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Mechanical versus Bioprosthetic Aortic Valve Replacement in Patients Aged between 50 and 70

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Abstract

Background

This study aims to compare the outcomes of aortic valve replacement (AVR) according to the prosthetic valve type in patients aged between 50 and 70 years.

Methods

In the present study, patients, aged ranging from 50 to 70, who underwent mechanical AVR were compared with those who underwent bioprosthetic AVR, between January 2000 and March 2019. Competing risk analysis and inverse-probability-of-treatment-weighting (IPTW) method were used for comparisons.

Results

This study enrolled a total of 1580 patients (Mechanical AVR group, 984 patients; Bioprosthetic AVR group, 596 patients). There was no significant difference in early mortality between Mechanical AVR and Bioprosthetic AVR groups (0.9% versus 1.7%, p=0.177). After adjustment with the IPTW method, all-cause mortality in Bioprosthetic AVR group was higher than in Mechanical AVR group (hazard ratio[HR], 1.39; 95% confidence interval [CI], 1.07-1.80; p = 0.014). Competing risk analysis revealed the risks of stroke (sub-distributional hazard ratio [sHR], 0.44; 95% CI, 0.28-0.67; p<0.001) and anticoagulation-related bleeding (sHR, 0.35; 95% CI, 0.23-0.52; p < 0.001) was higher in Mechanical AVR group. While the risk of reintervention was higher in Bioprosthetic AVR group (sHR, 6.14; 95% CI, 3.17-11.93; p < 0.001).

Conclusion

Among the patients aged 50 to 70 who underwent surgical AVR, the patients who received mechanical valves showed better survival than those who received bioprostheses. Mechanical AVR group exhibited a higher risk of stroke and anticoagulation-related bleeding. While

Bioprosthetic AVR group showed a higher risk of reintervention.

Keywords: Aortic valve replacement, Middle-aged, Prosthetic valve, Mechanical valve, Bioprosthesis

목 차

영문요약 ····· i

표 차례 ····· iv

그림 차례 ····· v

보충자료 차례 ····· vi

서론 ····· 1

연구대상 및 방법 ····· 2

결과 ····· 6

고찰 ····· 14

결론 ····· 18

참고문헌 ····· 19

국문요약 ····· 24

보충자료 ····· 25

표 차례

Table1. Baseline characteristics according to the prosthetic valve type ····· 7

Table2. Operative profiles according to the prosthetic valve type ····· 8

Table3. Clinical outcomes between the mechanical and the bioprosthetic valve groups ····· 10

그림 차례

Figure 1. Summary flow diagram of patients ····· 4

Figure 2. Survival after mechanical versus bioprosthetic AVR in (A) the original cohort and (B) the IPTW-adjusted cohort ····· 11

Figure 3. Time-to-event curve for (A) stroke, (B) anticoagulation-related bleeding, (C) infective endocarditis, and (D) reintervention in the IPTW-adjusted cohort between Mechanical versus Bioprosthetic AVR group ····· 12

Figure 4. Adjusted hazards of bioprosthesis for all-cause mortality according to various subgroups ····· 13

보충자료 차례

Supplement table 1-1. Mortality in reintervention patients ····· 26

Supplement table 1-2. Mortality in stroke patients ····· 26

Supplement table 1-3. Mortality in anticoagulation-related bleeding patients ····· 26

Supplement table 2. Bioprosthetic valve products and follow up duration ····· 27

Supplement table 3. Baseline characteristics according to the prosthetic valve type without concomitant CABG ····· 28

Supplement table 4. Operative profiles according to the prosthetic valve type without concomitant CABG ····· 29

Supplement table 5. Clinical outcomes between the mechanical and the bioprosthetic valve groups without concomitant CABG ····· 30

Supplement table 6. Operative profiles according to the bioprosthetic valve type ····· 31

INTRODUCTION

Aortic valve replacement (AVR) is the established treatment for severe aortic valve (AV) disease [1]. When performing AVR, the choice of prosthetic valve type should be based on the individual patient's clinical conditions and preferences [2,3]. Among various considerations, the patient's age is considered the most important factor. While a bioprosthetic valve is generally preferred for elderly patients with a short life expectancy and comorbidities that contraindicate long-term anticoagulation, a mechanical valve has traditionally been chosen for young patients due to its long-term durability.

However, recent times have witnessed an increased use of bioprosthetic valves in relatively young patients [4]. This trend may be attributed to the anticipation of the trans-catheter valve-in-valve option in case of prosthetic valve failure [5]. As the age threshold for the use of a mechanical valve is not clearly indicated, the guidelines from the U.S. and Europe also show differing views on this issue. The European guideline recommends the use of a mechanical valve for patients aged less than 60 years [6], while the U.S. guideline advocates a more liberal use of bioprosthetic valves, leaving a gray zone between the ages of 50 and 65 [7]. Moreover, the complexity surrounding the choice of prosthetic valves can be further compounded given the recent favorable clinical outcomes of mechanical valves in this middle-aged group [8].

In this context, this study aims to evaluate the early and long-term clinical outcomes in patients aged 50 to 70 who underwent AVR, according to the type of prosthetic valve used.

METHODS

Study Cohort

We searched the Institutional Cardiac Surgery Database to identify patients aged between 50 and 70 who underwent the first-time isolated surgical AVR with a mechanical or bioprosthetic valve between January 2000 and March 2019. The following exclusion criteria were applied to yield a patient cohort with reasonable comparability: (1) a history of prosthetic valve replacement, (2) concomitant aortic root replacement, and (3) AVR due to infective endocarditis or acute type A aortic dissection (Figure 1). Patients who underwent the following surgeries concomitant to AVR were included: coronary artery bypass grafting (CABG), ascending aorta or hemi-arch replacement, simple congenital heart defects repair and surgical atrial fibrillation (AF) ablation.

The study protocol was approved by the institutional review board (approval number: 2020-0122; date of approval: 2020-02-04) and the requirement for informed patient consent was waived considering the retrospective nature of the study.

Outcomes of Interest and Clinical Follow-Up

The primary outcome of interest was all-cause mortality, and the secondary outcomes of interests were early postoperative complications, stroke, anticoagulation-related bleeding, AV reintervention, operated valve endocarditis, and rehospitalization due to cardiovascular causes.

The definitions of each outcome are as follows: Early mortality encompasses periprocedural deaths occurring within 30 days after the index procedure or during the index hospitalization, as well as deaths occurring over 30 days but under 1 year after the index hospitalization. Other early outcomes also manifest within 30 days after the index procedure or during the index hospitalization. Stroke is defined to include both ischemic stroke and

hemorrhagic stroke. Anticoagulation-related bleeding encompasses not only overt bleeding that requires a transfusion of red blood cells but also overt bleeding that does not necessitate surgical or percutaneous intervention. Reintervention includes both percutaneous intervention and surgical reintervention. Hospitalization due to cardiac causes includes procedure-related or valve-related hospitalization and other cardiovascular hospitalization (e.g., ischemic heart disease, heart failure from other specific and proven etiologies, peripheral vascular disease).

The definition of each outcome utilized the endpoints definition in VARC-3 (Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research) for clear and homogenous reporting [7]. Clinical follow-up data were obtained until July 31, 2023. Data on the vital status was validated from the National Health Insurance System of South Korea.

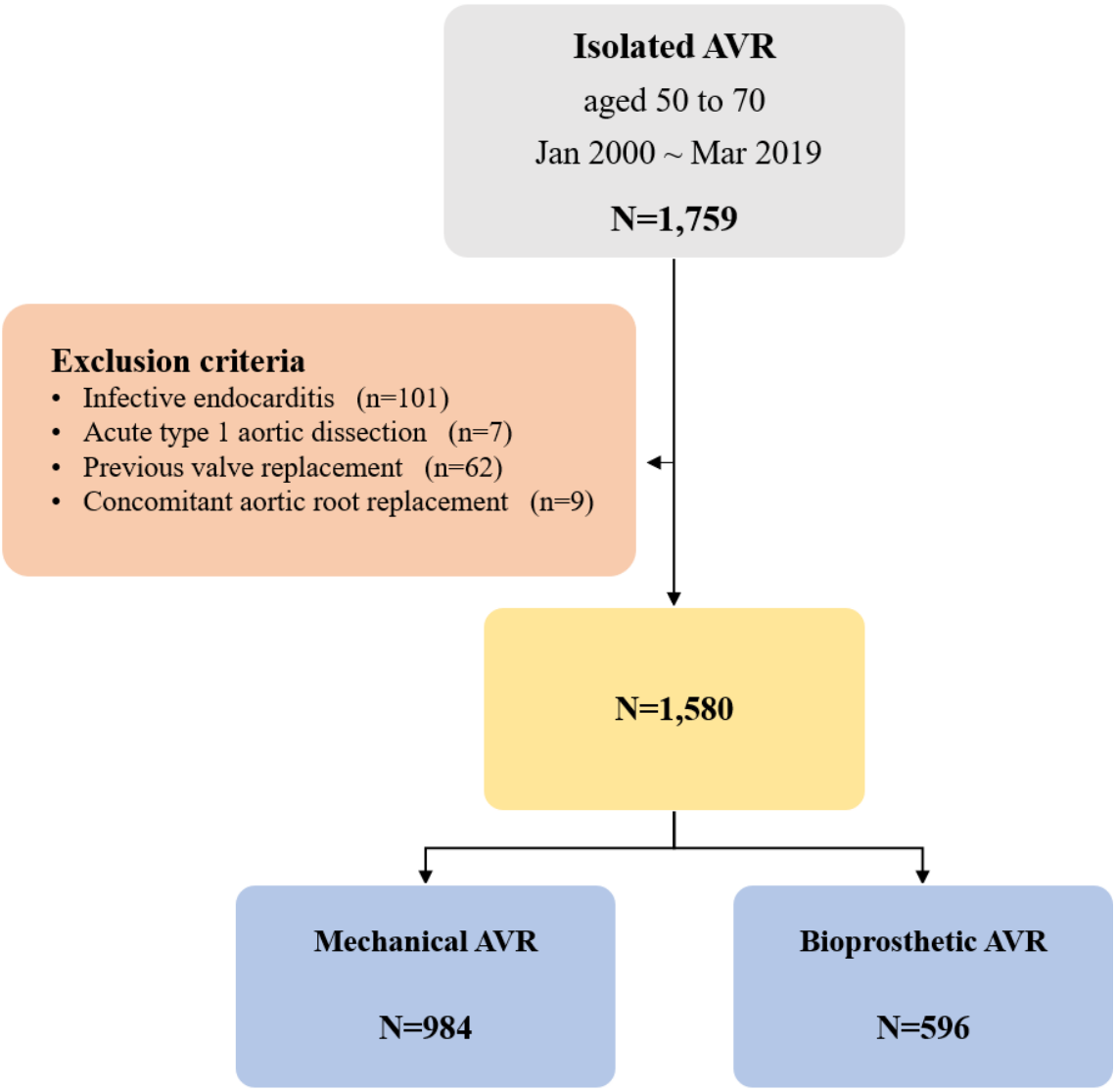

Figure 1 Summary flow diagram of patients. AVR, aortic valve replacement.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviations. Categorical variables were described as frequencies with percentages. Intergroup differences in the baseline characteristics were compared using Student t-tests for continuous variables and the chi-square test or Fisher exact test for categorical variables.

To address the differences in the baseline and operative profiles between Mechanical

and Bioprosthetic AVR groups, inverse-probability-of-treatment weighting (IPTW) based on propensity score (PS) modelling was performed. The PS was defined as the probability of a patient undergoing AVR with a bioprosthetic valve conditional on baseline and operative profiles, and was estimated from the logistic regression analysis incorporating all covariates listed in **Table 1** and **Table 2 (**except cardiopulmonary bypass time and aorta cross clamping time). The balance of the covariates was assessed by the standardized mean difference (SMD), in which a difference <10% was deemed to be a reasonable balance [9].

For the analyses of all-cause mortality, IPTW-adjusted Cox proportional hazard model was utilized to compute hazard ratio (HR) with 95% confidence intervals (CIs). The proportional hazard assumption was test using Schoenfeld residuals. Other time-related secondary outcomes of interest were analyzed using a competing risk model with all-cause mortality accounting as a competing risk. A sub-distributional hazard function was generated using the Fine-Gray model. The early postoperative outcomes were evaluated by using the logistic regression model.

Subgroup risk analysis for all-cause mortality was conducted within various subgroups to compare outcomes between mechanical and bioprosthetic valves. For these comparisons, the interaction between prosthesis types and each subgroup was assessed in IPTW-adjusted cohorts.

For all statistical analysis, a p-value < 0.05 was determined as significant. Statistical analyses were performed using R 4.1.2 (R Foundation for Statistical Computing).

RESULTS

Patient Characteristics

Among 1,759 patients who underwent isolated AVR, 1,580 were identified and 179 were excluded. A mechanical and bioprosthetic valve was implanted in 984 (62.3%) and 596 (37.7%) patients, respectively (**Figure 1**). The baseline characteristics according to the prosthetic valve type are summarized in **Table 1**. Compared with patients in Mechanical AVR group, those in Bioprosthetic AVR group was older, and had a higher prevalence of diabetes mellitus, kidney disease, or coronary artery disease. Bicuspid aortic valve, however, was more prevalent in Bioprosthetic AVR group.

Operative profiles according to the prosthetic valve type are summarized in **Table 2**. Minimally invasive approach was more frequently employed in Bioprosthetic AVR group than in Mechanical AVR group. Cardiopulmonary bypass (CPB) time and aortic cross-clamping (ACC) time was longer in Mechanical AVR group than in Bioprosthetic AVR group. Concomitant CABG was more frequently performed in Bioprosthetic AVR group, while ascending aorta replacement was more commonly performed in Mechanical AVR group.

After adjustments using the IPTW methods, most baseline and operative profiles were well-balanced with the standardized differences less than 10% for almost all variables, indicating only small differences between the two groups (**Table 1** and **Table 2**).

Table 1 Baseline characteristics according to the prosthetic valve type

Variable	Original				IPTW		
	Mechanical AVR (n = 984)	Bioprosthetic AVR (n = 596)	p-value	SMD (%)	Mechanical AVR (n=984)	Bioprosthetic AVR (n=596)	SMD (%)
Baseline demographics							
Age, years	59.8 ± 5.2	65.5 ± 4.0	<0.001	125.1	61.7 ± 5.3	62.4 ± 5.4	12.5
Female	376 (38.2)	236 (39.6)	0.621	2.8	38.1	39.0	1.9
Body mass index, kg/m^2	24.6 ± 3.2	24.5 ± 3.3	0.565	3.0	24.5 ± 3.1	24.4 ± 3.2	4.2
Baseline comorbidities							
Hypertension	503 (51.1)	332 (55.7)	0.086	9.2	53.4	52.0	2.8
Diabetes mellitus	171 (17.4)	151 (25.3)	<0.001	19.5	19.5	18.5	2.5
Dyslipidemia	354 (36.0)	233 (39.1)	0.234	6.4	36.7	36.9	0.3
eGFR < 30 mL/min/1.73 m^2	23 (2.3)	42 (7.0)	<0.001	22.4	3.9	3.9	<0.1
Dialysis	16 (1.6)	33 (5.5)	<0.001	21.2	2.4	3.1	4.3
Stroke or TIA	34 (3.5)	40 (6.7)	0.004	14.9	4.8	4.9	0.5
Coronary artery disease	160 (16.3)	141 (23.7)	<0.001	18.6	18.8	20.3	3.8
Previous PCI	35 (3.6)	39 (6.5)	0.009	13.7	4.0	4.1	0.6
Atrial fibrillation	86 (8.7)	52 (8.7)	1.000	0.1	8.6	7.7	3.3
Chronic lung disease	130 (13.2)	74 (12.4)	0.704	2.4	14.0	12.0	6.2
NYHA fc III or IV	204 (20.7)	127 (21.3)	0.834	1.4	21.1	18.8	5.7
Previous cardiac surgery	25 (2.5)	7 (1.2)	0.092	10.1	2.2	2.2	0.2
Hemoglobin, g/dl	13.4 ± 1.6	12.8 ± 1.7	<0.001	35.2	13.2 ± 1.7	13.0 ± 1.6	9.3
AV pathology			0.002	18.3			2.8
Stenosis	589 (59.9)	379 (63.6)			61.5	62.7	
Insufficiency	256 (26.0)	112 (18.8)			24.2	23.7	
Steno-insufficiency	139 (14.1)	105 (17.6)			14.3	13.6	
Echocardiographic Data							
Bicuspid AV	567 (57.6)	267 (44.8)	<0.001	25.9	53.5	51.5	4.0
Rheumatic pathology	75 (7.6)	40 (6.7)	0.565	3.5	7.5	7.0	1.7
LVEF, %	57.3 ± 11.6	57.8 ± 11.9	0.404	4.3	57.6 ± 11.3	58.2 ± 11.3	5.0
LVESD, mm	36.9 ± 11.4	35.2 ± 10.4	0.004	15.2	36.2 ± 11.1	35.5 ± 10.6	6.5
LVEDD, mm	55.1 ± 10.6	53.6 ± 9.4	0.005	14.7	54.6 ± 10.2	54.0 ± 9.9	5.6
LA diameter, mm	41.8 ± 7.4	42.0 ± 7.0	0.481	3.7	41.8 ± 7.2	41.4 ± 7.3	4.8
Peak RV-RA PG, mmHg	26.9 ± 9.9	26.9 ± 9.4	0.882	0.8	26.6 ± 9.7	26.3 ± 9.2	3.2
Significant MR[a)]	32 (3.3)	23 (3.9)	0.620	3.3	3.5	3.2	1.7
Significant TR[b)]	7 (0.7)	10 (1.7)	0.120	8.9	0.7	0.9	1.6

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.

[a)] Moderate to severe mitral regurgitation

[b)] Moderate to severe tricuspid regurgitation

IPTW, inverse-probability-of-treatment weighting; AVR, aortic valve replacement; SMD, standardized mean difference; eGFR, The estimated glomerular filtration rate; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; NYHA fc, New York Heart Association functional class; AV, aortic valve; LVEF, left ventricle ejection fraction; LVESD, left ventricle end-systolic dimension; LVEDD, left ventricle end-diastolic dimension; LA, left atrium; RV, right ventricle; RA, right atrium; PG, pressure gradient; MR, mitral regurgitation; TR, tricuspid regurgitation.

Table 2. Operative profiles according to the prosthetic valve type

Variable	Original				IPTW		
	Mechanical AVR (n =984)	Bioprosthetic AVR (n = 596)	p-value	SMD (%)	Mechanical AVR (n=984)	Bioprosthetic AVR (n=596)	SMD (%)
Emergency or urgency	32 (3.2)	14 (2.3)	0.446	6.8	2.8	1.8	6.2
Minimally invasive approach	129 (13.1)	149 (25.0)	<0.001	30.6	17.8	23.2	13.4
CPB time, minutes	123.5 ± 55.1	114.3 ± 45.7	0.001	18.2	124.4 ± 54.8	114.9 ± 47.6	18.5
ACC time, minutes	77.7 ± 33.7	73.7 ± 30.3	0.018	12.5	78.0 ± 33.7	75.7 ± 32.8	6.7
Concomitant procedure							
CABG	135 (13.7)	113 (19.0)	0.007	14.2	15.2	15.3	0.1
Surgical AF ablation	36 (3.7)	29 (4.9)	0.298	6.0	4.1	4.4	1.2
Ascending aorta replacement	159 (16.2)	66 (11.1)	0.006	14.9	14.2	13.8	1.1
Congenital correction	26 (2.6)	15 (2.5)	1.000	0.8	2.9	4.2	6.8

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.

IPTW, inverse-probability-of-treatment weighting; AVR, aortic valve replacement; SMD, standardized mean difference; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; CABG, coronary artery bypass grafting; AF, atrial fibrillation.

Clinical Outcomes

The incidence of early and long-term clinical outcomes and risk analyses between the two groups are summarized in **Table 3**. Early death occurred in 9 (0.9%) and 10 (1.7%) patients in Mechanical and Bioprosthetic AVR group, respectively (P=0.177). The risks of early complications between the two groups were comparable both in the original and the IPTW-adjusted cohort.

During a median follow-up period of 9.1 years (inter-quartile range, 6.0 to 13.4 years), the observed (crude) incidence of all-cause death (2.0% per patient-year [PY] versus 3.6%/PY; P<0.001) and AV reoperation (0.5%/PY versus 0.9%/PY; P<0.001) was significantly higher in Bioprosthetic AVR group than in Mechanical AVR group. The incidence of stroke and anticoagulation-related bleeding, however, was significantly higher in Mechanical AVR group than in Bioprosthetic group.

After an adjustment, the use of a bioprosthetic valve was associated with an increased risk of all-cause death (HR 1.39; 95% confidence interval [CI] 1.07-1.80; P=0.014) and AV reoperation (sub-distributional hazard ratio [sHR] 6.14; 95% CI 3.17-11.93; P<0.001) (**Figure 2B** and **Figure 3D**). However, using a bioprosthetic valve was associated with a significantly decreased risk of stroke (sHR 0.44; 95% CI 0.28-0.67; P<0.001) and anticoagulation-related bleeding (sHR 0.35; 95% CI 0.23-0.52; P<0.001) (**Figure 3A** and **3B**). The risks of endocarditis and readmission due to cardiac cause were comparable between the two groups (**Table 3**).

Subgroup risk analysis of all-cause mortality was conducted (**Figure 4**). There was no statistically significant difference among age groups (p for interaction = 0.111).

Table 3. Clinical outcomes between the mechanical and the bioprosthetic valve groups

Outcomes [a]	Original				IPTW			
	No. of events (rate)				No. of events (rate)			
	Mechanical AVR (N=984)	Bioprosthetic AVR (N=596)	OR or HR (95% CI)	p-value	Mechanical AVR (N=984)	Bioprosthetic AVR (N=596)	OR or HR/sHR (95% CI)	p-value
Early outcomes, n (%)								
Early death	9 (0.9)	10 (1.7)	1.85 (0.75-4.58)	0.177	1.0	1.1	1.19 (0.42-3.33)	0.741
Bleeding requiring exploration	35 (3.6)	27 (4.5)	1.29 (0.77-2.15)	0.330	3.7	3.8	1.05 (0.60-1.83)	0.856
LCOS requiring MCS [b]	11 (1.1)	11 (1.8)	1.66 (0.72-3.86)	0.230	1.1	1.2	1.08 (0.40-2.87)	0.885
Stroke	25 (2.5)	22 (3.7)	1.47 (0.82-2.63)	0.190	2.7	2.7	1.01 (0.53-1.95)	0.966
New onset dialysis	10 (1.0)	6 (1.0)	0.99 (0.36-2.74)	0.985	1.3	0.6	0.48 (0.15-1.59)	0.233
Sternal wound infection	12 (1.2)	8 (1.3)	1.10 (0.45-2.71)	0.830	1.2	1.3	1.14 (0.45-2.90)	0.787
Overall outcomes, n (%/PY)								
All-cause death	220 (2.0)	167 (3.6)	2.15 (1.74-2.64)	<0.001	2.3	2.9	1.39 (1.07-1.80)	0.014
Stroke	106 (1.3)	32 (0.9)	0.63 (0.43-0.94)	0.025	1.4	0.5	0.44 (0.28-0.67)	<0.001
Anticoagulation-related bleeding	119 (1.5)	31 (0.8)	0.55 (0.37-0.82)	0.004	1.5	0.6	0.35 (0.23-0.52)	<0.001
Operated valve endocarditis	20 (0.2)	14 (0.4)	1.44 (0.72-2.86)	0.300	0.2	0.4	1.31 (0.61-2.82)	0.490
AV reoperation	41 (0.5)	35 (0.9)	2.35 (1.48-3.74)	<0.001	0.4	0.8	6.14 (3.17-11.93)	<0.001
SVD	5 (0.1)	17 (0.5)			0.1	0.4		
Endocarditis	13 (0.2)	13 (0.3)			0.2	0.3		
Pannus	13 (0.2)	1 (0.0)			0.1	0.0		
Others	10 (0.1)	4 (0.1)			0.1	0.0		
Readmission due to cardiac cause	256 (3.6)	119 (3.5)	0.96 (0.77-1.20)	0.710	3.6	3.1	1.30 (0.86-1.97)	0.210

Values are presented as number (%) or number (% per patient-year) unless otherwise indicated.

Early outcomes are presented as odds ratios. Overall outcomes are presented as hazard ratios or sub-distributional hazard ratios.

IPTW, inverse-probability-of-treatment weighting; OR, odds ratio; HR, hazard ratio; sHR, sub-distributional hazard ratio; CI, confidence interval; LCOS, low cardiac output syndrome; MCS, mechanical circulatory support; PY, patient-year; AV, aortic valve; SVD, structural valve deterioration.

[a] Outcomes captured using a primary diagnosis during a visit to the emergency department or using any primary or secondary diagnosis during hospitalization.

[b] Included extracorporeal membrane oxygenation, intra-aortic balloon pump, and ventricular assist device.

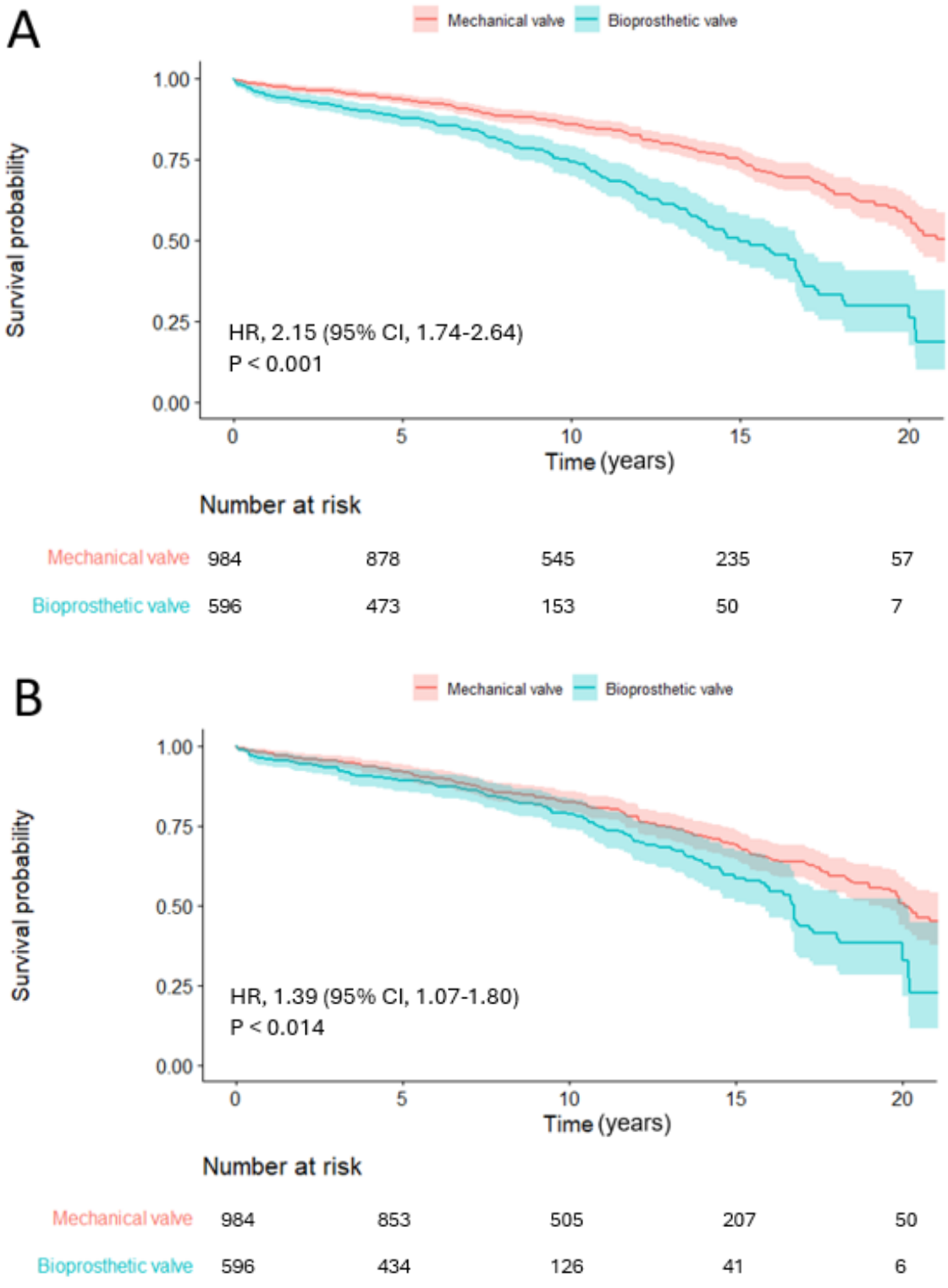

Figure 2. Survival after mechanical versus bioprosthetic AVR in (A) the original cohort and (B) the IPTW-adjusted cohort. IPTW, inverse-probability-of-treatment weighting; AVR, aortic valve replacement.

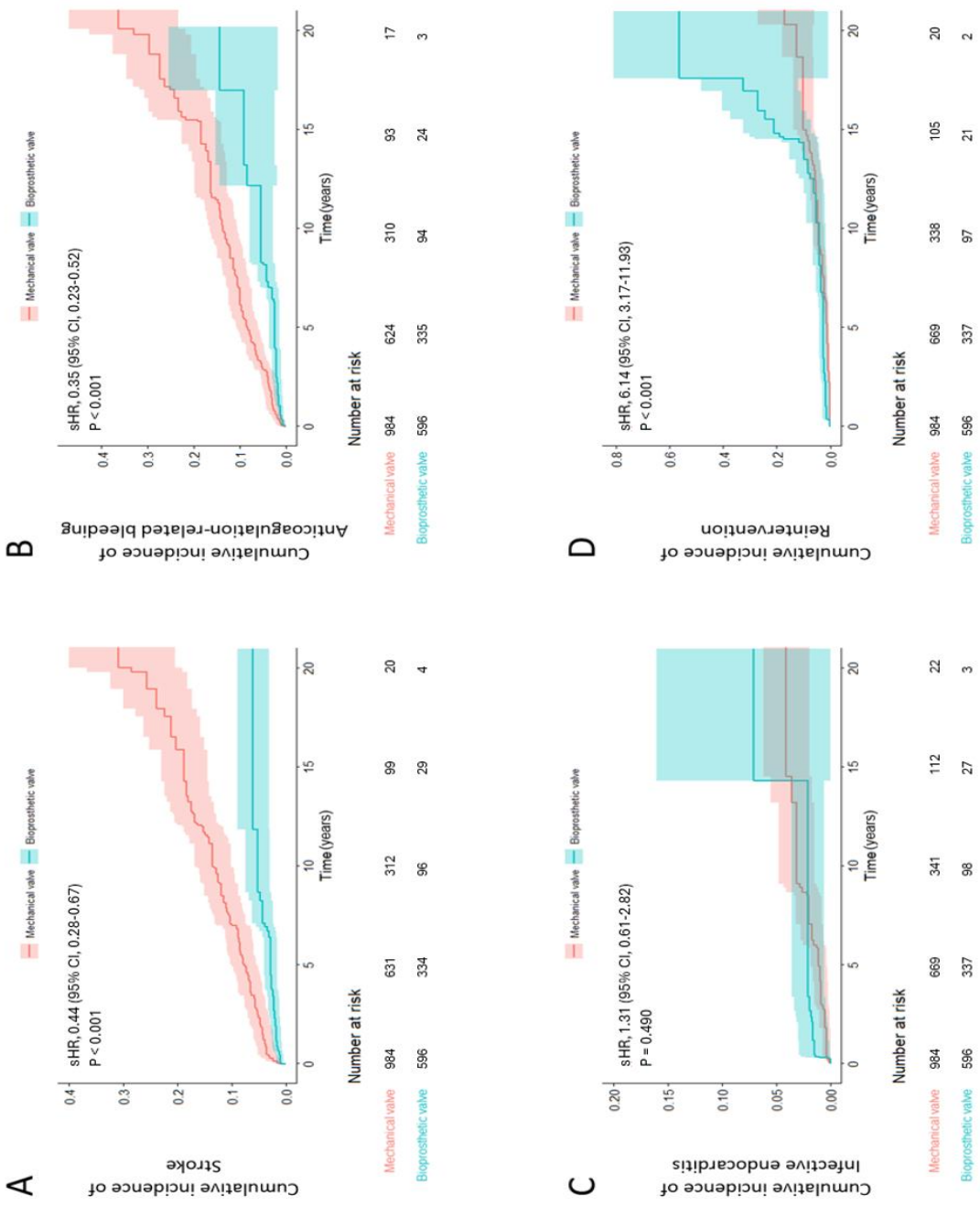

Figure 3. Time-to-event curve for (A) stroke, (B) anticoagulation-related bleeding, (C) infective endocarditis, and (D) reintervention in the IPTW-adjusted cohort between Mechanical versus Bioprosthetic AVR group. IPTW, inverse-probability-of-treatment weighting; AVR, aortic valve replacement.

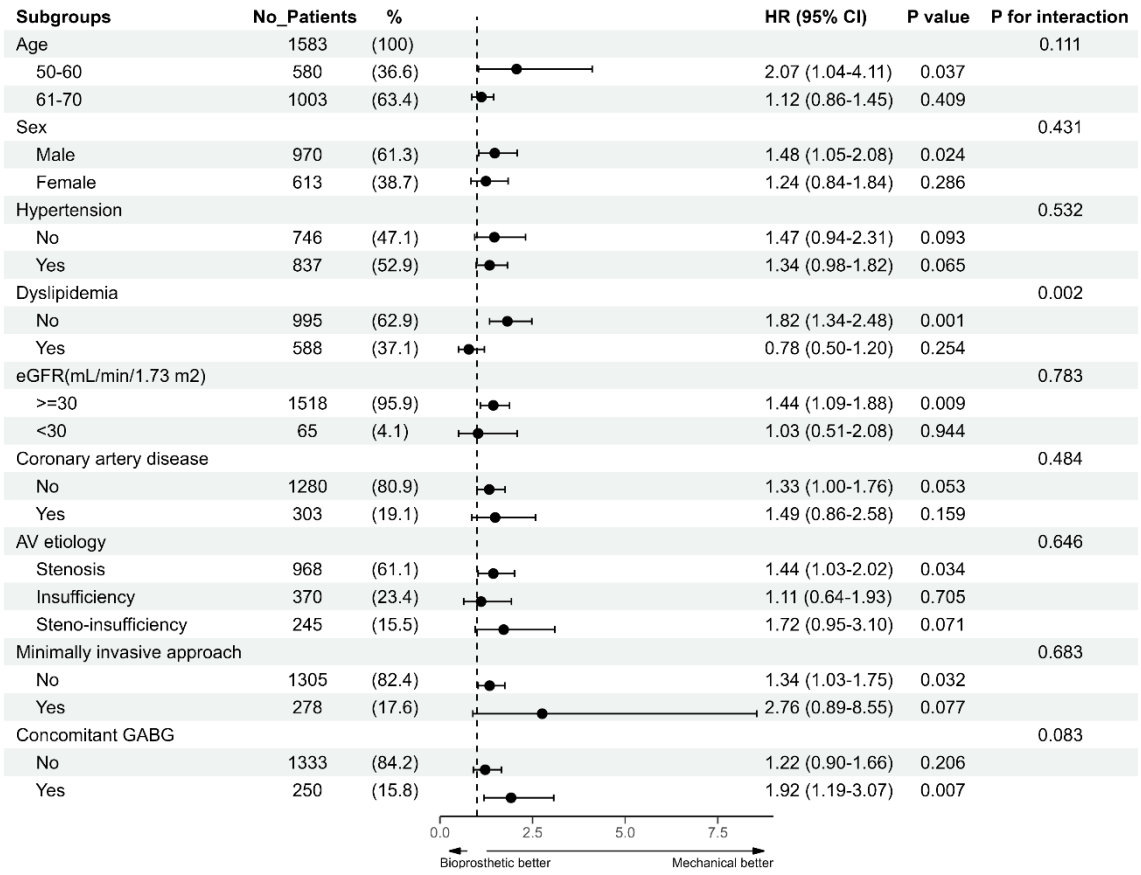

Figure 4. Adjusted hazards of bioprosthesis for all-cause mortality according to various subgroups. HR, hazard ratio; CI, confidence interval; AV, aortic valve; CABG, coronary artery bypass graft

DISCUSSION

In this study, we observed that patients aged 50 to 70 years who received a mechanical valve during surgical AVR had better survival rates than those who received a bioprosthetic valve (**Figure 2**). Meanwhile, Mechanical AVR group had a lower risk of reintervention, but had a higher risk of stroke and anticoagulation-related bleeding.

Among numerous studies comparing the clinical outcomes of mechanical and bioprosthetic AVR in middle-aged patients, some studies found that a long-term survival was significantly better with mechanical AVR than bioprosthetic AVR [3,8,10-17], whereas the others found no significant survival difference [18-20]. The most recent meta-analysis, which included 22 publications and involved 32,298 patients, reported better a long-term survival with mechanical AVR than bioprosthetic AVR among individuals aged between 50 and 70 [13]. However, they also reported that when they reduced the upper limit of the age range to 65 years, the survival benefit using a mechanical valve disappeared. The previous nationwide cohort study in Korea also demonstrated that the long-term survival benefit associated with mechanical prostheses versus bioprostheses persisted until the age of 65 years in AVR [8].

In the context of a better survival in Mechanical AVR group, the risk of each secondary outcome was analyzed. We found that the risks of stroke and anticoagulant-related bleeding were significantly higher, while the risk of AV reintervention was lower in Mechanical AVR group than in Bioprosthetic AVR group (**Table 3** and **Figure 3**). When assessing a possible association between each secondary outcome and overall mortality, the contribution of an increased risk due to reintervention after bioprosthetic AVR to mortality (sHR 6.14; 95% CI 3.71-11.93; P<0.001) may outweigh the benefits of a decreased risk of stroke and anticoagulation-related bleeding, which may explain the observed differences in mortality. We examined the outcomes of patients who underwent reintervention. It was observed that the mortality risk after reintervention was higher in Bioprosthetic AVR group compared to

Mechanical AVR group (HR 3.71; 95% CI 1.56-8.84; p = 0.003) (**Supplement Table 1-1**).

In the subgroup analysis, excluding dyslipidemia, there was no statistically significant difference in mortality based on the valve type in the remaining subgroups. While mechanical valves demonstrated a survival advantage in the absence of dyslipidemia, there was no significant difference in mortality based on valve type when dyslipidemia was present. Although the precise mechanism remains elusive, further research may be warranted to explore potential associations between statin use, valve type, and mortality.

Our study reconfirms well-established findings from previous studies regarding a higher risk of reoperation in patients who received bioprosthetic AVR [10,12,14,15,17,19-23] and an increased risk of bleeding related to continuing anticoagulation in those who underwent mechanical AVR [12,15,17,19,20]. Of note, we observed a sharp increase of AV reintervention starting at around 15 years after bioprosthetic AVR **(Figure 3D)**, which aligns with the findings of previous studies that reported a durability of bioprosthetic valves ≥ 15 years [24-26]. During the study period, 17 cases of SVD occurred. In investigating these cases, including the valves where SVD occurred (**Table 3**), we examined the brand and follow-up duration of all bioprosthetic valves (**Supplement Table 2**). Among these, 6 cases of SVD occurred within a follow-up duration of less than 10 years, with 4 cases occurring particularly within 5 years. However, all of early SVD cases had different products. Notably, in the case of the Trifecta valve, which had been discontinued due to early SVD issues[27], there was no SVD during a median follow-up of 5.5 years in this cohort.

In the present study, there was a significantly higher incidence of stroke associated with mechanical AVR (**Figure 3A**). Among the comparative studies of valve types in middle-aged AVR, there was few studies that reported a significant difference in stroke occurrence [12,13,15,18,20,23,28-30]. Stroke is a devastating complication that may occur early or late after operation in patients with prosthetic valve replacement and results from embolism,

intracranial hemorrhage, or both [31]. Considering a higher incidence of anticoagulation-related bleeding in Mechanical AVR group, stroke due to hemorrhage might have occurred more frequently in Mechanical AVR group than in Bioprosthetic AVR group.

Patients who undergo concurrent CABG are typically prescribed antiplatelet agents. To evaluate the impact, particularly on stroke and anticoagulation-related bleeding, we reanalyzed the data, focusing on patients without concomitant CABG (**Supplement tables 3 - 5**). When excluding CABG, similar outcomes were observed in terms of stroke and anticoagulation-related bleeding. In the IPTW-adjusted cohort, however, there was no significant difference in all-cause mortality and reintervention between the two groups (p=0.149; p=0.225; **Supplement table 5**). We also conducted subgroup mortality risk analysis based on the presence of concomitant CABG, but no statistically significant difference was observed (P for interaction = 0.083; **Figure 4**).

Bioprosthetic AVR group demonstrated a greater preference for a minimally invasive approach and shorter CPB and ACC times (**Table 2**). This observation may be attributed to the recent introduction of sutureless bioprosthetic valves, which have shown a distinctly more minimally invasive approach (63.5% versus 16.8%; p<0.001) and significantly shorter CPB time (88.4 minutes versus 120.3 minutes; p<0.001) and ACC time (78.8 minutes versus 51.5 minutes; p<0.001) compared to conventional bioprosthetic valves (**Supplement table 6**). The advantages of sutureless valves have been well-established in previous studies[32,33], and similar findings were observed in our study as well.

Recently, there has been an increasing trend in the use of bioprosthetic valves in younger patients [4]. However, our study highlights that mechanical valves offer better long-term survival in patients aged between 50 and 70. Therefore, caution should be still advised in selecting prosthetic valves in this middle-aged group. On the other hand, a transcatheter valve-in-valve for reintervention in bioprosthetic valve failure has shown lower procedure-related

mortality and morbidity compared to reoperative surgical AVR [5]. This suggests the potential improvement in the long-term outcomes of bioprosthetic valves, which necessitates further research.

This study has several limitations. First, since this was an observational retrospective study, addressing the concern of selection bias primarily relied on IPTW and regression adjustment. Second, since this study is a single-center study, it is essential to be cautious when applying the conclusions of this study to other centers. Additionally, considering the enrollment period for this study spans from 2000 to 2019, it should be noted that there have been improvements in surgical techniques and overall patient care during this period, which should be taken into consideration when interpreting the results. Additionally, considering the enrollment period for this study spans from 2000 to 2019, it should be noted that there have been improvements in surgical techniques and overall patient care during this period, which should be taken into consideration when interpreting the results.

CONCLUSIONS

Among patients aged 50 to 70 who underwent surgical AVR, those who received mechanical valves demonstrated a lower all-cause mortality, compared to those who received bioprostheses. Mechanical AVR group had a higher risk of stroke and bleeding related to anticoagulation than Bioprosthetic AVR group. Conversely, Bioprosthetic AVR group exhibited a higher rate of reintervention with the prosthetic aortic valve.

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국문 요약

배경

본 연구는 50세부터 70세 사이의 환자들을 대상으로 한 대동맥판막 치환술(Aortic valve replacement, AVR)의 결과를 인공판막 유형(기계판막 또는 조직판막)에 따라 비교하는 것을 목적으로 한다.

방법

본 연구에서는 2000년 1월부터 2019년 3월까지 50세부터 70세 사이의 AVR 시행받은 환자들 중 기계판막 AVR을 받은 환자들과 조직판막 AVR을 받은 환자들을 비교하였습니다. 경쟁 위험 분석 및 치료 가중치(inverse-probability-of-treatment-weighting, IPTW) 방법을 비교에 사용하였다.

결과

본 연구의 코호트는 총 1580명의 환자가 포함되었으며(기계판막 AVR 그룹 984명, 조직판막 AVR 그룹 596명), 초기 사망률에서는 기계판막 AVR 그룹과 조직판막 AVR 그룹 간에 유의한 차이는 없었다(0.9% 대 1.7%, p=0.177). IPTW 방법을 사용한 조정 후, 조직판막 AVR 그룹의 전체 사망률이 기계판막 AVR 그룹보다 높았다(Hazard ratio[HR], 1.39; 95% confidence interval [CI], 1.07-1.80; p = 0.014). 경쟁 위험 분석에서는 뇌졸중 위험(sub-distributional hazard ratio [sHR], 0.44; 95% CI, 0.28-0.67; p<0.001) 및 항응고제 관련 출혈 위험이 기계판막 AVR 그룹에서 더 높았다(sHR, 0.35; 95% CI, 0.23-0.52; p < 0.001). 반면, 조직판막 AVR 그룹에서는 재수술 위험이 더 높았다(sHR, 6.14; 95% CI, 3.17-11.93; p < 0.001).

결론

대동맥판막 치환술을 받은 50세부터 70세까지의 환자들 중에서 기계판막을 받은 환자들은 조직판막을 받은 환자들보다 더 우수한 생존율을 보였다. 기계판막 AVR 그룹은 뇌졸중 및 항응고제 관련 출혈 위험이 높았으며, 조직판막 AVR 그룹은 재수술 위험이 높았다.

Supplements

Supplement table 1-1. Mortality in reintervention patients

Outcomes [a)]	No. of events (rate)		HR (95% CI)	p-value
	Mechanical AVR (N=41)	Bioprosthetic AVR (N=35)		
All-cause death	7 (3.3)	17 (12.0)	3.71 (1.56-8.84)	0.003

Supplement table 1-2. Mortality in stroke patients

Outcomes [a)]	No. of events (rate)		HR (95% CI)	p-value
	Mechanical AVR (N=106)	Bioprosthetic AVR (N=32)		
All-cause death	41 (6.6)	16 (9.4)	1.49 (0.83-2.66)	0.178

Supplement table 1-3. Mortality in anticoagulation-related bleeding patients

Outcomes [a)]	No. of events (rate)		HR (95% CI)	p-value
	Mechanical AVR (N=119)	Bioprosthetic AVR (N=31)		
All-cause death	52 (6.8)	17 (9.2)	1.29 (0.74-2.24)	0.360

Values are presented as number (% per patient-year) unless otherwise indicated.

HR, hazard ratio; CI, confidence interval

[a)] Outcomes captured using a primary diagnosis during a visit to the emergency department or using any primary or secondary diagnosis during hospitalization.

Supplement table 2. Bioprosthetic valve products and follow up duration.

Valve name (Manufacture)	Bioprosthetic AVR (N=596)	Follow-up duration (years)	Reintervention due to SVD (N=17)	Duration until reintervention (years)
Conventional valve				
Magna (Carpentier-Edwards)	223 (37.4)	6.9 (0.0-21.3)	11 (64.7)	14.5 (2.3-17.8)
Hancock (Medtronic)	73 (12.2)	6.4 (0.1-16.9)	N/A	N/A
Magna Ease (Carpentier-Edwards)	59 (9.9)	4.5 (0.0-5.8)	N/A	N/A
Hancock II (Medtronic)	41 (6.9)	6.1 (0.4-12.5)	1 (5.9)	2.5 (2.5-2.5)
Trifecta (Abbott)	21 (3.5)	5.5 (2.2-8.1)	N/A	N/A
Perimaunt Magna (Carpentier-Edwards)	18 (3.0)	7.4 (0.0-14.8)	N/A	N/A
Biocor (St. Jude Medical)	18 (3.0)	12.8 (0.4-16.9)	1 (5.9)	14.8 (14.8-14.8)
Avalus (Medtronic)	14 (2.3)	3.6 (0.4-4.4)	N/A	N/A
Prima plus (Edwards)	10 (1.7)	9.2 (0.4-20.3)	1 (5.9)	6.9 (6.9-6.9)
Mitroflow (Sorin)	5 (0.8)	6.7 (2.8-7.5)	N/A	N/A
Freestyle (Medtronic)	5 (0.8)	7.9 (1.7-17.0)	1 (5.9)	8.2 (8.2-8.2)
Epic plus supra (Abbott)	3 (0.5)	8.9 (8.9-13.9)	N/A	N/A
Mosaic (Medtronic)	1 (0.2)	5.7 (5.7-5.7)	N/A	N/A
Soprano (Sorin)	1 (0.2)	1.1 (1.1-1.1)	N/A	N/A
Sutureless valve				
Intuity (Edwards)	77 (12.9)	5.2 (0.0-7.3)	1 (5.9)	2.3 (2.3-2.3)
Perceval (LivaNova)	26 (4.3)	4.7 (0.1-7.1)	1 (5.9)	2.9 (2.9-2.9)
3f enable (Medtronic)	1 (0.2)	0.0 (0.0-0.0)	N/A	N/A

Values are presented as number (%) or median (range) unless otherwise indicated.

SVD, structural valve deterioration.

Supplement table 3. Baseline characteristics according to the prosthetic valve type without concomitant CABG

Variable	Original				IPTW		
	Mechanical AVR (n = 850)	Bioprosthetic AVR (n = 483)	p-value	SMD (%)	Mechanical AVR (n=850)	Bioprosthetic AVR (n=483)	SMD (%)
Baseline demographics							
Age, years	59.6 ± 5.2	65.4 ± 4.1	<0.001	125.4	61.5 ± 5.4	62.2 ± 5.4	12.7
Female	333 (39.2)	191 (39.5)	0.941	0.8	38.9	40.5	3.2
Body mass index, kg/m^2	24.6 ± 3.2	24.5 ± 3.3	0.828	1.2	24.5 ± 3.1	24.3 ± 3.3	5.1
Baseline comorbidities							
Hypertension	413 (48.6)	259 (53.6)	0.087	10.1	50.7	49.6	2.2
Diabetes mellitus	130 (15.3)	105 (21.7)	0.004	16.6	16.5	15.7	2.1
Dyslipidemia	280 (32.9)	184 (38.1)	0.066	10.8	34.3	35.2	1.8
eGFR < 30 mL/min/1.73 m^2	19 (2.2)	27 (5.6)	0.002	17.4	3.4	3.3	0.6
Dialysis	15 (1.8)	23 (4.8)	0.003	16.9	2.5	2.7	1.3
Stroke or TIA	28 (3.3)	26 (5.4)	0.086	10.3	4.1	3.7	2.2
Coronary artery disease	47 (5.5)	51 (10.6)	0.001	18.6	7.0	8.7	6.0
Previous PCI	19 (2.2)	20 (4.1)	0.069	10.9	2.5	2.6	0.9
Atrial fibrillation	79 (9.3)	45 (9.3)	1.000	0.1	8.9	8.0	3.1
Chronic lung disease	114 (13.4)	55 (11.4)	0.326	6.1	14.0	11.7	7.1
NYHA fc III or IV	168 (19.8)	92 (19.0)	0.806	1.8	19.9	17.7	5.7
Previous cardiac surgery	22 (2.6)	6 (1.2)	0.147	9.8	2.1	1.6	3.7
Hemoglobin, g/dl	13.4 ± 1.6	12.9 ± 1.7	<0.001	30.5	13.3 ± 1.7	13.1 ± 1.6	9.7
AV pathology			0.003	19.9			8.5
Stenosis	502 (59.1)	299 (61.9)			59.6	62.3	
Insufficiency	224 (26.4)	91 (18.8)			26.2	22.6	
Steno-insufficiency	124 (14.6)	93 (19.3)			14.2	15.2	
Echocardiographic Data							

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.

[a)] Moderate to severe mitral regurgitation

[b)] Moderate to severe tricuspid regurgitation

IPTW, inverse-probability-of-treatment weighting; AVR, aortic valve replacement; SMD, standardized mean difference; eGFR, The estimated glomerular filtration rate; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; NYHA fc, New York Heart Association functional class; AV, aortic valve; LVEF, left ventricle ejection fraction; LVESD, left ventricle end-systolic dimension; LVEDD, left ventricle end-diastolic dimension; LA, left atrium; RV, right ventricle; RA, right atrium; PG, pressure gradient; MR, mitral regurgitation; TR, tricuspid regurgitation.

Supplement table 4. Operative profiles according to the prosthetic valve type without concomitant CABG

Variable	Original				IPTW		
	Mechanical AVR (n =850)	Bioprosthetic AVR (n = 483)	p-value	SMD (%)	Mechanical AVR (n=850)	Bioprosthetic AVR (n=483)	SMD (%)
Emergency or urgency	26 (3.1)	10 (2.0)	0.353	10.8	2.7	1.6	12.6
Minimally invasive approach	129 (15.2)	148 (30.6)	<0.001	37.4	21.0	27.2	14.6
CPB time, minutes	116.4 ± 48.7	107.5 ± 40.6	0.001	20.0	115.8 ± 46.6	108.5 ± 41.6	16.4
ACC time, minutes	74.2 ± 31.0	70.5 ± 27.8	0.027	12.8	73.9 ± 29.9	72.8 ± 29.3	3.9
Concomitant procedure							
CABG	0 (0.0)	0 (0.0)	N/A	N/A	0.0	0.0	N/A
Surgical AF ablation	34 (4.0)	28 (5.8)	0.173	8.3	4.7	4.9	1.2
Ascending aorta replacement	135 (15.9)	55 (11.4)	0.030	13.1	13.8	13.3	1.5
Congenital correction	21 (2.5)	14 (2.9)	0.771	2.6	3.0	4.4	7.3

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.

IPTW, inverse-probability-of-treatment weighting; AVR, aortic valve replacement; SMD, standardized mean difference; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; CABG, coronary artery bypass grafting; AF, atrial fibrillation.

Supplement table 5. Clinical outcomes between the mechanical and the bioprosthetic valve groups without concomitant CABG

Outcomes [a]	Original				IPTW			
	No. of events (rate)		OR or HR (95% CI)	p-value	No. of events (rate)		OR or HR/sHR (95% CI)	p-value
	Mechanical AVR (N=850)	Bioprosthetic AVR (N=483)			Mechanical AVR (N=850)	Bioprosthetic AVR (N=483)		
Early outcomes, n (%)								
Early death	8 (0.9)	8 (1.7)	1.77 (0.66-4.75)	0.255	0.8	1.3	1.69 (0.55-5.15)	0.356
Bleeding requiring exploration	27 (3.2)	22 (4.6)	1.46 (0.82-2.58)	0.201	3.5	4.0	1.15 (0.64-2.09)	0.639
LCOS requiring MCS [b]	9 (1.1)	8 (1.7)	1.57 (0.60-4.11)	0.354	0.9	1.1	1.28 (0.41-4.00)	0.665
Stroke	17 (2.0)	16 (3.3)	1.68 (0.84-3.35)	0.142	2.0	2.4	1.17 (0.54-2.52)	0.695
New onset dialysis	6 (0.7)	4 (0.8)	1.18 (0.33-4.18)	0.804	1.0	0.6	0.59 (0.15-2.36)	0.456
Sternal wound infection	8 (0.9)	5 (1.0)	1.10 (0.36-3.38)	0.867	0.8	1.1	1.50 (0.47-4.79)	0.494
Overall outcomes, n (%/PY)								
All-cause death	173 (1.8)	110 (2.89)	1.90 (1.49-2.44)	<0.001	2.1	2.3	1.25 (0.92-1.70)	0.149
Stroke	83 (1.2)	24 (0.8)	0.66 (0.41-1.04)	0.070	1.3	0.5	0.42 (0.24-0.72)	0.002
Anticoagulation-related bleeding	92 (1.3)	20 (0.7)	0.50 (0.31-0.82)	0.006	1.3	0.5	0.40 (0.24-0.67)	<0.001
Operated valve endocarditis	18 (0.2)	8 (0.3)	1.02 (0.44-2.38)	0.956	0.3	0.3	1.00 (0.34-2.92)	0.993
AV reoperation	39 (0.5)	23 (0.8)	1.73 (1.02-2.94)	0.042	0.5	0.6	1.26 (0.87-1.82)	0.225
Readmission due to cardiac cause	215 (3.5)	80 (2.9)	0.81 (0.63-1.05)	0.118	3.5	2.3	1.08 (0.66-1.75)	0.758

Values are presented as number (%) or number (% per patient-year) unless otherwise indicated.

Early outcomes are presented as odds ratios. Overall outcomes are presented as hazard ratios or sub-distributional hazard ratios.

IPTW, inverse-probability-of-treatment weighting; OR, odds ratio; HR, hazard ratio; sHR, sub-distributional hazard ratio; CI, confidence interval; LCOS, low cardiac output syndrome; MCS, mechanical circulatory support; PY, patient-year; AV, aortic valve; SVD, structural valve deterioration.

[a] Outcomes captured using a primary diagnosis during a visit to the emergency department or using any primary or secondary diagnosis during hospitalization.

[b] Included extracorporeal membrane oxygenation, intra-aortic balloon pump, and ventricular assist device.

Supplement table 6. Operative profiles according to the bioprosthetic valve type

Variables	Conventional B-AVR (n =494)	Sutureless B-AVR (n = 104)	p-value	SMD (%)
Minimally invasive approach	83 (16.8)	66 (63.5)	<0.001	108.2
CPB time, minutes	120.3 ± 47.0	88.4 ± 32.5	<0.001	78.9
ACC time, minutes	78.8 ± 31.0	51.5 ± 17.6	<0.001	108.3
Concomitant procedure				
CABG	100 (20.2)	15 (14.4)	0.218	15.4
Surgical AF ablation	20 (4.0)	9 (8.7)	0.083	19.0
Ascending aorta replacement	62 (12.6)	6 (5.8)	0.070	23.7
Congenital correction	12 (2.4)	3 (2.9)	1.000	2.8

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated.
B-AVR, Bioprosthetic aortic valve replacement; SMD, standardized mean difference; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; CABG, coronary artery bypass grafting; AF, atrial fibrillation.