Interactive CardioVascular and Thoracic Surgery 29 (2019) 386–392
doi:10.1093/icvts/ivz122 Advance Access publication 23 May 2019

ORIGINAL ARTICLE

Cite this article as: Kytö V, Ahtela E, Sipilä J, Rautava P, Gunn J. Mechanical versus biological valve prosthesis for surgical aortic valve replacement in patients with infective endocarditis. Interact CardioVasc Thorac Surg 2019;29:386–92.

Mechanical versus biological valve prosthesis for surgical aortic valve replacement in patients with infective endocarditis

Ville Kytö[a,b,c,*], Elina Ahtela [a,d], Jussi Sipilä[e,f], Päivi Rautava [g,h] and Jarmo Gunn [a]

[a] Heart Center, Turku University Hospital, University of Turku, Turku, Finland
[b] Centre for Population Health Research, Turku University Hospital, University of Turku, Turku, Finland
[c] Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland
[d] Department of Infectious Diseases, Turku University Hospital, University of Turku, Turku, Finland
[e] Siun sote, North Karelia Central Hospital, Joensuu, Finland
[f] Department of Neurology, University of Turku, Turku, Finland
[g] Department of Public Health, University of Turku, Turku, Finland
[h] Turku Clinical Research Centre, Turku University Hospital, Turku, Finland

* Corresponding author. Heart Center, Turku University Hospital, PO Box 52, 20521 Turku, Finland. Tel: +358-2-3130000; e-mail: ville.kyto@utu.fi (V. Kytö).

Received 5 February 2019; received in revised form 3 April 2019; accepted 17 April 2019

Key question

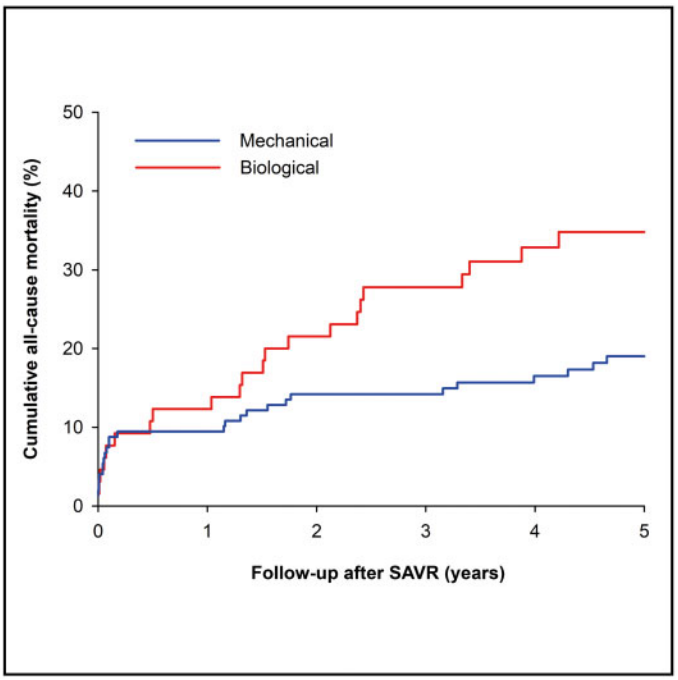
What is the optimal choice of valve prosthesis for surgical aortic valve replacement in patients with infective endocarditis (IE)?

Key findings

Mechanical valves were associated with a lower 5-year mortality rate compared to bioprostheses (19% vs 35%).

Take-home message

Results do not support routine choice of a biological aortic valve prosthesis in patients with IE aged ≤70 years.



Abstract

OBJECTIVES: The optimal choice of valve prosthesis in surgical aortic valve replacement for infective endocarditis (IE) is controversial. We studied outcomes after mechanical versus biological prosthetic valve surgical aortic valve replacement in IE patients.

METHODS: All patients with native-valve IE aged 16–70 years undergoing mechanical or biological surgical aortic valve replacement in Finland, between 2004 and 2014, were retrospectively studied ($n = 213$). Outcomes were all-cause mortality, ischaemic stroke, major bleeding and aortic valve reoperation at 1 year and 5 years. Results were adjusted for baseline features (age, sex, comorbidity burden, atrial fibrillation, valvular stenosis, concomitant coronary artery bypass grafting, extension, urgency, year and centre of operation). Median follow-up was 5 years.

Presented at the 99th Annual Meeting of the American Association for Thoracic Surgery, Toronto, ON, Canada, 6 May 2019.

RESULTS: The 5-year mortality rate was 19.0% with mechanical prostheses and 34.8% with biological prostheses [hazard ratio (HR) 0.47, 95% confidence interval (CI) 0.23–0.92; $P = 0.03$]. Ischaemic stroke rates were 8.3% with mechanical prostheses and 16.8% with biological prostheses at 5 years (HR 0.21, CI 0.06–0.79; $P = 0.01$). Results were comparable in patients aged 16–59 and 60–70 years (interaction $P = 0.84$). Major bleeding within 5 years was similar between mechanical (11.3%) and biological valve (13.4%) groups ($P = 0.95$) with comparable rates of both gastrointestinal and intracranial bleeds. Reoperation rates at 5 years were 5.0% for mechanical prostheses and 9.2% for biological prostheses ($P = 0.14$). The 1-year ischaemic stroke rate was lower with mechanical prostheses (3.6% vs 11.6%, $P = 0.03$), whereas mortality, major bleeding and reoperation rates were similar between groups.

CONCLUSIONS: The use of mechanical aortic valve is associated with lower mid-term mortality compared to biological prosthesis in patients with native-valve IE aged ≤70 years. Our results do not support the routine choice of a biological aortic valve prosthesis in this patient group.

Keywords: Endocarditis • Surgical aortic valve replacement • Mechanical valve • Bioprosthesis

INTRODUCTION

Infective endocarditis (IE) is a life-threatening disease associated with high mortality and morbidity. Surgical aortic valve replacement (SAVR) is the cornerstone of aortic valve IE treatment in the presence of severe valvular destruction or large vegetation [1]. The application of foreign material is recommended to be kept to a minimum in SAVR for IE [2]. The choice of prosthetic valve in SAVR for IE patients is, however, controversial. Studies comparing mechanical and biological prostheses in IE patients are few. Accordingly, guidelines give no specific recommendations for prosthesis selection in IE patients [1–4]. For SAVR patients in general, biological prosthesis is recommended in older patients, mechanical in younger and either in middle-aged with special reference to patient characteristics [3]. The choice of a prosthesis in middle-aged SAVR patients is also controversial with some studies reporting lower mortality with mechanical valve [5, 6], whereas others report similar mortality between prosthesis types [7, 8]. The use of a biological valve prosthesis for SAVR is, however, increasing in non-elderly SAVR patients in general [9], and also in IE patients undergoing valvular surgery [10].

To clarify the choice of aortic valve prosthesis in native-valve IE, we compared outcomes with mechanical or biological prostheses in a nationwide, population-based study of patients with IE aged ≤70 years old treated with SAVR in Finland.

METHODS

Study design and outcomes

All patients aged 16–70 years with IE, who underwent first-time aortic valve replacement surgery with a mechanical or biological prosthetic valve in Finland, between 1 January 2004 and 31 December 2014, were eligible for this nationwide, population-based study. The primary outcome of interest was 5-year all-cause mortality after the primary operation. Secondary outcomes were 5-year occurrence of non-perioperative ischaemic stroke, major bleeding and aortic valve reoperation. In addition, interim analyses at 1-year follow-up were performed. Outcome definitions are described in the Supplementary Material, Methods.

Study population

All IE patients ($n = 226$) aged 16–70 years, who underwent first-time aortic valve replacement surgery, between 1 January 2004 and 31 December 2014, were retrospectively identified from the Care Register for Healthcare in Finland (CRHF) registry held by The National Institute for Health and Welfare of Finland. This obligatory nationwide registry includes data on all hospital admissions in Finland. Cardiac surgery for endocarditis was performed in 6 public hospitals (5 university hospitals and 1 central hospital). Patients with prior valvular replacement surgery ($n = 12$) and a patient who underwent surgery with a homograft were excluded (Fig. 1). Mortality data was obtained from the nationwide and obligatory cause of death registry held by Statistics Finland. Mortality follow-up ended 5 years after the SAVR operation or on 31 December 2016, whichever came first. The National Institute for Health and Welfare of Finland (permissions no: THL/143/5.05.00/2015 and THL/1569/5.05.00/2016) and Statistics Finland (permission no: TK53-1410-15) approved the study.

Statistical analysis

Differences between groups were studied by the χ^2 test or *t*-test as appropriate. Follow-up was calculated for survivors. Comorbidity burden was evaluated by the Charlson comorbidity index (CCI) calculated according to a previously used algorithm [11]. Outcomes were studied using the Kaplan–Meier method and the Cox regression. Proportional hazard assumptions were evaluated using Schoenfeld residuals. Cox models were adjusted for baseline characteristics (age, sex, CCI, atrial fibrillation, aortic stenosis, concomitant coronary artery bypass grafting, extension of surgery to aorta or other valves, emergency/urgent operation, surgical centre) and stratified by the year of surgery. Results of unadjusted analyses are presented in the Supplementary Material, Table S1. Mortality was accounted for in analyses of secondary outcomes. Effect modification by age, was studied between patients aged 16–59 and 60–70 years (based on the European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines suggesting mechanical prosthesis for general SAVR patients aged <60 years [4]) using interaction-term analyses. Results are given as the mean, median, percentage or hazard ratio (HR) with 95% confidence interval (CI) or ± standard deviation. A *P*-value <0.05 was considered statistically significant. Analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The study included 213 IE patients with first-time SAVR. Of these patients 69.5% ($n = 148$) received a mechanical valve prosthesis and 30.5% ($n = 65$) received a biological valve prosthesis. Mean

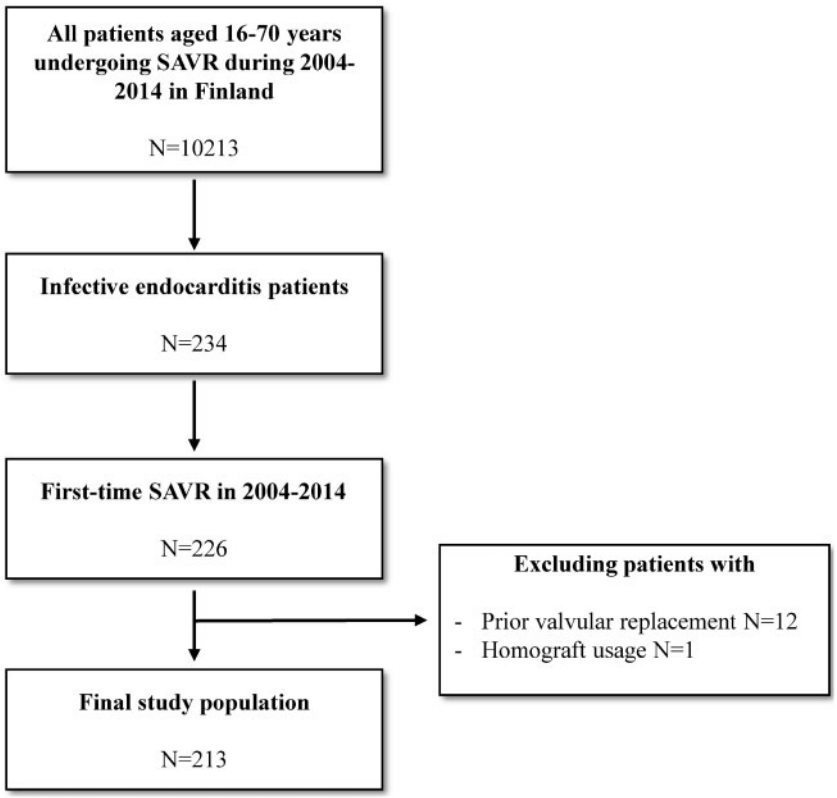


Figure 1: Study population flow-chart. SAVR: surgical aortic valve replacement.

Table 1: Features of infective endocarditis patients aged 16–70 years treated with first-time surgical aortic valve replacement using mechanical or biological valve prosthesis

Variables	All patients (*n* = 213)	Mechanical prosthesis (*n* = 148)	Biological prosthesis (*n* = 65)	*P*-value*
Age (years), mean ± SD	49.1 ± 13.8	47.1 ± 13.0	53.7 ± 14.7	0.001
Male gender, *n* (%)	177 (83.1)	130 (87.8)	47 (72.3)	0.005
Charlson comorbidity index score, *n* (%)				0.20
0	138 (64.8)	101 (68.2)	37 (56.9)	
1	45 (21.1)	31 (21.0)	14 (21.5)	
2	22 (10.3)	12 (8.1)	10 (15.4)	
≥3	8 (3.8)	4 (2.7)	4 (6.2)	
Atrial fibrillation, *n* (%)	21 (9.9)	14 (9.5)	7 (10.8)	0.77
Aortic stenosis, *n* (%)	45 (21.1)	29 (19.6)	16 (24.6)	0.41
Concomitant CABG, *n* (%)	12 (5.6)	7 (4.7)	5 (7.7)	0.39
Concomitant aortic surgery, *n* (%)	12 (6.1)	11 (7.4)	2 (3.1)	0.22
Concomitant surgery of other valves, *n* (%)	38 (17.8)	28 (18.9)	10 (15.4)	0.54
Mitral valve	35 (16.4)	27 (18.2)	8 (12.3)	
Tricuspid valve	3 (1.4)	1 (0.7)	2 (3.1)	
Emergency or urgent surgery, *n* (%)	70 (32.9)	46 (31.2)	24 (36.9)	0.40

*Comparing prosthetic valve types.

CABG: coronary artery bypass grafting; SD: standard deviation.

follow-up for mortality was 4.6 ± 0.7 years (median 1825 days) with no difference between groups (4.6 ± 0.7 years in both groups, $P = 0.683$). Patients treated with a mechanical prosthesis were younger compared to those treated with a biological valve (Table 1). Mechanical prosthesis was more commonly used in male patients. Mean age of men (49.1 ± 13.9 years) and women (49.4 ± 13.6 years) was similar ($P = 0.901$). The comorbidity burden (CCI), atrial fibrillation rate, rate of aortic stenosis and proportion of emergency/urgent operations were comparable between different valve prosthesis groups (Table 1). Surgery was extended beyond the aortic valve in 22.5% of patients (ascending aorta or aortic root in 6.1%, mitral valve in 16.4% and tricuspid valve in 1.4%) with no difference between mechanical and biological prosthesis groups (Table 1).

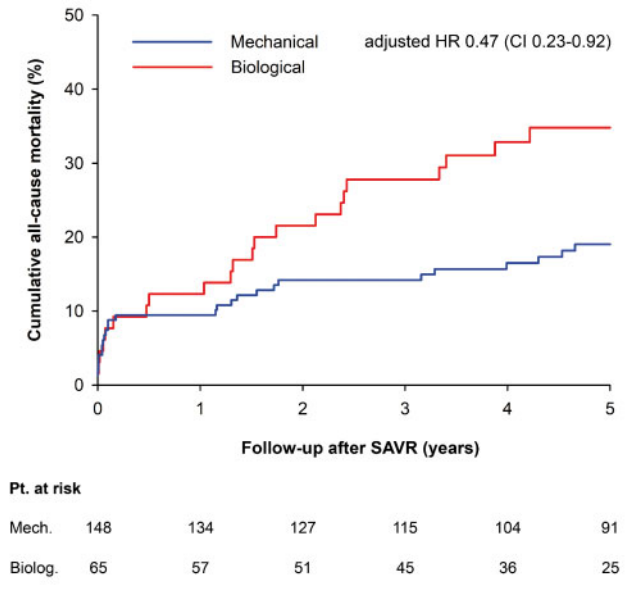


Figure 2: All-cause mortality of infective endocarditis patients aged 16–70 years treated with first-time SAVR by prosthetic valve type. Mechanical valve prosthesis in blue and biological valve prosthesis in red. CI: 95% confidence interval; HR: hazard ratio; SAVR: surgical aortic valve replacement. Please note the scale in vertical axis.

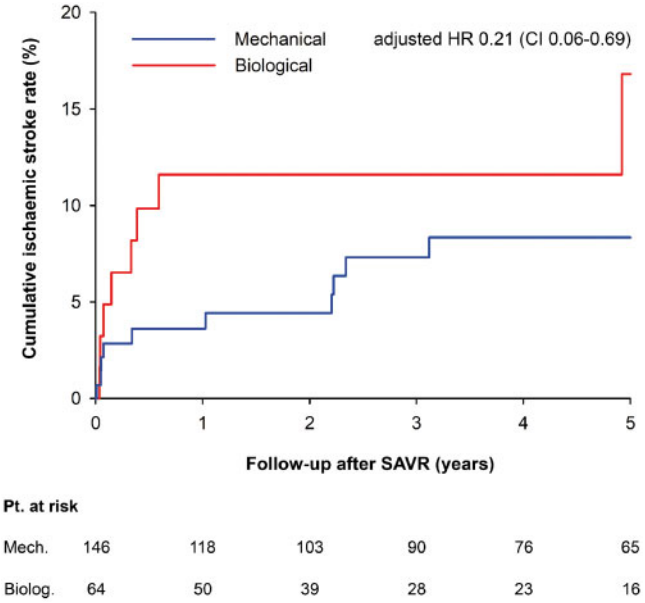


Figure 3: Ischaemic stroke occurrence among infective endocarditis patients aged 16–70 years treated with first-time SAVR by prosthetic valve type. Mechanical valve prosthesis in blue and biological valve prosthesis in red. CI: 95% confidence interval; HR: hazard ratio; SAVR: surgical aortic valve replacement. Please note the scale in vertical axis.

Mortality

All-cause mortality among all IE patients after SAVR was 7.5% at 30 days, 10.3% at 1 year and 23.9% at 5 years after SAVR (Fig. 2). Five-year mortality was lower among patients treated with a mechanical prosthesis (19.0%) than in those treated with a biological prosthesis (34.8%) (HR 0.47, CI 0.23–0.92; $P = 0.03$). Association was not modified by age (16–59 vs 60–70 years; interaction $P = 0.84$). Short-term mortality at 30 days did not differ between mechanical (7.4%) and biological valve (7.7%) patients. One-year mortality was also similar between groups (9.5% in the mechanical valve and 12.3% in the biological valve group; HR 1.13, CI 0.37–3.44; $P = 0.84$).

Ischaemic stroke

The ischaemic stroke rate after discharge from primary SAVR was 6.1% at 1 year and 10.6% at 5-year follow-up. Of the IE patients treated with a biological aortic valve prosthesis, 11.6% had experienced a stroke by the 1-year follow-up after primary AVR (Fig. 3). The 1-year ischaemic stroke rate was 3.6% among patients with mechanical prosthesis (HR 0.21 vs biological prosthesis, CI 0.05–0.87; $P = 0.03$). At 5-year follow-up, the stroke rate was 8.3% for patients with a mechanical prosthesis and 16.8% for patients with a biological prosthesis (HR 0.21, CI 0.06–0.69; $P = 0.01$). The association was not modified by age, 16–59 vs 60–70 years (interaction $P = 0.99$). The fatal ischaemic stroke rate was 1.0% at 1 year and 5 years, with similar rates between groups ($P = 1.000$).

Major bleeding

The cumulative major bleeding rate in IE patients was 5.3% at 1 year and 12.3% at 5 years after discharge from primary SAVR operation (Fig. 4). Major bleeding rates were similar in patients with a mechanical and biological prosthesis at 1 year (3.8% vs 9.0%, respectively; HR 0.96, CI 0.22–4.22; $P = 0.95$) and at 5 years follow-up (11.5% vs 13.5%, respectively; HR 1.09, CI 0.36–3.37; $P = 0.88$) with no effect modification by age group (16–59 vs 60–70 years, interaction $P = 0.80$). Major bleeding was most commonly gastrointestinal (57.9% of bleeds). Major gastrointestinal-bleeding rate was 8.7% with mechanical prosthesis and 4.3% with biological prosthesis, within 5-year follow-up (HR 2.62, CI 0.39–17.81; $P = 0.32$). Of all major bleeds, 15.8% were intracranial with similar 5-year rates between mechanical (2.1%) and biological (1.9%) prostheses ($P = 0.52$). Fatal bleeding was rare (1- and 5-year rate 0.7%), with no difference between study groups ($P = 1.00$).

Aortic valve reoperation

Aortic valve reoperation was performed to 3.7% of all IE patients by 1 year and to 6.1% of patients 5 years after SAVR. The reoperation rate was 3.7% for both mechanical and biological valves at 1 year after primary operation (Fig. 5). At 5-year follow-up, the reoperation rate was 5.0% for mechanical and 9.2% for biological prostheses (HR 0.11, CI 0.01–2.05; $P = 0.14$). The results did not differ by age (60–70 years of age vs <60 years, interaction $P = 0.11$).

DISCUSSION

This population-based study compared mid-term outcomes between mechanical and biological aortic valve prosthesis in patients with IE aged ≤70 years undergoing SAVR and demonstrated higher mortality and ischaemic stroke rates in patients treated with biological prostheses.

European guidelines recommend the use of a biological prosthesis for SAVR in patients aged >65 years, a mechanical

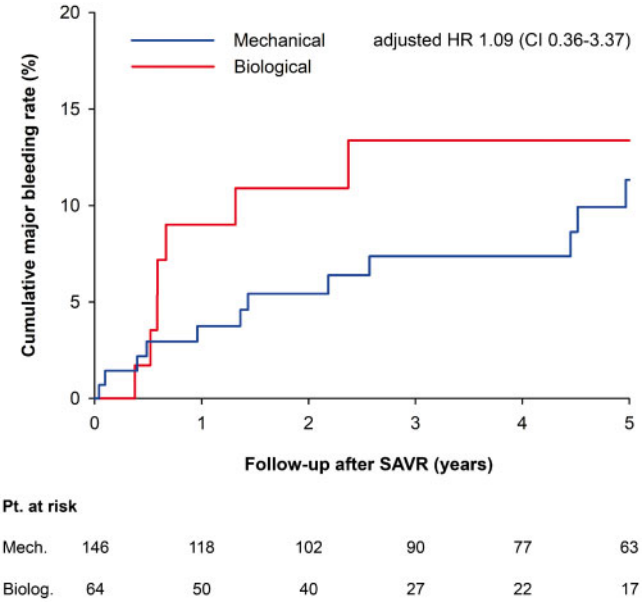


Figure 4: Occurrence of major bleeding among infective endocarditis patients aged 16–70 years treated with first-time SAVR by prosthetic valve type. Mechanical valve prosthesis in blue and biological valve prosthesis in red. CI: 95% confidence interval; HR: hazard ratio; SAVR: surgical aortic valve replacement. Please note the scale in vertical axis.

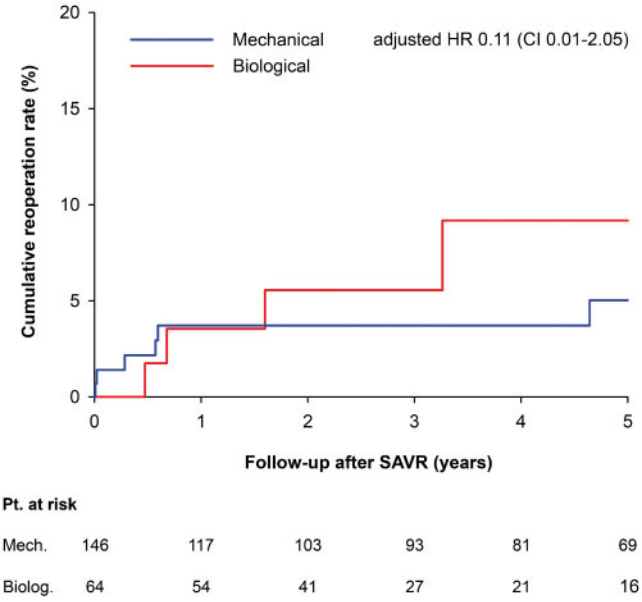


Figure 5: Aortic valve reoperation rate among infective endocarditis patients aged 16–70 years treated with first-time SAVR by prosthetic valve type. Mechanical valve prosthesis in blue and biological valve prosthesis in red. CI: 95% confidence interval; HR: hazard ratio; SAVR: surgical aortic valve replacement. Please note the scale in vertical axis.

prosthesis in those aged <60 years and either type for those aged 60–65 years old [4]. Most recent US guidelines suggest biological prosthesis for SAVR in patients aged >70 years, a mechanical prosthesis in patients aged <50 years and either prosthesis type in patients aged 50–70 years [3]. Patient-specific factors, especially those related to risks of long-term anticoagulation, should be weighted in the selection process. Comparative data on outcomes between prosthetic aortic valve types in IE patients are limited. Thus, there exists no specific guideline guidance for prosthesis selection in IE patients [1–4]. The usage of a biological valve prosthesis for IE surgery is, however, increasing [10] in general, and consequently also in specific population subsets such as IE patients.

The impact of the valve type on long-term outcomes after SAVR has been studied in 3 randomized trials, [8, 12, 13] which however, excluded all patients with active endocarditis. The Veterans Administration [12] and Edinburgh [13] trials compared mechanical Björk–Shiley and biological prostheses in adult patients of all ages. The 15-year mortality was significantly lower in patients with mechanical prostheses compared to those with biological prostheses (66% vs 79%) in the US study [12]. In the UK trial, there was no 20-year survival difference between valve types in all patients although the prognosis was better with a mechanical prosthesis in the absence of reoperation during follow-up [13]. In a more modern setting, Stassano *et al.* [8] compared bileaflet mechanical and biological prostheses after SAVR in Italian patients aged 55–70 years. Mortality was found to be comparable between mechanical and biological prostheses (31% vs 28%) during a mean follow-up of 9 years [8].

Observational studies of SAVR patients have reported improved survival with the mechanical valve after SAVR in non-elderly patients. Glaser *et al.* [5] found lower 15-year mortality with mechanical prostheses (50% vs 59%) in Swedish patients aged 50–69 years. The 15-year mortality was also lower with mechanical valves (26% vs 31%) in patients aged 45–54 years but did not significantly differ in those aged 55–64 years (32% vs 36%), in a US study of Goldstone *et al.* [14]. In another US study of patients aged 50–70 years, Brown *et al.* [6] found a lower 10-year mortality with mechanical prostheses (32% vs 50%). Similarly, Brennan *et al.* [15] found mechanical prostheses to be associated with lower 12-year mortality on SAVR patients aged 65–69 years. Chiang *et al.* [7], however, found no difference in 15-year mortality between valve types (39% with biological and 38% with mechanical) in a study of US SAVR patients aged 50–69 years. The incidence of endocarditis varied between <1% and 8% of SAVR patients in these studies [5, 14].

Studies comparing prosthetic valves in SAVR for endocarditis are scarce. A recent study of 1844 IE patients by Toyoda *et al.* [16] found no difference in 12-year survival after SAVR between mechanical and biological prostheses (mortality 52% vs 57%), when adjusted for patient characteristics. The study population differed, however, somewhat from the current study, as e.g. patients with concomitant surgery of other heart valves were excluded and there was no upper limit for age [16]. In another recent study of 801 IE patients of any valve involvement (50% isolated aortic valve), Said *et al.* [17] found 5-year mortality to be 58% with a biological valve prosthesis and 25% with a mechanical valve prosthesis, but long-term mortality was comparable after adjustment (HR 0.84, CI 0.65–1.09). We, however, found significantly lower 5-year mortality with mechanical prosthesis (19% vs 35%) with HR of 0.47 (CI 0.23–0.92). Notably, the association was not modified by age (<60 vs 60–70 years). Nguyen *et al.* [18] found a comparably lower 5-year mortality with mechanical prosthesis after SAVR for IE (HR 0.42, CI 0.19–0.92) among 140 French patients aged ≤65 years although mortality rates were higher compared to our study (58% with biological prosthesis and 24% with mechanical prosthesis). In our study, the mortality risk between prosthetic types started to differ after the first year following SAVR. This is in agreement with previous findings of comparable adjusted short-term survival between mechanical and biological prostheses after SAVR for IE [10].

Previous studies of general SAVR patients have found no difference in the stroke risk between mechanical and biological valve prostheses [6–8, 19]. IE increases the risk of stroke, with the 1-year stroke risk of aortic valve IE reported to be 9% with a majority of cerebrovascular accidents occurring early [20]. After SAVR for IE, the early postoperative stroke rate is previously found to be 3% with no difference between prosthesis types [10]. We found a significantly higher ischaemic stroke rate with biological prosthesis (17% vs 8%) during the 5-year follow-up after postoperative discharge. It is, however, unknown if this is related to increased prosthetic valve thrombogenicity or undetected atrial fibrillation in patients without anticoagulation, or other factors [21].

Mechanical valve prostheses have been associated with increased bleeding in both middle-aged patients [7, 14, 19] and elderly SAVR patients [15]. We found, however, no difference in occurrence of major bleeding, gastrointestinal or intracranial bleedings between mechanical and biological valves in non-elderly IE patients. This finding may be, in part, related to the universal health care system and consequently relatively good and uniform nationwide warfarin treatment balance in Finland [22]. It, however, appears that, in general, the long-term risk of major bleeding with anticoagulation should not be the major determinant for prosthesis selection in SAVR to non-elderly patients with IE.

The lifespan of a biological aortic valve prosthesis is estimated to be approximately 15 years in elderly patients [23, 24]. However, in younger patients, the risk of earlier degeneration of a biological valve prosthesis is higher due to a more pronounced immunological response and enhanced valvular calcification [25, 26], although the exact aetiology remains to be completely elucidated. Higher reoperation rates with biological prostheses in middle-aged patients have been shown in previous randomized [8] and observational [5, 7, 14] studies on general SAVR patients. Reoperation rates with biological prosthesis are also higher compared to mechanical prosthesis in IE patients aged <50 years but not in older patients treated with surgery [16]. We found no difference in mid-term reoperation rates in IE patients with a mean age of 49 years.

Limitations

There are limitations in this study. The retrospective design with no access to more detailed patient level clinical information, e.g. inflammatory data, microbiological data and data on intravenous illegal drug use is a major limitation. A previous investigation, however, found no difference in survival results for mechanical versus bioprosthesis after valvular surgery for IE between intravenous drug users and non-users [16]. Treating physicians, in this study, were responsible for diagnosis and operational codes and errors are possible, but it is unlikely that these limitations would have a different impact on the 2 study groups. End points and comorbidities were defined according to previous studies [11, 27] and study data were based on mandatory nationwide registries [28]. Specificity of ICD-10 codes for IE has, however, been found to be 100% in a study with a setting similar to ours [29]. Multivariate modelling was used to control for differences between study groups, although residual bias is possible. It is also possible that additional, non-recognized confounders may influence prosthesis selection and outcome. Randomized studies comparing mechanical and biological valve prostheses for SAVR in non-elderly IE patients are suggested. Furthermore, pathophysiological mechanisms of adverse outcomes after SAVR for IE require further studies.

CONCLUSION

In conclusion, this population-based study found lower mid-term mortality and ischaemic stroke rates with mechanical prostheses compared to biological prostheses after SAVR in native-valve IE patients aged ≤70 years. These results do not support the routine choice of a biological aortic valve prosthesis in non-elderly patients with native-valve IE undergoing SAVR.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Funding

This work was supported by the Finnish Cardiac Society, the Finnish Cultural Foundation and the Governmental VTR-funding.

Conflict of interest: Jarmo Gunn: Unrestricted research grant from Vifor Pharma. All other authors declared no conflict of interest.

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