Bioprosthetic aortic valve replacement: Revisiting prosthesis choice in patients younger than 50 years old

Samuel R. Schnittman, BA,[a] David H. Adams, MD,[a] Shinobu Itagaki, MD, MSc,[a] Nana Toyoda, MD, PhD,[a] Natalia N. Egorova, PhD,[b] and Joanna Chikwe, MD[a,c]

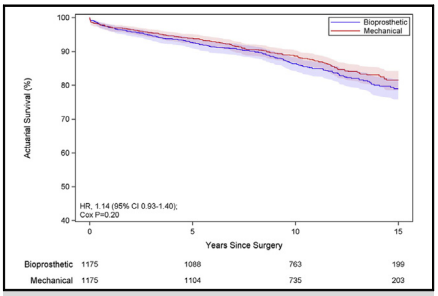
ABSTRACT

Objective: Aortic prosthesis choice is controversial in young adults because robust comparative outcome data are lacking. We therefore compared mortality and morbidity in young adults after bioprosthetic versus mechanical aortic valve replacement.

Methods: This was a retrospective analysis of 5111 patients aged 18 to 50 years undergoing primary aortic valve replacement in California and New York State from 1997 to 2006. Median follow-up time was 11.8 years (maximum 18.9 years). The primary endpoint was mortality; secondary endpoints were stroke, bleeding, and reoperation. Propensity score matching yielded 1175 patient pairs.

Results: Bioprosthetic valves increased from 14% to 47% of aortic valve replacements between 1997 and 2014 ($P < .001$). There was no survival difference with bioprosthetic versus mechanical aortic valves in the propensity score-matched cohort: actuarial 15-year survival was 79.0% (95% confidence interval [CI], 75.8%-81.8%) versus 81.5% (95% CI, 78.5%-84.2%) respectively (hazard ratio [HR], 1.14; 95% CI, 0.93-1.40, $P = .20$). No interaction was found between age and prosthesis choice on survival ($P_{interaction} = 0.16$). After bioprosthetic valve replacement, stroke rates were lower (5.4% [95% CI, 3.8%-7.2%] vs 8.1% [95% CI, 6.3%-10.2%], HR 0.62 [95% CI 0.43-0.91]), bleeding rates were lower (4.2% [95% CI, 3.0-5.6%] vs 8.4% [95% CI, 6.6-10.4%], HR 0.48 [95% CI, 0.33-0.69]), but reoperation rates were greater (24.5% [95% CI, 21.3%-27.8%] vs 9.3% [95% CI, 7.2%-11.7%], HR 5.9 [95% CI 3.2-11.0]) at 15 years versus mechanical valve replacement.

Conclusions: Although lifetime risks are represented incompletely, these findings suggest that in adults aged 18-50 years, bioprostheses are a reasonable alternative to mechanical valves for aortic valve replacement. (J Thorac Cardiovasc Surg 2018;155:539-47)



Survival in propensity score-matched patients aged 18 to 50 years according to aortic prosthesis.

Central Message

Bioprosthetic aortic valve replacement is associated with similar survival at 15 years in adults aged younger than 50 years compared with mechanical valves, supporting expanded use of bioprostheses in young adults.

Perspective

Prosthesis choice in young adults is controversial, primarily because of the lack of robust comparative data on long-term outcomes. We quantify the recent shift in practice toward implanting bioprosthetic valves in adults aged 18 to 50 years. The similar survival, and the differences in major morbidity at 15 years support this shift in practice and should inform the valve choice in this patient cohort.

See Editorial Commentary page 548.

See Editorial page 533.

Adults younger than 50 years of age comprise approximately 20% of patients undergoing aortic valve replacement surgery.[1] The optimal choice between bioprosthetic versus mechanical aortic valve replacement is unclear, primarily

Scanning this QR code will take you to the supplemental figures and tables. To view the AATS 2017 Webcast, see the URL next to the webcast thumbnail.

From the Departments of [a]Cardiovascular Surgery and [b]Population Health Science and Policy, Icahn School of Medicine at Mount Sinai; and [c]Division of Cardiothoracic Surgery, Stony Brook University Hospital, New York, NY.

Read at the 97th Annual Meeting of The American Association for Thoracic Surgery, Boston, Massachusetts, April 29-May 3, 2017.

Received for publication Jan 29, 2017; revisions received May 18, 2017; accepted for publication Aug 24, 2017; available ahead of print Oct 27, 2017.

Address for reprints: Joanna Chikwe, MD, Department of Cardiovascular Surgery, Mount Sinai Hospital, 1190 Fifth Ave, New York, NY 10029 (E-mail: Joanna.Chikwe@mountsinai.org).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2017.08.121

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*

because patients younger than 50 years of age have been underrepresented in the clinical trials and large registry analyses that have informed practice in older patients.[2-6] Traditionally, the increased risk of reoperation for bioprosthetic valve failure was the main rationale for recommending mechanical valve replacement in younger patients.[7,8] However, mechanical valves require life-long anticoagulation and substantial lifestyle modification and carry a greater long-term risk of major thromboembolic and hemorrhagic events, such as stroke, compared with bioprosthetic valves.

Consensus guideline recommendations recently were modified to include the patient's desire to avoid lifelong anticoagulation as a class I indication for implantation of a bioprosthetic rather than a mechanical valve.[9-11] These factors may have contributed to the recent and substantial increase in use of bioprosthetic valves in younger patients.[1] This major change in practice has occurred despite limited supporting data. We therefore designed this study with the aim of comparing long-term survival, stroke, major bleeding, and reoperation rates after bioprosthetic versus mechanical aortic valve replacement in adults aged 18 to 50 years.

METHODS

Study Design

This retrospective cohort study was conducted with the Office of Statewide Health Planning and Development in California State and the Statewide Planning and Research Cooperative System mandatory administrative databases, which capture all inpatient hospitalizations, ambulatory surgery records, and emergency department encounters in California and New York State. The study included all patients undergoing primary aortic valve replacement in California and New York State, aged 18 to 50 years, from January 1, 1997, to December 31, 2006. Exclusion criteria consisted of out-of-state residency; previous congenital cardiac history or procedures; previous or active endocarditis; previous valve replacement or repair or concomitant replacement or repair of any other valve; concomitant coronary bypass surgery; previous heart transplantation, and concomitant congenital cardiac procedures (Table E1).

The patient cohort was identified with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) procedure codes: 35.21 for bioprosthetic aortic valve replacement and 35.22 for mechanical aortic valve replacement. Baseline comorbidities were identified with ICD-9-CM procedure and diagnosis codes from both the index admission and previous inpatient hospitalizations within the past 2 years of the index visit (Table E2). The study was approved by the Program for Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai, the Committee for the Protection of Human Subjects of California State, and the New York State Department of Health data protection review board. These approvals included a waiver of informed consent.

Study End Points

The primary outcome measure was all-cause mortality. Secondary outcome measures included stroke, major bleeding, and reoperation on the aortic valve. Mortality in California and New York State was identified from each state's vital death records, which were linked to the datasets through each state's Department of Health. Mortality was further identified by discharge disposition from any inpatient, emergency department, or ambulatory surgery visits after the index admission. The Social Security Death Master File also was used. Stroke was defined as a postoperative cerebrovascular accident during the index admission or a primary diagnosis of hemorrhagic or ischemic cerebrovascular event during any subsequent admission. This definition did not include transient ischemic attacks. Major bleeding events were defined by a primary diagnosis of intracerebral hemorrhage, hemopericardium, cardiac tamponade, gastrointestinal hemorrhage, hematuria, hemarthrosis, hemoptysis, epistaxis, or ocular hemorrhage requiring inpatient admission (Tables E3 and E4). Reoperation was defined as any operation involving the aortic valve replacement. Any patient free from death, stroke, major bleeding, or reoperation was censored on December 31, 2015, which was the most recent follow-up date available for clinical events.

Statistical Analysis

Continuous variables are reported as means with standard deviations, whereas categorical variables are reported as proportions. Differences in baseline demographics between bioprosthetic and mechanical valve replacement group patients were detected with the t test for normally distributed continuous variables and the Pearson χ^2 test for categorical variables as appropriate. Normality was assessed in continuous variables by the Kolmogorov test, and non-normal continuous variables are reported with medians and interquartile ranges; differences in these variables were analyzed with the Wilcoxon-Mann-Whitney test. Trend analysis was performed with the Cochran-Armitage test on the patients who underwent aortic valve replacement between January 1, 1997, and December 31, 2014.

To adjust for confounding from intrinsic differences between the 2 valve replacement groups, propensity score matching was performed. Propensity scores were calculated with a hierarchical logistic regression with bioprosthetic valve implantation as the outcome and all patients clustered within their respective hospitals. All patient baseline characteristics (age, sex, race, coagulation defects, hypertension, diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, cancer), admission urgency, index surgery year, and concomitant operation of the aorta, were included as covariates. The area under the receiver operating characteristic curve for the model was 0.77. Patients were matched 1:1 using a caliper of 0.1 of the logit of the propensity score. Differences in baseline characteristics as well as 30-day complication rates were analyzed with the paired t test and the Wilcoxon signed rank sum test for normally distributed and non-normally distributed continuous variables, respectively; the McNemar test was used to detect differences between categorical variables. Standardized differences were reported as well.

Survival curves of the primary outcome of mortality were constructed with the Kaplan-Meier method; prostheses were compared with a marginal Cox model with a robust sandwich variance estimator. Competing risk analysis of the secondary outcomes—stroke, major bleeding, and reoperation—was performed by creating cumulative incidence functions and comparing them between prosthesis groups via the Gray test. For each end point, hazard ratios (HRs) were calculated with Cox proportional hazards models. The proportional hazards assumption was assessed in each model and found to be intact except reoperation and, if violated, the hazard ratios at different follow-up time points were reported.

To assess the robustness of the findings, all analyses were repeated in the full patient cohort as a sensitivity analysis via multivariable analysis with marginal Cox models with robust sandwich variance estimators, which we controlled for admission urgency, index surgery year, concomitant operation of the aorta, age, sex, race, coagulation defects, hypertension,

TABLE 1. Baseline characteristics of the propensity score-matched cohort, according to the aortic valve prosthesis type

Baseline characteristics	Prosthesis type, n (%)		Standardized difference, %	*P* value
	Bioprosthetic (N = 1175)	Mechanical (N = 1175)		
Demographics				
Age, y, median [IQR]	43 [36-47]	43 [37-47]	2.5	.55
18-30	140 (11.9)	137 (11.7)	0.8	.07
31-40	337 (28.7)	315 (26.8)	4.2	
41-50	698 (59.4)	723 (61.5)	4.4	
Men	891 (75.8)	879 (74.8)	2.4	.56
New York State resident	571 (48.6)	570 (48.5)	0.2	.97
Race/ethnicity				
White	852 (72.5)	865 (73.6)	2.5	.94
African-American	87 (7.4)	82 (7.0)	1.7	
Other race	236 (20.1)	228 (19.4)	1.7	
Emergent/urgent admission	328 (27.9)	320 (27.2)	1.5	.70
Comorbidities				
Coagulation/platelet disorders	38 (3.2)	40 (3.4)	1.0	.82
Hypertension	407 (34.6)	411 (35.0)	0.7	.86
Diabetes mellitus	79 (6.7)	70 (6.0)	3.1	.45
Coronary artery disease	123 (10.5)	123 (10.5)	0.0	1.00
Peripheral vascular disease	23 (2.0)	17 (1.4)	4.0	.33
Cerebrovascular disease	23 (2.0)	21 (1.8)	1.3	.75
Congestive heart failure	280 (23.8)	278 (23.7)	0.4	.92
Atrial fibrillation	77 (6.6)	60 (5.1)	6.2	.13
Chronic obstructive pulmonary disease	114 (9.7)	116 (9.9)	0.6	.89
Chronic kidney disease	39 (3.3)	38 (3.2)	0.5	.90
Dialysis dependent	26 (2.2)	23 (2.0)	1.8	.66
Liver disease	49 (4.2)	55 (4.7)	2.5	.54
Cancer	39 (3.3)	34 (2.9)	2.5	.55
Year of surgery				
1997	67 (5.7)	72 (6.1)	1.8	.85
1998	88 (7.5)	72 (6.1)	5.4	
1999	86 (7.3)	92 (7.8)	1.9	
2000	106 (9.0)	85 (7.2)	6.5	
2001	111 (9.4)	100 (8.5)	3.3	
2002	124 (10.6)	111 (9.4)	3.7	
2003	155 (13.2)	138 (11.7)	4.4	
2004	140 (11.9)	175 (14.9)	8.8	
2005	144 (12.3)	162 (13.8)	4.6	
2006	154 (13.1)	168 (14.3)	3.5	
Concomitant procedures				
Operations of the aorta	232 (19.7)	239 (20.3)	1.5	.71

IQR, Interquartile range.

diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, cancer, and clustering of patients within hospitals. We further conducted a sensitivity analysis for survival incorporating the interaction term between age and the prosthetic type in the survival model. All these sensitivity analyses confirmed the main findings and were included in the supplementary documents (Table E6 and Figure E2).

All statistical tests were 2-tailed with an α level of 0.05 consider statistically significant. The 95% confidence intervals (CIs) were provided where appropriate. All statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Study Population

A total of 10,055 patients aged 18 to 50 years who underwent primary aortic valve replacement were identified between January 1, 1997, and December 31, 2006. Of these patients, 4944 (49.2%) were excluded because they met one or more of the following criteria: out-of-state resident (6.5%, n = 650), previous or active endocarditis (15.4%, n = 1547), concomitant valve replacement or repair (22.8%, n = 2294), concomitant or previous congenital

TABLE 2. Thirty-day outcomes of propensity score-matched cohorts, according to aortic valve prosthesis type

Patient cohort	Outcome	Bioprosthetic (n = 1175)	Mechanical (n = 1175)	*P* value
Propensity score-matched patients	Mortality	9 (0.8)	16 (1.4)	.16
	Stroke	12 (1.0)	9 (0.8)	.51
	Atrial fibrillation	96 (8.2)	88 (7.5)	.54
	Acute kidney injury	24 (2.0)	24 (2.0)	1.00
	Respiratory failure	114 (9.7)	105 (8.9)	.51

cardiac surgery (3.6%, n = 361), concomitant coronary bypass surgery (9.9%, n = 995), or heart transplantation (<0.2%, n < 15). This left 5111 patients in the valve study cohort, comprising 1281 patients (25.1%) who underwent bioprosthetic aortic valve replacement and 3830 patients (74.9%) who underwent mechanical aortic valve replacement. Propensity score matching yielded 1175 patient pairs. The median follow-up time was 11.8 years (maximum 18.9 years).

Patient Characteristics

Bioprosthetic valve use in patients aged 18 to 50 years increased from 14.3% of aortic valve replacements in 1997 to 47.1% in 2014 ($P < .001$; Figure E1). In the overall cohort of patients before propensity score-matching, recipients of mechanical valves were more likely to have a history of coronary artery disease (12.8% vs 10.0%, $P = .007$) and congestive heart failure (28.1% vs 23.3%, $P = .001$) (Table E5). In the propensity score-matched group, there were no significant differences detected in patient characteristics, and 30-day outcomes were comparable (Tables 1 and 2).

Survival

There was no significant survival difference in 15-year follow-up in patients who underwent bioprosthetic aortic valve replacement compared with those who underwent mechanical aortic valve replacement in the propensity score-matched cohort (Figure 1). In the propensity score-matched cohort, actuarial 5-, 10-, and 15-year survival rates after bioprosthetic aortic valve replacement were 92.6% (95% CI, 90.9%-94.0%), 86.4% (95% CI, 84.3%-88.3%), and 79.0% (95% CI, 75.8%-81.8%) compared with 94.0% (95% CI, 92.4%-95.2%), 88.7% (95% CI, 86.7%-90.4%), and 81.5% (95% CI, 78.5%-84.2%) after mechanical valve replacement,

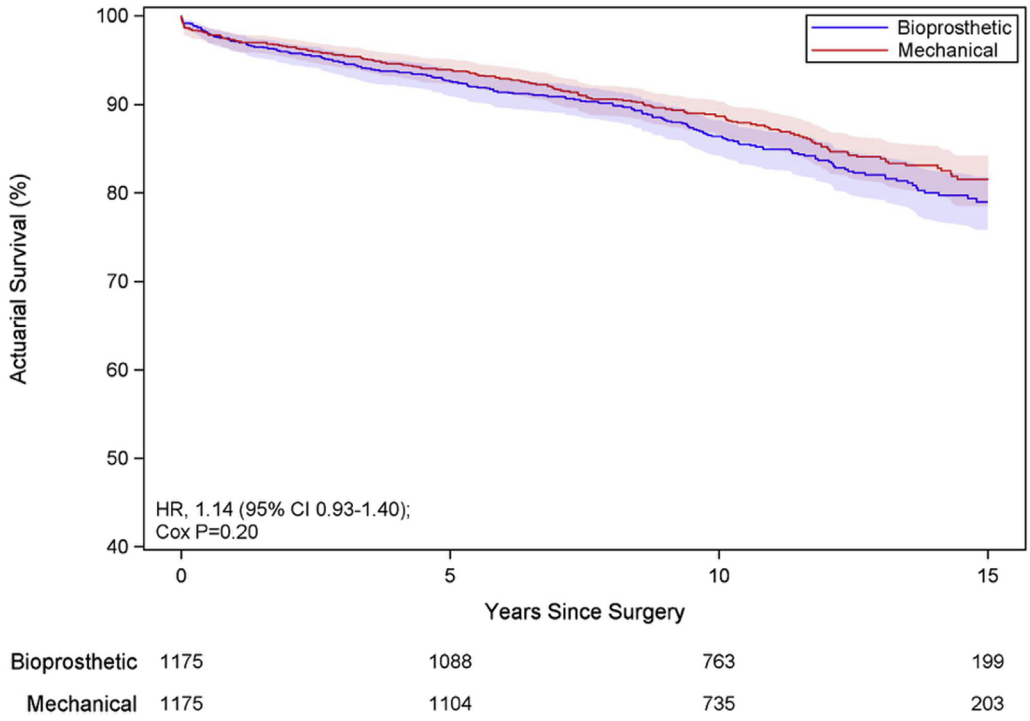


FIGURE 1. Kaplan-Meier survival curves in patients aged 18 to 50 years after aortic valve replacement according to the prosthesis type in propensity score-matched patients. *CI*, Confidence interval; *HR*, hazard ratio.

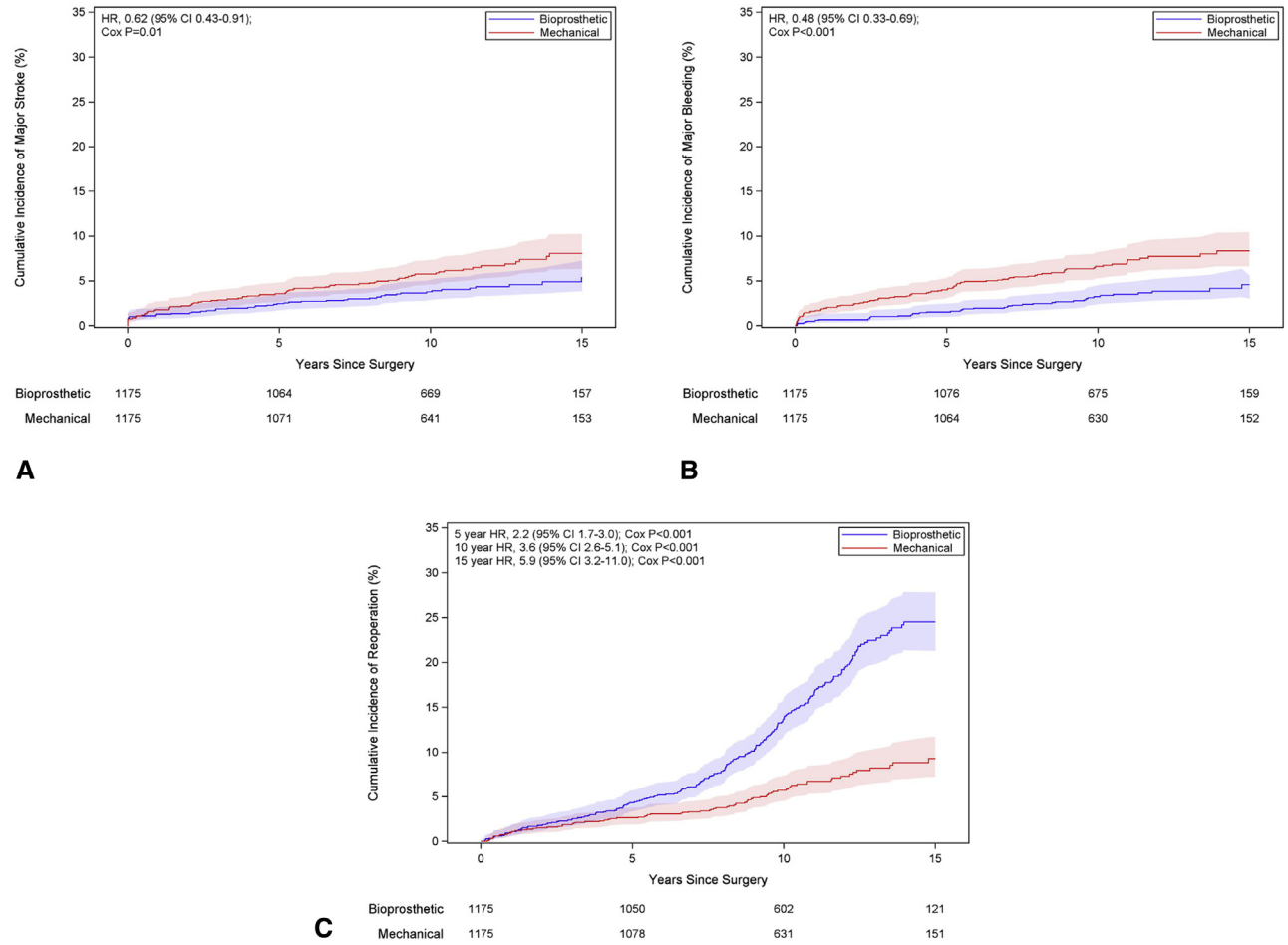


FIGURE 2. Cumulative incidence of major morbidity in patients aged 18 to 50 years after aortic valve replacement according to the prosthesis type: (A) stroke, (B) major bleeding, and (C) reoperation. *HR*, Hazard ratio; *CI*, confidence interval.

respectively. The hazard ratio (bioprosthetic vs mechanical) in the propensity score-matched cohort was 1.14 (95% CI, 0.93-1.40, $P = .20$). This finding was the case in each age strata by decade (Figure E2). A similar lack of survival difference was confirmed in the full cohort (HR, 1.16; 95% CI, 0.99-1.36, $P = .07$) (Table E6). There was no interaction detected between age and the prosthetic type ($P_{interaction} = 0.16$).

Stroke

The cumulative incidence of stroke was lower in propensity score-matched patients with bioprosthetic aortic valves compared with mechanical valves in 15-year follow-up (5.4% [95% CI, 3.8%-7.2%] vs 8.1% [95% CI, 6.3%-10.2%], HR, 0.62 [95% CI, 0.43-0.91], $P = .01$). The cumulative incidence of stroke at 5 and 10 years was 2.5% (95% CI, 1.7%-3.5%) and 3.8% (95% CI, 2.8%-5.0%) after bioprosthetic aortic valve replacement compared with 3.6% (95% CI, 2.6%-4.8%) and 5.7% (95% CI, 4.5%-7.2%) after mechanical aortic valve replacement, respectively (Figure 2, *A*). The 30-day mortality following stroke was 8.1%.

Major Bleeding

The cumulative incidence of major bleeding over 15 years was lower in propensity score-matched recipients of bioprosthetic aortic valves compared with mechanical valves (4.2% [95% CI, 3.0%-5.6%] vs 8.4% [95% CI, 6.6%-10.4%], HR, 0.48 [95% CI, 0.33-0.69], $P < .001$). The cumulative incidence of major bleeding at 5 and 10 years was 1.5% (95% CI, 0.9%-2.4%) and 3.2% (95% CI, 2.3%-4.4%) after bioprosthetic valve replacement compared with 4.0% (95% CI, 3.0%-5.2%) and 6.6% (95% CI, 5.2%-8.2%) after mechanical valve replacement, respectively (Figure 2, *B*). The 30-day mortality after major bleeding was 7.5%.

Reoperation

The cumulative incidence of reoperation was significantly greater in propensity score-matched recipients of bioprosthetic valves compared with mechanical valves at 15 years, with a steep increase in the rate of bioprosthetic valve reoperation starting at around 7 years ($P < .001$). The cumulative incidence of reoperation at 5, 10, and

15 years was 4.3% (95% CI, 3.3%-5.6%), 13.6% (95% CI, 11.6%-15.8%), and 24.5% (95% CI, 21.3%-27.8%) after bioprosthetic valve replacement compared with 2.6% (95% CI, 1.8%-3.7%), 5.7%, (95% CI, 4.4%-7.2%), and 9.3% (95% CI, 7.2%-11.7%) after mechanical valve replacement, respectively (Figure 2, *C*). The 5-, 10-, and 15-year hazard ratios in the propensity score-matched cohort were 2.2 (95% CI, 1.7-3.0), 3.6 (95% CI, 2.6-5.1), and 5.9 (95% CI, 3.2-11.0), respectively, after aortic valve replacement ($P < .001$). The 30-day mortality after reoperation was 4.8%. The cumulative incidences of reoperation after bioprosthetic valve replacement stratified by each age group was 28.0% (95% CI, 19.5%-37.1%) for 18 to 30 years, 24.2% (95% CI, 18.8%-30.0%) for 31 to 40 years, and 24.5% (95% CI, 20.3%-28.9%) for 41 to 50 years ($P = .11$).

DISCUSSION

The decision to implant a bioprosthetic or a mechanical prosthesis is based on factors including the patient's estimated life expectancy; the safety and feasibility of compliance with life-long anticoagulation; and patient preference.[9,10] Our study shows a substantial shift away from mechanical valve replacement in young adults during the last decade. This has occurred in the absence of robust long-term outcome data: patients younger than 50 years of age are represented poorly in randomized trials and registry series of valve replacement.[2-6] Our study indicates that aortic prosthesis choice appears to have minimal impact on survival at 15 years and suggests that bioprosthetic aortic valve replacement, which was associated with a lower risk of stroke and major bleeding, is a reasonable alternative to aortic mechanical valve replacement for adult patients younger than 50 years of age.

The lack of a survival benefit for mechanical aortic valve replacement over bioprosthetic aortic valve replacement is consistent with the few studies that include adults younger than 50 years of age and reporting long-term outcomes after valve replacement. In a meta-analysis of 32 studies including 17,439 patients Lund and Bland[12] found no difference in risk-adjusted mortality by aortic valve prosthesis type at any age. Two single-center analyses have found no difference in long-term survival between adult patients younger than 65 years receiving mechanical versus bioprosthetic aortic valves.[13,14] One single-center analysis of 172 matched patients aged 24 to 72 years reporting a survival benefit with mechanical over bioprosthetic valves did not adjust for major confounding variables, including major clinical comorbidity, valve position (mitral vs aortic), or year of surgery.[15]

The primary benefit of mechanical over bioprosthetic aortic valve replacement in our analysis was the almost 60% reduction in reoperation at 15 years, from 24.5% to 9.3%. This difference in reoperation did not appear to affect survival at 15 years: one reason for this may be that the 30-day mortality associated with reoperation on bioprosthetic valves was relatively low, at 4.8%. Transcatheter valve-in-valve replacement has been used as an alternative to surgical reoperation in older patients where the procedural mortality has been reported to be 7.6%.[16] The low mortality of reoperative valve surgery in our cohort suggests that the utility of transcatheter valve-in-valve as an alternative to reoperation in young patients may be limited to second or subsequent reoperative procedures where the risk of operative mortality increases.

The main implications of our data are for young adult patients unable or unwilling to comply with long-term anticoagulation after aortic valve replacement. Age younger than 55 years was one of the most important independent predictors of nonadherence to anticoagulation in an analysis of Medicaid patients, after comorbid conditions and ahead of barriers to health care.[17] Comorbid contraindications to anticoagulation are relatively uncommon in younger patients undergoing valve surgery, and reasons for nonadherence to lifelong anticoagulation in younger patients are more likely to be socioeconomic barriers to healthcare, childbearing, and patient preference. These factors are major considerations for several patient groups, including the growing number of patients in developing countries in which rheumatic valve disease is common in the younger population and long-term access to health care is most challenging. Safe management of anticoagulation during pregnancy presents substantial challenges, with maternal death rates in recipients of mechanical valves reported to be up to 5%.[18,19] In these contexts the immediate safety profile of bioprosthetic valves may offset the eventual risks of structural valve degeneration and need for reoperation. Finally, the importance of patient preference for bioprosthetic valve replacement and an anticoagulation-free lifestyle is indicated in a quality of life survey conducted in recipients of valve prostheses ages 18 to 50 years, who were significantly more likely to report continued perceived disability, dissatisfaction with the prosthesis and disruption of work, career, and income if they had a mechanical compared with a bioprosthetic valve.[13]

Limitations

The primary limitation of this analysis is the accuracy with which the variables of interest are recorded. First, the diagnoses and procedures in these databases are abstracted from clinical records by nonclinical personnel, which are a potential source of error, although we have previously validated ICD-9 codes using clinical records with a high degree of specificity and sensitivity.[6] Importantly, the absolute cumulative incidence of our secondary endpoints are likely to be underestimates because these databases do not contain data on patients that presented to hospitals outside California or New York State: however, we believe

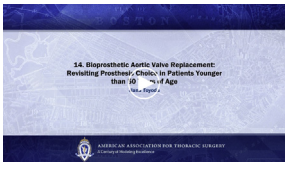
that the comparative findings are reliable because this limitation affects both valve types to the same extent. In addition, ICD-9 codes do not provide information on key baseline and outcome variables such as left ventricular dysfunction and functional status; no indication for choice of prosthesis; inaccurate data on anticoagulation; and no information on prosthesis size, model or type beyond bioprosthetic versus mechanical, so we were unable to account for these potential confounding variables. Finally, the 15-year follow-up time available to us does not fully capture the lifetime risks of patients in this young age group.

CONCLUSIONS

In patients aged 18 to 50 years undergoing aortic valve replacement in California and New York State, there was no significant difference in survival at 15 years with bioprosthetic versus mechanical valve replacement. The long-term risks of stroke and major bleeding events were greater with mechanical compared with bioprosthetic valves, whereas mechanical valve replacement had improved freedom from reoperation compared with bioprostheses. These findings suggest that in patients aged 18 to 50 years, bioprosthetic aortic valves represent a reasonable alternative to mechanical valve replacement.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/17AM/2017-05-01/BallroomABC/05-01-17_BallroomABC_1712_Toyoda.mp4.



Conflicts of Interest Statement

Samuel Schnittman was supported by The American Association for Thoracic Surgery's Summer Intern Scholarship. The Icahn School of Medicine at Mount Sinai receives royalty payments from Edwards Lifesciences and Medtronic for intellectual property related to Dr Adams' involvement in the development of 2 mitral valve repair rings and 1 tricuspid valve repair ring. Dr Adams is the National Co-Principal Investigator of the CoreValve United States Pivotal Trial, which is supported by Medtronic. Dr Chikwe received speaker honoraria from Edwards Lifesciences. None of the sponsoring organizations had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. All other authors have nothing to disclose with regard to commercial support.

References

1. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108, 687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg*. 2009;137:82-90.
2. Khan SS, Trento A, DeRobertis M, Kass RM, Sandhu M, Czer LS, et al. Twenty year comparison of tissue and mechanical valve replacement. *J Thorac Cardiovasc Surg*. 2001;122:257-69.
3. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, et al. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *Heart*. 2003;89:715-21.
4. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol*. 2000;36:1152-8.
5. Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients aged 55 to 70 years. *J Am Coll Cardiol*. 2009;54:1862-8.
6. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs. mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA*. 2014;312:1323-9.
7. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al. ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol*. 1998;32:1486-588.
8. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2006;48:e1-148.
9. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2438-88.
10. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;70:252-89.
11. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2012;33:2451-96.
12. Lund O, Bland M. Risk-corrected impact of mechanical versus bioprosthetic valves on long-term mortality after aortic valve replacement. *J Thorac Cardiovasc Surg*. 2006;132:20-6.
13. Ruel M, Chan V, Bedard P, Kulik A, Ressler L, Lam BK, et al. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. *Circulation*. 2007;116:294-300.
14. McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I, Wiegerinck EM, et al. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis. *J Thorac Cardiovasc Surg*. 2014;148:1931-9.
15. Badhwar V, Ofenloch JC, Rovin JD, van Gelder HM, Jacobs JP. Noninferiority of closely monitored mechanical valves to bioprostheses overshadowed by early mortality benefit in younger patients. *Ann Thorac Surg*. 2012;93:748-53.
16. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, et al. Transcather aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162-70.
17. Johnston JA, Cluxton RJ Jr, Heaton PC, Guo JJ, Moomaw CJ, Eckman MH. Predictors of warfarin use amoung Ohio Medicaid patients with new-onset nonvalvular atrial fibrillation. *Arch Intern Med*. 2003;163:1705-10.

18. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:3147-97.
19. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med*. 2000;160:191-6.

Key Words: aortic valve, aortic valve replacement, nonelderly patients, prosthetic valve choice, long-term outcomes

Discussion

Dr Mesana *(Ottawa, Ontario, Canada)*. First, I would like to congratulate Dr Toyoda and her coauthors for this important study on a controversial subject. The central message of your study is that patients younger than 50 years of age implanted with aortic bioprostheses have similar survival at 15 years compared with mechanical valves, around 80%. In addition, you found that patients with bioprostheses have fewer strokes, 5% versus 8.5%, and less bleeding complications. It seems that the only drawback is actually a reoperation rate of 24.6% at 15 years versus 8.1%. Your numbers are a bit different than the one I received in the article. That is all right; it is not so different. And you mentioned, an overall 5% risk of reoperations in these patients in your paper. Based on these results, I just wonder why surgeons with fewer than 15 years of life expectancy should be still using mechanical valves? I think it is not so simple. There are 3 elements for discussion and, please, can you answer them one at a time.

First of all, the clinical material was extracted from an administrative database in California and New York states. You acknowledge in your paper that the primary limitation of your study was the possible inaccuracy of the data, which are entered by nonclinical personnel. So my first question is simple and hopefully quickly answered. How accurate are these data, as the number of patients could be followed also outside California or New York state, and would you know if a patient had a complication or died outside these 2 states?

Dr Toyoda *(New York, NY)*. Thank you very much for your question. We used 3 sources to identify death. First, we used the vital statistics data linked with the discharge data, and, second, we searched the death disposition in the subsequent in-hospital admissions and also visits to the emergency department, and to identify death that occurred out of state, we used the Social Security death master file. However, we believe there were still remaining deaths that were not reported in these data. This would happen in both groups equally and this should not affect the conclusion of the analysis.

In terms of the secondary outcomes, we searched for a diagnosis in the subsequent admissions, in-hospitalizations, and we selected complications not caused admissions only, I mean, in-hospital care only.

Dr Mesana. Thank you. The second point is about the amount of valve information available. You indicated that codes did not provide information on key baseline and outcome variables such as left ventricular function, functional status, and more importantly, you had no information on prosthesis model at the time of the surgery or size, whether it was a mechanical or a tissue valve. There was no information on anticoagulation therapy and international normalized ratio monitoring of mechanical valves, and no information on prosthetic type implanted at the redo aortic valve replacement. I noted that 20% of your patients in both groups had concomitant ascending aorta surgery without any details.

Lacking these elements would present a serious drawback, in my opinion. We all know that measuring only reoperation rates for bioprostheses represents only the tip of the iceberg of prosthetic deterioration for tissue valves. In addition, we all know that small bioprostheses generate symptomatic prosthesis mismatch in patients who may not do well when they are not necessarily reoperated. This study unfortunately ignores entirely those critical aspects that are particularly relevant to quality of life for young and active patients beside their desire to avoid anticoagulation.

So my second question is, did you include stentless valves, homografts, the Ross procedure in your bioprosthetic group? Not all bioprostheses are alike, and I am concerned that you had compared not only apples and oranges but different apples with different oranges. So the question is, did you include all kind of bioprostheses in your group?

Dr Toyoda. Thank you very much. We excluded patients who had concomitant pulmonary valve surgery. So, I think Ross procedures were most likely excluded, although ICD-9 codes cannot detect Ross procedure. And homograft also cannot be detected with the ICD-9 codes but it is included in the tissue valve group in the study.

Dr Mesana. So you may have had a wide variety of stentless?

Dr Toyoda. Yes.

Dr Mesana. Okay. Thank you for your answer. My third point is about duration of follow-up and age stratification. We observed that only 27% of your patients were actually between 30 and 40 years old and actually 61% of your overall cohort is older than 40. Our group at the Ottawa Heart Institute published in *Circulation* in 2011 a long-term

longitudinal study of reoperations after bioprostheses below 60. We observed a striking difference for patients below or above 40 years of age. In our study, the median interval of reoperation in patients younger than 40 years old was about 8 years compared with13 years for patients between 40 and 60 years old—that's a very big difference—and actually only 34% of our patients younger than 40 years were free of reoperation at 15 years versus 78% for patients older than 60 years of age. So I noted that you observed a steep increase in your rate of reoperation around 7 years, although your rate of reoperation cumulated at about 25% at 15 years.

So my question is thus: could the rate of reoperation in your study have been impacted by the relatively low number of patients that you had below 40 and actually very few patients with bioprostheses below 40 compared with the other group could have reached the 15-year mark at 15 years? And did you stratify reoperation rate by group of age, like 40 to 50, 30 to 40, less than 40?

Dr Toyoda. Yes, we did.

Dr Mesana. It wasn't in your paper, though. It was stratified by survival but not reoperation.

Dr Toyoda. It will be put in the manuscript. We did further analysis on reoperation in stratified age group 18 to 30, 31 to 40, and 41 to 50; however, there was no significant difference between each age group in terms of the timing of the reoperation.

Dr Mesana. So you are saying that people between 30 and 40 are not operated earlier at 15 years than people more than 40? This is what you are saying now?

Dr Toyoda. In our data, we couldn't see a significant difference compared with patients in different age groups. However, each patient group had a small sample size, so maybe it might have contributed to this outcome.

Dr Mesana. So you may have a confounding factor of the low number of patients lower than 40 years old in your study, I am suspecting. This is very important.

Dr Toyoda. Yes.

Dr Mesana. My last point is that this study actually encourages surgeons to use fewer and fewer mechanical valves. I would like to raise a word of caution, because multiple reoperations are not a minor problem. We just had a paper from Mayo Clinic that shows that reoperations are not as safe. I think the young patients should be aware of the risk of multiple reoperations and the long-term outcomes of transcatheter aortic valve implantation and in particular with more surgical prostheses before making that choice. And actually they should be aware that you can have a reoperation with a mechanical valve but you are not free of stroke after a tissue valve.

Thank you. I would like to thank the Association for the privilege of discussing this paper.

Dr Toyoda. Thank you very much.

Dr R. Rocha *(Toronto, Ontario, Canada)*. First of all, my compliments for your presentation. It is an interesting US population study. There is a lack of population studies in cardiac surgery, which is a misfortune.

Dr Toyoda. Thank you very much.

Dr Rocha. I have some questions regarding, specifically, long-term mortality. This outcome was tracked by a combination of 3 coding strategies. One of them was using the Social Security index database. However, there has been several reports, including a publication from John Elefteriades and a review from Gene Blackstone, both at *The Journal of Thoracic and Cardiovascular Surgery*, indicating the low accuracy of this database. After you added the 2 other strategies to track mortality, have you done any validation of it? And for the validation of your ICD-9 codes for the secondary outcomes, did you do it in multi-institutions or just in your institution?

Dr Toyoda. We validated key ICD-9 codes, especially procedures, aortic valve replacement with tissue and mechanical, and for other outcomes we relied on previous literature from Medicaid showing the code validation of ICD-9 codes.

And for the Social Security death master file, it is only reporting 20% of deaths after 2011. We are aware of that. That is why we added vital statistics death data, which is stored in the department of health in both states, and also we searched death in the subsequent admissions after index admissions.

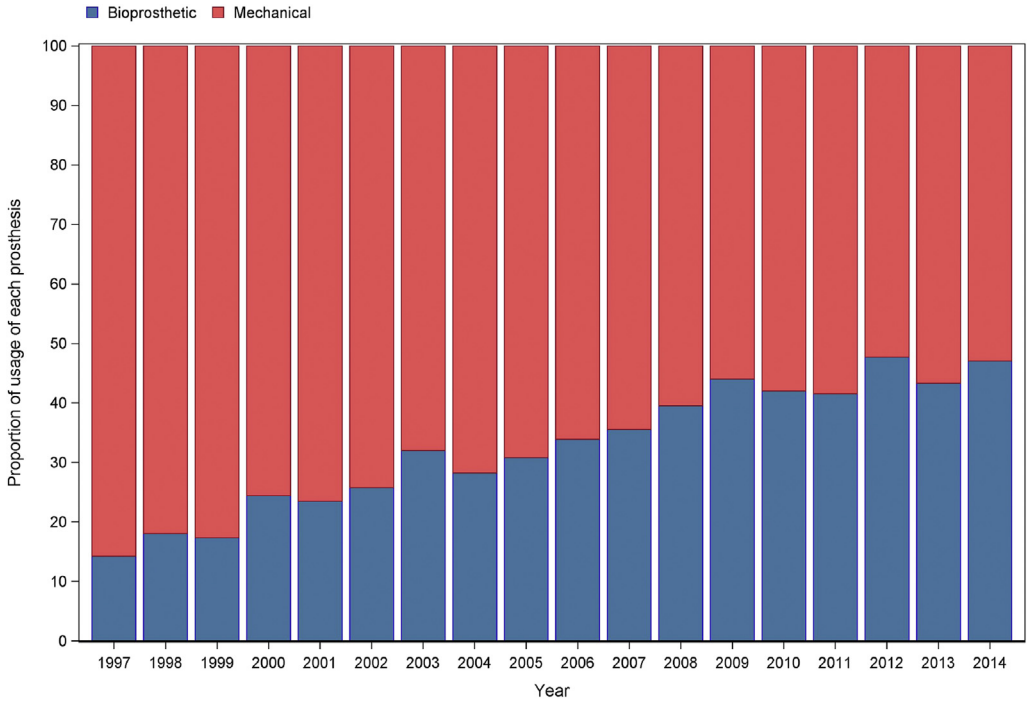


FIGURE E1. Trend in bioprosthetic or mechanical valve usage for aortic valve replacement in patients aged 18 to 50 years.

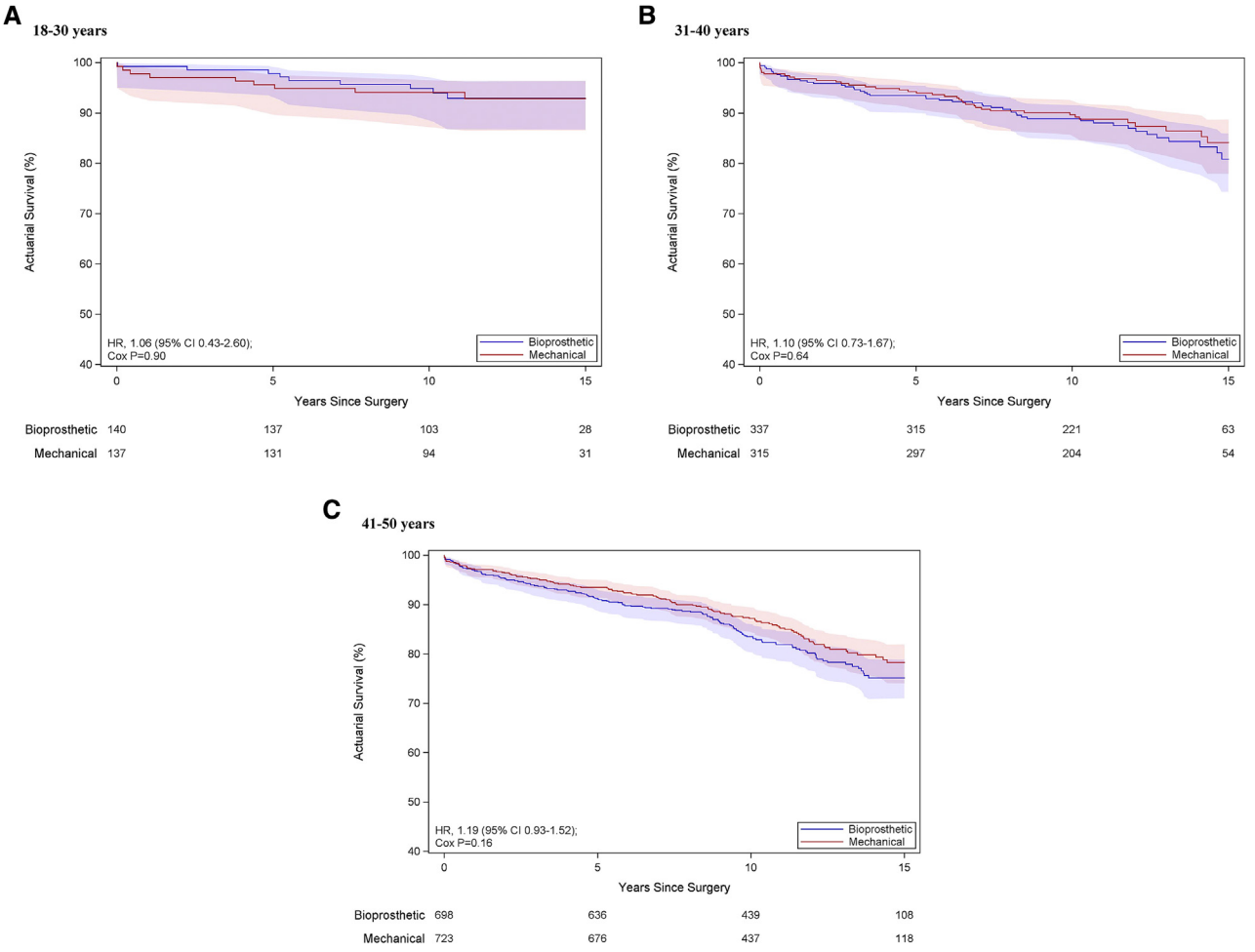


FIGURE E2. Survival curves in propensity score-matched patients aged 18 to 50 years according to prosthesis type stratified by age: (A) 18 to 30 years, (B) 31 to 40 years, (C) 41 to 50 years.

TABLE E1. Definitions of exclusion criteria

Exclusion criterion	*International Classification of Diseases, 9th Edition, Clinical Modification* codes
Endocarditis	Diagnosis codes (from index and previous admission) 421, 4210, 4211, 4219, 11281, 03642, 09884, 11504, 11514, and 11594
Previous valve replacement	Diagnosis code (from index admission) V433 Procedure codes (from previous admissions) 3520, 3521, 3522, 3523, 3524, 3525, 3526, 3527, and 3528
Previous valve repair	Procedure codes (from previous admissions) 3510, 3511, 3512, 3513, 3514 and 3533
Previous heart transplant	Procedure codes (from index and previous admissions) 336, 3751 Diagnosis codes (from index and previous admissions) V421, 99683
Congenital cardiac disease	Diagnosis code (from index and previous admission) 7450, 7451, 74510, 74511, 74512, 74519, 7451, 7453, 7467, 7457, 7456, 74560, 74561, 74569, 7460, 74601, 74602, 74609, 7461, 7462, 7473, 7474, 74740, 74741, 74742, 74749, 7458, 7459, 7475, 7468, 74681, 74682, 74683, 74684, 74689, 7469, 7479, and V1365 Procedure codes (from previous admission) 354, 3541, 3542, 3553, 3554, 3562, 3563, 3573, 358, 3581, 3582, 3583, 3584, 359, 3591, 3592, 3593, 3594, 3595, 3598, 3599, 390, and 3921
Concomitant congenital cardiac surgery	Procedure codes (from index admission) 354, 3541, 3542, 3553, 3554, 3562, 3563, 3573, 358, 3581, 3582, 3583, 3584, 359, 3591, 3592, 3593, 3594, 3595, 3598, 3599, 390, and 3921
Concomitant valve replacement	Procedure codes (from index admission) 3520, 3523, 3524, 3525, 3526, 3527, and 3528
Concomitant coronary artery bypass graft surgery	Procedure codes (from index admission) 361, 3610, 3611, 3612, 3613, 3614, 3615, 3615, 3617, and 3618

TABLE E2. Definitions of baseline characteristics

Baseline characteristic	*International Classification of Diseases, 9th Edition, Clinical Modification codes*
Coagulation or platelet disorders	Diagnosis codes (from index and previous admissions) 286, 2861-2865, 28652, 28653, 28659, 2866, 2867, 2869, 287, 2870-2873, 28730, 28731, 28732, 28733, 28739, 2874, 2875, 2878, and 2879
Hypertension	Diagnosis codes (from index and previous admissions) 401, 4011, 4019, 402, 4020, 40200, 40201, 4021, 4029, 40290, 40291, 403, 4030, 40300, 40301, 4031, 40310, 40311, 4039, 40390, 40391, 404, 4040, 40400, 40401, 40402, 40403, 4041, 40410, 40411, 40412, 40413, 4049, 40490, 40491, 40492, 40493, 405, 4050, 40501, 40509, 4051, 40511, 40519, 4059, 40591, 40599, and 4372
Diabetes	Diagnosis codes (from index and previous admissions) 249, 2490, 24900, 24901, 2491, 24910, 24911, 2492, 24920, 24921, 2493, 24930, 24931, 2494, 24940, 24941, 2495, 24950, 24951, 2496, 24960, 24961, 2497, 24970, 24971, 2498, 24980, 24981, 2499, 24990, 24991, 250, 2500, 25000, 25001, 25002, 25003, 2501, 25010, 25011, 25012, 25013, 2502, 25020, 25021, 25022, 25023, 2503, 25030, 25031, 25032, 25033, 2504, 25040, 25041, 25042, 25043, 2505, 25050, 25051, 25052, 25053, 2506, 25060, 25061, 25062, 25063, 2507, 25070, 25071, 25072, 25073, 2508, 25080, 25081, 25082, 25083, 2509, 25090, 25091, 25092, and 25093
Coronary artery disease	Un-revascularized Diagnosis codes (from index and previous admissions) 410, 4100, 41000, 41001, 41002, 4101, 41010, 41011, 41012, 4012, 40120, 41021, 41022, 4103, 41030, 41031, 41032, 4104, 41040, 41041, 41042, 4105, 41050, 41051, 41052, 4106, 41060, 41061, 41062, 4107, 41070, 41071, 41072, 4108, 41080, 41081, 41082, 4109, 41090, 41091, 41092, 411, 4110, 4111, 4118, 41181, 41189, 412, 413, 4130, 4131, 4139, 414, 4140, 41400, 41401, 41402, 41403, 41404, 41405, 41406, 41407, 4142, 4143, 4144, 4295, 4296, 4297, 42971, and 42979 Previous percutaneous coronary intervention Diagnosis codes (from index and previous admissions) V4582 Procedure codes (from previous admissions) 0066, 1755, 3601, 3602, 3603, 3604, 3605, 3606, 3607, 3608, and 3609 Previous coronary artery bypass grafting Diagnosis codes (from index and previous admissions) V4581 Procedure codes (from previous admissions) 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617, and 3619
Peripheral vascular disease	Diagnosis codes (from index and previous admissions) 4400, 4401, 4402, 44020, 44021, 44022, 44023, 44024, 44029, 4403, 44030, 44031, 44032, 4404, 4408, 4409, 4471, 9961, 99662, 99674, and V434
Cerebrovascular disease	Diagnosis codes (from index and previous admissions) 3623, 36230, 36231, 36232, 36233, 36234, 36235, 36236, 36237, 3466, 34660, 34661, 34662, 34663, 430, 431, 432, 4320, 4321, 4329, 433, 4330, 43300, 43301, 4331, 43310, 43311, 4332, 43320, 43321, 4333, 43330, 43331, 4338, 43380, 43381, 4339, 43390, 43391, 434, 4340, 43400, 43401, 4341, 43410, 43411, 4349, 43490, 43491, 435, 4350, 4351, 4352, 4353, 4358, 4359, 436, 437, 4370, 4371, 4372, 4373, 4374, 4375, 4376, 4377, 99702, 4378, 4379, 438, 4380, 4381, 43810, 43811, 43812, 43813, 43814, 43819, 4382, 43820, 43821, 43822, 4383, 43830, 43831, 43832, 4384, 43840, 43841, 43842, 4385, 43850, 43851, 43852, 4386, 4387, 4388, 43881, 43882, 43883, 43884, 43885, 43889, and 4389
Congestive heart failure	Diagnosis codes (from index and previous admissions) 39891, 428, 4280, 4281, 4282, 42820, 42821, 42822, 42823, 4283, 42830, 42831, 42832, 42833, 4284, 42840, 42841, 42842, 42843, 4289, 429, 4290, 4291, 4292, 4293, 4294, 4295, 4296, 4297, 42971, 42979, 4298, 42981, 42982, 42983, 42989, and 4299
Atrial fibrillation	Diagnosis codes (from index and previous admissions) 4273, 42731, 42732
	Diagnosis codes (from index and previous admissions)

(Continued)

TABLE E2. Continued

Baseline characteristic	*International Classification of Diseases, 9th Edition, Clinical Modification codes*
Chronic obstructive pulmonary disease	491, 4910, 4911, 4912, 49120, 49121, 49122, 4918, 4919, 492, 4920, 4928, 493, 4930, 49300, 49301, 49302, 4931, 49310, 49311, 49312, 4932, 49320, 49321, 49322, 4938, 49380, 49381, 49382, 4939, 49390, 49391, 49392, 494, 4940, 4941, and 496
Chronic kidney disease	Nondialysis-dependent Diagnosis codes (from index and previous admissions) 403, 4030, 40300, 40301, 4031, 40310, 40311, 4039, 40390, 40391, 404, 4040, 40400, 40401, 40402, 40403, 4041, 40410, 40411, 40412, 40413, 4049, 40490, 40491, 40492, 40493, 582, 5820, 5821, 5822, 5824, 5828, 58281, 58289, 5829, 583, 5830, 5831, 5832, 5834, 5836, 5837, 5838, 58381, 58389, 5839, 585, 5851, 5852, 5853, 5854, 5855, 5859, 586, 587, 588, 5880, 5881, 5888, 58881, 58888, 5889, V420, and V56 Dialysis-dependent Diagnosis codes (from index and previous admissions) V451, V4511, V4512, V560, V561, V562, V563, V5631, V5632, V568, and 5856
Liver disease	Diagnosis codes (from index and previous admissions) 070, 0700, 0701, 0702, 07020, 07021, 07022, 07023, 0703, 07030, 07031, 07032, 07033, 0704, 07041, 07042, 07043, 07044, 07049, 0705, 07051, 07052, 07053, 07054, 07059, 0706, 0707, 07070, 07071, 0709, 456, 4560, 4561, 4562, 45620, 45621, 4563, 4564, 4565, 4566, 4568, 570, 571, 5710, 5711, 5712, 5713, 5714, 57140, 57141, 57142, 57149, 5715, 5716, 5718, 5719, 572, 5720, 5721, 5722, 5723, 5724, 5728, 573, 5730, 5731, 5732, 5733, 5734, 5735, 5738, 5738, 7824, 7891, 7895, 78951, 78959, 7904, 7905, 7948, and V427
Cancer	Oropharyngeal cancers Diagnosis codes (from index and previous admissions) 140, 1400, 1401, 1403, 1404, 1405, 1406, 1408, 1409, 141, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1418, 1419, 142, 1420, 1421, 1422, 1428, 1429, 143, 1430, 1431, 1438, 1439, 144, 1440, 1441, 1448, 1449, 145, 1450, 1451, 1452, 1453, 1454, 1455, 1456, 1458, 1459, 146, 1460, 1461, 1462, 1463, 1464, 1465, 1466, 1467, 1468, 1469, 147, 1470, 1471, 1472, 1473, 1478, 1479, 148, 1480, 1481, 1482, 1483, 1488, 1489, 149, 1490, 1491, 1498, and 1499 Gastrointestinal cancers Diagnosis codes (from index and previous admissions) 150, 1500, 1501, 1502, 1503, 1504, 1505, 1506, 1508, 1509, 1510, 151, 1511, 15012, 1513, 1514, 1515, 1516, 1518, 1519, 152, 1520, 1521, 1522, 1523, 1528, 1529, 153, 1530, 1531, 1532, 1533, 1534, 1535, 1536, 1537, 1538, 1539, 154, 1540, 1541, 1542, 1543, 1548, 155, 1550, 1551, 1552, 156, 1560, 1561, 1562, 1568, 1569, 157, 1570, 1571, 1572, 1573, 1574, 1578, 1579, 158, 1580, 1588, 1589, 159, 1590, 1591, 1598, and 1599 Respiratory tract cancers Diagnosis codes (from index and previous admissions) 160, 1600, 1601, 1602, 1603, 1604, 1605, 1608, 1609, 161, 1610, 1611, 1612, 1613, 1618, 1619, 162, 1620, 1622, 1623, 1624, 1625, 1628, 1629, 163, 1630, 1631, 1638, 1639, 164, 1640, 1461, 1462, 1463, 1468, 1649, 165, 1650, 1658, and 1659 Bone and connective tissue cancer Diagnosis codes (from index and previous admissions) 170, 1700, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 171, 1710, 1712, 1713, 1714, 1715, 1716, 1717, 1718, 1719, 172, 1720, 1721, 1722, 1723, 1724, 1725, 1726, 1727, 1728, 1729, 173, 1730, 17300, 17301, 17302, 17309, 1731, 17310, 17311, 17312, 17319, 1732, 17320, 17321, 17322, 17329, 1733, 17330, 17331, 17332, 17339, 1734, 17340, 17341, 17342, 17349, 1735, 17350, 17351, 17352, 17359, 1736, 17360, 17361, 17362, 17369, 1737, 17370, 17371, 17372, 17379, 1738, 17380, 17381, 17382, 17389, 1739, 17390, 17391, 17392, 17399, 174, 1740, 1741, 1742, 1743, 1744, 1745, 1746, 1748, 1749, 175, 1750, 1759, 176, 1760, 1761, 1762, 1763, 1764, 1765, 1768, and 1769 Genitourinary cancers Diagnosis codes (from index and previous admissions) 179, 180, 1800, 1801, 1808, 1809, 181, 182, 1820, 1821, 1828, 183, 1830, 1832, 1833, 1834, 1835, 1838, 1839, 184, 1840, 1841, 1842, 1843, 1844, 1848, 1849, 185, 186, 1860, 1869, 187, 1871, 1872, 1873, 1874, 1875, 1876, 1877, 1878, 1879, 188, 1880, 1881, 1882, 1883, 1884, 1885, 1886, 1887, 1888, 1889, 189, 1890, 1891, 1892, 1893, 1894, 1898, and 1899

(Continued)

TABLE E2. Continued

Baseline characteristic	*International Classification of Diseases, 9th Edition, Clinical Modification codes*
	Lymphoid cancers
	Diagnosis codes (from index and previous admissions)
	200, 2000, 20000, 20001, 20002, 20003, 20004, 20005, 20006, 20007, 20008, 2001, 20010, 20011, 20012, 20013, 20014, 20015, 20016, 20017, 20018, 2002, 20020, 20021, 20022, 20023, 20024, 20025, 20026, 20027, 20028, 2003, 20030, 20031, 20032, 20033, 20034, 20035, 20036, 20037, 20038, 2004, 20040, 20041, 20042, 20043, 20044, 20045, 20046, 20047, 20048, 2005, 20050, 20051, 20052, 20053, 20054, 20055, 20056, 20057, 20058, 2006, 20060, 20061, 20062, 20063, 20064, 20065, 20066, 20067, 20068, 2007, 20070, 20071, 20072, 20073, 20074, 20075, 20076, 20076, 20077, 20078, 2008, 20080, 20081, 20082, 20083, 20084, 20085, 20086, 20087, 20088, 201, 2010, 20100, 20101, 20102, 20103, 20104, 20105, 20106, 20107, 20108, 2011, 20110, 20111, 20112, 20113, 20114, 20115, 20116, 20117, 20118, 2012, 20120, 20121, 20122, 20123, 20124, 20125, 20126, 20127, 20128, 2014, 20140, 20141, 20142, 20143, 20144, 20145, 20146, 20147, 20148, 2015, 20150, 20151, 20152, 20153, 20154, 20155, 20156, 20157, 20158, 2016, 20160, 20161, 20162, 20163, 20164, 20165, 20166, 20167, 20168, 2017, 20170, 20171, 20172, 20173, 20174, 20175, 20176, 20177, 20178, 2019, 20190, 20191, 20192, 20193, 20194, 20195, 20196, 20197, 20198, 202, 2020, 20200, 20201, 20202, 20203, 20204, 20205, 20206, 20207, 20208, 2021, 20210, 20211, 20212, 20213, 20214, 20215, 20216, 20217, 20218, 2022, 20220, 20221, 20222, 20223, 20224, 20225, 20226, 20227, 20228, 2023, 20230, 20231, 20232, 20233, 20234, 20235, 20236, 20237, 20238, 2024, 20240, 20241, 20242, 20243, 20244, 20245, 20246, 20247, 20248, 2025, 20250, 20251, 20252, 20253, 20254, 20255, 20256, 20257, 20258, 2026, 20260, 20261, 20262, 20263, 20264, 20265, 20266, 20267, 20268, 2027, 20270, 20271, 20272, 20273, 20274, 20275, 20276, 20277, 20278, 2028, 20280, 20281, 20282, 20283, 20284, 20285, 20286, 20287, 20288, 2029, 20290, 20291, 20292, 20293, 20294, 20295, 20296, 20297, 20298, 203, 2030, 20300, 20301, 20302, 2031, 20310, 20311, 20312, 2038, 20380, 20381, and 20382
	Hematologic cancers
	Diagnosis codes (from index and previous admissions)
	204, 2040, 20400, 20401, 20402, 2041, 20410, 20411, 20412, 2042, 20420, 20421, 20422, 2048, 20480, 20481, 20482, 2049, 20490, 20491, 20492, 205, 2050, 20500, 20501, 20502, 2051, 20510, 20511, 20512, 2052, 20520, 20521, 20522, 2053, 20530, 20531, 20532, 2058, 20580, 20581, 20582, 2059, 20590, 20591, 20592, 206, 2060, 20600, 20601, 20602, 2061, 20610, 20611, 20612, 2062, 20620, 20621, 20622, 2068, 20680, 20681, 20682, 2069, 20690, 20691, 20692, 207, 2070, 20700, 20701, 20702, 2071, 20710, 20711, 20712, 2072, 20720, 20721, 20722, 2078, 20780, 20781, 20782, 208, 2080, 20800, 20801, 20802, 2081, 20810, 20811, 20812, 2082, 20820, 20821, 20822, 2088, 20880, 20881, 20882, 2089, 20890, 20891, 20892, 209, 2090, 20900, 20901, 20902, 20903, 2091, 20910, 20911, 20912, 20913, 20914, 20915, 20916, 20917, 2092, 20920, 20921, 20922, 20923, 20924, 20925, 20926, 20927, 20929, 2093, 20930, 20931, 20932, 20933, 20934, 20935, 20936, 2094, 20940, 20941, 20942, 20943, 2095, 20950, 20951, 20952, 20953, 20954, 20955, 20956, 20957, 2096, 20960, 20961, 20962, 20963, 20964, 20965, 20966, 20967, 20969, 2097, 20970, 20971, 20972, 20973, 20974, 20975, and 20979
	Other cancers
	Diagnosis codes (from index and previous admissions)
	190, 1900, 1901, 1902, 1903, 1904, 1905, 1906, 1907, 1908, 1909, 191, 1910, 1911, 1912, 1913, 1914, 1915, 1916, 1917, 1918, 1919, 192, 1920, 1921, 1922, 1923, 1928, 1929, 193, 194, 1940, 1941, 1943, 1944, 1945, 1946, 1948, 195, 1950, 1951, 1952, 1953, 1954, 1955, 1958, 196, 1960, 1961, 1962, 1963, 1965, 1966, 1968, 1969, 197, 1970, 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978, 198, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988, 19881, 19882, 19889, 199, 1990, 1991, and 1992

TABLE E3. Definition of secondary endpoints

Outcome	*International Classification of Diseases, 9th Edition, Clinical Modification* codes
Stroke	Iatrogenic stroke Diagnosis code (from index hospitalization) 99702 Hemorrhagic stroke Diagnosis codes (primary diagnosis of subsequent admissions) 430, 431, 432, 4320, 4321, and 4329 Ischemic stroke Diagnosis codes (primary diagnosis of subsequent admissions) 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, and 43491
Reoperation	Procedure codes (subsequent admissions) 3521 and 3522
Major bleeding event	Intracerebral hemorrhage Diagnosis codes (primary diagnosis of subsequent admission) 430, 431, 432, 4320, 4321, and 4329 Hemopericardium or cardiac tamponade Diagnosis codes (primary diagnosis of subsequent admission) 4230 and 4233 Gastrointestinal hemorrhage Diagnosis codes (primary diagnosis of subsequent admission) 4560, 45620, 4590, 53021, 5310, 53100, 53101, 5312, 53120, 53121, 5314, 53140, 53141, 5316, 53160, 53161, 5320, 53200, 53201, 5322, 53220, 53221, 53241, 5326, 53260, 53261, 5330, 53300, 53301, 5332, 53320, 53321, 53340, 533401, 5336, 53360, 53361, 5340, 53400, 53401, 5342, 53420, 53421, 5344, 53440, 53441, 5346, 53501, 53511, 53521, 53531, 53541, 53561, 53571, 5693, 578, 5780, 5781, and 5789 Hematuria Diagnosis codes (primary diagnosis of subsequent admission) 5997, 59970, and 59971 Hemarthrosis Diagnosis codes (primary diagnosis of subsequent admission) 7191, 71910, 71911, 71912, 71913, 71914, 71915, 71916, 71917, 71918, and 71919 Hemoptysis Diagnosis codes (primary diagnosis of subsequent admission) 7848, 7863, 78630, and 78639 Epistaxis Diagnosis codes (primary diagnosis of subsequent admission) 7847 Retinal or choroidal hemorrhage Diagnosis codes (primary diagnosis of subsequent admission) 36281, 36243, 36361, and 36362

TABLE E4. Definition of 30-day complications

Outcome	*International Classification of Diseases, 9th Edition, Clinical Modification* codes
Stroke	Diagnosis code (from index admission) 99702 Diagnosis codes (from subsequent admissions) 430, 431, 432, 4320, 4321, 4329, 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, and 43491
Atrial fibrillation	Diagnosis code (from index and subsequent admissions) 4273, 42731, and 42732
Acute kidney injury	Diagnosis code (from index and subsequent admissions) 5939, 584, 5845, 5846, 5847, 5848, and 5849
Respiratory failure	Respiratory arrest Diagnosis codes (from index and subsequent admissions) 7991 Pulmonary insufficiency Diagnosis codes (from index and subsequent admissions) 5185, 51881, 51882, and 51884 Pulmonary collapse Diagnosis codes (from index and subsequent admissions) 5180 Lung edema Diagnosis codes (from index and subsequent admissions) 5184, 2766, 27661, and 27669 Pneumothorax Diagnosis codes (from index and subsequent admissions) 5120, 5121, and 5122 Pulmonary embolism Diagnosis codes (from index and subsequent admissions) 4151, 41511, 41512, 41513, and 41519 Pneumonia Diagnosis codes (from index and subsequent admissions) 00322, 0203, 0204, 0205, 0212, 0221, 0310, 0391, 0521, 0551, 0730, 0830, 1124, 1140, 1144, 1145, 11505, 11515, 11595, 1304, 1363, 4800, 4801, 4802, 4803, 4808, 4809, 481, 4820, 4821, 4822, 4823, 48230, 48231, 48232, 48239, 4824, 48240, 48241, 48242, 48249, 4828, 48281, 48282, 48283, 48284, 48289, 4829, 483, 4830, 4831, 4838, 4841, 4843, 4845, 4846, 4847, 4848, 485, 486, 5130, and 5171 Postoperative tracheostomy Procedure codes (from index admission) 311, 312, 3121, 3129 Continuous mechanical ventilation for 96 consecutive hours or more or unspecified duration Procedure codes (from index admission) 9670 and 9672 Reintubation Procedure codes (from index admission) 9604

TABLE E5. Baseline characteristics of the full study cohort, according to the aortic valve prosthesis type

Baseline characteristics	Prosthesis type, n (%)			Standardized difference (%)	*P* value
	All patients (n = 5111)	Bioprosthetic (n = 1281)	Mechanical (n = 3830)		
Demographics					
Age, y, median [IQR]	43 [36-47]	43 [36-47]	43 [37-47]	3.4	.22
18-30	600 (11.7)	148 (11.6)	452 (11.8)	0.77	.16
31-40	1371 (26.8)	370 (28.9)	1001 (26.1)	6.2	
41-50	3140 (61.4)	763 (59.6)	2377 (62.1)	5.1	
Men	3860 (75.5)	971 (75.8)	2889 (75.4)	0.86	.79
New York State resident	2261 (44.2)	604 (47.2)	1657 (43.3)	7.8	.02
Race/ethnicity					
White (non-Hispanic)	3700 (72.4)	937 (73.1)	2763 (72.1)	2.3	.67
African-American (non-Hispanic)	357 (7.0)	91 (7.1)	266 (6.9)	0.6	
Other	1054 (20.6)	253 (19.8)	801 (20.9)	2.9	
Emergent/urgent admission	1413 (27.6)	342 (26.7)	1071 (28.0)	2.8	.38
Comorbidities					
Coagulation/platelet disorders	157 (3.1)	45 (3.5)	112 (2.9)		.29
Hypertension	1850 (36.2)	441 (34.4)	1409 (36.8)	4.9	.13
Diabetes mellitus	346 (6.8)	81 (6.3)	265 (6.9)	2.4	.46
Coronary artery disease	620 (12.1)	128 (10.0)	492 (12.8)	9.0	.007
Peripheral vascular disease	105 (2.1)	24 (1.9)	81 (2.1)	1.7	.60
Cerebrovascular disease	120 (2.3)	24 (1.9)	96 (2.5)	4.3	.20
Congestive heart failure	1375 (26.9)	299 (23.3)	1076 (28.1)	10.9	.001
Atrial fibrillation	356 (7.0)	79 (6.2)	277 (7.2)	4.3	.19
Chronic obstructive pulmonary disease	496 (9.7)	122 (9.5)	374 (9.8)	0.82	.80
Chronic kidney disease	183 (3.6)	46 (3.6)	137 (3.6)	0.07	.98
Dialysis dependent	135 (2.6)	28 (2.2)	107 (2.8)	3.9	.24
Liver disease	191 (3.7)	56 (4.4)	135 (3.5)	4.4	.17
Cancer	129 (2.5)	43 (3.4)	86 (2.2)	6.7	.03
Year of surgery					
1997	477 (9.3)	68 (5.3)	409 (10.7)	19.9	<.001
1998	492 (9.6)	89 (6.9)	403 (10.5)	12.7	
1999	512 (10.0)	89 (6.9)	423 (11.0)	14.4	
2000	467 (9.1)	114 (8.9)	353 (9.2)	1.1	
2001	490 (9.6)	115 (9.0)	375 (9.8)	2.8	
2002	543 (10.6)	140 (10.9)	403 (10.5)	1.3	
2003	537 (10.5)	172 (13.4)	365 (9.5)	12.3	
2004	534 (10.4)	151 (11.8)	383 (10.0)	5.7	
2005	522 (10.2)	161 (12.6)	361 (9.4)	10.1	
2006	537 (10.5)	182 (14.2)	355 (9.3)	1.4	
Concomitant procedures					
Operations of the aorta	1019 (19.9)	254 (19.8)	765 (20.0)	0.36	.91

TABLE E6. Multivariable Cox regression results of survival in the full study cohort

Variable	Hazard ratio	95% CI	*P* value
Bioprosthesis	1.16	0.99-1.36	.07
Age	1.02	1.01-1.03	<.001
Male sex	0.95	0.80-1.12	.53
Race			.04
White	1.00	–	–
African-American	1.19	0.94-1.52	–
Other	0.85	0.70-1.02	–
Emergent/urgent admission	1.28	1.10-1.48	.001
New York State residency	0.95	0.80-1.11	.51
Coagulation/platelet disorders	1.16	0.83-1.11	.39
Hypertension	1.35	1.17-1.56	<.001
Diabetes mellitus	1.55	1.25-1.94	<.001
Coronary artery disease	1.05	0.85-1.30	.65
Peripheral vascular disease	1.58	1.05-2.36	.03
Cerebrovascular disease	1.20	0.84-1.70	.31
Congestive heart failure	1.48	1.29-1.70	<.001
Atrial fibrillation	1.31	1.04-1.65	.02
Chronic obstructive pulmonary disease	1.68	1.40-2.02	<.001
Chronic kidney disease	2.62	1.59-4.32	<.001
Dialysis dependent	3.87	2.94-5.07	
Liver disease	1.91	1.50-2.44	<.001
Cancer	2.56	1.87-3.51	<.001
Year of surgery	0.96	0.93-0.98	<.001
Operations of the aorta	1.09	0.93-1.29	.29

CI, Confidence interval.