Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis

Michael H. Criqui, Julie O. Denenberg, Robyn L. McClelland, Matthew A. Allison, Joachim H. Ix, Alan Guerci, Kevin P. Cohoon, Preethi Srikanthan, Karol E. Watson, Nathan D. Wong

Objective—To evaluate the predictive value of abdominal aortic calcium (AAC) for incident cardiovascular disease (CVD) independent of coronary artery calcium (CAC).

Approach and Results—We evaluated the association of AAC with CVD in 1974 men and women aged 45 to 84 years randomly selected from the Multi-Ethnic Study of Atherosclerosis participants who had complete AAC and CAC data from computed tomographic scans. AAC and CAC were each divided into following 3 percentile categories: 0 to 50th, 51st to 75th, and 76th to 100th. During a mean of 5.5 years of follow-up, there were 50 hard coronary heart disease events, 83 hard CVD events, 30 fatal CVD events, and 105 total deaths. In multivariable-adjusted Cox models including both AAC and CAC, comparing the fourth quartile with the ≤50th percentile, AAC and CAC were each significantly and independently predictive of hard coronary heart disease and hard CVD, with hazard ratios ranging from 2.4 to 4.4. For CVD mortality, the hazard ratio was highly significant for the fourth quartile of AAC, 5.9 (P≤0.01), whereas the association for the fourth quartile of CAC (hazard ratio, 2.1) was not significant. For total mortality, the fourth quartile hazard ratio for AAC was 2.7 (P=0.001), and for CAC, it was 1.9, P=0.04. Area under the receiver operating characteristic curve analyses showed improvement for both AAC and CAC separately, although improvement was greater with CAC for hard coronary heart disease and hard CVD, and greater with AAC for CVD mortality and total mortality. Sensitivity analyses defining AAC and CAC as continuous variables mirrored these results.

Conclusions—AAC and CAC predicted hard coronary heart disease and hard CVD events independent of one another. Only AAC was independently related to CVD mortality, and AAC showed a stronger association than CAC with total mortality. (Arterioscler Thromb Vasc Biol. 2014;34:1574-1579.)

Key Words: aortic diseases • calcium • cardiovascular diseases • diagnostic imaging • epidemiology

The standard methodology for predicting cardiovascular disease (CVD) risk has used risk scores consisting of traditional risk factors1-3 and, in some cases, novel markers as well. The General Framingham Risk Score is a risk score used for combined CVD end points. To improve CVD risk prediction beyond such risk scores, several subclinical CVD measures have been investigated. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) have demonstrated the incremental value of several subclinical CVD measures, including the ankle-brachial index,4 carotid intimal medial thickness by ultrasound,5 endothelial function,6 and coronary artery calcium (CAC).7 The incremental value of these measures ranges from modest (endothelial function) to high (CAC). However, among these, only CAC uses ionizing radiation. The independent value of CAC as a risk marker has now been confirmed in multiple studies.8 In addition, CAC has been shown to substantially improve classification of risk status in the MESA.9 Calcified atherosclerosis in the abdominal aorta (abdominal aortic calcium or AAC) measured in plain lumbar radiographs has also been shown to predict incident CVD.10-13 A recent meta-analysis of 10 studies concluded that the association of AAC with CVD was graded and consistent.13 However, minimal data exist for the relation of AAC, quantified by computed tomography, with CVD outcomes. In addition, whether AAC predicts CVD independent of CAC is unclear. We report here the association of AAC with cardiovascular morbidity and mortality in the MESA, when CAC was simultaneously considered in CVD risk prediction.

Materials and Methods

Materials and Methods are available in the online-only Supplement.
Results

Table 1 shows the distribution of CVD risk factors, including those used in the General Framingham Risk Score, across the 3 categories of AAC and 3 categories of CAC, and event rates for each of the 4 end points. The Agatston score ranges are given for each of the categories and illustrate the much higher scores for AAC versus CAC, and the skewed distribution of both AAC and CAC. At higher levels of AAC, participants were older, more likely to be white, and had higher blood pressure, and were more likely to be on hypotensive therapy. At higher levels of CAC, these trends were similarly present along with a greater male percentage, lower high-density lipoprotein-cholesterol, and a higher prevalence of diabetes mellitus. Statin use did not differ significantly by level of AAC or CAC. For both hard coronary heart disease (CHD) and hard CVD, incidence rates per 1000 person-years were 1.1 to 3.0 in the CAC and AAC 0 to 50th percentile categories, but increased to 11.1 and 12.1 for hard CHD in the fourth quartile of CAC and AAC, respectively, and 17.1 and 19.2 for hard CVD in the fourth quartile of CAC and AAC, respectively. Rates in the third quartiles were intermediate and higher for CAC than for AAC. For both CVD mortality and total mortality, higher rates were present for the fourth quartile of AAC, 7.0 and 21.3, respectively, compared with CAC, 5.5 and 18.0, respectively.

Of the 9 possible combined AAC/CAC categories (3 AAC categories multiplied by 3 CAC categories in Table 1), event rates were uniformly low in the 5 categories with either AAC or CAC ≤50th percentile, constituting 63% of the cohort. Thus, these categories were combined as the reference group for the Kaplan–Meier curves, and the remaining 4 groups were considered individually. Thirteen percent of the cohort was in the group with both AAC and CAC in the highest quartile, whereas in the remaining 3 groups, each contained 8% of the cohort. Figure A shows the rates for hard CHD, and Figure B shows the rates for hard CVD. The highest rates for both hard CHD and hard CVD occurred when both AAC and CAC were in the highest quartile, with the next highest rates for either AAC or CAC alone in the highest quartile, with intermediate

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>AAC 0–50th Percentile</th>
<th>AAC 51st–75th Percentile</th>
<th>AAC 76th–100th Percentile</th>
<th>CAC 0–50th Percentile</th>
<th>CAC 51st–75th Percentile</th>
<th>CAC 76th–100th Percentile</th>
<th>P Value Test for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agatston score range</td>
<td>0–241</td>
<td>242–1437</td>
<td>1438–20952</td>
<td>0–9</td>
<td>9–136</td>
<td>136–4508</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>n</td>
<td>983</td>
<td>491</td>
<td>492</td>
<td>983</td>
<td>491</td>
<td>492</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>60.4 (8.5)</td>
<td>66.5 (8.8)</td>
<td>71.4 (8.2)</td>
<td>&lt;0.01</td>
<td>60.9 (8.7)</td>
<td>67.0 (9.3)</td>
<td>69.9 (8.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>459 (46.7)</td>
<td>278 (56.6)</td>
<td>253 (51.4)</td>
<td>0.22</td>
<td>399 (40.6)</td>
<td>264 (53.8)</td>
<td>327 (66.5)</td>
</tr>
<tr>
<td>Non-Hispanic white, n (%)</td>
<td>324 (33.0)</td>
<td>204 (41.6)</td>
<td>262 (53.3)</td>
<td>&lt;0.01</td>
<td>336 (34.2)</td>
<td>200 (40.7)</td>
<td>254 (51.3)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>246 (25.0)</td>
<td>95 (19.4)</td>
<td>70 (14.2)</td>
<td>&lt;0.01</td>
<td>252 (25.6)</td>
<td>84 (17.1)</td>
<td>116 (23.6)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>271 (27.6)</td>
<td>127 (25.9)</td>
<td>108 (22.0)</td>
<td>0.02</td>
<td>258 (25.3)</td>
<td>136 (27.7)</td>
<td>112 (22.8)</td>
</tr>
<tr>
<td>Chinese, n (%)</td>
<td>142 (14.5)</td>
<td>65 (13.2)</td>
<td>52 (10.6)</td>
<td>0.04</td>
<td>137 (13.9)</td>
<td>71 (14.5)</td>
<td>51 (10.4)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>187.1 (35.4)</td>
<td>183.7 (34.3)</td>
<td>185.9 (37.6)</td>
<td>0.73</td>
<td>185.8 (34.7)</td>
<td>188.0 (35.7)</td>
<td>184.2 (37.6)</td>
</tr>
<tr>
<td>HDL-C, mean (SD), mg/dL</td>
<td>52.7 (15.4)</td>
<td>50.2 (14.6)</td>
<td>50.6 (15.2)</td>
<td>0.03</td>
<td>52.6 (15.4)</td>
<td>51.0 (15.0)</td>
<td>49.9 (14.8)</td>
</tr>
<tr>
<td>Systolic BP, mean (SD), mm Hg</td>
<td>119.7 (19.9)</td>
<td>127.3 (21.5)</td>
<td>129.4 (20.1)</td>
<td>&lt;0.01</td>
<td>120.6 (20.4)</td>
<td>126.6 (20.4)</td>
<td>128.2 (21.0)</td>
</tr>
<tr>
<td>BP treatment, n (%)</td>
<td>321 (32.7)</td>
<td>237 (48.3)</td>
<td>301 (61.2)</td>
<td>&lt;0.01</td>
<td>327 (33.3)</td>
<td>237 (48.3)</td>
<td>295 (60.0)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>94 (9.6)</td>
<td>70 (14.3)</td>
<td>56 (11.4)</td>
<td>0.50</td>
<td>121 (12.3)</td>
<td>52 (10.6)</td>
<td>47 (9.6)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>65 (6.6)</td>
<td>49 (10.0)</td>
<td>43 (8.7)</td>
<td>0.26</td>
<td>64 (6.5)</td>
<td>42 (8.6)</td>
<td>51 (10.4)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>234 (23.8)</td>
<td>94 (19.1)</td>
<td>135 (27.4)</td>
<td>0.29</td>
<td>232 (23.6)</td>
<td>115 (23.4)</td>
<td>116 (23.6)</td>
</tr>
</tbody>
</table>

Table 1. Ethnicity, Risk Factors for the General Framingham Risk Score, and Events by Categories of AAC and CAC

AAC indicates abdominal aortic calcium; BP, blood pressure; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; and HDL-C, high-density lipoprotein-cholesterol.

*Hard CHD indicates myocardial infarction, resuscitated cardiac arrest, and coronary heart disease death.
†Hard CVD indicates myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease death, and stroke death.
‡CVD mortality indicates death from atherosclerotic coronary heart disease, stroke, atherosclerotic disease other than coronary disease or stroke, or other cardiovascular disease not defined.
rates when AAC and CAC were both in the third quartile. The overall log-rank \( P \) value was <0.0001. Figure C shows the results for CVD mortality. Here, mortality was greatest for the 2 groups with AAC in the fourth quartile, and the group with only CAC in the fourth quartile showed intermediate risk, log-rank \( P \) value of <0.0001. Figure D shows the results for total mortality, where similarly mortality was highest with AAC in the fourth quartile, but with only CAC in the fourth quartile an intermediate risk was present, log-rank \( P \) value of <0.0001.

Table 2 shows the General Framingham Risk Score and ethnicity-adjusted Cox models. Models first show results for the AAC and CAC categories alone, and then to explore the independence of AAC and CAC, a model with AAC and CAC additionally adjusted for each other. Table 2 shows that for CHD, there were significant associations for the fourth quartiles of AAC and CAC, with hazard ratios (HRs) of 4.1 and 6.1, respectively, and that with mutual adjustment both HRs were attenuated but remained significant, with the HR for CAC (4.4) higher than that for AAC (2.4). For CVD, there were significant associations for the fourth quartiles of AAC and CAC, with HRs of 4.0 and 4.2, respectively, and with mutual adjustment both HRs were attenuated but remained significant, with the HR for AAC (2.7) similar to that for CAC (2.9). HRs were also elevated for the third quartile, but significant only for CAC. For CVD mortality, the fourth quartile of AAC showed a strong hazard, HR=7.8, with some attenuation after mutual adjustment, HR=5.9, \( P=0.01 \), whereas the fourth quartile of CAC showed no significant association after mutual adjustment, HR=2.1, \( P=NS \). For total mortality, the HR for the fourth quartile of AAC after mutual adjustment was 2.7, \( P<0.001 \), whereas the HR for the fourth quartile of CAC was 1.9, \( P=0.04 \).

Models exploring potential effect modification by sex or ethnicity showed nonsignificant interaction terms, and there was no significant interaction between the AAC and CAC categories. Tests for nonproportional hazards across AAC and CAC categories using Schoenfeld residuals were all nonsignificant.

Table 3 shows the receiver operating characteristic curve (area under the curve or AUC) analyses. Both AAC and CAC increased the AUC for both hard CHD and hard CVD, but the result was significant only for CAC, and when considered together, AAC added little to CAC. For CVD mortality, the results were reversed with only AAC significant and addition of CAC adding little to AAC. For total mortality, the increase for AAC was greater than CAC, but both were significant, and the highest AUC occurred when both were in the model.

The results of sensitivity analyses using log-transformed continuous measures of AAC and CAC, ln(AAC+1) and ln(CAC+1), mirrored these results. In models containing both variables, for ln(AAC+1), the HR per SD for CHD was 1.5 (\( P=0.11 \)), for CVD 1.5 (\( P=0.02 \)), for CVD mortality 3.3 (\( P<0.01 \)), and for
total mortality 1.8 ($P \leq 0.01$). For ln(CAC+1), the HRs were 1.9 ($P \leq 0.01$), 1.5 ($P = 0.02$), 1.2 ($P = 0.54$), and 1.3 ($P = 0.04$), respectively. These results confirm the somewhat stronger predictive power of CAC for hard CHD and the much stronger predictive power of AAC for CVD mortality and total mortality.

Following the recommendation of the recently published American College of Cardiology/the American Heart Association guideline on the assessment of cardiovascular risk to inform treatment decisions in patients considered uncertain by quantitative risk assessment,15 we compared a CAC cut point of 300 Agatston units (the 85th percentile in these data) with the same percentile cut point for AAC (2754). The results are shown in Table 4. With both AAC and CAC in the model, AAC was highly significantly associated for each of the 4 outcomes, with HRs ranging from 2.33 to 3.92, whereas CAC was not significantly associated with any of the 4 outcomes, with HRs ranging from 1.22 to 1.53.

### Discussion

Among subclinical CVD measures, CAC has shown the largest HRs for subsequent CVD events.7,8 In the MESA, participants with CAC scores in the top quartile (Agatston scores >100) had an ≈7-fold risk of a major coronary event during the first 5 years of follow-up.7 However, using relatively crude measures of AAC from standard lumbar radiographs, AAC has also been reported to be strongly associated with future CVD events.10–13 We have shown in the MESA that CAC was moderately correlated with AAC in participants with at least some AAC and CAC, with a Spearman correlation coefficient of 0.38 ($P <0.0001$).16 Here, each calcium measure attenuated the other somewhat, but the fourth quartile for both measures remained independently significant in predicting hard CHD and hard CVD. However, only AAC was predictive of CVD mortality. CAC showed higher AUC values for hard CHD and hard CVD, but AAC showed higher AUCs for CVD mortality and total mortality. There are no prior reports available that have directly evaluated the prognostic value of AAC measured by computed tomography for CVD events with adjustment for CAC and the General Framingham Risk Score simultaneously.

Several other subclinical CVD measures, including the ankle-brachial index,4,17,18 carotid intimal medial thickness,5,19 among others, have also been shown to be predictive of CVD events. However, the use of AAC instead of CAC in these models may provide additional information about the risk of CVD events.

### Table 2. Cox Models for Hard CHD, Hard CVD, CVD Mortality, and Total Mortality for Categorical Definition of AAC and CAC, Adjusted for the General Framingham Risk Score and Ethnicity

<table>
<thead>
<tr>
<th>Percentile categories</th>
<th>Hard CHD</th>
<th>Hard CVD</th>
<th>CVD Mortality</th>
<th>Total Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAC only, percentile</td>
<td>HR</td>
<td>$P$ Value</td>
<td>HR</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>0–50th</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>51st–75th</td>
<td>1.49</td>
<td>0.383</td>
<td>1.87</td>
<td>0.069</td>
</tr>
<tr>
<td>&gt;75th</td>
<td>4.06</td>
<td>&lt;0.001</td>
<td>4.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAC only, percentile</td>
<td>HR</td>
<td>$P$ Value</td>
<td>HR</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>0–50th</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>51st–75th</td>
<td>4.74</td>
<td>0.001</td>
<td>3.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;75th</td>
<td>6.14</td>
<td>&lt;0.001</td>
<td>4.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AAC and CAC, percentile</td>
<td>HR</td>
<td>$P$ Value</td>
<td>HR</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>AAC 0–50th</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>AAC 51st–75th</td>
<td>1.08</td>
<td>0.875</td>
<td>1.46</td>
<td>0.279</td>
</tr>
<tr>
<td>AAC &gt;75th</td>
<td>2.38</td>
<td>0.038</td>
<td>2.66</td>
<td>0.003</td>
</tr>
<tr>
<td>CAC 0–50th</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>CAC 51st–75th</td>
<td>3.91</td>
<td>0.006</td>
<td>2.92</td>
<td>0.003</td>
</tr>
<tr>
<td>CAC &gt;75th</td>
<td>4.35</td>
<td>0.004</td>
<td>2.90</td>
<td>0.003</td>
</tr>
</tbody>
</table>

AAC indicates abdominal aortic calcium; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; and HR, hazard ratio.

### Table 3. AUC for Each of the 4 Outcomes With Addition of Categorical Definitions of AAC and CAC to the Base Model*

<table>
<thead>
<tr>
<th>Percentile Categories</th>
<th>CHD Hard</th>
<th>CVD Hard</th>
<th>CVD Mortality</th>
<th>Total Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model†</td>
<td>0.749</td>
<td>0.749</td>
<td>0.768</td>
<td>0.716</td>
</tr>
<tr>
<td>AAC categories</td>
<td>0.772</td>
<td>0.210</td>
<td>0.816</td>
<td>0.753</td>
</tr>
<tr>
<td>CAC categories</td>
<td>0.807</td>
<td>&lt;0.001</td>
<td>0.802</td>
<td>0.743</td>
</tr>
<tr>
<td>Both</td>
<td>0.805</td>
<td>0.007</td>
<td>0.821</td>
<td>0.762</td>
</tr>
</tbody>
</table>

AAC indicates abdominal aortic calcium; CAC, coronary artery calcium; CHD, coronary heart disease; and CVD, cardiovascular disease.

*Vs base model.

†Adjusted for the General Framingham Risk Score and ethnicity.
endothelial function, subclavian stenosis, and thoracic aortic calcium have been reported to show independent predictive value for incident CVD events. Most of these measures have been reported to improve the area under the receiver operating characteristic curve. However, subclinical measures of CVD are correlated with each other, some highly so, and in evaluating a given subclinical CVD measure many reports have not adjusted for other correlated subclinical CVD measures, leaving the independence of the reported findings in doubt.

For CVD mortality, the independent HR for the fourth quartile of AAC was 5.9 versus 2.1 for CAC. For total mortality, the independent HR for AAC was 2.7, compared with 1.9 for CAC. AAC has been reported to be associated with both CVD and total mortality previously. However, these associations have been of variable strength. The reason for the discrepancy between hard CHD and hard CVD, and fatal outcomes here is unclear. AAC is more common, occurs earlier, is better correlated with risk factors than CAC, and seems to reflect atherosclerotic burden beyond CAC.

A possibility is that the strong mortality association for AAC reflects the known significance of the total atherosclerotic burden for mortality beyond the extent of coronary disease per se. Of interest, a recent report from the Framingham study showed that AAC, but not CAC, was significantly associated with total mortality.

Prior studies that have compared other subclinical CVD measures with CAC within the same cohort have not reported another subclinical measure equal to or superior to CAC in predicting CVD outcomes. Based on the data presented here, AAC could improve risk prediction. People below the 50th percentile for either measure had a low risk of events. These data suggest that AAC would add to CAC in predicting hard CVD and that AAC would be the stronger subclinical CVD measure for improving CVD mortality and total mortality risk prediction.

In the analyses of AAC and CAC in Table 4 where the CAC cut point of 300 recommended in the recent American College of Cardiology/the American Heart Association guideline was compared with the percentile equivalent for AAC, AAC was significant for each of the 4 end points, whereas CAC showed no significant association for any of the end points.

Strengths of this study include standardized and validated protocols in a multiethnic cohort, careful measurement of potentially confounding variables, and follow-up in a cohort free of CVD at baseline. Limitations include the modest number of CVD deaths, although the difference in the predictive value of AAC versus CAC for CVD mortality was marked. The cohort studied here was an ≈30% subset of the full MESA cohort. However, they were randomly selected and thus representative of the larger MESA cohort. To allow comparable assessment of the extent of AAC in participants, our AAC measure was limited to the distal 8 cm of the abdominal aorta. This choice seems reasonable because previous studies have shown the highest concentration of AAC is near the bifurcation. The MESA cohort was not a random sample of the US population, but MESA was structured for multiethnic representation. Finally, given the sparse data on the predictive value of AAC independent of CAC, our results will need to be replicated by others.

In conclusion, in a multiethnic cohort, both AAC and CAC were independently predictive for hard CHD and CVD. For CVD mortality, only AAC was independently predictive. The apparent predictive value of CAC for mortality was attenuated when AAC was added to the model. Given guidelines for screening for CAC in asymptomatic intermediate-risk people and the independent value of AAC in these data, further research should consider whether the added clinical use of AAC beyond CAC might warrant recommendations for CVD risk assessment.

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Table 4. Cox Models for Hard CHD, Hard CVD, CVD Mortality, and Total Mortality for ≥85th Percentile of AAC (2754) and CAC (300), Adjusted for the General Framingham Risk Score and Ethnicity

<table>
<thead>
<tr>
<th>Events</th>
<th>Hard CHD</th>
<th>Hard CVD</th>
<th>CVD Mortality</th>
<th>Total Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1930</td>
<td>1930</td>
<td>1966</td>
<td>1966</td>
</tr>
<tr>
<td>Percentile categories</td>
<td>HR</td>
<td>P Value</td>
<td>HR</td>
<td>P Value</td>
</tr>
<tr>
<td>0–84th</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>≥85th</td>
<td>4.34</td>
<td>&lt;0.001</td>
<td>2.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0–84th</td>
<td>1.00</td>
<td>Ref.</td>
<td>1.00</td>
<td>Ref.</td>
</tr>
<tr>
<td>≥85th</td>
<td>2.15</td>
<td>0.014</td>
<td>1.98</td>
<td>0.005</td>
</tr>
</tbody>
</table>

AAC indicates abdominal aortic calcium; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; and HR, hazard ratio.

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Disclosures
N. Wong is a Consultant (significant) at Re-Engineering Healthcare, Inc. The other authors report no conflicts.

References

Significance
In previous studies of subclinical atherosclerosis measures, CAC has shown the strongest independent relationship to CVD events and has similarly shown the greatest increase in CVD risk prediction above standard cardiovascular risk scores based on risk factors. This study is first to report a subclinical atherosclerosis measure, AAC, that shows a similar predictive value to CAC for hard CHD and hard CVD events, and a stronger association than CAC for CVD mortality. Importantly, the predictive values of AAC and CAC are independent and additive, such that overall risk prediction improved when both were measured simultaneously. These results, if conﬁrmed elsewhere, suggest that future recommendations for CVD risk assessment should consider the added clinical utility of AAC measurement.
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In the article by Criqui et al, which appeared in the July 2014 issue of the journal (Arterioscler Thromb Vasc Biol. 2014;34:1574–1579. DOI: 10.1161/ATVBAHA.114.303268), a correction was needed.

In the Figure, there are errors in the legend. The first category, “AAC 0–50% or CAC 0–50%” is correct. The other 4 categories all have the word “or” where the word “and” should be used in order for them to be mutually exclusive categories. Thus, the remaining categories should read as follows: “AAC 51–75% and CAC 51–75%,” “AAC 51–75% and CAC 76–100%,” “AAC 76–100% and CAC 51–75%,” and “AAC 76–100% and CAC 76–100%.”

The authors apologize for the error.

The online version of the article has been corrected and is available at http://atvb.ahajournals.org/content/34/7/1574.
Material and Methods Study

Participants
The MESA is an ongoing prospective cohort study in 6814 individuals aged 45 to 84 years, who were free of known clinical CVD at baseline. 47% were male and 38% were white, 28% black, 22% Hispanic, and 12% Chinese. Exam 1 was from 2000 to 2002 at six field centers: Baltimore, MD; Chicago, Ill; Los Angeles, CA; New York, NY; St Paul, MN; and Winston-Salem, NC. The study design, recruitment methods, examination components, and data collection have been described in detail and are available on line at http://www.mesa-nhlbi.org. After the MESA began, an ancillary study measured AAC and CAC in a random sample of MESA participants at Exams 2 and 3, conducted between August 2002 and September 2005, at five of the six MESA field centers (all except Baltimore, MD). Of 1990 participants satisfying eligibility criteria, 1974 had complete AAC and CAC data for these analyses. Both MESA and the Aortic Calcium Ancillary Study were approved by the IRBs at all participating centers and all participants gave written informed consent.

Risk Factor Assessment
Standardized questionnaires were used to obtain information about participant demographics, medical history, and medication usage, including current blood pressure and cholesterol-lowering medications. Resting blood pressure was measured in a standardized manner. Blood measures obtained after a 12-hour fast included glucose, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C). Diabetes was defined as a fasting blood glucose >125 mg/dL or use of hypoglycemic medications. Participants were classified by never, former, or current use of cigarettes.

AAC and CAC Assessment
AAC assessment has been previously described. AAC was measured using either an electron-beam CT scanner or a multidetector CT mode scanner. Images were reconstructed in a 35-cm field of view with a slice thickness of 6 mm (EBCT scanners) or a 5mm (multidetector scanners). A 15 cm segment of the abdominal aorta was scanned using the L5-S1 disc space as a reference point for the aortic bifurcation. Because of individual anatomic differences in the location of the bifurcation, calcium in the wall of the distal abdominal aorta in the 8-cm segment proximal to the aortic bifurcation was used as the AAC index value for these analyses, since all subjects had this 8 cm segment visualized. The Agatston score for AAC was calculated, and participants were given their score and told that the significance of AAC was unknown. Each participant was scanned twice for CAC, measured at the same exam using the same site-specific scanners. The methodology for acquisition and interpretation of the scans, as well as reproducibility of the readings, has been reported previously. The participants were told their CAC Agatston score, that the presence of CAC represented hardening of the coronary arteries, and that the amount of CAC was less than average, average, or greater than average. CAC and AAC scans were read centrally at the MESA CT Reading Center, and were brightness adjusted using a standard phantom to control for any scanner differences.

CVD and mortality follow-up
Follow-up began at the time of the AAC and CAC examination (Exam 2 or 3) and continued until the first CVD event, death, loss to follow-up, or the tenth follow-up call, which took place between May 2009 and June 2011. The mean follow-up was 5.5 years, with a median of 5.3 years. Details of CVD event ascertainment have been published. For this report, we analyzed four separate endpoints: 1) hard CHD, defined as myocardial infarction, resuscitated cardiac arrest or CHD death, 2) hard CVD, defined as hard CHD, stroke or stroke death, 3) CVD death, defined as coronary, stroke, or other atherosclerotic or CVD death; and 4) all-cause mortality. Softer CVD endpoints such as angina and revascularization were not analyzed since these outcomes could have been biased by knowledge of CAC status.
**Statistical analysis**

Of the 1974 participants, we excluded eight persons with missing data, leaving 1966 for mortality analysis. For hard CHD and hard CVD, we excluded an additional 36 persons who had had a nonfatal CVD event between Exam 1 and the baseline for follow-up for these analyses (Exam 2/3), leaving 1930 for analysis. Because AAC is much more extensive than CAC and thus shows much higher Agatston scores, percentile categories were used for these analyses, which allowed an unbiased comparison between AAC and CAC across the full distribution of participants’ scores. To allow unbiased comparisons across genders and ethnic groups, percentile cutpoints were derived using data from all 1974 participants. The cutpoints studied were 0-50th, 51-75th, or 76 -100th. Since about half the participants had CAC scores of zero, cutpoints below the 50th percentile were not possible. We calculated CVD event and mortality rates for these categories of AAC and CAC. Kaplan-Meier survival curves were constructed for combined categories of AAC and CAC. Cox proportional hazard regression was used to estimate hazard ratios (HR) for time to event, adjusting for covariates. Cox models were adjusted for ethnicity and the General Framingham Risk Score (GFRS). The variables in the GFRS are age, sex, TC, HDL-C, SBP, BP treatment, smoking, and diabetes. We used the GFRS to allow a standardized comparison with other reports of the incremental value of subclinical measures. We also included ethnicity in the multivariable model since the MESA was a multi-ethnic cohort. The incremental value of AAC and CAC for the prediction of CVD events was evaluated by the increase in the area under the Receiver Operating Characteristic (ROC) curve, which appears to be the most valid methodology for evaluating improvement in risk prediction given recent concerns about newer reclassification indices. All analyses were performed using STATA version 10.1 (StataCorp, College Station, Texas) statistical software or SAS version 9.2 (Cary, North Carolina).

In additional sensitivity analyses, we assessed the predictive value of AAC and CAC as continuous variables throughout the full range including zero scores, defined as ln(AAC+1) and ln(CAC+1). Again, since AAC is more extensive with much higher Agatston scores, we conducted an unbiased comparison by using standardized coefficients for hazard ratios.

The recently published AAC/AHA guideline on the assessment of cardiovascular risk recommended a CAC cutpoint of 300 Agatston units to inform treatment decisions in patients considered uncertain by quantitative risk assessment. In our data 300 Agatston units was the 85th percentile for CAC. Thus, in additional analyses we alternatively compared CAC defined dichotomously with this cutpoint with AAC also using an 85th percentile cutpoint (2754 Agatston units).
References


