Stroke

AHA/ASA SYSTEMATIC REVIEW

Benefits and Risks of Dual Versus Single Antiplatelet Therapy for Secondary Stroke Prevention

A Systematic Review for the 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

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BACKGROUND: Dual antiplatelet therapy (DAPT) after ischemic stroke or transient ischemic attack may reduce recurrent stroke but also increase severe bleeding compared with single antiplatelet therapy (SAPT). The American Heart Association/American Stroke Association convened an evidence review committee to perform a systematic review and meta-analysis of the benefits and risks of DAPT compared with SAPT for secondary ischemic stroke prevention.

METHODS: The Medline, Embase, and Cochrane databases were searched on December 5, 2019, to identify phase III or IV randomized controlled trials (n≥100) from December 1999 to December 2019. We calculated unadjusted relative risks (RRs) and performed meta-analyses of studies based on the duration of treatment (short [≤90 days] versus long [>90 days]).

RESULTS: Three short-duration randomized controlled trials were identified that enrolled mostly patients with minor stroke or high risk transient ischemic attack. In these trials, DAPT, compared with SAPT, was associated with a lower 90-day risk of recurrent ischemic stroke (pooled RR, 0.68 [95% CI, 0.55–0.83], I^2=37.1%). There was no significant increase in major bleeding with DAPT in short-duration trials (pooled RR, 1.88 [95% CI, 0.93–3.83], I^2=8.9%). In 2 long-duration treatment randomized controlled trials (mean treatment duration, 18-40 months), DAPT was not associated with a significant reduction in recurrent ischemic stroke (pooled RR, 0.89 [95% CI, 0.79–1.02], I^2=1.4%), but was associated with a higher risk of major bleeding (pooled RR, 2.42 [95% CI, 1.37–4.30], I^2=75.5%).

CONCLUSIONS: DAPT was more effective than SAPT for prevention of secondary ischemic stroke when initiated early after the onset of minor stroke/high-risk transient ischemic attack and treatment duration was <90 days. However, when the treatment duration was longer and initiated later after stroke or transient ischemic attack onset, DAPT was not more effective than SAPT for ischemic stroke prevention and it increased the risk of bleeding.

Key Words: AHA Scientific Statements ■ dual antiplatelet therapy ■ ischemic attack, transient ■ ischemic stroke

Antiplatelet therapy is a mainstay of secondary stroke prevention for noncardioembolic ischemic stroke and transient ischemic attack (TIA). Dual antiplatelet therapy (DAPT) may provide additional stroke risk reduction over single antiplatelet therapy (SAPT) through more potent inhibition of platelet activation pathways. However, clinical trials testing DAPT versus SAPT for secondary prevention have not shown a consistent reduction in recurrent stroke and often report increases in the incidence of bleeding.[1] The guideline writing group of the American Heart Association/American Stroke Association "2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack" commissioned an independent evidence review

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committee (ERC) to review evidence from randomized controlled trials (RCTs) regarding the relative efficacy and safety of DAPT compared with SAPT for secondary stroke prevention.

METHODS

This systematic review and meta-analysis addressed the following clinical question, in PICOTS format (Population, Intervention, Comparison, Outcomes, Timing, and Setting), posed by the guideline writing committee and revised by the ERC: "In patients with an ischemic stroke or TIA, what are the benefits and risks of DAPT compared to SAPT within 5 years for prevention of recurrent stroke?" This systematic review and meta-analysis complied with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[2]

Search Strategy

A literature search that included English language publications from December 1999 to December 5, 2019, was performed by an American Heart Association librarian on December 5, 2019, using PubMed (National Center for Biotechnology Information, US National Library of Medicine), Embase (Elsevier), the Cochrane Database of Systematic Reviews, and Cochrane Controlled Trials Register (EBSCOhost). The key search parameters included: Humans; Ethnic groups: All; Sex: Both; Ages: Adult; Publication type: Meta-analyses, Randomized controlled trials, Systematic reviews. Published meta-analyses and systematic reviews were also assessed manually to identify additional references missed by the search. The full search strategy and results are found in Table I in the Data Supplement.

Eligibility Criteria

Inclusion criteria were phase III or IV RCTs of DAPT compared with SAPT agents that enrolled at least 100 subjects with TIA or ischemic stroke. If trials included a mix of populations (participants with stroke/TIA with participants with other events, eg, myocardial infarction), only those trials that conducted stratified randomization by stroke/TIA status were included, even if the trial provided outcomes by stroke/TIA subgroup. Relevant clinical outcomes had to be reported within 5 years of randomization. Antiplatelet agents were not considered if they were administered intravenously, were not approved by the US Food and Drug Administration, were not available in the United States, or had other hypothesized modes of action that could contribute to stroke prevention in addition to antiplatelet effects (eg, dipyridamole, cilostazol).[3]

Review for Eligibility

Title/abstract and full-text reviews were done using the Indico Platform (Indico Solutions). All titles and abstracts were reviewed by 2 ERC members independently to determine eligibility for inclusion. Disagreements were resolved by an ERC chair. Similarly, full-text eligibility was performed by dual independent reviews, and differences were resolved by an ERC chair.

Quality Assessment

Each RCT was assessed for potential risk of bias using the Revised Cochrane Risk-of-Bias tool for randomized trials v2.0 (Table 1).[4] This assessed bias arising from the randomization process, deviations from assignment or adherence to the intended interventions, missing outcome data, measurement of the outcomes, and selective reporting of the result. Each of these domains was categorized as either low risk of bias, some concerns of bias, or high risk of bias. An overall risk-of-bias judgment was determined based on the individual domain assessments; the study was assigned a low risk of bias if all domains were low risk; some concerns of bias if at least 1 domain had some concerns, but no domain was high risk; and high risk of bias if at least 1 domain was high risk or multiple domains had some concern in ways that lowered the confidence in the results. Two ERC members independently applied the Revised Cochrane Risk-of-Bias tool v2.0 to each study, and individual domain and overall risk-of-bias discrepancies were resolved by the pair.

Data Abstraction

Data were abstracted independently within the Indico Platform by 2 ERC members and differences were resolved by the pair. For each RCT, information abstracted included study details, efficacy outcomes, and safety outcomes. When available, information was abstracted regarding the following outcomes: recurrent ischemic stroke (primary outcome), intracranial hemorrhage (intracerebral hemorrhage [ICH] was prespecified, but when it was not available, we used the trial definition of intracranial hemorrhage or hemorrhagic stroke), all recurrent strokes (ischemic stroke or ICH), myocardial infarction, major adverse cardiovascular events (MACE defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), all-cause mortality, vascular death, and major bleeding (as defined by each study; Table II in the Data Supplement). When available, data were abstracted for the following subpopulations identified a priori: randomization within 72 hours of stroke/TIA onset, major stroke, intracranial stenosis, extracranial stenosis, atrial fibrillation where anticoagulation was contraindicated, and duration of DAPT/SAPT treatment. After review of the duration of treatment in each trial, trials were divided post hoc into short-duration (≤90 days) and long-duration (>90 days) studies. Short-duration trials randomly assigned subjects within 7 days after stroke/TIA (Table 2).

Meta-Analysis

We estimated summary treatment effects across studies using random-effects meta-analyses for studies with

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Table 1. Risk of Bias Assessment for Each Article

Citation	Domain 1: Randomization process	Domain 2: Deviations from assignment to intervention	Domain 2: Deviations from adhering to intervention	Domain 3: Missing outcome data	Domain 4: Measurement of the outcome	Domain 5: Selection of reported results	Overall risk of bias
Benavente et al[12]	Low	Low	Some concerns	Low	Low	Low	Some concerns
Diener et al[13]	Low	Low	Some concerns	Low	Low	Low	Some concerns
He et al[9]	Low	High	High	Some concerns	High	Some concerns	High risk
Johnston et al[6]	Low	Low	Low	Low	Low	Low	Low risk
Li et al[22]	Low	Low	Low	Low	Low	Low	Low risk
Wang et al[10]	Low	High	High	Low	Some concerns	Some concerns	high risk
Wang et al[23]	Low	Low	Low	Low	Low	Low	Low risk
Wang et al[11]	Low	Low	Low	Low	Low	Some concerns	Low risk
Wang et al[7]	Low	Low	Low	Low	Low	Low	Low risk
Yi et al[14]	Low	Some concerns	High	High	Some concerns	Some concerns	High risk
Zuo et al[8]	Some concerns	Some concerns	High	Some concerns	Some concerns	Some concerns	High risk
Pan et al[24]	Low	Low	Low	Low	Low	Some concerns	Low risk
Tillman et al[25]	Low	Low	Some concerns	Low	Low	Low	Low risk
Johnston et al[26]	Low	Low	Low	Low	Low	Low	Low risk

similar durations of treatment (≤90 days, >90 days) and timing of outcome assessment (at 90 days for short-duration trials and longer-term outcomes for long-duration trials). For each RCT, we calculated the unadjusted relative risk (RR) of ischemic stroke and the secondary outcomes. In sensitivity analyses, we excluded any trial that had a high risk of bias. For each meta-analysis, we quantified heterogeneity with the I^2 index, where higher values suggest greater heterogeneity (25% often considered low; 50% moderate; and 75% high), and the Cochran Q test.[5] For all analyses, $P<0.05$ was considered significant with no adjustment for multiple comparisons. Meta-analyses were conducted using DerSimonian and Laird random-effects models implemented with the *metan* command in Stata, version 16.0 (StataCorp LLC). The protocol for this meta-analysis was not registered.

Table 2. Unique Trials Identified: 5 Short-Duration and 2 Long-Duration Treatment Trials

Trials	Randomization window	Treatment duration	Primary outcome assessment	Included in meta-analysis
Short-duration treatment				
CHANCE[7]	24 h	21 d	90 d	x
POINT[6]	12 h	90 d	90 d	x
Zuo et al[8]	7 d	90 d	90 d	x
He et al[9]	72 h	14 d	14 d	
Wang et al/Yi et al[10,15]	48 h	30 d	30 d	
Long-duration treatment				
MATCH[13]	3 mo	18 mo	18 mo	x
SPS3[12]	6 mo	Mean 3.4 y	Mean 3.4 y	x

CHANCE indicates Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events; MATCH, Management of Atherothrombosis With Clopidogrel in High-Risk Patients; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; and SPS3, Secondary Prevention of Small Subcortical Strokes-3.

RESULTS

The literature review identified 179 articles; 26 underwent full-text review (Figure 1) of which 13 reports of 7 trials were included. Details abstracted from these are found in Table III in the Data Supplement. Five short-duration treatment trials (14–90 days), each with early initiation of treatment (<7 days), reported short-term outcomes (14–90 days; Table 2).[6–10] In addition to its primary outcome time point at 90 days, CHANCE (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) also reported a 1-year outcome.[11] Two long-duration treatment trials, SPS3 (Secondary Prevention of Small Subcortical Strokes-3)[12] and MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients)[13] initiated treatment in a delayed fashion and reported long-term outcomes (Table 2).

Short-Duration Trials

The number of trials included in the systematic review (n=5) was greater than the number of trials included in the meta-analyses (n=3) because 2 trials did not report outcomes at required time points.

Five trials tested randomly allocated treatments for 14 to 90 days. Details are found in Table III in the Data Supplement. In all trials, participants were enrolled within 12 hours to 7 days after stroke/TIA. The risk of recurrent ischemic stroke was significantly lower in the DAPT than in the SAPT groups in the 2 larger trials,

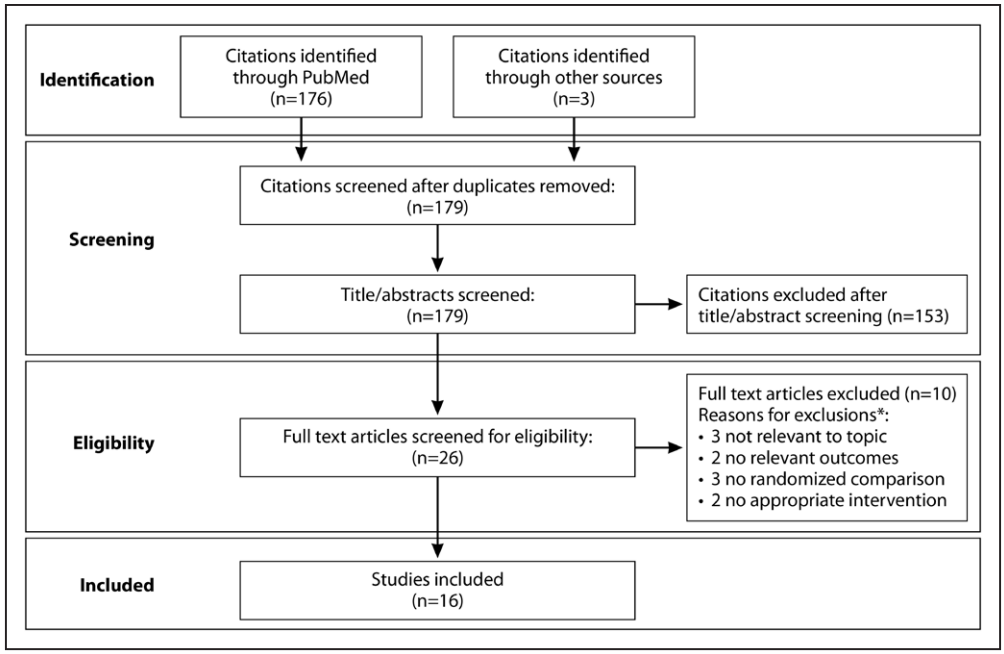

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram.
*Not relevant indicates primary prevention study; no relevant outcomes, observational study; no randomized comparison, randomization not stratified by stroke; no appropriate intervention, not approved by the US Food and Drug Administration, not available in the United States, trial is not phase III or IV.

POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)[6] and CHANCE,[7] both of which enrolled patients within 12 (POINT) or 24 (CHANCE) hours of symptom onset, respectively. The 3 smaller trials[8–10,14] also favored DAPT to SAPT with respect to lower recurrent ischemic stroke, significantly in 2 of the trials and without a significance test reported in the third.[9]

Results of Meta-Analyses

Three short-duration trials[6–8] were included in a meta-analysis because they reported outcomes at the same 90-day time point (although not all outcomes were available). The other 2 trials reported outcomes at different time points (14[9] and 30[10,15] days) and were therefore not included in the meta-analysis (Table 2). Based on the 3 trials, compared with SAPT, DAPT was associated with a lower risk of recurrent ischemic stroke by 90 days (pooled RR of 0.68 [95% CI, 0.55–0.83], I^2=37.1%; Figure 2A). Results were similar when the analysis was repeated excluding 1 trial with a high risk of bias[8]; of note, both trials retained in the analysis enrolled patients within 12 to 24 hours of symptom onset (Figure V in the Data Supplement). DAPT was associated with reduced total recurrent stroke (ischemic stroke plus ICH; pooled RR of 0.69 [95% CI, 0.56–0.85], I^2=41.5%; Figure 2B, 3 trials; Figure VI in the Data Supplement), and MACE (pooled RR, 0.76 [95% CI, 0.64–0.92], I^2=45.5%; Figure II in the Data Supplement, 2 trials). There was no difference between antiplatelet regimens for ICH (Figure 2C, 2 trials), myocardial infarction (Figure I in the Data Supplemental, 2 trials), all-cause mortality (Figure III in the Data Supplement, 2 trials), vascular death (Figure IV in the Data Supplement, 2 trials), or major bleeding (pooled RR of 1.88 [95% CI, 0.93–3.83], I^2=8.9%; Figure 2D, 2 trials). Three outcomes, MACE (Figure II in the Data Supplement), recurrent ischemic stroke (Figure 2A), and total recurrent stroke (Figure 2B) had a modest degree of heterogeneity. Although results for major bleeding were divergent, the I^2 did not indicate significant heterogeneity.

Long-Duration Trials

The number of trials included in the systematic review (n=2) was the same as the number of trials included in the meta-analyses (n=2).

Two trials tested randomly allocated treatments for an average of 18 to 40 months. Details of the 2 trials, SPS3[12] and MATCH,[13] are found in Table III in the Data Supplement. Participants were enrolled within the first 3 months of stroke/TIA in MATCH (mean time to randomization, 26.5 days) and within the first 6 months of lacunar stroke in SPS3 (median time to randomization, 62 days). In both trials, participants were randomly assigned to clopidogrel plus aspirin or SAPT for at least 18 months. Neither trial showed benefit of long-duration DAPT compared with SAPT for recurrent ischemic stroke. Major hemorrhages were significantly higher in the DAPT group in each trial.

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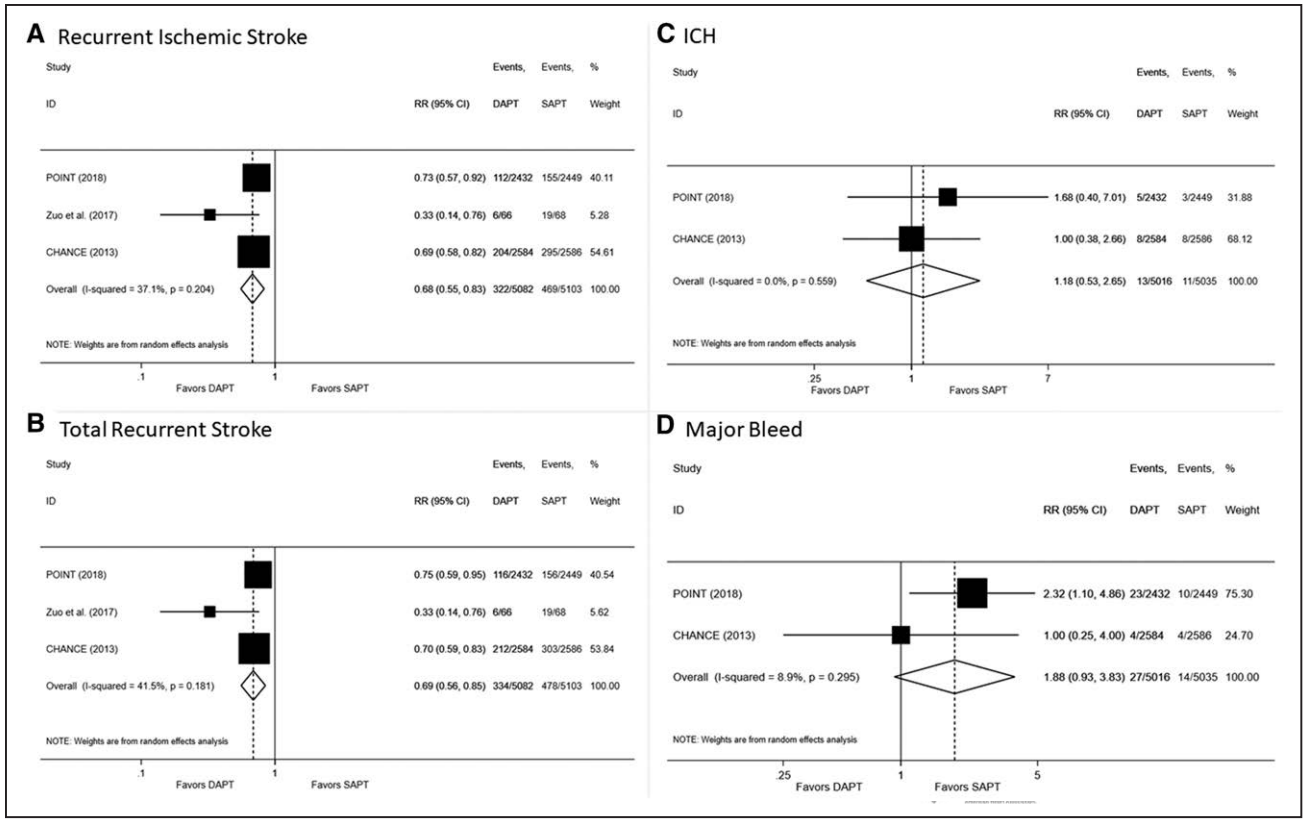

Figure 2. Forest plot for short-duration trials.
For short-duration trials, random-effects meta-analysis of relative risks from randomized controlled trials testing dual antiplatelet therapy compared with single antiplatelet therapy for the outcome of recurrent ischemic stroke (**A**), total recurrent stroke (recurrent ischemic stroke + ICH) (**B**), ICH (**C**), and major bleed (**D**). DAPT indicates dual antiplatelet therapy; ICH, intracranial hemorrhage; RR, relative risk; and SAPT, single antiplatelet therapy.

Results of Meta-Analyses

Both long-duration trials were included in a meta-analysis. Compared with SAPT, DAPT was not associated with a significant reduction in recurrent ischemic stroke (pooled RR, 0.89 [95% CI, 0.79–1.02], I^2=1.4%; Figure 3A). Similarly, DAPT was not associated with total recurrent stroke (ischemic and ICH combined; Figure 3B), myocardial infarction (Figure VII in the Data Supplement), MACE (Figure VIII in the Data Supplement), all-cause mortality (Figure IX in the Data Supplement), or vascular death (Figure X in the Data Supplement). However, DAPT was associated with both a higher risk of ICH (pooled RR, 1.76 [95% CI, 1.13–2.76], I^2=0.0%; Figure 3C) and a higher risk of major bleeding (pooled RR, 2.42 [95% CI, 1.37–4.30], I^2=75.5%; Figure 3D). A high degree of heterogeneity between trial effects was observed for all-cause mortality (I^2=78.5%) and major bleeding (I^2=75.5%) (Figure 3D and Figure IX in the Data Supplement).

Results by Subpopulation

No trial subpopulations qualified for meta-analysis. Individual trial results are therefore highlighted below.

Initiation of Treatment Within 72 Hours of Stroke/TIA Onset

Four trials randomly assigned subjects within 72 hours of symptom onset.[6,7,9,10,14] Two of the trials reported outcomes at 14[9] and 30[10,15] days and therefore were not included in the meta-analyses reported earlier. All 4 trials reported a lower risk of recurrent ischemic stroke for DAPT than SAPT. There were few events reported in He et al[9] and a between-treatment group comparison was not made, although DAPT was favored numerically. Both He et al[9] and Wang et al[10] were deemed at high risk for bias. Results of the meta-analysis that included only POINT and CHANCE, which both enrolled within 12 to 24 hours of symptom onset, were already described earlier (Figures V and VI in the Data Supplement).

Major Stroke

No trials provided data that pertained exclusively to this subpopulation.

Intracranial Stenosis/Extracranial Stenosis

No trials provided data exclusively on intracranial or extracranial stenosis subpopulations. However, 2 trials (3 articles) included only patients with large artery

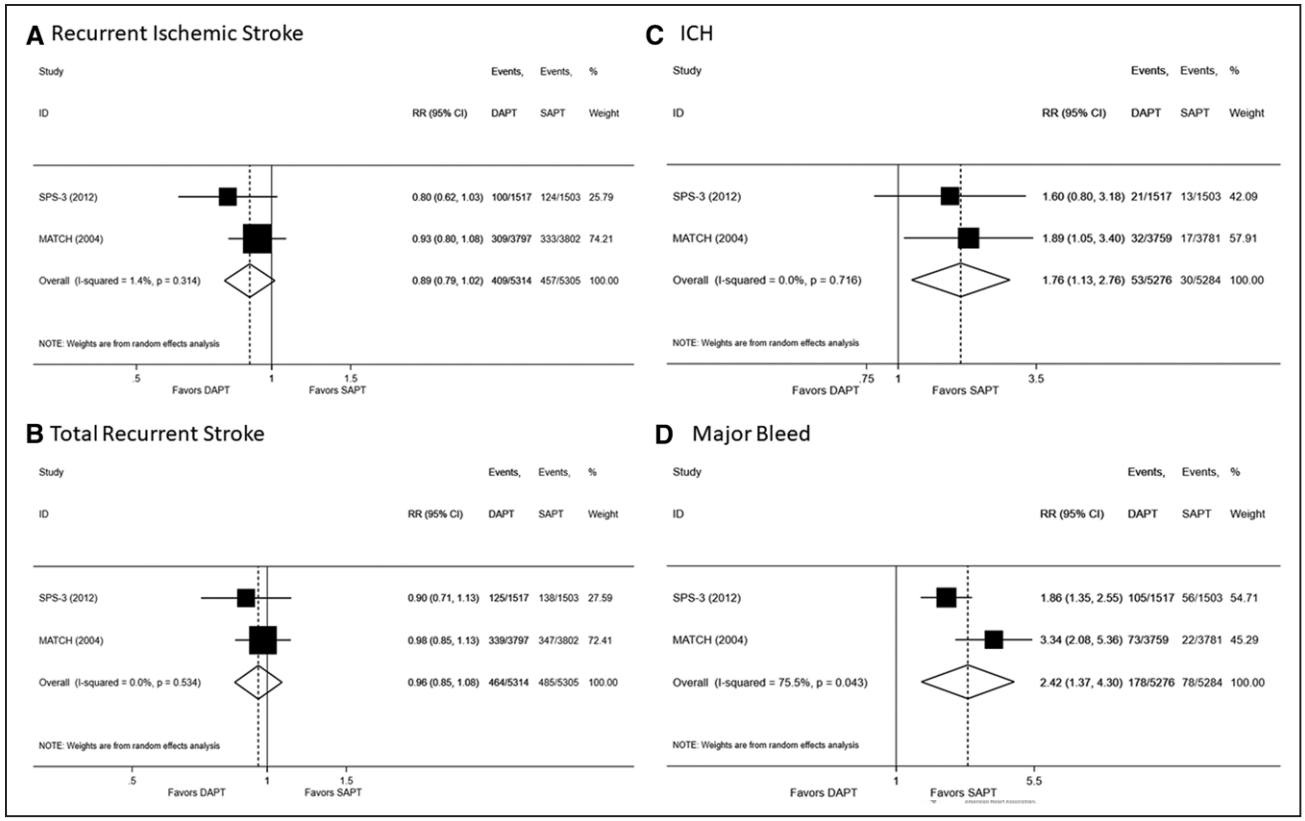

Figure 3. Forest plot for long-duration trials.
For long-duration trials, random-effects meta-analysis of relative risks from randomized controlled trials testing dual anti-platelet therapy compared with single antiplatelet therapy for the outcome of recurrent ischemic stroke (**A**), total recurrent stroke (recurrent ischemic stroke + ICH) (**B**), ICH (**C**), and major bleed (**D**). DAPT indicates dual antiplatelet therapy; ICH, intracranial hemorrhage; RR, relative risk; and SAPT, single antiplatelet therapy.

atherosclerosis (intracranial or extracranial disease).[8,10,14] These 2 trials enrolled subjects within the first 48 hours[10] or 7 days[8] and measured outcomes at 30 days[10] or 90 days.[8] Both trials showed a lower risk of recurrent ischemic stroke for DAPT than for SAPT, but also were deemed to have a high risk of bias.

Atrial Fibrillation Where Anticoagulation Is Contraindicated

No trials provided data that pertained exclusively to this subpopulation.

DISCUSSION

This systematic review and meta-analysis of trials that compared DAPT and SAPT for secondary stroke prevention had several findings. Based on 3 trials with early initiation (<1 week) and short-term treatment duration (<90 days), DAPT was superior to SAPT for prevention of recurrent ischemic stroke, any recurrent stroke, and MACE in people with minor stroke or high-risk TIA who were at low risk of bleeding. The meta-analysis of 2 trials found a pooled increase in risk of 88% for major bleeding with DAPT compared to SAPT, but with a wide confidence interval from a reduction of 7% to an increase of 283%. Significant heterogeneity was not identified for this outcome, but power was low given the low number of trials. POINT, a trial more generalizable to a US population, did identify an increased risk of major bleeding (RR, 2.32 [95% CI, 1.10–4.86]) with DAPT, whereas CHANCE did not (RR, 1.00 [95% CI, 0.25–4.00]). CHANCE classified very few bleeding events as severe, 4 in each arm, despite 20 ICH in the DAPT and 16 ICH in the SAPT groups.[16] A pooled analysis of POINT and CHANCE by the study investigators found an increased risk of "major or minor hemorrhage" and "minor hemorrhage."[17] Thus, use of DAPT in the early setting after high-risk TIA or minor ischemic stroke should take into consideration the potential for an increased risk of bleeding. For long-term secondary prevention, DAPT was not superior to SAPT for the prevention of recurrent ischemic stroke but was associated with a significantly increased risk of ICH and major bleeding. The 2 long-duration trials included in the meta-analysis enrolled either exclusively patients with lacunar stroke or patients with prior stroke or TIA who had at least 1 additional vascular risk factor. Therefore, results may not generalize to a broader stroke population.

Reasons for the benefits of DAPT compared with SAPT in short-duration trials, but not long-term trials,

may be attributable to the timing of treatment initiation. The short-duration trials initiated randomized treatment soon after stroke, within 12[6] or 24 hours[7] for 2 larger trials, or 72 hours[9,10,14] or 7 days[8] for the smaller trials. The long-term trials initiated randomized treatment within 3 months[13] or 6 months[12] of stroke onset (mean time to randomization as 27 and 62 days, respectively). The absolute risk of recurrent stroke is highest in the first few months of stroke[18] (although still modest) and therefore a benefit in risk reduction of recurrent stroke may be easier to identify in trials that initiate treatment soon after stroke. Similarly, the longer duration of DAPT may have made the subjects enrolled in the long-duration trials more vulnerable to bleeding complications that accumulate over time.

LIMITATIONS

We are unable to draw conclusions about the benefits and risks of DAPT compared with SAPT for the prespecified subpopulations of interest because no trial provided data that respected randomization by these groups. Although our results do not address the 2 subpopulations with intra- or extracranial stenosis individually, 2 short-duration trials did exclusively enroll subjects with large artery disease. The findings of these 2 trials, both with a high risk of bias, were in keeping with overall findings that DAPT is beneficial.

This meta-analysis included fewer trials than some other meta-analyses that addressed DAPT for secondary stroke prevention.[1,19–21] Compared with other systematic reviews and meta-analyses that included only clopidogrel and aspirin, fewer studies were included because we excluded phase 1 and 2 trials and trials that did not stratify randomization on stroke/TIA when mixed populations were enrolled.[1,19] This allowed us to focus on larger trials that were less susceptible to bias and had results specific to the secondary stroke prevention question. We excluded trials that included antiplatelet agents with additional potential stroke prevention mechanisms, such as vasodilation (eg, cilostazol, dipyridamole), to focus on antiplatelet effects on ischemic stroke prevention.

The strengths of this meta-analysis include our ERC with no relationships with industry, a prespecified meta-analysis plan, focus on drugs with only antiplatelet effects, and large trials available for inclusion. Limitations include the limited number of studies that were eligible for meta-analysis; the different doses of aspirin used across studies; different drugs used for the SAPT arm (aspirin or clopidogrel); heterogeneity of the timing of treatment initiation; heterogeneity of study samples; heterogeneity in the timing of the collection of outcomes; low power to identify heterogeneity between or among studies; and small differences in the definitions of MACE, major bleeding, and ICH used across trials.

CONCLUSIONS

When initiated soon after high-risk TIA or minor stroke, and continued for 21 to 90 days, DAPT is more effective than SAPT for the reduction of recurrent ischemic stroke and therefore has a role in early secondary stroke prevention. Although this meta-analysis did not identify a statistically significant higher pooled risk of bleeding associated with DAPT in the setting of early initiation and short-term treatment duration, POINT, the trial most representative of the US population, did demonstrate a statistically significant higher risk of major bleeding. Therefore, the risk of bleeding should be considered and weighed against the potential benefits of DAPT when initiated early after onset. When initiated within 1 to 2 months of stroke or TIA and continued for 2 to 3 years, DAPT is not associated with a lower risk of ischemic stroke but is associated with more bleeding events and therefore is not recommended in this setting. However, uncertainty surrounding these conclusions must be recognized given that few trials were identified in the systematic review and included in the meta-analyses. Additional research is needed to determine the optimal timing of starting treatment relative to the clinical event; the optimal duration of DAPT to maximize the risk-benefit ratio; whether additional populations excluded from POINT and CHANCE, such as those with major stroke, may also benefit from early DAPT; and whether certain genetic profiles eliminate the benefit of early DAPT.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Devin L. Brown	University of Michigan	NIH†	None	None	None	None	None	None
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*Modest.

†Significant.

‡The relationship with Bayer was added after the report was complete and had no bearing on the results of the evidence review committee report.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Mary Amatangelo	Massachusetts General	None	None	None	None	None	None	None
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Askiel Bruno	Medical College of Georgia at Augusta University	NINDS†; Georgia Rehabilitation Foundation†	None	Abbott Pharma*	None	None	None	None
Cheryl Bushnell	Wake Forest Baptist Health	None	None	None	None	Care Directions, LLC*	ZZ Biotech, Clinical Advisory Committee for RHAPSODY II trial*	None

(*Continued*)

Reviewer Disclosures Continued

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
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Clay Cauthen	University of Texas	None	None	Novartis	None	None	None	None
Tiffany Chen	University of Pennsylvania	None	None	None	None	None	None	None
Ephraim Church	Penn State Health	None	None	None	None	None	None	None
John Cole	University of Maryland	NIH/NINDS R01†	None	None	None	None	None	None
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Colin Derdeyn	University of Iowa	None	None	None	None	None	None	None
Marco R. Di Tullio	Columbia University	NIH/NINDS†	None	None	None	None	None	None
Kenneth Gaines	Vanderbilt University Medical Center	PCORI: C3FIT National PI†; USDA Distance Learning and Telemedicine Grant†	None	None	Expert witness for medical malpractice*	Stroke Link Health*	None	None
Philip B. Gorelick	Michigan State	Local Site PI for C3FIT recurrent stroke prevention trial funded by PCORI†	None	None	None	None	None	Bayer*; Novartis*
Virginia Howard	University of Alabama at Birmingham	NIH†	None	None	None	None	None	None
Judy Huang	Johns Hopkins University	None	None	None	Weber Gallagher*	Longeviti*	None	None
Silvio Inzuccchi	Yale School of Medicine	None	None	None	None	None	Boehringer Ingelheim*; AstraZeneca†; Novo Nordisk†; Merck*	None
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Salomeh Keyhani	University of California, San Francisco	None	None	None	None	None	None	None
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Christopher Kramer	University of Virginia	Regeneron†	None	None	None	None	None	None
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(*Continued*)

Reviewer Disclosures Continued

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Helmi Lutsep	Oregon Health & Science University	None	None	None	None	None	BMS*; Axiomatic -SSP trial*; Coherex Medical - Physician Advisory Board for Wavecrest*; NINDS/Mayo - Stroke Adjudication Committee for CREST2*; Medscape Neurology*	Modest*
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Prachi Mehndiratta	University of Maryland	None	None	None	None	None	None	None
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Sara Partington	University of Pennsylvania	None	None	None	None	None	None	None
Aman Patel	Massachusetts General Hospital	Siemens†	None	None	None	None	Microvention†; Medtronic*; Penumbra*	None
Sabrina Phillips	Mayo Clinic	None	None	None	None	None	None	None
Aleksandra Pikula	University of Toronto	Canadian Institute of Health Research*	Canadian Stroke Consortium*	None	None	None	None	None
Raymond Reichwein	Penn State Health	Athersys†	None	None	None	None	None	None
Gustavo Rodriguez	Texas Tech School of Medicine	None	None	None	None	None	None	None
Christianne Roumie	VA Tennessee Valley Healthcare System; Vanderbilt University	VA†; CSRD†; NIH/NHLBI†; AHRQ†; PCORI†	None	None	None	None	None	None
Julie Shulman	Boston University Medical Center	NIH†	None	None	None	None	None	None
James Siegler	Cooper University Hospital	None	None	None	None	None	Ceribell†	None
Brian Silver	University of Massachusetts Medical School	None	None	None	Law firms for expert review†	None	Women's Health Initiative review and committee work*; Best Doctors, Inc. case reviews*	Honoraria for reviews for Ebix, MedLink, Medscape*
Eric Smith	University of Calgary	Canadian Institutes of Health Research†; Brain Canada†	University of Ottawa Heart Institute†; McMaster University†	None	None	None	Bayer*; Biogen*; Cyclerion*; Javelin*	UpToDate*
Farzaneh Sorond	Feinberg School of Medicine Northwestern University	None	None	None	None	None	None	None

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Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Barney Stern	Johns Hopkins University	None	None	None	None	None	None	None
Jeffrey Switzer	Augusta University	None	None	None	None	None	None	None
Stavropoula Tjoumakaris	Thomas Jefferson University	None	None	None	None	None	None	None
Stanley Tuhrim	Mount Sinai Hospital	None	None	None	None	None	None	None
David Wang	Barrow Neurological Institute	None	None	Boehringer Ingelheim*	None	None	None	None
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Daniel Woo	University of Cincinnati	NIH2020†	None	None	None	None	None	None
Bradford Worrall	American Academy of Neurology	NIH†	None	None	None	None	None	None
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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