ORIGINAL ARTICLE

Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement

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ABSTRACT

BACKGROUND

In patients undergoing aortic-valve or mitral-valve replacement, either a mechanical or biologic prosthesis is used. Biologic prostheses have been increasingly favored despite limited evidence supporting this practice.

METHODS

We compared long-term mortality and rates of reoperation, stroke, and bleeding between inverse-probability-weighted cohorts of patients who underwent primary aortic-valve replacement or mitral-valve replacement with a mechanical or biologic prosthesis in California in the period from 1996 through 2013. Patients were stratified into different age groups on the basis of valve position (aortic vs. mitral valve).

RESULTS

From 1996 through 2013, the use of biologic prostheses increased substantially for aortic-valve and mitral-valve replacement, from 11.5% to 51.6% for aortic-valve replacement and from 16.8% to 53.7% for mitral-valve replacement. Among patients who underwent aortic-valve replacement, receipt of a biologic prosthesis was associated with significantly higher 15-year mortality than receipt of a mechanical prosthesis among patients 45 to 54 years of age (30.6% vs. 26.4% at 15 years; hazard ratio, 1.23; 95% confidence interval [CI], 1.02 to 1.48; P=0.03) but not among patients 55 to 64 years of age. Among patients who underwent mitral-valve replacement, receipt of a biologic prosthesis was associated with significantly higher mortality than receipt of a mechanical prosthesis among patients 40 to 49 years of age (44.1% vs. 27.1%; hazard ratio, 1.88; 95% CI, 1.35 to 2.63; P<0.001) and among those 50 to 69 years of age (50.0% vs. 45.3%; hazard ratio, 1.16; 95% CI, 1.04 to 1.30; P=0.01). The incidence of reoperation was significantly higher among recipients of a biologic prosthesis than among recipients of a mechanical prosthesis. Patients who received mechanical valves had a higher cumulative incidence of bleeding and, in some age groups, stroke than did recipients of a biologic prosthesis.

CONCLUSIONS

The long-term mortality benefit that was associated with a mechanical prosthesis, as compared with a biologic prosthesis, persisted until 70 years of age among patients undergoing mitral-valve replacement and until 55 years of age among those undergoing aortic-valve replacement. (Funded by the National Institutes of Health and the Agency for Healthcare Research and Quality.)

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Clinically significant aortic-valve disease or mitral-valve disease affects 2.5% of the population in the United States,[1] and valve replacement prolongs survival among patients with severe disease.[2] Valve prostheses are either mechanical or biologic, and each type has associated risks and benefits. Biologic prosthetic valves are associated with a higher risk of reoperation than mechanical valves because of structural valve deterioration, but mechanical valves typically necessitate lifelong anticoagulation, which increases the risk of hemorrhage and thromboembolism.[3-5]

Practice guidelines do not distinguish between aortic-valve and mitral-valve prostheses, and mechanical valves are recommended in persons younger than 50 years of age, biologic prosthetic valves in persons older than 70 years of age, and either type in persons 50 to 70 years of age.[6] However, these guidelines are based in part on data from underpowered, randomized trials of now-obsolete valves that were implanted more than 30 years ago.[7-10] Recent observational studies have shown equivalent mortality, regardless of valve type or position, among patients 50 to 69 years of age.[4,11] These results support the escalating use of biologic prosthetic valves in younger persons,[12,13] but the studies may have been underpowered to detect differences in mortality. We conducted a statewide retrospective cohort study to compare the long-term benefits and risks of mechanical and biologic prostheses for aortic-valve and mitral-valve replacement in California.

Methods

Study Design

We examined data from patients who underwent primary aortic-valve replacement or mitral-valve replacement at 142 nonfederal hospitals in California between January 1, 1996, and December 31, 2013, to evaluate the effect of prosthesis type on mortality and on the incidence of stroke, bleeding, and reoperation. The California Committee for the Protection of Human Subjects and the institutional review board at Stanford University approved this research. All the authors accept responsibility for the accuracy of the analyses.

Study Population

Patients were included in the study if they underwent primary aortic-valve replacement or mitral-valve replacement with a biologic prosthesis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 35.21 or 35.23, respectively) or a mechanical prosthesis (ICD-9-CM code 35.22 or 35.24, respectively) during the study period. We performed an internal validation study to compare the billed ICD-9-CM procedure code with the valve type that was received by each patient (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). Although we included only isolated aortic-valve replacements in the study, to improve statistical power, we included patients who underwent mitral-valve replacement with or without concomitant tricuspid-valve repair, ablation of atrial fibrillation, or coronary-artery bypass surgery. Exclusion criteria included out-of-state residency during the initial valve-replacement surgery, previous cardiac surgery, multiple valve replacement, aortic-valve repair, mitral-valve repair, and thoracic aortic surgery (Tables S1 and S2 in the Supplementary Appendix).

All the records were obtained from the California Office of Statewide Health Planning and Development (OSHPD) Patient Discharge, Emergency Department, and Ambulatory Surgery Center data sets. The characteristics of the patients at baseline were ascertained from previous hospitalizations or from diagnoses that were coded as "present on admission" during the index hospitalization. Definitions of coexisting conditions are provided in Table S3 in the Supplementary Appendix.

We stratified the study patients according to age: for aortic-valve replacement, the categories were 45 to 54 years and 55 to 64 years; and for mitral-valve replacement, the categories were 40 to 49 years, 50 to 69 years, and 70 to 79 years. For the analyses of aortic-valve replacement, we selected age strata that were consistent with recommendations from previous randomized trials.[7,10] For the analyses of mitral-valve replacement, we selected age strata to achieve appropriate power to assess current practice guidelines.[6] For mitral-valve replacement, we also performed exploratory analyses in which the subgroup of patients 50 to 69 years of age was split into two decades (50 to 59 years and 60 to 69 years).

Outcomes

The primary end point was mortality. The OSHPD patient-discharge database is linked to the California Department of Public Health Death Statis-

tical Master File, which is the annual state death record (and which is distinct from the Social Security Death Index). The performance of the linkage has been reported previously.[14] Longitudinal clinical follow-up was obtained by matching the record linkage number and birth year across all encounters. Secondary end points included perioperative mortality (≤30 days after surgery) and the cumulative incidence of stroke, bleeding, or reoperation, as defined in Table S4 in the Supplementary Appendix. Absent the event of interest, data from patients were censored on December 31, 2013.

STATISTICAL ANALYSIS

The study was designed to have a power of at least 85%, at an alpha level of 0.05, to detect a between-group hazard ratio of 1.15 for the analysis of mortality at 15 years among patients 55 to 64 years of age who underwent aortic-valve replacement and among patients 50 to 69 years of age who underwent mitral-valve replacement.[15] Patients in the younger and older age groups were included as contrasts. We expected mechanical valves to be associated with lower mortality among younger patients, and biologic prosthetic valves to be associated with lower mortality among older patients.

We used inverse probability weighting to limit confounding by indication (see the Methods section in the Supplementary Appendix). In each age group, nonparsimonious logistic regression was used to estimate each patient's probability of receiving a biologic prosthetic valve (Tables S5 and S6 and Figs. S1 and S2 in the Supplementary Appendix).[16] Stabilized weights were calculated by dividing the marginal probability of the observed treatment by the propensity score for the treatment received (Figs. S3 and S4 in the Supplementary Appendix).[17] Balance between treatment groups was assessed with the use of standardized mean differences. A standardized difference of 10% or less was deemed to be the ideal balance, and a standardized difference of 20% or less was deemed to be an acceptable balance.[18]

Weighted logistic regression with a robust variance estimator was used to determine the marginal effect of a biologic prosthetic valve on 30-day mortality. Weighted Cox proportional-hazards regression with a robust variance estimator was used to compare long-term mortality between groups. Separate analyses of the weighted population were adjusted for all baseline characteristics and concomitant procedures or included hospital as a random effect. To address nonproportional hazards, the restricted mean survival time (the average duration of event-free survival over a prespecified follow-up period, calculated as the area under the survival curve) was estimated to describe the overall effect of treatment during the study period (see the Methods section in the Supplementary Appendix).[19,20] As an exploratory analysis, the cumulative incidence of stroke, bleeding, and reoperation after the index valve replacement was compared between valve types with death as a competing risk. Subdistribution hazards in the weighted populations were estimated with the method of Fine and Gray.[21] Standard errors were estimated with the use of 500 bootstrap replicates. Stroke and bleeding were also evaluated as time-dependent variables to determine the effect of each complication on long-term mortality.

To explore the age-dependent effect of prosthesis type on mortality, a Cox proportional-hazards model was fit to the entire weighted study population with the use of an interaction term for age (modeled as a natural spline) and prosthesis type. Standard errors were computed from 1000 bootstrap replicates. Owing to changes in practice patterns over time, outcomes were also assessed for the primary age groups of interest after we stratified the 18-year study period into three 6-year intervals. Analyses were also conducted to determine the sensitivity of our results to prosthesis misclassification and unmeasured confounding. All the tests of treatment effect were two-tailed with an alpha threshold of 0.05. Statistical analyses were performed with the use of R software, version 3.2.3 (R Foundation), and data management was performed with the use of SAS software, version 9.2 (SAS Institute). Additional details regarding the statistical analysis are provided in the Methods section in the Supplementary Appendix.

RESULTS

PATIENTS

Of 45,639 patients who underwent aortic-valve replacement during the study period, 9942 were eligible for inclusion in the study, and of 38,431 patients who underwent mitral-valve replacement during the study period, 15,503 were eligible for inclusion (Figs. S5 and S6 in the Supplementary

Table 1. Baseline and Operative Characteristics of the Study Population before Inverse Probability Weighting.*

Characteristic	Aortic-Valve Replacement			Mitral-Valve Replacement		
	Mechanical Prosthesis (N=6097)	Biologic Prosthesis (N=3845)	SMD	Mechanical Prosthesis (N=9982)	Biologic Prosthesis (N=5521)	SMD
Age — yr	56.3±5.5	57.4±5.3	0.22	62.8±10.2	68.2±9.1	0.57
Year of surgery — yr†	2004.0±5.2	2006.8±4.6	0.58	2002.6±5.0	2005.2±5.0	0.52
Study period — no. (%)			0.56			0.51
1996–2001	2272 (37.3)	627 (16.3)		4967 (49.8)	1476 (26.7)	
2002–2007	2048 (33.6)	1232 (32.0)		2915 (29.2)	2001 (36.2)	
2008–2013	1777 (29.1)	1986 (51.7)		2100 (21.0)	2044 (37.0)	
Female sex — no. (%)	1980 (32.5)	1167 (30.4)	0.05	5214 (52.2)	2867 (51.9)	0.006
Race — no. (%)‡			0.08			0.11
Invalid data	—	—		1 (<0.1)	1 (<0.1)	
White	4719 (77.4)	3091 (80.4)		7251 (72.6)	4208 (76.2)	
Black	289 (4.7)	167 (4.3)		627 (6.3)	325 (5.9)	
Native American	25 (0.4)	20 (0.5)		29 (0.3)	17 (0.3)	
Asian or Pacific Islander	297 (4.9)	158 (4.1)		1120 (11.2)	449 (8.1)	
Other	683 (11.2)	362 (9.4)		805 (8.1)	450 (8.2)	
Unknown	84 (1.4)	47 (1.2)		149 (1.5)	71 (1.3)	
Valvular disease — no. (%)§						
Aortic stenosis	296 (4.9)	128 (3.3)	0.08	—	—	—
Aortic regurgitation	677 (11.1)	429 (11.2)	0.002	—	—	—
Aortic-valve disorder	4064 (66.7)	1879 (48.9)	0.37	—	—	—
Bicuspid aortic valve	438 (7.2)	329 (8.6)	0.05	—	—	—
Mitral stenosis	—	—	—	1279 (12.8)	400 (7.2)	0.19
Mitral regurgitation	—	—	—	962 (9.6)	636 (11.5)	0.06
Mitral stenosis and regurgitation	—	—	—	1196 (12.0)	423 (7.7)	0.15
Mitral-valve disorder	—	—	—	7168 (71.8)	4266 (77.3)	0.13
Tricuspid-valve disease	—	—	—	928 (9.3)	705 (12.8)	0.11
Endocarditis	347 (5.7)	275 (7.2)	0.06	714 (7.2)	477 (8.6)	0.06
Coexisting condition — no. (%)¶						
Hypertension	2526 (41.4)	1330 (34.6)	0.14	4408 (44.2)	2719 (49.2)	0.10
Diabetes mellitus	956 (15.7)	528 (13.7)	0.06	1814 (18.2)	1202 (21.8)	0.09
Coronary artery disease	1179 (19.3)	604 (15.7)	0.10	4398 (44.1)	2721 (49.3)	0.11
Peripheral vascular disease	129 (2.1)	63 (1.6)	0.04	325 (3.3)	307 (5.6)	0.11
Cerebrovascular disease	209 (3.4)	126 (3.3)	0.008	848 (8.5)	595 (10.8)	0.08
Congestive heart failure	1642 (26.9)	812 (21.1)	0.14	4974 (49.8)	2785 (50.4)	0.01
Atrial fibrillation	575 (9.4)	232 (6.0)	0.13	4112 (41.2)	1855 (33.6)	0.16
COPD	799 (13.1)	440 (11.4)	0.05	1854 (18.6)	1180 (21.4)	0.07
Chronic kidney disease	289 (4.7)	185 (4.8)	0.003	683 (6.8)	556 (10.1)	0.12
Renal dialysis	74 (1.2)	61 (1.6)	0.03	123 (1.2)	140 (2.5)	0.10
Liver disease	318 (5.2)	237 (6.2)	0.04	450 (4.5)	325 (5.9)	0.06
Cancer	95 (1.6)	89 (2.3)	0.06	213 (2.1)	204 (3.7)	0.09
Osteoporosis	32 (0.5)	27 (0.7)	0.02	160 (1.6)	178 (3.2)	0.11

Table 1. (Continued.)

Characteristic	Aortic-Valve Replacement			Mitral-Valve Replacement		
	Mechanical Prosthesis (N=6097)	Biologic Prosthesis (N=3845)	SMD	Mechanical Prosthesis (N=9982)	Biologic Prosthesis (N=5521)	SMD
Hip fracture	6 (0.1)	5 (0.1)	0.009	24 (0.2)	24 (0.4)	0.03
Malnutrition	113 (1.9)	92 (2.4)	0.04	270 (2.7)	242 (4.4)	0.09
Anemia	896 (14.7)	538 (14.0)	0.02	2088 (20.9)	1384 (25.1)	0.10
Hypothyroidism	324 (5.3)	215 (5.6)	0.01	802 (8.0)	604 (10.9)	0.10
Asthma	343 (5.6)	198 (5.1)	0.02	664 (6.7)	380 (6.9)	0.009
Previous myocardial infarction	207 (3.4)	106 (2.8)	0.04	1205 (12.1)	893 (16.2)	0.12
Dementia	5 (0.1)	4 (0.1)	0.007	30 (0.3)	36 (0.7)	0.05
History of smoking	1434 (23.5)	823 (21.4)	0.05	2196 (22.0)	1454 (26.3)	0.10
Obesity	793 (13.0)	449 (11.7)	0.04	856 (8.6)	539 (9.8)	0.04
Source of admission — no. (%)			0.05			0.11
Home	5262 (86.3)	3359 (87.4)		8416 (84.3)	4428 (80.2)	
Inpatient facility	791 (13.0)	457 (11.9)		1483 (14.9)	1028 (18.6)	
Other	29 (0.5)	14 (0.4)		23 (0.2)	21 (0.4)	
Subacute nursing facility	15 (0.2)	15 (0.4)		60 (0.6)	44 (0.8)	
Hospital admission type — no. (%)			0.09			0.06
Scheduled	4158 (68.2)	2768 (72.0)		6121 (61.3)	3239 (58.7)	
Unknown	9 (0.1)	2 (0.1)		12 (0.1)	4 (0.1)	
Unscheduled	1930 (31.7)	1075 (28.0)		3849 (38.6)	2278 (41.3)	
Concomitant procedure — no. (%)						
CABG	—	—	—	3250 (32.6)	2254 (40.8)	0.17
Tricuspid-valve repair	—	—	—	394 (3.9)	271 (4.9)	0.05
Atrial ablation	—	—	—	1223 (12.3)	1185 (21.5)	0.25

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, and SMD standardized mean difference.
† The year of surgery is shown as the calendar year, with the percentage of the following year represented by a decimal value.
‡ Race was reported by the patient.
§ Owing to idiosyncrasies of coding from the *International Classification of Diseases, Ninth Revision* (ICD-9), the categories of stenosis and regurgitation include only patients with either combined aortic-valve and mitral-valve disease or rheumatic disease. Patients with isolated stenosis or regurgitation of either the aortic or mitral valve have diagnoses that are often coded as "aortic-valve disorder" or "mitral-valve disorder," and the categories are not mutually exclusive.
¶ Coexisting conditions were determined with the use of ICD-9 codes.

Appendix). At baseline, recipients of biologic prostheses were older and had a higher incidence of coexisting conditions than recipients of mechanical prostheses (Table 1). Inverse probability weighting resulted in balanced baseline characteristics in each age group, but concomitant surgery for atrial fibrillation was slightly more frequent among recipients of mitral-valve biologic prostheses than among recipients of a mitral-valve mechanical prosthesis (standardized differences, <15%) (Tables S7 through S13 in the Supplementary Appendix). Among patients who underwent aortic-valve replacement, the median follow-up time was 5.0 years among recipients of a biologic prosthesis and 8.2 years among recipients of a mechanical prosthesis. Among patients who underwent mitral-valve replacement, the median follow-up time was 4.6 years among recipients of a biologic prosthesis and 7.6 years among recipients of a mechanical prosthesis.

From 1996 through 2013, the annual number of aortic-valve replacements increased while that of mitral-valve replacements declined. The latter was associated with a concurrent increase in

Table 2. Between-Group Differences in Mortality among Recipients of Mechanical and Biologic Aortic-Valve Prostheses.*

Variable	Patients 45 to 54 Yr of Age			Patients 55 to 64 Yr of Age		
	Biologic Prosthesis (N=1187.1)	Mechanical Prosthesis (N=2421.7)	P Value	Biologic Prosthesis (N=2636.0)	Mechanical Prosthesis (N=3684.7)	P Value
Mortality at 15 yr — %	30.6	26.4	0.03	36.1	32.1	0.60
Hazard ratio (95% CI)						
Weighted proportional-hazards model	1.23 (1.02 to 1.48)	Reference	0.03	1.04 (0.91 to 1.18)	Reference	0.60
Weighted proportional-hazards model, with multivariable adjustment†	1.25 (1.03 to 1.52)	Reference	0.02	1.05 (0.92 to 1.21)	Reference	0.47
Weighted proportional-hazards model, with hospital as random effect‡	1.28 (1.08 to 1.53)	Reference	0.005	1.11 (0.98 to 1.25)	Reference	0.12
Restricted mean survival time at 15 yr (95% CI)§						
Difference — days	−167.9 (−296.5 to −39.3)	Reference	0.01	−5.4 (−101.8 to 91.0)	Reference	0.91
Ratio	0.97 (0.94 to 0.99)	Reference	0.01	1.00 (0.98 to 1.02)	Reference	0.91
Ratio of restricted mean time lost	1.23 (1.05 to 1.42)	Reference	0.008	1.01 (0.91 to 1.12)	Reference	0.91

* The overall numbers of patients in each group are not necessarily integers owing to inverse probability weighting.
† The analysis was adjusted for all the baseline variables.
‡ The standard deviation of the random effect of hospital was 0.37 in the subgroup of patients 45 to 54 years of age and 0.33 in the subgroup of patients 55 to 64 years of age.
§ The restricted mean survival time is the average duration of survival in a cohort over a prespecified follow-up period (15 years is reported here), as estimated by the area under the curve. The difference in the restricted mean survival times is the average number of additional days gained in the treatment group (i.e., biologic-prosthesis group minus the mechanical-prosthesis group). The restricted mean time lost refers to the average number of days of life lost over a prespecified follow-up period; a ratio of more than 1.00 indicates that the treatment increased mortality (or decreased the survival rate).

mitral-valve repair (Fig. S7 in the Supplementary Appendix). The use of biologic prostheses increased over the study period with respect to both aortic-valve replacement and mitral-valve replacement. For aortic-valve replacement, the rate increased from 11.5% in 1996 to 51.6% in 2013 (P<0.001), and for mitral-valve replacement, the rate increased from 16.8% in 1996 to 53.7% in 2013 (P<0.001); this finding was also evident in the individual age groups (Figs. S8 and S9 in the Supplementary Appendix). The burden of coexisting conditions at baseline decreased over time (Tables S14 through S22 in the Supplementary Appendix).

MORTALITY AFTER AORTIC-VALVE REPLACEMENT

Mortality at 30 days did not differ significantly between recipients of a biologic aortic-valve prosthesis and recipients of a mechanical aortic-valve prosthesis (Table S23 in the Supplementary Appendix). Among recipients who were 45 to 54 years of age at the time of surgery, long-term mortality was higher among recipients of a biologic aortic-valve prosthesis than among recipients of a mechanical prosthesis (30.6% vs. 26.4% at 15 years; hazard ratio, 1.23; 95% confidence interval [CI], 1.02 to 1.48; P=0.03), but the difference was not significant among those 55 to 64 years of age (Table 2 and Fig. 1). These relationships were unaffected by multivariable adjustment or incorporation of hospital as a random effect. Despite evidence of nonproportional hazards, the results of the comparisons of the restricted mean survival time were consistent with the marginal hazard ratios (Table 2, and Fig. S10 in the Supplementary Appendix). When age was examined as a continuous variable, the relative mortality benefit that was associated with mechanical valves persisted until approximately 53 years of age (Fig. 2A). Additional sensitivity analyses are presented in the Methods section, Figures S11 and S12, and Tables S24 and S25 in the Supplementary Appendix.

COMPLICATIONS AFTER AORTIC-VALVE REPLACEMENT

Use of an aortic-valve biologic prosthesis was associated with a significantly lower cumulative incidence of stroke than was use of a mechanical prosthesis among patients 45 to 54 years of age and was associated with a significantly lower cumulative incidence of bleeding in the two age

groups. When examined as time-varying variables in the Cox proportional-hazards model, stroke and bleeding events were each associated with an increased hazard of death.

The hazard of reoperation was higher among patients who received a biologic prosthesis than among those who received a mechanical prosthesis during the index aortic-valve replacement, and this effect was more pronounced among younger persons. The 30-day mortality after reoperative aortic-valve replacement was 7.1%. Details regarding complications and reoperations are provided in Figures S13 through S21 and Tables S26 and S27 in the Supplementary Appendix.

MORTALITY AFTER MITRAL-VALVE REPLACEMENT

Mortality at 30 days did not differ significantly according to valve type among patients 50 to 69 years of age or 70 to 79 years of age who underwent mitral-valve replacement. However, implantation of a biologic prosthetic valve was associated with higher 30-day mortality among patients aged 40 to 49 years of age (5.6% vs. 2.2%; odds ratio, 2.62; 95% CI, 1.28 to 5.38) (Table S23 in the Supplementary Appendix).

Long-term mortality was higher among recipients of a biologic prosthesis than among recipients of a mechanical valve in the subgroup of patients who were 40 to 49 years of age (44.1% vs. 27.1% at 15 years; hazard ratio, 1.88; 95% CI, 1.35 to 2.63; P<0.001) or 50 to 69 years of age (50.0% vs. 45.3% at 15 years; hazard ratio, 1.16; 95% CI, 1.04 to 1.30; P=0.01) at the time of surgery (Table 3 and Fig. 3). However, mortality did not differ significantly between valve types among patients 70 to 79 years of age. These results were not affected by multivariable adjustment or incorporation of hospital as a random effect. The results of the comparisons of the restricted mean survival time were consistent with the results of the Cox proportional-hazards models (Table 3, and Fig. S22 in the Supplementary Appendix).

A similar trend was observed after we separated the group of patients who were 50 to 69 years of age into two groups according to decade (50 to 59 years and 60 to 69 years). Marginal hazard ratios for the two age groups were not significant, possibly owing to limited power. However, among patients 50 to 59 years of age and among those 60 to 69 years of age, the restricted mean survival time at 15 years was significantly lower among recipients of a biologic prosthesis than among recipients of a mechanical valve. When age was examined as a continuous variable, the relative mortality benefit that was associated with mechanical mitral valves persisted until approximately 68 years of age (Fig. 2B). Details are provided in Figures S23 and S24 and Table S28 in the Supplementary Appendix. Additional sensitivity analyses are also presented in the Methods section, Figure S25, and Tables S24 and S29 in the Supplementary Appendix.

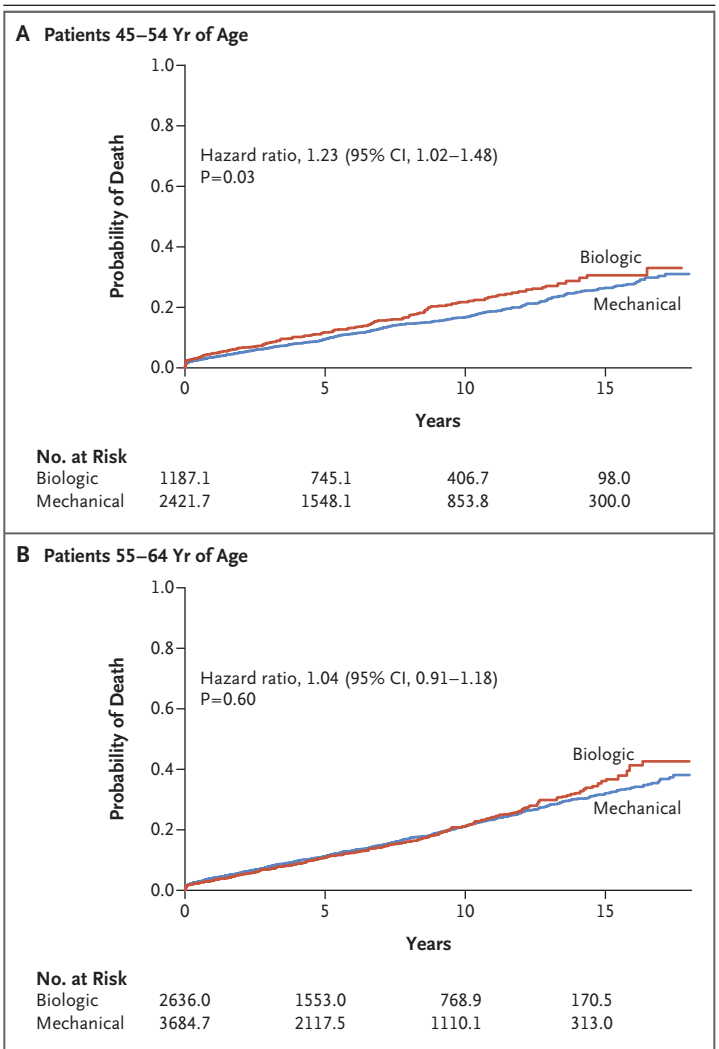

Figure 1. Mortality after Aortic-Valve Replacement with a Biologic or Mechanical Prosthesis.

All-cause mortality is plotted against time after surgery and stratified according to age group. The group of patients who received a mechanical valve is the reference group. The numbers of patients at risk are included below each graph. Note that the numbers are not necessarily integers owing to inverse probability weighting.

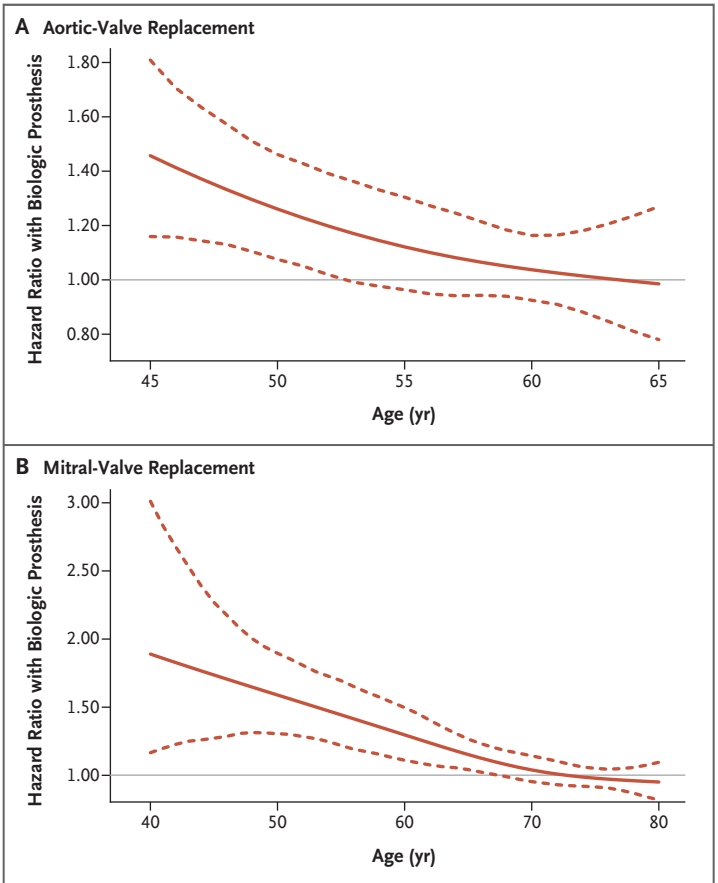

Figure 2. Age-Dependent Hazard of Death with a Biologic Prosthesis, as Compared with a Mechanical Prosthesis, in the Aortic-Valve or Mitral-Valve Position.

The hazard ratio for death among recipients of a biologic prosthesis, as compared with recipients of a mechanical valve, is plotted against age as a continuous variable (solid lines). Dashed lines represent the 95% confidence intervals that were obtained from bootstrap resampling. The horizontal line at 1.00 denotes no difference between valve types.

COMPLICATIONS AFTER MITRAL-VALVE REPLACEMENT

Use of a mitral-valve biologic prosthesis was associated with a significantly lower cumulative incidence of stroke than was use of a mechanical prosthesis during follow-up among patients 50 to 69 years of age but not in the other age groups. The cumulative incidence of bleeding was lower among patients 50 to 69 years of age and among those 70 to 79 years of age who received a biologic prosthesis than among those who received a mechanical prosthesis. When evaluated as time-varying exposures, a stroke or bleeding event during follow-up was a significant risk factor for death.

The cumulative incidence of reoperation was significantly higher among patients who received a biologic prosthesis during the index mitral-valve replacement than among those who received a mechanical prosthesis. This effect was more pronounced among younger patients, and younger patients also had reoperations sooner than older patients did, many within 10 years after the index operation. The 30-day mortality after reoperative mitral-valve replacement was 14.0%. Details regarding complications and reoperation are provided in Figures S26 through S31 and Tables S30 and S31 in the Supplementary Appendix.

DISCUSSION

In this population-level comparison of valve prostheses, mortality was lower among patients up to 70 years of age who received a mechanical mitral valve than among those who received a biologic prosthesis, whereas mechanical aortic valves were associated with lower mortality among patients up to 55 years of age. In both cases, the implantation of a mechanical prosthesis was associated with a significantly lower risk of reoperation but a greater risk of bleeding and, in some age groups, stroke than was implantation of a biologic prosthesis.

The choice of prosthesis for valve replacement is often determined by balancing the risks of anticoagulation and reoperation, and reports of improved durability of biologic prostheses have led to a substantial increase in their use.[12,13] However, this approach to the selection of a prosthesis assumes that mortality is equivalent between valve types, which was not the case in our analysis. Previous analyses comparing prosthesis types may not have been adequately powered to detect clinically relevant differences in mortality.[7,9,11]

Previous studies of aortic-valve replacement have had divergent results. A cohort study involving 1001 matched pairs of patients 50 to 69 years of age who underwent aortic-valve replacement in New York showed no difference in mortality between prosthesis types.[4] However, a subgroup analysis involving 287 matched pairs of patients in a similar study conducted in Sweden showed that mechanical prostheses were associated with substantially lower mortality than biologic prostheses among patients 50 to 59 years of age.[5]

Underlying differences between the populations may partially explain the divergent results. Longevity-related coexisting conditions, including hypertension, diabetes, and congestive heart failure, were less prevalent in the SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry than in the New York cohort. It is important for physicians to consider coexisting conditions that affect life expectancy — in addition to the risks associated with each valve type — when recommending valve prostheses to patients.

Previous studies of mitral-valve replacement have suggested that biologic prostheses may be safe in younger patients.[7,9,11,22-24] Our findings challenge this assertion and suggest that the current trend toward abandoning mechanical mitral valves in younger patients should be tempered. The large sample size that is required in order to detect a mortality difference in this population suggests that smaller studies were underpowered, and some studies lack generalizability because of strict exclusion criteria or restriction to a single center.[7,9,11,22-24] Our statewide study included patients who had undergone concomitant procedures. Although this approach increases generalizability, it may also introduce more systematic bias by encompassing a wider range of health states. This design feature also complicates comparisons between valve prostheses in the aortic-valve and mitral-valve positions because only isolated aortic-valve replacements were analyzed. However, the differences in outcomes that were seen in our study between patients who received a mitral-valve prosthesis and those who received an aortic-valve prosthesis suggest that the reinstatement of valve-specific guidelines for the selection of a prosthesis warrants further exploration.

Reoperation was more common among recipients of a biologic prosthesis than among those who received a mechanical valve, and this result has been reported previously.[4,5,7,9-11,25] Reoperation rates diverged as early as 6 to 8 years after the index valve replacement and coincided with the emergence of between-group differences in mortality in both the aortic-valve replacement cohort and the mitral-valve replacement cohort. Therefore, structural valve deterioration — which is underestimated by the cumulative incidence of

Table 3. Between-Group Differences in Mortality among Recipients of Mechanical and Biologic Mitral-Valve Prostheses.*

Variable	Patients 40 to 49 Yr of Age			Patients 50 to 69 Yr of Age			Patients 70 to 79 Yr of Age		
	Biologic Prosthesis (N = 285.9)	Mechanical Prosthesis (N = 1341.8)	P Value	Biologic Prosthesis (N = 2278.2)	Mechanical Prosthesis (N = 5748.9)	P Value	Biologic Prosthesis (N = 2919.9)	Mechanical Prosthesis (N = 2937.5)	P Value
Mortality at 15 yr — %	44.1	27.1	<0.001	50.0	45.3	0.01	78.3	77.3	0.97
Hazard ratio (95% CI)									
Weighted proportional-hazards model	1.88 (1.35 to 2.63)	Reference	<0.001	1.16 (1.04 to 1.30)	Reference	0.01	1.00 (0.93 to 1.08)	Reference	0.97
Weighted proportional-hazards model, with multivariable adjustment†	1.66 (1.22 to 2.27)	Reference	0.001	1.14 (1.02 to 1.27)	Reference	0.02	1.00 (0.92 to 1.07)	Reference	0.92
Weighted proportional-hazards model, with hospital as random effect‡	1.86 (1.45 to 2.38)	Reference	<0.001	1.17 (1.07 to 1.28)	Reference	<0.001	1.01 (0.94 to 1.08)	Reference	0.85
Restricted mean survival time at 15 yr (95% CI)									
Difference — days	−619.6 (−891.5 to −347.6)	Reference	<0.001	−191.3 (−298.1 to −84.5)	Reference	<0.001	10.4 (−101.6 to 122.5)	Reference	0.86
Ratio	0.87 (0.81 to 0.93)	Reference	<0.001	0.95 (0.93 to 0.98)	Reference	<0.001	1.00 (0.97 to 1.04)	Reference	0.86
Ratio of restricted mean time lost	1.70 (1.39 to 2.08)	Reference	<0.001	1.14 (1.06 to 1.22)	Reference	<0.001	1.00 (0.95 to 1.04)	Reference	0.86

* The overall numbers of patients in each group are not integers owing to inverse probability weighting.
† The analysis was adjusted for all the baseline variables.
‡ The standard deviation of the random effect of hospital was 0.30 in the subgroup of patients 40 to 49 years of age, 0.28 in the subgroup of patients 50 to 69 years of age, and 0.16 in the subgroup of patients 70 to 79 years of age.

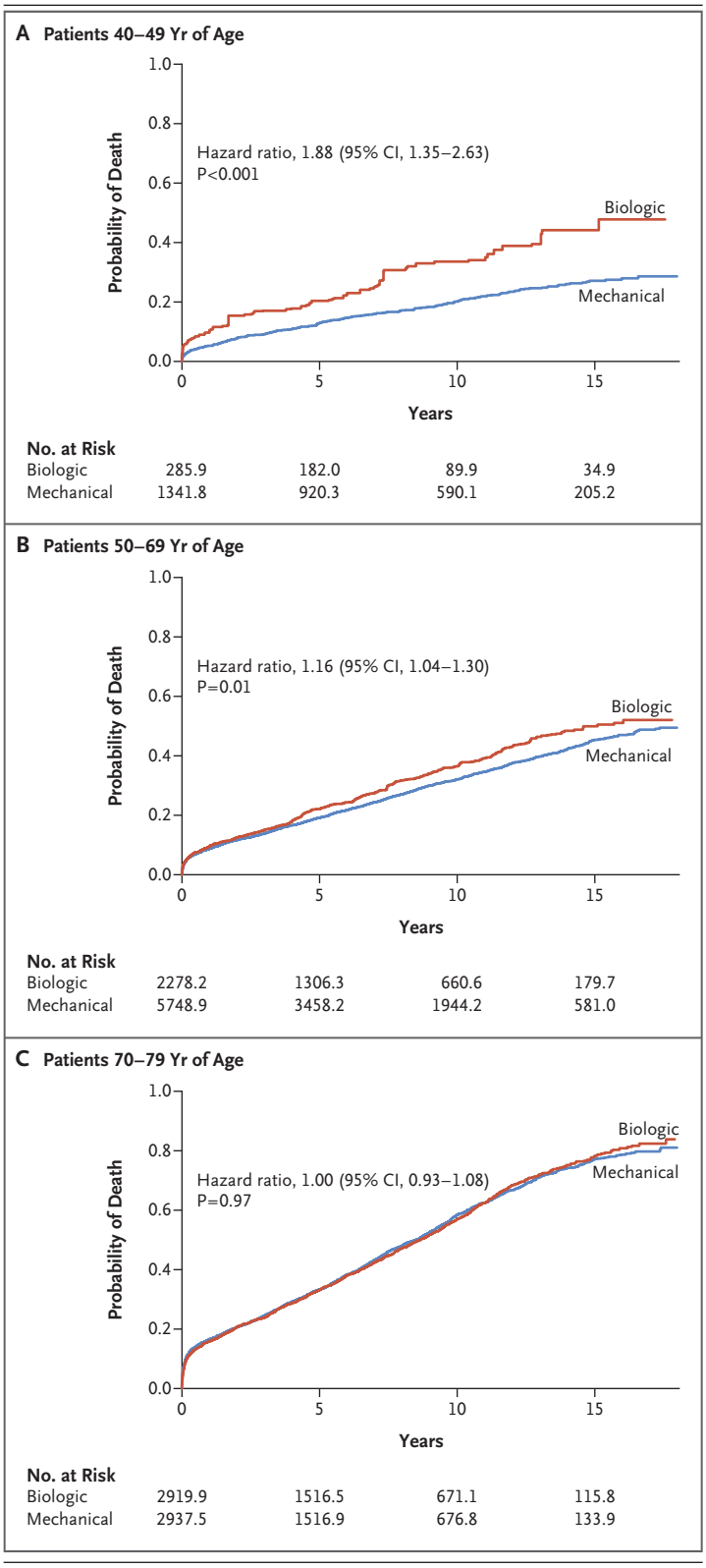

Figure 3. Mortality after Mitral-Valve Replacement with a Biologic or Mechanical Prosthesis.

All-cause mortality is plotted against time after surgery and stratified according to age group. The group of patients who received a mechanical valve is the reference group. The numbers of patients at risk are included below each graph. Note that numbers are not necessarily integers owing to inverse probability weighting.

reoperation — and subsequent reoperation may partially explain the difference in mortality.[26] As transcatheter technologies develop, the risk associated with reoperative surgery will change.

The mortality benefit that is afforded by mechanical prostheses comes at the cost of higher risks of bleeding and, in some age groups, stroke. Both events appeared to be associated with higher long-term mortality in our study and may be factors in the mortality advantage that was seen with biologic prostheses in older patients. However, for younger patients, these risks are clearly outweighed by the advantages of mechanical valves.

Our study used an administrative database rather than a clinical database. Therefore, it was subject to coding error and lacked important clinical details (e.g., cause of valve disease, ejection fraction, valve size, and medication and laboratory data). We used inverse probability weighting to account for observed differences in the incidence of coexisting conditions at baseline, but this technique cannot account for residual confounding owing to unmeasured variables. In particular, the potential bias introduced by frailer patients receiving biologic prostheses instead of mechanical prostheses could not be entirely assessed. Our study covered a period of 18 years, which introduces concern regarding changes in practice and interstate mobility. Secular trends in the use of biologic prostheses, the adoption of alternative treatments (e.g., mitral-valve repair and transcatheter aortic-valve replacement), and changes in indications for surgery may have biased our effect estimates.

In conclusion, in this population-level comparison of valve prostheses, mechanical mitral valves were associated with lower mortality than biologic valves among patients up to 70 years of age, whereas the benefit of a mechanical aortic

valve disappeared by 55 years of age. In both cases, the implantation of a mechanical prosthesis was associated with a significantly lower risk of reoperation than was the implantation of a biologic prosthesis; however, mechanical valves were associated with a higher risk of bleeding and, in some age groups, stroke.

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REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11.
2. Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. Circulation 1982;66:1105-10.
3. Russo A, Grigioni F, Avierinos JF, et al. Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. J Am Coll Cardiol 2008;51:1203-11.
4. 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.
5. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. Eur Heart J 2016;37:2658-67.
6. Nishimura RA, Otto CM, Bonow RO, 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.
7. 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.
8. Weber A, Noureddine H, Englberger L, et al. Ten-year comparison of pericardial tissue valves versus mechanical prostheses for aortic valve replacement in patients younger than 60 years of age. J Thorac Cardiovasc Surg 2012;144:1075-83.
9. Oxenham H, Bloomfield P, Wheatley DJ, et al. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. Heart 2003;89:715-21.
10. Stassano P, Di Tommaso L, Monaco M, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. J Am Coll Cardiol 2009;54:1862-8.
11. Chikwe J, Chiang YP, Egorova NN, Itagaki S, Adams DH. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. JAMA 2015;313:1435-42.
12. Gammie JS, Sheng S, Griffith BP, et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg 2009;87:1431-7.
13. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. J Thorac Cardiovasc Surg 2015;149(5):1262-1269.e3.
14. Zingmond DS, Ye Z, Ettner SL, Liu H. Linking hospital discharge and death records — accuracy and sources of bias. J Clin Epidemiol 2004;57:21-9.
15. Dupont WD, Plummer WD Jr. Power and sample size calculations: a review and computer program. Control Clin Trials 1990;11:116-28.
16. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55.
17. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008;168:656-64.
18. Silber JH, Rosenbaum PR, Trudeau ME, et al. Multivariate matching and bias reduction in the surgical outcomes study. Med Care 2001;39:1048-64.
19. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol 2014;32:2380-5.
20. Schermerhorn ML, Buck DB, O'Malley AJ, et al. Long-term outcomes of abdominal aortic aneurysm in the Medicare population. N Engl J Med 2015;373:328-38.
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
22. Cen YY, Glower DD, Landolfo K, et al. Comparison of survival after mitral valve replacement with biologic and mechanical valves in 1139 patients. J Thorac Cardiovasc Surg 2001;122:569-77.
23. Ruel M, Chan V, Bédard P, 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:Suppl:I-294–I-300.
24. 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.
25. Kaneko T, Aranki S, Javed Q, et al. Mechanical versus bioprosthetic mitral valve replacement in patients <65 years old. J Thorac Cardiovasc Surg 2014;147:117-26.
26. Kirali K, Güler M, Tuncer A, et al. Fifteen-year clinical experience with the biocor porcine bioprostheses in the mitral position. Ann Thorac Surg 2001;71:811-5.