Comparison of Coronary Artery Calcium Presence, Carotid Plaque Presence, and Carotid Intima-Media Thickness for Cardiovascular Disease Prediction in the Multi-Ethnic Study of Atherosclerosis

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Background—Presence of coronary artery calcium (CAC), carotid plaque, and increased carotid intima-media thickness (IMT) may indicate elevated cardiovascular disease (CVD) risk; however, no large studies have compared them directly. This study compares predictive uses of CAC presence, carotid artery plaque presence, and high IMT for incident CVD events.

Methods and Results—Participants were from the Multi-Ethnic Study of Atherosclerosis (MESA). Predictive values of carotid plaque, IMT, and CAC presence were compared using Cox proportional hazards models, c-statistics, and net reclassification indices. The 6779 participants were mean (SD) 62.2 (10.2) years old; 49.9% had CAC, and 46.7% had carotid plaque. The mean left and right IMT were 0.754 (0.210) mm and 0.751 (0.187) mm, respectively. After 9.5 years (mean), 538 CVD events, 388 coronary heart disease (CHD) events, and 196 stroke/transient ischemic attacks were observed. CAC presence was a stronger predictor of incident CVD and CHD than carotid ultrasound measures. Mean IMT ≥75th percentile (for age, sex, and race) alone did not predict events. Compared with traditional risk factors, c-statistics for CVD (c=0.756) and CHD (c=0.752) increased the most by the addition of CAC presence (CVD, 0.776; CHD, 0.784; P<0.001) followed by carotid plaque presence (CVD, c=0.760; CHD, c=0.757; P<0.05). Compared with risk factors (c=0.782), carotid plaque presence (c=0.787; P=0.045) but not CAC (c=0.785; P=0.438) improved prediction of stroke/transient ischemic attacks.

Conclusions—In adults without CVD, CAC presence improves prediction of CVD and CHD more than carotid plaque presence or high IMT. CAC and carotid ultrasound parameters performed similarly for stroke/transient ischemic attack event prediction. (Circ Cardiovasc Imaging. 2015;8:e002262. DOI: 10.1161/CIRCIMAGING.114.002262.)

Key Words: atherosclerosis • cardiovascular disease • carotid arteries • neuroimaging • risk factors

See Clinical Perspective

Multi-Ethnic Study of Atherosclerosis (MESA) investigators previously described superiority of CAC instead of IMT for coronary heart disease (CHD) and CVD risk prediction and superiority of IMT instead of CAC for prediction of stroke, but these analyses were limited by a short duration of follow-up with few CVD events.1,2 The predictive uses of CAC and IMT were compared in the Cardiovascular Health Study; however, participants were older, and the follow-up was short.3 Although the predictive uses of IMT, carotid plaque presence, and CAC presence have been described in several cohorts and meta-analyses,1,5,9 they have not been compared directly in a single cohort with extended follow-up and a large number of cardiovascular disease (CVD) events.

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MESA is a large, ethnically diverse cohort of individuals without clinically evident CVD at study baseline in whom participants had carotid ultrasound scans for IMT measurement and detection of carotid plaque presence, as well as and computed chest tomography (CT) scans for CAC presence. With a mean of 9.5 years of follow-up and >500 CVD events, this analysis directly compares IMT, carotid plaque presence, and CAC presence for predicting CVD events.

Methods

Study Participants and Design

The MESA is a large, prospective cohort study of the prevalence, causes, and progression of subclinical CVD. MESA is a population-based sample of 6814 men and women aged 45 to 84 years who were free of known CVD at baseline, recruited from 6 US communities. Study objectives and design have been previously published. All participants gave informed consent. It was approved by the institutional review boards of the field and reading centers.

This analysis was prespecified and included all MESA participants with examination 1 CAC evaluation and follow-up data (n=6799) who also had examination 1 common carotid artery (CCA) IMT measurements (n=3098) and carotid plaque assessment (n=3310) reread by the University of Wisconsin Ultrasound Reading Center. These 3310 participants were a subset of the original MESA cohort and had examination 1 IMT measurements reread because they subsequently had examination 5 ultrasound studies (mean, 9.5 years later), though examination 5 data were not used in this article. Of the 3310 participants with carotid ultrasounds, 266 were missing left CCA IMT and 212 were missing right CCA IMT. In this analysis, 418 (12.6%) participants with ultrasound evaluations were missing ≥ 1 IMT segment.

Follow-up data are described later in detail and in the Data Supplement (Tables I–VIII in the Data Supplement).

This analysis was performed using the University of Wisconsin CCA IMT readings because (1) the associations between CCA IMT measures and most traditional risk factors (age, systolic blood pressure, body-mass index, sex, African American race, and use of antihypertensive medications) were stronger than in the original IMT set; (2) reproducibility of IMT measurements was better than for the original readings (correlations, 0.96–0.99 versus 0.84–0.86) and (3) the University of Wisconsin readings provided standardized plaque scoring in accordance with clinical consensus recommendations. Because rereads only were available for a subset of MESA participants, multiple imputation was used to account for missing data from the entire MESA cohort (n=6779), which included the original IMT readings. Demographics, medical history, and laboratory data were obtained from July 2000 to August 2002.

Carotid Ultrasonography

At examination 1, B-mode ultrasound was used to image the near and far walls of the right and left distal CCA, carotid bulb, and proximal internal carotid using a Logiq 700 ultrasound system (General Electric Medical Systems, 13 MHz transducer). The carotid bifurcations and internal carotid arteries were interrogated thoroughly from both longitudinal and transverse approaches to identify the thickest regions. Images were stored on super-video home system videotape, digitized at a high resolution and frame rate using a Medical Digital Recording device (PACSGEAR, Pleasanton, CA), and converted into Digital Imaging and Communications in Medicine digital records. Mean and maximal IMT of the far wall of distal CCA (distal 1 cm, proximal to the carotid bifurcation point, where the distal CCA diameter remains uniform) and the proximal 1 cm of the proximal internal carotid were measured in triplicate at the University of Wisconsin using a semiautomated border detection program (Syngo Arterial Health package; Siemens Medical Solutions, Malvern, PA) blinded to subject demographic and medical information. The CCA IMT percentiles based on age, sex, and race/ethnicity were calculated (Table I in the Data Supplement). Carotid plaque presence was defined as a focal abnormal wall thickness (IMT, >1.5 mm) or a focal thickening of >50% of the surrounding IMT.4,12 The presence or absence of plaque acoustic shadowing was recorded. A total plaque score (range, 0–12) was calculated to describe carotid plaque burden. One point per plaque was allocated for the near and far walls of each segment (CCA, bulb, and proximal internal carotid) of each carotid artery that was interrogated. Ultrasound reproducibility is described in detail in the Data Supplement (IMT reproducibility).

CAC Presence and Score

Methods for CT scanning and interpretation have been previously reported.13 CAC was assessed at all 6 MESA sites at examination 1 by using either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles, and New York Field Centers) or a multi-detector CT system (Baltimore, Forsyth County, and St. Paul Field Centers). All scans were over-read by a trained radiologist or cardiologist using an interactive scoring system.1 CAC was categorized as present or absent, and the Agatston score was reported as a continuous variable with excellent reproducibility.14

CVD Events

Participants were followed from the baseline examination through October 2012. They were contacted by telephone every 9 to 12 months to inquire about interim hospital admissions, CVD outpatient diagnoses, and deaths. Events were verified with death certificates and medical records. Two physicians, blinded to study data, independently reviewed and classified CVD events. In cases of disagreement, a mortality and morbidity committee determined the final classification. CVD was defined as CHD (definite or probable myocardial infarction, CHD death, resuscitated cardiac arrest, definite angina, and probable angina—if followed by coronary revascularization), stroke (fetal or nonfatal), or other atherosclerotic CVD death.4 Stroke and transient ischemic attack (TIA) were adjudicated by neurologists. Stroke was defined as a focal neurological deficit lasting 24 hours or until death with a clinically relevant lesion on brain imaging, and no nonvascular cause was identified. TIA was defined as a focal neurological deficit lasting 30 seconds to 24 hours, without brain imaging, suggesting stroke. In the present analysis, the composite of TIA and stroke are reported because the number of strokes was small. A detailed description of the MESA follow-up methods is available at http://www.mesa-nhlbi.org.

Statistical Analysis

CAC was categorized as present or absent, and continuously as ln (CAC+25) because >50% of participants had zero CAC. The constant of 25 allows for a more symmetrical normal distribution and has been used before in MESA analyses.15 Carotid plaque was categorized as present or absent and as a carotid plaque score (0–12). Mean and maximum CCA and proximal internal carotid IMT were described as continuous variables. CCA IMT also was categorized as below or above the highest cohort quartile for age, sex, and race. Internal carotid artery IMT data are presented, for the sake of completeness, in the Data Supplement. Carotid plaque presence was our primary carotid plaque variable; carotid plaque score and shadowing were described for the sake of completeness. Cox proportional hazards models were used to assess the effect of multiple covariates on survival and to account for potential confounders. Multiple imputation was used to account for missing values. A model was developed that included traditional CVD risk factors, demographic information, original (noncore laboratory) IMT readings in the MESA population, CAC, and the known outcomes of the entire cohort over the follow-up period. All ultrasound
measurements were taken at baseline for event ascertainment, and data were imputed from individuals who died (Figure 1 in the Data Supplement). The IMT data from the rereads are missing at random and are highly correlated with the original IMT measurements included in the imputation model. Under these circumstances, multiple imputation performs well even with >90% missingness. The same imputation analysis was performed to account for missing carotid plaque data with 1 difference. Because the original carotid ultrasound readings did not provide plaque assessment in accordance with clinical consensus recommendations, those readings could not be imputed; however, all other participant data were included as in the carotid IMT models. Estimates for the Cox models were averaged across 100 datasets. The strength of association included as in the carotid IMT models. Estimates for the Cox models are reported, as in previous MESA publications. Areas under the receiver-operating characteristic curves (AUC) using Harrell c-statistics were estimated from 5 imputed datasets. Net reclassification improvement (NRI) analyses with bootstrapped SEs were used for all models. Sensitivity analyses combining the SEs were used for all models. Sensitivity analyses comparing complete case analysis with the imputed data are shown in Table 1.

Results

Participant Characteristics

Baseline characteristics are described in Table 2. Of those who underwent baseline carotid ultrasound evaluation (n=3310), ≥1 carotid plaque was found in 1544 (46.7%) participants with a mean (SD) total plaque score of 2.4 (1.6). CAC was present in 1479 (44.7%) with an average CAC score of 222.6 (417.0) units. The average left mean and maximum CCA IMT were 0.754 (0.210) mm and 0.930 (0.246) mm, respectively. The right mean and maximum CCA IMT were 0.751 (0.187) mm and 0.921 (0.219) mm, respectively. Carotid plaque or left or right mean CCA IMT ≥75th percentile for age, sex, and race/ethnicity (carotid plaque/carotid IMT) was found in 61.7% of participants with ultrasound data. The breakdown of CVD events is shown in Table 2.

Cox Regression Models for Predicting CVD Events

Cox regression models for CVD events with multiple imputation are shown in the Figure. After adjustment for traditional risk factors and multiple imputation for missing values, CAC presence was the strongest predictor of CVD events (HR, 3.12; 95% confidence interval [CI], 2.44–3.99; P<0.001). Carotid plaque presence (HR, 1.61; 95% CI, 1.17–2.21; P<0.003) was predictive of CVD events, but carotid plaque/CIMT75 (HR, 2.06; 95% CI, 1.46–2.91; P<0.003) performed better than carotid plaque alone (Figure; Table 1). CAC presence was a stronger predictor of CHD events (HR, 4.48; 95% CI, 3.24–6.17; P<0.001) than CVD events. CAC presence, carotid plaque presence, and carotid plaque/CIMT75 independently predicted stroke/TIA, with similar HRs. Carotid IMT ≥75th percentile without plaque did not predict stroke/TIA (HR, 1.01 [0.70–1.47]; Figure; Table 1). Analyses of the HRs for

Table 1. Risk Factor Adjusted Cox Regression Models for Predicting Incident Events

<table>
<thead>
<tr>
<th>Event</th>
<th>With Multiple Imputation†</th>
<th>Without Multiple Imputation†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>3.12 (2.44–3.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid plaque presence</td>
<td>1.61 (1.17–2.21)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean CCA IMT ≥75th percentile</td>
<td>1.20 (0.94–1.52)</td>
<td>0.141</td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>2.06 (1.46–2.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>4.48 (3.24–6.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid plaque presence</td>
<td>1.76 (1.23–2.52)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean CCA IMT ≥75th percentile</td>
<td>1.29 (0.98–1.68)</td>
<td>0.065</td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>2.33 (1.56–3.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>1.54 (1.09–2.18)</td>
<td>0.015</td>
</tr>
<tr>
<td>Carotid plaque presence</td>
<td>1.40 (1.35–1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean CCA IMT ≥75th percentile</td>
<td>1.01 (0.70–1.47)</td>
<td>0.944</td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>1.86 (1.10–3.13)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Carotid plaque/CIMT75=composite of any carotid plaque presence or CCA IMT ≥75th percentile. CAC indicates coronary artery calcium; CCA, common carotid artery; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; IMT, intima-media thickness; and TIA, transient ischemic attack.

*Multivariable models adjusted for age, sex, race/ethnicity, education, income, heart rate, body-mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication use, diabetes mellitus status, systolic blood pressure, and antihypertensive medication use.

†Multiple imputation sample size = 6779; without multiple imputation sample size=3310 (carotid plaque and CAC); 2892 for mean CCA IMT ≥75th percentile; and carotid plaque or carotid plaque or mean CCA IMT ≥75th percentile.
stroke alone (without TIA) were similar to stroke/TIA, but were limited by the low number of isolated stroke events. Because the HRs for CVD event prediction using CAC score (1.48; 95% CI, 1.20–1.86; P=0.001) and carotid plaque score (1.49; 95% CI, 1.39–1.58; P<0.001) were not better than CAC and carotid plaque presence, subsequent analyses focus on CAC and carotid plaque presence. Similar results were seen for the continuous CAC and carotid plaque measures for CHD and stroke/TIA events (data not shown).

Similar HR estimates were obtained in models restricted to those participants who were younger (men, <50 years old; women, <60 years old), and in each race/ethnicity category (Tables II and III in the Data Supplement). When participants with diabetes mellitus (n=850) were excluded from the analyses, similar HRs were obtained (data not shown). Mean, maximum, and combined internal carotid artery IMT did not predict CVD, CHD, or stroke/TIA (all P≥0.05; Table IV in the Data Supplement). Also, the presence of carotid plaque shadowing did not significantly predict CVD (0.92 [0.68–1.24]; P=0.6), CHD (0.97 [0.74–1.26]; P=0.8), or stroke (0.99 [0.58–1.67]; P=1.0) events, but predicted stroke/TIA events (1.65 [1.02–2.65]; P=0.04).

Receiver Operating Characteristic Curves and Net Reclassification Index

The areas under the receiver operator characteristic curves of the Cox regression models are shown in Table 4. For CVD events, traditional risk factors generated a c-statistic of 0.756. Addition of CAC presence to traditional risk factors increased the c-statistic to 0.776 (P<0.001). Addition of carotid plaque presence to traditional risk factors improved the c-statistic to 0.760 (P=0.033), but addition of carotid plaque presence to traditional risk factors improved the c-statistic to 0.787 (P=0.045). The NRI analysis results were similar to those AUC results; however, the only statistically significant improvement in NRI, in addition to traditional risk factors, was for CAC predicting CVD and CHD events (Table 4).

Discussion

Arterial imaging with CT (for CAC detection and scoring) and carotid ultrasound (for assessment of IMT and plaque presence) has been proposed as a strategy to better identify individuals who may have a higher CVD risk than is estimated by traditional risk prediction tools, to more efficiently use preventive resources. This is the first analysis, to our knowledge, that has directly compared carotid plaque presence, IMT, and CAC in a single cohort with extended follow-up and a large number of CVD events. It also is the only study to evaluate these parameters in a multi-ethnic cohort that is highly representative of the US population. Previous studies have directly compared the abilities of CAC and IMT to predict CVD events. A previous evaluation of 1330 MESA participants at intermediate Framingham CVD risk also demonstrated that CAC was a better predictor of CHD and CVD events compared with IMT. However, because both high risk and low risk participants were excluded from those analyses, the number of total events was far fewer than in this study and likely accounts for the differences between the calculated AUC and NRI data. That study also did not directly compare carotid plaque and IMT, though other cohorts have compared their predictive efficacy. Previous studies focused on IMT protocols developed for use in research settings, whereas this study is the first to compare the components of the carotid IMT/plaque examination currently recommended for clinical

Table 2. Baseline Characteristics* of MESA Participants, 2000 to 2002

<table>
<thead>
<tr>
<th></th>
<th>All Participants</th>
<th>Participants With Reread Carotid Ultrasounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytic sample size</td>
<td>6779</td>
<td>3310</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>62.2 (10.2)</td>
<td>60.3 (9.4)</td>
</tr>
<tr>
<td>Sex, male, % (n)</td>
<td>47.2 (3197)</td>
<td>47.1 (1559)</td>
</tr>
<tr>
<td>Race/ethnicity, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38.6 (2614)</td>
<td>39.5 (1306)</td>
</tr>
<tr>
<td>Chinese</td>
<td>11.8 (800)</td>
<td>13.2 (437)</td>
</tr>
<tr>
<td>Black</td>
<td>27.7 (1880)</td>
<td>25.4 (840)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21.9 (1485)</td>
<td>22.0 (727)</td>
</tr>
<tr>
<td>Education, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>18.0 (1215)</td>
<td>13.7 (453)</td>
</tr>
<tr>
<td>High school</td>
<td>46.7 (3153)</td>
<td>46.3 (1531)</td>
</tr>
<tr>
<td>More than high school</td>
<td>35.4 (2390)</td>
<td>40.1 (1326)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>28.3 (5.5)</td>
<td>28.2 (5.2)</td>
</tr>
<tr>
<td>Smoking, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>50.3 (3400)</td>
<td>52.2 (1729)</td>
</tr>
<tr>
<td>Former</td>
<td>36.6 (2475)</td>
<td>36.4 (1204)</td>
</tr>
<tr>
<td>Current</td>
<td>13.1 (884)</td>
<td>11.4 (377)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL, mean (SD)</td>
<td>194.2 (35.7)</td>
<td>194.1 (35.2)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL, mean (SD)</td>
<td>117.2 (31.5)</td>
<td>117.3 (31.0)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL, mean (SD)</td>
<td>51.0 (14.8)</td>
<td>51.0 (14.7)</td>
</tr>
<tr>
<td>Lipid-lowering medication, % (n)</td>
<td>16.2 (1096)</td>
<td>16.3 (539)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg mean (SD)</td>
<td>126.6 (21.5)</td>
<td>124.1 (20.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg, mean (SD)</td>
<td>71.9 (10.3)</td>
<td>71.9 (10.0)</td>
</tr>
<tr>
<td>Antihypertensive medication, % (n)</td>
<td>37.3 (2526)</td>
<td>34.2 (1133)</td>
</tr>
<tr>
<td>Diabetes mellitus status, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>73.6 (4972)</td>
<td>77.1 (2552)</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>13.8 (933)</td>
<td>13.0 (430)</td>
</tr>
<tr>
<td>Untreated diabetes mellitus</td>
<td>2.7 (179)</td>
<td>1.8 (60)</td>
</tr>
<tr>
<td>Treated diabetes mellitus</td>
<td>9.9 (671)</td>
<td>8.1 (268)</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and MESA, Multi-Ethnic Study of Atherosclerosis.

*Raw data without multiple imputation.
The results of our comprehensive analyses were consistent. CAC presence was a significantly better predictor of CVD and CHD events compared with any of the ultrasound measurements, including the consensus recommendation (carotid plaque/CIMT\textsuperscript{75}). Carotid plaque was a stronger predictor than IMT. Neither CCA nor internal carotid artery IMT values improved CVD or CHD event prediction more than the presence or the absence of carotid plaque. Regarding stroke/TIA, the point estimates of the HRs for CAC and carotid plaque presence were similar with overlapping CIs. Addition of carotid plaque presence to traditional risks factors improved prediction with a nominal level of statistical significance, whereas addition of CAC presence did not. Absolute differences in c-statistics and NRIs were small and not likely clinically significant.

In a subset of participants in the Cardiovascular Health Study, CAC and IMT seemed to predict CVD events in a similar manner, but IMT outperformed CAC for stroke prediction. They also were based on fewer events and shorter follow-up, with accordingly wider CIs. It is likely that the proximity of the carotid arteries to the brain and the coronary arteries to the heart explains the divergence of prediction between CAC scoring and carotid ultrasound measures. In this study, CAC clearly was a superior predictor of CVD and CHD events. Our data differ from earlier MESA publications\textsuperscript{1,2} by having longer follow-up and more clinically applicable IMT and plaque readings, as well as a wider range of CVD risk. Indeed, CAC was a better predictor of stroke/TIA than IMT alone and nearly as good as carotid plaque or the composite of carotid plaque and CIMT\textsubscript{≥}75th percentile. It is possible that with longer follow-up, the effect of risk-reducing medications, such as statins and antihypertensive medications, on IMT, the relative proximity of the arterial disease to the end-organ being assessed becomes less important. With long-term follow-up, the ability of CAC to predict CVD events remained strong but the differences between CAC and IMT in the ability to predict the type of event diminished. Also, the importance of carotid plaque—a further step along the pathway to clinical CVD—became more evident, likely because carotid plaque presence is less affected by medical therapy than IMT.

Accurate measurements of IMT and detection of carotid plaque are highly dependent on image quality and the sonographer’s skill.\textsuperscript{4} However, the reproducibility of these

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**Table 3. Numbers of Cardiovascular Disease Events and Descriptive Data on Carotid Plaque Presence, Coronary Artery Calcium, and Carotid Intima-Media Thickness**

<table>
<thead>
<tr>
<th></th>
<th>All Participants</th>
<th>All Participants With Reread Carotid Ultrasound</th>
<th>Participants With Reread Left CCA IMT Measurements</th>
<th>Participants With Reread Right CCA IMT Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analytic sample size</strong></td>
<td>6779</td>
<td>3310</td>
<td>3044</td>
<td>3098</td>
</tr>
<tr>
<td><strong>CVD event, % (n)</strong></td>
<td>7.9 (538)</td>
<td>5.0 (166)</td>
<td>5.0 (151)</td>
<td>5.0 (156)</td>
</tr>
<tr>
<td><strong>CVD death</strong></td>
<td>5.5 (370)</td>
<td>2.8 (91)</td>
<td>2.7 (82)</td>
<td>2.7 (83)</td>
</tr>
<tr>
<td><strong>CHD event, % (n)</strong></td>
<td>5.7 (388)</td>
<td>4.1 (136)</td>
<td>4.0 (121)</td>
<td>4.2 (130)</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>2.5 (171)</td>
<td>1.6 (54)</td>
<td>1.5 (46)</td>
<td>1.6 (50)</td>
</tr>
<tr>
<td><strong>CHD death</strong></td>
<td>3.5 (235)</td>
<td>1.7 (55)</td>
<td>1.5 (47)</td>
<td>1.7 (51)</td>
</tr>
<tr>
<td><strong>Cardiac arrest</strong></td>
<td>0.4 (24)</td>
<td>0.1 (2)</td>
<td>0.1 (2)</td>
<td>0.03 (1)</td>
</tr>
<tr>
<td><strong>Definite angina</strong></td>
<td>2.6 (175)</td>
<td>2.8 (92)</td>
<td>2.8 (84)</td>
<td>2.9 (89)</td>
</tr>
<tr>
<td><strong>Probable angina w/PCI</strong></td>
<td>1.1 (77)</td>
<td>1.2 (38)</td>
<td>1.2 (35)</td>
<td>1.1 (34)</td>
</tr>
<tr>
<td><strong>Stroke, % (n)</strong></td>
<td>2.2 (148)</td>
<td>1.1 (38)</td>
<td>1.2 (35)</td>
<td>1.0 (32)</td>
</tr>
<tr>
<td><strong>Stroke+TIA, % (n)</strong></td>
<td>2.9 (196)</td>
<td>1.7 (57)</td>
<td>1.8 (55)</td>
<td>1.6 (50)</td>
</tr>
<tr>
<td><strong>CAC present, % (n)</strong></td>
<td>49.9 (3382)</td>
<td>44.7 (1479)</td>
<td>44.2 (1345)</td>
<td>44.1 (1366)</td>
</tr>
<tr>
<td><strong>CAC score (if present), mean (SD)</strong></td>
<td>290.8 (545.9)</td>
<td>222.6 (417.0)</td>
<td>220.0 (415.4)</td>
<td>222.7 (422.7)</td>
</tr>
<tr>
<td><strong>Plaque present, % (n)</strong></td>
<td>...</td>
<td>46.7 (1544)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td><strong>Plaque score (if present), mean (SD)</strong></td>
<td>...</td>
<td>2.4 (1.6)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td><strong>Left CCA mean IMT (mm), mean (SD)</strong></td>
<td>0.743 (0.250)†</td>
<td>...</td>
<td>0.754 (0.210)</td>
<td>...</td>
</tr>
<tr>
<td><strong>Left CCA maximum IMT(mm), mean (SD)</strong></td>
<td>0.853 (0.279)†</td>
<td>...</td>
<td>0.930 (0.246)</td>
<td>...</td>
</tr>
<tr>
<td><strong>Right CCA mean IMT (mm), mean (SD)</strong></td>
<td>0.734 (0.232)†</td>
<td>...</td>
<td>...</td>
<td>0.751 (0.187)</td>
</tr>
<tr>
<td><strong>Right CCA maximum IMT (mm), mean (SD)</strong></td>
<td>0.846 (0.262)†</td>
<td>...</td>
<td>...</td>
<td>0.921 (0.220)</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium; CCA, common carotid artery; CHD, coronary heart disease; CVD, cardiovascular disease; IMT, intima media thickness; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*Raw data without multiple imputation.
†Left CCA mean IMT sample size=6570; left CCA maximum IMT sample size=6570; right CCA mean IMT sample size=6623; right CCA maximum IMT sample size=6623.
measures in this study approached that of CAC scoring. CAC scoring is less user dependent, and a score of zero may be less useful in individuals with high pretest likelihood of absent CAC, such as younger adults, women, and certain ethnic minorities. However, in our subgroup analyses of these individuals, CAC presence and the carotid ultrasound measures did not differ significantly from the primary analysis. Although previous studies have shown that CAC score and carotid plaque score can improve prediction of CVD events, in this study, the predictive ability of either CAC score or plaque score was similar to the presence or absence of CAC or carotid plaque for stroke/TIA and more easily directly compared given the differing scales of the scoring systems. Some studies have suggested that characterizing plaque based on echo characteristics may have predictive value; however, the definitions are not uniform, and correlations with histological findings of plaque have not been strong.

Limitations
This study shares the limitations of all observational research. However, this population is large, well described, and was followed prospectively with careful imaging, measurement, and event adjudication. The major drawback was the number of missing reread ultrasound studies. The imputation models included baseline IMT data from all 6779 (100%) MESA participants; however, the original MESA approach did not have a standardized plaque assessment. Thus, plaque assessment was imputed from the subset (n=3310) that survived until examination 5 and therefore had fewer events. However, because the original reads were included in the imputation model, it will accurately correct implausible baseline readings using the information available from the rereads, which was a major impetus for choosing an imputation approach. Table 4. Area Under the Curve and Net Reclassification Index for Cox Regression Models of Cardiovascular Disease End points

<table>
<thead>
<tr>
<th>Model</th>
<th>n=6779</th>
<th>c-Statistic</th>
<th>PValue*</th>
<th>Net Reclassification Index (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional risk factors alone</td>
<td>0.756</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>0.776</td>
<td>&lt;0.001</td>
<td>0.110 (0.060 to 0.159)</td>
<td></td>
</tr>
<tr>
<td>Carotid plaque presence</td>
<td>0.760</td>
<td>0.033</td>
<td>0.012 (−0.022 to 0.045)</td>
<td></td>
</tr>
<tr>
<td>Mean CCA IMT ≥ 75th percentile</td>
<td>0.757</td>
<td>0.111</td>
<td>−0.007 (−0.031 to 0.018)</td>
<td></td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>0.759</td>
<td>0.034</td>
<td>0.008 (−0.020 to 0.035)</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional risk factors alone</td>
<td>0.752</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>0.784</td>
<td>&lt;0.001</td>
<td>0.103 (0.052 to 0.155)</td>
<td></td>
</tr>
<tr>
<td>Carotid plaque presence</td>
<td>0.757</td>
<td>0.043</td>
<td>0.006 (−0.026 to 0.037)</td>
<td></td>
</tr>
<tr>
<td>Mean CCA IMT ≥75th percentile</td>
<td>0.754</td>
<td>0.153</td>
<td>−0.005 (−0.031 to 0.022)</td>
<td></td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>0.756</td>
<td>0.055</td>
<td>0.012 (−0.016 to 0.039)</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional risk factors alone</td>
<td>0.782</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>0.785</td>
<td>0.438</td>
<td>0.028 (−0.012 to 0.068)</td>
<td></td>
</tr>
<tr>
<td>Carotid plaque presence</td>
<td>0.787</td>
<td>0.045</td>
<td>0.015 (−0.017 to 0.048)</td>
<td></td>
</tr>
<tr>
<td>Mean CCA IMT 75th percentile</td>
<td>0.783</td>
<td>0.160</td>
<td>0.000 (−0.003 to 0.034)</td>
<td></td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>0.785</td>
<td>0.450</td>
<td>0.006 (−0.022 to 0.034)</td>
<td></td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium; CCA, common carotid artery; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; IMT, intima-media thickness; and TIA, transient ischemic attack.

*Compared with traditional risk factors alone.
strategy. The imputation model included carotid IMT readings from before all events. This approach was accepted because of the consensus recommendations for clinical use of carotid ultrasound, including measurement of carotid IMT and carotid plaque detection. It allowed all CVD, CHD, and stroke/TIA events to be included in the analysis and all data from all subjects (Tables V–VIII in the Data Supplement). The proportion of subjects with carotid plaque and CCA IMT >75th percentile was lower than in some but not all previous reports,8,21–23 likely because of differing scan protocols, definitions of plaque, reader variability, and characteristics of the different populations.

Conclusions
In middle-aged adults without preexisting CVD, CAC presence predicts incident CVD and CHD better than carotid plaque presence, carotid artery IMT, or their composite, for nearly a decade of follow-up. CAC and carotid ultrasound parameters performed in a similar manner for stroke/TIA event prediction. Similar observations were found in subgroup analyses of younger participants and ethnic minorities.

Acknowledgments
We thank the Multi-Ethnic Study of Atherosclerosis (MESA) investigators, staff, and participants for their valuable contributions. Participating MESA investigators/institutions can be found at http://www.mesa-nhlbi.org.

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Disclosures
Dr Stein received support from Wisconsin Alumni Research Foundation. The other authors report no conflicts.

References
The predictive uses of carotid intima-media thickness, carotid plaque presence, and coronary artery calcium (CAC) presence have been described in multiple cohorts but have not been directly compared in a single cohort with extended follow-up and a large number of cardiovascular disease (CVD) events. None have compared carotid intima-media thickness/carotid plaque examination currently recommended for clinical use to CAC presence. Participants were from the Multi-Ethnic Study of Atherosclerosis (MESA). This analysis included all MESA participants with examination 1 CAC evaluation and follow-up data (n=6799) and who also had examination 1 common carotid artery intima-media thickness measurements (n=3098) and carotid plaque assessment (n=3310) read by the University of Wisconsin Ultrasound Reading Center. Missing data were estimated by multiple imputation from the entire MESA cohort. For a median of 9.5 years, there were 538 CVD events, 388 coronary heart disease (CHD) events, and 196 stroke/transient ischemic attacks. CAC presence was a stronger predictor of incident CVD and CHD than carotid ultrasound measures. Compared with traditional risk factors, c-statistics for CVD ($c=0.756$) and CHD ($c=0.752$) increased most by addition of CAC presence (CVD, 0.776; CHD, 0.784; $P<0.001$) followed by carotid plaque presence (CVD, $c=0.760$; CHD, 0.757; $P<0.05$). Compared with risk factors ($c=0.782$), carotid plaque presence ($c=0.787$; $P=0.045$) but not CAC ($c=0.785$; $P=0.438$) improved prediction of stroke/transient ischemic attacks. In adults without CVD, CAC presence improves prediction of CVD and CHD more than carotid plaque presence or high intima-media thickness. CAC and carotid ultrasound parameters performed in a similar manner for stroke/transient ischemic attacks event prediction.
Comparison of Coronary Artery Calcium Presence, Carotid Plaque Presence, and Carotid Intima-Media Thickness for Cardiovascular Disease Prediction in the Multi-Ethnic Study of Atherosclerosis

Adam D. Gepner, Rebekah Young, Joseph A. Delaney, Matthew C. Tattersall, Michael J. Blaha, Wendy S. Post, Rebecca F. Gottesman, Richard Kronmal, Matthew J. Budoff, Gregory L. Burke, Aaron R. Folsom, Kiang Liu, Joel Kaufman and James H. Stein

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http://circimaging.ahajournals.org/content/suppl/2015/01/16/CIRCIMAGING.114.002262.DC1

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Supplemental Material – Reader Reproducibility

Reader reproducibility was assessed by having all 4 Wisconsin readers read 24 scans blinded to prior information, chosen as 4 per field center. Intra-reader reproducibility was excellent for maximum CCA-IMT (total error of the mean [TEM] 3-4%, intra-class correlation coefficients [ICCs] 0.93-0.99) and very good for maximum ICA-IMT (TEM 8-9%; ICC 0.86-0.96). Inter-reader reproducibility was excellent for maximum CCA-IMT (TEM 2-4%, ICC 0.96) and very good for maximum ICA-IMT (TEM 5-10%, ICCs 0.86-0.88). Scan-rescan reproducibility was evaluated by 44 repeated scans from 3 sonographers, measured by a single reader. Pearson correlations for matched segments ranged from 0.979-0.996. Mean (SD) differences were <0.01 (<0.05) mm with no outliers on limit of agreement (Bland-Altman) analysis for matched segments. For carotid plaque presence, intra-reader reproducibility was excellent (per reader Kappa = 0.82-1.0, overall Kappa = 0.83, 95% confidence interval [CI] 0.70-0.96), as was inter-reader reproducibility (Kappa = 0.89; 95% CI 0.72 – 1.00).
Supplementary Tables

Supplementary Table I. Estimates of Mean Common Carotid Intima–Media Thickness Percentiles by Age, Race, and Sex for the Mean

<table>
<thead>
<tr>
<th>Age</th>
<th>White</th>
<th>Chinese</th>
<th>Black</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>44-54</td>
<td>55-64</td>
<td>65-74</td>
<td>75-85</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44-54</td>
<td>55-64</td>
<td>65-74</td>
<td>75-85</td>
</tr>
<tr>
<td>P05</td>
<td>0.49</td>
<td>0.55</td>
<td>0.59</td>
<td>0.65</td>
</tr>
<tr>
<td>P10</td>
<td>0.51</td>
<td>0.56</td>
<td>0.63</td>
<td>0.73</td>
</tr>
<tr>
<td>P25</td>
<td>0.55</td>
<td>0.62</td>
<td>0.69</td>
<td>0.77</td>
</tr>
<tr>
<td>P50</td>
<td>0.61</td>
<td>0.69</td>
<td>0.78</td>
<td>0.86</td>
</tr>
<tr>
<td>P75</td>
<td>0.68</td>
<td>0.78</td>
<td>0.94</td>
<td>0.90</td>
</tr>
<tr>
<td>P90</td>
<td>0.76</td>
<td>0.88</td>
<td>1.01</td>
<td>1.10</td>
</tr>
<tr>
<td>P95</td>
<td>0.85</td>
<td>0.94</td>
<td>1.17</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td>44-54</td>
<td>55-64</td>
<td>65-74</td>
<td>75-85</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44-54</td>
<td>55-64</td>
<td>65-74</td>
<td>75-85</td>
</tr>
<tr>
<td>P05</td>
<td>0.48</td>
<td>0.55</td>
<td>0.60</td>
<td>0.69</td>
</tr>
<tr>
<td>P10</td>
<td>0.52</td>
<td>0.56</td>
<td>0.65</td>
<td>0.71</td>
</tr>
<tr>
<td>P25</td>
<td>0.58</td>
<td>0.63</td>
<td>0.72</td>
<td>0.75</td>
</tr>
<tr>
<td>P50</td>
<td>0.65</td>
<td>0.74</td>
<td>0.83</td>
<td>0.84</td>
</tr>
<tr>
<td>P75</td>
<td>0.73</td>
<td>0.87</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td>P90</td>
<td>0.83</td>
<td>0.97</td>
<td>1.12</td>
<td>1.08</td>
</tr>
<tr>
<td>P95</td>
<td>0.91</td>
<td>1.03</td>
<td>1.17</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Sample size = 6,779

Abbreviation: P = percentile

Multiple imputation was used for all missing values.
### Supplementary Table II. Multivariable Adjusted Cox Regression Models Predicting Events by Age Group*

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>(95% CI)</th>
<th>P-value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men ≤ 50 and Women ≤ 60 Years old</td>
<td>N=1954</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>2.53</td>
<td>(1.39 – 4.58)</td>
<td></td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>1.58</td>
<td>(0.65 – 3.82)</td>
<td></td>
</tr>
<tr>
<td>Men &gt; 50 and Women &gt; 60 Years old</td>
<td>N=4826</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>3.18</td>
<td>(2.42 – 4.18)</td>
<td>0.792</td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>1.95</td>
<td>(1.34 – 2.83)</td>
<td>0.984</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>3.07</td>
<td>(1.51 – 6.21)</td>
<td>0.502</td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>1.49</td>
<td>(0.57 – 3.89)</td>
<td>0.679</td>
</tr>
<tr>
<td><strong>Stroke/TIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>1.68</td>
<td>(1.02 – 2.78)</td>
<td>0.413</td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>1.75</td>
<td>(0.83 – 3.67)</td>
<td>0.707</td>
</tr>
</tbody>
</table>

*Multivariable models adjusted for age, gender, race/ethnicity, education, income, heart rate, body-mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication, diabetes mellitus status, systolic blood pressure and anti-hypertension medication.

Multiple imputation was used for all missing values.

Abbreviations: CI = confidence interval; CAC = coronary artery calcium; carotid plaque/CIMT75 = composite of any carotid plaque presence or common carotid artery intima-media thickness ≥75th percentile; CVD = cardiovascular disease; CHD = coronary heart disease; IA = transient ischemic attack.
**Supplementary Table III. Multivariable Adjusted Cox Regression Models Predicting Events by Race/Ethnicity***

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White N=2614</td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>2.93 (1.96–4.39)</td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>2.28 (1.34–3.89)</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
</tr>
<tr>
<td>CAC presence</td>
<td>4.62 (2.75–7.76)</td>
</tr>
<tr>
<td>Carotid plaque/CIMT75</td>
<td>2.51 (1.35–4.67)</td>
</tr>
</tbody>
</table>

*Multivariable models adjusted for age, gender, race/ethnicity, education, income, heart rate, body-mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication, diabetes mellitus status, systolic blood pressure and anti-hypertension medication.

**When hazard ratios were compared to White participants, all p-values >0.35.

Multiple imputation was used for all missing values.

Abbreviations as in Supplementary Table II
Supplementary Table IV. Multivariable Adjusted Cox Regression Models Predicting Events Using Internal Carotid Artery Intima Media Thickness*

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ICA Mean¹</td>
<td>1.50 (0.89 – 2.52)</td>
<td>0.126</td>
</tr>
<tr>
<td>Left ICA Max¹</td>
<td>1.20 (0.81 – 1.77)</td>
<td>0.371</td>
</tr>
<tr>
<td>Right ICA Mean²</td>
<td>0.91 (0.52 – 1.57)</td>
<td>0.730</td>
</tr>
<tr>
<td>Right ICA Max²</td>
<td>1.02 (0.70 – 1.47)</td>
<td>0.930</td>
</tr>
<tr>
<td>Average Mean ICA³</td>
<td>1.21 (0.63 – 2.31)</td>
<td>0.565</td>
</tr>
<tr>
<td>Average Max ICA³</td>
<td>1.14 (0.72 – 1.79)</td>
<td>0.579</td>
</tr>
<tr>
<td>Average Mean ICA ≥75th percentile³</td>
<td>1.12 (0.79 – 1.58)</td>
<td>0.523</td>
</tr>
<tr>
<td>Average Max ICA ≥75th percentile³</td>
<td>1.14 (0.82 – 1.59)</td>
<td>0.437</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ICA Mean¹</td>
<td>1.75 (1.00 – 3.08)</td>
<td>0.050</td>
</tr>
<tr>
<td>Left ICA Max¹</td>
<td>1.39 (0.91 – 2.12)</td>
<td>0.126</td>
</tr>
<tr>
<td>Right ICA Mean²</td>
<td>1.03 (0.57 – 1.86)</td>
<td>0.920</td>
</tr>
<tr>
<td>Right ICA Max²</td>
<td>1.17 (0.80 – 1.71)</td>
<td>0.421</td>
</tr>
<tr>
<td>Average Mean ICA³</td>
<td>1.49 (0.74 – 2.98)</td>
<td>0.263</td>
</tr>
<tr>
<td>Average Max ICA³</td>
<td>1.41 (0.88 – 2.25)</td>
<td>0.149</td>
</tr>
<tr>
<td>Average Mean ICA ≥75th percentile³</td>
<td>1.23 (0.83 – 1.81)</td>
<td>0.302</td>
</tr>
<tr>
<td>Average Max ICA ≥75th percentile³</td>
<td>1.31 (0.90 – 1.91)</td>
<td>0.163</td>
</tr>
<tr>
<td><strong>Stroke/TIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ICA Mean¹</td>
<td>1.26 (0.48 – 3.31)</td>
<td>0.643</td>
</tr>
<tr>
<td>Left ICA Max¹</td>
<td>0.95 (0.44 – 2.04)</td>
<td>0.889</td>
</tr>
<tr>
<td>Right ICA Mean²</td>
<td>0.62 (0.22 – 1.78)</td>
<td>0.375</td>
</tr>
<tr>
<td>Right ICA Max²</td>
<td>0.59 (0.27 – 1.28)</td>
<td>0.178</td>
</tr>
<tr>
<td>Average Mean ICA³</td>
<td>0.81 (0.22 – 2.92)</td>
<td>0.743</td>
</tr>
<tr>
<td>Average Max ICA³</td>
<td>0.61 (0.23 – 1.62)</td>
<td>0.319</td>
</tr>
<tr>
<td>Average Mean ICA ≥75th percentile³</td>
<td>0.96 (0.50 – 1.85)</td>
<td>0.903</td>
</tr>
<tr>
<td>Average Max ICA ≥75th percentile³</td>
<td>0.82 (0.43 – 1.55)</td>
<td>0.531</td>
</tr>
</tbody>
</table>

Sample size = 6,779 for CVD and CHD; sample size = 6,777 for Stroke/TIA. Multiple imputation was used for all missing values.

*Multivariable models adjusted for age, gender, race/ethnicity, education, income, heart rate, body-mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication, diabetes mellitus status, systolic blood pressure and anti-hypertension medication.

Abbreviations as in Supplementary Table II: ICA = Internal Carotid Artery
## Supplementary Table V. Comparison of Event Rates and Unadjusted Cox Proportional Hazards for Predicting Cardiovascular Disease Events: Full MESA Sample and the Imputed Subset

<table>
<thead>
<tr>
<th></th>
<th>Subset* with Multiple Imputation</th>
<th>Full Sample** with Multiple Imputation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD Event Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Events/1000 person-years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Max CCA IMT</td>
<td>10.6 [538/6779]</td>
<td>10.6 [538/6779]</td>
</tr>
<tr>
<td>Right Mean CCA IMT</td>
<td>10.6 [538/6779]</td>
<td>10.6 [538/6779]</td>
</tr>
<tr>
<td>Left Max CCA IMT</td>
<td>10.6 [538/6779]</td>
<td>10.6 [538/6779]</td>
</tr>
<tr>
<td>Left Mean CCA IMT</td>
<td>10.6 [538/6779]</td>
<td>10.6 [538/6779]</td>
</tr>
<tr>
<td><strong>Hazard Ratio (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Max CCA IMT</td>
<td>1.14‡ (1.11-1.17)</td>
<td>1.09‡ (1.07-1.11)</td>
</tr>
<tr>
<td>Right Mean CCA IMT</td>
<td>1.16‡ (1.12-1.20)</td>
<td>1.10‡ (1.08-1.12)</td>
</tr>
<tr>
<td>Left Max CCA IMT</td>
<td>1.11‡ (1.09-1.14)</td>
<td>1.10‡ (1.08-1.12)</td>
</tr>
<tr>
<td>Left Mean CCA IMT</td>
<td>1.14‡ (1.11-1.16)</td>
<td>1.11‡ (1.09-1.13)</td>
</tr>
</tbody>
</table>

Sample size=6,779
‡p<0.001 (two-tailed)

*Wisconsin re-reads, imputing all missing values for carotid IMT re-reads using Tufts original reads and all analysis variables

**Tufts original reads, imputing missing values for carotid IMT measures using all analysis variables (<1% of participants did not have an “original read” at Exam 1)

1Multiple imputation (chained equations); m=100; imputation model contained traditional CVD risk factors and Exam 1 reading center measures of CCA IMT as predictors.

Abbreviations as in Supplementary Table II: CCA = common carotid artery IMT = intima-media thickness; MESA = Multi-Ethnic Study of Atherosclerosis
Supplementary Table VI. Comparison of Event Rates and Unadjusted Cox Proportional Hazards for Predicting Coronary Heart Disease Events: Full MESA Sample and the Imputed Subset

<table>
<thead>
<tr>
<th>Coronary Heart Disease Event Rate (Events/1000 person-years)</th>
<th>Subset* with Multiple Imputation¹</th>
<th>Full Sample** with Multiple Imputation¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Max CCA IMT</td>
<td>7.54 [388/6779]</td>
<td>7.54 [388/6779]</td>
</tr>
<tr>
<td>Right Mean CCA IMT</td>
<td>7.54 [388/6779]</td>
<td>7.54 [388/6779]</td>
</tr>
<tr>
<td>Left Max CCA IMT</td>
<td>7.54 [388/6779]</td>
<td>7.54 [388/6779]</td>
</tr>
<tr>
<td>Left Mean CCA IMT</td>
<td>7.54 [388/6779]</td>
<td>7.54 [388/6779]</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Max CCA IMT</td>
<td>1.14‡ (1.10-1.18)</td>
<td>1.10‡ (1.08-1.12)</td>
</tr>
<tr>
<td>Right Mean CCA IMT</td>
<td>1.16‡ (1.12-1.20)</td>
<td>1.11‡ (1.08-1.13)</td>
</tr>
<tr>
<td>Left Max CCA IMT</td>
<td>1.11‡ (1.09-1.14)</td>
<td>1.10‡ (1.08-1.12)</td>
</tr>
<tr>
<td>Left Mean CCA IMT</td>
<td>1.14‡ (1.11-1.17)</td>
<td>1.12‡ (1.10-1.14)</td>
</tr>
</tbody>
</table>

Sample size=6,779

*Wisconsin re-reads, imputing all missing values for carotid IMT re-reads using Tufts original reads and all analysis variables

**Tufts original reads, imputing missing values for carotid IMT measures using all analysis variables (<1% of participants did not have an "original read" at Exam 1)

¹Multiple imputation (chained equations); m=100; imputation model contained traditional CVD risk factors and Exam 1 reading center measures of CCA IMT as predictors.

Abbreviations as in Supplementary Table IV.
Supplementary Table VII. Comparison of Event Rates and Unadjusted Cox Proportional Hazards for Predicting Stroke/ TIA Events: Full MESA Sample and the Imputed Subset

<table>
<thead>
<tr>
<th></th>
<th>Subset* with Multiple Imputation</th>
<th>Full Sample** with Multiple Imputation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke/TIA event rate</strong>&lt;sup&gt;2&lt;/sup&gt; (Events/1000 person-years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Max CCA IMT</td>
<td>3.7 [196/6777]</td>
<td>3.7 [196/6777]</td>
</tr>
<tr>
<td>Right Mean CCA IMT</td>
<td>3.7 [196/6777]</td>
<td>3.7 [196/6777]</td>
</tr>
<tr>
<td>Left Max CCA IMT</td>
<td>3.7 [196/6777]</td>
<td>3.7 [196/6777]</td>
</tr>
<tr>
<td>Left Mean CCA IMT</td>
<td>3.7 [196/6777]</td>
<td>3.7 [196/6777]</td>
</tr>
<tr>
<td><strong>Hazard Ratio (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Max CCA IMT</td>
<td>1.16‡ (1.10-1.21)</td>
<td>1.07‡ (1.03-1.12)</td>
</tr>
<tr>
<td>Right Mean CCA IMT</td>
<td>1.18‡ (1.12-1.25)</td>
<td>1.10‡ (1.05-1.43)</td>
</tr>
<tr>
<td>Left Max CCA IMT</td>
<td>1.10‡ (1.07-1.14)</td>
<td>1.08‡ (1.05-1.12)</td>
</tr>
<tr>
<td>Left Mean CCA IMT</td>
<td>1.11‡ (1.07-1.16)</td>
<td>1.09‡ (1.06-1.13)</td>
</tr>
</tbody>
</table>

Sample size=6,777

*Wisconsin re-reads, imputing all missing values for carotid IMT re-reads using Tufts original reads and all analysis variables

**Tufts original reads, imputing missing values for carotid IMT measures using all analysis variables (<1% of participants did not have an "original read" at Exam 1)

<sup>1</sup>Multiple imputation (chained equations); m=100; imputation model contained traditional CVD risk factors and Exam 1 reading center measures of CCA IMT as predictors.

Abbreviations as in Supplementary Table IV.
Supplementary Table VIII. Comparison of Hazard Ratios for Mean and Maximum Carotid Intima-Media Thickness Between the Full MESA Sample and the Subset with Augmentation

<table>
<thead>
<tr>
<th></th>
<th>Subset* with Multiple Imputation¹</th>
<th>Full Sample** with Multiple Imputation¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CCA IMT</td>
<td>1.064 (1.012-1.118)</td>
<td>0.016</td>
</tr>
<tr>
<td>Max CCA IMT</td>
<td>1.056 (1.011-1.012)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CCA IMT</td>
<td>1.086 (1.027-1.147)</td>
<td>0.004</td>
</tr>
<tr>
<td>Max CCA IMT</td>
<td>1.035 (0.988-1.085)</td>
<td>0.149</td>
</tr>
<tr>
<td><strong>Stroke/TIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CCA IMT</td>
<td>1.013 (0.933-1.110)</td>
<td>0.755</td>
</tr>
<tr>
<td>Max CCA IMT</td>
<td>1.032 (0.958-1.112)</td>
<td>0.409</td>
</tr>
</tbody>
</table>

Sample size = 6,779.

*Wisconsin re-reads, imputing all missing values for carotid IMT re-reads using Tufts original reads and all analysis variables

**Tufts original reads, imputing missing values for carotid IMT measures using all analysis variables (<1% of participants did not have an "original read" at Exam 1)

¹Multiple imputation (chained equations); m=100; imputation model contained traditional CVD risk factors and Exam 1 reading center measures of CCA IMT as predictors.

Abbreviations as in Supplementary Table II; CCA = common carotid artery IMT = intima-media thickness; MESA = Multi-Ethnic Study of Atherosclerosis
Supplementary Figure I: Imputation Strategy Flow Diagram

- All values present (used to improve imputation)
- Missing baseline values are imputed with multiple imputation
- New CCA IMT (UW) reads [Exam 1]
  - Imputed
  - Participants present at both Exam 1 and 5
- New CCA IMT reads [Exam 5]
  - These reads are not used in this paper or for imputation
  - Standardized plaque score available
  - These participants are not present in Exam 5

Study baseline (Time = 0)
[CAC measured here also]

Events are captured here during 9.5 years of MESA study follow-up. All CCA IMT values are baseline (before beginning event ascertainment).