Aortic stenosis

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In developed countries, aortic stenosis is the most prevalent of all valvular heart diseases. A manifestation of ageing, the disorder is becoming more frequent as the average age of the population increases. Symptomatic severe disease is universally fatal if left untreated yet is consistent with a typical lifespan when mechanical relief of the stenosis is provided in a timely fashion. Management of mild disease, severe asymptomatic disease, and far advanced disease, and the effect of new percutaneous treatments, provide both controversy and exciting promise to care of patients with aortic stenosis. We discuss these issues in this Review.

Epidemiology

Aortic valvular abnormalities are quite frequent in old patients. In the Cardiovascular Health Study, in which 5201 men and women older than 65 years were examined, 26% of study participants had aortic sclerosis (a thickening of the valve or calcification without significant obstruction). A slight predominance of the disorder was noted in men. 2% of all patients had frank aortic stenosis[1] A clear increase in prevalence of sclerosis was seen with age: 20% in patients aged 65–75 years, 35% in those aged 75–85 years, and 48% in patients older than 85 years. For the same age-groups, 1·3%, 2·4%, and 4% had frank aortic stenosis.

Causes

Calcific aortic stenosis

Once judged a degenerative disease, the mechanism by which a previously healthy tricuspid aortic valve becomes stenotic is now believed to be very similar to that of atherosclerosis. The initial plaque of aortic stenosis is alike that of coronary artery disease.[2] Risk factors associated with coronary artery disease—including age, male sex, hyperlipidaemia, and evidence of active inflammation—are held in common by the two disorders.[3] Further, there is a high coincidence of both diseases in the same individual.[4,5] Although debated, use of statins seems to retard progression of aortic stenosis early, but not late, in the disease course.[6–9] When tricuspid aortic valves do become stenotic, the process usually happens in the sixth, seventh, and eighth decades of life. Calcific aortic stenosis is mainly caused by solid calcium deposits within the valve cusps and less by fusion of the commissures. The location of these deposits helps to explain orifice variability in calcific aortic stenosis when cardiac output is raised by inotropic agents[10,11] or vasodilators.[12]

About 1–2% of babies are born with a bicuspid aortic valve, which is sometimes associated with coarctation of the aorta. Most of these affected infants are male. A bicuspid valve contributes more to the total number of cases of aortic stenosis than disease of tricuspid valves.[13,14] Processes that lead to stenosis of a bicuspid aortic valve are presumably similar to those noted above for tricuspid valves. However, stenosis in bicuspid valves arises about two decades before it does in tricuspid aortic valves. This earlier occurrence might develop because of less favourable haemodynamics of bicuspid valves. Even in healthy tricuspid valves, the three leaflets are rarely of equal area, with large variations in leaflet sizes.[15] Perhaps this variation could also have a bearing on the tendency for stenosis to develop.

Search strategy and selection criteria

We searched PubMed with the keyword "aortic stenosis". We identified citations that formed a mix of important older studies and those published since 2000. Citations from journals with high impact factors were given special weight, and we attempted to balance sources from the USA and Europe.

Congenital aortic stenosis

Most cases of severe congenital aortic stenosis are detected and treated in early childhood or adolescence. Occasionally, the disorder is diagnosed for the first time in adulthood. Some features of congenital aortic stenosis differ from those of acquired stenotic disease. First, anatomically, congenital aortic stenosis often features a unicuspid unicommissural valve and is virtually never associated with asymptomatic survival into adulthood; less typically, the disorder is attributable to a bicuspid valve.[13] Children with the condition either die in childhood or develop symptoms leading to aortic valve replacement. Second, angina and heart failure are unusual in congenital aortic stenosis, whereas sudden death in people without symptoms of aortic stenosis seems to be more common[16] and related to appearance of left-ventricular strain on the electrocardiogram. The absence of heart failure could be attributable in part to the fact that ejection performance is usually supranormal and wall stress is subnormal because concentric hypertrophy seems to overcompensate for the existing pressure overload.[17]

Rheumatic valve disease

In developed countries, rheumatic fever has become a very rare cause of aortic stenosis.[18] When the aortic valve is affected by rheumatic heart disease the mitral valve is almost always affected as well. Thus, diagnosis of rheumatic aortic stenosis should not be made without typical echocardiographic evidence of rheumatic mitral valve deformity. Further, in rheumatic aortic stenosis, commissural fusion is usually present, by contrast with calcific aortic stenosis.

Pathophysiology and relation to symptoms

Onset of severe symptoms of aortic stenosis—angina, syncope, and heart failure—remains the major demarcation point in the disease's course (figure 1).[19] The asymptomatic patient has a good outlook even with severe obstruction, whereas an individual with symptoms has a mortality rate of about 25% per year. Thus, knowing how the pathophysiology of aortic stenosis causes symptoms and death is paramount to understanding the disease.

Pressure overload hypertrophy

As the table shows, narrowing of the aortic orifice to half its usual 3 cm² causes little obstruction to left-ventricular outflow and, thus, only a small pressure gradient exists across the valve. However, further decreases in valve area result in progressively greater left-ventricular pressure overload. Although still debated, many researchers view development of left-ventricular hypertrophy as a major compensatory mechanism,[20–23] offsetting the pressure overload. Pressure overload by itself increases left-ventricular afterload, impairing ejection performance. Afterload is generally quantified as wall stress ( ) with the Laplace equation, in which =pr/2th and p is left-ventricular pressure, r is left-ventricular radius, and th is left-ventricular thickness. As pressure grows in the numerator of this equation it is offset by a rise in wall thickness (concentric left-ventricular hypertrophy) in the denominator, keeping afterload (wall stress) normal. Since afterload is a key determinant of ejection performance, its normalisation is important in maintaining normal ejection fraction and stroke volume.

Unfortunately, hypertrophy is a double-edged sword, beneficial in some respects and deleterious in others. Although it helps to preserve ejection performance, hypertrophy also impairs coronary blood-flow reserve, reduces diastolic function, and is associated with increased mortality.[24–30]

In all other circulatory beds, oxygen delivery to tissues can be augmented by both a boost in blood flow to the region and an increase in oxygen extraction from haemoglobin. The heart is unique among all organs in that its blood flow is received mainly during diastole and oxygen extraction is always close to maximum. Thus, the only way in which the myocardium can match enhanced oxygen demand with increased supply is by boosting coronary blood flow. In healthy individuals, coronary blood flow reserve is 500–800% over resting flow; however, in the presence of concentric hypertrophy, reserve is diminished, usually to about 200–300%.[26] This impairment could be secondary to reduced capillary ingrowth into the hypertrophied myocardium.[27] Additionally, the increased filling pressure needed to distend the thickened ventricular wall compresses the endocardium, further impairing blood flow to that layer of the myocardium. These abnormalities must contribute to the cause of angina in patients who develop it in the presence of normal epicardial coronary arteries. However, the explanation is not that simple because not all individuals with impaired flow reserve develop angina and angina does not correlate well with the extent of hypertrophy present. Angina does seem to accord with obstruction severity and diastolic filling time (the oxygen debt repayment period).[28,29]

Onset of dyspnoea and other symptoms of heart failure presage the worst outlook for the patient with aortic stenosis. Whereas concentric hypertrophy helps to maintain systolic performance, increased wall thickness impairs diastolic function. Diastole is typically divided into active relaxation and passive filling. During active relaxation, calcium is pumped back into the sarcoplasmic reticulum, causing the contractile interaction between actin and myosin to diminish. In concentric hypertrophy, this process is delayed, in turn holding up the onset of passive filling, shortening the time for blood to pass from the atria to the ventricles.[30] Furthermore, increased wall thickness needs amplified distending pressure to achieve the same diastolic volume as noted in a healthy individual.[31] This augmented diastolic pressure leads to pulmonary congestion and dyspnoea.

Concentric hypertrophy is not compensatory in all cases. In some patients, hypertrophy fails to normalise afterload[32], allowing the abnormal afterload to reduce ventricular ejection performance, reducing cardiac output, adding to the heart failure syndrome. Eventually, contractile function also fails (figure 2),[33] further restricting ejection

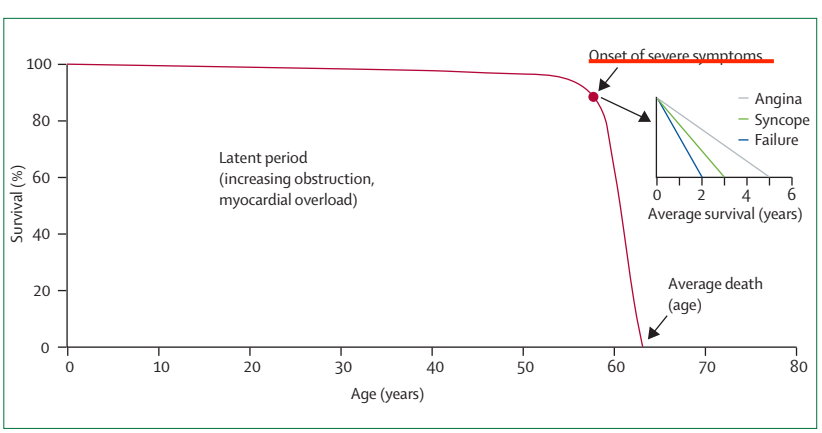

Figure 1: **Survival of patients with aortic stenosis over time**
After a long latent asymptomatic period, during which time survival is nearly normal, survival declines precipitously once symptoms develop. Adapted with permission from Ross and colleagues.[19]

Gradient (mm Hg)	Aortic valve area (cm²)	Cardiac output (L/min)
2	3·0	5·0
11	1·5	5·0
16	1·25	5·0
25	1·0	5·0
45	0·75	5·0
70	0·60	5·0
100	0·50	5·0

Table: **Aortic valve area versus gradient**

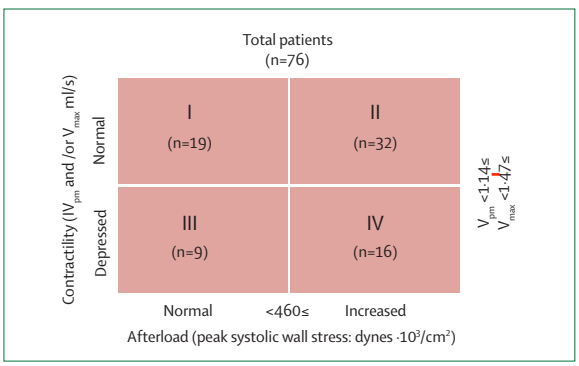

Figure 2: **Categories of patients with aortic stenosis**
Patients are divided into four groups. Group I have normal contractility and normal afterload. Group II have normal contractility and increased afterload. Group III have depressed contractility and normal afterload. Group IV have depressed contractility and increased afterload. Most patients with aortic stenosis have some element of afterload excess. Adapted with permission from Huber and colleagues.[33]

performance. Additionally, many long-held tenets of hypertrophy have been challenged. Provocative findings from a study showed that patients with aortic stenosis and left-ventricular hypertrophy had a higher prevalence of heart failure and depressed left-ventricular ejection fraction than did individuals with similar valve area and no left-ventricular hypertrophy.[34] However, in the people without hypertrophy, remodelling took place such that cavity size was reduced and relative wall thickness was increased compared with patients with diminished ejection fraction. Thus, wall stress was probably normalised by this very remarkable kind of remodelling, in which wall thickening arose without enhanced ventricular mass. This observation challenges the paradigm of adaptive left-ventricular hypertrophy in aortic stenosis,[35] although adaptive remodelling did happen. Further, the notion of classic evolution from adaptive hypertrophy to heart failure might not always hold. Microarray data indicated gene-expression patterns that differed widely in the initial stages of hypertrophy, shortly after imposition of the hypertrophy stimulus between animals that eventually developed adaptive versus maladaptive pressure-overload hypertrophy.[36] Similar phenotypic results were recorded by Koide and colleagues, in which adaptive versus maladaptive hypertrophy seemed distinct rather than one process evolving into the other.[21]

Mechanisms by which the hypertrophied heart develops a contractile deficit remain controversial and go well beyond the scope of this Review. Hypotheses include intermittent ischaemia,[37] abnormalities in calcium handling,[38] apoptosis,[39,40] neurohumoral activation,[41] and hyperpolymerisation of the myocardial cytoskeleton.[42]

Syncope

Another ominous symptom of aortic stenosis is syncope. Although probably unrelated to the presence of hypertrophy, the exact mechanism of syncope in aortic stenosis remains unclear. In patients with aortic stenosis, syncope usually arises during exercise. In healthy individuals, blood pressure rises during exercise. Blood pressure is equal to cardiac output multiplied by total peripheral resistance. In healthy people, total peripheral resistance falls during exercise but blood pressure increases because cardiac output rises more than total peripheral resistance diminishes. One theory is that the augmented stroke volume that usually accompanies exercise is limited in aortic stenosis by the narrowed outflow orifice. Since there is a requisite decrease in arterial resistance, blood pressure drops leading to syncope. Indeed, a fall in blood pressure during exercise has been noted in patients with aortic stenosis.[43] Other researchers[44] have postulated that the very high intraventricular pressure that develops during exercise in people with aortic stenosis causes a reflex depressor response, in turn causing syncope (ie, vasoplegic syncope). Finally, in some individuals, ventricular arrhythmias potentiated by exercise-induced ischaemia might also produce syncope. Such people are at risk for postoperative recurrence of arrhythmias and should be considered for further electrophysiological testing and eventual implantation of a cardioverter defibrillator.[45]

Diagnosis

Physical examination

Aortic stenosis is usually detected initially by auscultation that indicates the typical crescendo-decrescendo systolic ejection murmur radiating to the neck. In mild disease, the murmur peaks early in systole, S2 is physiologically split, and carotid upstrokes are normal. This condition—in which a thickened valve causes no appreciable obstruction to outflow—is termed aortic sclerosis. Although by itself benign, presence of aortic sclerosis is associated with a substantial increase in risk for cardiac death.[11] Since aortic stenosis and coronary disease seem to arise from similar cellular pathophysiologies, aortic sclerosis is presumed to be a marker for co-presence of coronary disease, which in turn causes the rise in mortality.

As aortic stenosis progresses, the murmur becomes louder, peaks progressively later in systole, and is associated with a thrill. With further worsening of stenosis, the murmur intensity lessens because stroke volume becomes reduced.[46] Carotid upstrokes are diminished in volume and the rate of rise is delayed (*parvus et tardus* figure 3).[47] In contradistinction, the left-ventricular apical impulse is forceful and slightly enlarged. The discrepancy between a powerful apex beat and diminished carotid pulses is good evidence of an obstruction between the two anatomic structures. Moreover, S2 is generally single without the aortic component, since the stenotic valve neither opens nor closes well. S4 is usually heard in patients in sinus rhythm.

Diagnostic studies

The electrocardiogram in patients with aortic stenosis is non-diagnostic. It usually shows evidence of left-

ventricular hypertrophy, but not all people with severe aortic stenosis have this feature. Left-atrial abnormality is typical as are non-specific ST-wave and T-wave abnormalities.

The chest radiograph in aortic stenosis is non-specific. The heart generally assumes a boot shape typical of concentric left-ventricular hypertrophy. In rare cases, calcification of the aortic valve can be seen in the lateral view.

The echocardiogram with doppler interrogation of the aortic valve serves as the mainstay of diagnosis. This study assesses left-ventricular function, extent of hypertrophy, amount of valve calcification, transvalvular pressure gradient, and aortic valve area. A good study can provide all data necessary to assess stenosis severity and its effect on the left ventricle. An accurate gradient can be obtained with the modified Bernoulli equation, $G=4V^2$, where G is gradient and V is peak transvalvular flow velocity. Valve area calculation uses the continuity equation,[47] which assumes flow (F) on both sides of the valve is equal ($F_1=F_2$). Flow is defined as area (A) multiplied by velocity (V), so $F_1=V_1\times A_1=F_2=V_2\times A_2$. Here, flow is equal to stroke volume, because V is the velocity-time integral (instead of peak velocity), which gives a mean velocity over the time the flow is taking place (units of v/t are cm/sec/sec, ie, cm). Thus, A×v/t gives $cm^2\times cm=cm^3$. As flow reaches the narrowed aortic valve, velocity must increase for flow to stay constant (figure 4).[47] The area of the outflow tract, outflow velocity, and velocity of flow at the valve are measurable and can be used to calculate the valve area that is not easily seen because the orifice is small and irregular. Although successful planimetry of aortic valve area has been reported,[48] difficulties in accurate visualisation of the orifice keep this technique from becoming mainstream in measurement of orifice area. Although echocardiographic and invasive haemodynamic assessment of severity of aortic stenosis are usually in agreement, downstream pressure recovery can alter both methods of gradient measurement.

Because of the danger of exercise testing in patients with symptoms of aortic stenosis, this method was deemed ill-advised for this group of people. However, findings of several studies[49] have shown the benefits of exercise testing of asymptomatic individuals with severe aortic stenosis. Das and co-workers[49] noted that more than a third of such patients developed symptoms during exercise. Most probably, these individuals either were denying their symptoms or simply failed to recognise them, and they should be reclassified as symptomatic. Observation of exercise-induced hypotension or ventricular tachycardia is also ominous. Such patients are likely to exercise as part of their daily routine, and detection of abnormalities is beneficial before they lead to catastrophe, although proof of this idea is currently absent.

Biomarkers and symptomatic status

Because of the importance of symptomatic status in predicting outcome in patients with aortic stenosis, and owing to imprecision in establishing symptom status in some individuals, objective prognostic variables have been sought. Brain natriuretic peptide (BNP) is thought to be a marker of both hypertrophy and use of preload reserve to maintain compensation, thus it has been studied extensively in patients with aortic stenosis.[50–53] Findings of these studies are concordant in showing that symptomatic patients have higher amounts of BNP or pro-BNP than individuals without symptoms. Further, asymptomatic patients who develop symptoms shortly after BNP measurement have higher concentrations of this peptide than do those who remain asymptomatic. Thus, BNP could become a useful marker in predicting onset of symptoms, potentially indicating that surgery would be advisable in a particular asymptomatic patient. Unfortunately at present, a wide range of values of this peptide portend symptom onset in various studies, preventing any cutoff from being sufficiently able to aid clinical management. Furthermore, presence of renal disease,[54] pulmonary hypertension,[55] and obesity[56] all interfere with the predictive value of BNP measurement.

Cardiac catheterisation

Because most patients with aortic stenosis are of an age at which coronary artery disease is prevalent, coronary arteriography is undertaken before surgical intervention so that existing obstructive coronary artery disease can be revascularised during aortic-valve replacement surgery. A full haemodynamic study with retrograde catheterisation of the aortic valve is no longer recommended if non-invasive assessment of the valve is completely adequate to assess valve haemodynamics. However, when a patient's history, physical examination, and

Figure 3: **Normal carotid pulse contour (left) versus pulse contour of patient with aortic stenosis (right)**
Reprinted with permission from Carabello and colleagues.[47]

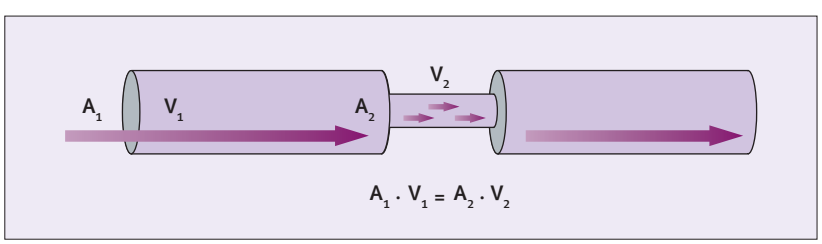

Figure 4: **Schematic of use of continuity equation**
Reprinted with permission from Carabello and colleagues.[47]

echocardiographic measurements are inconsistent and leave doubt about stenosis severity, a well-performed, invasive haemodynamic study remains the gold standard of diagnosis. To obtain an accurate diagnosis from data obtained invasively, a properly measured transvalvular gradient and correct cardiac-output assessment are essential, since this information will be applied to the Gorlin formula for calculating valve area.[57] The gradient should be measured with one catheter—transducer or lumen (depending on technique)—in the body of the left ventricle, with the second measuring device in the proximal aorta.[58,59] Although thermodilution cardiac output is acceptable in most cases, this method could provide inaccurate results in low-flow states, for which a properly undertaken Fick determination of cardiac output should be used.

Treatment

Medical treatment

Severe symptomatic aortic stenosis is a lethal obstruction to outflow that needs effective mechanical relief in the form of valve replacement for most patients. No medical treatment is effective for chronic disease. However, as noted above (see section on Causes), modern ideas about valve pathology (rather than the effects of stenosis on the heart and body) indicate that aortic stenosis is caused by an active inflammatory process akin to that of atherosclerosis.[60,61] Thus unsurprisingly, treatments for retarding progression of coronary disease have been investigated for similar effects in patients with aortic stenosis. Most prominent of these are 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors—statins.[6,7]

Findings of several retrospective studies and at least one prospective trial show that patients receiving statins have slower progression of stenosis severity than do individuals not receiving them.[6,7,9] However, in an important randomised trial of patients with moderately severe disease, Cowell and colleagues failed to record a benefit from statin use.[8] These researchers randomly allocated 165 people either placebo or atorvastatin (80 mg). The average concentration of LDL was 7·2 mmol/L and the average aortic valve area was 1·01 cm². After 25 months, no difference was seen in rate of progression in the two groups. Conversely, Moura and co-workers[9] administered 20 mg of rosuvastatin to patients with an average LDL amount of 8·8 mmol/L, while a second group with a lower LDL value (6·5 mmol/L) received no statin. Average valve area was 1·23 cm². For individuals receiving the statin, disease progression was slowed significantly. Therefore, for statins (and probably other drugs) to be effective, they must be given early for mild disease and perhaps are most effective in patients with high LDL concentrations.

If applied early, for how long will statins delay progression to severe surgical disease? In most patients likely to develop aortic stenosis, lipid abnormalities that by themselves mandate use of statins will usually be present. Thus, statin use will usually have the standard indications of coronary artery disease, which parenthetically will also help in retarding progression of aortic stenosis. An additional benefit of statins is that they might directly enhance diastolic left-ventricular function, an abnormality of which frequently triggers heart failure development in aortic stenosis.[62]

Standard teaching is that vasodilators in patients with aortic stenosis are dangerous because they can lead to hypotension and syncope; indeed, if these drugs are used in such individuals, great caution must be exercised. However, vasodilators have been used in two settings for people with aortic stenosis: concomitant hypertension and decompensated heart failure.

Because aortic stenosis typically arises in old patients, stiffening of the vasculature generally leads to systemic hypertension and, in the presence of obstruction, to outflow to a so-called double-loaded left ventricle.[63] Although no specific data are available, there is no reason to suppose that hypertension is any less a menace in patients with aortic stenosis than in the general population, and therefore hypertension must be treated. No clear recommendation for treatment in people with aortic stenosis is available, but in many instances, diuretics alone do not offer sufficient control and β blockers pose the danger of reduced inotropy in an already overloaded ventricle. Thus, vasodilators—typically angiotensin-converting-enzyme inhibitors—are usually administered. When used, these drugs must be initiated at a low dose then titrated upwards very cautiously. Similar to statins, angiotensin-converting-enzyme inhibitors have been suggested to slow progression of calcific valvular stenosis, but this idea has not been confirmed by findings of prospective studies.[64]

Sodium nitroprusside has been used successfully in patients with aortic stenosis and severely decompensated heart failure and pulmonary oedema.[65] Analysis of the mechanism of benefit indicated that peripheral resistance was not being reduced; rather, contractility was increased.[66] In severe decompensated aortic stenosis, amplified left-ventricular filling pressure probably compresses the endocardium and decreases coronary blood flow in the hypertrophied heart. As noted in the section on Pathophysiology, coronary flow reserve is already compromised in people with aortic stenosis. This fact, together with high diastolic filling pressure, presumably leads to subendocardial ischaemia and contractile impairment. Nitroprusside might reduce filling pressure and augment myocardial blood flow, in turn relieving ischaemia and enhancing contractility.

Experience with other vasodilators, such as calcium-channel blockers, is scarce in aortic stenosis. Accordingly, such drugs should be used with great caution.

Surgical treatment

One of the clearest decisions for a doctor is to recommend valve replacement for individuals with severe symptomatic aortic stenosis. As noted above, such patients have a dire outlook, with three-quarters dying within 3 years of symptom onset. As figure 5 shows, the mortality difference for people with symptoms of aortic stenosis treated with aortic valve replacement versus those not undergoing this procedure is one of the most striking in medicine.[67] Thus, aortic valve replacement can be withheld in such patients only when compelling contraindications exist. Further, there is some urgency about undertaking this procedure once symptoms ensue, since several reports have been published of sudden death within 3 months of onset of symptoms.[68,69] Indeed, the well-established 25% per year mortality rate in asymptomatic people who do not undergo valve replacement supports the inference that withholding surgery imposes a mortality risk of about 2% per month.

Because of the risk for an asymptomatic individual rapidly developing symptoms of aortic stenosis and dying suddenly, and owing to the possibility of people without symptoms dying unexpectedly (figure 6),[70] some researchers have advocated aortic valve replacement for severe asymptomatic disease. Indeed, the medical community is moving towards ever more liberal indications for this procedure in asymptomatic patients.[71] However, advocating valve replacement for all people with severe aortic stenosis but no symptoms is fraught with difficulty. First, the definition of what constitutes severe aortic stenosis is not agreed on universally. Generally, patients with an aortic valve area of less than 1·0 cm² who have a mean transvalvular gradient of more than 40 mm Hg are judged to have severe aortic stenosis.[71] However, as figure 7 shows, the valve area at which individuals become symptomatic is quite variable.[72] Indexing for body size is rational but there is less unanimity about what constitutes a severe aortic valve area index. However, a valve area index of 0·45 cm²/m² could be helpful in deciding severity in some cases. Further, undertaking aortic valve replacement in all asymptomatic patients would only benefit the fewer than 1% who would die suddenly before symptoms develop, while exposing almost 100% to risks of surgery and of complications from the substitute aortic valve. Therefore, the thrust should be to define a high-risk group of asymptomatic patients in whom risk of no intervention is higher than that of aortic valve replacement, thus making the procedure desirable. Once a high-risk group is identified, a randomised trial of no intervention versus aortic valve replacement could be done to establish evidence for superiority of one intervention over the other. Risk stratification might incorporate jet velocity, progression of valvular narrowing, response to exercise testing, comorbidity, abnormally raised biomarkers, and presence of ventricular dys-

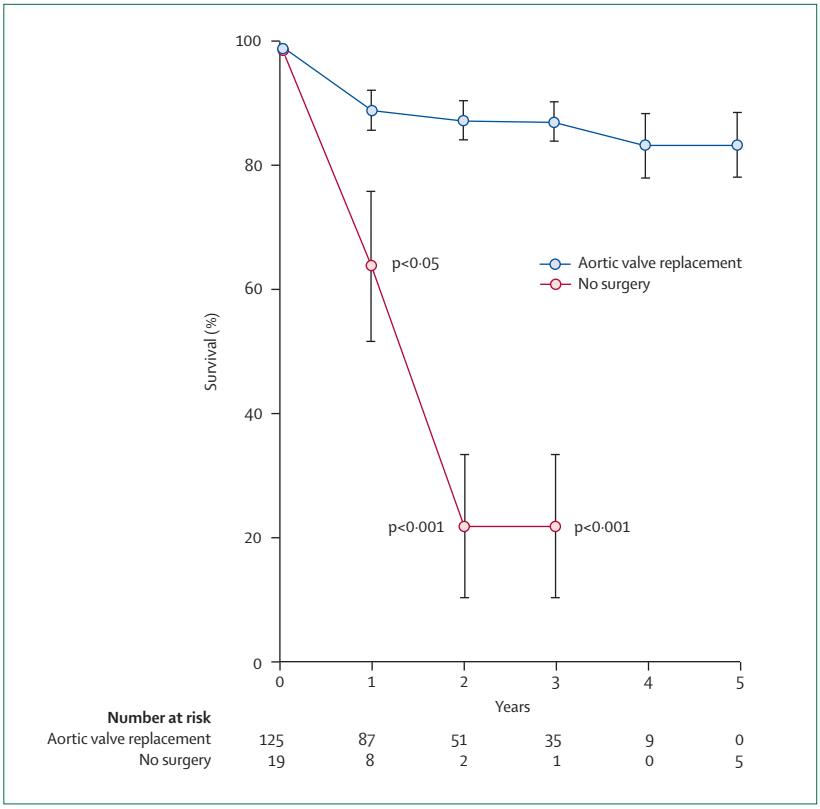

Figure 5: **Mean survival of patients with symptoms of aortic stenosis**
Adapted with permission from Schwartz and colleagues.[67]

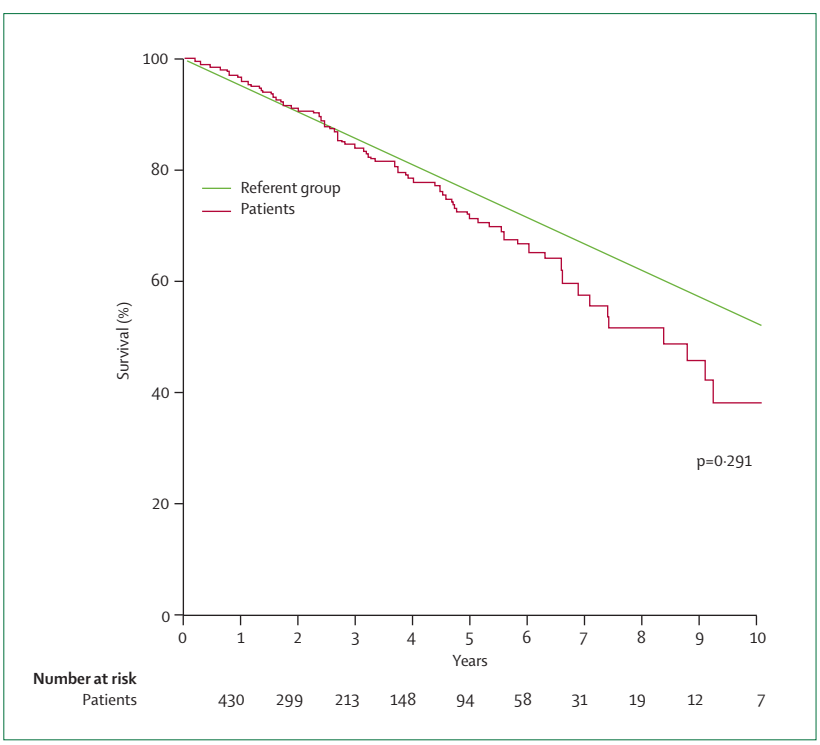

Figure 6: **Survival of asymptomatic patients with severe aortic stenosis versus age-matched US population**
Reprinted with permission from Pellikka and colleagues.[70]

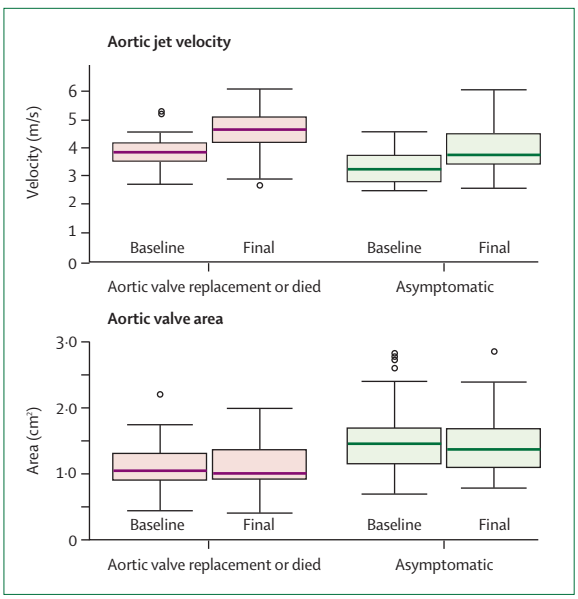

Figure 7: **Use of aortic jet velocity and aortic valve area to predict clinical outcome of asymptomatic patients with aortic stenosis**
Substantial overlap exists between patients who developed symptoms or died (left) and those who remained asymptomatic (right), so no specific jet velocity or valve area predicts outcome well. Adapted with permission from Otto and colleagues.[72]

function. Although progression is unpredictable and can be as rapid as a gradient increase of 20 mm Hg/year,[72] patients with an annual increase of aortic valve jet velocity in excess of 0·45 m/s had a significantly worse outcome in terms of survival and need for valve replacement.[73] Progression can be even more rapid in people with severe renal failure.[74] Whether or not individuals presenting with left-ventricular dysfunction are ever truly asymptomatic is a matter of considerable debate. Presence of certain comorbid disorders, such as metabolic syndrome, can also hasten symptom development in asymptomatic patients with aortic stenosis.[75]

Special considerations

Subnormal ejection fraction in aortic stenosis stems from afterload excess, contractile dysfunction, or both.[33] When afterload excess is the primary cause, prognosis after aortic valve replacement is usually good.[76] This procedure relieves the obstruction to outflow, afterload falls, and ejection fraction usually increases strikingly. However when muscle dysfunction prevents cardiac output from generating a mean gradient of more than 30 mm Hg, prognosis is greatly impaired (figure 8).[77] Although such patients have a poor outlook, some do get better after surgery, and the obvious challenge is to predict outcome preoperatively.[77,78]

The first issue is to decide either whether severe aortic stenosis has led to left-ventricular dysfunction, a low gradient, and a small calculated valve area or whether a ventricle weakened by an independent cardiomyopathy is unable to open an only mildly stenotic valve.[79] In the first situation, since severe aortic stenosis has caused the left-ventricular dysfunction, we can reasonably postulate that aortic valve replacement will be of benefit. In the second example, since the valve is not the primary cause of the contractile dysfunction, such patients are unlikely to benefit from aortic valve replacement, although data supporting this supposition are scarce.

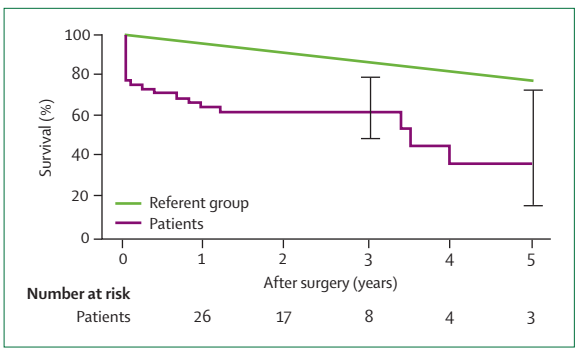

Figure 8: **Survival of patients with low gradient, low ejection fraction aortic stenosis versus a referent US population**
Reprinted with permission from Connolly and colleagues.[77]

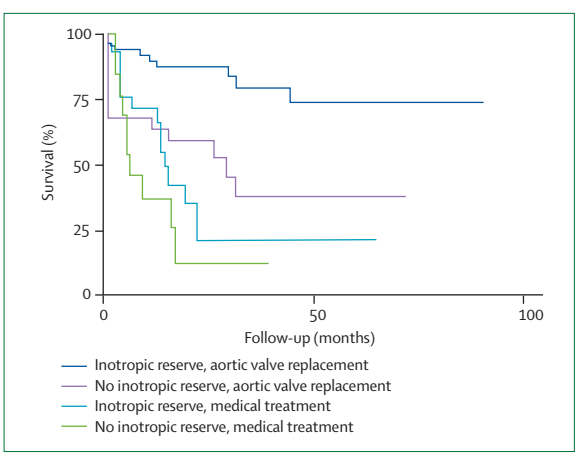

Figure 9: **Survival of patients with low gradient, low ejection fraction aortic stenosis with and without inotropic reserve treated medically or with surgery**
Reprinted with permission from Monin and colleagues.[80]

Currently, the best indicator of outcome in patients with aortic stenosis and a low gradient and low ejection fraction is presence or absence of inotropic reserve. As figure 9 shows, operative risk is reduced and long-term survival increased in people whose stroke volume rose by more than 20% during dobutamine infusion.[80] However, data suggest that the quality of life of individuals without inotropic reserve who survive surgery could still be enhanced after successful aortic valve replacement.[81] When this procedure is undertaken in patients with low ejection fraction and low gradient, a haemodynamically good prosthesis must be used, because any residual gradient has a negative effect on prognosis.[77]

As noted in the section on Causes, aortic stenosis and coronary artery disease have similar causes; thus, unsurprisingly, both disorders can coexist in the same

patient. A frequent challenge is how to manage people with mild-to-moderate aortic stenosis who need surgical coronary revascularisation. On one hand, the individual does not yet need aortic valve replacement; on the other, if aortic stenosis progresses rapidly and only bypass surgery is done, progression to severe aortic stenosis in as few as 3–4 years could expose the patient to risks of reoperation in that interval. Figure 10 shows that for people with an aortic valve area of more than 1·5 cm², whose corresponding mean gradient is usually less than 15 mm Hg,[82] concomitant aortic valve replacement at the time of bypass surgery provides no advantage. This fact is especially true for older patients whose lifespan is unlikely to encompass the years necessary to reach severe orifice narrowing.[83] Conversely, for individuals with an aortic valve area of 1·0–1·5 cm², aortic valve replacement at the time of coronary surgery probably confers a survival benefit. Awareness of an average aortic valve gradient progression of 6·5 mm Hg per year[84] can aid in clinical decision making, although variability in this rate is large.

As noted in the section on Epidemiology, aortic stenosis is a disease of ageing. Severe aortic stenosis can be present in patients older than 75 years. Even people age 90 years or older can have a good outcome after aortic valve replacement, and age by itself is not a contraindication for surgery.[85] However, old patients frequently have comorbid disorders that do affect prognosis. For example, cerebrovascular disease, coronary artery disease, and renal dysfunction lessen the chance for a good outcome while typically necessitating prolonged postoperative rehabilitation.[86–88]

Percutaneous approaches

Balloon aortic valvotomy was introduced more than 2 decades ago as a non-surgical alternative for treatment of aortic stenosis. After great initial enthusiasm, interest in the procedure waned once its high recurrence rate (50% within 6 months) and absence of any mortality benefit was recognised. Lack of benefit in adults with acquired disease probably stems from diffuse calcification of the valve, preventing balloon dilatation from substantially altering valve-leaflet morphology.

Stented valves placed either transapically or percutaneously are garnering much attention.[91–93] With these procedures, balloon aortic valvotomy is undertaken first, and a stented bioprothesis is then deployed over a balloon into the aortic annulus. Inflation of the balloon anchors the valve in place in the annulus, effectively achieving aortic valve replacement. By the transapical approach, a thoracotomy must still be done but the valve is deployed into the beating heart without extracorporeal circulation. By the percutaneous approach, the valve is deployed either antegradely, via the transseptal route, or retrogradely, across the native aortic valve. Early studies have been undertaken in patients deemed poor candidates for standard aortic valve replacement owing to the presence of severe comorbidity. This fact notwithstanding, results are encouraging and future technological refinements are likely to make the procedures more widely applicable.

Conclusions and future work

Symptomatic severe aortic stenosis is a fatal disease when treated medically, but after aortic valve replacement a patient's lifespan returns to near that of an unselected population.[94] Even individuals with advanced disease and left-ventricular dysfunction can have a good outcome, especially when the reason for the dysfunction is a large transvalvular gradient causing high afterload. In people with aortic stenosis and a low gradient and low ejection fraction, prognosis is worse but is still favourable in those manifesting inotropic reserve. Most difficulties arise in patients without inotropic reserve, in whom operative mortality is high,

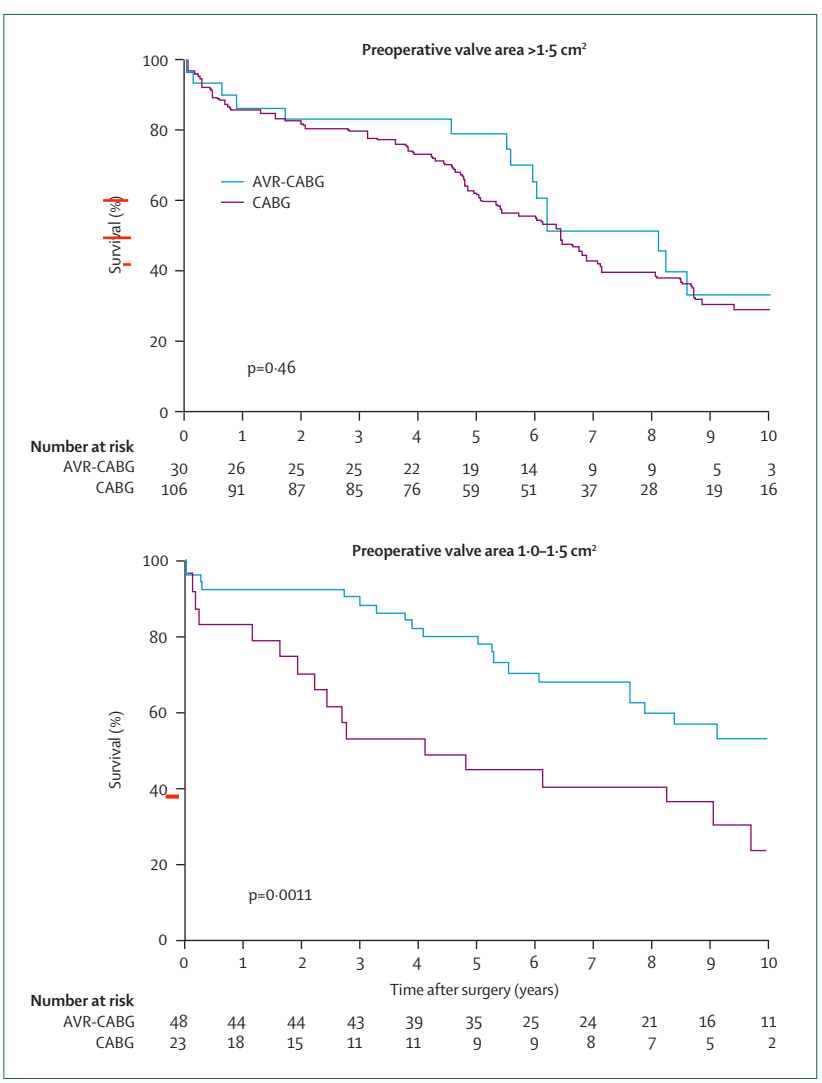

Figure 10: **Survival of patients with aortic stenosis undergoing coronary bypass surgery alone (CABG) and with aortic valve replacement (AVR-CABG)**
Reprinted with permission from Quéré and colleagues.[81]

but postoperative outcome can still be favourable in those surviving surgery.

The asymptomatic individual with severe aortic stenosis remains a management challenge. Most such patients have a good result with careful follow-up and urgent aortic valve replacement once symptoms develop. Some asymptomatic people probably should undergo aortic valve replacement, especially if exercise tolerance is reduced or exercise testing produces worrisome outcomes, such as hypotension or ventricular tachycardia. The role of biomarkers in helping to elucidate which asymptomatic patients will benefit from aortic valve replacement is not yet clear, but such factors are likely to play a part in future decision making.

Although, today, surgical aortic valve replacement is the only effective treatment for severe aortic stenosis, medical approaches for retarding progression of mild disease are likely to come to fruition. Percutaneously placed devices hold promise for future effective non-surgical treatment.

Conflict of interest statement

We declare that we have no conflict of interest.

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