Calcified Atherosclerosis in Different Vascular Beds and the Risk of Mortality

Matthew A. Allison, Stephanie Hsi, Christina L. Wassel, Cindy Morgan, Joachim H. Ix, C. Michael Wright, Michael H. Criqui

Objective—The goal of this study was to determine differences in risks for total and cause-specific mortality related to calcified atherosclerosis in different vascular beds.

Methods and Results—A total of 4544 patients underwent computed tomography scans that were interrogated for calcium in different vascular beds. Mortality assessment was conducted by death certificate adjudication. At baseline, the mean age was 56.8 years, and 43% were female. After an average of 7.8 years, there were 163 deaths. With full adjustment, the presence of calcium in the thoracic aorta (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.2–3.5), carotids (HR, 1.60; CI, 1.1–2.5), and iliac (HR, 1.67; CI, 1.0–2.9) arteries were associated with total mortality, whereas the presence of coronary calcium was associated with cardiovascular disease (CVD) mortality (HR, 3.4; CI, 0.8–10.9). For severity of calcium burden, a 1-SD increment in the iliac arteries was the strongest predictor for all types of mortality. C-statistics were not significantly larger when noncoronary vascular beds were added to models with CVD risk factors or CVD risk factors plus coronary artery calcium.

Conclusion—The associations between calcified atherosclerosis and mortality differ by vascular bed, suggesting that the location and severity of calcification in different vascular beds provide unique information for mortality. (Arterioscler Thromb Vasc Biol. 2012;32:00-00.)

Key Words: calcification □ coronary artery disease □ electron beam computed tomography □ outcomes □ peripheral arterial disease

Coronary artery calcium (CAC) is a significant predictor of future cardiac events independent of traditional risk factors.1 When added to the traditional cardiovascular disease (CVD) risk factors, CAC improves the ability to correctly classify individual risk for incident CVD.2 Similarly, the presence of calcified atherosclerosis in the thoracic aorta is independently associated with total mortality,3 with earlier studies showing that the presence of calcified atherosclerosis of the abdominal aorta is associated with incident fatal and nonfatal CVD.4 To our knowledge, no study has examined the association between calcified atherosclerosis in 5 distinct vascular beds and incident mortality. In this report, we present results of a study that tested the ability of calcified atherosclerosis from computed tomography (CT) in the carotid, coronary, thoracic aorta, abdominal aorta, and iliac vascular beds to predict incident total, CVD, and non-CVD mortality.

Methods

Subjects

From November 30, 2000, to July 30, 2003, 4544 consecutive patients underwent whole-body CT scanning as an adjunct to their preventive health care at a university-affiliated disease prevention center in San Diego, California. Most patients were asymptomatic and either self-referred or were referred on the recommendation of their personal physician. Participants completed a detailed health history questionnaire that collected information on hypertension, diabetes, high cholesterol, smoking, medications, family history of coronary heart disease, diet, exercise, and prior surgeries. The Human Research Protection Program at the University of California at San Diego approved the study protocol.

Imaging

CT was conducted using an Imatron C-150 scanner. At the time of the scan, calcium was quantified in the carotid and coronary arteries using the method described by Agatston et al.3 For the thoracic and abdominal aorta, as well as the iliac arteries, image files were retrospectively examined for the presence and extent of calcium due to atherosclerosis. Atherosclerotic calcification was defined as a plaque of ≥1 mm² (3 contiguous pixels) with a density of ≥130 Hounsfield units. Volume averaging was avoided by scoring each homogeneous slice thickness segment separately.

Data from the left and right sides were combined to give the extent of calcium in the carotid and iliac beds. The coronary calcium score consisted of calcified lesions in the left main, left anterior descending, left circumflex, and right coronary arteries. The thoracic aorta was defined as the segment from the aortic root to the diaphragm, and the abdominal aorta was the segment from the diaphragm to the iliac bifurcation.

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Table 1. Cohort Characteristics by Vital Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alive (n = 4291)</th>
<th>All Deceased* (n = 163)</th>
<th>Non-CVD Deceased† (n = 89)</th>
<th>CVD Deceased† (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y‡</td>
<td>56.3 (10.9)</td>
<td>69.2 (11.0)</td>
<td>67.6 (11.0)</td>
<td>73.3 (9.6)</td>
</tr>
<tr>
<td>Gender, female§</td>
<td>1862 (43.4)</td>
<td>62 (38)</td>
<td>37 (41.6)</td>
<td>12 (30.0)</td>
</tr>
<tr>
<td>BMI, kg/m²‡</td>
<td>27.0 (4.6)</td>
<td>26.7 (4.8)</td>
<td>26.7 (5.1)</td>
<td>26.9 (4.7)</td>
</tr>
<tr>
<td>Percentage body fat, %‡</td>
<td>29.7 (7.8)</td>
<td>31.4 (6.6)</td>
<td>31.3 (6.7)</td>
<td>32.7 (5.9)</td>
</tr>
<tr>
<td>Current smoker§</td>
<td>419 (9.8)</td>
<td>24 (14.7)</td>
<td>16 (18)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Former smoker§</td>
<td>1429 (33.3)</td>
<td>72 (44.2)</td>
<td>37 (41.6)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>Diabetes§</td>
<td>128 (3.0)</td>
<td>15 (9.2)</td>
<td>8 (9)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Dyslipidemia§</td>
<td>1403 (32.7)</td>
<td>62 (38)</td>
<td>33 (37.1)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Hypertension§</td>
<td>1196 (27.9)</td>
<td>80 (49.1)</td>
<td>47 (52.8)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Family history of CVD§</td>
<td>1059 (24.7)</td>
<td>46 (28.2)</td>
<td>22 (24.7)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Carotid calcium¶</td>
<td>31%/0</td>
<td>69%/90</td>
<td>69%/88</td>
<td>78%/160</td>
</tr>
<tr>
<td>Coronary calcium¶</td>
<td>55%/3</td>
<td>82%/190</td>
<td>79%/124</td>
<td>93%/252</td>
</tr>
<tr>
<td>Thoracic aortic calcium¶</td>
<td>37%/0</td>
<td>79%/461</td>
<td>78%/461</td>
<td>93%/535</td>
</tr>
<tr>
<td>Abdominal aortic calcium¶</td>
<td>54%/16</td>
<td>87%/1386</td>
<td>85%/1359</td>
<td>95%/1808</td>
</tr>
<tr>
<td>Iliac artery calcium¶</td>
<td>49%/0</td>
<td>82%/949</td>
<td>82%/1094</td>
<td>90%/1404</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; BMI, body mass index.
*From Social Security Death Index.
†From available death certificates.
‡Mean (SD).
§Frequency (%).
¶Prevalence/median.

Laboratory

Body mass index was determined by measuring the height and weight from patients who were lightly clothed (without shoes). Percentage of body fat was determined by electric bioimpedance (Omron, Schaumburg, IL). Randomly selected patients (i.e., potentially nonfasting) were obtained using the Cholestec LDX system (Hayward, CA). Diabetes was defined as having a fasting plasma glucose level greater than 126 mg/dL or use of antidiabetic medication. Dyslipidemia was defined as having a total cholesterol to high-density lipoprotein cholesterol ratio greater than 5 or use of a cholesterol-lowering medication. After the patient had rested for 5 minutes in the seated position, trained technicians obtained systolic and diastolic blood pressures in the right upper extremity. Hypertension was defined as having a systolic blood pressure greater than 140 or diastolic pressure greater than 90 or use of hypertension medication for this condition. A family history of premature coronary heart disease was defined as a first-degree family member (parent or sibling) diagnosed with heart disease before the age of 55.

Vital Status Ascertainment

Beginning in 2005 and continuing annually until August 31, 2009, the vital status of all patients was cross-referenced with the Social Security Death Index. Patients identified in the Social Security Death Index were cross-referenced with the study records to confirm their identity. Pertinent information from the Social Security Death Index was recorded and subsequently used with other patient identifiers for requesting death certificates from the appropriate institutions. Once received, the cause of death was adjudicated by a physician (M.A.A.) with expertise in coding causes of death for other collaborative studies. Using the underlying cause of death, the coding was then categorized into CVD and non-CVD causes.

Statistical Analysis

Normally distributed continuous variables were described by means/standard deviation (SD), and categorical variables were described as frequencies/percentage. As the distribution of calcium in the different vascular beds was highly skewed, we dichotomized these variables into present (score > 0) versus absent (score of 0) and also natural log-transformed these variables for the analyses when the quantity of calcium (plus 1) was used. Analysis of covariance was used to compute the age- and sex-adjusted differences in study variables by the presence versus absence of vascular calcium. Multivariable adjusted hazards of mortality were computed using Cox-proportional hazards models and satisfying the proportional hazards assumption. Differences in survival were tested using the log-rank (Mantel-Cox) test. Receiver operator characteristic analyses were conducted from logistic regression models, and the probability values were compared between different models using the method described by DeLong et al. Statistical significance was defined as a probability value < 0.05. Analyses were conducted using SPSS, version 16 (SPSS Inc, Chicago, IL), and SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

At the baseline clinic visit, the mean (SD) age was 56.8 (11.2) years, 43% were female, and 44% were either current or former smokers; 27% had a history of hypertension, 33% had a history of dyslipidemia, 3% had a history of diabetes, and 25% reported a family history of coronary heart disease. The prevalence of any calcium for the different vascular beds was as follows: carotid, 32.2%; coronary, 55.8%; thoracic aorta, 38.2%; abdominal aorta, 54.8%; and iliacs, 50.2%.

The average time from CT scan to censoring due to either mortality or end of study was 7.8 years. As of August 31, 2009, there were 163 (2.9%) deaths, for which we have received 129 death certificates. Of these, CVD was the underlying cause of death in 40 (31%), whereas 52 (40%) were due to cancer, 8 (6%) to infection, 7 (5%) to neurodegenerative disease, and the remainder (22 [18%]) to other causes.

Table 1 shows the characteristics of the patients by vital status. The mean age of those who died was 69.2 years, with...
those dying because of CVD being somewhat older (73.3). The rates of smoking, diabetes, dyslipidemia, hypertension, and family history of heart disease were higher in those who died from either non-CVD or CVD causes. Similarly, the prevalence and median calcium scores were higher in all vascular beds studied among those who died from either cause. Additionally, compared with the non-CVD and total mortality groups, calcium prevalence and scores were higher in the CVD mortality group.

For all of the vascular beds and compared with those with no calcium in a given bed, those who had any calcium in the different beds were significantly more likely to be older and male. With adjustment for age and sex, the prevalence of hypertension, diabetes, dyslipidemia, and former or current smoking was significantly higher in those with calcium in all of the different vascular beds. Body mass index was significantly higher in those with calcium in the carotids, coronaries, and iliac arteries, whereas the prevalence of a family history of CVD was significantly higher in those with calcium in any of the beds except for the carotids.

Figure. A, All-cause mortality for calcium in different vascular beds. CAR indicates carotid artery calcium; CAC, coronary artery calcium; TAC, thoracic aortic calcium; AAC, abdominal aortic calcium; ILIAC, iliac calcium. Significance of vascular bed comparisons: \( P < 0.05 \) for CAR vs CAC, CAR vs AAC, CAR vs ILIAC, CAC vs TAC, TAC vs AAC; \( P = 0.06 \) for TAC vs ILIAC. B, Noncardiovascular disease mortality for calcium in different vascular beds. Significance of vascular bed comparisons: \( P < 0.05 \) for CAR vs CAC, CAC vs TAC; \( P > 0.05 \) and \( P < 0.10 \) for CAR vs ILIAC, TAC vs AAC. C, Cardiovascular disease mortality for calcium in different vascular beds. Significance of vascular bed comparisons: \( P = 0.08 \) for CAC vs TAC.

Panels A through C of the Figure show Kaplan-Meier survival curves for total, CVD, and non-CVD mortality, respectively, as a function of calcium in the different vascular beds. For all vascular beds and compared with the absence of calcium in any given vascular bed, the presence of calcium in any vascular bed was associated with a significantly lower survival (\( P < 0.01 \) for all). For total mortality (Figure, A), those with any calcium in the carotid arteries had the lowest probability of survival, whereas those without any calcium in the abdominal aorta had the highest probability. The total mortality survival curves showed the least separation for those with CAC compared with those with no CAC and the largest separation for the presence/absence of calcium in the thoracic aorta. In comparing survival curves for the case when calcium was present in the different vascular beds, the curves for the carotid arteries and thoracic aorta were significantly different from the curves for the coronaries, abdominal aorta, and iliacs (\( P < 0.05 \) for all). The curves for these 3 beds were not significantly different from one another.
Conversely, when calcium was absent, there were no significant differences in the survival curves among the different vascular beds. The findings for non-CVD mortality (Figure, B) were essentially the same as those for total mortality.

The survival curves for CVD mortality (Figure, C) showed that those with any calcium in the thoracic aorta or carotid arteries had the lowest probability of survival, whereas those without any thoracic aortic calcium appeared to have the highest probability of CVD survival. As for total mortality, survival curves for CVD mortality showed the least separation for those with CAC compared with those with no CAC and the largest separation for the presence/absence of calcium in the thoracic aorta. However, pairwise comparisons of the different survival curves found only 1 case where the curves were marginally difference (P=0.08): the presence of calcium in the thoracic aorta compared with calcium in the coronary arteries.

The multivariable associations between the presence of calcium in a given vascular bed and total, CVD, and non-CVD mortality are provided in Table 2. With adjustment for age and sex, the presence of calcium in any of the different vascular beds, except the abdominal aorta, was associated with a significantly increased hazard for total mortality, with the largest magnitude of associations being for calcium in the thoracic aorta. Additional adjustment for body mass index and the traditional CVD risk factors attenuated the magnitudes of the associations such that only calcium in either the carotid arteries or thoracic aorta remained statistically significantly associated with incident total mortality. For the associations with non-CVD mortality, the magnitudes of the associations were somewhat less than those for total mortality, but in general, the patterns of the associations were similar. As before, the largest hazard ratio was found for the thoracic aorta. For CVD mortality and after adjustment for the CVD risk factors, the association was modestly stronger for CAC (hazard ratio [HR], 3.37; 95% CI, 1.79 to 6.03) than for thoracic aortic calcium (3.01, 95% CI, 1.67 to 5.37).

We also examined the associations between increasing increments of calcium in the different vascular beds and mortality. For total mortality (Table 3) and after adjustment for age, sex, body mass index, and the traditional CVD risk factors in model 3, a 1-SD increment of log-transformed calcium was significantly (P<0.01) associated with an increased mortality risk for all of the vascular beds. The hazard ratios ranged from 1.63 to 1.22, with the largest hazard being associated with calcium in the iliac arteries and the lowest being associated with the coronary arteries. For both CVD and non-CVD mortality, the largest association was found for calcium in the iliac arteries.

To account for the potential effect of systemic calcification, to model 3 in Tables 2 and 3 we added adjustment for the presence of calcium, as well as increasing increments of the total calcium score, in the other vascular beds (data not shown). For all types of mortality in Table 2, the results were not materially changed when we also adjusted for the presence of calcium in any of the beds that were not the primary predictor variable for a given model (eg, noncoronary calcium when CAC was the primary predictor variable). Conversely, for the calcium burden analyses, when we adjusted for increasing increments of calcium in the other vascular
beds that were not the primary predictor variable (Table 3), the associations were attenuated to statistical nonsignificance.

The results of the receiver operator characteristic analyses are presented in Supplemental Table I, available online at http://atvb.ahajournals.org. Compared with the area under the curve for when CAC was added to the traditional CVD risk factors and for total, non-CVD, and CVD mortality, the areas under the curve were larger (albeit modestly) for nearly all comparisons when the different noncoronary vascular beds were separately added to the CVD risk factors (Supplemental Table IA). In all cases, the areas under the curve increased when each noncoronary vascular bed was separately added to a model that contained both the CVD risk factors and CAC (Supplemental Table IB).

Interactions between gender and calcium in the different vascular beds for the 3 different types of mortality were assessed. None were significant.

**Discussion**

In this historical cohort study of individuals presenting for preventive medicine services at a university-affiliated disease prevention center, calcium in different vascular beds was associated with higher risk of total, non-CVD, and CVD mortality. Specifically, the presence of calcium in the thoracic aorta or the carotid arteries was significantly associated with an increased hazard of total and non-CVD mortality. The presence of calcium in the thoracic aorta was also associated with a higher risk for CVD mortality, but this association was smaller than that for the presence of calcium in the coronary arteries. Notably, C-statistics from receiver operator characteristic analyses revealed that the areas under the curves were not significantly larger when the noncoronary vascular beds were added to models with either the traditional CVD risk factors alone or those that also included CAC. In contrast and after adjustment for the CVD risk factors, increasing increments of calcium in any of the vascular beds were, in general, associated with total, CVD, and non-CVD mortality. In these analyses, the largest magnitude of the associations was found for calcium in the iliac arteries, followed by calcium in the abdominal aorta. Notably, addition of the traditional CVD risk factors to the multivariable models resulted in the associations becoming nonsignificant for a number of the vascular beds. This suggests that the association between calcium in the different vascular beds and incident mortality is partially mediated by the CVD risk factors. Taken together, these results indicate that the presence of or increasing increments of calcium are risk factors of not only CVD but also non-CVD causes of mortality. However, based on the receiver operator characteristic analyses, it appears that the presence of calcium in other vascular beds provides limited additional information for discriminating fatal events beyond that provided by traditional CVD risk factors or CAC alone.

An interesting finding from this study is that when calcium was dichotomized into present versus absent, the vascular beds significantly associated with the different types of mortality were different than when calcium was analyzed as a continuous variable. This suggests that the unit of measurement of calcium (ie, presence versus continuous increments) may provide distinct information with respect to the relevance of a given vascular bed to mortality risk. In this respect,
up to the age of 70 years, the prevalence of calcium in the thoracic aorta is less than that in the coronaries, iliacs, and abdominal aorta. After the age of 70, the prevalence of thoracic aortic calcium increases exponentially and surpasses that in all other vascular beds.\(^7\) The pattern for the carotid arteries is similar to that for the thoracic aorta.\(^9\) Moreover, those who have calcium in the thoracic aorta are likely to have calcium in other vascular beds, whereas those with calcium in the abdominal aorta or coronary arteries have a higher probability of having isolated disease.\(^9,10\) These results suggest that the presence of calcium in the thoracic aorta or carotid arteries is indicative of more extensive atherosclerotic burden and may therefore be associated with the highest risk of morbidity and mortality. However, in terms of extent of calcification, the iliac arteries showed the strongest association for all mortality end points, consistent with the well-known association between the severity of peripheral artery disease and both CVD and total mortality.\(^11\)

An important finding from our study is that the presence and extent of arterial calcification in several vascular beds were strongly associated with non-CVD mortality and that these associations were independent of age, body mass index, and smoking, which are risk factors for a number of non-CVD conditions. One potential explanation for this finding is a chronic inflammatory state that characterizes many chronic diseases, including cancer, infection, and neurodegenerative disorders,\(^12,13\) all of which are underlying causes of non-CVD death in our cohort. In support of this hypothesis, atherosclerotic calcification has been linked to higher levels of inflammatory markers, such as C-reactive protein, interleukin-6, and adipokines.\(^14,15\) However, these associations tend to be modest and often become nonsignificant with adjustment for traditional CVD risk factors. Alternatively, previous data have suggested that atherosclerosis represents an abnormality in innate (phagocytic leukocytes, complement, and proinflammatory cytokines) and adaptive (T cells, antibodies, and immunoregulatory cytokines) immune function.\(^16\) If this is true, immune function abnormalities may be a common pathophysiology in the association between calcified atherosclerosis and both CVD and non-CVD mortality. Investigation into other potential mediators of the association between arterial calcification and non-CVD chronic diseases is needed to clarify these relationships.

There have been many studies showing that CAC is significantly associated with both total and CVD mortality.\(^18,19\) The literature for noncoronary calcium and mortality is more limited. Previous studies have shown that thoracic aortic calcification is significantly associated with fatal and nonfatal CVD events\(^21\) and total mortality\(^3,22\) independently of CAC, whereas calcification in the abdominal aorta is significantly associated with CVD mortality.\(^4\) Importantly, in the latter study, the calcium deposits were detected by lateral radiographs, making comparisons with the results of studies using CT difficult. We are aware of no studies that have examined the association between calcium in either the carotid or iliac arteries and mortality. Therefore, our report extends findings for abdominal aortic calcium showing that results are similar irrespective of measurement by plain radiography or CT and provides new data for carotid and iliac calcification.

The results of this study should not be construed as support for conducting whole-body scans with the sole purpose of determining risk of different types of mortality. Rather, this study indicates that vascular calcium found on diagnostic CT scans may be used for assessing risk, and that those done for lung screening may be most relevant because they would capture images of the thoracic aorta, which was found to have strong and significant associations with all types of mortality in our study. This is particularly germane, as a recent trial using CT of the chest for screening of smokers (which imparts much less radiation than a cardiac CT scan) was stopped early because of a highly significant benefit.\(^23\) Therefore, from a clinical perspective, the information on calcified atherosclerosis in the thoracic aorta could be considered by the health care provider to improve morbidity and mortality risk stratification, estimation of “arterial age,” and a potential motivational tool for patients.

Strengths of this study include a relatively large sample that was free of extant clinical disease at baseline, measurement of calcified atherosclerosis that spans many vascular beds, the use of a single CT scanner, and assessment of both total and cause specific mortality. Conversely, there are some limitations. The study population was a clinical sample and may not generalize to the larger community-living population, especially given the lower prevalence of diabetes in this cohort. Calculation determined by CT cannot distinguish between intimal and medial calcification. However, as the prevalence of diabetes was quite low in our population and medial calcification is typically seen in those with diabetes or end stage renal disease, we believe the possibility of misclassification is low. Finally, the number of cases of CVD mortality was relatively small and may have limited our ability to find significant associations for this outcome. Importantly, as we used the underlying cause of death from the death certificates in these analyses, there were likely several cases where CVD may have been a contributing (but not underlying) cause of death. As such, the associations with CVD mortality are likely conservative.

In conclusion, the results of this study indicate that higher levels of calcium in different vascular beds are associated not only with CVD mortality but also with non-CVD and total mortality. Moreover, the location of the arterial calcification appears to be relevant to the strength of the association with mortality, and the CVD risk factors appear to mediate some of this association. Notably, there are current recommendations and guidelines for the use of CAC in the CVD risk stratification.\(^24\) Given the results of the current study, future research is warranted to determine whether current recommendations on CAC measurements should be expanded to include calcium in other vascular beds.

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**Disclosures**

None.
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Mortality and Systemic Calcified Atherosclerosis

References


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**SUPPLEMENTAL MATERIAL**

### TABLE I – AREAS UNDER THE CURVE FROM RECEIVER OPERATOR CHARACTERISTIC ANALYSES

<table>
<thead>
<tr>
<th>Model</th>
<th>Total Mortality*</th>
<th>p</th>
<th>Non-CVD Mortality*</th>
<th>p</th>
<th>CVD Mortality*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Panel A – Traditional CVD Risk Factors + Other Vascular Bed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traditional RFs**</td>
<td>0.820 (0.783, 0.858)</td>
<td>REF*</td>
<td>0.784 (0.736, 0.833)</td>
<td>REF*</td>
<td>0.922 (0.890, 0.955)</td>
<td>REF*</td>
</tr>
<tr>
<td>TR + Carotid presence</td>
<td>0.828 (0.791, 0.864)</td>
<td>0.10</td>
<td>0.793 (0.744, 0.842)</td>
<td>0.23</td>
<td>0.927 (0.898, 0.956)</td>
<td>0.13</td>
</tr>
<tr>
<td>TR + CAC presence</td>
<td>0.825 (0.789, 0.862)</td>
<td>0.18</td>
<td>0.788 (0.740, 0.837)</td>
<td>0.45</td>
<td>0.928 (0.900, 0.956)</td>
<td>0.13</td>
</tr>
<tr>
<td>TR + TAC presence</td>
<td>0.828 (0.791, 0.865)</td>
<td>0.07</td>
<td>0.791 (0.743, 0.840)</td>
<td>0.17</td>
<td>0.929 (0.903, 0.955)</td>
<td>0.35</td>
</tr>
<tr>
<td>TR + AAC presence</td>
<td>0.826 (0.790, 0.862)</td>
<td>0.06</td>
<td>0.791 (0.745, 0.838)</td>
<td>0.13</td>
<td>0.926 (0.898, 0.955)</td>
<td>0.14</td>
</tr>
<tr>
<td>TR + Iliac presence</td>
<td>0.826 (0.789, 0.862)</td>
<td>0.11</td>
<td>0.792 (0.745, 0.839)</td>
<td>0.14</td>
<td>0.925 (0.896, 0.955)</td>
<td>0.21</td>
</tr>
<tr>
<td>TR + all vascular beds</td>
<td>0.836 (0.801, 0.872)</td>
<td>0.01</td>
<td>0.803 (0.755, 0.850)</td>
<td>0.03</td>
<td>0.934 (0.912, 0.956)</td>
<td>0.13</td>
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<tr>
<td><strong>Panel B – Traditional CVD Risk Factors + CAC + Other Vascular Bed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR + CAC presence</td>
<td>0.825 (0.789, 0.862)</td>
<td>REF*</td>
<td>0.788 (0.740, 0.837)</td>
<td>REF*</td>
<td>0.928 (0.900, 0.956)</td>
<td>REF*</td>
</tr>
<tr>
<td>TR + CAC + Carotid</td>
<td>0.831 (0.794, 0.867)</td>
<td>0.19</td>
<td>0.796 (0.747, 0.844)</td>
<td>0.31</td>
<td>0.930 (0.905, 0.956)</td>
<td>0.22</td>
</tr>
<tr>
<td>TR + CAC + TAC</td>
<td>0.832 (0.796, 0.868)</td>
<td>0.09</td>
<td>0.794 (0.747, 0.842)</td>
<td>0.21</td>
<td>0.932 (0.909, 0.956)</td>
<td>0.44</td>
</tr>
<tr>
<td>TR + CAC + AAC</td>
<td>0.830 (0.801, 0.872)</td>
<td>0.13</td>
<td>0.794 (0.747, 0.840)</td>
<td>0.21</td>
<td>0.930 (0.905, 0.956)</td>
<td>0.14</td>
</tr>
<tr>
<td>TR + CAC + Iliac</td>
<td>0.830 (0.794, 0.865)</td>
<td>0.14</td>
<td>0.795 (0.747, 0.842)</td>
<td>0.18</td>
<td>0.929 (0.903, 0.956)</td>
<td>0.37</td>
</tr>
<tr>
<td>TR + all vascular beds</td>
<td>0.836 (0.801, 0.872)</td>
<td>0.04</td>
<td>0.803 (0.755, 0.850)</td>
<td>0.09</td>
<td>0.934 (0.912, 0.956)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*AUC (95% Confidence Interval), **Includes age, gender, BMI, smoking, dyslipidemia, hypertension, diabetes
* REF = Reference group for Panel A; b REF = Reference group for Panel B
TR = Traditional CVD Risk Factors, CAR = carotid calcium, CAC = coronary artery calcium, TAC = thoracic aortic calcium, AAC = abdominal aortic calcium, ILAC = iliac calcium
석회화된 죽상동맥경화증은 동맥의 부위에 따라 사망률의 차이를 보인다.

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Summary

배경
서로 다른 혈관에서의 석회화된 죽상동맥경화증(calcified atherosclerosis)과 연관된 총 사망률과 원인별 사망률에 대한 위험도의 차이를 알아보고자 하였다.

방법 및 결과
총 4,544명의 환자를 대상으로 CT를 이용하여 혈관별 칼슘을 측정하였다. 사망률은 사망 진단서에 근거하였다. 기저 검사상 대상자들의 평균 나이는 56.8세였고 43%가 여성으로 구성되어 있었다. 평균 7.8년 동안 163명의 사망자가 있었다. 다른 혼란변수를 보정한 후에 흉부대동맥(HR, 2.1; 95% CI, 1.2-3.5), 경동맥(HR, 1.60; CI, 1.1-2.5), 장골동맥(HR, 1.67; CI, 1.0-2.9)에서의 칼슘의 존재가 총 사망률과 유의한 관련성이 있었다. 심혈관 위험인자와 관상동맥의 칼슘을 포함한 모델에서 추가적으로 비관상동맥의 칼슘을 추가한 경우에는 C-statistics상 유의한 차이를 보이지 않았다.

결론
석회화된 죽상동맥경화증과 사망률간의 연관관계는 혈관마다 다른 양상을 보인다. 이는 석회화가 생긴 혈관의 부위 및 심한 정도가 사망률에 대한 고유한 정보를 제공할 수 있다는 것을 의미한다.
관상동맥의 칼슘은 앞으로 심혈관질환 발생의 기존 위험인자와 독립적인 예측인자이다. 또한 홍부대동맥의 석회화는 총 사망률과 연관성이 있고 복부대동맥의 석회화는 심혈관질환 발생과 관련 있다는 기존의 연구들이 있었다. 이 연구에서는 경동맥, 관상동맥, 흉부대동맥, 복부대동맥, 장골동맥 5개의 다른 동맥혈관의 석회화, 석회화의 정도와 사망률을 관찰하였다. 결론적으로 혈관의 높은 칼슘침착이 심혈관 사망률을 높일 뿐 아니라 비심혈관 사망률 및 총 사망률도 증가시켰다. 동맥 석회화의 위치는 사망률과 연관성을 가지고 있었다.

2010년 무증상 성인에서 심혈관 위험도를 평가하는 ACCF/AHA 가이드라인에서의 CT를 이용한 관상동맥의 칼슘 측정(coronary artery calcium score, CAC score)의 권고안을 살펴보면 다음과 같다.

CAC score가 증가한 중등도의 위험도를 가진 환자(중등도의 Framingham risk score: FRS & CAC >300)는 연 2.8%의 심혈관 사망 또는 심근경색을 보인다. 이 검사는 여러 장점을 가지고 있지만 방사선에 노출된다는 단점을 가지고 있다. 그러므로 검사로 얻을 수 있는 이득과 손해를 잘 고려해서 검사를 시행하는 것이 바람직하다.

1) Benefit >> Risk: 중등도 위험군(FRS: 10-20% 10-year risk)
2) Benefit ≥ Risk: 저-중등도 위험도(FRS: 6-10% 10-year risk)
3) No Benefit: 저위험군(FRS: <6% 10-year risk)
4) Benefit >> Risk: 40세 이상의 무증상인 당뇨병 환자에서 관상동맥 칼슘 측정은 합리적이다.

결론적으로 검사로 얻을 수 있는 이득이 더 큰 위험도가 높은 환자를 대상으로 한 관상동맥 칼슘 측정법은 심혈관관계 위험도를 좀 더 객관적으로 예측할 수 있다는 장점이 있다.

REFERENCES
Calcified Atherosclerosis in Different Vascular Beds and the Risk of Mortality

Matthew A. Allison, Stephanie Hsi, Christina L. Wassel, Cindy Morgan, Joachim H. Ix, C. Michael Wright, Michael H. Criqui

Objective—The goal of this study was to determine differences in risks for total and cause-specific mortality related to calcified atherosclerosis in different vascular beds.

Methods and Results—A total of 4544 patients underwent computed tomography scans that were interrogated for calcium in different vascular beds. Mortality assessment was conducted by death certificate adjudication. At baseline, the mean age was 56.8 years, and 43% were female. After an average of 7.8 years, there were 163 deaths. With full adjustment, the presence of calcium in the thoracic aorta (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.2–3.5), carotids (HR, 1.60; CI, 1.1–2.5), and iliac (HR, 1.67; CI, 1.0–2.9) arteries were associated with total mortality, whereas the presence of coronary calcium was associated with cardiovascular disease (CVD) mortality (HR, 3.4; CI, 0.8–10.9). For severity of calcium burden, a 1-SD increment in the iliac arteries was the strongest predictor for all types of mortality. C-statistics were not significantly larger when noncoronary vascular beds were added to models with CVD risk factors or CVD risk factors plus coronary artery calcium.

Conclusion—The associations between calcified atherosclerosis and mortality differ by vascular bed, suggesting that the location and severity of calcification in different vascular beds provide unique information for mortality. (Arterioscler Thromb Vasc Biol. 2012;32:140-146.)

Key Words: calcification □ coronary artery disease □ electron beam computed tomography □ outcomes □ peripheral arterial disease

Coronary artery calcium (CAC) is a significant predictor of future cardiac events independent of traditional risk factors.1 When added to the traditional cardiovascular disease (CVD) risk factors, CAC improves the ability to correctly classify individual risk for incident CVD.2 Similarly, the presence of calcified atherosclerosis in the thoracic aorta is independently associated with total mortality,3 with earlier studies showing that the presence of calcified atherosclerosis of the abdominal aorta is associated with incident fatal and nonfatal CVD.4 To our knowledge, no study has examined the association between calcified atherosclerosis in 5 distinct vascular beds and incident mortality. In this report, we present results of a study that tested the ability of calcified atherosclerosis from computed tomography (CT) in the carotid, coronary, thoracic aorta, abdominal aorta, and iliac vascular beds to predict incident total, CVD, and non-CVD mortality.

Methods

Subjects

From November 30, 2000, to July 30, 2003, 4544 consecutive patients underwent whole-body CT scanning as an adjunct to their preventive health care at a university-affiliated disease prevention center in San Diego, California. Most patients were asymptomatic and either self-referred or were referred on the recommendation of their personal physician. Participants completed a detailed health history questionnaire that collected information on hypertension, diabetes, high cholesterol, smoking, medications, family history of coronary heart disease, diet, exercise, and prior surgeries. The Human Research Protection Program at the University of California at San Diego approved the study protocol.

Imaging

CT was conducted using an Imatron C-150 scanner. At the time of the scan, calcium was quantified in the carotid and coronary arteries using the method described by Agatston et al5 For the thoracic and abdominal aorta, as well as the iliac arteries, image files were retrospectively examined for the presence and extent of calcium due to atherosclerosis. Atherosclerotic calcification was defined as a plaque of ≥1 mm² (3 contiguous pixels) with a density of ≥130 Hounsfield units. Volume averaging was avoided by scoring each homogeneous slice thickness segment separately.

Data from the left and right sides were combined to give the extent of calcium in the carotid and iliac beds. The coronary calcium score consisted of calcified lesions in the left main, left anterior descending, left circumflex, and right coronary arteries. The thoracic aorta was defined as the segment from the aortic root to the diaphragm, and the abdominal aorta was the segment from the diaphragm to the iliac bifurcation.

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Laboratory

Body mass index was determined by measuring the height and weight from patients who were lightly clothed (without shoes). Percentage of body fat was determined by using the leg impedance analysis (Omron, Schaumburg, IL). Random (ie, potentially nonfasting) serum lipid and glucose measurements were obtained by finger-stick using the Cholestec LDX system (Hayward, CA). Diabetes was defined as having a blood glucose level greater than 126 mg/dL or use of antihyperglycemic medication. Dyslipidemia was defined as a total cholesterol to high-density lipoprotein cholesterol greater than 5 or use of a cholesterol-lowering medication. After the patient had rested for 5 minutes in the seated position, trained technicians obtained systolic and diastolic blood pressures in the right upper extremity. Hypertension was defined as having a systolic blood pressure greater than 140 or diastolic pressure greater than 90 or use of hypertensive medication for this condition. A family history of premature coronary heart disease was defined as a first-degree family member (parent or sibling) diagnosed with heart disease before the age of 55.

Vital Status Ascertainment

Beginning in 2005 and continuing annually until August 31, 2009, the vital status of all patients was cross-referenced with the Social Security Death Index. Patients identified in the Social Security Death Index were cross-referenced with the study records to confirm their identity. Pertinent information from the Social Security Death Index was recorded and subsequently used with other patient identifiers for requesting death certificates from the appropriate institutions. Once received, the cause of death was adjudicated by a physician (M.A.A.) with expertise in coding causes of death for other collaborative studies. Using the underlying cause of death, the coding was then categorized into CVD and non-CVD causes.

Statistical Analysis

Normally distributed continuous variables were described by means/standard deviation (SD), and categorical variables were described as frequencies/percentage. As the distribution of calcium in the different vascular beds was highly skewed, we dichotomized these variables into present (score >0) versus absent (score of 0) and also natural log-transformed these variables for the analyses when the quantity of calcium (plus 1) was used. Analysis of covariance was used to compare the age- and sex-adjusted differences in study variables by the presence versus absence of vascular calcium. Multivariable adjusted hazards of mortality were computed using Cox-proportional hazards models and satisfying the proportional hazards assumption. Differences in survival were tested using the log-rank (Mantel-Cox) test. Receiver operator characteristic analyses were conducted from logistic regression models, and the probability values were compared between different models using the method described by DeLong et al. Statistical significance was defined as a probability value <0.05. Analyses were conducted using SPSS, version 16 (SPSS Inc, Chicago, IL), and SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

At the baseline clinic visit, the mean (SD) age was 56.8 (11.2) years, 43% were female, and 44% were either current or former smokers; 27% had a history of hypertension, 33% had a history of dyslipidemia, 3% had a history of diabetes, and 25% reported a family history of coronary heart disease. The prevalence of any calcium for the different vascular beds was as follows: carotid, 32.2%; coronary, 55.8%; thoracic aorta, 38.2%; abdominal aorta, 54.8%; and iliacs, 50.2%.

The average time from CT scan to censoring due to either mortality or end of study was 7.8 years. As of August 31, 2009, there were 163 (2.9%) deaths, for which we have received 129 death certificates. Of these, CVD was the underlying cause of death in 40 (31%), whereas 52 (40%) were due to cancer, 8 (6%) to infection, 7 (5%) to neurodegenerative disease, and the remainder (22 [18%]) to other causes.

Table 1 shows the characteristics of the patients by vital status. The mean age of those who died was 69.2 years, with

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alive (n=4291)</th>
<th>All Deceased* (n=163)</th>
<th>Non-CVD Deceased† (n=89)</th>
<th>CVD Deceased‡ (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y‡</td>
<td>56.3 (10.9)</td>
<td>69.2 (11.0)</td>
<td>67.6 (11.0)</td>
<td>73.3 (9.6)</td>
</tr>
<tr>
<td>Gender, female§</td>
<td>1862 (43.4)</td>
<td>62 (38)</td>
<td>37 (41.6)</td>
<td>12 (30.0)</td>
</tr>
<tr>
<td>BMI, kg/m²‡</td>
<td>27.0 (4.6)</td>
<td>26.7 (4.8)</td>
<td>26.7 (5.1)</td>
<td>26.9 (4.7)</td>
</tr>
<tr>
<td>Percentage body fat, %‡</td>
<td>29.7 (7.8)</td>
<td>31.4 (6.6)</td>
<td>31.3 (6.7)</td>
<td>32.7 (5.9)</td>
</tr>
<tr>
<td>Current smoker§</td>
<td>419 (9.8)</td>
<td>24 (14.7)</td>
<td>16 (18)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Former smoker§</td>
<td>1429 (33.3)</td>
<td>72 (44.2)</td>
<td>37 (41.6)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>Diabetes§</td>
<td>128 (3.0)</td>
<td>15 (9.2)</td>
<td>8 (9)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Dyslipidemia§</td>
<td>1403 (32.7)</td>
<td>62 (38)</td>
<td>33 (37.1)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Hypertension§</td>
<td>1196 (27.9)</td>
<td>80 (49.1)</td>
<td>47 (52.8)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Family history of CVD§</td>
<td>1059 (24.7)</td>
<td>46 (28.2)</td>
<td>22 (24.7)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Carotid calcium¶</td>
<td>31%0</td>
<td>69%90</td>
<td>69%88</td>
<td>78%160</td>
</tr>
<tr>
<td>Coronary calcium¶</td>
<td>55%3</td>
<td>82%190</td>
<td>79%124</td>
<td>93%252</td>
</tr>
<tr>
<td>Thoracic aortic calcium¶</td>
<td>37%0</td>
<td>79%461</td>
<td>78%461</td>
<td>93%535</td>
</tr>
<tr>
<td>Abdominal aortic calcium¶</td>
<td>54%16</td>
<td>87%1386</td>
<td>85%1359</td>
<td>95%1808</td>
</tr>
<tr>
<td>Iliac artery calcium¶</td>
<td>49%0</td>
<td>82%949</td>
<td>82%1094</td>
<td>90%1404</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; BMI, body mass index.

*From Social Security Death Index.
†From available death certificates.
‡Mean (SD).
§Frequency (%).
¶Prevalence/median.
those dying because of CVD being somewhat older (73.3).
The rates of smoking, diabetes, dyslipidemia, hypertension,
and family history of heart disease were higher in those who
died from either non-CVD or CVD causes. Similarly, the
prevalence and median calcium scores were higher in all
vascular beds studied among those who died from either
cause. Additionally, compared with the non-CVD and total
mortality groups, calcium prevalence and scores were higher
in the CVD mortality group.

For all of the vascular beds and compared with those with
no calcium in a given bed, those who had any calcium in the
different beds were significantly more likely to be older and
male. With adjustment for age and sex, the prevalence of
hypertension, diabetes, dyslipidemia, and former or current
smoking was significantly higher in those with calcium in all
of the different vascular beds. Body mass index was signifi-
cantly higher in those with calcium in the carotids, coronar-
ies, and iliac arteries, whereas the prevalence of a family
history of CVD was significantly higher in those with
calcium in any of the beds except for the carotids.

Panels A through C of the Figure show Kaplan-Meier
survival curves for total, CVD, and non-CVD mortality,
respectively, as a function of calcium in the different vascular
beds. For all vascular beds and compared with the absence
of calcium in any given vascular bed, the presence of calcium in
any vascular bed was associated with a significantly lower
survival (P < 0.01 for all). For total mortality (Figure, A),
those with any calcium in the carotid arteries had the lowest
probability of survival, whereas those without any calcium in
the abdominal aorta had the highest probability. The total
mortality survival curves showed the least separation for
those with CAC compared with those with no CAC and the
largest separation for the presence/absence of calcium in the
thoracic aorta. In comparing survival curves for the case
when calcium was present in the different vascular beds, the
curves for the carotid arteries and thoracic aorta were signif-
icantly different from the curves for the coronaries, abdomi-
nal aorta, and iliacs (P < 0.05 for all). The curves for these 3
beds were not significantly different from one another.

Figure. A, All-cause mortality for calcium in different vascular beds. CAR indicates carotid artery calcium; CAC, coronary artery cal-
cium; TAC, thoracic aortic calcium; AAC, abdominal aortic calcium; ILIAC, iliac calcium. Significance of vascular bed comparisons:
P < 0.05 for CAR vs CAC, CAR vs AAC, CAR vs ILIAC, CAC vs TAC, TAC vs AAC; P = 0.06 for TAC vs ILIAC. B, Noncardiovascular dis-
ease mortality for calcium in different vascular beds. Significance of vascular bed comparisons: P < 0.05 for CAR vs CAC, CAC vs TAC;
P > 0.05 and P < 0.10 for CAR vs ILIAC, TAC vs AAC. C, Cardiovascular disease mortality for calcium in different vascular beds. Signifi-
cance of vascular bed comparisons: P = 0.08 for CAC vs TAC.
Conversely, when calcium was absent, there were no significant differences in the survival curves among the different vascular beds. The findings for non-CVD mortality (Figure, B) were essentially the same as those for total mortality.

The survival curves for CVD mortality (Figure, C) showed that those with any calcium in the thoracic aorta or carotid arteries had the lowest probability of survival, whereas those without any thoracic aortic calcium appeared to have the highest probability of CVD survival. As for total mortality, survival curves for CVD mortality showed the least separation for those with CAC compared with those with no CAC and the largest separation for the presence/absence of calcium in the thoracic aorta. However, pairwise comparisons of the different survival curves found only 1 case where the curves were marginally difference (P=0.08): the presence of calcium in the thoracic aorta compared with calcium in the coronary arteries.

The multivariable associations between the presence of calcium in a given vascular bed and total, CVD, and non-CVD mortality are provided in Table 2. With adjustment for age and sex, the presence of calcium in any of the different vascular beds, except the abdominal aorta, was associated with a significantly increased hazard for total mortality, with the largest magnitude of associations being for calcium in the thoracic aorta. Additional adjustment for body mass index and the traditional CVD risk factors attenuated the magnitudes of the associations such that only calcium in either the carotid arteries or thoracic aorta remained statistically significantly associated with incident total mortality. For the associations with non-CVD mortality, the magnitudes of the associations were somewhat less than those for total mortality, but in general, the patterns of the associations were similar. As before, the largest hazard ratio was found for the thoracic aorta. For CVD mortality and after adjustment for the CVD risk factors, the association was modestly stronger for CAC (hazard ratio [HR], 3.37; P=0.10) than for thoracic aortic calcium (3.01, P=0.09).

We also examined the associations between increasing increments of calcium in the different vascular beds and mortality. For total mortality (Table 3) and after adjustment for age, sex, body mass index, and the traditional CVD risk factors (model 3), a 1-SD increment of log-transformed calcium was significantly (P<0.01) associated with an increased mortality risk for all of the vascular beds. The hazard ratios ranged from 1.63 to 1.22, with the largest hazard being associated with calcium in the iliac arteries and the lowest being associated with the coronary arteries. For both CVD and non-CVD mortality, the largest association was found for calcium in the iliac arteries.

To account for the potential effect of systemic calcification, to model 3 in Tables 2 and 3 we added adjustment for the presence of calcium, as well as increasing increments of the total calcium score, in the other vascular beds (data not shown). For all types of mortality in Table 2, the results were not materially changed when we also adjusted for the presence of calcium in any of the beds that were not the primary predictor variable for a given model (eg, noncoronary calcium when CAC was the primary predictor variable). Conversely, for the calcium burden analyses, when we adjusted for increasing increments of calcium in the other vascular beds, the findings for non-CVD mortality, the magnitudes of the associations were somewhat less than those for total mortality, but in general, the patterns of the associations were similar. As before, the largest hazard ratio was found for the thoracic aorta. For CVD mortality and after adjustment for the CVD risk factors, the association was modestly stronger for CAC (hazard ratio [HR], 3.37; P=0.10) than for thoracic aortic calcium (3.01, P=0.09).

Noncardiovascular disease mortality (n=4380)

Cardiovascular disease mortality (n=4331)

Table 2. Multivariable Associations Between the Presence of Vascular Calcium and Different Types of Mortality

<table>
<thead>
<tr>
<th>Vascular Bed</th>
<th>Model 1</th>
<th></th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th></th>
<th>Model 3</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P</td>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>P</td>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR</td>
<td>1.96</td>
<td>1.28–3.00</td>
<td>&lt;0.01</td>
<td></td>
<td>1.80</td>
<td>1.17–2.77</td>
<td>0.01</td>
<td></td>
<td>1.60</td>
<td>1.03–2.49</td>
<td>0.03</td>
</tr>
<tr>
<td>CAC</td>
<td>1.62</td>
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| Noncardiovascular disease mortality (n=4380)

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| Cardiovascular disease mortality (n=4331)

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Model 1: adjusted for age and sex; model 2: adjusted for age, sex, body mass index; model 3: adjusted for age, sex, body mass index, smoking, diabetes, hypertension, dyslipidemia, and family history of cardiovascular disease. HR indicates hazard ratio; CAR, carotid artery calcium; CAC, coronary artery calcium; TAC, thoracic aortic calcium; AAC, abdominal aortic calcium; ILAC, iliac calcium.
Table 3. Multivariable Associations Between Increasing Increments of Vascular Calcium* and Different Types of Mortality

<table>
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<td>Noncardiovascular disease mortality (n=4380)</td>
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<td>Cardiovascular disease mortality (n=4331)</td>
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Model 1: adjusted for age and sex; model 2: adjusted for age, sex, and body mass index; model 3: adjusted for age, sex, body mass index, smoking, diabetes, hypertension, dyslipidemia, and family history of cardiovascular disease. HR indicates hazard ratio; CAR, carotid artery calcium; CAC, coronary artery calcium; TAC, thoracic aortic calcium; AAC, abdominal aortic calcium; ILAC, iliac calcium.

*1-SD increment of log transformed calcium variable.

beds that were not the primary predictor variable (Table 3), the associations were attenuated to statistical nonsignificance.

The results of the receiver operator characteristic analyses are presented in Supplemental Table I, available online at http://atvb.ahajournals.org. Compared with the area under the curve for when CAC was added to the traditional CVD risk factors and for total, non-CVD, and CVD mortality, the areas under the curve were larger (albeit modestly) for nearly all comparisons when the different noncoronary vascular beds were separately added to the CVD risk factors (Supplemental Table IA). In all cases, the areas under the curve increased when each noncoronary vascular bed was separately added to a model that contained both the CVD risk factors and CAC (Supplemental Table IB).

Interactions between gender and calcium in the different vascular beds for the 3 different types of mortality were assessed. None were significant.

Discussion
In this historical cohort study of individuals presenting for preventive medicine services at a university-affiliated disease prevention center, calcium in different vascular beds was associated with higher risk of total, non-CVD, and CVD mortality. Specifically, the presence of calcium in the thoracic aorta or the carotid arteries was significantly associated with an increased hazard of total and non-CVD mortality. The presence of calcium in the thoracic aorta was also associated with a higher risk for CVD mortality, but this association was smaller than that for the presence of calcium in the coronary arteries. Notably, C-statistics from receiver operator characteristic analyses revealed that the areas under the curves were not significantly larger when the noncoronary vascular beds were added to models with either the traditional CVD risk factors alone or those that also included CAC. In contrast and after adjustment for the CVD risk factors, increasing increments of calcium in any of the vascular beds were, in general, associated with total, CVD, and non-CVD mortality. In these analyses, the largest magnitude of the associations was found for calcium in the iliac arteries, followed by calcium in the abdominal aorta. Notably, addition of the traditional CVD risk factors to the multivariable models resulted in the associations becoming nonsignificant for a number of the vascular beds. This suggests that the association between calcium in the different vascular beds and incident mortality is partially mediated by the CVD risk factors. Taken together, these results indicate that the presence of or increasing increments of calcium are risk factors of not only CVD but also non-CVD causes of mortality. However, based on the receiver operator characteristic analyses, it appears that the presence of calcium in other vascular beds provides limited additional information for discriminating fatal events beyond that provided by traditional CVD risk factors or CAC alone.

An interesting finding from this study is that when calcium was dichotomized into present versus absent, the vascular beds significantly associated with the different types of mortality were different than when calcium was analyzed as a continuous variable. This suggests that the unit of measurement of calcium (ie, presence versus continuous increments) may provide distinct information with respect to the relevance of a given vascular bed to mortality risk. In this respect,
up to the age of 70 years, the prevalence of calcium in the thoracic aorta is less than that in the coronaries, iliacs, and abdominal aorta. After the age of 70, the prevalence of thoracic aortic calcium increases exponentially and surpasses that in all other vascular beds. The pattern for the carotid arteries is similar to that for the thoracic aorta. Moreover, those who have calcium in the thoracic aorta are likely to have calcium in other vascular beds, whereas those with calcium in the abdominal aorta or coronary arteries have a higher probability of having isolated disease. These results suggest that the presence of calcium in the thoracic aorta or carotid arteries is indicative of more extensive atherosclerotic burden and may therefore be associated with the highest risk of morbidity and mortality. However, in terms of extent of calcification, the iliac arteries showed the strongest association for all mortality end points, consistent with the well-known association between the severity of peripheral artery disease and both CVD and total mortality.

An important finding from our study is that the presence and extent of arterial calcification in several vascular beds were strongly associated with non-CVD mortality and that these associations were independent of age, body mass index, and smoking, which are risk factors for a number of non-CVD conditions. One potential explanation for this finding is a chronic inflammatory state that characterizes many chronic diseases, including cancer, infection, and neurodegenerative disorders, all of which are underlying causes of non-CVD death in our cohort. In support of this hypothesis, atherosclerotic calcification has been linked to higher levels of inflammatory markers, such as C-reactive protein, interleukin-6, and adipokines. However, these associations tend to be modest and often become nonsignificant with adjustment for traditional CVD risk factors. Alternatively, previous data have suggested that atherosclerosis represents an abnormality in innate (phagocytic leukocytes, complement, and proinflammatory cytokines) and adaptive (T cells, antibodies, and immunoregulatory cytokines) immune function. If this is true, immune function abnormalities may be a common pathophysiology in the association between calcified atherosclerosis and both CVD and non-CVD mortality. Investigation into other potential mediators of the association between arterial calcification and non-CVD chronic diseases is needed to clarify these relationships.

There have been many studies showing that CAC is significantly associated with both total and CVD mortality. The literature for noncoronary calcium and mortality is more limited. Previous studies have shown that thoracic aortic calcification is significantly associated with fatal and nonfatal CVD events and total mortality independently of CAC, whereas calcium in the abdominal aorta is significantly associated with CVD mortality. Importantly, in the latter study, the calcium deposits were detected by lateral radiographs, making comparisons with the results of studies using CT difficult. We are aware of no studies that have examined the association between calcium in either the carotid or iliac arteries and mortality. Therefore, our report extends findings for abdominal aortic calcium showing that results are similar irrespective of measurement by plain radiography or CT and provides new data for carotid and iliac calcification.

The results of this study should not be construed as support for conducting whole-body scans with the sole purpose of determining risk of different types of mortality. Rather, this study indicates that vascular calcium found on diagnostic CT scans may be used for assessing risk, and that those done for lung screening may be most relevant because they would capture images of the thoracic aorta, which was found to have strong and significant associations with all types of mortality in our study. This is particularly germane, as a recent trial using CT of the chest for screening of smokers (which imparts much less radiation than a cardiac CT scan) was stopped early because of a highly significant benefit. Therefore, from a clinical perspective, the information on calcified atherosclerosis in the thoracic aorta could be considered by the health care provider to improve morbidity and mortality risk stratification, estimation of “arterial age,” and a potential motivational tool for patients.

Strengths of this study include a relatively large sample that was free of extant clinical disease at baseline, measurement of calcified atherosclerosis that spans many vascular beds, the use of a single CT scanner, and assessment of both total and cause specific mortality. Conversely, there are some limitations. The study population was a clinical sample and may not generalize to the larger community-living population, especially given the lower prevalence of diabetes in this cohort. Calcification determined by CT cannot distinguish between intimal and medial calcification. However, as the prevalence of diabetes was quite low in our population and medial calcification is typically seen in those with diabetes or end stage renal disease, we believe the possibility of misclassification is low. Finally, the number of cases of CVD mortality was relatively small and may have limited our ability to find significant associations for this outcome. Importantly, as we used the underlying cause of death from the death certificates in these analyses, there were likely several cases where CVD may have been a contributing (but not underlying) cause of death. As such, the associations with CVD mortality are likely conservative.

In conclusion, the results of this study indicate that higher levels of calcium in different vascular beds are associated not only with CVD mortality but also with non-CVD and total mortality. Moreover, the location of the arterial calcification appears to be relevant to the strength of the association with mortality, and the CVD risk factors appear to mediate some of this association. Notably, there are current recommendations and guidelines for the use of CAC in the CVD risk stratification. Given the results of the current study, future research is warranted to determine whether current recommendations on CAC measurements should be expanded to include calcium in other vascular beds.

**Sources of Funding**

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**Disclosures**

None.
References


