THE NATURAL HISTORY OF AORTIC SCLEROSIS

C.M. Otto, Professor of Medicine and K.D. O'Brien, Associate Professor of Medicine, Division of Cardiology, Department of Medicine, University of Washington, Seattle, Washington

PREVALENCE OF AORTIC SCLEROSIS IN THE ELDERLY

Increasing use of echocardiography has demonstrated a higher prevalence of mild aortic valve disease than was previously recognised. In the population-based Cardiovascular Health Study, echocardiography documented mild irregular thickening of the aortic valve leaflets in 25% of adults over the age of 65 years.[1] In this condition, termed 'aortic sclerosis', no obstruction occurs to left ventricular outflow. A similarly high prevalence of aortic sclerosis has been found in other studies; prevalence increases with ageing such that almost half of adults over the age of 84 have some degree of aortic valve sclerosis.[2] Aortic sclerosis is one end of a disease spectrum; severe aortic stenosis with significant narrowing of valve opening resulting in clinical symptoms is the end-stage of this disease process (Table 1).

TABLE 1
Echocardiographic prevalence of calcific aortic valve disease in the Cardiovascular Health Study (n = 5201).[1]

Age group	Normal aortic valve	Aortic stenosis	Aortic sclerosis
All subjects	72%	2%	26%
65–74 yrs	78%	1·3%	20%
75–84 yrs	62%	2·4%	35%
>84 yrs	48%	4%	48%

PATHOGENESIS OF AORTIC SCLEROSIS

Aortic sclerosis differs markedly from normal ageing changes which occur in the valve leaflets. On naked eye examination, the changes found in normal ageing include mild diffuse increased thickness and opacity of the leaflets with residual normal flexibility on palpation. Microscopically, increased numbers of adipose cells are seen in the basal portions of the ventricular aspect of the leaflets. In contrast, aortic sclerosis is characterised by the formation of irregular raised areas on the aortic side of the leaflet interspersed with normal leaflet tissue. On palpation, these areas are firm and may be calcified. Microscopically, these lesions are subendothelial, situated on the aortic side of the leaflet, with displacement of the elastic lamina.[3] These lesions extend into the adjacent fibrosa, i.e. the dense central collagenous layer of the aortic leaflets. While the initiating factors involved in the development of aortic sclerosis remain unclear, it is likely that high mechanical shear, as exemplified by patients with a bicuspid aortic valve, and low shear stress, based on diastolic fluid dynamics in the sinuses of Valsalva, are both important.

In early lesions of aortic sclerosis, inflammatory cells are present, predominantly macrophages, with smaller numbers of T-lymphocytes. Smooth muscle cells are not found in the body of the aortic leaflets, but some fibrocytes are present. Extracellular material is increased and it consists of protein, proteoglycans and lipids. Oil-Red-O staining of frozen specimens demonstrates large amounts of extracellular neutral lipid in this site which specific markers for apolipoproteins can identify as being consistent with low density lipoprotein (LDL) and lipoprotein(a) (Lp(a)).[4, 5] Oxidation of LDL is also demonstrable in the lesions of aortic sclerosis and stenosis (Figure 1).[6]

Even in early lesions, microscopic mineralisation is present, as seen on von Kossa staining for calcium. As the disease progresses, the amounts of calcification increase, with the end-stage disease seen in patients undergoing valve replacement being characterised by large amounts of extracellular calcification, as well as lipid accumulation. The calcification process appears to be active, with a subset of the local macrophages producing osteopontin, a protein involved in calcification.[7, 8] Most recently, our group has demonstrated the presence of angiotensin converting enzyme in the early lesions of aortic stenosis, again emphasising that this is an active disease process, not just an inevitable consequence of ageing.[9]

CLINICAL FACTORS ASSOCIATED WITH AORTIC SCLEROSIS

The similarities in the histopathology of aortic sclerosis and atherosclerosis suggest that these disease processes may also have similar clinical associations. The increased prevalence of aortic stenosis with age, and the higher prevalence in men compared to women, have been known for many years. More recent data also convincingly demonstrate that aortic valve calcification is associated with hypertension, current smoking, elevated serum LDL and Lp(a) levels, a short stature and diabetes (Table 2). These associations have a magnitude of risk similar to that seen for atherosclerosis and remain significant even when coexisting coronary artery disease is taken into account.[1, 10-12]

HAEMODYNAMIC PROGRESSION OF AORTIC SCLEROSIS/ STENOSIS

The severity of aortic valve disease is often described in haemodynamic terms. Historically, cardiac catheterisation was performed when severe stenosis was suspected in order to measure the pressure gradient between the left ventricle and aorta in systole, both as the peak-to-peak gradient and as the mean gradient over the systolic ejection period. In conjunction with measurement of cardiac output, valve area could be calculated using the Gorlin formula. Catheterisation-derived transvalvular pressure gradients and Gorlin valve areas provided useful data for clinical decision-making and are still occasionally measured when clinical and echocardiographic data are discrepant. Today, haemodynamic severity is measured non-invasively using Doppler echocardiography. The most useful measures in the clinical setting are the transvalvular jet velocity (normal about 1 m/s) and continuity equation valve area.[13] For

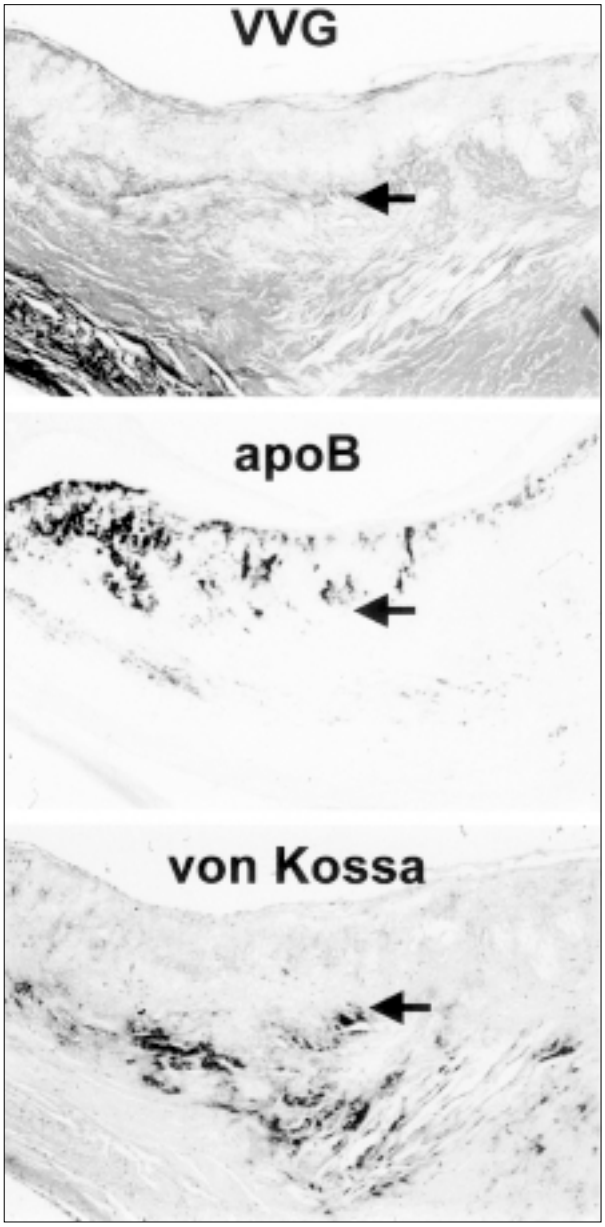

FIGURE 1
Typical early lesion of aortic stenosis. Shown are a morphological stain (VVG, upper panel) an immunohistochemical stain for the major protein of LDL, apolipoprotein B (apoB, middle panel) and a histochemical stain for calcium (von Kossa, lower panel). The aortic side of the valve leaflet is at the top of each panel. The early lesion of aortic stenosis develops on the aortic side of the leaflet and involves accumulation of inflammatory cells and proteins both in the subendothelial region above the elastic membrane shown with the VVG stain (black arrow) and below the elastic membrane in the collagen-rich fibrosa. Black arrows indicate the location of the elastic membrane in all panels. Plasma lipoproteins accumulate in the lesion, as shown by immunohistochemical staining for apoB (black reaction product, middle panel). In addition, the von Kossa stain demonstrates that calcification begins in areas of lipoprotein deposition (punctate black-brown staining, upper left region of the lower panel). In more advanced areas of calcification (dense black-brown staining, lower panel), there is less immunohistochemical evidence of lipoprotein deposition due to degradation of protein epitopes (comparison of central region of middle and lower panels).

TABLE 2
Clinical factors associated with calcific aortic valve disease in the Cardiovascular Health Study.[1]

	p-value	odds ratio
Age	<0·001	2·18*
Male Gender	<0·001	2·03
Lp(a)	<0·001	1·23†
Height	0·001	0·84‡
History of hypertension	0·002	1·23
Present smoking	0·006	1·35
LDLc (mg/d)	0·006	1·12†

*10 year increase; †10 unit increase; ‡75th vs 25th percentile; Lp(a)=lipoprotein (a); LDLc=low density lipoprotein cholesterol.

physicians more familiar with pressure gradient as a descriptor of stenosis severity, both maximum and mean transaortic pressure gradients can also be calculated based on the Bernoulli relationship that states that the pressure gradient across a narrowing is four times the velocity squared. Valve area calculations are most important when the jet velocity (or pressure gradient) is intermediate. In this situation, severe aortic stenosis may be present if the transvalvular volume flow rate is low, due to concurrent left ventricular systolic dysfunction or simply to a small hypertrophied ventricular chamber.

Both natural history studies and my own personal experience support the concept that aortic sclerosis is the early stage of the disease process that leads to severe aortic stenosis. In fact, aortic stenosis represents a disease continuum from very mild asymptomatic obstruction to severe obstruction requiring valve replacement. It is somewhat arbitrary and difficult to determine at which point aortic sclerosis becomes mild stenosis. My working definition for aortic stenosis is an antegrade jet velocity >2·5 m/s (two standard deviations above the normal value) in association with leaflet thickening. Irregular leaflet thickening with a jet velocity ≤2·5 m/s is defined as aortic sclerosis. In management of an individual patient, calculation of valve area is also needed; particularly as progressive disease may occur with no change in jet velocity due to a concurrent decrease in transvalvular volume flow rate as valve area decreases. For purposes of classifying groups of patients, mild stenosis is defined as a valve area >1·5 cm^2, moderate as a valve area of 1·0–1·5 cm^2 and severe as a valve area <1·0 cm^2. However, this classification only provides guidance and should not be used as absolute criteria for clinical decision-making in individual patients. The precise jet velocity or valve area at which an individual patient becomes symptomatic shows wide individual variability.

The rate of haemodynamic progression of aortic stenosis is highly variable from person to person.[14-21] The average rate of progression is an increase in jet velocity of 0·32 ± 0·34 m/s/yr, an increase in mean pressure gradient of 7 ± 7 mm Hg/yr and a decrease in valve area of 0·12 ± 0·19 cm^2/yr (Table 3). However, the standard deviation for the mean rates of progression are wide, such that some patients show little change over several years, while others have more rapid progression over one to two years of follow-up (Figure 2). Even so, progression is relatively slow and incremental so

TABLE 3
Haemodynamic progress of valvular aortic stenosis (selected studies) – update.

Series	Clinical status at entry	Type of study	n	Mean follow-up (yr)	↑ Mean ΔP (mmHg/yr)	↑ V_{max} (m/s per yr)	↓ AVA (cm^2/yr)	Predictors of haemodynamic progression
Otto *et al.* 1989[14]	Asymptomatic	Prospective	42	1·7	7·9 ± 7·1	0·36 ± 0·31	0·1 (0–0·5)	
Roger *et al.* 1990[15]	AS on echo	Retro cohort	112	2·1		0·23 ± 0·37		
Faggiano *et al.* 1992[16]	AS on echo	Prospective	45	1·5		0·4 ± 0·3	-0·1 ± 0·13 (-0·7–0·1)	
Peter *et al.* 1993[17]	AS on echo	Retrospective	49	2·7	7·2			
Brener *et al.* 1995[18]	AS on echo	Retrospective	394	3·1	6·3		0·14	
Otto 1997 *et al.*[19]	Asymptomatic	Prospective	123	2·5	7 ± 7	0·32 ± 0·34	0·12 ± 0·19	V_{max} at base line Rate of increase in V_{max} Functional status
Palta 2000 *et al.*[20]	AS on 2 echos	Retrospective	170	1·9			0·10 ± 0·27	Smoking, serum Ca^{++}, ↑cholesterol, ↑creatinine
Rosenhek 2000 *et al.*[21]	Asymptomatic	Prospective	128	Slow Rapid		0·14 ± 0·18 0·45 ± 0·38		Age diabetes, CAD Valve calcification Rate of increase in V_{max}

ΔP = pressure gradient; V_{max} = maximum aortic jet velocity; AVA = aortic valve replacement, CAD = coronary artery disease, Ca^{++} = calcium

TABLE 4
Suggested follow-up intervals for echocardiographic evaluation of asymptomatic aortic stenosis in the absence of a change in clinical status.

Aortic valve disease severity	Aortic jet velocity (m/s)	AVA (cm^2)	Follow-up interval
Aortic sclerosis	<2·5		4–5 years
Mild stenosis	2·5–3·0	>1x5	2–3 years
Moderate stenosis	3·0–4·0	1·0–1·5	Annually
Severe stenosis	>4·0	<1·0	Annually

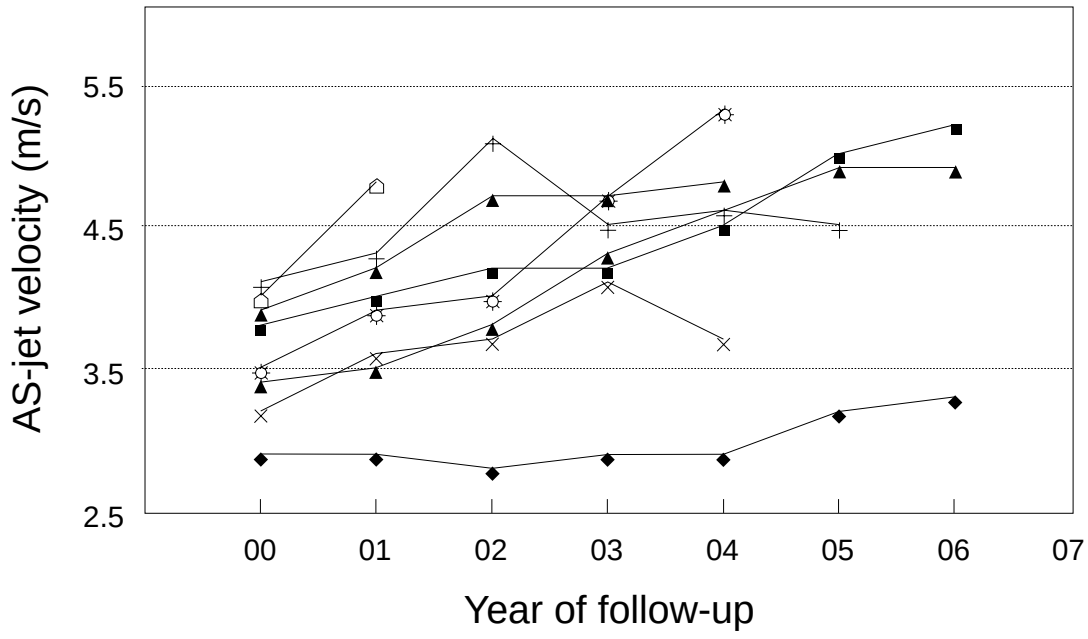

FIGURE 2

Examples of aortic stenosis (AS) jet velocity during prospective annual visits over a six year period in eight patients with asymptomatic AS, demonstrating the marked individual variability in the rate of hemodynamic progression. (Reproduced with permission from: Otto CM, Burwash IG, Legget ME *et al*. Prospective study of asymptomatic valvular aortic stenosis. *Circulation* 1997; **95:**2262.)

that diagnostic evaluation is rarely needed more often than annually, unless there is a significant change in the clinical situation (Table 4).

CLINICAL OUTCOME IN AORTIC STENOSIS

In adults with aortic stenosis, the strongest predictor of clinical outcome is symptom onset. Three classic symptoms of aortic stenosis are angina, syncope and heart failure. However, in educated patients followed prospectively, symptom onset is gradual, with most patients experiencing a gradual decrease in exercise tolerance as the initial symptom. In symptomatic adults with severe aortic stenosis, clinical outcome is very poor, with two year survival rates of only 50% and a high risk of sudden death,[22, 23] in contrast to asymptomatic patients in whom the risk of sudden death is low (less than 1% per year).[19, 23-26] Thus, the current consensus is that aortic valve replacement is indicated at the time of symptom onset.

Some clinicians advocate valve replacement prior to symptom onset if stenosis is severe; this is based on the argument that disease progression is inevitable and that a risk, albeit small, of sudden death always exists.[27] My own approach is to wait for symptom onset as valve surgery is not risk-free and prosthetic valves are not perfect. However, this approach depends on careful, periodic patient evaluation with emphasis on a detailed history, functional status assessment, and patient education.[28] Because symptom onset is insidious, the patient should be asked routinely to compare current maximal levels of exertion to specific time points in the past. If the history is unclear, an exercise stress test provides an objective measure of exercise tolerance, with a decreased exercise tolerance or blunted rise in blood pressure signaling symptom onset. When severe aortic stenosis is present, valve replacement should be recommended even for mild symptoms.

PREDICTORS OF HAEMODYNAMIC PROGRESSION AND CLINICAL OUTCOME

In our prospective study of 123 adults with initially asymptomatic aortic stenosis, the only multivariate predictors of clinical outcome were base line aortic jet velocity, the annual rate of increase in jet velocity and base line functional status score.[19] In those with an initial jet velocity <3·0 m/s, the rate of symptom onset is only about 8% per year. In contrast, in those with a jet velocity >4·0 m/s, 40% develop symptoms requiring valve replacement within one year, with a continued high rate of symptom onset over the next few years. In those with an initial jet velocity between 3·0 and 4·0 m/s, outcome is intermediate with an annual rate of symptom onset of 17% per year (Figure 3). In this study, there were no sudden deaths.

Other studies have confirmed the importance of jet velocity and the rate of increase in jet velocity as predictors of clinical outcome. In the study by Rosenhek *et al*.[21] carried out in patients with an annual increase in jet velocity >0·3 m/s/year, 80% developed symptoms requiring valve replacement or died within two years. Other factors associated with clinical outcome include coexisting coronary artery disease, left ventricular systolic dysfunction and other non-cardiac comorbid conditions.

Identification of factors that predict the rate of haemodynamic progression in individual patients has been more elusive. Although the extent of valve calcification is useful, this marker mainly distinguishes patients with rheumatic (less calcification) from those with calcific aortic valve disease. The clinical factors associated with aortic sclerosis (e.g. hypertension, diabetes, hypercholesterolemia, smoking) may be related to more rapid progression, but this association has been difficult to establish due to small sample sizes in studies with sequential Doppler data. It is likely that genetic factors that have not yet been

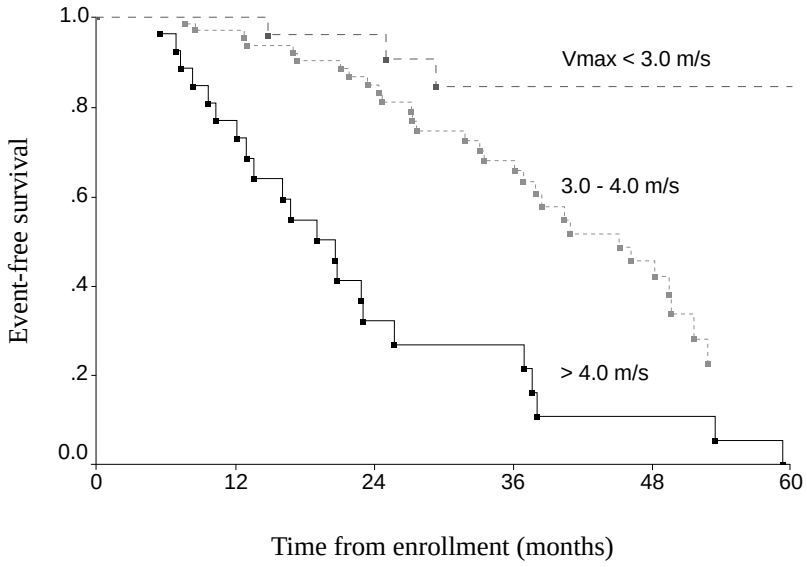

FIGURE 3
Cox regression analysis showing event-free survival in groups defined by aortic jet velocity at entry (p <0·0001 by log-rank test). (Reproduced with permission from: Otto CM, Burwash IG, Legget ME *et al.* Prospective study of asymptomatic valvular aortic stenosis. *Circulation* 1997; **95:**2262.)

identified are key elements in both an individual's susceptibility to the disease and in the rate of haemodynamic progression.

CLINICAL OUTCOME IN AORTIC SCLEROSIS

Until recently, aortic sclerosis on echocardiography was considered to be a benign incidental finding associated with ageing. As understanding of the disease process at the tissue level increased, and as the association of aortic sclerosis with clinical factors typically associated with atherosclerosis was better established, it became clear that aortic sclerosis is not a normal ageing change. The next question that had to be asked was: is the presence of aortic sclerosis on echocardiography associated with adverse cardiovascular outcomes? The population-based Cardiovascular Health Study offered an opportunity to address this question because base line echocardiography and clinical follow-up for an average of 5.5 years were available in 5,888 adults over age 65 years, randomly selected from all elderly adults at four locations in the US.[29]

In this study, outcome was defined as total mortality, cardiovascular (CV) mortality, and new CV events, including angina, myocardial infarction, congestive heart failure and stroke. A stepwise increase was demonstrated in both total and CV mortality rates comparing groups with a normal (total 14·9%, CV 6·1%), sclerotic (total 21·9%, CV 10·1%) or stenotic aortic valve (total 41·3%, CV 19·6%) (trend across groups p <0·001 for both total and CV mortality). After exclusion of subjects with known coronary disease at study entry, the relative risk for CV mortality was 1·66 (95% CI 1·23–2·23) for participants with a sclerotic valve compared to normal after adjustment for age and gender. This risk remained elevated even after further adjustment for other clinical factors associated with aortic sclerosis (1·52, 95% CI 1·12–2·05) (Table 5). The incidence of myocardial infarction also was higher in those with a sclerotic (8·6%) or stenotic (11·3%) versus a normal (6·0%) aortic valve (p <0·001) with a relative risk for myocardial infarction of 1·46 (95% CI 1·12–1·90) for a sclerotic valve compared to a normal aortic one.

The observed association between aortic sclerosis and adverse cardiovascular outcomes requires confirmation in other studies. In addition, the mechanism of the 50% increased risk of cardiovascular death and myocardial infarction in patients with aortic sclerosis compared to those with a normal valve cannot be deduced from this study. No obstruction to left ventricular outflow was shown on the base line study, so it is unlikely that a substantial number of subjects progressed to severe aortic stenosis over the follow-up interval. Instead, it is likely that aortic valve sclerosis is a marker of subclinical coronary artery disease in the elderly. The implication of this interpretation is that risk factor assessment and modification are needed in adults with aortic sclerosis. However, because risk factor modification is recommended for all adults, this does not represent a change in our current clinical approach. Whether more aggressive risk factor modification or other specific therapies would decrease the adverse outcomes associated with aortic sclerosis is unknown, and such therapy should await the results of well-designed randomised clinical trials.

RELATIONSHIP BETWEEN AORTIC SCLEROSIS AND CORONARY ARTERY DISEASE

Many similarities exist between aortic sclerosis and coronary artery disease. Both are associated with male gender, increasing age, hypercholesterolemia, hypertension, smoking and diabetes. At the tissue level, both occur at sites of increased tensile and decreased shear stress, and both are characterised by lipid accumulation, an inflammatory cell infiltrate, active production of proteins involved in tissue calcification and the presence of microscopic mineralisation. Clinically, both are associated with adverse outcomes including cardiovascular death and myocardial infarction (Table 6).

However, these diseases are not identical. At the tissue

TABLE 5
Event rates and relative risk for total and cardiovascular mortality in those with no Coronary Heart Disease* at study entry (2,958 participants with a normal valve and 1,115 participants with a sclerotic aortic one) in the Cardiovascular Health Study.[29]

All deaths	**Normal**	**Sclerosis**	**Relative risk**	**95% confidence intervals**
Event rate per 1,000 person – years	19	37		
Cox regression adjusted for age and gender			1·42	1·19–1·70
Cox regression adjusted for age, gender, and base line associated factors*			1·35	1·12–1·61
Cardiovascular deaths	**Normal**	**Sclerosis**	**Relative risk**	**95% confidence intervals**
Event rate per 1,000 person – years	6	14		
Cox regression adjusted for age and gender			1·66	1·23–2·23
Cox regression adjusted for age, gender, and baseline associated factors†			1·52	1·12–2·05

*Coronary Heart Disease; indicates participants with a history of myocardial infarction, angina, coronary bypass surgery or angioplasty prior to entry into the Cardiovascular Health Study.

†Factors associated with aortic valve sclerosis at base line which were included in this model were height, hypertension, present smoking, LDL levels, and diabetes.

TABLE 6
Comparison of calcific aortic valve disease and atherosclerosis.

	Calcific aortic valve disease	**Atherosclerosis**
Clinical		
• Increased prevalence with age	++++	++++
• Association with clinical factors	++++	++++
Pathologic		
• Inflammatory cells	+++	+++
• Lipoproteins	+++	+++
• Oxidized LDL	+++	+++
• Calcification	++++	++
• Smooth muscle cell proliferation	-	++
Genetic factors	?	+++
Mechanism of clinical events	Leaflet stiffness	Plaque instability

level, aortic sclerosis is characterised by earlier and more severe calcification. In addition, aortic sclerosis occurs on the broad surface of a valve leaflet, whereas atherosclerosis occurs within the lumen of a relatively small artery. The mechanism of clinical manifestations of the disease are also quite different. In atherosclerosis, most clinical events are acute and are related to plaque rupture with associated thrombosis. In aortic sclerosis, disease progression is slow with no likelihood of acute thrombosis. Furthermore, in aortic valve disease symptoms occur only when the bulky leaflet masses increase leaflet stiffness sufficiently to result in an impaired opening of the valve and, consequently, altered haemodynamics during ventricular systole.

Perhaps the most convincing evidence that these are two separate disease processes is the lack of concordance between severity of coronary and valvular disease in those patients (Figure 4). Most adults with significant coronary artery disease do not have aortic stenosis. Conversely, only about 50% of adults with aortic stenosis severe enough to require valve replacement have significant coexisting coronary artery disease.[30] Clearly, unidentified factors (possibly genetic) modulate the development and progression of these two disease processes in individual patients.

FUTURE DIRECTIONS

Aortic sclerosis is a prevalent disease that is associated with adverse cardiovascular outcomes. Many patients with aortic sclerosis will show progressive leaflet thickening and calcification, eventually requiring aortic valve replacement. As a clearer understanding of the clinical factors associated with aortic sclerosis has occured, accompanied by some understanding of the disease process at the cellular and molecular level, it is possible to begin to develop and test hypotheses about medical interventions that may prevent or slow the disease process. At this time, it is unclear whether therapy should consist of efforts to reduce 'risk factors' or whether more specific therapies can be developed.

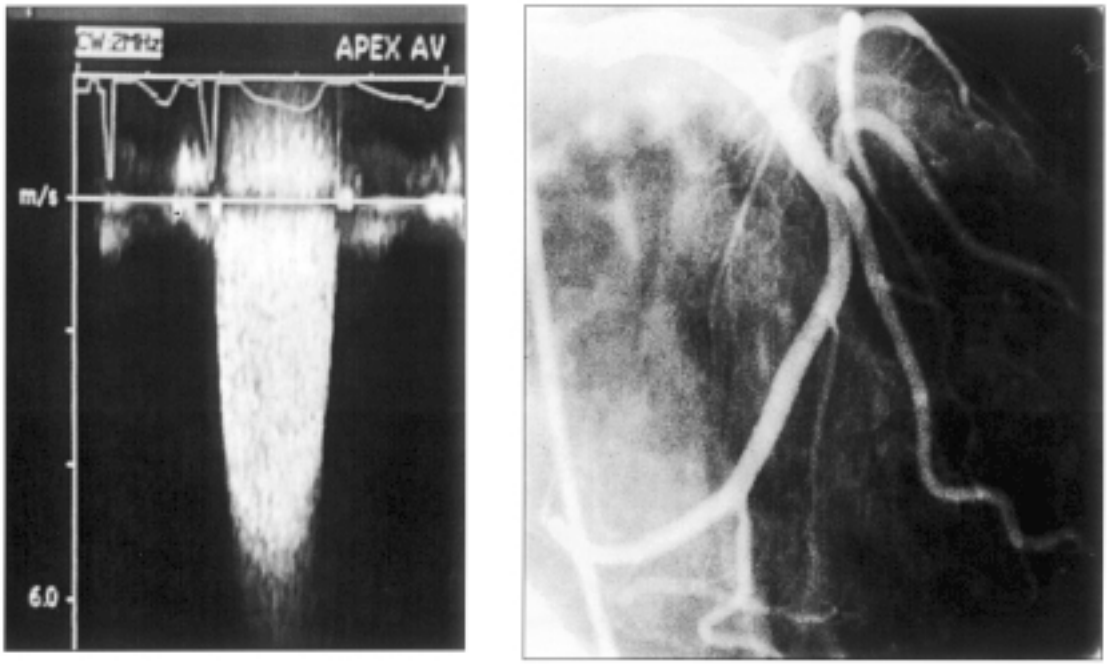

FIGURE 4
In this 84-year-old woman with exertional dyspnea, echocardiography showed severe aortic stenosis with an aortic jet velocity (LEFT) of 5·6 m/s and an aortic valve area of 0·6cm^2. However, coronary angiography (RIGHT) showed no significant coronary artery disease.

The optimal timing of medical therapy is also unclear. The goal would be to treat patients with enough disease to be at risk of adverse events and haemodynamic progression, but to treat them early enough in the disease process for the interventions to be effective.

REFERENCES

1 Stewart BF, Siscovick D, Lind BK *et al.* Clinical factors associated with calcific aortic valve disease. *J Am Coll Cardiol* 1997; **29:**630-4.

2 Lindroos M, Kupari M, Heikkila J *et al.* Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 1993; **21:**1220-5.

3 Otto CM, Kuusisto J, Reichenbach DD *et al.* Characterization of the early lesion of 'degenerative' valvular aortic stenosis: histologic and immunohistochemical studies. *Circulation* 1994; **90:**844-53.

4 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.

5 O'Brien KD, Reichenbach DD, Marcovina SM *et al.* Apolipoproteins B, (a) and E accumulate in the morphologically early lesion of "degenerative" valvular aortic stenosis. *Arterio and Thrombosis* 1996; **16:**523-32.

6 Olsson M, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. *Arterioscler Thromb Vasc Biol* 1999; **19(5):**1218-22.

7 O'Brien KD, Kuusisto J, Reichenbach DD *et al.* Osteopontin is expressed in human aortic valvular lesions. *Circulation* 1995; **92:**2163-8.

8 Mohler ERI, Adam LP, McClelland P *et al.* Detection of osteopontin in calcified human aortic valves. *Arterioscler Thromb Vasc Biol* 1997; **17:**547-52.

9 Shavelle DM, Eng KI, Probstfield JL *et al.* Angiotensin converting enzyme in human aortic valve lesions: production by macrophages and co-localization with low density lipoprotein. *Circulation* 2000;**102(II):**760. (Abstract)

10 Boon A, Cheriex E, Lodder J *et al.* Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. *Heart* 1997; **78:**472-4.

11 Aronow WS, Schwartz KS, Koenigsberg M. Correlation of serum lipids, calcium, and phosphorus, diabetes mellitus and history of systemic hypertension with presence or absence of calcified or thickened aortic cusps or root in elderly patients. *Am J Cardiol* 1987; **59:**998-9.

12 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.

13 Otto CM. *The Practice of Clinical Echocardiography*. Philadelphia: W.B. Saunders; 1997.

14 Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. *J Am Coll Cardiol* 1989; **13:**545-50.

15 Roger VL, Tajik AJ, Bailey KR *et al.* Progression of aortic stenosis in adults: new appraisal using Doppler echocardiography. *Am Heart J* 1990; **119:**331-8.

16 Faggiano P, Ghizzoni G, Sorgato A *et al.* Rate of progression of valvular aortic stenosis in adults. *Am J Cardiol* 1992; **70:**229-33.

17 Peter M, Hoffmann A, Parker C *et al.* Progression of aortic stenosis. Role of age and concomitant coronary artery disease. *Chest* 1993; **103:**1715-9.

18 Brener SJ, Duffy CI, Thomas JD *et al.* Progression of aortic stenosis in 394 patients: relation to changes in myocardial and mitral valve dysfunction. *J Am Coll Cardiol* 1995; **25(3):** 305-10.

19 Otto CM, Burwash IG, Legget ME *et al.* A prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997; **95:**2262-70.

20 Palta S, Pai AM, Gill KS *et al.* New insights into the progression of aortic stenosis: implications for secondary prevention. *Circulation* 2000; **101(21):**2497-502.

[21] Rosenhek R, Binder T, Porenta G *et al.* Predictors of outcome in severe asymptomatic aortic valve stenosis. *N Eng J Med* 2000; **643:**611-7.
[22] Kennedy KD, Nishimura RA, Holmes DRJ *et al.* Natural history of moderate aortic stenosis. *J Am Coll Cardiol* 1991; **17:**313-9.
[23] Turina J, Hess O, Sepulcri F *et al.* Spontaneous course of aortic valve disease. *Eur Heart J* 1987; **8:**471-83.
[24] Kelly TA, Rothbart RM, Cooper CM *et al.* Comparison of outcome of symptomatic to symptomatic patients older that 20 years of age with valvular aortic stenosis. *Am J Cardiol* 1988; **61:**123-30.
[25] Pellikka PA, Nishimura RA, Bailey KR *et al.* The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol* 1990; **15:**1012-7.
[26] Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J* 1988; **9(E):**57-64.
[27] Lund O. Valve replacement for aortic stenosis: the curative potential of early operation. *Scand J Thorac Cardiovasc Surg* 1993; **40(Suppl):**1-137.
[28] Otto CM. Aortic stenosis – listen to the patient, look at the valve (editorial). *N Engl J Med* 2000; **343(9):**652-4.
[29] 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(3):**142-7.
[30] Georgeson S, Meyer KB, Pauker SG. Decision analysis in clincal cardiology: when is coronary angiography required in aortic stenosis. *J Am Coll Cardiol* 1990; **15:**751-62.