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Mechanical aortic valve prostheses offer a survival benefit in 50–65 year olds: AUTHEARTVISIT study

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Abstract

Background: The present population-based cohort study investigated long-term mortality after surgical aortic valve replacement (AVR) with bioprosthetic (B) or mechanical aortic valve prostheses (M) in a European social welfare state.

Methods: We analysed patient data from health insurance records covering 98% of the Austrian population between 2010 and 2018. Subsequent patient-level record linkage with national health data provided patient characteristics and clinical outcomes. Further reoperation, myocardial infarction, heart failure and stroke were evaluated as secondary outcomes.

Results: A total of 13,993 patients were analysed and the following age groups were examined separately: <50 years (727 patients: 57.77% M, 42.23% B), 50–65 years (2612 patients: 26.88% M, 73.12% B) and >65 years (10,654 patients: 1.26% M, 98.74% B). Multivariable Cox regression revealed that the use of B-AVR was significantly associated with higher mortality in patients aged 50–65 years compared to M-AVR (HR = 1.676 [1.289–2.181], $p < 0.001$). B-AVR also

performed worse in a competing risk analysis regarding reoperation (HR = 3.483 [1.445–8.396], $p = 0.005$) and myocardial infarction (HR = 2.868 [1.255–6.555], $p = 0.012$). However, the risk of developing heart failure and stroke did not differ significantly after AVR in any age group.

Conclusions: Patients aged 50–65 years who underwent M-AVR had better long-term survival, and a lower risk of reoperation and myocardial infarction. Even though anticoagulation is crucial in patients with M-AVR, we did not observe significantly increased stroke rates in patients with M-AVR. This evident survival benefit in recipients of mechanical aortic valve prostheses aged <65 years critically questions current guideline recommendations.

KEYWORDS

aortic valve replacement, biological valve replacement, mechanical valve replacement, survival

1 | INTRODUCTION

Aortic valve replacement (AVR) represents the standard treatment option for severe aortic valve disease and is performed in approximately 280 000 patients annually worldwide.[1] Current guidelines of the European Society of Cardiology (ESC) advise a preference of mechanical aortic valve prosthesis (M) in patients <65 years.[2] In contrast, the American Heart Association/American College of Cardiology (AHA/ACC) guidelines[3] state that it is reasonable to implant bioprostheses (B) in patients aged >50 years. Interestingly, Chiang and colleagues published a large study that challenges ESC guidelines, showing similar long-term survival in patients aged 50–69 years who received either mechanical aortic valve prosthesis or a bioprosthesis.[4] These findings indicate that bioprostheses could be considered for patients ≥50 years of age and are supported by the findings reported by McClure et al.[5] However, contrary publications demonstrated that AVR with a bioprosthesis is associated with increased mortality in patients aged 50–65 years.[6–9]

This discrepancy in previously published studies shows that the optimal type of prosthesis for middle-aged patients remains controversial. Therefore, we conducted a population-based cohort study of the majority of all patients who underwent primary isolated AVR in Austria between 2010 and 2018 and evaluated three age groups: <50, 50–65 and >65 years. The primary objective was to compare long-term mortality between recipients of mechanical aortic valve prostheses and bioprostheses. The secondary objectives were to compare the risk of stroke, myocardial infarction, diagnosis of heart failure and reoperation between both types of valve.

2 | METHODS

2.1 | Study design

This study was a nationwide, population-based cohort study and complied with the Declaration of Helsinki. It was approved by the ethics committee of lower Austria (EC number: GS1-EK-4/722-2021). The trial was registered at clinicaltrials.gov (NCT: NCT04900909).

Our study population was generated by retrospectively retrieving data from the main social security carriers in Austria on the clinical and operative characteristics of the majority of all patients who underwent surgical heart valve replacement from 2010 to 2018 in Austria ($n = 17,658$). Patients <18 years old, and patient who underwent mitral, tricuspid or pulmonary valve replacement, concomitant heart surgery and transcatheter aortic valve replacement (TAVR) were excluded from our analysis ($n = 13,993$). Informed consent was not obtained from patients, as data were retrieved retrospectively from social security carriers.

2.2 | Outcomes

The primary outcome was all-cause mortality. Reoperation, stroke (I63.x—Cerebral infarction [including I63.0—Cerebral infarction due to thrombosis of precerebral arteries, I63.1—Cerebral infarction due to embolism of precerebral arteries, I63.2—Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries, I63.3—Cerebral infarction due to thrombosis of cerebral arteries, I63.4—Cerebral infarction due to embolism of cerebral arteries, I63.5—Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries, I63.6—Cerebral

infarction due to cerebral venous thrombosis, nonpyogenic, I63.8—Other cerebral infarction, I63.9—Cerebral infarction, unspecified and G45.9—Transient cerebral ischaemic attack, unspecified]), myocardial infarction (I21.x—Acute myocardial infarction [including I21.0—Acute transmural myocardial infarction of anterior wall, I21.1—Acute transmural myocardial infarction of inferior wall, I21.2—Acute transmural myocardial infarction of other sites, I21.3—Acute transmural myocardial infarction of unspecified site, I21.4—Acute subendocardial myocardial infarction, I21.9—Acute myocardial infarction, unspecified]) and risk of heart failure (I11.0—Hypertensive heart disease with (congestive) heart failure, I13.0—Hypertensive heart and renal disease with (congestive) heart failure, I13.2—Hypertensive heart and renal disease with both (congestive) heart failure and renal failure, I50—Heart failure, I50.0—Congestive heart failure, I50.1—Left ventricular failure and I50.9—Heart failure, unspecified were chosen as secondary outcomes. All endpoints were observed until 30 June 2020. Information on all outcomes was retrieved from the national social security carriers and evaluated in both the overall patient cohort and three age groups chosen according to the 2020 American College of Cardiology and American Heart Association (ACC/AHA) guidelines on management of patients with valvular heart disease[3]: <50 years, 50–65 years, and >65 years.

2.3 | Statistical analysis

Variables are presented descriptively as means ± standard deviation (SD) as well as medians with the interquartile range (IQR). Continuous variables were compared between M-AVR and B-AVR using Student's t-test or Mann-Whitney U test respectively. Categorical data were compared between groups using chi-squared test. p-values to compare baseline characteristics between heart valves groups were not adjusted for multiplicity and are therefore interpreted in an exploratory way.

Cox regression was used to evaluate whether the type of valve replacement had a significant impact on overall survival (0 = mechanical/1 = biological). For multivariable analyses, the following confounders were included: age (per one year increase), sex (0 = male, 1 = female) and diagnosis before heart valve replacement of diabetes, heart failure, myocardial infarction or stroke (0 = no prior diagnosis/1 = prior diagnosis). Heart failure, myocardial infarction and stroke were defined as stated above. Diabetes was defined as therapy ICD 10 codes E100-E149. To evaluate the secondary endpoints (time to reoperation, heart failure, myocardial infarction and stroke), we performed competing risk analyses using death as a competing event.

Multivariable analyses included the same confounders as stated above. The analysis was adjusted only for the secondary outcome heart failure; all patients with prior diagnosis of heart failure were excluded, as previously diagnosed patients cannot be diagnosed again.

Analyses were performed for the overall population as well as separately for the 3 subgroups based on age: <50 years, 50–65 years, >65 years.

Statistical analyses were carried out and graphs were generated in R (version 3.6.2), using the packages survival (version 3.1.11), survminer (version 0.4.6) and cmprsk (version 2.2.10). Due to multiple subgroup comparisons, the significance level was adjusted to 0.016 using Bonferroni correction (due to the 3 age groups). All tests were two sided.

3 | RESULTS

3.1 | Study population

A total of 13,993 patients >18 years of age who underwent isolated ARV in Austria between 2010 and 2018 were identified: 1256 (8.98%) received mechanical aortic valve prostheses and 12737 (91.02%) received bioprostheses.

According to current ACC/AHA guidelines, mechanical aortic valve prostheses are preferred in patients <50 years old and bioprostheses should be implanted in patients >65 years old. For patients between 50 and 65 years, no distinct recommendation is given.

In our cohort, 727 patients were <50 years old, out of which 420 (57.77%) received mechanical aortic valve prostheses and 307 (42.23%) received bioprostheses. In 2612 patients between 50 and 65 years of age, 702 (26.88%) were implanted with mechanical valves and 1910 (73.12%) with a bioprosthesis. The majority of our cohort was >65 years old (n = 10,654 patients). In this age group, most patients received bioprostheses (n = 10,520 [98.74%]) and only 134 patients (1.26%) were implanted with mechanical aortic valve prostheses (Figure 1).

3.2 | Patient characteristics

Baseline patient characteristics are given in Table 1. The median age of the overall cohort was 74 years (IQR: 66–79 years). The median age of patients who received mechanical aortic valve prostheses was 54 years (IQR: 46–60 years), and that of patients who received bioprostheses was 75 years (IQR: 69–80 years). The overall cohort included 5853 female patients (41.83%). The mechanical aortic valve prostheses cohort comprised 341 female
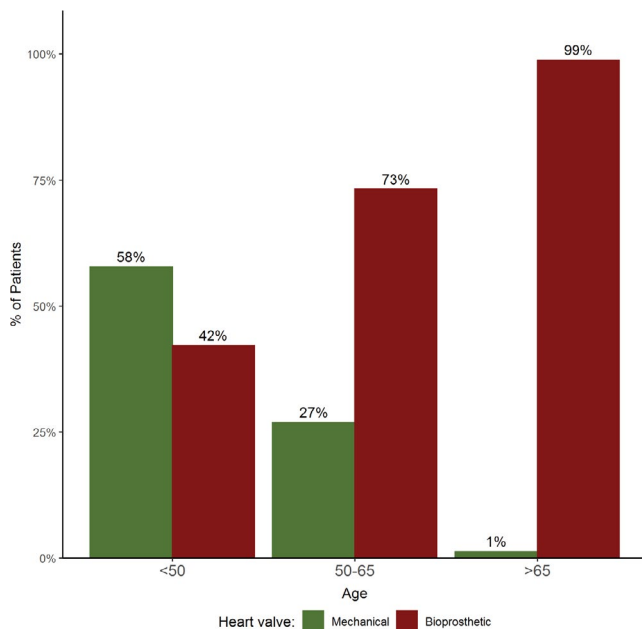
FIGURE 1 Proportions of implanted mechanical aortic valve prostheses and bioprostheses by age cohort. In patients under 50 years of age slightly more mechanical valves have been implanted. In the group of patients between 50 and 65 years more than two thirds received biological valves. According to the current guidelines almost only bioprostheses have been implanted in patients above 65 years of age

patients (27.15%) and the bioprostheses cohort 5512 female patients (43.28%). Regarding comorbidities, 580 patients (4.14%) had already had myocardial infarction and 182 patients (1.30%) a stroke prior to AVR. In addition, 1865 patients (13.33%) and 2556 patients (18.27%) suffered from heart failure and diabetes before the operation respectively. We found a significantly higher prevalence of comorbidities prior to valve replacement in the bioprostheses group.

A broader range of baseline characteristics for each age group with regard to pre-existing diseases and medication within the year prior to AVR is given in Tables S1 and S2. In the age group of interest (50–65 years) we observed a higher proportion of diagnosis of diabetes in the bioprostheses group, whereas more patients suffered from hyperuricaemia or gout, aortic diseases (eg aneurysms, dissections) and diseases of teeth or gingiva in the mechanical valve group. In terms of medication only anti-anaemic agents were consumed more often in the bioprosthesis group.

3.3 | Survival

A total of 4105 patients died during the follow-up period, including 157 in the mechanical aortic valve prosthesis

cohort and 3948 in the bioprosthesis cohort. The median observed time to death was 1031 days (IQR: 262–1947 days), detailed data on time to death per group are reported in the supplementary data (Table S3). Sixty-nine patients <50 years of age died; 31 had received a mechanical aortic valve prosthesis and 38 a bioprosthesis. The observed median time to death was 262 days (IQR: 43–1504 days). In the 50–65 years age group, 426 patients died during the follow-up period, including 72 patients who received a mechanical aortic valve prosthesis and 354 who underwent bioprosthetic valve replacement. The observed median time to death in this age group was 1214 days (IQR: 332–2164 days). Unsurprisingly, the mortality rate was highest in patients >65 years old; a total of 3610 patients died in this group, including 54 patients who received mechanical aortic valve prostheses and 3556 who received bioprostheses. The observed median time to death was 1019 days (IQR: 271–1925 days) (Table 2 and S8).

In the overall cohort, univariable Cox regression showed a clear favourable outcome of mechanical aortic valve prostheses (HR = 2.946 [2.512–3.456], $p < 0.001$, Figure 2A). However, after adjusting for age, sex and comorbidities (ie diabetes, heart failure, myocardial infarction and stroke), the benefit of mechanical aortic valve prostheses was no longer significant (HR = 1.115 [0.939–1.324], $p = 0.22$, Figure 2A) and age, sex and a history of diabetes, heart failure or stroke were stronger predictive factors. In patients younger than 50 years and older than 65 years of age, we did not identify the type of valve replacement as a significant influence factor for survival. In contrast, in patients between 50 and 65 years of age, mechanical aortic valve prosthesis replacement was a significant prognostic factor (univariable HR = 1.866 [1.448–2.404], $p < 0.001$; multivariable HR = 1.676 [1.289–2.181], $p < 0.001$, Figure 2B).

3.4 | Secondary outcomes

3.4.1 | Reoperation

Among all patients, 196 required reoperation. Of these patients, 15 had mechanical aortic valve prostheses and 181 had bioprostheses. Univariable competing risk regression showed no significant influence of the type of valve replacement (HR = 1.202 [0.710–2.033], $p = 0.49$, Figure 3A), but after adjusting for age, sex and comorbidities, a significantly increased risk of re-operation was observed in the bioprosthesis group (HR = 2.827 [1.562–5.115], $p < 0.001$, Figure 3A). Of the patients aged between 50 and 65 years, 62 needed to undergo a reoperation, including six patients with mechanical aortic valve prostheses and 56 with bioprostheses. In a univariable competing

TABLE 1 Patient characteristics

	All Patient n = 13993	<50 years n = 727	50–65 years n = 2612	>65 years n = 10654	p-value	Bioprostheses n = 12737	mechanical aortic valve prostheses n = 1256	p-value
Age (median, IQR)	74 (66–79)	43 (35–46)	60 (56–63)	76 (72–81)	<0.001	75 (69–80)	54 (46–60)	<0.001
Sex (n, % female)	5853 (41.83%)	181 (24.90%)	729 (27.91%)	4943 (46.40%)	<0.001	5512 (43.28%)	341 (27.15%)	<0.001
Type of surgical valve replacement (n, % mechanical/ % biological)	1256 (8.98%)/12737 (91.02%)	420 (57.77%)/307 (42.23%)	702 (26.88%)/1910 (73.12%)	134 (1.26%)/10520 (98.74%)	<0.001			
Comorbidities at time of surgery								
Heart failure	1865 (13.33%)	43 (5.94%)	238 (9.11%)	1584 (14.87%)	<0.001	1771 (13.90%)	94 (7.48%)	<0.001
Myocardial infarction	580 (4.14%)	11 (1.51%)	94 (3.60%)	475 (4.46%)	<0.001	550 (4.32%)	30 (2.39%)	0.001
Stroke	182 (1.30%)	10 (1.38%)	30 (1.15%)	142 (1.33%)	0.745	174 (1.37%)	8 (0.64%)	0.041
Diabetes	2556 (18.27%)	38 (5.23%)	446 (17.08%)	2072 (19.45%)	<0.001	2419 (18.99%)	137 (10.91%)	<0.001

risk regression, mechanical aortic valve prostheses performed significantly better (HR = 3.411 [1.470–7.912], $p < 0.01$, Figure 3B). This was also seen in the multivariable analysis (HR = 3.483, [1.445–8.396], $p < 0.01$, Figure 3B). In the younger patient group, we observed a trend favouring mechanical aortic valve prostheses, whereas in the older patient group, we observed no significant difference between the valve types (Table 2 and S9). Median observed times to reoperation overall and per age group are reported in Table S4.

3.4.2 | Heart failure

For the outcome incidence of heart failure, only 12,128 patients were included in the competing risk regression because all patients with previously diagnosed heart failure were excluded from the analysis. A total of 2078 patients developed heart failure during the follow-up period, including 113 patients with mechanical aortic valve prostheses and 1965 patients with bioprostheses. In the univariable competing risk regression, bioprostheses had poorer performance (HR = 1.927, [1.590–2.334], $p < 0.001$, Figure 3C), but this effect vanished in the multivariable analysis (HR = 1.068 [0.864–1.321], $p = 0.54$, Figure 3C) and other factors, such as age and diabetes, seemed to have a greater impact. In the 50–65 years age group, 256 patients were diagnosed with heart failure, including 51 patients with mechanical aortic valve prostheses and 205 patients with bioprostheses. Even though the univariable analysis revealed an advantage of mechanical aortic valve prostheses (HR = 1.538 [1.131–2.090], $p < 0.01$, Figure 3D), we observed only a trend towards worse performance of bioprostheses in the multivariable analysis (HR = 1.339 [0.971–1.846], $p = 0.08$) and pre-existing diabetes had a more prominent effect (Table 2 and S10). Observed median time to first diagnosis of heart failure overall and per age group is reported in Table S5.

3.4.3 | Myocardial infarction

A total of 282 patients had a myocardial infarction during the follow-up period. Of these patients, 14 had mechanical aortic valve prostheses and 268 had bioprostheses. In a univariable competing risk regression, no significantly increased risk of valve replacement was observed with bioprostheses (HR = 1.919 [1.122–3.282], $p = 0.02$, Figure 3E), but bioprostheses were less favourable in the multivariable analysis regarding the outcome myocardial infarction (HR = 2.198 [1.195–4.042], $p = 0.01$, Figure 3E). A similar pattern was observed in patients aged between 50 and 65 years. In this age group, 55 patients had a myocardial infarction after AVR, including 7 patients with

TABLE 2 Incidence rates and univariable and multivariable HR (95% CI) (M-AVR vs B-AVR) for the primary outcome death and the secondary outcomes reoperation, heart failure, myocardial infarction and stroke in the overall patient cohort and respective age groups (<50 years, 50–65 years, >65 years)

	Incidence rate		Univariable		Multivariable	
	Mechanical (*n*, %)	Biological (*n*, %)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Death (overall)	157 (12.50%)	3948 (31.00%)	2.946 (2.512–3.456)	**<0.001**	1.115 (0.939–1.324)	0.22
Death (<50 years)	31 (7.38%)	38 (12.38%)	1.572 (0.976–2.533)	0.06	1.465 (0.903–2.378)	0.12
Death (50–65 years)	72 (10.26%)	354 (18.53%)	1.866 (1.448–2.404)	**<0.001**	1.676 (1.289–2.181)	**<0.001**
Death (>65 years)	54 (40.30%)	3556 (33.8%)	1.194 (0.912–1.562)	0.20	0.851 (0.649–1.115)	0.24
Re-operation (overall)	15 (1.19%)	181 (1.42%)	1.202 (0.710–2.033)	0.49	2.827 (1.562–5.115)	**<0.001**
Re-operation (<50 years)	5 (1.19%)	13 (4.23%)	3.393 (1.202–9.577)	0.02	3.511 (1.240–9.938)	0.02
Re-operation (50–65 years)	6 (0.85%)	56 (2.93%)	3.411 (1.47–7.912)	**<0.01**	3.483 (1.445–8.396)	**<0.01**
Re-operation (>65 years)	4 (2.99%)	112 (1.06%)	0.415 (0.154–1.121)	0.08	0.569 (0.204–1.584)	0.28
Heart failure (overall)	113 (9.72%)	1965 (17.92%)	1.927 (1.590–2.334)	**<0.001**	1.068 (0.864–1.321)	0.54
Heart failure (<50 years)	34 (8.52%)	23 (8.07%)	0.911 (0.539–1.540)	0.73	0.897 (0.529–1.519)	0.68
Heart failure (50–65 years)	51 (7.87%)	205 (11.88%)	1.538 (1.131–2.090)	**<0.01**	1.339 (0.971–1.846)	0.08
Heart failure (>65 years)	28 (24.35%)	1737 (19.40%)	0.872 (0.597–1.274)	0.48	0.757 (0.518–1.106)	0.15
Myocardial infarction (overall)	14 (1.11%)	268 (2.10%)	1.919 (1.122–3.282)	0.02	2.198 (1.195–4.042)	**0.01**
Myocardial infarction (<50 years)	2 (0.48%)	5 (1.63%)	3.150 (0.608–16.326)	0.17	3.545 (0.706–17.796)	0.12
Myocardial infarction (50–65 years)	7 (1.00%)	48 (2.51%)	2.509 (1.135–5.544)	0.02	2.868 (1.255–6.555)	**0.01**
Myocardial infarction (>65 years)	5 (3.73%)	215 (2.04%)	0.638 (0.264–1.539)	0.32	0.721 (0.298–1.749)	0.47
Stroke (overall)	45 (3.58%)	677 (5.32%)	1.519 (1.124–2.052)	**<0.01**	0.960 (0.678–1.360)	0.82
Stroke (<50 years)	11 (2.62%)	10 (3.26%)	1.235 (0.529–2.883)	0.63	1.045 (0.403–2.711)	0.93
Stroke (50–65 years)	20 (2.85%)	70 (3.66%)	1.278 (0.778–2.099)	0.33	1.393 (0.808–2.402)	0.23
Stroke (>65 years)	14 (10.45%)	597 (5.67%)	0.642 (0.380–1.083)	0.10	0.569 (0.335–0.967)	0.04

Note: Statistically significant risk increase of B-AVR are marked bold.

mechanical aortic valve prostheses and 48 patients with bioprostheses. In a univariable competing risk analysis, no significant difference was observed between the two types of valves (HR = 2.509 [1.135–5.544], *p* = 0.02, Figure 3F). However, in a multivariable analysis, bioprostheses had a higher risk of myocardial infarction (HR = 2.868 [1.255–6.555], *p* = 0.01, Figure 3F). No significant differences were found in the other two age groups (Table 2 and Table S11). Observed median time to myocardial infarction overall and per age group is reported in Table S6.

3.4.4 | Stroke

In general, bioprostheses are often preferred because there is no need for anticoagulation with vitamin K antagonists, which reduces the risk of haemorrhagic stroke. In our patient cohort, 722 patients suffered from stroke after valve replacement. Of these patients, 45 had received mechanical

aortic valve prostheses and 677 had received bioprostheses. Even though bioprosthetic valves were associated with a higher risk in the univariable analysis (HR = 1.519 [1.124–2.052], *p* < 0.01, Figure 3G), this association was not sustained in the multivariable analysis (HR = 0.960 [0.678–1.360], *p* = 0.82, Figure 3G) and other factors, such as age and prior stroke, showed a stronger influence. The type of valve replacement was not a significant factor for stroke incidence after valve replacement in any of the three age groups (Figure 3H, Tables 2 and S12). Observed median time to stroke overall and per age group is reported in Table S7.

4 | DISCUSSION

We found that patients aged 50–65 years who received mechanical aortic valve prostheses during isolated AVR in Austria between 2010 and 2018 had significantly higher long-term survival than those who received bioprostheses.
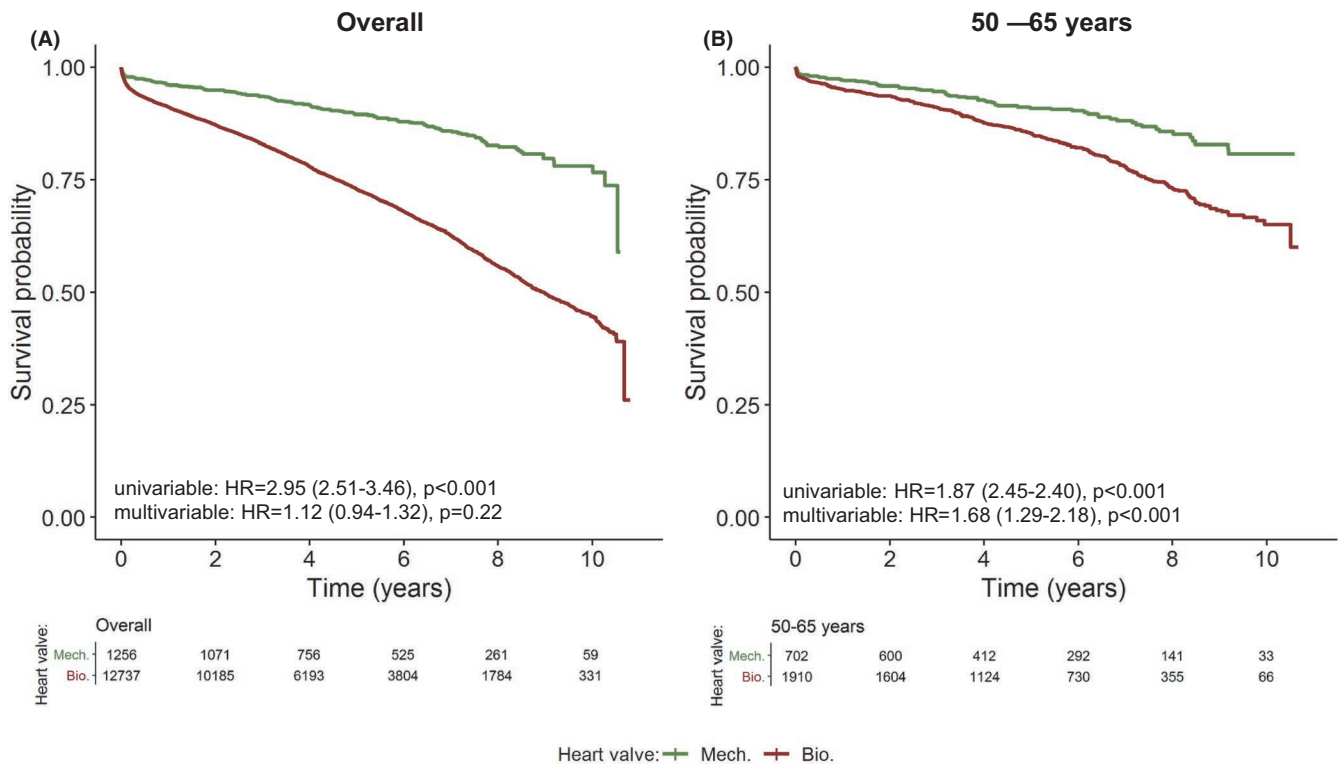
FIGURE 2 Kaplan-Meier survival curves for overall survival. Kaplan-Meier survival curve for the total patient cohort (A) and for patients aged 50–65 years (B). Significantly better survival was observed among patients who received mechanical aortic valve prostheses in patients between 50 and 65 years has been observed

Implantation of bioprostheses in this age group was also associated with a higher risk of reoperation and myocardial infarction after AVR, while risks of heart failure and stroke were similar for both types of valves. Bioprostheses outnumbered mechanical aortic valve prostheses in this age group, and even in patients <50 years old (42.23% received bioprostheses), against the recommendations of both the ESC and AHA/ACC guidelines. Currently accepted guidelines from the ESC recommend bioprostheses for patients aged >65 years. Between 60 and 65 years of age, both bioprostheses and mechanical aortic valve prostheses are considered acceptable options.[2] In contrast, the 2020 guidelines from the AHA/ACC lowered the recommended age limit for biologic heart valve implantation due to improved hemodynamic status, a lower risk of thromboembolic complications and the absence of requiring lifelong anticoagulant therapy compared to mechanical aortic valve prostheses.[3] In contrast to the above cited AHA/ACC guidelines, we found that patients aged 50–65 years who received mechanical valve prostheses had no significant increased incidence of stroke. Interestingly, we found that the implantation of bioprostheses in this age group resulted in an increased risk of myocardial infarction, reoperation, and death in a maximum follow-up of 8 years.

Based on AHA/ACC guidelines, the bioprosthesis implantation outnumbers mechanical aortic valve prosthesis implantation in young patients. The age limits for the implantation of biological valves decreased significantly in the last 15 years. It is pure speculation as to whether incentive-driven reimbursement schemes in hospitals or the relationship between professional societies and the medical device industry explain this clinical development.[10] Interestingly, a Nature Editorial bemoaned that surgical science is becoming increasingly irrelevant.[11] This denunciation is not supported by the situation with aortic valve diseases. Outcome studies in surgical aortic valve recipients are published regularly.[6-9] However, it is blatantly obvious that these insights do not delve too deeply into the daily best practice guidelines.[2,12]

As early as 2000, a double-blind randomized clinical trial confirmed that surgically implanted biological heart valves (BHVs) degenerate in an age-dependent manner.[13] In 2011, these data were confirmed by Weber et al.,[9] who showed that the implantation of bioprostheses correlated with increased mortality and the incidence of reoperation incidence in patients aged 50–60 years compared to mechanical aortic valve prostheses. Interestingly, recipients of bioprostheses presented with impaired haemodynamic performance in their postoperative echocardiographic follow-up.

Scarce information is available in the literature on the *de novo* occurrence of heart failure in recipients of biological
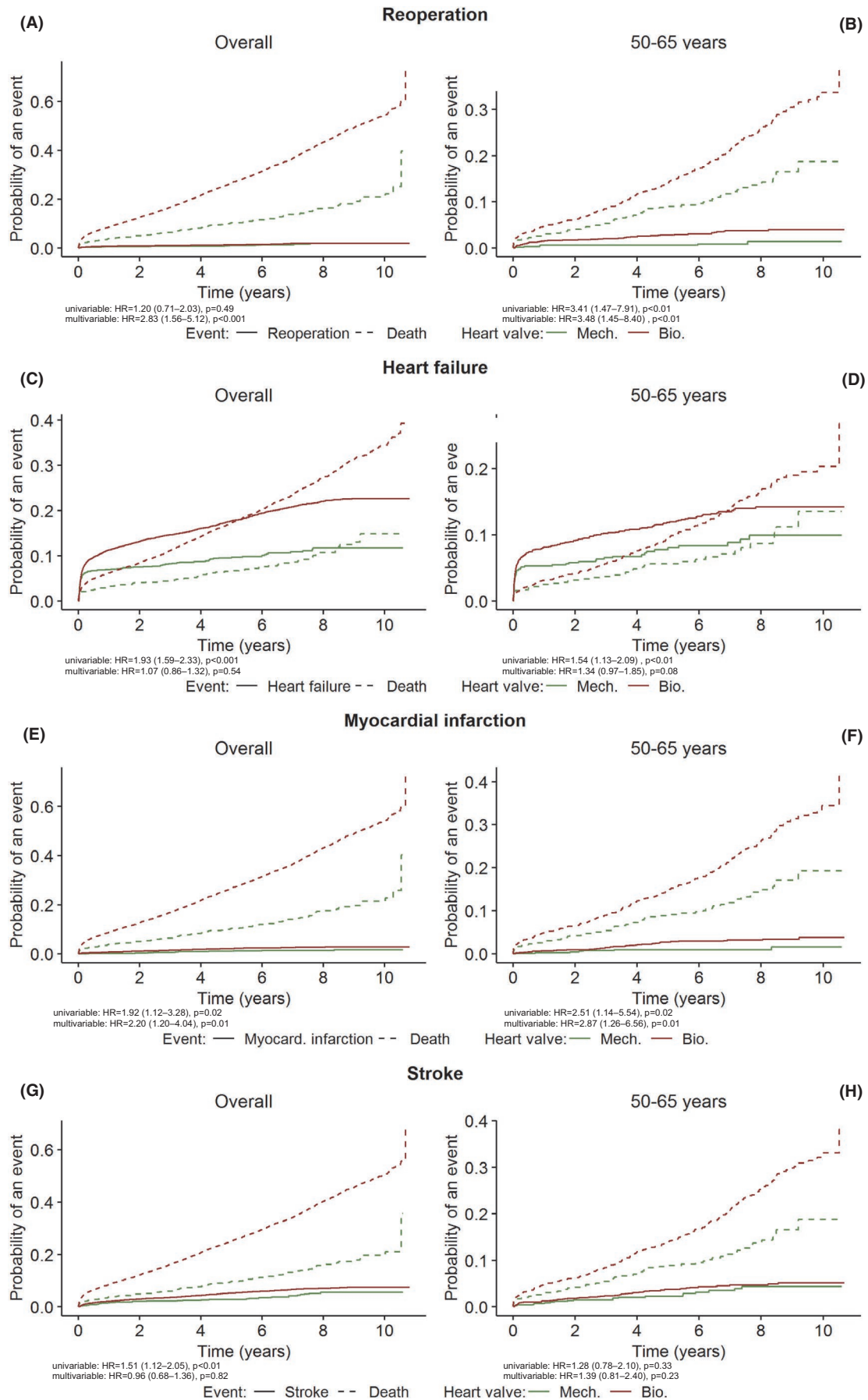
Reoperation

(A) Overall

(B) 50-65 years

univariable: HR=1.20 (0.71–2.03), p=0.49
multivariable: HR=2.83 (1.56–5.12), p<0.001

univariable: HR=3.41 (1.47–7.91), p<0.01
multivariable: HR=3.48 (1.45–8.40) , p<0.01

Event: —— Reoperation - - Death   Heart valve: —— Mech. —— Bio.

Heart failure

(C) Overall

(D) 50-65 years

univariable: HR=1.93 (1.59–2.33), p<0.001
multivariable: HR=1.07 (0.86–1.32), p=0.54

univariable: HR=1.54 (1.13–2.09) , p<0.01
multivariable: HR=1.34 (0.97–1.85), p=0.08

Event: —— Heart failure - - Death   Heart valve: —— Mech. —— Bio.

Myocardial infarction

(E) Overall

(F) 50-65 years

univariable: HR=1.92 (1.12–3.28), p=0.02
multivariable: HR=2.20 (1.20–4.04), p=0.01

univariable: HR=2.51 (1.14–5.54), p=0.02
multivariable: HR=2.87 (1.26–6.56), p=0.01

Event: —— Myocard. infarction - - Death   Heart valve: —— Mech. —— Bio.

Stroke

(G) Overall

(H) 50-65 years

univariable: HR=1.51 (1.12–2.05), p<0.01
multivariable: HR=0.96 (0.68–1.36), p=0.82

univariable: HR=1.28 (0.78–2.10), p=0.33
multivariable: HR=1.39 (0.81–2.40), p=0.23

Event: —— Stroke - - Death   Heart valve: —— Mech. —— Bio.

FIGURE 3 Legend on next page

FIGURE 3 Cumulative incidence plots for the secondary outcomes reoperation, heart failure, myocardial infarction and stroke for both all patients and patients between 50 and 65 years. Death has been included as a competing risk. (A) The chance of re-operation in the overall cohort and (B) patients aged 50–65 years was significantly increased in patients receiving bioprostheses. (C) The risk of heart failure was not significantly influenced by the choice of prostheses both in the overall cohort and (D) in patients aged 50–65 years. (E) Patients with bioprostheses had a higher risk of myocardial infarction aortic valve replacement, both in the overall cohort and (F) the 50–65 years age group. (G) After mechanical valve prosthesis implantation patients are forced to take anticoagulation daily, however, the risk of stroke was equal in the overall cohort and (H) patients aged 50–65 years

versus mechanical heart valves. Ruel et al. demonstrated that recipients of BHVs develop earlier NYHA 3–4 heart failure than recipients of mechanical aortic valve prostheses.[14] This observation makes sense given that Percy et al. and Salaun et al. showed that >40% of all patients aged <65 years who are implanted with bioprostheses develop subclinical structural valve degeneration, leading to increased cardiac strain.[15,16]

Early clinical and subclinical valve degeneration occurs in recipients of bioprostheses in an age-dependent manner. Leaflet thrombosis was assessed in both transcatheter aortic valve recipients and surgical aortic valve recipients. This group found an increased incidence of hypoattenuated leaflet thickening and reduced leaflet motion in recipients of biological scaffolds early after implantation.[17] Our investigation found a trend towards increased incidence of newly diagnosed heart failure in recipients of bioprostheses compared to mechanical aortic valve prostheses in the 50–65-year-old patient group. Regarding the observed decrease in survival and increased incidence of reoperation among recipients of bioprostheses who were 50–65 years old, an aggravated early immunological host-valve immune reaction can be expected.[18]

Our and previous studies have shown that the implantation of Gal-bearing bioprostheses elicits a short- and long-term alpha-Gal-specific immune response that is associated with clinically proven valve degeneration.[19–23] Recently, Veraar et al.[24] showed that the implantation of a Gal-bearing TAVR scaffold elicited a significant immune reaction via complement factor 3a, alpha-Gal-specific IgG3, NETosis-specific citrullinated histone H3 (CitH3) and the systemic inflammation marker soluble suppression of tumorigenicity 2 (sST2) 90 days after TAVR. Thus, it is important to acknowledge that complement activation, NETosis, the ST2 axis and IgG3 play a role in immune thrombosis.[25]

4.1 | How can this degenerative process of bioprostheses be modified in the future?

Several promising techniques have been reported to potentially increase the longevity of BHVs. In 2013, treatment of BHVs with alpha-galactosidase was shown to

effectively remove alpha-Gal epitopes from both bovine and porcine tissues.[26] Naso et al.[27] introduced a preservation technique (ie FACTA) that guarantees improved tissue biocompatibility by inactivating up to 95% of the alpha-Gal epitopes, thereby reducing the propensity of BHVs to calcify.

In addition to preservation techniques, there is growing interest in developing Gal-free BHVs from Gal-knockout pigs. Recently, Rahmani and colleagues[28] used Gal-knockout pigs to engineer BHVs out of porcine pericardial leaflets, with excellent haemodynamics, long-term durability and no thrombogenicity in a sheep model. Promising results of ongoing research on tissue-engineered heart valves for TAVR based on decellularized matrix in the pulmonary and aortic tissue were also recently published in humans.[29]

4.2 | Limitations

Our study aims to generate real-world evidence using administrative data from health insurance carriers, which reflect the current state in a European country with a well-established social welfare system. The observational design of this study has some limitations as is the case in most health service research projects.

First, our data were obtained retrospectively and do not meet the criteria of a prospective randomized study. We did not perform controlled treatment allocation. Second, some bias may result from the prosthesis type allocated to individual patients. Implantation of mechanical prostheses could have been more likely in younger patients with less comorbid conditions when compared to sicker patients in the same age category. However, we observed only diabetes mellitus to be more present in the bioprostheses group in patients aged 50–65 years. We included prior diagnosis of diabetes mellitus into the multivariable analyses to correct for this bias. Even though we attempted to limit bias by careful integration of comorbidities in the Cox regression analysis, some residual confounding is almost certainly present, as is the case in all observational studies. Finally, we did not perform propensity score matching in this retrospective research to avoid a reduction of the study population eligible for final analyses. However, we carefully applied multivariable adjustment to limit bias and confounding.

5 | CONCLUSIONS

We are convinced that biological scaffolds will supersede mechanical aortic valve prosthesis implantation in the future when appropriate 'humanized' valves are provided by the commercial valve industry. Based on our real-life data representing >98% of the Austrian population during follow-up, we feel that the overzealous implantation of bioprostheses in patients who are 50–65 years old has to undergo a critical appraisal and calls for a renaissance of mechanical aortic valve prosthesis implantation strategies in cardiac surgery. Professional societies and the national regulatory body will have to inform the public that lowering the age limits for bioprostheses is associated with increased mortality, as demonstrated in our 50–65-year-old patient cohort.

CONFLICT OF INTEREST

The Author(s) declare(s) that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

HJA is responsible for conceptualization. DT, PK, BR and HJA conceived the study and curated data. DT, HJA, ML and PK wrote the paper and visualized the data. PK and AG cleaned, analysed and verified the underlying data. HJA provided funding for the paper. All authors commented on the paper, oversaw the analysis and edited the final manuscript. All authors contributed to the study design. All authors contributed to drafting the paper and revised the manuscript for important intellectual content. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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