Management of Asymptomatic Severe Aortic Stenosis

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Patients with symptomatic severe aortic stenosis (AS) benefit from aortic valve replacement (AVR). Management of severe AS in the absence of symptoms is, however, controversial and often challenging. Unselected premature AVR carries the risks of cardiac surgery; delayed AVR due to unrecognized symptoms can result in a dismal outcome. Echocardiography is the standard tool to evaluate and follow patients with AS. Nevertheless, most of the current echocardiographic parameters have limitations in predicting symptom onset and clinical outcome. The same applies to clinical parameters, exercise stress testing, and other imaging modalities used in AS evaluation and serial follow-up. Predictors of outcome could, however, help to identify asymptomatic patients who would benefit from expedited AVR with the goal to reduce mortality. This review will discuss the most relevant clinical studies and guidelines on management of asymptomatic severe AS, with an emphasis on providing concise information for identifying patients at high risk. (J Am Coll Cardiol 2008;52:1279–92) © 2008 by the American College of Cardiology Foundation

Every fourth patient over age 65 years has evidence of aortic sclerosis (1), and more than 4% of the North American population age 75 years and older have aortic stenosis (AS) (2). Approximately 1 in 6 aortic sclerosis patients advances to AS (3), and in already established mild-to-moderate AS, one-half of those affected progress to hemodynamically severe AS (4).

Survival of patients with symptomatic AS is dismal (5–8), and the treatment of choice is aortic valve replacement (AVR) (9). Current AVR indication and timing is largely based on the development of angina, dyspnea, or syncope (10), and successful AVR results in good long-term prognosis (11,12). However, management of severe AS in the absence of symptoms is challenging. Whereas lack of symptom recognition portends a high risk of death (13), unselected, premature AVR is associated with the risks of cardiac surgery and valve prosthesis complications. At least every third—with estimates up to every second—patient with severe AS is asymptomatic (5,14,15). This makes reliable risk estimation and appropriate AVR indication and timing in patients with asymptomatic severe AS a common and important clinical challenge.

For this review we searched the MEDLINE database with PubMed. Our queries included the Medical Subject Heading term “Aortic Valve Stenosis” in various combinations with “asymptomatic,” “outcome,” “predictor,” “survival,” and “mortality.” Search results were restricted to original articles, reviews, and editorials in the English language. Additionally we retrieved articles referenced by published guidelines and comprehensive reviews.

Calcific Aortic Valve Disease: From Aortic Sclerosis to AS

Calcific aortic valve disease is the leading AS etiology in industrialized countries (2,16–18) and shares the atherosclerosis risk factors age, gender, hypertension, smoking, serum low-density lipoprotein, and lipoprotein (a) levels (1). Aortic valve calcification is a complex pathological process that starts at the base of the aortic cusp (10), primarily in response to endothelial damage caused by blood flow shear stress, and is followed by inflammatory cell infiltration, lipid and calcium deposition, and activation of osteoblast-like cells (19–25). Disease progression might be potentially modifiable by anti-inflammatory and lipid-lowering therapy (HMG-CoA reductase inhibitors) (26–30); however, if progressive, calcification usually spreads to the leaflet tips causing thickening, stiffening, and restricted movement of the aortic valve leaflets. Calcific aortic valve disease can be nonobstructive (= aortic sclerosis) or obstructive (= AS). Aortic stenosis can be graded, on the basis of the severity of obstruction, as mild, moderate, or severe (Table 1).

The average time interval from development of aortic sclerosis to moderate and severe AS is 6 and 8 years, respectively (3). This gives the left ventricle (LV) time to remodel for countering the increase in afterload (31,32). Reduction in LV longitudinal shortening due to subendo-
cardiac dysfunction (33) is accompanied with adaptive concentric wall hypertrophy (34) and exaggerated LV torsional mechanics (35) to keep LV systolic wall stress and left ventricular ejection fraction (LVEF) initially within the normal range. Once moderate AS is present, the average rate of aortic jet velocity progression by cardiac ultrasound is 0.3 m/s/year, with a concomitant increase in the mean transvalvular pressure gradient of 7 mm Hg/year and a parallel reduction in aortic valve area (AVA) of 0.1 cm²/year (11,36–38). Hemodynamic progression and calcification are accelerated in patients with congenital aortic valve disease (39). Patients with bicuspid aortic valve disease (BAV) present for AVR earlier (fourth decade) in comparison with patients with tricuspid AS (sixth decade) (18).

Natural History of Asymptomatic AS

Ross and Braunwald (40) published a comprehensive report on the natural history of AS, summarizing prospective and retrospective (post-mortem) studies and their experience. Patients with AS who developed angina and syncope survived 3 years, patients with dyspnea 2 years, and patients with heart failure survived 1.5 to 2 years, respectively. This landmark survival analysis from 1968 included symptomatic patients with heterogeneous AS etiologies (e.g., bicuspid AS, rheumatic AS [41]), which might limit applicability in patients with heterogeneous AS etiologies (e.g., bicuspid AS). landmark survival analysis from 1968 included symptomatic patients with heterogeneous AS etiologies (e.g., bicuspid AS, rheumatic AS [41]), which might limit applicability in patients with heterogeneous AS etiologies (e.g., bicuspid AS). 

Several retrospective (14,42) and prospective studies (11,43) have subsequently specifically evaluated the prognosis and management of patients with asymptomatic severe AS. It is important to note that these studies differed in design (e.g., patient age, exclusion criteria, mean transvalvular gradient). For example, Otto et al. (43) included patients with less than severe AS and bicuspid AS (28% of the study population). Secondly, AVR was considered as a clinical end point in each of these studies (Table 2). This makes survival data less conclusive, because AVR is a “soft” clinical end point compared with cardiac death. Moreover, referral for AVR might have been confounded by the primary physician’s treatment bias (“pre-emptive” AVR vs. true symptom development) or AVR performed concomitantly with coronary artery bypass grafting. Thirdly, coronary artery disease was not an exclusion criterion and potentially confounded cardiac death. Despite these limitations, it is worthwhile noting that approximately one-third of asymptomatic AS patients become symptomatic within 2 years (42). Within 4 to 5 years, two-thirds of patients have either an AVR due to symptom development or cardiac death (11,14,43). Survival in asymptomatic and unoperated patients is 99%, 98%, and 93% at 1, 2, and 5 years, respectively. Survival in these patients is actually similar to an age- and gender-matched healthy population; however, the prognosis worsens significantly as soon as symptoms develop (14). Overall survival of patients with asymptomatic severe AS including those who have AVR is 93 ± 2%, 91 ± 3%, and 87 ± 3% at 1, 2, and 5 years, respectively, which again does not differ statistically from an age- and gender-matched population (11). Early estimates of sudden death without preceding symptoms were approximately 3% to 5%/year (40). More recent evidence supports the concept that sudden death in truly asymptomatic AS patients is <1%/year (5,7,11,42,43). This conservative number, however, might be generated by heightened clinical vigilance, where patients are followed meticulously with serial echocardiography, and might not be representative of the ambient annual risk of sudden death in this group of patients.

Diagnosis of AS and Grading of Severity

On the basis of 2-dimensional echocardiography and Doppler measurements, AS can be graded as mild, moderate, and severe (Table 1) (10,44). In general, aortic jet velocity is the most reproducible measurement (45,46), because even small errors in LV outflow tract diameter and ultrasound beam alignment with respect to the aortic jet profoundly influence the calculated AVA and mean and peak transvalvular pressure gradient. Significant aortic regurgitation has limited impact on Doppler-calculated AVA, whereas a chaotic subvalvular velocity profile due to subvalvular obstruction (e.g., septal hypertrophy or subaortic membrane) results in erroneous AVA quantification (47). Furthermore, it needs to be emphasized that serial echocardiographic evaluation should be performed in a state of comparable hemodynamic range (46,48), because interexamination blood pressure differences, especially acute hypertension, can mask AS severity by influencing transvalvular pressure gradient and jet velocity (49).

Because noninvasive transvalvular gradients show excellent correlation with invasive transvalvular gradients, cardiac catheterization is rarely used to diagnose AS (50). Invasive

### Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology/American Heart Association</td>
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<tr>
<td>AS</td>
<td>aortic stenosis</td>
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<tr>
<td>AVA</td>
<td>aortic valve area</td>
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<td>AVR</td>
<td>aortic valve replacement</td>
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<td>BAV</td>
<td>bicuspid aortic valve</td>
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<tr>
<td>BNP</td>
<td>brain natriuretic peptide</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CR</td>
<td>contractile reserve</td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>LV</td>
<td>left ventricle/ventricular</td>
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<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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### Table 1: AS Severity Grading

<table>
<thead>
<tr>
<th></th>
<th>Mild AS</th>
<th>Moderate AS</th>
<th>Severe AS</th>
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<tbody>
<tr>
<td>AVA (cm²)</td>
<td>&gt;1.5</td>
<td>1.5–1.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>AVA index (cm²/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gradient (mm Hg)</td>
<td>&lt;25</td>
<td>25–40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Aortic jet velocity (m/s)</td>
<td>&lt;3.0</td>
<td>3.0–4.0</td>
<td>&gt;4.0</td>
</tr>
</tbody>
</table>

Adapted from Bonow et al. (10).

AS = aortic stenosis; AVA = aortic valve area.
Table 2 Natural History of Patients With Asymptomatic Severe AS

<table>
<thead>
<tr>
<th>n</th>
<th>Age (yrs)</th>
<th>Exclusion Criteria</th>
<th>Baseline Aortic Jet Velocity (m/s)</th>
<th>Mean Gradient (mm Hg)</th>
<th>Follow-Up</th>
<th>Symptom Definition</th>
<th>Cardiac Event/End Point Definition (n if Available)</th>
<th>Symptom-Free Survival (%)</th>
<th>Event-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Yr</td>
<td>2 Yrs</td>
<td>3 Yrs</td>
<td>4 Yrs</td>
<td>5 Yrs</td>
<td>1 Yr</td>
<td>2 Yrs</td>
</tr>
<tr>
<td>Pellikka et al. (42)</td>
<td>113</td>
<td>70 (40–94) Cardiac symptoms, multivalvular involvement, moderate-to-severe AR, documented MI, prior CABG, percutaneous aortic balloon valvuloplasty, valve replacement</td>
<td>4.3 (4–6)†</td>
<td>47</td>
<td>20 (6–48) months</td>
<td>Angina, dyspnea, syncope</td>
<td>AVR (20), cardiac death second to AS (3)</td>
<td>86 ± 3</td>
<td>62 ± 6</td>
</tr>
<tr>
<td>Otto et al. (43)</td>
<td>123</td>
<td>63 ± 16 Inability to return for follow-up (severe comorbid disease, distance of hospital from residence), patient refusal, AVR within 3 months of enrollment</td>
<td>3.6 ± 0.6‡</td>
<td>29 ± 11</td>
<td>2.5 ± 1.4 yrs</td>
<td>Angina, heart failure, syncope, or near syncope</td>
<td>AVR (48), cardiac death (4)</td>
<td>93 ± 5</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>Rosenhek et al. (11)</td>
<td>128</td>
<td>60 ± 18 Hemodynamically significant valvular lesions, symptoms at presentation</td>
<td>5.0 ± 0.6§</td>
<td>NA</td>
<td>22 ± 18 months</td>
<td>NA</td>
<td>AVR (59), cardiac death (6), noncardiac death (2)</td>
<td>67 ± 5</td>
<td>56 ± 5</td>
</tr>
<tr>
<td>Pellikka et al. (14)</td>
<td>622</td>
<td>72 ± 11 Multivalvular involvement, moderate-to-severe AR, documented MI, prior CABG, percutaneous aortic balloon valvuloplasty, valve replacement/cardiac surgery, history of cardiac symptoms, patient refusal, referral to surgery on initial evaluation</td>
<td>4.4 ± 0.4*</td>
<td>46 ± 11</td>
<td>5.4 ± 4.0 yrs</td>
<td>Angina, dyspnea, syncope</td>
<td>Symptom development (297), AVR (352), cardiac death (117)</td>
<td>82</td>
<td>67</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD or as range if indicated. *Peak aortic jet velocity; †aortic jet velocity range; ‡maximum aortic jet velocity; §mean aortic jet velocity.

AR = aortic regurgitation; AS = aortic stenosis; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MI = myocardial infarction; NA = data not available.
hemodynamics, however, might be of value in patients in need of coronary angiogram whose Doppler-derived transvalvular gradients are disproportionate to physical exam findings or patient history. An example is a patient with a small ascending aorta diameter (<3 cm) where pronounced pressure recovery might lead to significant Doppler overestimation of transvalvular gradient and therefore AS severity (51).

More recently, 3-dimensional echocardiography (52–55), cardiac computerized tomography (56,57), and cardiac magnetic resonance imaging (58–60) have been proposed as additional techniques to quantify AVA and AS severity. Because these imaging modalities measure the anatomic and not the functional effective AVA, AS severity is more likely to be underestimated. A new and exciting magnetic resonance technique, overcoming the limitations of anatomic quantification of the AVA, is velocity-encoded phase contrast imaging (Fig. 1) (60–62). This method allows AVA quantification with the continuity equation mimicking echocardiographic Doppler quantification and should be helpful in patients with poor echocardiographic windows, obesity, lung disease, or heavily calcified aortic valves. Contrary to current “crude” conventional measures such as LVEF, tissue Doppler imaging and speckle track imaging (Fig. 2) are superior in detecting subtle changes in myocardial function. Studies have shown reduced longitudinal systolic and early diastolic mitral annular velocities in patients with AS (63–65) and evidence of early LV systolic dysfunction if peak systolic mitral annular velocity increase after treadmill exercise is blunted (66). Longitudinal strain and strain rates are also reduced but show significant improvements after AVR, even before global LV function improves (67). Left ventricular torsion is a measure of the “wringing” motion of the heart and plays a critical role in efficient blood expulsion and filling. Systolic LV torsion is preserved or exaggerated in AS (35,68) and likely compensates for depressed intramyocardial circumferential strain (69) and decreased subendocardial contractile function (70) (Fig. 3). Diastolic untwisting is delayed, resulting in elevated LV end-diastolic filling pressures (35,68). Left ventricular torsion normalizes (69) and subendocardial contractile function significantly recovers within 3 month after AVR—even before LV remodeling is obvious (70). Early detection of myocardial dysfunction by tissue Doppler and speckle track imaging (Fig. 2) might be therefore potentially useful in optimizing the timing of AVR before the onset of global LV dysfunction and symptoms in patients with severe AS (33). However, this requires future investigation.

**Risk Estimation in Asymptomatic Severe AS**

A major clinical challenge is to manage asymptomatic patients with severe AS when the lack of clinical symptoms and echocardiographic findings do not support AVR per guidelines. The physician has to weigh the individual patient risks for AVR surgery versus watchful

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**Figure 1** Velocity-Encoded Phase Contrast Magnetic Resonance Imaging in Aortic Stenosis

Sampling planes in the left ventricular outflow tract and after the aortic valve allow measurement of quantitative flow by velocity time integration (gray area under the curve). Functional aortic valve area is then calculated by continuity equation. Adapted, with permission, from Caruthers et al. (62).
waiting with potential risk of sudden cardiac death or AVR at a more advanced age (71). Identifying at-risk patients would allow optimized AVR timing and “controlled” anticipation of AVR, while meeting the goals of avoiding unnecessary surgery and improving long-term mortality. The following section will elucidate the current concepts of risk estimation in patients with asymptomatic severe AS. Table 3 summarizes the predictors for symptoms, outcome, and operative mortality.

**Predictors of Symptom Development**

**Electrocardiography.** In a multivariate analysis, LV hypertrophy defined by Romhilt and Estes criteria (72) was found to be an independent predictor for the development of symptoms in asymptomatic severe AS patients (hazard ratio [HR]: 1.39; 95% confidence interval [CI]: 1.02 to 1.89; p = 0.04) (14). The sensitivity for detecting LV hypertrophy by electrocardiogram, however, might be as low as 40%.

**Echocardiography.** Patients with asymptomatic severe AS and a peak aortic jet velocity ≥4.5 m/s are more likely to develop symptoms compared with patients with a peak aortic jet velocity <4.5 m/s (relative risk [RR]: 1.34; 95% CI: 1.04 to 1.72; p = 0.03) (14). The same investigators showed that: 1) each 0.2-cm² decrease in AVA translates into an RR of 1.26 likelihood of developing symptoms (95% CI: 1.08 to 1.47; p = 0.004); and 2) AVA is an independent predictor for the development of symptoms (HR: 0.33 for a 1-cm² increase; 95% CI: 0.15 to 0.71; p = 0.005) (14). Although these data allow risk estimation of symptom development, there are no echocardiographic parameters to estimate the timing of symptom onset.

**Exercise stress testing.** Das et al. (73) prospectively evaluated 125 patients with asymptomatic mild (n = 11), moderate (n = 62), and severe AS (n = 52) to assess the accuracy of treadmill exercise testing in predicting symptom onset within 12 months. Twenty-one patients with a positive stress test met the combined end points of spontaneous exertional symptoms or cardiac death. Symptom-free survival at 12 months was 49% versus 89% for patients with a symptom limited exercise test compared with those without a symptom limited exercise test. In a multivariate analysis only the development of symptoms during stress testing was found to predict symptom onset within 12 months (odds ratio [OR]: 7.7; 95% CI: 2.79 to 21.39; p < 0.001). Analysis of the patient subgroup with severe AS
(n = 52) showed a positive and negative predictive accuracy of 65% and 73%, respectively, for subsequent symptom development after a symptom limited exercise test. Interestingly, however, the type of exercise-induced symptom seems to be important: compared with breathlessness or chest tightness, exertional dizziness seems to be a relatively

### Table 3  Predictors of High-Risk Patients With Asymptomatic Severe AS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistical Test</th>
<th>Result</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom predictor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV hypertrophy by ECG (14)</td>
<td>Present</td>
<td>HR</td>
<td>1.39</td>
<td>1.02-1.89</td>
</tr>
<tr>
<td>Peak aortic jet velocity (14)</td>
<td>≥4.5 m/s</td>
<td>RR</td>
<td>1.34</td>
<td>1.04-1.72</td>
</tr>
<tr>
<td>AVA decrease (14)</td>
<td>Per 0.2 cm²</td>
<td>RR</td>
<td>1.26</td>
<td>1.08-1.47</td>
</tr>
<tr>
<td>AVA (14)</td>
<td>Per 1 cm²</td>
<td>HR</td>
<td>0.33</td>
<td>0.15-0.71</td>
</tr>
<tr>
<td>Exercise stress test (73)</td>
<td>Positive</td>
<td>OR</td>
<td>7.7</td>
<td>2.79-21.39</td>
</tr>
<tr>
<td>N-terminal BNP (75)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome predictor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (11)</td>
<td>&gt;50 yrs</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline functional status score (43)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline aortic jet velocity (14)</td>
<td>≥4.5 m/s</td>
<td>RR</td>
<td>1.48</td>
<td>1.20-1.81</td>
</tr>
<tr>
<td>Rate of aortic jet velocity change over time (11)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF (42)</td>
<td>&lt;50%</td>
<td>RR</td>
<td>5.6</td>
<td>1.46-21.3</td>
</tr>
<tr>
<td>AVA decrease (14)</td>
<td>Per 0.2 cm²</td>
<td>RR</td>
<td>1.2</td>
<td>1.06-1.36</td>
</tr>
<tr>
<td>Stroke-work loss index (77)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise stress test (78)</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting to peak exercise mean aortic transvalvular gradient (79)</td>
<td>&gt;18 mm Hg</td>
<td>RR</td>
<td>1.06</td>
<td>1.02-1.10</td>
</tr>
<tr>
<td>Aortic valve calcification by EBCT (80)</td>
<td>Per 100 AU</td>
<td>RR</td>
<td>1.06</td>
<td>1.02-1.10</td>
</tr>
<tr>
<td><strong>Outcome predictor low-gradient AS</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Contractile reserve (106)</td>
<td>Present</td>
<td>HR</td>
<td>0.4</td>
<td>0.23-0.69</td>
</tr>
<tr>
<td>BNP (108)</td>
<td>≥550 pg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Operative mortality predictor low-gradient AS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractile reserve (106)</td>
<td>Absent</td>
<td>OR</td>
<td>10.9</td>
<td>2.6-43.4</td>
</tr>
<tr>
<td>Baseline mean transaortic gradient (106)</td>
<td>≤20 mm Hg</td>
<td>OR</td>
<td>4.7</td>
<td>1.1-21</td>
</tr>
</tbody>
</table>

Numbers in parentheses are the respective references.

† = increase; ‡ = decrease; AS = aortic stenosis; AU = Agatston unit; AVA = aortic valve area; BNP = brain natriuretic peptide; EBCT = electron beam computed tomography; ECG = electrocardiography; HR = hazard ratio; LV = left ventricular; LVEF = left ventricular ejection fraction; NA = data not available; OR = odds ratio; RR = relative risk.
reliable marker for subsequent symptom development (54% vs. 50% vs. 83%). Breathlessness and chest tightness seem to be nonspecific symptoms secondary to physical fitness and exercise tolerance rather than AS. Accordingly, stress testing has been found to be of higher diagnostic value in patients ≤70 years old in specific activity scale class I (patient can complete any activity requiring ≥7 metabolic equivalents [74]) (Table 4).

Cardiac biomarkers. Bergler-Klein et al. (75) reported that asymptomatic severe AS patients with brain natriuretic peptide (BNP) or N-terminal BNP concentrations of <130 pg/ml and 80 pmol/l, respectively, had a 9-month symptom-free survival of close to 90%. Patients with higher natriuretic peptide concentrations frequently required surgery (symptom-free survival <50%). Kaplan-Meier analysis in patients with BNP levels <130 pg/ml (n = 25) versus ≥130 pg/ml (n = 18) showed symptom-free survival of 100% versus 94 ± 5% at 3 months, 90 ± 7% versus 64 ± 12% at 6 months, 90 ± 7% versus 45 ± 14% at 9 months, and 66 ± 16% versus 34 ± 14% at 12 months (p < 0.05). Only N-terminal BNP independently predicted symptom-free survival. Asymptomatic status was defined as freedom of shortness of breath, angina, dizziness, and syncope with exertion and symptom status assessed blinded to the results of BNP and N-terminal BNP. Serial measurements of these markers might therefore add incremental information to help to identify optimal AVR timing (15).

Predictors of Clinical Outcome

Clinical parameters. Age: event-free survival (AVR, cardiac death, noncardiac death) for patients with asymptomatic severe AS and age 50 years or younger has been found to be significantly higher (85 ± 6% vs. 59 ± 6% at 1 year, 69 ± 8% vs. 49 ± 6% at 2 years, and 59 ± 9% vs. 21 ± 5% at 4 years [p < 0.001]) (11). Baseline functional status score: in a multivariate regression analysis model, Otto et al. (43) showed that the baseline Functional Status Questionnaire (76) score was predictive of clinical outcome (p = 0.002) (43). Patients who remained asymptomatic during follow-up had a significantly higher baseline and final Functional Status Questionnaire score (96 ± 7%; 95 ± 7%) compared with those meeting a clinical end point (92 ± 2%; 85 ± 16%) (patient population included asymptomatic patients with less than severe AS and BAV disease) (43).

Echocardiography. Baseline aortic jet velocity, the rate of change over time in aortic jet velocity, and baseline AVA have been found to predict clinical outcome (AVR, cardiac death) (43).

Patients with a baseline aortic jet velocity below 3.0 m/s and between 3.0 and 4.0 m/s have a 2-year event-free survival (without AVR) of 84 ± 16% and 66 ± 13%, respectively. Patients with an aortic jet velocity >4.0 m/s had a 21 ± 18% likelihood of being alive at 2 years (patient population included asymptomatic patients with less than severe AS and BAV disease) (43). Compared with patients with asymptomatic severe AS and a peak aortic jet velocity <4.5 m/s, patients with asymptomatic severe AS and a peak aortic jet velocity of ≥4.5 m/s have an increased RR of a cardiac event (AVR; cardiac death; RR: 1.48; 95% CI: 1.20 to 1.81; p = 0.0002) (14).

Aortic-jet velocity progression is significantly higher in patients with asymptomatic severe AS and cardiac events (AVR; cardiac death; noncardiac death) compared with those without a cardiac event (0.45 ± 0.38 m/s/year versus 0.14 ± 0.18 m/s/year, p < 0.001) (11).

Patients with asymptomatic severe AS and a reduced LVEF (<50%) have been found to have a higher RR of sustaining cardiac events (AVR; cardiac death second to AS; RR: 5.6; 95% CI: 1.46 to 21.3; p = 0.01) (42).

With regard to AVA, the RR of a cardiac event (AVR; cardiac death) has been found to increase per 0.2-cm² decrease in AVA (RR: 1.20; 95% CI: 1.06 to 1.36; p = 0.006) (14).

Event-free survival (AVR; cardiac death; noncardiac death) for patients without or with mild calcification versus patients with moderate or severe calcification has been found to be 92 ± 5% versus 60 ± 6% at 1 year, 84 ± 8% versus 47 ± 6% at 2 years, and 75 ± 9% versus 20 ± 5% at 4 years (p < 0.001) (11).

Stroke-work loss, the ratio of the mean transvalvular pressure gradient and LV pressure, has also been proposed to predict cardiac events (AVR; cardiac death) in asymptomatic AS patients. A stroke-work loss >26% results in a probability of cardiac death or AVR of >30% in the following 3 months (77).

Exercise stress testing. Several studies have evaluated the value of exercise stress testing in predicting clinical outcome in asymptomatic severe AS (Table 5). Amato et al. (78) prospectively followed 66 patients with asymptomatic severe AS (AVA ≤1.0 cm²) for a mean follow-up of 15 ± 12
months. Patients with a positive stress test (n = 44) had a 2-year event-free survival of only 19% compared with 85% if symptom-free during exercise. It is important to point out that event-free survival was defined as absence of symptoms in daily life and/or sudden death. Thirty-five patients met the combined end points (symptom development n = 31; sudden cardiac death n = 4). Positive and negative predictive values for a positive stress test and subsequent end point development were 0.79 and 0.86, respectively. The estimated risk to reach the combined end point for patients with a positive stress test and subsequent end point development was 7.6 times higher than in patients with a negative stress test. Every patient who died during the study follow-up had an event-free survival at 5 years was 92% versus 40% ± 18% comparing patients with calcification below and above 500 Agatston units, respectively (p = 0.0002). Aortic valve calcification also independently predicted event-free survival in patients with no or minimal symptoms (RR: 1.09/100 Agatston units; 95% CI: 1.05 to 1.15; p < 0.0001). Data further supporting the predictive value of calcification were recently reported by Feuchter et al. (81). Electron-beam computed tomography offers the advantage of objective calcification quantification (in Agatston units) as compared with the subjective grading by echocardiography.

When interpreting predictors of clinical outcome it is important to remember that survival outcomes included AVR as a clinical event, creating the conundrum that AVR is predictive of AVR.

### Management of Patients With Asymptomatic Severe AS

Onset of symptoms in a patient with AS who has been previously asymptomatic, if unnoticed even only for a few months, carries a bleak prognosis (6,13). Therefore, every patient with asymptomatic severe AS should be educated and advised to self-report onset of new symptoms (10). Some patients might subconsciously adapt and reduce their daily activities, and in these spuriously “asymptomatic” AS patients exercise stress testing has been shown to uncover symptoms in more than one-third of patients (73). There are, however, caveats in exercise stress testing symptom interpretation: 1) concurrent or unsuspected coronary artery disease potentially mimics AS symptoms (angina) (10); and 2) physical fitness influences reliable AS symptom interpretation. Close clinical follow-up in any patient with asymptomatic severe AS is recommended (6 to 12 months), and if there is no echocardiographic evidence of rapid progression

### Table 5

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age (yrs)</th>
<th>AS Grading</th>
<th>Test Modality</th>
<th>Criteria for Positive Stress Test</th>
<th>Follow-Up (Months)</th>
<th>Combined End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lancellotti et al. (79)</td>
<td>69</td>
<td>66 ± 12</td>
<td>AVA ≤1 cm²</td>
<td>Semi-supine bicycle on tilting table</td>
<td>≥1 of: angina; dyspnea; ≥2 mm ST-segment depression; fall or small rise in SBP compared with baseline (&lt; 20 mm Hg); significant arrhythmias</td>
<td>15 ± 7</td>
<td>Angina; dyspnea; syncope; hospital admission for heart failure; cardiac death; need for AVR</td>
</tr>
<tr>
<td>Das et al. (73)</td>
<td>125</td>
<td>65 (range: 56–74)</td>
<td>Mild (n = 11; EOA &gt; 1.2 cm²); moderate (n = 62; EOA 0.8–1.2 cm²); severe (n = 52; EOA &lt; 0.8 cm²)</td>
<td>Treadmill</td>
<td>Stopped prematurely due to: breathlessness; chest discomfort; dizziness; ST-segment depression &gt; 5 mm; &gt;3 consecutive VPCs; SBP decline &gt; 20 mm Hg from baseline</td>
<td>12</td>
<td>Spontaneous exertional symptoms or CV death</td>
</tr>
<tr>
<td>Amato et al. (78)</td>
<td>66</td>
<td>49 ± 14.9</td>
<td>AVA ≤1 cm²</td>
<td>Treadmill with mobile ramp</td>
<td>Horizontal or downsloping ST-segment depression ≥ 1 mm in men or ≥ 2 mm in women, or an upsloping ST-segment depression ≥ 3 mm in men; precordial chest pain or near syncope; complex ventricular arrhythmias; SBP raise from baseline &gt; 20 mm Hg</td>
<td>15 ± 12</td>
<td>Symptoms in daily life and/or sudden death</td>
</tr>
</tbody>
</table>

If available, data are presented as mean ± SD.

AS = aortic stenosis; AVA = aortic valve area; AVR = aortic valve replacement; CV = cardiovascular; EOA = effective orifice area; SBP = systolic blood pressure; VPC = ventricular premature contraction.
in 2 independent evaluations performed 6 months apart, patients should continue to follow up clinically with an annual echocardiographic examination. Expedited patient re-evaluation is warranted if there is a change in clinical status (10,82). Hypertension is common in patients with severe AS (approximately 30%) and should be aggressively treated in patients with asymptomatic AS (83). There is limited information regarding the role of statin therapy in delaying progression of asymptomatic AS (26–30). Two large, multicenter, double blinded, randomized, placebo-controlled trials—1) SEAS (Simvastatin and Ezetimibe in AS) and 2) ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effect of Rosuvastatin)—will hopefully clarify the role of statins in calcific AS.

Figure 4 provides a suggested stepwise approach in managing patients with asymptomatic severe AS on the basis of current American (American College of Cardiology/American Heart Association [ACC/AHA]) (10) and European (European Society of Cardiology) (84) AVR guidelines. It is worthwhile pointing out that even the recommendations with current best evidence are mainly based on expert consensus and/or small studies, retrospective studies, and registries.

Benefits, Risks, and Alternatives to AVR

Pre-emptive AVR in asymptomatic severe AS could theoretically reduce progressive myocardial dysfunction, which...
has been shown to be a predictor of heart failure and death after AVR (85). Iung et al. (86) speculated that nearly one-third of patients with symptomatic severe, single-valve heart disease who could benefit from AVR do not undergo surgical repair. Timely surgery at an asymptomatic stage could therefore potentially reduce the likelihood of being deemed a nonsurgical candidate when symptomatic.

Potential benefits of AVR in asymptomatic severe AS have to be weighed against short-term perioperative risks and the long-term risks of thromboembolism, anticoagulation-related bleeding, and infective endocarditis. Although no intervention, but observation only, has low risks (sudden cardiac death <1%/year), average surgical mortality for isolated AVR is approximately 3% to 4% (86) and 1% to 2% in high-volume and experienced medical centers (10). Surgical mortality, however, increases progressively with age and is up to 9% in octogenarians (87–92). Additional factors can further increase the risk of operative mortality in asymptomatic severe AS (e.g., emergent surgery, LV dysfunction, pulmonary hypertension, coexisting coronary artery disease, and previous bypass or valve surgery) (84). The ACC/AHA guidelines make the choice of AVR prosthesis type dependent on concurrent mitral or tricuspid mechanical valve, anticoagulation contraindications, thrombosis risk, and patient preferences (10). The incidence of thromboembolism and bleeding related to anticoagulation in the setting of a mechanical aortic valve prosthesis is 1.1 and 4.6/100 patient-years, respectively (93), with the latter increasing significantly if patients are ≥75 years of age (94). The incidence of infective endocarditis has been reported to be 0.27%/patient-year (95). These specific incidence rates, however, vary depending on the type of mechanical aortic valve prosthesis (96). Bioprosthetic aortic valves have the main risk of structural valve degeneration and therefore reduced valve life. Interestingly, however, a recent meta-analysis did not find any differences in mortality in patients with mechanical or bioprosthetic aortic valves (97). A bioprosthetic aortic valve is currently a reasonable choice in adult patients (approximately 65 years of age) who have contraindications to anticoagulation or who decline or do not require anticoagulation (10).

Aortic balloon valvotomy as an alternative to AVR is associated with significant procedural risk (98) and restenosis (99) and is currently only recommended for the unstable, severely comorbid adult patient with severe AS (10). In contrast, percutaneous AVR has attracted an unprecedented interest (100). One can speculate that the role of percutaneous AVR might be expanded to patients with asymptomatic severe AS who are “assumed” to be high-risk candidates for surgical AVR; however, this will need to be addressed in future studies.

Selected Clinical Scenarios

The asymptomatic patient with less than severe AS. Management of the asymptomatic patient with less than severe AS is challenging, and evidence to support “pre-emptive” AVR is limited. Current guidelines support AVR during coronary artery bypass grafting or ascending aorta surgery in: 1) patients with asymptomatic moderate AS (Class IIa–B); and 2) patients with mild AS and potential rapid AS progression (Class IIb–C) (10). Serial echocardiographic examinations might identify such “rapid progressors,” a high-risk group of patients with moderately or severely calcified aortic valves in whom aortic jet velocity increases by 0.3 m/s within 1 year (2-year risk of AVR or death of 79%) (11). The comorbid patient. Patients with asymptomatic and moderate-to-severe AS and progressive medical comorbidities (e.g., advanced age and impaired renal function) might be deemed inoperable once AVR is indicated (86). Pre-emptive AVR might be justified in some of these patients even at an asymptomatic stage. However, management strategies should be based on thorough risk estimation in regard to symptom development and AS progression (“rapid progressors”), medical center experience and surgery volume, and potential post-AVR benefit (e.g., reversibility/stabilization of renal function).

The patient in need of noncardiac surgery. Patients with asymptomatic severe AS who require emergent noncardiac surgery should proceed without AVR evaluation; in elective noncardiac surgery AVR management is dependent on coronary artery status (101). Depending on the type of noncardiac surgery and need for anticoagulation, AVR might be performed pre-emptively or simultaneously.

BAV disease. BAV disease is a disease of the aortic valve and ascending aorta (102) and frequently progresses to AS (18,103). Ascending aortic dilation is independent of AS severity (102) and affects up to 4 of 10 BAV patients over time (104). The most severe risk of aortic dilation, aortic dissection, has been reported to be 9 times higher in BAV compared with patients with tricuspid aortic valves (105). Evidence is scarce, but it seems reasonable to manage BAV patients similar to their tricuspid counterparts with the following additional criteria for follow-up of ascending aorta dilation. Aortic valve replacement should be considered if indicated by ACC/AHA (10) and European Society of Cardiology (84) guidelines with the addition of aortic root repair or ascending aorta replacement if more than 4.5 cm in diameter. Conversely, the aortic valve should be replaced in an asymptomatic patient with moderate or severe AS if aortic root repair or ascending aorta replacement is indicated due to ascending aorta diameter (>5.0 cm) or diameter increase by 0.5 cm/year or more (cut-off values should be adjusted depending on body stature) (10).

Low-gradient/low-flow AS. Patients with severe AS might have low-flow/low-gradient (<40 mm Hg) AS in the setting of reduced LVEF or preserved LVEF. Patients with severe AS and reduced LVEF are rarely asymptomatic, and therefore most of the available management data are derived from symptomatic patients (106–108). In patients with reduced LVEF it is important to determine whether the compromised LV function is attributable to a primary cardiomyopathy (e.g., scarred, fibrosed myocardium), isch-
such patients must be closely monitored by regular clinical
examinations. Low-dose dobutamine stress hemodynamic
ecocardiography (≥20 μg/kg/min) identifies these patients
demonstrating contractile reserve (CR) (defined as a ≥20% stroke volume increase from baseline on the basis of
LV outflow Doppler measurements [109]) and transvalvular
gradient increase (confirming severe AS). Monin et al.
(106) reported that presence of LV contractile reserve is
predictive for long-term survival (HR: 0.40; 95% CI: 0.23 to
0.69; p = 0.001). Absence of contractile reserve (OR: 10.9;
95% CI: 2.6 to 43.4; p = 0.001) and a baseline mean transaortic gradient ≤20 mm Hg (OR: 4.7; 95% CI: 1.1 to
21.0; p = 0.04) predicted perioperative mortality. Evidence
for contractile reserve resulted in reduced pre-operative
morality (CR+ vs. CR−: 5% vs. 32%) (106). Recovery of
LVEF and post-operative 2-year survival in the absence
of baseline contractile reserve, however, resembles that of
patients with contractile reserve once patients survive 30
days after surgery (107). Therefore, AVR should not be
contraindicated on the basis of documentation of exhausted
contractile reserve alone. Bergler-Klein et al. (108) evaluated
the prognostic value of BNP in 69 patients with low-flow,
low-gradient AS, 7 (10%) of whom were New York Heart
Association functional class I. One year after AVR, survival
was markedly lower in patients with BNP ≥550 pg/ml
(53 ± 13% vs. 92 ± 7%). Thus, BNP ≥550 pg/ml emerged
as a significant predictor of outcome (p < 0.001). One has
to note that patient numbers were low (n = 29), allowing
only univariate analysis of BNP as a predictor of outcome.
Nevertheless, these results could support AVR in patients
with asymptomatic AS and reduced LVEF, even in the
absence of contractile reserve if BNP levels are ≥550 pg/ml.

Low-flow severe AS patients have increased global LV
afterload leading to pronounced LV concentric remodeling
and a preserved LVEF, concealing impaired myocardial
function (110). In this patient group, low stroke volumes
reveal myocardial dysfunction and, due to reduced mean
and maximal flow velocities and gradients (111), might lead to
discrepancy low mean transvalvular gradients compared
with AVA (112). The exact prevalence and management of
asymptomatic patients with low-flow/low-gradient, severe
AS and preserved LVEF is less clear. However, a recent
retrospective study by Hachicha et al. (113) reported that
AVR in these patients led to significantly improved survival
and was preferable to medical treatment. The exact rele-
ance of this finding for patients with asymptomatic severe
AS who have low flow despite preserved LVEF remains to
be established.

Summary
In asymptomatic patients with severe AS, AVR mortality
and the yearly risks of prosthetic valve complications are
greater than the yearly risks of watchful waiting. However,
such patients must be closely monitored by regular clinical
and echocardiographic follow-up and should be educated
regarding symptom recognition and prompt self-reporting.
Exercise stress testing should be considered if symptom
status is unclear. Expedited AVR seems reasonable in
patients with a higher risk profile (extensive aortic valve
calcification, rapid aortic jet progression on serial echocar-
diograms, concomitant coronary artery disease, LV systolic
dysfunction, elevated BNP levels, and in some cases before
referral for major elective noncardiac surgery). Pre-emptive
AVR might emerge as the treatment of choice in the future;
however, this will be dependent on the (yet unproven)
superiority of noninvasive myocardial function assessment
and advances in prosthetic aortic valve design and percuta-
neous valve placement.

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Key Words: aortic stenosis • asymptomatic • management • outcome • predictor • severe.