Long-term Outcomes of Mechanical Vs Biologic Aortic Valve Prosthesis in Patients Older Than 70 Years

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Background. **Biologic prostheses are preferred for surgical aortic valve replacement (SAVR) in patients more than 70 years of age in clinical practice. This study investigated differences in long-term outcomes between SAVR-treated patients more than 70 years of age who received mechanical or biologic prosthetic valves.**

Methods. **All patients (excluding those with endocarditis) who were more than 70 years of age and who underwent isolated first-time SAVR (with or without coronary artery bypass grafting) in Finland between 2004 and 2014 were retrospectively studied (n = 4227). Propensity score matching (1:3) was used to account for baseline differences (n = 296 with mechanical prostheses and n = 888 with biologic prostheses). Outcomes were 10-year survival, major bleeding (all, gastrointestinal, intracranial), ischemic stroke, infective endocarditis, and aortic valve reoperation. Mean age was 75.8 years, and mean follow-up was 8.3 years.**

Results. **Survival at 10 years was 46.1% with mechanical prostheses and 57.8% with biologic prostheses (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.21 to 1.80; $P < .001$; number needed to harm = 7.0). The 10-year major bleeding rates were 37.0% with mechanical valves and 18.8% with biologic valves (HR, 1.77; 95% CI, 1.25 to 2.49; $P = .001$; number needed to harm = 7.4). Both gastrointestinal bleeding (26.5% vs 8.9%; HR, 2.63; 95% CI, 1.63 to 4.23; $P < .001$) and intracranial bleeding (8.8% vs 6.0%; HR, 2.12; 95% CI, 1.09 to 4.15; $P = .028$) were significantly more frequent with mechanical valve prosthesis. Occurrence of ischemic stroke (18.9% with mechanical prosthesis vs 16.1% with biologic prosthesis; $P = .341$), infective endocarditis (3.7% vs 2.8%; $P = .242$), or aortic valve reoperation (0.8% vs 2.8%; $P = .707$) did not differ between study groups.**

Conclusions. **Mechanical aortic valve prosthesis is associated with worse long-term survival and increased bleeding after SAVR in patients more than 70 years old. The study results suggest caution when considering mechanical aortic valve prostheses in elderly patients.**

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The optimal choice between biologic and mechanical prosthetic valves in surgical aortic valve replacement (SAVR) requires balancing between risks of life-long anticoagulation with a mechanical valve and gradual degeneration of a biologic valve. Aortic stenosis is predominantly a disease of elderly persons,[1] and age is the major determinant of valve choice.[2] Recent American Heart Association and American College of Cardiology guidelines recommend mechanical valve prosthesis for SAVR in patients more than 50 years old, biologic prosthesis for patients more than 70 years old, and either valve type in patients between those ages,[3] whereas European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines prioritize mechanical valves for patients less than 60 years old and biologic valves for patients older than 65 years.[4] Transcatheter aortic valve replacement is used increasingly for biologic aortic valve prosthesis implantation. Knowledge of long-term results with mechanical vs biologic aortic valve prostheses after SAVR in older patients is limited, however. Randomized studies focusing on older SAVR-treated patients have not been conducted.[2] Some observational studies have found similar survival with both

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prosthesis types,[5-7] whereas one study found modestly improved survival with biologic prostheses in the oldest patients.[8] Mechanical valves are commonly associated with increased bleeding risk in elderly patients,[7,8] although the impact on different bleeding locations is poorly known. Results on reoperation rate, stroke, and infective endocarditis risks are conflicting.[5-8]

To clarify the impact of aortic valve prosthesis choice in older patients, we compared long-term outcomes with mechanical or biologic prostheses in a nationwide, population-based propensity score–matched study of SAVR-treated patients who were more than 70 years old in Finland.

Patients and Methods

Study Design and Outcomes

We studied long-term outcomes of patients who were more than 70 years old and who had mechanical or biologic valve prosthesis implanted in first-time isolated SAVR with or without coronary artery bybass grafting (CABG). The primary outcome of interest was 10-year survival after operation. Secondary outcomes were 10-year occurrence of major bleeding, ischemic stroke, infective endocarditis, and aortic valve reoperation (Supplemental Material). Events occurring during initial surgical admission were excluded from secondary outcomes. Propensity score matching was used to identify comparable patient groups with mechanical or biologic valve prostheses. The study was approved and the need for patient consent waived by the National Institute for Health and Welfare of Finland (permissions nos. THL/143/5.05.00/2015 and THL/1569/5.05.00/2016) and Statistics Finland (TK53-1410-15).

Study Population

All patients more than 70 years old who underwent first-time SAVR with mechanical or biologic valve prosthesis as their primary operation between January 1, 2004 and December 31, 2014 (n = 4487) 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 nationwide, mandatory registry collects data from all hospital admissions in Finland. Aortic valve surgery was performed in 6 public (5 university hospitals and 1 central hospital) and 2 private hospitals during the study period. Patients with concomitant surgery of the aorta, other heart valves, or other cardiac or pulmonary vasculature defects, prior valvular replacement surgery, or infective endocarditis (IE) were excluded, resulting in 4227 patients with isolated SAVR (with or without CABG) (Supplemental Figure 1). Only bileaflet mechanical valves were used during the study period. Survival data of patients were obtained from a nationwide, mandatory cause of death registry held by Statistics Finland, with follow-up ending 10-years after the primary SAVR operation or on December 31, 2016, whichever came first.

Propensity Score Matching

Standardized difference scores were used for evaluation of differences in baseline characteristics between the groups.[9] Comorbidity burden was evaluated by the Charlson comorbidity index calculated according to a previously used algorithm.[10] Logistic regression was used to create a propensity score according to baseline characteristics (Table 1). This score was used for appropriate 1:3 nearest neighbor matching.[11]

Statistical Analysis

Differences between the groups were studied by *t* test or χ^2 tests as appropriate. Outcomes were studied using the Kaplan-Meier method and Cox regression with biologic prosthesis as reference. Cox models were adjusted for the baseline characteristics listed in Table 1. Results of unadjusted Cox analyses and subgroup analyses were comparable and are presented in Supplemental Tables 1 and 2. Absolute numbers of outcome events are presented in Supplemental Table 3. Subgroup analysis was performed to matched patients without concomitant CABG, and results are presented in Supplemental Table 2. Competitive hazard by mortality was accounted for in analyses of other outcomes. Number needed to harm (NNH) was estimated on basis of Cox modeling.[12] Follow-up was calculated for survivors. Results are presented as the mean, median, percentage, or hazard ratio (HR) with 95% confidence interval (CI) or ± SD. A *P* value <.05 was considered statistically significant. A standardized difference >.20 was considered as indicate imbalance in baseline characteristics. Analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Results

A biologic prosthesis was used significantly more often in older patients, and a mechanical valve was applied significantly more often in patients with atrial fibrillation (Table 1). Use of mechanical prostheses diminished during the study period from 18.3% in 2004 to 0.8% in 2014 (Table 1). The final study population after propensity score matching (1:3) consisted of 1184 patients, including 296 patients treated with mechanical valve prosthesis and 888 patients with biologic valve prosthesis, with comparable baseline characteristics between study groups (Supplemental Table 4). Mean follow-up of mortality was 8.4 ± 2.1 years (median, 3412 days), with no difference between mechanical and biologic prosthesis groups (8.3 ± 2.1 years for both).

Survival

Survival after SAVR was 86.5% at 1 year, 66.1% at 5 years, and 46.1% at 10 years after operation among patients with a mechanical prosthesis (Figure 1). Among patients with a biologic prosthesis, the

Table 1. Features of All Patients More Than 70 Years Old With First-Time Isolated Surgical Aortic Valve Replacement (With or Without Coronary Artery Bypass Grafting) With Mechanical or Biologic Valve Prostheses

	Original Cohort			
Variable	Mechanical Prosthesis (n = 296)	Biologic Prosthesis (n = 3931)	Standardized Difference	*P* Value
Age, y (SD)	75.8 (3.6)	77.4 (4.2)	.42	<.001
Female sex	152 (51.4)	2015 (51.3)	0	.976
Valvular stenosis	265 (89.5)	3675 (93.5)	.14	.009
Charlson comorbidity index score			.19	.066
0	179 (60.5)	2237 (56.7)		
1	76 (25.7)	1025 (26.1)		
2	34 (11.5)	441 (11.2)		
≥3	7 (2.4)	238 (6.1)		
Atrial fibrillation	86 (28.0)	671 (17.1)	.26	<.001
Concomitant CABG	122 (41.2)	1516 (38.6)	.05	.367
Use of ITA	69 (56.6)	868 (57.3)	.01	.881
Urgent or emergency surgery	9 (3.0)	226 (5.8)	.13	.0498
Surgical center	…	…	.61	<.001
Operation year			.91	<.001
2004	54 (18.2)	241 (6.1)		
2005	51 (17.2)	270 (6.9)		
2006	48 (16.2)	294 (7.5)		
2007	35 (11.8)	334 (8.5)		
2008	28 (9.5)	337 (8.6)		
2009	28 (9.5)	354 (9.0)		
2010	21 (7.1)	359 (9.1)		
2011	10 (3.4)	419 (10.7)		
2012	13 (4.4)	460 (11.7)		
2013	5 (1.7)	490 (12.5)		
2014	3 (1.0)	373 (9.5)		

Values are n (%) unless otherwise indicated.

CABG, coronary artery bypass grafting; ITA, internal thoracic artery.

survival rate was 91.9% at 1 year, 78.0% at 5 years, and 57.8% at 10 years after surgery (Figure 1). Mortality hazard within 10 years after surgery was significantly higher for patients with a mechanical valve prosthesis (HR, 1.48; 95% CI, 1.21 to 1.80; $P < .001$), with 10-year NNH of 7.0 (95% CI, 4.8 to 14.3) for use of a mechanical prosthesis. The result was similar in a subgroup of SAVR-treated patients without concomitant CABG (10-year survival, 45.1% with mechanical prosthesis and 59.3% with biologic prosthesis; HR, 1.43; 95% CI, 1.10 to 1.86; $P = .009$).

Major Bleeding

The cumulative major bleeding rate in patients with mechanical valves was 2.7% at 1-year, 12.2% at 5-year, and 37.0% at 10-year follow-up after SAVR (Figure 2). Major bleeding occurred in 1.9% of patients with a biologic prosthesis within 1 year, in 9.7% within 5 years, and in 18.8% within 10 years after SAVR (Figure 2). The HR for major bleeding, comparing patients with mechanical and biologic prostheses, was 1.77 (95% CI, 1.25 to 2.49; $P = .001$), and NNH of 7.4 (95% CI, 5.8 to 15.6) within 10 years after the primary aortic valve replacement. The gastrointestinal tract was the most common location of all major bleeding (47.9% of major bleeding). The rate of major gastrointestinal bleeding within 10 years after surgery was notably higher in the mechanical prosthesis group (26.5% vs 8.9% in the biologic prosthesis group; HR, 2.63; 95% CI, 1.63 to 4.23; $P < .001$), with NNH of 11.5 (95% CI, 11.2 to 14.4). Intracranial bleeding within 10 years after SAVR was also significantly more frequent among patients with mechanical prostheses (8.8%) than with biologic prostheses (6.0%; HR, 2.12; 95% CI, 1.09 to 4.15; $P = .028$), with NNH of 17.4 (95% CI, 16.7 to 74.5).

Ischemic Stroke

Ischemic stroke occurred within the first year after SAVR operation in 2.7% of patients with mechanical prostheses and in 2.4% of patients with biologic prostheses, whereas corresponding 5-year rates were

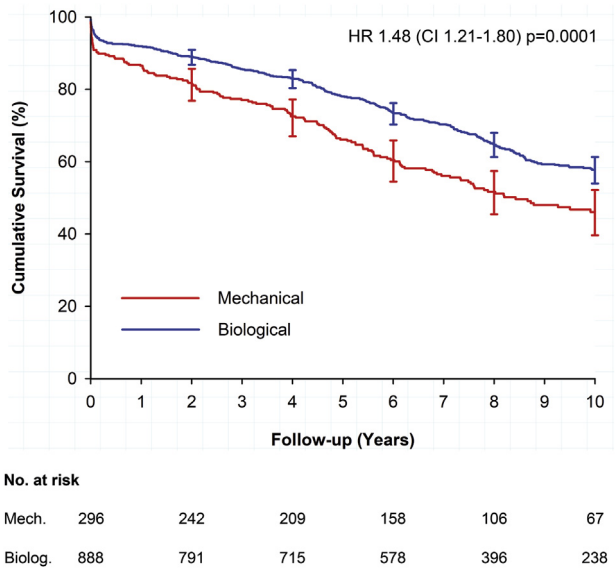

Figure 1. Survival after first-time isolated aortic valve replacement surgery (with or without coronary artery bypass grafting) for propensity-matched patients more than 70 years old with mechanical (Mech.) or biologic (Biolog.) valve prosthesis. Error bars represent 95% confidence intervals (CIs). (HR, hazard ratio; No., number.)

8.2% and 7.8% (Figure 3). The 10-year ischemic stroke rates were also comparable, with 18.9% for the mechanical prosthesis group and 16.1% for the biologic prosthesis group (HR, 1.25; 95% CI, .80 to 1.91; $P = .341$).

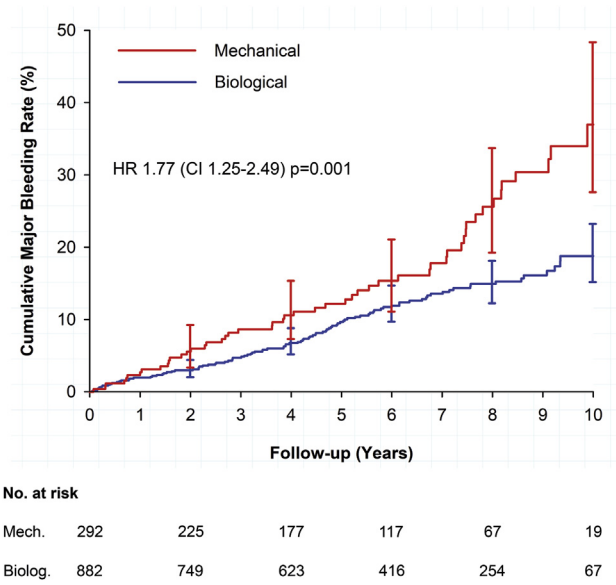

Figure 2. Occurrence of major bleeding after first-time isolated surgical aortic valve replacement (with or without coronary artery bypass grafting) in propensity-matched patients more than 70 years old with mechanical (Mech.) or biologic (Biolog.) valve prosthesis. Error bars represent 95% confidence intervals (CIs). (HR, hazard ratio; No., number.)

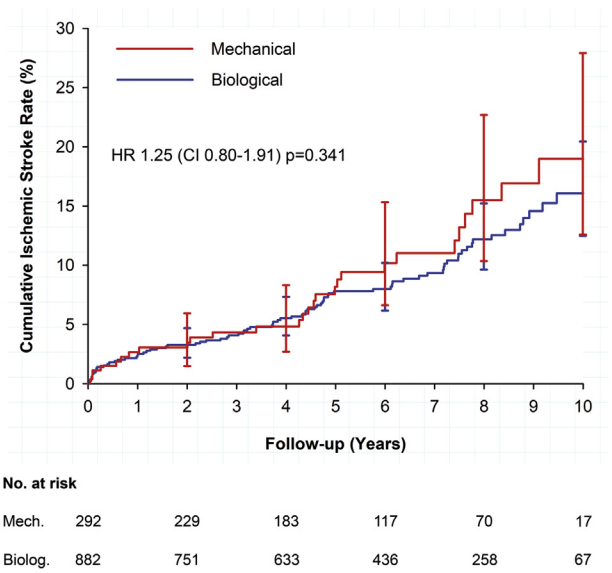

Figure 3. Occurrence of ischemic stroke after first-time isolated surgical aortic valve replacement (with or without coronary artery bypass grafting) in propensity-matched patients more than 70 years old with mechanical (Mech.) or biologic (Biolog.) valve prosthesis. Error bars represent 95% confidence intervals (CIs). (HR, hazard ratio; No., number.)

Infective Endocarditis

Among patients with mechanical valves the cumulative rate of IE was 2.3% at 1 year and 3.7% at 5 and 10 years after SAVR (Figure 4). Rates were similar among patients with biologic prosthesis (1.0% at 1-year, 2.2% at 5-year, and 2.8% at 10-year follow-up; HR, 1.63; 95% CI, .72 to 3.68; $P = .242$).

Reoperation of Aortic Valve Prosthesis

Aortic valve prosthesis reoperation was uncommon in patients more than 70 years old after SAVR regardless of prosthesis type (Figure 5). Reoperation for mechanical prostheses was performed in 0.4% of patients within 1-year follow-up, and in 0.8% of patients within 5- and 10-year follow-up. For biologic prostheses, the reoperation rate was 0.5% at 1-year, 1.0% at 5-year, and 2.8% at 10-year follow-up after SAVR (HR, 0.43; 95% CI, 0.10 to 1.89; $P = .262$). Aortic valve reoperations included surgery of the ascending aorta in 5.9% of reoperations with no difference between the study groups ($P = .707$).

Comment

Use of biologic valve prostheses is recommended in elderly SAVR-treated patients,[3,4] although knowledge of long-term outcomes is limited in this patient subgroup. This nationwide, population-based, propensity-scored study compared long-term outcomes between mechanical and biologic aortic valve prosthesis use in patients more than 70 years of age who underwent SAVR and observed poorer survival and increased bleeding in patients treated with mechanical prostheses.

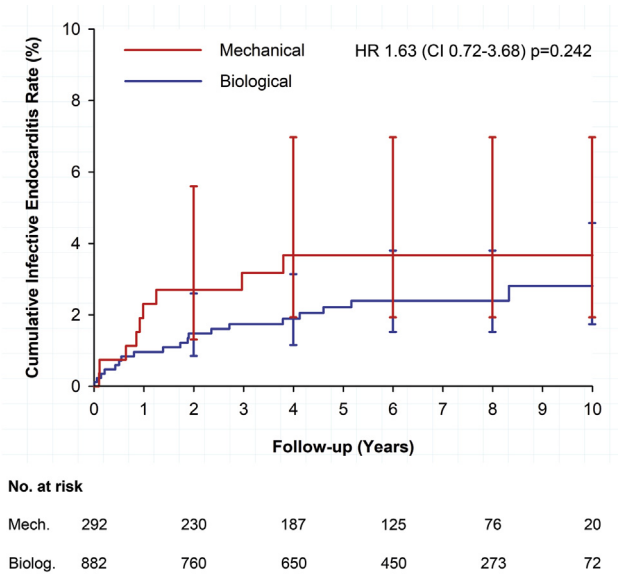

Figure 4. Occurrence of infective endocarditis after first-time isolated surgical aortic valve replacement (with or without coronary artery bypass grafting) in propensity-matched patients more than 70 years old with mechanical (Mech.) or biologic (Biolog.) valve prosthesis. Error bars represent 95% confidence intervals (CIs). (HR, hazard ratio; No., number.)

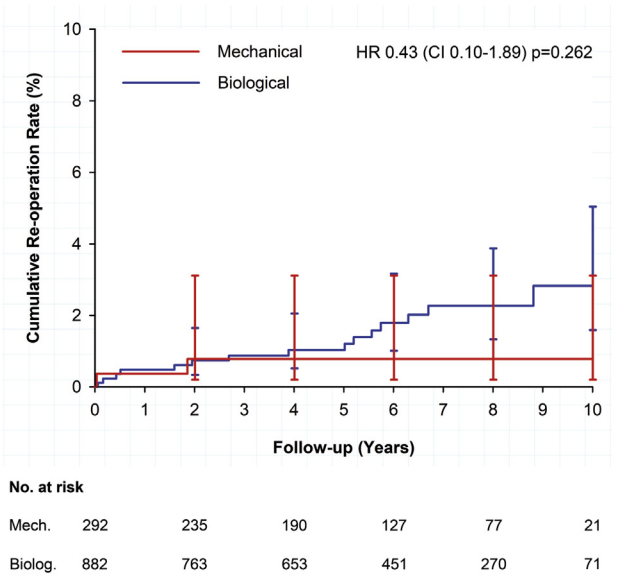

Figure 5. Aortic valve reoperation after first-time isolated surgical aortic valve replacement (with or without coronary artery bypass grafting) in patients more than 70 years old with mechanical (Mech.) or biologic (Biolog.) valve prosthesis. Error bars represent 95% confidence intervals (CIs). (HR, hazard ratio; No., number.)

Long-term outcomes between mechanical and biologic valve prostheses have been compared in 3 randomized trials, but none of these trials focused on older patients. The Edinburgh trial[13] and the US Veterans Affairs trial[14] included SAVR-treated patients with no age restrictions (mean age, 54 years[13] and 59 years[14]). During 20-year follow-up in the former study, there was no survival difference between prostheses types in all operated patients, but prognosis was significantly better with mechanical valves among patients who did not undergo reoperation.[13] In the Veterans Affairs study, the 15-year survival was significantly higher with a mechanical prosthesis (34%) compared with a biologic prosthesis (21%).[14] Stassano and colleagues[15] studied more modern mechanical prostheses vs biologic prostheses for SAVR in patients aged 55 to 70 years in Italy. During a mean follow-up of 8.8 years, these investigators found a survival of 72.5% with mechanical prostheses and 69.4% with biologic prostheses, but valve type per se was not a significant independent predictor of mortality,[15] although mortality rates were lower than those derived from power calculations.

We found the 10-year survival of elderly patients to be significantly better with biologic prostheses compared with mechanical valves after SAVR (57.8% vs 46.1%), with NNH of 7 for mechanical valves. Some previous observational studies on long-term outcomes after SAVR in elderly patients have been conducted, although propensity-matched studies are scarce. Okamoto and colleagues[5] studied 104 matched Japanese patients 75 years old or older and found the same survival (73%) for both mechanical and biologic prostheses during an 8-year follow-up. A US study by Ashikhmina and associates[6] found 10-year survival to be 40% with mechanical prostheses and 45% with biologic prostheses and 15-year survivals of 19% and 7%, respectively, with no statistical difference between groups in 458 matched patients 70 years old or older. A previous microsimulation study also found comparable life expectancy between aortic valve prostheses types in patients more than 70 years old.[7] In a large multivariate adjusted US study of more than 29,000 patients aged 70 to 80 years, Brennan and colleagues[8] found similar 12-year survival between mechanical and biologic prostheses in patients aged 70 to 74 years (38.4% vs 34.1%), but biologic prostheses were associated with a limited and statistically significant improvement in survival among SAVR-treated patients aged 75 to 80 years (23.8% vs 22.8%).

The major limitation of a mechanical valve prosthesis is the increased susceptibility to thrombogenicity requiring life-long anticoagulation with a vitamin K antagonist that renders patients susceptible to bleeding.[8,16] The bleeding risk associated with a mechanical valve prosthesis increases with aging.[7,17] Accordingly, we found the 10-year major bleeding risk to be significantly increased with mechanical prostheses, with NNH of 7.4 compared with biologic prostheses (bleeding rates, 37.0% vs 18.8%). The bleeding risk was elevated in the most feared category of intracranial bleeding, as well as the typically less severe category of gastrointestinal bleeding. This finding is contrast to that of a previous Japanese study that found very low long-term bleeding rates after SAVR in patients 75 years old or older with no difference

between prosthesis types at 8-year follow-up (0% with biologic prostheses and 4.3% with mechanical prostheses).[5]

Comparisons of the risk of thromboembolic events between valvular prosthesis types in older SAVR-treated patients are scarce. In a Japanese cohort of 104 propensity-matched patients 75 years old or older there was a nonsignificant trend toward increased thromboembolic events with mechanical prosthesis at 8-year follow-up (17.8% vs 1.9%).[5] Another Japanese study of 278 patients 70 years old or older found no difference between prosthetic types at 20 years after SAVR (10.1% vs 4.4%).[17] In agreement, we found comparable 10-year ischemic stroke rates between mechanical (18.9%) and biologic (16.1%) valve prostheses. Brennan and colleagues[8] found the 12-year stroke rate to be significantly higher with mechanical prostheses compared with bioprostheses in patients aged more than 65 years (14.7% vs 13.8%), but the comparison included both ischemic and hemorrhagic stroke types. It is plausible that the inherent thrombogenicity associated with a mechanical valve may be counterbalanced by the lack of anticoagulation in patients with biologic prostheses and the high prevalence of atrial fibrillation during follow-up after SAVR.[18,19] Currently, there is no convincing evidence supporting the use of long-term anticoagulation after SAVR with bioprosthesis in the absence of atrial fibrillation. A mechanical prosthesis was chosen for 18% of elder SAVR candidates at the beginning of our study period, but the proportion diminished during the study. This change was most likely related to accumulating evidence on bioprostheses in these patients and guideline guidance. The confidence in a universal health care system, and consequently a relatively good and uniform nationwide warfarin treatment balance in Finland,[20] may explain why mechanical prostheses were initially widely used.

A valvular prosthesis increases the risk of IE substantially.[21] Results on the impact of aortic valve prosthesis type on IE risk have been varied. Studies of middle-aged patients have found similar IE rates between mechanical and biologic prostheses.[15,22,23] Conversely, among US SAVR-treated patients aged 65 to 80 years, the 12-year IE rate was found to be lower with mechanical prostheses (1.4% vs 2.2%).[8] It is plausible that progressive calcification[24] and degeneration of a biologic valve prosthesis could increase susceptibility to valvular bacterial adhesion. However, we found comparable IE rates between mechanical and biologic prostheses (10-year rates, 3.7% and 2.8%) in SAVR-treated patients who were more than 70 years of age.

Gradual degeneration is the major limitation of biologic aortic valve prostheses.[25] The risk of earlier degeneration and reoperation is higher in younger patients because of their more pronounced immunologic response and enhanced valvular calcification.[26-28] In elderly patients, the life span of a biologic prosthesis is estimated to be approximately 15 years.[2,29] There also appear to be geographic differences in the reoperation rate. In middle-aged US patients the 15-year reoperation rate for biologic prosthesis was found to be 12.1% to 17.2%,[16,30] whereas the reoperation rate was 5.5% in a middle-aged Swedish SAVR-treated population.[31] We found the 10-year reoperation rate for biologic prosthesis to be 2.8% in elderly Finnish SAVR-treated patients, with similar reoperation rates compared with mechanical prostheses. US studies with populations comparable to those in our study have reported reoperation rates of 2.4% to 7%, with both similar reoperation rates between biologic and mechanical valve prostheses[6] and higher reoperation rates with biologic prostheses.[8] In Japanese patient cohorts with ages comparable to those in our study, the reoperation rate was 0% for both biologic and mechanical prostheses.[5,17] It is worth noticing that increasing frailty with aging[32] may preclude surgical reoperation of degenerated bioprostheses even in the presence of severe structural valve disease. Transcatheter valve-in-valve aortic valve replacement in this high-risk patient group could translate to improved long-term outcomes,[33] thus further underlying the superiority of bioprostheses in elderly patients.

The current study has some limitations. The major limitation is the retrospective design with no access to more detailed patient-level clinical information or therapeutic data. Diagnoses were made by treating physicians and coding errors are possible, but it is unlikely that these limitations would affect study groups differently. End points and comorbidities were defined according to previous studies,[34,35] and study data were based on nationwide, mandatory databases.[36] Propensity score matching with multivariate modeling was used to control for selection bias. It is nevertheless possible that additional, unrecognized confounders such as, for example, aortic root diameter, valve size, type of biologic prostheses, type of preoperative atrial fibrillation, or other preexisting conditions requiring anticoagulation, could have influenced prosthesis selection and outcome.

In conclusion, this population-based, propensity-scored study found worse long-term survival and more major bleeding with mechanical prostheses compared with biologic prostheses after SAVR in patients more than 70 years of age. Our results suggest careful consideration when contemplating a mechanical aortic valve prosthesis in SAVR for elderly patients.

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