From the Department of Thoracic and Cardiovascular Surgery

Saarland University Hospital, Homburg/Saar

Director: Univ.-Prof. Dr. med. Hans-Joachim Schäfers

The Ross Procedure: Outdated Or Up-To-Date?

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Submitted by: Karen Beatrix Abeln

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Dean: Univ.-Prof. Dr. med. Michael D.Menger

Reviewer: Univ.-Prof. Dr. med. Hans-Joachim Schäfers

Prof. Dr. med. Hashim Abdul-Khaliq

Abbreviations

AR	Aortic valve regurgitation
AS	Aortic valve stenosis
BAV	Bicuspid aortic valve
BSA	Body surface area
CABG	Coronary artery bypass graft
ESC/EACTS	European Society of Cardiology/~ Association for Cardio-Thoracic Surgery
EuroScore	**Euro**pean **S**ystem for **C**ardiac **O**perative **R**isk **E**valuation
I.E.	Infective endocarditis
i.v.	Intravenous
LAD	Left ventricular descending coronary artery
LVEDD	Left ventricular end diastolic diameter
LVESD	Left ventricular end systolic diameter
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
NYHA	New York Heart Association
PFO	Patent foramen ovale
PTFE	Polytetrafluoroethylene
RVAD	Right ventricular assist device
RVOT	Right ventricular outflow tract
RVPA	Right ventricular pulmonary artery
STJ	Sinotubular junction
TTE	Transthoracic echocardiogram
TEE	Transesophageal echocardiogram
UAV	Unicuspid aortic valve

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In dedication to my grandmother

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I. Abstract

Background: The Ross procedure uses a patient's own pulmonary valve to replace the diseased aortic valve. It is an alternative to conventional valve replacement especially in the younger patient population. This patient group, and patients with contraindications against conventional valve replacements, may benefit from a Ross procedure if it can be performed safely and with adequate durability. The aim of this study was to assess the reproducibility, survival, and durability of pulmonary autograft replacements in our institution.

Methods: Between December 1995 and December 2020, 202 patients (male 73%; mean age 35.4±11.4 years) underwent the Ross procedure at our institution. Eight patients were lost to follow-up and were excluded from the long-term analysis. One patient was intraoperatively converted to a Bentall procedure. Five patients underwent a cylinder Ross procedure and 196 patients a full root replacement. Aortic valve morphology was unicuspid in 87 (42%), bicuspid in 76 (39%), and tricuspid in 25 (12%) patients. Fourteen patients had undergone valve replacement previously, and the morphology could not be determined.

Results: Overall, 202 patients were analyzed, 10 patients died, and 8 patients were lost to follow-up. The pulmonary valve was replaced with a homograft in 156 patients, with a bovine jugular vein graft in 35 patients, and in 10 patients with a stentless biological valve prosthesis.
Mean myocardial ischemia time was 91±20minutes; mean perfusion time was 125±33 minutes. Fifty-eight patients required a concomitant procedure during their Ross operation, most commonly ascending aortic replacement (n=31). There was one perioperative death, no myocardial infarction, and one neurological complication. A permanent pacemaker was implanted in four cases (2%). There was one late death from a non-cardiac cause. Twenty-three patients required reinterventions after the Ross procedure (pulmonary autograft n=16, pulmonary conduit n= 7). A valve-sparing procedure was performed in the majority of cases. At 10 years, survival was 93%, similar to that of the age- and gender-matched German population. Freedom from autograft reintervention at 10 years was 89% and freedom from RV-PA reintervention was 93%. Median and mean follow-up were 5.7 [range 0.1 - 24.4] years and 7.8± 7 years. Clinical and echocardiography follow-up were 95% and 92% complete (1467 patient-years).

Conclusion: The Ross procedure represents a safe and valid option in young and middle-aged patients. It is associated with low perioperative morbidity and mortality. The probability of reinterventions is low and long-term survival is excellent, similar to that of the age - and gender-matched general German population.

II. Introduction

A. Historical development

The first replacement of an aortic valve, using a mechanical caged ball valve, was performed by Harken in 1960 [1]. These first valves, however, caused significant hemolysis and were associated with increased systolic gradients [1]. Subsequently, mechanical heart valves were progressively improved leading to the concept of the mechanical bileaflet valve [2], which has remained the standard of care to date (St Jude Medical Regent) [3]. The main disadvantages of these mechanical valves continue to be the risk of thromboembolism and the need for lifelong anticoagulation, with its associated peril of hemorrhagic complications [4]. Hence, certain patient groups, such as children and women of childbearing age, were per se excluded from its application.

In order to avoid these issues alternative valve prostheses were developed.
Barratt-Boyes introduced the concept of human aortic homografts for aortic valve replacement in 1960 [5]. In 1967, Ross used a patient's own pulmonary valve for aortic valve replacement [6], based on previous experimental work by Lower et al [7].

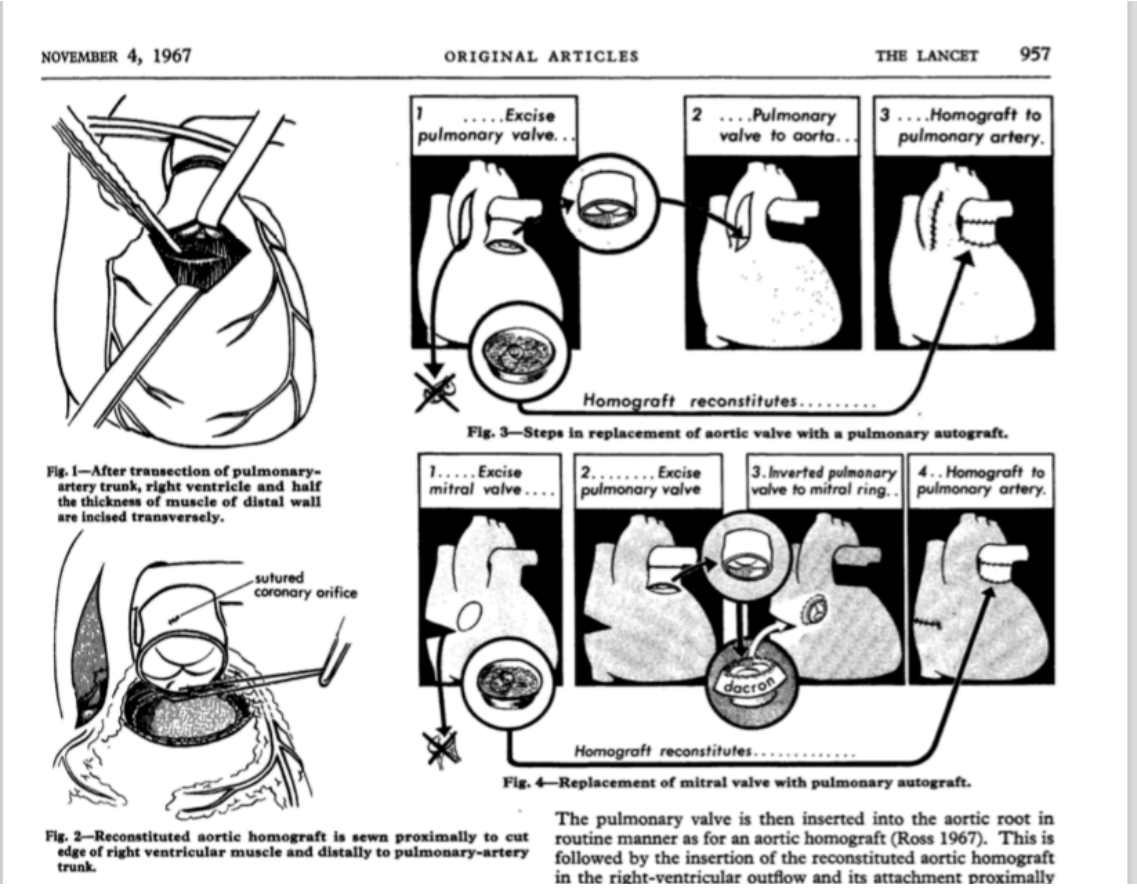

Figure 1 *Original publication of the Ross technique*

Source: Ross DN. Lancet 1967

To reconstitute the continuity of right ventricular outflow, Ross implanted a tubular vascular graft. In 1969, Carpentier introduced the concept of xenografts. However, these first xenografts degenerated quickly due to insufficient preservation [8].

In subsequent years, the use of homografts remained limited due to reduced availability.
In comparison, the autograft replacement remained a more complex, two-valve operation. In addition, Carpentier introduced a glutaraldehyde-preservation for stent-mounted porcine valves in 1969 [9], seemingly solving the issue of early degeneration of biological valves. Therefore, in the 1970s, almost only xenografts were implanted worldwide. In the 1980s, their suboptimal durability with need for reoperation was observed increasingly. It also became apparent that the durability was poor particularly in young patients [10].
Meanwhile, the Ross procedure was rarely performed until Ross published his first results with the pulmonary autograft in 1989, which lead to a renewed interest in the procedure.
Technical alternatives were developed and proposed by Elkins et al [11]. In the 1990s, different surgical techniques were developed and Matsuki et al [12] and Kouchoukos et al [13] published their first long-term results. Follow-up showed that the procedure improved life expectancy compared to other prostheses [14] and continuous postoperative observation lead to better recognition of failure of the autograft.

B. Valve-related complications

Choosing the most suitable valve replacement for the patient is difficult. Conventional valve prostheses are associated with high rates of valve-related complications and adverse events particularly in the younger patient population [15]. Thromboembolic events, such as stroke and valve thrombosis, occur at similar rates in biological and mechanical valve prostheses [15]. The main pitfall of mechanical valves is their thrombogenicity and subsequent need for anticoagulation while biological valve prostheses and allografts have a low durability.

Mechanical valve prostheses

Mechanical valves have long been the preferred replacement in young adults due to their long durability and relative ease of implantation. Since the introduction of the caged ball valve in the 1960s, their design has undergone several improvements [2]. Nevertheless, mechanical valves remain thrombogenic due to their high sheer stress. This can lead to platelet activation, which continuously exposes patients to thromboembolic and hemorrhagic complications. Lifelong anticoagulation is therefore required in order to avoid these complications (i.e., thrombosis, myocardial infarction, and stroke). The anticoagulation medicine itself bears substantial side effects. It can lead to osteoporosis, is teratogenic, and should be avoided in women of childbearing age [16–18]. Patients with high risk of falls or bleeding and terminal diseases should avoid its use as it increases the hemorrhagic risk [17].

Mechanical valves are universally considered the most durable valve substitute available; however, complication rates in long-term studies varied between 1.1% and 4.5% per patient-year [19]. There is a significant rate of reoperation due to thrombosis, infection, or non-structural valve dysfunction (i.e., pannus ingrowth, paravalvular leak) [20].
These valve-related complications convert into excess mortality. Studies have shown that mortality is inversely dependent on the age of the patient at the time of surgery [21]. Thus, younger patients have the highest observed mortality rates [21]. Long-term studies have reported mortality rates between 20% and 30% at 15 years [22].

The complexity of a possible reoperation remains a concern in heart valve surgery. In attempting to avoid high-risk reoperations, some centers may prefer the implantation of supposedly longer-lasting mechanical valves. However, mid-term studies have reported a suboptimal survival after mechanical valve reoperations [68% at 8 years] [23,24], ultimately putting the younger and middle-aged patient population in a predicament in the choice of valve prostheses.

Although they eliminate the drawback of low durability, especially in the younger patient population, mechanical valves are associated with a high risk of thromboembolic events. Thus, excess long-term mortality remains relatively high even in low-risk patient groups.

Biological valve prostheses

Biological valve prostheses have become more popular over the years. Unlike mechanical valves, they do not require anticoagulation thus eliminating the risk of hemorrhagic complications. However, biological valve prostheses are prone to several complications (i.e., structural deterioration, non-structural valve dysfunction, infective endocarditis, patient-prosthesis mismatch, and thromboembolism) [25]. These result in a limited durability particularly in younger patients.

Up to date, the most important predictor of failure remains age at implantation. Several studies have reported a poor durability with excess mortality when implanted in young and middle-aged adults (<60 years) [25–27]. Recently, mortality in patients aged 45 to 54 years was reported to be up to 31% at 15 years [22]. Studies have shown that valve hemodynamics often deteriorate in this patient group despite a lower risk of reoperation [28].
Freedom from reintervention at 15 years has been found to be 50% in patients < 60 years and 85% in patients > 60 years [22]. ESC/EACTS guidelines therefore recommend the use of biological valve prostheses for patients > 60 years [29].
Similar to mechanical valves, mortality is inversely dependent on patient age at the time of the operation (in childhood, valve failure occurs in 80% at 6 years) [30] and is further augmented by the presence of patient prosthesis-mismatch [30,31]. Clinically significant patient prosthesis-mismatch occurs in approximately 44% of patients undergoing prosthetic aortic valve replacement [32]. Further, the choice of valve (stented vs stentless) affects the rate of structural valve deterioration. Stentless valves are associated with increased rates of structural valve deterioration and endocarditis compared to their stented counterparts [31]. The risk of endocarditis has remained relatively constant in biological valve prostheses and has recently been reported at 0.57% per patient-year [33].

Biological valve prostheses eliminate the drawback of lifelong anticoagulation and implantation is considered less complex. However, they are associated with risks of patient-prosthesis-mismatch and poor durability in the younger patient population.

Allografts

Allografts continue to have satisfactory clinical results. However, the Yacoub group completed a randomized prospective trial in 2010 comparing biological valve prostheses for total aortic root replacement with allograft root replacements [34]. Tissue valves showed a significantly lower rate of structural valve deterioration and reintervention compared to homograft root replacement while allografts were less prone to endocarditis [35]. Another prospective cohort study by Arabkhani et al showed that durability was satisfactory up to 10 years [36]. However, structural valve deterioration, early calcification, and reintervention rates were elevated in the second decade (freedom from reoperation: 87% at 10 years, 40% at 20 years) [36]. In addition, availability remains limited and

costs are high reserving allografts for severe cases of endocarditis and complex aortic root pathology [34].

C. Ross operation and its complications

Creating a two-valve problem has long been perceived as the weakness of the Ross procedure. By 2010, the Ross procedure accounted for only <0.1% of all aortic valve replacements performed [37,38]. One of the most important factors driving this regression was the complexity of the procedure; despite adjustments to simplify it, it remains challenging and perioperative mortality in low-volume centers is non-negligible [37,39,40]. Studies also reported that the potential failure of two valves exposes patients to complex reoperations [38,41,42].

Several centers worldwide however continued to perform the operation as a complex alternative for conventional valve replacements. Long-term results and adaptation processes were closely monitored via retrospective and prospective studies and randomized trials. This persistent work led to iterative improvements of the surgical technique and several high-volume centers have reported favorable results [14,43–47].

These studies showed that the Ross procedure results in almost physiologic aortic valve hemodynamics and a low incidence of complications [34,48,49]. Histological findings showed that the pulmonary autograft undergoes adaptive remodeling resulting in normal hemodynamics both at rest and during exercise [34,42]. Thus, it shows the lowest rate of valve-related complications (i.e.,thromboembolic events and infective endocarditis) [50] as well as a superior quality of life [51] resulting in a long-term survival equivalent to that of the age- and gender-matched population. Further, results were superior to conventional valve prostheses [22,52]. On the other hand, the complexity of a potential redo procedure may be associated with increased perioperative mortality and morbidity. However, several contemporary studies have analyzed reoperations after the Ross procedure and reported excellent results [53-55]. In the majority of cases, the benefits of a living valve substitute could be retained by aortic valve repair [54,56], valve-sparing root replacement [53,56], or reversal of the procedure [55]. Further, mortality rates have been low (0% to 2.9%) [50-53].

Concerns remain regarding late autograft dilatation, particularly in patients with preoperative aortic regurgitation [38,57]. Almost all failed autograft replacements will have had regurgitation as the initial pathology [58]. Advocates of the Ross operation have therefore made refinements of the procedure aiming to mitigate autograft failure by dilatation or cusp deformation. The full-root replacement proposed by Elkins appeared to be more reproducible than the original subcoronary technique [11,59]. On the other hand, following the aortic root replacement progressive autograft dilatation was observed in a relevant proportion of cases [57,60]. Adjustments were later made to include the remnants of the native aortic wall for stabilization of the pulmonary autograft [61].

In particular, four possible techniques were developed over time: (i) subcoronary, (ii) subcoronary with retainment of the noncoronary sinus, (iii) cylinder, and (iv) freestanding full-root (**figure 2**) [62].

During the original technique (subcoronary), the pulmonary autograft is implanted in a subcoronary position in the aortic root. In order to support the annulus, the subcoronary technique was expanded to also retain the noncoronary sinus. This technique does not expose the autograft to the risk of secondary dilatation. It is, however, technically demanding.

The cylinder technique, during which the autograft is invaginated into the native aorta and wrapped by it entirely, proved to provide more support than solely maintaining the noncoronary sinus [63]. Some centers modified it by using a Dacron graft; both a straight graft and a prosthetic graft with an artificial Valsalva configuration have been used [64-67]. The full-root replacement allows for the most natural hemodynamics. It can be implanted in subannular or intraannular position. This technique has been complemented by different stabilization techniques in order to avoid secondary dilatation [68] and is the most frequently used technique [66].

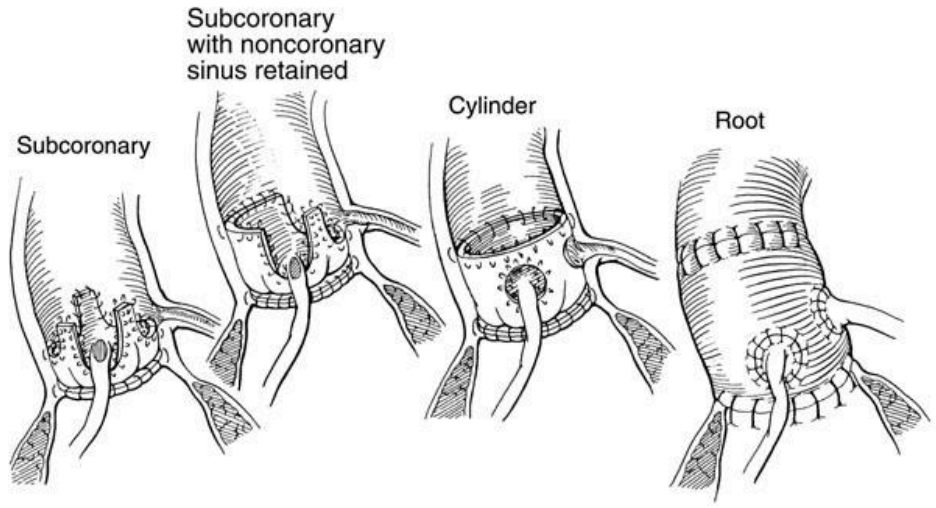

Figure 2 *Four different surgical techniques of the Ross procedure*

Source: Conklin LD, et al. Texas Heart Inst J. 2001.

In addition, several centers have adapted a strict blood pressure protocol for the first 6 months postoperatively in order to avoid dilatation in the phase of adaptive remodeling of the autograft [50,69]. Recent studies have reported low rates of reintervention with a freedom from reintervention between 85% and 95% at 10 years [50,70-74]. Interestingly, all series included a significant proportion of patients with isolated aortic regurgitation (20% to 50%) despite it being considered a predictor of late autograft failure [50,70-74]. According to Lavall et al., aortic regurgitation (AR) and a bicuspid valve morphology can lead to aortic root dilatation due to a reduced expression of the endothelial nitric oxide synthase and the asymmetric sheer wall stress [75]. However, at this stage, there is no proof of these factors constituting an appreciable risk for the pulmonary autograft [76,77]. In addition, recent studies have failed to find an association between isolated AR, a bicuspid valve morphology, and late failure of the pulmonary autograft [76].

There have been few comparative studies analyzing the results of the Ross procedure in comparison to conventional valve prostheses. A randomized controlled trial by the Yacoub group compared the Ross procedure to aortic homograft replacement [34]. This was the first study reporting a restored survival equivalent to that of the age- and gender-matched general population by using the Ross procedure. Few studies compared the Ross procedure to a mechanical valve replacement [52,78-80]. Patients undergoing the Ross procedure, in comparison to mechanical valve replacement, showed a significantly lower rate of cardiac- and valve-related deaths and thrombogenic complications [52,78-81]. Another large-scale study reported superior long-term survival in the Ross group (94% vs 84%, p=0.018) [78].

Despite these excellent results, the Ross procedure remains exclusive to highly experienced centers. Studies have reported an inverse relationship between surgical volume and results following aortic root surgery [40,82]. In summary, when performed in experienced high-volume centers, the Ross procedure shows excellent results in non-elderly patients. Survival is equivalent to that of the age- and gender-matched population, hemodynamics are normal, and there is no risk of patient-prosthesis-mismatch. Further, survival, valve-related complications, and quality of life are superior to conventional valve prostheses. For the pulmonary conduit, homografts show superior results compared to xenografts. If availability is limited, viable alternatives, such as stentless biological valve prostheses or xenografts, are accessible [83-86].

D. Pulmonary valve conduit

The first homografts were used as a replacement of the aortic valve by Ross and Barratt-Boyes [5,87]. Hemodynamics were outstanding and bleeding and thromboembolism rates were low. However, early degeneration was non-negligible. Meanwhile, Ross performed his first pulmonary autograft procedure using a stentless xenograft as a pulmonary conduit. However, durability of both xenograft and homograft used as a replacement of the aortic valve was poor [88,89]. This led to the idea that a homograft could be more durable in a lower pressure system and has been used as a pulmonary conduit since.

In Europe, homografts are taken from explanted hearts of a donor during a transplant or from hearts that do not qualify for a transplant. Availability stagnated due to a decrease in heart transplants but has significantly improved since the establishment of national and international homograft banks in 1989 [90].
Meanwhile, stentless xenografts and bovine jugular veins have been used as conduits. Reports however documented an appreciable number of reinterventions due to early degeneration [86,91].

Preservation of the pulmonary homograft was yet another limitation. The use of homografts remained difficult, as preservation techniques were not yet optimal. Historically, chemicals were used. However, durability was impaired and several different techniques of preservation were tested over time [92,93]. Cryopreservation eventually replaced chemical preservation due to its supe-

rior results. Indeed, cryopreserved and “wet valves” (i.e., valves that were treated with antibiotics and anti-fungal drugs kept in a nutrient solution at four degrees Celsius) were observed microscopically, and vital endothelial cells and fibroblasts were detected, which cause durability to increase [83,84,92].

However, recent studies have shown that an immunological response occurs against donor-specific HLA-molecules, which can lead to degeneration and calcification [94,95]. Therefore, decellularization of homografts has been tested showing a significant decrease in immunological responses and degeneration.

In our series, the majority of patients received a cryopreserved homograft. Studies have shown favorable results of decellularized homografts; they reported a significant decrease in immunological responses and degeneration [94,96], however, long-term results are not yet available.

E. Variability of techniques

There is no universally accepted technique for the Ross procedure, unlike there is for the implantation of mechanical or biological valves. While there is an increased need for studies analyzing different techniques in order to find the most optimal surgical technique, there have not been any comparative studies. A comparison was made with a meta-analysis reporting similar survival of the full-root replacement and subcoronary technique [62]. Mid-term freedom from reoperation was superior in the full-root replacement technique [47,62].

Reinforcement techniques were improved and a Dacron or pericardial strip at the level of the proximal suture line became popular [57,97,98]. Dilatation however did not affect the level of the root base in the majority of cases. Instead, it occurred at the level of the three sinuses and the sinotubular junction [57,63,99]. In order to prevent dilatation, several surgical techniques of autograft reinforcement have been developed. The root inclusion technique is one of the most recognized techniques during which the pulmonary root is included inside the native aortic root in its entirety [45,63,64,100]. This technique may prevent late dilatation; for objective assessment however there is a paucity of publications with long-term results [45,63,64,100]. In our cohort, the sinus was stabilized by wrapping the autograft root with remnants of the native aortic wall [61]. Additionally, an annuloplasty was applied according to patient and root characteristics. Overall, patients with sinus stabilization presented with a lower risk of secondary dilatation and regurgitation compared to their counterparts without stabilization. The annuloplasty material altered over time but showed no significant difference in freedom from reoperation. However, its application impeded the progression of autograft root dimensions.

F. Hypothesis

Although the Ross procedure offers numerous advantages, such as freedom from lifelong anticoagulation, survival comparable to that of the age-and gender matched general population, normal valve hemodynamics, and a superior quality of life, the incidence of reoperation remains a concern. The need for reoperation, along with its technical complexity, has been the main agenda in the international debate of whether the Ross procedure is a viable alternative to conventional valve prostheses.

We anticipate that the Ross procedure leads to excellent survival and favorable durability. In addition, hemodynamics are expected to be almost physiological with few adverse valve related events in the long-term. Further, external root support is expected to decrease the need for autograft reintervention and to influence the progression of root dimensions.

G. Study objective

The full-root Ross technique continues to be criticized for its potentially low durability. If not stabilized, the autograft root may dilate over time resulting in an increased rate of reintervention. Different stabilization techniques have been proposed but no long-term results have been published. The main aim of this retrospective study is to provide long-term results and discuss factors that may precede complications and valve failure.

The following questions will be discussed:

1. What are the long-term results of the full-root technique (survival, reintervention, aortic regurgitation)?
2. Is the autograft stabilization technique successful in preventing the progression of autograft root dimensions and subsequent reinterventions?
3. What are the long-term results in patients with prior aortic valve operations?
4. Does the rate of reintervention differ between the three types of pulmonary valve conduits used?

III. Material and methods

A. Patient population

We conducted a retrospective chart review of 202 consecutive patients (median age: 35.4±11.4 years, 73% male) who underwent a Ross procedure between December 1995 and December 2020 at our institution. Patients underwent a modified cylinder technique (n=5) or a full root replacement (n=196). A stabilization technique (native aortic wall inclusion) was added to the procedure in 146 cases. Patients were excluded from the long-term analysis if they were intraoperatively converted to a different procedure (n=1). Overall, 202 patients were analyzed and 8 patients were lost to follow-up. Baseline characteristics of the cohort are provided in **table 1**.

This study was conducted at Saarland University Hospital and was approved by the regional Ethics Committees (CEP 203/19.) and individual patient consent was waived for the analysis and publication in anonymized fashion.

The indication for surgery was isolated aortic stenosis in 42 (21%), isolated aortic regurgitation in 51 (25%), combined disease in 83 (41%), and active endocarditis in 26 (13%) patients. The most common infective organism was Staphylococcus aureus and Enterococcus faecalis.

The original aortic valve morphology was unicuspid in 87 (42%), bicuspid in 76 (39%), and tricuspid in 25 individuals (12%). Fourteen patients had undergone valve replacement previously, and the morphology could not be determined.
Mean left ventricular ejection fraction was 63 ± 12%. Thirty patients (17%) had a left ventricular ejection fraction < 50%. Preoperatively, 40 patients (20%) had annular enlargement (> 26mm).
The Ross procedure was a redo operation in 64 cases. Of those, 12 initially underwent a balloon valvuloplasty, 50 an aortic valve repair, and 14 an aortic valve replacement (some patients underwent more than one procedure). Patients with previous aortic valve repair underwent the Ross procedure after a median of 6.7 years [2.4-17.3 years].
The majority of patients (n=143, 71%) underwent the Ross procedure as an elective operation. If the valve dysfunction caused left ventricular dysfunction, the procedure was considered urgent (n=54, 27%). Five cases (3%) were emergent.
Median and mean follow-up were 5.7 years [range 0.1 - 24.4] and 7.8 ± 7 years, respectively. Clinical and echocardiography follow-up were 95% and 92% complete, respectively (1467 patient-years).

Table 1: Baseline characteristics

Patient characteristics	**N=202 n [%]**
Male sex	148 [73]
Age, mean ± SD, y	35.4 ± 11.4
<18 years	20 [10]
Cardiovascular risk factors	
BMI, mean ± SD	26 ± 5
Dyslipidemia	17 [10]
Diabetes	5 [2]
Art. Hypertension	59 [34]
Coronary artery disease	8 [5]
Chronic kidney disease	4 [2]
Smoker	33 [19]
i.v. drug abuse	8 [5]
Aortic valve lesion	
Isolated aortic stenosis	42 [21]
Isolated aortic regurgitation	51 [25]
Combined disease	83 [41]
Active endocarditis	26 [13]
Prior aortic valve intervention	**64 [32]**
Aortic valve replacement	14 [7]
Aortic valve repair	50 [25]
Valve morphology	
Unicuspid	87 [42]
Bicuspid	76 [39]
Tricuspid	25 [12]
Prosthesis (biological)	4 [2]
Prosthesis (mechanical)	10 [5]
Autograft regurgitation grade	
I	27 [13]
II	45 [22]
III or IV	85 [42]
Autograft root diameter, median [IQR], mm	
Annulus	25 [22-27]
Sinus	32 [29-35]
STJ	27 [24-31]
Aortic basal annulus >26mm	40 [20]

Patient characteristics	**N=202 n [%]**
LOS, median [IQR]	7 [6-8]
Euroscore II, median [IQR]	2.1 [1.4-4]
NYHA > II	24 [14]
LVEF %, mean ± SD	63 ± 12
LVEF <50%	30 [17]
LVEDd, mean ± SD mm	55 ± 11
AV gradient, mean ± SD mmHg	38 ± 21
AV gradient, max ± SD mmHg	65 ± 32
Urgency	
Elective	143 [71]
Urgent	54 [27]
Emergent	5 [3]

B. Follow-up and statistical methods

Follow-up

This is a retrospective analysis of prospectively collected data. All cardiac procedures from our institution were screened for patients who have undergone a Ross procedure since 1995. Functional state of the patient, concomitant diseases, and any previous cardiac procedures were collected from medical records. Preoperatively, the functional state of the aortic valve was determined by TTE and TEE in our own institution.

Postoperatively, all patients were seen regularly by their referring cardiologists or in our clinic. Echocardiograms (or their reports) from our institution and the patients' cardiologists were reviewed as well as surgical reports. In addition, patients were contacted via phone or seen in the clinic to determine current functional status. The cause of death was determined by review of the hospital chart or information from the primary care physician.

Parameters obtained

The following parameters were collected pre-, intra-, and postoperatively for further analysis (tables 1-3): Gender, age, prior cardiac operation, degree of pre- and postoperative aortic valve regurgitation and aortic stenosis, pre- and postoperative aortic valve endocarditis, pre - and postoperative aortic root diameters (basal ring, sinus of Valsalva, sinotubular junction), pre- and postoperative LVEDD, LVESD, and ejection fraction, body surface area, original valve morphology, stabilization and annuloplasty techniques used (aortic wall inclusion, suture annuloplasty or pericardium strip), replacement of the ascending aorta, pulmonary valve conduit and size (homograft, bovine jugular vein, porcine biological valve prosthesis), additional cardiac procedures performed, intraoperative times of extracorporeal circulation and myocardial ischemia, postoperative AV block III° and consecutive pacemaker implantation, time of death, time of reoperation, and time of aortic regurgitation first recorded.

Statistical analyses

Descriptive statistics are presented as median (interquartile range) or mean (± standard deviation). The date of first occurrence of AR grade > 2 was recorded for time-to-event calculation. The Fischer exact test was used for categorical variables and the Mann-Whitney test for continuous variables. Time-dependent data on survival and late adverse events were analyzed using the Kaplan-Meier method. Survival compared to the age- and gender-matched German population was obtained using the Ederer II method. The approximated gender, age, and year of surgery matched population survival curve was compared with the population of this study. Survival and freedom from reintervention were calculated at 1, 5, 10, 15, and 20 years.

Changes in autograft root dimensions were outlined using the linear Spline regression model and compared with a linear mixed-model analysis. They were measured over a span of 15 years. An

annulus diameter > 26mm, sinus diameter >34mm, and sinotubular diameter > 29mm were considered enlarged. A sinus diameter > 40mm was considered dilated.

Pulmonary valve stenosis was defined as mild (maximum gradient < 30 mmHg), moderate (maximum gradient 30–60 mmHg), and severe (maximum >60 mmHg).

Risk factors were identified by binary multivariate analysis (MANOVA) and a Cox regression analysis was completed for further differentiation. Differences between groups were compared using the log-rank test or t-test, as appropriate. P-values < 0.05 were considered significant for all analyses.

Data was statistically analyzed using Microsoft Office Excel (Microsoft Corp., Redmond, WA, USA), statistical package SPSS version 28.0 (233 S. Wacker Drive Chicago, IL 60606-6307), and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Mortality was defined as early (within 30 days of surgery) and late mortality and further classified as valve related, cardiac, or non-cardiac. Standard guidelines to define early and late mortality and valve-related events were followed. Valve-related mortality was considered any death caused by structural or non-structural valve deterioration, valve thrombosis or related embolism, valve endocarditis, bleeding, or death related to reintervention.

Reintervention was classified as any cardiac reoperation, autograft reintervention, and RVOT reoperation. Autograft reoperation was defined as any reintervention that concerns the reconstruction, repair, or replacement of the autograft valve and root.

Survival and freedom from reoperation commenced on the day of the operation and ended either at the fatal event, reoperative event, or at the last follow-up. If the reoperation concerned the pulmonary conduit or was an aortic valve repair (i.e., not replacement), follow-up did not cease with the date of that reoperation.

Valve morphology was individually assessed preoperatively by means of echocardiogram and was further confirmed intraoperatively. The configuration was classified according to Anderson [101] with modifications from Schäfers and de Kerchove [102,103]. The modifications consider the unicuspid valve a separate entity and not a variant of the bicuspid valve. Standard ESC/EACTS Guidelines were followed for classification of aortic stenosis and aortic regurgitation.

Concerning survival, freedom from reoperation, freedom from autograft dilatation, and freedom from aortic regurgitation the following groups were compared: Prior aortic valve repair versus aortic valve replacement, stabilization technique (supported versus unsupported).

C. Operative technique

The chest and pericardium were opened in standard fashion. The patient was connected to extra-corporeal circulation by aortic and right atrial cannulation in all instances. After cross clamping, the ascending aorta was cut approximately 10 mm by transverse incision above the commissures. Blood cardioplegia was introduced into the coronary ostia. Meanwhile, the valve was carefully inspected in order to eliminate the possibility of aortic valve repair.
Subsequently, the pulmonary trunk was cut approximately 10 mm above the pulmonary valve commissures and the valve morphology was inspected before mobilizing the trunk. In the most recent 30 instances, geometric height of the pulmonary valve was measured in a standard manner and found to be 20 mm, similar to what has been found for the tricuspid aortic valve. In 3 cases, a bicuspid pulmonary valve was detected, however, geometric height was adequate and the autograft was used in a standard fashion.

Eventually, both trunk and valve were excised. The dorsal part of the trunk was mobilized between the left and right ventricular part of the septal myocardium with an electrocautery. The anterior part was excised from an endoluminal view and lies approximately 5 to 10 mm below the valve. The right ventricular anterior wall was perforated with an instrument safely below the pulmonary valve. The opening was incised further to dissect the valve from the RVOT. The myocardium was divided by electrocautery with 5 to 8 mm of myocardium remaining on the autograft. This process was continued circumferentially. When preparing the dorsal part, it is important to stay between the right and left-ventricular myocardium in order to prevent possible damage to a septal branch of the LAD. The autograft was checked for its structural integrity and excess muscle was trimmed to 3 to 5 mm below the pulmonary valve sinus. The aortic root was then prepared for root replacement; the two coronary buttons were mobilized and the non-coronary sinus incised. The aortic valve was excised, possible calcifications were removed, and the annular diameter was measured by direct intubation using Hegar dilators. Any annular size (basal ring diameter) exceeding 26 mm triggered later use of external suture annuloplasty, irrespective of the surgical indication (i.e., AR or AS) [104].

Three stay sutures were placed below the commissures of the aortic root and the autograft to determine circumferential commissural orientation [61]. It is important to implant the autograft intraannularly whereby the native aortic annulus supports and stabilizes the autograft root, if the native aortic annulus is not itself dilated. A polypropylene 4-0 continuous suture was used, starting beneath the commissure between the right and left cusps. After a few stitches, the autograft was inverted into the LVOT and sutured to the basal annulus with a continuous 5-0 polypropylene over-and-over suture technique (**figure 3A**).

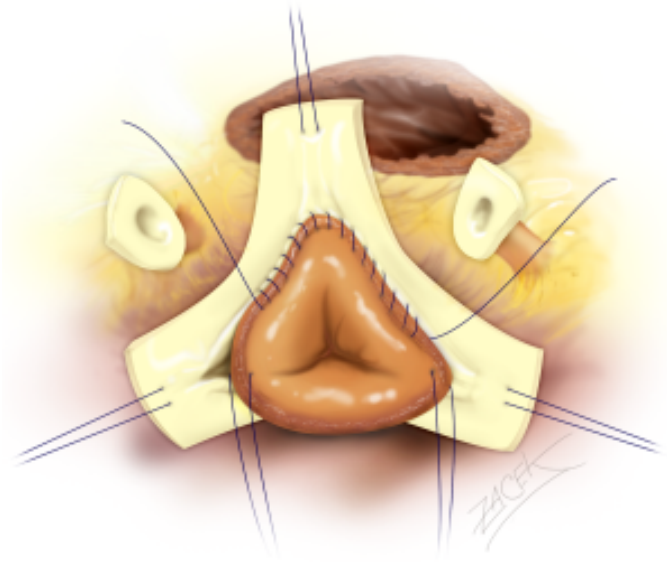

Figure 3A *Continuous over-and-over suture technique*

Source: Matsushima et al, Ann Thorac Surg. 2019

Further sutures were placed 120 degrees beneath the commissures of the autograft in the corresponding location in the LVOT. Every stitch has to include intact endocardium in order to prevent hemorrhage into the bulge of the muscle. The autograft valve was then pulled back, and additional stitches were inserted to secure the anastomosis if necessary (**figure 3B**).

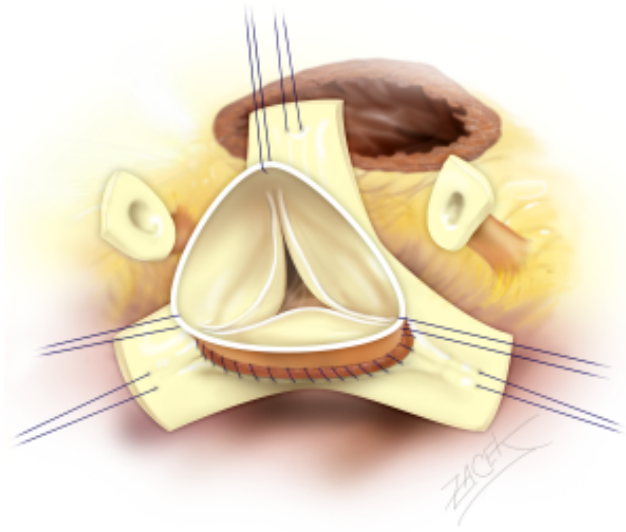

Figure 3B *Autograft valve pulled back*

Source: Matsushima et al, Ann Thorac Surg. 2019

For the external annuloplasty, a PTFE suture [105] was used. One needle of the ePTFE suture was passed around the posterior outer circumference of the aortic basal annulus beginning in the septal myocardium outside the commissure between the right and left cusps, ending at the aortomitral continuity outside the non-coronary sinus [61] (**figure 4A**).

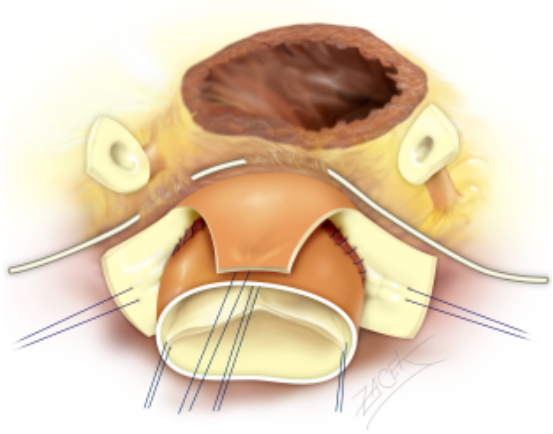

Figure 4A *External suture annuloplasty*

Source: Matsushima et al, Ann Thorac Surg. 2019

The other needle of the ePTFE suture was passed anteriorly through the right ventricular myocardium outside the nadir of the right cusp and tangentially passed through the aortic adventitia outside the nadir of the non-coronary cusp (**figure 4A**). The suture was tied around a Hegar dilator placed into the autograft (**figure 4B**). The size of the dilator was chosen according to the patient's body surface area (≥1.8 m2: 23 mm, <1.8 m2: 21 mm).

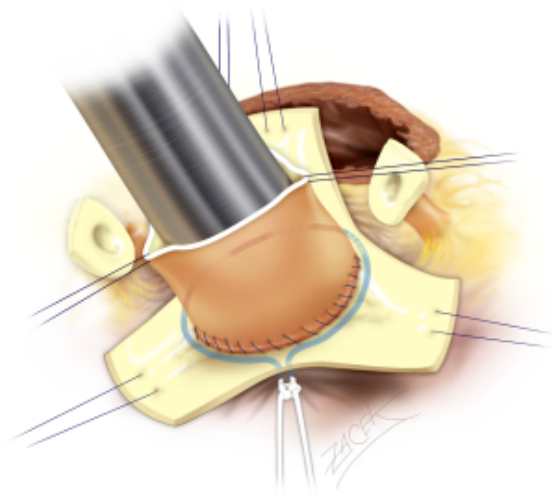

Figure 4B *Suture annuloplasty tied around a Hegar dilator*

Source: Matsushima et al, Ann Thorac Surg. 2019

Buttons for the coronary arteries were left attached to the aorta, which provides further support. Two incisions were made in the autograft for the anastomoses with the coronary arteries (Prolene 6-0). Both coronary buttons were implanted into the autograft, and the RVPA was reconstructed with a cryopreserved pulmonary homograft or other prostheses. The muscle was trimmed down to 5 to 8 mm, similar to the autograft. The RVPA prosthesis was then anastomosed to the distal pulmonary trunk.

In patients with a tubular diameter of the ascending aorta > 30 mm, its diameter was reduced with plication of the ascending aorta (31 - 35 mm) or replaced with a Dacron graft (≥ 35 mm) (size according to BSA) (n=31). This ensures stabilization of the autograft sinotubular junction [106]. During reduction aortoplasty, commissures were realigned (120 degrees) and effective cusp height was reduced. This is essential as a commissural orientation of >165 has a suboptimal outcome [103]. Finally, the distal end of the autograft was anastomosed to the ascending aorta or vascular graft with a 5-0 polypropylene continuous suture [61]. Thus, the suture is placed close to the sinotubular junction of the autograft. It is important to pay close attention to the 120-degree orientation of the commissures of the autograft when placing these sutures. The aortic wall in the area of aortic valve commissures and no more or less than 10 mm afar was included in this suture line (f**igure 5A**).

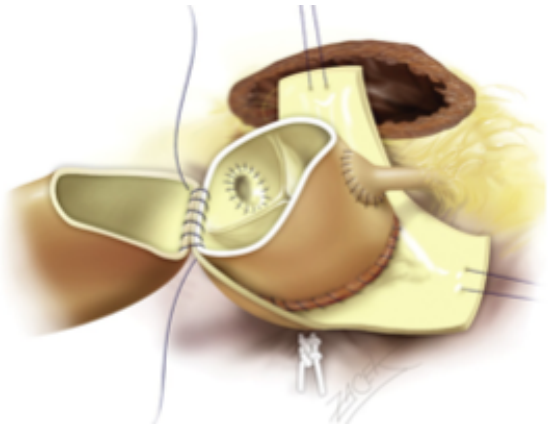

Figure 5A *Aortic wall included in suture line*

Source: Matsushima et al, Ann Thorac Surg. 2019

Thus, a 10 to 15 mm wide portion of native root tissue will lie outside the autograft commissures, on three parts between each Sinus of Valsalva, for external stabilization (**figure 5B**)

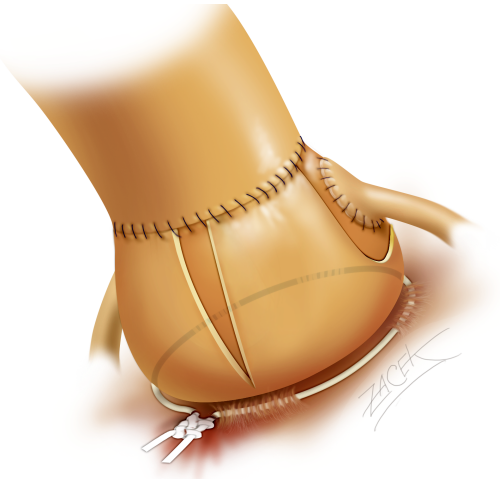

Figure 5B *Native aortic wall as stabilization*

Source: Matsushima et al, Ann Thorac Surg. 2019

After ventilation and release of coronary circulation, the function of the left ventricle and the autograft were scrutinized by performing a TEE. In case of a significant regurgitation of the autograft, the geometric height of the autograft has to be revised.

Postoperatively, systemic blood pressure was closely monitored and kept at a low normal level (100/60 mmHg) using ACE inhibitors, beta-blockers, and Ca channel blockers as needed. For the following 3 months, systemic blood pressure was monitored closely to stay below normal levels (120/80mmHg). This is imperative in order to avoid secondary dilatation.
Furthermore, the risk of endocarditis after valve replacement remains, thus necessitating a lifelong antibiotic prophylaxis for patients undergoing any type of dental, urological, and gastrointestinal treatment, surgical procedures, or who experience tonsillitis [107].
Replacement of the ascending aorta was managed by post-operative administration of Aspirin (100 mg/d) for eight weeks.

Between 1995 and 1997, a modified cylinder technique was used at our institution (n=5), whereby parts of the native aorta were preserved (commissures, noncoronary sinus). The autograft was implanted as a unit within these native structures and the upper edge of the autograft was fixated in a circular way. During the currently used inclusion technique, the autograft is inserted as a root replacement with the aorta verged around it to provide support. Since 1998, the full-root technique has been the standard procedure and was performed in 197 patients. In order to avoid autograft failure due to root dilatation or aortic regurgitation, the technique is complemented by an external stabilization of the annulus and/or sinus. The remnants of the aortic wall were first included as stabilization in 2001 (n=146) [61]. For the annuloplasty, pericardium was the standard of choice until 2009 (n=75). An expanded polytetrafluoroethylene (ePTFE) suture (Gore-Tex CV-0; W.L. Gore & Assoc., Flagstaff, AZ) [105] was first used in 2010 and has been the standard of choice since 2012 (n=40). As a pulmonary valve conduit, the majority of patients received a homograft (n=156). Between 2000 and 2010, a bovine jugular vein (Medtronic Contegra® Pulmonary Valve Conduit Model 200 (unsupported)) was used due to a shortage of homografts (n=35). In addition, few patients received a freestyle biological valve prosthesis (n=11). Intraoperative data are provided in **table 2**.

IV. Results

A. Early results

Operative data

Mean cross-clamp and perfusion times were 92 ± 20 minutes and 127 ± 34 minutes, respectively. Mean cross-clamp and perfusion times were significantly shorter in the group with stabilization (86±16 minutes vs 103 ± 24 minutes, p=0.0001; 116 ± 25 minutes vs 149 ± 43 minutes, p=0.0044).

Patients with primary autograft aortic valve replacement had shorter mean cross-clamp and perfusion times compared to patients with prior aortic valve replacement (87 ± 20 minutes vs 106 ±2 3 minutes, p=0.0003; 119 ± 30 minutes vs 157 ± 49 minutes, p=0.001). However, patients with prior aortic valve repair had similar cross-clamp and perfusion times compared to a primary Ross procedure (88 ± 13 minutes vs 92 ± 22 minutes, p=0.297; 126 ± 25 minutes vs 125 ± 37 minutes, p=0.812). The difference between prior aortic valve repair and replacement concerning cross-clamp and perfusion times was significant (p=0.001, p=0.004).

Patients with external root stabilization had shorter mean cross-clamp and perfusion times than those without stabilization (85 ± 17 minutes, 114 ± 24 minutes, p=0.0001 vs 105 ± 23 minutes, 149 ± 43 minutes, p=0.0044) (**table 2**).

Table 2: Intraoperative data

Parameters	**N=202**	**n [%]**
Myocardial ischemia, mean±SD min		91±20
Perfusion time, mean±SD min		125±33
Technique		
Modified cylinder (1995 -1997)		5 [2]
Full root replacement		196 [97]
Bentall conversion		1 [1]
Annular support		115 [57]
Pericardial strip		75 [37]
ePTFE suture		40 [20]
Aortic wall inclusion		146 [72]
RVPA prosthesis		
Bovine jugular vein		35 [17]
Homograft		156 [77]
Biological prosthesis		11 [6]
Concomitant procedure		58 [33]
Ascending aortic replacement		31 [15]
Septal myektomie		7 [4]
Hemi-arch using circulatory arrest		5 [2]
Coronary artery bypass		5 [2]
Tricuspid valve repair		3 [1]
Mitral valve repair		4 [1]
ASD, VSD, PFO closure		3 [1]

Survival

There was one early mortality. The patient underwent surgery (unsupported Ross technique) following 3 previous root replacements and had a history of heparin-induced thrombocytopenia. The patient developed unexpected rupture of the autograft, which was reexplored surgically without success. Thus, hospital survival was 99.5%.

Cardiac and neurological complications

There was no perioperative myocardial infarction. One neurological complication occurred in a patient with right coronary artery anomaly. Intraoperatively, he was treated by a coronary artery bypass after having developed right ventricular dysfunction and required a right ventricular assist device. He developed a thromboembolic stroke but could be weaned 5 days later. He recovered neurologically and has been well since. Another patient required a temporary left ventricular assist device for left ventricular dysfunction. He was weaned successfully on postoperative day 5 and continues to do well (**table 3**).

Four patients (2%) required permanent pacemaker implantation for atrioventricular block. In all four, the indication for surgery was active endocarditis with perivalvular root abscess; preoperatively, all of them presented with sinus rhythm.
Two additional patients underwent rethoracotomy for bleeding complications.

Table 3: Perioperative data

Parameters	**N=202**	**n [%]**
Bleeding complications		2 [1]
Myocardial infarction		0 [0]
Stroke		1 [0.5]
Permanent pacemaker implantation		4 [2]
Ventricular dysfunction requiring LVAD or RVAD		2 [1]

B. Late results

1. Survival

Nine patients died during follow-up, of which four died of cardiac causes (8 months to 4 years postoperatively). These included cardiac arrhythmia (n=2), pulmonary homograft endocarditis after intravenous drug abuse (n=1), and death from uncontrollable coagulopathy (n=1; presumed heparin-induced thrombocytopenia and thrombosis) after reoperation for autograft failure 8 months after the index operation.

Five patients died from non-cardiac causes (6 months to 11 years postoperatively) including pneumonia (n=1), sepsis from urinary tract infection (n=1), intravenous drug abuse (n=1), and oropharyngeal cancer (n=1). One cause of death remains unknown.

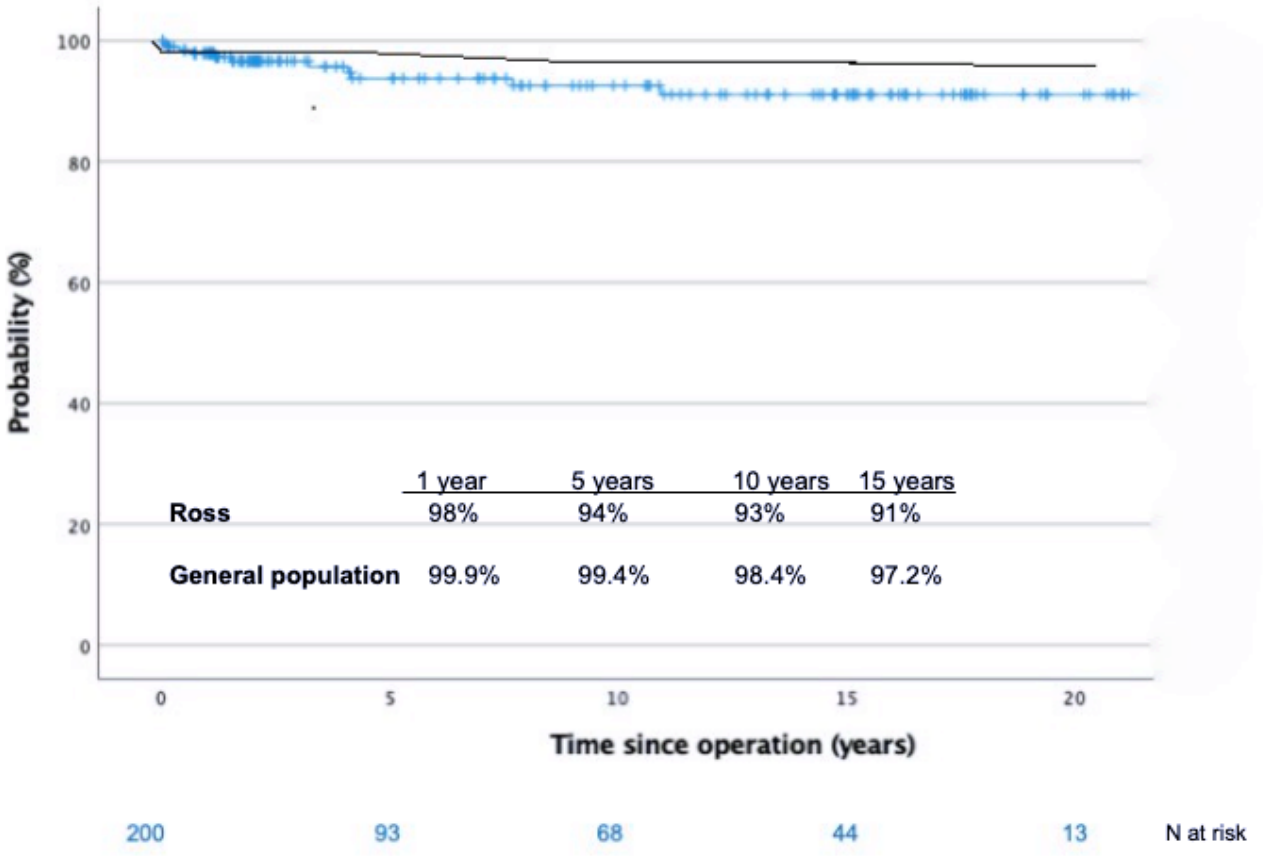

Figure 6A *Survival after the Ross procedure compared to the age-and gender-matched general population*

Overall survival was 98% at 1 year, 94% at 5 years, 93% at 10 years, and 91% at both 15 and 20 years. Freedom from cardiac death was 99% at 1 year, and 96% at both 10 and 20 years. This is comparable to that of the age- and gender-matched general population (**figure 6A**).

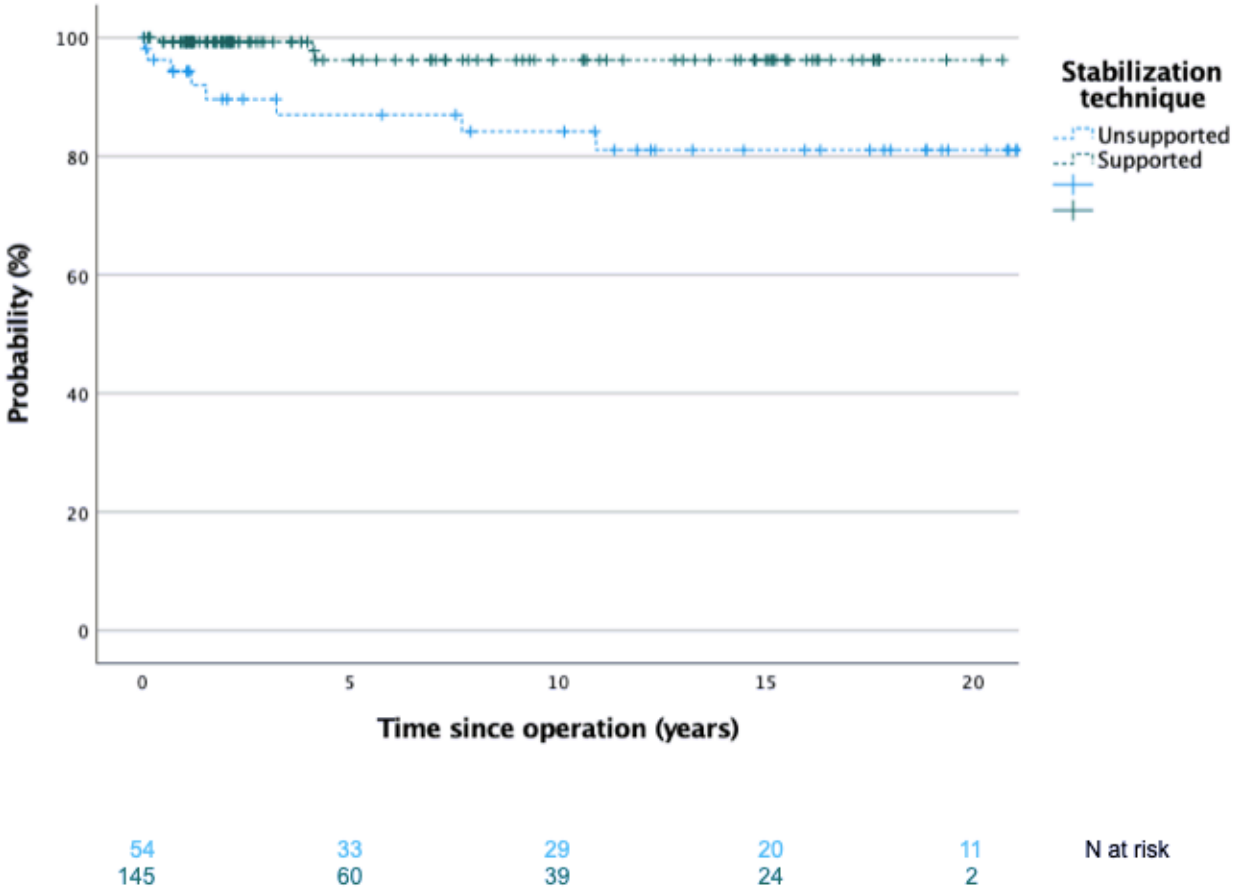

Figure 6B *Survival with and without autograft stabilization*

Three patients died after a supported (cardiac cause n=1) and six after an unsupported Ross operation (cardiac cause n=3). Survival was higher in the supported group (99% at 1 year, 95% at 10 and 15 years) than in the unsupported group (94% at 1 year, 85% at 10 years, and 81% at 15 years) (p=0.003) (**figure 6B**). Freedom from cardiac death was higher in the supported group (100% at 1 year and 98% at 10 and 15 years) compared to the unsupported group (98% at 1 year, 91% at 10 and 15 years) (p=0.045).

Predictors for cardiac death were endocarditis (acute or healed) [p=0.006, HR 6.3; 95% CI, 1.7–23.3] and prior conventional aortic valve replacement [p=0.02, HR 3.774; 95% CI, 1.2-11.8]. Survival was lower compared to patients without preoperative endocarditis (80% at 5 years, 72% at 15 years vs 97% at 5 years, 95% at 15 years; p=0.001).

Survival was higher in the group with prior aortic valve repair (100% at 15 years) compared to the group with prior aortic valve replacement (73% at 15 years) (p=0.001) (**figure 6C**).

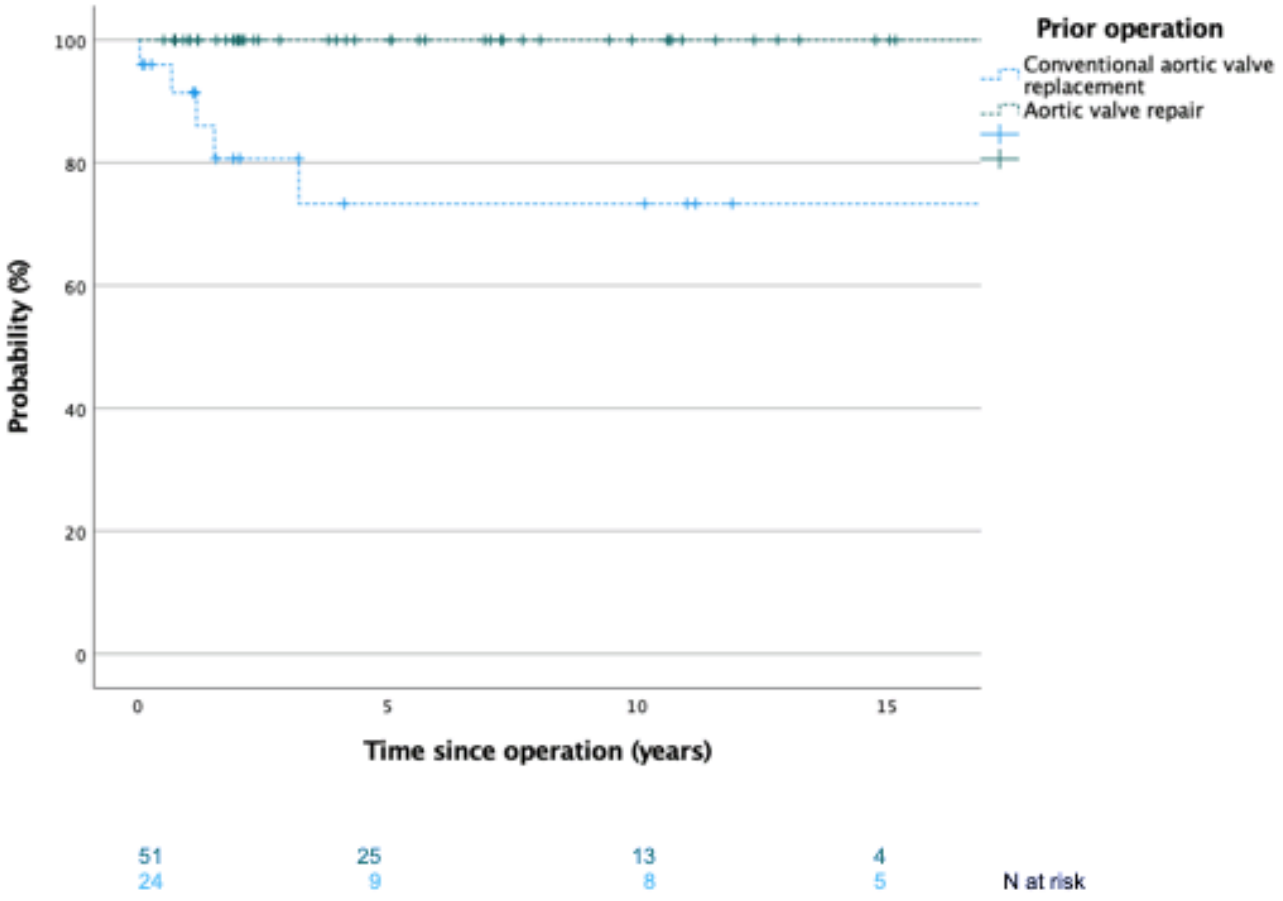

Figure 6C *Survival after conventional valve replacement and aortic valve repair*

2. Reoperation

Twenty-three patients (11.4%) underwent reoperations (autograft n=16, pulmonary conduit n= 7) between 0.1 and 21 years after surgery (median: 7.6 years).
An additional patient required a heart transplant 17 years after the surgery. The patient had coronary artery disease (3 vessels) and presented with a LVEF 16%. Both autograft and homograft were competent.

Overall freedom from reoperation was 96% at 1 year, 93% at 5 years, 81% at 10 years, and 78% at 15 years (**figure 7**).

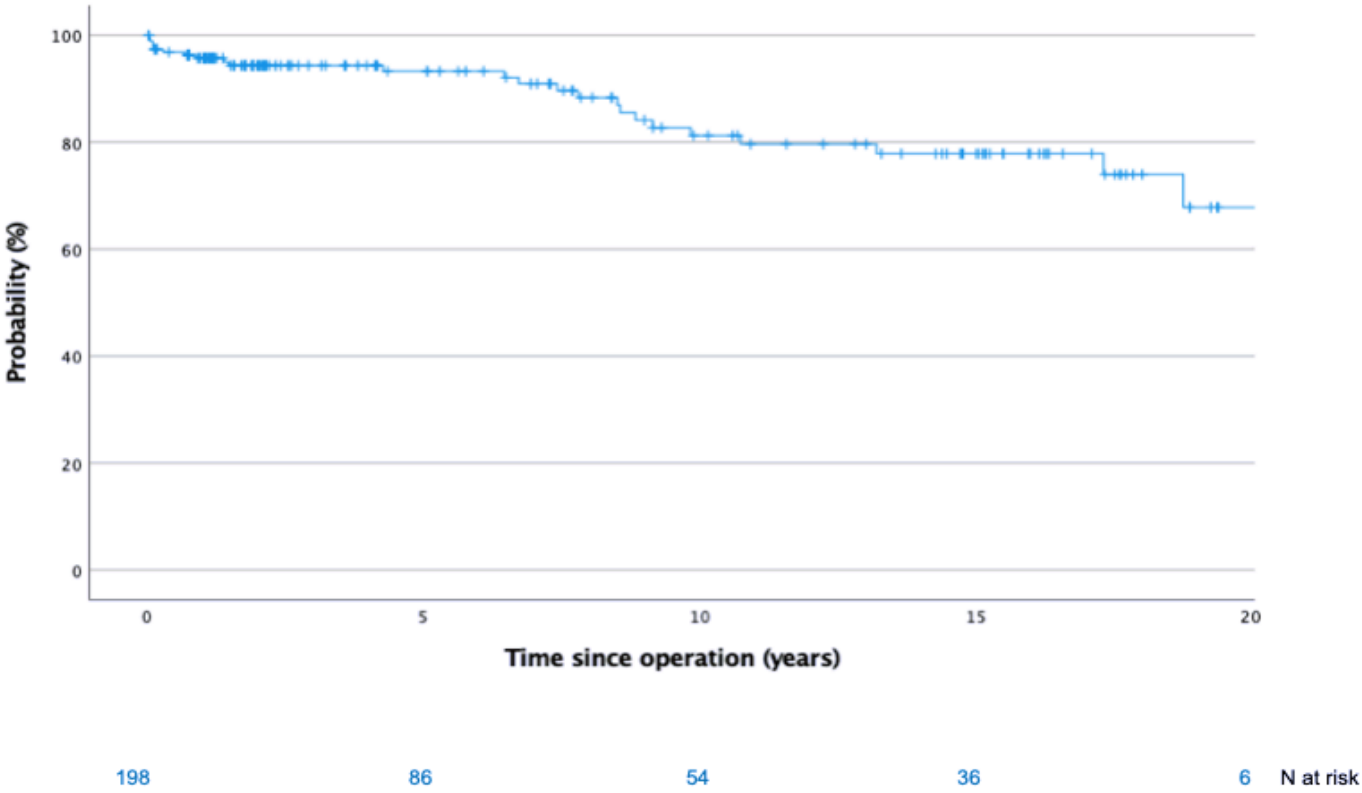

Figure 7 *Freedom from any cardiac reoperation*

a) Autograft

Sixteen patients (8.9%) underwent reoperation on the autograft (median: 7.8 years, range 0.1 to 21 years). Indications for reoperation were autograft dilatation with (n=4) or without relevant AR > 2 (n=2), isolated relevant AR (n=4), combined lesion (n=1), and active endocarditis (n=4, 3 after intravenous drug abuse). All patients who developed isolated AR presented with isolated aortic regurgitation at the time of the Ross procedure.

Four patients developed endocarditis postoperatively (mean 4.8 ± 3.4 years) requiring reoperation (unsupported n=3, supported n=1). Three of them were intravenous drug users. All of those required repair of a root abscess; one of them had a bicuspid autograft and the other two underwent the Ross procedure as a redo after aortic valve replacement.
In 3 additional instances (supported) endocarditis was suspected because of a localized perivalvular cavity resembling an endocarditic abscess. Blood cultures remained negative and the reoperations consisted of elimination of this cavity.
Overall risk of endocarditis was 0.54% per patient year (autograft: 0.27% per patient year, pulmonary conduit: 0.27% per patient year).

Reoperations included autograft valve replacement (n=5, 2.5%) and valve-sparing procedures (n=11, 5.5%). Of those, three patients (n=3/147) had received a stabilization as part of the Ross procedure, 9 (n=9/55) had no stabilization, and 2 (n=2/5) received a modified cylinder technique. All of the six patients that required a reoperation for autograft dilatation were in the unsupported group.

Six patients presented with autograft root dilatation with or without relevant AR between 9 to 21 years after surgery. One patient had previously undergone aortic valve reimplantation for root aneurysm of a regurgitant tricuspid valve. The other patient had previously undergone unicuspid valve repair and supracommissural replacement of the ascending aorta. External stabilization was not performed as part of the Ross procedure due to lack of sufficient tissue. Both patients were reoperated for autograft dilatation and cusp prolapse. A valve-sparing procedure (root remodeling) was performed in both cases.
The third patient underwent the Ross procedure as an emergency surgery for active endocarditis with root abscess. He received an annuloplasty (pericardium) without autograft stabilization. The patient presented with severe AR and autograft dilatation (46mm) 9.2 years postoperatively. The fourth patient presented with severe AR and autograft dilatation (47mm) 21 years postoperatively. External root stabilization had not been performed as part of the Ross procedure at that point in time. A valve-sparing procedure (root remodeling) was performed in both cases and there have been no complications since.
Another patient underwent the Ross procedure as reoperation after biological valve replacement. The patient had mild AR at discharge, which progressed to severe AR with autograft ectasia (40mm) 6 months postoperatively. The left cusp appeared hypoplastic and perforated. The auto-

graft was replaced and the patient was weaned from extracorporeal circulation but exhibited borderline low output syndrome. A coronary artery bypass on the LAD was performed for left ventricular dysfunction. The patient however developed uncontrollable coagulopathy and died one day after surgery.
The last patient underwent the Ross procedure for a combined lesion of a unicuspid valve at the age of 14. He presented with cusp prolapse and aortic dilatation (autograft 49mm, ascending aorta 51mm) 9 years postoperatively. A connective tissue disease was suspected. A valve-sparing procedure (root remodeling) was performed and there have been no complications since.

Overall, freedom from autograft reoperation was 96% at 1 year, 94% at 5 years, 89% at 10 years, and 85% at 15 years (**figure 8A).**

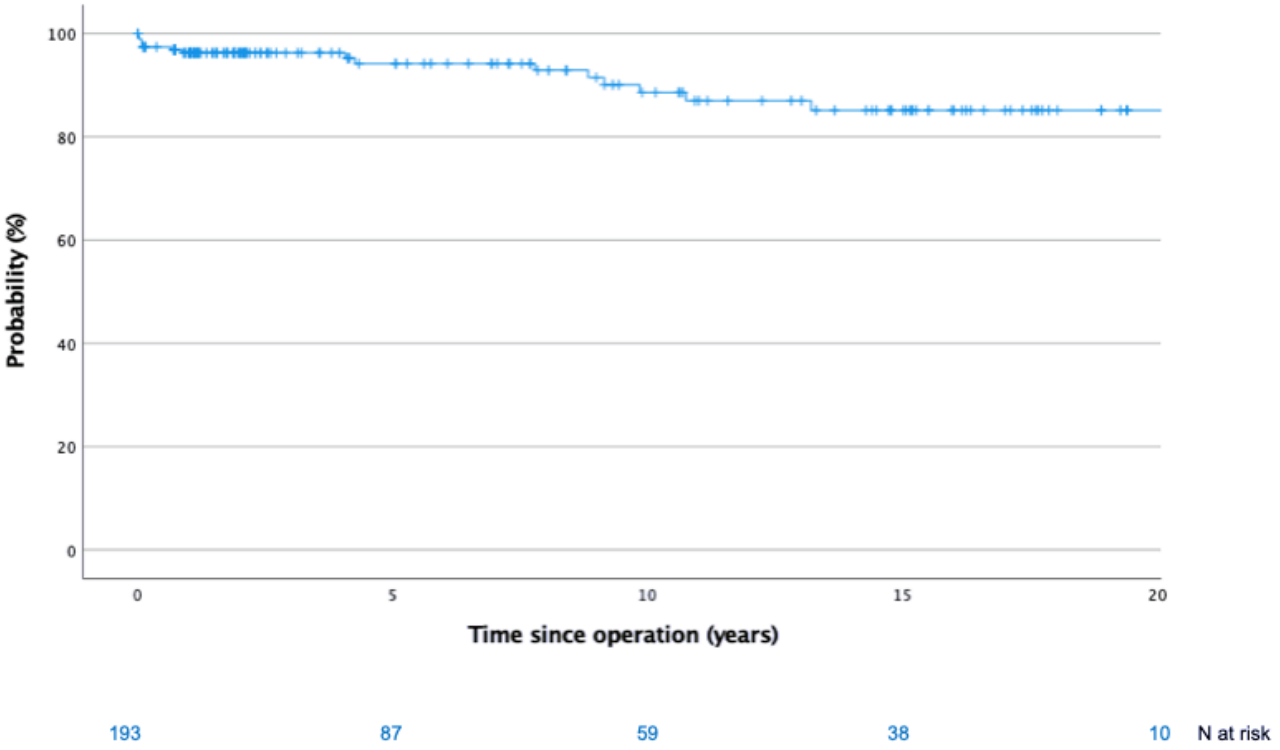

Figure 8A *Freedom from autograft reoperation*

Freedom from reoperation was higher in the supported group (99% at 1 year, and 93% at both 10 and 20 years) than in the unsupported group (89% at 1 year, 79% at 10 years, and 72% at 20 years) (p=0.003) (**figure 8B**).

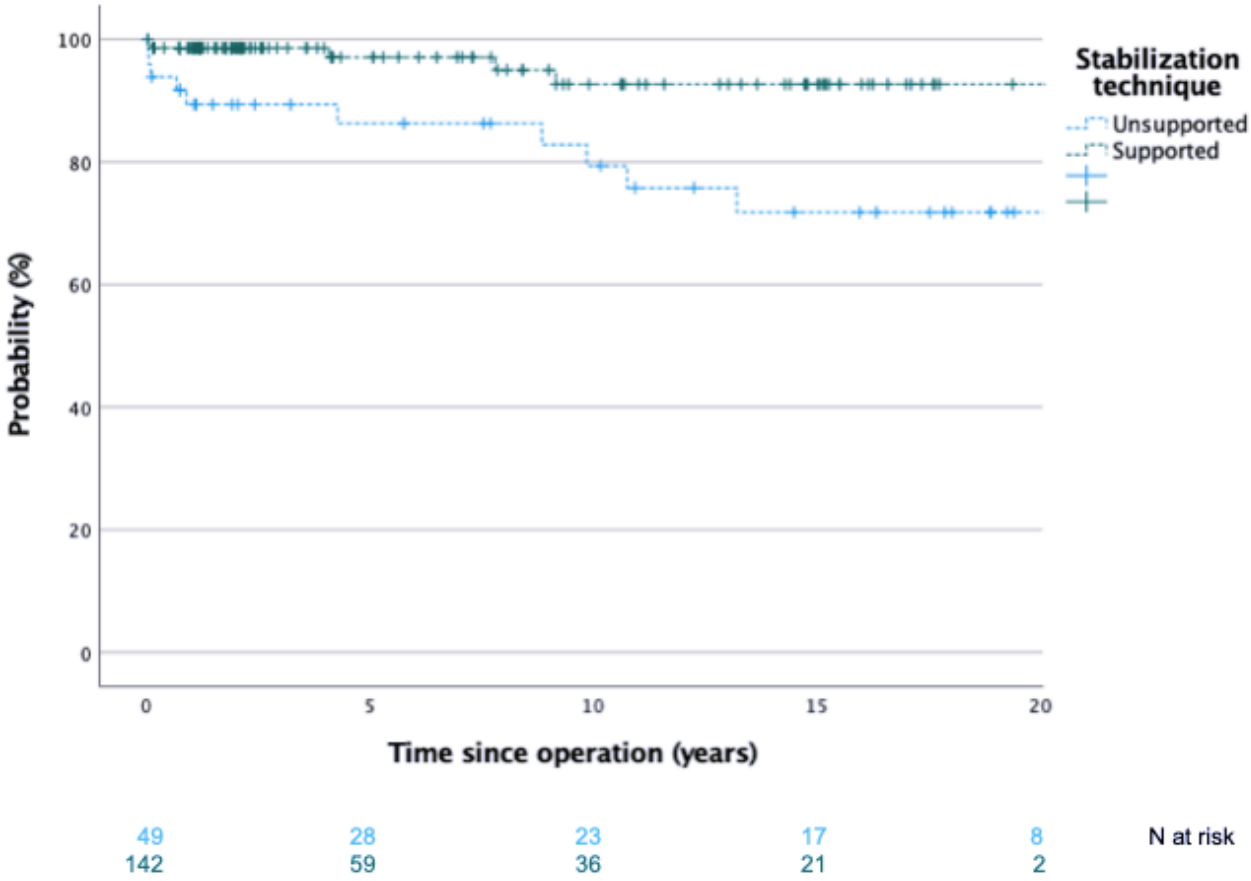

Figure 8B *Freedom from autograft reoperation with and without stabilization*

Freedom from reoperation showed a trend towards a superior outcome in the group with prior aortic valve repair (78% at 15 years) compared to the group with aortic valve replacement (73% at 15 years) (p=0.063) (**figure 8C**).

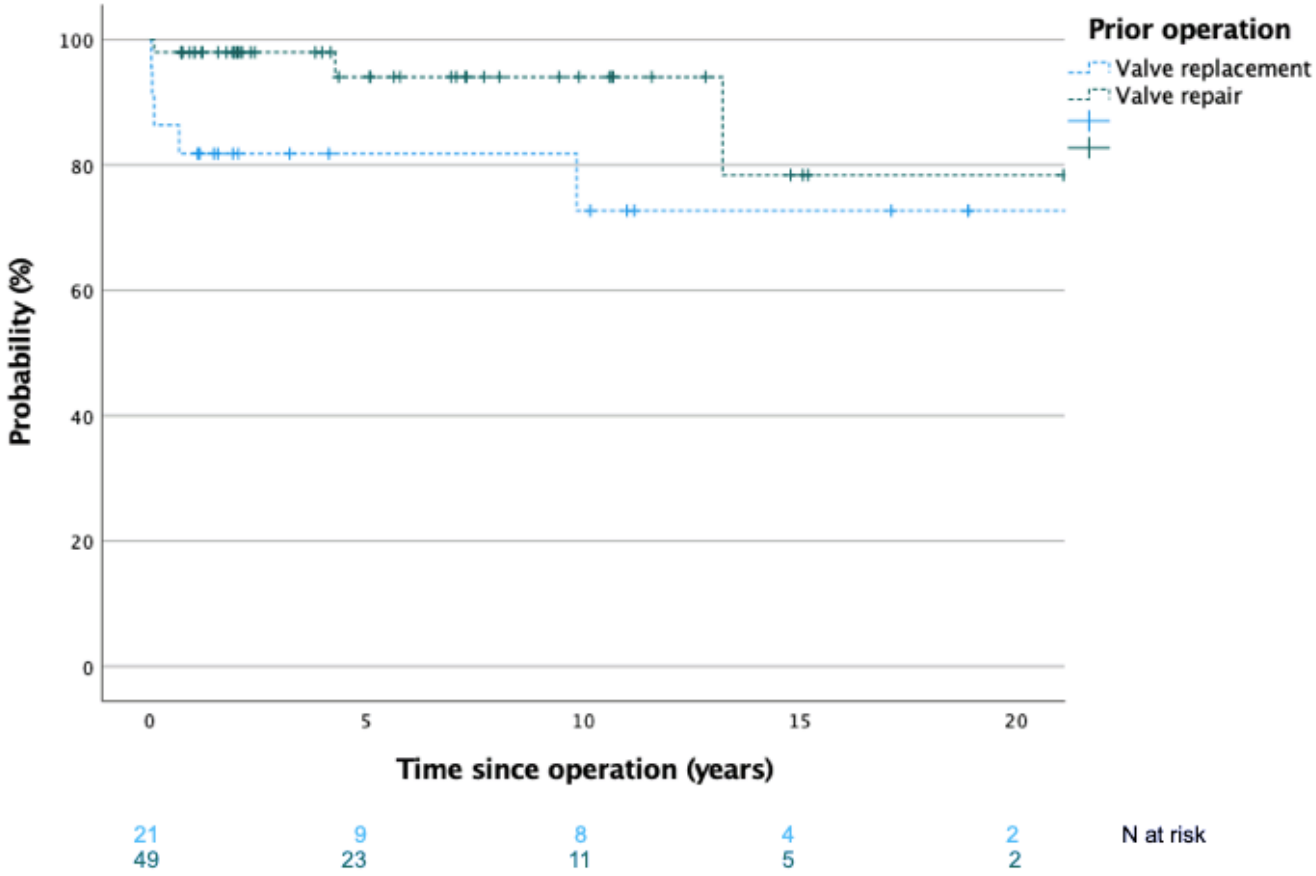

Figure 8C *Freedom from autograft reoperation with prior valve replacement or repair*

The analysis of underlying valve morphology showed a significant difference between cusp morphology (p=0.044). Ten-year freedom from reoperation was 79% in unicuspid morphology, 95% in bicuspid morphology, and 84% in tricuspid morphology (**figure 8D**).

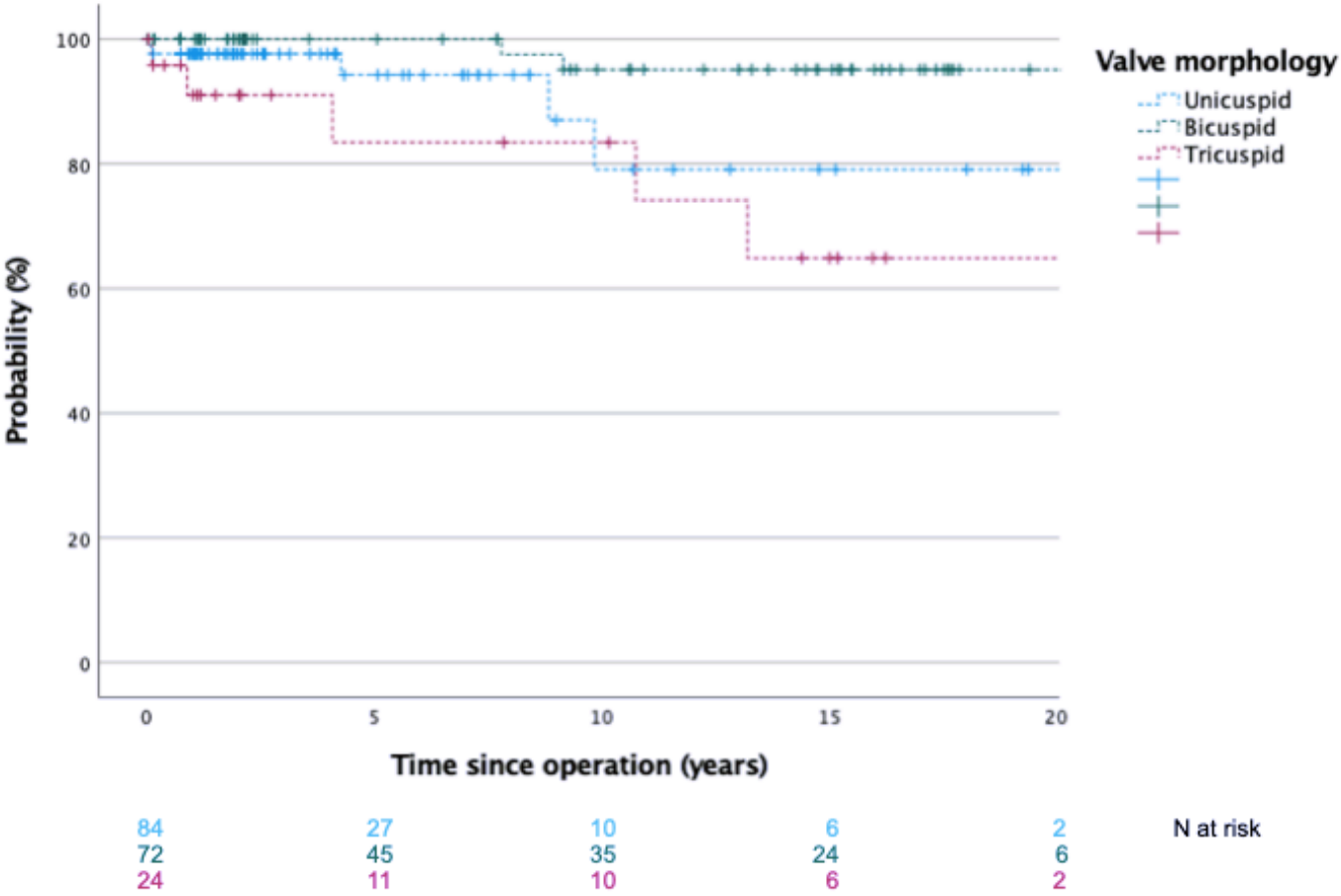

Figure 8D *Freedom from autograft reoperation according to valve morphology*

The analysis of surgical indication showed a significant difference between aortic valve regurgitation and stenosis (p=0.0004). At 10 years, freedom from reoperation was 76% with isolated regurgitation, 95% with isolated stenosis, and 92% with combined AR/AS (**figure 8E**).

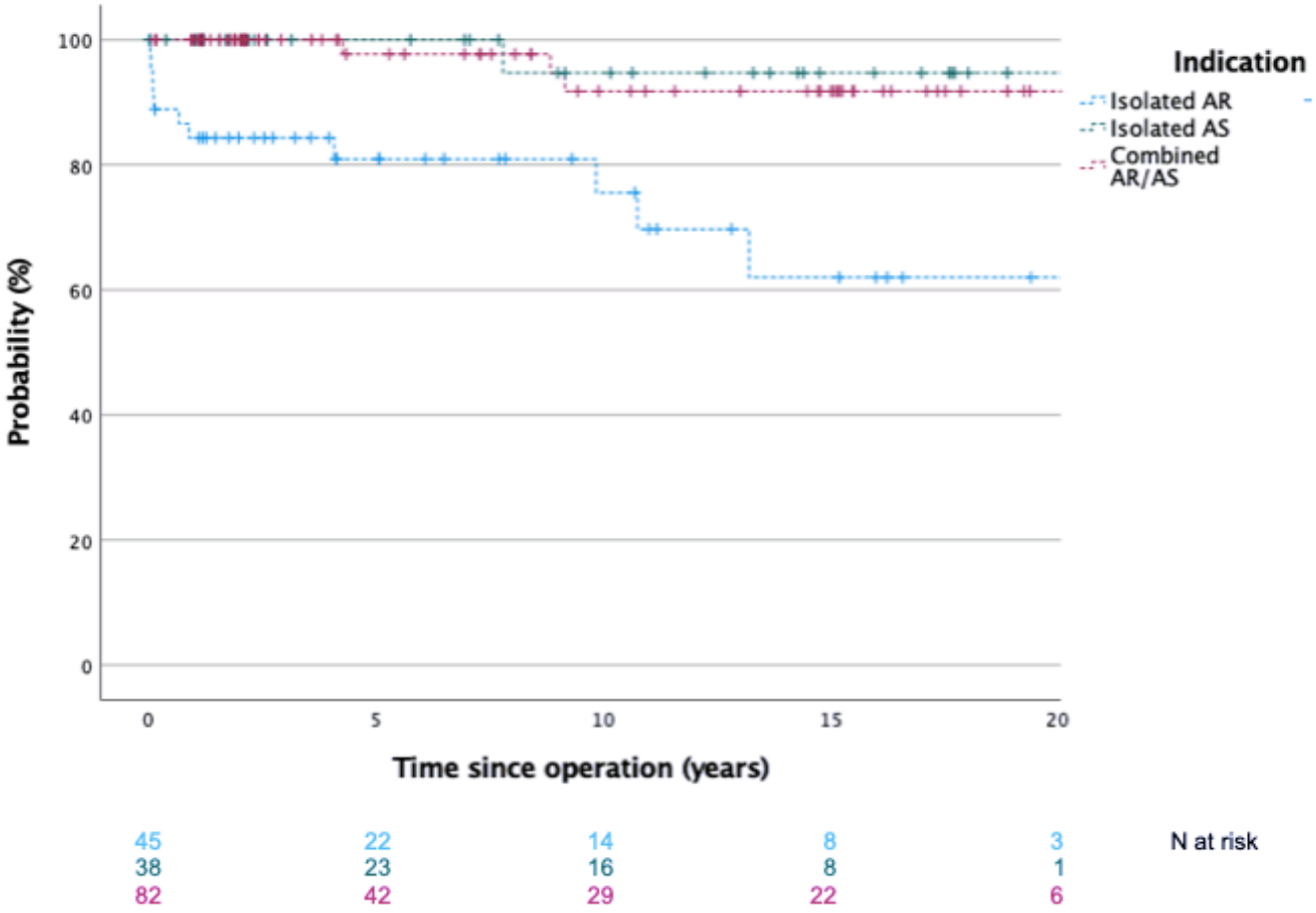

Figure 8E *Freedom from autograft reoperation according to surgical indication (AR=aortic regurgitation, AS=aortic stenosis)*

Interestingly, this difference only applied to patients who did not receive external root stabilization as part of the Ross procedure; freedom from reoperation (according to surgical indication) was higher in the group with external autograft stabilization (p=0.0012).

Patients without root stabilization showed a significant difference according to surgical indication (at 10 years, freedom from reoperation was 76% with isolated regurgitation, 95% with isolated stenosis, and 92% with combined AR/AS; p=0.006). Patients with root stabilization showed no difference according to surgical indication (at 10 years, freedom from reoperation was 88% with isolated regurgitation, 92% with isolated stenosis, and 95% with a combined AR/AS; p=0.587) (**figure 8F**).

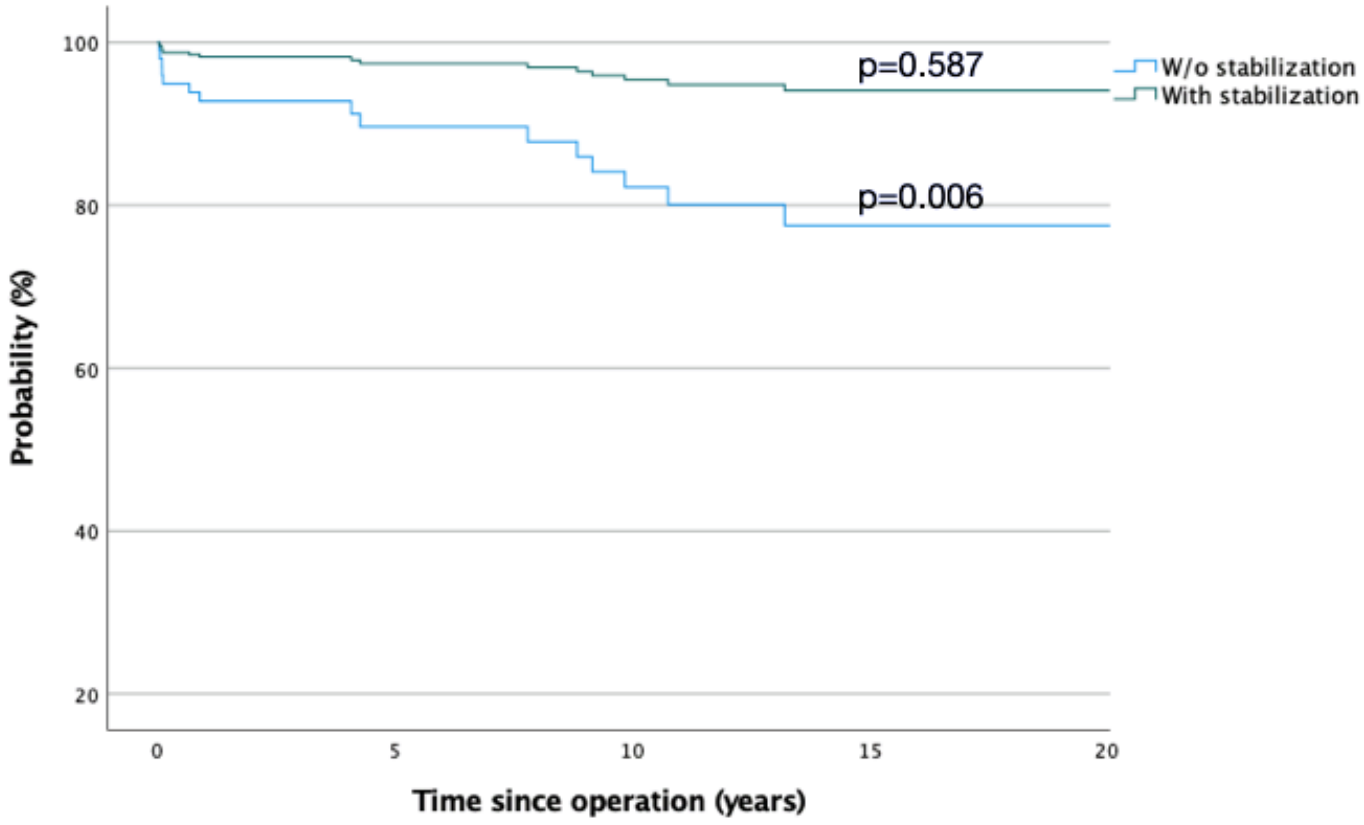

Figure 8F *Cox regression analyzing the impact of a stabilization technique on freedom from autograft reoperation according to surgical indication*

Freedom from reintervention was lower in the middle-aged patient population (18 to 40 years) (p=0.002; HR 0.864; 95% CI 0.788-0.949).

Freedom from reoperation was lower in patients with prior endocarditis compared to patients without (84% at 5 years and 69% at 15 years vs 96% at 5 years and 88% at 15 years; p=0.011) (**figure 8G**).

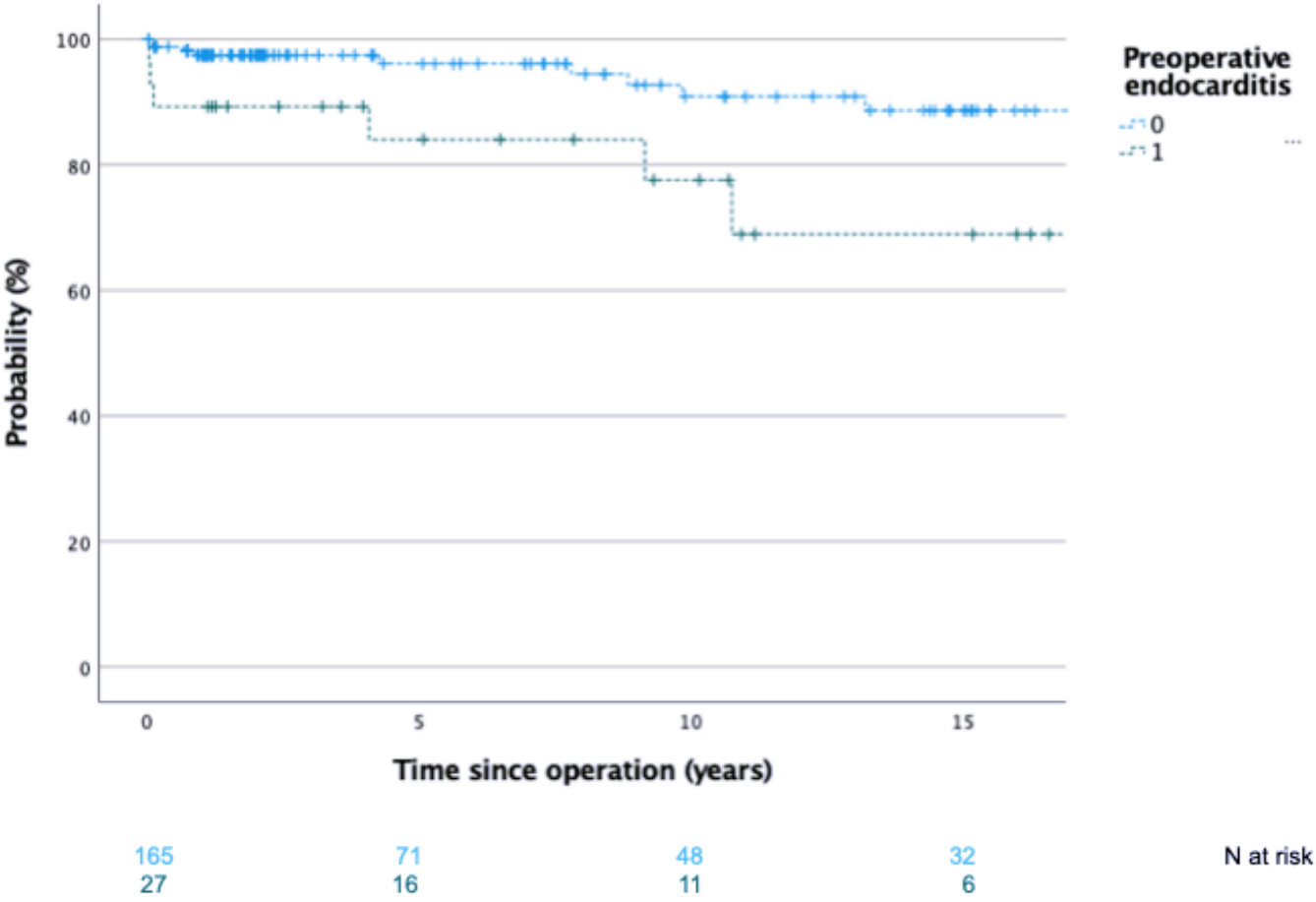

Figure 8G *Freedom from autograft reoperation in patients with preoperative endocarditis*

b) Right ventricular pulmonary artery

Seven patients (3.5%) underwent reoperations on the right ventricular pulmonary conduit (median: 7.4 years, range 1.4 to 18.8 years postoperatively). Of those, 2 patients (n=2/156; 1.3%) had a homograft, 4 (n=4/35; 11.4%) a bovine jugular vein, and 1 (n=1/10; 10%) a biological valve prosthesis.
The majority of the reinterventions were necessary in the pediatric patient population (n=4, 2%). Indication for reintervention was endocarditis (n=4) and degeneration (n=3).

Four (2%) patients presented with isolated pulmonary conduit endocarditis (mean 6.2 ± 3.4 years postoperatively). All patients affected were <18 years at the time of the Ross procedure. Three of those had a bovine jugular vein (Contegra) as a conduit. The overall risk of endocarditis on the pulmonary conduit was 0.27% per patient-year.
All patients received a pulmonary valve replacement and six patients required additional interventions (balloon dilatation) or implantation of a bovine transcatheter pulmonary valve ('Melody valve'). Overall freedom from RVPA reoperation was 100% at 1 year, 99% at 5 years, 93% at 10 years, and 87% at 15 years (**figure 9**).

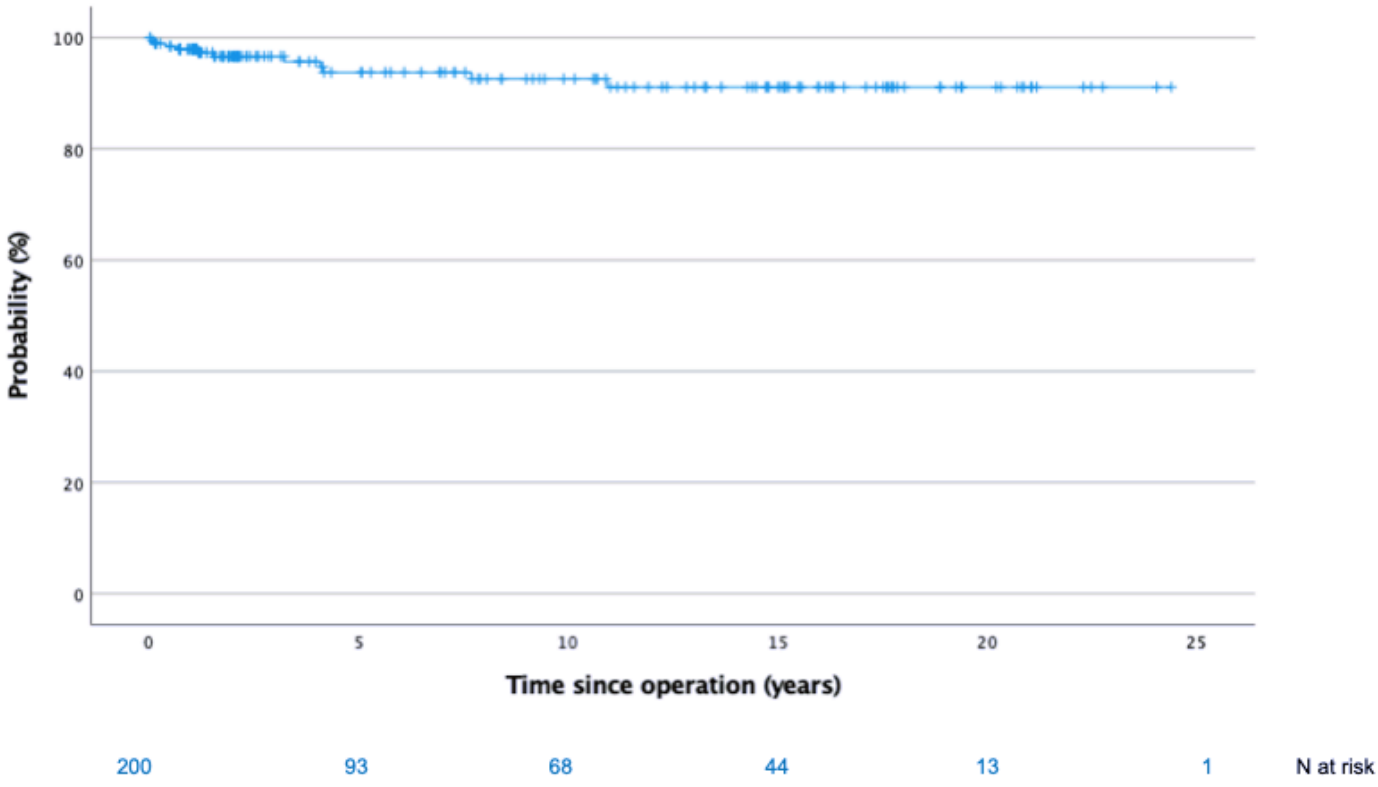

Figure 9 *Freedom from RV-PA reoperation*

The analysis of RVPA prosthesis showed a trend towards a higher freedom from reoperation in the Homograft (100% at 1 and 5 years, and 96% at 10 and 15 years) and the biological valve prosthesis group (and 100% up 15 years) compared to the Contegra group (100% at 1 year, 97% at 5 years, and 86% at 10 and 15 years) (p=0.069) (**figure 9A**).

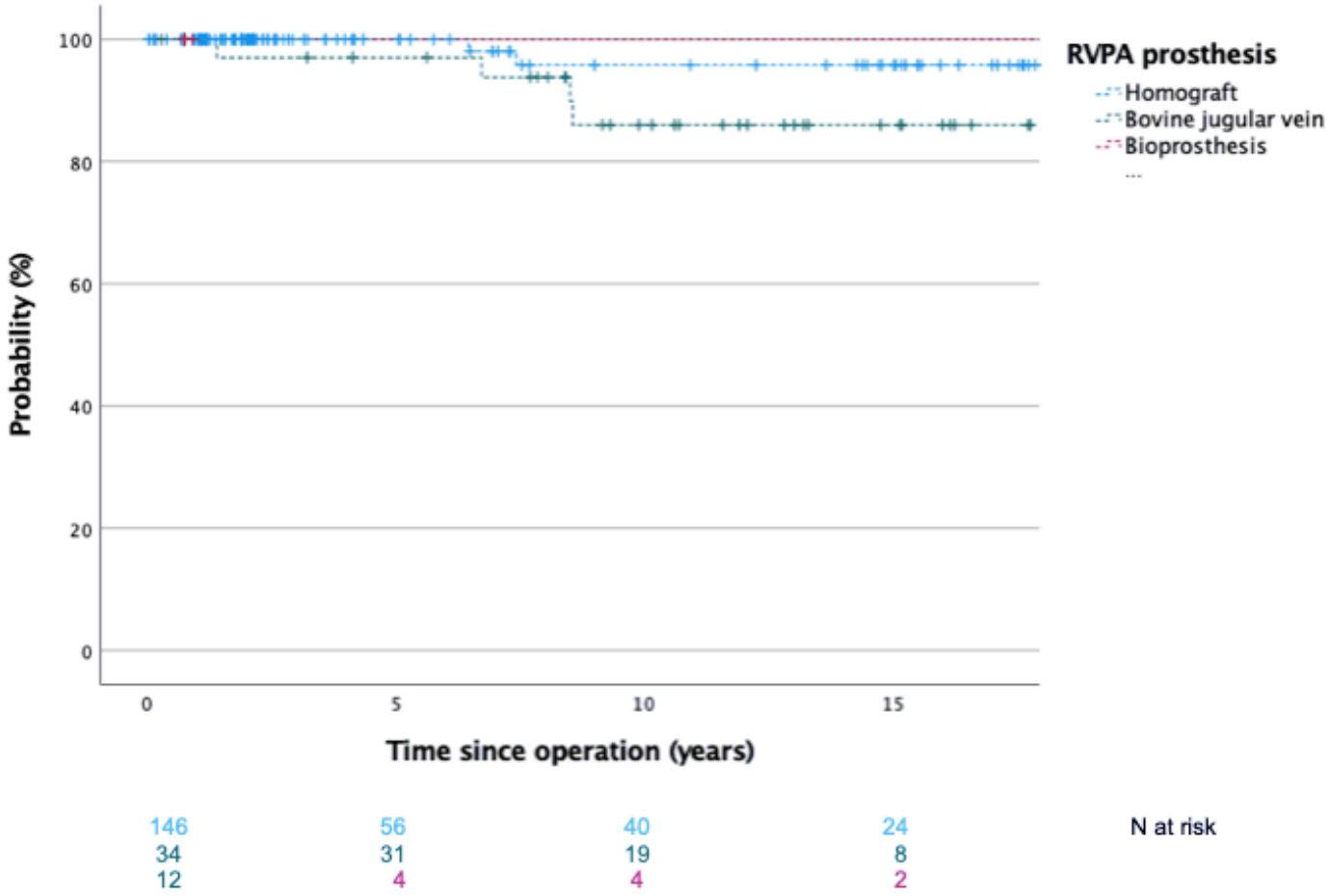

Figure 9A *Freedom from RV-PA reoperation according to conduit type (Homograft, bovine jugular vein, biological valve prosthesis)*

Freedom from reoperation differed significantly according to conduit type, with the homograft being superior to the bovine jugular vein [p=0.006; HR 0.93; 95% CI 0.17-0.504]. The risk of reoperation decreased with age (>18 years) [p=0.026; HR 0.864; 95% CI 0.788-0.949].

3. Autograft root dynamics

A relevant increase of autograft sinus diameter (>40mm) was observed in 23 (13%) patients (unicuspid n=8/87, bicuspid n=12/76, tricuspid n=2/25, unknown n=1/14). Of those, 12 (n=12/147) patients received root stabilization as part of the Ross procedure and 11 (n=11/55) did not.
Overall, freedom from autograft dilatation (>40mm) was 84% at 10 years and 75% at 15 years. Freedom from relevant autograft dilatation (>45mm) was 93% at 10 years and 90% at 15 years.

Freedom from autograft dilatation (>40mm) at 15 years was 77% with and 72% without stabilization (p=0.839). Freedom from marked autograft dilatation (>45mm) at 15 years was 94% with and 82% without stabilization (p=0.094) (**figure 10**). Only two patients developed sinus dilatation >50mm (both unsupported).

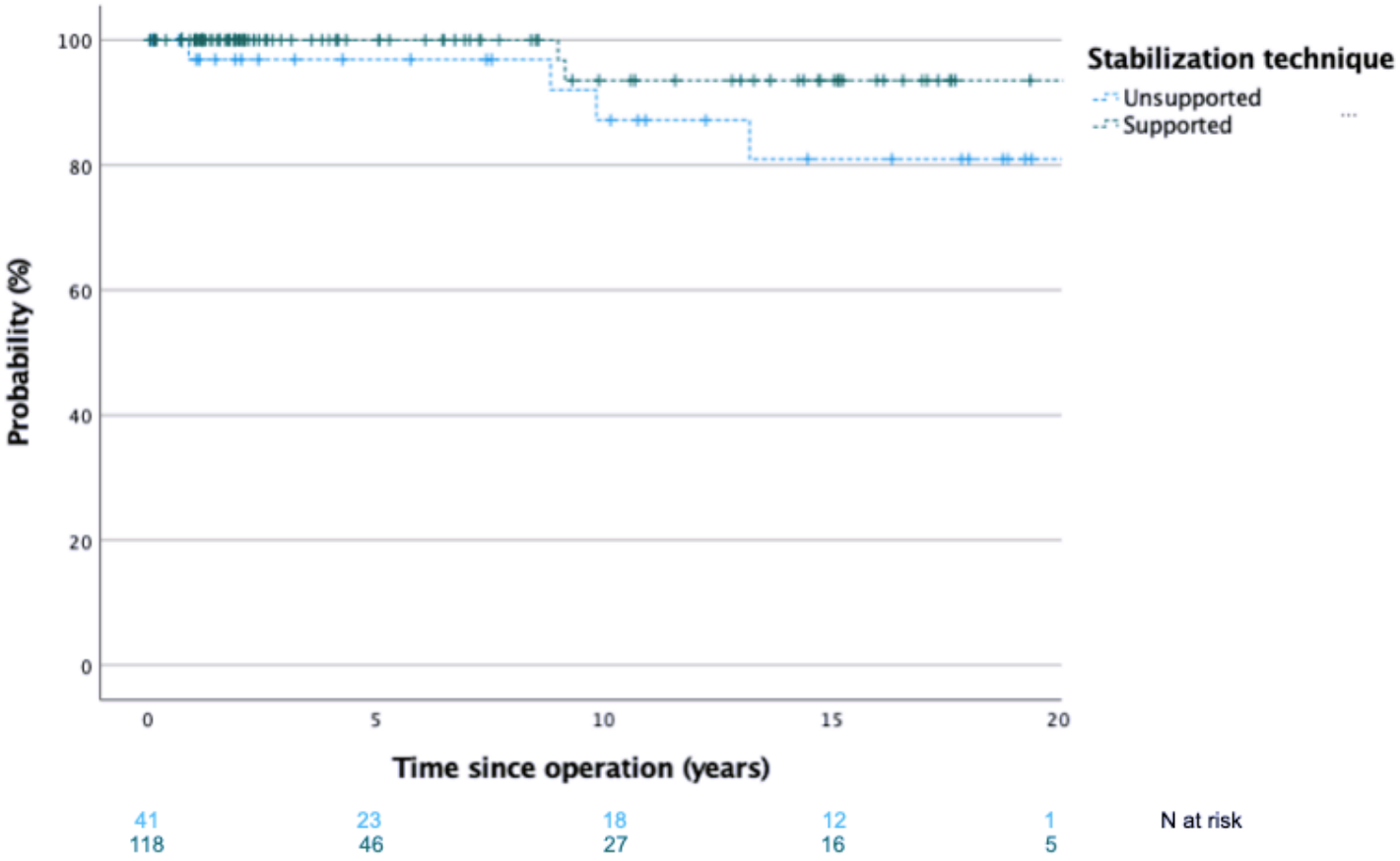

Figure 10 *Freedom from autograft dilatation (>45mm) with and without stabilization*

In a separate analysis, patients without any prior aortic valve operation had a higher ten-year freedom from dilatation (>40mm) (90%) compared to those with prior aortic valve repair (75%) and conventional aortic valve replacement (70%) (p=0.383).

The analysis of underlying valve morphology showed no significant difference in freedom from dilatation with and without support. Ten-year freedom from autograft dilatation (>45mm) for unicuspid valves was 83% with and 60% without stabilization (p=0.413), for bicuspid valves it was 96% with and 100% without stabilization (p=0.897), and for tricuspid valves it was 100% with and 86% without stabilization (p=0.218).

Progression of mean root dimensions was highest in the first 5 postoperative years. Patients with stabilization showed an indexed progression of 0.712 mm/(year*m), p=0.003, while patients without stabilization showed a progression of 1.554 mm/(year*m), p=0.001 (**figure 11**). The progression rates were higher in patients without compared to those with support in the first five years (p=0.045). After 5 years, progression rates were significant and similar in each group (0.248 mm/(year*m); p<0.001). They were however lower than in the first 5 years (p<0.001).

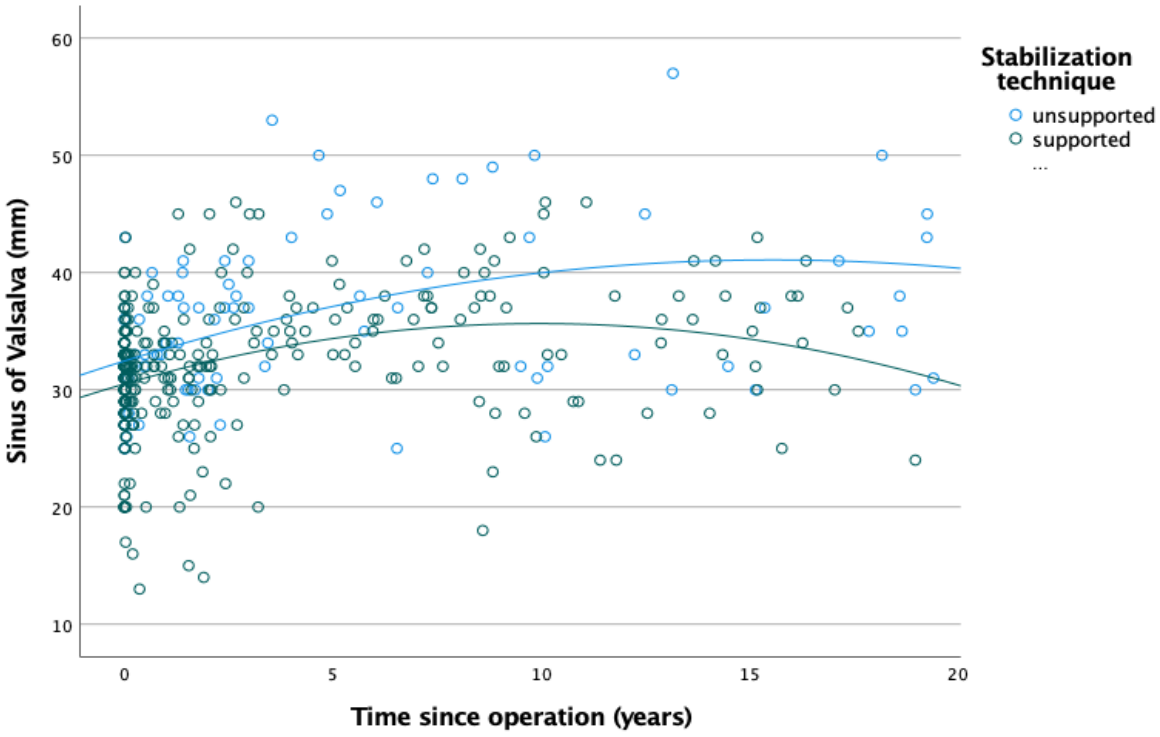

Figure 11 *Changes in autograft diameter with and without stabilization*

The significant difference observed between the groups in the first 5 years persisted for the remaining observation period. The findings were the same when absolute diameters or diameters indexed for BSA were used.

In a separate analysis, patients with tricuspid valves exhibited a significantly higher increase in the first 5 postoperative years (1.213 mm/(year*m); p=0.008) than patients with bicuspid valves (0.318 mm/(year*m)) and unicuspid valves (0.560 mm/(year*m)).

In patients with ascending aortic replacement (n=31), freedom from autograft dilatation (>40mm) was 100% at 10 years with and 83% without stabilization (p=0.102). In patients with preservation of the native ascending aorta, freedom from autograft dilatation (>40mm) at 15 years was 83% with and 76% without external support (p=0.892).

In a separate analysis, patients with aortic regurgitation and aortic stenosis showed a significant indexed root size progression over time (AR: 0.688mm/(year*m), p=0.038; AS: 0.991mm/(year*m), p=0.001) if they did not receive root stabilization. Patients with stabilization showed lower progression rates in both groups (AR: 0.019mm/(year*m), p=0.962; AS: 0.091mm/(year*m), p=0.707).

A lack of external stabilization was the only significant predictive factor for aortic root dilatation [p=0.001; HR 0.198; 95% CI 0.067-0.528]. Annuloplasty [p=0.161; HR 0.33; 95% CI 0.068-1.564] and replacement of the ascending aorta [p=0.05; HR 0.12; 95% CI 0.014-1.003] did not reach significance. Preoperative isolated aortic regurgitation [p=0.185; HR 1.96; 95% CI 0.724-5.32] or a bicuspid valve morphology [p=0.568; HR 1.486; 95% CI 0.382-5.784] did not show an increased risk of dilatation.

4. Autograft regurgitation

Eighteen patients developed AR ≥ 2 postoperatively (supported n=9, unsupported n=9) a median of 8.8 years [0.03-6.5] after surgery. Of these, 15 had no or only trivial AR at discharge (supported n= 9, unsupported n=6). The remaining three patients had AR 2 at discharge (unsupported). In two patients, the AR decreased and is now trivial (3 and 20 years postoperatively). The other patient developed severe AR and required a reoperation after 8 months.

AR increased over time and remained stable in 10 of those individuals; it progressed to relevant AR in 7 instances (4 in conjunction with autograft dilatation) and required reoperation (supported n=2, unsupported n=3).

Overall, freedom from AR ≥ 2 was 89% at 10 and 82% at 15 years. Freedom from AR ≥ 2 in the unsupported group was 88% at 10 years and 83% at 15 years. In the supported group, it was 88% at 10 years and 80% at 15 years (p=0.722) (**figure 12**). There was no difference between those without replacement (88%) and those with replacement of the ascending aorta (86%) (p=0.198).

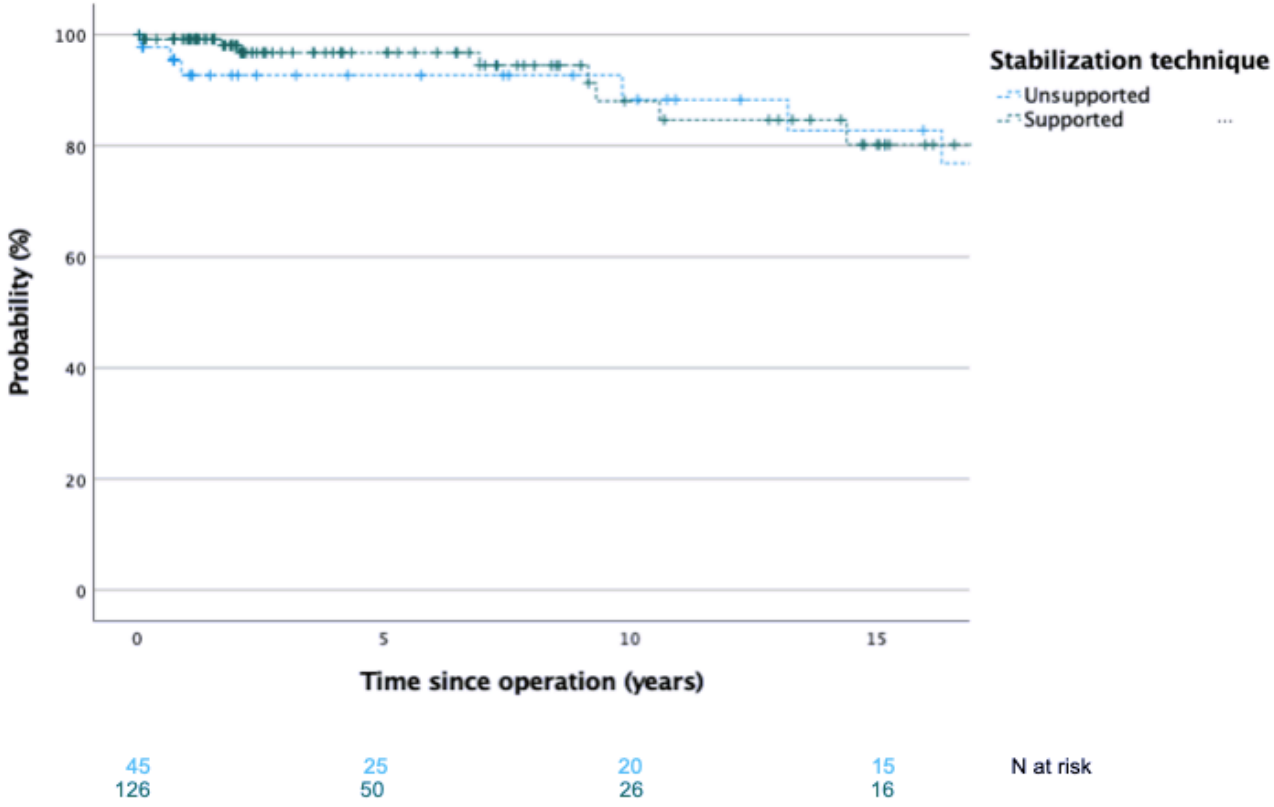

Figure 12 *Freedom from AR ≥ 2 with and without stabilization*

A preoperative LVEDd of more than 60mm was associated with a higher risk for recurrent AR [p= 0.020, HR 1.086, 95% CI 1.013 - 1.164].

Freedom from AR ≥ 2 in the group with a preoperative LVEDd >60mm was 67% at 10 and 15 years. In the group with a LVEDd <60mm, it was 96% at 10 years and 85% at 15 years (p=0.015) (**figure 12A**).

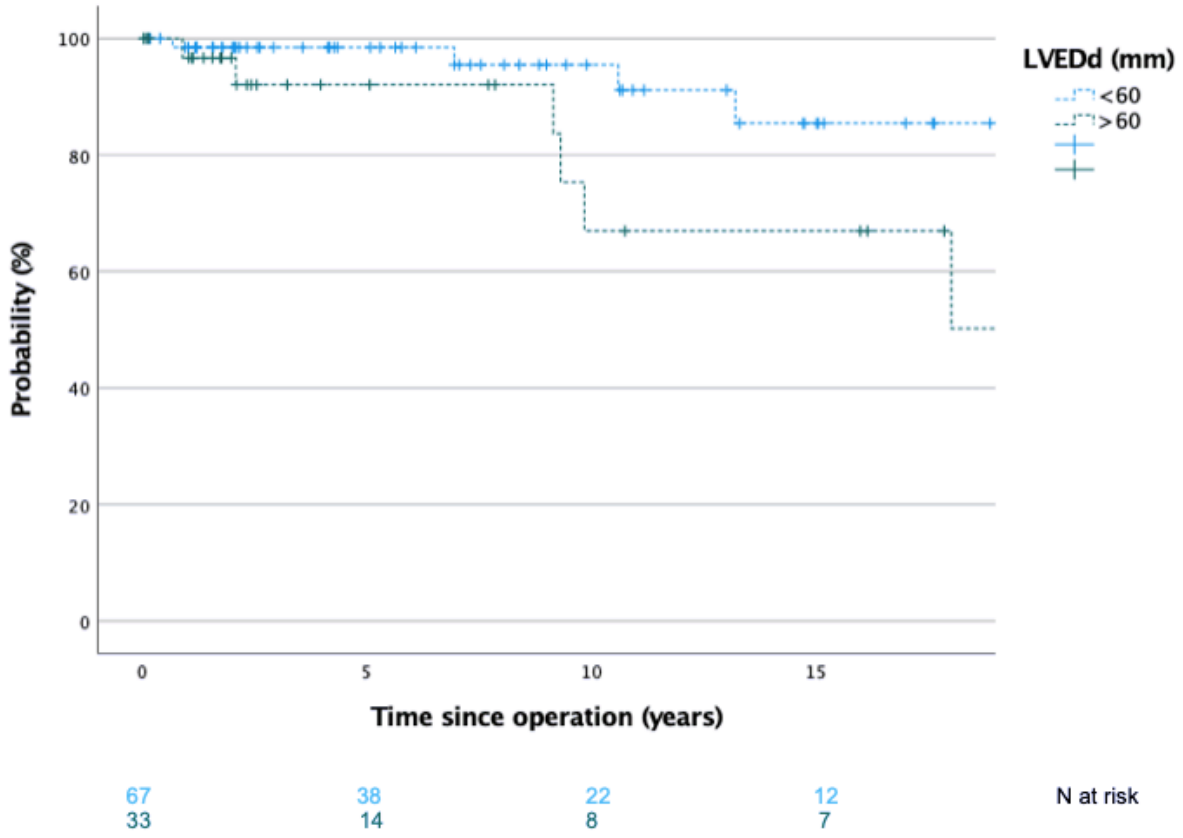

Figure 12A *Freedom from recurrent AR ≥ 2 with a LVEDd > or < than 60mm*

Cusp morphology did not affect the recurrence of AR [p=0.720, HR -0.356, 95% CI -0.179-0.123]. Hemodynamics were normal in all but one patient (mean gradient: 5.22 ± 5.17mmHg, maximum gradient 9.43 ± 9.4mmHg).

5. Pulmonary regurgitation and stenosis

Pulmonary regurgitation (PR)

Seven patients developed PR ≥ 2 (Homograft n=6, bovine jugular vein n=1) a mean of 10.3 ± 7.9 years after surgery. Three of those had no or only trivial PR at the time of discharge. Only one patient developed PR 3, which has remained stable.

Freedom from PR ≥ 2 was 96% at 10 years and 94% at 15 years. There was no difference between the different pulmonary conduits (freedom from PR ≥ 2 at 10 years: Homograft 96%, bovine jugular vein 97%, biological valve prosthesis 100%; p=0.764).

Pulmonary stenosis (PS)

Twenty-four (13%) patients developed mild to moderate stenosis (maximum gradient between 30 and 60mmHg) (Homograft n=15/142, bovine jugular vein n=8/32, biological valve prosthesis n=1/5) a mean of 11 ± 6.8 years after surgery. Median conduit size was 26mm.

Three of those required a reoperation (bovine jugular vein n=2, biological valve prosthesis n=1) and presented with a mean gradient of 45mmHg at the time of the reoperation. Pathology reports showed neovascularization (n=1) and chronic inflammation of the adventitia (n=1) of the pulmonary conduit (bovine jugular vein). The biological valve prosthesis showed calcification and chronic inflammation.

Freedom from relevant stenosis was 93% at 5 years, 75% at 10 years, and 68% at 15 years. Freedom from relevant stenosis was higher in the Homograft group (89% at 10 and 15 years) and in the biological valve prosthesis group (100% at 10 and 15 years) than in the bovine jugular vein group (97% at 10 years and 73% at 15 years) (p=0.382) (**figure 13**).

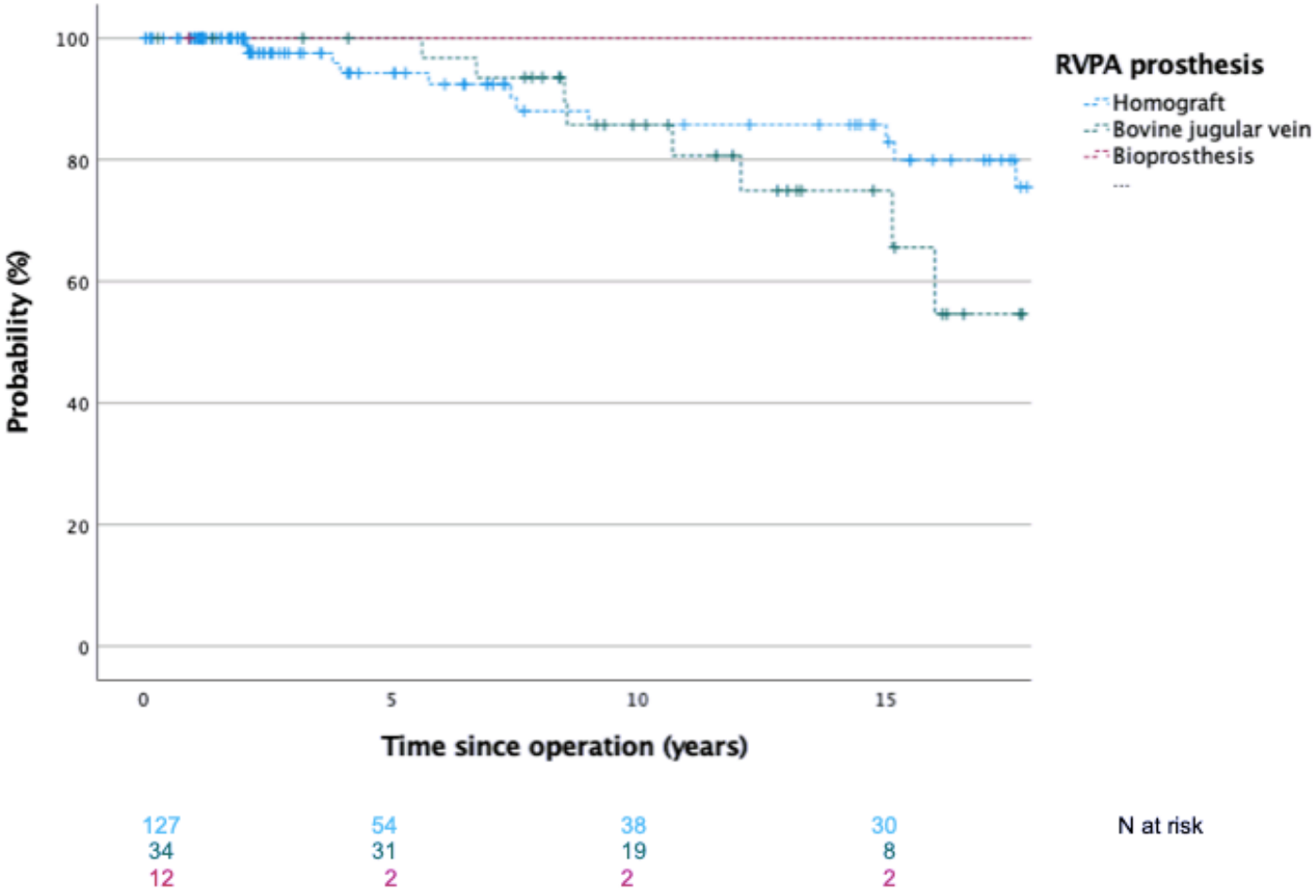

Figure 13 *Freedom from stenosis according to conduit type*

V. Discussion

The ideal treatment of aortic valve disease in the younger patient population remains debatable. Matching the patient to the most suitable aortic valve substitute is particularly important in the younger and middle-aged patient population.
While conventional valve replacements are less complex in implantation, the Ross procedure is the only aortic valve replacement using living tissue as a substitute. It thus allows for near physiological hemodynamics and adaptive remodeling [35,50,108]. It shows a superior quality of life [51,81], remarkable resistance to infection, and freedom from anticoagulation therapy.
Concerns that a univalvular disease is corrected by bivalvular surgery have faded into the background with several studies from high-volume centers reporting excellent mid- to long-term results [43,68,89,109]. The procedure achieves a long-term survival and quality of life equivalent to that of the age- and gender-matched general population [43-45,73,110,111]. Studies have also shown that good results are achieved when combined with other interventions or the treatment of complex cases [111-113].

Nevertheless, surgical complexity raises concerns about its perioperative risk and reproducibility [114]. Thus, we have attempted to simplify the procedure while applying a technique that provides the required stabilization to the autograft in order to increase its durability. In fact, long-term valve durability remains a concern after the Ross procedure. Autograft regurgitation may occur due to root dilatation and/or cusp deformation [115] and the pulmonary conduit may degenerate over time and require an additional reoperation. Reoperations are considered even more complex and may impair the procedure's advantages [116]. An in-depth understanding of the mechanisms of autograft and pulmonary conduit failure, and the protection against this drawback, are therefore necessary.

A. Comparison to alternative valve prostheses

The optimal valve prostheses should be carefully tailored to each patient, as this choice has been shown to affect long-term results and quality of life.

Biological valve prostheses are affiliated with a higher risk of reoperation than mechanical valves due to structural valve deterioration [22]. However, mechanical valves command lifelong anticoagulation, which increases the risk of thromboembolism and hemorrhage [117]. Hence, American guidelines recommended the use of mechanical valves in patients < 50 years and biological valve prostheses in patients > 70 years [3]. Earlier guidelines recommended mechanical valves for patients < 60 years. European guidelines recommend the use of mechanical prostheses in patients < 60 years and biological valve prostheses in patients > 65 years [29]. The discrepancy between American and European guidelines reflects the uncertainty in the choice of aortic valve replacement in the younger patient population. Despite several studies demonstrating superior results of

the Ross procedure in comparison to prosthetic valve replacement in the younger patient population, current American guidelines give the Ross procedure a class IIb recommendation [3]. Meanwhile, the European guidelines do not mention the Ross procedure as a surgical option [29].

Further, these guidelines are mainly based on historical randomized controlled trials [20,118]. A more recent randomized trial [119] and several observational studies comparing newer generation devices have further influenced these guidelines as of late. A recent publication systematically reviewed studies comparing long-term results between biological and mechanical valves in non-elderly patients [32]. Results were conflicting, with some showing improved survival after mechanical valve implantation and others showing no difference. Biological valves however continuously show a less optimal outcome in the non-elderly patient population. In comparison, the Ross procedure has recently been associated with a lower overall risk of reoperation [52]. In contrast, the risk of reoperation was higher than after mechanical valve replacement [52]. Despite these results, implantation of biological valve prostheses in particular has increased. This trend has somewhat been influenced by the promise of future transcatheter aortic valve implantation.

A randomized controlled trial by Yacoub et al. compared the Ross procedure to aortic homograft replacements [34]. In the Ross group, survival at 13 years was higher (95% vs 78%, p=0.006) and was identical to the age- and gender-matched general British population. Interestingly, half of the Ross patient population had a higher perioperative risk (42% with previous cardiac surgery, 8% with active endocarditis) [34]. Despite the fact that homografts are no longer considered a surgical option for elective aortic valve replacement, this study was the first to show the possibility of restoring late survival after aortic valve surgery in the younger patient population. Our cohort shows a similar risk profile and our results concur with these findings.

Mechanical valve prostheses

The choice of valve prosthesis often revolves around the durability issue, which explains the guideline recommendations favoring mechanical aortic valve replacement in patients aged <50 years. Nevertheless, the incidence and impact of other valve-related complications cannot be dismissed. Mechanical valves require lifelong anticoagulation, which increases the risk of thromboembolism and hemorrhage [20,21,117,118,120]. Studies have reported a cumulative incidence of stroke or major bleeding in patients undergoing mechanical valve replacement of 1% per year [52]. Further, the associated 30-day mortality after stroke or major bleeding showed sobering results at 5.6% and 2.6%, respectively [52]. These data are consistent with previously reported outcomes. The Toronto group reported a cumulative risk of stroke or major bleeding of 1% per year in young patients undergoing mechanical aortic replacement [78].
An important complication is the pannus formation with an occurrence of 0.24% per patient per year [121]. There have been few studies comparing mechanical valves and autograft valve replacement [78-80]. A study from 2016 reported that freedom from reintervention and overall sur-

vival are equivalent in the Ross and mechanical group [78]. However, freedom from valve-related mortality was superior in the Ross group (p=0.03) (97% vs 88% at 20 years after mechanical aortic valve replacement). Further, long-term freedom from complications was superior after the Ross procedure (Ross: 99% vs mechanical aortic valve replacement 91% at 20 years, p<0.001) [78]. More recently, autograft valve replacement showed an overall superior long-term survival at 20 years (Ross: 95%, mechanical aortic valve replacement: 68%, p < 0.001) despite a similar early mortality (Ross: 0.3%, mechanical aortic valve replacement: 0.8%; p=0.5) [80]. In a large long-term study, a mortality rate between 20% and 30% at 15 years was reported (compared to 5% at 15 years after the Ross procedure) [22]. Our results compare favorably to these studies. Survival was equivalent to that of the age-and gender-matched general population and freedom from complications was low. However, a reoperation in this young patient population is almost inevitable. A low reoperation rate is important; however, a slightly higher rate is acceptable. Therefore, the time between reoperations should be kept at a maximum, which the Ross procedure achieves in addition to an excellent survival rate and quality of life.

Further, given the negative side effects of anticoagulation medicine, non-vitamin K antagonist oral anticoagulants (NOACs) were suggested as an alternative. NOACs are currently contraindicated for mechanical valves (based on the RE-ALIGN randomized trial [Dabigatran versus Warfarin]) [122]. The trial was prematurely terminated due to excess bleeding and thromboembolic events in the Dabigatran group. The use of NOACs as an anticoagulation strategy for mechanical valves remains an area of interest despite the unfavorable results of the RE-ALIGN trial [123]. Recent prospective studies observing a relatively young patient population, who achieved adequate INR levels, reported a rate of adverse events (i.e., thromboembolism, thrombosis, bleeding) of 4.44% per patient-year in the lower INR group [123]. This postulates that mechanical valves carry a significant hemorrhagic and thromboembolic risk despite lower INR targets, which is particularly relevant for young patients. Further, mechanical valves that only require antiplatelet therapy are being tested. Early and mid-term results however are not yet available [123].

Biological valve prostheses

To date, the most important predictor of reoperation for biological valve degeneration remains age at implantation. The use of biological valve prostheses in non-elderly patients (<60 years) remains problematic. Several studies have shown poor durability with excess mortality when implanted in young adults [25-27]. Recently, mortality in patients aged 45 to 54 years at 15 years was found to be 30.6% [22].

In patients < 60 years, freedom from reintervention was found to be 70% at 10 years and 50% at 15 years [22,23]. In patients > 60 years, freedom from reintervention was found to be 85% at 15 years. ESC/EACTS guidelines therefore recommend the use of biological valve prostheses for patients > 60 years [29].

Further, similar to mechanical valves, the excess mortality is inversely proportional to patient age at the time of the operation. It is further augmented by the presence of patient prosthesis-mismatch [124]. While biological valves eliminate the drawback of lifelong anticoagulation, they are associated with the risk of patient–prosthesis mismatch. It is a frequently observed problem and is seen in up to 40% of patients at the time of hospital discharge [124,125]. Studies have shown that it leads to a decreased durability, both in terms of structural valve degeneration and survival in the younger patient population [126,127].
According to Etnel et al., a 45-year-old patient undergoing biological valve replacement has a life expectancy of 21 years (compared to 33 years in the age- and gender-matched general population) and a lifetime risk of structural valve deterioration (71%) or reoperation (78%) [128]. In comparison, the lifetime risk of reoperation is 25% in elderly patients [15]. A recent propensity-matched analysis comparing pulmonary autograft replacement to conventional valve replacement (biological, mechanical) showed that the cumulative risk of reintervention after the Ross procedure lies between that of biological and mechanical replacement (i.e., 1.2% per year) [52].

Recent studies have demonstrated that, despite the lower risk of reoperation, subclinical hemodynamic valve deterioration is common in this patient population [28].
Despite these data, biological valves are increasingly implanted, including in the younger adult patient population [129]. This trend is based on the notion that the increased mortality and morbidity in the younger patient population is attributed to the complexity of a potential reoperation. This issue is considered to be eliminated by the promise of valve-in-valve transcatheter aortic valve implantation. However, the obstructive nature of stented biological valve prostheses and its detrimental impact on left ventricular function is underestimated in this assessment [31,32].
In summary, the relative ease of implantation, the potential for future valve-in-valve procedures, and the lack of necessity of anticoagulation, have resulted in an overall decrease in the age of implantation of biological valve prostheses.

B. Mortality and morbidity

Perioperative complications were rare in our cohort. There was one perioperative death, no myocardial infarction, and one neurological complication. Only four patients with underlying hemophilia returned for bleeding complications. The incidence of permanent pacemaker implantation was 1.6% and only patients with preoperative endocarditis required its implantation.

Early mortality was low (n=1, 0.5%). Other studies have reported rates between 0.8 and 2% [14,44], which compares to conventional aortic valve replacement [22]. Our results may be attributable to the surgical expertise and short operative times in our institution. Studies have shown that > 5 years' experience of aortic valve surgery and sufficient case numbers should lead to a rate of < 2% [40].

As described by others [34,111], our cohort showed a long-term survival equivalent to that of the age- and gender-matched general population. Survival at 20 years was 90%, which compares favorably to other series (survival rates between 87% and 95% at 20 years) [34,73,110].

Endocarditis remains a continuous risk after conventional aortic valve replacement [33] but is rare after the Ross procedure [34]. In our cohort, the risk of autograft endocarditis was similar to other series [43,44] (0.27% per patient-year). The risk of pulmonary conduit endocarditis was also 0.27% per patient year with a notably increased risk after bovine jugular vein conduit implantation, which has been confirmed by other groups [44,43].
The Ross procedure for endocarditis leads to superior survival in comparison to other valve substitutes (80% at 10 years in our cohort). Several series have reported a survival of 63.6% at 10 years after allograft valve replacement [130], which is still favored by American Guidelines. Other studies have reported a survival of 39.7% at 10 years using biological valve prostheses [131]. The superiority of the Ross procedure may be attributable to the resistance of autologous valve tissue to infection [132].

Despite the expansion of the range of indications to include higher-risk patients, the procedure can be performed with a low perioperative risk. Several variables have long been considered perioperative risk factors, such as long operative times, preoperative active endocarditis, and prior conventional aortic valve replacement [110]. Operative times at our institution were short (mean cross-clamp time: 92 ± 20 minutes; mean perfusion time: 127 ± 34 minutes), eliminating the risks of long procedures. Patients with preoperative active endocarditis had significantly lower long-term survival. Further, patients with prior aortic valve replacement had an increased mortality rate, which may be attributable to increased ischemic times and complexity of the reoperation [114,116].

C. Autograft failure and reoperation

Despite achieving excellent results in experienced high-volume centers [34,43,46,50,52, 64,67,70-74,108,135], durability of the autograft remains a concern. Recurrent aortic regurgitation may occur over time based on cusp deformation and/or root dilatation [115] and a reoperation on the pulmonary conduit seems inevitable.

Studies on autograft reinterventions have reported freedom from such varying between 81% and 96% at 10 years [43,45-47,50,57,70-74]. This discrepancy may be attributable to the surgical implantation technique. Centers applying a stabilization technique to the autograft report lower failure rates. In our cohort, freedom from autograft reoperation was 79% at 10 years and 72% at 20 years without stabilization and 93% at both 10 and 20 years with stabilization.

Preoperative isolated aortic regurgitation and/or root aneurysm have long been considered risk factors for autograft failure [133]. Preoperative isolated aortic regurgitation affected the risk of reintervention significantly in our cohort, while patients with isolated aortic stenosis show a significantly higher freedom from reintervention. This may be related to the concomitant increase in annular size and thus potential stretching of the autograft at reimplantation. However, patients with preoperative aortic regurgitation and/or root dilatation only had an increased risk of reoperation without autograft stabilization. Results were significantly improved by complementing the procedure with a sinus stabilization technique. In fact, patients with AR and/or root dilatation and sinus stabilization showed equivalent results to patients with AS [134]. This confirms results from other series highlighting the importance of a tailored surgical approach [135]. Further, patients between the ages of 18 to 40 years had a lower risk of reoperation. It highlights that the younger patient population can profit from a stabilized autograft replacement despite their longer life expectancy with a prolonged period of postoperative complications.

Reoperations for root dilatation were (mostly) valve sparing, thus preserving the advantages the Ross procedure offers. Results of reoperations at our institution have been excellent using the concept of aortic valve repair and/or root remodeling (and reimplantation in one instance) [56].
There have been other attempts to maintain the advantages of the Ross operation by “reversing” the procedure in case of autograft failure. The pulmonary autograft is extracted and put back in its native position [55]. A mechanical or biological valve prosthesis is then used as aortic valve replacement. Results have been favorable, demonstrating that a regurgitant former pulmonary autograft still functions better in its native position than a homo- or xenograft. However, if the pulmonary conduit does not need replacement, it will be a bivalvular surgery for a univalvular disease.

Endocarditis remains a risk factor for increased mortality and reoperation rates and the infection largely destroys tissue [136]. Despite an adequate intravenous antibiotic treatment, some of these patients returned for reintervention due to dilatation of the ascending aorta and recurrent AR several years after the Ross procedure. Further, the risk profile of patients with endocarditis is often

considerable. In our cohort, 15% were i.v. drug users, 31% had endocarditis of a prosthetic valve, and more than a third of patients required drainage and closure of a peri-annular abscess. Concomitant procedures were also frequent.

Recurrent endocarditis of the autograft was rare; it only occurred in xenograft prostheses and the autograft was not affected. Patients who initially presented with endocarditis did not have an increased risk of postoperative infection. Only one patient had recurrent endocarditis, which reinforces the concept that autologous tissue is beneficial in patients who are at risk for recurrent endocarditis and can be performed in patients with more extensive infections.

Autograft root dilatation

Albeit being considered the most reproducible of the Ross techniques, the full-root replacement bears a risk of late autograft dilatation, which is a pivotal mechanism of failure [57]. In the majority of long-term studies, the lack of stabilization in the full-root technique has been associated with a higher risk of autograft reoperation due to root dilatation and/or autograft failure [53,57,108,137].

In attempting to explain this phenomenon, several studies have analyzed the differences in histological composition between the pulmonary artery and the native aorta [77,138,139]. Inherently, the pulmonary artery is thinner than the aortic root [49]. In addition, it has been reported that both fragmentation and loss of medial elastin fibers and increased adventitial collagen deposition occur immediately after implantation [49]. While this seemingly lays a ground stone for dilatation, a histological assimilation and transformation into an aortic phenotype has been demonstrated to occur in the first three months postoperatively [69,77]. Progressive dilatation of the pulmonary autograft may thus reflect the inadequate remodeling of the native pulmonary root in the systemic circulation [140]. This may lead to an impaired adaptability to the higher systemic pressure after the first decade [141-143] resulting in an increased risk of reoperation.

In our cohort, progressive dilatation mostly occurred within the first 5 years after surgery. Once the autograft has accustomed to the increased systemic pressure, the dimensions remain relatively stable. These results are in accordance with a study by Hokken, which showed that a significant proportion of dilatation had already occurred at the time of hospital discharge [144]. Some groups have proposed blood pressure control to limit autograft dilatation [49,135]. An increase of autograft dimensions, however, has been observed beyond the first year, although at a lower rate [137]. Similarly, the progression of root dimensions (mm/year) was a phenomenon of the first 5 postoperative years in our study, with minimal change thereafter.

Our study shows that late dilatation can potentially be counteracted by external stabilization. The expansion of the basal annulus is understood to be the source of autograft dilatation due to the increase of wall stress of the autograft according to the law of Laplace [145,146]. Wall stress leads

to degeneration, which then leads to plasticization and “weakening" of the aortic wall [147]. External stabilization of the annulus and/or sinotubular junction may thus prevent autograft dilatation and improve long-term results. Sinus stabilization decreased the progression of root dimensions (mm/year) significantly, thus also reducing the risk of reoperation in our cohort. Interestingly, the use of external annuloplasty alone did not reach significance. This may be related to the fact that dilatation may involve all three parts of the autograft root rather than just one. Evidently, some groups have shown excellent results when using the full-root technique with external support [45,148]. Further, the lower progression rates in patients with external support indicate that pressure control alone may not suffice in preventing autograft dilatation [72].

Regarding isolated aortic regurgitation as a risk factor for late autograft dilatation [149,150], some centers have conducted studies comparing AS and AR. Results showed a significant difference in impact on future root dimensions (AS superior) [135]. Thus, some centers advise against the use of the Ross procedure for isolated aortic regurgitation.
Our results showed a significant root size progression for both surgical indications. However, upon comparison between patients with aortic stenosis and aortic regurgitation, this holds true only for patients without sinus stabilization [134]. Patients with sinus stabilization showed no significant root size progression for either surgical indication.
This reinforces the statement that the determinant of dilatation is the surgical technique, independent of the valve lesion. The use of external stabilization appears to prevent autograft failure and excessive autograft dilatation following a Ross procedure, particularly in patients with aortic regurgitation. Therefore, the procedure can be offered to young adults with non-repairable aortic regurgitation.

A bicuspid aortic valve has been considered a risk factor for late autograft dilatation [147]. Some studies [76,138] however did not observe increased failure rates or noteworthy differences in the biomechanical properties of pulmonary arteries based on aortic valve morphology. A possible explanation for the increase risk of secondary AR and autograft dilatation may thus be the frequently observed dilated basal aortic annulus. A pathological sheer wall stress resulting in an asymmetric flow may be the cause of the dilatation [103]. Interestingly, we did not observe an increased risk of reintervention in bicuspid aortic valves in our analysis. A unicuspid morphology however was associated with a tendency towards autograft dilatation, even though with root support very few patients (n=4/145; 2.8%) developed autograft failure or dilatation. This postulates that annular dilatation may be more frequent in combination with a unicuspid morphology than previously thought [151,152]. Further, unicuspid valve are often stenotic; the associated secondary high blood pressure may be an additional risk factor in the early postoperative days.

Risk factors for autograft dilatation are annular [49] and sinotubular dilatation [57,106,153] as well as an inherent weakness of the “untrained” autograft. Annular stabilization has long been suggested [99,154] but has not eliminated dilatation entirely [57,73]. Sinotubular stabilization has previous-

ly been advocated for [38,57,135]; its sole effect has not been unequivocally proven [46,98,155]. David et al. found autograft dilatation (>45mm) in 8% of patients [73]. In our study, 14 patients with prior sinotubular dilatation underwent ascending aortic replacement, of whom 4 (29%) required re-operation. Limited autograft dilatation (>40mm) was observed in two patients. Thus, this concept seems to be of limited value. A combination of sinotubular and annular stabilization has been proposed [73,135]. However, mid- to long-term data are not available from all cohorts. Our current results suggest that a follow-up of more than 5 years is necessary to assess autograft dilatation, as autograft dilatation is most prominent in those early years.

The best durability in our study was achieved by the combined approach to support the annulus, the sinus portion of the autograft, and sinotubular junction (when necessary). Out of 136 patients treated in such a way, freedom from reoperation and pronounced root dilatation (> 45mm) at 10 years was 94% and 97%, respectively. Overall, freedom from aortic root dilatation was favorable compared to other series [135], highlighting the fact that an adapted surgical approach can minimize autograft dilatation.

Reports of autograft root dilatation over time have varied extensively. An important study by the Rotterdam group reported a 47% rate of autograft dilatation requiring reoperation at 13 years [38], however, they also demonstrated the importance of the surgical technique, and surgical expertise, in preventing long-term dilatation and autograft failure [137]. There have been attempts to quantify a learning curve for a Ross procedure. Reports showed an inverse relationship between surgical volumes and reintervention rates due to dilatation [39,40].

Autograft regurgitation

Significant autograft valve dysfunction and recurrent AR > 2 affected a minority of patients in our study. This may be attributable to our consistent use of external support, i.e., annuloplasty and sinus stabilization.

Further, cusp morphology affected neither the recurrence of AR nor the incidence of reintervention in our cohort. The lack of surgical stabilization technique however influenced the results significantly. The low number of recurrent AR may thus be attributable to our systematic use of external stabilization in patients with AR and an enlarged aortic root, which is predominant in abnormal valve morphology. Results concur with previous studies failing to find an association between bicuspid valve disease and recurrence of aortic regurgitation [76,133].
Isolated preoperative AR and left ventricular compliance influenced the recurrence of aortic regurgitation significantly**.** Patients with a LVEDd >60mm had a significantly higher risk of recurrent relevant AR. The decreased left ventricular compliance in patients with aortic regurgitation may contribute to the exacerbation of neoaortic regurgitation, highlighting the underestimated importance of left ventricular compliance on the fate of the autograft.

Patients who require surgery for AR due to rheumatic aortic valve disease face a predicament in finding the most appropriate treatment. The Ross procedure was first considered a good replacement option for the younger patient population; however, recent studies have reported high rates of recurrent AR in patients with rheumatic aortic valve disease [156,157]. This shows that the pulmonary autograft is susceptible to rheumatic involvement [156,158].

D. RVPA conduit failure and reoperation

Although concerns over durability focus on the pulmonary autograft, degeneration and infection are two important mechanisms of pulmonary conduit failure [42].

In the younger patient population (<18 years), most reinterventions in our study were caused by active endocarditis (n=4, 0.27% per patient-year). The increased sensitivity of the pulmonary conduit to endocarditis has often been described and differs according to conduit type [86,159]. In our cohort, the majority of infections occurred in patients with a bovine jugular vein conduit. One patient experienced endocarditis on the homograft; however, this patient was an intravenous drug user. These findings concur with a recent study reporting a high incidence of endocarditis in bovine jugular vein conduits [159].

Degeneration also occurred exclusively in the younger patient population. Younger patients are exposed to a prolonged period of cardiac-related complications and are more likely to exhibit accelerated degeneration of biological grafts. In addition, the majority of patients experiencing degeneration had a bovine jugular vein conduit. Pathology reports of explanted pulmonary valve prostheses showed neovascularization and chronic inflammation of the adventitia. Interestingly, this was mostly specific to the distal anastomosis. These results concur with other studies [86]. Histological studies of explanted conduits showed fibro-intimal proliferation in the area of the pulmonary anastomosis in combination with a mild autoimmune reaction at the outside layer of the conduit [91,160].

Few studies have compared the immunological response to cryopreserved and decellularized homografts. Early – to mid-term results showed similar durability after decellularized and cryopreserved pulmonary homografts [93,96]. Larger studies with longer-term follow-up are thus necessary to elucidate the efficacy of decellularized allografts compared to cryopreserved homografts.
Only cryopreserved homografts were used in our cohort. Despite our favorable results and similar results between different preservation techniques, decellularized pulmonary homografts have garnered increasing interest [95]. In an attempt to counteract the immunological response especially in the younger patient population, some groups prescribe non-steroidal anti-inflammatory medication for the first 6 months postoperatively [94]. Studies have reported an improved durability; however, long-term results are not yet available [161].
Further, durability of the pulmonary conduit has been associated with its size in relation to the RVOT. The RVOT is usually larger in diameter. By oversizing the pulmonary conduit, a patient-prosthesis-mismatch can be avoided. The implanted homograft should ideally be larger than the pulmonary autograft, and rarely < 25 mm in diameter. The Toronto group recently reported a 93% freedom from homograft reoperation at 20 years using this strategy [14]. This is not applicable when using a bovine jugular vein, which is offered in sizes 12 to 22 mm and has mostly been used in the pediatric patient population.

While active endocarditis potentially has to be treated by valve replacement and a rigorous antibiotic scheme, degeneration can potentially be treated by catheter reintervention, reducing the need for a conventional reoperation. However, studies on the long-term performance of these catheter valves are not yet available [162,163].

Overall, our results compare favorably to other series showing superior durability and lower sensitivity to infection of homografts in comparison to bovine jugular vein conduits [14,164]. Freedom from reoperation after biological valve implantation was similar to that of homograft conduits.

E. Ross as a reoperation

The Ross procedure achieves excellent results in experienced high-volume centers, with quality of life and long-term survival equivalent to that of the age- and gender-matched general population [34,43,46,50,52,64,67,70-74,108,135]. Nevertheless, the surgical complexity raises concerns about its perioperative risk and reproducibility, especially when performed as a reoperation [114]. The risk of the Ross procedure as a reoperation remains poorly defined [54,116].

The Ross procedure has become a replacement option for patients with prior aortic valve repair as well as prior conventional valve replacement. Over the past 20 years, aortic valve repair has become a more frequently used alternative to conventional valve replacement [165-168]. Hemodynamics, quality of life, and survival are favorable [81]. However, annular dilatation and recurrent regurgitation remain a concern, especially in patients with a challenging repair [115,169]. Repair failure remains the most frequent complication despite the fact that the incidence of valve-related complications is low [170]. At failure, many surgeons often prefer the implantation of conventional valve prostheses as a less complex procedure. The advantages of an autologous valve are thus eliminated, exposing patients to the long-term complications of conventional valve prostheses (i.e. excess mortality and hemorrhagic complications) [15,22]. In addition, studies have shown that patients who initially underwent aortic valve replacement have a higher mortality rate at reoperation [116]. A particularly high risk was seen in patients who received a conventional valve replacement as a reoperation. Patients who underwent a Ross procedure as a reoperation had a much lower perioperative risk and a superior long-term freedom from reoperation [22,52]. Some salvage options should therefore be considered, and the Ross procedure would be an ideal one. Current evidence provides little information on this topic.

In our study, there were no perioperative death, myocardial ischemic or cerebral complications, as well as a low incidence of postoperative atrioventricular block and new pacemaker implantation. Altogether, these results compare favorably with other series of redo aortic valve replacement [116]. Additionally, our cohort shows excellent survival at 15 years, which compares to other studies of primary autograft replacement [34,43,46,50,52,64,67,70-74,108,135]. It demonstrates that performing a Ross procedure as a reoperation after failed aortic valve repair is associated with the same long-term benefit [111]. Interestingly, survival after prior conventional valve replacement is significantly lower. This supports the value of our proposed strategy of initial valve repair followed by autograft valve replacement in case of failure [111].

The risk of reintervention is higher after aortic valve repair compared to Ross as a primary treatment option. However, the root and valve could be remodelled in all patients with autograft failure, thus preserving the proposed benefit of a living valve in the aortic position.

Relevant autograft valve dysfunction and AR > 2 affected a minority of patients in our study. Several series suggest that predominant aortic regurgitation and/or a dilated aortic annulus are con-

sidered risk factors for late failure in particular after the Ross procedure as a reoperation [133]. This could not be confirmed in our study.

F. Surgical variations of the Ross procedure

Unlike for the implantation of stented valves, there is no universally accepted technique for the Ross operation. The two most frequently used techniques are the full-root replacement and subcoronary implantation [62]. Both procedures bear a risk of reoperation [34,44,53,57]; however, the mechanisms differ. After subcoronary implantation, distortion of the commissural position may lead to prolapse and regurgitation [97]. Distortion can largely be avoided by using the full-root replacement technique, which provides near physiological root dynamics and early results have been favorable [43]. However, studies have shown that root replacement is associated with late autograft dilatation, which may lead to autograft aneurysm and/or regurgitation [57,108,137]. External autograft stabilization has been suggested to minimize the likelihood of late autograft failure [45,61,135,148].

An array of different stabilization techniques exists. Correction of annular dilatation by suture [99] or a strip of pericardium, Dacron, or Teflon in the proximal suture line [154,171] seem to have improved autograft stability. Sinotubular junction stabilization seems to have an additional supportive effect [154]. A more extensive variant has been used, keeping the native aortic root around the autograft as stabilization [45,61]. Other stabilization techniques have been proposed to forestall autograft root dilatation, such as encasing the autograft root in a Dacron graft [148,172,173]. Concerns remain that this technique may result in other complications, such as coronary artery distortion, inflammatory changes of the autograft similar to aortic wrapping [174], or a higher risk of infection [175,176]. Further, it does not allow for pulsatility of the autograft [63,64]. Carrel et al. modified this technique by using a prosthetic graft with an artificial Valsalva configuration [148]. It allows for improved hemodynamic patterns of the autograft and prevents secondary dilatation [65]. Long-term follow-up will be required in order to better assess the value of this approach. Its use in pediatric patients however will be limited due to the lack of growth potential.

An alternative support technique has been proposed by Skillington [45] (autograft within the native aorta as a vascular graft), which aims to minimize the use of prosthetic material and simultaneously to reduce all three aortic root diameters. Thus, this provides the advantage of an almost eliminated risk of endocarditis and the stabilization prevents dilatation. The long-term results have been favorable, as the dimensions of the autograft root (sinus) are stable up to 15 years after the procedure with 1.5% of patients exceeding a root diameter of 40 mm [45,148]. However, it seems that this technique provides limited exposure, making the operation somewhat more cumbersome. Myocardial ischemic times (172 ± 20 minutes) have been longer than in our series.

We have performed the full-root replacement since 1997. In order to avoid root dilatation in the second decade, particularly in patients with preoperative aortic regurgitation and a large aortic basal annulus, this technique has been complemented by an external autologous autograft stabilization since 2001.

Our root stabilization technique consists of simplified root wrapping and is composed of three posts with the native aortic wall. This technique provides several advantages. It is highly reproducible and preserves autograft valve geometry. It can be applied regardless of patients' age or indication for surgery (i.e., active endocarditis and root abscess). In addition, distortion of the autograft can be avoided by adjusting the height of the autograft and the aortic wall remnants and suturing the corresponding parts jointly at the distal anastomosis of the autograft [61]. Thus, this autologous reinforcement works as a longitudinal and horizontal support of the autograft, while it does not impair the implantation of the coronary buttons or the function of the autograft valve. Further, this technique is comparatively resistant to infection and can be used to surgically treat infective endocarditis. However, it only places partial support on the Sinus of Valsalva, as there is no prosthetic material support on the sinus or sinotubular junction.

Schäfers et al. introduced an external suture annuloplasty to the Ross operation in the same manner as it is practically used for aortic root remodeling and aortic valve repair [105]. The optimization of the aortic basal annulus with prosthetic material is essential because the expansion of the aortic basal plane is a risk factor for dilatation [177]. An external annuloplasty suture (i.e. Gore Tex suture) can be adjusted precisely by tying it around a Hegar dilator, preventing constriction of the annulus. An ePTFE suture is fixed at this target plane, and provides the suitable reduction of the neoaortic basal annulus without interfering with the left ventricular outflow tract and the autograft cusps. Further, this suture is less disruptive on the muscle due to its smooth texture. Studies have shown that its structure does not prevent the development of new extracellular matrix that takes place during remodeling [178]. Elastin and collagen fiber, Metalloproteinases-9 and Ki67, were found to be increased while apoptosis was reduced [139,178]. In comparison, the more commonly used technique of reinforcement with a Dacron Graft can lead to thinning of the underlying aortic wall with risk of dilatation [174,179].

In addition to the suture annuloplasty, the ascending aorta is replaced at lower threshold in our institution compared to others (>30 to 35mm compared to >38 to 40mm) [82]. If the tubular diameter of the ascending aorta exceeds 30mm, the diameter is reduced with plication of the ascending aorta (31 to 35 mm) or Dacron graft replacement (≥ 35mm). This ensures stabilization of the autograft sinotubular junction.
In summary, the full-root replacement with native aortic wall wrapping and an external annuloplasty achieves excellent results. It is highly reproducible, prevents secondary dilatation and aortic regurgitation, and is applicable in cases of endocarditis.

VI. Limitations of this study

The main limitation of this study is its observational design. Although data of consecutive procedures were collected prospectively, the analysis was done retrospectively, and treatment assignment was not randomized. Further, a highly experienced surgeon from a high-volume center performed most procedures. Thus, the reproducibility of our findings may be limited. However, surgical techniques are highly standardized at our institution in order to increase its reproducibility. The sample size for comparison of surgical stabilization techniques was relatively small but adequate and standardized techniques were used to support the findings. In order to support our results, a comparison should be conducted with larger patient groups. Despite these limitations, this analysis gives a clear insight into the results of a tailored surgical approach to the full-root Ross procedure. Further follow-up should be conducted to determine longer-term results.

VII. Conclusion

The full-root autograft replacement with a tailored autologous stabilization approach can be performed with low morbidity and a low incidence of reintervention. Long-term survival and quality of life are excellent, comparable to that of the age- and gender-matched population. The procedure bears a low risk of endocarditis and it does not require any anticoagulation. This particular technique is highly reproducible and can be tailored to each patient in order to mitigate the risk of autograft failure. Further, the implantation of a homograft or biological valve prosthesis as a pulmonary conduit leads to a low incidence of valve degeneration or endocarditis.

In case of failure, the advantages of autologous valve tissue can be maintained by performing a valve-sparing procedure. It is reproducible in the majority of cases and shows excellent results.

Meanwhile, newer studies of alternative valve prostheses have reported suboptimal survival, durability, and quality of life in non-elderly patients.

Altogether, these findings suggest that the Ross procedure is a safe and durable option that is associated with favorable perioperative and long-term results in non-elderly patients with aortic valve disease.

We therefore consider the Ross procedure an up-to-date and safe substitute for the younger patient population, and for some, as a salvage pathway for failed aortic valve repair.

VIII.References

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IX. Publications

During the course of this dissertation, the following publications were made:

1. Matsushima S, Abeln KB, Karliova I, Zacek P, Schäfers HJ. Suture Annuloplasty and Simplified Root Wrapping in the Full Root Ross Operation. Ann Thorac Surg. 2019 May;107(5):e361-e363.
2. Abeln KB, Chauvette V, Poirier N, Matsushima S, El-Hamamsy I, Schäfers HJ. Ross operation after failure of aortic valve repair. Ann Cardiothorac Surg. 2021 Jul;10(4):476-484.
3. Abeln KB, Ehrlich T, Hess A, Schäfers HJ. Valve-sparing procedure for a dilated pulmonary autograft. Ann Cardiothorac Surg. 2021 Jul;10(4):555-557.
4. Abeln KB, Schäfers S, Ehrlich T, Federspiel JM, Schäfers HJ. Ross Operation with Autologous External Autograft Stabilization - Long-term Results. Ann Thorac Surg. 2021 Oct 19:S0003-4975(21)01729-X.
5. Abeln KB, Schäfers HJ. Select or Adapt? Keep it Simple and Safe. Ann Thorac Surg. 2022 Jan 17:S0003-4975(22)00045-5.

Conference paper:

1. Abeln K, Federspiel J, Ehrlich T, Giebels C, Schäfers HJ. Ross Procedure after Failed Aortic Valve Repair - presented at the 50th Annual Meeting Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie e.V. (DGTHG), Wiesbaden, February 2021
2. Abeln K, Ehrlich T, Souko I, Brenner F, Schäfers HJ. Autograft Reoperations after the Ross Procedure - presented at the 35th Annual Meeting of the European Association for Cardio-Thoracic Surgery (EACTS), Barcelona, October 2021
3. Abeln KB, Giebels C, Ehrlich T, Federspiel JM, Froede L, Schäfers HJ. Ross Procedure for aortic regurgitation and stenosis- presented at the 51th Annual Meeting Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie e.V. (DGTHG), Hamburg, February 2022
4. Abeln KB, Ehrlich T, Froede L, Matsushisma S, Giebels C,Schäfers HJ. Ross versus Repair for Treatment of the Unicuspid Aortic Valve in Adults - presented at the 36th Annual Meeting of the European Association for Cardio-Thoracic Surgery (EACTS), Milan, October 2022

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XI. Statutory declaration

I hereby declare that I have composed this dissertation autonomously with no help of a third party and that no means other than those declared were used. The dissertation is in accordance with the dissertation regulation of Saarland University.
In every single case, I have indicated parts that were taken out of published or unpublished work, either verbatim or in a paraphrased manner, as such through a quotation.
The dissertation in the same or similar form has not been submitted to any examination body and has not been published.

XII. Curriculum vitae

For reasons of data protection, the curriculum vitae is not published in the electronic version of the dissertation.