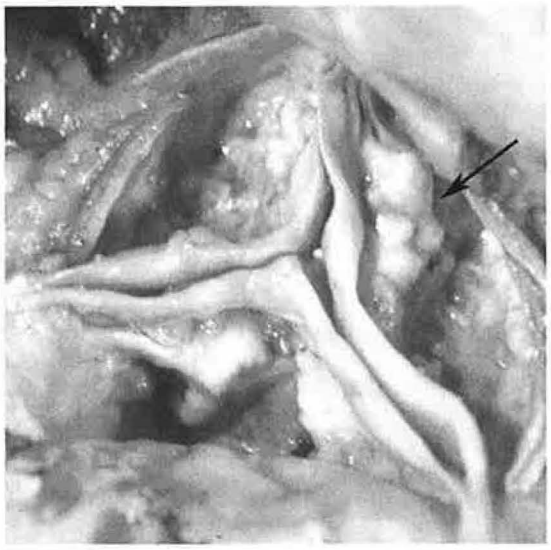
Update in the Management of Severe Asymptomatic Aortic Stenosis: Do we need a new paradigm?

Aortic Sclerosis[1]



Severe Aortic Stenosis[1]

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July 18, 2008

This is to acknowledge that Laura Collins, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Collins will not be discussing off-label uses in this presentation.

Introduction:

Degenerative or calcific aortic stenosis is the most common adult valvular disease. With the continued aging of the population, both primary care physicians and cardiologists will be faced with the longitudinal management of these patients, including the controversy of the appropriate timing of aortic valve replacement. The natural history of symptomatic aortic stenosis is preceded by a lengthy latent or asymptomatic period of decades during which there is progressive calcification of the valve, reduction in aortic valve area and compensatory hypertrophy of the left ventricle. The progression of aortic stenosis occurs at highly variable rates and is dependent on the underlying etiology of valve stenosis and still to be defined atherosclerotic and genetic risk factors. Analogous to the pathologic process, the onset of symptoms is insidious and often difficult to characterize for both the patient and physician. For well over 60 years it has been understood that the prognosis of severe aortic stenosis dramatically worsens after the development of symptoms with an *immediate* and significant increase in the risk of sudden cardiac death. Surgical valve replacement currently remains the only definitive therapy for symptomatic aortic stenosis. The dogma of waiting for the development of symptoms before proceeding with aortic valve replacement has been called in to question due to the improvements in surgical morbidity and mortality, technical advances in prosthetic valves, multiple studies indicating a less than benign outcome for the preoperative period of severe asymptomatic aortic stenosis and potentially worse outcomes in those patients operated on later in their clinical course. My goal will be to address the following:

1) Discuss how our current understanding of the natural history of severe asymptomatic aortic stenosis and has led to alterations in the management of these patients.
2) Based on current evidence do the valve guidelines adequately triage patients with severe asymptomatic aortic stenosis for the optimal timing of AVR?
3) Explore how emerging knowledge in the pathologic spectrum of aortic valve sclerosis to aortic valve calcification may translate to "medical therapy" for the treatment and prevention of aortic valve stenosis.

Etiologies/Incidence of Aortic Stenosis

Aortic stenosis is the most common valve disease in adults encountered in the developed world with an estimated incidence of 2-9% in the elderly population. [2-4] Aortic stenosis develops due to progressive calcification and thickening of either a congenitally abnormal valve or a normal trileaflet valve affected by rheumatic or degenerative disease with eventual obstruction to left ventricular outflow due to restricted leaflet motion. Congenital aortic stenosis is most commonly due to a bicuspid aortic valve and symptom onset is typically in the 6th decade, one to two decades earlier than those who develop aortic stenosis with a trileaflet valve. It is suspected that hemodynamic alterations and possible intrinsic biologic abnormalities of bicuspid valves may accelerate the calcification process. Rheumatic aortic stenosis due to fusion of the commissures and eventual calcification of the cups has become less common in the United States and if present is typically accompanied by rheumatic disease of the mitral valve.

Degenerative or calcific aortic stenosis of an originally normal trileaflet valve typically has symptom onset in the 7th or 8th decades and is the most common cause of aortic stenosis. We now view 'degenerative aortic valve disease as a continuum from its earliest stages of aortic sclerosis (defined as thickening of the valve leaflets without obstruction to outflow) to its latest stage of severe calcific aortic stenosis. Aortic sclerosis is present in 25% of the population over the age of 65 and 48% of people over 84.[2,3,5] Aortic sclerosis has been associated with progression to aortic stenosis and shares many of the same risk factors as atherosclerosis.[2] The Cardiovascular Health Study (Table 1) prospectively found that approximately 9% of patients with aortic sclerosis will progress to some degree of aortic stenosis within 5 years[6] and are at a 50% increased risk of a cardiovascular event.[5] It is suspected that these adverse outcomes in patients with aortic sclerosis are due to underlying atherosclerosis or a chronic systemic process (i.e. inflammation), thus the aortic sclerosis is a surrogate marker. [1]

Effect of Aortic Valve Sclerosis or Stenosis on Mortality and Morbidity in the Elderly: The Cardiovascular Health Study

Event	Normal Aortic Valves (n=3,919)	Aortic Sclerosis (n=1,610)	Aortic Stenosis (n=92)	p (for trend)
	n (%)			
Death from any cause	583 (14.9)	353 (21.9)*	38 (41.3)*	<0.001
Death from cardiovascular causes	238 (6.1)	162 (10.1)*	18 (19.6)*	<0.001
Myocardial infarction†	217 (6.0)	123 (8.6)‡	9 (11.3)‡	<0.001
Angina†	358 (11.0)	160 (13.0)	17 (24.3)*	0.001
Congestive heart failure†	337 (8.9)	192 (12.6)*	21 (24.7)*	<0.001
Stroke†	238 (6.3)	122 (8.0)§	10 (11.6)§	0.003

* p<0.001 for the comparison with the group with normal aortic valves.
† The rates were calculated for subjects at risk for new events.
‡ p<0.01 for the comparison with the group with normal aortic valves.
§ p=0.02 for the comparison with the group with normal aortic valves.

Table 1. Effect of Aortic Valve Sclerosis or Stenosis on Morbidity & Mortality in the Elderly[5]

Risk Factors for the Progression to Aortic Stenosis

The Cardiovascular Health Study identified several clinical factors by multivariate analysis which predicted progression to aortic stenosis from either a baseline normal or sclerotic valve. As in previous studies, age was found to be a significant risk factor for progression (OR 1.13, p<0.001). Male-gender was associated with a 3-fold increased risk, body stature was weakly inversely related and African-American ethnicity was found to be protective with a 51% lower risk. [6] Contrary to previous studies which implicated chronic inflammation in the pathogenesis of aortic valve calcification, C-reactive protein (CRP) was found to be a poor predictor of disease progression in either aortic sclerosis or stenosis in the Cardiovascular Health Study.[6] The lack of association between CRP and calcific aortic valve disease in this study may have been due to lack of referral bias in this larger population and inclusion of subjects with less advanced disease. Other risk factors which have been implicated in aortic valve calcification include hypertension, body mass index, metabolic syndrome, smoking, hypercholesterolemia, diabetes, and serum creatinine and calcium levels.[8]

Pathology of Aortic Valve Calcification

We should no longer refer to calcification of a normal trileaflet aortic valve as 'degenerative'. In the past, this was process was termed degenerative as it was felt to result from the mechanical stresses of the valve leaflets over time and the passive deposition of calcium. There is now emerging pathologic and clinical evidence that calcific aortic valve disease is a much more dynamic process sharing many similarities with atherosclerosis including chronic inflammation,[7] lipoprotein deposition,[7] active leaflet calcification, patient-related factors (i.e. dialysis, other conditions with altered calcium-phosphate metabolism) and still to be fully determined genetic factors.[8] (Fig 1)

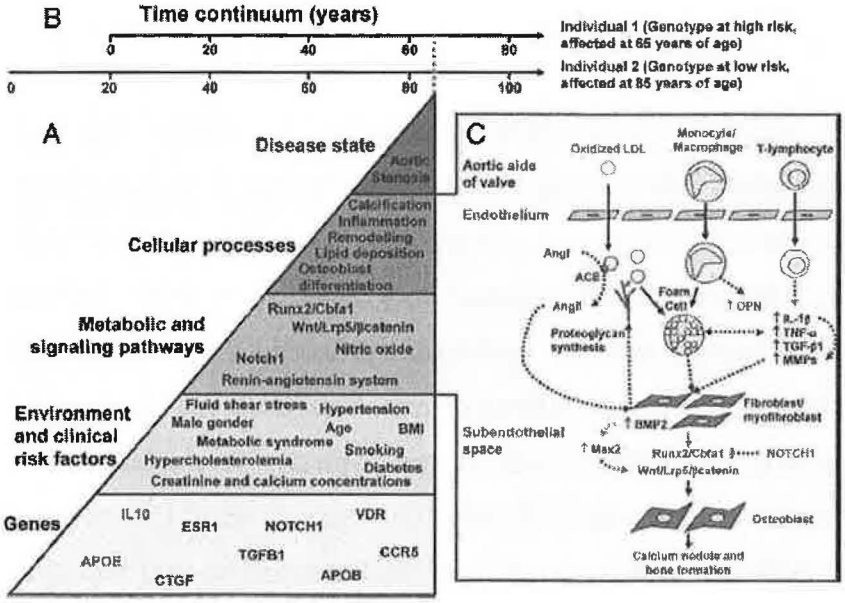


Fig. 1. Proposed mechanism for aortic valve calcification[8]

Pathophysiology of Severe Aortic Stenosis

In adults with severe aortic stenosis, the gradual obstruction to left ventricular outflow and slow rise in the transaortic pressure gradient allow for the maintenance of a normal cardiac output for several years. In most cases, the increasing pressure gradient across the aortic valve is balanced through the compensatory hypertrophy of the left ventricle without a significant increase in wall stress[9,10] (LaPlace's Law, fig. 2).

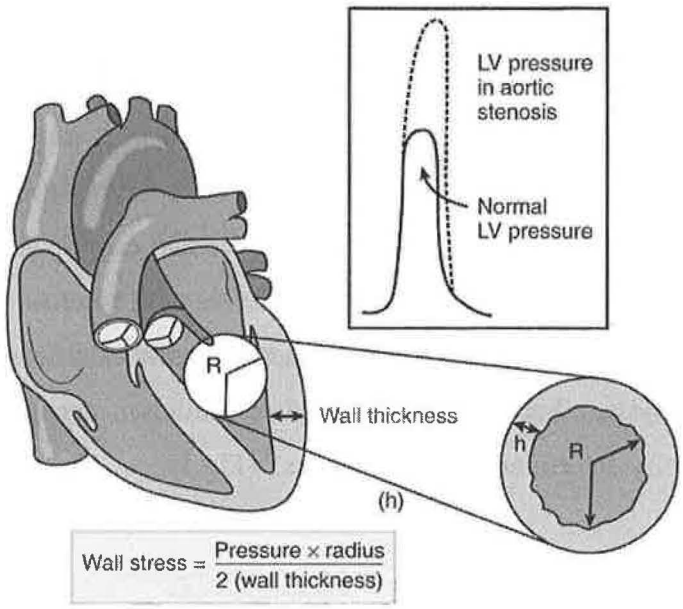


Fig. 2 LaPlace's Law

This is typically accomplished by myocyte hypertrophy and interstitial fibrosis within the extracellular matrix which subsequently lead to left ventricular diastolic impairment. Left ventricular (LV) systolic dysfunction may occur from "afterload mismatch" due to increased wall stress from inadequate compensatory hypertrophy and/or decreased contractility. In those patients with LV dysfunction primarily due to the latter, surgery is less effective. Interestingly, gender differences have been observed on how the left ventricle responds to severe aortic stenosis. Women typically develop significant concentric left ventricular hypertrophy (LVH) with relatively small LV cavities, have supernormal left ventricular systolic function, normal or below normal wall stress and more LV diastolic dysfunction. On the other hand, men are prone to larger LV cavities, eccentric LVH, increased wall stress and develop more left ventricular systolic dysfunction.[11] Clearly, there are other factors (i.e. genetic, hormonal) at play which determine the degree of left ventricular hypertrophy in aortic stenosis , aside from the degree of obstruction to left ventricular outflow.

Symptom Development

Asymptomatic disease is typically detected by auscultation of a heart murmur on routine physical exam. A lengthy latent period during which the patient is asymptomatic, but during which this pathological process proceeds is typical. The rate of progression is variable and not easily predicted among patients with aortic stenosis. In a cohort of mixed

degrees of stenosis the average rate of progression was reported as a decrease in aortic valve area of 0.12 ± 0.19 cm-sq per year, an increase in the mean gradient of 7 ± 7 mmHg per year, and an increase in the peak aortic velocity of 0.3 ± 0.34 m/sec per year.[12]

The onset of symptoms typically does not occur until the normal orifice area (3.0-4.0 cm^2) is reduced by 75% or more to an average valve area of 1.0 cm^2 or less. The age at which this process begins, and the rapidity of the progression is dependent on the etiology of the aortic stenosis and several factors which are not well understood. Symptoms including exertional angina, congestive heart failure (CHF) and syncope develop typically once the degree of stenosis is severe but their development is not uniform and develop much later in some. It is important to realize that more subtle symptoms such as exertional dyspnea, exertional dizziness, and decreased exercise tolerance are often more common and should be sought when obtaining a history. Patients routinely underreport symptoms and often curtail their physical activity to avoid symptom development. Since the landmark paper of Braunwald and Ross it has been understood that the onset of symptoms in aortic stenosis portends a poor prognosis. [13] After the development of these classic symptoms 50% of patients are dead within 2-3 years without surgical intervention. (Fig 3)

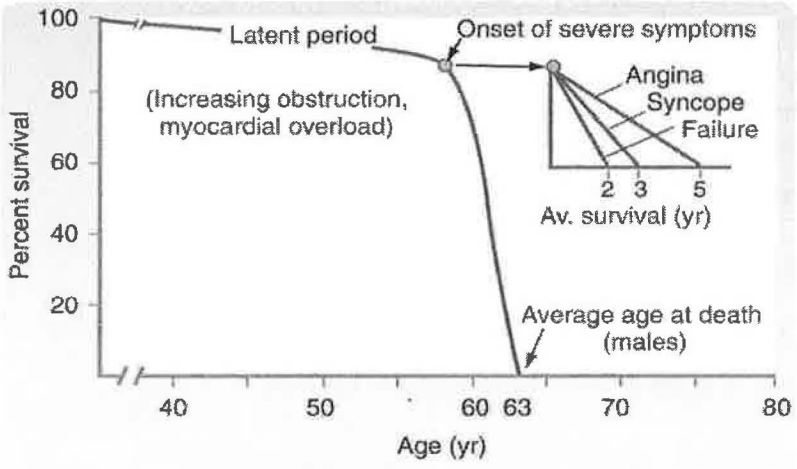


Fig. 3 Natural history of medically treated aortic stenosis[13]

Assessing Severity of Aortic Stenosis

It is crucial to have a reliable assessment regarding the severity of aortic stenosis as this will directly affect management decisions including surgical intervention, preoperative assessment for noncardiac surgery and intensity/frequency of routine clinical and echocardiographic follow-up. The current AHA/ACC Guidelines for Valvular Heart

Disease define severe aortic stenosis as a peak aortic velocity of >4.0 m/sec, mean gradient >40 mmHg and aortic valve area (AVA) of $\leq$1.0 cm^2 (or AVA index of 0.6 cm^2/m^2 (Table 2).[14] Note that 3 parameters are given to determine severity of stenosis. It is important to realize that gradient measurements are affected by both abnormally low or high cardiac outputs and significant aortic regurgitation, thus the actual aortic valve area becomes more important in determining the degree of stenosis in these situations. Consideration should be given to the size of the patient and aortic valve area should be

Classification of the Severity of Aortic Valve Disease in Adults

ACC/AHA 2006 Valvular Heart Disease Guidelines

Indicator	Mild	Moderate	Severe
Jet velocity (m per second)	<3.0	3.0-4.0	>4.0
Mean gradient (mm Hg)*	<25.0	25.0-40.0	>40.0
Valve area (cm^2)	>1.5	1.0-1.5	<1.0
Valve area index (cm^2 per m^2)	NA	NA	<0.6

*Valve gradients are flow dependent and when used as estimates of severity of valve stenosis should be assessed with knowledge of cardiac output or forward flow across the valve.

Table 2. Classification of Aortic Stenosis Severity in Adults[14]

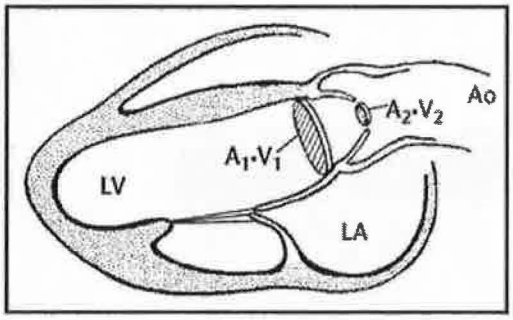
indexed to body surface area in those patients who are either well below or above the average body surface area. One should be cautious when indexing to body surface area as in the very obese patient this may lead to an overestimation of the severity of aortic stenosis.

Transthoracic echocardiography is currently the gold standard to assess the severity of valvular aortic stenosis. Both peak and mean gradients are measured by Doppler echocardiography and the aortic valve area is calculated by the continuity equation (Fig. 4) which is based upon the conservation of mass (flow) before and after a restrictive orifice. The precise measurement of the LVOT (left ventricular outflow tract) diameter is crucial to

the accurate determination of the aortic valve area as this measurement is squared in the determination of the LVOT area. Validation of aortic stenosis severity by cardiac cardiac catheterization is *only* necessary in those situations where the clinical history and/or physical examination are discordant with the degree of stenosis determined by transthoracic echocardiography or if echo quality does not allow for accurate determination.[14] Routine assessment of aortic stenosis severity is actually contraindicated at the time of cardiac catheterization due to the risk of stroke (1-2%) when crossing the valve. Alternatively, planimetry of the aortic valve area by transesophageal echocardiography may be helpful, but is less accurate in the setting of a heavily calcified valve. Finally, obtaining accurate pressure gradients by transesophageal echocardiography is not always possible due to the more difficult task of aligning the Doppler parallel to the transvalvular flow. Current guidelines recommend that follow-up echocardiograms be obtained yearly on a patient with severe aortic stenosis, every 1-2 years for moderate stenosis and every 3-5 years for those with mild aortic stenosis.

Continuity Equation

A_1V_1(or VTI_{LVOT})= A_2V_2 (or VTI_{Aov})



$$AVA=\frac{CSA_{LVOT} \times VTI_{LVOT}}{VTI_{AoV}}$$

CSA=cross sectional area

$CSA_{LVOT}= \pi D^2/4$

D=LVOT diameter

VTI=velocity time integral

Fig. 4. Echocardiographic Determination of Aortic Stenosis Severity by the Continuity Equation

Timing of Aortic Valve Replacement

Due to the poor prognosis after the development of symptoms in aortic stenosis there is no disagreement on proceeding with prompt surgical intervention. Ideally, if it were possible to predict the onset of symptoms with certainty, then the timing of surgical

intervention should be just prior to their onset. The original recommendation and now standard practice for greater than 40 years to defer aortic valve replacement until the onset of symptoms is grounded in the significant increase in the risk of sudden death after the onset of symptoms. Original autopsy series found a 15-20% rate of sudden death in patients with valvular aortic stenosis.[13,15] The majority of these patients (65-80%) were found to have preceding symptoms of angina, congestive heart failure or syncope;thus in those patient's without preceding symptoms the sudden death rate was estimated to be 3-5%.[13] More contemporary series estimate a 1% annual risk of sudden cardiac death in the asymptomatic patient with severe aortic stenosis.[16,17] The ability to proceed promptly to surgery after the onset of symptoms may be hindered by several factors including important personal obligations/commitments of the patient, development of comorbid illness which temporarily may delay surgery, and available surgical resources (more problematic in certain countries or even within certain socioeconomic groups in the U.S).

Outcome of Patients with Asymptomatic Aortic Stenosis

The lack of randomized clinical trials has made this period of asymptomatic, but severe aortic stenosis difficult to fully understand. Three important studies have significantly contributed to our knowledge of the rate or progression and predictive factors for progression and risk of sudden cardiac death.

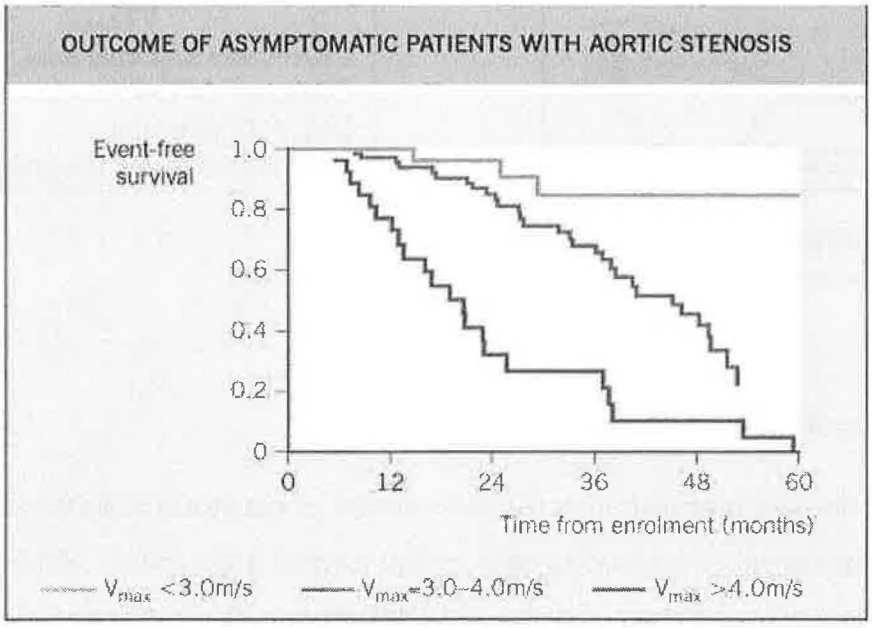


Fig.5 Outcome of Patients with Asymptomatic Aortic Stenosis[12]

Otto et al prospectively followed a group of 123 asymptomatic patients with aortic stenosis (note that not all of these patients had severe aortic stenosis; entry required an aortic jet velocity >2.5 m/sec). The majority of patients (71%) had calcific valve disease (28% had bicuspid vs 1% with rheumatic). Multivariate predictors of outcome included baseline jet velocity ($p<0.0001$), rate of change in jet velocity ($p<0.001$) and functional status ($p=0.002$) with the strongest being the baseline jet velocity.[12] Freedom from death or aortic valve replacement (AVR) at one, three and five years was 93, 62 and 26 percent respectively. The likelihood of remaining alive without AVR at 2 years was 21+/-18% for a jet velocity at entry >4 m/sec compared with 84 +/- 16% for a jet velocity <3 m/sec ($P<0.0001$) (Fig 5)[12]. No sudden cardiac deaths were noted in this cohort of mixed aortic stenosis severity.

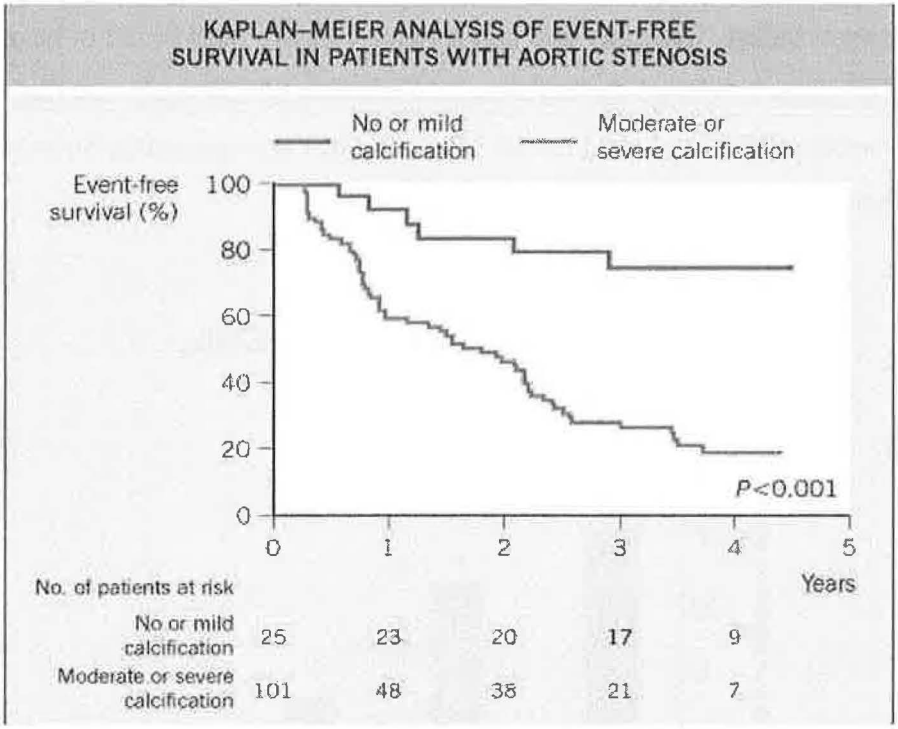


Fig 6. Degree of Aortic Valve Calcification as Predictor of Outcome in Severe AS[17]

Rosenhek and colleagues prospectively followed a cohort of 126 patients for a mean of 22 months with severe asymptomatic aortic stenosis (defined as an aortic velocity $\geq$4 m/sec) in Vienna. Similar to Otto's results they found event free survival to be 33% at 4 years.[17] Significant valve calcification (graded as moderate to severe by echo) was found to be the only

independent predictor of outcome (Fig 6) with those patients having lower rates of event free survival. Additionally they found that nearly 80% of patients with moderate to severe calcification and an increase in jet velocity of at least 0.3m/sec in one year had a cardiac event within 2 years. In this study, the risk of sudden cardiac death was found to be less than 1% per year (no preceding symptoms were noted in that one patient).

Finally, Pellikka and her colleagues at the Mayo Clinic retrospectively assessed the long-term outcome of a large (n=622) group of patients with severe asymptomatic aortic stenosis (defined as peak aortic jet velocity of $\geq$4 m/sec and mean aortic valve area of 0.9 cm^2). Similar to previous results[17] they found the risk of sudden cardiac death (not preceded by symptoms) to be less than 1% per year[16]. The rate of remaining free of symptoms and without valve replacement was 82, 67 and 33 percent at one, two and five years (Fig 7). [16] AVA and left ventricular hypertrophy predicted symptom development. Age, chronic renal failure, inactivity and aortic valve velocity were found to be multivariate predictors of all cause mortality. An unfortunate limitation of this study was that many patients who were underwent AVR (131 of 352) were still asymptomatic, but nevertheless referred by their physician for uncertain reasons.

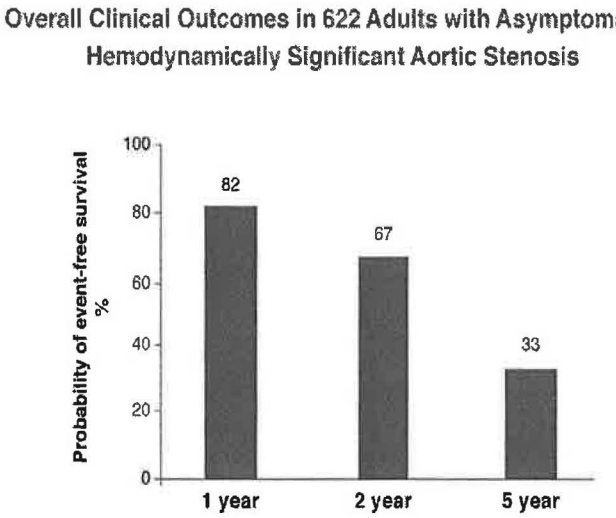


Fig 7. Event Free Survival in Patients with Asymptomatic Severe Aortic Stenosis[16]

Role of Exercise Testing

While exercise testing in severe, symptomatic aortic stenosis is contraindicated, exercise testing in those patients with moderate to severe asymptomatic aortic stenosis with nonspecific symptoms is relatively safe. In a cohort of 50,000 patients with suspected coronary artery disease and/or aortic stenosis the morbidity and mortality rates were 0.0005% and 0.00004% respectively.[18] Testing should always be symptom limited and discontinued if systolic blood pressure decreases by more than 20 mmHg, for the development of significant atrial or ventricular tachyarrhythmias or ST depression of more than 5 mm occurs.[12,19]

Exercise testing in severe asymptomatic aortic stenosis has been proposed as a potential tool to risk stratify those patients who are asymptomatic during routine activity. Functional capacity, which can be difficult to reliably quantitate by history becomes evident on the treadmill. Patients tend to overestimate their functional capacity and frequently curtail their level of physical exertion due to symptoms. It has been reported that up to 50% of previously asymptomatic patients with severe aortic stenosis develop their initial symptoms during exercise testing.[20,21] Only two small studies have assessed the role of exercise testing in severe asymptomatic aortic stenosis. Symptom-free survival was found to be significantly lower (49% vs 89% in those without limiting symptoms) in those with limiting symptoms[21] or a positive exercise test as defined by symptoms or EKG criteria[20] (Fig 8). In fact, the future development of spontaneous symptoms is related more to the development of limiting symptoms on exercise testing than to an abnormal blood pressure response or ST segment depression.[21] Interestingly, the majority of patients (83%) who experienced exertional dizziness on exercise testing developed spontaneous symptoms within 12 months compared to approximately half those with chest tightness or dyspnea on exercise testing. [21] In contrast, others have not found that data from exercise testing provided any additional predictive value over other variables (i.e. jet velocity, rate of change over time in jet velocity and functional status) in a Cox regression analysis.[12] Exercise echocardiography is able to objectively correlate symptoms (especially dyspnea) with the development of left ventricular systolic dysfunction. The majority (80%) of patients with an abnormal left ventricular response during exercise are more likely to develop symptoms during exercise compared to those with a normal LV response (27%),

{p<0.001} and cardiac free survival is lower in those patients with an abnormal LV response to exercise.[22] Currently, exercise testing in this group of patients is not routinely recommended for prognostic purposes. The ACC/AHA valve guidelines state that in those patients with uncertain or equivocal histories exercise testing can be considered to define functional capacity, elicit the objective development of symptoms and abnormal blood pressure response (Class IIb, Level of Evidence B).[14] Larger randomized trials are needed to better define the role of exercise testing in patients with severe asymptomatic aortic stenosis.

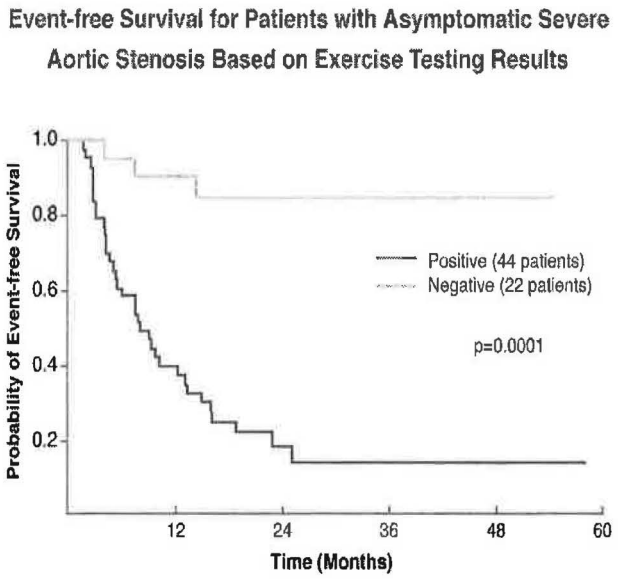


Fig 8. Kaplan-Meier analysis for probability of event-free survival over 60 months for patients with severe asymptomatic aortic stenosis, according to positive or negative stress testing results[20]

Operative and Long-term Morbidity and Mortality after AVR

The decision to proceed to surgery before the onset of symptoms must be weighed against the concern for operative mortality and resultant risks of prosthetic valve complications. Steady improvement in surgical mortality and the hemodynamic/safety profiles of bioprosthetic and mechanical valves along with our expanding knowledge of this period of "severe asymptomatic aortic stenosis" have called in to question this "watchful waiting" for the development of symptoms before considering AVR.

Currently the unadjusted operative mortality rate reported by several databases for isolated AVR ranges between 3.3 and 4.0%, while the rate for a combined AVR with coronary artery bypass grafting (CABG) ranges between 6.8 and 7.3% (Table 3).[23] Patients

undergoing combined AVR and CABG had a higher incidence of post-operative complications including permanent stroke (3.2 vs 1.6 % for isolated AVR) (Table 4). Many factors affect survival after AVR for aortic stenosis including age, left ventricular function, NYHA functional class, low gradient aortic stenosis, volume performed at the hospital, recent infarction, and renal failure.[24] Specifically those patients who undergo AVR on an emergency basis have nearly a 3.5 fold risk in operative mortality.[24] Thus, it is crucial that we define the parameters in patients with severe aortic stenosis that help define the optimal timing of AVR to avoid exposing our patients to this increased operative risk resulting from emergent surgery.

Table 3 *Comparative Operative Mortality (%)*[23]

	AVR	MVR	AVR/CABG	MVR/CABG
STS	4.0	6.0	6.8	13.3
CSCR	3.3	6.2	7.1	12.8
DVA	3.9	5.9	7.3	11.8

AVR=Aortic valve replacement, MVR=mitral valve replacement; CABG=Coronary artery bypass grafting, STS=Society of Thoracic Surgeons; CSCR= Ney York Cardiac Surgery Reporting System; DVA=Department of Veterans Affairs

Effect of Age

With regard to age, elderly patients usually tend to have higher perioperative mortalities. In one study, patients over the age of 80 were found to have a substantially higher perioperative mortality (14% vs 4% in those ages 65-75) and this in part was felt to be due to more concomitant risk factors (i.e. higher NYHA functional class) than actual age.[25] In fact, elderly patients who survive the early post-operative period tend to do quite well with similar survival as age-matched controls (after surviving the first 30 days) and enjoy an excellent functional recovery.[25,26]

Table 4: Complication Rate after AVR and combined AVR/CABG: STS Database [24]

Complication (%)	AVR	AVR + CABG
Permanent Stroke	1.58	3.15
Prolonged Ventilation	7.07	12.21
Reoperation for Bleeding	4.12	5.49
Renal Failure	3.7	6.48
Deep Sternal Infection	0.5	0.7

Effect of Left Ventricular Systolic Dysfunction

Both left ventricular systolic and diastolic dysfunction have been found to be risk factors for early and late mortality.[27] Patients with aortic stenosis and severe left ventricular dysfunction may have true low gradient aortic stenosis, defined as a transaortic mean pressure gradient less than 30 mmHg and calculated AVA <1.0 cm^2 in association with low flow. These patients typically have a higher perioperative mortality (10%),[28] however surgery is still recommended in most patients due to even worse outcomes with medical therapy. Overall 5-year survival rate was 49 ± 4%. A lower mean gradient, higher EuroSCORE (a score integrating patient-related, cardiac and operation-related factors), prior atrial fibrillation and multivessel disease were all found to be independent predictors of overall long-term mortality[28] (Fig 9).

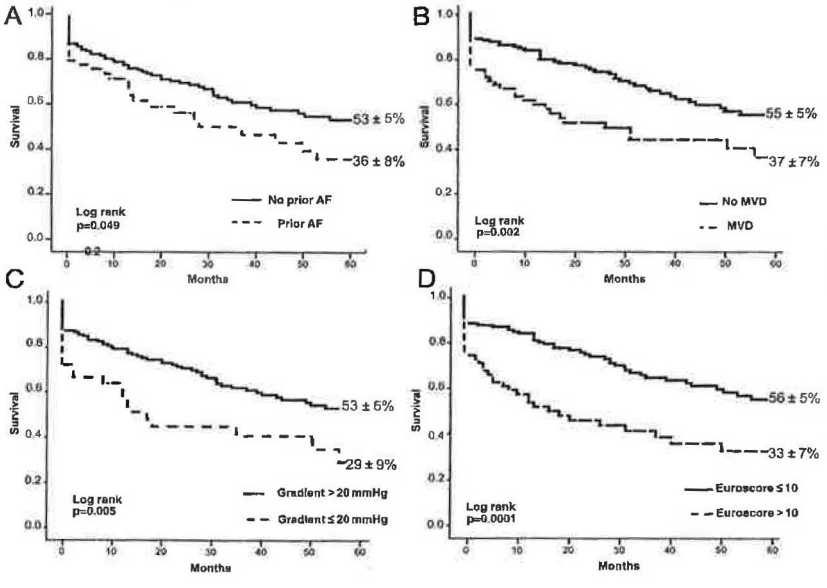


Fig 9. AVR for Low Gradient AS: 5 year overall survival curves. AF=Atrial fibrillation, MVD=multivessel disease, Euroscore (preoperative European System for Cardiac Operative Risk Evaluation)[28]

Morbidity after AVR

Aside from the obvious perioperative mortality assumed by the patient and physician considering aortic valve replacement, the ensuing complications from a heart valve prosthesis must be taken in to consideration when contemplating valve replacement in an asymptomatic patient. Depending upon the type of the prosthesis, complications range from valve thrombosis, bleeding, valve degeneration leading to valve stenosis or perivalvular leak, mechanical valve malfunction, prosthetic valve endocarditis, and arterial embolization. The actual prosthesis-related complication rate is reported to be 2-3% per year and dependent on a patient's clinical risk factors and whether a mechanical or bioprosthesis is placed. Prosthesis-related mortality rate is estimated to be at least 1% per year.[29-32]

Factors Affecting Long-term Survival after Aortic Valve Replacement

In the past, the decision to wait until the development of symptoms in severe aortic stenosis was based upon the operative mortality exceeding the risk of sudden cardiac death in an asymptomatic patient with aortic stenosis. However, we are now faced with increased knowledge that the deleterious effects caused by severe aortic stenosis on the left ventricle and development of more severe clinical symptoms may have direct impact on survival after AVR; thereby implying that earlier referral in certain patient's with severe asymptomatic aortic stenosis should be considered.

The Framingham Heart Study established that LVH from any etiology is a risk factor for cardiovascular morbidity and mortality.[33] Reduction in LV mass after AVR most commonly occurs within 3-4 months and typically averages 30%.[34] Failure to regress LVH or an increase in LVH after AVR is associated with a poor prognosis with 23% mortality and 38% CHF compared with no mortality and only 4% incidence of CHF for those who did show regression.[35] This study was unable to identify any preoperative predictors for which patients would show regression. In contrast, a minority (10%) of patients with severe aortic stenosis fail to develop LVH and this was more commonly found in those with a small body size.[36] The failure of the ventricle to adapt to the pressure overload posed by severe aortic stenosis and *not* hypertrophy has been found to be detrimental as well. A study of the impact of LVH six months after AVR found a J-shaped relationship (fig. 10)

with the highest mortality observed in patients with very low LV mass or very high LV mass.[37]

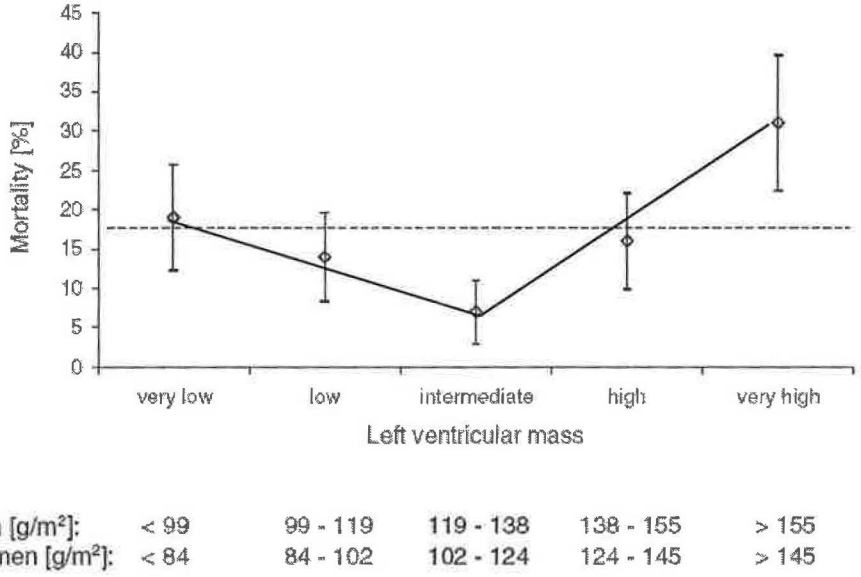


Figure 10: LVH & mortality 6 months after AVR[37]

A recent large scale, single-center observational study from the Cleveland Clinic in 3,049 patients who underwent aortic valve replacement with a single bioprosthesis has contributed to our understanding of how outcomes after AVR may be affected by the severity of the disease at the time of operation.[38] They found that the presence of severe left ventricular hypertrophy at the time of operation was associated with decreased long-term survival (Fig 11) and furthermore this effect was magnified by the severity of aortic stenosis ($p=0.02$) and the use of small valve prostheses. Furthermore, they found that approximately 50% of patients with mild or no symptoms had developed severe LVH and that 19% of asymptomatic patients and 26% of mildly symptomatic patients had developed some degree of left ventricular dysfunction. They speculated that the suboptimal results after AVR in these groups were likely the result of irreversible myocardial changes and fibrosis associated with severe left ventricular hypertrophy and stated that "LVH should not any longer be viewed as a benign side effect of aortic stenosis, which will be reversed after we replace the AV, but a significant contributor in pathology or bad outcomes of these patients even after a successful operation." They suggested that an LV mass index of > 135 g/m^2 in men and >100 g/m^2 in women should be used as a surgical indication for aortic

stenosis. Furthermore, their study suggests that patients with more severe asymptomatic aortic stenosis (AVA <0.6 and mean gradient of >60 mmHg) should be considered for surgery earlier (currently this would be a IIb criteria in the guidelines).

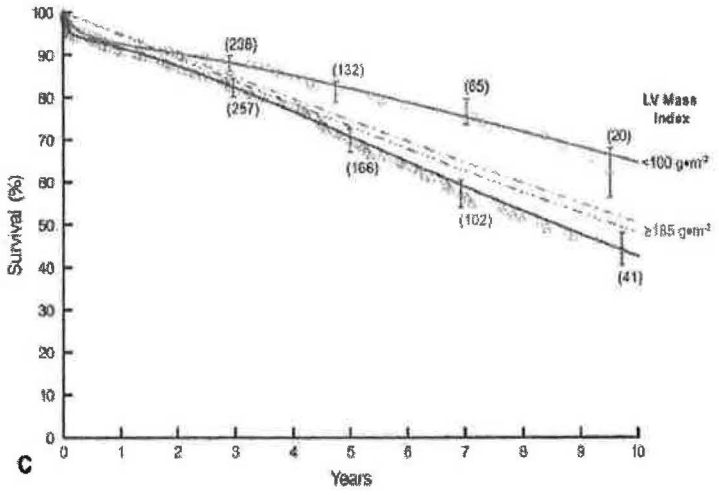


Fig 11. Survival after AVR according to LV Mass Index [38]

In agreement with previous studies, [27,28] they found that the presence of left ventricular dysfunction decreased survival; supporting the guidelines current 1C indication for this group of patients.[38] Clearly, this study will likely dictate an update of the current guidelines.

Current Guideline Recommendations

In 2006 the ACC/AHA task force on practice guidelines updated the guidelines for the management of patients with valvular heart disease.[14] It is important to note that none of the indications are based any randomized clinical data (all are Level of Evidence B or less). Class I indications for AVR include symptomatic patients with severe aortic stenosis, those with evidence of LV systolic dysfunction (defined at ejection fraction <50% and those with severe AS who are undergoing CABG, surgery on the aorta or other heart valves. A class IIa indication is given to those patients with a moderate degree of aortic stenosis undergoing CABG or other heart valve surgery. The current guidelines have four class IIb indications for AVR (all with level of evidence C). Remember that a IIb indication means that the usefulness/efficacy is less well established compared with a IIa indication which states that the weight of the evidence is in favor. Unfortunately, this is the category that most of our asymptomatic severe aortic stenosis patients would be in and for

the most part the guidelines are rather vague about further stratification among these patients. Currently, the ACC/AHA guidelines state that AVR may be considered (IIb indication) in those patients with severe aortic stenosis with an abnormal response to exercise (development of symptoms or asymptomatic hypotension). In contrast, the European Valve Guidelines[39] would classify exercise induced symptoms or asymptomatic hypotension as a Class I C indication for AVR. The remaining IIb indications include those patients with a high likelihood of rapid progression (age, heavy calcification, and concomitant CAD) or if surgery might be delayed at the time of symptom onset, those with mild aortic stenosis undergoing CABG when there is evidence that progression of stenosis may be rapid (ie heavy valve calcification) and finally those with critical aortic stenosis (aortic valve area <0.6 cm^2, mean gradient >60 mmHg, and jet velocity >5.0 m/sec when the patient's operative mortality is 1.0% or less. Please refer to the proposed management algorithm from the current ACC/AHA practice guidelines for valve disease. (Fig. 12)

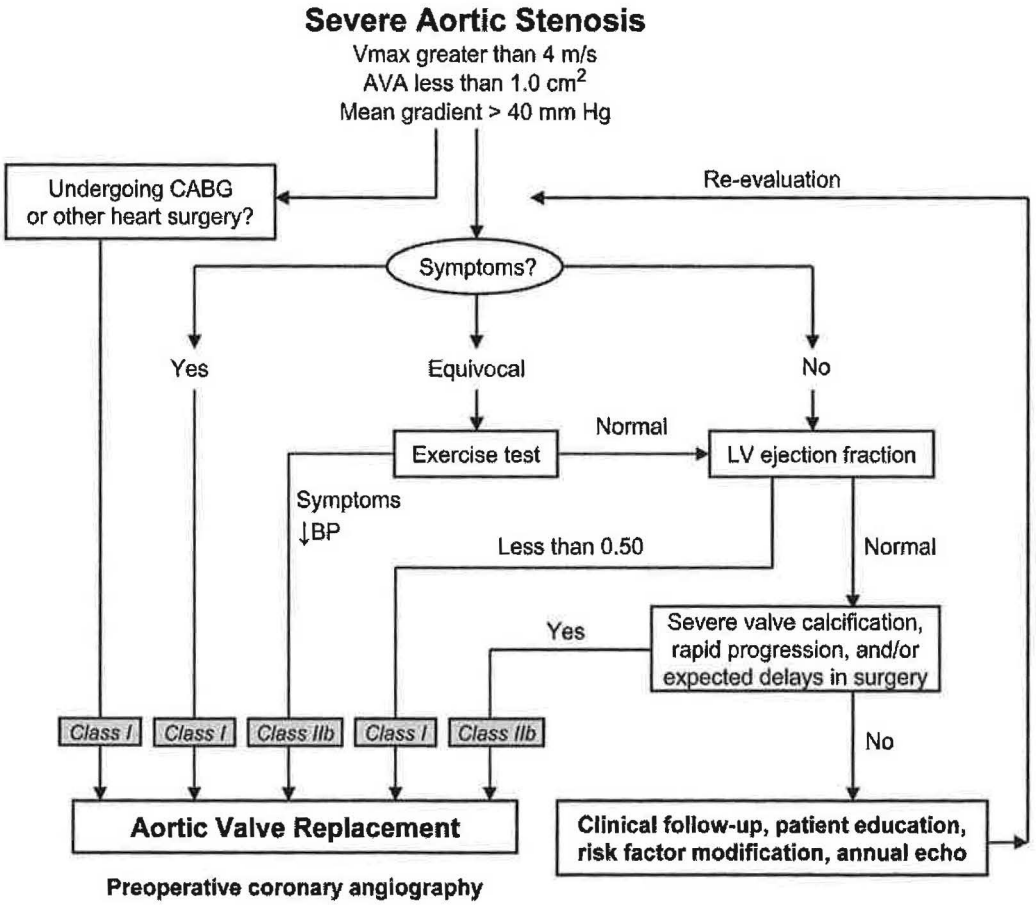


Fig 12. Management strategy for patients with severe aortic stenosis. [14]

Many feel that the current guidelines are not aggressive enough in identifying patients at risk for poor outcomes. Further definition of outcome predictors is needed in this group of asymptomatic patients. In particular, the guidelines do not recommend the best method to quantitate valve calcification. The study first demonstrating the correlation of valve calcification with poor outcome (rapid progression) used a qualitative grading method by echocardiography.[17] Other groups have applied EBCT (electron-beam computed tomography) to better quantitate the degree of valve calcification[40] (please refer to section on EBCT later in this document). There is increasing concern that compensatory left ventricular hypertrophy, while necessary, is associated with significant morbidity and mortality (see previous section on *Factors Affecting Long-Term Mortality after AVR*) and there is interest in factoring in the degree of LVH into the decision making process for proceeding with AVR. Finally, it is not clear why exercise induced symptoms or development of significant exercised induced hypotension is a IIB indication, as symptom development of any kind should be a class Ia indication.

Potential Future Tools

EBCT Measurement of Aortic Valve Calcium

Rosenhek and colleagues demonstrated the importance in the degree of aortic valve calcium qualitatively assessed by echocardiography in predicting outcomes in both mild to moderate and severe aortic stenosis.[17] Assessment of aortic valve calcium by echocardiography is a qualitative assessment which is subjective and may be significantly affected by ultrasound gain settings. Aortic valve calcium can be precisely quantified by EBCT with excellent intraobserver and interobserver variability in the assessment of aortic valve calcium scores.[40] A strong linear relation ($r=0.96$, $p<0.0001$) between EBCT score and calcium weight (as measured by tissue digestion) was demonstrated in thirty explanted valves of patients undergoing surgery for aortic stenosis or mixed aortic valve disease. The degree of aortic valve calcium was found to be strongly correlated to the hemodynamic severity (aortic valve area by echocardiography and peak aortic velocity) of the aortic stenosis by a curvilinear relationship. This curvilinear relationship suggests that aortic valve calcium and aortic valve area will likely provide complementary information which

may be important in predicting outcomes. EBCT was found to be sensitive in detecting severe aortic stenosis beginning with a score of 500 AU. An aortic valve calcium score ≥ 1100 AU had a 93% sensitivity and 82% specificity for the diagnosis of severe aortic stenosis (AVA <1 cm^2). Finally, they found that late event free survival (at 5 years) was predicted (92 ± 4% vs 40 ± 18% in patients with an AV calcium score below and ≥ 500 AU, respectively, p=0.0002) by a low aortic valve calcium score, independent of age, sex, aortic valve area, symptoms and left ventricular ejection fraction. Assessment of aortic valve calcium by echocardiography was found to be graded as more severe (compared to EBCT and pathologic analysis), suggesting that echocardiography may not be the optimal imaging method to use for quantification of aortic valve calcium. AV calcium score was found to be an independent predictor for event-free survival even after adjustment for echocardiographic calcification. The authors concluded that EBCT quantification of calcium may play a role in the evaluation of patients with aortic stenosis by providing further prognostic information and helping to determine aortic stenosis severity in patients with difficult echocardiographic windows or in those with severely depressed left ventricular systolic function and low gradient aortic stenosis in whom interpretation of the usual hemodynamic parameters by echocardiography are less reliable.[40]

Role of Brain Natriuretic Peptide

It is well established that levels of plasma BNP and N-terminal pro-BNP are higher in those patients with symptomatic severe aortic stenosis compared to those who are asymptomatic.[41,42] Additionally, in a group of 130 asymptomatic patients with severe aortic stenosis lower levels of pro-BNP (<80pmol/L) are able to predict a higher rate of symptom free survival at 12 months (69 vs 18%) while other variables such as age, transvalvular gradient and presence of coronary disease did not.[43] While it is premature to routinely measure neurohormones on a routine basis, it is interesting to speculate that interval measurement of these neurohormones might help guide the decision to consider valve replacement in an asymptomatic patient.

Medical Therapy for Aortic Stenosis

Statin Therapy

Currently, there is no recommended medical therapy to prevent progression of aortic stenosis. Due to the identification of hyperlipidemia as a possible risk factor for the development and progression of calcific aortic valve disease and the many similarities between the underlying pathology of degenerative aortic stenosis and atherosclerosis, interest developed as to whether statin therapy could slow the progression of aortic stenosis. Several retrospective studies have shown a benefit with the use of statin therapy in reducing the rate of progression in aortic stenosis.[44-48] While the majority of patients in these studies had mild to moderate degrees of stenosis, at least one study[48] showed an improvement even in those with severe degrees of stenosis. Disappointingly, there have been two prospective studies with discordant results. SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial Impact on Regression) was a prospective trial in 155 patients who were randomized to atorvastatin 80 mg or placebo. The average LDL cholesterol was 134 mg/dL and the average valve area was 1.0 cm-sq and heavily calcified at study onset. Despite a 50% reduction in the LDL cholesterol there was no effect on stenosis regression as measured by Doppler echocardiography or CT calcium score of the valve.[49] In the other prospective trial those patients with degenerative aortic stenosis having an AVA of >1.0 cm-sq for which a statin was indicated because of hyperlipidemia were placed in the treatment arm and given rosuvastatin 20 mg daily (not randomized) and the control arm were those patients not having an indication for statin therapy by guidelines.[50] The LDL did not significantly change in the nontreatment arm, but decreased by 40% in the statin arm. The annualized reduction in AVA in those treated with a statin was 0.05 cm-sq per year compared with 0.1 cm-sq in the control arm ($p=0.041$). Although many patients with aortic stenosis will have concomitant reasons for statin therapy, the question remains as to whether those without indications would benefit from therapy and of what intensity.

Two ongoing randomized trials will hopefully help clarify this question. The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) will randomize over 1800 patients with asymptomatic mild to moderate aortic stenosis to simvastatin 40 mg and ezetimibe 10 mg daily versus placebo[51]. The ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) trial, a multicenter trial to study the effect

of rosuvastatin on aortic stenosis progression will randomize 272 patients with mild to moderate aortic stenosis to receive 40 mg rosuvastatin daily or placebo.[52] For obvious ethical reason patients who had a valid indication for statin therapy were excluded from both of these trials. Results from ASTRONOMER should be available at the end of this year.

Potential Targets for Pharmacotherapy

Our developing understanding of the pathology of aortic valve stenosis/calcification has been instrumental in the identification of several pharmacotherapeutic targets. Strategies that have been identified as possible targets include leaflet endothelial layer disruption, activation of the inflammatory cascade, release of inflammatory cytokines, lipoprotein accumulation and deposition, lipid oxidation, angiotensin mediated effects, tissue calcification and osteogenesis. Ongoing and future research efforts will identify the most promising pathways to prevent the progression of aortic stenosis.

Is there a future role for percutaneous AVR?

Currently, the placement of a percutaneous aortic valve is limited only to those patients with severe symptomatic aortic stenosis who are not surgical candidates and can be enrolled in an approved clinical trial. Before consideration of utilizing this procedure for patients with severe asymptomatic aortic stenosis the morbidity and mortality from this procedure must be similar or better than that of open aortic valve replacement and long term outcomes of this procedure need to be defined.

Conclusions

Natural History of Severe Asymptomatic Aortic Stenosis

The three studies which have studied the natural history of severe asymptomatic stenosis have found that the majority of patients will develop symptoms within a five year period, however the actual risk of sudden cardiac death remains relatively low (1% per year) in the absence of symptoms. As we struggle to decide upon the most appropriate

timing of aortic valve replacement for our truly asymptomatic patients with aortic stenosis we must carefully individualize our advice to each patient based upon assessment of their predictors for disease progression, perioperative risk and whether the long term morbidity and mortality of living with a heart valve prosthesis is outweighed by potential benefits.

Current data have shown that a moderate to severe degree of aortic valve calcification is predictive of symptom onset within 2 years in most patients; however consensus is still needed on the best manner in which to quantify aortic valve calcium and parameters defined. An aortic jet velocity of more than 4.0 to 4.5 m/sec and the rate of change in this velocity have both been shown to be predictive of symptom development within 2 years. Both aortic valve area and left ventricular hypertrophy have been shown to be independent predictors of cardiac symptom development, as well as determinants of long term survival after AVR.

Future Suggestions

A future update of the current guidelines should factor in consideration of the deleterious effects of both abnormally low and high degrees of compensatory hypertrophy, more definitive recommendations on symptom development during exercise and guidance on the use of exercise for assessing prognosis, and provide stronger indications for those with the most severe degrees of stenosis (even in the absence of symptoms) . Clearly, the decision to refer someone for AVR in the absence of symptoms is complex and based upon imperfect and limited data. It would be helpful to develop a Markov decision analysis to help risk stratify our truly asymptomatic patients. The risk to benefit ratio of referring an asymptomatic patient with aortic stenosis will constantly evolve as further advances are realized in prosthetic valves and options for medical therapy to prevent progression become available.

Pathogenesis of Calcific Aortic Valve Disease & Clinical Implications

Finally, our understanding of the pathogenesis of aortic sclerosis/stenosis is rapidly evolving. The past decade of research has demonstrated many similarities between atherosclerosis and the development of calcific aortic valve disease. No longer can we think of the aortic valve as a passive bystander subjected to mechanical stress and inevitable deposition of calcium. The aortic valve is a dynamic canvas with complex pathobiology involving forces of mechanical and shear stress, the deposition of

inflammatory cells and lipoproteins resulting in the proliferation of valvular fibroblasts and bony formation. With our current knowledge we are now in a position to aggressively explore preventative strategies and pharmacotherapeutic options to prevent the progression of this very common valve disease. There is no equivalent of an acute coronary syndrome in aortic valve disease. This progressive valve disease often remains silent until its later stages and by then intervention to retard progression may be too late. It has yet to be determined whether early intervention (ie when aortic sclerosis is present in the absence of stenosis) will prove beneficial in the prevention of progression to valve stenosis. Death from cardiovascular disease has been significantly reduced largely through the efforts of prevention and treatment of coronary artery disease. It is now time to apply similar efforts toward calcific aortic valve disease and perhaps we will realize a decline in the incidence of aortic valve stenosis despite the aging of our population

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