View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Via Medica Journals

VIA MEDICA

HOW TO DO

Cardiology Journal
2007, Vol. 14, No. 5, pp. 510–517
Copyright © 2007 Via Medica
ISSN 1897–5593

How to manage patients with aortic stenosis?

Ewa Orłowska-Baranowska

Clinic of Valvular Heart Disease, Institute of Cardiology, Warsaw, Poland

Abstract

Aortic stenosis is a form of valvular heart disease that is bound to be seen more and more often by healthcare professionals in the coming years. This is due to the increasing life expectancy and the increasing rate of incidental echocardiographic diagnosis in asymptomatic patients. No effective drug treatment for AS is available. Symptomatic patients with significant AS should be referred for surgery. When deciding the method and timing of management, cardiologists and cardiac surgeons should take into consideration the symptoms present, the patient.'s age (life expectancy) and the echocardiographic evaluation of the severity of stenosis. The risk-to-benefit ratio of the various management options should be assessed individually. (Cardiol J 2007; 14: 510–517)

Key words: aortic stenosis, surgical management, echocardiography

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in adults. It is the third most common cause of cardiovascular disease after hypertension and coronary artery disease (CAD) [1–5].

Over the past few years the prevalence of rheumatic fever, and therefore that of rheumatic AS, has decreased. This has been paralleled by an increasing contribution of degenerative, atherosclerotic and calcific processes to the etiology of AS. Due to the increasing life expectancy in the general population, this form of valvular heart disease is now regarded as the coming plague of the 21st century. According to the most recent studies conducted in the United States, the prevalence of AS is 2.5% and it is estimated to affect about 5 million patients. The prevalence of the disease increases with age, ranging from 0.7% in the population of patients up to 45 years of age to over 13% among patients aged 75 years or more. In the elderly population, AS is more prevalent among men [6].

Aortic stenosis causes left ventricular outflow obstruction, increases left ventricular pressures and leads to compensatory left ventricular hypertrophy. Stroke volume is maintained within normal limits thanks to the increased left ventricular pressures, compensatory hypertrophy of the left ventricle and increased ejection time. Another mechanism that prevents the reduction of stroke volume and cardiac output involves peripheral vasoconstriction in less important tissues and organs, which enables larger amounts of blood to be directed to the cerebral, coronary and renal arteries. As the stenosis progresses, the left ventricle becomes increasingly dilated and insufficient, and a secondary transaortic pressure gradient reduction ensues [4].

The management of patients with AS in everyday practice is based on the guidelines developed by ACA/AHA in 2006 and ESC in January 2007 [1–3].

How to diagnose aortic stenosis?

Aortic stenosis is a valvular heart disease, which has highly characteristic signs and symptoms. Imaging studies, such as chest X-ray, ECG and echocardiography are useful in staging the disease. Sometimes transesophageal echocardiography is

Address for correspondence:
Ewa Orłowska-Baranowska, MD, PhD
Clinic of Valvular Heart Disease, Institute of Cardiology
Alpejska 42, 04–628 Warszawa, Poland
Tel: +48 22 343 44 47, fax: +48 22 343 4509
e-mail: eorlowska@ikard.pl

necessary. Cardiac catheterisation is important in doubtful cases. There is no consensus as to the role of computed tomography and magnetic resonance imaging in the standards of AS diagnosis. These studies are performed where the valve cannot be properly visualised and in order to assess the width of the ascending aorta [3, 4].

Symptoms

Aortic stenosis remains oligosymptomatic for many years, but once the typical manifestations develop (angina, syncope or heart failure) the clinical course becomes very dramatic. The symptoms reported by patients are highly characteristic and result from the body's inability to adjust the stroke volume and cardiac output as needed due to left ventricular outflow obstruction [4]. In 1968, Ross and Braunwald [7] analysed retrospective studies of the natural history of AS and evaluated the mean survival of patients following the onset of symptoms. The mean survival did not exceed 5 years in patients developing symptoms of coronary insufficiency, 3 years in patients developing syncope and 2 years in patients developing heart failure. These symptoms were therefore a signal pointing to the necessity of surgery (AVR, aortic valve replacement).

The typical symptoms of AS-vertigo (vision abnormalities, fainting and even syncope) initially develop only during exercise or with changes in body position, but later in the course of the disease, they also develop at rest. While they are principally caused by poor cerebral blood flow, they may also result from arrhythmias (significant left ventricular hypertrophy or reduced left ventricular ejection fraction) or conduction disturbances (calcifications extending onto elements of the conduction system).

Angina is present in over 50% of patients with AS. They are a manifestation of myocardial ischemia resulting from impaired coronary blood flow due to insufficient generation of coronary blood vessels relative to the degree of left ventricular hypertrophy or the associated atherosclerotic changes in the arteries.

Exertional dyspnoea, dyspnoea at rest and episodes of pulmonary oedema (manifestations of systolic and diastolic heart failure) develop relatively late in the course of aortic stenosis.

Signs

The auscultatory phenomena in aortic stenosis are highly characteristic. It should be emphasised that cardiac auscultation is the most accessible and the cheapest diagnostic method, yet, unfortunately, it is very often neglected in favour of state-of-the-art techniques. The heart murmur of AS is a typical crescendo-decrescendo (diamond-shaped) ejection murmur. The murmur is sometimes accompanied by a systolic thrill. The murmur is usually harsh, often even musical, and is most audible over the aortic area. The radiation of the murmur is quite extensive over both carotid arteries, left supra- and infraclavicular fosse and jugular fossa. It may also be heard over the back. Sometimes the murmur becomes quiet over the middle portion of the sternum and reappears at the apex. In the elderly, this may be the only area where it is heard [4].

Echocardiography

Echocardiography confirms the diagnosis and enables the severity of aortic stenosis and its consequences to be assessed. The examination should include: the measurement of blood flow velocity through the valve (V_{max}), definition of the pressure gradients through the valve (peak pressure gradient and mean pressure gradient), calculation of the aortic valve area (AVA), AVA indexed in relation to the body surface area (AVA//BSA) and the parameters describing the degree of left ventricular hypertrophy and left ventricular function (Table 1). Morphology of the valve is also important (presence of significant calcifications). The very value of transvalvular gradient may be misleading as it does not take into consideration the effect of cardiac output variability. Hemodynamically significant aortic stenosis is characterised by: AVA under 1 cm^2, AVA//BSA under 0/6 cm^2/m^2, V_{max} above 4 m/s and mean pressure gradient above 40 mm Hg [2, 3].

Table 1. Severity scale of aortic stenosis (ACC/AHA Practice Guidelines. J Am Coll Cardiol, 2006; 48: 3).

Aortic stenosis	V_{max} [m/s]	Mean gradient [mm Hg]	Aortic valve area [cm^2]
Mild	< 3.0	< 25	> 1.5
Moderate	3.0–4.0	20–40	1.0–1.5
Severe	> 4.0	> 40	< 1.0

Aortic valve area index < 0.6 cm^2/m^2

Table 2. Indications for aortic valve replacement in aortic stenosis according to ESC standards 2007.

Class I
1. Patients with significant aortic stenosis:
— and symptoms (B)
— qualified for coronary artery bypass grafting, surgery of the aorta or of other valves (C)
— without symptoms and with left ventricular dysfunction (ejection fraction < 50%) not due to other causes (C)
— without symptoms in whom the stress test caused symptoms (C)
Class IIa (C)
1. Asymptomatic patients with significant aortic stenosis in whom the stress test caused a fall in blood pressure
2. Asymptomatic patients with significant aortic stenosis, severe calcification of the valve and rapid progression V_{max} (> 0.3 m/s/year)
3. Patients with moderate aortic stenosis referred for coronary artery bypass grafting, surgery of the ascending aorta or of other valves
4. Patients with low transvalvular gradient (< 40 mm Hg), left ventricular dysfunction and preserved contractile reserve
Class IIb (C)
1. Patients with low transvalvular gradient (< 40 mm Hg), left ventricular dysfunction and no contractile reserve
2. Asymptomatic patients with significant aortic stenosis:
— with an abnormal stress test due to complex ventricular arrhythmias
— with significant left ventricular hypertrophy (>/15 mm) after exclusion of hypertension

Table 3. Indications for surgery in patients with aortic stenosis according to the ACC/AHA standards 2006.

Class I
1. AVR is indicated for symptomatic patients with severe AS (B)
2. AVR is indicated for patients with severe AS undergoing coronary artery bypass grafting (C)
3. AVR is indicated for patients with severe AS undergoing surgery on the aorta or other heart valves (C)
4. AVR is indicated for patients with severe AS and left ventricular systolic dysfunction (ejection fraction < 50%) (C)
Class IIa
1. AVR is justified in patients with moderate AS undergoing coronary artery bypass grafting or surgery on the aorta or other heart valves (B)
Class IIb
1. AVR may be considered for asymptomatic patients with severe AS and abnormal response to exercise (symptoms, hypotension) (C)
2. AVR may be considered for asymptomatic adults with severe AS if there is a high likelihood of rapid progression (age, calcification and coronary artery disease) or if surgery might be delayed at the time of symptom onset (C)
3. AVR may be considered in patients with mild AS undergoing coronary artery bypass grafting or surgery on other valves if there is high likelihood of rapid progression (moderate to severe valve calcification) (C)
4. AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area < 0.6 cm^2, mean gradient > 60 mm Hg and V_{max} > 5.0 m/s) if the risk of perioperative mortality is under 1.0% (C)
Class III
AVR does not prevent sudden cardiac death in patients with AS in whom none of the findings listed under Class IIa or Class IIb are seen

AS — aortic stenosis, AVR — aortic valve replacement

When should patients with aortic stenosis undergo surgery?

Development of symptoms (angina, syncope or heart failure) in patients with hemodynamically significant aortic stenosis is an indication for valve replacement (Tables 2 and 3). Treatment decisions should be based on the presence or absence of clinical manifestations rather than on the transvalvular gradient or the aortic valve area.

If the patient is being scheduled for coronary artery bypass grafting (CABG), surgery of the aorta or of other cardiac valves, the significantly/moderately stenosed aortic valve should also be replaced, even if the AS remains asymptomatic.

If the patient reports typical symptoms and the stenosis is significant, then the indications for surgery are justified beyond any doubt. However, in certain situations, decisions to implant an artificial valve or decisions regarding the timing of the

procedure are difficult to make and require more advanced investigations. This applies to patients with asymptomatic AS, low-gradient AS in patients with reduced left ventricular ejection fraction, coexistent CAD and elderly patients.

Should patients with asymptomatic aortic stenosis undergo surgery?

Despite the availability of numerous diagnostic tests, establishing the timing of surgery in asymptomatic or oligosymptomatic patients is still a difficult clinical decision to make. On the one hand, such patients have good compensatory mechanisms and live dozens of years symptom free, without having to undergo valve replacement. On the other hand, they are at risk of sudden cardiac death, development of irreversible changes and the absence of return of normal left ventricular function following surgical correction [5, 8, 9].

It is often difficult to establish if patients are experiencing cardiovascular symptoms or not. The gradual reduction of physical activity or sedentary lifestyle are considered to be typical of old age, which is when this type of valvular heart disease is most commonly diagnosed. There are patients who deny any symptoms, especially when vertigo or scotomata are rarely experienced.

It is still commonly held that patients should be referred for surgery sufficiently late to take the risk of operation and early enough to avoid irreversible damage to the left ventricular myocardium. In asymptomatic patients with AS, the combined risk of perioperative mortality, early complications and late complications following valve replacement does not justify valve implantation as a measure preventing sudden death, the prevalence of which does not exceed 1% a year. Asymptomatic patients have a similar prognosis to that in healthy adults matched for age. Patients with reduced left ventricular ejection fraction are an exception, and the group of patients with significant aortic stenosis should be referred for surgery despite the absence of symptoms.

One should also bear it mind that the progression of AS is unpredictable and varies considerably from patient to patient. The mean pressure gradient increases by an average of 7 mm Hg per year and the aortic valve area is reduced by 0.02–0.03 cm^2. Degenerative aortic stenosis usually progresses faster than bicuspid aortic valve disease or rheumatic aortic stenosis [2, 3, 10, 11].

The American standards concerning indications for AVR also include asymptomatic patients in whom the risk of rapid progression is high (age, CAD) and surgery after the onset of symptoms would be delayed as well as patients with critical AS (AVA $<$ $<$ 0.6 cm^2, mean pressure gradient $>$ 60 mm Hg and $V_{max} > 5$ m/s) and very low risk of AVR ($<$ 1%) (but Class IIB).

Can stress testing be helpful in qualification for surgical treatment?

Stress testing in symptomatic patients with significant aortic stenosis is contraindicated and in fact pointless, as it poses the risk of sudden death.

In asymptomatic patients, stress electrocardiography evaluates the risk of progression of AS within 12 months better than echocardiography [10]. The stress test is considered abnormal when dyspnoea, angina, syncope or presyncope develop, when the pressure during exercise increases by less than 20 mm Hg or decreases, when the patient is unable to attain 80% of the exercise limit appropriate for age and sex or when characteristic ST depression or complex ventricular arrhythmias develop [12].

However, it is the exercise-induced symptoms, blood pressure drop and complex forms of ventricular arrhythmias that are important when qualifying the patient for surgery.

The European recommendations point to the existence of certain clinical situations in which evaluation of a patient during exercise (which is inherent to everyday life) provides very important information and is logically justified. The availability of echo studies increases the number of cases of accidentally diagnosed valvular heart disease in otherwise healthy, professionally active individuals who do sports. These individuals expect to know if it is safe for them to carry on with their healthy lifestyle. Besides, patients with AS perform various forms of physical exercise during their everyday activities, and it is safer to evaluate their response to this exercise in the presence of a medical professional (at a specialist centre) in standard conditions. In these selected patients, the results of stress testing may help to formulate recommendations on further physical or professional activity. On the other hand, in patients with untypical symptoms and valvular heart disease of moderate severity, exercise stress testing enables one to verify these symptoms. In the American standards, stress ECG plays a smaller role — the indications and abnormal results consist of Class IIB [2, 13].

How often should a patient with asymptomatic aortic stenosis undergo follow-up examinations?

Each patient with asymptomatic AS should be followed up periodically by a cardiologist. The follow-up visits should be scheduled every 6–12 months and should include echocardiographic evaluation and stress ECG at least once a year, provided that the course of the disease is stable, of course. If even the slightest symptoms develop, the follow-up examinations should be performed more frequently.

Special attention should be paid to the education of patients and their families, giving due consideration to the significance of symptoms in the qualification for surgery and the need of contact with the doctor when such symptoms do develop. Risk factors which may accelerate the progression of AS require monitoring (such as the risk factors for atherosclerosis).

How should low-gradient aortic stenosis with reduced left ventricular ejection fraction be managed?

First of all, we must establish if the stenosis is significant despite the recorded low transvalvular gradients. This is very simple if a high transvalvular gradient was previously recorded (in this case the gradient reduction does not mean that the patient has improved).

In patients with normal left ventricular function, the transvalvular pressure gradient describes the severity of AS. In patients with reduced ejection fraction, evaluation of the severity of AS based on transvalvular gradients may be misleading. The degree of the aortic valve opening depends on transvalvular flow and left ventricular systolic pressures. In patients with left ventricular damage, the reduced force that opens the valve (as a result of the reduced cardiac output) may falsely suggest a stenosis. What is more, the low flow and the low pressure gradient affect the calculation of effective AVA, and such AS may falsely be regarded as hemodynamically significant (especially if there are organic changes within the valve). The test which (usually) enables differentiation between significant AS and a pseudostenosis susceptible to flow (a mild to moderate aortic stenosis) is dobutamine stress echocardiography. Improvement of left ventricular contractility and cardiac output in patients with anatomically significant AS results in only slight (or non-existent) increase in the valve area, and the mean pressure gradient increases to values exceeding 50 mm Hg. Such patients, despite the increased risk of AVR, benefit from surgery. In patients without considerable AS (pseudostenosis) undergoing dobutamine stress echocardiography, the improvement of cardiac output leads to a wider opening of the valve (AVA increases > 0.2 cm^2), while the gradients increase only slightly or not at all. Such patients should be managed conservatively.

The evaluation of whether cardiac output has improved enables one to evaluate left ventricular contractile reserve and provides information regarding prognosis following surgical management. In patients with preserved left ventricular contractile reserve, dobutamine leads to an improvement of contractility of over 20% from baseline.

In patients in whom contractility has not improved and the left ventricular ejection fraction has not increased (no contractile reserve), and the change in AVA and the mean pressure gradient is insignificant, prognosis is poor both during the qualification for surgery and for conservative management. In this group, treatment decisions should take into consideration the degree of valvular calcification (considerable calcification points in favour of surgery), the perioperative risk and co-morbidities.

Patients with narrow AS with heart failure consist of a group with poor prognosis. AVR is associated with high early and late mortality (8–21% and 21–35%, respectively) [14]. The European Society of Cardiology recommends valve replacement in patients with low-gradient AS (mean pressure gradient < 40 mm Hg), left ventricular dysfunction and confirmed left ventricular contractile reserve. Such patients, despite the elevated perioperative risk, should be referred for surgery. Surgical management in the case of impaired systolic function with no contractile reserve is arguable due to the high mortality rates. On the other hand, if the patient survives the operation, his/her prognosis improves. In these patients the decision regarding AVR should take into consideration co-morbidities, the degree of valve calcification, atherosclerotic changes in the coronary arteries and the possibility of performing revascularisation (Class IIB).

How to manage patients with aortic stenosis and co-existent coronary artery disease?

The diagnosis of co-existent CAD in patients with AS is difficult. On the one hand, angina is a typical symptom of AS and is not always associated with the presence of changes in the coronary arteries. Significant ST depression (caused by

Table 4. Indications for coronary angiography in patients with aortic stenosis.

Class 1
1. Before valve replacement in patients with chest pain, signs of ischemia, left ventricular systolic dysfunction, a history of coronary artery disease, risk factors for coronary artery disease (including the age: men > 35 years old, postmenopausal women)
2. Crescendo angina (> CCS class II), signs of ischemia, left ventricular systolic dysfunction, overt congestive heart failure in patients with mild to moderate aortic stenosis

subendocardial ischemia) is present in the resting ECG in 50–80% of the patients and does not correlate with coronary artery changes. Following surgical correction, the ST changes resolve in 80% of the patients. The value of stress ECG in the diagnosis of CAD in patients with AS is also limited (in symptomatic patients with significant AS, stress ECG is contraindicated). The pitfalls in the interpretation of stress ECG in patients with less severe AS result from the potential for false positive results caused by left ventricular hypertrophy and the potential for false negative results or the non-diagnostic test caused by insufficient degree of stress.

Despite reports of various diagnostic tests which facilitate the diagnosis of co-existent CAD (scintigraphy, CT), coronary arteriography remains the final examination confirming the diagnosis and extent of CAD. Coronary arteriography should be performed in all patients with suspected CAD referred for surgery (Table 4).

The selection of the management option in patients with AS and CAD depends on the severity of AS and on the morphology of changes in the coronary arteries.

If both the aortic and coronary artery stenoses are significant, it is recommended to combine AVR with CABG. Complete revascularisation should always be aimed for. If CABG cannot be performed for technical reasons, the patient should nevertheless undergo AVR.

In mild to moderate AS, the management decision is based on the morphology of the coronary arteries.

In patients referred for CABG due to coronary atherosclerosis, the significantly stenosed aortic valve should be replaced during the revascularisation procedure.

In patients with mild to moderate AS, the decision is more difficult: the performance of preventive prosthetic valve implantation during revascularisation is controversial. Valve replacement in patients with moderate AS is accepted, while more considerable controversy surrounds the indications for AVR during CABG in patients with milder forms of AS. Although it is difficult to predict the course of AS and the moment when it progresses, in most patients the progression is small or non-existent.

In patients with mild to moderate AS and changes in the coronary arteries whose morphology enables percutaneous transluminal coronary angioplasty (PTCA), the procedure should be performed and the AS should be followed up in accordance with the diagrams presented.

Despite the reports of good surgery outcomes where AVR was preceded by PTCA of significantly stenosed coronary arteries, this procedure is currently limited to selected patients with an acute coronary syndrome or insignificant AS.

How to manage aortic stenosis in the elderly?

The progress in the diagnosis and therapy of heart disease and the development of cardiac surgery have made heart operations feasible in patients in their 70s and 80s or even older. This group of patients is dominated by patients with aortic stenosis [5]. Old age is not a contraindication to the operation. AVR is technically possible irrespective of the patient's age, but the decision to operate should be made after an analysis of all the factors, including the patient's level of physical activity and expectations. It should be borne in mind that the risk of operation in the elderly is higher due to the higher rate of co-morbidity (diabetes, hypertension, renal failure, atherosclerosis of the cerebral arteries) and the higher risk of perioperative complications, especially in the central nervous system and the kidneys. Sometimes problems are posed by the necessity to dilate the aortic valve ring (narrow left ventricular outflow tract and narrow ring, especially in women) or the operation of the valve and the ascending aorta is hindered due to the massive calcifications of the aorta, which are common in the elderly.

In symptomatic patients with significant AS, implantation of the valve should be considered irrespective of age. Both the patient and his/her family should be informed of the perioperative risk. Before qualification for surgery, one should also take into consideration the risk of sudden cardiac death and heart failure and evaluate the perioperative risk and benefit gained by the patient (physical activity).

How should aortic stenosis be managed pharmacologically?

Asymptomatic patients with aortic stenosis of any severity do not require drug therapy.

The only effective treatment for symptomatic AS is surgery.

If surgery is contraindicated (or the consent to undergo surgery is refused), conservative treatment is very difficult. It should be remembered that aortic stenosis is in fact an obstruction in the left ventricular outflow tract. Drug therapy which affects the blood volume, peripheral resistance, heart rate and myocardial contractility may be harmful. Management must be very cautious. Drug treatment is usually effective only short-term.

Diuretics should only be used in the case of hypervolemia (as they may reduce left ventricular filling, cardiac output and blood pressure). The effectiveness of cardiac glycosides is poor in cases of left ventricular outflow obstruction and this drug class is often dangerous (especially in patients with considerable left ventricular hypertrophy). The use of cardiac glycosides is limited to patients with systolic dysfunction, reduced ejection fraction and atrial fibrillation.

Angiotensin-converting enzyme inhibitors (ACEIs) and other vasodilators that affect the total peripheral resistance and increase cardiac output in other heart diseases may exacerbate AS. Cardiac output in severe AS may not increase due to the obstruction caused by the stenosed valve, and the reduction in peripheral resistance leads to blood pressure drop, which may be fatal. If AS is accompanied by symptoms of heart failure, hypertension or diabetic nephropathy and ACEIs are well tolerated, they should not be discontinued.

If angina dominates the clinical picture of AS, careful use of nitrates and beta-blockers is acceptable and may lead to improvement.

For many years it was widely held that degenerative AS is a process which damages the valve due to cardiac tissue "wear and tear". However, recent studies have demonstrated that AS is caused by an active inflammation similar to atherosclerosis and the deposition of lipoproteins in the aortic valve, which lead to calcification of the valvular cusps and of the valve ring. Although it seemed that statins, which are well established in the treatment of atherosclerosis, would also prove effective in patients with AS, the preliminary reports of suppressed progression of AS by statins have not been confirmed in the recent randomised prospective studies.

Summary

Aortic stenosis is a form of valvular heart disease that is bound to be seen more and more often by healthcare professionals in the coming years. This is due to the increasing life expectancy and the increasing rate of incidental echocardiographic diagnosis in asymptomatic patients. No effective drug treatment for AS is available. Symptomatic patients with significant AS should be referred for surgery. When deciding the method and timing of management, cardiologists and cardiac surgeons should take into consideration the symptoms present, the patient's age (life expectancy) and the echocardiographic evaluation of the severity of stenosis. The risk-to-benefit ratio of the various management options should be assessed individually.

References

1. Bonow RO, Carabello B, deLeon AC et al. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on management of patients with valvular heart disease). J Am Coll Cardiol, 1998; 32: 1486–1588.
2. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. J Am Coll Cardiol, 2006; 48: 1–1472.
3. Guidelines on the management of valvular heart disease. The task force of the management of valvular heart disease of the European Society of Cardiology. Eur Heart J, 2007; 28: 230–268.
4. Braunwald E. Heart disease. Braunwald E, Zipes D (eds.) A textbook of cardiovascular medicine. 7th ed. Elsevier Sanders, Philadelphia 2005.
5. Iung B, Baron G, Butchart EG et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J, 2003; 24: 1231–1243.
6. Nkomo V, Skelton T, Gottdiener J et al. Burden of valvular heart disease: a population-based study. Lancet, 2006; 368: 1005–1011.

7. Ross J, Braunwald E. Aortic stenosis. Circulation, 1968; 38: 61–67.
8. Iung B, Gohlke-Barwolf C, Tornos P, Tribouilloy C, Hall R, Butchart H, Vahanian A. Recommendations on the management of the asymptomatic patient with valvular heart disease. Eur Heart J, 2002; 23: 1253–1266.
9. Otto CM. Timing of aortic valve surgery. Heart, 2000; 84: 211–218.
10. Rosenhek R, Klaar U, Schemper M et al. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. Eur Heart J, 2004; 25: 199–205.
11. Otto CM. Aortic stenosis. Clinical evaluation and optimal timing for surgery. Cardiol Clin, 1998; 16: 353–373.
12. Das P, Rimington H, Smeeton N et al. Determinants of symptoms and exercise capacity in aortic stenosis: a comparison of resting hemodynamics and valve compliance during dobutamine stress. Eur Heart J, 2003; 24: 1254–1263.
13. Gibbons RJ. ACC/AHA 2002 Guideline update for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Exercise Testing). Circulation, 2002; 106: 1883––1892.
14. Carabello BA. Evaluation and management of patients with aortic stenosis. Circulation, 2002; 105: 1746–1750.