When should patients with asymptomatic aortic stenosis be evaluated for valve replacement?

EVIDENCE-BASED ANSWER For patients whose echocardiograms show advanced calcification of the aortic valves, a jet velocity of > 4.0 m/s, or a progression in jet velocity of 0.3m/s/year; and for patients who have an abnormal exercise response or an impaired functional status, consider referral for valve replacement prior to the onset of symptoms (Grade of Recommendation: C).

EVIDENCE SUMMARY Aortic stenosis is a narrowing of the aortic valve. Degree of severity is judged by valve area: mild (1.5–2.0 cm^2), moderate (1.0–1.5 cm^2), severe (< 1.0 cm^2). Alternatively, stenosis may be classified by transvalvular gradient or jet velocity, the latter being the easier quantity to measure by echocardiogram. Prevalence of aortic stenosis increases with age; one series of 1243 elderly women (mean age of 82) found mild stenosis in 10%, moderate stenosis in 6%, and severe stenosis in 2%.[1] Natural history studies show that once classic symptoms develop, average survival decreases to 5 years with the onset of angina, 3 years after cardiac syncope, and 2 years after heart failure.[2] The incidence of sudden death increases from < 1% annually among asymptomatic patients to 15% to 20% among symptomatic patients.[3,4]

Aortic stenosis is suggested by such findings as a harsh systolic murmur at the right upper sternal border, pulsus parvus et tardus, and a sustained point of maximal impulse. Exercise stress testing may provide additional information. In one prospective study of 123 patients, those who had a greater increase in valve area, cardiac output, and blood pressure and a smaller decrease in stroke volume on stress echocardiogram were more likely to remain asymptomatic for the entire length of their time in the study, an average of 2.5 years.[5]

Asymptomatic patients with aortic stenosis who undergo coronary artery bypass grafting (CABG) often have their aortic valve replaced at the same time; the timing of aortic valve replacement in patients not requiring CABG is controversial. One prospective study found the severity of stenosis at baseline to be the strongest prognostic predictor. Patients with a jet velocity of < 3.0 m/s were unlikely to develop symptoms within 5 years; those with a jet velocity of ≥ 4.0 m/s had a > 50% likelihood of developing symptoms or dying within 2 years.[5] Another study followed 128 patients for 4 years and found that moderate to severe valvular calcification and an increase in jet velocity of ≥ 0.3 m/s/year were the best prognostic predictors.[6] Almost 80% of those with both calcification and a rapid change in jet velocity underwent surgery or died within 2 years[6] (Table).

TABLE

Indications for possible valve replacement with asymptomatic aortic stenosis

Predicting factor	Marker of worse prognosis
Calcification	Moderate to severe (multiple large calcified areas to extensive calcification of all cusps)
Jet velocity	> 4.0 m/s
Rate of jet velocity progression	≥ 0.3 m/s/year
Exercise response	Minimal to no change in valve area, cardiac output, and blood pressure; marked decrease in stroke volume
Functional status	Impaired initially or declining

RECOMMENDATIONS FROM OTHERS The American College of Cardiology/American Heart Association Task Force on Practice Guidelines recommends echocardiograms every 5 years for mild stenosis, every 2 years for moderate stenosis, and annually for severe stenosis.[4] There is no guideline for exercise testing. Aortic valve replacement is recommended for symptomatic patients and patients with severe stenosis undergoing CABG or other valvular or aortic surgery.

Michelle Colen, MD; Erik J. Lindbloom, MD, MSPH; and Susan Meadows, MLS
Department of Family and Community Medicine
University of Missouri-Columbia

Clinical Commentary by Ken Grauer, MD; and search strategy, at www.fpin.org.

REFERENCES
1. Aronow WS, Ahn C, Kronzon I. Am J Cardiol 1997; 79:379–80.
2. Ross J Jr., Braunwald E. . Circulation 1968; 38(1 Suppl):61–7.
3. Balentine J, Eisenhart A. Aortic Stenosis. EMedicine Journal 2002; 3:1.
4. Bonow RO, Carabello B, deLeon AC Jr., et al. Circulation 1998; 98:1949–84.
5. Otto CM, Burwash IG, Legget ME, et al. Circulation 1997; 95:2262–70.
6. Rosenhek R, Binder T, Porenta G, et al. N Engl J Med 2000; 343:611–7.

Members of the Family Practice Inquiries Network answer clinical questions with the best available evidence in a concise, reader-friendly format. Each peer-reviewed answer is based on a standard search of resources, including MEDLINE, the Cochrane Library, and InfoRetriever, and is graded for level of evidence (http://cebm.jr2.ox.ac.uk/docs/levels.html). The collected Clinical Inquiries can be found at http://www.jfponline.com and http://www.fpin.org; the latter site also includes the search strategy used for each answer.

What are effective treatments for panic disorder?

EVIDENCE-BASED ANSWER Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), benzodiazepines (BDZs), and cognitive behavioral therapy (CBT) are effective for panic disorder (PD) with or without agoraphobia (NNT≈5 for complete remission). SSRIs may be most effective, but BDZs work faster. Clomipramine is more effective than other TCAs. CBT improves response and decreases relapse rates when used with medication. Severe symptoms may warrant short-term use of a BDZ until other therapies take effect (Grade of recommendation: A, based on systematic reviews of randomized clinical trials (RCTs); high quality RCTs).

EVIDENCE SUMMARY SSRIs were more effective than imipramine or alprazolam in a meta-analysis,[1] but equivalent to these drugs in an effect-size analysis.[2] The absolute difference in efficacy is difficult to determine; few studies directly compare SSRIs with other drugs. In 2 randomized head-to-head trials,[3,4] remission rates (eliminating symptoms) were 50%–65% for paroxetine, 37%–53% for clomipramine, and 32%–34% for placebo after 9–12 weeks of therapy; differences between the 2 active drugs were not significant. Clomipramine is serotoninergic and was more effective than other tricyclics in an RCT.[5] Adding a BDZ to an SSRI for the first 3 weeks can rapidly stabilize symptoms[6] (Table).

Two meta-analyses concluded that CBT is as effective as antidepressants or BDZs during acute treatment[7] and during long-term follow-up (31–121 weeks).[8] CBT and imipramine each reduce symptoms in 45%–48% of patients; combining them reduces symptoms in 60%.[9] Imipramine is more effective initially; CBT is more durable[9] but effects may be therapist-dependent. When used in conjunction with medication, graded exposure to panic-inducing situations reduces agoraphobia[7] but does not improve relapse rates.[8] Behavioral therapy with exposure homework has good long-term results.[10]

An adequate trial of medication requires 6–8 weeks.[11] Before treating, evaluate patients for comorbid mood, anxiety, personality, substance use, or medical disorders, which affect 40%–50% of patients with panic disorder, and may influence the choice of treatment.[12] Current practice is to slowly taper and discontinue medication after 12–18 months of maintenance treatment[12] if there are no significant residual symptoms, no increased psychosocial stressors, and no history of severe or recurrent relapse.

RECOMMENDATIONS FROM OTHERS The American Psychiatric Association Guideline states that CBT and pharmacotherapy are equivalently effective, and that SSRIs, TCAs, BDZs, and MAOIs are equivalently effective.[12] The International Consensus Group on Depression and Anxiety concludes that SSRIs, TCAs, and BDZs are effective. SSRIs and BDZs are tolerated better than TCAs, and BDZs act faster (1 week vs. 4–8 weeks).[11]

TABLE

Drugs used to treat panic disorder

Drug Class	Side Effects	Other Considerations
Selective serotonin reuptake inhibitors	Nausea (10–30%), drowsiness (7–20%), insomnia (< 10%), nervousness(< 10%), sexual dysfunction (< 10% but underreported).	All equivalently effective. Some patients may respond to lower than usual doses. Start at half the usual dose.
Tricyclic antidepressants	Dry mouth (> 45%), dizziness (2%), constipation (15%), sweating (15%), tremors (15%), fatigue (< 10%)	Requires more time to titrate to treatment dose. Clomipramine more effective. Some patients with panic disorder are extremely sensitive both to the therapeutic and adverse effects of TCAs. Start at very low doses.
Benzodiazepines	Somnolence (15–34%) and impaired coordination (6–22%). Potential for physical dependence and withdrawal symptoms, but psychological addiction has not been a significant problem in clinical trials.	Faster onset of action than antidepressants, but do not treat comorbid depression and are more difficult to discontinue.

Deborah A. Sturpe, PharmD
Alicia M. Weissman, MD
University of Iowa, Iowa City

Read a Clinical Commentary by William A. Hensel, MD, at www.fpin.org.

REFERENCES

1. Boyer W. Int Clin Psychopharmacol 1995; 10:45–9.
2. Otto MW, Tuby KS, Gould RA, et al. Am J Psychiatry 2001; 158:1989–92.
3. Lecrubier Y, Bakker A, Dunbar G, et al. Acta Psychiatrica Scand 1997; 95:145–52.
4. Bakker A, van Dyck R, Spinhoven P, et al. J Clin Psychiatry 1999; 60:831–8.
5. Modigh K, Westberg P, Eriksson E. J Clin Psychopharmacol 1992; 12:251–61.
6. Goddard AW, Brouette T, Almai A, et al. Arch Gen Psychiatry 2001; 58:681–6.
7. van Balkom A, Bakker A, Spinhoven P, et al. J Nerv Ment Dis 1997; 185:510–6.
8. Bakker A, van Balkom A, Spinhoven P, et al. J Nerv Ment Dis 1998; 186:414–9.
9. Barlow D, Gorman J, Shear M, et al. JAMA 2000; 283:2529–36.
10. Fava GA, Rafanelli C, Grandi S, et al. Psychol Med 2001; 31(5):891–8.
11. Ballenger J, Davidson J, Lecrubier Y, et al. J Clin Psychiatry 1998;59(suppl 8):47–54.
12. American Psychiatric Association. Am J Psychiatry 1998; 155(5 Suppl):1S–34S.

Is there a role for theophylline in treating patients with asthma?

EVIDENCE-BASED ANSWER With adults, oral theophylline may help lower the dosage of inhaled steroids needed to control chronic asthma. It offers no benefit for acute asthma exacerbations. For children, intravenous aminophylline may improve the clinical course of severe asthma attacks. Side effects and toxicity limit use of these medications in most settings. (Grade of recommendation: A, based on systematic reviews and randomized control trials [RCTs]).

EVIDENCE SUMMARY Several systematic reviews help clarify theophylline's role in asthma management. When compared with placebo in the management of acute exacerbations, theophylline confers no added benefit to beta-agonist therapy (with or without steroids) in improving pulmonary function or reducing hospitalization rates. Side effects occurred more often in the theophylline group: palpitations/arrhythmias (OR = 2.9; 95% CI: 1.5 to 5.7) and vomiting (OR = 4.2; 95% CI: 2.4 to 7.4).[1] For moderately severe asthma in patients already receiving inhaled corticosteroids (ICS), theophylline as maintenance therapy equaled long-acting beta-2-agonists in increasing FEV_1 and PEFR, but was less effective in controlling night time symptoms. Use of long-acting beta-agonists resulted in fewer side effects (RR = 0.38; 95%CI: 0.25–0.57).[2] When added to low-dose ICS for maintenance, theophylline was as effective as high-dose ICS alone in improving FEV_1, decreasing day and night symptoms, and reducing the need for rescue medications and the incidence of attacks. This suggests theophylline has utility as a steroid sparing agent.[3]

Intravenous aminophylline does appear to be clinically beneficial for children with severe exacerbations, defined as an FEV_1 of 35%–40% of predicted value. Critically ill children receiving aminophylline in addition to usual care exhibited an improved FEV_1 at 24 hours (mean difference = 8.4%; 95% CI: 0.82 to 15.92) and reduced symptom scores at 6 hours.[4] The largest RCT of aminophylline in children demonstrated a reduced intubation rate (NNT = 14 CI: 7.8–77).[5] Children receiving aminophylline experienced more vomiting (RR = 3.69; 95%CI: 2.15–6.33). Treatment with aminophylline did not reduce length of hospital stay or the number of rescue nebulizers needed (Table).[4]

TABLE

Theophylline use in asthma

	Adults	Children
Acute Treatment	No added benefit to corticosteroids and beta-agonist therapy; increased GI and cardiac side effects.	24 hours of IV aminophylline improves symptom scores without reducing LOS or nebulizer requirements; may reduce intubation
Maintenance Therapy		
Mild	No clinical benefit	Not recommended
Moderate	Performs worse than long-acting beta-agonists and has more side effects; may limit the need for high-dose ICS if not using long beta agonists.	No advantage over long-acting beta agonists when added to ICS. More side effects
Severe	Same for moderate; does not limit the need for oral corticosteroids in this setting.	Same as moderate

LOS = length of stay; ICS = inhaled corticosteroids.

RECOMMENDATIONS FROM OTHERS Three evidence-supported guidelines concur that theophylline has a limited role as maintenance therapy for moderate-to-severe persistent asthma when symptom control with ICS alone is not adequate. Much stronger evidence supports the use of long-acting beta-2-agonists or leukotriene modifiers in this setting.[6–8] The guidelines do not recommend using theophylline to treat acute asthma exacerbations; nor do they address using theophylline in children.

Charissa Fotinos, MD
Swedish at Providence Family Medicine Residency
Seattle, Washington

Sherry Dodson, MLS
Health Sciences Libraries
University of Washington, Seattle

Read a Clinical Commentary by M. Lee Chambliss, MD, MSPH, at www.fpin.org.

REFERENCES

1. Wilson AJ, Gibson, PG, Coughlan J. The Cochrane Library, Issue 2, 2002. Oxford: Update Software.
2. Parameswaran K, Belda J, Rowe BH. The Cochrane Library, Issue 2, 2002. Oxford: Update Software.
3. Evans DJ, Taylor DA, Zetterstrom O, et al. N Engl J Med. 1997; 337:1412–8.
4. Mitra A, Bassler D, Ducharme FM. The Cochrane Library, Issue 2, 2002. Oxford: Update Software.
5. Yung M, South M. Arch Dis Child 1998;79: 405–410.
6. Management of Chronic Asthma. Evidence Report/Technology Assessment. Number 44. AHQR Publication Number 01-E043, September 2001.
7. Global Initiative for Asthma, National Heart, Lung and Blood Institute, (U.S.)/World Health Organization. 1995 Jan (revised 1998).
8. Expert Panel Report 2:Guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program/National Heart, Lung and Blood Institute (U.S.). 1997 Jul, (reprinted 1998 Apr, 1999 Mar).