Journal of the American College of Cardiology
© 2004 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 44, No. 6, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.06.031

Conditions Regarding Coronary Surgery

Should Coronary Artery Bypass Graft Surgery Patients With Mild or Moderate Aortic Stenosis Undergo Concomitant Aortic Valve Replacement?

A Decision Analysis Approach to the Surgical Dilemma

William T. Smith IV, MD,* T. Bruce Ferguson, JR, MD,† Thomas Ryan, MD, FACC,* Carolyn K. Landolfo, MD, FACC,* Eric D. Peterson, MD, MPH, FACC*

Durham, North Carolina; and New Orleans, Louisiana

OBJECTIVES This study utilizes Markov decision analysis to assess the relative benefits of prophylactic aortic valve replacement (AVR) at the time of coronary artery bypass graft surgery (CABG). Multiple sensitivity analyses were also performed to determine the variables that most profoundly affect outcome.

BACKGROUND The decision to perform CABG or concomitant CABG and AVR (CABG/AVR) in asymptomatic patients who need CABG surgery but have mild to moderate aortic stenosis (AS) is not clear-cut.

METHODS We performed Markov decision analysis comparing long-term, quality-adjusted life outcomes of patients with mild to moderate AS undergoing CABG versus CABG/AVR. Age-specific morbidity and mortality risks with CABG, CABG/AVR, and AVR after a prior CABG were based on the Society of Thoracic Surgeons national database (n = 1,344,100). Probabilities of progression to symptomatic AS, valve-related morbidity, and age-adjusted mortality rates were obtained from available published reports.

RESULTS For average AS progression, the decision to replace the aortic valve at the time of elective CABG should be based on patient age and severity of AS measured by echocardiography. For patients under age 70 years, an AVR for mild AS is preferred if the peak valve gradient is >25 to 30 mm Hg. For older patients, the threshold increases by 1 to 2 mm Hg/year, so that an 85-year-old patient undergoing CABG should have AVR only if the gradient exceeds 50 mm Hg. The AS progression rate also influences outcomes. With slow progression (<3 mm Hg/year), CABG is favored for all patients with AS gradients <50 mm Hg; with rapid progression (>10 mm Hg/year), CABG/AVR is favored except for patients >80 years old with a valve gradient <25 mm Hg.

CONCLUSIONS This study provides a decision aid for treating patients with mild to moderate AS requiring CABG surgery. Predictors of AS progression in individual patients need to be better defined. (J Am Coll Cardiol 2004;44:1241–7) © 2004 by the American College of Cardiology Foundation

Patients diagnosed with coronary disease requiring coronary artery bypass graft surgery (CABG) may also have mild to moderate aortic stenosis (AS) (1). Co-presentation with both coronary and valve disease is increasing as the age of patients referred for CABG surgery rises. If AS is severe (2,3) or the patient has symptoms, aortic valve replacement (AVR) should be performed in conjunction with CABG surgery (4,5). There is controversy, however, over the appropriate care of asymptomatic patients with mild or moderate stenosis (1,4–7). If no intervention is done at the time of CABG, AS symptoms may develop, necessitating a second open-heart procedure (AVR), with additional technical challenges and complications (1,6,8–10). Conversely, an initial CABG/AVR increases the initial operative risk and exposes patients to potential long-term valve-related complications (11). Numerous clinical factors, including severity and rate of progression of AS, patient life expectancy, and probability of valve- or operative-related complications, must be considered in making this decision.

This study utilizes Markov decision analysis to assess the relative benefits of prophylactic AVR. Multiple sensitivity analyses were also performed to determine the variables that most profoundly affect outcome, and to recommend treatment thresholds.

METHODS

Markov decision analysis. A Markov decision analysis synthesizes probabilities of multiple clinical outcomes in the assessment of competing treatment strategies (12). The Markov model structure utilized in this study is represented in Figure 1. The model evaluates CABG/AVR or CABG

From the *Duke University Medical Center, Durham, North Carolina; and †Louisiana State University, New Orleans, Louisiana. No support was received for this study. Dr. Peterson is a recipient of a Paul Beeson Career Development Award. Dr. Landolfo is currently affiliated with the Medical College of Georgia, Augusta, Georgia.

Manuscript received January 23, 2004; revised manuscript received April 20, 2004, accepted June 7, 2004.

JACC Vol. 44, No. 6, 2004
September 15, 2004:1241–7

Abbreviations and Acronyms

- ACC = American College of Cardiology
- AHA = American Heart Association
- AS = aortic stenosis
- AVR = aortic valve replacement
- CABG = coronary artery bypass graft surgery
- CAD = coronary artery disease
- QALY = quality-adjusted life year
- STS = Society of Thoracic Surgeons

alone as initial therapy in a patient with mild or moderate asymptomatic AS in whom a CABG is indicated. Patients who survive the index surgery without morbidity are initially in the "alive without events" state. Those who suffer operative morbidity are placed in the "alive with morbidity" state, and those who die as a result of operation are placed in the absorbing state, "dead."

There are potential transitions to other health states during each Markov cycle (one month in our model) that depend on the patients' current state of health. Those who survive CABG alone may develop AS symptoms, remain alive without symptoms, or die of other causes. If symptoms develop, a reoperation for AVR may be performed or the patient may not be an operative candidate, in which case he or she transitions to the "alive with symptomatic AS" state. Similarly, if AVR is performed (initially or when AS symptoms develop), patients may remain alive without complication, die of other causes, or develop complications related to the valve. In each health state, there are probabilities of transitioning to another state or dying of a competing morbidity, as shown in Figure 1.

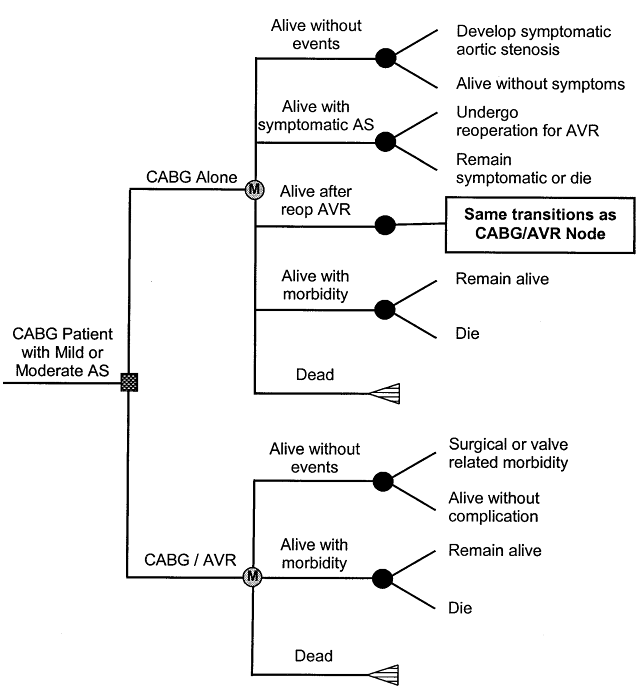

Figure 1. Schematic representation of Markov decision model structure. AS = aortic stenosis; AVR = aortic valve replacement; CABG = coronary artery bypass graft surgery.

Assumptions. Several assumptions were made to simplify the decision analysis. The population was assumed to be free from non-cardiac life-threatening morbidity. There were neither explicit indications nor contraindications for warfarin anticoagulation therapy. We also assumed all patients undergoing AVR would receive a mechanical prosthesis. In sensitivity analysis, the alternative strategy of using a bioprosthetic valve in patients over 70 years of age was assessed (13). With this strategy, the model was modified to eliminate valve-related complications, substituting the possibility of valve deterioration.

Input variables. All input variables and their sources are noted in Table 1. Age-specific mortality was obtained from the 1998 U.S. life tables (14). Excess mortality in patients with coronary artery disease and AS (15,16) as well as excess mortality in patients who develop morbidity (17) were added to these rates. Operative mortality was obtained from the Society of Thoracic Surgeons (STS) national database (18). Age- and procedure-specific mortality rates were grouped by decade as shown in Table 2, and linear interpolation was used to extrapolate an age-specific rate for a patient between the given age ranges. The rate of mortality among patients with symptomatic AS was abstracted from published reports (19), as were the likelihoods of complication or morbidity from a mechanical valve (20).

The risk of developing symptoms was modeled after Otto et al. (9). A linear least-squares regression was performed to define a rate of symptom development for patients at variable valve gradients. To interpolate over a continuous range of valve gradients, the probability of developing AS symptoms without any echo gradient was defined as 0, and the probability with a gradient of 5.5 m/s was 0.99. The fraction of patients who develop symptomatic AS but are no longer surgical candidates (or who decline surgery) was also modeled after the Otto et al. (9) data.

In the sensitivity analysis of bioprosthetic valves, the probability of spontaneous valve deterioration was modeled after Birkmeyer et al. (21) and varies according to patient age and the time since valve implant, or $3.48 \cdot \exp[-9.92 - 0.358 \cdot (\text{patient age} - 60/10) \cdot (\text{years since implant})^{2.48}]$. Mortality and morbidity of a repeat AVR for valve deterioration were assumed to be equal to those of an AVR following CABG.

Quality-of-life adjustments. Absolute survival and quality-adjusted survival were calculated for each management strategy. Future years of life were discounted at a rate of 3% per year (22). The utility of a year of life with significant morbidity, including symptomatic AS (23), stroke (24), permanent renal failure (24), and long-term morbidity from hemorrhagic complications (25), was discounted at a rate of 0.50. The relative utility of a year of life on chronic warfarin anticoagulation therapy was 0.99 relative to no anticoagulation therapy (26).

Table 1. Model Input Variables

	Value	Range	Source
Surgical mortality and morbidity	Age- and procedure-specific	75%–125% of rate	STS database
Age-related mortality	Age-specific	—	U.S. life tables (14)
Excess population mortality with CAD and AS (%)	1.4/yr	1.1–1.4	(15, 16)
Excess mortality with permanent morbidity (%)	3.75/yr	—	(17)
Mortality with symptomatic AS (%)	23.9/yr	9.6–35.8	(19)
Rate of AS progression (mm Hg/yr)	5	1–13	(1,9)
Probability of developing AS symptoms	Relates to baseline valve gradient	75%–125% of rate	(9)
Probability of refusing AVR or nonsurgical candidate when AS symptoms develop (%)	7.7	3.8–15.4	(9)
Serious bleeding after AVR (%/yr)	2.7	1.3–6.2	(20)
Permanent morbidity after bleeding complication (%)	22	—	(20)
Mortality after bleeding complication (%)	12.2	6–24	(20)
Thromboembolic risk after AVR (%/yr)	0.7	0.3–1.3	(20)
Permanent morbidity after thromboembolism (%)	67.5	—	(20)
Mortality after thromboembolism (%)	4.4	2.2–8.8	(20)
QALY survival with morbidity (yrs)	0.5	0.4–0.75	(23–25)
Utility of anticoagulation therapy (yrs)	0.99	0.9–1.0	(26)
Discount for future life-years relative to current year of life (%)	3 annually	1–5	(22)

AS = aortic stenosis; AVR = aortic valve replacement; CAD = coronary artery disease; QALY = quality-adjusted life year; STS = Society of Thoracic Surgeons.

Sensitivity analyses. Multiple sensitivity analyses were performed to test the stability of our model with variation of selected model input parameters within reasonable ranges (Table 1). The decision tree shown in Figure 1 was constructed, and all the analyses described above carried out using DATA (TreeAge Software Inc., Williamstown, Massachusetts).

RESULTS

Acute surgical risks. Between 1995 and 2000, 1,344,100 patients underwent CABG, CABG/AVR, or AVR after a prior CABG in the STS national database. Mortality and morbidity rates for these procedures stratified by patient age are shown in Table 2. The operative mortality increased with increasing age for each respective operation, from 1.33% for a patient under age 55 years undergoing CABG alone, to 11.34% for a patient over age 75 years undergoing AVR after a prior CABG. Operative mortality was higher for a patient undergoing AVR after CABG than for a patient undergoing simultaneous CABG/AVR, as was the risk of developing a morbid complication. The risk of permanent stroke or renal failure for a patient undergoing surgery that involved AVR (either at the time of CABG or subsequently) was about twice the risk of CABG alone.

Life expectancy from Markov modeling. A hypothetical 65-year-old patient with asymptomatic AS of varying severity demonstrates the model's major findings. The quality-adjusted life expectancy for such a patient undergoing CABG varies from 8.6 years with a baseline valve gradient of 50 mm Hg, to 9.1 years for a valve gradient of 10 mm Hg. Alternatively, the survival rate after initial CABG/AVR is 8.9 years. Therefore, CABG alone is superior at lower baseline valve gradients, and initial CABG/AVR is the best management if the gradient is over 30 mm Hg.

Absolute mathematical event rates for a 65-year-old patient with a baseline peak aortic gradient of 30 mm Hg and an average rate of AS progression (5 mm Hg/year) are shown in Table 3. Because of perioperative risks from

Table 2. Mortality and Morbidity Rates by Age With Various Operations From the STS National Database, 1995–2000

	Age Group (yrs)			
	<55	55–64	65–74	>75
CABG only (n)	231,448	332,938	437,500	260,452
Operative mortality (%)	1.33	1.85	3.17	5.69
Permanent stroke (%)	0.54	0.99	1.94	3.00
Renal failure complication (%)	1.59	2.35	4.02	6.5
CABG/AVR (n)	4,036	10,030	27,784	34,852
Operative mortality (%)	4.01	3.87	5.55	8.65
Permanent stroke (%)	0.89	1.73	2.87	4.59
Renal failure complication (%)	3.57	4.79	6.60	9.52
AVR only (with prior CABG) (n)	142	576	1,926	2,416
Operative mortality (%)	4.23	8.68	8.20	11.34
Permanent stroke (%)	4.23	3.47	3.01	4.55
Renal failure complication (%)	0.00	6.25	6.96	11.26

CABG = coronary artery bypass graft surgery; other abbreviations as in Table 1.

JACC Vol. 44, No. 6, 2004
September 15, 2004:1241–7

Table 3. Modeled Event Rates Over Time for a 65-Year-Old Patient With Baseline Peak Aortic Valve Gradient by Echo of 30 mm Hg and Progression Rate of AS of 5 mm Hg/Yr

	Immediate	1 yr	5 yrs	10 yrs	15 yrs
CABG (%)					
Event free	92.8	84.8	51.4	17.2	1.2
Successful reop AVR	0	4.0	19.8	31.6	29.3
Symptomatic AS	0	0.4	1.4	1.6	1.0
Morbid event	4.7	4.9	6.3	8.0	7.9
Death	2.5	5.9	21.1	41.6	60.6
CABG/AVR (%)					
Event free	87.3	83.5	68.7	51.2	35.1
Morbid event	8.0	8.3	9.4	9.2	7.7
Death	4.7	7.5	22.0	39.7	57.1

Abbreviations as in Tables 1 and 2.

combined CABG/AVR, the immediate post-surgical outcome is superior for patients receiving CABG alone. Over time, patients who initially receive CABG develop symptoms due to AS and require reoperation. Subsequent morbidity and mortality eventually exceed the up-front surgical risk of a combined CABG/AVR.

Effect of varying patient age and baseline aortic valve gradient. Patient age and peak aortic valve gradient by echo were important variables in determining treatment when progression of AS is constant. Figure 2 displays the threshold at which CABG alone is superior to CABG/AVR, varying age and peak valve gradient. Coronary artery bypass graft surgery alone is preferred in older patients because reduced life expectancy diminishes the likelihood that AS will progress to symptoms. A 60-year-old patient with a gradient of 30 mm Hg should have CABG/AVR, but an 80-year-old patient with the same gradient should undergo CABG alone, according to our data.

Mathematical differences in survival for patients undergoing CABG alone versus CABG/AVR are shown in Table 4 across a range of patient ages and baseline aortic valve gradients. Positive values indicate longer survival (in months) for patients undergoing CABG alone. For young patients with gradients above the threshold for performing CABG/AVR, about 21 days are gained for every 5-mm Hg increase in valve gradient. In older patients undergoing CABG, about 10 days of life expectancy are gained for each 5-mmHg decrease in valve gradient.

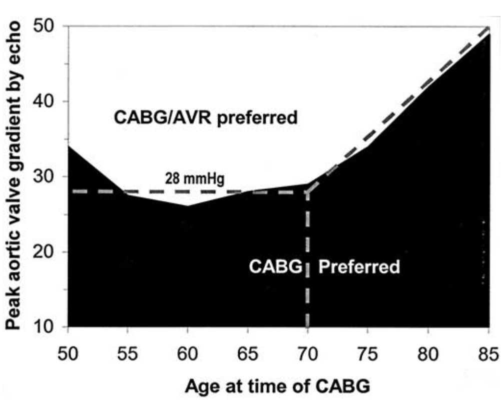

Figure 2. Using quality-adjusted survival as the outcome measure, at low baseline gradients and in older patients, CABG alone is the preferred strategy for management of a patient with mild, asymptomatic aortic stenosis undergoing coronary bypass surgery. CABG/AVR is favored for patients of all ages with a valve gradient over 50 mm Hg, and for patients under age 70 once their valve gradient reaches about 28 mm Hg. This assumes a constant rate of AS progression of 5 mm Hg/year. Abbreviations as in Figure 1.

Effect of variation in the rate of AS progression. Figure 3 illustrates the effect of varying AS progression rate on the decision to undergo CABG surgery or CABG/AVR. At a slow progression of 3 mm Hg/year, nearly all patients with asymptomatic AS should undergo CABG alone. As the rate of progression increases to 11 mm Hg/year, virtually all patients benefit from concomitant CABG/AVR.

Sensitivity analysis of other variables. Treatment decisions were not significantly affected by most other variables over clinical ranges (Table 1). Varying the rate of stroke or bleed from anticoagulation, probability of valve thrombosis, rate of death with symptomatic AS, and changes in rates of death from operative morbidity had little impact on treatment thresholds. Similarly, varying the quality-adjustment ratios for permanent morbidities made little difference in the overall decision.

We also found that the model results changed little when surgical morbidity and mortality rates were varied 20% above or below the STS national average. Finally, altering the decision analysis model to allow for insertion of a bioprosthesis in patients over age 70 years was superior, yet CABG/AVR with bioprosthesis still impacts only a few additional patient scenarios.

In contrast, the value of one year of life on anticoagulation therapy did affect the model's conclusions. Specifically, if patient displeasure from anticoagulation therapy reduces the value of one year of life on warfarin by 10% or more, then essentially all patients with a baseline valve gradient below 50 mm Hg should receive CABG alone, on the basis of the model data.

DISCUSSION

The clinical management of patients with mild or moderate AS at the time of coronary artery surgery remains a complex problem. This study is the first to incorporate a decision analysis approach as a means of simultaneously controlling for many factors that can affect the ultimate decision between CABG and CABG/AVR strategies.

Previous studies of AVR at the time of CABG. The American Heart Association/American College of Cardiology task force recommends valve replacement at the time of coronary surgery if asymptomatic patients have severe AS, but the task force acknowledges limited data to support a policy of replacing a valve that exhibits only mild or moderate AS (4). Small case series of CABG versus CABG/AVR for mild to moderate AS patients exist and have had conflicting treatment recommendations. In one series, only 8 of 51 patients with mild AS (16%) who had CABG alone required subsequent AVR at a mean of 71

Table 4. Absolute Differences in Quality-Adjusted Survival (in Months) Across Peak Aortic Valve Gradient **(Rows)** and Ages **(Columns)**

	Ages (yrs)							
	50	55	60	65	70	75	80	85
Peak aortic valve gradient (mm Hg)								
50	(3.15)	(5.26)	(5.62)	(4.44)	(3.85)	(2.81)	(1.14)	(0.11)
45	(2.19)	(4.15)	(4.47)	(3.44)	(2.95)	(1.97)	(0.45)	**0.40**
40	(1.21)	(3.03)	(3.33)	(2.45)	(2.06)	(1.15)	**0.21**	**0.88**
35	(0.19)	(1.88)	(2.19)	(1.45)	(1.16)	(0.34)	**0.85**	**1.34**
30	**0.89**	(0.69)	(1.02)	(0.43)	(0.23)	**0.48**	**1.49**	**.79**
25	**2.02**	**0.56**	**0.20**	**0.64**	**0.73**	**1.33**	**2.13**	**2.24**
20	**3.22**	**1.87**	**1.47**	**1.75**	**1.73**	**2.19**	**2.79**	**2.70**
15	**4.48**	**3.23**	**2.79**	**2.91**	**2.75**	**3.07**	**3.44**	**3.15**
10	**5.81**	**4.65**	**4.16**	**4.11**	**3.82**	**3.97**	**4.11**	**3.60**

Bold values indicate survival advantage for CABG-alone strategy. Parenthetical numbers indicate mean superior survival for CABG/AVR strategy.
Abbreviations as in Tables 1 and 2.

months (27). Additionally, no differences in overall or cardiac-related mortality were demonstrated among 476 patients with mild or moderate AS who underwent CABG/AVR (n = 414) or CABG but not AVR (n = 62), but the estimated need for AVR (based on Kaplan-Meier event-free survival curves) at 72 months of follow-up was 24% in patients who underwent CABG and only 3% in patients undergoing AVR (7). An analysis by Rahimtoola (28) used surgical mortality and post-operative survival rates for CABG or CABG/AVR from published reports to calculate that prophylactic AVR is contraindicated in most patients with mild or moderate AS. Unfortunately, this analysis used cohorts of patients with coronary disease only as the basis for the natural history after CABG surgery. Patients with any degree of AS are likely at higher risk, and comparing their outcomes with those of patients without AS biases this article in favor of CABG surgery alone.

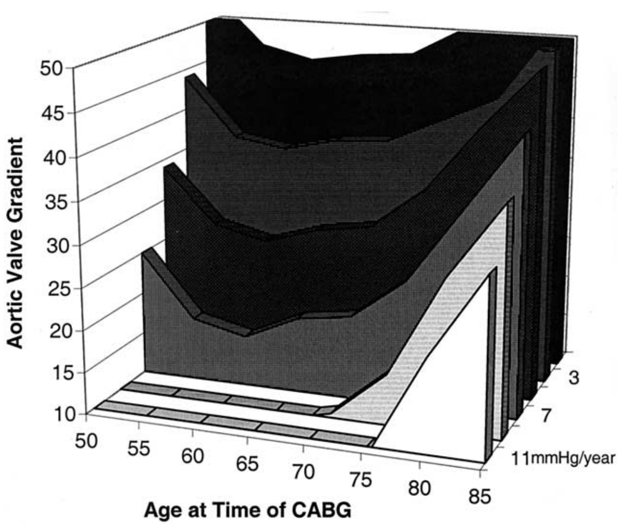

Figure 3. As the rate of progression of aortic stenosis increases from 3 mm Hg/year to 11 mm Hg/year, CABG alone **(hatched areas)** is favored in a smaller subset of patients. At a rate of 3 mm Hg/year, nearly all patients with mild AS should undergo CABG alone; at a rate of 11 mm Hg/year, only the elderly with very low gradients should be considered for CABG without coincident AVR. Abbreviations as in Figure 1.

Information from the current study. The decision model permits tailoring of recommendations on the basis of patient age and valve gradient as shown in Figure 2. Assuming an average rate of progression of AS (5 mm Hg/year [1,9,29]), patients under age 70 years with a valve gradient >30 mm Hg benefit from CABG/AVR. For older patients, competing mortalities gradually increase the gradient threshold at which an AVR should be performed by roughly 1 to 2 mm Hg/year. Although treatment decisions change, we should note that the absolute survival differences are generally small except at the extremes of age and valve gradient.

A major finding from our sensitivity analysis was that the rate of progression of AS greatly influences the model's treatment recommendations. Thus, this study emphasizes the need for tools to accurately assess AS progression for the individual patient. To date, case series have illustrated that the rate of progression may vary markedly among individuals (30–33). If known (by serial echocardiography), an individual's rate of AS progression should replace our population averages (Fig. 3). In addition, this individual variability emphasizes the need to determine reliable clinical predictors of AS progression for those lacking serial echo measurements. Although age, valve calcification, progressive symptoms, and concomitant coronary disease (30–33) have been cited as predictors of AS progression, no uniform, consistent risk factors for progression are currently in clinical use because of inconclusiveness of the above studies.

Roughly two-thirds of patients receive mechanical prostheses (34), but in patients over age 65 years a bioprosthesis is usually recommended. Altering the current model to reflect this practice had little effect because thromboembolic and anticoagulation-related complications were partially offset by the risk of valve failure. Although the favored valve did shift with age, other variables were more critical in determining whether to replace the valve.

Limitations of the current analysis. Our model had certain simplifying assumptions that should be noted. The risk of prosthetic-valve endocarditis was not included because of very low rates (<1% at year one) of prosthetic-valve endocarditis in recent series (35). Similarly, mechanical valve failure is uncommon in contemporary practice (36) and was not incorporated into the baseline model. Rates of mortality for redo CABG or redo AVR for valve failure were not considered because of the absence of reliable rates of these event occurrences, and because no reliable estimate of mortality and morbidity rates during a redo-redo operation exist. In addition, the possibility that a life-saving revascularization procedure (redo CABG) may be performed at the time of an AVR for progressive AS or valve malfunction was not modeled. Rates of CABG mortality and morbidity are from the general STS database population and do not reflect the fact that CABG patients with AS may actually have a higher mortality rate at the time of the index operation (6). Last, we chose to use valve gradient as our marker for progression and AS severity (rather than calculated valve area) because of the strong outcome data available regarding the progression and prognosis of patients with AS of varying degrees of severity (9), as well as the difficulties in calculating an accurate aortic valve area.

In addition, although patient age was an important factor in the treatment decision, the valve replacement threshold was directly dependent on life expectancy rather than age per se. Comorbidities such as diabetes, lung disease, or permanent renal failure should be considered when determining appropriate treatment. In general, the trends illustrated in this manuscript (that younger patients with higher baseline gradients or rapidly progressive AS should undergo AVR) and individual patient characteristics should have more bearing on the decision to replace a stenotic valve rather than using an absolute valve gradient threshold for a given patient age.

Clinical recommendations. The current study provides guidance to physicians and patients who are faced with a difficult clinical decision regarding replacement of a stenotic aortic valve during coronary surgery. Three major factors affect the decision to perform CABG/AVR or CABG alone: age (or life expectancy), baseline peak aortic valve gradient by echocardiography, and rate of AS progression. Assuming an average rate of progression, CABG/AVR should be considered once the baseline gradient exceeds 30 mm Hg. Individual patient characteristics, including comorbidities, local expertise in performing operations, and patient preference are still important when making this difficult decision.

Reprint requests and correspondence: Dr. Eric D. Peterson, Duke Clinical Research Institute, P.O. Box 17969, Durham, North Carolina 27715. E-mail: peter016@mc.duke.edu.

REFERENCES

1. Fiore AC, Swartz MT, Naunheim KS, et al. Management of asymptomatic mild aortic stenosis during coronary artery operations. Ann Thorac Surg 1996;61:1693–8.
2. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovik DS, for the Cardiovascular Health Study. Association of aortic valve stenosis with cardiovascular morbidity and mortality in the elderly. N Engl J Med 1999;341:142–7.
3. Ross J, Braunwald E. Aortic stenosis. Circulation 1968;38 Suppl: V61–7.
4. Bonow RO, Carabello B, de Leon AC, et al., Committee on Management of Patients With Valvular Heart Disease. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 1998;32:1486–588.
5. Lester SJ, Heilbron B, Gin K, Dodek A, Jue J. The natural history and rate of progression of aortic stenosis. Chest 1998;113:1109–14.
6. Rahimtoola SH. "Prophylactic" valve replacement for mild aortic valve disease at time of surgery for other cardiovascular disease? . . . No. J Am Coll Cardiol 1999;33:2009–15.
7. Hochrein J, Lucke JC, Harrison JK, et al. Mortality and need for reoperation in patients with mild-to-moderate asymptomatic aortic valve disease undergoing coronary artery bypass graft alone. Am Heart J 1999;138:791–7.
8. Fighali SF, Avendano A, Elayda MA, et al. Early and late mortality of patients undergoing aortic valve replacement after previous coronary artery bypass graft surgery. Circulation 1995;92 Suppl II:163–8.
9. Otto CM, Burwash IG, Leggett ME, et al. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic and exercise predictors of outcome. Circulation 1997;95:2262–70.
10. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611–7.
11. Carabello BA. Indications for valve surgery in asymptomatic patients with aortic and mitral stenosis. Chest 1995;108:1678–82.
12. Beck J, Pauker S. The Markov process in medical prognosis. Med Decis Making 1983;3:419–58.
13. O'Rourke RA. Aortic valve stenosis: a common clinical entity. Curr Probl Cardiol 1998;23:434–71.
14. Anderson RN. United States life tables, 1998. Natl Vital Stat Rep 2001;48:1–40.
15. Peterseim DS, Cen YY, Cheruvu S, et al. Long term outcome after biologic versus mechanical aortic valve replacement in 841 patients. J Thorac Cardiovasc Surg 1999;117:890–7.
16. Lindblom D, Lindblom U, Qvist J, Lundstrom H. Long-term relative survival rates after heart valve replacement. J Am Coll Cardiol 1990;15:566–73.
17. Brooks MM, Jones RH, Bach RG, et al. Predictors of mortality and mortality from cardiac causes in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial and registry. Circulation 2000;101:2682–9.
18. Ferguson TB, Hammill B, Peterson ED, DeLong ER, Grover FL. A decade of change: risk profiles for isolated CABG procedures, 1990–1999. A report from the STS National Database Committee and the Duke Clinical Research Institute. Ann Thorac Surg 2002;73:480–90.
19. Chizner MA, Pearle DL, deLeon AC. The natural history of aortic stenosis in adults. Am Heart J 1980;99:419–24.
20. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995;333:11–7.
21. Birkmeyer NJ, Birkmeyer JD, Tosteson ANA, Grunkemeier GL, Marrin CAS, O'Connor GT. Prosthetic valve type for patients undergoing aortic valve replacement: a decision analysis. Ann Thorac Surg 2000;70:1946–52.
22. Lipscomb J, Weinstein MC, Torrance GW. Time preferences. In: Gold M, Siegel JE, Russell LB, Weinstein MC, editors. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press, 1996.
23. Hummel S, Piercy J, Wright R. An economic analysis of the survival and ventricular enlargement study: application to the United Kingdom. Pharmacoeconomics 1997;12:182–92.
24. Katz DA, Cronenwett JL. The cost-effectiveness of early surgery versus watchful waiting in the management of small abdominal aortic aneurysms. J Vasc Surg 1994;19:980–90.
25. Sarasin FP, Eckman MH. Management and prevention of thromboembolic events in patients with cancer-related hypercoagulable states: a risky business. J Gen Intern Med 1993;8:476–86.

26. Gage BF, Cardinalli AB, Albers GW. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with non-valvular atrial fibrillation. JAMA 1995;274:1839–45.
27. Tam JW, Masters RG, Burwash IG, Mayhew AD, Chan KL. Management of patients with mild aortic stenosis undergoing coronary artery bypass grafting. Ann Thorac Surg 1998;65:1215–9.
28. Rahimtoola SH. Should patients with asymptomatic, mild or moderate aortic stenosis undergoing coronary artery bypass surgery also have valve replacement for their aortic stenosis? Heart 2001;85:337–41.
29. Faggiano P, Ghizzoni G, Sorgato A, et al. Rate of progression of valvular aortic stenosis in adults. Am J Cardiol 1992;70:229–33.
30. Otto C, Pearlman A, Gardner C. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. J Am Coll Cardiol 1989;13:545–50.
31. Roger VL, Tajik AJ, Bailey KR, Oh JK, Taylor CL, Seward JB. Progression of aortic stenosis in adults: new appraisal using Doppler echocardiography. Am Heart J 1990;2:331–8.
32. Peter M, Hoffmann A, Parker C, Luscher T, Burckhardt D. Progression of aortic stenosis. Role of age and concomitant coronary artery disease. Chest 1993;103:1715–9.
33. Nitta M, Nakamura T, Hultgren HN, Bilisoly J, Tovey DA. Progression of aortic stenosis in adult men. Detection by noninvasive methods. Chest 1987;92:40–3.
34. Garver D, Kaczmarek R, Silverman B, Gross T, Hamilton P. The epidemiology of prosthetic heart valves in the United States. Tex Heart Inst J 1995;22:86–91.
35. Podesser BK, Khuenl-Brady G, Eigenbauer EDE, et al. Long-term results of heart valve replacement with the Edwards Duromedics bileaflet prosthesis: a prospective ten-year clinical follow-up. J Thorac Cardiovasc Surg 1998;115:1121–9.
36. Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola S. A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. N Engl J Med 1993;328:1289–96.