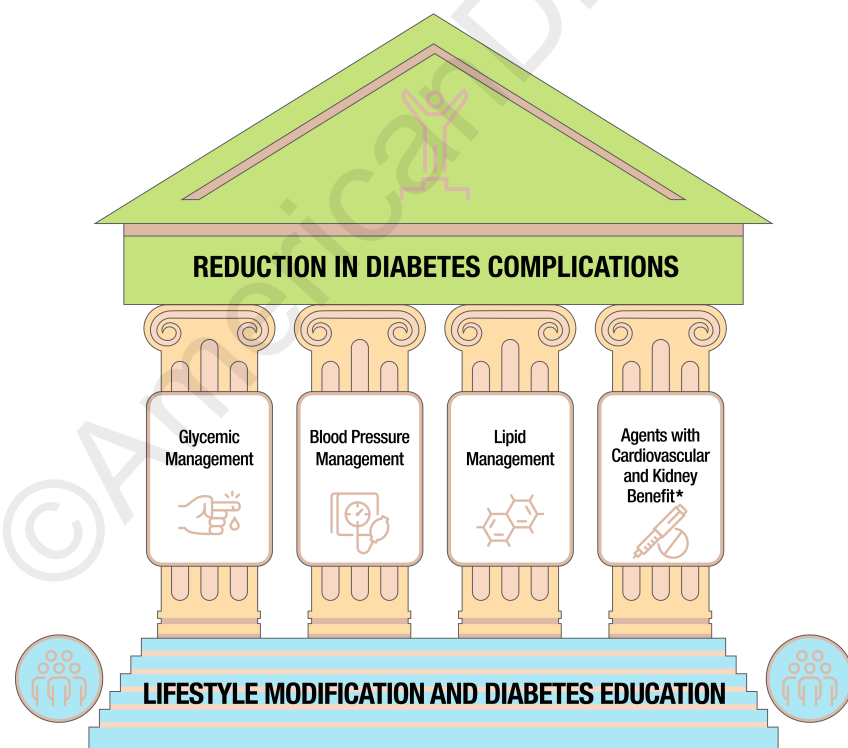


Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

on a separate day, to diagnose hypertension. **A** Hypertension is defined as a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 80 mmHg based on an average of ≥ 2 measurements obtained on ≥ 2 occasions. **A** Individuals with blood pressure $\geq 180/110$ mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. **E**

10.2 All people with hypertension and diabetes should monitor their blood pressure at home. **A**

Blood pressure should be measured at every routine clinical visit by a trained individual and should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference. Elevated values should preferably be confirmed on a separate day; however, in individuals with cardiovascular disease and blood pressure $\geq 180/110$ mmHg, it is reasonable to diagnose hypertension at a single visit (21). Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and “true” blood pressure (23,24). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. Studies of individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (23,24). Moreover, home blood pressure monitoring may improve patient medication taking and thus help reduce cardiovascular risk (25).

Treatment Goals

Recommendations

10.3 For people with diabetes and hypertension, blood pressure

targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. **B**

10.4 People with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated $\geq 130/80$ mmHg. The on-treatment target blood pressure goal is $<130/80$ mmHg, if it can be safely attained. **B**

10.5 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be lessened for blood pressure $<90/60$ mmHg. **E** A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

Randomized clinical trials have demonstrated unequivocally that treatment of hypertension reduces cardiovascular events as well as microvascular complications (26–32). There has been controversy on the recommendation of a specific blood pressure goal in people with diabetes. The committee recognizes that there has been no randomized controlled trial to specifically demonstrate a decreased incidence of cardiovascular events in people with diabetes by targeting a blood pressure $<130/80$ mmHg. The recommendation to support a blood pressure goal of $<130/80$ mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association (20), the International Society of Hypertension (21), and the European Society of Cardiology (22). The committee’s recommendation for the blood pressure target

of $<130/80$ mmHg derives primarily from the collective evidence of the following randomized controlled trials. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that treatment to a target systolic blood pressure of <120 mmHg decreases cardiovascular event rates by 25% in high-risk patients, although people with diabetes were excluded from this trial (33). The recently completed Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial included nearly 20% of people with diabetes and noted decreased cardiovascular events with treatment of hypertension to a blood pressure target of <130 mmHg (34). While the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial (ACCORD BP) did not confirm that targeting a systolic blood pressure of <120 mmHg in people with diabetes results in decreased cardiovascular event rates, the prespecified secondary outcome of stroke was reduced by 41% with intensive treatment (35). The Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial revealed that treatment with perindopril/indapamide to an achieved systolic blood pressure of ~ 135 mmHg significantly decreased cardiovascular event rates compared with a placebo treatment with an achieved blood pressure of 140 mmHg (36). Therefore, it is recommended that people with diabetes who have hypertension should be treated to blood pressure targets of $<130/80$ mmHg. Notably, there is an absence of high-quality data available to guide blood pressure targets in people with type 1 diabetes, but a similar blood pressure target of $<130/80$ mmHg is recommended in people with type 1 diabetes. As discussed below, treatment should be individualized and treatment should not be targeted to $<120/80$ mmHg, as a mean achieved blood pressure of $<120/80$ mmHg is associated with adverse events.

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control

SPRINT provides the strongest evidence to support lower blood pressure goals in patients at increased cardiovascular risk, although this trial excluded people with diabetes (33). The trial enrolled 9,361 patients with a systolic blood pressure of

≥ 130 mmHg and increased cardiovascular risk and treated to a systolic blood pressure target of <120 mmHg (intensive treatment) versus a target of <140 mmHg (standard treatment). The primary composite outcome of myocardial infarction (MI), coronary syndromes, stroke, heart failure, or death from cardiovascular causes was reduced by 25% in the intensive treatment group. The achieved systolic blood pressures in the trial were 121 mmHg and 136 mmHg in the intensive versus standard treatment group, respectively. Adverse outcomes, including hypotension, syncope, electrolyte abnormality, and acute kidney injury were more common in the intensive treatment arm; risk of adverse outcomes needs to be weighed against the cardiovascular benefit of more intensive blood pressure lowering.

ACCORD BP provides the strongest direct assessment of the benefits and risks of intensive blood pressure control in people with type 2 diabetes (35). In the study, a total of 4,733 with type 2 diabetes were assigned to intensive therapy (targeting a systolic blood pressure <120 mmHg) or standard therapy (targeting a systolic blood pressure <140 mmHg). The mean achieved systolic blood pressures were 119 mmHg and 133 mmHg in the intensive versus standard group, respectively. The primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes was not significantly reduced in the intensive treatment group. The prespecified secondary outcome of stroke was significantly reduced by 41% in the intensive treatment group. Adverse events attributed to blood pressure treatment, including hypotension, syncope, bradycardia, hyperkalemia, and elevations in serum creatinine occurred more frequently in the intensive treatment arm than in the standard therapy arm (Table 10.1).

Of note, the ACCORD BP and SPRINT trials targeted a similar systolic blood pressure <120 mmHg, but in contrast to SPRINT, the primary composite cardiovascular end point was nonsignificantly reduced in ACCORD BP. The results have been interpreted to be generally consistent between both trials, but ACCORD BP was viewed as underpowered due to the composite primary end point being less sensitive to blood pressure regulation (33).

The more recent STEP trial assigned 8,511 patients aged 60–80 years with

hypertension to a systolic blood pressure target of 110 to <130 mmHg (intensive treatment) or a target of 130 to <150 mmHg (34). In this trial, the primary composite outcome of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes was reduced by 26% in the intensive treatment group. In this trial, 18.9% of patients in the intensive treatment arm and 19.4% in the standard treatment arm had a diagnosis of type 2 diabetes. Hypotension occurred more frequently in the intensive treatment group (3.4%) compared with the standard treatment group (2.6%), without significant differences in other adverse events, including dizziness, syncope, or fractures.

In ADVANCE, 11,140 people with type 2 diabetes were randomized to receive either treatment with fixed combination perindopril/indapamide or matching placebo (36). The primary end point, a composite of cardiovascular death, nonfatal stroke infarction, or worsening renal or diabetic eye disease, was reduced by 9% in the combination treatment. The achieved systolic blood pressure was ~ 135 mmHg in the treatment group and 140 mmHg in the placebo group.

The Hypertension Optimal Treatment (HOT) trial enrolled 18,790 patients and targeted diastolic blood pressure <90 mmHg, <85 mmHg, or <80 mmHg (37). The cardiovascular event rates, defined as fatal or nonfatal MI, fatal and nonfatal strokes, and all other cardiovascular events, were not significantly different between diastolic blood pressure targets (≤ 90 mmHg, ≤ 85 mmHg, and ≤ 80 mmHg), although the lowest incidence of cardiovascular events occurred with an achieved diastolic blood pressure of 82 mmHg. However, in people with diabetes, there was a significant 51% reduction in the treatment group with a target diastolic blood pressure of <80 mmHg compared with a target diastolic blood pressure of <90 mmHg.

Meta-analyses of Trials

To clarify optimal blood pressure targets in people with diabetes, multiple meta-analyses have been performed. One of the largest meta-analyses included 73,913 people with diabetes. Compared with a less tight blood pressure control, allocation to a tighter blood pressure control

significantly reduced the risk of stroke by 31% but did not reduce the risk of MI (38). Another meta-analysis of 19 trials including 44,989 patients showed that a mean blood pressure of 133/76 mmHg is associated with a 14% risk reduction for major cardiovascular events compared with a mean blood pressure of 140/81 mmHg (32). This benefit was greatest in people with diabetes. An analysis of trials including people with type 2 diabetes and impaired glucose tolerance with achieved systolic blood pressures of <135 mmHg in the intensive blood pressure treatment group and <140 mmHg in the standard treatment group revealed a 10% reduction in all-cause mortality and a 17% reduction in stroke (30). More intensive reduction to <130 mmHg was associated with a further reduction in stroke but not other cardiovascular events.

Several meta-analyses stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention (or intensive treatment) arm. Based on these analyses, antihypertensive treatment appears to be most beneficial when mean baseline blood pressure is $\geq 140/90$ mmHg (19,26,27,29–31). Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident.

Individualization of Treatment Targets

Patients and clinicians should engage in a shared decision-making process to determine individual blood pressure targets (19). This approach acknowledges that the benefits and risks of intensive blood pressure targets are uncertain and may vary across patients and is consistent with a patient-focused approach to care that values patient priorities and health care professional judgment (39). Secondary analyses of ACCORD BP and SPRINT suggest that clinical factors can help determine individuals more likely to benefit and less likely to be harmed by intensive blood pressure control (40,41).

Absolute benefit from blood pressure reduction correlated with absolute baseline cardiovascular risk in SPRINT and in earlier clinical trials conducted at higher baseline blood pressure levels (13,41). Extrapolation of these studies suggests that people with diabetes may also be more likely to benefit from intensive blood

Table 10.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (35)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	<ul style="list-style-type: none"> No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE (36)	11,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	<ul style="list-style-type: none"> Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (242)
HOT (37)	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	DBP target: ≤90 mmHg	<ul style="list-style-type: none"> In the overall trial, there was no cardiovascular benefit with more intensive targets In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (43)	9,361 participants without diabetes	SBP target: <120 mmHg Achieved (mean): 121.4 mmHg	SBP target: <140 mmHg Achieved (mean): 136.2 mmHg	<ul style="list-style-type: none"> Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) Intensive target reduced risk of death 27% Intensive therapy increased risks of electrolyte abnormalities and AKI
STEP (34)	8,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150 mmHg Achieved (mean): 135.3 mmHg	<ul style="list-style-type: none"> Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) Intensive target reduced risk of cardiovascular death 28% Intensive therapy increased risks of hypotension

ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; STEP, Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; T2D, type 2 diabetes.

pressure control when they have high absolute cardiovascular risk. This approach is consistent with guidelines from the American College of Cardiology and American Heart Association, which also advocate a blood pressure target of <130/80 mmHg for all people, with or without diabetes (20).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, acute kidney injury, and electrolyte abnormalities) should also be taken into account (33,35,42,43). Individuals with older age, CKD, and frailty have been shown to be at higher risk of adverse effects of intensive blood

pressure control (43). In addition, individuals with orthostatic hypotension, substantial comorbidity, functional limitations, or polypharmacy may be at high risk of adverse effects, and some patients may prefer higher blood pressure targets to enhance quality of life. However, in ACCORD BP, it was found that intensive

blood pressure lowering decreased the risk of cardiovascular events irrespective of baseline diastolic blood pressure in patients who also received standard glycemic control (44). Therefore, the presence of low diastolic blood pressure is not necessarily a contraindication to more intensive blood pressure management in the context of otherwise standard care.

Pregnancy and Antihypertensive Medications

There are few randomized controlled trials of antihypertensive therapy in pregnant individuals with diabetes. A 2014 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension that included 49 trials and over 4,700 women did not find any conclusive evidence for or against blood pressure treatment to reduce the risk of preeclampsia for the mother or effects on perinatal outcomes such as preterm birth, small-for-gestational-age infants, or fetal death (45). The Control of Hypertension in Pregnancy Study (CHIPS) (46) enrolled mostly women with chronic hypertension. In CHIPS, targeting a diastolic blood pressure of 85 mmHg during pregnancy was associated with reduced likelihood of developing accelerated maternal hypertension and no demonstrable adverse outcome for infants compared with targeting a higher diastolic blood pressure. The mean systolic blood pressure achieved in the more intensively treated group was 133.1 ± 0.5 mmHg, and the mean diastolic blood pressure achieved in that group was 85.3 ± 0.3 mmHg. A similar approach is supported by the International Society for the Study of Hypertension in Pregnancy, which specifically recommends use of antihypertensive therapy to maintain systolic blood pressure between 110 and 140 mmHg and diastolic blood pressure between 80 and 85 mmHg (47).

The more recent Chronic Hypertension and Pregnancy (CHAP) trial assigned pregnant individuals with mild chronic hypertension to antihypertensive medications to target a blood pressure goal of $<140/90$ mmHg (active treatment group) or to control treatment, in which antihypertensive therapy was withheld unless severe hypertension (systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 105 mmHg) developed (control group) (48). The primary outcome, a composite of preeclampsia with severe features,

medically indicated preterm birth at <35 weeks of gestation, placental abruption, or fetal/neonatal death, occurred in 30.2% of female participants in the active treatment group vs. 37.0% in the control group ($P < 0.001$). The mean systolic blood pressure between randomization and delivery was 129.5 mmHg in the active treatment group and 132.6 mmHg in the control group.

Current evidence supports controlling blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension but also to minimize impairment of fetal growth. During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), and spironolactone are contraindicated as they may cause fetal damage. Special consideration should be taken for individuals of childbearing potential, and people intending to become pregnant should switch from an ACE inhibitor/ARB or spironolactone to an alternative antihypertensive medication approved during pregnancy. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine, while hydralazine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (49). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (49,50). The American College of Obstetricians and Gynecologists also recommends that postpartum individuals with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and for 7–10 days postpartum. Long-term follow-up is recommended for these individuals as they have increased lifetime cardiovascular risk (51). See Section 15, “Management of Diabetes in Pregnancy,” for additional information.

Treatment Strategies

Lifestyle Intervention

Recommendation

10.6 For people with blood pressure $>120/80$ mmHg, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and

increasing potassium intake, moderation of alcohol intake, and increased physical activity. **A**

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. Lifestyle therapy consists of reducing excess body weight through caloric restriction (see Section 8, “Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes”), at least 150 min of moderate-intensity aerobic activity per week (see Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities”), restricting sodium intake ($<2,300$ mg/day), increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (52), and increasing activity levels (53) (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”).

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic >120 mmHg or diastolic >80 mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (Fig. 10.2) (53). A lifestyle therapy plan should be developed in collaboration with the patient and discussed as part of diabetes management. Use of internet or mobile-based digital platforms to reinforce healthy behaviors may be considered as a component of care, as these interventions have been found to enhance the efficacy of medical therapy for hypertension (54,55).

Pharmacologic Interventions

Recommendations

10.7 Individuals with confirmed office-based blood pressure $\geq 130/80$ mmHg qualify for initiation and titration of pharmacologic therapy to achieve

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

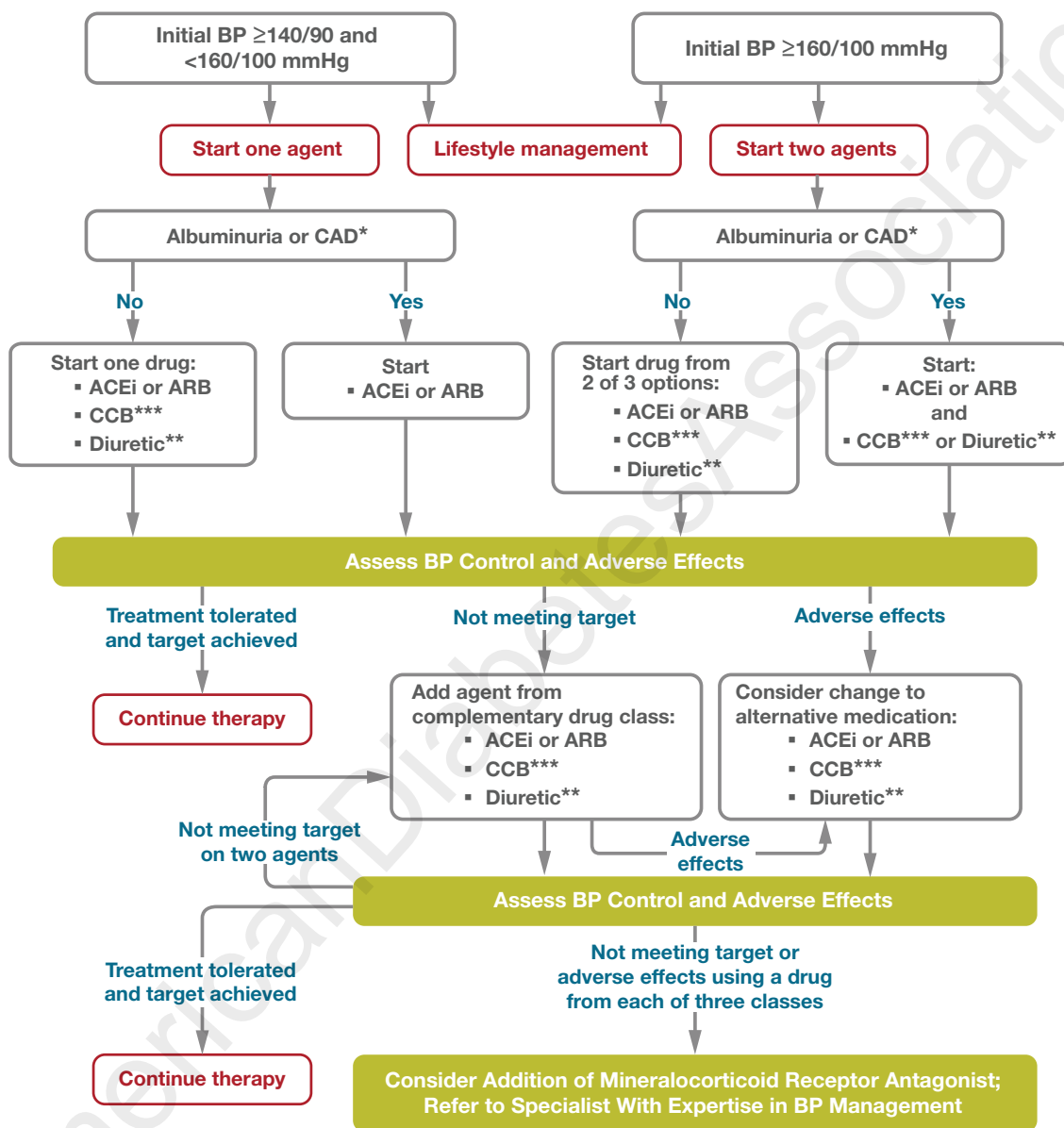


Figure 10.2—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for individuals with urine albumin-to-creatinine ratio ≥ 300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker (CCB). BP, blood pressure. Adapted from de Boer et al. (20).

10.8 the recommended blood pressure goal of $<130/80$ mmHg. **A** Individuals with confirmed office-based blood pressure $\geq 160/100$ mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs

10.9 or a single-pill combination of drugs demonstrated to reduce cardiovascular events in people with diabetes. **A** Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people

with diabetes. **A** ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. **A** **10.10** Multiple-drug therapy is generally required to achieve blood

pressure targets. However, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should not be used. **A**

10.11 An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in people with diabetes and urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine **A** or 30–299 mg/g creatinine. **B** If one class is not tolerated, the other should be substituted. **B**

10.12 For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. **B**

Initial Number of Antihypertensive Medications. Initial treatment for people with diabetes depends on the severity of hypertension (Fig. 10.2). Those with blood pressure between 130/80 mmHg and 160/100 mmHg may begin with a single drug. For patients with blood pressure $\geq 160/100$ mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended in order to more effectively achieve adequate blood pressure control (56–58). Single-pill antihypertensive combinations may improve medication taking in some patients (59).

Classes of Antihypertensive Medications. Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in people with diabetes: ACE inhibitors (60,61), ARBs (60,61), thiazide-like diuretics (62), or dihydropyridine calcium channel blockers (63). In people with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension (64–66). For patients with albuminuria (urine albumin-to-creatinine ratio [UACR] ≥ 30 mg/g), initial treatment should include an ACE inhibitor or ARB to

reduce the risk of progressive kidney disease (20) (Fig. 10.2). In patients receiving ACE inhibitor or ARB therapy, continuation of those medications as kidney function declines to estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² may provide cardiovascular benefit without significantly increasing the risk of end-stage kidney disease (67). In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection when compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (68). β -Blockers are indicated in the setting of prior MI, active angina, or HfrEF but have not been shown to reduce mortality as blood pressure-lowering agents in the absence of these conditions (28,69,70).

Multiple-Drug Therapy. Multiple-drug therapy is often required to achieve blood pressure targets (Fig. 10.2), particularly in the setting of diabetic kidney disease. However, the use of both ACE inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is contraindicated given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and acute kidney injury (AKI) (71–73). Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome therapeutic inertia in achieving blood pressure targets.

Bedtime Dosing. Although prior analyses of randomized clinical trials found a benefit to evening versus morning dosing of antihypertensive medications (74,75), these results have not been reproduced in subsequent trials. Therefore, preferential use of antihypertensives at bedtime is not recommended (76).

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors or ARBs can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (77,78). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (79). Therefore, serum creatinine and potassium should be monitored during treatment with an ACE inhibitor, ARB, or diuretic, particularly

among patients with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (77,78,80).

Resistant Hypertension

Recommendation

10.13 Individuals with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. **A**

Resistant hypertension is defined as blood pressure $\geq 140/90$ mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs with complementary mechanisms of action at adequate doses. Prior to diagnosing resistant hypertension, a number of other conditions should be excluded, including missed doses of antihypertensive medications, white coat hypertension, and secondary hypertension. In general, barriers to medication taking (such as cost and side effects) should be identified and addressed (Fig. 10.2). Mineralocorticoid receptor antagonists, including spironolactone and eplerenone, are effective for management of resistant hypertension in people with type 2 diabetes when added to existing treatment with an ACE inhibitor or ARB, thiazide-like diuretic, or dihydropyridine calcium channel blocker (81). In addition, mineralocorticoid receptor antagonists reduce albuminuria in people with diabetic nephropathy (82–84). However, adding a mineralocorticoid receptor antagonist to a regimen including an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these patients, and long-term outcome studies are needed to better evaluate the role of mineralocorticoid receptor antagonists in blood pressure management.

LIPID MANAGEMENT

Lifestyle Intervention

Recommendations

10.14 Lifestyle modification focusing on weight loss (if indicated);

application of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) eating pattern; reduction of saturated fat and *trans* fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease in people with diabetes. **A**

- 10.15** Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (≥ 150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (< 40 mg/dL [1.0 mmol/L] for men, < 50 mg/dL [1.3 mmol/L] for women). **C**

Lifestyle intervention, including weight loss in people with overweight or obesity (when appropriate) (85), increased physical activity, and medical nutrition therapy, allows some patients to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each patient's age, pharmacologic treatment, lipid levels, and medical conditions.

Recommendations should focus on application of a Mediterranean (83) or Dietary Approaches to Stop Hypertension (DASH) eating pattern, reducing saturated and *trans* fat intake and increasing plant stanols/sterols, n-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus) intake (86,87). Glycemic control may also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional nutrition information.

Ongoing Therapy and Monitoring With Lipid Panel

Recommendations

- 10.16** In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of

40 years, or more frequently if indicated. **E**

- 10.17** Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication taking. **E**

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in patients < 40 years of age. In younger people with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable. A lipid panel should also be obtained immediately before initiating statin therapy. Once a patient is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and on an individual basis (e.g., to monitor for medication taking and efficacy). If LDL cholesterol levels are not responding in spite of medication taking, clinical judgment is recommended to determine the need for and timing of lipid panels. In individual patients, the highly variable LDL cholesterol-lowering response seen with statins is poorly understood (88). Clinicians should attempt to find a dose or alternative statin that is tolerable if side effects occur. There is evidence for benefit from even extremely low, less than daily statin doses (89).

STATIN TREATMENT

Primary Prevention

Recommendations

- 10.18** For people with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. **A**
- 10.19** For people with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **C**

- 10.20** For people with diabetes aged 40–75 at higher cardiovascular risk, including those with one or more atherosclerotic cardiovascular disease risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by $\geq 50\%$ of baseline and to target an LDL cholesterol goal of < 70 mg/dL. **B**
- 10.21** For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple atherosclerotic cardiovascular disease risk factors and an LDL cholesterol ≥ 70 mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **C**

- 10.22** In adults with diabetes aged > 75 years already on statin therapy, it is reasonable to continue statin treatment. **B**
- 10.23** In adults with diabetes aged > 75 years, it may be reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks. **C**
- 10.24** Statin therapy is contraindicated in pregnancy. **B**

Secondary Prevention

Recommendations

- 10.25** For people of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. **A**
- 10.26** For people with diabetes and atherosclerotic cardiovascular disease, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of $\geq 50\%$ from baseline and an LDL cholesterol goal of < 55 mg/dL. Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. **B**
- 10.27** For individuals who do not tolerate the intended intensity, the maximum tolerated statin dose should be used. **E**

Table 10.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by $\geq 50\%$)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

*Once-daily dosing. XL, extended release.

Initiating Statin Therapy Based on Risk

People with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subjects with and without CHD (90,91). Subgroup analyses of people with diabetes in larger trials (92–96) and trials in people with diabetes (97,98) showed significant primary and secondary prevention of ASCVD events and CHD death in people with diabetes. Meta-analyses, including data from over 18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol (99). The cardiovascular benefit in this large meta-analysis did not depend on baseline LDL cholesterol levels and was linearly related to the LDL cholesterol reduction without a low threshold beyond which there was no benefit observed (99).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. **Table 10.2** shows the two statin dosing intensities that are recommended for use in clinical practice: high-intensity statin therapy will achieve approximately a $\geq 50\%$ reduction in LDL cholesterol, and moderate-intensity statin regimens achieve 30–49% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in people with diabetes but is sometimes the only dose of statin that a patient can tolerate. For patients who do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk

(known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD are convincing (100,101). The relative benefit of lipid-lowering therapy has been uniform across most subgroups tested (91,99), including subgroups that varied with respect to age and other risk factors.

Primary Prevention (People Without ASCVD)

For primary prevention, moderate-dose statin therapy is recommended for those aged ≥ 40 years (93,100,101), although high-intensity therapy should be considered in the context of additional ASCVD risk factors. The evidence is strong for people with diabetes aged 40–75 years, an age-group well represented in statin trials showing benefit. Since cardiovascular risk is enhanced in people with diabetes, as noted above, patients who also have multiple other coronary risk factors have increased risk, equivalent to that of those with ASCVD. Therefore, current guidelines recommend that in people with diabetes who are at higher cardiovascular risk, especially those with one or more ASCVD risk factors, high-intensity statin therapy should be prescribed to reduce LDL cholesterol by $\geq 50\%$ from baseline and to target an LDL cholesterol of <70 mg/dL (102–104). Since in clinical practice it is frequently difficult to ascertain the baseline LDL cholesterol level prior to statin therapy initiation, in those individuals, a focus on an LDL cholesterol target level of <70 mg/dL rather than the percent reduction in LDL cholesterol is recommended. In those individuals, it may also be reasonable to add ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy to maximum tolerated statin therapy if needed to reduce LDL cholesterol levels by $\geq 50\%$ and to achieve the recommended LDL cholesterol target of <70 mg/dL (14).

The evidence is lower for patients aged >75 years; relatively few older people with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants (91,98,99), and because older age confers higher risk, the absolute benefits are actually greater (91,105). Moderate-intensity statin therapy is recommended in people with diabetes who are ≥ 75 years of age. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of dose performed as needed. See Section 13, “Older Adults,” for more details on clinical considerations for this population.

Age <40 Years and/or Type 1 Diabetes. Very little clinical trial evidence exists for people with type 2 diabetes under the age of 40 years or for people with type 1 diabetes of any age. For pediatric recommendations, see Section 14, “Children and Adolescents.” In the Heart Protection Study (lower age limit 40 years), the subgroup of ~ 600 people with type 1 diabetes had a proportionately similar, although not statistically significant, reduction in risk to that in people with type 2 diabetes (93). Even though the data are not definitive, similar statin treatment approaches should be considered for people with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Patients <40 years of age have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and suffering an MI, stroke, or cardiovascular death is high. For people who are <40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the patient and health care professional discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy. Please refer to “Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association” (106) for additional discussion.

Secondary Prevention (People With ASCVD)

Because cardiovascular event rates are increased in people with diabetes and

established ASCVD, intensive therapy is indicated and has been shown to be of benefit in multiple large meta-analyses and randomized cardiovascular outcomes trials (91,99,105,107,108). High-intensity statin therapy is recommended for all people with diabetes and ASCVD to target an LDL cholesterol reduction of $\geq 50\%$ from baseline and an LDL cholesterol goal of < 55 mg/dL. Based on the evidence discussed below, addition of ezetimibe or a PCSK9 inhibitor is recommended if this goal is not achieved on maximum tolerated statin therapy. These recommendations are based on the observation that high-intensity versus moderate-intensity statin therapy reduces cardiovascular event rates in high-risk individuals with established cardiovascular disease in randomized trials (95,107). In addition, the Cholesterol Treatment Trialists' Collaboration involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins (99), showed a 21% reduction in major cardiovascular events in people with diabetes for every 39 mg/dL of LDL cholesterol lowering, irrespective of baseline LDL cholesterol or patient characteristics (99). However, the best evidence to support lower LDL cholesterol targets in people with diabetes and established cardiovascular disease derives from multiple large randomized trials investigating the benefits of adding nonstatin agents to statin therapy. As discussed in detail below, these include combination treatment with statins and ezetimibe (105,109) or PCSK9 inhibitors (108,110–112). Each trial found a significant benefit in the reduction of ASCVD events that was directly related to the degree of further LDL cholesterol lowering. These large trials included a significant number of participants with diabetes and prespecified analyses on cardiovascular outcomes in people with and without diabetes (109,111,112). The decision to add a nonstatin agent should be made following a clinician-patient discussion about the net benefit, safety, and cost of combination therapy.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial in 18,144 patients comparing the addition of ezetimibe to simvastatin

therapy versus simvastatin alone (105). Individuals were ≥ 50 years of age, had experienced a recent acute coronary syndrome (ACS) and were treated for an average of 6 years. Overall, the addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events (atherosclerotic cardiovascular events), with the degree of benefit being directly proportional to the change in LDL cholesterol, which was 70 mg/dL in the statin group on average and 54 mg/dL in the combination group (105). In those with diabetes (27% of participants), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45% cumulative incidence at 7 years) and a relative risk reduction of 14% (hazard ratio [HR] 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (109).

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the PCSK9 inhibitors evolocumab and alirocumab to maximum tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36 to 59%. These agents have been approved as adjunctive therapy for individuals with ASCVD or familial hypercholesterolemia who are receiving maximum tolerated statin therapy but require additional lowering of LDL cholesterol (113,114). No cardiovascular outcome trials have been performed to assess whether PCSK9 inhibitor therapy reduces ASCVD event rates in individuals without established cardiovascular disease (primary prevention).

The effects of PCSK9 inhibition on ASCVD outcomes was investigated in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, which enrolled 27,564 individuals with prior ASCVD and an additional high-risk feature who were receiving their maximum tolerated statin therapy (two-thirds were on high-intensity statin) but who still had LDL cholesterol ≥ 70 mg/dL or non-HDL cholesterol ≥ 100 mg/dL (108). Patients were randomized to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month based on patient

preference) versus placebo. Evolocumab reduced LDL cholesterol by 59% from a median of 92 to 30 mg/dL in the treatment arm.

During the median follow-up of 2.2 years, the composite outcome of cardiovascular death, MI, stroke, hospitalization for angina, or revascularization occurred in 11.3% vs. 9.8% of the placebo and evolocumab groups, respectively, representing a 15% relative risk reduction ($P < 0.001$). The combined end point of cardiovascular death, MI, or stroke was reduced by 20%, from 7.4 to 5.9% ($P < 0.001$). Evolocumab therapy also significantly reduced all strokes (1.5% vs. 1.9%; HR 0.79 [95% CI 0.66–0.95]; $P = 0.01$) and ischemic stroke (1.2% vs. 1.6%; HR 0.75 [95% CI 0.62–0.92]; $P = 0.005$) in the total population, with findings being consistent in individuals with or without a history of ischemic stroke at baseline (115). Importantly, similar benefits were seen in a prespecified subgroup of people with diabetes, comprising 11,031 patients (40% of the trial) (112).

In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 18,924 patients (28.8% of whom had diabetes) with recent acute coronary syndrome were randomized to the PCSK9 inhibitor alirocumab or placebo every 2 weeks in addition to maximum tolerated statin therapy, with alirocumab dosing titrated between 75 and 150 mg to achieve LDL cholesterol levels between 25 and 50 mg/dL (110). Over a median follow-up of 2.8 years, a composite primary end point (comprising death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospital admission) occurred in 903 patients (9.5%) in the alirocumab group and in 1,052 patients (11.1%) in the placebo group (HR 0.85 [95% CI 0.78–0.93]; $P < 0.001$). Combination therapy with alirocumab plus statin therapy resulted in a greater absolute reduction in the incidence of the primary end point in people with diabetes (2.3% [95% CI 0.4–4.2]) than in those with prediabetes (1.2% [0.0–2.4]) or normoglycemia (1.2% [–0.3 to 2.7]) (111).

In addition to monoclonal antibodies targeting PCSK9, the siRNA inclisiran has been developed and has recently become available in the U.S. In the Inclisiran for

Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10) and Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11) trials (116), individuals with established cardiovascular disease or ASCVD risk equivalent were randomized to receive inclisiran or placebo. Inclisiran allows less frequent administration compared with monoclonal antibodies and was administered on day 1, on day 90, and every 6 months in these trials. In the ORION-10 trial, 47.5% of patients in the inclisiran group and 42.4% in the placebo group had diabetes; in the ORION-11 trial, 36.5% of patients in the inclisiran group and 33.7% in the placebo group had diabetes. The coprimary end point of placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 was 52.3% in the ORION-10 trial and 49.9% in the ORION-11 trial. In an exploratory analysis, the prespecified cardiovascular end point, defined as a cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal MI, or stroke, occurred in 7.4% of the inclisiran group and 10.2% of the placebo group in the ORION-10 trial and in 7.8% of the inclisiran group and 10.3% of the placebo group in the ORION-11 trial. A cardiovascular outcome trial using inclisiran in people with established cardiovascular disease is currently ongoing (117).

Statins and Bempedoic Acid

Bempedoic acid is a novel LDL cholesterol-lowering agent that is indicated as an adjunct to diet and maximum tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of LDL cholesterol. A pooled analysis suggests that bempedoic acid therapy lowers LDL cholesterol levels by about 23% compared with placebo (118). At this time, there are no completed trials demonstrating a cardiovascular outcomes benefit to use of this medication; however, this agent may be considered for patients who cannot use or tolerate other evidence-based LDL cholesterol-lowering approaches, or for whom those other therapies are inadequately effective (119).

Treatment of Other Lipoprotein Fractions or Targets

Recommendations

- 10.28** For individuals with fasting triglyceride levels ≥ 500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**
- 10.29** In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. **C**
- 10.30** In individuals with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **A**

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including weight loss and abstinence from alcohol (120). Severe hypertriglyceridemia (fasting triglycerides ≥ 500 mg/dL and especially $>1,000$ mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis. Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see statin treatment). In people with moderate hypertriglyceridemia, lifestyle interventions, treatment of secondary factors, and avoidance of medications that might raise triglycerides are recommended.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) enrolled 8,179 adults receiving statin therapy with moderately elevated triglycerides (135–499 mg/dL, median baseline of 216 mg/dL) who had either established cardiovascular disease (secondary prevention cohort) or diabetes plus at least one other cardiovascular risk

factor (primary prevention cohort) (121). Patients were randomized to icosapent ethyl 4 g/day (2 g twice daily with food) versus placebo. The trial met its primary end point, demonstrating a 25% relative risk reduction ($P < 0.001$) for the primary end point composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. This reduction in risk was seen in people with or without diabetes at baseline. The composite of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 26% ($P < 0.001$). Additional ischemic end points were significantly lower in the icosapent ethyl group than in the placebo group, including cardiovascular death, which was reduced by 20% ($P = 0.03$). The proportions of patients experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups. It should be noted that data are lacking with other n-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products (121). As an example, the addition of 4 g per day of a carboxylic acid formulation of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n-3 carboxylic acid) to statin therapy in patients with atherogenic dyslipidemia and high cardiovascular risk, 70% of whom had diabetes, did not reduce the risk of major adverse cardiovascular events compared with the inert comparator of corn oil (122).

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in people with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy (123). In a large trial in people with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (124).

Other Combination Therapy

Recommendations

- 10.31** Statin plus fibrate combination therapy has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**
- 10.32** Statin plus niacin combination therapy has not been shown

to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

Statin and Fibrate Combination Therapy

Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate) (125).

In the ACCORD study, in people with type 2 diabetes who were at high risk for ASCVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared with simvastatin alone. Prespecified subgroup analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥ 204 mg/dL (2.3 mmol/L) and an HDL cholesterol level ≤ 34 mg/dL (0.9 mmol/L) (126).

Statin and Niacin Combination Therapy

The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized over 3,000 people (about one-third with diabetes) with established ASCVD, LDL cholesterol levels < 180 mg/dL [4.7 mmol/L], low HDL cholesterol levels (men < 40 mg/dL [1.0 mmol/L] and women < 50 mg/dL [1.3 mmol/L]), and triglyceride levels of 150–400 mg/dL (1.7–4.5 mmol/L) to statin therapy plus extended-release niacin or placebo. The trial was halted early due to lack of efficacy on the primary ASCVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (127).

The much larger Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial also failed to show a benefit of adding niacin to background statin

therapy (128). A total of 25,673 individuals with prior vascular disease were randomized to receive 2 g of extended-release niacin and 40 mg of laropiprant (an antagonist of the prostaglandin D2 receptor DP1 that has been shown to improve participation in niacin therapy) versus a matching placebo daily and followed for a median follow-up period of 3.9 years. There was no significant difference in the rate of coronary death, MI, stroke, or coronary revascularization with the addition of niacin–laropiprant versus placebo (13.2% vs. 13.7%; rate ratio 0.96; $P = 0.29$). Niacin–laropiprant was associated with an increased incidence of new-onset diabetes (absolute excess, 1.3 percentage points; $P < 0.001$) and disturbances in diabetes management among those with diabetes. In addition, there was an increase in serious adverse events associated with the gastrointestinal system, musculoskeletal system, skin, and, unexpectedly, infection and bleeding.

Therefore, combination therapy with a statin and niacin is not recommended given the lack of efficacy on major ASCVD outcomes and increased side effects.

Diabetes Risk With Statin Use

Several studies have reported a modestly increased risk of incident diabetes with statin use (129,130), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (131). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin developed diabetes) (131). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 patients (130).

Lipid-Lowering Agents and Cognitive Function

Although concerns regarding a potential adverse impact of lipid-lowering agents on cognitive function have been raised,

several lines of evidence point against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement (132). First, there are three large randomized trials of statin versus placebo where specific cognitive tests were performed, and no differences were seen between statin and placebo (133–136). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (105) or PCSK9 inhibitors (108,137) to statin therapy, including among patients treated to very low LDL cholesterol levels. In addition, the most recent systematic review of the U.S. Food and Drug Administration's (FDA's) postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data do not reveal an adverse effect of statins on cognition (138). Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD (138).

ANTIPLATELET AGENTS

Recommendations

- 10.33** Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**
- 10.34** For individuals with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- 10.35** Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome and may have benefits beyond this period. **A**
- 10.36** Long-term treatment with dual antiplatelet therapy should be considered for individuals with prior coronary intervention, high ischemic risk, and low bleeding risk to prevent major adverse cardiovascular events. **A**
- 10.37** Combination therapy with aspirin plus low-dose rivaroxaban

should be considered for individuals with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**

10.38 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. **A**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention) and is strongly recommended. In primary prevention, however, among patients with no previous cardiovascular events, its net benefit is more controversial (129,140).

Previous randomized controlled trials of aspirin specifically in people with diabetes failed to consistently show a significant reduction in overall ASCVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes, although some sex differences were suggested (141–143).

The Antithrombotic Trialists' Collaboration published an individual patient-level meta-analysis (139) of the six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (relative risk 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (relative risk 0.95 [95% CI 0.78–1.15]) or total stroke.

Most recently, the ASCEND (A Study of Cardiovascular Events in Diabetes) trial randomized 15,480 people with diabetes but no evident cardiovascular disease to aspirin 100 mg daily or placebo (144). The primary efficacy end point was vascular death, MI, or stroke or transient ischemic attack. The primary safety outcome was major bleeding (i.e., intracranial hemorrhage, sight-threatening bleeding in the eye, gastrointestinal

bleeding, or other serious bleeding). During a mean follow-up of 7.4 years, there was a significant 12% reduction in the primary efficacy end point (8.5% vs. 9.6%; $P = 0.01$). In contrast, major bleeding was significantly increased from 3.2 to 4.1% in the aspirin group (rate ratio 1.29; $P = 0.003$), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There were no significant differences by sex, weight, or duration of diabetes or other baseline factors including ASCVD risk score.

Two other large, randomized trials of aspirin for primary prevention, in people without diabetes (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) (145) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (146), which included 11% with diabetes, found no benefit of aspirin on the primary efficacy end point and an increased risk of bleeding. In ARRIVE, with 12,546 patients over a period of 60 months follow-up, the primary end point occurred in 4.29% vs. 4.48% of patients in the aspirin versus placebo groups (HR 0.96 [95% CI 0.81–1.13]; $P = 0.60$). Gastrointestinal bleeding events (characterized as mild) occurred in 0.97% of patients in the aspirin group vs. 0.46% in the placebo group (HR 2.11 [95% CI 1.36–3.28]; $P = 0.0007$). In ASPREE, including 19,114 individuals, for cardiovascular disease (fatal CHD, MI, stroke, or hospitalization for heart failure) after a median of 4.7 years of follow-up, the rates per 1,000 person-years were 10.7 vs. 11.3 events in aspirin vs. placebo groups (HR 0.95 [95% CI 0.83–1.08]). The rate of major hemorrhage per 1,000 person-years was 8.6 events vs. 6.2 events, respectively (HR 1.38 [95% CI 1.18–1.62]; $P < 0.001$).

Thus, aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk. The main adverse effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1,000 per year in real-world settings. However, for adults with ASCVD risk $>1\%$ per year, the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (147).

Recommendations for using aspirin as primary prevention include both men and women aged ≥ 50 years with diabetes and at least one additional major risk

factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease) (148–151). Noninvasive imaging techniques such as coronary calcium scoring may potentially help further tailor aspirin therapy, particularly in those at low risk (152,153). For people >70 years of age (with or without diabetes), the balance appears to have greater risk than benefit (144,146). Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk, but generally not in older adults. Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.

For people with documented ASCVD, use of aspirin for secondary prevention has far greater benefit than risk; for this indication, aspirin is still recommended (139).

Aspirin Use in People <50 Years of Age

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors) until further research is available. Patients' willingness to undergo long-term aspirin therapy should also be considered (154). Aspirin use in patients aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving people with diabetes ranged from 50 mg to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose but using the lowest possible dose may help to reduce side effects (155). In the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial of individuals with established cardiovascular disease, 38% of whom had

diabetes, there were no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily (156). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from people with diabetes have altered function, it is unclear what, if any, effect that finding has on the required dose of aspirin for cardioprotective effects in people with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A₂ and thus are not sensitive to the effects of aspirin (157). “Aspirin resistance” has been described in people with diabetes when measured by a variety of *ex vivo* and *in vitro* methods (platelet aggregometry, measurement of thromboxane B₂) (158), but other studies suggest no impairment in aspirin response among people with diabetes (159). A trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (160); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. Another meta-analysis raised the hypothesis that low-dose aspirin efficacy is reduced in those weighing >70 kg (161); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would thus not validate this suggested hypothesis (144). It appears that 75–162 mg/day is optimal.

Indications for P2Y₁₂ Receptor Antagonist Use

A P2Y₁₂ receptor antagonist in combination with aspirin is reasonable for at least 1 year in patients following an ACS and may have benefits beyond this period. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (162). In people with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events including cardiovascular and CHD death (163). Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in people with diabetes and stable coronary artery disease (164,165). However, a higher incidence of major bleeding,

including intracranial hemorrhage, was noted with dual antiplatelet therapy. The net clinical benefit (ischemic benefit vs. bleeding risk) was improved with ticagrelor therapy in the large prespecified subgroup of patients with history of percutaneous coronary intervention, while no net benefit was seen in patients without prior percutaneous coronary intervention (165). However, early aspirin discontinuation compared with continued dual antiplatelet therapy after coronary stenting may reduce the risk of bleeding without a corresponding increase in the risks of mortality and ischemic events, as shown in a prespecified analysis of people with diabetes enrolled in the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial and a recent meta-analysis (166,167).

Combination Antiplatelet and Anticoagulation Therapy

Combination therapy with aspirin plus low dose rivaroxaban may be considered for people with stable coronary and/or peripheral artery disease to prevent major adverse limb and cardiovascular complications. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial of 27,395 individuals with established coronary artery disease and/or peripheral artery disease, aspirin plus rivaroxaban 2.5 mg twice daily was superior to aspirin plus placebo in the reduction of cardiovascular ischemic events including major adverse limb events. The absolute benefits of combination therapy appeared larger in people with diabetes, who comprised 10,341 of the trial participants (168,169). A similar treatment strategy was evaluated in the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial (170), in which 6,564 individuals with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban 2.5 mg twice daily plus aspirin or placebo plus aspirin. Rivaroxaban treatment in this group of patients was also associated with a significantly lower incidence of ischemic cardiovascular events, including major adverse limb events. However, an increased risk of major bleeding was noted

with rivaroxaban added to aspirin treatment in both COMPASS and VOYAGER PAD.

The risks and benefits of dual antiplatelet or antiplatelet plus anticoagulant treatment strategies should be thoroughly discussed with eligible patients, and shared decision-making should be used to determine an individually appropriate treatment approach. This field of cardiovascular risk reduction is evolving rapidly, as are the definitions of optimal care for patients with differing types and circumstances of cardiovascular complications.

CARDIOVASCULAR DISEASE

Screening

Recommendations

10.39 In asymptomatic individuals, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. **A**

10.40 Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). **E**

Treatment

Recommendations

10.41 Among people with type 2 diabetes who have established atherosclerotic cardiovascular disease or established kidney disease, a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Table 10.3B** and **Table 10.3C**) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. **A**

Table 10.3A—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: DPP-4 inhibitors

	SAVOR-TIMI 53 (224) (n = 16,492)	EXAMINE (235) (n = 5,380)	TECOS (226) (n = 14,671)	CARMELINA (193,236) (n = 6,979)	CAROLINA (193,237) (n = 6,042)
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo	Linagliptin/placebo	Linagliptin/ glimepiride
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and high CV and renal risk	Type 2 diabetes and high CV risk
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	6.5–10.0	6.5–8.5
Age (years)†	65.1	61.0	65.4	65.8	64.0
Race (% White)	75.2	72.7	67.9	80.2	73.0
Sex (% male)	66.9	67.9	70.7	62.9	60.0
Diabetes duration (years)†	10.3	7.1	11.6	14.7	6.2
Median follow-up (years)	2.1	1.5	3.0	2.2	6.3
Statin use (%)	78	91	80	71.8	64.1
Metformin use (%)	70	66	82	54.8	82.5
Prior CVD/CHF (%)	78/13	100/28	74/18	57/26.8	34.5/4.5
Mean baseline A1C (%)	8.0	8.0	7.2	7.9	7.2
Mean difference in A1C between groups at end of treatment (%)	−0.3‡	−0.3‡	−0.3‡	−0.36‡	0
Year started/ reported	2010/2013	2009/2013	2008/2015	2013/2018	2010/2019
Primary outcome§	3-point MACE 1.00 (0.89–1.12)	3-point MACE 0.96 (95% UL ≤1.16)	4-point MACE 0.98 (0.89–1.08)	3-point MACE 1.02 (0.89–1.17)	3-point MACE 0.98 (0.84–1.14)
Key secondary outcome§	Expanded MACE 1.02 (0.94–1.11)	4-point MACE 0.95 (95% UL ≤1.14)	3-point MACE 0.99 (0.89–1.10)	Kidney composite (ESRD, sustained ≥40% decrease in eGFR, or renal death) 1.04 (0.89–1.22)	4-point MACE 0.99 (0.86–1.14)
Cardiovascular death§	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.96 (0.81–1.14)	1.00 (0.81–1.24)
MI§	0.95 (0.80–1.12)	1.08 (0.88–1.33)	0.95 (0.81–1.11)	1.12 (0.90–1.40)	1.03 (0.82–1.29)
Stroke§	1.11 (0.88–1.39)	0.91 (0.55–1.50)	0.97 (0.79–1.19)	0.91 (0.67–1.23)	0.86 (0.66–1.12)
HF hospitalization§	1.27 (1.07–1.51)	1.19 (0.90–1.58)	1.00 (0.83–1.20)	0.90 (0.74–1.08)	1.21 (0.92–1.59)
Unstable angina hospitalization§	1.19 (0.89–1.60)	0.90 (0.60–1.37)	0.90 (0.70–1.16)	0.87 (0.57–1.31)	1.07 (0.74–1.54)
All-cause mortality§	1.11 (0.96–1.27)	0.88 (0.71–1.09)	1.01 (0.90–1.14)	0.98 (0.84–1.13)	0.91 (0.78–1.06)
Worsening nephropathy§	1.08 (0.88–1.32)	—	—	Kidney composite (see above)	—

—, not assessed/reported; ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; UL, upper limit. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. †Age was reported as means in all trials except EXAMINE, which reported medians; diabetes duration was reported as means in all trials except SAVOR-TIMI 53 and EXAMINE, which reported medians. ‡Significant difference in A1C between groups ($P < 0.05$). §Outcomes reported as hazard ratio (95% CI). ||Worsening nephropathy is defined as a doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L) in SAVOR-TIMI 53. Worsening nephropathy was a prespecified exploratory adjudicated outcome in SAVOR-TIMI 53.

Table 10.3B—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists

Intervention	ELIXA (208) (n = 6,068)	LEADER (203) (n = 9,340)	SUSTAIN-6 (204)* (n = 3,297)	EXSCEL (209) (n = 14,752)	REWIND (207) (n = 9,901)	PIONEER-6 (205) (n = 3,183)
	Lixisenatide/placebo	Liraglutide/placebo	Semaglutide s.c. injection/placebo	Exenatide QW/placebo	Dulaglutide/placebo	Semaglutide oral/placebo
Main inclusion criteria	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes and prior ASCVD event or risk factors for ASCVD	Type 2 diabetes and high CV risk (age of ≥50 years with established CVD or CKD, or age of ≥60 years with CV risk factors only)
A1C inclusion criteria (%)	5.5–11.0	≥7.0	≥7.0	6.5–10.0	≤9.5	None
Age (years)†	60.3	64.3	64.6	62	66.2	66
Race (% White)	75.2	77.5	83.0	75.8	75.7	72.3
Sex (% male)	69.3	64.3	60.7	62	53.7	68.4
Diabetes duration (years)†	9.3	12.8	13.9	12	10.5	14.9
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3
Statin use (%)	93	72	73	74	66	85.2 (all lipid-lowering)
Metformin use (%)	66	76	73	77	81	77.4
Prior CVD/CHF (%)	100/22	81/18	60/24	73.1/16.2	32/9	84.7/12.2
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	7.4	8.2
Mean difference in A1C between groups at end of treatment (%)	−0.3±‡	−0.4‡	−0.7 or −1.0 [§]	−0.53± [¶]	−0.61±	−0.7
Year started/reported	2010/2015	2010/2016	2013/2016	2010/2017	2011/2019	2017/2019
Primary outcome§	4-point MACE 1.02 (0.89–1.17)	3-point MACE 0.87 (0.78–0.97)	3-point MACE 0.74 (0.58–0.95)	3-point MACE 0.91 (0.83–1.00)	3-point MACE 0.88 (0.79–0.99)	3-point MACE 0.79 (0.57–1.11)

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Table 10.3B—Continued

Key secondary outcome§	ELIXA (208) (n = 6,068) Expanded MACE 1.02 (0.90–1.11)	LEADER (203) (n = 9,340) Expanded MACE 0.88 (0.81–0.96)	SUSTAIN-6 (204)* (n = 3,297) Expanded MACE 0.74 (0.62–0.89)	EXSCEL (209) (n = 14,752) Individual components of MACE (see below)	REWIND (207) (n = 9,901) Composite microvascular outcome (eye or renal outcome) 0.87 (0.79–0.95)	PIONEER-6 (205) (n = 3,183) Expanded MACE or HF hospitalization 0.82 (0.61–1.10)
Cardiovascular death§	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
MI§	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79–1.15)	1.18 (0.73–1.90)
Stroke§	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.76 (0.61–0.95)	0.74 (0.35–1.57)
HF hospitalization§	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Unstable angina hospitalization§	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	1.14 (0.84–1.54)	1.56 (0.60–4.01)
All-cause mortality§	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
Worsening nephropathy§	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.85 (0.77–0.93)	—

—, not assessed/reported; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. *Powered to rule out a hazard ratio of 1.8; superiority hypothesis not prespecified. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EXSCEL, which reported medians. ‡Significant difference in A1C between groups ($P < 0.05$). ††AIC change of 0.66% with 0.5 mg and 1.05% with 1 mg dose of semaglutide. ‡‡Outcomes reported as hazard ratio (95% CI). ||Worsening nephropathy is defined as the new onset of urine albumin-to-creatinine ratio >300 mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of <45 mL/min/1.73 m², the need for continuous renal replacement therapy, or death from renal disease in LEADER and SUSTAIN-6 and as new macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy in REWIND. Worsening nephropathy was a prespecified exploratory adjudicated outcome in LEADER, SUSTAIN-6, and REWIND.

10.41a In people with type 2 diabetes and established atherosclerotic cardiovascular disease, multiple atherosclerotic cardiovascular disease risk factors, or diabetic kidney disease, a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. **A**

10.41b In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. **A**

10.41c In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, combined therapy with a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit and a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit may be considered for additive reduction in the risk of adverse cardiovascular and kidney events. **A**

10.42a In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. **A**

10.42b In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to improve

- symptoms, physical limitations, and quality of life. **A**
- 10.43** For people with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or angiotensin receptor blocker, addition of finerenone is recommended to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression. **A**
- 10.44** In people with known atherosclerotic cardiovascular disease, particularly coronary artery disease, ACE inhibitor or angiotensin receptor blocker therapy is recommended to reduce the risk of cardiovascular events. **A**
- 10.45** In people with prior myocardial infarction, β -blockers should be continued for 3 years after the event. **B**
- 10.46** Treatment of individuals with heart failure with reduced ejection fraction should include a β -blocker with proven cardiovascular outcomes benefit, unless otherwise contraindicated. **A**
- 10.47** In people with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if estimated glomerular filtration rate remains >30 mL/min/ 1.73 m² but should be avoided in unstable or hospitalized individuals with heart failure. **B**

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with 1) typical or atypical cardiac symptoms and 2) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥ 40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress

testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

Screening Asymptomatic Patients

The screening of asymptomatic patients with high ASCVD risk is not recommended (171), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides benefit similar to invasive revascularization (172,173). There is also some evidence that silent ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies (174). In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in people with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (175–177). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic people with type 2 diabetes and normal ECGs (178). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, indiscriminate screening is not considered cost-effective. Studies have found that a risk factor-based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which people with type 2 diabetes will have silent ischemia on screening tests (179,180).

Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven in asymptomatic people with diabetes, though research is ongoing. Since asymptomatic people with diabetes with higher coronary disease burden have more future cardiac events (175,181,182), these additional imaging tests may provide reasoning for treatment intensification and/or guide informed patient decision-making and willingness for medication initiation and participation.

While coronary artery screening methods, such as calcium scoring, may improve

cardiovascular risk assessment in people with type 2 diabetes (183), their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Lifestyle and Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Action for Health in Diabetes (Look AHEAD) trial may be considered for improving glucose control, fitness, and some ASCVD risk factors (184). Patients at increased ASCVD risk should receive statin, ACE inhibitor, or ARB therapy if the patient has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class. Clear benefit exists for ACE inhibitor or ARB therapy in people with diabetic kidney disease or hypertension, and these agents are recommended for hypertension management in people with known ASCVD (particularly coronary artery disease) (65,66,185). People with type 2 diabetes and CKD should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of CKD progression (186–189). β -Blockers should be used in individuals with active angina or HFrEF and for 3 years after MI in those with preserved left ventricular function (190,191).

Glucose-Lowering Therapies and Cardiovascular Outcomes

In 2008, the FDA issued a guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment for type 2 diabetes amid concerns of increased cardiovascular risk (192). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular and renal outcomes in people with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease (**Table 10.3A**, **Table 10.3B**, and **Table 10.3C**). An expanded review of the effects of glucose-lowering and other therapies

in people with CKD is included in Section 11, "Chronic Kidney Disease and Risk Management."

Cardiovascular outcomes trials of dipeptidyl peptidase 4 (DPP-4) inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. In addition, the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimpiride in Type 2 Diabetes) study demonstrated noninferiority between a DPP-4 inhibitor, linagliptin, and a sulfonyleurea, glimepiride, on cardiovascular outcomes despite lower rates of hypoglycemia in the linagliptin treatment group (193). However, results from other new agents have provided a mix of results.

SGLT2 Inhibitor Trials

The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, an SGLT2 inhibitor, versus placebo on cardiovascular outcomes in 7,020 people with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group, HR in the empagliflozin group 0.86 [95% CI 0.74–0.99]; $P = 0.04$ for superiority) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%, HR 0.62 [95% CI 0.49–0.77]; $P < 0.001$) (8).

Two large outcomes trials of the SGLT2 inhibitor canagliflozin have been conducted that separately assessed 1) the cardiovascular effects of treatment in patients at high risk for major adverse cardiovascular events (9) and 2) the impact of canagliflozin therapy on cardiorenal outcomes in people with diabetes-related CKD (194). First, the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program integrated data from two trials. The CANVAS trial that started in 2009 was partially unblinded prior to completion because of the need to file interim cardiovascular outcomes data for regulatory approval of the drug (195). Thereafter, the post approval CANVAS-Renal (CANVAS-R) trial was started in 2014. Combining both

trials, 10,142 participants with type 2 diabetes were randomized to canagliflozin or placebo and were followed for an average 3.6 years. The mean age of patients was 63 years, and 66% had a history of cardiovascular disease. The combined analysis of the two trials found that canagliflozin significantly reduced the composite outcome of cardiovascular death, MI, or stroke versus placebo (occurring in 26.9 vs. 31.5 participants per 1,000 patient-years; HR 0.86 [95% CI 0.75–0.97]). The specific estimates for canagliflozin versus placebo on the primary composite cardiovascular outcome were HR 0.88 (95% CI 0.75–1.03) for the CANVAS trial and 0.82 (0.66–1.01) for CANVAS-R, with no heterogeneity found between trials. Of note, there was an increased risk of lower-limb amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 patient-years; HR 1.97 [95% CI 1.41–2.75]) (9). Second, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CRENDENCE) trial randomized 4,401 people with type 2 diabetes and chronic diabetes-related kidney disease (UACR >300 mg/g and eGFR 30 to <90 mL/min/1.73 m²) to canagliflozin 100 mg daily or placebo (194). The primary outcome was a composite of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes. The trial was stopped early due to conclusive evidence of efficacy identified during a prespecified interim analysis with no unexpected safety signals. The risk of the primary composite outcome was 30% lower with canagliflozin treatment when compared with placebo (HR 0.70 [95% CI 0.59–0.82]). Moreover, it reduced the prespecified end point of end-stage kidney disease alone by 32% (HR 0.68 [95% CI 0.54–0.86]). Canagliflozin was additionally found to have a lower risk of the composite of cardiovascular death, MI, or stroke (HR 0.80 [95% CI 0.67–0.95]), as well as lower risk of hospitalizations for heart failure (HR 0.61 [95% CI 0.47–0.80]) and of the composite of cardiovascular death or hospitalization for heart failure (HR 0.69 [95% CI 0.57–0.83]). In terms of safety, no significant increase in lower-limb amputations, fractures, acute kidney injury, or hyperkalemia was noted for canagliflozin relative to placebo in CRENDENCE. An increased risk for diabetic ketoacidosis was noted, however, with 2.2 and 0.2 events per 1,000 patient-years noted

in the canagliflozin and placebo groups, respectively (HR 10.80 [95% CI 1.39–83.65]) (194).

The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial was another randomized, double-blind trial that assessed the effects of dapagliflozin versus placebo on cardiovascular and renal outcomes in 17,160 people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD (196). Study participants had a mean age of 64 years, with ~40% of study participants having established ASCVD at baseline—a characteristic of this trial that differs from other large cardiovascular trials where a majority of participants had established cardiovascular disease. DECLARE-TIMI 58 met the prespecified criteria for noninferiority to placebo with respect to major adverse cardiovascular events but did not show a lower rate of major adverse cardiovascular events when compared with placebo (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93 [95% CI 0.84–1.03]; $P = 0.17$). A lower rate of cardiovascular death or hospitalization for heart failure was noted (4.9% vs. 5.8%; HR 0.83 [95% CI 0.73–0.95]; $P = 0.005$), which reflected a lower rate of hospitalization for heart failure (HR 0.73 [95% CI 0.61–0.88]). No difference was seen in cardiovascular death between groups.

In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial (197), 4,304 individuals with CKD (UACR 200–5,000 mg/g and eGFR 25–75 mL/min/1.73 m²), with or without diabetes, were randomized to dapagliflozin 10 mg daily or placebo. The primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Over a median follow-up period of 2.4 years, a primary outcome event occurred in 9.2% of participants in the dapagliflozin group and 14.5% of those in the placebo group. The risk of the primary composite outcome was significantly lower with dapagliflozin therapy compared with placebo (HR 0.61 [95% CI 0.51–0.72]), as were the risks for a renal composite outcome of sustained decline in eGFR of at least 50%, endstage kidney disease, or death from renal causes (HR 0.56 [95% CI 0.45–0.68]), and a composite of cardiovascular death

Table 10.3C—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

Intervention	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 10,142)	DECLARE-TIMI 58 (196) (n = 17,160)	CREDESCENCE (194) (n = 4,401)	DAPA-CKD (197,239) (n = 4,304; 2,906 with diabetes)	VERTIS CV (201,240) (n = 8,246)	DAPA-HF (11) (n = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (200) (n = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (189,241) (n = 5,988; 2,938 with diabetes)	DELIVER (199) (n = 6,263; 2,807 with diabetes)
	Empagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Ertugliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo*	Empagliflozin/placebo	Dapagliflozin/placebo
Main inclusion criteria	Type 2 diabetes and preexisting CVD	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 CV risk factors at ≥50 years of age	Type 2 diabetes and established ASCVD or multiple risk factors for ASCVD	Type 2 diabetes and albuminuric kidney disease	Albuminuric kidney disease, with or without diabetes	Type 2 diabetes and ASCVD	IV heart failure and an ejection fraction ≤40%, with or without diabetes	IV heart failure and an ejection fraction >40%, with or without diabetes	heart failure and an ejection fraction >40%	NVHA class II, III, or IV heart failure and an ejection fraction >40% with or without diabetes
A1C inclusion criteria (%)	7.0–10.0	7.0–10.5	≥6.5	6.5–12	—	7.0–10.5	—	—	—	—
Age (years)†	63.1	63.3	64.0	63	61.8	64.4	66	67.2, 66.5	71.8, 71.9	71.7
Race (% White)	72.4	78.3	79.6	66.6	53.2	87.8	70.3	71.1, 69.8	76.3, 75.4	71.2
Sex (% male)	71.5	64.2	62.6	66.1	66.9	70	76.6	76.5, 75.6	55.4, 55.3	56.1
Diabetes duration (years)†	57% >10	13.5	11.0	15.8	—	12.9	—	—	—	—
Median follow-up (years)	3.1	3.6	4.2	2.6	2.4	3.5	1.5	1.3	2.2	2.3
Statin use (%)	77	75	75 (statin or ezetimibe use)	69	64.9	—	—	—	68.1, 68.8	—
Metformin use (%)	74	77	82	57.8	29	51.2% (of people with diabetes)	—	—	—	—
Prior CVD/CHF (%)	99/10	65.6/14.4	40/10	50.4/14.8	37.4/10.9	99.9/23.1	100% with CHF	100% with CHF	100% with CHF	100% with CHF
Mean baseline A1C (%)	8.1	8.2	8.3	8.3	7.1% (7.8% in those with diabetes)	8.2	—	—	—	6.6
Mean difference in A1C between groups at end of treatment (%)	−0.3 ^a	−0.58 [‡]	−0.43 [‡]	−0.31	—	−0.48 to −0.5	—	—	—	—
Year started/reported	2010/2015	2009/2017	2013/2018	2017/2019	2017/2020	2013/2020	2017/2019	2017/2020	2017/2020	2018/2022

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Table 10.3C—Continued

	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 10,142)	DECLARE-TIMI 58 (196) (n = 17,160)	CREDESCENCE (194) (n = 4,401)	DAPA-CKD (197,239) (n = 4,304; 2,906 with diabetes)	VERTIS CV (201,240) (n = 8,246)	DAPA-HF (11) (n = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (200) (n = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (189,241) (n = 5,988; 2,938 with diabetes)	DELIVER (199) (n = 6,263; 2,807 with diabetes)
Primary outcome\$	3-point MACE 0.86 (0.74–0.99)	3-point MACE 0.86 (0.75–0.97)	3-point MACE 0.93 (0.84–1.03) CV death or HF hospitalization 0.83 (0.73–0.95)	ESRD, doubling of creatinine, or death from renal or CV cause 0.70 (0.59–0.82)	≥50% decline in eGFR, ESKD, or death from renal or CV cause 0.61 (0.51–0.72)	3-point MACE 0.97 (0.85–1.11)	Worsening heart failure or death from CV causes 0.74 (0.65–0.85) Results did not differ by diabetes status	CV death or HF hospitalization 0.75 (0.65–0.86)	CV death or HF hospitalization 0.79 (0.69–0.90)	Worsening HF or CV death 0.82 (0.73–0.92)
Key secondary outcomes\$	4-point MACE 0.89 (0.78–1.01)	All-cause and CV mortality (see below)	Death from any cause 0.93 (0.82–1.04) Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m ² , new ESRD, or death from renal or CV causes 0.76 (0.67–0.87)	CV death or HF hospitalization 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95)	≥50% decline in eGFR, ESKD, or death from renal cause 0.56 (0.45–0.68) CV death or HF hospitalization 0.71 (0.55–0.92) Death from any cause 0.69 (0.53–0.88)	CV death or HF hospitalization 0.88 (0.75–1.03) CV death 0.92 (0.77–1.11) Renal death, renal replacement therapy, or doubling of creatinine 0.81 (0.63–1.04)	CV death or HF hospitalization 0.75 (0.65–0.85)	Total HF hospitalizations 0.70 (0.58–0.85) Mean slope of change in eGFR 1.73 (1.10–2.37)	All HF hospitalizations (first and recurrent) 0.73 (0.61–0.88) Rate of decline in eGFR (–1.25 vs. –2.62 mL/min/1.73 m ² ; P < 0.001)	Total number worsening HF and CV deaths 0.77 (0.67–0.89) Change in KCCQ TSS at month 8 1.11 (1.03–1.21) Mean change in KCCQ TSS 2.4 (1.5–3.4) All-cause mortality 0.94 (0.83–1.07)
Cardiovascular death\$	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.92 (0.77–1.11)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.91 (0.76–1.09)	0.88 (0.74–1.05)
MI\$	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	—	—	1.04 (0.86–1.26)	—	—	—	—
Strokes\$	1.18 (0.89–1.56)	87 (0.69–1.09)	1.01 (0.84–1.21)	—	—	1.06 (0.82–1.37)	—	—	—	—
HF hospitalization\$	0.65 (0.50–0.85)	67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	—	0.70 (0.54–0.90)	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.77 (0.67–0.89)
Unstable angina hospitalization\$	0.99 (0.74–1.34)	—	—	—	—	—	—	—	—	—
All-cause mortality\$	0.68 (0.57–0.82)	87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.93 (0.80–1.08)	0.83 (0.71–0.97)	0.92 (0.77–1.10)	1.00 (0.87–1.15)	0.94 (0.83–1.07)
Worsening nephropathy\$	0.61 (0.53–0.70)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	(See primary outcome)	(See primary outcome)	(See secondary outcomes)	0.71 (0.44–1.16)	Composite renal outcome 0.50 (0.32–0.77)	Composite renal outcome** 0.95 (0.73–1.24)	—

—, not assessed/reported; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; NYFIA, New York Heart Association. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. *Baseline characteristics for EMPEROR-Reduced displayed as empagliflozin, >10 years, and DECLARE-TIMI 58, which reported median. †Significant difference in A1C between groups (P < 0.05). ‡A1C change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin). §Outcomes reported as hazard ratio (95% CI). ||Definitions of worsening nephropathy differed between trials. **Composite outcome in EMPEROR-Preserved: time to first occurrence of chronic dialysis, renal transplantation; sustained reduction of ≥40% in eGFR, sustained eGFR <15 mL/min/1.73 m² for individuals with baseline eGFR ≥30 mL/min/1.73 m².

or hospitalization for heart failure (HR 0.71 [95% CI 0.55–0.92]). The effects of dapagliflozin therapy were similar in individuals with and without type 2 diabetes.

Results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF), and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER), which assessed the effects of dapagliflozin and empagliflozin in individuals with established heart failure (11,189,198,199,200), are described below in *GLUCOSE-LOWERING THERAPIES AND HEART FAILURE*.

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) (201) was a randomized, double-blind trial that established the effects of ertugliflozin versus placebo on cardiovascular outcomes in 8,246 people with type 2 diabetes and established ASCVD. Participants were assigned to the addition of 5 mg or 15 mg of ertugliflozin or to placebo once daily to background standard care. Study participants had a mean age of 64.4 years and a mean duration of diabetes of 13 years at baseline and were followed for a median of 3.0 years. VERTIS CV met the prespecified criteria for noninferiority of ertugliflozin to placebo with respect to the primary outcome of major adverse cardiovascular events (11.9% in the pooled ertugliflozin group and 11.9% in the placebo group; HR 0.97 [95% CI 0.85–1.11]; $P < 0.001$). Ertugliflozin was not superior to placebo for the key secondary outcomes of death from cardiovascular causes or hospitalization for heart failure; death from cardiovascular causes; or the composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level. The HR for a secondary outcome of hospitalization for heart failure (ertugliflozin vs. placebo) was 0.70 [95% CI 0.54–0.90], consistent with findings from other SGLT2 inhibitor cardiovascular outcomes trials.

Sotagliflozin, an SGLT1 and SGLT2 inhibitor not currently approved by the FDA in the U.S., lowers glucose via delayed glucose absorption in the gut in addition to increasing urinary glucose excretion and has been evaluated in the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial (202). A total of 10,584 people with type 2 diabetes, CKD, and additional cardiovascular risk were enrolled in SCORED and randomized to sotagliflozin 200 mg once daily (up-titrated to 400 mg once daily if tolerated) or placebo. SCORED ended early due to a lack of funding; thus, changes to the prespecified primary end points were made prior to unblinding to accommodate a lower than anticipated number of end point events. The primary end point of the trial was the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. After a median of 16 months of follow-up, the rate of primary end point events was reduced with sotagliflozin (5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group [HR 0.74 (95% CI 0.63–0.88); $P < 0.001$]). Sotagliflozin also reduced the risk of the secondary end point of total number of hospitalizations for heart failure and urgent visits for heart failure (3.5% in the sotagliflozin group and 5.1% in the placebo group; HR 0.67 [95% CI 0.55–0.82]; $P < 0.001$) but not the secondary end point of deaths from cardiovascular causes. No significant between-group differences were found for the outcome of all-cause mortality or for a composite renal outcome comprising the first occurrence of long-term dialysis, renal transplantation, or a sustained reduction in eGFR. In general, the adverse effects of sotagliflozin were similar to those seen with use of SGLT2 inhibitors, but they also included an increased rate of diarrhea potentially related to the inhibition of SGLT1.

GLP-1 Receptor Agonist Trials

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, versus placebo on cardiovascular outcomes in 9,340

people with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease (203). Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, LEADER showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) (HR 0.87 [95% CI 0.78–0.97]; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). Deaths from cardiovascular causes were significantly reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (HR 0.78 [95% CI 0.66–0.93]; $P = 0.007$) (203).

Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (204). Semaglutide is a once-weekly GLP-1 receptor agonist approved by the FDA for the treatment of type 2 diabetes. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) was the initial randomized trial powered to test noninferiority of semaglutide for the purpose of regulatory approval (204). In this study, 3,297 people with type 2 diabetes were randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 2 years. The primary outcome (the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) occurred in 108 patients (6.6%) in the semaglutide group vs. 146 patients (8.9%) in the placebo group (HR 0.74 [95% CI 0.58–0.95]; $P < 0.001$). More patients discontinued treatment in the semaglutide group because of adverse events, mainly gastrointestinal. The cardiovascular effects of the oral formulation of semaglutide compared with placebo have been assessed in Peptide Innovation for Early Diabetes Treatment (PIONEER) 6, a preapproval trial designed to rule out an unacceptable increase in cardiovascular risk (205). In this trial of 3,183 people with type 2 diabetes and high cardiovascular risk followed for a median of 15.9 months, oral semaglutide was noninferior to placebo for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (HR 0.79 [95% CI 0.57–1.11]; $P < 0.001$

for noninferiority) (205). The cardiovascular effects of this formulation of semaglutide will be further tested in a large, longer-term outcomes trial.

The Harmony Outcomes trial randomized 9,463 people with type 2 diabetes and cardiovascular disease to once-weekly subcutaneous albiglutide or matching placebo, in addition to their standard care (206). Over a median duration of 1.6 years, the GLP-1 receptor agonist reduced the risk of cardiovascular death, MI, or stroke to an incidence rate of 4.6 events per 100 person-years in the albiglutide group vs. 5.9 events in the placebo group (HR ratio 0.78, $P = 0.0006$ for superiority) (206). This agent is not currently available for clinical use.

The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial was a randomized, double-blind, placebo-controlled trial that assessed the effect of the once-weekly GLP-1 receptor agonist dulaglutide versus placebo on major adverse cardiovascular events in ~9,990 people with type 2 diabetes at risk for cardiovascular events or with a history of cardiovascular disease (207). Study participants had a mean age of 66 years and a mean duration of diabetes of ~10 years. Approximately 32% of participants had history of atherosclerotic cardiovascular events at baseline. After a median follow-up of 5.4 years, the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes occurred in 12.0% and 13.4% of participants in the dulaglutide and placebo treatment groups, respectively (HR 0.88 [95% CI 0.79–0.99]; $P = 0.026$). These findings equated to incidence rates of 2.4 and 2.7 events per 100 person-years, respectively. The results were consistent across the subgroups of patients with and without history of CV events. All-cause mortality did not differ between groups ($P = 0.067$).

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial studied the once-daily GLP-1 receptor agonist lixisenatide on cardiovascular outcomes in people with type 2 diabetes who had had a recent acute coronary event (208). A total of 6,068 people with type 2 diabetes with a recent hospitalization for MI or unstable angina within the previous 180 days were randomized to receive lixisenatide or placebo in addition to standard care and were followed for a median of ~2.1 years. The primary

outcome of cardiovascular death, MI, stroke, or hospitalization for unstable angina occurred in 406 patients (13.4%) in the lixisenatide group vs. 399 (13.2%) in the placebo group (HR 1.2 [95% CI 0.89–1.17]), which demonstrated the noninferiority of lixisenatide to placebo ($P < 0.001$) but did not show superiority ($P = 0.81$).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial also reported results with the once-weekly GLP-1 receptor agonist extended-release exenatide and found that major adverse cardiovascular events were numerically lower with use of extended-release exenatide compared with placebo, although this difference was not statistically significant (209). A total of 14,752 people with type 2 diabetes (of whom 10,782 [73.1%] had previous cardiovascular disease) were randomized to receive extended-release exenatide 2 mg or placebo and followed for a median of 3.2 years. The primary end point of cardiovascular death, MI, or stroke occurred in 839 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR 0.91 [95% CI 0.83–1.00]; $P < 0.001$ for noninferiority), but exenatide was not superior to placebo with respect to the primary end point ($P = 0.06$ for superiority). However, all-cause mortality was lower in the exenatide group (HR 0.86 [95% CI 0.77–0.97]). The incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

In summary, there are now numerous large randomized controlled trials reporting statistically significant reductions in cardiovascular events for three of the FDA-approved SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, with lesser benefits seen with ertugliflozin) and four FDA-approved GLP-1 receptor agonists (liraglutide, albiglutide [although that agent was removed from the market for business reasons], semaglutide [lower risk of cardiovascular events in a moderate-sized clinical trial but one not powered as a cardiovascular outcomes trial], and dulaglutide). Meta-analyses of the trials reported to date suggest that GLP-1 receptor agonists and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in people with type 2

diabetes and established ASCVD (210,211). SGLT2 inhibitors also reduce risk of heart failure hospitalization and progression of kidney disease in people with established ASCVD, multiple risk factors for ASCVD, or albuminuric kidney disease (212,213). In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. For many patients, use of either an SGLT2 inhibitor or a GLP-1 receptor agonist to reduce cardiovascular risk is appropriate. Emerging data suggest that use of both classes of drugs will provide an additive cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist may be considered to provide the complementary outcomes benefits associated with these classes of medication. Evidence to support such an approach includes findings from AMPLITUDE-O (Effect of Efglenatide on Cardiovascular Outcomes), an outcomes trial of people with type 2 diabetes and either cardiovascular or kidney disease plus at least one other risk factor randomized to the investigational GLP-1 receptor agonist efglenatide or placebo (214). Randomization was stratified by current or potential use of SGLT2 inhibitor therapy, a class ultimately used by >15% of the trial participants. Over a median follow-up of 1.8 years, efglenatide therapy reduced the risk of incident major adverse cardiovascular events by 27% and of a composite renal outcome event by 32%. Importantly, the effects of efglenatide did not vary by use of SGLT2 inhibitors, suggesting that the beneficial effects of the GLP-1 receptor agonist were independent of those provided by SGLT2 inhibitor therapy (215). Efglenatide is currently not approved by the FDA for use in the U.S.

Glucose-Lowering Therapies and Heart Failure

As many as 50% of people with type 2 diabetes may develop heart failure (216). These conditions, which are each

associated with increased morbidity and mortality, commonly coincide, and independently contribute to adverse outcomes (217). Strategies to mitigate these risks are needed, and the heart failure-related risks and benefits of glucose-lowering medications should be considered carefully when determining a regimen of care for people with diabetes and either established heart failure or high risk for the development of heart failure.

Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure (218–220). Therefore, thiazolidinedione use should be avoided in people with symptomatic heart failure. Restrictions to use of metformin in people with medically treated heart failure were removed by the FDA in 2006 (221). Observational studies of people with type 2 diabetes and heart failure suggest that metformin users have better outcomes than individuals treated with other antihyperglycemic agents (222); however, no randomized trial of metformin therapy has been conducted in people with heart failure. Metformin may be used for the management of hyperglycemia in people with stable heart failure as long as kidney function remains within the recommended range for use (223).

Recent studies examining the relationship between DPP-4 inhibitors and heart failure have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that patients treated with the DPP-4 inhibitor saxagliptin were more likely to be hospitalized for heart failure than those given placebo (3.5% vs. 2.8%, respectively) (224). However, three other cardiovascular outcomes trials—Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (225), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (226), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (193)—did not find a significant increase in risk of heart failure hospitalization with DPP-4 inhibitor use compared with placebo. No increased risk of heart failure hospitalization has been identified in the cardiovascular outcomes trials of the GLP-1 receptor

agonists lixisenatide, liraglutide, semaglutide, exenatide once-weekly, albiglutide, or dulaglutide compared with placebo (Table 10.3B) (203,204,207–209).

Reduced incidence of heart failure has been observed with the use of SGLT2 inhibitors (8,194,196). In EMPA-REG OUTCOME, the addition of empagliflozin to standard care led to a significant 35% reduction in hospitalization for heart failure compared with placebo (8). Although the majority of patients in the study did not have heart failure at baseline, this benefit was consistent in patients with and without a history of heart failure (10). Similarly, in CANVAS and DECLARE-TIMI 58, there were 33% and 27% reductions in hospitalization for heart failure, respectively, with SGLT2 inhibitor use versus placebo (9,196). Additional data from the CREDENCE trial with canagliflozin showed a 39% reduction in hospitalization for heart failure, and 31% reduction in the composite of cardiovascular death or hospitalization for heart failure, in a diabetic kidney disease population with albuminuria (UACR >300 to 5,000 mg/g) (194). These combined findings from four large outcomes trials of three different SGLT2 inhibitors are highly consistent and clearly indicate robust benefits of SGLT2 inhibitors in the prevention of heart failure hospitalizations. The EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE trials suggested, but did not prove, that SGLT2 inhibitors would be beneficial in the treatment of people with established heart failure. More recently, the placebo-controlled DAPA-HF trial evaluated the effects of dapagliflozin on the primary outcome of a composite of worsening heart failure or cardiovascular death in patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less. Of the 4,744 trial participants, 45% had a history of type 2 diabetes. Over a median of 18.2 months, the group assigned to dapagliflozin treatment had a lower risk of the primary outcome (HR 0.74 [95% CI 0.65–0.85]), lower risk of first worsening heart failure event (HR 0.70 [95% CI 0.59–0.83]), and lower risk of cardiovascular death (HR 0.82 [95% CI 0.69–0.98]) compared with placebo. The effect of dapagliflozin on the primary outcome was consistent regardless of the presence or absence of type 2 diabetes (11).

EMPEROR-Reduced assessed the effects of empagliflozin 10 mg once daily versus

placebo on a primary composite outcome of cardiovascular death or hospitalization for worsening heart failure in a population of 3,730 patients with NYHA class II, III, or IV heart failure and an ejection fraction of 40% or less (200). At baseline, 49.8% of participants had a history of diabetes. Over a median follow-up of 16 months, those in the empagliflozin-treated group had a reduced risk of the primary outcome (HR 0.75 [95% CI 0.65–0.86]; $P < 0.001$) and fewer total hospitalizations for heart failure (HR 0.70 [95% CI 0.58–0.85]; $P < 0.001$). The effect of empagliflozin on the primary outcome was consistent irrespective of diabetes diagnosis at baseline. The risk of a prespecified renal composite outcome (chronic dialysis, renal transplantation, or a sustained reduction in eGFR) was lower in the empagliflozin group than in the placebo group (1.6% in the empagliflozin group vs. 3.1% in the placebo group; HR 0.50 [95% CI 0.32–0.77]).

EMPEROR-Preserved, a randomized double-blinded placebo-controlled trial of 5,988 adults with NYHA functional class I–IV chronic HFpEF (left ventricular ejection fraction >40%), evaluated the efficacy of empagliflozin 10 mg daily versus placebo on top of standard of care on the primary outcome of composite cardiovascular death or hospitalization for heart failure (189). Approximately 50% of subjects had type 2 diabetes at baseline. Over a median of 26.2 months, there was a 21% reduction (HR 0.79 [95% CI 0.69–0.90]; $P < 0.001$) of the primary outcome. The effects of empagliflozin were consistent in people with or without diabetes (189).

In the DELIVER trial, 6,263 individuals with heart failure and an ejection fraction >40% were randomized to receive either dapagliflozin or placebo (199). The primary outcome of a composite of worsening heart failure, defined as hospitalization or urgent visit for heart failure, or cardiovascular death was reduced by 18% in patients treated with dapagliflozin compared with placebo (HR 0.82 [95% CI 0.73–0.92]; $P < 0.001$). Approximately 44% of patients randomized to either dapagliflozin or placebo had type 2 diabetes, and results were consistent regardless of the presence of type 2 diabetes.

A large recent meta-analysis (227) including data from EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, DELIVER, and Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes

Post Worsening Heart Failure (SOLOIST-WHF) included 21,947 patients and demonstrated reduced risk for the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, first hospitalization for heart failure, and all-cause mortality. The findings on the studied end points were consistent in both trials of heart failure with mildly reduced or preserved ejection fraction and in all five trials combined. Collectively, these studies indicate that SGLT2 inhibitors reduce the risk for heart failure hospitalization and cardiovascular death in a wide range of people with heart failure.

Additional data are accumulating regarding the effects of SGLT inhibition in people hospitalized for acute decompensated heart failure and in people with heart failure and HFpEF. As an example, the investigational SGLT1 and SGLT2 inhibitor sotagliflozin has also been studied in the SOLOIST-WHF trial (228). In SOLOIST-WHF, 1,222 people with type 2 diabetes who were recently hospitalized for worsening heart failure were randomized to sotagliflozin 200 mg once daily (with uptitration to 400 mg once daily if tolerated) or placebo either before or within 3 days after hospital discharge. Patients were eligible if hospitalized for signs and symptoms of heart failure (including elevated natriuretic peptide levels) requiring treatment with intravenous diuretic therapy. Exclusion criteria included end-stage heart failure or recent acute coronary syndrome or intervention, or an eGFR <30 mL/min/1.73 m². Patients were required to be clinically stable prior to randomization, defined as no use of supplemental oxygen, a systolic blood pressure ≥ 100 mmHg, and no need for intravenous inotropic or vasodilator therapy other than nitrates. Similar to SCORED, SOLOIST-WHF ended early due to a lack of funding, resulting in a change to the prespecified primary end point prior to unblinding to accommodate a lower than anticipated number of end point events. At a median follow-up of 9 months, the rate of primary end point events (the total number of cardiovascular deaths and hospitalizations and urgent visits for heart failure) was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; HR 0.67 [95% CI 0.52–0.85]; $P < 0.001$). No significant between-group differences were found in the rates of cardiovascular death or all-cause mortality. Both diarrhea (6.1%

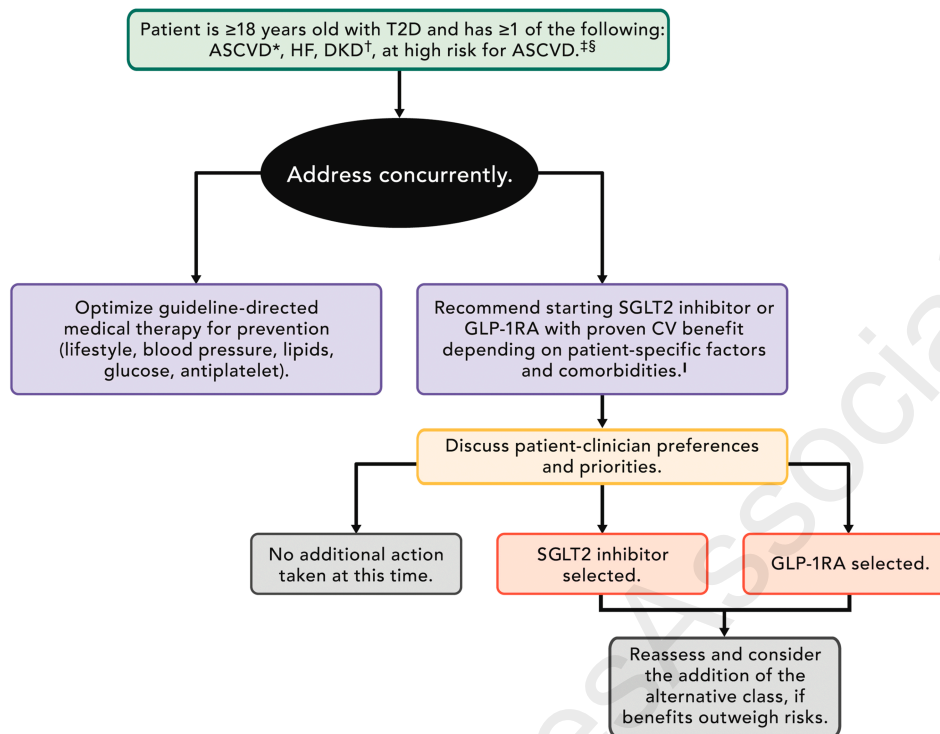
vs. 3.4%) and severe hypoglycemia (1.5% vs. 0.3%) were more common with sotagliflozin than with placebo. The trial was originally also intended to evaluate the effects of SGLT inhibition in people with HFpEF, and ultimately no evidence of heterogeneity of treatment effect by ejection fraction was noted. However, the relatively small percentage of such patients enrolled (only 21% of participants had ejection fraction $>50\%$) and the early termination of the trial limited the ability to determine the effects of sotagliflozin in HFpEF specifically.

In addition to the hospitalization and mortality benefit in people with heart failure, several recent analyses have addressed whether SGLT2 inhibitor treatment improves clinical stability and functional status in individuals with heart failure. In 3,730 patients with NYHA class II–IV heart failure with an ejection fraction of $\leq 40\%$, treatment with empagliflozin reduced the combined risk of death, hospitalization for heart failure, or an emergent/urgent heart failure visit requiring intravenous treatment and reduced the total number of hospitalizations for heart failure requiring intensive care, a vasopressor or positive inotropic drug, or mechanical or surgical intervention (229). In addition, patients treated with empagliflozin were more likely to experience an improvement in NYHA functional class (229). In people hospitalized for acute de novo or decompensated chronic heart failure, initiation of empagliflozin treatment during hospitalization reduced the primary outcome of a composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (230). Furthermore, PRESERVED-HF, a multicenter study (26 sites in the U.S.) showed that dapagliflozin treatment leads to significant improvement in both symptoms and physical limitation, as well as objective measures of exercise function in people with chronic HFpEF, regardless of diabetes status (198). Finally, canagliflozin improved heart failure symptoms assessed using the Kansas City Cardiomyopathy Questionnaire Total Symptom Score, irrespective of left ventricular ejection fraction or the presence of diabetes (231). Therefore, in people with type 2 diabetes and established HFpEF or HFrEF, an SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce the risk

of worsening heart failure and cardiovascular death. In addition, an SGLT2 inhibitor is recommended in this patient population to improve symptoms, physical limitations, and quality of life. The benefits seen in this patient population likely represent a class effect, and they appear unrelated to glucose lowering given comparable outcomes in people with heart failure with and without diabetes.

Finerenone in People With Type 2 Diabetes and Chronic Kidney Disease

As discussed in detail in Section 11, “Chronic Kidney Disease and Risk Management,” people with diabetes are at an increased risk for CKD, which increases cardiovascular risk (232). Finerenone, a selective nonsteroidal mineralocorticoid antagonist, has been shown in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial to improve CKD outcomes in people with type 2 diabetes with stage 3 or 4 CKD and severe albuminuria (233). In the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial, 7,437 patients with UACR 30–300 mg/g and eGFR 25–90 mL/min/1.73 m² or UACR 300–5,000 and eGFR ≥ 60 mL/min/1.73 m² on maximum dose of renin-angiotensin system blockade were randomized to receive finerenone or placebo (186). The HR of the primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization from heart failure was reduced by 13% in patients treated with finerenone. A prespecified subgroup analysis from FIGARO-DKD further revealed that in patients without symptomatic HFpEF, finerenone reduces the risk for new-onset heart failure and improves heart failure outcomes in people with type 2 diabetes and CKD (187). Finally, in the pooled analysis of 13,026 people with type 2 diabetes and CKD from both FIDELIO-DKD and FIGARO-DKD, the HRs for the composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure as well as a composite of kidney failure, a sustained $\geq 57\%$ decrease in eGFR from baseline over ≥ 4 weeks, or renal death were 0.86 and 0.77, respectively (188). These collective studies indicate that finerenone improves cardiovascular and renal outcomes in people with type 2 diabetes. Therefore, in people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE



*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

†DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

§Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

¶Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

Figure 10.3—Approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy. Reprinted with permission from Das et al. (234).

inhibitor or ARB, addition of finerenone should be considered to improve cardiovascular outcomes and reduce the risk of CKD progression.

Clinical Approach

As has been carefully outlined in **Fig. 9.3** in the preceding Section 9, “Pharmacologic Approaches to Glycemic Treatment,” people with type 2 diabetes with or at high risk for ASCVD, heart failure, or CKD should be treated with a cardioprotective SGLT2 inhibitor and/or GLP-1 receptor agonist as part of the comprehensive approach to cardiovascular and kidney risk reduction. Importantly, these agents should be included in the regimen of care irrespective of the need for additional glucose lowering, and irrespective of metformin use. Such an approach has also been described in the American Diabetes Association–endorsed American

College of Cardiology “2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes” (234). **Figure 10.3**, reproduced from that decision pathway, outlines the approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy.

Adoption of these agents should be reasonably straightforward in people with established cardiovascular or kidney disease who are later diagnosed with diabetes, as the cardioprotective agents can be used from the outset of diabetes management. On the other hand, incorporation of SGLT2 inhibitor or GLP-1 receptor agonist therapy in the care of

individuals with more long-standing diabetes may be more challenging, particularly if patients are using an already complex glucose-lowering regimen. In such patients, SGLT2 inhibitor or GLP-1 receptor agonist therapy may need to replace some or all of their existing medications to minimize risks of hypoglycemia and adverse side effects, and potentially to minimize medication costs. Close collaboration between primary and specialty care professionals can help to facilitate these transitions in clinical care and, in turn, improve outcomes for high-risk people with type 2 diabetes.

References

1. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care* 2018;41:917–928
2. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in

- U.S. diabetes care, 1999-2010. *N Engl J Med* 2013;368:1613-1624
3. Buse JB, Ginsberg HN, Bakris GL, et al.; American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2007;30:162-172
 4. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580-591
 5. Cavender MA, Steg PG, Smith SC Jr, et al.; REACH Registry Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation* 2015;132:923-931
 6. McAllister DA, Read SH, Kerssens J, et al. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. *Circulation* 2018;138:2774-2786
 7. Lam CSP, Voors AA, de Boer RA, Solomon SD, van Veldhuisen DJ. Heart failure with preserved ejection fraction: from mechanisms to therapies. *Eur Heart J* 2018;39:2780-2792
 8. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-2128
 9. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-657
 10. Fitchett D, Butler J, van de Borne P, et al.; EMPA-REG OUTCOME trial investigators. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME trial. *Eur Heart J* 2018;39:363-370
 11. McMurray JJV, Solomon SD, Inzucchi SE, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995-2008
 12. Arnott C, Li Q, Kang A, et al. Sodium-glucose cotransporter 2 inhibition for the prevention of cardiovascular events in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *J Am Heart Assoc* 2020;9:e014908
 13. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014;384:591-598
 14. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/Apha/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;73:3168-3209
 15. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. *JAMA* 2014;311:1406-1415
 16. DeFilippis AP, Young R, McEvoy JW, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. *Eur Heart J* 2017;38:598-608
 17. Bohula EA, Morrow DA, Giugliano RP, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. *J Am Coll Cardiol* 2017;69:911-921
 18. Bohula EA, Bonaca MP, Braunwald E, et al. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. *Circulation* 2016;134:304-313
 19. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/Apha/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71:e127-e248
 20. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:1273-1284
 21. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* 2020;75:1334-1357
 22. Williams B, Mancia G, Spiering W, et al.; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-3104
 23. Bobrie G, Genès N, Vaur L, et al. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? *Arch Intern Med* 2001;161:2205-2211
 24. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111:1777-1783
 25. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. *J Hypertens* 2013;31:455-467; discussion 467-468
 26. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015;313:603-615
 27. Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. *Cochrane Database Syst Rev* 2013;10:CD008277
 28. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957-967
 29. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016;352:i717
 30. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011;123:2799-2810
 31. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens* 2017;35:922-944
 32. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet* 2016;387:435-443
 33. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-2116
 34. Zhang W, Zhang S, Deng Y, et al.; STEP Study Group. Trial of intensive blood-pressure control in older patients with hypertension. *N Engl J Med* 2021;385:1268-1279
 35. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-1585
 36. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829-840
 37. Hansson L, Zanchetti A, Carruthers SG, et al.; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-1762
 38. Rebollo G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. *J Hypertens* 2011;29:1253-1269
 39. de Boer IH, Bakris G, Cannon CP. Individualizing blood pressure targets for people with diabetes and hypertension: comparing the ADA and the ACC/AHA recommendations. *JAMA* 2018;319:1319-1320
 40. Basu S, Sussman JB, Rigdon J, Steimle L, Denton BT, Hayward RA. Benefit and harm of intensive blood pressure treatment: derivation and validation of risk models using data from the SPRINT and ACCORD trials. *PLoS Med* 2017;14:e1002410
 41. Phillips RA, Xu J, Peterson LE, Arnold RM, Diamond JA, Schussheim AE. Impact of cardiovascular risk on the relative benefit and harm of intensive treatment of hypertension. *J Am Coll Cardiol* 2018;71:1601-1610
 42. Beddhu S, Greene T, Boucher R, et al. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. *Lancet Diabetes Endocrinol* 2018;6:555-563
 43. Sink KM, Evans GW, Shorr RI, et al. Syncope, hypotension, and falls in the treatment of hypertension: results from the randomized clinical systolic blood pressure intervention trial. *J Am Geriatr Soc* 2018;66:679-686
 44. Ilkun OL, Greene T, Cheung AK, et al. The influence of baseline diastolic blood pressure on the effects of intensive blood pressure lowering on

- cardiovascular outcomes and all-cause mortality in type 2 diabetes. *Diabetes Care* 2020;43:1878–1884
45. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014;2:CD002252
46. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;372:407–417
47. Brown MA, Magee LA, Kenny LC, et al.; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension* 2018;72:24–33
48. Tita AT, Szychowski JM, Boggess K, et al.; Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med* 2022;386:1781–1792
49. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;122:1122–1131
50. Al-Balas M, Bozzo P, Einarson A. Use of diuretics during pregnancy. *Can Fam Physician* 2009;55:44–45
51. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ* 2001;323:1213–1217
52. Sacks FM, Svetkey LP, Vollmer WM, et al.; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001;344:3–10
53. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507–520
54. Mao Y, Lin W, Wen J, Chen G. Impact and efficacy of mobile health intervention in the management of diabetes and hypertension: a systematic review and meta-analysis. *BMJ Open Diabetes Res Care* 2020;8:e001225
55. Stogios N, Kaur B, Huszti E, Vasanthan J, Nolan RP. Advancing digital health interventions as a clinically applied science for blood pressure reduction: a systematic review and meta-analysis. *Can J Cardiol* 2020;36:764–774
56. Bakris GL; Weir MR; Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) Investigators. Achieving goal blood pressure in patients with type 2 diabetes: conventional versus fixed-dose combination approaches. *J Clin Hypertens (Greenwich)* 2003;5:202–209
57. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SAE, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. *Hypertension* 2009;53:646–653
58. Webster R, Salam A, de Silva HA, et al.; TRIUMPH Study Group. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. *JAMA* 2018;320:566–579
59. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007;120:713–719
60. Catalá-López F, Macías Saint-Gerons D, González-Bermejo D, et al. Cardiovascular and renal outcomes of renin-angiotensin system blockade in adult patients with diabetes mellitus: a systematic review with network meta-analyses. *PLoS Med* 2016;13:e1001971
61. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* 2015;385:2047–2056
62. Barzilay JI, Davis BR, Bettencourt J, et al.; ALLHAT Collaborative Research Group. Cardiovascular outcomes using doxazosin vs. chlorthalidone for the treatment of hypertension in older adults with and without glucose disorders: a report from the ALLHAT study. *J Clin Hypertens (Greenwich)* 2004;6:116–125
63. Weber MA, Bakris GL, Jamerson K, et al.; ACCOMPLISH Investigators. Cardiovascular events during differing hypertension therapies in patients with diabetes. *J Am Coll Cardiol* 2010;56:77–85
64. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–259
65. Arnold SV, Bhatt DL, Barsness GW, et al.; American Heart Association Council on Lifestyle and Cardiometabolic Health and Council on Clinical Cardiology. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: a scientific statement from the American Heart Association. *Circulation* 2020;141:e779–e806
66. Yusuf S, Teo K, Anderson C, et al.; Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008;372:1174–1183
67. Qiao Y, Shin JI, Chen TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. *JAMA Intern Med* 2020;180:718–726
68. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* 2016;352:i438
69. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet* 2004;364:1684–1689
70. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart failure with reduced ejection fraction: a review. *JAMA* 2020;324:488–504
71. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–1559
72. Fried LF, Emanuele N, Zhang JH, et al.; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369:1892–1903
73. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ* 2013;346:f360
74. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. *Cochrane Database Syst Rev* 2011 (10):CD004184
75. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. *Diabetes Care* 2011;34:1270–1276
76. Rahman M, Greene T, Phillips RA, et al. A trial of 2 strategies to reduce nocturnal blood pressure in Blacks with chronic kidney disease. *Hypertension* 2013;61:82–88
77. Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol* 2017;245:277–284
78. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. *J Am Heart Assoc* 2017;6:e005428
79. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. *Clin J Am Soc Nephrol* 2017;12:245–252
80. James MT, Grams ME, Woodward M, et al.; CKD Prognosis Consortium. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis* 2015;66:602–612
81. Williams B, MacDonald TM, Morant S, et al.; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;386:2059–2068
82. Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. *Hypertension* 2003;41:64–68
83. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol* 2009;20:2641–2650
84. Bakris GL, Agarwal R, Chan JC, et al.; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* 2015;314:884–894
85. Jensen MD, Ryan DH, Apovian CM, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol* 2014;63(25 Pt B):2985–3023
86. Eckel RH, Jakicic JM, Ard JD, et al.; 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;129:S76–S99

87. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596–e646
88. Chasman DI, Posada D, Subrahmanyam L, Cook NR, Stanton VP Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA* 2004;291:2821–2827
89. Meek C, Wierzbicki AS, Jewkes C, et al. Daily and intermittent rosuvastatin 5 mg therapy in statin intolerant patients: an observational study. *Curr Med Res Opin* 2012;28:371–378
90. Mihaylova B, Emberson J, Blackwell L, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581–590
91. Baigent C, Keech A, Kearney PM, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–1278
92. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997;20:614–620
93. Collins R, Armitage J, Parish S, Sleight P; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361:2005–2016
94. Goldberg RB, Mellies MJ, Sacks FM, et al.; The Care Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 1998;98:2513–2519
95. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006;29:1220–1226
96. Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005;28:1151–1157
97. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006;29:1478–1485
98. Colhoun HM, Betteridge DJ, Durrington PN, et al.; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–696
99. Kearney PM, Blackwell L, Collins R, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;371:117–125
100. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013;1:CD004816
101. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ* 2013;346:f2610–f2610
102. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract* 2017;23(Suppl. 2):1–87
103. Goldberg RB, Stone NJ, Grundy SM. The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guidelines on the management of blood cholesterol in diabetes. *Diabetes Care* 2020;43:1673–1678
104. Mach F, Baigent C, Catapano AL, et al.; ESC Scientific Document Group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–188
105. Cannon CP, Blazing MA, Giugliano RP, et al.; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387–2397
106. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care* 2014;37:2843–2863
107. Cannon CP, Braunwald E, McCabe CH, et al.; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504
108. Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–1722
109. Giugliano RP, Cannon CP, Blazing MA, et al.; IMPROVE-IT (Improved Reduction of Outcomes: Vitorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vitorin Efficacy International Trial). *Circulation* 2018;137:1571–1582
110. Schwartz GG, Steg PG, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379:2097–2107
111. Ray KK, Colhoun HM, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;7:618–628
112. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;5:941–950
113. Moriarty PM, Jacobson TA, Bruckert E, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. *J Clin Lipidol* 2014;8:554–561
114. Zhang XL, Zhu QQ, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC Med* 2015;13:123
115. Giugliano RP, Pedersen TR, Saver JL, et al.; FOURIER Investigators. Stroke prevention with the PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitor evolocumab added to statin in high-risk patients with stable atherosclerosis. *Stroke* 2020;51:1546–1554
116. Ray KK, Wright RS, Kallend D, et al.; ORION-10 and ORION-11 Investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;382:1507–1519
117. University of Oxford. A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease (ORION-4). In: *ClinicalTrials.gov*. Bethesda, MD, National Library of Medicine. NLM Identifier: NCT03705234. Accessed 15 October 2022. Available from <https://clinicaltrials.gov/ct2/show/NCT03705234>
118. Dai L, Zuo Y, You Q, Zeng H, Cao S. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: a systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol* 2021;28:825–83
119. Di Minno A, Lupoli R, Calcaterra I, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia: systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2020;9:e016262
120. Berglund L, Brunzell JD, Goldberg AC, et al.; Endocrine society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2969–2989
121. Bhatt DL, Steg PG, Miller M, et al.; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;380:11–22
122. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA* 2020;324:2268–2280
123. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. *JAMA* 2007;298:786–798
124. Keech A, Simes RJ, Barter P, et al.; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–1861
125. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 2005;95:120–122
126. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination

- lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563–1574
127. Boden WE, Probstfield JL, Anderson T, et al.; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255–2267
128. Landray MJ, Haynes R, Hopewell JC, et al.; HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;371:203–212
129. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care* 2009;32:1924–1929
130. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735–742
131. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012;380:565–571
132. Mach F, Ray KK, Wiklund O, et al.; European Atherosclerosis Society Consensus Panel. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J* 2018;39:2526–2539
133. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22
134. Shepherd J, Blauw GJ, Murphy MB, et al.; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–1630
135. Trompet S, van Vliet P, de Craen AJM, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J Neurol* 2010;257:85–90
136. Yusuf S, Bosch J, Dagenais G, et al.; HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2021–2031
137. Giugliano RP, Mach F, Zavitz K, et al.; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med* 2017;377:633–643
138. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013;159:688–697
139. Baigent C, Blackwell L, Collins R, et al.; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–1860
140. Perk J, De Backer G, Gohlke H, et al.; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635–1701
141. Belch J, MacCuish A, Campbell I, et al.; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840–a1840
142. Zhang C, Sun A, Zhang P, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. *Diabetes Res Clin Pract* 2010;87:211–218
143. De Berardis G, Sacco M, Strippoli GFM, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* 2009;339:b4531
144. ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018;379:1529–1539
145. Gaziano JM, Brotons C, Coppolecchia R, et al.; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018;392:1036–1046
146. McNeil JJ, Wolfe R, Woods RL, et al.; ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018;379:1509–1518
147. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. *Ann Intern Med* 2006;144:326–336
148. Huxley RR, Peters SAE, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015;3:198–206
149. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia* 2014;57:1542–1551
150. Kalyani RR, Lazo M, Ouyang P, et al. Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults. *Diabetes Care* 2014;37:830–838
151. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet* 2014;383:1973–1980
152. Miedema MD, Duprez DA, Misialek JR, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Qual Outcomes* 2014;7:453–460
153. Dimitriu-Leen AC, Scholte AJHA, van Rosendaal AR, et al. Value of coronary computed tomography angiography in tailoring aspirin therapy for primary prevention of atherosclerotic events in patients at high risk with diabetes mellitus. *Am J Cardiol* 2016;117:887–893
154. Mora S, Ames JM, Manson JE. Low-dose aspirin in the primary prevention of cardiovascular disease: shared decision making in clinical practice. *JAMA* 2016;316:709–710
155. Campbell CL, Smyth S, Montalescot G, Steinhilber SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007;297:2018–2024
156. Jones WS, Mulder H, Wruck LM, et al.; ADAPTABLE Team. Comparative effectiveness of aspirin dosing in cardiovascular disease. *N Engl J Med* 2021;384:1981–1990
157. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007;357:2482–2494
158. Larsen SB, Grove EL, Neergaard-Petersen S, Würtz M, Hvas AM, Kristensen SD. Determinants of reduced antiplatelet effect of aspirin in patients with stable coronary artery disease. *PLoS One* 2015;10:e0126767
159. Zaccardi F, Rizzi A, Petrucci G, et al. In vivo platelet activation and aspirin responsiveness in type 1 diabetes. *Diabetes* 2016;65:503–509
160. Bethel MA, Harrison P, Sourij H, et al. Randomized controlled trial comparing impact on platelet reactivity of twice-daily with once-daily aspirin in people with type 2 diabetes. *Diabet Med* 2016;33:224–230
161. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* 2018;392:387–399
162. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(Suppl.):e637S–e668S
163. Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. *J Am Coll Cardiol* 2016;67:2732–2740
164. Steg PG, Bhatt DL, Simon T, et al.; THEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med* 2019;381:1309–1320
165. Bhatt DL, Steg PG, Mehta SR, et al.; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet* 2019;394:1169–1180
166. Angiolillo DJ, Baber U, Sartori S, et al. Ticagrelor with or without aspirin in high-risk patients with diabetes mellitus undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2020;75:2403–2413
167. Wiebe J, Ndrepepa G, Kufner S, et al. Early aspirin discontinuation after coronary stenting: a systematic review and meta-analysis. *J Am Heart Assoc* 2021;10:e018304
168. Bhatt DL, Eikelboom JW, Connolly SJ, et al.; COMPASS Steering Committee and Investigators. Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. *Circulation* 2020;141:1841–1854
169. Connolly SJ, Eikelboom JW, Bosch J, et al.; COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised,

- double-blind, placebo-controlled trial. *Lancet* 2018;391:205–218
170. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med* 2020;382:1994–2004
171. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO; ADA. Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 2007;30:2729–2736
172. Boden WE, O'Rourke RA, Teo KK, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–1516
173. Frye RL, August P, Brooks MM, et al.; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503–2515
174. Wackers FJT, Chyun DA, Young LH, et al.; Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Care* 2007;30:2892–2898
175. Elkeles RS, Godsland IF, Feher MD, et al.; PREDICT Study Group. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. *Eur Heart J* 2008;29:2244–2251
176. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol* 2004;43:1663–1669
177. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J* 2006;27:713–721
178. Young LH, Wackers FJT, Chyun DA, et al.; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009;301:1547–1555
179. Wackers FJT, Young LH, Inzucchi SE, et al.; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004;27:1954–1961
180. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol* 2006;47:65–71
181. Hadamitzky M, Hein F, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. *Diabetes Care* 2010;33:1358–1363
182. Choi EK, Chun EJ, Choi SI, et al. Assessment of subclinical coronary atherosclerosis in asymptomatic patients with type 2 diabetes mellitus with single photon emission computed tomography and coronary computed tomography angiography. *Am J Cardiol* 2009;104:890–896
183. Malik S, Zhao Y, Budoff M, et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the Multi-Ethnic Study of Atherosclerosis. *JAMA Cardiol* 2017;2:1332–1340
184. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–154
185. Braunwald E, Domanski MJ, Fowler SE, et al.; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058–2068
186. Pitt B, Filippatos G, Agarwal R, et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;385:2252–2263
187. Filippatos G, Anker SD, Agarwal R, et al.; FIGARO-DKD Investigators. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. *Circulation* 2022;145:437–447
188. Agarwal R, Filippatos G, Pitt B, et al.; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;43:474–484
189. Anker SD, Butler J, Filippatos G, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;385:1451–1461
190. Kezerashvili A, Marzo K, De Leon J. Beta blocker use after acute myocardial infarction in the patient with normal systolic function: when is it “ok” to discontinue? *Curr Cardiol Rev* 2012;8:77–84
191. Fihn SD, Gardin JM, Abrams J, et al.; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;60:e44–e164
192. U.S. Food and Drug Administration. Guidance for industry. Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD, 2008. Accessed 21 October 2022. Available from <https://www.federalregister.gov/documents/2008/12/19/E8-30086/guidance-for-industry-on-diabetes-mellitus-evaluating-cardiovascular-risk-in-new-antidiabetic>
193. Rosenstock J, Perkovic V, Johansen OE, et al.; CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA* 2019;321:69–79
194. Perkovic V, Jardine MJ, Neal B, et al.; CRENDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295–2306
195. Neal B, Perkovic V, Matthews DR, et al.; CANVAS-R Trial Collaborative Group. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): A randomized, placebo-controlled trial. *Diabetes Obes Metab* 2017;19:387–393
196. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347–357
197. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383:1436–1446
198. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med* 2021;27:1954–1960
199. Solomon SD, McMurray JJV, Claggett B, et al.; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;387:1089–1098
200. Packer M, Anker SD, Butler J, et al.; EMPEROR Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413–1424
201. Cannon CP, Pratley R, Dagogo-Jack S, et al.; VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;383:1425–1435
202. Bhatt DL, Szarek M, Pitt B, et al.; SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2021;384:129–139
203. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–322
204. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
205. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;381:841–851
206. Hernandez AF, Green JB, Janmohamed S, et al.; Harmony Outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;392:1519–1529
207. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394:121–130
208. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247–2257
209. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:1228–1239
210. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter

- 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation* 2019;139:2022–2031
211. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021;372:m4573
212. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;393:31–39
213. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021;6:148–158
214. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and renal outcomes with efglenatide in type 2 diabetes. *N Engl J Med* 2021;385:896–907
215. Lam CSP, Ramasundarahettige C, Branch KRH, et al. Efglenatide and clinical outcomes with and without concomitant sodium-glucose cotransporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O Trial. *Circulation* 2022;145:565–574
216. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29–34
217. Dunlay SM, Givertz MM, Aguilar D, et al.; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Heart Failure Society of America. Type 2 diabetes mellitus and heart failure, a scientific statement from the American Heart Association and Heart Failure Society of America. *J Card Fail* 2019;25:584–619
218. Dormandy JA, Charbonnel B, Eckland DJA, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279–1289
219. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007;298:1189–1195
220. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007;298:1180–1188
221. Inzucchi SE, Masoudi FA, McGuire DK. Metformin in heart failure. *Diabetes Care* 2007;30:e129–e129
222. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care* 2005;28:2345–2351
223. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function, 2016. Accessed 21 October 2022. Available from <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain>
224. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–1326
225. Zannad F, Cannon CP, Cushman WC, et al.; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015;385:2067–2076
226. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232–242
227. Vaduganathan M, Docherty KF, Claggett BL, et al.; SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet* 2022;400:757–767
228. Bhatt DL, Szarek M, Steg PG, et al.; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;384:117–128
229. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Circulation* 2021;143:326–336
230. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med* 2022;28:568–574
231. Spertus JA, Birmingham MC, Nassif M, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. *Nat Med* 2022;28:809–813
232. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;382:339–352
233. Bakris GL, Agarwal R, Anker SD, et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;383:2219–2229
234. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2020;76:1117–1145
235. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327–1335
236. Rosenstock J, Perkovic V, Alexander JH, et al.; CARMELINA investigators. Rationale, design, and baseline characteristics of the Cardiovascular safety and Renal Microvascular outcome study with LINagliptin (CARMELINA): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. *Cardiovasc Diabetol* 2018;17:39
237. Marx N, Rosenstock J, Kahn SE, et al. Design and baseline characteristics of the Cardiovascular Outcome Trial of LINagliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA®). *Diab Vasc Dis Res* 2015;12:164–174
238. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a *Diabetes Care* Editors' Expert Forum. *Diabetes Care* 2018;41:14–31
239. Wheeler DC, Stefansson BV, Batiushin M, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. *Nephrol Dial Transplant* 2020;35:1700–1711
240. Cannon CP, McGuire DK, Pratley R, et al.; VERTIS-CV Investigators. Design and baseline characteristics of the eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS-CV). *Am Heart J* 2018;206:11–23
241. Anker SD, Butler J, Filippatos G, et al.; EMPEROR-Preserved Trial Committees and Investigators. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. *Eur J Heart Fail* 2020;22:2383–2392
242. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392–1406

11. Chronic Kidney Disease and Risk Management: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, “Children and Adolescents.”

CHRONIC KIDNEY DISEASE

Screening

Recommendations

- 11.1a** At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be assessed in people with type 1 diabetes with duration of ≥ 5 years and in all people with type 2 diabetes regardless of treatment. **B**
- 11.1b** In people with established diabetic kidney disease, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be monitored 1–4 times per year depending on the stage of the disease (**Fig. 11.1**). **B**

Treatment

Recommendations

- 11.2** Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. **A**
- 11.3** Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of chronic kidney disease. **A**
- 11.4a** In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with moderately increased albuminuria (urinary albumin-to-creatinine ratio 30–299 mg/g creatinine) **B** and is strongly recommended for those

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CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 11.1—Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to a nephrologist according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal estimated GFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient, must be taken into account. “Refer” indicates that nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. Reprinted with permission from Vassalotti et al. (121).

with severely increased albuminuria (urinary albumin-to-creatinine ratio ≥300 mg/g creatinine) and/or estimated glomerular filtration rate <60 mL/min/1.73 m². **A**

11.4b Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. **B**

11.4c An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in people with diabetes who have normal blood pressure,

normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. **A**

11.4d Do not discontinue renin-angiotensin system blockade for increases in serum creatinine (≤30%) in the absence of volume depletion. **A**

11.5a For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m² and urinary albumin ≥200 mg/g creatinine. **A**

11.5b For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m² and urinary albumin ranging from normal to 200 mg/g creatinine. **B**

11.5c In people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m²), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration

rate is ≥ 25 mL/min/1.73 m²) additionally for cardiovascular risk reduction. **A**

- 11.5d** In people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events. **A**
- 11.6** In people with chronic kidney disease who have ≥ 300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow chronic kidney disease progression. **B**
- 11.7** For people with non-dialysis-dependent stage 3 or higher chronic kidney disease, dietary protein intake should be aimed to a target level of 0.8 g/kg body weight per day. **A** For patients on dialysis, higher levels of dietary protein intake should be considered since protein energy wasting is a major problem in some individuals on dialysis. **B**
- 11.8** Patients should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing estimated glomerular filtration rate and if the estimated glomerular filtration rate is < 30 mL/min/1.73 m². **A**
- 11.9** Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **A**

EPIDEMIOLOGY OF DIABETES AND CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is diagnosed by the persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1,2). In this section, the focus is on CKD attributed to diabetes

(diabetic kidney disease) in adults, which occurs in 20–40% of people with diabetes (1,3–5). Diabetic kidney disease typically develops after a diabetes duration of 10 years in type 1 diabetes (the most common presentation is 5–15 years after the diagnosis of type 1 diabetes) but may be present at diagnosis of type 2 diabetes. CKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD in the U.S. (6). In addition, among people with type 1 or type 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs (7). For details on the management of diabetic kidney disease in children, please see section 14, “Children and Adolescents.”

ASSESSMENT OF ALBUMINURIA AND ESTIMATED GLOMERULAR FILTRATION RATE

Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection (1,2). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration (8). Thus, to be useful for patient screening, semiquantitative or qualitative (dipstick) screening tests should be $> 85\%$ positive in those with moderately increased albuminuria (≥ 30 mg/g) and confirmed by albumin-to-creatinine values in an accredited laboratory (9,10). Hence, it is better to simply collect a spot urine sample for albumin-to-creatinine ratio because it will ultimately need to be done.

Normal albuminuria is defined as < 30 mg/g creatinine, moderately elevated albuminuria is defined as ≥ 30 – 300 mg/g creatinine, and severely elevated albuminuria is defined as ≥ 300 mg/g creatinine. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes (7,11,12). Furthermore, because of high biological variability of

$> 20\%$ between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have moderately or severely elevated albuminuria (1,2,13,14). Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (15).

Traditionally, eGFR is calculated from serum creatinine using a validated formula (16). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is preferred (2). eGFR is routinely reported by laboratories along with serum creatinine, and eGFR calculators are available online at nkdep.nih.gov. An eGFR persistently < 60 mL/min/1.73 m² in concert with a urinary albumin value of > 30 mg/g creatinine is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults over age 70 years (2,17). Historically, a correction factor for muscle mass was included in a modified equation for African American people; however, race is a social and not a biologic construct, making it problematic to apply race to clinical algorithms, and the need to advance health equity and social justice is clear. Thus, it was decided that the equation should be altered such that it applies to all (16). Hence, a committee was convened, resulting in the recommendation for immediate implementation of the CKD-EPI creatinine equation refit without the race variable in all laboratories in the U.S. Additionally, increased use of cystatin C (another marker of eGFR) is suggested in combination with the serum creatinine because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone.

DIAGNOSIS OF DIABETIC KIDNEY DISEASE

Diabetic kidney disease is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of

diabetic kidney disease may be present at diagnosis or without retinopathy in type 2 diabetes. Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (3,4,18,19).

An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or total proteinuria, the presence of nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease. For patients with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for people with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (20).

STAGING OF CHRONIC KIDNEY DISEASE

Stage 1 and stage 2 CKD are defined by evidence of high albuminuria with eGFR ≥ 60 mL/min/1.73 m², and stages 3–5 CKD are defined by progressively lower ranges of eGFR (21) (Fig. 11.1). At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease (CVD), CKD progression, and mortality (7). Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex and does not translate directly to treatment decisions (2). Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions. This is also important because eGFR levels are essential for modifications of drug dosages or restrictions of use (Fig. 11.1) (22,23). The degree of albuminuria should influence the choice of antihypertensive medications (see Section 10, “Cardiovascular Disease and Risk Management”) or glucose-lowering medications (see below). Observed history of eGFR loss (which is also associated with risk of CKD progression and other adverse health outcomes) and cause of kidney damage (including

possible causes other than diabetes) may also affect these decisions (24).

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is diagnosed by a 50% or greater sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR (25,26). People with diabetes are at higher risk of AKI than those without diabetes (27). Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), and the use of medications that alter renal blood flow and intrarenal hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized clinical outcome trials of advanced kidney disease (28) or high CVD risk with normal kidney function (29–31). It is also noteworthy that the nonsteroidal mineralocorticoid receptor antagonists (MRAs) do not increase the risk of AKI when used to slow kidney disease progression (32). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (33).

Elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system (RAS) blockers (such as ACE inhibitors and ARBs) must not be confused with AKI (34). An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrates that participants randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease (35–38). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (37). Accordingly, ACE inhibitors and ARBs should not be discontinued for increases in serum creatinine (<30%) in the absence of volume depletion.

Lastly, it should be noted that ACE inhibitors and ARBs are commonly not dosed at maximum tolerated doses because of fear that serum creatinine will rise. As noted above, this is an error. Note that in all clinical trials demonstrating efficacy of ACE inhibitors and ARBs in slowing kidney disease progression, the maximum tolerated doses were used—not very low doses that do not provide benefit. Moreover, there are now studies demonstrating outcome benefits on both mortality and slowed CKD progression in people with diabetes who have an eGFR <30 mL/min/1.73 m² (38). Additionally, when increases in serum creatinine reach 30% without associated hyperkalemia, RAS blockade should be continued (36,39).

SURVEILLANCE

Both albuminuria and eGFR should be monitored annually to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose drugs appropriately, and determine whether nephrology referral is needed. Among people with existing kidney disease, albuminuria and eGFR may change due to progression of CKD, development of a separate superimposed cause of kidney disease, AKI, or other effects of medications, as noted above. Serum potassium should also be monitored in patients treated with diuretics because these medications can cause hypokalemia, which is associated with cardiovascular risk and mortality (40–42). Patients with eGFR <60 mL/min/1.73 m² receiving ACE inhibitors, ARBs, or MRAs should have serum potassium measured periodically. Additionally, people with this lower range of eGFR should have their medication dosing verified, their exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and they should be evaluated for potential CKD complications (Table 11.1).

There is a clear need for annual quantitative assessment of urinary albumin excretion. This is especially true after a diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy to maximum tolerated doses, and achievement of blood pressure targets. Early changes in

Table 11.1—Selected complications of chronic kidney disease

Complication	Physical and laboratory evaluation
Blood pressure >130/80 mmHg	Blood pressure, weight
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m² (stage 3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage 3 CKD, every 3–5 months for stage 4 CKD, and every 1–3 months for stage 5 CKD, or as indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

kidney function may be detected by increases in albuminuria before changes in eGFR (43), and this also significantly affects cardiovascular risk. Moreover, an initial reduction of >30% from baseline, subsequently maintained over at least 2 years, is considered a valid surrogate for renal benefit by the Division of Cardiology and Nephrology of the U.S. Food and Drug Administration (FDA) (10). Continued surveillance can assess both response to therapy and disease progression and may aid in assessing participation in ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitors or ARB therapy in type 2 diabetes, reducing albuminuria to levels <300 mg/g creatinine or by >30% from baseline has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to maximize reduction in UACR. Data from post hoc analyses demonstrate less benefit on cardiorenal outcomes at half doses of RAS blockade (44). In type 1 diabetes, remission of albuminuria may occur spontaneously, and cohort studies evaluating associations of change in albuminuria with clinical outcomes have reported inconsistent results (45,46).

The prevalence of CKD complications correlates with eGFR (42). When eGFR is <60 mL/min/1.73 m², screening for complications of CKD is indicated (**Table 11.1**). Early vaccination against hepatitis B virus is indicated in individuals likely to progress to ESRD (see Section 4, “Comprehensive Medical Evaluation and

Assessment of Comorbidities,” for further information on immunization).

Prevention

The only proven primary prevention interventions for CKD are blood glucose and blood pressure control. There is no evidence that renin-angiotensin-aldosterone system (RAAS) inhibitors or any other interventions prevent the development of diabetic kidney disease. Thus, the American Diabetes Association does not recommend routine use of these medications solely for the purpose of prevention of the development of diabetic kidney disease.

INTERVENTIONS

Nutrition

For people with non-dialysis-dependent CKD, dietary protein intake should be ~0.8 g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter blood glucose levels, cardiovascular risk measures, or the course of GFR decline (47).

Restriction of dietary sodium (to <2,300 mg/day) may be useful to control blood

pressure and reduce cardiovascular risk (48,49), and individualization of dietary potassium may be necessary to control serum potassium concentrations (27,40–42). These interventions may be most important for individuals with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. For patients on dialysis, higher levels of dietary protein intake should be considered since malnutrition is a major problem for some patients on dialysis (50). Recommendations for dietary sodium and potassium intake should be individualized based on comorbid conditions, medication use, blood pressure, and laboratory data.

Glycemic Targets

Intensive lowering of blood glucose with the goal of achieving near-normoglycemia has been shown in large randomized studies to delay the onset and progression of albuminuria and reduce eGFR in people with type 1 diabetes (51,52) and type 2 diabetes (1,53–58). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that lowering blood glucose itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C targets (see **Table 6.2**).

The presence of CKD affects the risks and benefits of intensive lowering of blood glucose and a number of specific glucose-lowering medications. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of type 2 diabetes, adverse effects of intensive management of blood glucose levels (hypoglycemia and mortality) were increased among people with kidney disease at baseline (59,60). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (56,60,61). Therefore, in some people with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive (1,62).

Blood Pressure and Use of RAAS Inhibitors

RAAS inhibition remains a mainstay of management for people with diabetic kidney disease with albuminuria and for the treatment of hypertension in people with diabetes (with or without diabetic kidney disease). Indeed, all the trials that evaluated the benefits of SGLT2 inhibition or nonsteroidal mineralocorticoid receptor antagonist effects were done in individuals who were being treated with an ACE inhibitor or ARB, in some trials up to maximum tolerated doses.

Hypertension is a strong risk factor for the development and progression of CKD (63). Antihypertensive therapy reduces the risk of albuminuria (64–67), and among people with type 1 or 2 diabetes with established CKD (eGFR <60 mL/min/1.73 m² and UACR ≥300 mg/g creatinine), ACE inhibitor or ARB therapy reduces the risk of progression to ESRD (68–70,74–80). Moreover, antihypertensive therapy reduces the risk of cardiovascular events (64).

A blood pressure level <130/80 mmHg is recommended to reduce CVD mortality and slow CKD progression among all people with diabetes. Lower blood pressure targets (e.g., <130/80 mmHg) should be considered for patients based on individual anticipated benefits and risks. People with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD; therefore, lower blood pressure targets may be suitable in some cases, especially in individuals with severely elevated albuminuria (≥300 mg/g creatinine).

ACE inhibitors or ARBs are the preferred first-line agents for blood pressure treatment among people with diabetes, hypertension, eGFR <60 mL/min/1.73 m², and UACR ≥300 mg/g creatinine because of their proven benefits for prevention of CKD progression (68,69,74). ACE inhibitors and ARBs are considered to have similar benefits (75,76) and risks. In the setting of lower levels of albuminuria (30–299 mg/g creatinine), ACE inhibitor or ARB therapy at maximum tolerated doses in trials has reduced progression to more advanced albuminuria (≥300 mg/g creatinine), slowed CKD progression, and reduced cardiovascular events but has not reduced progression to ESRD (74,77). While ACE inhibitors or ARBs are often prescribed for

moderately increased albuminuria without hypertension, outcome trials have not been performed in this setting to determine whether they improve renal outcomes. Moreover, two long-term, double-blind studies demonstrated no renoprotective effect of either ACE inhibitors or ARBs in type 1 and type 2 diabetes among those who were normotensive with or without high albuminuria (formerly microalbuminuria) (78,79).

Absent kidney disease, ACE inhibitors or ARBs are useful to manage blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (80). In a trial of people with type 2 diabetes and normal urinary albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (81). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy (78). This was further supported by a similar trial in people with type 2 diabetes (79).

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or CKD, and the drug combination had higher adverse event rates (hyperkalemia and/or AKI) (82,83). Therefore, the combined use of ACE inhibitors and ARBs should be avoided.

Direct Renal Effects of Glucose-Lowering Medications

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (30,84–87). Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by >50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome activity (88–90). Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo (91–95). Renal effects should be considered when

selecting antihyperglycemia agents (see Section 9, “Pharmacologic Approaches to Glycemic Treatment”).

Selection of Glucose-Lowering Medications for People With Chronic Kidney Disease

For people with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate risks of CKD progression, CVD, and hypoglycemia (96,97). Drug dosing may require modification with eGFR <60 mL/min/1.73 m² (1).

The FDA revised its guidance for the use of metformin in CKD in 2016 (98), recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of people with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that 1) metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m², 2) eGFR should be monitored while taking metformin, 3) the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m² (99,100), 4) metformin should not be initiated for patients with an eGFR <45 mL/min/1.73 m², and 5) metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30–60 mL/min/1.73 m².

A number of recent studies have shown cardiovascular protection from SGLT2 inhibitors and GLP-1 RAs as well as renal protection from SGLT2 inhibitors and possibly from GLP-1 RAs. Selection of which glucose-lowering medications to use should be based on the usual criteria of an individual patient's risks (cardiovascular and renal in addition to glucose control) as well as convenience and cost.

SGLT2 inhibitors are recommended for people with stage 3 CKD or higher and type 2 diabetes, as they slow CKD progression and reduce heart failure risk independent of glucose management (101). GLP-1 RAs are suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression (102–105).

A number of large cardiovascular outcomes trials in people with type 2 diabetes at high risk for CVD or with existing CVD examined kidney effects as secondary outcomes. These trials include EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (71,86,91,94,102). Specifically, compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g creatinine, doubling of serum creatinine, ESRD, or death from ESRD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR \leq 45 mL/min/1.73 m² by 44%; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD, or death from ESRD by 40%; liraglutide reduced the risk of new or worsening nephropathy (a composite of persistent macroalbuminuria, doubling of serum creatinine, ESRD, or death from ESRD) by 22%; and semaglutide reduced the risk of new or worsening nephropathy (a composite of persistent UACR >300 mg/g creatinine, doubling of serum creatinine, or ESRD) by 36% (each $P < 0.01$). These analyses were limited by evaluation of study populations not selected primarily for CKD and examination of renal effects as secondary outcomes.

Some large clinical trials of SGLT2 inhibitors have focused on people with advanced CKD, and assessment of primary renal outcomes is either completed or ongoing. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CRENDENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR \geq 300–5,000 mg/g creatinine, and eGFR range 30–90 mL/min/1.73 m² (mean eGFR 56 mL/min/1.73 m² with a mean albuminuria level of >900 mg/day), had a primary composite end point of ESRD, doubling of serum creatinine, or renal or cardiovascular death (28,72). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESRD over control

(28). Additionally, the development of the primary end point, which included chronic dialysis for \geq 30 days, kidney transplantation or eGFR <15 mL/min/1.73 m² sustained for \geq 30 days by central laboratory assessment, doubling from the baseline serum creatinine average sustained for \geq 30 days by central laboratory assessment, or renal death or cardiovascular death, was reduced by 30%. This benefit was on background ACE inhibitor or ARB therapy in >99% of the patients (28). Moreover, in this advanced CKD group, there were clear benefits on cardiovascular outcomes demonstrating a 31% reduction in cardiovascular death or heart failure hospitalization and a 20% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (28,73,105).

A second trial in advanced diabetic kidney disease was the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study (106). This trial examined a cohort similar to that in CRENDENCE except 67.5% of the participants had type 2 diabetes and CKD (the other one-third had CKD without type 2 diabetes), and the end points were slightly different. The primary outcome was time to the first occurrence of any of the components of the composite, including \geq 50% sustained decline in eGFR or reaching ESRD or cardiovascular death, or renal death. Secondary outcome measures included time to the first occurrence of any of the components of the composite kidney outcome (\geq 50% sustained decline in eGFR or reaching ESRD or renal death), time to the first occurrence of either of the components of the cardiovascular composite (cardiovascular death or hospitalization for heart failure), and time to death from any cause. The trial had 4,304 participants with a mean eGFR at baseline of 43.1 ± 12.4 mL/min/1.73 m² (range 25–75 mL/min/1.73 m²) and a median UACR of 949 mg/g (range 200–5,000 mg/g). There was a significant benefit by dapagliflozin for the primary end point (hazard ratio [HR] 0.61 [95% CI 0.51–0.72]; $P < 0.001$) (106).

The HR for the kidney composite of a sustained decline in eGFR of \geq 50%, ESRD, or death from renal causes was 0.56 (95% CI 0.45–0.68; $P < 0.001$). The HR for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI

0.55–0.92; $P = 0.009$). Finally, all-cause mortality was decreased in the dapagliflozin group compared with the placebo group ($P < 0.004$).

In addition to renal effects, while SGLT2 inhibitors demonstrated reduced risk of heart failure hospitalizations, some also demonstrated cardiovascular risk reduction. GLP-1 RAs clearly demonstrated cardiovascular benefits. Namely, in the EMPA-REG OUTCOME, CANVAS, Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58), LEADER, and SUSTAIN-6 trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, and semaglutide, respectively, each reduced cardiovascular events, evaluated as primary outcomes, compared with placebo (see Section 10, “Cardiovascular Disease and Risk Management,” for further discussion). While the glucose-lowering effects of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m², the renal and cardiovascular benefits were still seen at eGFR levels of 25 mL/min/1.73 m² with no significant change in glucose (28,30, 51,62,71,94,106,107). Most participants with CKD in these trials also had diagnosed atherosclerotic cardiovascular disease (ASCVD) at baseline, although ~28% of CANVAS participants with CKD did not have diagnosed ASCVD (31).

Based on evidence from the CRENDENCE and DAPA-CKD trials, as well as secondary analyses of cardiovascular outcomes trials with SGLT2 inhibitors, cardio-vascular and renal events are reduced with SGLT2 inhibitor use in patients with an eGFR of 20 mL/min/1.73 m², independent of glucose-lowering effects (73,105).

While there is clear cardiovascular risk reduction associated with GLP-1 RA use in people with type 2 diabetes and CKD, the proof of benefit on renal outcomes will come with the results of the ongoing FLOW (A Research Study to See How Semaglutide Works Compared with Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial with injectable semaglutide (108). As noted above, published data address a limited group of people with CKD, mostly with coexisting ASCVD. Renal events, however, have been examined as both primary and secondary outcomes in large published trials. Adverse event profiles of these agents also must be considered. Please refer to **Table 9.2** for drug-specific factors, including adverse

event information, for these agents. Additional clinical trials focusing on CKD and cardiovascular outcomes in people with CKD are ongoing and will be reported in the next few years.

For people with type 2 diabetes and CKD, the selection of specific agents may depend on comorbidity and CKD stage. SGLT2 inhibitors may be more useful for individuals at high risk of CKD progression (i.e., with albuminuria or a history of documented eGFR loss) (Fig. 9.3) due to an apparent large beneficial effect on CKD incidence. However, for people with type 2 diabetes and diabetic kidney disease, use of an SGLT2 inhibitor in individuals with eGFR ≥ 20 mL/min/1.73 m² and UACR ≥ 200 mg/g creatinine is recommended to reduce CKD progression and cardiovascular events. This is a change in eGFR from previous recommendations that suggested an eGFR level > 25 mL/min/1.73 m². The reason for the lower limit of eGFR is as follows. The major clinical trials for SGLT2 inhibitors that showed benefit for people with diabetic kidney disease are CREDENCE and DAPA-CKD (28,105). CREDENCE enrollment criteria included an eGFR > 30 mL/min/1.73 m² and UACR > 300 mg/g (28,105). DAPA-CKD enrolled individuals with eGFR > 25 mL/min/1.73 m² and UACR > 200 mg/g. Subgroup analyses from DAPA-CKD (109) and analyses from the EMPEROR heart failure trials suggest that SGLT2 inhibitors are safe and effective at eGFR levels of > 20 mL/min/1.73 m². The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) enrolled 5,998 participants (110), and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) enrolled 3,730 participants (111); enrollment criteria included eGFR > 60 mL/min/1.73 m², but efficacy was seen at eGFR > 20 mL/min/1.73 m² in people with heart failure. Hence, the new recommendation is to use SGLT2 inhibitors in individuals with eGFR as low as 20 mL/min/1.73 m². In addition, the DECLARE-TIMI 58 trial suggested effectiveness in participants with normal urinary albumin levels (112). In sum, for people with type 2 diabetes and diabetic kidney disease, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events

in people with an eGFR ≥ 20 mL/min/1.73 m².

Of note, GLP-1 RAs may also be used at low eGFR for cardiovascular protection but may require dose adjustment (113).

Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease

MRAs historically have not been well studied in diabetic kidney disease because of the risk of hyperkalemia (114,115). However, data that do exist suggest sustained benefit on albuminuria reduction. There are two different classes of MRAs, steroidal and nonsteroidal, with one group not extrapolatable to the other (116). Late in 2020, the results of the first of two trials, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, which examined the renal effects of finerenone, demonstrated a significant reduction in diabetic kidney disease progression and cardiovascular events in people with advanced diabetic kidney disease (32,117). This trial had a primary end point of time to first occurrence of the composite end point of onset of kidney failure, a sustained decrease of eGFR $> 40\%$ from baseline over at least 4 weeks, or renal death. A prespecified secondary outcome was time to first occurrence of the composite end point cardiovascular death or nonfatal cardiovascular events (myocardial infarction, stroke, or hospitalization for heart failure). Other secondary outcomes included all-cause mortality, time to all-cause hospitalizations, and change in UACR from baseline to month 4, and time to first occurrence of the following composite end point: onset of kidney failure, a sustained decrease in eGFR of $\geq 57\%$ from baseline over at least 4 weeks, or renal death.

The double-blind, placebo-controlled trial randomized 5,734 people with CKD and type 2 diabetes to receive finerenone, a novel nonsteroidal MRA, or placebo. Eligible participants had a UACR of 30 to < 300 mg/g, an eGFR of 25 to < 60 mL/min/1.73 m², and diabetic retinopathy, or a UACR of 300–5,000 mg/g and an eGFR of 25 to < 75 mL/min/1.73 m². The mean age of participants was 65.6 years, and 30% were female. The mean eGFR was 44.3 mL/min/1.73 m²,

and the mean albuminuria was 852 mg/g (interquartile range 446–1,634 mg/g). The primary end point was reduced with finerenone compared with placebo (HR 0.82 [95% CI 0.73–0.93]; $P = 0.001$), as was the key secondary composite of cardiovascular outcome (HR 0.86 [95% CI 0.75–0.99]; $P = 0.03$). Hyperkalemia resulted in 2.3% discontinuation in the study group compared with 0.9% in the placebo group. However, the study was completed, and there were no deaths related to hyperkalemia. Of note, 4.5% of the total group were being treated with SGLT2 inhibitors.

The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial assessed the safety and efficacy of finerenone in reducing cardiovascular events among people with type 2 diabetes and CKD with elevated UACR (30 to < 300 mg/g creatinine) and eGFR 25–90 mL/min/1.73 m² (118). The study randomized eligible subjects to either finerenone ($n = 3,686$) or placebo ($n = 3,666$). Participants with an eGFR of 25–60 mL/min/1.73 m² at the screening visit received an initial dose at baseline of 10 mg once daily, and if eGFR at screening was ≥ 60 mL/min/1.73 m², the initial dose was 20 mg once daily. An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month, provided the serum potassium level was ≤ 4.8 mmol/L and eGFR was stable. The mean age of participants was 64.1 years (31% were female), and the median follow-up duration was 3.4 years. The median A1C was 7.7%, the mean systolic blood pressure was 136 mmHg, and the mean GFR was 67.8 mL/min/1.73 m². People with heart failure with a reduced ejection fraction and uncontrolled hypertension were excluded.

The primary composite outcome was cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. The finerenone group showed a 13% reduction in the primary end point compared with the placebo group (12.4% vs. 14.2%; HR 0.87 [95% CI 0.76–0.98]; $P = 0.03$). This benefit was primarily driven by a reduction in heart failure hospitalizations: 3.2% vs. 4.4% in the placebo group (HR 0.71 [95% CI 0.56–0.90]).

Of the secondary outcomes, the most noteworthy was a 36% reduction in end-stage kidney disease: 0.9% vs. 1.3% in

the placebo group (HR 0.64 [95% CI 0.41–0.995]). There was a higher incidence of hyperkalemia in the finerenone group, 10.8% vs. 5.3%, although only 1.2% of the 3,686 individuals on finerenone stopped the study due to hyperkalemia (0.6% vs. 0.4% of the placebo group).

The FIDELITY prespecified pooled efficacy and safety analysis incorporated individuals from both the FIGARO-DKD and FIDELIO-DKD trials ($N = 13,171$) to allow for evaluation across the spectrum of severity of CKD, since the populations were different (with a slight overlap) and the study designs were similar (119). The analysis showed a 14% reduction in composite cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure for finerenone vs. placebo (12.7% vs. 14.4%; HR 0.86 [95% CI 0.78–0.95]; $P = 0.0018$).

It also demonstrated a 23% reduction in the composite kidney outcome, consisting of sustained $\geq 57\%$ decrease in eGFR from baseline over ≥ 4 weeks, or renal death, for finerenone vs. placebo (5.5% vs. 7.1%; HR 0.77 [95% CI 0.67–0.88]; $P = 0.0002$).

The pooled FIDELITY trial analysis confirms and strengthens the positive cardiovascular and renal outcomes with finerenone across the spectrum of CKD, irrespective of baseline ASCVD history (with the exclusion of those with heart failure with reduced ejection fraction).

REFERRAL TO A NEPHROLOGIST

Health care professionals should consider referral to a nephrologist if the patient has continuously rising UACR levels and/or continuously declining eGFR, if there is uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria in spite of good blood pressure management, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or when there is advanced kidney disease (eGFR < 30 mL/min/1.73 m²) requiring discussion of renal replacement therapy for ESRD (2). The threshold for referral may vary depending on the frequency with which a health care professional encounters people with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR < 30 mL/min/1.73 m²) has been

found to reduce cost, improve quality of care, and delay dialysis (120). However, other specialists and health care professionals should also educate their patients about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

References

- Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care* 2014;37:2864–2883
- National Kidney Foundation. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;3:1–150
- Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. *JAMA* 2016;316:602–610
- de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011;305:2532–2539
- de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 2014;37:24–30
- Johansen KL, Chertow GM, Foley RN, et al. US Renal Data System 2020 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2021;77(Suppl. 1):A7–A8
- Fox CS, Matsushita K, Woodward M, et al.; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;380:1662–1673
- Yarnoff BO, Hoerger TJ, Simpson SK, et al.; Centers for Disease Control and Prevention CKD Initiative. The cost-effectiveness of using chronic kidney disease risk scores to screen for early-stage chronic kidney disease. *BMC Nephrol* 2017; 18:85
- Coresh J, Heerspink HJL, Sang Y, et al.; Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol* 2019;7:115–127
- Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis* 2020;75:84–104
- Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013;24: 302–308
- Groop P-H, Thomas MC, Moran JL, et al.; FinnDiane Study Group. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes* 2009;58:1651–1658
- Gomes MB, Gonçalves MF. Is there a physiological variability for albumin excretion rate? Study in patients with diabetes type 1 and non-diabetic individuals. *Clin Chim Acta* 2001;304: 117–123
- Naresh CN, Hayen A, Weening A, Craig JC, Chadban SJ. Day-to-day variability in spot urine albumin-creatinine ratio. *Am J Kidney Dis* 2013; 62:1095–1101
- Tankeu AT, Kaze FF, Noubiap JJ, Chelo D, Dehayem MY, Sobngwi E. Exercise-induced albuminuria and circadian blood pressure abnormalities in type 2 diabetes. *World J Nephrol* 2017;6:209–216
- Delanaye P, Glasscock RJ, Pottel H, Rule AD. An age-calibrated definition of chronic kidney disease: rationale and benefits. *Clin Biochem Rev* 2016;37:17–26
- Kramer HJ, Nguyen QD, Curhan G, Hsu C-Y. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA* 2003;289:3273–3277
- Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 2010;33: 1536–1543
- He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. *Diabetologia* 2013;56:457–466
- Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137–147
- Flynn C, Bakris GL. Noninsulin glucose-lowering agents for the treatment of patients on dialysis. *Nat Rev Nephrol* 2013;9:147–153
- Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011;80:1122–1137
- Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 2014;311:2518–2531
- Vassalotti JA, Centor R, Turner BJ, Greer RC, Choi M; National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Practical approach to detection and management of chronic kidney disease for the primary care clinician. *Am J Med* 2016;129:153–162.e7
- Zhou J, Liu Y, Tang Y, et al. A comparison of RIFLE, AKIN, KDIGO, and Cys-C criteria for the definition of acute kidney injury in critically ill patients. *Int Urol Nephrol* 2016;48:125–132
- Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018;14:607–625
- James MT, Grams ME, Woodward M, et al.; CKD Prognosis Consortium. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis* 2015;66:602–612
- Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2

- diabetes and nephropathy. *N Engl J Med* 2019;380:2295–2306
29. Nadkarni GN, Ferrandino R, Chang A, et al. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. *Diabetes Care* 2017;40:1479–1485
30. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–334
31. Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function: data from the CANVAS Program. *Circulation* 2018;138:1537–1550
32. Bakris GL, Agarwal R, Anker SD, et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;383:2219–2229
33. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. *Clin J Am Soc Nephrol* 2011;6:2567–2572
34. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160:685–693
35. Beddhu S, Greene T, Boucher R, et al. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. *Lancet Diabetes Endocrinol* 2018;6:555–563
36. Collard D, Brouwer TF, Peters RJG, Vogt L, van den Born BH. Creatinine rise during blood pressure therapy and the risk of adverse clinical outcomes in patients with type 2 diabetes mellitus. *Hypertension* 2018;72:1337–1344
37. Malhotra R, Craven T, Ambrosius WT, et al.; SPRINT Research Group. Effects of intensive blood pressure lowering on kidney tubule injury in CKD: a longitudinal subgroup analysis in SPRINT. *Am J Kidney Dis* 2019;73:21–30
38. Qiao Y, Shin J-I, Chen TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. *JAMA Intern Med* 2020;180:718–726
39. Ohkuma T, Jun M, Rodgers A, et al.; ADVANCE Collaborative Group. Acute increases in serum creatinine after starting angiotensin-converting enzyme inhibitor-based therapy and effects of its continuation on major clinical outcomes in type 2 diabetes mellitus. *Hypertension* 2019;73:84–91
40. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. *Clin J Am Soc Nephrol* 2017;12:245–252
41. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. *J Am Heart Assoc* 2017;6:e005428
42. Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol* 2017;245:277–284
43. Zelniker TA, Raz I, Mosenson O, et al. Effect of dapagliflozin on cardiovascular outcomes according to baseline kidney function and albuminuria status in patients with type 2 diabetes: a prespecified secondary analysis of a randomized clinical trial. *JAMA Cardiol* 2021;6:801–810
44. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015;21(Suppl.):S212–S220
45. de Boer IH, Gao X, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: the DCCT/EDIC study. *Clin J Am Soc Nephrol* 2016;11:1969–1977
46. Sumida K, Molnar MZ, Potukuchi PK, et al. Changes in albuminuria and subsequent risk of incident kidney disease. *Clin J Am Soc Nephrol* 2017;12:1941–1949
47. Klahr S, Levey AS, Beck GJ, et al.; Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 1994;330:877–884
48. Mills KT, Chen J, Yang W, et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA* 2016;315:2200–2210
49. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;71:1269–1324
50. Murray DP, Young L, Waller J, et al. Is dietary protein intake predictive of 1-year mortality in dialysis patients? *Am J Med Sci* 2018;356:234–243
51. DCCT/EDIC Research Group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. *Lancet Diabetes Endocrinol* 2014;2:793–800
52. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* 2011;365:2366–2376
53. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
54. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
55. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
56. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392–1406
57. Zoungas S, Arima H, Gerstein HC, et al.; Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017;5:431–437
58. Agrawal L, Azad N, Bahn GD, et al.; VADT Study Group. Long-term follow-up of intensive glycaemic control on renal outcomes in the Veterans Affairs Diabetes Trial (VADT). *Diabetologia* 2018;61:295–299
59. Papademetriou V, Lovato L, Doumas M, et al.; ACCORD Study Group. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int* 2015;87:649–659
60. Perkovic V, Heerspink HL, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int* 2013;83:517–523
61. Wong MG, Perkovic V, Chalmers J, et al.; ADVANCE-ON Collaborative Group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care* 2016;39:694–700
62. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;60:850–886
63. Leehey DJ, Zhang JH, Emanuele NV, et al.; VA NEPHRON-D Study Group. BP and renal outcomes in diabetic kidney disease: the Veterans Affairs Nephropathy in Diabetes Trial. *Clin J Am Soc Nephrol* 2015;10:2159–2169
64. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015;313:603–615
65. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–1585
66. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703–713
67. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:1273–1284
68. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–869
69. Lewis EJ, Hunsicker LG, Bain RP; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456–1462
70. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851–860
71. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–2128

72. Jardine MJ, Mahaffey KW, Neal B, et al.; CREDESCENCE study investigators. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE) study rationale, design, and baseline characteristics. *Am J Nephrol* 2017;46:462–472
73. Mahaffey KW, Jardine MJ, Bompont S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. *Circulation* 2019;140:739–750
74. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–259
75. Barnett AH, Bain SC, Bouter P, et al.; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;351:1952–1961
76. Wu HY, Peng CL, Chen PC, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers for major renal outcomes in patients with diabetes: a 15-year cohort study. *PLoS One* 2017;12:e0177654
77. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–878
78. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009;361:40–51
79. Weil EJ, Fufaa G, Jones LI, et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. *Diabetes* 2013;62:3224–3231
80. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. *BMJ* 2016;352:i438
81. Haller H, Ito S, Izzo JL Jr, et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011;364:907–917
82. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–1559
83. Fried LF, Emanuele N, Zhang JH, et al.; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369:1892–1903
84. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;129:587–597
85. Heerspink HJL, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independently of glycemic effects. *J Am Soc Nephrol* 2017;28:368–375
86. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–657
87. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;72:1845–1855
88. Woods TC, Satou R, Miyata K, et al. Canagliflozin prevents intrarenal angiotensinogen augmentation and mitigates kidney injury and hypertension in mouse model of type 2 diabetes mellitus. *Am J Nephrol* 2019;49:331–342
89. Heerspink HJL, Perco P, Mulder S, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. *Diabetologia* 2019;62:1154–1166
90. Yarbeygi H, Butler AE, Atkin SL, Katsiki N, Sahebkar A. Sodium-glucose cotransporter 2 inhibitors and inflammation in chronic kidney disease: possible molecular pathways. *J Cell Physiol* 2018;234:223–230
91. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311–322
92. Cooper ME, Perkovic V, McGill JB, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. *Am J Kidney Dis* 2015;66:441–449
93. Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;377:839–848
94. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
95. Shaman AM, Bain SC, Bakris GL, et al. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER. *Circulation* 2022;145:575–585
96. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. *JAMA Intern Med* 2017;177:1461–1470
97. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol* 2009;4:1121–1127
98. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function, 2017. Accessed 20 October 2022. Available from <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain>
99. Lalau JD, Kajbaf F, Bennis Y, Hurtel-Lemaire AS, Belpaire F, De Broe ME. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. *Diabetes Care* 2018;41:547–553
100. Chu PY, Hackstadt AJ, Chipman J, et al. Hospitalization for lactic acidosis among patients with reduced kidney function treated with metformin or sulfonylureas. *Diabetes Care* 2020;43:1462–1470
101. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021;6:148–158
102. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. *Circulation* 2019;139:2022–2031
103. Mann JFE, Hansen T, Idorn T, et al. Effects of once-weekly subcutaneous semaglutide on kidney function and safety in patients with type 2 diabetes: a post-hoc analysis of the SUSTAIN 1-7 randomised controlled trials. *Lancet Diabetes Endocrinol* 2020;8:880–893
104. Mann JFE, Muskiet MHA. Incretin-based drugs and the kidney in type 2 diabetes: choosing between DPP-4 inhibitors and GLP-1 receptor agonists. *Kidney Int* 2021;99:314–318
105. Bakris GL. Major advancements in slowing diabetic kidney disease progression: focus on SGLT2 inhibitors. *Am J Kidney Dis* 2019;74:573–575
106. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383:1436–1446
107. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347–357
108. Novo Nordisk A/S. A research study to see how semaglutide works compared to placebo in people with type 2 diabetes and chronic kidney disease (FLOW). In: [ClinicalTrials.gov](https://clinicaltrials.gov). Bethesda, MD, National Library of Medicine, 2019. Accessed 20 October 2022. Available from <https://clinicaltrials.gov/ct2/show/NCT03819153>
109. Chertow GM, Vart P, Jongs N, et al.; DAPA-CKD Trial Committees and Investigators. Effects of dapagliflozin in stage 4 chronic kidney disease. *J Am Soc Nephrol* 2021;32:2352–2361
110. Anker SD, Butler J, Filippatos G, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;385:1451–1461
111. Packer M, Anker SD, Butler J, et al.; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413–1424
112. Mosenzon O, Wiviott SD, Heerspink HJL, et al. The effect of dapagliflozin on albuminuria in DECLARE-TIMI 58. *Diabetes Care* 2021;44:1805–1815
113. Romera I, Cebrián-Cuenca A, Álvarez-Guisasaola F, Gomez-Peralta F, Reviriego J. A review of practical issues on the use of glucagon-like peptide-1 receptor agonists for the management of type 2 diabetes. *Diabetes Ther* 2019;10:5–19

114. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. *Am J Kidney Dis* 2008;51:199–211
115. Sarafidis P, Papadopoulos CE, Kamperidis V, Giannakoulas G, Doumas M. Cardiovascular protection with sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists in chronic kidney disease: a milestone achieved. *Hypertension* 2021;77:1442–1455
116. Agarwal R, Kolkhof P, Bakris G, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J* 2021;42:152–161
117. Filippatos G, Anker SD, Agarwal R, et al.; FIDELIO-DKD Investigators. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. *Circulation* 2021;143:540–552
118. Pitt B, Filippatos G, Agarwal R, et al.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;385:2252–2263
119. Agarwal R, Filippatos G, Pitt B, et al.; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;43:474–484
120. Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. *Cochrane Database Syst Rev* 2014;6:CD007333
121. Vassalotti JA, Centor R, Turner BJ, Greer RC, Choi M; National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Practical approach to detection and management of chronic kidney disease for the primary care clinician. *Am J Med* 2016;129:153–162.e7

12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2023

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, “Children and Adolescents.”

DIABETIC RETINOPATHY

Recommendations

- 12.1 Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**
- 12.2 Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control (1). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other eye disorders occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (2,3), nephropathy (4), hypertension (5), and dyslipidemia (6). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy, reduce the need for future ocular surgical procedures, and potentially improve patient-reported visual function (2,7–10). A meta-analysis of data from cardiovascular outcomes studies showed no association between glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment and retinopathy per se, except through the association between retinopathy and average A1C reduction at the 3-month and 1-year follow-up. Long-term impact of improved glycemic control on retinopathy was not studied

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in these trials. Retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy (11).

Screening

Recommendations

- 12.3** Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- 12.4** People with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**
- 12.5** If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- 12.6** Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**
- 12.7** Individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**
- 12.8** Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy and in the first

trimester and should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

The preventive effects of therapy and the fact that individuals with proliferative diabetic retinopathy (PDR) or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy. Prompt diagnosis allows triage of patients and timely intervention that may prevent vision loss in individuals who are asymptomatic despite advanced diabetic eye disease.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (12) (see Section 14, “Children and Adolescents”). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for individuals with type 1 or type 2 diabetes are generally repeated annually for individuals with minimal to no retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams. In a population with well-controlled type 2 diabetes, there was little risk of development of significant retinopathy within a 3-year interval after a normal examination (13), and less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in individuals without diabetic retinopathy (14). However, it is important to adjust screening intervals based on the presence of specific risk factors for retinopathy onset and worsening retinopathy. More frequent examinations by the ophthalmologist will be required if retinopathy is progressing or risk factors such as uncontrolled hyperglycemia, advanced baseline retinopathy, or diabetic macular edema are present.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (15–17). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care professional. Retinal

photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (15,18,19). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for dilated comprehensive eye exams, which should be performed at least initially and at yearly intervals thereafter or more frequently as recommended by an eye care professional. Artificial intelligence systems that detect more than mild diabetic retinopathy and diabetic macular edema, authorized for use by the U.S. Food and Drug Administration (FDA), represent an alternative to traditional screening approaches (20). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Results of all screening eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, people with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (21).

Type 2 Diabetes

People with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Individuals who develop gestational diabetes mellitus do not require eye examinations during pregnancy since they do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (22). However, individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the baseline prevalence and risk of development and/or progression of diabetic retinopathy. In a systematic review and meta-analysis of 18 observational studies of pregnant individuals with preexisting

type 1 or type 2 diabetes, the prevalence of any diabetic retinopathy and PDR in early pregnancy was 52.3% and 6.1%, respectively. The pooled progression rate per 100 pregnancies for new diabetic retinopathy development was 15.0 (95% CI 9.9–20.8), worsened nonproliferative diabetic retinopathy was 31.0 (95% CI 23.2–39.2), pooled sight-threatening progression rate from nonproliferative diabetic retinopathy to PDR was 6.3 (95% CI 3.3–10.0), and worsened PDR was 37.0 (95% CI 21.2–54.0), demonstrating that close follow-up should be maintained during pregnancy to prevent vision loss (23). In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (24).

A systematic review and meta-analysis and a controlled prospective study demonstrate that pregnancy in individuals with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor or retinopathy severity is advanced at the time of conception (23,24). Laser photocoagulation surgery can minimize the risk of vision loss during pregnancy for individuals with high-risk PDR or center-involved diabetic macular edema (24). Anti-vascular endothelial growth factor (anti-VEGF) medications should not be used in pregnant individuals with diabetes because of the theoretical risks to the vasculature of the developing fetus.

Treatment

Recommendations

- 12.9** Promptly refer individuals with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**
- 12.10** Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. **A**

12.11 Intravitreal injections of anti-vascular endothelial growth factor are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with proliferative diabetic retinopathy and also reduce the risk of vision loss in these individuals. **A**

12.12 Intravitreal injections of anti-vascular endothelial growth factor are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs vision acuity. **A**

12.13 Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-vascular endothelial growth factor therapy or eyes that are not candidates for this first-line approach. **A**

12.14 The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in individuals with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in individuals with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (25) showed in 1978 that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). In 1985, the ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset individuals with severe

nonproliferative diabetic retinopathy or less-than-high-risk PDR. Panretinal laser photocoagulation is still commonly used to manage complications of diabetic retinopathy that involve retinal neovascularization and its complications. A more gentle, macular focal/grid laser photocoagulation technique was shown in the ETDRS to be effective in treating eyes with clinically significant macular edema from diabetes (26), but this is now largely considered to be second-line treatment for diabetic macular edema.

Anti-Vascular Endothelial Growth Factor Treatment

Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others demonstrate that intravitreal injections of anti-VEGF agents are effective at regressing proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (27,28). In addition, it was observed that individuals treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing diabetic macular edema. However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that patients were required to have a greater number of visits and received a greater number of treatments than is typically required for management with panretinal laser, which may not be optimal for some individuals. The FDA has approved aflibercept and ranibizumab for the treatment of eyes with diabetic retinopathy. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. Anti-VEGF treatment of eyes with nonproliferative diabetic retinopathy has been demonstrated to reduce subsequent development of retinal neovascularization and diabetic macular edema but has not been shown to improve visual outcomes over 2 years of therapy and therefore is not routinely recommended for this indication (29).

While the ETDRS (26) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema

located at or threatening the macular center), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide a more effective treatment plan for center-involved diabetic macular edema than monotherapy with laser (30,31). Most patients require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from central-involved diabetic macular edema. There are currently three anti-VEGF agents commonly used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, and aflibercept (1)—and a comparative effectiveness study demonstrated that aflibercept provides vision outcomes superior to those of bevacizumab when eyes have moderate visual impairment (vision of 20/50 or worse) from diabetic macular edema (32). For eyes that have good vision (20/25 or better) despite diabetic macular edema, close monitoring with initiation of anti-VEGF therapy if vision worsens provides similar 2-year vision outcomes compared with immediate initiation of anti-VEGF therapy (33).

Eyes that have persistent diabetic macular edema despite anti-VEGF treatment may benefit from macular laser photocoagulation or intravitreal therapy with corticosteroids. Both of these therapies are also reasonable first-line approaches for individuals who are not candidates for anti-VEGF treatment due to systemic considerations such as pregnancy.

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit (8). In individuals with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (34,35).

NEUROPATHY

Screening

Recommendations

12.15 All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes

and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**

12.16 Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**

12.17 Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin. **E**

Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in people with diabetes is important. Points to be aware of include the following:

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in people with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers and amputations.
3. Recognition and treatment of autonomic neuropathy may improve

symptoms, reduce sequelae, and improve quality of life.

Specific treatment to reverse the underlying nerve damage is currently not available. Glycemic control can effectively prevent diabetic peripheral neuropathy (DPN) and cardiac autonomic neuropathy (CAN) in type 1 diabetes (36,37) and may modestly slow their progression in type 2 diabetes (38), but it does not reverse neuronal loss. Treatments of other modifiable risk factors (including lipids and blood pressure) can aid in prevention of DPN progression in type 2 diabetes and may reduce disease progression in type 1 diabetes (39–41). Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (42) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Individuals with a type 1 diabetes duration ≥ 5 years and all individuals with type 2 diabetes should be assessed annually for DPN using the medical history and simple clinical tests (42). Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensorimotor polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation.
2. Large-fiber function: lower-extremity reflexes, vibration perception, and 10-g monofilament.
3. Protective sensation: 10-g monofilament.

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations

where the clinical features are atypical or the diagnosis is unclear.

In all people with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, renal disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (43). See the American Diabetes Association position statement “Diabetic Neuropathy” for more details (42).

Diabetic Autonomic Neuropathy

Individuals who have had type 1 diabetes for ≥ 5 years and all individuals with type 2 diabetes should be assessed annually for autonomic neuropathy (42). The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating. Screening for symptoms of autonomic neuropathy includes asking about symptoms of orthostatic intolerance (dizziness, lightheadedness, or weakness with standing), syncope, exercise intolerance, constipation, diarrhea, urinary retention, urinary incontinence, or changes in sweat function. Further testing can be considered if symptoms are present and will depend on the end organ involved but might include cardiovascular autonomic testing, sweat testing, urodynamic studies, gastric emptying, or endoscopy/colonoscopy. Impaired counterregulatory responses to hypoglycemia in type 1 and type 2 diabetes can lead to hypoglycemia unawareness but are not directly linked to autonomic neuropathy.

Cardiovascular Autonomic Neuropathy. CAN is associated with mortality independently of other cardiovascular risk factors (44,45). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood

pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies. Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract, with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic control or with upper gastrointestinal symptoms without another identified cause. Exclusion of reversible/iatrogenic causes such as medications or organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is an approved alternative.

Genitourinary Disturbances. Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (42). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (46). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Recommendations

12.18 Optimize glucose control to prevent or delay the development of neuropathy in people with type 1 diabetes **A** and to slow the progression of

neuropathy in people with type 2 diabetes. **C** Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic neuropathy. **B**

12.19 Assess and treat pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy to improve quality of life. **E**

12.20 Gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A** Refer to neurologist or pain specialist when pain control is not achieved within the scope of practice of the treating physician. **E**

Glycemic Control

Near-normal glycemic control, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in people with type 1 diabetes (47–50). Although the evidence for the benefit of near-normal glycemic control is not as strong that for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (38,51). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea (52). Additionally, recent evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed clear benefit of intensive glucose and blood pressure control on the prevention of CAN in type 2 diabetes (53).

Lipid Control

Dyslipidemia is a key factor in the development of neuropathy in people with type 2 diabetes and may contribute to neuropathy risk in people with type 1 diabetes (54,55). Although the evidence for a relationship between lipids

and neuropathy development has become increasingly clear in type 2 diabetes, the optimal therapeutic intervention has not been identified. Positive effects of physical activity, weight loss, and bariatric surgery have been reported in individuals with DPN, but use of conventional lipid-lowering pharmacotherapy (such as statins or fenofibrates) does not appear to be effective in treating or preventing DPN development (56).

Blood Pressure Control

There are multiple reasons for blood pressure control in people with diabetes, but neuropathy progression (especially in type 2 diabetes) has now been added to this list. Although data from many studies have supported the role of hypertension in risk of neuropathy development, a recent meta-analysis of data from 14 countries in the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study revealed hypertension as an independent risk of DPN development with an odds ratio of 1.58 (57). In the ACCORD trial, intensive blood pressure intervention decreased CAN risk by 25% (53).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (58). No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (59). A recent guideline by the American Academy of Neurology recommends that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders because of increased frequency of these problems in individuals with DPN (60).

A number of pharmacologic therapies exist for treatment of pain in diabetes. The American Academy of Neurology update suggested that gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, tricyclic antidepressants (TCAs), and SNRI/opioid dual-mechanism agents could all be considered in the treatment of pain in DPN (60). These American Academy of Neurology recommendations offer a supplement to a recent American Diabetes Association pain monograph, although

some areas of disagreement exist, particularly around SNRI/opioid dual-mechanism agents (61). A recent head-to-head trial suggested therapeutic equivalency for TCAs, SNRIs, and gabapentinoids in the treatment of pain in DPN (62). The trial also supported the role of combination therapy over monotherapy for the treatment of pain in DPN.

Gabapentinoids. Gabapentinoids include several calcium channel $\alpha 2\text{-}\delta$ subunit ligands. Eight high-quality studies and seven medium-quality studies support the role of pregabalin in treatment of pain in DPN. One high-quality study and many small studies support the role of gabapentin in the treatment of pain in DPN. Two medium-quality studies suggest that microgabalin has a small effect on pain in DPN (60). Adverse effects may be more severe in older individuals (63) and may be attenuated by lower starting doses and more gradual titration.

SNRIs. SNRIs include duloxetine, venlafaxine, and desvenlafaxine, all selective SNRIs. Two high-quality studies and five medium-quality studies support the role of duloxetine in the treatment of pain in DPN. A high-quality study supports the role of venlafaxine in the treatment of pain in DPN. Only one medium-quality study supports a possible role for desvenlafaxine for treatment of pain in DPN (60). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tapentadol and Tramadol. Tapentadol and tramadol are centrally acting opioid analgesics that exert their analgesic effects through both μ -opioid receptor agonism and norepinephrine and serotonin reuptake inhibition. SNRI/opioid agents are probably effective in the treatment of pain in DPN. However, the use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided.

Tricyclic Antidepressants. Tricyclic antidepressants have been studied for treatment of pain, and most of the relevant data was acquired from trials of amitriptyline and include two high-quality studies and two medium-quality studies supporting the treatment of pain in DPN (60,62). Anticholinergic side effects may be dose limiting and restrict use in individuals ≥ 65 years of age.

Sodium Channel Blockers. Sodium channel blockers include lamotrigine, lacosamide, oxcarbazepine, and valproic acid. Five medium-quality studies support the role

of sodium channel blockers in treating pain in DPN (60).

Capsaicin. Capsaicin has received FDA approval for treatment of pain in DPN using an 8% patch, with one high-quality study reported. One medium-quality study of 0.075% capsaicin cream has been reported. In patients with contraindications to oral pharmacotherapy or who prefer topical treatments, the use of topical capsaicin can be considered.

Carbamazepine and α -Lipoic Acid. Carbamazepine and α -lipoic acid, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN (41,54,56).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. There have been clinical studies that assessed the impact of an approach incorporating the aforementioned nonpharmacologic measures. Additionally, supine blood pressure tends to be much higher in these individuals, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β -blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if an individual is unable to tolerate preferred agents (64–66). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment for diabetic gastroparesis may be very challenging. A low-fiber, low-fat eating plan provided in small frequent meals with a greater proportion of liquid calories may be useful (67–69). In addition, foods with small particle size may improve key symptoms (70). Withdrawing drugs with adverse effects on

gastrointestinal motility, including opioids, anticholinergics, tricyclic antidepressants, GLP-1 RAs, and pramlintide, may also improve intestinal motility (67,71). However, the risk of removal of GLP-1 RAs should be balanced against their potential benefits. In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA. It should be reserved for severe cases that are unresponsive to other therapies (71). Other treatment options include domperidone (available outside the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (72,73). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although its efficacy is variable and use is limited to individuals with severe symptoms that are refractory to other treatments (74).

Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve a person's quality of life.

FOOT CARE

Recommendations

- 12.21** Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **A**
- 12.22** The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment:

pinprick, temperature, vibration), and vascular assessment, including pulses in the legs and feet. **B**

- 12.23** Individuals with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **A**

- 12.24** Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**

- 12.25** Initial screening for peripheral arterial disease should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment as appropriate. **B**

- 12.26** A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., those on dialysis, those with Charcot foot, those with a history of prior ulcers or amputation, and those with peripheral arterial disease). **B**

- 12.27** Refer individuals who smoke and have a history of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and lifelong surveillance. **B**

- 12.28** Provide general preventive foot self-care education to all people with diabetes, including those with loss of protective sensation, on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. **B**

- 12.29** The use of specialized therapeutic footwear is recommended for people with diabetes at high risk for ulceration, including those with loss of protective sensation, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. **B**

- 12.30** For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial-proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy. **A**

Foot ulcerations and amputations are common complications associated with diabetes. These may be the consequences of several factors, including peripheral neuropathy, peripheral arterial disease (PAD), and foot deformities. They represent major causes of morbidity and mortality in people with diabetes. Early recognition of at-risk feet, preulcerative lesions, and prompt treatment of ulcerations and other lower-extremity complications can delay or prevent adverse outcomes.

Early recognition requires an understanding of those factors that put people with diabetes at increased risk for ulcerations and amputations. Factors that are associated with the at-risk foot include the following:

- Poor glycemic control
- Peripheral neuropathy/LOPS
- PAD
- Foot deformities (bunions, hammer-toes, Charcot joint, etc.)
- Preulcerative corns or calluses
- Prior ulceration
- Prior amputation
- Smoking
- Retinopathy
- Nephropathy (particularly individuals on dialysis or posttransplant)

Identifying the at-risk foot begins with a detailed history documenting diabetes control, smoking history, exercise tolerance, history of claudication or rest pain, and prior ulcerations or amputations. A thorough examination of the feet should be performed annually in all people with diabetes and more frequently in at-risk individuals (75). The examination should include assessment of skin integrity, assessment for LOPS using the 10-g monofilament along with at least one other neurological assessment tool, pulse examination of the dorsalis pedis and posterior tibial arteries, and assessment for foot deformities such as bunions, hammertoes, and prominent metatarsals, which increase plantar foot pressures and increase risk for ulcerations. At-risk individuals should be assessed at each visit and should be referred to foot care specialists for ongoing preventive care and surveillance. The physical examination can stratify patients into different categories and determine the frequency of these visits (76) (Table 12.1).

Evaluation for Loss of Protective Sensation

The presence of peripheral sensory neuropathy is the single most common component cause for foot ulceration. In a multicenter trial, peripheral neuropathy was found to be a component cause in 78% of people with diabetes with ulcerations and that the triad of peripheral sensory neuropathy, minor trauma, and foot deformity was present in >63% of participants (77). All people with diabetes should undergo a comprehensive foot examination at least annually, or

more frequently for those in higher-risk categories (75,76).

LOPS is vital to risk assessment. One of the most useful tests to determine LOPS is the 10-g monofilament test. Studies have shown that clinical examination and the 10-g monofilament test are the two most sensitive tests in identifying the foot at risk for ulceration (78). The monofilament test should be performed with at least one other neurologic assessment tool (e.g., pinprick, temperature perception, ankle reflexes, or vibratory perception with a 128-Hz tuning fork or similar device). Absent monofilament sensation and one other abnormal test confirms the presence of LOPS. Further neurological testing, such as nerve conduction, electromyography, nerve biopsy, or intraepidermal nerve fiber density biopsies, are rarely indicated for the diagnosis of peripheral sensory neuropathy (42).

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of leg fatigue, claudication, and rest pain relieved with dependency. Physical examination for PAD should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time (75,79). Any patient exhibiting signs and symptoms of PAD should be referred for noninvasive arterial studies in the form of Doppler ultrasound with pulse volume recordings. While ankle-brachial indices will be calculated, they should be interpreted carefully, as they are known to be inaccurate in people with diabetes due to

noncompressible vessels. Toe systolic blood pressure tends to be more accurate. Toe systolic blood pressures <30 mmHg are suggestive of PAD and an inability to heal foot ulcerations (80). Individuals with abnormal pulse volume recording tracings and toe pressures <30 mmHg with foot ulcers should be referred for immediate vascular evaluation. Due to the high prevalence of PAD in people with diabetes, it has been recommended by the Society for Vascular Surgery and the American Podiatric Medical Association in their 2016 guidelines that all people with diabetes >50 years of age should undergo screening via noninvasive arterial studies (79,81). If normal, these should be repeated every 5 years (79).

Patient Education

All people with diabetes (and their families), particularly those with the aforementioned high-risk conditions, should receive general foot care education, including appropriate management strategies (82–84). This education should be provided to all newly diagnosed people with diabetes as part of an annual comprehensive examination and to individuals with high-risk conditions at every visit. Recent studies have shown that while education improves knowledge of diabetic foot problems and self-care of the foot, it does not improve behaviors associated with active participation in their overall diabetes care and to achieve personal health goals (85). Evidence also suggests that while patient and family education are important, the knowledge is quickly forgotten and needs to be reinforced regularly (86).

Table 12.1—International Working Group on the Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and No PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: <ul style="list-style-type: none"> ● History of foot ulcer ● Amputation (minor or major) ● End-stage renal disease 	Every 1–3 months

Adapted with permission from Schaper et al. (76). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and patient-centered requirements.

Individuals considered at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot inspections on a daily basis. Individuals with LOPS should be educated on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. Patients should also be educated on the importance of referrals to foot care specialists. A recent study showed that people with diabetes and foot disease lacked awareness of their risk status and why they were being referred to a multidisciplinary team of foot care specialists. Further, they exhibited a variable degree of interest in learning further about foot complications (87).

Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Those with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

The selection of appropriate footwear and footwear behaviors at home should also be discussed (e.g., no walking barefoot, avoiding open-toed shoes). Therapeutic footwear with custom-made orthotic devices have been shown to reduce peak plantar pressures (84). Most studies use reduction in peak plantar pressures as an outcome as opposed to ulcer prevention. Certain design features of the orthoses, such as rocker soles and metatarsal accommodations, can reduce peak plantar pressures more significantly than insoles alone. A systematic review, however, showed there was no significant reduction in ulcer incidence after 18 months compared with standard insoles and extra-depth shoes. Further, it was also noted that evidence to prevent first ulcerations was non-existent (88).

Treatment

Treatment recommendations for people with diabetes will be determined by their risk category. No-risk or low-risk individuals can often be managed with

education and self-care. People in the moderate- to high-risk category should be referred to foot care specialists for further evaluation and regular surveillance as outlined in **Table 12.1**. This includes individuals with LOPS, PAD, and/or structural foot deformities, such as Charcot foot, bunions, or hammertoes. Individuals with any open ulceration or unexplained swelling, erythema, or increased skin temperature should be referred urgently to a foot care specialist or multidisciplinary team.

Initial treatment recommendations should include daily foot inspection, use of moisturizers for dry, scaly skin, and avoidance of self-care of ingrown nails and calluses. Well-fitted athletic or walking shoes with customized pressure-relieving orthoses should be part of initial recommendations for people with increased plantar pressures (as demonstrated by plantar calluses). Individuals with deformities such as bunions or hammertoes may require specialized footwear such as extra-depth shoes. Those with even more significant deformities, as in Charcot joint disease, may require custom-made footwear.

Special consideration should be given to individuals with neuropathy who present with a warm, swollen, red foot with or without a history of trauma and without an open ulceration. These individuals require a thorough workup for possible Charcot neuroarthropathy (89). Early diagnosis and treatment of this condition is of paramount importance in preventing deformities and instability that can lead to ulceration and amputation. These individuals require total non-weight-bearing and urgent referral to a foot care specialist for further management. Foot and ankle X-rays should be performed in all individuals presenting with the above clinical findings.

There have been a number of developments in the treatment of ulcerations over the years (90). These include negative-pressure therapy, growth factors, bioengineered tissue, acellular matrix tissue, stem cell therapy, hyperbaric oxygen therapy, and, most recently, topical oxygen therapy (91–93). While there is literature to support many modalities currently used to treat diabetic foot wounds, robust randomized controlled trials (RCTs) are often lacking. However, it is agreed that the initial treatment and evaluation of ulcerations

include the following five basic principles of ulcer treatment:

- Offloading of plantar ulcerations
- Debridement of necrotic, nonviable tissue
- Revascularization of ischemic wounds when necessary
- Management of infection: soft tissue or bone
- Use of physiologic, topical dressings

However, despite following the above principles, some ulcerations will become chronic and fail to heal. In those situations, advanced wound therapy can play a role. When to employ advanced wound therapy has been the subject of much discussion, as the therapy is often quite expensive. It has been determined that if a wound fails to show a reduction of 50% or more after 4 weeks of appropriate wound management (i.e., the five basic principles above), consideration should be given to the use of advanced wound therapy (94). Treatment of these chronic wounds is best managed in a multidisciplinary setting.

Evidence to support advanced wound therapy is challenging to produce and to assess. Randomization of trial participants is difficult, as there are many variables that can affect wound healing. In addition, many RCTs exclude certain cohorts of people, e.g., individuals with chronic renal disease or those on dialysis. Finally, blinding of participants and clinicians is not always possible. Meta-analyses and systematic reviews of observational studies are used to determine the clinical effectiveness of these modalities. Such studies can augment formal RCTs by including a greater variety of participants in various clinical settings who are typically excluded from the more rigidly structured clinical trials.

Advanced wound therapy can be categorized into nine broad categories (90) (**Table 12.2**). Topical growth factors, acellular matrix tissues, and bioengineered cellular therapies are commonly employed in offices and wound care centers to expedite healing of chronic, more superficial ulcerations. Numerous clinical reports and retrospective studies have demonstrated the clinical effectiveness of each of these modalities. Over the years, there has been increased evidence to support the use of these modalities.

Table 12.2—Categories of advanced wound therapies

Negative-pressure wound therapy
Standard electrically powered
Mechanically powered
Oxygen therapies
Hyperbaric oxygen therapy
Topical oxygen therapy
Oxygen-releasing sprays, dressings
Biophysical
Electrical stimulation, diathermy
Pulsed electromagnetic fields, pulsed radiofrequency energy
Low-frequency noncontact ultrasound
Extracorporeal shock wave therapy
Growth factors
Becaplermin: platelet-derived growth factor
Fibroblast growth factor
Epidermal growth factor
Autologous blood products
Platelet-rich plasma
Leukocyte, platelet, fibrin multilayered patches
Whole blood clot
Acellular matrix tissues
Xenograft dermis
Bovine dermis
Xenograft acellular matrices
Small intestine submucosa
Porcine urinary bladder matrix
Ovine forestomach
Equine pericardium
Bovine collagen
Bilayered dermal regeneration matrix
Human dermis products
Human pericardium
Placental tissues
Amniotic tissues/amniotic fluid
Umbilical cord
Bioengineered allogeneic cellular therapies
Bilayered skin equivalent (human keratinocytes and fibroblasts)
Dermal replacement therapy (human fibroblasts)
Stem cell therapies
Autogenous: bone marrow–derived stem cells
Allogeneic: amniotic matrix with mesenchymal stem cells
Miscellaneous active dressings
Hyaluronic acid, honey dressings, etc.
Sucrose octasulfate dressing
Adapted with permission from Frykberg and Banks (90).

Nonetheless, use of those products or agents with robust RCTs or systematic reviews should generally be preferred over those without level 1 evidence (Table 12.2).

Negative-pressure wound therapy was first introduced in the early to mid-1990s. It has become especially useful in wound preparation for skin grafts and flaps and assists in the closure of deep, large wounds (95,96). A variety of types exist in the marketplace and range from electrically powered to mechanically

powered in different sizes depending upon the specific wound requirements.

Electrical stimulation, pulsed radiofrequency energy, and extracorporeal shockwave therapy are biophysical modalities that are believed to upregulate growth factors or cytokines to stimulate wound healing, while low-frequency noncontact ultrasound is used to debride wounds. However, most of the studies advocating the use of these modalities have been retrospective observational or poor-quality RCTs.

Hyperbaric oxygen therapy is the delivery of oxygen through a chamber, either individual or multiperson, with the intention of increasing tissue oxygenation to increase tissue perfusion and neovascularization, combat resistant bacteria, and stimulate wound healing. While there had been great interest in this modality being able to expedite healing of chronic diabetic foot ulcers (DFUs), there has only been one positive RCT published in the last decade that reported increased healing rates at 9 and 12 months compared with control subjects (97). More recent studies with significant design deficiencies and participant dropouts have failed to provide corroborating evidence that hyperbaric oxygen therapy should be widely used for managing nonhealing DFUs (98,99). While there may be some benefit in prevention of amputation in selected chronic neuroischemic ulcers, recent studies have shown no benefit in healing DFUs in the absence of ischemia and/or infection (93,100).

Topical oxygen therapy has been studied rather vigorously in recent years, with several high-quality RCTs and at least five systematic reviews and meta-analyses all supporting its efficacy in healing chronic DFUs at 12 weeks (19,20,30–34,91,92,101–105). Three types of topical oxygen devices are available, including continuous-delivery, low-constant-pressure, and cyclical-pressure modalities. Importantly, topical oxygen therapy devices provide for home-based therapy rather than the need for daily visits to specialized centers. Very high participation with very few reported adverse events combined with improved healing rates makes this therapy another attractive option for advanced wound care.

If DFUs fail to heal despite appropriate wound care, adjunctive advanced therapies should be instituted and are best managed in a multidisciplinary manner. Once healed, all individuals should be enrolled in a formal comprehensive prevention program focused on reducing the incidence of recurrent ulcerations and subsequent amputations (75,106,107).

References

1. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:412–418

2. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
3. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. *Diabetologia* 2001;44:156–163
4. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. *Am J Kidney Dis* 1998;31:947–953
5. Yau JWY, Rogers SL, Kawasaki R, et al.; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35:556–564
6. Eid S, Sas KM, Abcouwer SF, et al. New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. *Diabetologia* 2019;62:1539–1549
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
8. Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233–244
9. Writing Team for the DCCT/EDIC Research Group; Gubitosi-Klug RA, Sun W, Cleary PA, et al. Effects of prior intensive insulin therapy and risk factors on patient-reported visual function outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. *JAMA Ophthalmol* 2016;134:137–145
10. Aiello LP, Sun W, Das A, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and ocular surgery in type 1 diabetes. *N Engl J Med* 2015;372:1722–1733
11. Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA_{1c} change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: a meta-analysis and meta-regression. *Diabetes Care* 2021;44:290–296
12. Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R, Dolan L, Imperatore G, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. *JAMA* 2017;317:825–835
13. Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. *Diabetes Care* 2011;34:1318–1319
14. Nathan DM, Bebu I, Hainsworth D, et al.; DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. *N Engl J Med* 2017;376:1507–1516
15. Silva PS, Horton MB, Clary D, et al. Identification of diabetic retinopathy and ungradable image rate with ultrawide field imaging in a national teleophthalmology program. *Ophthalmology* 2016;123:1360–1367
16. Bragge P, Gruen RL, Chau M, Forbes A, Taylor HR. Screening for presence or absence of diabetic retinopathy: a meta-analysis. *Arch Ophthalmol* 2011;129:435–444
17. Walton OB 4th, Garoon RB, Weng CY, et al. Evaluation of automated teleretinal screening program for diabetic retinopathy. *JAMA Ophthalmol* 2016;134:204–209
18. Daskivich LP, Vasquez C, Martinez C Jr, Tseng CH, Mangione CM. Implementation and evaluation of a large-scale teleretinal diabetic retinopathy screening program in the Los Angeles County Department of Health Services. *JAMA Intern Med* 2017;177:642–649
19. Sim DA, Mitry D, Alexander P, et al. The evolution of teleophthalmology programs in the United Kingdom: beyond diabetic retinopathy screening. *J Diabetes Sci Technol* 2016;10:308–317
20. Abramoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digit Med* 2018;1:1–8
21. Hooper P, Boucher MC, Cruess A, Dawson KG, Delpero W, Greve M, et al. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. *Can J Ophthalmol* 2012;47(2 Suppl):S1–S54
22. Gunderson EP, Lewis CE, Tsai AL, et al. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Diabetes* 2007;56:2990–2996
23. Widyaputri F, Rogers SL, Kandasamy R, Shub A, Symons RCA, Lim LL. Global estimates of diabetic retinopathy prevalence and progression in pregnant women with preexisting diabetes: a systematic review and meta-analysis. *JAMA Ophthalmol* 2022;140:486–494
24. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. *Diabetes Care* 2000;23:1084–1091
25. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383–396
26. Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796–1806
27. Gross JG, Glassman AR, Jampol LM, et al.; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015;314:2137–2146
28. Sivaprasad S, Prevost AT, Vasconcelos JC, et al.; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet* 2017;389:2193–2203
29. Maturi RK, Glassman AR, Josic K, et al.; DRCR Retina Network. Effect of intravitreal anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. *JAMA Ophthalmol* 2021;139:701–712
30. Elman MJ, Bressler NM, Qin H, et al.; Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118:609–614
31. Mitchell P, Bandello F, Schmidt-Erfurth U, et al.; RESTORE study group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615–625
32. Wells JA, Glassman AR, Ayala AR, et al.; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372:1193–1203
33. Baker CW, Glassman AR, Beaulieu WT, et al.; DRCR Retina Network. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA* 2019;321:1880–1894
34. Chew EY, Davis MD, Danis RP, et al.; Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study. *Ophthalmology* 2014;121:2443–2451
35. Shi R, Zhao L, Wang F, et al. Effects of lipid-lowering agents on diabetic retinopathy: a Meta-analysis and systematic review. *Int J Ophthalmol* 2018;11:287–295
36. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr Diab Rep* 2014;14:528
37. Martin CL, Albers JW; DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* 2014;37:31–38
38. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
39. Bashir M, Elhadd T, Dabbous Z, et al. Optimal glycaemic and blood pressure but not lipid targets are related to a lower prevalence of diabetic microvascular complications. *Diabetes Metab Syndr* 2021;15:102241
40. Look AHEAD Research Group. Effects of a long-term lifestyle modification programme on peripheral neuropathy in overweight or obese adults with type 2 diabetes: the Look AHEAD study. *Diabetologia* 2017;60:980–988
41. Callaghan BC, Reynolds EL, Banerjee M, et al. Dietary weight loss in people with severe obesity stabilizes neuropathy and improves symptomatology. *Obesity (Silver Spring)* 2021;29:2108–2118
42. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136–154

43. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. *Curr Diab Rep* 2009;9:423–431
44. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010;33:1578–1584
45. Pop-Busui R, Cleary PA, Braffett BH, et al.; DCCT/EDIC Research Group. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). *J Am Coll Cardiol* 2013;61:447–454
46. Smith AG, Lessard M, Reyna S, Doudova M, Singleton JR. The diagnostic utility of Sudoscan for distal symmetric peripheral neuropathy. *J Diabetes Complications* 2014;28:511–516
47. Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol* 1995;38:869–880
48. CDC Study Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998;41:416–423
49. Albers JW, Herman WH, Pop-Busui R, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *Diabetes Care* 2010;33:1090–1096
50. Pop-Busui R, Low PA, Waberski BH, et al.; DCCT/EDIC Research Group. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). *Circulation* 2009;119:2886–2893
51. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012;6:CD007543
52. Pop-Busui R, Lu J, Brooks MM, et al.; BARI 2D Study Group. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) cohort. *Diabetes Care* 2013;36:3208–3215
53. Tang Y, Shah H, Bueno Junior CR, et al. Intensive risk factor management and cardiovascular autonomic neuropathy in type 2 diabetes: the ACCORD trial. *Diabetes Care* 2021;44:164–173
54. Callaghan BC, Xia R, Banerjee M, et al.; Health ABC Study. Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. *Diabetes Care* 2016;39:801–807
55. Andersen ST, Witte DR, Dalsgaard EM, et al. Risk factors for incident diabetic polyneuropathy in a cohort with screen-detected type 2 diabetes followed for 13 years: ADDITION-Denmark. *Diabetes Care* 2018;41:1068–1075
56. Afshinnia F, Reynolds EL, Rajendiran TM, et al. Serum lipidomic determinants of human diabetic neuropathy in type 2 diabetes. *Ann Clin Transl Neurol* 2022;9:1392–1404
57. Lu Y, Xing P, Cai X, et al. Prevalence and risk factors for diabetic peripheral neuropathy in type 2 diabetic patients from 14 countries: estimates of the INTERPRET-DD study. *Front Public Health* 2020;8:534372
58. Sadosky A, Schaefer C, Mann R, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. *Diabetes Metab Syndr Obes* 2013;6:79–92
59. Waldfoegel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: a systematic review. *Neurology* 2017;88:1958–1967
60. Price R, Smith D, Franklin G, et al. Oral and topical treatment of painful diabetic polyneuropathy: practice guideline update summary: report of the AAN Guideline Subcommittee. *Neurology* 2022;98:31–43
61. Pop-Busui R, Ang L, Boulton AJM, et al. *Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy*. Arlington, VA, American Diabetes Association, 2022
62. Tesfaye S, Sloan G, Petrie J, et al.; OPTION-DM trial group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *Lancet* 2022;400:680–690
63. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. *J Pain* 2007;8:118–126
64. Briasoulis A, Silver A, Yano Y, Bakris GL. Orthostatic hypotension associated with baroreceptor dysfunction: treatment approaches. *J Clin Hypertens (Greenwich)* 2014;16:141–148
65. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: as easy as A, B, C. *Cleve Clin J Med* 2010;77:298–306
66. Jordan J, Fanciulli A, Tank J, et al. Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension. *J Hypertens* 2019;37:1541–1546
67. Camilleri M, Parkman HP, Shafi MA, Abell TL; American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108:18–37
68. Parrish CR, Pastors JG. Nutritional management of gastroparesis in people with diabetes. *Diabetes Spectr* 2007;20:231–234
69. Parkman HP, Yates KP, Hasler WL, et al.; NIDDK Gastroparesis Clinical Research Consortium. Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. *Gastroenterology* 2011;141:486–498, 498.e1–498.e7
70. Olausson EA, Störsrud S, Grundin H, Isaksson M, Attvall S, Simré M. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. *Am J Gastroenterol* 2014;109:375–385
71. Umpteirrez GE (Ed.) *Therapy for Diabetes Mellitus and Related Disorders*. 6th ed. Arlington, VA, American Diabetes Association; 2014
72. Sugumar A, Singh A, Pasricha PJ. A systematic review of the efficacy of domperidone for the treatment of diabetic gastroparesis. *Clin Gastroenterol Hepatol* 2008;6:726–733
73. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003;98:259–263
74. McCallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. *Clin Gastroenterol Hepatol* 2010;8:947–954; quiz e116
75. Boulton AJM, Armstrong DG, Albert SF, et al.; American Diabetes Association; American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* 2008;31:1679–1685
76. Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ; IWGDF Editorial Board. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020;36(Suppl. 1):e3266
77. Reiber GE, Vileikyte L, Boyko EJ, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 1999;22:157–162
78. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care* 2000;23:606–611
79. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg* 2016;63(Suppl.):35–215
80. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg* 2019;58(1S):S1–S109.e33
81. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26:3333–3341
82. Reaney M, Gladwin T, Churchill S. Information about foot care provided to people with diabetes with or without their partners: Impact on recommended foot care behavior. *Appl Psychol Health Well-Being* 2022;14:465–482
83. Heng ML, Kwan YH, Ilya N, et al. A collaborative approach in patient education for diabetes foot and wound care: A pragmatic randomised controlled trial. *Int Wound J* 2020;17:1678–1686
84. Bus SA, Lavery LA, Monteiro-Soares M, et al.; International Working Group on the Diabetic Foot. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020;36(Suppl. 1):e3269

85. Goodall RJ, Ellauzi J, Tan MKH, Onida S, Davies AH, Shalhoub J. A systematic review of the impact of foot care education on self efficacy and self care in patients with diabetes. *Eur J Vasc Endovasc Surg* 2020;60:282–292
86. Yuncken J, Williams CM, Stolwyk RJ, Haines TP. People with diabetes do not learn and recall their diabetes foot education: a cohort study. *Endocrine* 2018;62:250–258
87. Walton DV, Edmonds ME, Bates M, Vas PRJ, Petrova NL, Manu CA. People living with diabetes are unaware of their foot risk status or why they are referred to a multidisciplinary foot team. *J Wound Care* 2021;30:598–603
88. Bus SA, van Deursen RW, Armstrong DG, Lewis JE, Caravaggi CF; International Working Group on the Diabetic Foot. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl. 1):99–118
89. Rogers LC, Frykberg RG, Armstrong DG, et al. The Charcot foot in diabetes. *Diabetes Care* 2011;34:2123–2129
90. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care (New Rochelle)* 2015;4:560–582
91. Carter MJ, Frykberg RG, Oropallo A, Sen CK, Armstrong DG, Nair HKR, et al. Efficacy of topical wound oxygen therapy in healing chronic diabetic foot ulcers: systematic review and meta-analysis. *Adv Wound Care (New Rochelle)*. 21 June 2022 [Epub ahead of print]. DOI: 10.1089/wound.2022.0041
92. Frykberg RG, Franks PJ, Edmonds M, et al.; TWO2 Study Group. A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers: the TWO2 study. *Diabetes Care* 2020;43:616–624
93. Boulton AJM, Armstrong DG, Löndahl M, et al. *New Evidence-Based Therapies for Complex Diabetic Foot Wounds*. Arlington, VA, American Diabetes Association, 2022
94. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 2003;26:1879–1882
95. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008;31:631–636
96. Argenta LC, Morykwas MJ, Marks MW, DeFranzo AJ, Molnar JA, David LR. Vacuum-assisted closure: state of clinic art. *Plast Reconstr Surg* 2006;117(Suppl.):127S–142S
97. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010;33:998–1003
98. Santema KTB, Stoekenbroek RM, Koelemay MJW, et al.; DAMO2CLES Study Group. Hyperbaric oxygen therapy in the treatment of ischemic lower- extremity ulcers in patients with diabetes: results of the DAMO2CLES multicenter randomized clinical trial. *Diabetes Care* 2018;41:112–119
99. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. *Diabetes Care* 2016;39:392–399
100. Laliou RC, Brouwer RJ, Ubbink DT, Hoencamp R, Bol Raap R, van Hulst RA. Hyperbaric oxygen therapy for nonischemic diabetic ulcers: a systematic review. *Wound Repair Regen* 2020;28:266–275
101. Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. *J Wound Care* 2018;27(Suppl. 9):S30–S45
102. Serena TE, Bullock NM, Cole W, Lantis J, Li L, Moore S, et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. *J Wound Care* 2021;30(Suppl. 5):S7–S14
103. Sun XK, Li R, Yang XL, Yuan L. Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: an updated systematic review and meta-analysis. *Int Wound J*. 5 May 2022 [Epub ahead of print]. DOI: 10.1111/iwj.13830
104. Frykberg RG. Topical wound oxygen therapy in the treatment of chronic diabetic foot ulcers. *Medicina (Kaunas)* 2021;57:917
105. Sethi A, Khambhayta Y, Vas P. Topical oxygen therapy for healing diabetic foot ulcers: a systematic review and meta-analysis of randomised control trials. *Health Sci Rep* 2022;3:100028
106. van Netten JJ, Price PE, Lavery LA, et al.; International Working Group on the Diabetic Foot. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl. 1):84–98
107. Frykberg RG, Vileikyte L, Boulton AJM, Armstrong DG. The at-risk diabetic foot: time to focus on prevention. *Diabetes Care* 2022;45:e144–e145

13. Older Adults: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Recommendations

- 13.1** Consider the assessment of medical, psychological, functional (self-management abilities), and social domains in older adults to provide a framework to determine targets and therapeutic approaches for diabetes management. **B**
- 13.2** Screen for geriatric syndromes (i.e., polypharmacy, cognitive impairment, depression, urinary incontinence, falls, persistent pain, and frailty) in older adults, as they may affect diabetes self-management and diminish quality of life. **B**

Diabetes is a highly prevalent health condition in the aging population. Over one-quarter of people over the age of 65 years have diabetes, and one-half of older adults have prediabetes (1,2), and the number of older adults living with these conditions is expected to increase rapidly in the coming decades. Diabetes in older adults is also a highly heterogeneous condition. While type 2 diabetes predominates in the older population as much as in the younger population, improvements in insulin delivery, technology, and care over the last few decades have led to increasing numbers of people with childhood and adult-onset type 1 diabetes surviving and thriving into their later decades. Diabetes management in older adults requires regular assessment of medical, psychological, functional, and social domains. When assessing older adults with diabetes, it is important to accurately categorize the type of diabetes as well as other factors, including diabetes duration, the presence of complications, and treatment-related concerns, such as fear of hypoglycemia. Screening for diabetes complications in older adults should be individualized and periodically revisited, as the results of screening tests may impact targets and therapeutic approaches (3–5). Older adults with diabetes have higher rates of premature death, functional disability, accelerated muscle loss, and coexisting illnesses, such as hypertension, coronary heart disease, and stroke, than those

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without diabetes. At the same time, older adults with diabetes are also at greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, cognitive impairment, depression, urinary incontinence, injurious falls, persistent pain, and frailty (1). These conditions may impact older adults' diabetes self-management abilities and quality of life if left unaddressed (2,6,7). See Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for the full range of issues to consider when caring for older adults with diabetes.

The comprehensive assessment described above may provide a framework to determine targets and therapeutic approaches (8–10), including whether referral for diabetes self-management education is appropriate (when complicating factors arise or when transitions in care occur) or whether the current plan is too complex for the individual's self-management ability or the caregivers providing care (11). Particular attention should be paid to complications that can develop over short periods of time and/or would significantly impair functional status, such as visual and lower-extremity complications. Please refer to the American Diabetes Association (ADA) consensus report "Diabetes in Older Adults" for details (3).

NEUROCOGNITIVE FUNCTION

Recommendation

13.3 Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit, annually, and as appropriate. **B**

Older adults with diabetes are at higher risk of cognitive decline and institutionalization (12,13). The presentation of cognitive impairment ranges from subtle executive dysfunction to memory loss and overt dementia. People with diabetes have higher incidences of all-cause dementia, Alzheimer disease, and vascular dementia than people with normal glucose tolerance (14). The effects of hypoglycemia, hyperglycemia, and hyperinsulinemia on the brain are areas of intense research. Poor glycemic control

is associated with a decline in cognitive function (15,16), and longer duration of diabetes is associated with worsening cognitive function. There are ongoing studies evaluating whether preventing or delaying diabetes onset may help to maintain cognitive function in older adults. However, studies examining the effects of intensive glycemic and blood pressure control to achieve specific targets have not demonstrated a reduction in brain function decline (17,18).

Clinical trials of specific interventions—including cholinesterase inhibitors and glutamatergic antagonists—have not shown positive therapeutic benefit in maintaining or significantly improving cognitive function or in preventing cognitive decline (19). Pilot studies in individuals with mild cognitive impairment evaluating the potential benefits of intranasal insulin therapy and metformin therapy provide insights for future clinical trials and mechanistic studies (20–23).

Despite the paucity of therapies to prevent or remedy cognitive decline, identifying cognitive impairment early has important implications for diabetes care. The presence of cognitive impairment can make it challenging for clinicians to help their patients reach individualized glycemic, blood pressure, and lipid targets. Cognitive dysfunction makes it difficult for individuals to perform complex self-care tasks (24), such as monitoring glucose and adjusting insulin doses. It also hinders their ability to appropriately maintain the timing of meals and content of the diet. When clinicians are providing care for people with cognitive dysfunction, it is critical to simplify care plans and to facilitate and engage the appropriate support structure to assist individuals in all aspects of care.

Older adults with diabetes should be carefully screened and monitored for cognitive impairment (2). Several simple assessment tools are available to screen for cognitive impairment (24,25), such as the Mini-Mental State Examination (26), Mini-Cog (27), and the Montreal Cognitive Assessment (28), which may help to identify individuals requiring neuropsychological evaluation, particularly those in whom dementia is suspected (i.e., experiencing memory loss and decline in their basic and instrumental activities of daily living). Annual screening is indicated for adults 65 years of age or older for early detection of

mild cognitive impairment or dementia (4,29). Screening for cognitive impairment should additionally be considered when an individual presents with a significant decline in clinical status due to increased problems with self-care activities, such as errors in calculating insulin dose, difficulty counting carbohydrates, skipped meals, skipped insulin doses, and difficulty recognizing, preventing, or treating hypoglycemia. People who screen positive for cognitive impairment should receive diagnostic assessment as appropriate, including referral to a behavioral health professional for formal cognitive/neuropsychological evaluation (30).

HYPOGLYCEMIA

Recommendations

- 13.4** Because older adults with diabetes have a greater risk of hypoglycemia than younger adults, episodes of hypoglycemia should be ascertained and addressed at routine visits. **B**
- 13.5** For older adults with type 1 diabetes, continuous glucose monitoring is recommended to reduce hypoglycemia. **A**
- 13.6** For older adults with type 2 diabetes on multiple daily doses of insulin, continuous glucose monitoring should be considered to improve glycemic outcomes and decrease glucose variability. **B**
- 13.7** For older adults with type 1 diabetes, consider the use of automated insulin delivery systems **B** and other advanced insulin delivery devices such as connected pens **E** to reduce risk of hypoglycemia, based on individual ability.

Older adults are at higher risk of hypoglycemia for many reasons, including insulin deficiency necessitating insulin therapy and progressive renal insufficiency (31). As described above, older adults have higher rates of unidentified cognitive impairment and dementia, leading to difficulties in adhering to complex self-care activities (e.g., glucose monitoring, insulin dose adjustment). Cognitive decline has been associated with increased risk of hypoglycemia,

and conversely, severe hypoglycemia has been linked to increased risk of dementia (32,33). Therefore, as discussed in Recommendation 13.3, it is important to routinely screen older adults for cognitive impairment and dementia and discuss findings with the patients and their caregivers.

People with diabetes and their caregivers should be routinely queried about hypoglycemia (e.g., selected questions from the Diabetes Care Profile) (34) and hypoglycemia unawareness (35). Older adults can also be stratified for future risk for hypoglycemia with validated risk calculators (e.g., Kaiser Hypoglycemia Model) (36). An important step to mitigate hypoglycemia risk is to determine whether the person with diabetes is skipping meals or inadvertently repeating doses of their medications. Glycemic targets and pharmacologic treatments may need to be adjusted to minimize the occurrence of hypoglycemic events (2). This recommendation is supported by results from multiple randomized controlled trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Veterans Affairs Diabetes Trial (VADT), which showed that intensive treatment protocols targeting A1C <6.0% with complex drug regimens significantly increased the risk for hypoglycemia requiring assistance compared with standard treatment (37,38). However, these intensive treatment plans included extensive use of insulin and minimal use of glucagon-like peptide 1 (GLP-1) receptor agonists, and they preceded the availability of sodium–glucose cotransporter 2 (SGLT2) inhibitors.

For older people with type 1 diabetes, continuous glucose monitoring (CGM) is a useful approach to predicting and reducing the risk of hypoglycemia (39). In the Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial, adults over 60 years of age with type 1 diabetes were randomized to CGM or standard blood glucose monitoring. Over 6 months, use of CGM resulted in a small but statistically significant reduction in time spent with hypoglycemia (glucose level <70 mg/dL) compared with standard blood glucose monitoring (adjusted treatment difference –1.9% [–27 min/day]; 95% CI –2.8% to –1.1% [–40 to –16 min/day]; $P < 0.001$) (40,41). Among secondary outcomes, glycemic variability was reduced with CGM, as reflected by an

8% (95% CI 6.0–11.5) increase in time spent in range between 70 and 180 mg/dL. A 6-month extension of the trial demonstrated that these benefits were sustained for up to a year (42). These and other short-term trials are supported by observational data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study indicating that among older adults (mean age 58 years) with long-standing type 1 diabetes, routine CGM and insulin pump use was associated with fewer hypoglycemic events and hyperglycemic excursions and lower A1C levels (43). While the current evidence base for older adults is primarily in type 1 diabetes, the evidence demonstrating the clinical benefits of CGM for people with type 2 diabetes using insulin is growing (44) (see Section 7, “Diabetes Technology”). The DIAMOND (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes) study demonstrated that in adults ≥ 60 years of age with either type 1 or type 2 diabetes using multiple daily injections, CGM use was associated with improved A1C and reduced glycemic variability (45). Another population for which CGM may play an increasing role is older adults with physical or cognitive limitations who require monitoring of blood glucose by a surrogate.

The availability of accurate CGM devices that can communicate with insulin pumps through Bluetooth has enabled the development of advanced insulin delivery algorithms for pumps. These algorithms fall into two categories: predictive low-glucose suspend algorithms that automatically shut off insulin delivery if a hypoglycemic event is imminent and hybrid closed-loop algorithms that automatically adjust insulin infusion rates based on feedback from a CGM to keep glucose levels in a target range. Advanced insulin delivery devices have been shown to improve glycemic outcomes in both children and adults with type 1 diabetes. Most trials of these devices have included a broad range of people with type 1 diabetes but relatively few older adults. Recently, two small randomized controlled trials in older adults have been published. The Older Adult Closed Loop (ORACL) trial in 30 older adults (mean age 67 years) with type 1 diabetes found that a hybrid closed-loop insulin delivery strategy was associated with significant

improvements in time in range compared with sensor-augmented pump therapy (46). Moreover, they found small but significant decreases in hypoglycemia with the hybrid closed-loop strategy. Boughton et al. (47) reported results of an open-label, crossover design clinical trial in 37 older adults (≥ 60 years) in which 16 weeks of treatment with a hybrid closed-loop advanced insulin delivery system was compared with sensor-augmented pump therapy. They found that hybrid closed-loop insulin delivery improved the proportion of time glucose was in range largely due to decreases in hyperglycemia. In contrast to the ORACL study, no significant differences in hypoglycemia were observed. Both studies enrolled older individuals whose blood glucose was relatively well managed (mean A1C $\sim 7.4\%$), and both used a crossover design comparing hybrid closed-loop insulin delivery to sensor-augmented pump therapy. These trials provide the first evidence that older individuals with long-standing type 1 diabetes can successfully use advanced insulin delivery technologies to improve glycemic outcomes, as has been seen in younger populations. Use of such technologies should be periodically reassessed, as the burden may outweigh the benefits in those with declining cognitive or functional status.

TREATMENT GOALS

Recommendations

- 13.8** Older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as A1C <7.0–7.5% [53–58 mmol/mol]), while those with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less-stringent glycemic goals (such as A1C <8.0% [64 mmol/mol]). **C**
- 13.9** Glycemic goals for some older adults might reasonably be relaxed as part of individualized care, but hyperglycemia leading to symptoms or risk of acute hyperglycemia complications should be avoided in all people with diabetes. **C**

- 13.10** Screening for diabetes complications should be individualized in older adults. Particular attention should be paid to complications that would lead to functional impairment. **C**
- 13.11** Treatment of hypertension to individualized target levels is indicated in most older adults. **C**
- 13.12** Treatment of other cardiovascular risk factors should be individualized in older adults considering the time frame of benefit. Lipid-lowering therapy and aspirin therapy may benefit those with life expectancies at least equal to the time frame of primary prevention or secondary intervention trials. **E**

The care of older adults with diabetes is complicated by their clinical, cognitive, and functional heterogeneity. Some older individuals may have developed diabetes years earlier and have significant complications, others are newly diagnosed and may have had years of undiagnosed diabetes with resultant complications, and still, other older adults may have truly recent-onset disease with few or no complications (48). Some older adults with diabetes have other underlying chronic conditions, substantial diabetes-related comorbidity, limited cognitive or physical functioning, or frailty (49,50). Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable but are often longer than clinicians realize. Multiple prognostic tools for life expectancy for older adults are available (51), including tools specifically designed for older adults with diabetes (52). Older patients also vary in their preferences for the intensity and mode of glucose control (53). Health care professionals caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals (9,10) (**Table 13.1**). In addition, older adults with diabetes should be assessed for disease treatment and self-management knowledge, health literacy, and mathematical literacy (numeracy) at the onset of treatment. See **Fig. 6.2** for patient/disease-related factors to consider when

determining individualized glycemic targets.

A1C may have limitations in those who have medical conditions that impact red blood cell turnover (see Section 2, "Classification and Diagnosis of Diabetes," for additional details on the limitations of A1C) (54). Many conditions associated with increased red blood cell turnover, such as hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, are commonly seen in older adults and can falsely increase or decrease A1C. In these instances, plasma blood glucose fingerstick and sensor glucose readings should be used for goal setting (**Table 13.1**).

Older Adults With Good Functional Status and Without Complications

There are few long-term studies in older adults demonstrating the benefits of intensive glycemic, blood pressure, and lipid control. Older adults who can be expected to live long enough to realize the benefits of long-term intensive diabetes management, who have good cognitive and physical function, and who choose to do so via shared decision-making may be treated using therapeutic interventions and goals similar to those for younger adults with diabetes (**Table 13.1**).

As for all people with diabetes, diabetes self-management education and ongoing diabetes self-management support are vital components of diabetes care for older adults and their caregivers. Self-management knowledge and skills should be reassessed when treatment plan changes are made or an individual's functional abilities diminish. In addition, declining or impaired ability to perform diabetes self-care behaviors may be an indication that an older person with diabetes needs a referral for cognitive and physical functional assessment, using age-normalized evaluation tools, as well as help establishing a support structure for diabetes care (3,30).

Patients With Complications and Reduced Functionality

For people with advanced diabetes complications, life-limiting comorbid illnesses, or substantial cognitive or functional impairments, it is reasonable to set less-intensive glycemic goals (**Table 13.1**). Factors to consider in individualizing glycemic goals are outlined in **Fig. 6.2**.

Based on concepts of competing mortality and time to benefit, people with advanced diabetes complications are less likely to benefit from reducing the risk of microvascular complications (55). In addition, they are more likely to suffer serious adverse effects of therapeutics, such as hypoglycemia (56). However, those with poorly managed diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. Glycemic goals should, at a minimum, avoid these consequences.

While **Table 13.1** provides overall guidance for identifying complex and very complex patients, there is not yet global consensus on geriatric patient classification. Ongoing empiric research on the classification of older adults with diabetes based on comorbid illness has repeatedly found three major classes of patients: a healthy, a geriatric, and a cardiovascular class (9,57). The geriatric class has the highest prevalence of obesity, hypertension, arthritis, and incontinence, and the cardiovascular class has the highest prevalence of myocardial infarctions, heart failure, and stroke. Compared with the healthy class, the cardiovascular class has the highest risk of frailty and subsequent mortality. Additional research is needed to develop a reproducible classification scheme to distinguish the natural history of disease as well as differential response to glucose control and specific glucose-lowering agents (58).

Vulnerable Patients at the End of Life

For people with diabetes receiving palliative care and end-of-life care, the focus should be to avoid hypoglycemia and symptomatic hyperglycemia while reducing the burdens of glycemic management. Thus, as organ failure develops, several agents will have to be deintensified or discontinued. For a dying person, most agents for type 2 diabetes may be removed (59). There is, however, no consensus for the management of type 1 diabetes in this scenario (60). See the section **END-OF-LIFE CARE** below for additional information.

Beyond Glycemic Management

Although minimizing hyperglycemia may be important in older individuals with diabetes, greater reductions in

Table 13.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5% (53–58 mmol/mol)	80–130 mg/dL (4.4–7.2 mmol/L)	80–180 mg/dL (4.4–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or two or more instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or two or more ADL impairments)	Limited remaining life expectancy makes benefit uncertain	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<140/90 mmHg	Consider likelihood of benefit with statin

This table represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living; LTC, long-term care. ‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. "Multiple" means at least three, but many patients may have five or more (66). **The presence of a single end-stage chronic illness, such as stage 3–4 heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. Adapted from Kirkman et al. (3).

morbidity and mortality are likely to result from a clinical focus on comprehensive cardiovascular risk factor modification. There is strong evidence from clinical trials of the value of treating hypertension in older adults (61,62), with treatment of hypertension to individualized target levels indicated in most. There is less evidence for lipid-lowering therapy and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the time frames of the clinical trials (63). In the case of statins, the follow-up time of clinical trials ranged from 2 to 6 years. While the time frame of trials can be used to inform treatment decisions, a more specific concept is the time to benefit for a therapy. For statins, a meta-analysis of the previously mentioned trials showed that the time to benefit is 2.5 years (64).

LIFESTYLE MANAGEMENT

Recommendations

- 13.13** Optimal nutrition and protein intake is recommended for older adults; regular exercise, including aerobic activity, weight-bearing exercise, and/or resistance training, should be encouraged in all older adults who can safely engage in such activities. **B**
- 13.14** For older adults with type 2 diabetes, overweight/obesity, and capacity to safely exercise, an intensive lifestyle intervention focused on dietary changes, physical activity, and modest weight loss (e.g., 5–7%) should be considered for its benefits on quality of life, mobility and physical functioning, and cardiometabolic risk factor control. **A**

Lifestyle management in older adults should be tailored to frailty status. Diabetes in the aging population is associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass, which may result in sarcopenia and/or osteopenia (65,66). Diabetes is also recognized as an independent risk factor for frailty. Frailty is characterized by decline in physical performance and an increased risk of poor health outcomes due to physiologic vulnerability and functional or psychosocial stressors. Inadequate nutritional intake, particularly inadequate protein intake, can increase the risk of sarcopenia and frailty in older adults. Management of frailty in diabetes includes optimal nutrition with adequate protein intake combined with an exercise program that includes aerobic, weight-bearing, and resistance training. The benefits of a structured exercise program (as in the Lifestyle Interventions and Independence for Elders [LIFE] study) in frail

older adults include reducing sedentary time, preventing mobility disability, and reducing frailty (67,68). The goal of these programs is not weight loss but enhanced functional status.

For nonfrail older adults with type 2 diabetes and overweight or obesity, an intensive lifestyle intervention designed to reduce weight is beneficial across multiple outcomes. The Look AHEAD (Action for Health in Diabetes) trial is described in Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes." Look AHEAD specifically excluded individuals with a low functional status. It enrolled people between 45 and 74 years of age and required that they be able to perform a maximal exercise test (69,70). While the Look AHEAD trial did not achieve its primary outcome of reducing cardiovascular events, the intensive lifestyle intervention had multiple clinical benefits that are important to the quality of life of older adults. Benefits included weight loss, improved physical fitness, increased HDL cholesterol, lowered systolic blood pressure, reduced A1C levels, reduced waist circumference, and reduced need for medications (71). Additionally, several subgroups, including participants who lost at least 10% of baseline body weight at year 1, had improved cardiovascular outcomes (72). Risk factor control was improved with reduced utilization of antihypertensive medications, statins, and insulin (73). In age-stratified analyses, older adults in the trial (60 to early 70s) had similar benefits compared with younger people (74,75). In addition, lifestyle intervention produced benefits on aging-relevant outcomes such as reductions in multimorbidity and improvements in physical function and quality of life (76–79).

PHARMACOLOGIC THERAPY

Recommendations

- 13.15** In older adults with type 2 diabetes at increased risk of hypoglycemia, medication classes with low risk of hypoglycemia are preferred. **B**
- 13.16** Overtreatment of diabetes is common in older adults and should be avoided. **B**
- 13.17** Deintensification of treatment goals is recommended to reduce

the risk of hypoglycemia if it can be achieved within the individualized A1C target. **B**

- 13.18** Simplification of complex treatment plans (especially insulin) is recommended to reduce the risk of hypoglycemia and polypharmacy and decrease the burden of the disease if it can be achieved within the individualized A1C target. **B**

- 13.19** Consider costs of care and insurance coverage rules when developing treatment plans in order to reduce risk of cost-related barriers to adherence. **B**

Special care is required in prescribing and monitoring pharmacologic therapies in older adults (80). See **Fig. 9.3** for general recommendations regarding glucose-lowering treatment for adults with type 2 diabetes and **Table 9.2** for person- and drug-specific factors to consider when selecting glucose-lowering agents. Cost may be an especially important consideration, as older adults tend to be on many medications and live on fixed incomes (81). Accordingly, the costs of care and insurance coverage rules should be considered when developing treatment plans to reduce the risk of cost-related barriers to adherence (82,83). See **Table 9.3** and **Table 9.4** for median monthly cost in the U.S. of noninsulin glucose-lowering agents and insulin, respectively. It is important to match complexity of the treatment plan to the self-management ability of older adults with diabetes and their available social and medical support. Many older adults with diabetes struggle to maintain the frequent blood glucose monitoring and insulin injection regimens they previously followed, perhaps for many decades, as they develop medical conditions that may impair their ability to follow their treatment plan safely. Individualized glycemic goals should be established (**Fig. 6.2**) and periodically adjusted based on coexisting chronic illnesses, cognitive function, and functional status (2). Intensive glycemic control with regimens including insulin and sulfonylureas in older adults with complex or very complex medical conditions has been identified as overtreatment and found to be very common in clinical practice (84–88). Ultimately, the

determination of whether a person is considered overtreated requires an elicitation of the person's perceptions of the current medication burden and preferences for treatments. For those seeking to simplify their diabetes regimen, deintensification of regimens in individuals taking noninsulin glucose-lowering medications can be achieved by either lowering the dose or discontinuing some medications, as long as the individualized glycemic targets are maintained (89). When older adults are found to have an insulin regimen with complexity beyond their self-management abilities, lowering the dose of insulin may not be adequate (90). Simplification of the insulin plan to match an individual's self-management abilities and their available social and medical support in these situations has been shown to reduce hypoglycemia and disease-related distress without worsening glycemic outcomes (91–94). **Figure 13.1** depicts an algorithm that can be used to simplify the insulin regimen (93). There are now multiple studies evaluating deintensification protocols in diabetes as well as hypertension, demonstrating that deintensification is safe and possibly beneficial for older adults (89). **Table 13.2** provides examples of and rationale for situations where deintensification and/or insulin regimen simplification may be appropriate in older adults.

Metformin

Metformin is the first-line agent for older adults with type 2 diabetes. Recent studies have indicated that it may be used safely in individuals with estimated glomerular filtration rate ≥ 30 mL/min/1.73 m² (95). However, it is contraindicated in those with advanced renal insufficiency and should be used with caution in those with impaired hepatic function or heart failure because of the increased risk of lactic acidosis. Metformin may be temporarily discontinued before procedures, during hospitalizations, and when acute illness may compromise renal or liver function. Additionally, metformin can cause gastrointestinal side effects and a reduction in appetite that can be problematic for some older adults. Reduction or elimination of metformin may be necessary for those experiencing persistent gastrointestinal side effects. For those taking metformin long-term, monitoring for

Simplification of Complex Insulin Therapy

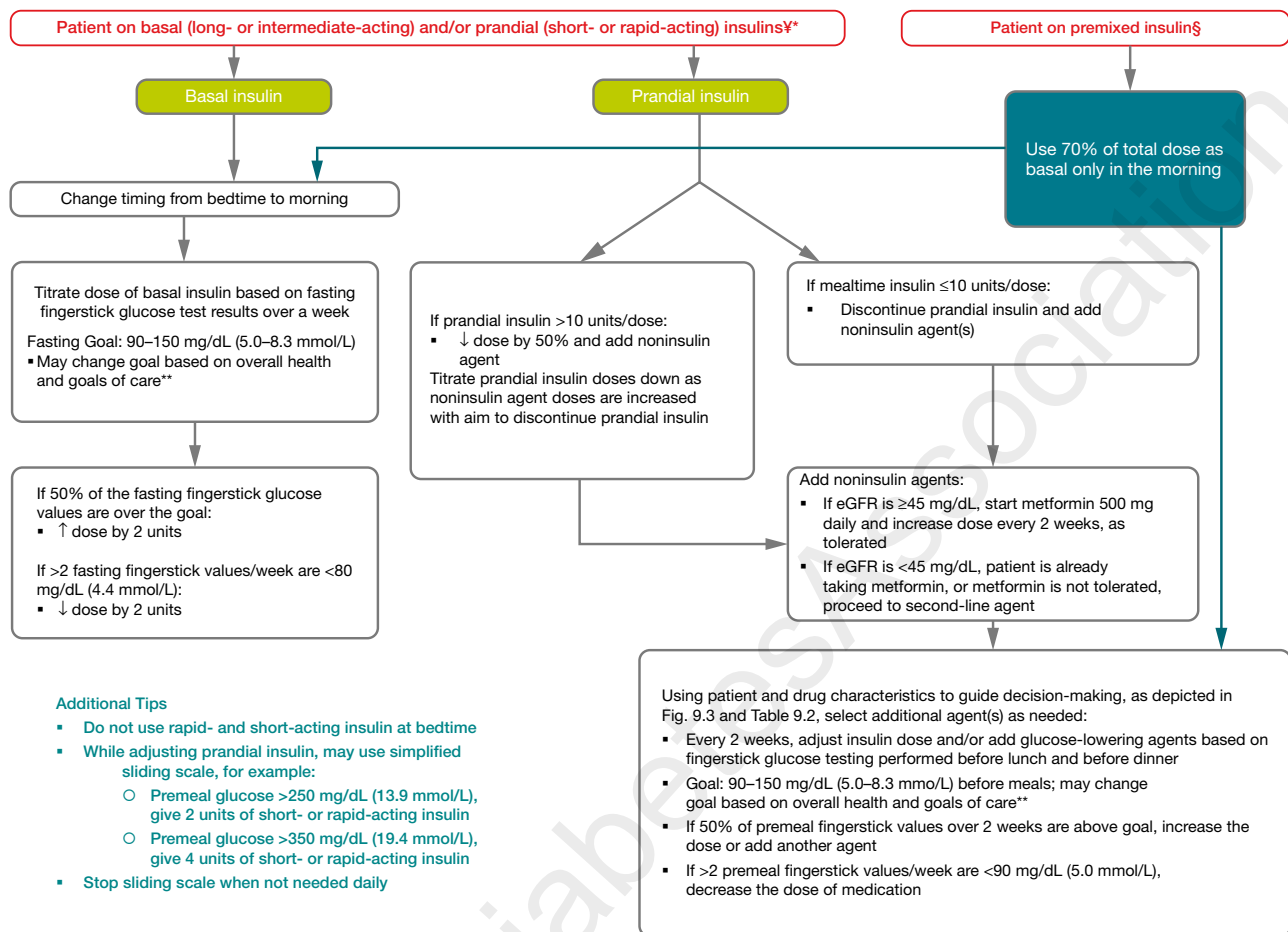


Figure 13.1—Algorithm to simplify insulin regimen for older adults with type 2 diabetes. eGFR, estimated glomerular filtration rate. *Basal insulins: glargine U-100 and U-300, detemir, degludec, and human NPH. **See Table 13.1. ¥Prandial insulins: short-acting (regular human insulin) or rapid-acting (lispro, aspart, and glulisine). §Premixed insulins: 70/30, 75/25, and 50/50 products. Adapted with permission from Munshi et al. (93).

vitamin B12 deficiency should be considered (96).

Thiazolidinediones

Thiazolidinediones, if used at all, should be used very cautiously in older adults on insulin therapy as well as in those with or at risk for heart failure, osteoporosis, falls or fractures, and/or macular edema (97,98). Lower doses of a thiazolidinedione in combination therapy may mitigate these side effects.

Insulin Secretagogues

Sulfonylureas and other insulin secretagogues are associated with hypoglycemia and should be used with caution. If used, sulfonylureas with a shorter duration of action, such as glipizide, are preferred. Glyburide is a longer-acting sulfonylurea and should be avoided in older adults (99).

Incretin-Based Therapies

Oral dipeptidyl peptidase 4 (DPP-4) inhibitors have few side effects and minimal risk of hypoglycemia, but their cost may be a barrier to some older adults. DPP-4 inhibitors do not reduce or increase major adverse cardiovascular outcomes (100). Across the trials of this drug class, there appears to be no interaction by age-group (101–103). A challenge of interpreting the age-stratified analyses of this drug class and other cardiovascular outcomes trials is that while most of these analyses were prespecified, they were not powered to detect differences.

GLP-1 receptor agonists have demonstrated cardiovascular benefits among people with diabetes and established atherosclerotic cardiovascular disease (ASCVD) and those at higher ASCVD risk, and newer trials are expanding our understanding of their benefits in

other populations (100). See Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," for a more extensive discussion regarding the specific indications for this class of agents. In a systematic review and meta-analysis of GLP-1 receptor agonist trials, these agents have been found to reduce major adverse cardiovascular events, cardiovascular deaths, stroke, and myocardial infarction to the same degree for people over and under 65 years of age (104). While the evidence for this class of agents for older adults continues to grow, there are a number of practical issues that should be considered specifically for older people. These drugs are injectable agents (with the exception of oral semaglutide) (105), which require visual, motor, and cognitive skills for appropriate administration. Agents with a weekly dosing schedule may reduce the

Table 13.2—Considerations for treatment regimen simplification and deintensification/deprescribing in older adults with diabetes (93,128)

Patient characteristics/ health status	Reasonable A1C/ treatment goal	Rationale/considerations	When may regimen simplification be required?	When may treatment deintensification/ deprescribing be required?
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	<7.0–7.5% (53–58 mmol/mol)	<ul style="list-style-type: none"> • Patients can generally perform complex tasks to maintain good glycemic control when health is stable • During acute illness, patients may be more at risk for administration or dosing errors that can result in hypoglycemia, falls, fractures, etc. 	<ul style="list-style-type: none"> • If severe or recurrent hypoglycemia occurs in patients on insulin therapy (regardless of A1C) • If wide glucose excursions are observed • If cognitive or functional decline occurs following acute illness 	<ul style="list-style-type: none"> • If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (regardless of A1C) • If wide glucose excursions are observed • In the presence of polypharmacy
Complex/intermediate (multiple coexisting chronic illnesses or two or more instrumental ADL impairments or mild-to-moderate cognitive impairment)	<8.0% (64 mmol/mol)	<ul style="list-style-type: none"> • Comorbidities may affect self-management abilities and capacity to avoid hypoglycemia • Long-acting medication formulations may decrease pill burden and complexity of medication regimen 	<ul style="list-style-type: none"> • If severe or recurrent hypoglycemia occurs in patients on insulin therapy (even if A1C is appropriate) • If unable to manage complexity of an insulin regimen • If there is a significant change in social circumstances, such as loss of caregiver, change in living situation, or financial difficulties 	<ul style="list-style-type: none"> • If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Community-dwelling patients receiving care in a skilled nursing facility for short-term rehabilitation	Avoid reliance on A1C, glucose target 100–200 mg/dL (5.55–11.1 mmol/L)	<ul style="list-style-type: none"> • Glycemic control is important for recovery, wound healing, hydration, and avoidance of infections • Patients recovering from illness may not have returned to baseline cognitive function at the time of discharge • Consider the type of support the patient will receive at home 	<ul style="list-style-type: none"> • If treatment regimen increased in complexity during hospitalization, it is reasonable, in many cases, to reinstate the prehospitalization medication regimen during the rehabilitation 	<ul style="list-style-type: none"> • If the hospitalization for acute illness resulted in weight loss, anorexia, short-term cognitive decline, and/or loss of physical functioning
Very complex/poor health (LTC or end-stage chronic illnesses or moderate-to-severe cognitive impairment or two or more ADL impairments)	Avoid reliance on A1C and avoid hypoglycemia and symptomatic hyperglycemia	<ul style="list-style-type: none"> • No benefits of tight glycemic control in this population • Hypoglycemia should be avoided • Most important outcomes are maintenance of cognitive and functional status 	<ul style="list-style-type: none"> • If on an insulin regimen and the patient would like to decrease the number of injections and fingerstick blood glucose monitoring events each day • If the patient has an inconsistent eating pattern 	<ul style="list-style-type: none"> • If on noninsulin agents with a high hypoglycemia risk in the context of cognitive dysfunction, depression, anorexia, or inconsistent eating pattern • If taking any medications without clear benefits
At the end of life	Avoid hypoglycemia and symptomatic hyperglycemia	<ul style="list-style-type: none"> • Goal is to provide comfort and avoid tasks or interventions that cause pain or discomfort • Caregivers are important in providing medical care and maintaining quality of life 	<ul style="list-style-type: none"> • If there is pain or discomfort caused by treatment (e.g., injections or finger sticks) • If there is excessive caregiver stress due to treatment complexity 	<ul style="list-style-type: none"> • If taking any medications without clear benefits in improving symptoms and/or comfort

Treatment regimen simplification refers to changing strategy to decrease the complexity of a medication regimen (e.g., fewer administration times, fewer blood glucose checks) and decreasing the need for calculations (such as sliding-scale insulin calculations or insulin-carbohydrate ratio calculations). Deintensification/deprescribing refers to decreasing the dose or frequency of administration of a treatment or discontinuing a treatment altogether. ADL, activities of daily living; LTC, long-term care.

burden of administration. GLP-1 receptor agonists may also be associated with nausea, vomiting, and diarrhea. Given the gastrointestinal side effects of this class, GLP-1 receptor agonists may not be preferred in older adults who are experiencing unexplained weight loss.

Sodium–Glucose Cotransporter 2 Inhibitors

SGLT2 inhibitors are administered orally, which may be convenient for older adults with diabetes. In those with established ASCVD, these agents have shown cardiovascular benefits (100). This class of agents has also been found to be beneficial for people with heart failure and to slow the progression of chronic kidney disease. See Section 9, “Pharmacologic Approaches to Glycemic Treatment,” and Section 10, “Cardiovascular Disease and Risk Management,” for a more extensive discussion regarding the indications for this class of agents. The stratified analyses of the trials of this drug class indicate that older adults have similar or greater benefits than younger people (106–108). While understanding of the clinical benefits of this class is evolving, side effects such as volume depletion, urinary tract infections, and worsening urinary incontinence may be more common among older people.

Insulin Therapy

The use of insulin therapy requires that individuals or their caregivers have good visual and motor skills and cognitive ability. Insulin therapy relies on the ability of the older person with diabetes to administer insulin on their own or with the assistance of a caregiver. Insulin doses should be titrated to meet individualized glycemic targets and to avoid hypoglycemia.

Once-daily basal insulin injection therapy is associated with minimal side effects and may be a reasonable option in many older adults (109). When choosing a basal insulin, long-acting insulin analogs have been found to be associated with a lower risk of hypoglycemia compared with NPH insulin in the Medicare population. Multiple daily injections of insulin may be too complex for an older person with advanced diabetes complications, life-limiting coexisting chronic illnesses, or limited functional status. **Figure 13.1** provides a potential approach to insulin regimen simplification.

Other Factors to Consider

The needs of older adults with diabetes and their caregivers should be evaluated to construct a tailored care plan. Impaired social functioning may reduce these individuals' quality of life and increase the risk of functional dependency (7). The person's living situation must be considered as it may affect diabetes management and support needs. Social and instrumental support networks (e.g., adult children, caretakers) that provide instrumental or emotional support for older adults with diabetes should be included in diabetes management discussions and shared decision-making.

The need for ongoing support of older adults becomes even greater when transitions to acute care and long-term care (LTC) become necessary. Unfortunately, these transitions can lead to discontinuity in goals of care, errors in dosing, and changes in nutrition and activity (110). Older adults in assisted living facilities may not have support to administer their own medications, whereas those living in a nursing home (community living centers) may rely completely on the care plan and nursing support. Those receiving palliative care (with or without hospice) may require an approach that emphasizes comfort and symptom management while de-emphasizing strict metabolic and blood pressure control.

SPECIAL CONSIDERATIONS FOR OLDER ADULTS WITH TYPE 1 DIABETES

Due in part to the success of modern diabetes management, people with type 1 diabetes are living longer, and the population of these people over 65 years of age is growing (111–113). Many of the recommendations in this section regarding a comprehensive geriatric assessment and personalization of goals and treatments are directly applicable to older adults with type 1 diabetes; however, this population has unique challenges and requires distinct treatment considerations (114). Insulin is an essential life-preserving therapy for people with type 1 diabetes, unlike for those with type 2 diabetes. To avoid diabetic ketoacidosis, older adults with type 1 diabetes need some form of basal insulin even when they are unable to ingest meals. Insulin may be delivered through an insulin pump or injections. CGM is approved for use by Medicare and can play a critical role in improving

A1C, reducing glycemic variability, and reducing risk of hypoglycemia (45) (see Section 7, “Diabetes Technology,” and Section 9, “Pharmacologic Approaches to Glycemic Treatment”). In older people with type 1 diabetes, administration of insulin may become more difficult as complications, cognitive impairment, and functional impairment arise. This increases the importance of caregivers in the lives of these individuals. Many older people with type 1 diabetes require placement in LTC settings (i.e., nursing homes and skilled nursing facilities) and unfortunately can encounter staff that are less familiar with insulin pumps or CGM. Some staff may be less knowledgeable about the differences between type 1 and type 2 diabetes. In these instances, the individual or the person's family may be more familiar with their diabetes management plan than the staff or health care professionals. Education of relevant support staff and health care professionals in rehabilitation and LTC settings regarding insulin dosing and use of pumps and CGM is recommended as part of general diabetes education (see Recommendations 13.20 and 13.21).

TREATMENT IN SKILLED NURSING FACILITIES AND NURSING HOMES

Recommendations

- 13.20** Consider diabetes education for the staff of long-term care and rehabilitation facilities to improve the management of older adults with diabetes. **E**
- 13.21** People with diabetes residing in long-term care facilities need careful assessment to establish individualized glycemic goals and to make appropriate choices of glucose-lowering agents based on their clinical and functional status. **E**
- 13.22** Consider use of continuous glucose monitoring to assess risk for hypoglycemia in older adults treated with sulfonylureas or insulin. **E**

Management of diabetes in the LTC setting is unique. Individualization of health care is important for all people with diabetes; however, practical guidance is needed for health care professionals as

well as the LTC staff and caregivers (115). Training should include diabetes detection and institutional quality assessment. LTC facilities should develop their own policies and procedures for prevention and management of hypoglycemia. With the increased longevity of populations, the care of people with diabetes and its complications in LTC is an area that warrants greater study.

Resources

Staff of LTC facilities should receive appropriate diabetes education to improve the management of older adults with diabetes. Treatments for each patient should be individualized. Special management considerations include the need to avoid both hypoglycemia and the complications of hyperglycemia (2,116). For more information, see the ADA position statement “Management of Diabetes in Long-term Care and Skilled Nursing Facilities” (115).

Nutritional Considerations

An older adult residing in an LTC facility may have irregular and unpredictable meal consumption, undernutrition, anorexia, and impaired swallowing. Furthermore, therapeutic diets may inadvertently lead to decreased food intake and contribute to unintentional weight loss and undernutrition. Meals tailored to a person’s culture, preferences, and personal goals may increase quality of life, satisfaction with meals, and nutrition status (117). It may be helpful to give insulin after meals to ensure that the dose is appropriate for the amount of carbohydrate the individual consumed in the meal.

Hypoglycemia

Older adults with diabetes in LTC are especially vulnerable to hypoglycemia. They have a disproportionately high number of clinical complications and comorbidities that can increase hypoglycemia risk: impaired cognitive and renal function, slowed hormonal regulation and counterregulation, suboptimal hydration, variable appetite and nutritional intake, polypharmacy, and slowed intestinal absorption (118). Oral agents may achieve glycemic outcomes similar to basal insulin in LTC populations (84,119). CGM may be a useful approach to monitoring for hypoglycemia among individuals treated with insulin in LTC, but the data are limited.

Another consideration for the LTC setting is that unlike in the hospital setting, health care professionals are not required to evaluate patients daily. According to federal guidelines, assessments should be done at least every 30 days for the first 90 days after admission and then at least once every 60 days. Although in practice patients may actually be seen more frequently, the concern is that these individuals may have uncontrolled glucose levels or wide excursions without the practitioner being notified. Health care professionals may adjust treatment plans by telephone, fax, or in person directly at the LTC facilities, provided they are given timely notification of blood glucose management issues from a standardized alert system.

The following alert strategy could be considered:

1. **Call health care professional immediately** in cases of low blood glucose levels (<70 mg/dL [3.9 mmol/L]).
2. **Call as soon as possible when**
 - a) glucose values are 70–100 mg/dL (3.9–5.6 mmol/L) (treatment plan may need to be adjusted),
 - b) glucose values are consistently >250 mg/dL (13.9 mmol/L) within a 24-h period,
 - c) glucose values are consistently >300 mg/dL (16.7 mmol/L) over 2 consecutive days,
 - d) any reading is too high for the glucose monitoring device, or
 - e) the person is sick, with vomiting, symptomatic hyperglycemia, or poor oral intake.

END-OF-LIFE CARE

Recommendations

- 13.23** When palliative care is needed in older adults with diabetes, health care professionals should initiate conversations regarding the goals and intensity of care. Strict glucose and blood pressure control are not necessary **E**, and simplification of regimens can be considered. Similarly, the intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate. **A**
- 13.24** Overall comfort, prevention of distressing symptoms, and preservation of quality of life

and dignity are primary goals for diabetes management at the end of life. **C**

The management of the older adult at the end of life receiving palliative medicine or hospice care is a unique situation. Overall, palliative medicine promotes comfort, symptom control and prevention (pain, hypoglycemia, hyperglycemia, and dehydration), and preservation of dignity and quality of life in older adults with limited life expectancy (116,120). In the setting of palliative care, health care professionals should initiate conversations regarding the goals and intensity of diabetes care; strict glucose and blood pressure control may not be consistent with achieving comfort and quality of life. Avoidance of severe hypertension and hyperglycemia aligns with the goals of palliative care. In a multicenter trial, withdrawal of statins among people with diabetes in palliative care was found to improve quality of life (121–123). The evidence for the safety and efficacy of de-intensification protocols in older adults is growing for both glucose and blood pressure control (88,124) and is clearly relevant for palliative care. An individual has the right to refuse testing and treatment, whereas health care professionals may consider withdrawing treatment and limiting diagnostic testing, including a reduction in the frequency of blood glucose monitoring (125,126). Glucose targets should aim to prevent hypoglycemia and hyperglycemia. Treatment interventions need to be mindful of quality of life. Careful monitoring of oral intake is warranted. The decision process may need to involve the individual, family, and caregivers, leading to a care plan that is both convenient and effective for the goals of care (127). The pharmacologic therapy may include oral agents as first line, followed by a simplified insulin regimen. If needed, basal insulin can be implemented, accompanied by oral agents and without rapid-acting insulin. Agents that can cause gastrointestinal symptoms such as nausea or excess weight loss may not be good choices in this setting. As symptoms progress, some agents may be slowly tapered and discontinued.

Different patient categories have been proposed for diabetes management in those with advanced disease (59).

1. A stable patient: Continue with the person's previous regimen, with a focus on 1) the prevention of hypoglycemia and 2) the management of hyperglycemia using blood glucose testing, keeping levels below the renal threshold of glucose, and hyperglycemia-mediated dehydration. There is no role for A1C monitoring.
2. A patient with organ failure: Preventing hypoglycemia is of greatest significance. Dehydration must be prevented and treated. In people with type 1 diabetes, insulin administration may be reduced as the oral intake of food decreases but should not be stopped. For those with type 2 diabetes, agents that may cause hypoglycemia should be reduced in dose. The main goal is to avoid hypoglycemia, allowing for glucose values in the upper level of the desired target range.
3. A dying patient: For people with type 2 diabetes, the discontinuation of all medications may be a reasonable approach, as these individuals are unlikely to have any oral intake. In people with type 1 diabetes, there is no consensus, but a small amount of basal insulin may maintain glucose levels and prevent acute hyperglycemic complications.

References

1. Laiteerapong N, Huang ES. Diabetes in older adults. In *Diabetes in America*. 3rd ed. Cowie CC, Casagrande SS, Menke A, et al., Eds. Bethesda, MD, National Institute of Diabetes and Digestive and Kidney Diseases (US), 2018. Accessed 19 October 2022. Available from <https://www.ncbi.nlm.nih.gov/books/NBK567980/>
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020: Estimates of Diabetes and its Burden in the United States. Accessed 19 October 2022. Available from <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>
3. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care* 2012;35:2650–2664
4. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2016;39:2126–2140
5. Institute of Medicine of the National Academies. Cognitive Aging: Progress in Understanding and Opportunities for Action. Accessed 22 October 2022. Available from <https://nationalacademies.org/hmd/Reports/2015/Cognitive-Aging.aspx>
6. Sudore RL, Karter AJ, Huang ES, et al. Symptom burden of adults with type 2 diabetes across the disease course: diabetes & aging study. *J Gen Intern Med* 2012;27:1674–1681
7. Laiteerapong N, Karter AJ, Liu JY, et al. Correlates of quality of life in older adults with diabetes: the diabetes & aging study. *Diabetes Care* 2011;34:1749–1753
8. McClintock MK, Dale W, Laumann EO, Waite L. Empirical redefinition of comprehensive health and well-being in the older adults of the United States. *Proc Natl Acad Sci U S A* 2016;113:E3071–E3080
9. Laiteerapong N, Iveniuk J, John PM, Laumann EO, Huang ES. Classification of older adults who have diabetes by comorbid conditions, United States, 2005–2006. *Prev Chronic Dis* 2012;9:E100
10. Blaum C, Cigolle CT, Boyd C, et al. Clinical complexity in middle-aged and older adults with diabetes: the Health and Retirement Study. *Med Care* 2010;48:327–334
11. Tinetti ME, Costello DM, Naik AD, et al. Outcome goals and health care preferences of older adults with multiple chronic conditions. *JAMA Netw Open* 2021;4:e211271
12. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. *Diabetologia* 2005;48:2460–2469
13. Roberts RO, Knopman DS, Przybelski SA, et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. *Neurology* 2014;82:1132–1141
14. Xu WL, von Strauss E, Qiu CX, Winblad B, Fratiglioni L. Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. *Diabetologia* 2009;52:1031–1039
15. Yaffe K, Falvey C, Hamilton N, et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Arch Neurol* 2012;69:1170–1175
16. Rawlings AM, Sharrett AR, Schneider ALC, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. *Ann Intern Med* 2014;161:785–793
17. Launer LJ, Miller ME, Williamson JD, et al.; ACCORD MIND investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol* 2011;10:969–977
18. Murray AM, Hsu FC, Williamson JD, et al.; Action to Control Cardiovascular Risk in Diabetes Follow-On Memory in Diabetes (ACCORDION MIND) Investigators. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. *Diabetologia* 2017;60:69–80
19. Ghezzi L, Scarpini E, Galimberti D. Disease-modifying drugs in Alzheimer's disease. *Drug Des Devel Ther* 2013;7:1471–1478
20. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnesic mild cognitive impairment: a pilot clinical trial. *Arch Neurol* 2012;69:29–38
21. Freiherr J, Hallschmid M, Frey WH 2nd, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. *CNS Drugs* 2013;27:505–514
22. Alagiakrishnan K, Sankaralingam S, Ghosh M, Mereu L, Senior P. Antidiabetic drugs and their potential role in treating mild cognitive impairment and Alzheimer's disease. *Discov Med* 2013;16:277–286
23. Tomlin A, Sinclair A. The influence of cognition on self-management of type 2 diabetes in older people. *Psychol Res Behav Manag* 2016;9:7–20
24. National Institute on Aging. Assessing Cognitive Impairment in Older Patients. Accessed 19 October 2022. Available from <https://www.nia.nih.gov/health/assessing-cognitive-impairment-older-patients>
25. Alzheimer's Association. Cognitive Assessment. Accessed 19 October 2022. Available from <https://alz.org/professionals/healthcare-professionals/cognitive-assessment>
26. Folstein MF, Folstein SE, McHugh PR. "Minimal state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198
27. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. *J Am Geriatr Soc* 2003;51:1451–1454
28. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–699
29. Moreno G, Mangione CM, Kimbro L; American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes Mellitus. Guidelines abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 update. *J Am Geriatr Soc* 2013;61:2020–2026
30. American Psychological Association. Guidelines for the Evaluation of Dementia and Age-Related Cognitive Change, 2021. Accessed 22 October 2022. Available from <https://www.apa.org/practice/guidelines/dementia.aspx>
31. Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk factors for severe hypoglycemia in black and white adults with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 2017;40:1661–1667
32. Feinkohl I, Aung PP, Keller M, et al.; Edinburgh Type 2 Diabetes Study (ET2DS) Investigators. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes Care* 2014;37:507–515
33. Lee AK, Rawlings AM, Lee CJ, et al. Severe hypoglycaemia, mild cognitive impairment, dementia and brain volumes in older adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) cohort study. *Diabetologia* 2018;61:1956–1965
34. Fitzgerald JT, Davis WK, Connell CM, Hess GE, Funnell MM, Hiss RG. Development and validation of the Diabetes Care Profile. *Eval Health Prof* 1996;19:208–230
35. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995;18:517–522
36. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. *JAMA Intern Med* 2017;177:1461–1470
37. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes

- Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–2559
38. Duckworth W, Abirra C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139
39. Toschi E, Slyné C, Sifre K, et al. The relationship between cgm-derived metrics, A1C, and risk of hypoglycemia in older adults with type 1 diabetes. *Diabetes Care* 2020;43:2349–2354
40. Carlson AL, Kanapka LG, Miller KM, et al. Hypoglycemia and glycemic control in older adults with type 1 diabetes: baseline results from the WISDM Study. *J Diabetes Sci Technol* 2021;15:582–592
41. Pratley RE, Kanapka LG, Rickels MR, Ahmann A, Aleppo G, Beck R, et al.; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study Group. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. *JAMA* 2020;323:2397–2406
42. Miller KM, Kanapka LG, Rickels MR, et al. Benefit of continuous glucose monitoring in reducing hypoglycemia is sustained through 12 months of use among older adults with type 1 diabetes. *Diabetes Technol Ther* 2022;24:424–434
43. Gubitosi-Klug RA, Braffett BH, Bebu I, et al. Continuous glucose monitoring in adults with type 1 diabetes with 35 years duration from the DCCT/EDIC Study. *Diabetes Care* 2022;45:659–665
44. Karter AJ, Parker MM, Moffet HH, Gilliam LK, Dlott R. Association of real-time continuous glucose monitoring with glycemic control and acute metabolic events among patients with insulin-treated diabetes. *JAMA* 2021;325:2273–2284
45. Ruedy KJ, Parkin CG, Riddlesworth TD; DIAMOND Study Group. Continuous glucose monitoring in older adults with type 1 and type 2 diabetes using multiple daily injections of insulin: results from the DIAMOND trial. *J Diabetes Sci Technol* 2017;11:1138–1146
46. McAuley SA, Trawley S, Vogrin S, et al. Closed-loop insulin delivery versus sensor-augmented pump therapy in older adults with type 1 diabetes (ORACL): a randomized, crossover trial. *Diabetes Care* 2022;45:381–390
47. Boughton CK, Hartnell S, Thabit H, et al. Hybrid closed-loop glucose control compared with sensor augmented pump therapy in older adults with type 1 diabetes: an open-label multicentre, multinational, randomised, crossover study. *Lancet Healthy Longev* 2022;3:e135–e142
48. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. *Diabetes Care* 2006;29:2415–2419
49. Banteen-Roche K, Seplaki CL, Huang J, et al. Frailty in older adults: a nationally representative profile in the United States. *J Gerontol A Biol Sci Med Sci* 2015;70:1427–1434
50. Kalyani RR, Tian J, Xue QL, et al. Hyperglycemia and incidence of frailty and lower extremity mobility limitations in older women. *J Am Geriatr Soc* 2012;60:1701–1707
51. Pilla SJ, Schoenborn NL, Maruthur NM, Huang ES. Approaches to risk assessment among older patients with diabetes. *Curr Diab Rep* 2019;19:59
52. Griffith KN, Prentice JC, Mohr DC, Conlin PR. Predicting 5- and 10-year mortality risk in older adults with diabetes. *Diabetes Care* 2020;43:1724–1731
53. Brown SES, Meltzer DO, Chin MH, Huang ES. Perceptions of quality-of-life effects of treatments for diabetes mellitus in vulnerable and nonvulnerable older patients. *J Am Geriatr Soc* 2008;56:1183–1190
54. NGSP. Factors that Interfere with HbA1c Test Results. Accessed 19 October 2022. Available from <http://www.ngsp.org/factors.asp>
55. Huang ES, Zhang Q, Gandra N, Chin MH, Meltzer DO. The effect of comorbid illness and functional status on the expected benefits of intensive glucose control in older patients with type 2 diabetes: a decision analysis. *Ann Intern Med* 2008;149:11–19
56. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med* 2014;174:251–258
57. Leung V, Wroblewski K, Schumm LP, Huisingh-Scheetz M, Huang ES. Re-examining the classification of older adults with diabetes by comorbidities and relationship with frailty, disability, and 5-year mortality. *J Gerontol A Biol Sci Med Sci* 2021;76:2071–2079
58. Rooney MR, Tang O, Echouffo Tcheugui JB, et al. American Diabetes Association framework for glycemic control in older adults: implications for risk of hospitalization and mortality. *Diabetes Care* 2021;44:1524–1531
59. Sinclair A, Dunning T, Colagiuri S. IDF Global Guideline For Managing Older People With Type 2 Diabetes. International Diabetes Federation, 2013
60. Angelo M, Ruchalski C, Spröge BJ. An approach to diabetes mellitus in hospice and palliative medicine. *J Palliat Med* 2011;14:83–87
61. Beckett NS, Peters R, Fletcher AE, et al.; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887–1898
62. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:1273–1284
63. Gencer B, Marston NA, Im K, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2020;396:1637–1643
64. Yourman LC, Censer IS, Boscardin WJ, et al. Evaluation of time to benefit of statins for the primary prevention of cardiovascular events in adults aged 50 to 75 years: a meta-analysis. *JAMA Intern Med* 2021;181:179–185
65. Park SW, Goodpaster BH, Strotmeyer ES, et al. Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. *Diabetes* 2006;55:1813–1818
66. Park SW, Goodpaster BH, Strotmeyer ES, et al.; Health, Aging, and Body Composition Study. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the health, aging, and body composition study. *Diabetes Care* 2007;30:1507–1512
67. Pahor M, Guralnik JM, Ambrosius WT, et al.; LIFE study investigators. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA* 2014;311:2387–2396
68. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons who live at home. *N Engl J Med* 2002;347:1068–1074
69. Curtis JM, Horton ES, Bahnson J, et al.; Look AHEAD Research Group. Prevalence and predictors of abnormal cardiovascular responses to exercise testing among individuals with type 2 diabetes: the Look AHEAD (Action for Health in Diabetes) study. *Diabetes Care* 2010;33:901–907
70. Bray G, Gregg E, Haffner S, et al.; Look Ahead Research Group. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res* 2006;3:202–215
71. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–154
72. Gregg EW, Jakicic JM, Blackburn G, et al.; Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2016;4:913–921
73. Gregg EW, Chen H, Wagenknecht LE, et al.; Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012;308:2489–2496
74. Rejeski WJ, Bray GA, Chen SH, et al.; Look AHEAD Research Group. Aging and physical function in type 2 diabetes: 8 years of an intensive lifestyle intervention. *J Gerontol A Biol Sci Med Sci* 2015;70:345–353
75. Espeland MA, Rejeski WJ, West DS, et al.; Action for Health in Diabetes Research Group. Intensive weight loss intervention in older individuals: results from the Action for Health in Diabetes Type 2 diabetes mellitus trial. *J Am Geriatr Soc* 2013;61:912–922
76. Houston DK, Neiberg RH, Miller ME, et al. Physical function following a long-term lifestyle intervention among middle aged and older adults with type 2 diabetes: the Look AHEAD Study. *J Gerontol A Biol Sci Med Sci* 2018;73:1552–1559
77. Simpson FR, Pajewski NM, Nicklas B, et al.; Indices for Accelerated Aging in Obesity and Diabetes Ancillary Study of the Action for Health in Diabetes (Look AHEAD) Trial. Impact of multidomain lifestyle intervention on frailty through the lens of deficit accumulation in adults with type 2 diabetes mellitus. *J Gerontol A Biol Sci Med Sci* 2020;75:1921–1927
78. Espeland MA, Gaussoin SA, Bahnson J, et al. Impact of an 8-year intensive lifestyle intervention on an index of multimorbidity. *J Am Geriatr Soc* 2020;68:2249–2256
79. Gregg EW, Lin J, Bardenheier B, et al.; Look AHEAD Study Group. Impact of intensive lifestyle intervention on disability-free life expectancy: the Look AHEAD Study. *Diabetes Care* 2018;41:1040–1048
80. Valencia WM, Florez H. Pharmacological treatment of diabetes in older people. *Diabetes Obes Metab* 2014;16:1192–1203
81. Zhang JX, Bhaumik D, Huang ES, Meltzer DO. Change in insurance status and cost-related

- medication non-adherence among older U.S. adults with diabetes from 2010 to 2014. *J Health Med Econ* 2018;4:7
82. Schmittiel JA, Steers N, Duru OK, et al. Patient-provider communication regarding drug costs in Medicare Part D beneficiaries with diabetes: a TRIAD Study. *BMC Health Serv Res* 2010;10:164
83. Patel MR, Resnicow K, Lang I, Kraus K, Heisler M. Solutions to address diabetes-related financial burden and cost-related nonadherence: results from a pilot study. *Health Educ Behav* 2018;45:101–111
84. Arnold SV, Lipska KJ, Wang J, Seman L, Mehta SN, Kosiborod M. Use of intensive glycemic management in older adults with diabetes mellitus. *J Am Geriatr Soc* 2018;66:1190–1194
85. Andreassen LM, Sandberg S, Kristensen GBB, Sølvik UØ, Kjøme RLS. Nursing home patients with diabetes: prevalence, drug treatment and glycemic control. *Diabetes Res Clin Pract* 2014; 105:102–109
86. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. *JAMA Intern Med* 2015;175:356–362
87. Thorpe CT, Gellad WF, Good CB, et al. Tight glycemic control and use of hypoglycemic medications in older veterans with type 2 diabetes and comorbid dementia. *Diabetes Care* 2015;38:588–595
88. McAlister FA, Youngson E, Eurich DT. Treatment deintensification is uncommon in adults with type 2 diabetes mellitus: a retrospective cohort study. *Circ Cardiovasc Qual Outcomes* 2017;10:e003514
89. Seidu S, Kunutsor SK, Topsever P, Hambling CE, Cos FX, Khunti K. Deintensification in older patients with type 2 diabetes: a systematic review of approaches, rates and outcomes. *Diabetes Obes Metab* 2019;21:1668–1679
90. Weiner JZ, Gopalan A, Mishra P, et al. Use and discontinuation of insulin treatment among adults aged 75 to 79 years with type 2 diabetes. *JAMA Intern Med* 2019;179:1633–1641
91. Abdelhafiz AH, Sinclair AJ. Deintensification of hypoglycaemic medications—use of a systematic review approach to highlight safety concerns in older people with type 2 diabetes. *J Diabetes Complications* 2018;32:444–450
92. Sussman JB, Kerr EA, Saini SD, et al. Rates of deintensification of blood pressure and glycemic medication treatment based on levels of control and life expectancy in older patients with diabetes mellitus. *JAMA Intern Med* 2015;175:1942–1949
93. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of insulin regimen in older adults and risk of hypoglycemia. *JAMA Intern Med* 2016;176:1023–1025
94. Jude EB, Malecki MT, Gomez Huelgas R, et al. Expert panel guidance and narrative review of treatment simplification of complex insulin regimens to improve outcomes in type 2 diabetes. *Diabetes Ther* 2022;13:619–634
95. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 2014;312:2668–2675
96. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab* 2016; 101:1754–1761
97. Schwartz AV, Chen H, Ambrosius WT, et al. Effects of TZD use and discontinuation on fracture rates in ACCORD Bone Study. *J Clin Endocrinol Metab* 2015;100:4059–4066
98. Billington EO, Grey A, Bolland MJ. The effect of thiazolidinediones on bone mineral density and bone turnover: systematic review and meta-analysis. *Diabetologia* 2015;58:2238–2246
99. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63:2227–2246
100. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41:2669–2701
101. Leiter LA, Teoh H, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Efficacy and safety of saxagliptin in older participants in the SAVOR-TIMI 53 trial. *Diabetes Care* 2015;38:1145–1153
102. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232–242
103. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327–1335
104. Karagiannis T, Tsapas A, Athanasiadou E, et al. GLP-1 receptor agonists and SGLT2 inhibitors for older people with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2021;174:108737
105. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;381:841–851
106. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–2128
107. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–657
108. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347–357
109. Bradley MC, Chillarige Y, Lee H, et al. Severe hypoglycemia risk with long-acting insulin analogs vs neutral protamine Hagedorn insulin. *JAMA Intern Med* 2021;181:598–607
110. Pandya N, Hames E, Sandhu S. Challenges and strategies for managing diabetes in the elderly in long-term care settings. *Diabetes Spectr* 2020;33:236–245
111. Livingstone SJ, Levin D, Looker HC, et al.; Scottish Diabetes Research Network Epidemiology Group; Scottish Renal Registry. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008–2010. *JAMA* 2015; 313:37–44
112. Miller RG, Secrest AM, Sharma RK, Songer TJ, Orchard TJ. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. *Diabetes* 2012;61:2987–2992
113. Bullard KM, Cowie CC, Lessem SE, et al. Prevalence of diagnosed diabetes in adults by diabetes type—United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67:359–361
114. Heise T, Nosek L, Rønn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 2004; 53:1614–1620
115. Munshi MN, Florez H, Huang ES, et al. Management of diabetes in long-term care and skilled nursing facilities: a position statement of the American Diabetes Association. *Diabetes Care* 2016;39:308–318
116. Sinclair A, Morley JE, Rodriguez-Mañás L, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. *J Am Med Dir Assoc* 2012;13: 497–502
117. Dorner B, Friedrich EK, Posthauer ME. Practice paper of the American Dietetic Association: individualized nutrition approaches for older adults in health care communities. *J Am Diet Assoc* 2010;110:1554–1563
118. Migdal A, Yarandi SS, Smiley D, Umpierrez GE. Update on diabetes in the elderly and in nursing home residents. *J Am Med Dir Assoc* 2011;12:627–632.e2
119. Pasquel FJ, Powell W, Peng L, et al. A randomized controlled trial comparing treatment with oral agents and basal insulin in elderly patients with type 2 diabetes in long-term care facilities. *BMJ Open Diabetes Res Care* 2015;3: e000104
120. Quinn K, Hudson P, Dunning T. Diabetes management in patients receiving palliative care. *J Pain Symptom Manage* 2006;32:275–286
121. Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med* 2015;175:691–700
122. Dunning T, Martin P. Palliative and end of life care of people with diabetes: issues, challenges and strategies. *Diabetes Res Clin Pract* 2018;143:454–463
123. Bouça-Machado R, Rosário M, Alarcão J, Correia-Guedes L, Abreu D, Ferreira JJ. Clinical trials in palliative care: a systematic review of their methodological characteristics and of the quality of their reporting. *BMC Palliat Care* 2017;16:10
124. Sheppard JP, Burt J, Lown M, et al.; OPTIMISE Investigators. Effect of antihypertensive medication reduction vs usual care on short-term blood pressure control in patients with hypertension aged 80 years and older: the OPTIMISE randomized clinical trial. *JAMA* 2020;323:2039–2051
125. Ford-Dunn S, Smith A, Quin J. Management of diabetes during the last days of life: attitudes of consultant diabetologists and consultant palliative care physicians in the UK. *Palliat Med* 2006;20:197–203
126. Petrillo LA, Gan S, Jing B, Lang-Brown S, Boscardin WJ, Lee SJ. Hypoglycemia in hospice

patients with type 2 diabetes in a national sample of nursing homes. *JAMA Intern Med* 2018;178:713–715

127. Mallery LH, Ransom T, Steeves B, Cook B, Dunbar P, Moorhouse P. Evidence-informed

guidelines for treating frail older adults with type 2 diabetes: from the Diabetes Care Program of Nova Scotia (DCPNS) and the Palliative and Therapeutic Harmonization (PATH) program. *J Am Med Dir Assoc* 2013;14:801–808

128. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Liberating A1C goals in older adults may not protect against the risk of hypoglycemia. *J Diabetes Complications* 2017;31:1197–1199

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14. Children and Adolescents: *Standards of Care in Diabetes—2023*

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Association

The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

The management of diabetes in children and adolescents (individuals <18 years of age) cannot simply be derived from care routinely provided to adults with diabetes. The epidemiology, pathophysiology, developmental considerations, and response to therapy in pediatric diabetes are often different from those of adult diabetes. There are also differences in recommended care for children and adolescents with type 1 diabetes, type 2 diabetes, and other forms of pediatric diabetes. This section is divided into two major parts: the first part addresses care for children and adolescents with type 1 diabetes, and the second part addresses care for children and adolescents with type 2 diabetes. Monogenic diabetes (neonatal diabetes and maturity-onset diabetes in the young [MODY]) and cystic fibrosis–related diabetes, which are often present in youth, are discussed in Section 2, “Classification and Diagnosis of Diabetes.” **Table 14.1A** and **Table 14.1B** provide an overview of the recommendations for screening and treatment of complications and related conditions in pediatric type 1 diabetes and type 2 diabetes, respectively. In addition to comprehensive diabetes care, youth with diabetes should receive age-appropriate and developmentally appropriate pediatric care, including vaccines and immunizations as recommended by the Centers for Disease Control and Prevention (CDC) (1). To ensure continuity of care as an adolescent with diabetes becomes an adult, guidance is provided at the end of this section on the transition from pediatric to adult diabetes care.

Due to the nature of pediatric clinical research, the recommendations for children and adolescents with diabetes are less likely to be based on clinical trial evidence. However, expert opinion and a review of available and relevant experimental data are summarized in the American Diabetes Association (ADA) position statements “Type 1 Diabetes in Children and Adolescents” (2) and “Evaluation and Management of Youth-Onset Type 2 Diabetes” (3). Finally, other sections in the Standards of Care may have recommendations that apply to youth with diabetes and are referenced in the narrative of this section.

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Table 14.14—Recommendations for screening and treatment of complications and related conditions in pediatric type 1 diabetes

Corresponding recommendations	Thyroid disease 14.29 and 14.30	Celiac disease 14.31–14.33	Hypertension 14.34–14.37	Dyslipidemia 14.38–14.42	Nephropathy 14.45 and 14.46	Retinopathy 14.47–14.49	Neuropathy 14.50
Method	Thyroid-stimulating hormone; consider antithyroglobulin and antithyroid peroxidase antibodies	igA tTG if total IgA normal; IgG tTG and deamidated gliadin antibodies if IgA antibodies deficient	Blood pressure monitoring	Lipid profile, nonfasting acceptable initially	Albumin-to-creatinine ratio; random sample acceptable initially	Dilated funduscopy or retinal photography of 3–5 years	Foot exam with foot pulses, pinprick, 10-g monofilament sensation tests, vibration, and ankle reflexes
When to start	Soon after diagnosis	Soon after diagnosis	At diagnosis	Soon after diagnosis; preferably after glycemia has improved and ≥ 2 years old	Puberty or >10 years old, whichever is earlier, and diabetes duration of 5 years	Puberty or ≥ 11 years old, whichever is earlier, and diabetes duration of 3–5 years	Puberty or ≥ 10 years old, whichever is earlier, and diabetes duration of 5 years
Follow-up frequency	Every 1–2 years if thyroid antibodies negative; more often if symptoms develop or presence of thyroid antibodies	Within 2 years and then at 5 years after diagnosis; sooner if symptoms develop	Every visit	If LDL ≤ 100 mg/dL, repeat at 9–11 years old; then, if <100 mg/dL, every 3 years	If normal, annually; if abnormal, repeat with confirmation in two of three samples over 6 months	If normal, every 2 years; consider less frequently (every 4 years) if A1C $<8\%$ and eye professional agrees	If normal, annually
Target	NA	NA	<90 th percentile for age, sex, and height; if ≥ 13 years old, $<120/80$ mmHg	LDL <100 mg/dL	Albumin-to-creatinine ratio <30 mg/g	No retinopathy	No neuropathy
Treatment	Appropriate treatment of underlying thyroid disorder	After confirmation, start gluten-free diet	Lifestyle modification for elevated blood pressure (90th to <95 th percentile for age, sex, and height or, if ≥ 13 years old, 120–129/ <80 mmHg); lifestyle modification and ACE inhibitor or ARB* for hypertension (≥ 95 th percentile for age, sex, and height or, if ≥ 13 years old, $\geq 130/80$ mmHg)	If abnormal, optimize glycemia and medical nutrition therapy; if >160 mg/dL or >130 mg/dL with cardiovascular risk factor(s), initiate statin therapy (for those aged >10 years)*	Optimize glycemia and blood pressure; ACE inhibitor* if albumin-to-creatinine ratio is elevated in two of three samples over 6 months	Optimize glycemia; treatment per ophthalmology	Optimize glycemia; referral to neurology

ARB, angiotensin receptor blocker; NA, not applicable; tTG, tissue transglutaminase. *Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

Table 14.1B—Recommendations for screening and treatment of complications and related conditions in pediatric type 2 diabetes

	Hypertension	Nephropathy	Neuropathy	Retinopathy	Nonalcoholic fatty liver disease	Obstructive sleep apnea	Polycystic ovarian syndrome (for adolescent female individuals)	Dyslipidemia
Corresponding recommendations	14.77–14.80	14.81–14.86	14.87 and 14.88	14.89–14.92	14.93 and 14.94	14.95	14.96–14.98	14.100–14.104
Method	Blood pressure monitoring	Albumin-to-creatinine ratio; random sample acceptable initially	Foot exam with foot pulses, pinprick, 10-g monofilament sensation tests, vibration, and ankle reflexes	Dilated fundoscopy	AST and ALT measurement	Screening for symptoms	Screening for symptoms; laboratory evaluation if positive symptoms	Lipid profile
When to start	At diagnosis	At diagnosis	At diagnosis	At/soon after diagnosis	At diagnosis	At diagnosis	At diagnosis	Soon after diagnosis, preferably after glycemia has improved
Follow-up frequency	Every visit	If normal, annually; if abnormal, repeat with confirmation in two of three samples over 6 months	No neuropathy	If normal, annually	Annually	Every visit	Every visit	Annually
Target	<90th percentile for age, sex, and height; if ≥13 years old, <130/80 mmHg	<30 mg/g	No neuropathy	No retinopathy	NA	NA	NA	LDL <100 mg/dL, HDL >35 mg/dL, triglycerides <150 mg/dL
Treatment	Lifestyle modification for elevated blood pressure (90th to <95th percentile for age, sex, and height or, if ≥13 years old, 120–129/<80 mmHg); lifestyle modification and ACE inhibitor or ARB* for hypertension (≥95th percentile for age, sex, and height or, if ≥13 years, ≥130/80 mmHg)	Optimize glycemia and blood pressure; ACE inhibitor* if albumin-to-creatinine ratio is elevated in two of three samples over 6 months	Optimize glycemia; referral to neurology	Optimize glycemia; treatment per ophthalmology	Refer to gastroenterology for persistently elevated or worsening transaminases	Refer to sleep specialist and polysomnogram	If no contraindications, oral contraceptive pills; medical nutrition therapy, metformin	If abnormal, optimize glycemia and medical nutrition therapy; if >130 mg/dL, initiate statin therapy (for those aged >10 years)*; if triglycerides >400 mg/dL fasting or >1,000 mg/dL nonfasting, begin fibrates

ARB, angiotensin receptor blocker; NA, not applicable. *Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

TYPE 1 DIABETES

Type 1 diabetes is the most common form of diabetes in youth (4), although data suggest that it may account for a large proportion of cases diagnosed in adult life (5). The health care professional must consider the unique aspects of care and management of children and adolescents with type 1 diabetes, such as changes in insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, supervision in the childcare and school environment, neurological vulnerability to hypoglycemia and hyperglycemia in young children, and possible adverse neurocognitive effects of diabetic ketoacidosis (DKA) (6,7). Attention to family dynamics, developmental stages, and physiologic differences related to sexual maturity is essential in developing and implementing an optimal diabetes treatment plan (8).

A multidisciplinary team trained in pediatric diabetes management and sensitive to the challenges of children and adolescents with type 1 diabetes and their families should provide diabetes-specific care for this population. It is essential that diabetes self-management education and support, medical nutrition therapy, and psychosocial support be provided at diagnosis and regularly thereafter in a developmentally appropriate format that builds on prior knowledge by a team of health care professionals experienced with the biological, educational, nutritional, behavioral, and emotional needs of the growing child and family. The diabetes team, taking into consideration the youth's developmental and psychosocial needs, should ask about and advise the youth and parents/caregivers about diabetes management responsibilities on an ongoing basis.

Diabetes Self-Management Education and Support

Recommendation

14.1 Youth with type 1 diabetes and their parents/caregivers (for patients aged <18 years) should receive culturally sensitive and developmentally appropriate individualized diabetes self-management education and support according to national standards at diagnosis and routinely thereafter. **B**

Self-management in pediatric diabetes involves both the youth and their parents/adult caregivers. No matter how sound the medical plan is, it can only be effective if the family and/or affected individuals are able to implement it. Family involvement is a vital component of optimal diabetes management throughout childhood and adolescence. As parents/caregivers are critical to diabetes self-management in youth, diabetes care requires an approach that places the youth and their parents/caregivers at the center of the care model. The pediatric diabetes care team must be capable of evaluating the educational, behavioral, emotional, and psychosocial factors that impact the implementation of a treatment plan and must work with the youth and family to overcome barriers or redefine goals as appropriate. Diabetes self-management education and support requires periodic reassessment, especially as the youth grows, develops, and acquires the need and desire for greater independent self-care skills. The pediatric diabetes team should work with the youth and their parents/caregivers to ensure there is not a premature transfer of self-management tasks to the youth during this time. In addition, it is necessary to assess the educational needs and skills of, and provide training to, day care workers, school nurses, and school personnel who are responsible for the care and supervision of the child with diabetes (9–11).

Nutrition Therapy

Recommendations

- 14.2** Individualized medical nutrition therapy is recommended for youth with type 1 diabetes as an essential component of the overall treatment plan. **A**
- 14.3** Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is a key component to optimizing glycemic management. **B**
- 14.4** Comprehensive nutrition education at diagnosis, with annual updates, by an experienced registered dietitian nutritionist, is recommended to assess caloric and nutrition intake in relation

to weight status and cardiovascular disease risk factors and to inform macronutrient choices. **E**

Nutrition management should be individualized: family habits, food preferences, religious or cultural needs, finances, schedules, physical activity, and the youth's and family's abilities in numeracy, literacy, and self-management should be considered. Visits with a registered dietitian nutritionist should include assessment for changes in food preferences over time, access to food, growth, and development, weight status, cardiovascular risk, and potential for disordered eating. Following recommended nutrition plans is associated with better glycemic outcomes in youth with type 1 diabetes (12).

Physical Activity and Exercise

Recommendations

- 14.5** Physical activity is recommended for all youth with type 1 diabetes with the goal of 60 min of moderate- to vigorous-intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week. **C**
- 14.6** Frequent glucose monitoring before, during, and after exercise, via blood glucose meter or continuous glucose monitoring, is important to prevent, detect, and treat hypoglycemia and hyperglycemia associated with exercise. **C**
- 14.7** Youth and their parents/caregivers should receive education on targets and management of glycemia before, during, and after physical activity, individualized according to the type and intensity of the planned physical activity. **E**
- 14.8** Youth and their parents/caregivers should be educated on strategies to prevent hypoglycemia during, after, and overnight following physical activity and exercise, which may include reducing prandial insulin dosing for the meal/snack preceding (and, if needed, following) exercise, reducing basal insulin doses, increasing carbohydrate intake, eating bedtime

snacks, and/or using continuous glucose monitoring. Treatment for hypoglycemia should be accessible before, during, and after engaging in activity. **C**

Physical activity and exercise positively impact metabolic and psychological health in children with type 1 diabetes (13). While it affects insulin sensitivity, physical fitness, strength building, weight management, social interaction, mood, self-esteem building, and the creation of healthful habits for adulthood, it also has the potential to cause both hypoglycemia and hyperglycemia.

See below for strategies to mitigate hypoglycemia risk and minimize hyperglycemia associated with exercise. For an in-depth discussion, see reviews and guidelines (14–16).

Overall, it is recommended that youth participate in 60 min of moderate-intensity (e.g., brisk walking, dancing) to vigorous-intensity (e.g., running, jumping rope) aerobic activity daily, including resistance and flexibility training (17). Although uncommon in the pediatric population, patients should be medically evaluated for comorbid conditions or diabetes complications that may restrict participation in an exercise program. As hyperglycemia can occur before, during, and after physical activity, it is important to ensure that the elevated glucose level is not related to insulin deficiency that would lead to worsening hyperglycemia with exercise and ketosis risk. Intense activity should be postponed with marked hyperglycemia (glucose ≥ 350 mg/dL [19.4 mmol/L]), moderate to large urine ketones, and/or β -hydroxybutyrate (B-OHB) > 1.5 mmol/L. Caution may be needed when B-OHB levels are ≥ 0.6 mmol/L (12,14).

The prevention and treatment of hypoglycemia associated with physical activity include decreasing the prandial insulin for the meal/snack before exercise and/or increasing food intake. Youth on insulin pumps can lower basal rates by ~ 10 – 50% or more or suspend for 1–2 h during exercise (18). Decreasing basal rates or long-acting insulin doses by $\sim 20\%$ after exercise may reduce delayed exercise-induced hypoglycemia (19). Accessible rapid-acting carbohydrates and frequent blood glucose monitoring before,

during, and after exercise, with or without continuous glucose monitoring (CGM), maximize safety with exercise. The use of hybrid closed-loop systems may improve time in range (70–180 mg/dL) during exercise, and youth can use “exercise mode” to prevent hypoglycemia (20).

Blood glucose targets prior to physical activity and exercise should be 126–180 mg/dL (7.0–10.0 mmol/L) but should be individualized based on the type, intensity, and duration of activity (14,16). Consider additional carbohydrate intake during and/or after exercise, depending on the duration and intensity of physical activity, to prevent hypoglycemia. For low- to moderate-intensity aerobic activities (30–60 min), and if the youth is fasting, 10–15 g of carbohydrate may prevent hypoglycemia (21). After insulin boluses (relative hyperinsulinemia), consider 0.5–1.0 g of carbohydrates/kg per hour of exercise (~ 30 – 60 g), which is similar to carbohydrate requirements to optimize performance in athletes without type 1 diabetes (22–24).

In addition, obesity is as common in youth with type 1 diabetes as in those without diabetes. It is associated with a higher frequency of cardiovascular risk factors, and it disproportionately affects racial/ethnic minorities in the U.S. (25–29). Therefore, diabetes health care professionals should monitor weight status and encourage a healthy eating pattern, physical activity, and healthy weight as key components of pediatric type 1 diabetes care.

School and Child Care

As a large portion of a youth’s day is spent in school and/or day care, training of school or day care personnel to provide care in accordance with the child’s individualized diabetes medical management plan is essential for optimal diabetes management and safe access to all school or day care-sponsored opportunities (10,11,30). In addition, federal and state laws require schools, day care facilities, and other entities to provide needed diabetes care to enable the child to safely access the school or day care environment. Refer to the ADA position statements “Diabetes Care in the School Setting” (10) and “Care of Young Children With Diabetes in the Child Care Setting” (11) and ADA’s Safe at School website (diabetes.org/resources/know-your-rights/safe-at-school-state-laws) for additional details.

Psychosocial Care

Recommendations

- 14.9** At diagnosis and during routine follow-up care, screen for psychosocial issues and family stresses that could impact diabetes management and provide appropriate referrals to trained mental health professionals, preferably experienced in childhood diabetes. **C**
- 14.10** Mental health professionals should be considered integral members of the pediatric diabetes multidisciplinary team. **E**
- 14.11** Encourage developmentally appropriate family involvement in diabetes management tasks for children and adolescents, recognizing that premature transfer of diabetes care responsibility to the youth can result in diabetes burnout, suboptimal diabetes management, and deterioration in glycemia. **A**
- 14.12** Health care professionals should screen for food security, housing stability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions. **E**
- 14.13** Health care professionals should consider asking youth and their parents/caregivers about social adjustment (peer relationships) and school performance to determine whether further intervention is needed. **B**
- 14.14** Screen youth with diabetes for psychosocial and diabetes-related distress, generally starting at 7–8 years of age. Refer to a qualified mental health professional for further assessment and treatment if indicated. **B**
- 14.15** Offer adolescents time by themselves with their health care professional(s) starting at age 12 years or when developmentally appropriate. **E**
- 14.16** Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all individuals of childbearing potential. **A**
- 14.17** Begin screening youth with type 1 diabetes for disordered

eating between 10 and 12 years of age. Refer to a qualified mental health professional for further assessment and treatment if indicated. **B**

Rapid and dynamic cognitive, developmental, and emotional changes occur during childhood, adolescence, and emerging adulthood. Diabetes management during childhood and adolescence places substantial burdens on the youth and family, necessitating ongoing assessment of psychosocial status, social determinants of health, and diabetes distress in the youth and the parents/caregivers during routine diabetes visits (31–41). It is important to consider the impact of diabetes on quality of life as well as the development of mental health problems related to diabetes distress, fear of hypoglycemia (and hyperglycemia), symptoms of anxiety, disordered eating behaviors and eating disorders, and symptoms of depression (42). Consider screening youth for diabetes distress, generally starting at 7 or 8 years of age (43). Consider screening for depression and disordered eating behaviors using available screening tools (44,45). Early detection of depression, anxiety, disordered eating, and learning disabilities can facilitate effective treatment options and help minimize adverse effects on diabetes management and disease outcomes (35,43). There are validated tools that can be used in assessing diabetes-specific distress in youth starting at age 8 years and in their parents/caregivers (36,46). Furthermore, the complexities of diabetes management require ongoing parental involvement in care throughout childhood with developmentally appropriate family teamwork between the growing child/teen and parent in order to maintain engagement in self-management behaviors and to prevent deterioration in glycemia (47,48). It is appropriate to inquire about diabetes-specific family conflict during visits and to either help to negotiate a plan for resolution or refer to an appropriate mental health professional (49). Such professionals can conduct further assessment and deliver evidence-based behavioral interventions to support developmentally appropriate, collaborative family involvement in diabetes self-management (50,51). Monitoring of

social adjustment (peer relationships) and school performance can facilitate both well-being and academic achievement (52). Elevated A1C is a risk factor for underperformance at school and increased absenteeism (53).

Shared decision-making with youth regarding the adoption of management plan components and self-management behaviors can improve diabetes self-efficacy, participation in diabetes care, and metabolic outcomes (26,54). Although cognitive abilities vary, the ethical position often adopted is the “mature minor rule,” whereby children after age 12 or 13 years who appear to be “mature” have the right to consent or withhold consent to general medical treatment, except in cases in which refusal would significantly endanger health (55).

Beginning at the onset of puberty or at diagnosis of diabetes, all individuals with childbearing potential should receive education about the risks of fetal malformations associated with elevated A1C and the use of effective contraception to prevent unplanned pregnancy. Preconception counseling using developmentally appropriate educational and behavioral strategies enables individuals of childbearing potential to make well-informed decisions (56). Preconception counseling resources tailored for adolescents are available at no cost through the ADA (57). Refer to the ADA position statement “Psychosocial Care for People With Diabetes” for further details (43).

Youth with type 1 diabetes have an increased risk of disordered eating behavior as well as clinical eating disorders with serious short-term and long-term negative effects on diabetes outcomes and health in general. It is important to recognize the unique and dangerous disordered eating behavior of insulin omission for weight management in type 1 diabetes (58) using tools such as the Diabetes Eating Problems Survey-Revised (DEPS-R) to allow for early diagnosis and intervention (45,59–61). Given the complexity of treating disordered eating behaviors, collaboration between the diabetes health care team and a mental health professional, ideally with expertise in disordered eating behaviors and diabetes, is recommended.

The presence of a mental health professional on pediatric multidisciplinary teams highlights the importance of attending to the psychosocial issues of

diabetes. These psychosocial factors are significantly related to self-management difficulties, elevated A1C, reduced quality of life, and higher rates of acute and chronic diabetes complications.

Glycemic Monitoring, Insulin Delivery, and Targets

Recommendations

- 14.18** All youth with type 1 diabetes should monitor glucose levels multiple times daily (up to 6–10 times/day by blood glucose meter or continuous glucose monitoring), including prior to meals and snacks, at bedtime, and as needed for safety in specific situations such as physical activity, driving, or the presence of symptoms of hypoglycemia. **B**
- 14.19** Real-time continuous glucose monitoring **B** or intermittently scanned continuous glucose monitoring **E** should be offered for diabetes management in youth with diabetes on multiple daily injections or insulin pump therapy who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual’s and family’s circumstances, desires, and needs.
- 14.20** Automated insulin delivery systems should be offered for diabetes management to youth with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual’s and family’s circumstances, desires, and needs. **A**
- 14.21** Insulin pump therapy alone should be offered for diabetes management to youth on multiple daily injections with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual’s and family’s circumstances, desires, and needs. **A**
- 14.22** Students must be supported at school in the use of diabetes

technology, including continuous glucose monitors, insulin pumps, connected insulin pens, and automated insulin delivery systems as prescribed by their diabetes care team. **E**

14.23 A1C goals must be individualized and reassessed over time. An A1C of <7% (53 mmol/mol) is appropriate for many children and adolescents. **B**

14.24 Less stringent A1C goals (such as <7.5% [58 mmol/mol]) may be appropriate for youth who cannot articulate symptoms of hypoglycemia; have hypoglycemia unawareness; lack access to analog insulins, advanced insulin delivery technology, and/or continuous glucose monitoring; cannot check blood glucose regularly; or have nonglycemic factors that increase A1C (e.g., high glycators). **B**

14.25 Even less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for individuals with a history of severe hypoglycemia, limited life expectancy, or where the harms of treatment are greater than the benefits. **B**

14.26 Health care professionals may reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individuals if they can be achieved without significant hypoglycemia, negative impacts on well-being, or undue burden of care or in those who have nonglycemic factors that decrease A1C (e.g., lower erythrocyte life span). Lower targets may also be appropriate during the honeymoon phase. **B**

14.27 Continuous glucose monitoring metrics derived from continuous glucose monitor use over the most recent 14 days (or longer for youth with more glycemic variability), including time in range (70–180 mg/dL), time below target (<70 and <54 mg/dL), and time above target (>180 and >250 mg/dL), are recommended to be used in

conjunction with A1C whenever possible. **E**

Current standards for diabetes management reflect the need to minimize hyperglycemia as safely as possible. The Diabetes Control and Complications Trial (DCCT), which did not enroll children <13 years of age, demonstrated that near normalization of blood glucose levels was more difficult to achieve in adolescents than in adults. Nevertheless, the increased use of basal-bolus regimens, insulin pumps, frequent blood glucose monitoring, CGM, automated insulin delivery systems, goal setting, and improved patient education has been associated with more children and adolescents reaching the blood glucose targets recommended by the ADA (62–64), particularly in families in which both the parents/caregivers and the child with diabetes participate jointly to perform the required diabetes-related tasks.

Lower A1C in adolescence and young adulthood is associated with a lower risk and rate of microvascular and macrovascular complications (65–68) and demonstrates the effects of metabolic memory (69–72).

In addition, type 1 diabetes can be associated with adverse effects on cognition during childhood and adolescence (6,73–75), and neurocognitive imaging differences related to hyperglycemia in children provide another motivation for achieving glycemic targets (6). DKA has been shown to cause adverse effects on brain development and function. Additional factors (76–79) that contribute to adverse effects on brain development and function include young age, severe hypoglycemia at <6 years of age, and chronic hyperglycemia (80–82). However, meticulous use of therapeutic modalities such as rapid- and long-acting insulin analogs, technological advances (e.g., CGM, sensor-augmented pump therapy, and automated insulin delivery systems), and intensive self-management education now make it more feasible to achieve glycemic goals while reducing the incidence of severe hypoglycemia (83–106). Please refer to Section 7, “Diabetes Technology,” for more information on technology to support people with diabetes.

In selecting individualized glycemic targets, the long-term health benefits of

achieving a lower A1C should be balanced against the risks of hypoglycemia and the developmental burdens of intensive treatment plans in youth (107). Recent data with newer devices and insulins indicate that the risk of hypoglycemia with lower A1C is less than it was before (108–117). Some data suggest that there could be a threshold where lower A1C is associated with more hypoglycemia (118,119); however, the confidence intervals were large, suggesting great variability. In addition, achieving lower A1C levels is likely facilitated by setting lower A1C targets (120,121). Lower goals may be possible during the “honeymoon” phase of type 1 diabetes. Special consideration should be given to the risk of hypoglycemia in young children (aged <6 years) who are often unable to recognize, articulate, and/or manage hypoglycemia. However, registry data indicate that A1C targets can be achieved in children, including those aged <6 years, without increased risk of severe hypoglycemia (109,120). Recent data have demonstrated that the use of real-time CGM lowered A1C and increased time in range in adolescents and young adults and, in children aged <8 years old, was associated with a lower risk of hypoglycemia (122,123). Please refer to Section 6, “Glycemic Targets,” for more information on glycemic assessment.

A strong relationship exists between the frequency of blood glucose monitoring and glycemic management (84–86, 124–130). Glucose levels for all children and adolescents with type 1 diabetes should be monitored multiple times daily by blood glucose monitoring and/or CGM. In the U.S., real-time CGM is approved for nonadjunctive use in children aged 2 years and older and intermittently scanned CGM is approved for nonadjunctive use in children aged 4 years and older. Parents/caregivers and youth should be offered initial and ongoing education and support for CGM use. Behavioral support may further improve ongoing CGM use (123). Metrics derived from CGM include percent time in target range, below target range, and above target range (131). While studies indicate a relationship between time in range and A1C (132, 133), it is still uncertain what the ideal target time in range should be for children, and further studies are needed.

Please refer to Section 7, “Diabetes Technology,” for more information on the use of blood glucose meters, CGM, and insulin pumps. More information on insulin injection technique can be found in Section 9, “Pharmacologic Approaches to Glycemic Treatment.”

Key Concepts in Setting Glycemic Targets

- Targets should be individualized, and lower targets may be reasonable based on a benefit–risk assessment.
- Blood glucose targets should be modified in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a discrepancy between preprandial blood glucose values and A1C levels and to assess preprandial insulin doses in those on basal-bolus or pump regimens.

Autoimmune Conditions

Recommendation

- 14.28** Assess for additional autoimmune conditions soon after the diagnosis of type 1 diabetes and if symptoms develop. **B**

Because of the increased frequency of other autoimmune diseases in type 1 diabetes, screening for thyroid dysfunction and celiac disease should be considered (134–138). Periodic screening in asymptomatic individuals has been recommended, but the optimal frequency of screening is unclear.

Although much less common than thyroid dysfunction and celiac disease, other autoimmune conditions, such as Addison disease (primary adrenal insufficiency), autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and myasthenia gravis, occur more commonly in the population with type 1 diabetes than in the general pediatric population and should be assessed and monitored as clinically indicated. In addition, relatives of youth with type 1 diabetes should be offered testing for islet autoantibodies through research studies (e.g., TrialNet) and national programs for early diagnosis of preclinical type 1 diabetes (stages 1 and 2).

Thyroid Disease

Recommendations

- 14.29** Consider testing children with type 1 diabetes for antithyroid

peroxidase and antithyroglobulin antibodies soon after diagnosis. **B**

- 14.30** Measure thyroid-stimulating hormone concentrations at diagnosis when clinically stable or soon after optimizing glycemia. If normal, suggest rechecking every 1–2 years or sooner if the youth has positive thyroid antibodies or develops symptoms or signs suggestive of thyroid dysfunction, thyromegaly, an abnormal growth rate, or unexplained glycemic variability. **B**

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of individuals with type 1 diabetes (135,139,140). At the time of diagnosis, ~25% of children with type 1 diabetes have thyroid autoantibodies (141), the presence of which is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of people with type 1 diabetes (142,143). For thyroid autoantibodies, a study from Sweden indicated that antithyroid peroxidase antibodies were more predictive than antithyroglobulin antibodies in multivariate analysis (144). Thyroid function tests may be misleading (euthyroid sick syndrome) if performed at the time of diagnosis owing to the effect of previous hyperglycemia, ketosis or ketoacidosis, weight loss, etc. Therefore, if performed at diagnosis and slightly abnormal, thyroid function tests should be repeated soon after a period of metabolic stability and achievement of glycemic targets. Subclinical hypothyroidism may be associated with an increased risk of symptomatic hypoglycemia (145) and a reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of glycemia.

Celiac Disease

Recommendations

- 14.31** Screen youth with type 1 diabetes for celiac disease by measuring IgA tissue transglutaminase (tTG) antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of

diabetes, or IgG tTG and deamidated gliadin antibodies if IgA is deficient. **B**

- 14.32** Repeat screening within 2 years of diabetes diagnosis and then again after 5 years and consider more frequent screening in youth who have symptoms or a first-degree relative with celiac disease. **B**

- 14.33** Individuals with confirmed celiac disease should be placed on a gluten-free diet for treatment and to avoid complications; they should also have a consultation with a registered dietitian nutritionist experienced in managing both diabetes and celiac disease. **B**

Celiac disease is an immune-mediated disorder that occurs with increased frequency in people with type 1 diabetes (1.6–16.4% of individuals compared with 0.3–1% in the general population) (134, 137,138,146–150). Screening people with type 1 diabetes for celiac disease is further justified by its association with osteoporosis, iron deficiency, growth failure, and potential increased risk of retinopathy and albuminuria (151–154).

Screening for celiac disease includes measuring serum levels of IgA and tissue transglutaminase (tTG) IgA antibodies, or, with IgA deficiency, screening can include measuring tTG IgG antibodies or deamidated gliadin peptide IgG antibodies. Because most cases of celiac disease are diagnosed within the first 5 years after the diagnosis of type 1 diabetes, screening should be considered at the time of diagnosis and repeated at 2 and then 5 years (148) or if clinical symptoms indicate, such as poor growth or increased hypoglycemia (149,151).

Although celiac disease can be diagnosed more than 10 years after diabetes diagnosis, there are insufficient data after 5 years to determine the optimal screening frequency. Measurement of tTG antibody should be considered at other times in individuals with symptoms suggestive of celiac disease (148). Monitoring for symptoms should include an assessment of linear growth and weight gain (149,151). A small bowel biopsy in antibody-positive children is recommended to confirm the diagnosis

(155). European guidelines on screening for celiac disease in children (not specific to children with type 1 diabetes) suggest that biopsy may not be necessary in symptomatic children with high antibody titers (i.e., greater than 10 times the upper limit of normal) provided that further testing is performed (verification of endomysial antibody positivity on a separate blood sample) (156). Whether this approach may be appropriate for asymptomatic children in high-risk groups remains an open question, though evidence is emerging (157). It is also advisable to check for celiac disease-associated HLA types in patients who are diagnosed without a small intestinal biopsy. In symptomatic children with type 1 diabetes and confirmed celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (158). The challenging dietary restrictions associated with having both type 1 diabetes and celiac disease place a significant burden on individuals. Therefore, a biopsy to confirm the diagnosis of celiac disease is recommended, especially in asymptomatic children, before establishing a diagnosis of celiac disease (159) and endorsing significant dietary changes. A gluten-free diet was beneficial in asymptomatic adults with positive antibodies confirmed by biopsy (160).

Management of Cardiovascular Risk Factors

Hypertension Screening

Recommendation

14.34 Blood pressure should be measured at every routine visit. In youth with high blood pressure (blood pressure \geq 90th percentile for age, sex, and height or, in adolescents aged \geq 13 years, blood pressure \geq 120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered. **B**

Hypertension Treatment

Recommendations

14.35 Treatment of elevated blood pressure (defined as 90th to $<$ 95th percentile for age, sex, and height or, in adolescents aged \geq 13 years, 120–129/ $<$ 80 mmHg) is lifestyle modification focused on healthy

nutrition, physical activity, sleep, and, if appropriate, weight management. **C**

14.36 In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently \geq 95th percentile for age, sex, and height or, in adolescents aged \geq 13 years, \geq 130/80 mmHg). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.37 The goal of treatment is blood pressure $<$ 90th percentile for age, sex, and height or, in adolescents aged \geq 13 years, $<$ 130/80 mmHg. **C**

Blood pressure measurements should be performed using the appropriate size cuff with the youth seated and relaxed. Elevated blood pressure should be confirmed on at least three separate days, and ambulatory blood pressure monitoring should be considered. Evaluation should proceed as clinically indicated (161,162). Treatment is generally initiated with an ACE inhibitor, but an angiotensin receptor blocker can be used if the ACE inhibitor is not tolerated (e.g., due to cough) (163).

Dyslipidemia Screening

Recommendations

14.38 Initial lipid profile should be performed soon after diagnosis, preferably after glycemia has improved and age is \geq 2 years. If initial LDL cholesterol is \leq 100 mg/dL (2.6 mmol/L), subsequent testing should be performed at 9–11 years of age. **B** Initial testing may be done with a nonfasting lipid level with confirmatory testing with a fasting lipid panel.

14.39 If LDL cholesterol values are within the accepted risk level

($<$ 100 mg/dL [2.6 mmol/L]), a lipid profile repeated every 3 years is reasonable. **E**

Dyslipidemia Treatment

Recommendations

14.40 If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutrition therapy to limit the amount of calories from fat to 25–30% and saturated fat to $<$ 7%, limit cholesterol to $<$ 200 mg/day, avoid *trans* fats, and aim for \sim 10% calories from monounsaturated fats. **A**

14.41 After the age of 10 years, addition of a statin may be considered in youth with type 1 diabetes who, despite medical nutrition therapy and lifestyle changes, continue to have LDL cholesterol $>$ 160 mg/dL (4.1 mmol/L) or LDL cholesterol $>$ 130 mg/dL (3.4 mmol/L) and one or more cardiovascular disease risk factors. **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.42 The goal of therapy is an LDL cholesterol value $<$ 100 mg/dL (2.6 mmol/L). **E**

Population-based studies estimate that 14–45% of children with type 1 diabetes have two or more atherosclerotic cardiovascular disease (ASCVD) risk factors (164–166), and the prevalence of cardiovascular disease (CVD) risk factors increase with age (166) and among racial/ethnic minorities (25), with girls having a higher risk burden than boys (165).

Pathophysiology. The atherosclerotic process begins in childhood, and although ASCVD events are not expected to occur during childhood, observations using a variety of methodologies show that youth with type 1 diabetes may have subclinical CVD within the first decade of diagnosis (167–169). Studies of carotid intima-

media thickness have yielded inconsistent results (162,163).

Screening. Diabetes predisposes to the development of accelerated arteriosclerosis. Lipid evaluation for these patients contributes to risk assessment and identifies an important proportion of those with dyslipidemia. Therefore, initial screening should be done soon after diagnosis. If the initial screen is normal, subsequent screening may be done at 9–11 years of age, which is a stable time for lipid assessment in children (170). Children with a primary lipid disorder (e.g., familial hyperlipidemia) should be referred to a lipid specialist. Non-HDL cholesterol level has been identified as a significant predictor of the presence of atherosclerosis—as powerful as any other lipoprotein cholesterol measure in children and adolescents. For both children and adults, non-HDL cholesterol level seems to be more predictive of persistent dyslipidemia and, therefore, atherosclerosis and future events than total cholesterol, LDL cholesterol, or HDL cholesterol levels alone. A major advantage of non-HDL cholesterol is that it can be accurately calculated in a nonfasting state and therefore is practical to obtain in clinical practice as a screening test (171). Youth with type 1 diabetes have a high prevalence of lipid abnormalities (164,172).

Even if normal, screening should be repeated within 3 years, as A1C and other cardiovascular risk factors can change dramatically during adolescence (173).

Treatment. Pediatric lipid guidelines provide some guidance relevant to children with type 1 diabetes and secondary dyslipidemia (162,170,174,175); however, there are few studies on modifying lipid levels in children with type 1 diabetes. A 6-month trial of dietary counseling produced a significant improvement in lipid levels (176); likewise, a lifestyle intervention trial with 6 months of exercise in adolescents demonstrated improvement in lipid levels (177). Data from the SEARCH for Diabetes in Youth (SEARCH) study show that improved glucose over a 2-year period is associated with a more favorable lipid profile; however, improved glycemia alone will not normalize lipids in youth with type 1 diabetes and dyslipidemia (173).

Although intervention data are sparse, the American Heart Association categorizes children with type 1 diabetes in the highest tier for cardiovascular risk and recommends both lifestyle and pharmacologic treatment for those with elevated LDL cholesterol levels (175,178). Initial therapy should include a nutrition plan that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day (170). Data from randomized clinical trials in children as young as 7 months of age indicate that this diet is safe and does not interfere with normal growth and development (179).

Neither long-term safety nor cardiovascular outcome efficacy of statin therapy has been established for children; however, studies have shown short-term safety equivalent to that seen in adults and efficacy in lowering LDL cholesterol levels in familial hypercholesterolemia or severe hyperlipidemia, improving endothelial function and causing regression of carotid intimal thickening (180,181). Statins are not approved for children aged <10 years, and statin treatment should generally not be used in children with type 1 diabetes before this age. Statins are contraindicated in pregnancy; therefore, the prevention of unplanned pregnancies is of paramount importance. Statins should be avoided in individuals of childbearing age who are not using reliable contraception (see Section 15, “Management of Diabetes in Pregnancy,” for more information). The multicenter, randomized, placebo-controlled Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) provides safety data on pharmacologic treatment with an ACE inhibitor and statin in adolescents with type 1 diabetes (162).

Smoking

Recommendations

- 14.43** Elicit a smoking history at initial and follow-up diabetes visits; discourage smoking in youth who do not smoke and encourage smoking cessation in those who do smoke. **A**
- 14.44** Electronic cigarette use should be discouraged. **A**

The adverse health effects of smoking are well recognized with respect to future cancer and CVD risk. Despite this,

smoking rates are significantly higher among youth with diabetes than among youth without diabetes (182,183). In youth with diabetes, it is important to avoid additional CVD risk factors. Smoking increases the risk of the onset of albuminuria; therefore, smoking avoidance is important to prevent both microvascular and macrovascular complications (170,184). Discouraging cigarette smoking, including electronic cigarettes (185, 186), is an important part of routine diabetes care. In light of CDC evidence of deaths related to electronic cigarette use (187,188), no individuals should be advised to use electronic cigarettes, either as a way to stop smoking tobacco or as a recreational drug. In younger children, it is important to assess exposure to cigarette smoke in the home because of the adverse effects of secondhand smoke and to discourage youth from ever smoking.

Microvascular Complications

Nephropathy Screening

Recommendation

- 14.45** Annual screening for albuminuria with a random (morning sample preferred to avoid effects of exercise) spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. **B**

Nephropathy Treatment

Recommendation

- 14.46** An ACE inhibitor or an angiotensin receptor blocker, titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio (>30 mg/g) is documented (two of three urine samples obtained over a 6-month interval following efforts to improve glycemia and normalize blood pressure). **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of

childbearing age who are not using reliable contraception. **B**

Data from 7,549 participants <20 years of age in the T1D Exchange clinic registry emphasize the importance of meeting glycemic and blood pressure goals, particularly as diabetes duration increases, in order to reduce the risk of diabetic kidney disease. The data also underscore the importance of routine screening to ensure early diagnosis and timely treatment of albuminuria (189). An estimation of glomerular filtration rate (GFR), calculated using GFR estimating equations from the serum creatinine, height, age, and sex (190), should be considered at baseline and repeated as indicated based on clinical status, age, diabetes duration, and therapies. Improved methods are needed to screen for early GFR loss since estimated GFR is inaccurate at $\text{GFR} > 60 \text{ mL/min/1.73 m}^2$ (190,191). The AddIT study in adolescents with type 1 diabetes demonstrated the safety of ACE inhibitor treatment, but the treatment did not change the albumin-to-creatinine ratio over the course of the study (162).

Retinopathy

Recommendations

- 14.47** An initial dilated and comprehensive eye examination is recommended once youth have had type 1 diabetes for 3–5 years, provided they are aged ≥ 11 years or puberty has started, whichever is earlier. **B**
- 14.48** After the initial examination, repeat dilated and comprehensive eye examination every 2 years. Less frequent examinations, every 4 years, may be acceptable on the advice of an eye care professional and based on risk factor assessment, including a history of $\text{A1C} < 8\%$. **B**
- 14.49** Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **E**

Retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (192). It is currently recognized that there is a low risk of development of vision-threatening retinal lesions prior to 12 years of age (193,194). A 2019 publication based on the follow-up of the DCCT adolescent cohort supports a lower frequency of eye examinations than previously recommended, particularly in adolescents with A1C closer to the target range (195,196). Referrals should be made to eye care professionals with expertise in diabetic retinopathy and experience in counseling pediatric patients and families on the importance of prevention, early detection, and intervention.

Neuropathy

Recommendation

- 14.50** Consider an annual comprehensive foot exam at the start of puberty or at age ≥ 10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years. The examination should include inspection, assessment of foot pulses, pinprick, and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. **B**

Diabetic neuropathy rarely occurs in prepubertal children or after only 1–2 years of diabetes (192), although data suggest a prevalence of distal peripheral neuropathy of 7% in 1,734 youth with type 1 diabetes and association with the presence of CVD risk factors (197,198). A comprehensive foot exam, including inspection, palpation of dorsalis pedis and posterior tibial pulses, and determination of proprioception, vibration, and monofilament sensation, should be performed annually along with an assessment of symptoms of neuropathic pain (198). Foot inspection can be performed at each visit to educate youth regarding the importance of foot care (see Section 12, “Retinopathy, Neuropathy, and Foot Care”).

TYPE 2 DIABETES

For information on risk-based screening for type 2 diabetes and prediabetes in children and adolescents, please refer to

Section 2, “Classification and Diagnosis of Diabetes.” For additional support for these recommendations, see the ADA position statement “Evaluation and Management of Youth-Onset Type 2 Diabetes” (3).

The prevalence of type 2 diabetes in youth has continued to increase over the past 20 years (4). The CDC published projections for type 2 diabetes prevalence using the SEARCH database; assuming a 2.3% annual increase, the prevalence in those under 20 years of age will quadruple in 40 years (199,200).

Evidence suggests that type 2 diabetes in youth is different not only from type 1 diabetes but also from type 2 diabetes in adults and has unique features, such as a more rapidly progressive decline in β -cell function and accelerated development of diabetes complications (3,201). Long-term follow-up data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study showed that a majority of individuals with type 2 diabetes diagnosed as youth had microvascular complications by young adulthood (202). Type 2 diabetes disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes and self-management behaviors (26,203–206). Additional risk factors associated with type 2 diabetes in youth include adiposity, family history of diabetes, female sex, and low socioeconomic status (201).

As with type 1 diabetes, youth with type 2 diabetes spend much of the day in school. Therefore, close communication with and the cooperation of school personnel are essential for optimal diabetes management, safety, and maximal academic opportunities.

Screening and Diagnosis

Recommendations

- 14.51** Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or ≥ 10 years of age, whichever occurs earlier, in youth with overweight ($\text{BMI} \geq 85\text{th}$ percentile) or obesity ($\text{BMI} \geq 95\text{th}$ percentile) and who have one or more additional risk factors for diabetes (see **Table 2.4** for evidence grading of other risk factors).

14.52 If screening is normal, repeat screening at a minimum of 3-year intervals **E**, or more frequently if BMI is increasing. **C**

14.53 Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1C can be used to test for prediabetes or diabetes in children and adolescents. **B**

14.54 Children and adolescents with overweight or obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes. **B**

In the last decade, the incidence and prevalence of type 2 diabetes in adolescents has increased dramatically, especially in racial and ethnic minority populations (170, 207). A few studies suggest oral glucose tolerance tests or fasting plasma glucose values as more suitable diagnostic tests than A1C in the pediatric population, especially among certain ethnicities (208), although fasting glucose alone may overdiagnose diabetes in children (209,210). In addition, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (211). An analysis of National Health and Nutrition Examination Survey (NHANES) data suggests using A1C for screening of high-risk youth (212).

The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes, and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this population (213,214).

Diagnostic Challenges

Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. Overweight and obesity are common in children with type 1 diabetes (27), and diabetes-associated autoantibodies and

ketosis may be present in pediatric individuals with clinical features of type 2 diabetes (including obesity and acanthosis nigricans) (209). The presence of islet autoantibodies has been associated with faster progression to insulin deficiency (209). At the onset, DKA occurs in ~6% of youth aged 10–19 years with type 2 diabetes (215). Although uncommon, type 2 diabetes has been observed in prepubertal children under the age of 10 years, and thus it should be part of the differential in children with suggestive symptoms (216). Finally, obesity contributes to the development of type 1 diabetes in some individuals (217), which further blurs the lines between diabetes types. However, accurate diagnosis is critical, as treatment plans, educational approaches, dietary advice, and outcomes differ markedly between patients with the two diagnoses. The significant diagnostic difficulties posed by MODY are discussed in Section 2, “Classification and Diagnosis of Diabetes.” In addition, there are rare and atypical diabetes cases that represent a challenge for clinicians and researchers.

Management

Lifestyle Management

Recommendations

14.55 All youth with type 2 diabetes and their families should receive comprehensive diabetes self-management education and support that is specific to youth with type 2 diabetes and is culturally appropriate. **B**

14.56 Youth with overweight/obesity and type 2 diabetes and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management to achieve a 7–10% decrease in excess weight. **C**

14.57 Given the necessity of long-term weight management for youth with type 2 diabetes, lifestyle intervention should be based on a chronic care model and offered in the context of diabetes care. **E**

14.58 Youth with prediabetes and type 2 diabetes, like all children

and adolescents, should be encouraged to participate in at least 60 min of moderate to vigorous physical activity daily (with muscle and bone strength training at least 3 days/week) **B** and to decrease sedentary behavior. **C**

14.59 Nutrition for youth with prediabetes and type 2 diabetes, like for all children and adolescents, should focus on healthy eating patterns that emphasize consumption of nutrient-dense, high-quality foods and decreased consumption of calorie-dense, nutrient-poor foods, particularly sugar-added beverages. **B**

Glycemic Targets

Recommendations

14.60 Blood glucose monitoring should be individualized, taking into consideration the pharmacologic treatment of the patient. **E**

14.61 Real-time continuous glucose monitoring or intermittently scanned continuous glucose monitoring should be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or insulin pumps who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on an individual’s and family’s circumstances, desires, and needs. **E**

14.62 Glycemic status should be assessed every 3 months. **E**

14.63 A reasonable A1C target for most children and adolescents with type 2 diabetes is <7% (53 mmol/mol). More stringent A1C targets (such as <6.5% [48 mmol/mol]) may be appropriate for selected individuals if they can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate individuals might include those with a short duration of diabetes and lesser degrees of β -cell dysfunction and individuals treated with

lifestyle or metformin only who achieve significant weight improvement. **E**

14.64 Less stringent A1C goals (such as 7.5% [58 mmol/mol]) may be appropriate if there is an increased risk of hypoglycemia. **E**

14.65 A1C targets for individuals on insulin should be individualized, taking into account the relatively low rates of hypoglycemia in youth-onset type 2 diabetes. **E**

Pharmacologic Management

Recommendations

14.66 Initiate pharmacologic therapy, in addition to behavioral counseling for healthful nutrition and physical activity changes, at diagnosis of type 2 diabetes. **A**

14.67 In individuals with incidentally diagnosed or metabolically stable diabetes (A1C <8.5% [69 mmol/mol] and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal. **A**

14.68 Youth with marked hyperglycemia (blood glucose \geq 250 mg/dL [13.9 mmol/L], A1C \geq 8.5% [69 mmol/mol]) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with long-acting insulin while metformin is initiated and titrated. **B**

14.69 In individuals with ketosis/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued. **A**

14.70 In individuals presenting with severe hyperglycemia (blood glucose \geq 600 mg/dL [33.3 mmol/L]), consider assessment for hyperglycemic hyperosmolar nonketotic syndrome. **A**

14.71 If glycemic targets are no longer met with metformin (with

or without long-acting insulin), glucagon-like peptide 1 receptor agonist therapy approved for youth with type 2 diabetes should be considered in children 10 years of age or older if they have no past medical history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. **A**

14.72 Individuals treated with metformin, a glucagon-like peptide 1 receptor agonist, and long-acting insulin who do not meet glycemic targets should be moved to multiple daily injections with long-acting and prandial insulins or insulin pump therapy. **E**

14.73 In individuals initially treated with insulin and metformin who are meeting glucose targets based on blood glucose monitoring, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days. **B**

14.74 Use of medications not approved by the U.S. Food and Drug Administration for youth with type 2 diabetes is not recommended outside of research trials. **B**

Treatment of youth-onset type 2 diabetes should include lifestyle management, diabetes self-management education and support, and pharmacologic treatment. Initial treatment of youth with obesity and diabetes must take into account that diabetes type is often uncertain in the first few weeks of treatment due to overlap in presentation and that a substantial percentage of youth with type 2 diabetes will present with clinically significant ketoacidosis (218). Therefore, initial therapy should address the hyperglycemia and associated metabolic derangements irrespective of ultimate diabetes type, with adjustment of therapy once metabolic compensation has been established and subsequent information, such as islet autoantibody results, becomes available. **Figure 14.1** provides an approach to the initial treatment of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes.

Glycemic targets should be individualized, taking into consideration the long-term health benefits of more stringent targets and risk for adverse effects, such as hypoglycemia. A lower target A1C in youth with type 2 diabetes when compared with those recommended in type 1 diabetes is justified by a lower risk of hypoglycemia and higher risk of complications (202,219–222).

Self-management in pediatric diabetes involves both the youth and their parents/adult caregivers. Individuals and their families should receive education and support for healthful nutrition and physical activity such as a balanced meal plan, achieving and maintaining a healthy weight, and regular physical activity. Physical activity should include aerobic, muscle-strengthening, and bone-strengthening activities (17). A family-centered approach to nutrition and lifestyle modification is essential in children and adolescents with type 2 diabetes, and nutrition recommendations should be culturally appropriate and sensitive to family resources (see Section 5, “Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes”). Given the complex social and environmental context surrounding youth with type 2 diabetes, individual-level lifestyle interventions may not be sufficient to target the complex interplay of family dynamics, mental health, community readiness, and the broader environmental system (3).

A multidisciplinary diabetes team, including a physician, diabetes care and education specialist, registered dietitian nutritionist, and psychologist or social worker, is essential. In addition to achieving glycemic targets and self-management education (223–225), initial treatment must include management of comorbidities such as obesity, dyslipidemia, hypertension, and microvascular complications.

Current pharmacologic treatment options for youth-onset type 2 diabetes are limited to three approved drug classes: insulin, metformin, and glucagon-like peptide 1 receptor agonists. Presentation with ketoacidosis or marked ketosis requires a period of insulin therapy until fasting and postprandial glycemia have been restored to normal or near-normal levels. Insulin pump therapy may be considered as an option for those on long-term multiple daily injections who are able

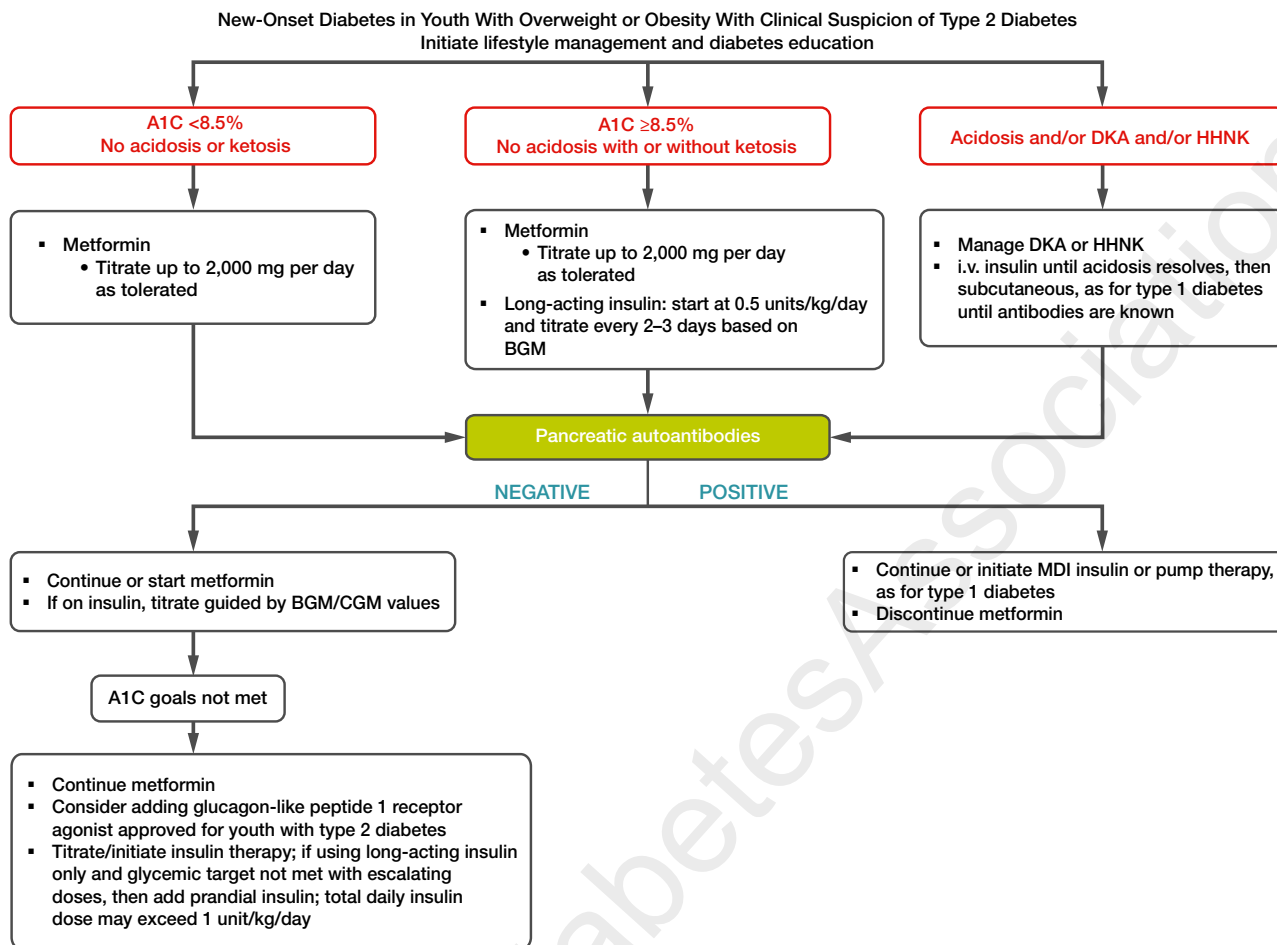


Figure 14.1—Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes. A1C 8.5% = 69 mmol/mol. Adapted from the ADA position statement “Evaluation and Management of Youth-Onset Type 2 Diabetes” (3). BGM, blood glucose monitoring; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; i.v., intravenous; MDI, multiple daily injections.

to safely manage the device. Initial treatment should also be with insulin when the distinction between type 1 diabetes and type 2 diabetes is unclear and in patients who have random blood glucose concentrations ≥ 250 mg/dL (13.9 mmol/L) and/or A1C $\geq 8.5\%$ (69 mmol/mol) (226). Metformin therapy should be added after resolution of ketosis/ketoacidosis.

When initial insulin treatment is not required, initiation of metformin is recommended. The TODAY study found that metformin alone provided durable glycemic control (A1C $\leq 8\%$ [64 mmol/mol] for 6 months) in approximately half of the subjects (227). The Restoring Insulin Secretion (RISE) Consortium study did not demonstrate differences in measures of glucose or β -cell function preservation between metformin and insulin, but there was more weight gain with insulin (228).

To date, the TODAY study is the only trial combining lifestyle and metformin

therapy in youth with type 2 diabetes; the combination did not perform better than metformin alone in achieving durable glycemic control (227).

A randomized clinical trial in youth aged 10–17 years with type 2 diabetes demonstrated the addition of subcutaneous liraglutide (up to 1.8 mg daily) to metformin (with or without long-acting insulin) as safe and effective to decrease A1C (estimated decrease of 1.06 percentage points at 26 weeks and 1.30 percentage points at 52 weeks), although it did increase the frequency of gastrointestinal side effects (229). Liraglutide and once-weekly exenatide extended release are approved for the treatment of type 2 diabetes in youth aged 10 years or older (230–232).

Blood glucose monitoring plans should be individualized, taking into consideration the pharmacologic treatment of the person. Although data on

CGM in youth with type 2 diabetes are sparse (233), CGM could be considered in individuals requiring frequent blood glucose monitoring for diabetes management.

Metabolic Surgery

Recommendations

14.75 Metabolic surgery may be considered for the treatment of adolescents with type 2 diabetes who have severe obesity (BMI > 35 kg/m²) and who have elevated A1C and/or serious comorbidities despite lifestyle and pharmacologic intervention. **A**

14.76 Metabolic surgery should be performed only by an experienced surgeon working as part of a well-organized and engaged multidisciplinary team, including a

surgeon, endocrinologist, registered dietitian nutritionist, behavioral health specialist, and nurse. **A**

The results of weight loss and lifestyle interventions for obesity in children and adolescents have been disappointing, and treatment options as adjuncts to lifestyle therapy are limited. Recent U.S. Food and Drug Administration–approved medications for youth ages 12 and older include phentermine and topiramate extended-release capsules and liraglutide (234–236). Over the last decade, weight loss surgery has been increasingly performed in adolescents with obesity. Small retrospective analyses and a prospective multicenter, nonrandomized study suggest that bariatric or metabolic surgery may have benefits in adolescents with obesity and type 2 diabetes similar to those observed in adults. Teenagers experience similar degrees of weight loss, diabetes remission, and improvement of cardiometabolic risk factors for at least 3 years after surgery (237). A secondary data analysis from the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and TODAY studies suggests surgical treatment of adolescents with severe obesity and type 2 diabetes is associated with improved glycemia (238); however, no randomized trials have yet compared the effectiveness and safety of surgery to those of conventional treatment options in adolescents (239). The guidelines used as an indication for metabolic surgery in adolescents generally include BMI >35 kg/m² with comorbidities or BMI >40 kg/m² with or without comorbidities (240–251). A number of groups, including the Pediatric Bariatric Study Group and Teen-LABS study, have demonstrated the effectiveness of metabolic surgery in adolescents (244–250).

Prevention and Management of Diabetes Complications

Hypertension

Recommendations

14.77 Blood pressure should be measured at every visit. In youth with high blood pressure (blood pressure ≥ 90 th percentile for age, sex, and height or, in adolescents aged ≥ 13 years, $\geq 120/80$ mmHg) on three separate measurements, ambulatory

blood pressure monitoring should be strongly considered. **B**

14.78 Treatment of elevated blood pressure (defined as 90th to <95 th percentile for age, sex, and height or, in adolescents aged ≥ 13 years, $120\text{--}129/ <80$ mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management. **C**

14.79 In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥ 95 th percentile for age, sex, and height or, in adolescents aged ≥ 13 years, $\geq 130/80$ mmHg). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.80 The goal of treatment is blood pressure <90 th percentile for age, sex, and height or, in adolescents aged ≥ 13 years, $<130/80$ mmHg. **C**

Nephropathy

Recommendations

14.81 Protein intake should be at the recommended daily allowance of 0.8 g/kg/day. **E**

14.82 Urine albumin-to-creatinine ratio should be obtained at the time of diagnosis and annually thereafter. An elevated urine albumin-to-creatinine ratio (>30 mg/g creatinine) should be confirmed on two of three samples. **B**

14.83 Estimated glomerular filtration rate should be determined at the time of diagnosis and annually thereafter. **E**

14.84 In youth with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated

urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) and is strongly recommended for those with urinary albumin-to-creatinine ratio >300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m². **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.85 For those with nephropathy, continued monitoring (yearly urinary albumin-to-creatinine ratio, estimated glomerular filtration rate, and serum potassium) may aid in assessing engagement and detecting progression of disease. **E**

14.86 Referral to nephrology is recommended in case of uncertainty of etiology, worsening urinary albumin-to-creatinine ratio, or decrease in estimated glomerular filtration rate. **E**

Neuropathy

Recommendations

14.87 Youth with type 2 diabetes should be screened for the presence of neuropathy by foot examination at diagnosis and annually. The examination should include inspection, assessment of foot pulses, pinprick and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. **C**

14.88 Prevention should focus on achieving glycemic targets. **C**

Retinopathy

Recommendations

14.89 Screening for retinopathy should be performed by dilated funduscopy at or soon after diagnosis and annually thereafter. **C**

14.90 Optimizing glycemia is recommended to decrease the risk

or slow the progression of retinopathy. **B**

14.91 Less frequent examination (every 2 years) may be considered if achieving glycemic targets and a normal eye exam. **C**

14.92 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **E**

Nonalcoholic Fatty Liver Disease

Recommendations

14.93 Evaluation for nonalcoholic fatty liver disease (by measuring AST and ALT) should be done at diagnosis and annually thereafter. **B**

14.94 Referral to gastroenterology should be considered for persistently elevated or worsening transaminases. **B**

Obstructive Sleep Apnea

Recommendation

14.95 Screening for symptoms of sleep apnea should be done at each visit, and referral to a pediatric sleep specialist for evaluation and a polysomnogram, if indicated, is recommended. Obstructive sleep apnea should be treated when documented. **B**

Polycystic Ovary Syndrome

Recommendations

14.96 Evaluate for polycystic ovary syndrome in female adolescents with type 2 diabetes, including laboratory studies, when indicated. **B**

14.97 Oral contraceptive pills for treatment of polycystic ovary syndrome are not contraindicated for female individuals with type 2 diabetes. **C**

14.98 Metformin, in addition to lifestyle modification, is likely to improve the menstrual cyclicity and hyperandrogenism in female individuals with type 2 diabetes. **E**

Cardiovascular Disease

Recommendation

14.99 Intensive lifestyle interventions focusing on weight loss, dyslipidemia, hypertension, and dysglycemia are important to prevent overt macrovascular disease in early adulthood. **E**

Dyslipidemia

Recommendations

14.100 Lipid screening should be performed initially after optimizing glycemia and annually thereafter. **B**

14.101 Optimal goals are LDL cholesterol <100 mg/dL (2.6 mmol/L), HDL cholesterol >35 mg/dL (0.91 mmol/L), and triglycerides <150 mg/dL (1.7 mmol/L). **E**

14.102 If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutritional therapy to limit the amount of calories from fat to 25–30% and saturated fat to <7%, limit cholesterol to <200 mg/day, avoid *trans* fats, and aim for ~10% calories from monounsaturated fats for elevated LDL. For elevated triglycerides, medical nutrition therapy should also focus on decreasing simple sugar intake and increasing dietary n-3 fatty acids in addition to the above changes. **A**

14.103 If LDL cholesterol remains >130 mg/dL after 6 months of dietary intervention, initiate therapy with statin, with a goal of LDL <100 mg/dL. Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing

age who are not using reliable contraception. **B**

14.104 If triglycerides are >400 mg/dL (4.7 mmol/L) fasting or >1,000 mg/dL (11.6 mmol/L) nonfasting, optimize glycemia and begin fibrates, with a goal of <400 mg/dL (4.7 mmol/L) fasting to reduce risk for pancreatitis. **C**

Cardiac Function Testing

Recommendation

14.105 Routine screening for heart disease with electrocardiogram, echocardiogram, or stress testing is not recommended in asymptomatic youth with type 2 diabetes. **B**

Comorbidities may already be present at the time of diagnosis of type 2 diabetes in youth (201,252). Therefore, blood pressure measurement, a fasting lipid panel, assessment of random urine albumin-to-creatinine ratio, and a dilated eye examination should be performed at diagnosis. Additional medical conditions that may need to be addressed include polycystic ovary disease and other comorbidities associated with pediatric obesity, such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns. The ADA position statement “Evaluation and Management of Youth-Onset Type 2 Diabetes” (3) provides guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in children and adolescents.

Youth-onset type 2 diabetes is associated with significant microvascular and macrovascular risk burden and a substantial increase in the risk of cardiovascular morbidity and mortality at an earlier age than in those diagnosed later in life (202,253). The higher complication risk in earlier-onset type 2 diabetes is likely related to prolonged lifetime exposure to hyperglycemia and other atherogenic risk factors, including insulin resistance, dyslipidemia, hypertension, and chronic inflammation. There is a low risk of hypoglycemia in youth with type 2 diabetes, even if they are being treated with insulin (254), and there are high rates of complications (219–222).

These diabetes comorbidities also appear to be higher than in youth with type 1 diabetes despite shorter diabetes duration and lower A1C (252). In addition, the progression of vascular abnormalities appears to be more pronounced in youth-onset type 2 diabetes than with type 1 diabetes of similar duration, including ischemic heart disease and stroke (255).

Psychosocial Factors

Recommendations

- 14.106** Health care professionals should screen for food insecurity, housing instability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions. **E**
- 14.107** Use age-appropriate standardized and validated tools to screen for diabetes distress, depressive symptoms, and mental/behavioral health in youth with type 2 diabetes, with attention to symptoms of depression and disordered eating, and refer to a qualified mental health professional when indicated. **B**
- 14.108** When choosing glucose-lowering or other medications for youth with overweight or obesity and type 2 diabetes, consider medication-taking behavior and the medications' effect on weight. **E**
- 14.109** Starting at puberty, preconception counseling should be incorporated into routine diabetes clinic visits for all individuals of childbearing potential because of the adverse pregnancy outcomes in this population. **A**
- 14.110** Adolescents and young adults should be screened for tobacco, electronic cigarettes, and alcohol use at diagnosis and regularly thereafter. **C**

Most youth with type 2 diabetes come from racial/ethnic minority groups, have low socioeconomic status, and often experience multiple psychosocial stressors (26,43,205,206). Consideration of the

sociocultural context and efforts to personalize diabetes management are of critical importance to minimize barriers to care, enhance participation, and maximize response to treatment.

Evidence about psychiatric disorders and symptoms in youth with type 2 diabetes is limited (256–260), but given the sociocultural context for many youth and the medical burden and obesity associated with type 2 diabetes, ongoing surveillance of mental health/behavioral health is indicated. Symptoms of depression and disordered eating are common and associated with poorer glycemic control (39,257,261,262).

Many of the medications prescribed for diabetes and psychiatric disorders are associated with weight gain and can increase concerns about eating, body shape, and weight (263,264).

The TODAY study documented high rates of maternal complications during pregnancy and low rates of preconception counseling and contraception use (265).

TRANSITION FROM PEDIATRIC TO ADULT CARE

Recommendations

- 14.111** Pediatric diabetes care teams should begin to prepare youth for transition to adult health care in early adolescence and, at the latest, at least 1 year before the transition. **E**
- 14.112** Both pediatric and adult diabetes care professionals should provide support and resources for transitioning young adults. **E**
- 14.113** Youth with type 2 diabetes should be transferred to an adult-oriented diabetes specialist when deemed appropriate by the young adult and health care professional. **E**

Care and close supervision of diabetes management are increasingly shifted from parents and other adults to the youth with type 1 or type 2 diabetes throughout childhood and adolescence. The shift from pediatric to adult health care professionals, however, often occurs abruptly as the older teen enters the next developmental stage, referred to as emerging adulthood (266), which is a critical period for young people

who have diabetes. During this period of major life transitions, youth may begin to move out of their parents' homes and become increasingly responsible for their diabetes care. Their new responsibilities include self-management of their diabetes, making medical appointments, and financing health care once they are no longer covered by their parents' health insurance plans (ongoing coverage until age 26 years is currently available under provisions of the U.S. Affordable Care Act). In addition to lapses in health care, this is also a period associated with deterioration in glycemic stability; increased occurrence of acute complications; psychosocial, emotional, and behavioral challenges; and the emergence of chronic complications (267–272). The transition period from pediatric to adult care is prone to fragmentation in health care delivery, which may adversely impact health care quality, cost, and outcomes (273). Worsening diabetes health outcomes during the transition to adult care and early adulthood have been documented (274,275).

Although scientific evidence is limited, it is clear that comprehensive and coordinated planning that begins in early adolescence is necessary to facilitate a seamless transition from pediatric to adult health care (267,268,276,277). New technologies and other interventions are being tried to support the transition to adult care in young adulthood (278–282). Given the behavioral, psychosocial, and developmental factors that relate to this transition, diabetes care teams addressing transition should include social workers, psychologists, and other behavioral health professionals, as available (51,283). A comprehensive discussion regarding the challenges faced during this period, including specific recommendations, is found in the ADA position statement "Diabetes Care for Emerging Adults: Recommendations for Transition From Pediatric to Adult Diabetes Care Systems" (268).

The Endocrine Society, in collaboration with the ADA and other organizations, has developed transition tools for clinicians and youth and families (277).

References

- Centers for Disease Control and Prevention. Vaccines site: Healthcare Providers/Professionals. 2021. Accessed 21 October 2022. Available from <https://www.cdc.gov/vaccines/hcp/index.html>

2. Chiang JL, Maahs DM, Garvey KC, et al. Type 1 diabetes in children and adolescents: a position statement by the American Diabetes Association. *Diabetes Care* 2018;41:2026–2044
3. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. *Diabetes Care* 2018;41:2648–2668
4. Lawrence JM, Divers J, Isom S, et al.; SEARCH for Diabetes in Youth Study Group. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001–2017. *JAMA* 2021;326:717–727
5. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. *Lancet Diabetes Endocrinol* 2018;6:122–129
6. Barnea-Goraly N, Raman M, Mazaika P, et al.; Diabetes Research in Children Network (DirecNet). Alterations in white matter structure in young children with type 1 diabetes. *Diabetes Care* 2014;37:332–340
7. Cameron FJ, Scratch SE, Nadebaum C, et al.; DKA Brain Injury Study Group. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. *Diabetes Care* 2014;37:1554–1562
8. Markowitz JT, Garvey KC, Laffel LMB. Developmental changes in the roles of patients and families in type 1 diabetes management. *Curr Diabetes Rev* 2015;11:231–238
9. Driscoll KA, Volkening LK, Haro H, et al. Are children with type 1 diabetes safe at school? Examining parent perceptions. *Pediatr Diabetes* 2014
10. Jackson CC, Albanese-O'Neill A, Butler KL, et al. Diabetes care in the school setting: a position statement of the American Diabetes Association. *Diabetes Care* 2015;38:1958–1963
11. Siminerio LM, Albanese-O'Neill A, Chiang JL, et al.; American Diabetes Association. Care of young children with diabetes in the child care setting: a position statement of the American Diabetes Association. *Diabetes Care* 2014;37:2834–2842
12. Mehta SN, Volkening LK, Anderson BJ, et al.; Family Management of Childhood Diabetes Study Steering Committee. Dietary behaviors predict glycemic control in youth with type 1 diabetes. *Diabetes Care* 2008;31:1318–1320
13. Absil H, Baudet L, Robert A, Lysy PA. Benefits of physical activity in children and adolescents with type 1 diabetes: a systematic review. *Diabetes Res Clin Pract* 2019;156:107810
14. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol* 2017;5:377–390
15. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2016;39:2065–2079
16. Moser O, Riddell MC, Eckstein ML, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) endorsed by JDREF and supported by the American Diabetes Association (ADA). *Diabetologia* 2020;63:2501–2520
17. U.S. Department of Health and Human Services. Physical activity guidelines for Americans, 2nd ed., 2018. Accessed 21 October 2022. Available from https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf
18. Tsalikian E, Kollman C, Tamborlane WB, et al.; Diabetes Research in Children Network (DirecNet) Study Group. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care* 2006;29:2200–2204
19. Taplin CE, Cobry E, Messer L, McFann K, Chase HP, Fiallo-Scharer R. Preventing post-exercise nocturnal hypoglycemia in children with type 1 diabetes. *J Pediatr* 2010;157:784–8.e1
20. Eckstein ML, Weigluni B, Tauschmann M, et al. Time in range for closed-loop systems versus standard of care during physical exercise in people with type 1 diabetes: a systematic review and meta-analysis. *J Clin Med* 2021;10:2445
21. Riddell MC, Milliken J. Preventing exercise-induced hypoglycemia in type 1 diabetes using real-time continuous glucose monitoring and a new carbohydrate intake algorithm: an observational field study. *Diabetes Technol Ther* 2011;13:819–825
22. Francescato MP, Stel G, Stenner E, Geat M. Prolonged exercise in type 1 diabetes: performance of a customizable algorithm to estimate the carbohydrate supplements to minimize glycemic imbalances. *PLoS One* 2015;10:e0125220
23. Baker LB, Rollo I, Stein KW, Jeukendrup AE. Acute effects of carbohydrate supplementation on intermittent sports performance. *Nutrients* 2015;7:5733–5763
24. Adolfsson P, Mattsson S, Jendle J. Evaluation of glucose control when a new strategy of increased carbohydrate supply is implemented during prolonged physical exercise in type 1 diabetes. *Eur J Appl Physiol* 2015;115:2599–2607
25. Redondo MJ, Libman I, Cheng P, et al.; Pediatric Diabetes Consortium. Racial/ethnic minority youth with recent-onset type 1 diabetes have poor prognostic factors. *Diabetes Care* 2018;41:1017–1024
26. Liu LL, Lawrence JM, Davis C, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. *Pediatr Diabetes* 2010;11:4–11
27. DuBose SN, Hermann JM, Tamborlane WV, Beck RW, Dost A, DiMeglio LA, et al. Obesity in youth with type 1 diabetes in Germany, Austria, and the United States. *J Pediatr* 2015;167:627–632.e1–4
28. Corbin KD, Driscoll KA, Pratley RE, Smith SR, Maahs DM; Advancing Care for Type 1 Diabetes and Obesity Network (ACT1ON). Obesity in type 1 diabetes: pathophysiology, clinical impact, and mechanisms. *Endocr Rev* 2018;39:629–663
29. Redondo MJ, Foster NC, Libman IM, et al. Prevalence of cardiovascular risk factors in youth with type 1 diabetes and elevated body mass index. *Acta Diabetol* 2016;53:271–277
30. American Association of Diabetes Educators. Management of children with diabetes in the school setting. *Diabetes Educ* 2019;45:54–59
31. Hood KK, Beavers DP, Yi-Frazier J, et al. Psychosocial burden and glycemic control during the first 6 years of diabetes: results from the SEARCH for Diabetes in Youth study. *J Adolesc Health* 2014;55:498–504
32. Ducat L, Philipson LH, Anderson BJ. The mental health comorbidities of diabetes. *JAMA* 2014;312:691–692
33. Hagger V, Hendrieckx C, Sturt J, Skinner TC, Speight J. Diabetes distress among adolescents with type 1 diabetes: a systematic review. *Curr Diab Rep* 2016;16:9
34. Anderson BJ, Laffel LM, Domenger C, et al. Factors associated with diabetes-specific health-related quality of life in youth with type 1 diabetes: the Global TEENs Study. *Diabetes Care* 2017;40:1002–1009
35. Hilliard ME, De Wit M, Wasserman RM, et al. Screening and support for emotional burdens of youth with type 1 diabetes: strategies for diabetes care providers. *Pediatr Diabetes* 2018;19:534–543
36. Shapiro JB, Vesco AT, Weil LEG, Evans MA, Hood KK, Weissberg-Benchell J. Psychometric properties of the problem areas in diabetes: teen and parent of teen versions. *J Pediatr Psychol* 2018;43:561–571
37. Iturralde E, Rausch JR, Weissberg-Benchell J, Hood KK. Diabetes-related emotional distress over time. *Pediatrics* 2019;143:e20183011
38. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. *Diabetes Care* 2020;44:258–279
39. Monaghan M, Mara CA, Kichler JC, et al. Multisite examination of depression screening scores and correlates among adolescents and young adults with type 2 diabetes. *Can J Diabetes* 2021;45:411–416
40. Mulvaney SA, Mara CA, Kichler JC, et al. A retrospective multisite examination of depression screening practices, scores, and correlates in pediatric diabetes care. *Transl Behav Med* 2021;11:122–131
41. Rechenberg K, Koerner R. Cognitive behavioral therapy in adolescents with type 1 diabetes: an integrative review. *J Pediatr Nurs* 2021;60:190–197
42. Lawrence JM, Yi-Frazier JP, Black MH, et al.; SEARCH for Diabetes in Youth Study Group. Demographic and clinical correlates of diabetes-related quality of life among youth with type 1 diabetes. *J Pediatr* 2012;161:201–207.e2
43. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2016;39:2126–2140
44. Corathers SD, Kichler J, Jones NHY, Houchen A, Jolly M, Morwessel N, et al. Improving depression screening for adolescents with type 1 diabetes. *Pediatrics* 2013;132:e1395–e1402
45. Markowitz JT, Butler DA, Volkening LK, Antisdal JE, Anderson BJ, Laffel LMB. Brief screening tool for disordered eating in diabetes: internal consistency and external validity in a contemporary sample of pediatric patients with type 1 diabetes. *Diabetes Care* 2010;33:495–500
46. Evans MA, Weil LEG, Shapiro JB, et al. Psychometric properties of the parent and child problem areas in diabetes measures. *J Pediatr Psychol* 2019;44:703–713
47. Katz ML, Volkening LK, Butler DA, Anderson BJ, Laffel LM. Family-based psychoeducation and Care

- Ambassador intervention to improve glycemic control in youth with type 1 diabetes: a randomized trial. *Pediatr Diabetes* 2014;15:142–150
48. Laffel LMB, Vangsness L, Connell A, Goebel-Fabbri A, Butler D, Anderson BJ. Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes. *J Pediatr* 2003;142:409–416
49. Anderson BJ, Vangsness L, Connell A, Butler D, Goebel-Fabbri A, Laffel LMB. Family conflict, adherence, and glycaemic control in youth with short duration type 1 diabetes. *Diabet Med* 2002;19:635–642
50. Hilliard ME, Powell PW, Anderson BJ. Evidence-based behavioral interventions to promote diabetes management in children, adolescents, and families. *Am Psychol* 2016;71:590–601
51. Kichler JC, Harris MA, Weissberg-Benchell J. Contemporary roles of the pediatric psychologist in diabetes care. *Curr Diabetes Rev* 2015;11:210–221
52. Helgeson VS, Palladino DK. Implications of psychosocial factors for diabetes outcomes among children with type 1 diabetes: a review. *Soc Personal Psychol Compass* 2012;6:228–242
53. McCarthy AM, Lindgren S, Mengeling MA, Tsalikian E, Engvall J. Factors associated with academic achievement in children with type 1 diabetes. *Diabetes Care* 2003;26:112–117
54. Kuther TL. Medical decision-making and minors: issues of consent and assent. *Adolescence* 2003;38:343–358
55. Coleman DL, Rosoff PM. The legal authority of mature minors to consent to general medical treatment. *Pediatrics* 2013;131:786–793
56. Charron-Prochownik D, Sereika SM, Becker D, et al. Long-term effects of the booster-enhanced READY-Girls preconception counseling program on intentions and behaviors for family planning in teens with diabetes. *Diabetes Care* 2013;36:3870–3874
57. Charron-Prochownik D, Downs J. Diabetes and Reproductive Health for Girls. Alexandria, VA, American Diabetes Association, 2016
58. Wisting L, Frøisland DH, Skriverhaug T, Dahl-Jørgensen K, Rø O. Disturbed eating behavior and omission of insulin in adolescents receiving intensified insulin treatment: a nationwide population-based study. *Diabetes Care* 2013;36:3382–3387
59. Goebel-Fabbri AE. Disturbed eating behaviors and eating disorders in type 1 diabetes: clinical significance and treatment recommendations. *Curr Diab Rep* 2009;9:133–139
60. Atik Altönok Y, Özgür S, Meseri R, Özen S, Darcan Ş, Gökşen D. Reliability and validity of the diabetes eating problem survey in Turkish children and adolescents with type 1 diabetes mellitus. *J Clin Res Pediatr Endocrinol* 2017;9:323–328
61. Saßmann H, Albrecht C, Busse-Widmann P, et al. Psychometric properties of the German version of the Diabetes Eating Problem Survey-Revised: additional benefit of disease-specific screening in adolescents with type 1 diabetes. *Diabet Med* 2015;32:1641–1647
62. Gerhardsson P, Schwandt A, Witsch M, et al. The SWEET Project 10-year benchmarking in 19 countries worldwide is associated with improved HbA1c and increased use of diabetes technology in youth with type 1 diabetes. *Diabetes Technol Ther* 2021;23:491–499
63. Cameron FJ, de Beaufort C, Aanstoot HJ, et al.; Hvidoere International Study Group. Lessons from the Hvidoere International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach. *Pediatr Diabetes* 2013;14:473–480
64. Miller KM, Beck RW, Foster NC, Maahs DM. HbA1c levels in type 1 diabetes from early childhood to older adults: a deeper dive into the influence of technology and socioeconomic status on HbA1c in the T1D Exchange clinic registry findings. *Diabetes Technol Ther* 2020;22:645–650
65. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 1994;125:177–188
66. White NH, Cleary PA, Dahms W, Goldstein D, Malone J; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 2001;139:804–812
67. Samuelsson U, Steineck I, Gubbjornsdottir S. A high mean-HbA1c value 3-15 months after diagnosis of type 1 diabetes in childhood is related to metabolic control, macroalbuminuria, and retinopathy in early adulthood—a pilot study using two nation-wide population based quality registries. *Pediatr Diabetes* 2014;15:229–235
68. Carlsen S, Skriverhaug T, Thue G, et al. Glycemic control and complications in patients with type 1 diabetes—a registry-based longitudinal study of adolescents and young adults. *Pediatr Diabetes* 2017;18:188–195
69. Genuth SM, Backlund JYC, Bayless M, et al.; DCCT/EDIC Research Group. Effects of prior intensive versus conventional therapy and history of glycemia on cardiac function in type 1 diabetes in the DCCT/EDIC. *Diabetes* 2013;62:3561–3569
70. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003;290:2159–2167
71. Writing Team for the DCCT/EDIC Research Group, Gubitosi-Klug RA, Sun W, Cleary PA, et al. Effects of prior intensive insulin therapy and risk factors on patient-reported visual function outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. *JAMA Ophthalmol* 2016;134:137–145
72. Orchard TJ, Nathan DM, Zinman B, et al.; Writing Group for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA* 2015;313:45–53
73. Folland-Ross LC, Reiss AL, Mazaika PK, et al.; Diabetes Research in Children Network (DirecNet). Longitudinal assessment of hippocampus structure in children with type 1 diabetes. *Pediatr Diabetes* 2018;19:1116–1123
74. Mauras N, Mazaika P, Buckingham B, et al.; Diabetes Research in Children Network (DirecNet). Longitudinal assessment of neuroanatomical and cognitive differences in young children with type 1 diabetes: association with hyperglycemia. *Diabetes* 2015;64:1770–1779
75. Folland-Ross LC, Tong G, Mauras N, et al.; Diabetes Research in Children Network (DirecNet). Brain function differences in children with type 1 diabetes: a functional MRI study of working memory. *Diabetes* 2020;69:1770–1778
76. Pourabbasi A, Tehrani-Doost M, Qavam SE, Arzaghi SM, Larjani B. Association of diabetes mellitus and structural changes in the central nervous system in children and adolescents: a systematic review. *J Diabetes Metab Disord* 2017;16:10
77. Perantie DC, Wu J, Koller JM, et al. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. *Diabetes Care* 2007;30:2331–2337
78. Arbelaez AM, Semenkovich K, Hershey T. Glycemic extremes in youth with T1DM: Effects on the developing brain's structural and functional integrity. *Pediatr Diabetes* 2013;14:541–553
79. Broadley MM, White MJ, Andrew B. A systematic review and meta-analysis of executive function performance in type 1 diabetes mellitus. *Psychosom Med* 2017;79:684–696
80. Ryan CM. Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. *Pediatr Diabetes* 2006;7:289–297
81. Cameron FJ. The impact of diabetes on brain function in childhood and adolescence. *Pediatr Clin North Am* 2015;62:911–927
82. Mauras N, Buckingham B, White NH, et al.; Diabetes Research in Children Network (DirecNet). Impact of type 1 diabetes in the developing brain in children: a longitudinal study. *Diabetes Care* 2021;44:983–992
83. Campbell MS, Schatz DA, Chen V, et al.; T1D Exchange Clinic Network. A contrast between children and adolescents with excellent and poor control: the T1D Exchange clinic registry experience. *Pediatr Diabetes* 2014;15:110–117
84. Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. *N Engl J Med* 2015;373:2129–2140
85. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA* 2016;316:1407–1408
86. Kovatchev B, Cheng P, Anderson SM, et al. Feasibility of long-term closed-loop control: a multicenter 6-month trial of 24/7 automated insulin delivery. *Diabetes Technol Ther* 2017;19:18–24
87. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med* 2019;381:1707–1717
88. Bergenstal RM, Nimri R, Beck RW, et al.; FLAIR Study Group. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. *Lancet* 2021;397:208–219
89. Breton MD, Kanapka LG, Beck RW, et al.; iDCL Trial Research Group. A randomized trial of

- closed-loop control in children with type 1 diabetes. *N Engl J Med* 2020;383:836–845
90. Dorando E, Haak T, Pieper D. Correction: continuous glucose monitoring for glycemic control in children and adolescents diagnosed with diabetes type 1: a systematic review and meta-analysis. *Exp Clin Endocrinol Diabetes* 2022;130:e1–e3
91. Brown SA, Forlenza GP, Bode BW, et al.; Omnipod 5 Research Group. Multicenter trial of a tubeless, on-body automated insulin delivery system with customizable glycemic targets in pediatric and adult participants with type 1 diabetes. *Diabetes Care* 2021;44:1630–1640
92. Carlson AL, Sherr JL, Shulman DI, et al. Safety and glycemic outcomes during the minimized advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2022;24:178–189
93. Prahald P, Ding VY, Zaharieva DP, et al. Teamwork, targets, technology, and tight control in newly diagnosed type 1 diabetes: the Pilot 4T Study. *J Clin Endocrinol Metab* 2022;107:998–1008
94. Champakanath A, Akturk HK, Alonso GT, Snell-Bergeon JK, Shah VN. Continuous glucose monitoring initiation within first year of type 1 diabetes diagnosis is associated with improved glycemic outcomes: 7-year follow-up study. *Diabetes Care* 2022;45:750–753
95. Johnson SR, Holmes-Walker DJ, Chee M, et al.; ADDN Study Group. Universal subsidized continuous glucose monitoring funding for young people with type 1 diabetes: uptake and outcomes over 2 years, a population-based study. *Diabetes Care* 2022;45:391–397
96. Rose S, Styles SE, Wiltshire EJ, et al. Use of intermittently scanned continuous glucose monitoring in young people with high-risk type 1 diabetes-Extension phase outcomes following a 6-month randomized control trial. *Diabet Med* 2022;39:e14756
97. Beato-Vibora PI, Gallego-Gamero F, Ambrojo-López A, Gil-Poch E, Martín-Romo I, Arroyo-Díez FJ. Rapid improvement in time in range after the implementation of an advanced hybrid closed-loop system in adolescents and adults with type 1 diabetes. *Diabetes Technol Ther* 2021;23:609–615
98. Breton MD, Kovatchev BP. One year real-world use of the Control-IQ advanced hybrid closed-loop technology. *Diabetes Technol Ther* 2021;23:601–608
99. Forlenza GP, Ekhlaspour L, DiMeglio LA, et al. Glycemic outcomes of children 2–6 years of age with type 1 diabetes during the pediatric MiniMed 670G system trial. *Pediatr Diabetes* 2022;23:324–329
100. Messer LH, Berget C, Pyle L, et al. Real-world use of a new hybrid closed loop improves glycemic control in youth with type 1 diabetes. *Diabetes Technol Ther* 2021;23:837–843
101. Varimo T, Pulkkinen MA, Hakonen E, Hero M, Miettinen PJ, Tuomaala AK. First year on commercial hybrid closed-loop system-experience on 111 children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2021;22:909–915
102. Ware J, Allen JM, Boughton CK, et al.; KidsAP Consortium. Randomized trial of closed-loop control in very young children with type 1 diabetes. *N Engl J Med* 2022;386:209–219
103. Isganaitis E, Raghinaru D, Ambler-Osborn L, et al.; iDCL Trial Research Group. Closed-loop insulin therapy improves glycemic control in adolescents and young adults: outcomes from the international diabetes closed-loop trial. *Diabetes Technol Ther* 2021;23:342–349
104. Schoelwer MJ, Kanapka LG, Wadwa RP, et al.; iDCL Trial Research Group. Predictors of time-in-range (70–180 mg/dL) achieved using a closed-loop control system. *Diabetes Technol Ther* 2021;23:475–481
105. Sherr JL, Bode BW, Forlenza GP, et al.; Omnipod 5 in Preschoolers Study Group. Safety and glycemic outcomes with a tubeless automated insulin delivery system in very young children with type 1 diabetes: a single-arm multicenter clinical trial. *Diabetes Care* 2022;45:1907–1910
106. Marigliano M, Eckert AJ, Guness PK, et al.; SWEET Study Group. Association of the use of diabetes technology with HbA_{1c} and BMI-SDS in an international cohort of children and adolescents with type 1 diabetes: the SWEET project experience. *Pediatr Diabetes* 2021;22:1120–1128
107. Redondo MJ, Libman I, Maahs DM, et al. The evolution of hemoglobin A_{1c} targets for youth with type 1 diabetes: rationale and supporting evidence. *Diabetes Care* 2021;44:301–312
108. Cooper MN, O’Connell SM, Davis EA, Jones TW. A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes. *Diabetologia* 2013;56:2164–2170
109. Haynes A, Hermann JM, Miller KM, et al.; T1D Exchange, WACDD and DPV Registries. Severe hypoglycemia rates are not associated with HbA_{1c}: a cross-sectional analysis of 3 contemporary pediatric diabetes registry databases. *Pediatr Diabetes* 2017;18:643–650
110. Haynes A, Hermann JM, Clapin H, et al.; WACDD and DPV Registries. Decreasing trends in mean HbA_{1c} are not associated with increasing rates of severe hypoglycemia in children: a longitudinal analysis of two contemporary population-based pediatric type 1 diabetes registries from Australia and Germany/Austria between 1995 and 2016. *Diabetes Care* 2019;42:1630–1636
111. Fredheim S, Johansen A, Thorsen SU, et al.; Danish Society for Diabetes in Childhood and Adolescence. Nationwide reduction in the frequency of severe hypoglycemia by half. *Acta Diabetol* 2015;52:591–599
112. Birkebaek NH, Drivvoll AK, Aakeson K, et al. Incidence of severe hypoglycemia in children with type 1 diabetes in the Nordic countries in the period 2008–2012: association with hemoglobin A_{1c} and treatment modality. *BMJ Open Diabetes Res Care* 2017;5:e000377
113. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA* 2013;310:1240–1247
114. Downie E, Craig ME, Hing S, Cusumano J, Chan AKF, Donaghue KC. Continued reduction in the prevalence of retinopathy in adolescents with type 1 diabetes: role of insulin therapy and glycemic control. *Diabetes Care* 2011;34:2368–2373
115. Karges B, Rosenbauer J, Kapellen T, et al. Hemoglobin A_{1c} levels and risk of severe hypoglycemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. *PLoS Med* 2014;11:e1001742
116. Johnson SR, Cooper MN, Jones TW, Davis EA. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. *Diabetologia* 2013;56:2392–2400
117. Karges B, Kapellen T, Wagner VM, et al.; DPV Initiative. Glycated hemoglobin A_{1c} as a risk factor for severe hypoglycemia in pediatric type 1 diabetes. *Pediatr Diabetes* 2017;18:51–58
118. Saydah S, Imperatore G, Divers J, et al. Occurrence of severe hypoglycaemic events among US youth and young adults with type 1 or type 2 diabetes. *Endocrinol Diabetes Metab* 2019;2:e00057
119. Ishtiak-Ahmed K, Carstensen B, Pedersen-Bjergaard U, Jørgensen ME. Incidence trends and predictors of hospitalization for hypoglycemia in 17,230 adult patients with type 1 diabetes: a Danish Register Linkage cohort study. *Diabetes Care* 2017;40:226–232
120. Maahs DM, Hermann JM, DuBose SN, et al.; DPV Initiative; T1D Exchange Clinic Network. Contrasting the clinical care and outcomes of 2,622 children with type 1 diabetes less than 6 years of age in the United States T1D Exchange and German/Austrian DPV registries. *Diabetologia* 2014;57:1578–1585
121. Swift PGF, Skinner TC, de Beaufort CE, et al.; Hvidoere Study Group on Childhood Diabetes. Target setting in intensive insulin management is associated with metabolic control: the Hvidoere childhood diabetes study group centre differences study 2005. *Pediatr Diabetes* 2010;11:271–278
122. Laffel LM, Kanapka LG, Beck RW, Bergamo K, Clements MA, Criego A, et al. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: a randomized clinical trial. *JAMA* 2020;323:2388–2396
123. Strategies to Enhance New CGM Use in Early Childhood (SENCE) Study Group. A randomized clinical trial assessing continuous glucose monitoring (CGM) use with standardized education with or without a family behavioral intervention compared with fingerstick blood glucose monitoring in very young children with type 1 diabetes. *Diabetes Care* 2021;44:464–472
124. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232
125. Abraham MB, Davey R, O’Grady MJ, et al. Effectiveness of a predictive algorithm in the prevention of exercise-induced hypoglycemia in type 1 diabetes. *Diabetes Technol Ther* 2016;18:543–550
126. Buckingham BA, Bailey TS, Christiansen M, et al. Evaluation of a predictive low-glucose management system in-clinic. *Diabetes Technol Ther* 2017;19:288–292
127. Nimri R, Muller I, Atlas E, et al. MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. *Diabetes Care* 2014;37:3025–3032
128. El-Khatib FH, Balliro C, Hillard MA, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. *Lancet* 2017;389:369–380

129. Levine BS, Anderson BJ, Butler DA, Antisdel JE, Brackett J, Laffel LM. Predictors of glycemic control and short-term adverse outcomes in youth with type 1 diabetes. *J Pediatr* 2001;139:197–203
130. Miller KM, Beck RW, Bergenstal RM, et al.; T1D Exchange Clinic Network. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care* 2013;36:2009–2014
131. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019;42:1593–1603
132. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technol Ther* 2019;21:81–85
133. Petersson J, Åkesson K, Sundberg F, Särnblad S. Translating glycosylated hemoglobin A1c into time spent in glucose target range: a multicenter study. *Pediatr Diabetes* 2019;20:339–344
134. Warncke K, Fröhlich-Reiterer EE, Thon A, Hofer SE, Wiemann D; DPV Initiative of the German Working Group for Pediatric Diabetology; German BMBF Competence Network for Diabetes Mellitus. Polyendocrinopathy in children, adolescents, and young adults with type 1 diabetes: a multicenter analysis of 28,671 patients from the German/Austrian DPV-Wiss database. *Diabetes Care* 2010;33:2010–2012
135. Nederstigt C, Uitbeijerse BS, Janssen LGM, Corssmit EPM, de Koning EJP, Dekkers OM. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. *Eur J Endocrinol* 2019;180:135–144
136. Kozhakhmetova A, Wyatt RC, Caygill C, et al. A quarter of patients with type 1 diabetes have co-existing non-islet autoimmunity: the findings of a UK population-based family study. *Clin Exp Immunol* 2018;192:251–258
137. Hughes JW, Riddlesworth TD, DiMeglio LA, Miller KM, Rickels MR, McGill JB. Autoimmune diseases in children and adults with type 1 diabetes from the T1D Exchange clinic registry. *J Clin Endocrinol Metab* 2016;101:4931–4937
138. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. *Autoimmun Rev* 2016;15:644–648
139. Roldán MB, Alonso M, Barrio R. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. *Diabetes Nutr Metab* 1999;12:27–31
140. Shun CB, Donaghue KC, Phelan H, Twigg SM, Craig ME. Thyroid autoimmunity in Type 1 diabetes: systematic review and meta-analysis. *Diabet Med* 2014;31:126–135
141. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 2011;34:1211–1213
142. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Grüters-Kieslich A. Predictivity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with type 1 diabetes. *Diabet Med* 2002;19:518–521
143. Dost A, Rohrer TR, Fröhlich-Reiterer E, et al.; DPV Initiative and the German Competence Network Diabetes Mellitus. Hyperthyroidism in 276 children and adolescents with type 1 diabetes from Germany and Austria. *Horm Res Paediatr* 2015;84:190–198
144. Jonsdottir B, Larsson C, Carlsson A, et al.; Better Diabetes Diagnosis Study Group. Thyroid and islet autoantibodies predict autoimmune thyroid disease at type 1 diabetes diagnosis. *J Clin Endocrinol Metab* 2017;102:1277–1285
145. Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F. The effect of subclinical hypothyroidism on metabolic control in children and adolescents with type 1 diabetes mellitus. *Diabet Med* 2002;19:70–73
146. Holmes GKT. Screening for coeliac disease in type 1 diabetes. *Arch Dis Child* 2002;87:495–498
147. Rewers M, Liu E, Simmons J, Redondo MJ, Hoffenberg EJ. Celiac disease associated with type 1 diabetes mellitus. *Endocrinol Metab Clin North Am* 2004;33:197–214
148. Pham-Short A, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME. Screening for celiac disease in type 1 diabetes: a systematic review. *Pediatrics* 2015;136:e170–e176
149. Craig ME, Prinz N, Boyle CT, et al.; Australasian Diabetes Data Network (ADDN); T1D Exchange Clinic Network (T1DX); National Paediatric Diabetes Audit (NPDA) and the Royal College of Paediatrics and Child Health; Prospective Diabetes Follow-up Registry (DPV) initiative. Prevalence of celiac disease in 52,721 youth with type 1 diabetes: international comparison across three continents. *Diabetes Care* 2017;40:1034–1040
150. Cerutti F, Bruno G, Chiarelli F, Lorini R, Meschi F; Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetology. Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. *Diabetes Care* 2004;27:1294–1298
151. Simmons JH, Foster NC, Riddlesworth TD, et al.; T1D Exchange Clinic Network. Sex- and age-dependent effects of celiac disease on growth and weight gain in children with type 1 diabetes: analysis of the Type 1 Diabetes Exchange clinic registry. *Pediatr Diabetes* 2018;19:741–748
152. Margoni D, Chouliaras G, Ducas G, et al. Bone health in children with celiac disease assessed by dual x-ray absorptiometry: effect of gluten-free diet and predictive value of serum biochemical indices. *J Pediatr Gastroenterol Nutr* 2012;54:680–684
153. Rohrer TR, Wolf J, Liptay S, et al.; DPV Initiative and the German BMBF Competence Network Diabetes Mellitus. Microvascular complications in childhood-onset type 1 diabetes and celiac disease: a multicenter longitudinal analysis of 56,514 patients from the German-Austrian DPV database. *Diabetes Care* 2015;38:801–807
154. Mollazadegan K, Kugelberg M, Montgomery SM, Sanders DS, Ludvigsson J, Ludvigsson JF. A population-based study of the risk of diabetic retinopathy in patients with type 1 diabetes and celiac disease. *Diabetes Care* 2013;36:316–321
155. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108:656–676
156. Husby S, Koletzko S, Korponay-Szabó IR, et al.; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54:136–160
157. Paul SP, Sandhu BK, Spray CH, Basude D, Ramani P. Evidence supporting serology-based pathway for diagnosing celiac disease in asymptomatic children from high-risk groups. *J Pediatr Gastroenterol Nutr* 2018;66:641–644
158. Abid N, McGlone O, Cardwell C, McCallion W, Carson D. Clinical and metabolic effects of gluten free diet in children with type 1 diabetes and coeliac disease. *Pediatr Diabetes* 2011;12:322–325
159. Husby S, Koletzko S, Korponay-Szabó IR, et al.; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54:136–160
160. Kurppa K, Paavola A, Collin P, et al. Benefits of a gluten-free diet for asymptomatic patients with serologic markers of celiac disease. *Gastroenterology* 2014;147:610–617.e1
161. Flynn JT, Kaelber DC, Baker-Smith CM, et al.; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017;140:e20171904
162. Marcovecchio ML, Chiesa ST, Bond S, et al.; AdDIT Study Group. ACE inhibitors and statins in adolescents with type 1 diabetes. *N Engl J Med* 2017;377:1733–1745
163. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care* 2014;37:2843–2863
164. Rodriguez BL, Fujimoto WY, Mayer-Davis EJ, et al. Prevalence of cardiovascular disease risk factors in U.S. children and adolescents with diabetes: the SEARCH for diabetes in youth study. *Diabetes Care* 2006;29:1891–1896
165. Margeisdottir HD, Larsen JR, Brunborg C, Overby NC; Norwegian Study Group for Childhood Diabetes. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. *Diabetologia* 2008;51:554–561
166. Schwab KO, Doerfer J, Hecker W, et al.; DPV Initiative of the German Working Group for Pediatric Diabetology. Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young adults with type 1 diabetes: cross-sectional data from the German diabetes documentation and quality management system (DPV). *Diabetes Care* 2006;29:218–225
167. Singh TP, Groehn H, Kazmers A. Vascular function and carotid intimal-medial thickness in children with insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 2003;41:661–665
168. Haller MJ, Stein J, Shuster J, et al. Peripheral artery tonometry demonstrates altered endothelial

- function in children with type 1 diabetes. *Pediatr Diabetes* 2007;8:193–198
169. Urbina EM, Wadwa RP, Davis C, et al. Prevalence of increased arterial stiffness in children with type 1 diabetes mellitus differs by measurement site and sex: the SEARCH for Diabetes in Youth Study. *J Pediatr* 2010;156:731–737
170. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011;128(Suppl. 5):S213–S256
171. Blaha MJ, Blumenthal RS, Brinton EA; National Lipid Association Taskforce on Non-HDL Cholesterol. The importance of non-HDL cholesterol reporting in lipid management. *J Clin Lipidol* 2008;2:267–273
172. Kershner AK, Daniels SR, Imperatore G, et al. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. *J Pediatr* 2006;149:314–319
173. Maahs DM, Dabelea D, D’Agostino RB Jr, et al.; SEARCH for Diabetes in Youth Study. Glucose control predicts 2-year change in lipid profile in youth with type 1 diabetes. *J Pediatr* 2013;162:101–7.e1
174. Daniels SR; Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics* 2008;122:198–208
152. Kavey R-EW, Allada V, Daniels SR, et al.; American Heart Association Expert Panel on Population and Prevention Science; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Nutrition, Physical Activity and Metabolism; American Heart Association Council on High Blood Pressure Research; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on the Kidney in Heart Disease; Interdisciplinary Working Group on Quality of Care and Outcomes Research. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2006;114:2710–2738
176. Cadario F, Prodam F, Pasqualicchio S, et al. Lipid profile and nutritional intake in children and adolescents with type 1 diabetes improve after a structured dietician training to a Mediterranean-style diet. *J Endocrinol Invest* 2012;35:160–168
177. Salem MA, AboElAsrar MA, Elbarbary NS, ElHilaly RA, Refaat YM. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. *Diabetol Metab Syndr* 2010;2:47
178. McCrindle BW, Urbina EM, Dennison BA, et al.; American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee; American Heart Association Council of Cardiovascular Disease in the Young; American Heart Association Council on Cardiovascular Nursing. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation* 2007;115:1948–1967
179. Salo P, Viikari J, Hämäläinen M, et al. Serum cholesterol ester fatty acids in 7- and 13-month-old children in a prospective randomized trial of a low-saturated fat, low-cholesterol diet: the STRIP baby project. Special Turku Coronary Risk Factor Intervention Project for Children. *Acta Paediatr* 1999;88:505–512
180. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003;143:74–80
181. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004;292:331–337
182. Karter AJ, Stevens MR, Gregg EW, et al. Educational disparities in rates of smoking among diabetic adults: the translating research into action for diabetes study. *Am J Public Health* 2008;98:365–370
183. Reynolds K, Liese AD, Anderson AM, et al. Prevalence of tobacco use and association between cardiometabolic risk factors and cigarette smoking in youth with type 1 or type 2 diabetes mellitus. *J Pediatr* 2011;158:594–601.e1
184. Scott LJ, Warram JH, Hanna LS, Laffel LM, Ryan L, Krolewski AS. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. *Diabetes* 2001;50:2842–2849
185. Chaffee BW, Watkins SL, Glantz SA. Electronic cigarette use and progression from experimentation to established smoking. *Pediatrics* 2018;141:e20173594
186. Audrain-McGovern J, Stone MD, Barrington-Trimis J, Unger JB, Leventhal AM. Adolescent E-cigarette, hookah, and conventional cigarette use and subsequent marijuana use. *Pediatrics* 2018;142:e20173616
187. Centers for Disease Control and Prevention. Smoking and tobacco use: outbreak of lung injury associated with e-cigarette use, or vaping. Accessed 21 October 2022. Available from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
188. Miech R, Johnston L, O’Malley PM, Bachman JG, Patrick ME. Trends in adolescent vaping, 2017–2019. *N Engl J Med* 2019;381:1490–1491
189. Daniels M, DuBose SN, Maahs DM, et al.; T1D Exchange Clinic Network. Factors associated with microalbuminuria in 7,549 children and adolescents with type 1 diabetes in the T1D Exchange clinic registry. *Diabetes Care* 2013;36:2639–2645
190. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol* 2009;4:1832–1843
191. Inker LA, Schmid CH, Tighiouart H, et al.; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012;367:20–29
192. Cho YH, Craig ME, Hing S, et al. Microvascular complications assessment in adolescents with 2- to 5-yr duration of type 1 diabetes from 1990 to 2006. *Pediatr Diabetes* 2011;12:682–689
193. Scanlon PH, Stratton IM, Bachmann MO, Jones C; Four Nations Diabetic Retinopathy Screening Study Group. Risk of diabetic retinopathy at first screen in children at 12 and 13 years of age. *Diabet Med* 2016;33:1655–1658
194. Beauchamp G, Boyle CT, Tamborlane WV, et al.; T1D Exchange Clinic Network. Treatable diabetic retinopathy is extremely rare among pediatric T1D Exchange clinic registry participants. *Diabetes Care* 2016;39:e218–e219
195. Nathan DM, Bebu I, Hainsworth D, et al.; DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. *N Engl J Med* 2017;376:1507–1516
196. Gubitosi-Klug RA, Bebu I, White NH, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Screening eye exams in youth with type 1 diabetes under 18 years of age: once may be enough? *Pediatr Diabetes* 2019;20:743–749
197. Jaiswal M, Divers J, Dabelea D, Isom S, Bell RA, Martin CL, et al. Prevalence of and risk factors for diabetic peripheral neuropathy in youth with type 1 and type 2 diabetes: SEARCH for Diabetes in Youth Study. *Diabetes Care* 2017;40:1226–1232
198. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136–154
199. Imperatore G, Boyle JP, Thompson TJ, et al.; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care* 2012;35:2515–2520
200. Pettitt DJ, Talton J, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. *Diabetes Care* 2014;37:402–408
201. Copeland KC, Zeitler P, Geffner M, et al.; TODAY Study Group. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. *J Clin Endocrinol Metab* 2011;96:159–167
202. Bjornstad P, Drews KL, Caprio S, et al.; TODAY Study Group. Long-term complications in youth-onset type 2 diabetes. *N Engl J Med* 2021;385:416–426
203. Arslanian SA. Metabolic differences between Caucasian and African-American children and the relationship to type 2 diabetes mellitus. *J Pediatr Endocrinol Metab* 2002;15(Suppl. 1):509–517
204. Naughton MJ, Ruggiero AM, Lawrence JM, et al.; SEARCH for Diabetes in Youth Study Group. Health-related quality of life of children and adolescents with type 1 or type 2 diabetes mellitus: SEARCH for Diabetes in Youth Study. *Arch Pediatr Adolesc Med* 2008;162:649–657
205. Wadden TA, Webb VL, Moran CH, Bailer BA. Lifestyle modification for obesity: new develop-

- ments in diet, physical activity, and behavior therapy. *Circulation* 2012;125:1157–1170
206. Whalen DJ, Belden AC, Tillman R, Barch DM, Luby JL. Early adversity, psychopathology, and latent class profiles of global physical health from preschool through early adolescence. *Psychosom Med* 2016;78:1008–1018
207. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 2014;311:1778–1786
208. Buse JB, Kaufman FR, Linder B, Hirst K, El Ghormli L; HEALTHY Study Group. Diabetes screening with hemoglobin A(1c) versus fasting plasma glucose in a multiethnic middle-school cohort. *Diabetes Care* 2013;36:429–435
209. Klingensmith GJ, Pyle L, Arslanian S, et al.; TODAY Study Group. The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. *Diabetes Care* 2010;33:1970–1975
210. Hannon TS, Arslanian SA. The changing face of diabetes in youth: lessons learned from studies of type 2 diabetes. *Ann N Y Acad Sci* 2015;1353:113–137
211. Kapadia C; Drugs and Therapeutics Committee of the Pediatric Endocrine Society. Hemoglobin A1c measurement for the diagnosis of type 2 diabetes in children. *Int J Pediatr Endocrinol* 2012;2012:31
212. Wallace AS, Wang D, Shin JI, Selvin E. Screening and diagnosis of prediabetes and diabetes in US children and adolescents. *Pediatrics* 2020;146:e20200265
213. Kester LM, Hey H, Hannon TS. Using hemoglobin A1c for prediabetes and diabetes diagnosis in adolescents: can adult recommendations be upheld for pediatric use? *J Adolesc Health* 2012;50:321–323
214. Wu EL, Kazzi NG, Lee JM. Cost-effectiveness of screening strategies for identifying pediatric diabetes mellitus and dysglycemia. *JAMA Pediatr* 2013;167:32–39
215. Dabelea D, Rewers A, Stafford JM, et al.; SEARCH for Diabetes in Youth Study Group. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. *Pediatrics* 2014;133:e938–e945
216. Hutchins J, Barajas RA, Hale D, Escaname E, Lynch J. Type 2 diabetes in a 5-year-old and single center experience of type 2 diabetes in youth under 10. *Pediatr Diabetes* 2017;18:674–677
217. Ferrara CT, Geyer SM, Liu YF, et al.; Type 1 Diabetes TrialNet Study Group. Excess BMI in childhood: a modifiable risk factor for type 1 diabetes development? *Diabetes Care* 2017;40:698–701
218. Pinhas-Hamiel O, Dolan LM, Zeitler PS. Diabetic ketoacidosis among obese African-American adolescents with NIDDM. *Diabetes Care* 1997;20:484–486
219. TODAY Study Group. Safety and tolerability of the treatment of youth-onset type 2 diabetes: the TODAY experience. *Diabetes Care* 2013;36:1765–1771
220. TODAY Study Group. Retinopathy in youth with type 2 diabetes participating in the TODAY clinical trial. *Diabetes Care* 2013;36:1772–1774
221. TODAY Study Group. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care* 2013;36:1758–1764
222. TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care* 2013;36:1735–1741
223. Grey M, Schreiner B, Pyle L. Development of a diabetes education program for youth with type 2 diabetes. *Diabetes Educ* 2009;35:108–116
224. American Diabetes Association. Be Healthy Today; Be Healthy For Life. Accessed 21 October 2022. Available from <http://main.diabetes.org/dorg/PDFs/Type-2-Diabetes-in-Youth/Type-2-Diabetes-in-Youth.pdf>
225. Atkinson A, Radjenovic D. Meeting quality standards for self-management education in pediatric type 2 diabetes. *Diabetes Spectr* 2007;20:40–46
226. Copeland KC, Silverstein J, Moore KR, et al.; American Academy of Pediatrics. Management of newly diagnosed type 2 Diabetes Mellitus (T2DM) in children and adolescents. *Pediatrics* 2013;131:364–382
227. Zeitler P, Hirst K, Pyle L, et al.; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* 2012;366:2247–2256
228. RISE Consortium. Impact of insulin and metformin versus metformin alone on β -cell function in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes. *Diabetes Care* 2018;41:1717–1725
229. Tamborlane WV, Barrientos-Pérez M, Fainberg U, Frimer-Larsen H, Hafez M, Hale PM, et al. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med* 2019;381:637–646
230. U.S. Food and Drug Administration. FDA approves treatment for pediatric patients with type 2 diabetes - drug information update. 2021. Accessed 21 October 2022. Available from <https://content.govdelivery.com/accounts/USFDA/bulletins/2e98d66>
231. U.S. Food and Drug Administration. FDA approves new treatment for pediatric patients with type 2 diabetes. 2019. Accessed 21 October 2022. Available from <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pediatric-patients-type-2-diabetes>
232. Tamborlane WV, Bishai R, Geller D, et al. Once-weekly exenatide in youth with type 2 diabetes. *Diabetes Care* 2022;45:1833–1840
233. Chan CL. Use of continuous glucose monitoring in youth-onset type 2 diabetes. *Curr Diab Rep* 2017;17:66
234. Kelly AS, Auerbach P, Barrientos-Perez M, et al.; NN8022-4180 Trial Investigators. A randomized, controlled trial of liraglutide for adolescents with obesity. *N Engl J Med* 2020;382:2117–2128
235. U.S. Food and Drug Administration. FDA approves weight management drug for patients aged 12 and older. 2021. Accessed 21 October 2022. Available from <https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-weight-management-drug-patients-aged-12-and-older>
236. U.S. Food and Drug Administration. FDA approves treatment for chronic weight management in pediatric patients aged 12 years and older. Accessed 27 August 2022. Available from <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-chronic-weight-management-pediatric-patients-aged-12-years-and-older>
237. Inge TH, Courcoulas AP, Jenkins TM, et al.; Teen-LABS Consortium. Weight loss and health status 3 years after bariatric surgery in adolescents. *N Engl J Med* 2016;374:113–123
238. Inge TH, Laffel LM, Jenkins TM, et al.; Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and Treatment Options of Type 2 Diabetes in Adolescents and Youth (TODAY) Consortia. Comparison of surgical and medical therapy for type 2 diabetes in severely obese adolescents. *JAMA Pediatr* 2018;172:452–460
239. Rubino F, Nathan DM, Eckel RH, et al.; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by International Diabetes Organizations. *Diabetes Care* 2016;39:861–877
240. Pratt JSA, Lenders CM, Dionne EA, et al. Best practice updates for pediatric/adolescent weight loss surgery. *Obesity (Silver Spring)* 2009;17:901–910
241. Dolan K, Creighton L, Hopkins G, Fielding G. Laparoscopic gastric banding in morbidly obese adolescents. *Obes Surg* 2003;13:101–104
242. Sugerman HJ, Sugerman EL, DeMaria EJ, et al. Bariatric surgery for severely obese adolescents. *J Gastrointest Surg* 2003;7:102–108
243. Inge TH, Garcia V, Daniels S, et al. A multidisciplinary approach to the adolescent bariatric surgical patient. *J Pediatr Surg* 2004;39:442–447
244. Lawson ML, Kirk S, Mitchell T, et al.; Pediatric Bariatric Study Group. One-year outcomes of Roux-en-Y gastric bypass for morbidly obese adolescents: a multicenter study from the Pediatric Bariatric Study Group. *J Pediatr Surg* 2006;41:137–143
245. Inge TH, Zeller M, Harmon C, et al. Teen-longitudinal assessment of bariatric surgery: methodological features of the first prospective multicenter study of adolescent bariatric surgery. *J Pediatr Surg* 2007;42:1969–1971
246. Ells LJ, Mead E, Atkinson G, et al. Surgery for the treatment of obesity in children and adolescents. *Cochrane Database Syst Rev* 2015;6:CD011740
247. Michalsky MP, Inge TH, Simmons M, et al.; Teen-LABS Consortium. Cardiovascular risk factors in severely obese adolescents: the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study. *JAMA Pediatr* 2015;169:438–444
248. Zeinoddini A, Heidari R, Talebpour M. Laparoscopic gastric plication in morbidly obese adolescents: a prospective study. *Surg Obes Relat Dis* 2014;10:1135–1139
249. Göthberg G, Gronowitz E, Flodmark CE, et al. Laparoscopic Roux-en-Y gastric bypass in adolescents with morbid obesity—surgical aspects and clinical outcome. *Semin Pediatr Surg* 2014;23:11–16
250. Inge TH, Prigeon RL, Elder DA, et al. Insulin sensitivity and β -cell function improve after gastric bypass in severely obese adolescents. *J Pediatr* 2015;167:1042–1048.e1
251. Styne DM, Arslanian SA, Connor EL, et al. Pediatric obesity-assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:709–757

252. Eppens MC, Craig ME, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care* 2006;29:1300–1306
253. Song SH, Hardisty CA. Early onset type 2 diabetes mellitus: a harbinger for complications in later years—clinical observation from a secondary care cohort. *QJM* 2009;102:799–806
254. Zeitler P, Fu J, Tandon N, et al.; International Society for Pediatric and Adolescent Diabetes. ISPAD clinical practice consensus guidelines 2014. Type 2 diabetes in the child and adolescent. *Pediatr Diabetes* 2014;15(Suppl. 20):26–46
255. Song SH. Complication characteristics between young-onset type 2 versus type 1 diabetes in a UK population. *BMJ Open Diabetes Res Care* 2015;3:e000044
256. Cefalu WT. “TODAY” reflects on the changing “faces” of type 2 diabetes. *Diabetes Care* 2013;36:1732–1734
257. Lawrence JM, Standiford DA, Loots B, et al.; SEARCH for Diabetes in Youth Study. Prevalence and correlates of depressed mood among youth with diabetes: the SEARCH for Diabetes in Youth study. *Pediatrics* 2006;117:1348–1358
258. Levitt Katz LE, Swami S, Abraham M, et al. Neuropsychiatric disorders at the presentation of type 2 diabetes mellitus in children. *Pediatr Diabetes* 2005;6:84–89
259. Lewis-Fernández R, Rotheram-Borus MJ, Betts VT, et al. Rethinking funding priorities in mental health research. *Br J Psychiatry* 2016; 208:507–509
260. Reinehr T. Type 2 diabetes mellitus in children and adolescents. *World J Diabetes* 2013; 4:270–281
261. Pinhas-Hamiel O, Hamiel U, Levy-Shraga Y. Eating disorders in adolescents with type 1 diabetes: challenges in diagnosis and treatment. *World J Diabetes* 2015;6:517–526
262. Wilfley D, Berkowitz R, Goebel-Fabbri A, et al.; TODAY Study Group. Binge eating, mood, and quality of life in youth with type 2 diabetes: baseline data from the today study. *Diabetes Care* 2011;34:858–860
263. Shelton RC. Depression, antidepressants, and weight gain in children. *Obesity (Silver Spring)* 2016;24:2450–2450
264. Baeza I, Vigo L, de la Serna E, et al. The effects of antipsychotics on weight gain, weight-related hormones and homocysteine in children and adolescents: a 1-year follow-up study. *Eur Child Adolesc Psychiatry* 2017;26:35–46
265. TODAY Study Group. Pregnancy outcomes in young women with youth-onset type 2 diabetes followed in the TODAY Study. *Diabetes Care* 2021;45:1038–1045
266. Arnett JJ. Emerging adulthood. A theory of development from the late teens through the twenties. *Am Psychol* 2000;55:469–480
267. Weissberg-Benchell J, Wolpert H, Anderson BJ. Transitioning from pediatric to adult care: a new approach to the post-adolescent young person with type 1 diabetes. *Diabetes Care* 2007;30:2441–2446
268. Peters A; American Diabetes Association Transitions Working Group. Diabetes care for emerging adults: recommendations for transition from pediatric to adult diabetes care systems: a position statement of the American Diabetes Association, with representation by the American College of Osteopathic Family Physicians, the American Academy of Pediatrics, the American Association of Clinical Endocrinologists, the American Osteopathic Association, the Centers for Disease Control and Prevention, Children with Diabetes, The Endocrine Society, the International Society for Pediatric and Adolescent Diabetes, Juvenile Diabetes Research Foundation International, the National Diabetes Education Program, and the Pediatric Endocrine Society (formerly Lawson Wilkins Pediatric Endocrine Society). *Diabetes Care* 2011;34: 2477–2485
269. Bryden KS, Peveler RC, Stein A, Neil A, Mayou RA, Dunger DB. Clinical and psychological course of diabetes from adolescence to young adulthood: a longitudinal cohort study. *Diabetes Care* 2001;24:1536–1540
270. Laing SP, Jones ME, Swerdlow AJ, Burden AC, Gatling W. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. *Diabetes Care* 2005;28: 1618–1623
271. Kapellen TM, Müther S, Schwandt A, et al.; DPV initiative and the Competence Network Diabetes Mellitus funded by the German Federal Ministry of Education and Research. Transition to adult diabetes care in Germany—high risk for acute complications and declining metabolic control during the transition phase. *Pediatr Diabetes* 2018;19:1094–1099
272. Agarwal S, Raymond JK, Isom S, et al. Transfer from paediatric to adult care for young adults with type 2 diabetes: the SEARCH for Diabetes in Youth Study. *Diabet Med* 2018;35: 504–512
273. Mays JA, Jackson KL, Derby TA, et al. An evaluation of recurrent diabetic ketoacidosis, fragmentation of care, and mortality across Chicago, Illinois. *Diabetes Care* 2016;39:1671–1676
274. Lotstein DS, Seid M, Klingensmith G, et al.; SEARCH for Diabetes in Youth Study Group. Transition from pediatric to adult care for youth diagnosed with type 1 diabetes in adolescence. *Pediatrics* 2013;131:e1062–e1070
275. Lyons SK, Becker DJ, Helgeson VS. Transfer from pediatric to adult health care: effects on diabetes outcomes. *Pediatr Diabetes* 2014;15:10–17
276. Garvey KC, Foster NC, Agarwal S, et al. Health care transition preparation and experiences in a U.S. national sample of young adults with type 1 diabetes. *Diabetes Care* 2017;40:317–324
277. The Endocrine Society. Transitions of Care. Accessed 21 October 2022. Available from <https://www.endocrine.org/improving-practice/transitions#t1d>
278. Reid MW, Krishnan S, Berget C, et al. CoYoT1 clinic: home telemedicine increases young adult engagement in diabetes care. *Diabetes Technol Ther* 2018;20:370–379
279. Spaic T, Robinson T, Goldbloom E, et al.; JDRF Canadian Clinical Trial CCTN1102 Study Group. Closing the gap: results of the multicenter Canadian randomized controlled trial of structured transition in young adults with type 1 diabetes. *Diabetes Care* 2019;42:1018–1026
280. White M, O’Connell MA, Cameron FJ. Clinic attendance and disengagement of young adults with type 1 diabetes after transition of care from paediatric to adult services (TrACeD): a randomised, open-label, controlled trial. *Lancet Child Adolesc Health* 2017;1:274–283
281. Schultz AT, Smaldone A. Components of interventions that improve transitions to adult care for adolescents with type 1 diabetes. *J Adolesc Health* 2017;60:133–146
282. Sequeira PA, Pyatak EA, Weigensberg MJ, et al. Let’s Empower and Prepare (LEAP): evaluation of a structured transition program for young adults with type 1 diabetes. *Diabetes Care* 2015;38:1412–1419
283. Monaghan M, Baumann K. Type 1 diabetes: addressing the transition from pediatric to adult-oriented health care. *Res Rep Endocr Disord* 2016;6:31–40

15. Management of Diabetes in Pregnancy: Standards of Care in Diabetes—2023

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. in parallel with the worldwide epidemic of obesity. Not only is the prevalence of type 1 diabetes and type 2 diabetes increasing in individuals of reproductive age, but there is also a dramatic increase in the reported rates of gestational diabetes mellitus (GDM). Diabetes confers significantly greater maternal and fetal risk largely related to the degree of hyperglycemia but also related to chronic complications and comorbidities of diabetes. In general, specific risks of diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, hyperbilirubinemia, and neonatal respiratory distress syndrome, among others. In addition, diabetes in pregnancy may increase the risk of obesity, hypertension, and type 2 diabetes in offspring later in life (1,2).

Preconception Counseling

Recommendations

- 15.1** Starting at puberty and continuing in all people with diabetes and reproductive potential, preconception counseling should be incorporated into routine diabetes care. **A**
- 15.2** Family planning should be discussed, and effective contraception (with consideration of long-acting, reversible contraception) should be prescribed and used until an individual’s treatment plan and A1C are optimized for pregnancy. **A**
- 15.3** Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C <6.5% (48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications. **A**

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All individuals with diabetes and reproductive potential should be informed about the importance of achieving and maintaining as near euglycemia as safely possible prior to conception and throughout pregnancy. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, renal anomalies, and caudal regression, directly proportional to elevations in A1C during the first 10 weeks of pregnancy (3). Although observational studies are confounded by the association between elevated preconceptional A1C and other engagement in self-care behaviors, the quantity and consistency of data are convincing and support the recommendation to optimize glycemia prior to conception, given that organogenesis occurs primarily at 5–8 weeks of gestation, with an A1C <6.5% (48 mmol/mol), which is associated with the lowest risk of congenital anomalies, preeclampsia, and preterm birth (3–7). A systematic review and meta-analysis of observational studies of preconception care for pregnant individuals with preexisting diabetes demonstrated lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age births, and neonatal intensive care unit admission (8).

There are opportunities to educate all adults and adolescents with diabetes and reproductive potential about the risks of unplanned pregnancies and about improved maternal and fetal outcomes with pregnancy planning (8). Effective preconception counseling could avert substantial health and associated cost burdens in offspring (9). Family planning should be discussed, including the benefits of long-acting, reversible contraception, and effective contraception should be prescribed and used until the individual is prepared and ready to become pregnant (10–14).

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all adults and adolescents with diabetes of childbearing potential should receive education about 1) the risks of malformations associated with unplanned pregnancies and even mild hyperglycemia and 2) the use of effective contraception at all times when preventing a pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescent girls

to make well-informed decisions (8). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (15).

Preconception Care

Recommendations

- 15.4** Individuals with preexisting diabetes who are planning a pregnancy should ideally begin receiving care in preconception at a multidisciplinary clinic including an endocrinologist, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes care and education specialist, when available. **B**
- 15.5** In addition to focused attention on achieving glycemic targets **A**, standard preconception care should be augmented with extra focus on nutrition, diabetes education, and screening for diabetes comorbidities and complications. **B**
- 15.6** Individuals with preexisting type 1 or type 2 diabetes who are planning a pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur ideally before pregnancy or in the first trimester, and then pregnant individuals should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the eye care health care professional. **B**

The importance of preconception care for all pregnant people is highlighted by American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 762, “Prepregnancy Counseling” (16). Preconception counseling for pregnant people with preexisting type 1 or type 2 diabetes is highly effective in reducing the risk of congenital malformations and decreasing the risk of preterm delivery and admission to neonatal intensive care units. Preconception counseling likely also reduces perinatal mortality and small-for-gestational-age birth weight (17). A key

point is the need to incorporate a question about plans for pregnancy into the routine primary and gynecologic care of people with diabetes. Preconception care for people with diabetes should include the standard screenings and care recommended for any person planning pregnancy (16). Prescription of prenatal vitamins with at least 400 µg of folic acid and 150 µg of potassium iodide (18) is recommended prior to conception. Review and counseling on the use of nicotine products, alcohol, and recreational drugs, including marijuana, is important. Standard care includes screening for sexually transmitted diseases and thyroid disease, recommended vaccinations, routine genetic screening, a careful review of all prescription and nonprescription medications and supplements used, and a review of travel history and plans with special attention to areas known to have Zika virus, as outlined by ACOG. See **Table 15.1** for additional details on elements of preconception care (16,19).

Counseling on the specific risks of obesity in pregnancy and lifestyle interventions to prevent and treat obesity, including referral to a registered dietitian nutritionist (RDN), is recommended.

Diabetes-specific counseling should include an explanation of the risks to mother and fetus related to pregnancy and the ways to reduce risk, including glycemic goal setting, lifestyle and behavioral management, and medical nutrition therapy (17). The most important diabetes-specific component of preconception care is the attainment of glycemic goals prior to conception. In addition, the presence of microvascular complications is associated with higher risk of disease progression and adverse pregnancy outcomes (20). Diabetes-specific testing should include A1C, creatinine, and urinary albumin-to-creatinine ratio. Special attention should be paid to the review of the medication list for potentially harmful drugs, i.e., ACE inhibitors (21,22), angiotensin receptor blockers (21), and statins (22,23). A referral for a comprehensive eye exam is recommended. Individuals with preexisting diabetic retinopathy will need close monitoring during pregnancy to assess for the progression of retinopathy and provide treatment if indicated (24).

GLYCEMIC TARGETS IN PREGNANCY

Recommendations

- 15.7** Fasting and postprandial blood glucose monitoring are recommended in both gestational diabetes mellitus and pre-existing diabetes in pregnancy to achieve optimal glucose levels. Glucose targets are fasting plasma glucose <95 mg/dL (5.3 mmol/L) and either 1-h postprandial glucose <140 mg/dL (7.8 mmol/L) or 2-h postprandial glucose <120 mg/dL (6.7 mmol/L). Some individuals with preexisting diabetes should also check blood glucose preprandially. **B**
- 15.8** Due to increased red blood cell turnover, A1C is slightly lower during pregnancy in people with and without diabetes. Ideally, the A1C target in pregnancy is <6% (42 mmol/mol) if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% (53 mmol/mol) if necessary to prevent hypoglycemia. **B**
- 15.9** When used in addition to pre- and postprandial blood glucose monitoring, continuous glucose monitoring can help to achieve the A1C target in diabetes and pregnancy. **B**
- 15.10** When used in addition to blood glucose monitoring, targeting traditional pre- and postprandial targets, real-time continuous glucose monitoring can reduce macrosomia and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes. **B**
- 15.11** Continuous glucose monitoring metrics may be used in addition to but should not be used as a substitute for blood glucose monitoring to achieve optimal pre- and postprandial glycemic targets. **E**
- 15.12** Commonly used estimated A1C and glucose management indicator calculations should not be used in pregnancy as estimates of A1C. **C**
- 15.13** Nutrition counseling should endorse a balance of macronutrients

Table 15.1—Checklist for preconception care for people with diabetes (16,19)

Preconception education should include:

- Comprehensive nutrition assessment and recommendations for:
 - Overweight/obesity or underweight
 - Meal planning
 - Correction of dietary nutritional deficiencies
 - Caffeine intake
 - Safe food preparation technique
- Lifestyle recommendations for:
 - Regular moderate exercise
 - Avoidance of hyperthermia (hot tubs)
 - Adequate sleep
- Comprehensive diabetes self-management education
- Counseling on diabetes in pregnancy per current standards, including natural history of insulin resistance in pregnancy and postpartum; preconception glycemic targets; avoidance of DKA/severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy; PCOS (if applicable); fertility in people with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, still birth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy, etc.
- Supplementation
 - Folic acid supplement (400 µg routine)
 - Appropriate use of over-the-counter medications and supplements

Health assessment and plan should include:

- General evaluation of overall health
- Evaluation of diabetes and its comorbidities and complications, including DKA/severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, NAFLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy
- Evaluation of obstetric/gynecologic history, including a history of: cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE)
- Review of current medications and appropriateness during pregnancy

Screening should include:

- Diabetes complications and comorbidities, including comprehensive foot exam; comprehensive ophthalmologic exam; ECG in individuals starting at age 35 years who have cardiac signs/symptoms or risk factors and, if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine protein-to-creatinine ratio
- Anemia
- Genetic carrier status (based on history):
 - Cystic fibrosis
 - Sickle cell anemia
 - Tay-Sachs disease
 - Thalassemia
 - Others if indicated
- Infectious disease
 - *Neisseria gonorrhoeae/Chlamydia trachomatis*
 - Hepatitis C
 - HIV
 - Pap smear
 - Syphilis

Immunizations should include:

- Rubella
- Varicella
- Hepatitis B
- Influenza
- Others if indicated

Preconception plan should include:

- Nutrition and medication plan to achieve glycemic targets prior to conception, including appropriate implementation of monitoring, continuous glucose monitoring, and pump technology
- Contraceptive plan to prevent pregnancy until glycemic targets are achieved
- Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction

DKA, diabetic ketoacidosis; DVT/PE, deep vein thrombosis/pulmonary embolism; ECG, electrocardiogram; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.

including nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish in the eating pattern. **E**

Pregnancy in people with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by mild postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental hormones. In people with preexisting diabetes, glycemic targets are usually achieved through a combination of insulin administration and medical nutrition therapy. Because glycemic targets in pregnancy are stricter than in nonpregnant individuals, it is important that pregnant people with diabetes eat consistent amounts of carbohydrates to match with insulin dosage and to avoid hyperglycemia or hypoglycemia. Referral to an RDN is important to establish a food plan and insulin-to-carbohydrate ratio and determine weight gain goals. The quality of the carbohydrates should be evaluated. A subgroup analysis of the Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes Trial (CONCEPTT) study demonstrated that the diets of individuals planning pregnancy and currently pregnant assessed during the run-in phase prior to randomization were characterized by high-fat, low-fiber, and poor-quality carbohydrate intakes. Fruit and vegetable consumption was inadequate, with one in four participants at risk for micronutrient deficiencies, highlighting the importance of medical nutrition therapy (25). An expert panel on nutrition in pregnancy recommends a balance of macronutrients. A diet that severely restricts any macronutrient class should be avoided, specifically the ketogenic diet that lacks carbohydrates, the Paleo diet because of dairy restriction, and any diet characterized by excess saturated fats. Nutrient-dense, whole foods are recommended, including fruits, vegetables, legumes, whole grains, and healthy fats with n-3 fatty acids that include nuts and seeds and fish, which are less likely to promote excessive weight gain.

Processed foods, fatty red meat, and sweetened foods and beverages should be limited (26).

Insulin Physiology

Given that early pregnancy is a time of enhanced insulin sensitivity and lower glucose levels, many people with type 1 diabetes will have lower insulin requirements and an increased risk for hypoglycemia (27). Around 16 weeks, insulin resistance begins to increase, and total daily insulin doses increase linearly ~5% per week through week 36. This usually results in a doubling of daily insulin dose compared with the prepregnancy requirement. The insulin requirement levels off toward the end of the third trimester with placental aging. A rapid reduction in insulin requirements can indicate the development of placental insufficiency (28). In people with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain normal glucose levels. However, in people with diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, fasting and postprandial blood glucose monitoring is recommended to achieve metabolic control in pregnant people with diabetes. Preprandial testing is also recommended when using insulin pumps or basal-bolus therapy so that premeal rapid-acting insulin dosage can be adjusted. Postprandial monitoring is associated with better glycemic outcomes and a lower risk of preeclampsia (29–31). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy.

Similar to the targets recommended by ACOG (upper limits are the same as for GDM, described below) (32), the ADA-recommended targets for pregnant people with type 1 or type 2 diabetes are as follows:

- Fasting glucose 70–95 mg/dL (3.9–5.3 mmol/L) and either
- One-hour postprandial glucose 110–140 mg/dL (6.1–7.8 mmol/L) or
- Two-hour postprandial glucose 100–120 mg/dL (5.6–6.7 mmol/L)

Lower limits are based on the mean of normal blood glucose in pregnancy (33). Lower limits do not apply to individuals with type 2 diabetes treated with nutrition alone. Hypoglycemia in pregnancy is as defined and treated in Recommendations 6.10–6.15 (Section 6, “Glycemic Targets”). These values represent optimal control if they can be achieved safely. In practice, it may be challenging for a person with type 1 diabetes to achieve these targets without hypoglycemia, particularly those with a history of recurrent hypoglycemia or hypoglycemia unawareness. If an individual cannot achieve these targets without significant hypoglycemia, the ADA suggests less-stringent targets based on clinical experience and individualization of care.

A1C in Pregnancy

In studies of individuals without preexisting diabetes, increasing A1C levels within the normal range are associated with adverse outcomes (34). In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, increasing levels of glycemia were also associated with worsening outcomes (35). Observational studies in preexisting diabetes and pregnancy show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (42–48 mmol/mol) early in gestation (4–6,36). Clinical trials have not evaluated the risks and benefits of achieving these targets, and treatment goals should account for the risk of maternal hypoglycemia in setting an individualized target of <6% (42 mmol/mol) to <7% (53 mmol/mol). Due to physiological increases in red blood cell turnover, A1C levels fall during normal pregnancy (37,38). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, although A1C may be useful, it should be used as a secondary measure of glycemic outcomes in pregnancy, after blood glucose monitoring.

In the second and third trimesters, A1C <6% (42 mmol/mol) has the lowest risk of large-for-gestational-age infants (36,39,40), preterm delivery (41), and preeclampsia (1,42). Taking all of this into account, a target of <6% (42 mmol/mol) is optimal during pregnancy if it can be achieved without significant hypoglycemia. The A1C target in a given individual

should be achieved without hypoglycemia, which, in addition to the usual adverse sequelae, may increase the risk of low birth weight (43). Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

Continuous Glucose Monitoring in Pregnancy

CONCEPTT was a randomized controlled trial (RCT) of real-time continuous glucose monitoring (CGM) in addition to standard care, including optimization of pre- and postprandial glucose targets versus standard care for pregnant people with type 1 diabetes. It demonstrated the value of real-time CGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C without an increase in hypoglycemia and reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia (44). An observational cohort study that evaluated the glycemic variables reported using CGM found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes (45). Use of the CGM-reported mean glucose is superior to the use of estimated A1C, glucose management indicator, and other calculations to estimate A1C, given the changes to A1C that occur in pregnancy (46). CGM time in range (TIR) can be used for assessment of glycemic outcomes in people with type 1 diabetes, but it does not provide actionable data to address fasting and postprandial hypoglycemia or hyperglycemia. The cost of CGM in pregnancies complicated by type 1 diabetes is offset by improved maternal and neonatal outcomes (47).

There are insufficient data to support the use of CGM in people with type 2 diabetes or GDM (48,49).

The international consensus on TIR (50) endorses pregnancy target ranges and goals for TIR for people with type 1 diabetes using CGM as reported on the ambulatory glucose profile; however, it does not specify the type or accuracy of the device or need for alarms and

alerts. A prospective, observational study including 20 pregnant people with type 1 diabetes simultaneously monitored with intermittently scanning CGM (isCGM) and real-time CGM (rtCGM) for 7 days in early pregnancy demonstrated a higher percentage of time below range in the isCGM group. Asymptomatic hypoglycemia measured by isCGM should therefore not necessarily lead to a reduction of insulin dose and/or increased carbohydrate intake at bedtime unless these episodes are confirmed by blood glucose meter measurements (51). Selection of CGM device should be based on an individual's circumstances, preferences, and needs.

- Target range 63–140 mg/dL (3.5–7.8 mmol/L): TIR, goal >70%
- Time below range (<63 mg/dL [3.5 mmol/L]), goal <4%
- Time below range (<54 mg/dL [3.0 mmol/L]), goal <1%
- Time above range (>140 mg/dL [7.8 mmol/L]), goal <25%

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

Recommendations

15.14 Lifestyle behavior change is an essential component of management of gestational diabetes mellitus and may suffice as treatment for many individuals. Insulin should be added if needed to achieve glycemic targets. **A**

15.15 Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus. Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus. **A** Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data.

15.16 Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester. **A**

15.17 Telehealth visits for pregnant people with gestational diabetes mellitus improve outcomes compared with standard in-person care. **A**

GDM is characterized by an increased risk of large-for-gestational-age birth weight and neonatal and pregnancy complications and an increased risk of long-term maternal type 2 diabetes and abnormal glucose metabolism of offspring in childhood. These associations with maternal oral glucose tolerance test (OGTT) results are continuous with no clear inflection points (35,52). Offspring with exposure to untreated GDM have reduced insulin sensitivity and β -cell compensation and are more likely to have impaired glucose tolerance in childhood (53). In other words, short-term and long-term risks increase with progressive maternal hyperglycemia. Therefore, all pregnant people should be screened as outlined in Section 2, "Classification and Diagnosis of Diabetes." Although there is some heterogeneity, many RCTs and a Cochrane review suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling, particularly when interventions are started during the first or early in the second trimester (54–56). There are no intervention trials in offspring of mothers with GDM. A meta-analysis of 11 RCTs demonstrated that metformin treatment in pregnancy does not reduce the risk of GDM in high-risk individuals with obesity, polycystic ovary syndrome, or preexisting insulin resistance (57). A meta-analysis of 32 RCTs evaluating the effectiveness of telehealth visits for GDM demonstrated reduction of incidences of cesarean delivery, neonatal hypoglycemia, premature rupture of membranes, macrosomia, pregnancy-induced hypertension or preeclampsia, preterm birth, neonatal asphyxia, and polyhydramnios compared with standard in-person care (58).

Lifestyle and Behavioral Management

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management, depending on pregestational weight, as outlined in the section below on preexisting type 2 diabetes, as well as glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (59):

- Fasting glucose <95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial glucose <140 mg/dL (7.8 mmol/L) or

- Two-hour postprandial glucose <120 mg/dL (6.7 mmol/L)

The glycemic target lower limits defined above for preexisting diabetes apply for GDM treated with insulin. Depending on the population, studies suggest that 70–85% of people diagnosed with GDM under Carpenter-Coustan criteria can manage GDM with lifestyle modification alone; it is anticipated that this proportion will be even higher if the lower International Association of the Diabetes and Pregnancy Study Groups (60) diagnostic thresholds are used.

Medical Nutrition Therapy

Medical nutrition therapy for GDM is an individualized nutrition plan developed between the pregnant person and an RDN familiar with the management of GDM (61,62). The food plan should provide adequate calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote weight gain, according to the 2009 Institute of Medicine recommendations (63). There is no definitive research that identifies a specific optimal calorie intake for people with GDM or suggests that their calorie needs are different from those of pregnant individuals without GDM. The food plan should be based on a nutrition assessment with dietary reference intake guidance from the National Institute of Medicine. The recommended dietary reference intake for all pregnant people is a minimum of 175 g of carbohydrate, a minimum of 71 g of protein, and 28 g of fiber (64). The nutrition plan should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding *trans* fats. As is true for all nutrition therapy in people with diabetes, the amount and type of carbohydrate will impact glucose levels. The current recommended amount of carbohydrates is 175 g, or ~35% of a 2,000-calorie diet. Liberalizing higher quality, nutrient-dense carbohydrates results in controlled fasting/postprandial glucose, lower free fatty acids, improved insulin action, and vascular benefits and may reduce excess infant adiposity. Individuals who substitute fat for carbohydrates may unintentionally enhance lipolysis, promote elevated free fatty acids, and worsen maternal insulin resistance (65,66). Fasting urine ketone

testing may be useful to identify those who are severely restricting carbohydrates to control blood glucose. Simple carbohydrates will result in higher postmeal excursions.

Physical Activity

A systematic review demonstrated improvements in glucose control and reductions in need to start insulin or insulin dose requirements with an exercise intervention. There was heterogeneity in the types of effective exercise (aerobic, resistance, or both) and duration of exercise (20–50 min/day, 2–7 days/week of moderate intensity) (67).

Pharmacologic Therapy

Treatment of GDM with lifestyle and insulin has been demonstrated to improve perinatal outcomes in two large randomized studies, as summarized in a U.S. Preventive Services Task Force review (68). Insulin is the first-line agent recommended for the treatment of GDM in the U.S. While individual RCTs support limited efficacy of metformin (69,70) and glyburide (71) in reducing glucose levels for the treatment of GDM, these agents are not recommended as the first-line treatment for GDM because they are known to cross the placenta and data on long-term safety for offspring is of some concern (32). Furthermore, in separate RCTs, glyburide and metformin failed to provide adequate glycemic outcomes in 23% and 25–28% of participants with GDM, respectively (72,73).

Sulfonylureas

Sulfonylureas are known to cross the placenta and have been associated with increased neonatal hypoglycemia. Concentrations of glyburide in umbilical cord plasma are approximately 50–70% of maternal levels (72,73). In meta-analyses and systematic reviews, glyburide was associated with a higher rate of neonatal hypoglycemia, macrosomia, and increased neonatal abdominal circumference than insulin or metformin (74,75).

Glyburide failed to be found noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia (76). Long-term safety data for offspring exposed to glyburide are not available (76).

Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews (74,77–79). However, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels (80,81). In the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study's analyses of 7- to 9-year-old offspring, the 9-year-old offspring exposed to metformin for the treatment of GDM in the Auckland cohort were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to insulin (82). This difference was not found in the Adelaide cohort. In two RCTs of metformin use in pregnancy for polycystic ovary syndrome, follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in the offspring exposed to metformin (83,84). A follow-up study at 5–10 years showed that the offspring had higher BMI, weight-to-height ratios, waist circumferences, and a borderline increase in fat mass (84,85). A recent meta-analysis concluded that metformin exposure resulted in smaller neonates with an acceleration of postnatal growth, resulting in higher BMI in childhood (84).

Randomized, double-blind, controlled trials comparing metformin with other therapies for ovulation induction in individuals with polycystic ovary syndrome have not demonstrated benefit in preventing spontaneous abortion or GDM (86), and there is no evidence-based need to continue metformin in these individuals (87–89).

There are some people with GDM requiring medical therapy who may not be able to use insulin safely or effectively during pregnancy due to cost, language barriers, comprehension, or cultural influences. Oral agents may be an alternative for these individuals after discussing the known risks and the need for more long-term safety data in offspring. However, due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in pregnant people with hypertension or preeclampsia or those at risk for intrauterine growth restriction (90,91).

Insulin

Insulin use should follow the guidelines below. Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable delivery strategies, and neither has been shown to be superior to the other during pregnancy (92).

MANAGEMENT OF PREEXISTING TYPE 1 DIABETES AND TYPE 2 DIABETES IN PREGNANCY

Insulin Use

Recommendations

- 15.18** Insulin should be used to manage type 1 diabetes in pregnancy. **A** Insulin is the preferred agent for the management of type 2 diabetes in pregnancy. **B**
- 15.19** Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes. **C**

The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent blood glucose monitoring. Due to the complexity of insulin management in pregnancy, referral to a specialized center offering team-based care (with team members including a maternal-fetal medicine specialist, endocrinologist or other health care professional experienced in managing pregnancy and preexisting diabetes, RDN, diabetes care and education specialist, and social worker, as needed) is recommended if this resource is available.

None of the currently available human insulin preparations have been demonstrated to cross the placenta (92–97). Insulins studied in RCTs are preferred (98–101) over those studied in cohort studies (102), which are preferred over those studied in case reports only.

While many health care professionals prefer insulin pumps in pregnancy, it is not clear that they are superior to multiple daily injections (103,104). None of the current hybrid closed-loop insulin pump systems approved by the U.S. Food and Drug Administration (FDA) achieve pregnancy targets. However, predictive low-glucose suspend (PLGS) technology has been shown in nonpregnant people to be better than sensor-augmented insulin pumps (SAP) for reducing low glucose values (105).

It may be suited for pregnancy because the predictive low-glucose threshold for suspending insulin is in the range of premeal and overnight glucose value targets in pregnancy and may allow for more aggressive prandial dosing. See *SENSOR-AUGMENTED PUMPS and AUTOMATED INSULIN DELIVERY SYSTEMS* in Section 7, “Diabetes Technology,” for more information on these systems.

Type 1 Diabetes

Pregnant individuals with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and, like all pregnant people, have altered counter-regulatory response in pregnancy that may decrease hypoglycemia awareness. Education for people with diabetes and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help prevent and manage hypoglycemia’s risks. Insulin resistance drops rapidly with the delivery of the placenta.

Pregnancy is a ketogenic state, and people with type 1 diabetes, and to a lesser extent those with type 2 diabetes, are at risk for diabetic ketoacidosis (DKA) at lower blood glucose levels than in the nonpregnant state. Pregnant people with type 1 diabetes should be prescribed ketone strips and receive education on DKA prevention and detection. DKA carries a high risk of stillbirth. Those in DKA who are unable to eat often require 10% dextrose with an insulin drip to adequately meet the higher carbohydrate demands of the placenta and fetus in the third trimester in order to resolve their ketosis.

Retinopathy is a special concern in pregnancy. The necessary rapid implementation of euglycemia in the setting of retinopathy is associated with worsening of retinopathy (106).

Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for people with overweight is 15–25 lb and for those with obesity is 10–20 lb (63). There are no adequate data on optimal weight gain versus weight maintenance in pregnant people with BMI >35 kg/m².

Optimal glycemic targets are often easier to achieve during pregnancy with type 2 diabetes than with type 1 diabetes

but can require much higher doses of insulin, sometimes necessitating concentrated insulin formulations. Insulin is the preferred treatment for type 2 diabetes in pregnancy. An RCT of metformin added to insulin for the treatment of type 2 diabetes found less maternal weight gain and fewer cesarean births. There were fewer macrosomic neonates, but there was a doubling of small-for-gestational-age neonates (107). As in type 1 diabetes, insulin requirements drop dramatically after delivery.

The risk for associated hypertension and other comorbidities may be as high or higher with type 2 diabetes as with type 1 diabetes, even if diabetes is better managed and of shorter apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in those with type 2 diabetes, compared with the first trimester in those with type 1 diabetes (108,109).

PRECLAMPSIA AND ASPIRIN

Insulin Use

Recommendation

- 15.20** Pregnant individuals with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia. **E** A dosage of 162 mg/day may be acceptable **E**; currently, in the U.S., low-dose aspirin is available in 81-mg tablets.

Diabetes in pregnancy is associated with an increased risk of preeclampsia (110). The U.S. Preventive Services Task Force recommends using low-dose aspirin (81 mg/day) as a preventive medication at 12 weeks of gestation in individuals at high risk for preeclampsia (111). However, a meta-analysis and an additional trial demonstrate that low-dose aspirin <100 mg is not effective in reducing preeclampsia. Low-dose aspirin >100 mg is required (112–114). A cost-benefit analysis has concluded that this approach would reduce morbidity, save lives, and lower health care costs (115). However, there is insufficient data regarding benefits of aspirin in pregnant people with preexisting diabetes (116,117). More

studies are needed to assess the long-term effects of prenatal aspirin exposure on offspring (116).

PREGNANCY AND DRUG CONSIDERATIONS

Recommendations

15.21 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational-age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be lessened for blood pressure <90/60 mmHg. **E** A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

15.22 Potentially harmful medications in pregnancy (i.e., ACE inhibitors, angiotensin receptor blockers, statins) should be stopped prior to conception and avoided in sexually active individuals of childbearing potential who are not using reliable contraception. **B**

In normal pregnancy, blood pressure is lower than in the nonpregnant state. The Chronic Hypertension and Pregnancy (CHAP) Trial Consortium's RCT on treatment for mild chronic hypertension during pregnancy demonstrated that a blood pressure of 140/90 mmHg, as the threshold for initiation or titration of treatment, reduces the incidence of adverse pregnancy outcomes without compromising fetal growth (118). The CHAP Consortium's study mitigates concerns about small-for-gestational-age birth weight. Attained mean \pm SD blood pressure measurements in the treated versus untreated groups were systolic 129.5 \pm 10.0 vs. 132.6 \pm 10.1 mmHg (between-group difference -3.11 [95% CI -3.95 to 2.28]) and diastolic 79.1 \pm 7.4 vs. 81.5 \pm 8.0 mmHg (-2.33 [-2.97 to 0.04]) (118). Individuals with diabetes

had an even better composite outcome score than those without diabetes (118).

As a result of the CHAP study, ACOG issued a Practice Advisory recommending a blood pressure of 140/90 mmHg as the threshold for initiation or titration of medical therapy for chronic hypertension in pregnancy (119) rather than their previously recommended threshold of 160/110 mmHg (120).

The CHAP study provides additional guidance for the management of hypertension in pregnancy. Data from the previously published Control of Hypertension in Pregnancy Study (CHIPS) supports a target blood pressure goal of 110–135/85 mmHg to reduce the risk of uncontrolled maternal hypertension and minimize impaired fetal growth (120–122). The 2015 study (121) excluded pregnancies complicated by preexisting diabetes, and only 6% of participants had GDM at enrollment. There was no difference in pregnancy loss, neonatal care, or other neonatal outcomes between the groups with tighter versus less tight control of hypertension (121).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated because they may cause fetal renal dysplasia, oligohydramnios, pulmonary hypoplasia, and intrauterine growth restriction (21).

A large study found that after adjusting for confounders, first trimester ACE inhibitor exposure does not appear to be associated with congenital malformations (123). However, ACE inhibitors and angiotensin receptor blockers should be stopped as soon as possible in the first trimester to avoid second and third trimester fetopathy (123). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, nifedipine, labetalol, diltiazem, clonidine, and prazosin. Atenolol is not recommended, but other β -blockers may be used, if necessary. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (124). On the basis of available evidence, statins should also be avoided in pregnancy (125).

See pregnancy and antihypertensive medications in Section 10, "Cardiovascular Disease and Risk Management," for more information on managing blood pressure in pregnancy.

POSTPARTUM CARE

Recommendations

15.23 Insulin resistance decreases dramatically immediately postpartum, and insulin requirements need to be evaluated and adjusted as they are often roughly half the prepregnancy requirements for the initial few days postpartum. **C**

15.24 A contraceptive plan should be discussed and implemented with all people with diabetes of reproductive potential. **A**

15.25 Screen individuals with a recent history of gestational diabetes mellitus at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**

15.26 Individuals with overweight/obesity and a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

15.27 Breastfeeding is recommended to reduce the risk of maternal type 2 diabetes and should be considered when choosing whether to breastfeed or formula feed. **B**

15.28 Individuals with a history of gestational diabetes mellitus should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years. **B**

15.29 Individuals with a history of gestational diabetes mellitus should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations. **E**

15.30 Postpartum care should include psychosocial assessment and support for self-care. **E**

Gestational Diabetes Mellitus

Initial Testing

Because GDM often represents previously undiagnosed prediabetes, type 2 diabetes, maturity-onset diabetes of the young, or even developing type 1 diabetes, individuals with GDM should be

tested for persistent diabetes or prediabetes at 4–12 weeks postpartum with a fasting 75-g OGTT using nonpregnancy criteria as outlined in Section 2, “Classification and Diagnosis of Diabetes,” specifically **Table 2.2**. In the absence of unequivocal hyperglycemia, a positive screen for diabetes requires two abnormal values. If both the fasting plasma glucose (≥ 126 mg/dL [7.0 mmol/L]) and 2-h plasma glucose (≥ 200 mg/dL [11.1 mmol/L]) are abnormal in a single screening test, then the diagnosis of diabetes is made. If only one abnormal value in the OGTT meets diabetes criteria, the test should be repeated to confirm that the abnormality persists. OGTT testing immediately postpartum, while still hospitalized, has demonstrated improved engagement in testing but also variably reduced sensitivity to the diagnosis of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes (126,127).

Postpartum Follow-up

The OGTT is recommended over A1C at 4–12 weeks postpartum because A1C may be persistently impacted (lowered) by the increased red blood cell turnover related to pregnancy, by blood loss at delivery, or by the preceding 3-month glucose profile. The OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes. Individuals of childbearing potential with prediabetes may develop type 2 diabetes by the time of their next pregnancy and will need preconception evaluation. Because GDM is associated with an increased lifetime maternal risk for diabetes estimated at 50–60% (128,129), individuals should also be tested every 1–3 years thereafter if the 4–12 weeks postpartum 75-g OGTT is normal. Ongoing evaluation may be performed with any recommended glycemic test (e.g., annual A1C, annual fasting plasma glucose, or triennial 75-g OGTT using nonpregnant thresholds).

Gestational Diabetes Mellitus and Type 2 Diabetes

Individuals with a history of GDM have a greatly increased risk of conversion to type 2 diabetes over time (129), and those with GDM have a 10-fold increased risk of developing type 2 diabetes compared with those without GDM (128). Absolute risk of developing type 2 diabetes after GDM increases linearly through a person's lifetime, being approximately

20% at 10 years, 30% at 20 years, 40% at 30 years, 50% at 40 years, and 60% at 50 years (129). In the prospective Nurses' Health Study II (NHS II), subsequent diabetes risk after a history of GDM was significantly lower in those who followed healthy eating patterns (130). Adjusting for BMI attenuated this association moderately, but not completely. Interpregnancy weight gain is associated with increased risk of adverse pregnancy outcomes (131) and higher risk of GDM, while in people with BMI > 25 kg/m², weight loss is associated with lower risk of developing GDM in the subsequent pregnancy (132). Development of type 2 diabetes is 18% higher per unit of BMI increase from prepregnancy BMI at follow-up, highlighting the importance of effective weight management after GDM (133). In addition, postdelivery lifestyle interventions are effective in reducing risk of type 2 diabetes (134).

Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in individuals with prediabetes and a history of GDM. Only five to six individuals with prediabetes and a history of GDM need to be treated with either intervention to prevent one case of diabetes over 3 years (135). In these individuals, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (136). If the pregnancy has motivated the adoption of healthy nutrition, building on these gains to support weight loss is recommended in the postpartum period. (See Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities.”)

Preexisting Type 1 and Type 2 Diabetes

Insulin sensitivity increases dramatically with the delivery of the placenta. In one study, insulin requirements in the immediate postpartum period are roughly 34% lower than prepregnancy insulin requirements (137). Insulin sensitivity then returns to prepregnancy levels over the following 1–2 weeks. For individuals taking insulin, particular attention should be directed to hypoglycemia prevention in the setting of breastfeeding and erratic sleep and eating schedules (138).

Lactation

Considering the immediate nutritional and immunological benefits of breastfeeding for the baby, all mothers, including

those with diabetes, should be supported in attempts to breastfeed. Breastfeeding may also confer longer-term metabolic benefits to both mother (139) and offspring (140). Breastfeeding reduces the risk of developing type 2 diabetes in mothers with previous GDM. It may improve the metabolic risk factors of offspring, but more studies are needed (141). However, lactation can increase the risk of overnight hypoglycemia, and insulin dosing may need to be adjusted.

Contraception

A major barrier to effective preconception care is the fact that the majority of pregnancies are unplanned. Planning pregnancy is critical in individuals with preexisting diabetes to achieve the optimal glycemic targets necessary to prevent congenital malformations and reduce the risk of other complications. Therefore, all individuals with diabetes of childbearing potential should have family planning options reviewed at regular intervals to make sure that effective contraception is implemented and maintained. This applies to individuals in the immediate postpartum period. Individuals with diabetes have the same contraception options and recommendations as those without diabetes. Long-acting, reversible contraception may be ideal for individuals with diabetes and childbearing potential. The risk of an unplanned pregnancy outweighs the risk of any currently available contraception option.

References

1. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 2000;49:2208–2211
2. Holmes VA, Young IS, Patterson CC, et al.; Diabetes and Pre-eclampsia Intervention Trial Study Group. Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. *Diabetes Care* 2011;34:1683–1688
3. Guerin A, Nisenbaum R, Ray JG. Use of maternal GHB concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. *Diabetes Care* 2007;30:1920–1925
4. Jensen DM, Korsholm L, Ovesen P, et al. Preconceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care* 2009;32:1046–1048
5. Nielsen GL, Møller M, Sørensen HT. HbA1c in early diabetic pregnancy and pregnancy outcomes:

- a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. *Diabetes Care* 2006;29:2612–2616
6. Suhonen L, Hillesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type 1 diabetes mellitus. *Diabetologia* 2000;43:79–82
 7. Ludvigsson JF, Neovius M, Söderling J, Gudbjörnsdóttir S, Svensson AM, Franzén S, et al. Maternal glycaemic control in type 1 diabetes and the risk for preterm birth: a population-based cohort study. *Ann Intern Med*. 2019;170:691–701
 8. Charron-Prochownik D, Sereika SM, Becker D, et al. Long-term effects of the booster-enhanced READY-Girls preconception counseling program on intentions and behaviors for family planning in teens with diabetes. *Diabetes Care* 2013;36:3870–3874
 9. Peterson C, Grosse SD, Li R, et al. Preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the United States. *Am J Obstet Gynecol* 2015;212:74.e1–74.e9
 10. Britton LE, Hussey JM, Berry DC, Crandell JL, Brooks JL, Bryant AG. Contraceptive use among women with prediabetes and diabetes in a US national sample. *J Midwifery Womens Health* 2019;64:36–45
 11. Morris JR, Tepper NK. Description and comparison of postpartum use of effective contraception among women with and without diabetes. *Contraception* 2019;100:474–479
 12. Goldstuck ND, Steyn PS. The intrauterine device in women with diabetes mellitus type i and ii: a systematic review. *ISRN Obstet Gynecol* 2013;2013:814062
 13. Wu JP, Moniz MH, Ursu AN. Long-acting reversible contraception—highly efficacious, safe, and underutilized. *JAMA*. 2018 24;320:397–398
 14. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 201: Pregestational diabetes mellitus. *Obstet Gynecol* 2018;132:e228–e248
 15. Charron-Prochownik D, Downs J. *Diabetes and Reproductive Health for Girls*. Alexandria, VA, American Diabetes Association, 2016
 16. ACOG Committee Opinion No. 762: Pre-pregnancy counseling. *Obstet Gynecol* 2019;133:e78–e89
 17. Wahabi HA, Fayed A, Esmaeil S, et al. Systematic review and meta-analysis of the effectiveness of pre-pregnancy care for women with diabetes for improving maternal and perinatal outcomes. *PLoS One* 2020;15:e0237571
 18. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017;27:315–389
 19. Ramos DE. Preconception health: changing the paradigm on well-woman health. *Obstet Gynecol Clin North Am* 2019;46:399–408
 20. Relph S, Patel T, Delaney L, Sobhy S, Thangaratinam S. Adverse pregnancy outcomes in women with diabetes-related microvascular disease and risks of disease progression in pregnancy: a systematic review and meta-analysis. *PLoS Med* 2021;18:e1003856
 21. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. *Hypertension* 2012;60:444–450
 22. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. *BMJ* 2015;350:h1035
 23. Taguchi N, Rubin ET, Hosokawa A, et al. Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes. *Reprod Toxicol* 2008;26:175–177
 24. Widyaputri F, Rogers SL, Kandasamy R, Shub A, Symons RCA, Lim LL. Global estimates of diabetic retinopathy prevalence and progression in pregnant women with preexisting diabetes: a systematic review and meta-analysis. *JAMA Ophthalmol* 2022;140:486–494
 25. Neoh SL, Grisoni JA, Feig DS; CONCEPT Collaborative Group. Dietary intakes of women with type 1 diabetes before and during pregnancy: a pre-specified secondary subgroup analysis among CONCEPT participants. *Diabet Med* 2020;37:1841–1848
 26. Marshall NE, Abrams B, Barbour LA, et al. The importance of nutrition in pregnancy and lactation: lifelong consequences. *Am J Obstet Gynecol* 2022;226:607–632
 27. García-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. *Diabetologia* 2010;53:446–451
 28. Padmanabhan S, Lee VW, Mclean M, et al. The association of falling insulin requirements with maternal biomarkers and placental dysfunction: a prospective study of women with preexisting diabetes in pregnancy. *Diabetes Care* 2017;40:1323–1330
 29. Manderson JG, Patterson CC, Hadden DR, Traub AI, Ennis C, McCance DR. Preprandial versus postprandial blood glucose monitoring in type 1 diabetic pregnancy: a randomized controlled clinical trial. *Am J Obstet Gynecol* 2003;189:507–512
 30. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 1995;333:1237–1241
 31. Jovanovic-Peterson L, Peterson CM, Reed GF, et al. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. The National Institute of Child Health and Human Development–Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 1991;164:103–111
 32. Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational diabetes mellitus. *Obstet Gynecol* 2018;131:e49–e64
 33. Hernandez TL, Friedman JE, Van Pelt RE, Barbour LA. Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? *Diabetes Care* 2011;34:1660–1668
 34. Ho YR, Wang P, Lu MC, Tseng ST, Yang CP, Yan YH. Associations of mid-pregnancy HbA1c with gestational diabetes and risk of adverse pregnancy outcomes in high-risk Taiwanese women. *PLoS One* 2017;12:e0177563
 35. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002
 36. Maresch MJA, Holmes VA, Patterson CC, et al.; Diabetes and Pre-eclampsia Intervention Trial Study Group. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. *Diabetes Care* 2015;38:34–42
 37. Nielsen LR, Ekbom P, Damm P, et al. HbA1c levels are significantly lower in early and late pregnancy. *Diabetes Care* 2004;27:1200–1201
 38. Mosca A, Palaria R, Dalfrà MG, et al. Reference intervals for hemoglobin A1c in pregnant women: data from an Italian multicenter study. *Clin Chem* 2006;52:1138–1143
 39. Hummel M, Marienfeld S, Huppmann M, et al. Fetal growth is increased by maternal type 1 diabetes and HLA DR4-related gene interactions. *Diabetologia* 2007;50:850–858
 40. Cyganek K, Skupien J, Katra B, et al. Risk of macrosomia remains glucose-dependent in a cohort of women with pregestational type 1 diabetes and good glycemic control. *Endocrine* 2017;55:447–455
 41. Abell SK, Boyle JA, de Courten B, et al. Impact of type 2 diabetes, obesity and glycaemic control on pregnancy outcomes. *Aust N Z J Obstet Gynaecol* 2017;57:308–314
 42. Temple RC, Aldridge V, Stanley K, Murphy HR. Glycaemic control throughout pregnancy and risk of pre-eclampsia in women with type 1 diabetes. *BJOG* 2006;113:1329–1332
 43. Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care* 1992;15:1251–1257
 44. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPT): a multicentre international randomised controlled trial. *Lancet* 2017;390:2347–2359
 45. Kristensen K, Ögge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. *Diabetologia* 2019;62:1143–1153
 46. Law GR, Gilthorpe MS, Secher AL, et al. Translating HbA_{1c} measurements into estimated average glucose values in pregnant women with diabetes. *Diabetologia* 2017;60:618–624
 47. Ahmed RJ, Gafni A, Hutton EK, et al.; CONCEPT Collaborative Group. The cost implications of continuous glucose monitoring in pregnant women with type 1 diabetes in 3 Canadian provinces: a posthoc cost analysis of the CONCEPT trial. *CMAJ Open* 2021;9:E627–E634
 48. García-Moreno RM, Benítez-Valderrama P, Barquiel B, et al. Efficacy of continuous glucose monitoring on maternal and neonatal outcomes in gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials. *Diabet Med* 2022;39:e14703
 49. Wyckoff JA, Brown FM. Time in range in pregnancy: is there a role? *Diabetes Spectr* 2021;34:119–132
 50. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. *Diabetes Care* 2019;42:1593–1603
 51. Nørgaard SK, Mathiesen ER, Nørgaard K, Ringholm L. Comparison of glycemic metrics

- measured simultaneously by intermittently scanned continuous glucose monitoring and real-time continuous glucose monitoring in pregnant women with type 1 diabetes. *Diabetes Technol Ther* 2021;23:665–672
52. Scholtens DM, Kuang A, Lowe LP, et al.; HAPO Follow-up Study Cooperative Research Group; HAPO Follow-Up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal glycemia and childhood glucose metabolism. *Diabetes Care* 2019;42:381–392
53. Lowe WL Jr, Scholtens DM, Kuang A, et al.; HAPO Follow-up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal gestational diabetes mellitus and childhood glucose metabolism. *Diabetes Care* 2019;42:372–380
54. Koivusalo SB, Rönö K, Klemetti MM, et al. Gestational diabetes mellitus can be prevented by lifestyle intervention: The Finnish Gestational Diabetes Prevention Study (RADIEL): a randomized controlled trial. *Diabetes Care* 2016;39:24–30
55. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. *Am J Obstet Gynecol* 2017;216:340–351
56. Griffith RJ, Alsweller J, Moore AE, et al. Interventions to prevent women from developing gestational diabetes mellitus: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2020;6:CD012394
57. Doi SAR, Furuya-Kanamori L, Toft E, et al. Metformin in pregnancy to avert gestational diabetes in women at high risk: Meta-analysis of randomized controlled trials. *Obes Rev* 2020;21:e12964
58. Xie W, Dai P, Qin Y, Wu M, Yang B, Yu X. Effectiveness of telemedicine for pregnant women with gestational diabetes mellitus: an updated meta-analysis of 32 randomized controlled trials with trial sequential analysis. *BMC Pregnancy Childbirth* 2020;20:198
59. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 2007;30(Suppl. 2):S251–S260
60. Mayo K, Melamed N, Vandenberghe H, Berger H. The impact of adoption of the International Association of Diabetes in Pregnancy Study Group criteria for the screening and diagnosis of gestational diabetes. *Am J Obstet Gynecol* 2015;212:224.e1–224.e9
61. Han S, Crowther CA, Middleton P, Heatley E. Different types of dietary advice for women with gestational diabetes mellitus. *Cochrane Database Syst Rev* 2013;3:CD009275
62. Viana LV, Gross JL, Azevedo MJ. Dietary intervention in patients with gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. *Diabetes Care* 2014;37:3345–3355
63. Weight GDP. Reexamining the Guidelines. Washington, D.C., National Academies Press, 2009. Accessed 5 October 2022. Available from <https://www.nap.edu/catalog/12584>
64. Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. The National Academies Press; Washington, DC, 2006. p. 1344
65. Hernandez TL, Mande A, Barbour LA. Nutrition therapy within and beyond gestational diabetes. *Diabetes Res Clin Pract* 2018;145:39–50
66. Hernandez TL, Van Pelt RE, Anderson MA, et al. A higher-complex carbohydrate diet in gestational diabetes mellitus achieves glucose targets and lowers postprandial lipids: a randomized crossover study. *Diabetes Care* 2014;37:1254–1262
67. Laredo-Aguilera JA, Gallardo-Bravo M, Rabanales-Sotos JA, Cobo-Cuenca AI, Carmona-Torres JM. Physical activity programs during pregnancy are effective for the control of gestational diabetes mellitus. *Int J Environ Res Public Health* 2020;17:E6151
68. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. *Ann Intern Med* 2013;159:123–129
69. Rowan JA, Hague WM, Gao W, Battin MR; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;358:2003–2015
70. Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. *PLoS One* 2013;8:e64585
71. Langer O, Conway DL, Berkus MD, Xenakis EMJ, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 2000;343:1134–1138
72. Hebert MF, Ma X, Narahariseti SB, et al.; Obstetric-Fetal Pharmacology Research Unit Network. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin Pharmacol Ther* 2009;85:607–614
73. Malek R, Davis SN. Pharmacokinetics, efficacy and safety of glyburide for treatment of gestational diabetes mellitus. *Expert Opin Drug Metab Toxicol* 2016;12:691–699
74. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ* 2015;350:h102
75. Tarry-Adkins JL, Aiken CE, Ozanne SE. Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry independent of maternal glycaemic control: a systematic review and meta-analysis. *PLoS Med* 2020;17:e1003126
76. Sénat MV, Affres H, Letourneau A, et al.; Groupe de Recherche en Obstétrique et Gynécologie (GROG). Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial. *JAMA* 2018;319:1773–1780
77. Silva JC, Pacheco C, Bizato J, de Souza BV, Ribeiro TE, Bertini AM. Metformin compared with glyburide for the management of gestational diabetes. *Int J Gynaecol Obstet* 2010;111:37–40
78. Nachum Z, Zafran N, Salim R, et al. Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: a randomized controlled study. *Diabetes Care* 2017;40:332–337
79. Jiang YF, Chen XY, Ding T, Wang XF, Zhu ZN, Su SW. Comparative efficacy and safety of OADs in management of GDM: network meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2015;100:2071–2080
80. Vanky E, Zahlsen K, Spigset O, Carlsen SM. Placental passage of metformin in women with polycystic ovary syndrome. *Fertil Steril* 2005;83:1575–1578
81. Charles B, Norris R, Xiao X, Hague W. Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit* 2006;28:67–72
82. Rowan JA, Rush EC, Plank LD, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7–9 years of age. *BMJ Open Diabetes Res Care* 2018;6:e000456
83. Hanem LGE, Stridsklev S, Júlíusson PB, et al. Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: follow-up of two RCTs. *J Clin Endocrinol Metab* 2018;103:1612–1621
84. Tarry-Adkins JL, Aiken CE, Ozanne SE. Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: a systematic review and meta-analysis. *PLoS Med* 2019;16:e1002848
85. Hanem LGE, Salvesen Ø, Júlíusson PB, et al. Intrauterine metformin exposure and offspring cardiometabolic risk factors (PedMet study): a 5–10 year follow-up of the PregMet randomised controlled trial. *Lancet Child Adolesc Health* 2019;3:166–174
86. Vanky E, Stridsklev S, Heimstad R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab* 2010;95:E448–E455
87. Legro RS, Barnhart HX, Schlaff WD, et al.; Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;356:551–566
88. Palomba S, Orio F Jr, Falbo A, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005;90:4068–4074
89. Palomba S, Orio F Jr, Nardo LG, et al. Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial. *J Clin Endocrinol Metab* 2004;89:4801–4809
90. Barbour LA, Scifres C, Valent AM, et al. A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. *Am J Obstet Gynecol* 2018;219:367.e1–367.e7
91. Barbour LA, Feig DS. Metformin for gestational diabetes mellitus: progeny, perspective, and a personalized approach. *Diabetes Care* 2019;42:396–399
92. Farrar D, Tuffnell DJ, West J, West HM. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant

- women with diabetes. *Cochrane Database Syst Rev* 2016;6:CD005542
93. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin glargine safety in pregnancy: a transplacental transfer study. *Diabetes Care* 2010; 33:29–33
 94. Holcberg G, Tsadkin-Tamir M, Sapir O, et al. Transfer of insulin lispro across the human placenta. *Eur J Obstet Gynecol Reprod Biol* 2004; 115:117–118
 95. Boskovic R, Feig DS, Derewlany L, Knie B, Portnoi G, Koren G. Transfer of insulin lispro across the human placenta: in vitro perfusion studies. *Diabetes Care* 2003;26:1390–1394
 96. McCance DR, Damm P, Mathiesen ER, et al. Evaluation of insulin antibodies and placental transfer of insulin aspart in pregnant women with type 1 diabetes mellitus. *Diabetologia* 2008; 51:2141–2143
 97. Suffecool K, Rosenn B, Niederkofler EE, et al. Insulin detemir does not cross the human placenta. *Diabetes Care* 2015;38:e20–e21
 98. Mathiesen ER, Hod M, Ivanisevic M, et al.; Detemir in Pregnancy Study Group. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care* 2012;35:2012–2017
 99. Hod M, Mathiesen ER, Jovanovic L, et al. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *J Matern Fetal Neonatal Med* 2014;27:7–13
 100. Hod M, Damm P, Kaaja R, et al.; Insulin Aspart Pregnancy Study Group. Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 2008;198:186.e1–186.e7
 101. Persson B, Swahn ML, Hjertberg R, et al. Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Res Clin Pract* 2002;58:115–121
 102. Pollex E, Moretti ME, Koren G, Feig DS. Safety of insulin glargine use in pregnancy: a systematic review and meta-analysis. *Ann Pharmacother* 2011;45:9–16
 103. Carta Q, Meriggi E, Trossarelli GF, et al. Continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in type I and type II diabetic pregnancy. *Diabetes Metab* 1986;12:121–129
 104. Kernaghan D, Farrell T, Hammond P, Owen P. Fetal growth in women managed with insulin pump therapy compared to conventional insulin. *Eur J Obstet Gynecol Reprod Biol* 2008;137: 47–49
 105. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG Trial. *Diabetes Care* 2018;41:2155–2161
 106. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. *Diabetes Care* 1995;18:631–637
 107. Feig DS, Donovan LE, Zinman B, et al.; MiTy Collaborative Group. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2020;8:834–844
 108. Clausen TD, Mathiesen ER, Ekbohm P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. *Diabetes Care* 2005;28:323–328
 109. Cundy T, Gamble G, Neale L, et al. Differing causes of pregnancy loss in type 1 and type 2 diabetes. *Diabetes Care* 2007;30:2603–2607
 110. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005;330:565
 111. Henderson JT, Whitlock EP, O’Conner E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Rockville, MD, Agency for Healthcare Research and Quality, 2014. Accessed 21 October 2022. Available from <https://www.ncbi.nlm.nih.gov/books/NBK196392/>
 112. Roberge S, Bujold E, Nicolaidis KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and meta-analysis. *Am J Obstet Gynecol* 2018;218:287–293.e1
 113. Rolnik DL, Wright D, Poon LC, O’Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017;377: 613–622
 114. Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2020 25;395: 285–293
 115. Werner EF, Hauspurg AK, Rouse DJ. A cost-benefit analysis of low-dose aspirin prophylaxis for the prevention of preeclampsia in the United States. *Obstet Gynecol* 2015;126:1242–1250
 116. Zen M, Haider R, Simmons D, et al. Aspirin for the prevention of pre-eclampsia in women with pre-existing diabetes: systematic review. *Aust N Z J Obstet Gynaecol* 2022;62:12–21
 117. Voutetakis A, Pervanidou P, Kanaka-Gantenbein C. Aspirin for the prevention of preeclampsia and potential consequences for fetal brain development. *JAMA Pediatr* 2019;173: 619–620
 118. Tita AT, Szychowski JM, Boggess K, et al.; Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med* 2022; 386:1781–1792
 119. American College of Obstetricians and Gynecologists: Clinical guidance for the integration of the findings of the Chronic Hypertension and Pregnancy (CHAP) study. Accessed 31 August 2022. Available from <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2022/04/clinical-guidance-for-the-integration-of-the-findings-of-the-chronic-hypertension-and-pregnancy-chap-study>
 120. American College of Obstetricians and Gynecologists’ Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 203: Chronic hypertension in pregnancy. *Obstet Gynecol* 2019; 133:e26–e50
 121. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;372:407–417
 122. Brown MA, Magee LA, Kenny LC, et al.; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension* 2018;72:24–43
 123. Bateman BT, Patorno E, Desai RJ, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. *Obstet Gynecol* 2017;129:174–184
 124. Sibai BM. Treatment of hypertension in pregnant women. *N Engl J Med* 1996;335:257–265
 125. Kazmin A, Garcia-Bournissen F, Koren G. Risks of statin use during pregnancy: a systematic review. *J Obstet Gynaecol Can* 2007;29:906–908
 126. Waters TP, Kim SY, Werner E, et al. Should women with gestational diabetes be screened at delivery hospitalization for type 2 diabetes? *Am J Obstet Gynecol* 2020;222:73.e1–73.e11
 127. Society for Maternal-Fetal Medicine (SMFM). Werner EF, Has P, Rouse D, Clark MA. Two-day postpartum compared with 4- to 12-week postpartum glucose tolerance testing for women with gestational diabetes. *Am J Obstet Gynecol* 2020;223:439.e1–439.e7
 128. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ* 2020;369:m1361
 129. Li Z, Cheng Y, Wang D, et al. Incidence rate of type 2 diabetes mellitus after gestational diabetes mellitus: a systematic review and meta-analysis of 170,139 women. *J Diabetes Res* 2020;2020:3076463
 130. Tobias DK, Hu FB, Chavarro J, Rosner B, Mozaffarian D, Zhang C. Healthful dietary patterns and type 2 diabetes mellitus risk among women with a history of gestational diabetes mellitus. *Arch Intern Med* 2012;172:1566–1572
 131. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. *Lancet* 2006;368:1164–1170
 132. Martínez-Hortelano JA, Cavero-Redondo I, Álvarez-Bueno C, Díez-Fernández A, Hernández-Luengo M, Martínez-Vizcaíno V. Interpregnancy weight change and gestational diabetes mellitus: a systematic review and meta-analysis. *Obesity (Silver Spring)* 2021;29:454–464
 133. Dennison RA, Chen ES, Green ME, et al. The absolute and relative risk of type 2 diabetes after gestational diabetes: a systematic review and meta-analysis of 129 studies. *Diabetes Res Clin Pract* 2021;171:108625
 134. Li N, Yang Y, Cui D, et al. Effects of lifestyle intervention on long-term risk of diabetes in women with prior gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev* 2021;22:e13122
 135. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774–4779
 136. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention

- Program outcomes study 10-year follow-up. *J Clin Endocrinol Metab* 2015;100:1646–1653
137. Achong N, Duncan EL, McIntyre HD, Callaway L. Peripartum management of glycemia in women with type 1 diabetes. *Diabetes Care* 2014;37:364–371
138. Riviello C, Mello G, Jovanovic LG. Breastfeeding and the basal insulin requirement in type 1 diabetic women. *Endocr Pract* 2009;15:187–193
139. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. *JAMA* 2005;294:2601–2610
140. Pereira PF, Alfenas R de CG, Araújo RMA. Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence. *J Pediatr (Rio J)* 2014;90:7–15
141. Pathirana MM, Ali A, Lassi ZS, Arstall MA, Roberts CT, Andraweera PH. Protective influence of breastfeeding on cardiovascular risk factors in women with previous gestational diabetes mellitus and their children: a systematic review and meta-analysis. *J Hum Lact* 2022;38:501–512

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16. Diabetes Care in the Hospital: Standards of Care in Diabetes—2023

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Among hospitalized patients, hyperglycemia, hypoglycemia, and glucose variability are associated with adverse outcomes, including increased morbidity and mortality (1). Careful management of people with diabetes during hospitalization has direct and immediate benefits. Diabetes management in the inpatient setting is facilitated by preadmission treatment of hyperglycemia in people with diabetes, having elective procedures, a dedicated inpatient diabetes service applying well-developed and validated standards of care, and careful transition to prearranged outpatient management. These steps can shorten hospital stays, reduce the need for readmission and emergency department visits, and improve outcomes. Some in-depth reviews of in-hospital care and care transitions for adults with diabetes have been published (2–4). For older hospitalized patients or for patients in long-term care facilities, please see Section 13, “Older Adults.”

HOSPITAL CARE DELIVERY STANDARDS

Recommendations

- 16.1** Perform an A1C test on all people with diabetes or hyperglycemia (blood glucose >140 mg/dL [7.8 mmol/L]) admitted to the hospital if not performed in the prior 3 months. **B**
- 16.2** Insulin should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin dosage based on glycemic fluctuations. **B**

Considerations on Admission

High-quality hospital care for diabetes requires standards for care delivery, which are best implemented using structured order sets and quality improvement strategies for process improvement. Unfortunately, “best practice” protocols, reviews, and guidelines (2,4) are inconsistently implemented within hospitals. To correct this, medical centers striving for optimal inpatient diabetes treatment should establish protocols and structured order sets, which include computerized provider order entry (CPOE).

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Initial orders should state the type of diabetes (i.e., type 1, type 2, gestational diabetes mellitus, pancreatogenic diabetes) when it is known. Because inpatient treatment and discharge planning are more effective if based on preadmission glycemia, A1C should be measured for all people with diabetes or hyperglycemia admitted to the hospital if an A1C test has not been performed in the previous 3 months (5–8). In addition, diabetes self-management knowledge and behaviors should be assessed on admission, and diabetes self-management education provided, especially if a new treatment plan is being considered. Diabetes self-management education should include appropriate skills needed after discharge, such as medication dosing and administration, glucose monitoring, and recognition and treatment of hypoglycemia (9,10). Evidence supports preadmission treatment of hyperglycemia in people scheduled for elective surgery as an effective means of reducing adverse outcomes (11–14).

The National Academy of Medicine recommends CPOE to prevent medication-related errors and increase medication administration efficiency (15). Systematic reviews of randomized controlled trials using computerized advice to improve glycemic outcomes in the hospital found significant improvement in the percentage of time individuals spent in the target glucose range, lower mean blood glucose levels, and no increase in hypoglycemia (16,17). Where feasible, there should be structured order sets that provide computerized guidance for glycemic management. Electronic insulin order templates also improve mean glucose levels without increasing hypoglycemia in people with type 2 diabetes, so structured insulin order sets incorporated into the CPOE can facilitate glycemic management (18,19). Insulin dosing algorithms using machine learning and data in the electronic health record (EHR) currently in development show great promise to more accurately predict insulin requirements during hospitalization compared with existing clinical practices (20).

Diabetes Care Specialists in the Hospital

Recommendation

16.3 When caring for hospitalized people with diabetes, consult with a specialized diabetes or glucose management team when possible. **C**

Appropriately trained specialists or specialty teams may reduce the length of stay and improve glycemic and other clinical outcomes (21–23). In addition, the increased risk of 30-day readmission following hospitalization that has been attributed to diabetes can be reduced, and costs saved when inpatient care is provided by a specialized diabetes management team (21,24,25). In a cross-sectional study comparing usual care to specialists reviewing diabetes cases and making recommendations virtually through the EHR, rates of both hyperglycemia and hypoglycemia were reduced by 30–40% (26). Providing inpatient diabetes education and developing a diabetes discharge plan that includes continued access to diabetes medications and supplies and ongoing education and support are key strategies to improve outcomes (27–29). Details of diabetes care team composition are available in the Joint Commission standards for programs and from the Society of Hospital Medicine (30,31).

Even the most efficacious orders may not be carried out in a way that improves quality, nor are they automatically updated when new evidence arises. The Joint Commission accreditation program for the hospital care of diabetes (31), the Society of Hospital Medicine workbook for program development (30), and the Joint British Diabetes Societies (JBDS) for Inpatient Care Group (32) are valuable resources.

GLYCEMIC TARGETS IN HOSPITALIZED ADULTS

Recommendations

- 16.4** Insulin therapy should be initiated for the treatment of persistent hyperglycemia starting at a threshold ≥ 180 mg/dL (10.0 mmol/L) (checked on two occasions). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill and noncritically ill patients. **A**
- 16.5** More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L) or 100–180 mg/dL (5.6–10.0 mmol/L), may be appropriate for selected patients and are acceptable if they can be achieved without significant hypoglycemia. **C**

Standard Definitions of Glucose Abnormalities

Hyperglycemia in hospitalized patients is defined as blood glucose levels >140 mg/dL (7.8 mmol/L) (33). Blood glucose levels persistently above this level warrant prompt interventions, such as alterations in nutrition or changes to medications that cause hyperglycemia. An admission A1C value $\geq 6.5\%$ (48 mmol/mol) suggests that the onset of diabetes preceded hospitalization (see Section 2, “Classification and Diagnosis of Diabetes”) (33,34). Hypoglycemia in hospitalized patients is categorized by blood glucose concentration and clinical correlates (Table 6.4) (35). Level 1 hypoglycemia is defined as a glucose concentration of 54–70 mg/dL (3.0–3.9 mmol/L). Level 2 hypoglycemia is defined as a blood glucose concentration <54 mg/dL (3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms. Level 3 hypoglycemia is defined as a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery. Levels 2 and 3 require immediate correction of low blood glucose. Prompt treatment of level 1 hypoglycemia can prevent progression to more significant level 2 and level 3 hypoglycemia.

Glycemic Targets

In a landmark clinical trial conducted in a surgical intensive care unit, Van den Berghe et al. (36) demonstrated that an intensive intravenous insulin protocol with a target glycemic range of 80–110 mg/dL (4.4–6.1 mmol/L) reduced mortality by 40% compared with a standard approach targeting blood glucose of 180–215 mg/dL (10–12 mmol/L) in critically ill hospitalized patients with recent surgery. This study provided robust evidence that active treatment to lower blood glucose in hospitalized patients could have immediate benefits. However, a large, multicenter follow-up study in critically ill hospitalized patients, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (37), led to a reconsideration of the optimal target range for glucose lowering in critical illness. In this trial, critically ill patients randomized to intensive glycemic management (80–110 mg/dL) derived no significant treatment advantage compared with a group with more moderate glycemic targets (140–180 mg/dL [7.8–10.0 mmol/L]) and had slightly but

significantly higher mortality (27.5% vs. 25%). The intensively treated group had 10- to 15-fold greater rates of hypoglycemia, which may have contributed to the adverse outcomes noted. The findings from NICE-SUGAR are supported by several meta-analyses and a randomized controlled trial, some of which suggest that tight glycemic management increases mortality compared with more moderate glycemic targets and generally causes higher rates of hypoglycemia (38–40).

Based on these results, insulin therapy should be initiated for the treatment of persistent hyperglycemia ≥ 180 mg/dL (10.0 mmol/L) and targeted to a glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) for the majority of critically ill patients. Although not as well supported by data from randomized controlled trials, these recommendations have been extended to hospitalized patients without critical illness. More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients (e.g., critically ill postsurgical patients or patients with cardiac surgery) as long as they can be achieved without significant hypoglycemia (41–43). For inpatient management of hyperglycemia in noncritical care, the expert consensus recommends a target range of 100–180 mg/dL (5.6–10.0 mmol/L) for noncritically ill patients with “new” hyperglycemia as well as people with known diabetes prior to admission. It has been found that fasting glucose levels < 100 mg/dL are predictors of hypoglycemia within the next 24 h (44). Glycemic levels > 250 mg/dL (13.9 mmol/L) may be acceptable in terminally ill patients with short life expectancy. In these individuals, less aggressive insulin regimens to minimize glucosuria, dehydration, and electrolyte disturbances are often more appropriate. Clinical judgment combined with ongoing assessment of clinical status, including changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids), may be incorporated into the day-to-day decisions regarding insulin dosing (42).

BLOOD GLUCOSE MONITORING

In hospitalized individuals with diabetes who are eating, point-of-care (POC) glucose monitoring should be performed before meals; in those not eating, glucose monitoring is advised every 4–6 h (33).

More frequent POC blood glucose monitoring ranging from every 30 min to every 2 h is the required standard for safe use of intravenous insulin. Safety standards for blood glucose monitoring that prohibit sharing lanceting devices, other testing materials, and needles are mandatory (45).

The vast majority of hospital glucose monitoring is performed with FDA-approved prescription POC glucose monitoring systems with and capillary blood taken from finger sticks, similar to the process performed by outpatients for home blood glucose monitoring (46). POC blood glucose meters are not as accurate or as precise as laboratory glucose analyzers, and capillary blood glucose readings are subject to artifacts due to perfusion, edema, anemia/erythrocytosis, and several medications commonly used in the hospital (47) (Table 7.1). The U.S. Food and Drug Administration (FDA) has established standards for capillary (finger-stick) blood glucose meters used in the ambulatory setting, as well as standards to be applied for POC measures in the hospital (47). The balance between analytic requirements (e.g., accuracy, precision, interference) and clinical requirements (rapidity, simplicity, point of care) has not been uniformly resolved (46,48), and most hospitals have arrived at their own policies to balance these parameters. It is critically important that devices selected for in-hospital use, and the workflow through which they are applied, have careful analysis of performance and reliability and ongoing quality assessments. Recent studies indicate that POC measures provide adequate information for usual practice, with only rare instances where care has been compromised (49,50). Best practice dictates that any glucose result that does not correlate with the patient’s clinical status should be confirmed by measuring a serum sample in the clinical laboratory.

Continuous Glucose Monitoring

Real-time continuous glucose monitoring (CGM) provides frequent measurements of interstitial glucose levels and the direction and magnitude of glucose trends. Even though CGM has theoretical advantages over POC glucose monitoring in detecting and reducing the incidence of hypoglycemia, it has not been approved by the FDA for inpatient use. Some hospitals with established glucose management

teams allow the use of CGM in selected people with diabetes on an individual basis, mostly in noncritical care settings, provided both the individual and the glucose management team are well educated in the use of this technology. CGM is not currently approved for intensive care unit use due to accuracy concerns such as hypovolemia, hypoperfusion, and use of therapies such as vasopressor agents.

During the coronavirus disease 2019 (COVID-19) pandemic, many institutions were able to use CGM to minimize contact between health care professionals and people with diabetes, especially those in the intensive care unit under an FDA policy of enforcement discretion during the pandemic (51–59). This approach has been helpful in that regard, as well as in minimizing the use of personal protective equipment. The availability of data about the safe and effective use of CGM in the inpatient setting is evolving. Preliminary data suggest that CGM can significantly improve glycemic management and other hospital outcomes (57,60–63).

For more information on CGM, see Section 7, “Diabetes Technology.”

GLUCOSE-LOWERING TREATMENT IN HOSPITALIZED PATIENTS

Recommendations

- 16.6** Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritically ill hospitalized patients with poor oral intake or those who are taking nothing by mouth. **A**
- 16.7** An insulin regimen with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized patients with adequate nutritional intake. **A**
- 16.8** Use of a correction or supplemental insulin without basal insulin (often referred to as a sliding scale) in the inpatient setting is discouraged. **A**

Insulin Therapy

Critical Care Setting

Continuous intravenous insulin infusion is the most effective method for achieving glycemic targets in the critical care setting. Intravenous insulin infusions should be administered based on validated

written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose (64).

Noncritical Care Setting

In most instances, insulin is the preferred treatment for hyperglycemia in hospitalized patients. However, in certain circumstances, it may be appropriate to continue home therapies, including oral glucose-lowering medications (64,65). If oral medications are held in the hospital but will be reinstated after discharge, there should be a protocol for guiding resumption of home medications 1–2 days prior to discharge. For people taking insulin, several reports indicate that inpatient use of insulin pens is safe and may be associated with improved nurse satisfaction compared with the use of insulin vials and syringes with safety protocols in place (66–68). Insulin pens have been the subject of an FDA warning because of potential blood-borne diseases if inadvertently shared with more than one person; the warning “For single patient use only” should be rigorously followed using strict safety measures such as barcoding to prevent errors (69,70).

Outside of critical care units, scheduled insulin orders are recommended to manage hyperglycemia in people with diabetes. Orders for insulin analogs or human insulin result in similar glycemic outcomes in the hospital setting (71). The use of subcutaneous rapid- or short-acting insulin before meals, or every 4–6 h if no meals are given or if the individual is receiving continuous enteral/parenteral nutrition, is indicated to correct or prevent hyperglycemia. Basal insulin, or a basal plus bolus correction schedule, is the preferred treatment for noncritically ill hospitalized patients with inadequate oral intake or those restricted from oral intake. An insulin schedule with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized people with diabetes with adequate nutritional intake (72). In people with diabetes with blood glucose <240 mg/dL, consider alternatives to basal-bolus therapy as discussed below (72,73).

For individuals who are eating, insulin injections should align with meals. In such instances, POC glucose monitoring should be performed immediately before meals. If oral intake is inadequate, a

safer procedure is administering prandial insulin immediately after eating, with the dose adjusted to be appropriate for the amount of carbohydrates ingested (71).

A randomized controlled trial has shown that basal-bolus treatment improved glycemic outcomes and reduced hospital complications compared with a correction or supplemental insulin without basal insulin (formerly known as sliding scale) in general surgery for people with type 2 diabetes (74). Prolonged use of correction or supplemental insulin without basal insulin as the sole treatment of hyperglycemia is strongly discouraged in the inpatient setting, with the exception of people with type 2 diabetes in noncritical care with mild hyperglycemia (23,75,76).

While there is evidence for using premixed insulin formulations in the outpatient setting (77), an inpatient study of 70/30 NPH/regular insulin versus basal-bolus therapy showed comparable glycemic outcomes but significantly increased hypoglycemia in the group receiving insulin mixtures (78). Therefore, insulin mixtures such as 75/25 or 70/30 insulins are not routinely recommended for in-hospital use.

Type 1 Diabetes

For people with type 1 diabetes, dosing insulin based solely on premeal glucose levels does not account for basal insulin requirements or caloric intake, increasing the risk of both hypoglycemia and hyperglycemia. Typically, basal insulin dosing is based on body weight, with some evidence that people with renal insufficiency should be treated with lower doses (79,80). An insulin schedule with basal and correction components is necessary for all hospitalized individuals with type 1 diabetes, even when taking nothing by mouth, with the addition of prandial insulin when eating.

Transitioning From Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is associated with less morbidity and lower costs of care (81,82) and is therefore recommended. A person with type 1 or type 2 diabetes being transitioned to a subcutaneous regimen should receive a dose of subcutaneous basal insulin 2 h before the intravenous infusion is discontinued. Prior to discontinuing an insulin infusion, initiation of subcutaneous basal insulin may

help minimize hyperglycemia and avoid rebound hypoglycemia (83,84). The dose of basal insulin is best calculated on the basis of the insulin infusion rate during the last 6 h when stable glycemic goals were achieved (85). For people being transitioned to concentrated insulin (U-200, U-300, or U-500) in the inpatient setting, it is important to ensure correct dosing by utilizing an individual pen or cartridge for each person and by meticulous pharmacy and nursing supervision of the dose administered (85,86).

Noninsulin Therapies

The safety and efficacy of noninsulin glucose-lowering therapies in the hospital setting is an area of active research (73,87–89). Several recent randomized trials have demonstrated the potential effectiveness of glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors in specific groups of hospitalized people with diabetes (90–93). However, an FDA bulletin states that health care professionals should consider discontinuing saxagliptin and alogliptin in people who develop heart failure (94).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors should be avoided in cases of severe illness, in people with ketonemia or ketonuria, and during prolonged fasting and surgical procedures (4). Until safety and efficacy are established, SGLT2 inhibitors are not recommended for routine in-hospital use for diabetes management, although they may be considered for the treatment of people with type 2 diabetes who have or are at risk for heart failure (95). Furthermore, the FDA has warned that SGLT2 inhibitors should be stopped 3 days before scheduled surgeries (4 days in the case of ertugliflozin) (96).

HYPOGLYCEMIA

Recommendations

16.9 A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system. A plan for preventing and treating hypoglycemia should be established for each individual. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked for quality improvement/quality assessment. **E**

16.10 Treatment regimens should be reviewed and changed as necessary to prevent further hypoglycemia when a blood glucose value of <70 mg/dL (3.9 mmol/L) is documented. **C**

People with or without diabetes may experience hypoglycemia in the hospital setting. While hypoglycemia is associated with increased mortality (97), in many cases, it is a marker of an underlying disease rather than the cause of fatality. However, hypoglycemia is a severe consequence of dysregulated metabolism and/or diabetes treatment, and it is imperative that it be minimized during hospitalization. Many episodes of inpatient hypoglycemia are preventable. Therefore, a hypoglycemia prevention and management protocol should be adopted and implemented by each hospital or hospital system. A standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol should be in place to immediately address blood glucose levels of <70 mg/dL (3.9 mmol/L) (98,99). In addition, individualized plans for preventing and treating hypoglycemia for each individual should also be developed. An American Diabetes Association consensus statement recommends that an individual's treatment plan be reviewed any time a blood glucose value of <70 mg/dL (3.9 mmol/L) occurs, as such readings often predict subsequent level 3 hypoglycemia. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked (1,2).

Triggering Events and Prevention of Hypoglycemia

Insulin is one of the most common drugs causing adverse events in hospitalized patients, and errors in insulin dosing and/or administration occur relatively frequently (97,100,101). Beyond insulin dosing errors, common preventable sources of iatrogenic hypoglycemia are improper prescribing of other glucose-lowering medications, inappropriate management of the first episode of hypoglycemia, and nutrition–insulin mismatch, often related to an unexpected interruption of nutrition (102). A recent study describes acute kidney injury as an important risk factor for hypoglycemia in

the hospital (103), possibly as a result of decreased insulin clearance. Studies of “bundled” preventive therapies, including proactive surveillance of glycemic outliers and an interdisciplinary data-driven approach to glycemic management, showed that hypoglycemic episodes in the hospital could be prevented. Compared with baseline, two such studies found that hypoglycemic events fell by 56–80% (99,104,105). The Joint Commission recommends that all hypoglycemic episodes be evaluated for a root cause and the episodes be aggregated and reviewed to address systemic issues (31).

In addition to errors with insulin treatment, iatrogenic hypoglycemia may be induced by a sudden reduction of corticosteroid dose, reduced oral intake, emesis, inappropriate timing of short- or rapid-acting insulin in relation to meals, reduced infusion rate of intravenous dextrose, unexpected interruption of enteral or parenteral feedings, delayed or missed blood glucose checks, and altered ability of the individual to report symptoms (106).

Recent inpatient CGM studies show promise for CGM as an early warning system to alert of impending hypoglycemia, offering an opportunity to mitigate it before it happens (60–63). The use of personal CGM and automated insulin delivery devices, such as insulin pumps that can automatically deliver correction doses and change basal delivery rates in real time, should be supported for ongoing use during hospitalization for individuals who are capable of using devices safely and independently when proper supervision is available. Hospitals should be encouraged to develop policies and protocols to support inpatient use of individual- and hospital-owned diabetes technology and have expert staff available for safe implementation. Hospital information technology teams are beginning to integrate CGM data into the electronic health record. The ability to download and interpret diabetes device data during hospitalization can inform insulin dosing during hospitalization and care transitions (107).

For more information on CGM, see Section 7, “Diabetes Technology.”

Predictors of Hypoglycemia

In people with diabetes in the ambulatory setting, it is well established that an episode of severe hypoglycemia increases

the risk for a subsequent event, partly because of impaired counterregulation (108,109). This relationship also holds true for people with diabetes in the inpatient setting. For example, in a study of hospitalized individuals treated for hyperglycemia, 84% who had an episode of “severe hypoglycemia” (defined in the study as <40 mg/dL [2.2 mmol/L]) had a preceding episode of hypoglycemia (<70 mg/dL [3.9 mmol/L]) during the same admission (110). In another study of hypoglycemic episodes (defined in the study as <50 mg/dL [2.8 mmol/L]), 78% of patients were using basal insulin, with the incidence of hypoglycemia peaking between midnight and 6:00 A.M. Despite recognition of hypoglycemia, 75% of individuals did not have their dose of basal insulin changed before the next insulin administration (111).

Recently, several groups have developed algorithms to predict episodes of hypoglycemia in the inpatient setting (112,113). Models such as these are potentially important and, once validated for general use, could provide a valuable tool to reduce rates of hypoglycemia in the hospital. In one retrospective cohort study data, a fasting blood glucose of <100 mg/dL was shown to be a predictor of next-day hypoglycemia (44).

MEDICAL NUTRITION THERAPY IN THE HOSPITAL

The goals of medical nutrition therapy in the hospital are to provide adequate calories to meet metabolic demands, optimize glycemic outcomes, address personal food preferences, and facilitate the creation of a discharge plan. The American Diabetes Association does not endorse any single meal plan or specified percentages of macronutrients. Current nutrition recommendations advise individualization based on treatment goals, physiological parameters, and medication use. Consistent carbohydrate meal plans are preferred by many hospitals as they facilitate matching the prandial insulin dose to the amount of carbohydrate given (114). Orders should also indicate that the meal delivery and nutritional insulin coverage should be coordinated, as their variability often creates the possibility of hyperglycemic and hypoglycemic events (28). Many hospitals offer “meals on demand,” where individuals may order meals from

the menu at any time during the day. This option improves patient satisfaction but complicates meal-insulin coordination. Finally, if the hospital food service supports carbohydrate counting, this option should be made available to people with diabetes counting carbohydrates at home (115,116).

SELF-MANAGEMENT IN THE HOSPITAL

Diabetes self-management in the hospital may be appropriate for specific individuals who wish to continue to perform self-care while acutely ill (117,118). Candidates include children with parental supervision, adolescents, and adults who successfully perform diabetes self-management at home and whose cognitive and physical skills needed to successfully self-administer insulin and perform glucose monitoring are not compromised (9,119). In addition, they should have adequate oral intake, be proficient in carbohydrate estimation, take multiple daily insulin injections or use insulin pumps, have stable insulin requirements, and understand sick-day management. If self-management is supported, a policy should include a requirement that people with diabetes and the care team agree that self-management is appropriate on a daily basis during hospitalization. Hospital personal medication policies may include guidance for people with diabetes who wish to take their own or hospital-dispensed diabetes medications during their hospital stay. A hospital policy for personal medication may consider a pharmacy exception on a case-by-case basis along with the care team. Pharmacy must verify any home medication and require a prescriber order for the individual to self-administer home or hospital-dispensed medication under the supervision of the registered nurse. If an insulin pump or CGM is worn, hospital policy and procedures delineating guidelines for wearing an insulin pump and/or CGM device should be developed according to consensus guidelines, including the changing of infusion sites and glucose sensors (107,120,121). As outlined in Recommendation 7.30, people with diabetes wearing diabetes devices should be supported to continue them in an inpatient setting when they are competent to perform self-care and proper supervision is available.

STANDARDS FOR SPECIAL SITUATIONS

Enteral/Parenteral Feedings

For individuals receiving enteral or parenteral feedings who require insulin, the insulin orders should include coverage of basal, prandial, and correctional needs (115,122,123). It is essential that people with type 1 diabetes continue to receive basal insulin even if feedings are discontinued.

Most adults receiving basal insulin should continue with their basal dose, while the insulin dose for the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g carbohydrate in the enteral and parenteral formulas. Commercially available cans of enteral nutrition contain variable amounts of carbohydrates and may be infused at different rates. All of this must be considered while calculating insulin doses to cover the nutritional component of enteral nutrition (116). Giving NPH insulin two or three times daily (every 8 or 12 h) to cover individual requirements is a reasonable option. Adjustments in insulin doses should be made frequently. Correctional insulin should also be administered subcutaneously every 6 h with human regular insulin or every 4 h with a rapid-acting insulin analog. If enteral nutrition is interrupted, a 10% dextrose infusion should be started immediately to prevent hypoglycemia and to allow time to select more appropriate insulin doses.

For adults receiving enteral bolus feedings, approximately 1 unit of regular human insulin or rapid-acting insulin per 10–15 g carbohydrate should be given subcutaneously before each feeding. Correctional insulin coverage should be added as needed before each feeding.

In individuals receiving nocturnal tube feeding, NPH insulin administered with the initiation of the feeding represents a reasonable approach to cover this nutritional load.

For individuals receiving continuous peripheral or central parenteral nutrition, human regular insulin may be added to the solution, particularly if >20 units of correctional insulin have been required in the past 24 h. A starting dose of 1 unit of human regular insulin for every 10 g dextrose has been recommended (115) and should be adjusted daily in the solution. Adding insulin to the parenteral

nutrition bag is the safest way to prevent hypoglycemia if the parenteral nutrition is stopped or interrupted. Correctional insulin should be administered subcutaneously to address any hyperglycemia. For full enteral/parenteral feeding guidance, please refer to review articles detailing this topic (122,124,125).

Because continuous enteral or parenteral nutrition results in a continuous postprandial state, efforts to bring blood glucose levels to below 140 mg/dL (7.8 mmol/L) substantially increase the risk of hypoglycemia in these patients.

Glucocorticoid Therapy

The prevalence of consistent use of glucocorticoid therapy in hospitalized patients can approach 10%, and these medications can induce hyperglycemia in 56–86% of these individuals with and without preexisting diabetes (126,127). If left untreated, this hyperglycemia increases mortality and morbidity risk, e.g., infections and cardiovascular events. Glucocorticoid type and duration of action must be considered in determining appropriate insulin treatments. Daily-ingested intermediate-acting glucocorticoids such as prednisone reach peak plasma levels in 4–6 h (128) but have pharmacologic actions that can last through the day. Individuals placed on morning steroid therapy have disproportionate hyperglycemia during the day but frequently reach target blood glucose levels overnight regardless of treatment (126). In subjects on once- or twice-daily steroids, administering intermediate-acting (NPH) insulin is a standard approach. NPH is usually administered in addition to daily basal-bolus insulin or in addition to oral glucose-lowering medications. Because NPH action peaks at 4–6 h after administration, it is recommended to administer it concomitantly with intermediate-acting steroids (129). For long-acting glucocorticoids such as dexamethasone and multidose or continuous glucocorticoid use, long-acting basal insulin may be required to manage fasting blood glucose levels (65,130). For higher doses of glucocorticoids, increasing doses of prandial (if eating) and correctional insulin, sometimes as much as 40–60% or more, are often needed in addition to basal insulin (72,131,132). A single-center retrospective study found that increasing the ratio of insulin to steroids was positively associated with

improved time in range (70–180 mg/dL); however, there was an increase in hypoglycemia (133). Whatever insulin orders are initiated, daily adjustments based on levels of glycemia and anticipated changes in type, doses, and duration of glucocorticoids, along with POC blood glucose monitoring, are critical to reducing rates of hypoglycemia and hyperglycemia.

Perioperative Care

It is estimated that up to 20% of general surgery patients have diabetes, and 23–60% have prediabetes or undiagnosed diabetes. Surgical stress and counterregulatory hormone release increase the risk of hyperglycemia as well as mortality, infection, and length of stay (134). There is little data available to guide care of people with diabetes through the perioperative period. To reduce surgical risk in people with diabetes, some institutions have A1C cutoffs for elective surgeries, and some have developed optimization programs to lower A1C before surgery (135).

The following approach (136–138) may be considered:

1. A preoperative risk assessment should be performed for people with diabetes who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
2. The A1C target for elective surgeries should be <8% (63.9 mmol/L) whenever possible (139,140).
3. The target range for blood glucose in the perioperative period should be 100–180 mg/dL (5.6–10.0 mmol/L) (139) within 4 h of the surgery (1).
4. Metformin should be held on the day of surgery.
5. SGLT2 inhibitors must be discontinued 3–4 days before surgery.
6. Hold any other oral glucose-lowering agents the morning of surgery or procedure and give half of NPH dose or 75–80% doses of long-acting analog or insulin pump basal insulin based on the type of diabetes and clinical judgment.
7. Monitor blood glucose at least every 2–4 h while the individual takes nothing by mouth and dose with short- or rapid-acting insulin as needed.
8. There are no data on the use and/or influence of glucagon-like peptide 1 receptor agonists or ultra-long-acting

insulin analogs on glycemia in perioperative care.

A recent review concluded that perioperative glycemic targets tighter than 80–180 mg/dL (4.4–10.0 mmol/L) did not improve outcomes and was associated with more hypoglycemia (137); therefore, in general, stricter glycemic targets are not advised. Evidence from a recent study indicates that compared with usual dosing, a reduction of insulin given the evening before surgery by ~25% was more likely to achieve perioperative blood glucose levels in the target range with a lower risk for hypoglycemia (141).

In noncardiac general surgery patients, basal insulin plus premeal short- or rapid-acting insulin (basal-bolus) coverage has been associated with improved glycemic outcomes and lower rates of perioperative complications compared with the reactive, correction-only short- or rapid-acting insulin coverage alone with no basal insulin dosing (74,134,142).

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

There is considerable variability in the presentation of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic states, ranging from euglycemia or mild hyperglycemia and acidosis to severe hyperglycemia, dehydration, and coma; therefore, individualization of treatment based on a careful clinical and laboratory assessment is needed (83,143–145).

Management goals include restoration of circulatory volume and tissue perfusion, resolution of hyperglycemia, and correction of electrolyte imbalance and acidosis. It is also essential to treat any correctable underlying cause of DKA, such as sepsis, myocardial infarction, or stroke. In critically ill and mentally obtunded individuals with DKA or hyperosmolar hyperglycemia, continuous intravenous insulin is the standard of care. Successful transition from intravenous to subcutaneous insulin requires administration of basal insulin 2–4 h before the intravenous insulin is stopped to prevent recurrence of ketoacidosis and rebound hyperglycemia (143). There is no significant difference in outcomes for intravenous human regular insulin versus subcutaneous rapid-acting analogs when combined with aggressive fluid management for treating mild or moderate DKA

(146). Individuals with uncomplicated DKA may sometimes be treated with subcutaneous insulin in the emergency department or step-down units (147). This approach may be safer and more cost-effective than treatment with intravenous insulin. If subcutaneous insulin administration is used, it is important to provide an adequate fluid replacement, frequent POC blood glucose monitoring, treatment of any concurrent infections, and appropriate follow-up to avoid recurrent DKA. Several studies have shown that the use of bicarbonate in patients with DKA made no difference in the resolution of acidosis or time to discharge, and its use is generally not recommended (148). For further treatment information, refer to recent in-depth reviews (4,106,149).

TRANSITION FROM THE HOSPITAL TO THE AMBULATORY SETTING

Recommendation

16.11 A structured discharge plan should be tailored to the individual with diabetes. **B**

A structured discharge plan tailored to the individual may reduce the length of hospital stay and readmission rates and increase satisfaction with the hospital experience (150). Multiple strategies are key, including diabetes education prior to discharge, diabetes medication reconciliation with attention to access, and scheduled virtual and/or face-to-face follow-up visits after discharge. Discharge planning should begin at admission and be updated as individual needs change (3,151).

The transition from the acute care setting presents risks for all people with diabetes. Individuals may be discharged to varied settings, including home (with or without visiting nurse services), assisted living, rehabilitation, or skilled nursing facilities. For individuals discharged to home or assisted living, the optimal discharge plan will need to consider diabetes type and severity, effects of the illness on blood glucose levels, and the individual's capabilities and preferences (29,152,153). See Section 13, "Older Adults," for more information.

An outpatient follow-up visit with the primary care clinician, endocrinologist, or diabetes care and education specialist

within 1 month of discharge is advised for all individuals experiencing hyperglycemia in the hospital. If glycemic medications are changed or glucose management is not optimal at discharge, an earlier appointment (in 1–2 weeks) is preferred, and frequent contact may be needed to avoid hyperglycemia and hypoglycemia. A discharge algorithm for glycemic medication adjustment based on admission A1C, diabetes medications before admission, and insulin usage during hospitalization was found useful to guide treatment decisions and significantly improved A1C after discharge (6). If an A1C from the prior 3 months is unavailable, measuring the A1C in all people with diabetes or hyperglycemia admitted to the hospital is recommended upon admission.

Clear communication with outpatient health care professionals directly or via hospital discharge summaries facilitates safe transitions to outpatient care. Providing information regarding the root cause of hyperglycemia (or the plan for determining the cause), related complications and comorbidities, and recommended treatments can assist outpatient health care professionals as they assume ongoing care.

The Agency for Healthcare Research and Quality recommends that, at a minimum, discharge plans include the following (154):

Medication Reconciliation

- Home and hospital medications must be cross-checked to ensure that no chronic medications are stopped and to ensure the safety of new and old prescriptions.
- Prescriptions for new or changed medication should be filled and reviewed with the individual and care partners at or before discharge.

Structured Discharge Communication

- Information on medication changes, pending tests and studies, and follow-up needs must be accurately and promptly communicated to outpatient health care professionals.
- Discharge summaries should be transmitted to the primary care clinician as soon as possible after discharge.
- Scheduling follow-up appointments prior to discharge with people with diabetes agreeing to the time and

place increases the likelihood that they will attend.

It is recommended that the following areas of knowledge be reviewed and addressed before hospital discharge:

- Identification of the health care professionals who will provide diabetes care after discharge.
- Level of understanding related to the diabetes diagnosis, glucose monitoring, home glucose goals, and when to call the health care professionals.
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia.
- Information on making healthy food choices at home and referral to an outpatient registered dietitian nutritionist or diabetes care and education specialist to guide individualization of the meal plan, if needed.
- When and how to take blood glucose-lowering medications, including insulin administration.
- Sick-day management (29,153).
- Proper use and disposal of diabetes supplies, e.g., insulin pen, pen needles, syringes, and lancets.

People with diabetes must be provided with appropriate durable medical equipment, medications, supplies (e.g., blood glucose test strips or CGM sensors), prescriptions, and appropriate education at the time of discharge to avoid a potentially dangerous hiatus in care.

PREVENTING ADMISSIONS AND READMISSIONS

In people with diabetes, the hospital readmission rate is between 14 and 20%, nearly twice that in people without diabetes (151,155). This may result in increased diabetes distress and has significant financial implications. Of people with diabetes who are hospitalized, 30% have two or more hospital stays, and these admissions account for over 50% of hospital costs for diabetes (156). Factors contributing to readmission include male sex, longer duration of prior hospitalization, number of previous hospitalizations, number and severity of comorbidities, and lower socioeconomic and/or educational status; scheduled home health visits and timely ambulatory follow-up

care reduce readmission rates (151,155). While there is no standard to prevent readmissions, several successful strategies have been reported (151). These include targeting ketosis-prone people with type 1 diabetes (157), insulin treatment of individuals with admission A1C >9% (75 mmol/mol) (158), and the use of a transitional care model (159). For people with diabetic kidney disease, collaborative patient-centered medical homes may decrease risk-adjusted readmission rates (160). A 2018 published algorithm based on demographic and clinical characteristics of people with diabetes had only moderate predictive power but identified a promising future strategy (161).

Age is also an important risk factor in hospitalization and readmission among people with diabetes (refer to Section 13, “Older Adults,” for detailed criteria).

References

1. Seisa MO, Saadi S, Nayfeh T, et al. A systematic review supporting the Endocrine Society clinical practice guideline for the management of hyperglycemia in adults hospitalized for noncritical illness or undergoing elective surgical procedures. *J Clin Endocrinol Metab* 2022;107:2139–2147
2. Korytkowski MT, Muniyappa R, Antinori-Lent K, et al. Management of hyperglycemia in hospitalized adult patients in non-critical care settings: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2022;107:2101–2128
3. Rubin DJ, Shah AA. Predicting and preventing acute care re-utilization by patients with diabetes. *Curr Diab Rep* 2021;21:34
4. Moghissi E, Inzucchi S. The evolution of glycemic control in the hospital setting. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Draznin B, Ed. Alexandria, VA, American Diabetes Association, 2016, pp. 1–10
5. Pasquel FJ, Gomez-Huelgas R, Anzola I, et al. Predictive value of admission hemoglobin a1c on inpatient glycemic control and response to insulin therapy in medicine and surgery patients with type 2 diabetes. *Diabetes Care* 2015;38:e202–e203
6. Umpierrez GE, Reyes D, Smiley D, et al. Hospital discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes. *Diabetes Care* 2014;37:2934–2939
7. Carpenter DL, Gregg SR, Xu K, Buchman TG, Coopersmith CM. Prevalence and impact of unknown diabetes in the ICU. *Crit Care Med* 2015;43:e541–e550
8. Nanayakkara N, Nguyen H, Churilov L, et al. Inpatient HbA1c testing: a prospective observational study. *BMJ Open Diabetes Res Care* 2015;3:e000113
9. Nassar CM, Montero A, Magee MF. Inpatient diabetes education in the real world: an overview of guidelines and delivery models. *Curr Diab Rep* 2019;19:103
10. Donihi AC. Practical recommendations for transitioning patients with type 2 diabetes from hospital to home. *Curr Diab Rep* 2017;17:52

11. Garg R, Schuman B, Bader A, et al. Effect of preoperative diabetes management on glycemic control and clinical outcomes after elective surgery. *Ann Surg* 2018;267:858–862
12. van den Boom W, Schroeder RA, Manning MW, Setji TL, Fiestan GO, Dunson DB. Effect of A1C and glucose on postoperative mortality in noncardiac and cardiac surgeries. *Diabetes Care* 2018;41:782–788
13. Setji T, Hopkins TJ, Jimenez M, et al. Rationalization, development, and implementation of a preoperative diabetes optimization program designed to improve perioperative outcomes and reduce cost. *Diabetes Spectr* 2017;30:217–223
14. Okabayashi T, Shima Y, Sumiyoshi T, et al. Intensive versus intermediate glucose control in surgical intensive care unit patients. *Diabetes Care* 2014;37:1516–1524
15. Institute of Medicine. *Preventing Medication Errors*. Aspden P, Wolcott J, Bootman JL, Cronenwett LR, Eds. Washington, DC, National Academies Press, 2007
16. Gillaizeau F, Chan E, Trinquart L, et al. Computerized advice on drug dosage to improve prescribing practice. *Cochrane Database Syst Rev* 2013;11:CD002894
17. Sly B, Russell AW, Sullivan C. Digital interventions to improve safety and quality of inpatient diabetes management: a systematic review. *Int J Med Inform* 2022;157:104596
18. Wexler DJ, Shrader P, Burns SM, Cagliero E. Effectiveness of a computerized insulin order template in general medical inpatients with type 2 diabetes: a cluster randomized trial. *Diabetes Care* 2010;33:2181–2183
19. Schnipper JL, Liang CL, Ndumele CD, Pendergrass ML. Effects of a computerized order set on the inpatient management of hyperglycemia: a cluster-randomized controlled trial. *Endocr Pract* 2010;16:209–218
20. Nguyen M, Jankovic I, Kalesinskas L, Baiocchi M, Chen JH. Machine learning for initial insulin estimation in hospitalized patients. *J Am Med Inform Assoc* 2021;28:2212–2219
21. Akiboye F, Sihre HK, Al Mulhem M, Rayman G, Nirantharakumar K, Adderley NJ. Impact of diabetes specialist nurses on inpatient care: a systematic review. *Diabet Med* 2021;38:e14573
22. Wang YJ, Seggelke S, Hawkins RM, et al. Impact of glucose management team on outcomes of hospitalization in patients with type 2 diabetes admitted to the medical service. *Endocr Pract* 2016;22:1401–1405
23. Draznin B, Gilden J, Golden SH, et al.; PRIDE investigators. Pathways to quality inpatient management of hyperglycemia and diabetes: a call to action. *Diabetes Care* 2013;36:1807–1814
24. Bansal V, Mottalib A, Pawar TK, et al. Inpatient diabetes management by specialized diabetes team versus primary service team in non-critical care units: impact on 30-day readmission rate and hospital cost. *BMJ Open Diabetes Res Care* 2018;6:e000460
25. Ostling S, Wyckoff J, Ciarkowski SL, et al. The relationship between diabetes mellitus and 30-day readmission rates. *Clin Diabetes Endocrinol* 2017;3:3
26. Rushakoff RJ, Sullivan MM, MacMaster HW, et al. Association between a virtual glucose management service and glycemic control in hospitalized adult patients: an observational study. *Ann Intern Med* 2017;166:621–627
27. Endocrine Society. Clinical Practice Guidelines. Accessed 30 August 2022. Available from <https://www.endocrine.org/clinical-practice-guidelines>
28. Magee MF, Baker KM, Bardsley JK, Wesley D, Smith KM. Diabetes to go-inpatient: pragmatic lessons learned from implementation of technology-enabled diabetes survival skills education within nursing unit workflow in an urban, tertiary care hospital. *Jt Comm J Qual Patient Saf* 2021;47:107–119
29. Pinkhasova D, Swami JB, Patel N, et al. Patient understanding of discharge instructions for home diabetes self-management and risk for hospital readmission and emergency department visits. *Endocr Pract* 2021;27:561–566
30. Society of Hospital Medicine. Glycemic control for hospitalists. Accessed 30 August 2022. Available from <https://www.hospitalmedicine.org/clinical-topics/glycemic-control/>
31. Arnold P, Scheurer D, Dake AW, et al. Hospital guidelines for diabetes management and the Joint Commission-American Diabetes Association Inpatient Diabetes Certification. *Am J Med Sci* 2016;351:333–341
32. Association of British Diabetologists. Joint British Diabetes Societies (JBDS) for Inpatient Care Group. Accessed 7 October 2022. Available from <https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group>
33. Moghissi ES, Korytkowski MT, DiNardo M, et al.; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009;32:1119–1131
34. Umpierrez GE, Hellman R, Korytkowski MT, et al.; Endocrine Society. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:16–38
35. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA_{1c} for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care* 2017;40:1622–1630
36. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359–1367
37. Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283–1297
38. Kansagara D, Fu R, Freeman M, Wolf F, Helfand M. Intensive insulin therapy in hospitalized patients: a systematic review. *Ann Intern Med* 2011;154:268–282
39. Sathya B, Davis R, Taveira T, Whitlatch H, Wu WC. Intensity of peri-operative glycemic control and postoperative outcomes in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2013;102:8–15
40. Umpierrez G, Cardona S, Pasquel F, et al. randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG trial. *Diabetes Care* 2015;38:1665–1672
41. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract* 2004;10(Suppl. 2):21–33
42. Low Wang CC, Draznin B. Practical approach to management of inpatient hyperglycemia in select patient populations. *Hosp Pract* (1995) 2013;41:45–53
43. Magaji V, Nayak S, Donihi AC, et al. Comparison of insulin infusion protocols targeting 110–140 mg/dL in patients after cardiac surgery. *Diabetes Technol Ther* 2012;14:1013–1017
44. Flory JH, Aleman JO, Furst J, Seley JJ. Basal insulin use in the non-critical care setting: is fasting hypoglycemia inevitable or preventable? *J Diabetes Sci Technol* 2014;8:427–428
45. Cobaugh DJ, Maynard G, Cooper L, et al. Enhancing insulin-use safety in hospitals: Practical recommendations from an ASHP Foundation expert consensus panel. *Am J Health Syst Pharm* 2013;70:1404–1413
46. Rice MJ, Coursin DB. Glucose meters: here today, gone tomorrow? *Crit Care Med* 2016;44:e97–e100
47. Rice MJ, Smith JL, Coursin DB. Glucose measurement in the ICU: regulatory intersects reality. *Crit Care Med* 2017;45:741–743
48. Klonoff DC, Draznin B, Drincic A, et al. PRIDE statement on the need for a moratorium on the CMS plan to cite hospitals for performing point-of-care capillary blood glucose monitoring on critically ill patients. *J Clin Endocrinol Metab* 2015;100:3607–3612
49. DuBois JA, Slingerland RJ, Fokkert M, et al. Bedside glucose monitoring—is it safe? A new, regulatory-compliant risk assessment evaluation protocol in critically ill patient care settings. *Crit Care Med* 2017;45:567–574
50. Zhang R, Isakow W, Kolfel MH, Scott MG. Performance of a modern glucose meter in ICU and general hospital inpatients: 3 years of real-world paired meter and central laboratory results. *Crit Care Med* 2017;45:1509–1514
51. Wallia A, Prince G, Touma E, El Muayed M, Seley JJ. Caring for hospitalized patients with diabetes mellitus, hyperglycemia, and COVID-19: bridging the remaining knowledge gaps. *Curr Diab Rep* 2020;20:77
52. Aljehani FA, Funke K, Hermayer KL. Inpatient diabetes and hyperglycemia management protocol in the COVID-19 era. *Am J Med Sci* 2020;360:423–426
53. Pasquel FJ, Umpierrez GE. Individualizing inpatient diabetes management during the coronavirus disease 2019 pandemic. *J Diabetes Sci Technol* 2020;14:705–707
54. Ceriello A, Standl E, Catrinou D, et al.; “Diabetes and Cardiovascular Disease (D&CVD)” Study Group of the European Association for the Study of Diabetes (EASD). Issues for the management of people with diabetes and COVID-19 in ICU. *Cardiovasc Diabetol* 2020;19:114
55. Korytkowski M, Antinori-Lent K, Drincic A, et al. A pragmatic approach to inpatient diabetes management during the COVID-19 pandemic. *J Clin Endocrinol Metab* 2020;105:dga342
56. Sadhu AR, Serrano IA, Xu J, et al. Continuous glucose monitoring in critically ill patients with

- COVID-19: results of an emergent pilot study. *J Diabetes Sci Technol* 2020;14:1065–1073
57. Galindo RJ, Aleppo G, Klonoff DC, et al. Implementation of continuous glucose monitoring in the hospital: emergent considerations for remote glucose monitoring during the COVID-19 pandemic. *J Diabetes Sci Technol* 2020;14:822–832
58. Agarwal S, Mathew J, Davis GM, et al. continuous glucose monitoring in the intensive care unit during the COVID-19 pandemic. *Diabetes Care* 2021;44:847–849
59. Faulds ER, Jones L, McNett M, et al. Facilitators and barriers to nursing implementation of continuous glucose monitoring (CGM) in critically ill patients with COVID-19. *Endocr Pract* 2021;27:354–361
60. Longo RR, Elias H, Khan M, Seley JJ. Use and accuracy of inpatient CGM during the COVID-19 pandemic: an observational study of general medicine and ICU patients. *J Diabetes Sci Technol* 2021;16:1136–1143
61. Davis GM, Spanakis EK, Migdal AL, et al. Accuracy of Dexcom G6 continuous glucose monitoring in non-critically ill hospitalized patients with diabetes. *Diabetes Care* 2021;44:1641–1646
62. Baker M, Musselman ME, Rogers R, Hellman R. Practical implementation of remote continuous glucose monitoring in hospitalized patients with diabetes. *Am J Health Syst Pharm* 2022;79:452–458
63. Wright JJ, Williams AJ, Friedman SB, et al. Accuracy of continuous glucose monitors for inpatient diabetes management. *J Diabetes Sci Technol*. 7 February 2022 [Epub ahead of print]. DOI: 10.1177/19322968221076562
64. Braithwaite SS, Clark LP, Idrees T, Qureshi F, Soetan OT. hypoglycemia prevention by algorithm design during intravenous insulin infusion. *Curr Diab Rep* 2018;18:26
65. Maynard G, Wesorick DH, O'Malley C; Society of Hospital Medicine Glycemic Control Task Force. Subcutaneous insulin order sets and protocols: effective design and implementation strategies. *J Hosp Med* 2008;3(Suppl.):29–41
66. Brown KE, Hertig JB. Determining current insulin pen use practices and errors in the inpatient setting. *Jt Comm J Qual Patient Saf* 2016;42:568–575, AP1–AP7
67. Horne J, Bond R, Sarangam P. Comparison of inpatient glycemic control with insulin vials versus insulin pens in general medicine patients. *Hosp Pharm* 2015;50:514–521
68. Veronesi G, Poerio CS, Braus A, et al. Determinants of nurse satisfaction using insulin pen devices with safety needles: an exploratory factor analysis. *Clin Diabetes Endocrinol* 2015;1:15
69. Najmi U, Haque WZ, Ansari U, et al. Inpatient insulin pen implementation, waste, and potential cost savings: a community hospital experience. *J Diabetes Sci Technol* 2021;15:741–747
70. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA requires label warnings to prohibit sharing of multi-dose diabetes pen devices among patients. Accessed 23 October 2022. Available from <https://www.fda.gov/Drugs/DrugSafety/ucm435271.htm>
71. Bueno E, Benitez A, Rufinelli JV, et al. Basal-bolus regimen with insulin analogues versus human insulin in medical patients with type 2 diabetes: a randomized controlled trial in Latin America. *Endocr Pract* 2015;21:807–813
72. Dhataria K, Corsino L, Umpierrez GE. Management of diabetes and hyperglycemia in hospitalized patients. In: Feingold KR, Anawalt B, Boyce A, et al., Eds. *Endotext*. South Dartmouth, MA, MDText.com, Inc. Accessed 30 August 2022. Available from <https://www.ncbi.nlm.nih.gov/books/NBK279093/>
73. Sadhu AR, Patham B, Vadhariya A, Chikermane SG, Johnson ML. Outcomes of “real-world” insulin strategies in the management of hospital hyperglycemia. *J Endocr Soc* 2021;5:bvab101
74. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011;34:256–261
75. Colunga-Lozano LE, Gonzalez Torres FJ, Delgado-Figueroa N, et al. Sliding scale insulin for non-critically ill hospitalized adults with diabetes mellitus. *Cochrane Database Syst Rev* 2018;11:CD011296
76. Migdal AL, Fortin-Leung C, Pasquel F, Wang H, Peng L, Umpierrez GE. Inpatient glycemic control with sliding scale insulin in noncritical patients with type 2 diabetes: who can slide? *J Hosp Med* 2021;16:462–468
77. Giugliano D, Chiodini P, Maiorino MI, Bellastella G, Esposito K. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Endocrine* 2016;51:417–428
78. Bellido V, Suarez L, Rodriguez MG, et al. Comparison of basal-bolus and premixed insulin regimens in hospitalized patients with type 2 diabetes. *Diabetes Care* 2015;38:2211–2216
79. Baldwin D, Zander J, Munoz C, et al. A randomized trial of two weight-based doses of insulin glargine and glulisine in hospitalized subjects with type 2 diabetes and renal insufficiency. *Diabetes Care* 2012;35:1970–1974
80. Iyengar R, Franzese J, Gianchandani R. Inpatient glycemic management in the setting of renal insufficiency/failure/dialysis. *Curr Diab Rep* 2018;18:75
81. Shomali ME, Herr DL, Hill PC, Pehlivanova M, Sharretts JM, Magee MF. Conversion from intravenous insulin to subcutaneous insulin after cardiovascular surgery: transition to target study. *Diabetes Technol Ther* 2011;13:121–126
82. Draznin B. Transitioning from intravenous to subcutaneous insulin. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Alexandria, VA, American Diabetes Association, 2016, p. 115–128
83. Hsia E, Seggelke S, Gibbs J, et al. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. *J Clin Endocrinol Metab* 2012;97:3132–3137
84. Lim Y, Ohn JH, Jeong J, et al. Effect of the concomitant use of subcutaneous basal insulin and intravenous insulin infusion in the treatment of severe hyperglycemic patients. *Endocrinol Metab (Seoul)* 2022;37:444–454
85. Tripathy PR, Lansang MC. U-500 regular insulin use in hospitalized patients. *Endocr Pract* 2015;21:54–58
86. Lansang MC, Umpierrez GE. Inpatient hyperglycemia management: a practical review for primary medical and surgical teams. *Cleve Clin J Med* 2016;83(Suppl. 1):S34–S43
87. Umpierrez GE, Gianchandani R, Smiley D, et al. Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized, controlled study. *Diabetes Care* 2013;36:3430–3435
88. Pasquel FJ, Fayman M, Umpierrez GE. Debate on insulin vs non-insulin use in the hospital setting—is it time to revise the guidelines for the management of inpatient diabetes? *Curr Diab Rep* 2019;19:65
89. Pasquel FJ, Lansang MC, Dhataria K, Umpierrez GE. Management of diabetes and hyperglycemia in the hospital. *Lancet Diabetes Endocrinol* 2021;9:174–188
90. Fushimi N, Shibuya T, Yoshida Y, Ito S, Hachiya H, Mori A. Dulaglutide-combined basal plus correction insulin therapy contributes to ideal glycemic control in non-critical hospitalized patients. *J Diabetes Investig* 2020;11:125–131
91. Fayman M, Galindo RJ, Rubin DJ, et al. A randomized controlled trial on the safety and efficacy of exenatide therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes. *Diabetes Care* 2019;42:450–456
92. Pérez-Belmonte LM, Osuna-Sánchez J, Millán-Gómez M, et al. Glycaemic efficacy and safety of linagliptin for the management of non-cardiac surgery patients with type 2 diabetes in a real-world setting: Lina-Surg study. *Ann Med* 2019;51:252–261
93. Vellanki P, Rasouli N, Baldwin D, et al. Glycaemic efficacy and safety of linagliptin compared to basal-bolus insulin regimen in patients with type 2 diabetes undergoing non-cardiac surgery: a multicenter randomized clinical trial. *Diabetes Obes Metab* 2019;21:837–843
94. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Accessed 23 October 2022. Available from <https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm>
95. Levine JA, Karam SL, Aleppo G. SGLT2-I in the hospital setting: diabetic ketoacidosis and other benefits and concerns. *Curr Diab Rep* 2017;17:54
96. U.S. Food and Drug Administration. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Accessed 30 August 2022. Available from <https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious>
97. Akirov A, Grossman A, Shochat T, Shimon I. Mortality among hospitalized patients with hypoglycemia: insulin related and noninsulin related. *J Clin Endocrinol Metab* 2017;102:416–424
98. Ilcewicz HN, Hennessey EK, Smith CB. Evaluation of the impact of an inpatient hyperglycemia protocol on glycemic control. *J Pharm Pharm Sci* 2019;22:85–92
99. Sinha Gregory N, Seley JJ, Gerber LM, Tang C, Brillou D. Decreased rates of hypoglycemia following implementation of a comprehensive computerized insulin order set and titration

algorithm in the inpatient setting. *Hosp Pract* (1995) 2016;44:260–265

100. Amori RE, Pittas AG, Siegel RD, et al. Inpatient medical errors involving glucose-lowering medications and their impact on patients: review of 2,598 incidents from a voluntary electronic error-reporting database. *Endocr Pract* 2008;14:535–542
101. Alwan D, Chipps E, Yen PY, Dungan K. Evaluation of the timing and coordination of prandial insulin administration in the hospital. *Diabetes Res Clin Pract* 2017;131:18–32
102. Korytkowski M, Dinardo M, Donihi AC, Bigi L, Devita M. Evolution of a diabetes inpatient safety committee. *Endocr Pract* 2006;12(Suppl. 3):91–99
103. Hung AM, Siew ED, Wilson OD, et al. Risk of hypoglycemia following hospital discharge in patients with diabetes and acute kidney injury. *Diabetes Care* 2018;41:503–512
104. Maynard G, Kulasa K, Ramos P, et al. Impact of a hypoglycemia reduction bundle and a systems approach to inpatient glycemic management. *Endocr Pract* 2015;21:355–367
105. Milligan PE, Bocox MC, Pratt E, Hoehner CM, Krettek JE, Dunagan WC. Multifaceted approach to reducing occurrence of severe hypoglycemia in a large healthcare system. *Am J Health Syst Pharm* 2015;72:1631–1641
106. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nat Rev Endocrinol* 2016;12:222–232
107. Galindo RJ, Umpierrez GE, Rushakoff RJ, et al. Continuous glucose monitors and automated insulin dosing systems in the hospital consensus guideline. *J Diabetes Sci Technol* 2020;14:1035–1064
108. Dagogo-Jack S. Hypoglycemia in type 1 diabetes mellitus: pathophysiology and prevention. *Treat Endocrinol* 2004;3:91–103
109. Rickels MR. Hypoglycemia-associated autonomic failure, counterregulatory responses, and therapeutic options in type 1 diabetes. *Ann N Y Acad Sci* 2019;1454:68–79
110. Dendy JA, Chockalingam V, Tirumalasetty NN, et al. Identifying risk factors for severe hypoglycemia in hospitalized patients with diabetes. *Endocr Pract* 2014;20:1051–1056
111. Ulmer BJ, Kara A, Mariash CN. Temporal occurrences and recurrence patterns of hypoglycemia during hospitalization. *Endocr Pract* 2015;21:501–507
112. Shah BR, Walji S, Kiss A, James JE, Lowe JM. Derivation and validation of a risk-prediction tool for hypoglycemia in hospitalized adults with diabetes: the Hypoglycemia During Hospitalization (HyDHo) score. *Can J Diabetes* 2019;43:278–282.e1
113. Mathioudakis NN, Everett E, Routh S, et al. Development and validation of a prediction model for insulin-associated hypoglycemia in non-critically ill hospitalized adults. *BMJ Open Diabetes Res Care* 2018;6:e000499
114. Curll M, Dinardo M, Noschese M, Korytkowski MT. Menu selection, glycaemic control and satisfaction with standard and patient-controlled consistent carbohydrate meal plans in hospitalised patients with diabetes. *Qual Saf Health Care* 2010;19:355–359
115. Drincic AT, Knezevich JT, Akkireddy P. Nutrition and hyperglycemia management in the inpatient setting (meals on demand, parenteral, or enteral nutrition). *Curr Diab Rep* 2017;17:59
116. Draznin B. Food, fasting, insulin, and glycemic control in the hospital. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Alexandria, VA, American Diabetes Association, 2016, p. 70–83
117. Mabrey ME, Setji TL. Patient self-management of diabetes care in the inpatient setting: pro. *J Diabetes Sci Technol* 2015;9:1152–1154
118. Shah AD, Rushakoff RJ. Patient self-management of diabetes care in the inpatient setting: con. *J Diabetes Sci Technol* 2015;9:1155–1157
119. Yeh T, Yeung M, Mendelsohn Curanaj FA. Managing patients with insulin pumps and continuous glucose monitors in the hospital: to wear or not to wear. *Curr Diab Rep* 2021;21:7
120. Umpierrez GE, Klonoff DC. Diabetes technology update: use of insulin pumps and continuous glucose monitoring in the hospital. *Diabetes Care* 2018;41:1579–1589
121. Houlden RL, Moore S. In-hospital management of adults using insulin pump therapy. *Can J Diabetes* 2014;38:126–133
122. Korytkowski MT, Salata RJ, Koerbel GL, et al. Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. *Diabetes Care* 2009;32:594–596
123. Hsia E, Seggelke SA, Gibbs J, Rasouli N, Draznin B. Comparison of 70/30 biphasic insulin with glargine/lispro regimen in non-critically ill diabetic patients on continuous enteral nutrition therapy. *Nutr Clin Pract* 2011;26:714–717
124. Oliveira G, Abuín J, López R, et al. Regular insulin added to total parenteral nutrition vs subcutaneous glargine in non-critically ill diabetic inpatients, a multicenter randomized clinical trial: INSUPAR trial. *Clin Nutr* 2020;39:388–394
125. Draznin B. Glycemic control in the setting of parenteral or enteral nutrition via tube feeding. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Alexandria, VA, American Diabetes Association, 2016, p. 84–98
126. Pichardo-Lowden AR, Fan CY, Gabbay RA. Management of hyperglycemia in the non-intensive care patient: featuring subcutaneous insulin protocols. *Endocr Pract* 2011;17:249–260
127. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocr Pract* 2006;12:358–362
128. Roberts A, James J; Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care Group. *Diabet Med* 2018;35:1011–1017
129. Kwon S, Hermayer KL, Hermayer K. Glucocorticoid-induced hyperglycemia. *Am J Med Sci* 2013;345:274–277
130. Seggelke SA, Gibbs J, Draznin B. Pilot study of using neutral protamine Hagedorn insulin to counteract the effect of methylprednisolone in hospitalized patients with diabetes. *J Hosp Med* 2011;6:175–176
131. Brady V, Thosani S, Zhou S, Bassett R, Busaidy NL, Lavis V. Safe and effective dosing of basal-bolus insulin in patients receiving high-dose steroids for hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone chemotherapy. *Diabetes Technol Ther* 2014;16:874–879
132. Cheng YC, Guerra Y, Morkos M, et al. Insulin management in hospitalized patients with diabetes mellitus on high-dose glucocorticoids: management of steroid-exacerbated hyperglycemia. *PLoS One* 2021;16:e0256682
133. Bajaj MA, Zale AD, Morgenlander WR, Abusamaan MS, Mathioudakis N. Insulin dosing and glycemic outcomes among steroid-treated hospitalized patients. *Endocr Pract* 2022;28:774–779
134. Todd LA, Vigersky RA. Evaluating perioperative glycemic control of non-cardiac surgical patients with diabetes. *Mil Med* 2021;186:e867–e872
135. Aronson S, Murray S, Martin G, et al; Perioperative Enhancement Team (POET). Roadmap for transforming preoperative assessment to preoperative optimization. *Anesth Analg* 2020;130:811–819
136. Smiley DD, Umpierrez GE. Perioperative glucose control in the diabetic or nondiabetic patient. *South Med J* 2006;99:580–589; quiz 590–591
137. Buchleitner AM, Martínez-Alonso M, Hernández M, Solà I, Mauricio D. Perioperative glycaemic control for diabetic patients undergoing surgery. *Cochrane Database Syst Rev* 2012;9:CD007315
138. Draznin B. Preoperative, intraoperative, and postoperative glucose management. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Alexandria, VA, American Diabetes Association, 2016, p. 129–144
139. Duggan EW, Carlson K, Umpierrez GE. Perioperative hyperglycemia management: an update. *Anesthesiology* 2017;126:547–560
140. Han HS, Kang SB. Relations between long-term glycemic control and postoperative wound and infectious complications after total knee arthroplasty in type 2 diabetics. *Clin Orthop Surg* 2013;5:118–123
141. Demma LJ, Carlson KT, Duggan EW, Morrow JG 3rd, Umpierrez G. Effect of basal insulin dosage on blood glucose concentration in ambulatory surgery patients with type 2 diabetes. *J Clin Anesth* 2017;36:184–188
142. Umpierrez GE, Smiley D, Hermayer K, et al. Randomized study comparing a Basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. *Diabetes Care* 2013;36:2169–2174
143. Harrison VS, Rustico S, Palladino AA, Ferrara C, Hawkes CP. Glargine co-administration with intravenous insulin in pediatric diabetic ketoacidosis is safe and facilitates transition to a subcutaneous regimen. *Pediatr Diabetes* 2017;18:742–748
144. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335–1343
145. Vellanki P, Umpierrez GE. Diabetic ketoacidosis: a common debut of diabetes among african americans with type 2 diabetes. *Endocr Pract* 2017;23:971–978
146. Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Gonzalez-Padilla DA. Subcutaneous rapid-acting insulin analogues for diabetic ketoacidosis. *Cochrane Database Syst Rev* 2016;1:CD011281

147. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *J Clin Endocrinol Metab* 2008;93:1541–1552
148. Karajgikar ND, Manroa P, Acharya R, et al. Addressing pitfalls in management of diabetic ketoacidosis with a standardized protocol. *Endocr Pract* 2019;25:407–412
149. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. *Nat Rev Dis Primers* 2020;6:40
150. Shepperd S, Lannin NA, Clemson LM, McCluskey A, Cameron ID, Barras SL. Discharge planning from hospital to home. *Cochrane Database Syst Rev* 1996;1:CD000313
151. Gregory NS, Seley JJ, Dargar SK, Galla N, Gerber LM, Lee JI. Strategies to prevent readmission in high-risk patients with diabetes: the importance of an interdisciplinary approach. *Curr Diab Rep* 2018;18:54
152. Rinaldi A, Snider M, James A, et al. The impact of a diabetes transitions of care clinic on hospital utilization and patient care. *Ann Pharmacother*. 9 June 2022 [Epub ahead of print]. DOI: 10.1177/10600280221102557
153. Patel N, Swami J, Pinkhasova D, et al. Sex differences in glycemic measures, complications, discharge disposition, and postdischarge emergency room visits and readmission among non-critically ill, hospitalized patients with diabetes. *BMJ Open Diabetes Res Care* 2022;10:e002722
154. Agency for Healthcare Research and Quality. Patient Safety Network – Readmissions and adverse events after discharge, 2019. Accessed 23 October 2022. Available from <https://psnet.ahrq.gov/primer.aspx?primerID=11>
155. Rubin DJ. Hospital readmission of patients with diabetes. *Curr Diab Rep* 2015;15:17
156. Jiang HJ, Stryer D, Friedman B, Andrews R. Multiple hospitalizations for patients with diabetes. *Diabetes Care* 2003;26:1421–1426
157. Maldonado MR, D’Amico S, Rodriguez L, Iyer D, Balasubramanyam A. Improved outcomes in indigent patients with ketosis-prone diabetes: effect of a dedicated diabetes treatment unit. *Endocr Pract* 2003;9:26–32
158. Wu EQ, Zhou S, Yu A, Lu M, Sharma H, Gill J, et al. Outcomes associated with post-discharge insulin continuity in US patients with type 2 diabetes mellitus initiating insulin in the hospital. *Hosp Pract (1995)* 2012;40:40–48
159. Hirschman KB, Bixby MB. Transitions in care from the hospital to home for patients with diabetes. *Diabetes Spectr* 2014;27:192–195
160. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care* 2014;37:2864–2883
161. Rubin DJ, Recco D, Turchin A, Zhao H, Golden SH. External Validation Of The Diabetes Early Re-Admission Risk Indicator (Derri). *Endocr Pract* 2018;24:527–541

17. Diabetes Advocacy: *Standards of Care in Diabetes—2023*

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The American Diabetes Association (ADA) “Standards of Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Managing the daily health demands of diabetes can be challenging. People living with diabetes should not have to face discrimination due to diabetes. By advocating for the rights of those with diabetes at all levels, the American Diabetes Association (ADA) can help to ensure that they live a healthy and productive life. A strategic goal of the ADA is for more children and adults with diabetes to live free from the burden of discrimination. The ADA is also focused on making sure cost is not a barrier to successful diabetes management.

One tactic for achieving these goals has been to implement the ADA Standards of Care through advocacy-oriented position statements. The ADA publishes evidence-based, peer-reviewed statements on topics such as diabetes and employment, diabetes and driving, insulin access and affordability, and diabetes management in certain settings such as schools, childcare programs, and detention facilities. In addition to the ADA’s clinical documents, these advocacy statements are important tools in educating schools, employers, licensing agencies, policy makers, and others about the intersection of diabetes management and the law and for providing scientifically supported policy recommendations.

ADVOCACY STATEMENTS

The following is a partial list of advocacy statements ordered by publication date, with the most recent statement appearing first. A comprehensive list of advocacy statements is available at professional.diabetes.org/content/key-statements-and-reports.

Insulin Access and Affordability

The ADA’s Insulin Access and Affordability Working Group compiled public information and convened a series of meetings with stakeholders throughout the insulin supply chain to learn how each entity affects the cost of insulin for the consumer. Their conclusions and recommendations are published in an ADA statement (1).

Diabetes Care in the School Setting

A sizable portion of a child’s day is spent in school, so close communication with and training and cooperation of school personnel are essential to optimize diabetes

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management, safety, and access to all school-sponsored opportunities. Refer to the published ADA position statement for diabetes management information for students with diabetes in elementary and secondary school settings (2).

Care of Young Children With Diabetes in the Childcare Setting

Very young children (aged <6 years) with diabetes have legal protections and can be safely cared for by childcare professionals with appropriate training, access to resources, and a communication system with parents and the child's diabetes health care professional. Refer to the published ADA position statement for information on young children aged <6 years in settings such as daycare centers, preschools, camps, and other programs (3).

Diabetes and Driving

People with diabetes who wish to operate motor vehicles are subject to various

licensing requirements applied by both state and federal jurisdictions. For an overview of existing licensing rules for people with diabetes, factors that impact driving for this population, and general guidelines for assessing driver fitness and determining appropriate licensing restrictions, refer to the published ADA position statement (4).

Editor's note: Federal commercial driving rules for individuals with insulin-treated diabetes changed on 19 November 2018. These changes will be reflected in a future updated ADA statement.

Diabetes and Employment

Any person with diabetes, whether insulin treated or noninsulin treated, should be eligible for any employment for which they are otherwise qualified. Employment decisions should never be based on generalizations or stereotypes regarding the effects of diabetes. For a general set of guidelines for evaluating individuals with

diabetes for employment, including how an assessment should be performed and what changes (accommodations) in the workplace may be needed for an individual with diabetes, refer to the published ADA position statement (5).

References

1. Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Insulin Access and Affordability Working Group: conclusions and recommendations [published correction appears in *Diabetes Care* 2018;41:1831]. *Diabetes Care* 2018;41:1299–1311
2. Jackson CC, Albanese-O'Neill A, Butler KL, et al. Diabetes care in the school setting: a position statement of the American Diabetes Association. *Diabetes Care* 2015;38:1958–1963
3. Siminerio LM, Albanese-O'Neill A, Chiang JL, et al.; Care of young children with diabetes in the child care setting: a position statement of the American Diabetes Association. *Diabetes Care* 2014;37:2834–2842
4. American Diabetes Association. Diabetes and driving. *Diabetes Care* 2014;37(Suppl. 1):S97–S103
5. American Diabetes Association. Diabetes and employment. *Diabetes Care* 2014;37(Suppl. 1):S112–S117

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Committee members disclosed the following financial or other conflicts of interest (COI) covering the period 12 months before December 2022

Member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
American Diabetes Association Professional Practice Committee							
Nuha A. ElSayed (Chair)§	American Diabetes Association	None	None	None	None	Expert, World Health Organization	Endocrinologist, Joslin Diabetes Center Chair, Diabetes Education for All
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Vanita R. Aroda	Brigham and Women's Hospital Faculty, Harvard Medical School	Applied Therapeutics#, Eli Lilly#, Fractyl#, Novo Nordisk#	None	None	None	Applied Therapeutics, Fractyl, Novo Nordisk*, Pfizer, Sanofi	Spouse Sandip Datta, MD, Senior Medical Director, Early Development, Infectious Diseases, May 2020 to present, Janssen Pharmaceutical Companies of Johnson & Johnson Consultant/educational activities: Associate Editor, <i>Diabetes Care</i> ; Member of the Writing Group for "Management of Hyperglycemia in Type 2 Diabetes, 2022. Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)" Novo Nordisk* (received other Industry benefits, such as travel)
Raveendhara R. Bannuru (Chief Methodologist)§	American Diabetes Association	None	None	None	None	None	None
Florence M. Brown	Joslin Diabetes Center	None	Dexcom	None	None	None	None

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Member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Ownership interest	Consultant/advisory board	Other
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Billy S. Collins	CDR, U.S. Public Health Service	None	None	None	None	None	None
Marisa E. Hilliard	Baylor College of Medicine Texas Children's Hospital	None	JDRF	None	None	None	Springer Publishing (book royalties) Associate Editor, American Psychological Association Member, Clinical & Research Advisory Committee; College Diabetes Network Member, External Registry & Research Committee; T1D Exchange Mental Health Diabetes Education Program
Diana Isaacs	Cleveland Clinic Endocrinology & Metabolism Institute	None	None	Abbott, Dexcom, Medtronic, Novo Nordisk, Bayer	None	Insulet, Eli Lilly, Sanofi, Klinio, Undermyfork	Board of Directors, Association of Diabetes Care and Education Specialists Clinical Practice Guideline Oversight Committee, American Association of Clinical Endocrinology
Eric L. Johnson	University of North Dakota School of Medicine and Health Sciences Altru Health System	None	None	None	None	None	Editorial Board, <i>Clinical Diabetes</i>
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Kamlesh Khunti	University of Leicester Leicester Diabetes Centre Leicester General Hospital	Boehringer Ingelheim#, Applied Therapeutics, AstraZeneca#, Novartis#, Novo Nordisk#, Oramed Pharmaceuticals, Sanofi#, Eli Lilly#, Merck Sharp & Dohme#	None	None	None	AstraZeneca, Bayer, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Boehringer Ingelheim	None
Jose Leon	National Center for Health in Public Housing	None	None	None	None	None	None

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Member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Ownership interest	Consultant/advisory board	Other
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Robert C. Stanton	Joslin Diabetes Center	None	None	None	None	None	None
Robert A. Gabbay§	American Diabetes Association	None	None	None	None	Onduo*, HealthReveal, Lark, Vida Health*	Spouse Christi Gabbay, CHSE, Managing Director, Major Gifts and Philanthropy at American Diabetes Association Senior volunteer, Joslin Diabetes Center
American College of Cardiology Designated Representatives and Staff (Section 10 "Cardiovascular Disease and Risk Management")							
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Member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Ownership interest	Consultant/advisory board	Other
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Laura S. Mitchell	American Diabetes Association	None	None	None	None	None	None
Designated Subject Matter Experts							
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Lisa Murdock	American Diabetes Association	None	None	None	None	None	None
Jennifer K. Sun	Joslin Diabetes Center		Novo Nordisk, Boehringer Ingelheim, Genentech/Roche	Jaeb Center for Health Research/ National Eye Insitute, JDRF	Genentech/ Roche	None	None
Crystal C. Woodward	American Diabetes Association	None	None	None	None	None	None
Deborah Young-Hyman	Office of Behavioral Health and Social Sciences Research, National Institutes of Health	None	None	None	None	None	None

*≥\$10,000 per year from company to individual. #Grant or contract is to university or other employer. †Disclosure made after committee member began work on the SOC 2022 update. §Nuha A. ElSayed, Raveendhara R. Bannuru, and Robert A. Gabbay are also American Diabetes Association staff.

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