Carotid Intima-Media Thickness as Surrogate for and Predictor of CVD

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ABSTRACT

Carotid artery intima-media thickness (IMT) is a noninvasive measurement of the artery wall thickness, inclusive of atherosclerotic plaque, obtained using ultrasound imaging. In the MESA (Multi-Ethnic Study of Atherosclerosis) study, IMT measurements are used as a surrogate for subclinical cardiovascular disease and as a variable predictive of cardiovascular events. IMT measurements of the common carotid artery are available in more than 99% of the MESA population and are predictive of cardiovascular events. More importantly, IMT and plaque thickness measurements made in the internal carotid artery and carotid bulb are also available in more than 98% of the population and are also strongly predictive of cardiovascular events. This article reviews the techniques used to obtain the MESA IMT values, compares them to those made in other epidemiological studies, and summarizes how they have been used in the MESA study as both surrogates for and predictors of cardiovascular disease.

In 1986, Pignoli et al. [1] published in the journal *Circulation* an article where they described an association between an ultrasound measurement of the aortic wall thickness and atherosclerotic lesions in pathological specimens. This observation was then expanded to the in vivo visualization of the carotid artery wall, or intima-media thickness (IMT), in a companion paper that focused on hypercholesterolemic patients [2]. This paper demonstrated that the common carotid IMT was larger in patients with elevated cholesterol levels [2]. Common carotid IMT (Fig. 1) measured by ultrasound was easily and noninvasively obtainable in almost all individuals and patients. Within a few years, the technique was investigated in patient cohorts, epidemiologic studies, and intervention trials [3-7].

At the inception of the MESA (Multi-Ethnic Study of Atherosclerosis) study, published results suggested that IMT was a predictor of cardiovascular events and showed promise for monitoring the effects of lipid-lowering medications [4,8-11]. The IMT protocols adopted in the MESA study built on that knowledge and were designed to confirm the results of prior studies showing the value of IMT for predicting cardiovascular events. The availability of coronary artery calcium scores in the MESA study population would also permit a side-to-side comparison of carotid IMT with coronary artery calcium scores for predicting cardiovascular events. Carotid IMT was also to serve as a surrogate measurement of atherosclerosis when investigating the effects of various risk factors or environmental exposures.

This review has 3 principal goals: 1) to describe the IMT protocols used in the MESA study, comparing them to those used in other epidemiologic studies and highlighting the specific scientific questions they were designed to answer; 2) to overview of cross-sectional associations of specific biochemical exposures, socioeconomic factors, and physiological measures with IMT used as a surrogate measurement for cardiovascular disease; and; 3) to overview the relative efficacy of common and internal carotid IMT for predicting coronary and cardiovascular events. The possibility of generating ethnic specific normative data for carotid IMT will then be touched on.

CAROTID ARTERY IMT IMAGING PROTOCOLS IN THE MESA STUDY: TECHNICAL ASPECTS

Overview and technical aspects

Two carotid ultrasound protocols were used in the MESA study. The first was a modified clinical imaging protocol typically used in noninvasive vascular laboratories throughout the United States. It was designed to survey both the common and internal carotid arteries. The main goal when imaging the common carotid artery (CCA) was to obtain both near wall and far wall IMT measurements. The imaging goals for the carotid bifurcation and proximal internal carotid artery (ICA) were to: 1) screen for hemodynamic significant plaque formation using color Doppler imaging and Doppler waveform analysis; 2) measure the dominant plaque in either the CCA bulb or the proximal ICA; and 3) measure IMT from 3 projections if a focal plaque was not present. The main purpose of the second carotid imaging protocol was to serve as a baseline study for the measurement of CCA IMT progression with the idea of repeat imaging at future the MESA study visits. It emulated the protocol originally used to show the effects of lipid-lowering therapy on the progression of IMT [4]. It was restricted to imaging the

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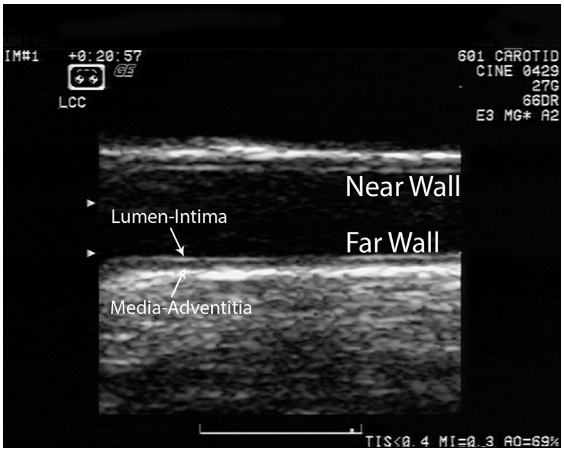

FIGURE 1. An example of a common carotid artery image acquired in the MESA (Multi-Ethnic Study of Atherosclerosis) study. The key interfaces used to measure common carotid artery intima-media thickness are the lumen-intima and the media-adventitia interfaces. The distance between these 2 interfaces is the intima-media thickness.

right CCA only on 1 projection with the internal jugular vein above the artery thereby offering a clear imaging window.

The precision of IMT measurements is dependent on slight variations in the location of imaging, the type of imaging device, the number of images acquired, the measurement process adopted, and the final value that the IMT measurement represents. The goals of the MESA study carotid IMT protocol were to standardize the IMT measurement process and to take account of as many of the sources of variability as possible because imaging was to be performed at 6 geographically distant sites in the United States. Factors such as the ultrasound imaging device, sonographer training, location of the acquired images, and the measurement process were kept as constant as possible to improve the reliability and accuracy of the resultant IMT values obtained at the 6 clinical sites.

Selection of the ultrasound device

The MESA study ultrasound device was selected from the commercially available devices of the time (late in the year 1999). Six candidate devices were brought to Boston (Massachusetts, USA) and used to image 2 volunteers, 1 with normal carotid walls and 1 with plaque formation. The same sonographer sequentially acquired on each device a CCA image at the same location and projection for the same volunteer. Six principal investigators and 6 IMT readers reviewed the images as they were being acquired and graded their quality. In the judgment of the 12 reviewers, 2 of the 6 devices fell short of delivering sufficient image quality and were not evaluated any further. Images of the CCA far wall taken on the remaining 4 devices were scaled to the same size. The 4 images were combined on 1 image and sent as e-mail attachment to the 12 evaluators (Online Fig. A1). The reviewers graded the quality of the images and focused on the distinctness of the carotid artery far wall interfaces. As a final step, each evaluator was asked to pick what they thought was the best image for measuring carotid IMT. This selection process identified 1 device that was subsequently used at all 6 clinic sites.

Lessons learned from the MESA study

The process used to select the MESA study ultrasound device showed significant differences in image quality between devices. In general, the more expensive devices gave better image quality. This subjective finding confirmed a report that indicated that the type of ultrasound device affected IMT reproducibility [12]. The MESA study experience was also consistent with the results of the EDIC (Epidemiology of Diabetes Interventions and Complications) study on carotid IMT progression where the results of a 26-center trial on young type 1 diabetics had to be adjusted for the type of ultrasound device used to obtain the IMT images [13].

Centralized training and certification

The same type of ultrasound devices and transducers, the same imaging presets, and the same imaging protocol were used at all 6 the MESA study clinical sites. All of the sonographers had to attend a central training session in Boston that included a review of the physics of ultrasound, specifics of using the ultrasound device keyboard and image controls (“knobology”), the pathophysiology of atherosclerosis, and a hands-on practice session. Upon return to their clinic site, they had to submit pilot studies performed on volunteers and perform at least 5 studies every 2 weeks to remain certified. These were reviewed for image quality and the ease of IMT measurement. These steps had to be followed and completed before a sonographer became certified and started acquiring carotid IMT studies on the MESA study participants.

Lessons learned from the MESA study

It is not possible to isolate the value of the MESA study training from other factors that affected the final results of the study. The training is likely to have contributed to the overall quality and completeness of the IMT measurements.

BASELINE CAROTID IMT IMAGING PROTOCOL: COMMON AND INTERNAL CAROTID IMT

The first MESA study ultrasound imaging protocol is similar to the CHS (Cardiovascular Health Study) study protocol [6], and is a shortened clinical carotid imaging protocol (Table 1). It starts with a transverse sweep from the base of the neck to the jaw along the course of the CCA

TABLE 1. Summary of the MESA study carotid ultrasound imaging protocols

	Clinical Carotid Protocol	MESA Study IMT	MESA Study Progression
Transverse sweep along the neck to confirm anatomy and identify plaque formation on transverse images	Optional but tends to be done routinely	Yes	Yes
At least 3 longitudinal images of the proximal, mid and distal common carotid with color Doppler and Doppler waveforms	Routine	Only the distal common carotid artery grayscale image; no Doppler evaluation	Only the distal right common carotid with Doppler and grayscale images
Color Doppler image of the bulb and internal carotid artery looking for sites of velocity elevation and plaque	Routine	Yes	No
Doppler evaluation of the mid and distal internal carotid artery	Routine	Only if there is elevation of Doppler velocities to find maximum	No
Grayscale images of plaques in at least 2 projections	Routine; can be done with transverse images	Three longitudinal images: anterior, lateral, and posterior angulation; at least 1 showing plaque interfaces clearly	No
External carotid artery Doppler and grayscale images	Routine	No	No
Vertebral artery Doppler imaging	Routine	No	No

IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis.

and its branches. This is used to gauge the overall extent of atherosclerotic changes and the location of the bifurcation. Images are then acquired with the ultrasound probe parallel to the artery walls. Color Doppler imaging and Doppler waveform acquisition are performed at the site of highest velocity near the carotid bifurcation. This is done to permit the grading of a possible carotid artery stenosis because grayscale imaging can underestimate the size of atherosclerotic plaques, especially in the case of an echolucent plaque [14]. The CCA and ICA IMT images are then acquired in a very standardized fashion.

One projection of the CCA was acquired with the patient's head rotated 45° to the side not being imaged (Fig. 2 and Online Fig. A2). The transducer face was held in a plane parallel to the CCA long axis, 45° from the horizontal, and an image loop lasting 2 to 3 cardiac cycles was acquired. The resolution was 180 pixels/cm and the edge of the carotid bulb was to the left of the image. In the MESA study, the ultrasound device was not equipped with an electrocardiographic trigger. We therefore opted to select the image frame having the smallest artery diameter during the cardiac cycle. The validity of this approach was subsequently tested by selectively analyzing images acquired at peak systole and end-diastole in the right CCA [15].

The ICA was then imaged in 3 projections: anterior, lateral, and posterior (Online Fig. A3). Images from the 3 projections were centered at the same level of the neck. If no plaque was visualized, the probe was rotated around the flow divider mid portion of the bulb, before the flow divider (Fig. 3). When a plaque was visualized, the

FIGURE 2. Image of the common carotid artery corresponds to the probe position shown in Online Figure A2. The vertical line corresponds to the location where the bulb begins based on the divergence of the outer wall of the common carotid artery.

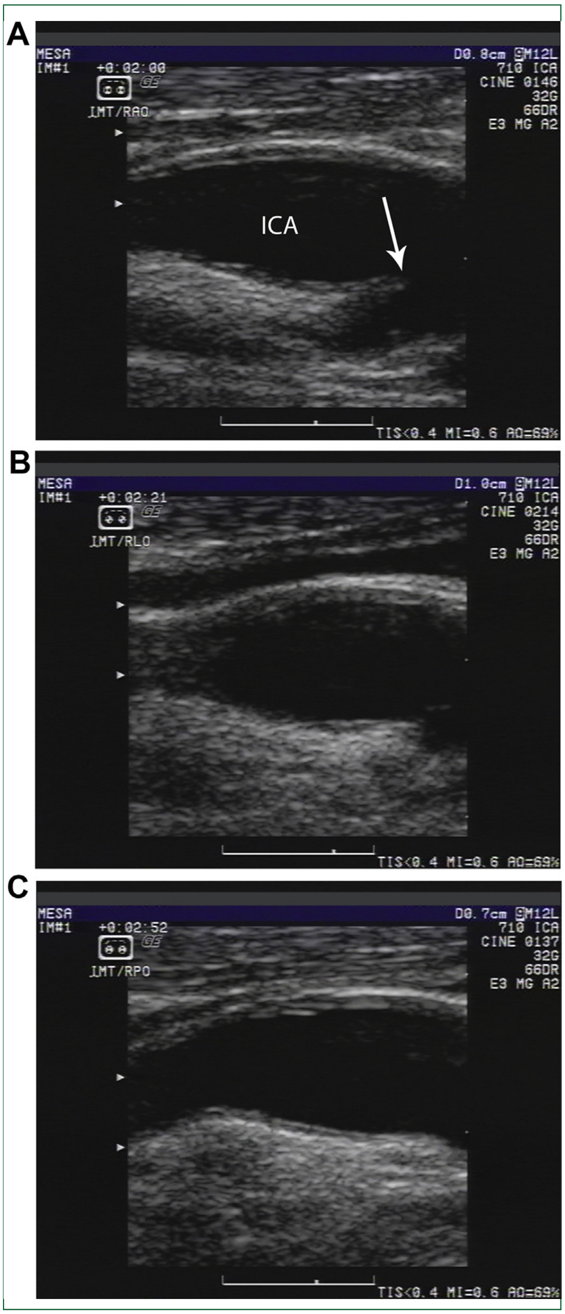

FIGURE 3. Images of the carotid bulb and proximal internal carotid corresponding to the projections shown in Online Figure A3. (A) The more anterior projection; the flow divider is clearly seen between the internal carotid artery (ICA) and external carotid artery (arrow). (B) The lateral projection; most of the image included the proximal internal carotid artery, and the flow divider is barely visible. (C) The flow divider is no longer visible on this posterior projection.

sonographer centered the imaging on the largest plaque seen in either the bulb or beyond the flow divider in the early ICA (Fig. 4). However, as occurs during a clinical carotid ultrasound examination, the sonographer could modify the angle of the acquired projections in order the better visualize any atherosclerotic plaque (Fig. 5).

All the MESA study images were stored on videotapes. The 8 images selected (4 on each side) for carotid IMT measurements were digitized and processed on a workstation. The IMT readers then drew lines approximately 1 cm long along the key wall interfaces (lumen-intima and media-adventitia) (Fig. 1). The lines are then processed by an algorithm that determined the mean IMT value, the standard deviation, and the minimum and the maximum [16]. The readers also reviewed the image sets and performed a qualitative evaluation of the extent of plaque formation (Table 2).

Lessons learned from the MESA study baseline IMT imaging protocol

Data completeness. The MESA study enrolled 6,814 participants with the requirement that they did not have evidence of prevalent cardiovascular disease [17]. No attempt was made to select individuals on the basis of being able to obtain ultrasound images of their carotid arteries. Because all participants needed to be imaged, failure to obtain data on some participants may have been due to a weakness of the carotid imaging protocol or to technical factors. Of the 6,814 MESA study participants, 6,739 presented themselves for the carotid examination. Common carotid IMT measurements were obtained in 99.7% (6,721 of 6,739) of participants and for the ICA in 98.4% (6,628 of 6,739) of participants.

Subjective evaluation of plaque severity and Doppler velocities. As indicated previously, the MESA IMT protocol is a simple protocol modified from a standard clinical carotid imaging protocol. The Doppler velocity measurements permit the detection of lesions that cause hemodynamic significant stenosis. As these lesions are associated with a high likelihood of future stroke, individuals likely to be candidates for surgical interventions can be identified. In the MESA study, the prevalence of lesions greater that 50% according to a Doppler velocity cutpoint of 125 cm/s compatible with stenosis grading in the North American Symptomatic Carotid Endarterectomy Trial is low, at 1.7% (113 individuals).

The MESA study protocol also adopts a qualitative method of evaluating plaque. This approach is based on the clinical premise that the dominant plaque is normally the 1 that is more likely to grow into a clinically significant stenosis [18]. The clinical carotid ultrasound examination uses Doppler velocity thresholds to identify “significant” plaques causing 50% or greater diameter narrowing. If the

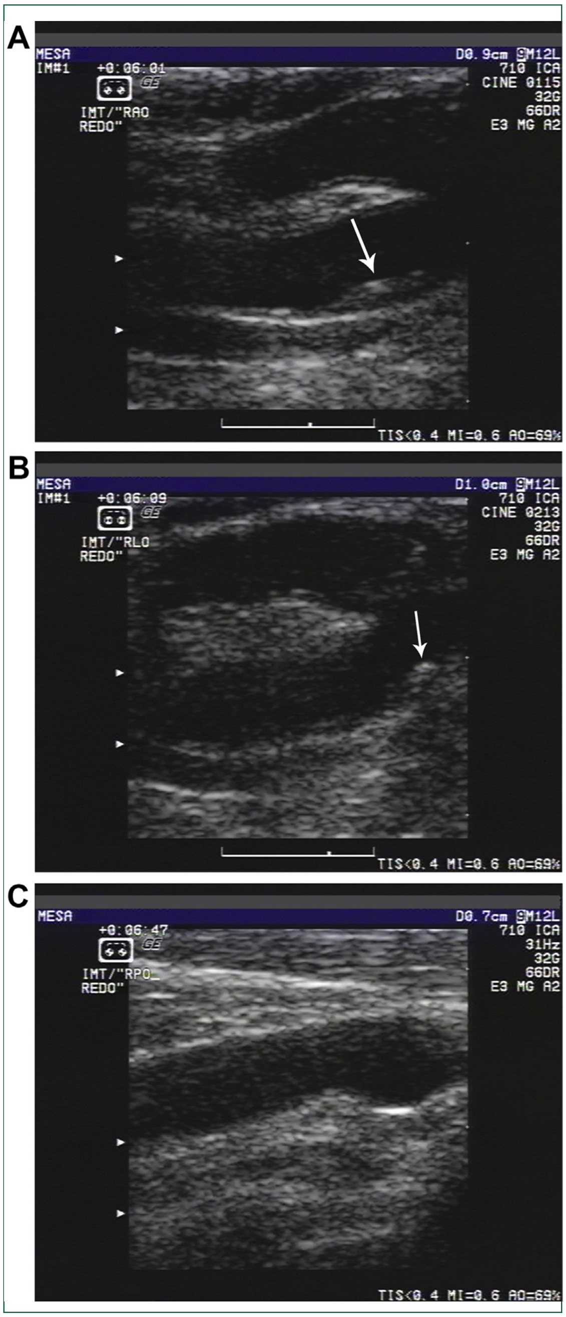

FIGURE 4. Images showing how plaque detection can depend on image projection. (A) The plaque (arrow) is best seen on the anterior projection. (B) The plaque (arrow) is not as well visualized on the lateral projection. (C) No plaque is seen on the posterior projection.

lesion is not significant, qualitative grading schemes use 0% for absence of plaque, and then give estimates of plaque size as a function of the percentage they protrude into the artery lumen. Depending on the vascular laboratory, in some cases plaques are graded as 1% to 15% and 16% to 49% [18] and in other instances as 1% to 24% and 25% to 49% [19]. In the MESA study, the subjective evaluation of plaque presence (0% vs. >0% or <25% vs. ≥25%) has been linked to the likelihood of future cardiovascular events [20].

Location of common carotid IMT measurement. The MESA study has also addressed some technical issues regarding the location where CCA IMT should be measured. This location had varied from study to study as reported by Lorenz et al. [21,22] in both a review of IMT imaging approaches and in a large meta-analysis. In their review, Lorenz et al. [21] noted variability in the site where CCA IMT measurements were made: sometimes close to the bulb, sometimes including the overhang into the bulb [23], and at other times at a site lower down in the CCA [24], often in a segment free of plaque (Fig. 6). The different IMT protocols that contributed data to another meta-analysis are summarized in graphical form as Figure 7 and described in Table 3. The figure and the contents of the table confirm the wide variation in the location chosen to measure common carotid IMT [36]. A MESA study analysis looked at the effects of performing a far wall common carotid IMT measurement close to or further away from the beginning of the carotid bulb. Measurements slightly lower (further away from the bulb corresponding to the right of line B in Fig. 6B) showed better associations with cardiovascular risk factors and had better predictive value for coronary heart disease events [37]. Although no strong explanation could be found for these differences, they likely reflect the low shear stress flow dynamics that occur at and near to the bulb [38,39].

Near wall versus far wall common carotid IMT measurements. The MESA study data have been used to determine if there are differences between near wall and far wall CCA IMT measurements and whether this affected their associations with cardiovascular risk factors and events. The near wall, closest to the skin (Fig. 1), is often believed to give unreliable results because of the physical process that generates reflected ultrasound waves at sharp interfaces between materials of different acoustic impedance [40]. The associations between risk factors and common carotid IMT have been noted to vary as a function of whether or not the common carotid IMT was measured on the near wall or the far wall [41]. Prior to the MESA study, no data existed on the separate association of the near and far wall IMT with cardiovascular events although there was wide variation on whether or not the near wall IMT was included in the IMT measurement (Table 3). We replicated the findings of the Rotterdam study for cross-sectional association with cardiovascular risk factors in the MESA study [41] and additionally found that near wall IMT showed

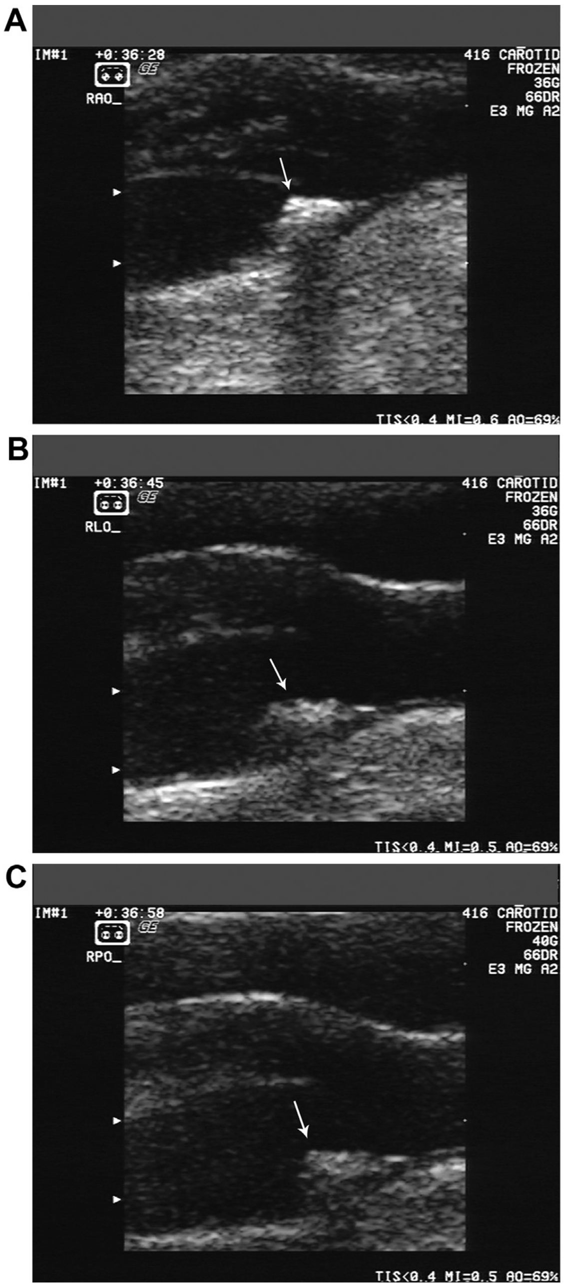

FIGURE 5. Images demonstrating how the sonographer attempted to better delineate a plaque by minimally changing the acquisition positions. (A, B, C) A plaque (arrow) and the flow divider are seen on all 3 projections.

slightly stronger associations with risk factors than far wall common carotid IMT measurements [42]. More importantly, the MESA study findings suggested that there is slightly greater predictive power for events when the far wall common carotid IMT measurements was used alone and not combined with the near wall [42].

Reproducibility of common and internal carotid IMT measurements. Reproducibility estimates were made for both the common carotid and the ICA IMT. Intrareader and inter-reader reproducibility estimates were made on the same set of already acquired images. Interscan reproducibility estimates were estimated from replicate carotid IMT studies randomly acquired on the same participants. In both cases, the IMT readers were blinded and the assignment for a replicate study was made by the study Coordinating Center at the University of Washington (Seattle, Washington, USA). Because of this design, there are few full replicate studies analyzed by different readers because readers tended to be assigned to the same the MESA study clinic.

The inter-reader Pearson correlation coefficient for comparing manual traced IMT of the right common carotid far wall was 0.78. However this process included review of a 20-s-long video loop, selection of an image and performance of an IMT measurement [43]. The reproducibility of the basic the MESA study CCA IMT measurements was evaluated more comprehensively [42]. For blinded replicate image acquisitions and measurements made by the same reader, the correlation coefficient between readings was 0.91 (95% confidence interval [CI]: 0.87 to 0.93). The intrareader correlation coefficient was high at 0.97 (95% CI: 0.96 to 0.98) whereas the inter-reader correlation coefficient was lower at 0.82 (95% CI: 0.73 to 0.88).

In the case of ICA plaque, the evaluation of reproducibility included kappa statistics for presence/absence of plaque defined according to 4 different criteria and ranged from the kappa values ranged from 0.83 to 0.94. For continuous estimates of the maximum ICA IMT, the correlation coefficient between measurements was 0.91. However, because of the blinded nature of the reading process the same reader was likely to read studies from the same clinical center, making the evaluation process one of intrareader variability in 141 studies [20].

THE MESA STUDY COMMON CAROTID IMT PROGRESSION PROTOCOL

The second MESA study carotid imaging protocol emulates the IMT progression protocol used by Hodis et al. [4]. The protocol consists of the acquisition of 1 image of the right common carotid with the ultrasound probe parallel to the artery walls but with the internal jugular vein above the artery. This improves physical resolution because there is no soft tissue attenuation as the ultrasound beam transits the vein lumen. If no jugular vein is visualized, the probe is held in a projection perpendicular to the neck. This progression protocol is predicated on obtaining images at the same orientation and location on at least 2 separate visits. In addition, at the second visit, the baseline images are available for review to facilitate concordance of image location. CCA images acquired with this imaging protocol

TABLE 2. Different IMT measurement variables derived from the MESA study

Metric	CCA	ICA	Comment
Basic MESA study protocol			
Mean of the maximum CCA IMT	Mean of the near wall and far wall maximum IMT		Up of 4 IMT measurements are averaged; plaque included
Mean of the maximum ICA IMT		Mean of the near wall and far wall maximum IMT	Up to 12 IMT measurements are averaged; plaque sought out
IMT *z*-score	*z*-score of the mean of the maximum IMT	*z*-score of the mean of the maximum IMT	Both *z*-scores are added to generate a global *z*-score
Mean of the mean CCA IMT	Mean of the near wall and far wall mean IMT		Up of 4 IMT measurements are averaged; plaque included
Maximum ICA IMT		Maximum ICA IMT in either wall or either side	Similar to a clinical protocol. The "tallest" plaque is measured; a 1.5-mm threshold is used to define plaque
Percent stenosis	Qualitative evaluation of plaque size given as absent (0%), visual lumen encroachment of 1–24%, 25–49%; elevated Doppler velocities ≥50% stenosis		Subjective measurement; typically reported as the most significant of both sides; additional category of probable occlusion based on absent color Doppler signals and Doppler waveforms
MESA study progression protocol			
Mean CCA IMT	Mean of the far wall IMT on the right side only		Plaque excluded

CCA, common carotid artery; ICA, internal carotid artery; other abbreviations as in Table 1.

had far wall CCA IMT measurements made with the application of an edge detector and by manual tracings at the interface lines [16,43].

The image sequence was acquired as a video stream of approximately 20 s in duration. This video stream was digitized. The video stream was processed with an edge detector to evaluate diameter changes during the cardiac cycle. The images with the smallest and largest diameter represented end-diastole and peak systole, respectively. Images corresponding to end-diastole were selected from the baseline acquisition and paired with a follow-up image also acquired at end-diastole [44].

Lessons learned from the MESA study common carotid IMT progression protocol

Data completeness. The follow-up period was randomly assigned to an average of 1.5 years in one half of the cohort and 3.0 years in the other half. Data completeness was judged by the number of paired IMT measurements made at baseline and on follow-up. All participants that had CCA IMT measurements made at follow-up were matched to the baseline studies for a total of 5,640 participants. Of these, paired IMT measurements were made in 5,633 (99.9%) participants [16]. This might reflect on the fact that the readers were able to review the 20 s of video loops at baseline and follow-up and then select what they considered to be the better quality CCA images.

Use of a common carotid IMT edge detector. Many experts and even consensus statements consider the use of an edge detector as essential for the measurements of common carotid IMT [24]. Despite this recommendation, no data compare the 2 measurement approaches with respect to their cross-sectional associations with risk factors or their predictive power for events. This wide variability in the use of edge detection and other means of measuring IMT is apparent when looking at the measurement processes (Table 4) used in a major meta-analysis on the value of common carotid IMT for predicting cardiovascular events [36]. In the MESA study, the progression protocol had manual common carotid IMT measurements and automated measurements in the same CCA segment. The readers performed their manual tracings in a rectangular region of interest and, when finished, activated an edge detector that automatically found the edges in the same region of interest and stored the results. In the MESA study, associations of manual traced and edge detected IMT with cardiovascular risk factors were very similar to each other [16]. Overall, the difference between edge detected and manual IMT measurements was 0.19 mm with a 0.15 mm standard deviation value in a Bland-Altman analysis [16]. In addition, the edge detected IMT values seem to have slightly stronger predictive power than manual tracings for coronary heart disease events although the differences between both approaches were minimal [43].

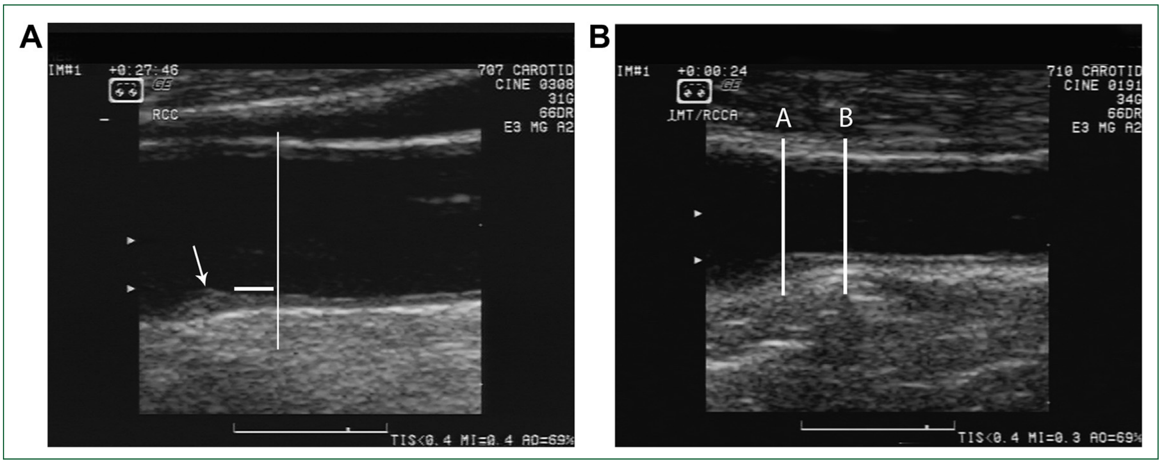

FIGURE 6. Two images showing how the MESA (Multi-Ethnic Study of Atherosclerosis) study protocol treated the common carotid artery intima-media thickness measurements. (A) The line indicates were the outer wall (adventitia) starts to diverge. In the Cardiovascular Health Study, the lesion indicated by the arrow would have been included in the measurement. In other protocols, the short segment indicated by the horizontal line would likely have been included because the divergence into the bulb would have been defined by the lumen-intima interface. In the MESA study, the measurement is made to the right of the vertical line. (B) Although there is no plaque, many protocols would have included the wall thickness between lines A and B as part of the intima-media thickness measurement because the wall defined as the lumen-intima interface is still horizontal and continues from the straight segment of the common carotid artery. In the MESA study, the measurement is made to the right of line B.

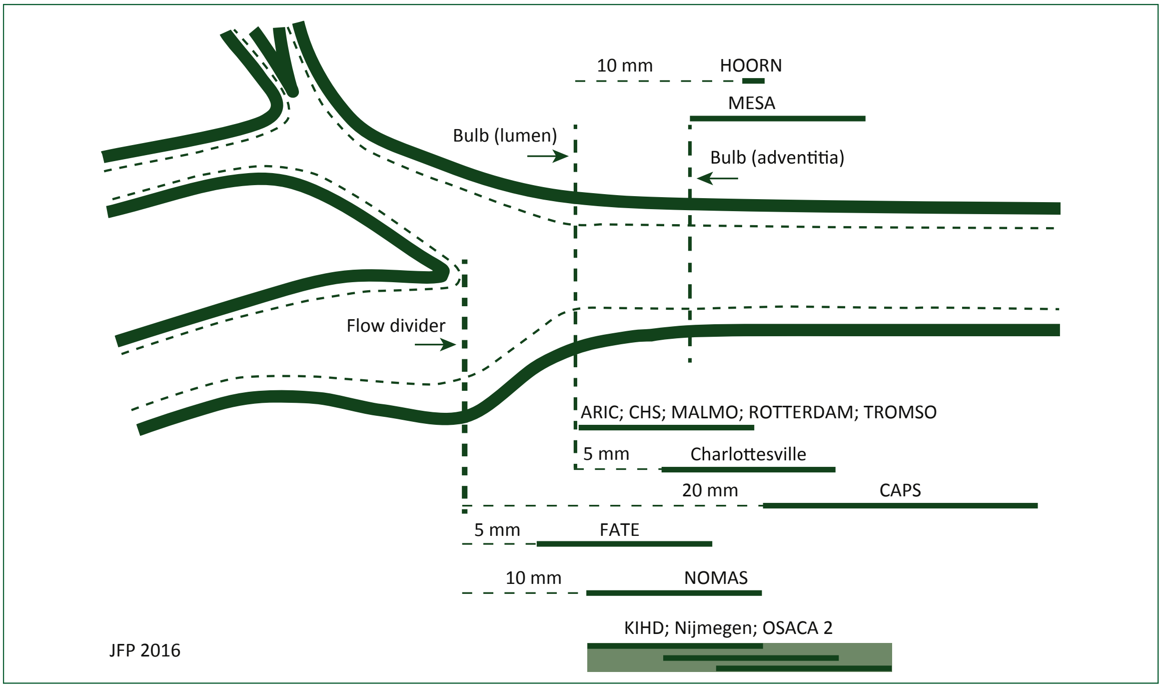

FIGURE 7. The differences in the common carotid intima-media thickness measurements made in the USE-IMT meta-analysis. The wide variability in the location of the common carotid artery intima-media thickness measurement as a function of 2 major fiduciary points: the common carotid artery flow divider and the beginning of the common carotid artery bulb. The pertinent references are listed in Table 5. ARIC, Atherosclerosis Risk in Communities; CAPS, Carotid Atherosclerosis Progression Study; CHS, Cardiovascular Health Study; FATE, Firefighters and Their Endothelium; KIHD, Kuopio Ischaemic Heart Disease; NOMAS, Northern Manhattan Study; MESA, Multi-Ethnic Study of Atherosclerosis; OSACA2, Osaka Follow-up Study for Carotid Atherosclerosis part 2; USE-IMT, Use Intima Media Thickness.

TABLE 3. Measurement approach for common carotid artery IMT in the USE-IMT meta-analysis

Study	Location	Number of Views	Plaque Included	IMT Variable
ARIC [23]	10 mm beginning of bulb based on lumen interfaces	3 angles; 1 frame each	Yes	Mean of mean far wall IMT right and left sides from a set of 11 cursors
CAPS [25]	20—60 mm below flow divider	1 angle; 1 frame	Yes	Mean of far wall mean IMT right and left sides from continuous tracings
Charlottesville [26]	10 mm segments starting 5 mm below the “bulb”	1 angle; 1 frame	Yes	Mean of mean IMT near and far wall right and left sides with cursors
CHS [6]	10 mm beginning of bulb based on lumen interfaces	1 angle; 1 frame	Yes	Mean of the maximum IMT near and far wall right and left sides from continuous tracings
FATE [27]	5 mm proximal to flow divider	1 angle; 3 frames	Yes	Mean far wall IMT of right side from continuous tracings; largest of 3 frames
Hoorn study [28]	Single location 10 mm below the bulb	1 angle; 3 acquisitions	No	Mean IMT integrated M-mode line data throughout the cardiac cycle; average of 3 frames
KIHD [29]	Common carotid not otherwise specified	1 angle; 1 frame	Yes	Mean of the maximum far wall IMT right and left sides from 3 pairs of manual cursors
Malmö [30]	10 mm beginning of bulb based on lumen interfaces	1 angle; 1 frame	Yes	Mean far wall IMT of the right side from continuous tracings
MESA standard [31]	10 mm beginning of bulb based on outer wall	1 angle; 1 frame	Yes	Mean of the maximum IMT near and far wall right and left sides from continuous tracings
Nijmegen study [32]	Distal 10 mm common carotid not otherwise specified	1 angle; 1 frame	No	Mean of mean IMT near and far wall right and left sides from continuous tracings
NOMAS [33]	10 to 20 mm from the flow divider	1 angle; 1 frame	Yes	Mean of the maximum IMT right and left sides from continuous tracings
OSACA2 study [34]	Common carotid not otherwise specified	1 angle; 1 frame	Yes	Mean of maximum right and left sides from 1 pair of manual cursors
Rotterdam study [8]	10 mm beginning of bulb based on lumen interfaces	1 angle; 3 frames	Yes	Mean of mean IMT near and far wall right and left sides from multiple manual cursors
Tromsø study [35]	10 mm beginning of bulb based on lumen interfaces	1 angle; 3 frames	Yes	Mean of mean IMT near and far wall right side from continuous tracings

ARIC, Atherosclerosis Risk in Communities; CAPS, Carotid Atherosclerosis Progression Study; CHS, Cardiovascular Health Study; FATE, Firefighters and Their Endothelium; KIHD, Kuopio Ischaemic Heart Disease; NOMAS, Northern Manhattan Study; OSACA2, Osaka Follow-up Study for Carotid Atherosclerosis part 2; USE-IMT, Use Intima Media Thickness; other abbreviations as in Table 1.

The edge-detected data also indicated that it would be possible to calibrate the manual traced IMT measurements thereby helping to generate IMT normative data [43]. An early report showed that individual readers making IMT measurements on the same images placed the lumen-intima and the media-adventitia interface lines in slightly different locations. These differences were consistent and therefore represent a systematic bias [45]. This systematic bias was also shown when the edge detected IMT results of a reader are compared to those made manually [43]. For example, the closest match between edge detected and manually traced IMT values was a mean ± SD difference of 0.09 ± 0.16 mm for 1 reader and the biggest discordance a mean difference of 0.25 ± 0.11 mm in another [43]. These findings would indicate that manual and edge-detected IMT measurements could be calibrated to generate normative common carotid IMT values as long as this bias term was accounted for [43]. When looking at the predictive power of edge-detected and manual traced IMT for coronary heart disease events, the hazard ratios were 1.63 (95% CI: 1.12 to 2.37) and 1.31 (95% CI: 0.84 to 2.06), respectively. Although the manual traced CCA IMT did not appear to predict events, the edge-detected values were significant at $p = 0.011$ [43]. The lack of predictive power for the manual traced IMT values was likely due to the positioning of the measurement site because manual traced far wall IMT has been shown to predict events in other MESA study analyses [42].

Effect of the cardiac cycle on common carotid IMT. Consensus statements have recommended that IMT be measured on an electrocardiographic gated image acquired at the peak of the R-wave (end-diastole). However, this recommendation was not followed in many of the key IMT studies that were part of a meta-analysis by Den Ruijter et al. [36], as shown in Table 4. In the MESA study, the ultrasound device was not equipped with an

TABLE 4. IMT estimation processes used in the USE-IMT meta-analysis: electrocardiographic gating and measurement approach

Study	ECG gating at Acquisition	Phase of Cardiac Cycle	Measurement Process
ARIC [23]	No	Systole from video loop	Manual crosshairs
CAPS [25]	Likely	Systole	Edge detection
Charlottesville [26]	Yes	Diastole	Likely manual crosshairs
CHS [6]	No	Not controlled	Manual continuous tracings
FATE [27]	No	Not controlled	Manual continuous tracings
Hoorn Study [28]	Yes	Average throughout the cardiac cycle	Pairs of edge detected points of 3 cardiac cycles
KIHD [29]	No	Not controlled	Manual crosshairs
Malmö [30]	No	Not controlled	Manual continuous tracings
MESA standard [31]	No	Diastole from video loop	Manual continuous tracings
Nijmegen study [32]	Yes	Diastole	Edge detection
NOMAS [33]	No	Not controlled	Manual continuous tracings
OSACA2 study [34]	No	Not controlled	Manual crosshairs
Rotterdam study [8]	Yes	Diastole	Manual continuous tracings
Tromsø study [35]	No	Not controlled	Edge detection

ECG, electrocardiogram; other abbreviations as in Tables 1 and 3.

electrocardiographic trigger. We therefore had opted to have the readers select the image frame with the smallest diameter for the IMT measurements. Although the sonographers were able to flag what they believed was the best image for the IMT measurements, the readers at the Ultrasound Reading Center (Boston, Massachusetts, USA) reviewed the video loops and did the final selection of the images used for the IMT analyses. We verified the robustness of this approach by performing a validation study using the video loops acquired as part of the CCA IMT progression protocol [15]. In essence, we looked at the effects of the cardiac cycle on the CCA IMT [15]. The first step was to generate diameter versus time tracings of the CCA using an edge detector to facilitate the identification of peak systole (maximal diameter) and of end-diastole (smallest diameter). We then measured the IMT on these 2 images. The difference in IMT due to the change in diameter between diastole and systole averaged 0.041 mm (95% CI: 0.039 to 0.042 mm). This difference in common carotid IMT between end-diastole and peak systole increased with pulse pressure and varied slightly with race-ethnicity [15].

These cardiac cycle differences might have affected individual patient cardiovascular risk assessment depending on the origin of the IMT normative data. For example, normative data from CCA IMT measurements generated by the ARIC (Atherosclerosis Risk in Communities) study were made at peak systole [23]. Consider a 55-year-old patient having an IMT measurement made at end-diastole (Fig. 8). The measurement falls just above the 75% value (high risk) for that age according to ARIC data. The patient IMT value, if measured at peak systole, will be approximately 0.04 mm lower [15], bringing the patient somewhere between the 50th and 75th percentile (moderate risk). Given that consensus statements recommend measurements made at end-diastole [24,46], the MESA study IMT data show that IMT normative values generated from ARIC study data would overestimate a patient's cardiovascular risk [15]. Considering that CCA IMT increases with age at a rate of approximately 0.007 mm/year, the difference in IMT values (Fig. 8) is equivalent to a 5- to 6-year age difference: (0.04 mm)/(0.007 mm/year).

SUMMARY OF THE MESA STUDY CAROTID IMT MEASUREMENTS

Baseline protocol

On the basis of the results of the CHS study, the key MESA study IMT variables were: 1) the mean of the maximum CCA IMT; and 2) the mean of the maximum internal carotid IMT. Both near and far walls were used (Table 2). The idea of using these aggregate averages was to reduce variability and improve statistical power. The MESA study IMT measurements also included separate mean far wall CCA IMT (Table 2) as recommended by consensus groups [24,46]. The ICA IMT protocol had a strong emphasis on detecting plaque and acquiring the image that best delineated plaque height. This measurement was specifically selected based on the findings from the Framingham Study Offspring cohort [47] where a similar IMT measurement process had been implemented. The following 2 IMT metrics were therefore also used in some MESA study analyses: 1) the mean of the mean far wall common carotid IMT [42]; and 2) the maximum of the internal carotid IMT [20]. Each IMT variable was, by itself, a strong predictor of cardiovascular events [20,42].

Progression protocol

The mean right CCA IMT and the change in IMT at follow-up were the 2 variables used in the MESA study IMT progression protocol. They emulated the previously validated protocol proposed by Hodis et al. [4]

USE OF CAROTID IMT AS A MEASURE OF SUBCLINICAL CARDIOVASCULAR DISEASE

Exposure: race or ethnicity

Common and internal carotid arteries show significant race-ethnicity differences in the MESA study cohort [48]. Chinese Americans have the lowest IMT in the common and internal carotid arteries. Although blacks have relatively high CCA IMTs, whites have the highest ICA IMTs [48]. Another analysis shows stronger differences in mean

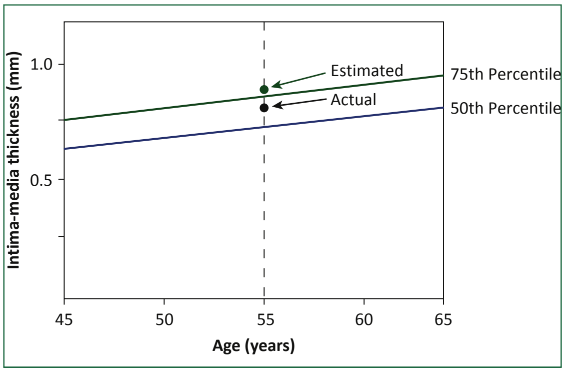

FIGURE 8. The effect of using common carotid artery intima-media thickness measurements made at systole, as was done in the ARIC (Atherosclerosis Risk in Communities), to generate 50th and 75th percentiles for normative data as a function of age. The intima-media thickness is then acquired and measured at end-diastole in a 55-year-old as recommended by current guidelines and gives the estimated value just above the 75th percentile. The intima-media thickness, if it had been measured at peak systole consistent with the method of acquisition in the ARIC study would have fallen between the 50th and the 75th percentiles.

of the maximum common carotid IMT and mean of the maximum internal carotid IMT between men and women than by race-ethnicity [49]. In diabetics both mean of the maximum common and internal carotid IMT are lower in Chinese than in other ethnicities [50].

Exposure: cholesterol and cholesterol particle sizes

Mora et al. [51] looked at the associations of small and large low-density lipoprotein particle size (LDL-p) as measured by proton nuclear magnetic resonance spectroscopy with IMT. The association between small LDL-p and an aggregate measurement of the mean of the maximum IMT in both the common and the internal carotid arteries remained strong even after statistical adjustments whereas no such association was seen for large LDL-p [51]. This was consistent with prior reports showing that small LDL-p had the strongest association with atherogenesis and outcomes, especially in women [52]. Mackey et al. [53] studied associations of high-density lipoprotein cholesterol (HDL-c) and HDL-c particles (HDL-p) with the combined mean of the maximum common and internal carotid IMT showing that HDL-p had stronger associations than HDL-c. This difference was noted when 4 lipoprotein moieties, triglycerides, LDL cholesterol, LDL-p, and HDL-c, were included with HDL-p in the same statistical model [53]. Paramsothy et al. [54] studied the associations between various lipoprotein profiles associated with dyslipidemia and mean of the maximum of the common and ICA IMT. Both hyperlipidemia and hypercholesterolemia were associated with IMT. These findings were consistent with the findings of concurrent analyses where coronary artery calcification served as a measure of subclinical disease instead of IMT [54].

Exposure: smoking, obesity, and markers of inflammation

The association between carotid IMT and smoking is well known [55,56]. In the MESA study, Sharrett et al. [57] found an association between the combined common and internal carotid IMT *z*-score and smoking. McEvoy et al. [58] sought to see if inflammatory markers altered this association. Carotid artery IMT was increased in smokers and former smokers and depended on the number of pack-years smoked [58].

Burke et al. [59] found that the mean of the maximum common and internal carotid IMT was associated with being overweight (body mass index between 25.0 kg/m^2 and 29.9 kg/m^2) or obese (body mass index >30kg/m^2). These investigators also found that both metrics were increased in overweight and obese individuals after accounting for cardiovascular risk factors [59]. Bertoni et al. [60] studied the associations of insulin resistance with mean of the maximum CCA IMT. They found weak associations of the highest IMT quartile when compared to the lowest quartile.

Associations between markers of inflammation and carotid IMT have been selectively investigated in the MESA study. The JUPITER (Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin) study had shown that the use of lipid-lowering therapy in individuals with low levels of LDL cholesterol (<130 mg/dl) had some benefit in individuals with elevated high-sensitivity C-reactive protein (hsCRP) >2 mg/L [61]. Blaha et al. [62] looked at associations between hsCRP in obese and nonobese individuals also stratifying by hsCRP <2 mg/L versus ≥2 mg/L. The mean of the maximum CCA IMT was used as a marker of subclinical cardiovascular disease [62]. Carotid IMT was associated with elevated hsCRP (≥2 mg/L) in obese individuals. Obesity and the metabolic syndrome were associated with increased carotid IMT [62]. Common carotid IMT was also associated with increased hsCRP in the absence of the metabolic syndrome [62].

Olson et al. [63] studied another aspect of inflammation, a plausible record of exposure to prior infection/inflammation as reflected by the CD4+ lymphocyte levels. An association was found between CD4+ levels and the mean of the maximum common carotid IMT in European-Americans [63]. No associations were found for ICA IMT.

Socioeconomic factors

The possible associations of socioeconomic factors with carotid artery IMT have been studied in the MESA study. These investigations suggested that low socioeconomic status and poor job control are associated with subclinical cardiovascular disease as measured by IMT.

The mean of the maximum CCA IMT was used as a marker of atherosclerosis by Lemelin et al. [64] to study whether socioeconomic status had an association with carotid IMT. They found inverse associations between childhood, adult, and neighborhood socioeconomic status and IMT [64]. Charles et al. [65] used mean of the maximum CCA and ICA IMT to study a plausible association between work hours and subclinical cardiovascular disease. They found a weak association between hours per week worked and common carotid IMT in women but no association for men [65]. No significant association was seen between work hours and the ICA IMT [65]. In a study looking at the effects of job control and demands on subclinical cardiovascular disease, Fujishiro et al. [66] noted an association between increasing mean of the maximum common carotid IMT and low job control. The mean of the maximum internal carotid IMT was increased in blue-collar workers [66] as compared to white-collar workers.

Associations with coronary artery calcium scores

Polak et al. [67] found a strong association between ICA plaque as well as maximum ICA IMT and a positive coronary artery calcium Agatston score. This confirmed the findings reported by Lee et al. that also showed an association between carotid artery plaque and the coronary artery calcium score [68]. In a longitudinal follow-up with a mean of 2.4 years. Polak et al. [67] found that maximum ICA IMT was associated with the development of a positive coronary artery calcium score in the MESA study participants with a score of zero at baseline. ICA IMT was also associated with increases in coronary artery calcium scores in individuals who had a positive score at baseline [67].

The MESA study findings build on a known association between carotid artery plaque and coronary artery lesions seen on angiography or at autopsy [69,70] and further support the linkage between atherosclerotic plaques in different arterial beds.

Associations with early markers of myocardial dysfunction

Polak et al. [71] observed an association between left ventricular mass, measured by magnetic resonance imaging, and CCA IMT. These findings suggested an association between the carotid artery IMT and the left ventricle that is likely mediated through elevations in blood pressure. A similar association had been shown in the CHS study with left ventricular mass measurements made by echocardiography [72].

Fernandes et al. [73] studied the associations of early markers of myocardial dysfunction as measured on cardiac magnetic resonance imaging with mean of the maximum common carotid IMT. They found an association between decreased myocardial strain (worsening left ventricular myocardial function) and increases in IMT [73]. The possibility that asymptomatic coronary artery lesions might have been the source of this association cannot be fully discounted. However, changes in cardiac strain might be reflective of early diastolic dysfunction. It is plausible that chronic elevations in blood pressure might have been the mediator of this association.

Associations with renal dysfunction

Chronic hypertension is known to lead to left ventricular hypertrophy and the development of renal dysfunction. Because CCA IMT is associated with left ventricular mass, it is likely associated with the progression of renal dysfunction as measured by changes in albumin-creatinine ratios. This is consistent with MESA study findings reported by Yu et al. [74]. Increased common carotid IMT was also shown to be associated with increases in albumin-creatinine ratios over time whereas ICA IMT was not [75]. The longitudinal associations were present despite the lack of a direct association of either common or ICA IMT with metrics of renal dysfunction in a cross-sectional analysis [76].

Exposure: air pollution

The MESA Air study is an ancillary study that included a large number of MESA study participants and enrolled additional participants [77]. Carotid IMT served as a surrogate for subclinical cardiovascular disease. Sun et al. [78] showed that the mean far wall common carotid IMT was associated with components of particulate matter in the atmosphere with an aerodynamic profile of 2.5 μm or less, specifically organic carbon and sulfur. These findings were confirmed with more sophisticated measures of exposures by Kim et al. [79]. Using data from the MESA study progression protocol, Adar et al. [80] showed a link between progression of right far wall mean carotid IMT and particulate matter in the atmosphere with an aerodynamic profile of 2.5 μm or less exposure levels. These findings support a plausible causal link between air pollution and subclinical cardiovascular disease.

ASSOCIATIONS OF COMMON AND ICA IMT WITH CARDIOVASCULAR OUTCOMES

Overview

The definition of cardiovascular outcomes in the MESA study is not identical to that adopted by other epidemiologic studies. For example in the Framingham Heart Study heart failure and the development of lower extremity arterial disease are part of the generic outcome of incident cardiovascular disease. In the MESA study, they are not. Incident cardiovascular disease is defined as incident myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by coronary revascularization), stroke, stroke death, coronary heart disease death, other atherosclerotic death, and other cardiovascular disease death.

Folsom et al. [31] first reported on the association between carotid artery IMT and cardiovascular events in

TABLE 5. Measurement process for the bulb and internal carotid artery IMT or plaque

Study	Location	Number of Views	IMT variable
ARIC [23]	2 measurements each side: 10 mm below and 10 mm above flow divider	I angle; 2 images 2 sides	Maximum distance between cursors $\geq$1.5 mm on far wall or subjective above 1.5 mm
CAPS [25]	2 measurements each side: 0-20 mm below and 0-20 mm above flow divider	1 angle; 2 images 2 sides	Mean of far wall mean IMT continuous tracings but not used as separate variable
Charlottesville [26]	2 measurements each side: center of bulb and 5 mm above end of bulb	1 angle; 2 images 2 sides	Mean of IMT near and far wall for bulb; mean far wall IMT for internal carotid artery Distance between cursors Not used as a separate variable
CHS [19]	1 measurement each image: centered on bulb; can shift center to flow divider if a plaque is seen	3 angles; 1 image each angle 2 sides	Mean of maximum IMT near and far wall from continuous tracings Subjective evaluation and semiquantitative grading
FATE [27]	Not done		Bulb measurement is considered common carotid IMT
Hoorn Study [28]	Not done		
KIHD [29]	Common carotid and carotid bulb		Subjective evaluation and semi-quantitative grading
Malmö [30]	Carotid bulb and proximal internal and external carotid arteries	Right side only	Subjective and >1.2 mm IMT
MESA standard [31]	1 measurement each image: centered on bulb; can shift center to flow divider if a plaque is seen	3 angles; 1 image each angle 2 sides	Mean of maximum IMT near and far wall from continuous tracings Subjective evaluation and semi-quantitative grading
Nijmegen Study [32]	Not done		
NOMAS [33]	0-10 mm below flow divider and 10 mm above flow divider	I angle; 2 images 2 sides	Mean of the maximum IMT right and left sides from continuous tracings; not used as separate variable
OSACA2 Study [34]	Carotid bifurcation and internal carotid artery; otherwise not specified	1 angle; 1 frame	Mean of maximum right and left sides from 1 pair of manual cursors; not used as separate variable
Rotterdam Study [82]	Carotid bifurcation and common carotid artery otherwise not specified	Not specified	Subjective: present/not present
Tromsø study [83]	Carotid bifurcation and common carotid artery otherwise not specified	Not specified	Subjective: present/not present in right carotid bifurcation

Abbreviations as in Tables 1 and 3.

the MESA study. They showed that the predictive power of IMT for coronary heart and cardiovascular disease was lower than that of the coronary artery calcium score. IMT values of the CCA and ICA were combined as a *z*-score (Table 2). In fully adjusted models, the hazard ratio of the *z*-score for coronary heart disease events was 1.2 (95% CI: 1.0 to 1.3) and for cardiovascular disease with angina was 1.1 (95% CI: 1.0 to 1.3). These findings were similar to the results reported in the CHS study (i.e., hazard ratio: 1.36; 95% CI: 1.25 to 1.47) for a combined outcome of myocardial infarction and stroke [11]. The MESA study findings indicated that the CHS study findings applied more broadly to a multiethnic cohort. Both IMT measurements were combined as a *z*-score to increase statistical power as was done in the CHS study [11]. The differences between both studies, specifically on the magnitude of the hazard ratios, might be due to including the coronary artery calcium scores and the carotid artery IMT *z*-scores in the same statistical model. The paper did not address the separate predictive power of the carotid IMT *z*-score in a model that did not include coronary artery calcium scores [31].

We have opted to study the results of the MESA study IMT data in the context of the results of a meta-analysis reported by Den Ruijter et al. [36]. This paper has been quoted as showing that carotid IMT does not incrementally add much to the Framingham risk factors in their current iteration as the pooled equation for predicting cardiovascular disease events [81]. The findings of this meta-analysis study are the main justification for not including carotid IMT as a predictor of cardiovascular disease outcomes in the most recent American Heart Association recommendations for the use of statin therapies in the general population [81]. The Den Ruijter et al. [36] paper concentrated its analyses on CCA IMT because most of the cohorts in the meta-analysis had not acquired ICA

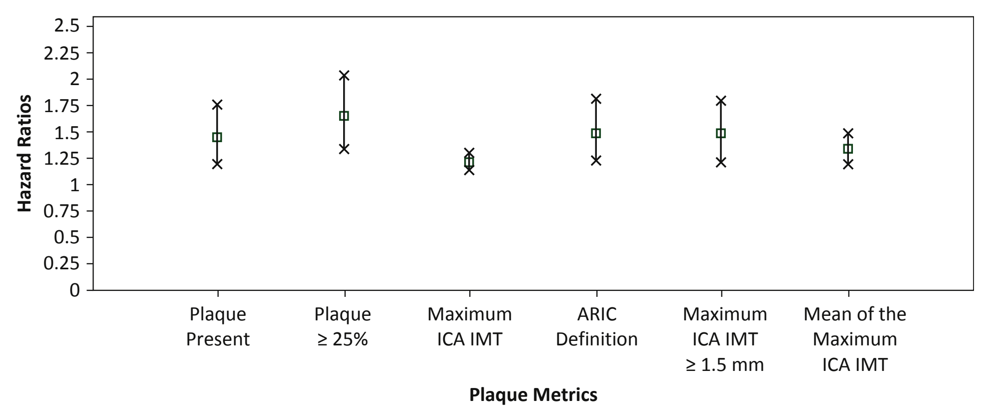

FIGURE 9. Hazard ratios (with 95% confidence intervals) of separate fully adjusted models with different definitions of plaque for predicting cardiovascular disease outcomes in the MESA (Multi-Ethnic Study of Atherosclerosis) study. All of the plaque metrics are independent predictors of events. ARIC, Atherosclerosis Risk in Communities; ICA, internal carotid artery; IMT, intima-media thickness.

IMT or plaque measurements (Table 5). Obvious differences in the studies selected by Den Ruijter et al. [36] were already mentioned and summarized in Tables 2 and 3. There was wide variation in the imaging protocols, the method used to obtain IMT measurements, and the IMT variables used. Analyses in the MESA study confirmed the hypothesis that the locations where common carotid IMT measurements were made with respect to the CCA bulb affected the association with outcomes [37]. The MESA study analyses rejected the hypothesis that adding the near wall IMT to the far wall IMT strengthened the association of IMT with events [42]. These 2 aspects of the IMT measurement process were different for the studies in the meta-analysis (Table 3). In addition, whereas the meta-analysis was limited to the CCA images, plaques were often included in the IMT variables (Table 3) [36]. The added heterogeneity of the resultant IMT variables likely decreased the statistical power of the meta-analysis [36] and might have given the impression that common carotid IMT had no value in cardiovascular risk assessment [81].

The meta-analysis did not include the ICA IMT [36] presumably because internal carotid IMT and plaque were either not evaluated or consistently defined in the different studies (Table 5). The predictive value of ICA IMT and plaque for cardiovascular events was therefore ignored despite findings from other studies. In both the ARIC study and the Framingham Offspring Study, the ICA IMT and plaque have shown stronger predictive value than CCA IMT for cardiovascular events [47,84]. We tested this hypothesis by performing additional analyses with the MESA study internal carotid IMT data.

ICA IMT and coronary heart disease events

The interface between the intima and the media of the artery walls is not consistently detectable on ultrasound imaging. Despite this limitation, coronary artery intravascular measurements of plaque or atheroma include the combined thickness of the intima and the media, in essence the IMT. As such, ICA IMT measurements and plaque measurement are interchangeable. The MESA study has available to it many ultrasound metrics of ICA plaque. The process used in the MESA study to obtain the ICA plaque metrics is similar to the approaches used in the CHS study [19] and the Framingham Offspring Study [85]. In both studies and in the MESA study, the sonographers are specifically instructed to focus on identifying the site of largest plaque formation in either the bulb or the ICA (Figs. 4 and 5).

In the MESA study, we tested the predictive value of 6 different plaque metrics (Table 4): subjectively defined as present [19], subjectively causing a relative diameter narrowing of 25% or more [86], measured as a continuous IMT value in the ICA [85], combining a subjective judgment of being present or far wall IMT >1.5 mm in the common and internal carotid arteries [84,87], measured as a maximum ICA IMT >1.5 mm [47], and calculated as the mean of the maximum ICA IMT [6,11].

As shown in Figure 9, the adjusted hazard ratios of the plaque metrics for predicting cardiovascular disease events were all >1, as were the lower 95% confidence intervals (CI). These data confirmed that the MESA study plaque metrics were all associated with events, either 1) when used as a continuous variable (maximum of any of the ICA IMTs or the mean of the maximum ICA IMTs), as a subjective measurement (plaque present or plaque causing an encroachment of ≥25% into the lumen), or above a quantitative threshold (≥1.5 mm ICA IMT); or 2) when used as a combination of both (subjective ≥0% or ≥1.5 mm ICA IMT). We also observed that all of the MESA study plaque measurements contributed in a statistically significant fashion to the prediction coronary

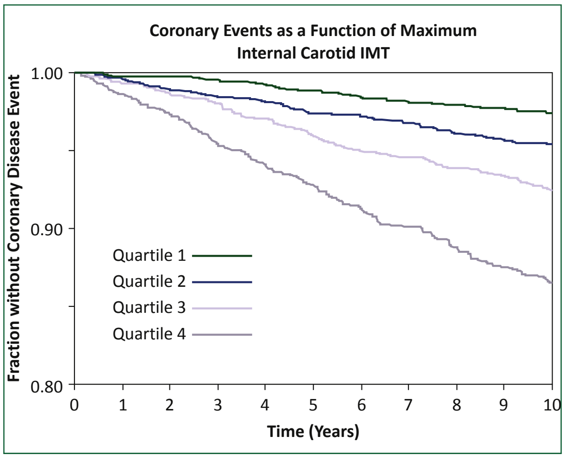

FIGURE 10. The Kaplan-Meier curves for the quartiles of maximum internal carotid artery intima-media thickness (IMT) show progressive increased risk of first-time coronary heart disease events. The highest quartile shows a distinct increase in the event rate.

heart disease events because the C-statistics of models with Framingham risk factors all increased significantly with the addition of the plaque metrics (Online Fig. A4). The Kaplan-Meier curves for quartiles of maximum ICA IMT is shown in Figure 10. Most of the discrimination for identifying individuals in a higher risk subgroup appears to be in the upper 2 IMT quartiles if not the highest quartile.

CCA IMT and cardiovascular outcomes

The ability of the CCA IMT measurements to predict coronary heart disease events was shown in a paper that compared the predictive values of the mean near wall IMT, mean far wall IMT, or the average of both near and far wall mean CCA IMT when added to the Framingham risk factors [42]. We used the mean of the mean CCA IMT instead of the mean of the maximum CCA IMT in keeping with other studies [22] but also based on the relative sensitivity of the IMT measurement with respect to proximity to the CCA bulb [37].

We found that a multivariable Cox proportional hazards model with Framingham risk factors, sex, and the 4 ethnic groups in the MESA study had a baseline C-statistic of 0.729 (95% CI: 0.708 to 0.749). There was no improvement in the C-statistic when the mean near wall IMT was added to the model (0.729; 95% CI: 0.708 to 0.749). Adding the mean far wall IMT and the mean of the near and far wall IMT to separate models increased the C-statistics to 0.740 (95% CI: 0.720 to 0.761; $p < 0.001$) and 0.735 (95% CI: 0.715 to 0.755; $p < 0.004$), respectively. Of the 3 variables, adding far wall mean CCA IMT had the most significant increase in the C-statistic by 0.012 (95% CI: 0.006 to 0.017) [42]. The Kaplan-Meier curves for quartiles of far wall IMT showed progressive increase in risk of coronary heart disease events as the quartiles increased (Online Fig. A5).

Association of common carotid IMT with stroke

The CHS study [11] and other cohort studies [8,88,89] had shown that common carotid IMT was associated with stroke. Because these findings were published a more than a decade ago, the findings from another cohort, the Tromsø study [90], have shown that CCA IMT was not a strong predictor of stroke although measures of ICA IMT and plaque area remained significant predictors [90]. Similarly, when the MESA study data were analyzed, in adjusted multivariable Cox proportional hazards models, CCA IMT did not appear to predict stroke [91,92]. Paradoxically, short-term progression of CCA IMT has been shown to be associated with stroke events in the MESA study [44]. The apparent discordance between both sets of findings has yet to be clarified. It is not clear why previously seen associations between ischemic stroke and CCA IMT appear to be changing. This might reflect differences in the imaging protocols and the fact that IMT measurements are being performed lower in the CCA than near to the carotid bulb. It is also possible that medical interventions such as statin use are having the effect of stabilizing plaque growth.

SUMMARY

The MESA study was designed to study plausible risk factors linked to subclinical cardiovascular disease and ascertain their predictive power in a population without clinical cardiovascular disease at baseline.

Carotid artery IMT is measured noninvasively and without radiation exposure. The MESA study showed strong associations with cardiovascular risk factors and with events. The data analyses confirm the observation that CCA IMT and internal carotid IMT are very separate phenotypes having different predictive values for coronary artery and cardiovascular disease events.

These findings are consistent with the belief that a clinical IMT protocol is close to being implemented. Our review has dealt more completely on the technical issues at hand than other reviews [93].

The MESA study has also helped clarify some of the technical aspects of the carotid IMT measurement process looking at ways to improve reproducibility as well as predictive power for future events. An untested hypothesis at this time is whether control of these technical steps should help develop a robust set of normative IMT data that could be applied as an adjunct to cardiovascular risk prediction for individuals of different ethnicities.

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APPENDIX

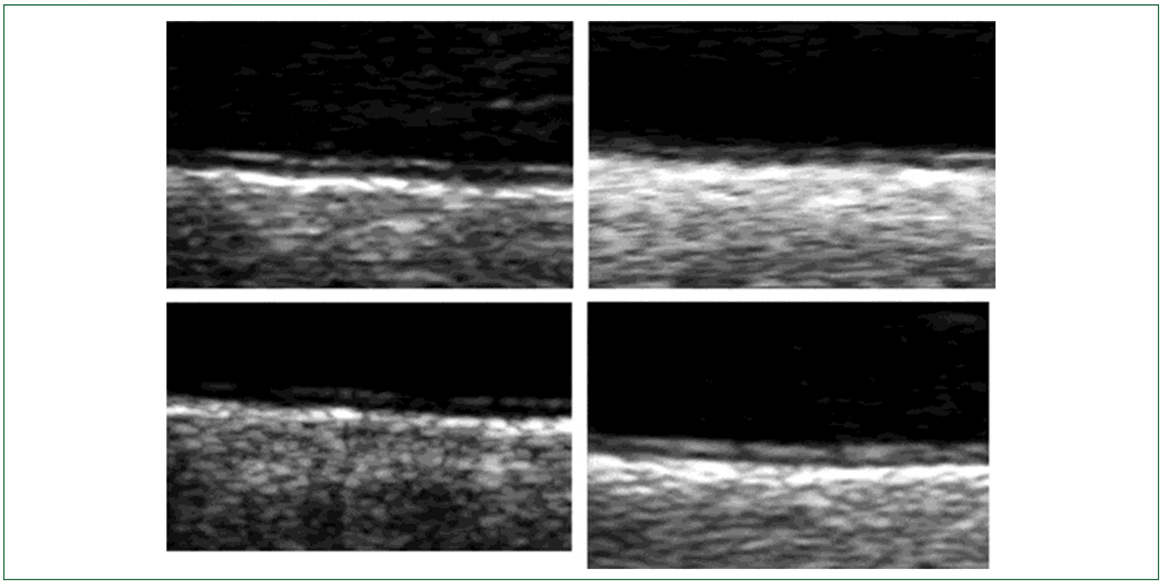

FIGURE A1. This image is a copy of an e-mail attachment sent to 12 evaluators given the task to review the image and select the 1 subimage that best demonstrated the near and far wall common carotid intima-media thickness.

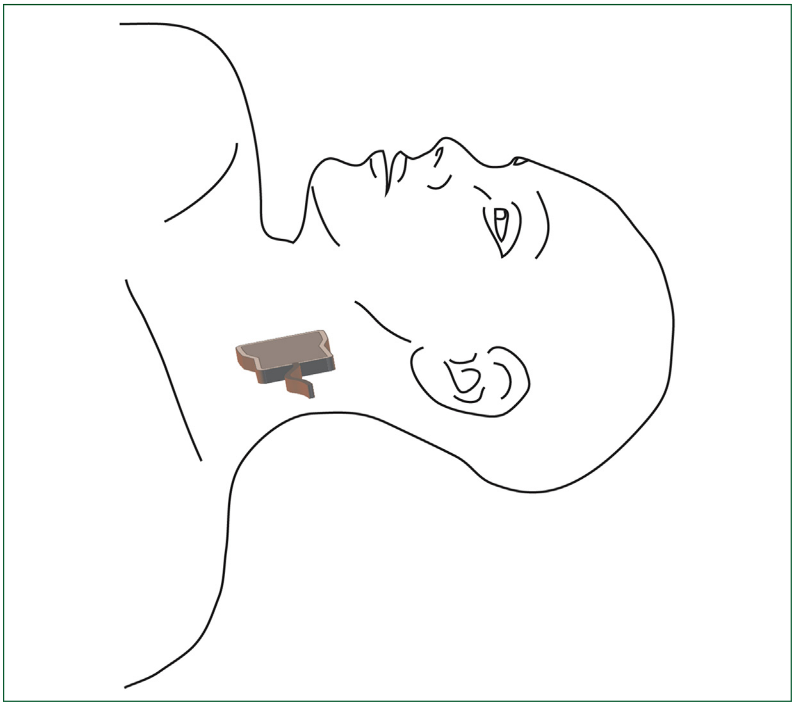

FIGURE A2. The ultrasound probe location and orientation used to image the common carotid artery. The probe is approximately 45° from the vertical and centered so that less than one-third of the carotid bulb is seen to the left of the image.

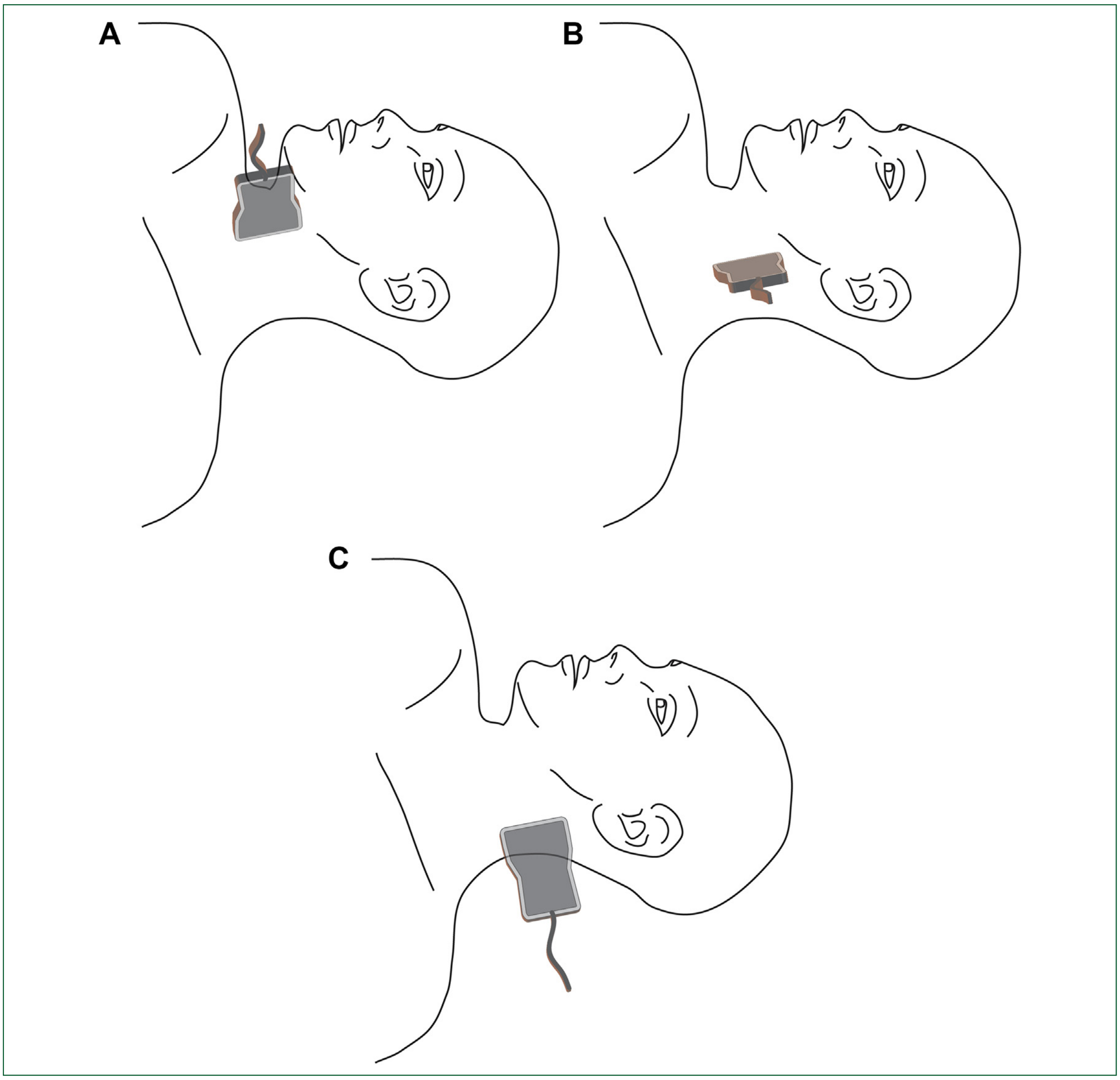

FIGURE A3. Diagrams showing the ultrasound probe locations and orientations used to image the bulb and proximal internal carotid artery. (A) The probe orientation for the anterior projection. (B) The orientation for the lateral projection. It is similar to the common carotid protocol (Online Fig. A2) but centered higher at the level of the bifurcation. (C) The orientation for the posterior projection.

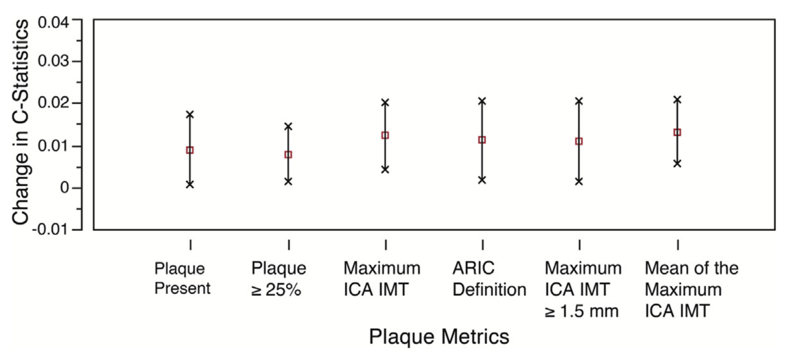

FIGURE A4. This diagram shows the change in C-statistic (with 95% confidence intervals) associated to individual plaque metrics when added to Framingham risk factors when predicting coronary artery heart disease events.

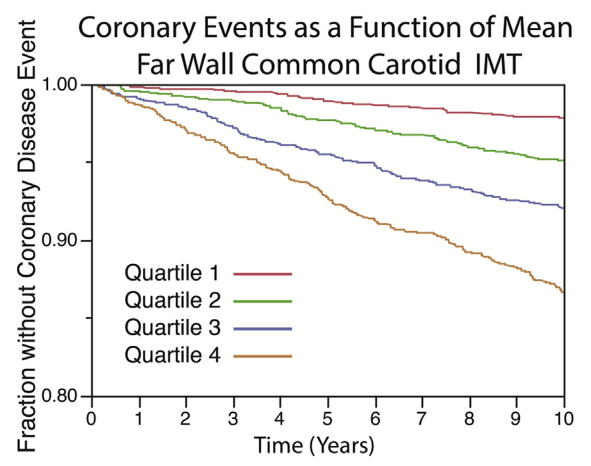

FIGURE A5. The Kaplan-Meier curves for the quartiles of mean far wall common carotid artery intima-media thickness show progressive increased risk of first-time coronary heart disease events. The highest quartile shows a distinct increase in the event rate.