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The Role of Carotid Intimal Thickness and Plaque Imaging in Risk Stratification for Coronary Heart Disease

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Abstract Improving the 10-year coronary heart disease (CHD) risk prediction beyond its current state is important as the current risk prediction schemes classify the majority of individuals who experience an incident CHD event as low or intermediate in risk. B-mode ultrasound-based carotid intima-media thickness (CIMT) measurement and carotid plaque detection is one of the surrogate markers of atherosclerosis that has shown value in CHD risk prediction. It has been shown that adding either CIMT, plaque, or both to traditional risk prediction models improves CHD risk prediction. Carotid ultrasound-based CIMT measurement and plaque identification is noninvasive, safe, and relatively inexpensive. Recent guidelines have given CIMT and plaque-based risk prediction a class II A recommendation. This article reviews the available data related to the use of CIMT and plaque information in CHD risk prediction.

Keywords Carotid intima media thickness · Carotid plaque · Atherosclerosis · Coronary artery disease

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Introduction

An acute myocardial event or sudden cardiac death may be the first manifestation of coronary heart disease (CHD) in almost one half of individuals [1]. Therefore, the role of screening, which will allow identification of "at risk" individuals and thereby potentially allow early institution of preventive therapeutic interventions to help reduce CHD events, cannot be over emphasized. Traditionally, several risk assessment scores have been used to determine the short-term (~ 10 year) CHD risk of an individual [2–4]. In the United States, the most commonly used among these is a modified form of the Framingham Risk Score (FRS) [2]. This risk scoring scheme that has been recommended for use by the National Cholesterol Education Panel categorizes individuals into low (10-year risk of < 10%), intermediate (10-year risk of 10–20%), and high (10-year risk of > 20%) risk for the development of CHD events. However, there are several inherent limitations to the use of these risk scores. First, they classify about 75% of the population into the low- or intermediate-risk categories, and about 60% of the CHD events (ie, the majority) occur in these risk groups [1, 5]. Further, traditional risk factor (TRF)-based risk estimation provides significant weight to the age of an individual and thus may not adequately predict risk in a younger population or in women [5–7]. Most TRF-based risk prediction models assess only a 10-year or short-term risk and do not address the long-term or life-time risk of an individual, sometimes giving a false sense of security. Due to these limitations, there exists a need to further refine risk factor assessment with the use of other methods of subclinical atherosclerosis detection.

Biomarker measurement, genetic testing, and imaging subclinical atherosclerosis are being evaluated as strategies for use in concert with TRFs to help improve CHD risk

prediction. Some of the commonly used vascular imaging modalities for CHD risk assessment include computed tomography (CT)-based coronary artery calcium (CAC) score [8] and ultrasound-based assessment of carotid intima-media thickness (CIMT) [9, 10••] and carotid plaque [10••].

Carotid Intima-Media Thickness

CIMT is defined as the distance between the lumen-intima and the media-adventitia interface [11]. Because atherosclerosis is a subintimal process, measurement of CIMT (which accounts for both the arterial media and intima) was thought to be a good surrogate measure of atherosclerotic burden. In mid 1980s, Pignoli et al. [12] reported results from an in vitro study of human aorta and common carotid arteries (CCA) comparing direct measurement of arterial wall thickness with the B-mode real-time imaging of the same specimen. They found a striking association of the distance between the two parallel echogenic lines separated by hypoechoic space with the thickness measured directly on the pathologic specimens [12]. This concept paved the way for the use of the B-mode ultrasound imaging for the measurement of CIMT in vivo.

Measurement of CIMT

The superficial location of the carotid artery (especially the common carotid artery [CCA]) in the neck makes it easily accessible to ultrasound examination. Carotid ultrasound imaging is generally performed using a linear-array transducer with a fundamental frequency of 7–10 MHz and a typical pixel size of approximately 0.11 mm at 4 cm depth [13]. B-mode imaging is preferred over M-mode imaging as the latter provides measurement of only a single point of thickness rather than a segmental measurement. Measurement of CIMT is best done in end-diastole [13] with the subject in supine position with head slightly hyperextended and rotated to the opposite side. Use of Meijer's arc to obtain a consistent angle and imaging from multiple angles is recommended [13]. Multiple longitudinal and transverse views are obtained. Blood-intima and media-adventitia interface of the far wall is traced using a leading edge–to–leading edge technique. The distal 1 cm of the CCA, bulb and proximal 1 cm of the internal carotid artery (ICA) are generally the segments of interest. Maximum and/or mean values can be obtained of near and/or far wall of each segment and averaged or used individually [13]. The distribution (percentiles) of CIMT values based on age, ethnic, and gender distributions have been described [13].

Definition of Carotid Plaque

The Mannheim consensus conference defined carotid plaque as "a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding CIMT value or demonstrates a thickness of 1.5 mm as measured from the media adventitia interference to the intima-lumen surface" [14]. Plaque surface characteristics (regular or irregular) and echogenicity should also be considered during the study. Due to the eccentric nature of plaques, a circumferential scan ranging from anterior to posterior angles, and imaging the near or far walls of the CCA, bulb, and ICA segments is required.

Association of CIMT and Carotid Plaque with Risk Factors for CHD

Given that CIMT/plaque reflects atherosclerosis, several efforts have aimed at associating TRF for atherosclerosis with CIMT. Traditional risk factors for CHD such as age [9], hypertension [9], diabetes [9], hyperlipidemia [9], and presence of metabolic syndrome [15] have all been associated with CIMT. Other newer risk factors/markers for atherosclerosis such as lipoprotein (a) [16], plasma homocysteine [9], and oxidized low density lipoprotein cholesterol (LDL-c) [17] have also been independently associated with CIMT. In the Framingham Heart Study, high-sensitivity C-reactive protein (hs-CRP) was associated with CIMT in women even after adjustment for TRF [18]. Similarly, the Rotterdam Study showed an incremental association of CIMT with hs-CRP [19].

Carotid plaque has also been associated with TRF including cholesterol levels [20, 21], smoking, diabetes, and apolipoprotein B [22, 23]. Plaque measured in the carotid bulb or ICA has been shown to be more strongly correlated with hyperlipidemia and smoking and to have a stronger association with CHD than the ones in CCA [22]. In the British Regional Heart Study (BRHS), the authors found a positive linear relationship between carotid plaque presence and increasing quintiles of the cardiovascular (CV) risk prediction score, which included years of smoking, systolic blood pressure, total cholesterol, family history, angina, diabetes mellitus, and diagnosis of ischemic heart disease [21]. Similarly, in the Atherosclerosis Risk in Communities (ARIC) study, Nambi et al. [10••] have shown plaque was not only related to increasing CIMT but also to increasing CHD risk. In this analysis of healthy individuals, they reported an increase in prevalence of carotid plaque from 13.6% in the overall population with a CIMT < 25th percentile (17.4% in men and 10.7% in women), to 26.2% in those with a CIMT between the 25th and 75th percentile (33.5% for men and 20.7% for women), and to 65.3% in those with a CIMT > 75th percentile (73.1% in men and 59.5% in women). On

evaluating plaque prevalence by 10-year CHD risk groups as defined by TRFs, plaque prevalence increased from 24% in the 0% to 5% risk group to 34.3% in the 5% to 10% risk group, 46.5% in the 10% to 20% risk group, and 54.6% in the > 20% risk group 10-year CHD (high) risk groups. Therefore, both CIMT and carotid plaque have been clearly shown to be associated with TRF for CHD.

Association of CIMT and Carotid Plaque with Prevalent and Incident CHD

Both CIMT and carotid plaque have been shown to be associated with incident and prevalent CHD. In the Cardiovascular Health Study (CHS), baseline measures of CIMT were strongly associated with CVD events even after adjustment for TRFs in 4476 subjects without clinical CVD (ie, CHD and stroke) followed for a median period of 6.2 years [24]. Dividing the CHS population into quintiles based on IMT, the investigators reported that the 7-year rate for myocardial infarction (MI) or stroke was > 25% for participants in the highest quintile compared with < 5% for those in the first quintile. When analyzed separately, there was a stronger association between the ICA IMT and incident MI than the CCA IMT, whereas the opposite was true for stroke [24]. The ARIC study examined the association between CIMT and incident CHD in 12,841 individuals aged 45–64 years who were clinically free of CHD at baseline [9]. After adjustment for age, ethnicity, and other risk factors, CIMT maintained an association with incident CHD over a follow-up of 4–7 years. In models with minimal adjustment (age, ethnicity, and center), individuals with CIMT ≥ 1 mm had a significantly higher hazard ratio (HR) for CHD in women (HR 5.07; 95% CI, 3.08–8.36) than in men (HR 1.85; 95% CI, 1.28–2.69) [9].

More recently, Lorenz et al. [25] conducted a meta-analysis of eight general population-based studies (n= 37,197 subjects, mean follow up 5.5 years) and reported that for an absolute CIMT increase of 0.1 mm, the future risk of an MI increased by 10–15% whereas the future risk of stroke increased by 13–18%.

In another meta-regression analysis of 28 randomized clinical trials (1990–2009, ~15,600 patients) that used CIMT as a surrogate endpoint, Goldberger et al. [26••] found that for every 0.01-mm-per-year smaller rate of progression in CIMT, there was a significant 18% reduction in the risk of nonfatal MI. However, in a subgroup analysis examining only statin-based trials, decreases in CIMT were not associated with a reduction in MI risk. The authors concluded that less progression in CIMT over time is associated with a lower likelihood of nonfatal MI in selected trials but recommended caution in using CIMT as a surrogate endpoint [26]. However, this study had some limitations. It consisted of heterogeneous trials with relatively short follow-up periods for the development of MIs. Further, CIMT were measured and reported in a number of ways and at different segments, and some studies reported the mean of the mean CIMT while others reported the mean of the maximum CIMT values. Because CIMT values vary in different segments and because the changes in mean and maximum CIMT values may be different, the results across these heterogeneous studies could be difficult to compare.

Finally, Polak et al. [27] recently reported that in the Multi-Ethnic Study of Atherosclerosis (MESA), common carotid IMT rate of change per year was strongly associated with the incidence of stroke (HR 1.23 per 0.05 mm/year; 95% CI, 1.02–1.48).

Association of Carotid Plaque Prevalence with CHD

Several studies have aimed to find an association between carotid plaque and prevalent and incident CVD. In the Northern Manhattan Study (NOMAS), 2189 subjects were followed for a combined endpoint of stroke, CHD events, and mortality from other vascular causes. The authors found a plaque prevalence of 58% in their cohort [28]. Subjects with maximum carotid plaque thickness greater than 1.9 mm had a 2.8-fold increased risk of combined vascular events in comparison to the subjects without carotid plaque (HR 2.80; 95% CI, 2.04–3.84) in unadjusted models and a HR of 1.48 (95% CI, 1.05–2.10) in models adjusted for demographics and risk factors. When the vascular events were separately considered, after adjustments, the results were nonsignificant.

Wyman et al. [29] performed a systematic literature review to determine whether the presence of carotid plaque was associated with future CV events. They included studies that had more than 300 subjects, were prospective, and reported HR or relative risk estimates of CV events. They included nine such studies and reported that carotid plaque presence was associated with the incidence of CV death and/or CHD event [29] Eight of the nine studies also reported associations with CIMT.

In the Kuopio Ischemic Heart Disease Study of 1288 Scandinavian men [30], although no significant association was found between CIMT and incident acute coronary events (relative risk 2.2; 95% CI, 0.7–6.7), the relative risk for CHD (95% CI) for individuals with small nonstenotic and large stenotic plaque when compared with those without plaque was 4.2 (1.5–11.5) and 6.7 (1.3–33.9), respectively.

Similarly, in the prospective population-based Tromsø study (over 6000 healthy participants) where measurements of both total plaque area and CIMT were available, baseline CCA-IMT was not associated with incident CHD events over a follow-up period of 6 years [31]. However, IMT in the bulb and total plaque area showed an association with incident CHD with the total plaque area having the strongest association.

In the Rotterdam Study, when a plaque score was developed based on the number of segments of the carotid artery with plaque, the authors found an incrementally increased risk for stroke as the plaque score increased, suggesting that as the burden of atherosclerosis increased so did the events [32].

Other investigators have evaluated if the quality of the plaque is associated with CHD. For example, the ARIC study [33, 34] evaluated the presence or absence of acoustic shadowing (defined as "a reduction in amplitude of echoes caused by intervening structures with high attenuation") and reported that after adjustment for the major CHD risk factors, the hazard ratio for CHD in women with plaques that had acoustic shadowing compared to women with plaques without acoustic shadowing was 1.73 (95% CI, 1.07–2.80) whereas the corresponding HR for men was 1.04 (95% CI, 0.72–1.51). Thus, association of carotid plaque with CHD was stronger for mineralized lesions in women but not in men.

Other efforts have tried to classify plaque based on their echogenicity or the gray scale pixel intensity (grey scale median). In one study involving 223 subjects [35], carotid plaque echogenicity was assessed by ultrasound at baseline and scored as echolucent, predominantly echolucent, predominantly echogenic, or echogenic based on a scale described by Gray-Weale et al. [36]. Plaque echogenicity as described on the Gray-Weale scale was independently associated with future CV event with the relative risk for CV events in subjects with echolucent plaques being 4.6 (95% CI, 1.1–18.9), even after adjustment for degree of carotid stenosis and TRF. There was also a significant linear trend, independent of the degree of stenosis and TRF, for higher CV risk with increasing plaque echolucency [35].

Therefore, overall, the preponderance of the data suggests that both plaque and CIMT are associated with prevalent and incident CHD, with presence of plaque, in general, having a stronger association with CVD compared to CIMT alone.

CIMT and Carotid Plaque in CHD Risk Prediction

Mere associations with prevalent and incident CHD, although important, do not automatically mean that adding CIMT (or any other marker) to traditional risk prediction schemes will improve CHD risk prediction. Additional statistical analyses that include statistical tests to discriminate and calibrate the different risk prediction models have been recommended. These parameters include tests of discrimination such as improvements in the area under the receiver operator characteristics curve (AUC), integrated discrimination improvement (IDI) and net reclassification index (NRI), and tests of model calibration such as the Hosmer-Lemeshow or Grønnesby-Borgan goodness of fit tests. Additionally, the number of individuals whose risk group will change (ie, will be reclassified) due to the addition of the new marker will also need to be described [37]. Given the association of CIMT/plaque with TRF and CHD, recent efforts have evaluated the value of CIMT/plaque in CHD risk prediction.

Nambi et al. [10••] reported the value of CIMT/plaque in CHD risk prediction in 13,145 (7463 women) healthy individuals between 45 and 64 years of age at the time of the baseline ARIC study visit (1987–1989) who were eligible for the analysis. Over a mean follow-up of 15.2 years, there were 1822 CHD events (MI, death, and revascularization). In women, the AUC increased from 0.759 (TRF alone) to 0.762 (95% CI for the difference in adjusted AUC, 0.002–0.006) when CIMT was added to TRF, whereas the AUC increased to 0.770 (95% CI for the difference in adjusted AUC, 0.005–0.016) when plaque alone was added to TRF. The TRF plus CIMT plus plaque model had a similar AUC of 0.770 (95% CI, 0.005–0.017). Conversely, adding CIMT had a more pronounced effect than adding plaque to TRF on the AUC for men. For men, the AUC increased from 0.674 (TRF alone) to 0.690 (95% CI for the difference in adjusted AUC, 0.009–0.022) when CIMT was added to TRF whereas the AUC increased to 0.686 (95% CI, 0.005–0.017) for plaque alone plus TRF. The TRF plus CIMT plus plaque model was associated with the most increase in AUC (increased to 0.694; 95% CI, 0.011–0.027)]. The TRF plus CIMT plus plaque model had the most significant NRI and clinical NRI (NRI in the intermediate groups in the overall sample), in men, and in women. Overall, the TRF plus CIMT plus plaque model when compared to the TRF-only model was associated with an NRI of 9.9% (clinical NRI 21.7%) in the overall sample, 8.9% (clinical NRI 16.4%) when men were considered separately, and 9.8% (clinical NRI 25.4%) when women were considered separately, suggesting effective reclassification. Although ~23% were reclassified, no one was reclassified from the high-risk group to the low-risk group or vice versa.

The IDI again showed that the model predictivity was significantly improved by adding CIMT and plaque to TRF in the overall population (IDI=0.011), in women (IDI=0.009), and in men (IDI=0.013). To test the model calibration, the observed and expected number of events within each estimated risk decile groups was compared using the Grønnesby-Borgan test statistic. A model with good fit will have lower chi-square statistic value and a nonsignificant *P* value, suggesting that there is no difference between the events expected (based on the risk prediction model) and the events observed. When the overall population was considered, although model fit improved with the addition of CIMT and/or plaque, none of the models had a good fit, with the chi-square statistic (*P* value) being 30.0 ($P=0.0004$),

23.7 (P=0.005), and 24.3 (P=0.004) for the TRF only model, TRF plus CIMT model, and TRF plus CIMT plus plaque model, respectively. When men and women were considered separately, the model fit improved. In men, the CIMT plus TRF model was a better fit (chi-square statistic= 14.12, P=0.11) compared to the CIMT plus TRF plus plaque model (chi-square statistic=17.9, P=0.04) and the TRF-only model (chi-square statistic=18.7, P=0.028]). Conversely, in women, the chi-square test statistics were 15.0 (P=0.09), 9.1 (P=0.43), and 8.7 (P=0.47) for the TRF only, TRF plus CIMT and TRF plus CIMT plus plaque models, respectively, which suggested that the TRF plus CIMT plus plaque model had the best model fit. A CHD risk calculator based on adding CIMT and plaque information to TRF as described in this manuscript is available online at http://www.ARICnews.net.

However, subsequent to the ARIC analysis, Lorenz et al. [38••] evaluated risk prediction with addition of CIMT to TRF in 4904 individuals without pre-existing vascular disease followed for 10 years in the Carotid Atherosclerosis Progression Study (CAPS) and reported that adding CIMT to different risk prediction models, including FRS and SCORE, did not result in a significant improvement of CVD risk prediction. Adding CCA-IMT to an FRS-based risk prediction model resulted in the reclassification of 357 subjects (8.1%) and an NRI of −1.41% (P=NS). More subjects were shifted to lower rather than to higher risk categories by the inclusion of CIMT. The Hosmer-Lemeshow test showed a lack of fit for all models examined (P=0.001). The authors concluded that CIMT, despite being associated with CV events, did not consistently improve the risk classification of individuals. However, this study had several limitations including the fact that incident events were not systematically collected but determined based on ICD codes and health care records. Furthermore, even in the highest-risk group (by traditional risk prediction methods), the event rates were low (observed 10-year risk in the high-risk group [ie, > 20% 10-year predicted risk] was 3.03%).

More recently, Polak et al. [39••] reported the value of adding the mean CCA-IMT and the maximum ICA-IMT to the FRS in 2965 members of the Framingham Offspring Study cohort followed for an average of 7.2 years. The NRI increased significantly after addition of ICA-IMT (7.6%, P<0.001) but not CCA-IMT (0.0%, P=0.99). Presence of plaque, which was defined as intima media thickness of ICA of more than 1.5 mm, increased NRI to 7.3% (P=0.01), with an increase in the C-statistic of 0.014 (95% CI, 0.003–0.025) [39••].

Overall, based on the available studies, it seems that CIMT and plaque can help improve CHD risk prediction, although the reported magnitude of this improvement has been variable.

Measurement of CIMT, as discussed, does have limitations. The technique assumes a uniform thickness along the blood vessel wall. This may lead to considerable variability. Even in trials that use CIMT as an endpoint, there has been a lack of consensus on the segment of carotid studied, angle of measurement, and whether to use the maximum of mean IMT value [40]. Because plaque progression occurs along the surface faster than circumferentially, CIMT alone may underestimate the atherosclerotic burden [41]. Similarly, the annual change in CIMT is on the order of 0.01 mm, and hence a great deal of precision is required to measure CIMT [42]. Despite these limitations, if carefully used and measured by trained personnel, CIMT and presence of plaque may help the clinician in better stratifying CHD risk. Currently, CIMT has been endorsed by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) with a class IIa recommendation, as a "reasonable study for cardiovascular risk assessment in asymptomatic adults at intermediate risk" [43].

Comparing Different CIMT Segments in Risk Prediction

A few studies have examined whether specific CIMT segments (ie, common versus internal or a combination of all segments versus one segment alone) are better in risk prediction. In the Cardiovascular Health Study, the combination of CCA-IMT and ICA-IMT had numerically higher relative risk (RR) for incident MI or stroke when compared with either CCA-IMT or ICA-IMT alone (RR 1.36 vs 1.27 and 1.30, respectively). When ICA-CIMT was compared with CCA-IMT, ICA-IMT had higher RR for incident CHD (1.34 vs 1.24) [24]. In the ARIC study, although there was some discordance in the risk groups to which individuals were classified, no differences in risk prediction were seen when CCA-IMT plus plaque was compared with all carotid segment IMT (A-CIMT) and plaque. Overall, there were 1722 incident CHD events in 12,576 individuals over a mean follow-up of 15.2 years. The AUC for TRF only, TRF plus A-CIMT plus plaque, and TRF plus CCA-IMT plus plaque models were 0.741, 0.754, and 0.753, respectively, and similarly there were no significant differences when percent individuals reclassified, NRI, and model calibration by the Grønnesby–Borgan test were estimated [44••]. In the Framingham Offspring Study cohort, Polak et al. [39••] found that the maximum ICA-IMT and mean CCA-IMT were associated cardiovascular outcomes, but only the maximum ICA-IMT and presence of carotid plaque in the ICA significantly improved CVD risk prediction.

However, as previously discussed, Lorenz et al. [40] not only reported that CIMT did not improve CHD risk prediction but also reported that there were no differences when individual carotid artery segments were examined for their

risk predictive abilities in CAPS. Overall, although studies such as the Framingham Offspring study have reported that ICA-IMT (maximum) may be superior to CCA-IMT, the ARIC study reported that CCA-IMT (mean) was as good as all IMT segments put together. Clinically, the measurement of the CCA-IMT is easier and more reliable. However, whichever approach is adopted, screening for plaque presence should be a critical component.

CIMT versus Carotid Plaque in CHD Risk Prediction

As previously noted, in the ARIC study, plaque was noted to be superior to CIMT in improving risk prediction in women but not in men. Overall, when men and women were considered together the combination of CIMT and plaque together offered the best improvements in CHD risk prediction [10••]. A recent meta-analysis of 11 population-based studies (54,336 subjects) by Inaba et al. [45] showed that carotid plaque, compared with CIMT, had a significantly higher diagnostic accuracy for the prediction of future CHD events (AUC 0.64 vs 0.61, relative diagnostic odds ratios (DOR) 1.35; 95% CI, 1.1–1.82; P=0.04). Similarly, on meta-analysis of 27 diagnostic cohort studies (n=4,878) a higher but nonsignificant increase in AUC for CAD prediction was seen when carotid plaque was compared with CIMT (AUC 0.76 vs 0.74, P=0.21 for relative DOR). The significant limitation of the meta-analysis was, once again, the presence of heterogeneity amongst the included studies. Another limitation was the difference in the scanning protocols of carotid ultrasound for the assessment of carotid plaque and CIMT between studies [45]. Furthermore, both the meta-analyses did not report on the other statistical tests required to evaluate improvements in risk prediction, such as NRI, IDI, percent reclassified, and model calibration. Overall, currently, a combination of both CIMT measurement and an evaluation for the presence or absence of plaque seems to be the most prudent approach.

CIMT and Lifetime Risk for CHD

Given that 10-year risk prediction schemes only represent a short-term risk estimate and younger individuals invariably have a low 10-year risk, Lloyd-Jones et al. [46] developed the concept of "lifetime risk," which estimates the lifetime risk of an individual at various ages and various levels of risk factors. Berry et al. [5] evaluated 4064 individuals from the Coronary Artery Risk Development in Young Adults (CARDIA) study and from the Multi-Ethnic Study of Atherosclerosis (MESA) and calculated their 10-year and lifetime risk for CHD, stratifying them into the following categories: low 10-year (< 10%, 10-year risk)/low lifetime (< 39% lifetime risk) risk; low 10-year (< 10%)/high lifetime risk (≥ 39%); and high 10-year risk (≥ 10%) or diagnosed diabetes mellitus. Baseline levels of subclinical atherosclerosis including CIMT were compared across risk strata. Among participants with low 10-year risk (91% of all participants), those with a high lifetime risk had a significantly greater CCA-IMT (0.83 vs 0.80 mm in men; 0.79 vs 0.75 mm in women) and ICA-IMT (0.85 vs 0.80 mm in men; 0.80 vs 0.76 mm in women) compared to those with a low lifetime risk, suggesting that even in subjects with low short-term (10-year) risk, individuals with an increased burden of subclinical atherosclerosis have a higher lifetime risk.

Future Directions

Several efforts are underway to improve the utility of carotid ultrasound in monitoring and/or assessing atherosclerotic burden and risk. Ultrasound contrast agents, which may provide better visualization of the luminal surfaces (especially the near wall-IMT), thereby allowing for more reliable CIMT measurements, are being evaluated for use in carotid ultrasound examination. In addition, contrast may visualize adventitial and intra-plaque angiogenesis (vasa vasorum), which is thought to be a marker of plaque vulnerability [47]. Similarly, techniques to improve border tracking which can serve to reduce intra- and inter-reader variability with CIMT measurement are being developed. Another new technology that is now available is one that uses a "GPS"-like software that can register points and thereby help serially track points on the image, allowing for improved reproducibility of IMT measurements [48]. Overall, these measures, if successful could help in further improvement in use of CIMT as a tool to monitor atherosclerosis.

Furthermore, there is growing interest in measuring plaque area and volume. Given that CIMT is a surrogate measure for the burden of atherosclerosis, measurement of atherosclerotic plaque area and volume may serve as an improved way to monitor atherosclerosis [49].

Three-dimensional ultrasound techniques that are now available may allow for reliable quantification and perhaps characterization of atherosclerotic plaques [50, 51]. This may clearly have significant clinical and research utility and further research in this area will be forthcoming.

Conclusions

The data on the utility of CIMT ± carotid plaque for CHD risk prediction continue to emerge. Overall current data would suggest that CIMT and information on plaque presence can help improve CHD risk prediction. Improving technology and future efforts, including evaluating the value

of plaque burden estimation and perhaps plaque characterization, will hopefully further help us in improving CVD risk prediction.

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