

# Aortic Valve Sclerosis and Aortic Atherosclerosis: Different Manifestations of the Same Disease?

## Insights From a Population-Based Study

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<b>OBJECTIVES</b>	The aim of this study was to examine the association between atherosclerosis risk factors, aortic atherosclerosis and aortic valve abnormalities in the general population.
<b>BACKGROUND</b>	Clinical and experimental studies suggest that aortic valve sclerosis (AVS) is a manifestation of the atherosclerotic process.
<b>METHODS</b>	Three hundred eighty-one subjects, a sample of the Olmsted County (Minnesota) population, were examined by transthoracic and transesophageal echocardiography. The presence of AVS (thickened valve leaflets), elevated transaortic flow velocities and aortic regurgitation (AR) was determined. The associations between atherosclerosis risk factors, aortic atherosclerosis (imaged by transesophageal echocardiography) and aortic valve abnormalities were examined.
<b>RESULTS</b>	Age, male gender, body mass index (odds ratio [OR]: 1.07 per kg/m <sup>2</sup> ; 95% confidence interval [CI]: 1.02 to 1.12), antihypertensive treatment (OR: 1.93; CI: 1.12 to 3.32) and plasma homocysteine levels (OR: 1.89 per twofold increase; CI: 0.99 to 3.61) were independently associated with an increased risk of AVS. Age, body mass index and pulse pressure (OR: 1.21 per 10 mm Hg; CI: 1.00 to 1.46) were associated with elevated (upper quintile) transaortic velocities, whereas only age was independently associated with AR. Sinotubular junction sclerosis (p = 0.001) and atherosclerosis of the ascending aorta (p = 0.03) were independently associated with AVS and elevated transaortic velocities, respectively.
<b>CONCLUSIONS</b>	Atherosclerosis risk factors and proximal aortic atherosclerosis are independently associated with aortic valve abnormalities in the general population. These observations suggest that AVS is an atherosclerosis-like process involving the aortic valve. (J Am Coll Cardiol 2001; 38:827-34) © 2001 by the American College of Cardiology

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Calcific ("degenerative") aortic valve disease is the most common etiology of acquired aortic valve stenosis (1). Histopathologically, the early lesions of aortic valve sclerosis (AVS) resemble arterial atherosclerotic plaques (2). Furthermore, atherosclerosis risk factors (3,4) and clinical atherosclerotic cardiovascular disease (5) are independently associated with AVS, suggesting that AVS represents an atherosclerosis-like process involving the aortic valve (6).

The objectives of our study were to examine the associations between atherosclerosis risk factors, anatomically defined atherosclerosis (atherosclerosis of the thoracic aorta imaged by transesophageal echocardiography [TEE]) and aortic valve abnormalities in the general population. Aortic

valve morphology and function were assessed comprehensively by a combination of transthoracic echocardiography (TTE) and TEE in a population-based cohort.

## METHODS

**Study population.** The study design and initial results of the first phase of the SPARC (Stroke Prevention: Assessment of Risk in a Community) study have been presented in detail (7,8). In brief, the SPARC study was designed to evaluate the prevalence of risk factors for stroke in the general population. The original study cohort consisted of 581 subjects, an age- and gender-stratified random sample of the Olmsted County (Minnesota) population ( $\geq 45$  years old), who were evaluated by multiple modalities, including echocardiography. Approximately four to five years after their initial evaluation (median: 4.6 years; range: 3.8 to 5.4 years), eligible participants were enrolled in the second phase of SPARC. Of 504 subjects eligible for the second study phase (excluding 3 subjects lost to follow-up, 54 deceased subjects and 20 with severe medical disabilities precluding participation), 392 (78%) agreed to participate (age of participants and subjects refusing to participate were

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**Abbreviations and Acronyms**

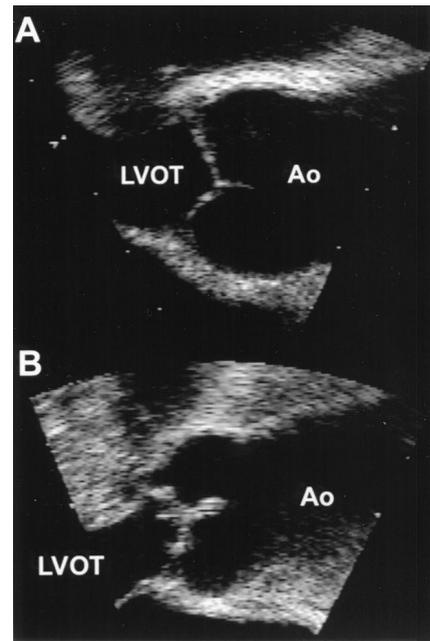
AR	=	aortic regurgitation
AVS	=	aortic valve sclerosis
CAD	=	coronary artery disease
CI	=	95% confidence interval(s)
HDL	=	high-density lipoprotein
LDL	=	low-density lipoprotein
OR	=	odds ratio(s)
SPARC	=	Stroke Prevention: Assessment of Risk in a Community study
TEE	=	transesophageal echocardiography
TTE	=	transthoracic echocardiography

not significantly different). Echocardiography was successfully repeated in 388 of the participants (99%). Seven subjects were excluded from the current analysis (three with aortic prostheses, three with bicuspid aortic valves and one patient with incomplete echocardiographic data). None were excluded because of rheumatic valve disease (none had mitral stenosis or have had mitral valve surgery for rheumatic valve disease). The final study group consisted of 381 subjects (median age: 67 years; range: 51 to 101; 52% men). The study was approved by the Institutional Review Board. Written, informed consent was obtained from all participants.

**Clinical and laboratory data.** Cardiovascular risk factors and clinical manifestations of coronary artery and cerebrovascular disease were assessed by an interview and by medical records abstracting (at Mayo Clinic and Olmsted Medical Center, the two primary health care providers in Olmsted County, Minnesota). Blood pressure measurements were taken during an office appointment related to SPARC. Two blood pressure measurements were taken in the sitting position, 5 to 10 min apart, and averaged. Pulse pressure was defined as the difference between mean systolic and mean diastolic measurements. Treatment of hypertension or hyperlipidemia was defined as current use of anti-hypertensive or lipid-lowering medications, respectively (self-reported during interview).

Fasting blood samples were collected on the day of the echocardiographic examination. Plasma lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides), apolipoprotein A-I, apolipoprotein B and homocysteine levels were determined using standard commercially available assays, and low-density lipoprotein (LDL) cholesterol levels were calculated.

**Echocardiographic evaluation.** Transthoracic echocardiography and multiplane TEE (9) were performed applying standard practice guidelines and using commercially available ultrasound instruments. Local pharyngeal anesthesia and intravenous sedation (midazolam and meperidine) were used during TEE, as clinically indicated. All TEE examinations were performed using an Acuson Sequoia ultrasound machine (Acuson, Mountain View, California).



**Figure 1.** Transesophageal echocardiographic examples of normal (A) and sclerotic (B) aortic valves. Note the irregular thickening of the sclerotic aortic valve leaflets. Ao = aorta; LVOT = left ventricular outflow tract.

**Aortic valve.** The morphology of the aortic valve was assessed during TEE by high-frequency (7 MHz), high-resolution imaging of the valve in multiple (short- and long-axis) echocardiographic views (9,10). “Aortic valve sclerosis” was defined as abnormal irregular thickening of the aortic valve leaflets (at least one abnormal leaflet per valve) (Fig. 1). A stratified random sample of 46 TEE studies was blindly reviewed off-line by the initial operator performing the echocardiographic studies and by a second reviewer. Given the good intraobserver agreement (comparison of initial and off-line interpretation: kappa = 0.63; 95% confidence interval [CI]: 0.40 to 0.85) and interobserver agreement (comparison of off-line interpretation by both reviewers: kappa = 0.63; CI: 0.43 to 0.84), the initial echocardiographic interpretation was taken for all subsequent analyses, as previously reported (4).

Peak transaortic flow velocities were measured during the TTE examination by continuous-wave Doppler (11) (average of triplicate measurements). The presence of aortic valve regurgitation (AR) was determined by color flow imaging in multiple planes during the TEE examination. Higher transaortic flow velocities (12) and AR (13) were examined as functional surrogates of AVS.

**Aortic atherosclerosis.** The ascending aorta, aortic arch and descending thoracic aorta were imaged by TEE in multiplane short- and long-axis views. “Atherosclerosis” was defined as irregular intimal thickening ( $\geq 2$  mm) with increased echogenicity. “Sinotubular junction sclerosis” was defined as focal, highly-echogenic thickening ( $\geq 2$  mm) of the sinotubular junction (14). The presence of aortic atherosclerosis (any degree of atherosclerosis in any segment of

**Table 1.** Clinical and Laboratory Characteristics of Subjects With Aortic Valve Sclerosis, Upper Quintile Transaortic Flow Velocities and Aortic Regurgitation

	Aortic Sclerosis		Transaortic Flow Velocities		Aortic Regurgitation	
	Present (n = 140; 36.7%)	Absent (n = 241; 63.3%)	Upper Quintile (n = 68)	Lower Quintiles (n = 302)	Present (n = 113; 29.8%)	Absent (n = 266; 70.2%)
Age, yr	76 (67-85)‡	63 (57-69)	71 (63-84)‡	65 (59-74)	73 (64-84)‡	64 (58-71)
Men, %	61*	47	46	53	57	51
Height, cm	167 (160-174)	167 (160-175)	164 (156-172)*	167 (160-174)	167 (158-175)	167 (161-174)
Weight, kg	81 (71-92)	80 (67-94)	79 (68-97)	81 (69-92)	79 (66-90)	81 (70-94)
BMI, kg/m <sup>2</sup>	28 (26-33)	28 (25-32)	28 (26-35)	28 (25-32)	27 (24-32)*	29 (26-33)
BSA, m <sup>2</sup>	1.9 (1.8-2.0)	1.9 (1.7-2.1)	1.9 (1.7-2.0)	1.9 (1.7-2.1)	1.9 (1.7-2.0)	1.9 (1.8-2.1)
Heart rate, beats/min	61 (54-70)	61 (54-69)	61 (52-71)	61 (54-69)	60 (52-69)	61 (54-69)
Systolic BP, mm Hg	139 (126-149)‡	128 (118-140)	142 (126-153)‡	131 (119-143)	136 (122-149)*	130 (119-143)
Diastolic BP, mm Hg	82 (75-87)	82 (76-88)	82 (75-87)	82 (75-88)	81 (73-87)	82 (76-88)
Pulse pressure, mm Hg	54 (46-71)‡	46 (38-56)	54 (46-74)‡	49 (40-59)	52 (47-67)‡	47 (39-58)
Antihypertensive drugs, %	53‡	25	51†	31	38	34
Diabetes mellitus, %	14	8	16	9	15*	8
Insulin treatment, %	2	2	4	2	2	3
Ever smoking, %	47	44	50	44	41	47
Current smoking, %	4	9	6	7	4	9
Total cholesterol, mg/dl	198 (175-218)	206 (182-226)	201 (174-225)	204 (180-223)	197 (178-216)	205 (181-226)
HDL cholesterol, mg/dl	51 (41-62)	53 (44-66)	54 (42-70)	53 (42-64)	54 (43-67)	51 (42-64)
Total cholesterol/ HDL cholesterol ratio	4.0 (3.2-4.9)	3.9 (3.0-4.7)	3.6 (2.9-4.6)	4.0 (3.1-4.8)	3.7 (2.9-4.6)	4.0 (3.1-4.9)
LDL cholesterol, mg/dl	110 (90-132)	118 (96-136)	110 (85-127)	117 (94-136)	112 (90-129)	118 (95-136)
Triglycerides, mg/dl	151 (116-206)	149 (113-193)	141 (103-196)	150 (117-195)	139 (110-178)	154 (115-203)
Apo A-I, mg/dl	145 (125-166)†	153 (133-175)	151 (129-171)	149 (131-171)	153 (130-171)	148 (130-171)
Apo B, mg/dl	103 (89-114)	102 (88-115)	99 (84-115)	103 (89-115)	100 (85-113)	103 (90-116)
Lipid lowering drugs, %	23	20	21	21	20	21
Homocysteine, μmol/l	11.1 (9.1-13.5)‡	8.9 (7.4-11.1)	10.7 (7.9-12.9)	9.6 (7.8-11.6)	10.4 (8.4-12.1)*	9.4 (7.6-11.8)
Coronary artery disease§, %	29‡	10	18	17	23*	15
Previous MI, %	16†	5	10	9	12	8
Angina pectoris, %	24‡	9	13	15	19	12
PTCA, %	6	2	3	4	5	3
CABG, %	10†	3	9	4	7	5
Cerebrovascular disease  , %	14*	6	18†	7	11	8
Stroke, %	5	3	10†	3	4	4
TIA, %	8	4	9	5	7	5
Carotid endarterectomy, %	3*	0	3	1	2	1

Continuous data presented as medians (interquartile ranges in parentheses); categorical data presented as percentages. \*p ≤ 0.05; †p < 0.01; ‡p < 0.001 for comparisons of subjects with aortic sclerosis, upper quintile transaortic velocities and aortic regurgitation to subjects without these abnormalities; §coronary artery disease defined as previous myocardial infarction, angina pectoris, PTCA or CABG; ||cerebrovascular disease defined as previous stroke, TIA or carotid endarterectomy.

Apo = apolipoprotein; BMI = body mass index; BP = blood pressure; BSA = body surface area; CABG = coronary artery bypass grafting; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TIA = transient ischemic attack.

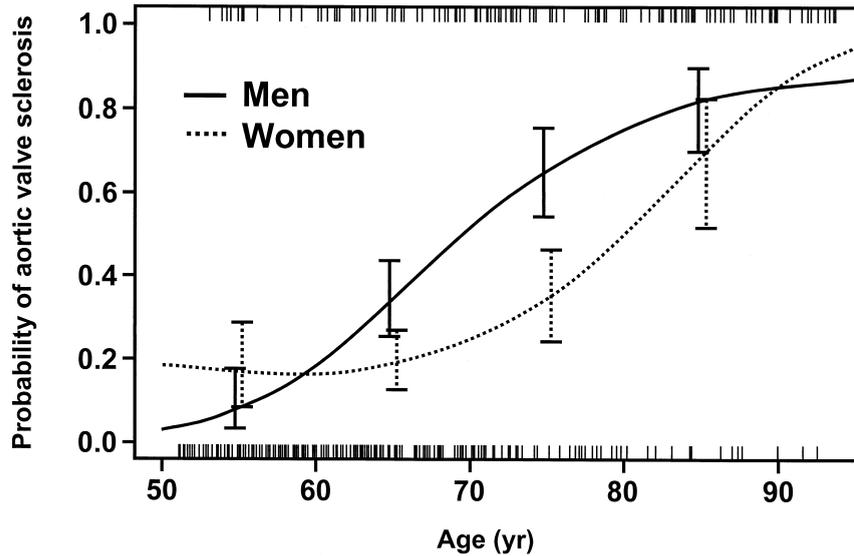
the thoracic aorta), proximal atherosclerosis (sinotubular junction sclerosis and atherosclerosis of the ascending aorta) and severe atherosclerosis (maximal plaque thickness ≥4 mm [15], plaque thickness ≥6 mm and mobile debris in any segment of the thoracic aorta) was determined.

**Statistical analysis.** Continuous data are summarized as medians and interquartile ranges (25% to 75%) and categorical data as percentages. Group comparisons involving continuous data were performed using Student *t* test or the Wilcoxon rank-sum test and comparisons involving categorical data using chi-square statistics or Fisher exact test, as appropriate.

The associations between atherosclerosis risk factors (Table 1) and aortic valve abnormalities (AVS, elevated transaortic velocities [in the upper quintile of the study

group] and AR) were examined by univariate and multivariate logistic regression. Initially, the age- and gender-adjusted associations were examined. Subsequently, multivariate risk factor models were developed by stepwise (forward and backward) logistic regression, allowing all atherosclerosis risk factors to compete for their entry into the models. Age and gender were forced into all models. The p value to enter and to leave the models was 0.05. All two-way interactions between the final variables in the models were examined.

The associations between aortic atherosclerosis variables and aortic valve abnormalities were examined by logistic regression, adjusting for age and gender and subsequently adjusting for age, gender and all additional variables in the multivariate risk factor models. The associations be-



**Figure 2.** Probability of aortic valve sclerosis by age and gender. Note the nonlinear relationship with age and the interaction between age and gender. There is approximately a decade difference between men and women in the age-associated increasing frequency of aortic valve sclerosis (earlier in men). The **marks at the top and the bottom** of the figure indicate individuals with and without aortic sclerosis, respectively.

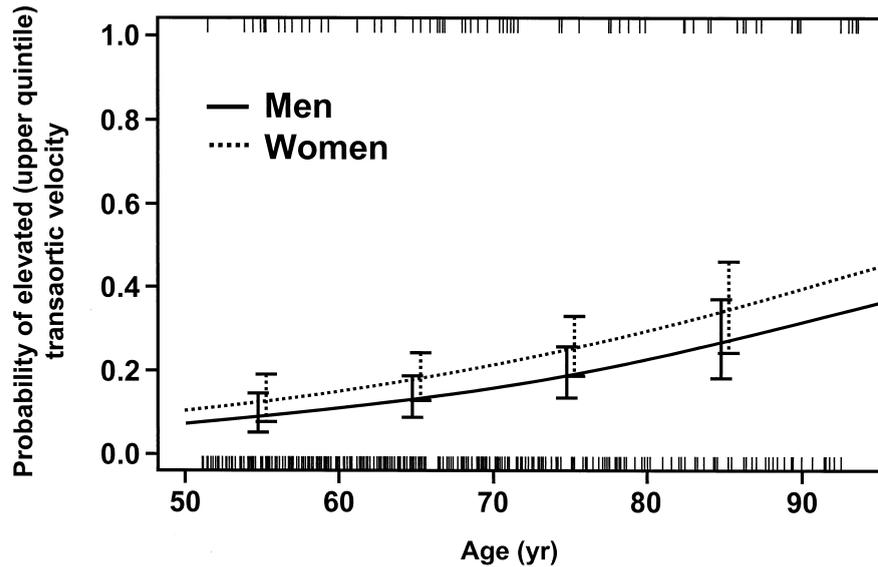
tween clinical coronary artery disease (CAD), cerebrovascular disease and aortic valve abnormalities were assessed similarly.

## RESULTS

**Atherosclerosis risk factors and aortic valve abnormalities.** AVS. The aortic valves were sclerotic in 140 subjects (36.7%). The clinical and laboratory characteristics of subjects with and without AVS are presented in Table 1. Subjects with AVS were significantly older than subjects without AVS (median age, 76 vs. 63 years, respectively;  $p < 0.001$ ) and were more commonly men (61 vs. 47%, respectively;  $p = 0.01$ ). Weight, body mass index, body surface area, antihypertensive drug treatment and plasma homocysteine levels were associated with AVS, adjusting for age and gender, whereas blood pressure measurements (systolic, diastolic or pulse pressure), diabetes mellitus, smoking and blood lipid levels were not. By multivariate analysis, age, male gender, body mass index, antihypertensive treatment and homocysteine levels were independently associated with AVS. A statistically significant interaction ( $p < 0.001$ ), best described graphically (Fig. 2), was apparent between age and gender regarding their association with AVS. There was approximately a decade difference between men and women in the age-associated increase in frequency of AVS (earlier increase in men). The odds of AVS were higher with higher body mass index (odds ratio [OR]: 1.07 for every 1 kg/m<sup>2</sup> increase in body mass index; CI: 1.02 to 1.12;  $p = 0.006$ ), were greater in subjects treated for hypertension (OR: 1.93; CI: 1.12 to 3.32;  $p = 0.02$ ) and were higher with higher homocysteine levels (OR: 1.89 per twofold increase in homocysteine levels; CI: 0.99 to 3.61;  $p = 0.05$ ).

**TRANSAORTIC FLOW VELOCITIES.** The median value of transaortic flow velocities (data available in 370 study participants) was 1.3 m/s. Transaortic velocities were dichotomized at approximately the 80th percentile of the study group (1.50 m/s). Velocities were in the upper quintile ( $\geq 1.50$  m/s) in 30% of subjects with AVS compared with 12% of subjects without AVS ( $p < 0.001$ ), supporting the use of transaortic velocities as hemodynamic surrogates of AVS. Velocities  $>2.5$  m/s, indicating aortic stenosis (4), were present in only five subjects, all with AVS.

The clinical and laboratory characteristics of subjects with and without elevated (upper quintile) transaortic velocities are presented in Table 1. Subjects with upper quintile velocities ( $\geq 1.50$  m/s) were significantly older than subjects with lower ( $<1.50$  m/s) velocities (median age: 71 years vs. 65 years, respectively;  $p < 0.001$ ) (Fig. 3). Weight, body mass index, pulse pressure and antihypertensive treatment were associated with upper quintile velocities, adjusting for age and gender, whereas heart rate and other atherosclerosis risk factors including diabetes mellitus, smoking and lipid levels were not. By multivariate analysis, age, body mass index and pulse pressure were independently associated with upper quintile transaortic velocities. A significant interaction was apparent between age and body mass index regarding their association with higher transaortic velocities ( $p = 0.01$ ). Age was associated with upper quintile velocities in subjects with low and intermediate body mass index; no pattern could be identified for the elderly with high body mass index because the study sample did not contain such subjects. The odds of upper quintile velocities increased with increasing pulse pressure (OR: 1.21 for every 10 mm Hg increase; CI: 1.00 to 1.46;  $p = 0.05$ ).



**Figure 3.** Probability of upper quintile transaortic velocities by age and gender. The marks at the top and the bottom of the figure indicate individuals with and without upper quintile velocities, respectively.

**AR.** Aortic regurgitation was detected in 113 subjects (30% of 379 subjects with available data). Aortic regurgitation was trivial-to-mild in 91 subjects (24%), moderate in 21 subjects (6%) and severe in 1 subject (0.3%). The proportion of subjects with AR was significantly higher among subjects with AVS (56%) than it was among subjects with morphologically normal aortic valves (15%) ( $p < 0.001$ ), supporting the use of AR as a surrogate of AVS. The clinical and laboratory characteristics of subjects with and without AR are presented in Table 1. Subjects with AR were significantly older than subjects without AR (median age, 73 years vs. 64 years, respectively;  $p < 0.001$ ). None of the other risk factors were significantly associated with AR after adjusting for age and gender.

**Association of aortic atherosclerosis and aortic valve abnormalities.** The proportion of subjects with aortic atherosclerosis was higher in subjects with aortic valve abnormalities (Table 2). Sinotubular junction sclerosis and thick ( $\geq 4$  mm) atherosclerotic plaques were associated with AVS, and atherosclerotic plaques in the ascending aorta were associated with upper quintile transaortic velocities, adjusting for age and gender (Table 3). Sinotubular junction sclerosis and atherosclerosis in the ascending aorta were

associated with AVS and upper quintile velocities, respectively, adjusting for age, gender and all additional variables in the final risk factor models (Table 3).

**Clinical CAD, cerebrovascular disease and aortic valve abnormalities.** The proportion of subjects with clinical coronary artery and cerebrovascular disease was higher in subjects with aortic valve abnormalities (Table 1). Angina pectoris and previous coronary artery bypass surgery were associated with AVS, and previous stroke was associated with upper quintile transaortic velocities, adjusting for age and gender (Table 4). These associations were no longer significant after adjusting for all the variables in the final risk factor models.

## DISCUSSION

Our population-based study demonstrates that multiple atherosclerosis risk factors (age, male gender, high blood pressure, obesity and homocysteine levels) are associated with AVS. Furthermore, anatomically defined atherosclerosis (echocardiographically delineated aortic atherosclerosis) is independently associated with AVS. These observations support the hypothesis that calcific (“degenerative”) aortic

**Table 2.** Aortic Atherosclerosis in Subjects With Aortic Valve Sclerosis and Upper Quintile Transaortic Velocities

	Aortic Sclerosis		Transaortic Velocities	
	Present	Absent	Upper Quintile	Lower Quintiles
Any aortic plaque	86‡	60	75	68
Sinotubular junction sclerosis	34‡	8	32‡	15
Plaque-ascending aorta	12‡	2	15†	4
Aortic plaque $\geq 4$ mm	54‡	16	43*	27
Aortic plaque $\geq 6$ mm	20‡	5	16	9
Mobile aortic debris	9*	3	6	5

Data presented as percentages. \* $p \leq 0.05$ ; † $p < 0.01$ ; ‡ $p < 0.001$ .

**Table 3.** Odds Ratios of Aortic Valve Sclerosis and Upper Quintile Transaortic Flow Velocities in Relation to Presence, Location and Severity of Aortic Atherosclerosis

	Aortic Sclerosis		Upper Quintile Transaortic Flow Velocities	
	Age- and Gender-Adjusted	Final Model-Adjusted	Age- and Gender-Adjusted	Final Model-Adjusted
Any aortic plaque	1.61 (0.82-3.13)	1.46 (0.74-2.89)	0.74 (0.36-1.52)	0.68 (0.32-1.43)
Sinotubular junction sclerosis	2.73 (1.40-5.31)†	3.24 (1.60-6.53)†	1.87 (0.96-3.65)	1.80 (0.89-3.62)
Plaque-ascending aorta	2.78 (0.93-8.36)	2.90 (0.92-9.13)	2.90 (1.14-7.36)*	2.97 (1.12-7.90)*
Aortic plaque $\geq 4$ mm	2.31 (1.28-4.17)†	1.70 (0.91-3.19)	1.33 (0.67-2.61)	0.99 (0.48-2.02)
Aortic plaque $\geq 6$ mm	1.65 (0.71-3.84)	1.28 (0.53-3.09)	1.19 (0.52-2.70)	1.03 (0.44-2.40)
Mobile aortic debris	1.67 (0.57-4.88)	1.27 (0.39-4.10)	0.79 (0.25-2.51)	0.71 (0.21-2.43)

Odds ratios adjusted for age and gender and adjusted for age, gender and additional significant variables in the final multivariate models. Data presented as odds ratios (95% confidence intervals in parentheses). \* $p \leq 0.05$ ; † $p < 0.01$ .

valve disease represents an atherosclerosis-like process involving the aortic valve (6).

Several unique features of our study design should be noted. First, we used TEE to assess aortic valve morphology in a population-based setting, an approach that consistently allows high-resolution imaging of the valves. Second, given the inherent limitations and subjectivity of qualitative evaluation of valve morphology (4), we examined the aortic valves both morphologically and functionally. Previous echocardiographic studies were based on transthoracic imaging (3,4) and, primarily, morphologic valve assessment (4). Importantly, to our knowledge, our study is the first to demonstrate an independent association between anatomically defined atherosclerosis and the morphophysiologic features of degenerative aortic valve disease in a population-based setting.

**Risk factors for AVS.** Multiple pathologic (16,17) and echocardiographic studies (3,4,12,13,18) have demonstrated a strong association between age and AVS, suggesting that AVS represents a nonspecific wear-and-tear (“degenerative”) phenomenon. Nevertheless, the risk of AVS is only partially explainable by age, and several additional risk factors may contribute to its development and progression (6). Male gender has been associated with AVS (4,19),

although not uniformly (17,18). An earlier age-associated increase in frequency of AVS in men was apparent in our study, a finding reminiscent of the relationship between age, gender and CAD.

An association between hypertension and AVS has been reported almost uniformly in multiple studies (3,4,18,20), as well as in our study, an association possibly resulting from chronic hypertension-related mechanical stress upon the aortic valve. Interestingly, our observation of the association between pulse pressure and elevated transaortic velocities, a surrogate for AVS, is similar to our recent description of the association between pulse pressure and aortic atherosclerosis (8), further emphasizing the similarity of these processes. Diabetes (18,20) and smoking (4,19) have been associated with AVS, although inconsistently (3). These associations were not observed in our study.

Familial hypercholesterolemia is associated with early-onset calcific aortic valve disease (21,22), suggesting a role for dyslipidemia in the pathogenesis of AVS. The histopathologic findings in early aortic valve lesions support this hypothesis (2), although the results of clinical studies have been less uniform. Increased total cholesterol (18,20), LDL cholesterol (4), lipoprotein(a) (4,23) and low HDL-cholesterol (20) have been associated with AVS. In the

**Table 4.** Odds Ratios of Aortic Valve Sclerosis and Upper Quintile Transaortic Velocities in Relation to Clinical Coronary Artery and Cerebrovascular Disease

	Aortic Sclerosis		Upper Quintile Transaortic Flow Velocities	
	Age- and Gender-Adjusted	Final Model-Adjusted	Age- and Gender-Adjusted	Final Model-Adjusted
Coronary artery disease	1.94 (1.01-3.76)*	1.69 (0.85-3.34)	0.78 (0.37-1.64)	0.66 (0.31-1.44)
Previous MI	1.27 (0.54-2.99)	0.92 (0.37-2.27)	0.83 (0.33-2.11)	0.70 (0.26-1.88)
Angina pectoris	2.17 (1.08-4.36)*	1.99 (0.97-4.09)	0.72 (0.32-1.61)	0.66 (0.29-1.53)
PTCA	2.26 (0.60-8.56)	2.06 (0.51-8.35)	0.77 (0.16-3.64)	0.71 (0.15-3.49)
CABG	3.02 (1.03-8.87)*	2.71 (0.89-8.21)	2.04 (0.72-5.82)	2.28 (0.76-6.85)
Cerebrovascular disease	0.79 (0.34-1.87)	0.63 (0.25-1.63)	1.92 (0.86-4.29)	2.00 (0.87-4.58)
Stroke	0.49 (0.14-1.72)	0.34 (0.09-1.33)	3.09 (1.03-9.26)*	2.80 (0.89-8.79)
TIA	0.63 (0.22-1.77)	0.49 (0.16-1.51)	1.24 (0.45-3.45)	1.40 (0.49-3.96)
Carotid endarterectomy, %	Not estimable†	Not estimable†	5.57 (0.75-41.4)	6.31 (0.81-48.9)

\* $p < 0.05$ ; †all subjects with carotid endarterectomy had aortic valve sclerosis. Odds ratios adjusted for age and gender and adjusted for age, gender and additional significant variables in the final multivariate models.

CABG = coronary artery bypass grafting; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TIA = transient ischemic attack.

Cardiovascular Health Study, increased LDL cholesterol and lipoprotein(a) were associated with AVS, although the association of LDL cholesterol was weak (4). As in the Helsinki Ageing Study (3), we did not detect any association between dyslipidemia and aortic valve abnormalities, suggesting a relatively lesser role for dyslipidemia in the pathogenesis of aortic valve disease compared with the other identified risk factors.

A strong association between increased body mass index and aortic valve abnormalities, assessed morphologically and functionally, was demonstrated in our study, whereas a lack of association (4) or even a negative association (3) has been previously reported. The discrepancy between these observations may be due to the limitation of TTE imaging in obese subjects (3), which was overcome in our study by using TEE. The relationship between obesity and aortic valve abnormalities may be due to obesity-associated metabolic abnormalities or increased mechanical stress upon the aortic valve due to obesity-related hemodynamic changes.

We observed an association between increasing homocysteine levels and AVS. This observation, which also supports the analogy between AVS and the atherosclerotic process, needs to be confirmed in additional studies.

**Atherosclerosis and AVS.** Aortic valve sclerosis is associated with clinical atherosclerotic cardiovascular disease (5), as also observed in our study. To date, the association of AVS with aortic atherosclerosis has only been described in selected patients (24,25). To our knowledge, our study is the first to demonstrate an independent association between aortic atherosclerosis and aortic valve abnormalities in the general population, suggesting that these disorders represent related processes in the spectrum of atherosclerotic cardiovascular disease.

Aortic atherosclerosis was associated with aortic valve abnormalities, adjusting for age and gender, supporting the hypothesis that both pathologies share common risk factors. Furthermore, aortic atherosclerosis was independently associated with aortic valve abnormalities, after adjusting for age, gender and other atherosclerosis risk factors, suggesting that additional "nontraditional" risk factors may predispose to both processes. Interestingly, atherosclerosis in proximity to the aortic valve (sinotubular sclerosis and atherosclerosis of the ascending aorta) was strongly associated with aortic valve abnormalities. This finding is supported by observations in patients with familial hypercholesterolemia, in whom aortic stenosis and supra-avalvular aortic atherosclerosis frequently coincide (21,22).

**Study limitations.** The SPARC study is the largest population-based TEE study published to date. The size of our study population, which is smaller than that of the Cardiovascular Health Study (4) but similar in size to the Helsinki Ageing Study (3,12), may have limited our ability to detect additional, albeit relatively less important, risk factors for AVS. Specifically, the relatively minor role of increased LDL cholesterol in the pathogenesis of AVS that was observed in the Cardiovascular Health Study (4) but not

in SPARC or the Helsinki Ageing Study (3) may have resulted from the smaller sample size of the latter two studies.

The reported frequency of AVS varies widely between studies (4,12,13,20,23), emphasizing the qualitative and subjective nature of this echocardiographic diagnosis. The frequency noted in our study (36.7%) is consistent with previous observations in populations of similar age. In addition to morphologic assessment, we examined the association between atherosclerosis risk factors, aortic atherosclerosis and subtle abnormalities of valve function (elevated transaortic flow velocities and AR, which were minor and clinically nonsignificant in the majority of subjects). Although flow velocities were higher and AR was more frequent in subjects with AVS, these functional variables may have been affected by other factors in addition to aortic valve structure. Nevertheless, the concordant results obtained by morphologic valve assessment and transaortic velocity measurements support our combined morphologic-functional analysis. Despite the strong association between AVS and AR (13), we were unable to detect any association of atherosclerosis risk factors and AR after adjusting for age, a finding concordant with previous data (26).

**Conclusions.** Multiple atherosclerosis risk factors and aortic atherosclerosis are independently associated with AVS in the general population. These observations support the hypothesis that AVS is an atherosclerosis-like process involving the aortic valve.

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