JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 70, NO. 15, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.08.030

Clinical Outcomes Following the Ross Procedure in Adults

A 25-Year Longitudinal Study

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ABSTRACT

BACKGROUND Very few reports of long-term outcomes of patients who underwent the Ross procedure have been published.

OBJECTIVES The authors reviewed their 25-year experience with the Ross procedure with the aim of defining very-long-term survival and factors associated with Ross-related failure.

METHODS Between January 1990 and December 2014, the Ross procedure was performed in 310 adults (mean age 40.8 years) at a single institution. All patients were prospectively added to a dedicated cardiac surgery registry. Complete post-operative clinical examination and history were obtained, and transthoracic echocardiography was performed according to a standardized protocol. There was no loss to follow-up. Median follow-up was 15.1 years and up to 25 years.

RESULTS Bicuspid aortic valve was diagnosed in 227 patients (73.2%), and the most common indication for surgery was aortic stenosis (n = 225 [72.6%]). Freedom from any Ross-related reintervention was 92.9% and 70.1% at 10 and 20 years, respectively. Independent risk factors for pulmonary autograft degeneration were pre-operative large aortic annulus (hazard ratio: 1.1; p = 0.01), pre-operative aortic insufficiency (hazard ratio: 2.7; p = 0.002), and concomitant replacement of the ascending aorta (hazard ratio: 7.7; p = 0.0003). There were 4 hospital deaths (1.3%), and overall survival at 10 and 20 years was 94.1% and 83.6%, respectively. Long-term survival was not significantly different in patients who required Ross-related reintervention (log-rank p = 0.70). However, compared with the general population, survival was significantly lower in patients following the Ross procedure when matched on age and sex (p < 0.0001).

CONCLUSIONS The Ross procedure was associated with excellent long-term valvular outcomes and survival, regardless of the need for reintervention. Adults presenting with aortic insufficiency or a dilated aortic annulus or ascending aorta were at greater risk for reintervention. Unlike previous reports, long-term survival was lower in Ross patients compared with matched subjects. (J Am Coll Cardiol 2017;70:1890–9)

The use of pulmonary autograft remains a controversial option for aortic valve replacement in adults. On the basis of the opinions of experts and a handful of reports, recent guidelines recommended that the Ross procedure may be considered for young patients with anticoagulation dilemma when performed by an experienced surgeon (1).

Benefits of this operation, such as low pulmonary autograft thrombogenicity, absence of anticoagulation, potential valvular growth for young patients, and favorable autograft hemodynamic measurements, have all been reported (2,3). Previous publications have also shown that patients survival following the Ross procedure was not significantly different from the general population, when matched on age and sex (4–6).

However, only very few long-term data are available, and despite all these advantages, we hypothesized that the technical challenges arising from 2 valvular replacements and coronary

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Manuscript received May 16, 2017; revised manuscript received August 5, 2017, accepted August 14, 2017.

reimplantations would likely engender negative late consequences. We also questioned why this complex operation and anticipated reinterventions from valvular degeneration would not affect long-term survival. Therefore, the purpose of this study was to assess very-long-term survival and echocardiographic findings following the Ross procedure, as well as late valve-related morbidities.

SEE PAGE 1900

METHODS

PATIENT SELECTION. From January 1990 to December 2014, 310 adults underwent the Ross procedure at the Quebec Heart and Lung Institute. The follow-up period lasted up to December 2015. Following patient preference and referral by the treating physician, the Ross procedure was proposed to adults younger than 55 years, those with a strong desire to avoid long-term anticoagulation, and women of childbearing age. Thirteen older adults (age >55 years) underwent the Ross procedure because of their strong preference for this surgery. One patient was >60 years of age, and the indication was severe bacterial endocarditis with failed medical therapy. Patients who required concomitant major interventions were investigated but frequently considered inappropriate. Four surgeons performed the Ross procedure at different time period, which represents 22.7% of all aortic valve replacements in adults <55 years of age.

SURGICAL PROCEDURE. Standard cardiopulmonary bypass was conducted with a 2-stage venous cannula and mild hypothermia. Myocardial diastolic arrest was induced with blood retrograde cardioplegia. Patients with large annuli (>27 mm) were frequently denied the procedure unless medical condition absolutely required the avoidance of anticoagulation. In those patients, reduction annuloplasty (n = 4 [1.3%]) was often performed.

The pulmonary artery was divided at the bifurcation, and the pulmonary valve was inspected for leaflet fenestration, severe prolapse, root dilation, extremely thin and translucent leaflets, and gross abnormalities. These patients were generally reassigned to different procedures. The pulmonary autograft implantation technique was selected according to surgeon preference and anatomic findings. Root replacement was the most commonly used technique (n = 259 [83.6%]). Right ventricular muscle at the proximal end of the pulmonary autograft was trimmed to leave a 2- to 3-mm sewing cuff. The proximal anastomosis was performed in a circular fashion with semicontinuous 4-0 Prolene suture, deep under the aortic annulus. We did not systematically stabilize the autograft.

A cryopreserved pulmonary homograft (Cryolife, Kennesaw, Georgia; and Héma-Québec, Quebec City, Quebec, Canada) or a decellularized pulmonary homograft (Synergraft, Cryolife) was implanted to reconstruct the right ventricular outflow tract. The homografts were not matched to patient blood type, and dimension was determined according to patient size and availability. Antiplatelet agents were given according to surgeon preference. We aggressively treated high blood pressure.

LONG-TERM FOLLOW-UP. Since 1990, patients were followed according to a rigorous post-operative protocol. For the first 3 years, clinical and echocardiographic examinations were performed yearly at our institution, or information was directly transferred from the patient's cardiologist to our dedicated Ross clinic. If the patient was medically stable following this 3-year period, the same follow-up procedure was applied but at a lower frequency of once every 2 years, up to 15 years post-operatively. Thereafter, yearly echocardiography and clinical examinations were performed. Over this study period, there was 0.68% echocardiogram per patient per year. A provincial health insurance number is provided at birth to each resident of the province of Quebec, and the Quebec Death Registry was used to validate patient survival status. Patient data from the registry were available up to December 31, 2014. Clinical follow-up was complete in 100% of patients, and duration ranged from 44 days to 25 years (median 15.1 years; IQR [interquartile range]: 5.5 to 18.4 years), and 15.2% of the cohort (n = 47) was followed for >20.0 years. A total of 3,881 person-years of clinical data and 3,563 person-years of echocardiographic data were accrued.

Our database is subject to periodic audit; errors and missing variables are random and affect <5% of fields. The study protocol was approved by the Institutional Review Board, and requirement to obtain patient consent was waived.

DEFINITIONS OF MORTALITY AND MORBIDITIES. The different causes of death and reinterventions were established according to the guidelines from the Councils of the American Association for Thoracic Surgery, the Society of Thoracic Surgeons, and the European Association for Cardio-Thoracic Surgery (7). Ross-related mortality was defined as any death directly resulting from the original surgery and from

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

SVD = structural valve degeneration

reoperations for structural or nonstructural degeneration of the pulmonary autograft or homograft. Death secondary to infective endocarditis, bleeding or embolic event, and unexplained sudden death were also considered Ross-related deaths. Cardiac non-Ross-related death included other acquired heart disease such as heart failure or coronary atherosclerosis and excluded mortality of Ross origin. Finally, all-cause mortality represents death of any cause in patients who underwent the Ross procedure.

We also assessed long-term degeneration of both the pulmonary autograft and the homograft and ensuing reinterventions. First, we defined pulmonary autograft failure as either degeneration of the pulmonary autograft or reinterventions. Degeneration of the autograft was diagnosed by means of 2-dimensional echocardiographic and/or computed tomographic imaging. Structural valve degeneration (SVD) was characterized by valvular regurgitation graded as moderate or severe, whereas nonstructural degeneration was defined by dilation of the neoaortic conduit (>50 mm), with or without associated autograft insufficiency (7,8).

Second, we defined homograft failure as either degeneration of the pulmonary homograft or reinterventions (surgery and percutaneous approach). Homograft SVD was determined following echocardiographic assessment and was characterized by either a peak systolic valvular gradient >40 mm Hg or valvular regurgitation, graded as moderate or severe (8). Infective endocarditis was not included in the Ross failure definitions but reported separately (7).

STATISTICAL ANALYSIS. Categorical variables are reported as counts and percentages. Continuous variables are presented as mean ± SD or as median with range. Nonparametric estimates of time-related events such as autograft and homograft degeneration, reinterventions, and survival were calculated using the Kaplan-Meier estimator and the log-rank test for comparisons. Patients in whom Ross-related events had not occurred were censored at their last known visits. The survival experience was compared with a reference population, and the 2011–2012 province of Quebec life tables stratified for sex were used as the reference population for survival comparison. All-cause mortality was used for comparison, and patients who required reoperations for any Ross-related valve failure were not excluded for survival comparison.

A multivariate Cox regression analysis was performed to identify independent variables associated with pulmonary autograft and homograft failure. We combined both valve degeneration and Ross-related reinterventions in each model to increase the number of adverse events. The independent variables presented to the model for homograft failure were age, sex, and pulmonary homograft size. The independent variables presented to the model for autograft failure were age, sex, pre-operative aortic annular size, pulmonary autograft implantation technique, pre-operative hypertension, infective endocarditis, surgical indication, valvular leaflet pathology, and concomitant procedure on the ascending aorta. Surgeon identity was not associated with the outcomes on univariate analysis and was therefore not included in the final models. Martingale residuals were used to assess the functional form of continuous variables. The proportionality assumption was examined with graphical representations. Statistical significance was defined as a p value <0.05. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PERIOPERATIVE DATA. Baseline patient characteristics are depicted in Table 1. Patient age ranged from 18 to 68 years (mean 40.8 years), and 13 patients (4.2%) were >55 years of age. There were 187 male patients (60.3%). Forty-seven patients (15.2%) previously underwent open heart surgery: aortic valve replacement was performed in 19 patients (6.1%) and aortic valvuloplasty in 25 patients (8.1%). Bicuspid aortic valve was found in 227 patients (73.2%), and isolated aortic stenosis was the predominant lesion in 72.6% of the cohort. Concomitant cardiac pathologies were addressed in 90 patients (29.0%). Associated procedures on a dilated ascending aorta were performed in 53 patients (17.1%), and only 9 patients (2.9%) known pre-operatively for coronary artery disease underwent concomitant coronary artery bypass graft surgery. Detailed operative characteristics are listed in Table 2.

EARLY CLINICAL OUTCOMES. Overall 30-day mortality was 1.3% (n = 4). The cause of early death was refractory cardiogenic shock in 3 patients who required extracorporeal membrane oxygenation support. The fourth patient died of hemorrhagic shock 10 days post-operatively, following the dehiscence of the pulmonary autograft distal anastomosis, which occurred 3 days after the patient was released from the hospital. All 4 early deaths occurred in the first 10 years of the Ross experience, and there has been no early death in the past 15 years. Unplanned coronary artery bypass graft surgery was necessary for 4 patients (1.3%) resulting from iatrogenic intraoperative coronary injuries. Sixteen patients (5.2%)

TABLE 1 Baseline Patient Characteristics (n = 310)

Age, yrs	40.8 ± 10.6
18-30	69 (22.3)
31-45	115 (37.1)
>45	126 (40.6)
Male	187 (60.3)
Redo sternotomy	47 (15.2)
Aortic valve replacement	19 (6.1)
LVOT obstruction repair	25 (8.1)
Other	3 (1.0)
History of aortic coarctation repair	7 (2.3)
Elective surgery	305 (98.4)
NYHA functional class III or IV	160 (51.6)
Chronic obstructive pulmonary disease	15 (4.8)
Hypertension	66 (21.3)
Dyslipidemia	94 (30.4)
Diabetes mellitus	16 (5.2)
Coronary artery disease	16 (5.2)
Obesity*	66 (21.3)
Active smoking	78 (25.2)
History of infective endocarditis	31 (10.0)
Active infective endocarditis	12 (3.9)
Left ventricular ejection fraction, %	62.2 ± 10.5
Aortic annular size, mm	23 ± 3
Pulmonary hypertension	29 (9.4)
Aortic valve leaflet characteristics	
Unicuspid	12 (3.9)
Bicuspid	227 (73.2)
Tricuspid	50 (16.1)
Quadricuspid	2 (0.7)
Prosthesis	19 (6.1)
Dominant aortic valve lesion	
Stenosis	225 (72.6)
Insufficiency	60 (19.4)
Mixed lesion	23 (7.4)
Prosthetic valve abscess	2 (0.7)

Values are mean ± SD or n (%). *Obesity was defined as body mass index >30 kg/m^2.
LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

TABLE 2 Procedural Characteristics (n = 310)

Autograft implantation technique	
Root replacement	259 (83.6)
Root inclusion	33 (10.7)
Subcoronary valve replacement	18 (5.8)
Concomitant procedures	
Ascending aorta replacement	39 (12.6)
Ascending aorta reconstruction	14 (4.5)
Aortic annuloplasty	4 (1.3)
Planned CABG	9 (2.9)
Unplanned CABG	4 (1.3)
Mitral valve intervention	9 (2.9)
Congenital intervention	9 (2.9)
Konno procedure	3 (1.0)
Other	8 (2.6)
Pulmonary homograft size, mm	25 (20-30)
Cardiopulmonary bypass time, min	173.3 ± 56.2
Aortic cross-clamp time, min	137.6 ± 44.4

Values are n (%), median (range), or mean ± SD.
CABG = coronary artery bypass grafting.

required surgical re-exploration for mediastinal bleeding. There was no early (pre-hospital discharge) autograft failure that required valvular replacement. Mortality and major post-operative complications are listed in Table 3.

LATE CLINICAL OUTCOMES. Autograft degeneration and reinterventions. Fifty-five patients (17.7%) developed pulmonary autograft failure. Among them, SVD was diagnosed in 36 patients. Isolated moderate or severe autograft insufficiency was therefore the primary finding in 30 patients, and one-half required surgery. The remaining 6 patients with SVD developed autograft insufficiency associated with only mild dilation of the ascending aorta, and reintervention was required in all but 1 patient. No patient developed pulmonary autograft stenosis. In most reintervention cases, patients had severe autograft insufficiency with nonsalvageable leaflets, and the Bentall procedure was performed in 13 patients. A valve-sparing aortic root replacement procedure was feasible in 2 patients, and the remaining 5 patients underwent aortic valve replacement.

Nineteen patients (6.1%) developed non-SVD of the pulmonary autograft. Isolated dilation of the ascending aorta was found in 10 patients (3.2%), and one-half underwent reoperation. Seven patients (2.3%) had a combination of both dilated ascending aorta and secondary autograft insufficiency; all of them required reintervention. A valve-sparing aortic root replacement procedure was performed in 7 of the 12 patients who required reintervention for non-SVD, and the well-functioning autograft leaflets were preserved.

Altogether, a total of 32 patients (10.3%) required autograft-related reoperations at a median of 13.8 years (IQR: 9.5 to 16.9 years) after the initial Ross procedure. Kaplan-Meier curves for autograft degeneration and reintervention are outlined in Figure 1. Freedom from all left-sided reinterventions, including reoperation for endocarditis (n = 2 [0.65%]), was 96.0%, 90.5%, and 76.1% at 10, 15, and 20 years, respectively (Table 4). Linearized rates for autograft degeneration and reintervention were 1.54% per patient-year and 0.82% per patient-year, respectively.

The root implantation technique did not influence autograft failure (hazard ratio [HR]: 1.1; 95% confidence interval [CI]: 0.6 to 2.1; p = 0.7), but preoperative aortic valve annulus >28 mm was associated with increased autograft failure (HR: 3.1;

TABLE 3 30-Day Outcomes (n = 310)

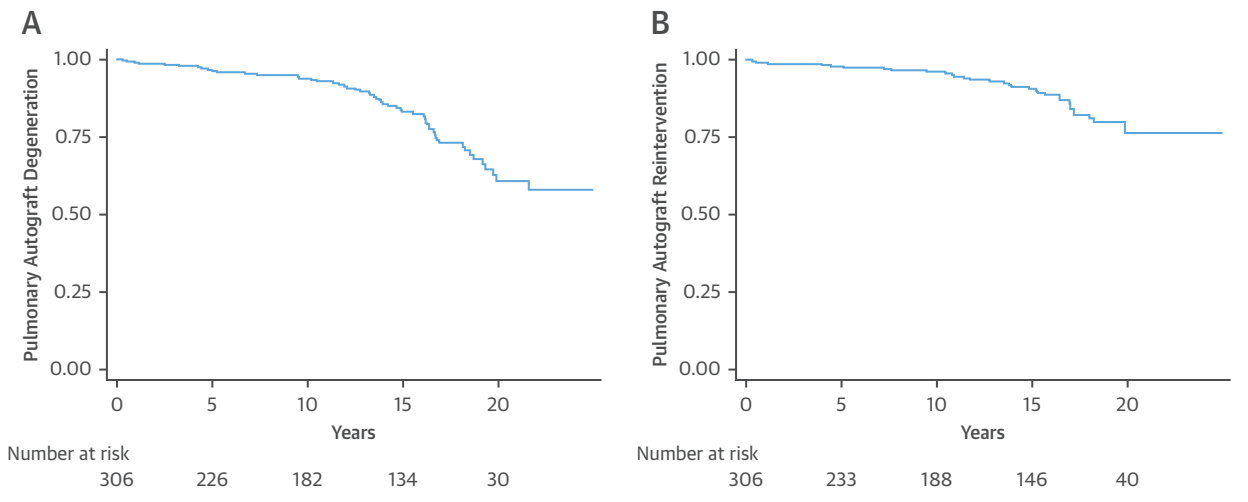
Neurological complications	
Seizures	2 (0.6)
Transient ischemic attack	3 (1.0)
Stroke	4 (1.3)
Permanent pacemaker insertion	4 (1.3)
Acute renal failure*	16 (5.2)
Hemodialysis	2 (0.6)
Re-exploration for mediastinal bleeding	16 (5.2)
Blood transfusion	182 (58.7)
New onset atrial fibrillation	51 (16.5)
Deep sternal wound infection	0 (0)
Sepsis	3 (1.0)
Assisted ventilation >48 h	6 (1.9)
ICU length of stay, days (n = 128)	1.8 (1.0–2.7)
Hospital length of stay, days	7.0 (5.0–8.0)
Mortality	4 (1.3)

Values are n (%) or median (interquartile range). *Acute renal failure defined as creatinine Δ50 mmol/l.
ICU = intensive care unit.

95% CI: 1.3 to 7.3; p = 0.02) on univariate analysis. Multivariate Cox regression analysis showed that a baseline large aortic valve annulus at initial operation (HR: 1.1; 95% CI: 1.03 to 1.27; p = 0.01) and pre-operative aortic valve insufficiency, graded as moderate or severe (HR: 2.7; 95% CI: 1.4 to 5.1; p = 0.002) were independent factors for pulmonary autograft failure. Concomitant replacement of a dilated ascending aorta at time of the Ross procedure was highly associated with autograft failure (n = 5) (HR: 7.7; 95% CI: 2.6 to 23.5; p < 0.0001).

PULMONARY HOMOGRAFT DEGENERATION AND REINTERVENTIONS. Sixty-seven patients (21.6%) developed pulmonary homograft SVD during the study period, and 21 patients underwent homograft reintervention (surgical replacement or transcatheter valve implantation) a median of 12.4 years (IQR: 6.9 to 17.2 years) after the initial Ross procedure. Homograft insufficiency was the most common pathology (n = 48), and reintervention was performed in 10 patients. Homograft stenosis was diagnosed in 18 patients, and 11 patients required valvular replacement. Finally, only 1 patient experienced both homograft insufficiency and stenosis. During reoperation for autograft failure, there were 4 well-functioning homografts that were damaged or excised during aortic root surgery. Kaplan-Meier curves for homograft degeneration and reintervention are shown in Figure 2. Freedom from all right ventricular outflow tract reintervention, including reoperations for endocarditis (n = 2 [0.65%]), was 96.6%, 92.1%, and 82.3% at 10, 15, and 20 years of follow-up, respectively (Table 4). Linearized rates for homograft degeneration and reintervention were 1.93% per patient-year and 0.54% per patient-year, respectively.

FIGURE 1 Freedom From Pulmonary Autograft Degeneration and Reintervention



(A) Freedom from pulmonary autograft degeneration. Kaplan-Meier curves of pulmonary autograft degeneration, which was defined as structural degeneration for valvular regurgitation graded as moderate or severe on transthoracic echocardiography, and nonstructural degeneration, which was defined as dilation of the neo-aortic conduit (>50 mm), with or without associated autograft insufficiency. No patient developed pulmonary autograft stenosis. Freedom from autograft degeneration was 93.9% and 60.8% at 10 and 20 years of follow-up, respectively. **(B)** Freedom from pulmonary autograft reintervention. Kaplan-Meier curves of all left-sided reinterventions, which included reoperation for endocarditis. A Bentall procedure was performed in 17 patients, a valve-sparing procedure in 9 patients, and aortic valve replacement in 6 patients. Freedom from surgical reintervention on the autograft was 96.0%, 90.5%, and 76.1% at 10, 15, and 20 years, respectively.

On multivariate Cox analysis, larger pulmonary homograft size was associated with significantly higher homograft failure (HR: 1.2; 95% CI: 1.02 to 1.39; p = 0.03) when patients were followed for >10 years. Homograft diameter >27 mm was associated with a significant increased reintervention (log-rank p = 0.001) and SVD rate (log-rank p = 0.006) at long-term follow-up. However, homograft size did not influence failure rate when post-operative follow-up duration was <10 years.

ROSS-RELATED AND NON-ROSS-RELATED REINTERVENTIONS. Over the study period, 56 patients (18.1%) required additional cardiac surgery: 44 patients (14.2%) underwent Ross-related reoperation at a median of 11.6 years (IQR: 6.6 to 16.4 years). Freedom from any Ross-related reintervention, including surgery for infective endocarditis (n = 3 [1%]), was 92.9%, 86.2%, and 70.1% at 10, 15, and 20 years, respectively (Figure 3, Table 4).

INFECTIVE ENDOCARDITIS. Twelve patients (3.9%) underwent the Ross procedure for active infective endocarditis. None of them required reintervention or experienced a second episode of endocarditis at a median of 3.9 years (IQR: 2.6 to 13.2 years). Three patients (1.0%) developed de novo infective endocarditis that required surgery. The linearized rate for endocarditis was 0.08% per patient-year.

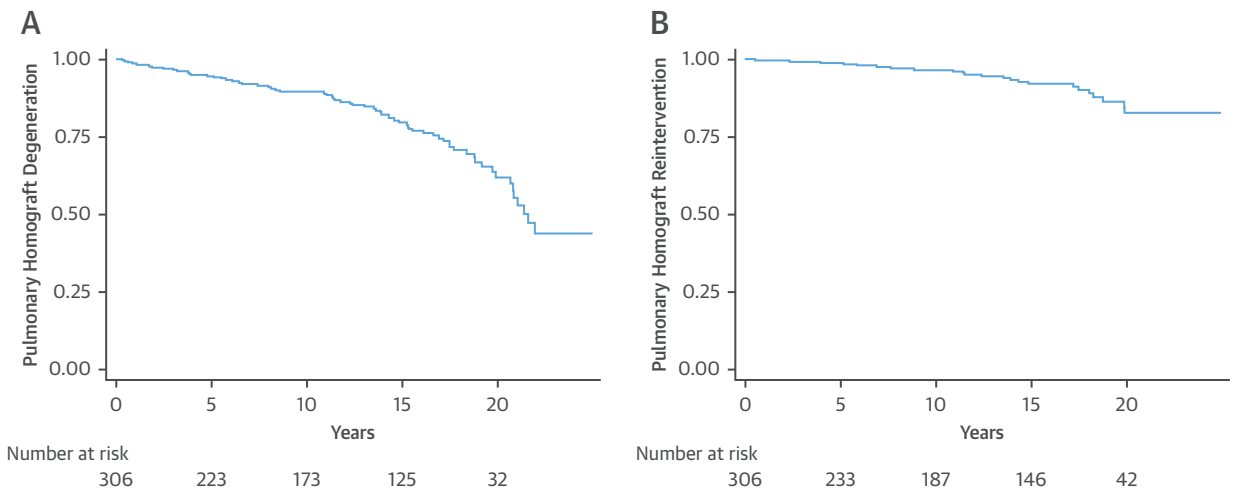
TABLE 4 Early and Late Survival and Cardiac Reinterventions

	1 Year of Follow-Up (95% CI)	10 Years of Follow-Up (95% CI)	20 Years of Follow-Up (95% CI)
Freedom from			
All-cause mortality	99.7 (97.7–100.0)	94.1 (90.2–96.5)	83.6 (76.3–88.8)
Ross-related mortality	99.7 (97.7–100.0)	99.2 (96.8–99.8)	97.4 (92.5–99.1)
Cardiac non-Ross-related mortality	–	98.1 (95.0–99.3)	91.5 (84.9–95.3)
Noncardiac mortality	–	96.7 (93.5–98.3)	93.7 (88.6–96.6)
Freedom from			
Any Ross-related failure	97.7 (95.2–98.9)	83.9 (78.6–88.0)	43.3 (33.9–52.3)
Pulmonary homograft failure	98.7 (96.5–99.5)	89.4 (84.8–92.7)	61.8 (52.0–70.2)
Pulmonary autograft failure	99.0 (96.9–99.7)	93.9 (90.0–96.3)	60.8 (50.2–69.8)
Freedom from			
Any Ross-related reintervention	99.0 (96.9–99.7)	92.9 (88.7–95.5)	70.1 (60.4–77.9)
Any homograft reintervention	99.7 (97.6–100.0)	96.6 (93.3–98.3)	82.6 (73.2–88.9)
Any autograft reintervention	99.0 (97.0–99.7)	96.0 (92.6–97.8)	76.1 (66.8–83.2)
Any cardiac reintervention	98.0 (95.6–99.1)	90.9 (86.4–94.0)	66.2 (56.6–74.2)
Pulmonary autograft insufficiency	99.3 (97.3–99.8)	94.7 (91.0–96.9)	66.9 (56.3–75.5)

CI = confidence interval.

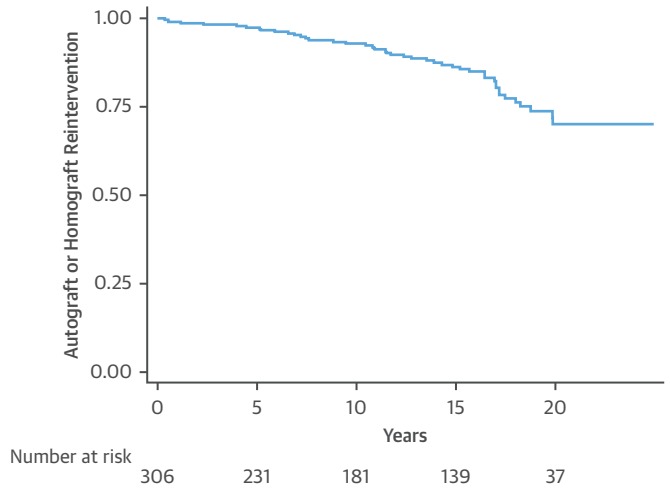
LONG-TERM SURVIVAL AND VALVE-RELATED MORTALITY. There were 28 late deaths (median survival 9.8 years): 12 patients died of noncardiac causes, 12 patients died of cardiac causes (not Ross related), and 4 deaths were considered Ross-related

FIGURE 2 Freedom From Pulmonary Homograft Degeneration and Reintervention



(A) Freedom from pulmonary homograft degeneration. Kaplan-Meier curves of pulmonary homograft structural degeneration, which was characterized by either a peak systolic valvular gradient >40 mm Hg or valvular regurgitation graded as moderate or severe. Homograft insufficiency was the most common pathology (n = 48). Freedom from homograft structural valve degeneration was 89.4% and 61.8% at 10 and 20 years of follow-up, respectively. **(B)** Freedom from pulmonary homograft reintervention. Kaplan-Meier curves of all reintervention (surgery or percutaneous) on the pulmonary homograft, which included reoperations for endocarditis and reoperation on a well-functioning homograft that was excised during concomitant reoperation on the pulmonary autograft. Freedom from all right ventricular outflow tract reintervention was 96.6%, 92.1%, and 82.3% at 10, 15, and 20 years of follow-up, respectively.

FIGURE 3 Freedom From Any Pulmonary Homograft or Autograft Reintervention



Kaplan-Meier curves of freedom from any Ross-related reintervention (on the pulmonary autograft, pulmonary homograft, or both), including surgery for infective endocarditis, was 92.9%, 86.2%, and 70.1% at 10, 15, and 20 years, respectively.

deaths. Three patients died following Ross-related reintervention, and overall mortality for reoperation was 5.6%. The fourth patient experienced a sudden and unexplained death while at work, 6 months post-operatively. Non-Ross-related cardiac deaths (median survival 14.3 years) were caused by acquired coronary atherosclerosis (n = 8) and malignant arrhythmias (n = 4).

In the noncardiac mortality group, malignant neoplasm was the predominant cause of death (n = 5), and 3 patients (ages 35, 41, and 54 years) committed suicide. Other causes of death were sepsis (n = 1), viral hepatitis (n = 1), severe chronic obstructive pulmonary disease (n = 1), and amyotrophic lateral sclerosis (n = 1).

There was no difference in survivorship for patients who required any Ross-related reinterventions (log-rank p = 0.70) or according to the initial autograft implantation technique (log-rank p = 0.60). Overall survival was 94.1%, 91.5%, and 83.6% at 10, 15, and 20 years, respectively (**Table 4**). Compared with the general population of the province of Quebec, long-term survival was significantly lower for our Ross patients (p < 0.0001), when matched on age and sex (**Central Illustration**). Expected survival was 94.7% at 15 years and 91.9% at 20 years for the matched population.

DISCUSSION

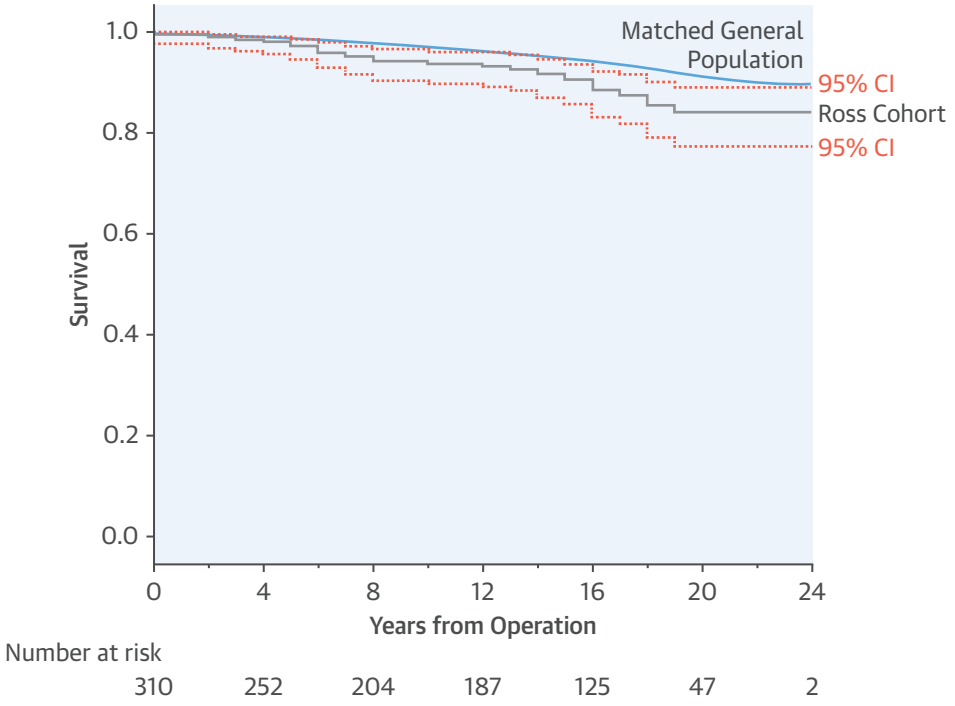
In this study, we report our 25-year experience of adults following the Ross procedure. Post-operative assessment was complete, with a median follow-up duration of >15 years, which appears to be the longest in the published research. Only a few Ross cohorts have been followed for >10 years (4,5,9). Most publications have reported short-term outcomes and combined results of adult and pediatric patients (10–15).

We report low periprocedural and long-term Ross-related mortality. At 20 years, freedom from Ross-related death was 97.4%, and overall survival was 83.6%. Survival is excellent considering the complexity of the surgery and the Ross-induced disease of both outflow tracts. Unlike what was revealed from a recent Society of Thoracic Surgeons database analysis, a lower operative mortality rate can be achieved at specialized institutions (16). We believe this study is the longest complete longitudinal assessment of clinical and echocardiographic outcomes following the Ross procedure in young adults.

David et al. (4) published the results of a younger population (median age 34 years) with a median follow-up period of 13.8 years (4). Freedom from all-cause mortality was 93.6% at 20 years. It appears that late survival was not significantly different compared with the general population of the province of Ontario, when matched on age and sex. However, only 13.2% of their original cohort remained at risk 18 years post-operatively, and it is difficult to assess how many patients were still followed 20 years post-operatively. In contrast to their findings, we found that all-cause mortality was higher in our Ross patients compared with a matched population. Of note, 3 patients committed suicide, representing 10.7% of all late deaths. This finding was unexpected, and it certainly has negatively affected long-term survival. Coronary atherosclerosis was also a major cause of late mortality, unlike what was described in previous reports (4,5). The mean age of our cohort is 41 years, and significant coronary artery disease may be expected as patients get older. Our population seems different, and comparison of late mortality should carefully be examined.

Mastrobuoni et al. (5) reported their 20-year experience with the Ross procedure in 306 patients. The median age of their cohort was comparable with ours, but follow-up duration was shorter, and late clinical assessment of their cohort was not complete. Survival estimates bifurcated at approximately 10 years, and all-cause mortality was significantly higher in the Ross patients compared with a matched population 15 years post-operatively. Freedom from Ross-related death was 96.8% at 16 years, which is largely similar to our results. However, we found a

CENTRAL ILLUSTRATION **Very-Long-Term Outcomes of the Ross Procedure**



Martin, E. et al. J Am Coll Cardiol. 2017;70(15):1890–9.

Long-term survival of Ross patients **(gray)** compared with the general population **(blue)** matched for sex and age (with 95% confidence interval [CI], in **orange**). Kaplan-Meier curves of patients who underwent the Ross procedure with 95% confidence limits and of the general population matched for age and sex. Compared with the general population, survival was significantly lower in patients following the Ross procedure ($p < 0.0001$). Overall survival for our cohort was 94.1%, 91.5%, and 83.6% at 10, 15, and 20 years, respectively.

lower frequency of Ross-related reinterventions (13.8%) on either the left- or right-sided valve at 15 years, compared with 25.5% at 16 years in their cohort.

By the end of our follow-up period, more than 50% of our cohort had developed valvular degeneration on echocardiographic imaging. Yet reinterventions on either valve occurred in <30% at 20 years and occurred more frequently at long-term follow-up. Similarly, David et al. (4) showed that reoperation on the homograft or autograft was uncommon in the first 10 years post-operatively, and 77.9% of their cohort was free of any Ross-related reoperation at 20 years. Accordingly, a careful appraisal of mid-term outcomes must be made because very few reinterventions are performed earlier than 10 years post-operatively and that mortality, although overall very uncommon, also occurred rarely in the first 10 years.

A recent update of the German Ross Registry reported the clinical outcomes of more than 1,500 patients (age >16 years) with a mean follow-up period of 8.3 years (6,17). Survival did not differ significantly between the Ross patients and the general German population. These findings are therefore not surprising, as we expect mortality and reoperations to occur at a much later period. Survival curves appeared to diverge at 15 years, and we can certainly assume that survival will soon be significantly lower in the Ross patients. Only 12% of the registry was followed for >15 years, and long-term follow-up is essential to better evaluate mortality.

The Ross procedure is a good addition to the therapeutic armamentarium for infective endocarditis treatment and may potentially be more resistant to infection compared with other conduits (5,18,19). In our study, all patients who underwent surgery for active infective endocarditis had no recurrence of the disease, but 1 patient eventually developed autograft SVD. Moreover, de novo endocarditis occurred in only 3 patients (1%) and represents a much lower endocarditis rate (0.08% per patient-year) compared with recent series (up to

0.52% per patient-year) of aortic valve replacement (20,21).

It is believed that properties of the neo-aortic root geometry are better preserved with the full root technique than the inclusion and subcoronary techniques, which both can deform the 3-dimensional integrity of the root and also damage the autograft leaflets. However, a previous study showed that the root technique was a predictor of proximal aorta dilation (odds ratio: 7.0; p = 0.003) on multivariate analysis (22). In our cohort, the pulmonary autograft implantation technique was not associated with autograft degeneration. However, replacement of the ascending aorta was highly significant for autograft degeneration. Very few patients developed autograft dysfunction but did so in their early postoperative period (3.3 years). One could hypothesize that the noncompliant synthetic aortic graft can no longer accommodate the aortic wall stress encountered during systole. The autograft root becomes the main actor compensating for the loss of aortic compliance. Patients who underwent ascending aorta remodeling (without synthetic graft replacement) did not develop autograft degeneration. The native, flexible, and living aortic wall may therefore help support the systemic pressure. In light of these results, we prioritize native aortic tissue and are considering an external prosthetic adjunct to stabilize the aortic annulus whenever a synthetic graft is used.

In recent years, there is a tendency to address the dilated autograft root sooner rather than later in an attempt to protect the autograft and decrease the chance of developing severe autograft insufficiency with nonsalvageable leaflets. A valve-sparing autograft reoperation was performed in one-half of the patients who developed dilated neo-aortic roots. At our institution, surgical expertise with valve-sparing surgery was first attained in patients with isolated root aneurysms and was later reproduced on Ross patients. To date, all 9 patients are alive and did not require additional surgery on the autograft, with a mean follow-up period of 2.2 years following the autograft leaflet-preserving surgery. Similarly, a multicenter study showed that preserving the autograft leaflets was appropriate and feasible in a subset of a Ross population (23). Eighty-six patients underwent valve-sparing surgery, and overall 30-day mortality was 1.2%. The autograft implantation technique at the time of the initial Ross procedure was found to influence durability of the valve-sparing surgery: the inclusion cylinder technique increased risk for reintervention on univariate analysis (HR: 4.4; p = 0.009).

Strict echocardiographic criteria were used to define pulmonary homograft SVD. These criteria have been previously described (4,5). In our study, homograft SVD was predominantly characterized by insufficiency. Although we report a higher rate of homograft SVD due to pulmonary insufficiency, moderate to severe pulmonary valve regurgitation can be extremely well tolerated for years. In our practice, we only intervene on the pulmonary homograft following the onset of right ventricular volume and function change.

Young adults requiring aortic valve surgery definitely represent a challenging situation, and all valve substitutes pose many disadvantages (1). To date, only 1 randomized trial has assessed outcomes following pulmonary autograft and homograft aortic root replacement. Results at 13 years showed significantly improved survival (95% vs. 78%) and fewer reoperations (94% vs. 51%) in Ross patients (9). A study by Ruel et al. (18) found that survival at 20 years was much lower (66% and 52%) in young adults who underwent either bioprosthetic or mechanical aortic valve implantation. Moreover, bioprosthetic valve degeneration requiring reoperations is common in young adults (19). Bourguignon et al. (20) reported their 20-year experience with the Carpentier-Edwards Perimount bioprosthesis in a large population and found a much higher reintervention rate (65.7% at 20 years) and mortality rate (34.4% at 15 years). Overall, it appears that the Ross procedure confers a solid survival advantage over commonly used valve substitutes.

STUDY LIMITATIONS. The present study has major important strengths. Long-term post-operative clinical and echocardiographic assessment was complete, with a median follow-up of more than 15 years. We were able to validate our survival data with those provided by province of Quebec. However, some causes of death, mainly suicide and coronary atherosclerosis, may indicate intrinsic differences in our Ross cohort and limit comparison with others. There are also limitations to our study that are inherent to any observational study. A few surgeons were involved in the procedure, but differences in surgical techniques were potentially not accounted for in our analysis. Adverse events were also quite low, and we did not perform individual regression models.

CONCLUSIONS

We report excellent long-term survival with very low valve-related mortality following the Ross procedure.

Yet all-cause mortality was higher than in a sex- and age-matched population. Although reoperation on the pulmonary autograft was more frequent than on the homograft, failing autograft can be successfully repaired in experienced hands. Young adults with aortic valve disease should be referred for the Ross procedure, and patients presenting with aortic regurgitation associated with a large aortic valve annulus and dilated ascending aorta should carefully be reviewed for optimal aortic valve surgery.

ACKNOWLEDGMENTS The authors acknowledge the technical assistance provided by Stéphanie Dionne and Serge Simard.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

For patients undergoing surgical aortic valve replacement, selection of a mechanical prosthesis is reasonable for those younger than 50 years with no contraindications to long-term anticoagulation. Although technically more challenging and not widely used, the Ross procedure provides excellent results when performed by experienced operators and should be considered for younger adults, as long the alternative options are discussed with the patient in the event the pulmonary valve autograft proves unsuitable.

TRANSLATIONAL OUTLOOK: Future studies should integrate data from multiple institutions to better define optimal autograft implantation techniques and postoperative management.

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KEY WORDS aortic valve surgery, pulmonary autograft, Ross