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Mitral valve replacement in children: balancing durability and risk with mechanical and bioprosthetic valves

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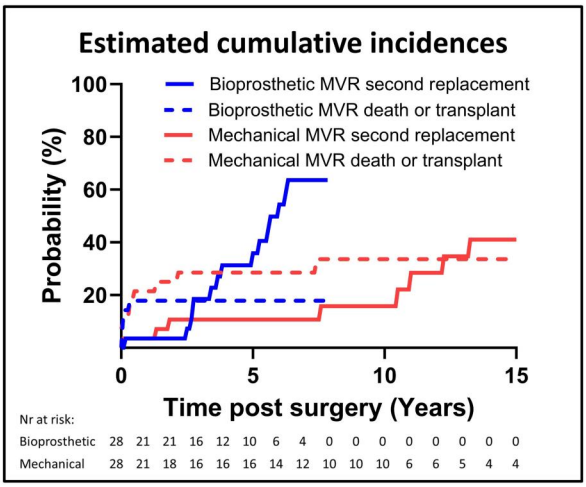
Mitral valve replacement in children: Balancing durability and risk with mechanical and bioprosthetic valves

Summary

A retrospective study of 56 children with mitral valve replacement (MVR) compared the durability and transplant-free survival between bioprosthetic and mechanical mitral valves. There is no difference in transplant-free survival between both groups. The lifespan of bioprosthetic mitral valves remains limited. After 15 years 40% of mechanical valves were replaced.



Legend: Estimated cumulative incidences with valve replacement and death or transplant as competing events

Abstract

OBJECTIVES: To investigate if there is still a place for bioprosthetic mitral valve replacement in children by comparing the prosthetic durability and transplant-free survival after bioprosthetic and mechanical mitral valve replacement.

METHODS: We reviewed all mitral valve replacements in children between 1981 and 2020. Bioprosthetic mitral valve replacement cases were individually matched to mechanical mitral valve replacement cases. The incidence rate of a 2nd replacement was calculated using the cumulative incidence function that considered death or transplantation as a competing risk.

RESULTS: The median age at implantation was 3.6 years (interquartile range 0.8–7.9) for the bioprosthetic valve cohort ($n = 28$) and 3 years (interquartile range 1.3–7.8) for the mechanical valve cohort ($n = 28$). Seven years after bioprosthetic mitral valve replacement, the cumulative incidence of death or transplantation was 17.9% [95% confidence interval (CI) 6.3–34.1] and the cumulative incidence of a 2nd replacement was 63.6% (95% CI 39.9–80.1). Seven years after mechanical mitral valve replacement, the cumulative incidence of death or transplantation

was 28.6% (95% CI 13.3–46) and the cumulative incidence of a 2nd replacement was 10.7% (95% CI 2.6–25.5). Fifteen years after mechanical mitral valve replacement, the cumulative incidence of death or transplantation was 33.6% (95% CI 16.2–52.1) and the cumulative incidence of a 2nd replacement was 41.1% (95% CI 18.4–62.7). The cumulative incidence curves for bioprosthetic and mechanical mitral valve replacement were statistically different for a 2nd valve replacement ($P < 0.001$) but not for death or transplantation ($P = 0.33$).

CONCLUSIONS: There is no difference in transplant-free survival after bioprosthetic and mechanical mitral valve replacement in children. The lifespan of bioprosthetic mitral valves remains limited in children because of structural valve failure due to calcification. After 15 years, 40% of mechanical valves were replaced, primarily because of patient–prosthesis mismatch related to somatic growth.

Keywords: Mitral valve replacement • Paediatric • Congenital • Mechanical mitral valve • Bioprosthetic mitral valve

ABBREVIATIONS

CI	Confidence interval
IQR	Interquartile range
MVR	Mitral valve replacement

INTRODUCTION

Mitral valve replacement (MVR) in children is a last resort option, in case valve repair fails or is technically unfeasible [1–5]. Despite surgical advances, MVR in young children remains a clinical and technical challenge and is associated with an early mortality of ∼5–14% [6–9]. Furthermore, over time, somatic growth will lead to patient–prosthesis size mismatch and a 2nd valve replacement becomes inevitable.

It is still debated which type of prosthesis is most suitable for these young patients as both options have major limitations. Mechanical valves typically have a low profile and good durability but are vulnerable to thromboembolism, haemolysis, infective endocarditis, the risks associated with lifetime anticoagulation and the risk of reoperation due to patient–prosthesis mismatch associated with somatic growth [7, 10–13]. Bioprosthetic valves on the other hand avoid the need for anticoagulation but are associated with accelerated calcification leading to failure and early reoperation, especially in young children [14]. It is also crucial to highlight the significant risk of endocarditis associated with bioprosthetic valves, especially following Melody valve implantation [13].

Mechanical valves have been the preferred prosthesis during the last decades because of their superior durability. However, the introduction of newer generation bioprosthetic valves led to an increased interest in bioprosthetic valves for young children. For instance, stented jugular vein grafts have the potential for catheter-based expansion in case of somatic outgrowth [14–16]. Furthermore, new tissue treatment techniques might slow down the degeneration process of the bioprosthetic valves, making them a more desirable option in the paediatric population [17].

Because mechanical valves were preferred during the last decades, the survival of bioprosthetic valves was not extensively studied. The objective of our single-centre, retrospective study was to compare the prosthetic durability and transplant-free survival of bioprosthetic and mechanical MVR in children.

PATIENTS AND METHODS

Ethics statement

This study was approved by the Institutional Review Board (Research Ethics Committee UZ/KU Leuven; MP009402; approved on 27 May 2019). The requirement for individual formal consent from the patients or relatives was waived considering the retrospective nature of the study and the respect of anonymity.

Study design

All paediatric patients (age ≤16 years) who underwent MVR with a bioprosthetic or mechanical mitral valve at the University Hospital Leuven, Belgium between January 1981 and December 2020 were included in this study. Patients were identified by a search of the surgical database for all cases of MVR and data were collected by retrospective chart review.

Case matching

A matched design was implemented to compare the prosthetic durability and transplant-free survival after bioprosthetic and mechanical MVR. Bioprosthetic MVR cases were individually matched as closely as possible to mechanical MVR cases, taking into account the age and weight of the patient at the time of surgery as well as the number of previously performed procedures on the mitral valve and the time period in which the surgery was performed.

Data analysis

Continuous data are reported as median and interquartile range (IQR). Discrete data are presented as frequency (percentage). P values <0.05 were considered statistically significant, all P values being two-sided. For tests of continuous variables that did not deviate significantly from a normal distribution (Shapiro–Wilk test $P > 0.05$), paired Student's t-tests were used. For non-parametrical data, a Wilcoxon sign-rank test was conducted. Patients' body surface area was calculated using the Dubois and Dubois formula [18]. Event-free survival, defined as freedom from death, transplantation or a 2nd valve replacement, curves were generated by the Kaplan–Meier method. Bioprosthetic and mechanical mitral valve durability, defined by the need for a 2nd MVR, was also evaluated in this study. Cardiac transplantation or death is considered a competing risk because it precludes a 2nd valve replacement. Competing risk events may overestimate the primary event of interest using the usual Kaplan–Meier method. Therefore, the estimated cumulative incidence of a 2nd valve replacement was calculated using the cumulative incidence function that considered all-cause death or transplantation as a competing risk, and the equality of distributions was tested with Gray's test for equality [19]. All statistical analyses were performed using IBM SPSS statistics version 29 (IBM corp., Armonk, NJ, USA), R version

4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 10.1.0 (Dotmatics, Boston, MA, USA).

RESULTS

Patient characteristics

We identified 96 MVR cases in 75 children of which 29 with bioprosthetic mitral valves and 67 with mechanical mitral valves. Ages varied between 21 days and 16 years (median 6.4 years; IQR 1.6–10.2). Indications for initial replacement were common atrioventricular canal ($n = 26$, 34.7%), congenital mitral stenosis ($n = 8$, 10.7%), congenital mitral insufficiency ($n = 25$, 33.3%), congenital mitral stenosis and insufficiency ($n = 5$, 6.7%), acquired mitral valve insufficiency ($n = 8$, 10.7%) and endocarditis ($n = 3$, 4%). In total, 12 patients (16%) had a genetic syndrome, of whom 7 had Down syndrome. The median number of previous mitral valve repair procedures per patient since birth was 1 (IQR 0–2) and 21 patients underwent at least 1 previous MVR. Postoperatively, every patient who received a mechanical mitral valve was prescribed Vitamin K antagonists. Similarly, the patients with bioprosthetic mitral valves were treated with aspirin therapy.

Overall outcomes

The median follow-up time after MVR was 5 years (IQR 1–16.5), with a median of 2.7 years (IQR 0.1–4.9) after bioprosthetic MVR and 8.3 years (IQR 1.9–18.6) after mechanical MVR. The hospital mortality rate for all patients who underwent MVR was 11.5% (11/96). The overall survival rate was 81.6% [95% confidence interval (CI) 72–88] at 1 year, 77.9% (95% CI 68–85) at 5 years and 74.1% (95% CI 63–82) at 10 years follow-up. The estimated event-free survival was 79.7% (95% CI 70–87) at 1 year, 66.9% (95% CI 56–76) at 5 years, 53.5% (95% CI 42–64) at 10 years and 38.6% (95% CI 27–50) at 20 years follow-up.

Matched cohorts: patient characteristics

Only 1 bioprosthetic MVR case of a small patient (age <2 years) could not be included in the matched analysis because no mechanical MVR patient was available with matching parameters within an acceptable range. The characteristics of the matched cohorts are shown in Table 1. The bioprosthetic MVR cohort was composed of 28 cases with a median age at implantation of 3.6 years (IQR 0.8–7.9), a median weight of 12.1 kg (IQR 7.6–18.7) and a median body surface area of 0.46 m^2 (IQR 0.37–0.77). The mechanical MVR cohort was composed of 28 cases with a median age at implantation of 3 years (IQR 1.3–7.8), a median weight of 13.5 kg (IQR 7.4–19.1) and a median body surface area of 0.7 m^2 (IQR 0.38–0.81). The median follow-up was 3.5 years (IQR 2–5.6) for the bioprosthetic MVR cohort and 6 years (IQR 1–10.4) for the mechanical MVR cohort. The median prosthesis size was 21 mm (IQR 19–25) for the bioprosthetic MVR cohort and 23 mm (IQR 19–25) for the mechanical MVR cohort (see Table 2 for specific models).

Event-free survival

The Kaplan–Meier plot for event-free survival for both groups is shown in Fig. 1. The estimated event-free survival for the bioprosthetic MVR cohort was 78.6% (95% CI 58–90) at 1 year, 46.3% (95% CI 26–64) at 5 years and 0% at 10 years follow-up. For the mechanical MVR cohort, the estimated event-free survival was 75% (95% CI 55–87) at 1 year, 60.7% (95% CI 40–76) at 5 years and 50.6% (95% CI 30–68) at 10 years follow-up.

Causes of death

There were 4 deaths in the bioprosthetic MVR cohort and 1 transplantation for end-stage heart failure following MVR in a patient with severe left ventricular dysfunction. One patient did not survive salvage MVR for cardiogenic shock with severe pulmonary oedema following failure of mitral valve repair. Another patient with severe hypertrophic cardiomyopathy required an extensive myectomy that led to mitral insufficiency requiring MVR. He required postoperative mechanical support and died from failure of cardiac recovery. A 3rd patient with left main coronary artery atresia, left ventricular dysfunction and mitral regurgitation underwent coronary artery bypass grafting but required postoperative mechanical support. After 1 month on mechanical support, MVR was performed, but she died from failure of cardiac recovery 1 month later. The 4th patient died from persistent multiple organ failure following urgent MVR after 2 failed mitral valve repair procedures.

There were 9 deaths in the mechanical MVR cohort. One Fontan patient died during emergency MVR after 2 failed mitral valve repair procedures. Another patient with a functionally univentricular heart did not survive MVR because of persistent bleeding and cardiac failure. There was 1 other early death related to multiple organ failure. Of the 6 late deaths, 1 was noncardiac, 1 was due to mechanical valve thrombosis and 4 were unexplained sudden deaths.

Modes of prosthesis failure

There were 16 second valve replacements in the bioprosthetic MVR cohort (Fig. 2A). Twelve bioprosthetic mitral valves were replaced for degenerative calcification and stenosis, 1 for regurgitation and 3 for mixed disease. Of the 6 balloon-expandable valves, 2 had a small paravalvular leak postoperatively that was successfully resolved after balloon dilation. Three patients underwent balloon dilation for mitral stenosis, successfully resolving the transmitral gradient without resulting in mitral insufficiency. However, one patient who underwent a 2nd balloon dilation for mitral stenosis 2 years later did not achieve successful resolution and had to undergo valve replacement.

There were 9 second valve replacements in the mechanical MVR cohort (Fig. 2B). In 1 patient, the left ventricular function was impaired and angiography showed a severe stenosis of the circumflex artery due to obstruction by the large mechanical prosthesis. He underwent early replacement with a smaller size prosthesis. Five prostheses were replaced because of mitral valve stenosis due to somatic growth. Two supra-annular placed prostheses were replaced with a larger size because the ventricularized atrium below the prosthesis dilated and impaired the ventricular function. There was 1 case of prosthetic valve thrombosis after 20 years requiring urgent valve replacement.

Table 1: Patient demographics and pre-operative and operative characteristics

Matched population	Bioprosthetic ($n = 28$)	Mechanical ($n = 28$)	P value
Patient characteristics			
Age at implantation (years), median (IQR)	3.6 (0.8–7.9)	3.0 (1.3–7.8)	0.45
Male, *n* (%)	16 (57)	19 (68)	0.44
Weight (kg), median (IQR)	12.1 (7.6–18.7)	13.5 (7.4–19.1)	0.33
Body surface area (m^2), median (IQR)	0.46 (0.37–0.77)	0.7 (0.38–0.81)	0.50
Cardiac diagnosis, *n* (%)			0.51
Atrioventricular canal defect	9 (32.1)	10 (35.7)	
Mitral regurgitation	9 (32.1)	4 (14.3)	
Mitral regurgitation and stenosis	1 (3.6)	3 (10.7)	
Mitral stenosis	2 (7.1)	3 (10.7)	
Endocarditis	1 (3.6)	0 (0)	
Prosthetic valve dysfunction	6 (21.4)	8 (28.6)	
Functionally univentricular circulation, *n* (%)	0 (0)	2 (7.1)	0.16
Time period of surgery, *n* (%)			0.79
1980–2000	4 (14.3)	5 (17.9)	
2001–2015	13 (46.4)	13 (46.4)	
2016–2020	11 (39.3)	10 (35.7)	
Previous valve repair or replacement, *n* (%)			0.69
No previous mitral valve procedure	6 (21.4)	7 (25)	
1 previous mitral valve procedure	8 (28.6)	8 (28.6)	
$\geq$2 previous mitral valve procedures	14 (50)	13 (46.4)	
Previous mitral valve replacement, *n* (%)	6 (21.4)	8 (28.6)	0.41
Prosthesis size (mm), median (IQR)	21 (19–25)	23 (19–25)	0.73
Valve size/body weight ratio, median (IQR)	1.74 (1.31–2.21)	1.71 (1.26–2.39)	0.90

IQR: interquartile range.

Table 2: Type of prosthetic valve at 1st mitral valve replacement

Prosthesis type	Patients, *n*
Biological	
Ionescu Shiley	1
Carpentier-Edwards	3
Biocor	1
Epic	10
Trifecta	2
Melody	5
Crown PRT	1
Sapien XT	1
Mosaic	2
Inspiris Resilia	2
Mechanical	
Bicarbon	2
Carbomedics	2
St. Jude	23
ON-X	1

Cumulative incidence of 2nd valve replacement and of death or transplant

The 2 cohorts were compared in a competing risk analysis for a 2nd valve replacement and for death or transplant (Fig. 3). Seven years after bioprosthetic MVR, the cumulative incidence of death or transplantation was 17.9% (95% CI 6.3–34.1) and the cumulative incidence of a 2nd replacement was 63.6% (95% CI 39.9–80.1). Seven years after mechanical MVR, the cumulative incidence of death or transplantation was 28.6% (95% CI 13.3–46) and the cumulative incidence of a 2nd replacement was 10.7% (95% CI 2.6–25.5). Fifteen years after mechanical MVR, the cumulative incidence of death or transplantation was 33.6% (95% CI 16.2–52.1) and the cumulative incidence of a 2nd replacement was 41.1% (95% CI 18.4–62.7). The cumulative incidence curves for bioprosthetic and mechanical MVR were statistically different for a 2nd valve replacement ($P < 0.001$) but not for death or transplantation ($P = 0.33$).

DISCUSSION

Every attempt should be made to repair a dysfunctional mitral valve, especially in children. Unfortunately, if previous attempts to avoid or delay valve replacement failed, the only viable course of action that remains is replacing the valve. Currently, there is no ideal prosthesis available, as both mechanical and bioprosthetic valves have major limitations. Bioprosthetic valves calcify and deteriorate over time, making a 2nd replacement inevitable. Mechanical prostheses need lifetime anticoagulation and require replacement once the patient's somatic growth leads to mitral valve stenosis due to patient–prosthesis mismatch [10]. Paediatric patients with mechanical heart valves are at a higher risk of developing thromboembolism than adults, and the optimal anticoagulation therapy remains unclear [20]. In addition, the quality of life can be impacted by frequent phlebotomies required to achieve and maintain therapeutic levels in children with age-related changes in drug metabolism and clearance.

Our study presents a single-centre experience with bioprosthetic and mechanical MVR in 75 children. We report an early mortality of 11.5%, which is in line with other studies and reflects the significant morbidity and mortality that remains associated with MVR in children [1–4]. Previous studies already illustrated the higher mortality risk associated with valve oversizing and with MVR in young children (<2 years) [6, 9, 21, 22].

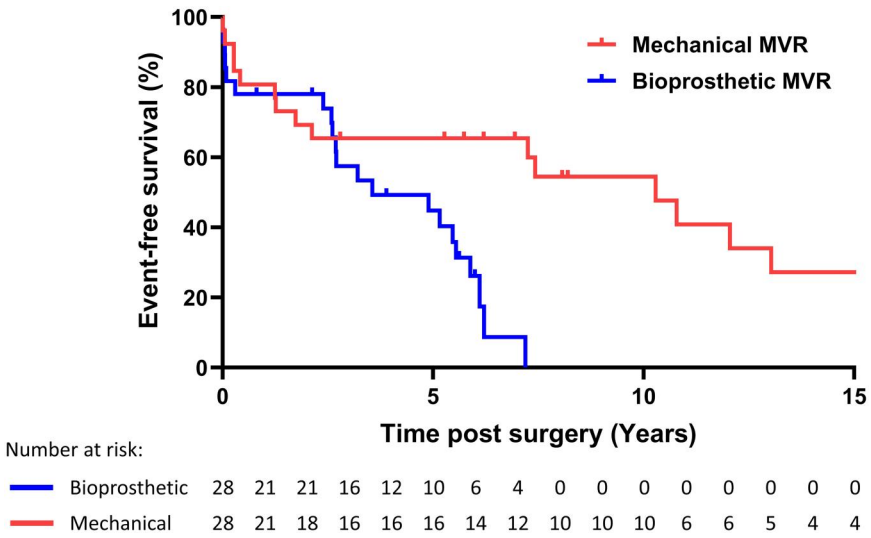


Figure 1: Kaplan–Meier curves showing event-free survival after bioprosthetic (blue line) and mechanical (red line) mitral valve replacement (MVR).

Bioprosthetic MVR patients in our study were on average younger and had a higher incidence of valve oversizing. Therefore, a matched design was chosen to compare the outcomes between bioprosthetic and mechanical MVR. Competing risk analysis was performed because the patients were simultaneously at risk for 2 mutually exclusive events: transplant-free survival and valve prosthetic valve replacement. Our results show that bioprosthetic MVR in children is not associated with an increased mortality risk. This is in line with recent studies examining risk factors after MVR in children [9, 14]. Choi *et al.* suggested that there may be a greater risk associated with porcine bioprosthetic valves; however, prosthesis type did not remain an independent risk factor in their multivariable analysis.

The superior durability of mechanical valves is a well-known fact. However, prosthetic durability will also be limited in growing children by the development of patient–prosthesis mismatch as the child outgrows the implanted valve. Our study confirms this, as 7 years after mechanical MVR, only 10% of patients required a 2nd valve replacement, but more than 40% of implanted mechanical valves were replaced after 15 years. This is similar to the results of Choi *et al.* who reported a median time to a 2nd valve replacement for mechanical valves of 11.2 years [14]. The incidence of a 2nd mechanical valve replacement could even be underestimated in our study because the median prosthesis size in our study was relatively large, at 23 mm. Additionally, we had no patients with the smallest size mechanical valves, the 15-mm St Jude Medical prosthesis (St Jude Medical, St Paul, MN). Intuitively, these smaller prostheses are more likely to require a 2nd valve replacement because of patient–prosthesis mismatch due to outgrowth. This was confirmed by IJsselhof *et al.*, who showed that 65% of 15-mm valves were replaced after a median follow-up time of 9.6 years [23]. Similarly, 44% of 15- to 17-mm valves required replacement after a median follow-up time of only 4 years [24].

To avoid the risk of patient–prosthesis mismatch, surgeons are inclined to place the largest prosthesis achievable. However, a high prosthetic valve size to patient weight ratio is a reported predictor for early mortality, as oversizing can induce left ventricular outflow tract obstruction, compression of the circumflex artery and injury to the conduction system [9, 25, 26]. Supra-annular placement of a larger prosthesis is also not the answer, because it is associated with worse survival and a higher risk of a 2nd valve replacement [27]. Following supra-annular valve placement, the volume and compliance of the left atrium are decreased, increasing the left atrial and pulmonary venous pressures. The ventricularized atrial tissue can dilate and develop into a systolic paradoxically moving aneurysm that impairs ventricular function [28].

During the last decade, an alternative emerged with the surgical implantation of expandable bioprosthetic valves. These valves can be tailored to fit annuli $<$15 mm and can be expanded by balloon dilation to accommodate somatic growth. However, there are also disadvantages of expandable bioprosthetic valves. Melody valves (Medtronic, Minnesota, USA) are at risk for structural valve deterioration requiring a 2nd replacement, predominantly caused by regurgitation because of paravalvular leaks or leaflet perforations [14, 15]. This was also illustrated by our experience, as we had 2 patients with a paravalvular leak after Melody valve implantation, both resolved after balloon dilation of the valve. More recently, the newest generation pericardial bioprosthesis, the Inspiris Resilia valve (Edwards Lifesciences LLC, Irvine, USA), became available and shows promising results in terms of reduced calcification [17]. Although designed as an aortic bioprosthesis, the use for MVR in children has also been described [29]. Both newest generation bioprosthetic valves from our series were still functional after a follow-up of more than 3 years. Still, the number of cases is too small and follow-up is too short to predict if the new tissue treatment techniques will result in a superior durability in the mitral position in children.

Limitations

Limitations of our study include its single-centre retrospective design over a long time period with a small, heterogeneous group of patients. In our overall study population, mechanical MVR cases were on average performed on older children and they were operated in an earlier era. To account for these confounding effects, we initially explored propensity score

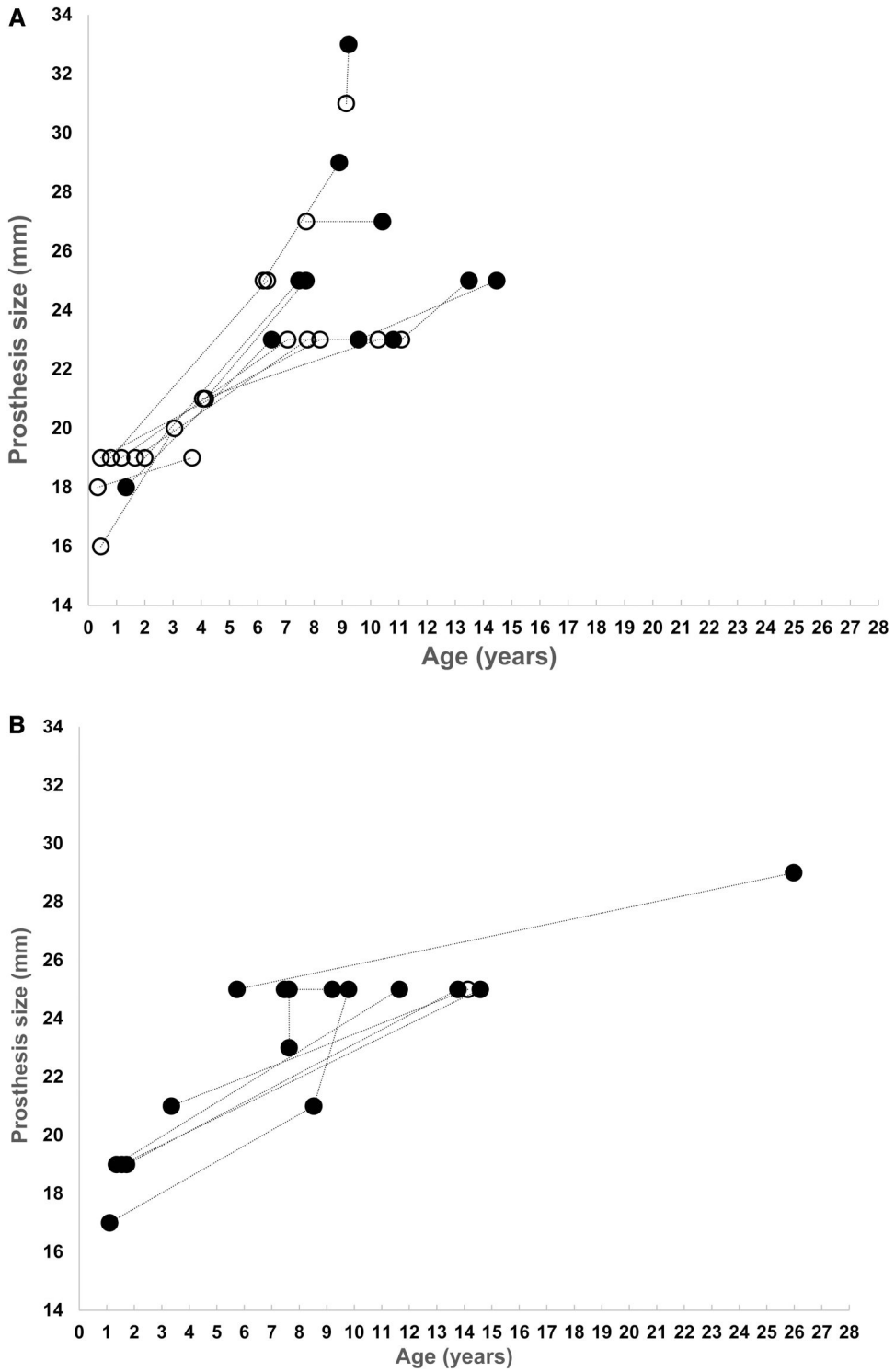


Figure 2: Valve size in millimetres plotted against age in years at each valve replacement for cases with a bioprosthetic valve at the initial replacement (**A**) and for cases with a mechanical valve at initial replacement (**B**). Each line represents a single case with the left side of the line representing the age and prosthetic valve size at the time of initial mitral valve replacement (MVR) and the right side of each individual line representing the age and prosthetic valve size at the time of the redo MVR. Full circles represent valve replacement with a mechanical valve and unfilled circled represent valve replacement with a bioprosthetic valve.

matching. Although propensity score matching seemed to be the most correct method available statistically, it neglected the overwhelming influence of age. In clinical reality, the patient's age, and consequently their size, predominantly dictates the choice of valve and prognosis following a MVR. As a result, we established matching primarily on age and weight, with secondary consideration given to other significant factors such as the count of prior procedures and the time frame of the surgery. Despite the careful consideration given to the selection of case matching as the method for addressing potential biases in our

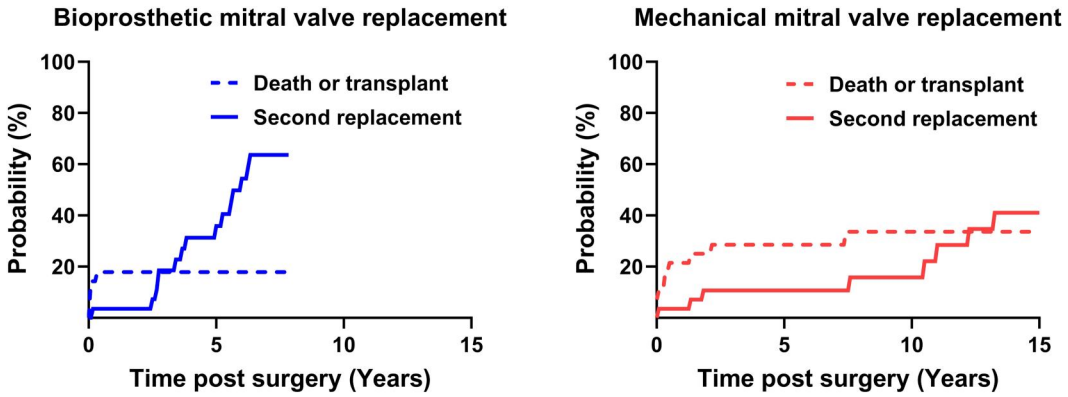


Figure 3: Estimated cumulative incidence curves with a 2nd valve replacement (solid line) and death or transplant (dashed line) as competing events for each type of prosthesis [bioprosthetic mitral valves (left side) or mechanical mitral valves (right side)].

study, it is important to acknowledge several limitations associated with this approach. Case matching introduces the risk of selection bias, as the process of selecting matched pairs may inherently introduce bias, potentially influencing the study outcomes. Furthermore, the use of case matching may lead to a reduction in the generalizability of the study findings, as the matched pairs may not fully represent the diversity of the overall patient population. Moreover, the approach may result in the loss of valuable information present in unmatched cases, limiting the inclusion of the entire dataset in the analysis. Additionally, case matching may not effectively address unmeasured confounders that could influence the outcomes of interest. Another limitation is the fact that follow-up was still ongoing in some cases. Additionally, our study is limited by the fact that only 40% of the included patients were below 2 years of age at the time of implantation. This particular patient subset poses a distinct challenge due to the limited availability of suitable prostheses for this age group and the potential implications for somatic growth and development. Regrettably, our study is unable to fully address the complexities associated with this challenging age group. Despite the peculiar difficulties in the younger age group, it is important to emphasize that even the older paediatric patients could potentially benefit from a bioprosthetic valve implantation, serving as an interim solution until they reach an appropriate size for an adult-sized mechanical valve implant.

In spite of these limitations, our data demonstrate that mechanical valves, despite their superior durability, have a high risk of requiring a 2nd valve replacement before adulthood, just as bioprosthetic valves. The gap in durability with mechanical valves could narrow in the future, as long-term results of the newest generation bioprosthetic valves and increased experience with expandable bioprosthetic valves become available. Redo valve replacement in children can be performed safely and, at the time of a 2nd replacement, a larger prosthetic valve can generally be implanted [9, 12]. In our experience, traditional, as well as expandable, bioprosthetic valves can be safely used as a 1st step. This grants the mitral annulus a chance to grow and allows subsequent placement of a mechanical prosthesis in adolescence. Delaying the implantation of a mechanical valve until an adult size mechanical valve can be placed has several advantages. Firstly, it avoids anticoagulation and its complications in young, active children. Secondly, during the initial procedure, an appropriately fitting bioprosthetic valve can be chosen. There is no need to risk valve oversizing or supra-annular valve placement to overcome the risk of somatic outgrowth associated with mechanical valves.

CONCLUSION

Bioprosthetic mitral valves are a feasible and patient-friendly option for surgical MVR in children. However, the lifespan of bioprosthetic mitral valves is limited and patients remain at risk for structural valve deterioration. It is important to note, however, that the explanted valves are of an older generation. Follow-up time is still too short to assess the degeneration process of the newer generation bioprosthetic valves, so long-term follow-up will determine their durability.

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Conflict of interest: none declared.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

Joeri Van Puyvelde: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing—original draft; Writing—review and editing. **Bart Meyns:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Supervision; Validation; Writing—review and editing. **Filip Rega:** Conceptualization; Methodology; Writing—review and editing. **Marc Gewillig:** Writing—review and editing. **Benedicte Eyskens:** Writing—review and editing. **Ruth Heying:** Writing—review and editing. **Bjorn Cools:** Writing—review and editing. **Thomas Salaets:** Writing—review and editing. **Peter-William Hellings:** Investigation. **Bart Meuris:** Conceptualization; Investigation; Methodology; Resources; Writing—review and editing.

Reviewer information

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