ARTIGO ORIGINAL ORIGINAL ARTICLE

EARLY AND MIDTERM OUTCOMES FOLLOWING AORTIC VALVE REPLACEMENT WITH MECHANICAL VERSUS BIOPROSTHETIC VALVES IN PATIENTS AGED 50 TO 70 YEARS

Rafael Rocha[1], Rui J. Cerqueira[1,2], Francisca A. Saraiva[1], Soraia Moreira[1,2], António S. Barros[2], Jorge Almeida[1,2], Mário J. Amorim[1,2], André P. Lourenço[1,3], Paulo Pinho[1,2], Adelino Leite-Moreira[1,2]

[1]Department of Surgery and Physiology, Cardiovascular Research and Development Center, Faculty of Medicine of the University of Porto, Porto, Portugal
[2]Department of Cardiothoracic Surgery, Centro Hospitalar Universitário São João, Porto, Portugal
[3]Department of Anesthesiology, Centro Hospitalar Universitário São João, Porto, Portugal

*Contacto Autor: amoreira@med.up.pt

Abstract

Objectives: *To compare 7-year survival and freedom from reoperation, as well as early clinical and hemodynamic outcomes, after surgical aortic valve replacement (SAVR) with mechanical or bioprosthetic valves in patients aged 50-70 years.*

Methods: *single-center retrospective cohort study including adults aged 50-70 years who underwent SAVR in 2012 with a mechanical or bioprosthetic valve. Median follow-up was 7 years. Univariable analyses were performed using Kaplan-Meier curves and Log-Rank tests for survival and freedom from reoperation analyses. Multivariable time-to-event analyses were conducted using Cox Regression.*

Results: *Of a total of 193 patients, 76 (39.4%) received mechanical valves and 117 (60.6%) received bioprosthetic valves. A trend for better survival was found for mechanical prostheses when adjusting for EuroSCORE II (HR: 0.35; 95%CI: 0.12-1.02, p=0.054), but using a backward stepwise Cox regression prosthesis type was not retained by the model as an independent predictor of survival. Moreover, mechanical prostheses showed trends for higher freedom from reoperation (100% vs. 95.5%, Log-Rank, p=0.076), higher median EuroSCORE II (2.52% vs. 1.95%, p=0.06) and early mortality (7.9% vs. 2.6%, p=0.086). However, after adjusting for EuroSCORE II, there was no significant difference in early mortality (OR: 2.3, 95%CI: 0.5-10.5, p=0.272). Regarding hemodynamic performance at follow-up echocardiogram, there were no differences other than left ventricular mass regression, which was not as pronounced in the mechanical group (-12% vs. -21%, p=0.002).*

Conclusion: *Mechanical and bioprosthetic aortic valves prostheses showed similar mid-term survival in the 50-70 age group. Further prospective and larger studies are needed to provide evidence-based recommendations on this topic.*

INTRODUCTION

The ideal type of prosthetic heart valve for Aortic Valve Replacement (AVR) in patients aged 50 to 70 years remains a matter of debate in Cardiac Surgery. In fact, the trade-off between durability and anticoagulation-related bleeding is the cornerstone of prosthesis choice and this decision requires weighing these factors on a case-by-case basis. Age, comorbidities and patient's lifestyle and preferences, among others, should be taken into account. As a rule of thumb, the perceived probability of the patient outliving a functional bioprostheses will drive the decision, and thus age is a major determinant to consider. However, there is still no agreement among leading scientific societies on the best age threshold to guide this decision.

Figure 1 represents the differences between European Society of Cardiology/European Society of Cardiothoracic Surgery Guidelines (ESC/EACTS)[1] and American Heart Association/American College of Cardiology (AHA/ACC)[2] recommendations for mechanical versus biological valves according to age. The gray zone for which both types of prostheses are appropriate is between 60 and 65 years old in ESC/EACTS Guidelines, as opposed to 50 to 70 years old in AHA/ACC guidelines. Mechanical valves were recommended as the best option for patients up to

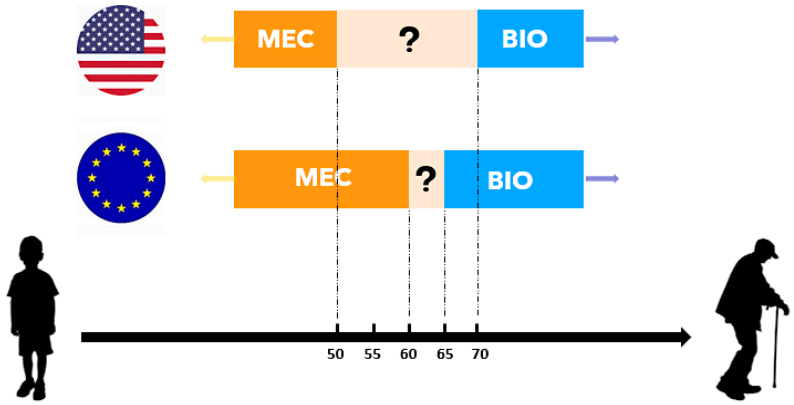

Figure 1 *Recommendations for use of a mechanical or bioprosthetic valve, according to current American (AHA/ACC) and European (ESC/EACTS) Guidelines on Management of Valvular Heart Disease.*

60 years old in the previous AHA/ACC guidelines and the evidence to support lowering the cut-off to 50 years has been questioned. On the one hand, several large, observational studies and a single recent randomized controlled trial (RCT)[3] showed similar long-term survival for the two types of prostheses in this patient population.[4-6] On the other hand, several other studies evidenced a survival benefit for mechanical prostheses in this age group[7-10], including a recent meta-analysis of propensity score-matched studies and RCT.[11]

Therefore, we aim to compare 7-year survival and freedom from reoperation, as well as early clinical and hemodynamic outcomes, after surgical aortic valve replacement (SAVR) with mechanical or bioprosthetic valves in a sample of patients aged 50-70 years.

METHODS

Study Design and Sample

We performed a single-center retrospective cohort study.

Patients aged 50 to 70 years old who underwent SAVR with a Mechanical or Freedom Solo®, Trifecta® or Perimount® bioprosthetic valves during one year (2012), at the Cardiothoracic Surgery Department of *Centro Hospitalar Universitário São João* (CHUSJ), Porto, Portugal, were consecutively included. Concomitant procedures were not excluded. Patients were grouped according to their aortic valve prosthesis – mechanical (MEC) or biological (BIO) –; the choice between MEC or BIO was an individualized, shared decision process between the patient and the surgeon.

Data Collection

Patients' data, including sociodemographic characteristics, comorbidities, echocardiography, admission status, intraoperative, and postoperative variables, were derived retrospectively from the patients' clinical records and the Department's informatics databases.

Data collected at baseline included age, sex, previous cardiac surgery, comorbidities (hypertension, diabetes, dyslipidemia, chronic pulmonary disease, atrial fibrillation (AF), coronary artery disease, cerebrovascular disease, peripheral artery disease, chronic renal disease), NYHA status, CCS status, history of smoking and obesity. From the preoperative echocardiogram, we obtained ejection fraction, mean and maximum transvalvular gradients, aortic valve pathology, and etiology. Surgical priority, procedures performed, cardiopulmonary bypass and aortic clamp times were recorded, and EuroSCORE II was calculated. Variables are defined in Table 1.

Outcomes

Survival and freedom from prosthesis-related reoperation were determined through the National Registry *Registo de Nacional de Utentes* (RNU) and consultation of informatics medical records, in May 2019. Median follow-up time was 7 years.

In the early postoperative period, we recorded reoperations and their respective reason, renal function worsening, severe thrombocytopenia, need of red blood cell transfusion, the need of inotrope support, prolonged invasive mechanical ventilation, stroke, *de novo* AF, permanent pacemaker implantation, length of intensive care unit stay, length of hospital stay and early mortality.

According to the local protocol, the postoperative transthoracic echocardiographic evaluation was performed 2 to 5 months after surgery, at a median of 3 months. Ejection fraction, mean and maximum transprosthetic gradients and patient-prosthesis mismatch (PPM) were registered.

Structural valve deterioration (SVD) was considered if any intrinsic changes in the valve occurred. A non-structural valve dysfunction (NSVD) was defined as any abnormality that did not directly involve valve components.[12]

Statistical Analysis

Statistical analyses were run on Statistical Package for the Social Sciences version 25 (SPSS) Software (IBM Corporation, Armonk, NY, USA). Categorical variables are presented as absolute and valid relative frequencies, excluding missing cases. The Chi-squared or Fisher's

Table 1 **Definition of variables and outcomes**

Variable	Definition
Chronic Pulmonary Disease	No/Yes - long term use of bronchodilators or steroids for lung disease
Coronary Artery Disease	No/Yes - >50% stenosis of 1,2 or 3 vessels
Cerebrovascular Disease	No/Yes - Stroke, transient ischemic attack, carotid surgery, carotid occlusion/>50% stenosis
Peripheral artery disease (PAD)	No/Yes – Claudication, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb arteries or carotids, abdominal aortic aneurysm, non-invasive test positive for PAD
Chronic renal disease	No/Yes, moderate - Creatinine Clearance < 85 mL/min/1.73m^2 or severe if Creatinine Clearance < 50 mL/min/1.73m^2 or Dialysis
Obesity	No/Yes – BMI ≥ 30kg/m^2
Left ventricle function	Normal-Mild: ejection fraction ≥40%; Moderate-Severe: ejection fraction <40%
Surgical Priority	Elective if admitted electively for a previously scheduled surgery; Urgent if not admitted electively and needed surgery before discharge or if required operation before the beginning of the next working day
Outcomes	**Definition**
Renal Function Worsening	Maximum post-operative creatinine > 1.5x preoperative creatinine
Need of Transfusion	No/Yes – Need of 2 or more units of Red Blood Cells
Need of Inotropic Support	No/Yes – Need of 2 or more inotropes or IABP
Prolonged Invasive Mechanical Ventilation	No/ Yes – >24 hours of mechanical ventilation
Stroke	No/Yes – Transient or Permanent Ischemic Attack
Postoperative Atrial Fibrillation	No/Yes – *de novo* Atrial Fibrillation in the postoperative period
Early Mortality	Death within 30 days after surgery or before hospital discharge
Early Reoperation	Reoperation within 30 days after surgery or before hospital discharge
Patient-Prosthesis Mismatch	Effective orifice area indexed to patient's body surface area: No / Yes, if moderate (0.85 cm^2/m^2 ≥ EOAi ≥ 0.65 cm^2/m^2) or severe (EOAi ≤ 0.65 cm^2/m^2)
Left Ventricle Mass Regression	(Pre-operative LV Mass – Post-operative LV mass) / (Pre-operative LV Mass)

exact test was used for categorical variables comparison between groups, as appropriate. Continuous variables are presented as mean (standard deviation) or median (interquartile range), according to data distribution, assessed by the Shapiro-Wilk test. The Student's t-test or the Mann-Whitney test were used for between-groups comparison of continuous variables.

Univariable survival and freedom from reoperation analyses were performed using Kaplan-Meier curves and Log-Rank tests. Multivariable time-to-event analyses were conducted using Cox Regression: 1) adjusted for EuroSCORE II, which combines many factors which could predictably cause confounding and 2) adjusting for all covariates $p<0.1$ at univariable analysis and prosthesis group using a backward stepwise Cox regression to identify potential predictor variables. Multivariable logistic regression was also used to estimate the impact of the type of prosthesis on early mortality.

Statistical models were checked for the association between covariates and dependent variables (Omnibus test, G^2) and calibration (Hosmer-Lemeshow – goodness of fit test). Discriminative power was assessed through the area under the Receiver Operating Characteristic (AUC ROC) curve (c-statistic) – considered good if >0.7. The proportional hazard assumption for Cox regression was assessed using interaction terms of time with group.

Ethics

This study was approved by the Ethics Committee and Administration Council of the CHUSJ. As this was a retrospective study, informed consent was waived. Anonymity and confidentiality were assured.

RESULTS

Study Sample

Of a total of 193 patients aged 50 to 70 years submitted to SAVR, 76 (39.4%) received mechanical valves (MEC) and 117 (60.6%) received bioprosthetic valves (BIO). Table 2 describes the main characteristics of the sample.

Table 2 **Characteristics of the sample at baseline**

	Total n=193	Bioprosthesis n= 117	Mechanical n=76	*p* value
Age, y, median (IQR)	63 (58-67)	66 (62-68)	59.5 (55-63)	<0.001
Male sex, n (%)	112 (58.0)	72 (61.5)	40 (52.6)	0.221
Obesity (BMI ≥30.00 kg/m²), n (%)	55 (28.5)	37 (31.6)	18 (23.7)	0.233
Hypertension, n (%)	140 (72.5)	91 (77.8)	49 (64.5)	0.043
Diabetes, n (%)	45 (23.3)	32 (27.4)	13 (17.1)	0.100
Dyslipidemia, n (%)	122 (64.2)	79 (68.1)	43 (58.1)	0.161
History of smoking, n (%)	51 (28.2)	34 (29.8)	17 (25.4)	0.520
Coronary artery disease, n (%)	51 (26.4)	38 (32.5)	13 (17.1)	0.018
Cerebrovascular disease, n (%)	21 (10.9)	20 (17.1)	1 (1.3)	0.001
Peripheral artery disease, n (%)	8 (4.1)	4 (3.4)	4 (5.3)	0.530
Chronic kidney disease, n (%) Moderate Severe	 61 (31.6) 14 (7.3)	 40 (34.2) 9 (7.7)	 21 (27.6) 5 (6.6)	0.653
Atrial fibrillation, n (%)	40 (20.9)	16 (13.8)	24 (32)	0.003
NYHA ≥ III, n (%)	48 (24.9)	33 (28.2)	15 (19.7)	0.184
CCS ≥ III, n (%)	14 (7.8)	9 (7.9)	5 (7.6)	0.939
Chronic Pulmonary Disease, n (%)	14 (7.3)	6 (5.1)	8 (10.5)	0.158
EuroSCORE II %, median (IQR)	2.03 (1.1 – 3.75)	1.95 (1.08 – 3.65)	2.52 (1.23 – 5.43)	0.158
Moderate to severe LV dysfunction	19 (10.0)	15 (12.8)	4 (5.5)	0.101
Reason for AV surgery, n(%)				
Aortic stenosis	123 (63.7)	88 (75.2)	35 (46.1)	0.001
Aortic regurgitation	38 (19.7)	16 (13.7)	22 (28.9)	
Stenosis and regurgitation	22 (11.4)	8 (6.8)	14 (18.4)	
Prosthetic Dysfunction	10 (5.2)	5 (4.3)	5 (6.6)	
Degenerative Aortic Disease, n (%)	91 (47.2)	75 (64.1)	16 (21.1)	<0.001
Rheumatic Aortic Disease, n (%)	28 (14.5)	8 (6.8)	20 (26.3)	<0.001
Bicuspid Aortic Valve, n (%)	35 (18.1)	20 (17.1)	15 (20.5)	0.642
Native Valve Infective Endocarditis, n (%)	7 (3.6)	6 (5.1)	1 (1.3)	0.248
Prosthetic Dysfunction, n (%)	10 (5,2)	5 (4.3)	5 (6.6)	0.519
Infective Endocarditis, n (%)	7 (3.6)	4 (3.4)	3 (3.9)	
Previous cardiac surgery, n (%)	23 (11.9)	7 (6.0)	16 (21.1)	0.002

Patients with MEC were significantly younger (60 (62-68) *vs* 66 years (55-63), p<0.001), and presented a lower prevalence of hypertension (64.5% *vs* 77.8%, p=0.043), coronary and cerebrovascular disease (17.1% *vs* 32.5%, p=0.018 and 1.3% *vs* 17.1%, p=0.001, respectively). On the other hand, they had a higher prevalence of atrial fibrillation (AF, 32% *vs* 13.8%, p=0.003), and a higher frequency of previous cardiac surgery (21.1% vs 6%, p=0.002). There

Table 3 **Surgical variables**

	Total n=193	Bioprosthesis n= 117	Mechanical n=76	*p* value
Urgent surgery, n (%)	56 (29.0)	35 (29.9)	21 (27.6)	0.733
Isolated AVR, n (%)	81 (42.0)	54 (46.2)	27 (35.5)	0.144
Multiple procedures, n (%)				
Mitral valve intervention	30 (15.5)	12 (10.3)	18 (23.7)	0.012
Tricuspid valve intervention	24 (12.4)	8 (6.8)	16 (21.1)	0.003
Multivalve	38 (19.7)	14 (12)	24 (31.6)	0.001
CABG	54 (28.0)	39 (33.3)	15 (19.7)	0.040
Ascending aorta Surgery	38 (19.7)	16 (13.7)	22 (28.9)	0.009

were no significant differences in NYHA Class, CCS class, diabetes, or chronic kidney disease. There was a trend for a higher median EuroSCORE II in the MEC group (2.52% (1.23-5.43) vs. 1.95% (1.08 – 3.65), p=0.06).

Regarding the indication for SAVR, there was a higher prevalence of Aortic Stenosis in the BIO group (75.2% *vs* 46.1%, p<0.001). The etiology of aortic valve pathology also differed – MEC patients had a higher prevalence of Rheumatic Aortic Disease (27.6% *vs* 6.8%, p<0.001), and BIO patients had a higher prevalence of Degenerative Aortic Disease (64.1% *vs* 21.1%, p<0.001). No differences regarding Bicuspid Aortic Valve or Infective Endocarditis were found.

Furthermore, intraoperatively, patients in the MEC group were more likely to undergo concomitant interventions on other valves (31.6% *vs* 12.0%, p=0.001) or the ascending aorta (28.9% *vs* 13.7%, p=0.009), but less likely to undergo simultaneous CABG (19.7% *vs* 33.3%, p=0.04) (Table 3).

Cardiopulmonary Bypass (CBP) and Aortic Cross Clamp times in the overall sample and patients undergoing isolated AVR are detailed in Figure 3. Considering isolated AVR, the groups presented similar cardiopulmonary bypass (CBP: 99 (84-112) vs 90 (80-114) minutes, p=0.339) and aortic cross-clamp times (AC: 69 (57-80) vs 65 (57-78) minutes, p=0.434).

Survival and Freedom from Reoperation

Excluding early mortality, 21 patients died during follow-up: 16 (14%) from the BIO group and 5 (7%) from the MEC group. The 7-years cumulative survival was 92.9% in the MEC group and 84.8% in the BIO group (Log-Rank test, p=0.173, Figure 2A).

Although we found a tendency for MEC to be protective of mortality after adjusting for EuroSCORE II (HR: 0.35, 95%CI: 0.12-1.02, p=0.054), adding age to the model mitigates this (HR: 0.46, 95%CI: 0.14-1.5, p=0.189) and prosthesis type was not one of the three variables identified as independent predictors of mortality in the backward method, which included prosthesis type, age, AF,

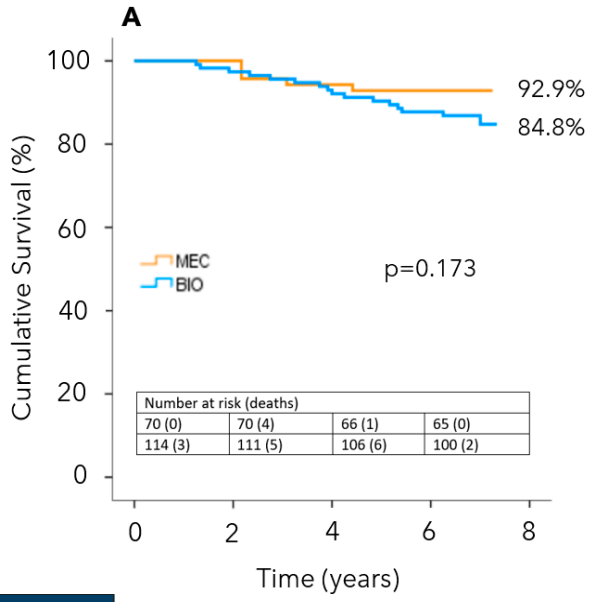

Figure 2A *Kaplan-Meier Curve for Survival (Log-rank test, p=0.173). MEC: Mechanical Prostheses. BIO: Bioprostheses.*

cerebrovascular disease, coronary artery disease, diabetes, hypertension. Atrial fibrillation (HR: 3.11, 95%CI: 1.28 – 7.55, p=0.012), diabetes (HR: 2.32, 95%CI: 0.98 – 5.53, p=0.058) and hypertension (HR: 6.88, 95%CI: 0.90 – 52.39, p=0.063) were the three variables retained by the model.

We found a trend for higher freedom from reoperation at 7 years in the MEC group (100% *vs* 95.5%, Log-Rank test, p=0.076): there were no reoperations in the MEC group, as opposed to 5 reoperations in the BIO group (Figure 2B). Four of these cases were due to Prosthetic Valve Endocarditis, and 1 due to Structural Valve Deterioration.

In-Hospital Outcomes

Table 4 summarizes in-hospital results. In the MEC group, we found a trend for a higher incidence of *de novo* postoperative atrial fibrillation (POAF, 42.6% *vs* 28.0%, p=0.079), and a higher need for inotropic support with 2

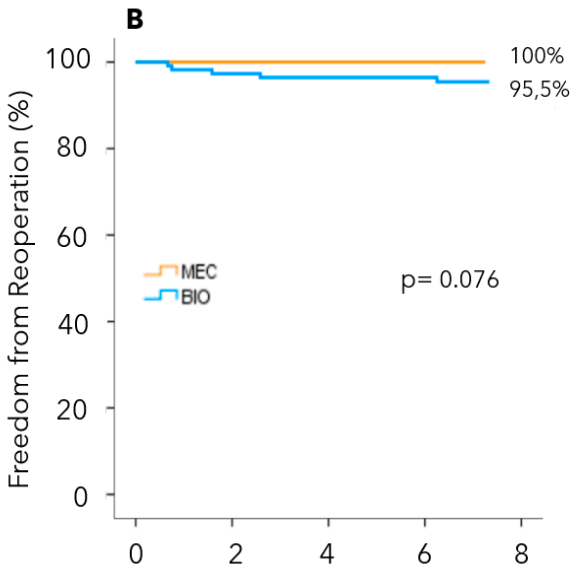

Figure 2B *Kaplan-Meier Curve for Freedom from Reoperation (Log-Rank Test=0.076). MEC: Mechanical Prostheses. BIO: Bioprostheses.*

or more inotropes (22.2% *vs* 10.9%, p=0.039). The median ICU stay was longer (6 (3-8) *vs* 3 (2-5) days, p<0.001).

There were no significant differences in renal function worsening, severe thrombocytopenia, prolonged invasive mechanical ventilation, stroke, permanent pacemaker implantation, or length of hospitalization. Reoperation in the early postoperative period was also similar between the two groups (3.9% MEC *vs* 4.3% BIO, p=0.912).

Regardless of the trend for higher early mortality in the MEC group - 7.9% *vs* 2.6%, p=0.086 -, after adjusting for the EuroSCORE II we did not find the type of prosthesis as an independent predictor of early mortality (OR MEC: 2.32, 95%CI: 0.52-10.50, p=0.272).

Hemodynamic Evaluation

Regarding hemodynamic performance assessed by echocardiography performed at 3 months (Table 4) there were no differences between MEC and BIO patients in mean transprosthetic gradient (14 *vs* 13 mmHg, p=0.115), indexed Effective Orifice Area (0.94 (0.84-1.04) *vs* 0.98 (0.86-1.11) cm^2/m^2, p=0.113) or Patient-Prosthesis Mismatch (29.2% vs 19.4%, p=0.146).

Table 4 **In-hospital outcomes and 3 months transthoracic echocardiographic outcomes**

	Total n=193	Bioprosthesis n= 117	Mechanical n=76	*p* value
In-Hospital Outcomes				
Early Mortality, n (%)	9 (4.7)	3 (2.6)	6 (7.9)	0.086
Early Reoperation n(%)	8 (4.1)	5 (4.3)	3 (3.9)	0.912
Re-exploration of thorax due to bleeding, n (%)	3 (1.6)	3 (2.6)	0 (0)	0.287
Sternal re-suturing, n (%)	2 (1.04)	1 (0.9)	1 (1.3)	0.757
Acute kidney injury, n (%)	20 (10.8)	13 (11.4)	7 (9.9)	0.742
Need of ≥ 2 RBC, n (%)	35 (20.1)	20 (19.4)	15 (21.1)	0.782
Need of ≥2 or inotropic or IABP, n (%)	28 (15.4)	12 (10.9)	16 (22.2)	0.039
Prolonged invasive mechanical ventilation, n (%)	15 (6.9)	10 (8.8)	5 (6.9)	0.656
Stroke, n (%)	5 (2.7)	4 (3.4)	1 (1.4)	0.651
Post-operative atrial fibrillation, n (%)	48 (32.7)	28 (28.0)	20 (42.6)	0.079
Permanent pacemaker implantation, n (%)	10 (5.4)	4 (3.5)	6 (8.5)	0.144
Length of ICU stay, median days (IQR)	3 (2-6)	3 (2-5)	6 (3-8)	<0.001
Length of Hospitalization, median days (IQR)	7 (6-11)	7 (6-10)	7 (6-12)	0.773
3 months Transthoracic Echocardiogram				
Left Ventricle Mass Regression, mean ± SD	-18 ± 17	-21 ± 16	-12 ± 16	0.002
EOAi, cm^2/m^2	0.96 (0.86 – 1.11)	0.98 (0.86 – 1.20)	0.94 (0.84 – 1.04)	0.113
Moderate to severe PPM, n(%)	38 (23.3)	19 (19.4)	19 (29.2)	0.146

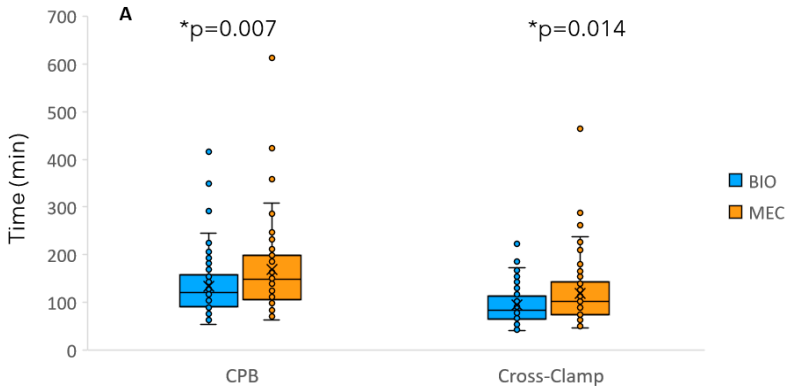

Figure 3A *Cardiopulmonary Bypass (CPB) and Aortic Cross-Clamp Time (min) in the overall sample.*

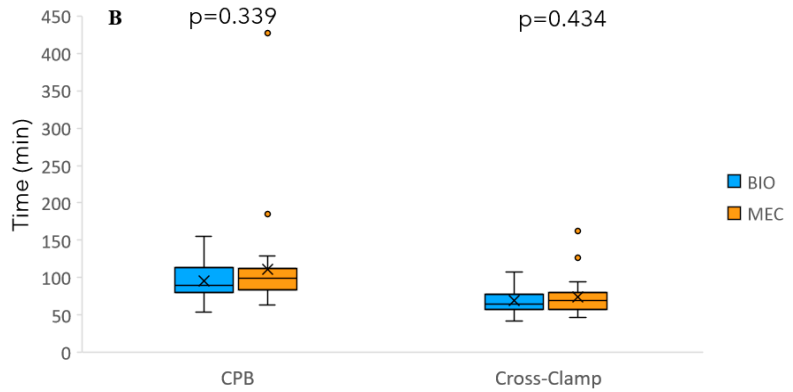

Figure 3B *Cardiopulmonary Bypass (CPB) and Aortic Cross-Clamp Time (min) for patients undergoing Isolated AVR.*

Left ventricular mass regression was more pronounced in the BIO group (-21% *vs* -12%, p=0.002) (Figure 4).

DISCUSSION

This single-center, single-year and retrospective study showed no significant differences in survival or in freedom from reoperation at 7-year follow-up, after SAVR with MEC or BIO valves, in patients aged 50 to 70 years (84.8% BIO *vs* 92.9% MEC and 95.5% BIO *vs*. 100% MEC, for cumulative survival and freedom from reoperation, respectively). However, there was a lower prevalence of postoperative complications, namely postoperative AF and need of inotropic support, and a shorter median ICU stay, as well as a trend for lower in-hospital mortality in the BIO group, which is in accordance with its lower EuroSCORE II 13 (1.95% BIO *vs* 2.52% MEC).

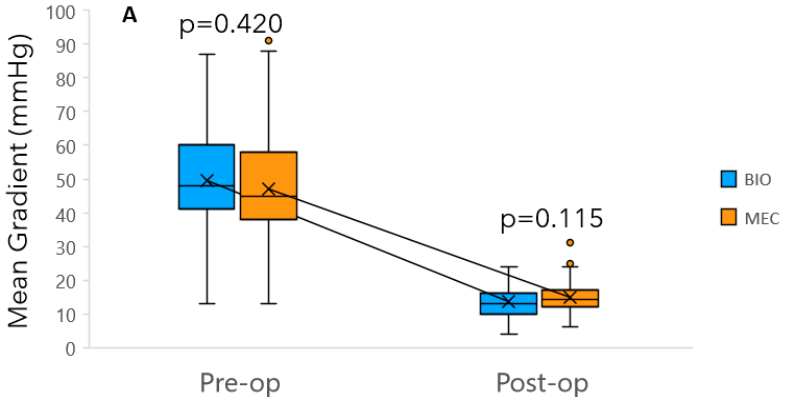

Figure 4A *Pre- and Post-operative transvalvular mean gradient (mmHg). MEC: Mechanical Prostheses. BIO: Bioprostheses.*

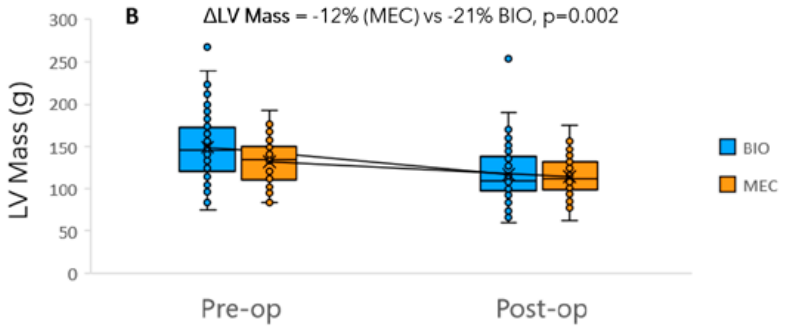

Figure 4B *Left Ventricular Pre- and Post-operative Mass. ΔLV Mass: left ventricle mass regression. MEC: Mechanical Prostheses. BIO: Bioprostheses.*

It should be noted that, by including all patients who underwent SAVR with a MEC or BIO prosthethic valve in 2012 (and not limiting our sample to primary, isolated SAVR), our study aims to provide an accurate representation of the real world setting. In fact, 59% of patients underwent multiple surgical procedures, including high risk cases such as aortic dissection and infective endocarditis.

Survival

Our study seems to support the current AHA/ACC Guidelines, according to which both types of valves are acceptable for patients aged 50-70 years, with respect to mid-term survival.

Similar conclusions have been drawn by other groups. The most recent RCT comparing mechanical and bioprosthetic valves in patients 55-70 years showed similar survival rates at 13 years (72.5% in the MEC group *vs* 69.4% in the BIO group), and type of valve was not an independent predictor of late mortality.[3] Also, in a propensity score-matched study, Chiang *et al* compared the two types of valves in patients aged 50 to 69 years undergoing primary, isolated AVR and concluded there was no significant 15-year difference in actuarial survival (62.1% in the MEC group *vs* 60.6% in the BIO group, HR: 0.97, 95% CI 0.83-1.14). Iribarne *et al* also found similar 15-year survival in both groups (60% in the MEC group *vs* 57% in the BIO group, HR: 0.87, 95% CI 0.67-1.13).[6]

However, other groups have found a survival advantage for mechanical prostheses in this age group: Glaser *et al* reported 5-, 10-, and 15-year survival of 92%, 79%, and 59% in the MEC group *vs.* 89%, 75%, and 50% in the BIO group (HR for BIO: 1.34, 95% CI: 1.09–1.66), in patients aged 50 to 69 years. A probable reason for this is the high quality of anticoagulation treatment in Sweden, which would positively influence the outcomes of the MEC group (leading to lower rates of bleeding and thromboembolic events) and distinguish it from studies performed in other countries.

It should be noted that within the 50 to 70 age group there could be subgroups whose outcomes differ and that might benefit from targeted approaches. For instance, Goldstone *et al.* compared the two types of valves in patients aged 45 to 659 and split patients into two age groups: 45-54 and 55-64, concluding that mortality at 15-years was lower in the MEC group only in the younger group (26.4% *vs* 30.6% at 15 years; p=0.03, HR:1.23, 95% CI 1.02-1.48), whereas in the older group the two types were comparable (32.1% *vs* 36.1% at 15 years, p=0.60, HR: 1.04, 95% CI 0.91-1.18).

Another point worth noting is that the benefits of MEC might only be noticeable at longer follow-up times: Kytö *et al.* compared mortality rates for the two type of valves in patients aged 50 to 70 at 1-, 5- and 10 years and found that, although there were no differences at 1- and 5- years (4.7% *vs* 4.9% and 12.7% *vs* 12%), at 10 years biological valves were associated with higher mortality – 27.6% *vs* 18.6% (HR: 1.39, 95% CI: 1.03-1.85, p=0.028).[14] Moreover, a recent meta-analysis of propensity score matched or RCT of patient ageds 50 to 70 years old, including 4648 patients, showed that mechanical valves are associated with survival benefit at 15 years (survival rate 62% *vs* 58%, MEC and BIO, respectively.[11]) These results are especially relevant for studies such as ours, as the lack of difference in survival could be due to a relatively short follow-up time, and may not hold true if we reexamine the same sample at 10 or 15-year follow-up.

Freedom from Reoperation

Unlike other studies, our results did not show a significant difference in freedom from reoperation, but a trend for higher freedom from reoperation at 7-years for the MEC group was reported (100% in the MEC group *vs* 95.5% in the BIO group, p=0.076). Both small sample size and the relatively short follow-up, which may not be sufficient for structural valve degeneration of bioprosthetic valves, could be reasons for not achieving statistical significance. Anselmi and colleagues showed that in patients under 60 years old fitted with a bioprosthetic valve, at 15 years 13.7% of patients had underwent reoperation for structural valve degeneration (SVD) and the average time for SVD was 11.9 years15 and in fact, in our study, only 1 patient was reoperated on for SVD. Other reports reinforce that the reoperation rates are consistently higher for bioprosthetic valves, especially for longer

follow-up periods: Kytö et al. presented reoperation rates of 8.5% *vs.* 1.4% at 10-years of follow-up9; Iribarne et al. showed a cumulative incidence of reoperation of 19.1% *vs* 3.0% at 15 years[6]; and a propensity score-matched study reported a cumulative incidence of reoperation of 45% *vs* 5% at 18 years.[5] Also, a recent meta-analysis by Diaz *et al* supported these findings, reporting a pooled incidence rate ratio of reoperation of 2.17 (1.67-2.86) for bioprosthetic valves, with reported mean follow-up time ranging from 6.6 to 9.8 years.[11]

However, it should be noted that reoperation does not seem to be an independent predictor of death in aortic valve replacement[16], and can be performed safely. Iribarne *et al.*, for example, showed a 30-day mortality rate of 2.4% for reoperative AVR. Chiang *et al.* interestingly, reported that the 30-day mortality rate after reoperation was lower than after a major bleeding event, 9.0% *vs* 13.2%, respectively, and the 15-year cumulative incidence of a major bleeding event occurred in 13% of MEC patients (as opposed to 6.6% in the BIO group).[4] Therefore, one should not rely solely on the assumption that, due to a higher risk of reoperation, biological valves are not the best option for a middle-aged patient.

In-Hospital Outcomes

In the unadjusted analysis, we found a trend for lower early mortality in the BIO group (2.6% *vs* 7.9%) related to the higher a priori risk of MEC group. Notwithstanding, after adjusting for EuroSCORE-II, we did not find prosthesis type to be an independent predictor of early mortality. Furthermore, there were significantly more postoperative complications (such as POAF, the need for inotropic support, or median ICU stay) in the MEC group, although this can also potentially be explained by the higher EuroSCORE-II. Several studies, including a randomized controlled trial, propensity score-matched studies, and an inverse-probability weighted study, showed no significant differences regarding these outcomes.[3-6]

Hemodynamic Performance

At follow-up echocardiogram at 3 months, both groups showed similar gradients, EOAi, and prevalence of PPM. Left ventricular mass regression, which has been suggested to be associated with improved long-term survival after AVR[17], was more pronounced in the BIO group (-21% *vs* -12%, p=0.002). However, it is not possible to ascribe these results solely to the type of prosthesis, as many factors are possibly contributing to left ventricular mass regression. For instance, patients in the BIO group were significantly older and had a higher prevalence of hypertension and coronary artery disease, as well as a higher rate of concomitant CABG. In contrast, patients in the MEC group showed a higher rate of multivalvular surgery, all of which could affect left ventricular mass regression.

Although the present study focused on age, there are other factors to consider when choosing the type of valve for a patient. For instance, a mechanical prosthesis is recommended for patients at risk of accelerated structural valve deterioration (such as patients with hyperparathyroidism). On the other hand, a bioprosthesis is recommended if there is a high bleeding risk or if good-quality anticoagulation is unlikely.[1] Moreover, patient preferences must be a crucial part of the decision.[1,2] Above all, the surgeon must aim to adequately provide all the relevant information to enable the patient to understand the compromises and make an informed decision.

In our study, aside from age, which was significantly different between the two groups, we found a higher preoperative prevalence of atrial fibrillation (AF) in patients with a mechanical prosthesis (32% *vs* 13.8%, p=0.003). This was not common in other studies.[4,8,9] The underlying reason might be that in 2012 non-vitamin K antagonist oral anticoagulant (NOACs) had not yet been widely adopted for atrial fibrillation, as only in the 2012 Focused Update of the ESC Guidelines for the management of atrial fibrillation were NOACs first recommended (and only for non-valvular AF, which was defined as AF not related to rheumatic valvular disease or prosthetic heart valves).[18] Therefore, these patients were already medicated with vitamin K antagonists, which might have tipped the balance in favor of MEC.

Although this single-year study did not address temporal changes in prosthetic valve selection at our centre, an increase in use of biological valves has been reported globally and across all age groups.[19,20] For instance, in the United States of America, the percentage of bioprosthetic valves implanted in adults rose from 37.7% in 1998-2001 to 63.6% in 2007-2011; this increased across all ages, having been most pronounced in patients aged 55 to 64 years21. There are several reasons for this trend: currently implanted bioprostheses are thought to last longer than past models, due to new anti-calcification and anti-immunogenicity strategies[22]; reoperation can be performed with low mortality rates (high-volume centers report mortality rates of 2-5% for reoperative AVR[4,6]) and there are emerging options such as Valve-in-Valve Technology (ViV, transcatheter valve implantation to replace a bioprosthetic valve), which offer safe alternatives to reoperation.[23] Thus, as bioprosthetic valves are becoming more durable and re-interventions safer, the balance between the risk of thrombotic/bleeding events versus the risk of reoperation seems to favor bioprosthetic valves in increasingly younger patients. However, it is important to keep in mind that solid evidence for widespread ViV usage and support for higher durability of recent biological valve iterations is still lacking, and that there is conflicting evidence regarding outcomes of bioprostheses in the 50 to 70 age group. Further larger and prospective studies should aim to provide evidence-based recommendations on this topic.

Limitations

It should be noted that this is a single-center study, including only a single year of SAVR, thus having a limited sample size, reducing statistical power of our results and precluding a generalization of results. Also, including all

patients aged 50 to 70 years old who underwent SAVR in 2012 reduces the comparability with other reports, many of which focus only on primary, isolated SAVR. Moreover, the type of valve for each patient was not randomized but left to the discretion of the surgeon and the patient, and we did not systematically register the motive for choice of valve type, although it would be pertinent to do so in future studies.

The retrospective nature of data precludes the inclusion of other valuable outcomes, such as bleeding events and hospitalizations during follow-up, and causes of death, which were not available, as patients' follow-up was often performed in other centers.

Despite having adjusted survival analyses for EuroSCORE II to mitigate confounding and selection bias, this score was designed towards predicting early mortality, not longer-term outcomes and only includes some of the relevant variables. Moreover, the small sample size and the small number of events limited the multivariable analysis performance. Furthermore, our median follow-up of 7 years could be insufficient to detect differences in outcomes in this sample.

CONCLUSION

In a real-world setting, in patients aged 50 to 70 years, both mechanical and bioprosthetic valves seem to be safe options, there being no relevant differences in terms of survival, at 7-year follow-up.

Ultimately, the choice of mechanical versus bioprosthetic valve replacement requires weighing the risk of bleeding and thrombotic events against the durability of the prosthesis and safety of reoperation. A shared and evidence-based decision process is key to maximize benefits for each patient. As of now, there is no single best answer. Further prospective and larger studies are needed to provide evidence-based recommendations on this topic.

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REFERENCES

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-2786. doi:10.1093/eurheartj/ehx391
2. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(25):e1159-e1195. doi:10.1161/CIR.0000000000000503
3. Stassano P, Di Tommaso L, Monaco M, et al. Aortic Valve Replacement. A Prospective Randomized Evaluation of Mechanical Versus Biological Valves in Patients Ages 55 to 70 Years. J Am Coll Cardiol. 2009;54(20):1862-1868. doi:10.1016/j.jacc.2009.07.032
4. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. JAMA - J Am Med Assoc. 2014;312(13):1323-1329. doi:10.1001/jama.2014.12679
5. Mcclure RS, Mcgurk S, Cevasco M, et al. Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position : A propensity-matched analysis. J Thorac Cardiovasc Surg. 2011;148(5):1931-1939. doi:10.1016/j.jtcvs.2013.12.042
6. Iribarne A, Leavitt BJ, Robich MP, et al. Tissue versus mechanical aortic valve replacement in younger patients: A multicenter analysis. In: Journal of Thoracic and Cardiovascular Surgery. Vol 158. Elsevier Inc.; 2019:1529-1538.e2. doi:10.1016/j.jtcvs.2019.02.076
7. Brown ML, Schaff H V, Lahr BD, et al. Aortic valve replacement in patients aged 50 to 70 years: Improved outcome with mechanical versus biologic prostheses. J Thorac Cardiovasc Surg. 2008;135(4):878-884. doi:10.1016/j.jtcvs.2007.10.065
8. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. Eur Heart J. 2016;37(34):2658-2667. doi:10.1093/eurheartj/ehv580
9. Goldstone AB, Chiu P, Baiocchi M, et al. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. N Engl J Med. 2017;377(19):1847-1857. doi:10.1056/NEJMoa1613792
10. Rodríguez-Caulo EA, Otero-Forero JJ, Sánchez-Espín G, et al. 15 years outcomes following bioprosthetic versus mechanical aortic valve replacement in patients aged 50–65 years with isolated aortic stenosis. Cir Cardiovasc. 2018;25(3):135-140. doi:10.1016/j.circv.2018.03.002
11. Diaz R, Hernandez-vaquero D, Alvarez-cabo R. Long-term outcomes of mechanical versus biological aortic valve prosthesis : Systematic review and meta-analysis. J Thorac Cardiovasc Surg. doi:10.1016/j.jtcvs.2018.10.146
12. Capodanno D, Petronio AS, Prendergast B, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: A consensus statement from the European Association of Percutaneous Cardiovascular Interven. Eur

Heart J. 2017. doi:10.1093/eurheartj/ehx303
13. Wang L, Han QQ, Qiao F, et al. Performance of euroSCORE II in patients who have undergone heart valve surgery: A multicentre study in a Chinese population. Eur J Cardio-thoracic Surg. 2014;45(2):359-364. doi:10.1093/ejcts/ezt264
14. Kytö V, Sipilä J, Ahtela E, Rautava P, Gunn J. Mechanical versus biological prostheses for surgical aortic valve replacement in patients aged 50-70. Ann Thorac Surg. 2019. doi:10.1016/j.athoracsur.2019.10.027
15. Anselmi A, Flecher E, Chabanne C, et al. Long-term follow-up of bioprosthetic aortic valve replacement in patients aged ≤60 years. J Thorac Cardiovasc Surg. 2017;154(5):1534-1541.e4. doi:10.1016/j.jtcvs.2017.05.103
16. Davierwala PM, Borger MA, David TE, Rao V, Maganti M, Yau TM. Reoperation is not an independent predictor of mortality during aortic valve surgery. J Thorac Cardiovasc Surg. 2006. doi:10.1016/j.jtcvs.2005.09.022
17. Ali A, Patel A, Ali Z, et al. Enhanced left ventricular mass regression after aortic valve replacement in patients with aortic stenosis is associated with improved long-term survival. J Thorac Cardiovasc Surg. 2011;142(2):285-291. doi:10.1016/j.jtcvs.2010.08.084
18. John Camm A, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J. 2012. doi:10.1093/eurheartj/ehs253
19. Siregar S, de Heer F, Groenwold RHH, et al. Trends and outcomes of valve surgery: 16-year results of Netherlands Cardiac Surgery National Database. Eur J Cardio-thoracic Surg. 2014;46(3):386-397. doi:10.1093/ejcts/ezu017
20. Head SJ, Çelik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. Eur Heart J. 2017;38(28):2183-2191. doi:10.1093/eurheartj/ehx141
21. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. J Thorac Cardiovasc Surg. 2015;149(5):1262-1269.e3. doi:10.1016/j.jtcvs.2015.01.052
22. Li KYC. Bioprosthetic Heart Valves: Upgrading a 50-Year Old Technology. Front Cardiovasc Med. 2019;6(April):1-6. doi:10.3389/fcvm.2019.00047
23. Ye J, Cheung A, Yamashita M, et al. Transcatheter aortic and mitral valve-in-valve implantation for failed surgical bioprosthetic valves an 8-year single-center experience. JACC Cardiovasc Interv. 2015;8(13):1735-1744. doi:10.1016/j.jcin.2015.08.012