Abdominal Aortic Calcific Deposits Are an Important Predictor of Vascular Morbidity and Mortality

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Background—The impact of abdominal arterial calcific deposits on the prediction of cardiovascular disease (CVD) over a long follow-up interval deserves greater scrutiny.

Methods and Results—Lateral lumbar radiographs were studied as a predictor of incident coronary heart disease (CHD), CVD, and CVD mortality in 1049 men and 1466 women (mean age, 61 years) who were followed from 1967 to 1989. Anterior and posterior wall calcific deposits in the aorta at the level of the first through fourth lumbar vertebrae were graded according to increasing severity using a previously validated rating scale for abdominal aortic calcium (AAC) that ranges from 0 to 24 points. There were 454 cases of CHD, 709 cases of CVD, and 365 CVD deaths. Proportional hazards logistic regression was used to test for associations between AAC and later events after adjustment for age, cigarette use, diabetes mellitus, systolic blood pressure, left ventricular hypertrophy, body mass index, cholesterol, and HDL cholesterol. In comparisons with the lowest AAC tertile, the multivariate age-adjusted relative risks (RR) for CVD were increased in tertile 2 (men: RR, 1.33; 95% confidence interval [CI], 1.02 to 1.74; women: RR, 1.25; 95% CI, 0.95 to 1.65) and tertile 3 (men: RR, 1.68; 95% CI, 1.25 to 2.27; women: RR, 1.78; 95% CI, 1.33 to 2.38). Similar results were obtained with CHD and CVD mortality.

Conclusions—AAC deposits, detected by lateral lumbar radiograms, are a marker of subclinical atherosclerotic disease and an independent predictor of subsequent vascular morbidity and mortality. **(*Circulation*. 2001;103:1529-1534.)**

Key Words: coronary disease ■ calcium ■ risk factors

Autopsy studies have noted that fatty streaks in the human aorta are common in children, coronary artery atherosclerotic lesions are often present in young soldiers who die in combat, and more severe disease (typified by plaques and calcified lesions) is frequent after the age of 30 years.[1] The presence of these atherosclerotic lesions has been correlated with a variety of environmental and genetic cardiovascular risk factors, and recent autopsy studies, such as the Pathological Determinants of Atherosclerosis in the Youth (PDAY), have reaffirmed that fatty streak formation continues to be very common during the teenage years.[2,3]

Although modern technology focuses on carotid and coronary arterial beds and new techniques such as electron beam and helical computerized tomography can now estimate the degree of coronary calcification,[4,5] imaging of the aorta has received less attention. Early methods of abdominal aortic assessment were largely confined to the study of necropsy specimens.[6] Autopsy studies of >600 middle-aged adults in the 1950s reported highly significant positive associations between the degree of abdominal aortic calcification and the presence of calcified plaque in the coronary arteries.[7] Although the investigations were confined to pathological materials, the authors felt the data were so strong that a high correlation between abdominal aortic calcification and advanced coronary atherosclerosis had to be present in the living population.[7] The authors of these studies concluded that there were "significant associations between the calcification of coronary arteries, and radiographic imaging should be able to provide information that would aid in the differential diagnosis of advanced coronary atherosclerosis."[6]

After aortic atherosclerosis has entered the plaque-forming phase, some of the calcified lesions are visible on standard radiographs of the thorax and abdomen.[8] The burden of atherosclerosis in the aorta was shown to correlate with the degree of atherosclerosis in other arterial beds,[6,7] but the role of aortic calcific deposits as determinants of later cardiovascular risk in living subjects has received less attention. A few studies have reported the impact of abdominal aortic calcification on cardiovascular death, but the information often lacked full lipoprotein cholesterol quantification, the outcome

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TABLE 1. Characteristics of the Study Cohort

Variable	Men (n=1049)	Women (n=1466)
Age, y	60.5 (7.9)	60.9 (8.1)
Cholesterol, mg/dL	221 (40.1)	243 (42.2)
HDL cholesterol, mg/dL	45.0 (12.9)	57.3 (15.7)
Systolic pressure, mm Hg	138.6 (21.8)	140.8 (24.7)
Diastolic pressure, mm Hg	81.3 (11.4)	80.2 (11.6)
Current smoking, %	36.7	32.3
Diabetes mellitus, %	5.9	4.8
Body mass index, kg/m^2	26.2 (3.5)	25.3 (4.2)
Left ventricular hypertrophy, %	2.7	2.3
AAC index	3.7 (4.4)	3.7 (4.9)

Values are mean (SD) or percent.

was restricted to cardiovascular death, and few cardiovascular events occurred in women.[9] Other studies have shown an association between the presence of aortic arch calcification and later vascular events, but the studies did not include all of the common vascular disease risk factors and protocols did not blind readers of the radiographs.[10] The current study investigated the prognostic features of abdominal aortic calcium (AAC) for various vascular disease outcomes, and it tests for an association between the severity of AAC and subsequent cardiovascular disease (CVD) and death in a population-based sample of Framingham Heart Study participants who were followed for ≥20 years.

Methods

The study participants were Framingham Heart Study subjects who attended routine examinations in 1967 through 1970. At that time, 2515 had lateral lumbar radiographs as part of a special osteoporosis examination. The clinical history included information on recognized risk factors for vascular morbidity and mortality, and subjects reported on cigarette smoking during the year before the examination. Blood pressure was measured with the subject in the sitting position for ≥5 minutes. Height and weight were measured, and the body mass index was calculated as the height in kilograms divided by the weight in meters squared. Left ventricular hypertrophy on the ECG was determined according to standard criteria.[11]

Blood tests at the time of the examination (or the examination immediately before or after the index examination) included measurements of blood cholesterol,[12] HDL cholesterol,[13] and blood glucose. Persons taking oral hypoglycemic agents or insulin, those with fasting glucose levels >140 mg/dL, or those with a history of casual glucose levels >200 mg/dL were considered diabetic.[14]

The lateral lumbar spine radiographs were acquired in the standing position, as previously described.[15] An AAC deposits index was developed to grade the severity of calcification in the aorta at the level of the first through fourth lumbar vertebrae. Radiographs were read without knowledge of any prevalent or incident clinical vascular disease. The radiodensity of the aortic wall was assessed systematically at each vertebral segment, and calcific deposits were regarded as present if densities were visible in an area parallel to the lumbar spine and anterior to the lower part of the spine. Densities overlapping the vertebrae were deemed as present only if they extended from or formed a clear pattern with those of the lower part of the aorta. Calcific densities were graded on a 0 to 3 scale at each lumbar vertebral segment. A score of 0 denoted no aortic calcific deposits;

TABLE 2. AAC Tertiles in Men and Women

Tertile	AAC Score	Men, n (%)	Women, n (%)	Total, n (%)
1	0	340 (32)	606 (43)	946 (38)
2	1–4	380 (36)	403 (28)	783 (31)
3	5–22	329 (31)	457 (29)	786 (31)
Total		1049 (100)	1466 (100)	2515 (100)

TABLE 3. Multivariate-Adjusted Relative Risk* Associated With Tertiles of AAC Vascular Events Over 22 Years of Follow-Up

	Men		Women		Total	
Event and Tertile Comparison	Age-Adjusted	Multivariate-Adjusted	Age-Adjusted	Multivariate-Adjusted	Age-Adjusted	Multivariate-Adjusted
CHD						
Tertile 2 vs 1	1.46 (1.10–1.93)	1.31 (0.95–1.80)	1.65 (1.20–2.28)	1.33 (0.90–1.94)	1.57 (1.27–1.94)	1.32 (1.03–1.68)
Tertile 3 vs 1	1.76 (1.29–2.39)	1.61 (1.13–2.30)	3.45 (2.52–4.73)	2.41 (1.64–3.55)	2.47 (1.98–3.07)	1.91 (1.48–2.47)
No. at risk	678		997		1675	
No. of events	249		205		454	
CVD						
Tertile 2 vs 1	1.45 (1.14–1.84)	1.33 (1.02–1.74)	1.59 (1.25–2.01)	1.25 (0.95–1.65)	1.53 (1.30–1.82)	1.29 (1.07–1.57)
Tertile 3 vs 1	1.82 (1.40–2.37)	1.68 (1.25–2.27)	2.47 (1.94–3.15)	1.78 (1.33–2.38)	2.17 (1.81–2.59)	1.70 (1.38–2.09)
No. at risk	653		973		1626	
No. of events	343		366		709	
CVD mortality						
Tertile 2 vs 1	1.72 (1.23–2.41)	1.74 (1.18–2.59)	2.22 (1.47–3.34)	1.89 (1.17–3.04)	1.98 (1.50–2.52)	1.77 (1.30–2.40)
Tertile 3 vs 1	2.21 (1.55–3.15)	2.24 (1.48–3.39)	3.67 (2.47–5.44)	2.42 (1.49–3.92)	2.82 (2.17–3.67)	2.26 (1.66–3.09)
No. at risk	784		1072		1856	
No. of events	203		162		365	

Values are relative risk (95% confidence intervals), unless otherwise indicated.

*Includes adjustment for age, cigarettes, diabetes mellitus, systolic pressure, left ventricular hypertrophy, body mass index, cholesterol, and HDL cholesterol.

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1, small scattered calcific deposits filled less than one-third of the longitudinal wall of the aorta; 2, one-third or more but less than two-thirds of the longitudinal wall of the aorta was calcified; and 3, two-thirds or more of the longitudinal wall of the aorta was calcified. A separate score was determined for the anterior and posterior aorta, and the values were summed across the 4 vertebrae, resulting in an AAC index that could range from 0 to 24 points, as previously described.[15]

In a previous study, the inter-rater agreement and reproducibility of a random selection of 50 films were estimated, and the AAC index measurements with this scoring had an inter-rater intraclass correlation of 0.93 and an intra-rater intraclass correlation of 0.98.[15] The calcification scoring methods depend on the height of the lumbar vertebrae. Older persons often have reduced vertebral height and may tend to have higher abdominal aortic scores that may be partly attributable to the assessment methods. This technique determines degree of calcification but does not distinguish between atherosclerotic plaque and medial calcification.

All study subjects were free of CVD at baseline and were followed over 20 years for the development of coronary heart disease (CHD), CVD, or CVD mortality using previously published end point criteria.[16] The diagnostic category for CHD included angina pectoris, unstable angina pectoris, myocardial infarction, and coronary disease death; CVD included transient ischemic attack, stroke, stroke death, or congestive heart failure in addition to all of the CHD end points. Cardiovascular mortality included death from CHD or cerebrovascular disease. Surveillance for CVD consisted of regular examinations at the Framingham Heart Study clinic and review of medical records from physician office visits and hospitalizations for heart and cerebrovascular disease.

The Cox proportional hazard regression model was used to test for the relation between various independent variables and the vascular disease outcomes.[17,18] Because approximately one-third of the participants had an AAC deposit index of 0, analyses were generally undertaken according to tertile categories of AAC deposits. Analyses included testing for proportionality, and multivariate adjusted odds ratios and their 95% confidence intervals were estimated from the β-coefficients and the standard error of the β-coefficients according to a specified number of units for the variables.[17] Subjects remained at risk as long as they were free of the outcome and alive during the 20 years of follow-up, and they were censored in the case of death or loss to follow-up. Less than 3% of subjects were lost to follow-up. Age-adjusted Kaplan-Meier methods were used to generate survival curves according to 3 AAC tertiles. Analyses were performed separately by sex for the vascular outcomes studied.

Results

Baseline characteristics for the 1049 men and 1466 women who participated in this study appear in Table 1. The mean age at baseline was ≈60 years, the mean cholesterol levels were 224 and 244 mg/dL in men and women, respectively, and the frequency of current smoking was in the range of 30% to 40%, reflecting the older age of the population and population experience in the early 1970s.

The AAC scores ranged from 0 to 22 points, and the approximate tertiles, developed from the scores in both sexes, were 0, 1 to 4, and 5 to 22 points (Table 2). Tertiles were used for the analysis because an AAC score of 0 was obtained in approximately one-third of the participants. The frequency of aortic calcific deposits according to tertile of AAC was relatively similar in men and women.

Multivariate models were used to assess the association between AAC and other variables with the outcomes CHD, CVD, and CVD mortality over 20 years of follow-up (Table 3). Separate models were used for used for each sex, and the Cox proportional hazards analysis included adjustment for age, cigarette use, diabetes mellitus, systolic pressure, left ventricular hypertrophy, body mass index, cholesterol, and HDL cholesterol. The presence of AAC was generally associated with an increased risk of subsequent CHD, CVD, and CVD mortality across tertiles of AAC in men and women. In comparisons that used the first tertile of AAC as the referent group, significant associations with vascular disease were usually found for persons in the second tertile of AAC. In all instances, the top tertile of AAC was associated with a significantly increased risk for adverse outcomes in these multivariate analyses for men, women, and both sexes combined. The corresponding Kaplan-Meier survival curves for men and women for CHD, CVD, and CVD mortality according to the tertile of AAC are shown in Figures 1 through 3, respectively.

An example of the multivariate analyses used to estimate risk for incident CHD in men and women is shown in Table 4. The adjusted risk and 95% confidence limits for that risk estimate appear in the table for a specified number of units for each factor. For instance, the top tertile of AAC was associated with a relative risk of 1.61 in men to develop CHD over the 20-year follow-up interval, and the 95% confidence interval around this estimate ranged from 1.13 to 2.30. Age was significantly associated with CHD risk only in men, and significant associations with later CHD were observed for diabetes, systolic pressure, cholesterol, HDL cholesterol, and AAC tertile 3 in both sexes. Current cigarette smoking was associated with the CHD outcome in multivariate analyses for men but not for women.

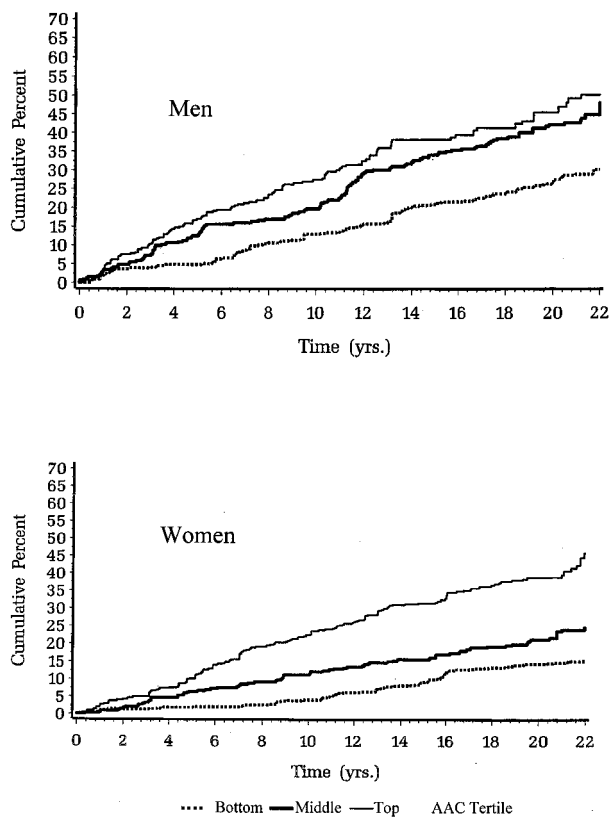

Figure 1. Age-adjusted incidence of CHD over 22 years of follow-up for men (top) and women (bottom) according to tertile of AAC at baseline.

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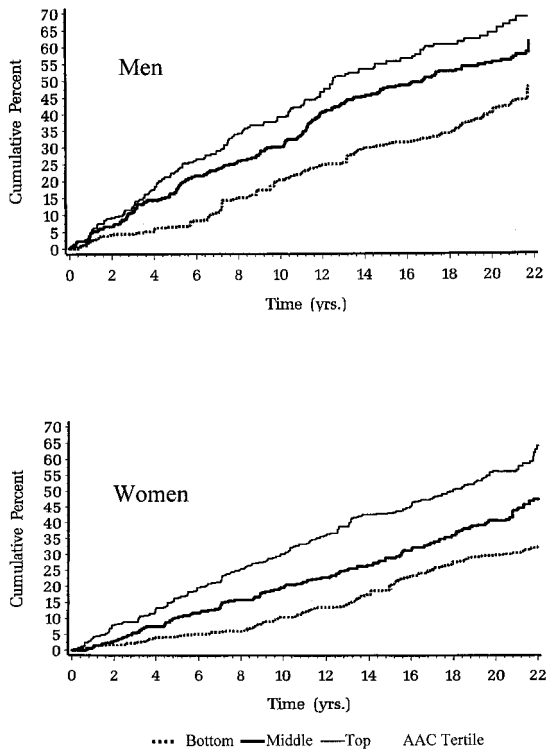

Figure 2. Age-adjusted incidence of CVD over 22 years of follow-up for men (top) and women (bottom) according to tertile of AAC at baseline.

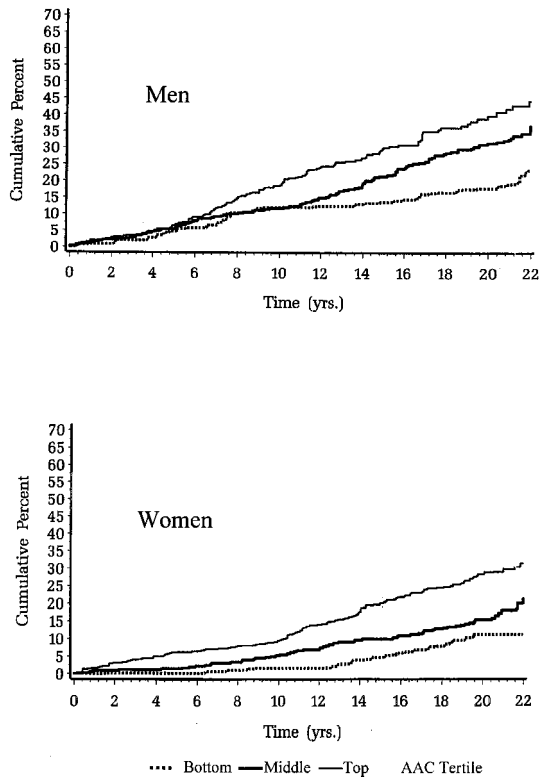

Figure 3. Age-adjusted incidence of CVD death over 22 years of follow-up for men (top) and women (bottom) according to tertile of AAC at baseline.

Discussion

The current study shows that middle-aged men and women with calcific disease in the abdominal aorta are more likely to develop CHD, CVD, and CVD mortality. The increased risk for vascular disease was present even after considering the effect of traditional cardiovascular risk factors, and the results were obtained during a period when there was relatively little intervention for dyslipidemia. Most of the traditional risk factors used in the multivariate analyses were associated with the vascular disease outcomes studied, but current cigarette smoking in women was not associated with CHD in this analysis and may be attributable to use of current smoking as the analytic variable. The results provide strong evidence that imaging of the vascular calcification using lumbar radiographs provides important prospective information on the role of vascular disease imaging to help assess risk of CVD.

Other reports have shown that calcification of the aortic arch, determined at the time of a conventional chest radiograph, is associated with an increased risk of vascular events.[9,10,19] For instance, a large study from the Kaiser Permanente Group showed that the relative risk of CHD was ≈25% greater in persons with aortic arch calcification compared with persons without the calcification. The prevalence of the abnormality was only ≈5% at 60 years, and this limited the utility. However, the current study showed that calcification in the abdominal aorta anterior to 4 lumbar vertebrae was common and affected two-thirds of the study population with mean age of 60 years.

Arterial lesions commence as fatty streaks, progress to raised lesions, and can become complicated by ulceration, calcification, or hemorrhage before occlusion and the development of clinical events such as a myocardial infarction. This sequence has been well documented, and the presence of raised lesions in young and middle-aged adults is highly associated with abnormal levels of cardiovascular risk factors.[20,21] It has also been demonstrated that the arterial wall of the human thoracic aorta undergoes progressive accumulation of calcium with aging; the region most affected by these changes is the elastin-rich layer of media and LDL cholesterol in arteries that acts to promote the calcium deposition.[22,23] The predominant mineral found in these lesions is apatite, and extracellular vesicles may serves as sites for calcification.[24] In the latter situation, intimal-medial thickening of the carotid artery provides added predictive yield over and above traditional cardiovascular risk factor assessment. More recently, electron beam computerized tomography has been used to identify and quantify the amount of calcium present in coronary arteries. Greater mineral density has been shown to be highly associated with the presence of clinical coronary artery disease, although the specific utility of the newer electron beam technology has not been demonstrated convincingly in population-based prospective studies.[25–27]

The available evidence on the risks of radiographically identified vascular calcific deposits has generally been focused on the aorta and the coronary arteries. The presence of calcific deposits in the aortic arch on plain chest radiography has been associated with increased CVD risks when using simple scoring systems for calcification of the aortic arch.[9,19] Studies from the Netherlands and from the earlier experience

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TABLE 4. Multivariate Relative Risks* for CHD According to AAC and Other Factors: 22 Years of Follow-Up

Factor	Units	Men	Women
Age	10 years	1.23 (1.02–1.49)	0.97 (0.78–1.20)
Current cigarette use	1 pack/day	1.03 (0.85–1.24)	0.98 (0.71–1.33)
Diabetes	Present/absent	1.60 (0.92–2.78)	2.04 (1.20–3.49)
Systolic pressure	10 mm Hg	1.10 (1.03–1.17)	1.08 (1.01–1.16)
Left ventricular hypertrophy	Present/absent	1.95 (0.88–4.35)	1.22 (0.44–3.38)
Body mass index	5 kg/m^2	0.97 (0.79–1.18)	1.01 (0.84–1.22)
Cholesterol	40 mg/dL	1.24 (1.10–1.41)	1.25 (1.09–1.42)
HDL cholesterol	5 mg/dL	0.88 (0.84–0.93)	0.92 (0.87–0.97)
AAC tertile 2 vs tertile 1	Present/absent	1.31 (0.95–1.80)	1.33 (0.90–1.94)
AAC tertile 3 vs tertile 1	Present/absent	1.61 (1.13–2.30)	2.41 (1.64–3.55)

Values are relative risks (95% confidence intervals).

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in Framingham reflect the presence or absence of calcified plaques in the thoracic aorta and did not include HDL cholesterol as a component of risk factor assessment. More recently, several studies representing the experience of electron beam computerized tomography groups showed an increased risk of CVD with greater coronary calcium scores, but these studies were generally conducted in selected populations.[25–27] One of these investigations demonstrated no added utility for computerized tomography scores over and above traditional risk factor measurement and risk factor assessment using Framingham Heart Study risk factor profiling.[27]

Although traditional cardiovascular risk factor levels are often abnormal in persons with calcified arterial tissue, a host of metabolic factors may also play a role in fostering arterial calcification. For example, higher levels of 25-OH vitamin D have been found in some persons with more arterial calcium, but parathyroid hormone levels were reported as normal.[28] Diminished vitamin K status may be accompanied by a decreased γ-carboxyglutamate content of proteins such as osteocalcin. It has been hypothesized that this metabolic effect reduces the affinity of osteocalcin for hydroxyapatite and may help account for lower bone mass and greater mineralization of atherosclerotic plaques.[29,30] Studies in rats have also suggested that osteopontin is present where arterial tissue undergoes calcification, but the exact role of osteopontin, an acidic glycoprotein associated with bone morphogenesis, is unclear at this time.[31–33] Finally, connective tissue collagen may play an important role, and variants in endothelial collagen may help to determine susceptibility to vascular calcification and, ultimately, to clinical CVD.

The current investigation does have several limitations that bear consideration. The data have been derived from the long-term experience of a community sample, and the baseline data were obtained in the late 1960s. It is not known whether middle-aged Americans have a similar risk factor and aortic calcium burden at the present time. The abdominal calcium was determined from radiographic techniques that are less sensitive in detecting atherosclerotic lesions than newer modalities such as ultrasound and computerized tomography.

Newer imaging modalities, such as electron beam and helical computed tomography imaging, now allow more detailed studies of subclinical disease in arterial beds. This article has focused on the prognostic utility of calcium in the abdominal aorta, providing one of the few long-term prospective follow-up studies with full cardiovascular risk factor profiling. These results suggest that vascular imaging will improve our ability to predict cardiovascular events, and further research using newer technologies should help us to define the utility of vascular calcium measures over and above established risk factors.[34]

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