A FRAMEWORK FOR THE EVALUATION AND REPORTING OF OUTCOMES AFTER COMPLEX HEART VALVE INTERVENTIONS

Applications to the European Ross Registry

Efstratios Charitos

Cover Page:

Two fundamental principles of the cumulative prospect theory (CPT) adapted from the works of Amos Tversky and Daniel Kahneman (Advances in prospect theory: Cumulative representation of uncertainty". *Journal of Risk and Uncertainty. 1992:* **5**: 297–323)

Front: A typical cumulative probability weighting function of the CPT. The objective probabilities are displayed on the x-axis and the subjective (perceived) probabilities (weighted probabilities) are displayed on the y-axis. Research shows a significant deviation in the way humans perceive the probability of certain events happening, with overestimation of low probability events and underestimation of high probability events (solid lines). Additionally, the perceived probability deviates even more from the objective probability (dotted diagonal), according to whether the prospect is associated with a gain or a loss (green, red line respectively; γ=.61; δ=.69). Since the original formulation, several other formulations have been proposed also allowing for additional elevation and curvature flexibility.

Back: A typical value function of the CPT. Three characteristics are apparent: First, every evaluation is relative to a reference point which differentiates gains from losses. Second, diminishing sensitivity takes place in both gains and losses (flattening of the gain and loss curves). Third, loss aversion is an important apparent feature. A k change resulting in a loss is perceived about $\lambda \approx 2$ times larger than a k change resulting in gain (higher slope of the loss curve; λ=2.3, $\alpha=\beta$=.88).

The work described in this thesis was conducted at the Department of Cardiac and Thoracic Vascular Surgery of the University of Lübeck, Lübeck and the Department of Cardiothoracic Surgery, Erasmus MC, Rotterdam.

A Framework for the Evaluation and Reporting of Outcomes after Complex Heart Valve Interventions

ISBN: 978-94-6182-463-9

Cover design, layout and printing: Off Page (www.offpage.nl)

A Framework for the Evaluation and Reporting of Outcomes after Complex Heart Valve Interventions

Applications to the European Ross Registry

Een kader voor de evaluatie en rapportage van resultaten na complexe hartklepinterventies.

Toepassingen op de Europese Ross registratie

Thesis

to obtain the degree of Doctor from the

Erasmus University Rotterdam

by command of the rector magnificus

Prof.dr. H.A.P Pols

and in accordance with the decision of the Doctorate Board.

The public defense shall be held on

Tuesday September 16, 2014 at 13:30 hrs

by

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»Στενά τα όρια των δυνάμεων του ανθρώπου και πολλά τα δεινά που στομώνουν τη σκέψη του.
Ένα τόσο δα κομμάτι της ζωής βλέπουν οι άνθρωποι όσο ζουν, κι ύστερα,
γοργοθάνατοι, πετούν σαν καπνός, σίγουροι μόνο γι' αυτό που σύντυχε ο καθένας
τους καθώς πλανιούνται εδώ κι εκεί.
Ποιος τάχα καυχιέται πως βρήκε το όλο;«

Ἐμπεδοκλῆς 490-430 π.Χ., „Περὶ φύσεως", απόσπ. 2

"Narrow are the limits of man's powers and many are the ills that obstruct his thinking.
People see only such a narrow part of life as they live, and then they quickly die, like smoke,
being only sure about what happened only to themselves, as they loom here and there.
Who can allegedly boast that he found the whole?"

Empedocles c.490-c.430 BC, "On Nature", 2

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Incidence of aortic valve disease

Operations on the aortic valve are the second most frequent cardiac surgical interventions. Surgical treatment of aortic valve disease remains the most effective therapeutic intervention in patients with severe aortic valve disease [1]. Although in the last 5 years transcatheter solutions have been utilized in patients who carry a high number of morbid conditions and who would be at high operative and postoperative risk for complications with a conventional procedure, the majority of patients will undergo conventional, open heart surgery. Despite an increasing interest in reconstructive surgery of the aortic valve in the latest years, the majority of aortic valve procedures replace the patient's diseased aortic valve, with a biological or mechanical prosthesis which bears significant disadvantages in comparison to the native human aortic valve. This is of special interest for young patients after aortic valve replacement since these patient will have to live a significant part of their life with the prosthetic heart valve. This patient population is the primary focus of the present thesis.

Limitations of currently used valve substitutes

Prior to an aortic valve replacement procedure, a patient is usually offered to choose between two options: either having a biological or mechanical valve implanted. Significant research has been performed in the last decades to evaluate the outcomes of patients after conventional aortic valve replacement. Due to the presence of foreign, thrombogenic material, patients with mechanical valves must receive lifelong anticoagulation in order to avoid life threatening thromboembolic complications or valve thrombosis and dysfunction. This automatically translates to an increase in bleeding complications as a consequence of coumadin prescription. However, even with the use of coumadin a certain risk for thromboembolic complications in these patients persists. Coumadin alternatives with better controllable pharmacodynamics and pharmacokinetics have shown poor results in patients with mechanical aortic valves, more or less failing to mitigate the high thrombogenic potential of the mechanical valves [2]. The lifetime risk for thromboembolic complication has been thoroughly evaluated by many research teams [3,4]. On an individual patient level the need for anticoagulation has several implications and brings limitations and restrictions especially in the young patients: performing competitive sports, considering childbirth for young females and certain professions (professional sports, aircraft pilot) are severely influenced or even contraindicated when receiving oral anticoagulation after mechanical valve implantation. Accordingly the need for anti-coagulation after aortic valve replacement has been shown to influence quality of life [5].

Biological valves on the other hand do not require lifelong anticoagulation, however in young patients the long term performance and durability of biological valves remains disappointing due to the very high prevalence of mid and late term structural valve deterioration, eventually mandating a valve re-replacement usually in the second postoperative decade [6–8].

The Ross procedure

An alternative to the conventional aortic valve replacement with a mechanical or biological valve is the Ross procedure (pulmonary autograft procedure). The pulmonary autograft procedure for the treatment of aortic valve disease, first performed by Donald Ross in 1967 [9],

theoretically at least, provides all advantages of a viable, autologous, tissue valve replacement warranting physiologic aortic valve hemodynamics and motion, as well as an unrestricted "cross talk to surrounding structures" [10] including the aortic root, the left ventricle and ascending aorta [10–13]. During the Ross procedure, the patient's native pulmonary valve is harvested and implanted in the aortic position, while a pulmonary homograft is implanted in the pulmonary position. This procedure is being performed in experienced centers with low operative mortality and is associated with lower incidence of macro- and micro embolism that any other mechanical or biological replacement [14] without the need for lifetime anticoagulation therapy.

Current status of the Ross procedure

After the limitations of mechanical and biological valves became apparent, especially in the young patients with aortic valve disease, a renewal of interest in the Ross procedure emerged in the 90's. Today the evaluation of this procedure and its place as the therapeutic modality in the young patients is even more pertinent since long-term results of these patient collectives and studies are beginning to emerge.

It is now well established that autograft function may, in some patients, deteriorate over time eventually requiring replacement [15–25]. Concerns surfaced lately regarding the ability of the isolated, unsupported pulmonary root to withstand the systemic circulation load over time and resist progressive dilatation, therefore threatening valve competence [18,23,26–30], and leading to an initially unexpected increased rate of reoperation beginning 7 to 8 years after the initial operation [26,28,30–32].

Although the above mentioned studies provide an important insight in the fate of the Ross procedure, there is significant controversy and variability regarding the mid and long term results and the results presented from the various teams are not easily generalizable. More importantly, due to the small sample size of single center experiences, inferences and comparisons are difficult to document and support from a statistical point of view, thus limiting the impact of these works to a more descriptive evaluation of usually single center results after the Ross procedure.

With these limitations in mind, the German-Dutch Ross Registry was established in January 2002 under the supervision of Prof. Dr. Ulrich Stierle, Prof. Dr. Hans-Hinrich Sievers and Prof. Dr. Johanna J. J. M Takkenberg. Aim of this effort was to collect information about Ross patients operated retrospectively up to 2002 and prospectively thereafter in a multi-center registry which would contain information about the outcomes after the Ross procedure in large number of patients that would allow a better understanding and evaluation of the outcomes after the Ross procedure in a form and degree that is generalizable. Currently the, now European, Ross Registry collects information on the outcomes of Ross patients operated in 15 cardiac surgery centers in 4 countries (Germany, The Netherlands, Austria, Czech Republic and Spain) with now more than 2200 patients followed for more than 15.000 patient*years. This effort has provided significant insights regarding the outcomes after the Ross procedure as well as valuable lessons in the methodological and statistical evaluation of patients after complex heart valve surgery.

CHALLENGES WITH THE EVALUATION OF OUTCOMES AFTER THE ROSS PROCEDURE

Influence of patient characteristics and surgical techniques

The Ross patient population presents a rather special patient population. Ross patients are mostly young, active adult, of higher socioeconomic status that are significantly concerned about quality of life and associated risks after valve replacement. Since only few centers offer the Ross procedure in young adult patients, a significant selection process underlies the referral process of a young patient prior to the Ross procedure. Additionally, not every patient referred or scheduled for a Ross procedure receives a Ross procedure. The final evaluation and decision of the feasibility of the Ross procedure in each individual patient takes place in the operating room. The intraoperative patient selection process is not well evidence based and consists of mostly experience-based criteria, biases and heuristics with some agreement between surgeons, centers or Ross "*schools of thought*". Some established – however not entirely unanimous – exclusion criteria exist such as connective tissue or active rheumatic disorders, structural defects of the pulmonary valve, as well as intractable systemic hypertension. In addition to patient selection, the Ross procedure has been performed using several techniques and technical modifications [32]. This is of particular importance when results of some technique are generalized as results of the Ross procedure itself. This diversity must be taken into consideration when analyzing outcomes and evaluating published series of Ross patients and more importantly when generalizing the results after each of the techniques, on the Ross procedure as a therapeutic option.

All factors mentioned above have a significant effect in the evaluation of outcomes after the Ross procedure and result in methodological difficulties when one attempts to perform comparisons between Ross patient populations and patients with conventional aortic valve replacement, since significant key patient characteristics and risk profiles differ between these groups to an extent that make a robust scientific methodological comparison precarious.

The absence of randomized controlled trials comparing outcomes between after the Ross procedure versus conventional alternatives may be attributed to the strong bias of the Ross community and the Ross patients for the Ross procedure. Patients referred for the Ross procedure are well informed about the benefits (as well as the risks) that the Ross procedure presents compared to the conventional aortic valve replacement options and are less willing to accept a randomization between a Ross procedure and a conventional aortic valve replacement. Additionally physicians with a strong preference for the Ross procedure are also less willing to randomize a patient to a conventional aortic valve replacement, knowing the limitations of biological valve durability in young patients, as well as the risks of lifelong anticoagulation and quality of life effect of mechanical valves in young patients. Of note, the only randomized controlled trial [33] to date compares the Ross patient collective to an aortic homograft collective. However, the homograft use as an aortic valve replacement conduit is limited and the results of this - otherwise seminal – study have a limited applicability to conventional aortic valve replacement options and decision making in the daily clinical routine.

Reporting of reoperations and outcomes

The accurate reporting of the reoperation incidence communicates two types of information. First, the need for and incidence of reoperations provides information about the **durability** of the initial procedure with time. Although it is known that sometimes not all patients requiring a reoperation will receive a reoperation for reasons such as extensive comorbidities, high risk or advanced age, overall the incidence of reoperations – especially in young populations - is a relative hard end point in clinical trials with less ambiguity than for example echocardiographic markers of conduit degeneration and valve function loss. Therefore accurate reporting of the need for and type of reoperation is important for the critical evaluation of the initial procedure especially under a comparative perspective with other alternatives.

Second, the exact type of reoperations and their outcomes communicate information about **the complexity, associated risk, morbidity and mortality of the reoperative procedure**. This is of especial interest in clinical decision making for the primary procedure because not only the potential incidence of future reoperations but also their risk, morbidity and mortality should be taken into consideration when evaluating options for the initial aortic valve replacement procedure. Therefore accurate reporting is an essential tool for the evaluation of any procedure.

In the setting of the Ross procedure, the accurate reporting of the incidence, type and complexity of reoperations can be challenging, especially in registries with large number of

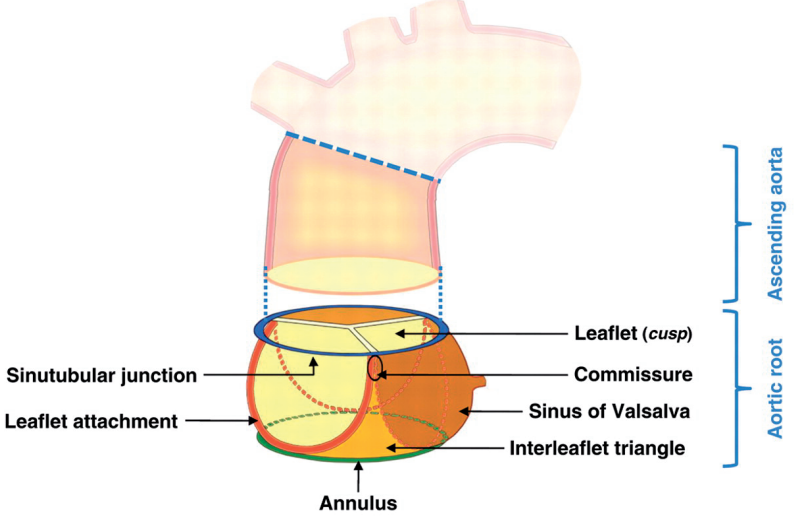

FIGURE 1. *The aortic root component nomenclature used in the European Ross Registry (modified from reference [36])*

patients followed over a considerable amount of time (>10 years) [14,24,32,34,35]. There are several reasons contributing to this complexity. First, the Ross procedure results in a double valve disease (autograft and homograft), both valves being at risk for failure and a failure of either of the two operated valves in time is usually seen as a sign of limited durability of the procedure. Second, reoperations can take variable forms such as valve replacement, or some kind of valve repair. Third, a renewal or repair of Ross valves can be performed in the same surgical session or at different surgical session, the former having a different operative risk profile than the latter procedure.

To reduce complexity the following definitions are utilized in the European Ross Registry [35]: A *Ross reintervention* is defined as any surgical or interventional procedure performed after the initial Ross procedure on the autograft or homograft. A *Ross reoperation* is defined as a surgical session that includes at least one Ross reintervention on the autograft or homograft, or both (1, 1, and 2 reinterventions, respectively) and may include concomitant interventions to other cardiac structures. In addition to this, a common nomenclature is required in order to classify the anatomic location of the interventions, and the classification of the reparative procedure. For data collection purposes the European Ross Registry follows the nomenclature proposed by Sievers and colleagues [36,37], Figure 1.

The importance of accurate data capture and evaluation of the patient history and the importance of accurate definitions can be illustrated with the help of *Figure 2* presenting the time course of a patient from the European Ross Registry.

This patient received an initial Ross procedure (A). Several years later he required an autograft repair and a homograft replacement which was performed as a combined procedure in one surgical session (B). Due to degeneration of the aortic valve an autograft valve sparing procedure was performed at a later time (C). Several years thereafter, due to degeneration of the second homograft conduit a transcatheter valve implantation was performed (D). For data collection and evaluation purposes it is important that the complete history of the patient is captured. This one patient experienced 4 Ross reinterventions (2 interventions at time B, on at C and one at D) in both Ross valves (autograft, AG; homograft, HG). Two Ross reinterventions were performed concomitantly in one Ross reoperation (B). Two reparative autograft Ross reinterventions were performed at different surgical sessions (B, C). One homograft exchange Ross reintervention was performed (B) and one transcatheter homograft Ross reintervention (D). The operative risk for the B, C, and D reinterventions and reoperations varies between the procedures. It is also important to note that even after this complex reoperative history, this patient still has the pulmonary autograft leaflets on the aortic valve position, therefore still

FIGURE 2. *Time course of a Ross patient*

exhibiting some of the benefits of the Ross procedure such as the freedom from the need of oral anticoagulation and normal transvalvular hemodynamics. With respect to the right heart and for risk evaluation purposes, this patient has a transcatheter valve (D) inside the second pulmonary homograft (B) both having separate risk processes for failure.

Evaluating Conduit Durability

Traditionally, two approaches to the evaluation of conduit durability are utilized in the reporting of outcomes after heart valve interventions. A first approach is the analysis of the incidence of reoperations in the form of actuarial analysis, reporting the actuarial freedom from autograft, homograft, and the combined outcome "autograft or homograft" reoperation. Although these methods provides an adequate description of the incidence and thus the need for reoperations in small trials, as the patient sample and the total follow-up duration becomes larger, several problems with this approach become apparent. First, reporting the need of reoperations as a measure of conduit durability ignores the functional status of the conduits. This means that at the time of closure of the database for analysis and reporting, several patients may have reached the level of conduit degeneration to warrant the need for a reoperation but may have not been reoperated yet. Second, especially in older patients, a reoperation may be deferred or postponed due to reduced general status of the patient, existing co-morbidities that may increase the objective or perceived operative risk of a reoperation, therefore overestimating the valve durability. Additional to this, in older populations and in large patient samples, the incidence of death represents a competing risk for reoperation (patients who die cannot be thereafter reoperated) a fact which further blurs the objective evaluation of conduit durability. Therefore, although the incidence of reoperation may be considered as a "*hard*" and unambiguous clinical endpoint regarding the durability of the heart valve replacement, important information is not considered or lost in this evaluation.

Combined, "*artificial*" endpoints providing freedom from reoperation or presence of a given functional valve deterioration may seem at first glance to alleviate some the above mentioned limitations. However, no consensus exists on the quantitative definition of valve degeneration especially for the homograft but also for the autograft. The second limitation of this approach is more or less an extension of the limitations and drawbacks of the use of actuarial methods in the evaluation of dynamic, reversible echocardiographic outcomes. Although some patients may reach a certain level of functional valve degeneration, this degeneration may appear at a slow progression rate or with minimal or no symptoms therefore the reoperative procedure may be deferred to a future time point. Especially with ordinal, reversible, dynamic echocardiographic outcomes, such as aortic or homograft insufficiency, asymptomatic patients may stay at a level of a certain functional valve degeneration for several years without progression. Therefore actuarial methods evaluating the combined endpoints "reoperation or significant functional valve degeneration" usually will overestimate the incidence and introduce a bias in the analysis and evaluation of these outcomes.

Several newer methodologies and statistical concepts aim at a more objective evaluation of combined incidence of reoperation and functional valve degeneration by providing a framework for the analysis and evaluation of time-to-event outcomes such as reoperation while utilizing information from serially acquired longitudinal measurement [38,39]. Despite

their complexity, these methods combine information obtained from serially correlated, repeated measurements in individual patients (such as echocardiographic outcomes) in order to evaluate their effects on time-to-event outcomes such as the incidence of reoperations, therefore providing a more objective insight for the durability of heart valve prostheses.

Reporting and evaluating echocardiographic outcomes

As mentioned above the evaluation of longitudinal collected echocardiographic information provides valuable insight in the postoperative function of the heart valve prostheses as well as durability information. The data collected from serially performed echocardiographic evaluations can be generally classified in two categories; continuous echocardiographic variables (such as transvalavular pressure gradients, valve area, aortic root dimensions) and ordinal echocardiographic variables (such as aortic or homograft regurgitation grade). Although there is a general consensus on the criteria for measurement and classification for each of the above mentioned information [40–42], a consensus on the appropriate methodologies to analyze and present these outcomes is less established. However it is now recognized that the analyses of these measurements require a methodological framework [43] that allows for the special nature of these measurements.

AIMS AND OUTLINE OF THE PRESENT THESIS

The present thesis studies various methodological aspects for the evaluation of outcomes after a complex heart valve interventions, using the Ross procedure and the data from the European Ross Registry to illustrate the evaluation of early and late clinical results and the durability of the procedure. The experience with the Ross procedure in the multi-center Ross registry as well as the single center experience with the subcoronary Ross procedure in the University of Lübeck is presented.

Chapter 1 is the general introduction of the thesis.

In **Chapter 2** a proposal on the nomenclature of the aortic root components is presented focusing on the following research questions:

- Does the currently used aortic root nomenclature accurately describe the components of the aortic root?
- Can the communication of surgical information be hindered by an ambiguous nomenclature?

The proposed nomenclature in the corresponding publication serves as a guide for data collection and evaluation purposes in the multicenter German-Dutch Ross registry.

In **Chapters 3 and 4** the single center results with the subcoronary Ross procedure are presented. Main focus points are the following:

- What is the survival of patients and the durability of the procedure after the subcoronary Ross procedure?

- How does patient survival after the subcoronary Ross procedure fare in relation to the general population?
- What are the technical considerations for the reproducibility of the subcoronary Ross procedures?
- What are the long-term results of the subcoronary Ross procedure?

Chapter 5 focuses on the durability of the Ross procedure observed in the large population of the German-Dutch Ross registry:

- What are the reoperation rates after the Ross procedure in the adult and in the pediatric population?
- Which factors affect the durability of the conduits?
- Which are the patient's options at the time of the reoperations and what are the outcomes of those?

Chapter 6 challenges a popular belief that the Ross procedure in the presence of a bicuspid aortic valves is associated with reduced durability:

- Is there evidence of higher rates of autograft regurgitation after the Ross procedure in patients with bicuspid aortic valves?
- Is there evidence of higher dilatation rates in patients with bicuspid aortic valves after the Ross procedure?

Chapter 7 discusses the problem of competing risks when evaluating conduit durability:

- How does ignoring patient survival impact the objective evaluation of conduit durability?

Chapter 8 presents the results of an effort to improve autograft durability after the Ross procedure:

- What are the main modes of failure of the Ross procedure?
- How do these mode of failure vary between the surgical techniques?
- What is the effect of autograft reinforcement on autograft durability?

Chapter 9 present clinical outcomes after the Ross procedure:

- What is the incidence of left and right sided endocarditis after the Ross procedure?
- What is the incidence of valve thrombosis and thromboembolic rates after the Ross procedure?
- What is the patients' survival after the Ross procedure?
- How does patient survival compare to that of the general population?

Chapter 10 presents a comparison of the survival of Ross patients with the survival of patient with mechanical valves after optimal and intensive anticoagulation monitoring:

- How does the survival of Ross patients compare to that of intensively monitored patients with mechanical aortic valves under optimal self-guided anticoagulation?

Chapters 11 and 12 focus on specific aspects of homograft durability:

- What is the durability of the homograft implanted in the right ventricular outflow tract?
- Which factors affect the homograft durability?
- How does the homograft function change with time and which factors influence these changes?
- What are the morphological and radiological characteristics of homograft dysfunction?

In the discussion (**Chapter 13**) the results and the knowledge obtained from the above mentioned studies and research questions are summarized and put in perspective. Pitfalls in the methodologies used to evaluate outcomes after the Ross procedure are presented with examples from the European Ross Registry and discussed, which are generalizable in the evaluation of outcomes after complex heart interventions.

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CHAPTER 2

THE EVERYDAY USED NOMENCLATURE OF THE AORTIC ROOT COMPONENTS: THE TOWER OF BABEL?

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Eur J Cardiothorac Surg. 2012;41:478-82
doi:10.1093/ejcts/ezr093 Advance Access publication 1 December 2011

SUMMARY

Modern analyses of data for scientific reporting and healthcare management purposes require standardized and consistent definitions, something which also holds true for aortic root surgery, as part of the cardiovascular surgery spectrum. The aim of the present study was to investigate the currently employed nomenclature of the aortic root components. A questionnaire was constructed on the terminology of aortic root components, providing a list of common definitions including anatomical descriptions, as well as fields for custom responses. Responses were received from 534 cardiothoracic surgeons registered at www.ctsnet.org. Remarkable variations in definitions were detected. The most unanimously accepted terms were: 'aortic leaflets', the freely moving parts (52.6% of responses); 'commissures', the distal part of the leaflet attachments plus the peripheral area of the free edges of the leaflets (52.2%); 'semi-lunar leaflet attachment', the anatomic site of leaflet attachment (58%); 'annulus', the circular line defined by the nadirs of the leaflets (38%); 'interleaflet triangle', the tissue between two leaflets and annulus (23%); 'aortic valve', the three leaflets only (55%); 'aortic root' as composed of sinuses, tissue between the leaflets, sinutubular junction, leaflets and their wall attachment (63%). The remarkable variability on the everyday-used definitions of the aortic root components can potentially lead to misinterpretation of data. More stringent adoption of consistent, standardized definitions of aortic root components is necessary in the modern era of data collection and management.

Key Words: Aortic root • Aortic valve • Anatomy

INTRODUCTION

The conduit between the left ventricle and the ascending aorta, once thought as a passive blood pathway moderated by an unadorned unidirectional gateway, is now being appreciated as a highly sophisticated and complex structure. The various components of this ensemble, although seemingly simplistic in their macroscopic morphology, are however strategically situated [1], endowed with the ability to adapt [2], renew [3], communicate [4], interact with each other [5, 6], so as to perfectly accommodate their objective as a whole [7–9]: the intermittent, unidirectional channelling of large volumes of fluid, while maintaining laminar flow, minimal resistance and least possible tissue stress and damage, over a widely and wildly varying haemodynamic conditions and demands [7–10].

It is the recognition of the overall superiority of this structure— far better than any man-made replacement—that has lead to the development of repair or 'sparing' surgical techniques respecting the functional and anatomical existence of its individual parts [11, 12]. Despite their complexity, these techniques and most importantly this surgical mentality are gaining increasing interest [12–18].

Sophisticated methods for data analyses of large registries for the quality assessment of surgical techniques, such as aortic root procedures, are being steadily developed and employed. A fundamental prerequisite for the reliable acquisition, evaluation and interpretation of these data is the adoption of standardized and consistent definitions of the surgical procedures and the respective anatomical structures. It has been shown recently that failure to use standardized and consistent definitions may jeopardize the quality of the data gathered [19].

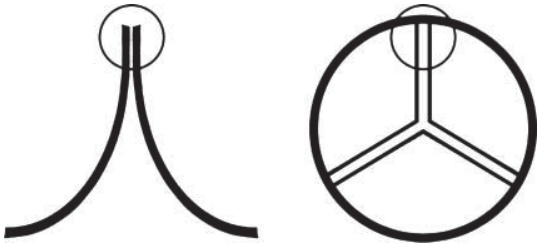

FIGURE 1. *Opened-out view of the lines of attachment of the cusps to the aortic wall (left) and the top-view on the free edges of the aortic valve cusps (right). The circles identify the areas of interest (Table 1).*

FIGURE 2. *A simplistic scheme of the opened-out aortic valve. Dashed lines, attachment of cusps; continuous line, the circular level defined by the nadirs of sinuses between cusps (Table 1).*

We aimed to investigate by means of an international survey the definitions that cardiac surgeons employ to describe the components of the aortic root, the second most frequent area of cardiac surgical interventions.

METHODS

We constructed a questionnaire on the terminology of the components of the aortic root including two overly simplistic schemes of the 'opened out aortic valve' (Figs 1 and 2). The questions and the predefined answers (Table 1) were compiled from—but not limited to—acknowledged textbooks of cardiac surgery [20], as well as vast literature including anatomical studies [1, 9, 12, 21–26]. Only the not unanimously used definitions were integrated in the survey. The term 'sinutubular junction' as the most distal part of the aortic root, the term 'sinuses of Valsalva' and their 'nadirs' as the most proximal point of the sinuses touching the 'annulus' were not included in the questionnaire because there seems to be no real disagreement on these terms. The questionnaire was sent via e-mail to cardiothoracic surgeons registered at www.ctsnet.org. All individuals were asked to identify their country where they practice and their position at their institution. We requested that only one answer per question should be selected and for all questions a blank field was provided in case no predefined answer was deemed satisfactory.

Statistical analysis of the results was performed using R (R Development Core Team 2011. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3–900051-07-0, http://www. R-project.org/). Comparisons were performed using χ^2 and ANOVA methods, where appropriate.

RESULTS

Demographics are displayed in Table 2 and the responses to the predefined answers of 534 responders in Table 1. Three hundred and thirty-six custom answers (9%) were provided in the blank fields. The most often provided answers in the blanks are presented in Table 3.

The term 'leaflet' was significantly more popular among heads of departments (58% of responses among heads of departments, $P < 0.01$). The majority of consultants responded that both terms can be used interchangeably (51% of responses) while surgeons in training choose equivalently between the terms 'leaflets' and 'cusps'. No regional differences could be observed. With all other questions there was no difference in responses with respect to the position of the responders or their nationality.

DISCUSSION

This international survey on the terminology of surgically important, however, not unanimously adapted definitions of aortic root components provides some evidence that there is a remarkable variability of definitions employed.

TABLE 1. Predefined questions and answers of the questionnaire and the distribution of received responses

Predefined question	Predefined answers	Results (% of answers)
(1) The freely moving parts of the valve (normally 3), warranting competence, are termed:	Leaflets	52
	Cusps	37
(2) The commissure is (think of the term 'subcommissural annuloplasty' and 'commissurotomy'):	The composition of the distal parts of the attachment of the leaflets/cusps to the aortic wall plus the peripheral area of the coapting parts of the free edges of the leaflets/cusps (Fig. 1, left and right)	52
	Only the short distance, where the most distal parts of the attachment of the leaflets/cusps to the aortic wall run in more or less parallel, almost conjoining (Fig. 1, left)	35
	Only the peripheral part of zones of apposition of the free edges of the leaflets/cusps (Fig. 1, right)	10
(3a) How do you term the dashed line in Fig. 2:	Semi-lunar leaflet/cusp attachment	58
	Semi-lunar ring	19
	Haemodynamic ventriculo-aortic junction	8
	'Crown-like' ring	8
(3b) How do you term the continuous line in Fig. 2, circular level (morphologically not existent) defined by the nadirs between leaflets/cusps:	Annulus	38
	Ventriculo-aortic junction	34
	Virtual annulus	12
	Base annulus	11
(4) The tissue of the aortic wall between two sinuses or two leaflets/cusps is termed:	Interleaflet/intercusp triangle	23
	Interleaflet/intercusp trigone	22
	Intercomissural trigone	18
	Intercomissural triangle	13
	Trigone	12
	Triangle	12
(5) The 'aortic valve' consists of:	The three leaflets/cusps only	55
	The sinuses, the tissue of the aortic wall between leaflets/cusps and the sinutubular junction and leaflets/cusps, and the attachment of leaflets/cusps to the aortic wall	28
(6) The 'aortic root' consists of:	The sinuses, the tissue of the aortic wall between leaflets/cusps and sinutubular junction and the leaflets/cusps, and the attachments of the leaflets/cusps to the aortic wall	63
	Only the sinuses, the tissue between leaflets/cusps and sinutubular junction, and the attachment of leaflets/cusps to the aortic wall	27

TABLE 2. Number of responses in relation to the international regions and the professional position of the responders

Region	Number of responses (% of total)
Europe	254 (47.6)
North America	126 (23.6)
Asia	91 (17.0)
Africa	24 (4.5)
South America	24 (4.5)
Australia	15 (2.8)
Position	
Head of Department	121 (22.7)
Consultant	235 (44)
Senior Registrar	46 (8.6)
Registrar	28 (5.2)
Resident	36 (6.7)
Other	59 (11)
Not specified	9 (1.7)

The moving parts, separating the aorta from the ventricle are called in the majority of the responses (52%) 'leaflets'. This seems reasonable because 'leaflet' essentially has the meaning of 'a small leaf' [Merriam-Webster Online Dictionary, http://www. merriam-webster.com/ (accessed 12 August 2011), Oxford Dictionaries, http://oxforddictionaries.com (accessed 12 August 2011)] which depicts the thin structure of these components. The term 'cusp' that is defined as 'a pointed end and where two curves meet' [Merriam-Webster Online Dictionary, http://www. merriam-webster.com/ (accessed 12 August 2011), Oxford Dictionaries, http://oxforddictionaries.com (accessed 12 August 2011)] was chosen by 37% of responders. Thus, two different terms are employed for the same anatomical structure. This is also reflected by the answers given in the blank fields where 42 answers point out that 'leaflet' and 'cusp' can be used interchangeably. For the sake of standardization of the nomenclature the term 'leaflet' should be preferred, something which is also supported recently by Frater and Anderson [23]; however, the term 'cusp' may lead to no significant misinterpretation.

The term 'commissure' originates from the Latin word 'commissura' indicating 'a point or line of union or junction especially between two anatomical parts' [Merriam-Webster Online Dictionary, http://www.merriam-webster.com/ (accessed 12 August 2011), Oxford Dictionaries, http://oxforddictionaries.com (accessed 12 August 2011)]. As depicted in the questionnaire, the term 'commissure' was used for two very different areas of the root (Table 1, Fig. 1). Fifty-two per cent of the responses defined the 'commissure' as 'the parallel course of the distal part of the semi-lunar leaflet attachment plus the peripheral area of the coapting parts of the free edges of the leaflets'. It remains open whether our hint in the questionnaire ('subcomissural annuloplasty' and 'commissurotomy'—two well-established operative

TABLE 3. Most frequent answers in the blank fields related to the different questions

Question	Most frequent answers in blank fields	n
1	Cusp and leaflet	42
	Semi-lunar cusp/leaflet	2
2	Complete contact line of the leaflets, not just periphery	3
	Zenith of the valve attachment	2
3a	Annulus	15
	Aortic annulus	4
	Anatomic annulus	2
	Ventriculo aortic junction	5
	Haemodynamic ventriculo aortic junction	2
	Hinge	5
3b	Annulus or ventriculo aortic junction, both	5
	No special term	13
	Subannular plane	5
4	Subcommissural triangle	10
	Subcommissural trigone	3
	Interleaflet triangle	4
	Commissural trigone	3
5	Leaflets, attachment of leaflets to aortic wall	31
	Different combinations between the terms leaflet/ cusp, commissures, annulus, sinuses	42
6	All components plus coronary ostia	12
	All components without leaflets	9
	Various combinations of the components including aortomitral curtain or proximal part of the ascending aorta	4

procedures) had influenced the results. Only few answers were provided in the blank fields, underlining that these terms, as given in the questionnaire, were appropriate in general. In a vernacular sense, the term 'commissures' could describe both areas. However, it is potentially troublesome that one term defines two different anatomical areas, therefore we propose the use of the term 'commissure' only for the distal parts of the leaflet attachment which reflects the common usage as recently published [23] (Fig. 3).

For the attachment of the leaflets to the wall of the aorta, the majority of responders (58%) found the term 'semi-lunar leaflet/ cusp attachment' most appropriate which is in accordance with anatomists [22, 25] and as such seems to be a well-established term, although 21 answers (4%) in the blank fields would like to name this area as 'annulus'. This may be ascribed to the fact that this area consists of dense fibrosis tissue and is in part used for surgically fixating prosthetic valves [27]. However, the elliptical insertion lines of the leaflets have more or less the form of a crown than a ring rendering perhaps the term 'annulus' less appropriate.

The circumference defined by the nadirs of the semi-lunar leaflet attachments is difficult to term because there is no real, anatomically or histologically distinct, circular structure [22]. The 'annulus' gathered 61% of all responses. This probably stems from the fact that this is the level measured by echocardiographers as 'aortic valve annulus'. In contrast, it has been shown that prosthetic valves are inserted somewhat more proximally, more towards the level of the anatomic ventriculo-arterial junction, which is due to the placement of the sutures predominently through the scalloped attachment of the excised leaflets, from the nadir of the sinus up to midway to the commissures [24, 27]. Furthermore, this is the area of the smallest diameter in the blood path between the left ventricle and the aorta and determines the fitting position of prosthetic valve sizers and therefore the size of the prosthetic valve to be implanted. In addition to this, the use of this definition gives a good impression of the employed operative techniques such as the positioning of the prostheses 'supra' or 'intra-annular'. Although this area presents a virtual ring, the term 'annulus' has a reasonable background. In the survey, the term 'annulus' was followed in popularity by the term 'ventriculo-aortic junction' (34% of responses). The term 'ventriculo-arterial junction' is rather ambiguous as the '*anatomical* ventriculo-arterial junction' represents the limit between the left ventricular myocardium and the arterial structure of the aorta, whereas the '*haemodynamic* ventriculo-arterial junction' is represented by the coronet shaped leaflet insertion and defines the separation level of the ventricular and arterial haemodynamics. From a strict anatomic point of view, the 'anatomic/histologic ventriculo-arterial' as well as the 'haemodynamic ventriculo-arterial' junction lie somewhat more distal to the 'annulus' [21, 22, 25] and define the area of interest less precisely. To avoid confusion that may arise with the terms 'haemodynamic' and 'anatomic/histologic ventriculo-arterial junction', we propose the use of the term 'annulus' to describe the virtual, circular ring defined by the nadirs of the semi-lunar leaflet attachments (Fig. 3).

The tissue between the semi-lunar attachments of the leaflets from their nadir up to the level of the commissure was most often termed 'interleaflet triangle' (23%). This is in line with other reports of anatomists [22, 23, 25]. However, no single term collected more than one-fourth of the total answers. Various terms were used to identify these structures; all expressions included the term 'triangle' or 'trigone'. However, because the term 'right and left trigone' is already employed to describe the fibrous components of the heart, the term 'triangle' may be more appropriate to describe the tissue between the leaflet attachments and the annulus, in order to prevent confusion.

The exact location and definition of term 'aortic valve'—the anatomic area where the second most frequent interventions in cardiac surgery are performed—was also defined variably. Fifty-five per cent of responders identified the aortic valve as comprising of only the three 'leaflet/cusps'. This seems logical since the aortic 'valve' replacement procedure—the most frequent valve operation—aims to replace the diseased or malfunctioning 'leaflets' in order to restore the normal function of the sealing mechanism. However, 28% of responses indicated that the 'aortic valve' is a more complex structure consisting of the 'sinuses, the tissue of the aortic wall between leaflet/cusps, the sinutubular junction, the leaflet/cusp and their attachments to the aortic wall' which is also supported by the large number of custom answers provided in the blank fields. Behind this extended definition could have been the notion that the aortic valve

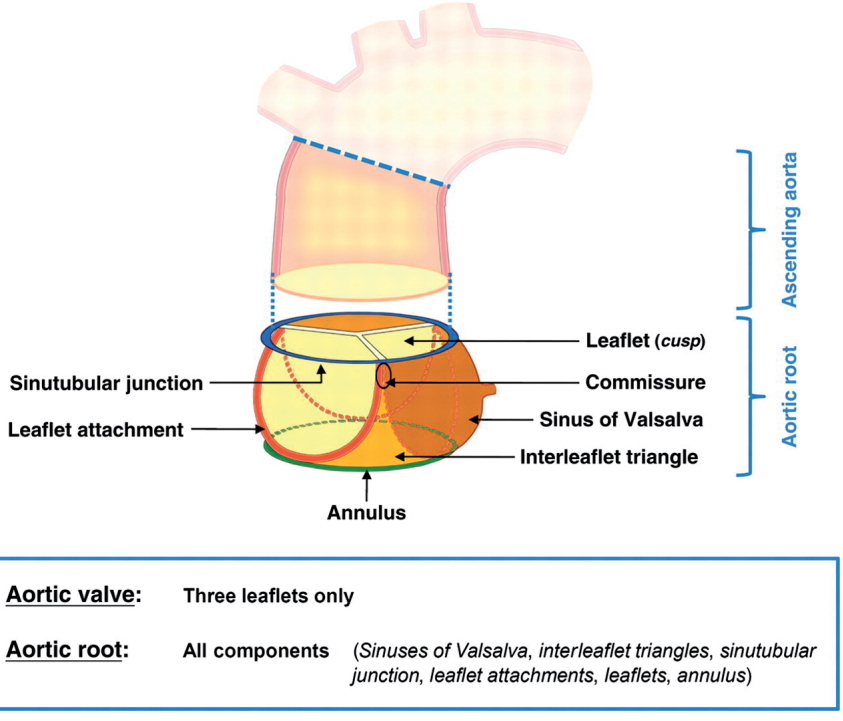

FIGURE 3. *Proposed terminology of the aortic root components. Modification of the scheme of the aortic root from reference [21, 22, 25] with one sinus of Valsalva excised.*

must be more than the leaflet since various pathologies that do not affect the leaflets (such as dilatation of the sinutubular junction) may render the valve incompetent, a notion that one cannot regard as illogical.

At first glance, it seems that this variability of definitions may not pose a problem in the everyday communication within the cardiac surgical community because experienced surgeons may know or suspect what is the true meaning or the exact anatomic location of each term or definition. But even between surgeons, there is disagreement, for example, if the 'aortic valve' consists of the leaflets only or if it is a broader, more complex structure (Table 3) or if the 'aortic root' is part of the 'ascending aorta' or not, indicating that there is a considerable potential for misinterpretation within the specialty itself. This becomes even more critical if non-specialists in the field are analysing or coding large databases for healthcare management or quality assessment purposes [19].

In summary, a considerable variation of definitions for aortic root components became evident in this international survey, potentially causing confusion, especially among non-specialists. For precise interpretation and reporting of data as well as for quality assessment of surgical procedures in a modern world of sophisticated data management, more consistent and eventually standardized definitions should be applied. Based on the research of the literature as

well as on the results of this survey, we propose a consensus on the definitions of the aortic root components (Fig. 3), perhaps as a first step towards a common, unequivocal terminology for aortic root components. With this consensus, the exact anatomic areas of surgical interest are clearly defined, and the terms used to describe complex procedures such as valve sparing aortic root replacement (David/ Yacoub operation, replacement of the root without replacement of the leaflets) and aortic root replacement (Bentall operation, replacement of the root and the leaflets) can be unequivocally employed.

ACKNOWLEDGEMENTS

We cordially thank all colleagues for answering the questionnaire and for many kind remarks in the blank fields. Unfortunately we could not present all of those comments but tried to integrate the most frequent and prominent thoughts and answers in the discussion. We remain thankful to Jana Engelmann and Anja Paap for the great support in writing this manuscript, as well as to Tobias Frin for the intuitive graphics.

Conflict of interest: none declared.

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CHAPTER 3

FOURTEEN YEARS' EXPERIENCE WITH 501 SUBCORONARY ROSS PROCEDURES: SURGICAL DETAILS AND RESULTS

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J Thorac Cardiovasc Surg. 2010;140:816-22

Objective

During the past decade the Ross procedure using the full root has become the predominant surgical technique. However, progressive autograft dilatation and eventual failure remain a concern. Here we report on the surgical techniques and results of the subcoronary technique over a 14-year period.

Methods

A total of 501 patients (mean age, 44.9 ± 12.9 years; 117 female; 384 male) were operated on from June 1994 to December 2007. The follow-up database, with a completeness of 98.2%, was closed on December 2008, comprising of 2931 patient-years with a mean follow-up of 5.9 ± 3.6 years (range, 0.1–14.1 years).

Results

Surgical details are presented. Early and late mortality were 0.4% (n = 2) and 4% (n = 20), respectively, valve-related mortality was 1.2% (n = 6), whereas the overall survival did not differ from that of the normal population. Neurologic events occurred in 22 patients, major bleeding in 9, autograft endocarditis in 8, and homograft endocarditis in 10. Freedom from autograft and homograft reoperation was 91.9% at 10 years. For the majority of patients, hemodynamics was excellent and no root dilatation was observed.

Conclusions

Midterm results after the original subcoronary Ross procedure are excellent, including normal survival and low risk of valve-related morbidity. Longer-term results are necessary for continuous judgment of the subcoronary technique.

Video clip is available online.

The pulmonary autograft procedure for the treatment of aortic valve disease, first performed by Donald Ross[1] in 1967, is the only aortic valve replacement procedure that theoretically provides all the advantages of a viable autologous tissue valve, achieving almost physiologic aortic valve hemodynamics and motion[2,3] with low incidence of macroembolism and microembolism[3-6] and without the need for lifelong anticoagulation. This makes the procedure especially attractive to young patients, whose quality of life may be limited by the valve-related morbidity of mechanical substitutes and the limited durability of biological prostheses in this age group.[7] Since the publication of excellent results in the early and late 1990s,[4,5,8] a renaissance of this surgical method has been lately observed.[3,9-12]

Although the Ross operation was initially performed as a subcoronary transplant,[1] the technical complexity of this technique made the reproduction of Ross's initial and late results[1,5] with the subcoronary technique difficult. This led to the development of the total root replacement technique, in which the complete aortic root is entirely replaced by the pulmonary root.[4,8,13] This technique has received broad acceptance in 81% of patients of the International Ross Registry.[14] However, concerns have surfaced lately regarding the ability of the isolated, unsupported pulmonary root to withstand the systemic circulation over time without progressive dilatation, leading to an unexpectedly increased reoperation rate 7 to 9 years after the initial operation.[9,10,15,16] We have performed the Ross operation with the subcoronary technique since 1994. Here we present a detailed description of the subcoronary surgical technique and our results in 501 patients.[17]

PATIENTS AND METHODS

From June 1994 through December 2007, the subcoronary Ross technique was performed in 501 consecutive patients, being 9.6% of the total number of aortic valve procedures in our center within that period. During this time period, 6 full root Ross procedures were performed (not included in this study), mainly in patients with severely malformed aortic roots, aortic roots destroyed by endocarditis, and reoperation after valve-sparing procedures and xenograft implantation. Thirty-three patients operated on with the root inclusion technique were included in this patient population. Because we did not find any difference between the root inclusion technique and the subcoronary technique in this study or in previous studies,[3,11,15] we decided to include these patients in the subcoronary population. The operative indications were in line with American Heart Association/American College of Cardiology guidelines.[17] The presence of markedly reduced left ventricular function, extensive coronary artery disease, connective tissue or active rheumatic disorders, severe deformation of the aortic root anatomy, or structural defects of the pulmonary valve, as well as intractable systemic hypertension, were considered contraindications for the Ross procedure. It is generally our philosophy that the Ross procedure is an extraordinary aortic valve replacement technique besides the commonly used alternatives and should not be performed if there are any doubts about the anatomy, the technical feasibility, or the attitude of the patient, the surgeon, or the cardiologist. Demographics and valve-related preoperative parameters are presented in Table 1. Early after the operation, antithrombotic treatment was initiated with

aspirin 100 mg per day and low molecular weight heparin for 1 week. Afterward, aspirin 100 mg per day was maintained for 3 months.

Abbreviations and Acronyms

CI confidence interval
LOR linearized occurrence rate

Surgical Technique

The surgical technique evolved mainly over the first 5 years, thereafter being by and large standardized (see Video 1). Nevertheless, increasing experience will lead to further modifications. Standard cardiopulmonary bypass with moderate systemic hypothermia was used. In the first years crystalloid cardioplegia was applied and later cold blood cardioplegia at 20-minute intervals. A detailed description of the surgical technique including 9 figures (Figures E1–E9) and a video is provided in the online E-Appendix.

Follow-up

Follow-up visits were performed prospectively on an outpatient basis 1, 3, 6, and 12 months after the operation and annually thereafter by clinical evaluation and serial standardized echocardiography.[11] All perioperative and postoperative events were defined according to the latest guidelines (2008) for reporting mortality and morbidity after cardiac valve interventions.[17] Details of the echocardiographic evaluation have been reported previously.[11,18,19] The study database was frozen on December 31, 2008. Follow-up was 98.2% complete at this time. The mean follow-up duration was 5.9 ± 3.6 years (range, 0.01–14.1 years) with a cumulative follow-up of 2931 patient-years.

Statistical Analysis

Continuous data were expressed as mean ± SD. Categorical variables were presented as absolute numbers and percentages. Estimation of longterm survival, freedom from morbid events, and valve function was made by the Kaplan–Meier method with truncation of the data at 12 years (when only 10% of patients remained at risk) so as to warrant statistical accuracy and sound conclusions. The survival time of each patient started at the time of surgery and ended at death (event) or at last follow-up (censoring). The long-term survival characteristics of the patient cohort were compared with the survival probabilities of the ageand gender-matched general population obtained from German Life Tables 2004/2006 (www.destatis.de). The analysis of event-free rates started at the time of operation and ended at the time of an event (eg, reoperation, thromboembolism, bleeding) or last follow-up or death (censoring). Statistics for patients with incomplete follow-up investigations were censored at the time of their last inquiry.

The SPSS 13.0 for Windows statistical software (SPSS, Inc, Chicago, Ill) was used for all analyses. The authors had full access to the data and take responsibility for their integrity. Informed consent was obtained from all patients preoperatively and before each follow-up visit. The local ethics committee approved the present study (Clinical Trials ID: NCT 00708409).

RESULTS

Mortality

Early mortality. All-cause early (<30 days) mortality was 0.4% (n = 2, owing to refractory ventricular arrhythmias 3 days postoperatively and to a thromboembolic occlusion of the left main coronary artery 7 days after valve replacement for infective endocarditis). The autograft function was excellent. No early mortalities occurred in the following 291 procedures.

Valve-related late mortality. Valve-related mortality was 1.2% (6 patients, linearized occurrence rate [LOR] 0.20%/ patient-year): 1 patient with coronary embolism, 1 with refractory ventricular arrhythmias, 1 with surgically treated valve endocarditis (primary mitral valve endocarditis, with eventual involvement of the autograft and homograft), 2 sudden, unexplained deaths (last follow-up examinations revealed no valvular problems in these patients), and 1 patient with heart failure with severe regurgitation of all 4 cardiac valves.

Cardiac death. The number of deaths of cardiac etiology was 8 (LOR, 0.27%/patient-year). Included are 6 valverelated deaths and 2 non–valve-related cardiac fatalities.

All-cause mortality. All-cause mortality, including early mortality, was 20 (4.0%, 0.68%/ patient-year): 8 cardiac deaths, 6 malignancies, 1 suicide, 1 multiorgan failure after noncardiac surgery, 1 renal failure, 2 bleeding events (hypertensive cerebral hemorrhage, bleeding of esophageal varices), and 1 intoxication. The cumulative overall survival compared with the expected number of deaths of the ageand gendermatched general German population is shown in Figure 1.

Morbidity

Five patients required the implantation of a permanent pacemaker in the immediate postoperative period (<14 days postoperatively).

Structural valve deterioration. Structural valve deterioration with impact on clinical functional capacity according to the New York Heart Association was present in 8 patients. Echocardiography revealed a relevant valvular impairment in these patients (aortic regurgitation grade II or III, n = 2; increase of mean pressure gradient across the pulmonary homograft, n = 6). In 6 patients a marked systolic left ventricular impairment was observed without obvious valvular dysfunction. Structural valve deterioration verified by reoperation was present in 13 patients (9 autografts, 4 homografts; see Reoperation section).

Nonstructural dysfunction. Nonstructural valve dysfunction[17] was confirmed in 2 homograft reoperations (1 patient–homograft mismatch, 1 annular ring dilatation) and 2 autograft reoperations (1 annular dilatation, 1 dilatation of the sinotubular junction).

Valve thrombosis. One patient required reoperation on the homograft 14 months after the primary procedure owing to obstruction caused by extensive leaflet-adherent thrombi in 2 sinuses (despite the patient receiving aspirin). Additionally, cusp laceration was present compatible with cured endocarditis. Autograft valve thrombosis was not detected. Embolism. Within 30 days postoperatively, stroke occurred in 1 patient (day 5; treated with aspirin and unfractionated heparin 22,500 IU/d) and a transient ischemic attack in 5 patients (all patients were treated with aspirin and unfractionated heparin 22 500, IU/d).

TABLE 1. Patient demographics and preoperative characteristics

n	**501**	
Mean age, y (range)	44.9 ± 12.9 (13.8–70.5)	
<20	19	3.8%
20–40	161	32.1%
41–60	274	54.7%
>60	47	9.4%
Gender		
Male	384	76.6%
Female	117	23.4% NYHA
I	144	28.7%
II	261	52.1%
III	93	18.6%
IV	3	0.6%
Ejection fraction (%)		
>50	458	91.4%
30–50	42	8.4%
<30	1	0.2%
Diabetes mellitus	22	4.4%
Hypertension	168	33.5%
Impaired renal function	32	6.4%
Rhythm		
Sinus	493	98.4%
Atrial fibrillation	7	1.4%
Pacemaker	1	0.2%
Hemodynamic diagnosis		
Stenosis	73	14.6%
Regurgitation	148	29.5%
Mixed lesion	279	55.7%
Prosthetic valve dysfunction	1	0.2%
Aortic valve morphology		
Tricuspid	128	25.5%
Bicuspid	344	68.7%
Unicuspid	15	3.0%
Other	14	2.8%
Etiology		
Congenital	345	68.9%
Degenerative	184	36.7%
Myxomatous	55	11.0%
Rheumatic	6	1.2%
Acute endocarditis	25	5.0%
Prior aortic valve interventions		
Valve replacement	6	1.2%
Valve reconstruction	13	2.6%

NYHA, New York Heart Association classification.

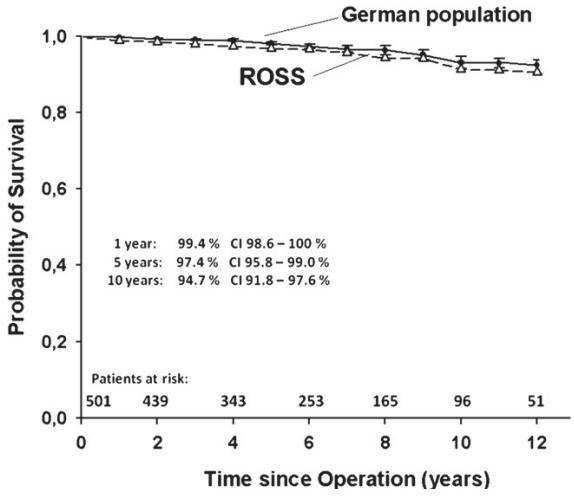

FIGURE 1. *Probability of survival comparing the Ross subcoronary patient group with the ageand gender-matched general population. CI, 95% confidence interval.*

After hospital discharge, 16 neurologic events occurred (3.2%; LOR, 0.55%/patient-year; 7 strokes, 9 transient ischemic attacks). In 5 patients with stroke, new onset of atrial fibrillation (without the patient receiving anticoagulation) was present, and in 2 patients, carotid artery disease was present. Transient ischemic attacks were associated with atrial arrhythmias in 5 or carotid artery disease/thromboa theromatosis of the aortic arch in 4.

Noncerebral embolic event. There was 1 coronary embolism complicated by refractory cardiogenic shock, leading to a fatal outcome in the early postoperative period (see Mortality). In 1 patient a thromboembolic femoral artery occlusion was detected (sinus rhythm, mitral stenosis, no anticoagulation).

Bleeding. Major internal or external bleeding occurred in 9 patients (1.8%; LOR, 0.31%/patient-year). One patient with atrial fibrillation receiving oral anticoagulation therapy had a head injury causing an epidural hematoma and 1 patient without anticoagulation had a subdural hematoma after a head trauma. Additionally, 1 patient receiving anticoagulation had a subdural hematoma and another had gastrointestinal bleeding. A hematothorax developed spontaneously in a patient receiving anticoagulation. Additionally, 2 patients with hemorrhages and fatal outcome (esophageal varices, hypertensive cerebral bleeding; no anticoagulants in both patients) and 2 patients with gastrointestinal bleeding were not treated with anticoagulants. Neither fatality was related to the cardiac condition or specific cardiac drug therapy.

Antithrombotic management. At the time of the last follow-up visit, 35 patients were being treated with oral anticoagulants (phenprocoumon; target international normalized ratio, 2.5–3.0) for chronic or paroxysmal atrial fibrillation (n = 26), embolic events of vascular or cardiac origin (n = 3), deep vein thrombosis (n = 3), pulmonary embolism (n = 2), and vascular surgery for chronic occlusive peripheral artery disease (n = 1). Antiplatelet drug therapy (100 mg aspirin daily) was used in all patients with coronary artery disease or

peripheral vascular disease (n = 33). For nonvalvular indications, 100 mg aspirin per day was used in 16 patients.

Composite thrombosis, embolism, and bleeding. A total of 34 patients had the composite end point of thrombosis, embolism, and bleeding (6.8%; LOR, 1.16%/patient-year). Operated valve endocarditis. No early endocarditis occurred (<30 days). Late autograft endocarditis with severe aortic regurgitation occurred in 5 patients (1.0%; LOR, 0.17%/patient-year): acute in 1, subacute in 2, and cured in 2. In 2 patients a mechanical prosthesis was implanted, and in another 3 a bioprosthesis. In 1 patient with additional infective endocarditis of the homograft, the conduit was also replaced by another homograft.

Homograft endocarditis occurred in 6 patients (1.2%; LOR, 0.20%/patient-year): 3 with acute endocarditis (1 patient with autograft and homograft endocarditis), 1 with subacute endocarditis, and 2 patients with valve destruction present after cured infective endocarditis. In 1 patient recurrent homograft endocarditis had to be treated with a second reoperation. In all cases the infected homograft was replaced by another homograft. Recurrent homograft endocarditis was treated with a stentless bioprosthesis.

One patient (not included in the above numbers) with primary mitral valve endocarditis after mitral valve replacement with a bioprosthesis had trivalvular endocarditis with involvement of the mitral bioprosthesis, the autograft, and the homograft. He died 1 week after mitral valve replacement in a septic shock state.

Medically treated valve endocarditis. Conservative medical treatment of autograft endocarditis was successful in 3 and homograft endocarditis in 4 patients (1.4%; LOR, 0.24%/patient-year).

The LOR for all operated and medically treated endocarditis events was 0.65%/patient-year Reoperation. Twenty-six reoperations on 28 Ross-related valves (pulmonary autograft, pulmonary homograft) were required in 23 patients (4.6%; 0.78%/patient-year); the time interval between the initial procedure and the reoperation was 4.82 ± 4.00 years (range, 0.01–11.7 years; median, 2.85 years). Thirteen interventions in 10 patients (1 patient had repeated interventions owing to recurrent infective endocarditis) were performed solely on the pulmonary conduit (2.6%; LOR, 0.44%/patient-year). Twelve patients underwent reinterventions on the autograft only (2.4%; LOR, 0.41%/patient-year) and 3 patients on both the autograft and homograft (0.6%; LOR, 0.10%/patient year).

Indications for 15 *autograft reinterventions* (including interventions on the autograft and homograft in 3 patients) included structural valve failure with pure aortic regurgitation in 10 patients as well as aortic valve endocarditis in 5 patients (2 acute interventions for annular abscess without regurgitation, 1 subacute, and 2 in patients with leaflet perforation and moderate-to-severe aortic regurgitation who were cured). Cusp prolapse (1 patient with acute endocarditis) was identified in 7 of 15 autograft reoperations (2/7 with concomitant annulus dilatation) and cusp perforations (1 patient with endocarditis) was identified in 3 reoperations. No reoperation owing to dilatation of the ascending aorta was observed. There was no correlation between autograft reoperation and valve morphologic features (bicuspid vs tricuspid aortic valve; $P = .3$). The autograft reoperation procedures were performed from 0.01 to 11.7 years (mean, 5.31 ± 4.25 years; median, 6.8 years) after the initial Ross operation.

In 7 patients a mechanical valve, in 6 a bioprosthesis, and in 1 a homograft was implanted; in 1 patient an autograft reconstruction was performed. Freedom from reoperation on the autograft is displayed in Figure 2. Among the 13 reinterventions on the *pulmonary homograft* (including 3 patients with replacement of the autograft and homograft and 1 patient with 3 reinterventions), 4 showed structural valve failure (in 4 pulmonary regurgitation grade III, in 1 pulmonary stenosis), 2 had nonstructural valve deterioration (patient–homograft mismatch in 1, annular dilatation in 1), and 7 had acute or cured infective endocarditis (2 with pure stenosis and 5 with pure regurgitation, with grade III in 4 and grade IV in 1). The homograft reoperation procedures were performed from 1.1 to 11.7 years (mean, 4.15 ± 3.73 years; median, 2.2 years) after the initial Ross operation. On 12 occasions another homograft was inserted; 1 patient with repeated homograft stenosis received a Shelhigh bioprosthesis (Shelhigh, Inc, Union, NJ) that degenerated within months and was replaced thereafter with a Carbomedics artificial valve (Carbomedics, Inc, Austin, Tex). No transcutaneous homograft procedures were performed. Freedom from reoperation on the homograft is displayed in Figure 3. Freedom from autograft and homograft reoperation is displayed in Figure 4. All patients survived the reoperation on Ross-related valves and were alive at the date of the last follow-up inquiry.

Major adverse valve-related events. Overall freedom from any major valve-related event (all valve-related mortality; valve-related morbidity: structural valve deterioration, nonstructural valve dysfunction, thrombosis, bleeding, embolism, neurologic events including transient ischemic attacks, endocarditis, reintervention; and need for pacemaker implantation within 14 days after operation[17]) was 95.8% at 1 year (95% confidence interval [CI], 94.0%–97.6%),

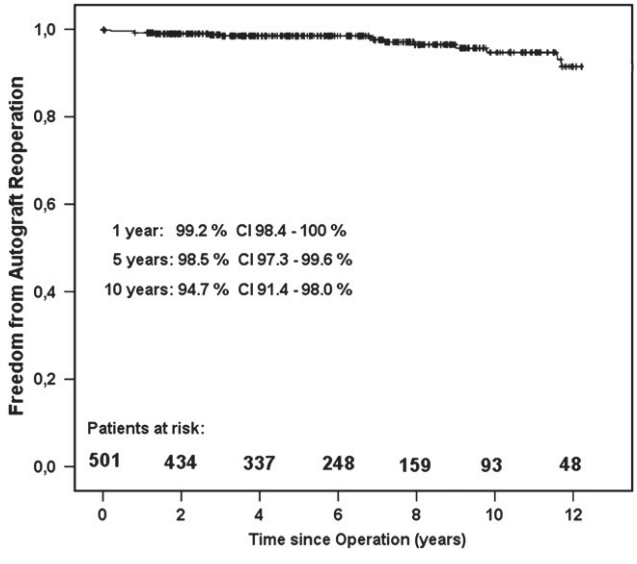

FIGURE 2. *Freedom from autograft reoperation. CI, 95% confidence interval.*

TABLE 2. Freedom from death and other morbid events at 10 years

Event	Freedom (%)	95% CI
Death	94.7	91.8–97.6
SVD, nSVD with AG or HG reoperation	91.9	87.9–95.8
Endocarditis	94.2	91.1–100
Thromboembolism (including TIAs)	95.1	92.9–100
Thromboembolism (excuding. TIAs)	97.5	95.9–100
Major bleeding	97.0	94.5–100

CI, Confidence interval; *SVD,* structural valve deterioration; *nSVD,* nonstructural valve deterioration; *AG,* autograft; *HG,* homograft; *TIAs,* transient ischemic attacks.

90.1% at 5 years (95% CI, 87.4%–92.8%), and 81.8% at 10 years (95 % CI, 76.9%–86.7%). The freedom from each of the aforementioned events at 10 years is displayed in Table 2.

Functional and echocardiographic status at last followup. Table 3 shows the functional capacity according to the New York Heart Association classification and the echocardiographic characteristics of the autograft and homograft at the last follow-up visit. At 5 years postoperatively, freedom from aortic insufficiency of grade II or more, pulmonary insufficiency of grade II or more, and homograft stenosis with a mean gradient of 25 mm Hg or more was 94.6% (CI, 92.2%–99.9%), 94.6% (CI, 92.4%–100%), and 95.2% (CI, 93.0%–100%), respectively, and at 10 years postoperatively 85.2% (CI, 80.3%–100%), 85.5% (CI, 81.0%–100%), and 89.9% (CI, 86.0%–100%), respectively. It must be stressed that the patients undergoing reoperation, with their hemodynamics at the time of the reoperation, are included in the aforementioned numbers.

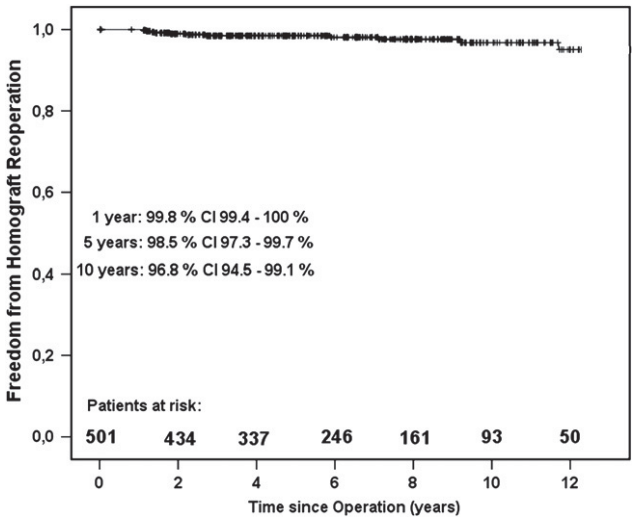

FIGURE 3. *Freedom from homograft reoperation, CI, 95% confidence interval.*

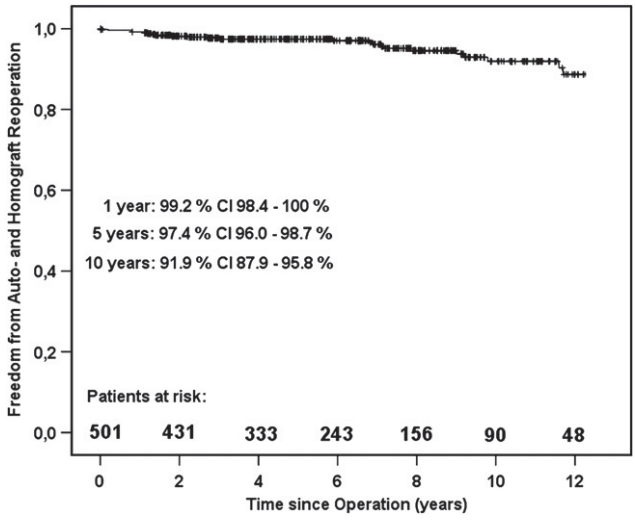

FIGURE 4. *Freedom from autograft and homograft reoperation. CI, 95% confidence interval.*

Patients with more than 10 years of follow-up. There were 105 patients with more than 10 years of follow-up. Of these patients, 5.3% had reoperations on the autograft and 3.8% on the homograft compared with 2.3% and 1.8% of patients with follow-up less than 10 years, respectively. The proportion of patients with aortic insufficiency of grade 2 or more was 8.6% in patients with more than 10 years of follow-up and 3.5% for those with less than 10 years of follow-up.

DISCUSSION

This study provides some evidence that the life expectancy of patients having the Ross operation is comparable with that of the normal population, at least in the first decade after the operation. This is astonishing to some extent inasmuch as the patients had significant valvular disease before the operation that may per se have a limiting effect on survival owing to disease-related structural alterations within the myocardium and connective tissue. However, patient selection by excluding those patients with severe heart failure, as well as the excellent postoperative hemodynamics with almost normal pressure gradients across the autograft and in most cases negligible regurgitation in conjunction with the low risk of valve-related extracardiac fatal events and the close regular follow-up, may have a protective effect on patient survival. In the full root technique, the adverse remodeling of the pulmonary root leads to progressive dilatation and aortic valve regurgitation, eventually mandating a reoperation in some patients. The incidence of reoperations increases 7 to 8 years after the initial operation.[9,10,15,16] In the present series, reoperations on the autograft were related to cusp prolapse and not to autograft dilatation.

The second reason for reoperations on the autograft and homograft was the occurrence of infective endocarditis.

TABLE 3. Functional and echocardiographic outcome at last follow-up visit

NYHA class			
I	449 (93.9%)		
II	27 (5.6%)		
III	2 (0.4%)		
IV	0		
Unknown	0		
Echocardiographic results			
AG gradient, mean (mm Hg)		AG regurgitation (grade)	
<5	338 (73.0%)	None	179 (38.7%)
5–10	119 (25.7%)	Trivial	166 (35.9%)
>10	0	1/4	88 (19.0%)
Unknown	6 (1.3%)	2/4	24 (5.2%)
3/4	3 (0.6%)		
4/4	0		
Unknown	2 (0.4%)		
HG gradient mean (mm Hg)		HG regurgitation (grade)	
<5	111 (23.8%)	None	215 (46.0%)
5–10	240 (51.4%)	Trivial	136 (29.1%)
11–15	66 (14.1%)	1/4	86 (18.4%)
16–20	25 (5.4%)	2/4	25 (5.4%)
21–25	12 (2.6%)	3/4	2 (0.4%)
>25	6 (1.3%)	4/4	0
Unknown	7 (1.5%)	Unknown	3 (0.6%)

Deceased (n = 20) and patients lost-to-follow-up (n = 3) are excluded. Reoperated valves are excluded from the corresponding valve function sections.

Whether this can be more favorably addressed with the appropriate use of endocarditis prophylaxis remains speculative. On the other hand, homograft degeneration with time remains an issue; however, novel decellularization protocols reducing the immunogenicity of homografts, with the potential to repopulate them with autologous cells, are promising.[20] Although decellularized xenografts are reported to yield excellent results in the right ventricular outflow tract,[21] our own experience with decellularized homografts is limited and does not support these promising reports.[22] This may be related to the different decellularization protocols and the fact that the allografts used in our study were additionally cryopreserved, which itself causes serious alterations to the leaflet tissue.[23]

Taken together, the risk of reoperation is a weak point in the Ross procedure. Although this risk is low (0.78%/ patient-year) for the observed time period of 0.1 to 14.1 years (mean, 5.9 ± 3.6 years), it remains a matter of concern.

Seven of our 501 patients have borderline hemodynamics (especially mean homograft gradients > 25 mm Hg) and may become candidates for possible reoperations in the future. Transfemoral approaches for pulmonary valve replacement in case of homograft failure can potentially reduce the need for conventional reoperations.[24] Interestingly, there is no exponential increase in reoperations in the longer term after 7 to 8 years, even in young patients, in contrast to reports with the full root technique.[9,10,15,16] However, the mean follow-up duration of our patients was 6 years, and only longer-term results can give more definite information on this subject. Although reoperation is a devastating problem for the patient, there was no fatal outcome or increased morbidity in our group during reoperations on the Ross-related valves. Morbidity is low and bleeding complications are most probably related to anticoagulant medication prescribed not for the Ross procedure itself but for other coexisting diseases, such as atrial fibrillation. If this was taken into account in the reporting guidelines, the incidence of strictly valve-related morbidity after the Ross procedure would be even lower than reported here, something that also holds true for bioprostheses.

Furthermore, quality of life is not considered, either in the guidelines or in this article. There are, however, aspects of quality of life, as measured by the 36 item Short-Form Health Survey, that are advantageous in the Ross procedure[25] compared with mechanical valves. These aspects are in addition to freedom from noise disturbance[26] and lifelong anticoagulation as well as unrestricted daily activities (sports, profession, and nutrition). Female patients of child-bearing age benefit from freedom from anticoagulation after the Ross procedure; for example, 8 female patients had uncomplicated delivery of 12 children in our patient group. Mechanical valve–related microembolism[6] with the potential for continuous cognitive impairment[27] is not considered in the new guidelines. Also not taken into account are hemodynamics like the near normal transvalvular pressure gradients at rest and exercise in Ross patients,[28] left ventricular mass regression,[18] and near normal flow turbulence characteristic downstream from the autograft,[29] in contrast to the altered coronary flow reserve in patients with mechanical valves.[30] Besides these objective parameters, how can we grade and evaluate the fear of a patient for adverse events after the Ross operation (mainly the need for reoperation), which does not occur suddenly and has a low risk of mortality and morbidity? On the other hand, there is the fear of sudden unexpected major events with a mechanical valve, mainly involving extracardiac organs, with the potential of lifelong disability (eg, stroke). How should we objectively measure the shortcomings of anticoagulation-related minor problems, such as troubles and uncertainties during dental procedures, nose bleeding, and minor and major accidents?

In conclusion, our experience with 501 subcoronary Ross operations shows excellent clinical and hemodynamic results with normal survival and low valve-related morbidity for the observed time period of 0.1 to 14.1 years (mean, 5.9 ± 3.6 years). The selection bias makes the comparison of the Ross operation with mechanical valves or bioprostheses difficult.

The use of randomization or propensity scoring techniques seems indispensible for comparison of the Ross operation with other alternatives. Although a certain risk for reoperation does exist with the subcoronary technique, for the observed time period of 0.1 to 14.1 years (mean, 5.9 ± 3.6 years) postoperatively this risk remains low and no exponential increase of the reoperation rate with time is observed, in contrast to the full root technique.[9,10,15,16] In

general, candidates for aortic valve replacement have to be thoroughly informed about the full spectrum of the aforementioned aspects. That holds true for the Ross operation and also for all other alternatives. Decision-making is difficult and is related not only to the valve substitute per se but also to the attitude of the patient, the surgeon/ cardiologist, and the technical details and postoperative care. All substitutes have their intrinsic advantages and disadvantages; we are far from an ideal solution. All efforts have to be concentrated on improving implants and techniques. For the final judgment of the subcoronary method reported in this article, there is no doubt that longer-term follow-up studies are needed.

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E-APPENDIX

Surgical Technique

Aortotomy and inspection of the aortic valve. The aortotomy is S-shaped, reaching into the noncoronary sinus, especially in patients with bicuspid aortic valves, because in these cases the noncoronary sinus is usually enlarged and can be adjusted by later aortotomy closure to the size of the autograft. If the sinotubular junction or the ascending aorta is larger than 50 mm, the ascending aorta is replaced by a supracommissural tube graft. Extensive and meticulous decalcification is necessary. The root anatomy of a tricuspid valve provides excellent conditions for the autograft implantation; bicuspid aortic valves, types I and II,[E1] have favorable root anatomy, whereas a subcoronary Ross procedure in a root of a bicuspid aortic valve type 0 is challenging and, in view of alternative substitutes, questionable. Hegar dilators are used for measurement of the size of the root. The sinotubular junction should be at least the same size as the tailored annulus (see later); some millimeters larger is of no concern, because resistance against dilatation-associated regurgitation is well preserved in autografts.[E2] A sinotubular junction diameter after implantation smaller than that of the autograft in the pulmonary position is potentially a risk factor for cusp prolapse–induced aortic insufficiency. This can be prevented by a small pericardial patch, normally 1 cm in width in the aortotomy suture line if necessary, or by not incising the noncoronary sinus during aortotomy. If the maximal diameter of the sinotubular junction or ascending aorta is larger than 50 mm, the ascending aorta is replaced by a supracommissural tube graft.

Excision of the pulmonary autograft. The trunk of the main pulmonary artery is incised anteriorly, half circumferentially and 0.5 cm distal to the anterior commissure, allowing for inspection of the valve. Large fenestrations, thickened and retracted leaflet tissue, and quadricuspid valves are considered contraindications. Only slight disproportions of leaflets and sinuses are accepted and adjusted by adequate positioning of the autograft in the aortic root. The pulmonary trunk is transected completely and tilted anteriorly to dissect the plane between the adventitia and the pulmonary trunk posteriorly. Care must be taken to stay close to the autograft. Usually an Overholt forceps placed through the pulmonary valve into the right ventricular outflow tract, indicating a level of 2 mm beneath the pulmonary annulus, is used to determine the right ventricular cross-sectional incision line. This incision is continued close to the semilunar attachment of the leaflets, trying to find a dissection plane posteriorly between the valve and right ventricular muscle. Special care has to be taken at the left lateral aspect of this dissection plane, where a typical right ventricular outflow tract muscle bundle indicates the position of the first septal branch (Merrick AF, Yacoub MH, Ho SY, Anderson RH. Anatomy of the muscular subpulmonary infundibulum with regard to the Ross procedure. *Ann Thorac Surg.* 2000;69:556-61) (Figure E1). The dissection at this area has to be kept very close to the pulmonary annulus, leaving only a small amount of muscle at the autograft. At this stage, there is a risk that the dissection level is too deep, causing problems with the coronary septal branches. After excision of the autograft, left coronary artery cardioplegia is given to identify and treat bleeding sites. The autograft is trimmed, leaving only a 1to 2-mm rim of muscular tissue while indicating the midpoint of the interleaflet triangles by a small, slightly scalloped incision (Figure E2).

Implantation of the pulmonary autograft. Normally the proximal autograft implantation suture line follows the scalloped semilunar attachment of the former aortic valve leaflets half the distance up to the commissure, usually starting at the left coronary sinus (Figure E3). The stitches in the autograft (4-0 polyfilament material) are placed directly at or through the attachment of pulmonary leaflets (Figure E4) following a line congruent to that in the aortic root, as shown in Figure E3. The autograft is placed side by side to the aortic root (Figure E5). The inversion technique may cause leaflet distortion. We start with a U-stitch followed by 3 regular single over-and-over stitches, and again the next series starts with a U-stitch (Figure E6). The U-stitches are very practical for later traction and positioning of the autograft into the aortic root. If the diameter of the annulus is more than roughly 25 mm, a 2-0 polytetrafluoroethylene suture (Gore-Tex suture; W. L. Gore & Associates, Inc, Flagstaff, Ariz) or Dacron strip is integrated in the suture line during tying of the knots. This polytetrafluoroethylene or Dacron strip is held under tension at each suture segment (1 U-stitch, 3 single stitches) so as to fix the annulus diameter or even reduce it (Figure E7). If a polytetrafluoroethylene 2-0 suture is used, both ends of these sutures are placed outside the nadir of the noncoronary cusp and fixed over a Teflon patch. Alternatively, the interleaflet trigone between the noncoronary and left coronary sinus can be plicated by a U-stitch from outside to reduce the size of the annulus. Next, 5-0 polypropylene U-stitches (Prolene; Ethicon, Inc, Somerville, NJ) buttressed with, for example, autologous pericardial pledgets inside and Teflon patches outside, are used to fix the commissures exactly above the former commissures of the aortic valve, trying to lift up the commissures, commonly by about 1 cm (Figure E8). Only small parts the left and right coronary sinuses of the autograft are excised before the attachment of the autograft sinuses in a subcoronary fashion to the sinuses of the aortic valve with a 5-0 Prolene polypropylene suture starting at the left coronary sinus—always at the most remote point from the surgeon—in a running over-and-over suture technique toward the surgeon. This is followed by the other end of the suture stitched in an inside–outside fashion through the wall of the aortic root, up to the commissure between the left and right coronary ostia (Figure E9).

Implantation of the pulmonary homograft. In almost all cases a long (up to the bifurcation) pulmonary homograft is used. The muscular tissue of the allograft is excised as much as possible, leaving only 2 or 3 mm of allogenic myocardium or replacing the complete muscle rim of the allograft by a pericardial or polytetrafluoroethylene strip. Latest investigations show only minor superiority of the pericardial patch,[3,11] leading to it now being applied only in small-sized homografts. The distal suture line is performed with 5-0 Prolene polypropylene suture whereby the stitches are placed close together to ameliorate constriction by the suture line.

For the proximal anastomosis, 5-0 or 4-0 Prolene polypropylene sutures, depending on the allograft material, are used, with special care not to injure the area of the septal branch where the stitches are placed superficially. The size of the homograft is chosen to be 25 mm in diameter or larger.

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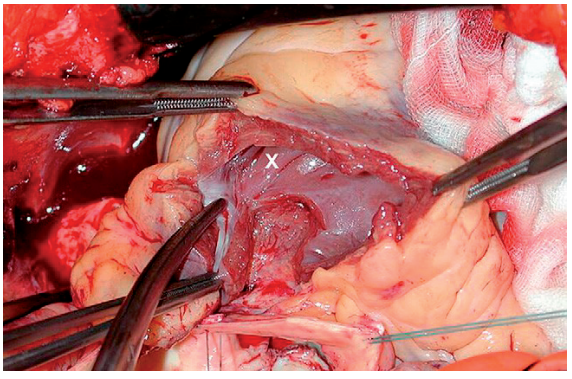

FIGURE E1. *Excision of the autograft. Usually a muscle band (X) in the right ventricular outflow tract indicates the location of the septal branches (tip of scissors).*

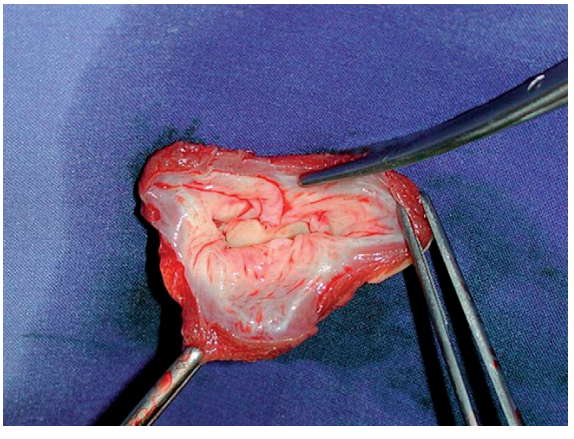

FIGURE E2. *Preparation of the autograft. The autograft is trimmed leaving only a 12-mm rim of muscular tissue and incising the interleaflet triangle slightly in a scalloped fashion.*

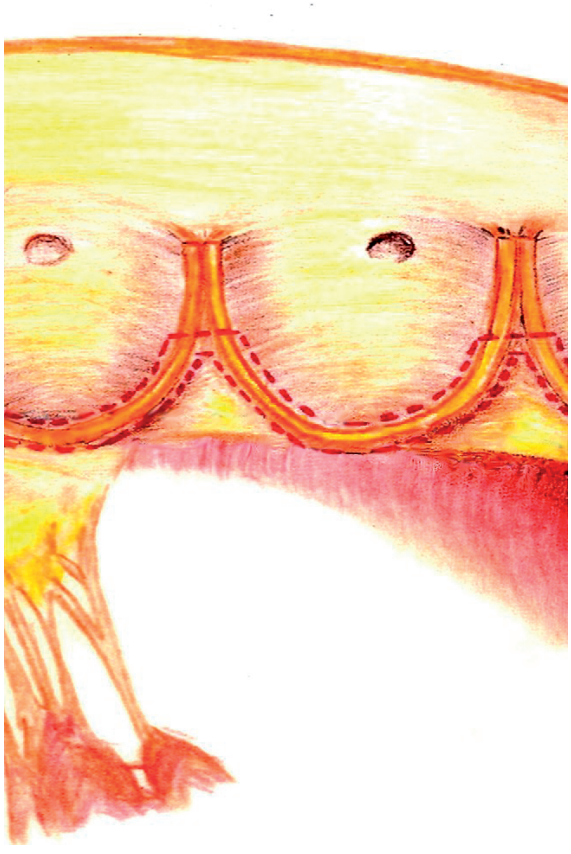

FIGURE E3. *Implantation of the autograft. This schematic drawing shows the suture line (broken red lines) following the attachment of the former aortic valve leaflets halfway up to the commissures.*

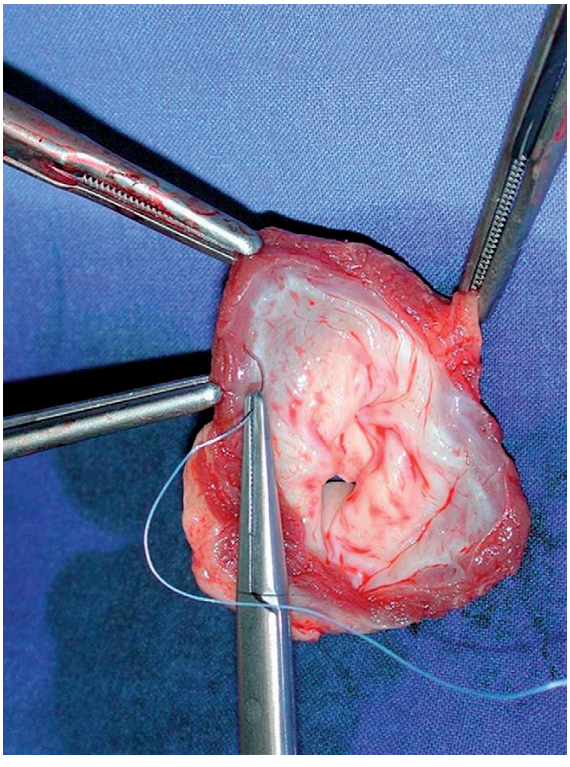

FIGURE E4. *Implantation of the autograft. Sutures of the proximal suture line are placed close to the scalloped attachment of the semilunar leaflets of the pulmonary autograft.*

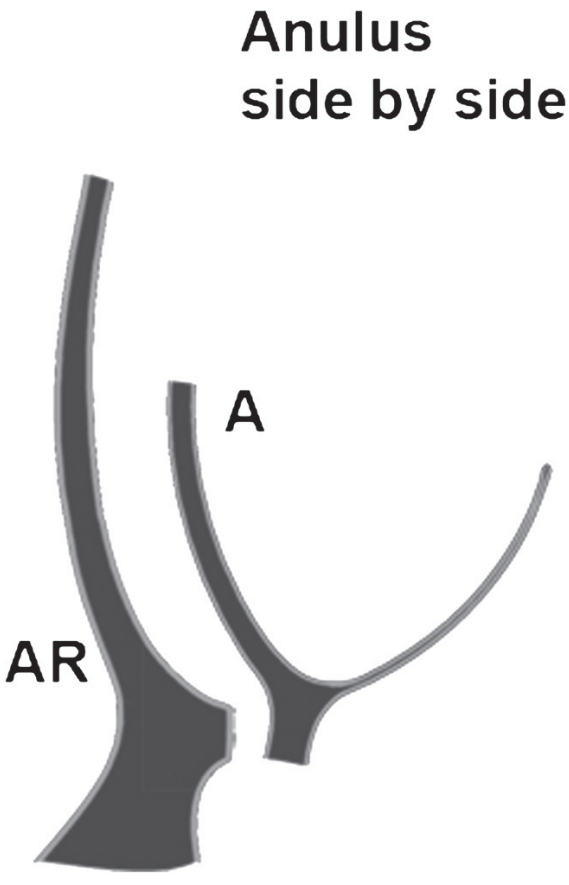

FIGURE E5. *Implantation of the autograft. The autograft (A) is sutured side by side to the annulus of the aortic root (AR).*

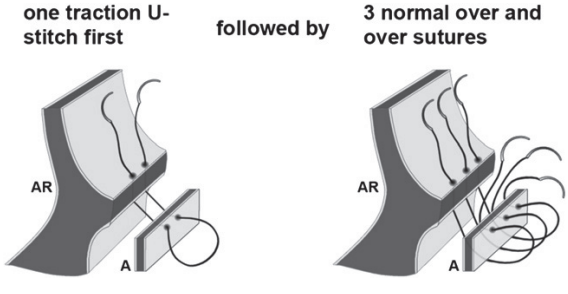

FIGURE E6. *Implantation of the autograft. One U-stitch is used first, followed by 3 over-and-over single stitches. This series of sutures is then repeated all around the annulus (A, autograft; AR, aortic root). The U-stitches are helpful for traction and positioning the autograft into the root.*

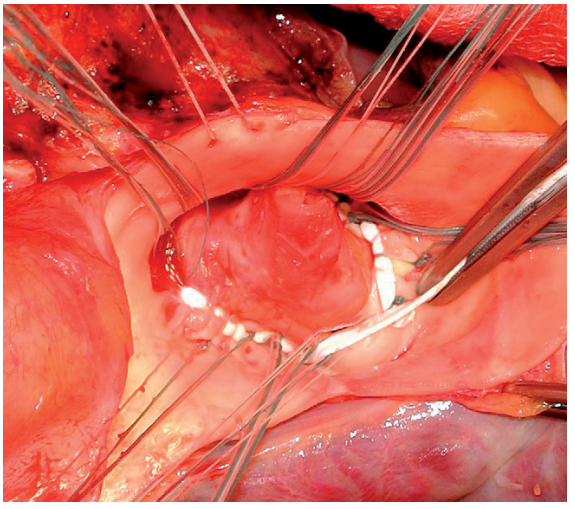

FIGURE E7. *Implantation of the autograft. A strip of polytetrafluoroethylene or a 2-0 polytetrafluoroethylene suture is integrated in the proximal suture line to reduce and stabilize a dilated annulus.*

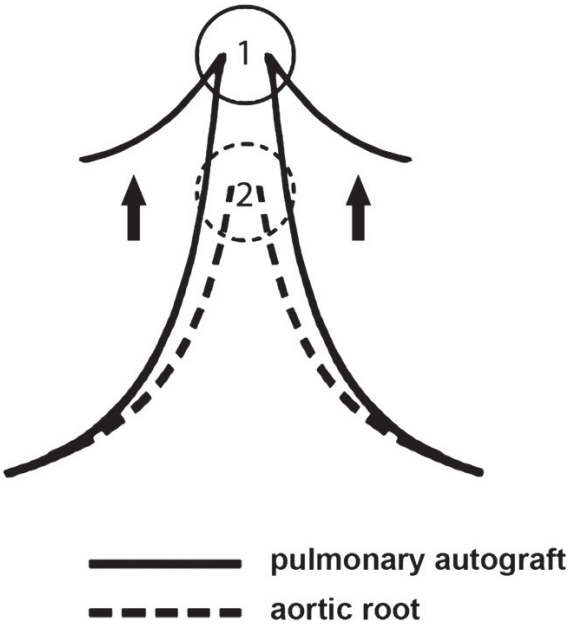

FIGURE E8. *Implantation ofthe autograft. The commissure of the autograft (1) is hitched up roughly 1cm above the commissure of the corresponding aortic root (2).*

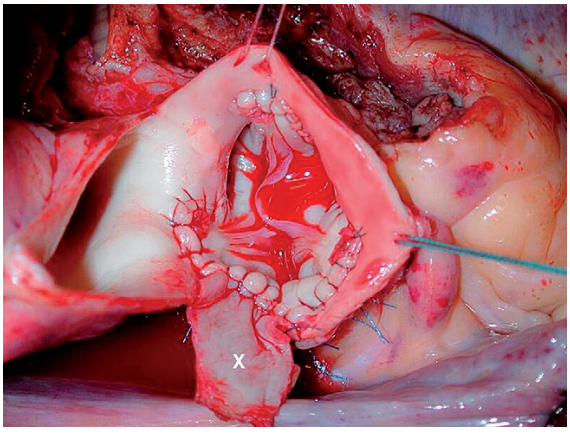

FIGURE E9. *Implantation of the autograft. The distal sinus suture line using 5-0 Prolene polypropylene continuously is completed. A pericardial patch (X) is integrated in this case into aortotomy closure line to adjust a narrowed sinotubular junction of the aortic root to the autograft dimensions.*

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CHAPTER 4

LONG-TERM RESULTS OF 203 YOUNG AND MIDDLE-AGED PATIENTS WITH MORE THAN 10 YEARS OF FOLLOW-UP AFTER THE ORIGINAL SUBCORONARY ROSS OPERATION

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Ann Thorac Surg. 2012;93:495-502

Background

The choice of prosthesis for aortic valve replacement in young and middle-aged patients remains challenging owing to the accelerated degeneration of bioprostheses in these age groups and the risks of thromboembolism and bleeding with mechanical valves. Theoretically, the living pulmonary autograft (Ross operation) would be advantageous. Long-term results of the various Ross techniques are needed for defining the value of this surgical concept.

Methods

Of a total of 576 subcoronary Ross patients operated on between June 1994 and June 2011, we report on 203 consecutive subcoronary patients (mean age, 47.2 ± 13.6 years, 155 male, 2,491 patient-years) with a follow-up of at least 10 years (mean, 12.3 ± 2.9 years).

Results

Early and late mortality were 0.98% (n = 2) and 11.4% (n = 23). Valve-related mortality was 2.5% (n = 5). Survival did not differ from that of the general German population. Freedom from autograft or allograft reoperation was 92.2% at 10 years and 87.1% at 15 years. Five major bleeding (0.20%/patient-year) and 11 thromboembolic events (0.44%/patient-year) occurred in 5 and 10 patients, respectively. Neither a systematic increase in aortic regurgitation nor an increase in root dimensions with time could be observed. In the vast majority of patients, valvular hemodynamics at latest echocardiographic follow-up were excellent.

Conclusions

Long-term results of the original subcoronary Ross operation reveal normal survival, excellent hemodynamics, low risk of thromboembolism or bleeding, and small risk for reoperation. These results favor the pulmonary autograft concept in young and middleaged patients in experienced centers and may serve to better define its role in surgical treatment of aortic valve disease in these patients.

The Ross operation, initially performed in 1967 by Donald Ross, uses the autologous pulmonary valve as a subcoronary aortic valve replacement. Theoretically, this living material provides the best potential for normal aortic valve function and durability. Indeed the midterm results are favorable after the aortic root preserving subcoronary technique [1–3] as well as after the reinforced full root technique [4]. The survival of the Ross patients is similar to that of the general population, with low rates of valve-related complications [3] and near normal hemodynamics at rest and exercise [5], leading to an anticoagulation-free, high-quality lifestyle [6]. Especially for active, young and middle-aged patients, for women at childbearing age, patients at risk for injuries and bleeding, and patients who do not want to accept lifelong anticoagulation or the low durability of bioprostheses at a young age, the Ross operation has appealing aspects.

The pulmonary autograft technique, however, is sensitive to several factors, including the macroscopic and microscopic characteristics of the pulmonary valve, its adaptation to systemic pressure, the antihypertensive postoperative treatment, the fate of the allograft, and especially the surgical technique and experience. In this context, some publications have recently reported an increased rate of reoperations 7 to 8 years after the supported or unsupported full root replacement technique [4, 7–10], calling into question the Ross operation altogether [11]. Reliable longer-term follow-up studies, particularly after the first decade after the different Ross techniques, are eagerly awaited for further judgment of this surgical concept.

In this study we present results of the original subcoronary Ross procedure in 203 patients with more than 10 years of follow-up.

PATIENTS AND METHODS

Of a series of 576 subcoronary Ross patients operated on between 1994 and 2011, we evaluated 203 patients who underwent this operation between 1994 and 2001, therefore having more than 10 years of follow-up. Eight full root Ross operations were performed in that period and are not included in this study. Operative indications for aortic valve replacement and for ascending aorta replacement or repair at the time of the initial operation were in accordance with American Heart Association/American College of Cardiology guidelines [12, 13]. Every patient was examined by noninvasive (echocardiography) as well as invasive studies (left-heart catheterization and coronary angiography), and before the procedure a thorough discussion with the patient took place regarding the risks, benefits, and expectations after the Ross procedure including the risk for reoperation. The study was approved by the local ethics committee, and all authors had full access to and take full responsibility for the integrity of the data and the present article.

Demographics and valve-related preoperative characteristics are presented in Table 1. The Ross cohort comprised 7% of the total aortic valve replacements in our institution during this period. In our institution we offer the Ross procedure as an alternative to conventional aortic valve replacement to all patients who are skeptical about lifelong oral anticoagulation and the risks of thromboembolism and bleeding as well as noise disturbance with mechanical valves, to women of childbearing age, to patients at risk for injuries and bleeding during professional

TABLE 1. Demographics and Preoperative Data

Variable	N 203	%
Mean age (± SD; range; y)	47.2 ± 13.6 (15.1–70.5)	
<20	9	4.4
20–40	55	27.1
41–60	102	50.3
>60	37	18.2
Sex		
Male	155	76.4
Female	48	23.6
NYHA class		
I	51	25.1
II	108	53.2
III	41	20.2
IV	2	1.0
Unknown	1	0.5
Left ventricular ejection fraction		
>0.50	167	82.3
0.26–0.49	36	17.7
Diabetes mellitus	12	5.9
Systemic hypertension	76	37.4
Rheumatic disease	1	0.5
Impaired renal function	25	12.3
Rhythm		
Sinus	197	97.0
Atrial fibrillation	5	2.5
Pacemaker	1	0.5
Predominant aortic hemodynamics		
Stenosis	33	16.3
Regurgitation	62	30.5
Mixed lesions	108	53.2
Acute endocarditis	17	8.4
Aortic valve morphology		
Tricuspid	92	45.3
Bicuspid	96	47.3
Other	15	7.4
Previous aortic valve interventions	6	3.0
Valve replacement	5	2.5
Valve reconstruction	1	0.5

NYHA = New York Heart Association; SD = standard deviation.

or other activities, and to young patients who consider the premature failure of bioprostheses as a problem. The extended spectrum of indications in selected patients included the correction of concurrent valve lesions or other interventions (eg, coronary artery bypass grafting, replacement of the ascending aorta, Maze procedure), reoperations after aortic valve repair or replacement, and acute endocarditis (Tables 1 and 2). Exclusion criteria were mainly anatomic or structural defects of the pulmonary valve (fenestration, asymmetry, shrinkage), presence of significant comorbidities such as connective tissue disorders (eg, Marfan syndrome), severe coronary artery disease, calcification of the coronary ostia, reduced general condition, severely reduced left ventricular function, patients with chronic inflammatory disease (scleroderma, juvenile rheumatoid arthritis, lupus erythematosus), persistent untreatable hypertension, and older age. In approximately 5% of patients who were candidates for the Ross procedure (11 of 214), the intraoperative inspection of the pulmonary valve revealed findings unsuitable for the Ross operation (fenestrations, gross leaflet asymmetry, or malformations), and a conventional aortic valve replacement was performed. Operative data are presented in Table 2, and the surgical techniques have been described in detail previously [3, 14]. In 37.4% of patients additional procedures were performed (Table 2).

Follow-Up Evaluation

Follow-up data were documented in a prospective outpatient basis 1, 3, 6, and 12 months after operation and annually thereafter. For this study, a database freeze was performed June 2011. The standardized follow-up visits include clinical evaluation and serial echocardiography. Details of the echocardiographic evaluation have been reported previously [3, 14]. All perioperative and postoperative events were defined and reported according to the latest guidelines [15]. Mean follow-up was 12.3 ± 2.9 years (range, 0.05 to 17.0 years), and age at latest follow-up was 59.5 ± 14.0 years (range, 27.6 to 85.2 years). Two patients were lost to follow-up, resulting in a 97% completeness of clinical follow-up with a total cumulative follow-up of 2,491 patient-years.

Statistical Analysis

Continuous data were expressed as mean ± standard deviation. Categorical variables were described as absolute numbers and percentages. Kaplan-Meier estimates of freedom from morbid events were calculated. The survival of the Ross patients was compared with that of the ageand sex-matched German general population (www.destatis.de). The relative survival was calculated [16] and expressed as the ratio of expected versus observed numbers of death. For the longitudinal analysis of the echocardiographic measurements, continuous data were modeled using a random effects model, assuming correlation between repeated follow-up measurements, a random patient effect, and a piecewise linear relation with follow-up time, with knots at {1, 3, 5, . . . 17} years. Aortic regurgitation was modeled using a multinomial ordinal model, with a random patient effect and a piecewise linear relationship with follow-up time. The instantaneous risk for reoperation is presented as the smoothed instantaneous probability that a patient will experience a reoperation in the time interval (t, $t + dt$) provided that the patient has not been censored until the beginning of t [17, 18]. Statistical analyses

TABLE 2. Operative Data

Variable[a]		
Bypass time (mean ± SD; range; min)	212 ± 31	153–433
Cross-clamp time (mean ± SD; range; min)	163 ± 25	104–240
Additional procedures	76	37.4
Ascending aorta aortoplasty	32	15.8
Ascending aorta replacement	9	4.4
Coronary artery bypass grafting	6	3.0
Mitral valve reconstruction	7	3.5
LVOT myotomy or myectomy	8	3.9
Maze procedure (cut and sew Cox Maze III)	2	1.0
Other	12	5.9
RVOT conduit diameter (mean ± SD; range; mm)	25.6 ± 1.94	22–31
22–23	18	8.9
24–25	91	44.8
26–27	61	30.0
28–31	27	13.3
Unknown	6	3.0

[a] Values are numbers and percentages, except as indicated. LVOT = left ventricular outflow tract; RVOT = right ventricular outflow tract; SD = standard deviation.

were performed using R version 2.13.1 (Development Core Team; 2011; R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/).

RESULTS

In-Hospital Course

Two patients died (hospital death, 0.98%) 1 of coronary thromboembolism with myocardial infarction, and 1 of malignant arrhythmia. There were 9 reoperations owing to bleeding, 1 autograft reoperation owing to technical failure (included in the reoperation estimates), 1 transient ischemic attack, and 1 completed stroke. In 4 patients (2%), persistent, early postoperative, complete atrioventricular block mandated the need for permanent pacemaker implantation.

Late Survival

All-cause late mortality (>30 days) was 23 (11.4%; 0.9%/patient-year): 5 were cardiac valvular (1 endocarditis, 1 heart failure, 3 sudden death), 3 were cardiac nonvalvular (1 acute myocardial infarction, 2 heart failure), and 15 were noncardiac (8 malignancy, 1 pneumonia, 1 esophageal bleeding, 1 cerebral bleeding, 1 multiorgan failure, 2 renal failure, 1 liver cirrhosis). The overall as well as the relative survival did not differ from that of the general German population (Fig 1).

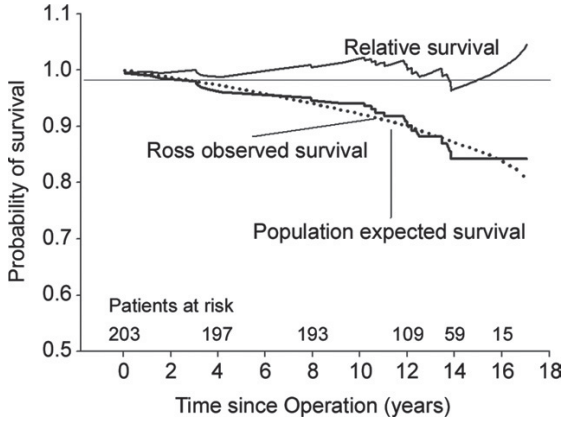

FIGURE 1. *Expected versus observed survival in Ross patients (solid line, actuarial estimates) and ageand sex-matched normal population (dotted line). Relative survival is the ratio of observed and expected survival: 1.0 represents the line of identity.*

Reoperation

Twenty-six reoperations on Ross-related valves were performed in 19 patients (9.35%; linear occurrence rate, 1.04%/patient-year); 14 patients underwent 14 reoperations on the autograft (linear occurrence rate, 0.56%/ patient-year), and 9 patients underwent 12 reoperations on the allograft (linear occurrence rate, 0.48%/patientyear). Four patients underwent a concomitant autograft and allograft reoperation (included in the above estimates).

Indications for reoperations on the autograft were regurgitation owing to leaflet prolapse or endocarditis. Structural valve deterioration was seen in 9 patients, with cusp prolapse in 7 cases (all patients had preoperative aortic annular diameter > 28 mm and neoaortic regurgitation > I° (first grade) early after the operation). Reoperation because of infective endocarditis was observed in 5 patients. Nonstructural valve deterioration was not detected. The autografts were replaced by mechanical valves in 8 patients and by a bioprosthesis in 6 patients. No autograft reconstruction was performed.

Indications for reoperations on the allograft were regurgitation in 9 patients (associated with acute endocarditis in 4 patients), stenosis in 2 patients, and a combined lesion in 1 patient. In 7 patients acute or healed infective endocarditis was the cause of valve failure, in 4 patients a structural valve deterioration, and in 1 patient nonstructural valve deterioration owing to annular ring dilatation.

Kaplan-Meier estimates of freedom from autograft, allograft, and autograft or allograft reoperation are shown in Figures 2 through 4. Freedom from reoperation at 15 years was 89.6% (95% confidence interval, 83.8 to 95.9) for the autograft, 92.8% (95% confidence interval, 87.5 to 98.3) for the allograft, and 87.1% (95% confidence interval, 81.0 to 93.6) for the combined autograft or allograft. All patients survived the reoperations. The time points of the reoperations seemed to have a random pattern of appearance, and neither a late aggregation of failures nor an increase of the instantaneous risk for reoperations of the Ross valves could be detected (Figs 2– 4).

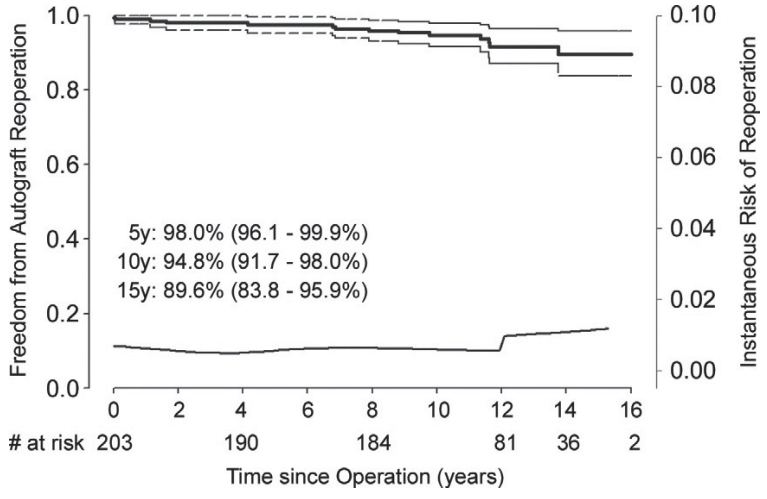

FIGURE 2. *Actuarial estimates of freedom from autograft reoperation (left y axis) and instantaneous risk of autograft reoperation (right y axis). Patients at risk and the estimated probabilities (with 95% confidence intervals) are shown.*

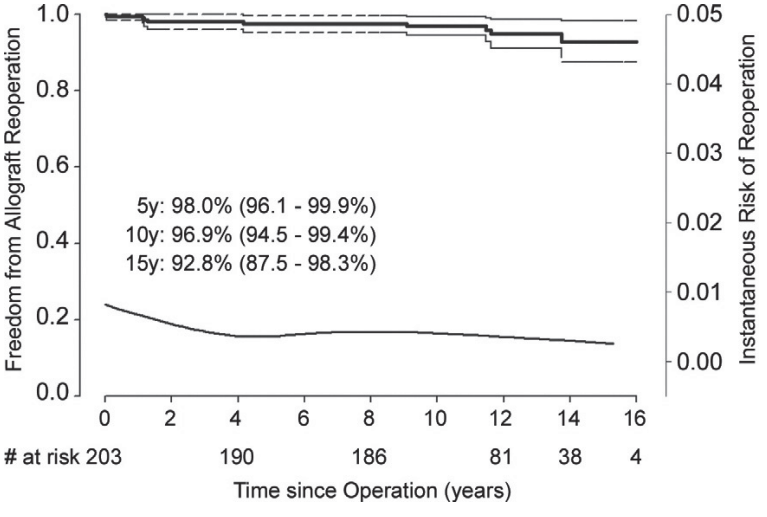

FIGURE 3. *Actuarial estimates of freedom from allograft reoperation (left y axis) and instantaneous risk of allograft reoperation (right y axis). Patients at risk and the estimated probabilities (with 95% confidence intervals) are shown.*

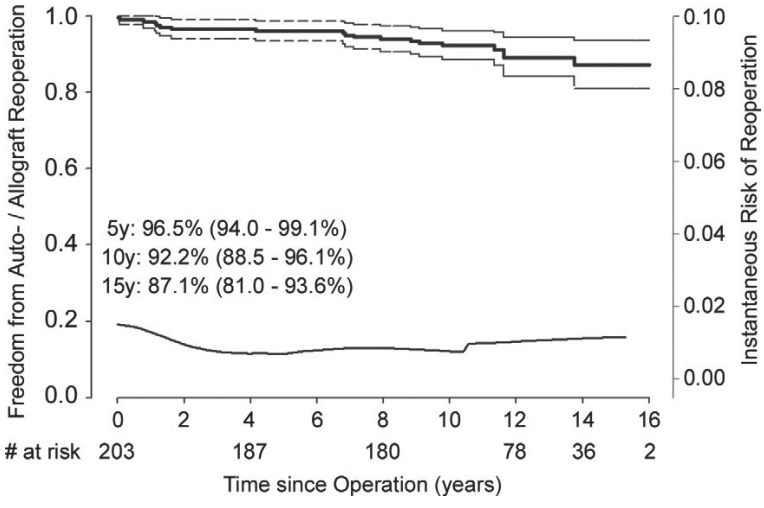

FIGURE 4. *Actuarial estimates of freedom from autograft and allograft reoperation (left y axis) and instantaneous risk of reoperation (right y axis). Patients at risk and the estimated probabilities (with 95% confidence intervals) are shown.*

Embolism, Bleeding, and Endocarditis

Eleven thromboembolic events after hospital discharge occurred in 10 patients (4.9%): transient ischemic attack in 3, a completed stroke in 6 (7 events in 6 patients), and a noncerebral embolic event in 1, resulting in a linearized occurrence rate of 0.44%/patientyear for thromboembolic events. Major internal or external bleeding events were detected in 5 patients (2.5%; occurrence rate, 0.20%/patient-year). A total of 15 patients with 16 events had the composite end point of embolism, thrombosis, and bleeding (7.4%; occurrence rate, 0.64%/patient-year). Conservative treatment of autograft endocarditis was successful in 2 patients, and allograft endocarditis also in 2 patients, respectively (2.0%, 0.16%/patient-year). In 5 patients a reoperation was indicated because of autograft endocarditis and in 7 patients because of allograft endocarditis (acute or cured, 5.9%; 0.48%/patient-year).

Echocardiographic Status at Last Follow-Up Visit

The longitudinal changes of aortic root dimensions with time are displayed in Figure 5. A small (<1 mm/decade; $p < 0.001$) increase in annulus and sinotubular junction diameters could be statistically observed; however, there was no clinical significance or implications. The longitudinal percentage of patients being in each of the aortic insufficiency grades as a function of time is displayed in Figure 6. For the group overall, there appeared to be no significant evidence of a systematic increase in aortic insufficiency with time. Information about the valvular performance at the time of the last follow-up visit is displayed in Table 3. The proportion of patients with autograft regurgitation of grade 2 or more was 6.9%, with 1 patient having grade III and none having grade IV. Autograft stenosis with clinical impact was not detected. Allograft regurgitation of grade II or more was present in 9.5%, a transvalvular mean

gradient of the conduit more than 15 mm Hg was observed in 12.8% of patients. Four patients (2%) had a transvalvular allograft pressure gradient of more than 25 mm Hg.

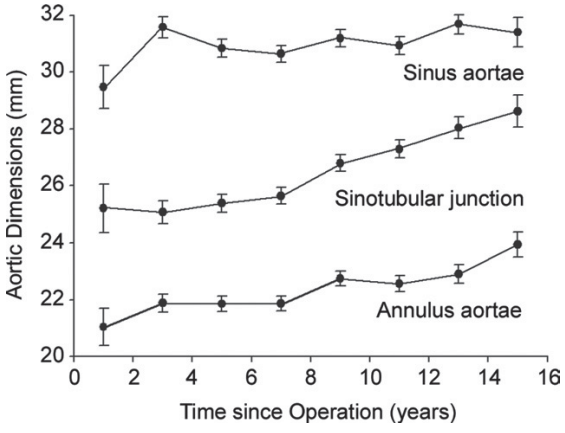

FIGURE 5. *Mixed effects model on the longitudinal changes of aortic root dimensions with time. A small (<1 mm/ decade) increase in annulus and sinotubular junction diameters could be statistically observed; however, there was no clinical significance or implications. Error bars indicate one standard error of the mean.*

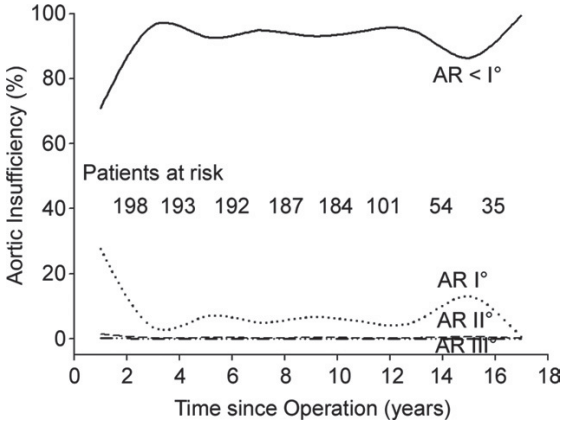

FIGURE 6. *Multinomial ordinal mixed effect model of the aortic insufficiency as a function of time. The percentage of patients being in each of the four aortic insufficiency grades with time is shown. No significant evidence of a systematic increase in aortic insufficiency with time could be observed. (AR = aortic regurgitation.)*

TABLE 3. Follow-Up Data[a]

Variable[b]		
Follow-up (y; mean ± SD; range)	12.3 ± 2.9	0.05–17.0
Age at latest follow-up (y; mean ± SD; range)	59.5 ± 14.0	27.6–85.2
Allograft performance		
Pressure gradient (mean ± SD; range, in mm Hg)	9.9 ± 5.7	2–31
<5	22	13.5
5–10	79	48.5
11–15	35	21.5
16–20	12	7.4
21–25	4	2.4
>25	4	2.4
Unknown	7	4.3
Regurgitation		
None	67	41.1
Trace	49	30.0
Grade I	27	16.6
Grade II	13	8.0
Grade III	2	1.2
Grade IV	0	0
Unknown	5	3.1
Autograft performance		
Pressure gradient (mean ± SD; range, in mm Hg)	3.7 ± 1.4	2–8
<5	114	72.2
5–10	35	22.1
>10	0	0
Unknown	9	5.7
Regurgitation		
None	60	38.0
Trace	59	37.3
Grade I	26	16.5
Grade II	10	6.4
Grade III	1	0.6
Grade IV	0	0
Unknown	2	1.2

[a] Deceased, reoperated on, and lost-to-follow-up patients were exclu- ded. [b] Except as indicated, values are reported as numbers and percentages.
SD = standard deviation.

COMMENT

This study reports on more than 200 patients followed for more than 10 years after the subcoronary Ross procedure. Operative mortality was low (approximately 1%) and compares favorably with other valve replacement alternatives. In the 373 consecutive patients operated on after June 2001 there was no hospital death, indicating that this procedure can be performed with low operative mortality. Long-term survival is similar to that of the German general population, resulting in a near 100% relative survival. This is remarkable because these patients had for several years had a significant valvular disease before the operation. Thus, one should expect a higher long-term mortality than normal. Most late deaths were noncardiac and nonvalverelated. With longer follow-up and thus aging of the patients, the age-related and nonvalve-related mortality indicates that the vast majority of these Ross patients will reach their life expectancy. In an elegant study by Van Geldorp and colleagues [19], the life expectancy in young patients after biologic or mechanical aortic valve replacement was substantially lower than that of the ageand sex-matched general population (a patient in the late 40s has a life expectancy of about 17 years, which is far below the normal life expectancy of roughly 30 years). However, the follow-up time in the present study may be too short to uncover differences in postoperative survival, or the excellent hemodynamics after the Ross procedure may have some beneficial effects on ventricular recovery and maybe also on survival as indicated by the excellent regression of left ventricular hypertrophy [20]. When comparing these ideal survival rates with other techniques, it must be considered that the inclusion criteria for the Ross operation might have a positive bias. Nevertheless 36% of patients had preoperatively a reduced left ventricular ejection fraction between 0.26 and 0.49, and 8% had acute endocarditis, partially ameliorating this selection bias.

Although reoperations remain a potential shortcoming of the Ross procedure, the late increase in autograft reoperations [8, 21] observed in other studies seems to be related to the operative technique used, and it is not observed in the original subcoronary technique [14] (Figs 2–4) or the reinforced full root technique [4]. The combined autograft or allograft freedom from reoperation was 87.1% at 15 years. This incidence is significantly lower when compared with patients of similar age with bioprostheses as reported by Tanaka and associates [22], one of the few recent reports on the fate of bioprostheses in the young and middle-aged patients. In that series, freedom from reoperation at 15 years was 39%, and reoperation was common even for patients receiving newer-generation bioprosthetic valves, showing that young age is probably the most significant determinate for the unfavorable durability of bioprostheses.

The reoperation rate of the subcoronary Ross proce dure may be even reduced with the application of novel surgical techniques to prevent the major cause of reoperation in the subcoronary technique, which is prolapse of one cusp. These techniques were less rigorously used during the evolving phase at the beginning of our Ross experience in this series. Of note is that all patients with cusp prolapse and reoperation had an aortic annular diameter greater than 28 mm before the procedure, and these patients had at least a mild neoaortic regurgitation early after the procedure. Both findings are strong markers of valve failure and can be neutralized by refined surgical techniques, especially annulus and sinotubular junction

reduction and stabilization similar to the full root technique, providing excellent long-term free reoperation rates as reported in a large multicenter series of 1,335 patients in the German-Dutch Ross Registry [4] and recently by Brown and coworkers [23].

With a small number of reoperation events in the present study, these findings are more of descriptive nature mainly because a sophisticated statistical analysis on this small number of events would have little power. A still unresolved problem is the high rate of infective endocarditis as the cause of valve failure with need for reoperation. Nearly half of all autograft reoperations and allograft reoperations were related to acute or healed infective endocarditis. As a consequence, strict adherence to life-long endocarditis prophylaxis is mandatory. Adequate information of patients and their physicians might have the potential to reduce the rate of reoperations further. Hypertension as a risk factor for autograft failure [24] was not considered during the early days of our series. The positive effect of antihypertensive treatment could potentially reduce the rate of reoperation in the future and also improve left ventricular mass regression [20]. The fact that allograft malfunction is treated more and more nowadays by noninvasive techniques adds to reducing the need for open, conventional reoperations. Nevertheless, the risk for reoperation still exists and is related to two valves, and as such, careful follow-up is necessary to assess whether these favorable results are durable even beyond the observed period of this study.

Valve-related morbidity such as bleeding and thromboembolism occurred in 15 patients. Of those 15 patients, 9 (60%) had atrial fibrillation (diagnosed some time after the procedure) or were on oral anticoagulation for other conditions. Thus, it remains questionable whether these adverse events can be related to the Ross procedure itself or to the concomitant diseases, such as atrial fibrillation, occurring with increasing age.

In conclusion, our data of patients with more than 10 years of follow-up show that the subcoronary technique has excellent results up to 16 years after the operation. These results may help to better determine the role of the Ross concept as a surgical option for aortic valve replacement in the young and middle-aged patient. Consequent adherence to refined surgical techniques like annulus and sinotubular junction reduction and stabilization as well as prevention and adequate treatment of postoperative hypertension and endocarditis may further improve results. Nevertheless longer follow-up data are necessary to judge this method against the conventional aortic valve replacement. From these results with the original subcoronary Ross procedure, the theory of using autologous pulmonary valve tissue for aortic valve replacement in young and middle-aged patients seems to be valid at least for this time span, favoring its use in experienced centers.

This work has been registered with the US National Institutes of Health: Clinical Trial Registration, URL: http://www.clinicaltrials. gov. Identifier: NCT00708409.

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INVITED COMMENTARY

Dr Charitos and colleagues [1] are to be congratulated on their excellent results with the subcoronary Ross operation in young adults. In the second postoperative decade, patient survival remains comparable to the age-matched general population—a feature that seems unique to the Ross operation— [2, 3], and autograft and right ventricular outflow tract conduit reintervention rates are low and echocardiographic valve function adequate. Undoubtedly, these patient survival and valve durability results are superior to any other biological valve substitute.

Nevertheless, the role of the Ross operation for young adult patients who require aortic valve replacement (AVR) remains a matter of debate, and only a fraction of all AVRs in this age group involves a Ross operation. Compared with other surgical options, the Ross operation reportedly carries an increased early mortality risk and treats single-valve disease with double prosthetic valve disease. In addition, widely varying durability results are obtained with Ross root replacement, illustrating the technical complexity of the procedure and the requirement of a particular surgical expertise with the procedure [3].

The other surgical options for young adult patients who require AVR are far from perfect. Although early mortality risk is low, we are basically offering the patient the choice between different hazards: considerable anticoagulation-related hazards with mechanical prostheses versus high reoperation hazards with bioprosthetic valves. In a recent analysis regarding the Ross operation, Dr Tom Treasure posed the intriguing question of whether there is a risk in early mortality risk avoidance for younger patients who require AVR. He stated that "in case of the Ross operation, intolerance of even a small increase in immediate risk could impede access to a better long-term solution"[4]. This statement is indeed true for the subcoronary Ross experience reported by Charitos and colleagues, as well for the Ross root replacement experience from Sir Magdi Yacoub [2]. In experienced dedicated hands, the Ross operation provides excellent results, both with regard to early mortality and late outcome. The challenge is to translate this expertise to other surgeons who are interested in and dedicated to acquiring the skills to perform a durable Ross operation. It requires well-organized mentoring and

supervision of dedicated surgeons in dedicated centers to learn a Ross operation technique that has been proved durable. This is a basic requirement for the Ross operation to survive on the surgical menu for young adults who require AVR.

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Read at the 92nd Annual Meeting of The American Association for Thoracic Surgery, San Francisco, California,

CHAPTER 5

REOPERATIONS ON THE PULMONARY AUTOGRAFT AND PULMONARY HOMOGRAFT AFTER THE ROSS PROCEDURE: AN UPDATE ON THE GERMAN DUTCH ROSS REGISTRY

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Reoperations on the pulmonary autograft and pulmonary homograft after the Ross procedure: An update on the German Dutch Ross Registry.
J Thorac Cardiovasc Surg. 2012;144:813-21

http://dx.doi.org/10.1016/j.jtcvs.2012.07.005

Objectives

Reinterventions after the Ross procedure are a concern for patients and treating physicians. The scope of the present report was to provide an update on the reinterventions observed in the large patient population of the German-Dutch Ross Registry.

Patients and Methods

From 1988 to 2011, 2023 patients (age, 39.05 ± 16.5 years; male patients, 1502; adults, 1642) underwent a Ross procedure in 13 centers. The mean follow-up was 7.1 ± 4.6 years (range, 0-22 years; 13,168 patient-years).

Results

In the adult population, 120 autograft reinterventions in 113 patients (1.03%/patient-year) and 76 homograft reinterventions in 67 patients (0.65%/patient-year) and, in the pediatric population, 14 autograft reinterventions in 13 patients (0.91%/patient-year) and 42 homograft reinterventions in 31 patients (2.72%/patient-year) were observed. Of the autograft and homograft reinterventions, 17.9% and 21.2% were performed because of endocarditis, respectively. The subcoronary technique in the adult population resulted in significantly superior autograft durability (freedom from autograft reintervention: 97% at 10 years and 91% at 12 years; $P<.001$). The root replacement technique without root reinforcement (hazard ratio, 2.4; 95% confidence interval, 1.4-4.1) and the presence of pure aortic insufficiency preoperatively (hazard ratio, 2.3; 95% confidence interval, 1.5-3.5) were statistically significant predictors for a shorter time to reoperation. The center volume had a significant influence on the long-term results. The freedom from homograft reoperation for the adults and pediatric population was 97% and 87% at 5 years and 93% and 79% at 12 years, respectively ($P<.001$), with younger recipient and donor age being significant predictors of a shorter time to homograft reoperation.

Conclusions

The autograft principle remains a valid option for young patients requiring aortic valve replacement. The risk of reoperation depends largely on the surgical technique used and the preoperative hemodynamics. Center experience and expertise also influence the long-term results. Adequate endocarditis prophylaxis might further reduce the need for reoperation.

Although the Ross procedure has been shown to offer numerous advantages, including freedom from lifelong anticoagulation, survival comparable to that of the general population, superior quality of life, unrestricted daily activities, and normal aortic valve hemodynamics,[1-10] the incidence of reoperation remains a concern. Together with the technical complexity of the procedure, the need for reoperations, on the autograft, the homograft, or both, has been the cornerstone of debate of whether the Ross procedure should be performed, especially in adult patients.

The aim of the present study was to present in detail the incidence of, reasons for, outcomes of, and factors that influence, reoperation after the Ross procedure observed in the multicenter German-Dutch Ross Registry. Although a detailed analysis of the adult and pediatric populations is presented, the main focus of the present study was the adult patient. The information presented could facilitate decision making when informing young patients with aortic valve disease before surgical intervention and could serve as a basis for comparing the outcomes after the Ross procedure with that of alternative therapeutic options for the treatment of aortic valve disease.

Abbreviations and Acronyms

SC subcoronary
RR root replacement without additional root reinforcement
RR+R root replacement with additional root reinforcement

PATIENTS AND METHODS

The German-Dutch Ross Registry collects data from 13 departments of cardiac surgery, retrospectively for 1988 to 2001 and prospectively from 2002 onward (clinical trial no. NCT00708409). For the purposes of the present study, the study database was frozen in August 2011 and included 2023 patients.

The operating surgeon at each center determined the surgical technique (subcoronary [SC] or root replacement with [RR+R] or without [RR] additional root reinforcement procedures). Reinforcement interventions in the RR+R group were performed either in the annulus only (n = 394), the sinotubular junction only (n = 35), or at both levels (n = 214). A total of 30 patients who underwent the root inclusion (miniroot) technique were included in the SC group to create a group with all native root-preserving procedures. The details of the operative techniques and the reasons for including the root inclusion technique patients in the SC group have been reported previously.[1,2,6] All the patients provided informed consent; the local ethics committee approved the study; all authors had full access to, and take full responsibility for, the integrity of the data.

All indications for the primary operation and for all reoperations were in accordance with the 2008 guidelines.[11] Clinical follow-up examinations were performed at discharge and yearly thereafter. The reporting and analysis of the outcomes and major adverse cardiac and cerebrovascular events were according to published guidelines.[12]

The present report focused on the need for cardiac, valve-related reinterventions on the autograft or homograft after the Ross procedure. Cardiac nonvalvular, as well as cardiac, valvular, non–Ross-related interventions, are not presented. Cases of pacemaker implantation within 14 days after the Ross procedure were not included in the present study and have been previously reported.[1,6] A Ross reintervention was defined as any surgical or interventional procedure performed after the initial Ross procedure on the autograft or homograft. A Ross reoperation was defined as a surgical session that included at least 1 Ross reintervention on the autograft or homograft, or both (1, 1, and 2 reinterventions, respectively) and could include concomitant interventions to other cardiac structures.

The adult and pediatric population of the Registry were analyzed and reported separately. The cutoff point of 16 years was chosen to differentiate the adult and pediatric populations, because at this age, the patients were regarded from a surgical viewpoint as adults and the technical aspects of the procedure were those of the adult population.

Frequencies are given as absolute numbers and percentages. Continuous data are expressed as the mean ± standard deviation. The actuarial estimates of freedom from reoperation events were made using the KaplanMeier method. The instantaneous risk of reoperation is presented as the smoothed instantaneous rate that a patient will require reoperation within the interval $(t,\ t + dt)$ provided the patient was not censored until the beginning of t.[13-15] To identify the predictive variables for a shorter time to reoperation on the autograft or homograft, we performed univariate analyses using the Cox proportional hazard regression model. Multivariate Cox proportional hazard models were used to confirm whether significant ($P < .10$) univariate predictors persisted in the presence of other preoperative variables. The following factors were analyzed as potential risk factors for autograft or homograft reoperation: age, year of surgery, gender, presence of co-morbidities (eg, diabetes, hypertension, renal failure, coronary artery disease, pulmonary disease, peripheral vascular disease), previous cardiac surgery, preoperative hemodynamics, aortic valve morphology, center experience (number of operated patients per center), year of surgery, and homograft donor parameters (eg, diameter, donor recipient age and blood group mismatch).

Given the data obtained to date from the German-Dutch Ross Registry and our understanding of the risk of autograft and homograft reintervention that patients undergoing the Ross procedure face, we attempted to extrapolate the estimated risk of reoperation for a Ross patient up to 70 years of age according to the patient's age at the initial Ross procedure, taking into consideration the probability of survival up to 70 years old. The survival of the Ross patients was assumed to be similar to that of the German general population (data available from: https://www.destatis.de), because several studies have failed to show excess mortality for the Ross population compared with that of the general population.[3,6,7,15] For the calculation of the estimated risk of reoperation with the SC and RR techniques, the hazards for autograft and homograft reoperation were assumed to be independent, and the Ross-related reoperation hazard rate was evaluated as the sum of the hazard rate for the autograft and homograft reoperation functions. The homograft hazard rate in the adults was assumed to be linear (see Figure 2). For the SC technique, a constant autograft reoperation hazard rate was assumed for the period after 17 years of follow-up $h_{SC}(t>17)=0.014$. For the RR group, significant

evidence was seen for an increase in the autograft hazard rate with time (see Figure 3),[1,6] and an exponential hazard rate was assumed $h_{RR}(t)=0.01+0.01*exp(t/5.9)$ (see Figure 3).

RESULTS

The patient characteristics and operative data are presented in Table 1. Completeness of follow-up for the outcomes presented in the present study was 96%.

A detailed listing of the reoperations and reinterventions observed in the total population, stratified by technique and population subgroup, is presented in Table 2. The reoperative mortality rate is also listed in Table 2.

The choice of autograft or homograft replacement material used in the respective reinterventions is listed in Table 3.

The actuarial estimates for freedom for autograft, homograft, and combined reoperation for the subpopulations of the present study are listed in Table 4. The survival estimates for the adult and pediatric populations are also listed in Table 4. No significant difference was seen between the survival of the adult Ross population and that of the ageand gender-matched general population ($P = .3$). However, the survival of the pediatric population was significantly inferior to that of the age- and gender-matched general population ($P < .0001$).

The results of the multivariate Cox proportional hazards model for a shorter time to autograft and homograft reoperation in the adult population are listed in Table 5.

Freedom from autograft, homograft, or combined reoperation in the population groups and the technique subgroups are displayed in Figures 1 to 5.

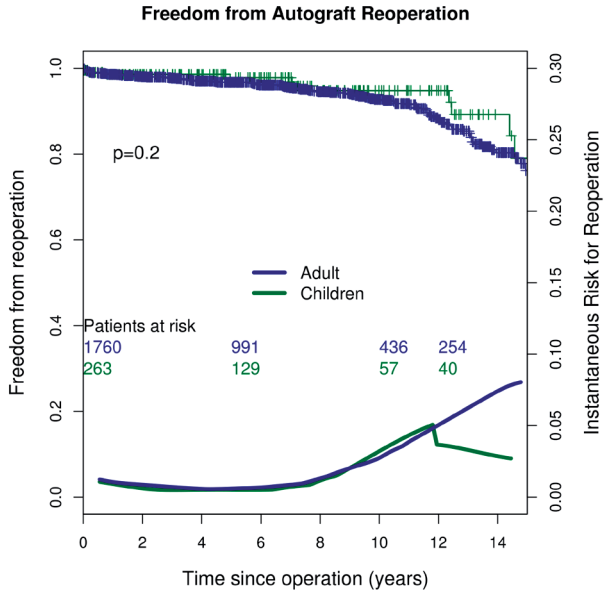

FIGURE 1. *Freedom from autograft reintervention in the pediatric and adult (all techniques) population.*

TABLE 1. Patient characteristics and operative

				Adults		
	Total	**Adults**	**Pediatric**	**SC**	**RR**	**RR+R**
Patients (n)	2023	1760	263	771	346	643
Follow-up (y)						
Mean	7.1	7.1	6.9	7	9.1	6.1
Range	0-22.4	0-22.4	0-21.8	0-18.5	0-22.4	0-15
Age (y)	39 ± 16.5	43.7 ± 12.0	8 ± 5.2	45.2 ± 11.3	37.6 ± 12.6	45.1 ± 11.3
Male gender	1502 (74%)	1315 (75%)	187 (71%)	585 (76%)	253 (73%)	477 (74%)
Age group (y)						
<16	263 (13%)	(0%)	263 (100%)			
16-40	661 (33%)	661 (38%)		255 (33%)	198 (57%)	208 (33%)
41-60	1019 (50%)	1019 (58%)		470 (61%)	141 (41%)	408 (63%)
>60	80 (4%)	80 (4%)		46 (6%)	7 (2%)	27 (4%)
Predominant aortic hemodynamics						
Regurgitation	469 (23%)	423 (24%)	46 (17%)	197 (26%)	87 (25%)	139 (22%)
Stenosis	457 (23%)	408 (23%)	49 (19%)	143 (19%)	79 (23%)	186 (29%)
Combined	1048 (52%)	894 (51%)	154 (59%)	419 (54%)	172 (50%)	303 (47%)
Aortic valve type						
Bicuspid	1254 (62%)	1105 (63%)	149 (56%)	532 (69%)	189 (55%)	384 (60%)
Tricuspid	480 (24%)	410 (23%)	70 (27%)	170 (22%)	110 (32%)	130 (20%)
Other	175 (9%)	157 (9%)	18 (7%)	34 (4%)	23 (7%)	100 (16%)
Unknown	111 (5%)	85 (5%)	26 (10%)	35 (5%)	22 (6%)	28 (4%)
Atrial fibrillation	16 (1%)	16 (1%)	0 (0%)	11 (1%)	2 (1%)	3 (0%)
Concomitant procedures (n)						
Total	884 (44%)	813 (46%)	71 (27%)	333 (43%)	99 (29%)	381 (59%)
CABG	102 (5%)	100 (6%)	2 (1%)	30 (4%)	19 (5%)	51 (8%)
Previous cardiac interventions (n)	299 (15%)	158 (9%)	141 (54%)	40 (5%)	40 (12%)	57 (9%)
Circulatory arrest						
Patients (n)	106 (5%)	97 (6%)	9 (3%)	62 (8%)	62 (18%)	30 (5%)
Mean ± SD	18.2 ± 10.8	17.4 ± 9	39.7 ± 29.3	17.9 ± 4	17.9 ± 4	13.2 ± 4.6
Range	2-72	2-64	15-72	11-33	11-33	3-23
CPB time (min)						
Mean ± SD	189.1 ± 47.6	191.2 ± 45.6	175.7 ± 57.1	211 ± 35.2	211 ± 35.2	170.7 ± 41.9
Range	61-685	71-685	61-495	71-433	71-433	95-482
Cross-clamp time (min)						
Mean ± SD	146.2 ± 36.1	150.4 ± 34.9	119.7 ± 31.8	172.2 ± 34.1	172.2 ± 34.1	135.1 ± 24.9
Range	17-293	38-293	17-265	43-293	43-293	79-258
In-hospital (<30 d) mortality	29 (1.4%)	20 (1.1%)	9 (3.4%)	8 (1%)	2 (0.6%)	10 (1.6%)

CABG, Coronary artery bypass grafting; *CPB,* cardiopulmonary bypass; *RR,* root replacement without additional root reinforcement; *RR+R,* root replacement with additional root reinforcement; *SC,* subcoronary; *SD*, standard deviation. n = Number of patients.

DISCUSSION

The main scope of the present study was to provide a detailed presentation of the reasons, incidence, results, and outcomes of reoperations on the autograft or homograft after the Ross procedure in the adult and pediatric populations of the German-Dutch Ross Registry. The incidence of other major adverse cardiac and cerebrovascular events has been previously reported.[6] The information provided in the present study might facilitate patient–physician discussions before aortic valve interventions and outline patient expectations after the Ross procedure regarding the probability, incidence, and outcomes of reoperations. The present results could also serve as a basis for a comparison of the outcomes after the Ross procedure with those after other novel or conventional therapeutic options for the treatment of aortic valve disease.

Although the first Ross procedure was performed as an SC transplant,[16] the technical complexity of this procedure eventually led to the development of the RR technique, which provided, at least for the early to midterm, satisfactory results.[17] The initial enthusiasm for the RR Ross procedure soon waned, after several reports of the increased incidence of reoperations because of autograft dilatation starting 7 to 10 years after the initial procedure.[18-25] Research on the modes of failure of the pulmonary autograft has shown a technique-specific pattern of autograft failure.[1] In the RR technique, the main mode of autograft failure seems to be nonstructural valve deterioration (Table 2), mainly because of dilatation of the unsupported pulmonary root under systemic pressure, leading to progressive loss of valve coaptation and the development of autograft insufficiency. However, when the autograft is implanted as an SC transplant, the main cause of failure is leaflet-related degeneration (structural valve deterioration; Table 2).

TABLE 2. Reinterventions observed in German-Dutch Ross

	Technique			
Registry	**RR**	**RR+R**	**SC**	**Total**
Adults				
Patients with Ross-related reoperation (% of total)	64 (18.5%)	39 (6.1%)	53 (6.9%)	156 (8.9%)
Follow-up (y)				
Mean ± SD	9.1 ± 5.4	6.1 ± 3.9	7 ± 4.3	7.1 ± 4.5
Range	0-22.4	0-15	0-18.5	0-22.4
Cumulative follow-up (pt-y)	2925.3	3481.7	5218.7	11,625.7
Ross-related reoperations	69	43	62	174
Reoperation mortality (n)	0	1	5	6
Ross-related reinterventions	79	45	72	196
Reoperation type				
Autograft	44	27	27	98
Homograft	15	14	25	54

TABLE 2. Reinterventions observed in German-Dutch Ross (*continued*)

	Technique			
Registry	**RR**	**RR+R**	**SC**	**Total**
Combined	10	2	10	22
Autograft reinterventions	54	29	37	120
Endocarditis	1	11	11	23
SVD	4	7	20	31
NSVD	49	10	6	65
Technical	1	1	0	2
Homograft reinterventions				76
SVD				
Stenosis				44
Regurgitation				10
NSVD				6
Endocarditis				16
Pediatric				
Patients with Ross-related reoperation (% of total)	28 (16.6%)	7 (18.9%)	6 (10.5%)	41 (15.6%)
Follow-up (y)				
Mean ± SD	6.4 ± 5.7	8.5 ± 2.8	7.2 ± 4.3	6.9 ± 5.2
Range	0-21.8	0.2-13.5	0-16.4	0-21.8
Cumulative follow-up (pt-y)	933.1	306.4	303.3	1542.7
Ross-related reoperations	37	8	9	54
Reoperation mortality (n)	0	0	0	0
Ross-related reinterventions	38	9	9	56
Reoperation type				
Autograft	9	2	1	12
Homograft	27	5	8	40
Combined	1	1	0	2
Autograft reintervention	10	3	1	14
NSVD	10	3	0	13
Endocarditis	0	0	1	1
Homograft reinterventions				42
SVD				
Stenosis				25
Regurgitation				7
NSVD				1
Endocarditis				9

NSVD, Nonstructural valve deterioration; *pt-y,* patient-year; *RR,* root replacement without additional root reinforcement; *RR+R,* root replacement with additional root reinforcement; *SC,* subcoronary; *SVD,* structural valve deterioration; *SD*, standard deviation.

Although some prominent series have been published with excellent results after the RR Ross procedure,[23,25,26] the high failure rate after the first decade has initiated either a switch back to the original SC technique or a search for technical modifications to prevent root dilatation.[1,6-8,17,27,28] During the past decade, several groups have reported satisfactory results with the modified RR Ross procedure, using autograft root reinforcement with various techniques and materials in an attempt to stabilize the tissue and the areas of the aortic root that have been shown to dilate and result in progressive autograft insufficiency late after the Ross procedure.[1,17,27,28] This change has also been observed in the German-Dutch Ross Registry, with most active centers having switched now to either the SC technique or to RR with aggressive reinforcement of the autograft annulus or sinotubular junction, or both.[1] A small increase in the risk of reoperation in the RR+R group after the first decade has been observed (Figure 3). However, to date, no statistically significant difference in the freedom from autograft reoperation can be observed between the RR+R and SC groups. Because RR+R is a relatively new technique, only a few (<6%) of patients have completed a follow-up period of longer than 12 years. Therefore, reliable conclusions about the second decade could not be made for the RR+R group.

TABLE 3. Choice of replacement material at reintervention

	Biologic	Homograft	Mechanical	Repair	Valve sparing	Catheter	Unknown/ not coded
Adults							
Autograft (n)	26	8	45	19	7	1	14
Age at reoperation (y)							
Mean ± SD	47.3 ± 12.9	38.5 ± 12.5	32.0 ± 12.5	44.0 ± 10.8	39.7 ± 9.79		
Range	21.9-64.9	18.9-52.0	16.2-66.0	20.2-58.3	23.4-50.9		
RR	5	4	35	3	1	1	5
RR+R	9	3	1	9	6		1
SC	12	1	9	7			8
Homograft	6	39	1	2		16	12
Pediatric							
Autograft	0	4	3	2	2	0	3
RR		3	3		1		3
RR+R		1		1	1		
SC				1			
Homograft	1	19	2	3		11	6

The decision for the type of prosthesis at reoperation was the result of a thorough informed consent process after taking into consideration the recommendations and patientspecific needs and wishes. *RR,* Root replacement without additional root reinforcement; *RR+R,* root replacement with additional root reinforcement; *SC,* subcoronary; *SD,* standard deviation.

TABLE 4. Actuarial estimates for freedom from autograft, homograft, or any Ross reintervention (with and without endocarditis) and survival estimates in adult and pediatric population

Variable	5 y	12 y
Freedom from reoperation		
Endocarditis included		
Autograft		
Adult		
SC	97% (96-98)	91% (88-95)
RR	97% (95-99)	82% (76-88)
RR+R	96% (94-98)	91% (86-96)
Pediatric	98% (96-100)	95% (91-99)
Homograft		
Adult	97% (97-98)	93% (91-95)
Pediatric	87% (82-92)	79% (72-87)
Combined		
Adult		
SC	95% (94-97)	88% (84-92)
RR	95% (92-97)	77% (71-83)
RR+R	94% (92-96)	87% (81-93)
Pediatric	86% (81-91)	76% (69-84)
Endocarditis excluded		
Autograft		
Adult		
SC	98% (97-99)	94% (91-97)
RR	97% (95-99)	82% (76-88)
RR+R	98% (96-99)	93% (88-98)
Pediatric	98% (96-100)	95% (91-99)
Homograft		
Adult	98% (97-99)	95% (93-96)
Pediatric	90% (85-94)	83% (90-76)
Combined		
Adult		
SC	97% (95-98)	91% (87-95)
RR	95% (92-97)	78% (72-84)
RR+R	96% (94-98)	90% (84-95)
Pediatric	89% (84-94)	80% (74-88)
Survival		
Adult	98% (97-99)	93% (91-95)
Pediatric	97% (94-99)	95% (91-99)

Data in parentheses are 95% confidence intervals. RR, Root replacement without ad- ditional root reinforcement; RR+R, root replacement with additional root reinforce- ment; SC, subcoronary.

Endocarditis remains a significant cause of reoperation after the Ross procedure. Although it was initially believed that the Ross procedure, by using only biologic (autologous and allogenic) material, might be resistant to postoperative endocarditis, data from the German-Dutch Ross registry have shown that almost 20% of all interventions on the autograft or homograft were performed because of endocarditis (Table 2). This should be of interest to the treating physician and for the follow-up of Ross patients, because aggressive endocarditis prophylaxis could lead to a reduction in the incidence of endocarditis and, thus, the need for reoperations. The understanding that endocarditis can occur in patients with autologous and allograft material, together with a high clinical suspicion, is required to diagnose nonfulminant autograft or homograft endocarditis and prevent valve deterioration. This is especially important for Ross patients, because 2 valves are at risk and because the latest guidelines are more restrictive regarding the use of antibiotic prophylaxis.[29]

Several groups have demonstrated that patients with pure aortic insufficiency with or without aortic dilatation seem to have a much greater incidence of autograft deterioration.[30-36] Although the data from the German-Dutch Ross Registry have shown that although pure aortic insufficiency is an independent predictor for a shorter time to reoperation, this effect (Table 5) appears to be milder than that reported in other series.[33,35,36] Also, its effect seems to be more pronounced with the RR technique without active reinforcement. Although many patients with pure aortic insufficiency currently undergo aortic valve reconstruction, we believe that aortic insufficiency should not be regarded as a contraindication to the Ross procedure. Similarly, the presence of a bicuspid aortic valve did not have any influence on the incidence of autograft reoperation.

TABLE 5. Multivariate Cox proportional hazard model for shorter time to autograft or homograft reoperation in adult population

Variable	HR	95% CI	P value
Autograft			
Technique			
SC	Baseline		
RR+R	1.4	0.8-2.3	.25
RR	2.4	1.4-4.1	.001
Center volume	0.998/patient	0.997-0.999	.001
Preoperative hemodynamics			
Pure aortic regurgitation	2.3	1.5-3.5	<.001
Homograft			
Patient age group (y)			
<16	5.1	2.1-12.4	<.001
16-40	2.2	0.9-5.0	.08
41-60	Baseline		
>60		0.9-5.0	.08
Donor age (y)	0.975	0.96-0.99	<.001

CI, Confidence interval; *HR,* hazard ratio; *RR,* root replacement without additional root reinforcement; *RR+R,* root replacement with additional root reinforcement; *SC,* subcoronary.

In the pediatric population, the effect of the surgical technique on autograft durability was less pronounced. Autograft reoperations in the first decade were rare (Figure 1)[37] but could become necessary after the first decade. Most reoperations and reinterventions in the pediatric population were for homograft deterioration (Figure 2 and Table 2).[38] Also, younger homograft donor and recipient age appeared to lead to significantly inferior homograft durability (Table 5). Catheter reinterventions on the homograft might reduce the need for conventional reoperation (Table 3). However, the long-term performance of this therapeutic option remains unknown.

As with any operation, the major determinants of the operative outcome include not only the type and complexity of the operation itself, but also the status of the patient at surgery. During the 224 reoperations observed in the German-Dutch Ross Registry, 6 patients died of postoperative complications (2.6%). This low reoperative mortality rate has also been observed by other groups.[39-43] However, it is important to note that all these patients presented with a critical status (5 patients because of endocarditis and 1 patient for technical reasons) requiring either urgent or emergency surgery. No reoperative mortality was observed in the patients presenting or scheduled for an elective reoperation.

In the young patient requiring aortic valve surgery, the lifetime risk of valve-related complications with mechanical valves is neither 0% nor rare.[44-46] If the Ross procedure manages to bridge the young patient with aortic valve disease from an age when a conventional biologic solution is questionable (age, 20-60 years) to an age at which a biologic or even transcatheter (age, >65-70 years) solution is feasible, this, we believe, also constitutes a success of the Ross procedure. However, even when an autograft reoperation becomes necessary, in about 22%

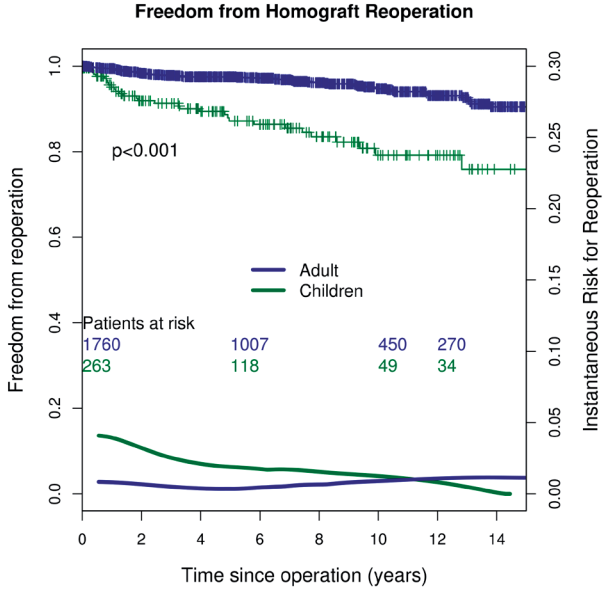

FIGURE 2. *Freedom from homograft reintervention in the pediatric and adult population.*

of cases, the autograft can be either repaired or spared (Table 3), thus retaining some of the benefits the pulmonary autograft has to offer. Elective reoperation in the case of autograft or homograft deterioration can be performed with remarkable safety in experienced centers. Also, catheter interventions will probably reduce the incidence and the need for open conventional procedures further.

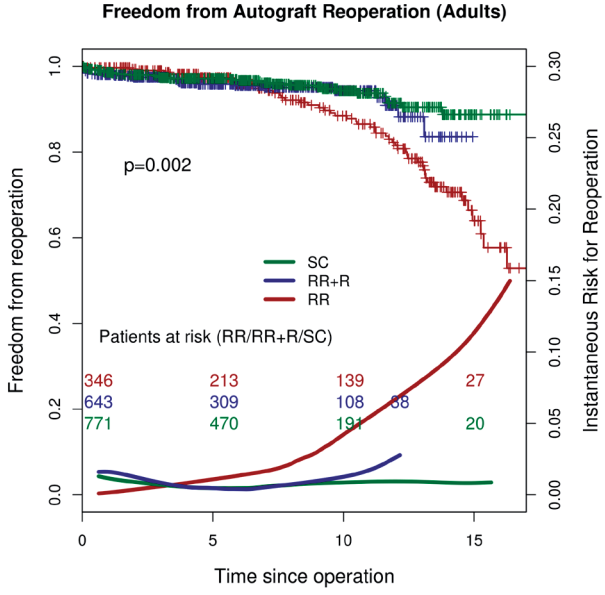

FIGURE 3. *Freedom from autograft reintervention in the adult population stratified by the operative technique. RR, Root replacement without additional root reinforcement; RR+R, root replacement with additional root reinforcement; SC, subcoronary.*

Despite all therapeutic options and modalities, even today, aortic valve replacement, remains a palliative treatment. Mechanical and biologic prostheses bring advantages and disadvantages that the patient and physician should weigh carefully before making an important, informed decision. Eventually, patients requiring aortic valve replacement face some risk of procedural or postoperative valve-related complications. From the view of the treating surgeon, and especially for the Ross procedure, the wish for risk avoidance or risk intolerance, might deny a great proportion of young patients with aortic valve disease all the benefits the Ross procedure has to offer.[47,48]

Study Limitations

The present study is a retrospective analysis of an ongoing nonrandomized registry. The intention of the surgeon when performing reinforcement was either to treat an underlying pathology or to prophylactically stabilize key elements of the aortic root to prevent dilatation.

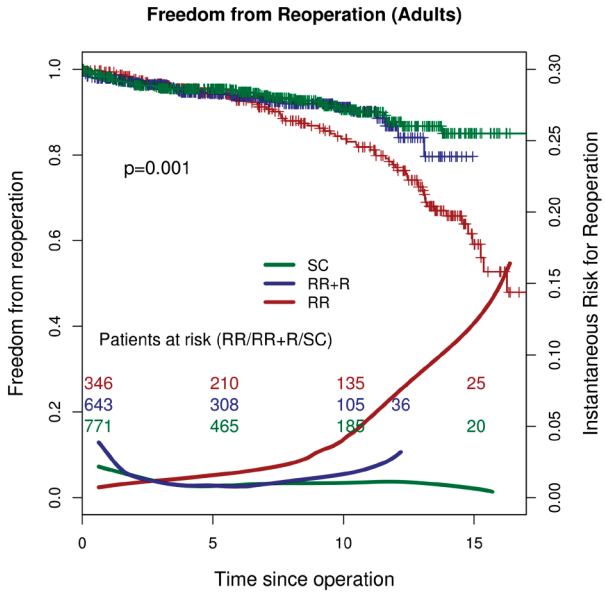

FIGURE 4. *Freedom from autograft or homograft reintervention in the adult population stratified by the operative technique. RR, Root replacement without additional root reinforcement; RR+R, root replacement with additional root reinforcement; SC, subcoronary.*

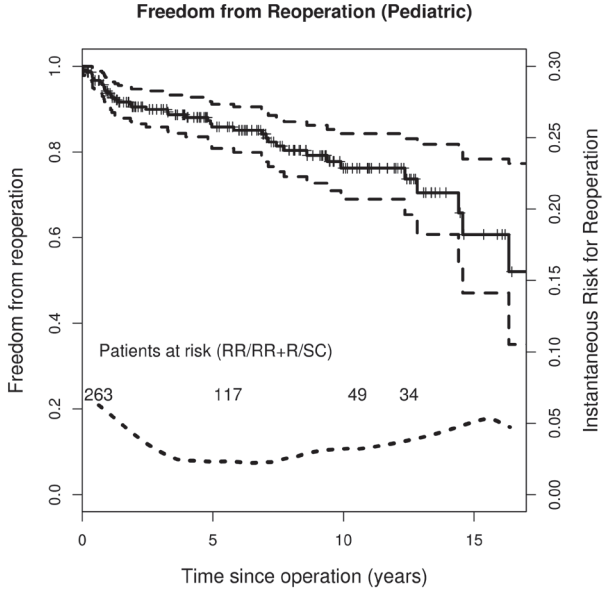

FIGURE 5. *Freedom from autograft or homograft reintervention in the pediatric population.*

For the estimation of the probability of reoperation to the age of 70 years, the risk of autograft or homograft reoperation until age 70 years was extrapolated from the data obtained to date. The survival of the Ross patients was assumed to be comparable to that of the general population. Although evidence has shown that this holds true for the first 2 decades after the Ross procedure,[3,6,7,15] it is unclear whether this persists beyond that point. However if the survival of Ross patients after the second decade is inferior to that of the general population, the probability of reoperation would have been even smaller owing to the competing risk of death.[49-51]

CONCLUSIONS

The present report has outlined the most frequently discussed complication after the Ross procedure, namely, the need for reoperation. Although we see several reasons for a focused presentation on the incidence of reoperation after the Ross procedure, one should evaluate and weigh the need for reoperations under the prism of their relative frequency and against the many benefits the Ross procedure offers to the patient. These benefits include survival comparable to that of the general population, freedom from lifelong anticoagulation, a superior quality of life, unrestricted daily activities, and normal aortic valve hemodynamics.[3-7,10] According to our current knowledge and estimations, not all Ross patients will require reoperation when treated with the SC technique (Figure 6), which, at least in the period of the present study, provided the most robust longterm results.

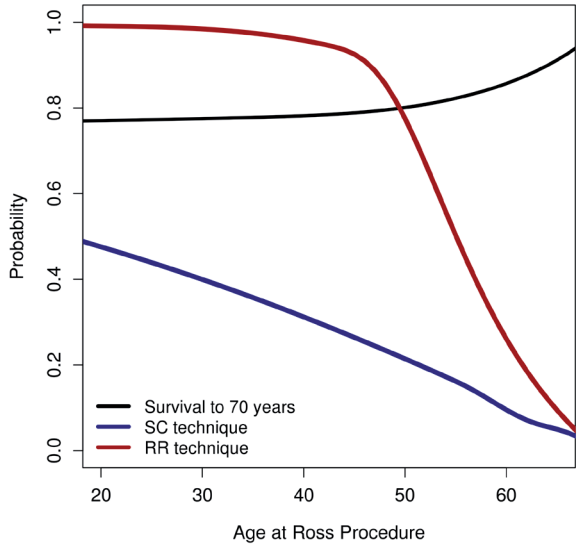

FIGURE 6. *Estimation of the probability of autograft or homograft reintervention until 70 years of age according to the age at the Ross procedure for patients treated with the subcoronary (SC) and root replacement (RR) techniques.*

The risk of reoperation after the Ross procedure depends largely on the surgical technique used and the preoperative hemodynamics. Also, significant research and technical modifications have been successful in progressively reducing the need for reoperation, especially in centers with experience in the treatment of young patients with aortic valve disease. Adequate endocarditis prophylaxis to prevent autograft or homograft endocarditis and increased clinical suspicion might reduce the need for reoperation further. The Ross procedure remains a valid option with many benefits and small risks for the young patient requiring aortic valve replacement.

DISCUSSION

Dr Joseph A. Dearani (*Rochester, Minn*). I have no disclosures. Congratulations on the remarkable results. One of our previous AATS [American Association for Thoracic Surgery] presidents, Dr Tirone David, has acknowledged in the literature that the Ross procedure is a "complex operation and one should not be surprised that reoperations are more complicated." In contrast, standard aortic valve replacement is generally a straightforward operation that most residents would be allowed to perform. The Ross procedure in children is not controversial. In fact, it is the procedure of choice when aortic valve replacement is required. However, in adults, the low early mortality of isolated aortic valve replacement and relative good durability of bioprostheses or low incidence of thromboembolic complications with "point of care" testing in mechanical valve replacements makes the Ross procedure more controversial. My comments will focus on 3 aspects of your results in the adult age bracket, and I will ask 3 questions at the end.

First, at the initial glance, superior autograft durability with the SC implantation technique might imply that this is the technique of choice for Ross implantation. However, a more detailed consideration of the results demonstrated a high early mortality of 8% to 9% for reoperation in this group. In addition, when reoperation was necessary in the SC group, most required replacement and none underwent valve-sparing root replacement. Thus, although reoperation was less likely with the SC technique, the greater operative mortality associated with reoperation might temper enthusiasm to apply it more frequently.

Second, the finding of the relatively high incidence of endocarditis of either the autograft or homograft is eye opening, counterintuitive, and unexpected, particularly because some centers believe the Ross is the preferred operation for the initial treatment of aortic valve endocarditis. Although no obvious explanation is present in your report, I wonder whether the homograft preservation and preparation techniques in Europe could have potentially influenced the susceptibility to infection.

Finally, the cumulative number of reinterventions or reoperation for any given patient in the Ross population can be numerous. Your results will add to the abundant data reporting the reoperation rates after the Ross procedure. However, the reoperation rates alone do not reflect the valve disease that many Ross patients are harboring but for which they have not yet required reoperation.

Although isolated biologic or mechanical aortic valve replacement is not free of subsequent interventions, when they are required, it is more likely related to isolated aortic valve issues and complexity, and the risk of reoperation is often less than that after the Ross. With that

said, your report today of low early mortality for the Ross procedure and low early mortality with reoperation and the excellent late survival make a persuasive argument for more liberal application of the Ross procedure in the young and in middle-age adults, particularly when surgical services are centralized.

My questions are the following. First, what is the Ross implantation technique of choice? Second, do you believe the Ross procedure is a legitimate contender in the current era of excellent outcomes with minimally invasive aortic valve replacement? Finally, although not the focus of your review, do you have any echocardiographic data about autograft or homograft abnormalities in patients who are ''on the way'' to reoperation?

Thank you to the Association for the privilege of this discussion and congratulations on the remarkable results.

Dr Charitos. Thank you very much. These are very pertinent questions. The Ross technique of choice is more or less a matter of debate. Obviously I am biased toward the SC technique. I come from Luebeck; Professor Sievers has probably the most extensive experience with the SC technique. I do believe that the Ross procedure should be performed with the SC technique. This seems logical. We have now more than 600 patients with a complete follow-up rate of 98%. We know exactly what happens to all our patients. The SC technique seems to be technically more demanding; one should know which items one should pay special attention to and which to avoid during the procedure, but the SC technique does provide more robust results.

Some surgeons might prefer other techniques, such as the root replacement technique or root replacement with reinforcement. Some prominent root replacement series have been published, with very good results. However, in general and in the multicenter Ross registry, the root replacement technique without reinforcement has generally underperformed, and I think the data are consistent that the SC provides the best and the most robust results in the long term.

Your second question has to do with minimally invasive aortic valve replacement in this era. Minimally invasive aortic valve replacement does not offer many advantages for the 20-, 30-, or 35-year-old patient. Perhaps cosmetically; however, the problem of valve choice in the patient who is 20 or 25 years old does not depend on the type of surgical access.

The problem these patients face is mainly from the type of prosthesis. If one implants a biologic valve in a 20-year-old patient, one will probably see the patient again in 5 to 7 years. However; a mechanical valve will change the patient's lifestyle, and the patient will face a certain lifetime risk of significant complications. Thus, the type of surgical access for aortic valve replacement in young patients I do not believe has a major effect for a young patient with aortic valve disease, other than, perhaps, cosmetic implications.

And the third question?

Dr Dearani. Whether you have any information about echocardiographic data on the hemodynamic abnormalities in patients that many have but who have not yet required reoperation.

Dr Charitos. This is also a very pertinent question. We do have echocardiographic data. There are patients who have some autograft or homograft dysfunction that might eventually require reoperation but who have, at least for now, not reached the indications for reoperation. The indications for reoperation are much more clear with the autograft and slightly more hazy for the homograft, but certainly we had patients in the study with valve dysfunction at risk of reoperation.

Dr Azhar Hossain (*Miami, Fla*). My question is regarding the bicuspid valve in the young adult, say 20 years old, with severe regurgitation. Would you recommend the Ross procedure for that patient? If so, what procedure would you choose, the classic Ross, which is the SC, or the root replacement?

Dr Charitos. A bicuspid aortic valve is not a contraindication for the Ross procedure. Patients with pure aortic regurgitation do have a greater risk of reoperation; the hazard ratio is about 2.4 to 2.9. But we do not consider patients with a bicuspid aortic valve to have a contraindication to the Ross procedure. Currently, I think the tendency is to repair these valves, but certainly we do not regard a bicuspid aortic valve as a contraindication for the Ross procedure.

The choice of procedure is more or less surgeon specific. We have found that if a center uses 1 specific technique, it usually sticks to that technique. Whether the surgeon will perform additional interventions, for example, to stabilize the aortic annulus or the sinotubular junction in patients with pure aortic insufficiency who have some malformation of the aortic root, this is something one must decide in the operating room. But the choice of technique is mostly surgeon specific.

Dr Hossain. Thus, in other words, you are not concerned that in a bicuspid aortic valve, there is additional risk of root dilatation if you do a root replacement as opposed to an SC procedure?

Dr Charitos. No. We have extensively studied the effects of bicuspid aortic valve in terms of aortic insufficiency and dilatation of the aortic root. We published these findings about 3 or 4 years ago. We have found no clinically significant difference in terms of root dilatation or progression of aortic insufficiency in patients with a bicuspid aortic valve, irrespective of the technique. Dr Hossain. I was referring to the pulmonary autograft that you are going to use in the aortic position. That has the same disease as the native aortic root, which has been reported by many well-published investigators. Thus, if you use a pulmonary autograft, which has a tendency to undergo dilatation, would you still use root replacement, as opposed to the SC, in a Ross procedure, which is the classic Ross?

Dr Charitos. I do not think there is much evidence that the pulmonary autograft in the aortic position in a patient with a bicuspid valve has a greater failure rate. There is only 1 report from the team of Tirone David stating that in some patients with bicuspid aortic valves there are some histologic abnormalities, but that is a very long way to proving that if this patient has a pulmonary autograft in the bicuspid aortic valve position, that the autograft will fail. If one wants to determine whether in a patient with bicuspid aortic valve the autograft fails to a greater extent, one must investigate exactly that assumption. One cannot state that because we have seen some histologic abnormalities in the pulmonary valve of some bicuspid aortic valve patients, then implanting this pulmonary autograft in the aortic position would be the cause of the failure. That is a very big leap.

We have extensively analyzed the effect of bicuspid valves and we have seen no clinically significant influence of the bicuspid aortic valve on the durability of the autograft.

Dr Andre Vincentelli (*Lille, France*). Congratulations for your outstanding series. What was the proportion of patients receiving the SC technique coming from Leubeck in your series?

Dr Charitos. I think I can say we contributed most of the patients treated with the SC technique. From the 750 patients in the Ross registry treated with the SC technique, about 580 were from Leubeck.

Dr Vincentelli. This experience seems to be quite unique in Leubeck and the very good results with the SC technique that you have reported remain hardly reproducible elsewhere. In our series of 394 patients undergoing a Ross operation, we have used the modified root inclusion with a Dacron Valsalva prostheses in 69 patients since 2003. We had no reoperation with this technique that has become routinely used since April 2010 in our institution. Do you have such experience?

Dr Charitos. We have few patients with Dacron root inclusion and 30 patients with the miniroot inclusion technique in the Ross registry. That was too small a population to analyze it separately. Thus, we included the miniroot inclusion patients with the SC patients. Most of these patients with the SC technique were patients in whom the noncoronary sinus was preserved. So it could be considered is a root-preserving technique; the SC technique or the miniroot technique is a type of native root-preserving technique.

Dr Nicholas T. Kouchoukos (*St. Louis, Mo*). Just a follow-up to Dr Dearani's questions. Regarding the SC technique, you have a large experience with this, and it is fairly clear that the failure rates will be different between the SC technique and the root replacement technique, and he asked you about echocardiographic follow-up. Have you seen increases in the degree of aortic regurgitation with the SC technique in patients who have not yet required reoperation, because this is an important consideration. My second question relates to the techniques of preservation of the homograft. Were different techniques used among the different institutions? Were these available commercially or were they prepared in your own hospital?

Dr Charitos. Regarding your first question, we recently published our experience with 200 patients with more than 10 years of follow-up, and we had complete echocardiographic data available. We follow-up every patient; we examine every patient, every year. We have a complete follow-up rate of more than 98% in Luebeck, so we know exactly what happens to the patients.

In the SC technique, we have not seen this gradual increase in the dimensions and aortic regurgitation one sees with the root replacement technique. When the SC technique fails, it is usually abrupt and mostly due to isolated leaflet problems, cusp prolapse or cusp tear, or endocarditis. Nevertheless, there are few patients with moderate aortic regurgitation who might may require reoperation in the future.

Regarding your second question, the evaluation of the homograft is a very complex topic. There are many factors that could potentially have an influence. The factors we have presented were factors influencing, not the function of the homograft, but the incidence of reoperation as an event. Drs Mokhles and Takkenberg are analyzing the homograft data with the cooperation of Dr Blackstone. We hope we will have some high-quality data and results on the durability of the homograft and homograft function and the risk for deterioration within this year.

But I just want to say that the evaluation of the homograft is a very, very complex topic.

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CHAPTER 6

THE ROSS OPERATION — A FEASIBLE AND SAFE OPTION IN THE SETTING OF A BICUSPID AORTIC VALVE?

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Eur J Cardiothorac Surg. 2010;38:333-9
www.elsevier.com/locate/ejcts

ABSTRACT

Objectives

The Ross operation in the setting of a bicuspid aortic valve (BAV) remains controversial. Using data from the German Ross Registry, we sought to investigate the effect of the presence of a BAV on autograft function and diameters over time after the Ross operation compared with the presence of a tricuspid aortic valve (TAV). Methods: A total of 1277 patients (mean age 42.2 ± 15.3 years) with intraoperatively documented aortic valve morphology during the Ross operation were analysed in the present study (sub-coronary technique, n = 648, root replacement technique, n = 629 patients). A BAV was present in 70.9% of patients. Clinical and echocardiographic follow-up was performed preoperatively and at pre-specified intervals (mean follow-up 5.7 ± 3.8 years, 6806 patient-years). Hierarchical multilevel modelling techniques were used for the statistical analysis of serial measurements and comparisons among groups. Results: Initial neoaortic regurgitation was lower in the BAV group (0.52 vs 0.62 aortic insufficiency (AI) grades, p = 0.008), whereas the annual increase of it did not differ among groups. In both surgical techniques, no significant development of neo-aortic regurgitation (<0.02 AI grades per year) could be detected. Initial aortic annulus and sinus dimensions did not differ in the presence of a BAV. However, BAV patients developed a higher degree of annulus and sinus dilatation over time (0.20 mm per year vs 0.06 mm per year, p = 0.003; 0.24 vs 0.11 mm per year, p = 0.013). This effect persisted when allowing for the two different surgical techniques. Baseline sinotubular junction (STJ) diameters did not differ among groups and annual increase thereof was similar (29.15 mm vs 28.9 mm, p = 0.69; 0.44 mm vs 0.35 mm, p = 0.15). Conclusions: For the observed time period, postoperative neo-aortic regurgitation after the Ross procedure did not differ between patients with a BAV or a TAV. Root dimensions, although clinically not relevant, increased in both valve entities supporting surgical reinforcement strategies. We cannot consider a BAV as a contraindication for the Ross operation.

Key Words: Ross operation • Bicuspid aortic valve • Autograft dimensions • Autograft regurgitation

INTRODUCTION

The bicuspid aortic valve (BAV) is the most common congenital heart-valve disorder, present in 1—2% of the population [1]. This aortic valve morphology incorporates different phenotypes, in which a BAV with one raphe represents the most frequent one [24]. The presence of a BAV may be associated with significant valvular dysfunction, which may manifest either as aortic stenosis or as aortic regurgitation (AV), mandating surgical therapy at a relative young age in a significant percentage of patients [2]. The pulmonary autograft procedure, initially described by Donald Ross in 1967 [3], has been shown to result in favourable haemodynamics; it allows an anticoagulation-free life and places the patient at a significantly lower risk for thromboembolism than any other alternative valve prosthesis [4—6]. Due to the concomitant aortic root and ascending aorta pathology observed in many patients with BAV [7], and the common embryological origin of the aortic and pulmonary root, the Ross operation in the setting of a BAV remains controversial, with several groups reporting premature autograft dysfunction or even failure [8,9], whereas others report no relation between a BAV and early or late autograft failure [10—12]. However, most of these studies feature a small number of patients and/or short postoperative follow-up.

The aim of this present study is to investigate the influence of a BAV on the midterm outcome after the Ross operation in a large adult population of the German Ross Registry.

PATIENTS AND METHODS

Study population and operative data

All patient data from the German Ross Registry database were queried and analysed. The registry collects data from 13 cardiac surgery departments in Germany. Historic followup data from each centre were entered into the database for the period 1991—2002, and a common, systematic, prospective registry was initiated in January 2002 (Clinical trial ID NCT 00708409). A total of 1475 patients underwent the Ross procedure between February 1990 and June 2009. In 1277 patients, the aortic valve morphology was documented intra-operatively and these patients were included in the study. Two main implantation techniques were used: the subcoronary (SC, n = 648) technique and the root replacement (RR, n = 629) technique. The choice of operative technique was according to the surgeon's preference. A detailed description of each technique has been provided elsewhere [13]. A bicuspid valve was present in 70.9% of patients (SC, n = 474, RR = 432, p = 0.08). Table 1 summarises the preoperative characteristics of patients with BAV and with a tricuspid aortic valve (TAV), as well as data on the intraoperative and early postoperative course. Informed consent was obtained from all patients and the study protocol was approved by the ethics committee of the registry site. All authors had full access and take full responsibility for the integrity of the data.

Clinical and echocardiographic follow-up

Clinical and echocardiographic follow-up was performed at discharge and on a yearly basis thereafter. The echocardiographic data acquisition protocol of the study has been published

TABLE 1. Demographics, preand operative characteristics (n = 1277). Absolute values (± standard deviation, SD; CVA: cerebro vascular accident).

	Bicuspid aortic valve (*n* = 906)	**Tricuspid aortic valve (*n* = 371)**	**Overall Group (*n* = 1277)**	***p* Value**
Mean age (years)	41.5 ± 14.4	42.1 ± 16.5	41.6 ± 15.1	0.5
<20	97	48	145	0.2
20—40	260	97	357	0.3
41—60	512	192	704	0.12
>61	37	34	71	0.001
Gender				
Male	202	102	304	0.051
Female	704	269	973	
NYHA functional class				
I	269	90	359	0.055
II	382	152	534	0.7
III	180	89	269	0.1
IV	27	21	48	0.034
Unknown	48	19	67	1.0
Left ventricular ejection fraction				
>50%	699	270	969	0.098
30—50%	87	38	125	0.5
<30%	5	0	5	0.3
Unknown	115	63	178	0.05
Cardiovascular risk factors				
Diabetes	24	17	41	0.082
Systemic hypertension	250	116	366	0.2
Impaired renal function	27	22	49	0.016
Rheumatic disease	5	14	19	0.001
Coronary artery disease	50	28	78	0.2
Predominant aortic haemodynamics				
Stenosis	188	60	248	0.062
Regurgitation	207	145	352	0.001
Mixed	486	166	652	0.005
Other — unknown	25	0	25	0.000
Previous aortic valve intervention	76	33	109	0.7
Bypass time (min)				
Mean ± SD	190 ± 42	177 ± 43	187 ± 43	<0.001
Range	71—372	81—460	71—460	
Cross-clamp time (min)				
Mean ± SD	154 ± 38	135 ± 33	149 ± 43	<0.001
Range	43—293	38—273	38—293	

TABLE 1. Demographics, preand operative characteristics (n = 1277). Absolute values (± standard deviation, SD; CVA: cerebro vascular accident). (*Continued*)

	Bicuspid aortic valve (*n* = 906)	Tricuspid aortic valve (*n* = 371)	Overall Group (*n* = 1277)	*p* Value
Circulatory arrest				
n	44	1	45	
Time mean ± SD, range (min)	17 ± 4, 10—33	12	17 ± 4, 10—33	0.2
Surgical technique				
Sub-coronary	474	174	648	0.084
Root replacement	432	197	629	
Clinical course <30 days				
Intra-operative death	0	1	1	0.3
In hospital death	9	2	11	0.5
Low cardiac output syndrome	7	5	12	0.3
Myocardial infarction	11	3	14	0.8
CVA	7	5	12	0.3

elsewhere [6]. In brief, the autograft dimensions at four levels (annulus, sinus of Valsalva, sinotubular junction (STJ) and proximal ascending aorta) were measured as described by Roman et al. [14]. AR was graded on a scale from 0 to 4 according to Perry et al. [15]. Trace (trivial) aortic insufficiency (AI) defined as a tiny AR jet in the early diastole near the detection limit was included in the analysis and was coded as grade 0.5. Mean follow-up was 5.72 ± 3.76 years, ranging from 0.01 to 19.41 years and a cumulative follow-up of 6806 patient-years was collected.

Statistical analysis

Frequencies are provided as absolute numbers and percentages. Continuous data are expressed as mean ± SD. Depending on the surgical technique employed, all patients were grouped either as SC (*n* = 648) or RR (*n* = 629). Forty patients with the root inclusion technique were included in the SC group. Comparisons between the surgical technique groups were performed using the Mann—Whitney *U* test and the Fisher's exact test (SPSS 15.0 for Windows; SPSS; Chicago, IL, USA).

In accordance with the newly revised 'Guidelines for reporting mortality and morbidity after cardiac valve interventions' [16], autograft echocardiographic performance over time was analysed and reported with the use of longitudinal modelling (MLWin 2.0, Centre for Multilevel Modeling, London, UK). The methodology for multilevel hierarchical modelling for the analysis of valvular function over time has been described previously [6,16]. Various regression models were tested on the study's dataset and the linear model provided the best fit for the study. This model provides a linear regression line with an intercept and slope for each individual patient and it estimates the mean intercept and slope across patients. The intercept and slope are assumed to vary randomly for the different patients. The intercept

(±SE) corresponds to the notional value at the time of surgery; the slope (±SE) represents the annual progression of these measurements. Comparisons between slopes/ intercepts and the corresponding *p* values represent the comparisons of the difference between slopes/ intercepts. The intercept and slopes provided represent the mean values across the population or subgroups throughout the period of the study and should not be extrapolated beyond this. Since it is a multicentre study, a centre variable was included in the model allowing for the effect which the different centres may have on the results of this study. This model was applied to analyse AR and aortic root dimensions over time.

RESULTS

Re-operations

Detailed data regarding re-operation and complication rates observed in both morphologies are summarised in Table 2.

Development of neo-aortic regurgitation in BAV and TAV patients

The BAV morphology had a significantly lower grade of initial neo-aortic regurgitation (nAR; 0.52 vs 0.62 AR grade, respectively, $p = 0.008$; 95% confidence interval (CI) of the difference: -0.1867 to 0.0275). A trend towards a higher, although clinically not relevant, nAR development over time was observed in BAV patients (0.01 vs -0.001 AR grade per year, $p = 0.089$; 95% CI of the difference: -0.0019 to 0.0267) (Fig. 1). No significant differences with respect to nAR development could be detected when accounting for the different preoperative valvular haemodynamics (pure AR vs patients with stenotic or combined predominant aortic valve haemodynamics).

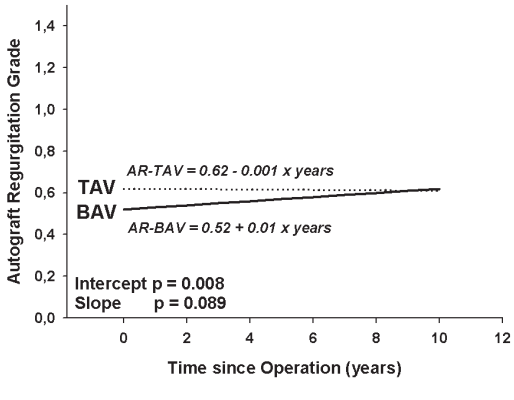

FIGURE 1. *Autograft regurgitation (AR) with time in Ross patients with a bicuspid aortic valve (BAV) and a tricuspid aortic valve (TAV).*

TABLE 2. Survey on mortality, morbidity and re-operation.

	Bicuspid aortic valve (*n* = 906)	Tricuspid aortic valve (*n* = 371)	Overall group (*n* = 1277)	*p* Value
Complication				
Thrombo-embolism	13	18	31	0.001
Valve thrombosis	4	4	8	0.2
Peripheral thrombosis	1	2	3	0.2
CVA	9	13	22	0.007
TIA	7	5	12	0.3
Stroke	2	8	10	0.001
Bleeding	10	7	17	0.3
Endocarditis	25	10	35	1.0
Surgery				
Cardiac	92	59	151	0.005
Ross related	86	44	130	0.2
AG explant	17	17	34	0.011
HG explant	30	10	40	0.7
AG reconstruction	13	6	19	0.8
HG reconstruction	14	0	14	0.014
Death	30	27	57	0.003
Cardiac	20	17	37	0.027
HF	7	7	14	0.1
Arrhythmia	3	1	4	1.0
MI	3	2	5	0.6
Bleeding	2	1	3	1.0
Endocarditis	2	2	4	0.6
Thrombo-embolism	2	1	3	1.0
Sudden	5	6	11	0.090
Non-cardiac	9	11	20	0.022

CVA: cerebro vascular accident, TIA: transient ischaemic attack, AG: auto- graft, HG: homograft, HF: heart failure, MI: myocardial infarction

Influence of surgical technique in the development of nAR in BAV and TAV

When the applied surgical technique was taken into consideration, significant differences between the BAV and TAV groups were observed. The initial nAR was higher in the TAV-RR group than in the BAV-RR group (RR-BAV: 0.59 AR group vs RR-TAV: 0.77 AR group, $p = 0.05$; 95% CI of the difference: -0.29 to 0.05). However, its linear progression did not differ (<0.025 AR group per year in both morphologies, $p = 0.7$; 95% CI of the difference: -0.02 to 0.03). In

the SC group, neither the initial nAR nor its development over time differed between BAV and TAV patients (Fig. 2(a) and (b)).

In the BAV morphology, both techniques had comparable initial nAR (SC: 0.46 AR group, RR: 0.55 AR group, p = 0.22; 95% CI of the difference: -0.23 to 0.05); however, the development of nAR over time was significantly higher in the SC group, albeit not clinically relevant (0.03 vs -0.02 ARg per year, p < 0.001; 95% CI of the difference: 0.03—0.07). In the TAV morphology, initial nAR was lower with the SC technique (0.57 vs 0.81, p = 0.036; 95% CI of the difference: -0.48 to -0.02); however, the rate of increase was lower within the RR group (-0.02 vs 0.012 ARg per year, p < 0.001; 95% CI of the difference: 0.02—0.06). No clinically relevant conclusion could be drawn when comparing patients with pure AR with patients presenting stenotic or combined predominant aortic valve haemodynamics irrespective of the surgical technique employed.

Aortic root dimensions

Aortic annulus

In both morphologies, the initial aortic annulus diameter was comparable (BAV 23.8 vs TAV 24.3 mm, p = 0.14; 95% CI of the difference: -1.1 to 0.16); however, a greater annual increase in annulus diameters was observed in BAV patients (0.20 vs 0.06 mm per year, p = 0.003, 95% CI of the difference: 0.05—0.23; Fig. 3). This effect of progressive dilatation persisted when analysing BAV and TAV patients within each technique. Within the RR group, TAV patients had a higher initial diameter (24.06 vs 25.63, p = 0.006; 95% CI of the difference: -2.69 to -0.45). BAV patients revealed an eightfold greater increase in annulus diameters over time (0.15 vs -0.02 mm per year, p = 0.049; 95% CI of the difference: 0.0006—0.35). Within the SC group, initial annulus diameters were comparable between BAV and TAV patients (22.89 vs 22.82 mm, respectively, p = 0.87; 95% CI of the difference: -0.76 to 0.90), whereas BAV patients had a threefold progressive increase in annulus diameter over time (0.24 vs 0.07 mm per year, p = 0.0049; 95% CI of the difference: 0.05—0.28).

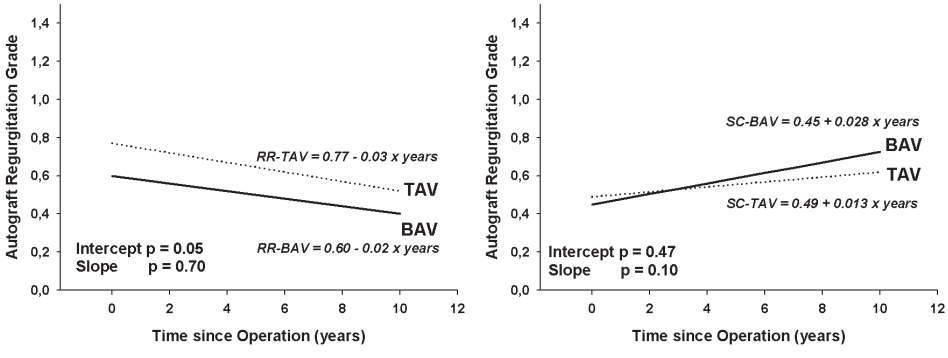

FIGURE 2. *(a) Autograft regurgitation (AR) with time in Ross patients with the root replacement technique with a bicuspid aortic valve (RR-BAV) or with a tricuspid aortic valve (RR-TAV). (b) Autograft regurgitation (AR) with time in Ross patients with the sub-coronary technique and a bicuspid aortic valve (SC-BAV) or with a tricuspid aortic valve (SC-TAV).*

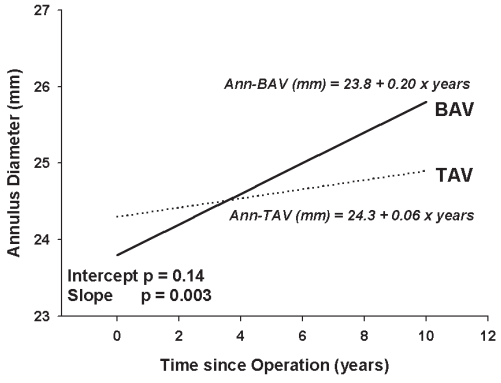

FIGURE 3. *Estimation of the diameters at the annular (Ann) level with time for the two different aortic valve morphologies (BAV: bicuspid aortic valve, TAV: tricuspid aortic valve).*

When comparing the two techniques with respect to aortic valve morphology, no significant differences in initial diameters or diameter increase over time could be observed.

Sinuses of Valsalva

In both morphologies, the initial sinus diameter was slightly higher in the TAV group (BAV 32.4 vs TAV 33.2 mm, p = 0.052; 95% CI of the difference: -1.62 to 0.006). However, a greater increase in sinus diameter was observed in BAV patients (0.24 vs 0.11 mm per year, p = 0.013; 95% CI of the difference: 0.03—0.24) (Fig. 4). This effect of progressive dilatation persisted when analysing BAV and TAV patients within each technique. Within the RR group, TAV patients had a higher initial sinus diameter (35.03 vs 32.87, p = 0.004; 95% CI of the difference: -3.64 to -0.68); however, BAV patients had a 3.5-fold greater increase in sinus diameters over time (0.41 vs 0.12 mm per year, p = 0.016; 95% CI of the difference: 0.05—0.51). Within the

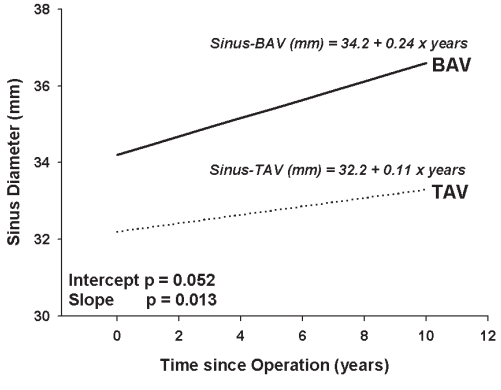

FIGURE 4. *Estimation of the diameters at the sinus level with time for the two different aortic valve morphologies (BAV: bicuspid aortic valve, TAV: tricuspid aortic valve).*

SC group, initial sinus diameters were similar in BAV and TAV patients (31.95 mm in both, p = 0.99; 95% CI of the difference: -0.96 to 0.98), whereas in BAV patients a trend towards a greater increase in annulus diameter over time was observed (0.19 vs 0.08 mm per year, p = 0.07; 95% CI of the difference: -0.01 to 0.23).

When comparing the two techniques within each aortic valve morphology, in BAV patients, the initial sinus diameters were comparable between SC and RR (33.02 vs 31.57, p = 0.11; 95% CI of the difference: -0.31 to 3.23), whereas a higher degree of sinus dilatation in the RR patients was observed (0.41 vs 0.20, p = 0.003; 95% CI of the difference: -0.35 to -0.07). In TAV patients, the SC technique provided a lower initial sinus diameter (30.04 vs 37.14, p < 0.001; 95% CI of the difference: -8.87 to -5.33), whereas there was no difference in the development over time between SC and RR techniques (0.07 vs 0.10 mm per year, p = 0.77; 95% CI of the difference: -0.24 to 0.18).

STJ diameters

Initial STJ diameter (29.15 vs 28.9 mm, p = 0.69; 95% CI of the difference: -0.69 to 1.04) as well as development over time thereof (0.44 vs 0.35 mm, p = 0.15; 95% CI of the difference: -0.03 to 0.22) were similar in BAV and TAV morphologies (Fig. 5). In the SC group, no difference between BAV and TAV could be observed, whereas in the RR group, initial diameter (29.94 vs 32.33 mm, p = 0.043; 95% CI of the difference: -4.71 to -0.07) as well as increase over time (0.73 vs 0.26 mm per year, p = 0.023; 95% CI of the difference: 0.07—0.87) was greater in the BAV group. Within the BAV morphology, initial diameters were similar in SC and RR groups; however, RR patients had a greater diameter increase over time (0.76 vs 0.43 mm per year, p = 0.004; 95% CI of the difference: -0.57 to -0.11). In the TAV group, SC patients had smaller initial diameters (27.96 vs 32.60 mm, p = 0.022; 95% CI of the difference: -8.60 to -0.67), whereas the increase over time did not differ (<0.3 mm per year, p = 0.69; 95% CI of the difference: -0.22 to 0.35).

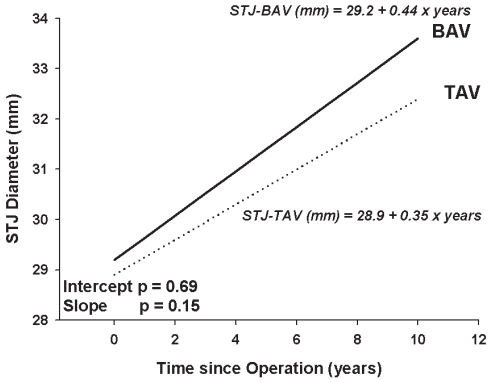

FIGURE 5. *Estimation of the diameters at the sinotubular junction (STJ) level with time for the two different aortic valve morphologies (BAV: bicuspid aortic valve, TAV: tricuspid aortic valve).*

Effect of ascending aorta replacement on nAR and aortic root dimensions

Concomitant replacement of the ascending aorta did not influence the initial postoperative nAR or its development regardless of the aortic valve morphology. No difference could be observed when surgical technique was taken into consideration. The same was true for the longitudinal analysis of the aortic root diameters over time, where the replacement of the ascending aorta did not seem to have a significant influence at all levels of the aortic root, irrespective of the morphology of the aortic valve and the surgical technique.

DISCUSSION

Numerous reports indicate that, in experienced centres, the Ross operation results in favourable clinical outcomes and ventricular haemodynamics; and it offers an anticoagulationfree life and poses a significantly lower risk of thromboembolism than any other valve prosthesis [4—6,17,18]. Given, however, the common embryologic origin of the aortic and pulmonary roots, concerns have been raised regarding the safety, feasibility and the long-term results of the Ross operation in patients with a BAV [11]. There is some evidence that BAV might be associated with progressive aortic root enlargement [19], which, although initially thought to be a result of post-stenotic dilatation, is nowadays attributed to a 'BAV-associated aortopathy', due to abnormal connective tissue properties and dysfunctional collagen metabolism present in some patients with BAV [20]. This process appears to be present irrespective of the valvular dysfunction [21] and may support the hypothesis of a common developmental deviation associated between bicuspid aortic valve and aortic wall abnormalities. Degenerative changes have been found in the wall of the aortic and pulmonary arteries in patients with BAV [22] and although some groups report no relation between a BAV and early or late autograft failure [10—14] some authors report premature autograft dysfunction or even failure in BAV patients after a Ross operation [8,9]; they recommend against the Ross procedure in the presence of a BAV [23].

In the present study, the presence of a BAV was prospectively documented and defined as a congenitally malformed aortic valve comprising a spectrum of deformed aortic valves presenting on gross, intra-operative examination as two functional cusps forming a mechanism with less than three zones of parallel apposition between the cusps [24]. Further sub-typing or sub-classification of the BAV phenotype was not always possible. The wide variety of the BAV phenotype may present a technical challenge to the operating surgeon, as is the case with the Type 0 BAV (two cusps, no raphe and two commissures) [24] operated with the sub-coronary technique. However, the determination of the feasibility as well as the final decision to perform the Ross procedure in each individual case was left to the discretion of the operating surgeon. During the past years, the use of various reinforcement techniques to reduce anatomic mismatch — including the mismatch caused by the presence of a BAV or to prevent autograft deterioration — has increased in the centres participating in the German Ross Registry with favourable results, especially in patients operated with the RR technique [25]. For the patients being studied and operated with the Ross procedure in the presence of a BAV, we could not detect any clinical influence of the aortic valve morphology on the postoperative outcomes or the autograft function. In addition, the

preoperative valvular pathology (pure AR, pure aortic valve stenosis and combined lesion) had no influence on nAR or aortic root dimension at the time of surgery and on annular development.

During the time period of this study, we did observe a numerically higher degree of aortic root dilatation over time for the BAV patients; however, this did not translate into an adverse clinical outcome in terms of risk or need for reoperation. As a group, patients with BAV, irrespective of the surgical technique applied, did not show any clinically relevant difference regarding early postoperative nAR, its increase over time (<0.2 AI grades per decade) or aortic root dilatation. Nonetheless, due to the numerical increase of the STJ diameter over time, especially in patients being operated with the root replacement technique, additional refined surgical stabilisation techniques may be favourable to prevent further dilatation.

In conclusion, a BAV does not influence the clinical outcome after a Ross operation irrespective of the surgical technique applied. Therefore, we cannot consider a BAV as an absolute contraindication for the Ross operation. However, when performing the Ross procedure in patients with a BAV, all possible surgical manoeuvres ought to be performed to stabilise the aortic root and patients need to be followed closely and regularly by thorough echocardiographic followup strategies.

LIMITATIONS

The current study presents several limitations. The mean follow-up time (5.7 ± 3.8 years) is limited. The intercept and slopes provided represent the mean values across the population or subgroups throughout the period of the study, and should not be extrapolated beyond this. The analysis presented in this study is not an intention-to-treat analysis and the final decision to perform or not the Ross procedure in each individual case was left to the discretion of the operating surgeon. As with all multicentre echocardiographic follow-up studies without a core lab, a bias cannot be excluded. To mitigate this problem, we integrated in our model a centre variable, allowing for the effect which the different centres may have on the results of this study, in all statistical analyses performed.

In this study, ordinal data (grade of AR) were treated by the model as nominal data. As a more appropriate statistical approach, the cumulative logit proportional odds model is specifically designed to deal with ordinal data (such as regurgitation grades) but it is less easy for clinicians to interpret the estimated parameters and results. We feel that with such a large amount of data, the central limit theorem allows us to be confident in the fitted models, even though the normality assumptions clearly do not hold exactly. The advantages of a simple interpretation of parameters (mean at time of operation and mean increase per year) should not be disregarded.

ACKNOWLEDGEMENTS

The authors thank Katrin Meyer for the excellent data management at the Registry Site in the Department of Cardiac and Thoracic Vascular Surgery, University Hospitals Schleswig-Holstein, Campus Lu¨beck. The manuscript was written on behalf of the German Ross Registry. The authors thank all participants.

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CHAPTER 7

LETTER BY CHARITOS ET AL REGARDING ARTICLE, "REOPERATION OF LEFT HEART VALVE BIOPROSTHESES ACCORDING TO AGE AT IMPLANTATION"

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Circulation. 2012;125:e583.

Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.111.071993 e583

TO THE EDITOR

We read with great interest the work of Chan and colleagues[1] on the age-stratified incidence of reoperations after left heart biological valve implantation. Results on this area of research were greatly anticipated because previous works in this field were sparse and often plagued by small patient populations or older valve prostheses that are now off the market.

We have some concerns, however, about the graphical representation of freedom from reoperation as a continuous function of patient age at the time of operation (Figure 2).[1] There seems to be a discrepancy between the actuarial freedom from reoperation estimates in Figure 1A and the age-stratified estimates in Figure 2A. If Figure 2 presents actuarial estimates, the authors should provide more information on how these estimates were obtained. If Figure 2 represents predictions of a Cox proportional hazards model, the estimates for freedom from reoperation in young patients based on a model averaging risk factors from a population heavily skewed toward older patients may provide dysfunctional estimates. The authors should explain the discrepancy between Figures 1 and 2 in the young patients, because this bears the potential of misinterpretation both from clinicians and patients.

We believe that the data presented in this work will facilitate decision making when informing patients before heart valve replacement, and we congratulate the authors for undertaking this project.

Disclosures

None.

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Presented in part at American Heart Association Scientific Sessions 2008, November 8 –12, 2008, New Orleans, La.
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CHAPTER 8

AUTOGRAFT REINFORCEMENT TO PRESERVE AUTOGRAFT FUNCTION AFTER THE ROSS PROCEDURE: A REPORT FROM THE GERMAN-DUTCH ROSS REGISTRY

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Circulation. 2009;120:S146-54

Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.108.843391

Background

Autograft reinforcement interventions (R) during the Ross procedure are intended to preserve autograft function and improve durability. The aim of this study is to evaluate this hypothesis.

Methods and Results

1335 adult patients (mean age:43.5±12.0 years) underwent a Ross procedure (subcoronary, SC, n=637; root replacement, Root, n=698). 592 patients received R of the annulus, sinotubular junction, or both. Regular clinical and echocardiographic follow-up was performed (mean:6.09±3.97, range:0.01 to 19.2 years). Longitudinal assessment of autograft function with time was performed using multilevel modeling techniques. The Root without R (Root-R) group was associated with a 6X increased reoperation rate compared to Root with R (Root+R), SC with R (SC+R), and without R (SC-R; 12.9% versus 2.3% versus 2.5%.versus 2.6%, respectively; $P<0.001$). SC and Root groups had similar rate of aortic regurgitation (AR) development over time. Root+R patients had no progression of AR, whereas Root-R had 6 times higher AR development compared to Root+R. In SC, R had no remarkable effect on the annual AR progression. The SC technique was associated with lower rates of autograft dilatation at all levels of the aortic root compared to the Root techniques. R did not influence autograft dilatation rates in the Root group.

Conclusions

For the time period of the study surgical autograft stabilization techniques preserve autograft function and result in significantly lower reoperation rates. The nonreinforced Root was associated with significant adverse outcome. Therefore, surgical stabilization of the autograft is advisable to preserve long-term autograft function, especially in the Root Ross procedure.

Key Words: valves • autograft • echocardiography • surgery • registry

The Ross operation is an alternative to conventional aortic valve replacement in selected patients. It can be performed with low mortality, and provides excellent hemodynamics and low rates of thromboembolism, avoiding the need for anticoagulation therapy and its consequences.[1–5] After a renewal of interest in this procedure in the early 90s, long-term results of these procedures are beginning to emerge, and it is well established that autograft function may deteriorate over time eventually requiring replacement.[1–8]

Several teams have used autograft reinforcement interventions (R) to treat underlying abnormalities and to stabilize the components of the aortic root [8–11] in an attempt to prevent autograft failure. These reports include small number of patients and provide short follow-up, which in combination with the low incidence of autograft failure itself may be insufficient to evaluate the effects of such additional procedures.

Using data from the adult population of the German-Dutch Ross Registry, we sought to investigate the effect of R on postoperative outcome, the need for reoperation, and the longitudinal autograft performance over time.

PATIENTS AND METHODS

Study Population and Operative Data

Data from the German-Dutch Ross Registry were analyzed. The registry includes data from 12 departments of cardiac surgery since 1988. Follow-up data from each center were entered in the database and a systematic prospective registry was started in January 2002 (Clinical trial ID NCT 00708409). The used surgical technique was according to the surgeon's preference, with more or less each center having adopted the one or the other technique. The operative technique (SC/Root) was specific for each institution and remained the same throughout the time period of the study. The vast majority of SC procedures were performed in one center. In the Root technique, one center performed no reinforcement procedures at all, whereas the incidence of prophylactically performed reinforcement procedures increased with time in all other centers performing the Root Ross procedure. Thirty patient operated with the root inclusion technique were included in the subcoronary group (SC), to create a group with all native root preserving procedures. A total of 1335 patients were entered in the registry as of January 2008. Patients' preoperative characteristics as well as operative technique (subcoronary, SC; root replacement, Root) and presence (+R) or absence (-R) of R are summarized in Tables 1 and 2, respectively.

Indications and contraindications for the Ross procedure have been described in detail elsewhere.[4,9,12] As R was regarded any additional procedure performed at the aortic annulus, sinotubular junction, or both. Usually, at the level of the annulus, a 4-mm wide strip of pericardium, Dacron, or a 2/0 GoreTex^{R} suture was placed between donor and recipient tissues to stabilize or to prevent dilatation. In the Root group, R with mainly a Dacron strip, was used in almost all patients in the last 8 years. In the SC group, as R, a 2/0 GoreTex^{R} suture was incorporated in the annulus suture line, if the annulus diameter exceeded 28 to 30 mm as measured before autograft implantation. In the Root group, autograft R consisted also of an additional second suture line fixating circumferentially the remnants of the wall of the native aortic root to the autograft, 4 mm distal to the proximal suture line. In both groups (Root, SC),

TABLE 1. Demographics and Preoperative Characteristics (n=1335)

	Total Group	SC+R	SC-R	Root+R	Root-R
No. of patients	1335	152	485	443	255
Mean age±SD	43.5±12.0	44.9±10.6	45.1±11.8	44.4±11.5	38±12.2*
Range	16 to 70.5	16.7 to 65.6	16.3 to 70.5	16.1 to 67.7	16 to 65.4
<20	50 (3.7)	2 (1.3)	12 (2.5)	17 (3.8)	19 (7.4)*
20 to 40	443 (33.2)	48 (31.6)	147 (30.3)	128 (28.9)	120 (47.1)*
41 to 60	765 (57.3)	95 (62.5)	282 (58.1)	276 (62.3)	112 (43.9)*
>60	77 (5.8)	7 (4.6)	44 (9.1)	22 (5.0)	4 (1.6)*
Gender					
Male	1013 (75.9)	128 (84.2)	365 (75.3)	331 (74.7)	189 (74.1)*
Female	322 (24.1)	24 (15.8)	120 (24.7)	112 (25.3)	66 (25.9)*
LV ejection fraction					
>50%	1034 (77.4)	136 (89.5)	392 (80.8)	316 (71.3)	190 (74.5)
26–49%	141 (10.6)	12 (7.9)	52 (10.7)	43 (9.7)	34 (13.3)*
<25%	5 (0.4)	2 (1.3)	1 (0.2)	2 (0.5)	0 (0)
Unknown	155 (11.6)	2 (1.3)	40 (8.3)	82 (18.5)	31 (12.2)*
Predominant aortic hemodynamics†					
Stenosis	283 (21.5)	15 (10.0)	98 (20.4)	111 (25.8)	59 (23.3)*
Regurgitation	381 (29.0)	43 (28.9)	142 (29.5)	123 (28.5)	73 (28.8)
Mixed lesion	650 (49.5)	91 (61.1)	241 (50.1)	197 (45.7)	121 (47.8)*
Aortic valve morphology					
Nonbicuspid	460 (34.5)	17 (11.2)	173 (35.7)	162 (36.6)	108 (42.4)*
Bicuspid	820 (61.4)	133 (87.5)	291 (60)	259 (58.5)	137 (53.7)*
Other	55 (4.1)	2 (1.3)	21 (4.3)	22 (4.9)	10 (3.9)
Previous aortic valve interventions	98 (7.3)	9 (5.9)	16 (3.3)	36 (8.1)	37 (14.5)*

Absolute values (±SD). Relative values (in %) in brackets. SC indicates subcoronary implantation technique; Root, root replacement technique; +/-R, with/without reinforcement; LV, left ventricle. *P<0.01. †Prosthetic valve dysfunction and acute endocarditis not included.

R of the sinotubular junction was performed by suturing a Dacron prosthesis directly distal to the commissures, if an ascending aorta replacement was indicated.

Informed consent was obtained from all patients. The study was approved by the local ethics committee. All authors had full access to and take full responsibility for the integrity of the data.

Clinical and Echocardiographic Follow-Up

Clinical and echocardiographic follow-up was performed at discharge and on a yearly basis. The standardized echocardiographic data acquisition protocol of the registry has

been published elsewhere.[3] Autograft dimensions were measured at 3 levels (annulus, sinus of Valsalva, sinutubular junction) as described by Roman et al.[13] Aortic regurgitation (AR) was graded on a scale from 0 to 4 according to Perry et al.[14] Mean duration of follow-up was 6.09±3.97 years (median 5.6 years; range 0.01 to 19.2 years; 8205 patient-years). Follow-up completeness was 93%. The 7% missing follow up visits were evenly distributed across the groups. Classification of the mode of valve failure has been performed according to the latest guidelines for reporting outcome after valve interventions.[15] All indications for autograft reoperations were in accordance with the ACC/AHA guidelines.[16] In 2 patients subvalvular aortic aneurysms were the primary indication for reoperation.

TABLE 2. Operative Data and Early Postoperative Course (n=1335)

	Total Group	SC+R	SC-R	Root+R	Root-R
No. of patients	1335	152	485	443	255
Cardiopulmonary bypass time, mean±SD, min	189.8±45.4	215.8±39.5	207.4±32.8	163.2±37.3	191.4±56.2*
Range, min	71 to 685	71 to 345	81 to 433	95 to 372	71 to 685
Cross clamp time, mean±SD, min	150.5±35.4	182.2±40.2	167.1±30.1	130.9±24.9	136.2±28.2*
Range, min	38 to 293	43 to 293	65 to 273	79 to 258	38 to 238
Circulatory Arrest, n	48 (3.6)	34 (22.4)	0 (0)	12 (2.7)	2 (0.8)*
Additional procedures					
None	758 (56.8)	39 (25.7)	329 (67.8)	209 (47.2)	181 (71.0)*
Ascending aorta replacement	233 (17.5)	80 (52.6)	0 (0)	153 (34.5)	0 (0)
Ascending aorta reconstruction	162 (12.1)	18 (11.8)	65 (13.4)	48 (10.8)	31 (12.2)
Valve intervention other than aortic	48 (3.6)	9 (5.9)	27 (5.6)	6 (1.4)	6 (2.4)*
CABG	79 (5.9)	6 (4.0)	19 (3.9)	36 (8.1)	18 (7.1)*
LV Outflow Tract Enlargement	50 (3.7)	14 (9.2)	34 (7)	3 (0.7)	5 (2.0)*
Other	37 (2.7)	1 (0.7)	30 (6.2)	4 (0.9)	2 (0.8)*
Autograft reinforcement					
Annulus	514 (38.5)	93 (61.2)	0 (0)	421 (95)	0 (0)
Sinotubular junction	259 (19.4)	91 (59.9)	0 (0)	168 (37.9)	0 (0)
Annulus and sinotubular junction	180 (13.4)	33 (21.7)	0 (0)	147 (33.1)	0 (0)
Early postoperative z-value (aortic annulus)	0.4±2.1	-0.5±1.7	-0.6±1.7	1.4±1.5	1.7±2.5†
Clinical course <30 days					
In-hospital death	15 (1.1)	2 (1.3)	7 (1.4)	3 (0.7)	3 (1.2)
Reoperation on autograft	6 (0.4)	2 (1.3)	1 (0.2)	3 (0.7)	0 (0)
Reoperation on homograft	0 (0)				

Absolute values (±SD). SC indicates subcoronary implantation technique; Root, root replacement technique; +/-R, with/without reinforcement; CABG, coronary artery bypass grafting. *P<0.01, †P<0.0001 between SC and Root groups.

STATISTICAL ANALYSIS

Frequencies are given as absolute numbers and percentages. Continuous data are expressed as mean±SD. Patients were classified according to the operative technique (SC, Root) and the presence (+R) or absence (-R) of R. Comparisons between the groups were performed using the Mann–Whitney *U* test and the Fisher exact test. Actuarial estimates of survival and freedom from autograft reoperation were accomplished with Kaplan–Meier methods. Survival curves were compared using the log-rank test (SPSS 11.0 for Windows, SPSS, Inc). The Cox model was used to assess the consistency of treatment effect by testing for interactions between the type of surgery (technique and presence of autograft reinforcement) and prespecified baseline characteristics. To identify predictive variables for shorter time to autograft reoperation, we first performed a univariate analyses by using the Cox proportional hazard regression model. Multivariable Cox proportional hazard models were used to confirm whether differences between the operative groups persisted in the presence of preoperative variables. The presence of interactions and the proportionality of hazards assumption was checked for the final model, including operative group and significant preoperative variables. The following factors were analyzed as potential risk factors for autograft reoperation attributable to structural and nonstructural failure (infective endocarditis as a reoperation indication in 8 patients was excluded): age, sex, year of surgery, predominant aortic hemodynamics, hypertension, previous aortic valve intervention, presence of bicuspid aortic valve, technique, and presence of reinforcement procedures.

In accordance with the new guidelines,[15] autograft performance over time was analyzed and reported with the use of longitudinal modeling as previously described.[3,15,17] The echocardiographic data were analyzed by using a multi-level linear model (MLWin 2.0, Centre for Multilevel Modeling). Various regression models were tested on the study's dataset, and the linear model provided an appropriate fit for the study. This model provides a linear regression line with an intercept and slope for each individual patient, and it estimates the mean intercept and slope across patients. The intercept and slope are assumed to vary randomly for the different patients. The intercept (±SE) corresponds to the notional value at the time of surgery, the slope (±SE) represents the annual progression of these measurements. Because this is a multicenter study, it reflects the daily practice of the Registry sites, nevertheless the uniformity of the preoperative data are not warranted and may have an influence in the statistical evaluation of the results. In an attempt to neutralize this center-specific influence, we integrated a center variable, allowing for the effect which the different centers may have to the results of this study, in all statistical analyses performed. This model was applied to analyze AR and aortic root dimensions over time, as well as AR as a function of aortic root dimensions for the surgical subgroups Root and SC and subgroups with and without R. The intercept and slopes provided represent the mean values across the population or subgroups throughout the period of the study and should not be extrapolated beyond this. For the small subgroup of 30 patients with root inclusion technique, separate estimation of the AR development and AR dimensions over time was also performed.

TABLE 3. Survey on Mortality and Reoperation

	Total	SC+R	SC-R	Root+R	Root-R	*P*
No. of patients	1335	152	485	443	255	
Follow-up, y	6.09±3.97	3.31±2.37	6.44±3.56	5.06±3.07	9.08±4.84	*
All cause mortality	35 (2.6)	1 (0.7)	19 (3.9)	8 (1.8)	7 (2.7)	
Cardiac death	16 (1.2)	0 (0)	7 (1.4)	3 (0.7)	6 (2.4)	
Valve related mortality	12 (0.9)	0 (0)	5 (1)	2 (0.5)	5 (2.0)	
Other	19 (1.4)	1 (0.7)	12 (2.5)	5 (1.1)	1 (0.4)	
Reoperation						
Autograft	67 (5)	4 2.6)	18 (3.7)	11 (2.5)	34 (13.3)	*
SVD	18 (1.4)	4 (2.6)	10 (2.1)	3 (0.7)	1 (0.4)	
nSVD	41 (3.1)	0 (0)	2 (0.4)	7 (1.6)	32 (12.6)	*
Endocarditis	8 (0.6)	0 (0)	6 (1.2)	1 (0.2)	1 (0.4)	
Homograft	31 (2.3)	4 (2.6)	12 (2.5)	6 (1.4)	9 (3.5)	
SVD	19 (1.4)	1 (0.7)	3 (0.6)	6 (1.4)	9 (3.5)	*
nSVD	3 (0.2)	1 (0.7)	2 (0.4)	0 (0)	0 (0)	
Endocarditis	9 (0.7)	2 (1.3)	7 (1.4)	0 (0)	0 (0)	

SC indicates subcoronary implantation technique; Root, root replacement technique; +/-R, with/without reinforcement; SVD, structural valve deterioration; nSVD, nonstructural valve deterioration. *P<0.01.

RESULTS

Clinical Outcome (>30 Days) and Autograft Reoperations

Table 3 provides information on the observed mortality and reoperations. Overall cumulative survival was 94.6% (95% CI 92.8 to 96.4%) at 10 years, freedom from autograft reoperation (with the exclusion of 8 patients operated for infective endocarditis[15]) was 96.8% (95% CI 95.5 to 99.0%) at 5 and 89.6% (95% CI 86.1 to 93.0%) at 10 years. When allowing for technique and presence of R, the SC and the Root+R revealed a significantly better freedom from reoperation at 10 years in comparison with Root-R (94.2% [95% CI 90.4 to 97.9%] and 93.2% [95% CI 88.2 to 98.2%] versus 88.3% [95% CI 76.5 to 90.1%], respectively, P=0.001; Figure 1). Autograft reoperation rates for structural (26.9% of all reoperations) and nonstructural valve failure (61.2% of all reoperations) were significantly higher in Root-R in comparison with Root+R, SC-R, SC+R (12.5% versus 2.3%, 2.6%, 2.5%, respectively, P<0.0001). The Root-R group accounted for 55.9% of all reoperations (Table 3). The instantaneous hazard for reoperation for all subgroups is displayed in Figure 2. The multivariable Cox proportional hazard model of the 4 operative groups showed strong evidence that patients operated with the Root technique without the use of reinforcement techniques tend to have shorter times to reoperation (Table 4). The effect of including a number of preoperative variables in the model is shown in Table 5. The differences between the operative groups persist in the presence of these variables. Details of the final model including operative group and the only significant preoperative variable, aortic

regurgitation, are given in Table 6. There was no significant evidence of an interaction between the variables in the final model or that the proportionality assumptions were violated.

Development of Aortic Regurgitation Over Time

AR grade was found to develop approximately linearly with follow-up time. Based on 3803 measurements, the mean initial AR grade was 0.531 (±0.094) with an average increase of AR grade of 0.032 (±0.005) per year. There is significant evidence that AR increases with time ($P<0.0001$), but the amount of this increase is clinically not substantial.

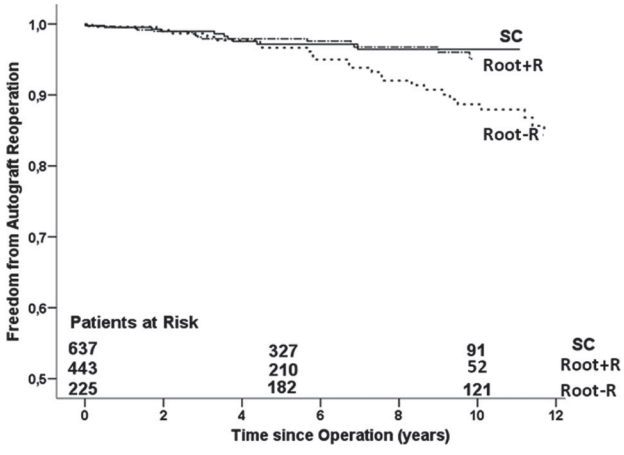

FIGURE 1. *Estimated freedom from autograft reoperation comparing the surgical subgroubs subcoronary implantation (SC), root replacement with root reinforcement (Root+R), and root replacement without root (Root-R) reinforcement (log rank P=0.001, not adjusting for confounding variables). For the comparison between the groups, the data were censored at the 10-year mark.*

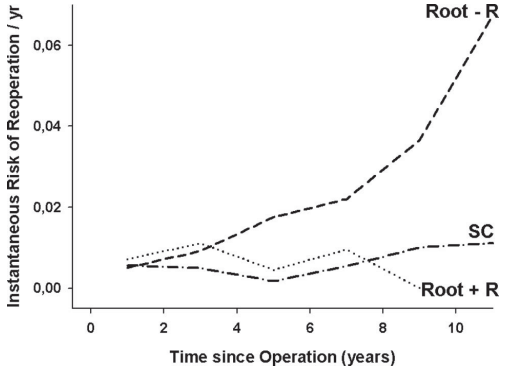

FIGURE 2. *Instanteneous hazard for autograft reoperation per year for the surgical subgroups subcoronary implantation (SC), root replacement with root interventions (Root+R), and root replacement without root interventions (Root-R). Because of the low number of reoperations in the SC+R group, the SC group is depicted as a total.*

TABLE 4. Multivariable Cox Proportional Hazard Model for Shorter Time to Reoperation for the Operative Groups: SC Without Reinforcement (Baseline), SC With Reinforcement, Root Without Reinforcement, and Root With Reinforcement

Predictor	Hazard Ratio (95 % CI)	*P* Value
SC without reinforcement	Baseline	
SC with reinforcement	2.589 (0.818–8.192)	0.11
Root without reinforcement	3.007 (1.516–5.957	0.0016
Root with reinforcement	1.345 (0.577–3.137)	0.49

TABLE 5. Multivariable Cox Proportional Hazard Models for Shorter Time to Reoperation Allowing for Preoperative Characteristics and Operative Groups

Predictor	Multivariate Hazard Ratio (95 % CI)	*P* Value
Age	0.992 (0.97 to 1.01)	0.45
Female gender	0.735 (0.39 to 1.39)	0.34
Operation after 01.01.2001	0.671 (0.31 to 1.46)	0.32
Previous aortic intervention	0.927 (0.43 to 2.02)	0.85
Hypertension	0.953 (0.48 to 1.88)	0.89
Bicuspid aortic valve	0.885 (0.52 to 1.49)	0.65
Pre-op aortic hemodynamics		
Aortic regurgitation	2.334 (1.29 to 4.24)	0.0054
Aortic stenosis	1.303 (0.61 to 2.79)	0.50
Combined lesion	Baseline	

TABLE 6. Multivariable Cox Proportional Hazard Models for Shorter Time to Reoperation for Operative Groups and Preoperative AR

Predictor	Hazard Ratio (95 % CI)	*P* Value
SC without reinforcement	Baseline	
Pre-op aortic regurgitation	2.121 (1.265 to 3.555)	0.0043
SC with reinforcement	1.966 (0.545 to 7.088)	0.30
Root without reinforcement	3.034 (1.533 to 6.002)	0.0014
Root with reinforcement	1.365 (0.585 to 3.182)	0.47

In the current analysis, and allowing for a random center effect, no difference between the Root and SC groups could be observed in terms of initial AR grade (0.519±0.10 versus 0.543±0.101; P=0.71) and annual progression rate (0.035±0.007 versus 0.029±0.006; P=0.49). Allowing for annulus reinforcement, in the SC groups, SC+R had higher initial AR grade compared to SC-R (0.667±0.112 versus 0.491±0.100; P=0.0045), whereas no difference could

be observed in the annual progression of AR (P=0.57, Figure 3a). In the Root subgroups, a higher initial AR grade in Root+R was observed (0.678±0.125 versus 0.471±0.116; P=0.031), however in the presence of annulus R, AR remained stable for the first decade, in contrast to Root-R, in which AR increased at 6-fold rate compared to Root+R (Root-R: 0.067±0.010 AR grade/yr versus Root+R: -0.013±0.012 AR grade/yr; P<0.001, Figure 3b). No significant differences between the SC and root inclusion technique could be observed in terms of initial AR grade and the annual increase of it. All models remained robust after adjusting for cofounding preoperative variables.

Changes of Autograft Dimensions Over Time

An appropriate regression model to study diameter changes at the level of the aortic annulus, sinus, and sinotubular junction with time was a linear model:

Diameter (time)=(Initial diameter±SE)+(Annual increase of diameter±SE)Xtime (yr).

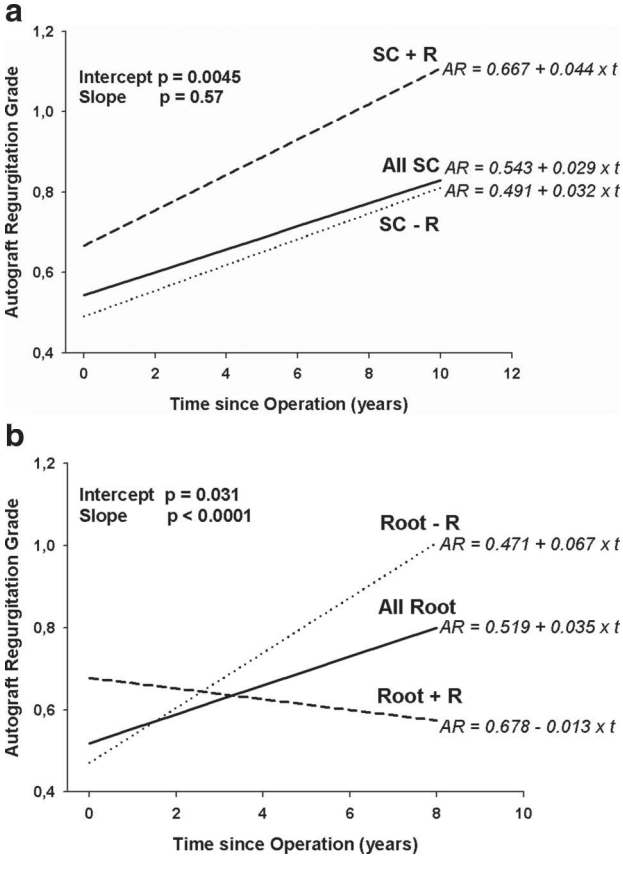

FIGURE 3. *a, Autograft regurgitation with time in Ross patients with the subcoronary implantation technique (SC) with (SC+R) or without (SC-R) annulus reinforcement of the autograft. b, Autograft regurgitation with time in Ross patients with the root replacement technique (Root) with (Root+R) or without (Root-R) annulus reinforcement of the autograft.*

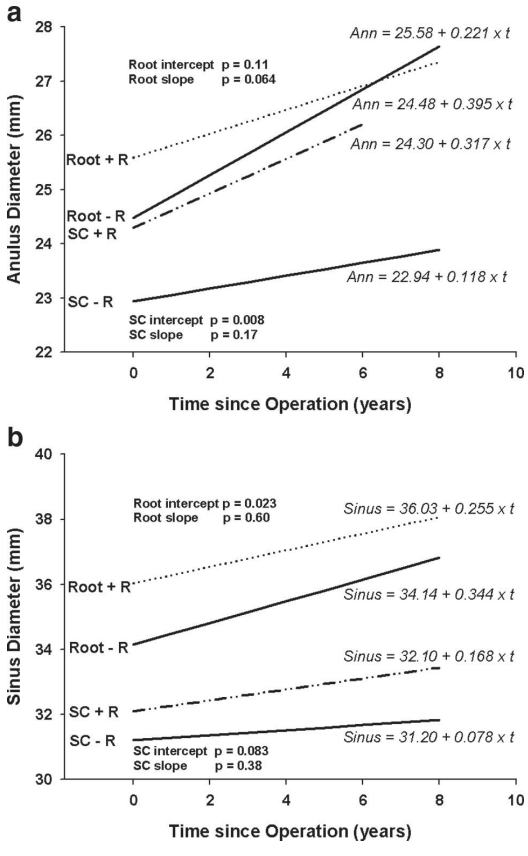

FIGURE 4. *Multilevel modeling of the diameters of the aortic root. Estimation of the diameters (in mm) at the annular (a) and sinus (b) with time for the 2 different implantation techniques (SC, subcoronary implantation; Root, root replacement) and allowing for reinforcement of the root (+R, with reinforcement, -R, without reinforcement) at the respective aortic root level (annulus reinforcement at the annulus level, combined reinforcement at the sinus level).*

Aortic Annulus

Initial dimensions were comparable between Root and SC (25.18±1.05 mm versus 24.49±1.06 mm; P=0.26). The Root group dilated 3 times faster in the first decade (0.316±0.046 mm/yr versus 0.103±0.039 mm/yr, P<0.0004). Taking the presence of annulus R into consideration, no difference could be observed between the Root subgroups. In SC, the presence of R led to higher initial annulus diameter (24.30±0.657 mm versus 24.94±0.837 mm, P=0.008), the rate of annulus dilatation did not differ (Figure 4a).

Sinuses of Valsalva

Initial dimensions were comparable between Root and SC (33.81±1.09 mm versus 32.43±1.050 mm; P=0.10). During the first decade Root dilated 4 times faster than SC (0.259±0.063 mm versus 0.064±0.039 mm/yr respectively, P=0.008). No differences of the

annual diameter increase within the subgroups of each technique could be observed when allowing for the presence of R (Figure 4b).

Sinotubular Junction

A tendency toward lower initial diameters were observed in SC (29.54±1.58 versus 31.11±1.59 mm; P=0.067), in the Root group the sinotubular junction (STJ) tended to dilate almost 3-fold faster than in SC during the first decade (0.602±0.058 mm/yr versus 0.219±0.047 mm/yr, P<0.0001). When allowing for STJ R, no differences between the subgroups of each technique (with or without STJ reinforcement) could be observed.

No significant differences between SC and root inclusion technique could be observed in terms of autograft dilatation over time. All models remained robust after adjusting for cofounding preoperative variables.

Change of Dimensions and Autograft Regurgitation

The Root technique resulted in wider range of annulus and STJ diameters and a trend toward a higher slope of AR development with increasing diameters compared to the SC technique. AR development with increasing annulus or STJ diameters was lower in SC, which, together with the narrower range and lower slope of diameters in SC, makes this technique more robust against AR development with increasing annulus or STJ diameters. (Figure 5a and 5b).

DISCUSSION

The Ross procedure can be performed as an attractive alternative in selected patients, however various groups present midto long-term results indicating that the autograft function may deteriorate over time with the hazard of eventually mandating a reoperation.[1–3,6]

Previous Studies

Significant research has been conducted regarding the mode of autograft failure after the Ross procedure. Early autograft failure is often attributed to technical errors, as was the case with the technically demanding and difficult to reproduce subcoronary technique.[18] The introduction of the root replacement technique[19] seems to ameliorate this early autograft failure, however reports of progressive autograft dilatation[3,7,20,21] and subsequent late autograft failure have recently emerged.[2,7]

Understanding the modes of autograft failure after the Ross procedure, many groups have used modified techniques or R to correct abnormalities in the aortic root area and thus prevent anatomic mismatch,[21,22] or to stabilize parts of the aortic annulus prone to dilatation.[8–11] The long-term impact of R on the autograft function and durability remains largely unknown. Thus main focus of the present study was to unveil the effect of such R on autograft function. The presence of 2 different techniques in the Ross Registry (SC and Root) presents a challenge for this analysis, mainly because the evolution of the native aortic root pathology hosting a subcoronary implant is very different than the evolution of the freestanding pulmonary autograft root technique, and as such, reinforcement techniques might play different roles and serve different purposes in each of these techniques.

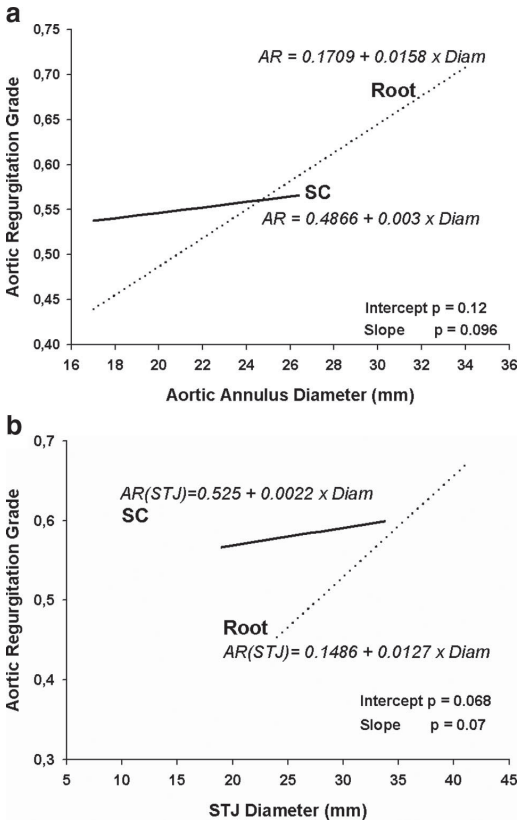

FIGURE 5. *a, Multilevel modeling of the autograft regurgitation grade for the various postoperative aortic annulus diameters for the 2 surgical technique groups. Mean diameter ±2SD of each group are represented. The Root technique resulted in wider range of annulus diameters and a trend toward a higher slope of AR development with increasing diameters compared to the SC technique. b, Multilevel modeling of the autograft regurgitation grade for the various postoperative sinotubular junction diameters for the 2 surgical technique groups. Mean diameter ±2SD of each group are represented. The Root technique resulted in wider range of STJ diameters and a trend toward a higher slope of AR development with increasing diameters compared to the SC technique.*

Present Study

R in this study were performed to correct anatomic abnormalities or mismatch, or prophylactically to stabilize the aortic root and prevent postoperative autograft dilatation. The intention of the operating surgeon and the indication for performing R was determined by the operating surgeon at each institution.

Reoperation Rates

Our main observation was that a significant proportion of the Root-R subgroup required reoperation in comparison to the 3 other subgroups. The Root-R group contributed 57% of all reoperations observed in the registry. The leading cause of reoperation in the Root group was nonstructural valve deterioration[15] (87% of all reoperations in this group) presenting in the

form of autograft dilatation, whereas in the SC group 63% of all reoperations were attributed to structural valve deterioration,[15] mainly as cusp prolapse. The addition of R seemed to decrease reoperation rates because of nonstructural valve deterioration in the Root+R group leading to reoperation rates similar to the SC technique. In the SC group, we could not show a significant impact of R on reoperation rates attributable to either structural or nonstructural valve deterioration.

Autograft failure appears after the first 6 to 8 years in the Root-R group with an exponentially rising instantaneous hazard rate, while remaining stable throughout the observational period in the SC group. For the time period studied, the Root+R subgroup had similar reoperation risk rates as the SC group. This finding is in concordance with previous studies.[23] From our data it could be hypothesized that the larger the preoperative annulus dimensions, the lower the ability of the autograft to provide adequate leaflet coaptation with progressive root dilatation. In the Root group, R leads to smaller annulus diameters, and thus they may act prophylactically. It is however unknown whether in the long term reinforcement procedures prevent or postpone autograft function deterioration.

Autograft Function

In this study we could not observe a significant difference with regards to AR development over time between the SC and the Root as overall groups. This is in contrast to a previous report of ours,[3] where we found a significantly increased initial AR in the Root patients. This difference, however, could be attributed to the additional 321 patients (32% more than the 2006 report[3]) added to the registry in the last 2 years. Moreover, because of the nonuniformity of the preoperative data, in this analysis we allowed for a center effect to mitigate any systematic reporting error between the registry sites. The presence of R effectively prevented AR development over time in the Root group, whereas in the SC R had no effect on the AR increase, albeit for a greater initial AR. R in SC was implemented only in large annulus observed at operation to reduce or reshape the effective annular size to improve cusp coaptation. Here, the indication for R was not prophylactically but therapeutic.

Autograft Dimensions

A consistent finding in this study is the larger initial postoperative aortic root diameters in patients undergoing R in both groups (Figure 4a and 4b), although this does not always reach the level of statistical significance. Given, however, that R are most likely to reduce the aortic root diameters, one can argue that R are often performed to treat underlying abnormalities, thus reducing aortic root dimension to restore the ideal anatomic relations. Although in our series R had a positive effect in terms of autograft durability, there are in the literature notable series of patients operated with the Root technique without R with excellent long-term outcome.[1,5] The effects of proper patient selection bias, however, cannot be ruled out because an often intraoperative selection of the appropriate patient pathology is common in the setting of the Ross procedure. It may well be that in patients with an ideal aortic root pathology, a Root-R technique may have excellent outcome. In addition, it cannot be ruled out that special modifications on individual patient basis in very experienced hands can prevent postoperative dilatation without the need for R with synthetic material.[5]

The SC technique was associated with significantly reduced rates of aortic root dilatation at all levels of the aortic root. In the Root technique, R did not influence the progressive autograft dilatation over time for the time period of the study. In this study we could observe an increased AR in patients with increased annulus and STJ diameters. Although a causal effect could not be established, this could be explained by the observational nature of this study and the increased reserve of the aortic root in terms of dilatation[24] that would lead to AR, and as such the time frame of this study could be insufficient to show that the AR increase is solely caused by root dilatation.

Limitations

The present study is a retrospective nonrandomized study. The intention of the surgeon when performing R in SC was primarily to treat an underlying pathology, whereas in Root, R was mainly applied routinely as a part of root replacement. Early postoperative z values are provided only for the aortic annulus, mainly because of the fact that large databases of normal values in the adult population do not exist for the other counterparts of the aortic root components. No technique to support the sinus of Valsalva was performed in this patient population. A further post-hoc subgroup analysis to identify the most appropriate type of reinforcement material and or specific operative techniques was regarded statistically inappropriate because of the retrospective nature of this study. We believe that this should be performed in the setting of a prospective randomized trial. A small surgical subgroup operated with the root inclusion technique was included in the SC group. Subanalysis of key items (AR, autograft dimensions, reoperations) did not reveal any difference between the SC and the root inclusion technique group. A possible limitation may be the different follow-up times of the various study groups, with R in the Root, being mostly implemented in the last 8 years, having the shortest follow-up time. However the differences observed in outcome and autograft function were statistically and clinically significant for the time period studied.

Clinical Implications

We can conclude that in patients undergoing the Ross procedure, autograft reinforcement procedures performed either prophylactically to prevent autograft dilatation, or therapeutically to correct an underlying a suboptimal anatomy, lead to lower development of AR over time. Surgical autograft reinforcement is able to reduce reoperation rates for autograft failure because of nonstructural valve deterioration in the root replacement Ross procedure for the time period of this study. These procedures appear to be safe, present with good long-term outcome, and should strongly be taken into consideration.

ACKNOWLEDGMENTS

The authors thank Katrin Meyer for her excellent data management and secretarial support at the Registry Site in the Department of Cardiac and Thoracic Vascular Surgery, University Clinics Schleswig-Holstein, Campus Lu¨beck. We thank Petra Lingens and Ilse Beyer for their secretarial support as well as Jana Engelmann and Anja Paap for their documentation support

at the Department of Cardiac and Thoracic Vascular Surgery, University Clinics Schleswig-Holstein, Campus Lübeck.

DISCLOSURES

C.A.B Serves as medical director of the South Africa Homograft Bank.

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Presented at the 2009 American Heart Association meeting in Orlando, Fla, November 14 –18, 2009.
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CHAPTER 9

MAJOR ADVERSE CARDIAC AND CEREBROVASCULAR EVENTS AFTER THE ROSS PROCEDURE: A REPORT FROM THE GERMAN-DUTCH ROSS REGISTRY

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Circulation. 2010;122:S216-23

Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.109.925800

Background

The purpose of the study is to report major cardiac and cerebrovascular events after the Ross procedure in the large adult and pediatric population of the German-Dutch Ross registry. These data could provide an additional basis for discussions among physicians and a source of information for patients.

Methods and Results

One thousand six hundred twenty patients (1420 adults; 1211 male; mean age, 39.2±16.2 years) underwent a Ross procedure between 1988 and 2008. Follow-up was performed on an annual basis (median, 6.2 years; 10 747 patient-years). Early and late mortality were 1.2% (n=19) and 3.6% (n=58; 0.54%/patient-year), respectively. Ninety-three patients underwent 99 reinterventions on the autograft (0.92%/patient-year); 78 reinterventions in 63 patients on the pulmonary conduit were performed (0.73%/patient-year). Freedom from autograft or pulmonary conduit reoperation was 98.2%, 95.1%, and 89% at 1, 5, and 10 years, respectively. Preoperative aortic regurgitation and the root replacement technique without surgical autograft reinforcement were associated with a greater hazard for autograft reoperation. Major internal or external bleeding occurred in 17 (0.15%/patient-year), and a total of 38 patients had composite end point of thrombosis, embolism, or bleeding (0.35%/patient-year). Late endocarditis with medical (n=16) or surgical treatment (n=29) was observed in 38 patients (0.38%/patient-year). Freedom from any valve-related event was 94.9% at 1 year, 90.7% at 5 years, and 82.5% at 10 years.

Conclusions

Although longer follow-up of patients who undergo Ross operation is needed, the present series confirms that the autograft procedure is a valid option to treat aortic valve disease in selected patients. The nonreinforced full root technique and preoperative aortic regurgitation are predictors for autograft failure and warrant further consideration.

Clinical Trial Registration

URL: http://www.clinicaltrials.gov. Unique identifier: NCT00708409.

(Circulation. 2010;122[suppl 1]:S216 –S223.)

Key Words: registries • surgery • valves

The Ross operation is an acceptable alternative to conventional aortic valve replacement in selected patients. Advantages of this therapeutic option are the use of the patients' own valve with favorable hemodynamic characteristics, avoidance of anticoagulant therapy, low thrombogenicity, and the potential to grow in children. Factors contributing to a limited acceptance are the complexity of the operation and the necessity of replacing both the aortic and pulmonary valves. In addition, little clinical long-term information is available regarding the durability of the autograft in the aortic position and the durability of pulmonary conduit substitute. After a renewal of interest in this procedure in the early 1990s, longer-term results are beginning to emerge, focusing mainly on the durability of the procedure and the valve substitutes. However, data on other major cardiac or cerebrovascular events in this patient population remain sparse, coming mainly from small single-center reports with limited follow-up durations. Using data from the large patient population of the German-Dutch Ross Registry, we sought to report on major cardiac or cerebrovascular events observed in 1620 Ross-operated patients over a follow-up of 10 747 patient-years. We believe that the data presented herein could provide a basis for the further judgment of this procedure and could assist physician–patient discussion about the risks, benefits, and expectations after the Ross procedure.

PATIENTS AND METHODS

Study Population and Operative Data

The German-Dutch Ross Registry includes data from 12 departments of cardiac surgery since 1988 and the systematic prospective registry that was started in January 2002 (Clinical trial ID NCT 00708409). The study database was frozen in November 2009 and, for the purposes of the present report, all events until December 31, 2008 were analyzed. A total of 1620 patients were included in the database and their baseline and follow-up data were analyzed. The responsible surgeon at each center determined the surgical technique (subcoronary; root replacement with or without additional reinforcement procedures). A small subgroup of 30 patients undergoing operation with the root inclusion technique was included in the subcoronary group to create a group with all native root-preserving procedures. Details of the operative techniques and the reasons behind the inclusion of the root inclusion technique patients in the subcoronary group and the separate analysis of the root replacement technique patients with and without reinforcements have been reported previously.[1–4] Informed consent was obtained from all patients; the study was approved by the local ethics committee and the authors had full access to and take full responsibility for the integrity of the data and the present article.

Clinical Follow-Up

Clinical follow-up was performed at discharge and on a yearly basis. As a result of the different regional provenance of the patients and to support adherence to the program, complete clinical examinations from the referring cardiologists or general practitioners were also accepted. Major adverse cardiac and cerebrovascular events were reported according to the 2008 guidelines.[5] All indications for autograft or pulmonary conduit reoperations were in accordance with the American College of Cardiology/American Heart Association guidelines.

Statistical Analysis

The adult and the pediatric population (younger than 16 years) of the Registry are analyzed and reported separately. The cut-off point of 16 years was chosen because at this age the patients are regarded as adults and the technical aspects of the procedure are those of the adult population. Frequencies are given as absolute numbers and percentages. Continuous data are expressed as the mean±SD. Actuarial estimates of survival and freedom from morbid events are made using the Kaplan–Meier method. The survival time of a patient started at the time of surgery and ended at death (event) or at last follow-up (censoring). The long-term survival characteristics of the patient cohort were compared with survival probabilities of the general population obtained from German Life Tables 2005 (Statistisches Bundesamt, Wiesbaden Germany; http://www.destatis.de) and Dutch Life Tables 2008 (http://www.cbs.nl/L-NL/menu/home/ default.htm). The contribution of every patient's follow-up time within each age year is added to obtain the cumulative number of years at risk in each age year for the whole study population. Thereafter, the expected number of deaths (assuming their death rates were the same as the national figure) in each age year is found by multiplying the numbers of years at risk by the ageand gender-matched hazard provided by the life tables. The expected deaths for each age year are added to calculate the total expected deaths in the patient collective. The survival times were simulated based on the patients' ages and genders but using the life table hazard rates in the simulation. If the simulated time until death exceeds the follow-up time for the corresponding patient, then the follow-up time is recorded and the value is regarded as censored. A Kaplan–Meier curve is fitted to the simulated times. This procedure was repeated enough times and an average curve was calculated and was compared to the Kaplan–Meier survival curve of the actual data. For the various operative technique groups, the instantaneous risk for reoperation was also calculated.

To identify predictive variables for shorter time to reoperation of the autograft or allograft, we performed univariate analyses using the Cox proportional hazard regression model. Multivariate Cox proportional hazard models were used to confirm whether significant (P<0.10) univariate predictors persisted in the presence of preoperative variables. The presence of interaction and the proportionality of hazards assumption were checked in the final model. The following factors were analyzed as potential risk factors for death or autograft or allograft reoperation: age, year of surgery, gender, presence of comorbidities (diabetes, hypertension, renal failure, coronary artery disease, pulmonary disease, peripheral vascular disease), previous cardiac surgery, preoperative hemodynamics, aortic valve morphology, and homograft donor parameters (diameter, donor recipient age and blood group mismatch, cryopreservation).

RESULTS

Study Population

Patients, characteristics and operative data are listed in Table 1. Follow-up completeness was 95%, with a mean follow-up of 6.6±4.2 years (range, 0 –20.3 years) with 10 747 patient-years.

TABLE 1. Preoperative and Operative Characteristics of the Patient Population

			Adults			
	Total	**Children**	**SC**	**RR+R**	**RR-R**	*P*
N of patients	1620	200	665	464	291	
Mean age, y	39.2±16.2	8.4±5.1	50.0±11.4	44.4±11.5	38.9±12.4	<0.001
Range, y	0.01–70.5	0.01–15.9	16.3–70.5	16.1–67.7	16.0–65.4	
<16 y	200	200				
16–40 y	521		219	152	150	<0.001
41–60 y	819		394	288	137	<0.001
>60 y	80		52	24	4	<0.001
Gender						
Male	1211	141	510	346	214	0.3
Female	409	59	155	118	77	0.3
Left ventricular ejection fraction						
>50%	1263	123	573	341	226	<0.001
26%–49%	122	18	48	29	27	0.37
<25%	2	0	2	0	0	0.41
Unknown	233	59	42	94	38	<0.001
Predominant hemodynamics						
Stenosis	555	45	219	197	94	<0.001
Regurgitation	507	57	227	137	86	0.23
Mixed	534	90	214	121	109	<0.001
Other	24	8	5	9	2	<0.01
Aortic valve morphology						
Bicuspid	994	114	448	271	161	<0.001
Nonbicuspid	553	70	194	170	119	<0.01
Unknown	73	16	23	23	11	0.05
Previous aortic valve intervention	212	104	28	38	42	<0.001
Cardiopulmonary bypass time						
Mean	188±47	170±50	211±35	164±38	191±55	<0.001
Range	71–685	99–465	71–433	95–383	71–685	
Cross-clamp time						
Mean	147±37	118±31	172±34	132±25	137±27	<0.001
Range	38–293	45–240	43–293	79–258	38–238	
Circulatory arrest	60	5	39	14	2	<0.001
Additional procedures	683	54	284	244	101	<0.001

RR+R indicates root replacement technique with additional reinforcement procedures; RR-R, root replacement without additional reinforcement procedures; SC, subcoronary technique.
Choice of pulmonary conduit: homograft (n=1503), bioprosthesis (n=97), bovine vein conduit (n=16), unknown (n=4).

Survival

All-cause early (<30 days) mortality was 1.2% (n=19). Allcause late (>30 days) mortality was 58 (3.6%; 0.54%/patientyear): 34 (0.32%/patient-year) cardiac deaths, 22 noncardiac deaths (0.20%/patient-year), and 2 unknown. Valve-related mortality was 1.2% (20 patients; 0.19%/ patient-year). Actuarial cumulative overall survival (including early mortality) for adults was 98.6% at 1 year (95% confidence interval (CI), 98.0%–99.2%), 96.9% at 5 years (95% CI, 95.2%–97.9%), and 94.7 at 10 years (95% CI, 93.1%–93.6%); for children it was 95.0% at 1 year (95% CI, 92.1%–97.9%), 94.4% at 5 years (95% CI, 91.3%–97.5%), and 92.5% at 10 years (95% CI, 88.4%–96.6%).

Actual vs Expected Death Rate

In this comparison, all patients with follow-up >30 days were included. Observed fatal events were compared with the expected deaths in the ageand gender-matched general German and Dutch populations (Table 2). The Kaplan–Meier actuarial estimates and the estimates of expected survival for the adult and the pediatric populations are displayed in Figures 1 and 2, respectively. In the univariate Cox proportional hazard model, younger age among children (hazard ratio [HR] per year, 0.86; 95% CI, 0.80 – 0.93; $P<0.0001$), older age among adults (HR per year, 1.04; 95% CI, 1.02– 1.06; $P<0.0001$), and presence of preoperative risk factors (HR, 1.38; 95% CI, 1.05–1.83; $P=0.023$) were associated with increased risk for late mortality.

Reoperation Including Endocarditis

One hundred sixty reoperations on Ross-related valves (pulmonary autograft, pulmonary conduit) were required in 137 patients (8.5%; 1.49%/patient-year); the time interval between the initial procedure and the first reoperation was 5.7±4.7 years (range, 0.0 –16.3 years; median, 4.9 years). Ninety-three patients underwent 99 reinterventions on the autograft (5.7%; (linearized occurrence rates [LOR], 0.92%/ patient-year). Seventy-eight interventions in 63 patients were performed on the pulmonary conduit (3.9%; LOR, 0.72%/ patient-year). Of these, 17 procedures with simultaneous autograft and pulmonary conduit interventions were performed in 17 patients.

TABLE 2. Observed vs Expected Deaths in the Study Population

	Cumulative Years of Follow-Up	Observed Deaths	Expected Deaths	*P*
Total	10 747	58	49.9	0.28
Male	8135	44	42.4	0.85
Female	2612	14	7.5	0.044
Age group, y				
<16	1510	8	0.5	<0.001
16–40	3863	11	4.6	0.015
41–60	4756	29	33.1	0.54
>60	618	10	11.8	0.75

FIGURE 1. *Expected vs observed survival in adult Ross patients (actuarial estimates with 95% confidence intervals) and ageand gender-matched normal population.*

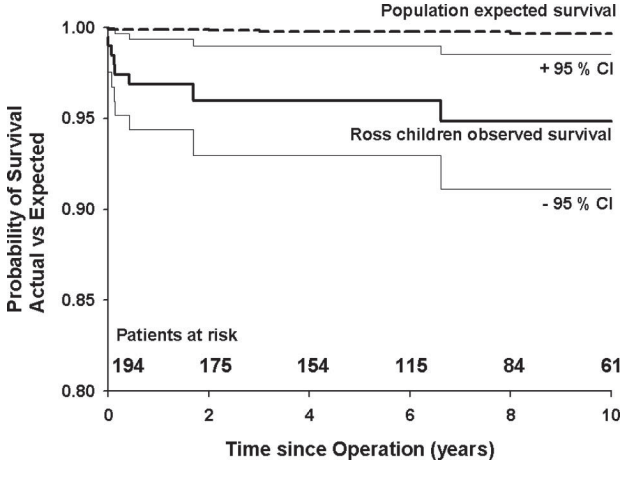

FIGURE 2. *Expected vs observed survival in Ross children (actuarial estimates with 95% confidence intervals) and ageand gender-matched normal population.*

Table 3 summarizes the indications for 99 autograft reinterventions (including 17 cases of interventions on the autograft and pulmonary conduit). The autograft reoperation procedures (time to first reoperation) were performed 0 to 16.3 years (mean, 6.6±4.9 years; median, 6.8 years) after the initial Ross operation. In 47 patients a mechanical valve was used, in 14 a bioprosthesis was used, and in 6 a homograft was implanted; in 23 patients, an autograft reconstruction was performed. Freedom from reoperation on the autograft and the instantaneous risk of reoperation in children are displayed in Figure 3; the estimates in adults

for the different surgical techniques are shown in Figure 4. The univariate Cox proportional hazard model showed evidence that in age group 16 to 40 years (HR, 1.78; 95% CI, 1.12–2.83;

TABLE 3. Major Adverse Cardiac and Cerebrovascular Events in the Study Population

			Adults			
	Total	**Children**	**SC**	**RR+R**	**RR-R**	***P***
N of patients	1620	200	665	464	291	
Follow-up						
Mean	6.6±4.18	7.55±4.65	6.2±3.66	5.46±3.25	8.87±5.19	<0.001
Patient-years	10 747	1510	4124	2532	2580	
Clinical course <30 days						
Death	19	5	6	4	4	0.27
Autograft reoperation	7	0	3	4	0	0.25
Allograft reoperation	2	1	0	1	0	0.28
Clinical course >30 days						
Death	58	8	29	10	11	0.26
Autograft reoperation	92	7	26	10	49	<0.001
nSVD	57	6	3	4	44	<0.001
SVD	21	0	15	3	3	0.03
Endocarditis	14	1	8	3	2	0.7
Other	0	0	0	0	0	
Pulmonary conduit reoperation	76	34	20	6	16	<0.001
Stenosis	43	25	5	5	8	<0.001
Regurgitation	9	2	2	1	4	0.11
Combined	5	1	1	0	3	0.07
Endocarditis	15	4	10	0	1	0.02
Other	4	2	2	0	0	0.09
Endocarditis conservatively treated						
Autograft	5	0	2	1	2	0.55
Pulmonary conduit	11	2	5	0	4	0.13
Thromboembolism	21	3	11	5	2	0.62
Valve thrombosis	6	3	1	2	0	0.03
Peripheral embolism	4	0	2	1	1	0.87
Completed stroke	11	0	8	2	1	0.17
Bleeding	17	0	9	6	2	0.34
Cerebral	6	0	4	2	0	0.41

nSVD indicates nonstructural valve deterioration; RR+R, root replacement technique with additional reinforcement procedures; RR-R, root replacement without additional reinforcement procedures; SC, subcoronary technique; SVD, structural valve deterioration.

P=0.015, in comparison to age group 41 to 60 years), root replacement without surgical reinforcement (HR, 1.82; 95% CI, 1.12– 2.95; *P*=0.015, in comparison to the subcoronary technique) and preoperative aortic regurgitation (HR, 2.07; 95% CI, 1.21–3.55; *P*=0.0079, in comparison to aortic stenosis as predominant preoperative hemodynamics) were associated with shorter times to reoperation. The multivariate model is displayed in Table 4.

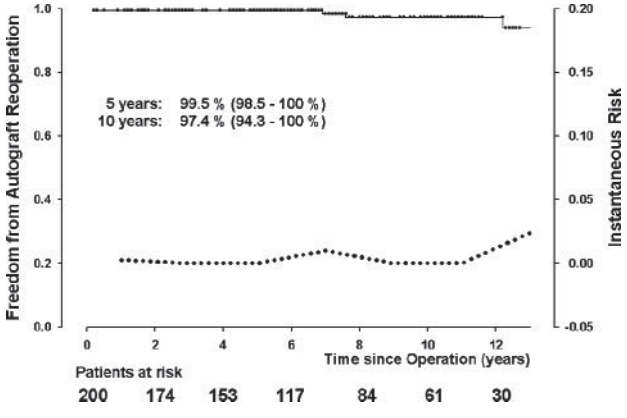

FIGURE 3. *Actuarial estimates of freedom from autograft reoperation (left, y-axis) in children and instantaneous risk of autograft reoperation (right, y-axis; events/censorings: 6/194).*

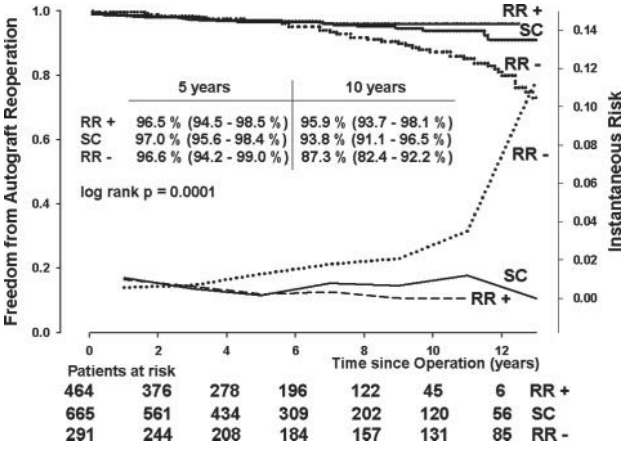

FIGURE 4. *Actuarial estimates of freedom from autograft reoperation with different surgical techniques in the adult cohort (left, y-axis) and instantaneous risk of autograft reoperation (right, y-axis). Reoperations of adult patients who underwent operation with the root replacement technique without autograft reinforcement are also displayed, although this technique is being abandoned with time among the participating centers (events/cencorings: 82/13 389; events for subgroups: SC, 27; RR+, 14; RR-, 41; SC, subcoronary technique; RR+R, root replacement technique with additional reinforcement procedures; RR-R, root replacement without additional reinforcement procedures).*

TABLE 4. Multivariate Cox Modeling for Shorter Time to First Autograft and Allograft Reoperation

	HR	95% CI	*P*
Shorter time to autograft reoperation			
Age group			
41–60 y	Baseline		
<16 y	0.47	0.19–1.09	0.078
>60 y	2.22	0.95–5.17	0.066
Surgical technique			
Subcoronary	Baseline		
Root replacement without reinforcement*	2.17	1.32–3.57	0.0024
Predominant preoperative hemodynamics			
Aortic stenosis	Baseline		
Aortic insufficiency	1.98	1.15–3.42	0.014
Shorter time to allograft reoperation			
Age group			
<16 y	5.06	2.07–12.38	<0.001
16–40 y	2.155	0.92–5.03	0.076
41–60 y	Baseline		
>60 y	4.2	0.89–19.79	0.070
Donor age	0.975	0.96–0.99	0.016

*The hazard ration (HR) for the root replacement without reinforcement techniques represents the average HR, because there is evidence that the HR increases with time (Figure 4).

Indications for the 78 reinterventions on the pulmonary conduit (including 17 patients with replacement of the autograft and pulmonary conduit) are presented in Table 3. The pulmonary conduit reoperation procedures (time to first reoperation) were performed from 0 to 16.3 years (mean, 4.7±4.4 years; median, 2.7 years) after the initial Ross operation. No percutaneous procedures were performed. Freedom from reoperation on the pulmonary conduit and the instantaneous risk of reoperation are displayed in Figure 5. The univariate Cox proportional hazard model showed evidence that the younger patient age (HR, 0.97 per year; 95% CI, 0.95–0.98; $P<0.0001$), younger donor age (HR, 0.96 per year; 95% CI, 0.94 – 0.98; $P=0.0001$), absolute age difference between donor and patient (HR per year, 1.06; 95% CI, 1.002–1.048; $P=0.032$), smaller allograft diameters (HR per mm, 0.87; 95% CI, 0.800 – 0.95; $P=0.0012$) were associated with shorter times to allograft reoperation. The multivariable model is displayed in Table 4. Freedom from autograft and pulmonary conduit reoperation and the instantaneous risk of reoperation are displayed in Figure 6. All patients survived the reoperation on Ross-related valves and were alive at the date of the last follow-up inquiry.

Infective Endocarditis

Four early endocarditis occurred. Late endocarditis with medical (n=16) or surgical treatment (n=29) was observed in 38 patients (2.3%; LOR, 0.38%/patient-year). Overall, 18 autograft

reoperations attributable to endocarditis were performed (1.1%; LOR, 0.18%/patient-year). Pulmonary conduit endocarditis with medical (n=11) or surgical treatment (n=15) occurred in 24 patients (1.5%; LOR, 0.26%/patient-year).

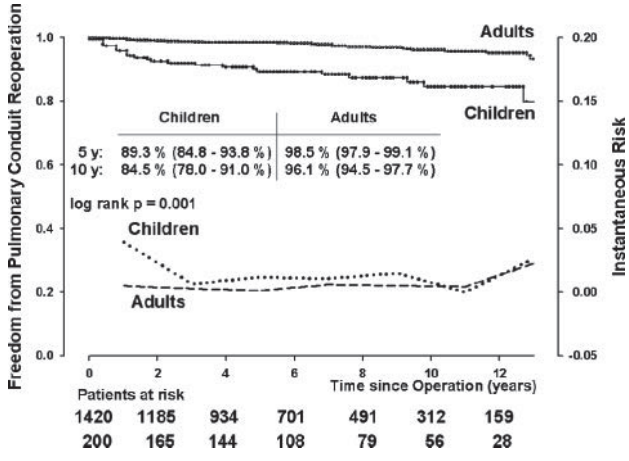

FIGURE 5. *Actuarial estimates of freedom from pulmonary conduit reoperation in children and adults (left, y-axis) and instantaneous risk of pulmonary conduit reoperation (right, y-axis; children: events/cencorings, 24/176; adults: events/cencorings, 38/1382).*

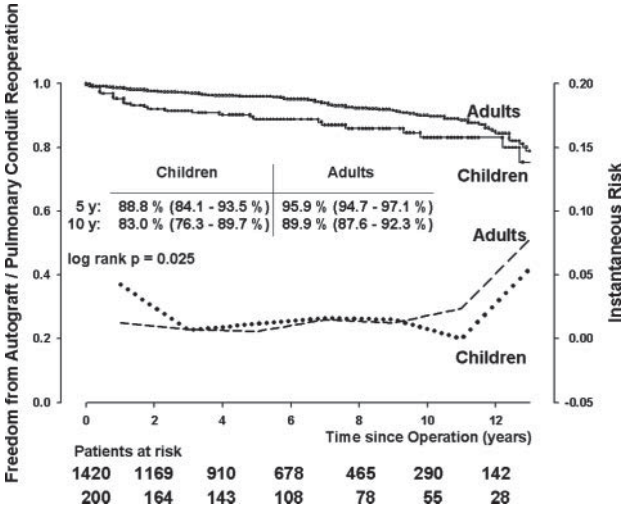

FIGURE 6. *Actuarial estimates of freedom from autograft or pulmonary conduit reoperation in children and adults (left, y-axis) and instantaneous risk of autograft or pulmonary conduit reoperation (right, y-axis). (children: events/cencorings, 27/173; adults: events/cencorings, 103/1317).*

Thrombosis and Bleeding

Valve-related thrombotic and thromboembolic events occurred in 21 patients (Table 3). Major internal or external bleeding occurred in 17 patients (1.05%; LOR, 0.15%/ patient-year). A total of 38 patients experienced the composite end point of thrombosis, embolism, or bleeding (2.3%; LOR, 0.35%/patient-year).

Major Adverse Valve-Related Events

Overall freedom from any major valve-related event (all valve-related mortality; valve-related morbidity: structural and nonstructural valve dysfunction with the need of reoperation, thrombosis, bleeding, embolism, neurological events, endocarditis, and the need for pacemaker implantation within 14 days after operation) was 94.9% at 1 year (95% CI, 95.9%–93.9%), 90.7% at 5 years (95% CI, 92.3%– 89.1%), and 82.5% at 10 years (95% CI, 85.0%– 80.0%).

DISCUSSION

The prospective German-Dutch Ross Registry with a considerable number of patients, good midterm follow-up completeness, and follow-up time of >10 000 patient-years offers the opportunity to address key question of major cardiac and cerebrovascular events.

Survival in the Pediatric Population

In most case-series studies addressing the survival of pediatric patients, encouraging results have been published. In the series published by Elkins et al,[6] actuarial survival at 8 years was 97%,[7] and their updated series showed an actuarial survival of 92% at 12 years.[8] Kouchoukos et al[9] showed a 10-year actuarial survival of 96%, and in a systematic review the pooled outcome estimate for late mortality in pediatric series was 0.62%/patient-year.[10] The reported numbers are similar to the actuarial survival in the registry with 94.4% at 5 years and 92.5% at 13 years. After excluding the early mortality, a comparison to the expected survival based on national hazard rates revealed significant differences, with lower observed patient survival mainly attributable to fatalities occurring within the first year after the procedure. These results are inferior to the results in adult patients. In contrast to adult Ross patients, pediatric patients are more often critically ill, and almost all undergo the procedure after failing previous interventions for congenital aortic stenosis. Furthermore, these patients are more likely to present with complex left ventricular disease and other associated anomalies.

Survival in the Adult Population

In the adult population of the Registry, the observed 94.9% 10-year actuarial survival estimate is comparable to the estimates reported in other large series[8] and to the pooled outcome survival estimates of a recently published meta-analysis (0.64%/patient-year[10]). After the initial survival decrease associated with in-hospital mortality, the observed survival parallels the expected survival calculated from the national hazard rates. Excluding all early fatalities (within 30 days of the initial operation), no significant differences in survival could be observed between the adult Ross patients and the normal population, a fact that underlines

the overall good prognosis of the adult Ross-operated patients, after overcoming the early postoperative hazard.

In contrast, in the present pediatric series reoperations on the autograft are rare within the first decade with an actuarial freedom from reoperation of 100% at 5 years and 97.9% at 10 years, respectively, reflecting a LOR of 0.40% per patientyear. However, graft failure may become apparent thereafter. This is in accordance with an actuarial estimate of 93.8% at 13 years in our series, which is also supported by the data of the series published by Elkins et al.[8,11] Aortic regurgitation was the leading cause of reoperation based on nonstructural valve failure with root dilatation; other indications were rare in this pediatric series (no structural valve deterioration, infective endocarditis in 1). The dilatation of the autograft must be prevented to improve the durability of the neoaortic root. In adults and adolescents, this could be effectively achieved by applying reinforcement techniques or by the use of the subcoronary implantation technique.[2] The routine use of reinforcement techniques or other implantation techniques failed to improve autograft durability[12] or was not applicable, especially in small children. Additionally, the growth potential of the neoaortic root is one of the major advantages of the Ross procedure, which will be unfavorably influenced by all available stabilizing measures.[7,13] This limitation and the necessity of reoperation attributable to outgrowth are still an unsolved issue in the pediatric patient undergoing Ross procedure.

In adult patients, the pooled estimates of structural and nonstructural autograft deterioration with the need for reoperation was reported to range between 0.15% and 1.90% per patient-year, with a pooled mean of 0.78% per patient-year.[10] These estimates are congruent with the present actuarial freedom from reoperation probability of 97.6% at 5 years and 93.7% at 10 years, reflecting a linearized rate of 0.74% per patient-year. The actuarial data are convincing up to 12 years; beyond this cut-off point, no robust data are available. Because the definition of autograft failure differs in numerous reports in literature, comparisons with other series are limited[8] and thus we restricted our estimates on the hard end point "reoperation." Aortic regurgitation was the leading cause of reoperation in 90% of all reoperations. The mechanisms of graft failure differs between the surgical implantation techniques; autograft procedures as root replacements without reinforcement interventions are prone to nonstructural valve deterioration caused by root dilatation in 41 of 47 (LOR, 1.82%/patient-year), whereas root replacement with reinforcement (LOR, 0.32%/patient-year) or the subcoronary technique (LOR, 0.48%/patient-year) revealed dilated root with the need for reoperation only in 2 of 8 and 0, respectively. The practical benefit of stabilization measures at the annular level of the neoaortic root has been reported previously based on the large database of the registry.[2] The leading cause of autograft valve failure with the need for reoperation in the subcoronary group is structural valve deterioration (80% of all reoperations), mainly as cusp prolapse (69% of all structural valve deteriorations). This problem remains a surgical challenge in the subcoronary implantation technique. Additionally, our data suggest that patients with primary aortic regurgitation have an increased risk for autograft failure and might have an increased risk for reoperation. This potential limitation of the procedure is apparent in the pediatric and adult populations and has been reported by various groups.[8]

Reoperation on the Pulmonary Conduit Excluding Endocarditis

For the combined end point structural and nonstructural degeneration of the pulmonary conduit with the need for reoperation in pediatric patients, a LOR between 0.40% and 4.9% per patient-year (pooled mean, 1.6%/ patient-year) was estimated.[10] In accordance with this meta-analysis, we also observed an apparently higher reoperation rate of the pulmonary conduit compared to autograft reoperations. The present series revealed actuarial estimates of freedom from conduit reoperation of 90.6% at 5 years and 87.1% at 10 years, respectively, which correspond to a LOR of 1.32% per patient-year. As in other series, the predominant indication for reoperation of the pulmonary conduit was stenosis (57%). Pure regurgitation is uncommon (12%). Several predictors of conduit failure have been reported;[14–19] however, most of them cannot be taken into clinical consideration because of the limited availability of donor grafts.

In the adult population, the LOR estimates of structural and nonstructural pulmonary conduit deterioration with the need for reoperation has been reported to range between 0.12% and 1.27% per patient-year (pooled mean, 0.55%/patient-year).[10] The present actuarial freedom from pulmonary conduit reoperation probability of 99.0% at 5 years and 97.0% at 10 years results in a linearized rate of 0.30% per patient-year. In most cases, a pulmonary allograft was the first choice for reconstruction of the right ventricular outflow tract. Similar to the pediatric population, predictors of pulmonary conduit failure in multivariate analyses could hardly be considered in the choice of the graft.

Autograft and Pulmonary Conduit Endocarditis

The observed numbers of autograft endocarditis in the present series are low, with a LOR in the pediatric patients of 0.07% per patient-year (compared to a pooled mean estimate of 0.15%/patient-year[10]); pediatric pulmonary conduit endocarditis was seen with LOR of 0.40% per patient-year (pooled mean estimate, 0.26%/patient-year). In our adult series, autograft and pulmonary conduit endocarditis are similar to that reported by Takkenberg et al.[10] Although the absolute numbers are low, it must be emphasized that 15% of all autograft reoperations and 20% of all pulmonary conduit reoperations were caused by infective endocarditis. All cases of endocarditis during follow-up were unrelated to active aortic valve endocarditis before the procedure supporting the use of the Ross operation for treating patients with infective endocarditis of the aortic valve. In most cases, precipitating factors (hematologic disorders, corticosteroid therapy, diabetes mellitus, drug or alcohol abuse) could be identified.

Thrombosis, Thromboembolism, and Bleeding

Valve thrombosis, thromboembolism, and bleeding events are uncommon in patients who underwent the Ross procedure. The LOR of 0.18% per year in the pediatric series and 0.35% per patient-year in the adults (normal adult population, 0.13%/patient-year) are identical with the reported pooled data.[10] Especially in the adult series, the composite event related more to other cardiac and extracardiac factors than to the valve itself (eg, embolism in atrial fibrillation, anticoagulation-related bleedings).

Limitations

The German-Dutch Ross Registry is a nonrandomized registry, prospectively recruiting patients since 2002 and all historical Ross patients for the period 1988 to 2002. The operative volume and experience varies across the 13 centers. A small subgroup of patients undergoing operation with the root inclusion technique, as well as patients undergoing operation with a modification of the subcoronary technique (preservation of the non coronary sinus), are included in the subcoronary root population. Analysis showed no difference regarding major outcomes within these techniques. The various operative groups (children, subcoronary technique, root replacement technique with additional reinforcement procedures, root replacement without additional reinforcement procedures) have different follow-up durations. In the reported LOR, reoperations in adult patients who underwent operation with the root replacement technique without autograft reinforcement have been included, although this technique is being abandoned among the participating centers.

CONCLUSION

The present series confirms that the autograft procedure is a valuable option to treat aortic valve disease in children, adolescents, and young adults. Preoperative aortic regurgitation and the nonreinforced full root technique are predictors for autograft reoperation and require special consideration.

ACKNOWLEDGMENTS

The authors thank Mrs. Katrin Meyer for her excellent data management and secretarial support at the Registry Site in the Department of Cardiac and Thoracic Vascular Surgery, University Clinics Schleswig-Holstein, Campus Lu¨beck.

DISCLOSURES

Lange is a Consultant/Advisory Board member (<$10 000) for Medtronic, Edwards, and MDS. G. Ziemer is an expert witness in medical malpractice case (one-quarter year, <$10 000). H.-H. Sievers received honoraria (<$10 000) from the Ross meeting 2009 (Atlanta, GA) and Cryolife.

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Received February 19, 2010; accepted October 19, 2010.
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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.947341/DC1.
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CHAPTER 10

SURVIVAL COMPARISON OF THE ROSS PROCEDURE AND MECHANICAL VALVE REPLACEMENT WITH OPTIMAL SELF-MANAGEMENT ANTICOAGULATION THERAPY: PROPENSITY-MATCHED COHORT STUDY

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Circulation. 2011;123:31-8

DOI: 10.1161/CIRCULATIONAHA.110.947341

Background

It is suggested that in young adults the Ross procedure results in better late patient survival compared with mechanical prosthesis implantation. We performed a propensity score–matched study that assessed late survival in young adult patients after a Ross procedure versus that after mechanical aortic valve replacement with optimal self-management anticoagulation therapy.

Methods and Results

We selected 918 Ross patients and 406 mechanical valve patients 18 to 60 years of age without dissection, aneurysm, or mitral valve replacement who survived an elective procedure (1994 to 2008). With the use of propensity score matching, late survival was compared between the 2 groups. Two hundred fifty-three patients with a mechanical valve (mean follow-up, 6.3 years) could be propensity matched to a Ross patient (mean follow-up, 5.1 years). Mean age of the matched cohort was 47.3 years in the Ross procedure group and 48.0 years in the mechanical valve group (P=0.17); the ratio of male to female patients was 3.2 in the Ross procedure group and 2.7 in the mechanical valve group (P=0.46). Linearized all-cause mortality rate was 0.53% per patient-year in the Ross procedure group compared with 0.30% per patient-year in the mechanical valve group (matched hazard ratio, 1.86; 95% confidence interval, 0.58 to 5.91; P=0.32). Late survival was comparable to that of the general German population.

Conclusions

In comparable patients, there is no late survival difference in the first postoperative decade between the Ross procedure and mechanical aortic valve implantation with optimal anticoagulation self-management. Survival in these selected young adult patients closely resembles that of the general population, possibly as a result of highly specialized anticoagulation self-management, better timing of surgery, and improved patient selection in recent years.

Key Words: aorta • aortic valve • autograft • coagulation • surgery • survival • valves

Survival after aortic valve replacement is reported to be significantly lower compared with the general agematched population, especially in younger adult patients.[1–3] An exception is survival after the Ross procedure, which seems to be comparable to that of the general age-matched population.[4] It remains unclear whether this excellent survival is a consequence of the autograft attributes[5] (living valve with superior hemodynamics and low valve-related event occurrence rates) or the careful selection of patients for the Ross procedure.[6] To obtain an answer to this puzzling question, the method of choice would be a randomized controlled trial. However, few centers are willing to randomize young adult patients among the Ross procedure, a mechanical prosthesis, a stentless bioprosthesis, or a stented bioprosthesis. Most surgeons or young adults have a clear preference for a particular prosthesis in young adult patients, and only a handful of surgeons are experienced with the Ross procedure.

Clinical Perspective on page 174

In the absence of a randomized trial, we performed a propensity score–matched study that assessed late survival in young adult patients after a Ross procedure compared with mechanical aortic valve replacement. Given that optimal postoperative anticoagulation treatment can potentially contribute to a better patient survival, we have included in this study patients with mechanical valves who receive a specialized self-management anticoagulation treatment.

METHODS

Source of Study Data

For this study, we used data from the German-Dutch Ross Registry[7–10] and the Early Self Controlled Anticoagulation Trial-II (ESCAT II) trial.[11,12] The German-Dutch Ross Registry is a prospective multicenter cohort study with 1742 patients. Started in February 1991, the registry includes data from 12 cardiothoracic surgery departments in the Netherlands and Germany[7–10] (see the online-only Data Supplement for a list of participating centers). The ESCAT II trial is a prospective controlled randomized multicenter study. A total of 2162 patients were enrolled in the ESCAT II trial between 1994 and 2002. Follow-up of all patients was assessed for the last time in 2006. Patients were randomized between a conventional group (international normalized ratio [INR] target range, 2.5 to 4.5) and a low-dose group (for aortic valve recipients, the INR target range was 1.8 to 2.8). The Bad Oeynhausen concept of INR self-management consists of a postoperative training, a second training =6 months later, and a 24-hour telemedicine care and consultation. The center provides the patients with an anticoagulation monitor with test strips and lancets. A weekly determination and feedback to the telemedicine center allow sensitive INR adjustment during the long-term anticoagulation therapy. Two large randomized prospective studies have demonstrated that the Bad Oeynhausen concept results in well-trained patients with a high percentage of their measured INR values lying within the predetermined therapeutic range, thus resulting in a low rate of complications such as bleeding and thromboembolism.[11,13] Six different centers across Germany participated in the ESCAT II study.[11,12] We included only patients from the Bad Oeynhausen center (881 patients) because this was the only center that had collected

the detailed patient and perioperative information that we needed for our study. During patient selection for the propensity score analysis, we did not make a distinction between the 2 groups in the ESCAT II trial because there were no differences between the groups that were relevant for this study.[14] The authors had full access to and take full responsibility for the integrity of the data and the present article.

Study Population

Patients with isolated aortic valve pathology who were 18 through 60 years of age at the time of operation and were operated on between 1994 and 2008 were included. Patients who underwent an urgent operation (within 24 hours after admission), patients with an aortic dissection or aortic aneurysm, and those who required concomitant mitral valve replacement were excluded from this study. Concomitant mitral valve reconstruction and concomitant coronary artery bypass graft were not considered exclusion criteria. The remaining study population consisted of 406 patients in the mechanical valve group and 918 patients in the Ross procedure group. The baseline characteristics of this initial cohort are shown in Table 1.

Study Outcomes

The outcome of interest was late mortality (defined as any death occurring >30 days after surgery). The occurrence of events during follow-up and the cause of death were registered and reported according to the guidelines for reporting mortality and morbidity after cardiac valve interventions.[15] Only grade III thromboembolism and grade III bleeding complications were used for the analyses. Briefly, grade III thromboembolism was defined as heart valve prosthesis thrombosis or severe thromboembolism requiring inpatient treatment or causing long-term impairment (including transient ischemic attacks). Grade III bleeding was defined as severe bleeding requiring transfusion, surgical or endoscopic intervention, or inpatient care or causing long-term impairment. Each death and its cause were documented during follow-up.[11]

Propensity Score Construction and Analyses

In our initial cohort, most baseline characteristics were significantly different between the Ross procedure group and the mechanical prosthesis group (Table 1). To achieve a more balanced group, we used propensity score balancing. Propensity score matching offers a way to achieve more balanced groups by matching treatment and control units on the basis of a set of baseline characteristics.[16–18] Before matching the 2 treatment groups, we excluded all hospital mortality. The overall early mortality in the German-Dutch registry was 0.8% (7 deaths). The overall early mortality in mechanical prosthesis group was 0.5% (2 deaths). After exclusion of hospital mortality, the cohort consisted of 918 patients in the Ross procedure group and 406 patients in the mechanical prosthesis group (Figure 1). The propensity score for our combined cohort of 1324 patients (with the Ross procedure or mechanical prosthesis) was constructed with the use of a nonparsimonious multivariable logistic regression model. In the model, the choice of operation (Ross procedure or mechanical prosthesis) was used as the dependent variable, and all statistically significant baseline characteristics displayed in Table 1 except left ventricular end-systolic diameter were included as covariates. Left ventricular end-systolic diameter was

TABLE 1. Baseline Characteristics: Unmatched Cohort

Covariates	Cohort (n=1324)	Mechanical AVR (n=406)	Ross Procedure (n=918)	*P*
Male gender, n (%)	1001 (75.6)	310 (76.4)	691 (75.3)	0.672
Mean age at surgical intervention, y	44.0±11.3	49.5±10.3	41.6±11.0	<0.001
Cause, n (%)				
Rheumatic	60 (4.5)	23 (5.7)	37 (4.0)	0.054
Missing	58 (4.4)	58 (14.3)		
Calcified/degenerative	644 (48.6)	311 (76.6)	333 (36.3)	<0.001
Missing	55 (4.2)	55 (13.5)		
Endocarditis				
Active endocarditis	32 (2.4)	0 (0)	32 (3.5)	<0.001
Hemodynamic manifestation, n (%)				
Stenosis	339 (25.6)	129 (31.8)	210 (22.9)	<0.001
Regurgitation	401 (30.3)	102 (25.1)	299 (32.6)	0.028
Mixed	554 (41.8)	155 (38.2)	399 (43.5)	0.270
Missing	30 (2.3)	20 (4.9)	10 (1.1)	
Preoperative NYHA grade, n (%)				
I/II	813 (61.4)	202 (49.8)	611 (66.6)	<0.001
III/IV	463 (35.0)	191 (47.0)	272 (29.6)	
Missing	48 (3.6)	13 (3.2)	35 (3.8)	
Preoperative creatinine, μmol/L	83.8±60.4	93.6±89.1	76.7±20.9	<0.001
Preoperative rhythm, n (%)				0.003
Sinus	1268 (95.8)	374 (92.1)	894 (97.4)	
Other	24 (1.8)	15 (3.7)	9 (1.0)	
Missing	32 (2.4)	17 (4.2)	15 (1.6)	
Preoperative DM, n (%)	46 (3.5)	20 (4.9)	26 (2.8)	0.055
Preoperative hypertension, n (%)	406 (30.7)	161 (39.7)	245 (26.7)	<0.001
Preoperative lung disease, n (%)	29 (2.2)	7 (1.7)	22 (2.4)	0.441
Preoperative LVEF, %	64.0±12.3	65.3±13.8	63.2±11.2	0.013
Missing	156 (11.8)	24 (5.9)	132 (14.4)	
Preoperative LVH, n (%)	726 (54.8)	354 (87.6)	372 (40.5)	<0.001
Missing	47 (3.5)		47 (5.1)	
Preoperative LVEDD, mm	55.9±10.6	57.2±10.7	55.2±10.4	0.009
Preoperative LVESD, mm	37.1±10.1	39.2±10.4	35.8±9.6	<0.001
Previous cardiac operation, n (%)	88 (6.6)	27 (6.7)	61 (6.6)	0.997
Previous aortic valve operation, n (%)	59 (4.5)	9 (2.2)	50 (5.4)	0.009
Concomitant CABG, n (%)	183 (13.8)	145 (35.7)	38 (4.1)	<0.001
Concomitant MV reconstruction, n (%)	16 (1.2)	0 (0.0)	16 (1.7)	<0.001

AVR indicates aortic valve replacement; NYHA, New York Heart Association; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; CABG, coronary artery bypass grafting; and MV, mitral valve.

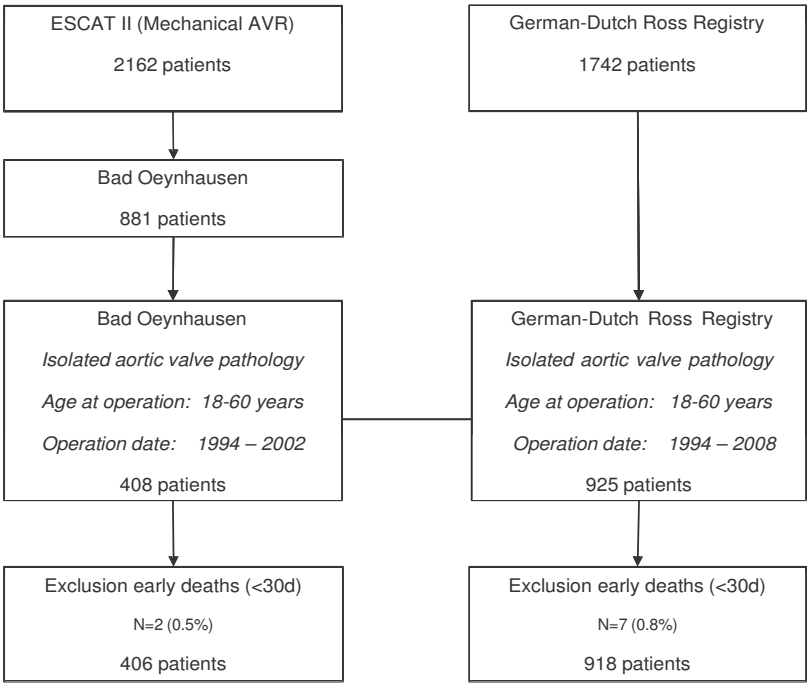

FIGURE 1. *Flowchart of patient selection. AVR indicates aortic valve replacement.*

not included as a covariate in the propensity model because it was highly correlated with left ventricular end-diastolic diameter (Spearman correlation coefficient=0.815).

The propensity score was entered into a Cox proportional hazards model for late mortality, together with the variable Ross procedure versus mechanical prosthesis. Additionally, the patients were matched according to the method of nearest neighbor matching.[19] Patients within the mechanical valve group were assigned a random number. Then, starting with lowest random number, the first patient with a mechanical valve was matched to a Ross patient with the closest propensity score. A propensity score difference of 0.25 was used as a maximum caliper width for matching the 2 treatment groups. If no Ross patients could be found as a match to a patient with a mechanical prosthesis, then this patient with mechanical prosthesis was left unmatched and was not used in subsequent analyses. Ross patients who could be matched to patients with a mechanical prosthesis were no longer considered a possible match for subsequent patients with a mechanical prosthesis. This process was repeated until all possible matches were formed. The baseline characteristics of this final matched cohort are shown in Table 2.

Statistical Analyses

Using survival analysis power calculation (Power and Precision version 2.1), we estimated that =238 patients in each group were needed to reject the null hypothesis that there is no late survival difference between the groups. The required sample size of 238 patients in each

TABLE 2. Baseline Characteristics: Matched Cohort

Covariates	Cohort (n=506)	Mechanical AVR (n=253)	Ross Procedure (n=253)	*P*
Male gender, n (%)	378 (74.7)	185 (73.1)	193 (76.3)	0.461
Mean age at surgical intervention, y	47.6±9.8	48.0±11.0	47.3±8.5	0.169
Cause, n (%)				
Rheumatic	34 (6.7)	17 (6.7)	17 (6.7)	0.571
Missing	33 (6.5)	33 (13.0)		
Calcified/degenerative	403 (79.6)	188 (74.3)	215 (85.0)	>0.99
Missing	30 (5.9)	30 (11.9)		
Endocarditis, n (%)				
Active endocarditis	0 (0.0)	0 (0)	0 (0.0%)	. . .
Hemodynamic manifestation, n (%)				
Stenosis	164 (32.4)	82 (32.4)	80 (31.6)	0.769
Regurgitation	90 (17.8)	44 (17.4)	47 (18.6)	0.724
Mixed	237 (46.8)	112 (44.3)	126 (49.8)	0.516
Missing	15 (3.0)	15 (5.9%)		
Preoperative NYHA grade, n (%)				0.497
I/II	297 (58.7)	145 (57.3)	152 (60.1)	
III/IV	185 (36.6)	95 (37.5)	90 (35.6)	
Missing	24 (4.7)	13 (5.1)	11 (4.3)	
Preoperative creatinine, μmol/L	82.2±22.8	82.9±16.9	80.7±31.6	0.206
Preoperative rhythm, n (%)				0.508
Sinus	480 (94.9)	232 (91.7)	248 (98.0)	
Other	9 (1.8)	6 (2.4)	3 (1.2)	
Missing	17 (3.4)	15 (5.9)	2 (0.8)	
Preoperative DM, n (%)	20 (4.0)	9 (3.6)	11 (4.3)	0.824
Preoperative hypertension, n (%)	166 (32.8)	86 (34.0)	80 (31.6)	0.645
Preoperative lung disease, n (%)	14 (2.8)	5 (2.0)	9 (3.6)	0.424
Preoperative LVEF, %	64.8±12.9	65.6±14.2	64.0±11.2	0.169
Missing	48 (9.5)	22 (8.7)	26 (10.3)	
Preoperative LVH, n (%)	382 (75.5)	194 (76.7)	188 (74.3)	0.807
Missing	5 (1.0)		5 (2.0)	
Preoperative LVEDD, mm	55.3±10.1	55.7±10.2	54.8±10.2	0.386
Preoperative LVESD, mm	36.5±8.7	36.7±8.8	36.3±8.6	0.745
Previous cardiac operation, n (%)	16 (3.2)	10 (4.0)	6 (2.4)	0.454
Previous aortic valve operation, n (%)	9 (1.8)	5 (2.0)	4 (1.6)	>0.99
Concomitant CABG, n (%)	67 (13.2)	36 (14.2)	31 (12.3)	0.542
Concomitant MV reconstruction, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	. . .

Abbreviations as in Table 1.

treatment group was based on the use of a 2-tailed value of P=0.05 to indicate statistical significance for late survival with a minimum power of 0.80. We assumed a late mortality rate of 0.45%/y for patients with the Ross procedure[20] and of 1.40%/y for patients with a mechanical prosthesis[6] with a study duration of 14 years (1994 to 2008) and a constant accrual of patients.

Continuous data are presented as means (SD and range), and comparison in the unmatched cohort was done with the unpaired t test unless the data were not normally distributed (KolmogorovSmirnov test); in these instances, we used the Mann-Whitney U test for comparison. Categorical data are presented as proportions, and comparison in the unmatched cohort was done with the x test or the Fisher exact test when appropriate. All tests were 2 sided with an CY level of 0.05. Comparison in the matched cohort was done with the McNemar test and paired sample t test or Wilcoxon signed-rank test when appropriate. A Cox regression model, taking pair into account (by correcting the SEs), has been used to compare survival between the different surgical techniques. The Cox proportional hazards model was also used for univariate and multivariate analyses of late survival. Comparison of patient survival with the general ageand gender-matched population was done with the German population life tables.[21] All statistical tests were 2 sided, and tests with a value of P<0.05 were considered significant. Survival comparison of the matched cohort was done with R statistical software (R, version 2.11.1, 2010; R Development Core Team 2006, R Foundation for Statistical Computing, Vienna, Austria). All other statistical analyses were done with SPSS for Windows, version 15 (SPSS Inc, Chicago, IL).

RESULTS

Outcomes in the Unmatched Cohort

In the initial unmatched cohort of 1324 patients, 36 late deaths occurred during a follow-up of 8066 patient-years (0.45% per patient-year). Late mortality occurred in 0.49% per patient-year (n=27) in the Ross procedure group compared with 0.32% per patient-year (n=9) in the mechanical prosthesis group (unmatched hazard ratio, 1.33; 95% confidence interval, 0.61 to 2.91; P=0.47; Table 3). Addition of the propensity score to the Cox regression model resulted in a propensity-matched hazard ratio of 3.64 (95% confidence interval, 1.22 to 10.88). Exploration of the propensity score distribution of the 2 treatment groups revealed extreme skewness of the propensity score of Ross patients.

Outcomes in the Propensity Score–Matched Cohort

Direct matching of patients according to propensity score resulted in a cohort that consisted of 253 patients in the Ross procedure group (mean follow-up time, 5.1 years) and of 253 patients in the mechanical valve group (mean follow-up time, 6.3 years). The baseline characteristics of this final matched cohort are shown in Table 2. Absolute standardized differences for all measured covariates were <10%, suggesting substantial covariate balance across the groups (Figure 2).[22]

TABLE 3. Association of Procedure With Late Mortality

	Mechanical Valve	Ross Procedure	Hazard Ratio (95% Confidence Interval)	*P*
Before matching, n	406	918		
All-cause mortality	9/2574	27/5492	1.33 (0.61–2.91)	0.47
Valve-related mortality	0	13/5492		
Non–valve-related cardiac mortality	6/2574	6/5492		
Non–valve-related noncardiac mortality	1/2574	7/5492		
Unknown	2/2574	1/5492		
After matching, n	253	253		
All-cause mortality	5/1682	7/1310	1.86 (0.58–5.91)	0.29
Valve-related mortality	0	4/1310		
Non–valve-related cardiac mortality	3/1682	1/1310		
Non–valve-related noncardiac mortality	1/1682	2/1310		
Unknown	1/1682	0		

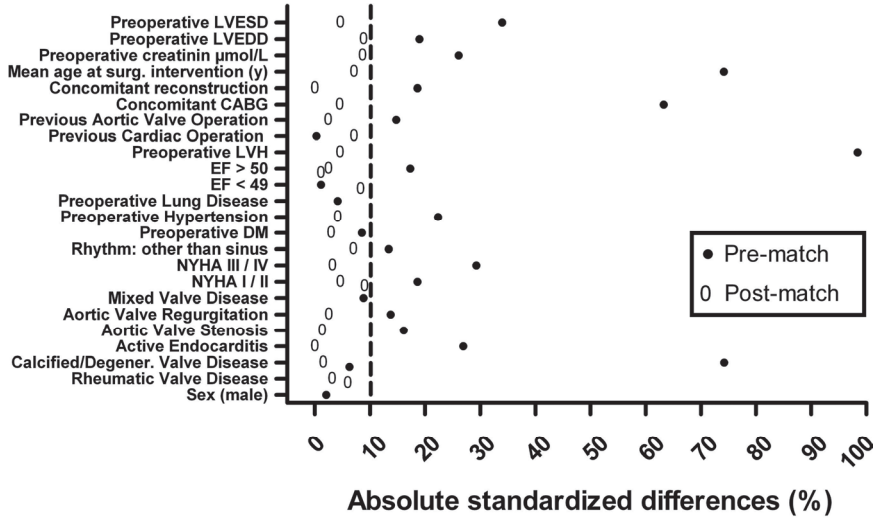

FIGURE 2. *Love plots for absolute standardized differences for baseline covariates between patients with mechanical valve and patients with the Ross procedure, before and after propensity score matching. DM indicates diabetes mellitus; EF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; MV, mitral valve; and LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVH, left ventricular hypertrophy; and NYHA, New York Heart Association.*

In the cohort of 253 matched pairs, during 2899 patient-years of follow-up, 12 participants (2.4%) died (Table 3). Valverelated mortality was observed only in patients who underwent a Ross procedure. The 4 valve-related deaths were 2 sudden, unexplained, unexpected deaths without further clinical data or autopsy, 1 death resulting from a coronary embolus and subsequent myocardial infarction, and 1 death resulting from stroke. During follow-up, 8 Ross patients in the matched cohort required an aortic valve replacement. None of the patients with a mechanical valve required reoperation in the matched cohort. Linearized all-cause reoperation rate was 0.61% per patient-year in the Ross procedure group compared with 0.00% per patient-year in the mechanical valve group (P=0.01). Two bleeding events were observed in the matched cohort of Ross patients, and 6 bleeding events were observed in the matched cohort of the patients with a mechanical valve. The linearized bleeding rate was 0.15% per patient-year in the Ross procedure group compared with 0.36% per patient-year in the mechanical valve group (P=0.15). During follow-up, 5 Ross patients and 1 patient with a mechanical valve experienced a thromboembolic event. The linearized thromboembolism rate was 0.38% per patient-year in the Ross procedure group compared with 0.06% per patient-year in the mechanical valve group (P=0.10). Endocarditis was diagnosed in 2 patients who underwent a Ross procedure and in none of the patients who underwent a mechanical aortic valve replacement. The linearized endocarditis rate was 0.15% per patient-year in the Ross procedure group compared with 0.00% per patient-year in the mechanical valve group (P=0.16). All-cause mortality occurred in 0.54% per patient-year (n=7) in the Ross procedure group compared with 0.31% per patientyear (n=5) in the mechanical prosthesis group (matched hazard ratio, 1.86; 95% confidence interval, 0.58 to 5.91; P=0.32; Table 3). Cumulative survival is displayed in Figure 3. Ageand gender-matched late survival for young adult patients after aortic valve replacement was comparable to that of the general German population (96% versus 95% at 8 years).

DISCUSSION

Our study results suggest that survival of mechanical valve patients with highly specialized anticoagulation selfmanagement is comparable to that of Ross patients. It also illustrates the vast differences in patient characteristics between the 2 patient groups. Finally, the present study shows that late survival after both the Ross procedure and mechanical prosthesis implantation is excellent and comparable to that of the general population.

The choice for particular valve prosthesis for aortic valve replacement in young adults has an important impact on the lives of these patients. Both the Ross procedure and mechanical prosthesis implantation have important advantages and disadvantages. Because of the increased thrombogenicity of mechanical prostheses, the choice for this valve substitute implies lifelong anticoagulation and is associated with an increased risk for thromboembolic and bleeding events. The use of anticoagulation may also complicate pregnancy because of the fetal and maternal complications of taking warfarin[23,24] and may require lifestyle adjustments in this relatively young and active patient group. The clinical association between microemboli, generated by mechanical valves, and neurocognitive dysfunction is still a source of controversy.[25,26]

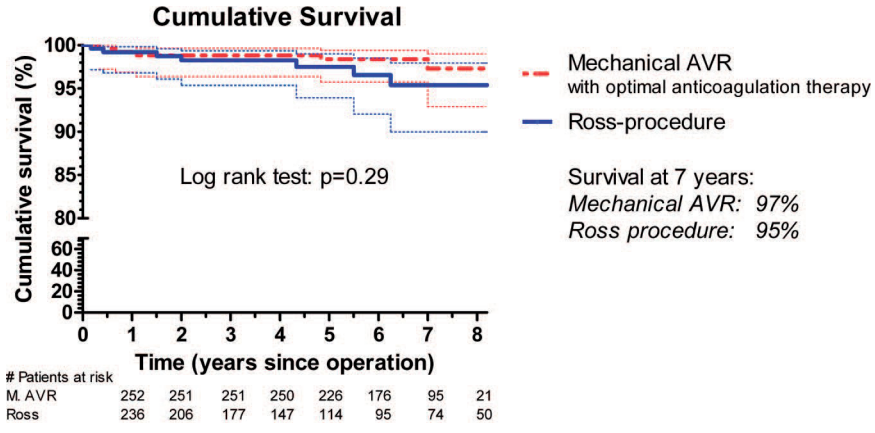

FIGURE 3. *Kaplan-Meier plot for all-cause mortality by procedure (Ross procedure vs mechanical valve replacement with optimal self-management anticoagulation therapy). AVR indicates aortic valve replacement.*

Furthermore, compared with autograft valves, the hemodynamic performance of mechanical valves is less favorable,[27] and mechanical valve noise can negatively affect the patient's quality of life.[28] The advantage of a mechanical prosthesis is the excellent durability and low reoperative hazard. The choice for a Ross procedure, on the other hand, would mean a limited durability of the aortic valve autograft and pulmonary valve allograft and implies a certain risk of reoperation during the patient's life, depending on the technique used and the follow-up time. The advantages of the Ross procedure are the superior hemodynamic performance, low valve-related event occurrence rates, and no need for lifelong anticoagulation.[29]

Surprisingly, we found not only that there was no survival advantage for the Ross procedure over the use of mechanical prosthesis with optimal anticoagulation self-management but also that there was even a tendency toward a survival advantage in patients who received a mechanical prosthesis. Of course, given the few late deaths in these series, this observation should be interpreted cautiously, and a hazard ratio up to 5.91 cannot be excluded.

Possible explanations for our findings include the highly specialized anticoagulation self-management treatment that patients receive in Bad Oeynhausen and the advances in recent years in the selection and timing of treatment in this young adult patient group. To receive anticoagulation selfmanagement treatment, mechanical valve patients have to be psychically and mentally able to attend the anticoagulation self-management training session and able to control their INR. Theoretically, this may have caused selection bias, although the effect of such bias is expected to be very small in the present study because we have included only patients between the age of 18 and 60 years. It should be stated explicitly that our study results cannot automatically be generalized to all mechanical valve recipients. In the unmatched subset of ESCAT II patients from Bad Oeynhausen, mortality is lower than mortality in the entire ESCAT II cohort (linearized occurrence rate, 2.90 per year).[14] This suggests that the innovative postoperative management of patients in Bad Oeynhausen is extraordinarily effective in terms of complication and survival rates.

Of note, in the mechanical prosthesis group, none of the late deaths were valve related, whereas 4 (2 valve related with acute myocardial infarction and stroke, 2 unknown but attributed to valve related according to the guidelines) of the 7 late deaths in the Ross group were. This observation suggests that the optimized anticoagulation self-management treatment that mechanical prosthesis patients receive in Bad Oeynhausen has resulted in a minimization of thromboembolic and bleeding events and decreased valve-related mortality compared with older reports.[30] The definition of previous cured endocarditis differed between the mechanical prosthesis cohort and the Ross patient cohort. In the cohort of patients with a mechanical prosthesis, the pathologist classified in explanted valves any sign of inflammation that might indicate previous endocarditis as cured endocarditis (71% of explanted valves). In the cohort of Ross patients, only those who experienced clinically manifest endocarditis were classified as having cured endo carditis (12% of the patients). Because of this significant discrepancy in the definitions of previous cured endocarditis between the cohorts, we decided not to include this variable in the analyses of the present study.

Without the use of an additional statistical strategy to achieve more comparable treatment groups, it was not possible to compare late survival between young adults undergoing a Ross procedure and young adults receiving a mechanical prosthesis. Ross patients, for example, were on average 7 years younger, more often had aortic valve stenosis, and were in better physical condition than patients who received a mechanical prosthesis. Patients who received a mechanical prosthesis more often had diabetes, hypertension, and, besides aortic valve disease, other cardiac conditions requiring concomitant cardiac surgery. All these differences have an important impact on late survival in these patient groups.[31–33] The fact that only 253 of 406 mechanical valve patients (62%) could be matched to a Ross patient illustrates that there is strict selection of patients for these 2 treatment options. This is also reflected by the distribution differences of propensity score between the 2 groups.

It is remarkable that for the duration of the follow-up period, survival after aortic valve replacement was comparable to that of the age-matched German population in both Ross patients and mechanical prosthesis patients. This observation supports the hypothesis that late mortality after aortic valve replacement is driven mainly by patient characteristics and that prosthesis selection plays only a minor role, if any. This observation implies that in patients who are good candidates for both a Ross procedure and mechanical aortic valve replacement, the choice for a particular treatment strategy should be determined by patient preferences. One patient's unacceptable risk may be another patient's acceptable risk; for some, a reoperation in the distant future may be more acceptable than the limitations and risks imposed by anticoagulant treatment, whereas others prefer the opposite. With the ongoing improvement in the current anticoagulant treatment and the introduction of novel anticoagulant drugs, the rates of bleeding and thromboembolic events may decrease further.[14,34] As a consequence, in the future, patient preference may more often shift toward a mechanical valve. Of course, it needs to be taken into account that the results from the present study apply only to the first postoperative decade. The effect on late survival of the increasing reoperative hazard for the Ross procedure in the second postoperative decade still needs to be determined.

Limitations

This study was performed in the setting of elective European patients without aortic dissection, aortic aneurysm, and concomitant mitral valve replacement. It is possible that some baseline differences between the groups were not taken into account (and thus are not included in the propensity score). Because the 2 treatment groups were treated in different centers, the possible existence of "center effect" cannot be ruled out. However, the purpose of this study was to compare these 2 patient populations in the setting of optimal treatment, and we managed to obtain and use data from very dedicated centers. Although the power calculation was based on literature, it might have been too optimistic because we have observed fewer deaths than expected. An additional limitation is that mechanical valves are from a single center, whereas the Ross patients were from several centers. Finally, the generalizability of our study results requires further investigation.

Conclusions

In comparable patients, there appears to be no late survival advantage in the first postoperative decade for the Ross procedure over mechanical aortic valve implantation with highly specialized anticoagulation self-management treatment. In contrast to older reports, relative survival in these selected young adult patients closely resembles that of the general population, possibly a result of highly specialized self-management anticoagulation treatment, better timing of surgery, and improved patient selection in more recent years. Careful prosthetic valve selection remains an important issue to ensure optimal patient-tailored quality of life.

ACKNOWLEDGMENTS

We thank Tanja Feige (Heart and Diabetes Center North Rhine– Westphalia, Department of Thoracic and Cardiovascular Surgery, Bad Oeynhausen, Germany) and Katrin Meyer (University of Luebeck, Department of Cardiac and Thoracic Vascular Surgery, Luebeck, Germany) for their support in data collection and data management.

SOURCE OF FUNDING

Mokhles is funded by a Mosaic grant from the Netherlands Organisation for Scientific Research (NWO 017.006.058).

DISCLOSURES

Hans-Hinrich Sievers received a honoraria payment at Cryolife Symposium. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Survival in young adult patients after mechanical aortic valve replacement is reported to be significantly reduced compared with the general ageand gender-matched population, whereas survival after the Ross procedure is excellent and comparable to that in the general population. There is ongoing debate about whether the excellent survival rates observed in Ross patients are a consequence of a hemodynamically superior valve and low valve-related complication rates or of patient selection. This is the first study to compare survival in young adult patients after mechanical aortic valve replacement and the Ross procedure using propensity score matching. In comparable patients, there was no late survival advantage in the first postoperative decade for the Ross procedure over mechanical aortic valve implantation with optimal anticoagulation self-management. In contrast to older reports, the relative survival in these selected young adult patients closely resembles that of the general population, possibly a result of better timing of surgery, improved patient selection, and highly specialized self-management anticoagulation treatment in more recent years. In the absence of late mortality differences between comparable patients who received either a mechanical prosthesis or the Ross procedure, the weight of the prosthetic valve selection decision making process shifts toward quality of life and patient preference. Clinicians are therefore encouraged to systematically elicit patient preferences when discussing prosthetic valve selection in this young adult population.

Additional material is published online only. To view please visit the journal online
(http://dx.doi.org/10.1136/ heartjnl-2013-304425).
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CHAPTER 11

THE FATE OF PULMONARY CONDUIT AFTER THE ROSS OPERATION: LONGITUDINAL ANALYSIS OF THE GERMAN-DUTCH ROSS REGISTRY EXPERIENCE

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Heart doi:10.1136/heartjnl-2013-304425

ABSTRACT

Objective

To assess allograft function over time after the Ross procedure.

Design

Prospective multicentre registry.

Setting

10 cardiac surgery departments in Germany and the Netherlands.

Patients

Among 1775 consecutive adult patients (mean age 43.7±12.0) who underwent the Ross procedure, 1645 (93%) received an allograft (pulmonary=1612, aortic=12, unknown=21), 120 (6%) a bioprosthesis, and 5 (0.3%) a bovine jugular vein for right ventricular outflow tract reconstruction.

Intervention

Ross procedure.

Main outcome measures

Using non-linear longitudinal models, serial echocardiographic records (N=6950) were studied to assess pulmonary conduit function over time in patients who had undergone the Ross procedure, with a maximum echocardiographic follow-up of 22.4 years (5.5±4.3 years).

Results

A slight increase in pulmonary conduit regurgitation grade was observed during follow-up. Freedom from regurgitation grade ≥2+ was 95% after 14 years. Female patient gender, allograft use (compared to bioprosthesis), male donor gender, antibiotic treatment of the allograft, and specific surgical adjustments were associated with a significantly higher regurgitation grade. Mean conduit gradient increased from 4.7 mm Hg at 1 month to 10 mm Hg by 14 years, while peak gradient increased from 8.4 to 18.5 mm Hg. Smaller conduit diameter, male patient gender, younger patient age, younger donor age, and use of a bioprosthesis were associated with a significantly higher mean and peak gradient. During follow-up, 76 reinterventions were required on the pulmonary conduit in 67 patients. Freedom from pulmonary conduit reintervention or dysfunction was 90.6% (95% CI 87.7% to 93.6%) and 79.5% (95% CI 75.2% to 84.0%) at 15 years, respectively.

Conclusions

Echocardiographic follow-up of pulmonary conduits shows good conduit durability. Clinically important conduit regurgitation and stenosis are rare in adult patients after the Ross operation.

INTRODUCTION

Although initially there was concern about the outcome of the Ross procedure, several short and mid term studies have proven that the procedure can be performed with low operative risk and with survival rates comparable to the general population.[1–4] The need for specific surgical expertise to perform this complex operation and concerns about early and late failure led to its limited usage.[3] With growing experience, however, the advantages of the Ross procedure have become more fully appreciated.

The long term fate of the pulmonary conduit is largely unknown but it is crucial for a more comprehensive judgment of this operation to be made. This is because this procedure results in the treatment of a single aortic valve disease with a twovalve procedure, subsequently placing two valves at risk of failure. In this regard, it is essential to understand how the pulmonary conduits in Ross patients function over time and to determine the factors associated with poor conduit performance. This knowledge can potentially lead to better patient management and improved outcomes in these young adult patients.

The durability of the pulmonary autograft depends on an appropriate surgical technique applied systematically and tailored to the individual patient.[5–8] The long term durability of the reconstructed right ventricular outflow tract (RVOT) is predominantly related to non-surgical factors including degenerative processes.

The prevalence and predictors of late pulmonary conduit failure after the Ross procedure in adults have been addressed in only a few reports with small patient numbers.[3 9–11] The natural dynamics of conduit stenosis and/or regurgitation are poorly understood. In the present multicentre study the availability of large numbers of patients and systematically collected echocardiographic records, and the use of sophisticated statistical methods, offer the unique opportunity to study extensively pulmonary conduit function over time in Ross patients and to explore potential risk factors associated with poor performance of the pulmonary conduits. Therefore, the objective of this study was to assess allograft function over time after the Ross procedure.

METHODS

Study population

Data from 2038 patients who underwent a Ross procedure between November 1988 and September 2011 were collected and analysed from the German-Dutch Ross Registry database. All patients aged ≥16 years (n=1775) were entered into the study. Baseline characteristics are shown in table 1. The prospective registry was started in January 2002 and includes patient data from 10 cardiac surgery departments in Germany and the Netherlands.

Institutional review board approval was obtained to conduct this prospective follow-up study in each participating centre (clinical trial ID NCT 00708409).

Surgical technique

The surgical technique was determined by the surgeon responsible at each centre. Details of the operative technique have been described elsewhere.[6 7] Perioperative and pulmonary

TABLE 1. Baseline patient characteristics

	Patient cohort (n=1775)	
Characteristic	**Data available n (%)***	**No. (%) or mean±SD**
Demography		
Age (years)	1775 (100)	43.7±12
Height	1698 (96)	175±9.42
Weight	1698 (96)	78.2±14.5
Gender	1775 (100)	
Male		1326 (75)
Female		449 (25)
Symptoms		
NYHA functional class	1657 (93)	
I		453 (27)
II		744 (45)
III		406 (25)
IV		54 (3.3)
Ventilation support	1775 (100)	2 (0.11)
Predominant aortic haemodynamics	1775 (100)	
Regurgitation		430 (24)
Stenosis		411 (23)
Combined		898 (51)
Other		36 (2)
Aortic valve type	1775 (100)	
Bicuspid		1116 (63)
Tricuspid		411 (23)
Other		159 (9)
Unknown		89 (5)
Timing of surgery	1775 (100)	
Surgery within 24 h		32 (1.8)
Elective surgery		1739 (98)
Cardiac comorbidity		
History of angina	1696 (96)	411 (24)
Preoperative coronary artery disease	1775 (100)	57 (3.2)
Previous heart operations (eg, aortic valve and arch surgery, VSD repair)	1775 (100)	161 (9.1)
Rhythm	1775 (100)	
Sinus rhythm		1753 (99)
Atrial fibrillation		16 (0.9)
Other (eg, heart block, pacemaker)		6 (0.34)

TABLE 1. Baseline patient characteristics (*continued*)

	Patient cohort (n=1775)	
Characteristic	**Data available n (%)***	**No. (%) or mean±SD**
Left ventricular function	1189 (67)	
EF ≥50%		1051 (88)
EF 26–49%		134 (11)
EF ≤25%		4 (0.34)
EF (continuous, %)	1276 (72)	63.5±11.3

*Number of patients from whom data are available.
EF, ejection fraction; NYHA, New York Heart Association; VSD, ventricular septal defect.

conduit characteristics are shown in table 2. The presence of allograft sclerosis or fibrosis were determined by the tissue bank (pathology finding) during the harvesting and treatment of the homograft (the large majority) or as noted by the surgeon intraoperatively (minority). Of the implanted allografts, approximately 1.5% of fresh pulmonary allografts and approximately 15% of cryopreserved allografts received antibiotic treatment.

Although five percutaneous pulmonary valve implantations were performed during the follow-up of our patient population, the long term results of the Melody valve in adults are unknown at this moment and there is some reservation regarding the use of Melody valves in adults. Currently, we reserve the percutaneous pulmonary valve implantations for older and sick patients. For young adults, homograft is still the procedure of choice.

Clinical follow-up and echocardiographic data acquisition and measurements

Follow-up investigations were scheduled at discharge and on a yearly basis thereafter.

Conduit regurgitation was graded by mapping the dimensions of the regurgitation jet with pulsed and colour flow Doppler echocardiography, analogous to the semiquantitative method described by Perry and colleagues.[12] The width of the proximal pulmonary regurgitation jet and the density and deceleration rate of the spectral Doppler flow signal were included in the assessment of regurgitation severity. This was graded from 0 to 4 (0 none, 1 mild, 2 moderate, 3 moderate-to-severe, 4 severe).

Additionally, trace (trivial) insufficiency—defined as a very small regurgitation jet in early diastole near the detection limit—was included in the analyses as grade 0.5. Because of the low frequency of patients in grade 4 (n=7), this grade was combined with grade 3 and treated as one category. Because this is a multicentre study, the final decision regarding regurgitation grading was left to the attending echocardiographer. Maximum velocities across the pulmonary conduit were obtained by continuous Doppler in the basal short axis. Pressure gradients across the RVOT were calculated by the modified Bernoulli equation.

The prospective echocardiographic database was frozen on 1 November 2011, and echocardiographic data on all patients aged ≥16 years at the time of the Ross procedure were extracted (n=1775, mean age 43.7±12.0, range 16.1–70.5 years). Based on the distribution of

the echocardiographic measurements, we could reliably assess overall temporal trend up to 14 years postoperatively.

For the analysis of 'hard' clinical end points (eg, death and reoperation), all consecutive patients were included in the study. However, there were also patients in whom no echocardiographic follow-up was available due to several reasons (eg, did not reach 12 months postoperative follow-up at the time the database was frozen). These patients were, therefore, not included in the echocardiographic analyses. For the echo analyses, only patients with at least one echocardiographic follow-up were included. A total of 6950 standardised echocardiographic measurements were analysed. The mean echocardiographic follow-up duration was 5.5 years (median 4.8 years, SD 4.25, range 0–22.4 years). At least one echocardiographic follow-up was obtained in 93.5% of patients (166 patients did not have any follow-up due to various reasons, eg, did not reach 12 months postoperative follow-up at the time the database was frozen, lost to follow-up).

The mean clinical follow-up duration was 7.2 years (median 6.7 years, SD 4.6, range 0–22.4 years).

Valve related events were defined according to the guidelines for reporting morbidity and mortality after cardiac valvular operations.[13] Any degeneration of function not attributable to the valve leaflets (eg, the valve leaflets being intact) was considered as non-structural dysfunction (eg, regurgitation due to dilatation), whereas dysfunction due to leaflet degeneration was considered as structural valve failure (eg, retraction, calcification). Reconstruction was defined as the restoration of valve function without the exchange of the valve (or implantation of a new one)—that is, valve repair.

Statistical analyses

Simple descriptive statistics were used to summarise the data. Continuous variables are presented as mean±SD. Categorical data are described using frequencies and percentages. Parametric estimates of the postoperative echo derivatives are accompanied by an asymmetric 95% confidence interval (CI), comparable to ±2 SE. The CI is obtained by the bootstrap percentile method.[14]

Analyses of clinical data

Actuarial estimates of freedom from conduit reintervention and conduit failure were accomplished using Kaplan-Meier methods (SPSS V.11.0 for Windows, SPSS Inc, Chicago, Illinois, USA). The indications for reintervention were clinically overt right heart failure, medically intractable infective endocarditis, or maximal pressure gradients across the RVOT of one half of the systemic systolic pressure even in asymptomatic patients but with right ventricular hypertrophy and dilatation. Conduit dysfunction was defined as conduit reintervention, mean pressure gradient ≥25 mm Hg or regurgitation grade III or IV. This composite end point takes into consideration patients who have developed significant allograft dysfunction but for various reasons have not yet undergone reoperation by the database closure date. This end point better reflects the true incidence of significant and clinically relevant allograft dysfunction.

TABLE 2. Perioperative characteristics

	Patient cohort (n=1775)	
Characteristic	**Data available n (%)***	**No. (%) or mean±SD**
Type of conduit implanted	1770 (99.7)	
Allograft		1645 (93)
Bioprosthesis		120 (6.8)
Bovine vein		5 (0.28)
Conduit diameter (mm)	1700 (96)	26±2.15
Allograft properties (n=1645)		
Female gender donor allograft	1301 (79.0)	440 (34)
Age donor allograft	1275 (77.5)	45.9±12.2
Presence of sclerosis or fibrosis donor allograft	1645 (100)	338 (20.5)
Presence of fenestrations donor allograft	1645 (100)	298 (18.1)
Cryopreserved donor allograft	1645 (100)	1411 (85.8)
Antibiotic treatment of donor allograft	1645 (100)	216 (13.1)
Donor allograft length†	1583 (96.2)	
Short		779 (47.4)
Long		804 (48.9)
Type of allograft implanted	1624 (98.7)	
Pulmonary allograft		1612 (98.0)
Aortic allograft		12 (0.7)
Procedure		
Perfusion time	1583 (89)	191±45.7
Cross clamp time	1595 (90)	151±35.2
Circulatory arrest	82 (100)	17.5±8.83
Concomitant procedures		
CABG	1775 (100)	100 (5.6)
Mitral valve surgery	1775 (100)	52 (2.9)
Tricuspid valve surgery	1775 (100)	3 (0.17)
Ascending aorta and/or arch reconstruction	1775 (100)	601 (34)
Specific surgical adjustments of the allograft‡	1775 (100)	215 (12)

*Number of patients from whom data are available.
†Distance between pulmonary artery bifurcation resection line and sinutubular junction of the pulmonary valve ≤20 mm (short) or >20 mm (long).
‡Resection of the allograft's subvalvular muscle with or without replacement with a stripe of pericardium, GoreTex membrane, or Dacron prosthesis.
CABG, coronary artery bypass grafting.

Analyses of echocardiographic data

Categorical echocardiographic measurement

To assess the temporal trend of likelihood of conduit regurgitation grades over time after surgery, follow-up transthoracic echocardiograms were analysed longitudinally for change in percentages of patients in each aortic regurgitation grade across time.

Continuous echocardiographic measurement

To assess the temporal trend of mean conduit gradient and peak conduit gradient over time after surgery, follow-up transthoracic echocardiographic measurements were analysed longitudinally for change in mean response across time.[15] A non-linear longitudinal mixed model regression[16 17] (SAS PROC NLMIXED) was used to analyse these continuous repeated measurements.

A focused unadjusted analysis (two separate analyses) was performed to assess the association between the postoperative mean and peak gradients, and pulmonary valve regurgitation. In the cumulative logistic mixed effects model for pulmonary valve regurgitation, we treated postoperative mean and peak gradients as the time varying covariates and assessed the effect of these gradients on the likelihood of higher pulmonary valve regurgitation grades.

Variable selection and risk factor analyses

Patient characteristics, conduit properties, and procedure related variables that are shown in tables 1 and 2 (and various transformations of these variables) were screened for association with postoperative conduit regurgitation, mean conduit gradient, and peak conduit gradient. In addition, year of surgery and recipient–donor blood group mismatch were also included in the model as a potential risk factor.

Variable selection utilised bootstrap bagging (bootstrap aggregation).[16-18] The purpose behind the use of bootstrapping is simply to test the reliability of p values that are generated via statistical models. If bootstrap reliability of a variable is, for example, calculated as 30%, then—even though the p value is significant— it is judged to be significant in only ~30% of datasets pertaining to the Ross operation. Our over-arching aim is to be as conservative as possible when reporting significant variables.

A detailed description of the statistical analyses can be found in the online supplementary appendix. All statistical tests with a p value of 0.05 or lower were considered significant. The longitudinal analyses of echocardiographic data were performed using SAS V.9.1 (SAS, Cary, North Carolina, USA).

RESULTS

Reinterventions on the pulmonary conduit

During follow-up, 76 reinterventions (56 explants, 20 reconstructions) were required on the pulmonary conduit in 67 patients. Mean time to reintervention was 5.6±4.5 years (range 0.1–16.7 years). Structural valve failure was present in 53 reinterventions and non-structural failure in seven reinterventions. Pulmonary conduit endocarditis was present in 16

reinterventions. Freedom from pulmonary conduit reintervention was 99.4% at 1 year (95% CI 99.1% to 99.8%), 94.7% at 10 years (95% CI 93.3% to 96.2%), and 90.6% at 15 years (95% CI 87.7% to 93.6%). Freedom from pulmonary conduit dysfunction (defined as conduit intervention or regurgitation >2 or mean gradient >25) was 98.5% at 1 year (95% CI 97.9% to 99.1%), 88.5% at 10 years (95% CI 86.4% to 90.6%), and 79.5% at 15 years (95% CI 75.2% to 84.0%).

With regard to allografts, during follow-up 63 reinterventions (48 explants, 15 reconstructions) were required on the pulmonary conduit in 54 patients. Mean time to reintervention was 6.9 ±4.5 years (range 0.04–16.3 years). Structural valve failure was present in 43 reinterventions and non-structural failure in six reinterventions. Pulmonary conduit endocarditis was present in 14 reinterventions. The mean time for endocarditis incidence was 6.3 years (SD 4.5, range 0.06–16.25). Freedom from pulmonary conduit reintervention was 99.5% at 1 year (95% CI 99.2% to 99.9%), 95.5% at 10 years (95% CI 94.1% to 97.0%), and 91.4% at 15 years (95% CI 88.5% to 94.3%).

Freedom from pulmonary conduit failure was 98.4% at 1 year (95% CI 97.8% to 99.0%), 88.4% at 10 years (95% CI 86.4% to 90.5%), and 78.1% at 15 years (95% CI 74.6% to 83.1%). With regard to bioprostheses, during follow-up 13 reinterventions (eight explants, five reconstructions/dilatation) were required on the pulmonary conduit in 13 patients. Mean time to reintervention was 1.8±0.9 years (range 0.17–3.4 years). Structural valve failure was present in 10 reinterventions and non-structural failure in one reintervention. Pulmonary conduit endocarditis was present in two reinterventions. In patients with bioprostheses freedom from reintervention was 98.2% at 1 year (95% CI 95.8% to 100.0%) and 85.4% at 10 years (95% CI 78.0% to 93.6%).

Freedom from dysfunction was 91.4% at 1 year (95% CI 86.8% to 96.2%) and 66.8% at 5 years (95% CI 55.3 to 80.6).

The clinical outcomes of these patients and reinterventions have been extensively presented in previous publications of the Registry.[19–24]

Pulmonary conduit regurgitation over time

The percentage of patients in each grade of pulmonary conduit regurgitation changed significantly over time (p=0.003). During follow-up, the percentage of patients with pulmonary conduit regurgitation grade 0 or trace decreased from about 88% at 1 month to about 66% by 14 years after the procedure. The percentage of patients with grade 1+ increased from about 11% to about 29% during the same time period. The percentage of patients with grade 2+ or higher increased from about 1.1% to about 4.7% during the same time period.

The temporal trend of pulmonary regurgitation over time is non-linear. There is an early hazard phase evident within the initial 2 years; beyond that, the risk is relatively constant and low (figure 1A).

The risk factors associated with a greater risk of higher pulmonary conduit regurgitation grade are shown in table 3. Overall, female patient gender was associated with a significantly greater risk of higher pulmonary conduit regurgitation grade compared to males (p<0.001). Furthermore, with respect to allograft properties, antibiotic treatment of the allograft (p<0.001) and male donor gender (p=0.032) were associated with a higher risk of higher

pulmonary conduit regurgitation grade. In addition, the use of an allograft (as compared to a bioprosthesis) was correlated with a significantly higher grade of pulmonary conduit regurgitation grade during follow-up of Ross patients ($p<0.001$). Specific surgical adjustments of the allograft (resection of the allograft's subvalvular muscle with or without replacement with a stripe of pericardium, GoreTex membrane, or Dacron prosthesis) were associated with a significantly higher regurgitation grade ($p<0.001$) (figure 1B).

The presence of allograft sclerosis or fibrosis appeared to be associated with a lower pulmonary conduit regurgitation grade ($p<0.001$). However, this effect was only significant in the first 2 years after the Ross operation. The presence of allograft fenestration, on the other hand, was only significantly associated ($p=0.012$) with a lower regurgitation grade late in the follow-up (>2 years after surgery).

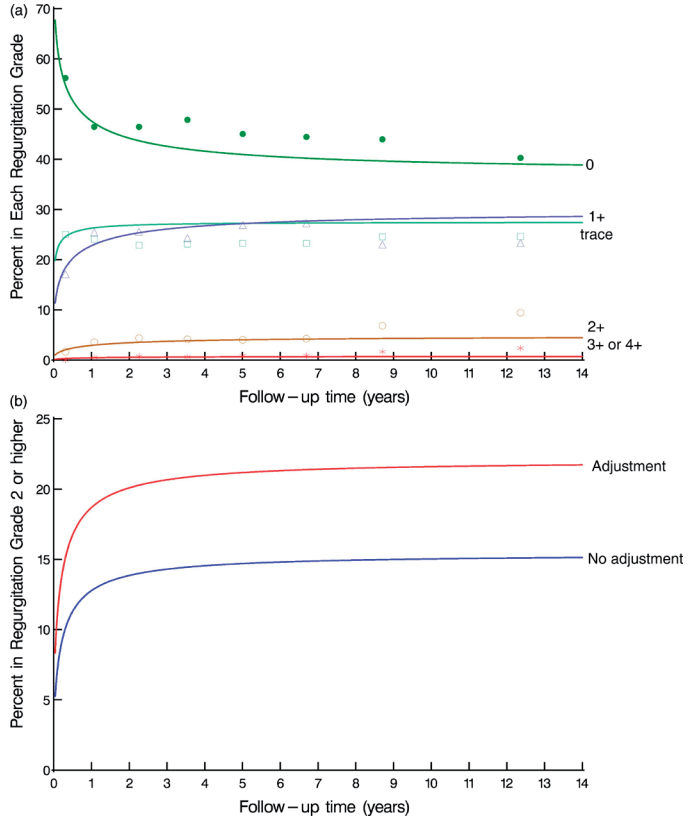

FIGURE 1. *(A) Temporal trend of pulmonary regurgitation grade after the Ross procedure. Solid lines represent percentage of patients (mean effect) in each grade at various time points. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting. (B) Predicted percentages of patients in regurgitation grade 2 or higher stratified by specific surgical adjustments of the allograft. The nomogram was solved for patients with a high risk profile with the following values for variables in the model: type of prosthesis=allograft; antibiotic treatment of the allograft=yes; female donor gender; female recipient gender; absence of sclerosis or fibrosis; absence of fenestrations. Access the article online to view this figure in colour.*

TABLE 3. Risk factors associated with increased likelihood of higher conduit regurgitation grade and increased mean/peak conduit gradient

Factor	Estimate±SE	*p* Value	Reliability
Pulmonary conduit regurgitation grade			
Overall phase			
Risk factors related to all conduits			
Use of allograft (as compared to bioprosthesis)	1.35±0.34	<0.001	50.8
Female patient gender	0.90±0.16	<0.001	89.3
Risk factors related to allografts only			
Surgical adjustment of allograft	0.64±0.20	0.001	100
Antibiotic treatment of allograft	1.01±0.23	<0.001	83.3
Male gender of donor allograft	0.33±0.15	0.032	99.4
Early phase			
Absence of allograft sclerosis or fibrosis	−2.30±0.39	<0.001	69.9
Late phase			
Absence of allograft fenestrations	−0.57±0.23	0.012	92.3
Mean conduit gradient			
Risk factors related to all conduits			
Male patient gender	0.07±0.01	<0.001	95
Younger patient age*	−0.16±0.02	<0.001	100
Use of bioprosthesis (as compared to allograft)	0.21±0.04	<0.001	96
Smaller conduit diameter†	−0.27±0.06	<0.001	96
Risk factors related to allografts only			
Younger age of allograft donor‡	−0.07±0.02	0.012	100
Peak conduit gradient			
Risk factors related to all conduits			
Smaller conduit diameter†	−1.42±0.27	<0.001	98
Use of bioprosthesis (as compared to allograft)	0.81±0.17	0.002	76
Younger patient age*	−0.75±0.08	<0.001	100
Male patient gender	0.41±0.05	<0.001	59
Recent date of surgery§	0.16±0.08	0.039	73
Interrupted proximal suture line	0.42±0.18	0.017	100
Risk factors related to allografts only			
Non-heart beating donor of allograft	0.14±0.07	0.024	96
Younger age of allograft donor‡	−0.35±0.10	<0.001	100

*Patient age/40.
†Conduit diameter/25.
‡Donor age/47.
§Interval first–last surgery in database/15.

Pulmonary conduit obstruction over time

Mean pulmonary conduit gradient

Mean pulmonary conduit gradient increased from about 4.7 mm Hg at 1 month to about 10 mm Hg by 14 years after the procedure (figure 2A). The change in mean gradient was mainly observed in the first 2 years after surgery. The increase was statistically significant ($p<0.001$).

Both younger age of the recipient ($p<0.001$) and younger age of the allograft donor ($p=0.012$) were associated with a significantly higher mean pulmonary conduit gradient. Male patient gender ($p<0.001$) (figure 2B) and the use of smaller conduit diameters ($p<0.001$) were correlated with a higher mean pulmonary conduit gradient. Furthermore, the use of a bioprosthesis (as compared to an allograft) ($p<0.001$) appeared to be associated with higher pulmonary conduit gradient.

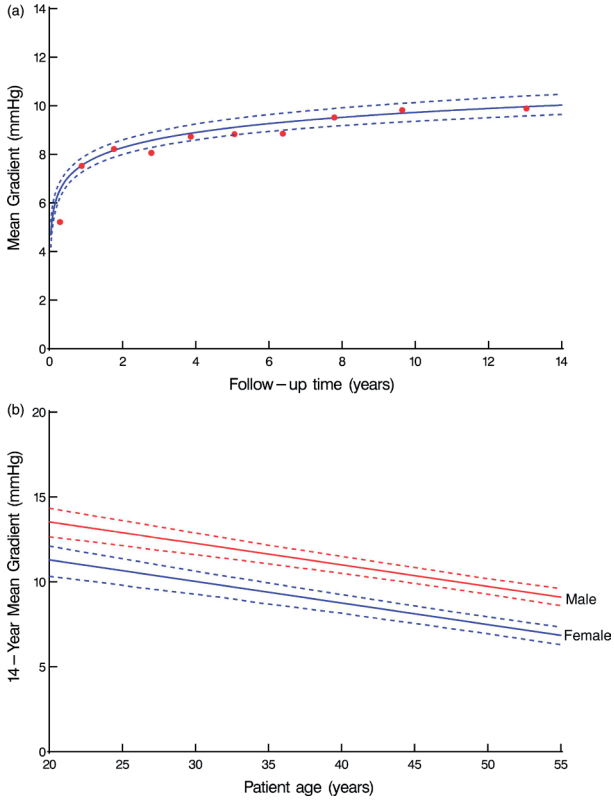

FIGURE 2. *(A) Solid lines are parametric estimates of mean gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting. (B) Fourteen year predicted mean gradient by age, stratified by gender. The nomogram was solved for the following values for variables in the model: type of prosthesis=allograft; mean conduit diameter (25 mm); mean donor age (47 years). Access the article online to view this figure in colour.*

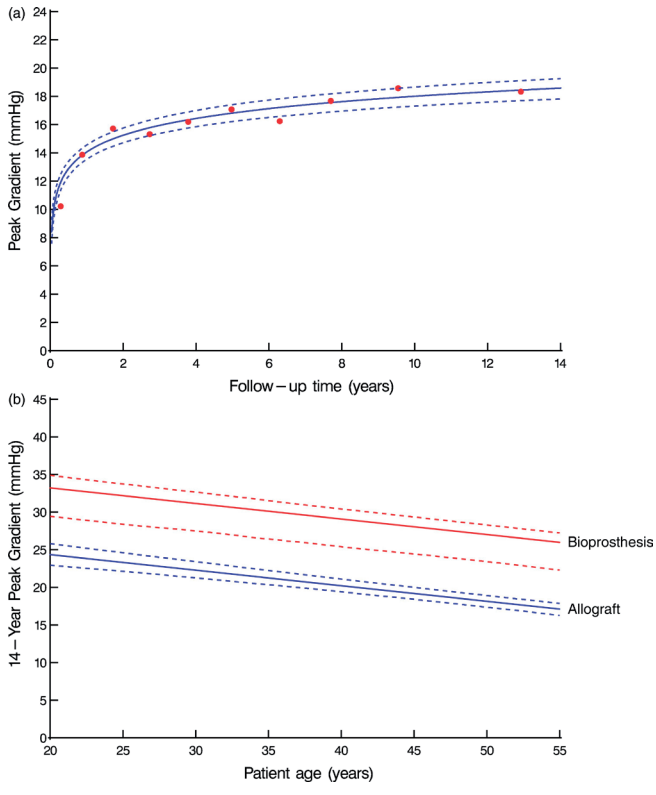

FIGURE 3. *(A) Solid lines are parametric estimates of peak gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting. (B) Fourteen year predicted peak gradient by age, stratified by type of prosthesis used. The nomogram was solved for the following values for variables in the model: mean conduit diameter (25 mm); continuous proximal suture line; allograft harvested from non-heart beating donor; male patient gender; mean donor age (47 years). Access the article online to view this figure in colour.*

Donor gender, allograft quality (presence of fenestrations, sclerosis or fibrosis), allograft adjustments by surgical means (yes vs no, different surgical techniques), allograft length (distance between pulmonary artery bifurcation resection line and sinutubular junction of the pulmonary valve ≤20 mm (short) or >20 mm (long)), allograft diameter (absolute value), year of surgery, and recipient–donor blood group mismatch had no substantial effect on the annual progression of the mean pulmonary conduit gradient.

The focused unadjusted analysis to assess the association between mean gradient and PVR during follow-up showed that early postoperative mean gradient does not have any impact ($p=0.1$) on the early return of PVR. However, higher postoperative mean gradient is associated with an increased likelihood of higher grade of late PVR ($p<0.0001$).

Peak pulmonary conduit gradient

Peak pulmonary conduit gradient appears to be slightly increased from about 8.4 mm Hg at 1 month to about 18.5 mm Hg by 14 years after the procedure (figures 3A). The increase was statistically significant ($p<0.001$) and was mainly observed in the first 2 years after surgery.

As with the mean pulmonary conduit gradient, younger age of the recipient ($p<0.001$) (figure 3B) and the use of bioprosthesis (as compared to allograft) ($p<0.001$) (figure 3B) were associated with a significantly higher peak pulmonary conduit gradient after 14 years of follow-up. Figure 3B shows on the x-axis that younger patient age (for both allograft and bioprosthesis recipients) is correlated with a higher peak conduit gradient after 14 years of follow-up (shown on the y-axis). The older the patient at the time of the procedure, the lower the peak gradient is after 14 years of follow-up. In addition, this figure also shows that although younger patient age is correlated with higher peak conduit gradient after 14 years of follow-up, the use of a bioprosthesis is correlated with a higher gradient compared to the use of allografts, independent of how old the patient is at the time of the procedure (shown by the two stratified lines in the figure).

Younger age of the allograft donor ($p=0.012$), male patient gender ($p<0.001$), and smaller conduit diameter were associated with a significantly higher peak pulmonary conduit gradient ($p<0.001$). In addition, it appears that the use of an interrupted suture line (as compared to continuous) ($p=0.017$), allografts harvested from non-heart beating donors ($p=0.024$), and a recent date of surgery ($p=0.039$) were also associated with a higher peak gradient after RVOT reconstruction with a conduit.

Donor gender, allograft quality, allograft adjustments by surgical means, allograft length, and recipient–donor blood group mismatch had no substantial effect on the annual progression of the peak pulmonary conduit gradient.

The focused unadjusted analysis to assess the association between peak gradient and PVR during follow-up showed that early postoperative peak gradient does not have any impact ($p=0.1$) on the early return of PVR. However, higher postoperative peak gradient is associated with an increased likelihood of a higher grade of late PVR ($p<0.0001$).

DISCUSSION

The results of the present study show that both pulmonary conduit pressure gradient and pulmonary conduit regurgitation grade increases predominantly within the first two postoperative years. Clinically important pulmonary conduit regurgitation is rare in adult patients after the Ross procedure, with the number of patients with clinically significant pulmonary conduit regurgitation being <5% after 14 years of follow-up. In addition, conduit obstruction of potential clinical impact occurs in a minority of patients (3.2%). Furthermore, in the present study we were able to identify several patient, donor, and procedure related factors influencing the pulmonary conduit function during the follow-up of the Ross patients.

The use of allografts in the reconstruction of the RVOT is widely accepted and this conduit is considered as the 'gold standard' in patients undergoing the Ross operation. However, the limited availability and the high costs involved in the preparation and

storage of these valves have led to the use of bioprostheses as a suitable alternatives. Some studies investigating hard clinical end points showed comparable intermediate results between allografts and bioprostheses,[25 26] while others reported a significantly higher risk of reintervention with bioprosthetic valves as compared to allografts.[27] The results of the present study show that the use of bioprosthetic valves is correlated with significantly higher mean and peak gradients as compared to allografts. Patients with an allograft, on the other hand, had a significantly greater risk of higher regurgitation grade as compared to patients with bioprosthetic valves. The difference in regurgitation grade and gradient between allografts and bioprosthetic valves occurred mainly in the first 2 years after surgery and remained constant after this period.

An allograft related factor that has been found to play a role in the chronic degeneration process of the allograft is younger donor age.[9 10 28] We observed a clear age dependent association between donor age and mean/peak allograft gradient: the younger the donor allograft, the higher the allograft mean and peak gradient. This is in accordance with communications in the literature which report on the entire age range from infants to adults.[29] In most studies, younger donor age is also related to a smaller allograft diameter. The present report includes only young adult and adult patients, thus the issue of age related small allografts in children and adolescents does not play any role. It may be speculated that this age dependency is related to the amount of viable cells with pronounced immunogenic properties.[29]

The effect of conduit diameter on valve failure has been extensively studied, but no generally accepted consensus has been reached.[30 31] Previous reports have shown that smaller conduit diameter is associated with limited longevity, while others have not found any relation between absolute allograft diameter and its longevity.[32–34] In the present study, smaller conduit diameter was correlated with a significantly increased risk of higher mean and peak conduit gradient over time. We can only speculate that with larger implanted allografts, the expected shrinkage process induced by immunologically active material is less obstructive since a diameter reserve works protective. The length of the allograft had no effect on the changes of the pressure gradient or allograft regurgitation grade. This is in contrast to other studies which stressed the occurrence of an extensive fibroproliferative process with consecutive compression and/or shrinkage of the tubular part of the allograft as a major mechanism of deteriorating graft haemodynamics.[11]

Shrinkage of the allograft was pronounced in the proximal annulus area,[35] suggesting that implantation of a glutaraldehyde fixed pericardial strip after donor muscle resection might reduce allograft annulus shrinkage with a haemodynamic benefit. In the present study allograft adjustments resulted in a significantly greater risk of higher allograft regurgitation grade compared to the allografts without any surgical adjustment interventions. Allograft adjustments were not correlated at all with allograft stenosis. Since no large scale reports on allograft adjustments to prevent the occurrence of allograft shrinkage are available, long term echocardiographic follow-up studies are necessary to confirm the modelled results.

A more recent year of operation correlated with a significantly higher peak conduit gradient. This finding has also been previously reported.[28] Although patient gender and antibiotic treatment of the allografts were also found to be significantly associated with

allograft function over time, the clinical relevance of these factors is negligible since the difference in mean gradient between male and female patients was ±2 mm Hg.

There is uncertainty about the role of blood group compatibility in relation to accelerated allograft failure. While some investigators have suggested that blood group incompatible allografts have a significantly higher early reoperation rate compared to blood group compatible allografts,[36] other investigators were not able to find any association at all.[37–39] In the present study, we were not able to identify any correlation between recipient–donor blood group mismatch and allograft function over time.

Clinical implications

Thus far the number of reinterventions on the pulmonary conduits for haemodynamic deterioration is low, although a considerable number of conduit failures were due to infective endocarditis. Strict adherence to endocarditis prophylaxis guidelines and high clinical suspicion to detect and diagnose non-fulminant allograft endocarditis may decrease the incidence of endocarditis and further improve the postoperative outcomes. Our echocardiographic analyses showed that a small but not negligible subset of patients is at risk for progressive valve failure. Thus, not only overt failures (with the need for reoperation) have to be reported, but also the number of conduits at risk with an expected high failure rate in the longer term need reporting. An almost linear increase of the mean transvalvular gradient occurred within the first 2 years and flattened out in a steady state afterwards. In contrast, a small gradual increase in conduit regurgitation over time is detectable, but the progression rate is sustained and clinically insubstantial. Using non-linear longitudinal models, we were able to define several patient and conduit related factors that are associated with increased dysfunction and/or progression of conduit dysfunction over time. These insights may be helpful in applying the optimal surgical technique (conduit type, suturing, donor/patient characteristics mismatch, sizing, and surgical adjustments) and to monitor patients more adequately who present with an increased risk of allograft failure.

We find that the pulmonary allograft, together with consideration of allograft related risk factors, constitutes the most appropriate valve substitute in the setting of the Ross operation, although it is challenging to take into account risk related allograft factors given the limited availability of pulmonary allografts. Alternative valve substitutes depict no optimal RVOT substitute so far, due to the lack of scientific evaluation with respect to large patient cohorts and mid term or even long term observations.

Study strengths and limitations

Some reports on institutional experiences tried to define prognostic factors for pulmonary conduit dysfunction in the mid term. These reports have included relatively low numbers of patients, they mainly focused on the development of allograft stenosis, the follow-up time was limited, and serial longitudinal analysis of haemodynamic conduit function over time was not considered.

One of the major strengths of the present study is the systematic echocardiographic follow-up of a large group of Ross patients. In addition, the surgical procedure was performed

in 10 cardiac surgery departments in Germany and the Netherlands which increases the generalisability of the results presented. Furthermore, using longitudinal methods in the present study, we were able to explicitly model the temporal trend of the echocardiographic measurements. Using this method we were able to visualise the temporal trend of each conduit regurgitation grade over time during follow-up, which enabled the clinicians to determine how conduit regurgitation on average developed over time after valve implantation. These methods are superior to dichotomising outcomes and analysing them with actuarial methods as if they were events, such as freedom from grade 1+ or 3+ conduit regurgitation after valve surgery, where only a snapshot image of valve function is expressed.[40–42] Modelling of the temporal trend and identifying factors that influence this temporal trend can be of particular importance since it can help clinicians understand how a certain process changes over time and thus can contribute to better patient management (eg, by determining which patients should be monitored more closely by their physicians and at which time interval).

The current study presents several limitations. The echocardiographic examinations were not reviewed independently or blindly. However, the echocardiographic examination protocol was standardised, and forms designed specifically for this registry were completed at each examination. The echocardiographic examination data were, therefore, collected prospectively. The mean echocardiographic follow-up time is 5.5 ±4.2 years. Furthermore, a slow-going haemodynamic deterioration of the RVOT conduit is well compensated clinically for a long time. Therefore, long term studies are necessary. As with all multicentre echocardiographic follow-up studies, a bias cannot be excluded and may have influenced the results. The lack of an echo core laboratory is an additional potential weakness of the present study. Finally, the applied longitudinal statistical methods are relatively new and therefore there is no widespread general knowledge about their use.

Key messages

What is already known on this subject?
Although initially there was concern about the outcome of the Ross procedure, several short and mid term studies have proven that the procedure can be performed with low operative risk and survival rates comparable to the general population. The need for specific surgical expertise to perform this complex operation and concerns about early and late failure led to its limited usage.
With growing experience, however, the advantages of the Ross procedure have become more fully appreciated.
How might this impact on clinical practice?
The long term fate of the pulmonary conduit is largely unknown, but it is crucial for a more comprehensive judgment of this operation since this procedure results in the treatment of a single aortic valve disease with a two-valve procedure, subsequently placing two valves at risk of failure. In this regard, it is crucial to understand how the pulmonary conduits in Ross patients function over time and to determine the factors associated with poor conduit performance.
What this study adds?
This knowledge can potentially lead to better patient management and improved outcomes in these young adult patients.

CONCLUSION

Echocardiographic follow-up of pulmonary conduits shows good conduit durability. Clinically important pulmonary conduit regurgitation is rare in adult patients after the Ross procedure. Conduit obstruction with a potential clinical impact occurs in a minority of patients. While conduit pressure gradient development occurs predominantly during the first 2 years postoperatively, conduit regurgitation increases gradually over time yet is clinically insignificant on average. Consideration of risk associated predictors may improve both conduit and patient outcome.

ACKNOWLEDGEMENTS

We thank Mrs Katrin Meyer for her excellent data management and secretarial support at the Registry Site in the Department of Cardiac and Thoracic Vascular Surgery, University of Lübeck, Germany.

CONTRIBUTORS

MMM: conception, design, analysis, interpretation of data, and drafting the article. EIC: conception, design, interpretation of data, drafting the article, final approval of the version to be published. US, AdJJCB and H-HS: conception, design, final approval of the version to be published. JR and EHB: analysis and final approval of the version to be published. JJMT conception, design, interpretation of data, final approval of the version to be published.

Funding MMM is funded by a Mosaic grant of the Netherlands Organisation for Scientific Research (NWO 017.006.058).

Competing interests None

Ethics approval Institutional review board approval was obtained to conduct this prospective follow-up study in each participating centre (clinical trial ID NCT 00708409).
Provenance and peer review Not commissioned; externally peer reviewed.

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CHAPTER 12

PULMONARY HOMOGRAFT MORPHOLOGY AFTER THE ROSS PROCEDURE: A COMPUTED TOMOGRAPHY STUDY

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J Heart Valve Dis. 2011;20:688-94

Background and aim of the study

In patients undergoing the Ross procedure the autograft morphological characteristics have been well studied, but those of the homograft are less clear. The study aim was to describe the radiomorphological homograft characteristics in Ross patients, and to compare them with such characteristics in normal (control) subjects.

Methods

A total of 79 Ross patients (68 males, 11 females; mean age 43 ± 12.3 years) underwent a computed tomography (CT) scan at a mean of 31 ± 26 months after surgery. A group of 123 patients without cardiovascular disease served as controls. Cryopreserved homografts were implanted in all Ross patients, with the majority being obtained from a single source.

Results

The mean donor age was 47 ± 11 years, and the mean homograft diameter 25.4 ± 1.3 mm (as provided at source). Electrocardiographic-gated CT reconstructions were used for the measurements.

The smallest diameters were at the proximal anastomosis, and maximum diameters at the distal anastomosis ($p < 0.001$). In controls, the minimum diameter was just proximal to the pulmonary valve annulus. In Ross patients, the homograft diameters were significantly smaller at all levels compared to controls. This effect persisted after taking into consideration patient age, height, gender, body surface area, and time since surgery. Notably, the measured homograft diameters were significantly smaller than those provided at source.

Conclusion

The study results provided evidence of homograft shrinkage at all levels after the Ross procedure but, most prominently, at the level of the proximal suture line. This may have implications for novel preservation methods, as well as homograft size selection and implantation techniques.

In young, active patients, the Ross procedure is considered to be an acceptable alternative to conventional aortic valve replacement with either a mechanical or a biological aortic valve. The implantation of the patient's native pulmonary valve in the aortic position eliminates the need for lifelong anticoagulation and provides an excellent postoperative neoaortic valve function, while the valve also has the ability to grow. Taken together, these benefits appear very appealing, especially in young patients. However, it has now been well established in large studies that, in a minority of patients, the autograft or homograft function can deteriorate with time, such that eventually reoperation will be required (1-5). While many previous studies have focused on the incidence and modes of failure of the autograft, the exact process and the pathophysiology of homograft degeneration have been less well described.

With regards to the homograft it is well known that, after the Ross procedure, a minority of patients develop significant pressure gradients that are attributed to a decrease in the effective homograft valve area (6-9). It is interesting that this process develops mainly in the first two postoperative years, but thereafter the situation remains relatively stable. Whilst the exact mechanism of the process remains unclear, it has been shown that an immunological rejection process takes place, which may be partially influenced by the process of cryopreservation prior to implantation of the homograft. Although the result of this process – which is seen mainly as an increase in homograft pressure gradient over time has been described in detail, the morphological characteristics of the homograft's effective valve area reduction remain largely unidentified. Hence, the aim of the present study was to describe the radiomorphological characteristics of the homograft stenosis that develops in some patients after the Ross procedure.

CLINICAL MATERIAL AND METHODS

Patient population

Between February 1990 and May 2003, a total of 289 patients underwent a Ross procedure at the authors' institution. During the same period, 79 (27.3%) of these patients (68 males, 11 females; mean age 43 ± 12.3 years) underwent computed tomography (CT) angiography, the indications for which were: a newly developed pressure gradient over the homograft or a significant deviation from the previous examination; late fever of unknown etiology; and/or clinical or echocardiographic suspicion of homograft endocarditis.

The decision to perform CT rather than magnetic resonance tomography was based on the fact that CT allows the in vivo measurement of homograft diameters, as well as an identification of the potential presence of calcium in degenerated homografts. The mean time interval between the initial surgery and CT angiography was 31 ± 26 months (range: 5 to 156 months). At that time, the mean maximum homograft gradient was 20.9 ± 11.2 mmHg, and the average 10.8 ± 6.5 mmHg. The mean gradient was <10 mmHg in 37 patients, 10-15 mmHg in 28, and >16 mmHg in 11 (the gradient was unknown in three cases). Eight patients had grade I homograft regurgitation, and three had grade II; all other patients had no homograft regurgitation. At the time of the latest follow up (during 2010), eight homograft reoperations had been carried out; three due to homograft stenosis, one to regurgitation, two to combined stenosis and regurgitation, and two to endocarditis. For purposes of comparison, a group

of 123 patients without prior cardiovascular manifestations or interventions underwent CT angiography, and served as controls.

All patients provided their informed consent for the collection and use of the respective data. The study was approved by the local ethics committee (Clinical Trials ID: NCT 00708409).

Operative technique

The detailed operative technique of the subcoronary Ross procedure has been described elsewhere (4,5). All patients were operated on by three surgeons, using the same technique with regards to autograft harvesting/implantation and homograft preparation/implantation. For reconstruction of the right ventricular outflow tract (RVOT), a cryopreserved pulmonary homograft was used that consisted of a proximal muscle band, the pulmonary valve, and the main pulmonary artery. The major proportion of the proximal muscle band, as well as the pulmonary artery proximal to the bifurcation, was resected prior to implantation in all patients. A complete homograft muscle resection was performed in five patients. The distal homograft anastomosis was performed using a 5/0 Prolene suture (running suture in 70 cases, single interrupted in two, mixed in two, and unknown in five). In all patients the proximal anastomosis was performed using a running 4/0 Prolene suture; there was no hooded augmentation of the proximal anastomosis in any of the patients.

Homograft characteristics

The homografts used were from five different sources, with the majority (n = 51) being obtained from a single source (CryoLife Inc., Kennesaw, GA, USA). A decellularized homograft (SynerGraft, CryoLife Inc.) was implanted in 13 patients. The mean donor age was 47 ± 11 years (n = 61), and the mean homograft diameter (as provided from source) was 25.4 ± 1.3 mm. Small fenestrations, as well as sclerotic and atheromatic lesions, were observed in 43%, 37%, and 9% of the homografts, respectively. No significant patient-prosthesis mismatch was observed since, during the early postoperative period all patients had normal homograft gradients. In addition, no significant difference was observed between the size of the implanted homograft and the pulmonary valve diameter (25.4 ± 1.3 versus 25.4 ± 1.2 mm; p = 0.9) in the body surface area (BSA)-matched control population (10).

CT angiography examination

All CT angiographies were performed during apnea, using the same settings (Toshiba Medical Systems, Aquilion Multi; length of scan 12 cm, 2 mm slices, 0.5 s rotation time, 120 kV, 150 mA). A CT scan either without contrast agent (to localize and quantify any calcified lesions) or with contrast agent (to evaluate the RVOT and pulmonary artery lumen morphology) was performed in all patients. In each patient, 120 ml of contrast agent (Ultravist 370®; Bayer HealthCare Pharmaceuticals) was injected via a peripheral vein, at an infusion rate of 3.5 ml/s.

In order to evaluate the examinations, electrocardiographic-gated CT reconstructions were performed. Multiplane reconstructions in the para-axial, parasagittal and paracoronary planes were carried out to evaluate the RVOT and the main pulmonary artery, up to the level of the bifurcation.

Measurements

The homograft lumen dimensions were measured at the paracoronary projection. The diameters at the following levels were evaluated: proximal anastomosis just proximal to the pulmonary valve (A-B), and the distal anastomosis just prior to the bifurcation (C-D). The distance in between was divided into three equal segments, and the diameter of each segment measured (proximal: E-F; middle: G-H; and distal tubular segment: I-J) (see Fig. 1).

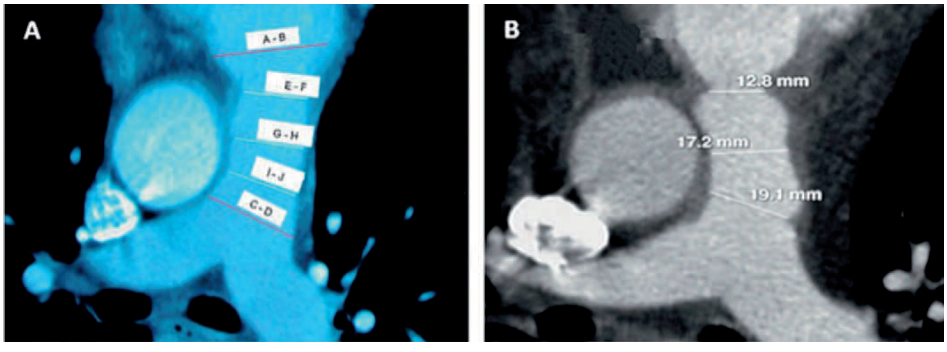

FIGURE 1. *Paracoronary projection of the CT angiography in (A) a normal subject and (B) a Ross patient who developed significant homograft stenosis. Illustration of the five levels of measurement: proximal anastomosis (A-B); distal anastomosis (C-D); proximal, middle, and distal tubular segments (E-F, G-H, and I-J, respectively).*

Statistical analysis

Frequencies were presented as absolute numbers and percentages, and continuous data as mean ± SD. For comparisons, either Fisher's exact test or the Mann-Whitney *U*-test was employed as appropriate, whilst for the comparison of two or more groups the Wilcoxon and Friedman tests were utilized, respectively. Bivariate correlations were analyzed with Pearson's correlation coefficients. A p-value <0.05 was considered to be statistically significant.

For all subgroup analyses, the Bonferroni correction was taken into consideration and incorporated into the analyses and p-values presented herein. In order to control for demographic differences between the Ross and control groups, multiple linear regression analyses were performed. In these analyses the measured distances were treated as a dependent variable, while the demographic variables (age, gender, body weight, height, BSA, group [Ross or control]) were treated as independent variables. To correct for multiple comparisons the Bonferroni correction was used, with p-values <0.001 denoting statistical significance.

All statistical analyses were performed using SPSS software (Version 15; SPSS Inc.).

RESULTS

Differences were identified between the homograft and control groups in terms of age (43 ± 12 versus 63 ± 14 years, p <0.001), height (178 ± 8 versus 173 ± 10 cm, p = 0.001), body weight

(81 ± 15 versus 78 ± 17 kg, p = 0.18), BSA (2.0 ± 0.2 versus 1.9 ± 0.2 m^2, p = 0.05), and gender (44% female versus 14% female, p <0.001).

Homograft dimensions

Among the Ross patients, the smallest diameters were found at the site of the proximal anastomosis, and maximum diameters at the site of distal anastomosis, just proximal to the pulmonary artery bifurcation (p <0.001, Friedman test; Table I).

No correlation was found between the measured diameters and patient age, BSA, donor age, or time between surgery and CT angiography. Neither was any correlation found between patient gender, gender concordance, source of homograft, homograft alterations (presence of fenestrations, sclerosis, or atheromatic lesions), use of a decellularized homograft, or the surgical technique employed for the distal anastomosis. The measured homograft diameter (segment A-B in Fig. 1) at the time of the CT examination was significantly smaller than the homograft diameter as provided at source (21.1 ± 4.5 versus 25.4 ± 1.3 mm, p <0.01).

TABLE I. Comparison of homograft diameters at the five measured distances within the Ross and control groups.

	Measured distance+				
Group	**A-B**	**E-F**	**G-H**	**I-J**	**C-D**
Homograft (Ross)					
Diameter (mm)	21.1 ± 4.5	21.9 ± 3.8	22.0 ± 3.7	23.3 ± 4.1	25.9 ± 5.3
Friedman test				p <0.001	
Pairwise Wilcoxon test					
A-B versus		NS	*	*	*
E-F versus			NS	NS	*
G-H versus				*	*
I-J versus					*
Control					
Diameter	27.8 ± 4.3	27.2 ± 4.0	28.3 ± 4.1	29.5 ± 4.2	31.4 ± 3.7
Friedman test				p <0.001	
Pairwise Wilcoxon test					
A-B versus		NS	NS	*	*
E-F versus			*	*	*
G-H versus				*	*
I-J versus					*

+A-B, proximal anastomosis; C-D, distal anastomosis; E-F, proximal tubular segment; G-H, middle tubular segment; I-J, distal tubular segment.
*p <0.05.
NS: Not significant.

Normal (control) pulmonary artery dimensions

In the control group, the minimal diameter was just proximal to the valve attachments (A-B), and at the proximal third of the tubular segment of the pulmonary artery (Table I). The maximal diameter was observed at the level of the bifurcation (C-D).

No correlation was found between the pulmonary artery dimensions and patient age. A weak (r = 0.22), albeit statistically significant, correlation was observed between the pulmonary artery dimensions and the somatometric characteristics (height, body weight, BSA). A significant difference in the pulmonary artery diameters was identified between male and female subjects.

Comparison between Ross patients and normal (control) subjects

The homograft diameters in Ross patients were significantly smaller at all levels (Table II). In an attempt to mitigate the differences between Ross patients and normal subjects in terms of preoperative characteristics and demographics, multiple regression analyses were performed. The characteristics that differed in the two populations served as independent variables, and the measurement dimensions as dependent variables.

TABLE II. Comparison of homograft diameters (mm) between Ross patients and control subjects.

	Measured distance[+]				
Group	**A-B**	**E-F**	**G-H**	**I-J**	**C-D**
Homograft					
Mean (± SD)	21.1 ± 4.5	21.9 ± 3.8	22.0 ± 3.7	23.3 ± 4.1	25.9 ± 5.3
Range (mm)	12.2-31.8	14.6-32.7	13.9-32.2	15.2-34.1	15.1-38.8
Control					
Mean (± SD)	27.8 ± 4.3	27.2 ± 4.0	28.3 ± 4.1	29.5 ± 4.2	31.4 ± 3.7
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

[+]A-B, proximal anastomosis; C-D, distal anastomosis; E-F, proximal tubular segment; G-H, middle tubular segment; I-J, distal tubular segment.

After considering age, height, gender, and BSA, a significant group effect was identified which confirmed the fact that, independent of any demographic differences, the Ross population had significantly smaller diameters than did normal subjects (Table III).

DISCUSSION

The results of the present study indicated that the diameters along the homograft were significantly smaller than those in normal subjects, and that this situation persisted after correcting for demographic differences between the two groups. Typically, the smaller diameter in the pulmonary conduit was at the site of the proximal anastomosis.

TABLE III. Multiple linear regression analyses between measured distances and patient demographics.*

	Measured distance[+]				
Variable	**A-B**	**E-F**	**G-H**	**I-J**	**C-D**
Constant	13.7 ± 9.8	23.0 ± 8.9	12.5 ± 8.8	4.2 ± 8.9	8.2 ± 10.0
Age	0.1 ± 0.1	0.03 ± 0.0	0.02 ± 0.01	0.02 ± 0.03	0.03 ± 0.03
Height	-0.1 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1	-0.1 ± 0.1	0.1 ± 0.1
Gender	-0.1 ± 1.0	-0.7 ± 0.9	-0.3 ± 0.9	0.2 ± 0.9	-0.9 ± 1.0
BSA	5.3 ± 2.5	5.9 ± 2.3	4.4 ± 2.2	6.7 ± 2.3	4.1 ± 2.5
Group effect					
(Ross vs. Control)	5.5 ± 0.9	5.0 ± 0.8	6.2 ± 0.8	6.4 ± 0.8	5.8 ± 0.9
p-value	<0.001	<0.001	<0.001	<0.001	<0.001

*Values are unstandardized coefficients ± SE.
+A-B, proximal anastomosis; C-D, distal anastomosis; E-F, proximal tubular segment; G-H, middle tubular segment; I-J, distal tubular segment.
BSA: Body surface area.

One potential methodological concern for the study was the choice of controls, since some conditions (e.g., pulmonary hypertension) may affect the size of the pulmonary artery. When searching retrospectively for CT examinations to use as control group, special attention was paid to an absence of any cardiopulmonary manifestations in the history and discharge diagnosis of these patients before their inclusion in the study. Among a large pool of CT angiographies performed in these patients, for reasons other than cardiovascular manifestations between 2002 and 2003, those were selected in whom a gated reconstruction was possible in order to evaluate the RVOT. The majority of these 'control' examinations was performed as part of complex medical evaluations for malignancy detection, unclear chest pain, or other non-cardiovascular diagnoses. Although the control cohort was not prospectively selected, it is believed that they were representative of a normal collective without significant bias, as the diameters measured were within the normal range (11-14). It was also believed that this methodology did not insert any significant bias, as pulmonary hypertension may lead to increased pulmonary artery internal diameters (15,16), or to an immunological reaction to the homograft, which in turn leads to shrinkage of the homograft lumen, as observed in the present study.

A second potential concern was the lack of follow up CT examinations. The study aim was not to describe the rate of deterioration, as evaluated with CT angiography, but rather to present and discuss the information that could be derived from the snapshot CT examinations of this population. When all conclusions had been derived from the examinations, it was deemed improper and unethical to perform additional CT investigations, as this involved significant radiation exposure in this young population. Currently, an abundance of information is available regarding the rate of homograft degeneration, the time after surgery when such degeneration takes place, and the development of pressure gradients over time (17,18). Hence, it was considered that a demonstration of the same issue via another diagnostic modality

would have little or no scientific value, and would reveal no new findings. Thus, the study was limited to a snapshot analysis of homograft morphology, using CT.

It seems that, at some time point between cryopreservation of the homograft and implantation (or even postoperatively), a process occurs that leads to shrinkage of the homograft (Figs 1 and 2), and this is in accordance with previous observations (6-8,19). The results of this slow reduction in effective homograft diameter has been verified in many echocardiography studies demonstrating an increase in the homograft pressure gradient that evolves mainly during the first months after implantation. In most adult patients, however, this development of homograft pressure gradient remained stable thereafter (17,18). While the exact mechanisms behind this process remain unknown, the results of many studies have indicated an immunologically mediated inflammatory process, similar to that of chronic rejection, although questions remain as to the exact nature of the mechanism involved. Although chronic lymphocytic infiltration, increased postoperative patient temperatures (with normalization of these on administration of non-steroid anti-inflammatory medication) and microscopic signs of inflammatory cell proliferation support the hypothesis of a rejection process, no influence of panel-reactive antibodies or HLA histocompatibility studies on this rejection process and development of stenosis has been documented previously (20,21).

One interesting finding in the present study was that no calcifications were identified in the pulmonary homograft of these adult patients. This contrasted with the pulmonary homograft degeneration observed among the pediatric population, and the aortic homograft degeneration in adults, in which various studies have shown significant calcification to occur during the degeneration process (22). This may imply that the rejection model may not be the sole cause of homograft degeneration, as both the anatomic position of the homograft and the patient's age (which may translate to immunologic reactivity) also seem to play significant roles (22,23). Previously, Carr-White et al. (21), by using magnetic resonance imaging, observed evidence of tissue growth around the homograft that they speculated as

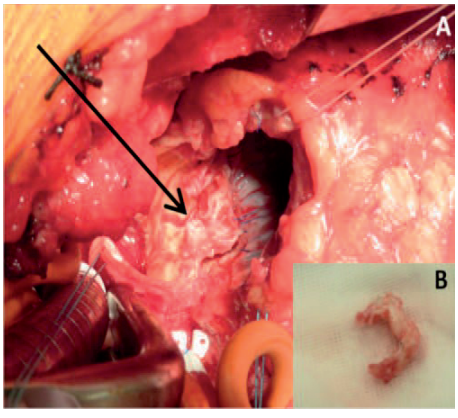

FIGURE 2. *A) Fibrous tissue growth (arrow) at the site of the proximal anastomosis in a patient reoperated on due to homograft stenosis. B) The tissue specimen, isolated.*

being the cause of external compression of the tubular part of the homograft. These authors postulated that the postoperative inflammatory reaction to the homograft would lead to a fibroproliferative processes that would promote tissue growth around the homograft, and shrinkage of the homograft itself. It is possible that pulmonary homograft degeneration in the pulmonary position in the adult population may also be caused by fibroproliferative degeneration. However, in the present study and in contrast to other reports (21) no form of external homograft compression due to perivascular and adventitial fibroproliferative processes could be identified.

Among the present patients, 13 received a decellularized cryopreserved homograft. Although this decellularization process aims at reducing (or even abolishing) the immunological stimulus that may cause not only an inflammatory reaction but also a possible shrinkage of the homograft diameters, the present data failed to reveal any differences between patients implanted with a decellularized and a non-decellularized homograft, in terms of homograft diameter or reduction in homograft size. In a previous study, the pressure gradients and effective orifice areas did not differ among patients with decellularized homografts (24,25).

The observation that the smallest homograft diameter is constantly observed at the proximal suture line, leads to the theory that the muscle cells just proximal to the pulmonary valve attachments can provide a strong immunologic stimulus that could eventually lead to a diameter reduction in this respective area. In the present series, only five patients underwent a complete muscle resection of the homograft, and this did not allow for a meaningful subgroup analysis. Previous studies conducted by the present authors' group, in which the proximal homograft muscle band was completely resected and replaced with either an autologous pericardial strip or a Gore-Tex membrane (W. L. Gore & Associates, Inc., Flagstaff, AZ, USA), indicated a somewhat lower pressure gradient development across the homograft within the first two years after surgery (26). However, this modification does not alleviate the problem of homograft shrinkage and degeneration in the long term, and additional studies are required before any final judgment can be made of this modification.

Notably, the measured diameters obtained with CT angiography were significantly smaller that those provided at source ($p < 0.001$). This was also true in patients without prominent high-grade homograft stenosis. This observation may have some implication for homograft size selection. For example, Brown et al. (27,28) have reported that the RVOT conduit size was an independent risk factor for conduit dysfunction and eventual failure, and postulated that homograft conduit oversizing might have a protective effect. This would apply especially to the pediatric population, where body growth in conjunction with a stronger immunological reaction may lead to functional and anatomic homograft stenosis, respectively. These authors also postulated that an intentional oversizing of the homograft might compensate for the expected homograft shrinkage observed during the first postoperative months. Although the beneficial effect of deliberately oversizing the homograft remains to be confirmed, studies conducted in pediatric populations have indicated that homograft oversizing may lead to a higher annual increase in homograft regurgitation (23).

In conclusion, a significant shrinkage of the homograft was observed after the Ross procedure, compared to normal diameters and to the homograft dimensions as provided at

source. This occurred at all levels of the homograft, but was most prominent at the level of the proximal suture line. No signs of external compression of calcification of the homograft were observed. The process of homograft shrinkage should perhaps be taken into consideration when selecting the homograft size at the time of surgery

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CHAPTER 13

GENERAL DISCUSSION

SURVIVAL AFTER AORTIC VALVE REPLACEMENT

Current knowledge on patient survival after aortic valve replacement

Although it is now well known that survival of patients with symptomatic aortic valve stenosis or aortic valve insufficiency is severely impaired without surgery [44], even after the alleviation of the pathological cardiovascular hemodynamics with aortic valve replacement, the survival of the patients does not seem to return to that of the normal general population [3,4,45]. In fact, patients with either a biological or mechanical valve have a significantly reduced expected survival compared to the age and gender matched general population. Martijn van Geldorp and colleagues calculated that patients with either mechanical or biological valve have a reduced survival compared to the matched general population and its effect ranges between -2 to -15 years [4]. Additionally, Kvidal and colleagues have shown that the survival penalty after aortic valve replacement in comparison to the expected survival of the matched general population is higher in young patients, patients with more prominent symptoms, patient who develop concomitant atrial fibrillation at some point during the natural history of the aortic valve lesion and patients in which the history of the disease resulted in depressed ventricular function [45–47]. Patients referred for aortic valve surgery due to aortic valve insufficiency seem to fare worse than patients with aortic valve stenosis [45]. The above mentioned factors seem to be independently associated with reduced long term postoperative survival.

Of special interest is the influence of the patient's age at the time of the initial operation on the postoperative survival. It seems that even in the presence of few or no other comorbidities, patients of young age after aortic valve replacement will also face a reduced survival compared to the age adjusted general population. Kvidal and colleagues have shown that the only group in which aortic valve replacement restores survival to that of the matched general population is the patient group >70 years old [45], although selection bias could have influenced this finding.

These findings raise interesting and important questions. There are several factors influencing late postoperative survival in the context of a prospective or retrospective study. First, the patient's comorbidities and preoperative characteristics can affect the postoperative survival. Patients referred late during the natural history of aortic valve disease, even with signs of mild cardiovascular symptoms or asymptomatic concomitant atrial fibrillation, seem to fare worse in terms of postoperative long term survival [48]. This raises the question of optimal timing for aortic valve replacement surgery and whether the current indications for aortic valve replacement should be individualized taking into consideration patient age or the presence of biomarkers indicating structural heart disease accompanying the valvular lesion. Second, the mortality and morbidity associated with the operation may play role in defining each patient's postoperative course. Although perioperative survival is conventionally excluded from long term survival reporting, the higher morbidity accompanying high(er) risk aortic valve replacement procedures seems to impact postoperative survival. Third, there is now evidence that significant mortality and morbidity is associated directly with the consequences of the type of conventional aortic valve replacement implanted. This effect is more pronounced in young patients, since their life expectancy is longer thus the potential time to develop such complications is greater. Both mechanical valves (with anticoagulation)

and biological valves (without oral anticoagulation) are associated with significant incidence of thromboembolic complications [3,4,49]. In young patients there is now significant evidence of a higher degeneration rate of biological valves usually which mandate a reoperation (and thus a higher morbidity and mortality risk) within the first decade [6–8]. The renewed cardiac burden associated with degeneration of a prosthetic heart valve may induce further structural heart disease and impact long term mortality. Although mechanical valves have an excellent structural durability, the need for reoperations due to complications is not uncommon [50].

In the setting of a clinical trial and for the evaluation of the survival characteristics of therapeutic interventions as well as for drawing inferences from the sample level to the population, chance may also have a significant influence. Survival trials require usually a high number of patients in order to provide reliable inferences, because not only should the patient sample characteristics should be representative of the patient population but also the postoperative course of the patient sample should be representative of the patient population. This is of particular interest from an epidemiological point of view in younger patients since, the incidence and frequency of mortal events is per se low and as such a higher sample sizes are required to provide a reliable estimates and inferences. Additionally when performing comparisons regarding survival estimates between groups and between interventions group and the general population, one should not forget that the primary force of mortality in the young patient populations is accidents (chance) followed by malignancies, thus a greater sample size is required to provide reliable, population representative estimates of the difference in cardiac related survival that the various types of aortic valve replacement conduits may result in.

Survival after the Ross procedure

Although there is a plethora of studies indicating that patient survival after conventional aortic valve replacement is inferior to the expected survival of the general population and thus, aortic valve replacement does not restore postoperative survival to that of the general population, almost all publications on Ross patients, show a postoperative survival that is comparable or statistically indifferent from that of the general population [14,24,25,34]. This automatically raises the question whether the benefits associated with the Ross procedure (such as normal hemodynamics, anticoagulation free life etc.) have a beneficial impact on patient survival.

Before attributing this survival benefit to the Ross procedure, several issues must first be taken into consideration. First, death has a low incidence in the young population, even in adults after aortic valve replacement. This mandates that clinical reports having as endpoint the survival in the Ross population would require a larger sample size in order to document statistically significant differences. Second, the mean follow-up of the above mentioned trials is relatively short, in most cases under 10 years. This in conjunction to the previously mentioned point means that the expected number of events in small trials will be relatively low, the statistical power of such survival analyses will be reduced and thus the probability of Type II error (failing to reject a null hypothesis that is false) is high. Third, there seems to be some kind of selection bias in patients who are treated with a Ross procedure. The incidence of significant co-morbidities at the time of the initial operation in the Ross population is relative low [14,35], Ross patients have usually a higher socioeconomic status and thus a more favorable

survival. Importantly, patients receiving a Ross procedure have more often aortic stenosis, normal left ventricular, absence of coronary artery disease and atrial fibrillation [14], all being factors that have been shown to positively influence postoperative survival after aortic valve replacement [45]. All the above mentioned issues combined may affect the survival of Ross patients as documented in studies in the literature. This makes answering the question whether the superior survival which has been observed in the Ross patients [14,24,34,35,51] can be attributed to the uniqueness of the autograft particularly difficult.

In recent years there are some indications that the overall survival of the Ross population will statistically deviate from that of the general population. Although the major driving force of mortality in the general population of similar age to the Ross collective is non-cardiovascular related mortality (accidents, malignancies) [52,53], cardiac related mortality in the Ross collective accounts for about 50% of the mortality observed in the Registry [14]. Since one can reasonably assume that the Ross procedure cannot influence non-cardiac causes of mortality this implies that the high - for the general population standards - incidence of cardiac and cardiac valve related mortality in the Ross registry should be in addition to the non-cardiac force of mortality the patients at the age of 30-40 experience. Thus with the addition of more patients and follow-up years the survival of the Ross patients is expected to deviate from that of the general population.

The deviation of the survival of the patients enrolled in the European Ross Registry from that of the age, gender, and nationality matched general population is displayed in Figure 1. Although the survival of the Ross population closely follows the general population (Figure 1 left), it appears that a progressive deviation takes place with an increase in the number of excess deaths in the Ross collective in comparison to the expected in the matched general population (Figure 1 right). It can be postulated that this will reach in the years to come the level of statistical significance.

Although the majority of publications indicate that for a mean follow-up time of usually <10 years the survival of the Ross patients is similar or closely comparable to the general population, the relatively high number of cardiac and cardiac- valve related deaths observed in the Registry [14] coupled with the fact the in the age-matched general populations non-cardiac deaths are the major force of mortality indicate that in the longer term, the survival of the Ross collective will deviate from that of the general population. Of importance however is the effect size of this deviation and more importantly its comparison to the reduced survival observed with conventional aortic valve replacement using biological or mechanical conduits.

Large published series of Ross patients, usually present higher survival probabilities [14,24,34] than other series of either mechanical or biological valves [3,4,6–8,31,50], however a direct comparison is difficult. Outcomes after mechanical aortic valve implantation versus the Ross procedure have not been comparatively investigated in the setting randomized controlled trial investigating. Several reasons cited for the higher survival rates of Ross patients are usually the normal transvalvular hemodynamics after the Ross procedure, the freedom from anticoagulation and superior durability compared to mechanical and biological prostheses respectively. However there is significant evidence that patient selection plays a role in this comparison. Mokhles and colleagues have investigated the survival of the European

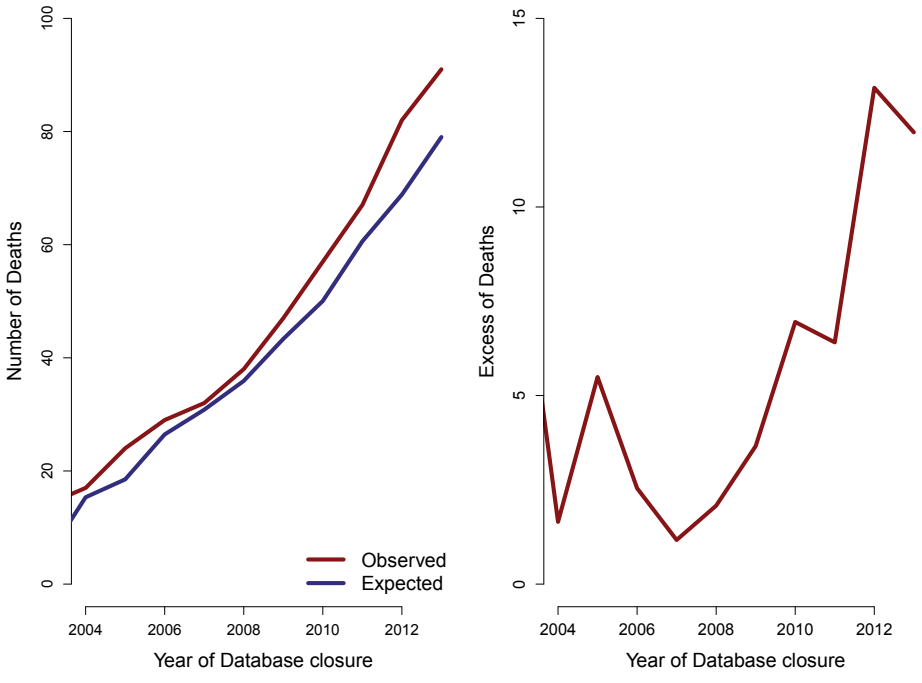


FIGURE 1. Left: *Evolution of observed and expected deaths in the European Ross Registry.* ***Right:*** *Evolution of excess mortality compared to the general population*

Ross Registry collective and compared it with patients from the Bad Oeynhausen [54] experience using propensity score matching to control for patient characteristics that may affect postoperative survival [51]. With all the limitations of this methodology in mind, in this study no survival benefit of the Ross collective could be documented. It is unclear if this is due to the difficulty of patient matching, therefore including somewhat different preoperative characteristics, or if the intensive anti-coagulation controls and optimal therapy that the patients in Bad Oeynhausen receive [54–56] may lead to superior survival probabilities than other published series of mechanical valves.

REOPERATIONS AFTER THE ROSS PROCEDURES

Definitions and challenges for the accurate reporting of reinterventions and reoperations

As mentioned in the Introduction section an accurate nomenclature of the type of reintervention or reoperation simplifies the storing of information and the accurate reporting of the need for repeated events, the associated conduit durability as well as information about the risk profile of the repeated events. In the European Ross Registry the following nomenclature has served this purpose satisfactorily [35]: A *Ross reintervention* is defined as any surgical

or interventional procedure performed after the initial Ross procedure on the autograft or homograft. A *Ross reoperation* is defined as a surgical session that included at least 1 Ross reintervention on the autograft or homograft, or both (1, 1, and 2 reinterventions, respectively) and may include concomitant interventions to other cardiac structures.

Additionally the classification of morbidity and morbid events in the European Ross Registry follows the classification proposed by Akins et al. [43]

General incidence and risk factors for autograft reoperations after the Ross procedure

The incidence of reoperations in the European Ross Registry has been evaluated to be at about 1.5% per patient*year [35] which may be regarded as an acceptable failure rate of a cardiac valve procedure. The subanalysis of the reoperative incidence provides valuable information for the understanding of the risk for reoperation.

One of the first important findings regarding the reoperative incidence of the Ross population which had been diluted in the clinical experience but has been more formally and scientifically depicted and demonstrated in the publications of the European Ross Registry, is the effect of the operative technique [14,32,35]. The initial Ross procedure performed as a free root replacement has been shown to be prone to acute and chronic dilatation under the systemic arterial pressure [26,26,28,29,57,58]. The late consequences of these geometric changes usually become clinically relevant leading to increased risk of events 6-8 years after the initial procedure (Figure 2), with the vast majority of these failures being categorized as non-structural [35,36,43] valve deterioration (loss of competent valve function with morphologically intact valve leaflets). This knowledge has led to the development of the supported or reinforced root technique in which key elements of the aortic root (aortic annulus, sinotubular junction) that had been shown to be prone to dilatation are reinforce with non-compliant material. Early experience with this technique has shown promising results for the first postoperative decade [32,35] (Figure 2). On the other hand the mechanism of autograft failure in the subcoronary technique is fundamentally different from the root replacement technique. Here the main mode of failure is structural valve deterioration (leaflet problems such as leaflet cusp, leaflet tears) as well as endocarditis.

Risk decomposition of autograft failure incidence (Figure 2, middle panel) provides some interesting information. The risk evaluation of the root replacement technique (Figure 2, middle panel) identifies a significant wear out effect taking place postoperatively, and an accelerated failure rate starting after 6-8 years postoperatively. The reinforced root replacement technique, does seem to ameliorate this acceleration, however it is important to note that this technique is relative new and inferences after the 8-10 year mark are precarious. On the contrary, the risk decomposition of the subcoronary Ross procedure exhibits a flat risk function (Figure 2, middle panel), indicating constant risk of failure with no identifiable temporal evolution up to 15 years postoperatively. The autograft reoperative events in the subcoronary procedure seem to exhibit a random, memory-less pattern (Figure 2, middle panel, green line) with the instantaneous risk for failure at any time during the postoperative course being independent of the risk up to that time, at least for the first 15 years. Aside from the effect of the operative technique

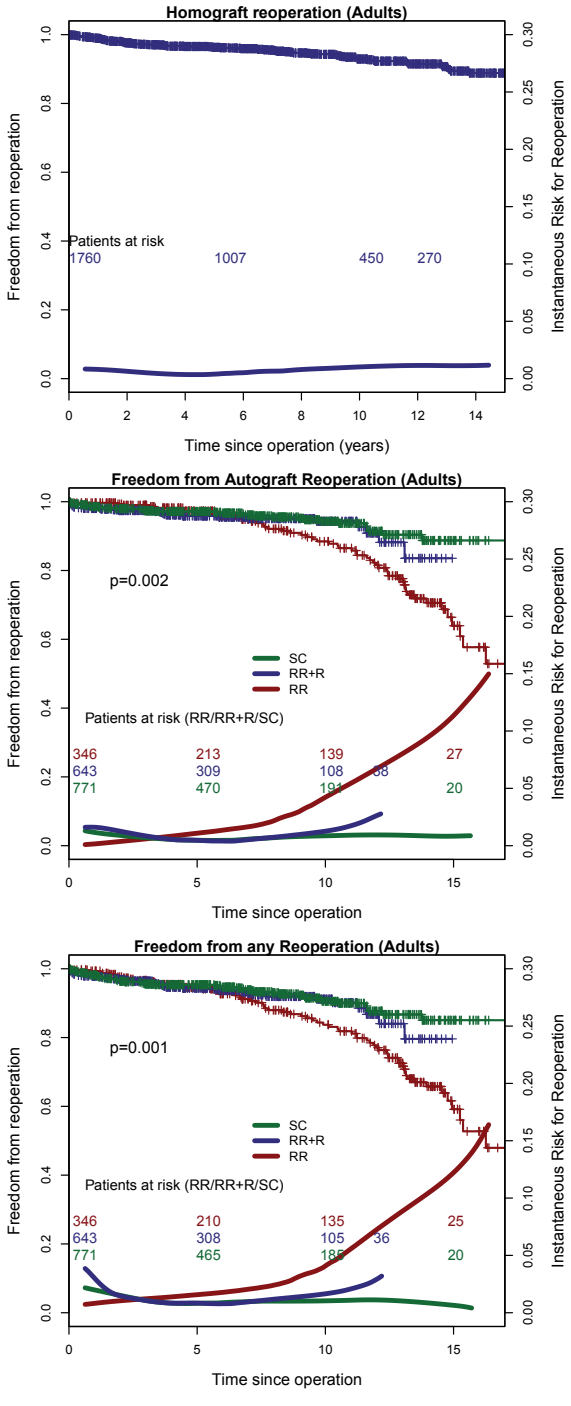


FIGURE 2. *Actuarial analysis of homograft (**upper**), autograft (**middle**) and combined (**lower**) reoperations.*

several other risk factors for failure have been identified. Center experience also seems to positively influence the incidence of reoperations[35]. The presence of preoperative pure aortic insufficiency has been identified as an independent risk factor for failure, with hazard ratio estimates of about 2.3 (95% CI 1.5-3.5) [35]. The mechanism behind this is assumed to be that patients with pure aortic insufficiency and no calcification of the aortic annulus, may have an intrinsic connective tissue disorder that makes the native aortic root as well as its surrounding structures prone to dilatation. This increase risk for failure has been also identified from other groups [18,27,30,59,60], however, due to the small absolute reoperative risk per se, pure aortic insufficiency should not be regarded as a contraindication for the Ross procedure [35,60].

An interesting discussion regarding autograft durability is whether the presence of a bicuspid aortic valve leads to an increased incidence of autograft reoperations. The main driving force behind this hypothesis is a single observational report [61] in which the authors have observed vague histological abnormalities in the pulmonary artery of bicuspid aortic valve patients, thereafter postulating that increased incidence of failures observed in the young Ross patients (the majority of whom have some kind of bicuspid aortic valve disease) should be attributed to the presence of the BAV associated histological abnormalities found in the autograft. This has led to a recommendation against performing the Ross procedure in the setting of a bicuspid aortic valve [62]. However, from a scientific point of view, there seems to be no evidence of such association. Data from the large population of the European Ross Registry do not support the theory that bicuspid aortic valve is a risk factor for autograft failure and current knowledge based on the multicenter evaluation of results after the Ross procedure indicate that patients with bicuspid aortic valve do not exhibit a higher reoperation risk than patients with tricuspid aortic valves [14,32,35,63].

Risk factors for homograft reinterventions are well known but less modifiable. The most significant risk factor for homograft deterioration is the age mismatch between donor and recipient [35]. Older homografts implanted in older patients seem to fare significantly better than younger homografts implanted in young patients, especially in the pediatric population. The reasons behind this age dependent homograft degeneration have been shown to be of immunologic nature[64–69], with younger patients and younger homograft exhibiting a greater immunologic response. Although the patient's age is not a modifiable risk factor, homograft shortage also limits choice when selecting the appropriate homograft for each Ross patient.

Results of reoperations

Reports focusing on the type of reoperative procedures as well as on their results have yielded interesting information. Although the Ross procedure has a certain risk for autograft reoperation, a great number of these reoperations can take the form of some kind of reparative or sparing procedure on the autograft [35,70]. Recent publications of the European Ross Registry have shown that almost 20% of all autograft reoperations can be performed as either aortic valve repair or as a valve sparing procedure. This has significant benefits for the patient since the main advantages of the Ross procedure (avoidance of chronic anticoagulation, limited durability of biological prosthesis, normal transvalvular hemodynamics) are carried on even after an autograft repair or valve sparing procedure. The ability to repair or spare a

valve is greater in the root replacement procedure since the primary mode of failure of the root replacement procedure (non-structural valve deterioration) leave the autograft leaflets intact, thus enabling a reparative strategy. This is in contrast to the subcoronary procedure in which structural valve deterioration (leaflet issues) mandate usually a replacement of the autograft with mostly either a mechanical or a biological valve[35].

Reoperations after the Ross procedure when performed in experienced centers have a remarkably low morbidity and mortality. Data from the European Ross Registry have shown an unadjusted reoperative mortality of 6%; however it is important to note that all deaths have been observed in patients who required emergency or urgent surgery and were in critical condition. In patients electively reoperated or scheduled for an elective reoperation no mortality was observed. The feasibility and low risk for reoperations after the Ross procedure in experienced centers have been reported also by others in the literature [71–76]. Close clinical and echocardiographic follow-up of these patients is of paramount importance in order to recognize potential valve deterioration early and identify patients that potentially may require a reoperation, thus avoiding performing these reoperations on urgent or emergency basis.

Interpretations of the results under a competing risk framework

When evaluating the incidence of an event, one has to bear in mind that other events may prevent the appearance of the event of interest. The most common such setting in cardiovascular research is the risk for death which prevents the appearance of other events of interest such as reoperation (a patient who dies cannot experience a future reoperation, thus the true durability of this patient's valve conduit is masked through the competing event of death). These risks that may prevent the appearance of events of primary interest are called competing risks and the analysis of the events of interests under the knowledge that other events may prevent evaluating their true incidence mandate a different analytical framework.

Although there is significant and solid mathematical background for the competing risk analyses [77–84], the cardiothoracic community was primarily exposed to this issue during the late 90's through the seminal comments and works of Grunkemeier and colleagues [50,85–89]. These comments and works have generated over the time significant discussion in the cardiac surgical literature.

The Kaplan-Meier estimator [90] represents a flexible way of obtaining estimates of survival probabilities in cohorts of patients while simultaneously incorporating information form censored observations. Its ease of use and interpretation, together with the feasibility of comparisons between groups [91,92] led to an explosion of its application. Although initially devised to describe survival estimates from a terminal, non-recurrent event (death), its applications has been expanded – sometimes ill-advised – to the analysis and presentation of competing events, recurrent events, longitudinal data of various forms. The estimation and the mathematical formulations of the Kaplan-Meier estimator have been described elsewhere [77,79,84,90].

An initially not apparent fact when presenting or analyzing results using the Kaplan-Meier estimator is that it assumes that all individuals of a cohort **will eventually experience** the event of interest even if the time of these events is after the discontinuation of the study

and therefore is unobservable (Figure 3, panel A). The clinically relevance lies with the fact that when this estimator is employed to calculate "*survival*" estimates for binary events other than death (reoperation, freedom from valve dysfunction above a certain threshold), **the individuals are assumed to be immortal**. No absorbing state other than the primary event is allowed or accounted for.

On the other hand, the cumulative incidence analysis assumes not only the state of the event of interest (Figure 3, panel B) but also for at least one other, competing and absorbing states that prevent the occurrence of the event of interest. A pathway from the event of interest to a competing absorbing state may be included and is calculable; however it is usually not the primary focus of interest (Figure 3).

When more than one absorbing states are allowed a distinction is made between the causes and cause specific hazards (event of interest or other competing risks) are calculated. The calculation of the risk set and the corresponding cause specific hazard is straightforward and is presented in Figure 4, left panel.

Under a competing risk framework the subdistribution hazard is defined as the probability of the event given that an individual has survived up to time t without any event or has had the competing event prior to time t.

The main difference between the cause specific hazard and the subdistribution hazard is the way events from causes other than the cause of interest are treated. In the cause specific hazard (Figure 4, left) patients failing from the competing risk **are removed** from the *at risk* set. On the contrary, for the calculation of the subdistribution hazard, patients failing from causes other than the cause of interest **act as placeholders and remain in the risk set** (Figure 4). Although initially counter-intuitive, this places a constraint in the estimation of the

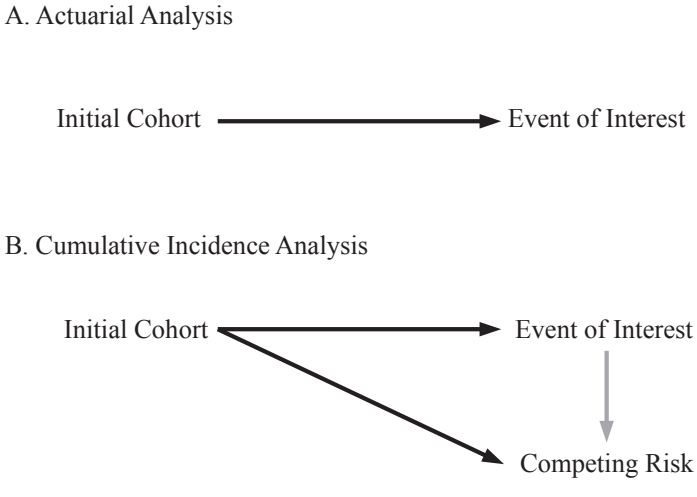


FIGURE 3. *Distribution of events in Actuarial (A) and Cumulative Incidence (B) analyses. In the actuarial analysis, the event of interest is the only absorbing state allowed. In the cumulative incidence analysis, other absorbing states are allowed and accounted for.*

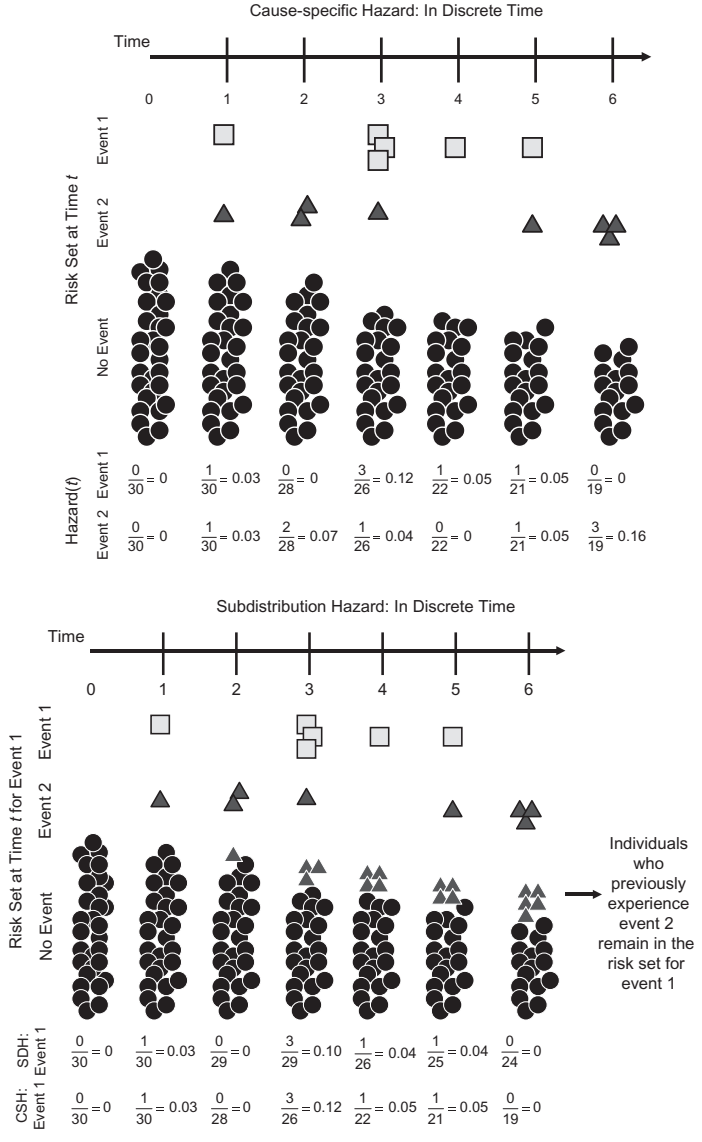


FIGURE 4. *Risk sets for the construction of the cause specific (left) and the subdistribution hazards (right) in discrete time.* ***Upper:*** *Cause-specific hazard schematic. The risk set starts with 30 individuals (solid circles). Over time, individuals have either event 1 (square) or event 2 (triangle). As individuals have either event, they are removed from the remaining risk sets. The calculation for the cause-specific hazard is given at the bottom of the figure.*
Lower: *Subdistribution hazard schematic. The risk set starts with 30 individuals (solid circles). Over time, individuals have either event 1 (square) or event 2 (triangle). As individuals have the competing event (event 2, triangle), they are maintained in the risk set as triangles. Thus, over time, a greater proportion of the risk set becomes full of triangles that are individuals who have had the competing event prior to that time. The subdistribution hazard (SDH) for event 1 is given near the bottom of the figure along with the cause-specific hazard (CSH) for event 1 for comparison. Note that, because individuals are maintained in the risk set, the SDH tends to be lower than the CSH. Reproduced with permission from [145].*

subdistribution hazard allowing for absorbing states other than the event of primary interest. Due to the fact that anytime a competing event takes place the *risk set* of the subdistribution hazard is larger than the risk set of the cause specific hazard, the estimates of subdistribution hazard tend to be smaller than the cause specific hazard estimates. As the hazard for the competing events tends to zero, the cause-specific hazard and the subdistribution hazard tend to equalize. As a consequence of the fact that the subdistribution hazard is smaller than the cause specific hazard, other estimates depending on the subdistribution hazard like the cumulative incidence function (CIF) and its complement (1-CIF) will lead to lower (for the CIF) and higher (for the 1-CIF) estimates, respectively.

This fact has been misused in the cardiothoracic literature when presenting results on the durability of the heart valve conduits and more specific on the durability of biological heart valves which has generated significant discussion and controversies [82,93,94]. Estimates generated using the cause specific hazards isolate other causes of failure, do not allow the existence of absorbing states other than that of the primary event, and thus the main focus of this methodology is to try to identify the intrinsic durability and failure characteristics of the device of interest *while isolating all other possible causes of death*. Since all individuals are assumed to fail (will be reoperated), and no other absorbing state is allowed (death), "survival" probabilities generated from cause-specific hazard estimations are lower than those estimated under a competing risk framework (subdistribution hazard).

On the other hand, if the interest is not the intrinsic property of the implanted device (i.e. heart valve) to fail, but to understand the probability that an individual will actually experiencing the event of interest (or not, due to the competing events) then the competing risk framework and the estimates obtained using the subdistribution hazards may be more appropriate. The latter have been used to derive information on the probability of patients experiencing certain events from the perspective of resource allocation and organization, exactly because these estimates, while taking into consideration that due to the competing risk(s) not all individuals will experience an event, provide more realistic estimates of the actual – real life - incidence and probabilities for failure, which can be of primary interest in studies focusing on resource utilization.

Eventually the decision between the well established and mathematically sound methodologies has to do with several factors. If the interest for the estimated probabilities is the intrinsic durability of the valve, the appropriate methodology for this type of question is the actuarial analysis, which isolates competing risks and tries to unmask the intrinsic durability information of the valve while disallowing other absorbing states. When the primary study interest is resource utilization, estimates based on the subdistribution hazard, taking into consideration that not all individuals will experience the event of interested due to competing risks, provide more appropriate, and accurate estimates.

Some controversy might arise when the primary research question is the probability that a prospective individual patient will experience the event of interest (for example valve failure) while using estimates derived from another published patient cohort. In this case actuarial estimates based on the cause specific hazard overestimate the probability of event occurrence. However to justify the use of estimates based on the subdistribution hazards,

the characteristics of the incidence of the competing risk event (death) have to be similar to that that the prospective patient will face. For example, if the published estimates have been estimated from a patient cohort with high mortality rates, using the subdistribution probability estimates to infer reoperation incidence information in a healthy prospective patient will **underestimate** the probability that this prospective patient has to experience the event of interest. On the other hand, if the subdistribution hazard has been evaluated in a relative healthy cohort and one is using these estimates to derive incidence information for a prospective patient with a high risk for mortality, this will **overestimate** the probability that this patient will experience the event of interest.

The characteristics of the incidence of the competing events (in the cardiac surgical literature focusing on heart valve outcomes, the most common competing risk is death) are also important when attempting to assess estimates of event occurrence published from different populations. In this case, while actuarial estimates, by not allowing absorbing states other than the event of interest, reduce the amount of bias in the comparison of estimates published from different populations. However, when using estimates of event occurrence for this cause, one has to be certain that the competing risk incidence and characteristics (death and risk of death) between the two groups are similar or at least comparable, in order for estimates calculated from subdistribution hazards to provide a meaningful comparisons. Since this is rarely the case, and because the various published cohorts have different mortality rates, different risk profiles and risk for death, estimates derived from subdistribution hazards should not be used to place results of different studies under a comparative perspective.

The Ross collective presents an interesting example for the methodology of choice for the estimation of failure occurrence.

Projections for the need of reoperation in the future

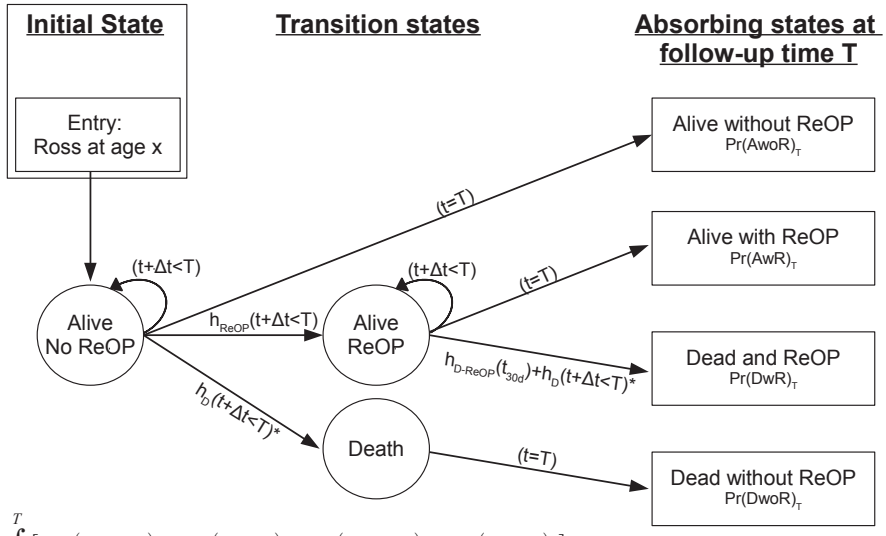
A major interest to the patient is the probability that she or he will experience a reoperation regardless of the type of the reoperation or the specific valve failing (autograft or homograft). The European Ross Registry provides a good amount of information to attempt to provide prospective Ross patients an objective estimate for the probability of reoperations.

Key elements for such calculation are the intrinsic, actuarial hazard for autograft failure $h_{AG}(t)$, the intrinsic actuarial hazard for homograft failure $h_{HG}(t)$ and the survival probabilities of the Ross population $S(t)$ and corresponding hazard estimated $h_{D}(t)$. Since the European Ross Registry includes information for the first two postoperative decades some degree of extrapolation of the obtained information into the future is necessary in order to derive such estimates. Until the point of this writing, survival of the European Ross Registry collective is similar to the general population (Figure 1) and for the calculation of the lifetime reoperation probabilities we continued to assume that the survival of the Ross population will be similar to that of the general population. We assumed that the Ross population will continue to closely follow the survival of the general population and even if this deviates at some point in the future, this effect size will most likely be rather small. However, it should be noted, that even if the survival estimates of the Ross population

deviate from the age and gender matched general population, this, under the competing risk framework will lower the observed probability for reoperation since patient who die cannot experience a reoperation.

Regarding the intrinsic hazard for autograft or homograft failure the following assumptions were made. In the adult population, we observed minimal temporal variation of the homograft reoperation hazard, and for the lifetime reoperation probability the last observed smoothed hazard rate was carried on through the end of patient life. For the autograft hazard, due to the great effect of the operative technique, we differentiated accordingly. For the root replacement technique according to the observed hazard patterns from the data (Figure 2) we assumed an accelerated failure of the AG with an exponential hazard rate $h_{AG\text{-}RR}(t)=0.01+0.01*\exp(t/5.9)$ (accelerated failure model). For the subcoronary technique we used the observed smoothed hazard estimates for times<17 years and thereafter assumed a constant hazard rate $h_{AG\text{-}SC}(t)=0.014$. The hazard for either autograft or homograft reoperation was obtained as follows $h(t)=h_{HG}(t)+h_{AG}(t)$. We built and evaluated a Markov process as displayed in Figure 5.

The estimated lifetime risk for reoperation in the Ross patients and for the subcoronary and root replacement technique according to the patient age at the Ross procedure is displayed in Figure 6.



$$\int_0^T [Pr(AwoR)_t + Pr(AwR)_t + Pr(DwoR)_t + Pr(DwR)_t]\,dt = T$$

$$Pr(AwoR)_t + Pr(AwR)_t + Pr(DwoR)_t + Pr(DwR)_t = 1 \;\forall\, t \in T$$

FIGURE 5. *Markov Chain for the estimation of the lifetime risk for reoperation after the Ross procedure. h_D: hazard for death as obtained from the life tables and penalized as required; $h_{D\text{-}ReOP}$: reoperative mortality; h_{ReOP}: hazard for reoperation as obtained from the Ross Registry and extrapolated in the future; $h_{D\text{-}ReOP}(t_{30d})$: early reoperative (thirty day) mortality.*

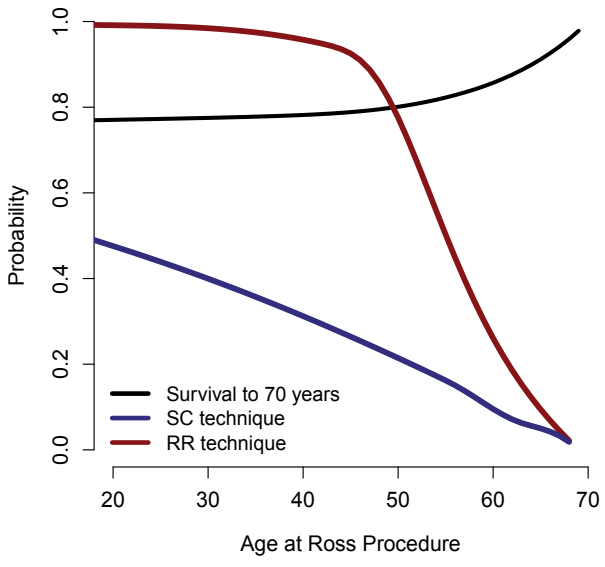


FIGURE 6. *Estimation of the risk for reoperation up to the age of 70, after a Ross procedure according to the patient's age at the initial operation[35]*

OTHER CLINICAL ENDPOINTS

Incidence of endocarditis in the Ross patient

The Ross procedure, especially when performed with the original root replacement technique or the subcoronary technique, results in minimal implantation of foreign material in the aortic root. Therefore it has been speculated that the Ross procedure may be a valid therapeutic choice in the setting of aortic valve endocarditis. While extended destruction of the aortic root anatomy may be regarded as a contraindication for the subcoronary Ross procedure [24], the root replacement technique can be performed even in the setting of significant aortic root involvement.

The diagnosis of an autograft or homograft endocarditis is a challenging task. Especially in the subclinical form, non-destructive endocarditis without gross morphological changes requires good knowledge of the patient's echocardiographic and functional valve history to document whether a certain degree of valve dysfunction is preexisting or should be attributed to the presence of a Ross valve infection. The latter task is particularly difficult since several Ross patients have some form of mild Ross valve dysfunction (trivial or first grade aortic insufficiency, or some mild degree of homograft stenosis or regurgitation). Also, strict adherence to the Duke criteria for the diagnosis of Ross valve endocarditis may lead to the underestimation of the incidence of endocarditis. In the non-acute setting (chronic/healed valve endocarditis) often the diagnosis is set after the resolution of the symptoms, or at the time of the reoperation. All the above indicate that there might be some risk and bias for under

or over diagnosis of endocarditis in Ross patients, particularly in the setting of a multicenter Registry, such as the European Ross Registry.

When evaluating the incidence of endocarditis in patients after heart valve replacement and especially after a complex heart valve replacement such as the Ross procedure, two primary research questions can be formulated. First, how do patients operated on the ground of aortic valve endocarditis fare in comparison to the patients who had their initial Ross procedure for other indications? and second, what is the incidence of autograft or homograft endocarditis after the Ross procedure?

Regarding the first research question, results from the European Ross Registry [14,35] as well as from other groups [24,95–98] show that the Ross procedure is a valid therapeutic option for the patient with aortic valve endocarditis with satisfactory results. Data from the European Ross Registry [14,35] suggest that the presence of aortic valve endocarditis at the time of the initial Ross procedure is not a risk factor for the development of future autograft endocarditis or valve deterioration (Figure 7).

Regarding the incidence of Ross related (autograft or homograft) endocarditis after the Ross procedure, it was initially believed that due to the biologic (homograft) or autologous (autograft) nature of the conduits, the Ross procedure would show a higher resistance to postoperative endocarditis. Data from the European Ross Registry show that although the incidence of Ross valve endocarditis seems to be lower than the endocarditis incidence in mechanical or biological valves, endocarditis is not an uncommon cause of Ross related reoperations [14,35]. Approximately 20% of all reoperation observed in the European Ross

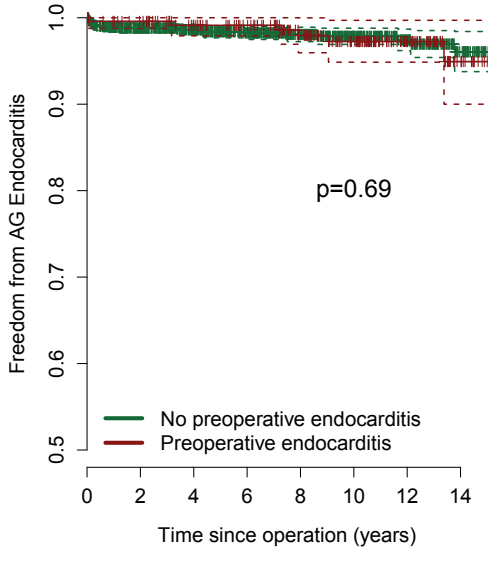


FIGURE 7. *The presence of aortic valve endocarditis at the primary Ross procedure is not a risk factor for postoperative autograft endocarditis. Log rank P=0.69*

Registry are performed on the grounds of endocarditis. Risk decomposition of the hazard for endocarditis for the autograft (Figure 8, left) identifies an early vulnerability phase taking place within the early postoperative phase (0-3 years after the initial procedure), a plateau (4-10 years) and a late increase (>11 years). Speculatively one may attribute the early vulnerability phase of the autograft and homograph endocarditis hazard to the operation. The late increase in the risk for autograft endocarditis may be attributed to vulnerability to endocarditis due to structural valve deterioration, or failure to comply with endocarditis prevention guidelines especially during invasive examinations.

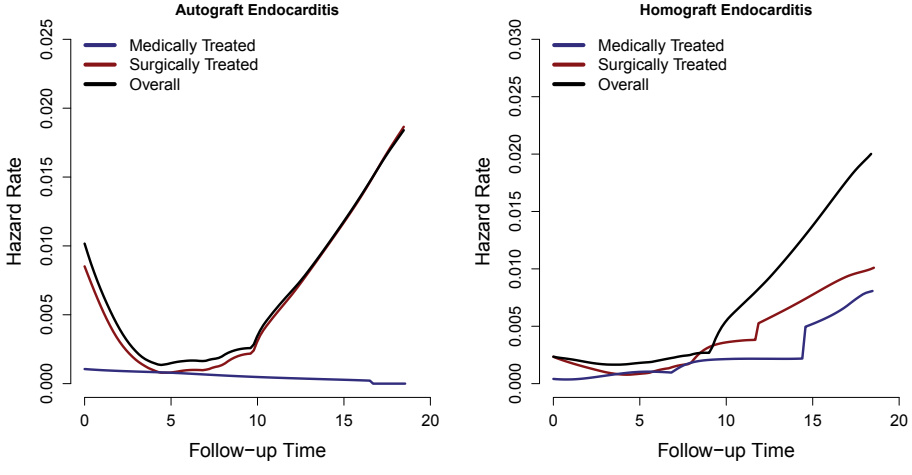


FIGURE 8. *Development of the hazard rate for medical and surgically treated autograft (left) and homograft (right) endocarditis*

Thromboembolic and bleeding complications

Thromboembolic and bleeding complications are important endpoints for the evaluation of outcomes after heart valve interventions. These complications are particularly important to postoperative quality of life and patient status and may lead to a wide range of symptomatology ranging from mild transient discomfort to severe permanent disability and death.

Traditionally, the thromboembolic risk an individual patient faces after a heart valve procedure is attributed to three factors: the patient's intrinsic thromboembolic risk due to factors unrelated with the valve pathology or the prosthesis, the intrinsic thrombogenicity of the prosthesis, and the risk for thromboembolic complications (as well as bleeding) attributed to the degree of anticoagulation that the patient achieves over time. Because of variations in these three factors, result of various studies and estimation of the incidence of thromboembolic or bleeding complications cannot be always transferred to other patient populations. Furthermore comparisons of the incidence of bleeding or thromboembolic

complications across different studies and patient populations, as well as inferences for each of the three above mentioned factors across different populations are precarious.

Pooled estimates from various studies have calculated the linearized occurrence rate for thromboembolic and bleeding complications (thromboembolism, major bleeding, valve thrombosis[43]) to be 1.6, 1.6, 0.16 % per patient*year [3,49] with a mechanical valve in the aortic position. On the contrary, pooled estimates for the above mentioned complication for biological valves have been calculated to be 1.3, 0.4, 0.01% per patient*year, showing lower incidence of complications especially of the bleeding and valve thrombosis type, which become very rare in the setting of a patient implanted with a biological valve.

In patients implanted with mechanical valves, especially in the aortic position it has been shown that significant improvement in the incidence of thromboembolic and bleeding complications can be achieved with aggressive follow-up of mechanical valve patients combined with anticoagulation self-management as well as centralized telemetry for anticoagulation monitoring. The ESCAT trial and the Bad Oeynhausen experience have shown that this specialized – albeit not widely used and applicable – patient care can improve the real-life warfarin therapeutic levels, therefore allowing lower INR levels [54–56,99,100] and therefore lowering furthermore the incidence complications. The Bad Oeynhausen experience which has been recently compared to a propensity score matched Ross population [51] has shown that for patients with mechanical valves in the aortic position and with a target INR of 1.8-2.8 and the incidence (LOR) of thrombotic complications can be reduce to 0.06% for thromboembolic, 0.16% for bleeding events per patient*year.

Data from the European Ross Registry affirm the very low incidence of thromboembolic complications in the Ross collective while allowing for these patients to enjoy and anticoagulation free life. In the latest report of the European Ross Registry (1620 adult patients, 10747 patient*years), the linearized occurrence rate for the **composite endpoint** that included bleeding, thromboembolism or valve thrombosis was 0.35%/patient*year. However it is important to note that these patients do not routinely receive either oral anticoagulation of the coumadin derivative type or any anti platelet agents (some clinics prescribe anti-platelet agents for the first 6 weeks postoperatively). Freedom from oral anticoagulation therapy is important in young patients since the need for this medication may have consequences for the patients' lifestyle (intensive sport activities, childbearing and family planning) as well as the patient's profession (professional sports, professions with high injury potential, airplane flying). Additionally a large percentage of the thromboembolic complications observed in the Ross Registry have occurred in patients who have developed atrial fibrillation at some time during the follow-up. Similarly, a large percentage of the Ross patients that experienced bleeding complications are patients that have been required to receive coumadin derivatives for other non-valve related diseases requiring oral anticoagulation [14,24].

ANALYSIS OF CONTINUOUS, LONGITUDINAL HEART VALVE INFORMATION

Challenges in analyzing continuous echocardiographic longitudinal outcomes

The analysis of serially collected longitudinal collected measurements in each individual represent a somewhat smaller deviation from the classical analytical and methodological framework that health care researchers are usually accustomed to employing. Analyses and inferences made on these measurements can be obtained using modification of well-established methods such as generalized linear models. The major modification that longitudinally collected data mandate stems from the fact that measurements of longitudinal data are usually auto-correlated and heteroscedastic within each measured individual. Therefore, traditional regression strategies such as ordinary least square regression, which assume independence and homoscedasticity of residuals are less appropriate. Mixed or multilevel models provide the framework for the analysis of continuous echocardiographic longitudinal measurements encountered in patients after heart valve replacement, with focus on modeling the change of these measurements throughout the time. Another advantage of this approach is that the models do not only describe the sample behavior but extend more flexible to the underlying population process that generated the sample data [101,102].

Mixed models, theory advantages and applications

Mixed or multilevel models allow for a greater flexibility in modeling the underlying population process generating the sampled data as well as model the variation and obtain regression coefficient on an individual level. On an individual level, the usual assumptions of least squares regression apply, however the coefficients obtained address the within patient correlation of the obtained measurements[103]. Furthermore, this information and variability of the individual level evolutions is taken into consideration and is accounted for, together with the group level variation when estimating the group level regression coefficients that the researches usually pursue[102,103]. An attractive advantage of this approach is that mixed level modeling can obtain adequate estimates for subgroups of the population having themselves small sample sizes. Potential disadvantages of mixed modeling is the additional complexity of fitting models with several fixed and random effects and error structures as well as the complexity in the interpretation of these findings[101–103]. Complexity in computations required to fit the models is nowadays rarely an issue since fitting is performed using freely available software and routines [104].Additionally, one should bear in mind that each level of the model, as a separate regression of its own has the usual assumptions (linearity, independence, homoscedasticity and normality), assumptions which should be examined[103]. Given the benefits and the flexibility of mixed models, there is little motivation not to benefit from this methodology and there seems to be little risk from applying these methods in applicable data sets [103].

Mixed modeling for the evaluation of continuous longitudinal outcomes after complex heart valve replacement usually utilize a patient level model (level 1 model: modeling the

trajectories of each individuals using random intercept and random slope; random effects) and an inter-individual level, usually modeling the effect of the parameters the investigator wishes to measure their influence (fixed effects). In the setting of multicenter studies, like the Ross registry, where the investigator may want to allow a "center" influence on the desired outcome, an additional center random effect (grouping structure or nested effect) can be introduced.

Evaluation of autograft diameters after the Ross procedure

Using the above mentioned methodology, several important conclusions based on the data of the Ross registry were obtained. In an attempt to interpret the high rate of failure of the root replacement Ross technique [29], the presence of a bicuspid aortic valve at the time of the initial Ross procedure was proposed as a risk for failure, either in the form of dilatation or development of significant regurgitation [28] and an attractive pathophysiological mechanism has been proposed [61]. However statistical analyses of these hypotheses and proposed risk factors has not been positive and several different groups have published opposite results [24,35,63,105]. With the use of the data from the Ross Registry it could be shown that patients with bicuspid aortic valves do not experience a higher rate of autograft dilatation ([63], Figures 9 and 10) and that patients with bicuspid and tricuspid aortic valves experience similar autograft growth rates ([32,63], Figure 11).

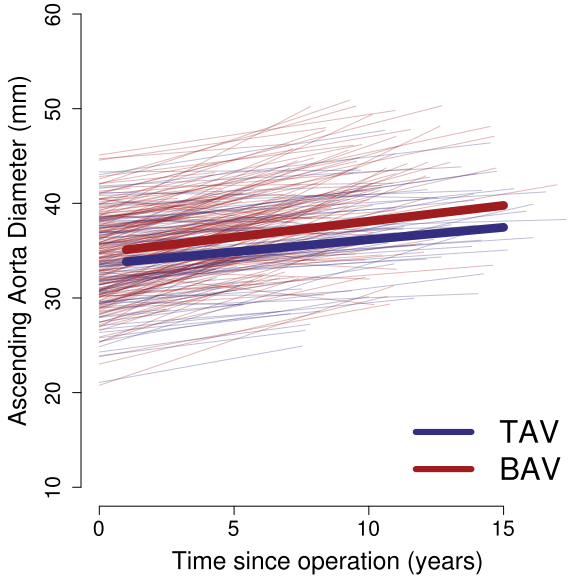


FIGURE 9. *Linear Mixed Model on the longitudinal changes of the ascending aorta dimensions with time. The individual patient trajectories as well as the level-2 (population) trajectories for the tricuspid (TAV) and bicuspid (BAV) aortic valve groups are presented.*

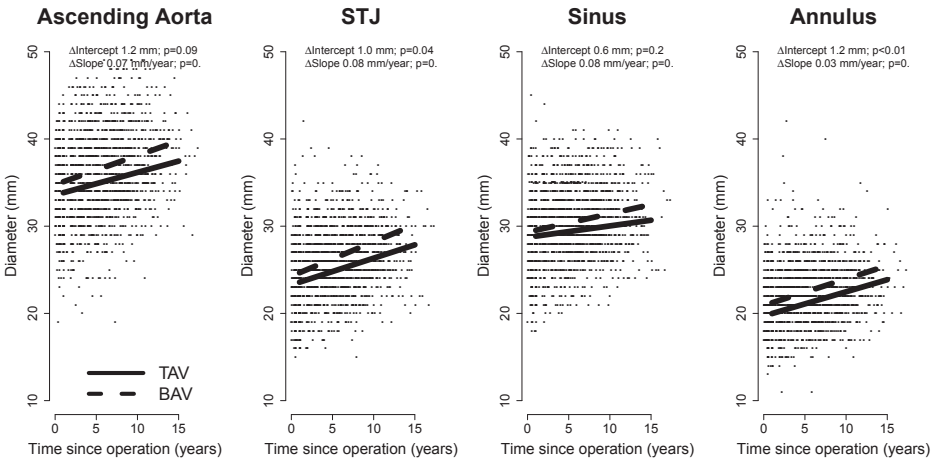


FIGURE 10. *Evolution of autograft diameters after the Ross procedure in patients with bicuspid and tricuspid valves. No statistically differences could be observed between patients with bicuspid and tricuspid aortic valves.*

Additionally, data from the European Ross Registry show that the longitudinal evolution of autograft diameters patients after the subcoronary Ross technique little differs from the expected evolution of the aortic root diameters in the general population [106] (Figure 11).

Development of homograft stenosis

The development of pressure gradients across the homograft manifest as one of the two main homograft degeneration mechanisms. The pulmonary homograft being a foreign material is more or less expected to develop a form of foreign material immunologic reaction [69]. Degeneration of the homograft with development of significant pressure gradients is the results of calcification of the valves which usually takes place at the level of the valve of just proximal to it [107], Figure 12. However the process of homograft gradient development takes place very slowly (Figure 12), in mostly two phases: one early gradient development phase taking place within the first two years after the Ross procedure, in which most patients develop relative rapidly a low gradients (maximum homograph gradient ≈10mmHg) and a later latent phase with a flattened slope (≈1.0 mmHg /year, Figure 12).

ANALYSIS OF ORDINAL HEART VALVE INFORMATION

The postoperative follow-up of patients with heart valve prosthesis as well as the interrogation of the prosthesis function often results in categorical data and variables that characterize the patient's or the valve's functional status. Important information is being communicated through these variables and clinically relevant inferences about the well-being of the patients, the success and status of the procedure and the functional characteristics of the implanted prosthesis can be drawn from this categorical information. Although an elaborate and well-established methodology for the evaluation and presentation of categorical results

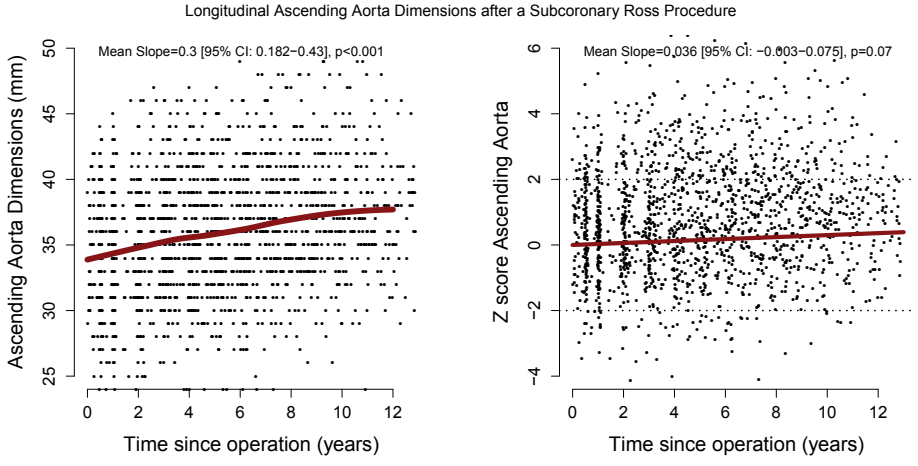


FIGURE 11. *Longitudinal modeling of the absolute ascending aorta diameters (left) after the subcoronary Ross procedure and z-values calculated from the age, gender and BSA adjusted general population (right) [106]*

and variables exists in the literature [108–110], more often than not in the cardiac surgical literature and especially for the evaluation of outcomes there is significant misuse of established methodologies or even use of inappropriate methods for the analysis, evaluation and presentation of categorical outcomes.

Valve regurgitation as a dynamic variable

While failure of mechanical or biological valves can manifest usually as the development of either significant stenosis or regurgitation, reparative aortic valve procedures as well as the pulmonary autograft after the Ross procedure rarely develop significant transvalvular pressure gradients. The main hemodynamic mode of failure of the pulmonary autograft is the development of autograft regurgitation either due to structural or non-structural valve deterioration[32,35,43].

The objective estimation of the degree of valve regurgitation presents several challenges. Valve regurgitation as a physical phenomenon is a continuous outcome that depends on the geometrical characteristics of the leaflet coaptation defect as well as the transvalvular pressure gradient. Changes in volume, peripheral systemic resistance, contractility or heart rate have been shown to affect the quantitative severity of valve regurgitation [42,111–113]. Additionally changes in the echocardiographic interrogation of the heart structures and substrate velocities can also severely affect the obtained measurements [42,113–116]. Interrogating, assessing, storing, analyzing and presenting this information in an objective fashion without loss of information represents a significant challenge.

Current approaches in classification and evaluation

Although several new approaches to a quantitative evaluation of valve insufficiency have been proposed and at least partly used in the clinical practice [42,115], the most often used method for

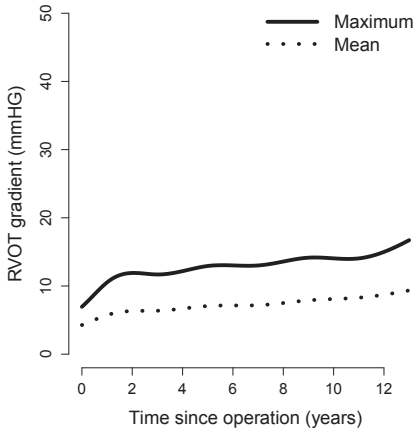


FIGURE 12. *Development of Homograft Gradients in the European Ross Registry. Linear mixed model using natural splines at knows 1,2,3..,11 years postoperatively*

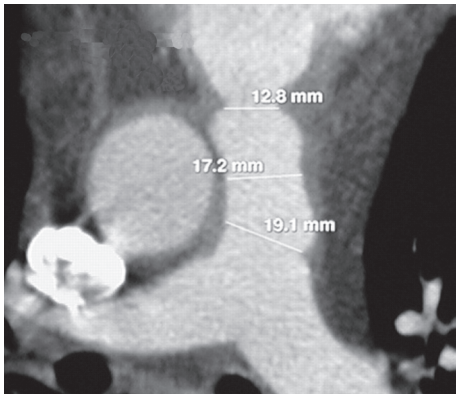


FIGURE 13. *Typical location of the homograft stenosis at the level of the valve or just prior to it [107]*

data classification, storage and analysis of the severity of valve insufficiency is the classification method of Perry et al [117], who proposed the ratio (%) of thickness of the regurgitation stream at its origin to the size of the LVOT as classification measure for the severity of aortic insufficiency into grades I (<25%), II (25-45%), III (46-64%) and IV (≥65%) [42,115,117]. The methods proposed by Perry and represent a simple method of quantifying valve regurgitation that has shown good correlation with patient related events and outcomes in clinical practice.

However, the use of the categorical classification as an endpoints presents several drawbacks. Aside from technical measurement considerations and examination quality issues, the categorization of a continuous variable for any statistical analysis – although sometimes intuitively benign – often leads to methodological issues. Categorization inevitably leads to information loss which in turns leads to reduce statistical power [118,119] (Figurers 14 and 15).

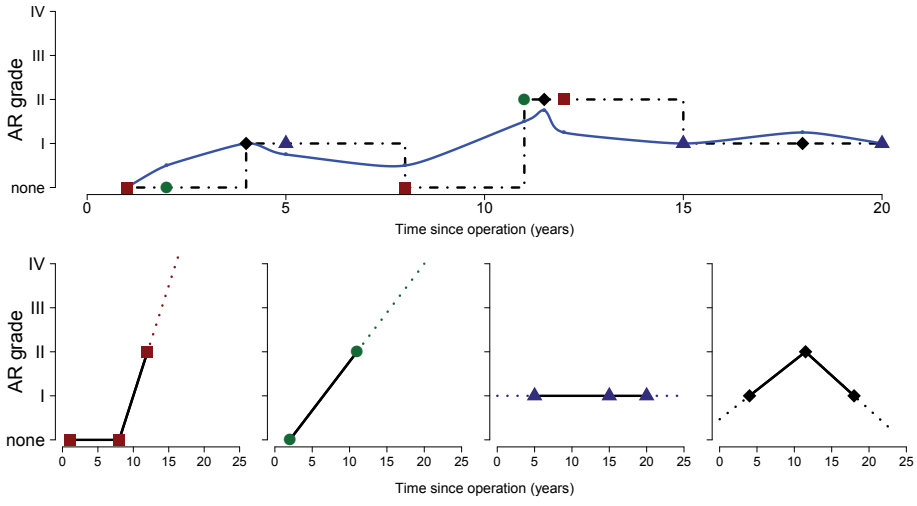


FIGURE 14. *Inferences via intermittent follow-up of a categorized continuous outcome (autograft regurgitation)*
Upper panel: *The real, continuous scale – unobserved – time course of aortic regurgitation is depicted with the blue line. The observed values at the intermittent follow-up examinations are depicted via the colored points. The black line depicts the inferred time course of the aortic regurgitation severity (last value carried on method). At times where the unobservable blue line does not touch the colored points loss of information due to categorization of a continuous variable takes place.*
Lower panel: *Intermittent follow-up with incomplete longitudinal information can severely affect the interpretation and the inferences for the past and future trajectory of the aortic regurgitation severity as well as the clinical conclusions. For the trajectory of the patient in the upper panel and for four intermittent follow-up schemes (red, green, blue, black), four very different trajectories can be assumed.*

Categorization increases the inhomogeneity of some individuals, with individuals being close (on the continuous scale) but on the opposite sides of the cutoff (on the categorical scale) being characterized as being more different than similar. The problems regarding choice of cutoffs and the associated increase in false positive findings and the need for multiple testing between the categories have also been denoted as drawbacks of categorization [120–124].

Figure 14 (upper panel), presents this problem. The real – however unobservable – degree of autograft regurgitation on a continuous scale is shown with the blue line. At some points during the follow-up period the valve function is interrogated, and the continuous outcome is quantified in an ordinal scale (triangle, square, circle and rhombus points). Inferences about the longitudinal development of autograft regurgitation over time are obtained from the intermittent follow-up with last observation carried forward methods (dotted black line). At the times of follow-up in which the blue – unobservable – line does not meet the quantified autograft regurgitation grade (for example at 2, 5, 7, 11, 12 years) loss of information takes place due to categorization of a continuous variable. Although in small patient populations, with limited follow-up duration this loss of information may have limited consequences, in large Registries like the European Ross Registry which now has more than 15.000 echocardiographic follow-up information and valve function interrogations this information loss can lead to errors in the evaluation of the longitudinal evolution of categorical outcomes both in patient specific but also in population level.

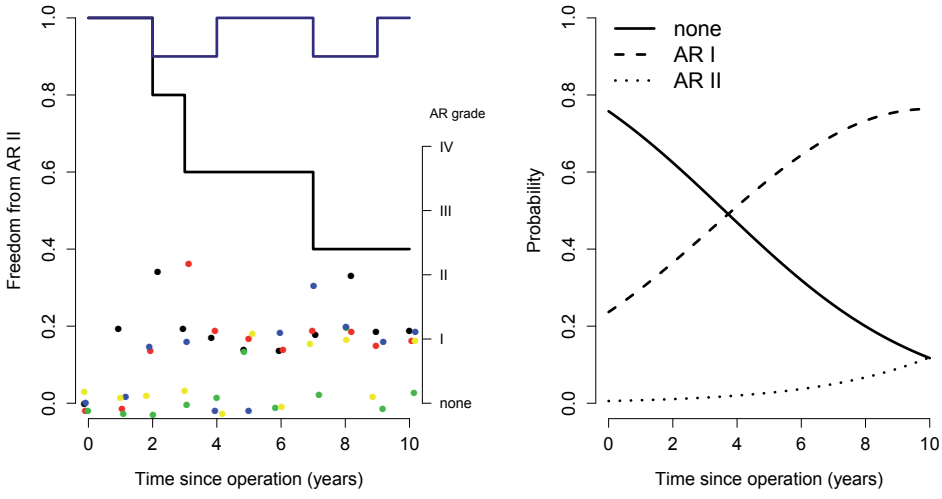


FIGURE 15. *Analysis of aortic regurgitation development with time (actuarial left, ordinal longitudinal right)*
Left panel: *The analysis of the development of aortic regurgitation of five sample patients (colored dots), three of them reach at some point the AR grade II. An arbitrary cutoff (AR grade II) is usually chosen to denote a clinically significant threshold. The blue line shows at every time the proportion of patients not being at AR grade II. The black solid line shows the estimate obtained when analyzing the longitudinal ordinal measurements of these patients using an inappropriate methodology (Kaplan-Meier). Severe overestimation of the probability of reaching AR grade II is seen with this methodology.*
Right panel: *Modeling of the probability of being in each of the ordinal aortic regurgitation grades, continuous time. Continuation ratio models depict the conditional probability than an individual moves to a greater AR grade once a given AR grade has been reached. This analysis reflects more accurately the limited evolution of patients to the AR II grade, in contrast to the actuarial estimates depicted in left panel.*

Intermittent follow-up with intermittent interrogation of valve function, missing follow-up visits and the analysis of categorical outcomes with the last observation carried forwards method, as is common in studies of outcomes after heart valve replacement can lead to variable interpretations of the same longitudinal process. This is depicted in Figure 14, lower panel. For the same longitudinal process (Figure 14, upper panel) and according to choice of interrogation points in time (triangle, square, circle and rhombus points) different inferences about the longitudinal dynamic of the underlying process can be inferred (Figure 14 lower panel).

Methodological considerations in analyzing aortic regurgitation grade over time

With respect to the presentation and analysis of categorical outcomes such aortic regurgitation in the cardiac surgical literature, not only the method of measurement and information storage but also the methods for analyzing this information is more often than not, inappropriate. Significant misrepresentation can occur when statistical methods are misused.

The most often used methodologies in the literature for the evaluation of aortic regurgitation over time in a population of patients are actuarial methods. These methods however are inappropriate to analyze functional, longitudinal, repeated, reversible outcomes.

First, actuarial methods, regard the reaching of a certain state as a permanent non-reversible event, whereas patients usually experience a transition between aortic regurgitation grades. Thus by using actuarial methods, the time that individuals reach the predetermined cutoff (usually aortic regurgitation grade 2) is grossly underestimated. Second, even if there is positive, increasing dynamic in a categorical outcome such as aortic regurgitation, patients usually require longer time intervals to stabilize in a certain grade, and more often they fluctuate between grades during a considerable amount of time. Patients who develop a progressive valve failure and increase of aortic regurgitation over time, may move between the cutoff and lower (or even higher) categories for a considerable amount of time before stabilizing at a certain grade or permanently exceeding the arbitrary cutoff grade. A significant degree of variation in the categorical outcome such as autograft regurgitation may be attributed to errors or variability of measurement, biological variation, or the dynamic nature of the aortic regurgitation that may mask the underlying longitudinal process. This induces a further underestimation of the time to reach the determined cutoff (Figure 16). Additionally all limitations of actuarial methods with respect to competing risks and other absorbing states also apply to the evaluation of the development of aortic regurgitation with actuarial methods. Thus, actuarial methods using an arbitrary cutoff to denote a significant event, or the reaching of a certain degree of valve dysfunction are not only inappropriate for analysis, evaluation and presentation of longitudinal ordinal outcomes, but may also severely distort the underlying longitudinal process, usually by over-reporting and underestimating the time to reaching a certain degree of valve dysfunction.

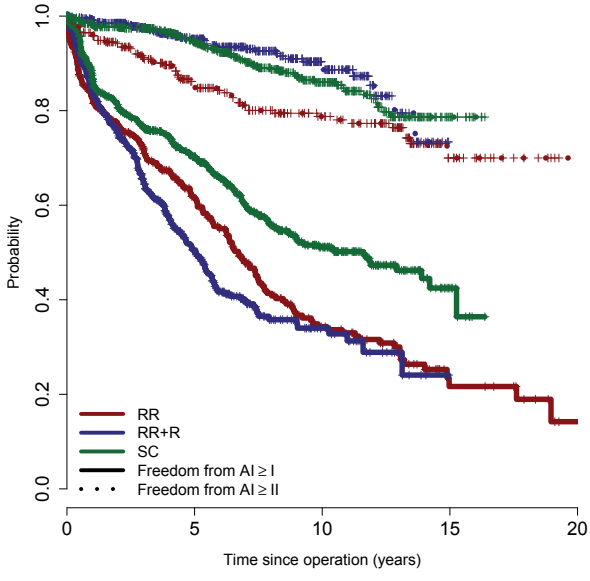


FIGURE 16. *Analysis of longitudinal ordinal outcomes with time-to-event methods. Various cut-offs to denote "events" yield dramatically different results*

Alternative approaches for the evaluation ordinal outcomes over time such as the development of aortic regurgitation with time focus, not on the time to reach a certain prespecified (and often arbitrary) cutoff, but on modeling the probability of a patient being in each of the observed categories (Figure 15, right panel) [38,108,110]. These analyses represents extensions of the mixed model methodology described in previous sections on ordinal outcomes, and thus can capture the longitudinal information of each patient and account for the correlation between serial measurements of regurgitation grades within each patient.

Ordinal regression models, essentially estimate within a single model the effect of explanatory variables on different ways of partitioning the data of the *j* outcome categories. An assumption of all models is that the effect of the explanatory variables (β) is the same on the calculated odds, regardless of the odds studied. Although the models provide a j specific intercept (θ_j), the effect of the β remains the same regardless of the corresponding splits (j). Although several test exists to investigate violations of these assumptions, these test tend to be overly strict especially when the number of explanatory variable is large [125], the sample size is large [108,126] or in the presence of continuous variables [126]. Violation of the proportionality assumption indicates that variables in the model have different effects (β) across the outcome levels (j). Fitting separate binary logistic models and comparing the estimated effects may help identifying variables that have differential effect across separate levels. Partial proportional odds models [108,110,126] allow for interactions between the independent variables and the different logit studies, therefore allowing the effect of the explanatory variable to vary (β_j) across the different outcome levels. Fitting such models requires the restructure of the data set, with multiple lines (responses) for each patient at the j levels and additional variables indicating if the individual is at – the now replicated – level of outcome. Additionally, due to the correlation of the replicated dataset (with several observation in each individual) generalized estimating equations are used to fit the non-proportional and the partial proportional odds model [108,126].

In addition to the above it should be noted that the advantages of mixed models, to allow for correlation of serially obtained measurements within each patient, are applicable to the linear predictor function therefore allowing for random – patient (m) specific – intercepts (θ_{jm}) and slopes (b_{jm}).

Development of autograft valve insufficiency after the Ross procedure

As depicted in Figure 15, the diffusion of patients into higher AR grades is overestimated with use of actuarial methods, and the time to the development of clinically relevant AR is underestimated even in small patient populations.

This error is usually inflated in large patient populations and longer follow-up durations. Figure 16 presents an analysis of the development of autograft regurgitation grade I and grade II with time-to-event methods in the three surgical techniques coded in the European Ross Registry. Inspection of Figure 16 leaves the reader with the impression of a significant dynamic in the development of clinically relevant autograft regurgitation. Although the

comparison between the techniques for both the AR≥I and AR≥II indicate statistically significant differences, for the (more relevant) AR≥II outcome at 10 years there seem to be small differences between the surgical techniques. All the above mentioned drawbacks of time-to-event methods (disallowing other absorbing states, regarding outcomes are irreversible, modeling the time to first occurrence of a dynamic reversible outcome such as aortic insufficiency) lead to severe overestimation of the dynamic of the development of autograft insufficiency in patients after the Ross procedure.

When the development of autograft insufficiency is modeled as an ordinal variable, taking into consideration the dynamic nature of this phenomenon, the reversibility of the severity grade, allowing for patients to move between usually adjacent categories for a large amount of time before stabilizing in a certain category a different, a more appropriate and more realistic picture is obtained. Figure 17, showing a plot of the probability of a patient being in a certain AR grade against time in the three surgical techniques used in the Ross registry. In the subcoronary and root replacement with reinforcement technique (Figure 18, left and middle panel) the majority of patients remain in the AR≤I category throughout the observation period. In the subcoronary technique, some diffusion of the patient population in the AR I grade category can be observed after the 8 year mark, however the development of clinically relevant autograft regurgitation of grade II is minimal. Similar conclusions can be drawn for the relative new root replacement technique with autograft reinforcement (Figure 17, middle panel). On the contrary in the root replacement technique (Figure 17, right panel) significant progression in higher autograft regurgitation grades can be observed for the patient population. Similarly the development of regurgitation grades in the homograft over time are displayed in Figure 18.

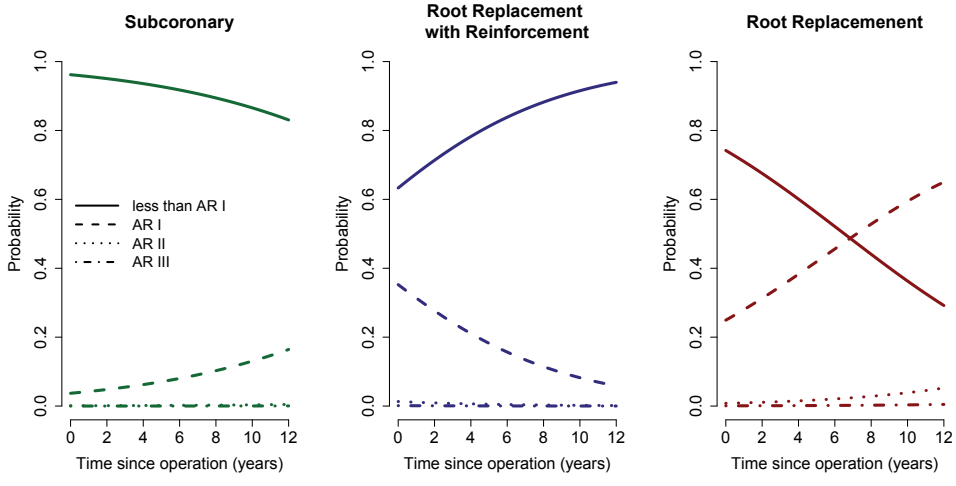


FIGURE 17. *Development of autograft regurgitation after the Ross procedure. Cumulative link mixed model longitudinal ordinal regression.*

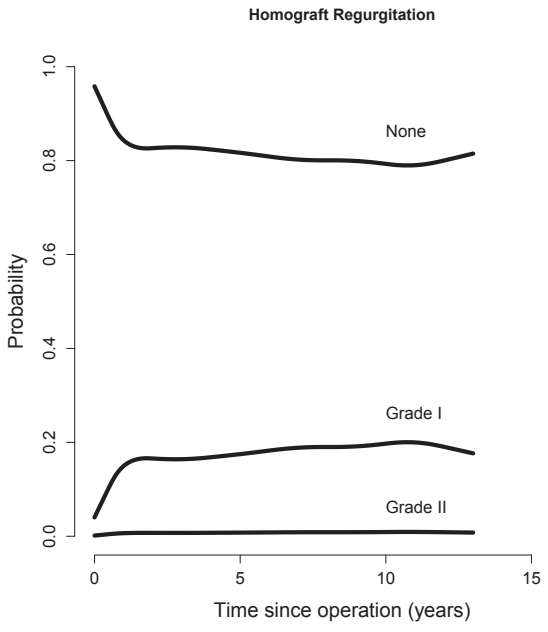


FIGURE 18. *Development of homograft regurgitation after the Ross procedure. Multinomial ordinal model, with a random patient effect and a piecewise linear relationship with follow-up time.*

COMBINING LONGITUDINAL AND TIME-TO-EVENT INFORMATION

Exogenous and endogenous (bio)markers

The follow-up of patients after medical interventions and procedures is a process generating a wealth of information. Usually in the cardiothoracic follow-up setting the primary interest lies in whether patients have experienced or not a usually binary event of interest (e.g. death, reoperation). However several other usually quantitative parameters collected at the time of follow-up may be associated or may include prognostic information about the event of interest and the probability of experiencing the event of interest in the future. For example, although patients may not have experienced a valve failure or reoparations, increased or increasing transvalvular gradients as measured by echocardiography through time are strong indications of a potential valve failure or reoperation in the near future. Similarly, although patients may not have experienced a heart failure decompensation, increased or increasing blood levels of NT-proBNP may indicate worsening of heart failure, and provide valuable prognostic information.

Usually, time-to-event outcomes and longitudinal measurements of biomarkers of interests are treated and analyzed separately. While the most frequently used methodological framework for the analysis of time to event data has been published several decades ago [90,127], the methodological framework for the analysis and evaluation of measurements of

biomarkers obtained through time is only recently being utilized in the medical literature with increasing interest.

Extensions of the Cox model provide some flexibility in including (*external* or *exogenous*) time-dependent variables in the survival models, however the application of this framework in the setting of (*internal* or *endogenous*) biomarkers obtained from individuals under study and their association to time-to-event outcomes may be problematic for several reasons [39], and have been presented in detail by Rizopoulos [39]. In summary, endogenous biomarkers (such as aortic valve transvalular gradients for the study of valve failure) are generated by the individuals in contrast to exogenous markers (air pollution for the study of asthma attacks) and as such they require the survival of the individual as an information generating process. Exogenous markers (air pollution) can be measured after the event of interest takes place on an individual or after the death of an individual, endogenous however biomarkers (ie transvalvular homograft gradients) cannot be evaluated in the same context after the event of interest takes place, or cannot be obtained after the death of the patient. Due to the dependency of the information generating process of the endogenous biomarkers on the survival of the individual, the hazard function in the presence of endogenous markers is not directly related to the survival function, and functions such as the conventional formulation of the survival function, do not anymore represent a survival function [39].

Therefore the evaluation of the information context in the longitudinal process of an endogenous biomarker on a patient bound event of interest requires a different framework. Additionally, endogenous biomarkers usually have biological variability, which is not always solely a consequence of measurement error (which is also present in exogenous biomarkers) but can be partially attributed to the underlying variability that every biological system has. Thirdly, in contrast to the continuous measurement ability of exogenous markers (air pollution can be monitored continuously during the study of asthma attacks and irrespective of the occurrence of events), endogenous biomarkers practically are measured intermittently during follow-up examinations. This has direct implications when the extended Cox model is used to model endogenous markers, as the "last value carried forward" that the extended Cox model employs might be inappropriate in many modeling strategies of endogenous markers [39].

As a measure to overcome the limitations of the extended Cox model when evaluating endogenous biomarkers, the joint model framework has been proposed [39,128–131]. Details of the advantages of joint models, with applications to biological hypotheses, have been published previously in great depth [39] and are beyond the scope of the present thesis.

Using the joint model framework we investigated the association of homograft gradient development after the Ross procedure on the risk for homograft reoperation. Natural cubic splines with four internal knots (at the corresponding percentiles of the follow-up duration) were employed when modeling the longitudinal trajectories of the mean homograft gradient. The graphical representation of the results are displayed in Figure 19.

Increased homograft gradients, especially within the first 2 years postoperatively (Figure 19) are associated with an increased risk for reoperation on the homograft. This information can be used to evaluate expectations after the Ross procedure based on the observed longitudinal trajectory of the individual patients.

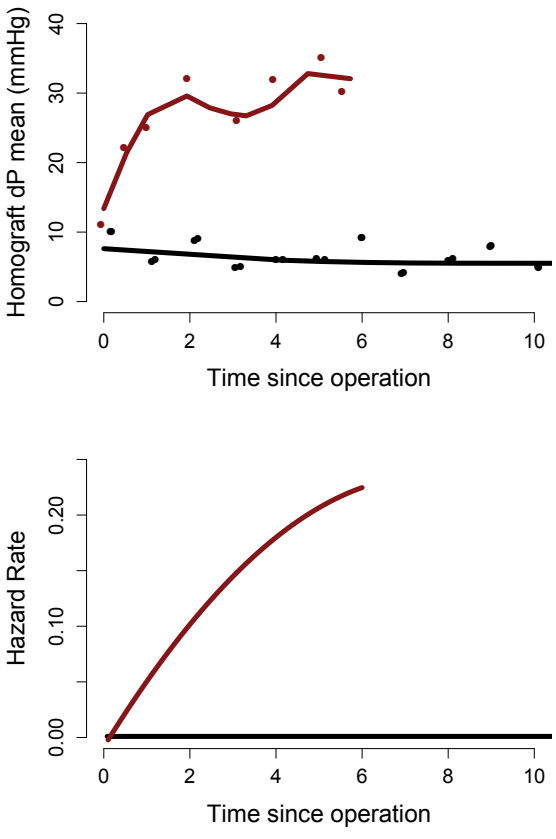


FIGURE 19. *Upper Panel: The longitudinal evolution of homograft gradients in two sample patients. A patient with low postoperative gradient development (black trajectory) and a patient high early development of high homograft gradients indicative of an immunological reaction (red trajectory). Lower panel: The hazard for reopeation (survival submodel of the joint model) in the two mentioned patients as a function of time.*

On an individual patient basis, the joint model framework allows prediction of survival probabilities to be obtained, at time points T>t in patients that have provided some biomarkers up to time point t. For the homograft evaluation, based on the joint modeling of the homograft data, dynamic prediction of survival allows us to use the obtained results from the complete patient collective on new individuals that have provided some trajectory of homograft gradients up to time t in order to derive their individualized risk for reoperation at times T>t (Figure 20).

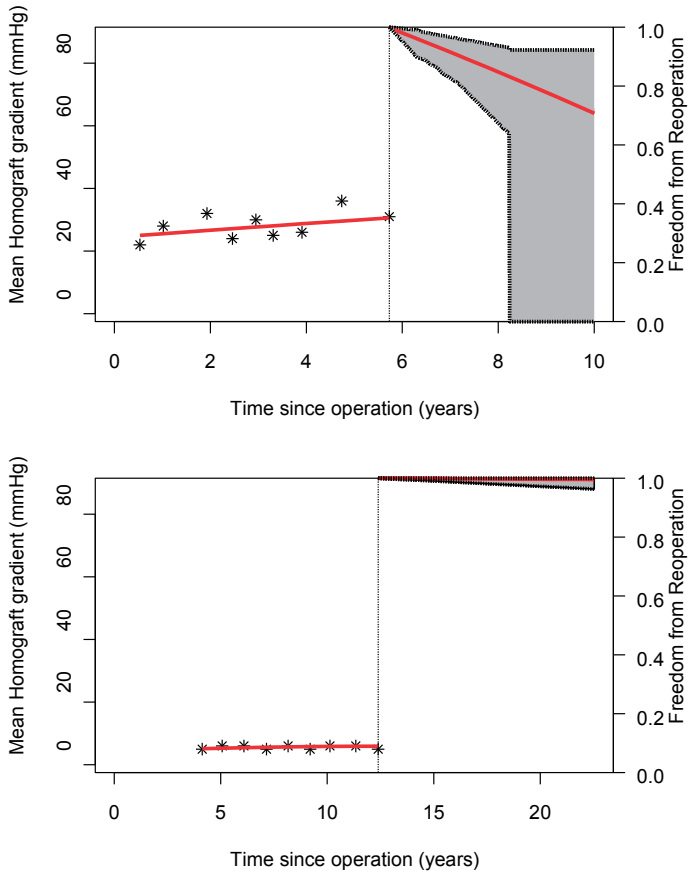


FIGURE 20. *Dynamic risk prediction on a patients with early development of significant homograft gradient (upper panel) and a patient without significant development of homograft gradients (lower panel). In each panel, on the left side is the longitudinal development of the mean homograft gradient in each patient up to the last observation, and on the right side the predicted survival probabilities for a reoperation in the future. The shaded areas correspond to the 95% confidence intervals of the survival estimates.*

CONCLUSIONS

The present thesis studied the evaluation of outcomes after a complex heart valve interventions, such as the Ross procedure, using data from the European Ross Registry with focus on the early and late clinical results, the patients' survival and the durability of the procedure. Simultaneously, various methodological aspects for the analysis of these outcomes are depicted.

Knowledge obtained from this thesis

The following new knowledge has been obtained and documented through the works and scientific publications of the present thesis:

1. Despite its complexity, when performed in experienced centers the Ross procedure has a low initial risk [14,35] for mortality and morbidity.
2. The Ross Registry has presented durability information of the Ross procedure, in a multi-center fashion to allow comparisons with other alternatives and outline expectations after the Ross procedure for patients and physicians [32,35]
3. Survival of the Ross patients is excellent and the data up to now indicate that it is similar or follows very closely the expected survival of the age and gender adjusted general population [14,35,51,63].
4. Patients after the Ross procedure face a low risk for reoperation, however these reoperations when performed in experienced centers can be performed with low morbidity and mortality [35].
5. Patients after the Ross procedure can enjoy a quality of life that is superior to other alternatives, with low incidence of valve-related morbidity and unrestricted level of activities [14,132]. In young women, the Ross procedure allows unproblematic childbearing, avoiding the need for anticoagulation and the associated risks that mechanical valves would enforce and with far superior durability than xenograft alternatives.
6. Analyses of the large population of the Ross Registry has identified technical factors associated with reduced autograft durability [14,32,58] and confirmed the success of alternative[24], novel techniques to preserve autograft function and increase durability [32,133]
7. Analyses of the Ross Registry have confirmed the excellent functional status of the Ross valves [14,32,134], the beneficial effect of this valve performance on left ventricular mass reduction[135] and transvalvular hemodynamics [32,57,134,136]. Reports including Ross patients well into the second decade after the Ross procedure confirm the durability of this excellent valve performance [34,133].
8. In contrast to popular beliefs and hypotheses [61] the presence of a bicuspid aortic valve is not risk factor for autograft deterioration after the Ross procedure [14,32,35,63]. Up to the point of the present writing, the presence of a bicuspid aortic valve in patients undergoing the Ross procedure is not associated with adverse durability or functional valve performance. Due to the large number of patients included in the Registry this fact is not likely to change its clinical significance at least for the first 15 years after the Ross procedure.
9. In contrast to previous popular beliefs that the Ross procedure is immune to postoperative endocarditis, results and analyses of the Ross Registry have shown than almost 20% of all reoperation in are performed on the grounds of endocarditis, and may be preventable. Knowledge of this fact together with high clinical suspicion required to detect non-fulminant homograft or autograft endocarditis and prevent valve deterioration may further improve outcomes after the Ross procedure.

Improvements in clinical decision making for young patients with aortic valve disease

Despite all efforts and medical progress that took place in the last 50 years, the treatment of young patients with aortic valve disease still remains a significantly problematic. Although it is well known that avoidance of an aortic valve intervention leads to reduced survival [111], for the choice of optimal timing of intervention, this risk should be weighed against the risks associated with either mechanical or biological valves [4,49,50,137]. Despite efforts in lowering the incidence of thromboembolic complications in mechanical valves and efforts to increase the hemodynamic performance and durability of biological valves, both these alternatives under-perform when compared to the native aortic valve and are associated with significant valve related morbidity[4,49]. This is even more important in the young patient with aortic valve disease who will spend a significant part of his lifetime with the aortic prosthesis and thus faces an increased risk for prosthetic valve related morbidity. Because of the suboptimal performance of valve prostheses, in young patients with significant aortic valve disease, without the presence of symptoms or signs of ventricular dysfunction, a "watchful waiting" strategy may be considered in order to gain time and postpone the replacement of the native aortic valve [138,139].

However even if a reoperation may become necessary, the Ross patient enjoys an unrestricted quality of life, and regular follow-up of these patients can identify the need for a reinterventions, well in time to ensure an elective, low risk, reintervention. Whether a reintervention, or a need for reintervention constitutes a "failure" of the Ross procedure remains debatable. If the Ross procedure manages to bridge the young patient with aortic valve disease from an age when a conventional biologic solution is questionable (age, 20-60 years) to an age at which a biologic or even transcatheter (age>70 years) solution is feasible, this, can also be considered as a success of the Ross procedure. However, even when an autograft reoperation becomes necessary, in about 22% of cases, the autograft can be either repaired or spared[35], thus retaining some of the benefits the pulmonary autograft has to offer. Elective reoperation in the case of autograft or homograft deterioration can be performed with remarkable safety in experienced centers. Also, catheter interventions will probably reduce the incidence and the need for open conventional procedures further.

Future perspectives

Currently, the European Ross Registry provides an excellent insight in the first postoperative decade after the Ross procedure with a significant number of patients being now in the second postoperative decade. Although this in terms of clinical trials constitutes already "long-term" evaluations, results or outcomes, for the young patient with aortic valve disease this follow-up constitutes a small amount of time that the patient will live with the implanted prostheses. Longer follow-up of these patients together with the evaluation of these results with proper and scientifically sound methodologies will help crystalize the benefits, risks and expectations after the Ross procedure in young patients.

In terms of the procedure per se, the long term results (>2 decades) of novel techniques[32] still remain to be seen. Further technical modifications of the autograft procedure [32,133]

or novel homograft preservation[67,140,141] or implantation [142] techniques may lead to an improved durability of the respective valve substitutes and the Ross procedure altogether. Moreover the long term results of reoperations after the Ross procedure[35], especially those sparing or repairing the autograft, as well as catheter based interventions on the homograft remain to be seen.

Despite all therapeutic options and modalities, even today, aortic valve replacement, remains a palliative treatment. Mechanical and biologic prostheses bring advantages and disadvantages that the patient and physician should weigh carefully before making an important, informed decision. In concordance to this mentality the current European guidelines have emphasized the importance that the preference of the well-informed patient has in deciding the optimal, and perhaps individualized therapeutic strategy[143]. Eventually, patients requiring aortic valve replacement face some risk of procedural or postoperative valve-related complications. From the view of the treating surgeon, and especially for the Ross procedure, the wish for risk avoidance or risk intolerance, might deny a great proportion of young patients with aortic valve disease all the benefits the Ross procedure has to offer[144].

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CHAPTER 14

SUMMARY

NEDERLANDSE SAMENVATTING

ACKNOWLEDGEMENTS

CURRICULUM VITAE

LIST OF PUBLICATIONS

PHD PORTFOLIO

SUMMARY

Chapter 1 is the general introduction of the thesis. The aims of our studies are presented and an outline of the thesis is given.

Chapter 2 presents a proposal on the nomenclature of the aortic root components is presented focusing on the following research questions. The proposed nomenclature in the corresponding publication serves as a guide for data collection and evaluation purposes in the multicenter German-Dutch Ross registry.

Chapters 3 and 4 the single center results with the subcoronary Ross procedure are presented in the University of Lübeck. The Ross procedure has a low operative mortality and patients after the Ross procedure enjoy a survival comparable to that of the general populations. Freedom from any reoperation was 92% at 10 years and 87% at 15 years. Important steps and technical considerations of the subcoronary Ross procedure are presented.

Chapter 5 the durability of the autograft and homograft as observed in the large population of the German-Dutch Ross registry are presented. Modes of autograft and homograft failure are presented as well as detailed outcomes of the observed reoperations. The risk of reoperation depends largely on the surgical technique used, the preoperative hemodynamics and center experience and expertise.

Chapter 6 challenges a popular belief that the Ross procedure in the presence of a bicuspid aortic valve is associated with reduced durability. For the observed time period, postoperative neo-aortic regurgitation after the Ross procedure did not differ between patients with a BAV or a TAV. Patients with a BAV did not exhibit higher rates of ascending aorta dilatation after AVR than patients with TAV.

Chapter 7 discusses the problem of competing risks when evaluating conduit durability. Patient survival is seemingly important when evaluating conduit durability and ignoring patient survival impacts the objective evaluation of conduit durability.

Chapter 8 presents the results of an effort to improve autograft durability after the Ross procedure. The various techniques utilized in the German Dutch Ross Registry have different modes of failure. Surgical reinforcement techniques introduced to address dilatation of the autograft in the root replacement technique appear to have a beneficial effect on autograft durability.

Chapter 9 presents clinical outcomes after the Ross procedure and provides a basis for the further judgment of this procedure and assist physician–patient discussion about the risks, benefits, and expectations after the Ross procedure.

Chapter 10 presents a comparison of the survival of Ross patients with the survival of patient with mechanical valves after optimal and intensive anticoagulation monitoring. In this propensity-score matched study no late survival benefit could be observed between Ross patients and patients with mechanical aortic valves and optimal self-managed anticoagulation therapy.

Chapters 11 and 12 focus on specific aspects of homograft durability. Echocardiographic follow-up of the pulmonary conduits shows good conduit durability and clinically important conduit regurgitation and stenosis are rare in adult patients after the Ross operation. When

homograft deterioration takes place, this appears to affect all levels of the homograft but most prominently, at the level of the proximal suture line, which may have implications for novel preservation methods, as well as homograft size selection and implantation techniques.

Chapter 13 discusses the results and the knowledge obtained from the above mentioned studies and research questions are summarized and put in perspective. Pitfalls in the methodologies used to evaluate outcomes after the Ross procedure are presented with examples from the European Ross Registry and discussed, which are generalizable in the evaluation of outcomes after complex heart interventions.

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 is de algemene introductie van het proefschrift. De doelen van onze studies worden gepresenteerd en een beschrijving van de inhoud van het proefschrift wordt gegeven.

Hoofdstuk 2 doet een voorstel voor de nomenclatuur van de verschillende componenten van de aortawortel. De voorgestelde nomenclatuur wordt gebruikt als richtlijn voor dataverzameling en beoordeling in de multicenter Duits-Nederlandse Ross registratie.

Hoofdstukken 3 en 4 presenteren de resultaten met de subcoronaire Ross procedure van de Universiteit van Lubeck, Duitsland. De Ross procedure heeft een lage operatieve sterfte en de overleving van patienten na de Ross procedure is vergelijkbaar met de algemene bevolking. Vrijheid van reoperatie op 10 en 15 jaar na de operatie was respectievelijk 92% en 87%. Belangrijke stappen en technische overwegingen voor de subcoronaire Ross operatie worden gepresenteerd.

Hoofdstuk 5 beschrijft de duurzaamheid van de autograft en homograft zoals waargenomen in de grote patientenpopulatie van de Duits-Nederlandse Ross registratie. De karakteristieken van autograft- en homograftfalen worden gepresenteerd, alsmede de gedetailleerde uitkomsten van de geobserveerde reoperaties. Het risico op een reoperatie is grotendeels afhankelijk van de toegepaste chirurgische techniek, de preoperatieve hemodynamiek van het kleplijden, en de ervaring en expertise van het chirurgische centrum.

Hoofdstuk 6 spreekt de populaire gedachte tegen dat de Ross procedure minder duurzaam is als er sprake is van een bicuspide aortaklep. Tijdens de observatieperiode was er geen verschil in postoperatieve neo-aortaregurgitatie na de Ross procedure tussen patienten met een bicuspide versus tricuspide aortaklep. Patienten met bicuspide aortakleppen hadden een vergelijkbare snelheid van aorta ascendensdilatatie na de Ross procedure in vergelijking met patienten met een tricuspide aortaklep.

Hoofdstuk 7 bediscussieert het probleem van concurrerende risico's bij het evalueren van de duurzaamheid van een conduit. Overleving van patienten is een belangrijke factor bij het evalueren van de duurzaamheid van een conduit, en het negeren van overleving van patienten heeft effect op de objectieve evaluatie van de duurzaamheid van een conduit.

Hoofdstuk 8 presenteert de resultaten van een inspanning om de duurzaamheid van de autograft na de Ross procedure te verbeteren. De verschillende toegepaste chirurgische technieken in de Duits-Nederlandse Ross registratie hebben verschillende manieren van falen. De chirurgische verstevigingstechnieken die zijn geintroduceerd voor de aortawortelvervangingstechniek om verwijding van de neo-aortawortel tegen te gaan, lijken een postief effect te hebben op de duurzaamheid van de autograft.

Hoofdstuk 9 beschrijft de klinische uitkomsten na de Ross procedure en voorziet in een basis voor de evaluatie van deze procedure, en ondersteunt de discussie tussen arts en patient over de risico's, voordelen en verwachtingen na de Ross procedure.

Hoofdstuk 10 presenteert een vergelijking van overleving van Ross patienten en patienten met mechanische klepprotheses die een optimale en intensieve controle hebben van hun antistollingmedicatie. Deze propensityscore gematchte studie toont geen laat

overlevingsvoordeel voor Ross patienten in vergelijking met patienten met mechanische aortakleppen en optimale zelfbeheer antistollingmedicatie.

Hoofdstukken 11 en 12 richten zich op specifieke aspecten van de duurzaamheid van homografts. Echocardiografische follow-up van de pulmonale conduits toont een goede duurzaamheid, en klinisch belangrijke conduit regurgitatie en stenose komen zelden voor in patienten na de Ross procedure. Wanneer er sprake is van homograft degeneratie, dan lijkt dit op alle niveaus van de homograft zichtbaar, maar met name op het niveau van de proximale hechtnaad, hetgeen een belangrijk gegeven kan zijn voor nieuwe preservatiemethoden, maar ook selectie van de grootte van de homograft en implantatietechnieken.

Hoofdstuk 13 bediscussieert de resultaten en kennis die is verkregen uit bovengenoemde studies, en de onderzoeksvragen worden samengevat en in perspectief geplaatst. Valkuilen van de methodologieen die worden gebruikt om de resultaten van de Ross procedure te evalueren, worden gepresenteerd en bediscussieerd met voorbeelden uit de Europese Ross Registratie. Deze valkuilen zijn generaliseerbaar naar de evaluatie van uitkomsten van complexe interventies aan het hart.

ACKNOWLEDGMENTS

I remain thankful to Professor Dr. Takkenberg for the opportunity complete my Thesis under her supervision. For all her thoughtful mentorship throughout the years and the works of this PhD thesis. It is impossible for one to ask for better supervision. An additional thank you for all your help with the administrative part of this process.

To all the colleagues of the German Dutch Ross Registry for their hard work building and maintaining this wonderful collection of data. For their interest in cardiovascular research and for their affection and sympathy to the young patient with aortic valve disease.

To all the patients of the German Dutch Ross Registry who entrusted us with their data, in the hope that our analyses and the knowledge we obtained might benefit others.

To Professor Ad Bogers for entrusting me with the completion of this Thesis in his department at the Erasmus MC Thoraxcenter.

To Professor Dr. Hans-Hinrich Sievers for the opportunity to work and learn under his supervision in the department of cardiac and thoracic vascular surgery of the University of Lübeck. For introducing me to the concepts of the evaluation of outcomes after heart valve surgery and his thoughtful mentorship throughout the years and the works of this thesis.

To Professor Dr. Ulrich Stierle for introducing me to the principles of cardiovascular research and to the research of outcomes after the Ross procedure.

To Dr. Mostafa Mokhles for his help and thoughtful comments throughout the process and for the collaboration on several papers of included in the present Thesis.

To Professor Dimitris Rizopoulous and Dr. Elrozy Adrinopoulou for their statistical consultancy on several methodological aspects of the analysis of outcomes after heart valve interventions. Σας ευχαριστώ πολύ!

To Dr. Derek R. Robinson for his statistical consultancy, his invaluable help and support throughout the publications of this Thesis.

To my spouse, Martina Tandetzki for her support, patience and motivation. Thank you for your understanding.

To all the above mentioned individuals for their perseverance in proofing and commenting on the manuscripts, figures and tables of our published works as well as the present thesis, zealously pointing out all the small, annoying errors.

Those errors that still remain, are mine.

CURRICULUM VITAE

Efstratios I. Charitos was born on December 12th, 1981 in Nea Smyrni, Athens, Greece. After completing basic education he was admitted to the Medical School of the University of Athens in September 1999 and completed his medical training in June 2005. From September 2005 until September 2007 he worked as a research fellow in the combined program of the Department of Clinical Therapeutics of the University of Athens (supervisor: Prof. J. Nanas) and the Harefield Athens Recovery Program (supervisor: Prof. Sir M. H. Yacoub) in the field of heart failure and mechanical cardiac support in end-stage heart failure patients. From September 2007 until March 2014 he received training in cardiac and thoracic vascular surgery in the Department of cardiac and thoracic vascular surgery of the University of Lübeck (director: Prof. Dr. H.-H. Sievers). In 2010 he receive the title "Doktor der Medizin" (dr. med) from the University of Lübeck (supervisor: Prof. Dr. U. Stierle). In 2014 he obtained his board certification in cardiac and thoracic vascular surgery. From 2014 till present he is working as a specialist in the Department of Cardiac and Thoracic Vascular Surgery of the University of Lübeck (director: Prof. Dr. H.-H. Sievers).

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rhythm status after surgical atrial fibrillation ablation therapy: up to 12 months experience with a novel permanently implantable heart rhythm monitor device. Circulation. 2009 Sep 15;120(11 Suppl):S177-84.

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PHD PORTFOLIO

Name of PhD student:	Efstratios I. Charitos, MD
Erasmus MC department:	Cardiothoracic Surgery
Research School:	Cardiovascular Research School
PhD Period:	November 2009 – February 2014
Thesis Title:	A Framework for the Evaluation and Reporting of Outcomes after Complex Heart Valve Interventions – Applications to the European Ross Registry
Date of Thesis Defense:	Tuesday September 16, 2014 at 13:30 hrs

Academic education

1999 - 2005:	MD, University of Athens Medical School
2005 - 2007:	Research Fellow, University of Athens, Harefield Athens Recovery Program (Prof. M.H. Yacoub, Prof. J Nanas)
2007 - 2014:	Resident, Department of Cardiac and Thoracic Vascular Surgery, University of Lübeck (Prof. H.-H. Sievers)
2010:	Doktor der Medizin ("*Dr. med*"), University of Lübeck (Prof. U. Stierle)
2014:	Board Certification in Cardiac Surgery
2014 - present	Specialist, Department of Cardiac and Thoracic Vascular Surgery, University of Lübeck (Prof. H.-H. Sievers)

PhD Training	**Year**	**Workload**
Oral Presentations		
• Update on the German-Dutch Ross Registry (AATS, San Frascisco)	2012	0.6
• Effect of Autograft Reinforcement on Autograft Durability (AHA, New Orleans)	2009	0.6
• Single Center Experience with 545 Subcoronary Ross procedures (WSCTS, Berlin)	2011	0.6
• After the Ross Procedure the Patients' Survival is Similar to that of the Normal Population (DGTHG, Stuttgart)	2010	0.6
• Up to 16 years experience with the subcoronary Ross procedure (DGTHG, Stuttgart)	2011	0.6
• Impact of Endocarditis Before and After the Ross Procedure (DGTHG, Stuttgart)	2012	0.6
• German – Dutch Ross Registry Update (DGTHG, Stuttgart)	2012	0.6
• The Fate of the Bicuspid Valve Aortopathy After Aortic Valve Replacement (EACTS, Vienna)	2013	0.6

• Current Status of the Ross Procedure (Istanbul Meeting Practice and Science in Cardiology and Cardiovascular Surgery, *Invited Presentation*)	2012	1.5
• Bicuspid Aortic Valve Classification (Ross Meeting Atlanta, *Invited Presentation*)	2011	1.5
• The impact of Endocarditis before and after the Ross procedure (Ross Meeting Atlanta, *Invited Presentation*)	2011	1.5
• Left sided hemdynamics after various aortic valve procedures (Ross Meeting Atlanta, *Invited Presentation*)	2011	1.5
• German-Dutch Ross Registry Update (Atlanta, *Invited Presentation*)	2011	1.5
• Technical considerations of the subcoronary Ross procedure (Ross Meeting Atlanta, *Invited Presentation*)	2011	1.5
• An 2012 update on the German-Dutch Ross Registry (Ross Meeting Atlanta, *Invited Presentation*)	2012	1.5
• The Subcoronary Ross technique (Ross Meeting Atlanta, *Invited Presentation*)	2012	1.5
• Biological aortic valve replacement (Barcelona SHVD, *Invited Talk, Postgraduate Cours*e)	2011	1.5
• Epidemiology, classification, and clinical relevance of bicuspid aortic valve disease (Barcelona SHVD, *Invited Talk, Postgraduate Cours*e)	2011	
• Is a physiological aortic valve function feasible after aortic valve replacement procedures (Barcelona SHVD)	2011	0.6
• Does Type of Aortic Root Repair In Acute Type A Dissection Matter (Barcelona SHVD)	2011	0.6
• The Ross procedure in the Second Decade (3. Stuttgarter Aortentage, *Invited Talk*)	2013	1.5
• A survey on the nomenclature of the components of the aortic root: The tower of Babel? (DGTHG Stuttgart)	2009	0.6

Poster presentations

• Aortic Valve Replacement in 1854 Young Adults with the Autograft Principle (DKG Mannheim)	2013	0.6
• Rhythm monitoring after therapies for atrial fibrillation (ESC, Munich)	2012	0.3
• The surgical Cox Maze III procedure for the treatment of atrial fibrillation (ESC Munich)	2012	0.3

In-depth courses

• An Introduction to the Joint Modeling of Longitudinal and Survival Outcomes with applications in R (Erasmus MC)	2013	0.6
• Scientific Integrity Course (Erasmus MC)	2014	0.3

International Meetings

• German Society of Cardiac and Thoracic Surgery (Stuttgart)	2009	1.2
• German Society of Cardiac and Thoracic Surgery (Stuttgart)	2010	1.2
• German Society of Cardiac and Thoracic Surgery (Stuttgart)	2011	1.2
• German Society of Cardiac and Thoracic Surgery (Freiburg)	2012	1.2
• German Society of Cardiac and Thoracic Surgery (Freiburg)	2013	1.2
• German Society of Cardiac and Thoracic Surgery (Freiburg)	2014	0.9
• European Association for Cardio-Thoracic Surgery (Vienna)	2013	0.9
• World Society of Cardio Thoracic Surgery (Berlin)	2011	0.9
• American Heart Association (New Orleans)	2009	1.2
• American Assocoation for Thoracic Surgery (San Franscisco)	2012	1.2
• American Heart Association (Dallas)	2013	1.2
• European Heart Rhythm Association (Athens)	2013	0.9
• European Society of Cardiology (Munich)	2012	0.6
• Istanbul Meeting Practice and Science in Cardiology and Cardiovascular Surgery	2012	0.9
• The Ross Summit (Atlanta)	2011	0.6
• The Ross Summit (Atlanta)	2012	0.6
• Society of Heart Valve Disease Meeting (Barcelona)	2011	0.9

Peer Reviewer in International Scientific Journals

• Journal of Pediatric Infectious Disease	2012-...	0.3
• Journal Heart Valve Disease	2012-...	0.6
• PloS One	2013-...	0.3
• Cardiovascular Revascularization Medicine	2010-...	0.3

Total Workload (ECTS)	42