JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 79, NO. 10, 2022

PUBLISHED BY ELSEVIER

Improved Outcomes Following the Ross Procedure Compared With Bioprosthetic Aortic Valve Replacement

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ABSTRACT

BACKGROUND The ideal aortic valve substitute for young and middle-aged adults remains elusive.

OBJECTIVES This study sought to compare the long-term outcomes of patients undergoing the Ross procedure and those receiving bioprosthetic aortic valve replacements (AVRs).

METHODS Consecutive patients aged 16-60 years who underwent a Ross procedure or surgical bioprosthetic AVR at the Toronto General Hospital between 1990 and 2014 were identified. Propensity score matching was used to account for differences in baseline characteristics. The primary outcome was all-cause mortality. Secondary outcomes included valve reintervention, valve deterioration, endocarditis, thromboembolic events, and permanent pacemaker implantation.

RESULTS Propensity score matching yielded 108 pairs of patients. The median age was 41 years (IQR: 34-47 years). Baseline characteristics were similar between the matched groups. There was no operative mortality in either group. Mean follow-up was 14.5 ± 7.2 years. All-cause mortality was lower following the Ross procedure (HR: 0.35; 95% CI: 0.14-0.90; $P = 0.028$). Using death as a competing risk, the Ross procedure was associated with lower rates of reintervention (HR: 0.21; 95% CI: 0.10-0.41; $P < 0.001$), valve deterioration (HR: 0.25; 95% CI: 0.14-0.45; $P < 0.001$), thromboembolic events (HR: 0.15; 95% CI: 0.05-0.50; $P = 0.002$), and permanent pacemaker implantation (HR: 0.22; 95% CI: 0.07-0.64; $P = 0.006$).

CONCLUSIONS In this propensity-matched study, the Ross procedure was associated with better long-term survival and freedom from adverse valve-related events compared with bioprosthetic AVR. In specialized centers with sufficient expertise, the Ross procedure should be considered the primary option for young and middle-aged adults undergoing AVR. (J Am Coll Cardiol 2022;79:993-1005) © 2022 by the American College of Cardiology Foundation.

Mechanical prostheses have long been the preferred option for aortic valve replacement (AVR) in young and middle-aged adults. However, over the last 2 decades, there has been a significant increase in the use of bioprosthetic valves in this patient population.[1,2] This trend was born from a desire to avoid the lifelong anticoagulation mandated by mechanical AVR and its associated complications. It was further accentuated by the introduction of percutaneous therapies and the promise of valve-in-valve transcatheter aortic valve replacement (TAVR) to treat the main perceived drawback of bioprosthetic AVR, namely, a predictable higher rate of structural valve deterioration in young adults.

The Ross procedure (pulmonary autograft replacement) is an alternative to prosthetic AVR. Unlike mechanical and bioprosthetic valves—which are nonliving substitutes—the Ross procedure allows for long-term viability of the neo-aortic valve. The

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 21, 2021; revised manuscript received November 15, 2021, accepted December 8, 2021.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2021.12.026

ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

TAVR = transcatheter aortic valve replacement

living nature of the pulmonary autograft allows for adaptive remodeling and confers a hemodynamic profile similar to that of the native aortic valve.[3,4] These unique properties translate into excellent long-term clinical outcomes, as shown in several contemporary longitudinal studies conducted across the world.[5-8] Despite this, the Ross procedure continues to be criticized because of concerns over surgical complexity, exposure to a broad spectrum of complex reoperations, and the notion of transforming a single-valve disease into a double-valve disease.[9-11] As a result of these concerns—and despite the growing body of evidence showing excellent long-term outcomes—the Ross procedure remains a Class IIb recommendation in the most recent 2020 American College of Cardiology/American Heart Association valve guidelines.[12]

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In recent years, several studies have shown superior long-term outcomes of the Ross procedure over mechanical AVR.[13-15] In contrast, there is a paucity of comparative data between the Ross procedure and bioprosthetic AVR, and no longitudinal study comparing long-term (≥20 years) outcomes between these 2 techniques has been published.[16] In light of the contemporary increase in the use of bioprosthetic AVR in young and middle-aged adults, such data are pressingly needed. Given the limited number of surgeons currently performing the Ross procedure and the long follow-up required to study meaningful outcomes in young adults, a randomized trial comparing bioprosthetic AVR and the Ross procedure is unlikely to yield these data in the foreseeable future. Hence, we conducted a propensity-matched cohort study with the objective of comparing long-term survival and adverse valve-related events among patients receiving bioprosthetic AVR and those undergoing the Ross procedure.

METHODS

PATIENT POPULATION. All patients aged 16-60 years who underwent a Ross procedure or surgical bioprosthetic AVR at the Toronto General Hospital between 1990 and 2014 were identified. Patients with active endocarditis, acute aortic dissection, end-stage renal disease, or requiring emergency surgery were excluded from the present study. Patients who received an aortic homograft or a Toronto SPV bioprosthesis (St Jude Medical, St Paul, Minnesota) were also excluded. To mitigate the effects of measurable baseline confounders, patients were matched using propensity score matching (Supplemental Figure 1). The vast majority of the Ross procedures (97%) were performed by a single surgeon (T.E.D.) who also performed a majority (60%) of the bioprosthetic AVRs.

SURGICAL TECHNIQUE. Patients in the bioprosthetic AVR group received either a stented porcine or pericardial bioprosthesis, or a stentless porcine bioprosthesis. The operative techniques used in patients who underwent the Ross procedure have been described elsewhere.[17-19] Briefly, the autograft was secured in the aortic position with a modified subcoronary or aortic root inclusion technique, or as a freestanding neo-aortic root.[17] The choice of surgical technique was primarily dictated by the pathology of the aortic root, sizes of the aortic and pulmonary roots, and the anatomy of the coronary arteries. In an attempt to prevent late failure of the pulmonary autograft, surgical reduction of the aortic annulus and/or sinotubular junction was performed before autograft implantation whenever the aortic root was larger than the pulmonary root by more than 2-3 mm.[20]

DATA SOURCES. This observational, single-center, cohort study was approved by the Review Ethics Board of the University Health Network (Toronto, Ontario, Canada) (REB approval #19-6367), and consent was required from all patients. Perioperative data were prospectively entered into an institutional database and extracted for the purpose of this study. Patients' vital status was assessed using vital statistics data from the Office of the Registrar General of Ontario's death registry, a comprehensive database that captures all deaths registered in Ontario. Patients and their cardiologists were contacted by phone or electronically to confirm vital status and to determine the incidence of morbid outcomes at follow-up. In addition, all medical records and echocardiogram reports were reviewed to document valve-related complications (Supplemental Methods).

STUDY OUTCOMES. All outcomes of interest are reported according to the American Association for Thoracic Surgery/European Association for Cardio-Thoracic Surgery/Society of Thoracic Surgeons Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions.[21] The primary outcome of this study was death from any cause and was divided into early mortality (occurring within 30 days of surgery or during the index hospitalization) and late mortality. The cause of death was determined by review of the hospital chart, death certificates, or information from the physician who was caring for the patient at the time of death. Mortality was classified as valve-related, cardiac-related,

or noncardiac. All sudden or unknown causes of death were considered valve-related.

Secondary outcomes of interest included valve reintervention, valve deterioration, endocarditis, thromboembolic events (eg, stroke, transient ischemic attack, and noncerebral systemic embolism), and permanent pacemaker implantation. Valve reintervention was defined as any surgical or percutaneous reintervention on any operated valve. In the Ross group, this includes reinterventions on either the pulmonary autograft or the pulmonary homograft. Valve deterioration was defined as a composite endpoint that included structural and nonstructural valve deterioration, as well as valve deterioration resulting from endocarditis. Structural valve deterioration refers to changes intrinsic to the valve (eg, wear, calcification, or leaflet tear), whereas nonstructural dysfunction is a problem that does not directly involve valve components yet results in dysfunction of an operated valve (eg, entrapment by pannus or paravalvular leak). In addition, nonstructural dysfunction includes development of aortic or pulmonic regurgitation as a result of technical errors, dilatation of the sinotubular junction, or dilatation of the valve annulus. Valve deterioration also includes any recurrent or new insufficiency (moderate or severe) and/or stenosis (mean systolic gradient ≥20 mm Hg) of any operated valve (eg, bioprosthetic aortic valve, pulmonary autograft, or pulmonary homograft). Valve deterioration was determined by periodic echocardiographic surveillance according to the valve-reporting guidelines and confirmed by surgical findings at the time of reoperation, when available.[21] Where applicable, outcomes of interest in the Ross group were reported separately for the aortic and pulmonary positions.

STATISTICAL ANALYSIS. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R. Statistical significance was set at $\alpha = 0.05$. Continuous variables are expressed as mean ± SD when normally distributed and median (IQR) when non-normally distributed. Dichotomous and polytomous variables are expressed in terms of frequency (percentage). Differences in baseline characteristics were assessed using 2-sample Student's *t*-tests for continuous variables and Pearson's chi-square test or Fisher exact test for dichotomous and polytomous variables, as appropriate.

Propensity score matching was used to select comparable cohorts of patients who underwent the Ross procedure versus bioprosthetic AVR. The propensity score was calculated using a multivariable logistic regression model. In the model, the choice of operation (Ross procedure or bioprosthetic AVR) was the dependent variable. The independent variables used for propensity score derivation were as follows: age at surgery, sex, year of surgery, weight, body surface area, preoperative diabetes, congestive heart failure, angina, severe chronic obstructive pulmonary

TABLE 1 Baseline Characteristics of the Matched Cohort

	Bioprosthetic AVR (n = 108)	Ross Procedure (n = 108)	*P* Value
Median age at surgery, y	41 (34-47)	40 (33-47)	0.93
Age at surgery, y			0.82
≤20	2 (2)	3 (3)	
21-30	18 (17)	14 (13)	
31-40	32 (30)	39 (36)	
41-50	40 (37)	38 (35)	
51-60	16 (15)	14 (13)	
Year of surgery			0.29
1990-1995	12 (11)	14 (13)	
1996-2000	23 (21)	29 (27)	
2001-2005	34 (32)	27 (25)	
2006-2010	32 (30)	24 (22)	
2011-2014	7 (7)	14 (13)	
Male	80 (74)	69 (64)	0.11
Median weight, kg	79 (67-91)	76 (63-86)	0.20
Median body surface area, m^2	1.9 (1.8-2.1)	1.9 (1.7-2.0)	0.24
Previous cardiac surgery			
Any previous cardiac surgery	19 (18)	10 (9)	0.11
Previous aortic valve surgery	12 (11)	5 (5)	0.13
Cardiovascular risk factors			
Hypertension	19 (18)	19 (18)	1.00
Dyslipidemia	11 (10)	17 (16)	0.31
Diabetes mellitus	2 (2)	3 (3)	1.00
Current or previous smoker	49 (45)	49 (45)	1.00
Associated conditions			
Chronic obstructive pulmonary disease	1 (1)	1 (1)	1.00
Previous stroke or TIA	1 (1)	3 (3)	0.62
Atrial fibrillation or flutter	1 (1)	1 (1)	1.00
Complete heart block/pacemaker	0 (0)	2 (2)	0.50
Ejection fraction <40%	7 (7)	6 (6)	1.00
Clinical presentation			
Angina pectoris	17 (16)	19 (18)	0.86
Congestive heart failure	11 (10)	11 (10)	1.00
Syncopal episodes	6 (6)	6 (6)	1.00
NYHA functional class			1.00
I	27 (25)	26 (24)	
II	64 (59)	65 (60)	
III	14 (13)	15 (14)	
IV	3 (3)	2 (2)	
Aortic valve lesion			0.28
Stenosis	48 (44)	57 (52)	
Insufficiency	40 (37)	29 (26)	
Mixed lesion	20 (18)	22 (20)	
Bicuspid aortic valve	75 (69)	87 (81)	0.083
Unicuspid/quadricuspid aortic valve	8 (7)	7 (6)	1.00

Values are median (IQR) or n (%).
AVR = aortic valve replacement; NYHA = New York Heart Association; TIA = transient ischemic attack.

TABLE 2 Operative Characteristics and Early Outcomes of the Matched Cohort

	Bioprosthetic AVR (n = 108)	Ross Procedure (n = 108)	*P* Value
Type of bioprosthesis			–
Carpentier-Edwards pericardial valve	22 (20)	–	
Freestyle stentless bioprosthesis	37 (34)	–	
Hancock II porcine valve	40 (37)	–	
Other stented bioprosthesis	9 (8)	–	
Bioprosthesis size, mm			–
19	1 (1)	–	
21	4 (4)	–	
23	19 (18)	–	
25	24 (22)	–	
27	43 (40)	–	
29	17 (16)	–	
Concomitant procedures			
Coronary artery bypass grafting	2 (2)	4 (4)	0.68
Mitral valve surgery	1 (1)	4 (4)	0.12
Ascending aortic replacement	63 (58)	45 (42)	0.06
Median cross-clamp time, min	76 (62-93)	125 (115-138)	<0.001
Median CPB time, min	96 (80-117)	146 (135-160)	<0.001
In-hospital outcomes			
Operative mortality	0 (0)	0 (0)	1.00
Myocardial infarction	2 (2)	4 (4)	0.62
Low output syndrome	2 (2)	4 (4)	0.69
Permanent pacemaker insertion	8 (7)	2 (2)	0.109
Atrial fibrillation	13 (12)	9 (8)	0.42
Ventricular dysrhythmias	3 (3)	4 (4)	1.00
Transient ischemic attack	0 (0)	1 (1)	1.00
Stroke	1 (1)	1 (1)	1.00
Pulmonary complications	4 (4)	3 (3)	1.00
Renal failure	0 (0)	2 (2)	0.50
Sepsis	1 (1)	2 (2)	1.00
Reopening after surgery	7 (7)	7 (7)	0.50
Bleeding	5 (5)	3 (3)	
Tamponade	1 (1)	2 (2)	
Infection	1 (1)	0 (0)	
Redo surgery	0 (0)	1 (1)	
Other	0 (0)	1 (1)	
Median ventilatory support duration, h	5.3 (4.1-6.9)	5.1 (4.1-7.0)	0.89
Median intensive care unit stay, h	24 (20-28)	23 (20-25)	0.96
Predischarge echocardiography[a]			
Mean peak aortic gradient, mm Hg	27.0 ± 9.8	11.5 ± 5.4	<0.001
Mean aortic gradient, mm Hg	14.4 ± 5.3	6.0 ± 3.0	<0.001
Median aortic valve area, cm^2	1.4 (1.3-1.7)	2.0 (1.9-2.3)	<0.001
Median iEOA, cm^2/m^2	0.73 (0.61-0.90)	1.12 (0.88-1.33)	<0.001
Patient prosthesis mismatch[a]			
Moderate: iEOA 0.65-0.85 cm^2/m^2	20 (31)	7 (17)	0.11
Severe: iEOA <0.65 cm^2/m^2	22 (34)	2 (5)	<0.001

Values are n (%), median (IQR), or mean ± SD. [a]Data available for patients operated after 2002.
CPB = cardiopulmonary bypass; iEOA = indexed effective orifice area; other abbreviation as in Table 1.

disease, hypertension, medically treated hyperlipidemia, previous stroke or transient ischemic attack, atrial fibrillation or complete heart block preoperatively, ascending aortic disease, use of aspirin or statins within 7 days before surgery, concurrent coronary artery bypass grafting, concurrent mitral and/or tricuspid valve procedure, and history of cardiac intervention (ie, previous aortic or mitral valve surgery, any other cardiac surgery, or nonsurgical cardiac intervention).

Upon calculation of the propensity score, patients in the Ross group were matched to those in the bioprosthetic AVR group in a 1:1 fashion using a greedy matching algorithm. The matched-paired sample was constructed using a caliper size of 0.2 times the pooled standard deviation of the logit of the propensity score, as well as a precise match of age at surgery (within 5 years) and year of surgery (within 5 years).[22]

The incidence of perioperative adverse events was compared between the matched groups using McNemar's test for paired categorical data. Perioperative continuous variables were compared using paired sample Student's *t*-tests. Survival estimates were obtained using the Kaplan-Meier method, and were compared between the groups using a stratified log-rank test. Administrative censoring was applied when there remained <10% of the original cohort at risk. All other long-term adverse events are presented as cumulative incidence function curves and were analyzed with death as a competing risk using the Fine and Gray methodology.[23] In the case of cardiac-related and/or valve-related death, death from any other cause was considered a competing risk. The cumulative incidence of time-to-event outcomes was compared between the groups while accounting for clustering by matched pair using a stratified Gray's test.[24] Patients who had reoperations or other adverse events continued to be followed and were entered into the survival analysis using an intention-to-treat approach.

RESULTS

PATIENTS AND PROCEDURES. A total of 789 patients aged 16-60 years met the inclusion criteria for this study (Ross, n = 233; bioprosthetic AVR, n = 556). Baseline and operative characteristics of the entire cohort are available in Supplemental Tables 1 and 2, respectively. Propensity score matching yielded 108 pairs of patients. Baseline characteristics of the propensity-matched cohort are presented in **Table 1**. Median age was 41 years (IQR: 34-47 years; range: 17-59 years) and 148 patients (69%) were male. The indication for surgery was aortic stenosis in 105 patients (49%), aortic insufficiency in 69 (32%), and mixed pathology in 42 (19%). A bicuspid aortic valve was seen in 162 patients (75%). All baseline characteristics were similar between the groups (**Table 1**).

Operative characteristics of the propensity-matched cohort are presented in **Table 2**. In the

bioprosthetic AVR group, 71 patients (66%) received a stented bioprosthesis and 37 (34%) a stentless bioprosthesis. The median implanted bioprosthesis size was 27 mm (IQR: 25-27 mm; range: 19-29 mm). In the Ross group, 63 patients (58%) underwent a modified subcoronary or aortic root inclusion technique and 45 (42%) underwent a freestanding neo-aortic root implantation. Aortic cross-clamp and cardiopulmonary bypass times were longer in the Ross group (Table 2).

PERIOPERATIVE OUTCOMES. Perioperative outcomes are presented in Table 2. There was no operative mortality in either group in the matched cohort. The frequency of all early complications was similar between the groups, including myocardial infarction ($P = 0.62$), low output syndrome ($P = 0.69$), permanent pacemaker insertion ($P = 0.11$), atrial fibrillation ($P = 0.42$), medically treated ventricular dysrhythmias ($P = 1.00$), transient ischemic attack ($P = 1.00$), stroke ($P = 1.00$), pulmonary complications ($P = 1.00$), renal failure ($P = 0.50$), sepsis ($P = 1.00$), and reopening after surgery ($P = 0.50$). There were no significant differences in the length of mechanical ventilatory support ($P = 0.89$), nor in the duration of intensive care unit stay ($P = 0.96$). On predischarge echocardiography, patients in the Ross group had lower peak and mean transaortic gradients ($P < 0.001$), larger aortic valve area and indexed effective orifice area ($P < 0.001$), as well as a lower incidence of severe patient-prosthesis mismatch ($P < 0.001$).

LONG-TERM MORTALITY. The mean follow-up duration was 14.5 ± 7.2 years. A total of 28 patients died during follow-up, with 7 deaths (6.5%) occurring in the Ross group and 21 deaths (19.4%) in the bioprosthetic AVR group. All-cause mortality at 20 years was 9.6% in the Ross group versus 25.1% in the bioprosthetic AVR group (Table 3). All-cause mortality was significantly lower after the Ross procedure (Ross vs bioprosthetic AVR HR: 0.35; 95% CI: 0.14-0.90; $P = 0.022$) (Central Illustration).

CAUSE OF DEATH. In the Ross group, late mortality was valve-related in 1 patient (14%) and noncardiac in 6 patients (86%). In the bioprosthetic AVR group, late mortality was valve-related in 16 patients (76%), cardiac but not valve-related in 4 patients (19%) and noncardiac in 1 patient (5%). Late malignancy accounted for all noncardiac deaths in the matched cohort. The cumulative incidence of valve-related death is presented in Table 3 and was lower following the Ross procedure (Ross 1.3% vs bioprosthetic AVR 17.2% at 20 years). Patients undergoing the Ross procedure had lower rates of valve-related mortality (HR: 0.05; 95% CI: 0.01-0.37; $P = 0.004$) (Supplemental Figure 2). The cumulative incidence of cardiac- or valve-related death is presented in Table 3 and was lower following the Ross procedure (Ross 1.3% vs bioprosthetic AVR 23.8% at 20 years). Patients undergoing the Ross procedure

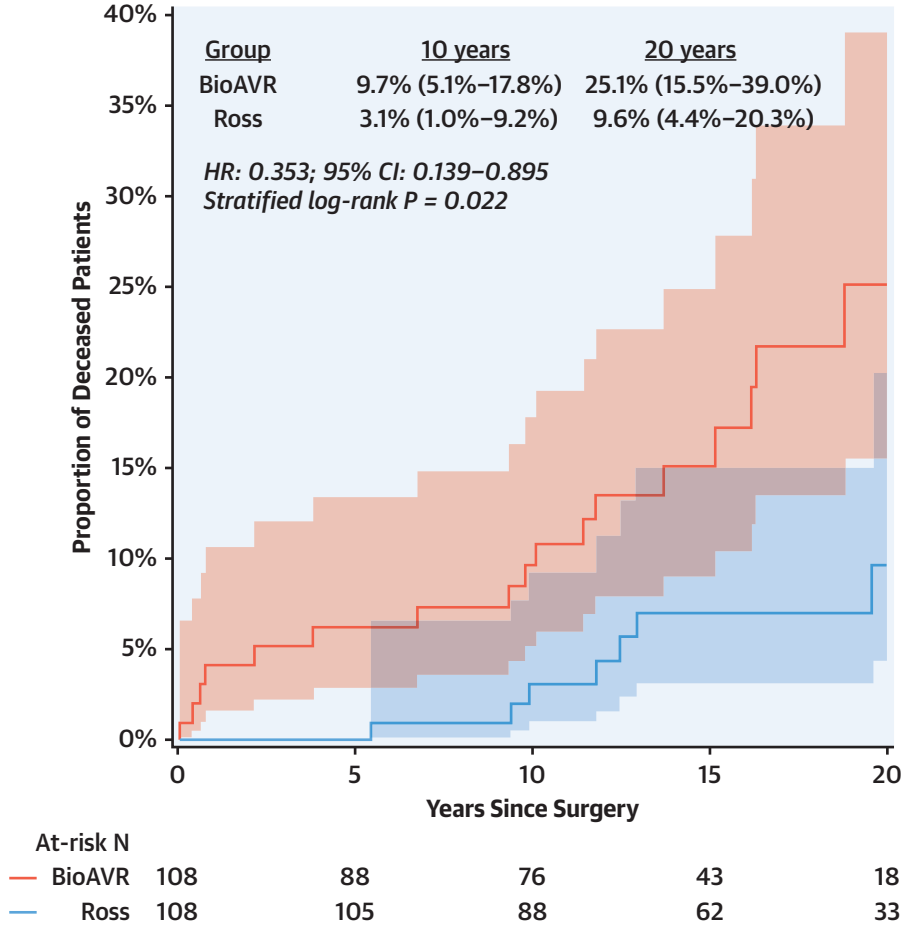
TABLE 3 Cumulative Incidence of Adverse Events at Various Time Intervals

Outcome[a]	No. of Years	Bioprosthetic AVR	Ross Procedure	*P* Value
All-cause mortality	5	6.2 (2.9-13.4)	0.0 (0.0-0.0)	0.028
	10	9.7 (5.1-17.8)	3.1 (1.0-9.2)	
	15	15.1 (9.0-24.9)	7.0 (3.2-15.0)	
	20	25.1 (15.5-39.0)	9.6 (4.4-20.3)	
Valve-related mortality	5	5.2 (2.2-12.2)	0.0 (0.0-0.0)	0.002
	10	7.5 (3.6-15.2)	0.0 (0.0-0.0)	
	15	11.6 (6.4-21.0)	1.3 (0.2-9.1)	
	20	17.2 (9.6-30.9)	1.3 (0.2-9.1)	
Cardiac- or valve-related mortality	5	6.2 (2.9-13.6)	0.0 (0.0-0.0)	<0.001
	10	9.7 (5.2-18.0)	0.0 (0.0-0.0)	
	15	13.8 (8.1-23.6)	1.3 (0.2-9.1)	
	20	23.8 (14.7-38.5)	1.3 (0.2-9.1)	
Operated valve reintervention[b]	5	1.1 (0.2-7.8)	3.8 (1.4-9.9)	0.002
	10	9.4 (4.8-18.2)	5.9 (2.7-12.9)	
	15	37.3 (27.3-51.0)	8.8 (4.5-17.3)	
	20	56.8 (44.7-72.3)	11.3 (5.8-22.0)	
Any valve deterioration[c]	5	2.3 (0.6-8.9)	3.8 (1.4-9.9)	0.001
	10	13.1 (7.6-22.8)	9.0 (4.8-16.8)	
	15	49.4 (38.7-62.9)	12.8 (7.5-21.8)	
	20	63.4 (52.3-76.8)	14.5 (8.7-24.3)	
Structural valve deterioration[d]	5	1.1 (0.2-7.8)	1.9 (0.5-7.6)	<0.001
	10	10.9 (5.9-20.2)	1.9 (0.5-7.6)	
	15	43.2 (32.8-57.0)	3.1 (1.0-9.5)	
	20	58.2 (46.7-72.6)	3.1 (1.0-9.5)	
Nonstructural valve dysfunction[d]	5	2.3 (0.6-8.9)	1.9 (0.5-7.3)	0.62
	10	5.8 (2.5-13.6)	7.0 (3.4-14.4)	
	15	11.9 (6.4-22.3)	9.7 (5.2-18.2)	
	20	14.0 (7.8-25.4)	11.4 (6.3-20.8)	
Endocarditis	5	1.1 (0.2-7.8)	0.0 (0.0-0.0)	0.71
	10	2.3 (0.6-8.9)	2.0 (0.5-8.0)	
	15	3.8 (1.2-11.6)	3.2 (1.0-9.7)	
	20	8.9 (3.6-21.9)	5.5 (2.0-15.6)	
Thromboembolic event	5	3.4 (1.1-10.2)	0.0 (0.0-0.0)	0.012
	10	9.4 (4.9-18.2)	0.0 (0.0-0.0)	
	15	14.1 (8.1-24.7)	0.0 (0.0-0.0)	
	20	21.3 (12.9-35.2)	7.7 (2.5-23.5)	
Permanent pacemaker implantation	5	7.9 (4.1-15.4)	1.9 (0.5-7.3)	<0.001
	10	10.3 (5.7-18.6)	1.9 (0.5-7.3)	
	15	15.9 (9.8-26.1)	1.9 (0.5-7.3)	
	20	18.1 (11.2-29.2)	1.9 (0.5-7.3)	

Values are cumulative incidence (95% CI) %, unless otherwise indicated. [a]The cumulative incidence of long-term adverse events was calculated with death as a competing risk using the Fine and Gray methodology.[23] In the case of cardiac- and/or valve-related death, death from any other cause was considered a competing risk. [b]In the Ross group, it includes any percutaneous or surgical reintervention on the pulmonary autograft and/or pulmonary homograft. [c]Valve deterioration was defined as pulmonary or aortic insufficiency of moderate or severe degree and/or a mean systolic gradient ≥20 mm Hg, respectively. Includes both structural valve deterioration and nonstructural valve dysfunction. In the Ross group, it includes deterioration of the pulmonary autograft and/or pulmonary homograft. [d]In the Ross group, it includes deterioration of the pulmonary autograft and/or pulmonary homograft.

Abbreviation as in Table 1.

CENTRAL ILLUSTRATION **All-Cause Mortality Following the Ross Procedure vs Bioprosthetic Aortic Valve Replacement**



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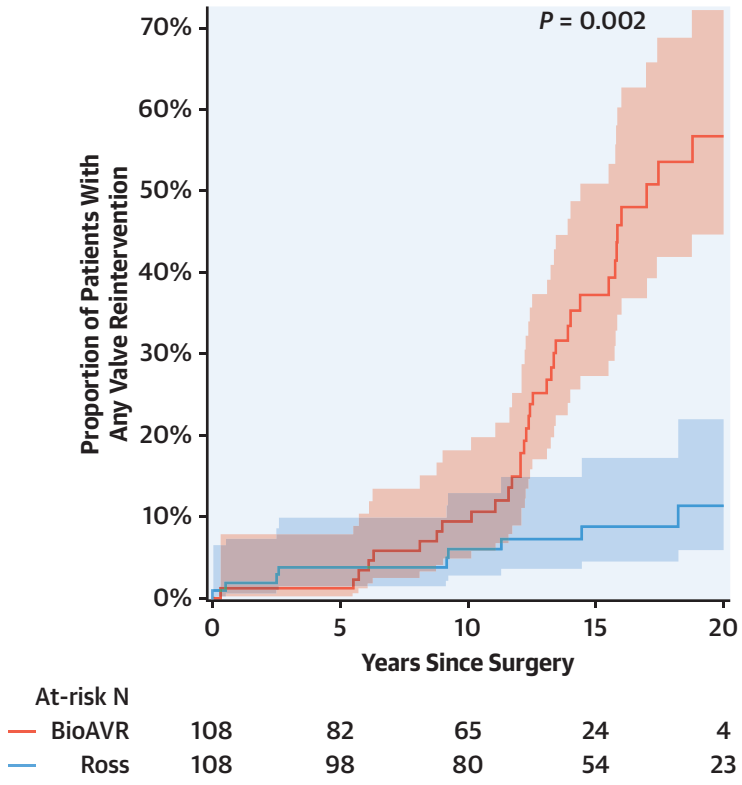
Cumulative incidence of all-cause mortality in the propensity-matched cohort. The **blue and red lines** represent the cumulative incidence estimates for patients who underwent the Ross procedure and bioprosthetic aortic valve replacement, respectively. **Color shading** shows the 95% CIs. The numbers of patients at risk are included below the graph. AVR = aortic valve replacement; BioAVR = bioprosthetic aortic valve replacement.

had lower rates of cardiac- or valve-related mortality (HR: 0.04; 95% CI: 0.01-0.28; $P = 0.001$) (Supplemental Figure 3).

REINTERVENTION. In the Ross group, a total of 15 valve reinterventions occurred (12 surgical and 3 percutaneous) in 11 patients. In the bioprosthetic AVR group, a total of 37 reinterventions (36 surgical and 1 percutaneous) occurred in 35 patients. The cumulative incidence of operated valve reintervention (aortic valve in the bioprosthetic AVR group and aortic or pulmonary valve in the Ross group) is presented in **Table 3** and was lower in the Ross group (Ross 11.3% vs bioprosthetic AVR 56.8% at 20 years). For the Ross group, the incidence of aortic and pulmonary valve reintervention (either surgical or percutaneous) is presented in Supplemental Table 3. Patients undergoing the Ross procedure had lower rates of reintervention (HR: 0.21; 95% CI: 0.10-0.41; $P < 0.001$) (**Figure 1**). There were no operative mortalities among the 11 patients in the Ross group who required valve reintervention. Among the 35 patients in the bioprosthetic AVR group who required valve reintervention, only 1 patient died at reoperation. This patient had developed a large aortic root abscess that extended to the tricuspid valve and involved the entire left main coronary artery.

FIGURE 1 Cumulative Incidence of Reintervention



Cumulative incidence of reintervention in the propensity-matched cohort. The **blue and red lines** represent the first event estimates for patients who underwent the Ross procedure and bioprosthetic aortic valve replacement (BioAVR), respectively. In the Ross group, this includes percutaneous or surgical reintervention on the pulmonary autograft and/or pulmonary homograft. **Color shading** shows the 95% CIs. Death was treated as a competing risk using the Fine and Gray methodology.[23] The numbers of patients at risk are included below the graph.

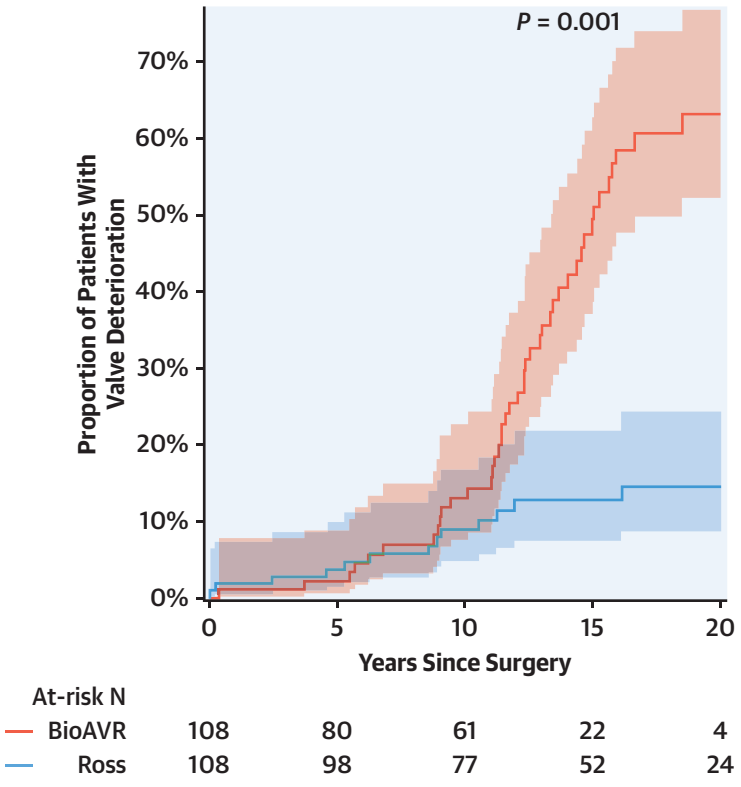
VALVE DETERIORATION. The cumulative incidence of any operated valve deterioration (aortic valve in the bioprosthetic AVR group and aortic or pulmonary valve in the Ross group) is presented in **Table 3** and was lower in the Ross group (Ross 14.5% vs bioprosthetic AVR 63.4% at 20 years). For the Ross group, the incidence of aortic and pulmonary valve deterioration is presented in Supplemental Table 3. Patients undergoing the Ross procedure had lower rates of valve deterioration (HR: 0.25; 95% CI: 0.14-0.45; $P < 0.001$) (**Figure 2**). This was driven by lower rates of structural valve deterioration (HR: 0.08; 95% CI: 0.03-0.21; $P < 0.001$) (Supplemental Figure 4) as rates of nonstructural valve dysfunction were similar between the groups (Ross vs bioprosthetic AVR: HR: 1.04; 95% CI: 0.45-2.39; $P = 0.93$) (Supplemental Figure 5, **Table 3**). Details of valve deterioration are presented in the Supplemental Results.

OTHER ADVERSE EVENTS. The cumulative incidence of other adverse events is presented in **Table 3**. Rates of endocarditis were low and not significantly different between the groups (Ross vs bioprosthetic AVR HR: 0.64; 95% CI: 0.17-2.42; $P = 0.51$) (**Figure 3**). Patients undergoing the Ross procedure had lower rates of thromboembolic events (HR: 0.15; 95% CI: 0.05-0.50; $P = 0.002$) (**Figure 4**). Patients undergoing the Ross procedure also had lower rates of permanent pacemaker implantation (HR: 0.22; 95% CI: 0.07-0.64; $P = 0.006$) (**Figure 5**). Details of these adverse events are presented in the Supplemental Results.

DISCUSSION

Herein, we report a propensity-matched cohort study comparing the long-term outcomes of the Ross procedure vs bioprosthetic AVR. The study's main finding is that the Ross procedure is associated with

FIGURE 2 Cumulative Incidence of Valve Deterioration

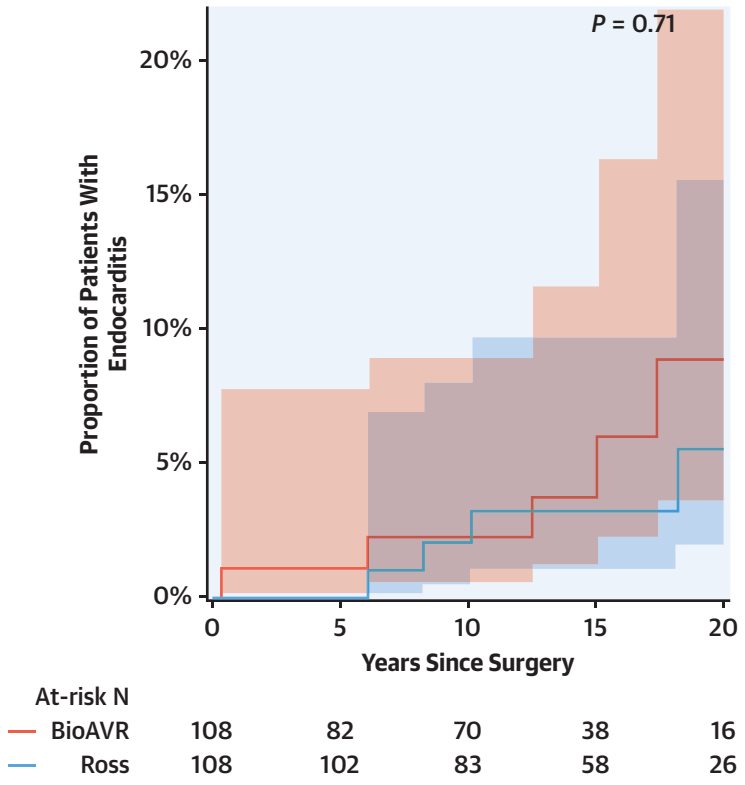


Cumulative incidence of valve deterioration in the propensity-matched cohort. The **blue and red lines** represent the first event estimates for patients who underwent the Ross procedure and BioAVR, respectively. In the Ross group, this includes any deterioration of the pulmonary autograft and/or pulmonary homograft. **Color shading** shows the 95% Cis. Death was treated as a competing risk using the Fine and Gray methodology.[23] The numbers of patients at risk are included below the graph. Abbreviation as in Figure 1.

better long-term survival compared with bioprosthetic AVR, driven by lower rates of valve-related complications. To our knowledge, this is the first report comparing late (>20-year) outcomes between these 2 treatment options in adults.

SURVIVAL. Young and middle-aged adults with aortic valve disease represent a challenging population. The primary goal of AVR in these patients should be to restore their life expectancy to that of the general population. Studies have shown that when implanted in nonelderly adults, bioprosthetic aortic valves fail to restore normal life expectancy.[25-27] In contrast, several contemporary studies have consistently shown that the Ross procedure has the potential to restore survival of young and middle-aged adults with aortic valve disease to that of the general population.[5,6] However, patients in the Ross series tend to be carefully selected. Some have argued that the excellent long-term outcomes observed in these cohorts may be related to favorable patient characteristics rather than the operation itself. We used propensity score matching to obtain comparable cohorts of patients who underwent a Ross procedure or bioprosthetic AVR. Although propensity score matching does not account for potential unmeasured confounders, patients in both groups were young, generally healthy, and presented a low surgical risk. Despite this, we observed a striking difference in long-term survival rate favoring the Ross procedure. Furthermore, the majority of deaths in the Ross group were noncardiac (ie, malignancy in all but 1 patient) whereas in the bioprosthetic AVR group, all but 1 death were cardiac- or valve-related. The observed difference in long-term mortality is likely multifactorial. Importantly, the survival advantage of the Ross procedure cannot be solely explained by the higher rates of reintervention in the bioprosthetic AVR group, as only 1 patient in the entire cohort died at reoperation. Rather, it is likely that the unique biological and hemodynamic properties of the

FIGURE 3 Cumulative Incidence of Endocarditis

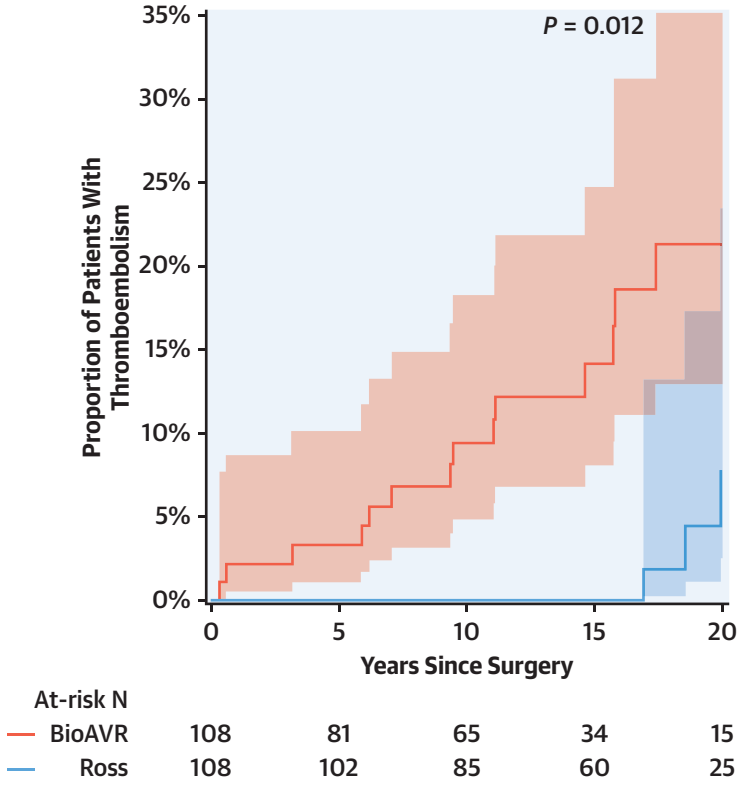


Cumulative incidence of endocarditis in the propensity-matched cohort. The **blue and red lines** represent the first event estimates for patients who underwent the Ross procedure and BioAVR, respectively. In the Ross group, this includes endocarditis of the pulmonary autograft and/or pulmonary homograft. **Color shading** shows the 95% CIs. Death was treated as a competing risk using the Fine and Gray methodology.[23] The numbers of patients at risk are included below the graph. Abbreviation as in Figure 1.

pulmonary autograft may have played a role. Indeed, it is well established that the pulmonary autograft closely approximates the hemodynamics of the native valve.[4] In contrast, stented bioprosthetic valves are by definition obstructive—because of the presence of an intraluminal sewing ring—and lead to varying degrees of patient-prosthesis mismatch.[28] Although less critical in elderly patients, patient-prosthesis mismatch is associated with long-term mortality in young and middle-aged adults.[29] In the present study, the incidence of severe patient-prosthesis mismatch was higher in the bioprosthetic AVR group, and it stands to reason that this factor—along with higher rates of other valve-related complications—would have contributed to the lower survival observed in this group.

REINTERVENTION AND VALVE DETERIORATION. The potential failure of 2 valves—and subsequent risk of reintervention—after the Ross procedure is considered by many to be its Achilles' heel.[11] Similarly, the durability of bioprosthetic AVR in young patients is known to be significantly lower than in their elderly counterparts.[30] In the present study, the risk of reintervention was much higher after bioprosthetic AVR compared with the Ross procedure. This was observed despite the fact that reinterventions in the Ross group included any surgical or percutaneous reintervention on either the autograft or homograft. Furthermore, one-half of the patients in the Ross group presented with preoperative aortic insufficiency, a known predictor of decreased durability after the Ross operation.[19] Despite this, rates of reintervention were low after the Ross procedure (11% at 20 years), in keeping with several contemporary series that have reported a rate of reintervention (for the pulmonary autograft and/or pulmonary homograft) ranging between 0.5% and 1.5% per patient-year.[6] This supports the view—held by our group and others—that with proper technical refinements, the Ross procedure can yield excellent

FIGURE 4 Cumulative Incidence of Thromboembolic Events



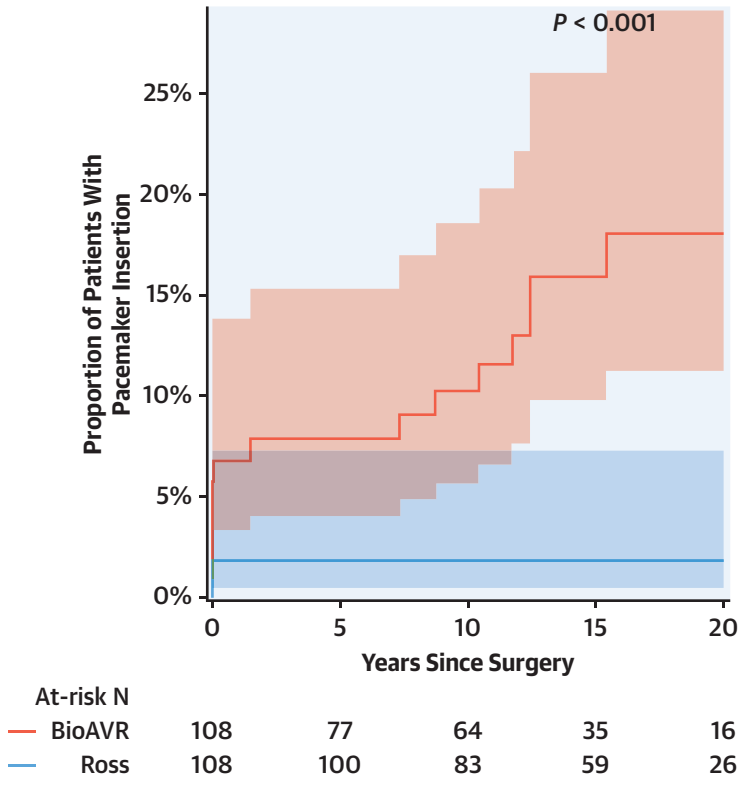
Cumulative incidence of thromboembolic events in the propensity-matched cohort. The **blue and red lines** represent the first event estimates for patients who underwent the Ross procedure and BioAVR, respectively. **Color shading** shows the 95% CIs. Death was treated as a competing risk using the Fine and Gray methodology.[23] The numbers of patients at risk are included below the graph. Abbreviation as in Figure 1.

durability, including in patients with suboptimal anatomical substrates.[31] Furthermore, no operative mortality was observed among the 11 patients in the Ross group who required reintervention. As such, our findings also argue against the notion that the Ross procedure invariably exposes patients to a wide range of complex reoperations associated with substantial mortality.

In the present study, the rates of structural valve deterioration observed in the bioprosthetic AVR group were comparable to those reported in the literature.[32-34] Bioprosthesis size is an important predictor of structural valve deterioration, with smaller prostheses degenerating at a faster rate.[35] The most frequently implanted prosthesis size in this study was 27 mm, and that more than three-quarters of patients received a prosthesis measuring 25 mm or greater. Nonetheless, half of the implanted bioprostheses had deteriorated by 15 years.

Despite their limited durability, bioprosthetic aortic valves are increasingly being used in young and middle-aged adults.[1,2] This trend has been fueled by the promise of valve-in-valve TAVR to treat structural bioprosthetic valve deterioration. This strategy is predicated on the notion that the surgical risk of reoperation is the main driver of mortality in young patients who undergo bioprosthetic AVR. Our findings do not support this notion. Indeed, in the present study, despite high rates of reintervention, there was only 1 death at reoperation in the bioprosthetic AVR group. Furthermore, this death occurred in a patient who developed an aortic root abscess and would therefore not have been a candidate for valve-in-valve TAVR. Thus, it appears that other factors—for example, patient-prosthesis mismatch—drive the excess mortality observed in the bioprosthetic AVR group. Such factors would not be addressed by valve-in-valve TAVR. As a result—and given the lack of data

FIGURE 5 Cumulative Incidence of Permanent Pacemaker Implantation



Cumulative incidence of permanent pacemaker implantation in the propensity-matched cohort. The **blue and red lines** represent the first event estimates for patients who underwent the Ross procedure and BioAVR, respectively. **Color shading** shows the 95% CIs. Death was treated as a competing risk using the Fine and Gray methodology.[23] The numbers of patients at risk are included below the graph. Abbreviation as in Figure 1.

on the durability of valve-in-valve TAVR in non-elderly patients—we strongly caution against any prospective strategy in which a young patient is advised to undergo bioprosthetic AVR with the hope of performing valve-in-valve TAVR if the first valve fails.

OTHER ADVERSE EVENTS. There were no differences in the incidence of perioperative adverse events, despite the fact that patients in the Ross group had longer cardiopulmonary bypass and aortic cross-clamp times. This confirms previous observations that in dedicated centers, the long-term benefits of the Ross procedure do not come at the cost of an increased early risk.[36]

Although less thrombogenic than mechanical valves, bioprosthetic valves present a small but continuous hazard of thromboembolic complications.[33,34] In young patients with a long anticipated life expectancy, this continuous hazard translates into a non-negligible cumulative lifetime risk. In this study, the rate of thromboembolic complications in the bioprosthetic AVR group was 1% per patient-year and was significantly higher than that observed in the Ross group. This higher incidence of thromboembolic complications may have contributed to the inferior survival observed in bioprosthetic AVR group. The higher rates of permanent pacemaker implantation observed after bioprosthetic AVR could also have contributed to the excess mortality seen in this group. Indeed, permanent pacemaker implantation after surgical AVR is not a trivial complication and is associated with reduced long-term survival.[37] This higher incidence of pacemaker requirement could be explained by the rigid nature of the bioprosthetic valve sewing ring, which can compress the conduction system as opposed to the soft autograft. It could also be partially explained by higher rates of reintervention in the bioprosthetic AVR group, as repeat cardiac surgery is a known risk factor for pacemaker implantation.[38]

STUDY LIMITATIONS. The main limitations of this study are its observational design and the fact that treatment allocation was nonrandomized. Although propensity score matching mitigates the impact of a potential selection bias, it does not entirely alleviate it and does not consider potential unmeasured confounders. To obtain the most comparable cohorts possible, we used a stringent matching algorithm that resulted in a relatively small sample size. In addition, this was a single-center study performed at a tertiary academic hospital and the majority of the procedures were performed by a single surgeon. The generalizability of our findings will therefore need to be confirmed by other groups. Finally, our assessment of echocardiographic data at follow-up was limited to the incidence of valve deterioration, defined as a mean systolic gradient ≥20 mm Hg or moderate/severe aortic insufficiency. As such, we did not evaluate the progression of transaortic gradients over time.

These limitations notwithstanding, the present report represents the longest available comparative longitudinal study examining long-term outcomes of the Ross procedure versus bioprosthetic AVR. The excellent availability of comprehensive long-term follow-up make the results relevant and add important comparative data to the current body of literature.

CONCLUSIONS

In this propensity-matched cohort study, the Ross procedure was associated with better long-term survival and lower rates of reintervention, valve deterioration, thromboembolic events, and permanent pacemaker implantation compared with bioprosthetic AVR. If these findings are reproduced in other specialized centers with sufficient expertise, the Ross procedure may be considered the preferred option for selected young and middle-aged adults undergoing AVR.

ACKNOWLEDGMENTS The authors thank Karamvir Deol and Valerie Ojha for their help with data collection.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Ouzounian is partially supported by the Antonio & Helga DeGasperis Chair in Clinical Trials and Outcomes Research at University Health Network; and has consulting agreements with Cryolife, Terumo Aortic, Medtronic, and Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In young and middle-aged patients with aortic valve disease, the Ross procedure is associated with better clinical outcomes than bioprosthetic AVR.

TRANSLATIONAL OUTLOOK: Further studies are needed to explain the excess mortality in patients undergoing bioprosthetic AVR and confirm the generalizability of the survival advantage associated with the Ross procedure in other surgical centers.

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KEY WORDS aortic valve replacement, bioprosthesis, pulmonary autograft, Ross procedure, young adults

APPENDIX For supplemental text, figures, and tables, please see the online version of this paper.