Calcific aortic stenosis is the third most common cause of aortic valve disease in developed countries. This condition increases in prevalence with advancing age, affecting 2–3% of the population by the age of 65 years. The aging US population has led to a burgeoning number of valve replacements per year, which in turn costs the USA approximately $1 billion. The natural history, as described by Ross and Braunwald, shows that severe symptomatic aortic stenosis is associated with a life expectancy less than five years. Despite the high prevalence of this condition and the increasing morbidity and mortality, very little is known regarding the cellular basis of calcific aortic stenosis.

Pathologically, progressive aortic stenosis may produce left ventricular hypertrophy, left ventricular diastolic and systolic dysfunction, congestive heart failure, angina, arrhythmias, and syncope. Recent studies demonstrate an association between atherosclerosis and its risk factors and aortic valve disease. Although a unifying hypothesis for the role of atherosclerotic risk factors in the mechanism of vascular and aortic valve disease is emerging, progress in studying the cell biology of this disease has been limited by the paucity of experimental models available. A crucial question to ask is whether the same risk factors for vascular disease that initiate an atherosclerotic type injury in the coronary arteries initiate a similar injury in the aortic valve. If this is the case, it raises the possibility that the treatments used in slowing the progression of vascular atherosclerosis may be effective in patients with aortic sclerosis. Current management of calcific aortic valve disease focuses on defining patients with valvar disease and the development of symptoms to determine the timing of surgical valve replacement. This article will review the pathogenesis, natural history, evaluation, and management of patients with calcific aortic stenosis, taking into account emerging studies important in the understanding of the cellular mechanisms of calcific aortic stenosis. It will also address diagnostic studies for the detection and diagnosis of aortic valve calcium and summarise the current standard of treatment for calcific aortic stenosis and the potential for cholesterol lowering treatment to prevent progression or aortic valve calcification.

AETIOLOGY AND PATHOGENESIS

In 1854 William Stokes described in his textbook, *The diseases of the heart and the aorta*, specific pathological descriptions of calcific aortic valve disease, including: (1) permanent patency of the valve in which the diameter may be increased or diminished; (2) an extreme ossific growth along the valve surrounding the ventricle, at which the valves are often destroyed; and (3) an atheromatous deposit on the ventricular surface of the valve which is often seen in the context of fatty degeneration of the heart. In 2003, the aetiologies of calcific aortic stenosis (table 1) include bicuspid aortic valves, degeneration, familial hypercholesterolemia, hyperuricaemia, hyperparathyroidism, Paget's disease, ochronosis, Fabry's disease, systemic lupus erythematosus, and drug induced valvar disease. Currently, there are many proposed theories for the cellular causation of this disease: (1) mechanical shear stress leading to calcific injury as in bicuspid aortic valves; (2) autoimmune phenomena causing degeneration; and (3) cardiovascular risk factors initiating a “response to injury” similar to that seen in atherosclerosis. Other modifying factors that are associated with an increased prevalence of aortic stenosis include conditions with a chronically raised stroke volume and altered calcium metabolism (for example, Paget's disease, renal failure associated with arteriovenous fistula). Figure 1 shows an aortic valve removed at the time of surgical valve replacement, demonstrating valve leaflet nodule formation and thickening. These gross pathologic findings are responsible for the classic symptoms of chest pain, dyspnoea, and syncope in patients who have symptomatic severe aortic stenosis.

NATURAL HISTORY

Asymptomatic patients

Patients with severe calcific aortic stenosis develop left ventricular obstruction that occurs gradually over several years. Over time the left ventricle compensates for the persistent gradient between the left ventricle and the aorta, resulting in left ventricular hypertrophy and an increase in left
progression of aortic stenosis before to the onset of symptoms. Defining the rate of progression of this valvar lesion. There is an increasing amount of information demonstrating the association between clinical risk factors for atherosclerosis and the development of aortic stenosis (see box). Homozygous familial hypercholesterolemia (FH) produces a particularly severe form of aortic stenosis often with supravalvar narrowing in children. In this specific condition extremely high low density lipoprotein cholesterol (LDL-c) concentrations are seen without the presence of symptoms with unequivocal evidence of severe stenosis, but this is a complex issue and needs to be individualised, particularly in younger active patients. Recommendations for the use of echocardiography, cardiac catheterisation, and indication for aortic valve replacement in aortic stenosis have been described in the ACC/AHA guidelines (table 2).

MANAGEMENT
Currently, no medical treatment is required for the asymptomatic patient with valvar aortic stenosis. Management of patients with symptomatic aortic stenosis would include selected laboratory examinations, including an ECG, chest radiograph, and an echocardiogram. The echocardiogram will confirm the presence of aortic valve disease and delineate left ventricular (LV) size and function. The American College of Cardiology and American Heart Association (ACC/AHA) guidelines have defined severe aortic stenosis as an aortic valve area of < 1.0 cm$^2$ and a mean gradient of > 50 mm Hg. The decision to replace the valve is dependent on the presence or absence of symptoms with unequivocal evidence of severe stenosis, but this is a complex issue and needs to be individualised, particularly in younger active patients. Recommendations for the use of echocardiography, cardiac catheterisation, and indication for aortic valve replacement in aortic stenosis have been described in the ACC/AHA guidelines (table 2).

EMERGING CLINICAL AND EXPERIMENTAL DATA FOR THE ATHEROSCLEROTIC HYPOTHESIS
Clinical risk factors for the atherosclerosis hypothesis
Emerging epidemiological studies are revealing convincing clinical evidence towards an atherosclerotic hypothesis for the cellular mechanism of this valvar lesion. There is an increasing amount of information demonstrating the association between clinical risk factors for atherosclerosis and the development of aortic stenosis (see box). Homozygous familial hypercholesterolemia (FH) produces a particularly severe form of aortic stenosis often with supravalvar narrowing in children. In this specific condition extremely high low density lipoprotein cholesterol (LDL-c) concentrations are seen without the other traditional risk factors for coronary artery disease. Stewart and others from the cardiovascular health study identified several risk factors for calcific aortic valve disease:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptomatic patients with severe AS</td>
<td>I</td>
</tr>
<tr>
<td>2. Patients with severe AS before undergoing coronary artery bypass surgery</td>
<td>I</td>
</tr>
<tr>
<td>3. Patients with severe AS undergoing surgery on the aorta or other heart valves</td>
<td>I</td>
</tr>
<tr>
<td>4. Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves</td>
<td>IIa</td>
</tr>
<tr>
<td>5. Asymptomatic patients with severe AS and:</td>
<td></td>
</tr>
<tr>
<td>- left ventricular (LV) systolic dysfunction</td>
<td>IIa</td>
</tr>
<tr>
<td>- abnormal response to exercise (for example, hypotension)</td>
<td>IIa</td>
</tr>
<tr>
<td>- ventricular tachycardia</td>
<td>III</td>
</tr>
<tr>
<td>- pronounced or excessive LV hypertrophy ($\geq$15 mm)</td>
<td>III</td>
</tr>
<tr>
<td>- valve area &lt;0.6 cm$^2$</td>
<td>III</td>
</tr>
<tr>
<td>6. Prevention of sudden death in asymptomatic patients with none of the findings listed under indication 5</td>
<td>III</td>
</tr>
</tbody>
</table>
male sex, hypertension, raised LDL-c, and smoking. Furthermore, Palta and colleagues correlated the progression of aortic valve disease with smoking, raised serum creatinine, cholesterol, and calcium concentrations. These studies demonstrate that many of the same risk factors initiating vascular atherosclerosis are also implicated in aortic valve disease. Recently, Otto and colleagues reported that aortic sclerosis, which is described as focal areas of increased echogenicity and thickening of aortic valve leaflets without restricted leaflets, is found in 29% of subjects in the cardiovascular health study. In a five year follow up, aortic sclerosis was associated with an increase of approximately 50% in the risk of death from cardiovascular causes and the risk of myocardial infarction, even in the absence of haemodynamically significant obstruction to left ventricular outflow. These findings provide further evidence that the early lesion of aortic valve sclerosis may be associated with coronary artery disease and vascular atherosclerosis. Galante and co-workers have also demonstrated an increase in C reactive protein concentrations in patients with aortic valve stenosis. Finally, the extent of aortic valve calcification has been noted as an important predictor of poor outcome in patients with aortic stenosis. Together, these clinical studies suggest that aortic valve calcification is an inflammatory process promoted by atherosclerotic risk factors.

**Histologic evidence for atherosclerosis**

Many surgical pathological studies of human aortic valves demonstrate the presence of LDL and atherosclerosis in calcified valves, suggesting that there may be a common cellular basis for the genesis of valvar and vascular disease. O’Brien and colleagues have characterised early degenerative valve lesions in human valves and demonstrated an associated inflammatory infiltrate composed of non-foam cell and foam cell macrophages, occasional T cells, and rare α-actin positive cells. A prominent feature of degenerative valvar aortic stenosis is the accumulation of lipid, particularly in the fibrosa, the anatomic layer of the valve located immediately below the endothelium on the aortic side of the valve. Co-localisation of neutral lipid with immunohistochemical staining for LDL and other proteins implicated in atherogenesis such as lipoprotein(a), and apoE containing lipoproteins might be present in aortic valvar lesions. These histologic studies support the hypothesis that degenerative valvar aortic stenosis is the result of an active inflammatory disease process with some similarities to atherosclerosis. These similar findings are also found in more advanced lesions but in this setting smaller amounts of α-actin smooth muscles cells and more advanced calcification is present. Emerging experimental models in vitro and in vivo have demonstrated that atherosclerosis and bone-like features are also present in experimental valve calcification. Figure 2 compares a normal aortic valve with an experimental hypercholesterolaemic aortic valve in an animal model of hypercholesterolaemic diet. The normal aortic valve shows the presence of a normal clear glistening valve leaflet attached to the vascular aorta. The hypercholesterolaemic aortic valve shows atherosclerotic lipid deposition on the valve leaflet as well as the vascular aorta.

**Mechanisms of calcification**

Although calcification and ossification in aortic valves has been described in the literature for over 100 years, little is known about the synthesis of bone matrix proteins in calcific aortic valve stenosis. Until recently, only descriptive histologic and protein expression studies delineating the development of calcification in the aortic valve existed. Demer and colleagues have defined cardiovascular calcification as being composed of hydroxyapatite deposited on a bone-like matrix of collagen, osteopontin, and other minor bone matrix proteins. Osteopontin expression has been demonstrated in the mineralisation zones of heavily calcified aortic valves obtained at
Table 3: Retrospective studies of statin treatment in calcific aortic valve stenosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Radiological assessment</th>
<th>Degree of regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow et al</td>
<td>2001</td>
<td>180</td>
<td>Echo</td>
<td>Statin treatment</td>
</tr>
<tr>
<td>Novaro et al</td>
<td>2001</td>
<td>174</td>
<td>Echo</td>
<td>Change in peak systolic gradient across the aortic valve [−0.370 mm Hg/year]</td>
</tr>
<tr>
<td>Shavelle et al</td>
<td>2002</td>
<td>65</td>
<td>EBCT</td>
<td>Aortic valve area</td>
</tr>
<tr>
<td>Bellamy et al</td>
<td>2001</td>
<td>156</td>
<td>Echo</td>
<td>Non-statin</td>
</tr>
</tbody>
</table>

EBCT, electron beam computed tomography.

Table 3 summarises the retrospective data for the use of statins in the treatment of calcific aortic valve stenosis. These retrospective studies, combined with the experimental data, suggest that statin treatment may have a role in the inhibition of bone matrix production and end stage calcification, as proven in the regression of coronary artery calcification.

SUMMARY

This new evidence agrees with the original descriptions of Dr Stokes in that there is an atherosclerotic ossified lesion contributing to the pathogenesis of this disease. Recent epidemiological clinical studies have revealed that the risk factors for arterial atherosclerosis—male sex, smoking, and raised serum cholesterol—are similar to the risk factors associated with development of aortic valve stenosis. Experimental studies in vitro and in vivo support the hypothesis that the development of aortic valve calcification is similar to that of vascular calcification. Preliminary data are also emerging towards the potential possibility of primary and/or secondary prevention of aortic stenosis. Moreover, future clinical studies using statins in the treatment of aortic valve disease are also necessary to determine their potential for slowing this disease process in patients.
REFERENCES


The first study indicating the natural progression of patients with severe aortic stenosis.

3 Stokes W. The diseases of the heart and aorta. Dublin: Hodges & Smith, 1845:211–12.


Important echo study defining the echo parameters important in the development of severe aortic stenosis.


Current ACC/AHA guidelines for cardiac evaluation for patients with valvular heart disease. Contains a very thorough review of the entire English language literature.


First in vivo model of valve atherosclerosis demonstrating the effects of cholesterol and statins in the aortic valve.


First study to evaluate retrospectively the progression of aortic stenosis in patients who are taking statin agents.

CALCIFIC AORTIC STENOSIS: FROM BENCH TO THE BEDSIDE—EMERGING CLINICAL AND CELLULAR CONCEPTS

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