Most Important Outcomes Research Papers on Valvular Heart Disease

Juliani F. Lampropulos, MD; Behnood Bikdeli, MD; Aakriti Gupta, MBBS; Purav Mody, MBBS; Vivek T. Kulkarni, AB; RuiJun Chen, BA; Kumar Dharmarajan, MD, MBA; for the Editor

The following are highlights from the new series, Circulation: Cardiovascular Quality and Outcomes Topic Reviews. This series will summarize the most important manuscripts, as selected by the Editor, which have been published in the Circulation portfolio. The objective of this new series is to provide our readership with a timely, comprehensive selection of important papers that are relevant to the quality and outcomes as well as general cardiology audience. The studies included in this article represent the most significant research in the area of valvular heart disease. (Circ Cardiovasc Qual Outcomes. 2012;5:e95-e103.)

In recent years, no field of clinical cardiology has experienced a great influx of transformational therapeutic options as has the area of valvular heart disease. Treatment of severe aortic stenosis (AS) has been revolutionized by transcatheter aortic valve replacement (TAVR), which has been shown to improve life expectancy and functional outcomes in patients with inoperable AS1,2 and to have short-term outcomes comparable to surgical aortic valve replacement (AVR) in patients at high perioperative risk.3,4 Analogously, mitral valve disease has been amenable to percutaneous valve replacement,5,6 as well as clipping procedures7 that can substantially reduce severe mitral regurgitation (MR) and improve functional outcomes. Even right-sided outcomes in patients with inoperable AS1,2 and to have short-term follow-up of 63.6 months. Relative to patients undergoing valve replacement only, thromboembolism was less in maze patients with a European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 0 to 3 (HR, 0.61; 95% CI, 0.17–2.18). Patients undergoing the maze procedure had superior left ventricular function (P<0.001) and less tricuspid regurgitation (P<0.001) at a median follow-up of 52.7 months. Conclusion: The addition of the maze procedure to mechanical valve replacement is a reasonable strategy to reduce thromboembolic events in lower-risk patients with chronic atrial fibrillation requiring lifelong anticoagulation. However, this approach cannot be recommended universally because both death and the composite end point including death were not different between treatment groups. It is possible that the 2 treatment groups were incompletely matched, because the lower age and symptomatology among patients undergoing the maze procedure point to potentially important underlying differences between groups. Finally, because patients in the maze group also underwent a rhythm control strategy after surgery, it may be that pharmacologic therapy drove differences in outcomes between the treatment groups, not the maze procedure itself.50

Long-term Outcomes of Mechanical Valve Replacement in Patients With Atrial Fibrillation: Impact of the Maze Procedure

Summary: The long-term benefits of the maze procedure in patients with chronic atrial fibrillation requiring lifelong anticoagulation who are undergoing mechanical valve replacement are unknown. The authors evaluated adverse outcomes including death, thromboembolic events, and a composite measure including death, thromboembolism, heart failure (HF), and valve-related complications in 569 patients with atrial fibrillation–related valvular heart disease undergoing mechanical valve replacement with (n=317) or without (n=252) the maze procedure. Patients were recruited from 1 center between 1999 and 2000. Those undergoing the maze procedure were placed on a postoperative rhythm control strategy, whereas others were placed on a rate control strategy. Propensity matching was used to minimize preoperative differences between groups. The authors found that patients undergoing the maze procedure were younger and less symptomatic than patients undergoing valve-only surgery. Patients undergoing maze were at similar risk of death and the composite outcome but at lower risk for thromboembolic events (hazard ratio [HR], 0.29; 95% confidence interval [CI], 0.12–0.73) compared with patients undergoing valve replacement alone at a median follow-up of 63.6 months. Relative to patients undergoing valve replacement only, thromboembolism was less in maze patients with a European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 0 to 3 (HR, 0.61; 95% CI, 0.17–2.18). Patients undergoing the maze procedure had superior left ventricular function (P<0.001) and less tricuspid regurgitation (P<0.001) at a median follow-up of 52.7 months. Conclusion: The addition of the maze procedure to mechanical valve replacement is a reasonable strategy to reduce thromboembolic events in lower-risk patients with chronic atrial fibrillation requiring lifelong anticoagulation. However, this approach cannot be recommended universally because both death and the composite end point including death were not different between treatment groups. It is possible that the 2 treatment groups were incompletely matched, because the lower age and symptomatology among patients undergoing the maze procedure point to potentially important underlying differences between groups. Finally, because patients in the maze group also underwent a rhythm control strategy after surgery, it may be that pharmacologic therapy drove differences in outcomes between the treatment groups, not the maze procedure itself.50

Survival of Kidney Transplantation Patients in the United States After Cardiac Valve Replacement

Summary: This study assessed survival of US kidney transplantation recipients after cardiac valve replacement and compared outcomes...
among patients receiving bioprosthetic versus mechanical heart valves. Using the US Renal Data System, the authors identified 1335 kidney transplantation recipients hospitalized between 1991 and 2004 that underwent replacement of mitral and aortic valves. Mean follow-up was 34.4±3.45 months. Most patients (50.3%) were between 45 and 64 years of age. Most valve surgeries (52.4%) were performed between 2000 and 2004. Tissue valves were used in 28% of patients. Survival was estimated using the life-table method. The log-rank test was used to compare survival between groups receiving bioprosthetic and mechanical valves. A Cox proportional hazard model was used to identify predictors of survival with additional propensity matching to confirm results. For the entire cohort, estimated survival at 0.5, 1, 2, 3, 5, and 10 years was 75.3%, 70.8%, 60.1%, 52.8%, 38.4%, and 16.0%, respectively. Predictors of death included age >75 years (HR, 3.76; 95% CI, 2.62–5.39), age 65 to 74 years (HR, 2.11; 95% CI, 1.65–2.68), end-stage renal disease duration, and increased comorbidity. Mortality was lower for patients receiving tissue valves (HR, 0.83; 95% CI, 0.70–0.99). Estimates did not change significantly with additional propensity matching.

Conclusion: Mortality rates are extremely high after left-sided valve replacement in kidney transplant recipients. In this study, more than one quarter of patients are dead at 1 year after surgery, and almost one half are dead at 3 years. This finding will gain increased importance as the mean age of kidney transplant recipients continues to rise and valvular heart disease becomes more common. The improved outcomes associated with the use of bioprosthetic valves are of interest because patients with renal disease are at higher risk of hemorrhage when taking anticoagulation. However, these results will need to be confirmed because the US Renal Data System database provides relatively few clinical data that may be important in risk adjustment.

Preoperative Factors Associated With Adverse Outcome After TVR

Summary: Little is known about the preoperative clinical and echocardiographic factors associated with increased mortality after TVR in patients with severe tricuspid regurgitation. The authors examined 189 patients (mean age, 67.5 years) with severe tricuspid regurgitation who underwent TVR at the Mayo Clinic (Minneapolis, MN) between 1997 and 2007. Patients were excluded if they had undergone previous tricuspid valve surgery, had congenital tricuspid valve disease, had carcinoid heart disease, had tricuspid stenosis, or underwent tricuspid valve repair rather than replacement. Operative mortality was 0% in New York Heart Association (NYHA) class II patients, 8.9% in NYHA class III patients, and 17.9% in NYHA class IV patients. NYHA class was the only significant predictor of early mortality when evaluating outcomes in all TVR patients, as well as the subset undergoing isolated TVR (68 patients). At a mean follow-up of 29.3±27.1 months, 30% of patients had died and 41% remained event free without death, hospital readmission for HF, or repeat tricuspid valve surgery. Increased NYHA class, increased comorbidity by the Charlson Index, and increased creatinine-predicted death on follow-up. Adjusted Cox analyses that included echocardiographic parameters showed that the right index of myocardial performance, a global estimate of right ventricular systolic and diastolic function, also predicted death and cardiac events. Five-year survival rates were 69.3%, 63.5%, and 36.3% in patients with NYHA functional class II, III, and IV, respectively.

Conclusion: Overall mortality at 29 months after TVR is high and is strongly correlated with NYHA functional class and other easily assessed patient characteristics, including comorbidities and serum creatinine. The additional use of echocardiographic parameters of right ventricular function can provide additional prognostic use. Although the authors indicate that surgery should be considered before the development of advanced HF or echocardiographic evidence of increased right ventricular filling pressure, these data cannot be used to plan timing of surgery in the absence of a control group; it is not surprising that sicker patients are more likely to experience adverse events.

Mitrail Valve Disease

Mitrail valve disease, especially MR, is relatively common among Americans. More than 19% of participants in the Framingham Heart Study were found to have at least mild MR. In the year 2000, it was estimated that 2 to 2.5 million Americans had moderate to severe MR, with the number expected to increase because of population aging. Although mitral stenosis has declined in both incidence and prevalence in the United States and other industrialized countries because rheumatic fever has become increasingly rare, mitral stenosis remains an important valvular problem in the developing world.

Research continues to define the clinical significance of mitral valve disease and opportunities for its correction. For example, ischemic MR has been found to be associated with worse outcomes among patients with coronary artery disease. However, it is unclear whether concomitant mitral surgery improves outcomes among patients undergoing coronary artery bypass grafting (CABG). Similarly, although PMC has been a major treatment option for patients with moderate to severe mitral stenosis and anatomy amenable to intervention, long-term follow-up data concerning the efficacy and safety of this procedure are limited.

The summaries in this section pertain to articles examining outcomes related to concomitant mitral valve surgery in patients undergoing CABG, mitral valve repair and replacement in the elderly, and PMC.

Outcomes for Mitrail Valve Surgery Among Medicare Fee-for-Service Beneficiaries, 1999–2008

Summary: The authors sought to analyze changes over time in rates of mitral valve surgery, postprocedural mortality, and 30-day readmissions through examination of a 100% sample of Medicare Fee-for-Service beneficiaries undergoing mitral valve surgery between 1999 and 2008. All patients were ≥65 years of age. Over the time period of analysis, the overall rate of mitral valve surgery per 100 000 beneficiary-years declined (56 per 100 000 beneficiary-years to 51 per 100 000 beneficiary-years). The proportion of patients undergoing surgery who had mitral valve repair versus replacement increased from 24.7% to 46.9% (P=0.001). Among patients undergoing isolated mitral valve surgery, there were significant declines in risk-adjusted 30-day mortality (8.1%–4.2%; P<0.001 for trend) and 1-year mortality (15.3%–9.2%; P=0.003 for trend) over the study period. There also was a slight decline in rates of risk-adjusted 30-day readmission (23.0%–21.0%; P=0.035 for trend). Mortality rates decreased in all age, sex, and race subgroups, as well as among patients undergoing mitral valve repair or replacement. However, mortality remained high among patients ≥85 years of age, women, and nonwhites.

Conclusion: Using real-world data, the authors point to an encouraging trend of reduced 30-day and 1-year mortality among elderly patients undergoing mitral valve surgery. The reasons for this reduction are unknown, although it may be related to increased use of valve repair versus replacement and improved patient selection because we see that overall surgical rates are declining with time. Interestingly, readmission rates have remained relatively constant, indicating that the determinants of postprocedural mortality and readmission may differ. Reductions in readmissions may therefore be an appropriate target for further intervention.

Influence of MR Repair on Survival in the Surgical Treatment for Ischemic Heart Failure Trial

Summary: MR can adversely affect the outcomes of patients undergoing CABG. Using data from the Surgical Treatment for Ischemic Heart Failure (STICH) trial, the authors reported multiple outcomes for patients in the medical therapy, CABG only, and CABG plus PMC.
valve repair treatment groups as related to the underlying degree of MR. Of the 1212 patients in STICH, noltrace MR, mild MR, moderate MR, and severe MR were reported in 435, 554, 181, and 39 cases, respectively. Among the patients in the medical therapy arm, mortality was proportionally greater with increasing MR severity (32%, 44%, and 50% in patients with no/trace, mild, and moderate to severe MR, respectively). Among the surgical patients undergoing CABG only or CABG plus mitral valve repair, the mortality benefit for concomitant mitral valve surgery was significant only after adjustment for other prognostic factors (adjusted HR, 0.41; 95% CI, 0.22–0.77; P=0.006). There was also a nonsignificant trend toward reduced mortality with CABG plus mitral valve surgery compared with medical therapy alone.

Conclusion: This study provides a large amount of information about medical and surgical outcomes in patients with various degrees of MR. Natural history data in patients who were medically managed are particularly useful. However, because the decision to perform mitral valve repair was not randomized and the criteria for distinction of MR severity may have varied across enrolling sites, it would be prudent to use additional data when making treatment decisions. Two ongoing studies by the Cardiothoracic Surgical Trials Network should be better able to clarify the benefits of treatment of ischemic MR during CABG.20,22

Late Results of PMC up to 20 Years: Development and Validation of a Risk Score Predicting Late Functional Results From a Series of 912 Patients

Summary: PMC is a standard procedure in areas with a high prevalence of mitral stenosis. In a single-center study, the authors determined the 20-year outcomes in a population of 1024 patients who underwent PMC. In patients with good immediate PMC results (n=912, with postprocedure valve area ≥1.5 cm2 and MR ≤2/4), the 20-year rate of good functional outcome (survival free from repeat PMC, mitral surgery, or NYHA functional class of III or IV) was 30.2±2.0%. The median duration between PMC and a second intervention (survival free from repeat PMC, mitral surgery, or NYHA functional class of III or IV) was 20±2.2 years. In a Cox model with interaction terms, the authors determined the predictors of late outcomes, six of which consisted of interactions between variables, including age–valve area interaction (P<0.0001) with lower impact at higher age and sex–valve calcification interaction (P<0.0001) with stronger impact of calcification in men. High residual transmural gradient also predicted poor functional outcomes (P<0.0001). The authors additionally developed a risk score for prediction of favorable outcomes among 609 randomly selected patients. The risk score was validated in the remaining 303 patients, with an overall C index of 0.71 (95% CI, 0.58–0.80).

Conclusion: This study provides unique insight into natural history of patients undergoing PMC. Successful intervention can delay further procedures for ≥8 years. However, fewer than one third of patients maintain a good functional status at 20 years postprocedure. Study findings are limited by the fact that results can be extrapolated only to highly experienced centers. In addition, the derived risk score is very complex to interpret with multiple interaction terms. Finally, no investigation was done to identify the predictors of poor short-term results.

Aortic Valve Disease

Aortic valve disease is common in the United States and affects ≥5.2 million adults ≥65 years of age.38,39 Patients with symptomatic AS have a limited lifespan after the onset of symptoms such as angina, syncope, or dyspnea,3 and prognosis is poor when these patients are treated medically.46 For this reason, surgical AVR has long been the standard of care. Prognosis in younger elderly patients without significant comorbidities is excellent after surgical AVR and mirrors age-matched control subjects without aortic valve disease.39 Prognosis after surgical AVR is also very good even in high-risk patients ≥70 years of age in whom median survival is ≥6 years.39 Yet some patients still remain ineligible for surgery because of high operative risks.39

However, the choice of therapeutic options has increased in recent years with the development of TAVR. In 2002, Cribier et al42 successfully performed the first human TAVR in a 57-year-old male patient with severe calcific AS who was ineligible for surgical AVR because of significant comorbidities. Since then, TAVR has been performed many thousands of times with good short-term results.41 Randomized data with the Edwards SAPIEN valve43 have shown better short-term outcomes with TAVR compared with medical management in patients with inoperable AS,43 as well as a 1-year outcome comparable to surgical AVR in patients with high perioperative risk.44 Further trials are testing the safety and efficacy of the Medtronic CoreValve for patients with symptomatic AS at high risk for surgical AVR. Additional postmarketing surveillance of both Edwards and Medtronic valves is ongoing in Europe.45

In light of the expanding therapeutic options for aortic valve disease, increased attention is being directed to patients with severe but asymptomatic AS. Despite being asymptomatic, this population has been found to have a yearly risk of sudden death of ≥1%44,45 and a risk of postoperative mortality of ≥3% to 4%.46 Although some retrospective data suggest a possible benefit to early surgical AVR in patients with asymptomatic severe AS,47 this intervention does not receive a Class I or IIa recommendation from European48 or US guidelines.49 Further prospective studies are needed to identify subsets of asymptomatic patients who are at higher risk of cardiac events and may therefore benefit from early intervention.

Given the explosion of articles pertinent to AS with the increasing focus on TAVR, we have included multiple articles on aortic valve disease. Topics include long-term outcomes after surgical AVR,48 the cost-effectiveness of TAVR in patients with severe AS,43,49 predictors of mortality after TAVR, the natural history of asymptomatic AS, and many others.


Summary: AVR has long been the standard of care for patients with operable aortic valve disease. However, there exists no benchmark of long-term survival after surgical AVR in elderly patients. This study examined long-term survival in 145 911 patients ≥65 years of age (median, 76 years of age) undergoing AVR (61 530 isolated AVR; 84 381 AVR with CABG) at 1026 centers included in the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database during 1991–2007. To identify long-term outcomes, patient records were linked to Medicare claims files using indirect patient identifiers in a previously validated algorithm, and results were stratified by age, comorbidities, and STS perioperative risk of mortality. The authors found that median survival for patients 65 to 69, 70 to 79, and ≥80 years of age undergoing isolated AVR was 13, 9, and 6 years, respectively, which was nearly identical to the age-matched general population for the 70 to 79- and ≥80-year age groups. Median survival of patients in each group undergoing AVR plus CABG was slightly worse at 10, 8, and 6 years, respectively. Severe lung disease, renal failure, left ventricular dysfunction, and prior cardiac surgery were associated with significant reductions in median survival. STS perioperative risk of mortality was moderately predictive of long-term survival overall (C index, 0.71 over 10 years). However, intermediate- and high-risk patients by STS perioperative risk of mortality were found to have similar median survival times.

Conclusion: Study results support AVR as the standard of care for operative aortic valve disease because long-term survival is excellent for all patients ≥65 years of age. In particular, the survival of patients...
70 to 79 and 280 years of age is nearly identical to that of the age-matched general population. A limitation of the study was the indirect identifier approach used to match patients in the STS database to Medicare denominator files; 25% of patients were unable to be matched, resulting in a study cohort that may not be representative of the overall surgical population with possible unmeasured confounders. Interestingly, STS perioperative risk of mortality did not appear to accurately differentiate intermediate- and high-risk patients when median survival was considered, implying that perioperative and long-term outcomes may be influenced by different factors.38

**AVR in the Elderly: Determinants of Late Outcome**

**Summary:** AVR is common in the elderly, but few studies have evaluated long-term outcomes in older patients undergoing AVR. The authors studied late survival and complications of 2890 patients ≥70 years of age (mean, 78±5 years) who underwent AVR (92% bioprostheses; 8% mechanical valves) at the Mayo Clinic between 1993 and 2007. Five-, 10-, and 15-year survival rates were 68%, 34%, and 8%, respectively. Multivariable analysis identified 11 significant risk factors for late death, with age and renal failure being the 2 most important by HR. When risk-stratified by these factors, the lowest-risk group showed a survival rate (55%) similar to that of a matched general population, whereas higher-risk groups had lower-than-expected survival. A comparison of patients receiving mechanical and bioprosthetic valves showed no significant difference in overall survival but found lower survival in the highest-risk patients receiving mechanical prostheses. The overall incidence of bioprosthetic valve deterioration was found to be low at 2.9% over the 15-year follow-up period based on the combined end points of reoperation or echocardiographic evidence of either prosthetic stenosis or moderate to severe regurgitation. However, late echocardiographic follow-up (mean interval, 4.4±3.2 years) was available in only 63% of patients.

**Conclusion:** The overall survival of patients after AVR is strongly influenced by age and several other mostly nonmodifiable factors, suggesting that earlier surgical referral may be a strategy that merits further testing. Attention to risk in patients with chronic kidney disease also seems to be particularly important. The lack of validation of risk of death, with age and renal failure being the 2 most important by HR. When risk-stratified by these factors, the lowest-risk group showed a survival rate (55%) similar to that of a matched general population, whereas higher-risk groups had lower-than-expected survival. A comparison of patients receiving mechanical and bioprosthetic valves showed no significant difference in overall survival but found lower survival in the highest-risk patients receiving mechanical prostheses. The overall incidence of bioprosthetic valve deterioration was found to be low at 2.9% over the 15-year follow-up period based on the combined end points of reoperation or echocardiographic evidence of either prosthetic stenosis or moderate to severe regurgitation. However, late echocardiographic follow-up (mean interval, 4.4±3.2 years) was available in only 63% of patients.

**Conclusion:** The overall survival of patients after AVR is strongly influenced by age and several other mostly nonmodifiable factors, suggesting that earlier surgical referral may be a strategy that merits further testing. Attention to risk in patients with chronic kidney disease also seems to be particularly important. The lack of validation of risk of death, with age and renal failure being the 2 most important by HR. When risk-stratified by these factors, the lowest-risk group showed a survival rate (55%) similar to that of a matched general population, whereas higher-risk groups had lower-than-expected survival. A comparison of patients receiving mechanical and bioprosthetic valves showed no significant difference in overall survival but found lower survival in the highest-risk patients receiving mechanical prostheses. The overall incidence of bioprosthetic valve deterioration was found to be low at 2.9% over the 15-year follow-up period based on the combined end points of reoperation or echocardiographic evidence of either prosthetic stenosis or moderate to severe regurgitation. However, late echocardiographic follow-up (mean interval, 4.4±3.2 years) was available in only 63% of patients.

**Cost-effectiveness of TAVR Compared With Standard Care Among Inoperable Patients With Severe AS: Results From the Placement of Aortic Transcatheter Valves Trial (Cohort B)**

**Summary:** The Placement of Aortic Transcatheter Valve (PARTNER) trial randomized patients to receive TAVR (n=179) or standard therapy that consisted of medical management or percutaneous aortic valveoplasty as required (n=179). This substudy from the PARTNER trial evaluates the cost-effectiveness of TAVR in symptomatic patients with inoperable severe AS (cohort B) compared with standard therapy. Life expectancy, quality-adjusted life expectancy, and lifetime medical care costs were calculated on the basis of the survival, quality of life, medical resource use, and hospital cost data collected during the duration of the trial. The authors also calculated incremental cost-effectiveness for TAVR in the US context. For patients treated with TAVR, mean cost for the initial hospitalization was $78 542. Follow-up cost through 12 months was lower with TAVR compared with routine therapy ($29 289 versus $53 621) because of reduced hospitalization rates, but cumulative 1-year cost remained higher ($106 076 versus $53 621) because of the increased initial cost of the procedure. Discounted life expectancy was projected to be increased by 1.6 years (1.3 quality-adjusted life-years) at an incremental cost of $79 837 by TAVR. The incremental cost-effectiveness ratio for TAVR was thus estimated at $50 200 per year of life gained or $61 889 per quality-adjusted life-year gained. These results were stable across a broad range of uncertainty and sensitivity analyses.

**Conclusion:** In the current challenging financial context, studies assisting physicians in the delivery of high-value, cost-conscious care are critical. This analysis finds that TAVR is a justifiable intervention from a cost-effectiveness perspective because it meets the commonly accepted incremental cost-effectiveness ratio threshold of $50 000. Because improved technology and operator experience improve valve function and procedure-related morbidity, respectively, incremental cost-effectiveness may further improve with time. Limitations of this study include the lack of long-term follow-up and its inclusion of a highly selected clinical trial population.40

**Health-Related Quality of Life After TAVR in Inoperable Patients With Severe AS**

**Summary:** The authors sought to evaluate improvement in health-related quality of life with TAVR compared with routine therapy consisting of medical management or aortic valvuloplasty in patients with inoperable symptomatic severe AS of the PARTNER trial. Health-related quality of life was assessed at baseline and at 1, 6, and 12 months with the Kansas City Cardiomyopathy Questionnaire and the 12-item Short Form-12 General Health Survey. The mean Kansas City Cardiomyopathy Questionnaire summary scores (35±20) and 12-item Short Form-12 General Health Survey physical summary scores (28±7) at baseline were markedly depressed in the study population compared with the general US population. The improvement of summary scores was greater after TAVR compared with routine therapy at 1 month (mean between-group difference, 13 points; 95% CI, 8–19; P<0.001) with larger benefits at 6 months (mean difference, 21 points; 95% CI, 15–27; P<0.001) and 12 months (mean difference, 26 points; 95% CI, 19–33; P<0.001). At 12 months, TAVR patients also reported higher 12-item Short Form-12 General Health Survey physical and mental health scores with mean differences compared with standard care of 5.7 and 6.4 points, respectively (P<0.001).

**Conclusion:** In this preplanned substudy from the PARTNER trial, TAVR was associated with a significant improvement in quality of life among patients with symptomatic severe AS who were deemed inoperable. Because studies have shown that the great majority of inoperable patients undergoing TAVR survive beyond 1 year postprocedure,14,27 it is important to know whether quality-of-life benefits are sustained beyond the 12 months studied in this article. Because TAVR technology improves and the procedure becomes less morbid, it is likely that quality-of-life improvement relative to medical management will become further pronounced.22

**Incidence and Predictors of Early and Late Mortality After Transcatheter Aortic Valve Implantation in 663 Patients With Severe AS**

**Summary:** Information on the incidence and predictors of both early mortality at 30 days and late mortality between 30 days and 1 year after transcatheter aortic valve implantation (TAVI) with the self-expanding CoreValve Revalving prosthesis remains scarce. Using data from a multicenter registry, the authors sought to provide information on incidence and predictors of early and late mortality in a total of 663 patients (mean age, 81.0±7.3 years) with symptomatic severe AS undergoing TAVI at 14 Italian centers. Procedural success and intraprocedural death occurred in 98% and 0.9% of patients, respectively. The cumulative incidence of mortality was 5.4% at 30 days, 12.2% at 6 months, and 15.0% at 1 year. Independent predictors of mortality at 30 days included conversion to open heart surgery (odds ratio [OR], 38.68), cardiac tamponade (OR, 10.97), major...
access site complications (OR, 8.47), left ventricular ejection fraction <40% (OR, 3.51), prior balloon valvuloplasty (OR, 2.87), and diabetes mellitus (OR, 2.66). Prior stroke (HR, 5.47), postprocedural paravalvular leak ≥2+ (HR, 3.79), prior acute pulmonary edema (HR, 2.70), and chronic kidney disease (HR, 2.53) were independent predictors of mortality between 30 days and 1 year. The discriminative ability of the logistic EuroSCORE for predicting risks of 30-day and 1-year mortality was weak (c statistic 0.55 for both).

Conclusion: This study describes long-term predictors of success after TAVI with the third-generation CoreValve Revalving System. Not surprisingly, the data indicate that early mortality was largely affected by procedural complications, whereas late mortality was influenced significantly by comorbidities. Importantly, the logistic EuroSCORE showed a weak discriminative ability in predicting both 30-day and 1-year mortality, highlighting the need for novel TAVI-specific scores such as the recently proposed Karmofsky index used in the post-TAVI setting. Comparative study of the predictors of mortality when using different TAVI bioprostheses would provide additional light on whether the covariates identified in this article maintain their significance across different device types.

Correlates and Causes of Death in Patients With Severe Symptomatic AS Who Are Not Eligible to Participate in a Clinical Trial of TAVI

Summary: This single-center study aimed to detect the incidence and correlates of mortality in patients ineligible to participate in TAVI trial. From April 2007 to July 2009, 362 patients with severe AS who did not meet the necessary inclusion criteria for TAVI were screened and classified into 2 groups: Group 1 received medical treatment with or without balloon aortic valvuloplasty, and group 2 was intended to receive surgery. Groups 1 and 2 included 274 and 88 patients, respectively. In group 1, 97 patients (35.4%) were treated medically and 177 patients (64.6%) were treated with valvuloplasty. This group was of significantly higher peri-procedural risk than the surgical group, with significantly higher STS scores (12.8±7.0 versus 8.5±5.1; P<0.001) and logistic EuroSCORE (42.4±22.8 versus 24.4±18.1; P<0.001). After 1-year follow-up, mortality rate in group 1 was 37.2%, and mortality rate in group 2 was 21.5%. After multivariate adjustment, renal failure (HR, 5.60) and NYHA class IV (HR, 2.53) were independent correlates for mortality in the medical group, whereas renal failure (HR, 7.45), STS score (HR, 1.09), and logistic EuroSCORE (HR, 1.45) were correlates of mortality in the surgical group.

Conclusion: Study results demonstrate that patients with severe symptomatic AS formerly ineligible for TAVI trials will experience high mortality rates even when undergoing surgical AVR. Renal failure was an important predictor of risk in both surgical and nonsurgical patients. It is possible that indication creep in typical practice may lead to a number of these medically managed patients receiving TAVI in the future. For these patients, it is unknown whether outcomes would be similar to those receiving TAVI the PARTNER B trial.

One-year Outcome of Cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome Registry: The European Registry of TAVI Using the Edwards SAPIEN Valve

Summary: In this study, the authors have reported the 1-year outcome of TAVI using data from the Edwards SAPIEN Aortic Bioprosthesis European Outcome registry. The cohort consisted of 1038 patients who underwent TAVI at 32 centers by either transfemoral (n=575) or transapical approach (n=463). Differences in baseline characteristics of the 2 subgroups precluded any direct comparisons. Kaplan-Meier 1-year survival rates were 76.1%, 72.1%, and 81.1% for the entire cohort, transapical patients, and transfemoral patients, respectively. Definitive cardiac causes accounted for 25% (45 of 179) of all deaths, most commonly HF (62%), whereas definitive noncardiac causes accounted for nearly 50% (88 of 179) of deaths. Twenty-five percent (46 of 179) of deaths had an unknown cause. Multivariable analysis identified higher logistic EuroSCORE, renal disease, liver disease, and smoking as variables associated with higher 1-year mortality, whereas carotid artery stenosis, hyperlipidemia, and hypertension were associated with lower mortality. The authors also report that surviving patients in both the transfemoral and transapical groups have substantial improvements in functional status as measured by NYHA class.

Conclusion: Interestingly, the authors find that the majority of deaths within 1 year of TAVI resulted from noncardiac causes, thereby suggesting the need to consider the substantial comorbidity burden in the population both preprocedure and postprocedure. Risk factors for increased mortality identified in this study may allow the eventual development of TAVI-specific risk scores such as the recently proposed Karmofsky index used in the post-TAVI setting. Comparative study of the predictors of mortality when using different TAVI bioprostheses would provide additional light on whether the covariates identified in this article maintain their significance across different device types.

Prosthesis-Patient Mismatch Predicts Structural Valve Degeneration in Bioprosthetic Heart Valves

Summary: The authors sought to understand the relationship between structural valve deterioration (SVD) of bioprosthetic heart valves, classified as either stenosis type or incompetence type, and prosthesis-patient mismatch (P-Pm), which was defined by an effective orifice index <0.85 cm²/m². They analyzed 564 consecutive patients who underwent single AVR with a bioprosthetic valve. Median follow-up was 6.1 years (maximum, 16.4 years). SVD was noted in 7% of patients. In multivariable analysis, P-Pm increased (HR, 2.29; 95% CI, 1.03–5.06) and anti-calciﬁcation treatment of the bioprostheses with chemical compounds such as α-amino oleic acid decreased (HR, 0.34; 95% CI 0.17–0.66) the likelihood of SVD. Stenosis-type SVD occurred beginning 2 to 3 years after implantation and was found predominantly in patients with P-Pm, whereas incompetence-type SVD did not occur until 9 years after implantation and was more common in patients without P-Pm.

Conclusion: This study helps clarify the relationship between P-Pm and SVD by separating stenosis-type from incompetence-type SVD and identifying an association between P-Pm and earlier stenosis-type SVD. This finding indirectly supports the use of strategies that facilitate proper valve sizing. In addition, the finding that anti-calciﬁcation treatment is important in preventing valve deterioration suggests the importance of valve tissue processing to improve durability. The number of patients with SVD was very small, limiting the generalizability of these results.

Survival Comparison of the Ross Procedure and Mechanical Valve Replacement With Optimal Self-Management Anticoagulation Therapy: Propensity-Matched Cohort Study

Summary: Prior studies have suggested that the Ross procedure results in better late patient survival compared with mechanical prosthesis implantation in young adults. The authors performed a propensity score–matched study that assessed late survival (defined as survival >30 days after surgery) through the use of a cohort of 918 patients undergoing the Ross procedure and 406 patients undergoing mechanical AVR with optimal self-management anticoagulation therapy who were 18 to 60 years of age and survived the index operation (1994–2008). Data were obtained from the German-Dutch Ross Registry and the Early Self-Controlled Anticoagulation Trial-II. With the use of propensity score matching, late survival after ≥5 years of follow-up was compared between 253 patients who underwent the Ross procedure and the same number of patients who underwent mechanical valve replacement. Mean age of the matched cohort was 47.3 years in the Ross procedure.
group and 48.0 years in the mechanical valve group ($P=0.17$); the ratio of male/female patients was 3.2 in the Ross procedure group and 2.7 in the mechanical valve group ($P=0.46$). Linearized all-cause mortality rate was 0.53% per patient-year in the Ross procedure group compared with 0.30% per patient-year in the mechanical valve group (matched HR, 1.86; 95% CI, 0.58 to 5.91; $P=0.32$). Late survival was comparable to that of the general German population.

**Conclusion:** More than 45 years after Donald Ross first performed the pulmonary autograft procedure bearing his name, the comparative effectiveness of the Ross technique relative to other forms of AVR remains unclear. Using a propensity-matched cohort, the authors of this study demonstrate comparable survival in the first postoperative decade after the Ross procedure. These results contrast with a previous study demonstrating superior survival with the Ross procedure after 16 years of follow-up. The reasons for this difference in study results are unknown and may result from improved anticoagulation practices in recent years for patients with mechanical prosthesis and differences in patient selection with time. Ultimately, individual patient preferences with regard to anticoagulation and possibilities of reoperation as well as operator experience should affect the choice of procedure.

### Major Adverse Cardiac and Cerebrovascular Events After the Ross Procedure: A Report From the German-Dutch Ross Registry

**Summary:** The objective of this study was to report major cardiac and cerebrovascular events after the Ross procedure in the large adult and pediatric population of the German-Dutch Ross Registry. The authors included 1620 patients (1420 adults; 1211 male; mean age, 39.2±16.2 years) who underwent a Ross procedure between 1988 and 2008 and were followed up on an annual basis (median, 6.2 years; 10,747 patient-years). Early and late mortality were 1.2% and 3.6% (0.54% per patient-year), respectively. Ninety-three patients underwent 99 reinterventions on the autograft (0.92% per patient-year), and 63 patients underwent 78 reinterventions on the pulmonary conduit (0.73% per patient-year). Freedom from autograft or pulmonary conduit reoperation was 98.2%, 95.1%, and 89% at 1, 5, and 10 years, respectively. Preoperative aortic regurgitation and root replacement without surgical autograft reinforcement were associated with a greater hazard for autograft reoperation. Major internal or external bleeding occurred in 17 patients (0.15% per patient-year), and a total of 38 patients had composite end point of thrombosis, embolism, or bleeding (0.35% per patient-year). Late endocarditis with mediastinitis (n=16) or surgical (n=29) treatment was observed in 38 patients (0.38% per patient-year). Freedom from any valve-related event was 94.9% at 1 year, 90.7% at 5 years, and 82.5% at 10 years. Kaplan-Meier survival curves showed a lower survival rate for the pediatric population but comparable survival rate for the adult population (after excluding fatalities within 30 days) with the estimated expected survival of normal pediatric and adult populations, respectively.

**Conclusion:** The authors have characterized major adverse cardiac and cerebrovascular events after the Ross procedure through use of a relatively large registry of patients undergoing the operation. Survival rates in the pediatric population were significantly lower than expected, possibly because children are more likely to be critically ill when undergoing the operation or are having a repeat procedure after failing previous interventions for congenital AS. In contrast, survival in adults was similar to that of the normal population, thereby underscoring expectations of overall good prognosis in adults undergoing the operation. Preoperative aortic regurgitation was identified as a predictor of autograft failure and may help guide patient selection toward alternative treatment strategies including mechanical AVR.

### Quality-of-Life Implications of Immediate Surgery and Watchful Waiting in Asymptomatic AS: A Decision-Analytic Model

**Summary:** The present study examined the effectiveness of aggressive management defined as early surgical AVR compared with watchful waiting with close follow-up in patients with asymptomatic severe AS. To compare these options, the authors developed a decision-analytic model (Markov model) incorporating a reference case of a patient 65 years of age with post-AVR use of 0.9, annual pre-AVR mortality of 1%, and post-AVR HF of 11.3%. Assumptions about risks, transitions, uses, and costs associated with aortic valve (mechanical and tissue valve) replacement and watchful waiting were derived from previous studies. Sensitivity analyses based on a wide range of risk of preoperative death and postoperative HF were performed to compare the effectiveness of early surgery and watchful waiting. The use of watchful waiting was superior to that of immediate mechanical or tissue AVR (quality-adjusted life-years, 7.4 versus 5.3, respectively). Sensitivity analyses showed watchful waiting to be more effective than immediate surgery regardless of the yearly probability of post-AVR HF in the watchful waiting group (range, 0%–80%). However, immediate surgery would be preferred to watchful waiting when pre-AVR annual mortality reached 13%.

**Conclusion:** The decision of when to operate on a patient with severe asymptomatic AS is a difficult one. Study results in favor of watchful waiting are consistent with American College of Cardiology/American Heart Association guidelines and may reduce short-term healthcare costs. However, with the advent and improvement of newer technologies such as TAVR, there is a possibility of shifting treatment thresholds toward more aggressive, early replacement of the aortic valve.

### Early Surgery Versus Conventional Treatment in Asymptomatic Very Severe AS

**Summary:** The authors sought to compare the long-term results of early surgical AVR and a conventional treatment strategy among 197 asymptomatic patients (99 men; age, 63±12 years) with asymptomatic yet very severe AS. Very severe AS was defined as an aortic valve area ≤0.75 cm² accomplished by a peak aortic jet velocity ≥4.5 m/s or a mean transaortic pressure gradient ≥50 mm Hg on Doppler echocardiography. The choice of early surgery or conventional treatment was at the discretion of the attending physician. Early elective surgery was performed on 102 patients, and the conventional treatment strategy was used in 95 patients. During a median follow-up of 1501 days, there were 3 noncardiac deaths in the operated group and 18 cardiac and 10 noncardiac deaths in the conventional treatment group. The estimated 6-year mortality rate in the operated group was 0% for cardiac mortality and 2±1% for all-cause mortality, and the estimated 6-year mortality rate in the conventional treatment group was 24±5% for cardiac mortality and 32±6% for all-cause mortality. The risk of all-cause mortality for 57 propensity score–matched pairs was significantly lower in the operated group than in the conventional treatment group (HR, 0.135; 95% CI, 0.030–0.597; $P=0.008$).

**Conclusion:** The management of asymptomatic patients with very severe AS remains a controversy. There are no randomized, controlled trials to inform the management of these patients, and there are discrepancies between current guidelines. Although study results favor early surgery, they mandate careful interpretation because findings may not be applicable to low-volume centers or asymptomatic patients with high operative risk. In addition, it is unclear as to what percentage of medically managed patients with very severe AS were truly asymptomatic because symptomatic patients without high operative risk would be expected to have better outcomes with surgery.
Natural History of Very Severe AS

Summary: Although the natural history of asymptomatic AS has been under investigation for decades, little is known about asymptomatic very severe AS, with no evidence-based consensus between European and American guidelines on this topic.17 The authors prospectively followed up 116 patients with asymptomatic very severe AS (peak aortic jet velocity ≥5.0 m/s). Over a median follow-up period of 41 months, 90 patients developed an indication for AVR (mainly development of symptoms) and 6 patients had cardiac death. Event-free survival (no cardiovascular death and no guideline-recommended indication for valve surgery) was 64%, 36%, 25%, 12%, and 3% at 1, 2, 3, 4, and 6 years, respectively. Higher aortic jet velocities were associated with lower likelihood of event-free survival. The outcome was not significantly different for patients with aortic valve area <0.6 versus ≥0.6 cm² (P=0.12).

Conclusion: In this study, the authors called for early AVR for patients with asymptomatic very severe AS in light of the low rate of event-free survival. However, the mortality rates reported in this study were low and were markedly lower compared with a previous US study.44 Possible reasons for the difference in outcomes among these studies may include younger age of participants in the present study and consideration of noncardiac deaths in the previous study. To better determine the use of AVR in this population, it will be important to compare outcomes between patients with symptomatic and asymptomatic severe AS to understand the relative benefits of early intervention in a patient group without clinical symptoms.17

Outcome of Patients With Low-Gradient Severe AS and Preserved Ejection Fraction

Summary: Retrospective studies have suggested that patients with a low transvalvular gradient in the presence of an aortic valve area <1.0 cm² and normal ejection fraction may represent a subgroup with an advanced stage of aortic valve disease, reduced stroke volume, and poor prognosis requiring early surgery. The authors evaluated the outcomes of 1525 asymptomatic patients (mean age, 67 years; ejection fraction, ≥55%) with low-gradient severe AS (defined as aortic valve area <1.0 cm² and mean gradient <40 mm Hg) in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Aortic valve events (defined as AVR, congostric HF because of AS, or death resulting from cardiovascular causes) in the study cohort were compared with those in patients with moderate stenosis (aortic valve area, 1.0–1.5 cm²; mean gradient, 25–40 mm Hg). Baseline echocardiography revealed low-gradient severe stenosis in 435 patients (29%) and moderate stenosis in 184 (12%). Left ventricular mass was lower in patients with low-gradient severe stenosis than in those with moderate stenosis. During 46 months of follow-up, aortic valve events occurred in 48.5% versus 44.6%, respectively (P=0.37; major cardiovascular events, 50.9% versus 48.5%, P=0.58; cardiovascular death, 7.8% versus 4.9%, P=0.19). Low-gradient severe AS patients with reduced stroke volume index (<35 ml/m²; n=223) had aortic valve events comparable to those in patients with normal stroke volume index (46.2% versus 50.9%; P=0.53).

Conclusion: Contrary to previous reports suggesting a very poor prognosis with low-gradient aortic valve stenosis,6162 the authors demonstrated outcomes similar to those of patients having moderate aortic valve stenosis. Although inclusion of only asymptomatic patients in this study may be partly responsible, it is possible that the traditional definition of severe AS as an aortic valve area <1.0 cm² may lead to overestimation of disease severity. Recent studies46 have shown that the cutoffs for peak velocity and mean gradient incorporated in the American Heart Association/American College of Cardiology definition of severe AS do not correspond well with the valve area cutoff of 1 cm², which may need to be redefined to increase its specificity.21

Five-Year Clinical and Economic Outcomes Among Patients With Medically Managed Severe AS: Results From a Medicare Claims Analysis

Summary: Limited data exist on the medical resource use and costs incurred by Medicare patients who do not undergo valve replacement surgery despite having severe, symptomatic AS. The authors used data from the 2003 Medicare 5% standard analytic files to identify patients with AS and a recent hospitalization for HF who did not undergo valve replacement surgery within the ensuing 2 calendar quarters. These 2150 patients were considered to have medically managed severe AS and were tracked over 5 years to measure clinical outcomes, medical resource use, and costs from the perspective of the Medicare Program. The mean age of the cohort was 82 years; 64% were female; and the estimated logistic EuroSCORE, a measure of predicted mortality with cardiac surgery, was 17%. During 5 years of follow-up, overall mortality was 88.4% with a mean survival duration of 1.8 years. During this time period, patients experienced an average of 4.4 hospital admissions. Fifty-two percent of patients were admitted to skilled nursing care, and 28% had hospice care. The total 5-year costs were $63,844 per patient, whereas the mean annual follow-up costs (excluding the index quarter) per year alive were $29,278.

Conclusion: The authors demonstrate that elderly patients with severe AS undergoing medical management alone have a limited lifespan yet incur substantial costs to the Medicare program. These findings are especially important given the advent and dissemination of TAVR, a potential treatment option for many of these patients that has been associated with decreased mortality and improved functional outcomes compared with medical management. Although TAVR is projected to generate >$2.4 billion in sales by 2015 in the United States,45 it may still be cost-effective because of its associated decreased mortality and improved quality of life.46 Greater experience with TAVR in the real-world setting will provide more precise point estimates regarding hospital and skilled nursing admissions averted and the overall costs saved from the procedure.46

Sources of Funding
Dr Dharmarajan is supported by a National Institutes of Health T32 training grant (2T32HL070854-16A1) from Columbia University, New York, NY.

Disclosures
None.

References

Downloaded from http://circoutcomes.ahajournals.org/ by guest on December 11, 2017


Most Important Outcomes Research Papers on Valvular Heart Disease
Julianna F. Lampropulos, Behnood Bikdeli, Aakriti Gupta, Purav Mody, Vivek T. Kulkarni, RuiJun Chen, Kumar Dharmarajan and for the Editor

Circ Cardiovasc Qual Outcomes. 2012;5:e95-e103
doi: 10.1161/CIRCOUTCOMES.112.969766
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/5/6/e95

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org//subscriptions/