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Adverse Outcome in Aortic Sclerosis Is Associated With Coronary Artery Disease and Inflammation

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OBJECTIVES The present study was designed to evaluate the relationship between the presence of aortic sclerosis, serologic markers of inflammation, and adverse cardiovascular outcomes.

BACKGROUND Aortic sclerosis is associated with adverse cardiovascular outcomes. However, the mechanism by which such nonobstructive valve lesions impart excess cardiovascular risk has not been delineated.

METHODS In 425 patients (mean age 68 ± 15 years, 54% men) presenting to the emergency room with chest pain, we studied the relationship among aortic sclerosis, the presence and acuity of coronary artery disease, serologic markers of inflammation, and cardiovascular outcomes. Patients underwent echocardiography and serologic testing including C-reactive protein (CRP). Aortic valves were graded for the degree of sclerosis, and cardiovascular outcomes including cardiac death and nonfatal myocardial infarction (MI) were analyzed over one year.

RESULTS Aortic sclerosis was identified in 203 patients (49%) , whereas 212 (51%) had normal aortic valves. On univariate analysis at one year, patients with aortic sclerosis had a higher incidence of cardiovascular events (16.8% vs. 7.1%, p = 0.002) and worse event-free survival (normal valves = 93%, mild aortic sclerosis = 85%, and moderate to severe aortic sclerosis = 77%, p = 0.002). However, by multivariable analysis aortic sclerosis was not independently associated with adverse cardiovascular outcomes; the only independent predictors of cardiac death or MI at one year were coronary artery disease (hazard ratio [HR] 3.23, p = 0.003), MI at index admission (HR 2.77, p = 0.008), ascending tertiles of CRP (HR 2.2, p = 0.001), congestive heart failure (HR 2.15, p = 0.02) and age (HR 1.03, p = 0.04).

CONCLUSIONS The increased incidence of adverse cardiovascular events in patients with aortic sclerosis is associated with coronary artery disease and inflammation, not a result of the effects of valvular heart disease per se. (J Am Coll Cardiol 2004;43:169–75) © 2004 by the American College of Cardiology Foundation

Aortic sclerosis was until recently considered a benign degenerative process of the elderly. However, recent observations demonstrate that aortic sclerosis is associated with an increased incidence of myocardial infarction (MI) and cardiovascular death (1–3). Because aortic sclerosis does not itself cause sufficient hemodynamic perturbations to impact cardiovascular function, the mechanisms underlying its association with adverse cardiovascular outcomes are unclear.

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Histopathologic studies have shown striking similarities between degenerative aortic valve disease and coronary atherosclerosis (4–6), with evidence of inflammation common to both conditions. Inflammation is an important mechanism underlying the pathophysiology of chronic atherosclerosis (7–10) and has also been implicated in the precipitation of coronary plaque rupture (8,11–15). Observations in patients with acute coronary syndromes suggest that plaque inflammation is a multifocal coronary process associated with elevated systemic markers of inflammation (16,17).

Whether systemic activation of inflammatory processes secondarily exerts extrinsic adverse influences on coronary atherosclerosis and plaque stability, or whether these serologic findings are merely systemic markers of primary coronary inflammation triggered by intrinsic arterial mechanisms, has not been fully elucidated. Regardless of the nature of the link, the association between elevation of serologic markers of inflammation and increased cardiovascular events in patients with both chronic coronary artery disease (CAD) and in those with acute coronary syndromes is well documented (18–22). Recent evidence suggests that chronic inflammation may play a role in the pathogenesis of aortic sclerosis as well (4–6). On the basis of these observations, we hypothesized that the association between aortic sclerosis and adverse cardiovascular events is unlikely to be a direct pathophysiologic link, but may be attributable to active CAD with an inflammatory link.

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Abbreviations and Acronyms
CAD = coronary artery disease
CRP = C-reactive protein
ECG = electrocardiogram
IgG = immunoglobulin G
MI = myocardial infarction

METHODS

We studied the relationship among aortic sclerosis, the presence and acuity of CAD, serologic markers of inflammation, and cardiovascular outcomes in patients presenting with chest pain to the emergency room by prospective follow-up of a cohort of patients from an observational cross-sectional study, Chlamydia Pneumoniae Exposure and Inflammatory Markers in Acute Coronary Syndrome (CIMACS); the detailed methodology of the study has been published earlier (23). In brief, patients were enrolled at William Beaumont Hospital from March to June 1999. Patients had a 12-lead electrocardiogram (ECG) and cardiac enzymes evaluation. A subset of patients underwent two-dimensional echocardiographic evaluation at the discretion of the attending physician. Patients were excluded for aortic stenosis (peak velocity ≥2 m/s, prosthetic aortic valves, age <18 years, any malignancy requiring treatment within the previous two months, acquired immunodeficiency syndrome, chronic steroid use, immunosuppressive therapy (such as for transplantation), chronic liver disease, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erethematosis, and any major surgery within the past two months. Patients with multiple visits during the period were enrolled only at their first visit.

Echocardiography. Two-dimensional Doppler echocardiograms (HP5500 or HP5000, Agilent Technologies, Andover, Massachusetts) were blindly reviewed by three experienced observers. The aortic valve was analyzed using parasternal long- and short-axis views. Aortic sclerosis was defined as increased echogenicity, thickening, or calcification of the leaflets. Although no prior study has graded aortic sclerosis, we noted significant variations in echogenicity, thickening, or calcification of the valve leaflets on echocardiography and found it reasonable to employ these features to construct a qualitative grading system. The severity of aortic sclerosis was graded on a scale of 0 to 3: 0 = normal (no involvement), 1 = mild (minor involvement of one leaflet), 2 = moderate (minor involvement of two leaflets or extensive involvement of one leaflet), and 3 = severe (extensive involvement of two leaflets or involvement of all three leaflets). Discrepancies in scoring were resolved by consensus among the observers. Peak Doppler velocity across the valve was measured.

Serologic testing. Complete blood count, blood urea nitrogen, and creatinine were obtained. Creatinine kinase (CK), CK-MB, and troponin-T were measured using electrochemiluminescence immunoassay (Roche Elecsys 1010/2010, Tokyo, Japan). High sensitivity C-reactive protein (CRP) levels were determined employing a commercial assay (Dade Behring BN II system, Newark, Delaware). Fibrinogen was measured using the MDA 180 method (Organon Teknika MDA 180 coagulometer, Oklahoma City, Oklahoma). In order to test whether prior infection with *Chlamydia pneumoniae* was associated with the conditions studied, immunoglobulin G (IgG) antibodies against *C. pneumoniae* were measured using microimmunofluorescent assay (ARUP Laboratory, Salt Lake City, Utah).

Clinical outcomes. Clinical outcomes were analyzed by chart review. Acute coronary syndromes included MI and unstable angina. Myocardial infarction was defined as chest discomfort with abnormal cardiac enzymes (twofold increase in total creatine kinase enzyme with creatine kinase-MB fraction ≥3.9%). Unstable angina was defined as chest discomfort with or without ECG changes, together with either noninvasive stress imaging (sestamibi or two-dimensional echocardiographic) documentation of ischemia or angiographic evidence of significant (≥70%) coronary artery stenoses. Charts were reviewed to analyze clinical variables. To analyze one-year cardiovascular outcomes (MI or death from cardiovascular causes), patients (or family members) were contacted by telephone and findings were confirmed by review of medical records.

Statistical analysis. Moderate and severe aortic sclerosis groups were combined for the analysis. Recognizing the limitations of echocardiographic qualitative grading, we compared normal valves with any aortic sclerosis and with groups with increasing severity of aortic sclerosis. All normally distributed continuous variables were compared using Student *t* test . Categorical variables were compared using chi-square test (or Fisher exact test where appropriate). Alpha of 0.05 was used to define statistical significance.

All inflammatory markers (CRP, fibrinogen, and leukocyte counts) were non-normally distributed and hence were compared as continuous variables after log normalization and computation of geometric means. Median values of these variables were computed and compared using Wilcoxon's rank-sum test. Tertiles of the inflammatory markers were also computed and used for relative ratio analysis for adverse outcome at one year. IgG antibody titers against *C. pneumoniae* were compared both as a continuous variable (using reciprocal of the titer) and as a dichotomous variable at different levels: < or ≥1:64, < or ≥1:128, < or ≥1:256, < or ≥1:512, and < or ≥1:1,024 (instead of using an arbitrary definition of seropositivity).

Multivariable logistic regression was done using presence or absence of aortic sclerosis as the dependent variable, and clinical, laboratory, and inpatient outcome variables found to have an association on univariate analysis at alpha ≤0.10. Using logistic regression analysis (where the dependent variable was adverse cardiovascular outcome at one year), the unadjusted relative risks with 95% confidence interval were computed for variables of clinical interest. Kaplan-Meier survival analyses were performed to evaluate the

Table 1. Univariate Association Between Baseline Clinical and Laboratory Variables and Aortic Sclerosis

Variables	Normal Aortic Valve (n = 212)	Any Aortic Sclerosis (n = 203)	Mild Aortic Sclerosis (n = 149)	Moderate-Severe Aortic Sclerosis (n = 54)
Clinical variables				
Age, yrs (mean ± SD)	61.8 ± 14.3	73.9 ± 12*	73.5 ± 12.7*	74.9 ± 10.3*
Male gender	118 (56%)	105 (52%)	73 (49%)	32 (59%)
Caucasian race	176 (84%)	180 (89%)	133 (89%)	47 (90%)
History of hypertension	132 (63%)	151 (74%)†	112 (75%)†	39 (72%)
History of diabetes mellitus	51 (24%)	57 (28%)	38 (26%)	19 (35%)
History of hyperlipidemia	84 (40%)	85 (52%)	61 (41%)	24 (44%)
History of coronary heart disease‡	101 (48%)	115 (57%)	84 (56%)	31 (57%)
History of congestive heart failure	22 (10%)	50 (25%)*	37 (25%)*	13 (24%)*
Smoking status				
Current	35 (17%)	23 (12%)	20 (14%)	3 (6%)
Ever§	117 (57%)	80 (40%)	75 (51%)	27 (50%)
Laboratory evaluation at baseline				
C-reactive protein				
Geometric mean (mg/dl)	0.55	0.78†	0.71	1.04†
Median (mg/dl)	0.48	0.8†	0.77†	1.05†
Fibrinogen				
Geometric mean (mg/dl)	312	339†	334	351†
Median (mg/dl)	305	344†	344†	352†
Leukocyte count				
Geometric mean (10^9/l)	7.8	7.9	8.1	7.6
Median (10^9/l)	7.9	7.6	7.8	7.25
Elevated troponin T (≥ 0.2 ng/ml)	31 (15%)	14 (7%)	31 (22%)	16 (30%)†
Total cholesterol (mg/dl, mean ± SD)	180 ± 43	173 ± 38	175 ± 38	168 ± 35
LDL (mg/dl, mean ± SD)	120 ± 76	107 ± 50†	108 ± 48	104 ± 54†
HDL (mg/dl, mean ± SD)	44 ± 13	46 ± 15	47 ± 15	43 ± 14
Triglycerides (mg/dl, mean ± SD)	175 ± 180	133 ± 93*	129 ± 88†	147 ± 107*

*$p < 0.001$; †$p < 0.05$ vs. normal aortic valve; ‡angiographic evidence of >50% lesion in at least one coronary artery or evidence of myocardial ischemia on non-invasive testing; §>10 pack-year smoking anytime in the past.
LDL = low density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol.

one-year outcome according to the severity of aortic sclerosis, and tertiles of CRP in patients with aortic sclerosis. The Cochran-Mantel-Haenszel statistic was used for analysis of trend. Cox proportional hazard model was used for multivariable regression analysis using variables found to have univariate association with adverse cardiovascular outcome at one year at alpha ≤0.10. Statistical analysis was performed using SAS version 6.12.

The study was approved by the institutional Human Investigation Committee. All patients provided informed consent.

RESULTS

We screened 830 patients with chest pain to identify 425 who underwent echocardiography. Five patients were subsequently excluded because of inadequate echocardiographic views of the aortic valve and three were excluded because of aortic stenosis, as were two others with prosthetic aortic valves. The remaining 415 patients constitute the population analyzed in this study, of whom 212 (51%) patients had normal aortic valves, 149 (36%) had mild aortic sclerosis, 47 (11%) had moderate aortic sclerosis, and seven (2%) had severe aortic sclerosis. Coronary artery disease was documented in 315 (76%) of the patients, of whom 225 (54%) presented with acute coronary syndromes, including MI in 74 (33%) and unstable angina in 151 (67%).

Aortic sclerosis and cardiovascular outcomes. By univariate analysis, the presence of aortic sclerosis was associated with age, hypertension, congestive heart failure, elevated CRP, fibrinogen, and lower triglyceride levels (Table 1). However, by multivariable analysis only age was associated with the presence of aortic sclerosis (odds ratio = 1.07, $p < 0.0001$). There were no differences in the incidence of acute coronary syndromes on index admission between the groups with normal and sclerotic aortic valves. However, a tendency toward increased cardiovascular deaths during the index admission was noted in patients with aortic sclerosis ($p = 0.06$) (Table 2).

Over one year, both the presence and severity of aortic sclerosis were strongly associated with adverse cardiovascular outcomes (Table 2). At one-year follow-up, those with aortic valve involvement suffered an increased incidence of overall mortality compared to those without aortic sclerosis (18.7% vs. 2.4%, $p < 0.0001$) and cardiovascular mortality in particular (14.7% vs. 1.4%, $p < 0.0001$). The incidence of nonfatal MI was no different between the two groups. The combined end point of cardiovascular death or nonfatal MI at one year was higher in patients with aortic sclerosis (16.7% vs. 7.1%, p =

Table 2. Aortic Sclerosis and Cardiovascular Outcomes

Variables	Normal Aortic Valve (n = 212)	Any Aortic Sclerosis (n = 203)	Mild Sclerosis (n = 149)	Moderate-Severe Sclerosis (n = 54)
Outcome at index admission				
Acute coronary syndrome	121 (57%)	104 (51%)	74 (50%)	30 (56%)
Myocardial infarction	39 (18%)	35 (17%)	25 (17%)	10 (19%)
Unstable angina	82 (39%)	69 (34%)	49 (33%)	20 (37%)
In-hospital death	1 (0.5%)	7 (3%)	6 (4.0%)†	1 (1.9%)
Cardiovascular	1 (0.5%)	7 (3%)	6 (4.0%)†	1 (1.9%)
Noncardiovascular	0	0	0	0
Outcome at 12 months				
Nonfatal myocardial infarction	12 (5.7%)	7 (3.4%)	2 (1.3%)	5 (9.3%)
Death	5 (2.4%)	38 (18.7%)*	27 (18.1%)*	11 (20.4%)*
Cardiovascular	3 (1.4%)	30 (14.7%)*	21 (14.1%)*	9 (16.7%)*
Noncardiovascular	2 (0.9%)	8 (3.9%)	6 (4.9%)	2 (4.0%)
Combined end point‡				
(Cardiovascular death + MI)	15 (7.1%)	34 (16.7%)†	22 (14.8%)†	12 (22.2%)†

*$p < 0.001$; †$p < 0.05$ vs. normal aortic valve; ‡p for trend <0.005.
MI = myocardial infarction.

0.003). Furthermore, Kaplan-Meier analysis showed a strong association between increasing severity of aortic sclerosis and adverse cardiovascular events at one year (Fig. 1), with event-free survival of 93% in patients without aortic sclerosis, 85% in mild aortic sclerosis, and 77% in moderate to severe aortic sclerosis ($p = 0.0002$). Adverse cardiovascular events were also associated with CAD, elevated troponin-T (>0.2 ng/ml), increasing tertiles of CRP, fibrinogen and leukocyte counts, age, hypertension, diabetes mellitus, and congestive heart failure (Table 3).

CAD, inflammatory markers, and cardiovascular outcomes. There was an incremental increase in adverse cardiovascular events with both increasing magnitude of elevation of inflammatory markers as well as severity of aortic sclerosis (Fig. 2). In patients with moderate to severe aortic sclerosis and the highest tertile CRP (>1.18 mg/dl), there was a striking fivefold increase in adverse events at one year compared with the lowest tertile (<0.32 mg/dl). The event-free survival in patients with aortic sclerosis varied inversely with increasing tertiles of CRP (Fig. 3).

Figure 4 depicts the cumulative incidence of cardiac death and nonfatal MI either at index admission or at one-year follow-up in patients with and without aortic sclerosis on echocardiographic evaluation, with respect to their history of documented CAD and the status of their systemic inflammation at the time of admission. In 98 patients without documented CAD (24%), we found a higher incidence of cumulative events in the aortic sclerosis group (9% vs. 0%, $p = 0.04$), all of which were in those who also had elevated CRP.

However, despite these findings by univariate and bivariate analyses, aortic sclerosis was not found to be an independent predictor of adverse cardiovascular outcome (Fig. 5). On multivariable analysis, independent predictors of adverse cardiovascular outcomes at one year were documented CAD, presentation with acute MI at the time of index admission, increasing tertiles of CRP, congestive heart failure, and age.

CPIgG titers were available in 408 patients, of whom 314

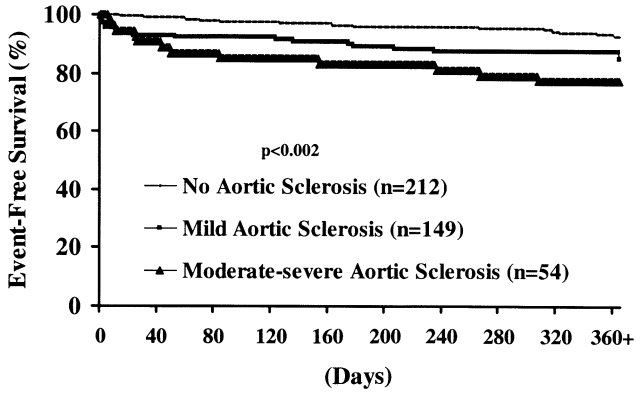

Figure 1. Kaplan-Meier analysis of event-free survival in patients according to the severity of aortic sclerosis. Event-free survival = freedom from cardiac death and nonfatal myocardial infarction.

Table 3. Unadjusted Risk of Adverse Cardiovascular Events at 12 Months

Variables	Relative Risk	95% CI
Age	1.05	(1.02, 1.07)
Hypertension	2.21	(1.04, 4.71)
Diabetes mellitus	2.16	(1.17, 4.01)
Coronary heart disease	4.12	(2.0, 8.47)
Congestive heart failure	2.97	(1.55, 5.72)
Elevated troponin T (>0.2 ng/ml)	2.68	(1.40, 5.14)
CRP (each tertile increase)*	1.52	(1.22, 1.88)
Fibrinogen (each tertile increase)†	1.88	(1.26, 2.80)
Lekocyte count (each tertile increase)‡	1.7	(1.15, 2.50)
Aortic sclerosis		
None	1	
Mild	2.28	(1.14, 4.55)
Mod-severe	3.75	(1.64, 8.59)
Any	3.11	(1.71, 5.67)

*C-reactive protein tertiles: <0.32; 0.32–1.18; >1.18 (mg/dl); ‡leukocyte count tertiles: <6.8; 6.8–9.0; >9.0 (10^9/l); and †fibrinogen tertiles: <282; 282–359.40; >359.40 (mg/dl).
CI = confidence interval; CRP = C-reactive protein.

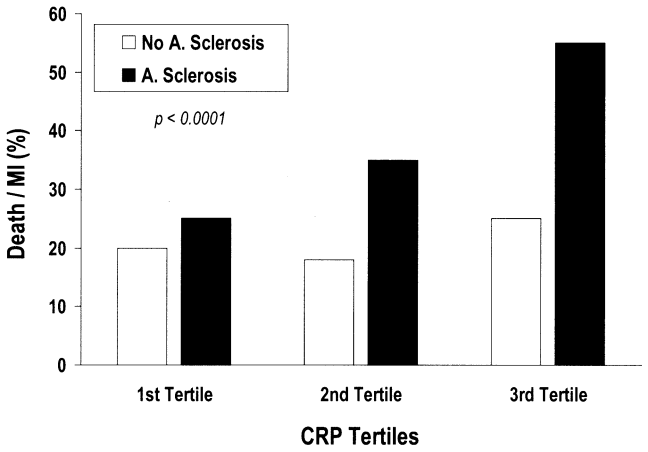

Figure 2. Incidence of cardiac death and nonfatal myocardial infarction (MI) at one year by severity of aortic (A.) sclerosis and C-reactive protein (CRP) tertiles. Tertiles: <0.32; 0.32 to 1.18; >1.18 (mg/dl); levels available on 395 of 415 patients.

(77%) were positive at the lowest titer (≥1:64) and 122 (30%) were positive at or above the highest titer (≥1:1,024). However, CPIgG titers were associated neither with aortic sclerosis nor with outcomes either at index admission or at one year. Furthermore, there was no association between the CPIgG titers and the levels of inflammatory markers.

DISCUSSION

Observations from the present study suggest that the increased incidence of adverse cardiovascular outcomes in patients with aortic sclerosis is attributable to the effects of CAD and inflammation, not a result of the effects of valvular heart disease per se.

The present findings are consistent with and extend those of prior studies documenting that patients with aortic sclerosis are at increased risk of adverse cardiovascular events (1–3). In this study, as in prior reports, patients with aortic sclerosis suffered an increased incidence of adverse cardiovascular events. However, the present results demonstrate

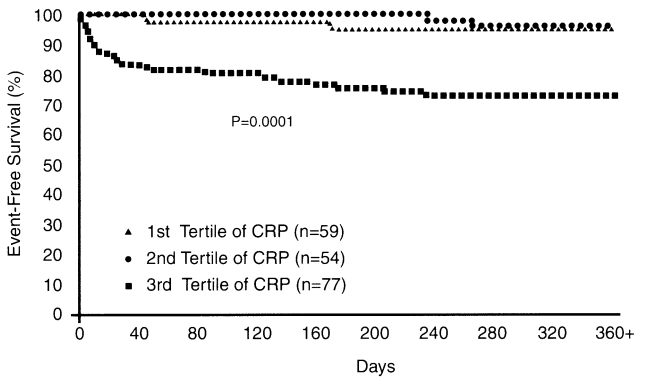

Figure 3. Kaplan-Meier analysis of event-free survival in patients with aortic sclerosis with respect to C-reactive protein (CRP) levels. Event-free survival = freedom from cardiac death and nonfatal myocardial infarction. Tertiles: <0.32; 0.32 to 1.18; >1.18 (mg/dl); levels available on 190 of 203 patients with aortic sclerosis.

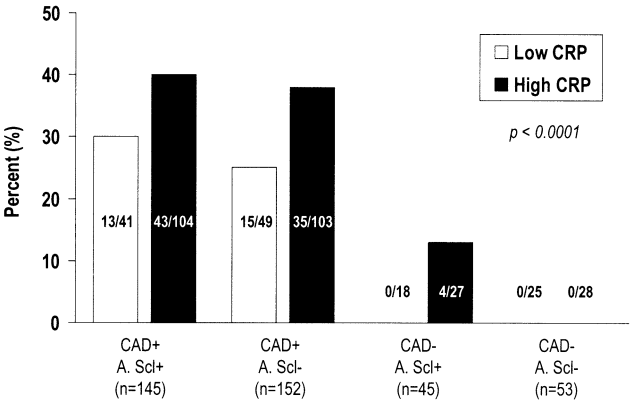

Figure 4. Cumulative incidence of cardiac death and nonfatal myocardial infarction either at index admission or at one year in patients with and without known coronary artery disease (CAD) in relation to their aortic valves (normal or any sclerosis by echocardiography) and systemic inflammation (low C-reactive protein [CRP] = 1st tertile, <0.32 vs. high CRP = 2nd and 3rd tertiles, ≥0.32 mg/dl); levels available on 395 of 415 patients; A.Scl = aortic sclerosis, + = present, − = absent.

that aortic sclerosis is not the mediator of adverse outcomes but rather a marker of the presence of CAD and inflammation, which together appear to be predominantly associated with the increased incidence of cardiovascular events. Our data demonstrate that patients with acute coronary syndromes, the greatest elevation of systemic inflammatory markers, and more severe aortic sclerosis suffered the highest incidence of adverse cardiovascular events. Multivariable analysis demonstrated that aortic sclerosis was not independently associated with adverse cardiovascular events. The strong relationship between aortic sclerosis and adverse cardiovascular events noted on univariate analysis was explained by the presence of CAD and concomitant elevation of inflammatory markers. Given the absence of a direct association between aortic sclerosis and adverse outcomes by

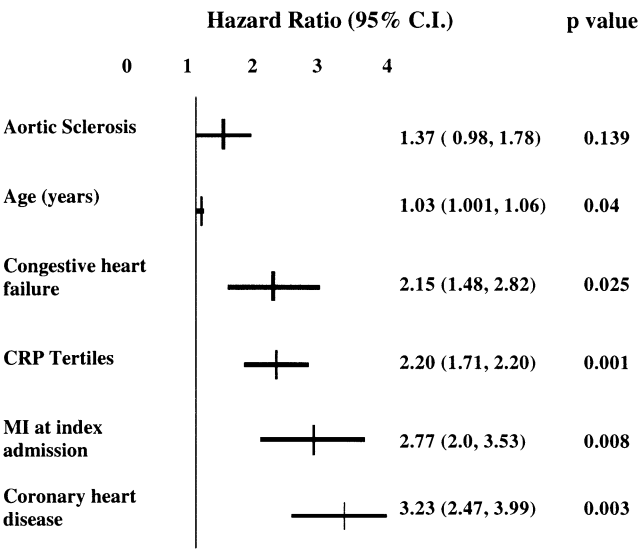

Figure 5. Cox multivariate analysis: one-year outcome of cardiac death and nonfatal myocardial infarction (MI). C.I. = confidence interval; CRP = C-reactive protein. Tertiles <0.32; 0.32 to 1.18; >1.18 (mg/dl).

multivariable analysis and the lack of a plausible independent pathophysiologic link between nonobstructive aortic sclerosis and cardiovascular events, the present data suggest that aortic sclerosis is merely an indicator for the presence of CAD and systemic inflammation, which constitute the factors associated with adverse coronary events.

In the present study, in patients with aortic sclerosis the presence and magnitude of elevated CRP was an independent predictor of adverse cardiovascular events, a link likely predominantly attributable to the direct pathophysiologic association between CAD and active inflammation. Local coronary inflammation is thought to play a fundamental pathophysiologic role in the induction and progression of chronic CAD (7–9). Acute plaque inflammation has been implicated as a key factor precipitating plaque instability resulting in acute coronary syndromes (8,9,11–15,24). Furthermore, observations from angiographic and pathologic studies support the concept that acute coronary artery instability is a multifocal coronary process, likely reflecting factors such as inflammation that adversely influence a diffusely atherosclerotic coronary vasculature (16,17). Whether elevation of systemic markers of inflammation in patients with acute coronary syndromes reflects primary local activation of inflammation in the coronary tree or systemic activation of the immune system that secondarily precipitates plaque instability is a subject of ongoing debate. Regardless, such serologic markers are prognosticators of short and long-term adverse cardiovascular events (18–22). Furthermore, recent data suggest that CRP may also play a complex modulatory function in the development and evolution of inflammation/atherosclerosis by directly inducing expression of adhesion molecules in human endothelial cells (25).

The present findings documenting elevated inflammatory markers and their association with adverse outcomes in patients with aortic sclerosis are novel and provide the basis for speculation regarding the mechanisms by which inflammation imparts increased risk in such patients. It is likely that the association between aortic sclerosis, cardiovascular events, and inflammatory markers reflects a shared pathophysiologic bond whereby inflammation plays a key role in the pathogenesis of both aortic sclerosis and atherosclerosis. Histopathologic studies in patients with aortic sclerosis document the presence of lipid particles and inflammatory infiltrates, including macrophages, T-lymphocytes, and matrix metalloproteinase, features that are strikingly similar to those seen in atherosclerosis (4–6). Risk factors implicated as stimuli for inflammation, including smoking, elevated low density lipoprotein cholesterol levels, hypertension, and obesity, are common to both CAD and degenerative aortic valve disease (1–3,26). Furthermore, endothelial injury at sites of hemodynamic stress has been postulated as the key factor inducing both coronary atherosclerosis and aortic sclerosis (8,11,15,24). The present study demonstrates associations, not cause and effect, but together with these observations the study provides the basis for speculation that the inflammatory process that initiates, promotes, and destabilizes coronary atherosclerosis also impacts the aortic valve and contributes to the development of aortic sclerosis. Thus, aortic sclerosis appears to be both a result of and a marker for the adverse effects of inflammation in the cardiovascular system. It is beyond the scope of the present study to determine whether the local coronary and aortic valve inflammation that appears to be common to the pathophysiology of coronary atherosclerosis and aortic sclerosis reflects a single pathogenetic stimulus inducing injury and inflammation in both vessel and valve or whether inflammation (and its reflection in serologic markers) is a coincidental response to independent unrelated injuries from hyperlipidemia, smoking, hypertension, diabetes, or infection.

There are important considerations pertinent to the methods of this study. The emergency room chest pain population may represent a group at higher risk for cardiovascular events. Echocardiographic evaluation was performed in 51% of cases, which may constitute a selection bias. Qualitative grading of aortic sclerosis is novel and needs to be replicated in further studies. The present study lacks angiographic and histopathologic data. On multivariable analysis the hazard ratio of 1.37 for aortic sclerosis showed a tendency toward statistical significance ($p = 0.139$). It is possible that a larger sample size would have shown aortic sclerosis to be an independent predictor of adverse cardiovascular events.

The present study has potential prognostic and therapeutic implications. On the basis of the present observations, patients with aortic sclerosis may need to be considered for testing to exclude CAD and analyze inflammatory markers. Anti-inflammatory agents such as aspirin, known to exert salutary effects on cardiovascular events in patients with CAD (27), and statins, which reduce cardiovascular events and lower the magnitude of systemic inflammation (28), could be beneficial in patients with aortic sclerosis and elevated inflammatory markers. Prospective studies will be necessary to determine whether such diagnostic and therapeutic strategies can improve outcomes in these patients. The severity of inflammation, which influences lesion progression and the clinical course in patients with unstable coronary plaques (11,12,14,18,19,21) may also determine the rate at which aortic sclerosis progresses. The present study found a linear association between inflammatory markers and severity of aortic sclerosis. Prospective longitudinal studies correlating levels of inflammatory markers with rates of aortic sclerosis progression will be necessary to determine whether the severity and duration of systemic inflammation influence which sclerotic valves will progress to become clinically stenotic.

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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. Aronow WS, Ahn C, Shirani J, et al. Comparison of frequency of new coronary events in older subjects with and without valvular aortic sclerosis. Am J Cardiol 1999;83:599–600.
3. Otto CM, Lind BK, Kitzman DW, et al. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142–7.
4. Otto CM, Kuusisto J, Reichenbach DD, et al. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994;90:844–53.
5. Olsson M, Dalsgaard CJ, Haegerstrand A, et al. Accumulation of T lymphocytes and expression of interleukin-2 receptors in nonrheumatic stenotic aortic valves. J Am Coll Cardiol 1994;23:1162–70.
6. Edep ME, Shirani J, Wolf P, et al. Matrix metalloproteinase expression in nonrheumatic aortic stenosis. Cardiovasc Pathol 2000;9:281–6.
7. Jang IK, Lassila R, Fuster V. Atherogenesis and inflammation. Eur Heart J 1993;14 Suppl K:2–6.
8. Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995;91:2844–50.
9. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115–26.
10. Danesh J, Collins R, Appleby P, et al. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477–82.
11. Fuster V, Stein B, Ambrose JA, et al. Atherosclerotic plaque rupture and thrombosis. Evolving concepts. Circulation 1990;82 Suppl:II47–59.
12. Moreno PR, Falk E, Palacios IF, et al. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994;90:775–8.
13. van der Wal AC, Becker AE. Atherosclerotic plaque rupture—pathologic basis of plaque stability and instability. Cardiovasc Res 1999;41:334–44.
14. Kovanen PT, Kaartinen M, Paavonen T. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. Circulation 1995;92:1084–8.
15. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. Circulation 1990;82 Suppl:II38–46.
16. Garcia-Moll X, Coccolo F, Cole D, et al. Serum neopterin and complex stenosis morphology in patients with unstable angina. J Am Coll Cardiol 2000;35:956–62.
17. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000;343:915–22.
18. Ridker PM, Rifai N, Stampfer MJ, et al. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000;101:1767–72.
19. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836–43.
20. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 1998;97:2007–11.
21. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med 2000;343:1139–47.
22. Anzai T, Yoshikawa T, Shiraki H, et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. Circulation 1997;96:778–84.
23. Chandra HR, Choudhary N, O'Neill C, et al. Chlamydia pneumoniae exposure and inflammatory markers in acute coronary syndrome (CIMACS). Am J Cardiol 2001;88:214–8.
24. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657–71.
25. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 2000;102:2165–8.
26. Mohler ER, Sheridan MJ, Nichols R, et al. Development and progression of aortic valve stenosis: atherosclerosis risk factors—a causal relationship? A clinical morphologic study. Clin Cardiol 1991;14:995–9.
27. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.
28. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1998;98:839–44.