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Relation of Aortic Valve Sclerosis to Risk of Coronary Heart Disease in African-Americans

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To assess the relation between aortic valve sclerosis (AVS) and subsequent occurrence of coronary heart disease (CHD) events, we analyzed echocardiographic data obtained from 2,279 middle-aged African-Americans enrolled in the Jackson Mississippi Atherosclerosis Risk in Communities study cohort who were free of known CHD at the time of the examination. Cox regression analyses demonstrated a hazard ratio of 3.8 for incident first myocardial infarction or fatal CHD after adjusted for multiple risk factors, including markers of inflammation. An amplification of CHD risk in the AVS subgroup with high levels of serum inflammatory markers (the highest quartile of fibrinogen and von Willebrand Factor levels) demonstrated greater than fivefold higher risk of CHD associated with AVS than risk in the lowest quartile. ©2005 by Excerpta Medica Inc.

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We analyzed data from the African-American cohort of the Atherosclerosis Risk in Communities (ARIC) study in Jackson, Mississppi[1] to assess the prevalence of aortic valve sclerosis (AVS) and its potential role as a predictor of coronary heart disease (CHD) among a population distinguished by its high prevalence of subclinical cardiovascular disease[2] and high cardiovascular mortality.[3]

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The ARIC study is a prospective epidemiologic investigation of the etiology and natural history of atherosclerosis. Objectives of the study include understanding the causes of subclinical and clinical manifestations of atherosclerosis, and the variation in cardiovascular risk factors, medical care, and disease by gender, race, geographic location, and time.[4] The ARIC cohort is made up of patients from 4 United States communities including Forsyth County, North Carolina, the northwestern suburbs of Minneapolis, Minnesota, Washington County, Maryland, and the city of Jackson, Mississippi. The ARIC study was designed to examine and follow approximately 16,000 men and women aged 45 to 64 years: 4,000 were selected from each of the 4 communities. Probability sampling was used to identify participants who would be representative of 3 of these communities, and in the case of Jackson, Mississippi, a representative sample was drawn among only African-Americans. Details of the selection procedures have been previously reported.[1] In all, 3,728 African-American participants enrolled, and 9 years later (1996 to 1998), 2,445 returned for echocardiographic examination. Participants were also interviewed by trained personnel to obtain information about tobacco and alcohol use; physical examination included anthropometry, blood pressure measurement, and phlebotomy for multiple analyses.

The echocardiographic examinations were conducted in the ARIC Jackson Center Clinic facilities in Jackson, Mississippi. Two staff nurses were trained to perform the studies, following a standardized protocol with the Acuson XP128/10c echocardiographic machine (Siemens AG, Malvern, Pennsylvania). Additional details of the methods are reported elsewhere.[5] AVS was defined by focal areas of increased echoge-

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TABLE 1 Distribution of Cardiovascular Disease Risk Factors by Aortic Valve Sclerosis Status

Variable	Nonaortic Sclerosis (n = 2,104)	Aortic Sclerosis (n = 175)	p Value
Age (yrs)	58.7 ± 5.6	64.0 ± 5.3	<0.001
Body mass index (kg/m^2)	30.5 ± 6.3	30.0 ± 6.2	0.30
Men (%)	34%	47%	<0.001
High-density lipoprotein (mg/dl)	56.8 ± 18.8	52.8 ± 18.0	0.006
Low-density lipoprotein (mg/dl)	125.7 ± 36.6	137.8 ± 40.1	0.07
Diabetes mellitus*	23%	35%	<0.001
Systolic blood pressure, (mm Hg)	131 ± 20.1	138 ± 23.7	<0.001
Hypertension medication	47%	58%	0.004
Current smoker	19%	24%	0.13
Fibrinogen (mg/dl)	311 ± 68	329 ± 69	0.001
von Willebrand factor (%)	130 ± 53	143 ± 61	0.002
Intimal-medial thickness (mm)	0.71 ± 0.14	0.81 ± 0.16	<0.001

*Fasting glucose ≥126 mg/dl, or history of diabetes mellitus, or taking antidiabetic medication. Values are expressed as mean ± SD.

TABLE 2 Age-adjusted Incident Coronary Heart Disease (CHD) Events by Aortic Valve Status

Incident* Events Type	Incidence Rate: Nonaortic Sclerosis (n = 2,104)	Incidence Rate: Aortic Valve Sclerosis (n = 175)
Hospitalized myocardial infarction or fatal CHD	4.3	26.7
Hospitalized myocardial infarction, fatal CHD, or procedure†	5.2	29.7
Hospitalized myocardial infarction, fatal CHD, Procedure† or silent myocardial infarction‡	5.9	30.6

*Incidence reported as age-adjusted incident CHD events/1,000 person-years. Participants with known prevalent CHD at time of echocardiographic examination were excluded.

†Procedures include coronary artery bypass graft surgery or angioplasty.

‡Silent myocardial infarctions are infarctions that were only detected on electrocardiography when participants came to the routine clinic visit; however, no symptoms were ever expressed by these participants.

nicity and thickening of the aortic valve leaflets without restriction of leaflet motion.[6] Ninety-eight percent of participants had adequate visualization of the aortic valve to assess for AVS on 2-dimensional imaging. Of the remaining participants, those who had any degree of restriction of leaflet motion suggesting aortic stenosis and those who developed incident CHD events before the date of echocardiographic examination (n = 119) were excluded from analysis. A total of 2,279 participants were used for the present analyses after applying exclusion criteria.

Incident CHD was defined as (1) definite or probable hospitalized myocardial infarction, (2) electrocardiographic evidence of a silent myocardial infarction, (3) definite CHD death, and (4) coronary bypass surgery or coronary angioplasty. Standard ARIC events review and adjudication procedures were used as described in previous reports.[4,7,8]

General characteristics of the study population are summarized by mean ± SDs for continuous data and percentages for categorical data. Univariate contrasts between subgroups were based on *t* tests and chi-square tests, or Fisher's exact test when appropriate. Cox proportional-hazard models were used to estimate the hazard ratio for incident CHD in relation to the presence or absence of AVS. For participants who developed CHD, the time of follow-up was the time between echocardiographic examination and date of the event. For all other participants, December 31, 1999 was the date for the end point for follow-up. Potential covariates were tested one at a time using the age-adjusted simple model and were chosen to be entered into the final multivariable-adjusted model if they were significant in the simple model. Covariates of interest included age, gender, diabetes status, systolic blood pressure and hypertension medication, smoking status, carotid artery intimal-medial thickness, fibrinogen levels, von Willebrand factor, lipoprotein cholesterol levels, triglycerides, cigarette-years of smoking, current drinker, ethanol intake/week, and left ventricular hypertrophy. The assumption of proportionality of hazards using the Cox model was validated. To further investigate the potential modification effect of inflammation factors on the AVS-CHD association, similar analyses were performed, stratifying for fibrinogen and von Willebrand factor status. Quartiles of these 2 factors were obtained, and the lower 3 quartiles for both factors were grouped into a single category due to few CHD events in the lower 3 quartiles. The hazard ratio for CHD given the AVS status within each fibrinogen and von Willebrand factor stratum was calculated after adjustment of other covariates. All data analyses were performed using SAS, version 9 (SAS Inc., Cary North Carolina).

Table 1 lists the distribution of disease risk factors for those with sclerotic and nonsclerotic aortic valves. Those with AVS were significantly older, and disproportionately men. For those aged 65 to 74 years, the prevalence of AVS was 18.6%. Additionally, those with AVS had lower mean levels of high-density lipoprotein, and higher levels of systolic blood pressure, low-density lipoprotein, fibrinogen, and carotid intimal medial thickness. Diabetes mellitus, hypertension medication users, and those with higher von Willebrand factor levels were also significantly more likely to be among the AVS group. All these differences were statistically significant at the 99% confidence level. Age-adjusted CHD incidence rates were >4 times higher for those with AVS than for those without AVS, for all 3 definitions of CHD (Table 2).

Age-adjusted simple models displayed in Table 3 show that those with AVS were 4.26 times more likely to have had a CHD incident event than those without AVS. Men, diabetics, hypertension medication users,

TABLE 3 Hazard Ratio (HR) Estimates for Age-adjusted Simple Models and Multivariable Model for Aortic Valve Sclerosis as a Predictor of Incident Coronary Heart Disease*

Variables	Age-adjusted Simple Models†	Multivariable Model
Aortic valve sclerosis	4.26 (2.15–8.04)	3.82 (1.83–7.97)
Women	0.59 (0.36–0.99)	0.80 (0.41–1.54)
Diabetes mellitus (%)	1.92 (1.13–3.25)	1.80 (0.96–3.38)
Systolic blood pressure (mm Hg)	1.02 (1.01–1.03)	1.02 (1.00–1.03)
Hypertension medication status	2.00 (1.13–3.53)	1.68 (0.85–3.32)
Current smoker status	3.30 (1.78–6.15)	2.65 (1.41–4.97)
High-density lipoprotein (mg/dl)	0.97 (0.96–0.99)	0.99 (0.97–1.01)
Low-density lipoprotein (10 mg/dl)	1.1 (0.99–1.02)	1.1 (0.99–1.01)
Intimal-medial thickness (mm)	4.83 (1.03–22.62)	0.67 (0.01–5.08)
Fibrinogen (10 mg/dl)	1.1 (1.0–1.2)	1.1 (1.0–11.2)
von Willebrand Factor (10%)	1.01 (1.00–1.02)	1.03 (1.00–1.05)

*Hospitalized myocardial infarction or fatal CHD.

†Covariates as major risk factors of CHD are put into the model one at a time, along with the age variable. If a covariate was significant in the simple model, it was put into the multivariable model. Also, variables that have relevant clinical meanings from previous studies, although not significant in the present analyses, are still included in the model.

Values are expressed as hazard ratio (95% confidence interval).

TABLE 4 Hazard Ratio (HR) Estimates for Aortic Valve Sclerosis as a Predictor of Incident Coronary Heart Disease (CHD) Events* Stratified by Fibrinogen and von Willebrand Factor

Quartiles†	Patients at Risk (n)	No. of CHD Events*	HR (95% CI)‡	p Value
Fibrinogen				
Highest	552	25	5.8 (1.9–17.4)	0.002
Lower 3	1,727	34	2.7 (0.9–8.0)	0.07
Von Willebrand factor				
Highest	534	24	7.1 (12.7–16.7)	<0.001
Lower 3	1,745	35	1.6 (0.4–6.4)	0.51

*Incident CHD events include myocardial infarction and CHD death.

†The cut point of the highest quartile is 349 mg/dl for fibrinogen and 161% for von Willebrand factor. The p values for the interactions between AVS status and inflammatory marker categories are 0.39 for fibrinogen, and 0.07 for von Willebrand factor.

‡Covariates adjusted in the model include age, gender, systolic blood pressure and hypertension medication status, diabetics, current smoking status, high-density lipoprotein, intimal-medial thickness, fibrinogen (except for fibrinogen stratified models), von Willebrand factor (except for von Willibrand factor–stratified models).

CI = confidence interval; HR = hazard ratio.

and those with elevated von Willebrand factor levels were more likely to have had a CHD event. In addition, those with higher systolic blood pressures, lower high-density lipoprotein levels, higher carotid intimal medial thickness levels, and higher fibrinogen levels were more likely to have had CHD events. After adjusting for age, gender, diabetes mellitus status, systolic blood pressure, hypertension medication status, smoking status, high-density lipoprotein levels, carotid intimal-medial thickness, fibrinogen levels, and von Willebrand factor levels, those with AVS were still 3.82 times more likely to have had a CHD event than the AVS-free population. Among the covariates, only smoking status, systolic blood pressure, and von Willebrand factor levels remained significant in this multivariable model.

Table 4 lists hazard ratio estimates for AVS as a predictor of incident CHD events stratified by fibrinogen and von Willebrand factor levels. Von Willebrand factor and fibrinogen thresholds for the fourth quartile are listed in Table 4. Although interactions were not found to be statistically significant, hazard ratios for CHD were much higher for the fourth quartile than for the 3 lower quartiles of fibrinogen and von Willebrand factors.

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These analyses suggest that AVS, a disorder studied primarily in elderly, white populations, is a lesion of significant prevalence and prognostic importance among a younger, African-American sample. The risk of CHD events associated with AVS is not accounted for by the presence of established CHD risk factors, although these factors were more common among subjects with AVS. We also show evidence that inflammation, as measured by the presence of elevated levels of serum inflammatory markers, dramatically increases the risk of CHD in those with AVS. In the absence of elevated fibrinogen and von Willebrand factor, AVS-related CHD events appear to occur much less often. This report is the first to identify a synergy with inflammation and AVS for CHD risk.

Much of our data are consistent with previous reports. Our analysis reveals a high prevalence of AVS among African- Americans aged >65 years, a rate similar to that reported in a study of elderly white patients.[1] Men in our study were more likely to have AVS than women at comparable ages. Also, our data are consistent with earlier reports that show a higher prevalence of traditional cardiovascular disease risk factors among patients with AVS.[5,9]

Our cohort and our results add to the findings from previous studies in important ways. The average age of the Jackson-ARIC cohort is relatively young—approximately 10 years younger than that of the Cardiovascular Health Study (CHS). Although the CHS cohort was aged ≥65 years, the prevalence of AVS in our sample (8%) was similar to that of CHS. Although AVS clearly occurs more often among older adults, our analysis demonstrates that this lesion is not exclusively a problem of advanced age.

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Use of *Amiodarone* for Atrial Fibrillation in Patients With Preexisting Pulmonary Disease in the AFFIRM Study

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In the Atrial Fibrillation Follow-up Investigation of Rhythm Management study, preexisting pulmonary disease did not preclude the use of amiodarone. Preexisting pulmonary disease was associated with a higher risk of pulmonary death and had a higher risk of diagnosed amiodarone pulmonary toxicity. However, use of amiodarone in the presence of preexisting pulmonary disease did not increase pulmonary death and all-cause mortality rates. Cautious use of amiodarone to treat atrial fibrillation appears acceptable in elderly patients with atrial fibrillation, even if preexisting pulmonary disease is present. ©2005 by Excerpta Medica Inc.

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Amiodarone can cause serious, even fatal, pulmonary toxicity, perhaps at a greater rate if preexisting pulmonary disease is present. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study compared a rate-control strategy with a rhythm-control strategy for patients with atrial fibrillation (AF) who had a high risk for stroke or death.[1] Details of the methods and the results have been reported.[1,2] We assessed the risk of pulmonary toxicity, pulmonary-related death, and total death in patients prescribed amiodarone in the AFFIRM study based on the presence or absence of underlying pulmonary disease.

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In the rhythm-control arm of the AFFIRM study, amiodarone was frequently prescribed. This was true even if preexisting pulmonary disease was present. Doses were not reported, except at the time of a patient's death or other serious adverse event causing drug discontinuation. Investigators were allowed to report presumed pulmonary toxicity and discontinue amiodarone without supporting documentation. Therapy with amiodarone could be restarted if the diagnosis was later confirmed not to be pulmonary toxicity. Only when death occurred was supporting documentation required. An events committee, blinded to drug use, adjudicated all deaths.

Patients were classified by (1) presence or absence of pulmonary disease on entry into the study, (2) exposure to amiodarone and temporary or permanent discontinuation of amiodarone for suspected pulmonary toxicity, (3) development of amiodarone-related pulmonary toxicity, (4) pulmonary-related death (all pulmonary causes including cancer), and (5) all-cause mortality.

Groups were compared with chi-square and Fisher's exact tests, as appropriate. Standard Kaplan-Meier analysis was used to assess event-free survival, and groups were compared using the log-rank statistic. All tests were 2-sided.

Pulmonary disease was present in 591 of 4,060 patients (15%) at study onset. Patients with underlying pulmonary disease were more often men, had a higher incidence of coronary artery disease, angina pectoris, myocardial infarction, coronary artery bypass graft surgery or other interventional procedure, hypertension, and hepatic or renal disease ($p < 0.0001$ for each). They were more likely to have cardiomyopathy, to have a history of systemic embolism, to smoke, and to have a worse left ventricular ejection fraction ($p < 0.0001$).

Amiodarone was given to 1,468 of 4,060 patients

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