GUIDELINES AND STANDARDS

Recommendations for the Assessment of Carotid Arterial Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk: From the American Society of Echocardiography

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Atherosclerotic plaque detection by carotid ultrasound provides cardiovascular disease risk stratification. The advantages and disadvantages of two-dimensional (2D) and three-dimensional (3D) ultrasound methods for carotid arterial plaque quantification are reviewed. Advanced and emerging methods of carotid arterial plaque activity and composition analysis by ultrasound are considered. Recommendations for the standardization of focused 2D and 3D carotid arterial plaque ultrasound image acquisition and measurement for the purpose of cardiovascular disease stratification are formulated. Potential clinical application towards cardiovascular risk stratification of recommended focused carotid arterial plaque quantification approaches are summarized. (J Am Soc Echocardiogr 2020;■:■-■.)

Keywords: Carotid plaque, Atherosclerosis, Risk stratification

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BACKGROUND

Atherosclerotic cardiovascular disease (CVD) remains the leading global cause of morbidity and mortality.[1] Ultrasound imaging of the carotid artery has the ability to provide a unique "window" into the identification of a patient's underlying cardiovascular risk.[2] The presence and degree of atherosclerosis, as defined by plaque presence detected in the carotid arterial system, has been used to estimate and classify or reclassify an individual's cardiovascular risk. Beyond overall risk stratification, carotid atherosclerosis is also a known predictor of other CVD events, such as stroke resulting from luminal vessel stenosis and plaque rupture.[3,4]

RATIONALE

Several methods have been used to assess risk for CVD using carotid ultrasound, including the following two distinct approaches: measurement of carotid intima-media thickness (CIMT) and assessment of carotid arterial plaque.[3,5] CIMT measurement identifies areas of increased carotid artery wall thickness[6], which provide an easily accessible imaging biomarker for the classification of cardiovascular risk for individuals, as well as population cohorts. However, questions about the precision of CIMT measurements remain, and there is now recognition that the assessment of carotid arterial plaque offers an even greater risk stratification benefit than CIMT. This has led to a paradigm shift in the carotid ultrasound parameters used in risk prediction, specifically, the greater benefit seen with plaque assessment compared with CIMT for risk prediction.[7]

It is now recognized that CIMT may represent more than one distinct morphologic process while plaque primarily reflects atherosclerosis. CIMT may predominantly reflect the presence of cardiovascular risk factors (such as hypertension), whereas carotid plaque, a sub-intimal process, may be more reflective of atherosclerosis, as it correlates with overall atherosclerotic burden in the coronary vascular bed.[8,9] The high prevalence of carotid atherosclerosis in subjects with an otherwise low Framingham risk score has potential implications for screening of subclinical atherosclerosis.[8] Thus, quantification of carotid arterial plaque has emerged as an important tool for CVD risk stratification beyond what is offered by CIMT. This document focuses on the methods to quantify carotid arterial plaque, when present, for the purpose of risk stratification.

CIMT can still provide useful information even if no plaque is present. Currently, CIMT assessment is well described in "The ASE Consensus Statement on the Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Risk".[5] The CIMT related recommendations from this consensus continue to be endorsed by this writing panel. Henceforth, recommendations under the following headings from the previous consensus will not be revisited in the current document: 1) Rationale for Carotid Ultrasound to Identify Subclinical Vascular Disease, 2) Instrumentation, Display and Scanning Technique, 3) Reporting of Carotid Ultrasound Study Results, and 4) Training and Certification of Sonographers and Readers.[5] The current document complements the previous consensus in its provision of a standardized approach to defining and quantifying carotid arterial plaque by ultrasound beyond the technical approach to CIMT measurement. Specifically the previous consensus did not provide a standardized approach to plaque quantification. Since the publication of the previous consensus in 2008, carotid ultrasound technology has advanced tremendously, first from the widespread availability of a dedicated three-dimensional vascular ultrasound probe, and now more recently, following the release of a 3D matrix array probe for carotid ultrasound with concomitant analysis software. The current document is the first to provide systematic recommendations for standardization of the quantification of carotid arterial plaque for the purposes of CVD risk stratification.

SCOPE

This consensus statement provides recommendations for the 2- and 3-dimensional quantification of carotid arterial plaque by ultrasound for the basis of CVD risk stratification. Emerging techniques, including the role of ultrasound enhancing agents (UEA) for assessment of intraplaque neovascularization and composition analysis, are also discussed.

Abbreviations and Acronyms
2D = two-dimensional
3D = three-dimensional
ASE = American Society of Echocardiography
CCA = common carotid artery
CIMT = carotid intima-media thickness
CT = computed tomography
CVD = cardiovascular disease
FDG = fluorodeoxyglucose
GSM = grayscale median
ICA = internal carotid artery
IPN = intra-plaque neovascularization
MACE = major adverse cardiovascular events
MRI = magnetic resonance imaging
PDA = pixel distribution analysis
PET = positron emission tomography
UEA = ultrasound enhancing agent
VWV = vessel wall volume

DEFINITION OF PLAQUE - PROTUBERANT AND DIFFUSE TYPES

Carotid arterial atherosclerosis is thought to develop beneath the intimal layer in the sub-intima. In contrast, the medial layer is subject to non-atherosclerotic medial hypertrophy commonly induced by aging and hypertension. Since the largest portion of CIMT (~99% in healthy individuals and ~80% when diseased) consists of the medial layer, CIMT has not been shown to consistently add to CVD risk prediction. Carotid plaque, on the other hand, represents the atherosclerotic process itself, and starts in the intimal layer and has thus been shown to predict CVD events better than CIMT.[7,10] Despite this difference in carotid arterial phenotypes, which have been used to describe associations with CVD events and risks[4,11], it can be difficult to discern medial thickening from diffuse atherosclerotic plaque. Though some atherosclerotic plaques are discrete lesions that can be easily distinguished from the surrounding wall, plaque can also be eccentric and spread over the surface of the wall, appearing indistinct from the media. In such cases it is difficult to determine whether there is simply medial thickening present or eccentric, diffuse plaque. Thus, arbitrary definitions to define the presence of diffuse plaque beyond a certain CIMT threshold have been proposed.[12] Adding to this complexity is the debate as to whether the transition from increased CIMT to plaque formation is a continuous process[13], or if CIMT and plaque are truly separate phenotypes.[14]

A commonly reported threshold value to define diffuse plaque is a CIMT value greater than 1.5 mm or a focal intimal medial thickening of greater than 50% of the surrounding area.[15,16] However, confusion occurs because ultrasound resolution now allows for the visualization of distinct protuberant plaque lesions that could be smaller than this threshold value. Furthermore, even the threshold CIMT value signifying plaque varies among studies. For example, in one study, plaque was defined as a focal thickening of the intima-media greater than 1 mm, protruding into the lumen, that was at least twice as thick as the surrounding normal CIMT, thus providing varying definitions of plaque ranging from 0.5 mm to >1.5 mm.[17] In comparison, another study defined plaque as CIMT >1.2 mm.[18] In contrast, the European Mannheim consensus defined plaque as a focal thickening that encroaches into the lumen by 0.5 mm or by 50% of the surrounding intimal-medial thickness or where CIMT is >1.5 mm.[19]

Our writing panel selected a CIMT threshold value signifying plaque that is slightly more conservative than the Mannheim consensus[16,19] by recommending ≥1.5 mm (vs >1.5 mm) as the cut-off CIMT threshold value for the presence of diffuse plaque. This newly established Plaque Grading Consensus, described in detail below, now allows for the identification and characterization of protuberant plaque lesions smaller than the CIMT threshold value for identifying diffuse plaque. In other words, we recognize that plaque lesions smaller than 1.5 mm can be highly resolved with today's technology. Advances in ultrasound now allow for identification of such small lesions in exquisite detail, allowing for both quantification and even potential analysis of composition. Thus this modern grading system sets a framework for continued outcomes-based research across the spectrum of plaque lesion shapes, sizes, and types.

Recommendation #1: *We recommend that carotid arterial plaque visualized by ultrasound (with or without use of an ultrasound enhancing agent [UEA]) be defined in one of the following 2 ways: 1) any focal thickening thought to be atherosclerotic in origin and encroaching into the lumen of any segment of the carotid artery (protuberant-type plaque) or 2) in the case of diffuse vessel wall atherosclerosis, when carotid intima-media thickness (CIMT) measures ≥1.5 mm in any segment of the carotid artery (diffuse-type plaque).*

Recommendation #2*: We recommend the evaluation of both protuberant and diffuse types of carotid arterial plaque for cardiovascular risk stratification and the serial assessment of atherosclerosis.*

Recommendation #3: *We recommend that* ***first****, the carotid arterial wall be visually scanned for the presence of protuberant plaque, and* ***if absent, then*** *carotid intima-media thickness (CIMT) measurement be performed to identify the presence of diffuse plaque (defined as CIMT ≥1.5 mm). If performed, CIMT should be measured as described in the ASE Consensus Statement on the Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Risk.*[5]

CLINICALLY SIGNIFICANT CAROTID ARTERIAL PLAQUE OR CIMT

It is recognized that in some centers, repeat evaluation of CIMT in the absence of plaque is considered if CIMT is >75th percentile for age, race, and gender.[20] Despite the lack of evidence surrounding the frequency of repeat testing, an interval for repeat testing of 2-5 years has been utilized in population studies, although published evidence suggests that more frequent CIMT measurements could increase the precision of the assessment of CIMT progression.[21] Methodological limitations of this study notwithstanding, our expert panel *recommends against* serial CIMT measurements for CVD risk stratification especially when not meeting the threshold for diffuse plaque (*≥1.5 mm)*. We recognized that based on limited or anecdotal evidence, there may be value in serial CIMT measurements in the hands of some experts for research,[22,23], monitoring of progression or regression in specific cases [24,25], and as a potential tool to alter patient

behavior.[26] Additionally, it is possible that over time, an individual patient may have a CIMT value that has increased to ≥1.5 mm, signifying the development of diffuse atherosclerotic plaque by our definition; however the clinical utility of such long term CIMT monitoring is not yet established.

We have suggested that a CIMT ≥1.5 mm be considered a clinically significant lesion for patients less than 65 years of age. The thickness (also known as height in the long axis view) of a carotid arterial plaque lesion, whether it is protuberant or diffuse, was chosen as the initial measure to define plaque because of its widespread availability and because this variable can be measured in both protuberant or diffuse types of plaque lesions (Figure 1). Additional quantification techniques such as area and volume apply mostly to protuberant-type plaque lesions, and are difficult to define in atherosclerotic lesions that are diffusely layered along the intimal wall. Such lesions may be focal or diffuse wall calcification layered in a concentric or eccentric manner and may represent atherosclerotic or non-atherosclerotic processes. Accordingly, our panel suggests the grading system for both protuberant and diffuse plaque lesions as described in Figure 1.

The grading system does not reflect the degree of vessel occlusion but attempts to standardize the size of an individual plaque lesion for the purpose of comparison across studies. It is important to note that Grade I characterization applies only to small protuberant types of plaque lesions. This is because, though ultrasound can now resolve such small protuberant lesions, if the plaque is non-protuberant (diffuse or eccentric) and less than 1.5 mm in thickness, it is currently not possible to distinguish whether this is entirely due to medial thickening or is intimal. However at a CIMT value of 1.5 mm or greater (Grades II and III), this framework attributes the thickness to be due to diffuse atherosclerotic plaque (mostly intimal rather than medial) and is thus considered a plaque equivalent. The Grades II and III measurements are applied to obviously protuberant plaque in the same manner for simplicity (Figure 1).

Recommendation #4*: We recommend against serial carotid intima-media thickness (CIMT) measurements in an asymptomatic patient. Repeat measurements are not recommended unless the Grade and (CIMT) meets criteria for diffuse-type plaque (Grades II or III, and CIMT ≥1.5 mm) in which case it is a plaque equivalent.*

QUANTIFICATION METHODS

Two-Dimensional Techniques for Quantifying Plaque

Interest in plaque quantification significantly grew when it was discovered that the presence or absence of plaque conferred additional advantage to risk stratification beyond that provided by CIMT alone (ARIC Study).[27] It was recognized that if simply the presence or absence of plaque re-stratified patients beyond traditional risk factors, then examining the amount of plaque may further personalize a patient's risk assessment.

An early, highly variable approach, was to quantifying plaque using a visual **plaque score,** which evaluated and reported the total number of plaques or affected segments occurring anywhere in the common carotid artery (CCA), carotid bulb, or internal carotid artery (ICA) in any wall (near, far, lateral). More precise methods include 2-dimensional (2D) quantification techniques such as the **maximal plaque height** or thickness. Another common 2D approach has been the calculation of the **plaque area** where the area of one or multiple plaques is measured, and the total value reported. The advantages, disadvantages, and data with respect to outcomes for these 2D quantitative measures are briefly summarized followed by recommendations for performance.

Plaque score. The plaque score is a semi-quantitative approach where the total number of sites containing plaque along the CCA, carotid bulb, and ICA are visualized and summed. This approach varies greatly among studies - some investigators count plaque lesions in any visualized segment, whereas others count only the lesions seen in easily identified segments such as the distal first centimeter (cm) of the CCA, bulb, and proximal ICA. Two important analyses from the Rotterdam Study, a prospective, population-based cohort that aimed to determine the occurrence of CVD (among other disease) in elderly people, calculated plaque score using a unique process. Both studies (n_1=4217 and n_2=6389) measured the presence of carotid plaques at 6 locations in the carotid arteries (two sides each of the CCA, bifurcation, and ICA). The total plaque score ranged from 0 to 6 and was calculated by adding the number of sites at which a plaque was detected, divided by the total number of sites for which an ultrasound image was available, and multiplying by 6 (maximum number of sites).[28,29] In the second study (n=6389), patients with a plaque score of 0, 1, 2, and ≥3 points were considered to have no, mild, moderate, or severe carotid atherosclerosis, respectively.[28,29]

For the purposes of risk prediction, and in order to attempt standardization, we recommend that if a plaque score is being calculated, then lesions limited to the distal 1 cm of the CCA, bulb, and proximal 1 cm of the ICA be included in the counting.[29] The need for further effort toward standardization of the plaque score is recognized.

Clinical studies have shown an association between plaque score and incident CVD. In the Three-city study of 5895 individuals (aged 65-85 years) free of CVD, the presence of plaque in one site was associated with a hazard ratio (HR) of 1.5 [95% confidence interval (CI) = 1.0-2.2] while the HR for plaque at ≥ 2 sites was 2.2 (95% CI = 1.6-3.1; $p_{for\ trend} < 0.001$).[30] The addition of plaque information to traditional risk factors also improved the area under the curve (AUC) for CVD prediction from 0.728 to 0.745 ($p = 0.04$) with a net reclassification index (NRI) of 13.7%. Another study showed that in 367 men (mean age 78±4 years) the hazard ratio for mortality over 4 years increased from 2.89 for a plaque score of 1-2 to 4.53 for a plaque score of 7-12.[31]

Advantages. An important advantage of the plaque score is its ease of performance and lack of need for advanced quantification software. Additionally, as a distinct plaque lesion is not quantified with this method, but simply visualized and counted, the angle or plane of imaging is less critical. Despite the plaque score being a relatively gross reflection of the extent of plaque development, it has more predictive utility than simply reporting the absence or presence of plaque.

Disadvantages. The plaque score is a semi-quantitative method that simply counts the number of lesions. This method does not consider additional parameters such as the size of an individual plaque lesion which would then otherwise better reflect the overall extent of atherosclerosis. Additionally, because the number of plaque lesions at distinct sites is counted in this method, the score may not be clear as to whether two distinct plaque lesions are in fact contiguous, thus providing an overestimation. Similarly, there may be a significant degree of protuberant contiguous plaque, but if this is just one large lesion, the plaque score will underestimate the extent of atherosclerosis.

Plaque height/thickness. Carotid plaque thickness or height may be considered a variation of the maximal CIMT measurement but differs in that it represents the degree to which the plaque protrudes in a radial manner from its origin, along the vessel wall, into the lumen. To conduct this measurement, some investigators suggest

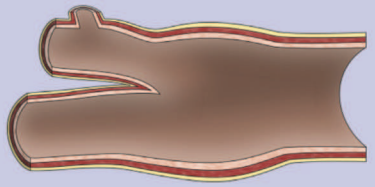
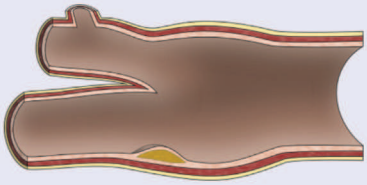
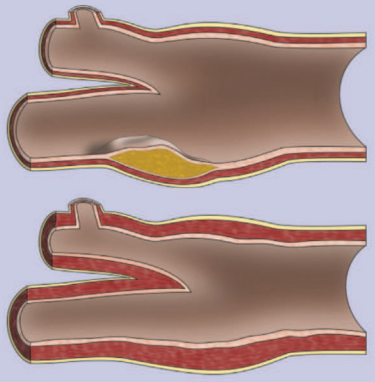
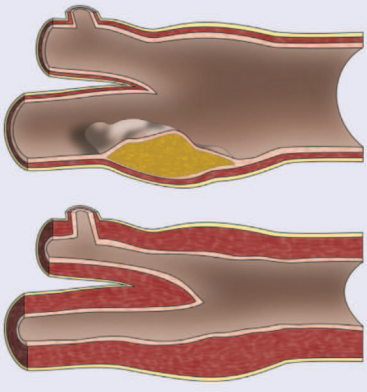
Grade	Plaque Type		Plaque Thickness
0		No plaque	IMT < 1.5 mm
I		Protuberant (Focal thickening of vessel wall)	< 1.5 mm
II		Protuberant or Diffuse (Vessel wall thickened throughout; (CIMT ≥1.5 mm)	1.5 – 2.4 mm
III		Protuberant or Diffuse (CIMT ≥ 2.5 mm)	≥ 2.5 mm

Figure 1 Plaque Grading Consensus: carotid medial thickening and intimal plaque. Carotid intimal-medial thickening is thought to involve thickening of the medial layer whereas plaque is thought to be an intimal process as suggested in this schematic. However, diffuse intimal thickening may also occur that is difficult to distinguish from a medial process, and though not protuberant, eccentric or concentric thickening of 1.5 mm or greater is suggested to be a plaque equivalent by this system.

electrocardiographic gating in order to measure at the same phase of the cardiac cycle. Typically, cross-sectional (transverse) sweeps to evaluate for the presence of plaque are made and then once a plaque lesion is identified, electronic calipers (available with most software) are placed beginning along the origin of the plaque at the vessel wall, into the lumen (at right angles to the wall) along the most protuberant aspect of that particular plaque. The maximum plaque height or thickness among all identified plaque lesions, visualized in both the right and the left carotid arteries, is then reported. It is important to note that studies utilizing this method do not sum the plaque heights measured but report the single largest plaque height measured from any plaque identified in the patient. Plaque height measured in this manner is highly reproducible. The intra-class correlation coefficient for inter-observer and intra-observer reliability were 0.77 and 0.94, respectively, in the Northern Manhattan Study (NOMAS).[32] Variability in this method is related to identification of the location within the vessel wall, where plaque height measurement should begin. To reduce variability across studies, we recommend beginning the measurement at the adventitial-medial layer, similar to CIMT measurement.

Association of Plaque Height with Outcomes. Maximum plaque height ≥1.54 mm has been shown to be associated with significant coronary artery disease.[33] Similarly, asymptomatic subjects with advanced atherosclerosis of the carotid artery (carotid plaques with a CIMT ≥ 3.5 mm and flat carotid plaques with a CIMT > 2 mm) have been shown to have a high risk of coronary heart disease.[34] In the High Risk Plaque (HRP) Bioimage study, hazard ratios for major adverse cardiovascular events (MACE) for the maximum carotid plaque thickness were 1.96 (95% CI 0.91-4.25, $p = 0.015$) for primary MACE [cardiovascular death, myocardial infarction, or stroke] and 3.13 (95% CI 1.80-5.51, $p < 0.001$) for secondary MACE (all-cause death, MI, ischemic stroke, unstable angina, or coronary revascularization).[35]

Advantages. The main advantage of using maximum plaque thickness is that it is a precise quantitative measurement but remains very simple to perform using a standard 2D linear probe. It is usually easy to visualize the largest plaque from any segment of the right and left common carotid arteries, and then one only needs to measure the height of the largest plaque. Furthermore, this method has supportive data demonstrating association with outcomes.[36]

Disadvantages. Some of the same disadvantages associated with CIMT measurement occur with measurement of plaque thickness as well. It is recognized that common to all two-dimensional ultrasound techniques, the maximal plaque height may be out of plane and underestimated, or overestimated if scanning is not performed through the center of the artery.[37] Whether a long- or short-axis view of the artery is obtained, the maximal plaque height will be an underestimate if the acquisition is not through the plane bisecting the largest or most protuberant component of the plaque. Another disadvantage of 2D plaque height is that thickness may not truly reflect the burden of disease, because such lesions also have *width*. For example, a very small or minor plaque lesion that is protuberant, will have a higher thickness value compared with an extensive and heavily layered plaque that may not be as protuberant but is more eccentric and has a greater overall volume burden. Many of these disadvantages can be overcome through the acquisition of a three-dimensional image if technology is available (described in detail below). On balance, the writing group concluded that there are sufficient advantages (especially simplicity) to performing 2D plaque thickness measurement whether this is acquired from a 2D or 3D imaging probe.

Recommendation #5: *We recommend that plaque thickness (also known as height) be measured as the initial 2-dimensional approach* for quantification of carotid ultrasound plaque.*

**Though plaque height is often measured from 2D images, it can be obtained from a 3D image acquisition when available, to overcome the out-of-plane limitations of 2D imaging.*

Recommendation #6: *The maximal plaque height should be measured from the side in which a plaque is detected (unilateral) or from both the right and left carotid arterial segments (bilateral) using a caliper placed at the adventitial plane**, and extending into the center of the lumen at right angles to the vessel wall. For the purposes of standardization, this measurement should be taken from any segment of the long and short axis of the carotid artery (bulb, ICA, CCA) and the view and segment reported accordingly.*

***This measurement begins at the same plane as where the carotid intima-media thickness (CIMT) measurement begins in order to be consistent with defining plaque beyond the CIMT threshold of >1.5 mm.*

Plaque Area. Carotid plaque area is the most advanced of the 2D quantification methods. This method begins with a manual sweep of the carotid artery, typically scanning the artery in cross section, to initially identify plaque lesions. Once identified, the lesion is imaged in a manner that would provide its largest area, usually in the longitudinal view (long axis) of the carotid artery. The lesion is then manually traced using basic software present in most analysis packages. A more advanced analysis can occur if semi-automated or automated software is available. For example, in the High Risk Plaque study protocol, the media-adventitia boundary and the lumen-intima boundary are marked manually and then the plaque area is traced in an automated manner. If multiple plaques (same artery or bilateral) were present, they would be summed to define the total plaque area. The semi-automated method has been validated with CVD outcomes.[38]

Advantages. Carotid plaque area provides the most information on plaque "quantity" or burden that is available through 2D ultrasound techniques. For example, compared with plaque height, plaque area would be a better indicator of overall plaque burden in distinguishing an eccentric or large layered plaque from a small, protuberant plaque. There are good data demonstrating the association with incident events and also response to therapy.[39,40] Measurement can be performed with commercially available software.

Disadvantages. Two-dimensional imaging measurements are affected by the imaging plane and can introduce variability into area measurements. Cross-sectional imaging helps mitigate this to an extent. Additionally, judging the extent of plaque, i.e., the area surrounding the maximal plaque thickness can be subjective and hence associated with inherent measurement errors. Other general but important limitations associated with standard 2D imaging of arterial plaque include the operator dependence of this method, variable image quality, out-of-plane registration errors and the time requirement, limiting its use in clinical practice.[41] On balance, the writing group concluded that the disadvantages of measuring plaque area outweigh the current limitations of 2D height measurement, and we have not identified this approach as a recommended technique (See recommendations #5 and #6). Figure 2 provides a summary of current 2D methods, including plaque height and area.

Three-dimensional Plaque Quantification

The emergence of three-dimensional (3D) plaque quantification has overcome many of the disadvantages of 2D techniques. Recent

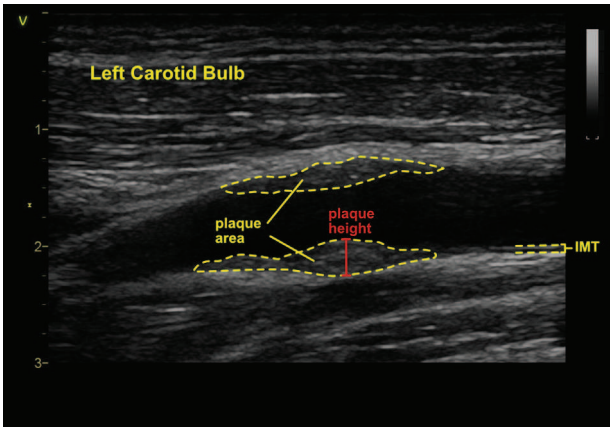


Figure 2 2D methods of plaque assessment. Two-dimensional methods of quantifying arterial plaque, including plaque area and plaque height. Intimal-medial thickening is also shown for demonstration but is suggested to be measured in the absence of plaque. As demonstrated in this figure, plaque thickness is measured beginning from the adventitial plane (same plane as where CIMT begins). It is recognized that in some cases the plaque may be mostly intimal, appear distinct from the underlying medial layer, and not extend fully to the medial-adventitial border, however the measurement should still begin from this medial-adventitial plane for the purposes of standardization.

technological developments now permit 3D volumetric characterization of arterial wall anatomy and function, including plaque characterization, with enhanced spatial resolution.[35,42-45]

Three-dimensional ultrasound techniques were initially developed using a 2D linear array transducer. Carotid plaque burden was calculated in approximately 6000 U.S. participants without known CVD by summarizing all carotid plaque areas after "sweeping" over the carotid artery from proximal CCA to distal ICA in cross section and adding values from the 2 sides. Carotid plaque burden was shown to predict future major CVD events similarly to coronary calcium score and much better than traditional risk factors.[36,46] In another study, carotid plaque volume was calculated by moving a 2D ultrasound transducer manually in cross section and serial scans over time using this method demonstrated that progression in volume (increasing plaque volume) was found to predict future cerebrovascular events and death.[40] Similarly, changes in carotid plaque volume and texture were found to predict future vascular events.[47] Using a 2D ultrasound transducer mounted on a motorized rail placed on the neck, carotid plaque volume was calculated reproducibly.[48] Similarly, using a 2D transducer translated into 3D capture by controlling the speed of movement in short axis along the carotid artery has demonstrated that total plaque volume, captured from the distal 1.5 mm of the CCA until 1 cm distal to the bifurcation, predicted future CVD events.[40] Understandably, methods using a mounted probe or registration following a manual sweep introduced operator dependence and/or artifact, affecting variability.

In contrast to the above mounted probes, the first use of a mechanical 3D ultrasound transducer to assess carotid plaque volume was in patients undergoing coronary angiography using a repurposed breast-imaging probe. This study found that the prediction of coronary atherosclerosis by the 3D method was superior to 2D ultrasound.[37] This study used a 'stacked contour' method to calculate plaque volume. Using the same equipment, carotid plaque volume assessment was shown to be reproducible with an average variability of 5% between measurements, although a considerable number of cases had to be excluded.[49] Subsequent modifications allowed for a mechanical 3D transducer dedicated to vascular imaging. Recently, a 3D matrix array probe for carotid plaque assessment has been developed and is now available. Studies using this novel technology are emerging.[43]

The main advantage of 3D quantification is the ability to measure a specific lesion in all planes. This technique provides an opportunity to follow the disease process over time, for example in order to monitor and assess the response to treatment of an individual lesion. The pitfalls of 2D imaging, where the maximal height or area can be missed if out of plane, are now overcome with a full volume assessment of the arterial lesion. Thus the maximal 2D plaque height (as recommended above) can be more accurately obtained if the full shape and extent of the plaque is visualized by 3D. The 'X-plane' function of novel matrix array technology is especially useful for this determination.

Finally, visualization of plaque in 2 planes often demonstrates the complex morphology and shape of plaque, which hitherto has not been well described (Figure 3). Plaque ulceration and surface irregularity are known contributors to plaque vulnerability and are strongly associated with the presence of rupture, plaque hemorrhage, a large lipid core, reduced fibrous tissue, and overall instability.[50] Three-dimensional (3D) ultrasound allows for complete visualization of the plaque geometry and surface, allowing for the differentiation between ulceration and gaps between contiguous plaques.[51] 3D ultrasound has been used to detect changes in the progression and regression of ulceration over a mean observation period of 17 months.[52] The use of 3D ultrasound imaging for the identification and quantification of ulcers in the carotid arteries of patients with carotid stenosis ≥60% has been noted; the authors found that the presence of 3 or more ulcers correlated with a risk of stroke or death, similar to that predicted by the presence of microemboli.[53] *Further research into the characterization of plaque surface morphology by 3D ultrasound to identify plaque vulnerability and inform cardiovascular risk stratification is required before a recommendation can be made.*

The few disadvantages of the 3D technique include the size and weight of the transducer, which is slightly wider than the usual 2D array. Also, performing a 3D acquisition takes from 1-2 seconds for a matrix transducer. Finally, at its current price, the need for specialized quantification software to process a 3D image may be a limitation for its use (Figure 4, Panels A-C). Currently, data for grading of plaque volume is limited, and further study is needed to develop threshold cut-off values that best predict CVD risk. Finally, 3D imaging may add value to CIMT measurement (3D vessel wall volume [VWV] technique), but further study is needed, and our panel does not recommend this approach for clinical practice.

3D Plaque Volume Acquisition Protocols. Three-dimensional plaque volume of the carotid artery may be acquired using 2 different approaches, depending upon the equipment available – either the single-region protocol where only one segment, such as the arterial bulb, is acquired in 3D, or full-vessel protocol where multiple 3D datasets acquired along the length of the vessel are registered. Following acquisition, volume of plaque may be quantified using either the stacked-contour method in multiplanar reconstruction, or with the use of semi-automated software that collates the plaque area of a series of short-axis images from the acquired 3D volume set (Figure 4, Panels A and B). More rapid and user-friendly quantification tools for plaque volume determination are currently under development.

Single-region protocol. In this approach, the 3D dataset is acquired by centering on a single plaque or selected region or vessel landmark, most often the carotid arterial bulb/bifurcation.

Advantages. This protocol facilitates land-marking and identification of an individual lesion that can be serially tracked with repeated

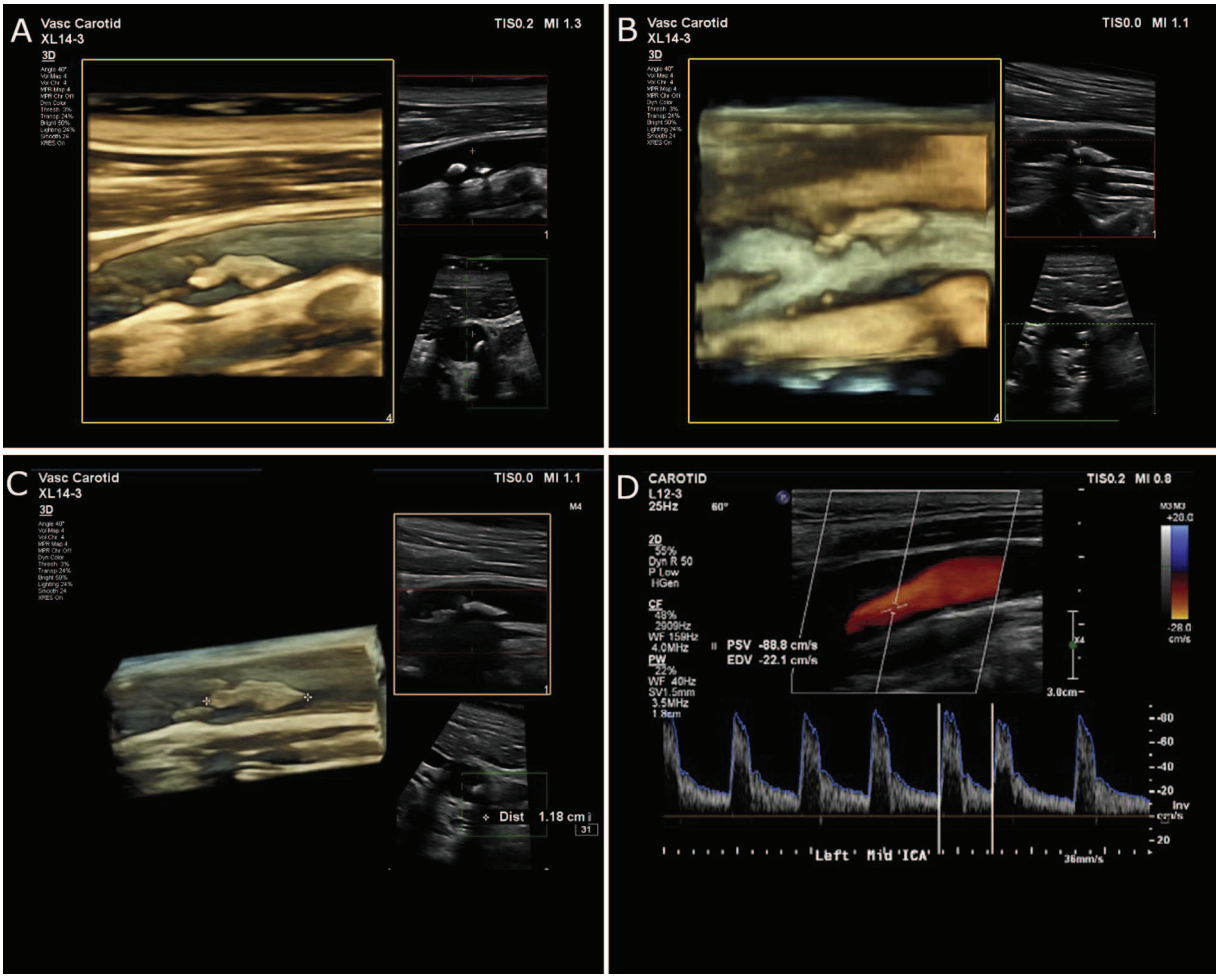


Figure 3 3D plaque acquisition. Three-dimensional imaging of the carotid artery, providing plaque lesion morphology. **A-C**: Images acquired by a matrix array vascular probe of the left carotid artery. **D**: The protocol was preceded by a two-dimensional image and Doppler velocity assessment that suggested 40% stenosis. The three-dimensional images demonstrated the complexity of the arterial plaque, not appreciated by two-dimensional imaging. Three-dimensional imaging may explain why the velocities were lower than expected, by detailing the complexity of the plaque and identifying additional flow channels through the body of the lesion not visualized by two-dimensional imaging. The degree of protuberance seen by three-dimensional imaging was also not appreciated by two-dimensional imaging alone.

measurements. Additionally, selection of one region for acquisition allows for rapid off-line analysis. For example, it has been shown that plaque found in the arterial bulb alone predicts disease and hence simplifies risk assessment.[37] A single-region protocol does not require registration of overlapping regions as would be required with multiple acquisitions from multiple sites along the vessel.

Disadvantages. The main disadvantage of this approach would be missing quantification of plaque that is outside of the region selected for imaging. A second disadvantage may occur related to the equipment available. Using a mechanical transducer, where a 2D linear array is moved along a curved arc, the highest quality of the image occurs around the center of the acquired 3D volume due to the mechanical principle that the angle of the beam formed will not be perpendicular to the vessel further from the center. The use of a matrix transducer eliminates this problem and theoretically provides higher quality imaging with the single-region protocol.

Full-vessel protocol. In this approach, multiple 3D datasets are acquired along all visualized portions of the common and internal carotid arteries.

Advantages. The advantage of this approach is that the volume of all plaque lesions within the carotid artery can be visualized and the total plaque burden can be summed.

Disadvantages. While the time for additional image acquisition is not significantly increased during the scanning procedure, greater expertise, time, and resources are required for off-line analysis and registration of these multiple acquisitions. For example, there is the theoretical risk of quantifying a single plaque lesion twice if it is visualized in 2 contiguous acquisitions due to overlap of the regions scanned. Currently there are no techniques to register multiple contiguous 3D acquisitions in order to avoid overlapping of regions. The other disadvantage is the difficulty in standardizing a protocol across patients due to the anatomic variability in the lengths of the visualized segments of the common and internal carotid arteries. Future work, where plaque burden is indexed to the length the vessel visualized, may help standardize quantification of total plaque burden. The development of automated software may also help to eliminate the problem of registering multiple acquisitions along the entire length of the carotid artery. Outcomes data comparing the

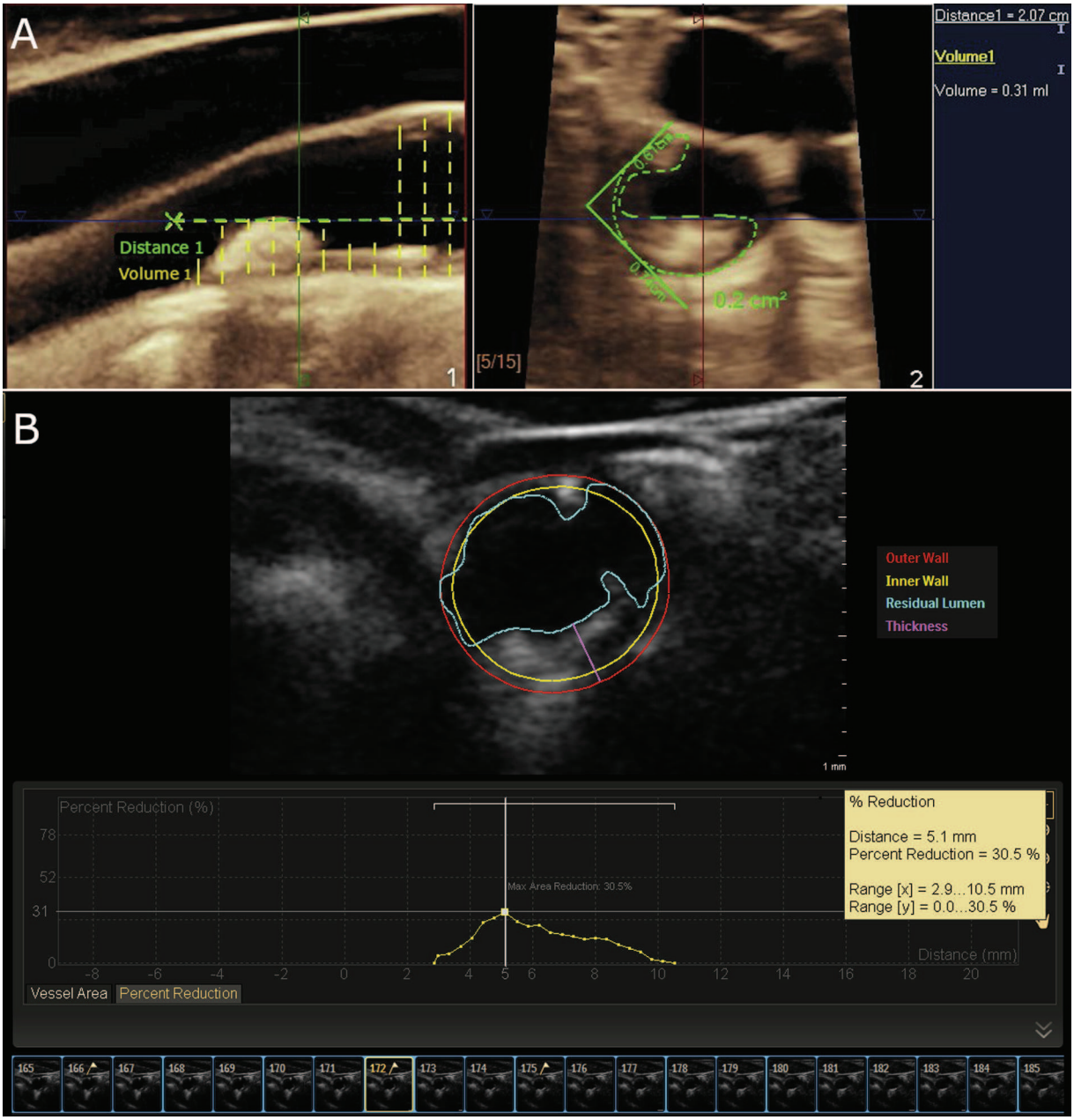


Figure 4 **A** and **B**. 3D plaque volume analysis. Panel **A**: Carotid arterial plaque, acquired by 3D ultrasound and quantified by the stacked contour method. The arterial plaque is identified in the 3D volume dataset using multi-planar reconstruction (MPR) mode. The length of the plaque is identified, and the stacked contour method allows for area calculation of orthogonal views of the plaque along a series of 'slices.' The slices are integrated by the software to provide a volume measurement. Panel **B**: Carotid arterial plaque, acquired by 3D ultrasound and quantified using specialized semi-automated software (Philips Healthcare VPQ). The acquisition begins with a short-axis view of the bifurcation in a series of image frames (similar to a video segment). The start (first frame) and end (last frame) of the plaque are outlined in short-axis using an ellipse and represent "no plaque", then the key frame in the center of the plaque is outlined to represent "plaque". The total plaque volume, maximum thickness, and % lumen reduction are automatically calculated. Reference frames can be manually modified as necessary. The software places the outer wall at the medial-adventitial layer (*red circle*). Following input of the estimated size of the medial thickness (typically 0.5 mm), the software creates the yellow circle representing the intimal-medial thickness 0.5 mm in from the outer wall. Using a form of edge detection, the software traces the residual lumen as echogenic areas extending beyond the inner wall (*cyan line*). The area between the residual lumen and the inner wall (intimal-medial plane) represents plaque. The software models these parameters for each slice derived from the three-dimensional reconstruction, each of which can be manually reviewed and adjusted. Automated registration of this modeling and slices through the full-volume acquisition provide plaque volume and % lumen reduction.

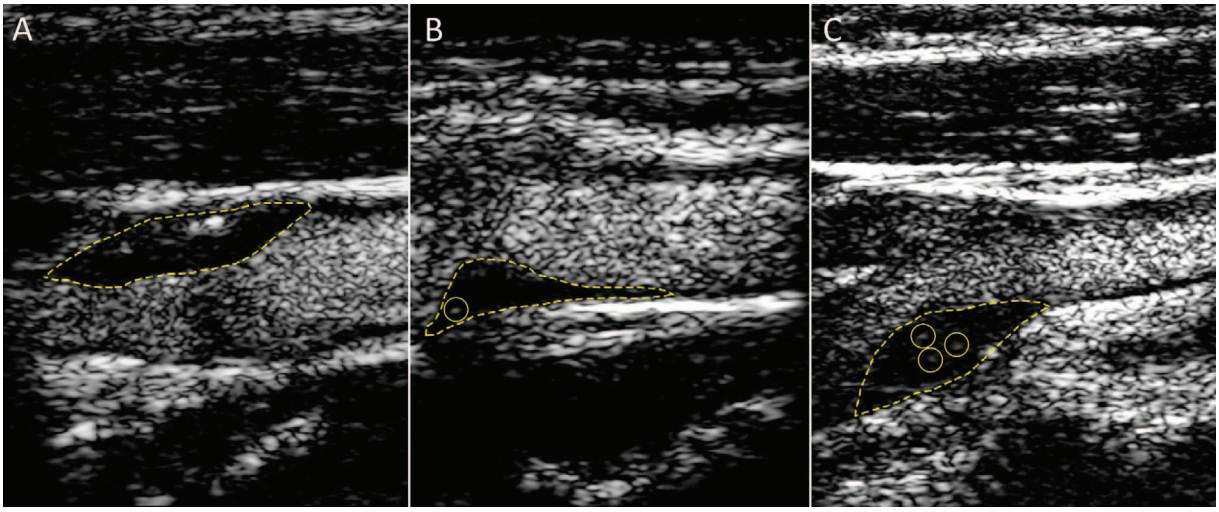


Figure 5 Contrast-enhanced carotid ultrasound for the detection of plaque neovascularization. Adapted from Mantella *et al*.[60] with permission. Carotid intraplaque neovascularization scoring method. Representative contrast-enhanced ultrasound images of carotid plaques. **(A)** demonstrates a plaque score of 0, no visible microbubbles within the plaque; **(B)** demonstrates a plaque score of 1, minimal microbubbles confined to peri-adventitial area; **(C)** demonstrates a plaque score of 2, microbubbles present throughout the plaque core. The yellow dotted line outlines the plaque lesion. Yellow circles depict intraplaque contrast microbubbles.

full-vessel and single-region 3D protocols have not been reported, and thus our panel acknowledges that the following recommendations are based on expert opinion and consensus.

Recommendation #7: *We recommend the quantification of plaque volume for an individual plaque lesion when required (e.g., morphologic assessment, serial assessment, or pre-operative consideration), using either the stacked-contour method or specialized semi-automated tools.*

Recommendation #8: *We recommend the quantification of right and/or left carotid arterial plaque volume using 3-dimensional ultrasound for cardiovascular risk stratification.*

Recommendation #9*: We recommend the single-plaque or single-region protocol where the 3-dimensional volume acquisition is centered over the identified plaque or the right and left carotid arterial bulb, allowing for quantification of total plaque volume in the distal common carotid artery (CCA), bulb, and bifurcation, as well as in the portion of the internal carotid artery (ICA) that can be visualized.*

Recommendation #10: *We recommend the consideration of a full-vessel protocol* ***provided the following criteria are met:*** *time, expertise, equipment, and analytic software are available for accurate registration of multiple 3-dimensional volume acquisitions. In this latter protocol, total carotid arterial plaque is calculated by summing the volume of plaque seen in all major segments of the right and left carotid arteries.*

Plaque Assessment Beyond Quantification- the Concept of Vulnerability. It is increasingly recognized that major cardiovascular clinical events are not solely a result of linear progression of atherosclerotic vascular narrowing that culminates in an acute luminal obstruction. Rather, acute events are often triggered by pathologic events within an unstable plaque, characterized by increased intraplaque neovascularization driven by local hypoxia, inflammation, etc.[40,49,54,55] This re-assessment of vulnerable plaque physiology has ignited interest in developing an *a priori* biomarker for the identification of plaque features that confer higher risk for subsequent adverse events. In a landmark study in 2010, it was reported that the presence of high intra-plaque vessel density and intra-plaque hemorrhage were the only significant histological findings associated with plaque vulnerability and subsequent clinical cardiovascular events in a prospective analysis of 818 patients who underwent carotid endarterectomy.[56] The authors further noted that the presence of macrophage infiltration, a large lipid core, calcification, and smooth muscle cell infiltration within the plaques were not associated with cardiovascular outcomes. These recent observations[56] are consistent with an earlier cross-sectional study of patients who had undergone carotid endarterectomy and were found to have increased intraplaque neovascularity compared to patients with no history of CVD events.[57] This concept has been further supported by the reported association between increased [^{18}F]-fluorodeoxyglucose (FDG) uptake in patients with symptomatic carotid stenosis as compared to asymptomatic lesions.[58]

Plaque neovascularization, anatomy, and contrast-enhanced ultrasound. The applications of an ultrasound enhancing agent (UEA) in relation to plaque composition are based on its use to enhance overall image quality, resulting in better definition of plaque anatomy, including vessel wall ulcerations. The administration of UEAs in combination with changes required in the technical/power settings are outlined in detail from a past ASE Guidelines Update.[59] Further, UEAs provide an unparalleled approach to identifying that spatial and temporal heterogeneity of intra-plaque neovascularization (IPN) directly correlated with vulnerable plaque and adverse clinical outcomes (Figure 5).[60] The commercial UEAs used in this application are a solution of gas-filled bubbles that appear hyperechoic on an ultrasound image.[61] In addition to the assessment of IPN, a simpler use of a UEA is to enhance the luminal border, which can reveal echolucent plaque, and assist in identifying plaque surface irregularities and ulcerations.[41,62,63]

At the present time, administration of UEAs, either for IPN assessment or plaque border detection, is off-label and is not mentioned in the most recent ASE guidelines on UEAs.[64] However, the writing panel recognizes the critical value of UEAs for delineation of echolucent areas of plaque as well as accurate plaque quantification, and their emerging role in detection of plaque vulnerability. Although some outcomes-based research is now published[60], additional studies are needed to support the inclusion of UEA administration in clinical

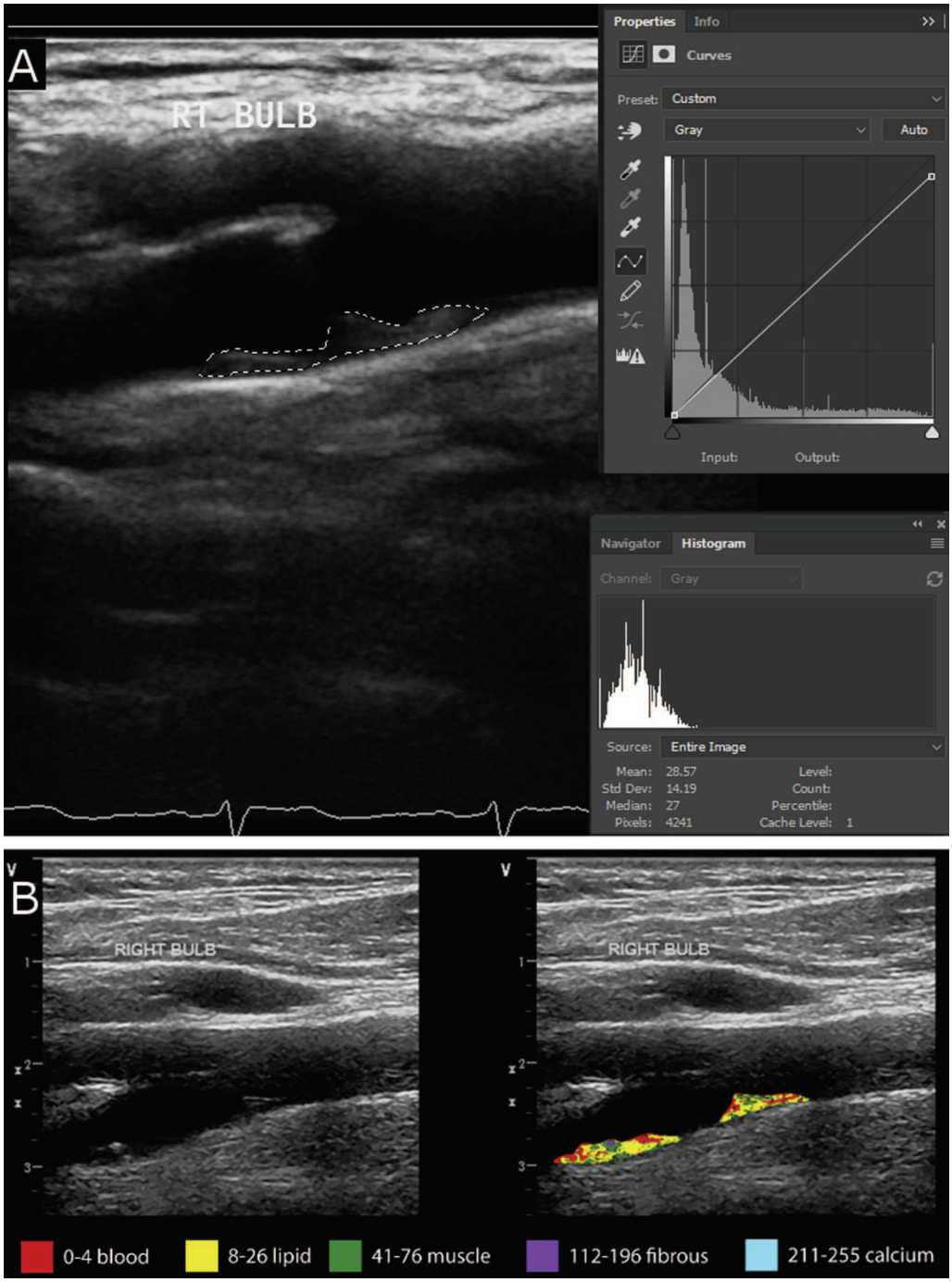


Figure 6 Plaque composition analysis by GSM and pixel distribution analysis (PDA). **(A)**: Grayscale median (GSM) analysis of carotid plaque is conducted by creating a region of interest outlining the plaque, normalizing the plaque so that the lumen is 0 and the adventitia is 190, and obtaining the GSM from the histogram of gray value distribution in the normalized plaque. Adapted from Johri *et al*.[69] with permission. **(B)**: Pixel distribution analysis (PDA) showing the color-mapped grayscale ranges representative of different tissue types. Adapted from Herr *et al*.[70] with permission.

practice recommendations. *The writing panel calls for additional research demonstrating the added value of ultrasound enhancing agents (UEAs) for plaque border delineation and for assessment of IPN to identify vulnerability and enhancement of cardiovascular risk stratification.*

Gray Scale Median Analysis. Different tissue types have differing levels of echogenicity to produce a range of gray scale values in an ultrasound image. Characterization of these gray scale values may be used to provide information about tissue composition in a region of interest such as an arterial plaque lesion. [65] While plaque characteristics were initially assessed qualitatively based on appearance and graded according to echogenicity and heterogeneity[66-68], the quantitative method of grayscale median (GSM) analysis was developed to extract and quantify the median grayscale value of the plaque from an ultrasound image. The grayscale median is the median gray value of the pixels in the plaque ultrasound image (Figure 6A).[71]

Table 1 Comparison of multi-modality imaging techniques for the assessment of arterial plaque

Modality	Advantages	Disadvantages	Developing Techniques
Ultrasound	• Widely available • Non-invasive • Portable • Low cost • Identification of ulceration, intraplaque hemorrhage • 2D and 3D quantification	• Operator dependent • Technical challenges ◦ Acoustic shadowing from calcification ◦ Vessel tortuosity	• UEA • GSM analysis • 3D lumen assessment
Multidector Computer Tomography (MDCT)	• Image from aortic arch to distal cervical vessels • Identification of plaque ulceration, intraplaque hemorrhage • Identification and quantification of calcification • Quantification of plaque volume	• Radiation exposure • Iodinated contrast exposure • Blooming artifact from calcification	• 3D lumen geometry for shear stress
Magnetic Resonance Imaging (MR)	• Image from aortic arch to distal cervical vessels • High soft tissue contrast • High resolution • High reproducibility • Identification of plaque ulceration, intraplaque hemorrhage	• Low availability • High cost • Long procedure time • Multiple sequences and protocols • Not portable • Complex training • Safety requirements	• 3D based techniques • Molecular MRI
Fluoro-deoxyglucose Positron Emission Tomography (^{18}FDG PET)	• Direct imaging of plaque inflammation	• Lacks anatomic precision • Limited spatial resolution • Non-specific uptake by surrounding tissues • Cost, lack of portability, complex training needs	• Co-registration with CT and MRI • Novel molecular PET tracers

2D, two-dimensional; *3D*, three-dimensional; *CT*, computed tomography; *FDG*, fluorodeoxyglucose; *GSM*, grayscale median; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography; *UEA*, ultrasound enhancing agent.

In addition to overall GSM assessment, other attempts have been made to divide the grayscale into ranges to better represent heterogeneity within a plaque; a feature that is lost when the median grayscale value alone is used. To overcome this limitation, the pixel distribution analysis (PDA) method was introduced, which assigned grayscale ranges to various tissues types including blood, lipid, muscle, fibrous tissue, and calcification, demonstrating good correlation to histology.[65]

Current GSM approaches quantify echogenicity to determine a threshold value for predicting high risk plaque. The ICAROS (Imaging in Carotid Angioplasty and Risk of Stroke) study was a large-scale investigation into the relationship between carotid plaque echolucency as measured by overall GSM and the risk of stroke during carotid artery stenting.[72] The ICAROS study demonstrated that the rate of stroke and transient ischemic attack was greater in patients with GSM values ≤25 compared with patients with plaque of GSM >25. Echolucent plaque was more likely to result in embolism in association with angioplasty and stenting, during or following the procedure.[72] Furthermore, subjects with echolucent atherosclerotic plaques have been shown to be at increased risk of ischemic cerebrovascular events, such as stroke.[73,74] A previous study has reported that plaque with a median GSM of 25.5 was associated with cerebral infarction, and reported the threshold value for risk assessment as a GSM of 35.[75] While there has been no consensus on an exact threshold value for classifying plaque as vulnerable, symptomatic plaque is often correlated to GSM values of 30-40.[76]

A recent study used a method of mapping grayscale value ranges across a plaque using PDA (Figure 6B) in patients assessed for CVD.[70] The authors concluded that increased carotid plaque echogenicity from fibrous and calcium-like tissues correlated with increased coronary artery disease; however, a combination of plaque height, % calcium, and/or % fat increased risk for cardiovascular events. This work points to the potential for incorporating ultrasound carotid plaque composition to enhance risk stratification. Thus, the *pattern* of gray scale values across a plaque lesion using techniques such as PDA may confer greater risk prediction benefit than a gross GSM value representing the global echogenicity of a plaque. Machine learning techniques analyzing such patterns or plaque texture with risk factors and correlation to outcomes offers attractive avenues of future research to define the relationship between ultrasound-detected gray scale values, additional signals (such as radiofrequency), and the atherosclerotic process. *The writing panel calls for further research into the emerging role of gray scale median analysis to identify plaque vulnerability and inform cardiovascular risk stratification.*

Multi-Modality Assessment of Plaque Characterization. Plaque characterization has also been investigated using other imaging modalities. Compared to surgical specimens, multidetector computed tomography (CT) has shown a 94% sensitivity and 99% specificity for the detection of ulcerated plaques.[77] When compared to histology, a 100% sensitivity and 64% specificity for the detection of intraplaque hemorrhage has been reported[78] Carotid plaque characteristics assessed by CT have been correlated to acute stroke events.[79,80] The major

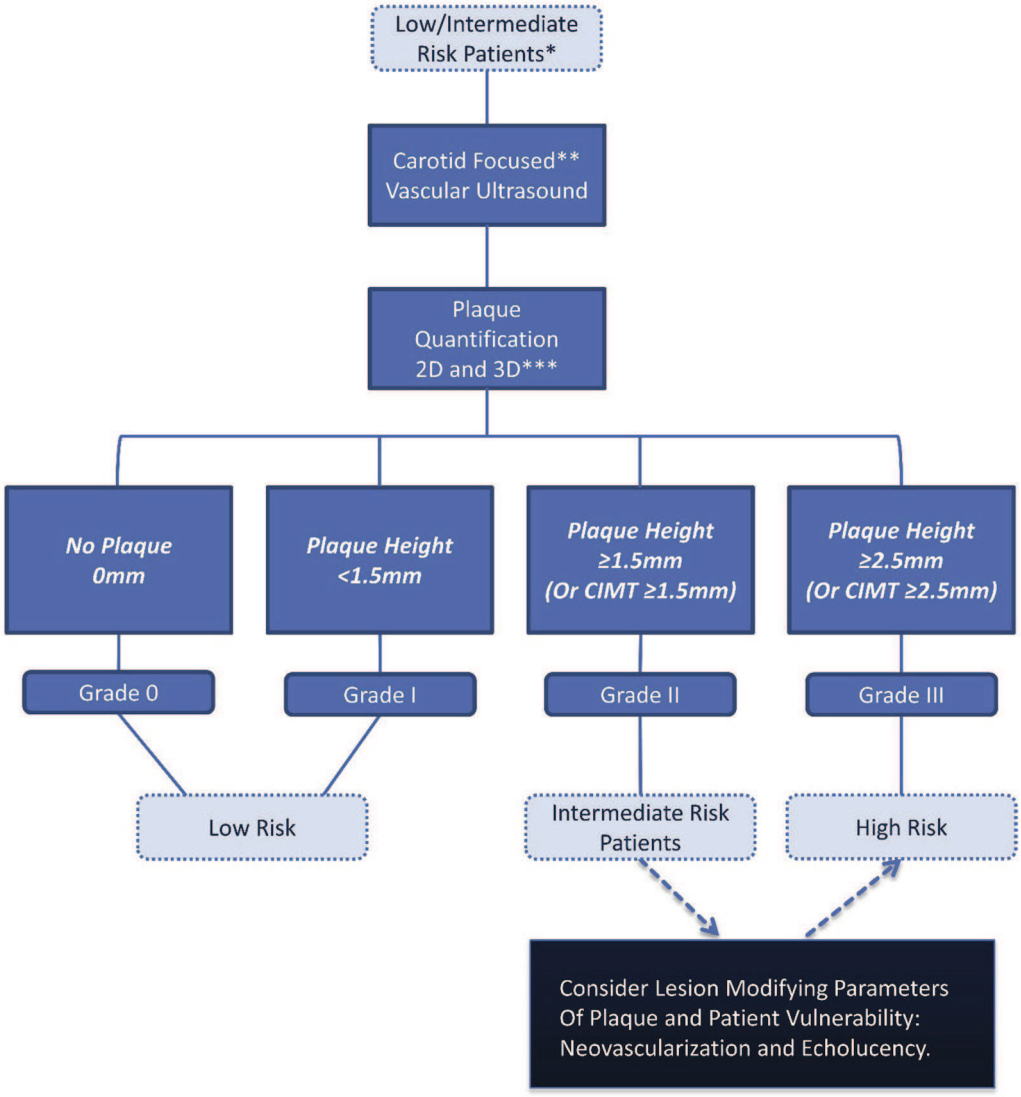


Figure 7 Cardiovascular risk stratification pathway using plaque grading by 2D/3D ultrasound. *Risk Score (Asymptomatic At-Risk Population) adapted from Greenland *et al*. (2010)[95]: *Low Risk:* <6% Framingham Risk Score (FRS), *Intermediate Risk:* Grey Area (6-10% to ≤20% FRS), *High Risk:* ≥20% FRS. **European Guidelines on CVD Prevention in Clinical Practice (Class IIb, Level B); adapted from Piepoli *et al*. (2016).[91] ***3D quantification is recommended to determine the maximal plaque height value from either the left or right carotid arterial bulb. 3D volume should also be measured however, a threshold volume has not yet been determined in large outcome studies. The value of 0.08 ml was found to be associated with significant CAD in a selected population. This algorithm requires updating following further 3D plaque volume investigations.

disadvantages of CT for plaque assessment are the radiation exposure and need for iodinated contrast.

Similar to CT, magnetic resonance imaging (MRI) has also demonstrated good correlation with histology for identification of calcification (sensitivity as high as 100%)[81], unstable fibrous cap (sensitivity 81%, specificity 90%)[82], and lipid-rich necrotic core (sensitivity 91.6% and specificity 95%).[83] Plaque characterization by MRI has been associated with subsequent neurologic events[84], but the heterogeneity of imaging protocols and magnet strength used in previous studies, along with high cost and low availability, limit the use of MRI as a routine risk stratification tool.[84,85]

Enhanced FDG uptake on carotid positron emission tomography (PET) imaging has been shown to correlate with regions of inflammatory cells (macrophages and foam cells) and, to a lesser degree, loose extracellular matrix and neovascularization in atherosclerotic plaque.[86] Symptomatic unstable carotid plaques demonstrate increased FDG uptake compared to asymptomatic plaques[87,88], thus potentially providing a means to identify the vulnerable plaque. Similarly, increased FDG uptake on PET/CT was shown to correlate with decreasing GSM on 2D ultrasound, indicating greater activity in hypoechoic lesions.[89] The disadvantage of PET for carotid plaque characterization is the limited ability to localize tracer to a precise anatomic structure, but hybrid imaging with CT or MRI have the potential to overcome this limitation. A position paper on PET imaging of atherosclerosis was recently published in an effort to optimize and standardize protocols for imaging and interpretation of PET scans in atherosclerosis.[90] While hybrid PET/CT and PET/MRI hold promise for carotid plaque characterization, further work is required before

these techniques are ready for widespread clinical use.[88,90] Table 1 summarizes the advantages and disadvantages of these modalities in comparison to ultrasound. Of note, the non-ultrasound-based methods are valuable for mechanistic research, but given their relative cost, cannot be recommended for serial clinical assessment of atherosclerosis.

APPLICATION OF CAROTID ARTERIAL PLAQUE IMAGING IN CLINICAL PRACTICE

Primary prevention/asymptomatic patients

It appears reasonable to combine established risk scores with plaque imaging. The 2016 European Society of Cardiology Guidelines on Cardiovascular Disease Prevention have included plaque detection as a modifier in cardiovascular risk assessment (class IIb, level B) after the initial assessment has been performed using established risk scores.[91] The same recommendation (class IIb, level B) is given for coronary calcium scoring. A risk modifier is likely to have reclassification potential.[91] Previous work has showed that ultrasound examination allowed improved identification of individuals who could be targeted for prophylactic medical intervention.[92] However, the 2019 American Heart Association/American College of Cardiology guidelines[93] and Canadian Guidelines for the Management of Dyslipidemia for the Prevention of in the Adult[94] have only included coronary calcium scoring but not carotid plaque imaging as a risk modifier. Further studies are needed to obtain more evidence for using plaque assessment as a risk modifier and to define which groups benefit from a combined assessment. This document facilitates this work by recommending standard plaque assessment approaches for comparison across studies. In the assessment of asymptomatic at-risk patients, we suggest a stepwise approach to cardiovascular risk stratification using plaque grading via a focused carotid vascular ultrasound and subsequent 2D or 3D plaque quantification (Figure 7).

Symptoms suspicious of coronary artery disease, but normal non-invasive tests

The functional tests for assessment of coronary artery disease (e.g., stress electrocardiogram, stress echocardiography, stress MRI, and nuclear imaging) cannot detect coronary artery obstruction between 50 and 70%. Although the short-term prognosis of patients with a normal stress test is good, direct assessment of atherosclerosis may be helpful for long-term prognosis and prevention. Recent studies suggest that carotid plaque imaging in patients with normal stress tests provides improved prognostic information: patients without plaque have an excellent prognosis, whereas patients with a normal imaging test for myocardial ischemia, but atherosclerotic plaques in the carotid artery, may benefit from more aggressive medical treatment.[96-100] The combination of carotid plaque assessment with stress testing is a promising area offering enhanced risk stratification. Further multicenter confirmation will allow for consideration of practice recommendations in the future. Monitoring and adjusting treatment of atherosclerosis by repetitive plaque measurements appears to be an attractive application that needs further development of reliable, user friendly tools to assess the carotid plaque burden and clinical studies to define the time intervals and changes in dosing of statins and other medications. *The writing panel calls for further development and study of application tools for the integration of carotid plaque assessment into existing risk stratification algorithms and testing.*

SUMMARY

This document provides recommendations for the definition and quantification of carotid arterial plaque. A framework for grading atherosclerotic plaque based on thickness is provided to facilitate comparison across studies and monitoring of patient outcomes. Of 2D techniques, plaque height is recommended as the preferred approach and formulated to promote standardization. Three-dimensional volumetric ultrasound quantification is preferred when available, and a recommendation for plaque volume quantification is provided to promote standardization. The role of composition analysis to assess plaque vulnerability and tissue types continues to emerge. The important role of plaque analysis by ultrasound in cardiovascular risk stratification continues to require innovative approaches to dissemination of this knowledge and greater efforts toward translation to practice.

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