JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 24, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.04.021

Aortic Valve Replacement and the Ross Operation in Children and Young Adults

Mansour T.A. Sharabiani, PhD,[a] Dan M. Dorobantu, MD,[b,c] Alireza S. Mahani, PhD,[d] Mark Turner, PhD,[b] Andrew J. Peter Tometzki, MBChB,[b] Gianni D. Angelini, MD,[a,b] Andrew J. Parry, MBChB,[b] Massimo Caputo, MD,[b] Serban C. Stoica, MD[b]

ABSTRACT

BACKGROUND There are several options available for aortic valve replacement (AVR), with few comparative reports in the literature. The optimal choice for AVR in each age group is not clear.

OBJECTIVES The study sought to report and compare outcomes after AVR in the young using data from a national database.

METHODS AVR procedures were compared after advanced matching, both in pairs and in a 3-way manner, using a Bayesian dynamic survival model.

RESULTS A total of 1,501 patients who underwent AVR in the United Kingdom between 2000 and 2012 were included. Of these, 47.8% had a Ross procedure, 37.8% a mechanical AVR, 10.9% a bioprosthesis AVR, and 3.5% a homograft AVR, with Ross patients being significantly younger when compared to the other groups. Overall survival at 12 years was 94.6%. In children, the Ross procedure had a 12.7% higher event-free probability (death or any reintervention) at 10 years when compared to mechanical AVR ($p = 0.05$). We also compared all procedures except the homograft in a matched population of young adults, where the bioprosthesis had the lowest event-free probability of 78.8%, followed by comparable results in mechanical AVR and Ross, with 86.3% and 89.6%, respectively. Younger age was associated with mortality and pulmonary reintervention in the Ross group and with aortic reintervention in the mechanical AVR. Of all 3 options, only the patients undergoing the Ross procedure approached the survival of the general population.

CONCLUSIONS AVR in the young achieves good results, with the Ross being overall better suited for this age group, especially in children. Although freedom from aortic valve reintervention is superior after the Ross procedure, the need for homograft reinterventions is an issue to take into account. All methods have advantages and limitations, with reinterventions being an issue in the long term for all, more crucially in smaller children. (J Am Coll Cardiol 2016;67:2858–70)

Young patients with aortic valve (AoV) disease can be palliated by transcatheter or surgical methods but most will eventually require an aortic valve replacement (AVR). There are several options available for children and young adults: mechanical valve replacement (M-AVR), pulmonary autograft or the Ross procedure (R-AVR), biological heterograft (B-AVR), and homograft valves (H-AVR).

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From the [a]Department of Cardiothoracic Surgery, Imperial College, London, United Kingdom; [b]Department of Cardiothoracic Surgery, University Hospitals Bristol NHS Trust, Bristol, United Kingdom; [c]Cardiology Department, "Prof. C.C. Iliescu" Emergency Institute for Cardiovascular Diseases, Bucharest, Romania; and [d]Sentrana Inc., Washington, DC. This research was supported by National Institute for Health Research (NIHR) Bristol Cardiovascular Biomedical Research Unit and used data provided by the National Institute for Cardiovascular Outcomes Research, as part of the National Congenital Heart Disease Audit (NCHDA). The NCHDA is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme (NCAPOP) and within the National Health Service, United Kingdom. The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR, or Department of Health. Dr. Turner has served as a proctor for Medtronic and Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Sharabiani and Dorobantu contributed equally to this work.

Manuscript received February 18, 2016; revised manuscript received March 29, 2016, accepted April 5, 2016.

Each has its uses and limitations and, more importantly, no option is perfect. There is a set of qualities an AoV substitute should have, and presently there is no choice that can achieve them all, with many factors influencing the choice and long-term results of an AVR. Data on outcomes vary, with few national and even fewer comparative studies. Multicenter studies would be best suited to describe and compare modern results. The objective of the current study is to describe early and long-term survival and freedom from reintervention in a national population of consecutive, unselected young patients, to compare the results of the main types of AVR in appropriately matched populations and to identify factors influencing outcome for each procedure type.

SEE PAGE 2871

METHODS

The National Congenital Heart Disease Audit collects validated key data on cardiac procedures from all the UK units, using a mechanism for data capture, cleaning, and validation similar to that for adult cardiac surgery (1).

Using linkage with census records at the Office of National Statistics, the audit database publicly reports survival rates at 30 days and 1 year following the index procedure online. Linkage with survival registries of Northern Ireland and Scotland cannot be done consistently with the patient's personal identification number, whereas a minority of them either have errors in their social data or are foreign. This resulted in 10.6% of patients not having data beyond 30 days, due to administrative reasons. The remaining patients have long-term follow-up from either the Office of National Statistics or from other entries in the database.

Indications for each operation were established by multidisciplinary teams at each center. Diagnosis and procedure codes from the European Pediatric Cardiac Code Short List are used for reporting of data. The quality index for key procedure fields is above 95%. The completeness and accuracy of noncritical data fields cannot be estimated without detailed patient-level data from each center, but there is no indication of systematic, persistent errors in reporting. The need for patient-level consent to participate in this retrospective study was waived by the National Institute for Cardiovascular Outcomes Research Board.

PATIENT SELECTION. All available data on patients undergoing an AoV procedure for a congenital cause between April 2000 and March 2012 were selected and anonymized. Out of these, 2,767 had an AVR.

We excluded 671 patients who were >40 years of age, as we considered that above this age degenerative disease is more prevalent. We also excluded those patients with associated complex heart abnormalities (n = 193), rheumatic fever (n = 15), unclassified AVR procedures (n = 313), and unknown age at index procedure (n = 74). The excluded complex heart abnormalities were univentricular conditions, valvar atresias, interrupted aortic arch, atrioventricular septal defect, transposition of great arteries, common arterial trunk, Fallot-type defects, severe vascular abnormalities (e.g., major aortopulmonary collaterals), and atrial isomerism. Unclassified AVR procedures were due to errors in reporting (i.e., using a general "Aortic valve replacement" code).

Reinterventions were defined as either reoperations or catheter-based procedures related to the AoV or root and to the pulmonary valve and right ventricle outflow tract (RVOT) for the Ross operation group. Not included were early reinterventions (within 30 days, considered connected to intraoperative events and not prosthesis durability) and those aorta dilation/aneurysm repairs that were related to previous conditions (e.g., Marfan syndrome). When comparing the procedures, separate calculations were made for AoV reinterventions and any reinterventions, due to the fact that the Ross procedure is at risk of both AoV and RVOT reinterventions. This was done to ensure that the comparisons between procedures can be properly interpreted, with both AoV and overall freedom from reintervention comparisons.

STATISTICAL ANALYSIS. Frequencies are given as absolute numbers and percentages, continuous values as median (interquartile range). Short-term mortality is calculated on the basis of 30-day life status. Population characteristics were compared using the Mann-Whitney *U* test, Kruskall-Wallis test, Student *t* test, and Fisher exact test. Descriptive estimates of long-term outcomes by AVR category and also for neonates are made with the Kaplan Meier method using mortality (all-cause) and reintervention, death being censoring for reintervention. Risk factor analysis for the B-AVR and H-AVR groups was performed using the log-rank test and Cox proportional hazards regression.

In addition to aggregate, nonparametric analysis of short- and long-term survival rates, we used a Bayesian dynamic survival model to perform Variable Importance Analysis and Procedure Comparison Analysis (2). The resulting dynamic HRs allowed us to

ABBREVIATIONS AND ACRONYMS

AoV = aortic valve
AVR = aortic valve replacement
B-AVR = biological heterograft
CI = confidence interval
H-AVR = homograft valve
HR = hazard ratio
M-AVR = mechanical valve replacement
R-AVR = Ross procedure
RVOT = right ventricle outflow tract

differentiate early-phase and late-phase impact of variables on mortality and reintervention, providing a measure of significance for the trend in the HR, if any is present. For Procedure Comparison Analysis (2- and 3-way), a combination of propensity score matching, restriction matching, and stochastic augmentation was used to implement matching without replacement and ensure balanced distribution of age, sex, aortic disease type, and subaortic stenosis across different procedure types (3). Separate models for mortality, AoV reintervention, and overall reintervention were built, treating death and reintervention as competing, and combined using the cause-specific hazard approach to competing-risk analysis. R-AVR versus M-AVR comparison was done after matching as described previously, adjusting by age, AVR type, and interaction between the two. The other comparisons are done adjusting only by AVR type. Variable importance analysis used a multivariable model including age (continuous), age group, sex, aortic disease type, mitral disease, coarctation, subaortic stenosis, genetic syndrome, mitral valve procedure, coarctation repair, and subaortic stenosis repair at index, with hypothetical patient profiles being used to provide context for each plot. Model coefficients are estimated using Markov chain Monte Carlo sampling of posterior distribution, and HRs are plotted versus follow-up time (dynamic HRs), with corresponding, sampled-based p values indicating their significance. Bayesian Lasso shrinkage was used as a built-in variable selection mechanism to minimize the degrees-of-freedom problem in light of increased model parameters. Missing data regarding aortic disease type were not imputed, as not enough data was available to ensure this is done properly. Instead a separate category was created ("Undetermined").

For further methodological details, please see the Online Appendix. Statistical analyses were done with STATA/IC version 11.2 (StataCorp LP, College Station, Texas) and R version 3.1 (R Development Core Team).

RESULTS

A total of 1,501 patients <40 years of age who underwent an AVR procedure were included in the analysis. Of these, 718 (47.8%) had R-AVR, 567 (37.8%) had M-AVR, 163 (10.9%) had B-AVR, and 53 (3.5%) had H-AVR. Table 1 shows data completeness and Table 2 shows demographic, clinical, and procedure-related data. From the 289 patients (19.2%) with no specific data on AoV hemodynamics, 86 (29.7%) had only bicuspid morphology noted, as some centers do not systematically report aortic disease type when a bicuspid valve is seen, assuming there will be mixed aortic disease.

TABLE 1 Data Completeness

National Health System ID	100.0%
Aortic valve hemodynamics	80.7%
Diagnosis	97.9%
Weight	92.8%
Sternotomy number	79.8%
Hospitalization period	97.5%
Discharge status	99.9%
30-day status	89.3%

There were significant differences in age and sex between groups, most notably R-AVR patients being younger than in the other 3 groups (R-AVR mean 13.7 years of age vs. M-AVR 25.5 years of age, B-AVR 25.7 years of age, and H-AVR 18.8 years of age; $p < 0.001$) (Figure 1), whereas more men were operated using M-AVR rather B-AVR (30.9% vs. 21.3%; $p < 0.001$).

Significantly fewer patients with documented aortic regurgitation had R-AVR when compared to the rest of the group (R-AVR 23% vs. 32.7% otherwise; $p < 0.001$). No significant differences in patient distribution by lesion type were observed between the remaining 3 groups. Of the 4 main associated abnormalities and corresponding concomitant procedures (Table 2) there were several significant differences between the R-AVR group and the remainder of the patients: subaortic stenosis had a higher frequency in the R-AVR group, with 16.2% versus 8.3% ($p < 0.001$), as did the procedure to correct it at index, with 12% versus 5.2% ($p < 0.001$). Also, slightly fewer R-AVR patients had a ventricular septal defect (4.3% vs. 8.9%; $p < 0.001$) or a ventricular septal defect closure at index (0.7% vs. 3.2%; $p = 0.001$). No differences in mitral valve disease or aortic coarctation prevalence were found between groups.

The short- and long-term outcome estimates are shown in Table 3. The best results were achieved in the R-AVR group, with 97.3% survival and 94.7% freedom from aortic reintervention at 12 years. The H-AVR group had a poor freedom from reintervention, with 73.8% at 5 years and 59.8% at 12 years, but survival was comparable with the other 3 groups, being 93.4% at 12 years.

INFANTS AND CHILDREN. The majority of infants and neonates (55 of 61) underwent R-AVR. Overall, the 30-day and 1-year mortality were 10.5% and 14.3%, respectively; 1 patient died beyond 1 year. Overall freedom from aortic reintervention is 84.7% (95% confidence interval [CI]: 67.9% to 93.2%) and

TABLE 2 Patient Characteristics and Procedure Data by AVR Type

	Total (n = 1,501)	Ross Autograft (n = 718)	Mechanical AVR (n = 567)	Bioprosthetic AVR (n = 163)	Homograft AVR (n = 53)
Age, yrs	17.8 (12.1–28.7)	13.1 (7.5–17.0)	26.3 (17.6–33.6)	24.8 (20.1–31.0)	16.4 (12.0–27.6)
Male	1,091 (72.7)	514 (71.6)	446 (78.7)	104 (63.8)	27 (51.0)
Age group					
Neonate (<30 days)	8 (0.5)	6 (0.9)	0 (0.0)	0 (0.0)	2 (3.8)
Infant (1–12 months)	53 (3.5)	49 (6.8)	1 (0.2)	1 (0.6)	2 (3.8)
Child (1–16 yrs)	568 (37.9)	439 (61.1)	98 (17.3)	10 (6.1)	21 (39.6)
Young adult (16–40 yrs)	872 (58.1)	224 (31.2)	468 (82.5)	152 (93.3)	28 (52.8)
Follow-up, yrs	5.3 (2.1–8.6)	6.6 (2.5–9.6)	4.7 (1.8–7.5)	3.5 (2.0–5.6)	5.6 (1.1–8.5)
Aortic valve disease					
Stenosis	492 (32.8)	268 (37.3)	148 (26.1)	25 (15.3)	8 (15.1)
Regurgitation	421 (28.0)	165 (23.0)	181 (31.9)	58 (35.6)	17 (32.1)
Mixed	299 (19.9)	190 (26.5)	76 (13.4)	59 (36.2)	17 (32.1)
Unknown	289 (19.3)	95 (13.2)	162 (28.6)	21 (12.9)	11 (20.7)
Marfan syndrome	41 (2.7)	0 (0.0)	37 (6.5)	1 (0.6)	3 (5.7)
Concomitant procedures					
Mitral valve	58 (3.9)	22 (3.1)	29 (5.1)	5 (3.1)	2 (3.8)
Subaortic	127 (8.5)	86 (12.0)	32 (5.6)	5 (3.1)	4 (7.5)
Ventricular septal defect repair	30 (2.0)	5 (0.7)	15 (2.6)	7 (4.3)	3. (5.7)
Coarctation/hypoplasia repair	18 (1.2)	7 (1.0)	8 (1.4)	3 (1.8)	0 (0)

Values are median (interquartile range) or n (%).
AVR = aortic valve replacement.

FIGURE 1 Age Distribution Histogram by Procedure Type

The **columns** represent fraction from total for 1-year-wide bins. The **continuous line** represents the kernel density.

TABLE 3 Survival and Freedom From Reintervention by AVR Type

	Overall (n = 1,501)	Ross Procedure (n = 718)	Mechanical AVR (n = 567)	Bioprosthetic AVR (n = 163)	Homograft AVR (n = 53)
Survival					
30-day	98.4	98.9	98.0	97.4	97.9
5-yr estimate	96.2 (95.0–97.2)	97.6 (96.0–98.6)	95.0 (92.4–96.7)	94.9 (89.3–97.6)	93.4 (81.0–97.8)
12-yr estimate	94.6 (92.8–95.9)	97.3 (95.6–98.4)	90.6 (85.8–93.9)	92.6 (84.2–96.7)	93.4 (81.0–97.8)
Freedom from aortic reintervention					
5-yr estimate	96.0 (94.6–97.0)	97.2 (95.5–98.3)	96.2 (93.7–97.6)	94.3 (86.0–97.7)	73.8 (55.3–85.6)
12-yr estimate	90.4 (87.1–93.0)	94.7 (91.7–96.6)	91.8 (86.8–94.9)	75.0 (53.2–87.8)	59.5 (37.9–75.7)
Freedom from pulmonary valve reintervention					
5-yr estimate		98.0 (96.4–98.9)			
12-yr estimate		91.1 (87.3–93.8)			

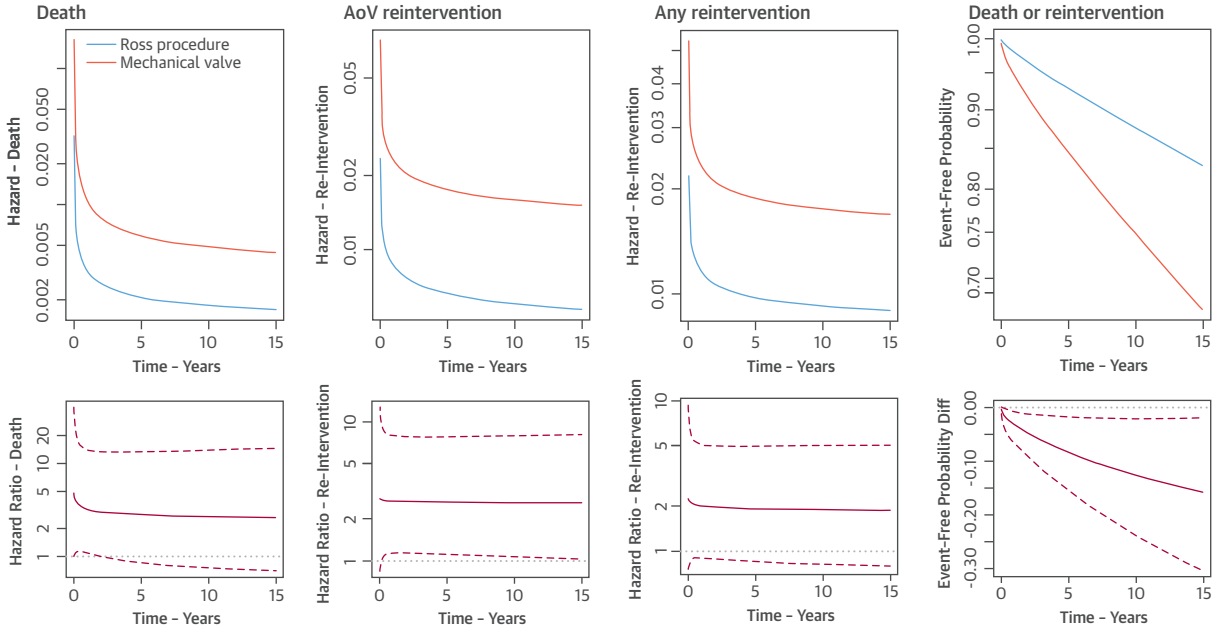
Values are % or % (95% confidence interval). Unadjusted Kaplan-Meier estimated values with death and reintervention (aortic and pulmonary) as failures; death is censoring for reintervention.

AVR = aortic valve repair.

freedom from pulmonary valve and RVOT reintervention for the Ross operation is 72.5% (95% CI: 52.5% to 85.2%).

In children between 1 and 16 years of age (n = 568), the 2 most-used AVR options are R-AVR (77.2%) and M-AVR (17.3%). We examined them after matching using the Procedure Comparison Analysis (Figure 2). Median M-AVR to R-AVR HR for death starts at 4.8 after the procedure (p = 0.09) (Figure 2) and in 10 years decreases to 2.7 (p = 0.20). However, this decline is not statistically significant (p value for difference in HR is 0.65). The difference in

FIGURE 2 Comparison of Long-Term Outcomes Between Ross AVR and Mechanical AVR in Children Using Matched Groups



Hazard functions **(top row)** and dynamic hazard ratios/event-free probability differences (**bottom row**, with confidence intervals) are shown, derived from a Bayesian Mixture Survival Model using the additive mixture of 2 Weibull hazards. Samples are matched by sex, age, aortic disease type, and association of subaortic stenosis, using a stochastic algorithm with propensity score matching. The model was adjusted by age group and the interaction between age group and aortic valve replacement (AVR) type was included. AoV = aortic valve.

cumulative incidence of death between R-AVR and M-AVR is 5.1% at 10 years (M-AVR being higher; p = 0.10). In terms of AoV reintervention risk, M-AVR to R-AVR HR starts at 2.8 (p = 0.15) and reaches 2.6 at 10 years (p = 0.08), without a significant dynamic trend (Figure 2). The difference in cumulative incidence of AoV reintervention between R-AVR and M-AVR is 9.9% at 10 years (M-AVR being higher; p = 0.07). When considering all reinterventions (Figure 2), the M-AVR to R-AVR HR starts at 2.2 (p = 0.21) and reaches 1.9 at 10 years (p = 0.21), with a difference in cumulative incidence of 7.7% at 10 years (p = 0.19). Finally, overall event-free probability for R-AVR is 12.7% higher than M-AVR at 10 years (p = 0.05) (Figure 2).

Ten children underwent B-AVR and 21 had H-AVR with no deaths during follow-up. In terms of AoV reintervention, 1 of 10 with B-AVR required a reintervention at 2.7 years (actuarial freedom from reintervention 80%), whereas 7 of 21 from the H-AVR group did (actuarial freedom from reintervention 38.4%). No other comparisons were possible between these groups and the other 2 in this age due to small sample sizes.

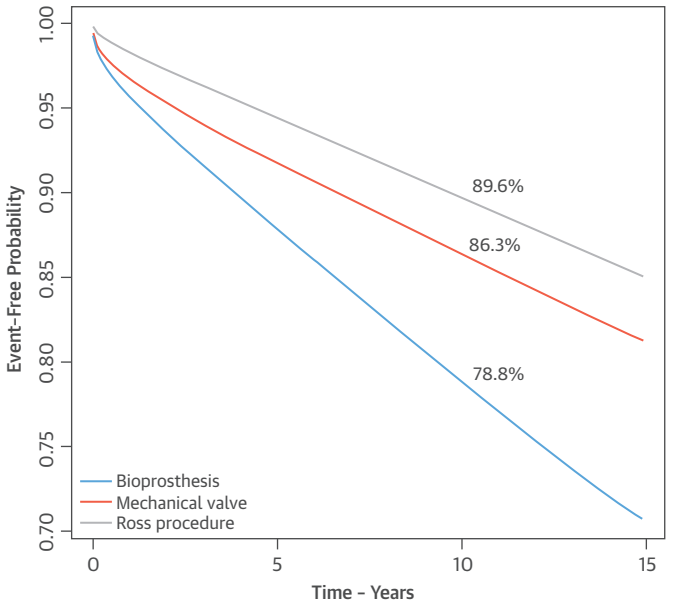
YOUNG ADULTS. Of the 872 patients between 16 and 40 years old, 224 (25.7%) had R-AVR, 468 (53.7%) had M-AVR, 152 (17.4%) had B-AVR, and 28 (3.2%) had H-AVR. All 3 main choices for AVR are used in young adults so we were able to analyze outcomes both in a 3-way comparison and also in pairs. This was necessary due to the particular overlapping pattern in age distribution (Figure 1), which led to different ends of this age group being matched in different comparisons (e.g., younger for R-AVR vs. M-AVR, older for M-AVR vs. B-AVR).

Ross operation versus mechanical prosthesis versus bioprosthesis. Mortality and reintervention are highest in the B-AVR group, followed by M-AVR, being lowest in the R-AVR group, with a 10-year event-free probability after matching of 78.8% (B-AVR), 86.3% (M-AVR), and 89.6% (R-AVR) respectively (Figure 3).

Ross operation versus mechanical prosthesis. After matching, M-AVR has a higher hazard for both death and reintervention but not statistically significant, with the exception of early mortality where HR is 3.0 (p = 0.09) (Figure 4). Overall, this does not translate into significant differences in the event-free probabilities (Figure 4). Similar to children, we do not see significant dynamic trends for the HR.

Ross operation versus bioprosthesis. In the matched group comparison, The mortality risk is significantly higher for B-AVR within the first 5 years after the index, with the median HR starting at 5.4 (p = 0.04) and reaching 2.5 at 10 years (p = 0.12) (Figure 5). The risk for AoV reintervention was significantly higher for the B-AVR group, with an HR starting at 2.2 early after the index, becoming statistically significant at around 1 year of follow-up and reaching 4.1 at 10 years (p = 0.01) (Figure 5). When considering overall reintervention risks, we see the same pattern (Figure 5), albeit with smaller HR values. These differences are reflected in the higher event-free probability for the R-AVR (Figure 5). No significant time dependence for death or reintervention HR was found.

FIGURE 3 Comparison of Long-Term Outcomes Among the Ross Operation, Mechanical Aortic Valve Replacement, and Bioprosthesis for Young Adults (16 to 40 Years of Age)

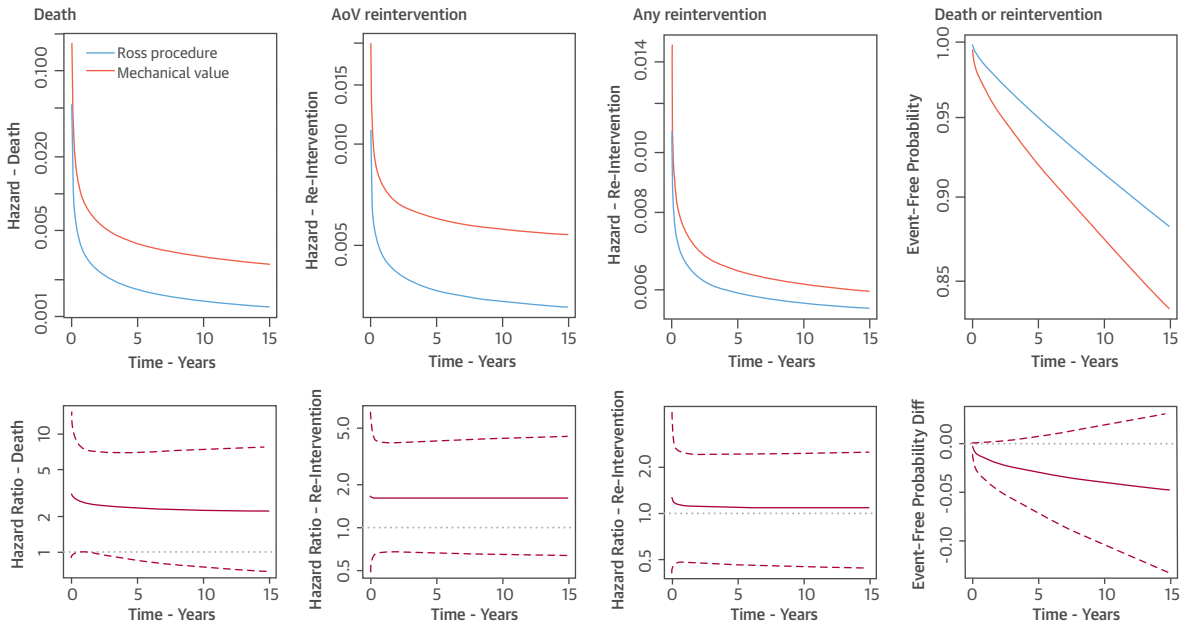


Confidence bands are not included to avoid clutter. These are unadjusted event curves after matching using a 3-way composite algorithm (described in Methods section).

MECHANICAL PROSTHESIS VERSUS BIOPROSTHESIS. Although death hazard is similar in B-AVR and M-AVR matched groups (Figure 6), reintervention hazard becomes higher in B-AVR starting from 5 years after the index, with 10-year HR being 2.3 (p = 0.12) (Figure 6). Correspondingly, cumulative incidence of reintervention is 8.8% higher in B-AVR compared to M-AVR (p = 0.12) (Figure 6).

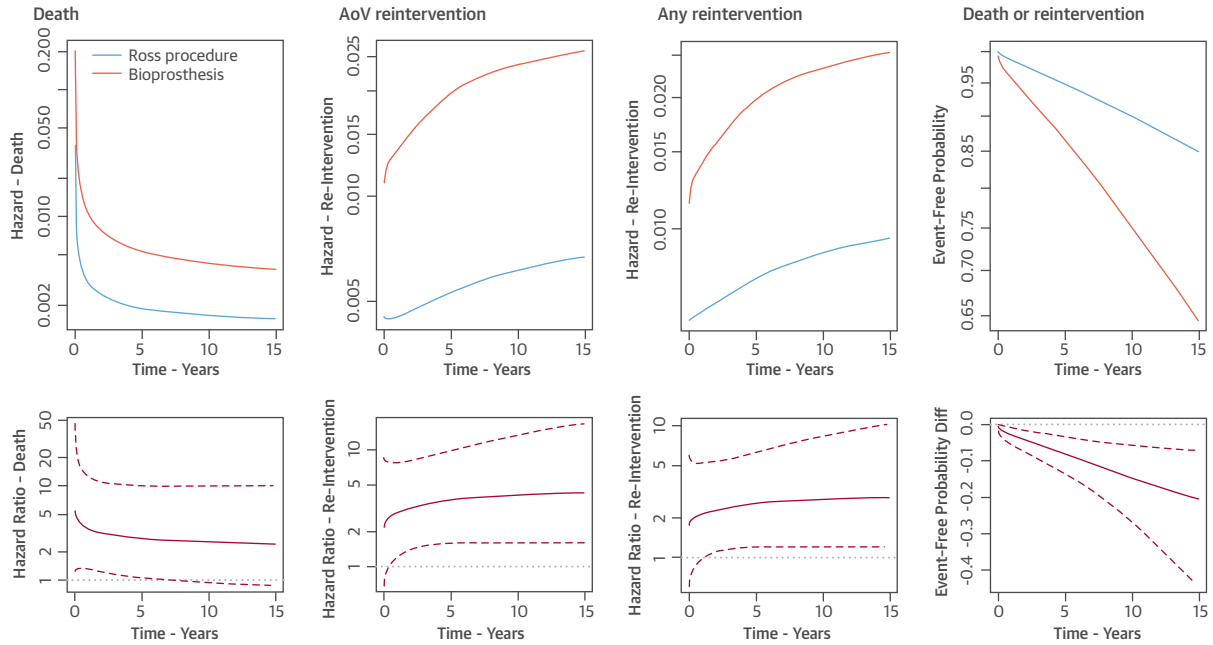
RISK FACTORS ASSOCIATED WITH AVR. Ross procedure. Although the risk of aortic reintervention shows no statistically significant difference across age groups, mortality risk is higher for

FIGURE 4 Comparison of Long-Term Outcomes Between Ross AVR and Mechanical AVR in Young Adults Using Matched Groups



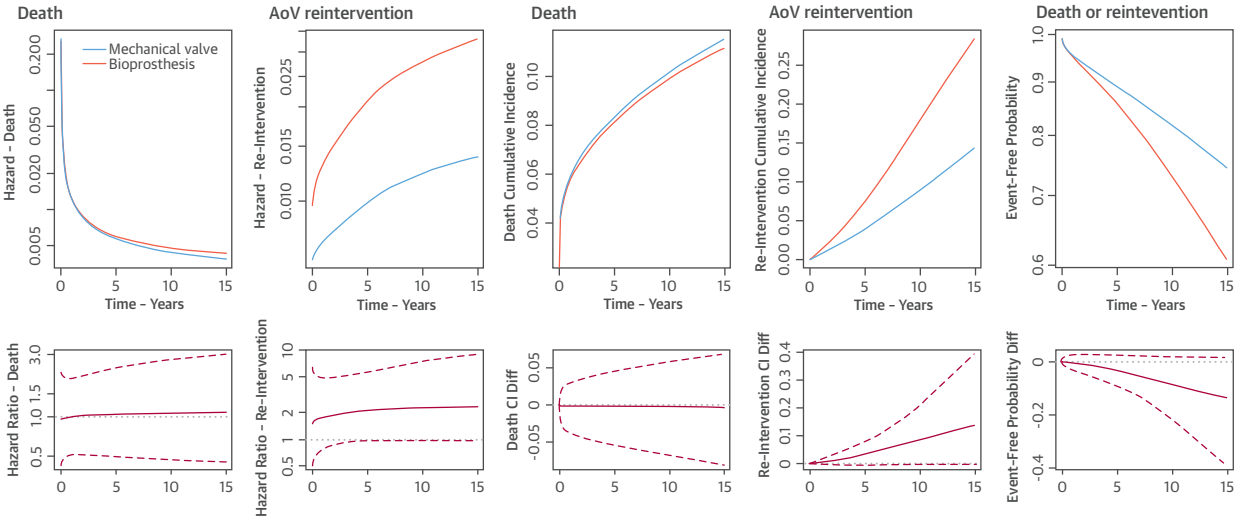
See caption of Figure 2 for details on panel rows, model, and matching. The model is unadjusted. Abbreviations as in Figure 2.

FIGURE 5 Comparison of Long-Term Outcomes Between the Ross Operation and Bioprosthesis AVR in Young Adults Using Matched Groups



See caption of Figure 2 for details on panel rows, model, and matching. The model is unadjusted. Abbreviations as in Figure 2.

FIGURE 6 Comparison of the Mechanical AVR and Bioprosthesis in Young Adults in Terms of Long-Term Outcomes in Matched Groups



See caption of Figure 2 for details on panel rows, model, and matching. The model is unadjusted. Abbreviations as in Figure 2.

neonates and infants compared to children and young adults, especially within the early phase of the first 3 years of follow-up (Figure 7A). AoV regurgitation is associated with higher reintervention risk, compared to mixed disease and stenosis (Figure 7B). The risk becomes statistically significant shortly after surgery but does not exhibit a dynamic behavior. Age appears to have a steady impact on pulmonary reintervention: the younger the patient, the higher the risk (Figure 7C). The HRs are steady and statistically significant over time. This is in contrast to the early-phase impact of age on mortality risk (Figure 7A). Time independence of age HR for pulmonary reintervention suggests that the increased risk with younger age is related to the procedure performed and is not influenced by time-varying factors. We did not find sex to be a predictor of pulmonary reintervention or death.

Mechanical prosthesis. No predictors for mortality were found in this group. Younger age was associated with significantly higher hazard and cumulative incidence for aortic reintervention (Figure 7D).

Biopsrosthesis. Mitral valve abnormalities (HR: 7.1; 95% CI: 1.4 to 35.9; p = 0.014) and subaortic stenosis (HR: 6.3; 95% CI: 1.2 to 31.5; p = 0.025) were associated with higher mortality risk in this group but we were limited to univariable analysis. No predictors for mortality were found.

Homograft. A total of 3 of 53 patients died in this group, 2 of them also being the only 2 neonates operated with a homograft AVR, pointing to age under 30 days being a risk factor. Younger age was also identified as a risk for aortic reintervention (univariate analysis HR: 1.08/year; 95% CI: 1.01 to 1.15; p = 0.02).

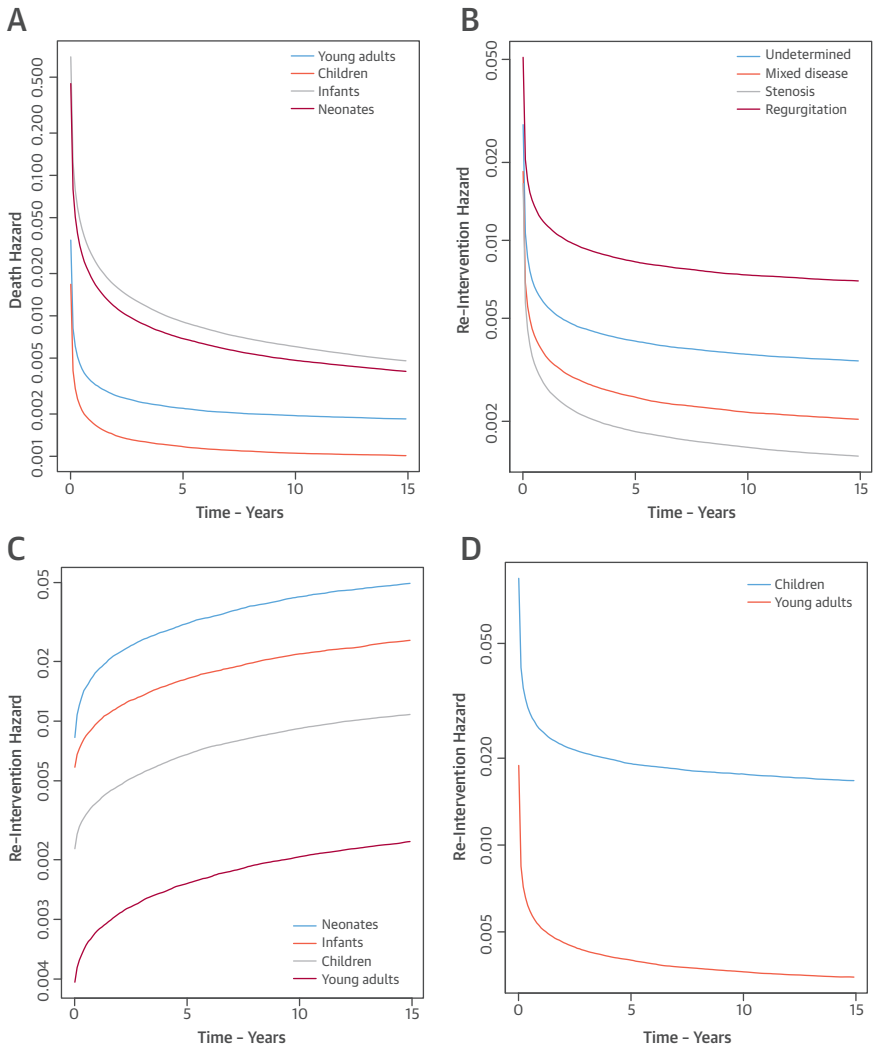
COMPARISON WITH THE MATCHED GENERAL POPULATION. Survival after R-AVR, B-AVR, and M-AVR was compared with that of the general population, with R-AVR being the only method having a survival pattern closely similar to that of the general population. The method, results, and discussions are available in the Online Appendix.

DISCUSSION

This study shows that the prevalence of various AVR options is in keeping with what is known and expected in children and young adults (Central Illustration). The Ross procedure is the most common option in children due to its growth potential but its utilization decreases in young adults. All valves achieved good survival, the lowest 12-year estimate being for M-AVR at 90.6%. The 12-year freedom from reintervention is over 90% for R-AVR and M-AVR but only 75% and 59.5% for B-AVR and H-AVR, respectively (Table 3).

More insight was gained by detailed subgroup analyses, in which R-AVR emerged as overall superior, at worst comparable to M-AVR in young adults. In a separate analysis examining UK trends we found that the Ross procedure has excellent results in young

FIGURE 7 Risk Factors for Death or Reintervention in Ross and Mechanical AVR

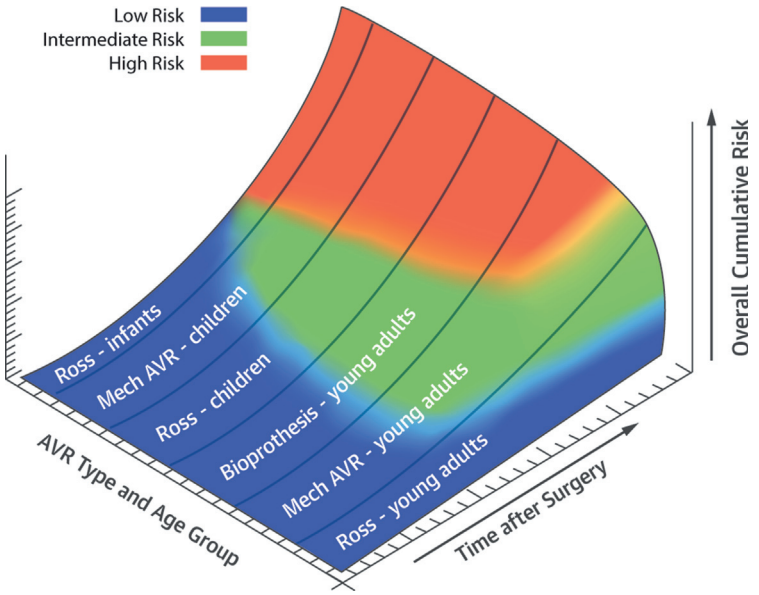


Hazard functions are derived from multivariable Bayesian mixture survival models (separate for Ross and mechanical aortic valve replacement [AVR]), using the additive mixture of 2 Weibull hazards, adjusted by age (continuous), age group, sex, aortic disease type, mitral disease, coarctation, subaortic stenosis, genetic syndrome, mitral valve procedure, coarctation repair, and subaortic stenosis repair at index. The midpoint of each age group was chosen as the age of its corresponding hypothetical patient, whereas the rest of the categorical variables were set as zero. **(A)** Impact of age on mortality risk for Ross procedure. **(B)** Impact of aortic disease type on reintervention risk for Ross procedure. **(C)** Impact of age on risk of pulmonary reintervention for Ross procedure. **(D)** Impact of age on reintervention risk for the mechanical AVR procedure in young adults. Dynamic hazard ratios, CI differences, event-free probability differences, and their corresponding p values can be seen in the Online Appendix.

patients but, curiously, its usage is gradually decreasing over time, the main competitors being balloon valvuloplasty in children and M-AVR in young adults (4).

Most of the data available on long-term outcomes in AVR in children and young adults comes from single-center studies, with just a few multicenter reports and even fewer comparative ones. The German-Dutch registry reports excellent results with the Ross procedure in older patients (5), whereas the Society of Thoracic Surgeons reports short-term results from a national database in infants (6). Published data on outcomes after each individual AVR type is readily available, but patient age, clinical

CENTRAL ILLUSTRATION **AVR and the Ross Operation in Children and Young Adults**



Sharabiani, M.T.A. et al. J Am Coll Cardiol. 2016;67(24):2858–70.

Dynamic changes of risk of mortality or reintervention during follow-up period after aortic valve replacement (AVR) operation by the procedure types and the age groups. Risk of both mortality and reintervention decrease with the patient age and increase during follow-up. The overall increase of risk differs depending on the AVR procedure type and the speed of increase in risk during the various stages of follow-up time is not proportional across the AVR types. Distances and the levels of increase in risk are drawn schematically and, therefore, are not precise.

status, and methodology vary widely. Comparative studies in the young are scarce and confronted with the same limitations we encountered, specifically differences in patient characteristics. No randomized AVR studies were performed in children and only a few were done in adults. A review of modern literature on AVR in the young shows a particular interest in the Ross procedure, in some reports survival being comparable with that of the general adult population (7–9). Careful patient selection and technical modifications are most likely responsible for the improved results (5,9,10). This naturally leads to the question: Is the Ross procedure the gold standard in AVR in the young? And if so, where do we stand in regard to the other 3 options?

NEONATES AND INFANTS. In our study the majority of neonates and infants underwent R-AVR. But the Ross operation is not always seen as first choice for small children. Surgical or transcatheter repair are sometimes preferred to postpone AVR, on the grounds that palliation can achieve good results (11,12), whereas AVR mortality in these patients is high, ranging from 15% to 50% (12–14). We have seen a lower early mortality in this age group (10%) but still we found that age under 1 year is a risk factor in the R-AVR overall. The lower mortality may be related to excluding patients with complex associated defects, like interrupted arch, specifically found to be a risk factor by others (6,15). Hickey et al. (10) report high mortality in neonates and infants undergoing a Ross procedure, but these patients had either critical stenosis or a failed previous repair, the results being otherwise acceptable for patients older than 3 months presenting electively. In other words performing a Ross procedure in unfavorable circumstances may lead to unfavorable results, but these are situations where alternatives are limited.

We found that <1 year of age was a significant risk factor for pulmonary conduit reintervention, as previously reported, in keeping with the notion that a small conduit is rapidly outgrown (5). Examining the best treatment sequence in small children (including palliation by valve repair and balloon dilation) was beyond the scope of this paper, but the small number

of AVRs in infants nationally suggests this option is considered after all other treatment paths are exhausted.

CHILDREN. It has previously been shown that hetero- and homografts are not suitable in the long term in the pediatric population and should be used with caution. Bioprosthesis valves have been associated with a risk of rapid deterioration and explantation (16), or even catastrophic early failure (17). Results achieved with H-AVR have been variable, but a high incidence of reoperation has been reported (16,18). This was mirrored in our group by the majority of children receiving either a Ross autograft or a mechanical valve. Compared to R-AVR, M-AVR has higher mortality, especially in the early phase, and slightly higher aortic reintervention risks. Taking into consideration the RVOT reinterventions, it results in a 12.7% difference in event-free probability at 10 years in favor of the Ross procedure (**Figure 2**). Alsoufi et al. (19) also found a significantly higher mortality risk after M-AVR, but a higher risk of aortic reintervention in the Ross group, noting that patients with rheumatic disease were included and found to be at increased risk for reintervention. Ruzmetov et al. (16) reported a single center series with similar results as our national audit. In a study with 10 years of follow-up Lupinetti et al. (20) also found that mechanical AVR in children had worse results when compared to autograft/allograft.

YOUNG ADULTS. In young adults, all 3 main choices of valves are available, patients receiving a Ross autograft being the youngest in our group, those having a mechanical AVR the oldest, with the bioprosthesis in between (**Figure 1**). In a 3-way matched comparison, we found that biological valves are associated with the worst results, followed by mechanical valves and Ross with comparable results, albeit slightly better for the latter (**Figure 3**). These results persist in pairwise comparisons, which broaden the matched groups depending on the particular overlap in age (**Figures 4 to 6**).

Comparing the Ross procedure and mechanical AVR we found a slightly higher mortality and aortic reintervention risk in M-AVR, but overall event-free probabilities are comparable after considering the RVOT reinterventions (**Figure 4**). Mokhles et al. (21) compared the R-AVR and optimally anticoagulated M-AVR in propensity score matched groups for the nonelderly adult population, finding no differences in mortality and significantly higher aortic reintervention rates in the Ross group. There are several differences between this study and ours: our patients are younger, we did not use propensity matching but rather a composite approach, and finally our M-AVR patients were not under highly specialized anticoagulation but under real-life conditions when compliance is variable.

Few reports compare the Ross procedure with the bioprosthetic valve in the young. Ruzmetov et al. (22) reported better survival with Ross at 15 years (91% vs. 84%) (but children were also included and noted to have higher mortality), comparable freedom from aortic reintervention, and higher risk of AoV explantation in the bioprosthesis group. We found no differences in long-term mortality in our matched groups (the difference being we compared only young adults), but we did find a higher risk for AoV reintervention in the B-AVR group, especially starting after 2 years of follow-up (**Figure 5**).

Comparing the mechanical to bioprosthetic valves in matched young adults groups, we found modest differences in mortality and aortic reintervention, the risks being slightly higher in the latter (**Figure 6**). Ruel et al. (23) examined mechanical prostheses with biological (heterograft and homograft) in a population of young adults and found comparable results in long-term mortality but significantly worse freedom from reintervention in the biological valve group (worse in the heterograft vs. homograft). In addition there was a lower overall quality of life in the mechanical group. Interestingly, when patients of similar ages are compared in our study, the differences are not as striking as previously reported, but this might also be due to the small sample size. The results suggest that B-AVR remains a reasonable option for young adults, particularly in keen patients such as women contemplating pregnancy.

RISK FACTORS ASSOCIATED WITH AVR. Our data originated in a procedure-based audit, and therefore we had few other variables to consider as predictors. The focus became age, valve disease type, and concomitant defects and procedures, also looking into the dynamic effect they might have during follow-up. The choice to apply dynamic survival analysis was influenced by the belief that some key drivers of outcome may not have the same impact in various stages of follow-up. Our results highlighted 3 cases of age influencing outcome: mortality risk and pulmonary reintervention for the Ross procedure, and aortic reintervention for M-AVR (**Figure 7**). In the first case, we saw a strong early-phase hazard for neonates and infants compared to children and young adults, consistent with the more severe clinical condition associated with presentation at earlier ages. In the other 2 cases, an increased hazard for younger

patients was noted which lasted long into follow-up. This is consistent with an inherently higher risk due to the initial surgery. A dynamic model allowed us to differentiate these 2 patterns and hypothesize about the different root-causes of each. Of course an alternative is to build independent models for different age groups to allow for arbitrary HRs between them, but this would not be as efficient a use of data as building a single model that contains all age groups.

STUDY LIMITATIONS. The study is limited by absence of more clinical data such as operative timing and echocardiography, as well as by relatively short follow-up. The small proportion of patients with incomplete follow-up could be a source of errors, even though the missing data is due to administrative reasons. In addition, being a retrospective study, it shares the limitations inherent to such a design, and also of the retrospective matching methods.

CONCLUSIONS

The UK national dataset allowed complete procedural and survival follow-up for AVR carried out in the young. The Ross procedure has multiple advantages that seem to extend beyond childhood, being superior to other AVR types when compared in matched groups, especially in children, but all prostheses perform reasonably well overall. Future planned research revolves around linkage with other UK valve registries to obtain longer follow-up as well as examining the role of surgical and balloon valvuloplasty in delaying AVR. Cost and quality of life analyses would similarly add to the quest for finding the most advantageous valve substitutes for individual patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Dan M. Dorobantu, Department of Cardiology, "Prof. C.C. Iliescu" Emergency Institute for Cardiovascular Diseases, 022322 Sos Fundeni 258, Bucharest, Romania. E-mail: dn.dorobantu@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although most methods of AVR in children and young adults are associated with good outcomes, the Ross procedure achieves better survival than other valve replacement options, but is associated with more frequent need for subsequent interventions.

TRANSLATIONAL OUTLOOK: Longer follow-up studies may identify high- and low-risk subgroups and better inform selection of optimum approaches for individual patients.

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KEY WORDS aortic valve disease, aortic valve replacement, congenital heart disease, Ross procedure

APPENDIX For expanded Methods, Results, Discussion, and Reference sections as well as supplemental figures, please see the online version of this article.