

Clinical Practice

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

AORTIC STENOSIS

BLASE A. CARABELLO, M.D.

A 60-year-old man is evaluated for a heart murmur. He jogs 3 mi (5 km) per day and is asymptomatic. Physical examination reveals a delayed carotid upstroke, a 3/6 late-peaking systolic ejection murmur that radiates to the neck, and a single S₂. An echocardiogram shows normal systolic function and a heavily calcified aortic valve. The patient's peak Doppler transvalvular gradient is 64 mm Hg, with a mean gradient of 50 mm Hg. His calculated valve area is 0.7 cm². How should this patient be treated?

THE CLINICAL PROBLEM

Aortic stenosis is the most common cardiac-valve lesion in the United States. Two factors account for its common occurrence: approximately 1 to 2 percent of the population is born with a bicuspid aortic valve, which is prone to stenosis; and aortic stenosis develops with age, and the population is aging.

The clinician is usually first alerted to the presence of aortic stenosis by the finding of a systolic ejection murmur at the right upper sternal border that radiates to the neck. Clues that the disease is at least moderate in severity are peaking of the murmur late in systole, palpable delay of the carotid upstroke, and a soft single second heart sound, because the aortic component of S₂ disappears when the valve no longer opens or closes well.

Although once thought of as a degenerative lesion, calcific aortic stenosis has many features in common with coronary disease.¹ Both conditions are more common in men, older persons, and patients with hyper-

cholesterolemia, and both derive in part from an active inflammatory process.²

Aortic stenosis is distinguished from aortic sclerosis by the degree of valve impairment. In aortic sclerosis, the valve leaflets are abnormally thickened, but obstruction to outflow is minimal, whereas in aortic stenosis, the functional area of the valve has decreased enough to cause measurable obstruction of outflow. Little hemodynamic disturbance occurs as the valve area is reduced from the normal 3 to 4 cm² to 1.5 to 2 cm². However, as shown in Table 1, an additional reduction in the valve area from half its normal size to one quarter of its normal size produces severe obstruction to flow and a progressive pressure overload on the left ventricle. The concentric hypertrophy that develops in response to this overload is both adaptive and maladaptive. Whereas the increased muscle mass allows the ventricle to generate the increased force necessary to propel blood past the obstruction, the hypertrophied myocardium has decreased coronary blood flow reserve³ (even in the presence of normal epicardial coronary arteries) and can also cause both diastolic and systolic left ventricular dysfunction, producing the symptoms of congestive heart failure.^{4,5} The obvious question for the physician is when is the optimal time for clinical intervention? Although aor-

TABLE 1. RELATION OF THE AORTIC-VALVE AREA TO THE MEAN GRADIENT.*

AORTIC-VALVE AREA	MEAN GRADIENT
cm ²	mm Hg
4	1.7
3	2.9
2	6.6
1	26
0.9	32
0.8	41
0.7	53
0.6	73
0.5	105

*Data were derived with the Gorlin formula: aortic-valve area =

$$\frac{\text{cardiac output} \div (\text{systolic ejection period} \times \text{heart rate})}{44.3 \sqrt{\text{mean gradient}}}$$

where the cardiac output was assumed to be 6 liters per minute, the systolic ejection period was assumed to be 0.33 second, and the heart rate was assumed to be 80 beats per minute.

From the Department of Medicine, Baylor College of Medicine, and the Veterans Affairs Medical Center, Houston. Address reprint requests to Dr. Carabello at the Veterans Affairs Medical Center Medical Service (111), 2002 Holcombe Blvd., Houston, TX 77030, or at blaseanthony.carabello@med.va.gov.

tic stenosis often coexists with other valvular diseases, this review focuses on isolated aortic stenosis.

STRATEGIES AND EVIDENCE

There is no effective medical therapy for severe aortic stenosis; aortic stenosis is a mechanical obstruction to blood flow that requires mechanical correction. In children with congenital aortic stenosis, the valve leaflets are merely fused, and balloon valvotomy may offer substantial benefit.⁶ In adults with calcified valves, however, balloon valvotomy only temporarily relieves symptoms and does not prolong survival.⁷ Thus, the intervention required in adults, other than standard prophylactic antibiotics against infective endocarditis,⁸ is the replacement of the valve. The risks of replacing that valve must be weighed against the risks of delaying the procedure. The procedure can usually be delayed until symptoms develop.^{9,10} Studies of aortic stenosis uniformly demonstrate that once angina, syncope, dyspnea, or other symptoms of heart failure develop and are found to be due to aortic stenosis, the patient's life span is drastically shortened unless the valve is replaced (Fig. 1). Of the 35 percent of patients with aortic stenosis who present with angina, half will die within five years in the absence of aortic-valve replacement. Of the 15 percent of patients who present with syncope, half will die within three years, and of the 50 percent of patients who present with dyspnea, half will die within two years, unless the aortic valve is replaced. In contrast, 10-year age-corrected rates of survival among patients who have undergone aortic-valve replacement approach the rate in the normal population.^{11,12}

The striking contrast between the excellent prognosis after aortic-valve replacement and the dismal prognosis in the absence of replacement in symptomatic patients makes the presence or absence of symptoms the crucial factor with respect to management. In general, the clinician can be confident that, in a given patient, the symptoms are due to aortic stenosis if the mean aortic-valve gradient exceeds 50 mm Hg or if the aortic-valve area is no larger than 1 cm². I will use these as criteria for severe disease, although there is no universally accepted definition that relies on valve area or gradient.

AREAS OF UNCERTAINTY

Management of Severe Asymptomatic Aortic Stenosis

There is overwhelming evidence that patients with severe aortic stenosis who become symptomatic require prompt aortic-valve replacement. Conversely, asymptomatic patients, even those with severe disease, generally have an excellent prognosis without aortic-valve replacement. Unfortunately, approximately 1 to 2 percent of asymptomatic patients die suddenly or have a very rapid rate of progression to the sympto-

matic state and then to sudden death.^{9,10,13,14} Thus, the question arises whether patients with severe asymptomatic aortic stenosis should undergo aortic-valve replacement to protect them from sudden death. Although some experts advocate this approach, this strategy exposes the entire group of asymptomatic patients with severe aortic stenosis to the risk of perioperative and valve-related complications and death. Even in the best of circumstances, the surgical mortality rate is approximately 1 percent and the risk of a valve-related complication (including thromboembolism; bleeding during therapy with anticoagulants; deterioration of the prosthetic valve, requiring reoperation; and infective endocarditis) is 1 percent per year.¹⁵

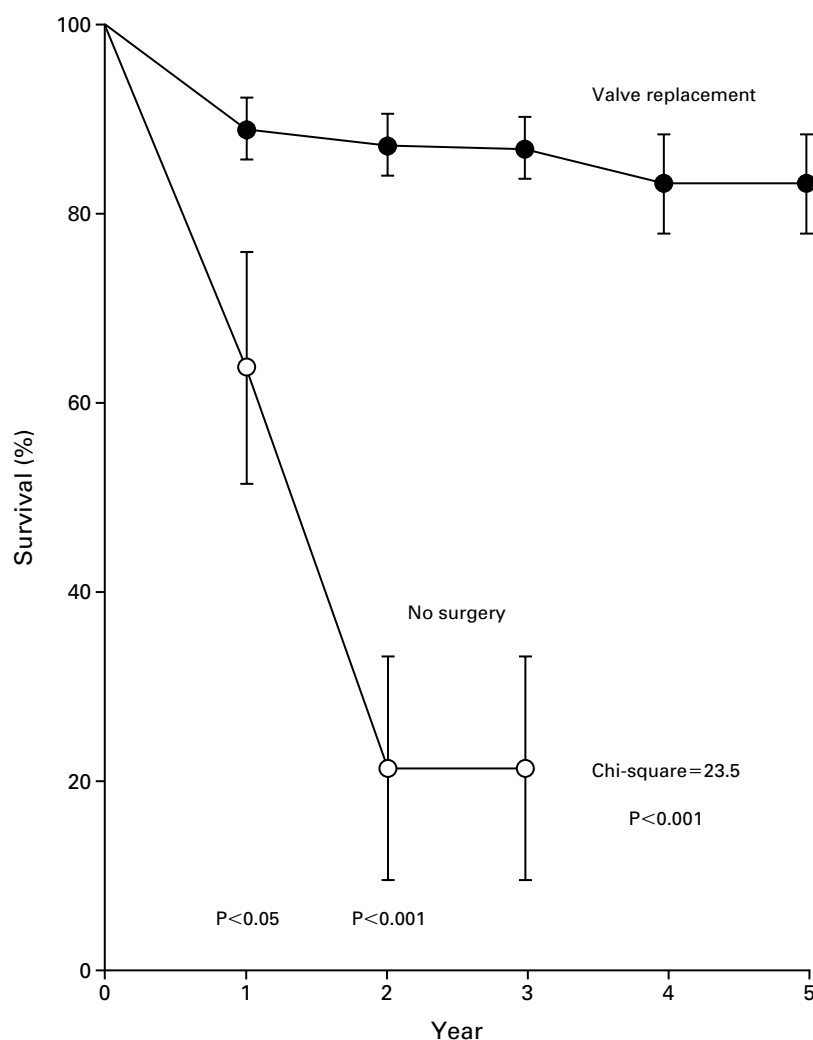
Echocardiography and exercise testing may identify asymptomatic patients who are likely to benefit from surgery. Otto et al.¹⁶ found that patients with asymptomatic aortic stenosis whose peak transaortic blood flow velocity exceeded 4 m per second (a peak gradient of 64 mm Hg) had a risk of becoming symptomatic and requiring aortic-valve replacement of 70 percent within two years. None of the patients in this moderate-sized series died suddenly, and all underwent exercise testing.

Although exercise testing is unwarranted and dangerous in patients with symptomatic aortic stenosis, it has proved safe in patients with moderate-to-severe asymptomatic aortic stenosis.^{16,17} A preliminary report suggests that exercise testing may identify some patients with latent symptoms or exercise-induced hemodynamic instability, facilitating timely aortic-valve replacement. In a study of 58 asymptomatic patients,¹⁸ 21 had symptoms for the first time during the exercise test. Most likely, these patients had failed to recognize the symptoms previously or had not engaged in activities that would have precipitated symptoms. Although patients with asymptomatic aortic stenosis can exercise safely under a physician's scrutiny, it seems most unwise to permit patients with moderate-to-severe aortic stenosis to engage in vigorous, unmonitored exercise in view of the limitations imposed by left ventricular hypertrophy on coronary blood flow.

Treatment of the Patient with a Low Gradient and Reduced Ejection Fraction

In patients with left ventricular dysfunction who have a substantial transvalvular gradient (a mean gradient of more than 40 mm Hg), the outcome of surgery is excellent despite the presence of a reduced ejection fraction preoperatively.¹⁹ In these patients, the excessive afterload generated by the obstructing valve is a prime contributor to the left ventricular dysfunction. Once the obstruction is removed and the afterload is reduced, left ventricular function returns to or approaches normal.

Patients with a reduced ejection fraction and a small



No. AT Risk	0	1	2	3	4	5
Valve replacement	125	87	51	35	9	0
No surgery	19	8	2	1	0	0

Figure 1. Survival among Patients with Severe Symptomatic Aortic Stenosis Who Underwent Valve Replacement and Similar Patients Who Declined to Undergo Surgery.

The overall and individual P values are shown, as is the overall chi-square value. Reprinted from Schwarz et al.¹¹ with the permission of the publisher.

transvalvular gradient (less than 30 mm Hg)^{19,20} have a high operative risk, and only half such patients are alive three to four years after surgery.²¹ The poor outcome in these patients is related to the presence of both severely depressed myocardial contractility and the excessive afterload.¹⁹

Although the overall prognosis for this group of patients is poor, some patients in this category, presumably those with severe valve obstruction, benefit

from surgery.^{21,22} In other patients, the calculated valve area may be severely reduced because cardiomyopathy inhibits the left ventricle from completely opening a mildly but not a severely stenotic valve. The presence of low output may lead clinicians to the false conclusion that the valve is severely stenotic (aortic pseudo-stenosis).²³⁻²⁵ The best method for distinguishing these two conditions is to increase cardiac output during Doppler echocardiography or cardiac catheterization

and to use the new data to recalculate the valve area. In the case of pseudostenosis, increased output causes a large increase in the calculated valve area, often to more than 1 cm². In this group of patients, valve replacement is unlikely to be beneficial. Conversely, patients in whom increased cardiac output produces a substantial increase in gradient have a true outflow obstruction and may benefit from surgery. Patients with a low gradient who have no response to inotropic stimulation have a poor outcome, presumably because the myocardial damage is so far advanced.²⁶

Safety of Cardiac Surgery in Patients with Mild-to-Moderate Aortic Stenosis

Controversy also exists regarding the optimal approach to patients with mild-to-moderate aortic stenosis (as indicated by a transvalvular gradient in the range of 10 to 30 mm Hg and a valve area of more than 1 cm²) who require cardiac surgery for some other cause, usually coronary revascularization. Concomitant aortic-valve replacement increases the risk of both perioperative death and complications related to the prosthetic valve. However, if the native valve is left in place, aortic stenosis may progress so rapidly that another cardiac surgery is required despite the fact that the bypass grafts are functioning normally.²⁷ Unfortunately, there is wide individual variability in the rate of disease progression,²⁷⁻²⁹ virtually precluding prognostication of the course of a given patient. Concomitant aortic-valve replacement is considered unwise if it is likely to increase the gradient even further.

Safety of Noncardiac Surgery in Patients with Severe Asymptomatic Aortic Stenosis

On the basis of a small number of adverse events, one study indicated that noncardiac surgery posed an increased risk among patients with aortic stenosis.³⁰ However, O'Keefe et al. examined the course of 48 patients with severe aortic stenosis who underwent noncardiac surgery³¹ and found that there were no complications in the 25 patients who had local anesthesia and only one complication in the 23 patients who received general anesthesia. Thus, although intraoperative hemodynamics must be closely monitored during noncardiac surgery in patients with asymptomatic aortic stenosis, there is no apparent need for concomitant aortic-valve intervention.

Ability to Slow or Halt Progression of the Valve Lesion

As noted above, the lesion of aortic stenosis shares many features with coronary disease. Although recent data suggest that hydroxymethylglutaryl coenzyme A reductase inhibitors (referred to as "statins") can retard the progression of aortic stenosis,³² in my opinion it is a bit too early to begin prescribing statins for this purpose.

GUIDELINES

Guidelines for the use of valve replacement in patients with aortic stenosis are provided in Table 2. In 1998 the American Heart Association and American College of Cardiology issued guidelines for the treatment of valvular heart disease (available at <http://www.americanheart.org>).⁸ These guidelines recommend the use of standard antibiotic prophylaxis against infective endocarditis. Doppler echocardiography is recommended for the initial diagnosis and assessment of the severity of aortic stenosis and the function and hemodynamics of the left ventricle, as well as for the reevaluation of patients whose symptoms and signs are changing and of patients known to have severe asymptomatic aortic stenosis.

CONCLUSIONS AND RECOMMENDATIONS

Doppler echocardiography is indicated for the initial evaluation in all patients suspected of having aortic stenosis, as well as in patients with established disease if symptoms develop or physical signs change. The development of angina, syncope, or dyspnea in a patient with severe aortic stenosis constitutes a grave medical condition, requiring prompt aortic-valve replacement. For patients with severe asymptomatic disease, such as the patient described in the clinical vignette, the presence of an aortic-jet velocity of at least 4 m per second on Doppler echocardiography indicates the need for close scrutiny. I routinely recommend exercise testing in this group (but never in symptomatic patients), since it may help identify which of these patients are at high enough risk to warrant undergoing surgery (Fig. 2).

The postoperative prognosis of patients with a reduced ejection fraction is good if the mean transvalvular pressure gradient exceeds 40 mm Hg. Thus, a low ejection fraction alone should never be an abso-

TABLE 2. RECOMMENDATIONS FOR THE USE OF AORTIC-VALVE REPLACEMENT IN PATIENTS WITH AORTIC STENOSIS.

Aortic-valve replacement indicated

Patients with severe aortic stenosis and any of its classic symptoms (angina, syncope, or dyspnea)
 Patients with severe aortic stenosis who are undergoing coronary-artery bypass surgery
 Patients with severe aortic stenosis who are undergoing surgery on the aorta or other heart valves

Aortic-valve replacement possibly indicated

Patients with only moderate aortic stenosis who require coronary-artery bypass surgery or surgery on the aorta or other heart valves
 Asymptomatic patients with severe aortic stenosis and at least one of the following: an ejection fraction of no more than 0.50, hemodynamic instability during exercise (e.g., hypotension), or ventricular tachycardia*

*Aortic-valve replacement is not indicated to prevent sudden death in asymptomatic patients who have none of the findings listed.

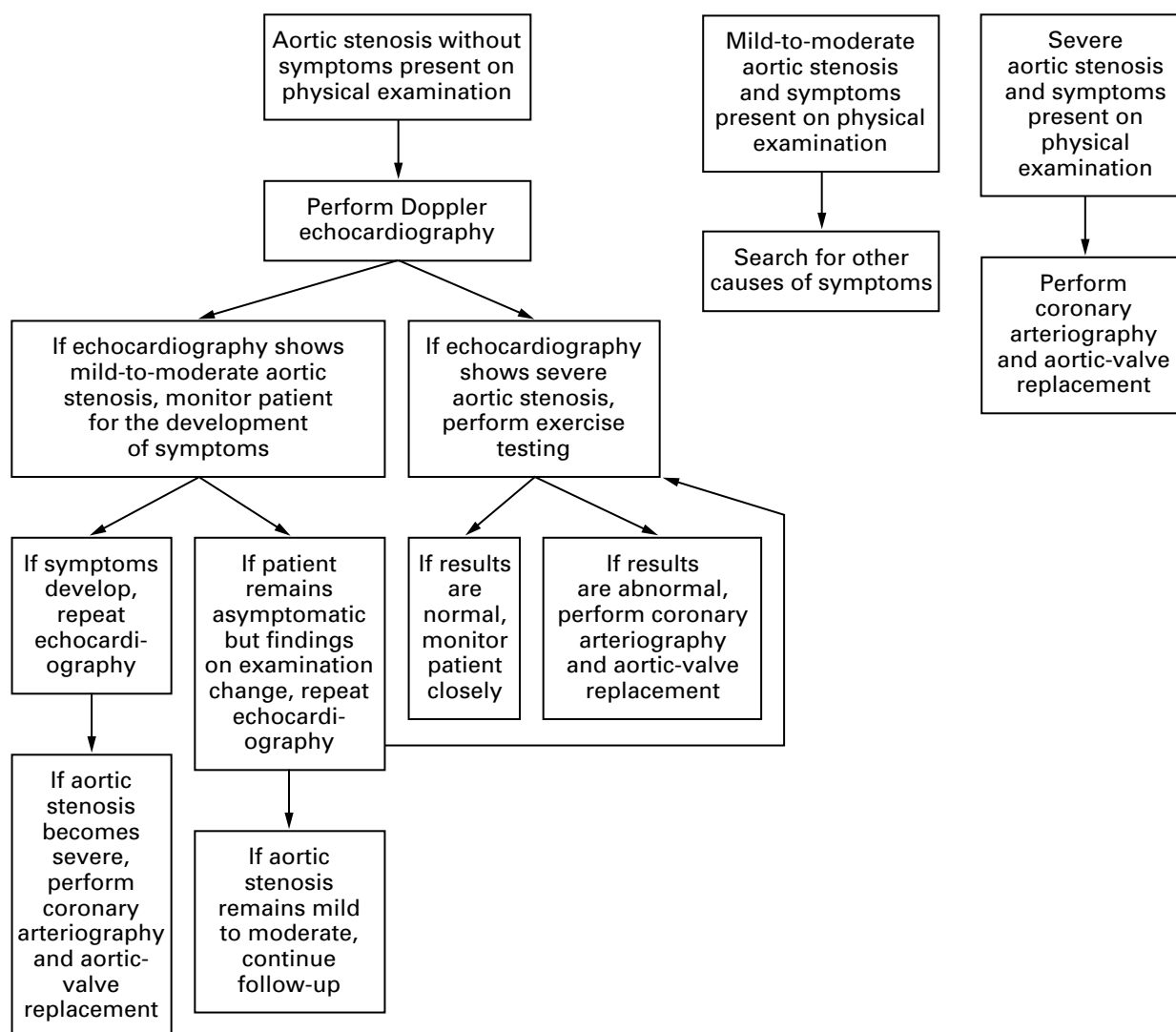


Figure 2. Algorithm for the Management of Aortic Stenosis.

lute contraindication to surgery. However, the prognosis of patients with a low gradient and a low ejection fraction is worse. For such patients I recommend hemodynamic manipulation in the catheterization or echocardiographic laboratory to help determine which patients are more likely to benefit from surgery.

Preliminary evidence indicates that patients who have moderate aortic stenosis (as indicated by a gradient of more than 20 mm Hg and a valve area of less than 1.2 cm²) but who require heart surgery for other diseases should probably undergo concomitant aortic-valve replacement. Further study of this approach is required.

REFERENCES

1. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of "degenerative" valvular aortic stenosis: histological and immunohistochemical studies. *Circulation* 1994;90:844-53.
2. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve stenosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999;341:142-7.
3. Marcus ML, Doty DB, Hiratzka LE, et al. Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. *N Engl J Med* 1982;307:1362-7.
4. Hess OM, Ritter M, Schneider J, Grimm J, Turina M, Krayenbuehl HP. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. *Circulation* 1984;69:855-65.
5. Huber D, Grimm J, Koch R, Krayenbuehl HP. Determinants of ejection performance in aortic stenosis. *Circulation* 1981;64:126-34.
6. McCrindle BW. Independent predictors of immediate results of percu-

- taneous balloon aortic valvotomy in children. *Am J Cardiol* 1996;77:286-93.
7. Otto CM, Mickel MC, Kennedy JW, et al. Three-year outcome after balloon aortic valvuloplasty: insights into prognosis of valvular aortic stenosis. *Circulation* 1994;89:642-50.
 8. 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;32:1486-588.
 9. Ross J Jr, Braunwald E. Aortic stenosis. *Circulation* 1968;38:Suppl V:V-61-V-67.
 10. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol* 1990;15:1012-7.
 11. Schwarz E, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. *Circulation* 1982;66:1105-10.
 12. Lindblom D, Lindblom U, Qvist J, Lundstrom H. Long-term relative survival rates after heart valve replacement. *J Am Coll Cardiol* 1990;15:566-73.
 13. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. *Am J Cardiol* 1988;61:123-30.
 14. Pellikka PA, Nishimura RA, Bailey KR, et al. Natural history of 610 adults with asymptomatic hemodynamically significant aortic stenosis over prolonged follow-up. *J Am Coll Cardiol* 2001;37:Suppl A:489A. abstract.
 15. Thai HM, Gore JM. Prosthetic heart valves. In: Alpert JS, Dalen JE, Rahimtoola SH, eds. *Valvular heart disease*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:393-407.
 16. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;95:2262-70.
 17. Linderholm H, Osterman G, Teien D. Detection of coronary artery disease by means of exercise ECG in patients with aortic stenosis. *Acta Med Scand* 1985;218:181-8.
 18. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;297:845-50.
 19. Carabello BA, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ Jr. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. *Circulation* 1980;62:42-8.
 20. Lund O. Preoperative risk evaluation and stratification of long-term survival after valve replacement for aortic stenosis: reasons for earlier operative intervention. *Circulation* 1990;82:124-39.
 21. Connolly HM, Oh JK, Schaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation* 2000;101:1940-6.
 22. Brogan WC III, Grayburn PA, Lange RA, Hillis LD. Prognosis after valve replacement in patients with severe aortic stenosis and a low transvalvular pressure gradient. *J Am Coll Cardiol* 1993;21:1657-60.
 23. Cannon JD Jr, Zile MR, Crawford FA Jr, Carabello BA. Aortic valve resistance as an adjunct to the Gorlin formula in assessing the severity of aortic stenosis in symptomatic patients. *J Am Coll Cardiol* 1992;20:1517-23.
 24. deFilippi CR, Willett DL, Brickner ME, et al. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol* 1995;75:191-4.
 25. Burwash IG, Pearlman AS, Kraft CD, Miyake-Hull C, Healy NL, Otto CM. Flow dependence of measures of aortic stenosis severity during exercise. *J Am Coll Cardiol* 1994;24:1342-50.
 26. Monin JL, Monchi M, Gest V, Duval-Moulin AM, Dubois-Rande JL, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose dobutamine echocardiography. *J Am Coll Cardiol* 2001;37:2101-7.
 27. Faggiano P, Aurigemma GP, Rusconi C, Gaasch WH. Progression of valvular aortic stenosis in adults: literature review and clinical implications. *Am Heart J* 1996;132:408-17.
 28. Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. *J Am Coll Cardiol* 1989;13:545-50.
 29. Nestico PF, DePace NL, Kimbiris D, et al. Progression of isolated aortic stenosis: analysis of 29 patients having more than 1 cardiac catheterization. *Am J Cardiol* 1983;52:1054-8.
 30. Das P, Rimington H, McGrane K, Chambers J. The value of treadmill exercise testing in apparently asymptomatic aortic stenosis. *J Am Coll Cardiol* 2001;37:Suppl A:489A. abstract.
 31. O'Keefe JH Jr, Shub C, Rettke SR. Risk of noncardiac surgical procedures in patients with aortic stenosis. *Mayo Clin Proc* 1989;64:400-5.
 32. Novaro GM, Tiong IY, Pearce GL, Lauer MS, Sprecher DL, Griffin BP. Effect of hydroxymethylglutaryl coenzyme A reductase inhibitors on the progression of calcific aortic stenosis. *Circulation* 2001;104:2205-9.

Copyright © 2002 Massachusetts Medical Society.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* Web site at <http://www.nejm.org>. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.
