

## ASSOCIATION OF AORTIC-VALVE SCLEROSIS WITH CARDIOVASCULAR MORTALITY AND MORBIDITY IN THE ELDERLY

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### ABSTRACT

**Background** Although aortic-valve stenosis is clearly associated with adverse cardiovascular outcomes, it is unclear whether valve sclerosis increases the risk of cardiovascular events.

**Methods** We assessed echocardiograms obtained at base line from 5621 men and women 65 years of age or older who were enrolled in a population-based prospective study. On echocardiography, the aortic valve was normal in 70 percent (3919 subjects), sclerotic without outflow obstruction in 29 percent (1610), and stenotic in 2 percent (92). The subjects were followed for a mean of 5.0 years to assess the risk of death from any cause and of death from cardiovascular causes. Cardiovascular morbidity was defined as new episodes of myocardial infarction, angina pectoris, congestive heart failure, or stroke.

**Results** There was a stepwise increase in deaths from any cause ( $P$  for trend,  $<0.001$ ) and deaths from cardiovascular causes ( $P$  for trend,  $<0.001$ ) with increasing aortic-valve abnormality; the respective rates were 14.9 and 6.1 percent in the group with normal aortic valves, 21.9 and 10.1 percent in the group with aortic sclerosis, and 41.3 and 19.6 percent in the group with aortic stenosis. The relative risk of death from cardiovascular causes among subjects without coronary heart disease at base line was 1.66 (95 percent confidence interval, 1.23 to 2.23) for those with sclerotic valves as compared with those with normal valves, after adjustment for age and sex. The relative risk remained elevated after further adjustment for clinical factors associated with sclerosis (relative risk, 1.52; 95 percent confidence interval, 1.12 to 2.05). The relative risk of myocardial infarction was 1.40 (95 percent confidence interval, 1.07 to 1.83) among subjects with aortic sclerosis, as compared with those with normal aortic valves.

**Conclusions** Aortic sclerosis is common in the elderly and is associated with an increase of approximately 50 percent in the risk of death from cardiovascular causes and the risk of myocardial infarction, even in the absence of hemodynamically significant obstruction of left ventricular outflow. (N Engl J Med 1999;341:142-7.)

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**A**ORTIC-VALVE sclerosis, calcification and thickening of a trileaflet aortic valve in the absence of obstruction of ventricular outflow, is common in the elderly, affecting 21 to 26 percent of adults over 65 years of age.<sup>1,2</sup> When calcification and thickening are severe, the increased stiffness of the valve leaflets results in ob-

struction at the valvular level, causing aortic stenosis in 2 to 9 percent of elderly adults.<sup>1,2</sup> The prevalences of both aortic sclerosis and aortic stenosis increase with age, being present in 48 percent and 4 percent, respectively, of adults over 85 years of age.<sup>1</sup>

On the basis of autopsy studies and small clinical series of patients who declined valve replacement, it is clear that severe symptomatic aortic stenosis carries a poor prognosis unless treated surgically.<sup>3-7</sup> In addition, prospective clinical studies suggest that aortic sclerosis gradually progresses to clinically significant stenosis in many patients.<sup>8-13</sup>

However, although the poor clinical prognosis of patients with aortic stenosis and hemodynamically significant obstruction of left ventricular outflow is well established, the clinical prognosis of adults with aortic sclerosis in whom valvular obstruction has not yet developed has not been defined. We hypothesized that since the valve abnormality represents a spectrum of disease, the presence of "asymptomatic" aortic sclerosis may have clinical importance and may not be benign over time. The Cardiovascular Health Study offered an opportunity to address this question, since it includes a large cohort of adults over the age of 65 years who have undergone two-dimensional echocardiography, with assessment of aortic-valve anatomy.<sup>1</sup> We hypothesized that the presence of aortic sclerosis at base line on two-dimensional echocardiography would be associated with an increased risk of cardiovascular events, including myocardial infarction, angina pectoris, congestive heart failure, stroke, and death from cardiovascular causes.

### METHODS

#### Study Population

The Cardiovascular Health Study is a prospective study of 5888 men and women 65 years of age or older who were randomly selected from households identified on Medicare-eligibility lists in four communities in the United States: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania. From 1989 to 1990, 5201 subjects were recruited and examined; an additional 687 blacks were recruited and examined from 1992 to 1993. Of the 5653 subjects with adequate echocardiograms in this cohort, 32 with endocarditis, rheumatic valve disease, a prosthetic valve,

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or hypertrophic cardiomyopathy were excluded, leaving a total of 5621 subjects. The study was approved by the institutional review board at each participating center, and informed consent was obtained.

Details of the study design and its objectives have been published previously.<sup>14</sup> In brief, the base-line examination, conducted in 1989 and 1990, consisted of an extensive history-taking, physical examination, 12-lead electrocardiography, spirometry, and M-mode, two-dimensional, and Doppler echocardiography. Laboratory examination included serum-chemistry tests, an oral glucose-tolerance test, and assessment of levels of plasma lipids after fasting, Lp(a) lipoprotein, and hemostatic factors. In addition, carotid-wall thickness was measured by ultrasonography, with the mean thickness of the internal-carotid-artery wall defined as the average of the maximal thickness of the near and far walls. The supplemental cohort of black subjects underwent a similar base-line examination in 1992 and 1993; however, echocardiography was performed in 1994 and 1995. At study entry, subjects were classified as having prevalent coronary heart disease if they had a clinical history of myocardial infarction, angina, coronary-artery bypass grafting, or angioplasty.

### Echocardiography

Two-dimensional echocardiographic studies were recorded on videotape with use of a cardiac ultrasound machine (model SSH-160A, Toshiba, Tustin, Calif.) as previously described.<sup>15</sup> Two-dimensional assessment of the aortic valve was performed on the basis of the parasternal long-axis and short-axis views. Base-line videotapes were sent to the echocardiography reading center (located at the University of California, Irvine, for the original cohort and at Georgetown University, Washington, D.C., for the supplemental cohort), where abnormalities of the aortic valve were coded as representing aortic stenosis, a bicuspid aortic valve, aortic sclerosis, or aortic-valve vegetation, or the valve was coded as prosthetic. Left ventricular mass was calculated from the M-mode echocardiographic data.

Sclerosis was defined by focal areas of increased echogenicity and thickening of the aortic-valve leaflets without restriction of leaflet motion. Aortic stenosis was defined as thickened leaflets with reduced systolic opening on two-dimensional imaging and an increased velocity across the aortic valve ( $\geq 2.5$  m per second in the original cohort and  $> 2.0$  m per second in the supplemental cohort). The results of 96 percent of the imaging studies were adequate and were classified as normal, indicative of sclerosis, or indicative of stenosis. As previously reported, aortic-valve morphology was reanalyzed in detail in a subgroup of 201 base-line studies from the original cohort, including all 92 coded as indicating aortic stenosis as well as 109 randomly selected studies. Given the acceptable level of agreement between the results from the reading center and the results of the reanalysis ( $\kappa = 0.62$ ), the reading-center results were used for all subsequent analyses.<sup>1</sup>

### Clinical Outcome

Follow-up consisted of annual clinic visits followed by a telephone call six months later. Subjects were queried regarding any hospitalizations at each contact. The mean length of follow-up was 5.5 years for the original cohort, 1.25 years for the supplemental cohort, and 5.0 years overall; follow-up was complete for 95 percent of the cohort. Outcomes of interest were death (from cardiac and noncardiac causes) and new cardiovascular events. The following new (incident) cardiovascular events were considered during follow-up: myocardial infarction, angina pectoris, congestive heart failure, and stroke.<sup>16</sup>

### Statistical Analysis

Analysis of variance was used to compare the base-line characteristics of the subjects according to the echocardiographic findings (normal, sclerotic, or stenotic aortic valves). Chi-square analysis was used to compare the frequency of events in each group. Mantel-Haenszel tests were used to assess linear trends.

In order to assess the association between aortic-valve sclerosis and clinical outcome, we calculated both the rates of events per 1000 person-years and the relative risks (including 95 percent confidence intervals). In the Cox regression analysis, the variable of interest was aortic-valve sclerosis; data on subjects with stenosis were excluded. Cox regression analysis was performed separately for those with prevalent coronary heart disease and those without it, since coexisting coronary disease might confound or modify the relation between aortic sclerosis and clinical outcomes. First, Cox regression analysis adjusted only for age and sex was performed to evaluate the relative risk associated with the presence of aortic sclerosis. Then, in order to evaluate the independent contribution of aortic sclerosis to clinical outcome, base-line clinical factors known to be associated with aortic sclerosis or stenosis were forced into the analysis. These factors, as defined in our previous study,<sup>1</sup> were older age, male sex, shorter height, presence of hypertension, current smoking, elevated low-density lipoprotein cholesterol levels, and presence of diabetes. Because of the short follow-up interval and the small number of events in the supplemental cohort, the initial and supplemental cohorts were combined in the analysis. Statistical analysis was performed with SPSS software (version 7.5, SPSS, Chicago) with default settings.

## RESULTS

### Base-Line Characteristics

The base-line characteristics of the 3919 subjects with normal aortic valves (70 percent), the 1610 subjects with sclerotic valves (29 percent), and the 92 with stenotic aortic valves (2 percent) are shown in Table 1. There was a progressive increase in age, proportion of male subjects, and prevalence of hypertension, coronary heart disease, chronic renal disease, and impaired functional status (P for trend,  $< 0.001$ ) with increasing aortic-valve abnormality.

Mean left ventricular mass was greater in subjects with aortic stenosis than in those with sclerotic or normal aortic valves (183.0, 157.5, and 148.6 g, respectively;  $P < 0.001$ ). The average ( $\pm$ SD) thickness of the wall of the internal carotid artery was  $1.64 \pm 0.60$  mm in subjects with aortic stenosis, as compared with  $1.56 \pm 0.61$  mm in those with sclerosis and  $1.38 \pm 0.54$  mm in those with normal aortic valves ( $P < 0.001$ ).

### Survival

The numbers of deaths and incident cardiovascular events during a mean of 5.0 years of follow-up are shown in Table 2. There was a consistent stepwise increase in deaths from any cause and deaths from cardiovascular causes with increasing aortic-valve abnormality (P for trend,  $< 0.001$ ). There was also a consistent pattern of an increased number of events with increasing abnormality of the aortic valve with respect to myocardial infarction, angina pectoris, congestive heart failure, and stroke.

The rates of death from any cause and death from cardiovascular causes per 1000 person-years of follow-up among subjects with sclerotic valves were approximately twice those among subjects with normal aortic valves. We used Cox regression analysis to evaluate the relative risk of death associated with a sclerotic as compared with a normal aortic valve among

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE SUBJECTS WITH NORMAL AORTIC VALVES, THOSE WITH SCLEROTIC VALVES, AND THOSE WITH STENOTIC VALVES.

CHARACTERISTIC	NORMAL AORTIC VALVES (N=3919)	AORTIC SCLEROSIS (N=1610)	AORTIC STENOSIS (N=92)	P VALUE FOR TREND
Mean ±SD age — yr	72.1±5.2	74.7±6.0	75.8±6.1	<0.001
Sex — no. (%)				
Female	2372 (60.5)	818 (50.8)	45 (48.9)	<0.001
Male	1547 (39.5)	792 (49.2)	47 (51.1)	
Current smoking — no. (%)	452 (11.6)	191 (11.9)	13 (14.1)	0.43
History of hypertension — no. (%)	1724 (44.0)	833 (51.7)	47 (51.1)	<0.001
History of diabetes — no. (%)	446 (11.4)	211 (13.1)	6 (6.5)	0.90
Coronary heart disease — no. (%)	673 (17.2)	383 (23.8)	22 (23.9)	<0.001
Renal insufficiency — no. (%)*	182 (4.8)	123 (8.1)	16 (17.8)	<0.001
Impaired ability to perform activities of daily living — no. (%)†	1039 (26.6)	526 (32.8)	28 (30.8)	<0.001

\*Data were missing for 131 patients with normal aortic valves, 88 patients with aortic sclerosis, and 2 patients with aortic stenosis.

†Data were missing for 7 patients with normal aortic valves, 4 patients with aortic sclerosis, and 1 patient with aortic stenosis.

**TABLE 2.** EVENT RATES IN THE THREE GROUPS.

EVENT	NORMAL AORTIC VALVES (N=3919)	AORTIC SCLEROSIS (N=1610)	AORTIC STENOSIS (N=92)	P VALUE FOR TREND
	number (percent)			
Death from any cause	583 (14.9)	353 (21.9)*	38 (41.3)*	<0.001
Death from cardiovascular causes	238 (6.1)	162 (10.1)*	18 (19.6)*	<0.001
Myocardial infarction†	217 (6.0)	123 (8.6)‡	9 (11.3)‡	<0.001
Angina†	358 (11.0)	160 (13.0)	17 (24.3)*	0.001
Congestive heart failure†	337 (8.9)	192 (12.6)*	21 (24.7)*	<0.001
Stroke†	238 (6.3)	122 (8.0)§	10 (11.6)§	0.003

\*P<0.001 for the comparison with the group with normal aortic valves.

†The rates were calculated for subjects at risk for new events.

‡P<0.01 for the comparison with the group with normal aortic valves.

§P=0.02 for the comparison with the group with normal aortic valves.

subjects without known coronary heart disease at entry into the study, thereby excluding the potential effect of clinically recognized coronary heart disease. After adjustment for age and sex, the risk of death from any cause and death from cardiovascular causes was higher among adults with aortic sclerosis than among subjects with normal aortic-valve leaflets (Table 3). Even when the model was also adjusted for base-line factors associated with aortic sclerosis, there was still an independent increased risk of death from any cause and of death from cardiovascular causes among adults with aortic sclerosis but not coronary heart disease. The risk associated with

sclerosis was not altered by the addition of left ventricular mass or carotid-wall thickness to the model. Risk ratios for men and women were similar, although the statistical power of the study to detect differences on the basis of sex was limited (data not shown).

As expected, the rates of events were higher among subjects with documented coronary heart disease at base line, whether or not they had aortic sclerosis. For each outcome, however, there were only small increases in the estimated relative risks associated with aortic sclerosis, and the 95 percent confidence intervals for these estimates overlapped 1.0 (Table 4).

**TABLE 3.** RATES AND RELATIVE RISKS OF DEATH FROM ANY CAUSE AND OF DEATH FROM CARDIOVASCULAR CAUSES AMONG THE 4073 SUBJECTS WITH NO CORONARY HEART DISEASE AT ENTRY, ACCORDING TO THE PRESENCE OR ABSENCE OF AORTIC SCLEROSIS.\*

VARIABLE	TOTAL NO. OF SUBJECTS	RATE/1000 PERSON-YR	RELATIVE RISK (95% CONFIDENCE INTERVAL)	
			ADJUSTED FOR AGE AND SEX	ADJUSTED FOR AGE, SEX, AND ASSOCIATED BASE-LINE FACTORS†
Death from any cause			1.42 (1.19–1.70)	1.35 (1.12–1.61)
Normal aortic valves	2958	19		
Aortic sclerosis	1115	37		
Death from cardiovascular causes			1.66 (1.23–2.23)	1.52 (1.12–2.05)
Normal aortic valves	2958	6		
Aortic sclerosis	1115	14		

\*Coronary heart disease was defined as a history of myocardial infarction, angina, or coronary artery bypass grafting or angioplasty.

†Factors associated with aortic-valve sclerosis at base line that were included in the model were shorter height, presence of hypertension, current smoking, elevated low-density lipoprotein cholesterol levels, and presence of diabetes.

**TABLE 4.** RATES AND RELATIVE RISKS OF DEATH FROM ANY CAUSE AND OF DEATH FROM CARDIOVASCULAR CAUSES AMONG 1456 SUBJECTS WITH CORONARY HEART DISEASE AT ENTRY, ACCORDING TO THE PRESENCE OR ABSENCE OF AORTIC SCLEROSIS.\*

VARIABLE	TOTAL NO. OF SUBJECTS	RATE/1000 PERSON-YR	RELATIVE RISK (95% CONFIDENCE INTERVAL)	
			ADJUSTED FOR AGE AND SEX	ADJUSTED FOR AGE, SEX, AND ASSOCIATED BASE-LINE FACTORS†
Death from any cause			1.16 (0.94–1.43)	1.14 (0.92–1.41)
Normal aortic valves	961	45		
Aortic sclerosis	495	61		
Death from cardiovascular causes			1.25 (0.94–1.65)	1.21 (0.91–1.61)
Normal aortic valves	961	25		
Aortic sclerosis	495	35		

\*The 92 subjects with aortic stenosis were not included in the analysis. Coronary heart disease was defined as a history of myocardial infarction, angina, or coronary-artery bypass grafting or angioplasty.

†Factors associated with aortic-valve sclerosis at base line that were included in the model were shorter height, presence of hypertension, current smoking, elevated low-density lipoprotein cholesterol levels, and presence of diabetes.

### New Cardiovascular Events

The rates of various cardiovascular events per 1000 person-years of follow-up among subjects without cardiovascular disease at entry into the study and the relative risks of these events among subjects with aortic sclerosis, as compared with those with normal aortic valves, are shown in Table 5. After adjustment for age, sex, and associated base-line factors, sclerosis was associated with a relative risk of myocardial infarction of 1.40 (95 percent confidence interval, 1.07 to 1.83). There was a moderate association with con-

gestive heart failure (relative risk, 1.28; 95 percent confidence interval, 1.01 to 1.63). There was also a trend toward an increased risk of angina pectoris and stroke among subjects with sclerotic aortic valves, although the 95 percent confidence intervals overlapped 1.0.

### DISCUSSION

Our results indicate that elderly adults with abnormal aortic valves on two-dimensional echocardiography have an increased risk of cardiovascular events and of death from cardiovascular causes. This asso-

**TABLE 5. RATES AND RELATIVE RISK OF CARDIOVASCULAR EVENTS AMONG THE 4271 SUBJECTS WITHOUT PREVALENT CARDIOVASCULAR DISEASE AT ENTRY, ACCORDING TO THE PRESENCE OR ABSENCE OF AORTIC SCLEROSIS.\***

EVENT	TOTAL NO. OF EVENTS	NORMAL VALVES	AORTIC SCLEROSIS	RELATIVE RISK (95% CONFIDENCE INTERVAL)	
				ADJUSTED FOR AGE AND SEX	ADJUSTED FOR AGE, SEX, AND ASSOCIATED BASE-LINE FACTORS†
Myocardial infarction	254			1.46 (1.12–1.90)	1.40 (1.07–1.83)
No. of events		166	88		
Event rate/1000 person-yr		9	16		
Angina	478			1.23 (1.00–1.50)	1.17 (0.95–1.43)
No. of events		338	140		
Event rate/1000 person-yr		19	26		
Congestive heart failure	326			1.33 (1.05–1.68)	1.28 (1.01–1.63)
No. of events		215	111		
Event rate/1000 person-yr		12	20		
Stroke	260			1.31 (1.01–1.71)	1.25 (0.96–1.64)
No. of events		173	87		
Event rate/1000 person-yr		10	16		

\*Cardiovascular disease was defined as a history of myocardial infarction, angina, congestive heart failure, or stroke.

†Factors associated with aortic-valve sclerosis at base line that were included in the model were elevated Lp(a) lipoprotein levels, shorter height, presence of hypertension, current smoking, elevated low-density lipoprotein cholesterol levels, and presence of diabetes.

ciation was observed not only in subjects with restricted leaflet motion and obstruction of outflow (aortic stenosis), but also in those with milder degrees of valve thickening and calcification (aortic-valve sclerosis).

The presence of aortic sclerosis was associated with an increase of approximately 50 percent in the risk of both death from cardiovascular causes and new myocardial infarction, even though there was no demonstrable obstruction of blood flow across the aortic valve in these subjects. This increase in risk was apparent even though the follow-up period was relatively short. A similarly increased risk of death has been noted in a preliminary report.<sup>17</sup> Although we do not have data on the possible hemodynamic progression of aortic-valve disease in our subjects, the development of clinically significant obstruction is likely to be of only minimal importance given that the estimated rate of progression to symptomatic aortic stenosis in adults with a jet velocity below 3.0 m per second is 8 percent per year or less.<sup>8,10-13</sup> Although there was some degree of discordance between the results from the reading center and a detailed reanalysis of aortic-valve morphology, any misclassification would attenuate the results, so the true relations are likely to be even stronger than reported.

The increase in risk associated with aortic sclerosis was most evident in subjects without clinically evident coronary heart disease at entry into the study. Even after adjustment for other clinical factors associated with aortic sclerosis, including age, blood pres-

sure, serum lipid levels, height, and smoking status, aortic sclerosis was associated with an increased risk of death from cardiovascular causes. These data suggest that aortic sclerosis may not be simply a benign incidental finding on echocardiography but instead may be a marker for an increased risk of cardiovascular events.

Somewhat surprisingly, aortic sclerosis was associated with an increased risk of myocardial infarction among subjects without known cardiovascular disease, suggesting that the degree of unrecognized coronary atherosclerosis in these subjects may have been higher than expected. It is unlikely that the valve abnormality itself led to myocardial infarction, since there are no data to suggest that embolic coronary occlusions occur in adults with aortic stenosis.

The association between aortic-valve disease and coronary artery disease is complex. First, the relation between the presence of coronary artery and aortic-valve disease is not 1 to 1: only about 50 percent of adults with aortic stenosis have clinically significant luminal narrowing on coronary angiography.<sup>8,18</sup> Second, patterns of coronary blood flow are altered in patients with severe aortic stenosis, even in the absence of atherosclerotic coronary artery disease.<sup>19-24</sup> Third, clinical factors associated with aortic sclerosis or stenosis are similar to those associated with coronary atherosclerosis and include older age, male sex, elevated Lp(a) lipoprotein levels, shorter height, presence of hypertension, current smoking, and elevated low-density lipoprotein cholesterol levels.<sup>1,25-30</sup>

However, although the disease process in the aortic-valve leaflets of patients with aortic sclerosis or stenosis has some similarities to that of atherosclerosis, including the presence of oxidized lipoproteins, inflammatory cells, and microscopic calcification and the production of proteins by activated macrophages, there are substantial differences as well, including the absence of smooth-muscle cells and the accumulation of larger amounts of calcium and protein than are seen with coronary atherosclerosis.<sup>31-35</sup> Furthermore, clinical events in patients with coronary atherosclerosis are typically related to the instability of the plaques and associated formation of thrombus. In contrast, the clinical effects of aortic-valve disease result from ventricular-outflow obstruction caused by the increased stiffness and thickness of the leaflets.

Studies exploring potential pathophysiologic mechanisms of the association between aortic sclerosis and adverse cardiovascular outcomes are needed, since it is unclear whether aortic sclerosis is simply a marker of increased risk or has a direct effect on clinical outcome. Studies evaluating intermediate cardiac end points in conjunction with an evaluation of the degree of leaflet thickening and calcification may provide insight into the relation between valve anatomy and clinical outcome. Studies are also needed on the possible association of aortic sclerosis with other clinical outcomes, such as endocarditis, that were not addressed in this study.

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