

# Aortic stenosis

Aortic stenosis (AS) is a narrowing or obstruction of the aortic valve and is the third most prevalent form of cardiovascular disease in the Western world after hypertension and coronary artery disease. AS is a potentially life-threatening condition that may present with symptoms related to valve obstruction or heart failure or may be diagnosed incidentally on "routine" clinical examination.

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Although the leading cause of aortic stenosis (AS) worldwide is rheumatic disease, in the western world "senile" degenerative AS is more common.<sup>1</sup> Degenerative AS has now become the commonest indication for valve replacement surgery and its prevalence increases with age; affecting about 2% of the population with a mean age of 72 years and up to 13% between the ages of 75 and 85 years.<sup>2</sup>

## Pathogenesis

Degenerative AS can occur either in patients with a normal tricuspid aortic valve (AV) or earlier in patients with a congenitally abnormal valve (figure 1).<sup>1</sup> The earliest histological changes resemble an active inflammatory process similar to that seen in coronary artery atheroma.<sup>3</sup> This presumably explains why diabetes, hypertension, smoking and elevated levels of low-density lipoprotein cholesterol have all been identified as risk factors for the development of degenerative AS.<sup>4</sup> These changes are the precursor to thickening or "sclerosis" of the valve which occurs as a result of the increased mechanical stress<sup>5</sup> and left ventricular (LV) outflow obstruction as valve leaflet opening becomes restricted. Progressive LV outflow tract obstruction results in greater wall stress and compensatory increased LV mass and hypertrophy. Initially LV systolic function and cardiac output are preserved but over time depression of myocardial contractility results in impaired LV systolic function and left ventricular systolic failure. Myocardial ischaemia occurs due to an imbalance between myocardial blood flow and demand. Myocardial blood flow may be reduced because of increased LV systolic pressures, reduction in capillary density and prolongation of systolic ejection phase, whilst myocardial oxygen requirements are

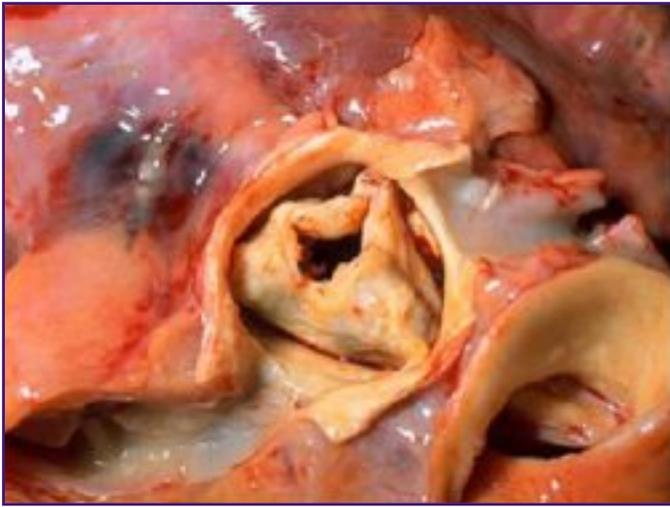
increased as a result of hypertrophied myocardium. Diastolic dysfunction is common and likely to be a consequence of ventricular hypertrophy, elevated end diastolic pressures and ischaemia.

The most common congenital abnormality of the AV is the bicuspid valve (figure 2). Other recognised abnormalities include unicuspid, quadricuspid valves and commissural fusion. These abnormalities lead to turbulent flow with continuous trauma to the leaflets and narrowing of the valve orifice.

## Symptoms and natural history

Patients with rheumatic AS tend to present with symptoms in their sixth decade or beyond. Patients with degenerative AS typically present later in their seventh decade unless the degeneration is associated with a congenitally abnormal valve in which case presentation may be sooner in midlife. The classically recognised symptoms associated with AS such as angina, syncope and heart failure are attributable to the pathological consequences of AS (ie. an increase in LV afterload, progressive LV hypertrophy and a decrease in systemic and coronary blood flow) and are more likely to occur as LV outflow tract obstruction increases. Angina results from myocardial ischaemia but concomitant coronary artery disease is also common. Syncope may be caused by either an inability to augment stroke volume during exercise as a result of outflow tract obstruction or inappropriate peripheral vasodilatation during exercise. Symptoms of heart failure may occur because of systolic or diastolic dysfunction.

The natural history of AS is well documented. It is classically associated with a long latent phase where patients remain asymptomatic. In general the onset of



**Figure 1:** Macroscopic appearance of stenotic aortic valve

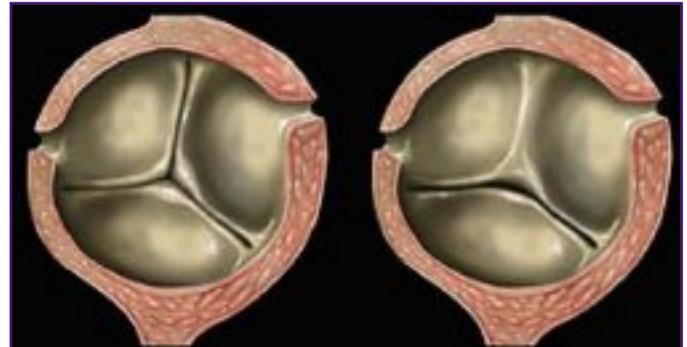
symptoms predicts a poor prognosis; the approximate time interval from the onset of symptoms to death is two years for congestive heart failure, three years for syncope, and five years for angina. These are the figures on which the recommendation to operate on severe symptomatic AS is based.<sup>6</sup> Sudden cardiac death is a frequent cause of death in symptomatic patients but occurs in less than 1% of asymptomatic individuals per year.<sup>7,8</sup>

## Diagnosis

A diagnosis of AS may be suspected based on the medical history and clinical examination. The classical signs of severe AS are a slow-rising carotid arterial pulse, crescendo-decrescendo systolic murmur and absence of the aortic component of the second heart sound (S2) but their presence varies with the severity of valve calcification, the severity of stenosis and the degree of LV dysfunction. Lateral displacement of the apex beat, the presence of a third heart sound and elevation of the jugular venous pressure are suggestive of the development of heart failure. However, clinical examination findings are often unreliable.<sup>9</sup>

## Electrocardiography (ECG)

Left ventricular hypertrophy with associated repolarisation abnormality is the most commonly recognised ECG feature of AS. Other common abnormalities include conduction abnormalities, bundle branch block and axis deviation. However, a normal resting ECG does not exclude a diagnosis of severe AS.



**Figure 2:** Example of a normal tri leaflet (left) and bicuspid aortic valve (right)

## Transthoracic echocardiography (TTE)

Transthoracic echocardiography (TTE) remains the imaging modality of choice when investigating and assessing the severity of AS. Two-dimensional TTE allows identification of a bicuspid valve and can provide information on the appearance of the valve leaflets and the pattern and extent of disease while measurements of haemodynamic gradients and effective valve orifice area (EOA) can be determined from Doppler echocardiography. Additional information with regards to left ventricular size and function, the presence of associated mitral valve pathology, aortic dimensions and assessment of pulmonary artery pressure can also be obtained with TTE. An instantaneous peak gradient across the valve of greater than 65mmHg, a mean gradient greater than 50mmHg and an EOA of less than 1cm<sup>2</sup> (or 0.6cm<sup>2</sup>/m<sup>2</sup> body surface area) is considered to represent severe AS.<sup>10</sup>

## Dobutamine stress echocardiography

The calculation of aortic valve area on TTE is based on the Gorlin or continuity equation, both of which are flow dependent and therefore dependent on the patient's cardiac output at the time. Thus in patients with reduced cardiac output due to LV dysfunction TTE alone may underestimate the degree of AS. In these patients low dose dobutamine can be used to augment cardiac output, and therefore flow rates across the stenotic valve, allowing more accurate assessment of severity. Those patients that demonstrate improved LV ejection fraction and increased outflow tract gradient after dobutamine are also more likely to respond favourably to valve replacement.

## Transoesophageal echocardiography

Transoesophageal echocardiography (TOE) is rarely required

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for straightforward diagnosis of AS. It allows superior spatial resolution and is useful in those patients in whom TTE image quality is poor or assessment of co-existing mitral valve disease is difficult with TTE. More recently, TOE has been used to make accurate measurements of aortic root size prior to transcatheter valve interventions.

## Computed tomography (CT)

Early data suggests that CT may be useful in quantifying valve calcification and measuring anatomic valve area,<sup>11</sup> both of which may be useful prognostic information. However, it does not allow assessment of gradients or EOA. At present its main clinical use is to measure the aortic root in cases where aortic root enlargement is suspected or to quantify the amount of calcium in the aorta prior to surgical replacement.

## Cardiac catheterisation

The main indications for cardiac catheterisation in AS

is to document the extent of any coexistent coronary artery disease prior to valve replacement or to assess the transvalvular pressure gradient by taking simultaneous LV and aortic pressure measurements when clinical findings are not consistent with Doppler TTE results.

## Management

### Non-interventional management

Non medical intervention has yet been proven to prevent or reverse AS in humans. Experimental animal models have suggested a role for lowering of plasma cholesterol levels in reversing progression of aortic valve disease in mice<sup>12</sup> but the large prospective randomised SALTIRE and SEAS trials of lipid-lowering therapies in humans have been discouraging.<sup>13,14</sup> Medical treatment is therefore currently reserved for treating complications of AS such as heart failure or angina pectoris.

Outpatient management of AS is mainly directed

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Bydureon should be discontinued at least 3 months before a planned pregnancy. Bydureon should not be used during pregnancy and the use of insulin is recommended. Bydureon should not be used during breastfeeding. **Driving, etc.** No studies on the effects on the ability to drive and use machines have been performed. When Bydureon is used in combination with a sulphonylurea, avoid hypoglycaemia while driving and using machines. **Undesirable Effects** Adverse Reactions Reported From Clinical Studies Very common Hypoglycaemia (with a sulphonylurea), constipation, diarrhoea, nausea, vomiting, injection site pruritus, injection site nodules. Common Decreased appetite, dizziness, headache, abdominal distension, abdominal pain, dyspepsia, eructation, flatulence, gastro-oesophageal reflux, fatigue, injection site erythema, injection site itch, soreness. Rapid weight loss has been reported with Bydureon. Patients may develop anti-exenatide antibodies following treatment with Bydureon. These patients tend to have more injection site reactions (eg, skin redness, itching). Acute pancreatitis and acute renal failure have been reported rarely and anaphylactic reaction has been reported very rarely in spontaneous post-marketing reports with exenatide twice daily. For full details of these and other side effects, please see the Summary of Product Characteristics, which is available at <http://emc.medicines.org.uk/>. **Legal Category** POM. **Marketing Authorisation Number** EU/1/11/005/001 **Basic NHS Cost** £73.36 per 4 weekly pack **Date of Information or Last Review** June 2011

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**References** 1. National Institute for Health and Clinical Excellence. Exenatide prolonged release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. Technology Appraisal Guidance No. 248. London: NICE, 2012 ([www.nice.org.uk](http://www.nice.org.uk)). 2. Buse JB, Mack MA, Forst T et al. Efficacy and safety of exenatide once weekly versus liraglutide in subjects with type 2 diabetes. EXAMINATION-6: a randomised, open-label study. *Diabetologia* 2011; 54(Suppl 1): S38-4. 3. BYDUREON<sup>®</sup> (Summary of Product Characteristics).

at recognition of symptoms and optimal timing of surgery. All asymptomatic patients without significant medical comorbidities to preclude a valve replacement procedure should be assessed annually (moderate AS) or every six months (severe AS), ideally in a specialist valve clinic.<sup>15</sup> Predictors of accelerated progression of AS include older age, presence of atherosclerotic risk factors, rapid haemodynamic progression and the presence of valve calcification at echocardiography.<sup>6</sup> Antibiotic prophylaxis before dental treatment is no longer routinely recommended in the UK.<sup>16</sup>

### Surgical aortic valve replacement

Surgical aortic valve replacement surgery is the definitive management of severe AS with expected in-hospital mortality in the region of 3%. Indications for surgery are severe AS, either in the presence of symptoms or LV impairment in asymptomatic patients. Careful exercise testing can be undertaken to provoke symptoms in those patients with severe AS who deny any limitation of exercise on questioning. Aortic valve replacement should also be undertaken in patients with moderate AS undergoing coronary artery bypass surgery, aortic root or arch replacement or other valve surgery.<sup>6</sup>

### Aortic balloon valvuloplasty

Initially devised in the 1980s as a less invasive alternative to surgical treatment of AS,<sup>17</sup> aortic balloon valvuloplasty has a high complication rate and an unacceptably high restenosis rate to be considered as an alternative to surgery.<sup>18</sup> The use of aortic valvuloplasty should be restricted to haemodynamically unstable patients at high risk for surgery as a bridge to definitive treatment or as a palliative measure in patients in whom definitive treatment is contraindicated because of significant comorbidities.

### Transcatheter aortic valve intervention (TAVI)

The development of a percutaneous valve replacement procedure was motivated by the observation that almost a third of patients with severe AS in Europe did not undergo surgical valve replacement because of significant co-existing comorbidities.<sup>19</sup> The procedure is performed via a catheter inserted into either the femoral artery or the apex of the heart and a compressible bioprosthetic valve (see figure 3 and 4) is inflated within the native valve orifice. Overall 30-day major adverse cardiovascular complication



**Figure 3:** Percutaneous aortic valve (Edwards Lifesciences Inc, Irvine, CA, USA)

rate in high-risk patients (ie. those deemed at too high risk to undergo conventional surgical aortic valve replacement) ranges from 3-35%.<sup>20</sup> Although these results suggest that this is an inferior procedure in terms of morbidity when compared to surgical aortic valve replacement, it is worth remembering that TAVI is usually undertaken in patients with high anticipated surgical mortality.

Transcatheter aortic valve replacement is currently restricted to elderly patients who are considered at high risk for conventional surgery but remains a promising focus of future studies.

NICE has recently updated its guidance for the NHS on TAVI procedures. The guidance updates and replaces previous guidance from 2008.<sup>21</sup> The main updates are recommendations on the use of TAVI for people who would be considered unsuitable for open heart surgery (eg. because of poor health) and on when to consider TAVI as an option for people who could have the more invasive option instead. NICE did not advise on the use of TAVI for these patient groups in 2008 because there was insufficient evidence at the time.

## Conclusion

AS is a potentially life-threatening condition that may present with symptoms related to valve obstruction or heart failure or may be diagnosed incidentally on "routine" clinical examination. The management of AS is



**Figure 4:** Fluoroscopic image taken at the time of TAVI, the valve is positioned over the native aortic annulus. A temporary pacing wire can be seen in the right ventricle, fast ventricular pacing for a short period of time results in a reduction in cardiac output and provides greater stability as the valve is delivered. A transoesophageal echo probe can also be seen.

predominantly aimed at early diagnosis, serial follow up and timing of a definitive valve replacement procedure, of which conventional (surgical) aortic valve replacement remains the gold-standard. However, TAVI is increasingly becoming an option for patients with high surgical morbidity and mortality.

**Conflict of interest:** none declared

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