의학석사 학위논문

이중 판막 치환술에서의 소 심낭 조직 판막과 돼지 심장 판막의 장기성적 비교

: 건강보험 빅데이터를 활용한 연구

Long-term Comparison of Bovine Pericardial and Porcine Bioprosthetic Valves in Double Valve Replacement: A Nationwide Population-based Cohort Study in Korea

울산대학교 대학원

의 학 과

오 하 은

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이 논문을 의학석사 학위 논문으로 제출함

2024 년 2 월

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의 학 과

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오하은의 의학석사 학위 논문을 인준함

심사위원　　김 준 범　　인

심사위원　　송 종 민　　인

심사위원　　김 대 희　　인

울 산 대 학 교　대 학 원

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국문요약

연구배경: 현재까지 대동맥 판막 치환술이나 승모 판막 치환술에서 소 심낭 조직 판막과 돼지 조직 판막을 비교한 연구는 있었으나, 이중 판막 치환술에서 두 조직 판막의 사망률과 합병증 발생률을 비교한 연구는 없었다. 이에 본 연구에서는 이중 판막 치환술에서 두 조직 판막의 심혈관 질환 사망률과 합병증 발생률에 유의한 차이가 있는지 알아보고자 하였다.

연구 방법: 국민건강보험공단 자료를 바탕으로, 2003 년부터 2018 년까지 조직판막을 사용하여 이중 판막 치환술을 받은 889 명의 환자들을 후향적으로 분석하였다. 889 명 중 608 (68.3%)명이 소 심낭 판막을 사용하였고, 281 (31.6%)명이 돼지 심장 판막을 사용하였다. 일차 평가변수 (primary end point)는 심혈관계 질환 사망률로 설정하였다. 성향점수 매칭(Propensity score matching)을 통해 두 군의 기저 변수를 보정하였다. 하위집단분석(Subgroup analysis)에 역 확률 가중치 방법(IPTW method)를 사용하였다.

연구결과: 보정 전 데이터를 이용한 전체사망률 분석에서, 소 심낭 판막군에서 238 명 (7.5%/PY), 돼지 조직 판막군에서 136 명 (8.0%/PY)의 사망이 발생하였다. 심혈관계 질환 사망률 분석에서 소 심낭 판막군에서 152 명 (4.8%/PY), 돼지 조직 판막군에서 83 명 (4.9%/PY)의 사망이 발생하였다. 어떤 조직 판막을 사용하는지는 전체 사망률 (95% 신뢰구간 0.94-1.43), 심혈관계 질환 사망률 (95% 신뢰구간 1.07-7.45)에 유의한 영향을 미치지 않았다. 성향점수 매칭 시행 후에도, 소 심낭 판막군과 돼지 조직 판막군에서 전체 사망률 [조정 위험률(adjusted hazard ratio) 0.87, 95% 신뢰구간 0.65-1.17]과 심혈관계 질환 사망률 (조정 위험률 0.74, (95% 신뢰구간 0.50-1.07)의 유의한 차이가 없었다. 감염 심내막염, 혈전 색전증, 출혈을 포함한 판막관련 합병증에서 두 군간의 유의한 차이는 없었으나, 돼지 조직 판막군에서 재수술률이 유의하게 높았다 (조정 위험률 2.08, 95% 신뢰구간 1.30-4.40). 하위분석에서 당뇨병이 없는 환자군에서 돼지 판막을 받은 환자의 재수술률이 소 판막을 받은 환자보다 높았다 (p for interaction=0.027). 또한 Charlson 동반 질환 지수 (Charlson comorbidity index, CCI)가 2 미만으로 낮은 환자군에서 돼지 판막을 받은 환자의 재수술률이 소 판막을 받은 환자보다 높았다 (p for interaction=0.043).

연구결론: 전국적인 후향적 관찰 연구를 통해 이중 판막 치환술에서 조직 판막의 유형이 심혈관계 사망률 및 감염 심내막염, 혈전 색전증, 출혈과 같은 판막 관련 합병증에 영향을 미칠 수 있는지를 알아보았다. 전체 사망률, 심혈관계 질환 사망률에는 유의한 차이가 없었으나 돼지 조직 판막을 받은 환자에서 소 심낭 판막을 받은 환자보다 재수술률이 유의하게 높았다.

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Introduction

Multivalvular heart disease is an intricate medical condition that results in substantial morbidity and mortality among individuals suffering from valvular heart disease. According to The Euro Heart Survey on Valvular Heart Disease, almost 17% of patients who require valve surgery have multiple affected heart valves, making it a challenging and complex medical issue to manage (1, 2). Various approaches are available for surgical intervention for concomitant aortic and mitral valve diseases. Double valve replacement (DVR) is a widely accepted method with satisfactory survival rates, although it may require strict anticoagulation regimens for patients with mechanical prostheses (3).

Elderly patients often favor bioprosthetic valves due to their ability to reduce major bleeding events without requiring anticoagulation therapy (4). Similarly, younger patients who wish to avoid anticoagulation therapy may opt for tissue valves (5). However, it is important to note that while these valves may offer certain advantages, they are limited in their durability due to structural valve degeneration (SVD). This serious condition may ultimately require a major surgical intervention. Bioprosthetic valves are typically crafted from animal sources such as bovine pericardium or porcine heart valves.

There have been numerous studies that compare the efficacy of bovine and porcine prosthetic valves in both the aortic and mitral positions. While the outcomes in the aortic position have been somewhat controversial, recent research has shown that there is no significant difference in all-cause mortality between the two valve types. However, there is still some debate over which valve is superior in terms of reoperation (6, 7, 8). In contrast, there is a consensus that there is no difference in all-cause mortality in mitral position (9, 10). Despite this, there is currently little data to guide surgical decisions regarding DVR and which bioprosthetic valve - bovine or porcine - is the better option.

To address this gap, we conducted a large-scale nationwide cohort study using the Korean National Administrative database of the National Health Insurance Service (NHIS) to compare the long-term outcomes of these two valve types in DVR.

Method

1. Data collection

Study data was obtained from the Korean National Administrative database of the National Health Insurance Service (NHIS). In South Korea, the NHIS is the single institution that covers almost (97%) all the national population (approximately 52 million in 2022). Adults above the age of 19 are required to undergo biannual regular health examinations. Regular health examinations included height, weight, body mass index (BMI), blood pressure, pulse rate, complete blood count, serum glucose, serum cholesterol/ triglyceride, serum creatinine, liver function test, electrocardiogram, chest x-ray, and a self-reported questionnaire on health behavior (e.g., smoking and, alcohol use, etc). National Health Information Database (NHID) includes comprehensive medical insurance service information such as demographic information, diagnosis, treatment, prescription, procedure, and operation. All diagnoses were recorded using the International Classification of Disease, 10th Revision (ICD-10) codes.

2. Study design and study patient

Adults (age ≥ 40 years old) who underwent DVR (aortic and mitral valves) using a bioprosthetic valve from January 2003 to December 2018 were enrolled in this study. The exclusion criteria were 1) previous aortic valve replacement (AVR) or previous mitral valve replacement (MVR), 2) concomitant other valve surgery; 3) concomitant aorta surgery, 4) preoperative extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump (IABP), 5) preoperative mechanical ventilator, 6) aortic valve (AV) or mitral valve (MV) repair, 7) concomitant cardiac tumor removal surgery, 8) AVR with sutureless valve, or 9) different aortic and mitral bioprosthetic valve material. All exclusion criteria are listed in Figure. 1. Further details on the types of valves used in this study are provided in Supplementary Table S1.

3. Ethics

This study was granted approval by the Institutional Review Board of Asan Medical Center; under study number 2022-0345. Since the NHID provides anonymized datasets, personal information cannot be identified. Consequently, informed consent was waived.

4. Outcomes

The primary outcome was cardiovascular mortality. The secondary outcome was all-cause mortality and valve-related events, including endocarditis, reoperation, thromboembolism, and major bleeding. Reoperation was defined as a repeated surgical valve (mitral or aortic position) intervention during the follow-up period.

The information regarding mortality and its causes was obtained from Statistic Korea, which maintains records of residents in South Korea using personal identification numbers. Cardiovascular mortality was classified as a disease of the circulatory system with no exceptions: ICD I10-99. Thromboembolism was identified as a combination of ischemic stroke and systemic thromboembolism (ICD I63, I64, I74). Ischemic stroke was confirmed using ICD-10 (ICD I63-64) and NHIS claim codes, and brain imaging (CT or MRI) during hospitalization. Systemic thromboembolism was defined as arterial embolism and thrombosis (ICD I74) and confirmed by imaging during hospitalization. Major bleeding included image-confirmed brain hemorrhage, gastrointestinal bleeding, and other site bleeding requiring hospitalization. Supplementary Tables S2, S3 provide detailed definitions of the variables and outcomes according to ICD-10 and NHIS codes.

5. Definition of covariate and outcomes

Each covariate was defined as follows. Dyslipidemia was defined as total cholesterol of 240 mg/dL or more of the use of a lipid-lowering drug, low-density lipoprotein cholesterol (LDL-C) of 160 or more or the use of a lipid-lowering drug, triglycerides of 200 of more; or high-density lipoprotein cholesterol (HDL-C) under 40 mg/Dl (ICD E78) (11). Dialysis included hemodialysis and peritoneal dialysis. Ischemic heart disease included stable angina, acute coronary syndrome, and ischemic cardiomyopathy (ICD I20-I25). Previous percutaneous coronary intervention (PCI) was defined as those who underwent balloon dilatation, stent insertion, or thrombectomy in the coronary artery. Charlson comorbidity index (CCI) predicts one year and ten year survival in patients with multiple comorbidities (12). A higher score in the CCI indicates a poor prognosis, Charlson et al. suggested one year mortality rates for the different scores: "0", 12%; "1-2", 26%; "3-4", 52%; and "≥ 5", 85% (13). We established the cut-off value of the CCI to be 2. BMI was categorized according to the WHO BMI classification for adults (14). For alcohol use, mild to moderate was defined as drinking once a month to two or three times a week, and heavy drinking was defined as drinking more than four times a week. Health screening data (e.g., BMI, systolic blood pressure, diastolic blood pressure, smoking, alcohol use, and creatinine), was unavailable in 39.0~53.5% of the patients.

6. Statistical analysis

Categorical variables are presented as numerical percentages, while continuous variables are presented as the means. To compare the categorical variables, a chi-square test or Fisher's exact test was used, and a Student's t-test was used to compare the continuous variables.

To minimize bias due to confounding variables and balance baseline characteristics between the bovine pericardial and porcine groups, propensity score (PS) matching was utilized. The PS was estimated

using a logistic regression model and applied to incorporate the baseline characteristics and outcomes listed in Tables 1 and 2. After adjusting by the PS matching, a Cox proportional hazard model with robust standard error was used to compare the risk of all-cause mortality between the two groups. Our criterion for balance was achieved when the absolute value of the standardized mean difference (SMD) was less than 0.1. In addition, the Inverse Probability of Treatment Weighting (IPTW) based on the PS score was used to compare baseline characteristics and outcomes. An IPTW-adjusted Cox proportional hazard model was utilized to compare the risk of cardiovascular mortality between the bovine pericardial and porcine groups. As in the PS matching cohort, the Fine and Gray method was used to analyze the risk of time-related outcomes, considering cardiovascular mortality as a competitive event.

Subgroup analyses were also conducted to compare the outcomes of the two bioprosthetic valve groups according to various baseline characteristics. The IPTW method was used for these subgroup analyses.

All *P*-values were two-tailed, and statistical significance was considered at a *P*-value of less than 0.05. All statistical analyses were performed using R software, version 4.0.3.

Results

1. Study population and baseline characteristics

The median follow-up duration of this study was 5.74 years (IQR [Inter Quartile Range], 3.19-9.79). During the initial enrollment, a total of 3901 patients who underwent DVR with a bioprosthetic valve were identified. After excluding patients who were not linked to the NHIS database, were under 40 years old, or had missing information about the level of institution, 3454 patients were included in this. After applying additional exclusion criteria related to cardiac surgery, a final of 889 patients were included. (Fig. 1). Among the patients, 608 (68.3%) received a bovine pericardial valve, while 281 (31.6%) received a porcine valve. Table 1 lists the baseline characteristics of the patients. Before matching, those who received a bovine pericardial valve tended to have chronic kidney disease, mitral stenosis, and mitral regurgitation, compared with patients who received a porcine valve. However, after using propensity score matching, a well-balanced distribution of baseline characteristics between the two groups was achieved.

2. Clinical outcomes

Table 2 displays the incidence and risk analyses of unadjusted and adjusted data for the covariates. In

the unadjusted analysis, the cardiovascular mortality rates were 4.8%/ patient-year (PY) in the bovine groups and 4.9%/PY in the porcine group. The all-cause mortality rates were 7.5%/PY in the bovine groups and 8.0%/PY in the porcine group. However, there were no statistically significant differences between the types of bioprosthetic valves used in terms of cardiovascular mortality (hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.94-1.43) or all-cause mortality (HR, 1.10; 95% CI, 0.84-1.45). Endocarditis was less common in the bovine groups (HR, 2.82; 95% CI, 1.07-7.45), whereas no significant differences were observed in the other valve-related events (e.g., reoperation, thromboembolism, or hemorrhage).

After PS matching, the cardiovascular mortality (adjusted hazard ratio [aHR], 0.74; 95% CI, 0.50-1.07) and all-cause mortality (aHR, 0.87; 95% CI, 0.65-1.17) did not significantly differ between the bovine and porcine groups. Furthermore, no significant differences were found in the other valve-related events, including endocarditis (HR, 2.31; 95% CI, 0.59-9.10), thromboembolism (aHR, 0.88; 95% CI, 0.40-1.93), and hemorrhage (aHR, 1.07; 95% CI, 0.76-1.53). However, patients with porcine valves had a higher risk of reoperation (aHR, 2.08; 95% CI, 1.10-3.94). Supplement Table S4 summarizes which valves were reoperated in patients who underwent reoperation.

Additionally, the 30-day mortality after reoperation was analyzed. There was no significant difference in the 30-day mortality after reoperation between the bovine and porcine groups (OR [odds ratio], 1.19; 95% CI, 0.071-20.011, *P*-value = 0.903).

Similarly, after adjusting using the IPTW method, there were no significant differences in cardiovascular mortality (aHR, 0.84; 95% CI, 0.60-1.19), all-cause mortality (aHR, 0.82; 95% CI, 0.62-1.08), and valve-related events, including endocarditis (aHR, 2.86; 95% CI, 0.87-9.44), thromboembolism (aHR, 1.00; 95% CI, 0.47-2.17), and hemorrhage (aHR, 1.14; 95% CI, 0.80-1.61) between bovine and porcine groups. However, as with the PS matching, the risk of reoperation was higher for patients with porcine valves (HR, 2.40; 95% CI, 1.30-4.40).

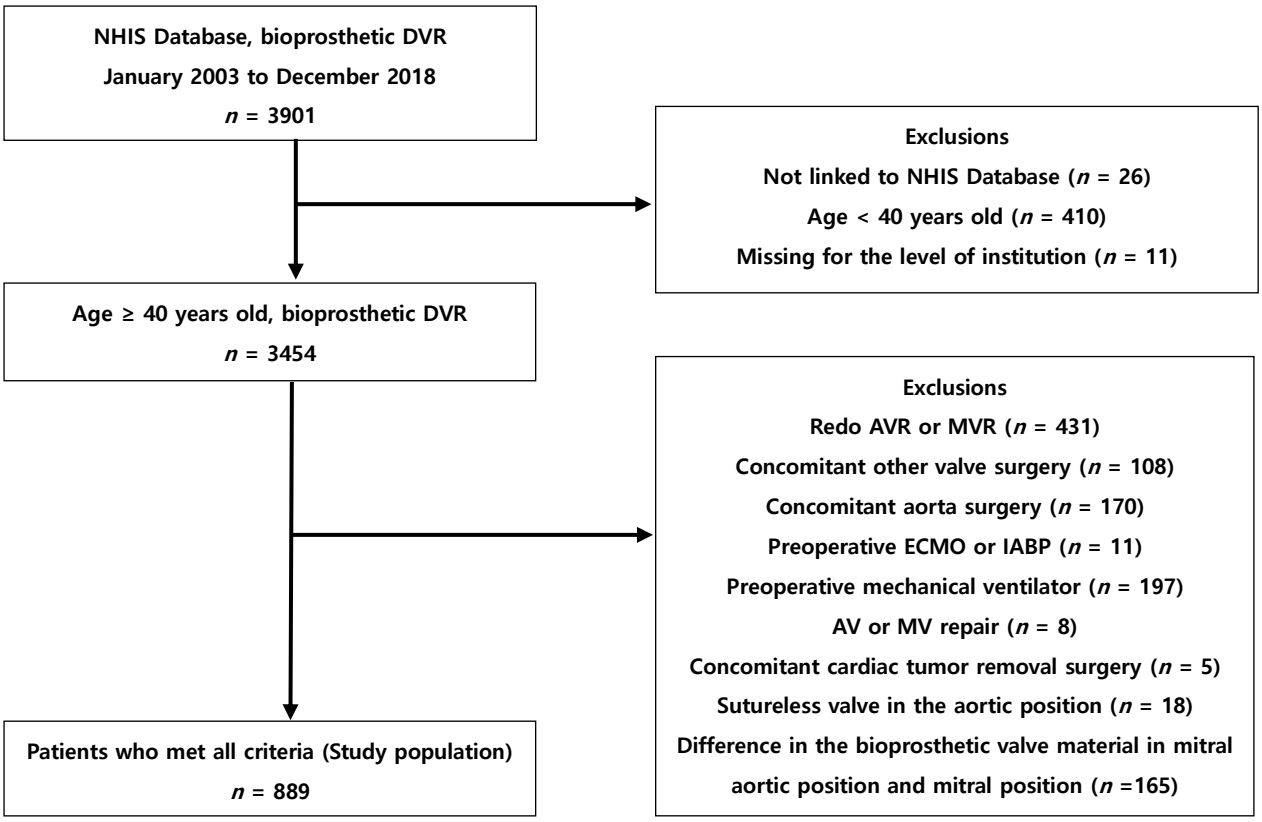

Figure 1. The flowchart of the study enrollment

AVR = aortic valve replacement; MVR = mitral valve replacement; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; AV = aortic valve; MV = mitral valve

Table 1. Baseline characteristics

Variable	Unadjusted data				Propensity score matching (PSM)			Inverse probability of treatment weighting (IPTW)		
	Bovine (*n* = 608)	Porcine (*n* = 281)	*P*-value	SMD	Bovine (*n* = 195)	Porcine (*n* = 195)	SMD	Bovine (*n* = 608)	Porcine (*n* = 281)	SMD
Baseline demographics										
Age (years)	69.56 (SD: 7.83)	70.64 (SD: 5.93)	0.029	0.150	70.30 (SD: 6.81)	70.36 (SD: 6.28)	0.009	69.95 (SD: 7.42)	70.31 (SD: 6.9)	0.05
Female, n (%)	365 (60.0)	161 (27.3)	0.110	0.056	114 (58.5)	115 (59.0)	0.01	367.3 (60.4)	171.2 (60.9)	0.011
Baseline comorbidities, n (%)										
Hypertension	395 (65.0)	196 (69.8)	0.160	0.102	134 (38.7)	133 (68.2)	0.011	389.7 (65.6)	185.8 (66.1)	0.011
Diabetes mellitus	138 (22.7)	65 (23.1)	0.886	0.010	39 (20.0)	42 (21.5)	0.038	129.5 (21.3)	61.5 (21.9)	0.014
Dyslipidemia	103 (16.9)	49 (17.4)	0.855	0.013	37 (19.0)	35 (17.9)	0.026	101.3 (16.7)	60.9 (21.7)	0.128
Atrial fibrillation	246 (40.5)	112 (39.9)	0.865	0.012	83 (42.6)	78 (40.0)	0.052	246.1 (40.5)	116.2 (41.4)	0.018
Chronic kidney disease	45 (7.4)	8 (2.8)	0.008	0.208	8 (4.1)	6 (3.1)	0.055	351 (5.8)	10.7 (3.8)	0.092
Dialysis	27 (4.4)	6 (2.1)	0.091	0.130	7 (3.6)	4 (2.1)	0.093	22 (3.6)	6.3 (2.2)	0.081
Ischemic stroke	100 (16.4)	45 (16.0)	0.871	0.012	32 (16.4)	31 (15.9)	0.014	96.5 (15.9)	49.4 (17.6)	0.046
Ischemic heart disease	201 (33.1)	96 (34.2)	0.745	0.023	66 (33.8)	65 (33.3)	0.011	201.8 (33.2)	90.8 (32.3)	0.018
Myocardial infarction	19 (3.1)	12 (4.3)	0.387	0.061	8 (4.1)	7 (3.6)	0.027	19.3 (3.2)	8.3 (3.0)	0.012
Previous PCI	25 (4.1)	13 (4.6)	0.724	0.025	8 (4.1)	11 (5.6)	0.072	26.5 (4.4)	11.9 (4.2)	0.006
Congestive heart failure	302 (49.7)	132 (47.0)	0.455	0.054	89 (45.6)	97 (49.7)	0.082	291.9 (48.0)	126 (44.8)	0.064
Anemia	89 (14.6)	31 (11.0)	0.143	0.108	22 (11.3)	22 (11.3)	<0.001	79.9 (13.1)	31.9 (11.4)	0.054
COPD	38 (6.3)	27 (9.6)	0.074	0.125	16 (8.2)	14 (7.2)	0.038	43.6 (7.2)	22.9 (8.1)	0.036
Asthma	137 (22.5)	59 (21.0)	0.607	0.037	41 (21.0)	41 (21.0)	<0.001	127(20.9)	53 (18.9)	0.051
Peripheral vascular disease	45 (7.4)	23 (8.2)	0.683	0.029	14 (7.2)	13 (6.7)	0.02	45.1 (7.4)	16.8 (6.0)	0.057
Previous cancer	43 (7.1)	15 (5.3)	0.330	0.072	15 (7.7)	14 (7.2)	0.059	40.3 (6.6)	23 (8.2)	0.059
Charlson comorbidity index			0.753	0.099			0.103			0.049
0	100 (16.4)	44 (15.7)			35 (17.9)	33 (16.9)		97.3 (16.0)	47.3 (16.8)	
1	137 (22.5)	62 (22.1)			42 (21.5)	46 (23.6)		142.6 (23.5)	68.6 (24.4)	
2	119 (19.6)	66 (23.5)			47 (24.1)	40 (20.5)		127.8 (21.0)	56.9 (20.2)	
3-4	163 (26.8)	72 (25.6)			49 (25.1)	51 (26.2)		161.2 (26.5)	69.9 (24.9)	
≥5	89 (14.6)	37 (13.2)			22 (11.3)	25 (12.5)		79 (13.0)	38.3 (13.6)	
Mode of valve disease. n (%)										
Aortic stenosis	289 (47.5)	121 (43.1)	0.214	0.090	93 (47.7)	84 (43.1)	0.093	279.3 (45.9)	128.6 (45.8)	0.004
Aortic regurgitation	267 (43.9)	116 (41.3)	0.461	0.053	83 (42.6)	82 (42.1)	0.01	271.1 (44.6)	131.5 (46.8)	0.044
Combined (Aortic valve)	131 (21.5)	63 (22.4)	0.769	0.021	45 (23.1)	37 (20.0)	0.075	129.1 (21.2)	61.8 (22.0)	0.019
Mitral stenosis	451 (74.2)	186 (66.2)	0.014	0.175	138 (70.8)	139 (71.3)	0.011	439.6 (72.3)	209.3 (74.5)	0.05
Mitral regurgitation	57 (9.4)	40 (14.2)	0.031	0.151	25 (12.8)	23 (11.8)	0.031	72.8 (12.0)	33.9 (12.1)	0.003
Combined (Mitral valve)	150 (24.7)	70 (24.9)	0.939	0.006	48 (24.6)	50 (25.6)	0.024	144.8 (23.8)	64 (22.8)	0.025
Health screening data										

Table 1. Continued

BMI (kg/m^2)	23.51 (SD: 3.43)	22.86 (SD: 2.84)	0.024	0.206	22.75 (SD: 3.05)	22.92 (SD: 2.87)	0.058	23.22 (SD: 3.31)	23.34 (SD: 2.97)	0.041
<18.5	24 (3.9)	11 (3.9)	0.151	0.222	10 (5.1)	8 (4.1)	0.128	26 (4.3)	10.7 (3.8)	
≥18.5 and <23	137 (22.5)	71 (25.3)			47 (24.1)	50 (25.6)		146.1 (24.0)	61.7 (22.0)	
≥23 and <25	106 (17.4)	45 (16.0)			30 (15.4)	33 (16.9)		103.4 (17.0)	48.4 (17.2)	
≥25 and <30	90 (14.8)	31 (11.0)			24 (12.3)	22 (11.3)		78.3 (12.9)	40.9 (14.6)	
≥30	14 (2.3)	1 (0.4)			0 (0.0)	1 (0.5)		10.4 (1.7)	1.8 (0.6)	
Not available	237 (39.0)	122 (43.4)			84 (43.1)	81 (41.5)		243.7 (40.1)	117.6 (41.9)	
Systolic blood pressure (mmHg)			0.920	0.009			0.034			0.058
<120	125 (20.6)	57 (20.3)			41 (21.0)	42 (21.5)		124.6 (20.5)	52.3 (18.6)	
≥120 and <140	177 (29.1)	72 (25.6)			47 (24.1)	51 (26.2)		170.6 (28.1)	72.9 (25.9)	
≥140	69 (11.3)	30 (10.7)			23 (11.8)	21 (10.8)		69.1 (11.4)	38.2 (13.6)	
Not available	237 (39.0)	122 (43.4)			84 (43.1)	81 (41.5)		243.7 (40.1)	117.6 (41.9)	
Diastolic blood pressure (mmHg)			0.593	0.051			0.08			0.062
<80	232 (38.2)	99 (35.2)			62 (31.8)	69 (35.4)		225.6 (37.1)	94 (33.5)	
≥80 and <90	101 (16.6)	45 (16.0)			34 (17.4)	33 (16.9)		103.2 (17.0)	50.2 (17.9)	
≥90	38 (6.3)	15 (15.3)			15 (7.7)	12 (6.2)		35.4 (5.8)	19.2 (6.8)	
Not available	237 (39.0)	122 (43.4)			84 (43.1)	81 (41.5)		243.7 (40.1)	117.6 (41.9)	
Smoking			0.601	0.100			0.036			0.051
Never smoking	276 (45.4)	125 (44.5)			84 (43.1)	86 (44.1)		278.9 (45.9)	126.1 (44.9)	
Previous smoker	50 (8.2)	17 (6.0)			15 (7.7)	15 (7.7)		46.7 (7.7)	24 (8.5)	
Current smoker	35 (5.8)	15 (5.3)			10 (5.1)	11 (5.6)		31.1 (5.1)	12.1 (4.3)	
Not available	247 (40.6)	124 (44.1)			86 (44.1)	83 (42.6)		251.4 (41.3)	118.8 (42.3)	
Alcohol use			0.014	0.236			0.036			0.049
None	237 (39.1)	83 (29.5)			58 (29.7)	61 (31.3))		222.8 (36.6)	102.8 (36.6)	
Mild to moderate	107 (17.6)	69 (24.6)			48 (24.6)	48 (24.6)		120.2 (19.8)	55.3 (19.7)	
Heavy	16 (2.6)	5 (1.8)			3 (1.5)	3 (1.5)		13 (2.1)	4.2 (1.5)	
Not available	248 (40.8)	124 (44.1)			86 (44.1)	83 (42.6)		252 (41.4)	118.8 (42.3)	
Creatinine (mg/dl)			0.014	0.217			0.055			0.111
≤1.5	266 (43.8)	101 (35.9)			68 (34.9)	72 (36.9)		254.7 (41.9)	112.6 (40.1)	
>1.5	17 (2.8)	3 (1.1)			4 (2.1)	3 (1.5)		13.3 (2.2)	2.7 (1.0)	
Not available	325 (53.5)	177 (63.0)			123 (63.1)	120 (61.5)		340 (55.9)	165.7 (59.0)	

PCI = percutaneous coronary intervention; COPD = chronic obstructive pulmonary disease; BMI = body mass index; SD = standard deviation; SMD = standardized mean difference.

Table 2. Clinical outcomes between the bovine and porcine groups

Outcomes	Unadjusted data				Propensity score matching				Inverse probability of treatment weighting			
	No. of events (%/PY)		HR (95% CI)	*P*-value	No. of events (%/PY)		aHR (95% CI)	*P*-value	No. of events (%/PY)		aHR (95% CI)	*P*-value
	Bovine (*n* = 608)	Porcine (*n* = 281)			Bovine (*n* = 608)	Porcine (*n* = 281)			Bovine (*n* = 608)	Porcine (*n* = 281)		
Outcomes, n (%/PY)												
Mortality	238 (7.5)	136 (8.0)	1.16 (0.94, 1.43)	0.172	100 (8.5)	87 (7.4)	0.87 (0.65, 1.17)	0.369	259 (7.8)	104 (6.1)	0.82 (0.623, 1.08)	0.163
Cardiovascular mortality	152 (4.8)	83 (4.9)	1.10 (0.84, 1.45)	0.446	68 (5.8)	51 (4.3)	0.74 (0.50, 1.07)	0.104	169 (5.1)	67 (4.0)	0.84 (0.60, 1.19)	0.323
Non-cardiovascular mortality	86 (2.7)	53 (3.1)	1.15 (0.83, 1.62)	0.395	32 (2.7)	36 (3.1)	1.20 (0.76, 1.92)	0.430	90 (2.7)	37 (2.2)	0.86 (0.58, 1.28)	0.445
Valve-related events												
Endocarditis	7 (0.3)	10 (0.7)	2.82 (1.07, 7.45)	0.036	3 (0.3)	7 (0.7)	2.31 (0.59, 9.10)	0.228	8 (0.3)	11 (0.7)	2.86 (0.87, 9.44)	0.085
Reoperation	32 (1.2)	27 (1.8)	1.56 (0.94, 2.58)	0.084	12 (1.2)	23 (2.3)	2.08 (1.10, 3.94)	0.025	32 (1.1)	35 (2.5)	2.40 (1.30, 4.40)	0.005
Thromboembolism	39 (1.5)	21 (1.4)	0.97 (0.57, 1.65)	0.910	13 (1.3)	11 (1.1)	0.88 (0.40, 1.93)	0.743	39 (1.4)	18 (1.2)	1.00 (0.47, 2.17)	0.988
Hemorrhage	156 (7.2)	83 (6.7)	0.98 (0.75, 1.27)	0.855	56 (7.1)	59 (6.9)	1.07 (0.76, 1.53)	0.697	162 (7.0)	86 (7.2)	1.14 (0.80, 1.61)	0.468

Hazard ratio was calculated by setting the bovine group as a control group.

PY = patient-year; HR = hazard ratio; aHR = adjusted hazard ratio; CI = confidence interval; COPD = chronic obstructive pulmonary disease

3. Subgroup analysis for the primary end point

Table 3 provides a detailed analysis of the subgroups comparing the two types of bioprosthetic valves using IPTW-adjusted HRs for cardiovascular mortality and reoperation. Patients who received a porcine valve and did not have diabetes mellitus had a higher risk of reoperation (with a p-value for interaction of 0.027), and those with a Charlson comorbidity index < 2 who received porcine valve had a higher risk of reoperation (with a p-value for interaction of 0.043). There were no significant interactions observed between the type of bioprosthetic valve and the other baseline characteristics, except for diabetes mellitus and Charlson comorbidity index, in relation to both cardiovascular mortality and reoperation.

Table 3. Subgroup analysis for the primary end point using IPTW-adjusted HRs

(A: Cardiovascular mortality, B: Reoperation)

DVR (*n* = 889)	Bovine (*n* = 608)	Porcine (*n* = 281)	Hazard ratio (HR)	95% CI	*P-v*alue	*P*-value for interaction
A: Cardiovascular mortality						
Age						
<70 years	66/254	22/116	0.683	0.375, 1.246	0.214	0.437
≥70 years	103/354	46/165	0.918	0.590, 1.427	0.703	
Sex						
Male	79/241	33/110	0.839	0.527, 1.337	0.410	0.906
Female	90/367	34/171	0.805	0.480, 1.350	0.410	
Diabetes mellitus						
No	135/478	45/219	0.690	0.467, 1.020	0.063	0.076
Yes	34/130	23/62	1.352	0.718, 2.547	0.350	
Stroke, SE						
No	139/511	52/231	0.764	0.521, 1.120	0.168	0.404
Yes	30/97	16/50	1.126	0.492, 2.578	0.779	
Congestive heart failure						
No	79/316	42/155	1.073	0.653, 1.761	0.782	0.101
Yes	90/292	26/126	0.604	0.376, 0.971	0.037	
Atrial fibrillation						
No	115/362	42/165	0.779	0.512, 1.184	0.242	0.657
Yes	54/246	25/116	0.926	0.491, 1.749	0.813	
Charlson comorbidity index						
<2	59/240	26/116	0.915	0.520, 1.612	0.760	0.651
≥2	110/368	41/165	0.777	0.501, 1.205	0.259	

Table 3: Continued

DVR (n = 889)	Bovine (n = 608)	Porcine (n = 281)	Hazard ratio (HR)	95% CI	*P*-value	*P*-value for interaction
B: Reoperation						
Age						
<70 years	22/254	22/116	2.293	1.08, 4.88	0.031	0.788
≥70 years	10/354	13/165	2.736	0.96, 7.78	0.059	
Sex						
Male	18/241	12/110	1.391	0.55, 3.53	0.488	0.123
Female	14/367	23/171	3.740	1.61, 8.70	0.002	
Diabetes mellitus						
No	25/478	33/219	3.133	1.64, 5.99	0.001	0.027
Yes	7/130	2/62	0.539	0.13, 2.23	0.393	
Stroke, SE						
No	29/511	33/231	2.503	1.32, 4.75	0.005	0.559
Yes	3/97	2/50	1.483	0.30, 7.60	0.636	
Congestive heart failure						
No	17/316	20/155	2.595	1.24, 5.44	0.012	0.780
Yes	15/292	15/126	2.169	0.80, 5.96	0.133	
Atrial fibrillation						
No	23/362	22/165	2.145	1.03, 4.47	0.041	0.605
Yes	9/246	14/116	3.047	1.00, 9.30	0.050	
Charlson comorbidity index						
<2	15/240	26/116	4.094	1.97, 8.50	0.000	0.043
≥2	17/368	9/165	1.131	0.42, 3.07	0.809	

Hazard ratio was calculated by setting the bovine group as the control group. A *P*- value for interaction less than 0.05 was considered statistically significant.

CI = confidence interval; SE = systemic embolization

Discussion

This nationwide cohort study demonstrates that the types of bioprosthetic valve had no effect on cardiovascular mortality, all-cause mortality, and valve-related events such as endocarditis, thromboembolism, and hemorrhage, except for reoperation. In the subgroup analysis using the IPTW method, patients who received a porcine valve and did not have diabetes mellitus had a higher risk of reoperation, and those with a Charlson comorbidity index less than 2 who received a porcine valve had a higher risk of reoperation (with a p-value for interaction = 0.043).

Numerous studies have been conducted comparing the efficacy of bovine pericardial valves versus porcine bioprosthetic valves in both mitral and aortic positions. However, to date, less data or research has been published comparing the two types of tissue valves in terms of all-cause mortality and valve-

related events in double valve replacement procedures.

While transcatheter procedures such as transcatheter aortic valve replacement (TAVR) and transcatheter mitral valve repair or replacement (TMVR) have seen a rapid increase in popularity, surgical valve replacement remains a crucial aspect of treating valve disease. Bioprosthetic valves are now preferred over mechanical valves due to changes in lifestyle and a desire to avoid anticoagulants.

The guidelines provided by the American College of Cardiology and American Heart Association (ACC/AHA) and the European Society of Cardiology and European Association for Cardio-Thoracic Surgery (ESC/EACTS) recommend a bioprosthetic AVR for patients above the age of 65 years (15, 16). In contrast, the ESC/EACTS guidelines suggest a mechanical AVR for patients younger than 60 years, while the ACC/AHA guidelines propose that either a bioprosthetic or mechanical AVR is reasonable for patients aged 50 to 65 years, depending on several factors such as comorbid conditions, risk of repeat valve surgery, patient preferences, and shared decision-making. Furthermore, the ACC/AHA guidelines recommend a mechanical AVR for patients younger than 50. Regarding patients undergoing MVR, the ACC/AHA and ESC/EACTS guidelines advocate for a mechanical valve in patients below the age of 65, instead of younger than 70. However, the ESC/EACTS guidelines do recommend a bioprosthetic MVR only for patients older than 70 years. However, it is important to note that bioprosthetic valves may require reoperation due to valve degeneration. As the human lifespan continues to increase, the durability of these valves has become a significant concern. There are currently no guidelines or data indicating the optimal age for valve selection in patients undergoing DVR. American guidelines recommend that a bioprosthetic should be considered for patients of any age who are contraindicated for anticoagulant therapy, are unable to manage it appropriately, or do not desire it (15).

According to research on aortic position using the same database, there was no notable difference in cardiovascular mortality (17). However, the group that received porcine bioprosthetic valves had a higher risk of reoperation. In the case of mitral position, there were no significant differences in cardiovascular mortality or valve-related events, including reoperation (18). When it comes to double valve replacement with a bioprosthetic valve, there was no significant difference in cardiovascular mortality, but patients who received porcine valves had a higher rate of reoperation than those who received bovine pericardial valves. Christian's et al (19) independently linked the use of porcine tissue valves to valve hemodynamic deterioration in patients with bioprosthetic valves. Porcine valves were found to have a lower durability when compared with bovine valves, which is consistent with the outcomes of another study that address bioprosthetic AVR (6). Thus, the aortic position is likely a crucial factor in the outcome after DVR, even more so than the mitral position.

The study discovered that the bovine and porcine groups had similar rates of diabetes mellitus (22.7% and 23.1%, respectively). Previous studies have shown that patients with diabetes have a significantly higher prevalence of cardiovascular disorders than non-diabetic patients. (20, 21). Additionally, Briand et al. (22) found that the combination of type 2 diabetes mellitus and metabolic syndrome was associated with a rapid progression of mean gradient in aortic valve replacement. Another study by Lorusso et al. (23) suggested that patients with type 2 DM who underwent bioprosthetic valve replacement (including AVR and MVR) were at higher risk of short-term and long-term mortality, and that type 2 diabetes mellitus was a strong predictor of structural valve degeneration (SVD).

After analyzing the subgroups, it was found that there was no significant difference in cardiovascular mortality risk between the bovine and porcine groups, regardless of whether the patient had diabetes. However, it was observed that patients who received a porcine valve without diabetes were at a higher risk of reoperation. This is because diabetes can accelerate SVD, leading to poor prognosis regardless of the type of tissue valve used. Patients without diabetes have a better prognosis, but it was determined that a longer survival period may necessitate a reoperation in those who received a bioprosthetic valve. Therefore, patients who received a porcine valve without diabetes were found to have a higher risk of reoperation compared with those who received a bovine valve without diabetes. However, there was no difference in cardiovascular mortality risk between the two groups.

In the bovine group, 38.9% of patients had Charlson comorbidity index (CCI) less than 2. and 37.8% of patients in the porcine group had a CCI of less than 2. Among the low CCI porcine group, there was no difference in cardiovascular mortality risk, but the reoperation risk was higher. As the CCI becomes lower, life expectancy lengthens, and the corresponding reoperation rate is expected to increase. We initially thought that a higher reoperation rate could lead to more postoperative complications and cardiovascular mortality. However, this was not the case for the low CCI porcine group. Therefore, our subgroup analysis suggests that diabetes mellitus and CCI affect the risk of reoperation between bovine and porcine groups in DVR, but do not affect the risk of cardiovascular mortality.

Similar to the diabetes mellitus and CCI mentioned previously, a longer lifespan appears to correlate with an increased likelihood of requiring a subsequent operation. The age of the recipient is a crucial determinant of SVD onset, with younger individuals being at higher risk (24). In the subgroup analysis, we observed no significant differences in the risk of reoperation between the bovine and porcine bioprosthetic valve groups within the younger age group.

Strengths and limitations

This study examined a large, nationwide population, leveraging data from NHIS, an insurance program covering nearly the entire population of South Korean. One key advantage of this dataset is its ability to enable long-term follow-up, even if patients move or switch healthcare providers. Additionally, NHID contains a wealth of health screening data, including baseline blood tests, body measurements, and self-reported questionnaires. To analyze clinical outcomes, we used propensity score matching and the IPTW method to balance baseline characteristics. Notably, the results from both methods were identical, strengthening the reliability of our clinical outcomes. This study focused on cardiovascular mortality and valve-related events related to the tissue valve type in double valve replacement surgery - a topic that has not been well studied in the past.

We defined cardiovascular outcomes as ICD I10-99, without exclusionary diagnoses. However, this means that several diagnoses unrelated to the valve operation were included. Additionally, some health screening data were missing, and ICD codes could differ depending on the healthcare provider. Self-reported questionnaires can be subjective, and we were unable to analyze certain patient data, such as echocardiographic data or detailed tissue valve product information. As a retrospective observational study, we leveraged propensity score matching to balance baseline covariates between the groups. However, unmeasured confounders could still exist and affect the study results.

Furthermore, SVD shares common risk factors with atherosclerosis, such as metabolic syndrome, diabetes mellitus, smoking, and dyslipidemia (25). However, for the subgroup analysis, we only included diabetes mellitus as a covariate, leaving out other risk factors like smoking and dyslipidemia. As a result, our subgroup analysis results could vary depending on the presence or absence of these factors.

In the subgroup analysis, chronic kidney disease and dialysis as covariates were excluded because those sample sizes were too small.

Conclusion

This nationwide retrospective observational study investigated the potential impact of different types of bioprosthetic valves in DVR on cardiovascular mortality and valve-related events, including endocarditis, reoperation, thromboembolism, and hemorrhage. These results revealed that although there was no significant difference in cardiovascular mortality, patients who received a porcine bioprosthetic valve had a higher reoperation rate compared with those who received a bovine pericardial

valve, as indicated by adjusted data using PS matching and IPTW method. Therefore, this study suggests that porcine valves may have lower durability than bovine valve.

Supplementary Table S1 Details of bioprosthetic valves

Prosthesis name	NHIS claim code
Porcine valve	
HANCOCK II VALVE	G2001003
MOSAIC TISSUE VALVE	G2001103
SJM EPIC VALVE	G2001121
EPIC SUPRA VALVE	G2001221
SJM BIOCOR PROCINE VALVE	G2001021
TORONTO SPV VALVE	G2001007
Bovine pericardial valve	
SOPRANO PERICARDIAL HEART VALVE	G2001034
CARPENTIER EDWARDS PERIMOUNT MAGNA TFX VALVE	G2001102
CARPENTIER EDWARDS PERIMOUNT VALVE	G2001002
PERICARBON MORE PERICARDIAL HEART VALVE	G2001134
AVALUS BIOPROSTHESIS	G2001203
TRIFECTA VALVE	G2001321
MITROFLOW AORTIC PERICARDIAL HEART VALVE, CROWN PRTAORTIC PERICARDIAL HEART VALVE	G2001234

Supplementary Table S2. Definition of baseline characteristic covariates

Comorbidities	ICD-10 codes	NHIS claim code	Number of diagnoses/Additional definition
Hypertension	I10-I13, I15	-	Admission or outpatient clinic ≥ 3
Diabetes mellitus	E10-E14	-	Admission or outpatient clinic ≥ 3
Dyslipidemia	E78	-	Admission or outpatient clinic ≥ 3
Atrial fibrillation	I48		Admission or outpatient clinic ≥ 1
Chronic kidney disease	N18	-	Admission or outpatient clinic ≥ 2
Dialysis	-	O701x-O708x	Admission or outpatient clinic ≥ 1
Stroke/TIA/SE	I63, I64, I67.8, I67.9, G45, I74		Admission or outpatient clinic ≥ 2
Ischemic heart disease	I20-I25	-	Admission or outpatient clinic ≥ 2
Myocardial infarction	I21-I23	-	Admission or outpatient clinic ≥ 2
Previous PCI	-	M6551, M6552, M6561-M6564, M6571, M6572	Admission or outpatient clinic ≥ 1
Congestive heart failure	I50, I42, I11.0, I13.0,	-	Admission or outpatient clinic ≥ 2

	I13.2		
Anemia	D50-D64	-	Admission or outpatient clinic ≥ 2
COPD	J44	-	Admission or outpatient clinic ≥ 2
Asthma	J45	-	Admission or outpatient clinic ≥ 2
Peripheral vascular disease	I70	-	Admission or outpatient clinic ≥ 2
Previous cardiac surgery	-	O1660, O1671, O1672, O1680, O1701-O1705, O1710, O1711, O1721-O1723, O1730, O1740, O1750, O1760, O1770, O1781-O1783, O1791, O1800, O1810, O1821-O1826, O1830, O1840, O1851, O1852, O1861, O1873-O1875, O1878, O1879, O0881-O0883, O1940, O1950, O1960, O1970, O1981, O1982, O2001, O2004, O2006, O2007, O1640, O1641, OA640, OA641, O1648, OA648, O1649, OA649, O1647, OA647, O2031-O2033	Admission ≥ 1
Previous cancer	C00-C97	-	Admission or outpatient clinic ≥ 1, and cancer registration codes (V027, V193, V194)
Concomitant procedure			
Surgical ablation		O2006	
TV repair		O1781	
CABG		O1641, O1642, O1647, OA641, OA642, OA647	

Supplementary Table S3. Definition of clinical outcomes

Comorbidities	**ICD-10 codes**	**NHIS claim code**	**Additional definition**
Outcomes			
Endocarditis	T82.7, T826 I33, I38, I39.0, I39.1, I39.4, I39.8		Until the end of follow-up Operated valve endocarditis
Reoperation	-	O1795	Until the end of follow-up Mitral valve reoperation

Thromboembolism	I63,64,74	HE101, HE201, HE501, HE102, HE502, HE135, HE235, HE535, HE136, HE236, HE301, E302, HF101, HF201, HF102, HF202, HF103, HF203, HF104, F105, HF35, HF106, HF306, HF107, HA441, HA45, HA461, HA471, HA851, HA601, HA60, HA603, HA604, HA605	Hospitalization, brain imaging (CT or MRI code), primary or subsidiary diagnosis
Hemorrhage	-		
Hemorrhagic stroke	I60-I62	HE101, HE201, HE501, HE102, HE502, HE135, HE235, HE535, HE136, HE236, HE301, E302, HF101, HF201, HF102, HF202, HF103, HF203, HF104, F105, HF35, HF106, HF306, HF107, HA441, HA45, HA461, HA471, HA851, HA601, HA60, HA603, HA604, HA605	Hospitalization, brain imaging (CT or MRI) with primary or subsidiary diagnosis
Major bleeding	I85.0, K22.1, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.8, K55.2, K57.0, K57.1-K57.5, K57.8, K57.9, K62.5, K66.1, K92.0, K92.1, K92.2, D62, H05.2, H35.6, H43.1, J94.2, M25.0, R04		Hospitalization with primary or subsidiary diagnosis, gastrointestinal bleeding or hemorrhagic event occurring at unclassified sites (e.g., extracranial, intraocular, intra-articular, hemothorax, etc.) requiring hospitalization.

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Abstract

Background: There have been several studies comparing bovine pericardial and porcine prosthetic valves for aortic position or mitral position in terms of long-term survival and valve related events. However, there has been little research on which bioprosthetic valve is better for surgical double valve replacement (DVR). This study aimed to determine whether the type of tissue valves used in DVR affected cardiovascular mortality and valve-related events.

Methods: We constructed a large nationwide cohort and enrolled adults (≥ 40 years) who underwent DVR with a bioprosthetic valve from January 2003 to December 2018, based on data from National Health Insurance Service (NHIS). The primary outcome was cardiovascular mortality. Propensity score matching was used to minimize the bias due to confounding variables and balance baseline characteristics between bovine pericardial group and porcine groups.

Results: In unadjusted analysis, cardiovascular mortality occurred in 152 (4.8%/PY) in the bovine groups, 83 (4.9%/PY) in the porcine group. All-cause mortality occurred in 238 (7.5%/PY [patient-year]) in the bovine group, 136 (8.0%/PY) in the porcine group. Which bioprosthetic valve to use did not show statistically significant differences in the all-cause mortality (hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.94-1.43] or cardiovascular mortality (HR, 1.10; 95% CI, 0.84-1.45). After PS matching, there were no significant differences between the bovine and porcine groups for cardiovascular mortality (aHR, 0.74; 95% CI, 0.50-1.07) and all-cause mortality (adjusted hazard ratio [aHR], 0.87; 95% CI, 0.65-1.17). There were no significant differences in the other valve-related events, including endocarditis (HR, 2.31; 95% CI, 0.59-9.10), thromboembolism (aHR, 0.88; 95% CI, 0.40-1.93), and hemorrhage (aHR, 1.07; 95% CI, 0.76-1.53). However, the porcine group had a higher risk of reoperation (aHR, 2.08; 95% CI, 1.10-3.94).

Conclusion: There was no significant difference in cardiovascular mortality, but reoperation was higher in the patients who received a porcine bioprosthetic valve than those who received a bovine pericardial valve.