Long-Term Safety and Effectiveness of Mechanical versus Biologic Aortic Valve Prostheses in Older Patients: Results from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery National Database

Running title: Brennan et al.; Aortic prostheses in an elderly cohort

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Journal Subject Code: Ethics and policy:[100] Health policy and outcome research
Abstract:

**Background**—There is a paucity of long-term data comparing biologic versus mechanical aortic valve prostheses in older individuals.

**Methods and Results**—We followed patients aged 65-80 years undergoing aortic valve replacement (AVR) with a biologic (n=24,410) or mechanical prosthesis (n=14,789) from 1991-1999 at 605 centers within the Society of Thoracic Surgeons Adult Cardiac Surgery Database using Medicare inpatient claims (mean, 12.6 years; max, 17 years; min, 8 years), and outcomes were compared using propensity methods. Among Medicare-linked AVR patients (mean age, 73 years), both reoperation (4.0%) and endocarditis (1.9%) were uncommon to 12 years; however, the risk for other adverse outcomes was high, including death (66.5%), stroke (14.1%), and bleeding (17.9%). Compared with those receiving a mechanical valve, bioprostheses patients had a similar adjusted risk for death (hazard ratio [HR] 1.04; 95% confidence interval [CI] 1.01-1.07), higher risks for reoperation (HR 2.55; 95% CI 2.14-3.03) and endocarditis (HR 1.60; 95% CI 1.31-1.94), and lower risks for stroke (HR 0.87; 95% CI 0.82-0.93) and bleeding (HR 0.66; 95% CI 0.62-0.70). While these results were generally consistent among patient subgroups, bioprostheses aged 65 to 69 years had a substantially elevated 12-year absolute risk of reoperation (10.5%).

**Conclusions**—Among AVR patients, long-term mortality rates were similar for bioprosthetic versus mechanical valve patients. Bioprostheses were associated with a higher long-term risk of reoperation and endocarditis, but a lower risk of stroke and hemorrhage. These risks vary as a function of a patient’s age and comorbidities.

**Key words:** aortic valve replacement; comparative effectiveness research; valve prostheses
In recent years, nearly 80,000 aortic valve replacements (AVRs) have been performed annually in the United States\(^1\) in an increasingly older and sicker patient population.\(^2\) Among older patients, bioprostheses are an attractive alternative to the more thrombogenic mechanical prostheses;\(^3\)\(^-\)\(^5\) however, data regarding the long-term safety and effectiveness of biologic versus mechanical prostheses among elderly AVR patients is limited. Most clinical trial data\(^6\)\(^,\)\(^7\) are now three decades old and no longer reflect the current state of technology, nor the population characteristics encountered in clinical practice. Furthermore, observational analyses have been limited, lacking both: (1) clinical and procedural details necessary for accurate treatment assignment and risk-adjustment;\(^8\) and (2) sufficient power and generalizability to provide reliable comparisons.\(^9\)\(^,\)\(^10\)

In response to the need for better data on the relative safety and effectiveness of aortic valve prostheses in older patients, we identified a cohort of Medicare-linked AVR patients within the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD). Using this cohort, we sought to: (1) evaluate long-term mortality and valve-related complications in older individuals treated with bioprosthetic versus mechanical aortic valves; and (2) examine the consistency of these findings among strata of commonly encountered patient subgroups.

**Methods**

Since 1991, the STS ACSD has collected detailed in-hospital data on adult patients undergoing cardiac surgery with the aim of improving quality of care and post-operative outcomes,\(^11\) with more than 1,000 currently participating institutions throughout the United States.

For the purposes of this study, we identified a cohort of Medicare-linked fee-for-service (FFS) patients between 65 and 80 years of age undergoing elective or urgent AVR with a mechanical or
biologic prosthesis from January 1, 1991 to December 28, 1999; therefore, each patient in the analysis cohort had at least eight years of available follow-up data. From this cohort, we excluded patients undergoing concomitant non-coronary artery bypass graft (CABG) cardiac surgical procedures and those with a prior history of any valve replacement. Additionally, we excluded patients at health maintenance organizations (HMOs) and military hospitals where no patients linked to Medicare records, those with potential linkage to multiple Medicare files, and those with index procedures occurring outside a period of FFS Medicare enrollment.

Follow-up Information

To obtain follow-up information on the study cohort, we linked de-identified STS patient records with research-identifiable Medicare inpatient standard analytic claims files through December 31, 2007, by using combinations of indirect identifiers including age, sex, and dates of birth, admission, and discharge (linkage rate, 76.8%).12 Compared with patients in the Medicare-linked population, eligible patients who were not linked were on average slightly younger (75 vs. 76 years), less often female (39.0% vs. 40.8%), less often Caucasian (86.2% vs. 92.1%), less often undergoing elective procedures (73.4% vs. 75.5%), and less likely to receive biologic prostheses (80.7% vs. 82.8%). Otherwise, matched and unmatched patients were similar across demographics and comorbidities of interest. The Duke University School of Medicine Institutional Review Board granted a waiver of informed consent and authorization for this study.

Clinical Endpoints

The primary endpoint was all-cause mortality, identified using the Medicare denominator file. Secondary endpoints were identified using primary hospital diagnosis International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and
included rehospitalization for aortic valve reoperation, cerebrovascular accident (CVA), hemorrhagic CVA, hemorrhage, and endocarditis as identified using ICD-9-CM codes (Supplemental Appendix 1).

**Statistical Analysis**

Summary statistics for baseline patient characteristics, based on non-missing values, were stratified by device type, and presented as percentages for categorical variables and means with standard deviation (SD) for continuous variables. The frequency of missing data was also summarized for those baseline characteristics. The Mantel-Haenszel test was used to compare the distribution of categorical variables between groups, whereas the Wilcoxon rank sum test was used to compare continuous variable distributions. SAS statistical software (version 9.1; SAS Institute, Cary, NC) was used for all calculations.

Temporal trends in the use of bioprosthetic valves in the aortic position among 65 to 80 year old patients in the overall STS ACSD and the Medicare-linked cohort from 1991 to 1999 were calculated as a function of the total AVR volume to account for the increasing penetrance of the database across this timeframe. The frequency of the specific valve prostheses used in this cohort are presented in **Supplemental Table 1**.

Patients receiving biologic and mechanical aortic prostheses were compared using propensity scores with inverse probability-weighting (IPW) to adjust for differences in baseline characteristics between the two treatment groups. The propensity score represents the estimated probability of patients receiving a biologic (vs. mechanical) prosthesis as a function of the covariates in the propensity model.\(^\text{13}\) Propensity scores were estimated using a non-parsimonious logistic regression model, including each of the variables listed in Supplemental Appendix 2. The propensity model included interactions between the year of surgery and each of the other
variables in the model. To account for changes in data definitions and quality over the study period, we estimated a separate set of regression coefficients for each calendar year.

The ability of the propensity model to balance the two treatment groups was assessed in two ways. First, we compared the distribution of estimated propensity scores in the two treatment groups to ensure that there was a high degree of overlap. The 5-number summaries (min, 25th, 50th, 75th, max) of the propensity distributions in each treatment group were similar (bioprosthetic: 6.20%, 57.84%, 72.25%, 81.53%, 97.80%; mechanical: 3.38%, 36.64%, 51.85%, 68.14%, 96.43%), suggesting that comparisons based on the propensity score were statistically appropriate. To further increase the comparability between the two groups, patients with propensity scores that were not in the range of overlapping propensity distributions (i.e., <6.20% or >96.43%) were omitted from the risk-adjusted analysis. Next, we compared the distribution of patient characteristics across the two treatment groups before and after propensity score weighting; the observed differences in covariates were small, and in all cases were less than 5% of the estimated standard deviation.14

The time-to-event analysis assumes non-informative censoring. Patient follow-up was considered censored at the end of the study period (December 31, 2007) or on the first month of HMO enrollment (whichever occurred first). The unadjusted hazard ratio (HR) comparing mortality risk for biologic versus mechanical prostheses was estimated in a Cox regression model with a single treatment group indicator. Adjusted HRs (biologic versus mechanical prostheses) were estimated by fitting a Cox regression model with a single treatment group indicator and weighting each observation by the inverse of the estimated propensity score.15 The association between valve type and each non-fatal endpoint was analyzed by modeling the cause-specific hazard function in each treatment group. Specifically, we assumed that the cause-
specific hazard functions were proportional. This methodology was equivalent to fitting a standard Cox model and treating mortality as a censoring variable. The proportional hazards (PH) assumption was evaluated for each outcome using visual inspection of both cumulative hazards plots and log cumulative hazards plots. By visual inspection, the PH assumption was satisfied for stroke, bleeding, and endocarditis. For aortic valve reoperation, the PH assumption was less clearly satisfied; however, we elected to present a single combined estimate for this outcome because the treatment effect is in the same direction over time without overlap of the hazards function. For mortality, survival curves clearly violated the PH assumption (with overlap shown in Figure 1). Therefore, for this endpoint, we have presented time-dependent HRs for each of three time periods, corresponding to early follow-up (0–3 months), mid-term follow-up (3mo–9 years), and late follow-up (>9 years). Robust sandwich variance estimates\(^\text{16}\) were used to obtain 95% confidence intervals (CIs) of coefficients.

The unadjusted cumulative incidence of mortality was estimated for each treatment group using the product-limit method of Kaplan & Meier\(^\text{17}\), the propensity-adjusted incidence of mortality was calculated for each treatment group using the Breslow estimator\(^\text{18}\) based on the IPW Cox model. A similar approach was also used for the aortic valve repair or replacement endpoint. The cumulative incidence rate for other non-fatal rehospitalization endpoints was analyzed using competing risk methods of Kalbfleisch & Prentice to account for the role of death in preventing subsequent hospitalizations.\(^\text{19}\) For hemorrhage, hemorrhagic stroke, stroke, congestive heart failure (CHF), and endocarditis, our analyses focused on estimating the actual probability of the event (i.e., the probability that it will occur before a patient dies); whereas analyses of aortic valve repair or replacement focused on estimating the probability of valve failure in a death-free environment.\(^\text{20,21}\)
The cumulative incidence of adverse events is reported at 12 years in the primary manuscript text; however, the cumulative incidence for each endpoint is reported annually through 15 years of follow-up in Supplemental Table 2 to facilitate comparisons with other available studies. Hazards ratios represent data from the full follow-up interval.

**Analysis of Missing Data**

Missing data in the baseline characteristics (used for adjusted analyses) were handled by multiple imputations under the assumption of missing at random (MAR). The multiple imputation procedure was performed using R software (www.R-project.org) with the add-on library package Multivariate Imputation by Chained Equations (MICE). This package generates multiple imputations for incomplete multivariate data by Gibbs sampling. Imputation was performed separately for each calendar year using the covariates from the propensity model plus valve type, pre-op digitalis, pre-op diuretic, or pre-op beta blocker. Ten complete imputed datasets were created. The standard analyses, including the baseline characteristic summary statistics and the risk-adjusted analyses (described above), were performed separately for each of the completed datasets. The ten sets of results were then combined using the method proposed by Rubin.

**Subgroup Analyses**

Prospectively derived subgroups were identified using STS data files, including: age (65–69, 70–74, and 75–80 years), sex, preoperative left ventricular ejection fraction (LVEF; <50%, ≥50%), and pre-operative renal function. Consistent with STS ACSD data definitions, renal failure was defined as a serum creatinine >2.0 mg/dl or dialysis. The IPW Cox model was applied within each strata of these four pre-specified groups to estimate strata-specific treatment effects.
Results

Population Characteristics

The Medicare-linked study cohort (age 65–80 years) included 39,199 patients who received biologic (n=24,410) or mechanical (n=14,789) aortic valve prostheses from 605 hospital centers (Figure 2), with a median age of 73 years and a mean follow-up of 12.6 years (max, 17 years; min, 8 years). Bioprostheses were used with increasing frequency among progressively older patients, and a 20% absolute increase in the use of bioprostheses was observed across the spectrum of age from 1991 to 1999 (Figure 3). Compared with mechanical valve patients, bioprosthetic valve patients were on average older (74 vs. 71 years) with a higher prevalence of both heart failure (43.7% vs. 39.9%) and significant coronary artery disease (70.1% vs. 65.6%), but a similar prevalence of most other comorbidities (Table 1).

Intra-operative characteristics were similar for bioprosthetic versus mechanical valve patients, with a similar proportion of patients undergoing elective procedures (82.5% vs. 82.8%) and a similar mean time on cardiopulmonary bypass (132.9 vs. 132.3 minutes). Bioprosthetic valve patients were more likely to undergo concomitant CABG surgery (60.1% vs. 55.2%) and slightly more likely to receive a larger size prosthesis (>21mm: 58.8% vs. 56.6%). After propensity weighting, patient and operative characteristics were well balanced across treatment groups (Table 1).

Long-term Outcomes

All-cause Mortality

In this Medicare-linked cohort, the 12-year incidence of all-cause mortality following AVR was 70.5% for bioprosthetic valve patients and 60.3% for mechanical valve patients (unadjusted HR 1.29; 95% CI 1.26–1.32). Following risk adjustment, patients receiving bioprosthetic valves
experienced a similar long-term mortality rate compared with mechanical valve patients (adjusted HR 1.04; 95% CI 1.01–1.07; Figure 1). However, mortality rates were higher beyond 9 years of follow-up in patients treated with bioprosthetic than mechanical valves (Figures 1 and 4), a result that differed significantly from earlier time periods (p<0.002, comparing the adjusted HR in late follow-up vs. either early or mid-term follow-up).

The absolute risk of long-term mortality varied widely across patient subgroups and was particularly high among patients with either pre-operative renal failure (12-year mortality, 65.2%) or reduced LVEF (12-year, 74.1%; Figure 4). The relative mortality rate associated with valve type varied according to patient age and comorbidities (p-interaction was significant [<0.05] across all subgroups of interest, including age, sex, LVEF, and renal function). For example, bioprostheses were associated with a 23% increased mortality rate among the youngest patients (65–69 years; adjusted HR 1.23, 95% CI 1.16–1.31), without a meaningful difference among 70 to 80 year old patients (Figure 4).

Aortic Valve Reoperation

The incidence of aortic valve reoperation was higher among bioprosthetic than mechanical valve patients throughout follow-up (unadjusted HR 1.91; 95% CI 1.64–2.22). By 12 years, reoperation was observed in 5.2% of bioprosthetic valve and 2.3% of mechanical valve patients. Among the youngest patients (65–69 years), the incidence of bioprosthetic valve reoperation was 10.5%, which was more than three times the incidence observed among the oldest patients (75–80 years, 2.9%; Figure 5). Following risk-adjustment, bioprosthetic valves were associated with more than a two-fold increase in the long-term rate of reoperation compared with mechanical valves in the overall population (adjusted HR 2.55; 95% CI 2.14–3.03; Figure 1) and across
most patient subgroups. This effect was larger among younger (compared with older) patients (p-interaction <0.05), but was similar across strata of other subgroups of interest.

**Stroke**

The 12-year incidence of stroke (all-cause) requiring rehospitalization was high among patients receiving either bioprosthesis or mechanical aortic valves (13.8% vs. 14.7%; unadjusted HR 1.00; 95% CI 0.95–1.06). After adjusting for baseline risk, the rate of stroke was significantly lower among bioprosthetic than mechanical valve patients in the overall cohort (adjusted HR 0.87; 95% CI 0.82–0.93) and in most of the pre-specified subgroups (**Supplemental Figure 1**).

**Bleeding**

By 12 years, rehospitalization for a bleeding event occurred in 15.5% of bioprosthetic valve and 21.8% of mechanical valve patients (unadjusted HR 0.75; 95% CI 0.71–0.78), with hemorrhagic stroke in 2.2% and 3.7%, respectively (unadjusted HR 0.64; 95% CI 0.57–0.73). Compared with those receiving mechanical valves, bioprosthetic valve patients experienced a lower adjusted rate of both all-cause bleeding (adjusted HR 0.66, 95% CI 0.62–0.70) and hemorrhagic stroke (adjusted HR 0.57, 95% CI 0.49–0.65)—a finding which was consistent across each of the pre-specified subgroups (**Supplemental Figures 2 and 3**).

**Endocarditis**

The 12-year incidence of rehospitalization for endocarditis was 2.2% for bioprosthetic valve and 1.4% for mechanical valve patients (unadjusted HR 1.69; 95% CI 1.43–2.00). Following risk adjustment, bioprosthetic valve patients experienced a higher risk of endocarditis than mechanical valve patients in the overall cohort (adjusted HR 1.60; 95% CI 1.31–1.94) and in each of the pre-specified subgroups, except among the oldest patients (75–80 years, adjusted HR
1.17; 95% CI 0.85–1.60) and those with renal failure (adjusted HR 0.69; 95% CI 0.29–1.66) 
(Supplemental Figure 4).

Discussion

This study provides a contemporary view of long-term outcomes with biologic versus mechanical prostheses for AVR in older individuals in the United States. Several important findings stem from these results. Although overall mortality was similar between bioprosthetic and mechanical valve patients, mechanical valves were generally associated with a lower risk-adjusted mortality rate beyond 9 years. The incidence of aortic valve reoperation was substantially higher among bioprosthetic than mechanical valve patients, and this difference was especially pronounced among the youngest AVR patients (65–69 years) in whom the observed 12-year bioprosthetic valve reoperative rate reached 10.5%. Finally, rehospitalization for both bleeding and stroke was higher among patients with mechanical aortic valves, although endocarditis was more common among bioprosthetic valve patients. These data highlight the complexity of selecting an appropriate prosthesis in elderly patients undergoing AVR.

Mortality

The 12-year incidence of mortality (66.5%) was high in this older Medicare-linked AVR cohort. This risk was age-dependent, ranging from 53% among 65 to 69 year-olds to 77% among those 75 to 80 years old. Direct comparison with clinical trial results is limited by the substantially younger age of patients tested in the Edinburgh (1975–1979; mean age, 54 years)\textsuperscript{7} and Veterans Affairs Cooperative (1977–1982; mean age, 59 years)\textsuperscript{6} studies; however, the decision analysis of Birkmeyer et al.\textsuperscript{24} does provide some insight. Based on a pooled analysis of the Edinburgh and Veterans Affairs Cooperative study data, Birkmeyer et al. reported 12-year mortality estimates of
62% for patients 70 years of age. These results are nearly identical to those observed in the STS Medicare-linked cohort (70–74 year olds, 64%), suggesting very little improvement in long-term patient outcomes following AVR from the 1970s to 1990s. Nevertheless, caution should be used in the interpretation of these data, as previous work has demonstrated that both: (1) the burden of comorbidities in patients undergoing AVR has increased over time;\(^2\) and (2) long-term mortality following AVR is more closely related to complications associated with patient comorbidities than with prosthesis failure.\(^6\)

In the overall study cohort, long-term mortality rates were similar across prostheses (HR 1.04); however, the prosthesis-associated relative risk varied across patient subgroups and over the duration of follow-up. For example, among the youngest patients (65 to 69 years of age), mechanical valves were associated with a 23% relative reduction in the risk-adjusted long-term mortality rate when compared with bioprostheses; however, this benefit was not observed among patients 70 to 80 years of age. Additionally, among patients surviving to 9 years after AVR, bioprosthetic valves were associated with a significantly higher mortality rate in the overall cohort and among most patient subgroups. This finding is consistent with those of both the Veterans Affairs Cooperative study and the Edinburgh trial\(^7\) which reported a late (10 to 15 year) increase in excess mortality among bioprosthetic valve patients.

**Aortic Valve Reoperation**

Valve degeneration remains an important concern in the selection of appropriate aortic valve prosthesis. In this older cohort, the 12-year incidence of bioprosthetic aortic valve reoperation (4.0%) was substantially lower than that reported from either the Edinburgh study\(^7\) (11.3% at 10 years) or the Veterans Affairs Cooperative study\(^6\) (29% at 15 years). While this risk was similar across most subgroups, the 12-year incidence of aortic valve reoperation in our study was
substantially higher among the youngest (65–69 years) bioprosthetic valve patients (10.5% at 12 years)—a result which is consistent with previous randomized\textsuperscript{6} and observational\textsuperscript{25} data. In keeping with prior recommendations,\textsuperscript{20,21} this estimate is based on the probability of valve failure in a “death-free” environment (i.e., “actuarial probability”). As a result, reoperative rates described here approximate valve durability, with limited influence by patient survival. In other words, the high-risk of reoperation observed among the youngest patients is not explained by the expectation that these patients will live longer (and, therefore, have more time at risk) than the older patients. Nevertheless, two alternative explanations remain. First, the durability of bioprosthetic valves may truly be reduced in younger patients,\textsuperscript{26} perhaps as a function of differences in calcium metabolism or increased mechanical stress inflicted on the valve by a more active, younger cohort.\textsuperscript{27} Alternatively, this finding may be due in part to a referral bias favoring reoperation among younger patients with a lower expected operative risk.\textsuperscript{28}

Compared with mechanical valve patients, those receiving bioprostheses experienced a significantly higher risk for reoperation (HR 2.55)—a result which persisted across the spectrum of patient age. Unlike prior studies, this difference was observed throughout the follow-up interval; however, similar to previous reports, this difference appeared to accelerate beyond seven to eight years of follow-up.

**Stroke and Bleeding**

The risk of rehospitalization for either stroke or bleeding was high in this elderly cohort. Offsetting the late survival and durability advantages of mechanical valves, both stroke and bleeding were less common among bioprosthetic valve patients. For example, in the overall cohort, bioprostheses were associated with a 13% relative reduction in the risk of stroke. While the absolute magnitude of this risk is consistent with prior analyses,\textsuperscript{6,7} randomized comparisons
have not previously demonstrated a significantly lower risk of thromboembolism in patients treated with bioprostheses (versus those with mechanical valves on warfarin therapy). Despite a low perceived risk of stroke in patients with bioprostheses, its incidence remains high in this group. It is unclear whether this risk is concentrated within a group of patients who carry or develop traditional risk factors for ischemic stroke after AVR (e.g., atrial fibrillation or reduced LVEF); it is also unknown whether the benefits of vitamin K inhibition or alternative anticoagulation regimens (i.e., direct thrombin inhibitors or factor Xa inhibitors) would outweigh their risks in this cohort, especially given the demonstrated risk of hemorrhagic stroke (3.7% by 12 years) in those patients who were presumably treated with warfarin therapy in the setting of a mechanical valve prostheses.

**Practical Applications**

The results presented in this analysis demonstrate the complexities and trade-offs of selecting an aortic valve prosthesis in older patients. This decision is ultimately one that must be made in conjunction with the patient; however, examination of results from three important subgroups may help inform this discussion. First, among patients **70 years of age or older**, bioprostheses offer at least equivalent survival to mechanical valves with a lower risk of stroke and hemorrhage, yet the use of bioprostheses in these patients comes at the expense of a slightly higher absolute risk of both reoperation and endocarditis. Second, for patients between **65 and 69 years of age**, mechanical valves are associated with a slightly lower long-term relative risk of mortality and a substantially lower risk (both absolute and relative) of reoperation when compared with bioprosthetic valves, yet the use of mechanical valves in this younger cohort carries an increased long-term risk of rehospitalization for hemorrhage and stroke. Finally, among **older patients with renal failure**, bioprostheses are associated with a lower long-term risk
of mortality, hemorrhage, and stroke than mechanical valves without an associated increase in the risk of either reoperation or endocarditis.

Limitations

This study is among the largest evaluations of valve-specific long-term outcomes following AVR in contemporary practice, and builds on the recent claims-based analysis of Schelbert et al. through the use of clinical (rather than claims) data for both risk adjustment and treatment assessment. The limitations of claims data for the assessment of baseline risk have been well documented. Here, we have also demonstrated the limitations of claims data for the assessment of treatment status. Between 1991 and 1999, bioprostheses were used in 62% of AVR operations in Medicare-linked STS patients 65 to 80 years of age, with increasing frequency across this interval. By comparison, only 39% of AVR operations during a similar time period (1997–1999) were classified as involving bioprostheses when a claims-based ICD-9-CM algorithm was used for device identification in the Schelbert et al. analysis. This finding highlights an important advantage of registry-based comparative analyses, and it may account for inconsistencies between the data reported here and those previously reported from the overall Medicare cohort.

While this study has several inherent strengths, it also has important limitations. First, the comparisons presented here are not randomized. We have attempted to limit selection bias by choosing a patient cohort in which some degree of equipoise exists for the use of either a mechanical or bioprosthetic valve. The reasonable degree of baseline overlap in the propensity distributions across the two treatment groups and the balance achieved across observed covariates in these two groups following inverse probability weighting suggests that we have achieved this goal. Despite these efforts, as with any observational analysis, unmeasured confounders may have influenced the accuracy of the reported comparisons. Since mechanical
prostheses tend to be used only in healthier elderly patients, the direction of this potential bias would be expected to favor patients receiving mechanical valves. Second, while use of the 1991–1999 data has ensured that all patients have a minimum of eight years of follow-up, recent advances in bioprosthetic and mechanical valve technology may have altered the relative treatment effects in contemporary practice. Third, this analysis assumes consistency of effect across the various biologic and mechanical prostheses. While potential differences in model-specific outcomes may be the focus of future efforts, this analysis was not designed to compare outcomes across specific valve models. Fourth, while the linkage rate between STS and Medicare files was within expected bounds,\textsuperscript{12,30} it is not perfect. A comparison of matched and unmatched patients demonstrated a high level of overlap between these two groups, but enhanced the generalizability of these findings. Finally, the results presented here were drawn from a 65 to 80 year old patient cohort. Our results build on a substantial body of knowledge which suggests that the relative effectiveness of bioprosthetic versus mechanical valves is highly dependent on patient age at the time of implantation. Therefore, these results should not be viewed as generalizable to younger patients.

**Conclusions**

Among older individuals, the incidence of both mortality and valve-associated morbidities is high in the first 12 years after AVR. Mechanical valves are associated with improved late survival and long-term prosthesis durability; however, these gains are achieved at the cost of an increased incidence of bleeding and stroke among patients receiving mechanical valves. The comparative safety and effectiveness of prosthetic heart valves is highly dependent on patient age and underlying comorbidities, and the choice of an appropriate prosthesis remains complex.
Ultimately, the most appropriate prosthesis for a given patient can only be determined through careful discussion between patients and their healthcare providers.

Acknowledgments: The authors would like to thank Erin LoFrese for her editorial contributions to this manuscript. Ms. LoFrese did not receive compensation for her contributions, apart from her employment at the institution where this study was conducted.

Funding Sources: This project was sponsored by the Agency for Healthcare Research and Quality, US Department of Health and Human Services, Rockville, MD as part of the Cardiovascular Consortium and funded under Project ID: 20-DKE-13 and Work Assignment Number: HHSA290-2005-0032-I-TO2-WA3 as part of the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the US Department of Health and Human Services.

Conflict of Interest Disclosures: Dr. Edwards reports grant support from the University of Florida (significant). Dr. Peterson reports grant support from the Society of Thoracic Surgeons Data Warehouse Coordinating Center (significant). The remaining authors do not report any relevant disclosures. Role of the Sponsor: The funding organization had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

References:


### Table 1. Population Characteristics Stratified by Valve Type

<table>
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<th>Patient Characteristics, %</th>
<th>Missing (%)</th>
<th>Mechanical (n=14,789)</th>
<th>Bioprosthetic (n=24,410)</th>
<th>Baseline* p-value</th>
<th>Mechanical (n=14,789)</th>
<th>Bioprosthetic (n=24,410)</th>
<th>Post-IPW p-value</th>
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<td>74.20 (3.94)</td>
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<td>73.07 (4.29)</td>
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<td>Race</td>
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<td>94.42</td>
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<td>White</td>
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<td>1.87 (0.24)</td>
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<td>51.07 (14.73)</td>
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<td>51.48 (14.79)</td>
<td>51.45 (14.88)</td>
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<td>2.54</td>
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<td>Mean follow-up (SD)</td>
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<td>4754 (804)</td>
<td>4525 (791)</td>
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<td>82.76</td>
<td>82.45</td>
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<tr>
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<tr>
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<td>41.21</td>
<td>41.86</td>
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<tr>
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<td>58.14</td>
<td>58.50</td>
<td>58.34</td>
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<td>Time on cardiopulmonary bypass, mean (SD)</td>
<td>1.18</td>
<td>132.31 (54.11)</td>
<td>132.87 (53.09)</td>
<td>0.012</td>
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</table>

*Summary statistics are based on non-missing values.

AVR indicates aortic valve replacement; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; SD, standard deviation.
Figure Legends:

**Figure 1.** Risk-adjusted mortality and aortic valve reoperation following aortic valve replacement with mechanical vs. biologic prostheses. Beginning at the time of valve implantation, the patients treated with biologic aortic prostheses experienced a higher risk of valve reoperation compared with mechanical valve patients. Although the overall mortality rates were similar for biologic and mechanical prosthesis patients, the relative risk of mortality for biologic valve patients increased beyond 9 years when compared to mechanical valve patients.

**Figure 2.** Population flow diagram. Beginning with a cohort of 266,690 AVR procedures occurring in the STS ACSD between 1991 and 2007 on patients 65 years or older and following exclusions, 193,839 AVR admissions were eligible for Medicare linkage. Following Medicare linkage (76.8% linked), 39,199 patients between the ages of 65 and 79 years from 605 hospital centers were included in the final study cohort. ACSD indicates Adult Cardiac Surgery Database; AVR, aortic valve replacement; STS, Society of Thoracic Surgeons.

**Figure 3.** Temporal trends in the use of aortic valve bioprostheses among Medicare-linked STS ACSD patients, 1991-1999. Across the cohort inception interval, the use of bioprosthetic aortic valves increased within each of the three patient subgroups (65-69 years, 70-74 years, 75-80 years).

**Figure 4.** Comparison of long-term mortality with biologic vs. mechanical prostheses by patient subgroup. The risk of mortality varied substantially across patient characteristics. In general,
while patients treated with biologic and mechanical valves experienced a similar mortality risk to 9 years, those treated with biologic valves experienced an increased relative risk of mortality beyond 9 years of follow-up. This trend was not consistent among either: (1) the younger patients (65-69 years) who experienced an early (3 months to 9 years) reduction in the relative risk of mortality with mechanical prostheses; or (2) the oldest patients (75-80 years) who experienced an early (3 months to 9 years) reduction in the relative risk of mortality with bioprosthetic valves.

**Figure 5.** Comparison of long-term aortic valve reoperation with biologic vs. mechanical prostheses by patient subgroup. With the exception of patients with renal failure, the long-term risk of reoperation was substantially higher among most subgroups of patients treated with bioprosthetic (vs. mechanical) aortic valve prostheses.
Figure 1

Adjusted Probability (in %) for Death

Time since surgery (in years)

<table>
<thead>
<tr>
<th>At Risk</th>
<th>2 yrs</th>
<th>4 yrs</th>
<th>6 yrs</th>
<th>8 yrs</th>
<th>10 yrs</th>
<th>12 yrs</th>
<th>14 yrs</th>
<th>16 yrs</th>
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<tr>
<td>Bio</td>
<td>20,889</td>
<td>18,563</td>
<td>15,822</td>
<td>12,822</td>
<td>8,380</td>
<td>3,549</td>
<td>1,128</td>
<td>262</td>
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<td>Mech</td>
<td>12,884</td>
<td>11,709</td>
<td>10,307</td>
<td>8,807</td>
<td>6,646</td>
<td>3,717</td>
<td>1,458</td>
<td>421</td>
</tr>
</tbody>
</table>

Mortality

AV Reoperation

| Bio     | 19,943| 17,162| 14,304| 11,205| 6,976  | 2,772  | 845    | 184    |
| Mech    | 12,334| 10,791| 9,258 | 7,716 | 5,583  | 2,993  | 1,109  | 312    |
Figure 2

STS AVR Operations, ≥65 years, 1991-2007
266,690 AVR admissions

Exclude patients with other non-CABG operations

AVR admissions +/-CABG only, ≥65y/o, 1991-2007
204,349 AVR admissions

Exclude prior valve surgery, emergent and salvage status

AVR admissions +/-CABG only, ≥65y/o, 1991-2007
193,839 AVR admissions

NOT Medicare-Linked
45,037 AVR admissions

STS Medicare-Linked Cohort
148,802 AVR admissions, 1,453 hospitals

Exclude patients with one CMS claim matching to 2 different STS admissions, non-index admission, and HMO patients

STS Medicare-Linked Cohort
1:1 STS:CMS match
145,984 AVR patients, 1,453 hospitals

Exclude years 2000-2007

STS Medicare-Linked Cohort, 1991-1999
1:1 STS:CMS match
48,764 AVR patients, 622 hospitals

Exclude Age ≥80 years

Final Study Population
39,199 patients, 605 hospitals
Figure 3

Bioprosthetic Valve Use (as % of total AVR procedures)

- 65-69 yrs
- 70-74 yrs
- 75-80 yrs

Year:
- 1991
- 1992
- 1993
- 1994
- 1995
- 1996
- 1997
- 1998
- 1999

Journal of the American Heart Association
<table>
<thead>
<tr>
<th></th>
<th>Mechanical AVR</th>
<th></th>
<th>Bioprosthetic AVR</th>
<th></th>
<th></th>
<th>0-3 months</th>
<th>3 mo – 9 yrs</th>
<th>&gt;9 years</th>
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<tr>
<td></td>
<td>n</td>
<td>12 yrs Unadjusted Incidence (%)</td>
<td>n</td>
<td>12 yrs Unadjusted Incidence (%)</td>
<td>IPW Adjusted HR (95% CI)</td>
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<td></td>
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<tr>
<td>Age 65-69</td>
<td>5,949</td>
<td>49.7</td>
<td>3,505</td>
<td>58.1</td>
<td>1.23 (1.16, 1.31)</td>
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<tr>
<td>Age 70-74</td>
<td>5,306</td>
<td>61.6</td>
<td>8,367</td>
<td>65.8</td>
<td>1.04 (0.99, 1.09)</td>
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<tr>
<td>Age 75-80</td>
<td>2,821</td>
<td>76.2</td>
<td>12,538</td>
<td>77.2</td>
<td>0.95 (0.90, 0.99)</td>
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<tr>
<td>Male</td>
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<td>60.5</td>
<td>14,882</td>
<td>71.1</td>
<td>1.06 (1.02, 1.10)</td>
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<tr>
<td>Female</td>
<td>5,756</td>
<td>60.0</td>
<td>9,513</td>
<td>69.6</td>
<td>1.01 (0.97, 1.06)</td>
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<tr>
<td>EF &lt;50%</td>
<td>4,230</td>
<td>69.1</td>
<td>7,226</td>
<td>77.1</td>
<td>1.03 (0.98, 1.08)</td>
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<tr>
<td>EF &gt;=50%</td>
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<td>13,231</td>
<td>58.7</td>
<td>21,764</td>
<td>69.4</td>
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<td>Renal Failure</td>
<td>704</td>
<td>92.2</td>
<td>1,330</td>
<td>90.1</td>
<td>0.86 (0.77, 0.96)</td>
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<tr>
<td>Isolated AVR</td>
<td>6,624</td>
<td>54.6</td>
<td>9,734</td>
<td>65.7</td>
<td>1.06 (1.02, 1.11)</td>
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<tr>
<td>Overall</td>
<td>14,789</td>
<td>60.3</td>
<td>24,410</td>
<td>70.5</td>
<td>1.04 (1.01, 1.07)</td>
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HR >1.0 favors Mechanical Valves, whereas a HR<1.0 favors Bioprosthetic Valves
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<th>Bioprosthetic AVR</th>
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<tr>
<td></td>
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<td>Unadjusted Incidence (%)</td>
<td>n</td>
<td>Unadjusted Incidence (%)</td>
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<tr>
<td>Age 65-69</td>
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<td>3,505</td>
<td>10.5</td>
<td>3.31 (2.62, 4.19)</td>
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<td>Age 70-74</td>
<td>5,306</td>
<td>2.3*</td>
<td>8,867</td>
<td>6.2</td>
<td>2.31 (1.78, 3.00)</td>
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<td>Age 75-80</td>
<td>2,821</td>
<td>1.0*</td>
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<td>2.4</td>
<td>2.03 (1.27, 3.26)</td>
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<tr>
<td>Male</td>
<td>9,024</td>
<td>2.0</td>
<td>14,882</td>
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<td>2.69 (2.12, 3.41)</td>
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<td>5,756</td>
<td>2.8</td>
<td>9,513</td>
<td>5.3</td>
<td>2.34 (1.81, 3.04)</td>
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<td>EF &lt;50%</td>
<td>4,230</td>
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<td>12,029</td>
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<td>No Renal Failure</td>
<td>13,231</td>
<td>2.4</td>
<td>21,764</td>
<td>5.3</td>
<td>2.64 (2.22, 3.14)</td>
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<td>Renal Failure</td>
<td>704</td>
<td>0.6*</td>
<td>1,330</td>
<td>3.9</td>
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<td>9,734</td>
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<td>2.63 (2.08, 3.32)</td>
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<tr>
<td>Overall</td>
<td>14,789</td>
<td>2.3</td>
<td>24,410</td>
<td>5.2</td>
<td>2.55 (2.14, 3.03)</td>
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HR >1.0 favors Mechanical Valves, whereas a HR<1.0 favors Bioprosthetic Valves

Figure 5