Coronary Artery Calcification Compared With Carotid Intima-Media Thickness in the Prediction of Cardiovascular Disease Incidence

The Multi-Ethnic Study of Atherosclerosis (MESA)

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Background: Coronary artery calcium (CAC) and carotid intima-media thickness (IMT) are noninvasive measures of atherosclerosis that consensus panels have recommended as possible additions to risk factor assessment for predicting the probability of cardiovascular disease (CVD) occurrence. Our objective was to assess whether maximum carotid IMT or CAC (Agatston score) is the better predictor of incident CVD.

Methods: A prospective cohort study of subjects aged 45 to 84 years in 4 ethnic groups, who were initially free of CVD (n=6698) was performed, with standardized carotid IMT and CAC measures at baseline, in 6 field centers of the Multi-Ethnic Study of Atherosclerosis (MESA). The main outcome measure was the risk of incident CVD events (coronary heart disease, stroke, and fatal CVD) over a maximum of 5.3 years of follow-up.

Results: There were 222 CVD events during follow-up. Coronary artery calcium was associated more strongly than carotid IMT with the risk of incident CVD. After adjustment for each other (CAC score and IMT) and traditional CVD risk factors, the hazard ratio of CVD increased 2.1-fold (95% confidence interval [CI], 1.8-2.5) for each 1-standard deviation (SD) increment of log-transformed CAC score, vs 1.3-fold (95% CI, 1.1-1.4) for each 1-SD increment of the maximum IMT. For coronary heart disease, the hazard ratios per 1-SD increment increased 2.5-fold (95% CI, 2.1-3.1) for CAC score and 1.2-fold (95% CI, 1.0-1.4) for IMT. A receiver operating characteristic curve analysis also suggested that CAC score was a better predictor of incident CVD than was IMT, with areas under the curve of 0.81 vs 0.78, respectively.

Conclusion: Although whether and how to clinically use bioimaging tests of subclinical atherosclerosis remains a topic of debate, this study found that CAC score is a better predictor of subsequent CVD events than carotid IMT.

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associated more strongly than IMT with prevalent coronary artery stenosis. Brook et al confirmed this but found that an estimate of carotid plaque area predicted coronary stenosis somewhat more strongly than even CAC. Neither of these cross-sectional studies assessed CVD incidence. The prospective Rotterdam Study found that carotid plaques, increased IMT, aortic calcium, and low ankle-brachial blood pressure index predicted incident myocardial infarction (MI) fairly comparably, and the more subclinical measures present, the greater the risk. Their study did not examine CAC. Very recently, the first prospective study assessed the potential utility of measuring CAC vs IMT for global CVD risk prediction. Newman et al found that CAC and common carotid IMT similarly predicted CVD and CHD in adults 70 years or older, but IMT was the better predictor of stroke. Herein, we also adddress this question, prospectively, in the Multi-Ethnic Study of Atherosclerosis (MESA).

METHODS

MESA COHORT AND RISK FACTOR ASSESSMENTS

MESA recruited 6814 adults aged 43 to 84 years from the populations near 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St Paul, Minnesota) to a baseline examination between July 2000 and September 2002. The study participants were white (38%), African American (28%), Hispanic (22%), and Chinese American (12%) and free of clinically recognized CVD and were drawn from households in geographically defined areas (5 centers) or in an occupational union (New York). MESA conducted 3 subsequent examinations of the cohort between 2002 and 2007. Institutional review boards at each site approved the study, and all participants gave written informed consent.

Centrally trained clinical teams collected information on cardiovascular risk factors during the baseline examination. They measured resting blood pressure 3 times in seated participants with a Dinamap model Pro 1000 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida). A central laboratory measured total and high-density lipoprotein cholesterol and glucose levels from blood samples obtained after a 12-hour fast. We defined diabetes as a fasting glucose level of 126 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0555) or use of hypoglycemic medication.

CAC ASSESSMENT

Scanning centers assessed CAC by chest computed tomography using either a cardiac-gated electron-beam computed tomography scanner (Chicago, Los Angeles, and New York field centers) or a multidetector computed tomography system (Baltimore, Forsyth County, and St Paul field centers). Certified technologists scanned all participants twice. A phantom of known physical calcium concentration was included in the field of view. A radiologist or cardiologist read all computed tomographic scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center in Torrance, California) using an interactive scoring system similar to that used by Yaghoubi et al. The reader–work station interface identified and quantified CAC from images calibrated according to the readings of the calcium phantom. The Agatston score, which is a pseudo–continuous variable derived from plaque densities and their areas in all coronary arteries, was computed. We used the mean phantom-adjusted Agatston score for the 2 scans in all analyses. Carr et al have reported the details of the MESA computed tomographic scanning and interpretation methods. Each participant and his or her physicians were notified whether the CAC scores were below average, average, or above average for the participant’s age. No recommendation was made about treatment.

CAROTID IMT ASSESSMENT

Trained technicians in each field center performed B-mode ultrasonography of the right and left common and internal carotid arteries. They used the Logiq 700 ultrasound device (General Electric Medical Systems, Waukesha, Wisconsin) to record images. An ultrasound reading center (Department of Radiology, Tufts–New England Medical Center, Boston, Massachusetts) measured maximal IMT of the internal and common carotid sites as the mean of the maximum IMT of the near and far walls of the right and left sides. In addition, for this article, we created a composite z score for overall maximal IMT by summing the values of the 2 carotid IMT sites (if both were measured) after standardization (subtraction of the mean and division by the SD of each measure) and then dividing by the SD of the sum. If only 1 of the 2 measures was available, it was used. The resulting variable, hereafter referred to as z score maximum IMT, has a mean of 0 and an SD of 1. Each participant and his or her physicians were notified whether an accompanying Doppler assessment suggested significant carotid stenosis (≥50%), but no recommendation was made about treatment.

CVD FOLLOW-UP

We followed the cohort for incident CVD events for a median of 3.9 years (maximum, 5.3 years). At intervals of 9 to 12 months, a telephone interviewer contacted each participant to inquire about interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. To verify self-reported diagnoses, we requested copies of all death certificates and medical records for hospitalizations and outpatient cardiovascular diagnoses. We also conducted next-of-kin interviews for out-of-hospital cardiovascular deaths. We obtained records on an estimated 98% of reported hospitalized cardiovascular events and some information on 95% of reported outpatient diagnostic encounters. Two physicians, blinded to the CAC and IMT data, independently reviewed and classified CVD events and assigned incidence dates. If, after review and adjudication, disagreements persisted, a full mortality and morbidity review committee made the final classification. MESA criteria for events were adopted from the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Women’s Health Initiative. Reviewers classified MI as definite, probable, or absent, based primarily on combinations of symptoms, electrocardiographic findings, and levels of cardiac biomarkers (generally, troponins or creatine kinase myocardial band). Reviewers graded angina based on their clinical judgment as definite, probable, or absent. Probable angina required symptoms of ischemia, as well as documentation that a physician had diagnosed and treated angina. Definite angina also required objective diagnostic evidence of CHD. In this article, we only included definite angina (n = 76) plus probable angina when accompanied by coronary revascularization (n = 5). The reviewers classified CHD or CVD death as present or absent based on hospital records and interviews with families. Definite fatal CHD required an MI within 28 days of death, chest pain within the 72 hours before death, or a history of CHD and the absence of a known non-
atherosclerotic or noncardiac cause of death. Neurologists re-
viewed and classified stroke as present if there was a focal neu-
rologic deficit lasting 24 hours or until death, with a clinically
relevant lesion on brain imaging and no nonvascular cause.

For this report, we defined incident CVD as CHD (definite
and probable MI, definite CHD death, resuscitated cardiac ar-
rest, definite angina, and probable angina associated with coro-
nary revascularization), stroke (fetal or nonfatal), or other
atherosclerotic CVD death. Follow-up went from the baseline
examination until the first CVD event, loss to follow-up, death,
or January 12, 2005, whichever came first.

STATISTICAL ANALYSIS

From the 6814 MESA participants, we excluded 77 who were
missing both of the carotid IMT measures, 5 who were discov-
ered to have had CVD events before baseline, and 34 with no
follow-up data, leaving 6698 participants for analysis. For most
analyses, we either (1) categorized carotid IMT and CAC into
3 groups (the bottom 50% and the 2 upper quartiles) to ac-
commodate the fact that 50% of participants had a CAC score
of 0 or (2) treated IMT and the natural logarithm (ln) of (CAC
score + 1) as continuous variables. The ln(CAC score + 1) trans-
f ormation better normalized the CAC distribution. We used Cox
proportional hazard regression to estimate hazard ratios (HRs).
We performed tests for nonproportional hazards using Shoen-
feld residuals; all results were nonsignificant. Covariates for mul-
tiple variables models included age (continuous), sex, race/ethnicity (4 groups), smoking (current, former, or never),
diabetes (yes or no), blood pressure (6 categories according to
the Sixth Report of the Joint National Committee on Preven-
tion, Detection, Evaluation, and Treatment of High Blood
Pressure, including medications), high-density lipoprotein and total
cholesterol level (continuous), and use of lipid-lowering medica-
tion (yes or no). We compared the strength of the associa-
t ion for IMT vs CAC score based on the relative size of their
HRs and the corresponding χ² or z score of the HRs. We
also compared IMT and CAC associations with receiver oper-
at ing characteristic curves modeling carotid IMT and ln(CAC
score + 1) as continuous variables in Cox models. In the
Figure, rates were calculated for “low, medium, and high” values of
z score maximum IMT and CAC score using intervals as previ-
ously described. All analyses were performed using STATA 9.2
(StataCorp, College Station, Texas) statistical software.

RESULTS

The MESA sample for this analysis comprised 6698 adults
aged 45 to 84 years at baseline (3161 men and 3537 women).
During 23735 person-years of follow-up, we identi-
 fied 222 incident CVD events (159 CHD events [61 MI,
81 angina, 3 resuscitated cardiac arrest, 13 CHD deaths];
59 stroke events [3 of which included a CHD event];
and 7 other atherosclerotic CVD deaths). Of the MESA
sample, 50% had detectable CAC. The mean (SD) value
was 2.2 (2.5) for ln(CAC score + 1), 1.0 (0.6) mm for
maximum internal carotid IMT, 0.8 (0.19) mm for maxi-
 mum common carotid IMT, and 0.00 (1.00) for z score
maximum IMT.

As given in Table 1, the 3 measures of carotid IMT
were all positively associated with incident CVD, with age-
, race/ethnicity-, and sex-adjusted HRs for the high-
est vs lowest quartile of 3.3 (95% confidence interval [CI],
2.1-5.2) for the maximum internal carotid IMT, 2.7 (95%
CI, 1.4-3.8) for the maximum common carotid IMT, and
3.8 (95% CI, 2.2-6.4) for the z score maximum IMT (all
P < .001). The remaining IMT analyses therefore fo-
cused on z score maximum IMT. For CAC score (Table 1),
the HRs of CVD increased across categories, with the age-
, race/ethnicity-, and sex-adjusted HR being 6.0 (95% CI,
3.9-9.1) for the highest CAC score quartile vs a CAC score
of 0 (P < .001). The results for CHD risk (data not shown)
were similar. For reference to recommended clinical cut points for CAC score,1,3 the age-, race/ethnicity-, and sex-
adjusted HRs for CAC scores of 0, 1 to 99, 100 to 399,
and 400 or greater were 1 [Reference], 4.7 (95% CI,
2.5-8.7), 11.5 (95% CI, 6.2-21.5), and 16.1 (95% CI,
8.5-30.8), respectively (data not shown in tables).

When put in the same model, CAC score was more
strongly associated with both CVD and CHD compared
with IMT (Table 2). The multivariable-adjusted HRs
of CVD and CHD per 1-SD increment were 1.9 (95% CI,
1.6-2.2) and 2.3 (95% CI, 1.9-3.8), respectively, for
ln(CAC score + 1), compared with 1.2 (95% CI, 1.0-
1.3) and 1.1 (95% CI, 1.0-1.3) for z score maximum IMT.
Furthermore, the scores were larger and P values were
smaller for the CAC association. In contrast, for stroke,
only z score maximum IMT was statistically significant
(P = .01) with multivariable-adjusted HR of 1.3 (95% CI,
1.1-1.7), while the HR for ln(CAC + 1) was 1.1 (95% CI,
0.8-1.4).

A categorical analysis (Table 3) also suggested that CAC
score was a better predictor of incident CVD and CHD than
was IMT. For example, the multivariable-adjusted HRs of
CAC for the highest quartile vs lowest 50th percentile were
8.2 (95% CI, 4.5-15.1; P < .001) for CAC and 1.7 (95% CI,
1.1-2.7; P = .07) for z score maximum IMT.

In supplemental research, we restricted our analyses to
subjects at intermediate CHD risk, based on a Framing-
ham risk score of 1% to 2% per year (n = 1841, with 54
### Table 1. Hazard Ratios (HRs) for an Incident Cardiovascular Disease Event in Relation to Quartiles of Maximal Carotid IMT or CAC Score (MESA, 2000-2004)

<table>
<thead>
<tr>
<th>Measure&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Quartile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td><strong>Max internal IMT</strong></td>
<td></td>
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<tr>
<td>Range, mm</td>
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<tr>
<td>0.37 to 0.68</td>
<td>0.68 to 0.85</td>
<td>0.85 to 1.28</td>
<td>1.28 to 5.66</td>
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<td></td>
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<tr>
<td>No. of events</td>
<td>24</td>
<td>33</td>
<td>39</td>
<td>122</td>
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<tr>
<td>Person-years</td>
<td>5745</td>
<td>6130</td>
<td>5977</td>
<td>5510</td>
<td></td>
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<tr>
<td>Crude HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.3 (0.8-2.2)</td>
<td>1.6 (0.9-2.6)</td>
<td>5.3 (3.4-8.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, race-, and sex-adjusted HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.2 (0.7-2.1)</td>
<td>1.3 (0.7-2.1)</td>
<td>3.3 (2.1-5.2)</td>
<td></td>
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<tr>
<td><strong>Max common IMT</strong></td>
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<tr>
<td>Range, mm</td>
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<td>0.40 to 0.74</td>
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<td>0.97 to 2.45</td>
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<tr>
<td>No. of events</td>
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<td>37</td>
<td>61</td>
<td>102</td>
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<tr>
<td>Person-years</td>
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<td>5843</td>
<td>6133</td>
<td>5705</td>
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<tr>
<td>Crude HR (95% CI)</td>
<td>1 [Reference]</td>
<td>2.1 (1.1-4.0)</td>
<td>2.1 (1.1-3.9)</td>
<td>4.9 (2.7-8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, race-, and sex-adjusted HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.3 (0.8-2.2)</td>
<td>1.7 (1.0-2.8)</td>
<td>2.3 (1.4-3.8)</td>
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<tr>
<td><strong>z Score max IMT</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Range</td>
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</tr>
<tr>
<td>-2.06 to -0.70</td>
<td>-0.70 to -0.20</td>
<td>-0.20 to 0.49</td>
<td>0.49 to 9.51</td>
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<tr>
<td>No. of events</td>
<td>18</td>
<td>31</td>
<td>52</td>
<td>121</td>
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</tr>
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<td>Person-years</td>
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<td>6036</td>
<td>6052</td>
<td>5621</td>
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</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.7 (1.0-3.1)</td>
<td>2.9 (1.7-4.9)</td>
<td>7.2 (4.4-11.8)</td>
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<tr>
<td>Age-, race-, and sex-adjusted HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.4 (0.8-2.5)</td>
<td>1.9 (1.1-3.5)</td>
<td>3.8 (2.2-6.4)</td>
<td></td>
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<tr>
<td><strong>CAC score</strong></td>
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<td></td>
</tr>
<tr>
<td>Range</td>
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</tr>
<tr>
<td>0</td>
<td>1 to 880</td>
<td>88 to 6315</td>
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</tr>
<tr>
<td>No. of events</td>
<td>33</td>
<td>53</td>
<td>141</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>12,420</td>
<td>5995</td>
<td>5572</td>
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</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>1 [Reference]</td>
<td>3.3 (2.1-5.1)</td>
<td>9.5 (6.5-13.9)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age-, race-, and sex-adjusted HR (95% CI)</td>
<td>1 [Reference]</td>
<td>2.6 (1.6-4.0)</td>
<td>6.0 (3.9-9.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAC, coronary artery calcium; CI, confidence interval; IMT, intima-media thickness; max, maximum; MESA, Multi-Ethnic Study of Atherosclerosis.

<sup>a</sup>Coronary artery calcium score and each IMT variable were in separate models.

### Table 2. Hazard Ratios (HRs) for an Incident CVD, CHD, or Stroke Event in Relation to a 1-SD Increment of Maximal Carotid IMT or CAC Score (MESA, 2000-2004)

<table>
<thead>
<tr>
<th>Measure&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HR Per 1-SD Increment (95% CI)</th>
<th>z Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD (n = 222)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, race-, and sex-adjusted</td>
<td>1.3 (1.1-1.4)</td>
<td>4.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>z Score max IMT</td>
<td>1.2 (1.0-1.3)</td>
<td>2.7</td>
<td>.007</td>
</tr>
<tr>
<td>ln(CAC score + 1)</td>
<td>1.9 (1.6-2.2)</td>
<td>7.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>CHD (n = 159)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, race-, and sex-adjusted</td>
<td>1.2 (1.0-1.4)</td>
<td>2.5</td>
<td>.01</td>
</tr>
<tr>
<td>z Score max IMT</td>
<td>1.1 (1.0-1.3)</td>
<td>1.5</td>
<td>.12</td>
</tr>
<tr>
<td>ln(CAC score + 1)</td>
<td>2.3 (1.9-2.8)</td>
<td>7.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Stroke (n = 59)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, race-, and sex-adjusted</td>
<td>1.4 (1.2-1.8)</td>
<td>3.5</td>
<td>.001</td>
</tr>
<tr>
<td>z Score max IMT</td>
<td>1.1 (0.8-1.5)</td>
<td>0.8</td>
<td>.41</td>
</tr>
<tr>
<td>ln(CAC score + 1)</td>
<td>1.3 (1.1-1.7)</td>
<td>2.5</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; IMT, intima-media thickness; ln, natural logarithm; max, maximum; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.

<sup>a</sup>Coronary artery calcium and IMT were included as continuous variables in the same model. A 1-SD increment was 1.0 for z score max IMT and 2.5 for ln(CAC score + 1).

Adjusted as described in the “Methods” section.
CHD events). Among them, the multivariable-adjusted HRs of CHD per 1-SD increment were 2.4 (95% CI, 1.7-3.3; \( P < .001 \)) for ln(CAC score + 1) and 1.3 (95% CI, 1.0-1.6; \( P < .05 \)) for z score maximum IMT when both were included in the model. In the same subgroup at intermediate Framingham risk, for CVD (81 events), the multivariable-adjusted HRs were 1.8 (95% CI, 1.4-2.2; \( P < .001 \)) for ln(CAC score + 1) and 1.4 (95% CI, 1.1-1.6; \( P = .001 \)) for z score maximum IMT.

The Figure shows crude rates of incident CVD by 9 joint categories of z score maximum IMT and CAC score. Rates of CVD were between 1% and 2% per year for those with (1) a moderate level of CAC and high IMT or (2) a high level of CAC and low IMT. Rates of CVD were greater than 2% per year for those with a high level of CAC and either a moderate or high level of IMT. Those with a CAC score of 0 and either low or moderate IMT had almost no events during this follow-up period. Findings for CHD were similar (data not shown).

Findings from receiver operating characteristic curve analysis suggested that CAC score was a better predictor of CVD incidence than was carotid IMT. With the multiple risk factors in the model for CVD, the area under the curve (AUC) was 0.772 (95% CI, 0.74-0.80). After adding z score maximum IMT, the AUC was 0.782 (95% CI, 0.75-0.81); after substituting CAC score for IMT, the AUC was 0.808 (95% CI, 0.78-0.83); and after including both IMT and CAC score, the AUC was 0.811 (95% CI, 0.78-0.84). A similar receiver operating characteristic curve analysis for CHD produced AUCs of 0.771 (95% CI, 0.74-0.80) for risk factors alone, 0.782 (95% CI, 0.75-0.82) for risk factors plus IMT, 0.823 (95% CI, 0.79-0.85) for risk factors plus CAC score, and 0.824 (95% CI, 0.79-0.85) for risk factors plus CAC score and IMT.

### Table 3. Hazard Ratios (HRs) for an Incident CVD, CHD, or Stroke Event in Relation to Quartiles of Maximal Carotid IMT or CAC Score (MESA, 2000-2004)

<table>
<thead>
<tr>
<th>Measure(^a)</th>
<th>&lt;.50th Percentile</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>( \chi^2 ) Statistic</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD (n = 222)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age-, race-, and sex-adjusted</td>
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</tr>
<tr>
<td>z Score max IMT</td>
<td>1 [Reference]</td>
<td>1.4 (0.9-2.0)</td>
<td>2.2 (1.5-3.2)</td>
<td>20.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAC score</td>
<td>1 [Reference]</td>
<td>2.6 (1.6-4.1)</td>
<td>5.3 (3.4-8.2)</td>
<td>58.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariable-adjusted(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>z Score max IMT</td>
<td>1 [Reference]</td>
<td>1.3 (0.9-2.0)</td>
<td>1.7 (1.2-2.5)</td>
<td>8.7</td>
<td>.01</td>
</tr>
<tr>
<td>CAC score</td>
<td>1 [Reference]</td>
<td>2.3 (1.5-3.7)</td>
<td>4.4 (2.8-6.8)</td>
<td>44.7</td>
<td>&lt;.001</td>
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<tr>
<td><strong>CHD (n = 159)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, race-, and sex-adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>z Score max IMT</td>
<td>1 [Reference]</td>
<td>1.5 (1.0-2.4)</td>
<td>2.1 (1.4-3.3)</td>
<td>11.5</td>
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</tr>
<tr>
<td>CAC score</td>
<td>1 [Reference]</td>
<td>4.1 (2.2-7.7)</td>
<td>10.3 (5.6-18.9)</td>
<td>63.8</td>
<td>&lt;.001</td>
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<tr>
<td>Multivariable-adjusted(^b)</td>
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</tr>
<tr>
<td>z Score max IMT</td>
<td>1 [Reference]</td>
<td>1.5 (0.9-2.3)</td>
<td>1.7 (1.1-2.7)</td>
<td>5.4</td>
<td>.07</td>
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<tr>
<td>CAC score</td>
<td>1 [Reference]</td>
<td>3.5 (1.9-6.6)</td>
<td>8.2 (4.5-15.1)</td>
<td>51.5</td>
<td>&lt;.001</td>
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<tr>
<td><strong>Stroke (n = 59)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-, race-, and sex-adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>z Score max IMT</td>
<td>1 [Reference]</td>
<td>0.9 (0.4-2.0)</td>
<td>2.4 (1.2-4.7)</td>
<td>9.9</td>
<td>&lt;.01</td>
</tr>
<tr>
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<td>1 [Reference]</td>
<td>1.4 (0.8-2.7)</td>
<td>1.2 (0.6-2.4)</td>
<td>0.7</td>
<td>.70</td>
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<tr>
<td>Multivariable-adjusted(^b)</td>
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</tr>
<tr>
<td>z Score max IMT</td>
<td>1 [Reference]</td>
<td>0.9 (0.4-2.0)</td>
<td>1.8 (0.9-3.6)</td>
<td>4.7</td>
<td>.10</td>
</tr>
<tr>
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<td>1.3 (0.6-2.1)</td>
<td>1.0 (0.5-2.1)</td>
<td>0.6</td>
<td>.73</td>
</tr>
</tbody>
</table>

Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; IMT, intima-media thickness; max, maximum; MESA, Multi-Ethnic Study of Atherosclerosis.\(^a\)

**COMMENT**

This prospective analysis of the MESA cohort who were initially free of symptomatic CVD found that carotid maximum IMT and CAC score, 2 measures of subclinical atherosclerosis, predicted future CVD events. However, CAC score was the better predictor for CHD and total CVD. Intima-media thickness was a modestly better predictor of stroke than CAC score, although there were few stroke events. The associations observed were consistent with those reported by meta-analyses of prospective studies of each subclinical measure of atherosclerosis studied separately.\(^1,2\) They were somewhat inconsistent with a small prospective study in elderly people, in which common carotid IMT was similar to CAC in predicting CVD and CHD.\(^13\) It may be that IMT becomes more predictive of CVD in old age, but the smaller sample size of that study also may have limited its ability to show differences between CAC and IMT associations with CVD.

Although previous consensus statements indicated that CAC score and IMT are global atherosclerosis measures and either might be used clinically for refinement of CVD risk assessment,\(^1,20\) our data suggest that in asymptomatic 45- to 84-year-old US adults, CAC score may be the better choice over IMT. As judged by proportional hazards modeling and by the AUC, CAC score added more to CVD prediction,
beyond traditional risk factors, than did IMT. Coronary artery calcium was also associated with CHD more strongly than IMT within the group of individuals at intermediate risk, for whom a subclinical atherosclerosis assessment may be most appropriate. When more CVD events accrue in MESA, we can more thoroughly address the issue of what novel measures (eg, CAC score, IMT, C-reactive protein level, and others) might improve CVD risk prediction in intermediate-risk patients.

The modestly better prediction of stroke by IMT and clearly better prediction of CHD by CAC score likely reflects their different vascular territories. The potential choice between measuring CAC or IMT or neither in preventive cardiology depends on other considerations as well (eg, differences in radiation exposure, cost, and availability). The CAC score may be most relevant in the United States, where CHD is common. If risk of stroke in families with histories of early stroke were a concern, then carotid IMT may be very relevant. Also, in MESA, there are substantial ethnic differences in CAC score (highest in whites), and to a lesser degree for IMT (highest in African Americans), which may have an impact on clinical use.

Strengths of this study include its multiethnic sample, standardized subclinical atherosclerosis assessments and risk factor measurements, and its reliance on symptomatic end points to avoid detection bias related to CVD events being diagnosed more readily in subjects with known subclinical atherosclerosis. Limitations include, first, the relatively short follow-up period and the relatively small number of strokes to date. Results could be different for long-term CVD prediction, especially as this population ages and the ratio of strokes to CHD events increases. Second, the shapes of distributions differ for IMT and CAC, with many 0 values for CAC score. However, our analyses using both categorical and continuous measures of IMT and CAC placed them on a more comparable footing. Third, although all end points were symptomatic, we included both “hard” CHD (MI and CHD death) and “soft” CHD (angina) to provide adequate statistical power. Fourth, for ethical reasons, we felt compelled to report high CAC and IMT values to participants and refer them to their physicians. More participants were referred for high CAC score (17%) than for high IMT (1%), which could have affected our findings if participants changed risk factors differentially. Yet, this seems unlikely, since a clinical trial suggested that telling patients their CAC score does not motivate significant health behavior change.

In conclusion, although whether and how to use bioimaging tests for subclinical atherosclerosis remains a topic of debate, this study found that CAC score was a better predictor of subsequent CVD events than was carotid IMT.

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Author Contributions: Dr Folsom had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Folsom, Kronmal, Detrano, O’Leary, Bild, Bluemke, Shea, and Tracy. Acquisition of data: Folsom, Kronmal, Detrano, O’Leary, Budoff, Liu, Shea, Szkoł, Tracy, Watson, and Burke. Analysis and interpretation of data: Folsom, Kronmal, O’Leary, Bild, Budoff, Liu, and Burke. Drafting of the manuscript: Folsom, Kronmal, and O’Leary. Critical revision of the manuscript for important intellectual content: Kronmal, O’Leary, Bild, Bluemke, Budoff, Liu, Shea, Szkoł, Tracy, Watson, and Burke. Statistical analysis: Kronmal and Liu. Obtained funding: Kronmal, O’Leary, Bluemke, Shea, Tracy, and Burke. Administrative, technical, and material support: Kronmal, O’Leary, Bild, Shea, and Tracy. Study supervision: O’Leary, Budoff, Shea, and Watson.

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1. Greenland P, Bonow RO, Brundage BH, et al; American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACC/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography); Society of Atherosclerosis Imaging and Prevention; Soci-
Coronary artery calcium outperforms carotid intima-media thickness as a noninvasive index of prevalent coronary artery stenosis.


