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JACC STATE-OF-THE-ART REVIEW

Ross Procedure in Adults for Cardiologists and Cardiac Surgeons

JACC State-of-the-Art Review

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ABSTRACT

The ideal aortic valve substitute for young and middle-aged adults remains elusive. The Ross procedure (pulmonary autograft replacement) is the only operation that allows replacement of the diseased aortic valve with a living substitute. However, use of this procedure has declined significantly due to concerns over increased surgical risk and potential long-term failure of the operation. Several recent publications from expert centers have shown that in the current era, the Ross procedure can be performed safely and reproducibly in appropriately selected patients. Furthermore, an increasing body of evidence suggests that the Ross procedure is associated with better long-term outcomes compared with conventional aortic valve replacement in young and middle-aged adults. In this paper, the authors review the indications and technical considerations of the Ross procedure, describe its advantages and drawbacks, and discuss patient selection criteria. Finally, the authors provide a comprehensive synthesis of the current Ross published reports to enable cardiologists and surgeons to make appropriate decisions for their patients with aortic valve disease. (J Am Coll Cardiol 2018;72:2761–77)

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ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

BAV = bicuspid aortic valve

TAVR = transcatheter aortic valve replacement

Aortic valve replacement (AVR) is the most common form of valve surgery, with approximately 85,000 procedures performed annually in the United States (1). Replacement options include bioprosthetic valves, mechanical valves, aortic valve homografts, or a pulmonary autograft (i.e., the Ross procedure). The choice of aortic valve substitute has important implications for long-term outcomes, and it must be carefully tailored to the individual patient (2). In North America, the majority of patients undergoing AVR are elderly. The choice of an adequate valve substitute in these patients is often straightforward, as surgical or transcatheter bioprosthetic valves are associated with excellent outcomes in this age group (3). By contrast, young and middle-aged adults with aortic valve disease represent a challenging population. Due to a longer life expectancy, these patients are exposed to a higher cumulative lifetime hazard of valve-related complications. Furthermore, compared with older patients, many young and middle-aged adults wish to pursue higher levels of physical activity after their operation. In addition to restoring normal survival and minimizing the risk of valve-related complications, the ideal aortic valve substitute in these young patients should therefore also provide durable hemodynamic properties that permit an active lifestyle with excellent quality of life.

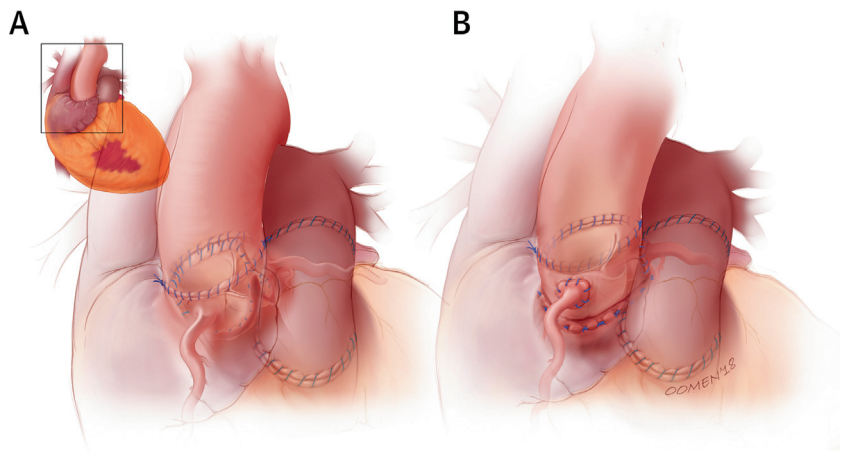
The ideal aortic valve substitute remains elusive. Mechanical prostheses are the most frequently implanted valves in young and middle-aged adults primarily because they are easy to implant and are durable (4). However, these valves are thrombogenic and require lifelong anticoagulation, exposing patients to a continuous hazard of thromboembolic and hemorrhagic complications (5). The management of anticoagulation requirements of a mechanical valve is also problematic in women of childbearing age contemplating pregnancy (6–8). By contrast, bioprosthetic valves and aortic valve homografts alleviate the need for lifelong anticoagulation. However, when implanted in young adults, these biological substitutes are associated with predictable higher rates of structural valve deterioration requiring reoperation (9–11). Although several studies—both randomized and observational—have demonstrated superior outcomes with the use of mechanical valves versus bioprosthetic valves in young and middle-aged adults (12–14), there has been a significant increase in the use of bioprostheses for AVR over the last 2 decades in this age group (4,15). The promise of transcatheter valve-in-valve therapy has been in part responsible for accentuating the trend of implanting bioprosthetic valves in younger patients, although this trend preceded the introduction of transcatheter aortic valve replacement (TAVR). Although valve-in-valve TAVR represents an exciting avenue, the impact of this approach on long-term survival and valve-related complications has not been determined, such that a 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 cannot be recommended at this time, based on best available evidence (16). Furthermore, contemporary data suggest that neither prosthetic valves—biological or mechanical—nor aortic valve homografts can restore normal life expectancy in young and middle-aged adults undergoing AVR (9,17–20). Importantly, several studies have shown that the excess mortality observed is inversely proportional to patient age at the time of surgery (i.e., the youngest patients have the largest excess mortality), presumably because of the higher functional demand and longer exposure to potential valve-related complications in young adults with prosthetic valves (21–23). Transcatheter aortic valve replacement has been used with increasing frequency for aortic stenosis, though the durability of TAVR valves is unknown, especially given potential concerns about subclinical leaflet thrombosis (24–28), which has implications in younger patients.

Against this backdrop, there has been renewed interest within the cardiovascular community regarding the Ross procedure (1). Indeed, in recent years, numerous studies showing excellent long-term outcomes with the Ross procedure have been published (9,29–33), leading to renewed interest for this operation. Herein, we present a primer on various aspects of the Ross procedure and review the contemporary evidence supporting its use in selected young and middle-aged adults with aortic valve disease. We delineate patients who stand to benefit the most from this operation, and those in whom it should be avoided. Finally, we critically examine current practice guidelines as they pertain to the Ross procedure.

HISTORICAL BACKGROUND

Replacement of a diseased aortic valve with a pulmonary autograft—and placement of a homograft in the pulmonary position—was first described in humans by Donald Ross in 1967 (34), based on previous experimental work by Lower et al. (35). The popularity of this operation peaked in the early 1990s, followed by a gradual decline in use over the subsequent 2 decades. By 2010, the Ross procedure

FIGURE 1 The Ross Procedure



(A) Subcoronary technique; **(B)** full root replacement technique (Online Videos 1, 2, 3, 4 and 5). Regardless of the technique chosen, the pulmonary autograft should be inserted within the annulus of the native aortic root (Online Video 3).

accounted for <0.1% of all AVRs performed in the United States (36). The 2 most important factors driving this decline in popularity were the increased complexity of the operation, which increases operative risk in low-volume centers (36), as well as the potential long-term failure of 2 valves (37), which exposes patients to complex reoperations (38).

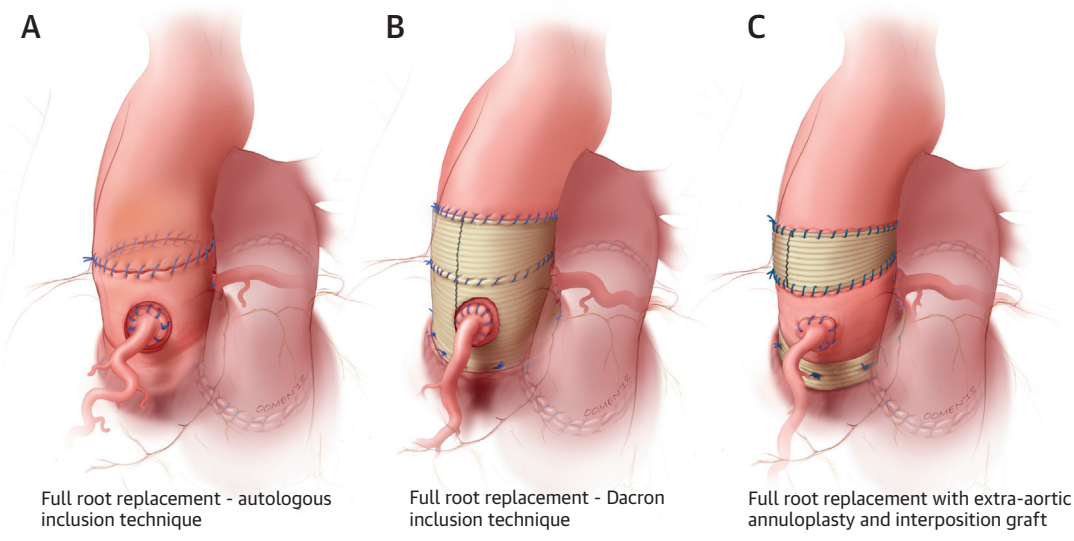
Nevertheless, numerous centers worldwide persisted with the operation while closely analyzing long-term outcomes. This led to improved understanding of pulmonary autograft adaptation to systemic conditions, as well as mechanisms of pulmonary autograft and homograft failure. Together, this resulted in iterative improvements and tailoring of the surgical technique, and translated into excellent reported durability in contemporary series from high-volume, experienced centers (9,29–33). This accumulating body of evidence showing favorable long-term outcomes with the Ross procedure—in conjunction with the suboptimal outcomes associated with conventional AVR in young and middle-aged adults—has led to a renewed interest in the operation.

TECHNICAL CONSIDERATIONS

The Ross procedure represents an "evolutionary tale" (39). Although the operation was described >50 years ago, it has continued to evolve through gradual understanding of the complex anatomic and physiological processes involved in its execution (39). An in-depth discussion on the technical subtleties of the Ross procedure is beyond the scope of this review. However, a few salient points should be highlighted. The Ross procedure is a more complex operation than standard AVR with prosthetic valves. Some of the steps that are required in the Ross procedure—but not conventional AVR—include dissection of the aortic root, mobilization of the coronary arteries (Online Video 1), harvesting of the pulmonary autograft (Online Video 2), proximal autograft anastomosis (Online Video 3), coronary artery reimplantation (Online Video 4), and pulmonary homograft implantation (Online Video 5). Each of these steps carries numerous pitfalls that must be carefully avoided. Detailed descriptions of the steps involved in conducting the Ross procedure are available elsewhere (40,41).

Implantation of the pulmonary autograft in the aortic position can be performed using 2 main techniques: the subcoronary and root replacement techniques (**Figures 1A and 1B**). Various studies have compared the relative benefits and drawbacks of these 2 strategies (32,42). In his original description of the procedure, Donald Ross described implantation of the autograft in the subcoronary position (**Figure 1A**) (34). Because the aortic and pulmonary roots often have different dimensions and commissural distribution—particularly in patients with aortic insufficiency or bicuspid/unicuspid aortic valves—this approach can be technically challenging. As a result, over the years, numerous surgeons performing the Ross procedure have shifted toward a full root replacement technique (**Figure 1B**). However, implanting the pulmonary autograft as a full

FIGURE 2 Technical Modifications of the Ross Procedure Aimed at Mitigating Late Autograft Dilatation and Insufficiency



(A) Autologous inclusion technique; **(B)** Dacron inclusion technique; **(C)** extra-aortic annuloplasty and interposition graft (Online Video 6).

root exposes the unsupported pulmonary sinuses to systemic pressures, potentially leading to late pulmonary autograft dilatation (43). To avoid this complication, a number of technical modifications have been proposed, including implanting the pulmonary autograft within the patient's own aortic root (33,41)—the so-called inclusion technique (**Figure 2A**). More recently, reinforcement of the pulmonary autograft with a prosthetic Dacron graft has been proposed to prevent late dilatation, but data on the long-term results of this approach are lacking (44) (**Figure 2B**).

Another common mechanism of failure of the Ross procedure is annular dilatation with subsequent late autograft insufficiency. Patients who undergo the Ross procedure for aortic insufficiency, and those who present with a dilated annulus (>26 mm) preoperatively are at highest risk of this complication (45). Reducing the size of the aortic annulus with suture plication can mitigate early dilatation (46), but does not prevent late failure (45). Systematic performance of an extra-aortic annuloplasty using a circular Dacron ring in patients with aortic insufficiency may be more effective in reducing the risk of late annular dilatation, but longer follow-up is needed to confirm this hypothesis (47) (**Figure 2C**, Online Video 6). Regardless of the technique chosen, it is critical to implant the pulmonary autograft within the native aortic annulus. Indeed, unlike the aortic root—which has a true fibrous annulus—the pulmonary valve is directly attached to infundibular muscle around its entire circumference. Once harvested, this muscle is devascularized and provides no structural support, hence the importance of trimming this infundibular muscle and implanting the pulmonary autograft deep within the left ventricular outflow tract to ensure native aortic annular support to the autograft (40) (Online Video 3).

In patients with progressive native ascending aortic dilatation, the pulmonary autograft may dilate at the level of the sinotubular junction, leading to autograft insufficiency. To mitigate this risk, some advocate proactive management of the ascending aorta in patients with an ascending aortic diameter >38 to 40 mm at the time of surgery. This can be done by interposing a short Dacron graft between the autograft and the ascending aorta, which stabilizes the sinotubular junction (48,49) (**Figure 2C**). Any subsequent increase in ascending aortic diameter would not impact sinotubular junction diameters.

PROPOSED ADVANTAGES OF THE PULMONARY AUTOGRAFT AS A VALVE SUBSTITUTE

THE LIVING AORTIC ROOT. The aortic root is a sophisticated structure composed of 4 main components: the aortic annulus, the aortic leaflets, the sinuses of Valsalva, and the sinotubular junction. Although the aortic valve is often regarded as a

passive structure that opens and closes in response to transvalvular pressure gradients, clinical and experimental evidence has demonstrated that each component of the aortic root is a living dynamic structure acting together to form a cohesive functional unit. Functional studies have shown that the aortic root undergoes a series of complex 3-dimensional deformations throughout the cardiac cycle. These expansile and contractile deformations—which occur at the level of the annulus, sinuses of Valsalva, and sinotubular junction—play an important role in minimizing aortic cusp stress, promoting laminar flow during systole, and enhancing coronary flow reserve in systole and diastole (50).

Examination of the microstructure of aortic valve leaflets reveals additional complexity and sophistication of the aortic root. A monolayer of valvular endothelial cells line the ventricular and aortic sides of the cusps, whereas as a mixed population of valvular interstitial cells (i.e., smooth muscle cells, fibroblasts, and myofibroblasts) comprise the extracellular matrix in the body of the cusp (51). Valvular endothelial cells sense and respond to changes in shear stress by a mechanism called mechanotransduction, translating mechanical stimuli into biological signals. Similarly, endothelium-dependent signals can modulate the mechanical properties of aortic valve leaflets in response to their humoral environment (52). In addition, valvular interstitial cells possess both secretory and contractile properties, allowing generation, maintenance, and repair of the extracellular matrix, which is mainly composed of elastin, collagen, and glycosaminoglycans (51). Finally, microscopic evaluation of aortic valve leaflets reveals a rich network of intrinsic nerves, which are thought to play a significant role in the modulation of aortic valve responses to different hemodynamic and humoral stimuli (53).

These observations on the complex architecture and function of the aortic root serve as the basis for the Ross principle: that replacement of the diseased aortic valve with a living substitute that preserves the structural and functional unity of the neo-aortic root translates into better long-term clinical outcomes. The pulmonary autograft is the only substitute that guarantees long-term viability of the neo-aortic valve. By contrast, all other aortic valve substitutes represent non-living tissue. Even homovital homografts (i.e., unprocessed homografts, harvested under sterile conditions, kept in tissue-culture medium, and inserted at the first available opportunity) once thought to maintain long-term viability, have been shown to become acellular a few weeks after implantation.

ADAPTIVE REMODELING OF THE PULMONARY AUTOGRAFT. The viability of the pulmonary autograft allows it to undergo adaptive remodeling when implanted in the aortic position. This adaptive remodeling allows the pulmonary autograft to mimic the highly sophisticated anatomy and function of the native aortic root. This remodeling is largely mediated by valvular endothelial and interstitial cells, which undergo activation and phenotypic changes when exposed to the systemic circulation (54). For example, endothelial cells of pulmonary autografts implanted in the aortic position start expressing EphrinB2, a marker of left-sided, but not right-sided, heart valve endothelium. This induced expression of EphrinB2 leads to extracellular matrix remodeling, in the form of increased smooth muscle actin production (54). This is 1 of several mechanisms by which pulmonary autograft leaflets, when placed in the aortic position, adapt to the mechanical stresses of their new environment by means of reversible phenotypic changes, and adopt characteristics of normal aortic valve leaflets. As a result, pulmonary autograft leaflet thickness and breaking strain become more akin to those of native aortic valve leaflets (55).

HEMODYNAMIC PERFORMANCE. In contrast to mechanical and bioprosthetic valves that fix the annulus and are inherently obstructive, the pulmonary autograft preserves the mobility of all components of the aortic root. This contributes to the superior hemodynamic performance observed after a Ross procedure compared with conventional AVR (56). In a recent systematic review and meta-analysis, the Ross procedure was associated with significantly lower mean aortic gradients at discharge and follow-up compared with conventional AVR (56). These findings are potentially important, because even small reductions in mean aortic gradients have been shown to significantly reduce the risk of persistent or recurrent congestive heart failure in patients undergoing AVR (57). Furthermore, it has been suggested that due to its ability to more closely replicate normal physiology, the Ross procedure may result in improved coronary flow reserve (58) and superior left ventricular mass regression (59) compared with standard AVR, although these hypotheses have yet to be adequately tested with comparative studies.

In a study assessing flow patterns using magnetic resonance imaging 10 or more years after various types of aortic root replacement procedures, the pattern and velocity of blood flow through pulmonary autografts most closely resembled that of normal control subjects compared with aortic homografts and

bioprosthetic roots (60). Hemodynamic performance early after the Ross procedure is similar to that of aortic homografts, with mean and peak transaortic gradients <10 mm Hg in the vast majority of patients (56). However, gradients remain consistently low at long-term follow-up after the Ross procedure because the pulmonary autograft rarely shows any signs of calcification or degeneration, whereas many patients develop high transaortic gradients following bioprosthesis or homograft implantation. A randomized controlled trial comparing the Ross procedure to aortic homograft replacement demonstrated important differences in mean transaortic gradients at long-term follow-up: 5 mm Hg in the Ross group versus 30 mm Hg in the homograft group at 13 years (9). In addition to lower gradients at rest that approximate normal aortic valve function, the Ross procedure is associated with excellent hemodynamic performance with exercise, a benefit that is particularly important for this patient population of predominantly active young adults. Several studies have shown that gradients across the pulmonary autograft do not increase with maximal exercise, closely mirroring the hemodynamic performance of native aortic valves in healthy individuals (61–63).

AVOIDANCE OF LIFELONG ANTICOAGULATION. Another major advantage of the Ross procedure is avoidance of lifelong anticoagulation and the attendant continuous hazard of valve thrombosis, thromboembolism, and bleeding. Large cohort studies with >20 years of follow-up in patients who are chronically anticoagulated after mechanical AVR have documented a linearized rate of thromboembolic complications or major bleeding ranging from 1.1% to 4.5% per patient-year (64,65). Because direct oral anticoagulant agents are contraindicated in patients with mechanical valves, warfarin remains the only choice for anticoagulation. Warfarin has a narrow therapeutic window that exposes patients to thrombotic and bleeding complications when the international normalized ratio is infra- or supra-therapeutic, respectively (66,67). Although self-monitoring of oral anticoagulation (68) and newer generation, potentially less thrombogenic, mechanical valves requiring lower international normalized ratio targets (69) may reduce some of this risk, thromboembolic and hemorrhagic complications will remain an unavoidable drawback to the use of mechanical valves. Avoidance of these complications with the Ross procedure may translate into better cost-effectiveness (70). Although bioprostheses have long been thought to obviate the need for anticoagulation, increased recognition of subclinical leaflet thrombosis following implantation of bioprosthetic valves is challenging this widely held practice (24–28). Emerging data linking subclinical leaflet thrombosis to neurological complications and early valve deterioration have reinforced the notion that patients with bioprosthetic valves should be anticoagulated for at least 3 months after surgery—as recommended by current practice guidelines (71,72)—as both warfarin and direct oral anticoagulant agents have been shown to prevent and treat subclinical leaflet thrombosis (24–28).

Furthermore, the Ross procedure is an especially attractive option for women contemplating pregnancy who require AVR, as prosthetic valves pose major risks in these patients. The risk of thrombosis is significantly increased during pregnancy in women with mechanical valves, and the various options for anticoagulation all pose significant risks to the mother and fetus (6–8,73). Although bioprosthetic valves eliminate this risk, their limited durability in this age group and the potential for accelerated degeneration with pregnancy limit their usefulness in this patient population (6,73).

QUALITY OF LIFE. Young and middle-aged adults who undergo AVR are often more physically and professionally active than their older counterparts. As a result, quality of life is an important consideration in these patients. Due to excellent hemodynamic performance and avoidance of anticoagulation, patients who undergo the Ross procedure enjoy enhanced quality of life compared with those who undergo mechanical AVR, evidenced by higher scores on both the physical and psychological health subscales of the short-form health survey (74–76). By contrast, more than one-half of patients after mechanical AVR report being disturbed by the valve sound and a similar number express concern about potential bleeding complications related to anticoagulation (75). These issues are of little to no concern in patients undergoing the Ross procedure, in whom no anticoagulation or antiplatelet therapy is required (unless otherwise indicated). Similarly, in the randomized controlled trial comparing the Ross procedure to aortic homograft replacement, patients in the Ross group had significantly better short-form health survey quality-of-life scores (9).

POTENTIAL PITFALLS OF THE ROSS PROCEDURE

Despite its proposed benefits, the Ross procedure has remained limited to a few expert centers worldwide. Barriers to widespread adoption include concerns over increased operative risk, technical complexity, the potential long-term failure of 2 valves, and

complexity of reoperation with an attendant high mortality at reintervention.

TECHNICAL COMPLEXITY AND OPERATIVE RISK. The Ross procedure is undoubtedly a more complex operation than conventional AVR. In a study reporting on all Ross procedures performed between 1994 and 2010 across the Society of Thoracic Surgeons' database, Reece et al. (36) reported a 3-fold increase in operative mortality compared with conventional AVR. It is important to point out that the increased mortality was observed in predominantly low-volume centers. Indeed, the median annual number of Ross procedures performed per center was <1, and only 6 of the 231 centers included in this study performed ≥5 Ross procedures per year (36). These suboptimal outcomes are therefore not surprising, given the well-established inverse relationship between surgical volumes and outcomes of cardiac surgical procedures, especially more complex procedures such as aortic root replacement (77). In contrast to the findings by Reece et al., several series from experienced, high-volume centers, have shown that the Ross procedure can be performed with an operative mortality ranging from 0.3% to 1.1%, similar to that of conventional prosthetic AVR (32,33,78,79). The disparity between excellent outcomes in high-volume centers and increased mortality in low-volume centers underscores the importance of surgeon expertise and adequate surgical volumes to achieve excellent outcomes with the Ross procedure.

POTENTIAL LONG-TERM FAILURE OF 2 VALVES. The potential long-term failure of 2 valves (aortic and pulmonary) in a patient initially presenting with single-valve disease has long been considered the Achilles' heel of the Ross procedure (37). When failure requiring reintervention occurs, it involves the pulmonary autograft in most cases (29). Several mechanisms of failure of the pulmonary autograft have been described (43,80), including primary leaflet failure and dilatation of the annulus, sinuses of Valsalva, or sinotubular junction. Certain groups have reported unacceptable rates of autograft dilatation requiring reoperation (37). Studies from these same groups have shown that in patients who experience autograft dilatation leading to aortic insufficiency after the Ross procedure, most of the increase in neo-aortic root diameter has already occurred by the time patients are discharged from hospital, suggesting technical issues (46,80).

Proponents of the Ross procedure have argued that technical refinements lessen the risk of early and late autograft dilatation. Techniques that may improve long-term autograft function and protect against failure include modifications such as suturing the autograft in an intra-annular position thereby allowing the native aortic annulus to support and stabilize the neo-aortic root, if the native aortic annulus is not itself dilated. Furthermore, cumulative experience has allowed identification of patients at higher risk of autograft dilatation and failure: patients presenting with aortic insufficiency, a dilated aortic annulus, a dilated ascending aorta, and pulmonary/aortic size mismatch (45). Additional technical modifications such as annular and/or sinotubular junction stabilization, as well as synthetic or autologous reinforcement of the autograft (**Figure 2**) may be important in minimizing risk of failure in this subset of patients. Furthermore, recent evidence suggests that increased systemic and pulmonary arterial pressures are independently associated with premature degeneration of the autograft and homograft, respectively (81). Thus, irrespective of the technique chosen, all patients undergoing the Ross procedure should be screened for the presence of systemic or pulmonary hypertension. Importantly, strict blood pressure control is mandatory in the first 6 to 12 months after surgery to avoid early autograft dilatation, and instead promote autograft adaptation. Target systolic blood pressure should be <110 to 115 mm Hg using beta-blockade as first-line therapy to reduce autograft wall stress and allow positive remodeling of the neo-aortic root.

A number of contemporary series have demonstrated excellent long-term durability of the pulmonary autograft using the aforementioned technical refinements and adjunctive measures (29–33). Beside autograft failure, patients are also at risk of homograft dysfunction, manifesting predominantly as progressive valvular or supravalvular pulmonary stenosis—most frequently at the level of the distal anastomosis—driven by what appears to be an inflammatory process (82). Pulmonary insufficiency, due to homograft leaflet prolapse, occurs to a lesser extent (80,83). Pre-operative pulmonary hypertension—especially when it is severe and/or irreversible—is a risk factor for premature homograft degeneration. On the other hand, patients with mild pulmonary hypertension may be at lower risk of autograft dilatation because of "pre-conditioning" of the pulmonary root. Pulmonary homograft stenosis follows a bimodal presentation, with an early hazard phase (first 12 to 18 months) followed by a low and constant long-term hazard phase (82). Therefore, it is imperative to examine gradients across the homograft at the 1-year echocardiographic evaluation. Most often, early increases in transpulmonary gradients subsequently plateau and remain stable for many years with

a minority of patients requiring reintervention (either for symptoms or right ventricular dilatation/dysfunction). In addition to echocardiography, right heart catheterization can be useful to ascertain pulmonary gradients, and cardiac magnetic resonance imaging helps better evaluate right ventricular structure and function. Thus, homograft failure is rarely an acutely life-threatening problem, as right ventricular volume and/or pressure overload is usually tolerated for a long time before requiring reintervention. In the current era, homograft failure is increasingly treated with percutaneous approaches (84), using predominantly the Melody valve (Medtronic, Dublin, Ireland) (85) or the Sapien system (Edwards Lifesciences, Irvine, California) (86).

The durability of homografts used in the context of the Ross procedure can be enhanced by systematic oversizing of the homograft. Ideally, the implanted homograft should always be larger than the pulmonary autograft, and rarely <25 mm in diameter. Using this strategy, the Toronto group recently reported 93% freedom from homograft reoperation at 20 years in a cohort of 212 patients undergoing the Ross procedure (29). However, nearly one-half of the cohort demonstrated varying degrees of homograft dysfunction on echocardiography, and it is likely that many of these patients will require reintervention in the future.

The type of conduit chosen to reconstruct the right ventricular outflow tract may play a role in determining durability. Pulmonary homografts are more durable than aortic homografts in the pulmonary position (87). For many years, cryopreserved homografts have been considered the best available option (88). More recently, decellularized pulmonary homografts have garnered increasing interest (89), but longer follow-up is required to determine whether these conduits will achieve superior durability compared with cryopreserved homografts (90). In recent years, tightening regulations surrounding human tissue harvesting and banking have led to a worldwide shortage in pulmonary homografts. In this context, stentless xenograft roots such as the Freestyle porcine aortic root (Medtronic) have been used as an alternative to reconstruct the right ventricular outflow tract during the Ross procedure (91). Long-term data on the durability of aortic xenografts in the pulmonary position are lacking (92).

Given the continuous hazard of pulmonary autograft and/or homograft failure following the Ross procedure, lifelong follow-up and monitoring are warranted. Patients should be followed with annual or biennial clinical and echocardiographic evaluation, focusing on aortic and pulmonary valve function (i.e., mean gradient and degree of insufficiency) and dimension (particularly of the neo-aortic root) to screen for dilatation. We do not recommend routine CT scan follow-up unless otherwise indicated.

Indications for reintervention on a failing autograft are identical to those for native aortic valve insufficiency. In the setting of autograft dilatation with a competent neo-aortic valve, the diameter threshold for surgical reintervention remains unclear because of the scarcity of reported cases of autograft dissection. Surgery should be considered when the autograft diameter reaches 50 mm, especially if the likelihood of autograft valve-sparing is high. Reintervention on the homograft is indicated when there is evidence of pulmonary valve dysfunction combined with symptoms of right ventricular failure and/or evidence of right ventricular dilatation/dysfunction on imaging.

COMPLEXITY OF REOPERATIONS. Despite the aforementioned measures aimed at enhancing the durability of the Ross procedure, a small subset of patients who undergo this operation will invariably require reintervention. Unlike reoperations after standard AVR, reoperative surgery after a Ross procedure is more complex and may be associated with a higher operative risk, especially in cases requiring reintervention on both valves. Stulak et al. (38) reported on a series of 56 patients who underwent reoperation after a failed Ross and concluded that "a broad spectrum of complex reoperations may be required after the Ross procedure." The authors reported 1 in-hospital mortality (1.8%) and 4 additional deaths (7.1%) within a median follow-up of 8 months (38). Nevertheless, other series have shown better results. Sievers et al. (32) reported data on 1,779 patients in the German Ross Registry from 1990 to 2013. Of these, 147 patients had a total of 175 Ross-related reoperations (84 on the autograft, 69 on the homograft, and 22 combined). Mortality at reoperation occurred in 5 patients (2.9%) (32). Similarly, Mastrobuoni et al. (31) reported their single-center 20-year experience with the Ross procedure in 306 consecutive patients. There were 39 late reinterventions, with 1 death at reoperation (2.6%). In the Toronto experience of 212 patients with a median follow-up of 14 years, there was no mortality at reintervention among 17 patients who required reoperation after a Ross procedure, including 14 patients who underwent reintervention on the pulmonary autograft (79). A similar volume-outcome relationship likely exists for Ross reoperations as it does for the original Ross operation, and may in part explain the improved results with reoperation in these expert centers.

TABLE 1 Summary of Contemporary Series Reporting Long-Term Outcomes (≥15 Years) of the Ross Procedure in Adults

First Author (Year) (Ref. #)	Design	Patients, n	Mean Age, yrs	BAV, %	Pure AI/ Mixed AS-AI, %/%	Mean Follow-Up, yrs	Operative Mortality, %	10-yr Survival, %	15-yr Survival, %	20-yr Survival, %	10-yr Freedom From Reintervention, %*	15-yr Freedom From Reintervention, %*	20-yr Freedom From Reintervention, %*
El-Hamamsy et al. (2010) (9)	RCT	108	38	49	45/27	10.2	0.9	97	95†	–	95	94	–
David et al. (2014) (29)	Single-center	212	34	72	36/13	13.8‡	0.4	98	94	94‡	AG 97 HG 98	AG 93 HG 96	AG 82 HG 93
Da Costa et al. (2014) (101)	Single-center	414	31	50	39/31	8.2	2.7	92	89†	–	90	81	–
Andreas et al. (2014) (100)	Single-center	246	29	75	40/31	10.0‡	1.6	95	91†	–	88	81	–
Skillington et al. (2015) (33)	Single-center	322	39	92	32/22	9.8	0.3	98	97	97†	94	93	–
Mastrobuoni et al. (2016) (31)	Single-center	306	42	59	31/0	10.6‡	2.3	97	88	–	–	75	–
Sievers et al. (2016) (32)	Multicenter (prospective)	1,779	45	65	22/52	8.3	1.1	96	90†	–	91	83	–
Martin et al. (2017) (30)	Single-center	310	41	73	19/7	15.1‡	1.3	94	92	84	93	86	70
Sievers et al. (2018) (128)	Single-center	630	45	78	24/–	12.5‡	0.3	95	87	73†	AG 96 HG 97	AG 94 HG 94	AG 90 HG 91

*Includes any reintervention on the pulmonary autograft and/or pulmonary homograft. †Survival equivalent to age- and sex-matched general population. ‡Median (rather than mean) follow-up.
AG = autograft; AI = aortic insufficiency; AS = aortic stenosis; BAV = bicuspid aortic valve; HG = homograft; RCT = randomized controlled trial.

Collectively, these data suggest that reoperations after failure of the Ross procedure, although inherently more complex than reoperation after standard AVR, can be carried out with good results in experienced centers. Furthermore, the pulmonary autograft valve can often be salvaged at the time of reintervention, thus retaining its benefits as a living valve substitute. This can be achieved through isolated valve repair (when autograft failure is due to leaflet pathology) (93), valve-sparing root replacement (when autograft failure is due to dilatation of the neosinuses) (94–96), or by placing the pulmonary autograft back into the native pulmonary position, the so-called "Ross reversal" procedure (97). Using these techniques, several groups have reported rates of successful autograft salvage ranging from 50% to 90% (31,93,97–99).

LONG-TERM CLINICAL OUTCOMES OF THE ROSS PROCEDURE

COHORT STUDIES WITH LONG-TERM FOLLOW-UP. Although focusing primarily on in-hospital outcomes and early survival might be appropriate for elderly patients undergoing AVR, these metrics are incomplete when evaluating outcomes of AVR in young adults who, because of their longer life expectancy, are exposed to a continuous hazard of valve-related complications for many years. As previously mentioned, both mechanical and bioprosthetic valves are associated with excess long-term mortality compared with the matched general population when implanted in young and middle-aged adults (17,20–23). By contrast, several contemporary cohort studies with long-term follow-up have demonstrated excellent survival well into the second post-operative decade after the Ross procedure (9,29–33,100–102). The majority of these studies have reported a survival that was similar to that of the age- and sex-matched general population. A summary of contemporary series with ≥15 years of follow-up is presented in **Table 1**. Aside from these Ross series, no other study on AVR in young and middle-aged adults has demonstrated restored survival compared with the matched general population, including highly selected series of patients undergoing conventional AVR (17,19). Although this may be partly explained by careful patient selection, it is more likely attributable to the unique hemodynamic, biological, and adaptive features of the living pulmonary autograft.

Large contemporary series from expert centers have consistently demonstrated excellent long-term survival—ranging from 87% to 95% at 15 years—whereas rates of freedom from Ross-related reintervention have been more variable—ranging from 75% to 94% at 15 years (**Table 1**). This variability may be explained by different patient selection criteria (e.g., proportion of patients with aortic insufficiency) and different surgical techniques between studies.

Nevertheless, considering that the mean age of patients in long-term Ross series ranges from 34 years to 44 years, a 1% to 2% per patient-year reoperation rate compares very favorably to any biological valve substitute (11).

A major advantage of the Ross procedure is the low rate of long-term valve-related complications. A meta-analysis of observational studies reporting on outcomes of the Ross procedure in adults has shown low linearized rates of autograft deterioration (0.78% per patient-year), homograft deterioration (0.55% per patient-year), autograft endocarditis (0.26% per patient-year), homograft endocarditis (0.20% per patient-year), and thromboembolism, bleeding, or valve thrombosis (0.36% per patient-year) (103).

COMPARATIVE STUDIES. There is a growing number of comparative studies between the Ross procedure and other AVR options in adults. In a randomized controlled trial comparing the Ross operation with aortic homograft replacement in an "all-comer" cohort of 216 young adults (mean age 39 years; mean follow-up 11 years; completeness of follow-up 97%), survival in the Ross group was significantly higher compared with the homograft group (95% vs. 78% at 13 years; hazard ratio: 0.22; $p = 0.006$) (9). The survival difference favoring the Ross procedure was even more impressive considering that 42% of patients in the Ross group had had previous cardiac surgery (most of which were homograft aortic root replacements) and 8% were operated on for active endocarditis. In addition, the 13-year survival after the Ross procedure was identical to that of the age- and sex-matched British general population (**Figure 3A**).

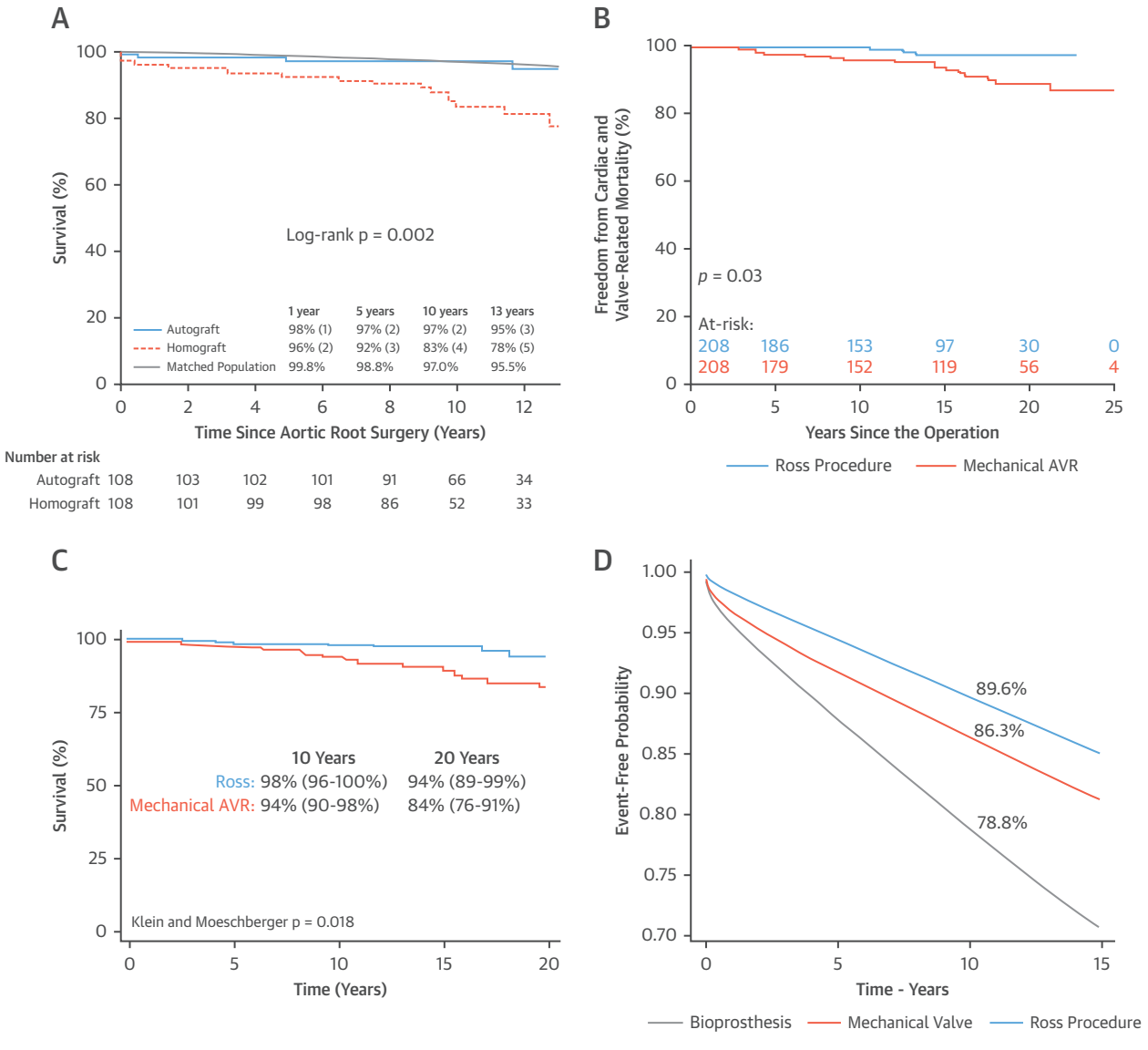
The longest available longitudinal study comparing outcomes of the Ross procedure versus mechanical AVR comes from a propensity-matched cohort of 416 young and middle-aged adults (208 per group) who underwent surgery between 1990 and 2014 (mean age 37 years; mean follow-up 14 years; completeness of follow-up 98%) (79). Although early outcomes and overall survival were equivalent between groups, Ross patients had a significantly higher freedom from cardiac- and valve-related mortality (97% vs. 89% at 20 years; hazard ratio: 0.22; $p = 0.03$) (**Figure 3B**). Surprisingly, long-term freedom from reintervention was not different between the groups (87% in the Ross group vs. 94% in the mechanical AVR group at 20 years; hazard ratio: 1.86; $p = 0.19$), despite the fact that 43% of patients in the Ross group had aortic insufficiency pre-operatively, and that reinterventions in the Ross group included any surgical or percutaneous reintervention on the aortic and/or pulmonary position. Not surprisingly, patients in the Ross group enjoyed higher freedom from thromboembolic and/or major hemorrhagic complications (99% vs. 80% at 20 years; hazard ratio: 0.09; $p < 0.001$).

More recently, Buratto et al. (104) reported a risk-adjusted analysis comparing the outcomes of 392 patients undergoing the Ross procedure with those of a contemporaneous cohort of 1,928 patients undergoing isolated mechanical AVR over a 25-year period (1992 to 2016). Among 275 propensity-score matched pairs (mean age 44 years; mean follow-up 10 years), 30-day mortality was similar (Ross 0%; mechanical AVR 0.4%; $p > 0.99$), but patients in the Ross group were found to have superior survival at 20 years (94% vs. 84%; $p = 0.018$) (**Figure 3C**). This study is the first large propensity-matched analysis to demonstrate higher freedom from all-cause mortality with the Ross procedure versus mechanical AVR (105).

No direct comparison between the Ross procedure and bioprosthetic AVR has been published to date. Sharabiani et al. (2) examined early and late survival and freedom from reintervention in 872 unselected young adults (age 17 to 40 years) who underwent AVR in the United Kingdom between 2000 and 2012. Of these, 26% underwent a Ross procedure, 54% mechanical AVR, and 17% bioprosthetic AVR. Data were extracted from the National Congenital Heart Disease Audit of the United Kingdom, and were linked to the census of the Office of National Statistics to obtain long-term outcomes. Using a Bayesian dynamic survival model and a combination of propensity score matching, restriction matching, and stochastic augmentation to match patients from the 3 groups, the authors demonstrated that the Ross procedure was associated with superior event-free survival compared with mechanical AVR, which itself was superior to bioprosthetic AVR (**Figure 3D**). Of the 3 types of surgical AVR examined in this study, the Ross procedure was the only one that resulted in survival similar to that of the matched general population (2).

Bioprosthetic valves have been associated with worse outcomes in young adults compared with mechanical AVR (12–14). However, recent practice trends have challenged this assumption (106,107). Given the increased usage of bioprosthetic valves in the current era (4)—and with the emergence of valve-in-valve TAVR as a proposed option for the treatment of bioprosthetic valve degeneration (108)—a comparative study between the Ross procedure and bioprosthetic AVR in young adults is needed.

FIGURE 3 **Outcomes of the Ross Procedure Versus Conventional AVR**

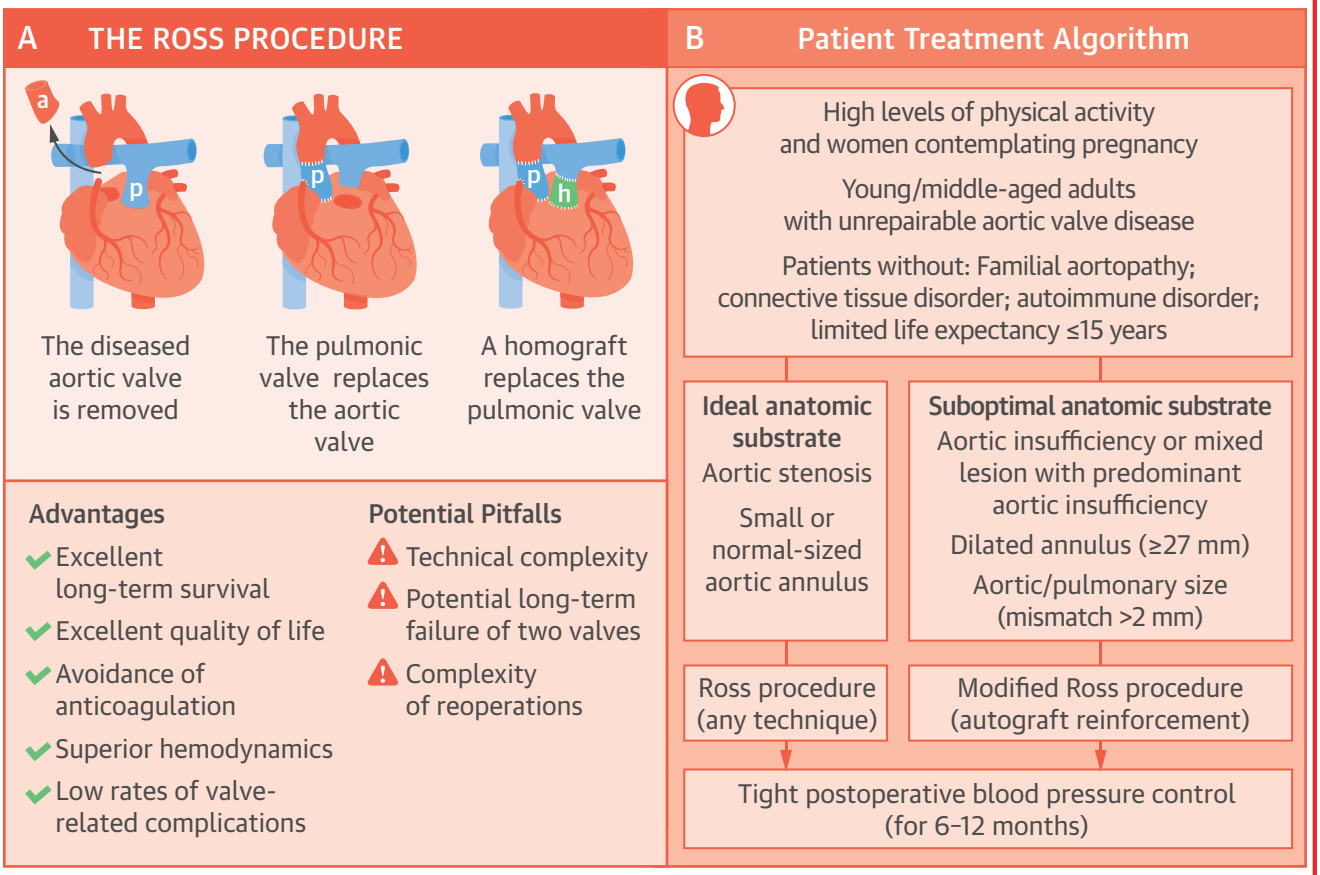


(A) Ross procedure versus aortic homograft. Reproduced with permission from El-Hamamsy et al. (9). **(B)** Ross procedure versus mechanical aortic valve replacement (AVR) (Canadian study). Reproduced with permission from Mazine et al. (79). **(C)** Ross procedure versus mechanical aortic valve replacement (Australian study). Reproduced with permission from Buratto et al. (104). **(D)** Ross procedure versus mechanical and biological aortic valve replacement. Reproduced with permission from Sharabiani et al. (2).

PATIENT SELECTION

The clinical experience accumulated over the last few decades has led to better defined predictors of long-term benefit and success after the Ross procedure, as well as risk factors for failure (**Central Illustration**). It bears emphasizing that the Ross procedure is reserved for patients with non-repairable, non-spareable aortic valves. Otherwise, isolated aortic valve repair or valve-sparing root replacement should be favored (109). The ideal candidate for the Ross operation is a young or middle-aged (<50 years old), otherwise healthy patient with aortic stenosis and a small or normal-sized aortic annulus (110). In these patients, the Ross procedure is expected to provide a durable solution—particularly in women (45)—and

CENTRAL ILLUSTRATION **Algorithm for Patient Selection for the Ross Procedure**



Mazine, A. et al. J Am Coll Cardiol. 2018;72(22):2761–77.

(A) Advantages and pitfalls of the Ross procedure; **(B)** indications and contraindications for the Ross procedure. This proposed algorithm remains to be further validated and supported by practice guidelines. a = aortic; p = pulmonic; h = homograft.

restore normal life expectancy with excellent quality of life and a low rate of valve-related complications. For patients 50 to 60 years of age, the Ross procedure should be reserved to those most likely to derive a benefit from the operation. Specifically, these are patients with a projected life expectancy of ≤15 years, an active lifestyle, favorable anatomy, no major concomitant cardiac disease, and few comorbidities.

The main predictors of late failure of the pulmonary autograft include pre-operative aortic insufficiency, an aortic annulus ≥27 mm, and aortic/pulmonary size mismatch (45). As detailed in the *Technical Considerations* section, numerous technical modifications and adjunct measures have been proposed to mitigate the risk of late failure in these patients, who present a suboptimal anatomic substrate. Despite these mitigating measures, these patients are unlikely to achieve as durable a result with the Ross procedure as ideal candidates. Furthermore, because many of the proposed technical modifications—for example, inclusion of the autograft in a Dacron tube—limit the expansibility and motion of the pulmonary autograft, some of the theoretical benefits of the operation are lost, potentially decreasing the benefits derived from the operation. These considerations notwithstanding, it is noteworthy that all large contemporary Ross series with long-term follow-up have included a significant proportion of patients with pure aortic insufficiency—ranging from 20% to 50%—and yet rates of reoperation have been low, ranging between 1% to 2% per patient-year (**Table 1**). In a consecutive series of 129 patients (mean age 35 years; mean follow-up 10 years; completeness of follow-up 98%) presenting with bicuspid aortic valve (BAV) and pure aortic insufficiency, Poh et al. (111) reported a 20-year freedom

from reoperation and/or greater-than-mild aortic insufficiency of 85%, demonstrating that the Ross procedure (inclusion technique) can be carried out with good durability including in patients with aortic insufficiency. Therefore, in light of the known results with prosthetic AVR in young patients, a tailored Ross procedure in patients with aortic insufficiency may still be the best option.

The Ross procedure is contraindicated in patients with a familial aortopathy or connective tissue disease, regardless of aortic valve phenotype, due to a prohibitive risk of autograft dilatation and failure. By contrast, BAV—in the absence of inherited aortopathy or connective tissue disease—is not a contraindication to the Ross procedure (112). There were early theoretical concerns about a potentially higher risk of autograft dilatation in patients with BAV undergoing the Ross procedure, analogous to the phenomenon of BAV aortopathy (113,114). These concerns were put to rest following the publication of various studies showing no significant differences in the biomechanical properties of pulmonary autografts harvested from patients with bicuspid versus tricuspid aortic valves (115), as well as clinical studies demonstrating equivalent outcomes up to 19 years after the Ross procedure, regardless of aortic valve phenotype (112). In fact, the majority (50% to 90%) of patients who undergo the Ross procedure have congenital aortic valve disease, predominantly BAV (**Table 1**), and yet the rates of late aortopathy or dissection have been exceedingly low in large series with long-term follow-up (2,9,30–32,79). It is important to emphasize that BAV is a heterogeneous disorder, and a small subset of patients with BAV—usually presenting with annuloaortic ectasia and aortic insufficiency—have an associated inherited aortopathy. The Ross procedure is contraindicated in these patients. Finally, certain patients with BAV present with a dilated ascending aorta (≥40 mm), without evidence of connective tissue disease or familial aortopathy. These patients should undergo proactive management of the ascending aorta with an interposition Dacron graft at the time of the Ross procedure to stabilize the sinotubular junction and thus minimize the risk of late aortic insufficiency and autograft failure (**Figure 2C**).

Other contraindications to the Ross procedure include any co-existing condition that limits life expectancy to <15 years (such as chronic renal failure on dialysis or radiation-induced valve disease), as well as certain autoimmune disorders (e.g., lupus erythematosus or rheumatoid arthritis) because of concerns over autograft valve durability. Data on outcomes of the Ross procedure in the setting of rheumatic valve disease are scarce, and its use for this indication is controversial, particularly in the active phase (116). By contrast, there is increasing acceptance for a role for the pulmonary autograft in the management of aortic valve infective endocarditis, where avoidance of prosthetic material is desirable. When used in this setting, the Ross procedure carries an acceptable risk of early mortality and excellent long-term survival free from recurrent endocarditis (117–119).

TABLE 2 Summary of Current Guideline Recommendations on the Ross Procedure

Year Guideline (Ref. #)	Recommendation	Class of Recommendation	LOE	First Author (Year) (Ref. #)
2014 AHA/ACC (120)*	Replacement of the aortic valve by a pulmonary autograft (the Ross procedure), when performed by an experienced surgeon, may be considered for young patients when VKA anticoagulation is contraindicated or undesirable	IIb	C	Mokhles et al. (2012) (129) Charitos et al. (2012) (130) El-Hamamsy et al. (2010) (9)
2017 ESC/EACTS (72)	No mention of the Ross procedure	—	—	—

*No change in the 2017 AHA/ACC focused update (71).

ACC = American College of Cardiology; AHA = American Heart Association; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; LOE = Level of Evidence.

CURRENT GUIDELINES

Despite a convergence of cumulative evidence showing excellent long-term outcomes associated with the Ross procedure, and its potential superiority over other forms of AVR in young adults—including data from a randomized controlled trial (9), a systematic review and meta-analysis (103), as well as several large cohort studies with long-term follow-up (9,29–33,100,101,104)—practice guidelines from major societies either omit to mention the Ross procedure as a surgical option (72), or place it as a Class IIb recommendation (120). This is explained by the potential for increased operative risk and hazard of late failure. However, we believe that the recent evidence demonstrating the long-term clinically relevant benefits of the Ross operation should be considered in future iterations of these guidelines, with the same caveat as with other complex surgical procedures, that these should be performed in high-volume experienced centers (**Table 2**).

HOW TO SET UP A SUCCESSFUL ROSS PROGRAM

The Ross procedure is a complex operation, with wide variability in published results. In addition to

patient selection and appropriate technique, a successful Ross program hinges on a number of factors including a systematic surgical technique tailored to patient pathology, adequate surgical volumes, prior expertise in aortic root surgery, availability of mentorship, and patient management by an experienced and dedicated multidisciplinary team (121). This also entails remote monitoring of blood pressure and prompt therapeutic adjustments during the first 6 to 12 months after surgery to ensure positive remodeling of the pulmonary autograft. Several studies have shown that under the right circumstances, the Ross procedure can be performed safely and reproducibly, with excellent early and late outcomes (9,29,30,32,33), including by early-career surgeons (122).

The learning curve of the Ross operation should be mitigated through special training programs—ideally sponsored by established cardiovascular societies—and careful proctoring, in a process akin to that which led to the widespread dissemination of TAVR. Furthermore, close monitoring of short- and long-term outcomes is of the utmost importance for any group wishing to start a Ross program. Ideally, such monitoring should be performed within large multicenter prospective registries, such as the German Ross Registry, or the more recent Canadian Ross Registry, which currently includes >450 patients from 5 centers that have started Ross programs since 2010.

In recent years, there have been calls to concentrate complex cardiovascular surgical procedures into high-volume centers of excellence, in an effort to standardize care and optimize outcomes (123–125). Though the definition of centers of excellence is an area of debate, there is little doubt that young and middle-aged adults who may be eligible for the Ross procedure should be referred to high-volume aortic centers with expertise in complex aortic root surgery (126). This would help avoid the mistakes of the past and ensure optimal patient selection and surgical technique.

FUTURE DIRECTIONS

One randomized controlled trial comparing the Ross procedure with aortic homograft replacement has been published to date (9), yet no randomized comparison between the Ross procedure and prosthetic AVR has been performed. The challenges involved in conducting a randomized controlled trial comparing the Ross procedure with conventional AVR are significant. First, the Ross procedure is performed in a small number of centers and by a limited number of surgeons necessitating a long recruitment period. Second, because young and middle-aged adults who undergo AVR are typically otherwise healthy, a long follow-up period would be required to detect any significant difference in outcomes. Third, the implications of each treatment arm on the patient's life are drastically different (lifelong anticoagulation with mechanical valves, risk of early degeneration with bioprostheses, need for long-term monitoring of both the aortic and pulmonary valves with the Ross procedure). As a result, patients, cardiologists and, a fortiori, surgeons often have strong biases in favor or against different AVR options, so that many are unwilling to participate in randomization. Some of these challenges may be overcome with the use of expertise-based randomized controlled trials (127), although the need for such costly studies to address the benefits of the Ross procedure has been questioned in light of the presented evidence from long-term cohort studies. Nevertheless, continued systematic follow-up of these cohorts is critical to evaluate outcomes into the third decade after the Ross procedure.

CONCLUSIONS

The ideal aortic valve substitute in young and middle-aged adults remains elusive. The pulmonary autograft is the only aortic valve substitute that confers long-term viability to the aortic root. This has translated into the Ross procedure being the only AVR intervention that has shown the potential to restore long-term survival, matching that of the age- and sex-matched general population. In appropriately selected patients, the Ross procedure can be performed safely and reproducibly—with excellent long-term freedom from death and valve-related complications—in centers of excellence where high volumes of aortic root surgery are performed. The accumulating evidence favoring the Ross procedure over other forms of AVR in young and middle-aged adults raises the question of whether the role of this operation in the surgical armamentarium should be revisited, while stressing the importance of concentrating care of these patients in expert centers.

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

APPENDIX For supplemental videos, please see the online version of this paper.