Valvular Aortic Stenosis in the Elderly

Wilbert S. Aronow, MD, FACC, FAHA

Abstract: Elderly patients with valvular aortic stenosis have an increased prevalence of coronary risk factors, of coronary artery disease, and evidence of other atherosclerotic vascular diseases. Statins may reduce the progression of aortic stenosis (AS). Angina pectoris, syncope or near syncope, and congestive heart failure are the 3 classic manifestations of severe AS. Prolonged duration and late peaking of an aortic systolic ejection murmur best differentiate severe AS from mild AS on physical examination. Doppler echocardiography is used to diagnose the prevalence and severity of AS. The indications for cardiac catheterization and the medical management of AS are discussed. Once symptoms develop, aortic valve replacement (AVR) should be performed in patients with severe or moderate AS. Other indications for AVR are discussed. Warfarin should be administered indefinitely after AVR in patients with a mechanical aortic valve and in patients with a bioprosthetic aortic valve who have either atrial fibrillation, prior thromboembolism, left ventricular systolic dysfunction, or a hypercoagulable condition. Patients with a bioprosthetic aortic valve without any of these 4 risk factors should be treated with aspirin 75–100 mg daily.

Key Words: aortic stenosis, Doppler echocardiography, heart failure, angina, syncope, cardiovascular surgery, coronary artery disease, heart murmurs, mechanical prosthetic valve, porcine bioprosthesis, anticoagulant therapy, aspirin

(*Cardiology in Review* 2007;15: 217–225)

Aortic stenosis (AS) is a major cause of cardiovascular morbidity in older subjects. In this article, the etiology, epidemiology, and pathophysiology of AS are discussed, along with the various therapeutic options that are available to treat this cardiac condition.

ETIOLOGY AND PREVALENCE

Valvular aortic stenosis (VAS) in elderly patients is usually due to stiffening, scarring, and calcification of the aortic valve leaflets. The commissures are not fused as in rheumatic AS. Calcific deposits in the aortic valve are common in elderly persons and may lead to VAS.[1–7] Aortic cuspal calcium was present in 295 of 752 men (36%), mean age 80, and in 672 of 1663 women (40%), mean age 82.[6] Of 2358 patients, mean age 81, 378 (16%) had VAS, 981 (42%) had valvular aortic sclerosis (thickening of or calcific deposits on the aortic valve cusps with a peak flow velocity across the aortic valve $\leq$1.5 m/s), and 999 (42%) had no VAS or aortic sclerosis.[7] Calcific deposits in the aortic valve were present in 22 of 40 necropsy patients (55%) age 90–103.[2] Calcium of the aortic valve and mitral annulus may coexist.[1–3,8,9]

In the Helsinki Aging study, calcification of the aortic valve was diagnosed by Doppler echocardiography in 28% of 76 patients age 55–71, in 48% of 197 patients age 75–76, in 55% of 155 patients age 80–81, and in 75% of 124 patients age 85–86.[5] Aortic valve calcification, aortic sclerosis, and mitral annular calcium are degenerative processes,[1,2,10–12] accounting for their high prevalence in an older population.

Otto et al[11] showed that the early lesion of degenerative AS is an active inflammatory process with some similarities to atherosclerosis, including lipid deposition, macrophage and T-cell infiltration, and basement membrane disruption. In a prospective study of 571 unselected patients, mean age 82, 292 patients (51%) had calcified or thickened aortic cusps or root.[13] A serum total cholesterol $\geq$200 mg/dL, diabetes mellitus, a history of hypertension, and a serum high-density lipoprotein (HDL)-cholesterol $<$35 mg/dL were more prevalent in elderly patients with calcified or thickened aortic cusps or root than in elderly patients having normal aortic cusps and root.

In the Helsinki Aging Study, age, hypertension, and a low body mass index were independent predictors of aortic valve calcification.[14] In 5201 patients more than 65 years old in the Cardiovascular Health Study, independent clinical factors associated with degenerative aortic valve disease included age, male gender, smoking, history of hypertension, height, and high lipoprotein (a) and low-density lipoprotein (LDL)-cholesterol levels.[12] In 1275 elderly patients, mean age 81, AS was present in 52 of 202 patients (26%) with 40–100% extracranial carotid arterial disease and in 162 of 1073 patients (15%) with 0–39% extracranial carotid arterial disease.[15] Adler et al[16] also demonstrated a significant association between aortic valve calcium and carotid atherosclerotic disease. In 2987 elderly patients, mean age 81, symptomatic peripheral arterial disease was present in 193 of 462 patients (42%) with AS and in 639 of 2525 patients (25%) without AS.[17]

In 290 patients, mean age 79, with VAS who had follow-up Doppler echocardiograms, elderly patients with mitral annular calcium had a greater reduction in aortic valve area per

From the Cardiology Division, Department of Medicine, New York Medical College, Valhalla, New York.
Correspondence: Wilbert S. Aronow, MD, Cardiology Division, New York Medical College, Macy Pavilion, Room 138, Valhalla, NY 10595. E-mail: wsaronow@aol.com.

ISSN: 1061-5377/07/1505-0217
DOI: 10.1097/CRD.0b013e31805f6796

year than elderly patients without mitral annular calcium.[18] There was a reduction in aortic valve area of 0.12 cm^2/y after 36-month follow-up in patients with mild aortic stenosis, of 0.11 cm^2/y after 30-month follow-up in patients with moderate aortic stenosis, and of 0.11 cm^2/y after 15-month follow-up in patients with severe AS.[18]

Significant independent risk factors for progression of VAS in 102 patients, mean age 76, who had follow-up Doppler echocardiograms were cigarette smoking and hypercholesterolemia.[19] Palta et al[20] also found that cigarette smoking and hypercholesterolemia accelerate the progression of AS. These and other data suggest that aortic valve calcium, mitral annular calcium, and coronary atherosclerosis in elderly patients have similar predisposing factors.[11–22]

A retrospective analysis of 180 elderly patients with mild AS who had follow-up Doppler echocardiograms at ≥2 years showed at 33-month follow-up that if the initial serum LDL-cholesterol was >125 mg/dL, the increase in peak systolic gradient across the aortic valve each year was 6.3 mm Hg in patients not treated with statins compared with 3.4 mm Hg in patients treated with statins.[23] Significant independent predictors of the progression of AS were male gender, cigarette smoking, hypertension, diabetes mellitus, a serum low-density lipoprotein cholesterol ≥125 mg/dL at follow-up, a serum HDL-cholesterol <35 mg/dL at follow-up, and use of statins (inverse association).[23]

Novaro et al[24] reported in a retrospective analysis of 174 patients, mean age 68, with mild-to-moderate AS that statin therapy reduced the progression of AS. In a retrospective study of 156 patients, mean age 77, with AS, at 3.7-year follow-up statin therapy reduced the progression of AS by 54%.[25] Pai et al[26] found in their database that 99 of 338 patients (29%), mean age 71, with asymptomatic severe AS had aortic valve replacement (AVR) during the 3.5-year follow-up. Unoperated patients treated with statins had a significant 48% reduction in mortality, and unoperated patients treated with β-blockers had a significant 48% reduction in mortality.[26]

In an open-label, prospective study of 121 patients, mean age 74, with an aortic valve area between 1.0 and 1.5 cm^2, 61 patients with a serum LDL-cholesterol >130 mg/dL were treated with rosuvastatin, and 60 patients with a serum LDL-cholesterol <130 mg/dL did not receive statin therapy.[27] At 73-week follow-up, there was significantly less progression of AS in patients treated with rosuvastatin.[27] These data differ from the results reported in 155 patients in the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression study, which included patients with an average aortic valve area of 1 cm^2 and extensive calcification of the aortic valve.[28]

Many patients with AS will be treated with statins because they have coronary artery disease (CAD), other atherosclerotic vascular disease, or diabetes mellitus, and will be treated according to the updated National Cholesterol Education Program III guidelines.[29] There is need for data from a long-term, large, prospective, randomized controlled trial of intensive statin therapy in patients with AS, especially in patients with mild AS. The Simvastatin and Ezetimibe in Aortic Stenosis trial, currently in progress, is randomizing 1800 patients with asymptomatic AS to simvastatin 40 mg daily and ezetimibe 10 mg daily versus placebo to determine the effect of lipid-lowering therapy on mortality or the need for aortic valve surgery.[30]

The frequency of AS increases with age.[5,31,32] VAS diagnosed by Doppler echocardiography was present in 141 of 924 men (15%), mean age 80, and in 322 of 1881 women (17%), mean age 81.[31] Severe VAS (peak gradient across aortic valve of ≥50 mm Hg or aortic valve area <0.75 cm^2) was diagnosed in 62 of 2805 elderly patients (2%).[31] Moderate VAS (peak gradient across aortic valve of 26 to 49 mm Hg or aortic valve area of 0.75 to 1.49 cm^2) was present in 149 of 2805 elderly patients (5%).[31] Mild VAS (peak gradient across aortic valve of 10 to 25 mm Hg or aortic valve area ≥1.50 cm^2) occurred in 25 of 2805 elderly patients (9%).[31] In 924 elderly men, mean age 80, AS was present in 36 of 236 African Americans (15%), in 19 of 135 Hispanics (14%), and in 86 of 553 whites (16%).[31] In 1881 elderly women, mean age 81, AS was present in 84 of 494 African Americans (17%), in 33 of 188 Hispanics (18%), and in 205 of 1199 white women (17%).[31] In 501 unselected patients age 75–86 in the Helsinki Aging Study, critical AS was present in 3% and moderate-to-severe AS in 5% of the 501 elderly patients.[5]

PATHOPHYSIOLOGY

In VAS there is resistance to ejection of blood from the left ventricle (LV) into the aorta, with a pressure gradient across the aortic valve during systole and an increase in LV systolic pressure. The pressure overload on the LV leads to concentric LV hypertrophy (LVH), with an increase in LV wall thickness and mass, normalizing systolic wall stress, and maintenance of normal LV ejection fraction (LVEF) and cardiac output.[33,34] A compensated hyperdynamic response is common in elderly women.[35] Elderly patients with a comparable degree of AS have more impairment of LV diastolic function than do younger patients.[36] Coronary vasodilator reserve is more severely impaired in the subendocardium in patients with LVH caused by severe AS.[37]

The compensatory concentric LVH leads to abnormal LV compliance, LV diastolic dysfunction with reduced LV diastolic filling, and increased LV end-diastolic pressure, further increased by left atrial systole. Left atrial enlargement develops. Atrial systole plays an important role in diastolic filling of the LV in patients with AS.[38] Loss of effective atrial contraction may cause immediate clinical deterioration in patients with severe AS.

Sustained LVH eventually leads to LV chamber dilatation with decreased LVEF and, ultimately, congestive heart failure (CHF). The stroke volume and cardiac output decrease, the mean left atrial and pulmonary capillary pressures increase, and pulmonary hypertension occurs. Elderly patients with both obstructive and nonobstructive CAD have an increased incidence of LV enlargement and LV systolic dysfunction.[39] In a percentage of elderly patients with AS, the LVEF will remain normal and LV diastolic dysfunction will be the main problem.

In 48 elderly patients with CHF associated with unoperated severe VAS, the LVEF was normal in 30 patients (63%).[40] The prognosis of patients with AS and LV diastolic

dysfunction is usually better than that of patients with AS and LV systolic dysfunction, but is worse than that of patients without LV diastolic dysfunction.[40,41]

SYMPTOMS

Angina pectoris, syncope or near syncope, and CHF are the 3 classic manifestations of severe AS. Angina pectoris is the most common symptom associated with AS in elderly patients. Coexistent CAD is frequently present in these patients. However, angina pectoris may occur in the absence of CAD as a result of an increase in myocardial oxygen demand with a reduction in myocardial oxygen supply at the subendocardial level. Myocardial ischemia in patients with severe AS and normal coronary arteries is due to inadequate LVH with increased LV systolic and diastolic wall stresses causing a reduced coronary flow reserve.[42] Of 160 patients with AS and angina pectoris, 91 (57%) did not have CAD.[43]

Syncope in patients with AS may be caused by decreased cerebral perfusion after exertion when arterial pressure drops because of systemic vasodilatation in the presence of a fixed cardiac output. LV failure with a decrease in cardiac output may also cause syncope. In addition, syncope at rest may be caused by a marked reduction in cardiac output secondary to transient ventricular fibrillation or transient atrial fibrillation or transient atrioventricular block related to extension of the valve calcification into the conduction system. Coexistent cerebrovascular disease with transient cerebral ischemia may contribute to syncope in elderly patients with AS.

Exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and pulmonary edema may be caused by pulmonary venous hypertension associated with AS. Coexistent CAD and hypertension may contribute to CHF in elderly patients with AS. Atrial fibrillation may also precipitate CHF in these patients.

CHF, syncope, or angina pectoris was present in 36 of 40 elderly patients (90%) with severe AS, in 66 of 96 elderly patients (69%) with moderate VAS, and in 45 of 165 elderly patients (27%) with mild VAS.[44]

Sudden death occurs mainly in symptomatic VAS patients.[40,44–47] It may also occur in 3–5% of asymptomatic patients with AS.[45,47] Marked fatigue and peripheral cyanosis in patients with AS may be caused by a low cardiac output. Cerebral emboli causing stroke or transient cerebral ischemic attack, bacterial endocarditis, and gastrointestinal bleeding may also occur in elderly patients with AS.

SIGNS

A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward the apex, or at the apex is classified as an aortic systolic ejection murmur (ASEM).[3,4,48,49] An ASEM is commonly heard in elderly patients,[1,3,48] occurring in 265 of 565 unselected elderly patients (47%).[3] Of 220 elderly patients with an ASEM and technically adequate M-mode and 2-dimensional echocardiograms of the aortic valve, 207 (94%) had aortic cuspal or root calcification or thickening.[3] Of 75 elderly patients with an ASEM, valvular AS was diagnosed by continuous-wave Doppler echocardiography in 42 patients (56%).[49]

TABLE 1. Physical Signs of Valvular Aortic Stenosis Correlated With the Severity of Aortic Stenosis in Elderly Patients

	Severity of Aortic Stenosis (%)		
Physical Sign	**Mild (n = 74)**	**Moderate (n = 49)**	**Severe (n = 19)**
ASEM	95	100	100
Prolonged duration ASEM	3	63	84
Late-peaking ASEM	3	63	84
Prolonged carotid upstroke time	3	33	53
A_2 absent	0	10	16
A_2 decreased or absent	5	49	74

A_2 indicates aortic component of second heart sound.

Adapted from *Am J Cardiol*, Vol. 67, Aronow WS, Kronzon I, Prevalence and severity of valvular aortic stenosis determined by Doppler echocardiography and its association with echocardiographic and electrocardiographic left ventricular hypertrophy and physical signs of aortic stenosis in elderly patients, pages 776–777, Copyright (1991), with permission from Elsevier.[4]

Table 1 shows that an ASEM was heard in 100% of 19 elderly patients with severe AS, in 100% of 49 elderly patients with moderate AS, and in 95% of 74 elderly patients with mild AS.[4] However, the ASEM may become softer or absent in patients with CHF associated with severe AS because of a low cardiac output. The intensity and maximal location of the ASEM and transmission of the ASEM to the right carotid artery do not differentiate among mild, moderate, and severe AS.[3,4,49] The ASEM may be heard only at the apex in some elderly patients with AS. The apical systolic ejection murmur may also be louder and more musical than the basal systolic ejection murmur in some elderly patients with AS. The intensity of the ASEM in VAS increases with squatting and by inhalation of amyl nitrite, and decreases during the Valsalva maneuver.

Prolonged duration of the ASEM and late peaking of the ASEM best differentiate severe AS from mild AS.[3,4,49] However, the physical signs do not distinguish between severe and moderate AS (Table 1).[4,49]

A prolonged carotid upstroke time does not differentiate between severe and moderate AS in elderly patients.[4] A prolonged carotid upstroke time was palpable in 3% of elderly patients with mild AS, in 33% of elderly patients with moderate AS, and in 53% of elderly patients with severe AS (Table 1).[4] Stiff noncompliant arteries may mask a prolonged carotid upstroke time in elderly patients with severe AS. The pulse pressure may also be normal or wide rather than narrow in elderly patients with severe AS because of loss of vascular elasticity. An aortic ejection click is rare in elderly patients with severe AS because of loss of vascular elasticity, and because the valve cusps are immobile.[4,49]

An absent or reduced A_2 (aortic component of second heart sound) occurs more frequently in elderly patients with severe or moderate AS than in patients with mild AS (Table 1).[4,49] However, an absent or decreased A_2 does not differentiate between severe and moderate AS.[4,49] The presence of atrial fibrillation, reversed splitting of S_2, or an audible fourth heart

sound at the apex also does not differentiate between severe and moderate AS in elderly patients.[49] The presence of a third heart sound in elderly patients with AS usually indicates the presence of LV systolic dysfunction and an elevated LV filling pressure.[50]

ELECTROCARDIOGRAPHY AND CHEST ROENTGENOGRAPHY

Table 2 shows that echocardiography is more sensitive than electrocardiography in detecting LVH in an elderly person with AS.[4] Rounding of the LV border and apex may occur as a result of concentric LVH. Poststenotic dilatation of the ascending aorta is commonly seen. Calcification of the aortic valve is best seen by echocardiography or fluoroscopy.

Involvement of the conduction system by calcific deposits may occur in elderly patients with AS. In a study of 51 elderly patients with AS who underwent AVR, conduction defects occurred in 58% of 31 patients with mitral anular calcium and in 25% of 20 patients without mitral anular calcium.[9] In another study of 77 elderly patients with AS, first-degree atrioventricular block occurred in 18% of patients, left bundle branch block in 10% of patients, intraventricular conduction defect in 6% of patients, right bundle branch block in 4% of patients, and left axis deviation in 17% of patients.[51]

Complex ventricular arrhythmias may be detected by 24-hour ambulatory electrocardiograms in patients with AS. Elderly patients with complex ventricular arrhythmias associated with AS have a higher incidence of new coronary events than elderly patients with AS and no complex ventricular arrhythmias.[52]

ECHOCARDIOGRAPHY AND DOPPLER ECHOCARDIOGRAPHY

M-mode and 2-dimensional echocardiography and Doppler echocardiography are very useful in the diagnosis of AS. Of 83 patients with CHF or angina pectoris and a systolic precordial murmur in whom severe AS was diagnosed by Doppler echocardiography, AS was not clinically diagnosed in 28 patients (34%).[53] Echocardiography can detect thickening, calcification, and a reduced excursion of aortic valve leaflets.[3] LVH is best diagnosed by echocardiography.[4] Chamber dimensions and measurements of LV end-systolic and end-diastolic volumes, LVEF, and assessment of global and regional LV wall motion give important information on LV systolic function.

Doppler echocardiography is used to measure peak and mean transvalvular gradients across the aortic valve and to identify associated valve lesions. Aortic valve area can be calculated by the continuity equation using pulsed Doppler echocardiography to measure LV outflow tract velocity, continuous-wave Doppler echocardiography to measure transvalvular flow velocity, and 2-dimensional long-axis view to measure LV outflow tract area.[54,55] Aortic valve area can be detected reliably by the continuity equation in elderly patients with AS.[55]

Shah and Graham[56] reported that the agreement in quantitation of the severity of AS between Doppler echocardiography and cardiac catheterization was greater than 95%. Patients with a peak jet velocity $\geq$4.5 m/s had critical AS, and those with a peak jet velocity $<$3.0 m/s had noncritical AS. Slater et al[57] demonstrated a concordance between Doppler echocardiography and cardiac catheterization in the decision to operate or not to operate in 61 of 73 patients (84%) with VAS. In 75 patients with VAS, mean age 76, the Bland-Altman plot showed that 4 of the 75 patients (5%) had disagreement between cardiac catheterization and Doppler echocardiography that was outside the 95% confidence limits.[58] Aortic valve area measured by Doppler echocardiography and cardiac catheterization was identical in 31% of the 75 elderly patients with AS.[58]

Cardiac catheterization was performed in 105 patients in which Doppler echocardiography demonstrated an aortic valve area $\leq$0.75 cm^2 or a peak jet velocity $\geq$4.5 m/s, consistent with critical AS.[59] Doppler echocardiography was 97% accurate in this subgroup. Cardiac catheterization was performed in this study in 133 patients with noncritical AS. Doppler echocardiography was 95% accurate in this subgroup. Although most elderly patients do not require cardiac catheterization before aortic valve surgery, they require selective coronary arteriography before aortic valve surgery (Table 3).[60] Patients in whom Doppler echocardiography shows a peak jet velocity between 3.6 and 4.4 m/s and an aortic valve area $>$0.8 cm^2 should undergo cardiac catheter-

TABLE 2. Prevalence of Electrocardiographic and Echocardiographic Left Ventricular Hypertrophy (LVH) in 142 Older Patients With Mild, Moderate, and Severe Valvular Aortic Stenosis

	Severity of Valvular Aortic Stenosis (%)		
	Mild (n = 74)	Moderate (n = 49)	Severe (n = 19)
Electrocardiographic LVH	11	31	58
Echocardiographic LVH	74	96	100

Adapted from *Am J Cardiol*, Vol. 67, Aronow WS, Kronzon I, Prevalence and severity of valvular aortic stenosis determined by Doppler echocardiography and its association with echocardiographic and electrocardiographic left ventricular hypertrophy and physical signs of aortic stenosis in elderly patients, pages 776–777, Copyright (1991), with permission from Elsevier.[4]

TABLE 3. American College of Cardiology/American Heart Association Class I Indications for Cardiac Catheterization in Patients With Aortic Stenosis

1. Coronary angiography should be performed before aortic valve replacement in patients with aortic stenosis at risk for coronary artery disease
2. Cardiac catheterization for hemodynamic measurements is recommended for assessment of severity of aortic stenosis in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of aortic stenosis

Data from Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 practice guidelines for the management of patients with valvular heart disease: Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). Developed in collaboration with the Society of Cardiovascular Anesthesiologists. Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006;48:598–675.[60]

ization if they have cardiac symptoms attributable to AS.[55,60] Patients with a peak jet velocity between 3.0 and 3.5 m/s and an LVEF <50% may have severe AS, requiring AVR, and should undergo cardiac catheterization.[60] Patients with a peak jet velocity between 3.0 and 3.5 m/s and an LVEF >50% probably do not need AVR but should undergo cardiac catheterization if they have symptoms of severe AS.[56] Cardiac catheterization for hemodynamic measurements is recommended for assessment of severity of AS in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding the severity of AS (Table 3).[60]

NATURAL HISTORY

Ross and Braunwald[45] found that the average survival rate after the onset of angina pectoris was 3 years in patients with severe AS; the average survival rate after the onset of syncope was also 3 years, and the average survival rate after the onset of CHF was 1.5–2 years.

Patients with symptomatic severe VAS have a poor prognosis.[44–47,61] At the National Institutes of Health, 52% of patients with symptomatic severe VAS not operated on were dead at 5 years.[46,47] At 10-year follow-up, 90% of these patients were dead. Patients with severe AS and pulmonary hypertension who do not undergo AVR have an 80% mortality at a median follow-up of 436 days.[62]

At 4-year follow-up of patients age 75–86 in the Helsinki Aging Study, the incidence of cardiovascular mortality was 62% in patients with severe AS and 35% in patients with moderate AS.[63] At 4-year follow-up the incidence of total mortality was 76% in patients with severe AS and 50% in patients with moderate AS.[63]

In a prospective study, at 19-month follow-up (range, 2–36 months), 90% of 30 patients with CHF associated with unoperated severe AS and a normal LVEF were dead.[41] At 13-month follow-up (range, 2–24 months), 100% of 18 patients with CHF associated with unoperated severe AS and an abnormal LVEF were dead.[41]

Table 4 shows the incidence of new coronary events in elderly patients with no, mild, moderate, and severe AS. Independent risk factors for new coronary events in this study were prior myocardial infarction, AS, male gender, and increasing age.[44] In this prospective study, at 20-month follow-up of 40 elderly patients with severe AS, CHF, syncope, or angina pectoris was present in 36 of 37 patients (97%) who developed new coronary events and in none of 3 patients (0%) without new coronary events.[44] At 32-month follow-up of 96 elderly patients with moderate VAS, CHF, syncope, or angina pectoris was present in 65 of 77 patients (84%) who developed new coronary events and in 1 of 19 patients (5%) without new coronary events.[44] At the 52-month follow-up of 165 elderly patients with mild AS, CHF, syncope, or angina pectoris was present in 40 of 103 patients (39%) who developed new coronary events and in 5 of 62 patients (8%) without new coronary events.[44]

TABLE 4. Incidence of New Coronary Events in 1797 Elderly Persons With No, Mild, Moderate, and Severe Aortic Stenosis (AS)

	No AS (n = 1496)	Mild AS (n = 165)	Moderate AS (n = 96)	Severe AS (n = 40)
Age (yrs)	81	84	85	85
Follow-up (mo)	49	52	32	20
New coronary events	41%	62%	80%	93%

Adapted from *Am J Cardiol,* Vol 81, Aronow WS, Ahn C, Shirani J, et al. Comparison of frequency of new coronary events in elderly patients with mild, moderate, and severe valvular aortic stenosis with those without aortic stenosis, pages 647–649, Copyright (1998), with permission from Elsevier.[44]

In a prospective study of 981 patients, mean age 82, with aortic sclerosis and of 999 patients, mean age 80, without valvular aortic sclerosis, elderly patients with aortic sclerosis had a 1.8 times higher chance of developing a new coronary event than those without valvular aortic sclerosis at 46-month follow up.[7] Otto et al[64] also reported on 5621 men and women ≥65 years old, that AS and aortic sclerosis increased cardiovascular morbidity and mortality. Of 400 patients with aortic sclerosis, 33% developed AS during 4-year follow-up.[65]

Kennedy et al[66] followed 66 patients with moderate AS diagnosed by cardiac catheterization (aortic valve area 0.7–1.2 cm^2). In 38 patients with symptomatic moderate AS and 28 patients with minimally symptomatic moderate AS, the probabilities of avoiding death from AS were 0.86 for patients with symptomatic AS and 1.0 for patients with minimally symptomatic moderate AS at 1-year follow-up, 0.77 for patients with symptomatic AS and 1.0 for patients with minimally symptomatic AS at 2 years, 0.77 for patients with symptomatic AS and 0.96 for patients with minimally symptomatic AS at 3 years, and 0.70 for patients with symptomatic AS and 0.90 for patients with minimally symptomatic AS at 4 years.[66] During 35-month mean follow-up in this study, 21 patients underwent AVR.

Hammermeister et al[67] followed 106 patients with unoperated AS in the Veterans Administration Cooperative Study on Valvular Heart Disease for 5 years. During follow-up, 60 of 106 patients (57%) died. Multivariate analysis demonstrated that measures of the severity of the AS, the presence of CAD, and the presence of CHF were the important predictors of survival in unoperated patients.

Studies have shown that patients with asymptomatic severe AS are at low risk for death and can be followed until symptoms develop.[68–71] Turina et al[68] followed 17 patients with asymptomatic or mildly symptomatic AS. During the first 2 years, none died or had aortic valve surgery. At 5-year follow-up, 94% were alive and 75% were free of cardiac events. Kelly et al[69] followed 51 asymptomatic patients with severe AS. During 17-month follow-up, 21 (41%) of the patients became symptomatic. Only 2 of the 51 patients (4%) died of cardiac causes. In both patients, death was preceded by the development of angina pectoris or CHF. Pellikka et al[70] found that 113 of 143 patients (79%), mean age 72, with asymptomatic severe AS were not initially referred for AVR or percutaneous aortic balloon valvuloplasty. During 20-month follow-up, 37 of the 113 patients (33%) became symptomatic. The actuarial probability of remaining free of cardiac events associated with AS, including cardiac death and aortic valve surgery, was 95% at 6 months, 93% at 1 year,

and 74% at 2 years. No asymptomatic person with severe AS developed sudden death while asymptomatic.

Rosenhek et al[71] followed 126 patients with asymptomatic severe AS for 22 months. Eight patients died and 59 patients developed symptoms necessitating AVR. Event-free survival was 67% at 1 year, 56% at 2 years, and 33% at 4 years. Five of the 6 deaths from cardiac disease were preceded by symptoms. Of the patients with moderately or severely calcified aortic valves whose aortic jet velocity increased by 0.3 m/s or more within 1 year, 79% underwent AVR or died within 2 years of the observed increase.

When patients with low gradient AS due to abnormal LVEF are considered for AVR, failure to respond to dobutamine and large preoperative LV end-systolic and end-diastolic volumes are poor prognostic signs.[72–74] The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines state that dobutamine stress echocardiography is reasonable to evaluate patients with low-flow/low-gradient AS and abnormal LVEF.[60]

MEDICAL MANAGEMENT

Prophylactic antibiotics should be used to prevent bacterial endocarditis in patients with AS regardless of severity, according to AHA guidelines.[75] Patients with CHF, exertional syncope, or angina pectoris associated with moderate or severe AS should undergo AVR promptly. Valvular surgery is the only definitive therapy in these elderly patients.[60,76] Medical therapy does not relieve the mechanical obstruction to LV outflow and does not relieve symptoms or progression of the disorder. Patients with asymptomatic AS should report the development of symptoms possibly related to AS immediately to the physician. If significant AS is present in asymptomatic elderly patients, clinical examination, electrocardiogram, and Doppler echocardiogram should be performed at 6-month intervals. Nitrates should be used with caution in patients with angina pectoris and AS to prevent the occurrence of orthostatic hypotension and syncope. Diuretics should be used with caution in patients with CHF to prevent a decrease in cardiac output and hypotension. Vasodilators should be avoided. Digitalis should not be used in patients with CHF and a normal LVEF unless needed to control a rapid ventricular rate associated with atrial fibrillation. Intravenous nitroprusside improves cardiac function in patients with decompensated CHF due to severe LV systolic dysfunction and severe AS.[77] It provides a bridge to AVR or oral vasodilator therapy in these critically ill patients.[77]

AORTIC VALVE REPLACEMENT

Table 5 lists 4 class I indications and 1 class II_a indication for performing AVR in elderly patients with AS.[60] AVR is the procedure of choice for symptomatic elderly patients with severe AS. Other class I indications for AVR in elderly patients with severe AS include those undergoing coronary artery bypass graft (CABG) surgery, undergoing surgery on the aorta or other heart valves, and those with an LVEF <50%.[60] Patients with moderate AS undergoing CABG or surgery on the aorta or other heart valves have a class II_a indication for AVR.[60]

TABLE 5. American College of Cardiology/American Heart Association Class I Indications for Aortic Valve Replacement in Patients With Severe Aortic Stenosis (AS)

1. Patients with symptomatic severe AS
2. Patients with severe AS undergoing coronary artery bypass surgery
3. Patients with severe AS undergoing surgery on the aorta or other heart valves
4. Patients with severe AS and a left ventricular ejection fraction <50%
5. Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves (class II_a indication)

Data from Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 practice guidelines for the management of patients with valvular heart disease: Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). Developed in collaboration with the Society of Cardiovascular Anesthesiologists. Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006;48:598–675.[60]

Although the ACC/AHA guidelines do not recommend AVR in patients with asymptomatic severe AS and normal LVEF, there are some data suggesting otherwise.[26] Pai et al[26] found in their database that 99 of 338 patients (29%), mean age 71, with asymptomatic severe AS had AVR during 3.5-year follow-up. Survival at 1, 2, and 5 years was 67%, 56%, and 38%, respectively for nonoperated patients and 94%, 93%, and 90%, respectively for those who had AVR.[26]

Echocardiography is recommended in asymptomatic patients with AS every year for severe AS, every 1–2 years for moderate AS, and every 3–5 years for mild AS.[60] Echocardiography is also recommended for re-evaluation of patients with known AS and changing symptoms or signs.[60]

The bioprosthesis has less structural failure in elderly patients than in younger patients and may be preferable to the mechanical prosthetic valve for AVR in the elderly due to the anticoagulation issue.[78,79] Patients with mechanical prostheses need anticoagulant therapy indefinitely. Patients with porcine bioprostheses may be treated with aspirin at a dose of 75–100 mg daily, unless the patient has atrial fibrillation, abnormal LVEF, previous thromboembolism, or a hypercoagulable condition.[60,80] Table 6 lists 4 class I indications and 2 class II_a indications for antithrombotic therapy in patients with AVR.[60]

Of 241 patients undergoing biologic AVR, mean age 71, 141 received warfarin and 108 patients received aspirin for the first 3 months after AVR.[81] The rate of major bleeding events, stroke-free survival, and survival rates were not different between the 2 groups.[81]

Arom et al[82] performed AVR in 273 patients age 70–89 (mean age 75), 162 with AVR alone and 111 with AVR plus CABG. Operative mortality was 5%. Late mortality at 33-month follow-up was 18%. Actuarial analysis showed at 5-year follow-up that overall survival was 66% for patients with AVR alone, 76% for patients with AVR plus CABG, and 74% for a similar age group in the general population.

A United Kingdom heart valve registry observed in 1100 patients age ≥80 (56% women) who underwent AVR that the

TABLE 6. Class I Indications For Antithrombotic Therapy In Patients After Aortic Valve Replacement (AVR)

1. After AVR with bileaflet mechanical or Medtronic Hall prostheses, in patients with no risk factors, administer warfarin to maintain INR between 2.0 and 3.0; if risk factors are present, the INR should be maintained between 2.5 and 3.5
2. After AVR with Starr-Edwards valves or mechanical disc valves (other than Medtronic Hall prostheses), in patients with no risk factors, warfarin should be given to maintain INR between 2.5 and 3.5
3. After AVR with a bioprosthesis and no risk factors, administer aspirin in a dose of 75–100 mg daily
4. After AVR with a bioprosthesis and risk factors, administer warfarin to maintain an INR between 2.0 and 3.0
5. During the first 3 mo after AVR with a mechanical prosthesis, it is reasonable to give warfarin to maintain an INR between 2.5 and 3.5 (Class II_a indication)
6. During the first 3 mo after AVR with a bioprosthesis in patients with no risk factors, it is reasonable to administer warfarin to maintain an INR between 2.0 and 3.0 (Class II_a indication)

Risk factors include atrial fibrillation, prior thromboembolism, left ventricular systolic dysfunction, and hypercoagulable condition

INR indicates international normalized ratio.

Data from Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 practice guidelines for the management of patients with valvular heart disease: Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). Developed in collaboration with the Society of Cardiovascular Anesthesiologists. Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006;48:598–675.[60]

30-day mortality was 6.6%.[83] The actuarial survival was 89% at 1 year, 79% at 3 years, 69% at 5 years, and 46% at 8 years.

The survival of patients with severe AS, an LVEF <35%, and a low transvalvular gradient at 1 year and at 4 years was 82% and 78% respectively in 39 patients, mean age 73, who underwent AVR versus 41% and 15% respectively in 56 patients, mean age 75, in a control group.[84] In 242 patients, mean age 83, with AS who had AVR, actuarial survival was 92% at 1 year and 66% at 5 years.[85] Concomitant CABG did not affect late survival.[85]

Paroxysmal or chronic atrial fibrillation is a risk factor for mortality in patients with severe AS and an LVEF ≤35% undergoing AVR.[86] Of 83 patients, mean age 70, with severe AS and an LVEF ≤35%, 29 (35%) had paroxysmal or chronic atrial fibrillation.[86] The perioperative mortality was 24% in the group with atrial fibrillation versus 5.5% in the group without atrial fibrillation.[86]

AVR is associated with a decrease in LV mass and in improvement of LV diastolic filling.[87–89] However, LV diastolic dysfunction may develop 10 years after AVR.[90]

Hoffman and Burckhardt[91] performed a prospective study in 100 patients who had AVR. At 41-month follow-up, the yearly cardiac mortality rate was 8% in patients with electrocardiographic LVH and repetitive ventricular premature complexes ≥2 couplets per 24 hours during 24-hour ambulatory monitoring and 0.6% in patients without either of these findings.[91]

If LV systolic dysfunction in patients with severe AS is associated with critical narrowing of the aortic valve rather than myocardial fibrosis, it often improves after successful AVR.[92] In 154 patients, mean age 73, with AS and an LVEF ≤35% who underwent AVR, the 30-day mortality was 9%. The 5-year survival was 69% in patients without significant CAD and 39% in patients with significant CAD. New York Heart Association (NYHA) functional class III or IV was present in 58% of patients before surgery versus 7% of patients after surgery. Postoperative LVEF was measured in 76% of survivors at a mean of 14 months after surgery. Improvement in LVEF was found in 76% of patients.[92]

BALLOON AORTIC VALVULOPLASTY

AVR is the procedure of choice for symptomatic elderly patients with severe AS. In a Mayo Clinic study, the actuarial survival of 50 elderly patients, mean age 77, with symptomatic severe AS in whom AVR was refused (45 patients) or deferred (5 patients) was 57% at 1 year, 37% at 2 years, and 25% at 3 years.[93] Because of the poor survival in this group of patients, balloon aortic valvuloplasty should be considered when operative intervention is refused or deferred. On the basis of the available data, balloon aortic valvuloplasty should be considered for elderly patients with symptomatic severe AS who are not candidates for aortic valve surgery and possibly for patients with severe LV dysfunction as a bridge to subsequent valve surgery.[94–96]

PERCUTANEOUS TRANSCATHETER IMPLANTATION OF AORTIC VALVE PROSTHESES

Percutaneous heart valve implantation may be performed in nonsurgical patients with end-stage calcific AS.[97,98] Ongoing trials will define the clinical role for this therapy. Percutaneous transcatheter implantation of an aortic valve prosthesis would be of great value for elderly high-risk patients with severe comorbidities.

HYBRID APPROACH

Eighteen high-risk patients, mean age 76, with severe AS and moderate CAD amenable to percutaneous coronary intervention (PCI) had combined PCI followed by minimally invasive AVR.[99] One of 18 patients (6%) died postoperatively with no late mortality after a mean follow-up of 19 months.[99] This hybrid strategy may be a new therapeutic approach for elderly high-risk patients with combined CAD and severe AS.

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