Quality-of-Life Implications of Immediate Surgery and Watchful Waiting in Asymptomatic Aortic Stenosis
A Decision-Analytic Model

Hemal Gada, MD, MBA; Paul A. Scuffham, PhD; Brian Griffin, MD; Thomas H. Marwick, MD, PhD

Background—Traditional management of severe aortic stenosis (AS) is based on delay in aortic valve replacement (AVR) until the development of symptoms. Surgery for asymptomatic AS has been proposed to reduce the small risk of sudden death before AVR and avoid heart failure (HF) after AVR. Because a trial to compare these options is unlikely, we developed a Markov model to inform the choice between immediate surgery and watchful waiting in asymptomatic AS.

Methods and Results—We defined health states as preoperative, postoperative, postcomplication, and death. We calculated the implications of watchful waiting, tissue and mechanical AVR-based on risks, transitions, utilities, and cost derived from literature review. Further analyses evaluated situations thought to favor immediate surgery and watchful waiting. Sensitivity analyses were based on the likelihood of preoperative death and HF in follow-up. In the reference case (age, 65 years; post-AVR utility, 0.9; annualized pre-AVR mortality, 1%; and post-AVR HF, 11.3%), the utility of watchful waiting was superior to that of immediate mechanical or tissue AVR (quality-adjusted life-years, 7.4 versus 5.3 versus 5.3, respectively), and the cost was less than immediate surgery. Sensitivity analyses showed immediate surgery was not likely to be more effective regardless of the yearly probability of post-AVR HF in the watchful waiting group (range, 0% to 80%). Immediate surgery was likely to be effective when pre-AVR annual mortality reached 13%.

Conclusions—Immediate surgery in asymptomatic severe AS does not improve outcomes unless risk of sudden death pre-AVR and HF after AVR are higher than currently reported. (Circ Cardiovasc Qual Outcomes. 2011;4:541-548.)

Key Words: aortic stenosis □ aortic valve replacement □ decision analysis □ cost-effectiveness

The aging of the population has made aortic stenosis (AS) one of the most frequently encountered cardiovascular diseases.1 Symptomatic patients with severe AS have a poor prognosis without aortic valve replacement (AVR), with mortality exceeding 70% within a few years of symptom onset.2 Asymptomatic patients with severe AS do not share this level of risk,3 and the timing of isolated AVR in the absence of symptoms and in the setting of preserved left ventricular (LV) systolic function remains controversial. The current guidelines support a policy of watchful waiting (WW)—frequent monitoring for the development of the cardinal symptoms of angina, syncope, and heart failure (HF)—as the cornerstone of managing asymptomatic severe AS.4,5 The most frequent concerns about WW in AS are the risks of sudden death and the development of subclinical LV dysfunction. The incidence of sudden cardiac death in patients with asymptomatic severe aortic stenosis has been reported between 0% to 4.1% per year,6 though it appears to be most often cited as less than 1% per year.3 This is thought not to justify the risk of AVR prior to the development of cardiac symptoms. Immediate performance of AVR surgery (IS) may reduce the risk of persistent HF symptoms after AVR, due to prolonged LV pressure load imposed by unoperated AS.8 On the other hand, AVR itself presents risk of both morbidity and mortality. Because this question of timing involves the risks of surgical delay on not only mortality but also morbidity, and because it is unlikely that this will be resolved by a clinical trial, we sought to compare the strategies of WW and IS for asymptomatic severe AS using a decision-analytic model, from the perspective of costs to the health care payer.

Methods

Model Development

This decision-analytic model evaluated the morbidity, mortality, and costs inherent in IS and WW for the treatment of patients with severe but asymptomatic AS. The typical clinical setting would correspond to an asymptomatic patient in whom a systolic murmur is a coincidental finding, and in whom an echocardiogram confirms the presence of severe AS with preserved LV systolic function. In this setting, IS would involve AVR, based on the echocardiographic findings alone, whereas WW would involve yearly clinical and echocardiographic review and performance of surgery with the development of symptoms or LV systolic dysfunction.

A Markov model with Monte Carlo simulations9 (TreeAge Pro 2008, TreeAge, Williamstown, MA) was used to study a hypothetical cohort of 10,000 patients through a number of health states that
arose as consequences of WW, surgery or their combination (Figure 1). The model was used to estimate quality-adjusted life years (QALY) and lifetime cost, with the most efficient as the strategy with the lowest incremental cost-effectiveness ratio (ICER). We included all medical care costs and costs incurred due to increased survival associated with cardiac disease. All future costs and outcomes were discounted at 3.0% per year, with costs estimated in 2010 US dollars. Discounting is a standard strategy used in cost-effectiveness analysis to allow comparison of present and future costs and health consequences. Cycle length is the time frame of transition from one state to the next, during which period all information is held constant. For the purposes of this analysis, cycle length was assumed to be 1 year. Patients had an initial age of 65 years, and the rest of life was simulated.

**WHAT IS KNOWN**

- Traditionally, aortic valve replacement (AVR) for severe but asymptomatic aortic stenosis is delayed until the development of symptoms.
- Earlier surgery may reduce the small risk of sudden death before AVR and avoid heart failure after AVR, but a trial to compare these options has not been performed and seems unlikely.
- Novel therapeutic strategies, such as percutaneous aortic valve insertions, may cause practitioners to rethink current recommendations.

**WHAT THE STUDY ADDS**

- A Markov model, using literature-derived parameters for a representative 65-year-old patient, shows that the utility with watchful waiting is superior to that of immediate mechanical or tissue AVR (quality-adjusted life-years, 7.4 versus 5.3 versus 5.3), at a lower cost.
- Sensitivity analyses show that immediate surgery is unlikely to be justified, on basis of preventing heart failure, unless the pre-AVR annual mortality reaches 13%.
- This decision-analysis supports the current guidelines of frequent clinical follow-up in asymptomatic aortic stenosis.

### Health States and Transitions

Data on transitions between health states were obtained from the literature and supplemented with outcomes of aortic valve surgery from the literature. The following health states and transitions were defined (Table 1).

#### Asymptomatic AS

All patients entered the model with asymptomatic severe AS. The rate of development of cardiac symptoms (and thus progression to a surgical indication) was identified from a weighted average across studies of asymptomatic AS (Table 2). This showed progression to AVR in 25% of patients in year 1 after diagnosis and 12% per year thereafter. Background age-specific mortality was used to define noncardiac death in all limbs of the model.

#### Aortic Valve Surgery

We investigated 2 postoperative states: after tissue (tAVR) and mechanical aortic valve replacement (mAVR). The performance of AVR carries a perioperative mortality risk of 3% to 4%, per the Society of Thoracic Surgery database, and in a large 20-year comparison of tAVR and mAVR there was a linearized mortality risk of 3.8% after AVR. Mortality rates appear largely dependent on a hospital’s surgical volume. In addition, the decision of whether to perform tAVR versus mAVR may be dependent on the individual surgical center. However, there is no significant difference in operative mortality between tAVR and mAVR.

#### Heart Failure

The development of HF before surgery was considered an indication for AVR and therefore not quantified in this study. The frequency of post-AVR HF was obtained from the report of Váňky et al. This reported prevalence of 11.3% may be inflated by inclusion of patients experiencing difficulty in weaning from cardiopulmonary bypass or with echocardiographic evidence of left and/or right ventricular dysfunction. For this reason, this figure was subject to sensitivity analysis.

#### Perioperative Stroke

Perioperative stroke is defined as any new temporary or permanent focal or global neurological deficit as described in published guidelines. The risk of perioperative stroke from aortic valve surgery was used was 4.8%, 21, 24 Given variability in published data, much of which may be dependent on differences in surgical volume, this figure was subject to sensitivity analysis.

#### Post-AVR Complications

The risk of post-AVR complications, including endocarditis, hemorrhage from anticoagulation, valve thrombosis, and thromboembolism, was estimated by means of linearized event rates noted in a large, 20-year comparison of tAVR (4.8±0.7%) and mAVR (5.2±0.7%).

#### Reoperation

The reoperation rate for tAVR and mAVR is reported to be approximately 1.2% at 5 years after AVR, with no significant difference between mechanical and tissue valve recipients. The reoperation rate for tAVR was anticipated to follow a previously described Weibull distribution for tissue valves.

#### Death

The background mortality rate was calculated from USA life tables. Further details regarding mortality in each health state is
Table 1. Annual Transition Probabilities and Mortality Rates (±SEM)

<table>
<thead>
<tr>
<th>Health State</th>
<th>Immediate Surgery</th>
<th>Watchful Waiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual transition probabilities for patients to experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>100% at outset</td>
<td>Year 1: 25% Subsequent years: 10% (estimated from 7 studies of asymptomatic severe AS)</td>
</tr>
<tr>
<td>Post-AVR heart failure</td>
<td>11.3%21</td>
<td>Year 1: 18% Subsequent years: 15%16</td>
</tr>
<tr>
<td>Stroke, peroperative†</td>
<td>4.8%23,24</td>
<td></td>
</tr>
<tr>
<td>Stroke, postoperative</td>
<td>Mechanical AVR: 2.5% per year</td>
<td>Tissue AVR: 2.1% per year19</td>
</tr>
<tr>
<td>Post-AVR complications*</td>
<td>Mechanical AVR: 5.2±0.7% per year</td>
<td>Tissue AVR: 4.8±0.7% per year19</td>
</tr>
<tr>
<td>Reoperation‡</td>
<td>1.2% at 5 y19</td>
<td></td>
</tr>
<tr>
<td>Annual mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death during WW in asymptomatic severe AS§</td>
<td>N/A</td>
<td>1%7</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Post-AVR21</td>
<td>8.9%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1st year: 11±2%</td>
<td>Subsequent years: 11±11%20</td>
</tr>
<tr>
<td>Post-AVR</td>
<td>3.8%18–20</td>
<td></td>
</tr>
</tbody>
</table>

AS indicates aortic stenosis; AVR, aortic valve replacement; and WW, watchful waiting. 
*Complications include endocarditis, hemorrhage, valve thrombosis, and thromboembolism. 
†Substantial variations reported for stroke, submitted to sensitivity analysis.25,26 
‡Follow-up costs for 1 outpatient visit. 
§USA life tables used to calculate the background mortality rate.28

provided in the next section. The risk of mortality in post-AVR HF was 10% per year.21 The risk of death in nonoperative stroke is 11%, and we assumed it to be similar in operative stroke.29 After the acute phase, the yearly mortality due to stroke is 11%.20

Health Outcome Information

Information regarding health outcomes was obtained from the literature, by performing searches with the words “utility” and “quality of life” (QOL) in conjunction with the health states. Table

Table 2. Utility Values for Each Health State

<table>
<thead>
<tr>
<th>Health State</th>
<th>Utility Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic AS</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.67±0.01221</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.455±0.0132</td>
</tr>
<tr>
<td>Post-AVR</td>
<td>10% disutility20</td>
</tr>
</tbody>
</table>

AS indicates aortic stenosis; AVR, aortic valve replacement. Utility is age-adjusted, declining by 0.3% per year of age.

Table 3. Costs Associated With Each Health State

<table>
<thead>
<tr>
<th>Health State</th>
<th>Mean Cost, $/y; ±SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic severe AS</td>
<td>Annual follow-up costs: $336.41*</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Yearly costs after diagnosis: $10 83227</td>
</tr>
<tr>
<td>Stroke</td>
<td>$14 155±453 (acute treatment)24</td>
</tr>
<tr>
<td>AVR (tissue)</td>
<td>Annual follow-up costs: $14 561±14 69038</td>
</tr>
<tr>
<td>AVR (mechanical)</td>
<td>$49 106±12834</td>
</tr>
<tr>
<td></td>
<td>Annual follow-up costs: $99.01 1st 5 y†</td>
</tr>
<tr>
<td></td>
<td>Annual follow-up costs: $336.41 thereafter*</td>
</tr>
<tr>
<td></td>
<td>$49 158±14164</td>
</tr>
<tr>
<td></td>
<td>Annual follow-up costs: $612‡</td>
</tr>
</tbody>
</table>

AS indicates aortic stenosis; AVR, aortic valve replacement.
*Follow-up costs for transthoracic echocardiogram plus 1 outpatient visit.33
†Follow-up costs for 1 outpatient visit.
‡Follow-up costs for 1 outpatient visit as well as annual cost of anticoagulant therapy and monitoring ($51335,36).

2 lists the findings for utilities (values obtained from preferences associated with health-related QOL, in which full health = 1.0 and dead = 0.0).30–32 Utility weights were multiplied by the duration in each health state to calculate QALYs.

Asymptomatic AS

Age-specific utility data, drawn from the Medical Expenditure Panel Survey of 38 678 individuals with valid responses, has been used to define QOL in the general population.30 These are derived from the general population using a validated questionnaire (EQ5D), the results of which are linked to utilities. This age adjustment leads utility to decline by 0.3% per year of age.

Heart Failure

The utility weight from the Cardiovascular Outcomes Research Consortium measured with the EQ-5D (the most widely used utility instrument) was 0.67 in HF patients in New York Heart Association functional classes II and III.31

Stroke

Utilities of stroke survivors vary widely; however, based on a comprehensive systematic review, we used a mean utility weight of 0.455 for disabling stroke from time trade-off and standard gamble methods.32 Stroke after open heart surgery would make it unlikely that reoperation would be considered.

After AVR

Independent of the post-AVR complications described above, utilities are compromised after AVR. We applied a 10% reduction in utility for both mAVR and tAVR, given similar complication rates.

Cost Information

The analysis took the perspective of the healthcare payer and consequently used the amount reimbursed to the provider as the cost of care (rather than the charges claimed by the providers). Information regarding costs was obtained primarily from the literature, including diagnostic-related groups, and Medicare payments for current procedural terminology codes (Table 3).33–36 Costs were converted to 2010 US$ using the health care inflation index. A willingness to pay threshold of $50 000 per QALY was applied; this threshold recognizes a societal acceptance of how much can reasonably be spent to save each QALY.

Asymptomatic AS

The cost of asymptomatic AS comprises the costs of clinical review and transthoracic echocardiography but has not been reported in the
literature. These were assumed to include the costs for an echocardiogram and follow-up consultation annually.33

AV Replacement
The weighted national estimates from the Healthcare Cost and Utilization Project nationwide inpatient sample 2010, were used to identify costs associated with AVR procedures. These data are collected by individual States and provided to the Agency for Healthcare Research and Quality (AHRQ).34 ICD-9 procedure codes were used to identify costs associated with procedures. Patients undergoing implantation of a mAVR or tAVR were attributed the different initial costs and follow-up costs, related to disparate frequency of follow-up imaging and costs associated with anticoagulation.35,36

Complications
The costs of HF include the cost of procedures and provider visits.37 The cost for the acute treatment of perioperative stroke was incorporated in the global cost of surgery. We identified the annual costs of follow-up ($14 651)—including outpatient care, rehabilitation, physician consultations, skilled nursing facility care, and home health care from a study of Medicare beneficiaries.38

Scenario Analysis
A scenario analysis was conducted based on studies reporting relatively high annual rates of symptoms (Table 2), which would then merit AVR, with a major reduction of risk from intervention given the high mortality in medical management of the symptomatic patient.39

Sensitivity Analysis
One-way sensitivity analyses were performed to identify the critical sources of variation in the input data, such as mortality in the WW arm, and the balance of post-AVR HF risk in each group. Each input factor was varied by its standard error. A threshold analysis was performed on the most influential factors to identify the point where the additional cost per QALY gained from IS was <100 000. Because of clinical concerns regarding the roles of sudden death, postoperative heart failure and perioperative stroke, these were subject to 2-way sensitivity analyses.

Probabilistic sensitivity analyses were performed from the Markov model using a Monte Carlo analysis. Distributions were assigned to probabilities and utility weights, and y distributions were assigned to costs, based on standard errors derived from the associated literature. Means and 95% credible intervals (95% CI) for each of the posterior distributions were computed on the basis of 10 000 iterations. Cost-effectiveness acceptability curves (CEACs, a method to quantify and graphically represent uncertainty in economic evaluation studies of health care technologies) were used to report the probability that the ICER for an intervention was below the predefined willingness to pay threshold of $100 000/QALY gained. The Net Health Benefit was defined as the difference between the gain in QALYs and the ratio between the difference in cost and the willingness to pay threshold.

Results
Health Outcomes and Costs of IS and WW
In the reference case (age, 65 years; post-AVR utility, 0.9; annualized pre-AVR mortality, 1%; and post-AVR HF, 11.3%), the outcomes of WW were superior to that of IS. There is a large difference in quality-adjusted survival between WW (7.4 QALYs) and both mAVR and tAVR (5.3 QALYs).

Monte Carlo Simulation
The impact of variability in the frequency of transition probabilities, utilities, and costs were examined using a Monte Carlo analysis. Figure 2 illustrates the results the costs and QALYs from 10 000 simulations for WW and IS. CEACs for the reference case and all scenarios show that IS reaches acceptability limits for funding in <50% of simulations, regardless of willingness to pay.

Sensitivity Analyses
One-way sensitivity analyses were performed for all variables, based on a clinically plausible range. The impact of these variations in expected probabilities on health outcomes in severe asymptomatic aortic stenosis; the impact of this variation is depicted in a tornado diagram (Figure 3). This analysis emphasizes that variation in the risk of sudden death, late mortality after valve replacement, HF, and surgical threshold are the main causes of variation in outcomes of IS. The impact of variability in the frequency of SD and risk of post-AVR HF were studied further in additional 1-way sensitivity analyses (Figure 4). The effect of variations in the frequency of SD on expected outcomes shows that unless the risk of sudden death in the WW arm exceeds 12% per year, WW has superior utility compared with IS (Figure 4A). However, increasing risk of post-AVR HF demonstrated no threshold value at which IS would be superior to WW (Figure 4B).

These variables were combined in 2-way sensitivity analyses incorporating the probability of stroke, sudden death and post-AVR HF (Figure 5A and 5B). In either circumstance, WW was justifiable if the risk of sudden death is <10%. The threshold was closer to this value if the risk of HF without surgery was greater, or the risk of stroke lower.

Finally, even if the utility of a post-AVR state rises to 1, the utility of an asymptomatic patient would need to be approximately 0.5 or lower for net health benefit to favor immediate surgery (Figure 6).
Discussion

This decision-analytic model, which accounts for not only mortality but also nonfatal adverse effects from aortic valve surgery, as well as cost associated with each strategy, favors watchful waiting as the superior course of action in asymptomatic patients with severe AS. Unless the currently cited rate of sudden cardiac death (approximately 1% per year) in asymptomatic patients with severe AS is significantly higher, WW is superior to IS. Although concerns about the risk of post-AVR HF are considered in the decision to send the patient for early surgery, this phenomenon did not substantially impact outcomes in this decision-analytic model in asymptomatic patients.
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with diminished LV systolic dysfunction are recommended to yearly transthoracic echocardiography, as severe AS patients in this setting have focused on outcome, but, given the age, they would be indicated to undergo concomitant AVR. Recent discussions of surgery in only 33% of patients remain free of cardiac symptoms to approximate 50% without AVR.

The outcomes of asymptomatic patients are cited to be more benign, with a mortality <1.0% per year, although only 33% of patients remain free of cardiac symptoms meriting AVR at 5 years. Recent discussions of surgery in this setting have focused on outcome, but, given the age, comorbidities, and risk of complications of these patients, analysis of symptoms or abnormal hemodynamic response during exercise testing is of value in certain patients, in whom the clinical history is unclear. Guidelines support at least yearly transthoracic echocardiography, as severe AS patients with diminished LV systolic dysfunction are recommended to undergo AVR. Should patients undergo coronary artery bypass grafting or surgery on the aorta or other heart valves, they would be indicated to undergo concomitant AVR.

There are more controversial indications mentioned in both the ACC/AHA and ESC guidelines, derived from smaller, single-center studies that would suggest benefit of isolated AVR even in the absence of unprovoked symptoms. ESC guidelines delineate asymptomatic patients with severe AS and moderate to severe valve calcification with rapid progression of peak velocity (>0.3 m/s per year) a class IIa indication for AVR. ACC/AHA guidelines assign a class IIb indication to asymptomatic patients with “extremely severe AS” (defined as an aortic valve area less than 0.6 cm², mean gradient greater than 60 mm Hg, and peak velocity greater than 5 m/s) when the patient’s operative mortality is expected to be ≤1%. Finally, LV hypertrophy may be a clue that the lesion is hemodynamically important, and ESC guidelines propose excessive LV hypertrophy (≥15 mm) in the absence of hypertension to be a class IIb indication for AVR in asymptomatic patients with severe AS.

Assumptions in the Model
The literature shows significant variation of data around the assumptions selected to populate this decision-analytic model. The assumed mortality of asymptomatic AS has been recorded as 1.4% to 4.0% in other studies than that selected but is not reported to be anywhere near the threshold of 13% shown to influence the results in the sensitivity analysis (Figure 4A). Likewise, of the 7 most recent studies of asymptomatic severe AS, the largest by Pellikka et al was a retrospective study of 622 patients, whereas the remainder of studies were prospective. This may account for the variation in requirement for AVR, which may also be driven by the knowledge of the diagnosis, as much as the development of symptoms.

The perioperative stroke rate of 4.8% is cited from a large prospective study of 16 184 patients, of whom 1830 received aortic valve surgery. It is uncertain what portion of these patients received tAVR versus mAVR, though other large studies suggest no difference between the incidence of perioperative stroke in these subgroups. Because of the recorded variation in stroke rates (to as low as 1.4% in the STS database), this was subjected to sensitivity analysis, which confirmed the minor effect of perioperative stroke on the preferred treatment.

The 10% disutility after AVR is assumed from literature assessing EQ-5D Index scores after valve surgery. It is unknown whether utility after AVR significantly differs from that of other valve surgery. Given the uncertainty regarding utility after AVR, as well as the assumption that utility of an asymptomatic patient with severe AS is that of an age-matched member of the general population, sensitivity analysis was performed. This showed that reasonable ranges of variability in these utility values do not change the outcome of the decision-analytic model.

There is only one study that has defined a risk of post-AVR HF and the mortality therein, but this does not take into account the possible additive risk, and deleterious impact on LV morphology, of WW. However, the sensitivity analysis that was used largely obviated this uncertainty, given that even a large risk of post-AVR HF in the WW arm does not affect its superior utility over IS.

Limitations
Creation of a decision-analytic model involves simplifications and assumptions from existing literature, not taking into account the variation in practice and costs between different healthcare institutions. The quantitative values quoted are, in instances, estimates drawn from means and weighted averages. This is well exemplified by the rate of postoperative HF, which is undefined in asymptomatic patients with severe AS.
AS with preserved ejection fraction. The study used to inform the model likely overestimates this problem, as 37% of patients in that study had preoperative HF and nearly 60% had NYHA FC III-IV symptoms. However, a sensitivity analysis relating to the risk of postoperative HF showed no significant impact on the difference in QALY between watchful waiting and immediate surgery (Figure 4B).

The potential contributions of comorbidities (hypertension, diabetes mellitus) were not included in the model, based on the lack of evidence of effect on outcome in observational studies. The presence of coronary artery disease was not predictive of outcome in the paper by Rosenhek et al, but there is a clear need for further research to define the role of concomitant coronary disease in determining outcomes and treatment responses in asymptomatic severe AS. Finally, idiosyncrasies of individual patient outcomes cannot be taken into account.

Conclusion
Decision-analytic models are useful tools to further understand the potential drivers of outcomes based on the current literature and may be useful in guiding therapy in situations in which a clinical trial is unlikely. The results of this analysis support the current guidelines of frequent clinical follow-up of asymptomatic patients.

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None.

References


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