JACC: CARDIOVASCULAR IMAGING VOL. 5, NO. 6, 2012

ISSN 1936-878X/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcmg.2011.12.023

Aortic Valve Calcium Independently Predicts Coronary and Cardiovascular Events in a Primary Prevention Population

David S. Owens, MD,* Matthew J. Budoff, MD,† Ronit Katz, DPHIL,‡ Junichiro Takasu, MD, PHD,† David M. Shavelle, MD,§ J. Jeffrey Carr, MD, MS,‖ Susan R. Heckbert, MD, PHD,¶ Catherine M. Otto, MD,* Jeffrey L. Probstfield, MD,* Richard A. Kronmal, PHD,‡ Kevin D. O'Brien, MD*

Seattle, Washington; Los Angeles, California; and Winston-Salem, North Carolina

OBJECTIVES This study sought to test whether aortic valve calcium (AVC) is independently associated with coronary and cardiovascular events in a primary-prevention population.

BACKGROUND Aortic sclerosis is associated with increased cardiovascular morbidity and mortality among the elderly, but the mechanisms underlying this association remain controversial. Also, it is unknown whether this association extends to younger individuals.

METHODS We performed a prospective analysis of 6,685 participants in MESA (Multi-Ethnic Study of Atherosclerosis). All subjects, ages 45 to 84 years and free of clinical cardiovascular disease at baseline, underwent computed tomography for AVC and coronary artery calcium scoring. The primary, prespecified combined endpoint of cardiovascular events included myocardial infarctions, fatal and nonfatal strokes, resuscitated cardiac arrest, and cardiovascular death, whereas a secondary combined endpoint of coronary events excluded strokes. The association between AVC and clinical events was assessed using Cox proportional hazards regression with incremental adjustments for demographics, cardiovascular risk factors, inflammatory biomarkers, and subclinical coronary atherosclerosis.

RESULTS Over a median follow-up of 5.8 years (interquartile range: 5.6 to 5.9 years), adjusting for demographics and cardiovascular risk factors, subjects with AVC (n = 894, 13.4%) had higher risks of cardiovascular (hazard ratio [HR]: 1.50; 95% confidence interval [CI]: 1.10 to 2.03) and coronary (HR: 1.72; 95% CI: 1.19 to 2.49) events compared with those without AVC. Adjustments for inflammatory biomarkers did not alter these associations, but adjustment for coronary artery calcium substantially attenuated both cardiovascular (HR: 1.32; 95% CI: 0.98 to 1.78) and coronary (HR: 1.41; 95% CI: 0.98 to 2.02) event risk. AVC remained predictive of cardiovascular mortality even after full adjustment (HR: 2.51; 95% CI: 1.22 to 5.21).

CONCLUSIONS In this MESA cohort, free of clinical cardiovascular disease, AVC predicts cardiovascular and coronary event risk independent of traditional risk factors and inflammatory biomarkers, likely due to the strong correlation between AVC and subclinical atherosclerosis. The association of AVC with excess cardiovascular mortality beyond coronary atherosclerosis risk merits further investigation. (Multi-Ethnic Study of Atherosclerosis [MESA]; NCT00005487) (J Am Coll Cardiol Img 2012;5:619–25)

From the *Department of Medicine, University of Washington, Seattle, Washington; †Department of Medicine, Harbor-UCLA, Los Angeles, California; ‡Department of Biostatistics, University of Washington, Seattle, Washington; §Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles, California; ‖Department of Radiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina; and the ¶Department of Epidemiology, University of Washington, Seattle, Washington. This research was supported by R01-HL-63963-01A1 and by contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI participated in the design and conduct of MESA, but did not take part in manuscript preparation or the decision to submit for publication. The NHLBI did not review this manuscript before submission. Dr. Owens had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Budoff has received speaking honoraria from General Electric. Dr. O'Brien has received speaking honoraria from AstraZeneca and Merck. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Dr. Shavelle is currently affiliated with the Department of Medicine, University of Southern California, Los Angeles, California.

Manuscript received December 1, 2011; accepted December 14, 2011.

JACC: CARDIOVASCULAR IMAGING, VOL. 5, NO. 6, 2012
JUNE 2012:619–25

Calcific aortic valve disease is common in older adults, with an estimated prevalence of 25% in individuals older than 65 years of age (1). Thought previously to be a degenerative disorder, the disease is now recognized to be an actively regulated biological process sharing many epidemiological (1–4) and histopathological (5) similarities to coronary atherosclerosis.

In older adults without known cardiovascular disease, aortic sclerosis (the presence of valve calcium without hemodynamic obstruction) is associated with a 50% increase in risk of cardiovascular events (6). Hypothesized mechanisms underlying this association include inflammation, subclinical atherosclerosis, and other shared biological mechanisms.

To determine whether the presence of aortic valve calcium (AVC), detected on computed tomography (CT) scans, predicts cardiovascular events in a younger cohort and to identify mechanisms underlying this association, we performed a prospective analysis in MESA (Multi-Ethnic Study of Atherosclerosis).

ABBREVIATIONS AND ACRONYMS

AVC = aortic valve calcium
CAC = coronary artery calcium
CI = confidence interval
CRP = C-reactive protein
CT = computed tomography
HR = hazard ratio
MI = myocardial infarction

METHODS

Study population: MESA is a National Heart, Lung, and Blood Institute–sponsored, population-based investigation of subclinical cardiovascular disease and its progression (7). In this study, a total of 6,814 individuals, ages 45 to 84 years, were recruited from 6 U.S. communities (Baltimore City and County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota) between July 2000 and August 2002. Pre-specified recruitment plans targeted 4 ethnic groups (white, black, Hispanic, and Chinese). Participants were excluded if they had physician-diagnosed cardiovascular disease before enrollment, including angina, myocardial infarction (MI), heart failure, stroke or transient ischemic attack, resuscitated cardiac arrest, or a cardiovascular intervention (e.g., coronary artery bypass graft, angioplasty, valve replacement, pacemaker/defibrillator placement). Subjects with subclinical aortic valve disease (e.g., bicuspid valves) were thus eligible for participation. The institutional review board at each participating institution approved MESA, and each participant provided informed written consent before enrollment.

Demographic and covariate data. The comprehensive baseline MESA examination included a clinic visit, serum analyses, and a CT scan of the chest and heart. Information regarding the participants' demographic data and medical history, including medication use, was obtained by questionnaire. Ethnicity was self-reported. Baseline testing for and definitions of cardiovascular risk factors were described previously (8). Serum samples were obtained after a 12-h fast and analyzed in a central laboratory (University of Vermont, Burlington, Vermont). C-reactive protein (CRP) concentrations were analyzed using the BNII high-sensitivity nephelometer (Dade Behring, Inc., Deerfield, Illinois). Diabetes and impaired fasting glucose were defined according to the 2003 American Diabetes Association fasting criteria algorithm or a history of diabetes treatment. Renal function was estimated using the Modification of Diet in Renal Disease equation.

CT analysis. All MESA participants underwent baseline CT scans that were analyzed for both coronary artery calcium (CAC) and AVC. Three institutions used an electron beam tomography Imatron C150 scanner (GE Medical Systems, Milwaukee, Wisconsin), whereas 3 institutions used 4-slice multidetector CT scanners. Spatial resolution was 1.38 mm^3 for electron beam tomography (0.68 × 0.68 × 3.00 mm) and 1.15 mm^3 for multidetector CT (0.68 × 0.68 × 2.50 mm). Full details concerning the equipment, scanning methods, and quality control, including image calibration, phantom adjustment, and interscanner reproducibility, were reported previously (9,10).

All scans were sent to a central MESA CT reading center (Harbor-UCLA Research and Education Institute, Los Angeles, California). Calcium strongly attenuates x-rays, appears bright on CT scans, and is readily differentiated from surrounding tissue. The methods for CAC scoring in MESA were described previously (11). Consistent with accepted methodology (10,12–14), lesions were classified as AVC if they resided within the aortic valve leaflets, exclusive of the aortic annulus or coronary arteries, and contained ≥3 contiguous pixels of ≥130 Hounsfield units of brightness. Using Agatston methodology (15), single-lesion calcium contents were summed to give a total AVC score. If no lesions reached threshold, the AVC score was 0.

Outcomes assessment. MESA participants were followed prospectively from the time of enrollment. To capture unreported events, telephone interviews were conducted every 9 to 12 months. More than 99% of self-reported hospitalizations and 97% of cardiovascular outpatient diagnoses and procedures were investigated through medical record review, and incident aortic valve disease and valve replace-

ments were identified by ICD-9 diagnosis and procedure codes. Death investigations included examination of death certificates and next-of-kin interviews. Each event was adjudicated by 2 physicians, with committee review of disagreements. Deaths potentially due to cardiovascular causes were adjudicated by the full committee.

The combined endpoints of major coronary events (MI, resuscitated cardiac arrest, and cardiovascular death) and major cardiovascular events (coronary events plus nonfatal or fatal stroke) were pre-specified by MESA. Definite or probable MIs were defined by symptoms, electrocardiographic findings, and abnormal cardiac biomarker levels (>2 times upper limits of normal). Strokes were defined as neurological deficits lasting >24 h or lesions on brain imaging consistent with a localized ischemic or hemorrhagic event.

Data analyses. MESA participants were categorized according to the presence (AVC score >0) or absence (AVC score = 0) of AVC on baseline examination. Differences in baseline demographic features were compared using chi-square test of proportions or the Student *t* test comparison of means where appropriate. Event rates were described and displayed using Kaplan-Meier cumulative events methods. The risks associated with the presence of AVC, adjusted for baseline demographic features,

Table 1. Baseline Demographics and Risk Factors According to the Presence of AVC

	All Subjects (N = 6,685)	No AVC (n = 5,791)	AVC (n = 894)	p Value
Age, yrs	62 ± 10	61 ± 10	70 ± 8	<0.0001
Male	3,157 (47)	2,621 (45)	536 (60)	<0.0001
Race/ethnicity				<0.0001
White	2,583 (39)	2,181 (38)	402 (45)	
Chinese	795 (12)	729 (13)	66 (7)	
Black	1,832 (27)	1,605 (28)	227 (25)	
Hispanic	1,475 (22)	1,276 (22)	199 (22)	
Body mass index, kg/m^2	28.3 ± 5.5	28.3 ± 5.5	28.5 ± 5.0	0.26
Hypertension	2,997 (45)	2,421 (42)	576 (64)	<0.0001
Medical therapy	2,486 (37)	1,991 (34)	495 (55)	<0.0001
Blood pressure, mm Hg				
Systolic	127 ± 22	125 ± 21	135 ± 22	<0.0001
Diastolic	72 ± 10	72 ± 10	72 ± 10	0.52
Diabetes status				<0.0001
Normal	4,922 (74)	4,350 (75)	572 (64)	
Impaired fasting glucose	924 (14)	783 (14)	141 (16)	
Diabetes	839 (13)	648 (11)	181 (20)	
Smoking status				<0.0001
Never	3,362 (50)	2,972 (51)	390 (44)	
Former	2,455 (37)	2,044 (35)	411 (46)	
Current	868 (13)	775 (13)	93 (10)	
Pack-years smoking	16 (6–32)	15 (6–31)	20 (7–44)	<0.0001
Family history of MI	2,680 (40)	2,277 (39)	403 (45)	<0.0001
Cholesterol, mg/dl				
Total	194 ± 36	194 ± 35	195 ± 38	0.37
Low density	117 ± 31	117 ± 31	119 ± 31	0.11
High density	51 ± 15	51 ± 15	49 ± 14	<0.0001
Triglycerides†	111 (78–161)	110 (77–159)	120 (83–172)	0.0006
Cholesterol/HDL ratio	4.1 (1.2)	4.0 (1.2)	4.2 (1.2)	<0.0001
Lipid-lowering medications	1,088 (16)	856 (15)	232 (26)	<0.0001
CRP, mg/dl	1.91 (0.84–4.24)	1.89 (0.82–4.26)	2.05 (0.95–4.09)	0.04
Estimated GFR, ml × min^{-1} × (1.73 m^2)$^{-1}$	81 (18)	82 (18)	76 (19)	<0.0001
CAC	3,339 (50)	2,609 (45)	730 (82)	<0.0001

Values are mean ± SD, n (%), or median (interquartile range). SI conversion factors: to convert cholesterol concentrations to mmol/l, multiply by 0.0259; to convert triglyceride concentrations to mmol/l, multiply by 0.01129; to convert creatinine to μmol/l, multiply by 88.4.

AVC = aortic valve calcium; CAC = coronary artery calcium; CFP = C-reactive protein; GFR = glomerular filtration rate; HDL = high-density lipoprotein; MI = myocardial infarction.

were estimated using Cox proportional hazards regression. Schoenfeld residual and log-minus-log survival plots were used to confirm the proportional hazards assumptions of these models.

Incremental model building was performed to demonstrate the impact of baseline factors on overall risk. Model 1 included adjustments for age, sex, and race. Model 2 additionally adjusted for body size, cardiovascular risk factors, and renal function. Model 3 additionally included adjustment for CRP, which was log-transformed before inclusion due to its skewed distribution. Exploratory models adding fibrinogen and interleukin-6 were also performed, but did not substantively alter the results.

Model 4 included adjustment for baseline CAC score, modeled as a log-transformed variable using the sum of the CAC score plus 1 (i.e., log[CAC + 1]) to permit inclusion of subjects with CAC scores of 0. Exploratory analyses using alternative CAC transformations were performed, including Greenland categories (0, 1 to 100, 100 to 300, and >300) (16) and a square root transformation, but these did not substantively alter the analytical results.

All statistical analyses were performed with Stata version 11.0 for Windows (StataCorp, College Station, Texas). Statistical significance was defined as $p < 0.05$, and hazard ratios (HRs) are reported with 95% confidence intervals (CIs).

RESULTS

Study subjects. Of the 6,814 participants initially recruited into MESA, 6,685 were included in these analyses. Participants were excluded because of cardiovascular events before enrollment (n = 5, 0.1%), lost to follow-up (n = 33, 0.5%), no baseline AVC scoring (n = 1, 0.01%), and missing covariate data (n = 90, 1.3%). Two excluded subjects had strokes during follow-up, 1 each with and without AVC at baseline.

The baseline characteristics of the study cohort are shown in Table 1. AVC was observed in 13% of the cohort at baseline, with a median Agatston score of 58 (interquartile range: 20 to 149). Subjects with AVC were older and more likely to be male and had worse overall cardiovascular risk factor profiles. Additionally, subjects with AVC were more likely to have CAC and to have higher CAC scores (Fig. 1).

Subjects were followed for a median of 5.8 years (interquartile range: 5.6 to 5.9 years), with a maximum follow-up of 7.1 years. During this period, there were 40 cases of incident aortic valve disease and 22 aortic valve replacements, as well as 160 coronary and 255 cardiovascular events.

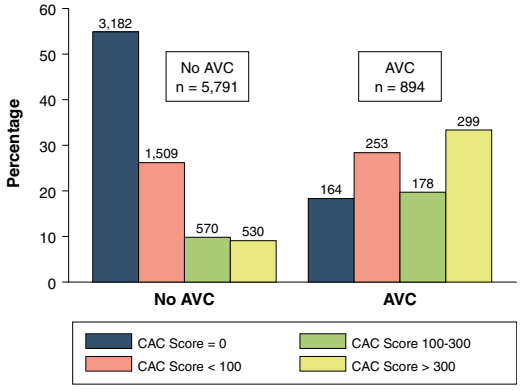

Figure 1. Distribution of CAC Scores, Stratified by Presence of AVC

The prevalence of coronary artery calcium (CAC) categories (CAC score = 0, <100, 100 to 300, and >300) among MESA participants with (n = 894) and without (n = 5,791) aortic valve calcium (AVC) at baseline. Participants with baseline AVC had a higher prevalence of CAC (87.1% vs. 45.1%, $p < 0.0001$) compared with those without AVC, with skewing of the distribution of CAC scores toward more severe calcification.

Risk of coronary and cardiovascular events. Figure 2 depicts the unadjusted Kaplan-Meier cumulative event curves for major coronary and cardiovascular events, respectively. After adjusting for age, race, and sex (Table 2, model 1), the presence of AVC was a strong predictor of both cardiovascular and coronary events. Although these risks were attenuated after adjusting for known atherosclerotic risk factors (Table 2, model 2), AVC remained predictive of both cardiovascular (HR: 1.50; 95% CI: 1.10 to 2.04) and coronary (HR: 1.72; 95% CI: 1.19 to 2.49) events.

The inclusion of CRP in the model (Table 2, model 3) did not alter these findings. However, in the fully adjusted model that included adjustments for both CRP and CAC scores (Table 2, model 4), AVC demonstrated a borderline association with cardiovascular (HRL 1.32; 95% CI: 0.98 to 1.78) and coronary (HR: 1.41; 95% CI: 0.98 to 2.02) events. Additionally, there was no significant trend in risk across AVC tertiles for either outcome (HR: 1.17, p = 0.32 and HR = 1.09, p = 0.66, respectively).

Risk by event type. In fully adjusted models incorporating demographics, cardiovascular risk factors, inflammatory biomarkers, and CAC scores, the presence of AVC was not associated with increased risk of MI or stroke (Table 3), but was associated with a 2.76-fold (95% CI: 1.44 to 5.30) higher risk of cardiovascular death or resuscitated cardiac arrest. These results were unaltered (HR: 2.72; 95%

CI: 1.37 to 5.40; p = 0.004) when subjects with clinical progression (incident clinical valve disease or valve replacement, n = 54) or higher baseline calcium (AVC score >100, n = 293) were excluded. Increasing tertiles of AVC were observed to have increased event rates (Fig. 3). Compared with those without AVC, those with AVC scores of 1.9 to 29.2, 29.4 to 107, and 107.5 to 7,672 had a 2.18-fold (95% CI: 0.93 to 5.12), 3.10-fold (95% CI: 1.31 to 7.37), and 3.02-fold (95% CI: 1.22 to 7.43) higher risk of cardiovascular death, respectively, after full adjustment.

Risk by race/ethnicity. After adjustment for demographics, cardiovascular risk factors, inflammation, and CAC score, there were no significant differences by race/ethnicity in the association of AVC with either cardiovascular (p interaction = 0.12) or coronary (p interaction = 0.13) events.

DISCUSSION

Calcific aortic valve disease begins in midlife as a clinically latent but progressive disorder and often is detected incidentally. Yet even in this latent, preobstructive phase, the presence of aortic valve calcium appears to be a marker of increased cardiovascular risk. Previous results from the CHS (Cardiovascular Health Study) showed that, among adults older than 65 years of age, echocardiographically detected aortic sclerosis was associated with a 50% increased risk of cardiovascular mortality (6). In that study, aortic sclerosis also was associated with a 42% increase in risk of MI. However, these analyses were unable to control for the presence of subclinical atherosclerosis and systemic inflammation, plausible mediators of these associations.

Our results extend these previous findings to a younger, healthier, and multiethnic population and offer a partial explanation for the observed association between aortic sclerosis and coronary events. Among participants age 45 to 84 years and free of cardiovascular disease at baseline and after adjustment for demographics and cardiovascular risk profiles, the presence of AVC on CT was associated with a significant, 50% higher risk of cardiovascular events and a 72% higher risk of coronary events. Notably, these results are similar in magnitude to echocardiographically detected aortic sclerosis in CHS. These risk estimates were unaltered by adjustment for inflammatory biomarkers, suggesting that systemic inflammation did not account for these associations.

Conversely, the risk estimates were attenuated substantially after adjusting for the severity of subclinical atherosclerosis, as estimated by CAC scores. CAC has been strongly and independently associated with cardiovascular events across a range of age, ethnic, and

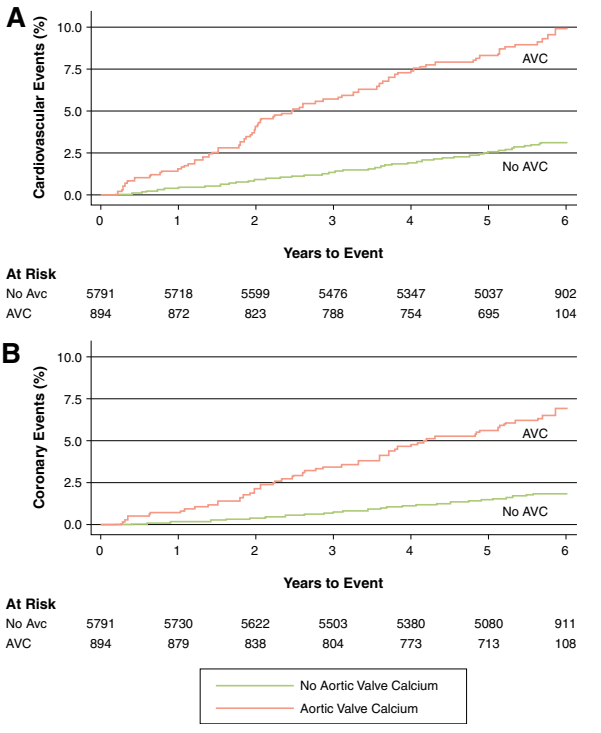

Figure 2. Kaplan-Meier Event Curves for Primary and Secondary Outcomes

Unadjusted Kaplan-Meier cumulative event curves depicting the cardiovascular **(A)** and coronary **(B)** events rates among participants with **(red)** and without **(green)** aortic valve calcium (AVC) at baseline. At the median 5.8 years of follow-up, participants with AVC had higher unadjusted rates of both cardiovascular (3.2% vs. 10.2%, p < 0.0001) and coronary (1.9% vs. 6.9%, p < 0.0001) events compared with participants without AVC.

Table 2. Incrementally Adjusted Risks of Cardiovascular Events Associated With the Presence of Aortic Valve Calcification

	Major Cardiovascular Event (n = 255)		Major Coronary Event (n = 160)	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Model 1	1.82 (1.37–2.42)	<0.001	2.07 (1.45–2.95)	<0.001
Model 2	1.50 (1.10–2.04)	0.009	1.72 (1.19–2.49)	0.004
Model 3	1.50 (1.10–2.03)	0.01	1.72 (1.19–2.49)	0.004
Model 4	1.32 (0.98–1.78)	0.07	1.41 (0.98–2.02)	0.07

Model 1 included adjustments for age, sex, and race. Model 2 included all variables in model 1 plus adjustments for body mass index, systolic and diastolic blood pressure, diabetes status, use of antihypertensive therapy, smoking status, family history of heart attack, total cholesterol, high-density lipoprotein cholesterol, triglycerides, use of cholesterol-lowering medications, and renal function. Model 3 included all variables in model 2 plus adjustment for log(C-reactive protein). Model 4 included all variables in model 3 plus adjustment for log(coronary artery calcium score + 1).
CI = confidence interval; HR = hazard ratio.

Table 3. Number of Pre-Specified Events by Event Type, Stratified by the Presence or Absence of AVC at Baseline

	Total (N = 6,685)	No AVC (n = 5,791)	AVC (n = 894)	HR (95% CI)	
				Age, Race, Sex	Fully Adjusted*
Coronary, n (%)					
MI	126 (1.9)	87 (1.5)	39 (4.3)	1.67 (1.11–2.52)	1.11 (0.73–1.68)
Resuscitated cardiac arrest	17 (0.3)	8 (0.1)	9 (1.0)	5.94 (2.05–17.2)	5.37 (1.43–20.1)
Cardiovascular death†	36 (0.5)	18 (0.3)	18 (2.2)	3.66 (1.79–7.48)	2.51 (1.22–5.21)
Cardiovascular, n (%)					
Any stroke	103 (1.5)	71 (1.2)	32 (3.6)	1.75 (1.11–2.74)	1.38 (0.84–2.27)
Fatal stroke	13 (0.2)	10 (0.2)	3 (0.4)	0.74 (0.19–2.82)	0.59 (0.14–2.51)

Events may not add up due to synchronous events (e.g., MI resulting in cardiovascular death would be classified as a single coronary event). *HRs are adjusted for age, race, sex, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes status, smoking status, pack-years smoked, total cholesterol, high-density lipoprotein cholesterol, triglycerides, use of lipid-lowering medications, renal function, C-reactive protein, and log of coronary calcium scores. †Cardiovascular deaths excluding strokes.
Abbreviations as in Tables 1 and 2.

risk profiles (8,16–18). We found a strong association between the presence of AVC and both the prevalence and severity of CAC in MESA (Fig. 1), and after adjusting for CAC, the observed risk of MI approached unity. These findings suggest that CAC scores are an effective marker of coronary event risk and that a substantial portion of the increased risk of cardiovascular morbidity seen with AVC is due to coexistent subclinical atherosclerosis.

To test whether AVC was associated with clinical events, we performed extensive adjustments beyond the standard Framingham risk factors, including adjustments for body mass index, diabetes, impaired fasting glucose, pack-years of smoking, family history of MI, use of lipid-lowering therapy, and renal function. Thus, our findings do not preclude the possibility that AVC adds to Framingham risk prediction. Among 5,877 nondiabetic subjects in MESA, AVC remained strongly associated with coronary events after adjustment for Framingham risk factors alone (HR: 1.85; 95% CI: 1.33 to 2.59) and Framingham risk factors plus CAC (HR: 1.42; 95% CI: 1.02 to 1.98). Whether AVC improves risk categorization beyond Framingham risk calculations requires more detailed analyses beyond the scope of the present investigation.

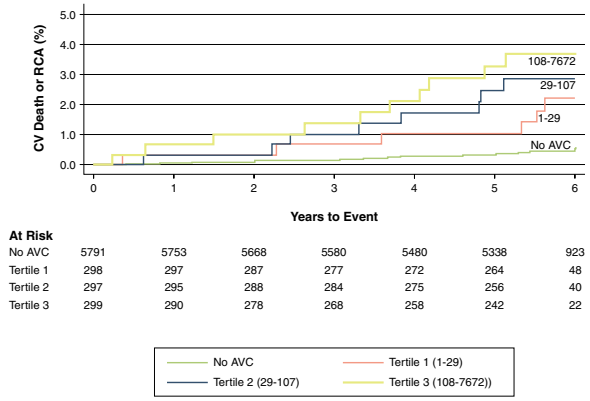

Figure 3. Kaplan-Meier Event Curves for CV Mortality

Unadjusted Kaplan-Meier cumulative event curves for the combined endpoint of cardiovascular (CV) death or resuscitated cardiac arrest (RCA), stratified by tertiles of baseline aortic valve calcium (AVC) score. At the median 5.8 years of follow-up, the unadjusted event rate for participants without baseline AVC was 0.5% compared with event rates of 2.1% (tertile 1), 3.2% (tertile 2), and 3.7% (tertile 3) for those with increasing severity of baseline AVC. After full adjustment for age, sex, cardiovascular risk factors, renal function, and coronary artery calcium scores, there remained a 1.48-fold (95% confidence interval: 1.14 to 1.95; p = 0.004) increase in risk of CV death or RCA per-tertile increase in AVC score.

In pre-specified exploratory analyses, AVC remained an independent predictor of cardiovascular mortality after adjustment for risk factors and CAC severity. Given the low event rate, this finding must be interpreted with caution. Nonetheless, this finding is intriguing because this excess mortality may be unrelated to progressive valve disease. Participants with substantial calcium progression likely would have developed symptoms and undergone valve replacement, whereas death from asymptomatic aortic stenosis is relatively uncommon (19), even in very severe aortic stenosis (20). Previous studies suggest that aortic stenosis is uncommon with AVC scores <150 (13,14), and exclusion of those with known progression and those with AVC scores >100 did not alter the risk association. The mechanisms underlying this observed association remain unexplained, and further investigations are warranted.

Study limitations. First, AVC was not a pre-specified variable in MESA, and CT scans obtained for the purpose of CAC scoring were analyzed retrospectively. Second, only baseline risk factor profiles were included as covariates, and changes in profiles were not evaluated. Third, the rate of cardiovascular events in MESA was low, reducing

the power to detect risk associations. Finally, participants and their physicians were informed of high CAC scores, knowledge that may have prompted therapy to reduce cardiovascular risk; however, such treatment would likely bias results toward the null.

CONCLUSIONS

In a multiethnic cohort without clinical cardiovascular disease at baseline, AVC was associated with risks of coronary and cardiovascular events beyond those predicted by traditional risk factors. These risk associations were attenuated after adjustment for CAC but not for inflammatory markers, suggesting that AVC partly serves as a marker of subclinical atherosclerosis severity. Whether AVC adds to cardiovascular risk prediction beyond Framingham risk categorization merits additional investigation. Finally, through mechanisms yet to be elucidated, the association of AVC with excess cardiovascular mortality remained, even after adjustment for risk factors, inflammation, and subclinical atherosclerosis.

Acknowledgments

The authors thank the other investigators, staff, and participants of MESA for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Reprint requests and correspondence: Dr. Kevin D. O'Brien, Division of Cardiology, Box 356422, University of Washington, 1959 N.E. Pacific Street, Seattle, Washington 98195-6422. *E-mail: cardiac@u.washington.edu.*

REFERENCES

1. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol 1997;29:630–4.
2. Agmon Y, Khandheria BK, Meissner I, et al. Aortic valve sclerosis and aortic atherosclerosis: different manifestations of the same disease? Insights from a population-based study. J Am Coll Cardiol 2001;38:827–34.
3. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkila J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. Eur Heart J 1994;15:865–70.
4. Owens DS, Katz R, Takasu J, Kronmal R, Budoff MJ, O'Brien KD. Incidence and progression of aortic valve calcium in the Multi-ethnic Study of Atherosclerosis (MESA). Am J Cardiol 2010;105:701–8.
5. O'Brien KD. Pathogenesis of calcific aortic valve disease. A disease process comes of age (and a good deal more). Arterioscler Thromb Vasc Biol 2006; 26:1721–8.
6. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142–7.
7. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
8. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358: 1336–45.
9. Budoff MJ, Katz R, Wong ND, et al. Effect of scanner type on the reproducibility of extracoronary measures of calcification: the multi-ethnic study of atherosclerosis. Acad Radiol 2007;14: 1043–9.
10. Budoff MJ, Takasu J, Katz R, et al. Reproducibility of CT measurements of aortic valve calcification, mitral annulus calcification, and aortic wall calcification in the multi-ethnic study of atherosclerosis. Acad Radiol 2006;13:166–72.
11. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology 2005;234:35–43.
12. Budoff MJ, Mao S, Takasu J, Shavelle DM, Zhao XQ, O'Brien KD. Reproducibility of electron-beam CT measures of aortic valve calcification. Acad Radiol 2002;9:1122–7.
13. Shavelle DM, Budoff MJ, Buljubasic N, et al. Usefulness of aortic valve calcium scores by electron beam computed tomography as a marker for aortic stenosis. Am J Cardiol 2003;92:349–53.
14. Messika-Zeitoun D, Aubry MC, Detaint D, et al. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. Circulation 2004; 110:356–62.
15. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
16. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210–5.
17. Raggi P, Gongora MC, Gopal A, Callister TQ, Budoff M, Shaw LJ. Coronary artery calcium to predict all-cause mortality in elderly men and women. J Am Coll Cardiol 2008;52:17–23.
18. Nasir K, Shaw LJ, Liu ST, et al. Ethnic differences in the prognostic value of coronary artery calcification for all-cause mortality. J Am Coll Cardiol 2007;50:953–60.
19. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611–7.
20. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. Circulation 2010;121:151–6.

Key Words: aortic sclerosis ■ aortic valve calcium ■ atherosclerosis ■ cardiovascular death ■ cardiovascular events ■ computed tomography ■ coronary artery calcium ■ coronary events.