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Long-term outcomes of mechanical versus biological valve prosthesis in native mitral valve infective endocarditis

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ABSTRACT

Objectives. To study the long-term outcomes of mitral valve replacement with mechanical or biological valve prostheses in native mitral valve infective endocarditis patients. *Desing*. We conducted a retrospective, nationwide, multicenter cohort study with patients aged ≤ 70 years who were treated with mitral valve replacement for native mitral valve infective endocarditis in Finland between 2004 and 2017. *Results*. The endpoints were all-cause mortality, ischemic stroke, major bleeding, and mitral valve reoperations. The results were adjusted for baseline features (age, gender, comorbidities, history of drug abuse, concomitant surgeries, operational urgency, and surgical center). The median follow-up time was 6.1 years. The 12-year cumulative mortality rates were 36% for mechanical prostheses and 74% for biological prostheses (adj. HR 0.40; CI: 0.17–0.91; $p = 0.03$). At follow-up, the ischemic stroke had occurred in 19% of patients with mechanical prosthesis and 33% of those with a biological prosthesis (adj. $p = 0.52$). The major bleeding rates within the 12-year follow-up period were 30% for mechanical prosthesis and 13% for a biological prosthesis (adj. $p = 0.29$). The mitral valve reoperation rates were 13% for mechanical prosthesis and 12% for a biological prosthesis (adj. $p = 0.50$). Drug abuse history did not have a significant modifying impact on the results (interaction $p = 0.51$ for mortality and ≥ 0.13 for secondary outcomes). *Conclusion*. The use of mechanical mitral valve prosthesis is associated with lower long-term mortality compared to the biological prosthesis in non-elder native mitral valve infective endocarditis patients. The routine choice of biological mitral valve prostheses for this patient group is not supported by the results.

Introduction

Patients with native valve infective endocarditis (IE) are at an increased risk of mortality and morbidity, even with current treatment options [1–3]. Although aggressive antimicrobial therapy is the cornerstone of treatment for these patients, up to 50% of these patients undergo surgical intervention [1,4,5]. In native mitral valve endocarditis, surgical correction often requires the replacement of the infected valve (mitral valve replacement, MVR) [6]. Deciding whether MVR should be performed with a mechanical or biological valve prosthesis can be difficult, despite current guidelines and recommendations [4,5,7]. There is limited data on the long-term outcomes of choosing mechanical or biological valve prostheses. Therefore, we aimed to investigate the long-term outcomes of MVR in patients with native mitral valve endocarditis.

Methods

Study design and population

All native valve IE patients aged 16–70 years who had been treated with first-time MVR surgery between January 1, 2004, and December 31, 2017, in Finland ($n = 151$) were retrospectively identified from the Care Register for Healthcare in Finland (CRHF). Surgical IE treatments performed in six hospitals (five university hospitals and one central hospital) were included in the present study. Patients with histories of prior cardiac surgery ($n = 11$) or missing mortality data ($n = 1$) were excluded. The outcomes were all-cause mortality (primary outcome), ischemic stroke, major bleeding, and mitral valve reoperation. These outcomes are described in greater detail in the Supplement. Perioperative ischemic stroke and bleeding events were excluded. The ICD-10 diagnostic codes I33, I38, and I39 were used to identify primary (85% of all patients),

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ⓘ Supplemental data for this article can be accessed here.

secondary (8%), and tertiary (7%) discharge diagnoses of IE upon surgical admission. Mortality data were obtained from the nationwide cause-of-death registry held by Statistics Finland. Comorbidities were identified in the CRHF admission records and the Finnish Cancer Registry from the beginning of the study to the end of the index admission period, as described previously [8]. The follow-up period ended on December 31, 2018. The registries used in this study are mandated by law in Finland and include full coverage of all hospital admissions, major surgical procedures, and deaths in the Finnish population. This study was approved by the National Institute for Health and Welfare of Finland (permission no. THL/2245/5.05.00/2019) and Statistics Finland (TK-53-484-20). This was a retrospective register study; thus, informed consent was not required, and the participants were not contacted. The legal basis for processing personal data was public interest and scientific research; see EU General Data Protection Regulation 2016/679 (GDPR), Articles 6(1)(e) and 9(2)(j), and Data Protection Act Sections 4 and 6.

Statistical analysis

Differences between the study groups were examined with Fisher's exact tests or t-tests, as appropriate. The outcomes were studied using the Kaplan–Meier method and Cox regression. The multivariable Cox models included age and covariables associated with the outcome at $p < 0.25$ (Supplement Table 1). Variables analyzed included gender, alcohol abuse, anemia, atrial fibrillation, cerebrovascular disease, chronic pulmonary disease, coagulopathy, dementia, diabetes, drug abuse, heart failure, hypertension, liver disease, malignancy, peripheral vascular disease, prior myocardial infarction, psychotic disorder, systemic rheumatic disease, renal failure, concomitant procedure (coronary artery bypass grafting, aortic, aortic valve, and tricuspid valve surgeries), the urgency of operation, and surgical center. Proportional hazard assumptions were evaluated using Schoenfeld residuals. Cause-specific hazard models were applied in the outcome analyses. The median follow-up time of the survivors was 6.1 years (min = 1 year, max = 12 years). The numbers of patients at risk are presented in Supplement Table 2. Association modification by recorded drug abuse history was evaluated using interaction-term analyses. The extent of unmeasured confounding was estimated using the E-value calculated for the primary outcome analysis [9]. The results are presented as means, medians, percentages, and hazard ratios (HRs) with 95% confidence intervals (CIs) or ± standard deviations (SDs). Statistical significance was inferred for p-values < 0.05. Analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 139 native mitral valves IE patients treated with MVR were included in this study. Of these patients, 63% ($n = 88$) received mechanical valve prosthesis and 37% ($n = 51$) received biological prosthesis. The mean age of all the included patients was 51 (SD = 13.9) years, 74% of the patients were men, and there were no age or gender differences between the study groups (Table 1). Patients with

Table 1. Features of native-valve infective endocarditis patients aged 16–70 years treated with mitral valve replacement surgery using mechanical or biological valve prosthesis.

Variable	All patients $n = 139$	Mechanical prosthesis $n = 88$	Biological prosthesis $n = 51$	P-value*
Age, years (SD)	50.7 (13.9)	50.2 (12.0)	51.5 (16.8)	0.63
Men	103 (74.1%)	70 (79.6%)	33 (64.7%)	0.03
Co-morbidites				
Alcohol abuse	18 (13.0%)	11 (12.5%)	7 (13.7%)	0.20
Anemia (history of)	5 (3.6%)	4 (4.6%)	1 (2.0%)	0.30
Atrial fibrillation	13 (9.4%)	8 (9.1%)	5 (9.8%)	0.23
Cerebrovascular disease	25 (18.0%)	12 (13.6%)	13 (25.5%)	0.04
Chronic pulmonary disease	9 (6.5%)	3 (3.4%)	6 (11.8%)	0.05
Coagulopathy	7 (5.0%)	4 (4.6%)	3 (5.9%)	0.29
Dementia	2 (1.4%)	0 (0.0%)	2 (3.9%)	0.13
Diabetes	14 (10.1%)	6 (6.8%)	8 (15.7%)	0.06
Drug abuse	19 (13.7%)	8 (9.1%)	11 (21.6%)	0.03
Heart failure	14 (10.1%)	8 (9.1%)	6 (11.8%)	0.20
Hypertension	28 (20.1%)	17 (19.3%)	11 (21.6%)	0.16
Liver disease	18 (13.0%)	6 (6.8%)	12 (23.5%)	0.01
Malignancy (history of)	9 (6.5%)	4 (4.6%)	5 (9.8%)	0.13
Peripheral vascular disease	3 (2.2%)	2 (2.3%)	1 (2.0%)	0.45
Prior myocardial infarction	4 (2.9%)	1 (1.1%)	3 (5.9%)	0.12
Psychotic disorder	5 (3.6%)	3 (3.4%)	2 (3.9%)	0.35
Systemic rheumatic disease	6 (4.3%)	6 (6.8%)	0 (0.0%)	0.06
Renal failure	6 (4.3%)	4 (4.6%)	2 (3.9%)	0.33
Concomitant CABG	13 (9.4%)	4 (4.6%)	9 (17.7%)	0.01
Extended surgery	38 (27.3%)	22 (25.0%)	16 (31.4%)	0.11
Aorta	2 (1.4%)	2 (2.3%)	0 (0.0%)	0.40
Aortic valve	32 (23.0%)	20 (22.7%)	12 (37.5%)	0.16
Tricuspid valve	5 (3.6%)	1 (1.1%)	4 (7.8%)	0.06
Pulmonary valve	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Emergency or urgent surgery	75 (54.0%)	42 (56.0%)	33 (64.7%)	0.02

SD: Standard deviation; CABG: coronary artery bypass grafting surgery.
*Comparing prosthetic valve types.

known histories of drug abuse were less frequently treated with a mechanical prosthesis (9% vs. 22% of all operated patients, $p = 0.03$). Cerebrovascular disease and liver disease were more frequent in the biological prosthesis group (Table 1). Surgery for IE was extended beyond the mitral valve in 27% of the patients (ascending aorta or aortic root in 1%, aortic valve in 23%, and tricuspid valve in 4%), with no significant differences between the study groups (Table 1).

Mortality

There was a total of 48 deaths (25 in the mechanical valve group) during the 12-year follow-up period. The cumulative all-cause mortality rates of all the IE patients were 8.6% at 30 days, 15% at one year, 23% at five years, and 48% at 12 years after MVR (Figure 1). The 12-year mortality rate was lower in patients treated with a mechanical prosthesis

(36%) than in patients treated with a biological prosthesis (74%; adj. HR 0.40; CI: 0.17–0.91; $p = 0.03$). The E-value was 4.50 (CI: 1.43–11.14). The association between the mechanical valve and decreased mortality was not modified by known drug abuse history (interaction $p = 0.51$). The short-term mortality rates at 30 days were 8% in the mechanical valve group and 10% in the biological valve group (adj. $p = 0.63$). The one-year mortality rates were 14% for mechanical prostheses and 18% for biological prostheses (adj. $p = 0.75$; Table 2). The underlying cause of death was an infection in 35.4% of the deceased patients (Supplement Table 3).

Ischemic stroke

At follow-up, the ischemic stroke had occurred in 20 patients ($n = 12$ in the mechanical valve group). The overall cumulative stroke rates after MVR were 10% at one year,
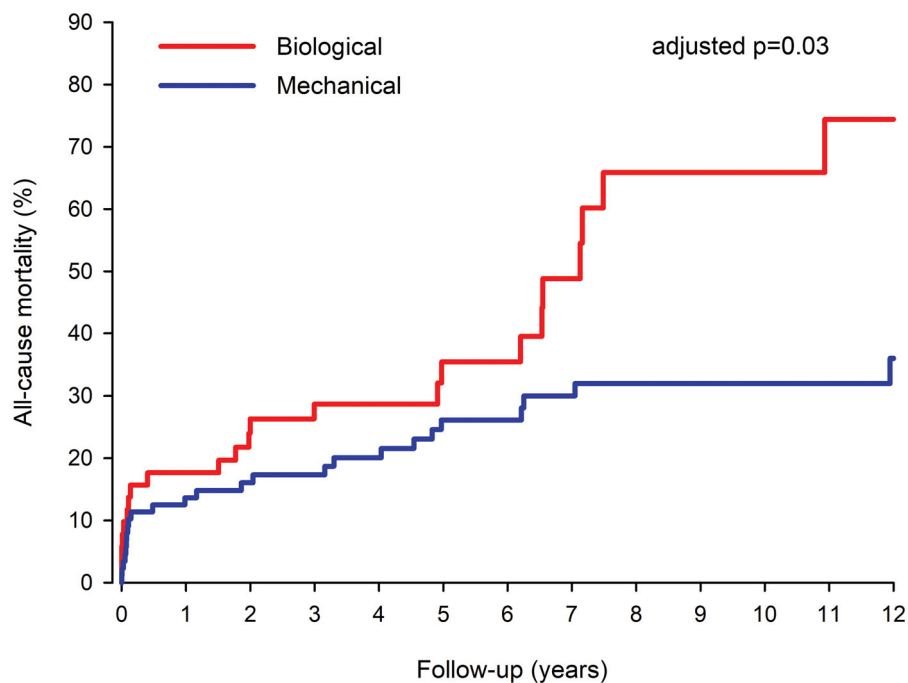

Figure 1. Cumulative all-cause mortality of native mitral valve infective endocarditis patients aged 16–70 years treated with mitral valve replacement by prosthetic valve type. Mechanical valve prosthesis in blue, and biological valve prosthesis in red.

Table 2. Hazard ratios (HR) with 95% confidence intervals (CI) for 1- and 12-year outcomes comparing mechanical and biological prosthetic valves for mitral valve replacement to patients with native-valve infective endocarditis.

	Prosthetic valve				
	Biological $n = 51$	Mechanical $n = 88$			
		Unadjusted		Adjusted	
Outcome	HR (CI)	HR (CI)	P-value	HR (CI)	P-value
Within 1 year					
All-cause mortality	1 (reference)	0.41 (0.16–1.06)	0.08	0.82 (0.24–2.78)	0.75
Ischemic stroke	1 (reference)	0.64 (0.22–1.90)	0.42	1.68 (0.41–6.93)	0.47
Major bleeding	1 (reference)	0.74 (0.17–3.30)	0.69	0.95 (0.21–4.38)	0.95
Re-operation	1 (reference)	2.21 (0.25–19.80)	0.48	5.37 (0.44–65.61)	0.19
Within 12-years					
All-cause mortality	1 (reference)	0.33 (0.17–0.62)	<0.001	0.40 (0.17–0.91)	0.03
Ischemic stroke	1 (reference)	0.74 (0.30–1.83)	0.52	1.44 (0.48–4.38)	0.52
Major bleeding	1 (reference)	1.68 (0.55–5.15)	0.36	1.84 (0.59–5.67)	0.29
Re-operation	1 (reference)	0.89 (0.26–3.08)	0.86	1.72 (0.36–8.32)	0.50

Results of univariable and multivariable analyses. Covariables used in adjusted models are presented in Supplement Table 1.
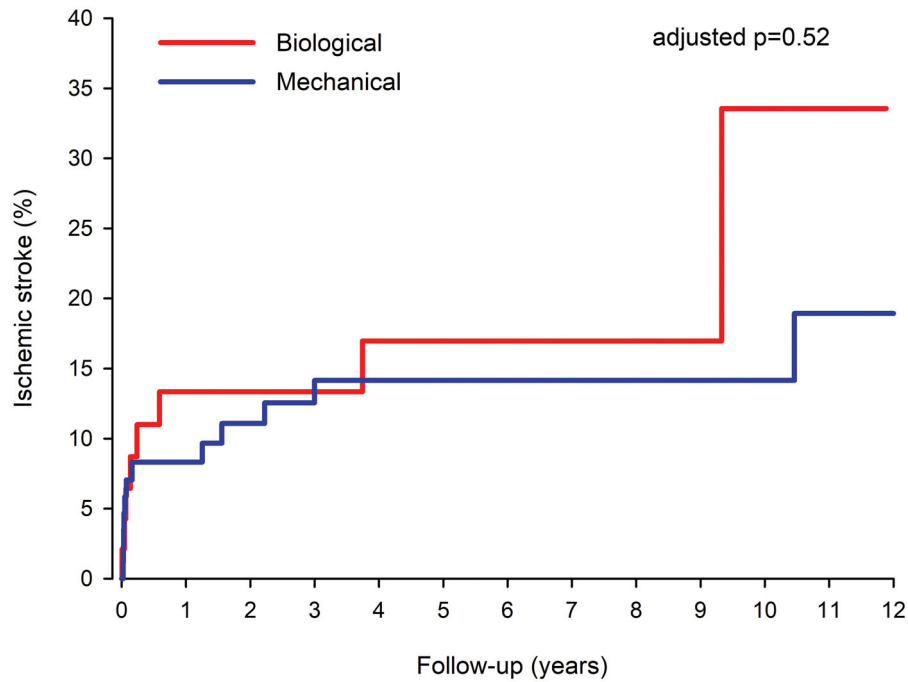
Figure 2. Cumulative occurrence of ischemic stroke in native mitral valve infective endocarditis patients aged 16–70 years treated with mitral valve replacement by prosthetic valve type. Mechanical valve prosthesis in blue, and biological valve prosthesis in red.
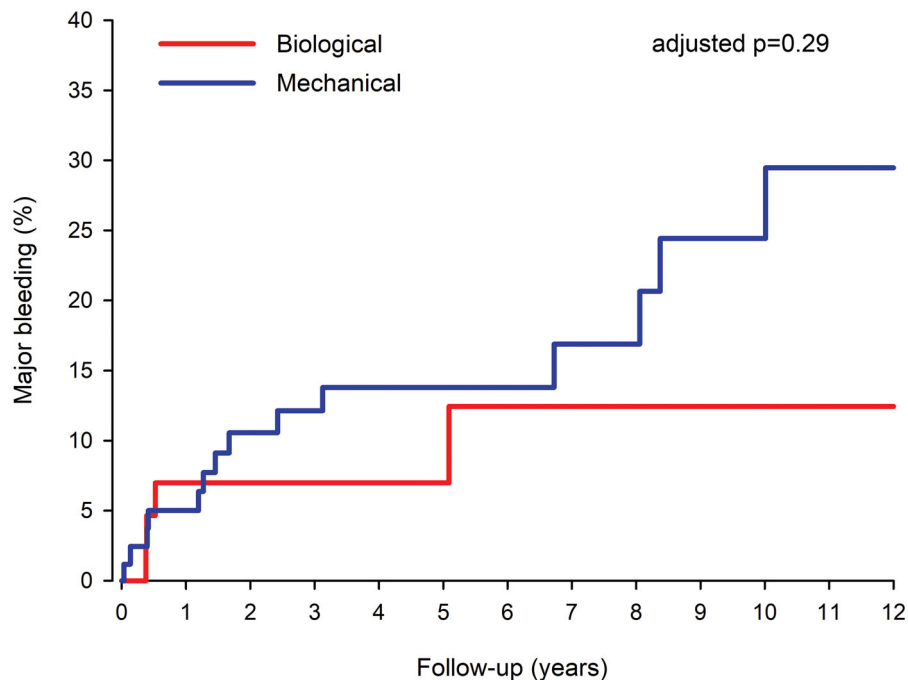

Figure 3. Cumulative occurrence of major bleeding in native mitral valve infective endocarditis patients aged 16–70 years treated with mitral valve replacement by prosthetic valve type. Mechanical valve prosthesis in blue, and biological valve prosthesis in red.

15% at five years, and 22% at 12 years. Of the IE patients who were treated with mechanical mitral valve prosthesis, 8% had experienced strokes one year after primary MVR (Figure 2). The one-year ischemic stroke rate was 13% among patients with a biological prosthesis (Table 2). At 12 years, the cumulative stroke rates were 19% in patients with mechanical prosthesis and 34% in patients with a biological prosthesis (adj. HR 1.44; CI: 0.48–4.38; $p = 0.52$). This association was not modified by drug abuse history (interaction $p = 0.13$). The fatal ischemic stroke rates within the 12-year follow-up period were 1% in the mechanical valve group and 5% in the biological valve group (adj. $p = 0.76$).

Major bleeding

The major bleeding event occurred in 18 patients ($n = 14$ in the mechanical valve group) during the follow-up. The cumulative major bleeding rates of all the operated IE patients were 6% at one year, 11% at five years, and 26% at 12 years after the MVR operation (Figure 3). The major

bleeding rates at one year were 5% in the mechanical valve group and 7% in the biological valve group (Table 2). The long-term major bleeding rates were 30% for patients who received mechanical valves and 13% for patients who received biological valves (adj. HR 1.84; CI: 0.59–5.67; $p = 0.29$). Drug abuse history did not modify these results (interaction $p = 0.78$). Of the 18 first-time major bleeding events during the follow-up period, 22% were intracranial, 22% were gastrointestinal, and 51% were located elsewhere, with no differences in bleeding site distribution between the study groups ($p = 0.16$). Fatal bleeding occurred in 2% of the patients with biological prosthesis and in none of the patients with a mechanical prosthesis (adj. $p = 0.37$).

Mitral valve reoperation

Mitral valve reoperation had been performed on 4% of all IE patients at one year and 13% of the patients ($n = 11$) at 12 years after primary MVR. The reoperation rates were 5% in the mechanical valve group and 2% in the biological valve group one year after the primary operation. At the end of the 12-year follow-up period, the reoperation rates were 13% for mechanical prostheses and 12% for biological prostheses (adj. $p = 0.50$). These results were not modified by drug abuse history (interaction $p = 0.58$). The indication for reoperation was prosthetic valve infection in 57.1% of the mechanical valve group and 75.0% of the biological valve group ($p = 0.42$); other indications for reoperation included prosthetic valve deterioration, malfunction, and insufficiency.

Discussion

This retrospective, nationwide, population-based cohort study found that in patients who underwent mitral valve replacement for native valve IE, biological valves were associated with increased long-term mortality. Deciding between mechanical and biological valve prostheses for patients requiring MVR can be challenging. According to current guidelines, a mechanical mitral valve prosthesis should be considered for a patient under 65 years of age if there is no contraindication to long-term anticoagulation, taking into account the patient's medical history and personal preference [7,10]. However, there are no specific guidelines to support a decision when selecting a prosthesis type for surgical IE treatment; rather, this judgement is made individually according to general guidelines and the patient's overall medical status and lifestyle [4,5,7,10]. In experienced hands, mitral valve repair with good long-term results can be feasible in cases of native mitral valve IE; however, IE patients often require infected valve replacement [6,11].

A recent meta-analysis of over 20,000 patients by Yanagawa et al. showed that mechanical mitral valve prostheses were associated with lower long-term mortality in patients under 70 years of age compared to bioprostheses [12]. Additionally, a propensity score-matched analysis by Hu et al. showed lower long-term mortality after MVR with mechanical prostheses compared to bioprostheses in IE

patients aged 50–69 years [13]. On the other hand, a retrospective study by Toyoda et al. indicated no significant difference in the rates of IE recurrence between mechanical and biological valve prostheses 12 years after MVR [14]. Instead, a recent meta-analysis of more than 40,000 patients indicated that a higher rate of recurrence was associated with left-sided IE with bioprostheses in both the aortic and mitral valves [15]. The present results are in line with these findings, as they do not encourage the systematic use of bioprostheses in the surgical treatment of native mitral valve IE.

The present data indicated that patients with a known history of drug abuse were more frequently treated with biological valve prosthesis. Although drug abuse is associated with higher mortality [16], known drug abuse did not significantly modify the association between survival and valve type in the interaction analysis. However, there was no long-term difference in mitral valve-related reoperation rates between the study groups; this may partly explain the survival difference between patients with different valve types.

Although the numbers of ischemic strokes and major bleeding events that occurred during the long-term follow-up period were remarkable, no significant differences in these were found between the study groups. Recent reports have indicated that patients with IE are at an increased risk of both ischemic stroke and bleeding events [17–19]. Although no medication usage data were available for the present study, the results indicated that the oral anticoagulant required for a mechanical valve prosthesis does not necessarily provide sufficient protection from ischemic stroke. On the other hand, oral anticoagulant use with a mechanical valve did not appear to significantly increase the risk of major bleeding compared to the biological valve group during the follow-up period. It remains to be determined whether this finding would persist with a longer follow-up period.

This study had several limitations. The registries used for data collection are considered reliable; however, sources of bias still might have been present [20]. Coding and reporting errors could have been made, and the diagnoses were made by the treating clinicians. A previous validation study showed that the IE diagnoses in the CRHF registry have 96.8% specificity for the Duke criteria [2]. Interpretation of the present results could have been limited by the retrospective nature of the study, and unrecognized residual cofounders might have had an impact on the results. The retrospective design of this register study did not allow access to more detailed in-hospital or operative data (e.g. regarding left ventricle ejection fraction, medical therapy, microbiology, or the EuroSCORE). Non-recognized residual confounders are possible. The observed HR of 0.40 for all-cause mortality could be explained away by unmeasured confounders associated with both the prosthetic valve type and death by a risk ratio of 5.0-fold each, above and beyond the measured confounders; however, a weaker confounding could not do so [9]. Despite the nationwide design and the 14-year catchment period, the rarity of the studied condition

resulted in a relatively small number of included patients and thus limited the power of the study.

In conclusion, the findings of this study suggest that patients with native mitral valve IE undergoing MVR have better long-term survival with mechanical valve prosthesis than with bioprosthesis. The results do not support the routine choice of biological mitral valve prostheses for the surgical treatment of mitral valve IE.

Disclosure statement

Funding

Data availability statement

The data and study materials will be made available to those who fulfill requirements of applicable Finnish laws and regulations for purposes of reproducing the results or replicating the procedure (from the corresponding author).

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