ORIGINAL RESEARCH

Edge-Detected Common Carotid Artery Intima–Media Thickness and Incident Coronary Heart Disease in the Multi-Ethnic Study of Atherosclerosis

Joseph F. Polak, MD, MPH; Daniel H. O'Leary, MD

***Background*—**Common carotid artery intima–media thickness (IMT) can be measured either by hand or with an automated edge detector. We performed a direct comparison of these 2 approaches and studied their respective associations with coronary heart disease outcomes.

***Methods and Results*—**We studied 5468 participants of the Multi-Ethnic Study of Atherosclerosis, composed of white, Chinese, Hispanic, and black participants with an average age of 61.9 years (47.8% men) and who were free of coronary heart disease at baseline. Manual-traced and edge-detected IMT measurements were made in the same location on ultrasound images of the right common carotid artery far wall in an area free of plaque. Manual-traced and edge-detected common carotid artery IMT measurements were added separately to multivariable Cox proportional hazards models with time to incident coronary heart disease as the outcome and adjusted for traditional coronary heart disease Framingham risk factors, lipid-lowering therapy, blood pressure–lowering therapy, and race or ethnicity. Additional models were generated after adding clinic site and reader. There were 349 events during a median follow-up of 10.2 years. In adjusted models, the hazard ratio was not significant (1.31; 95% CI 0.84 to 2.06) for each millimeter increase in manual-traced IMT but was significant for edge-detected IMT (hazard ratio 1.63; 95% CI 1.12 to 2.37). Edge-detected IMT remained statistically associated with outcomes after additional adjustment for clinic site and reader performing the IMT measurement (hazard ratio 1.59; 95% CI 1.07 to 2.35).

***Conclusions*—**Edge-detected common carotid artery far wall IMT has similar if not stronger associations with coronary heart disease outcomes when compared with manual-traced IMT.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov/. Unique identifier: NCT00063440. **(*J Am Heart Assoc*. 2015;4: e001492 doi: 10.1161/JAHA.114.001492)**

Key Words: atherosclerosis • carotid arteries • epidemiology • risk factors • ultrasonics

Common carotid artery (CCA) intima–media thickness (IMT) is a marker of coronary heart disease (CHD). The distance between the lumen–intima and media–adventitia interfaces of the artery wall can be measured by readers (1) who place calipers and record measurements,[1] (2) who place calipers at selected intervals along the key interfaces and record the measurements,[2] (3) who trace continuous lines along the wall interfaces[3] and then have an algorithm calculate the distances,[4] or (4) who use edge detectors to automatically detect the key wall interfaces.[4–10]

Manual-traced and edge-detected IMT measurements have been shown to have similar cross-sectional associations with cardiovascular risk factors[4] and similar statistical power for determining the outcome of intervention trials.[11]

In most cases, manual-traced and edge-detected IMT measurements have shown positive associations with cardiovascular outcomes; however, individual studies could have used either edge-detected or manual-traced IMT measurements.[12] A side-by-side comparison of the associations between cardiovascular outcomes and these 2 approaches has yet to be reported.

We compared the associations of CHD events with edge-detected and manual-traced IMT measurements in a large multiethnic cohort that was free of cardiovascular disease at baseline and followed longitudinally in the Multi-Ethnic Study of Atherosclerosis (MESA).

From the Department of Radiology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA (J.F.P.); Saint Elizabeth's Medical Center, Boston, MA (D.H.O.).

Correspondence to: Joseph F. Polak, MD, MPH, Department of Radiology, # 299, Tufts Medical Center, 800 Washington Street, Boston, MA 02111. E-mail: jpolak@tuftsmedicalcenter.org

Received October 3, 2014; accepted May 13, 2015.

Materials and Methods

Population

MESA recruited and examined a multiethnic population of 6814 men and women aged 45 to 84 years with no history of clinical cardiovascular disease between July 2000 and August 2002 at 6 separate clinic sites in the United States.[13] The MESA cohort is a multiethnic cohort including white, black, Hispanic, and Chinese participants. Participants were excluded if they had a physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, angina, or atrial fibrillation; history of any cardiovascular procedure; weight >300 lb; pregnancy; or any medical condition that would prevent long-term participation. MESA protocols and all studies described in this paper were approved by the institutional review boards of all collaborating institutions, and all participants gave informed consent. Of the 6814 participants studied, 5641 underwent edge-detected IMT measurements in addition to manual measurements as part of an ancillary study (ClinicalTrials.gov identifier NCT00063440).[4]

Risk Factors and Anthropomorphic Variables

The risk factors used in this paper were derived from the updated Framingham risk score as presented by D'Agostino et al,[14] comprising age, sex, smoking and diabetes status, systolic blood pressure, and low- and high-density lipoprotein cholesterol, to which race or ethnicity and use of lipid-lowering therapy were added.

Age, sex, race or ethnicity, and medical history were self-reported and included use of blood pressure–lowering medications and lipid-lowering medications. Current smoking was defined as self-report of a cigarette in the past 30 days. Resting blood pressure was measured at rest in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon), using the average of the last 2 of 3 serial measurements. Lipid levels were measured after a 12-hour fast. The presence of treated diabetes mellitus was based on self-reported physician diagnosis, use of insulin, and/or use of an oral hypoglycemic agent. A fasting glucose value ≥126 mg/dL was coded as untreated diabetes. Total cholesterol was measured using a cholesterol oxidase method (Roche Diagnostics), as was high-density lipoprotein after precipitation of non–high-density lipoprotein cholesterol with magnesium and dextran.

Carotid Artery Measures

Carotid ultrasound examinations were made at the baseline visit. Participants were examined supine with the head rotated 45° toward the left side. The arms were held slightly abducted from the body. Imaging was done in the plane parallel to the artery with the jugular vein lying immediately above the CCA (or at 45° from the vertical if the internal jugular vein was not present). Images of the right CCA were centered below (caudad to) the right CCA bulb.[6] A matrix array probe (M12L; General Electric) was used, with the frequency set at 13 MHz and 2 focal zones selected, and the frame rate was set at 32 frames per second. A super-VHS videotape recording was then made for 20 seconds. Images were digitized at 30 frames per second, and automated diameter measurements were made from this video segment using customized software. End-diastolic images (smallest diameter of the artery) were captured based on measurements of diameter during the cardiac cycle.[15]

The selected image had a region of interest defined along the far wall of ≈10 mm starting at least 5 to 10 mm below (caudad to) the right CCA bulb. The region was adjusted to exclude any carotid artery plaque. Trained readers traced lines along the 2 key interfaces, the lumen–intima and media–adventitia. An automated edge-detection algorithm was then used to determine these same 2 key interfaces in the same region of interest. The tracings for manual-traced and edge-detected interfaces were applied to the same algorithm to calculate the respective mean IMT values[4] and were entered directly into a database. Four readers performed the measurements.

Reproducibility was assessed by blinded replicate rereads performed by 2 readers on a set of 114 studies read by another reader.[4] Correlations between readers were 0.78 for manual-traced IMT and 0.71 for edge-detected IMT. The correlation coefficient between manual tracings and edge-detected IMT values was 0.76. Rereads were done by having the readers redigitize the videotapes, choose an image from the 20-second segment, define a region of interest on the far wall, and perform the measurements.

Image acquisition of both common and internal carotid arteries was also performed at a separate imaging session. The participants were supine with the head rotated 45° toward the side opposite that being imaged. After acquisition of 1 CCA image, 3 images centered on the internal carotid artery bulb were taken on each side and from 3 projections: 1 anterior, 1 lateral (at 45°), and 1 posterior. A matrix array probe (M12L; General Electric) was used with the frequency set at 9 MHz and 2 focal zones selected and at a frame rate of 32 frames per second. Internal carotid artery IMT measurements were made on near and far walls of the CCA (1 projection) and the internal carotid artery (3 projections) using hand-drawn continuous tracings of the intima–lumen and media–adventitia interfaces that were then processed using a previously described algorithm.[4] The maximum internal carotid artery IMT from either the right or left side and near or far wall was used for a measurement of plaque. Maximal internal carotid artery IMT >1.5 mm was considered to represent plaque.[16,17]

We investigated the presence of a possible bias between readers as follows. We calculated the mean difference between the IMT measurements made by each of the 4 readers and those obtained by edge detection. We calibrated the original manual-traced measurements by adding this difference to the individual measurements made by each reader.

Outcome

All cardiovascular events were adjudicated and classified by 2 members of the MESA mortality and morbidity review committee. Events were identified during follow-up examinations and by telephone interviews conducted every 9 to 12 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Copies of all death certificates and all medical records for hospitalizations and outpatient cardiovascular diagnoses were obtained.

The review process included all generated International Classification of Diseases (ICD-9) definitions, but the final adjudication of MESA end points was based on specific criteria applied to data obtained from medical records by 2 committee members or by the whole study events committee in case of disagreement.

CHD events included myocardial infarction, death due to CHD, resuscitated cardiac arrest, definite or probable angina followed by coronary revascularization, and definite angina not followed by coronary revascularization. Cases of coronary artery revascularization that did not have a concurrent diagnosis of angina were not included.

The diagnosis of myocardial infarction was based on a combination of symptoms, electrocardiographic findings, and circulating cardiac biomarkers. Death was considered to be related to CHD if it occurred within 28 days after a myocardial infarct, if the participant experienced chest pain within the 72 hours preceding death, or if the participant had a history of CHD and died without documentation of any other cause of death. Resuscitated cardiac arrest included participants who successfully recovered from full cardiac arrest through cardiopulmonary resuscitation. Adjudicators graded the presence of angina based on the following criteria: Definite or probable angina required clear and definite documentation of symptoms without the development of myocardial infarction. Definite angina also required objective evidence of reversible myocardial ischemia or obstructive coronary artery disease.

Statistical Analyses

The mean (and standard deviation) values of continuous variables are presented. The distribution of dichotomous variables is also shown as a percentage in each group.

Separate Kaplan–Meier curves were generated for manual-traced and edge-detected IMTs using the respective IMT quartile values.

Multivariable Cox proportional hazards models were constructed with time to CHD as the outcome and using robust error handling. Manual-traced and edge-detected IMT measurements were used separately as independent variables in adjusted Cox proportional hazards models (age, sex, race or ethnicity, systolic pressure, total cholesterol, high-density lipoprotein cholesterol, smoking history, diabetes status, and lipid-lowering, and blood pressure–lowering therapies). The reader performing the measurement and the clinic site were added as covariates to the fully adjusted models in a sensitivity analysis.

We performed a sensitivity analysis to address the possibility that clustering effects might have affected our results when clinic site and reader were entered into our models. Consequently, we treated both variables as separate sources of variance, entering them as random effects in a hierarchical multivariable logistic regression analysis that included the IMT variables, race or ethnicity, and risk factors. The results of the multivariable logistic regression model without reader and clinic entered into the model were compared with those of the hierarchical multivariable logistic regression model using a conservative likelihood ratio test. We also evaluated associations with events when reader and clinic were entered as dummy variables in the multivariable logistic regression models.

We performed a sensitivity analysis of all participants with internal carotid artery IMT plaque measurements with a definition of plaque as an IMT value >1.5 mm.[16,17] We used a multivariable Cox proportional hazards model with the following predictor variables: Framingham risk factors plus race or ethnicity, internal carotid artery plaque, and either manual-traced or edge-detected CCA IMT.

We used minimally adjusted Cox proportional hazards models to test whether the calibrated IMT values we generated for each reader manual-traced IMT value affected the predictive value of the measurements.

Statistical analyses were performed using Stata 11.2 (StataCorp). The level of statistical significance was set at $P\leq 0.05$ (2-sided).

Results

There were 5468 participants with manual-traced IMT measurements (mean 0.68 ± 0.19 mm) and edge-detected IMT values (mean 0.87 ± 0.22 mm). The mean age was 61.9 years (Table 1). The proportion of men was 47.8%. The largest ethnicity represented was white at 39.7% of participants, and the smallest was Chinese (12.2%). There were 349 first CHD events at a median follow-up of 10.2 years.

Table 1. Demographics and Key Variables of the Population Studied (n=5468)

	Value
Age, y, mean (SD)	61.9 (10.2)
Sex, men, % (n)	47.8 (2615)
Race or ethnicity, % (n)	
White	39.7 (2168)
Chinese	12.2 (667)
Black	26.4 (1445)
Hispanic	21.7 (1188)
HDL cholesterol, mg/dL, mean (SD)	51.2 (14.7)
Total cholesterol, mg/dL, mean (SD)	193.5 (34.1)
Systolic blood pressure, mm Hg, mean (SD)	125.9 (21.2)
Smoker, yes, % (n)	12.5 (683)
Diabetes, yes, % (n)	11.6 (636)
Lipid-lowering therapy, yes, % (n)	16.1 (878)
Blood pressure–lowering therapy, yes, % (n)	36.1 (1974)
Hand-measured IMT, mm, mean (SD)	0.68 (0.19)
Edge-detected IMT, mm, mean (SD)	0.87 (0.23)

HDL indicates high-density lipoprotein; IMT, intima–media thickness.

Results of the adjusted Cox proportional hazards model for manual-traced and edge-detected IMTs are shown in Tables 2 and 3. The hazard ratios (HRs) were significant for edge-detected IMT (Table 3), with a value of 1.63 per millimeter increase (95% CI 1.12 to 2.37), but not for manual-traced IMT (Table 2), with a value of 1.31 per millimeter increase (95% CI 0.84 to 2.06). The HRs for the various predictor variables were all within 10% of each other when the baseline model was modified by separately entering manual-traced IMT (Table 2) and edge-detected IMT (Table 3). All variables were significant predictors of events. There was a slight difference between Hispanic and white participants for the model without IMT and for the model with manual-traced IMT. Although this difference was no longer significant when edge-detected IMT was entered into the model, the effect size did not change.

Inclusion of clinic site and reader (data not shown) slightly weakened the association of edge-detected IMT with CHD, with a HR of 1.59 per millimeter increase (95% CI 1.07 to 2.35). The HR for manual-traced IMT increased slightly (HR 1.45; 95% CI 0.90 to 2.35) but did not become significant. Associations with events were weaker for 1 of the clinic sites (P=0.003) in the models with and without IMT. There were no significant interreader differences.

The respective Kaplan–Meier curves for manual and edge-detected tracings plotted out as quartiles (unadjusted) are shown as Figures 1 and 2, respectively. Although both sets of curves show the increased risk of events as the IMT quartile increases, there is slightly better scaling between quartiles and events for the edge-detected IMT values (Figure 2) compared with the manual-traced measurements (Figure 1).

The multivariable logistic regression models with reader and clinic included (data not shown) as predictor variables for events gave a significant (P=0.025) odds ratio for

Table 2. Results of Multivariable Cox Proportional Hazards Models for Incident Coronary Heart Disease Without and With Manual-Traced IMT Measurements

Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, y	1.05	1.04 to 1.06	<0.001	1.05	1.04 to 1.06	<0.001
Sex (male)	2.17	1.70 to 2.77	<0.001	2.15	1.69 to 2.75	<0.001
Race or ethnicity (white)						
Chinese	0.61	0.42 to 0.90	0.013	0.62	0.42 to 0.90	0.013
Black	0.72	0.54 to 0.95	0.019	0.71	0.54 to 0.94	0.017
Hispanic	0.75	0.56 to 0.99	0.041	0.75	0.57 to 1.00	0.049
HDL cholesterol, mg/dL	0.98	0.97 to 0.99	<0.001	0.98	0.97 to 0.99	0.001
Total cholesterol, mg/dL	1.01	1.00 to 1.01	<0.001	1.01	1.00 to 1.02	<0.001
Systolic pressure, mm Hg	1.01	1.01 to 1.02	<0.001	1.01	1.00 to 1.01	<0.001
Smoker (yes)	1.65	1.22 to 2.24	0.001	1.62	1.19 to 2.21	0.002
Diabetes (yes)	1.73	1.32 to 2.27	<0.001	1.73	1.32 to 2.26	<0.001
Lipid Rx (yes)	1.49	1.15 to 1.93	0.002	1.49	1.15 to 1.93	0.002
Blood pressure Rx (yes)	1.40	1.10 to 1.79	0.006	1.40	1.10 to 1.79	0.006
Manual IMT, mm				1.31	0.84 to 2.06	0.236

HDL indicates high-density lipoprotein; HR, hazard ratio; IMT, intima–media thickness; Rx, prescription.

Table 3. Results of Multivariable Cox Proportional Hazards Models for Incident Coronary Heart Disease Without and With Edge-Detected IMT Measurements

Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, y	1.05	1.04 to 1.06	<0.001	1.05	1.03 to 1.06	<0.001
Sex (male)	2.17	1.70 to 2.77	<0.001	2.15	1.68 to 2.74	<0.001
Race or ethnicity (white)						
Chinese	0.61	0.42 to 0.90	0.013	0.61	0.42 to 0.90	0.012
Black	0.72	0.54 to 0.95	0.019	0.70	0.53 to 0.93	0.012
Hispanic	0.75	0.56 to 0.99	0.041	0.77	0.58 to 1.02	0.065
HDL cholesterol, mg/dL	0.98	0.97 to 0.99	<0.001	0.98	0.97 to 0.99	0.001
Total cholesterol, mg/dL	1.01	1.00 to 1.01	<0.001	1.01	1.00 to 1.01	<0.001
Systolic pressure, mm Hg	1.01	1.01 to 1.02	<0.001	1.01	1.00 to 1.01	<0.001
Smoker (yes)	1.65	1.22 to 2.24	0.001	1.62	1.19 to 2.20	0.002
Diabetes (yes)	1.73	1.32 to 2.27	<0.001	1.70	1.30 to 2.23	<0.001
Lipid Rx (yes)	1.49	1.15 to 1.93	0.002	1.49	1.15 to 1.93	0.002
Blood pressure Rx (yes)	1.40	1.10 to 1.79	0.006	1.41	1.11 to 1.80	0.005
Edge-detected IMT, mm				1.63	1.12 to 2.37	0.011

HDL indicates high-density lipoprotein; HR, hazard ratio; IMT, intima–media thickness; Rx, prescription.

edge-detected IMT of 1.70 (95% CI 1.07 to 2.72) and a nonsignificant (*P*=0.10) odds ratio of 1.64 (95% CI 0.91 to 2.95) for manual-traced IMT. Treating clinic site and reader as random effects did not significantly alter the predictive value of the logistic regression model compared with models that did not factor in both of these variables (*P*=0.46 for the model with edge-detected IMT; *P*=0.37 for the model with manual-traced IMT).

The results of the multivariable Cox proportional hazards model with internal carotid artery plaque added are shown in Tables 4 and 5. There were 338 CHD events in 5342 participants with internal carotid artery IMT measurements. The addition of internal carotid artery plaque to the model with manual-traced IMT did not improve the predictive value of manual-traced IMT (HR 1.34; 95% CI 0.83 to 2.18), whereas plaque was a significant (*P*=0.003) predictor of events (HR

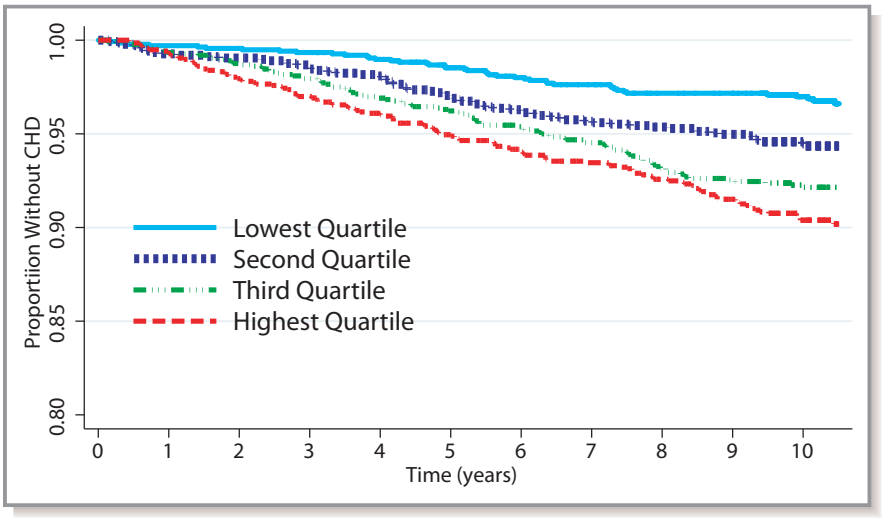

Figure 1. Kaplan–Meier (failure) curves for incident coronary heart disease using the quartiles of manual-traced common carotid artery intima–media thickness. Quartile ranges were as follows: 0.316 to 0.547, 0.547 to 0.643, 0.643 to 0.768, and >0.768 mm. CHD indicates coronary heart disease.

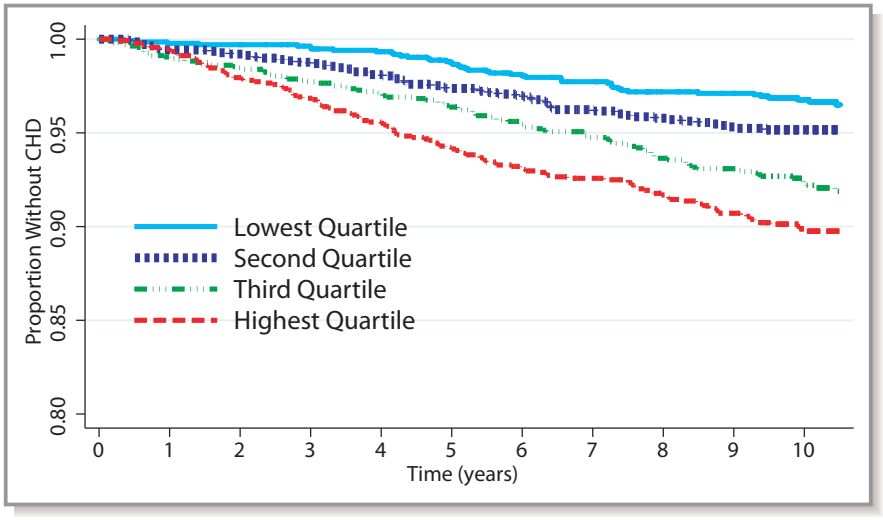

Figure 2. Kaplan–Meier (failure) curves for incident coronary heart disease using the quartiles of edge-detected common carotid artery intima–media thickness. Quartile ranges were as follows: 0.219 to 0.722, 0.722 to 0.837, 0.837 to 0.987, and >0.987 mm. CHD indicates coronary heart disease.

1.43; 95% CI 1.13 to 1.82). Edge-detected CCA IMT remained a significant predictor of events, with an HR of 1.56 (95% CI 1.06 to 2.29), and plaque was also a significant predictor of events, with an HR of 1.41 (95% CI 1.11 to 1.80).

As shown in Figure 3, we observed significant interreader differences when manual-traced IMT values were compared with edge-detected measurements. Interreader differences were readily apparent, with the measurements for reader D being the closest to those obtained with edge detection (a difference of 0.09±0.16 mm) and the farthest (0.25±0.11 mm) being those for reader C. Results of using calibrated IMT values in Cox proportional hazards models predicting CHD events are shown in Table 6. The manual-traced IMT values gave a lower HR than the "calibrated" values. In addition, the magnitude of the reader effect was decreased after calibration because (1) a dummy variable representing the readers was no longer a statistically significant predictor (P=0.08) and (2) the HR before and after adjustment for reader was essentially constant for the calibrated IMT values (2.35 before and 2.33 after adjustment).

Table 4. Associations of Manual-Traced Common Carotid Artery IMT With Coronary Artery Disease Events (n=338) in the Subset of Participants (5342 of 5468) Having Measurements of Internal Carotid Artery Plaque

	Hazard Ratio	95% CI	*P* Value
Manual-traced IMT, mm*	2.14	1.39 to 3.31	0.001
Manual-traced IMT, mm†	1.83	1.16 to 2.87	0.009
Internal carotid artery plaque, >1.5 mm†	1.75	1.38 to 2.22	<0.001
Manual-traced IMT, mm‡	1.34	0.83 to 2.18	0.23
Internal carotid artery plaque, >1.5 mm‡	1.43	1.13 to 1.82	0.003

IMT indicates intima–media thickness.
*Adjusted for age, sex, and reader.
†IMT and plaque in the model; adjusted for age, sex, and reader.
‡IMT and plaque in the model; adjusted for age, sex, reader, high-density lipoprotein cholesterol, total cholesterol, systolic blood pressure, smoking status, diabetes, use of lipid-lowering medications, and use of blood pressure–lowering medications.

Table 5. Associations of Edge-Detected Common Carotid Artery IMT With Coronary Artery Disease Events (n=338) in the Subset of Participants (5342 of 5468) Having Measurements of Internal Carotid Artery Plaque

	Hazard Ratio	95% CI	*P* Value
Edge-detected IMT, mm*	2.44	1.67 to 3.56	<0.001
Edge-detected IMT, mm†	2.10	1.41 to 3.12	<0.001
Internal carotid artery plaque, >1.5 mm†	1.72	1.35 to 2.18	<0.001
Edge-detected IMT, mm‡	1.56	1.06 to 2.29	0.025
Internal carotid artery plaque, >1.5 mm‡	1.41	1.11 to 1.80	0.005

IMT indicates intima–media thickness.
*Adjusted for age, sex, and reader.
†IMT and plaque in the model; adjusted for age, sex, and reader.
‡IMT and plaque in the model; adjusted for age, sex, reader, high-density lipoprotein cholesterol, total cholesterol, systolic blood pressure, smoking status, diabetes, use of lipid-lowering medications, and use of blood pressure–lowering medications.

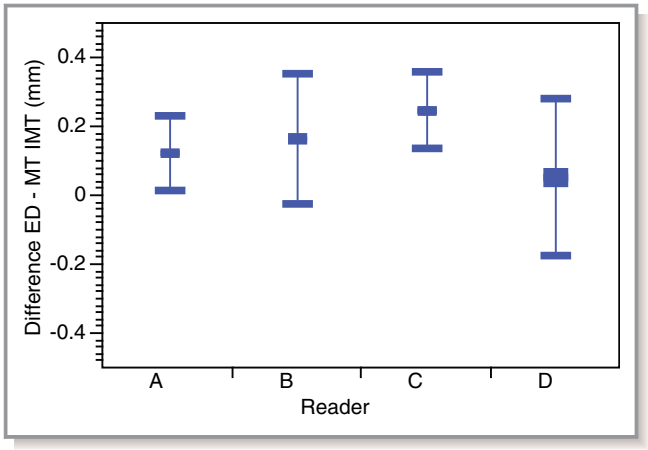

Figure 3. Plot graph showing the difference between the mean IMT measured by manual tracing and edge detection (*y*-axis) for each reader (*y*-axis). The numbers on the *y*-axis are the mean of the paired differences between IMT measurements made for each participant as calculated by subtracting manual-traced IMT values from the edge-detected values. Ranges between brackets are standard deviation values. ED indicates edge detected; IMT, intima–media thickness; MT, manual traced.

Discussion

We found that edge-detected IMT measurements of the CCA far wall appear to have similar if not stronger associations with CHD events than manual-traced IMT measurements. These results apply to the right CCA in an area selected as being free of plaque.

Our prior observations have shown that manual-traced and edge-detected IMT measurements were similarly associated with cardiovascular risk factors.[4] We had hypothesized that edge-detected IMT measurements would have weaker associations with events than manual-traced IMT values based on a review of the published results of epidemiological studies. The majority of studies linking IMT with cardiovascular outcomes had IMT values derived from manual tracings. A recent large meta-analysis combining various IMT studies, for example, included data on the associations between outcomes and edge-detected IMT or manual-traced IMT.[12] Of the 14 studies used in the analyses, 1 of 5 studies using edge-detected IMT and 4 of 9 studies using manual-traced IMT showed positive associations between IMT and cardiovascular events.[12]

Two limitations of the general applicability of our study are the use of 1 type of ultrasound device and the use of 1 type of edge detector. The images acquired with our ultrasound device might differ from the images acquired with other devices. This might affect visual perception of the interfaces by the readers or performance of the edge detector. In addition to affecting variability, this approach might introduce a fixed bias compared with the results of other studies.[18] Although it is likely that the interreader bias term would tend to be constant,[19] it could affect the strength of the associations between the IMT measurements and outcomes.[18] The use of only 1 type of edge detector also restricts the general applicability of our results. We used an algorithm based on dynamic programming that resembles that developed by Wendelhag et al.[10] This algorithm processes data based on pixel intensity and gradients and is different from algorithms based on polynomial fitting of intensity curves perpendicular to interfaces or algorithms using template matching.[8,9,20] It is plausible that the results presented in this paper are specific to the algorithm used and might not apply to other edge-detection algorithms.

An underlying limitation of our study is the location of the CCA selected for IMT measurements. These measurements were made with the intent of assessing IMT progression; therefore, the site of IMT measurements was paired with follow-up ultrasound images. In addition, the measurements were made in an area that was free of plaque and below the beginning of the carotid bulb. Determining whether or not a plaque was present was dependent on the sonographer and on the reader doing the IMT measurement. This approach could have introduced a selection bias toward performing measurements that would optimize progression estimates but that could have blunted associations between baseline IMT and cardiovascular events.

A basic strength of our study is the observation that edge detection works well for IMT measurements in a multiethnic

Table 6. Prediction of Coronary Heart Disease Events in Models Adjusted for Age, Sex, and Race or Ethnicity Using Manual-Traced Common Carotid Artery IMT Values Before and After Calibration Against Edge-Detected IMT Values

Variable	Hazard Ratio	95% CI	*P* Value
Before calibration*			
Manual-traced IMT, mm†	2.04	1.31 to 3.16	0.001
Reader‡	1.06	1.01 to 1.12	0.03
Manual-traced IMT, mm‡	2.12	1.38 to 3.26	0.001
After calibration*			
Calibrated manual-traced IMT, mm†	2.35	1.51 to 3.67	<0.001
Reader‡	1.05	0.99 to 1.11	0.08
Calibrated manual-traced IMT, mm‡	2.33	1.50 to 3.64	<0.001

Data on all 5468 participants and the 349 events were used. IMT indicates intima–media thickness.

*Adding to manual-traced IMT measurements made by each reader the mean difference between edge-detected IMT values and the manual-traced IMT measurements made by that reader.

†Not adjusted for reader.

‡Adjusted for reader (n=4).

cohort with an age range between 45 and 84 years and composed of 4 ethnic groups. We believe our results suggest that the use of edge detection is a way of compensating for interreader bias terms, which seem to represent a constant difference between the measurements made by different readers and likely dilute the associations between IMT and events.[18]

We considered the possibility that clustering effects might affect our results because of the distribution between readers and clinic sites and the possibility of unaccounted-for sources of variance. We tested this possibility with hierarchical modeling and found that this was not the case. This result suggests that the variability in the process of IMT measurement of the CCA far wall due to clinic and readers, although present, might be of lower magnitude than expected.[18]

It is still possible that interreader differences might have affected our results. We noted that differences between manual-traced and edge-detected IMT values (Figure 3) varied by reader. These interreader differences are likely due to the visual perception of edges between the key artery wall interfaces. We have shown previously that this effect leads to a bias that is mostly due to the perception of the location at which the media–adventitia interface is located.[19] We have now investigated whether this bias term is consistent enough to be used to calibrate the manual-traced IMT values made by each reader. The results shown in Table 6 indicate that this form of calibration is possible because the calibrated IMT values gave an HR for predicting events similar to that of the model adjusted for readers (2.35 before and 2.33 after adjustment). Without calibration, the HR was weaker and a reader effect was statistically significant. Further research into this topic is needed.

The sensitivity analyses we performed by adding plaque to our models suggest that CCA IMT captures a different facet of atherosclerosis than measurements of carotid plaque. Differences between CCA and internal carotid artery IMT measurements have been shown previously for cross-sectional associations with risk factors and for predicting events.[16,21]

We concluded that the associations of CHD events with edge-detected IMT were at least similar to if not stronger than manual-traced IMT measurements. These findings need confirmation by other studies, given the specific imaging protocol that we used and our focus on measuring the CCA far wall IMT in an area free of plaque.

Acknowledgments

The authors would like to thank the investigators, the staff, and the participants of the Multi-Ethnic Study of Atherosclerosis (MESA) study for their valuable contributions. A full list of participating MESA investigators and institutions can be found online (http://www.mesa-nhlbi.org).

Sources of Funding

This research was supported by National Institutes of Health contracts N01- HC-95159 through N01-HC-95165 and N01-HC-95167 as well as R01 HL069003 and R01 HL081352.

Disclosures

O'Leary owns stock in Medpace, Inc, and is a vice president.

References

1. Bots ML, Breslau PJ, Briet E, de Bruyn AM, van Vliet HHDM, van der Ouweland FA, de Jong PTVM, Hofman A, Grobbee DE. Cardiovascular determinants of carotid artery disease. The Rotterdam Elderly Study. *Stroke*. 1992;19:717–720.
2. Anonymous. Atherosclerosis Risk in Communities study protocol manual 6 version 1 ultrasound assessment: part B: ultrasound reading. In: The National Heart L, and Blood Institute of the National Institutes of Health, ed. Available at: www.cscc.unc.edu/aric/visit/Ultrasound_Assessment-_Reading_Procedures.1_6b.pdf. Accessed June 12, 2015.
3. O'Leary DH, Polak JF, Wolfson SKJ, Bond MG, Bommer W, Sheh S, Psaty BM, Sharrett AR, Manolio TA. The use of sonography to evaluate carotid atherosclerosis in the elderly: the Cardiovascular Health Study. *Stroke*. 1991;22:1155–1163.
4. Polak JF, Pencina MJ, Herrington D, O'Leary DH. Associations of edge-detected and manual-traced common carotid intima-media thickness measurements with Framingham risk factors: the Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2011;42:1912–1916.
5. Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation*. 2001;103:1721–1726.
6. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu C, Alaupovic P, Kwong-Fu H, Azen SP. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med*. 1996;124:548–556.
7. Schmidt C, Wendelhag I. How can the variability in ultrasound measurement of intima-media thickness be reduced? Studies of interobserver variability in carotid and femoral arteries. *Clin Physiol*. 1999;19:45–55.
8. Selzer RH, Hodis HN, Kwong-Fu H, Mack WJ, Lee PL, Liu CR, Liu CH. Evaluation of computerized edge tracking for quantifying intima-media thickness of the common carotid artery from B-mode ultrasound images. *Atherosclerosis*. 1994;111:1–11.
9. Touboul PJ, Prati P, Scarabin PY, Adrai V, Thibout E, Ducimetiere P. Use of monitoring software to improve the measurement of carotid wall thickness by B-mode imaging. *J Hypertens Suppl*. 1992;10:S37–S41.
10. Wendelhag I, Liang Q, Gustavsson T, Wikstrand J. A new automated computerized analyzing system simplifies readings and reduces the variability in ultrasound measurement of intima-media thickness. *Stroke*. 1997;28:2195–2200.
11. Peters SAE, den Ruijter HM, Palmer MK, Grobbee DE, Crouse JR III, O'Leary DH, Evans GW, Raichlen JS, Lind L, Bots ML; Group MS. Manual or semi-automated edge detection of the maximal far wall common carotid intima-media thickness: a direct comparison. *J Intern Med*. 2012;271:247–256.
12. Den Ruijter HM, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engstrom G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CDA, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012;308:796–803.
13. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871–881.

14. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB, D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.

15. Polak JF, Johnson C, Harrington A, Wong Q, O'Leary DH, Burke G, Yanez ND. Changes in carotid intima-media thickness during the cardiac cycle: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2012;1:e001420 doi: 10.1161/JAHA.112.001420.

16. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med*. 2011;365:213–221.

17. Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AEH, O'Leary DH. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2013;2:e000087 doi: 10.1161/JAHA.113.000087.

18. Delaney JAC, Scherzer R, Polak J, Biggs ML, Kronmal R, Chen H, Sidney S, Grunfeld C. Effect of inter-reader variability on outcomes in studies using carotid intima media thickness quantified by carotid ultrasonography. *Eur J Epidemiol*. 2010;25:385–392.

19. Polak JF, Funk LC, O'Leary DH. Inter-reader differences in common carotid artery intima-media thickness: implications for cardiovascular risk assessment and vascular age determination. *J Ultrasound Med*. 2011;30:915–920.

20. Graf S, Gariepy J, Massonneau M, Armentano RL, Mansour S, Barra JG, Simon A, Levenson J. Experimental and clinical validation of arterial diameter waveform and intimal media thickness obtained from B-mode ultrasound image processing. *Ultrasound Med Biol*. 1999;25:1353–1363.

21. O'Leary DH, Polak JF, Kronmal RA, Savage PJ, Borhani NO, Kittner SJ, Tracy R, Gardin JM, Price TR, Furberg CD; for the Cardiovascular Health Study Collaborative research Group. Thickening of the carotid wall. A marker for atherosclerosis in the elderly? *Stroke*. 1996;27:224–231.