European Journal of Cardio-Thoracic Surgery 2024, 66(1), ezae267
https://doi.org/10.1093/ejcts/ezae267 Advance Access publication 11 July 2024

ORIGINAL ARTICLE

Cite this article as: Van Hoof L, Rooyackers B, Schuermans A, Duponselle J, Van De Bruaene A, De Meester P *et al.* Long-term outcome after the Ross procedure in 173 adults with up to 25 years of follow-up. Eur J Cardiothorac Surg 2024; doi:10.1093/ejcts/ezae267.

Long-term outcome after the Ross procedure in 173 adults with up to 25 years of follow-up

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Received 20 March 2024; received in revised form 9 June 2024

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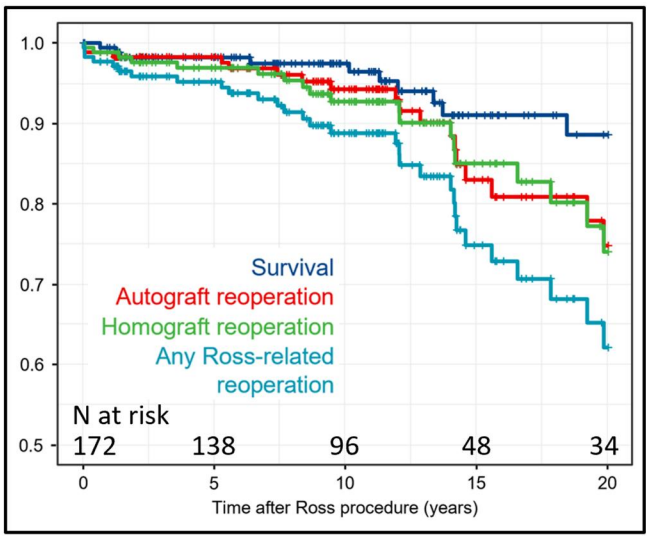
Summary

With up to 25 years of follow-up, this retrospective study shows that the Ross procedure offers young adults long-term survival similar to that of the matched population. Excellent reintervention-free survival can be achieved. The Ross procedure should be considered on an individual basis.



Legend: the figure shows Kaplan-Meier estimates of survival and reintervention after the Ross procedure.

Abstract

OBJECTIVES: The potential risk of autograft dilatation and homograft stenosis after the Ross procedure mandates lifelong follow-up. This retrospective cohort study aimed to determine long-term outcome of the Ross procedure, investigating autograft and homograft failure patterns leading to reintervention.

†The first two authors contributed equally to this study.

METHODS: All adults who underwent the Ross procedure between 1991 and 2018 at the University Hospitals Leuven were included, with follow-up data collected retrospectively. Autograft implantation was performed using the full root replacement technique. The primary end-point was long-term survival. Secondary end-points were survival free from any reintervention, autograft or homograft reintervention-free survival, and evolution of autograft diameter, homograft gradient and aortic regurgitation grade over time.

RESULTS: A total of 173 adult patients (66% male) with a median age of 32 years (range 18–58 years) were included. External support at both the annulus and sinotubular junction was used in 38.7% (67/173). Median follow-up duration was 11.1 years (IQR, 6.4–15.9; 2065 patient-years) with 95% follow-up completeness. There was one (0.6%) perioperative death. Kaplan–Meier estimate for 15-year survival was 91.1% and Ross-related reintervention-free survival was 75.7% (autograft: 83.5%, homograft: 85%). Regression analyses demonstrated progressive neoaortic root dilatation (0.56 mm/year) and increase in homograft gradient (0.72 mmHg/year).

CONCLUSIONS: The Ross procedure has the potential to offer excellent long-term survival and reintervention-free survival. These long-term data further confirm that the Ross procedure is a suitable option in young adults with aortic valve disease which should be considered on an individual basis.

Keywords: Ross procedure • Reintervention • Pulmonary autograft • Pulmonary homograft

ABBREVIATIONS

AR	Aortic regurgitation
AS	Aortic stenosis
AV	Aortic valve
CI	Confidence interval
HR	Hazard ratio
TTE	Transthoracic echocardiography

INTRODUCTION

The pulmonary autograft procedure—commonly known as the Ross procedure—was introduced in the 1960s and remains the only type of aortic valve (AV) replacement known to restore survival to that of the age- and sex-matched general population [1–6]. As it provides a living valve substitute, the Ross procedure offers excellent haemodynamic outcome, low thrombogenicity and low risk of endocarditis [7]. The operation itself presents a technical challenge and should be performed in centres with sufficient expertise [5, 8]. After the freestanding root technique, follow-up is warranted regarding the risk of progressive autograft dilatation, which may lead to neoaortic regurgitation and require reoperation. Both autologous aortic inclusion and external support using vascular graft material can be used to prevent dilatation and subsequent reintervention [5, 9–12]. Pulmonary homograft dysfunction—including pulmonary homograft regurgitation or stenosis—is another potential consequence of the Ross procedure [2]. Continued data collection is needed from as many high-volume centres as possible to gain insight into the outcomes associated with the Ross procedure, including mortality, autograft and pulmonary homograft failure and reintervention. While clinical series often represent the experience of renowned centres, reproducibility of their outcomes remains uncertain [3, 6, 13, 14]. In addition, the evidence regarding long-term follow-up after the Ross procedure in Belgium is limited [15, 16]. The current study presents the long-term outcomes of patients who underwent the Ross procedure at the University Hospitals of Leuven, Belgium.

METHODS

Study design and ethical statement

A longitudinal single-centre single-arm cohort study was carried out. All adults (≥18 years) who underwent the Ross procedure from July 1991 to November 2018 at the University Hospitals Leuven were included. Clinical follow-up data until March 2020 were retrospectively collected. The Ethics Committee Research UZ/KU Leuven approved the current study (S63569) and due to the retrospective design, the need for patient consent was waived.

Data collection

Perioperative and follow-up data were collected from electronic medical records. The last documented clinical visit was consulted to determine survival. If no recent visit (2019—March 2020) was available, the national health register was consulted. During follow-up, imaging was performed at the discretion of the monitoring cardiologist, including transthoracic echocardiography (TTE), computed tomography (CT), and magnetic resonance imaging (MRI). TTE reports were screened to define neoaortic root diameter at sinus level, aortic regurgitation (AR) grade and peak pulmonary homograft gradient in the first two months postoperatively. TTE, CT or MRI—whichever was performed last during follow-up—was used to define the last neoaortic root diameter before a potential reintervention. To define AR grade and peak homograft gradient during last follow-up before a potential reintervention, the last available TTE report was consulted.

Endpoints

The primary end-point was long-term survival. Secondary endpoints included operative mortality and in-hospital complications, autograft reintervention-free survival, survival free from surgical or percutaneous homograft reintervention and any Ross-related reintervention-free survival (on autograft and/or homograft, combined or separate). Furthermore, evolution of autograft diameter, homograft gradient, occurrence of pulmonary homograft failure and aortic regurgitation grade over time was evaluated.

Definitions

Patients were categorised based on haemodynamic lesion type: aortic stenosis (AS), aortic regurgitation (AR), or mixed AV disease (AS and AR). Patients with severe preoperative AR (≥grade 3/4) and a peak trans-AV gradient ≤40 mmHg (mild AS) were included in the AR group. Patients with moderate-severe AS (peak gradient >40 mmHg) and up to moderate AR (≤grade 2/4) were included in the AS group. Severe AR in combination with moderate or greater AS was defined as mixed AV disease [17].

Statistical analysis

Continuous variables were reported as median [interquartile range, IQR], while categorical variables were reported as *n* (%). Completeness of follow-up was defined as the follow-up index for the entire study population, calculated by dividing the documented postoperative years by the optimal follow-up, as previously reported [18]. Risk factors for mortality and reintervention were expressed by hazard ratios (HRs) with 95% confidence interval (CI) and *P*-values and obtained by univariate Cox regression analyses. To account for potential confounding, a multivariate Cox regression model was constructed using all significant predictors identified by univariate Cox regression analysis. Kaplan–Meier curves were used to obtain survival percentage estimates and visually summarize time-to-event data. In addition, mortality rates were compared between the study population and the general population. To this end, a Kaplan–Meier estimate was constructed for the general population matched for sex, age, calendar year, and country of birth, based on publicly available life tables published by the Human Mortality Database [19]. All time-to-event data were truncated at 20 years of follow-up.

A Kaplan–Meier estimate was constructed for survival free from at least moderate AR (grade ≥2/4) during follow-up. Neoaortic root diameter and peak pulmonary homograft gradient were plotted against their respective postoperative time-point, with drop-out due to loss of follow-up, death, or reoperation. Linear regression was performed to assess the global changes in these parameters over time, and unstandardized coefficients (*B*) with 95% CIs and *P*-values were reported. Analyses were exploratory in nature, 95% confidence intervals were not adjusted for multiple comparisons and inferences drawn from them may not be reproducible. *P*-values ≤ 0.05 were considered statistically significant throughout the study, and all tests were two-sided. Analyses were executed using Microsoft Excel (Microsoft) or R (R Foundation for Statistical Computing).

RESULTS

Study population and patient characteristics

From July 1991 to November 2018, 173 patients (65.9% male; median age 32 years, IQR 25–41 years, range 18–58 years) underwent the Ross procedure via the freestanding root technique. Five surgeons carried out a median of 26 operations, ranging from 14–57. Most operations (67.1%) were performed in the second half of the study period (2005–2018) (Supplementary Material, Fig. S1). Patients were followed for a median of 11.1 [IQR: 6.4–15.9] years. In total, 2065 postoperative patient-years were documented, while optimal clinical follow-up for the 172 patients (excluding 1 early death) corresponded with 2168 postoperative patient-years. Therefore, follow-up completeness amounted to 95%. Twelve patients (6.9%) had follow-up beyond 25 years and 33 (19.1%) had a follow-up beyond 20 years.

Patients predominantly had a bicuspid aortic valve (105, 60.7%), 38.7% had an isolated AR, 18.5% of patients previously underwent AV surgery, and 16.2% received a percutaneous balloon dilatation during childhood. A complete overview of baseline patient characteristics and echocardiographic parameters is listed in Table 1. In our study, external support (83/173, 48%) using a ring of Dacron graft was employed systematically since 2009, with 80.7% (67/83) of patients receiving support at both the aortic annulus and sinotubular junction, with a technique similar to that later proposed by El-Hamamsy [5]. The choice of external support was independent of haemodynamic lesion, such that approximately half of all patients with either AS, AR or mixed AV disease received support. For patients in whom external support was not used, median follow-up was 13.6 years, while for patients with external support, median follow-up was 6.4 years. Operative details are listed in Table 2. A descriptive overview of baseline patient characteristics, echocardiographic parameters and operative details can be found in Supplementary Material, Results section.

Early mortality and in-hospital outcomes

One patient (0.6% early mortality), a 25-year-old male with a prior mechanical valve and patient-prosthesis mismatch, died 3 days after the Ross procedure due to LV failure. A complete overview of early outcomes is shown in Table 3. The mean neoaortic root diameter at sinus level on first postoperative echocardiography, at most 2 months postoperatively, was 33 (IQR: 30–35.5) mm. Four patients (2.3%) demonstrated early neoaortic root dilatation >40mm. Six patients (3.5%) had moderate AR on their first postoperative echocardiography. The median peak pulmonary homograft gradient was 8 (IQR: 4–14) mmHg, with 5 patients (2.9%) showing a pulmonary homograft gradient ≥25mmHg. Two patients (1.2%) demonstrated pulmonary homograft regurgitation ≥grade 2.

Survival

Among 172 patients, excluding 1 early death, 10 patients (5.8%) died during follow-up. Causes of death were sepsis ($n = 2$), prosthetic aortic valve endocarditis complicated by intracranial bleeding in a patient who received a mechanical valve 7 years after the Ross procedure ($n = 1$), multiple organ failure not otherwise specified ($n = 1$), malignancy ($n = 3$), and unknown cause ($n = 3$). The Kaplan–Meier estimate for survival is shown in Fig. 1A. Estimates for 10-, 15- and 20-year survival were 97.4, 91 and 88.5%, respectively. Kaplan–Meier analysis of long-term

Table 1: Baseline patient characteristics and echocardiographic data

Variable	All patients ($n = 173$)
Demographics and clinical characteristics	
Age (y)	32 [25–41]
Male	114 (65.9)
NYHA functional class	
I–II	142 (82.1)
III–IV	31 (17.9)
Preoperative comorbidities	
Pulmonary hypertension	18 (10.4)
Transient ischaemic attack or stroke	4 (2.3)
Renal failure	2 (1.2)
Myocardial infarction	2 (1.2)
Previous interventions	
Patients with previous AV procedure(s)	55 (31.8)
Patients with percutaneous balloon dilatation(s)	28 (16.2)
Patients with previous AV surgery	32 (18.5)
Valvotomy/-plasty	28 (16.2)
Mechanical valve replacement	4 (2.3)
Aortic homograft	3 (1.7)
Coarctation repair	5 (2.9)
AV haemodynamics	
Aortic regurgitation	67 (38.7)
Aortic stenosis	59 (34.1)
Mixed—primary	21 (12.1)
Mixed—iatrogenic[a]	26 (15.1)
AV morphology at time of Ross	
Bicuspid	105 (60.7)
Tricuspid	43 (24.9)
Dysplastic/unicuspid	12 (7.0)
Prosthetic valve	7 (4.0)
Unknown	6 (3.5)
Acute infective aortic valve endocarditis	8 (4.6)
Dilated LV: LVEDD (>59 mm/>53 mm)[b]	49 (28.3)
LVEF	
Normal (≥55%)	125 (72.3)
Reduced (<55%)	24 (13.9)
Unknown	24 (13.9)

Continuous and categorical variables presented as median [IQR] and *n* (%), respectively.

[a]Occurring in patients with primary aortic stenosis who underwent a balloon valvuloplasty.

[b]LVEDD > 59 mm and > 53 mm in male and female patients, respectively.

AV: aortic valve; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction.

survival in Ross patients vs the sex- and age-matched population suggested that survival in the Ross group at 10 and 20 years postoperatively was slightly lower than that of the age- and sex-matched population (97.4 vs 97.9% and 88.5 vs 93.3%, respectively, Log-rank $P = 0.047$). Univariate Cox regression identified higher age at the Ross procedure (HR: 1.06; 95% CI: 1.01–1.13; $P = 0.032$), a native tricuspid AV (HR: 14.26; 95% CI: 1.71–118.67; $P = 0.013$), non-congenital AV disease (HR: 5.12; 95% CI: 1.27–20.59; $P = 0.027$), and a smaller pulmonary homograft size (HR: 0.68; 95% CI: 0.47–0.99; $P = 0.042$) as the only baseline, procedural or early postoperative risk factors for long-term mortality (Supplementary Material, Table S1). In a multivariable Cox regression model which incorporated all the significant univariate predictors, only the presence of a native tricuspid AV remained significantly associated with long-term mortality (HR: 10.27; 95% CI: 1.68–244.14; $P = 0.031$; Fig. 1B; Supplementary Material, Table S2).

Table 2: Operative characteristics

Variable	All patients ($n = 173$)
Aortic dimensions	
Aortic annulus diameter (mm)	23.3 [21–26]
Aortic root diameter (mm)	32 [29–36]
Sino-tubular junction diameter (mm)	29 [26–32]
Preoperative aortic dilatation	80 (46.2)
Ascending aorta	55 (31.8)
Root	13 (7.5)
Both	12 (6.9)
Freestanding root replacement	173 (100)
External autograft support	83 (48.0)
Annulus	13 (7.5)
Sino-tubular junction	3 (1.7)
Both	67 (38.7)
Patients undergoing concomitant procedures	55 (31.8)
Ascending aorta replacement	48 (27.7)
Mitral valve repair	3 (1.7)
Coronary artery bypass grafting	2 (1.2)
Preoperatively planned	1 (0.6)
Due to right ventricular ischaemia	1 (0.6)
Ventricular septal defect repair	1 (0.6)
Cardiopulmonary bypass time (min)	138 [127–157]
Cross-clamp time (min)	115 [105–125]
Pulmonary homograft size (mm)	23 [25–26]

Continuous and categorical variables presented as median [IQR] and *n* (%), respectively.

Table 3: Early postoperative outcomes

Variable	All patients ($n = 173$)
In-hospital adverse events	
In-hospital death	1 (0.6)
Severe, non-fatal postoperative complications	
Pacemaker implantation	9 (5.2)
Myocardial infarction	5 (2.9)
Transient ischaemic attack or stroke	3 (1.7)
Endocarditis	3 (1.7)
Deep sternal wound infection	2 (1.2)
Hospitalisation time (days)	9 [8–11]
Early echocardiographic follow-up (*<2 months*)	
Autograft regurgitation	
Grade 0	36 (20.8)
Grade 1	97 (56.1)
Grade 2	6 (3.5)
Grade 3–4	0 (0.0)
Unknown	34 (19.7)
Neo-aortic root diameter (mm)	33 [30–36]
Normal (≤40 mm)	116 (67.1)
Dilated (>40 mm)	4 (2.3)
Unknown	53 (30.6)
Mean pulmonary homograft gradient (mmHg)	8 [4–14]
≤25 mmHg	127 (73.4)
>25 mmHg	3 (1.7)
Unknown	43 (24.9)

Continuous and categorical variables presented as median [IQR] and *n* (%), respectively.

Reintervention

Thirty-seven patients (21.5%) needed a reintervention after a median of 12.8 [IQR: 6.7–19.2] years. Twenty-five patients (14.5%) had an autograft reoperation, 24 (14.0%) underwent a

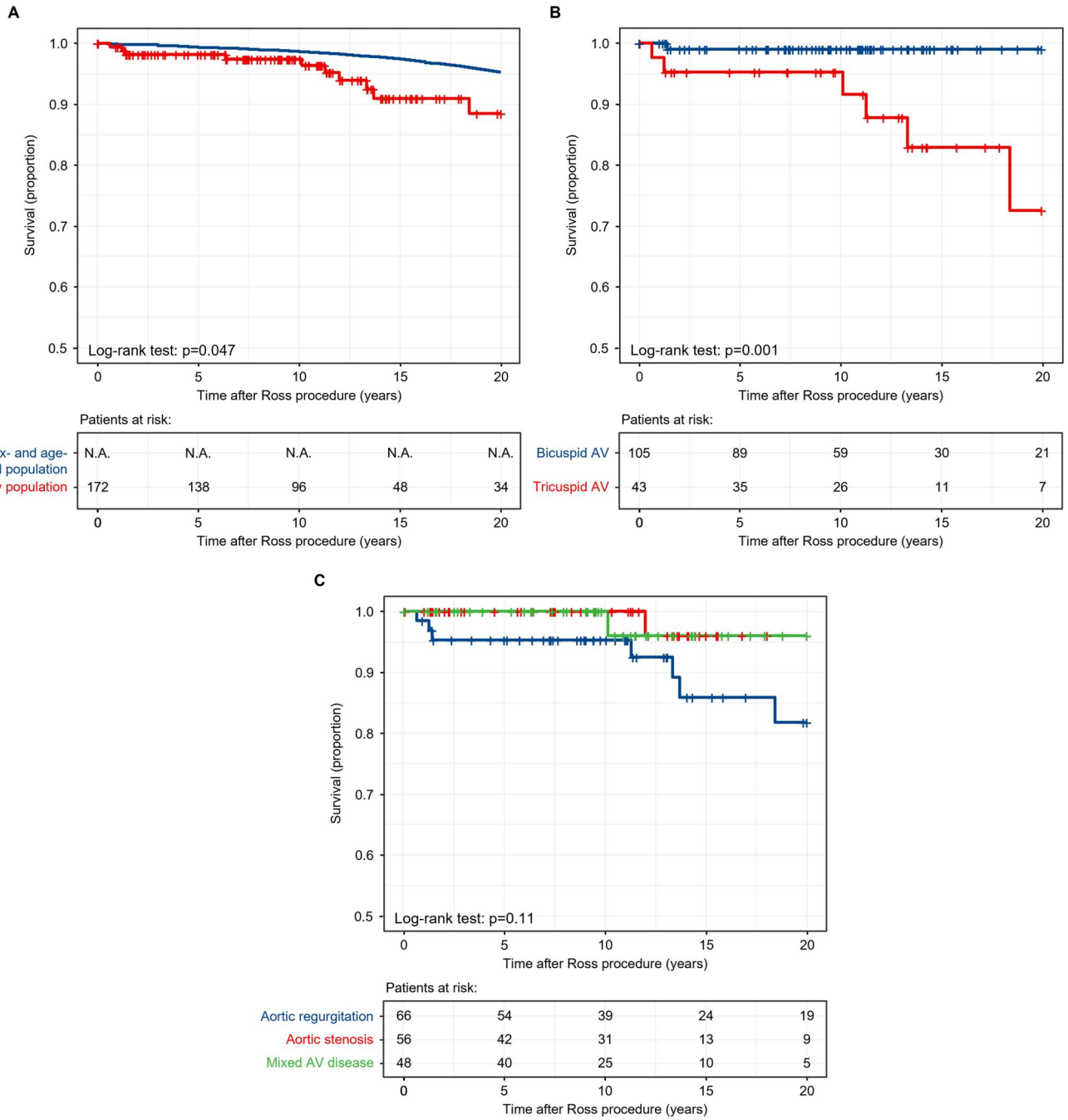


Figure 1: (**A**) Kaplan–Meier estimate of survival in the study population vs the age- and sex-matched general population. (**B**) Survival according to native AV morphology. (**C**) Survival based on preoperative AV haemodynamic lesion. Time-to-event data were compared between groups using the log-rank test.

homograft reintervention (surgical: 15 [8.7%]; transcatheter: 9 [5.2%]), and 12 (7.0%) had a reintervention on both the autograft and the homograft. The main indication for autograft reoperation was root dilatation with AR (16/25, 64%, with mean root diameter 53 ± 7mm at 15 ± 5 years), followed by AR without root dilatation (4/25, 16%, with mean root diameter 36 ± 5mm at 22 ± 2 years). In accordance, the most common modality of autograft reintervention was mechanical valved root replacement in fifteen patients, five patients underwent mechanical valve replacement, three patients received a biological valve replacement and 2 patients underwent valve-sparing root replacement. The most common indication for homograft reintervention was progressive stenosis (15/24, 62.5%) with an average peak gradient of 63 ± 14 mmHg at 12 ± 8 years. Five patients underwent surgical homograft replacement during a reoperation with as main indication autograft failure. There were three reoperations for homograft endocarditis and one percutaneous valve replacement for severe homograft regurgitation.

Kaplan–Meier estimates for autograft, homograft and any Ross-related reintervention-free survival are shown in Fig. 2A. Autograft reintervention-free survival was 94.2, 82.9 and 74.7% at 10, 15 and 20 years, respectively, while homograft reintervention-free survival was 92.7, 84.9 and 73.9% at 10, 15 and 20 years. Estimates for any Ross-related reintervention-free survival at 10, 15 and 20 years were 88.7, 74.7 and 61.9%, respectively.

Early postoperative pulmonary homograft gradient was the only parameter significantly associated with homograft reintervention (HR: 1.05; 95% CI: 1.02–1.08; $P = 0.004$). Univariate Cox regression identified early postoperative grade 2/4 autograft regurgitation as the only significant predictor of autograft reintervention (HR: 3.6; 95% CI: 1.0–12.9; $P = 0.04$; Supplementary Material, Table S2). The use of external support (HR: 1.18; 95% CI: 0.5–2.9; $P = 0.72$) was not associated with lower need for autograft reintervention.

Autograft and pulmonary homograft function. An overview of echocardiographic data at last follow-up (median 9.9, IQR 5.7–15.3 years) is shown in Table 4. Survival free from AR grade ≥2/4 was 95.1, 88.7, 74.7 and 61.9% at 5, 10, 15 and 20 years, respectively. There was no significant difference based on preoperative AV type or haemodynamic lesion (Fig. 3).

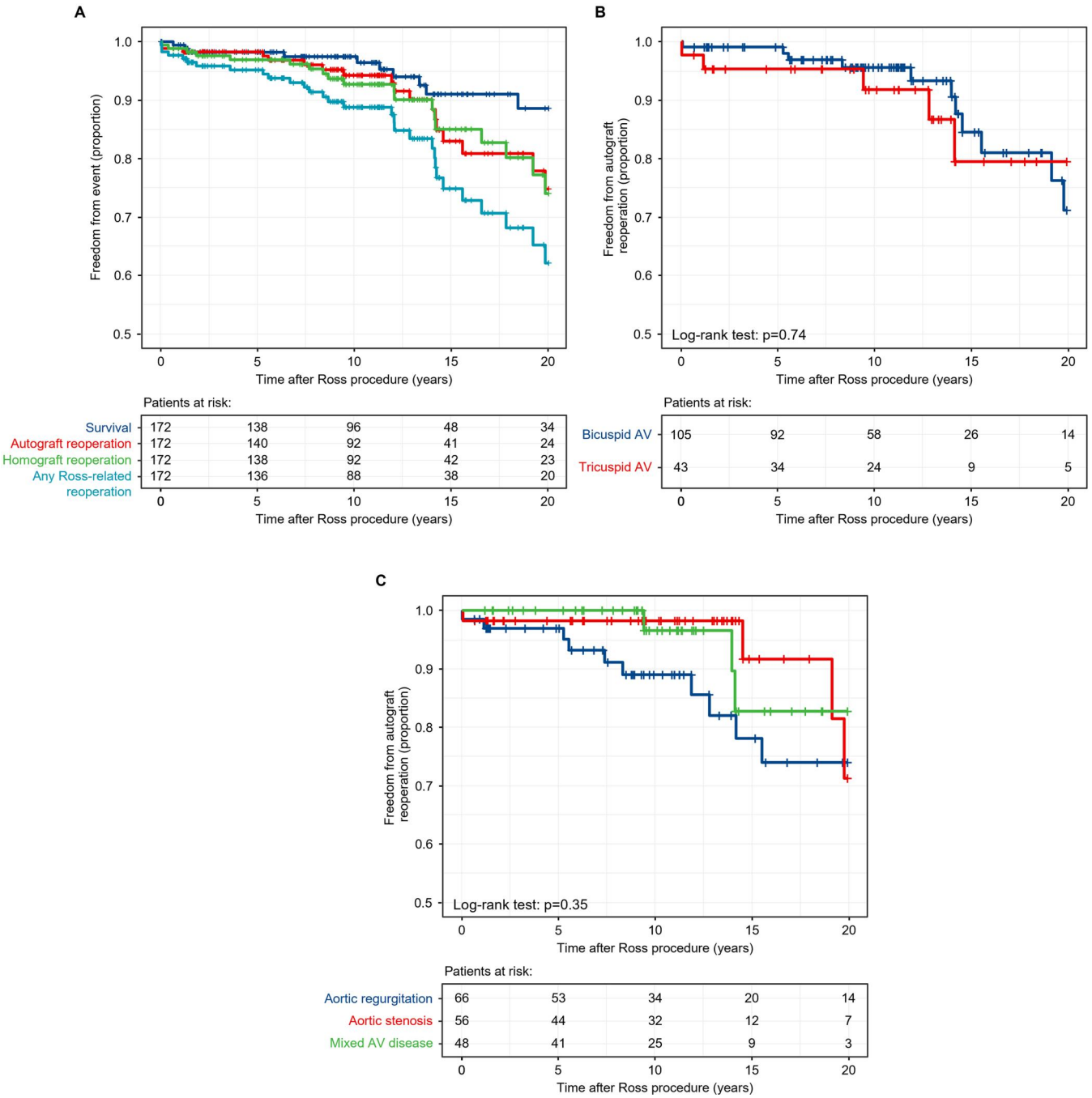


Figure 2: (**A**) Reintervention-free survival. (**B**) Autograft reintervention-free survival according to native AV morphology. (**C**) Autograft reintervention-free survival by preoperative AV haemodynamic lesion. Time-to-event data were compared between groups using the log-rank test. AV: aortic valve.

Mean neoaortic root diameter increased significantly over time; for each additional year of follow-up, the root diameter increased on average by 0.56 mm ($B = 0.56$ mm/year; 95% CI: 0.46–0.67; $P < 0.001$). The growth rate was 1.35, 1.04, 0.31 and 1.67 mm/year for <5, 5–<10, 10–<15 and 15–<20 postoperative years, respectively. In this linear regression model of root diameter over time, there was no nominally significant interaction between presence of external support and follow-up time ($P = 0.45$), suggesting no difference in root diameter evolution in the presence of support. Linear regression demonstrated that peak pulmonary homograft gradient significantly increased over time ($B = 0.72$ mmHg per year of follow-up; 95% CI: 0.55–0.88; $P < 0.001$). This gradient increased by 2.93 mm/year, 0.12 mmHg/year and 1.91 mmHg/year for 0–<5, 5–<10 and 10–<20 postoperative years, respectively.

Table 4: Outcomes at last echocardiographic follow-up (median 9.9, IQR 5.7–15.3 years)

Variable	All patients with late follow-up ($n = 172$)
Autograft regurgitation	
Grade 0	57 (32.9)
Grade 1	56 (32.4)
Grade 2	19 (11.0)
Grade 3	3 (1.7)
Grade 4	1 (0.6)
Underwent reoperation	25 (14.5)
Unknown	11 (6.3)
Neo-aortic root diameter (mm)	39 [35–44]
≤40mm	60 (34.8)
>40mm	46 (26.7)
Underwent reoperation	25 (14.5)
Unknown	41 (23.8)
Mean pulmonary homograft gradient (mmHg)	16 [10–24]
≤25 mmHg	105 (61)
>25 mmHg	28 (16.3)
Underwent reintervention	24 (13.9)
Unknown	15 (8.7)

Continuous and categorical variables presented as median [IQR] and *n* (%), respectively.

DISCUSSION

In this longitudinal study with over 25 years of follow-up in adults, we confirm the excellent survival as well as the established concerns regarding autograft and homograft dysfunction over time. In addition, we demonstrate reintervention-free survival rates in line with national and international series of the Ross procedure [2, 15, 20, 21]. Overall demographics in our study were typical of patients undergoing the Ross procedure in other series [2–4, 8, 15, 20]. Approximately 11.2% of all adult Ross patients had a previous history of AV surgery in a recent meta-analysis by Etnel *et al.*, as opposed to 18.5% in our study [22]. The prevalence of endocarditis was lower in our study (4.6 vs 19.4%) than in the meta-analysis by Etnel *et al.*

Early and late mortality

In our cohort of 173 Ross patients, 11 deaths (6.4%) were noted during the follow-up period, including 1 early and 10 late deaths. The early mortality of 0.6% was in line with that observed in other experienced, high-volume centres of 0.3–1.1% [2, 3, 8]. Several short- and midterm studies have shown that the Ross procedure can offer excellent long-term survival equivalent to that of the general population [2, 4, 15]. We equally found that the chance of being alive 20 years after the Ross procedure was slightly lower than that of the general population, with excellent long-term survival rates of 97.5 and 88.7% at 10 and 20 years postoperatively, respectively. Similarly, other Belgian Ross studies demonstrated 10-year survival estimates of approximately 95% [15, 16]. Likewise, Martin *et al.* recently performed a similar investigation of 310

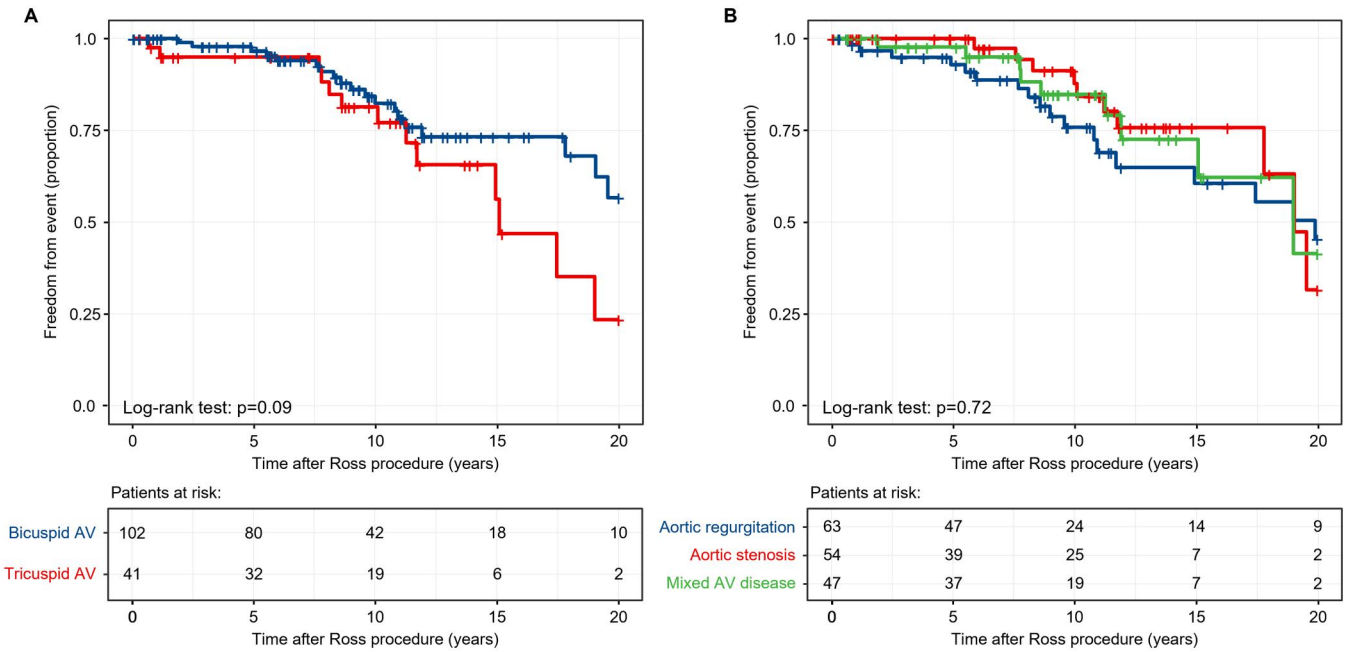


Figure 3: (**A**) Survival free from AR grade ≥ 2/4 for patients with preoperative bicuspid aortic valve (BAV) versus tricuspid aortic valve (TAV). (**B**) Survival free from AR grade ≥ 2/4 stratified by preoperative haemodynamic lesion.

patients, showing survival rates of 94.1 and 83.6% after 10 and 20 years [20]. In contrast, for young patients receiving a bioprosthetic or mechanical AVR, life expectancy may be significantly reduced due to the cumulative risk of thrombo-embolism, endocarditis, bleeding and reintervention [3, 23–25]. With optimal self-management of anti-coagulation and newest generation bileaflet valves, however, there may be no late survival difference after mechanical valve replacement compared to the Ross procedure [26]. In this study, only the presence of a native tricuspid AV was a risk factor for long-term mortality in a multivariable Cox regression model. We suspect that this is a coincidental finding as there were only 10 late deaths with limited cardiovascular mortality, and that our study is likely underpowered to reliably identify and discriminate between risk factors for survival and reintervention.

Reintervention-free survival

We found 94.8 and 75.6% autograft reintervention-free survival at 10 and 20 years, respectively, while homograft reintervention-free survival was 92.7 and 73.9% at 10 and 20 years. Our autograft reintervention-free survival is nearly identical to that in recent meta-analyses reporting 84–85% freedom from autograft reintervention at 15 years, as compared to 83.5% in our study [21, 22]. Homograft reintervention-free survival at 15 years in our study was slightly lower than in recent meta-analyses (85 vs 91–93.5%) [21, 22]. Importantly, the largest study included in these meta-analyses only reports on surgical homograft reoperation [2]. Furthermore, comparison is challenging as studies including decellularized homografts and bioprosthetic conduits implanted into the right ventricular outflow tract were involved, with decellularized allografts recently showing promising results, and the latter having a significantly greater reintervention rate [21, 27]. As previously established, early postoperative homograft gradient was a major predictor of homograft longevity [28, 29].

We observed a gradual increase in neoaortic sinus diameter and pulmonary homograft gradient over time without evident break-point after which failure rates begin to increase, similar to previous reports [2, 28–32]. In our study, survival free from neoaortic AR $\geq$2/4 was 88.7% at 10 years and 61.9% at 20 years, similar to a large single-surgeon experience by David *et al.* with 90.3 and 62.6% freedom from neoaortic AR $\geq$2/4 at 10 and 20 years, respectively [33].

As commonly reported, neoaortic root dilatation with autograft regurgitation was the most common cause of autograft failure and reintervention [21, 22, 34]. There are three main surgical approaches to prevent dilatation and subsequent reintervention after the freestanding Ross. Inclusion of the autograft within the patient's native aortic wall may produce excellent outcomes, yet this technique is not applicable in case of size mismatch [11]. Wrapping the autograft within a vascular tube graft has shown to prevent long-term dilatation and may reduce the risk of reintervention [10, 12]. Personalized support using a macroporous mesh is a recent and promising technique aiming avoid the potential risks of wall atrophy, loss of compliance and seroma formation associated with vascular tube grafts [35]. Most commonly performed nowadays, support at the aortic annulus and sinotubular junction is proposed by El-Hamamsy in patients at risk for dilatation [12, 36]. Similarly, in our study, external support at both the aortic annulus and sinotubular junction was systematically performed since 2009 (38.7%, 67/173).

We did not observe a significant difference in neoaortic sinus dilatation or reintervention free survival with use of external support. Here we must note a crucial historical bias with patients receiving external support having shorter follow-up (median follow-up 13.6 years vs 6.4 years) so that it may be too soon to observe differences. Accordingly, in the German-Dutch Ross registry, most reinterventions for dilatation were after 12 years postoperatively [34]. Furthermore, the aim of support at the annulus and sinotubular junction is primarily to preserve valve geometry while preserving sinus geometry and compliance. We believe that the progressive dilatation observed in this study further supports the importance of external support and, perhaps even more important, minimizing the amount of wall tissue exposed to aortic pressures, by trimming and by sub-annular implantation [32]. In most recent years, our group has put more emphasis on this last aspect while also suturing the remnant aortic commissures to the distal anastomosis to provide longitudinal support.

Limitations

While our study presents long-term data with near-complete follow-up and a comprehensive evaluation of survival, reintervention, as well as autograft and homograft function, several limitations must be considered. First, all operations were performed in one single centre by five different surgeons. While this may reduce the generalizability of the results presented in the current study, our baseline characteristics, perioperative parameters, and outcome rates were similar to those of many recent studies. Second, the echocardiographic data during follow-up were obtained without standardised protocol and provided by various referring cardiologists, likely increasing the heterogeneity and decreasing the signal-to-noise ratio of the imaging parameters assessed in this study. Third, we were confronted with missing data due to gaps in medical reports, which limited the statistical power of the analyses. Therefore, we focused on survival and reintervention-free survival. Due to sample size and limited event rate, we consider our study underpowered to deliver robust regression analyses for survival and reintervention. Finally, it should be noted that our findings apply to the freestanding Ross procedure, as no other variations on the Ross procedure were included.

CONCLUSIONS

This study with up to 25 years of follow-up shows that the Ross procedure offers long-term survival similar to that of the sex- and age-matched general population. Continued surveillance of autograft and homograft function is needed, yet excellent reintervention-free survival can be achieved. More research is needed to identify the role of external support in promoting autograft adaptation and longevity. Our long-term data further confirm that the Ross procedure is a suitable option in young adults with AV disease which should be considered on an individual basis.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

FUNDING

Lucas Van Hoof is the holder of a pre-doctoral grant 'Strategic basic research' (SB 1S70220N) from the Research Foundation Flanders (FWO). Art Schuermans was supported by the Belgian American Educational Foundation.

Conflict of interest: none declared.

DATA AVAILABILITY

Underlying data will be made available upon reasonable request.

Author contributions

Lucas Van Hoof: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review and editing. **Bert Rooyackers:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing—original draft. **Art Schuermans:** Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing—original draft; Writing—review and editing. **Jolien Duponselle:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—review and editing. **Alexander Van De Bruaene:** Data curation; Investigation; Methodology; Writing—review and editing. **Pieter De Meester:** Data curation; Investigation; Methodology; Writing—review and editing. **Els Troost:** Data curation; Investigation; Methodology; Writing—review and editing. **Bart Meuris:** Investigation; Methodology; Supervision; Writing—review and editing. **Werner Budts:** Conceptualization; Data curation; Investigation; Methodology; Supervision; Writing—review and editing. **Marc Gewillig:** Conceptualization; Data curation; Investigation; Methodology; Supervision; Writing—review and editing. **Willem Flameng:** Conceptualization; Data curation; Project administration; Writing—review and editing. **Willem Daenen:** Conceptualization; Data curation; Project administration; Writing—review and editing. **Bart Meyns:** Conceptualization; Data curation; Project administration; Supervision; Writing—review and editing. **Peter Verbrugghe:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing—review and editing. **Filip Rega:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Visualization; Writing—original draft; Writing—review and editing.

Reviewer information

European Journal of Cardio-Thoracic Surgery thanks Antonios Kallikourdis, Manan Himanshu Desai, Fatos Ballazhi, Karen Beatrix Abeln and the other anonymous reviewers for their contribution to the peer review process of this article.

REFERENCES

[1] Ross DN. Replacement of aortic and mitral valves with a pulmonary autograft. Lancet 1967;2:956–8. doi:10.1016/S0140-6736(67)90794-5

[2] Sievers H-H, Stierle U, Charitos EI, Takkenberg JJM, Hörer J, Lange R *et al.* A multicentre evaluation of the autograft procedure for young patients undergoing aortic valve replacement: update on the German Ross Registry. Eur J Cardiothorac Surg 2016;49:212–8. doi:10.1093/ejcts/ezv001

[3] Buratto E, Shi WY, Wynne R, Poh CL, Larobina M, O'Keefe M *et al.* Improved survival after the Ross procedure compared with mechanical aortic valve replacement. J Am Coll Cardiol 2018;71:1337–44. doi:10.1016/j.jacc.2018.01.048

[4] El-Hamamsy I, Eryigit Z, Stevens L-M, Sarang Z, George R, Clark L *et al.* Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 2010;376:524–31. doi:10.1016/S0140-6736(10)60828-8

[5] Mazine A, El-Hamamsy I, Verma S, Peterson MD, Bonow RO, Yacoub MH *et al.* Ross procedure in adults for cardiologists and cardiac surgeons. J Am Coll Cardiol 2018;72:2761–77. doi:10.1016/j.jacc.2018.08.2200

[6] Notenboom ML, Melina G, Veen KM, De Robertis F, Coppola G, De Siena P *et al.* Long-term clinical and echocardiographic outcomes following the Ross procedure: a post hoc analysis of a randomized clinical trial. JAMA Cardiol 2023;9:6–14. doi:10.1001/jamacardio.2023.4090

[7] Van Hoof L, Verbrugghe P, Jones EAV, Humphrey JD, Janssens S, Famaey N *et al.* Understanding pulmonary autograft remodeling after the Ross procedure: stick to the facts. Front Cardiovasc Med 2022;9:829120. doi:10.3389/fcvm.2022.829120

[8] Bouhout I, Noly P-E, Ghoneim A, Stevens L-M, Cartier R, Poirier N *et al.* Is the Ross procedure a riskier operation? Perioperative outcome comparison with mechanical aortic valve replacement in a propensity-matched cohort. Interact CardioVasc Thorac Surg 2017;24:41–7. doi:10.1093/icvts/ivw325

[9] Abeln KB, Schäfers S, Ehrlich T, Federspiel JM, Schäfers H-J. Ross operation with autologous external autograft stabilization—long-term results. Ann Thorac Surg 2022;114:502–9. doi:10.1016/j.athoracsur.2021.09.017

[10] Starnes VA, Elsayed RS, Cohen RG, Olds AP, Bojko MM, Mack WJ *et al.* Long-term outcomes with the pulmonary autograft inclusion technique in adults with bicuspid aortic valves undergoing the Ross procedure. J Thorac Cardiovasc Surg 2023;165:43.e2–52.e2. doi:10.1016/j.jtcvs.2021.01.101

[11] Skillington PD, Mokhles MM, Takkenberg JJM, Larobina M, O'Keefe M, Wynne R *et al.* The Ross procedure using autologous support of the pulmonary autograft: techniques and late results. J Thorac Cardiovasc Surg 2015;149:S46–52. doi:10.1016/j.jtcvs.2014.08.068

[12] Carrel T, Kadner A. Long-term clinical and imaging follow-up after reinforced pulmonary autograft Ross procedure. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2016;19:59–62. doi:10.1053/j.pcsu.2015.11.005

[13] Sievers H-H, Stierle U, Petersen M, Klotz S, Richardt D, Diwoky M *et al.* Valve performance classification in 630 subcoronary Ross patients over 22 years. J Thorac Cardiovasc Surg 2018;156:79.e2–86.e2. doi:10.1016/j.jtcvs.2018.03.015

[14] David TE, Ouzounian M, David CM, Lafreniere-Roula M, Manlhiot C. Late results of the Ross procedure. J Thorac Cardiovasc Surg 2019;157:201–8. doi:10.1016/j.jtcvs.2018.06.037

[15] Mastrobuoni S, de Kerchove L, Solari S, Astarci P, Poncelet A, Noirhomme P *et al.* The Ross procedure in young adults: over 20 years of experience in our institution. Eur J Cardiothorac Surg 2016;49:507–13. doi:10.1093/ejcts/ezv053

[16] Bové T, Bradt N, Martens T, De Wolf D, François K, de Beco G *et al.* The pulmonary autograft after the Ross operation: results of 25-year follow-up in a pediatric cohort. Ann Thorac Surg 2021;111:159–67. doi:10.1016/j.athoracsur.2020.06.027

[17] Rajani R, Hancock J, Chambers JB. The art of assessing aortic stenosis. Heart 2012;98 Suppl 4:iv14–iv22. doi:10.1136/heartjnl-2012-302392

[18] von Allmen RS, Weiss S, Tevaearai HT, Kuemmerli C, Tinner C, Carrel TP *et al.* Completeness of follow-up determines validity of study findings: results of a prospective repeated measures cohort study. PLoS One 2015;10:e0140817. doi:10.1371/journal.pone.0140817

[19] Max Planck Institute for Demographic Research (Aug 2022) Belgium Mortality data. https://mortality.org/Country/Country?cntr=BEL.

[20] Martin E, Mohammadi S, Jacques F, Kalavrouziotis D, Voisine P, Doyle D *et al.* Clinical outcomes following the Ross procedure in adults: a 25-year longitudinal study. J Am Coll Cardiol 2017;70:1890–9. doi:10.1016/j.jacc.2017.08.030

[21] Flynn CD, De Bono JH, Muston B, Rattan N, Tian DH, Larobina M *et al.* Systematic review and meta-analysis of long-term outcomes in adults undergoing the Ross procedure. Ann Cardiothorac Surg 2021;10:411–9. doi:10.21037/acs-2021-rp-30

[22] Etnel JRG, Grashuis P, Huygens SA, Pekbay B, Papageorgiou G, Helbing WA *et al.* The Ross procedure: a systematic review, meta-analysis, and microsimulation. Circ Cardiovasc Qual Outcomes 2018;11:e004748. doi:10.1161/circoutcomes.118.004748

[23] Sharabiani MTA, Dorobantu DM, Mahani AS, Turner M, Peter Tometzki AJ, Angelini GD *et al.* Aortic valve replacement and the Ross operation in children and young adults. J Am Coll Cardiol 2016;67:2858–70. doi:10.1016/j.jacc.2016.04.021

[24] Bourguignon T, El Khoury R, Candolfi P, Loardi C, Mirza A, Boulanger-Lothion J *et al.* Very long-term outcomes of the Carpentier-Edwards perimount aortic valve in patients aged 60 or younger. Ann Thorac Surg 2015;100:853–9. doi:10.1016/j.athoracsur.2015.03.105

[25] El-Hamamsy I, Toyoda N, Itagaki S, Stelzer P, Varghese R, Williams EE et al Propensity-matched comparison of the Ross procedure and prosthetic aortic valve replacement in adults. J Am Coll Cardiol 2022;79:805–15. doi:10.1016/j.jacc.2021.11.057

[26] Mokhles MM, Körtke H, Stierle U, Wagner O, Charitos EI, Bogers AJJC et al Survival comparison of the ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. Circulation 2011;123:31–8. doi:10.1161/CIRCULATIONAHA.110.947341

[27] Bobylev D, Horke A, Boethig D, Hazekamp M, Meyns B, Rega F *et al.* 5-Year results from the prospective European multi-centre study on decellularized homografts for pulmonary valve replacement ESPOIR trial and ESPOIR Registry data. Eur J Cardiothorac Surg 2022;62:1–11. doi:10.1093/ejcts/ezac219

[28] Troost E, Meyns B, Daenen W, Van de Werf F, Gewillig M, Van Deyk K et al Homograft survival after tetralogy of Fallot repair: determinants of accelerated homograft degeneration. Eur Heart J 2007;28:2503–9. doi:10.1093/eurheartj/ehm376

[29] Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Hazekamp MG *et al.* Individualised prediction of pulmonary homograft durability in tetralogy of Fallot. Heart 2015;101:1717–23. doi:10.1136/heartjnl-2015-307754

[30] Kouchoukos NT, Masetti P, Nickerson NJ, Castner CF, Shannon WD, Dávila-Román VG *et al.* The Ross procedure: long-term clinical and echocardiographic follow-up. Ann Thorac Surg 2004;78:773–81. doi:10.1016/j.athoracsur.2004.02.033

[31] Frigiola A, Ranucci M, Carlucci C, Giamberti A, Abella R, Di Donato M et al The Ross procedure in adults: long-term follow-up and echocardiographic changes leading to pulmonary autograft reoperation. Ann Thorac Surg 2008;86:482–9. doi:10.1016/j.athoracsur.2008.04.001

[32] Takkenberg JJM, van Herwerden LA, Galema TW, Bekkers JA, Kleyburg-Linkers VA, Eijkemans MJ *et al.* Serial echocardiographic assessment of neo-aortic regurgitation and root dimensions after the modified Ross procedure. J Hear Valve Dis 2006;15:100–6. http://www.ncbi.nlm.nih.gov/pubmed/?term=Takkenberg+JJ%2C+van+Herwerden+LA%2C+Galema+TW%2C+Bekkers+JA%2C+Kleyburg-+Linkers+VE%2C+Eijkemans+MJ%2C+Bogers+AJ.+Serial+echocardiographic+assessment+of+neo-aortic+regurgitation+and+root+dimensions+after+the+modif

[33] David TE, David C, Woo A, Manlhiot C. The Ross procedure: outcomes at 20 years. J Thorac Cardiovasc Surg 2014;147:85–93. doi:10.1016/j.jtcvs.2013.08.007

[34] Charitos EI, Takkenberg JJM, Hanke T, Gorski A, Botha C, Franke U *et al.* Reoperations on the pulmonary autograft and pulmonary homograft after the Ross procedure: an update on the German Dutch Ross Registry. J Thorac Cardiovasc Surg 2012;144:813–23. doi:10.1016/j.jtcvs.2012.07.005

[35] Redondo A, Austin C. Our 7-year experience supporting the Ross autograft with the novel technique of personalized external aortic root support. JTCVS Tech 2024;24:121–7. doi:10.1016/j.xjtc.2024.02.004

[36] Bouhout I, Ghoneim A, Tousch M, Stevens LM, Semplonius T, Tarabzoni M *et al.* Impact of a tailored surgical approach on autograft root dimensions in patients undergoing the Ross procedure for aortic regurgitation. Eur J Cardiothorac Surg 2019;56:959–67. doi:10.1093/ejcts/ezz105

European Journal of Cardio-Thoracic Surgery, 2024, 66, 1–10
https://doi.org/10.1093/ejcts/ezae267
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