Revisiting Prosthesis Choice in Mitral Valve Replacement in Children: Durable Alternatives to Traditional Bioprosthe

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Student Name: Perry S. Choi, BA

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Mentor Name(s) and Affiliations:

Sitaram Emani, MD, Dept of Cardiac Surgery, Boston Children's Hospital

Collaborators, with Affiliations:

Lynn A. Sleeper, ScD, Dept of Cardiology, Boston Children's Hospital

Minmin Lu, MS, Dept of Cardiology, Boston Children's Hospital

Patrick Upchurch, MD, Dept of Anesthesiology, Johns Hopkins School of Medicine

Christopher Baird, MD, Dept of Cardiac Surgery, Boston Children's Hospital

Abstract

Revisiting Prosthesis Choice in Mitral Valve Replacement in Children: Durable Alternatives to Traditional Bioprostheses

Perry S. Choi, BA, Lynn A. Sleeper, ScD, Minmin Lu, MS, Patrick Upchurch, MD, Christopher Baird, MD, Sitaram Emani, MD

Purpose: To determine risk factors for re-replacement and death or transplant following mitral valve replacement (MVR) in children

Methods: This is a retrospective 26-year review of patients less than 20 years undergoing MVR between 1992 and 2018 at single institution. Outcomes included freedom from re-MVR and transplant-free survival. Cox proportional hazards regression models assessed association between outcomes and potential risk factors.

Results: At median age 4.2 years, 190 children underwent 290 MVR: 180 mechanical, 63 porcine, 13 pericardial, 34 stented bovine jugular vein valves. Re-MVR occurred in 100 valves. Freedom from re-MVR at 5 and 10 years was 76% and 44%. Times to re-MVR were associated with prosthesis type ($p<.001$), with porcine and pericardial valves at highest risk. Other risk factors for prosthetic failure included smaller prosthesis size and LV hypoplasia. There were 9 transplants and 44 deaths. Transplant-free survival at 5 and 10 years was 81% and 76%. Prosthesis type was significantly associated with time to death/transplant in univariate analysis only ($p=0.021$), with porcine at higher risk than mechanical. Independent risk factors for death/transplant included larger indexed geometric orifice area and longer bypass time.

Conclusion: In pediatric patients undergoing MVR, mechanical and stented bovine jugular vein valves were associated with increased durability compared to fixed-diameter bioprosthetic alternatives.

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Glossary of Abbreviations

BSA = body surface area

CAVC = complete atrioventricular canal

CPB = cardiopulmonary bypass

ECMO = extracorporeal membrane oxygenator

GOA = geometric orifice area

LV = left ventricle

MR = mitral regurgitation

MS = mitral stenosis

MVR = mitral valve replacement

PVF = prosthetic valve failure

TE = thromboembolus/thromboembolic

Contributions

The primary question of this scholarly project concerned the comparative durability of mitral valve prostheses in the pediatric population, particularly mechanical, porcine, pericardial, and surgically implanted Melody valves. I played a role in the study design, data collection, analytic strategy, writing, and presentation of the research project. Importantly, this was not a single-handed effort. I received immense support in preliminary design and data collection from Dr. Upchurch, statistical analysis from Lynn Sleeper and Minmin Lu, and writing and presentation from Drs. Emani and Baird. The present work is currently conditionally accepted at the Journal of Cardiovascular and Thoracic Surgery (JTCVS) and undergoing appropriate revisions.

Appendix

Introduction

Mitral valve replacement (MVR) is an operation reserved for patients with irreparable mitral valve disease. Direct repair of the native valve is preferable to replacement, especially for young children in whom somatic growth predisposes to early prosthetic failure. Hospital mortality rate for MVR in children is approximately 10%[1–3]. Risk factors include younger age, smaller prosthesis size, increased prosthesis-patient mismatch, supraannular implantation, longer cardiopulmonary bypass (CPB) time, concurrent procedure, requirement of permanent pacemaker, presence of left-sided lesions, and diagnosis of Shone's complex or complete atrioventricular canal (CAVC)[2,4–9]. Similarly, smaller prosthesis size, younger age, and presence of left-sided lesions have been associated with decreased freedom from re-replacement[10–14].

Ideal prosthesis choice for MVR in children remains debated. Mechanical valves are considered more durable than bioprosthetic valves in young adults and have relatively low incidence of thromboembolic (TE) events[7,10,15]. Nevertheless, complications associated with anticoagulation present a significant disadvantage, and several institutions have advocated for bioprosthetic valve replacement, particularly for patients in whom long-term anticoagulation may be contraindicated or difficult to manage[16,17].

Another complicating factor for MVR in children is the limited prosthesis options for annulus size less than 15 mm. Techniques such as supraannular placement or oversizing have been associated with increased mortality risk. Given the poor outcomes and paucity of available prostheses <15 mm, stented jugular vein valves (Melody) have been implanted in the mitral position as off-label use, with potential for catheter-based expansion following somatic growth[18]. The aim of this study was to comparatively assess prosthetic durability and transplant-free survival of MVR in children for mechanical, fixed-diameter porcine and pericardial, and surgically-implanted Melody valves in a single institutional experience.

Methods

Study Design

Retrospective review of patients less than 20 years who underwent MVR between 1/1/1992 and 7/15/2018 at Boston Children's Hospital was performed following approval by the Boston Children's Hospital Institutional Review Board. Primary outcome was freedom from re-replacement. Each prosthesis was followed from date of implantation until prosthesis explant,

unless interrupted by death or transplant. In the case of re-MVR, the newly implanted prosthesis was followed from a new time zero. Prostheses implanted prior to 1/1/1992 were excluded to focus on contemporary prosthesis models.

Composite secondary outcomes were transplant-free survival and incidence of bleeding/TE events. Determination of bleeding event was based on the International Society of Thrombosis and Haemostasis definitions for major bleeding event[19] and clinically relevant non-major bleeding event[20]. TE event was defined as valve thrombosis, intracardiac thrombus, deep vein thrombosis, embolic stroke, or septic embolus. Bleeding/TE events within 30 days of surgery were excluded to avoid confounding events from post-operative inpatient management.

Data Collection

Study candidates were identified by query of Boston Children's Hospital's heart center database. Initial search yielded 310 surgeries in 210 patients. After exclusion of candidates with insufficient information, 290 surgeries in 190 patients entered final analysis. Patient characteristics and pre- and post-operative information were obtained via Boston Children's Hospital's electronic medical records system as well as review of paper records. Additional information regarding bleeding/TE events was obtained from an internal database (Alere Standing Stone CoagClinic) with prospectively collected data from the monitoring team following all anticoagulated patients at Boston Children's Hospital. Follow-up information was either complete or as recent as 2016 for 156 (82%) patients with median follow-up of 4.4 years per patient.

Statistical Analysis

Kaplan-Meier methodology was used to estimate the distributions of time to re-MVR. Where median survival times are reported, the associated 95% confidence intervals assume independence of procedures. Conditional Cox proportional hazards regression modeling was performed, accounting for repeated surgeries on the same subject; the unit of analysis was the valve replacement, and follow-up time for a given procedure was censored at time of subsequent procedure. Where applicable, predictor values associated with the surgery were incorporated. The modeling assessed association between the primary outcomes and all risk factors as shown in Table 1. Pairwise comparisons between prosthesis types were unadjusted for multiple comparisons. P-value <0.05 was considered statistically significant for main comparisons. All risk factors in univariate analysis with p-value <0.15 became candidate predictors in stepwise selection for

multivariable Cox regression analysis. Non-linearity of covariate effects with respect to the log hazard ratio was assessed using restricted cubic splines.

Similarly, Kaplan-Meier survival curves were generated to estimate incidence rate of death/transplant, and univariate and multivariable Cox regression models assessed association between outcome and predictors. Analyzed risk factors included all covariates in prosthetic durability analysis, as well as cardiopulmonary bypass and aortic cross-clamp durations, diagnosis of CAVC, and concurrent procedure. Candidate predictors met a threshold of $p<0.15$ from the univariate model. Mean imputation specific to concurrent procedure status was applied to unknown bypass and cross-clamp times. A Firth adjustment was required for parameter estimation for prosthesis type, due to the absence of deaths and transplants in the pericardial cohort.

Given significant prosthesis size differences with little overlap between Melody and non-Melody groups and the different choice of commercially available prostheses for sizes smaller than 19 mm, analysis restricted to the <19 mm subgroup was conducted to determine whether findings from non-stratified models were robust.

SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.1 were used for analysis.

Results

Patient and Valve Characteristics

At median age 4.2 years, 190 children (49% male) underwent 290 MVR: 180 mechanical, 63 porcine, 13 pericardial, 34 Melody valves (see Supplement 1 for specific models). Of the 290 MVRs, 171 were initial replacements. Indications for initial MVR were MS alone (n=42, 22.1%), MR alone (n=77, 40.5%), and combined MS/MR (n=59, 31.1%). Median number of MVRs per patient since birth was 2, varying from 1 to 6. 51 patients (26.8%) had a genetic syndrome, the most common being Down syndrome (n=23). Fundamental cardiac diagnoses included congenital mitral stenosis (n=70), hypoplastic left heart syndrome/Shone's (n=49), coarctation of the aorta (n=41), congenital mitral insufficiency (n=39), and CAVC (n=35) (See Supplement 2 for complete list).

Table 1 displays the distribution of characteristics stratified by prosthesis type. Age at surgery was positively associated with prosthesis size ($r=0.73$, $p<.001$). Significant differences in distribution were detected across prosthesis types for prosthesis size and age at surgery, with both measures being lowest in the Melody valve group ($p<.001$). Indexed geometric orifice area (GOA)

was also significantly different across prosthesis types (p<.001), with median ratio of 4.0 for Melody, 5.1 for porcine, 3.3 for mechanical, and 4.1 for pericardial.

MVR was associated with complications of bleeding in 12% (29/246) and TE events in 11% (28/246) of surgeries. Crude incidence rates for bleeding events were not significantly different among valve types (p=0.51), with 2.4 events/100 valve-years for mechanical and 3.2 events/100 valve-years for non-mechanical valves. Similarly, crude incidence rates for independent TE events were not different among valve types (p=0.31), with 2.1 events/100 valve-years for mechanical and 3.2 events/100 valve-years for non-mechanical valves. Anticoagulation in patients undergoing mechanical MVR included long-term warfarin in 98.7% (n=151) and additional antiplatelet therapy in 60 patients. Anticoagulation management in the non-mechanical group included no therapy (n=4 patients), aspirin only (n=61), dual antiplatelet (n=6), short-term (<4 months) warfarin (n=19), long-term warfarin (n=2).

Prosthetic Durability: Re-MVR

Re-replacement occurred in 100 (35%) valves. Freedom from re-MVR at 5 and 10 years was 76% (95%CI: 69%, 82%) and 44% (95%CI: 35%, 53%) (Figure 1). Median time to re-MVR (50% of surgeries) was different among valve types with 11.2 (95%CI: 9.1, 12.2) years for mechanical, 5.3 (95%CI: 3.9, 7.8) for porcine, and 3.7 (95%CI: 2.8, 5.0) for Melody valve (event rate below 50% for pericardial group) (p<.001) (Figure 2). Reasons for re-MVR (non-exclusive) included mitral stenosis (n=74), valve thrombosis (n=10), leaflet entrapment (n=8), mitral regurgitation (n=13), and perivalvar leak (n=4). Among the 37 bioprosthetic valves that were re-replaced in the study, 36 (97%) had information on explant or intraoperative findings. 100% (20/20) of porcine and pericardial valves were found to have significant pannus or leaflet calcification upon explant, compared to only 23.5% (4/17) of Melody valves. The most common finding at explant for Melody valves was perforated leaflet (47.1%, 8/17).

To adjust for confounding risk factors, Cox regression modeling was performed. Potential non-linear associations were first investigated to improve model accuracy. The relationship between indexed GOA and time to re-MVR was non-linear, with risk increasing up to values of 4.5 for re-MVR and then increasing at slower rates (non-linear p=0.004). Prosthesis size was also non-linear with time to re-MVR, with size-related decrease in risk being greater among surgeries with prosthesis size ≥19 mm (non-linear p=0.032). Table 2 shows significant risk factors for re-MVR after univariate Cox regression analysis. Time to re-MVR was associated with prosthesis

type (p<.001), with mechanical valves associated with lowest risk among all valve types. Hazard differences between Melody and porcine or pericardial were not statistically significant. Other significant risk factors for re-MVR in univariate analysis included younger age (p<0.001), smaller prosthesis size (p<0.001), first-time MVR (p<0.001), LV hypoplasia (p<0.001), and larger indexed GOA (p=0.002).

Table 3 displays stepwise multivariable Cox regression modeling for all univariate risk factors with p≤0.15. Prosthesis type remained an independent risk factor (p<.001), with mechanical valves associated with lower risk for re-MVR compared to porcine and pericardial valves. However, hazard differences between mechanical and Melody valves were not statistically significant for re-MVR. Smaller prosthesis size and LV hypoplasia remained independent risk factors for re-MVR.

For prosthesis size <19 mm subgroup, median time to re-MVR (50% of valves) was 7.0 (95%CI: 5.4, 11.7) years for mechanical, 0.5 (95%CI: 0.2, non-estimable) for porcine, and 3.7 (95%CI: 2.8, 5.0) for Melody valve (p<.001) (Supplement 3). Both univariate and multivariable Cox regression models for prosthesis size subgroup revealed times to re-MVR were associated with prosthesis type (p<.001), with porcine valves at higher risk than both Melody and mechanical valves (Table 3). Melody valves had higher risk than mechanical for re-MVR (p=0.001). Other significant risk factors included smaller prosthesis size and LV hypoplasia in univariate analysis, and LV hypoplasia alone in multivariable analysis.

Balloon-Dilation Interventions

Of the 34 Melody valves, 26 (76%) underwent balloon dilation in the setting of mitral stenosis, with an average of 1.92 ± 1.0 dilations per valve. Of the 50 total balloon dilations done across implanted Melody valves, 50 (100%) were successful in resolving or decreasing transmitral gradient and 4 (8%) resulted in mitral insufficiency. Median time to first balloon dilation was 0.83 years (IQR: 0.38, 1.40).

Transplant-Free Survival

There were 9 transplants and 44 deaths distributed across 50 patients (see Supplement 4 for list of conditions proximate to time of death/transplant). Operative mortality as defined by the Society of Thoracic Surgeons[21] occurred in 15 of 44 deaths. Transplant-free survival at 5 and 10 years was 81% (95%CI: 75%, 85%) and 75% (95%CI: 68%, 81%) (Figure 1), and composite event rate remained below 50% across all prosthesis types. Times whereby 25% of surgeries met the

composite end point were 19.8 (95%CI: 8.0, non-estimable) years for mechanical, 1.4 (95%CI: 0.4, 3.4) for porcine, and 4.7 (95%CI: 0.4, non-estimable) for Melody (p=0.021) (Figure 2). There were no deaths or transplants associated with the 13 pericardial valves.

Table 4 illustrates the univariate Cox regression models for transplant-free survival. Time to death/transplant was associated with prosthesis type (p=0.021). Porcine valves were at highest risk. Pairwise comparisons with pericardial and Melody valves were not statistically significant. Other risk factors included higher indexed GOA (p=0.013), longer imputed CPB time (p<.001), and concurrent procedure (p=0.017). In the multivariable model, higher indexed GOA and longer imputed CPB time remained independent risk factors, while prosthesis type was not significantly associated with transplant-free survival (p=0.60) (Table 5).

In prosthesis size <19 mm subgroup, median time to death or transplant (50% of valves) was 1.2 (95%CI: 0.1, 1.2) years for porcine valves, while fewer than 50% of mechanical and Melody valves were associated with a death or transplant (Supplement 3). In univariate analysis, prosthesis type was significantly associated with time to death/transplant (p=0.043) with porcine at higher risk than both Melody and mechanical valves. Diagnosis of CAVC (p=0.003) and longer imputed CPB time (p=0.003) were additional risk factors. In the final multivariable model, diagnosis of CAVC and longer imputed CPB time remained independent risk factors, but there was no significant difference among prosthesis types (p=0.94) (Table 5).

Discussion

Although prosthetic durability for MVR has been studied extensively in adults, there is limited data regarding clinical outcomes among pediatric patients, particularly for those with a small annulus. Furthermore, ideal prosthesis choice remains unclear in this population. After adjusting for confounding factors, this retrospective study found that prosthesis type was significantly associated with times to re-MVR and death/transplant, with fixed-diameter bioprosthetic valves demonstrating worse outcomes compared to mechanical and Melody valves.

Prosthetic Durability

Consistent with previous studies, our results confirm prosthetic durability is significantly influenced by risk factors such as prosthesis size, age at surgery, and LV hypoplasia. Moreover, this study confirmed the durability advantage of mechanical valves over traditional, fixed-diameter bioprosthetic valves. Despite being associated with significantly younger age and smaller mitral annulus, the Melody valve was also associated with increased durability compared to fixed-

diameter bioprosthetic valves. Prosthesis type remained a risk factor for re-MVR in the <19 mm subgroup analysis, consistent with results from the overall cohort.

The most common type of prosthetic failure observed for porcine and pericardial valves was mitral stenosis, and explant analysis suggested these valves likely failed earliest due to increased susceptibility to calcification and pannus formation[22]. In contrast, Melody valves were re-replaced predominantly due to mitral regurgitation related to perivalvar leak and leaflet perforation, consistent with previous reports.[18] In line with these findings, a recent report by Carreon et al. demonstrated lack of leaflet calcification or pannus in venous-valved grafts, with retained pliability and coaptation of leaflets in 75% of specimens examined.[23] Leaflet perforation may be related to balloon dilation interventions, but further investigation is required to elucidate exact etiology. Surgical modifications made prior to implantation (e.g., pericardial skirt creation)[24] may make these valves susceptible to perivalvar leak. A commercially designed sewing cuff would obviate the need for pre-operative modifications and may reduce risk of perivalvar leaks.

Transplant-free Survival

The enhanced durability of mechanical valves compared to traditional bioprosthetic valves is well understood, but bioprosthetic valves have continued to be utilized due to their ability to circumvent long-term anticoagulation. An important assumption in this reasoning is that despite shorter durability bioprosthetic valves do not confer higher mortality risk. Recent studies have suggested this to be a dangerous assumption in the adult population[25,26]. The present results showing that porcine valves were associated with higher risk to death/transplant suggest that prosthesis choice may be associated with transplant-free survival in children. This study was unable to further characterize this association, which could reflect a selection bias rather than a cause-effect relationship. Indeed, survival analyses in both the overall cohort and prosthesis size <19 mm subgroup did not reveal a statistically significant association between prosthesis type and transplant-free survival in the multivariable model. Notably, small number of events detected in these subgroups may have contributed to inadequate power.

Bleeding and Thromboembolic Events

Despite numerous studies demonstrating relatively low bleeding/TE event rates in patients undergoing mechanical MVR, perceived risks of anticoagulation and the promise of transcatheter valve-in-valve replacement may drive the ongoing trend of bioprosthetic MVR[27–29]. In this study, comparison of incidence rates for bleeding and TE events between mechanical and non-

mechanical groups did not detect a significant difference at mid to late-term follow-up. However, follow-up time was significantly shorter for non-mechanical valves, and bias may have led to overestimation of event incidence. Although further investigation is necessary, these results suggest in this population mechanical valves are not at significantly higher risk for bleeding or TE compared non-mechanical valves.

Study Limitations

As with all retrospective studies, key limitations include potential selection bias and incomplete data from missing records or incomplete follow-up. Although the study's valve groupings and additional subgroup analysis for prosthesis size <19 mm were based on clinical approach to prosthesis choice, it is possible that grouping differently, such as a model-based approach, would have been more specific, but this was not feasible due to limited sample size.

Because several patients in the dataset had multiple MVR surgeries, individual valves—not patients—were the unit of analysis for transplant-free survival, thereby complicating attribution of death/transplant for patients who had received different prosthesis types. Moreover, there were a number of MVRs in which patients in extremis (e.g., acute arrest, ECMO, ventricular assist device) received MVR and accurate attribution of death or transplant is complex (see Supplement 5 for clinical descriptions), but the vast majority of patients (86%, 43/50) had MVR with a single prosthesis type.

In this study, multivariable analysis showed no difference between Melody and mechanical valves in durability for the overall cohort, but subgroup analysis suggested increased durability for mechanical valves. The significant differences in follow-up time and patient characteristics between these two groups makes head-to-head comparison challenging. The smallest mechanical valve used in this study was 15 mm, whereas most Melody valves were implanted at sizes less than 15 mm. Although attempts at decreasing non-overlap through subgroup and adjusted analyses were made, the lack of significant overlap in prosthesis sizes complicates direct comparison.

The majority of literature on MVR in children defines prosthetic durability as freedom from re-replacement. Although time to re-MVR is easily accessible and a reasonable estimate of prosthetic durability, it fails to account for practice variabilities that affect the subjective decision regarding timing of valve replacement, as well as indications for re-MVR unrelated to true prosthetic failure (e.g., perivalvar leak from imperfect implantation). Indeed, although perivalvar leak is an indication for reoperation, it may not be an indicator of intrinsic prosthesis dysfunction

but rather a reflection of surgical technique. Importantly, Melody valves had the highest incidence of perivalvar leak (14.7%, 5/34): 1.1% (n=2) for mechanical, 1.6% (n=1) for porcine, 7.7% (n=1) for pericardial). This is likely related to the need for surgical modification prior to implantation. Furthermore, Melody valve implantation in the mitral position is a relatively new procedure and unfamiliarity with the prosthesis may have biased the surgeon toward re-replacing sooner than a traditional valve. For these reasons, Melody valve durability is likely underestimated in this re-replacement analysis.

Conclusions

Prosthesis choice is an integral component of decision making for mitral valve replacement in children. The data herein suggest greater durability of mechanical valves and stented bovine jugular vein grafts over traditional bioprosthetic valves in this patient population. Moreover, this study shows that for children with a particularly small annulus who face limited prosthesis options, stented bovine jugular venous valves offer a promising alternative to traditional prostheses (Figure 3). The association between prosthesis choice and survival and the etiology of failure for these jugular vein grafts deserve further investigation.

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Tables

Table 1

	Overall	Mechanical	Porcine	Pericardial	Melody	P
N of surgeries	290	180	63	13	34	
Age at surgery, yr						**<.001**
Median (IQR)	4.2 (1.3, 10.8)	6.0 (2.1, 12.4)	4.5 (1.6, 8.4)	12.3 (4.2, 18.3)	0.7 (0.4, 1.8)	
Range	0.1, 37.1	0.1, 37.1	0.1, 18.7	0.5, 19.9	0.1, 3.4	
Age group						**<.001**
< 3.5 yrs	130 (44.8%)	65 (36.1%)	28 (44.4%)	3 (23.1%)	34 (100%)	
3.5 – 9.9 yrs	82 (28.3%)	55 (30.6%)	24 (38.1%)	3 (23.1%)	0 (0%)	
10 – 19.9 yrs	78 (26.9%)	60 (33.3%)	11 (17.5%)	7 (53.8%)	0 (0%)	
Prosthesis size, mm						**<.001**
N of surgeries	289	179	63	13	34	
Mean ± SD	20.5 ± 4.6	21.4 ± 3.9	21.1 ± 4.6	23.2 ± 4.0	13.7 ± 2.0	
Median (IQR)	21 (17, 23)	21 (19, 25)	21 (19, 25)	23 (19, 27)	14 (12, 14)	
Range	9, 33	15, 33	12, 33	19, 29	9, 18	
Prosthesis size, mm						**<.001**
< 19 mm	88 (30.4%)	43 (24.0%)	11 (17.5%)	0 (0%)	34 (100%)	
≥ 19 mm	201 (69.6%)	136 (76.0%)	52 (82.5%)	13 (100%)	0 (0%)	
GOA/BSA, cm^2/ m^2						**<.001**
N of surgeries	290	180	63	13	34	
Mean ± SD	4.1 ± 1.6	3.6 ± 1.4	5.4 ± 1.8	4.4 ± 1.3	4.2 ± 1.0	
Median (IQR)	3.8 (2.9, 5.0)	3.3 (2.6, 4.3)	5.1 (4.2, 6.0)	4.1 (3.6, 5.0)	4.0 (3.4, 4.8)	
Range	0.1,10.2	7.9,0.1	2.7, 10.1	2.6, 7.9	2.5, 7.2	
BSA, m^2						**<.001**
N of surgeries	274	166	62	12	34	

Mean ± SD	0.8 ± 1.1	0.9 ± 1.3	0.7 ± 0.4	1.0 ± 0.5	0.4 ± 0.1	
Median (IQR)	0.6 (0.4, 1.1)	0.7 (0.5, 1.2)	0.6 (0.5, 0.9)	0.9 (0.6, 1.4)	0.3 (0.3, 0.5)	
Range	0.2, 17.1	0.2, 17.1	0.2, 1.7	0.3, 1.8	0.2, 0.6	
CPB time, min						0.141
N of surgeries	232	124	62	12	34	
Mean ± SD	163.1 ± 67.5	156.3 ± 69.7	162.9 ± 61.4	219.8 ± 75.2	168.4 ± 59.8	
Median (IQR)	144 (114.5, 189)	140 (110, 183)	149.5 (125, 194)	217.5 (142, 273)	155 (128, 196)	
Range	33, 435	33, 435	68, 360	134, 355	75, 303	
AoXC time, min						0.183
N of surgeries	233	125	62	12	34	
Mean ± SD	97.8 ± 54.6	94.0 ± 50.6	89.9 ± 51.2	157.2 ± 67.2	105.2 ± 58.8	
Median (IQR)	93 (63, 123)	85 (66, 116)	92.5 (48, 118)	146.5 (103, 202)	106.5 (76, 123)	
Range	0, 284	0, 252	0, 213	70, 284	0, 257	
Imputed CPB time						**0.048**
N of surgeries	281	173	62	12	34	
Mean ± SD	157.8 ± 63.6	149.7 ± 62.0	162.9 ± 61.4	219.8 ± 75.2	168.4 ± 59.8	
Median (IQR)	140 (111.1, 181)	129 (111.1, 174.1)	149.5 (125, 194)	217.5 (142, 273)	155 (128, 196)	
Range	33, 435	33, 435	68, 360	134, 355	75, 303	
Imputed AoXC time						0.134
N of surgeries	281	173	62	12	34	
Mean ± SD	95.0 ± 50.5	90.5 ± 44.1	89.9 ± 51.2	157.2 ± 67.2	105.2 ± 58.8	
Median (IQR)	88 (70, 116)	80 (70.8, 103)	92.5 (48, 118)	146.5 (103, 202)	106.5 (76, 123)	
Range	0, 284	0, 252	0, 213	70, 284	0, 257	
Concurrent procedure						**0.003**
Yes	190 (67.4%)	106 (61.3%)	43 (68.3%)	11 (91.7%)	30 (88.2%)	
No	92 (32.6%)	67 (38.7%)	20 (31.7%)	1 (8.3%)	4 (11.8%)	
Supraannular MVR	31 (11.1%)	27 (15.9%)	3 (4.8%)	1 (8.3%)	0 (0%)	**<.001**

Intrannular MVR	248 (88.9%)	143 (84.1%)	60 (95.2%)	11 (91.7%)	34 (100%)	
LV hypoplasia						0.453
Yes	116 (40.0%)	65 (36.1%)	27 (42.9%)	7 (53.8%)	17 (50.0%)	
No	174 (60.0%)	115 (63.9%)	36 (57.1%)	6 (46.2%)	17 (50.0%)	
Left-sided lesion						**0.016**
Yes	100 (35.1%)	71 (40.6%)	14 (22.2%)	8 (61.5%)	7 (20.6%)	
No	185 (64.9%)	104 (59.4%)	49 (77.8%)	5 (38.5%)	27 (79.4%)	
CAVC						0.925
Yes	100 (35.1%)	71 (40.6%)	14 (22.2%)	8 (61.5%)	7 (20.6%)	
No	185 (64.9%)	104 (59.4%)	49 (77.8%)	5 (38.5%)	27 (79.4%)	
Previous MVRs						**<.001**
0	171 (59.0%)	97 (53.9%)	38 (60.3%)	6 (46.2%)	30 (88.2%)	
1	95 (32.8%)	66 (36.7%)	21 (33.3%)	5 (38.5%)	3 (8.8%)	
2	18 (6.2%)	12 (6.7%)	3 (4.8%)	2 (15.4%)	1 (2.9%)	
3	4 (1.4%)	3 (1.7%)	1 (1.6%)	0 (0%)	0 (0%)	
4	1 (0.3%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	
5	1 (0.3%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	

Table 1: Valve characteristics by prosthesis type (N=290 MVR Surgeries). Significant differences in distribution were detected across prosthesis types for prosthesis size and age at surgery, with both measures being lowest in the Melody valve group ($p<.001$). Indexed geometric orifice area was also significantly different across prosthesis types ($p<.001$), with mechanical valves with lowest value. Other significant covariates included BSA, imputed CPB time, concurrent procedure, supraannular implantation, presence of left-sided lesion, and number of previous MVR. LV hypoplasia included Shone's syndrome, right dominant CAVC and any variant of hypoplastic left heart syndrome. Left-sided lesion included aortic stenosis and regurgitation, coarctation of the aorta, and hypoplastic arch. Abbreviations: AoXC = aortic cross-clamp, BSA = body surface area, CAVC = complete atrioventricular canal, CPB = cardiopulmonary bypass, GOA = geometric orifice area, IQR = interquartile range, LV = left ventricle, MVR = mitral valve replacement, SD = standard deviation

Table 2

Re-MVR	Yes (n=100)	No (n=190)	HR (95% CI)	P
Prosthesis type				**<.001**
Mechanical	63 (35.0%)	117 (65.0%)	**Ref**	
Porcine	17 (27.0%)	46 (73.0%)	4.76 (2.72, 8.32)	
Pericardial	3 (23.1%)	10 (76.9%)	3.67 (1.06, 12.71)	
Melody	17 (50.0%)	17 (50.0%)	7.95 (4.01, 15.77)	
Porcine vs. Melody			0.60 (0.31, 1.16)	
Pericardial vs. Melody			0.46 (0.14, 1.49)	
Pericardial vs. Porcine			0.77 (0.22, 2.76)	
Age at surgery, yr			0.86 (0.81, 0.91)	**<.001**
Mean ± SD	3.5 ± 4.0	8.1 ± 6.6		
Median (IQR)	2.3 (0.8, 3.8)	6.7 (2.4, 13.3)		
Prosthesis size, mm			0.81 (0.77, 0.85)	**<.001**
Mean ± SD	18.2 ± 3.4	21.7 ± 4.8		
Median (IQR)	19.0 (16.0, 20.5)	23.0 (19.0, 25.0)		
Prosthesis size				**<.001**
< 19 mm	49 (55.7%)	39 (44.3%)	2.77 (1.83, 4.20)	
≥ 19 mm	51 (25.4%)	150 (74.6%)	**Ref**	
Prosthesis size piecewise linear terms				0.101
< 19 mm			0.87 (0.79, 0.96)	
≥ 19 mm			0.74 (0.64, 0.85)	
Supraannular MVR				0.407
Yes	18 (58.1%)	13 (41.9%)	1.25 (0.73, 2.14)	
No	81 (32.0%)	172 (68.0%)	**Ref**	
LV hypoplasia				**<.001**
Yes	49 (42.2%)	67 (57.8%)	2.20 (1.41, 3.44)	
No	51 (29.3%)	123 (70.7%)	**Ref**	
Left-sided lesion				0.758
Yes	36 (36.0%)	64 (64.0%)	1.06 (0.72, 1.56)	
No	64 (34.6%)	121 (65.4%)	**Ref**	
CAVC				0.320
Yes	19 (26.0%)	54 (74.0%)	0.76 (0.45, 1.30)	
No	81 (37.3%)	136 (62.7%)	**Ref**	
Previous MVR				**<.001**
Yes	20 (16.8%)	99 (83.2%)	0.12 (0.05, 0.34)	
No	80 (46.8%)	91 (53.2%)	**Ref**	
BSA, m_2			0.10 (0.05, 0.21)	**<.001**

Re-MVR	Yes (n=100)	No (n=190)	HR (95% CI)	P
Mean ± SD	0.54 ± 0.26	0.94 ± 1.26		
Median (IQR)	0.49 (0.37, 0.60)	0.76 (0.46, 1.21)		
GOA/BSA, cm^2/ m^2			1.25 (1.08, 1.44)	**0.002**
Mean ± SD	4.14 ± 1.36	4.12 ± 1.71		
Median (IQR)	3.85 (3.21, 4.81)	3.81 (2.80, 5.14)		
GOA/BSA piecewise linear terms				**0.003**
< 4.5			1.98 (1.39, 2.83)	<.001
≥ 4.5			0.83 (0.55, 1.26)	0.38

Table 2: Univariate Cox regression model for Re-MVR (N=290). Time to re-MVR was associated with prosthesis type (p<.001), with mechanical valves associated with lowest risk. Hazard differences between Melody and porcine or pericardial valves were not statistically significant. Other significant risk factors for re-MVR included younger age, smaller prosthesis size, LV hypoplasia, previous MVR, smaller BSA, and larger indexed geometric orifice area. Abbreviations: BSA = body surface area, CI = confidence interval, GOA = geometric orifice area, HR = hazard ratio, IQR = interquartile range, LV = left ventricle, MVR = mitral valve replacement, PVF = prosthetic valve failure, SD = standard deviation

Table 3

Re-MVR **Overall Cohort**	**HR**	**95% CI**	**P**
Prosthesis type			**<.001**
Mechanical	**Ref**		
Porcine	5.60	2.55, 12.29	
Pericardial	8.08	2.28, 28.63	
Melody	2.91	0.97, 8.74	
Porcine vs. Melody	1.92	0.57, 6.46	
Pericardial vs. Melody	2.77	0.58, 13.17	
Pericardial vs. Porcine	0.69	0.19, 2.51	
Prosthesis size			**<.001**
< 19 mm	0.89	0.75, 1.06	
≥ 19 mm	0.75	0.66, 0.85	
LV hypoplasia	1.58	1.01, 2.49	**0.046**
Prosthesis size <19 mm	**HR**	**95% CI**	**P**
Prosthesis type			**0.001**
Mechanical	**Ref**		
Porcine	12.79	3.15, 51.93	
Melody	3.21	1.45, 7.13	
Porcine vs. Melody	3.98	1.26, 12.59	
LV hypoplasia	1.84	1.04, 3.24	**0.037**

Table 3: Final multivariable Cox regression models for Re-MVR. Top) Overall cohort model (N= 290, 100 events for Re-MVR). Prosthesis type was an independent risk factor (p<.001), with mechanical valves associated with significantly lower risk for re-MVR compared to porcine and pericardial valves. Hazard difference between mechanical and Melody valves was not significant. Smaller prosthesis size and LV hypoplasia remained independent risk factors. Bottom) Models for prosthesis size <19 mm subgroup (N=84, 48 events). Time to re-MVR was associated with prosthesis type (p<.001), with porcine valves at higher risk than both Melody and mechanical valves. Melody valves had higher risk than mechanical valves. LV hypoplasia was also an independent risk factor (p=0.037). Abbreviations: CI = confidence interval, HR = hazard ratio, LV = left ventricle, MVR = mitral valve replacement, PVF = prosthetic valve failure

Table 4

Death/Transplant	Yes (n=50)	No (n=240)	HR (95% CI)	P
Prosthesis type				**0.021**
Mechanical	29 (16.1%)	151 (83.9%)	**Ref**	
Porcine	15 (23.8%)	48 (76.2%)	2.70 (1.39, 5.27)	
Pericardial	0 (0%)	13 (100%)	0.29 (0.02, 5.32)	
Melody	6 (17.6%)	28 (82.4%)	1.48 (0.60, 3.67)	
Porcine vs. Melody			1.82 (0.71, 4.69)	
Pericardial vs. Melody			0.20 (0.01, 3.91)	
Pericardial vs. Porcine			0.11 (0.006, 2.00)	
Age at surgery, yr			0.95 (0.90, 1.00)	0.062
Mean ± SD	5.6 ± 5.8	6.7 ± 6.2		
Median (IQR)	3.5 (0.8, 8.7)	4.4 (1.5, 11.1)		
Prosthesis size, mm			0.98 (0.91, 1.05)	0.563
Mean ± SD	20.3 ± 5.4	20.5 ± 4.5		
Median (IQR)	21 (17, 23)	21.0 (17.0, 23.0)		
Prosthesis size				0.496
< 19 mm	17 (19.3%)	71 (80.7%)	1.24 (0.66, 2.33)	
≥ 19 mm	33 (17.6%)	168 (83.6%)	**Ref**	
Imputed CPB time, min			1.24 (1.10, 1.38)	**<.001**
Mean ± SD	185.6 ± 79.3	152.4 ± 58.8	Per 30-min ↑	
Median (IQR)	169 (133, 223)	137 (111, 174)		
Imputed AoXC time, min			1.05 (0.86, 1.27)	0.637
Mean ± SD	98.0 ± 53.2	96.2 ± 49.8	Per 30-min ↑	
Median (IQR)	97.5 (63.0, 124.0)	85.0 (70.0, 114.0)		
Concurrent procedure				**0.017**
Yes	37 (20.7%)	153 (80.5%)	2.41 (1.17, 4.96)	
No	10 (11.0%)	82 (89.1%)	**Ref**	
Supraannular MVR				0.893
Yes	5 (16.7%)	26 (83.9%)	0.94 (0.36, 2.44)	
No	42 (17.4%)	211 (83.4%)	**Ref**	
LV hypoplasia				0.443
Yes	21 (19.3%)	95 (81.9%)	1.25 (0.70, 2.23)	
No	29 (17.3%)	145 (83.3%)	**Ref**	
Left-sided lesion				0.717
Yes	18 (19.6%)	82 (82.0%)	1.11 (0.62, 1.99)	
No	30 (16.7%)	155 (83.8%)	**Ref**	
CAVC				0.092
Yes	17 (24.3%)	56 (76.7%)	1.67 (0.92, 3.05)	
No	33 (15.9%)	184 (84.8%)	**Ref**	

Death/Transplant	Yes (n=50)	No (n=240)	HR (95% CI)	P
Pacemaker				0.482
Yes	9 (15.8%)	49 (84.5%)	0.76 (0.36, 1.63)	
No	39 (18.1%)	189 (82.9%)	**Ref**	
Previous MVR>0				0.065
Yes	16 (14.3%)	103 (86.6%)	0.31 (0.09, 1.07)	
No	34 (20.6%)	137 (80.1%)	**Ref**	
BSA, m^2			0.44 (0.19, 1.02)	0.056
Mean ± SD	0.68 ± 0.42	0.84 ± 1.17		
Median (IQR)	0.56 (0.33, 0.88)	0.65 (0.43, 1.10)		
GOA/BSA, cm^2/ m^2			1.33 (1.14, 1.54)	**<.001**
Mean ± SD	4.6 ± 1.9	4.0 ± 1.5		
Median (IQR)	4.0 (3.2, 6.0)	3.8 (2.9, 4.9)		

Table 4: Univariate Cox models for death/transplant (N=290 surgeries). Time to death/transplant was significantly associated with prosthesis type (p=0.021), with porcine valves associated with highest risk and mechanical valves with lowest risk. Pairwise comparisons with the pericardial and Melody valves were not statistically significant. Other significant risk factors included larger indexed geometric orifice area, longer CPB time, and concurrent procedure. Abbreviations: AoXC = aortic cross-clamp, BSA = body surface area, CAVC = complete atrioventricular canal, CPB = cardiopulmonary bypass, GOA = geometric orifice area, HR = hazard ratio, IQR = interquartile range, LV = left ventricle, MVR = mitral valve replacement

Table 5

Death/Transplant Overall Cohort	**Hazard ratio**	**95% CI**	**P**
Prosthesis type			0.601
Mechanical	**Ref**		
Porcine	1.18	0.48, 2.88	
Pericardial	0.16	0.01, 2.85	
Melody	0.96	0.37, 2.46	
Porcine vs. Melody	1.23	0.43, 3.50	
Pericardial vs. Melody	0.16	0.008, 3.20	
Pericardial vs. Porcine	0.13	0.007, 2.50	
Imputed CPB time, per 30-min↑	1.25	1.10, 1.41	**<.001**
GOA/BSA, cm^2/ m^2	1.32	1.09, 1.59	**0.005**
Valve size <19 mm	**Hazard ratio**	**95% CI**	**P**
Prosthesis Type			0.944
Mechanical	**Ref**		
Porcine	1.25	0.29, 5.30	0.766
Melody	0.99	0.34, 2.92	0.988
Porcine vs. Melody	1.26	0.32, 4.93	0.743
CAVC			**0.006**
Yes	4.58	1.55, 13.56	
No	**Ref**		
Imputed CPB time, per 30-min↑	1.34	1.09, 1.63	**0.005**

Table 5: Final multivariable Cox regression models for death/transplant. Top) Overall cohort model (N=267 surgeries, 46 events). Prosthesis type was not associated with time to death/transplant. However, larger indexed geometric orifice area (p=0.005) and longer CPB time (p<.001) were independent risk factors. Bottom) Model for prosthesis size <19 mm subgroup (N=88 surgeries, 17 events). There was no significant difference among prosthesis types (p=0.94), but CAVC (p=0.006) and longer CPB time (p=0.005) were significant independent risk factors. Abbreviations: BSA = body surface area, CAVC = complete atrioventricular canal, CI = confidence interval, CPB = cardiopulmonary bypass, GOA = geometric orifice area

Figure Legends

Central Picture: Mechanical and Melody valves in mitral position outperformed bioprosthetic alternatives.

Fig. 1: Kaplan-Meier survival curves for prosthetic durability and transplant-free survival in overall cohort. Number of valves free from event per timepoint shown below the graph. Left) Freedom from re-replacement at 5 and 10 years was 76% (95%CI: 69%, 82%) and 44% (95%CI: 35%, 53%). Right) Transplant-free survival at 5 and 10 years was 81% (95%CI: 75%, 85%) and 75% (68%, 81%).

Fig. 2: Kaplan-Meier survival curves for prosthetic durability and transplant-free survival across prosthesis types in overall cohort. Number of valves free from event per timepoint shown below the graph. Left) Freedom from re-replacement at 5 and 10 years was 88% (95%CI: 81%, 93%) and 55% (95%CI: 45%, 65%) for mechanical, 55% (95%CI: 32%, 73%) and 0% for porcine, 66% (95%CI: 24%, 89%) for pericardial, and 30% (95%CI: 12%, 52%) and 0% for Melody. Median time to re-MVR (50% of surgeries) was 11.2 (95%CI: 9.1, 12.2) years for mechanical, 5.3 (95%CI: 3.9, 7.8) years for porcine, and 3.7 (95%CI: 2.8, 5.0) years for Melody valve (event rate below 50% for pericardial group) ($p<.001$). Right) Freedom from death/transplant at 5 and 10 years was 86% (95%CI: 79%, 91%) and 80% (95%CI: 72, 86%) for mechanical, 60% (95%CI: 41, 75%) for porcine, 0% for pericardial, and 63% (95%CI: 19%, 88%) for Melody. Composite event rate remained below 50% across all prosthesis types, and pericardial group did not experience any events. Times whereby 25% of surgeries met the composite end point were 19.8 (95%CI: 8.0, non-estimable) years for mechanical, 1.4 (95%CI: 0.4, 3.4) for porcine, non-estimable for pericardial, and 4.7 (95%CI: 0.4, non-estimable) for Melody ($p=0.014$).

Fig. 3: Graphical Abstract. Mechanical valve cohort was associated with increased freedoms from re-replacement and death or transplant compared to traditional bioprosthetic alternatives. Although associated with significantly smaller prosthesis size (median 14 mm vs 21-23 mm), Melody valve cohort was also associated with improved prosthetic durability compared to bioprosthetic alternatives.

Figure 1

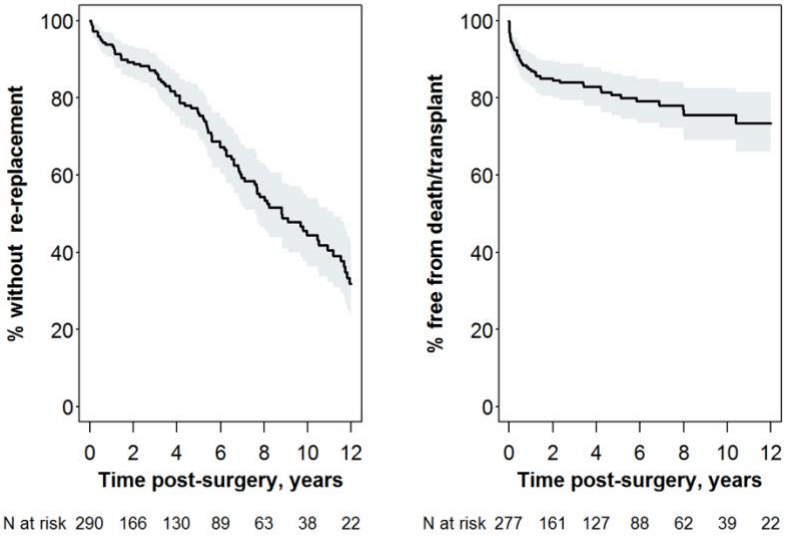

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Figure 2

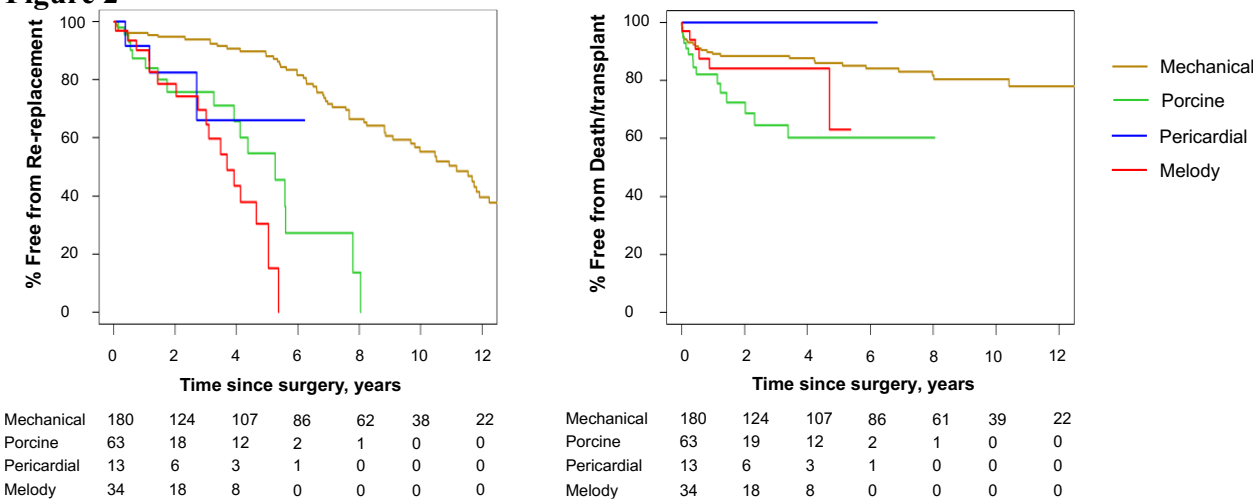

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Figure 3

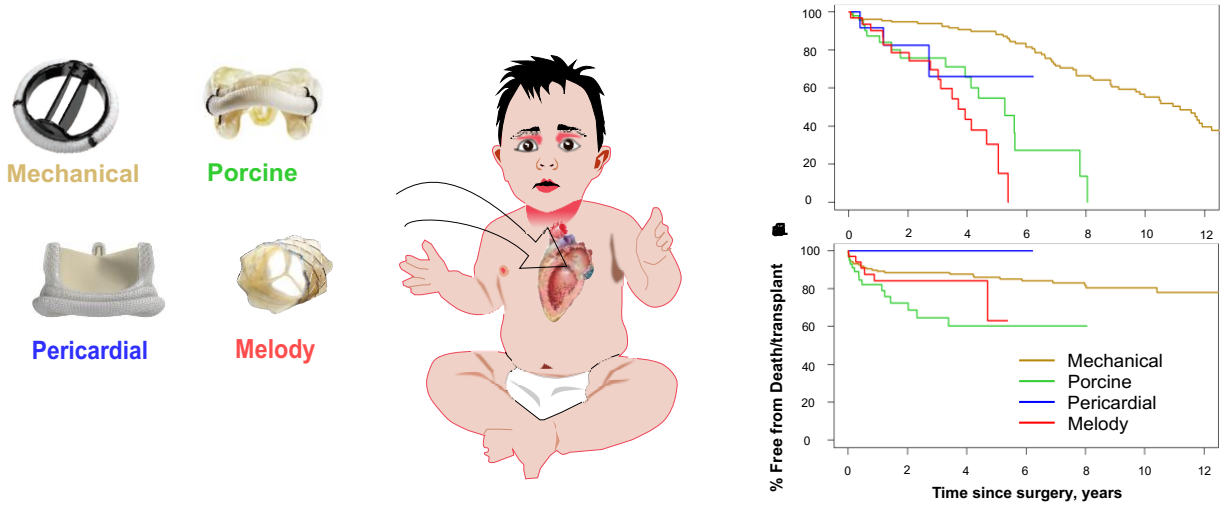


Fig. 3: Graphical Abstract. Mechanical valve cohort was associated with increased freedoms from re-replacement and death or transplant compared to traditional bioprosthetic alternatives. Although associated with significantly smaller prosthesis size (median 14 mm vs 21-23 mm), Melody valve cohort was also associated with improved prosthetic durability compared to bioprosthetic alternatives.

Supplemental Material

Supplement 1

Prosthesis Type	Prosthesis Model	# of valves	Size Range (mm)
Mechanical	St. Jude HP	63	15 - 27
	St. Jude standard	80	17 - 33
	Carbomedics	22	16 - 18
	On-X	15	21 - 27
Porcine	Hancock valved conduit	4	12 - 16
	Carpentier-Edwards valved conduit	8	12 – 20
	St. Jude Epic Supra	18	19 - 25
	St. Jude Epic	18	19 – 27
	Medtronic Mosaic	11	21 - 27
	Carpentier-Edwards Other	4	25 - 33
Pericardial	Carpentier-Edwards Perimount	13	19 - 29
Melody	Medtronic Melody	34	9 - 18

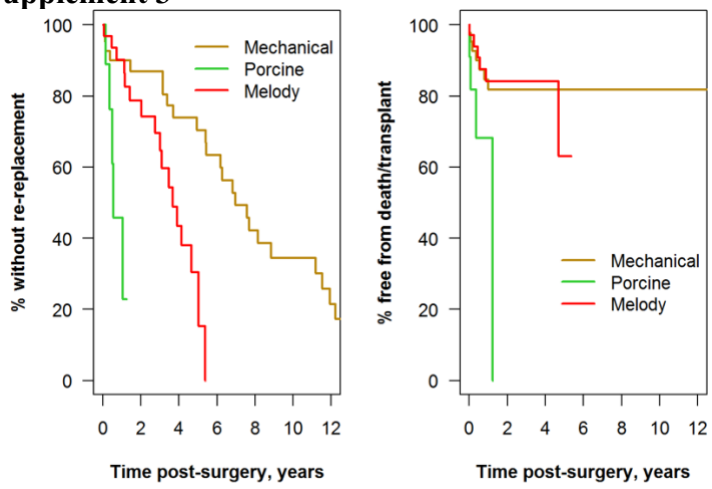
Supplement 1: Distribution of prosthesis models for each prosthesis type. Prostheses were grouped into mechanical, porcine, pericardial, and Melody valve groups, with varying models within each group. In total there were 180 mechanical, 63 porcine, 13 pericardial, and 34 Melody valves in this study cohort.

Supplement 2

Fundamental Cardiac Diagnosis	# of Patients
Congenital mitral stenosis	70
Hypoplastic left heart syndrome/Shone's	49
Coarctation of the aorta	41
Congenital mitral insufficiency	39
Complete atrioventricular canal defect	35
Congenital aortic stenosis	21
Partial/transitional atrioventricular canal defect	20
Right dominant complete atrioventricular canal defect	19
Double outlet right ventricle/D-transposition of the great arteries	11
Cardiomyopathy	11
Heterotaxy	11
Endocarditis	11
Acquired mitral insufficiency	11
Tetralogy of Fallot	6
Total/partial anomalous pulmonary vein	5
L-transposition of the great arteries	3
Marfan syndrome	3
Anomalous left coronary artery from the pulmonary artery	2
Tricuspid atresia	1

Supplement 2: Distribution of fundamental cardiac diagnoses (non-exclusive).

Supplement 3



Supplement 3: Kaplan-Meier curves for prosthesis size <19 mm subgroup. All pericardial valves were ≥19 mm and therefore excluded from these curves. Left) Freedom from re-replacement at 5 and 10 years was 70% (95%CI: 51%, 83%) and 34% (95%CI: 18%, 52%) for mechanical, 23% (95%CI: 1%, 61%) for porcine, and 30% (95%CI: 12%, 52%) and 0% for Melody (n = 88, event = 49) Median time to re-replacement (50% of valves) was 7.0 (95%CI: 5.4, 11.7) years for mechanical, 0.5 (95%CI: 0.2, non-estimable) for porcine, and 3.7 (95%CI: 2.8, 5.0) for Melody valve (p<.001). Right) Freedom from death/transplant at 5 and 10 years was 82% (95%CI: 65%, 91%) for mechanical, 0% for porcine, and 63% (95%CI: 19%, 88%) for Melody (n = 88, event = 17). Median time to death or transplant (50% of valves) was 1.2 (95%CI: 0.1, 1.2) years for porcine valve (event rate below 50% for mechanical and Melody group) (p=0.043).

Supplement 4:

Condition	# of Patients
Right or Left ventricular dysfunction	14
Hemorrhage (intracranial, pulmonary, gastrointestinal)	12
Cardiac arrest	10
Multiorgan Failure/Sepsis	10
Congestive heart failure	5
Pulmonary hypertension	3
Endocarditis	1
Unknown	17

Supplement 4: Conditions proximate to death or transplant (non-exclusive).

Supplement 5:

Patient #	Prosthesis at Event	Clinical Description
36	Porcine	Presented with acute thrombus of previous mechanical valve and put on ECMO emergently. MVR with porcine prosthesis attempted, but unable to wean off ECMO. Endured pulmonary and intracranial hemorrhage.
53	Porcine	Patient with mechanical valve who underwent concurrent placement of biventricular assist device with porcine re-MVR. Received transplant post-operative day 173.
109	Mechanical	Hypotensive arrest post mitral valvuloplasty. MVR with mechanical valve. Suffered from multiple cardiac arrests soon after transfer to ICU
112	Porcine	Placed on ECMO after cardiac arrest. MVR with porcine valve, but persistent ventricular dysfunction.
115	Mechanical	Ventricular tachycardia arrest in ICU after mitral valvuloplasty and Senning takedown/arterial switch. Put on ECMO. ECHO showed severe mitral regurgitation. MVR with mechanical prosthesis, but unable to wean off ECMO. Anuric and septic with disseminated intravascular coagulation.
121	Melody	ECMO for ventricular dysfunction on post-operative day 1 from biventricular repair. ECHO showed severe mitral regurgitation. MVR with Melody prosthesis, but unable to wean from ECMO. Ventricular dysfunction despite maximal medical therapy.
135	Mechanical	Severe mitral regurgitation and multiple cardiac arrests status post mitral valvuloplasty. MVR with mechanical prosthesis, but unable to wean off bypass and placed on ECMO. Weaned from ECMO, but persistent low cardiac output state.

Supplement 5: Clinical Descriptions for Deaths and Transplants after Emergent MVR or MVR on ECMO/ventricular assist device. Abbreviations: ECHO = echocardiogram, ECMO = extracorporeal membrane oxygenator, ICU = intensive care unit, MVR = mitral valve replacement