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 0.3 m/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 cm²), moderate (1.0–1.5 cm²), severe (< 1.0 cm²). 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%. 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. The incidence of sudden death increases from < 1% annually among asymptomatic patients to 15% to 20% among symptomatic patients.

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 125 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.

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 unlike-ly 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. 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. Almost 80% of

### Table

**Indications for possible valve replacement with asymptomatic aortic stenosis**

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

**REFERENCES**

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, but equivalent to these drugs in effect-size analysis. The absolute difference in efficacy is difficult to determine; few studies directly compare SSRIs with other drugs. In 2 randomized head-to-head trials, remission rates (eliminating symptoms) were 50%-65% for paroxetine, 37%-53% for clomipramine, and 52%-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. Adding a BDZ to an SSRI for the first 3 weeks can rapidly stabilize symptoms (Table).

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

An adequate trial of medication requires 6–8 weeks. 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. Current practice is to slowly taper and discontinue medication after 12–18 months of maintenance treatment 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. 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).

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


REFERENCES
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 conferred 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 FEV₁ and PEFR, but was less effective in controlling night time symptoms. Use of long-acting beta-2-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 FEV₁, 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 FEV₁ of 35%–40% of predicted value. Critically ill children receiving aminophylline in addition to usual care exhibited an improved FEV₁ 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

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


REFERENCES