Carotid Intima-Media Thickness and Plaque in Cardiovascular Risk Assessment

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ABSTRACT

Carotid intima-media thickness (CIMT) has been shown to predict cardiovascular (CV) risk in multiple large studies. Careful evaluation of CIMT studies reveals discrepancies in the comprehensiveness with which CIMT is assessed—the number of carotid segments evaluated (common carotid artery [CCA], internal carotid artery [ICA], or the carotid bulb), the type of measurements made (mean or maximum of single measurements, mean of the mean, or mean of the maximum for multiple measurements), the number of imaging angles used, whether plaques were included in the intima-media thickness (IMT) measurement, the report of adjusted or unadjusted models, risk association versus risk prediction, and the arbitrary cutoff points for CIMT and for plaque to predict risk. Measuring the far wall of the CCA was shown to be the least variable method for assessing IMT. However, meta-analyses suggest that CCA-IMT alone only minimally improves predictive power beyond traditional risk factors, whereas inclusion of the carotid bulb and ICA-IMT improves prediction of both cardiac risk and stroke risk. Carotid plaque appears to be a more powerful predictor of CV risk compared with CIMT alone. Quantitative measures of plaques such as plaque number, plaque thickness, plaque area, and 3-dimensional assessment of plaque volume appear to be progressively more sensitive in predicting CV risk than mere assessment of plaque presence. Limited data show that plaque characteristics including plaque vascularity may improve CV disease risk stratification further. IMT measurement at the CCA, carotid bulb, and ICA that allows inclusion of plaque in the IMT measurement or CCA-IMT measurement along with plaque assessment in all carotid segments is emerging as the focus of carotid artery ultrasound imaging for CV risk prediction. (J Am Coll Cardiol Img 2014;7:1025–38) © 2014 by the American College of Cardiology Foundation.

Recent American Heart Association/American College of Cardiology guidelines designated carotid intima-media thickness (CIMT) along with coronary artery calcium (CAC) score a class IIa recommendation for cardiovascular (CV) risk assessment in asymptomatic adults at intermediate risk of cardiovascular disease (CVD) (1). In addition, consensus documents from the national societies (2) and from the American Society of Echocardiography have simplified intima-media thickness (IMT) and plaque assessment methodology (3). Dedicated ultrasound systems for IMT assessment now incorporate IMT datasets from large clinical studies, which allows generation of CIMT percentile values for individual patients. These recent developments have made IMT and plaque assessment a useful method for CVD risk reclassification in clinical practice (4). Nonetheless, most insurers consider CIMT and plaque assessment as investigational and the data to be insufficient and contradictory to justify reimbursement of CIMT for CV risk assessment (5). This is similar to assessment for CAC, which is considered investigational by insurers (6). Along the same lines the recent US national guidelines recommend against performing CIMT in routine

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imaging of a single segment (13); others imaged multiple segments (14–16). Some studies imaged the far wall of multiple segments (17), whereas others imaged both near and far walls (4,18,19). Far wall measurements of the CCA alone have been favored because the CCA is perpendicular to the ultrasound beam, easily assessable, and reproducible (8–10), whereas the carotid bulb and ICA lie at an oblique angle and are more difficult to image (12). Studies also differed in the type of IMT measurements made (mean or maximum for single measurements, mean of the mean, or mean of the maximum for multiple measurements), varying definition of plaque, whether plaques were included in the IMT measurements, and the different arbitrary cutoff points for CIMT to predict risk. Because of the focal nature of the atherosclerotic process (Figures 2 and 3A), IMT measurements at 1 site can be very different from those taken at another site (14); hence, measuring CIMT from a single site can lower the sensitivity of detecting atherosclerotic changes. Other differences in imaging protocol include the angle from which CIMT is assessed. Some studies imaged only from a single angle (13,20), whereas others imaged from multiple angles (17,18,21). Imaging from a single angle does not completely evaluate the carotid artery in 3 dimensions. Atherosclerosis tends to form at the carotid bulb, particularly toward the outer wall where the shear stresses are low and oscillations in shear stresses are high (22). Extensive ultrasound protocols are required to fully evaluate the degree of atherosclerotic burden and observe a treatment effect (23). The phase of the cardiac cycle (end-systole vs. end-diastole) when CIMT is measured also differs among studies. Because of systolic lumen diameter expansion that leads to thinning of CIMT during systole, CIMT values obtained from end-systole are lower than those obtained in end-diastole (24).

The Kuopio Ischaemic Heart Disease study was the first study to demonstrate an association of CIMT with future coronary events. In this study, every 0.1-mm increment of IMT was associated with an 11% increased risk of myocardial infarction (MI) during follow-up (25). Subsequently, several other large clinical studies, including the ARIC (Atherosclerosis Risk in Communities) study (17), the CHS (Cardiovascular Health Study) (26), the CAPS (Carotid Atherosclerosis Progression Study) (27), the MDCS (Malmo Diet and Cancer Study) (28), and the Rotterdam Study (29), all showed that CIMT can be used to assess incident CVD risk. Plaque presence seemed to have a more profound effect on improving risk prediction in women than in men.

Studies that evaluated whether CIMT provided additional prognostic information over and above clinical practice for prediction of CV events (7). This article reviews studies that evaluated CIMT for CV risk stratification and risk prediction and discusses methodological variability that accounts for differences in findings among studies that has caused confusion about the role of IMT in CV risk prediction. The article summarizes studies using CIMT and plaque in CVD risk association or prediction and discusses the emerging role of carotid plaque as a better marker of CV risk than CIMT.

**CIMT MEASUREMENT**

CIMT is measured between the intimal-luminal and the medial-adventitial interfaces of the carotid artery wall represented as a double-line density on an ultrasound image (Figure 1). The accuracy of the common carotid artery (CCA) far wall IMT measurement was validated against histological specimens (8) as representing the true biological thickness of the vessel wall, whereas the near-wall IMT measurement was shown to have a systematic measurement error because of the echogenicity of the adventitial layer masking the adventitial-medial boundary (9,10) as well as being affected by gain settings (10). The annual changes in IMT are small, and the differences between 25th and 75th percentiles are <1 mm, and, therefore, a high degree of precision is required in CIMT measurement. With sonographer training and strict adherence to quality control of IMT scanning protocol including the angles at which CIMT measurements are made, CIMT offers good interscan and interobserver reproducibility with an intraclass correlation coefficient >0.90 (11), indicating good test characteristics.

The development of automated edge-tracking software, which obviated the need to perform manual measurements, further improved the reproducibility of CIMT measurements (12).

**CIMT ASSESSMENT IN CLINICAL STUDIES OF CVD RISK PREDICTION**

The carotid artery includes 4 segments, beginning with the CCA. This gives rise to the carotid bulb from which arise the external carotid artery and the internal carotid artery (ICA) (Figure 2). Large clinical studies that measured CIMT to determine its value in predicting incident CVD are listed in Table 1. These CIMT studies varied in the comprehensiveness with which CIMT was assessed. Some imaged only 1 side of the neck, whereas others imaged bilaterally (Table 1).
Framingham risk score (FRS) have been largely negative. In the MESA (Multi-Ethnic Study of Atherosclerosis), CCA-IMT did not predict either coronary artery disease or stroke risk after adjusting for the FRS (area under the curve of 0.78 for risk factors plus CIMT vs. 0.77 for risk factors alone in both models) (30). Another study found the area under the curve of 0.69 for CIMT and FRS versus 0.66 for FRS (31). The CAPS showed that even though CIMT was significantly and independently predictive of CV events, when added to the FRS and the European cardiovascular disease risk assessment model systemic coronary risk evaluation (SCORE) models, it did not consistently improve the risk classification of individuals (27). A review of the CIMT studies by Simon et al. (32) shows that in some studies, CIMT added little to the coronary heart disease (CHD) prediction by risk factors, as judged by c-statistic and receiver-operating characteristic curve analysis and that the CHD prediction by CIMT was inferior to that by carotid plaque. Meta-analyses of CIMT studies have also yielded contradictory results. The first meta-analysis that included major clinical studies with CIMT assessment of single or multiple carotid segments showed that for every 0.1-mm increase in CIMT, the future risk of myocardial infarction (MI) increases by 10% to 15% (33). A second meta-analysis that evaluated CCA-IMT alone and excluded CCA or bulb IMT or plaques in 45,828 patients from 14 population-based studies showed that the addition of CIMT does not add clinically meaningful information to the standard prediction modalities (34,35). The Net Reclassification Index (NRI) with the addition of CCA-IMT was only 0.8% for the overall cohort and 3.6% for those at intermediate risk. The NRI examines the net effect of adding a biomarker to the risk-prediction model, and the clinical NRI is the NRI in intermediate-risk patients only. This meta-analysis (34) limited to the evaluation of predictive value of CCA IMT alone was the basis for the recent recommendation of downgrading of CIMT test by the 2013 ACC/AHA prevention guidelines (7). Both meta-analyses (33,34) noted a significant variability in the CIMT methodologies and in reporting of mean or maximal CIMT of single or multiple segments, making it difficult to compare studies or to combine the results from different studies. The findings of this meta-analysis are in contrast to the findings of the ARIC study, which found no significant difference in CHD risk prediction when CCA-IMT alone was added to plaque and traditional risk factors (TRFs) versus the mean combined IMT of all carotid segments added to plaque and TRFs (36). These differences can partly be explained by the fact that in the ARIC study, ICA IMT was only measurable in 43% of study subjects (17).

Hence, in majority of subjects, combined IMT essentially represented CCA and bulb IMT, and plaque can be a representative of bulb IMT because majority of plaques form at the bulb. More recent studies, with better...
<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Sample Size, No. (% Women)</th>
<th>Age of Subjects, yrs</th>
<th>Follow-Up</th>
<th>Carotid Ultrasound Parameters</th>
<th>Plaque</th>
<th>Endpoints</th>
<th>CIMT, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIHDS (25)</td>
<td>1,257 (0)</td>
<td>42-60 yrs</td>
<td>1 month to 2.5 yrs</td>
<td>CCA-IMT, mean of maximal IMT, near and far wall, bilateral</td>
<td>Focal calcified plaque not included</td>
<td>AMI</td>
<td>CCA-IMT increment, 0.1 mm; RR: 2.14 (1.08–4.26)</td>
</tr>
<tr>
<td>CHS (16)</td>
<td>5,020 (60)</td>
<td>72.6 ± 5.5 yrs</td>
<td>5 days to 12 yrs (median, 11 yrs)</td>
<td>CCA and ICA-IMT, mean of maximal IMT, near and far wall, bilateral</td>
<td>Plaque included</td>
<td>MI, stroke, CV death, all-cause mortality</td>
<td>Highest tertile: RR: 1.84 (1.54–2.20)</td>
</tr>
<tr>
<td>ARIC (17)</td>
<td>12,841 (57)</td>
<td>45-64 yrs</td>
<td>Mean follow-up, 15.1 yrs</td>
<td>Mean far wall IMT at 6 sites (CCA, bulb, ICA, bilateral)</td>
<td>Plaque included</td>
<td>MI, CV death</td>
<td>IMT ≥1.0 mm: women: RR: 5.07 (3.08–8.36); men: 1.85 (1.28–2.69)</td>
</tr>
<tr>
<td>CAPS (95)</td>
<td>5,056 (51)</td>
<td>19-90 yrs</td>
<td>Mean follow-up, 4.2 yrs</td>
<td>Mean far wall IMT bilaterally at CCA, carotid BIF, ICA bulb</td>
<td>Not specified</td>
<td>MI, stroke, death</td>
<td>RR for 1 SD: RR 1.17 (1.08–1.24) for CCA-IMT; RR 1.14 (1.05–1.24), for carotid bulb-IMT; RR 1.09 (1.01–1.18) for ICA-IMT.</td>
</tr>
<tr>
<td>MDCS (28)</td>
<td>5,163 (59)</td>
<td>46-68 yrs</td>
<td>Median, 7 yrs</td>
<td>Mean far wall right distal CCA</td>
<td>Plaque included</td>
<td>MI, CV death</td>
<td>RR for highest tertile: 1.50 (0.81–2.59)</td>
</tr>
<tr>
<td>Rotterdam Study (15)</td>
<td>6,389 (61.9)</td>
<td>69.3 ± 9.2 yrs</td>
<td>7-10 yrs</td>
<td>Average of maximal CCA-IMT of near and far wall, bilateral</td>
<td>Not specified</td>
<td>MI</td>
<td>RR: 1.95 (1.19–3.19)</td>
</tr>
<tr>
<td>LILAC (96)</td>
<td>298 (60)</td>
<td>Mean, 79.6 yrs</td>
<td>Mean, 1,152 days</td>
<td>Average of CCA bilaterally, near and far wall</td>
<td>Not specified</td>
<td>All-cause mortality</td>
<td>For 0.3-mm increase in left IMT, RR: 1.65 (1.08–2.5), right IMT, RR: 3.3 (1.4–7.7)</td>
</tr>
<tr>
<td>Three-City Study (52)</td>
<td>5,895 (62.9)</td>
<td>65-85 yrs</td>
<td>Median, 5.4 yrs</td>
<td>Mean CCA-IMT bilaterally, near and far wall</td>
<td>Plaque excluded</td>
<td>MI, angina, CV death, revascularization</td>
<td>HR for fifth quintile: 0.8 (0.5–1.2)</td>
</tr>
<tr>
<td>IMPROVE (69)</td>
<td>3,703 (52)</td>
<td>Median, 64.4 yrs</td>
<td>Median, 36.2 months</td>
<td>Maximal and mean CCA, ICA, BIF, bilateral</td>
<td>Plaque included</td>
<td>MI, SCD, angina, stroke, TIA, revascularization</td>
<td>HR for 1-SD increase: mean CCA-IMT: 1.33 (1.18–1.50); mean ICA-IMT: 1.34 (1.18–1.51)</td>
</tr>
<tr>
<td>MESA (30)</td>
<td>6,814 (33.3)</td>
<td>45-84 yrs</td>
<td>Median, 7.6 yrs</td>
<td>Mean of maximal right CCA-IMT, far wall</td>
<td>Plaque excluded</td>
<td>MI, revascularization, SCD, CV death</td>
<td>RR: 1.17 (0.95–1.45)</td>
</tr>
<tr>
<td>The Edinburgh Artery Study (13)</td>
<td>1,007 (51.7)</td>
<td>Mean, 69.4 yrs</td>
<td>12 yrs</td>
<td>Maximal far wall CCA-IMT, bilateral</td>
<td>Not specified</td>
<td>MI, stroke, angina, claudication</td>
<td>IMT ≥0.9 mm, OR: 1.59 (1.07–2.37)</td>
</tr>
<tr>
<td>Framingham Offspring Study (84)</td>
<td>2,965 (55.3)</td>
<td>58 ± 10 yrs</td>
<td>Average, 7.2 yrs</td>
<td>Mean CCA-IMT, or maximal CCA-IMT, maximal ICA-IMT, bilateral</td>
<td>Plaque excluded</td>
<td>MI, angina, CV death, stroke, claudication, heart failure</td>
<td>HR for 1-SD mean CCA-IMT: 1.13 (1.02–1.24); HR for 1-SD maximal ICA-IMT: 1.21 (1.13–1.29); HR for 1-SD maximal ICA-IMT: 1.21 (1.13–1.29)</td>
</tr>
<tr>
<td>Charlottesville study (42)</td>
<td>727 (45)</td>
<td>16-85 yrs</td>
<td>Mean, 4.78 yrs</td>
<td>Mean CCA-IMT, bulb-IMT, ICA-IMT, near and far wall, bilateral</td>
<td>Plaque included</td>
<td>MI, revascularization, stroke, TIA</td>
<td>OR for highest quartile of carotid bulb IMT: 5.8 (1.3–26.6)</td>
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<tr>
<td>FATE (97)</td>
<td>1,574 (0)</td>
<td>49.4 ± 9.9 yrs</td>
<td>Mean, 7.2 yrs</td>
<td>Right CCA-IMT</td>
<td>Plaque excluded</td>
<td>CV death, revascularization, MI, angina, stroke</td>
<td>HR: 1.45 (1.15–1.83)</td>
</tr>
<tr>
<td>OSACA2 (98)</td>
<td>574 (45.2)</td>
<td>65.3 ± 9.5 yrs</td>
<td>Mean, 2.6 yrs</td>
<td>Mean maximal CCA-IMT, BIF-IMT, ICA-IMT, near and far, bilateral</td>
<td>Plaque included</td>
<td>MI, CABG, angioplasty, PAD, stroke</td>
<td>For 1-SD increase, RR: 1.57 (1.11–2.20)</td>
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<tr>
<td>Tromso Study (54)</td>
<td>6,226 (44)</td>
<td>25-84 yrs</td>
<td>6 yrs</td>
<td>Mean of near and far wall right CCA-IMT, near and far wall of the bulb</td>
<td>Plaque included</td>
<td>MI</td>
<td>Highest IMT quintile, 1.73 (0.98–3.06) in men and 2.86 (1.07–7.65) in women</td>
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<td>CCCC (99)</td>
<td>2,190 (55)</td>
<td>≈35 yrs</td>
<td>Median, 10.5 yrs</td>
<td>Maximal CCA-IMT, far wall, bilateral</td>
<td>Plaque excluded</td>
<td>MI, CV death, PCI, CABG</td>
<td>RR: 1 SD; 1.38 (1.12–1.70)</td>
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<tr>
<td>APSIS (100)</td>
<td>558 (33)</td>
<td>60 ± 7 yrs</td>
<td>Median, 3.0 yrs</td>
<td>Maximal left CCA-IMT, far wall</td>
<td>Not specified</td>
<td>CV death, MI, revascularization</td>
<td>IMT &gt;1.02 mm; RR: 0.78 (0.36–1.70) for CV death or MI; RR: 1.07 (0.56–2.04) for revascularization</td>
</tr>
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<td>Cournot et al. (101)</td>
<td>2,561 (38.2)</td>
<td>51.6 ± 10.5 yrs</td>
<td>2-10 yrs</td>
<td>CCA-IMT, ICA-IMT bilaterally</td>
<td>Plaque excluded</td>
<td>CV death, MI, angina</td>
<td>OR for highest tertile: 1.50 (0.81–2.59)</td>
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</table>

AMI = acute myocardial infarction; APSIS = the Angina Prognosis Study in Stockholm; BIF = bifurcation; CABG = coronary artery bypass graft; CCA = common carotid artery; CCCC = Chin-Shan Community Cardiovascular Cohort Study; CI = confidence interval; CIMT = carotid intima-media thickness; CV = cardiovascular; ICA = internal carotid artery; FATE = Firefighters and Their Endothelium study; IMT = intima-media thickness; CV = cardiovascular; HR = hazard ratio; MDCS Malmo = Malmo Die and Cancer Study; MI = myocardial infarction; NOMAS = Northern Manhattan Study; OR = odds ratio; OSACA2 = Osaka Follow-up Study for Carotid Atherosclerosis; PCI = percutaneous coronary intervention; PAD = peripheral artery disease; RR = relative risk; SCF = sudden cardiac death; TIA = transient ischemic attack.
ability to image ICA-IMT due to an improvement in ultrasound imaging techniques and pixel resolution, found that ICA-IMT is associated with higher relative risk of incident CVD compared with CCA-IMT (37).

Studies have found greater prediction of stroke by CCA-IMT (30), whereas ICA-IMT appears to predict atherosclerotic cardiac events better (16). In the MESA study (38), age-, race-, and sex-adjusted risk of stroke per SD increase was 2.5 for CIMT versus 0.4 for CAC after multivariable adjustment of risk factors including age, race, sex, ethnicity, smoking, diabetes, blood pressure, low-density lipoprotein, total cholesterol, and use of lipid-lowering medication. The influence of blood pressure on CCA-IMT was indirectly observed in the RADIANCE (Rating Atherosclerotic Disease by Imaging with A New CEPP inhibitor) study in which torcetrapib treatment was associated with an increase in blood pressure and a nearly significant increase in mean CCA-IMT during study period (p = 0.06), without a net yearly rate of change in the maximal IMT of 12 carotid segments (21), suggesting that CCA-IMT is more affected by blood pressure than by atherosclerosis. Besides intimal thickening, CIMT represents smooth muscle hypertrophy and/or hyperplasia, which may be induced by pressure overload and/or age-related sclerosis (39-41). CIMT is a measurement of the combined thickness of the intima and the media of the carotid vessel wall. This combined thickness is chosen because current ultrasound instruments with the standard transducers have insufficient axial resolution to discriminate between the intimal and the medial layers that comprise 20% and 80% of IMT, respectively (8-10).

**QUANTIFYING CIMT**

The definition of an abnormal IMT also differs between studies. Some use a definition of an IMT greater than the 75th percentile (3,42). Others definitions include an IMT that is >1 SD from the mean or IMT at the upper quartile or upper tertile, or an absolute IMT value of ≥0.9 mm or ≥1 mm (13,17). An American Society of Echocardiography consensus statement recommends the use of CIMT greater than the 75th percentile for age, ethnicity, and sex as being abnormal (3).

**CAROTID PLAQUE.** Perhaps the most important difference in the methodology between studies is how plaque is treated when assessing CIMT. Different pathophysiology underlies the development of carotid plaque and CIMT. Unlike CIMT, carotid plaque represents predominantly intimal thickening with foam cells, smooth muscle cells, macrophages, lipid core, and fibrous cap depending on the stage of plaque development (43). Not all CIMT studies include plaque in the CIMT measurements (Table 1). Some studies specifically exclude plaque and selectively measure CIMT in a plaque-free region (44). Others include plaque when measuring CIMT (17). Figure 3A shows a patient with a focal nonobstructive carotid plaque with acoustic shadowing at the far wall of the carotid bulb. In this case, the CCA-IMT is thin and normal. If CIMT is measured in the plaque-free common carotid artery intima-media thickness (CCA-IMT), if only CCA-IMT is measured for risk stratification, this patient would be misclassified as having low cardiovascular risk. (B) This patient has a focal long homogeneous plaque at the region of the carotid bifurcation, but also thickening of the near and far wall carotid IMT. (C) Predominantly noncalcified multiple plaques in the carotid bulb. (D) A large calcified plaque layered along the vessel wall.

**FIGURE 3 Plaque Phenotypes**

Images showing variation in plaque morphology. (A) Focal plaque at the far wall of the carotid bulb with calcification and acoustic shadowing. Note the entirely normal common carotid artery intima-media thickness (CCA-IMT). If only CCA-IMT is measured for risk stratification, this patient would be misclassified as having low cardiovascular risk. (B) This patient has a focal long homogeneous plaque at the region of the carotid bifurcation, but also thickening of the near and far wall carotid IMT. (C) Predominantly noncalcified multiple plaques in the carotid bulb. (D) A large calcified plaque layered along the vessel wall.
increased IMT. Some studies define plaque as a focal thickening of the intima-media >1 mm, protruding into the lumen, which is at least twice as thick as the IMT on either side (46). Other studies define plaques as carotid IMT >1.2 mm (47). Yet others subjectively define plaques as present or absent (48). 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 IMT or where IMT is >1.5 mm (49). Other common criteria for plaque identification are shadowing in wall texture, roughness, and inconsistency in the visualization of structural boundaries along with bright echogenicity (44).

In studies in which plaques are taken into consideration, the way in which plaques are analyzed differs. Table 2 lists studies in which carotid plaque was evaluated as a prognostic predictor of CV events. In some studies, plaque assessment is qualitative, in which the presence or absence of plaques was recorded and analyzed categorically as either “yes” or “no” (50). Others rely on visual assessment of plaque size and burden, classifying plaque burden as none, mild, moderate, or severe (51). Other studies are more quantitative and include detailed analysis of plaque burden, in which the number of plaques (52), plaque thickness (53), and plaque area (54-56) are assessed. Some studies show that “plaque phenotypes” such as plaque irregularity (57), and plaque calcification (44) add to CV risk prediction. Figure 3 illustrates the variability in plaque size and appearance. Figure 3C shows a patient with multiple plaques in the carotid bulb, and Figure 3D shows a patient with a large calcified layered plaque along the carotid vessel wall. Thus, plaques differ in their morphology and composition, and simply categorizing plaque as “yes” and “no” clearly fails to capture plaque complexity and its implications for CV risk.

New technology may aid in the ultrasound characterization of complex plaques. Computerized algorithms based on gray-scale pixel analysis have been developed for texture analysis of plaques. Pixel-distribution analysis further provides a quantitative method for assessing plaque composition (58). These tools have been validated against tissue characteristics of endarterectomy specimens (58,59) as well as clinical endpoints. Echolucent carotid plaques and plaques with surface irregularity are associated with a higher risk of future ischemic stroke and a low level of high-density lipoprotein cholesterol level (60). Furthermore, plaque lucency is more reproducible than plaque thickness measurement (61). Three-dimensional measurement of plaque volume (62) and vessel volume (63) has shown promise in determining regression of atherosclerosis and is being tested for CV risk prediction (64). Plaque vascularity, which relates to activity of atherosclerosis, can be assessed with the use of ultrasound contrast agents, but its use has not been tested in a prognostic setting (65). Colli et al. (66) demonstrated that quantitative evaluation of vasa vasorum on pathology correlated with qualitative assessment of plaque vascularity by ultrasound. Additionally, increased plaque vascularity by ultrasound correlated well with B-mode echolucency, which is a sign of a vulnerable plaque.

**PREDICTIVE VALUE OF IMT VERSUS PLAQUE IN POPULATION-BASED STUDIES IN PREDICTING FUTURE MI.** Given that plaque formation is a manifestation of atherosclerosis, it is not surprising that the presence of plaques predicts future CV events. A meta-analysis of 11 population-based studies including 54,336 patients showed that carotid plaque, when compared with CIMT (inclusive of CCA, bulb, and/or ICA depending on the study), had a significantly higher diagnostic accuracy for the prediction of future MI (67). After adjusting for Framingham risk factors, the relative diagnostic odds ratio comparing plaques and CIMT assessment was 1.35, suggesting that plaque assessment was 35% better than CIMT in predicting future cardiac events. The specificity of event prediction was also higher with carotid plaque. The 10-year event rates of MI after negative results were lower with carotid plaques compared with a normal CIMT.

These studies suggest that varying results among studies are likely related to methodology and that CCA-IMT measurement at sites not containing plaque, versus IMT measurement in the carotid bulb and ICA, inclusive of plaque, if present, represent 2 separate phenotypes. Measurement of carotid plaque alone was more predictive of CV events than either IMT phenotype in a meta-analysis (67,68). In addition, assessment of CIMT at multiple angles evaluates the asymmetrical nature of atherosclerosis better than measurement at a single angle only.

Analyses of individual studies also suggest that plaque is more effective than CIMT in predicting future CV events. Mean CIMT of all segments when added to TRFs and plaque significantly increased CHD risk prediction in men but not in women in the ARIC study (50). The ARIC study (Table 1) included 13,145 healthy subjects (7,463 women) between 45 and 64 years of age at the time of the baseline study visit (50). Over a mean follow-up of 15.2 years, there were 1,822 CV events that included MI, death, and revascularization. The model that performed the best included TRFs plus CIMT plus plaque. When the TRFs plus CIMT plus plaque model was compared with the TRFs-only model, the NRI was 9.9% in the overall sample (8.9% in men and 9.8% in women) and
<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Sample Size, No. (% Women)</th>
<th>Age of Subjects, yrs</th>
<th>Follow-Up</th>
<th>Definition of Plaque</th>
<th>Endpoints</th>
<th>Plaque RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tromso Study (54)</td>
<td>6,226 (44)</td>
<td>25-84</td>
<td>6 yrs</td>
<td>Localized protrusion of the vessel wall into the lumen</td>
<td>MI</td>
<td>Highest plaque area tertile, RR: 1.56 (1.04-2.36) in men and RR: 3.95 (2.16-7.19) in women</td>
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<td>APSIS (100)</td>
<td>558 (33)</td>
<td>60 ± 7</td>
<td>Median, 3.0 yrs</td>
<td>Distinct area with IMT more than twice that of neighboring sites</td>
<td>CV death, MI</td>
<td>Presence of plaque, RR: 1.83 (0.96-3.51)</td>
</tr>
<tr>
<td>KIHD (25)</td>
<td>1,288 (0)</td>
<td>42-60</td>
<td>1 month to 2.5 yrs</td>
<td>Area with mineralization or focal protrusion into the lumen, measured at the carotid bulb</td>
<td>MI</td>
<td>Small plaque, RR: 4.15 (1.51-11.47); large plaque, 6.71 (1.33-33.91)</td>
</tr>
<tr>
<td>Rotterdam Study (15)</td>
<td>6,389 (61.9)</td>
<td>69.3 ± 9.2</td>
<td>7-10 yrs</td>
<td>Focal widening relative to adjacent segments with protrusion into the lumen</td>
<td>MI</td>
<td>HR for severe plaque: 1.83 (1.27-2.62)</td>
</tr>
<tr>
<td>ARIC (50)</td>
<td>13,145 (57)</td>
<td>54.0 ± 1.8</td>
<td>Mean, 15.1 yrs</td>
<td>Plaque defined as meeting 2 of 3 criteria: 1) CIMT &gt;1.5 mm; 2) protrusion into the lumen; and 3) abnormal wall texture</td>
<td>MI, CV death, revascularization</td>
<td>HR varied depending on risk factors. Model with plaque and CIMT improved area under the curve from 0.742 to 0.755</td>
</tr>
<tr>
<td>MDCS (28)</td>
<td>5,163 (59)</td>
<td>46-68</td>
<td>Median, 7 yrs</td>
<td>Focal IMT &gt;1.2 mm</td>
<td>MI, CV death</td>
<td>RR for presence of plaque: 1.81 (1.14-2.87)</td>
</tr>
<tr>
<td>Cournot et al. (101)</td>
<td>2,561 (38.2)</td>
<td>51.6 ± 10.5</td>
<td>2-10 yrs</td>
<td>Focal protrusion into the vessel lumen</td>
<td>CV death, MI, angina</td>
<td>RR for the presence of plaque 2.81 (1.84-4.29)</td>
</tr>
<tr>
<td>NOMAS (44)</td>
<td>1,118 (59)</td>
<td>68 ± 8</td>
<td>Mean 2.7 years</td>
<td>Graded based on stenosis. Grade 1, &lt;30%; grade 2, 30%-49%; grade 3, 50%-99%; grade 4, 100%</td>
<td>MI, CV death, PCI, CABG, stroke</td>
<td>Calcified plaque, RR: 2.4 (1.0-5.8); noncalcified plaques, RR: 1.5 (0.7-3.4)</td>
</tr>
<tr>
<td>Three-City Study (52)</td>
<td>5,895 (62.9)</td>
<td>65-85</td>
<td>Median, 5.4 yrs</td>
<td>Wall thickening ≥50% compared with surrounding vessel wall</td>
<td>MI, angina, CV death, revascularization</td>
<td>Any plaques, HR: 1.5 (1.0-2.2); plaques at ≥2 sites, HR: 2.2 (1.6-3.1)</td>
</tr>
<tr>
<td>CHS (16)</td>
<td>5,020 (60)</td>
<td>72.6 ± 5.5</td>
<td>5 days to 12 years (median, 11 yrs)</td>
<td>High-risk plaques were defined as markedly irregular, ulcerated surface, hypodense, heterogeneous plaques &gt;50% of total plaque volume</td>
<td>MI, stroke, CV death and all-cause mortality</td>
<td>High-risk plaque, RR: 1.38 (1.14-1.67); RR for mortality: 1.23 (1.04-1.44)</td>
</tr>
<tr>
<td>Framingham Offspring Study (84)</td>
<td>2,965 (55.3)</td>
<td>58 ± 10</td>
<td>Average, 7.2 yrs</td>
<td>ICA-IMT ≥1.5 mm</td>
<td>MI, angina, CV death, stroke, claudication, heart failure</td>
<td>Presence of plaque, HR: 1.91 (1.49-2.47)</td>
</tr>
<tr>
<td>Prati et al. (57)</td>
<td>1,348 (53)</td>
<td>18-99</td>
<td>Average, 12 yrs</td>
<td>Focal structure encroaching into the lumen with maximal thickness &gt;1.5 mm</td>
<td>Vascular death, stroke</td>
<td>Event incidence for group with high total plaque score: 50-75 yrs, 2.9% (1.1-7.5); &gt;75 yrs, 9.6% (5.6-17.0)</td>
</tr>
<tr>
<td>Stork et al. (102)</td>
<td>403 (0)</td>
<td>77.7 ± 3.5</td>
<td>48 months</td>
<td>Focal widening with protrusion into the lumen</td>
<td>CV death</td>
<td>RR: 1.16 (1.03-1.31)</td>
</tr>
<tr>
<td>Xie et al. (103)</td>
<td>3,258 (59)</td>
<td>38-79</td>
<td>5 yrs</td>
<td>IMT ≥1.5 mm</td>
<td>MI, CVA</td>
<td>CCA plaque, RR: 1.90 (1.15-3.33); BIF plaque, RR: 1.26 (0.86-1.83)</td>
</tr>
<tr>
<td>CAFES-CAVE (88)</td>
<td>10,000 (30.5)</td>
<td>53.2 ± 6.3</td>
<td>10 yrs</td>
<td>Class I, normal; class II, IMT &gt;1 mm; class III, plaque defined as IMT 1 mm with irregular increased echogenicity; class IV, stenotic plaque with stenosis &gt;50%</td>
<td>MI, CV death, revascularization</td>
<td>Event rate by class: class I, 0.1%; class II, 8.6%; class III, 39.28%; class IV, 81.5%</td>
</tr>
<tr>
<td>MESA (85)</td>
<td>6,562 (52.6)</td>
<td>61.1 ± 10.2</td>
<td>Mean, 7.8 yrs</td>
<td>0%, 1%-24% narrowing, 25%-49% narrowing, and &gt;50% narrowing (defined as peak systolic velocities ≥125 cm/s)</td>
<td>CHD (MI, CV death, angina, revascularization), stroke, death after stroke</td>
<td>Plaque &lt;0%, HR: 1.67 (1.33-2.10); plaque 25%, HR: 1.67 (1.30-2.13)</td>
</tr>
</tbody>
</table>

CAFES-CAVE = carotid-femoral morphology and cardiovascular events; CHD = coronary heart disease; CVA = cerebrovascular accident; other abbreviations as in Table 1.
21.7% in the intermediate-risk groups (16.4% in men and 25.4% in women). None of the subjects were reclassified from the high-risk group to the low-risk group or vice versa. In this study, the ICA IMT could not be measured in more than one-half of the cases, and plaques were classified categorically as “yes” or “no.” Despite these limitations, this study showed that when plaque data are added to any level of IMT (at less than the 25th percentile, 25th to 75th percentiles, or higher than the 75th percentile), there was an added improvement in risk CHD prediction in both men and women. It should be noted that, in this study, plaque data were obtained from the near and far wall of all carotid segments, whereas IMT data were obtained only from the far wall of all segments and was inclusive of plaque in the far wall. In this study, adding plaque and CIMT data best improved risk prediction in men and women in the intermediate-risk group; however, plaque presence had a more profound effect on improving risk prediction in women than in men. It may be that CIMT (of the far wall of all carotid segments) in men had already included plaques, which are more prevalent in men, whereas additional assessment of plaque in the near wall in women, who might have small plaque burden overall, improved assessment of atherosclerosis that might not have been represented by CIMT of the far wall alone.

The Three-City Study evaluated older individuals 65 to 85 years of age over a median follow-up period of 5.4 years. Among 5,895 adults with no history of coronary artery disease, the presence of carotid plaque, but not CCA-IMT measured at a plaque-free site, was found to be an independent predictor of a first cardiac event (52). On multivariate analysis, carotid plaque at 1 site was associated with a hazard ratio (HR) of 1.5 (95% confidence interval: 1.0 to 2.2), and the presence of plaques at ≥2 sites was associated with an HR of 2.2 (95% confidence interval: 1.6 to 3.1). Adding carotid plaques to conventional risk factors significantly improved cardiac risk prediction, with an NRI of 13.7%. This study highlights the methodological issue of differentiation of CIMT at plaque-free sites versus IMT inclusive of plaque.

The Tromso Study evaluated total plaque area in 6,226 individuals 25 to 84 years of age with no history of MI. Plaque burden was separated into tertiles. After a 6-year follow-up, MI occurred in 6.6% of men and 3.0% of women. Men in the highest tertile of plaque had a 56% higher risk of MI compared with those with no plaque. For women, those in the highest tertile had a 3.9-fold higher risk. This study also analyzed carotid IMT and found that IMT did have predictive power, but when carotid bulb IMT was excluded from the analyses, IMT did not predict MI in either sex (54). Because plaque develops in the carotid bulb, presumably the loss of predictive power was due to the exclusion of plaque from the analysis. Extending the analysis to 10 years, the Tromso group found that plaque, but not IMT, was predictive of first-ever ischemic stroke. The multivariable-adjusted HR in the highest quartile of plaque area versus no plaque was 1.73 (p = 0.004) in men and 1.62 (p = 0.09) in women. There was no difference in stroke risk across quartiles of IMT in multivariate analysis (55).

The investigators for the Three-City Study showed that plaque but not CIMT added to CVD risk prediction over TRFs (52), and the HRs for incident CVD events increased as the number of sites with plaque increased. Similar findings were observed in the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study (69), where the mean of maximum measurements of all carotid ICA IMT segments performed significantly better than CCA far-wall mean IMT in reclassification of coronary or CV events in models adjusted for risk factors. In this study, the presence of at least 1 plaque, defined as maximal IMT >1.5 mm, performed significantly better than mean IMT only when the latter was measured in plaque-free areas; otherwise, the predictive value of the plaque presence alone was always significantly worse. This is likely because, in this study, mean or maximal IMT was inclusive of plaque in all segments and was representative of combined CIMT and plaque.

These studies suggest that carotid plaque has predictive power for incident atherosclerotic heart disease. Plaques tend to form at the carotid bulb and at the ICA. This may explain why IMT measurements from these segments are good predictors of CV events, whereas IMT measurements from the CCA alone or IMT measurements that specifically exclude plaque are less predictive of atherosclerotic cardiac disease. Because increased CCA-IMT is associated with an increased stroke risk, combined assessment of FRS, IMT, and plaque may enhance prediction of total CVD (70).

**ASSOCIATION OF CIMT AND PLAQUE WITH RISK FACTORS**

Another clue to the link between CIMT and plaque in CVD risk prediction comes from their association with risk factors. The British Regional Heart Study, in which CCA far-wall IMT was measured along with bulb IMT and plaque, found that CCA-IMT and bulb IMT were correlated with each other but showed differing patterns of association with risk factors and prevalent atherosclerotic disease (71). CCA-IMT was strongly
associated with risk factors for stroke and with prevalent stroke, whereas bulb IMT and plaque were more directly associated with ischemic heart disease risk factors and prevalent ischemic heart disease. IMT is strongly influenced by genetic determinants, but plaque appears to be determined by common CHD risk factors such as age, sex, hypertension, diabetes mellitus, hypercholesterolemia, amount of nicotine consumed, factor VIII, and von Willebrand factor but not genetic inheritance (72). Plaques also correlate with other measures of atherosclerotic vascular disease, such as aortic stiffness, whereas no such association was found for CIMT (73). In particular, echogenic plaques are associated with increased arterial stiffness (74). In multivariable linear regression, traditional coronary risk factors explain only 15% to 17% of IMT, as assessed by the $R^2$ statistic (75) but account for 52% of the carotid total plaque area (76).

Besides association with TRFs and a predictive role for CVD risk, an important question in the development of a new biomarker is its clinical utility (i.e., does the novel risk marker change predicted risk sufficiently to change recommended therapy). Single-center studies suggest such imaging results lead to changes in physician prescribing pattern (77), although larger studies are needed in this area. Whether the use of CIMT and plaque assessment will improve clinical outcomes in a randomized clinical trial remains to be tested and may never be performed, given the costs involved. Cost-effectiveness analyses have suggested justification of the additional costs of testing with CIMT and plaque assessment and treatment (78).

3-DIMENSIONAL PLAQUE ASSESSMENT FOR CORONARY ARTERY DISEASE AND PLAQUE PROGRESSION AND REGRESSION. The advent of 3-dimensional (3D) ultrasound allows more accurate quantification of plaque burden. Plaques are outlined on cross-sectional images, and plaque areas are summed up to obtain the total plaque burden (64) (Figure 4). An advantage of performing 3D measurements is the large dynamic scale range of plaque volume or plaque area that enables the assessment of progression or regression of disease in individual subjects. With CIMT measurements, most measurements fall in the submillimeter range. The annual change of CIMT value is roughly 0.01 to 0.04 mm per year in health (26) and disease (79,80), which is lower than the current-generation ultrasound pixel resolution of 0.1 to 0.2 mm, making it very difficult to follow CIMT change in individual subjects in the short term. A meta-analysis that included 16 studies with 36,984 participants in whom CIMT was assessed at least twice showed that even though the CIMT value itself at both time points was associated with future CV risk, there was no association between the progression of CIMT and future CV risk (81). Compared with CIMT, total plaque area has a dynamic range of 5 to 500 mm³, ~2 orders of magnitude higher than the range for CIMT measurements (82). The average change in total plaque area is 10 mm² per year, so progression or regression of disease can be easily measured in months (56), allowing assessment of the effect of therapy with a short follow-up. As an example, using 3D plaque volume assessment, 1 group has been able to show large effects of therapy on atherosclerosis within 3 months with a sample size of only ~20 patients per group (62).

Carotid vessel wall volume, as assessed using carotid 3D ultrasound, is another parameter that has a good dynamic range. This was used successfully in a dietary intervention trial to evaluate the effect of different diets on atherosclerosis (63). 3D plaque volume was also shown to have a high negative predictive value to...
exclude significant coronary artery disease compared with 2-dimensional assessment of plaque by indicating its potential role as a clinical screening tool to help identify patients who are at low risk of significant coronary artery disease (83).

**3D Plaque Characteristics.** Apart from improving quantification of plaque burden, contemporary studies have also started to focus on better characterization of plaque morphology. A plaque scoring system was developed that incorporates stenosis degree, plaque surface irregularity, echolucency, and plaque texture. Individuals in the San Daniele study who had high plaque scores, which correspond to plaques that are stenotic, with high echogenicity, complex heterogeneous echocardiographic pattern, and irregular plaque contours, had a higher risk of the development of CV events (57). This plaque score was shown to significantly increase the predictive power of using TRFs alone.

**NRI of CAC Versus IMT Versus Plaque in CVD Risk Reclassification**

Studies that have compared CIMT and CAC scores head to head in asymptomatic individuals have in general found that IMT and plaque assessment is more sensitive to detect atherosclerosis than the CAC score (4,64). Unlike the CAC score cutoff values of <100, 100 to 400, and >400 (64), the abnormal IMT value is not as defined. IMT is a normal structure, whereas CAC is pathological. Varying measures have been used to define IMT from single or multiple sites from the near or far wall including, maximal IMT and mean IMT. IMT cutoff that is 75th percentile for age, race, and sex is the most widely used definition, although quintiles, SD, and upper and lower quartiles or tertiles are also used. Hence, what is an abnormal IMT is more difficult to define than the CAC score. In a recent study, Polak et al. (84) evaluated the 2,965-member Framingham Offspring Study cohort for an average follow-up of 7.2 years. The NRI increased significantly after the addition of IMT of the ICA (7.6%) but not IMT of the CCA (0.0%). Because plaques form in the ICA, this was analyzed specifically and the presence of plaque, which was defined as IMT of the ICA >1.5 mm, was associated with an NRI of 7.3%. The analysis of the MESA study data by Polak et al. (85) also showed an NRI of 7% for the mean of maximum measurements of ICA IMT added to TRFs.

IMT and CAC do not appear comparable for risk prediction. The annual NRI and clinical NRI of plaque and CIMT combined with the FRS were 9.9% and 21.7%, respectively, in the ARIC study. CAC studies, on the other hand, have shown NRIs of 21.7% and 30.6% at CAC cutoff points of 100 and 400, respectively (86). CV event rates of 1.431% per year occurred during prospective follow-up of patients who had a CAC score of >100 in the MESA (38), in which adjustment for TRFs showed that each 1-SD increase in log-transformed CAC was associated with an HR of CV events of 2.1, whereas for CIMT, it was 1.3; however, CIMT predicted stroke risk modestly better in this study (HR: 2.1 for CIMT vs. 1.2 for CAC) Plaque was not included in this CIMT analysis. A more comparable HR for incident CVD was found in the Pittsburgh Field Center of the Cardiovascular Health Study for CIMT (HR: 2.3) and CAC score (HR: 2.1) in subjects with a mean age of 80 years (87). This suggests that the mere presence of 1 or more 1.5-mm plaque does not comparably represent atherosclerotic burden as a CAC score of 100 or 400. A much larger plaque burden as a nonhemodynamically obstructive plaque or an obstructive plaque was associated with CV event rates of 39% and 81%, respectively, at 10 years (88). These event rates are comparable to those predicted by CAC scores of 400 in the MESA (38) and St. Francis Heart Study (89). IMT and plaque assessment as used at present is a 2-dimensional technique, whereas CAC is a 3D technique. 3D ultrasound assessment of plaque area or volume was found to correlate more strongly with CAC score (chi-square: 450) than CIMT (chi-square: 24) and would be more reliable in CV risk prediction (64).

**Follow-up IMT Measurement**

The theoretical axial resolution of an ultrasound system varies from 0.08 to 0.11 mm for 12-MHz and 7-MHz transducer frequency, respectively. A small change in IMT cannot be measured in individuals (on the order of 0.01 to 0.1 mm) in clinically meaningful timeframes, especially taking into consideration reader error and patient factors leading to variability. Follow-up measurement of IMT is only recommended in large research studies in which standardized IMT protocols including multiple angles, anatomic landmarks, and automated edge detection software technology are used to assess IMT progression or regression on serial measurements in a large dataset. Duplicate measurement of IMT at baseline and follow-up reduces this error.

**Utility of IMT in Youths**

CIMT provides a measurable reliable marker of the atherosclerotic disease process in the young, a group in whom vascular events will not occur for decades and in whom plaque formation or calcification has not occurred (90). Mean CCA-IMT, bulb, and ICA-IMT were
increased in children with type 1 diabetes mellitus and obese children compared with lean children (91).

**RELATIVE MERITS/DEMERITS OF CIMT/PLAQUE MEASUREMENT VERSUS CAC IN ASSESSING CV RISK IN ASYMPTOMATIC INDIVIDUALS.** One of the limitations of ultrasound is image quality, which depends highly on the sonographer’s ability to provide a comprehensive scan using appropriate standardized angles, and the like. CAC measurement, on the other hand, is fairly automated and easy to perform. Patient body habitus can similarly have a greater impact on ultrasound images relative to other imaging modalities. Finally, because CIMT measurements are exacting, small changes (which may occur with minor changes in the angle of imaging) can have an impact on the measured value and hence the interpretation of the test. The advantages of ultrasound scanning are several: there are no major side effects to the test (minimal heating of tissue is possible), no radiation is involved, scans can be done on portable devices, and the overall acquisition time is fast, which offers the possibility of higher throughput, lower cost, and relative safety.

**ASSESSMENT OF IMT AND PLAQUE IN CLINICAL PRACTICE**

Previous studies required offline measurements of IMT using calipers or edge detection software in a core laboratory, making IMT measurement cumbersome and time-consuming. Recent advances including the use of dedicated IMT ultrasound systems (92) and simplification of IMT protocols have made IMT measurement practical (3). Measurement of CCA-IMT has become automated and is standardized and reproducible if a careful protocol is followed. Our own experience shows good interobserver agreement in IMT and plaque assessment when nonsonographer physician residents are trained in IMT acquisition on more recent generation ultrasound systems that perform online edge detection of IMT (93). On the other hand, assessment of plaque burden is more qualitative at present, and reproducibility of carotid plaque quantification has not been well studied. Use of anatomic landmarks, similar angles at baseline and follow up as well as development of technology that tracks imaging angle and annotates it on the screen may be used to more precisely assess IMT progression or regression on serial measurements (93).

**FUTURE DEVELOPMENT**

It appears that plaque detection by ultrasound imaging may not require the intensive training that is required for measurement of CIMT and that plaque screening may be more easily accomplished in the outpatient setting. Plaque reproducibility needs to be defined in large multicenter studies. Abnormal cutoff values for plaque presence and size or volume adjusted for age, race, and sex and plaque measurement variability need to be defined. Effect of plaque characteristics on outcome is not well defined in large studies, although preliminary data suggest the utility of contrast imaging in assessing plaque neovascularization (94). Considerable research is needed to illuminate the conditions and/or cohorts where one methodology may be superior to the other. Current methodologies are relatively silent on plaque vulnerability and triggering conditions, limiting attainable improvements in risk classification.

**CONCLUSIONS**

The controversy surrounding the usefulness of CIMT measurement in risk stratification appears to result from the lack of uniform methodology used in CIMT studies. Measurements of IMT at the carotid bulb and at the ICA are more useful than CCA-IMT, both for risk classification and risk prediction, likely because intimal thickening and plaques form at the bulb and at the ICA. Assessment of plaque burden is a better measure of atherosclerosis and CV risk than is a simple assessment of the presence or absence of plaques. Combined CIMT and plaque assessment appear better than either measure alone. 3D plaque volume correlates with CAC score. In the future, plaque progression and regression assessed by 3D ultrasound may serve as a powerful tool to evaluate the effect of CV therapy.

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IMT, Plaque, and Cardiovascular Risk

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1036 Naqui and Lee


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