Strategies to minimise need for prosthetic aortic valve replacement in congenital aortic stenosis – value of the Ross procedure

Ivanov, Yaroslav; Drury, Nigel; Stickley, John; Botha, Phil; Khan, Natasha; Jones, Timothy; Brawn, William; Barron, David

DOI:
10.1053/j.semtcvs.2020.02.015

Title: Strategies to Minimise Need for Prosthetic Aortic Valve Replacement in Congenital Aortic Stenosis – Value of the Ross Procedure

Authors: Yaroslav Ivanov [1] MD PhD, Nigel E Drury [1,2] MD PhD, John Stickley [1] BSc, Phil Botha [1] MD PhD, Natasha E Khan [1] MD, Timothy J Jones [1,2] MD, William J Brawn [1] MD, David J Barron [1] MD

Conflict of interest: none

Source of funding: The authors received no specific funding for this study. Nigel Drury is funded by an Intermediate Clinical Research Fellowship from the British Heart Foundation (FS/15/49/31612).

Affiliations: [1] Department of Paediatric Cardiac Surgery, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK; [2] Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK.

Corresponding author: Yaroslav Ivanov, iyaroslav@ukr.net, +61434520933

Word count: 4070

List of abbreviations:

AoV – aortic valve

AS – congenital aortic stenosis

BV – balloon valvuloplasty

pAVR – prosthetic aortic valve replacement

RVOT – right ventricular outflow tract

SV – surgical valvotomy

SR – surgical repair

Abstract

Objectives: To examine the role and outcomes of all interventions for aortic stenosis in children, with focus on freedom from reintervention and the aim to minimise prosthetic aortic valve replacement (pAVR) during childhood.

Methods: Retrospective analysis of 194 consecutive children who underwent any aortic valve intervention for a biventricular repair strategy at a single institution between 1995-2017. Data were obtained from hospital records and follow-up was 100% complete.

Results: Over a 22-year period, 194 children underwent total 313 aortic valve procedures: Primary interventions were surgical valvotomy (SV)/surgical repair (SR) in 94 (48.5%), balloon valvuloplasty (BV) in 60 (30.9%), pAVR in 8 (4.1%) and Ross/Ross-Konno procedure in 32 (16.5%). Median age at first intervention was 1.1 years (IQR 0.1-9.4) and varied with type of intervention: SV/SR were most common in neonates (33, 75%) and infants (35, 68%), whilst BV was most frequent in older children (42, 42%). Operative survival was 99% (2 early deaths, both in neonates with critical aortic stenosis and poor left ventricular function) and 15-year survival was 95%. A Ross procedure was performed in 79 (40.7%) patients over the 15-year study period, one of whom required late pAVR for autograft failure. Freedom from any reintervention after SV/SR and BV was 41% and 40% at 10 years, compared to 90% at 10 years with the Ross procedure ($p<0.001$). Amongst neonatal SV/SR and BV, 98% required reintervention during childhood with no difference between groups. Valve morphology did not influence freedom from ultimate valve replacement. In patients who went on to have a Ross procedure, median time from initial intervention to Ross was 2.8 years (IQR 0.1-11.9) in neonates and 6.0 years (IQR 3.1-7.5) in all other age groups. Overall freedom from pAVR was 97% at 10 years and was similar in the SV/SR and BV groups.

Conclusion: A strategy of simple valve repair and primary Ross procedure provides excellent survival and good freedom from pAVR. However, reintervention rates after simple interventions for congenital AS are high, especially in younger age groups. The Ross procedure offers the best freedom from reintervention of any technique and wider use of primary Ross in younger age groups should be considered

Abstract word count: 352

Central message: The burden of aortic valve reintervention could be reduced by wider use of the Ross procedure in childhood.

Perspective statement: Combination of simple repair techniques and the Ross procedure provide excellent survival for congenital aortic stenosis and minimise the need for prosthetic aortic valve replacement in children. Wider use of the Ross procedure could reduce the burden of aortic valve reintervention during childhood.

Introduction

Congenital aortic stenosis (AS) in children presents a significant challenge due to variability in clinical presentation and commonly requires a series of interventions during childhood[1]. Optimal management of symptomatic patients with AS still remains controversial; however, in majority of scenarios it consists of the first line treatment that can be either balloon valvuloplasty (BV) or surgical valvulotomy (SV)[1–3] with destination interventions most commonly being the Ross procedure[4–7], prosthetic aortic valve replacement (pAVR)[8–10] or surgical aortic valve (AoV) reconstruction [8,10–12]. The choice and timing of ultimate destination for the AoV is also a matter of ongoing debate[13]. Recent reports show that AoV substitute with autograft is superior to pAVR[14], despite being criticised for its complexity, risks of autograft dilatation and right ventricular outflow tract (RVOT) reoperation. In contrast, three-cusp reconstruction techniques are an attractive alternative to any AoV replacement, but with concerns over limited long-term durability and performance of leaflet material and suitability in younger children.

The aim of this study was to analyse the clinical outcomes for patients presenting with congenital AS, the burden of reinterventions with each pathway, and the roles of BV, SV and primary Ross procedure in providing long-term freedom from prosthetic AoV replacement. Outcomes were analysed not only in terms of survival but also freedom from reintervention with each treatment strategy.

Material and methods

All patients presenting with a primary diagnosis of AS between 1995-2017 were included in the study. All patients were treated at a single institution (Birmingham Children's Hospital, United Kingdom). The start date was chosen as this was when all hospital records and imaging data became established in the hospital digital database to enable accurate review of original data. This study was registered with the Institution's Research & Development office; however, in accordance with UK NHS National Research Ethics Service guidance, neither individual informed consent not formal research ethics committee review was required as the study was undertaken by the direct clinical care team using information previously collected in the course of routine care.

Patients were only included in the study if they underwent biventricular repair. Patients with associated ventricular septal defect, mitral valve disease and the coarctation of the aorta were also included into the study. Patients with predominant AoV regurgitation were excluded. Neonatal period was defined as an age from birth to 28 days inclusive with infancy as an age between 28 days and one year and childhood until 18 years old. Follow up was complete to September 2018, obtained from hospital electronic patient records (HeartSuite, Systeria, Glasgow, United Kingdom) and through structured enquiry with referring cardiac surgeons or cardiologists when patients has been transferred to another institution.

A bicuspid aortic valve was defined as either a truly bileaflet, bicommissural valve or a functionally bicuspid valve with a completely fused false commissure. The first interventions were defined as any initial AoV procedures performed after the diagnosis of AS was established and included the following interventions: surgical valvotomy (SV), surgical repair (SR), balloon valvuloplasty (BV), Ross/Ross-Konno procedure, or pAVR. The choice of BV vs SV/SR was made by a multi-disciplinary decision but with a strong institutional bias towards surgical intervention in neonates (see below). This reflects the institutional preference for SV in neonates to create a controlled opening of the valve and minimise the risk of creating aortic regurgitation. Our operative technique for SV has been described previously[12] and involves opening up of fused commissures, thinning of the leaflets and excision of nodules and areas of thickening on the aortic leaflets. Policy was to achieve a peak velocity across the valve at completion of at least less than <30mmHg. In this study, surgical repair (SR) was defined as performing valvotomy as described above, but with the addition of a single patch (of bovine pericardium) to re-create a single commissure or part of an unsupported leaflet. Multiple AoV leaflet extensions and three leaflet reconstruction techniques were ***not*** used throughout the time of the study as an institutional preference. The Ross procedure was preferred for any valves requiring more than a single patch commissural repair. Our current technique for the Ross procedure has also been described previously[7]and was performed as root replacement without external prosthetic support.

Statistical methods

Exploratory analyses incorporating graphical and tabular displays assessed evidence in favour of trends and associations. Data that is skewed is presented as median and interquartile range. Categorical data are expressed as counts and percentages where appropriate.

Overall survival was estimated using the Kaplan-Meier method. The log rank test was used to compare survival and re-intervention between subgroups. R version 3.5.3 was used for the analysis and packages for survival, survminer and ggplot2 along with those in the base version were used for presenting data and for analysis. Significance testing was 2-sided with the significance level set at $p<0.05$.

Results

A total of 194 patients with a primarily diagnosis of AS underwent 313 AoV interventions between 1995 and 2017, of whom 141 (72.7%) were male. The median weight at the first intervention was 9.7kg (IQR 4.0-31.4) and median age 1.1 years (IQR 0.1-9.4). Initial valve morphology was bicuspid in 144 (74.2%) patients, trileaflet in 41 (21.1%) and unicuspid in two (1.0%), with no quadricuspid aortic valves identified; in seven (3.6%) cases, valve morphology could not be defined, all of whom had undergone initial balloon intervention. The average number of AoV interventions was 1.6 per patient with 59 (30.4%) patients undergoing two interventions, 22 (11.3%) with three interventions, 4 (2.1%) with four interventions, and one (0.5%) with five interventions. At first intervention, 44 (22.7%) were neonates, 51 (26.3%) were infants, and 99 (51.0%) were children; median age at first intervention in children was 9.0 years (IQR 3.9-13.7). Procedures were performed by or under the supervision of 7 Consultant interventional cardiologists and 6 Consultant surgeons, all of whom performed Ross procedures. A flow diagram of primary and subsequent aortic valve interventions in this cohort, including the number of prosthetic AVR/root replacements and Ross procedures by primary intervention, is shown in the graphical abstract (figure 8).

The overall survival was 95% at 15 years (Figure 1A), with a hospital mortality of 1.0%; only two hospital deaths occurred, both in the neonatal group in the setting of severely impaired ventricular function. One patient presented with critical AS and underwent SV, then, due to inadequate AS relief, the Ross-Konno procedure was performed on postoperative day 21. The patient died of intractable heart failure on postoperative day 23. The second case had persistent poor LV function and low cardiac output state after urgent SV, despite good relief of gradient and no aortic incompetence, and died on postoperative day 12. Late mortality was 3.1%, with six late non-procedural deaths, with the causes as follows: chronic heart failure in a patient who died at age 2.8 years after initial SV twice in neonatal period; late infective endocarditis after pAVR in a patient with Shone complex and severe pulmonary hypertension at age 8.4 years; respiratory failure in context of multiply birth anomalies after good surgical result and two lost to follow up 12 y after SV and 3 months after BV. The cause of death in last patient was unknown, a sudden death at home at age 2.4 years with documented good heart function, no residual AoV stenosis but moderate regurgitation after neonatal SV.

Median time of follow-up was 12.4 years (11 days to 28.1 years) and was 100 % complete.

First AoV intervention

The most common initial AoV intervention was SV/SR performed in 94 (48.5%) patients followed by BV as the second most common AoV intervention in 60 (30.9%) patients. Primary Ross/Ross-Konno procedure was performed in 32 (16.5%) cases and pAVR required in 8 (4.1%) patients. The spectrum of age at first AoV intervention is presented in Figure 2. Median age at first intervention was 1.1 years (IQR 0.1-9.4) and varied with type of intervention: surgical repair was the most frequent primary intervention in neonates (33, 75%) and infants (35, 68%), whilst BV was the most common in older children (42, 42%). The institutional preference for SV (or repair) in neonates is clearly shown in Figure 2 with 85% of neonates undergoing surgery compared to 15% having BV as the first intervention.

The median age at primary pAVR was 15.4 years (IQR 13.5-16.0), all of which were mechanical valves (St Jude, Abbott Cardiovascular, Minnesota). The indications for choosing pAVR over Ross procedure in these 8 patients were: patient preference in 3, dilated aortic root with aortopathy in 3, abnormal pulmonary valve in 1, and unfavourable anatomy in 1

(LAD passing around the annulus of the pulmonary valve). The freedom from pAVR was 95% at 10 years and 88% at 15 years in the entire cohort as shown in Figure 1B.

Freedom from prosthetic AVR: In total 21 (10.8%) patients required pAVR including 8 (4.1%) cases as a primary pAVR. One patient required pAVR due to autograft failure at 14.5 years after primary Ross procedure. The other reasons for pAVR were mainly due to non-feasibility of the Ross procedure in 16 (80%) cases and patient choice in 4 (20%). The instances when we performed pAVR were as follows: abnormal pulmonary valve in 7 (30%) cases, aortopathy with ascending aorta dilatation in 5 (25%), and deteriorated clinical condition due to renal failure in one (5%) patient. Primary Ross/Ross-Konno procedure provided the highest freedom from subsequent pAVR compared with other primary AoV interventions (100 % vs 94 % in BV group and 93 % in SV/SR group at 10 years, p=0.5) (Figure 3).

The Ross/Ross-Konno procedures were used constantly throughout the study period across a wide age range, as shown in Figure 2. 79 (40.7%) patients underwent the Ross procedure, 32 as a primary procedure (ie, as their first intervention) and 47 as a secondary procedure (i.e. after one or more previous AoV interventions). The median age at primary Ross was 8.3 (IQR 3.0-11.2) years and at secondary Ross was 7.0 (IQR 2.6-12.5) years. There was zero mortality amongst the primary Ross group, and one death in the secondary Ross group, as described above in a critically ill neonate.

Primary Ross procedure, SV/SR and BV and were equally good in protecting from ultimate pAVR, noting that there was 100% freedom from need for pAVR in the primary Ross procedure group at 10 years (Figure 3).

Subsequent AoV interventions

Median time between interventions was 2.5 years (1 day to 15 years). Freedom from reintervention with respect to age at original procedure is shown in Figure 4. In neonatal groups of SV/SR and BV, freedom from subsequent AoV intervention was 47% and 43 % at 1 year. When the first intervention was performed in infancy, the freedom from subsequent reintervention was 61% in the SV/SR group compared to 78% with BV at 5 years (p=ns). Finally, when the first intervention was at an age older than 1 year, freedom from subsequent reintervention after SV/SR or BV were 81% and 63% at 5 years, respectively (p=ns). The results again emphasise that neonatal interventions (whether SV/SR or BV) are associated with higher reintervention rates and shorter time to reintervention than in the older age groups. More detailed analysis of the time spent in each intervention state showed that there was no difference in the sequence or duration of freedom from reinterventions when comparing BV with SV/SR (supplementary figure). Of the 94 patients who underwent initial SV/SR, 34 (35%) had a subsequent Ross procedure, 8 (8%) had BV, 5 (5%) had repeated SV, 4 (4%) had pAVR, and 3 (3%) have undergone aortic root replacement . In the BV group, 33 (55%) patients required one or more subsequent AoV interventions and by the time they reached adulthood, the most recent procedure was the Ross procedure in 13 (22%), SV in 8 (13%), repeated BV in 5 (8%) and pAVR in 5 (8%) patients. BV was avoided if there was >mild regurgitation or if the morphology of the valve suggested fused commissures that were good targets for surgical valvotomy.

Amongst all patients who underwent neonatal ‘repair’ procedures (SV/SR or BV) almost all required at least one further reintervention during childhood. Freedom from ultimate AoV replacement (whether autograft or prosthetic) is shown in Figure 5, comparing those who require initial neonatal intervention with those whose first intervention was beyond the neonatal period; 15-year freedom from valve replacement (either Ross or pAVR) was 3% in the neonatal group compared to 39% in the older age groups ($p<0.003$) (Figure 5).

Comparison of balloon valvuloplasty and surgical repair/valvotomy in terms of freedom from any type of AoV replacement (Ross or pAVR) is shown in Figure 6A. Taking all age-groups together, initial BV provided improved freedom from AoV replacement when compared to initial surgery ($p=0.005$), but did not show any benefit in freedom from overall reintervention (Figure 4). This potential benefit of BV is mainly within the older patients, as shown when comparing to Figure 4 where the outcomes within neonates for both BV and SV/SR were similar. Surgical valvotomy and repair, when performed in neonatal period as primary AoV procedures, were associated with significantly lower freedom from subsequent AoV intervention (25% at 5 years, $p<0.001$) compared with infant and children (65% and 80% at 5 years, respectively). In neonates who underwent primary BV, the numbers were small, and it did not reach statistical significance ($p=0.10$). Overall, 97% of all neonatal SV/SR and BV required subsequent reintervention during childhood.

The impact of valve morphology on the need for valve replacement is shown in Figure 6B. Bicuspid/unicuspid AoV morphology did not influence the freedom from AoV replacement when compared to trileaflet valves.

Ross Procedure: Ross procedure was performed in 79 (40.7%) patients over the study period. Freedom from any AoV intervention in the entire group of Ross/Ross-Konno procedure was 90% at 10 years, which was significantly better outcome ($p<0.001$) compared with reintervention rates in BV and SV/SR groups where the freedom from any AoV intervention was 40% and 41% at 10 years, respectively (Figure 7A). Analysis of the patients that ultimately received the Ross procedure showed that the mean time between initial intervention and the Ross procedure was 6.1 years with a mean of 1.5 interventions prior to the Ross procedure. The median time from initial intervention to the Ross procedure also depended on the age at first intervention: if the first intervention was in childhood, median time to Ross procedure was 5.2 years (IQR 2.8-8.9), if during infancy, median time was 6.3 years (IQR 3.1-6.7) and if performed as a neonate, median time was 2.8 years (IQR 0.0-13.4).

The need for surgical reintervention on the RVOT amongst the entire Ross procedure cohort was 7 conduit replacements in 6 (7.7%) patients over the duration of the study. Freedom from surgical RVOT reintervention is shown in Figure 7B, with a freedom from conduit replacement of 88% at 10 years.

Discussion

The management of congenital AS in children is a challenging task due to a lack of well-established guidelines, heterogeneity in practice and various patterns of presentation[15]. The initial treatment strategy remains an area of debate but evidence suggests that both BV and SV as primary intervention in neonates and infants yields equivalent results in terms of survival[1] and also, it is commonly accepted that they are palliative procedures in the sense that the majority of patients will come to need further intervention in the future[2]. In contemporary series, freedom from AoV reintervention after AoV surgery in the paediatric population ranges between 50% and 80% at 10 years, with a median time to next AoV reintervention between 4 and 6 years[8–10,12]. Freedom from reintervention was only 33% at 10 years for AS with a bileaflet AoV phenotype[12]. Similarly, initial BV provides freedom from subsequent AoV intervention between 30% and 50% at 10 years,[2,3,16,17] most commonly due to significant AoV regurgitation. These outcomes are generally accepted, given that the aim of BV and SV is to delay the need for subsequent AoV substitute until the child is grown sufficiently[2]. In general, studies have focused on the outcomes for critical AS in the neonatal period, and there is limited data on the relative benefits/performance of BV vs SV in older age groups within childhood. This study highlights the overall burden of reinterventions within this population and describes similar high reintervention rates in the neonatal population, with 97% of cases requiring further surgical intervention during childhood.

An important component of this study is our institutional policy regarding initial AoV interventions which has evolved to strongly favour surgical valvotomy in neonates. The rationale is that this is felt to be more a more controlled procedure with less risk of significant AoV regurgitation, which can be difficult to manage in neonates. Beyond the neonatal period, we would still favour surgical valvotomy when AoV presented with at least two well-defined commissures while BV would be reserved for the more dysplastic AoV with poorly defined commissures, or as a second line intervention for those patients who had previous SV. Therefore, surgical valvotomy was the most common procedure in neonates (33, 75%) and infants (35, 68%) whilst BV was more frequent in older children (42, 42%). This study has shown that using this selective policy can yield very encouraging outcomes, with 98% survival at 15 years across the entire spectrum of AS (excluding univentricular circulations). This study cannot tell us whether SV or BV is preferable in neonates due to the small numbers of patients in the BV group, only that a policy of favouring surgery appears to be safe and provides excellent survival.

Given that such good survival can be achieved, the focus becomes more on the burden of reinterventions in this patient group and whether there may be ways of minimising reintervention. This study reinforced the finding that almost all patients who require neonatal intervention will come to need eventual AoV replacement during childhood. However, in older patients (first intervention during or after infancy) the story is not the same, and it would be expected that two-thirds of all infants and children will require some reintervention, and only half will need AoV replacement during childhood. An important observation from this study is that, beyond the neonatal period, freedom from eventual AoV replacement (Ross procedure or pAVR) was improved (p=0.05) in BV group compared with SV group; however, this may reflect our selective policy of reserving BV for the older age-groups and its use as a secondary procedure subsequent to initial SV. Although BV appeared to reduce the need for eventual valve replacement in these older children, the need for reintervention was similar to the SV group.

In the current literature there are few studies which directly compare BV and SV in neonates and infants[2,3]. Siddiqui et al[3] reported outcome in 123 infants and neonates who underwent BV and SR for critical AoS. Surgical valvotomy was associated with a significantly higher freedom from next AoV intervention when compared to BV (27% vs 65% at 5 years). In contrast, Benson et al[2] reported comparable long-term outcomes in 79 neonates undergoing BV or SV; freedom from re-intervention in the BV group was 52% versus 78% for SV at 5 years, but this was not significant (p =0.09). This study shows comparable outcomes between BV and SV in neonates, but the small numbers in the BV group prohibit any further analysis beyond this observation.

In managing congenital AS, a key aim is to avoid the need for pAVR during childhood whenever possible. In this study, we found that a 96% freedom from pAVR can be achieved at 10 years using the combination approach of simple SV, BV and the Ross procedure. Mechanical pAVR has generally been reserved for children with AoV disease who are not good candidates for the Ross procedure or for valve-sparing AoV surgery[4], but in many studies it is still used as the definitive AoV substitute[18,19], despite the disadvantages of poorer haemodynamics that the Ross procedure, the issue of no growth potential and significant morbidity related to the need for lifelong anticoagulation. In contrast, the Ross procedure is the preferred AoV substitute in children as it offers growth potential, excellent hemodynamics and avoids the risk of anticoagulation[15] in spite of being criticized for its complexity, risks related to autograft dilatation[5,6] and the need for RVOT reinterventions. The Ross/Ross-Konno procedure also has the advantage that it can be used at any age, including neonates and that it retains full growth potential regardless of the age at which it is performed. An important observation within this study is the remarkable freedom from the need for any reintervention on the AoV following the Ross procedure (whether primary or secondary), which is considerably better than that seen with SV/SR or BV. Thus, in terms of minimising the burden of reintervention on the AoV, there could be an argument for wider use of the Ross procedure, especially in the younger age groups where there is an extremely high likelihood of coming to need valve replacement during childhood. This argument is strengthened by evidence that the Ross procedure performed at a younger age has extremely good long-term performance with a lower incidence of autograft dilatation and better long-term preservation of autograft function[7]. This creates a potential dilemma in the younger patient as the Ross/Ross-Konno procedure is a major and complex procedure and the use of a simpler SV or even BV can be very appealing. Having said this, the operative outcomes of the Ross procedure in infants, particularly in the setting of good ventricular function, are extremely good and would support a strategy of wider use of the Ross procedure in younger patients. The attraction of such a strategy might not only reduce the burden of AoV reinterventions but may also preserve better long-term left ventricular function by avoiding interim periods with sub-optimal haemodynamic between multiple interventions.

This argument must be balanced by the potential drawbacks of the Ross procedure, which include the likely need for right sided conduit interventions[4,6] and a recognised failure rate and dilatation of the autograft. However, the need for surgical RVOT reintervention was low in this study despite many patients being in younger age groups (88% freedom at 10 years), and the use of homografts for RVOT reintervention in the setting of the Ross procedure have traditionally performed extremely well.

The biggest challenge in management of congenital AS is to better predict which patients are likely to come to need AoV replacement and which are likely to do well with simple repair (BV or SV), or at least to be able to identify the group who are likely to get good mid-long term palliation with simple repair. This may help us to design treatment models favouring earlier Ross procedure in certain patient groups.

Limitations of the study

As an observational study, our institutional bias towards using SV in neonates and BV in older patients limits an objective comparison between techniques by age group. The retrospective nature of the study and the variability in pre-operative characteristics limits the capability to objectively compare SV to Ross as there are too many compounding variables – a randomised prospective study would be needed to examine this. Only patients who underwent a biventricular repair were included and as such, our results do not reflect the outcomes of all neonates with critical aortic stenosis. Some patients underwent multiple BV or SV procedures, including cross-over between groups, which makes subsequent analysis of outcomes more clouded. As follow-up was limited to childhood, this study does not address the late freedom from pAVR, performance of the Ross autograft or need for RVOT reintervention into adulthood. In addition, there was missing data on valve morphology in seven (3.6%) cases.

This study did not attempt to evaluate the role of more complex AoV reconstructive procedures; we have avoided these procedures in children due to concerns over the durability of the techniques and materials used,[8] although we acknowledge that there has been renewed interest in these procedures with greater success of the Ozaki procedure[20], even in younger children[21]. This may become an additional option in managing the pathway of congenital AS, although are still less likely to be offered in the younger age group, where the controversy over the best strategy is greatest.

Conclusion

A combined approach of simple valvotomy/repair, judicious use of balloon valvuloplasty and the Ross procedure can provide excellent outcomes in congenital AS and minimise the need for pAVR during childhood. There is a considerable burden of reintervention, particularly in patients needing neonatal intervention, who have a 97% likelihood of needing valve replacement during childhood. The Ross procedure carries the lowest need for reintervention of any treatment modality, and wider use of the primary Ross in the younger age-group should be considered.

References

1. Hill GD, Ginde S, Rios R, Frommelt PC, Hill KD. Surgical valvotomy versus balloon valvuloplasty for congenital aortic valve stenosis: a systematic review and meta-analysis. J Am Heart Assoc. 2016;5(8).

2. Benson L. Neonatal aortic stenosis is a surgical disease: an interventional cardiologist view. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2016;19: 6-9.

3. Siddiqui J, Brizard CP, Galati JC, et al. Surgical valvotomy and repair for neonatal and infant congenital aortic stenosis achieves better results than interventional catheterization. J Am Coll Cardiol. 2013;62(22):2134-2140.

4. Takkenberg JJM, Klieverik LMA, Schoof PH, et al. The Ross procedure: a systematic review and meta-analysis. Circulation. 2009;119(2):222-228.

5. Brancaccio G, Polito A, Hoxha S, et al. The Ross procedure in patients aged less than 18 years: The midterm results. J Thorac Cardiovasc Surg. 2014;147(1):383-388.

6. Schneider AW, Putter H, Klautz RJM, et al. Long-term follow-up after the Ross procedure: a single center 22-Year experience. Ann Thorac Surg. 2017;103(6):1976-1983.

7. Lo Rito M, Davies B, Brawn WJ, et al. Comparison of the Ross/Ross-Konno aortic root in children before and after the age of 18 months. Eur J Cardiothorac Surg. 2014;46(3):450-457.

8. d'Udekem Y, Siddiqui J, Seaman CS, et al. Long-term results of a strategy of aortic valve repair in the pediatric population. J Thorac Cardiovasc Surg. 2013;145(2):461-469.

9. Vergnat M, Asfour B, Arenz C, et al. Contemporary results of aortic valve repair for congenital disease: lessons for management and staged strategy. Eur J Cardiothorac Surg. 2017;52(3):581-587.

10. Poncelet AJ, El Khoury G, De Kerchove L, et al. Aortic valve repair in the paediatric population: insights from a 38-year single-centre experience. Eur J Cardiothorac Surg. 2017;51(1):43-49.

11. Hawkins JA, Kouretas PC, Holubkov R, et al. Intermediate-term results of repair for aortic, neoaortic, and truncal valve insufficiency in children. J Thorac Cardiovasc Surg. 2007;133(5):1311-1317.

12. Bhabra MS, Dhillon R, Bhudia S, et al. Surgical aortic valvotomy in infancy: impact of leaflet morphology on long-term outcomes. Ann Thorac Surg. 2003;76(5):1412-1416.

13. Alsoufi B, Al-Halees Z, Manlhiot C, et al. Mechanical valves versus the Ross procedure for aortic valve replacement in children: Propensity-adjusted comparison of long-term outcomes. J Thorac Cardiovasc Surg. 2009;137(2):362-370.

14. Buratto E, Shi WY, Wynne R, et al. Improved survival after the Ross procedure compared with mechanical aortic valve replacement. J Am Coll Cardiol. 2018;71(12):1337-1344.

15. Bouhout I, Ba PS, El-Hamamsy I, Poirier N. Aortic valve interventions in pediatric patients. Semin Thorac Cardiovasc Surg. November 2018.

16. Petit CJ, Ing FF, Mattamal R, Pignatelli RH, Mullins CE, Justino H. Diminished left ventricular function is associated with poor mid-term outcomes in neonates after balloon aortic valvuloplasty. Catheter Cardiovasc Interv. 2012;80(7):1190-1199.

17. Sullivan PM, Rubio AE, Johnston TA, Jones TK. Long-term outcomes and re-interventions following balloon aortic valvuloplasty in pediatric patients with congenital aortic stenosis: a single-center study: outcomes after pediatric balloon aortic valvuloplasty. Catheter Cardiovasc Interv. 2017;89(2):288-296.

18. Arnold R, Ley-Zaporozhan J, Ley S, et al. Outcome after mechanical aortic valve replacement in children and young adults. Ann Thorac Surg. 2008;85(2):604-610.

19. Masuda M, Kado H, Ando Y, et al. Intermediate-term results after the aortic valve replacement using bileaflet mechanical prosthetic valve in children. Eur J Cardiothorac Surg. 2008;34(1):42-47.

20. Ozaki S, Kawase I, Yamashita H, et al. A total of 404 cases of aortic valve reconstructionwith glutaraldehyde-treated autologous pericardium. J Thorac Cardiovasc Surg 2014;147: 301–6.

21. Mazzitelli D, MD, Nobauer C, MD, Rankin JS, MD et al. Complete aortic valve cusp replacement in the pediatric population using tissue-engineered bovine pericardium. Ann Thorac Surg 2015;100:1923–5

Figure Legends

Figure 1. Kaplan-Meier survival (A) and freedom from prosthetic aortic valve replacement (B) following aortic valve interventions, showing excellent survival and good freedom from prosthetic valve replacement during childhood.

Figure 2. Trends in age at first aortic valve intervention: balloon valvuloplasty, surgical valvotomy/repair, Ross procedure, and prosthetic aortic valve replacement, demonstrating our preference for surgical intervention in neonates.

Figure 3. Freedom from prosthetic aortic valve replacement, stratified by the type of first aortic valve intervention: balloon valvuloplasty, surgical valvotomy/repair, or Ross procedure, showing equally good avoidance of prosthetic valve replacement during childhood.

Figure 4. Freedom from any aortic valve reintervention, stratified by age-group at the time of primary aortic valve intervention: neonate, infant, or child, revealing a higher rate of reintervention in those whose first intervention was as a neonate.

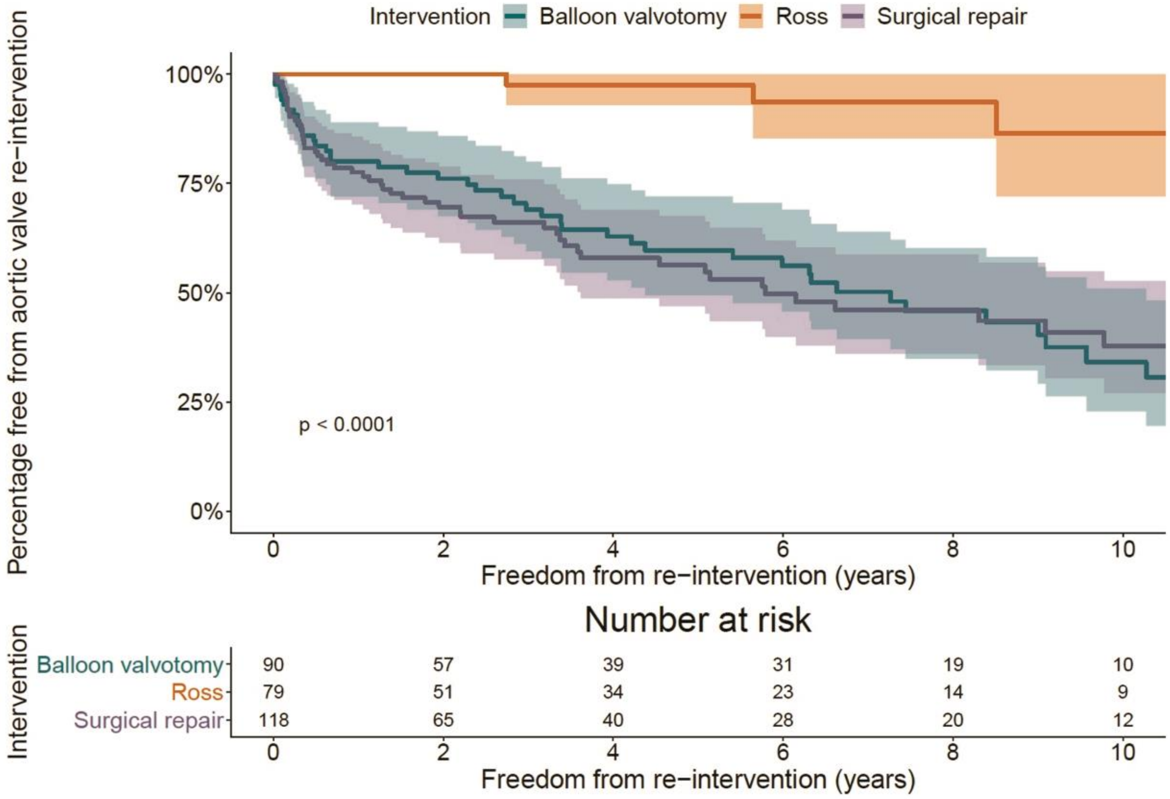
Figure 5. Freedom from any aortic valve replacement (Ross procedure or prosthetic valve), stratified by whether the initial aortic valve intervention was performed during or after the neonatal period, demonstrating a high rate of valve replacement in those whose first intervention was as a neonate.

Figure 6. Freedom from (A) any aortic valve replacement (Ross procedure or prosthetic valve), stratified by the initial aortic valve intervention, or (B) any aortic valve replacement, stratified by whether the valve morphology was bicuspid/unicuspid or trileaflet, showing no difference by initial intervention or valve morphology; those in whom valve morphology was unknown were excluded.

Figure 7. Freedom from (A) any subsequent aortic valve reintervention, stratified by type of primary aortic valve intervention: balloon valvuloplasty or surgical valvotomy/repair, compared with the Ross procedure (primary or secondary) and (B) surgical right ventricular outflow tract reintervention following the Ross procedure, demonstrating the low rates of reintervention during childhood following the Ross procedure.

Figure 8. Graphical abstract, including a flow diagram of primary and subsequent aortic valve interventions demonstrating that prosthetic aortic valve replacement (AVR) or root replacement can be minimized during childhood and, and a plot of freedom from aortic valve reintervention following primary balloon valvuloplasty, primary surgical valvotomy/repair, and the Ross procedure (primary or secondary).

Supplementary Figure. Length of time spent in each intervention state for those patients undergoing initial surgical valvotomy (upper panels) or balloon valvuloplasty (lower panels). Each panel shows the number of patients who required subsequent interventions and a Kaplan-Meier estimate of the time to reintervention.



Central image

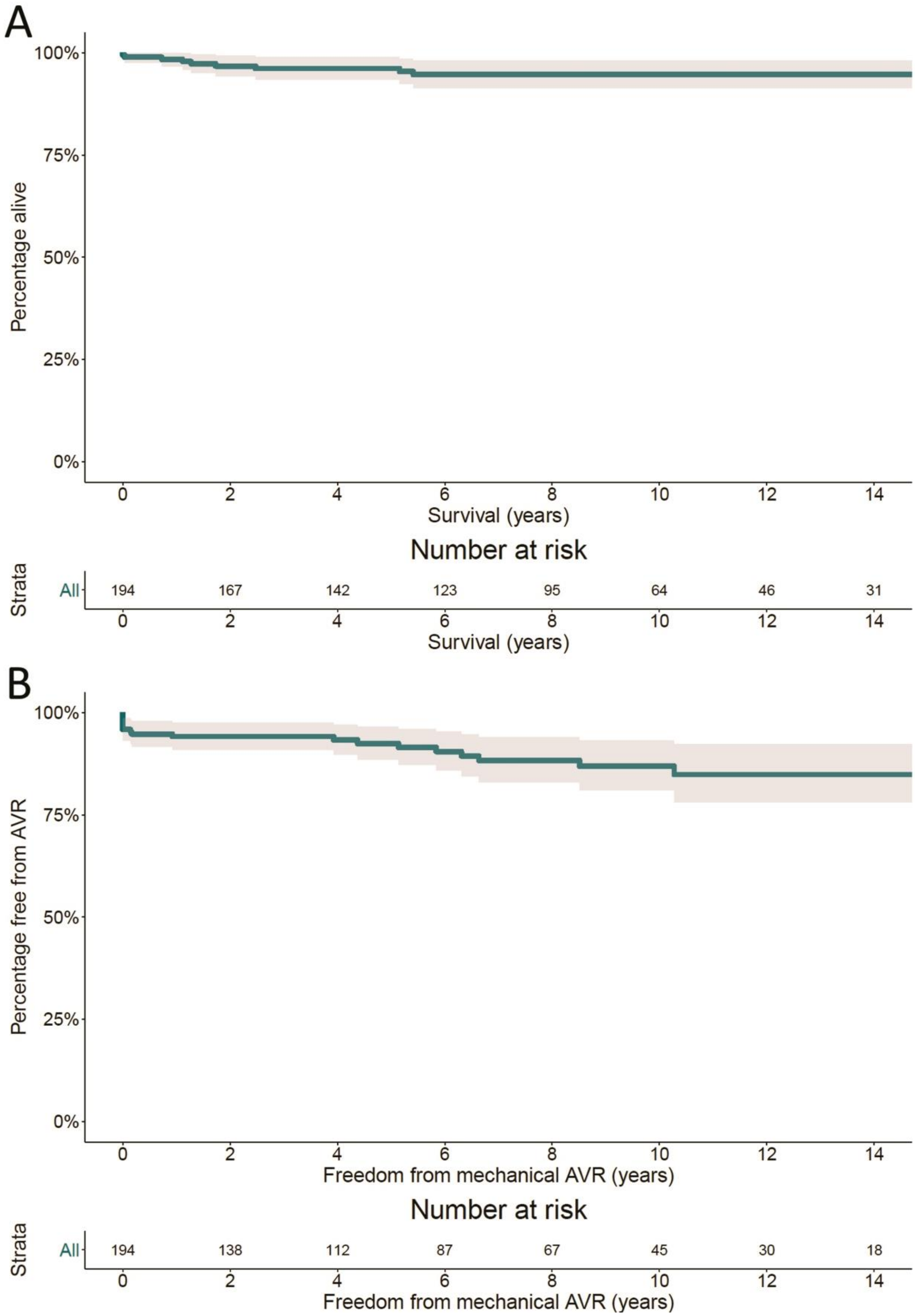

A
100%
75%
50%
25%
0%
Percentage alive
0 2 4 6 8 10 12 14
Survival (years)
Number at risk
Strata
All
194 167 142 123 95 64 46 31
0 2 4 6 8 10 12 14
Survival (years)
B
100%
75%
50%
25%
0%
Percentage free from AVR
0 2 4 6 8 10 12 14
Freedom from mechanical AVR (years)
Number at risk
Strata
All
194 138 112 87 67 45 30 18
0 2 4 6 8 10 12 14
Freedom from mechanical AVR (years)

Figure 1

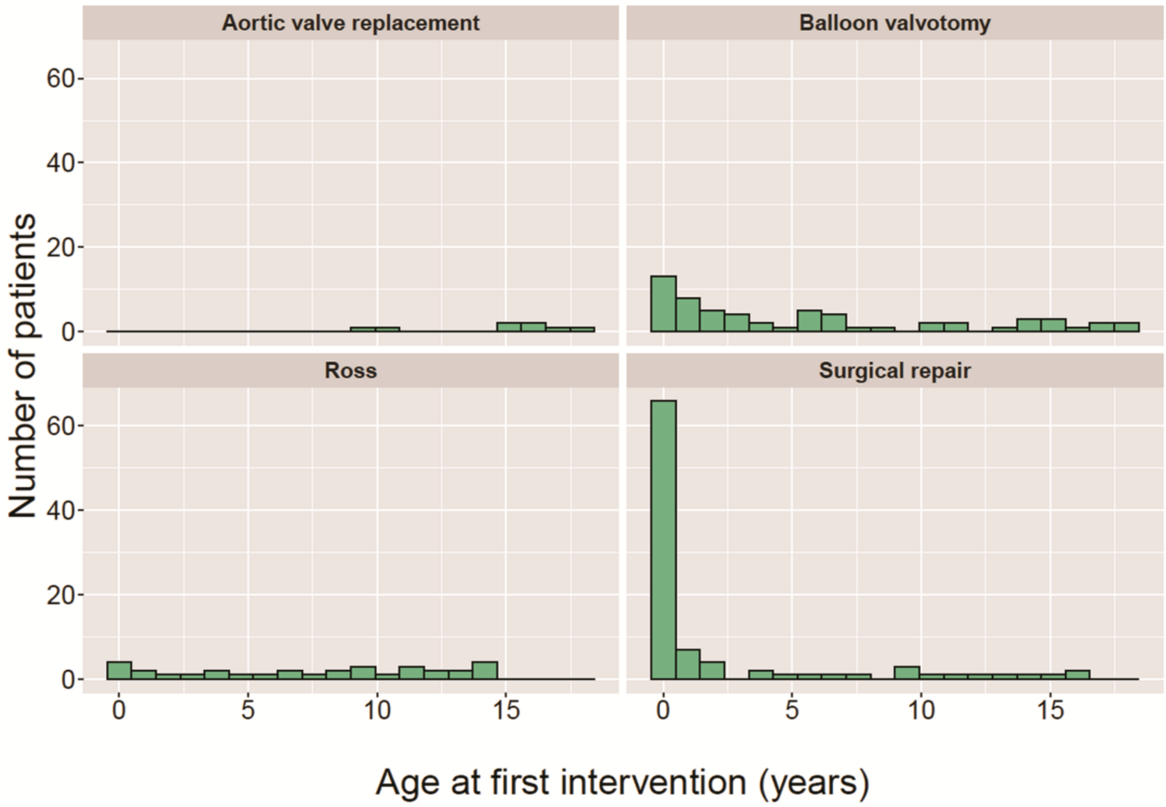

Aortic valve replacement
Balloon valvotomy
Ross
Surgical repair
Number of patients
0
20
40
60
0
5
10
15
Age at first intervention (years)

Figure 2

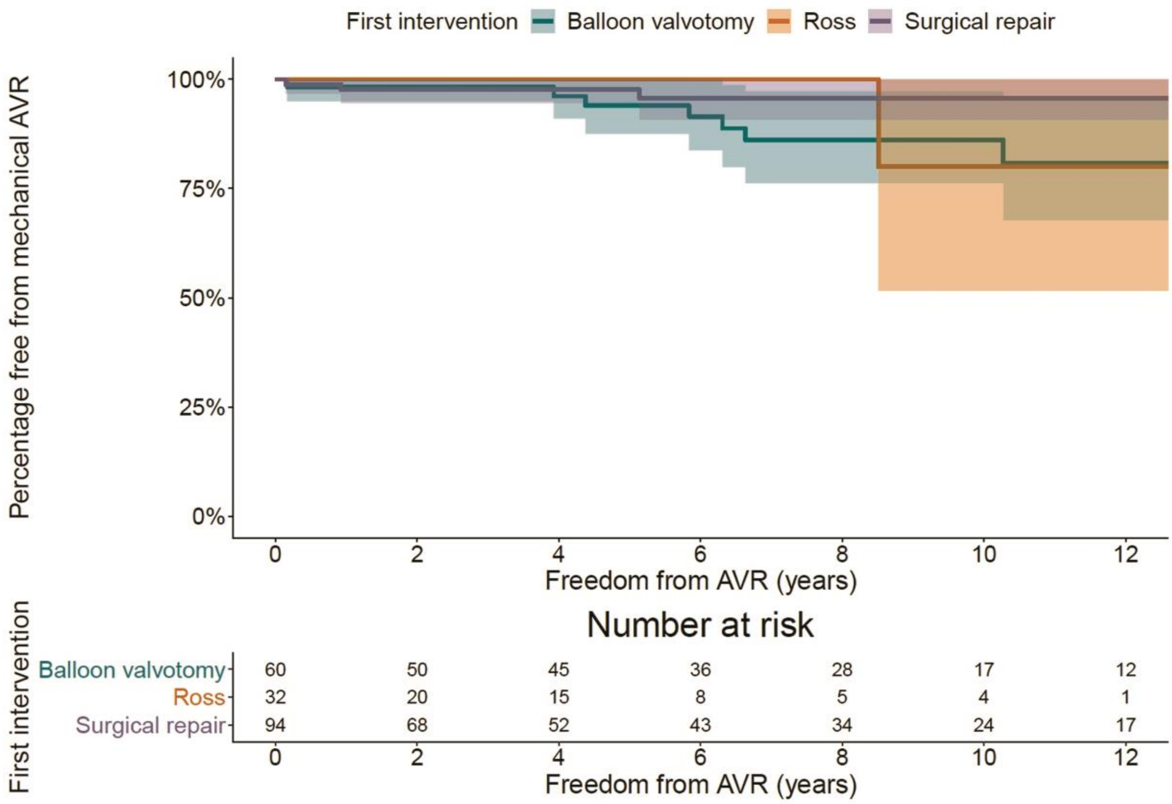

First intervention
Balloon valvotomy
Ross
Surgical repair
Percentage free from mechanical AVR
100%
75%
50%
25%
0%
0
2
4
6
8
10
12
Freedom from AVR (years)
Number at risk
First intervention
Balloon valvotomy 60 50 45 36 28 17 12
Ross 32 20 15 8 5 4 1
Surgical repair 94 68 52 43 34 24 17
0
2
4
6
8
10
12
Freedom from AVR (years)

Figure 3

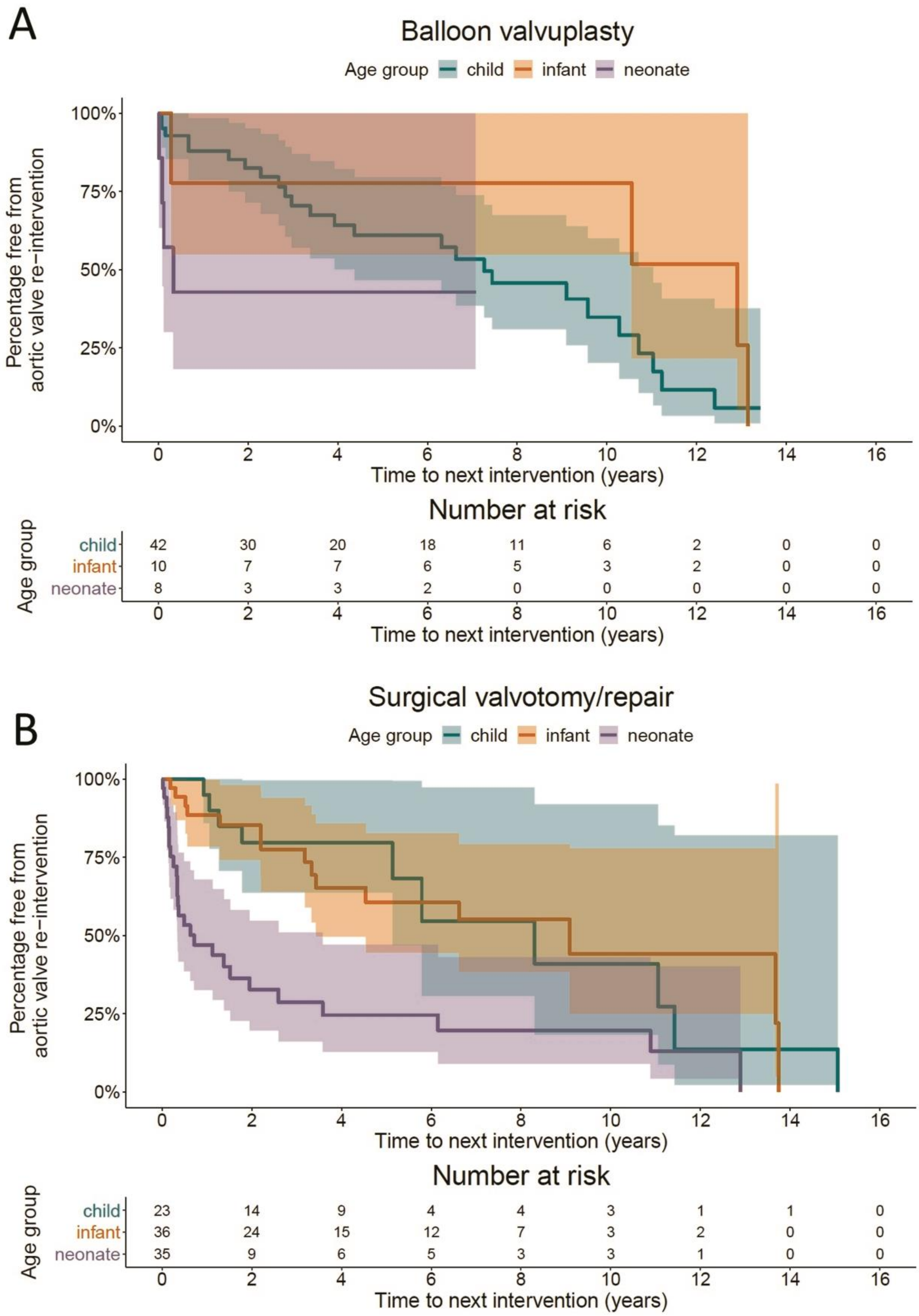
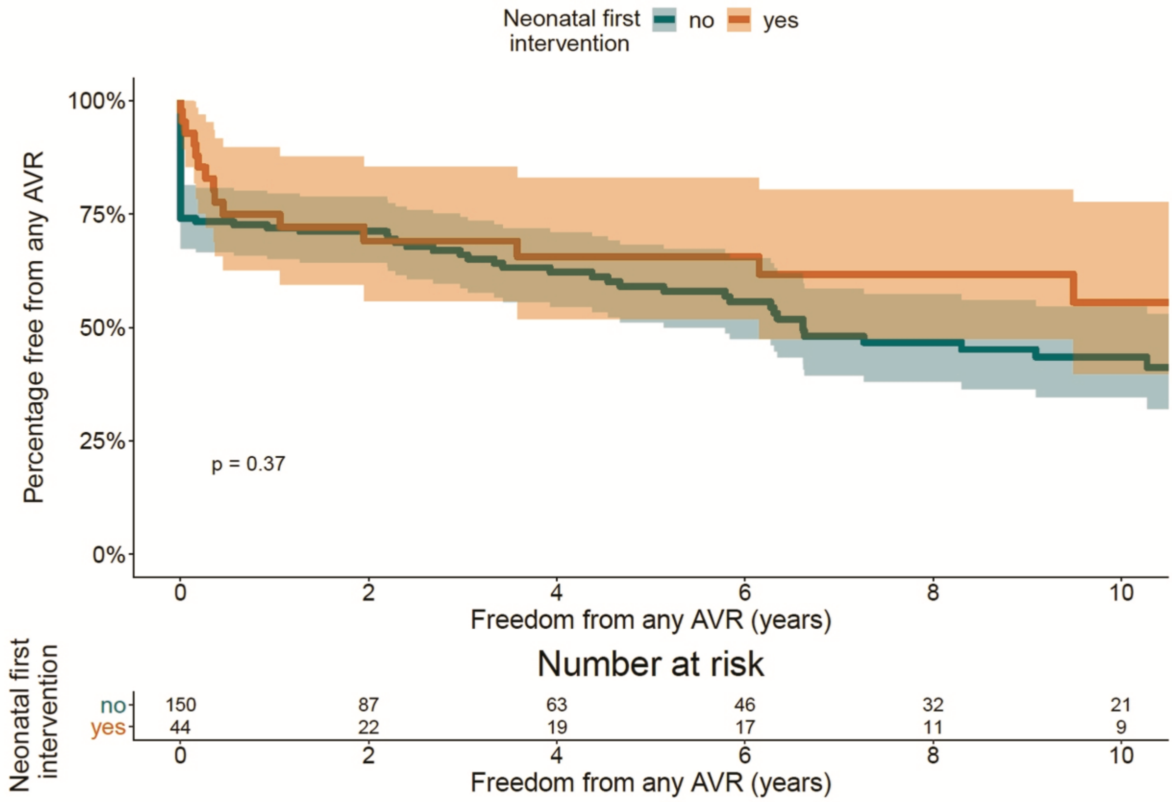

A
Balloon valvuplasty
Age group child infant neonate
100%
75%
50%
25%
0%
Percentage free from aortic valve re−intervention
0 2 4 6 8 10 12 14 16
Time to next intervention (years)
Number at risk
Age group
child 42 30 20 18 11 6 2 0 0
infant 10 7 7 6 5 3 2 0 0
neonate 8 3 3 2 0 0 0 0 0
0 2 4 6 8 10 12 14 16
Time to next intervention (years)
B
Surgical valvotomy/repair
Age group child infant neonate
100%
75%
50%
25%
0%
Percentage free from aortic valve re−intervention
0 2 4 6 8 10 12 14 16
Time to next intervention (years)
Number at risk
Age group
child 23 14 9 4 4 3 1 1 0
infant 36 24 15 12 7 3 2 0 0
neonate 35 9 6 5 3 3 1 0 0
0 2 4 6 8 10 12 14 16
Time to next intervention (years)

Figure 4



538

539 Figure 5

540

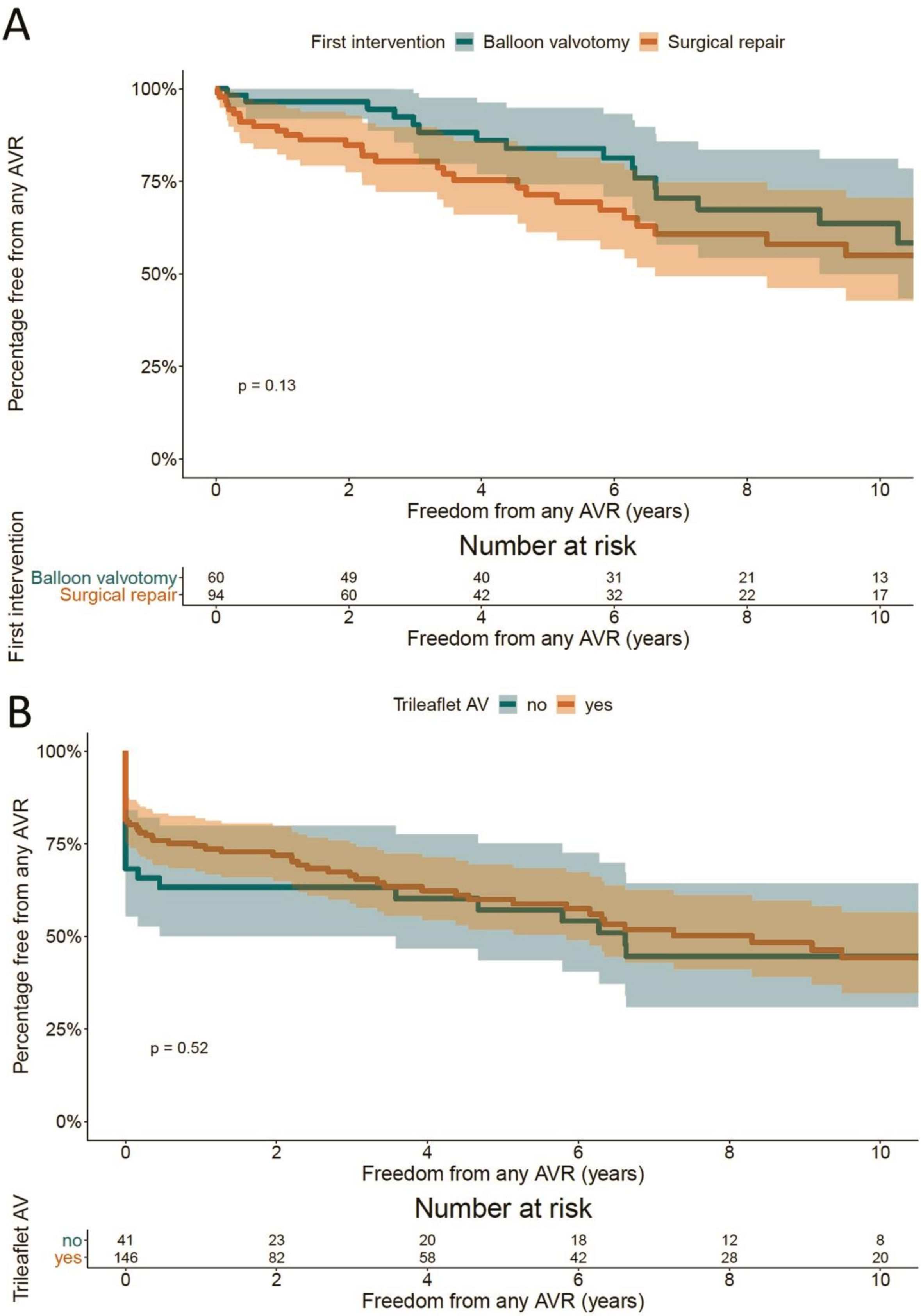

A
First intervention
Balloon valvotomy
Surgical repair
Percentage free from any AVR
100%
75%
50%
25%
0%
p = 0.13
0
2
4
6
8
10
Freedom from any AVR (years)
Number at risk
First intervention
Balloon valvotomy 60 49 40 31 21 13
Surgical repair 94 60 42 32 22 17
B
Trileaflet AV
no
yes
p = 0.52
Number at risk
Trileaflet AV
no 41 23 20 18 12 8
yes 146 82 58 42 28 20

Figure 6

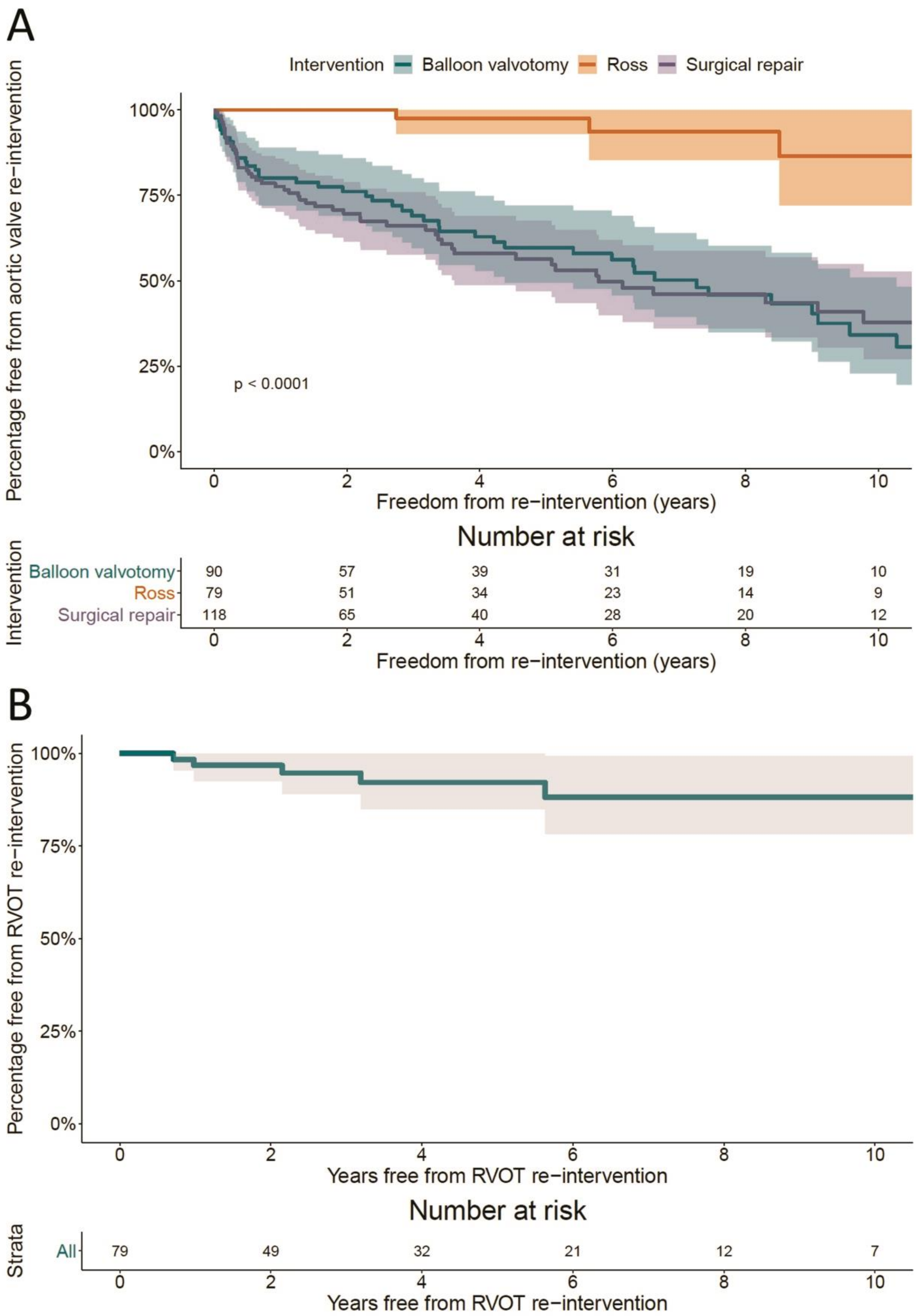
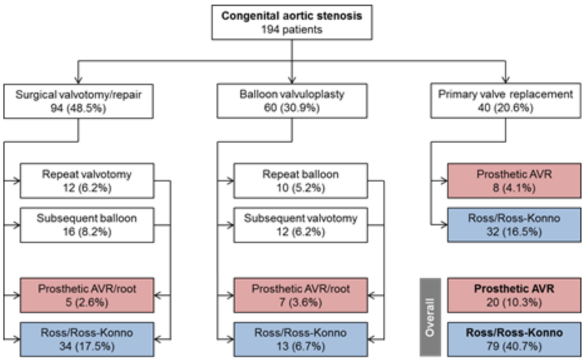
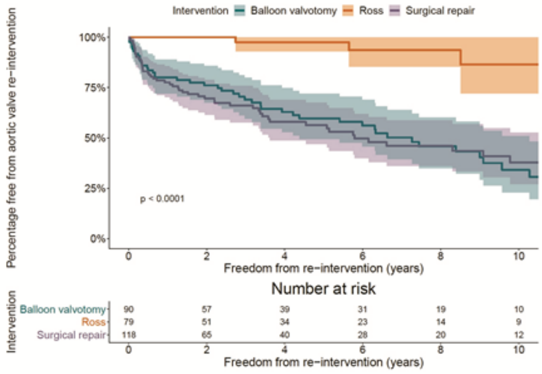

A
Intervention
Balloon valvotomy
Ross
Surgical repair
Percentage free from aortic valve re−intervention
100%
75%
50%
25%
0%
p < 0.0001
0
2
4
6
8
10
Freedom from re−intervention (years)
Number at risk
Intervention
Balloon valvotomy 90 57 39 31 19 10
Ross 79 51 34 23 14 9
Surgical repair 118 65 40 28 20 12
Freedom from re−intervention (years)
B
Percentage free from RVOT re−intervention
100%
75%
50%
25%
0%
0
2
4
6
8
10
Years free from RVOT re−intervention
Number at risk
Strata
All 79 49 32 21 12 7
Years free from RVOT re−intervention

Figure 7

Strategies to minimize need for Prosthetic Aortic Valve Replacement in Congenital Aortic Stenosis – value of the Ross Procedure

Retrospective analysis of 194 consecutive children who underwent any aortic valve intervention for a biventricular repair strategy at a single institution between 1995 and 2017.



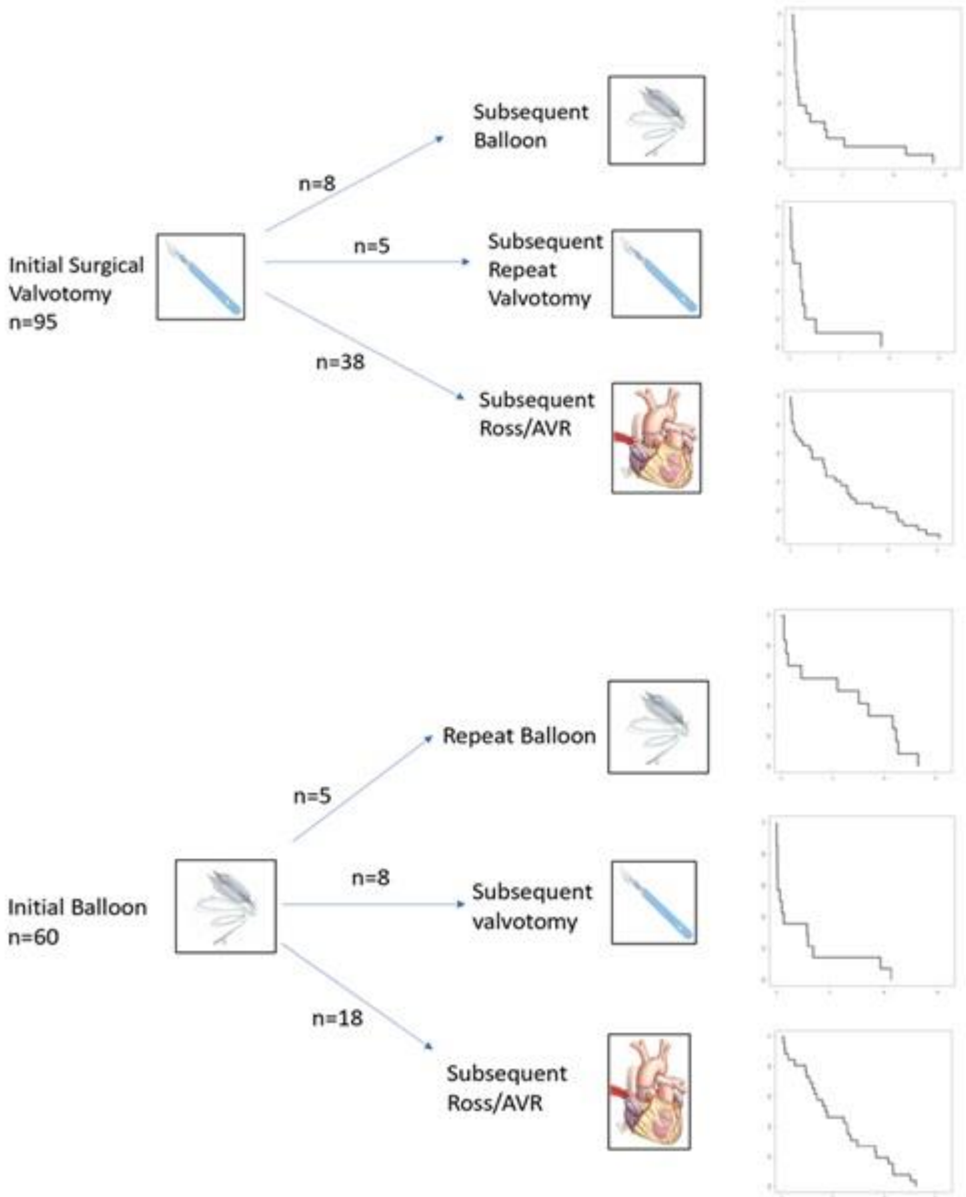


Prosthetic AVR/root replacement during childhood can be minimized by the use of the Ross procedure.

Reintervention is much greater after balloon valvuloplasty or surgical valvotomy/repair than after Ross procedure.

Our strategy of simple valve repair & primary Ross procedure provides excellent survival & good freedom from prosthetic AVR/root replacement. The Ross procedure offers the best freedom from reintervention of any technique and wider use of primary Ross in younger age groups should be considered.

Figure 8 graphical abstract



Supplementary figure