

Relation of Aortic Valve Calcium Detected by Cardiac Computed Tomography to All-Cause Mortality

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Aortic valve calcium (AVC) can be quantified on the same computed tomographic scan as coronary artery calcium (CAC). Although CAC is an established predictor of cardiovascular events, limited evidence is available for an independent predictive value for AVC. We studied a cohort of 8,401 asymptomatic subjects (mean age 53 ± 10 years, 69% men), who were free of known coronary heart disease and were undergoing electron beam computed tomography for assessment of subclinical atherosclerosis. The patients were followed for a median of 5 years (range 1 to 7) for the occurrence of mortality from any cause. Multivariate Cox regression models were developed to predict all-cause mortality according to the presence of AVC. A total of 517 patients (6%) had AVC on electron beam computed tomography. During follow-up, 124 patients died (1.5%), for an overall survival rate of 96.1% and 98.7% for those with and without AVC, respectively (hazard ratio 3.39, 95% confidence interval 2.09 to 5.49). After adjustment for age, gender, hypertension, dyslipidemia, diabetes mellitus, smoking, and a family history of premature coronary heart disease, AVC remained a significant predictor of mortality (hazard ratio 1.82, 95% confidence interval 1.11 to 2.98). Likelihood ratio chi-square statistics demonstrated that the addition of AVC contributed significantly to the prediction of mortality in a model adjusted for traditional risk factors (chi-square = 5.03, $p = 0.03$) as well as traditional risk factors plus the presence of CAC (chi-square = 3.58, $p = 0.05$). In conclusion, AVC was associated with increased all-cause mortality, independent of the traditional risk factors and the presence of CAC. © 2010 Published by Elsevier Inc. (Am J Cardiol 2010;106:1787–1791)

Coronary artery calcium (CAC), thoracic aortic calcium (TAC), and aortic valve calcium (AVC) can be reliably measured on the same cardiac computed tomographic scan.¹ CAC is an established predictor of adverse coronary heart disease (CHD) events across diverse populations,² and TAC predicts overall mortality and adds prognostic information to CAC.³ Although echocardiographic studies have been suggestive,⁴ limited evidence is currently available of an association between AVC and poor outcomes. In the present study, we sought to describe the association of AVC with mortality in a large cohort before and after adjustment for CAC. If AVC, as measured by computed tomography, is shown to predict adverse events, an argument could be

made to explore routine quantification of AVC on cardiac computed tomographic scans. If AVC adds predictive value beyond CAC, an argument can be made for more complete reporting of “total cardiovascular calcium” for comprehensive risk assessment.

Methods

The study cohort consisted of 8,401 asymptomatic subjects free of known CHD and overt aortic valve disease referred for single electron beam computed tomography (EBCT) at a facility in Columbus, Ohio from 1999 to 2003 for the assessment of subclinical atherosclerosis. All screened subjects had provided informed consent to undergo EBCT and for the use of their de-identified data for epidemiologic research. The Human Investigations Committee approved the present study. Furthermore, separate approval and informed consent was obtained for the patient interviews, collection of baseline and follow-up data, and corroboration of death.

Baseline demographic and risk factor data were obtained by self-report at EBCT. The prevalence of occult bicuspid aortic valve was not available. Cigarette smoking was considered present if a subject reported a history of smoking or was a smoker at scanning. Dyslipidemia was coded as present for any subject self-reporting a history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides,

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and/or current use of lipid-lowering therapy. Patients were considered to have diabetes if they had endorsed a diabetes history or reported using oral antidiabetes medications or insulin. Hypertension was considered present if a patient reported a history of a hypertension diagnosis or used an antihypertensive medication. A family history of early CHD was obtained by asking patients whether any member of their immediate family (parents or siblings) had had nonfatal myocardial infarction, coronary revascularization, or fatal cardiovascular event ≤ 55 years of age.

EBCT was performed using either a C-100 or C-150 scanner (Imatron, San Francisco, California). Using a 100 ms/slice scanning time and 3-mm slice thickness, 40 separate slices were obtained, starting at the level of the carina and proceeding to the level of the diaphragm. Image acquisition was electrocardiographically triggered at 60% to 80% of the RR interval. After data processing, each image was assessed for the presence of both CAC and AVC. A calcified lesion was defined as ≥ 3 contiguous pixels with a peak Hounsfield attenuation of >130 . The presence of CAC and CAC scores were calculated using the method described by Agatston et al.⁵ The presence of AVC was defined as any calcified lesion detected within the aortic valve leaflet area or extending to the aortic root⁶; the aortic valve was identified as the structure lying within the contiguous plane that extended from the left ventricle to the ascending aorta present within 3 to 4 consecutive images. Calcium in the aortic valve was distinguished from coronary calcium by the anatomic location of calcium, as previously described.⁶ Calcium within the aortic sinuses or thoracic aorta (equivalent to TAC), or both, was excluded from analysis and not measured as AVC, consistent with the method used in the Multi-Ethnic Study of Atherosclerosis (MESA).⁷ AVC severity was not scored in the cohort used for the present study.

The subjects were followed for a median of 5 years (range 1 to 7). The primary outcome for the present study was the occurrence of death from any cause, which was determined by cross-reference with the Social Security Death Index. Ascertainment of mortality was conducted by persons who were unaware of the baseline data and electron beam computed tomographic results. The details on the cause and mechanism of death were not available for this registry.

The baseline characteristics of the study population are presented stratified by the absence or presence of AVC. Age is presented as a continuous measure $\pm$ SD; the remaining baseline characteristics are presented as frequencies. Age was compared between groups using a 2-sample *t* test. The categorical risk factors were compared using the Pearson chi-square test. Survival analysis was conducted using the individual time-to-all-cause mortality data. Curves representing cumulative survival were constructed using Kaplan-Meier estimates of the survival function. Additional curves were generated after stratifying by 2 prespecified categories of CAC (<100 and ≥ 100).⁸ The Cox proportional hazards model was used to calculate univariate and multivariate hazard ratios (HRs) for the occurrence of death according to AVC. The independent predictive value of AVC was assessed in the following hierarchical models: model 1, unadjusted; model 2, adjusted for age and gender; model 3,

Table 1

Clinical characteristics of those with and without aortic valve calcium (AVC)

Variable	AVC		p Value
	No (n = 7,884)	Yes (n = 517)	
Age (years)	52 $\pm$ 10	61 $\pm$ 10	<0.0001
Gender (women)	31%	30%	0.62
Hypertension	27%	45%	<0.0001
Diabetes mellitus	6%	10%	<0.0001
Dyslipidemia*	25%	35%	<0.0001
Smoking	9%	11%	0.04

* Dyslipidemia defined as self-report of history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, and/or current use of lipid-lowering therapy.

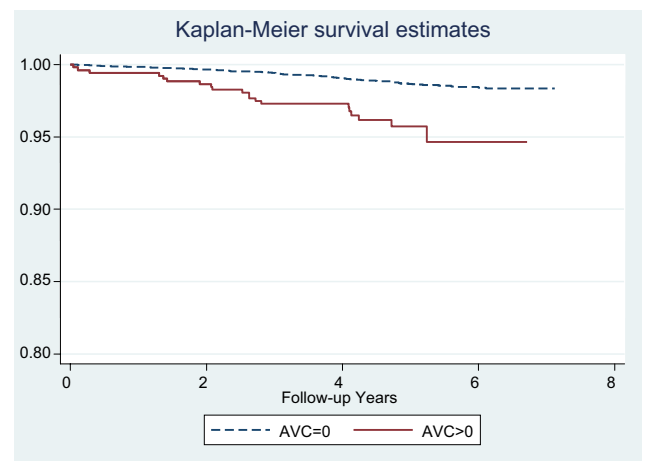


Figure 1. Kaplan-Meier estimates of cumulative survival for those with (AVC+) or without (AVC-) AVC. $p < 0.0001$ by log-rank test.

model 2 plus hypertension, dyslipidemia, diabetes mellitus, smoking, and family history of CHD; and model 4, model 3 plus the presence of CAC.

To further test the hypothesis that AVC adds predictive value to a risk factor and CAC-adjusted model, we calculated the likelihood ratio chi-square statistics. The likelihood-ratio test rejects the null hypothesis if the value of the chi-square statistic is large and statistically significant. The level of significance was set at $p < 0.05$ (2-tailed). All statistical analyses were performed with Stata, version 10.0 (StataCorp, Austin, Texas).

Results

The study population consisted of 8,401 asymptomatic subjects without previous manifestation of CHD or aortic valve disease (Table 1). The mean age of the population was 53 ± 10 years, and most were men (69%). A total of 35% had no major CHD risk factors, and 36%, 20%, and 9% had 1, 2, and 3 major risk factors, respectively.

A total of 517 patients (6%) had AVC on electron beam computed tomographic scanning. The patients with AVC were older, with an increased prevalence of hypertension, diabetes, and dyslipidemia (all $p < 0.0001$). These patients

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