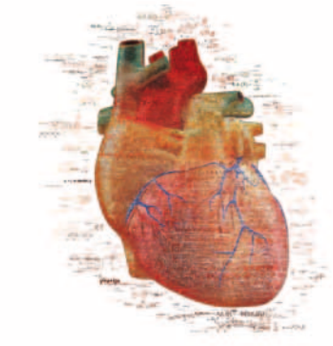
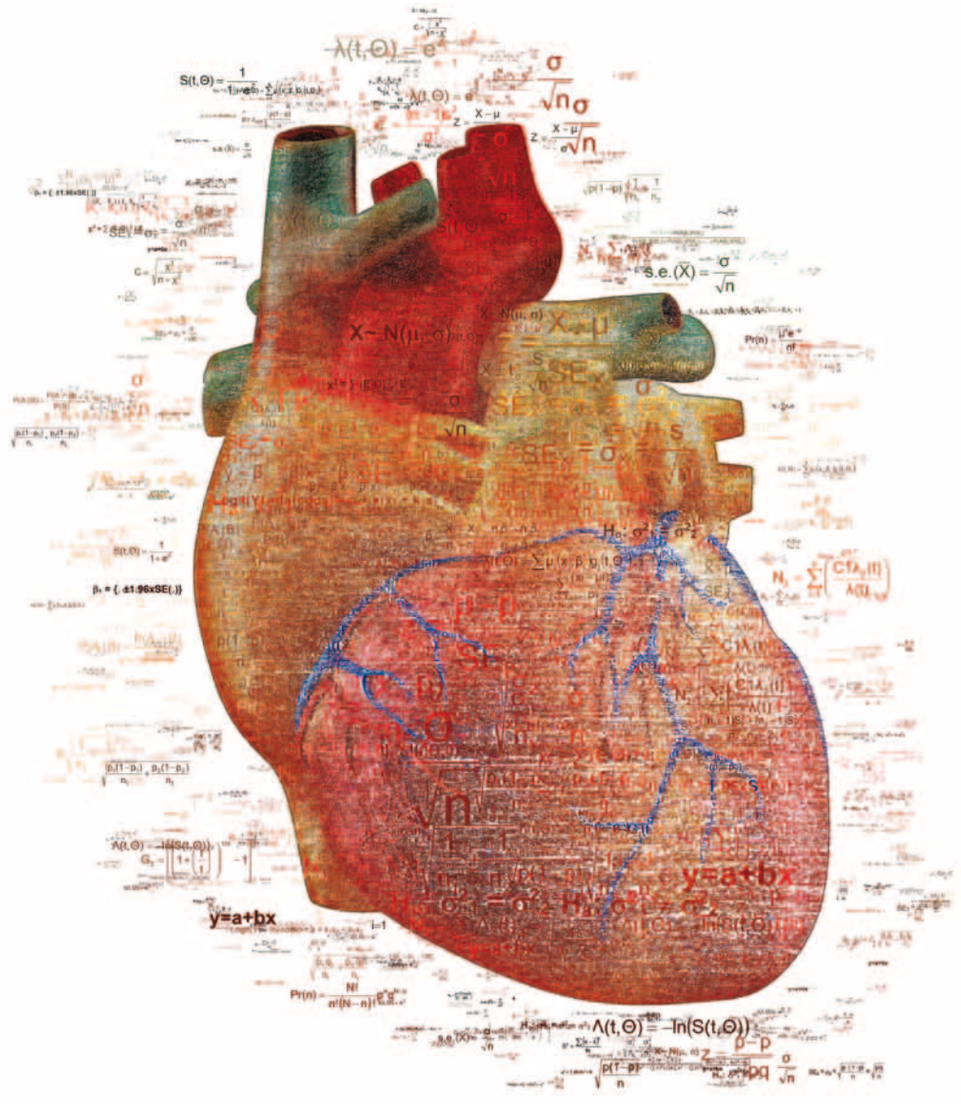


ISBN: 978-94-6169-441-6

INNOVATIVE MODELING OF OUTCOME IN CARDIAC SURGERY

M. Mostafa Mokhles

INNOVATIVE MODELING OF OUTCOME IN CARDIAC SURGERY



M. Mostafa Mokhles

INNOVATIVE MODELING OF OUTCOME IN CARDIAC SURGERY

M. Mostafa Mokhles

Lay out and printed by: Optima Grafische Communicatie, Rotterdam, The Netherlands
Cover design: Juan Osborne

ISBN: 978-94-6169-441-6

INNOVATIVE MODELING OF OUTCOME IN CARDIAC SURGERY

Innovatief modelleren van cardiochirurgische uitkomsten

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 decision of the Doctorate Board
The public defence shall be held on

Wednesday the 18th of December 2013 at 9:30 am

by

Mohammad Mostafa Mokhles
born in Kabul, Afghanistan

Doctoral Committee

Promotors:	Prof.dr. A.J.J.C. Bogers
	Prof.dr. J.J.M. Takkenberg
Other members:	Prof.dr. R.J.M. Klautz
	Prof.dr. J.W. Roos-Hesselink
	Prof.dr. E.W. Steyerberg

The research described in this thesis was financially supported by the Netherlands Organization for Scientific research (NWO), Mosaic grant, project number NWO 017.006.058.

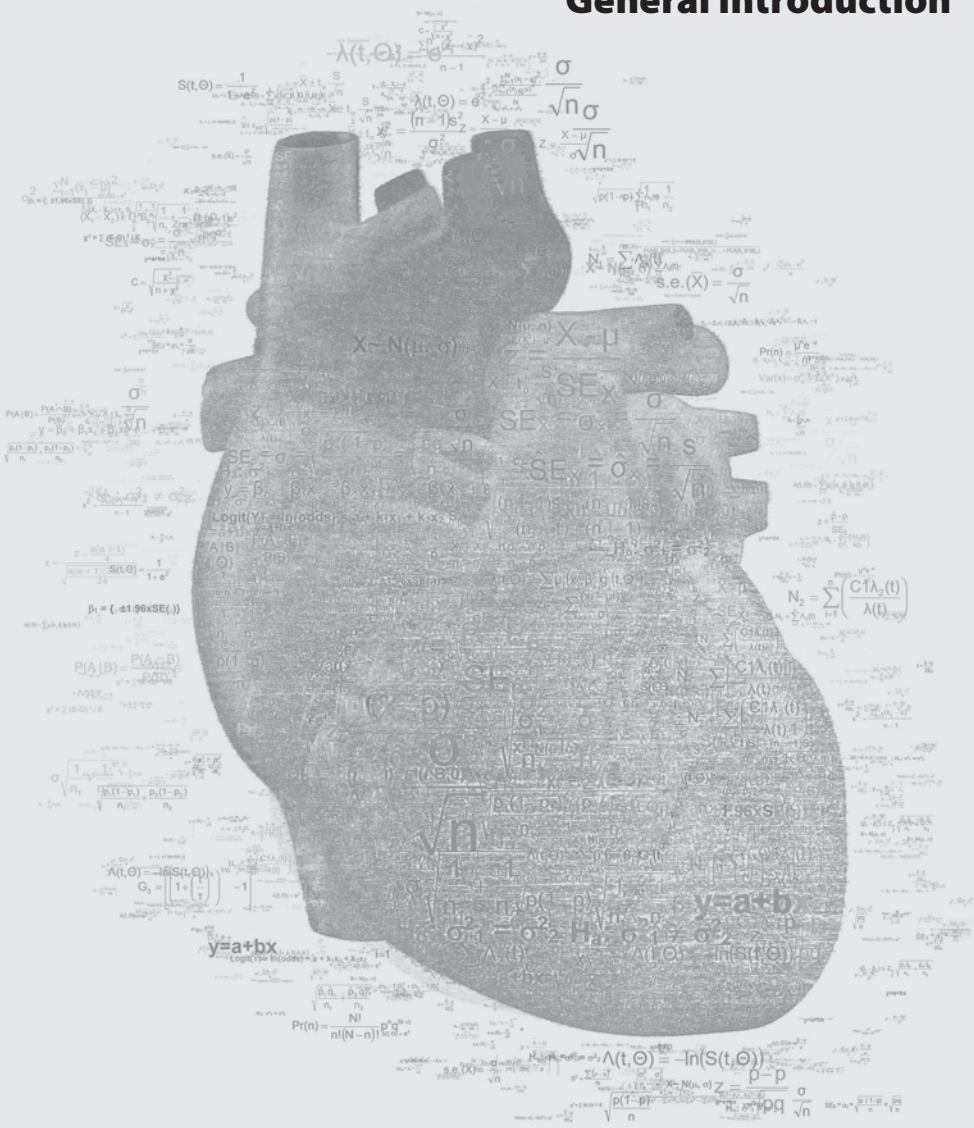
Financial support by the Dutch Heart Foundation and H.Huysmans foundation for the publication of this thesis is gratefully acknowledged.

For my parents

TABLE OF CONTENTS

Chapter 1

General Introduction



HEART VALVES

In the normal heart both left and right ventricle have a valve at the atrio-ventricular connection and at the ventriculo-arterial connection. In the left ventricle the inflow valve is the mitral valve and the outflow valve is the aortic valve. In the right ventricle the inflow valve is the tricuspid valve and the outflow valve is the pulmonary valve. These heart valves ascertain that blood only flows in one direction through the heart. The valves are made of strong, thin flaps of tissue, called leaflets. The valves control the blood flow through the heart by opening and closing the leaflets during the contractions of the heart.

Heart valve disease occurs when one or more of the heart valves do not work correctly because of valvular stenosis or valvular regurgitation, or a combination of the two. Valvular stenosis occurs when a heart valve doesn't fully open due to stiff or fused leaflets or when a valve is congenitally too small. This limits the amount of blood that can flow through the valve. Valvular regurgitation, also known as valvular insufficiency, occurs when a valve does not close properly. This will lead to blood leaking back through the valve when it should be closed. All four heart valves can develop stenosis, regurgitation of a combination of both stenosis and regurgitation. In case heart valve disease is not treated, it can have negative impact on a person's quality of life and may even become life-threatening. During the past decades, great advances in the surgical treatment of heart valves disease have been achieved. This thesis will focus on the surgical treatment of aortic and pulmonary valve disease.

AORTIC VALVE DISEASE AND VALVE REPLACEMENT OPTIONS

The aortic valve is the outflow valve of the left ventricle that regulates the blood supply to all of the major vessels of the body. It normally has three leaflets, although in 1% of the population it is found to congenitally have two leaflets (1). The aortic valve allows blood to flow from the left ventricle to the aorta and prevents regurgitation of blood from aorta back into the left ventricle.

Only in a minority of patients it is possible to repair a disease aortic valve. There are several options available for patients in whom the aortic valve needs to be replaced. The four most implanted valve substitutes are: mechanical prosthesis, bioprosthesis, allograft and autograft (also known as the Ross procedure).

The major advantage of mechanical valve prostheses is that it provides excellent durability and a low reoperative hazard (2, 3). However, because of their increased thrombogenicity, the choice for the mechanical valve implies lifelong anticoagulation and is associated with an increased risk for thromboembolic and bleeding events (4,

5). The use of anticoagulation may also complicate pregnancy because of the fetal and maternal complications associated with the use of warfarin (6, 7), and may require lifestyle adjustments. The main advantage of biological valve substitutes (bioprostheses, allografts and autografts) is that there is no need for long-term anticoagulation. The major downside of biological valve types is, on the other hand, the structural deterioration of these prostheses which can lead to regurgitation and/or stenosis of the valve leaflets, necessitating a reoperation or reintervention.

PULMONARY VALVE DISEASE AND VALVE REPLACEMENT OPTIONS

The pulmonary valve allows blood to flow from the right ventricle to the pulmonary artery and lungs, and prevents regurgitation of blood from pulmonary artery back into the right ventricle. In case of regurgitant dysfunction of the pulmonary valve there is a large amount of regurgitant blood flow from the pulmonary circulation back into the right ventricle resulting in right ventricle volume overload. More than 30% of all patients with congenital heart defects have a dysfunctional or absent pulmonary valve and need a pulmonary valve replacement at some point in their life. In addition, reconstruction of the right ventricular outflow tract (RVOT) with a pulmonary allograft is not only necessary in a broad range of congenital heart diseases (e.g. tetralogy of Fallot, truncus arteriosus, pulmonary atresia with ventricular septal defect, double outlet right ventricle) but also during the autograft procedure where a diseased aortic valve is replaced with the patient's own pulmonary valve. The autograft patients need therefore a donor allograft for the reconstruction of the RVOT.

There are several types of prostheses available for pulmonary valve replacement which includes: bioprosthetic valves, mechanical prostheses and allografts. Frequently used bioprosthetic valves for pulmonary valve replacement are bovine jugular vein grafts, porcine pulmonary valve conduits and porcine aortic roots. The most important advantages of bioprosthetic valves are the adequate supply of the valves, relatively low preparation costs and availability of smaller sizes for neonates. On the other hand, the rate of reintervention after bioprosthetic valve implantation in the RVOT position have been reported to be higher compared to allografts (8). Although mechanical valves theoretically provide several important advantages (e.g. durability, absent need of anticoagulation) their application is limited in patients who are in need of pulmonary valve replacement largely owing to frequent thromboembolic events, bleeding complications and valve failure (9-11). Allografts are currently the preferred type of conduit for pulmonary valve replacement, and most experiences has been acquired with these allografts. The use of an aortic valve allograft for pulmonary valve replacement was introduced in 1966 (12). It was not until 1983 that Ross et al. introduced the pulmonary valve al-

lograft for pulmonary valve replacement (13). This has resulted in an ever increasing application of allografts. Nevertheless, a tendency toward allograft degeneration over the years is still apparent (14) and long-term results of RVOT reconstruction with pulmonary allografts have been scarcely reported thus far. Degeneration of the pulmonary valve allograft can eventually lead to clinically relevant pulmonary stenosis (PS) and pulmonary regurgitation (PR). PS can range from mild and asymptomatic, not requiring intervention, to severe. The stenosis can become even more severe in growing children in whom the implanted allograft does not (entirely) follow the somatic growth of the child. PR is usually well tolerated in childhood. However, recent long-term studies have demonstrated that in adults PR leads to progressive right ventricular (RV) dilatation and, with time, to RV dysfunction, exercise intolerance and an increased risk of ventricular tachycardia and sudden cardiac death (15-17). Further improvements for, this still growing, population of patients with congenital heart diseases are mandatory to be able to optimize their life expectancy and quality of life. Long-term results of RVOT reconstruction with pulmonary allografts have been scarcely reported thus far. An important aim of this thesis was to assess the outcome of patients, with congenital heart defects or autograft patients, after pulmonary valve implantation in the RVOT position.

A more recent development in the treatment of the diseased pulmonary valve is the application of percutaneous approach (18). This approach will be discussed more extensively in **Chapter 20**.

INNOVATIVE OUTCOME MODELING

The tremendous development and application of biostatistics over the past few decades and the evolution of computational power have been a vital tool for the rise of evidence-based medicine. Although several (innovative) statistical methods have been developed and are currently available for the analyses of outcome in cardiac surgery, only a few of these methods are widely used. The success of evidence-based medicine depends, however, to a great extent on the correct statistical analysis of the data arising from a study. Ignoring this important aspect of research may result in wrong statistical inferences and conclusions how interesting the study design and data may be.

OUTLINE OF THIS THESIS AND AIMS

The primary aim of this thesis is to illustrate the use of innovative statistical methods for the assessment of patient outcome and heart valve function after aortic or pulmonary valve replacement. The application of the following statistical methods, from simple to

more advanced, is illustrated in this thesis while studying patient outcome (**Chapters 1-12**) and prosthesis durability (**Chapters 13-18**) after aortic or pulmonary valve replacement:

'Conventional' statistical methods for outcome assessment in cardiac surgery

The application of conventional and most widely used statistical methods is illustrated in **Chapters 2-7** during the assessment of patient and prosthesis outcome after heart valve replacement. The aim of **Chapter 2** is to assess the clinical outcome and health-related quality of life after RVOT reconstruction with an allograft conduit. The objective of **Chapter 3** is to describe the long-term experience with the use of allograft conduits for RVOT reconstruction after correction of tetralogy of Fallot in our institution. The improper application of survival- and risk factor analyses will be illustrated in **Chapters 4 and 5**. The outcome of Ross patients in whom a variant of the inclusion cylinder technique was utilized whereby the aortic root size was adjusted to match the autograft will be described in **Chapter 6**. The aim of **Chapter 7** is to determine the long-term survival prognosis of patients with infective endocarditis.

The application of systematic reviews and meta-analyses

Systematic reviews and meta-analyses are powerful statistical tools available in the pursuit of evidence-based medicine. The Cochrane Handbook defines a systematic review as 'A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarize the results of the included studies (19). In addition to systematic reviews, meta-analyses contain pooled and reanalyzed results based on the data from the individual studies. The rationale for a meta-analysis is that well conducted meta-analysis allows for a more objective appraisal of the evidence because of the improved statistical power and precision of the estimates of treatment effects.

The aim of **Chapter 8** is to (1) systematically review the current literature with regard to infective endocarditis, comparing medical to surgical therapy to evaluate if surgery is the preferred option, (2) to perform a meta-analysis of studies who reported propensity matched analyses, and (3), to briefly summarize the current indications for surgery in patients with infective endocarditis. The objective of **Chapter 9** is to explore the association of prosthesis-patient mismatch and long-term survival after aortic valve replacement in adults by performing a systematic review and meta-analysis.

Propensity Score analyses

Although randomized controlled trials (RCTs) are considered to be the 'gold standard' and provide the strongest evidence for the efficacy of preventive and therapeutic procedures in the clinical setting (20), it is not always possible or feasible to perform an RCT because of medical or ethical reasons. The propensity score technique was introduced by Rosenbaum and Rubin in the early in 1980's and offers a way to achieve more comparable groups in observational studies (21-23). The calculated propensity score for each individual reflects that person's probability to receive a certain treatment based conditional on observed baseline characteristics.

Since few centers are willing to randomize young adult patients between the Ross procedure, a mechanical prosthesis, a stentless or stented bioprosthesis, the objective of **Chapter 10** is to assess late survival in young adult patients after a Ross procedure versus mechanical aortic valve replacement by performing a propensity score matched study.

Matching patient survival with the general population

Matching of patient survival with that of the general population is very common in medical research. This is done in order to obtain an objective measure of survival probability after a certain diagnosis or treatment (e.g. infective endocarditis or aortic valve replacement) while controlling for differences in mortality as a result of other causes. Only reporting long-term survival in a certain patient population can lead to wrong conclusions since the background mortality of the general population is not taken into account. Although researchers often attempt to compare the survival of specific patient population with that of the general- or reference population, comparison is not always performed methodologically correct (24).

Using different survival matching methods, the aim of **Chapter 11** is to evaluate the long-term mortality of surgically treated infective endocarditis patients in relation to the age- and gender matched general population.

Assessment of valve function over time

Modeling of the temporal trend of (human) valve function over time and identifying factors that influence this temporal trend can be of particular importance since it can help the clinicians understand how a certain process changes over time and thus can contribute to a better patient management (e.g. by determining which patients should be monitored more closely by their physicians and at which time interval). Two different longitudinal methods will be employed in this thesis in order to model the temporal trend of allograft or autograft valve function over time: the linear- and the non-linear model.

Linear models will be employed in order to assess valve function over time in **Chapters 12-14**. The aim of **Chapter 12** is to determine and compare long term allograft function after surgical procedures which a standard or bicuspidalized homograft was used in the RV-PA position in infants younger than 12 months. The objective of **Chapter 13** is to report our ongoing prospective cohort of autograft recipients with up to 21 years of follow-up, with a special emphasis on autograft and allograft valve function over time. The aim of **Chapter 14** is to assess the influence of pregnancy on durability of allografts and pulmonary autografts in aortic position.

Non-linear models will be used for assessment of valve function over time in **Chapters 15-18**. The objective of **Chapter 15** is to report our experience with the Ross operation in patients with predominant aortic stenosis using an inclusion cylinder method. The aim of **Chapter 16** is to determine the natural dynamics of pulmonary conduit stenosis and regurgitation after the Ross procedure. **Chapter 17** focusses on the echocardiographic allograft valve function over time in a cohort of patients that underwent right ventricular outflow tract reconstruction with an allograft conduit. **Chapter 18** describes echocardiographic allograft valve function over time in a cohort of patients who were prospectively followed after allograft aortic valve or root replacement.

Multiple imputation of missing values

Missing data are commonly encountered in clinical research. This is particularly the case in observational studies. The consequence of missing data in such studies is not only loss of information, but also loss of efficiency and power. More importantly, another consequence of missing data is the potential existence of bias, and therefore wrong conclusions, because of differences between the observed and unobserved data. Multiple imputation provides a useful strategy for dealing with data sets with missing values. The application of this method will be illustrated in **Chapters 16 and 17**.

Variable selection using bootstrap

In observational studies, the appropriate selection of potential predictors of a certain outcome is extremely important since differential selection processes can bias estimated treatment effects. Particularly in case of datasets that contain a large number of variables and a relatively small number of observations is the appropriate selection of correct set of variables for the model important. Different methods exist for the selection of the best possible subset of predictors of a certain outcome. One of the aims of this thesis is to illustrate the use of bootstrap bagging for the selection of a correct set of variables for the model **(Chapters 15-18)**.

Competing risks analyses

Standard survival analysis methods, such as Kaplan Meier curves, log-rank test and Cox proportional hazard model, are widely accepted tools to compare the cause-specific hazards when there is only one event of interest and the time to event and time to censoring are independent. However, competing risks are often encountered in clinical research, where multiple failure types exist and one type of event either precludes the occurrence of another event or fundamentally alters the probability of occurrence of the other event. In the analysis of competing risks data, the standard analysis methods may lead to biased results by treating the competing event as censored at the time this event occurs. This way, it is assumed that the patients failing from a competing risk are no more or less likely to fail from the cause of interest than the patients still at risk beyond this time. The application of statistical method for taking into account competing events will be illustrated in **Chapter 18**.

SHARED DECISION MAKING: PUTTING RISKS AND BENEFITS INTO PERSPECTIVE

The choice for particular valve prosthesis for aortic valve replacement in young adults has an important impact on the lives of these patients. The importance of active involvement of patients in the selection of the most appropriate prosthesis for them will be discussed in **Chapter 19**.

DISCUSSION

The most important findings of this thesis will be discussed in **Chapter 20**. In addition, the possible clinical implications and future perspectives will be discussed.

REFERENCES

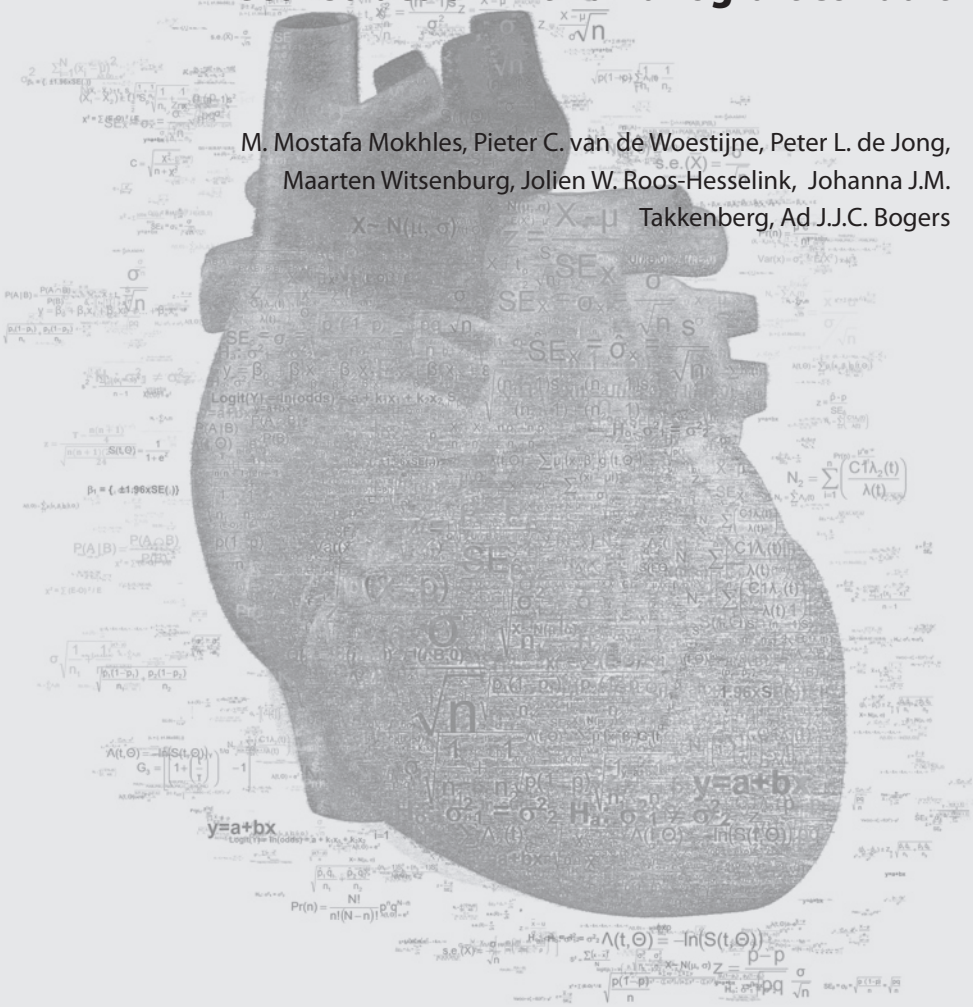
1. Ward C. Clinical significance of the bicuspid aortic valve. Heart 2000; 83(1):81-85.
2. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. N Engl J Med 1996; 335(6):407-416.
3. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol 2000; 36(4):1152-1158.
4. Vink R, Kraaijenhagen RA, Hutten BA, van den Brink RB, de Mol BA, Buller HR, Levi M. The optimal intensity of vitamin K antagonists in patients with mechanical heart valves: a meta-analysis. J Am Coll Cardiol 2003; 42(12):2042-2048.
5. Takkenberg JJ, Puvimanasinghe JP, van Herwerden LA. Optimal target international normalized ratio for patients with mechanical heart valves. J Am Coll Cardiol 2004; 44(5):1142-1143; author reply 1144-1145.
6. Wong V, Cheng CH, Chan KC. Fetal and neonatal outcome of exposure to anticoagulants during pregnancy. Am J Med Genet 1993; 45(1):17-21.
7. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 2000; 160(2):191-196.
8. Miskovic A, Monsefi N, Doss M, Ozaslan F, Karimian A, Moritz A. Comparison between homografts and Freestyle(R) bioprosthesis for right ventricular outflow tract replacement in Ross procedures. Eur J Cardiothorac Surg 2012.
9. Ilbawi MN, Lockhart CG, Idriss FS, DeLeon SY, Muster AJ, Duffy CE, Paul MH. Experience with St. Jude Medical valve prosthesis in children. A word of caution regarding right-sided placement. J Thorac Cardiovasc Surg 1987; 93(1):73-79.
10. Kiyota Y, Shiroyama T, Akamatsu T, Yokota Y, Ban T. In vitro closing behavior of the St. Jude Medical heart valve in the pulmonary position. Valve incompetence originating in the prosthesis itself. J Thorac Cardiovasc Surg 1992; 104(3):779-785.
11. Pass HI, Sade RM, Crawford FA, Hohn AR. Cardiac valve prostheses in children without anticoagulation. J Thorac Cardiovasc Surg 1984; 87(6):832-835.
12. Ross DN, Somerville J. Correction of pulmonary atresia with a homograft aortic valve. Lancet 1966; 2(7479):1446-1447.
13. Livi U, Kay P, Ross D. The pulmonary homograft: an improved conduit for RVOT reconstruction. Circulation 1986; 74(suppl 2):250.
14. Cleveland DC, Williams WG, Razzouk AJ, Trusler GA, Rebeyka IM, Duffy L, Kan Z, Coles JG, Freedom RM. Failure of cryopreserved homograft valved conduits in the pulmonary circulation. Circulation 1992; 86(5 Suppl):II150-153.
15. Wessel HU, Cunningham WJ, Paul MH, Bastanier CK, Muster AJ, Idriss FS. Exercise performance in tetralogy of Fallot after intracardiac repair. J Thorac Cardiovasc Surg 1980; 80(4):582-593.
16. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. Br Heart J 1992; 67(6):470-473.
17. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000; 356(9234):975-981.
18. Bonhoeffer P, Boudjemline Y, Saliba Z, Merckx J, Aggoun Y, Bonnet D, Acar P, Le Bidois J, Sidi D, Kachaner J. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 2000; 356(9239):1403-1405.

19. Alderson P, Green S, Higgins JPT, ed. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]. In: The Cochrane Library, Issue 1. Chichester, UK: John Wiley & Sons, Ltd., 2004.
20. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. Lancet 2001; 357(9253):373-380.
21. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
22. Rubin DB. Using propensity score to help design observational studies: application to the tobacco litigation. Health Services and Outcomes Research Methodology 2001;2:169–188.
23. Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg 2002; 123(1):8-15.
24. Osnabrugge RL, Head SJ, Kappetein AP. Methodologic issues regarding background mortality in observational studies. J Thorac Cardiovasc Surg 2011; 142(5):1289-1290; author reply 1290.

Chapter 2

Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit

M. Mostafa Mokhles, Pieter C. van de Woestijne, Peter L. de Jong, Maarten Witsenburg, Jolien W. Roos-Hesselink, Johanna J.M. Takkenberg, Ad J.J.C. Bogers



Eur J Cardiothorac Surg. 2011;40:571-8

ABSTRACT

Objective

Allograft conduits are used for reconstruction of the right ventricular outflow tract in congenital heart malformations (biventricular repair) and autograft procedures. A retrospective evaluation of allograft reconstruction of the Right ventricular outflow tract reconstruction was conducted and a cross-sectional Quality of life study was performed.

Methods

Between August 1986 and March 2009, 509 allografts (435 pulmonary, 74 aortic) were implanted in 463 pediatric and adult patients (308 right-sided congenital heart malformations, 155 autograft procedures). Peri-operative and follow-up data were collected and analyzed. Kaplan-Meier analyses were done for survival, valve-related reoperation, and valve-related events. Cox-regression analysis was used for evaluation of potential risk factors. In addition, the Short Form-36 was presented to patients to assess the perceived Quality of life. The results of the Short Form-36 were compared to age adjusted Dutch population norms.

Results

The mean age at allograft implantation was 19 years (1 week-66 years). Mean follow-up was 9 years (2 days-22 years). Forty-eight patients died during follow-up. Patient survival was 93% at 10 years and 88% at 15 years. Sixty-three reoperations were required for allograft dysfunction in 58 patients. Freedom from valve-related reoperation was 89% at 10 years and 81% at 15 years. Freedom from valve related events was 86% at 10 years and 74% at 15 years. Younger patient age ($p=0.007$) and the use of an aortic allograft ($p<0.001$) were identified as independent risk factors for allograft reoperation.

Patients between 14 and 40 years scored significantly lower on 'physical functioning' and 'general health' subscales than the general Dutch population, but scored better on subscales 'emotional role functioning' and 'bodily pain'. Except for the subscale 'general health', on which patients within our study population scored lower, patients between 41 and 60 years had comparable average scores as the general Dutch population. The older patient group (61 years or older) had a better average score on subscale 'bodily pain' and similar scores on other subscales as the general Dutch population.

Conclusions

Right ventricular outflow tract reconstruction with an allograft conduit can be performed with good patient survival, acceptable long-term allograft durability, and good perceived quality of life.

INTRODUCTION

Reconstruction of the right ventricular outflow tract (RVOT) is performed in patients with congenital heart disease when there is no adequate continuity between the right ventricle and the pulmonary circulation. The use of an aortic valve allograft for pulmonary valve replacement was introduced in 1966 (1). But it was not until 1983 that Ross et al. introduced the pulmonary valve allograft for pulmonary valve replacement (2). This has resulted in an ever increasing application of allografts. Nevertheless, a tendency toward allograft degeneration over the years is still apparent (3). Degeneration of the pulmonary valve allograft can eventually lead to clinically relevant pulmonary stenosis (PS) and pulmonary regurgitation (PR). PR is usually well tolerated in childhood. However, recent long-term studies have demonstrated that in adults PR may lead to progressive right ventricular (RV) dilatation and, with time, to RV dysfunction, exercise intolerance, ventricular tachycardia, and sudden cardiac death (4-6). Further improvement for, this still growing, population of patients with congenital heart disease, is mandatory to be able to optimize their life expectancy and quality of life (QoL).

Long-term results of RVOT reconstruction with pulmonary allografts have been scarcely reported thus far. Furthermore, no study has reported on QoL in patients after RVOT reconstruction. QoL has emerged as an increasingly important outcome parameter for several reasons: it provides a precise indicator of overall health status of the individual patient and higher QoL is associated with improved disease specific prognosis and also with increased survival (7, 8).

The aim of the present study was to assess clinical outcome over time in patients who received an allograft in the RVOT at our institution. In addition, a cross-sectional assessment of QoL in these patients was done.

METHODS

Patient Population

Between August 1986 and March 2009, 509 allografts (435 pulmonary, 74 aortic) were implanted in 463 pediatric and adult patients (308 right-sided congenital heart malformations, 155 autograft procedures). Our series represents a heterogeneous group in which the common denominator was the need for a right-sided allograft conduit. Patients were classified according to their primary diagnosis (Table 1). A first allograft was implanted in 463 patients, a second in 41, a third in 4, and a fourth in 1.

Operative Techniques

Timing of surgery was determined in a regular heart team meeting between the (congenital) cardiologists and cardiac surgeons during which all cases were discussed. The decision to whether to operate or not was based on contemporary clinical practice. The surgical procedures were performed using standard cardiopulmonary bypass with moderate hypothermia, myocardial protection with crystalloid cardioplegia (St. Thomas Hospital solution), and in most cases topical cooling. If associated intracardiac procedures were not required, the reconstruction was done without cross-clamping of the aorta. Using the interposition technique the allograft was sewn between the right ventricle and pulmonary artery in most cases (n=502). In 7 patients the allograft was implanted between the right-sided left ventricle and the pulmonary artery. Distal and proximal anastomoses were made with a running polypropylene suture. Twenty one patients needed a distal extension to ensure proper connection. For this purpose an allograft patch (n=12), an autologous pericardial patch (n=3), or a prosthetic patch (n=6) was used. A proximal extension of the allograft was necessary in 112 patients. In these cases an allograft patch (n=47), the anterior mitral valve leaflet of the aortic allograft (n=26), a pericardial patch (n=27), or a prosthetic patch (n=12) was used. In all cases attempts

Table 1. Baseline Characteristics and Primary Diagnosis at Time of Allograft Implantation.

Characteristics	Mean ±SD or Total No.	Range or Percentage
Age	19 ± 15	1 week – 66 years
Age < 1 year	60	12 %
Age 1-18 years	208	41 %
Age > 18 years	241	47 %
Gender		
Male	301	59 %
Female	208	41 %
Weight (kg)	46 ± 27	
Height (m)	1.41 ± 0.43	
Diagnosis		
Aortic valve pathology	170	33.4 %
Tetralogy of Fallot	152	29.9 %
PA or PS, VSD	63	12.4 %
Discordant ventriculoarterial connection with PA or PS	51	10.0 %
Common arterial trunk	44	8.6 %
PA or PS with intact septum	26	5.1 %
Aortic atresia with biventricular heart	3	0.6 %
Total	**509**	**100 %**

PA, pulmonary atresia; PS, pulmonary stenosis; VSD, ventricle septum defect

were made to implant the allograft away from the sternum to prevent compression or distortion.

Allograft Properties

The Rotterdam Heart Valve Bank provided most of the allografts (n=410), which were allocated by Bio Implant Services, Leiden, The Netherlands. Preparation and storage methods have been described earlier (9). The National Heart Hospital, London, England, provided 19 fresh and 4 cryopreserved allograft conduits. The remaining allografts were shipped from the Hospital Clinic I, Barcelona, Spain (n=47), the Karolinska Homograft bank, Stockholm, Sweden (n=6), the Deutsches Herzzentrum, Berlin, Germany (n=26), and Herzzentrum Nord Rhein Westphalen, Bad Oeynhausen, Germany (n=1). Patient's body surface area was used as a guideline to determine the allograft diameter. No attempt was made to achieve ABO blood type or HLA type matching.

Data collection

All patients who receive an allograft for RVOT reconstruction at Erasmus MC are systematically registered in a dedicated relational database (Microsoft Access 2007). After implantation of the allograft, patients were seen at regular intervals by their cardiologists, with the exception of 12 patients who migrated to other countries or were living abroad. In September 2009, vital status of all patients was acquired from municipal civil registries with a response rate of 97%.

All follow-up data of patients with congenital heart malformations (biventricular repair) were collected retrospectively from hospital records. The autograft patients are part of a prospective cohort study. In addition, questionnaires with information about occurrence of any cardiovascular event since last known follow-up were sent to all living patients in October 2009. These questionnaires were completed and returned back by 94% of the patients. Patients who did not complete and returned the questionnaires (6%) were censored at most recent known follow-up. The day of implantation was considered the starting point of patient survival. End points in patient survival were death or last follow-up date. Patients lost to follow-up were censored at last date of follow-up. Starting point of allograft survival was the day of implantation; end points the occurrence of events during follow-up or last follow-up date. The cause of death was registered and reported according to the Guidelines for reporting mortality and morbidity after cardiac valve interventions (10). This study was approved by the institutional review board of Erasmus University Medical Center (MEC-2008-371) and all patients provided informed consent.

Quality of life assessment

Quality of life was measured with the Short Form 36-Item Health Survey (SF-36) (11). The SF-36 is the most widely used and evaluated health outcomes measure and has extensive evidence for its validity and reliability in multiple populations. The SF-36 assesses 8 health status domains (ie, physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the raw scores to a scale from 0 to 100 (11). A higher score on the SF-36 subdomains represents a better functioning; a high score on the bodily pain scale indicates the absence of pain. The scale has good reliability, with Cronbach α ranging from 0.65 to 0.96 for all subscales (12).

In August 2009, all surviving patients who were 14 years or older (N=236) received the SF-36 (Dutch version) questionnaire by mail and were asked to return the completed questionnaire. Patients living abroad or of whom up-to-date contact specifications were not available were excluded. One-hundred-ninety-eight (84%) patients completed the SF-36 questionnaire. The results of perceived QoL in the patients after RVOT reconstruction were compared to Dutch population norms (13). In order to be able to compare the QoL assessed in patients after RVOT reconstruction with the QoL of general Dutch population, we subdivided the study group in different age categories (14-40 years, 41-60 years and 61-70 years).

Statistical analyses

Patient data were entered into a computerized relational database (Microsoft Access 2000). Statistical software SPSS for Windows version 10 (SPSS Inc, Chicago, IL.) was used for data analysis. Actuarial survival was determined using the Kaplan-Meier method (14). For all tests, a p-value of less than 0.05 was considered significant.

The log-rank test was used for univariate assessment of the effect of potential risk factors on patient survival, freedom from valve-related reoperation, and freedom from valve-related events. To investigate independent risk factors for mortality and morbidity caused by allograft failure, the Cox proportional hazard model was used. Risk factors were selected with a backward stepwise method (required significance of $p>0.10$ for elimination from the model and $p<0.05$ for retention in the model). With regard to implantation position, all autograft procedures were labeled as anatomic, and any other allograft implantation for reconstruction of the RVOT was labeled as extra-anatomic. Young age at time of implantation (Figure 1a), small allograft diameter (Figure 1b), extra-anatomic position of the allograft, young donor age (Fig 1c), and an aortic allograft were considered to be potential risk factors for allograft dysfunction (3, 15-17).

The results of SF-36 questionnaire were compared with the population norms by the Wilcoxon rank-sum test with Bonferroni correction. This latter correction indicates that the allowable significance level for each SF-36 subscales was $p<0.00625$ (0.05/8 subscales).

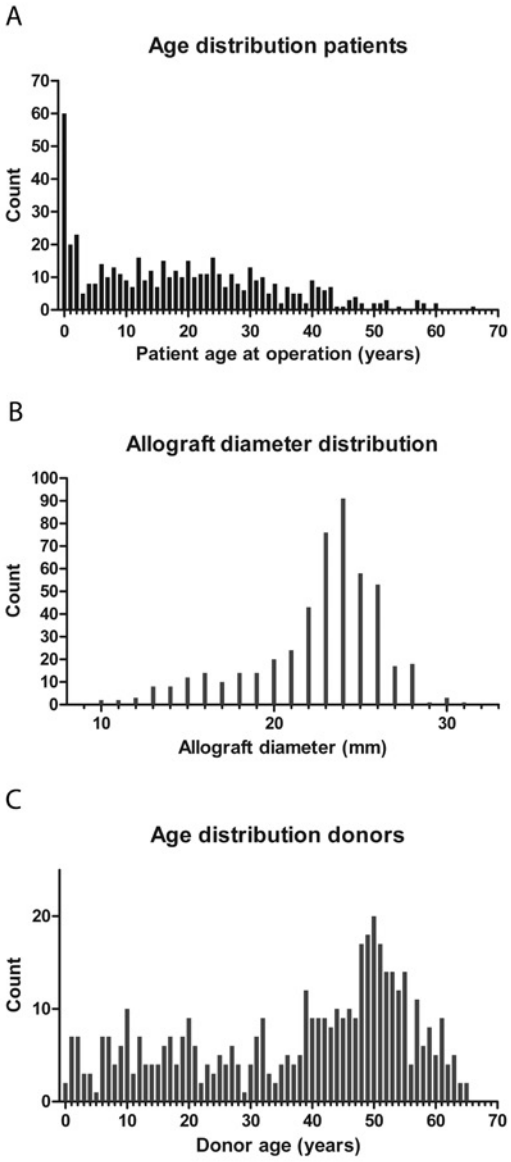


Figure 1. Frequency distribution of patient age at operation (A), allograft diameter (B), and donor age (C).

RESULTS

Patient and Donor Characteristics

Baseline characteristics of the study population are shown by Table 1. The donor group consisted of 280 male and 214 female donors with a mean age of 37 ± 18 years (median, 42; range, 0 to 65 years). The characteristics of 15 donors could not be traced. Mean allograft diameter was 22 ± 4 mm (median, 23; range 10-31 mm). Of the 509 allografts, 493 were cryopreserved, and 16 were fresh. Nineteen (3.7%) allografts were reduced in size by bicuspidalisation before they were used for RVOT reconstruction, their size was included as 2/3 of the original size.

Follow-up

The mean follow-up time was 9 ± 6 years (median, 9; range 0 to 22 years). Total number of patient-years was 4,680.

Mortality

Fifteen patients (3%) died within 30 days of operation. Causes of early death were heart failure (n=5), bleeding (n=4), hypoxic encephalopathy (n=1), respiratory insufficiency (n=1), pulmonary thromboembolism (n=1), multi organ failure (n=1), severe congenital bronchomalacia (n=1), and arrhythmia (n=1). All deaths were non valve-related. None of these allografts showed signs of degeneration at pathologic examination. Univariable logistic regression analysis revealed that the need of preoperative ventilation support (HR 6.08; 95% CI 1.23-29.95; p=0.027), the need of preoperative inotropic drug support (HR 8.38; 95% CI 2.12-33.03; p=0.002), and undergoing urgent or semi-urgent operation (HR 6.56; 95% CI 2.19-19.66; p=0.001) are independent risk factors of early mortality. In a multivariable logistic regression analysis only undergoing urgent or semi-urgent operation (HR 5.02; 95% CI 1.41-17.88; p=0.013) could be identified as an independent risk factor of early mortality.

Thirty-three patients died later than 30 days after implantation. Six of these deaths were valve-related. In 1 patient calcification of the allograft valve conduit caused stenosis resulting in acute right heart failure 1.2 years after the operation. Endocarditis destroyed the allograft in two other patients after 51 days and 7.4 years, respectively, resulting in right ventricular failure. One patient died due severe pulmonary valve insufficiency and arrhythmia 3 months after the operation. One patient died due severe pulmonary valve insufficiency resulting in heart failure 2 years after the operation. One patient died from sudden, unexplained, unexpected death without further clinical data or autopsy 5.5 years after the operation.

Causes of non–valve related late death were heart failure (n=12), respiratory insufficiency (n=2), sepsis (n=2), myocardial infarction (n=1), arrhythmia (n=1), pulmonary

hypertension (n=1), pancreatitis and heart failure (n=1), hypoxic encephalopathy (n=1), the cause was unknown in 6 patients. Patient survival was 97% (95% CI 95-98%) at 1 year, 93% (95% CI 90-95%) at 10 years and 88% (95% CI 83-92%) at 15 years (Fig 2).

Univariable Cox-regression analysis revealed that undergoing urgent or semi-urgent operation was the only risk factor for late death (HR 3.94; 95% CI 1.83-8.48; p<0.001).

Morbidity

During follow-up 99 valve-related events were reported. Sixty-three allograft replacements were required for allograft dysfunction in 58 patients (mean age 18.8 ± 11.2 years).

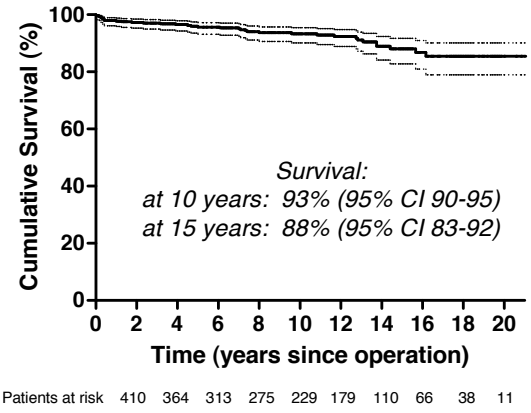


Figure 2. Kaplan-Meier plot of patient survival after RVOT reconstruction with an allograft conduit (RVOT, Right Ventricular Outflow Tract).

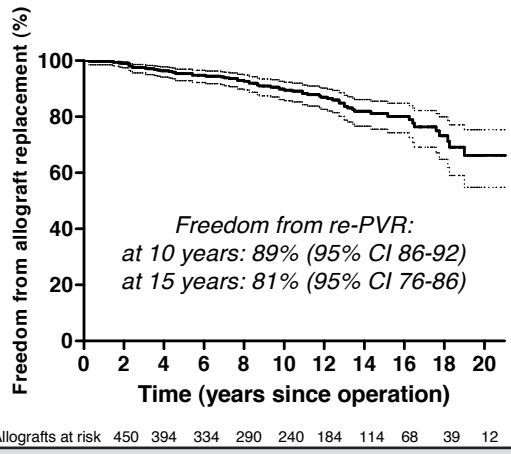


Figure 3. Kaplan-Meier plot of freedom from allograft replacement.

Among the patients who needed an allograft replacement, allograft dysfunction was related to structural valve failure in 56 reoperations, non-structural failure in 3 reoperations and allograft endocarditis in 4 patients. In the group of patients with structural valve failure, 42 valves were replaced due to stenosis, 8 valves due to regurgitation and 6 valves because of both stenosis and regurgitation.

In the group of patients with non-structural valve failure, the extension of the conduit caused stenosis near the proximal anastomosis of the allograft in one patient, one patient suffered from supravalvular stenosis near the distal anastomosis, and in one allograft a false aneurysm in one sinus was responsible for the regurgitation. Freedom from valve-related reoperation was 89% (95% CI 86-92%) at 10 years and 81% (95% CI 76-86%) at 15 years (Fig 3).

Three patients underwent a reoperation for allograft failure but without replacement of the allograft. In two of these patients extension material causing allograft stenosis was removed, and in 1 patient a pulmonary allograft patch was used for enlargement of the RVOT. Endocarditis was diagnosed in 8 patients. Thirteen patients underwent a percutaneous pulmonary valve replacement. Balloon dilatation of the pulmonary allograft was needed in 9 patients and in three patients the diagnosis of cerebrovascular accident was made. Freedom from any valve related event or reoperation was 86% (95% CI 82-89%) at 10 years and 74% (95% CI 68-78%) at 15 years (Fig 4).

Risk factors

Univariate analysis identified younger patient age (HR 1.06; 95% CI 1.04-1.09; p<0.001), extra-anatomic position of the allograft (HR 2.67; 95% CI 1.42-5.02; p=0.002), the use of aortic allograft (HR 6.40; 95% CI 3.89-10.53; p<0.001), younger donor age (HR 1.05;

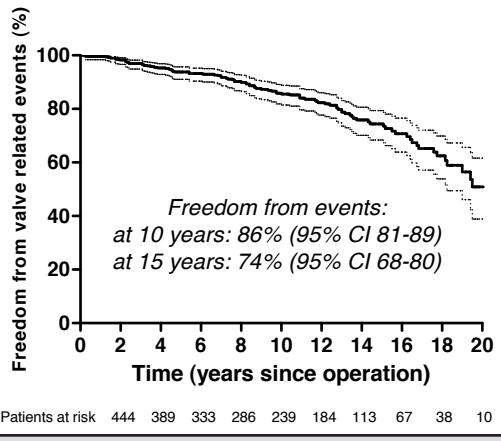


Figure 4. Kaplan-Meier plot of freedom from valve related events.

95% CI 1.03-1.06; p<0.001) and smaller allograft diameter (HR 1.21; 95% CI 1.14-1.27; p<0.001) as potential risk factors for valve-related reoperation.

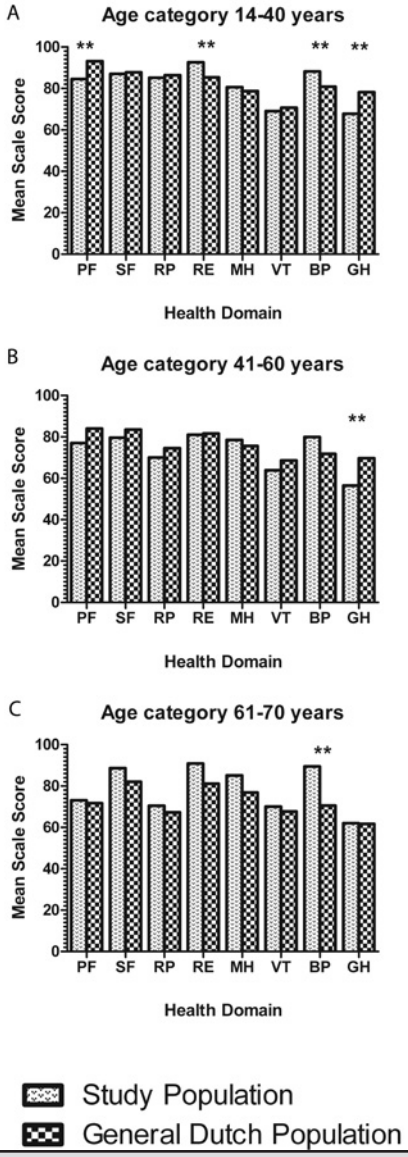


Figure 5. Averaged SF-36 scores for different age groups, who underwent a right ventricular outflow tract reconstruction (PF = physical functioning; SF = social functioning; RP = physical role functioning; RE = emotional role functioning; MH = mental health; VT = vitality; BP = bodily pain; GH = general health); ** significant p-value (p-value < 0.00625).

Donor age and allograft diameter were not included in a multivariable analysis since they were significantly correlated with patient age at the time of operation ($p<0.01$).

After multivariable analysis, younger patient age (HR 1.04; 95% CI 1.01-1.06; $p=0.007$) and the use of aortic allograft (HR 4.17; 95% CI 2.39-7.27; $p<0.001$) were identified as independent risk factors for allograft reoperation.

Quality of Life

After Bonferroni correction for multiple tests, young adult patients (age category 14 to 40 years) who underwent an RVOT reconstruction, scored significantly lower on 'physical functioning' and 'general health' scales. However, compared to general Dutch population, this patient group scored better on 'emotional role functioning' and 'bodily pain' scales. No major differences could be found between the perceived QoL in this patient group and the QoL of general Dutch population for the other measured SF-36 scales (Figure 5a).

In adult patients (age category 41 to 60 years), no substantial differences could be found for the most scales between the perceived QoL of our study population and the general Dutch population, except for 'general health' scale on which the study population scored a lower average (Figure 5b).

Compared to general Dutch population, patients older than 61 years of age scored significantly better on 'bodily pain' scale. No major differences could be found in this group for other scales between the study population and the general Dutch population (Figure 5c).

DISCUSSION

The present study evaluated the long term clinical outcome of RVOT reconstruction with an allograft conduit. Our results show that this procedure can be performed with excellent results in terms of patient survival and acceptable long-term allograft durability. The results of our experience with RVOT reconstruction have been reported earlier by our institution (18). The additional value of the present study is reporting the long term clinical outcome of RVOT reconstruction in a larger group of patients with a follow-up time up to 22 years. Furthermore, the health-related quality of life in patients after RVOT reconstruction has been assessed in the present study.

Survival

In the present study patient survival was 93% (95% CI 90-95%) at 10 years and 88% (95% CI 83-92%) at 15 years. These survival rates seem to be slightly better than those reported in the previous studies (16, 18-21). Tweddell and colleagues reported a survival rate of 88% at 10 years in 205 patients receiving a cryopreserved homograft valve (19).

Bando et al. observed a survival rate of 86% in patients receiving a pulmonary allograft and a survival rate of 80% in patients receiving an aortic allograft after a follow-up period of 5 years (16). Hawkins and coworkers reported a survival rate which was 81% at 33 months of follow-up (20). Brown and colleagues reported recently a survival rate of 80% at 15 years in a non-Ross patient population receiving an allograft conduit (21). Furthermore, the survival rates in the present study have improved compared to the survival rates reported previously by our own institution (18, 22). Possible explanations for this improvement could be the increasing experience of RVOT reconstruction and improved overall management of this patient population.

Reoperation

Compared to previous reports on this patient population we observed good long term results in terms of freedom from valve-related reoperations. In the present study, freedom from valve-related reoperation was 89% (95% CI 86-92%) at 10 years and 81% (95% CI 76- 86%) at 15 years. Even when taking into account any valve related event that occurred in our study population the results were still good. Freedom from valve related events was 86% (95% CI 82-89%) at 10 years and 74% (95% CI 68-78%) at 15 years. The observed results in our study are more encouraging than those reported by other investigators. In a recent publication, Brown and colleagues reported a freedom from allograft failure of 60% at 5 years and 43% at 15 years (21). Niwaya and coworkers reported a freedom from allograft failure of 82% at 8 years (17). Stark and colleagues described 58% and 31% freedom from conduit replacement at 10 and 15 years, respectively (23). Their relatively young patient population, a large amount of aortic allografts used in the latter series, and use of non-cryopreserved allografts in the early implantation period may perhaps explain these findings.

In an earlier report from our own institution the freedom from reoperation was 90% at 5 years and 86% at 8 years (18), which was lower than in the present study. Possible explanation for this improvement could be the increasing experience of RVOT reconstruction with an allograft conduit at our institution. Furthermore, we have observed a change in the population of patients receiving an allograft. The number of patients undergoing an autograft procedure or receiving an allograft after a primary tetralogy of Fallot correction has increased.

Risk factors for accelerated allograft failure

In the Cox regression multivariate analysis younger patient age and the use of aortic allograft were identified as independent risk factors for accelerated allograft failure. The use of aortic allograft is indeed a well-known independent risk factor in the literature for accelerated graft failure (15, 16, 18, 19). It has been postulated that a lower content of

elastic tissue and a lower amount of total calcium in the wall of the pulmonary allograft in comparison to the aortic allograft can be responsible for this difference (24).

Younger patient age was another independent risk factor for accelerated graft failure in the present study. A plausible explanation for this observation is the fact that the heart will outgrow the allograft after a few years, resulting in the need for reoperation. To prevent this some authors advise using an allograft with a relatively large diameter (25). However, implanting too large an allograft entails a risk for compression or kinking of the allograft.

Allografts implanted in extra-anatomic position could only be identified as a potential risk factor in the univariate analysis and not in the multivariate analysis. This is in contrast to an earlier report from our institution (18) and to what other investigators have reported in the past (3, 17).

Quality of Life

With the development of advanced surgical techniques and patient survival, QoL is of increasing interest in health care, especially in patients undergoing major surgical operations. The present study shows that the perceived QoL in young adult patients after RVOT reconstruction is impaired on subscales 'physical functioning'. This implies that patients experience more often limitations in lifting, climbing, bending, kneeling, walking, or running than the general Dutch population. Furthermore, this patient group has an impaired score on the 'general health' subscale, indicating that they evaluate their overall health to be lower than in the general population. However, these patients scored better on 'emotional role functioning' subscale: this indicates that the personal feelings of job performance or work or other activities are perceived to be better than in the general population. Furthermore, the intensity and duration of bodily pain and limitations in activities due to pain ('bodily pain' subscale) were perceived to be lower. The latter was also the case in patients of 61 years and older. The explanation of a better score on 'bodily pain' subscale could be the fact that a proportion of our patients had experienced limitations in their daily activity before the operation. Symptom relief and the return to previous lifestyle can probably increase the perception of own health status.

It was interesting to see that with increasing age the perceived QoL was more in accordance with the QoL of the general Dutch population. This can be caused by the fact that healthy elderly individuals tend to unconsciously compare their current physical and psychologic performances with those during younger years.

Conclusions

Right ventricular outflow tract reconstruction with an allograft conduit can be performed with good patient survival, acceptable allograft durability and good perceived quality of life. Progressive allograft dysfunction with increasing patient follow-up can be

expected. Continued long term surveillance is, therefore, necessary and careful monitoring of patients with pulmonary allografts is warranted.

REFERENCES

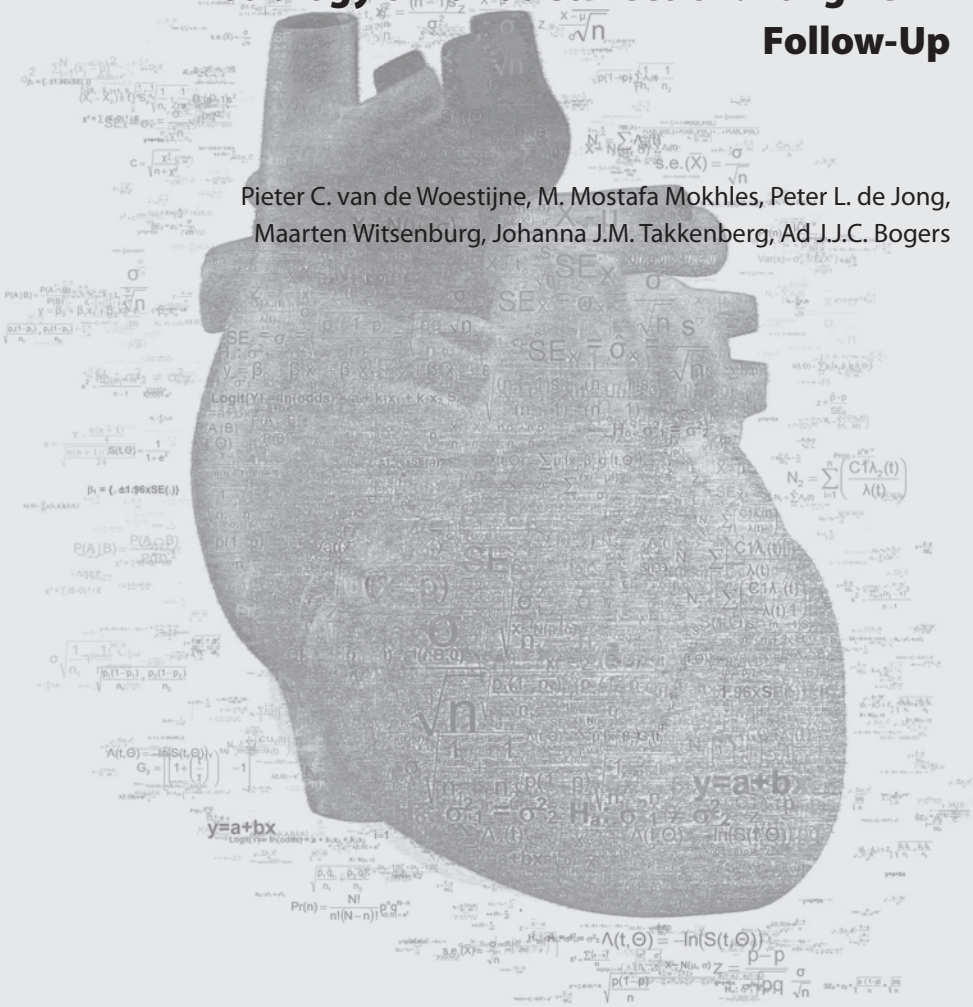
1. Ross DN, Somerville J. Correction of pulmonary atresia with a homograft aortic valve. Lancet 1966; 2(7479):1446-1447.
2. Livi U, Kay P, Ross D. The pulmonary homograft: an improved conduit for RVOT reconstruction. Circulation 1986; 74(suppl 2):250.
3. Cleveland DC, Williams WG, Razzouk AJ, Trusler GA, Rebeyka IM, Duffy L, Kan Z, Coles JG, Freedom RM. Failure of cryopreserved homograft valved conduits in the pulmonary circulation. Circulation 1992; 86(5 Suppl):II150-153.
4. Wessel HU, Cunningham WJ, Paul MH, Bastanier CK, Muster AJ, Idriss FS. Exercise performance in tetralogy of Fallot after intracardiac repair. J Thorac Cardiovasc Surg 1980; 80(4):582-593.
5. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. Br Heart J 1992; 67(6):470-473.
6. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000; 356(9234):975-981.
7. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995; 41(10):1403-1409.
8. Koch CG, Li L, Lauer M, Sabik J, Starr NJ, Blackstone EH. Effect of functional health-related quality of life on long-term survival after cardiac surgery. Circulation 2007; 115(6):692-699.
9. H.J.M. Thijsen, E. Bos, W. Konertz, R.J. Van Suylen and T.M.M.H. De By, Kryokonservierung humaner Spenderherzklappen in der Herzklappenbank in Rotterdam. Z Herz- Thorax- Gefäßchir 6 Suppl 1 (1992), pp. 49–55.
10. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 2008; 85(4):1490-1495.
11. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30(6):473-483.
12. Smith HJ, Taylor R, Mitchell A. A comparison of four quality of life instruments in cardiac patients: SF-36, QLI, QLMI, and SEIQoL. Heart 2000; 84(4):390-394.
13. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51(11):1055-1068.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457– 81.
15. Albert JD, Bishop DA, Fullerton DA, Campbell DN, Clarke DR. Conduit reconstruction of the right ventricular outflow tract. Lessons learned in a twelve-year experience. J Thorac Cardiovasc Surg 1993; 106(2):228-235; discussion 235-226.
16. Bando K, Danielson GK, Schaff HV, Mair DD, Julsrud PR, Puga FJ. Outcome of pulmonary and aortic homografts for right ventricular outflow tract reconstruction. J Thorac Cardiovasc Surg 1995; 109(3):509-517; discussion 517-508.

17. Niwaya K, Knott-Craig CJ, Lane MM, Chandrasekaren K, Overholt ED, Elkins RC. Cryopreserved homograft valves in the pulmonary position: risk analysis for intermediate-term failure. J Thorac Cardiovasc Surg 1999; 117(1):141-146; discussion 146-147.
18. Gerestein CG, Takkenberg JJ, Oei FB, Cromme-Dijkhuis AH, Spitaels SE, van Herwerden LA, Steyerberg EW, Bogers AJ. Right ventricular outflow tract reconstruction with an allograft conduit. Ann Thorac Surg 2001; 71(3):911-917; discussion 917-918.
19. Tweddell JS, Pelech AN, Frommelt PC, Mussatto KA, Wyman JD, Fedderly RT, Berger S, Frommelt MA, Lewis DA, Friedberg DZ, Thomas JP, Jr., Sachdeva R, Litwin SB. Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. Circulation 2000; 102(19 Suppl 3):III130-135.
20. Hawkins JA, Bailey WW, Dillon T, Schwartz DC. Midterm results with cryopreserved allograft valved conduits from the right ventricle to the pulmonary arteries. J Thorac Cardiovasc Surg 1992; 104(4):910-916.
21. Brown JW, Ruzmetov M, Rodefeld MD, Vijay P, Turrentine MW. Right ventricular outflow tract reconstruction with an allograft conduit in non-ross patients: risk factors for allograft dysfunction and failure. Ann Thorac Surg 2005; 80(2):655-663; discussion 663-654.
22. Willems TP, Bogers AJ, Cromme-Dijkhuis AH, Steyerberg EW, van Herwerden LA, Hokken RB, Hess J, Bos E. Allograft reconstruction of the right ventricular outflow tract. Eur J Cardiothorac Surg 1996; 10(8):609-614; discussion 614-605.
23. Stark J, Bull C, Stajevic M, Jothi M, Elliott M, de Leval M. Fate of subpulmonary homograft conduits: determinants of late homograft failure. J Thorac Cardiovasc Surg 1998; 115(3):506-514; discussion 514-506.
24. Livi U, Abdulla AK, Parker R, Olsen EJ, Ross DN. Viability and morphology of aortic and pulmonary homografts. A comparative study. J Thorac Cardiovasc Surg 1987; 93(5):755-760.
25. Tam RK, Tolan MJ, Zamvar VY, Slavik Z, Pickering R, Keeton BR, Salmon AP, Webber SA, Tsang V, Lamb RK, et al. Use of larger sized aortic homograft conduits in right ventricular outflow tract reconstruction. J Heart Valve Dis 1995; 4(6):660-664.

Chapter 3

Right Ventricular Outflow Tract Reconstruction with an Allograft Conduit in Patients after Tetralogy of Fallot Correction: Long-Term Follow-Up

Pieter C. van de Woestijne, M. Mostafa Mokhles, Peter L. de Jong, Maarten Witsenburg, Johanna J.M. Takkenberg, Ad J.J.C. Bogers



Ann Thorac Surg. 2011;92:161-6

ABSTRACT

Background

In Tetralogy of Fallot (ToF) pulmonary regurgitation is a frequent complication after initial repair. The objective of present study was to describe the long-term experience with the use of allograft conduits for right ventricular outflow tract (RVOT) reconstruction after correction of ToF in our institution.

Methods

Between 1987 and 2009, 133 allografts were implanted in 126 patients (mean age 27.8 years). The mean time from initial ToF repair to allograft implantation was 20.8 ± 8.8 years. Kaplan-Meier analyses were done for patient survival, freedom from allograft replacement and freedom from any cardiovascular event.

Results

Hospital mortality was 1.5% (2 patients). Mean follow-up was 8.1 years. Ten other patients died during late follow-up, in eight cases due to heart failure. Patient survival was 95% at 5 years, 91% at 10 years and 80% at 15 years. Male gender, older patient age at the time of operation, and the use of preoperative diuretics were associated with increased risk of mortality during follow-up. Freedom from allograft replacement was 83% at 10 years and 70% at 15 years. Freedom from any valve-related event was 80% at 10 years and 67% at 15 years.

Conclusions

RVOT reconstruction after previous ToF repair can be performed with low risk and a low re-intervention rate. Allograft conduits function satisfactorily in the pulmonary position at longer term follow-up. Functional status after allograft implantation in patients with a previous correction of ToF remains good. There is concern about the long-term survival and the occurrence of heart failure.

INTRODUCTION

Tetralogy of Fallot (ToF) is a common congenital heart defect. Surgical intervention of right ventricular outflow tract (RVOT) obstruction in ToF patients often consists of RVOT enlargement with frequently a transannular patch extending from the muscular infundibulum to the main pulmonary artery. On the other hand, progressive pulmonary regurgitation (PR) is also a well-known side effect after total surgical correction of ToF with a transannular patch (1). PR can result in progressive right ventricular (RV) dilatation and, with time, to RV dysfunction, exercise intolerance, ventricular tachycardia, and sudden cardiac death (2-5).

A timely reconstruction of the RVOT with insertion of an allograft in the RVOT may limit these problems. The use of an aortic valve allograft for RVOT reconstruction was introduced in 1966 (6). But it was not until 1983 that Ross et al. introduced the pulmonary valve allograft for RVOT reconstruction (7). This has resulted in an ever increasing application of allografts. Nevertheless, a tendency toward allograft degeneration over the years is still apparent (8).

Long-term results of RVOT reconstruction with an allograft after previous correction of ToF have been scarcely reported thus far. The objective of present study was to describe the long-term experience with the use of allograft conduits for RVOT reconstruction after correction of ToF in our institution.

PATIENTS AND METHODS

Between August 1986 and March 2009, 133 allografts (126 pulmonary, 7 aortic) were implanted in 126 patients for reconstruction of the RVOT after previous Tetralogy of Fallot correction at the Erasmus University Hospital Rotterdam, Rotterdam, The Nederlands. This study was approved by the institutional review board of Erasmus University Medical Center (MEC-2008-208) and all patients provided informed consent.

Patient characteristics

All children and adults who underwent an RVOT reconstruction with an allograft after primary correction of ToF were included in the study. We excluded in this series patients with an absent pulmonary valve syndrome, pulmonary atresia and those who received an allograft during initial correction of ToF. A first allograft was implanted in 126 patients, a second in 5, a third in 1, and a fourth in 1.

Allograft Properties

The Rotterdam Heart Valve Bank provided most of the allografts (n=114), which were allocated by Bio Implant Services, Leiden, The Netherlands. Preparation and storage

methods have been described earlier (9). The remaining allografts were shipped from the Hospital Clinic I, Barcelona, Spain (n=7), the Karolinska Homograft bank, Stockholm, Sweden (n=1), the Deutsches Herzzentrum, Berlin, Germany (n=3), Herzzentrum Nord Rhein Westphalen, Bad Oeynhausen, Germany (n=7), and the National Heart Hospital, London, England, provided (n=1). In case of (small) children we have used normograms (e.g. patient's body surface area) to assess the normalized diameter of the allograft. In case of adult patients we have tried to use an allograft diameter which was considered to be 'normal' for that patient's age. Whenever necessary, a reduction plasty of the RVOT has been performed to avoid any tension on the implanted allograft. No attempt was made to achieve ABO blood type or HLA type matching.

Indications for allograft implantation

Selection criteria for allograft implantation in patients with corrected ToF were clinically determined. The indication for allograft implantation was severe PR in combination with progressive RV dilatation, systolic dysfunction, and/or a decrease in objective exercise capacity, as previously described (10).

Operative techniques

The surgical procedures were performed through median sternotomy on beating heart, using standard cardiopulmonary bypass with mild hypothermia or normothermia. If associated intra-cardiac procedures were required the aorta was cross-clamped and myocardial protection was performed using crystalloid cardioplegia (St. Thomas solution). Using the interposition technique the allograft was sewn between the right ventricle and pulmonary artery. The anastomoses were made with a running polypropylene suture. A reduction plasty of the right ventricular outflow tract was performed if this was indicated to accommodate the allograft or whenever the RVOT was too large or aneurysmatic. We have a selective approach with performing tricuspid valve repair in patients undergoing RVOT reconstruction. We only perform this procedure when the clinical condition of these patients necessitates it (10).

Data collection

All tetralogy of Fallot patients who receive an allograft for RVOT reconstruction at Erasmus University Medical Center are systematically registered in a dedicated relational database (Microsoft Access 2000). After implantation of the allograft, patients were seen at regular intervals by their cardiologists, with the exception of three patients who migrated to other countries and were living abroad.

Follow-up data of patients with corrected ToF who underwent an RVOT reconstruction with an allograft were collected retrospectively from hospital records. In September 2009, vital status of all patients was acquired from municipal civil registries. In addition, question-

naires with information about occurrence of any cardiovascular event since last known follow-up were sent to all living patients in October 2009. Non-responders were contacted by phone. Completeness of follow-up was 94% within 6 months of study closure.

The day of implantation was considered the starting point of patient survival. End points in patient survival were death or last follow-up date. Patients lost to follow-up were censored at last date of follow-up. Starting point of allograft survival also was the day of implantation. End points were the occurrence of events during follow-up or last follow-up date. The cause of death was registered and reported according to the Guidelines for reporting mortality and morbidity after cardiac valve interventions (11).

Statistical analysis

Patient data were entered into a computerized relational database (Microsoft Access 2000). Continuous data are presented as mean with standard deviation or median with range. Categorical data are presented as proportions. All tests were 2-sided, with an α-level of 0.05.

Actuarial survival was determined using the Kaplan-Meier method (12). To investigate potential risk factors for mortality and morbidity caused by allograft failure, the Cox proportional hazard model was used. Statistical software SPSS for Windows version 10 (SPSS Inc, Chicago, IL.) was used for data analysis. GraphPad Prism 5.00 for Windows (GraphPad Software, La Jolla, California) was used to obtain life tables and corresponding Kaplan-Meier survival curves.

RESULTS

Baseline characteristics of the study population are shown by Table 1. The donor group consisted of 77 male and 56 female donors with a mean age of 43.8 ± 14.5 years. The characteristics of 3 donors could not be traced. Mean allograft diameter was 24 ± 2.3 mm (range 14-28 mm). Of the 133 allografts, 130 were cryopreserved, and 3 were fresh. None of the allografts were reduced in size by bicuspidalisation before they were used for RVOT reconstruction.

Allograft implantation

RVOT reconstruction with a first allograft was performed at a mean age of 28.1 ±1 2.2 years (range 2 to 66 years), with a mean time from ToF repair to RVOT reconstruction of 20.8 ± 8.8 years (range 2 weeks to 44 years). Additional procedures performed at the time of RVOT reconstruction with an allograft are listed in Table 2.

Postoperative course

Two patients (1.5%) died within 30 days after the operation. One patient (18 years old) died at home 14 days after the allograft implantation. The cause of death was presumed to be arrhythmia since the patient was known with rhythm disturbances. During pathological examination signs of hemorrhage were found in the left lung. The second patient (43 years old) died in the hospital 14 days after the operation which consisted of allograft implantation combined with tracheal reconstruction for acquired tracheal stenosis and additional anastomosis. The cause of death was hypovolemic shock due persistent bleeding from proximal esophagus and hypopharynx. None of these deaths were valve-related and the two explanted valves did not showed signs of degeneration at pathologic examination.

Six patients had an early reexploration for bleeding. An overview of post-operative complications is given in Table 3.

Table 1. Demographic and preoperative data of 133 patients undergoing RVOT reconstruction with an allograft after ToF repair.

Baseline characteristic	Mean ± SD or Number	Range or Percentage
Age at ToF correction (years)	7.22 (±7.1)	0.1 – 57
Age at first PVR (years)	28.1 (±12.2)	2 – 66
Interval ToF repair-PVR (years)	20.8 (±8.8)	0.04 - 44
Gender		
Male	72	54.1%
Female	61	45.9%
Height at PVR (m)	1.7 (±1.9)	0.8 – 1.9
Weight at PVR (kg)	61.4 (±18.4)	10.0 – 105.0
Creatinin	69.2 (±18.5)	18.0 – 137.0
RVH[a]		
Yes	31	23.3
No	68	51.1
Unknown	34	25.6
LVH[a]		
Yes	6	4.5
No	114	85.7
Unknown	13	9.8
Growth delay	2	1.5
Preoperative use of diuretics	19	14.3
Problems with feeding	1	0.8
Ventilation support	1	0.8

[a]Defined by echocardiography; LVH, Left Ventricular Hypertrophy; PVR, Pulmonary valve replacement; RVH, Right Ventricular Hypertrophy; ToF, tetralogy of Fallot

Late mortality

During a mean follow-up time of 8.1 ± 5.6 years (range 0.04 to 21.2 years) ten late (>30 days) deaths were observed. Causes of late death were heart failure or cardiogenic shock (n=6), heart failure complicated by pancreatitis (n=1) and heart failure complicated by renal failure (n=1). The cause of death was unknown in two patients. The mean age of patients who died during was follow-up was 45.8 ± 11.4 years (median 49.5, range 18 to 56).

Overall, patient survival was 95% (95% CI 90-98%) at 5 years, 91% (95% CI 83-96%) at 10 years and 80% (95% CI 66-89%) at 15 years (Fig 1).

Table 2. Associated procedures performed at allograft implantation.[a]

Associated proceduresa	No. of patients (%)
VSD closure	19 (14.3)
Infundibular muscle resection [b]	15 (11.3)
PA plasty	12 (9.0)
Tricuspid valve repair	8 (6.0)
ASD closure	3 (2.3)
Tricuspid valve replacement	3 (2.3)
Residual shunt closure	3 (2.3)
AVR	1 (0.8)
CABG	1 (0.8)
Resection tracheal stenosis	1 (0.8)

[a] Some patients had more than one associated procedure; [b] With associated valvotomy or valvectomy; ASD, Atrial septal defect; AVR, aortic valve replacement, CABG: coronary artery bypass grafting; PA, pulmonary artery; PVR, pulmonary valve replacement; ToF, tetralogy of Fallot; VSD, ventricular septal defect

Table 3. Operative data of patients undergoing RVOT reconstruction after primary ToF repair.

Parameter	Value (range or percentage)
Aorta occlusion time (min) (N=51)	38 (0 – 178)
Perfusion time (min)	123 (33 – 264)
Circulatory arrest (min) (N=3)	31 (6 – 74)
Complications	
Bleeding requiring reexploration	6 (4.5)
Pneumothorax	5 (3.8)
Ventricular fibrillation	2 (1.5)
Ventricular tachycardia	2 (1.5)
Subdural hematoma	1 (0.8)
Post-anoxic encephalopathy	1 (0.8)
Operative mortality	2 (1.5)

Univariate analyses revealed that male gender (HR 8.62, 95% CI 1.86-39.87), older patient age (continuous variable) (HR 1.08, 95% CI 1.03-1.13), larger allograft diameter (HR 1.55, 95% CI 1.11-2.16), the preoperative use of diuretics (HR 8.14, 95% CI 2.73-24.34) and preoperative high serum creatinin (HR 1.05, 95% CI 1.02-1.08) were significantly associated with increased risk of mortality during follow-up.

Adverse events and morbidity

Seventeen patients (12.8%) experienced one or more adverse events during follow-up. Seven allograft replacements were required for allograft dysfunction in five patients. Furthermore, five patients underwent a percutaneous pulmonary valve replacement. The mean interval between the initial allograft implantation and the allograft replacement was 6.3 ± 4.8 years (range 1.8 to 16.5). The mean age of these patients requiring valve replacement was 28.8 ± 9.9 years (median 28.0, range 16 to 51). Freedom from valve replacement was 83% (95% CI 74-89%) at 10 years and 70% (95% CI 57-80%) at 15 years (Fig 2).

Endocarditis was diagnosed in two patients. These patients were conservatively treated and survived the active period of endocarditis. Balloon dilatation of the pulmonary allograft was needed in 2 patients and in one patient the diagnosis of cerebrovascular accident was made. Freedom from any valve related event or replacement was 80% (95% CI 70-87%) at 10 years and 67% (95% CI 54-78%) at 15 years (Fig 3). At most recent follow-up more than 90% of the patients were in NYHA classification I or II.

Patient gender (HR 0.38, 95% CI 0.11-1.30), patient age at the time of allograft implantation (HR 0.97, 95% CI 0.92-1.02), donor gender (HR 1.78, 95% CI 0.57-5.56), diameter of the implanted allograft (HR 0.98, 95% CI 0.76-1.26), quality code of the allograft (HR

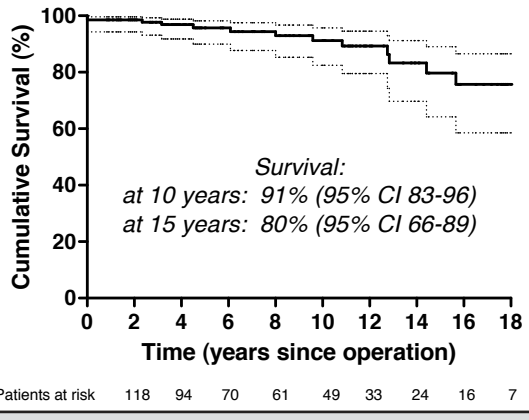


Figure 1. Kaplan-Meier plot of patient survival after right ventricular outflow tract reconstruction with an allograft conduit.

0.75, 95% CI 0.36-1.56) and the use of aortic allograft (HR 0.38, 95% CI 0.08-1.79) were not associated with allograft failure requiring replacement.

COMMENTS

The present study shows that right ventricular outflow tract reconstruction with an allograft conduit after primary correction of Tetralogy of Fallot can be performed with a relatively low operative risk, good patient survival and acceptable long-term allograft durability. The allografts are doing better than previously assumed (13-15).

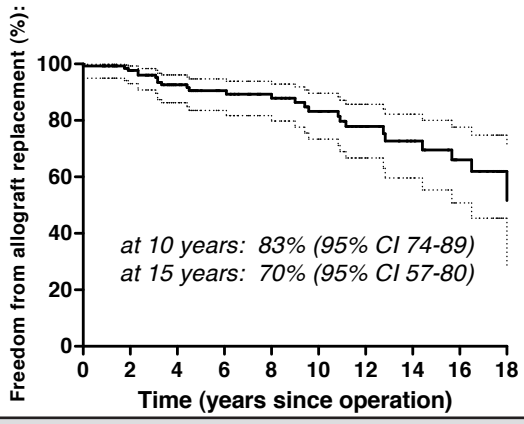


Figure 2. Kaplan-Meier plot of patient survival with freedom from reoperation after right ventricular outflow tract reconstruction with an allograft conduit.

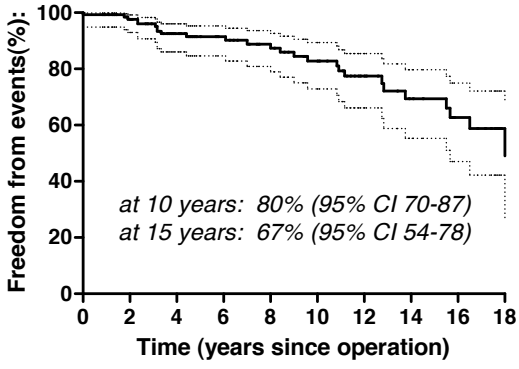


Figure 3. Kaplan-Meier plot of patient survival with freedom from any event after right ventricular outflow tract reconstruction with an allograft conduit.

Survival

The observed long-term survival in the present study was 95% at 5 years, 91% at 10 years and 80% at 15 years. Overall, these survival rates are comparable of even slightly higher than those reported by other investigators (16-22) Therrien and colleagues (16) reported 92% survival at 5 years and 86% at 10 years in their series of 70 adult patients with ToF that underwent a pulmonary valve replacement. Discigil and colleagues (17) reported 95% survival at 5 years and 76% at 10 years in 42 patients. Yemets and colleagues (18) reported a survival rate of 95% at 10 years in their patient population which is slightly higher than the survival rate in our patient population after 10 years of follow-up. A possible explanation for this observation could be fact that our patient population was older at the time of allograft implantation compared to the patient population of the latter study.

Our study and those published by other investigators suggest that RVOT reconstruction with an allograft can be performed with low operative mortality (2, 20, 23). The results in term of long-term survival are good in this patient population with 10 year patient survival varying between 90% and 95% (16-21).

Functional status

It has been previously reported by other investigators that RVOT reconstruction with an allograft results in functional status improvement in patients with corrected ToF (2, 16, 18, 19). At most recent follow-up more that 90% of our patients were in NYHA class I or II. This indicates that functional status of patients with corrected ToF that undergo an RVOT reconstruction remains good even after a long period of time.

Reoperation

The average life span of a pulmonary allograft have been reported to vary between 7 and 15 years (24). The observed freedom from valve-related reoperation in the present study was 83% at 10 years and 70% at 15. These results are more encouraging than those reported by other investigators (13-15). Brown and colleagues reported a freedom from allograft failure of 60% at 5 years and 43% at 15 years (13). Niwaya and coworkers reported a freedom from allograft failure of 82% at 8 years (14). Stark and colleagues described 58% and 31% freedom from conduit replacement at 10 and 15 years, respectively (15). We are aware of the differences that exist between other patient populations reported and our patient population. Being aware of that, we think that the use of a relatively larger number of aortic allografts in the latter series, and use of non-cryopreserved allografts in the early implantation period may perhaps explain these findings.

In the present study we could not identify independent predictors of accelerated allograft failure.

Conclusions

Allograft implantation after previous ToF repair can be performed with low risk and a low re-intervention rate. The results of allograft durability are acceptable at long-term follow-up. Functional improvement after allograft implantation in patients with a previous correction of ToF is good, even after a relatively long period of follow-up. However, there is concern about the long-term patient survival and the occurrence of heart failure as a cause of late mortality and this will be subject of further investigations.

REFERENCES

1. Oosterhof T, Hazekamp MG, Mulder BJ. Opportunities in pulmonary valve replacement. Expert Rev Cardiovasc Ther 2009; 7(9):1117-1122.
2. Bove EL, Kavey RE, Byrum CJ, Sondheimer HM, Blackman MS, Thomas FD. Improved right ventricular function following late pulmonary valve replacement for residual pulmonary insufficiency or stenosis. J Thorac Cardiovasc Surg 1985; 90(1):50-55.
3. Wessel HU, Cunningham WJ, Paul MH, Bastanier CK, Muster AJ, Idriss FS. Exercise performance in tetralogy of Fallot after intracardiac repair. J Thorac Cardiovasc Surg 1980; 80(4):582-593.
4. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. Br Heart J 1992; 67(6):470-473.
5. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000; 356(9234):975-981.
6. Ross DN, Somerville J. Correction of pulmonary atresia with a homograft aortic valve. Lancet 1966; 2(7479):1446-1447.
7. Livi U, Kay P, Ross D. The pulmonary homograft: an improved conduit for RVOT reconstruction. Circulation 1986; 74(suppl 2):250.
8. Cleveland DC, Williams WG, Razzouk AJ, Trusler GA, Rebeyka IM, Duffy L, Kan Z, Coles JG, Freedom RM. Failure of cryopreserved homograft valved conduits in the pulmonary circulation. Circulation 1992; 86(5 Suppl):II150-153.
9. H.J.M. Thijsen, E. Bos, W. Konertz, R.J. Van Suylen and T.M.M.H. De By, Kryokonservierung humaner Spenderherzklappen in der Herzklappenbank in Rotterdam. Z Herz- Thorax- Gefäβchir 6 Suppl 1 (1992), pp. 49–55.
10. Meijboom FJ, Roos-Hesselink JW, McGhie JS, Spitaels SE, van Domburg RT, Utens LM, Simoons ML, Bogers AJ. Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. J Thorac Cardiovasc Surg 2008; 135(1):50-55.
11. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 2008; 85(4):1490-1495.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457– 81.
13. Brown JW, Ruzmetov M, Rodefeld MD, Vijay P, Turrentine MW. Right ventricular outflow tract reconstruction with an allograft conduit in non-ross patients: risk factors for allograft dysfunction and failure. Ann Thorac Surg 2005; 80(2):655-663; discussion 663-654.
14. Niwaya K, Knott-Craig CJ, Lane MM, Chandrasekaren K, Overholt ED, Elkins RC. Cryopreserved homograft valves in the pulmonary position: risk analysis for intermediate-term failure. J Thorac Cardiovasc Surg 1999; 117(1):141-146; discussion 146-147.
15. Stark J, Bull C, Stajevic M, Jothi M, Elliott M, de Leval M. Fate of subpulmonary homograft conduits: determinants of late homograft failure. J Thorac Cardiovasc Surg 1998; 115(3):506-514; discussion 514-506.

16. Therrien J, Siu SC, Harris L, Dore A, Niwa K, Janousek J, Williams WG, Webb G, Gatzoulis MA. Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. Circulation 2001; 103(20):2489-2494.
17. Discigil B, Dearani JA, Puga FJ, Schaff HV, Hagler DJ, Warnes CA, Danielson GK. Late pulmonary valve replacement after repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 2001; 121(2):344-351.
18. Yemets IM, Williams WG, Webb GD, Harrison DA, McLaughlin PR, Trusler GA, Coles JG, Rebeyka IM, Freedom RM. Pulmonary valve replacement late after repair of tetralogy of Fallot. Ann Thorac Surg 1997; 64(2):526-530.
19. Warner KG, Anderson JE, Fulton DR, Payne DD, Geggel RL, Marx GR. Restoration of the pulmonary valve reduces right ventricular volume overload after previous repair of tetralogy of Fallot. Circulation 1993; 88(5 Pt 2):II189-197.
20. d'Udekem Y, Rubay J, Shango-Lody P, Ovaert C, Vliers A, Caliteaux M, Sluysmans T. Late homograft valve insertion after transannular patch repair of tetralogy of Fallot. J Heart Valve Dis 1998; 7(4):450-454.
21. Oechslin EN, Harrison DA, Harris L, Downar E, Webb GD, Siu SS, Williams WG. Reoperation in adults with repair of tetralogy of fallot: indications and outcomes. J Thorac Cardiovasc Surg 1999; 118(2):245-251.
22. Scherptong RW, Hazekamp MG, Mulder BJ, Wijers O, Swenne CA, van der Wall EE, Schalij MJ, Vliegen HW. Follow-up after pulmonary valve replacement in adults with tetralogy of Fallot: association between QRS duration and outcome. J Am Coll Cardiol; 56(18):1486-1492.
23. Vliegen HW, van Straten A, de Roos A, Roest AA, Schoof PH, Zwinderman AH, Ottenkamp J, van der Wall EE, Hazekamp MG. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of fallot. Circulation 2002; 106(13):1703-1707.
24. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. N Engl J Med 1996; 335(6):407-416.

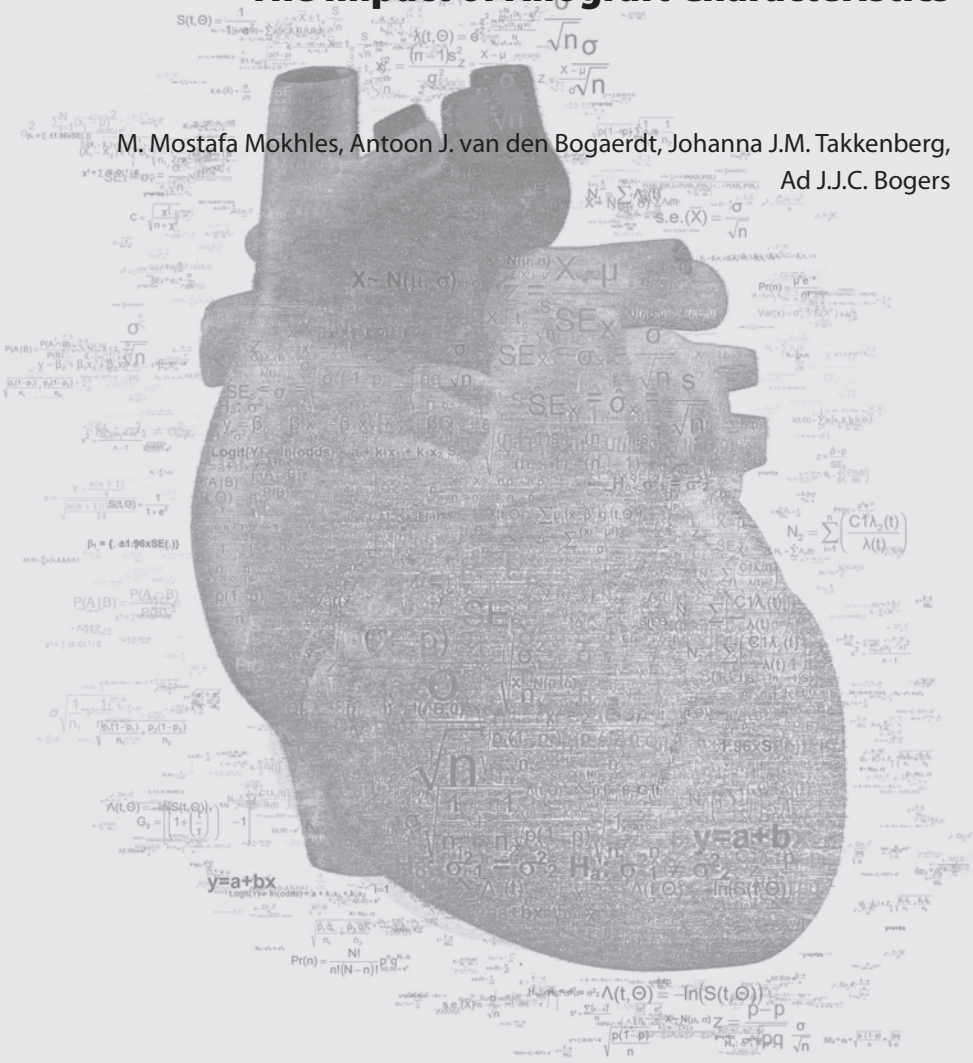
LIST OF ABBREVIATIONS

CI	Confidence Interval
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
KM	Kaplan-Meier
NYHA	New York Heart Association
PR	Pulmonary Regurgitation
RV	Right Ventricular
RVOT	Right Ventricular Outflow Tract
ToF	Tetralogy of Fallot

Chapter 4

Right Ventricular Outflow Tract Reconstruction: The Impact of Allograft Characteristics

M. Mostafa Mokhles, Antoon J. van den Bogaerdt, Johanna J.M. Takkenberg, Ad J.J.C. Bogers



Ann Thorac Surg. 2011;91:2025

Dear Editor,

We read with great interest the recent article by Christenson and colleagues (1) addressing the impact of ABO blood group compatibility on the reoperation rate of allograft conduits used for right ventricular outflow tract (RVOT) reconstruction. They show that blood group non-compatible allografts have a significantly higher early reoperation rate compared to blood group compatible allografts.

In Table 4 Christenson et al. report the impact of age and different conduits used on the reoperation rate during follow-up by calculating and comparing risk estimates. However, by doing this the authors do not take into account the time-dependency of the event (reoperation). If one is interested in investigating the impact of certain variables on a time-dependent event, a more appropriate approach would be to calculate and compare rate estimates, in this case hazard ratios. Furthermore, the total follow-up period differed significantly between the Contegra group and the allograft group. Therefore, not the log-rank test but the Tarone-Ware test would be a more appropriate statistical test to compare these groups.

We have investigated the issue of blood group compatibility in our own patient population, as well as the influence of allograft quality code assignment. All patients who receive an allograft for RVOT reconstruction at our institution are systematically registered. Between August 1986 and March 2009, 509 allografts were implanted in 463 pediatric and adult patients. The mean age of donors was 37 ± 18 years (range 0-65 years). The mean age of patients was 19 ± 15 years (range 0,02 - 66 years). The mean follow-up time was 9 years.

Seventy-six allograft re-interventions were required in 69 patients (including thirteen percutaneous stented valve implantations). Allograft dysfunction was related to structural valve failure in 69 patients, non-structural failure in 3 patients and endocarditis in 4 patients. Freedom from allograft re-intervention was 88% (95% CI 84-91%) at 10 years and 78% (95% CI 72-83%) at 15 years. Overall, the reoperation rate was not significantly higher in the group of non-ABO compatible allografts as compared to ABO compatible allografts (HR 0.63, 95% CI 0.36-1.10). Christenson and colleagues have observed a strong correlation between non-ABO compatible allografts and increased reoperation rate in patients younger than 3 years. In our patient population, also in this group (N=102 of which 31 patients required an allograft re-intervention) the re-intervention rate was not significantly higher in the group of non-ABO compatible allografts as compared to ABO compatible allografts (HR 0.76, 95% CI 0.33-1.73).

Furthermore, our results indicate that assignment of allograft quality codes is not associated with the durability of allografts used for RVOT reconstruction. Allografts with the highest quality code 1 (N=184) showed a performance comparable to allografts with quality code 2 (N=164) (HR 0.61, 95% CI 0.34-1.10) and to allografts with quality code ≥3

(N=112) (HR 1.03, 95%CI 0.50-2.12). From 49 allografts (9.6 %) the quality code could not be retrieved.

In conclusion, in our experience blood group compatibility and assignment of quality codes do not have an impact on allograft durability.

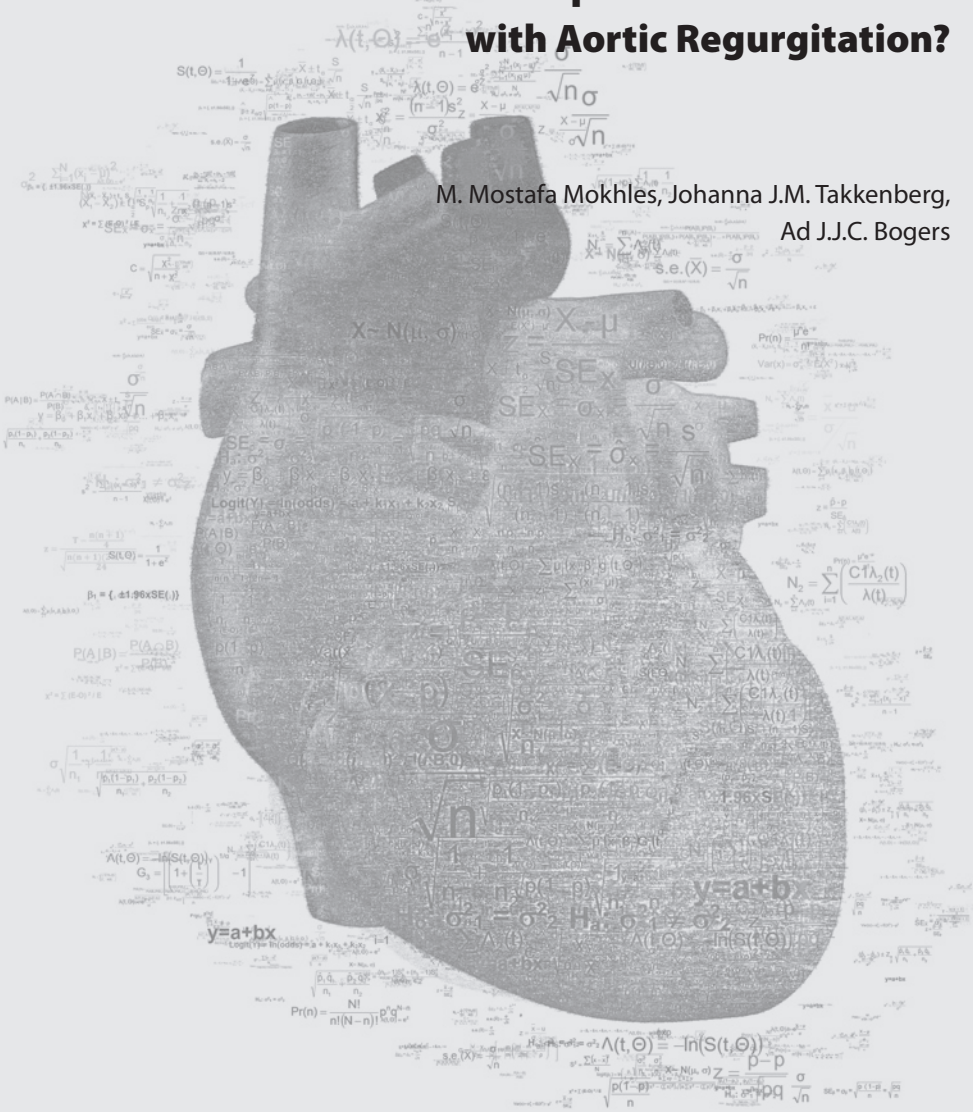
REFERENCE

1. Christenson JT, Sierra J, Colina Manzano NE, Jolou J, Beghetti M, Kalangos A. Homografts and xenografts for right ventricular outflow tract reconstruction: long-term results. Ann Thorac Surg; 90(4):1287-1293.

Chapter 5

No Ross Operation for Patients with Aortic Regurgitation?

M. Mostafa Mokhles, Johanna J.M. Takkenberg, Ad J.J.C. Bogers



Ann Thorac Surg. 2011;92:1156-7

Dear Editor,

We read with interest the recent article by Ryan and colleagues (1) discussing the results of the Ross procedure in their adult patient population. Dr. Ryan and colleagues conclude in their paper that the Ross procedure in adults provides excellent freedom from autograft failure in patients operated for aortic stenosis, but advice strongly to consider other options in adults presenting with aortic insufficiency (AI). Their series and the 100% follow-up of their patients are excellent, but this report leaves us with a few outstanding questions that we would like to address.

The authors report that 4 out of 15 reoperations were for noncoronory sinus dissection. This is an incidentally reported but potentially serious condition and we would like to request the authors to provide more information about these patients. How were the dissections diagnosed? What was the morphology of the dissections? What did the histology reports show? This information would be valuable to increase our understanding of noncoronary sinus dissection. In addition, we would be grateful if the authors could provide us with more details on the timing of the individual reoperations. Is there a time-dependent pattern in the reason for reoperation (for example autograft dysfunction in the first decade and dilatation and dissection in the second decade)? This would provide clinicians with valuable information on how autograft recipients should be monitored over time (perhaps more often in the second decade than in the first decade?).

The title of the paper and the freedom from reoperation curves (Figure 2) may be misleading. The title of the paper suggests that pre-operative AI is associated with a higher reoperation hazard. This statement is not uniformly supported by the results of the study. Although according to the log-rank test the AI patients have lower freedom from reoperation rate, this observation is not confirmed by the Cox-regression analyses. In addition, the authors investigated the risk of pre-operative AI by calculating and comparing risk estimates (odds ratios). However, this does not take into account the time-dependency of the event and is inadequate. Furthermore, the upper 95% confidence interval limit of the reoperation hazard for pre-operative AI is 105.9, which indicates that freedom from reoperation curves are based on very few patients, especially after 8 years of follow-up. These small sample sizes may increase the effect of assumption violations, which may result in incorrect or uninterpretable Kaplan-Meier results. In order to achieve reliable estimates of the three major functions (survival, probability density, hazard) and to ensure that the standard error of the survival estimate is less than 10%, the number of subjects remaining at risk in this study should be at least 13 at the time of the last survival estimate (2).

Finally, the authors' conclusion that other approaches should be considered for patients with AI should be interpreted in light of some other important issues. Even if the durability of autografts is less in patients with pre-operative AI, the decision whether to perform the Ross procedures depends also on technical considerations and informed patient preferences (3).

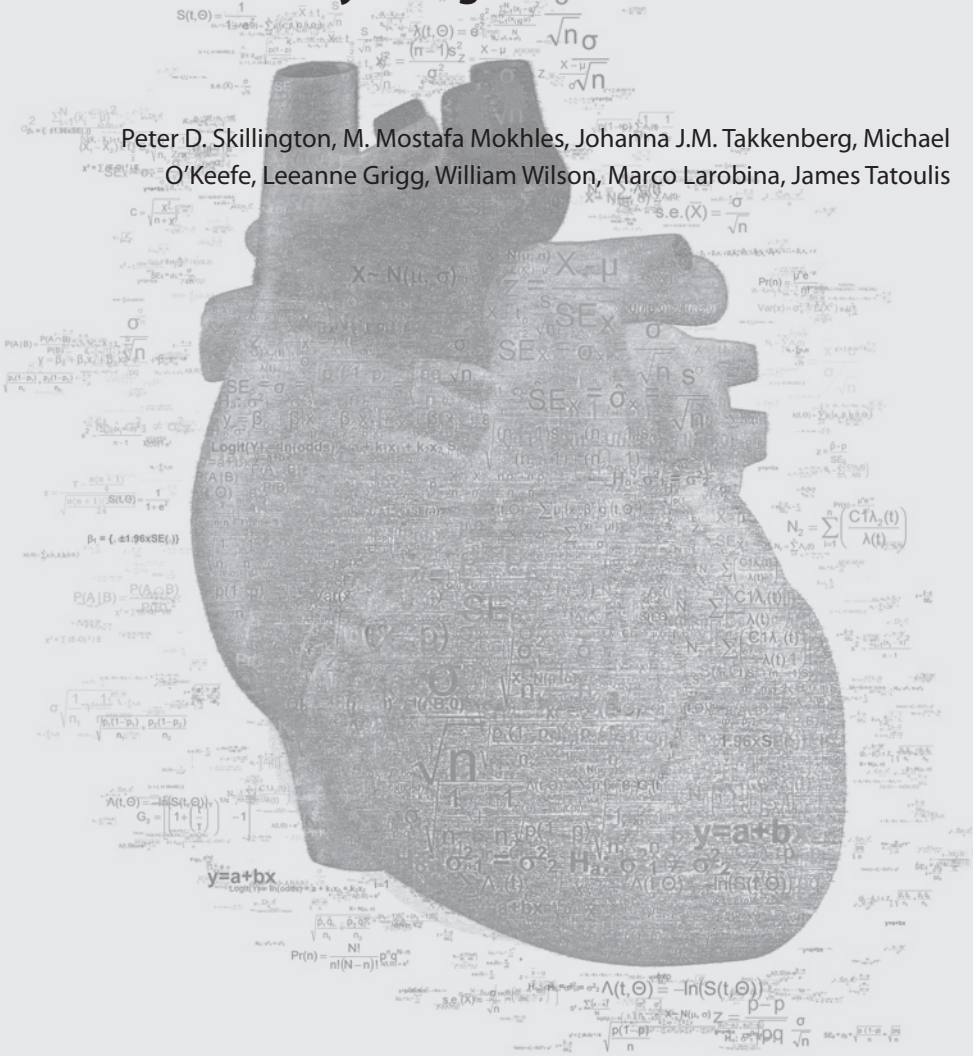
REFERENCES

1. Ryan WH, Prince SL, Culica D, Herbert MA. The Ross procedure performed for aortic insufficiency is associated with increased autograft reoperation. Ann Thorac Surg; 91(1):64-69; discussion 69-70.
2. Karrison TG. Use of Irwin's restricted mean as an index for comparing survival in different treatment groups--interpretation and power considerations. Control Clin Trials 1997; 18(2):151-167.
3. Mokhles MM, Kortke H, Stierle U, Wagner O, Charitos EI, Bogers AJ, Gummert J, Sievers HH, Takkenberg JJ. Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. Circulation; 123(1):31-38.

Chapter 6

Twenty-Year Analysis of Autologous Support of the Pulmonary Autograft in the Ross Procedure

Peter D. Skillington, M. Mostafa Mokhles, Johanna J.M. Takkenberg, Michael O'Keefe, Leeanne Grigg, William Wilson, Marco Larobina, James Tatoulis



Ann Thorac Surg 2013; Epub ahead of print (PubMed PMID: 23870828)

ABSTRACT

Background

The Ross procedure is seldom offered to adults less than 60 years of age who require aortic valve replacement except in a few high-volume centers with documented expertise. Inserting the pulmonary autograft as an unsupported root replacement may lead to increasing reoperations on the aortic valve in the second decade.

Methods

Of 333 patients undergoing the Ross procedure between October 1992 and June 2012, the study group of 310 consecutive patients (mean age ± standard deviation, 39.3 ± 12.7 years (limits 16–63) had the aortic root size adjusted to match the pulmonary autograft, which was inserted as a root replacement, with the aorta closed up around it to provide autologous support.

Results

The mean follow-up time was 9.4 years; the actuarial survival was 97% at 16 years; and freedom from the composite of all reoperations on the aortic valve and late echocardiographic-detected aortic regurgitation greater than mild was 95% at 5 years, 94% at 10 years, and 93% at 15 years. Overall freedom from all reoperations on aortic and pulmonary valves was 97% at 5 years, 94% at 10 years, and 93% at 15 years. All results were better for the patients presenting with predominant aortic stenosis (98% freedom at 15 years) than for those with aortic regurgitation (p=0.01).

Conclusions

Autologous support of the pulmonary autograft leads to excellent results in the groups presenting with aortic stenosis and mixed aortic stenosis/regurgitation and to good results for those presenting with pure aortic regurgitation. The Ross procedure, using one of the proven, durable techniques available, should be considered for more widespread adoption.

INTRODUCTION

The Ross operation for treatment of aortic valve disease in younger patients has a lot of advantages when compared with other aortic valve replacement (AVR) options, particularly with regard to improved survival (1-3), hemodynamic performance similar to that in patients with a normal aortic valve (4,5), and the lack of necessity to take oral anticoagulant drugs.

However, the Ross procedure (RP) is not often performed unless the patient is operated on in one of the few high-volume centers that have documented expertise with this operation. The main reason is a variability in the durability of the pulmonary autograft (PA) in the aortic position, and this in turn is also influenced by the technique of PA insertion. The known techniques that have led to good long-term outcomes include the subcoronary technique (6, 7) and root replacement methods (2, 3, 8). With the root replacement method, however, it is very important that the PA root is trimmed distally to just above the commissures to achieve good aortic valve function in the long term. When this has not been done, late PA root dilatation early in the second decade of follow-up has been increasingly reported, leading to aortic regurgitation (AR) and reoperation (9-12).

Treatment of this series of patients used a variant of the inclusion cylinder (IC) technique whereby the aortic root size was adjusted to match the PA, which was inserted as a root replacement with the aorta closed up around it to provide autologous support (13, 14). It is different from other previously described IC methods (15, 16).

MATERIAL AND METHODS

Between October 1992 and June 2012, 333 consecutive patients underwent the RP as a surgical treatment for aortic valve disease. Of these, in 310 patients, a variant IC method was used to insert the PA, and these patients constituted the study patients. Of the 23 patients in whom this IC method was not used, a root replacement (unsupported) was used in 8 patients and a subcoronary technique in 2. In 13 patients, the PA was inserted inside a Valsalva Dacron graft. The ethics committee at the Royal Melbourne Hospital approved the study of these patients, and each individual patient gave informed consent for participation in this study.

The demographics of the patients operated on can be seen in Table I. Patients classified as having pure aortic stenosis (AS) had either severe aortic valve stenosis or symptomatic moderate to severe AS, with less than moderate regurgitation. Those with mixed AS/AR had at least moderate stenosis and regurgitation combined, and those presenting with pure AR had no additional significant AS. The technique used has been

previously described (13). All operations were performed by use of median sternotomy, cardiopulmonary bypass, and cardiac arrest with tepid blood cardioplegia delivered both antegradely and retrogradely. The sequence of events after aortic cross-clamping was as previously described (13). With respect to the aortic root procedure, the sequence of steps was as follows:

1. Transverse aortotomy with transection of the aorta 5 mm above the sinotubular junction (STJ).
2. Aortic valve excision and debridement of aortic annulus.
3. Measurement of aortic annulus and STJ diameter.
4. Vertical extension of aortotomy down into the non coronary sinus, all the way to aortic annulus.
5. Reduction of aortic annulus using partial circumference external Dacron ring and reduction of aortic sinus and STJ if required using wedge or quadrangular excision to achieve aortic annulus diameter of 24 mm – 26 mm (male patients) and 22 mm – 24 mm (female), similar STJ diameter.
6. If the aortic annulus or STJ diameter exceeds 32 mm to 34 mm, indicating excessive mismatch between the aortic and pulmonary roots, the variant IC method described is inappropriate, and the PA is inserted either by root replacement, or inside a valsalva Dacron graft, or the RP is abandoned in favour of either a mechanical or other bioprosthetic valve.
7. Insertion of the PA root with interrupted (predominantly) or continuous 4/0 Prolene suture.
8. Coronary anastomosis to the PA as previously described (13).
9. Closure of vertical extension of aortotomy using 5/0 Prolene, thus enclosing the PA root inside the aortic root.
10. Anastomosis of the PA root distally to the ascending aorta, including part or all of the aortic root remnant in this suture line.

The aortic cross-clamp and cardiopulmonary bypass times, and adjunctive aortic root manipulation and concomitant other cardiac procedures, are listed in Table 2. Enlargement of the aortic annulus, if required, used the Manougian technique (2 patients). When the aortic sinuses or STJ required enlargement, this was performed by using autologous pericardial patch enlargement (21 patients). The diagram of the completed standard operation can be seen in Figure 1.

All patients have been followed up with clinical review by the surgeon and/or cardiologist yearly, and follow-up echocardiograms have been obtained before hospital discharge, 6 to 12 months after the operation, and every second year thereafter. Echo-

Table 1. **Patient Demographics.**		
No. Patients	**310**	
Age	Mean±SD (years)	Limits (years)
	39.3±12.7	16-63
Gender	Male	Female
	216 (69.7 %)	94 (30.3%)
Aortic valve lesion		
AS	141 (45.5%)	
AS/AR	68 (21.9%)	
AR	101 (32.6 %)	
Bicuspid aortic valve	285 (92.0%)	
NHYA Class		
I	58 (18.7%)	
II	193 (62.3 %)	
III	57 (18.4 %)	
IV	2 (0.6%)	
Previous surgery	30 (9.7%)	
Aortic valve repair	13 (4.2%)	
AVR	9 (2.9%)	

AS, aortic stenosis; AR, aortic regurgitation; NHYA, New York Heart Association; AVR, aortic valve replacement

Table 2. **Operative Data.**		
	Mean±SD (mins)	**Limits (mins)**
Aortic cross clamp time	172.9±20.4	122-247
Cardiopulmonary bypass time	199±22.4	139-290
Adjunctive aortic root procedure		
External Dacron partial circumference ring reduction annuloplasty	168 (54.2%)	
Wedge or quadrangular reduction aortic non-coronary sinus and sinotubular juntion (STJ)	109 (35.2 %)	
Enlargement aortic annulus or aortic root	23 (7.4%)	
Concommitant procedures		
Ascending aorta replacement	43 (13.9 %)	
Tailoring aortoplasty	65 (21.0%)	
Subaortic resection/Myomectomy	4 (1.3 %)	
CABG	3 (1.0%)	
ASD/PFO	4 (1.3 %)	
Miscellaneous	4 (1.3 %)	

CABG, coronary artery bypass graft; ASD/PFO, Atrial Septal Defect/ Patent Foramen Ovale

cardiographic parameters assessed include aortic and pulmonary valve function, left ventricular size and function, and aortic root size.

Statistical Analysis

Cumulative survival and freedom from events were analyzed by the Kaplan-Meier method. The log-rank test was used to compare survival between different groups.

All statistical tests were two-sided, and tests with p values of 0.05 or lower were considered significant. All statistical analyses were done with the Statistical Package for Social Sciences software, version 20.0 (SPSS, Chicago, IL). GraphPad Prism 5.00 for Windows (GraphPad Software, La Jolla, CA) was used to obtain life tables and corresponding Kaplan-Meier survival curves.

RESULTS

Early and late mortality

There were no in-hospital deaths, but there was one death within 30 days, from myocardial infarction, an early mortality of 0.3%. Late follow-up is 97%, complete with 9 patients lost to clinical follow-up. There have been 5 late deaths, all from noncardiovascular

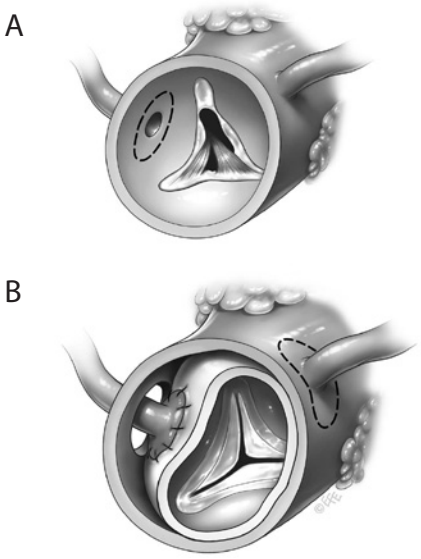


Figure 1. Variant inclusion cylinder method with autologous support of the pulmonary autograft. (A) Site and size of left coronary button. (B) Left coronary artery implantation into pulmonary autograft showing inclusion cylinder technique.

causes at 3, 4, 5, 10, and 12 years postoperatively (ie, no late cardiac deaths). As can be seen from Figure 2, late actuarial survival is 97% at 16 years. The mean follow-up time is 9.4 years and encompasses 2/915 patient-years.

In-hospital complications

For a group of adult patients less than 60 years of age, in-hospital complications were as expected. Please refer to Table 3 for a full list of these.

Late aortic valve function

1. Re-operation for progressive AR: Ten patients required reoperation and AVR. Nine of these were in the group presenting with pure AR before surgery. Thus freedom from re-do AVR can be seen in Figure 3, 96%, at 15 years.
2. Late Doppler echocardiography detected AR: only 2 patients, other than those that have already undergone re-do AVR for progressive AR, have greater than mild AR detected during serial follow-up Doppler echocardiography.
3. Endocarditis affecting aortic valve. Two patients required surgery for late endocarditis affecting the aortic valve. In one, this was a consequence of primary pulmonary valve endocarditis, where paravalvular infection also involved the neo-aortic valve. In this patient both aortic and pulmonary valves were replaced with Medtronic freestyle valves. In the other patient, infection involved a partial circumferential external Dacron ring around the aortic annulus. Surgery was required, although the ring, which was surrounded by purulent material, was excised, and the normally functioning neo-aortic PA valve was able to be left in situ. These operations were

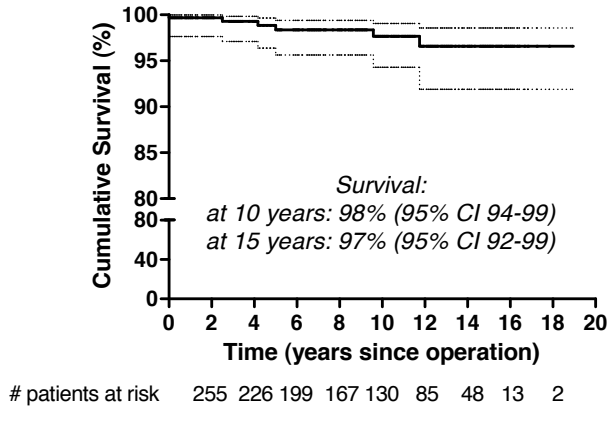


Figure 2. Actuarial patient survival.

performed at seven and nine years post operatively respectively. Both patients survived re-operation.

4. Composite of freedom from all re-operations on the aortic valve and greater that mild post-operative AR can be seen in Figure 4, 93% at 15 years. There is a significant (p=0.01) difference in this outcome measure between those patients presenting with AS and AS/AR, compared to those presenting with the AR (at 15 years, 98% for AS, 98% for AS/AR, and 82% for AR presentation) as can be seen in Figure 5.

Late pulmonary valve function

Late assessment and management of pulmonary valve function has been as follows.

1. Doppler echocardiography:

The mean ± SD pulmonary valve gradient measured by Doppler echocardiography, is 10 ± 5.3 mmHg (limited 2-44). The indication for re-do pulmonary vale replacement (PVR) in these patients is mean pulmonary valve gradient exceeding 40 mmHg or development of right ventricular (RV) hypertrophy, or enlargement, or symptoms associated with a lower gradient than that described. Only one patient has met these criteria and underwent successful re-do PVR at 11 years post-operative. With regard to late pulmonary regurgitation (PR), only 12 patients (4%) have more than mild PR detected during follow-up (all moderate in degree), and none have required re-operation for this problem. The

Table 3. In-hospital Complications.

CVA	1 (0.3%)
Bleeding	5 (1.6%)
Deep sternal wound infection	1 (0.3%)
Low CO needing inotropes	1 (0.3%)
Ventricular Arrhythmias	1 (0.3%)
Atrial Arrhythmias	31 (1%)
Pericardial effusion/tamponade	2 (0.6%)
Re-exploration for low cardiac output	1 (0.3%)
Renal impairment	3 (1.0%)
HB/PPM	1 (0.3%)
Antibiotic/positive Homograft culture	1 (0.3%)
Repair/graft septal perforated artery	1 (0.3%)
Re-intubation	1 (0.3%)
Pneumothorax	2 (0.6%)
AMI	1 (0.3%)
Coronary artery kink	1 (0.3%)
Other	15 (4.8%)

CVA, cerebrovascular accident; CO, cardiac output; HB/PPM, heart block / permanent pacemaker; AMI, acute myocardial infarction

indication for re-do PVR, is the development of severe PR, in association with significant enlargement and/or reduced RV systolic function, or development of symptoms.

2. Endocarditis of the pulmonary valve:

Three patients developed endocarditis affecting the pulmonary valve, one already mentioned who required re-do AVR and re-do PVR. The other two developed endocarditis isolated to the pulmonary valve at three and seven years post-operative, and both required re-do PVR. Both survived re-operation.

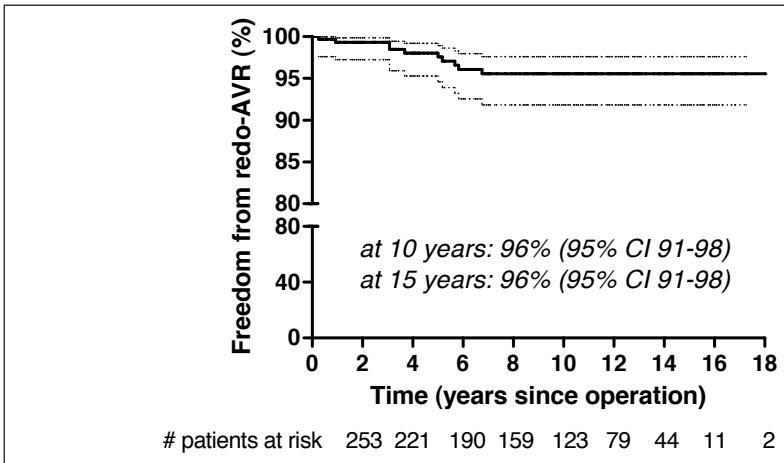


Figure 3. Actuarial freedom from redo aortic valve replacement (AVR).

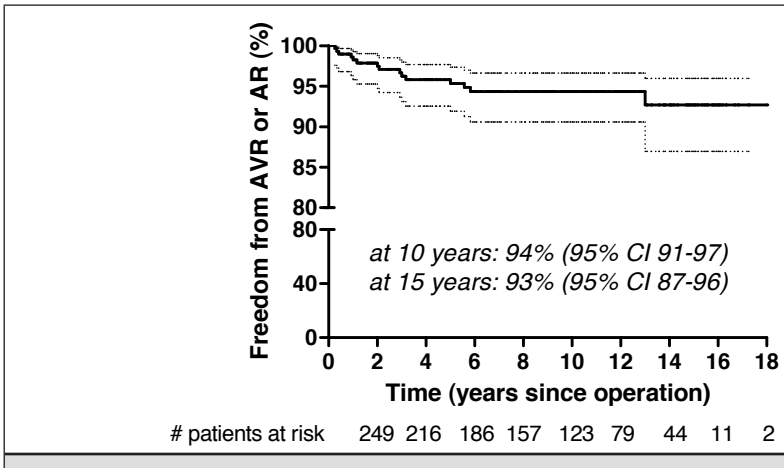


Figure 4. Actuarial freedom from redo aortic valve replacement (AVR) and greater than mild post-operative aortic regurgitation (AR).

3. Freedom from re-operation on both the aortic and pulmonary valves during follow-up:

Including all causes (i.e. structural degeneration and endocarditis), a total of 15 patients have required re-operation on either valve (or in the case of one patient, both), as can be seen in Figure 6. Once again, the outcome is significantly better for AS and AS/AR presentations, as shown in Figure 7. The respective freedoms at 15 years are: 98% for AS, 98%, for AS/AR, and 82% for AR presentation (p=0.01).

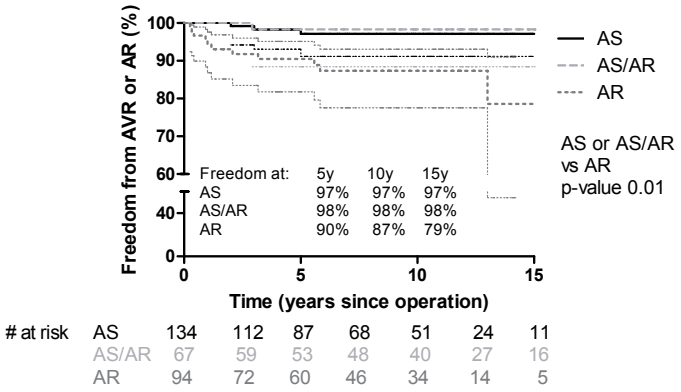


Figure 5. Freedom from redo aortic valve replacement (AVR) and greater than mild postoperative aortic regurgitation (AR): aortic stenosis (AS) vs AS/AR vs AR.

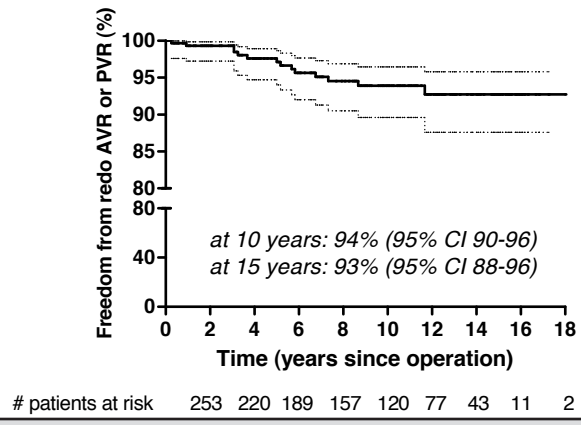


Figure 6. Actuarial freedom from redo aortic valve replacement (AVR) and/or pulmonary valve replacement (PVR).

COMMENT

The variant IC method described has been used in 310 of 333 consecutive patients undergoing the RP during the past 20 years, most of whom presented with congenital bicuspid aortic valve disease. Early in the authors' experience, during the initial 10 RPs performed, 4 patients underwent an unsupported root replacement (RR) method to insert the PA, and in 6 patients, an IC method was used. In the patients undergoing RR, it was noted that after release of the aortic cross-clamp, the neoaortic root dilated significantly. Although no AR was associated with this enlargement, because of concern about further potential aortic root enlargement later, the RR method was abandoned. It was only used in another 4 patients subsequently in special circumstances dictated by unusual technical factors.

After that observation, the authors decided to use an IC method nearly exclusively. This method differs from previously described IC methods in two significant ways. First, as described by the senior author in 1995 (14), the coronary arteries are excised as buttons, brought inside the aortic root, and anastomosed to the PA root as shown in Figure 1. Second, the aortic root is adjusted in size, incorporating an external Dacron ring annuloplasty, mostly partial circumference only, and reduction in the aortic sinus diameter and STJ by the use of longitudinal excision of noncoronary sinus tissue, as described in the Methods section. In 1999, the senior author showed that these maneuvers were successful in maintaining normal aortic root size, in comparison with the 4 earlier patients in whom a RR method was used for PA implantation, in whom the aortic root significantly dilated (13).

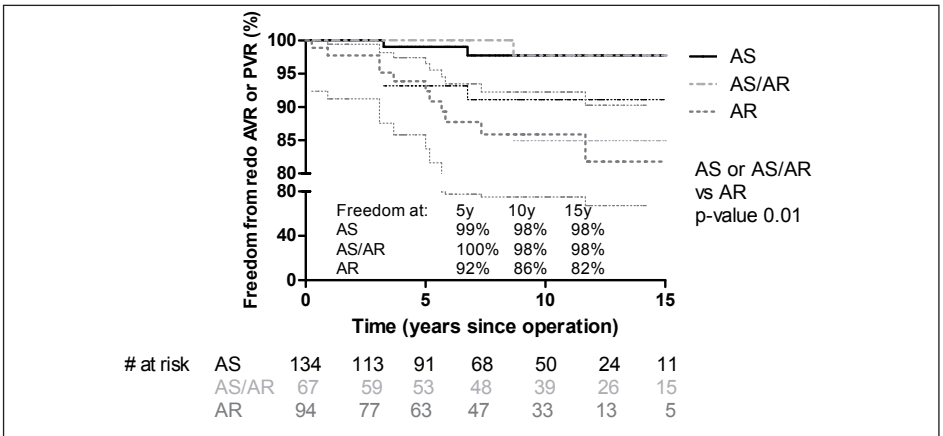


Figure 7. Freedom from redo aortic valve replacement (AVR) and/or pulmonary valve replacement (PVR): AS vs AS/AR vs AR (AR = aortic regurgitation; AS = aortic stenosis).

It is highly likely that supporting the PA root with the patient's own aorta in this manner, which has been adjusted to the correct size, is responsible for the very durable results reported in this study. By closing the patient's aorta up around the PA, this autologous support does away with the need for prosthetic material to support the aortic sinuses and STJ. The only situation in which prosthetic support has been used more recently is when aortic dilatation is marked, and with such excessive mismatch of aorta to pulmonary artery size; if an RP is to be performed, the PA has been inserted inside a Valsalva Dacron graft. These patients are not included in the study group as mentioned in the Methods section.

The method used has given outstanding results both in patients with AS and those with mixed AS/AR. In both these groups, the composite freedom from reoperation on the aortic valve and late AR greater than mild is 97% and 98%, respectively at 15 years after operation. Excluding 2 patients who have required aortic valve reoperation because of late endocarditis, this composite freedom would be 99%. Thus, there is no late tendency for increasing postoperative AR. For this procedure to be compared with mechanical AVR, one needs to take into account patients who have also had to undergo reoperation on the pulmonary valve. There have been four of these procedures, three of which were for endocarditis. Allowing for this, the 15-year freedom from reoperation on both aortic and pulmonary valves is 98% for both the AS group and the AS/AR group. This compares very favorably with the incidence of late redo AVR, after mechanical AVR, which varies from 91% to 97% (17-20).

The results obtained with this IC method have not been as good when applied to patients presenting with pure AR, with 79% composite freedom from re-operation on the aortic valve and postoperative AR greater than mild. In this group, progressive AR led to redo AVR in 9 patients, all within 6 years of operation, with no failures beyond that time frame. During the initial few years of the senior author's experience (1992 to 1998 inclusive), all patients presenting with AR underwent the RP. Six of the 30 patients with AR operated on in that time, the majority of whom had marked aortic root enlargement, needed redo AVR. At the end of 1998, when it was appreciated that excessive aortic root dilatation was a significant risk factor for the development of postoperative AR, the RP was abandoned in this subset of patients presenting with excessively dilated aortic root. For the past 3 years, the authors again offered the RP to patients in this group, albeit with insertion of the PA inside a Valsalva Dacron graft, although these patients have not been analyzed as part of this study because the follow-up period is too short to allow a meaningful analysis. Other groups have also noted worse late results in patients presenting with AR (8, 12). With regard this IC method in patients presenting with AR, if the aortic root is not excessively dilated (>32 to 34 mm at the aortic annulus, the STJ, or both), good results have been obtained.

If a reoperation is required for progressive AR in patients having this IC method, a mechanical AVR has been performed. Valve-sparing surgical procedures have not been possible in this situation, as has been reported after a failed RR method (9). Fortunately, this is seldom required, particularly with AS or AS/AR. Also, of note in the group presenting with AR, if failure and redo AVR are necessary, this becomes apparent early, and all reoperations are performed within 6 years, with no late failures. Thus, if failure has not occurred early, stable aortic valve function has been observed even in the group presenting with AR. This is in stark contrast to failure after the RR method, when increasing failures occur during the second decade of follow-up (9, 10, 12), and an earlier failure phase, related to technical factors (11).

When reoperations after the RP are considered, the pulmonary allograft also needs mention. Four patients required redo PVR, and in 3, the indication was endocarditis. Admittedly 5% to 6% of patients do have mild to moderate tubular pulmonary stenosis of the conduit that develops 6 to 12 months after operation, and fortunately, these patients have stable Doppler echocardiography parameters across the pulmonary valve, up to 17 years postoperatively, in this series. No doubt with further follow-up into the second and third decades, some of these patients will come to reoperation, either by further open procedures, or via percutaneous methods.

The other options for patients in this age group (15 to 60 years) who require AVR are mechanical valve replacement and tissue AVR, both xenograft and aortic allograft. Not only do mechanical AVR recipients require oral anticoagulants such as warfarin indefinitely, but their long-term survival is worse than that of an age-matched and sex-matched population (21). When one takes into account valve-related deaths and thromboembolic and bleeding complications, fewer than 50% of patients after mechanical AVR are free of valve-related complications 15 years after operation (17, 19). In this series of 310 patients followed up over a 20-year period, there have been no late valve-related deaths.

With regard to bioprosthetic AVR, not many studies have analyzed survival rates in the younger patient group reported on here. However, those that have, show reduced life expectancy in comparison with the general population (22, 23). There is also the problem of poor durability in younger patients (22). The modern trend toward bioprosthetic AVR insertion in patients under 60 years, with the plan to insert "valve-in-valve" transcatheter AVR, is as yet untested, but it is difficult to see how this will lead to comparable survival and subsequent reoperation rates, considering that a smaller valve will have to be inserted inside the original prosthesis each time this is done. There may be a place for bioprosthetic AVR in a patient between 50 and 60 years of age, in whom the aortic annulus is dilated more than 32 to 34 mm if this anatomic substrate is present in a patient within this age group, a larger valve-in-valve subsequent procedure could be performed without causing significant patient–prosthesis mismatch. An AVR using an

aortic allograft does give better durability than bioprosthetic AVR in younger patients (24), although the important recent randomized controlled trial comparing the PA with the aortic allograft, reported in 2010 in the Lancet by Yacoub's group, showed worse survival and reoperation rates in the allograft group than in the RP group (1).

Conclusions

In summary, this variant of the IC method, which incorporates autologous support of PA in 310 adult patients younger than 60 years, operated on over a 20-year period, has led to excellent durability with very low reoperation rates and nearly perfect long-term aortic valve function as determined by echocardiography. The outcomes are outstanding in patients presenting with AS and AS/AR, and good in those presenting with AR. Considering the discussed and known disadvantages associated with the use of bioprosthetic and mechanical valves in this age group, the RP using either the method discussed or one of the other proven, durable techniques available should be considered for more widespread adoption.

ACKNOWLEDGEMENTS

The authors would like to thank Tonia Iacuone for typing the manuscript, Mardi Malone for assistance with submission of the manuscript. The authors would also like to thank Rochelle Wynne for help in maintaining the Ross procedure database.

FUNDING SOURCE

The Ross Procedure and Cardiac Surgery Trust.

REFERENCES

1. El-Hamamsy I, Eryigit Z, Stevens LM, et al. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. The Lancet 2010;376:9740:524-531.
2. Yacoub MH, Klieverik LMA, Melina G, et al. An Evaluation of the Ross Operation in Adults. J Heart Valve Dis 2006;15:531-539 .
3. Brown JW, Ruzmetov M, Shahriari A, Rodefeld MD, Mahomed Y, Turrentine MW. Midterm Results of Ross Aortic Valve Replacement: A Single-Institution Experience. Ann Thorac Surg 2009;88:601.608.
4. Oury JH, Doty D, Oswalt JD, Knapp JF, Mackey SK, Duran CMG. Cardiopulmonary response to maximal exercise in young athletes following the Ross procedure. Ann Thorac Surg 1998;66:S153-4.
5. Porter GF, Skillington PD, Bjorksten AR, Morgan JG, Yapanis AG. Exercise Hemodynamic Performance of the Pulmonary Autograft Following the Ross Procedure. J Heart Valve Dis 1998;8:516-521.
6. Sievers HH, Hanke T, Stierle U, et al. A Critical Reappraisal of the Ross Operation Renaissance of the Subcoronary Implantation Technique? Circulation 2006;114[suppl I]:I-504-I-511.
7. Sievers HH, Stierle U, Charitos EI, et al. Fourteen years' experience with 501 subcoronary Ross procedures: Surgical details and results. J Thorac Cardiovasc Surg 2010;140:816-822.
8. David, TE, Woo A, Armstrong S, Maganti M. When is the Ross operation a good option to treat aortic valve disease? J Thorac Cardiovasc Surg 2010;139:68-75.
9. de Kerchove L, Rubay J, Pasquet A, et al. Ross Operation in the Adult: Long-Term Outcomes After Root Replacement and Inclusion Techniques. Ann Thorac Surg 2009; 87: 95-102.
10. Klieverik LMA, Takkenberg JJM, Bekkers JA, Roos-Hesselink JW, Witsenburg M, Bogers AJJC. The Ross operation: a Trojan horse? Eur Heart J 2007;28:1993-2000.
11. Frigiola A, Ranucci M, Carlucci C, Giamberti A, Abella R, Di Donato M. The Ross Procedure in Adults: Long-Term Follow-Up and Echocardiographic Changes Leading to Pulmonary Autograft Reoperation. Ann Thorac Surg 2008;86:482-489.
12. Elkins RC, Thompson DM, Lane MM, Elkins CC, Peyton MD. Ross operation: 16-year experience. J Thorac Cardiovasc Surg 2008;136:623-630.
13. Skillington PD, Fuller JA, Grigg LE, Yapanis AG, Porter GF. Ross procedure: Inserting the autograft using a fully supported root replacement method; techniques and results. J Heart Valve Dis 1999;8:593-600.
14. Skillington PD, Grigg LE. Insertion of the pulmonary autograft as an inclusion cylinder – modifications to existing techniques. J Heart Valve Dis 1995;4:374-378.
15. Elkins RC, Santangelo K, Stelzer P, Randolph JD, Knott-Craig CJ. Pulmonary autograft replacement of the aortic valve: an evolution of technique. J Card Surg 1992;7:108-116.
16. Pacifico AD, Kirklin JK, McGiffin DC, Matter GJ, Nanda NZC, Diethelm AG. The Ross operation – early echocardiographic comparison of different operative techniques. J Heart Valve Dis 1994; 3:365-370.
17. Zellner JL, Kratz JM, Crumbley AJ, et al. Long-term experience with the St. Jude medical valve prosthesis. Ann Thorac Surg 1999;68:1210-1218.
18. Butchart EG, Li HH, Payne N, Buchan K, Grunkemeier, GL. Twenty years' experience with the Medtronic Hall valve. J Thorac Cardiovasc Surg 2001;121:1090-1100a.

19. Lund O, Nielsen SL, Arildsen H, Ilkjaer LB, Pilegaard HK. Standard aortic St. Jude valve at 18 years: performance profile and determinants of outcome. Ann Thorac Surg 2000;69:1459-1465.
20. Emery RW, Krogh CC, Arom KV, et al. The St. Jude Medical Cardiac Valve Prosthesis: A 25-Year Experience With Single Valve Replacement. Ann Thorac Surg 2005;79:776-782.
21. Kvidal P, Bergstrom R, Horte, LG, Stahle, E. Observed and relative survival after aortic valve replacement. JACC 2000;35:747-756.
22. Puvimanasinghe JPA, Takkenberg JJM, Eijkemans MJC, et al. Prognosis After Aortic Valve Replacement With the Carpentier-Edwards Pericardial Valve: Use of Microsimulation. Ann Thorac Surg 2005;80:825-831.
23. David TE, Puschmann R, Ivanov J, et al. Aortic valve replacement with stentless and stented porcine valves: a case-match study. J Thorac Cardiovasc Surg 1998;116:236-240.
24. O'Brien M, Stafford EG, Gardner MAH, et al. Allograft aortic valve replacement: Long-term follow-up. Ann Thorac Surg 1995;60:S65-70.

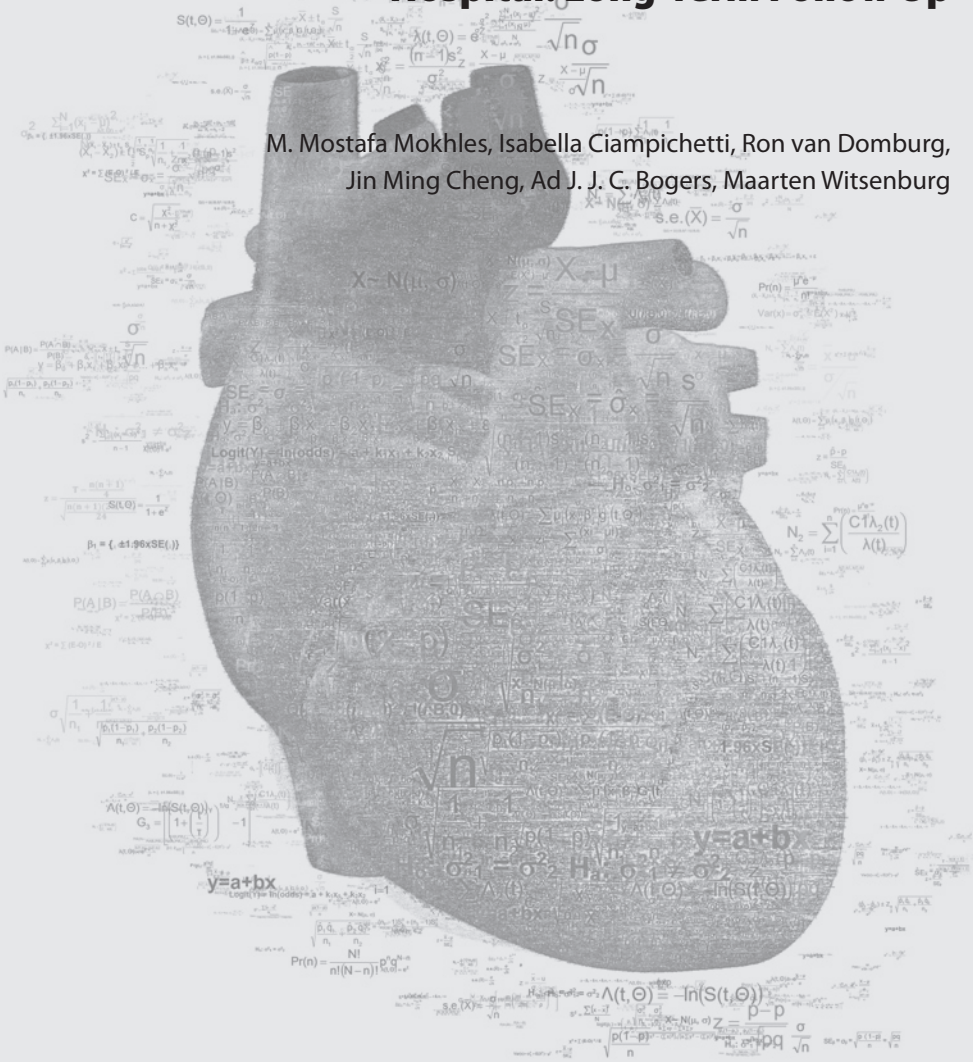
LIST OF ABBREVIATIONS

AMI	Acute Myocardial Infarction
AR	Aortic Regurgitation
AS	Aortic Stenosis
ASD/PFO	Atrial Septal Defect/ Patent Foramen Ovale
AVR	Aortic Valve Replacement
CABG	Coronary Artery Bypass Graft
CO	Cardiac Output
CVA	Cerebrovascular Accident
HB/PPM	Heart Block / Permanent Pacemaker
IC	Inclusion Cylinder
NHYA	New York Heart Association
PA	Pulmonary Autograft
PR	Pulmonary Regurgitation
PVR	Pulmonary Vale Replacement
RP	Ross Procedure
RR	Root Replacement
RV	Right Ventricular
STJ	Sinotubular Junction

Chapter 7

Infective Endocarditis in a Tertiary Referral Hospital: Long-Term Follow Up

M. Mostafa Mokhles, Isabella Ciampichetti, Ron van Domburg, Jin Ming Cheng, Ad J. J. C. Bogers, Maarten Witsenburg



J Heart Valve Dis. 2012;21:118-24

ABSTRACT

Background and aim of the study

Infective endocarditis (IE) is associated with significant mortality and morbidity. The objective of present study was to assess long-term survival of patients with infective endocarditis. In addition, we aimed to objectify the mortality in these patients by comparing their survival with age- and gender matched survival rate of the general population.

Materials and methods

A retrospective observational cohort study of adults with IE, determined by the modified Duke criteria, who were admitted between January 1, 1998 and December 31, 2007 to a tertiary-referral center. Cumulative survival was analyzed using the Kaplan—Meier method. The Log-rank test was used to compare different groups. Multivariate Cox proportional hazards regression analyses were performed to identify predictors of long-term all-cause mortality.

Results

One-hundred-ninety-one consecutive patients with IE were evaluated (176 left-sided, 15 right-sided). Cardiac surgery was performed in 72% of the cases. Median follow-up was 6.3 years. Cumulative long-term survival was 59% after 10 years of follow-up, the main causes of death being congestive heart failure (28%) and different type of malignancies (17%). Age- and gender matched survival in the general population was 98%, 92% and 80% after a follow-up period of one, five and ten years, respectively. Predictor of long-term mortality was cancer. Surgery had a positive effect on long-term survival.

Conclusions

Despite diagnostic and therapeutic advances, IE is associated with high long-term mortality. Compared to the general Dutch population, the survival of patients with IE was significantly lower. Even if the IE is cured, the survival of these patients may be diminished compared to that of the general population. Careful follow-up of these patients is therefore warranted.

INTRODUCTION

During the past decades the prognosis of infective endocarditis (IE) improved considerably and the disease is no longer by definition fatal (1, 2). However, IE still remains a serious condition characterized by high morbidity and mortality. The in-hospital mortality has been reported in large series to range between 15% and 20% (3, 4) with one year mortality of almost 40% (4, 5).

The clinical diagnosis of IE is often difficult due to highly variable manifestation of this disease. IE can manifest with cardiac, pulmonary, ophthalmic, central nervous system, renal, orthopedic, and peripheral vascular disorders. In addition, IE may affect patients' own native heart valves or a surgically implanted prosthetic valve, but can also be associated with various types of structural and congenital heart diseases as well. Several predisposing factors, e.g. mitral prolapse, aortic valve disease and congenital heart disease, have been reported to be associated with a risk for development of IE (6-8). Moreover, the clinical diagnosis of IE is hampered by a lack of epidemiological characteristics and the variety of microbiological organisms.

Immediate identification of patients with IE, who are at high risk of death or complications, can contribute to improved outcome of this disease. Unfortunately, definitive studies on IE are still rather limited, especially studies determining long-term survival of patients after IE. In addition, survival of patients with IE has never been put into perspective by comparing the survival rate of these patients with that of the matched general population.

The aim of present study was to determine long-term survival prognosis of patients with IE. Furthermore, we aimed to objectify the survival of these patients by comparing it to the matched survival of the general population.

METHODS

Study population

From January 1998 to December 2008, all consecutive adult patients (n=256), presenting with suspected IE at our tertiary referral center, were included. Hospital records of these patients were retrospectively evaluated for having definite IE according to the modified Duke criteria (9). One-hundred-ninety-one patients that fulfilled the modified Duke criteria of definite IE were included in this study.

Data collection

Using standardized forms, all necessary data were collected by retrospectively reviewing the medical records and hospital database. Follow-up started at the day of admission in our

center. The follow-up of patients in the present study consisted of obtaining mortality status from the civil registries and obtaining the causes of death from the general practitioners.

In March 2010, vital status of all patients was acquired from municipal civil registries with a response rate of 100%. Furthermore, we have conducted phone interviews with the general practitioners to obtain the causes of death.

Local research ethics committee approval was not required for this retrospective study. The authors had full access to and take full responsibility for the integrity of the data and the present manuscript.

Statistical Analyses

Continuous data are presented as mean (standard deviation; range), and comparison was done using the unpaired T-test unless the data were not normally distributed (Kolmogorov-Smirnov test); in these instances we used the Mann-Whitney U-test for comparison. Categorical data are presented as proportions, and comparison was done using the Chi-Square test or the Fisher Exact test where appropriate. All tests were 2-sided, with an α-level of 0.05. Cumulative survival was analyzed using the Kaplan-Meier method. The Log-rank test was used to compare different groups. Multivariate Cox proportional hazards regression analyses were performed to identify predictors of long-term all-cause mortality. Due limited amount of in-hospital deaths (n=26), the number of variables in the multivariate analysis were restricted to five ($=\sqrt{26}$). We used univariate analysis to identify the best predictors of death. Together with age and gender, additional three predictors were subsequently entered in a multivariate analysis to identify independent predictors of in-hospital death. Comparison of patient survival with the general age-matched population was done using the Dutch population life table (10). All statistical tests were two-sided, and tests with P value of 0.05 or lower were considered significant. All statistical analyses were done using the Statistical Package for Social Sciences software, version 15.0 (SPSS, Chicago, Illinois).

RESULTS

Baseline characteristics of 191 patients with definite IE are shown in Table 1. Mean age was 55 years and 72% were male.

Microbiologic characteristics

Causative microorganisms were identified through blood cultures in 177 patients (93%). From 6 of these patients with confirmed positive blood cultures the hospital record did not contain information about the causative agent. The blood cultures of 14 (7%) patients were negative (Table 1).

Table 1. Baseline Characteristics and Microbiologic Etiology of 191 Patients with Definite Endocarditis.

Baseline characteristics	Patients, No. (%)
Mean age ± SD (years)	55 (15)
Gender	
Males	138 (72)
Females	53 (28)
Hypertension	42 (22)
Diabetes mellitus	20 (11)
Myocardial infarction	25 (13)
Extracardiac arteriopathy	8 (4)
Aorta ascendens aneurysm	3 (2)
CVA	25 (13)
TIA	11 (6)
Renal failure	16 (8)
Hemodialysis dependent	8 (4)
COPD	14 (7)
HIV positive	1 (1)
Chronic immunosuppressive therapy	4 (2)
Cancer	17 (9)
Rheumatoid arthritis	3 (2)
Pacemaker/ICD	10 (5)
Congenital heart disease	25 (13)
Native valve predisposition*	44 (23)
Previous endocarditis	27 (14)
Intravenous drug abuse	1 (1)
Dental procedures <60 days to admission	18 (9)
Other invasive procedures <60 days to admission	17 (9)
Central venous catheter as suspected cause	7 (4)
Prior valve surgery or CABG†	71 (37)
Prior Valve surgery	60 (31)
Prior CABG	16 (8)
Prior PCI	7 (4)
Fever, temperature >38°C	91 (48)
Left ventricular function ≤ 49%	47 (25)
Elevated ESR	111 (58)
Elevated C-reactive protein	143 (75)

CABG, Coronary artery bypass grafting; COPD, Chronic Obstructive Pulmonary Disease; CVA, Cerebro Vasculair Accident; ESR, Erythrocyte Sedimentation Rate; HIV, Human Immunodeficiency Virus; ICD, Implantable Cardioverter Defibrillator; PCI, Percutaneous coronary intervention; TIA, Transient Ischaemic Attack; *Prior valve regurgitation and/or fibrosis; †Some patient had a history of both valve surgery and CABG.

Overall, the majority of IE was caused by Staphyloccocus Aureus (n=43, 23%) followed by Viridans group streptococci (n=42, 22%). Coagulase-negative staphylococcus (n=26, 14%), other streptococcus (n=38, 20%), Enteroccocus species (n=14, 7%), Gamella Morbillorum (n=4, 2%), Propionibacterium Acnes (n=2, 1%), Escherichia coli (n=2, 1%), Aeroccocus viridans (n=1, 1%) and Klebsiella species (n=1, 1%) could be identified as other causes of infective endocarditis.

In almost half of the patients who were operated, streptococcus could be identified as the causative organism, while in non-surgical patients streptococcus were responsible in 25% of the cases. In non-surgical patients more than half of the cases of endocarditis were caused by staphylococcus aureus and coagulase-negative staphylococci (Figure 1).

Clinical and Echocardiographical findings

Fever was present in 91 (48%) patients at the time of admission. The majority of the patients had an elevated serum level C-reactive protein (n=143; 75%) and elevated serum level erythrocyte sedimentation rate (n=111; 58%) (Table 1).

Echocardiography was performed in all patients with suspected IE. Table 2 summarizes the localization of IE and type of valve affected. The valves of the left side of the heart (n=176) were more frequently affected than the valves of the right side of the heart (n=15).

The pulmonary valve was affected in 7 patients and in 8 patients the tricuspid valve was affected. In the group of patients with pulmonary valve endocarditis, 4 patients had operated congenitally corrected transposition of the great arteries, two patients had surgically corrected tetralogy of Fallot and one patient underwent a Ross operation nine years before the diagnosis of the endocarditis. In the group of patients with tricuspid valve endocarditis, 2 patients had Ebstein's Anomaly, one patient was a intravenous drug abuser, one patient developed endocarditis after orthopedic hand surgery, one patient developed endocarditis shortly after tricuspid valve replacement, one patient

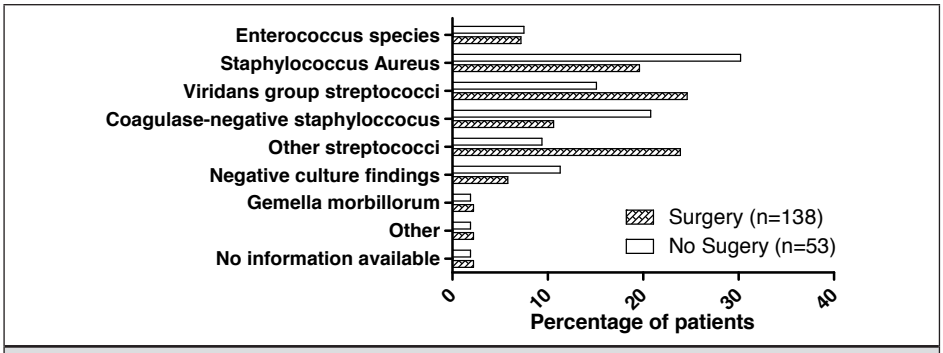


Figure 1. Microbiologic etiology of surgical and non-surgical patients.

developed endocarditis of the tricuspid valve after endocarditis of VSD-patch, and from two patients the exact location of endocarditis could not be retrieved.

In the group of patients with aortic valve endocarditis, eight patients had a bicuspid aortic valve and two patients had a congenital aortic valve stenosis. There were no congenital valve lesions in the group of patients with mitral valve endocarditis. None of the patients with left sided IE was an intravenous drug abuser.

In the majority of cases a native valve was affected (73%). Prosthetic valve IE was present in 25% of the cases (Table 2).

Complications and outcome

During median admission of 26 days (range, 0-160 days), 120 (63%) patients developed at least one complication. The most frequently observed complications were neurologic events (18%), renal failure (16%) and heart failure (9%).

Surgery was performed in 138 (72%) patients. The main indications for surgery were a large persistent vegetation (25%), severe valve regurgitation (20%), heart failure (18%), abscess formation (6%) and systemic embolization (3%). Within this group of 138 patients, who underwent surgery, 8 (6%) patients developed atrioventricular block post operatively, and 10 patients needed a rethoracotomy (mainly due to persistent blood loss).

During hospital admission 26 (14%) patients died, of whom 15 patients underwent surgery for their endocarditis during admission and 11 patients were treated conservatively. Causes of death were congestive heart failure or cardiogenic shock in nine patients, progressive renal failure in three patients, uncontrolled infection in another three patients, and gastrointestinal bleeding in two patients. Multiple organ failure, electromechanical dissociation, cerebral hemorrhage, cardiac tamponade, basilar artery thrombosis and ventricular fibrillation were other causes for death. Three patients died during surgery because severe tissue damage prevented valve replacement.

Table 2. Type and frequency of affected valves in 191 Patients with Definite Endocarditis.

	Main affected valve				
	Aortic valve*	**Mitral valve†**	**Pulmonary valve**	**Tricuspid valve**	**Total**
Native valve	84 (44%)	49 (26%)	3 (2%)	7 (4%)	140 (73%)
Mechanical valve	17 (9%)	14 (7%)	0 (0%)	1 (1%)	32 (17%)
Homograft	3 (2%)	0 (0%)	4 (2%)	0 (0%)	7(4%)
Bioprosthesis	8 (4%)	1 (1%)	0 (0%)	0 (0%)	9 (5%)
Total	112^ (57%)	64 (34%)	7 (4%)	8 (4%)	191 (100%)

* 24 patients with IE of mainly aortic valve had also concomitant mitral valve IE which is not taken into account in this table; † 3 patients with IE of mainly mitral valve had also concomitant aortic valve IE which is not taken into account in this table

Long-term survival after infective endocarditis

There were 165 (86%) hospital survivors. During a median follow-up of 6.3 years (range, 0 days-12.2 years) 46 patients died (39 left-sided endocarditis, 7 right-sided endocarditis). Cause of late death were congestive heart failure in thirteen patients, various type of malignancies in eight patients, renal failure in six patients, and cerebrovascular accident in three patients. Multiple organ failure, sepsis in two patients, acute coronary syndrome, post-anoxic encephalopathy, trauma capitis, acute heart failure after cardiac transplantation, pneumonia, peritonitis were other causes for death. There were two sudden, unexplained, unexpected deaths without further clinical data or autopsy. From five patients the cause of death could not be retrieved. In the group of patients with right-sided endocarditis heart failure was by far the most common cause of death (4 out of 7 deaths).

The overall survival after infective endocarditis was 76% at 1 year, 65% at 5 years and 59% at 10 years (Figure 2A). A survival difference was observed between different types of causative organisms of IE. Patients presenting with Staphylococcus Aureus or coagulase-negative staphylococci IE had lower survival compared to patients presenting with other microbiological organisms ($p<0.001$) (Figure 2B). Patients with IE of a prosthetic valve had a lower survival compared to patients with native valve endocarditis ($p=0.03$) (Figure 2C). No differences were observed in late survival between right-sided and left-sided IE ($p=0.88$) (Figure 2D).

Survival comparison

Age- and gender matched survival in the general population was 98%, 92% and 80% after a follow-up period of one, five and ten years, respectively. Compared to age- and gender matched Dutch population norms, the survival of patients with IE was significantly impaired. After 10 years of follow-up only 59% of the patients with IE were still alive while the survival rate in the age- and gender matched general population was 80% (Figure 3A).

After exclusion of in-hospital mortality, age- and gender matched survival in the general population was 93% and 81% after a follow-up period of five and ten years, respectively. The survival of our patient population, after exclusion of in-hospital mortality, was 75% and 69% after a follow-up period of five and ten years, respectively (Figure 3B).

Factors affecting long-term mortality

Using Cox proportional hazards model we identified that age (HR 1.04, 95% CI 1.02-1.06), cancer (HR 3.37, 95% CI 1.74-6.55), poor left ventricular function (EF ≤ 49%) (HR 2.77, 95% CI 1.00-7.71), history of myocardial infarction (HR 2.14, 95% CI 1.21-3.78), development of renal (HR 1.99, 95% CI 1.11-3.56) or heart failure (HR 2.01, 95% CI 1.00-4.04) during admission are associated with long-term mortality. Surgery (HR 0.33, 95% CI 0.21-0.53) had a protective effect on long-term mortality.

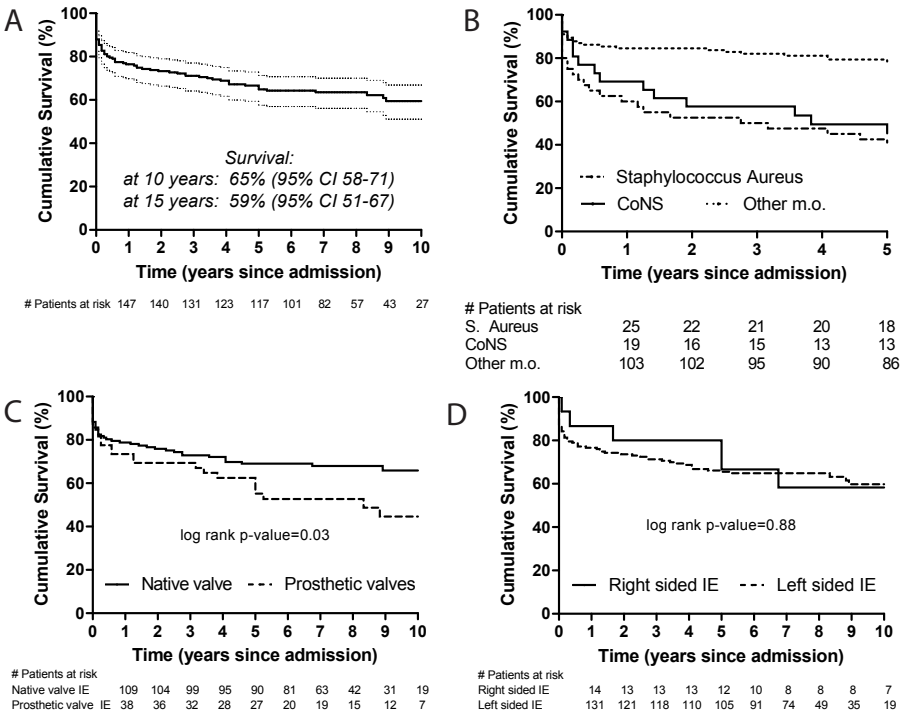


Figure 2. Survival after Infective Endocarditis; A) KM survival curve with 95% CI, B) KM survival curves stratified by different causative organisms, C) KM survival curves stratified between native valve and prosthetic valve, D) KM survival curves stratified between left-sided and right-sided IE. S. Aureus, Staphyloccocus Aureus, CoNS, coagulase- negative staphylococcus, m.o., micro-organisms, IE, Infective Endocarditis.

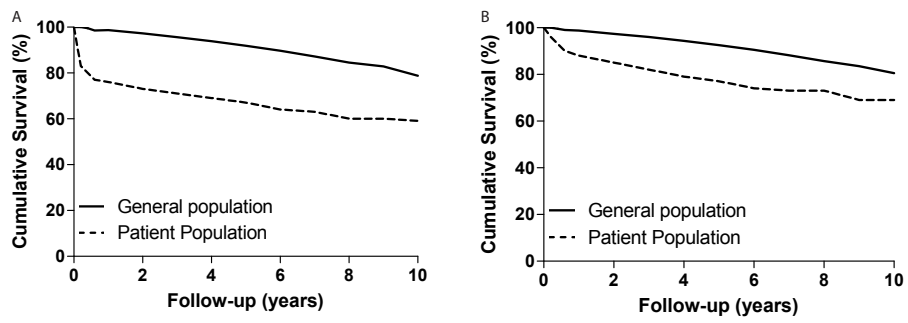


Figure 3. Survival comparison with the general Dutch population; A) KM survival including in-hospital mortality, B) KM survival curves without in-hospital mortality.

After adjustment, cancer (HR 3.37, 95% CI 1.70-6.70) was associated with higher mortality during long-term follow up. Surgery (HR 0.41, 95% CI 0.23-0.73) could also in multivariate analysis be identified to have a protective effect on long-term mortality.

DISCUSSION

To our knowledge, this is the first study which objectifies the survival of IE patients by comparing it to the survival of age- and gender matched population.

Overall, the present study shows that long-term survival after diagnosis of IE is relatively low with 59% of the patients being alive after a follow-up period of 10 years. We observed a considerable difference between the long-term survival of patient with IE and the survival of age and gender matched general population. The discrepancy in survival rates between patients with IE and the general Dutch population also remained considerable after the exclusion of in-hospital mortality.

The five year survival within our study population is comparable with the five year survival rate of 71% reported by Castillo et al. (11) and higher compared with the five year survival rate of 57% reported by Delahaye et al. (12). The five year survival rate of native valve endocarditis in the present study was 73% which is lower compared to five year survival rates of 88% and 96% reported in other series (11, 13). The five year survival rate of prosthetic valve endocarditis in our series was 61% which is comparable with survival rate of 60% reported by Calderwood et al. (14).

The mean age of our study population was 55 years (range, 18-79 years). Of these patients 30% were older than 65 years. This finding is in accordance with previous studies on IE and confirms that patients presenting with IE in the last decades are getting older (3, 5, 15, 16). This finding may be explained by an increased life expectancy which leads to higher incidence of degenerative valvular diseases and increased exposure to nosocomial bacteremia (17).

In the majority of cases left-sided heart valves were affected. However, 15 (8%) patients were treated for right-sided endocarditis. In western countries right-sided endocarditis most often occurs in persons using intravenous drug, but in the present study only one patient was an intravenous drug abuser. Therefore, intravenous drug abuse was not a major cause of right-sided endocarditis in our patient population. In the present study, the right-sided endocarditis, especially endocarditis of the pulmonary valve, seems to be predominantly a disease of patients with preexisting congenital valvular abnormalities.

Study limitations

The present study is based on a single center tertiary-care university hospital patient population and, therefore, could be subject to referral bias limiting the generalization of

our results. Acute infections are also treated in other regional hospitals in the area, but more severe or complicated cases, which may need surgery, may have been referred to our hospital.

Conclusions

In conclusion, despite diagnostic and therapeutic advances, infective endocarditis is still associated with high long-term mortality. Compared to the general Dutch population, the survival of patients with IE was significantly lower. Even if the IE is cured, the survival of these patients may be diminished compared to that of the general population. Careful follow-up of these patients is, therefore, warranted. In a minority of patients the right-sided heart valves were affected. This was predominantly a disease of patients with preexisting valvular abnormalities.

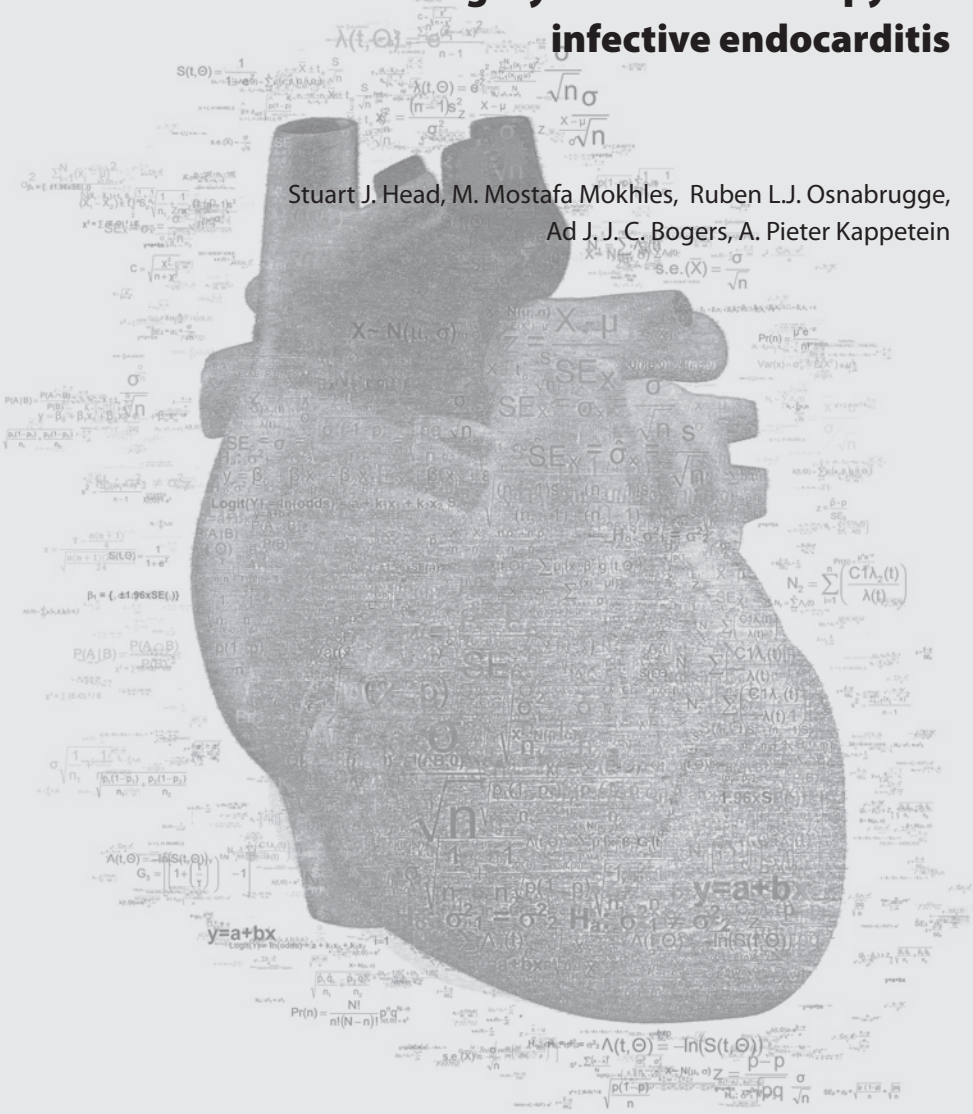
REFERENCES

1. Lowes JA, Hamer J, Williams G, Houang E, Tabaqchali S, Shaw EJ, Hill IM, Rees GM. 10 Years of infective endocarditis at St. Bartholomew's Hospital: analysis of clinical features and treatment in relation to prognosis and mortality. Lancet 1980; 1(8160):133-136.
2. McCartney AC. Changing trends in infective endocarditis. J Clin Pathol 1992; 45(11):945-948.
3. Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, Casalta JP, Danchin N, Delahaye F, Etienne J, Le Moing V, Leport C, Mainardi JL, Ruimy R, Vandenesch F. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA 2002; 288(1):75-81.
4. Cabell CH, Jollis JG, Peterson GE, Corey GR, Anderson DJ, Sexton DJ, Woods CW, Reller LB, Ryan T, Fowler VG, Jr. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 2002; 162(1):90-94.
5. Benn M, Hagelskjaer LH, Tvede M. Infective endocarditis, 1984 through 1993: a clinical and microbiological survey. J Intern Med 1997; 242(1):15-22.
6. Michel PL, Acar J. Native cardiac disease predisposing to infective endocarditis. Eur Heart J 1995; 16 Suppl B:2-6.
7. Weinberger I, Rotenberg Z, Zacharovitch D, Fuchs J, Davidson E, Agmon J. Native valve infective endocarditis in the 1970s versus the 1980s: underlying cardiac lesions and infecting organisms. Clin Cardiol 1990; 13(2):94-98.
8. Habib G. Management of infective endocarditis. Heart 2006; 92(1):124-130.
9. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30(4):633-638.
10. Dutch Life Tables 2009 (Centraal Bureau voor de Statitiek, The Hague, The Netherlands; http://statline.cbs.nl).
11. Castillo JC, Anguita MP, Ramirez A, Siles JR, Torres F, Mesa D, Franco M, Munoz I, Concha M, Valles F. Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. Heart 2000; 83(5):525-530.
12. Delahaye F, Rial MO, de Gevigney G, Ecochard R, Delaye J. A critical appraisal of the quality of the management of infective endocarditis. J Am Coll Cardiol 1999; 33(3):788-793.
13. Tornos MP, Permanyer-Miralda G, Olona M, Gil M, Galve E, Almirante B, Soler-Soler J. Long-term complications of native valve infective endocarditis in non-addicts. A 15-year follow-up study. Ann Intern Med 1992; 117(7):567-572.
14. Calderwood SB, Swinski LA, Karchmer AW, Waternaux CM, Buckley MJ. Prosthetic valve endocarditis. Analysis of factors affecting outcome of therapy. J Thorac Cardiovasc Surg 1986; 92(4):776-783.
15. Watanakunakorn C, Burkert T. Infective endocarditis at a large community teaching hospital, 1980-1990. A review of 210 episodes. Medicine (Baltimore) 1993; 72(2):90-102.
16. Bogers AJ, van Vreeswijk H, Verbaan CJ, Kappetein AP, van Herwerden LA, Mochtar B, Bos E. Early surgery for active infective endocarditis improves early and late results. Thorac Cardiovasc Surg 1991; 39(5):284-288.
17. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med 2001; 345(18):1318-1330.

Chapter 8

Surgery in current therapy for infective endocarditis

Stuart J. Head, M. Mostafa Mokhles, Ruben L.J. Osnabrugge, Ad J. J. C. Bogers, A. Pieter Kappetein



Vasc Health Risk Manag. 2011;7:255-63

ABSTRACT

The introduction of the Duke criteria and transesophageal echocardiography has improved early recognition of infective endocarditis but patients are still at high risk for severe morbidity or death. Whether an exclusively antibiotic regimen is superior to surgical intervention is subject to ongoing debate. Current guidelines indicate when surgery is the preferred treatment, but decisions are often based on physician preferences. Surgery has shown to decrease the risk of short-term mortality in patients who present with specific symptoms or microorganisms; nevertheless even then it often remains unclear when surgery should be performed. In this review we i) systematically reviewed the current literature comparing medical to surgical therapy to evaluate if surgery is the preferred option, ii) performed a meta-analysis of studies reporting propensity matched analyses, and iii), briefly summarized the current indications for surgery.

INTRODUCTION

Over the last decades infective endocarditis (IE) has been described extensively (1). This has identified risk factors, clinical features, and predictors of outcome, which led to the prescription of antibiotic prophylaxis during the perioperative stage of dental and cardiovascular surgery (2, 3). Furthermore, the development of the Duke criteria as a diagnostic tool (4) and the use of transesophageal echocardiography (TEE) have contributed significantly to early recognition. Despite these developments, outcomes nonetheless remain unsatisfactory (5-7). Peripheral or cerebrovascular embolisms and acute heart failure can cause a drastic decrease of the quality of life. Moreover, mortality rates continue to be as high as 50% in some studies.

The usage of an antibiotic regimen alone or in combination with surgical intervention is an ongoing debate. Studies investigating the best treatment have shown that surgery in combination with antibiotics is superior in some indications (8). The decision whether and when to treat endocarditis surgically often depends on local practice. Uniform recommendations are therefore difficult to make and an overall superiority of medical or surgical treatment is not yet established. In a propensity matched analysis surgery seemed to be superior regarding in-hospital mortality (9, 10), but at long-term follow-up data suggests no benefit of surgical therapy compared to an exclusively medical regimen (11, 12). A better outcome with surgical therapy was recently demonstrated in the largest reported matched cohorts (13). Still, these studies with propensity matched analysis do not produce unambiguous results (14).

Timing of surgery is important. This issue has been extensively addressed and there is substantial evidence that early surgery can be performed safely, but no consensus exists on the optimal timing of valve replacement in the active phase of endocarditis (15, 16). Waiting increases the risk of stroke or peripheral emboli while early surgery increases the risk of procedure-related complications and longer antibiotic treatment can potentially avoid valve replacement.

It is clear that the optimal treatment for IE remains challenging. The ongoing ENDO-VAL trial will be the first to report results of patients treated medically or surgically in a randomized fashion and can provide important data (17). Before these results will be presented treatment preferences are based on current data. This review systematically evaluates studies comparing medical to surgical therapy and discusses the timing of surgery.

CURRENT DATA

Systematic Review: Medical or Surgical Therapy?

We performed a systematic review of studies reporting hospital mortality of medical and surgical treatment separately. The Medline database, web-of-science, and The Cochrane Library were consulted with search entries of "endocarditis" and "treatment or therapy or surgery or medical" and "outcome or survival or mortality or hazard ratio" in all possible combinations. Studies were excluded if they focused on a specific aspect of endocarditis, reported results of an exclusive patient cohort, or included less than 50 patients. Multiple studies overlapped in patient populations; only the study with the largest number of patients was included.

Forty eligible studies were identified (9-11, 12-13, 18-52). Data was pooled to obtain an overall view of the studied population; a total of 11,348 IE episodes were analyzed (Table 1, Figure 1). The largest study on endocarditis to date is from the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS), which was a prospective, multicenter, international registry with 2,781 patients from over 50 centers (53). The combined data of the 40 studies had similar baseline characteristics as gender, PVE (%), and periannular abscess (%). Vegetations were visualized less in the combined data (87% compared to 70% in our data). The cause of endocarditis was also similar, although the number of Staphylococcus aureus infections was 21% in the combined series as to 31% in the registry, and viridans streptococci was identified in 20% compared to 17% in the ICE-PCS registry. Results were remarkably similar; occurrence of stroke and non-stroke embolism were almost identical. Furthermore, heart failure was diagnosed in 34% compared to 32% in ICE-PCS, and in-hospital mortality was 19% versus 18% respectively.

One limitation of the ICE-PCS registry is that the indications for surgery were not reported. In our combined data of the 40 studies, surgery was performed in 4714 episodes of endocarditis. Seventeen studies reported indications for surgery; heart failure (50%) was the main reason, others were large vegetation on echocardiography (21.5%), persistent infection (18.8%), embolic complication (17.8%), or abscess formation (17.4%). Although it is likely that more complex cases of endocarditis underwent surgery, the in-hospital mortality was significantly lower in these patients compared to those medically treated (15.8% versus 20.3%). This could be explained by the fact that patients deemed too high risk for surgery due to their condition were treated non-surgically, thereby increasing the observed mortality in the medically treated patient cohort. As a result of treatment preferences, most studies include significant treatment bias and robust evidence-based conclusions are unavailable. Predicting which treatment is most beneficial for the individual patient remains challenging.

Meta-analysis: Propensity Score Studies

A number of studies used propensity matching to compare medical to surgical therapy (Table 2) (9-14, 54). Studies that report in-hospital mortality either show results favoring

Table 1. Characteristics and Outcome of IE in Pooled Analysis of 40 Systematically Included Studies.

	Episodes (N=11,348) (%)	Number of Studies (N)
Characteristics		
Definite infective endocarditis according to Duke criteria	95.4%	(33)
Males	65.5%	(39)
Prosthetic valve endocarditis (all studies)	20.2%	(39)
Prosthetic valve endocarditis (natural)	21.9%	(28)
Surgery	41.5%	(40)
Echocardiographic findings		
Vegetations	69.4%	(32)
Mobile vegetations	51.7%	(7)
New valve regurgitation	47.6%	(7)
Periannular complications	16.2%	(4)
Abscess	12.7%	(16)
Perforation	10.4%	(8)
Prosthetic valve dehiscence	6.9%	(12)
Indications for surgery		
Heart failure	49.7%	(17)
Emboli	17.8%	(16)
Persistent infection	18.8%	(14)
Abscess	17.4%	(12)
Large vegetation	21.5%	(6)
Complications		
Emboli		
Brain	14.9%	(14)
Systemic/peripheral	21.2%	(21)
Unspecified	33.0%	(9)
Heart failure	34.1%	(34)
Neurological events	24.0%	(7)
Stroke	16.3%	(6)
In-hospital mortality	19.2%	(40)
Surgical treatment	15.8%	(40)
Medical treatment	20.3%	(40)

Prosthetic valve endocarditis "all studies" shows the incidence in all episodes. The "natural" occurrence of prosthetic valve endocarditis is the percentage in studies including all cases of endocarditis, and not studies specifically including prosthetic or native valve cases.

surgical therapy over medical therapy or no statistical difference (Table 2). Combined data reveal an overall odds ratio of 0.47 (95% confidence interval (CI) 0.38-0.58) supporting surgery. There is however a marked statistically significant heterogeneity (I^2=65%, P=0.005 (Figure 2)), meaning that there is excessive variation in the results. The largest study encompassed 1500 patients from the large ICE-PCS registry and is therefore weighted with 48.7% in the analysis (13).

Bias

Even though both the pooled and meta-analysis limit bias to some extent, included studies that report results after IE treatment are inherent to treatment and referral bias.

First of all, studies comparing medical to surgical treatment in a randomized fashion are not yet available. Baseline characteristics are therefore incomparable between groups. Even with propensity matched analyses, patients can only be matched considering the collected variables. Characteristics such as frailty are not available but can influence outcome. Other certain endocarditis-specific variables warrant surgical intervention and these variables will not be available in the medical group. These variables can therefore not be matched, and while groups are allegedly 'matched', they often are not completely. A recent study demonstrated that adjustment for an additional survivor bias factor is needed, as it can significantly alter the results (55).

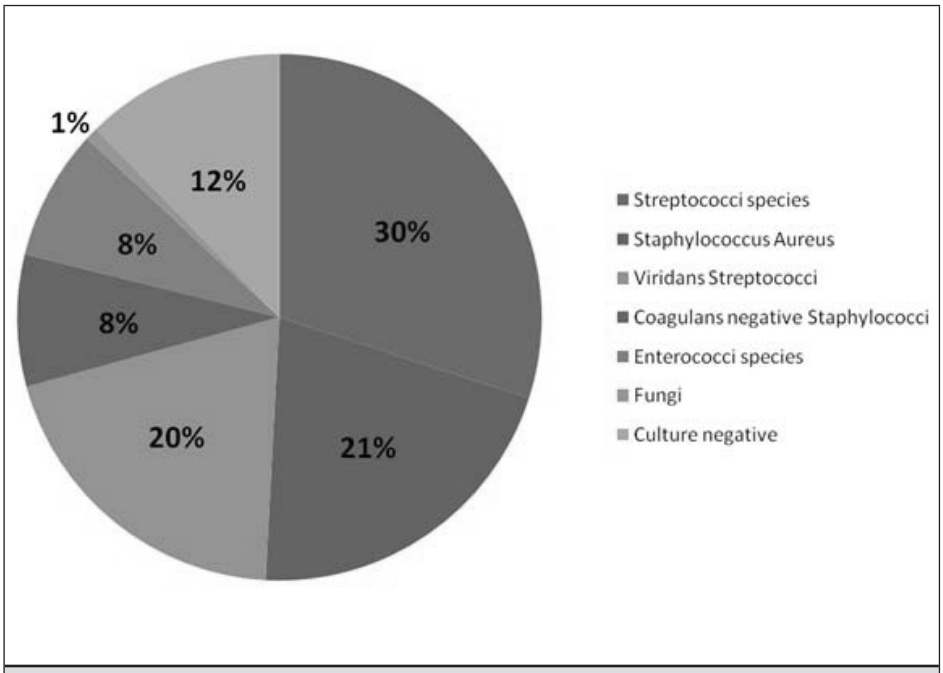


Figure 1. Causative microorganisms from pooled data of 11,348 IE episodes.

Referral bias embodies another bias that is often present in the included studies. Patients from the ICE-PCS registry transferred to tertiary care centers more frequently underwent surgery and had higher rates of complications such as stroke, heart failure, or valve regurgitation (56). Results from certain centers can therefore be skewed in relation to other outcomes, and this should be kept in mind when evaluating these studies.

The studies included in the meta-analysis have previously been shown to be incomparable on multiple fronts. Inconsistent results are therefore likely to be not only dependable of the given treatment, but also due to used methods of data acquirement, co-morbidity definitions, the number of variables matched for, reporting of data, and statistical methods (57). Furthermore, the deliberate decision whether to treat medically or surgically is based on certain specific characteristics of the patient, and no study without or with propensity analysis can adjust for clinical judgment.

Indications and Timing for Surgery

In the pooled data surgery was performed in 41.5% of IE cases. Apart from studies comparing medical to surgical therapy, extensive results of surgical series have been described. These studies have furthermore provided data on surgical indications and many of these indications have now been included in current guidelines (3, 58, 59).

Congestive Heart failure

Infective endocarditis often causes heart failure as a result of valve regurgitation, or sometimes because of valve obstruction or prosthetic valve dehiscence. Heart failure is a prognostic factor of impaired survival, independent of the causative microorganism or the status of infection. Many surgeons consider it as the main indication to perform surgery (60).

The timing of surgery depends on the progression of heart failure. Urgent surgery is needed if acute regurgitation of the aortic valve is present. A slower progressive presentation gives the opportunity to postpone surgery and await the effect of medical therapy.

Periannular Extension

In native valve endocarditis periannular extension is present in 10-40%, but in prosthetic valve endocarditis (PVE) this is as high as 56-100% (61). Annulus involvement is associated with development of heart failure and increases mortality. Surgery is often indicated, especially when an abscess is present. The pooled data (Table 1) suggests that this is the case in almost 13%, but a recent study focusing exclusively on surgical patients showed a rate of 38% (62). Medical therapy is insufficient if an abscess has been detected on TEE, and guidelines therefore suggest that these patients should undergo

Table 2. Studies reporting propensity matched analysis.

First Author, year	*Follow-up*	*Total No. of Patients (N)*	*Matched No. of Patients (N)*	*Mean Age (years)*	*Prosthetic Valve Endocarditis (%)*	*Mortality Surgical (%)*	*Mortality Medical (%)*	*Hazard Ratio / Odd Ratio Surgery (95% CI)*
Lalani, 2010	In-hospital	1552	619:619	53:53	0:0	11.8	17.4	0.44 (0.33-0.59)
Aksoy, 2007	In-hospital	426	51:51	58:59	18:26	11.8	21.6	0.27 (0.13-0.55)
Wang, 2005	In-hospital	355	68:68	…	100:100	22.1	32.4	0.56 (0.23-1.36)
Cabell, 2009 *	In-hospital	1516	299:300:299:300:299	…	0:0	not reported		2.38 (0.83-6.88) **
								0.49 (0.19-1.22)
								0.52 (0.23-1.18)
								0.79 (0.46-1.35)
								0.21 (0.10-0.41) ***
Vikram, 2003	6 months	513	109:109	53:55	0:0	15	28	0.40 (0.18-0.91)
Tleyjeh, 2009	6 months	546	93:93	…	…	not reported		1.3 (0.5-3.1)
Sy, 2009	median 5.2 years	223	62:161	47:58	19:26	not reported		0.77 (0.42-1.40)

Multiple values in one entry are listed as 'surgical patients : medical patients'. * Patients were divided in five cohorts depending on the likelihood of undergoing surgery. **Patients not likely to undergo surgery. *** Patients very likely to undergo surgery.

surgery (3). If early surgical intervention is not performed an abscess can progress into fistulous cavities resulting in a mortality rate as high as 41% (63).

Periannular extension is likely in case of persistent infection despite antibiotic therapy and surgery should be considered. An advantage of surgery over an antibiotic regimen is expressed in the completeness of therapy. Open-heart surgery gives the opportunity to extensively remove infected tissue to prevent relapses.

Emboli

One of the major complications of IE is the development of systemic emboli in 22-50% of the patients (64, 65). Common affected sites are the lungs, spleen and peripheral arteries, but the most affected (65%) is the central nervous system (CNS) (65). Not only morbidity is high, but CNS emboli significantly increase the risk of mortality.

The prevention of events is difficult, since the event itself can be the initial presentation of IE. These patients have a clear indication for urgent surgery. This however carries an increased risk of intracranial hemorrhage while waiting and medical therapy increases the risk of recurrent emboli. Current recommendations therefore suggest a 2-4 week antibiotic regimen before surgery can be performed safely. In patients that present with transient ischemic attacks or "silent" embolisms early surgery appears safe. No prospective studies have confirmed these findings, and more data is needed (66).

Large vegetations on TEE are often of prognostic value of embolic events. Although there is not a uniform cut-off value, vegetations between 10-15 mm are an indication to perform urgent surgery.

Persistent Sepsis

An ongoing infection despite antibiotic therapy is common with aggressive microorganisms, abscess formation, or large vegetations. Patients with persistent sepsis are at

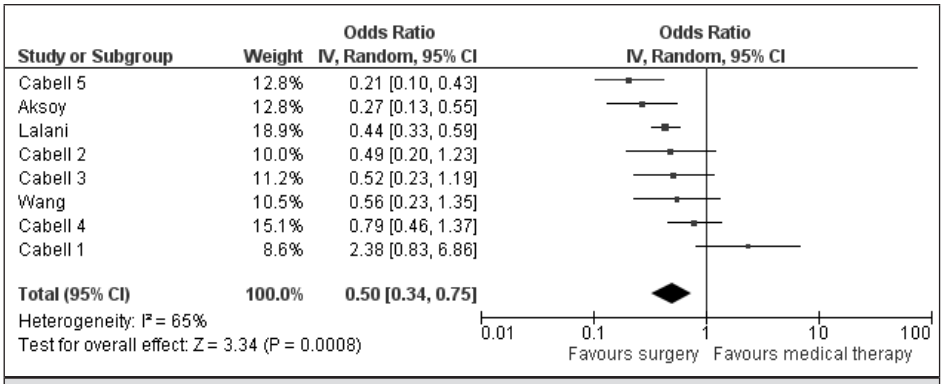


Figure 2. Meta-analysis of studies with propensity analysis.

high risk to develop multi-organ failure and guidelines indicate that surgery is needed in these patients if cultures persist to be positive after 7 days of medical therapy (59, 62). Some caution is however advised in patients that develop recurrent fever after an initially good response to antibiotics, because the fever could be explained by other reasons than the endocarditic valve. Surgery is only indicated if further diagnostics confirm persistent infection of the valve (61).

Microorganism

A fungal cause often marks a complex case of IE. First of all, the diagnosis is delayed due to recurring negative blood cultures. Once IE is established medical therapy with antifungals is frequently unsatisfactory, resulting in the need for surgery in a large percentage of patients. Other indications for surgery are large vegetations and periannular extension that regularly complicates fungal IE.

Endocarditis caused by bacteria can be challenging as well, especially Staphylococcus aureus (67). These complicated infections with large vegetations and embolic manifestations result in an increased risk of mortality. If multi-resistant S aureus is detected, surgery is the only conclusive therapy and is always indicated.

Several other micro-organisms such as Brucella, Q fever, Pseudomonas aeruginosa, and Staphylococcus lugdunensis indicate surgical intervention, but are rare in presentation (68-71).

Prosthetic Valve Endocarditis (PVE)

In approximately 20% of IE a prosthetic valve is involved (72). A distinction is often made between early and late cases based on the time of diagnosis after initial surgery. The prognosis of PVE is worse than in native valve IE (72). Several studies have compared outcomes after medical and surgical therapy in PVE (14,22,25,33,38,51). A large cohort study of 367 prospectively followed patients showed that in-hospital mortality rates were similar: 23.4% in medical and 25% in surgical patients (14). Six months survival in a different study also showed no favorable result for surgery in 80 patients (70% survival in medical and 73% in surgical patients) (73). Surgery for PVE is often indicated, but is a troublesome procedure which is reflected in a high recurrent IE rate of up to 15% (74, 75).

Right-Sided Endocarditis

The incidence of right-sided IE represents less than 10% of all cases of IE (76, 77). Right-sided endocarditis mainly occurs in patients with intravenous drug use, pacemaker or central venous lines, or congenital heart disease. The majority of cases involve the tricuspid valve, while isolated pulmonary valve endocarditis is rare (78).

Isolated right-sided endocarditis has a favorable prognosis with low in-hospital mortality and the primary approach in these patients should therefore be conservative. Most cases respond to medical therapy and surgery is only necessary in a small minority of patients (79).

The 10 and 20 year survival rate after surgery for isolated right-sided endocarditis has been reported to be 70% and 58% respectively, which is better than patients with left-sided IE (80).

Device-Related Endocarditis

The use of pacemakers, defibrillators, and other implants has grown significantly over the last decades. As a result, endocarditis is more frequently associated to these devices (81). These types of endocarditis require excision of the infected device and complete eradication of the infection. Only thereafter a new device can be implanted.

Percutaneous techniques allow the cardiologist to perform this procedure, and surgeon involvement is therefore not necessary.

Risk Stratification

Due to the variability in the complexity of IE, the prognosis strongly depends on the individual patients' characteristics. Some patients benefit more from surgery than others, and to identify in which group of patients surgery can be performed safely and with an adequate result, a recent study developed a simplified risk scoring system including 13 variables (82). Although this model is noteworthy, one should be reminded that data is from the Society of Thoracic Surgeons (STS) database in which >19,000 patients surgically treated for IE were analyzed to relate baseline characteristics to 30-day outcomes. The database only includes general characteristics, but endocarditis-specific variables such as vegetation size, prosthetic valve endocarditis, or periannular extension are lacking. The model therefore is similar to the STS score, and is not specific for endocarditis. Also, this score is only based on surgical patients, and therefore it cannot be used to identify those who would benefit most.

Another recent study showed that additive and logarithmic EuroSCORE have a predictive value of 0.84 and 0.85 respectively, confirming that available risk models not specific for endocarditis can be sufficient to predict mortality (77).

Transcatheter Aortic Valve Endocarditis

The introduction of transcatheter aortic valve implantation (TAVI) to treat severe aortic stenosis could change the face of PVE. The occurrence of early PVE could be influenced by the difference of a sternotomy and access through the groin. The increased prevalence of paravalvular leakage raises concerns because of the associated risk of endocarditis. Little is known about the true incidence of endocarditis after TAVI; to date

it has only been anecdotally described (83, 84). Follow-up has been short, and late PVE has therefore not yet been fully addressed. TAVI has recently shown positive results in the PARTNER (Placement of Aortic Transcatheter Valves) trial (85), and more randomized trials will start enrollment soon to broaden the indication to lower risk patients (86). Further data will contribute to the unknown prevalence of endocarditis after TAVI.

New Insights

Late 2011 the first randomized data from the ENDOVAL trial on surgical or medical treatment for IE will be available. The trial will only include high-risk patients with (1) periannular complications, (2) new onset aortic-ventricular block, (3) new onset severe valve regurgitation, (4) early-onset PVE, or (5) Staphylococcus aureus endocarditis. The trial will likely lead to treatment preferences for most endocarditis patients. Too high-risk patients with an EuroSCORE >40% or an emergent/urgent indication for surgery because of heart failure due to valvular insufficiency, fungal endocarditis, or septic shock are excluded (17). It is these patients that lead treatment bias when comparing studies from different centers. Some surgeons are willing to operate in the very high-risk patients, while others are reticent. To evaluate the need for surgery in high risk patients, another trial in high-risk patients is preferable. The ENDOVAL trial is the first and only trial assessing the use of early surgery in endocarditis, and could be a boost for others to follow.

Conclusions

Endocarditis has been extensively described over the last decades and treatment with surgery is established for certain indications associated with improved survival. Surgical treatment of PVE carries quite a high mortality and requires close follow-up due to a continued postoperative risk. The selection of patients who benefit most from valve replacement is becoming more transparent, but treatment often remains biased because of surgeon preferences. A large number of ongoing studies and randomized trials will produce stronger evidence.

REFERENCES

1. Cabell CH, Abrutyn E. Progress towards a global understanding of infective endocarditis. Early lessons from the International Collaboration on Endocarditis investigation. Infect Dis Clin North Am. 2002;16(2):255-272.
2. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group . Circulation 2007;116(5):1736-1754.
3. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. Circulation 2008;118(15):e523-661.
4. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994;96(3):200-209.
5. Heiro M, Helenius H, Mäkilä S, et al. Infective endocarditis in a Finnish teaching hospital: a study on 326 episodes treated during 1980-2004. Heart 2006;92(10):1457-1462.
6. Durante-Mangoni E, Bradley S, Selton-Suty C, et al. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med 2008;168(19):2095-2103.
7. Mansur AJ, Dal Bó CM, Fukushima JT, Issa VS, Grinberg M, Pomerantzeff PM. Relapses, recurrences, valve replacements, and mortality during the long-term follow-up after infective endocarditis. Am Heart J 2001;141(1):78-86.
8. Yu VL, Fang GD, Keys TF, et al. Prosthetic valve endocarditis: superiority of surgical valve replacement versus medical therapy alone. Ann Thorac Surg 1994;58(4):1073-1077.
9. Cabell CH, Abrutyn E, Fowler VG Jr, et al. Use of surgery in patients with native valve infective endocarditis: results from the International Collaboration on Endocarditis Merged Database. Am Heart J 2005;150(5):1092-1098.
10. Aksoy O, Sexton DJ, Wang A, et al. Early Surgery in Patients with Infective Endocarditis: A Propensity Score Analysis. Clin Infect Dis 2007;44(3):364-372.
11. Tleyjeh IM, Ghomrawi HM, Steckelberg JM, et al. The impact of valve surgery on 6-month mortality in left-sided infective endocarditis. Circulation 2007;115(13):1721-1728.
12. Sy RW, Bannon PG, Bayfield MS, Brown C, Kritharides L. Survivor treatment selection bias and outcomes research: a case study of surgery in infective endocarditis. Circ Cardiovasc Qual Outcomes 2009;2(5):469-474.
13. Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation 2010;121(8):1005-1013.
14. Wang A, Pappas P, Anstrom KJ, et al. The use and effect of surgical therapy for prosthetic valve infective endocarditis: a propensity analysis of a multicenter, international cohort. Am Heart J 2005;150(5):1086-1091.

15. Bogers AJ, van Vreeswijk H, Verbaan CJ, Kappetein AP, van Herwerden LA, Mochtar B, Bos E. Early surgery for active infective endocarditis improves early and late results. Thorac Cardiovasc Surg 1991;39(5):284-288.
16. Thuny F, Beurtheret S, Mancini J, et al. The timing of surgery influence mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis. Eur Heart J 2009; doi:10.1093/eurheartj/ehp089.
17. San Román JA, López J, Revilla A, al. Rationale, design, and methods for the early surgery in infective endocarditis study (ENDOVAL 1): a multicenter, prospective, randomized trial comparing the state-of-the-art therapeutic strategy versus early surgery strategy in infective endocarditis. Am Heart J 2008;156(3):431-436.
18. Tornos MP, Olona M, Permanyer-Miralda G, Almirante B, Evangelista A, Soler-Soler J. Is the clinical spectrum and prognosis of native valve infective endocarditis in non-addicts changing? Eur Heart J 1995;16(11):1686-1691.
19. Schulz R, Werner GS, Fuchs JB, et al. Clinical outcome and echocardiographic findings of native and prosthetic valve endocarditis in the 1990's. Eur Heart J 1996;17(2):281-288.
20. Sandre RM, Shafran SD. Infective endocarditis: review of 135 cases over 9 years. Clin Infect Dis 1996;22(2):276-286.
21. Olaison L, Hogevik H, Myken P, Oden A, Alestig K. Early surgery in infective endocarditis. QJM 1996;89(4):267-278.
22. Tornos P, Almirante B, Olona M, et al. Clinical outcome and long-term prognosis of late prosthetic valve endocarditis: a 20-year experience. Clin Infect Dis 1997;24(3):381-386.
23. Hricak V, Kovacik J, Marx P, et al. Etiology and risk factors of 180 cases of native valve endocarditis. Report from a 5-year national prospective survey in Slovak Republic. Diagn Microbiol Infect Dis 1998;31(3):431-435.
24. Castillo JC, Anguita MP, Ramírez A, et al. Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. Heart 2000;83(5):525-530.
25. Gordon SM, Serkey JM, Longworth DL, Lytle BW, Cosgrove DM 3rd. Early onset prosthetic valve endocarditis: the Cleveland Clinic experience 1992-1997. Ann Thorac Surg 2000;69(5):1388-1392.
26. Bishara J, Leibovici L, Gartman-Israel D, et al. Long-term outcome of infective endocarditis: the impact of early surgical intervention. Clin Infect Dis 2001;33(10):1636-1643.
27. Wallace SM, Walton BI, Kharbanda RK, Hardy R, Wilson AP, Swanton RH. Mortality from infective endocarditis: clinical predictors of outcome. Heart 2002;88(1):53-60.
28. Mouly S, Ruimy R, Launay R, et al. The changing clinical aspects of infective endocarditis: descriptive review of 90 episodes in a French teaching hospital and risk factors for death. J Infect 2002;45(4):246-256.
29. Hoen B, Alla F, Selton-Suty C, et al. Changing Profile of Infective Endocarditis: Results of a 1-Year Survey in France. JAMA 2002;288(1):75-81.
30. Pachirat O, Chetchotisakd P, Klungboonkrong V, Taweesangsuksakul P, Tantisirin C, Loapiboon M. Infective endocarditis: prevalence, characteristics and mortality in Khon Kaen, 1990-1999. J Med Addoc Thai 2002;85(1):1-10.
31. Di Salvo G, Thuny F, Rosenberg V, et al. Endocarditis in the elderly: clinical, echocardiographic, and prognostic features. Eur Heart J 2003;24(17):1576-1583.
32. Ako J, Ikari Y, Hatori M, Hara K, Ouchi Y. Changing spectrum of infective endocarditis: review of 194 episodes over 20 years. Circ J 2003;67(1):3-7.
33. Akowuah EF, Davies W, Oliver S, et al. Prosthetic valve endocarditis: early and late outcome following medical or surgical treatment. Heart 2003;89(3):269-272.

34. Krcmery V, Gogová M, Ondrusová A, et al. Etiology and risk factors of 339 cases of infective endocarditis: report from a 10-year national prospective survey in the SLovak Republic. J Chemother 2003;15(6):579-583.
35. Mourvillier B, Trouillet JL, Timsit JF, et al. Infective endocarditis in the intensive care unit: clinical spectrum and prognostic factors in 228 consecutive patients. Intensive Care Med 2004;30(11):2046-2052.
36. Zamorano J, de Isla LP, Moura L, et al. Impact of echocardiography in the short- and long-term prognosis of patients with infective endocarditis and negative blood cultures. J Heart Valve Dis 2004;13(6):997-1004.
37. Cecchi E, Forno D, Imazio M, et al. New trends in the epidemiological and clinical features of infective endocarditis: results of a multicenter prospective study. Ital Heart J 2004;5(4):249-256.
38. Habib G, Tribouilloy C, Thuny F, et al. Prosthetic valve endocarditis: who needs surgery? A multicentre study of 104 cases. Heart 2005;91(7):954-959.
39. Garg N, Kandpal B, Garg N, et al. Characteristics of infective endocarditis in a developing country-clinical profile and outcome in 192 Indian patients, 1992-2001. Int J Cardiol 2005;98(2):253-260.
40. Tornos P, Iung B, Permanyer-Miralda G, et al. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 2005;91(5):571-575.
41. Ferreiros E, Nacinovich F, Casabé JH, et al. Epidemiologic, clinical, and microbiologic profile of infective endocarditis in Argentina: a national survey. The Endocarditis Infecciosa en la República Argentina-2 (EIRA-2) Study. Am Heart J 2006;151(2):545-552.
42. Leblebicioglu H, Yilmaz H, Tasova Y, et al. Characteristics and analysis of risk factors for mortality in infective endocarditis. Eur J Epidemiol 2006;21(1):25-31.
43. Abramczuk E, Hryniewiecki T, Stepińska J. Influence of pathogenetic factors on prognosis in patients with native valve infective endocarditis. Kardiol Pol 2006;64(7):675-681.
44. Slater MS, Komanapalli CB, Tripathy U, Ravichandran PS, Ungerleider RM. Treatment of endocarditis: a decade of experience. Ann Thorac Surg 2007;83(6):2074-2079.
45. Delahaye F, Alla F, Béguinot I, et al. In-hospital mortality of infective endocarditis: prognostic factors and evolution over an 8-year period. Scand J Infect Dis 2007;39(10):849-857.
46. Heiro M, Helenius H, Hurme S, et al. Short-term and one-year outcome of infective endocarditis in adult patients treated in a Finnish teaching hospital during 1980-2004. BMC Infect Dis 2007;7:78.
47. Krecki R, Drozdz J, Ibata G, et al. Clinical profile, prognosis and treatment of patients with infective endocarditis--a 14-year follow-up study. Pol Arch Med Wewn 2007;117(11-12):512-520.
48. Trabelsi I, Rekik S, Znazen A, et al. Native valve infective endocarditis in a tertiary care center in a developing country (Tunisia). Am J Cardiol 2008;102(9):1247-1251.
49. Pazdernik M, Baddour LM, Pelouch R. Infective endocarditis in the Czech Republic: eight years of experience at one of the country's largest medical centers. J Heart Valve Dis 2009;18(4):395-400.
50. Nunes MC, Gelape CL, Ferrari TC. Profile of infective endocarditis at a tertiary care center in Brazil during a seven-year period: prognostic factors and in-hospital outcome. Int J Infect Dis 2010;14(5):e394-398.
51. Alonso-Valle H, Fariñas-Alvarez C, García-Palomo JD, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. J Thorac Cardiovasc Surg 2010;139(4):887-893.
52. López J, Revilla A, Vilacosta I, et al. Age-dependent profile of left-sided infective endocarditis: a 3-center experience. Circulation 2010;121(7):892-897.

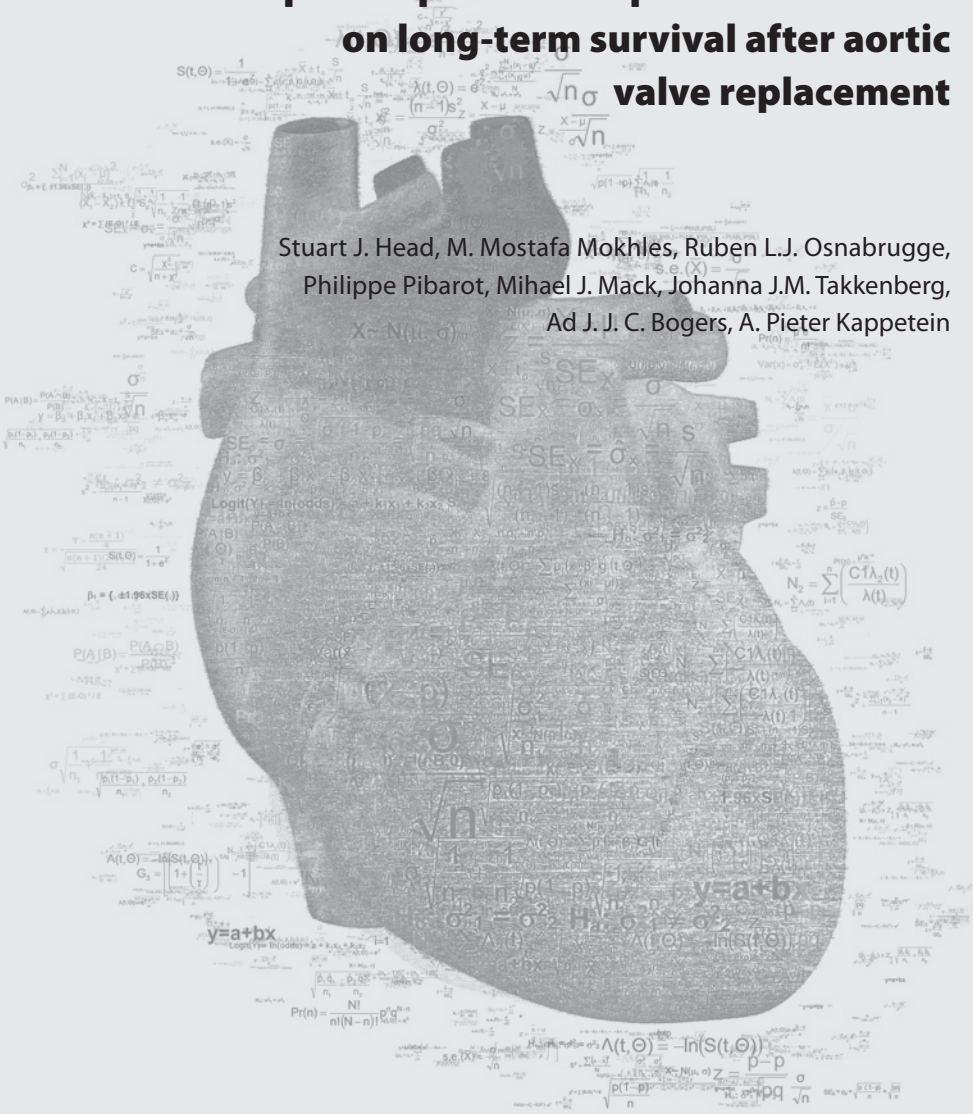
53. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169(5):463-473.
54. Vikram HR, Buenconsejo J, Hasbun R, Quagliarello VJ. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. JAMA 2003;290(24):3207-3214.
55. Tleyjeh IM, Ghomrawi HM, Steckelberg JM, et al. Conclusion about the association between valve surgery and mortality in an infective endocarditis cohort changed after adjusting for survivor bias. J Clin Epidemiol 2010;63(2):130-135.
56. Kanafani ZA, Kanj SS, Cabell CH, et al. Revisiting the effect of referral bias on the clinical spectrum of infective endocarditis in adults. Eur J Clin Microbiol Infect Dis 2010;29(10):1203-1210.
57. Tleyjeh IM, Kashour T, Zimmerman V, Steckelberg JM, Wilson WR, Baddour LM. The role of valve surgery in infective endocarditis management: a systematic review of observational studies that included propensity score analysis. Am Heart J 2008;156(5):901-909.
58. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J 2009;30(19):2369-2413.
59. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005;111(23):e395-434.
60. Revilla A, López J, Villacosta I, et al. Clinical and prognostic profile of patients with infective endocarditis who need urgent surgery. Eur Heart J 2007;28(1):65-71.
61. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? Circulation 2010;121(9):1141-1152.
62. Klieverik LM, Yacoub MH, Edwards S, et al. Surgical treatment of active native aortic valve endocarditis with allografts and mechanical prostheses. Ann Thorac Surg 2009;88(6):1814-1821.
63. Anguera I, Miro JM, Vilacosta I, et al. Aorto-cavitary fistulous tract formation in infective endocarditis: clinical and echocardiographic features of 76 cases and risk factors for mortality. Eur Heart J 2005;26(3):288-297.
64. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter. Circulation 2005;112(1):69-75.
65. Heiro M, Nikoskelainen J, Engblom E, Kotilainen E, Marttila R, Kotilainen P. Neurologic manifestations of infective endocarditis: a 17 year experience in a teaching hospital in Finland. Arch Intern Med 2000;160(18):2781-2787.
66. Derex L, Bonnefoy E, Delahaye F. Impact of stroke on therapeutic decision making in infective endocarditis. J Neurol 2010;257:315-321.
67. Remadi JP, Habib G, Nadji G, et al. Predictors of death and impact of surgery in Staphylococcus aureus infective endocarditis. Ann Thorac Surg 2007;83(4):1295-1302.
68. Morpeth S, Murdoch D, Cabell CH, et al. Non-HACEK gram-negative bacillus endocarditis. Ann Intern Med 2007;147(12):829-835.
69. Raoult D, Marrie T. Q Fever. Clin Infect Dis 1995;20(3):489-495.

70. Jacobs F, Abramowicz D, Vereerstraeten P, Le Clerc JL, Zech F, Thys JP. Brucella endocarditis: the role of combined medical and surgical treatment. Rev Infect Dis 1990;12(5):740-744.
71. Anguera I, Del Río A, Miró JM, et al. Staphylococcus lugdunensis infective endocarditis: description of 10 cases and analysis of native valve, prosthetic valve, and pacemaker lead endocarditis clinical profiles. Heart 2005;91(2):e10.
72. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA 2007;297(12):1354-1361.
73. Hill EE, Herregods MC, Vanderschueren S, Claus P, Peetermans WE, Herijgers P. Management of prosthetic valve infective endocarditis. Am J Cardiol 2008;101(8):1174-1178.
74. Lytle BW, Priest BP, Taylor PC, et al. Surgical treatment of prosthetic valve endocarditis. J Thorac Cardiovasc Surg 1996;111(1):198-207.
75. Pansini S, di Summa M, Patane F, Forsenatti PG, Serra M, Del Ponte S. Risk of recurrence after reoperation for prosthetic valve endocarditis. J Heart Valve Dis 1997;6(1):84-87.
76. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med2001;345(18):1318-1330.
77. Mokhles MM, Ciampichetti I, Head SJ, Takkenberg JJM, Bogers AJJC. Survival of surgically treated infective endocarditis: a comparison with the general Dutch population. Ann Thorac Surg. 2011. doi:10.1016/j.athoracsur.2011.02.007.
78. Nishida K, Fukuyama O, Nakamura DS. Pulmonary valve endocarditis caused by right ventricular outflow obstruction in association with sinus of valsalva aneurysm: a case report. J Cardiothorac Surg. 2008;3:46.
79. Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users. Prognostic features in 102 episodes. Ann Intern Med 1992;117(7):560-566.
80. Musci M, Siniawski H, Pasic M, Grauhan O, Weng Y, Meyer R et al. Surgical treatment of right-sided active infective endocarditis with or without involvement of the left heart: 20-year single center experience. Eur J Cardiothor Surg 2007;32:118–125.
81. Baddour LM, Bettmann MA, Bolger AF, et al. Nonvalvular cardiovascular device related infections. Circulation 2003;108(16):2015–2031.
82. Gaca JG, Sheng S, Daneshmand MA, et al. Outcomes for endocarditis surgery in North America: a simplified risk scoring system. J Thorac Cardiovasc Surg 2011;141(1):98-106.
83. Piazza N, Marra S, Webb J, et al. Two cases of aneurysm of the anterior mitral valve leaflet associated with transcatheter aortic valve endocarditis: a mere coincidence? J Thorac Cardiovasc Surg 2010;140(3):e36-83.
84. Head SJ, Dewey TM, Mack MJ. Fungal endocarditis after transfemoral aortic valve implantation. Catheter Cardiovasc Interv 2011; doi:10.1002/ccd.23038.
85. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363(17):1597-1607.
86. Head SJ, Kappetein AP. Transcatheter aortic valve implantation after PARTNER: what is up next? EuroIntervention 2010;6(5):560-561.

Chapter 9

The impact of prosthesis–patient mismatch on long-term survival after aortic valve replacement

Stuart J. Head, M. Mostafa Mokhles, Ruben L.J. Osnabrugge, Philippe Pibarot, Mihael J. Mack, Johanna J.M. Takkenberg, Ad J. J. C. Bogers, A. Pieter Kappetein



Eur Heart J. 2012;33:1518-29

ABSTRACT

Aims

Numerous studies have linked prosthesis-patient mismatch (PPM) after aortic valve replacement (AVR) to adverse outcomes. Its correlation with long-term survival has been described but with contradicting results. This systematic review and meta-analysis of observational studies aims to determine the hazard of PPM after AVR.

Methods and Results

The Medline and EMBase databases were searched for English-language original publications. Two researchers independently screened studies and extracted data. Pooled estimates were obtained by random-effects model. Subgroup analyses were performed to detect sources of heterogeneity. The search yielded 348 potentially relevant studies; 34 were included comprising 27,186 patients and 133,141 patient-years. Defined by the universally accredited indexed effective orifice area of <0.85 cm^2/m^2, 44.2% of patients were categorized as having PPM. In 34.2% moderate (0.65-0.85 cm^2/m^2) and 9.8% severe (<0.65 cm^2/m^2) PPM was present. PPM was associated with a statistically significant increase of all-cause mortality (HR=1.34, 95% 1.18-1.51), but only a trend to an increase in cardiac-related mortality (HR=1.51, 95% 0.88-2.60) was recognized. Analysis by severity of PPM demonstrated that both moderate and severe PPM increased all-cause mortality (HR=1.19, 95% 1.07-1.33 and HR=1.84, 95% 1.38-2.45) and cardiac-related mortality (HR=1.32, 95% 1.02-1.71 and HR=6.46, 95% 2.79-14.97). Further analyses showed a consistent effect over separate time-intervals during follow-up.

Conclusions

PPM is associated with an increase in all-cause and cardiac-related mortality over long-term follow-up. We recommend that current efforts to prevent PPM should receive more emphasis and a widespread acceptance to improve long-term survival after AVR.

BACKGROUND

The problem of prosthesis-patient mismatch (PPM) after valvular surgery has been a topic of discussion ever since it was first described in 1978 (1). PPM occurs when the effective orifice area (EOA) of the prosthesis is physiologically too small in relation to the patient's body size, thus resulting in abnormally high postoperative gradients. Hence, the parameter that has been used to characterize PPM is the indexed EOA (iEOA), i.e. the EOA of the prosthesis divided by the patient's body surface area (2-4).

Results from clinical studies demonstrated the negative effect of PPM following aortic valve replacement (AVR) on left ventricular (LV) mass regression, recovery of LV systolic function, New York Heart Association functional class, quality of life, and bioprosthetic valve durability (5, 6). Furthermore, aortic PPM has been associated with increased incidence of operative mortality and late cardiac events (7-11).

Although patients with PPM have been shown to have worse hemodynamic and functional outcomes following AVR, survival analyses have not yet uniformly demonstrated that PPM is a predictor of increased mortality (12, 13). In an attempt to further explore the association of PPM and long-term survival after AVR in adults, a systematic review and meta-analysis was performed of both retro-and prospective cohort studies that stratify survival by the presence of PPM.

METHODS

The reporting of this systematic review and meta-analysis is according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (14).

Search Strategy

In January 2011 the Medline and EMBase databases were systematically searched to identify published full-length English studies reporting the long-term survival of patients after AVR, stratified by the presence of PPM. No year of publication exclusion was implied. Studies were identified by a search using the following key words in all fields: "mismatch OR PPM" AND "AVR OR aortic valve replacement". To ensure that no potentially valid studies were missed, the reference lists from reviews and included studies were checked.

Study Inclusion

The title and abstract of studies identified by the search were independently screened by two investigators (S.J.H. and M.M.M) using the following steps: 1) the publication was an original full-article contribution in a peer-reviewed journal; 2) patients were adults;

3) patients had undergone AVR with a bioprosthetic or mechanical valve; 4) PPM was assessed; and 5) long-term follow-up of minimal 5 years was available and stratified for PPM. Studies reporting only a specific patient group (e.g. patients with renal failure) were excluded. For studies that met these criteria, or in case of uncertainty, the full texts were further evaluated.

Finally, the study site(s), inclusion period, patient demographics (e.g. age), and diagnosis of potential studies were compared to ensure minimal patient overlap in different publications. If extensive overlap existed, included was only the publication with the largest or diagnostically most complete cohort (e.g. all patients instead of only patients with aortic stenosis).

Data Extraction

From each study we collected the design, number of patients, patient baseline characteristics, type of implanted valve, presence of PPM according to the corresponding iEOA cut-off threshold, follow-up, and patient-years of follow-up. If the number of patient-years was not mentioned, it was calculated by multiplying the number of patients with the mean follow-up. If data was unclear or unavailable, the authors were contacted by e-mail.

Studies that reported results of a PPM (iEOA <0.85, <0.80, or <0.75 cm^2/m^2) versus no PPM group were included in the "any PPM" analysis. Studies that reported results for moderate PPM (iEOA 0.65/0.60 - 0.90/0.85 cm^2/m^2) or severe PPM (iEOA <0.65 or <0.60 cm^2/m^2) separately were included in "moderate PPM" and "severe PPM" pooled analyses.

All-cause mortality and cardiac-related mortality were evaluated. Mortality was extracted as a HR. For studies that did not report a HR with corresponding variance, this was extracted per 6 month period from the Kaplan-Meier survival curve by two independent investigators (S.J.H. and R.L.J.O). Survival was obtained up to a representative number of patients at risk (15, 16). The method described by Williamson et al. (17) was used to estimate a logarithmic HR with corresponding variance when the number of patients at risk was given at each time frame. If this data was not provided, the method by Parmar et al. (18) was used. For each study, we used a spreadsheet programmed to estimate the overall HR with 95% confidence intervals (CI) using an inverse variance-weighted average (19, 20).

Statistical Analysis

Statistical analyses were performed using Review Manager version 5.0 for Windows (The Cochrane Collaboration, 2008). A random-effect model was used to obtain pooled estimates. Weighing of studies was based on the standard error (SE) of the logarithmic HR, in which studies with a large SE are weighed less than studies with a small SE. Heterogeneity was examined with the I^2 statistic; whether this was statistically significant in subgroup analyses was explored with the Q test. Sources of heterogeneity were explored by subgroup analyses of study characteristics (study design, study location, year

of publication, mean follow-up), patient characteristics (age, type of valve implanted), and the method used to define PPM. Sensitivity analyses were performed for year of patient inclusion to study the effect of characteristics that may have changed over time.

A separate analysis was performed with obtained HRs and corresponding SEs per one-year period, calculated with the extraction spreadsheet. An overall pooled HR estimate per separate time-period was obtained with a random-effects model. Subsequently, the pooled year-estimates were again combined to assess whether the HRs were different between intervals.

Funnel plots were produced for visualization of possible publication bias (21).

RESULTS

The database search yielded 348 potentially relevant studies (Figure 1). After the title and abstract were screened, 176 studies were excluded because they did not focus on aortic valve replacement with bioprosthesis or mechanical valve and the association of

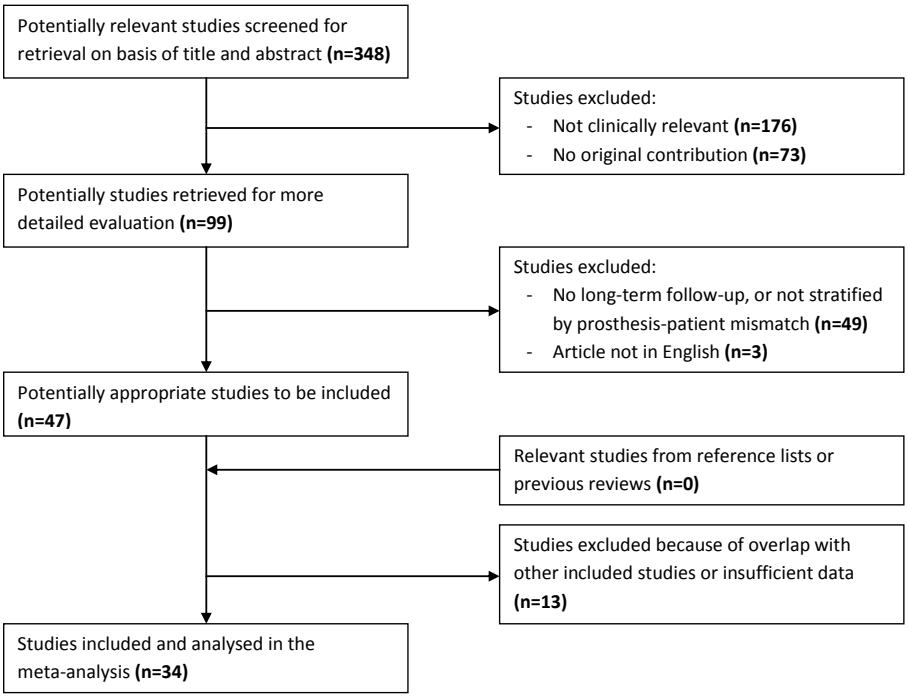


Figure 1. Flow diagram - systematic inclusion of studies for meta-analysis.

Table 1. Study Characteristics.

First Author	Year of Publication	Study Location	Inclusion	Study Design	No. of Patients	Male Gender (%)	Mean Age (Years)	Type of Valve	iEOA Cut-off (cm2/m2)	PPM (%)	Mean Follow-up (years)	Mortality Analysis
Sakamoto	2010	Japan	1996-2008	retrospective	342	61.7	69.7	bioprosthetic	<0.85	28	3.2	overall
Jamieson	2010	Canada	1982-2003	retrospective	3343	65.7	68.1	mix	≤0.85	54	6.2	overall
Flameng	2010	Belgium	1991-2003	retrospective	564	51	73.6	bioprosthetic	<0.85	51	6.1*	overall
Bleiziffer	2010	Germany	2000-2007	retrospective	645	56.4	72.3	bioprosthetic	<0.85	40	2.7	cardiac
Urso	2009	Spain	2000-2007	retrospective	163	49.7	78.0	mix	≤0.85	43	3.1	overall
Mrowczynksi	2009	Germany	1995-2004	retrospective	309	63.6	71.6	mix	<0.85	66	2.8*	overall
Moon	2009	USA	1992-2007	retrospective	1399	58.5	71.1	bioprosthetic	<0.85	62	3.8	overall
Mohty	2009	Canada	1992-2005	retrospective	2576	61	68.5	mix	≤0.85	32	4.8	both
Mannacio	2009	Italy	1997-2002	retrospective	157	67.4	66.7	mix	≤0.75	61	7.0	overall
Vicchio	2008	Italy	1988-2006	retrospective	345	33.0	74.5	mechanical	<0.85	60	4.2	overall
Tsutsumi	2008	Japan	1990-2009	retrospective	124	50.8	59.3	mechanical	<0.85	20	9.1	cardiac
Ryomoto	2008	Japan	1990-2007	retrospective	101	45.5	72.4	mix	≤0.85	34	3.1	overall
Mascherbauer	2008	Austria	1998-2005	prospective	361	47.4	69.5	mix	≤0.80	54	4.2	overall
Kohsaka	2008	USA	1993-1998	prospective	469	66.7	56.1	mechanical	≤0.85	43	7.9*	overall
Kato	2008	Japan	1986-2006	retrospective	84	50	68.5	mix	≤0.85	25	4.5	both
Florath	2008	Germany	1996-2005	retrospective	533	54.2	71.1	mix	≤0.85	80	4.7	overall
Tao	2007	Japan	2000-2005	retrospective	150	45.3	68.7	mechanical	≤0.85	23	2.5	both
Nozohoor	2007	Sweden	1996-2006	retrospective	1797	…	…	mix	≤0.85	53	4.3	overall
Monin	2007	France	1994-2005	prospective	139	74.1	72	mix	≤0.85	57	3.7*	overall
Kato	2007	Japan	1990-2005	retrospective	146	56.8	68.2	mix	≤0.85	45	4.5	both
Garcia Fuster	2007	Spain	1994-2005	retrospective	339	55.8	66.5	mix	≤0.85	38	6.9	cardiac
Walther	2006	Germany	1996-2004	prospective	4131	62.8	58.9	mix	<0.85	29	5.2	overall

Table 1. (Continued).

First Author	Year of Publication	Study Location	Inclusion	Study Design	No. of Patients	Male Gender (%)	Mean Age (Years)	Type of Valve	iEOA Cut-off (cm2/m2)	PPM (%)	Mean Follow-up (years)	Mortality Analysis
Tasca	2006	Italy	1997-2003	prospective	315	49.8	70.8	mix	≤0.80	47	3.7	overall
Moon	2006	USA	1992-2004	retrospective	1400	57.2	66.8	mix	<0.75	38	3.8	overall
Mohty	2006	USA	1985-2000	retrospective	388	31.4	62.3	mechanical	≤0.85	43	5.3	overall
Howell	2006	UK	1997-2005	prospective	1418	61.6	65.5	mix	<0.85	56	3*	overall
Flameng	2006	Belgium	1985-2003	retrospective	506	50	73.3	bioprosthetic	<0.85	20	6.1	overall
Penta de Peppo	2005	Italy	1991-2002	prospective	83	71.1	46.5	mechanical	<0.85	28	6.7	cardiac
Ruel	2004	Canada	1976-2001	prospective	1226	58.6	63.8	mix	≤0.85	77	4.3	cardiac
Milano	2002	Italy	1981-1995	retrospective	229	20.1	63.7	mechanical	≤0.90	73	10	both
Hanayama	2002	Canada	1990-2000	prospective	768	66.0	64.7	mix	<0.60	10	3.5	overall
Frapier	2000	France	1986-1990	retrospective	90	62.2	72.6	bioprosthetic	≤0.85	71	7.3*	both
Rao	2000	Canada	1976-1996	prospective	2154	60.1	66.1	bioprosthetic	≤0.75	11	6.2	both
Pibarot	1998	Canada	1986-1995	prospective	392	71.7	68.4	bioprosthetic	≤0.85	45	...	overall

*median follow-up; iEOA, indexed effective orifice area; PPM, prosthesis-patient mismatch.

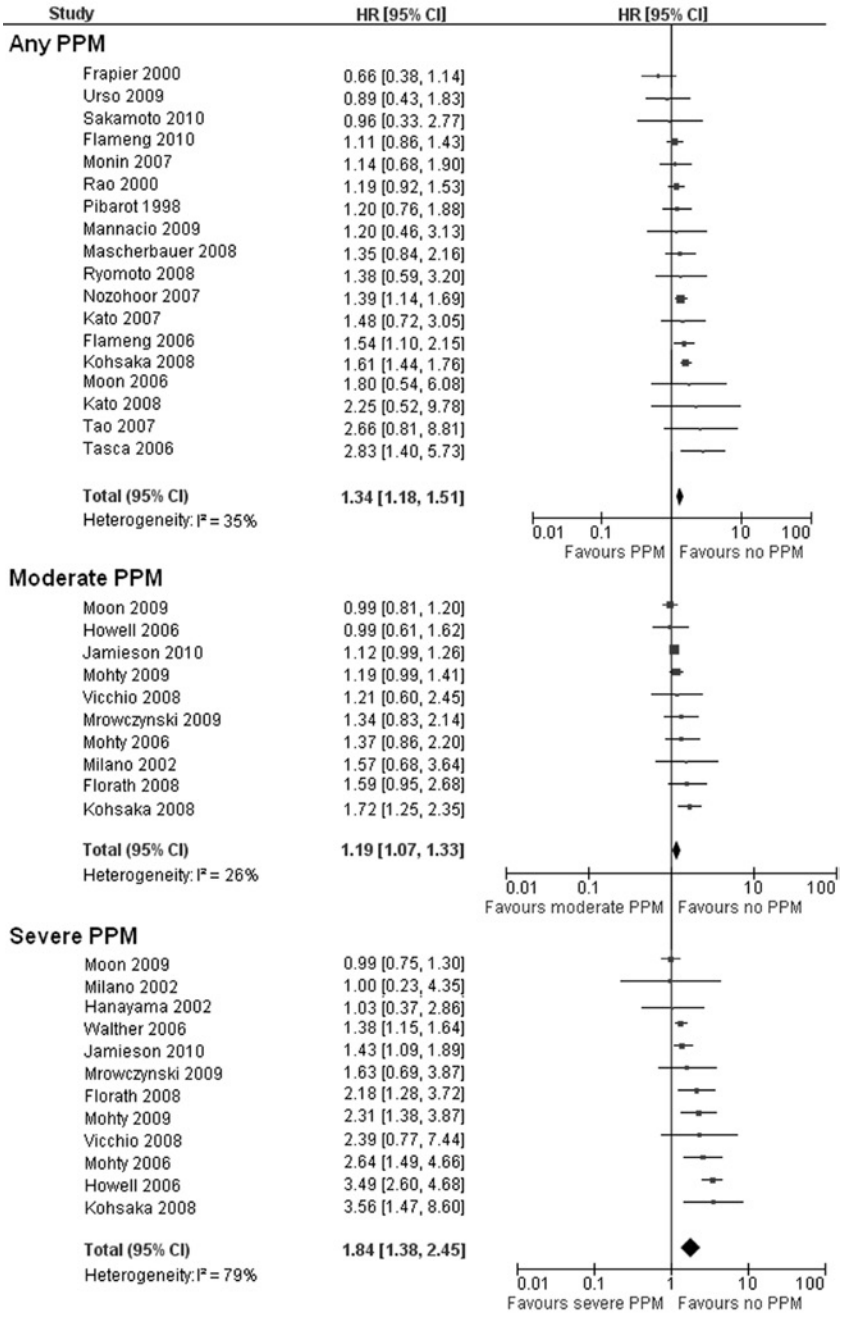


Figure 2. Pooled estimate for all-cause mortality - ratio's demonstrate the additional hazard with PPM in relation to a no PPM reference group. Studies that stratified results according to the severity of PPM are analyzed individually. HR, hazard ratio; CI, confidence interval; PPM, prosthesis-patient mismatch.

PPM with survival. Another 73 studies were excluded because they were not original full-length contributions.

Ninety-nine full-text original articles were reviewed in more detail. Studies were further excluded for various reasons (Figure 1), and a remaining 34 studies were included in the present systematic review (Table 1) (4, 5, 8, 10, 11, 22-50). They comprised a total of 27,186 patients and 133,141 patient-years. In 27 studies with 21,802 patients the iEOA threshold of 0.85 cm^2/m^2 was used, and 44.2% of patients were diagnosed with PPM. Seven studies found that 34.2% of patients had moderate PPM (>0.65 - >0.85 cm^2/m^2), and 9.8% had severe PPM (<0.65 cm^2/m^2).

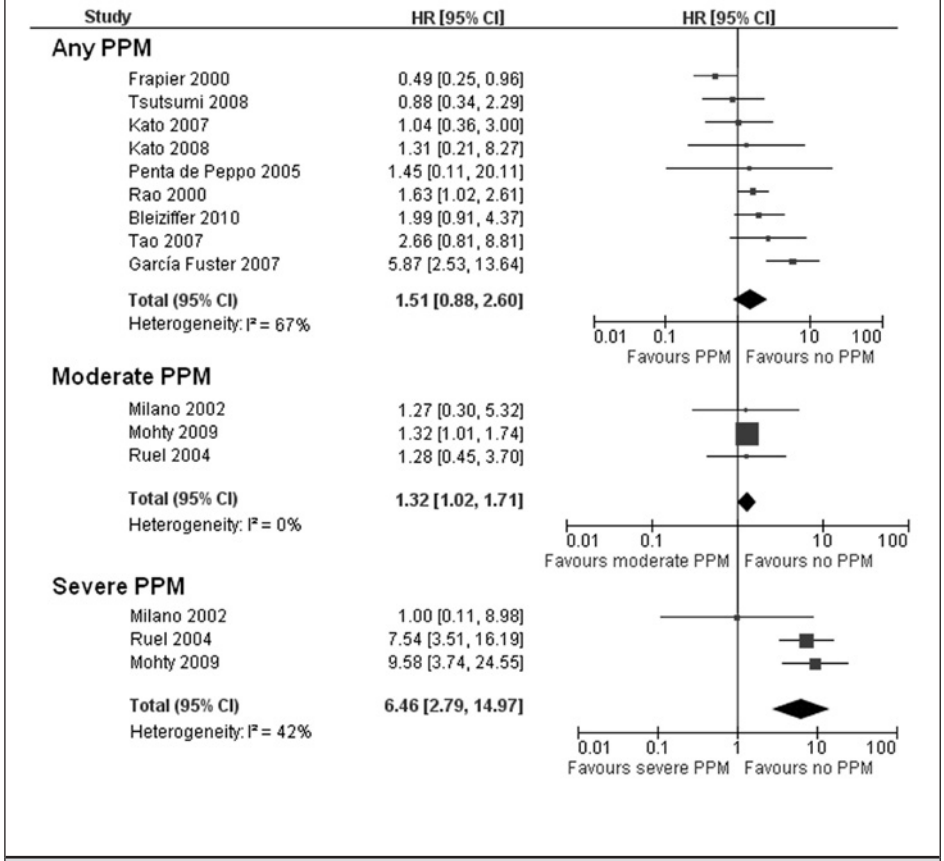


Figure 3. Pooled estimate for cardiac-related mortality - ratio's demonstrate the additional hazard with PPM in relation to a no PPM reference group. Studies that stratified results according to the severity of PPM are analyzed individually. HR, hazard ratio; CI, confidence interval; PPM, prosthesis-patient mismatch.

Long-Term Outcomes

PPM was associated with decreased long-term survival (HR=1.34, 95% CI 1.18-1.51) when compared to patients without PPM (Figure 2). In studies that stratified outcomes by the severity of PPM, both moderate (HR=1.19, 95% CI 1.07-1.33) and severe (HR=1.84, 95% CI 1.38-2.45) PPM showed a statistically significant increase of all-cause mortality.

PPM was associated with a 1.51-fold (95% CI 0.88-2.60) non-significant increase of cardiac-related mortality (Figure 3). Differentiation by moderate and severe PPM demonstrated HRs of 1.32 (95% CI 1.02-1.71) and 6.46 (95% CI 2.79-14.97), respectively.

There was a constant hazard over time for all-cause mortality (p=0.93) (Figure 4). The cardiac-related analysis showed more variation in HRs over time.

Sensitivity analysis with studies that included patients operated after 1990 and after 1995 demonstrated that the effect was slightly higher with later inclusion, but this difference was not statistically significant (Table 2). No analyses were performed for the moderate and severe PPM group for cardiac-related mortality, due to the low number of studies included (n=3).

Sources of Heterogeneity

The subgroup analysis detected statistical heterogeneity between bioprosthetic and mechanical valves (Figure 5). There was also a statistical significant heterogeneity in the all-cause mortality analysis by determining the EOA, but this is likely due to the low number of studied that used echocardiographic measurement because this heterogeneity was not significant in other analyses. Again, no analyses were performed for the moderate and severe PPM group for cardiac-related mortality.

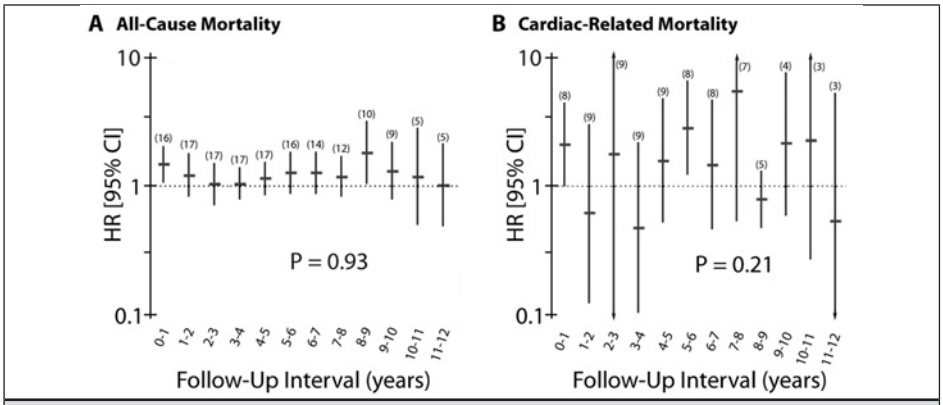


Figure 4. Hazard of mortality in separate time-intervals - pooled estimates of studies to detect variance in all-cause (A) and cardiac-related (B) hazard over separate intervals during follow-up. Within the first year of follow-up, studies were excluded if analyses were performed without hospital mortality. The number of studies with corresponding lengths of follow-up are indicated between brackets. HR, hazard ratio; CI, confidence interval.

Publication Bias

There was no evidence of publication bias in funnel plots of all-cause and cardiac-related mortality survival assessments (Figure 1 of the online-only data supplement).

DISCUSSION

Prosthesis-patient mismatch has been associated with reduced LV mass regression, impaired physical recovery, and higher incidence of adverse cardiac events after AVR, however, no consistent association between PPM and long-term survival has been established (13). The current unprecedented meta-analysis shows a significant reduction in overall and cardiac-related long-term survival for patients with PPM after AVR. Moreover, this association increases with PPM severity and appears constant over time. These results have important clinical implications given that PPM is a potentially modifiable risk factor.

Table 2. Sensitivity analysis with patient inclusion after 1990 and 1995.

	HR (95% CI)	P for Heterogeneity
All-cause Mortality		
Any PPM		0.71
All studies (n=18)	1.34 (1.18-1.51)	
Patient inclusion >1990 (n=13)	1.43 (1.27-1.61)	
Patient inclusion >1995 (n=7)	1.42 (1.13-1.77)	
Moderate PPM		0.87
All studies (n=10)	1.19 (1.07-1.33)	
Patient inclusion >1990 (n=6)	1.24 (1.03-1.49)	
Patient inclusion >1995 (n=3)	1.27 (0.96-1.69)	
Severe PPM		0.94
All studies (n=12)	1.84 (1.38-2.45)	
Patient inclusion >1990 (n=8)	1.86 (1.26-2.73)	
Patient inclusion >1995 (n=4)	2.06 (1.33-2.39)	
Cardiac-related Mortality		
Any PPM		0.67
All studies (n=9)	1.51 (0.88-2.60)	
Patient inclusion >1990 (n=6)	1.97 (1.04-3.74)	
Patient inclusion >1995 (n=2)	2.18 (1.13-4.19)	
Moderate PPM	…*	
Severe PPM	…*	

*Not assessed due to low number of studies; PPM, prosthesis-patient mismatch.

The marked statistical significant heterogeneity in the explorative subgroup analyses is mainly related to the type of prosthesis, whether this was a bioprosthetic or mechanical valve. The type of prosthesis could be a confounding factor, as mechanical valves are implanted more often in younger patients. These patients generally have a more active life-style and higher metabolic rate, thereby increasing the flow and thus the gradient across the valve in case of PPM (13). In this regard, some studies have suggested that the impact of PPM on postoperative survival is more pronounced in younger patients

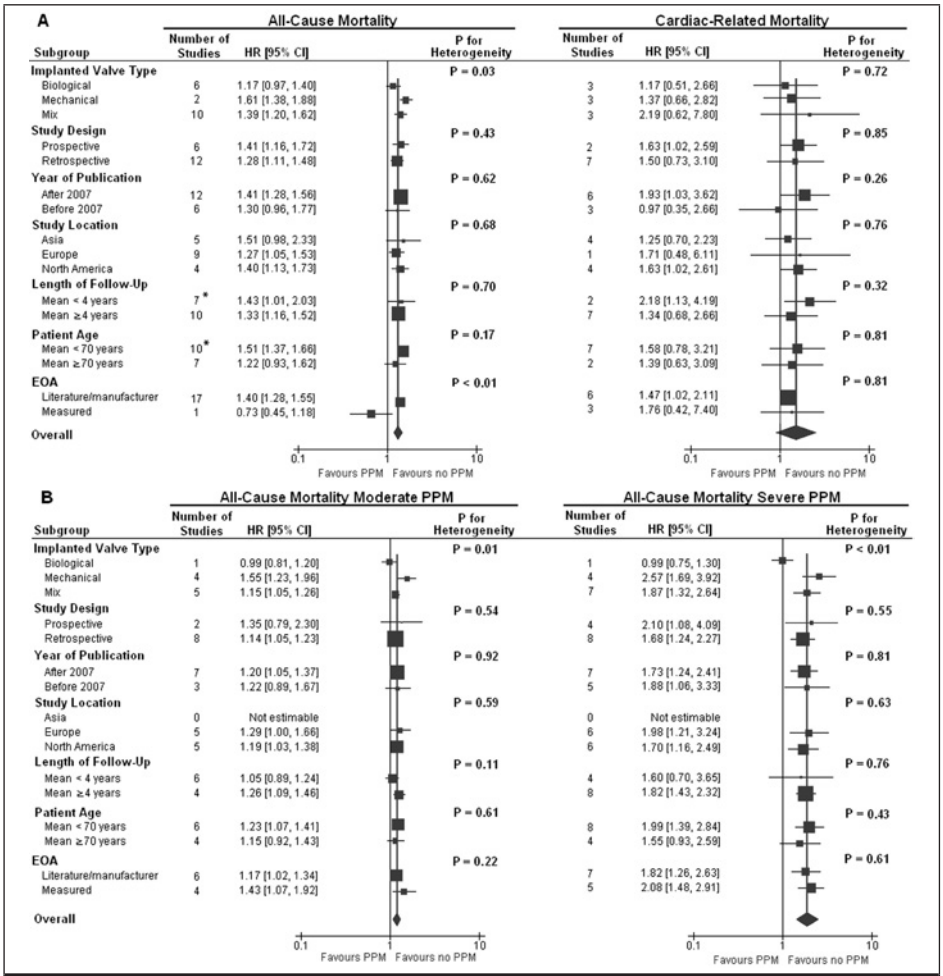


Figure 5. Subgroup analyses to explore the source of heterogeneity - all-cause and cardiac-related results were analyzed according to baseline- and study-related factors (A). Moderate and severe analyses (B) were also performed for all-cause mortality, but not for cardiac-related mortality due to the low number of studies included (n=3). HR, hazard ratio; CI, confidence interval; PPM, prosthesis-patient mismatch. *Analysis excluded 1 study because of missing data.

than in older ones (31, 45). In this study individual patient data was unavailable and the results from subgroup analyses should be regarded as hypothesis-generating. Future PPM studies should report the incidence and outcomes of patients with a mechanical and bioprosthetic valve separately, so that evidence is more substantiated.

Several factors may explain the association between PPM and reduced survival after AVR. The persistent LV afterload imposed by PPM may impair the postoperative recovery of coronary flow reserve (51) and the regression of LV hypertrophy and dysfunction (8, 27, 52). Other negative outcomes previously reported in association with aortic PPM may have contributed to increase postoperative mortality, including: abnormalities of the Von Willebrand factor and associated bleeding complications (53, 54), higher occurrence of exercise-induced arrhythmias (44), and higher incidence of late congestive heart failure (8). Unger et al. also observed that, in patients with severe aortic stenosis and concomitant mild mitral regurgitation, PPM is associated with more important residual regurgitation after operation (55). A recent study showed that PPM is an important risk factor for early structural valve deterioration of aortic bioprosthesis (5). Finally, PPM may also be a surrogate marker for other co-morbidities (e.g. small calcified aortic root).

Prevention of PPM

The observed increased mortality hazard should encourage surgeons to avoid PPM. As opposed to most other risk factors for postoperative mortality, PPM may be avoided or its severity may be reduced by the application of a preventive strategy at the time of operation (6, 56, 57). The first step in this strategy is to calculate the minimal prosthetic valve EOA required to avoid PPM by multiplying patient's BSA by 0.85 (6). The second step is to select a prosthetic valve model and size that fits into the patient's aortic annulus/root and that meets the minimum EOA calculated in the first step. It is important to emphasize that the currently available prosthetic valve models are not equivalent in terms of sizing and hemodynamic performance (6, 58). For example, the implantation of a 21mm valve can produce an EOA ranging between 1.2 ± 0.1 and 2.0 ± 0.7 cm^2, depending on the type of prosthesis (13, 58). Given the significant improvements in prostheses design, contemporary prevention of PPM can largely be accomplished by the implantation of prosthetic valve models providing a better hemodynamic performance. In cases where severe PPM cannot be avoided with the use of currently available prosthetic valves, aortic root enlargement may be contemplated if risk-benefit ratio is considered acceptable. Root enlargement is a surgical technique to accommodate a valve with a larger EOA and thereby avoiding PPM. This procedure has shown to be effective in reducing rates of PPM, although none of these studies have shown that annulus enlargement results in improved long-term survival (59, 60).

Two recent studies have reported that valve hemodynamics are superior with transcatheter aortic valve implantation (TAVI) than with surgical AVR, especially in the subset

of patients with small aortic root (61, 62). In these studies, PPM was less frequently present in TAVI patients (11% and 17.8%) than those who underwent AVR (27% and 30.5%, respectively) (61, 63). TAVI may thus provide another potential alternative to avoid PPM in high risk patients and yet provide a less invasive procedure. Although, initial results with TAVI are promising, studies to date have only included a small number of patients. These results should thus be interpreted with caution and further studies in larger series of patients are needed to corroborate the usefulness of this procedure for the prevention of PPM.

Prevention of PPM needs to be stressed especially in younger patients. These patients often receive a mechanical valve, and PPM may have a higher impact on survival. Other studies have also emphasized the importance of avoiding PPM in patients with depressed LV systolic function given that they are most vulnerable to the residual LV afterload associated with PPM (7, 64, 65).

Hemodynamics and EOA

There is a strong inverse relationship between pressure gradients and iEOA, which has led to widely accepted iEOA cut-off for defining PPM at 0.85 cm^2/m^2 for moderate and 0.65 cm^2/m^2 for severe PPM. Significant valve gradients at rest or during exercise can be avoided with an iEOA >0.85 cm^2/m^2 (13). It has been shown that patients without PPM have stable hemodynamics, while an increase in gradients has been demonstrated in patients with an iEOA ≤0.85 cm^2/m^2 which is even worse in patients with severe PPM (≤0.65 cm^2/m^2) (4). Hence, the difference in gradient that is observed at rest between patients with PPM versus those with no PPM increases dramatically with exercise and associated increase in flow rate. It should however be emphasized that some patients may exhibit a relatively low gradient despite the presence of a small iEOA. This "pseudo-normalization" of gradient is related to the presence of a low flow state, similar to what occurs in patients with low flow, low-gradient aortic stenosis. And the patients with PPM and low gradient are likely at higher risk for adverse events.

Over time valve companies have developed prosthetic valves with better hemodynamic performance and thus with larger EOAs. The older generation of prosthesis tends to have smaller EOAs for a given prosthesis size (Table 3). This meta-analysis includes studies with a long time period of patient inclusion. Many centers, however, are still using certain popular valves (e.g. St Jude Medical Standard mechanical valve, CarboMedics mechanical valve, Perimount bioprosthesis, etc). The use of a newer generation of valve prosthesis may influence the prevalence of PPM, but the effect of PPM on mortality will not change.

Company-provided iEAO charts should be interpreted with caution. There are no standards for creating these charts and it has been shown that the most optimistic EOA values are often chosen to be reported (56, 66, 67). A more reliable and manufacturer-

independent source of reference EOA data has been published by Pibarot et al. and is displayed in Table 3 (68). This table can be used to predict the average postoperative EOA for each given model and size of prosthesis. This information is particularly useful to anticipate the risk of PPM at the time of operation. If, after calculating the predicted iEOA from Table 3 (with information of valve model and sizing) and patient's body surface area, the surgeon concludes that there is risk of PPM, and especially of severe PPM, an alternative prosthesis model and/or surgical technique could be used to avoid PPM or, at least, reduce its severity. A comparison of the different models of prostheses on a label size per size basis in Table 3 may be misleading given that the dimensions of the sizers and the correspondence with the label prosthesis size may vary from one manufacturer to the other. The establishment of universal sizers and sizing process that would be the same for all prosthetic valves of all manufacturers would certainly help to implement operative strategies for the prevention of PPM.

Table 3. Literature derived effective orifice areas of popular valves.

	Valve size (mm)					
	19	**21**	**23**	**25**	**27**	**29**
Stented bioprostheses						
Mosaic	1.1 ± 0.2	1.2 ± 0.3	1.4 ± 0.3	1.7 ± 0.4	1.8 ± 0.4	2.0 ± 0.4
Hancock II	…	1.2 ± 0.1	1.3 ± 0.2	1.5 ± 0.3	1.6 ± 0.2	1.6 ± 0.2
CE Perimount	1.1 ± 0.3	1.3 ± 0.4	1.5 ± 0.4	1.8 ± 0.4	2.1 ± 0.4	2.2 ± 0.4
CR Magna*	1.3 ± 0.3	1.7 ± 0.3	2.1 ± 0.4	2.3 ± 0.5	…	…
Biocor (Epic)*	…	1.3 ± 0.3	1.6 ± 0.3	1.8 ± 0.4	…	…
Mitroflow*	1.1 ± 0.1	1.3 ± 0.1	1.5 ± 0.2	1.8 ± 0.2	…	…
Stentless bioprostheses						
Medtronic Freestyle	1.2 ± 0.2	1,4 ± 0.2	1.5 ± 0.3	2.0 ± 0.4	2.3 ± 0.5	…
SJM Toronto SPV	…	1.3 ± 0.3	1.5 ± 0.5	1.7 ± 0.8	2.1 ± 0.7	2.7 ± 1.0
Mechanical prostheses						
Medtronic Hall	1.2 ± 0.2	1.3 ± 0.2	…	…	…	…
Medtronic Advantage*	…	1.7 ± 0.2	2.2 ± 0.3	2.8 ± 0.6	3.3 ± 0.7	3.9 ± 0.7
SJM Standard	1.0 ± 0.2	1.4 ± 0.2	1.5 ± 0.5	2.1 ± 0.4	2.7 ± 0.6	3.2 ± 0.3
SJM Regent	1.6 ± 0.4	2.0 ± 0.7	2.2 ± 0.9	2.5 ± 0.9	3.6 ± .13	4.4 ± 0.6
On-X	1.5 ± 0.2	1.7 ± 0.4	2.0 ± 0.6	2.4 ± 0.8	3.2 ± 0.6	3.2 ± 0.6
CarboMedics	1.0 ± 0.4	1.5 ± 0.3	1.7 ± 0.3	2.0 ± 0.4	2.5 ± 0.4	2.6 ± 0.4

CE, Carpentier-Edwards; SJM, St Jude Medical; *Results are based on a limited number of patients.
Reproduced with permission of Pibarot et al.[67]

Study Limitations

To reduce the limitations inherent to meta-analysis, we included multiple databases in the literature search, and used minimal exclusion criteria. As a result, a wide time horizon of patient inclusion is present which some consider problematic due to changes in cardiac surgery and echocardiography. However, a sensitivity analysis by years of patient inclusion could not demonstrate a difference in HRs when only studies with inclusion of patients operated after 1990 and 1995 were used.

First of all, many of the studies were retrospective by design and therefore follow-up was incomplete. The method by Williamson et al. (17) to extrapolate HRs from Kaplan-Meier is a widely-accepted method recommended in the PRISMA guidelines (19), but the corresponding HR is not as accurate as to when reported in the original paper. Nonetheless, a subgroup analysis by study design was unable to detect a difference in effect between retro-and prospective studies. The quality of studies was generally high because completion of follow-up was often >95%.

Second, only 8 of the 34 studies used EOAs determined by echocardiographic measurement. Although direct measurement is considered a more appropriate method, the other studies used previously reported reference values of the EOA to calculate the iEOA, due to a lack of postoperative echocardiographic data (5, 13). It is possible that some patients may thus have been mis-classified with the use of this "projected" iEOA. However, the utilization of the iEOA measured by Doppler-echocardiography early after operation also has limitations. Its accuracy may be altered by LV outflow or chronotropic conditions and by technical pitfalls or measurements errors. Furthermore, data is not available in patients who died in the operative or early postoperative periods. Nevertheless, the subgroup analysis demonstrated no difference in outcomes in studies using measured or reference values, and long-term survival is significantly impaired in both categories of studies (Figure 5).

Third, despite significant efforts to instruct authors to report results according to guidelines (69), outcome reporting in the included studies differed considerably. In some studies hospital or procedure-related mortality was in-or excluded. In several instances the in-or exclusion was not even specified. Both authors and editors of journals should be encouraged to use uniform definitions and reporting of outcomes. Meta-analysis is an important method in clinical research. With standardized methods and reporting, a larger number of studies can be included in meta-analyses and evidence can be more accurately and less spuriously defined (70).

Conclusions

Although the adverse effect of PPM on long-term survival has been denied in some studies, this meta-analysis of 34 studies with 27,186 patients demonstrates a significant increase in all-cause and cardiac-related mortality over long-term follow-up after AVR.

Current efforts to prevent PPM should therefore receive more emphasis and a widespread acceptance to improve long-term survival.

REFERENCES

1. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. Circulation 1978;58:20-4.
2. Dumesnil JG, Honos GN, Lemieux M, Beauchemin J. Validation and applications of indexed aortic prosthetic valve areas calculated by Doppler echocardiography. J Am Coll Cardiol 1990;16:637-643.
3. Dumesnil JG, Yoganathan AP. Valve prosthesis hemodynamics and the problem of high transprosthetic pressure gradients. Eur J Cardiothorac Surg 1992;6:S34-S37.
4. Pibarot P, Dumesnil JG, Lemieux M, Cartier P, Metras J, Durand LG. Impact of prosthesis-patient mismatch on hemodynamic and symptomatic status, morbidity and mortality after aortic valve replacement with a bioprosthetic heart valve. J Heart Valve Dis 1998;7:211-218.
5. Flameng W, Herregods MC, Vercalsteren M, Herijgers P, Bogaerts K, Meuris B. Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. Circulation 2010;121:2123-2129.
6. Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: definition, clinical impact, and prevention. Heart 2006;92:1022-1029.
7. Blais C, Dumesnil JG, Baillot R, Simard S, Doyle D, Pibarot P. Impact of valve prosthesis-patient mismatch on short-term mortality after aortic valve replacement. Circulation 2003;108:983-988.
8. Ruel M, Rubens FD, Masters RG, Pipe AL, Bedard P, Hendry PJ, Lam BK, Burwash IG, Goldstein WG, Brais MP, Keon WJ, Mesana TG. Late incidence and predictors of persistent or recurrent heart failure in patients with aortic prosthetic valves. J Thorac Cardiovasc Surg 2004;127:149-159.
9. Tasca G, Mhagna Z, Perotti S, Centurini PB, Sabatini T, Amaducci A, Brunelli F, Cirillo M, Dalla Tomba M, Quaini E, Troise G, Pibarot P. Impact of prosthesis-patient mismatch on cardiac events and midterm mortality after aortic valve replacement in patients with pure aortic stenosis. Circulation 2006;113:570-576.
10. Urso S, Sadaba R, Vives M, Trujillo J, Beltrame S, Soriano B, Piqueras L, Aldamiz-Echevarria G. Patient-prosthesis mismatch in elderly patients undergoing aortic valve replacement: impact on quality of life and survival. J Heart Valve Dis 2009;18:248-255.
11. Walther T, Rastan A, Falk V, Lehmann S, Garbade J, Funkat AK, Mohr FW, Gummert JF. Patient prosthesis mismatch affects short- and long-term outcomes after aortic valve replacement. Eur J Cardiothorac Surg 2006;30:15-19.
12. Blackstone EH, Cosgrove DM, Jamieson WR, Birkmeyer NJ, Lemmer JH, Jr., Miller DC, Butchart EG, Rizzoli G, Yacoub M, Chai A. Prosthesis size and long-term survival after aortic valve replacement. J Thorac Cardiovasc Surg 2003;126:783-796.
13. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. J Am Coll Cardiol 2000;36:1131-1141.
14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
15. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002;359:1686-1689.
16. Karrison TG. Use of Irwin's restricted mean as an index for comparing survival in different treatment groups--interpretation and power considerations. Control Clin Trials 1997;18:151-167.
17. Williamson PR, Smith CT, Hutton JL, Marson AG. Aggregate data meta-analysis with time-to-event outcomes. Stat Med 2002;21:3337-3351.

18. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-2834.
19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65-W94.
20. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634.
22. Rao V, Jamieson WR, Ivanov J, Armstrong S, David TE. Prosthesis-patient mismatch affects survival after aortic valve replacement. Circulation 2000;102:III5-III9.
23. Frapier JM, Rouviere P, Razcka F, Aymard T, Albat B, Chaptal PA. Influence of patient-prosthesis mismatch on long-term results after aortic valve replacement with a stented bioprosthesis. J Heart Valve Dis 2002;11:543-551.
24. Hanayama N, Christakis GT, Mallidi HR, Joyner CD, Fremes SE, Morgan CD, Mitoff PR, Goldman BS. Patient prosthesis mismatch is rare after aortic valve replacement: valve size may be irrelevant. Ann Thorac Surg 2002;73:1822-1829.
25. Milano AD, De Carlo M, Mecozzi G, D'Alfonso A, Scioti G, Nardi C, Bortolotti U. Clinical outcome in patients with 19-mm and 21-mm St. Jude aortic prostheses: comparison at long-term follow-up. Ann Thorac Surg 2002;73:37-43.
26. Penta de Peppo A, Zeitani J, Nardi P, Iaci G, Polisca P, De Paulis R, Chiariello L. Small "functional" size after mechanical aortic valve replacement: no risk in young to middle-age patients. Ann Thorac Surg 2005;79:1915-1920.
27. Tasca G, Brunelli F, Cirillo M, DallaTomba M, Mhagna Z, Troise G, Quaini E. Impact of valve prosthesis-patient mismatch on left ventricular mass regression following aortic valve replacement. Ann Thorac Surg 2005;79:505-510.
28. Flameng W, Meuris B, Herijgers P, Herregods MC. Prosthesis-patient mismatch is not clinically relevant in aortic valve replacement using the Carpentier-Edwards Perimount valve. Ann Thorac Surg 2006;82:530-536.
29. Howell NJ, Keogh BE, Barnet V, Bonser RS, Graham TR, Rooney SJ, Wilson IC, Pagano D. Patient-prosthesis mismatch does not affect survival following aortic valve replacement. Eur J Cardiothorac Surg 2006;30:10-14.
30. Mohty D, Malouf JF, Girard SE, Schaff HV, Grill DE, Enriquez-Sarano ME, Miller FA Jr. Impact of prosthesis-patient mismatch on long-term survival in patients with small St Jude Medical mechanical prostheses in the aortic position. Circulation 2006;113:420-426.
31. Moon MR, Pasque MK, Munfakh NA, Melby SJ, Lawton JS, Moazami N, Codd JE, Crabtree TD, Barner HB, Damiano RJ Jr. Prosthesis-patient mismatch after aortic valve replacement: impact of age and body size on late survival. Ann Thorac Surg 2006;81:481-488.
32. Garcia Fuster R, Estevez V, Rodriguez I, Canovas S, Gil O, Hornero F, Martínes-León J. Prosthesis - patient mismatch with latest generation supra-annular prostheses. The beginning of the end? Interact Cardiovasc Thorac Surg 2007;6:462-469.
33. Kato Y, Suehiro S, Shibata T, Sasaki Y, Hirai H. Impact of valve prosthesis-patient mismatch on long-term survival and left ventricular mass regression after aortic valve replacement for aortic stenosis. J Card Surg 2007;22:314-319.

34. Monin JL, Monchi M, Kirsch ME, Petit-Eisenmann H, Baleynaud S, Chauvel C, Metz D, Adams C, Quere JP, Gueret P, Tribouilloy C. Low-gradient aortic stenosis: impact of prosthesis-patient mismatch on survival. Eur Heart J 2007;28:2620-2626.
35. Nozohoor S, Nilsson J, Luhrs C, Roijer A, Sjogren J. The influence of patient-prosthesis mismatch on in-hospital complications and early mortality after aortic valve replacement. J Heart Valve Dis 2007;16:475-482.
36. Tao K, Sakata R, Iguro Y, Ueno M, Tanaka Y, Otsuji Y, Tei C. Impact of valve prosthesis-patient mismatch on intermediate-term outcome and regression of left ventricular mass following aortic valve replacement with mechanical prosthesis. J Card Surg 2007;22:486-492.
37. Florath I, Albert A, Rosendahl U, Ennker IC, Ennker J. Impact of valve prosthesis-patient mismatch estimated by echocardiographic-determined effective orifice area on long-term outcome after aortic valve replacement. Am Heart J 2008;155:1135-1142.
38. Kato Y, Tsutsumi Y, Kawai T, Goto T, Takahashi Y, Ohashi H. Aortic valve replacement for aortic stenosis in the elderly: influence of prosthesis-patient mismatch on late survival and left ventricular mass regression. Gen Thorac Cardiovasc Surg 2008;56:397-403.
39. Kohsaka S, Mohan S, Virani S, Lee VV, Contreras A, Reul GJ, Coulter SA. Prosthesis-patient mismatch affects long-term survival after mechanical valve replacement. J Thorac Cardiovasc Surg 2008;135:1076-1080.
40. Mascherbauer J, Rosenhek R, Fuchs C, Pernicka E, Klaar U, Scholten C, Heger M, Wollenek G, Maurer G, Baumgartner H. Moderate patient-prosthesis mismatch after valve replacement for severe aortic stenosis has no impact on short-term and long-term mortality. Heart 2008;94:1639-1645.
41. Ryomoto M, Mitsuno M, Yamamura M, Tanaka H, Kobayashi Y, Fukui S, Tsujiya N, Kajiyama T, Miyamoto Y. Patient-prosthesis mismatch after aortic valve replacement in the elderly. Gen Thorac Cardiovasc Surg 2008;56:330-334.
42. Tsutsumi K, Nagumo M, Nishikawa K, Takahashi R. Effect of prosthesis-patient mismatch on survival after aortic valve replacement using mechanical prostheses in patients with aortic stenosis. Gen Thorac Cardiovasc Surg 2008;56:577-583.
43. Vicchio M, Della Corte A, De Santo LS, De Feo M, Caianiello G, Scardone M, Cotrufo M. Prosthesis-patient mismatch in the elderly: survival, ventricular mass regression, and quality of life. Ann Thorac Surg 2008;86:1791-1797.
44. Mannacio VA, De Amicis V, Di Tommaso L, Iorio F, Vosa C. Influence of prosthesis-patient mismatch on exercise-induced arrhythmias: a further aspect after aortic valve replacement. J Thorac Cardiovasc Surg 2009;138:632-638.
45. Mohty D, Dumesnil JG, Echahidi N, Mathieu P, Dagenais F, Voisine P, Pibarot P. Impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: influence of age, obesity, and left ventricular dysfunction. J Am Coll Cardiol 2009;53:39-47.
46. Moon MR, Lawton JS, Moazami N, Munfakh NA, Pasque MK, Damiano RJ, Jr. POINT: Prosthesis-patient mismatch does not affect survival for patients greater than 70 years of age undergoing bioprosthetic aortic valve replacement. J Thorac Cardiovasc Surg 2009;137:278-283.
47. Mrowczynski W, Lutter G, Attmann T, Hoffmann G, Quaden R, Cremer J, Böning A. Does patient-prosthesis mismatch influence the results of combined aortic valve replacement and coronary bypass grafting? Kardiol Pol 2009;67:865-873.
48. Bleiziffer S, Ali A, Hettich IM, Akdere D, Laubender RP, Ruzicka D, Boehm J, Lange R, Eichinger W. Impact of the indexed effective orifice area on mid-term cardiac-related mortality after aortic valve replacement. Heart 2010;96:865-871.

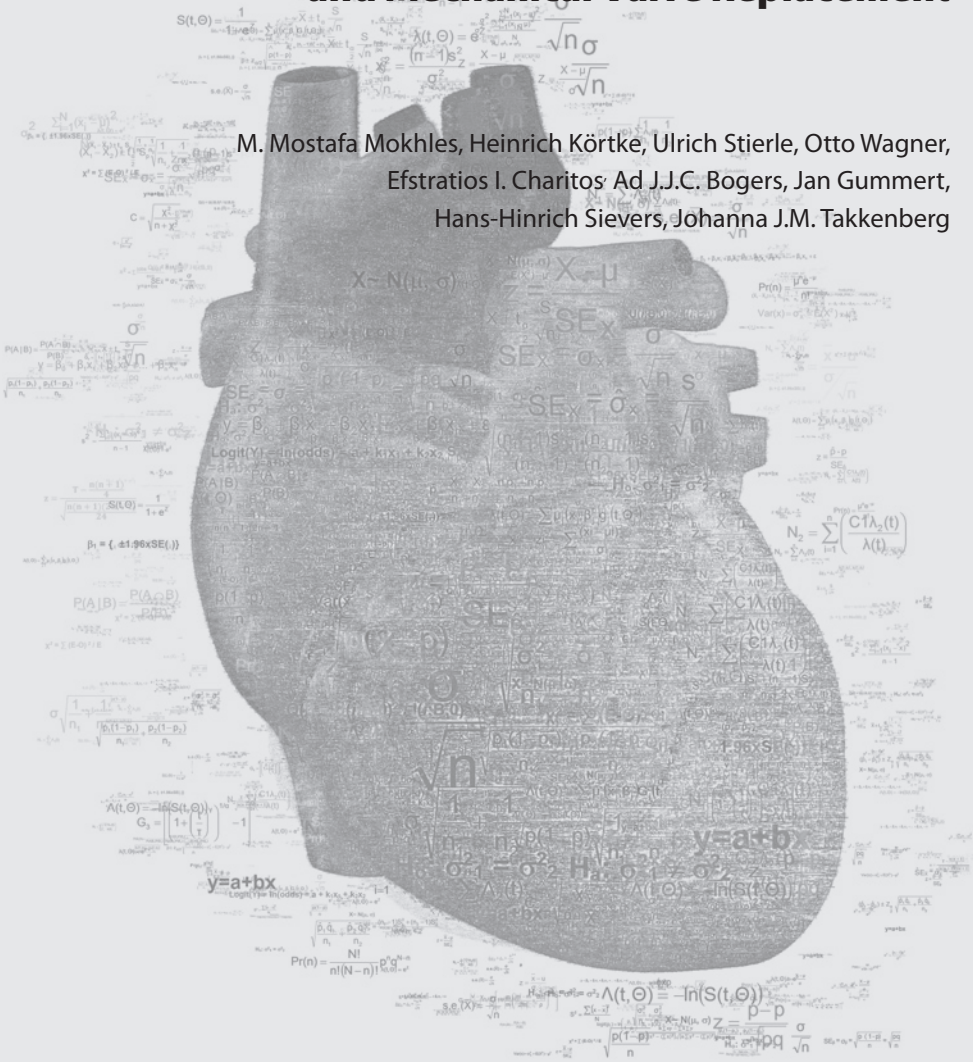
49. Jamieson WR, Ye J, Higgins J, Cheung A, Fradet GJ, Skarsgard P, Germann E, Chan F, Lichtenstein SV. Effect of prosthesis-patient mismatch on long-term survival with aortic valve replacement: assessment to 15 years. Ann Thorac Surg 2010;89:51-59.
50. Sakamoto Y, Yoshitake M, Naganuma H, Kawada N, Kinouchi K, Hashimoto K. Reconsideration of patient-prosthesis mismatch definition from the valve indexed effective orifice area. Ann Thorac Surg 2010;89:1951-1955.
51. Bakhtiary F, Schiemann M, Dzemali O, Dogan S, Schachinger V, Ackermann H, Moritz A, Kleine P. Impact of patient-prosthesis mismatch and aortic valve design on coronary flow reserve after aortic valve replacement. J Am Coll Cardiol 2007;49:790-796.
52. Pibarot P, Honos GN, Durand LG, Dumesnil JG. The effect of prosthesis-patient mismatch on aortic bioprosthetic valve hemodynamic performance and patient clinical status. Can J Cardiol 1996;12:379-387.
53. Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, Bauters A, Decoene C, Goudemand J, Prat A, Jude B. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med 2003;349:343-349.
54. Yoshida K, Tobe S, Kawata M, Yamaguchi M. Acquired and reversible von Willebrand disease with high shear stress aortic valve stenosis. Ann Thorac Surg 2006;81:490-494.
55. Unger P, Magne J, Vanden Eynden F, Plein D, Van Camp G, Pasquet A,Cosyns B, Dedobbeleer C, Lancellotti P. Impact of prosthesis-patient mismatch on mitral regurgitation after aortic valve replacement. Heart 2010;96:1627-1632.
56. Bleiziffer S, Eichinger WB, Hettich I, Guenzinger R, Ruzicka D, Bauernschmitt R, Lange R. Prediction of valve prosthesis-patient mismatch prior to aortic valve replacement: which is the best method? Heart 2007;93:615-620.
57. Castro LJ, Arcidi JM, Jr., Fisher AL, Gaudiani VA. Routine enlargement of the small aortic root: a preventive strategy to minimize mismatch. Ann Thorac Surg 2002;74:31-6; discussion 36.
58. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation 2009;119:1034-1048.
59. Kulik A, Al-Saigh M, Chan V, Masters RG, Bedard P, Lam BK, Rubens FD, Hendry PJ, Mesana TG, Ruel M. Enlargement of the small aortic root during aortic valve replacement: is there a benefit? Ann Thorac Surg 2008;85:94-100.
60. Peterson MD, Borger MA, Feindel CM, David TE. Aortic annular enlargement during aortic valve replacement: improving results with time. Ann Thorac Surg 2007;83:2044-2049.
61. Clavel MA, Webb JG, Pibarot P, Altwegg L, Dumont E, Thompson C, De Larochellière R, Doyle D, Masson JB, Bergeron S, Bertrand OF, Rodés-Cabau J. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol 2009;53:1883-1891.
62. Jilaihawi H, Chin D, Spyt T, Jeilan M, Vasa-Nicotera M, Bence J, Logtens E, Kovac J. Prosthesis-patient mismatch after transcatheter aortic valve implantation with the Medtronic-Corevalve bioprosthesis. Eur Heart J 2010;31:857-864.
63. Sherif MA, Abdel-Wahab M, Awad O, Geist V, El-Shahed G, Semmler R, Tawfik M, Khattab AA, Richardt D, Richardt G, Tölg R. Early hemodynamic and neurohormonal response after transcatheter aortic valve implantation. Am Heart J 2010;160:862-869.
64. Kulik A, Burwash IG, Kapila V, Mesana TG, Ruel M. Long-term outcomes after valve replacement for low-gradient aortic stenosis: impact of prosthesis-patient mismatch. Circulation 2006;114:I553-I558.

65. Ruel M, Al-Faleh H, Kulik A, Chan KL, Mesana TG, Burwash IG. Prosthesis-patient mismatch after aortic valve replacement predominantly affects patients with preexisting left ventricular dysfunction: effect on survival, freedom from heart failure, and left ventricular mass regression. J Thorac Cardiovasc Surg 2006;131:1036-1044.
66. Cohen RG, Bourne ET. Industry-generated charts for the selection of stented aortic valve prostheses: clinical tool or marketing ploy? Ann Thorac Surg 2011;91:1001-1002.
67. Pibarot P, Dumesnil JG. Prevention of valve prosthesis-patient mismatch before aortic valve replacement: does it matter and is it feasible? Heart 2007;93:549-551.
68. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation 2009;119:1034-1048.
69. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Eur J Cardiothorac Surg 2008;33:523-528.
70. Egger M, Davey Smith G, Altman D. Systematic reviews in health care: meta-analysis in context. London: BMJ Publishing Group; 2001.

Chapter 10

Survival Comparison of the Ross Procedure and Mechanical Valve Replacement

M. Mostafa Mokhles, Heinrich Körtke, Ulrich Stierle, Otto Wagner, Efstratios I. Charitos, Ad J.J.C. Bogers, Jan Gummert, Hans-Hinrich Sievers, Johanna J.M. Takkenberg



Circulation. 2011;123:31-8

ABSTRACT

Background

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

Methods and Results

We selected 918 Ross patients and 406 mechanical valve patients aged 18-60 years without dissection, aneurysm or mitral valve replacement who survived an elective procedure (1994-2008). Using 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), M/F ratio 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%/patient-year in the Ross procedure group compared to 0.30%/patient-year in the mechanical valve group (matched hazard ratio 1.86, 95% confidence interval 0.58-5.91, p=0.32). Late survival was comparable to 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 the general population, possibly as a result of highly specialized anticoagulation self-management, better timing of surgery, and improved patient selection in more recent years.

INTRODUCTION

Survival after aortic valve replacement is reported to be significantly lower compared to the general age-matched population—especially in younger adult patients (1-3). An exception is survival after the Ross procedure, which seems to be comparable to 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 between the Ross procedure, a mechanical prosthesis, a stentless or 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.

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 versus mechanical aortic valve replacement. Given the fact 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 ESCAT II trial (11, 12). The German-Dutch Ross Registry is a prospective multicenter cohort study with 1742 patients. The Registry includes data from 12 departments of cardiothoracic surgery in The Netherlands and Germany, and started in February 1991 (7-10). The ESCAT II trial is a prospective controlled randomized multicenter study. A total of 2162 patients were enrolled in the ESCAT II trial between the years 1994 and 2002. Follow-up of all patients was assessed for the last time in 2006. Patients were randomized between a conventional group (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 approximately six months later, and a 24 h telemedicine care and consultation. The centre provides the patients an anticoagulation monitor with test strips and the lancets. A weekly determination and feedback to the telemedicine centre allows a sensitive INR adjustment during the long-term anticoagulation therapy. Two large randomised 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) since this was the only center that had collected the detailed patient and peri-operative information that we needed for the purpose of our study. During patient selection for the propensity score analysis we didn't make a distinction between the two groups in the ESCAT II trial because there were no differences between the groups relevant for this study (14). The authors had full access to and take full responsibility for the integrity of the data and the present manuscript.

Study population

Patients with isolated aortic valve pathology aged 18 through 60 years at the time of operation that were operated 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 patients who required concomitant mitral valve replacement were excluded from this study. Concomitant mitral valve reconstruction and concomitant coronary artery bypass graft were not considered as exclusion criteria. The remaining study population consisted of 406 patients within the mechanical valve group and of 918 patients within 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 more than 30 days after surgery). The occurrence of events during follow-up and the cause of death was registered and reported according to the Guidelines for reporting mortality and morbidity after cardiac valve interventions (15). Only grade III thrombo-embolism and grade III bleeding complications were used for the analyses. Briefly, grade III thrombo-embolism was defined as heart valve prosthesis thrombosis or severe thrombo-embolism 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, and inpatient care or causing long-term impairment. Moreover, 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

Table 1. Baseline Characteristics Unmatched Cohort.

Covariates	Cohort (N = 1324)	Mechanical AVR (N = 406)	Ross Procedure (N = 918)	P value
Sex (male)	1001 (75.6 %)	310 (76.4 %)	691 (75.3 %)	.672
Mean age at surgical intervention (y)	44.0 ± 11.3	49.5 ± 10.3	41.6 ± 11.0	< .001
Cause				
Rheumatic	60 (4.5 %)	23 (5.7 %)	37 (4.0 %)	.054
Missing	58 (4.4 %)	58 (14.3 %)		
Calcified/Degenerative	644 (48.6 %)	311 (76.6 %)	333 (36.3 %)	< .001
Missing	55 (4.2 %)	55 (13.5 %)		
Endocarditis				
Active Endocarditis	32 (2.4 %)	0 (0 %)	32 (3.5 %)	< .001
Hemodynamic manifestation				
Stenosis	339 (25.6 %)	129 (31.8 %)	210 (22.9 %)	< .001
Regurgitation	401 (30.3 %)	102 (25.1 %)	299 (32.6 %)	.028
Mixed	554 (41.8 %)	155 (38.2 %)	399 (43.5 %)	.270
Missing	30 (2.3 %)	20 (4.9%)	10 (1.1 %)	
Preoperative NYHA				< .001
NYHA I / II	813 (61.4 %)	202 (49.8 %)	611 (66.6 %)	
NYHA III / IV	463 (35.0 %)	191 (47.0 %)	272 (29.6 %)	
Missing	48 (3.6 %)	13 (3.2 %)	35 (3.8 %)	
Preoperative creatinin µmol/L	83.8 ± 60.4	93.6 ± 89.1	76.7 ± 20.9	< .001
Preoperative rhythm				.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	46 (3.5 %)	20 (4.9 %)	26 (2.8 %)	.055
Preoperative Hypertension	406 (30.7 %)	161 (39.7 %)	245 (26.7 %)	< .001
Preoperative Lung Disease	29 (2.2 %)	7 (1.7 %)	22 (2.4 %)	.441
Preoperative LVEF (%)	64.0 ± 12.3	65.3 ± 13.8	63.2 ± 11.2	.013
Missing	156 (11.8 %)	24 (5.9 %)	132 (14.4 %)	
Preoperative LVH	726 (54.8 %)	354 (87.6 %)	372 (40.5 %)	< .001
Missing	47 (3.5 %)		47 (5.1 %)	
Preoperative LVEDD	55.9 ± 10.6	57.2 ± 10.7	55.2 ± 10.4	.009
Preoperative LVESD	37.1 ± 10.1	39.2 ± 10.4	35.8 ± 9.6	< .001
Previous Cardiac Operation	88 (6.6 %)	27 (6.7 %)	61 (6.6 %)	.997
Previous Aortic Valve Operation	59 (4.5 %)	9 (2.2 %)	50 (5.4 %)	.009
Concomitant CABG	183 (13.8)	145 (35.7)	38 (4.1)	< .001
Concomitant MV reconstruction	16 (1.2)	0 (0.0)	16 (1.7)	< .001

DM, diabetes mellitus; EF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameters**;** CABG, coronary artery bypass grafting; MV, mitral valve

offers a way to achieve more balanced groups by matching treatment and control units based on a set of baseline characteristics (16-18). Before matching the two 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 the exclusion of hospital mortality the cohort consisted of 918 patients in the Ross procedure group and of 406 patients in the mechanical prosthesis group (Figure 1).

The propensity score for our combined cohort of 1324 patients (with Ross procedure or mechanical prosthesis) was constructed using 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 for LVESD, were included as covariates. LVESD was not included as covariate in the propensity model because it was highly correlated with LVEDD (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 two 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 that could be matched to patients with a mechanical prosthesis were no longer considered as 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 approximately 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 treatment group was based on the use of a two-tailed P value of 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% per year for patients with the Ross procedure (20) and a late mortality rate of 1.40% per year for patients with a mechanical prosthesis (6), and study duration of 14 years (1994-2008) with a constant accrual of patients.

Continuous data are presented as means (standard deviation; range), and comparison in the unmatched cohort was done using the unpaired T-test unless the data were not normally distributed (Kolmogorov-Smirnov 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 using the Chi-Square test or the Fisher Exact test where appropriate. All tests were 2-sided, with an α-level of 0.05. Comparison in the matched cohort was done using McNemar's test and paired sample t-test or Wilcoxon signed-rank test, where appropriate. A Cox-regression model, taking pair into account (by correcting the standard errors), has been used to compare survival between the different surgical techniques. The Cox proportional hazards model was also used for univariate and multivariate analysis of late survival. Comparison of patient survival with the general age and gender matched population was done using the German population life tables (21). All statistical tests were two-sided, and tests with a p-value of 0.05 or lower were considered significant. Survival comparison of the matched cohort was done using 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 using SPSS for windows version 15 (SPSS Inc.; Chicago, IL).

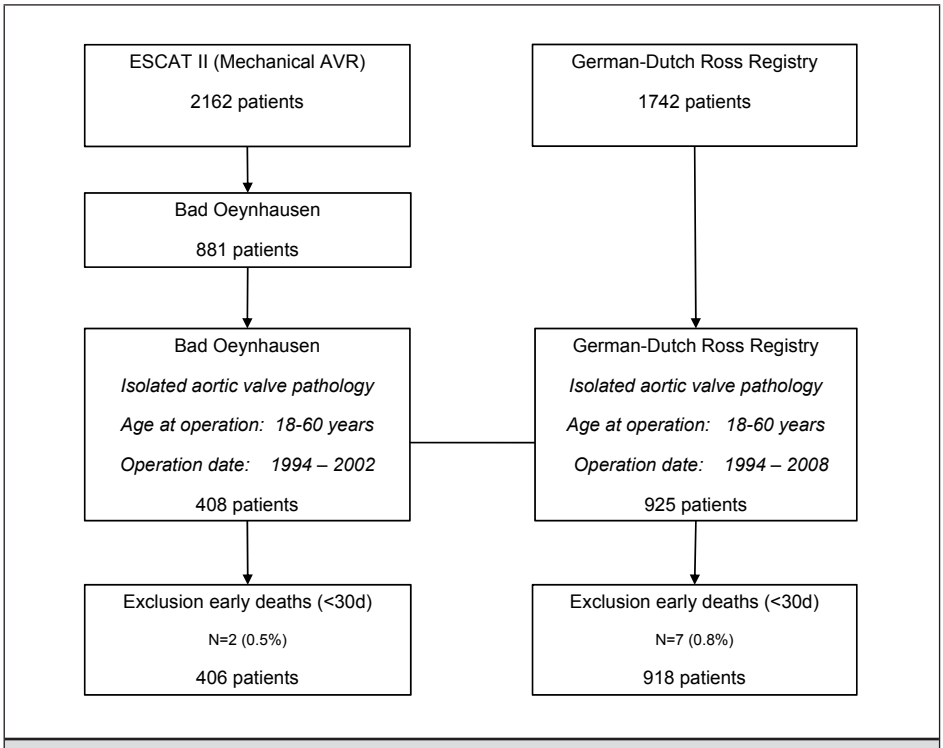


Figure 1. Flow chart patient selection.

Table 2. Baseline Characteristics Matched Cohort.

Covariates	Cohort (N = 506)	Mechanical AVR (N = 253)	Ross Procedure (N = 253)	P value
Sex (male)	378 (74.7 %)	185 (73.1 %)	193 (76.3 %)	.461
Mean age at surgical intervention (y)	47.6 ± 9.8	48.0 ± 11.0	47.3 ± 8.5	.169
Cause				
Rheumatic	34 (6.7 %)	17 (6.7 %)	17 (6.7 %)	.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				
Active Endocarditis	0 (0.0 %)	0 (0 %)	0 (0.0%)	-
Hemodynamic manifestation				
Stenosis	164 (32.4 %)	82 (32.4 %)	80 (31.6 %)	.769
Regurgitation	90 (17.8 %)	44 (17.4 %)	47 (18.6 %)	.724
Mixed	237 (46.8 %)	112 (44.3 %)	126 (49.8 %)	.516
Missing	15 (3.0 %)	15 (5.9%)		
Preoperative NYHA				.497
NYHA I / II	297 (58.7 %)	145 (57.3 %)	152 (60.1 %)	
NYHA III / IV	185 (36.6 %)	95 (37.5 %)	90 (35.6 %)	
Missing	24 (4.7 %)	13 (5.1 %)	11 (4.3 %)	
Preoperative creatinin µmol/L	82.2 ± 22.8	82.9 ± 16.9	80.7 ± 31.6	.206
Preoperative rhythm				.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	20 (4.0 %)	9 (3.6 %)	11 (4.3 %)	.824
Preoperative Hypertension	166 (32.8 %)	86 (34.0 %)	80 (31.6 %)	.645
Preoperative Lung Disease	14 (2.8 %)	5 (2.0 %)	9 (3.6 %)	.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	382 (75.5 %)	194 (76.7 %)	188 (74.3 %)	.807
Missing	5 (1.0 %)		5 (2.0 %)	
Preoperative LVEDD	55.3 ± 10.1	55.7 ± 10.2	54.8 ± 10.2	.386
Preoperative LVESD	36.5 ± 8.7	36.7 ± 8.8	36.3 ± 8.6	.745
Previous Cardiac Operation	16 (3.2 %)	10 (4.0 %)	6 (2.4 %)	.454
Previous Aortic Valve Operation	9 (1.8 %)	5 (2.0 %)	4 (1.6 %)	> 0.99
Concomitant CABG	67 (13.2 %)	36 (14.2)	31 (12.3)	.542
Concomitant MV reconstruction	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-

DM, diabetes mellitus; EF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameters**;** CABG, coronary artery bypass grafting; MV, mitral valve

RESULTS

Outcomes in the unmatched cohort

In the initial unmatched cohort of 1324 patients there were 36 late deaths during a follow-up of 8,066 patient-years (0.45%/patient year). Late mortality occurred in 0.49%/patient-year (N=27) in the Ross procedure group compared to 0.32%/patient-year (N=9) in the mechanical prosthesis group (unmatched hazard ratio [HR] 1.33, 95% confidence interval [CI] 0.61-2.91, p=0.47; Table 3). Addition of the propensity score to the Cox regression model resulted in a propensity matched HR of 3.64 (95% CI 1.22-10.88). 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 within the Ross procedure group (mean follow-up time 5.1 years) and of 253 patients within 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).

In the 253 matched-pair cohort, during 2,899 patient-years of follow-up, 12 participants (2.4%) died (Table 3). Valve-related mortality was only observed in patients who underwent a Ross procedure. The four valve-related deaths were two sudden, unexplained, unexpected deaths without further clinical data or autopsy, one death due to a coronary embolus and subsequent myocardial infarction, and one stroke.

During follow-up eight Ross patients in the matched cohort required an aortic valve replacement. None of the patients with a mechanical valve required a reoperation in the matched cohort. Linearized all-cause reoperation rate was 0.61%/patient-year in the Ross procedure group compared 0.00%/patient-year in the mechanical valve group (p=0.01). Two bleeding events were observed in the matched cohort of Ross patients and six bleeding events were observed in the matched cohort of the patients with a mechanical valve. Linearized bleeding rate was 0.15%/patient-year in the Ross procedure group compared to 0.36/patient-year in the mechanical valve group (p=0.15). During follow-up five Ross patients and one patient with a mechanical valve experienced a thromboembolic event. Linearized thromboembolism rate was 0.38%/patient-year in the Ross procedure group compared to 0.06/patient-year in the mechanical valve group (p=0.10). Endocarditis was diagnosed in two patients who underwent a Ross procedure and in none of the patients who underwent a mechanical aortic valve replacement. Linearized endocarditis rate was 0.15%/patient-year in the Ross procedure group compared to 0.00%/patient-year in the mechanical valve group (p=0.16).

All-cause mortality occurred in 0.54%/patient-year (N=7) in the Ross procedure group compared to 0.31%/patient-year (N=5) in the mechanical prosthesis group (matched hazard ratio [HR] 1.86, 95% confidence interval [CI] 0.58 to 5.91, p=0.32; Table 3). Cumu-

Table 3. Association of procedure with late mortality.

	Events/ total follow-up years		Matched hazard ratio (95% confidence interval)	P-value
	Mechanical Valve	Ross Procedure		
Before matching	n=406	n=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 non-cardiac mortality	1/2574	7/5492		
Unknown	2/2574	1/5492		
After matching	n=253	n=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 non-cardiac mortality	1/1682	2/1310		
Unknown	1/1682	0		

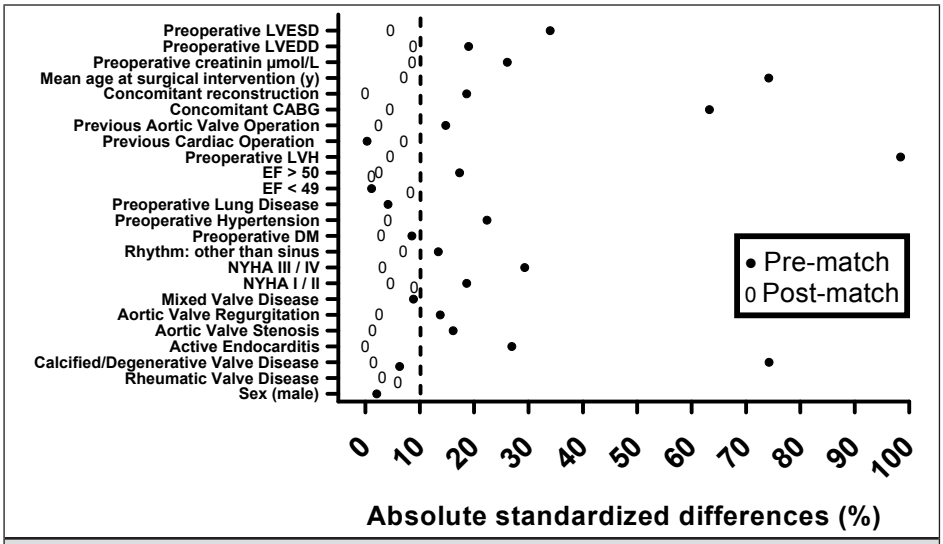


Figure 2. Love plots for absolute standardized differences for baseline covariates between patients with mechanical valve and patients with Ross procedure, before and after propensity score matching (DM, diabetes mellitus; EF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; MV, mitral valve; LVEDD, left ventricular end diastolic diameter).

lative survival is displayed in Figure 3. Age and gender matched late survival for young adult patients after aortic valve replacement was comparable to the general German population (96% vs. 95% at 8 years).

DISCUSSION

Our study results suggest that survival of mechanical valve patients, with highly specialized anticoagulation-self-management, is comparable to 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 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. Due to 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 warfarin (23, 24) and may require life style adjustments in this relatively young and active patient group. The clinical association between micro-emboli, generated by mechanical valves, and neurocognitive dysfunction is still a source of controversy (25, 26). Furthermore, compared to autograft valves, the hemodynamic performance of mechanical valves are less favorable (27), and mechanical valve noise can negatively affect patient's quality of life (28). The

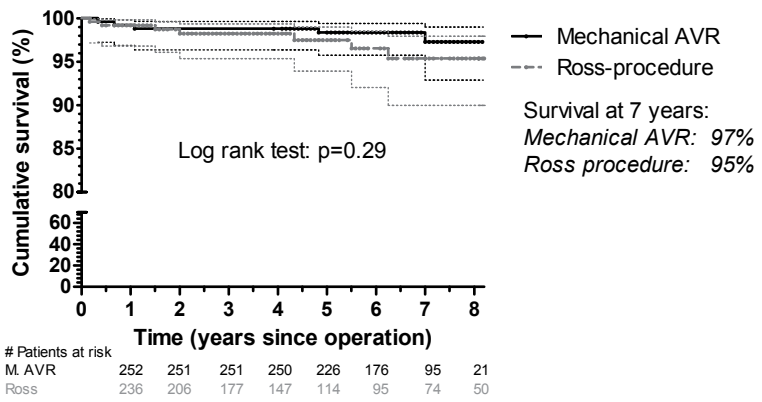


Figure 3. Kaplan-Meier plot for all-cause mortality by procedure (Ross procedure versus mechanical valve replacement with optimal self-management anticoagulation therapy).

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 advantage of the Ross procedure is the superior hemodynamic performance, low valve-related event occurrence rates and absent need for lifelong anticoagulation (29).

Surprisingly, we did not only find that there was no survival advantage for the Ross procedure over the use of mechanical prosthesis with optimal anticoagulation-self-management, but 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. In order to receive anticoagulation self-management 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 as we have only included patients between the age of 18 and 60 years. It should explicitly be stated 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 (LOR 2.90/year) (14). This suggests that the innovative postoperative management of patients in Bad Oeynhausen is extraordinary effective in terms of complication and survival rates.

Of note, in the mechanical prosthesis group none of the late deaths was valve-related while four (two valve related with AMI and stroke, two unknown but attributed as 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 mechanical prosthesis patients receive in Bad Oeynhausen has resulted in a minimization of thrombo-embolic and bleeding events and decreased valve-related mortality in comparison to 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). While in the cohort of Ross patients only those who experienced clinically manifest endocarditis were classified as having cured endocarditis (12% of the patients). Because

of this significant discrepancy in definition of previous cured endocarditis between the cohorts we decided to not include this variable in the analyses of present study.

Without using 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 were for example on average seven years younger, had more often aortic valve stenosis and had better physical condition compared to patients that received a mechanical prosthesis. Patients that received a mechanical prosthesis had more often diabetes, hypertension, and next to aortic valve disease also 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 out 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 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 mainly driven by patient characteristics, and prosthesis selection plays only a minor role, if any.

It implies that in patients who are good candidate 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, while others prefer the opposite. With the ongoing improvement in the current anticoagulant treatment and the introduction of novel anticoagulant drugs the rate of bleeding and thromboembolic events may further decrease (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 current study only apply to the first postoperative decade, and 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). Since the two treatment groups were treated in different centers a possible existence of 'center effect' cannot be ruled out. However,

the purpose of this study was to compare these two 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 since 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 generalisability of our study results requires further investigation.

Conclusions

In comparable patients there appears 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 the general population, possibly a result of highly specialized self-management anticoagulation treatment, and 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

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

REFERENCES

1. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. J Am Coll Cardiol 2000; 35(3):747-756.
2. Lytle BW, Cosgrove DM, Taylor PC, Goormastic M, Stewart RW, Golding LA, Gill CC, Loop FD. Primary isolated aortic valve replacement. Early and late results. J Thorac Cardiovasc Surg 1989; 97(5):675-694.
3. Ruel M, Kulik A, Lam BK, Rubens FD, Hendry PJ, Masters RG, Bedard P, Mesana TG. Long-term outcomes of valve replacement with modern prostheses in young adults. Eur J Cardiothorac Surg 2005; 27(3):425-433; discussion 433.
4. Takkenberg JJ, Klieverik LM, Schoof PH, van Suylen RJ, van Herwerden LA, Zondervan PE, Roos-Hesselink JW, Eijkemans MJ, Yacoub MH, Bogers AJ. The Ross procedure: a systematic review and meta-analysis. Circulation 2009; 119(2):222-228.
5. El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G, Takkenberg JJ, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet; 376(9740):524-531.
6. Klieverik LM, Noorlander M, Takkenberg JJ, Kappetein AP, Bekkers JA, van Herwerden LA, Bogers AJ. Outcome after aortic valve replacement in young adults: is patient profile more important than prosthesis type? J Heart Valve Dis 2006; 15(4):479-487; discussion 487.
7. Charitos EI, Hanke T, Stierle U, Robinson DR, Bogers AJ, Hemmer W, Bechtel M, Misfeld M, Gorski A, Boehm JO, Rein JG, Botha CA, Lange R, Hoerer J, Moritz A, Wahlers T, Franke UF, Breuer M, Ferrari-Kuehne K, Hetzer R, Huebler M, Ziemer G, Takkenberg JJ, Sievers HH. Autograft reinforcement to preserve autograft function after the ross procedure: a report from the german-dutch ross registry. Circulation 2009; 120(11 Suppl):S146-154.
8. Hanke T, Stierle U, Boehm JO, Botha CA, Matthias Bechtel JF, Erasmi A, Misfeld M, Hemmer W, Rein JG, Robinson DR, Lange R, Horer J, Moritz A, Ozaslan F, Wahlers T, Franke UF, Hetzer R, Hubler M, Ziemer G, Graf B, Ross DN, Sievers HH, German Ross R. Autograft regurgitation and aortic root dimensions after the Ross procedure: the German Ross Registry experience. Circulation 2007; 116(11 Suppl):I251-258.
9. Horer J, Hanke T, Stierle U, Takkenberg JJ, Bogers AJ, Hemmer W, Rein JG, Hetzer R, Hubler M, Robinson DR, Sievers HH, Lange R. Homograft performance in children after the Ross operation. Ann Thorac Surg 2009; 88(2):609-615.
10. Horer J, Hanke T, Stierle U, Takkenberg JJ, Bogers AJ, Hemmer W, Rein JG, Hetzer R, Hubler M, Robinson DR, Sievers HH, Lange R. Neoaortic root diameters and aortic regurgitation in children after the Ross operation. Ann Thorac Surg 2009; 88(2):594-600; discussion 600.
11. Koertke H, Minami K, Boethig D, Breymann T, Seifert D, Wagner O, Atmacha N, Krian A, Ennker J, Taborski U, Klovekorn WP, Moosdorf R, Saggau W, Koerfer R. INR self-management permits lower anticoagulation levels after mechanical heart valve replacement. Circulation 2003; 108 Suppl 1:II75-78.
12. Koerfer R, Reiss N, Koertke H. International normalized ratio patient self-management for mechanical valves: is it safe enough? Curr Opin Cardiol 2009; 24(2):130-135.
13. Kortke H, Korfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? Ann Thorac Surg 2001; 72(1):44-48.
14. Koertke H, Zittermann A, Tenderich G, Wagner O, El-Arousy M, Krian A, Ennker J, Taborski U, Klovekorn WP, Moosdorf R, Saggau W, Koerfer R. Low-dose oral anticoagulation in patients with

mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J 2007; 28(20):2479-2484.
15. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 2008; 85(4):1490-1495.
16. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
17. Rubin DB. Using propensity score to help design observational studies: application to the tobacco litigation. Health Services and Outcomes Research Methodology 2001;2:169–188.
18. Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg 2002; 123(1):8-15.
19. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J Thorac Cardiovasc Surg 2007; 134(5):1128-1135.
20. Sievers HH, Hanke T, Stierle U, Bechtel MF, Graf B, Robinson DR, Ross DN. A critical reappraisal of the Ross operation: renaissance of the subcoronary implantation technique? Circulation 2006; 114(1 Suppl):I504-511.
21. German Life Tables 2005 (Statistisches Bundesamt, Wiesbaden Germany; http://www.destatis.de).
22. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol 2001; 54(4):387-398.
23. Wong V, Cheng CH, Chan KC. Fetal and neonatal outcome of exposure to anticoagulants during pregnancy. Am J Med Genet 1993; 45(1):17-21.
24. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 2000; 160(2):191-196.
25. Skjelland M, Michelsen A, Brosstad F, Svennevig JL, Brucher R, Russell D. Solid cerebral microemboli and cerebrovascular symptoms in patients with prosthetic heart valves. Stroke 2008; 39(4):1159-1164.
26. Zimpfer D, Czerny M, Schuch P, Fakin R, Madl C, Wolner E, Grimm M. Long-term neurocognitive function after mechanical aortic valve replacement. Ann Thorac Surg 2006; 81(1):29-33.
27. Porter GF, Skillington PD, Bjorksten AR, Morgan JG, Yapanis AG, Grigg LE. Exercise hemodynamic performance of the pulmonary autograft following the Ross procedure. J Heart Valve Dis 1999; 8(5):516-521.
28. Blome-Eberwein SA, Mrowinski D, Hofmeister J, Hetzer R. Impact of mechanical heart valve prosthesis sound on patients' quality of life. Ann Thorac Surg 1996; 61(2):594-602.
29. Elkins RC, Knott-Craig CJ, Ward KE, McCue C, Lane MM. Pulmonary autograft in children: realized growth potential. Ann Thorac Surg 1994; 57(6):1387-1393; discussion 1393-1384.
30. Takkenberg JJ, Puvimanasinghe JP, van Herwerden LA, Steyerberg EW, Eijkemans MJ, Habbema JD, Bogers AJJC. Prognosis after aortic valve replacement with SJM bileaflet prostheses: Impact on outcome of varying thrombo-embolic and bleeding hazard. Eur Heart J Supplements. 2001;3 (Suppl Q):Q27-32.)
31. Tjang YS, van Hees Y, Korfer R, Grobbee DE, van der Heijden GJ. Predictors of mortality after aortic valve replacement. Eur J Cardiothorac Surg 2007; 32(3):469-474.

32. Toumpoulis IK, Chamogeorgakis TP, Angouras DC, Swistel DG, Anagnostopoulos CE, Rokkas CK. Independent predictors for early and long-term mortality after heart valve surgery. J Heart Valve Dis 2008; 17(5):548-556.
33. Hannan EL, Samadashvili Z, Lahey SJ, Smith CR, Culliford AT, Higgins RS, Gold JP, Jones RH. Aortic valve replacement for patients with severe aortic stenosis: risk factors and their impact on 30-month mortality. Ann Thorac Surg 2009; 87(6):1741-1749.
34. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361(12):1139-1151.

APPENDIX: PARTICIPATING CENTERS ROSS REGISTRY

University of Luebeck, Department of Cardiac and Thoracic Vascular Surgery, Luebeck, Germany, Registry Site
Thorsten Hanke, MD
J.F Matthias Bechtel, MD
Armin Gorski, MD

Erasmus University Medical Center, Department of Cardiothoracic Surgery, Rotterdam, The Netherlands
Ad JJC Bogers, MD PhD
Johanna JM Takkenberg, MD PhD

Sana Herzchirurgische Klinik, Stuttgart, Germany
Wolfgang Hemmer

Herzzentrum Bodensee, Konstanz, Germany
Cornelius A. Botha, MD

Robert-Bosch-Hospital, Stuttgart, Germany
Ulrich F. W. Franke, MD
Marc Albert, MD

University Wuerzburg, Department of Cardiothoracic Surgery, Wuerzburg, Germany
Armin Gorski, MD

University Heart Center Hamburg, Hamburg, Germany
Siegmar Sachweh, MD
Arlindo Riso, MD

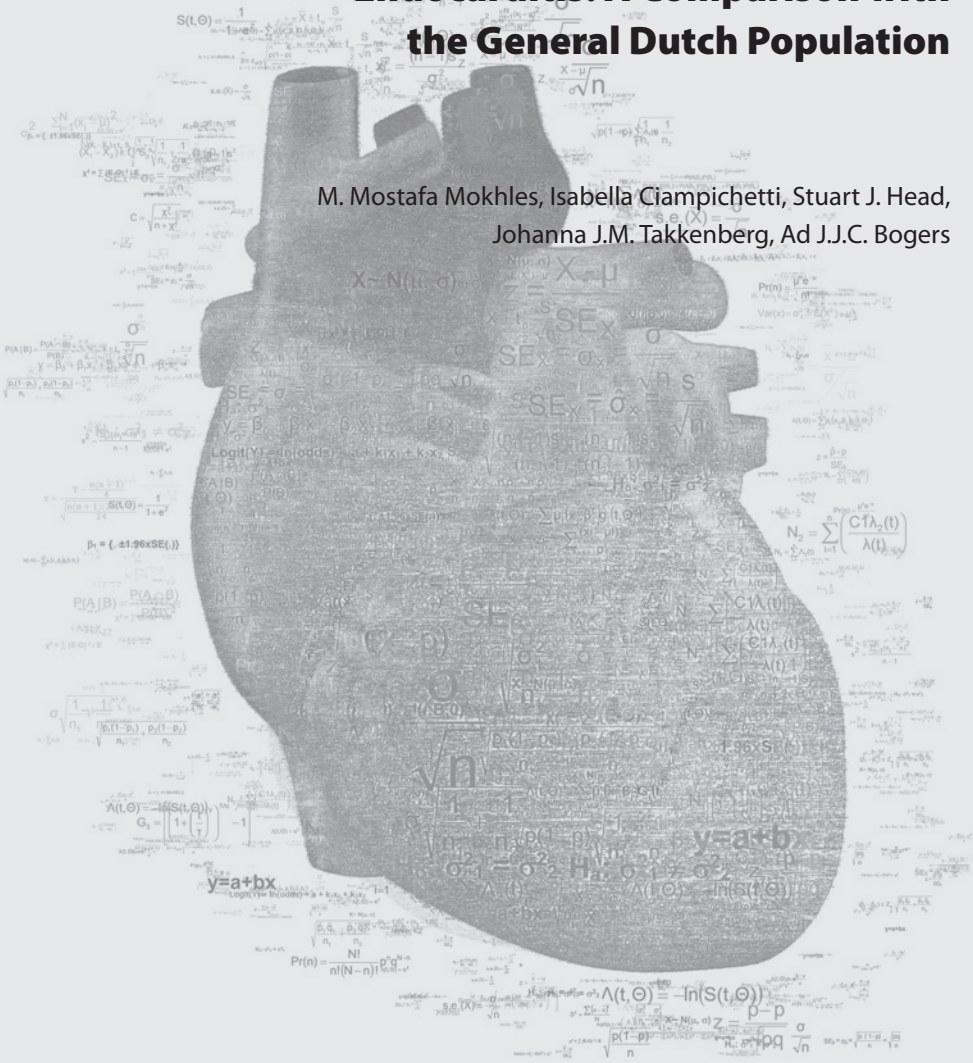
Johann-Wolfgang-Goethe-University, Frankfurt/Main, Germany
Anton Moritz, MD

German Heart Center, Berlin, Germany
Roland Hetzer, MD PhD

Chapter 11

Survival of Surgically Treated Infective Endocarditis: A Comparison with the General Dutch Population

M. Mostafa Mokhles, Isabella Ciampichetti, Stuart J. Head, Johanna J.M. Takkenberg, Ad J.J.C. Bogers



Ann Thorac Surg. 2011;91:1407-12

ABSTRACT

Background

Infective endocarditis remains associated with high in-hospital and long-term mortality. The outcome of surgically treated infective endocarditis patients has never been put into perspective by comparing it to the age- and gender matched general population.

The aim of present study was to evaluate the long-term mortality of surgically treated infective endocarditis patients in relation to the age- and gender matched general population.

Methods

A retrospective observational cohort study of all 138 consecutive surgically treated infective endocarditis patients (1998-2007) was conducted. Cumulative survival was analyzed using the Kaplan-Meier method. Comparison of patient survival with the general population was done using the Dutch population life table. Standardized mortality ratio was used to assess the degree of late deaths.

Results

Observed in-hospital mortality risk was 10.9%. Observed long-term survival was 85% (95% CI 78-90), 74% (95% CI 65-79), 71% (95% CI 62-78) after one, five and ten years, respectively. Age- and gender matched survival in the general population was 99%, 93% and 80% after a follow-up period of one, five and ten years, respectively. The standardized mortality ratio was 0.99 (95% confidence interval 0.67-1.31).

Conclusions

Although mortality of surgically treated infective endocarditis patients remains considerable during the immediate post-operative period, the mortality of hospital survivors is, with increasing follow-up time, comparable with the general population.

INTRODUCTION

During the past decades prognosis of infective endocarditis (IE) improved considerably. However, IE still remains a serious condition characterized by high morbidity and mortality. Overall in-hospital mortality has been reported in large series to range between 15% and 20% (1, 2).

Approximately fifty percent of the patients undergo surgery, which is often performed on an emergent or urgent basis (1, 3). It has been suggested that surgical intervention may contribute to a better patient outcome (4-6). The ESC guidelines recommend performing surgery in order to avoid progressive heart failure, irreversible structural damage caused by severe infection and to prevent systemic embolism (7).

Few investigators have reported long-term outcome of surgically treated IE patients, and most of these studies have relatively short follow-up time. It is generally known that (long-term) survival after IE is relatively low (2, 8). However, although the long-term outcome of patients with IE undergoing cardiac surgery with different types of valve substitutes has been studied before (9), the survival of these patients has never been put into perspective by comparing the survival rate of these patients with that of the matched general population.

The objective of the present study was to evaluate the long-term survival of patients with IE undergoing cardiac surgery. Furthermore, we aimed to objectify the survival of these patients by comparing it to the matched survival of the general population.

METHODS

Study population

From January 1998 to December 2007, a total of 191 patients were treated conservatively or surgically for IE at our institution. All consecutive adult patients (n=138), that underwent cardiac surgery for IE, were included. Only patients having definite IE according to the modified Duke criteria were included in the study (10). Erasmus Medical Centre is a tertiary-care university hospital and serves as a referral center for other local hospitals. Out of 138 patients surgically treated for infective endocarditis, 94 patients were referred for surgery by hospitals in the area. Urgent surgery was defined as surgery performed within <48 hours after admission in patients in whom the unfavorable clinical course necessitated surgical intervention (heart failure unresponsive to medication, vegetation or repeat embolism).

Data collection

Using standardized forms, all patient characteristics and perioperative data were collected by retrospectively reviewing the medical records and hospital database. The standard of care at our institution is to perform transesophageal echocardiogram in case a patient is suspected to have IE. Follow-up started at the day of admission in our centre. In March 2010, vital status of all patients was acquired from municipal civil registries with a response rate of 100%. The latter was used to assess the long-term survival in patients who are operated for IE. The causes of late death were obtained from the general practitioners.

Endocarditis

Endocarditis was considered active if patients underwent operations before completing a 6-week course of antibiotic treatment. Endocarditis was considered recently cured if clinical symptoms had resolved (no symptoms of IE), blood cultures were negative, antibiotic treatment was complete, and surgery of the valve was needed within one year after the diagnosis of IE.

Operative Technique

All operations were performed on cardiopulmonary bypass with moderate hypothermia. Circulatory arrest with deep hypothermia was needed in 3 patients because of ascending aorta and arch interventions. The root replacement technique was used in all patients who received a homograft. All surgical interventions were performed by the same team throughout the study period.

EuroSCORE

The EuroSCORE was calculated based on a set of pre-defined pre-operative risk factors (11, 12). The additive and logistic EuroSCORE models were applied to all patients undergoing cardiac surgery for IE.

Outcome

The main outcome of interest was late mortality. In-hospital mortality was defined as mortality during hospitalization. Outcome was reported according to the AATS/EACTS/STS guidelines (13).

Statistical Analyses

Continuous data are presented as mean (standard deviation; range). Categorical data are presented as proportions. To investigate independent risk factors for long-term mortality, the Cox proportional hazard model was used. Risk factors for multivariate model were selected with a backward stepwise method (required significance of $p>0.10$ for

elimination from the model and $p<0.05$ for retention in the model). Correlation between variables was assessed with Pearson- or Spearman correlation coefficient, whenever appropriate. In case of significant correlation, the clinically most important variable was chosen to be included in the model. Cumulative survival was analyzed using the Kaplan—Meier method. The Log-rank test was used to compare survival between different groups. Comparison of patient survival with the general age-matched population was done using the Dutch population life table (14). In order to assess, in an objective manner, whether mortality rate was indeed higher in our patient population (as compared to the general population) the standardized mortality ratio (SMR) method was applied (15). SMR represents a proportional comparison to the numbers of deaths that would have been expected if the population had been of a standard composition in terms of age and gender. An SMR over 1 indicates that the mortality rate is higher than in the general population.

Model discrimination (statistical accuracy) of the EuroSCORE was tested with the receiver operating characteristic (ROC) curve (16). Model calibration (statistical precision) of the EuroSCORE was determined with Hosmer–Lemeshow goodness-of-fit statistic (17). All statistical tests were two-sided, and tests with p-value of 0.05 or lower were considered significant. All statistical analyses were done using the Statistical Package for Social Sciences software, version 15.0 (SPSS, Chicago, Illinois). GraphPad Prism 5.00 for Windows (GraphPad Software, La Jolla, California) was used to obtain life tables and corresponding Kaplan-Meier survival curves.

RESULTS

Baseline characteristics of the 138 patients with definite IE are shown in Table 1. The vast majority concerned left sided heart valves (Table 2). The indications for performing an urgent operation (22 (15.9%) patients) were heart failure unresponsive to medication (N=15) and vegetation or repeat embolism (N=7). The mean time between (first) admission for IE and surgery was 17 days (range, 0-330 days).

Microbiologic characteristics

The causative microorganisms found in the cohort of patients are described in more detail in Table 3.

Echocardiographical findings

Echocardiography was performed in all patients with suspected IE. Table 2 summarizes the localization of IE and type of valve affected. In the majority of patients the valves of the left side of the heart (n=134) were affected.

Table 1. Baseline Characteristics and Microbiologic Etiology of 138 Patients Undergoing Cardiac Surgery for Infective Endocarditis.

Baseline characteristics	Patients, No. (%)
Mean age ± SD (years)	54.4 (14.2)
Gender	
Males	106 (76.8)
Females	32 (23.2)
Hypertension	34 (24.6)
Diabetes mellitus	12 (8.7)
Myocardial infarction	17 (12.3)
Extracardiac arteriopathy	7 (5.1)
Aorta ascendens aneurysm	3 (2.2)
CVA	19 (13.8)
Recent CVA	6 (4.4)
TIA	6 (4.3)
Renal failure	10 (7.2)
Hemodialysis dependent	4 (2.9)
COPD	10 (7.2)
Chronic immunosuppressive therapy	1 (0.7)
Cancer	10 (7.2)
Rheumatoid arthritis	2 (1.4)
Pacemaker/ICD	3 (2.2)
Congenital heart disease	16 (11.6)
Native valve predisposition[a]	28 (20.3)
Previous endocarditis	18 (13.0)
Intravenous drug abuse	1 (0.7)
Dental procedures <60 days to admission	18 (13.0)
Other invasive procedures <60 days to admission	4 (2.9)
Central venous catheter as suspected cause	2 (1.4)
Prior valve surgery or CABG[bc]	38 (27.5)
Prior Valve surgery	31 (22.5)
Prior CABG	7 (5.1)
Prior PCI	5 (3.6)
Fever, temperature >38°C	62 (44.9)
Left ventricular function ≤ 49%	39 (28.2)
Elevated ESR	80 (58.0)
Elevated C-reactive protein	97 (70.3)
Active endocarditis at the time of surgery	103 (74.6)
Urgent operation	22 (15.9)

CABG, Coronary artery bypass grafting; COPD, Chronic Obstructive Pulmonary Disease; CVA, Cerebro Vasculair Accident; ESR, Erythrocyte Sedimentation Rate; HIV, Human Immunodeficiency Virus; ICD, Implantable Cardioverter Defibrillator; PCI, Percutaneous coronary intervention; TIA, Transient Ischaemic Attack; [a]prior valve regurgitation and/or stenosis; [b]Some patient had a history of both valve surgery and CABG. [c]In the group of patients with prior valve surgery, 29 were replacements and 2 were repairs

Type of surgery

In 132 patients the following valve procedures were performed: a single valve was replaced in 108 patients, which was combined in nine patients with the reconstruction of a second valve that was also affected. In another 10 patients two valves were replaced and in 14 patients the affected valve was reconstructed. In total, 72 mechanical valves, 41 homografts and 15 bioprosthetic valves were implanted (some patients received a combination of these valves during a double valve replacement procedure). In 6 patients no valve procedure was initiated (see Complications and outcome section). Coronary artery bypass graft surgery was performed as a concomitant procedure in 13 patients.

Complications and outcome

The main indications for surgery were a large persistent vegetation (34.8%), severe valve regurgitation (27.5%), heart failure (24.6%), abscess formation (8.0%) and systemic

Table 2. Type and frequency of affected valves in 138 Patients Undergoing Cardiac Surgery for Infective Endocarditis.

	Main affected valve				
	Aortic valve[a]	Mitral valve[b]	Pulmonary valve	Tricuspid valve	**Total**
Native valve	66 (47.8%)	41 (29.7%)	1 (0.7%)	2 (1.4%)	110 (79.7%)
Mechanical valve	13 (9.4%)	9 (6.5%)	0 (0%)	0 (0.0%)	22 (15.9%)
Homograft	2 (1.4%)	0 (0%)	1 (0.7%)	0 (0%)	3 (2.2%)
Bioprosthesis	2 (1.4%)	1 (0.7%)	0 (0%)	0 (0%)	3 (2.2%)
Total	83^ (60.1%)	51 (37.0%)	2 (1.4%)	2 (1.4%)	138 (100.0%)

[a]18 patients with IE of mainly aortic valve had also concomitant mitral valve IE which is not taken into account in this table; [b]2 patients with IE of mainly mitral valve had also concomitant aortic valve IE which is not taken into account in this table

Table 3. Type of Microorganisms found in 138 Patients with Definite Endocarditis Undergoing Cardiac Surgery.

Cause of Endocarditis	**No. (%)**
Viridans group streptococci	34 (24.6)
Other streptococci	33 (23.9)
S. aureus	27 (19.6)
Coagulase-negative staphylococci	15 (10.9)
Enterococcus species	10 (7.2)
G. morbillorum	3 (2.2)
P. acnes	2 (1.4)
Negative culture findings	8 (5.8)
Other[a]	6 (4.4)
Total	**138 (100%)**

[a]Includes 3 patients with missing data

embolization (4.3%). Eight (5.8%) patients developed atrioventricular block post operatively, and 10 patients needed a rethoracotomy (mainly due to persistent blood loss).

Fifteen patients (10.9%) died during a median admission of 23 days (range: 0-34). Six of these patients died during surgery. Of these six patients, three patients died because severe tissue damage prevented valve replacement, two patients died due heart failure and one patient died due bradycardia and cardiogenic shock during the initiation of the operation. Causes of post-operative in-hospital death were congestive heart failure or cardiogenic shock in three patients. Progressive hemodynamic instability in two patients. Electromechanical dissociation, basilar artery thrombosis, and hypoxia combined with arrhythmia were other causes for death. One patient died due permanent vegetative state with sepsis. All patients that died during hospitalization had active endocarditis at the time of operation. The hospital mortality for active IE was, therefore, 14.6% (15/103). The hospital mortality for treated IE was 0%. In-hospital mortality was similar between patients with prosthetic valve IE and patients with native valve IE (p=0.21).

During the follow-up a total of seven patients underwent a valve reoperation. Two of these patients were operated within 1 year after the initial operation for IE. Six patients underwent a reoperation for aortic valve replacement and one patient underwent a reoperation for mitral valve replacement. All re-operations were due non-IE valvular causes.

Predictive power of EuroSCORE

The observed hospital mortality in our patient population was 10.9%. The additive EuroSCORE predicted a post-operative in-hospital mortality risk of 8.0% (range 2% - 18%). The logistic EuroScore predicted a mortality risk of 17.4% (range 1.5% - 83.8%). The AUC for the additive model was 0.85 (95% CI [CI] 0.76-0.95). The AUC for the logistic model was 0.84 (95% CI 0.75-0.94) (Figure 1). Calibration of the model resulted in a p-value of 0.80 for the additive model and a p-value of 0.12 for the logistic model.

Late survival after IE

There were 123 (89.1%) hospital survivors. Median follow-up was 6.8 years and 821 patient-years accumulated. Twenty-two patients died during the follow-up. Causes of late death were various type of malignancies in five patients, congestive heart failure in three patients, multiple organ failure in two patients and renal failure in two patients. Sepsis, acute heart failure after cardiac transplantation, peritonitis, intra-cerebral bleeding in a patient using anticoagulant medication for a mechanical valve were other causes for death, each in one patient. There were two sudden, unexplained, unexpected deaths without further clinical data or autopsy. For four patients the cause of death could not be retrieved. The overall survival after IE was 85% (95% CI 78-90) at 1 year, 74% (95% CI 65-79) at 5 years and 71% (95% CI 62-78) at 10 years (Figure 2).

Predictors of late mortality

Patients presenting with S. aureus or coagulase-negative staphylococci IE had lower survival compared to patients presenting with other microbiological organisms (HR 3.26, 95% CI 1.70-6.22, p<0.001). An urgent operation indication (OR 2.74, 95% CI 1.07-7.00) was also associated with a higher long-term mortality rate in the univariate model. Patients with IE of a prosthetic valve had a long-term survival comparable to patients with native valve endocarditis (p=0.61).

Multivariate Cox proportional hazards model showed that only cancer (at the time of IE diagnosis) was associated with higher mortality during long-term follow up (HR 3.87, 95% CI 1.38-10.84).

Survival comparison

Age- and gender matched survival in the general population was 99%, 93% and 80% after a follow-up period of one, five and ten years, respectively. Compared to age- and gender matched Dutch population norms, the survival of patients with IE undergoing cardiac surgery was significantly impaired. After 10 years of follow-up only 71% of the patients with IE were still alive while the survival rate in the age- and gender matched general population was 80% (Figure 3A).

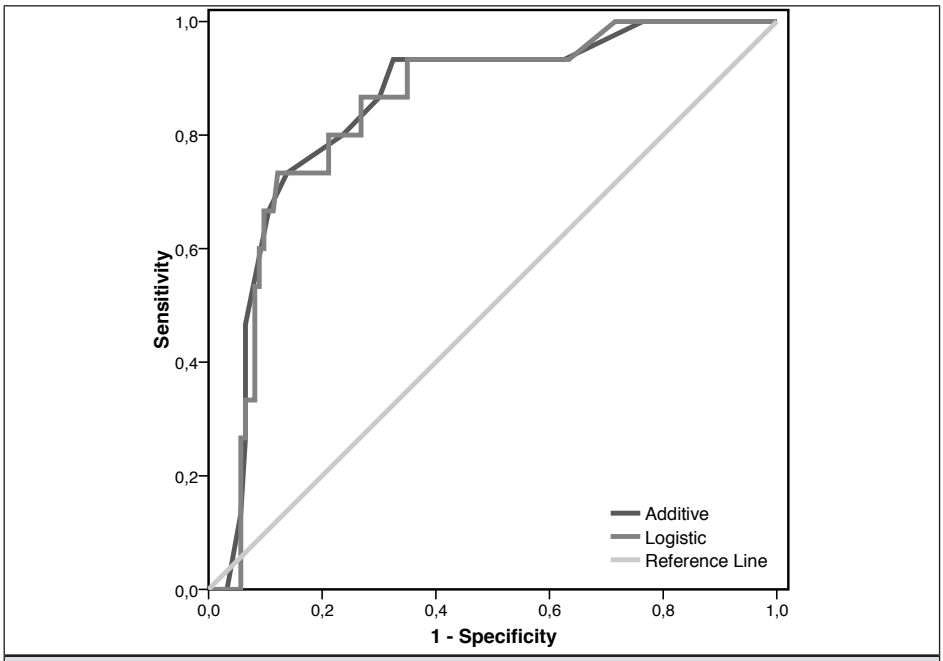


Figure 1. Receiver operating characteristic curves for the additive (area = 0.85) and logistic (area = 0.84) model.

After exclusion of in-hospital mortality, the mortality hazard was 5% in the first year for patients with IE undergoing cardiac surgery. Thereafter, the annualized mortality hazard was 2.3%/year. The survival rate of our patient population was comparable with the survival rate of age- and gender matched general population after 10 years of follow-up (Figure 3B).

These results did not changed substantially when we only examined the survival of patients with active IE at the time of operation. After excluding in-hospital mortality, the survival rate of patients with active IE at the time of operation was 77% after 10 years of follow-up, while the survival rate in the age- and gender matched general population was 79% after the same period of follow-up time.

During 821 patient-years of follow-up 37 deaths were documented. According to the age- and gender matched general Dutch survival rates the expected number of deaths should be 37.5. The assessed standardized mortality ratio (SMR) was 0.99 (95% CI 0.67-1.31).

COMMENT

Mortality of surgically treated IE patients is considerable during the immediate post-operative period. Nevertheless, our study shows that patients who survive this immediate period have a relatively low late mortality rate. Although hospital survivors still had a higher mortality hazard in the first year (18), the annualized mortality hazard after the first year decreased by ~50%. With increasing follow-up time, the survival of hospital survivors becomes comparable with that of the general population. Overall, the late

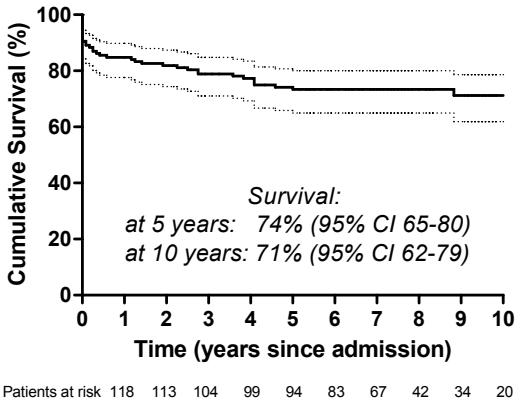


Figure 2. Long-Term survival of patients undergoing cardiac surgery for infective endocarditis.

mortality rate was comparable to the general population in the first decade after cardiac surgery.

Survival after valve surgery for IE

Cumulative long-term survival in the present study was 74% and 71% after respectively five and ten years. These survival rates are higher than those reported by other investigators (19, 20) and higher than those reported by our institution two decades ago (21). Advancement in the medical treatment, diagnostic tools, development of guidelines, and better timing of surgery may have contributed to these improved results. It should, however, be noted that direct comparison of different studies is difficult because of the variation in the characteristics of patient populations. Our own institutional policy for operating on patients with IE follows the ESC guidelines (7).

Compared to the general Dutch population, the survival of patients with IE undergoing cardiac surgery was significantly lower. However, the discrepancy in survival rates between our patient population and the general population was mainly due in-hospital mortality and mortality during the first year of follow-up. Patients who survived the

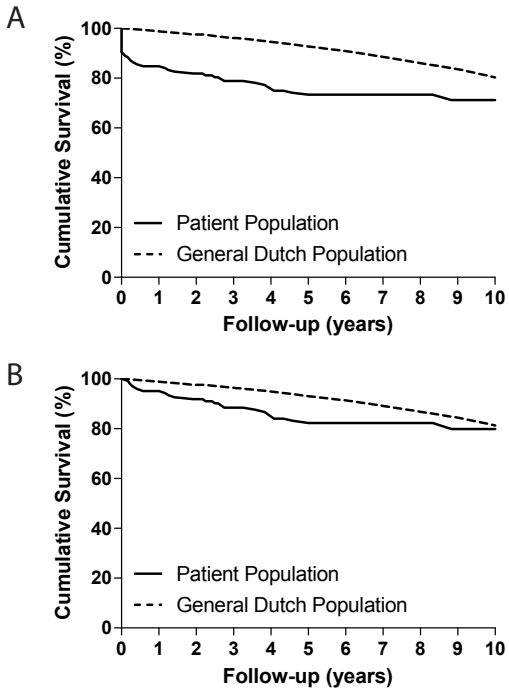


Figure 3. Survival comparison of patients undergoing cardiac surgery for infective endocarditis with general Dutch population; A) KM survival including in-hospital mortality, B) KM survival curves without in-hospital mortality.

immediate period after the surgical procedure had a low late mortality rate in the first postoperative decade, comparable to the age- and gender matched general population (19, 22). Some considerations have to be taken into account when interpreting this observation. Several investigators have reported that early surgery can be of importance in improving survival in patients with definite IE (23, 24). Therefore, the results of present study do not apply to the total cohort of patients with IE. The mortality rate may still be higher in the group of patients who were only treated medically and did not receive a combination of medical and surgical treatment.

EuroSCORE risk model

While the original EuroSCORE seems to be no longer able to accurately predict the risk of in-hospital mortality for the overall group of patients undergoing cardiac surgery, the results of present study indicate that EuroSCORE might be very well of use in more complex pathologies like IE. This finding is in accordance with a previous publication from Mestres and colleagues (25). Both statistical accuracy (discrimination) and statistical precision (calibration) were good in our series of patients. However, the predictive ability of additive EuroSCORE was better than the predictive ability of logistic EuroSCORE in our series. The logistic EuroSCORE overestimated the observed in-hospital mortality. This was reflected by the observation that the calibration of additive EuroSCORE (HL p=0.80) was far better than the calibration of logistic EuroSCORE (HL p=0.12).

Limitations

The present study has several limitations. First, it is a retrospective observational study from a single center. Second, the results are based on patients with IE who were selected to undergo surgery and, therefore, could be subject to selection bias. Furthermore, as with many other statistics, the standardized mortality ratio has to be interpreted with full consciousness of the possible effects of random variation. It should also be noted that the size of our patient population is modest and may not be sufficient to accurately assess the predictive ability of the EuroSCORE. Future studies with larger sample size are needed to confirm the results of present study, and to assess whether our observations can be confirmed in other institutions.

Conclusions

In conclusion, although hospital mortality is considerable for patients who are surgically treated for IE in our institution, those patients who survive the immediate postoperative period after the diagnosis of IE have a survival rate similar to the age- and gender matched general population. Furthermore, both the additive EuroSCORE model and the logistic EuroSCORE model were able to accurately predict the risk of in-hospital mortality in surgically treated IE patients.

REFERENCES

1. Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, Casalta JP, Danchin N, Delahaye F, Etienne J, Le Moing V, Leport C, Mainardi JL, Ruimy R, Vandenesch F. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA 2002; 288(1):75-81.
2. Cabell CH, Jollis JG, Peterson GE, Corey GR, Anderson DJ, Sexton DJ, Woods CW, Reller LB, Ryan T, Fowler VG, Jr. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 2002; 162(1):90-94.
3. Tornos P, Iung B, Permanyer-Miralda G, Baron G, Delahaye F, Gohlke-Barwolf C, Butchart EG, Ravaud P, Vahanian A. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 2005; 91(5):571-575.
4. Croft CH, Woodward W, Elliott A, Commerford PJ, Barnard CN, Beck W. Analysis of surgical versus medical therapy in active complicated native valve infective endocarditis. Am J Cardiol 1983; 51(10):1650-1655.
5. Vikram HR, Buenconsejo J, Hasbun R, Quagliarello VJ. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. JAMA 2003; 290(24):3207-3214.
6. Lalani T, Cabell CH, Benjamin DK, Lasca O, Naber C, Fowler VG, Jr., Corey GR, Chu VH, Fenely M, Pachirat O, Tan RS, Watkin R, Ionac A, Moreno A, Mestres CA, Casabe J, Chipigina N, Eisen DP, Spelman D, Delahaye F, Peterson G, Olaison L, Wang A. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation; 121(8):1005-1013.
7. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Muller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009; 30(19):2369-2413.
8. Benn M, Hagelskjaer LH, Tvede M. Infective endocarditis, 1984 through 1993: a clinical and microbiological survey. J Intern Med 1997; 242(1):15-22.
9. Nguyen DT, Delahaye F, Obadia JF, Duval X, Selton-Suty C, Carteaux JP, Hoen B, Alla F. Aortic valve replacement for active infective endocarditis: 5-year survival comparison of bioprostheses, homografts and mechanical prostheses. Eur J Cardiothorac Surg; 37(5):1025-1032.
10. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30(4):633-638.
11. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999; 16(1):9-13.
12. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003; 24(9):881-882.
13. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 2008; 85(4):1490-1495.

14. Dutch Life Tables 2009 (Centraal Bureau voor de Statitiek, The Hague, The Netherlands; http://statline.cbs.nl).
15. Curtin LR, Klein RJ. Direct standardization (age-adjusted death rates). Healthy People 2000 Stat Notes 1995; (6):1-10.
16. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143(1):29-36.
17. Lemeshow S, Hosmer DW, Jr. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982; 115(1):92-106.
18. Blackstone EH, Kirklin JW. Death and other time-related events after valve replacement. Circulation 1985; 72(4):753-767.
19. Netzer RO, Altwegg SC, Zollinger E, Tauber M, Carrel T, Seiler C. Infective endocarditis: determinants of long term outcome. Heart 2002; 88(1):61-66.
20. Klieverik LM, Yacoub MH, Edwards S, Bekkers JA, Roos-Hesselink JW, Kappetein AP, Takkenberg JJ, Bogers AJ. Surgical treatment of active native aortic valve endocarditis with allografts and mechanical prostheses. Ann Thorac Surg 2009; 88(6):1814-1821.
21. Bogers AJ, van Vreeswijk H, Verbaan CJ, Kappetein AP, van Herwerden LA, Mochtar B, Bos E. Early surgery for active infective endocarditis improves early and late results. Thorac Cardiovasc Surg 1991; 39(5):284-288.
22. Tornos MP, Permanyer-Miralda G, Olona M, Gil M, Galve E, Almirante B, Soler-Soler J. Long-term complications of native valve infective endocarditis in non-addicts. A 15-year follow-up study. Ann Intern Med 1992; 117(7):567-572.
23. Bishara J, Leibovici L, Gartman-Israel D, Sagie A, Kazakov A, Miroshnik E, Ashkenazi S, Pitlik S. Long-term outcome of infective endocarditis: the impact of early surgical intervention. Clin Infect Dis 2001; 33(10):1636-1643.
24. Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG, Jr., Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, Chambers ST, Chu VH, Falco V, Holland DJ, Jones P, Klein JL, Raymond NJ, Read KM, Tripodi MF, Utili R, Wang A, Woods CW, Cabell CH. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009; 169(5):463-473.
25. Mestres CA, Castro MA, Bernabeu E, Josa M, Cartana R, Pomar JL, Miro JM, Mulet J. Preoperative risk stratification in infective endocarditis. Does the EuroSCORE model work? Preliminary results. Eur J Cardiothorac Surg 2007; 32(2):281-285.

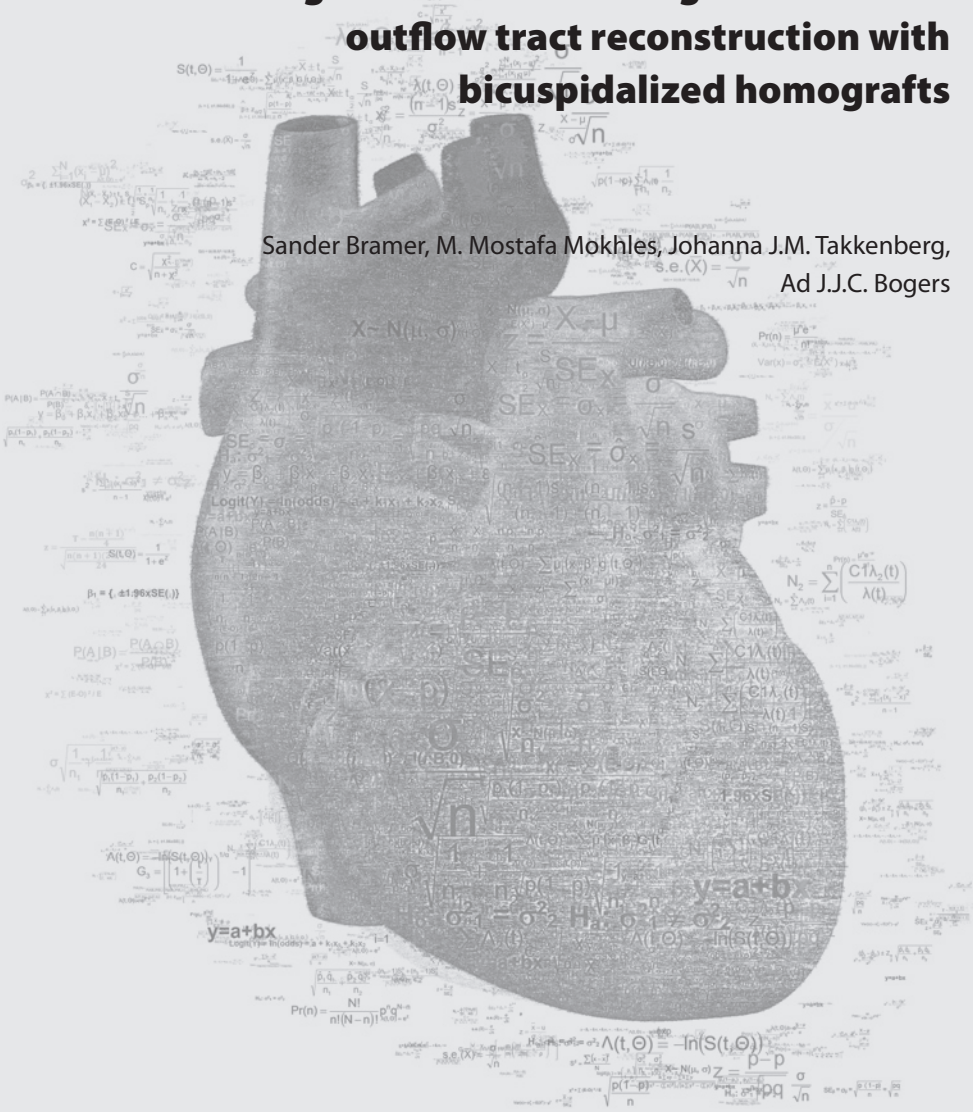
LIST OF ABBREVIATIONS

AATS	American Association for Thoracic Surgery
CI	Confidence Interval
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
HL	Hosmer-Lemeshow
IE	Infective Endocarditis
KM	Kaplan-Meier
ROC	Receiver Operating Characteristic
SMR	Standardized Mortality Ratio
STS	Society of Thoracic Surgeons

Chapter 12

Long-term outcome of right ventricular outflow tract reconstruction with bicuspidalized homografts

Sander Bramer, M. Mostafa Mokhles, Johanna J.M. Takkenberg, Ad J.J.C. Bogers



Eur J Cardiothorac Surg. 2011;40:1392-5

ABSTRACT

Objectives

Given the shortage of small-sized cryopreserved homografts for right ventricle (RV) to pulmonary artery (PA) reconstructions, more readily available larger-sized homografts can be used after size reduction by bicuspidalization. The aim of our study was to determine and compare function over time of standard and bicuspidalized homografts in infants younger than 12 months, including patients with a Ross or extended Ross procedure.

Methods

All consecutives infants under the age of 1 year, who underwent a surgical procedure in which a homograft was placed in the RV-PA position between January 1994 and April 2009, were included. Prospectively collected data from serial, standardized echocardiography from all patients were extracted from the database, and hospital records were retrospectively reviewed.

Results

A total of 40 infants had a valved homograft conduit placed in the RV-PA position. In 20 of those patients, a bicuspidalized homograft was used. Twelve patients underwent a Ross procedure, of whom seven had an additional Konno-type aortic annulus enlargement. Median follow-up was 146 months (interquartile range (IQR), 117-170; total patient years: 178) in the group with standard use of the homograft and 95 months (IQR, 11-104; total patient years: 78) in the group with bicuspidalized conduits. Freedom from re-intervention (re-operation or percutaneous) was not different in the standard and bicuspidalized groups for all and Ross or Konno-Ross procedures (Tarone-Ware, p=0.65 and p=0.47, respectively). Consecutive echocardiographic maximum velocities in the right ventricular outflow tract were similar in the standard and bicuspidalized groups.

Conclusions

When proper sized cryopreserved homografts for placement in the RV-PA position in Ross, Konno-Ross, and other procedures in infants under the age of 1 year are not readily available, bicuspidalized homografts provide an acceptable alternative.

INTRODUCTION

Cryopreserved aortic and pulmonary valve homografts are widely used as a conduit in right ventricle (RV) to pulmonary artery (PA) reconstructions for different congenital anomalies (1). Given the shortage of small-sized conduits for these reconstructions in young infants, more readily available larger-sized grafts can be used after size reduction by bicuspidalization (2, 3). The long-term functionality of bicuspidalized grafts in the RV outflow tract (RVOT) has been described by few groups (4-7). The results in children with Ross or extended Ross (Konno) procedures have only been reported anecdotally (4, 7).

The aim of this study was to determine and compare long term allograft function after surgical procedures in which a standard or bicuspidalized homograft was used in the RV-PA position in infants younger than 12 months, including patients with a Ross or extended Ross procedure.

MATERIAL AND METHODS

Patient population

All consecutives infants under the age of 1 year, who underwent a surgical procedure in which a homograft was placed in the RV-PA position at the Erasmus University Medical Center in Rotterdam, the Netherlands, between January 1994 and April 2009, were included. Since 1987, serial, standardized echocardiography has been carried out on all patients, who received human tissue valves (8, 9). The prospective echocardiographic database was frozen on July 2009, and echocardiographic data on all studied patients was extracted. Hospital records were retrospectively reviewed. The Dutch civil registry was consulted for survival data of the patients. Our local ethical committee approved of the study and waived the need for informed consent.

Procedure

Two attending surgeons performed all the procedures. The conduits were bicuspidalized by excising a longitudinal strip containing one of the three leaflets, and consecutively reapproximating the free edges. The homograft was proximally implanted on an autologous pericardial patch placed in the defect after ventriculotomy in the RVOT, and distally connected to the PA. The underlying pathology of the infant determined the other steps in the procedure.

Timing of (re-)intervention was determined in a weekly scheduled heart team meeting between the (congenital) cardiologists and cardiac surgeons during which all cases were discussed. The decision to whether operate or not was based on contemporary clinical practice.

Definitions

Early mortality was defined as death within 30 days after the operation. In-hospital death was defined as early mortality or mortality within the initial hospitalization. The cause of death was registered and reported according to the guidelines for reporting mortality and morbidity after cardiac valve interventions (10).

Statistical analyses

Continuous data are presented as mean with standard deviation or median with range or interquartile range (25^{th}-75^{th} percentile), and comparison between groups was done using the unpaired t-test. Categorical data are presented as proportions, and comparison was done using the chi-square test or the Fisher's exact test, where appropriate. All tests were two-sided, with an α-level of 0.05. Gradients over the RVOT were calculated from the maximum velocity (4 times the square of the maximum velocity (Vmax). Vmax in the RVOT was plotted against days after the initial operation for both patients with bicuspidalized and non-bicuspidalized homografts in two different panels. To assess the possible association between bicuspidalization and Vmax over time, a linear mixed model for longitudinal data was constructed with random effects for slopes. This model has proven in the past to provide an appropriate fit for the type of data that we have analyzed in the present study (11). Based on the linear mixed model for both groups, a mean regression line was calculated and plotted. Freedom from re-intervention and freedom from death were calculated using the Kaplan-Meier method. The Tarone-Ware test was used to compare Kaplan-Meier curves between surgical techniques (correcting for the differences in follow-up time between the groups). All statistical tests were two-sided, and tests with p value of 0.05 or lower were considered significant. All statistical analyses were done using Statistical Package for Social Sciences (SPSS) for Windows version 15 (SPSS Inc.; Chicago, IL, USA).

RESULTS

Population and procedures

In the study period, a total of 40 infants under the age of 1 year had a valved homograft conduit placed in the RV- position. In 20 of those patients, a bicuspidalized homograft was used; the other 20 patients received a non-bicuspidalized homograft. The preoperative diagnoses are shown in Table 1.

Patient demographics and intra-operative data are shown in Table 2. The use of pulmonary grafts was more frequent in the bicuspidalized group. No bicuspidalized allografts were implanted before the year 2000. Other described intraoperative data and demographics were similar in both groups.

The mean diameter of the bicuspidalized conduits was 14.6 mm (median 14 mm, range 14-16 mm). The conduits were constructed from homografts with a mean diameter of 22.6 mm (median 23 mm, range 19-24 mm). The bicuspidalized grafts were relatively undersized with an indexed size of 54 compared with 65 mm m^{-2} in the non-bicuspidalized group (p=0.030).

Follow up

Early death occurred in nine patients. One patient died during initial hospital stay 125 days post-operatively. There were five in-hospital deaths in both groups (p=1.00). No deaths were directly related to homograft dysfunction. Follow-up was complete in 29 of 30 survivors. One patient was lost to follow-up due to emigration. Median follow-up was 146 months (IQR, 117-170; total patient years: 178) in the group with standard use

Table 1. Preoperative Diagnosis.

	Type of Homograft Conduit	
	Bicuspidalized	**Standard**
Truncus Arteriosis	6	10
Aortic Stenosis/Regurgitation	10	2
Tetralogy of Fallot/DORV	2	3
Pulmonary Atresia with VSD	2	2
Aortic Atresia with VSD	0	3

DORV, double outlet right ventricle; VSD, ventricle septum defect

Table 2. Patient Demografics and Intraoperative Data.

	Type of Homograft Conduit		
	Bicuspid	**Standard**	
	n=20	**n=20**	**P Value**
Male : Female	14 : 6	13 : 7	0.74
Age, days (range)	144 (20-347)	104 (7-333)	0.24
Weigth, kg	5.3 ± 2.1	4.2 ± 1.8	0.08
BSA, m^2	0.29 ± 0.08	0.25 ± 0.07	0.067
CPB time, minutes	153 ± 49	185 ± 100	0.21
Cross-clamp time, minutes	104 ± 33	100 ± 26	0.69
Type of Homograft			
Pulmonary : Aortic	19 : 1	8 : 12	<0.001
Allograft size, mm (range)	14 (14-16)	16 (13-19)	0.16
Indexed allograft size, mm/m^2 (range)	54 (35-86)	65 (42-94)	0.030
Operation before the year 2000	0	18	<0.001

BSA, body surface area; CPB, cardio-pulmonary bypass

of the homograft and 95 months (IQR, 11-104; total patient years: 78) in the group with bicuspidalized conduits. No late deaths occurred.

A total of 214 serial echocardiographic measurements of homograft valve function were available in 30 patients (mean seven echocardiographic measurements per patient; range 1-13). Initial overall Vmax was 1.7 m s^{-1} (standard error (SE) 0.13) and overall Vmax progression was 0.21 m s^{-1} $year^{-1}$ (SE 0.02). The linear mixed model fitted best and was

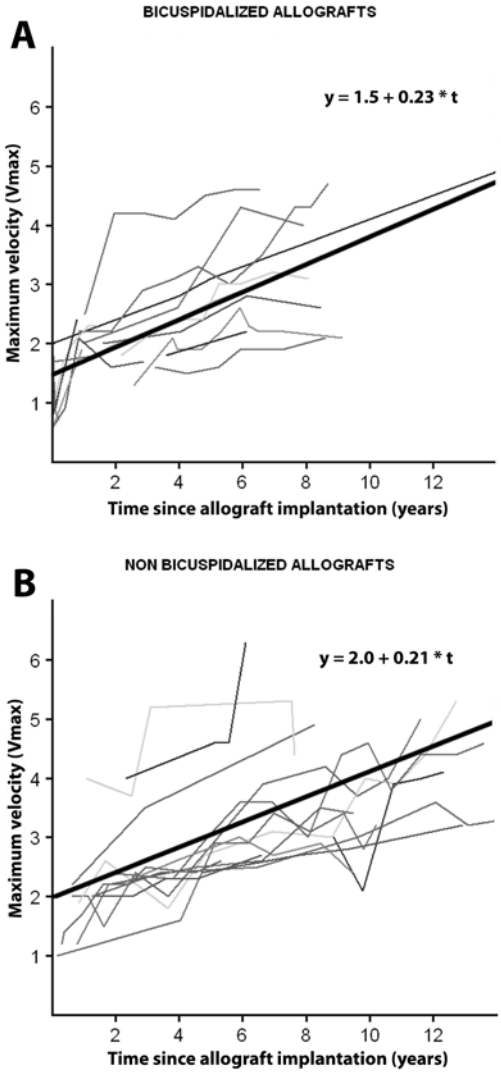


Figure 1. Maximum velocity (Vmax) at echocardiographic examinations in patients with bicuspidalized homografts (panel a) and standard (non bicuspidalized) homografts (panel b).

used. There was a trend toward a smaller initial Vmax in bicuspidalized patients versus non-bicuspidalized patients (1.5 vs 2.0 m s^{-1}, respectively; p=0.07) while there was no significant difference in annual progression rates (0.23 vs 0.21 m s^{-1} $year^{-1}$, respectively; p = 0.61). Echocardiographic Vmax in the RVOT for each consecutive investigation for patients with non-bicuspidalized and bicuspidalized homografts is shown in Figure 1(A) and (B). No significant difference between both groups could be found.

Two patients in the bicuspidalized group versus six patients in the standard group underwent a re-operation or percutaneous balloon dilatation for homograft failure due to stenosis. No endocarditis occurred. Freedom from reintervention was not different between the standard and bicuspidalized group (Tarone-Ware test, p=0.653) (Figure 2).

Ross group

Twelve patients underwent a Ross procedure (12), of whom seven had an additional Konno-type aortic annulus enlargement. Ten out of 12 infants received a bicuspidalized prosthesis. One of the patients from the Ross group died in hospital (8%). This patient concomitantly underwent a mitral valve replacement because of severe mitral valve re-

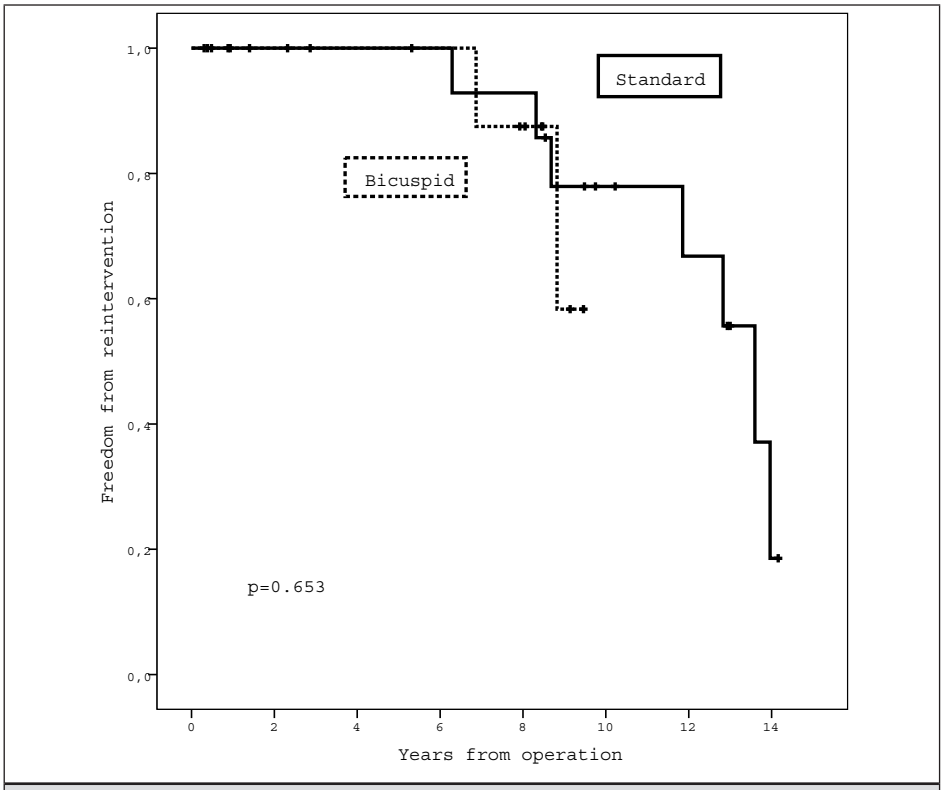


Figure 2. Freedom from reintervention for graft failure.

gurgitation and stenosis. This was a redo procedure, after a previously performed mitral valve repair. Median follow-up in the Ross group was 80 months (IQR, 9-109 months). Two of the survivors (18%) were re-operated because of homograft failure at 82 and 106 months after the first procedure. Both patients had a bicuspidalized conduit.

DISCUSSION

In most institutions, cryopreserved homografts are the first choice for implantation in the RV-PA position in many surgical procedures for congenital heart defects. Shortage of small-sized homografts for implantation in infants has initiated the search for more readily available alternatives, such as bovine jugular vein grafts (13-16) and bicuspidalisation of homografts (2, 3). Especially infants, with inherent small diameter of the conduit, are prone to conduit stenosis (17), eventually necessitating re-intervention (18). To our knowledge, the performance of bicuspidalized homografts in infants <1 year in whom a Ross or extended Ross procedure is performed is only reported anecdotally.

The results of present study show that stenosis in bicuspidalized homografts in the RV-PA position in infants younger than a year does not progress faster than in non-bicuspidalized homografts. In addition, no difference could be found in freedom from re-intervention between these groups of patients.

Heterogeneity in confounding factors necessitates careful interpretation of the data: more pulmonary graft use and more Ross patients in the bicuspidalized group could favor the results in that group, whereas, on the other hand, relative undersized conduits could be a potential disadvantage in the same group.

Results of the use of bicuspidalized valves in the RV-PA position in infants <1 year are described by few other groups. McMullan et al. (5) show no difference in freedom from reintervention in 13 infants with bicuspidalized and 21 infants with standard used homografts in surgical repair for truncus arteriosus with a median follow-up of 66 months. Koirala et al. (4) describe a group of 21 children up to 2.5 years of age compared with a matched group of children aged up to 5.1 years in which the use of a bicuspidalized graft does not have a worse freedom from re-intervention compared with the matched group. Mean follow-up was 54 months and the patients underwent various procedures; four of these patients (two in both groups) underwent surgery for aortic regurgitation or stenosis. The results of present study show that the bicuspidalisation technique is an adequate solution, beside the use of bovine jugular vein grafts, to circumvent the shortage of small conduits for Ross or extended Ross procedures in infants.

Conclusions

When proper sized cryopreserved homografts for placement in the RV-PA position in Ross, Konno-Ross, and other procedures in infants are not readily available, bicuspidalized homografts provide an acceptable alternative. Structural deterioration of the conduit over time is comparable to non-bicuspidalized valves as are re-interventions for graft failure.

REFERENCES

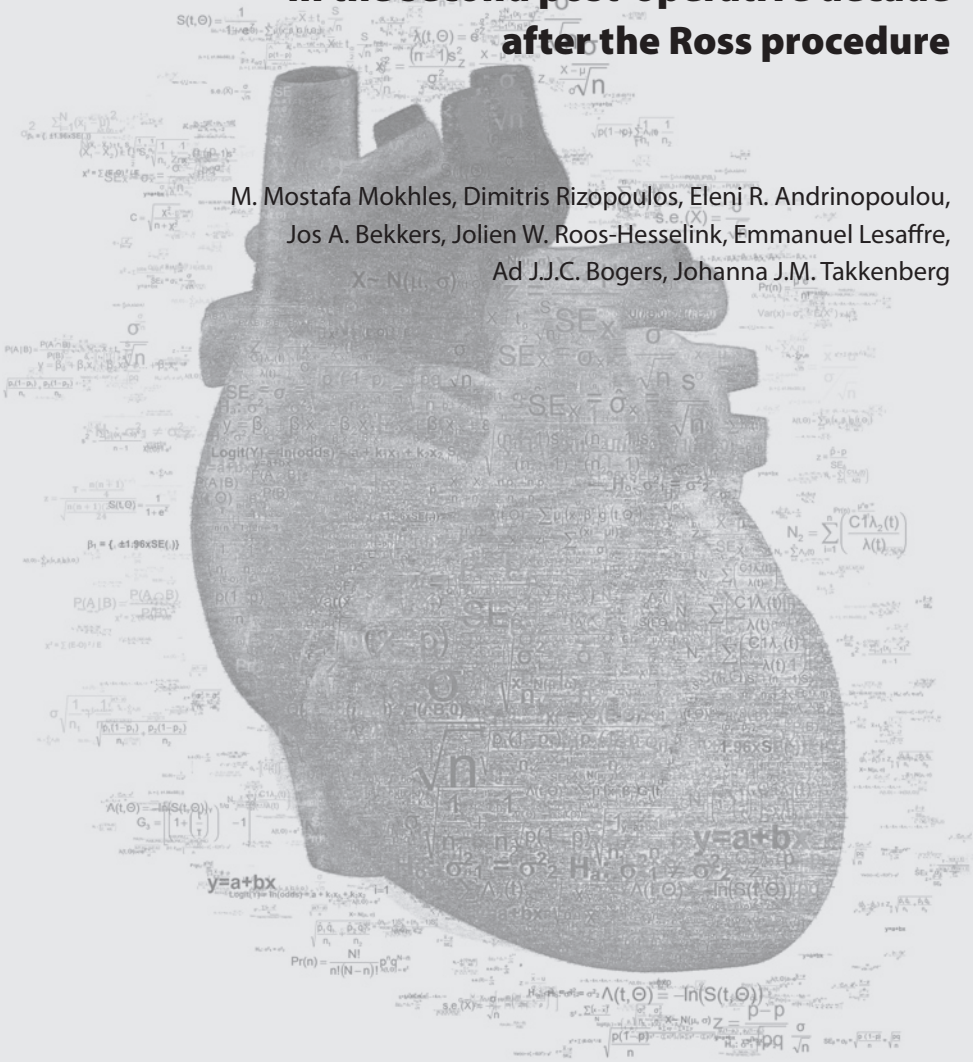
1. Mokhles MM, van de Woestijne PC, de Jong PL, Witsenburg M, Roos-Hesselink JW, Takkenberg JJ, Bogers AJ. Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg.
2. Michler RE, Chen JM, Quaegebeur JM. Novel technique for extending the use of allografts in cardiac operations. Ann Thorac Surg 1994; 57(1):83-87.
3. Santini F, Mazzucco A. Bicuspid homograft reconstruction of the right ventricular outflow tract in infants. Ann Thorac Surg 1995; 60(6 Suppl):S624-625.
4. Koirala B, Merklinger SL, Van Arsdell GS, McCrindle BW, Borger MA, Caldarone CA, Coles JG, Williams WG. Extending the usable size range of homografts in the pulmonary circulation: outcome of bicuspid homografts. Ann Thorac Surg 2002; 73(3):866-869; discussion 869-870.
5. McMullan DM, Oppido G, Alphonso N, Cochrane AD, d'Acoz Y, Brizard CP. Evaluation of downsized homograft conduits for right ventricle-to-pulmonary artery reconstruction. J Thorac Cardiovasc Surg 2006; 132(1):66-71.
6. Benjacholamas V, Namchaisiri J, Khongphatthanayothin A, Lertsapcharoen P. Bicuspidized pulmonary homograft for truncus arteriosus repair. Asian Cardiovasc Thorac Ann 2008; 16(3):189-193.
7. Shih T, Gurney JG, Bove EL, Devaney EJ, Hirsch JC, Ohye RG. Performance of bicuspidized pulmonary allografts compared with standard trileaflet allografts. Ann Thorac Surg; 90(2):610-613.
8. Willems TP, Takkenberg JJ, Steyerberg EW, Kleyburg-Linkers VE, Roelandt JR, Bos E, van Herwerden LA. Human tissue valves in aortic position: determinants of reoperation and valve regurgitation. Circulation 2001; 103(11):1515-1521.
9. Kappetein AP, Puvimanasinghe JP, Takkenberg JJ, Steyerberg EW, Bogers AJ. Predicted patient outcome after aortic valve replacement with Medtronic Stentless Freestyle bioprostheses. J Heart Valve Dis 2007; 16(4):423-428; discussion 429.
10. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 2008; 85(4):1490-1495.
11. Charitos EI, Hanke T, Stierle U, Robinson DR, Bogers AJ, Hemmer W, Bechtel M, Misfeld M, Gorski A, Boehm JO, Rein JG, Botha CA, Lange R, Hoerer J, Moritz A, Wahlers T, Franke UF, Breuer M, Ferrari-Kuehne K, Hetzer R, Huebler M, Ziemer G, Takkenberg JJ, Sievers HH. Autograft reinforcement to preserve autograft function after the ross procedure: a report from the german-dutch ross registry. Circulation 2009; 120(11 Suppl):S146-154.
12. Ross DN. Replacement of aortic and mitral valves with a pulmonary autograft. Lancet 1967; 2(7523):956-958.
13. Levine AJ, Miller PA, Stumper OS, Wright JG, Silove ED, De Giovanni JV, Sethia B, Brawn WJ. Early results of right ventricular-pulmonary artery conduits in patients under 1 year of age. Eur J Cardiothorac Surg 2001; 19(2):122-126.
14. Brown JW, Ruzmetov M, Vijay P, Rodefeld MD, Turrentine MW. Surgical treatment of absent pulmonary valve syndrome associated with bronchial obstruction. Ann Thorac Surg 2006; 82(6):2221-2226.
15. Breymann T, Thies WR, Boethig D, Goerg R, Blanz U, Koerfer R. Bovine valved venous xenografts for RVOT reconstruction: results after 71 implantations. Eur J Cardiothorac Surg 2002; 21(4):703-710; discussion 710.

16. Homann M, Haehnel JC, Mendler N, Paek SU, Holper K, Meisner H, Lange R. Reconstruction of the RVOT with valved biological conduits: 25 years experience with allografts and xenografts. Eur J Cardiothorac Surg 2000; 17(6):624-630.
17. Caldarone CA, McCrindle BW, Van Arsdell GS, Coles JG, Webb G, Freedom RM, Williams WG. Independent factors associated with longevity of prosthetic pulmonary valves and valved conduits. J Thorac Cardiovasc Surg 2000; 120(6):1022-1030; discussion 1031.
18. Wells WJ, Arroyo H, Jr., Bremner RM, Wood J, Starnes VA. Homograft conduit failure in infants is not due to somatic outgrowth. J Thorac Cardiovasc Surg 2002; 124(1):88-96.

Chapter 13

Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure

M. Mostafa Mokhles, Dimitris Rizopoulos, Eleni R. Andrinopoulou, Jos A. Bekkers, Jolien W. Roos-Hesselink, Emmanuel Lesaffre, Ad J.J.C. Bogers, Johanna J.M. Takkenberg



Eur Heart J. 2012;33:2213-24

ABSTRACT

Aims

The objective of present study was to report our ongoing prospective cohort of autograft recipients with up to 21 years of follow-up.

Methods and Results

All consecutive patients (n=161), operated between 1988 and 2010, were analyzed. Mixed-effects models were used to assess changes in echocardiographic measurements (n=1023) over time in both the autograft and the pulmonary allograft.

Mean patient age was 20.9 years (range 0.05-52.7), 66.5% were male. Early mortality was 2.5% (n=4) and 8 additional patients died during a mean follow-up of 11.6 ± 5.7 years (range, 0-21.5). Patient survival was 90% (95%Confidence Interval [CI], 78-95) up to 18 years. During follow-up, 57 patients required a re-intervention related to the Ross operation. Freedom from autograft reoperation and allograft re-intervention was 51% (95%CI, 38-63) and 82% (95%CI, 71-89) after 18 years, respectively.

No major changes were observed over time in autograft gradient, and allograft gradient and regurgitation. An initial increase of sinotubular junction and aortic annulus diameter was observed in the first 5 years after surgery.

The only factor associated with an increased autograft reoperation rate was preoperative pure aortic regurgitation (hazard ratio 1.88; 95%CI, 1.04-3.39; p=0.037).

Conclusions

We observed good late survival in patients undergoing autograft procedure without reinforcement techniques. However, over half of the autografts failed prior to the end of the second decade. The reoperation rate and the results of echocardiographic measurements over time underline the importance of careful monitoring especially in the second decade after the initial autograft operation and in particular in patients with preoperative aortic regurgitation.

INTRODUCTION

The Ross procedure (or pulmonary autograft procedure), first introduced by Donald Ross in 1967, has become a widely accepted option for aortic valve replacement in a selected group of patients (1-3).

Although the operative mortality and long term survival have been satisfactory, a major drawback of this procedure is the progressive dilatation of the autograft root, often combined with autograft valve insufficiency, necessitating reoperation (4-8).

Data on patient survival, durability of the autograft and the pulmonary allograft, and the incidence of potential risk factors for valve dysfunction and reoperation after the Ross procedure are scarce beyond the first decade (9, 10). In this regard, we report the results of the longest and most complete ongoing prospective cohort of autograft recipients, with a follow-up now reaching up to an unprecedented 21 years.

METHODS

Patient Population

Between September 1988 and November 2010, 161 consecutive patients underwent the autograft procedure in our institution. The patients included in this study are also part of the German-Ross registry (11). Approval from the Institutional Review Board was obtained for this prospective follow-up study; all patients gave written informed consent.

Operative Techniques

Timing of surgery was determined in a regular heart team meeting between (congenital) cardiologists and cardiac surgeons during which all cases were discussed. The decision whether to operate or not was based on contemporary clinical practice. Most procedures (72%) were performed by two surgeons. The remainder of the procedures was performed by another 4 surgeons. The surgical procedures were performed using standard cardiopulmonary bypass with moderate hypothermia, myocardial protection with crystalloid cardioplegia (St. Thomas Hospital solution), and topical cooling. Additional deep hypothermia with total circulatory arrest was employed for surgery on the aortic arch.

In 155 patients, the root replacement technique was employed, and the pulmonary autograft was inserted at the level of the annulus, with care taken to reduce the subannular muscular rim of the autograft to 3 to 4 mm. The proximal suture line of the autograft was constructed, with interrupted sutures in 19% (n=30) of the procedures and running sutures in the remainder. In 159 of the 161 patients no root reinforcement

measures were taken. In 2 patients, an autologous pericardial strip supported the proximal suture line.

Three patients required concomitant coronary artery bypass grafting (CABG) due to a procedural complication. The details of these patients have been previously reported (6).

Allograft Properties

In all patients the right ventricular outflow tract (RVOT) was reconstructed using an allograft. The Rotterdam Heart Valve Bank provided most of the allografts (n=131), which were allocated by Bio Implant Services, Leiden, The Netherlands. The remaining allografts were shipped from Hospital Clinic I, Barcelona, (N=16), Deutsches Herzzentrum, Berlin, Germany (n=7), the Karolinska Homograft bank, Stockholm, Sweden (n=4) and the National Heart Hospital, London, England (n=3). In 98% a pulmonary allograft was used and 99% of the allografts were cryopreserved. Patient's body surface area was used as a guideline to determine the allograft diameter. No attempt was made to achieve ABO blood type or HLA type matching. Previous publication from our center showed that blood group compatibility and assignment of quality codes do not have an impact on allograft durability (12).

Data collection

Hospital mortality and morbidity were registered and the causes of death were documented. Hospital mortality was defined as death of the patient within hospital or within 30 days after surgery. All patients were followed-up prospectively, contacted annually and interviewed over telephone. Patients over 16 years underwent standardized echocardiography biannually (13). In case of suspected complications the attending physician was contacted for verification. Total follow-up was 1875 patient years and was 98.1% complete. Three patients moved abroad and were lost to follow-up (data from these patients was included in the analyses until the moment when they moved abroad). Valve-related events were defined according to the guidelines for reporting morbidity and mortality after cardiac valvular operations (14). Sudden, unexplained, unexpected deaths (SUUD) without further clinical data or autopsy were classified as valve-related death according these guidelines (14). Failure of the autograft or pulmonary allograft was determined at the time of reoperation or death. Patient survival started at the time of Ross operation and ended at the time of death or at last follow-up. Survival of the autograft or pulmonary allograft started at the time of operation and ended when a reoperation or re-intervention was done, when the patient died or at last follow-up. Echocardiographic measurements were systematically and prospectively obtained for all patients until the time of death or autograft explant. The echocardiographic follow-up was 94% complete. The database was frozen on December 31, 2010.

Statistical analyses

Analyses of clinical data

Patient data were entered into a computerized relational database (Microsoft Access 2000). Statistical software SPSS for Windows version 10 (SPSS Inc, Chicago, IL.) was used for data analysis. Patient survival was estimated using the Kaplan-Meier method (15). The log-rank test was used to assess the effect of potential risk factors on patient survival, freedom from valve-related reoperation, and freedom from valve-related events. To investigate independent risk factors for mortality and morbidity caused by allograft failure, the Cox proportional hazard model was used. Risk factors were selected with a backward stepwise method (required significance of $p>0.10$ for elimination from the model and $p<0.05$ for retention in the model). Given the relatively small number of deaths, no multivariable analysis was performed for mortality in our patient population. Kaplan-Meier survival estimates were compared with survival of the general population matched for age, sex, year of surgery, and years of follow-up using the Dutch population life table (16).

Analyses of serial echocardiographic data

While the statistical analysis of serial echocardiographic data is often performed by means of the Kaplan-Meier method, the echocardiographic data in the present study were analyzed with mixed-effects model instead. Mixed-effects modeling allow for more accurate analyses of dependent data such as hierarchical data, observations taken on related individuals (e.g. siblings) or measurements collected over time on the same individuals (e.g. echocardiographic measurements) (17, 18). This approach of longitudinal data analyses is also proposed by the 2008 guidelines for reporting mortality and morbidity after cardiac valvular interventions (14).

Mixed-effects models were used to assess changes in echocardiographic measurements over time while accounting for the correlation between repeated follow-up measurements in each patient. For the continuous outcomes, linear mixed models were used, whereas for the ordinal outcomes mixed-effects continuation ratio models were employed. To allow for more flexibility in the specification of the patient-specific longitudinal trajectories we utilized natural cubic splines with three internal knots placed at the corresponding percentiles of the follow-up times. Residual plots were used to validate the model's assumption, and when appropriate transformations of the outcome variables were performed. Missing echocardiogram measurements were assumed to be missing at random (19, 20). In both the univariable and multivariable analyses, F-tests were used to assess which variables/prognostic factors were most associated with the echocardiographic measurements.

All analyses were performed with the R statistical software (version 2.13.2, R Development Core Team 2011, R Foundation for Statistical Computing, Vienna, Austria).

All statistical tests with a p-value of 0.05 or lower were considered significant.

RESULTS

Patient and operation characteristics

The mean age of the patients was 20.9 ± 13.7 years (range, 0.05-52.7). Patient characteristics are shown in Table 1. Twelve patients underwent previous AVR: six subcoronary allografts, three biological prostheses, and three mechanical prostheses were used. Perioperative data are shown in Table 2.

Hospital mortality and late survival

Hospital mortality was 2.5% (four patients) (Table 2). Two patients, both female, died peri-operatively. One 26-year-old male patient died due to massive pulmonary emboli shortly after the operation. Furthermore, one 24-year-old female patient with Turner syndrome and extreme LV hypertrophy died due to mediastinitis and sepsis 13 days after surgery.

Mean follow-up duration was 11.6 ± 5.7 years (range 0-21.5 years; median, 12.7 years; interquartile range, 8.6-15.3 years). During follow-up eight more patients died. There were three valve-related. One patient suddenly died 13.9 years after autograft operation at the age of 50 years. The other patient with sudden, unexplained, unexpected death died 10.7 years after autograft operation at the age of 39 years. The third patient with valve-related death was a 12-year-old girl with severe juvenile rheumatic disease and severe aortic valve regurgitation and mitral valve incompetence resulting in progressive heart failure. She died 6 months after operation. Furthermore, there were five non-valve-related deaths of which four were cardiac deaths. Causes of the non-valve-related deaths included septic shock (Candida albicans) in one infant 51 days after autograft operation, heart failure resulting in cardiogenic shock in another infant 1.7 years after autograft operation, gastroenteritis (Staphylococcus aureus) resulting in septic shock and multi-organ failure 14.6 years after autograft operation, heart failure due restrictive cardiomyopathy 16.3 years after autograft operation, and an acute myocardial infarction in an adult patient 4.7 years after autograft operation and 2 months after autograft reoperation for structural valve deterioration with implantation of a mechanical prosthesis.

Overall, survival was 89% (95% Confidence Interval [CI] 78-95) up to 18-years of follow-up (Figure 1A).

Table 1. Preoperative Characteristics of 161 patients.

Baseline characteristics	All patients (n=161), No. (%)	< 18 years (n=75) No. (%)	18-30 years (n=43) No. (%)	> 30 years (n=43) No. (%)
Median age [± SD; range (years)]	20.9±13.7 (0.05-52.7)	8.6±5.9 (0.05-17.8)	24.7±3.3 (18.33-24.69)	38.5±6.1 (30.0-52.7)
Gender				
Males	107 (66.5)	54 (72.0)	26 (60.5)	27 (62.8)
Females	54 (33.5)	21 (28.0)	17 (39.5)	16 (37.2)
Prior cardiac surgery				
Prior AVR	12 (7.5)	0 (0.0)	6 (14.0)	6 (14.0)
Etiology				
Endocarditis	8 (4.9)	3 (4.0)	1 (2.3)	4 (9.4)
Congenital (including bicuspid)	123 (76.4)	70 (93.3)	30 (69.8)	23 (53.5)
Other (mainly prosthetic valve)	18 (11.2)	2 (2.7)	10 (23.3)	6 (14.0)
Degenerative/ rheumatic	11 (6.8)	0 (0.0)	1 (2.3)	10 (23.3)
Aneurysm/ dissection	1 (0.6)	0 (0.0)	1 (2.3)	0 (0.0)
Diagnosis				
Aortic valve regurgitation (AR)	46 (28.6)	13 (17.3)	15 (34.9)	18 (41.9)
Aortic valve stenosis (AS)	47 (29.2)	19 (25.3)	14 (32.6)	14 (32.6)
AR + AS	68 (42.2)	43 (57.3)	14 (32.6)	11 (25.6)
Systolic LVF				
Good (EF > 50%)	135 (83.8)	63 (84.0)	36 (83.7)	35 (81.4)
Impaired (EF 40-50%)	17 (10.6)	9 (12.0)	3 (7.0)	5 (11.6)
Moderate/bad (EF < 40%)	9 (5.5)	2 (2.6)	4 (9.3)	3 (7.0)
Sinus rhythm	161 (100)	75 (100)	43 (100)	43 (100)
Creatinine (µmol/L)	61.7±24.4 (12-157)	41.4±15.9 (12-89)	75.6±19.5 (49-157)	78.6±15.4 (42-121)
NYHA class				
I	68 (42.2)	42 (56.0)	15 (34.9)	11 (25.6)
II	60 (37.3)	20 (26.7)	18 (41.9)	22 (51.2)
III	25 (15.5)	7 (9.3)	9 (20.9)	9 (20.9)
IV	8 (4.9)	6 (8.0)	1 (2.3)	1 (2.3)
Type of operation				
Emergency	2 (1.2)	1 (1.3)	1 (2.3)	0 (0.0)
Urgent	25 (15.5)	18 (24.0)	2 (4.7)	5 (11.6)
Elective	134 (83.2)	56 (74.7)	40 (93.0)	38 (88.4)

AS, Aortic Stenosis; AR, Aortic Regurgitation; AVR, Aortic Valve Replacement; EF, Ejection Fraction; LVF, Left Ventricular Function

The instantaneous hazard of mortality was highest in the immediate postoperative period. This hazard then declined in the first 6 years after surgery, but started to slightly increase again after this period (Figure 1A).

At most recent follow-up, 81 (54%) of our patients were in NYHA functional class I, 38 (26%) were in NYHA functional class II, 16 (11%) were in NYHA functional class III and 5 (3%) were in NYHA functional class IV. NYHA functional class was unknown in 9 (6%) patients at most recent follow-up.

Table 3 displays the risk factors associated with long-term mortality after autograft procedure that were identified in univariate analyses.

Long-term mortality rates of our patient population are relatively low and comparable with that of the general population in the first decade. However, the survival rate of Ross patients shows, in our experience, a decline in the second postoperative decade compared with the general population (Figure 1B).

Table 2. Perioperative Characteristics of 161 patients.

	All patients (n=161), No. (%)	< 18 years (n=75) No. (%)	18-30 years No. (%)	> 30 years No. (%)
Aortic valve				
Bicuspid	99 (61.5)	49 (65.3)	27 (62.8)	23 (53.5)
Tricuspid	51 (31.7)	26 (34.7)	10 (23.3)	15 (34.9)
Prosthesis	11 (6.8)	0 (0.0)	6 (13.9)	5 (11.6)
Surgical technique				
Autograft root replacement	155 (96.3)	75 (100)	43 (100)	37 (86.0)
Inlay autograft	6 (3.7)	0 (0.0)	0 (0.0)	6 (14.0)
Concomitant procedures				
CABG	3 (1.9)	0 (0.0)	1 (2.3)	2 (4.7)
LVOT enlargement	16 (9.9)	10 (13.3)	4 (9.3)	2 (4.7)
Mitral valve surgery	2 (1.2)	1 (1.3)	0 (0.0)	1 (1.3)
Other*	20 (12.4)	12 (16.0)	4 (9.3)	4 (9.3)
CPB time (min)	200±68 (114-685)	175±54 (118-465)	214±55 (114-366)	227±84 (142-685)
Cross-clamp time (min)	141±32 (90-240)	125±28 (90-240)	151±33 (90-238)	156±27 (117-225)
Circulatory arrest (min)	30±29 (11-64) (n=3)	15 (n=1)	64 (n=1)	11 (n=1)
Complications				
Bleeding/Tamponade	21 (13.0)	2 (2.7)	10 (23.3)	9 (20.9)
Pacemaker	2 (1.2)	1 (1.3)	0 (0.0)	1 (2.3)
Perioperative MI	1 (0.6)	0	1 (2.3)	0 (0.0)
Early mortality	4 (2.5)	1 (1.3)	2 (4.7)	1 (2.3)

* Includes patients requiring tailoring of the ascending aorta or subvalvular membrane resection. CABG, Coronary Artery Bypass Graft; CPB, Cardiopulmonary Bypass; LVOT, Left Ventricular Outflow Tract; MI, Myocardial Infarction

Survival rate in different age categories

Patient survival in the age category 2 weeks to 18 years was 94% (95% CI 87-99) at both 10 years as well as up to 18 years of follow-up. Univariate analyses indicated that previous aortic valve surgery (p-value 0.030) and preoperative aortic annulus aneurysm (p-value 0.048) were associated with impaired survival during follow-up in this patient group.

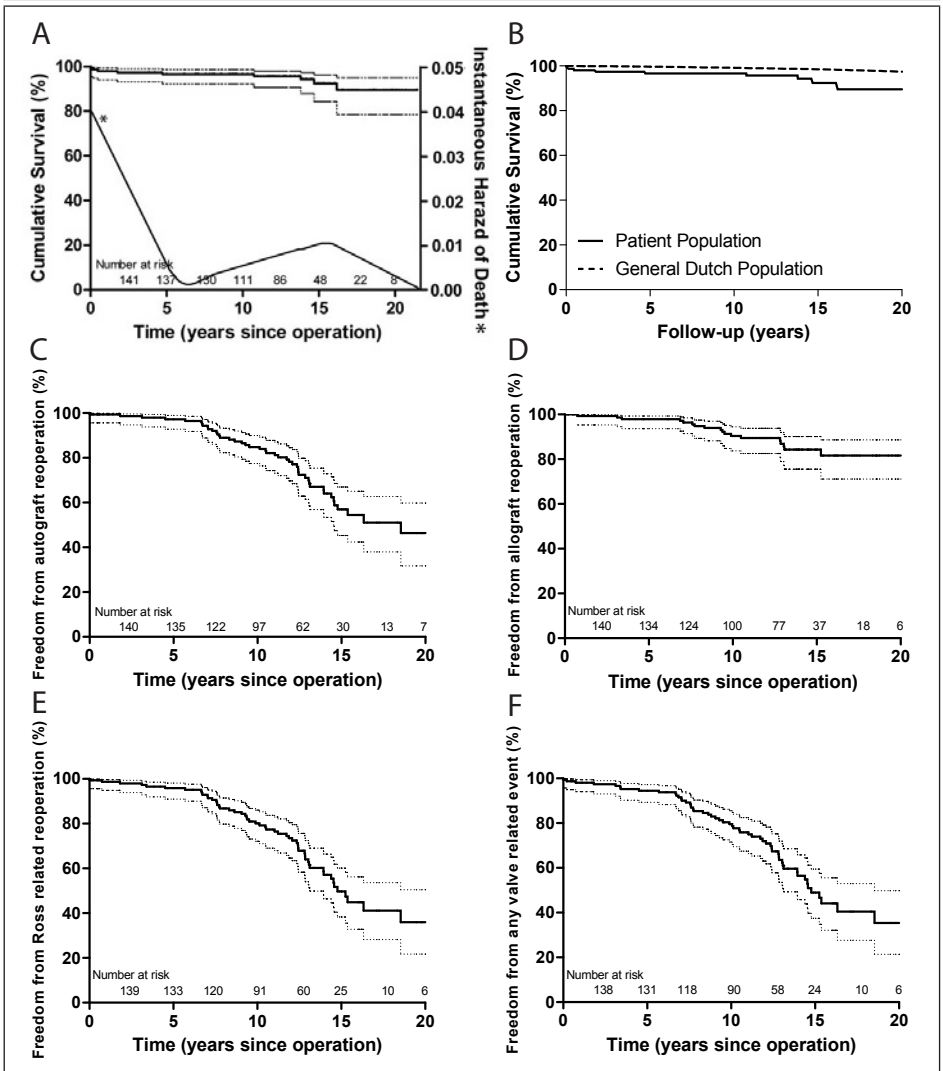


Figure 1. Kaplan-Meier plot of: A) patient survival after autograft procedure (* represents instantaneous hazard of death); B) survival comparison of autograft patients with that of general population; C) freedom from autograft reoperation; D) freedom from allograft reoperation; E) freedom from autograft or allograft reoperation; F) freedom from any valve related event.

Patient survival in the age category 18 to 30 years was 98% (95% CI 84-99) after 10 years of follow-up and 95% (95% CI 80-98) up to 18 years of follow-up. Hypertension (p-value 0.011), previous aortic valve surgery (p-value 0.030), bicuspid aortic valve (p-value 0.007) and preoperative aortic annulus aneurysm (p-value 0.043) were correlated with impaired survival in this patient group.

Patient survival in the age category 30 years and older was 100% after 10 years of follow-up and 76% (95% CI 24-95) up to 18 years of follow-up. The use of inclusion technique (p-value 0.038) and preoperative aortic annulus aneurysm (p-value 0.043) were associated with impaired survival in this group of patients.

Table 3. Potential predictors of mortality, autograft reoperation and allograft reoperation. Results obtained from univariate analyses.

Predictor	Survival		Autograft reoperation		Allograft reoperation	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender	1.78 (0.44-7.17)	0.24	0.63 (0.32-1.22)	0.16	0.87 (0.33-2.30)	0.77
Age	0.99 (0.94-1.05)	0.99	1.02 (0.99-1.04)	0.20	0.98 (0.95-1.02)	0.29
NYHA						
I	reference		reference		reference	
II	2.39 (0.22-26.44)	0.29	1.17 (0.60-2.29)	0.67	0.59 (0.18-1.96)	0.38
III or IV	**10.58 (1.23-90.67)**	**0.02**	1.88 (0.90-3.95)	0.11	1.55 (0.51-4.76)	0.45
Hypertension	**11.07 (1.23-99.42)**	**0.03**	1.08 (0.15-7.85)	0.95	NA	NA
Previous AV surgery	0.02 (0.00-11.37)	0.24	0.53 (0.27-1.06)	0.48	0.60 (0.20-1.83)	0.49
Creatinine	1.01 (0.97-1.04)	0.84	1.01 (0.99-1.03)	0.13	0.99 (0.97-1.01)	0.29
LV function	1.03 (0.39-2.75)	0.87	1.34 (0.92-1.94)	0.13	1.04 (0.55-1.97)	0.91
Timing						
Elective	reference		reference		reference	
Urgent	3.13 (0.74-13.25)	0.99	0.89 (0.37-2.11)	0.99	1.97 (0.65-6.01)	0.99
Inclusion technique	NA	NA	0.45 (0.06-3.24)	0.42	-	-
Cross-clamp time	1.01 (0.99-1.03)	0.89	1.00 (0.99-1.01)	0.83	1.00 (0.98-1.02)	0.99
Perfusion time	1.01 (0.99-1.02)	0.17	1.00 (0.99-1.01)	0.79	1.00 (0.99-1.01)	0.73
Bicuspid AV	0.33 (0.08-1.38)	0.27	0.97 (0.52-1.78)	0.88	-	-
Aorta ascendens aneurysm	NA	NA	1.58 (0.67-3.75)	0.30	1.15 (0.27-5.03)	0.85
Aortic regurgitation	**7.40 (1.49-36.85)**	**0.03**	**1.88 (1.04-3.39)**	**0.03**	-	-
Adult age (>18 years)	1.05 (0.25-4.47)	0.86	1.63 (0.84-3.17)	0.15	0.75 (0.30-1.89)	0.55

AV, Aortic Valve; CI, Confidence Interval; HR, Hazard Ratio; LV, Left Ventricle; NA, not assessable; NYHA, New York Heart Association Class.

Reoperation

Fifty-seven patients required a re-intervention related to the Ross operation. Of these, 33 patients required isolated pulmonary autograft replacement, 9 patients required simultaneous replacement of both the pulmonary autograft and allograft, 5 patients required isolated pulmonary allograft replacement, 2 patients with neo-aortic root dilatation required re-implantation of the autograft after replacement of aortic root with Vascutec prostheses, 1 patient underwent autograft repair according to Yacoub's method (21), and 1 patient underwent reoperation after a recurrent episode of rheumatic fever involving the autograft. Furthermore, 2 patients underwent a reoperation without valve replacement (one patient underwent enlargement of the pulmonary outflow tract due to supravalvular pulmonary stenosis and the other patient required reoperation for constrictive pericarditis). In addition, two patients underwent balloon valvuloplasty of the RVOT to relieve supravalvular pulmonary stenosis.

Percutaneous pulmonary allograft replacement with the Melody valve was required in 2 patients.

Progressive dilatation of the neo-aortic root was the main cause for autograft reoperation (n=40). Causes for pulmonary allograft reintervention were mainly structural failure, calcification, or degeneration of the valve. In our study group, 4 patients required a second reintervention on the pulmonary allograft during follow-up.

All reoperations on the autograft were performed through a median sternotomy, with cardiopulmonary bypass and moderate hypothermia. We mostly used central canulation in the ascending aorta and right atrium or caval veins. To anticipate possible perforation of the heart or aorta when reopening the chest, we instituted cardiopulmonary bypass with canulation of the femoralvessels and deep cooling in 4 patients before performing the sternotomy. Crystalloid cardioplegia and topical cooling were used for myocardial protection. Total circulatory arrest with deep hypothermia was needed in 11 patients, with ascending aorta or arch reconstruction. In patients without aortic root dilatation, the valve leaflets were excised, followed by mechanical valve implantation. The neo-aortic root was in most cases dilated without any signs of root or valve calcification. After opening the autograft root, the autograft valve leaflets were inspected, and most of them were excised and the coronary buttons mobilized. Excess autograft wall tissue was removed, leaving parts of the autograft at the annular level in situ. Standard valved conduit implantation was performed. When appropriate, the valve leaflets were spared, using the aortic valve reimplantation technique.

Freedom from reoperation for autograft failure was 84% (95% CI 77-92) and 51% (95% CI 38-62) after 10 and 18 years, respectively (Figure 1C). Freedom from reintervention for allograft failure was 90% (95% CI 83-94) and 81% (95% CI 71-88) after 10 and 18 years, respectively (Figure 1D). Freedom from reintervention for autograft or allograft failure

was 80% (95% CI 72-86) and 41% (95% CI 28-53) after 10 and 18 years, respectively (Figure 1E).

Risk factors that were associated with autograft reoperation in the univariate analyses are shown in Table 3. There was no reoperative mortality.

Reoperation rate in different age categories

In young patients up to 18 years of age at the time of the Ross procedure, freedom from reoperation for autograft failure was 84% (95% CI 71-92) and 62% (95% CI 39-79) after 10 and 18 years of follow, respectively. In the univariate analyses, preoperative aortic regurgitation (p-value 0.041), higher creatinin (p-value 0.031) and higher age (p-value 0.009) were associated with autograft failure in these young patients. However, none of these factors remained significant in the multivariate analyses. Freedom from reintervention for allograft failure was 86% (95% CI 71-94) and 81% (95% CI 64-91) after 10 and 18 years of follow-up, respectively. No potential risk factors could be identified for allograft failure in this specific patient group. Freedom from reintervention for autograft or allograft failure was 77% (95% CI 62-87) and 49% (95% CI 25-68) after 10 and 18 years, respectively.

In young adults patients between 18 and 30 years of age, freedom from reoperation for autograft failure was 80% (95% CI 64-90) and 37% (95% CI 19-56) after 10 and 18 years of follow, respectively. Preoperative aortic sinus aneurysm (p-value 0.025) was the only risk factor found to be associated with autograft failure. Freedom from reintervention for allograft failure was 87% (95% CI 72-94) and 81% (95% CI 64-91) after 10 and 18 years of follow-up, respectively. No risk factors were found for allograft failure. Freedom from reintervention for autograft or allograft failure was 73% (95% CI 56-84) and 32% (95% CI 15-50) after 10 and 18 years, respectively.

In patients of 30 years and older, freedom from reoperation for autograft failure was 90% (95% CI 76-96) and 58% (95% CI 19-56) after 10 and 18 years of follow, respectively. Freedom from reintervention for allograft failure was 98% (95% CI 84-99) and 76% (95% CI 40-92) after 10 and 18 years of follow-up, respectively. No risk factors were found for autograft or allograft failure. Freedom from reintervention for autograft or allograft failure was 90% (95% CI 76-96) and 45% (95% CI 22-66) after 10 and 18 years, respectively.

Other valve-related events

Two patients developed endocarditis of the autograft during follow-up (0.11%/patient year). In one patient the endocarditis was complicated by stroke. Furthermore, one patient developed endocarditis of the allograft (0.05%/patient-year) which was treated with antibiotics. One patient developed pulmonary emboli (0.05%/patient year). Bleeding events, valve thrombosis, or non-structural failure were not observed.

Freedom from any valve related event was 79% (95% CI 71-85) and 40% (95% CI 27-52) after 10 and 18 years, respectively (Figure 1F).

Functional performance of the autograft and allograft over time

During the study period, 1023 echocardiograms were reviewed for 161 subjects. Figure 2 shows time-related changes in autograft gradient (Figure 2a), allograft gradient (Figure 2b), autograft regurgitation (Figure 2c) and allograft regurgitation (Figure 2d). Figure 3 shows time-related changes in aortic annulus diameter (Figure 3a) and STJ (Figure 3b).

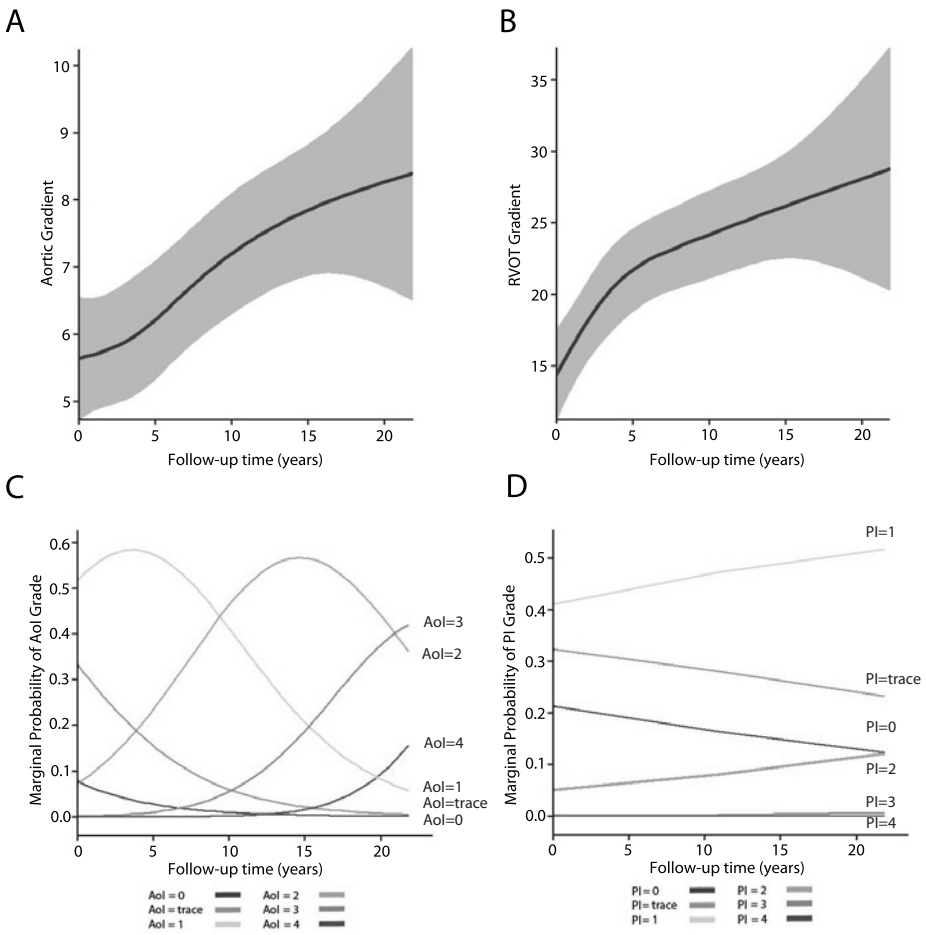


Figure 2. Mixed-effects models of echocardiogram variables after autograft procedure: A) transaortic gradients; B) transpulmonary gradient; C) marginal probability of aortic insufficiency grades; D) marginal probability of pulmonary insufficiency grades.

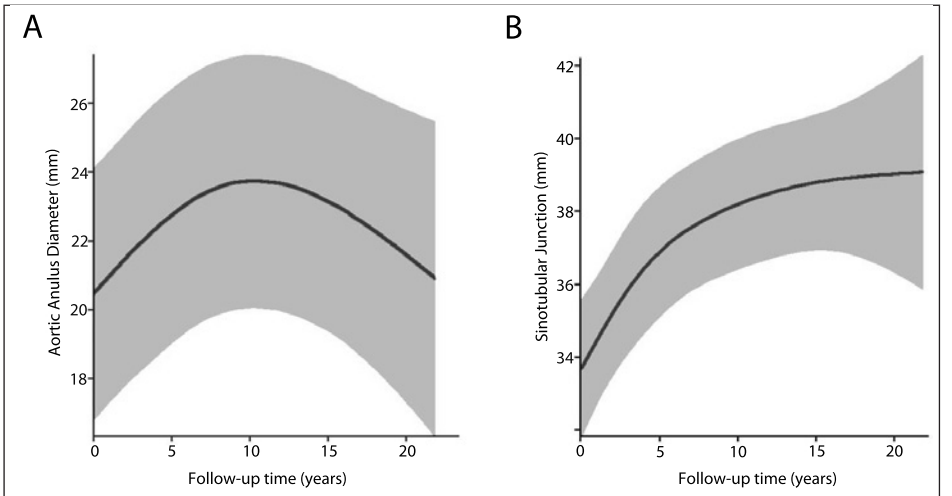


Figure 3. Mixed-effects models of: A) aortic annulus diameter increase over time; and B) Sinotubular Junction diameter increase over time.

Table 4. Risk factors associated with changes in echocardiographic measurements during follow-up.

Echocardiographic Measurement	Risk factors	Univariable Analyses Estimate (±SE)	p-value	Multivariable analyses Estimate (±SE)	p-value
Aortic Gradient	Female gender	0.39 (0.14)	0.007	0.40 (0.14)	0.005
	Older age	0.01 (0.01)	0.014	0.01 (0.01)	0.009
Aortic Regurgitation	Impaired LVF	-0.70 (0.24)	0.003	#	#
Aortic Annulus	Female gender	-4.54 (0.81)	<0.001	-3.77 (0.79)	<0.001
	Preoperative creatinine	0.06 (0.02)	0.015	0.04 (0.02)	0.02
	Preoperative AR	2.24 (0.90)	0.01	1.83 (0.83)	0.028
STJ	Female gender	-5.31 (1.02)	<0.001	#	#
Allograft Gradient	Female gender	-0.63 (0.29)	0.029	#	#
Allograft Regurgitation	Hypertension	2.21 (1.02)	0.030	0.02 (0.01)	0.02
	Older age	0.03 (0.01)	0.008	#	#

No longer significant in the multivariable model; AR, Aortic Regurgitation; LVF, Left Ventricular Function; SE, Standard Error; STJ, Sinotubular Junction

Risk factors associated with changes in echocardiographic measurements during follow-up are shown in Table 4. Female gender was found to be consistently associated with better echocardiographic outcomes. Preoperative AR was found to be consistently associated with worse echocardiographic outcomes

DISCUSSION

The present study is the first to show that long-term patient survival after the Ross procedure is relatively good in contemporary practice, even at the end of the second postoperative decade. Compared to the original pioneer series by Donald Ross (1967-1984), that reported an early mortality of 13% and a 20-year survival of only 61% in hospital survivors, our results illustrate the tremendous innovations that have taken place in cardiac surgery over the past decades. The present study also shows that, with increasing follow-up time, in particular the autograft has a limited durability. In addition, mixed-effects models analyses of echocardiographic measurements do not show major changes in transaortic gradients during the follow-up period. The results of mixed-effects models do, however, show that freedom from autograft regurgitation grade 3–4 was only 66% after 18 years of follow-up. Regarding neo-aortic dimensions the mixed-effects model shows an initial increase in STJ diameter in the first 5 postoperative years, which was then followed by a constant phase. Furthermore, an initial slight increase in aortic annulus diameter was observed in the first 10 postoperative years.

Survival after the Ross procedure

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 (6, 22, 23).

It remains unclear whether this excellent survival is a consequence of autograft attributes (living valve with superior hemodynamics and low valve-related event occurrence rates) (20), or the careful selection of patients for the Ross procedure (24).

The present study adds to current knowledge that although long-term mortality rates are relatively low and comparable with that of the general population in the first decade, as reported by several other authors (6, 11, 23), the survival rate of Ross patients in our experience shows a decline in the second postoperative decade compared with the general population. Of the 4 observed deaths in the second postoperative decade, 2 were valve-related (SUUD). Although the numbers are small, this observation suggests that valve-related mortality hazard may increase in the second postoperative decade after the Ross procedure.

Autograft performance

The longevity of the autograft within our patient population is a point of concern. At the end of the second decade, over half of patients were re-operated for autograft failure.

The main cause for reoperation after the Ross operation is dilatation of the neo-aortic root. Due to this dilatation, coaptation of the cusps is lost and AR occurs. The exact cause of autograft root dilatation is unknown. It is speculated that several factor may contribute to dilatation of the aortic root. Younger patient age (22), congenital aortic valve disease (25), rheumatic valve disease (26), and preoperative AR (27) and dilatation (22) are the most commonly reported patient-related determinants of durability of the autograft valve. It should also be noted that the outcome of the Ross procedure varies considerably between different centers (23) and surgical techniques employed and by individual variation of the application of the root replacement technique (28). Furthermore, due to significantly increased mechanical stress postoperatively hypertension may potentially have a negative effect on autograft durability (29, 30).

The presence of preoperative AR was independent risk factor of autograft failure during follow-up. Furthermore, the longitudinal analyses of echocardiographic data indicated that the presence of preoperative AR was significantly associated with increased aortic annulus diameter during follow-up. Preoperative AR was not associated with STJ diameter during follow-up at all. This suggests that preoperative AR might specially be a risk factor for the dilatation of the aortic annulus after the Ross procedure.

The association between preoperative aortic regurgitation and autograft failure is in agreement with other recent publications on this subject (10, 27, 31, 32). Two studies hypothesize that annular dilatation associated with aortic regurgitation may be a factor, and 1 suggests a role for altered geometry and tissue characteristics of the subvalvular left ventricular outflow tract resulting from chronic aortic regurgitation (27, 32).

Allograft performance

In contrast to autograft performance, the allografts performed adequately within our patient population with freedom from reoperation for allograft failure of 81% after 18 years of follow-up. Although there are no studies at the moment with such a long-term follow-up as the present study, the freedom from allograft failure that we have observed after 10 years of follow-up in our patient population was comparable to that of the other series (4, 33). The main reason for allograft reoperation in the present study was degeneration with calcification of the allograft. Pulmonary allograft stenosis is indeed another important issue that has to be taken into account when considering the Ross procedure. The stenosis appears to represent an early postoperative inflammatory reaction to the pulmonary allograft that leads to extrinsic compression and/or shrinkage and is characterized by intimal hyperplasia at the distal anastomosis and an inflammatory-mediated external compression by fibrous tissue (34).

Clinical Implications

The observed high reoperation rate after the Ross procedure has tempered our initial enthusiasm for the procedure: in our early experience we applied the Ross procedure generously in children and young adults performing up to 18 Ross procedures per year, while in more recent years this number has gone down to 1 or 2 per year, mainly in young children.

In most of our patients (n=159, 99%) no reinforcement procedures were taken. It has been shown that in patients undergoing the Ross procedure autograft reinforcement procedures are associated with lower AR development rates and reduced reoperation rates for autograft failure (35). This is of particular importance since autograft reoperation rate in the present study was mainly driven by root dilatation. Furthermore, it should be noted that surgical techniques employed can considerably influence the outcome after the Ross procedure. In a recent publication from the German-Dutch Ross registry showed that freedom from autograft or allograft reoperation was 92% at 10 years and 87% at 15 years in young and middle-aged patients operated with the subcoronary technique (36). These reported results are better than those observed in our study population where mainly (96%) root replacement technique was used. The widely varying durability results obtained with different surgical techniques applied in the Ross procedure illustrates the technical complexity of the procedure and the requirement of a particular surgical expertise with this procedure.

The Ross procedure represents only a fraction of all aortic valve replacement in contemporary practice (37). Obviously, surgical expertise required to perform a Ross procedure is a limiting factor, although one may hypothesize that by avoiding this technically challenging procedure with potentially increased early risks, we are withholding young adult patients from a potentially better solution in the long run (37). Several other options exist in replacement of the diseased aortic valve in young adult patients: mechanical prostheses, biological prostheses or homografts.

Although mechanical valves provide excellent durability and low reoperative hazard (38, 39), the choice for the mechanical valve implies lifelong anticoagulation and is associated with an increased risk for thromboembolic and bleeding events (40, 41). The use of anticoagulation may also complicate pregnancy because of the fetal and maternal complications of taking warfarin (42, 43), and may require lifestyle adjustments in this relatively young and active patient group. Also the hemodynamic performance of mechanical valves is less favorable compared to autograft valves (44). Furthermore, prosthetic valve endocarditis occurs in up to six percent of mechanical valve recipients and is associated with considerable mortality (38). However, it still remains unclear whether the excellent survival observed in Ross patients is a consequence of autograft attributes (living valve with superior hemodynamics and low valve-related event occurrence) or the careful selection of patients for the Ross procedure. A recent publication

from our group showed that 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 (24).

Bioprostheses are frequently used as an aortic valve substitute and have a low thrombogenicity and absent need for lifelong anti-thrombotic therapy. Recently published studies reporting the results of Hancock II bioprosthesis have shown a freedom from reoperation of only 30%-50% after 20 years of follow-up (45, 46).

Homograft valves have, similar to the autograft procedure, the advantage of a low risk for thromboembolism and absent need of lifelong anticoagulation. However, the results of a recently published prospective randomized trial between the Ross procedure and the aortic homograft, both implanted as full roots, showed that the performance of allografts was inferior to that of autografts (23). Furthermore, the performance of the homograft valves have also been shown to be inferior compared to xenografts with more modern tissue processing including anticalcification processes (47).

In light of the limitations of contemporary prosthetic valve options, the optimal prosthesis choice for young adults remains controversial. Therefore, an individualized approach is needed in the selection of the optimal prosthetic valve. This approach should combine the evidence on outcome with different therapeutic strategies with the preferences of the informed patient since the inherent limitations of each prosthetic valve can be valued differently by individual patients.

Strengths and Limitations

The present study is the longest and most complete prospective cohort study allowing for new insights into patient outcome and autograft and pulmonary allograft function well into the second postoperative decade. In addition of reporting hard clinical endpoints, the number of available echocardiograms and the powerful longitudinal data analysis techniques enabled us to be the first to provide insight into autograft and allograft valve function over time until the end of second decade. The long-term evidence of patient outcome and valve performance is helpful in the selection of most optimal prosthetic aortic valve since it provides an unprecedented time horizon regarding the Ross procedure.

The present study has several limitations. The survival of patients is reported at 18 years of follow-up and future studies are required to confirm the results of present study. An additional limitation is the absence of a control group in the present study. Furthermore, the results of present study only apply to the unsupported root replacement technique, which is both a strength and a limitation of the data. Finally, the generalizability of our study results requires further investigation.

Conclusions

The present study shows that, in patients that undergo autograft procedure without any reinforcement techniques, the autograft procedure indeed meets the prospect with respect to relatively good long-term survival. However, the observation that over half of the autografts failed prior the end of the second decade is a point of concern. The reoperation rate and echocardiographic function over time underline the importance of careful monitoring, especially in the second decade after the initial autograft operation and particularly in patients with preoperative AR.

REFERENCES

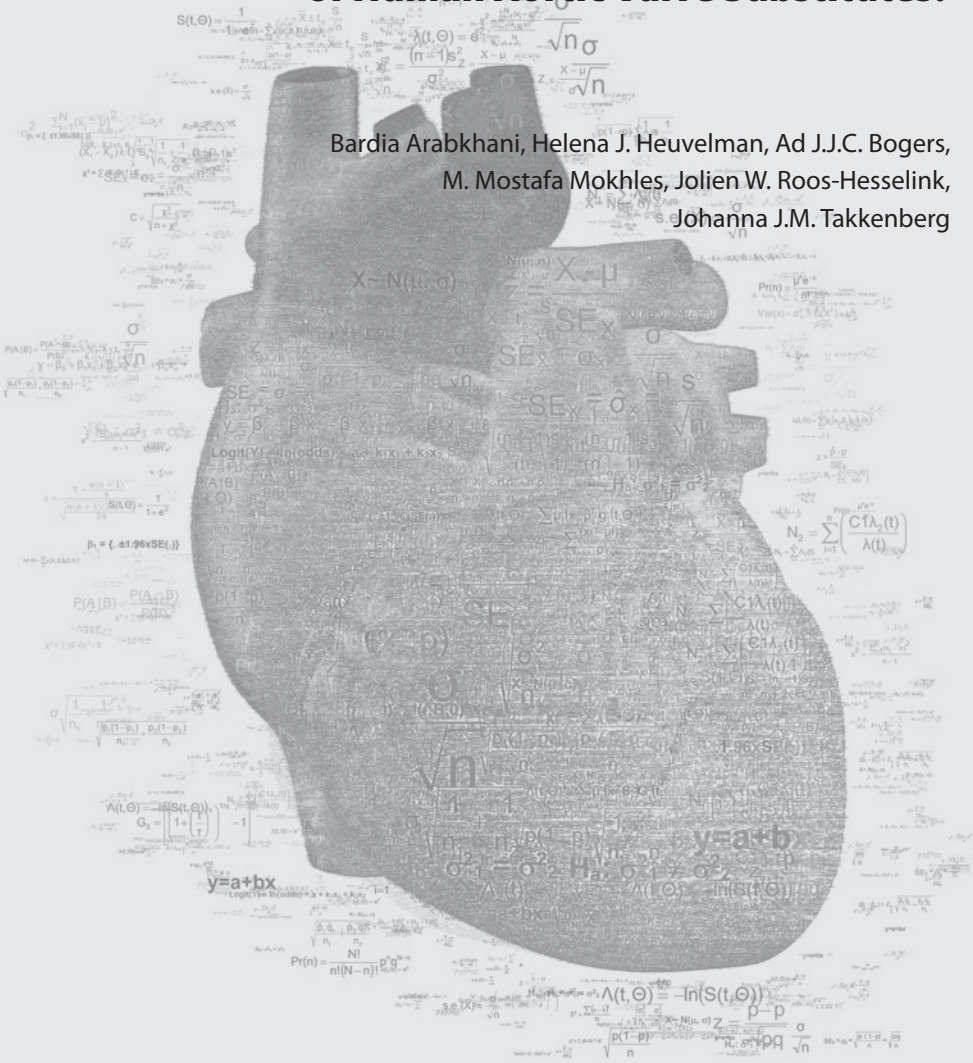
1. Ross DN. Replacement of aortic and mitral valves with a pulmonary autograft. Lancet 1967; 2(7523):956-958.
2. Ross D, Jackson M, Davies J. The pulmonary autograft--a permanent aortic valve. Eur J Cardiothorac Surg 1992; 6(3):113-116; discussion 117.
3. Kouchoukos NT, Davila-Roman VG, Spray TL, Murphy SF, Perrillo JB. Replacement of the aortic root with a pulmonary autograft in children and young adults with aortic-valve disease. N Engl J Med 1994; 330(1):1-6.
4. Kouchoukos NT, Masetti P, Nickerson NJ, Castner CF, Shannon WD, Davila-Roman VG. The Ross procedure: long-term clinical and echocardiographic follow-up. Ann Thorac Surg 2004; 78(3):773-781; discussion 773-781.
5. Luciani GB, Casali G, Favaro A, Prioli MA, Barozzi L, Santini F, Mazzucco A. Fate of the aortic root late after Ross operation. Circulation 2003; 108 Suppl 1:II61-67.
6. Klieverik LM, Takkenberg JJ, Bekkers JA, Roos-Hesselink JW, Witsenburg M, Bogers AJ. The Ross operation: a Trojan horse? Eur Heart J 2007; 28(16):1993-2000.
7. Stulak JM, Burkhart HM, Sundt TM, 3rd, Connolly HM, Suri RM, Schaff HV, Dearani JA. Spectrum and outcome of reoperations after the Ross procedure. Circulation 2010; 122(12):1153-1158.
8. Bekkers JA, Klieverik LM, Raap GB, Takkenberg JJ, Bogers AJ. Aortic root reoperations after pulmonary autograft implantation. J Thorac Cardiovasc Surg 2010; 140(6 Suppl):S58-63; discussion S86-91.
9. Klieverik LM, Takkenberg JJ, Elbers BC, Oei FB, van Herwerden LA, Bogers AJ. Dissection of a dilated autograft root. J Thorac Cardiovasc Surg 2007; 133(3):817-818.
10. David TE, Woo A, Armstrong S, Maganti M. When is the Ross operation a good option to treat aortic valve disease? J Thorac Cardiovasc Surg 2010; 139(1):68-73; discussion 73-65.
11. Sievers HH, Stierle U, Charitos EI, Hanke T, Misfeld M, Matthias Bechtel JF, Gorski A, Franke UF, Graf B, Robinson DR, Bogers AJ, Dodge-Khatami A, Boehm JO, Rein JG, Botha CA, Lange R, Hoerer J, Moritz A, Wahlers T, Breuer M, Ferrari-Kuehne K, Hetzer R, Huebler M, Ziemer G, Takkenberg JJ, Hemmer W. Major adverse cardiac and cerebrovascular events after the Ross procedure: a report from the German-Dutch Ross Registry. Circulation 2010; 122(11 Suppl):S216-223.
12. Mokhles MM, van den Bogaerdt AJ, Takkenberg JJ, Bogers AJ. Right ventricular outflow tract reconstruction: the impact of allograft characteristics. Ann Thorac Surg 2011; 91(6):2025.
13. Willems TP, Takkenberg JJ, Steyerberg EW, Kleyburg-Linkers VE, Roelandt JR, Bos E, van Herwerden LA. Human tissue valves in aortic position: determinants of reoperation and valve regurgitation. Circulation 2001; 103(11):1515-1521.
14. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008; 135(4):732-738.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457– 81.
16. Dutch Life Tables 2009 (Centraal Bureau voor de Statitiek, The Hague, The Netherlands http://statline.cbs.nl.
17. Pinheiro, J. C. & D. M Bates. 2000. Mixed-Effects Models in S and S-PLUS. New York: Springer.
18. Verbeke G & Molenberghs G. 2009. Linear Mixed Models for Longitudinal Data. New York. Springer.

19. Frank, E. and Harrell, Jr. Regression Modeling Strategies (2001 published). Springer: New York.
20. Verbeke, G and Molenberghs, G. Linear Mixed Models for Longitudinal Data (2000 published). Springer: New York.
21. Yacoub MH, Gehle P, Chandrasekaran V, Birks EJ, Child A, Radley-Smith R. Late results of a valve-preserving operation in patients with aneurysms of the ascending aorta and root. J Thorac Cardiovasc Surg 1998; 115(5):1080-1090.
22. Luciani GB, Favaro A, Casali G, Santini F, Mazzucco A. Ross operation in the young: a ten-year experience. Ann Thorac Surg 2005; 80(6):2271-2277.
23. El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G, Takkenberg JJ, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 2010; 376(9740):524-531.
24. van de Woestijne PC, Mokhles MM, de Jong PL, Witsenburg M, Takkenberg JJ, Bogers AJ. Right ventricular outflow tract reconstruction with an allograft conduit in patients after tetralogy of Fallot correction: long-term follow-up. Ann Thorac Surg 2011; 92(1):161-166.
25. Settepani F, Kaya A, Morshuis WJ, Schepens MA, Heijmen RH, Dossche KM. The Ross operation: an evaluation of a single institution's experience. Ann Thorac Surg 2005; 79(2):499-504.
26. Sampath Kumar A, Talwar S, Saxena A, Singh R. Ross procedure in rheumatic aortic valve disease. Eur J Cardiothorac Surg 2006; 29(2):156-161.
27. Laudito A, Brook MM, Suleman S, Bleiweis MS, Thompson LD, Hanley FL, Reddy VM. The Ross procedure in children and young adults: a word of caution. J Thorac Cardiovasc Surg 2001; 122(1):147-153.
28. Takkenberg JJ, Klieverik LM, Schoof PH, van Suylen RJ, van Herwerden LA, Zondervan PE, Roos-Hesselink JW, Eijkemans MJ, Yacoub MH, Bogers AJ. The Ross procedure: a systematic review and meta-analysis. Circulation 2009; 119(2):222-228.
29. Carr-White GS, Afoke A, Birks EJ, Hughes S, O'Halloran A, Glennen S, Edwards S, Eastwood M, Yacoub MH. Aortic root characteristics of human pulmonary autografts. Circulation 2000; 102(19 Suppl 3):III15-21.
30. Yacoub MH, Klieverik LM, Melina G, Edwards SE, Sarathchandra P, Bogers AJ, Squarcia U, Sani G, van Herwerden LA, Takkenberg JJ. An evaluation of the Ross operation in adults. J Heart Valve Dis 2006; 15(4):531-539.
31. Ryan WH, Prince SL, Culica D, Herbert MA. The Ross procedure performed for aortic insufficiency is associated with increased autograft reoperation. Ann Thorac Surg 2011; 91(1):64-69; discussion 69-70.
32. Elkins RC, Lane MM, McCue C. Ross operation in children: late results. J Heart Valve Dis 2001; 10(6):736-741.
33. Elkins RC. The Ross operation: a 12-year experience. Ann Thorac Surg 1999; 68(3 Suppl):S14-18.
34. Carr-White GS, Kilner PJ, Hon JK, Rutledge T, Edwards S, Burman ED, Pennell DJ, Yacoub MH. Incidence, location, pathology, and significance of pulmonary homograft stenosis after the Ross operation. Circulation 2001; 104(12 Suppl 1):I16-20.
35. Charitos EI, Hanke T, Stierle U, Robinson DR, Bogers AJ, Hemmer W, Bechtel M, Misfeld M, Gorski A, Boehm JO, Rein JG, Botha CA, Lange R, Hoerer J, Moritz A, Wahlers T, Franke UF, Breuer M, Ferrari-Kuehne K, Hetzer R, Huebler M, Ziemer G, Takkenberg JJ, Sievers HH. Autograft reinforcement to preserve autograft function after the ross procedure: a report from the german-dutch ross registry. Circulation 2009; 120(11 Suppl):S146-154.

36. Charitos EI, Stierle U, Hanke T, Schmidtke C, Sievers HH, Richardt D. Long-term results of 203 young and middle-aged patients with more than 10 years of follow-up after the original subcoronary ross operation. Ann Thorac Surg 2012; 93(2):495-502.
37. Treasure T, Hasan A, Yacoub M. Is there a risk in avoiding risk for younger patients with aortic valve disease? BMJ 2011; 342:d2466.
38. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. N Engl J Med 1996; 335(6):407-416.
39. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol 2000; 36(4):1152-1158.
40. Vink R, Kraaijenhagen RA, Hutten BA, van den Brink RB, de Mol BA, Buller HR, Levi M. The optimal intensity of vitamin K antagonists in patients with mechanical heart valves: a meta-analysis. J Am Coll Cardiol 2003; 42(12):2042-2048.
41. Takkenberg JJ, Puvimanasinghe JP, van Herwerden LA. Optimal target international normalized ratio for patients with mechanical heart valves. J Am Coll Cardiol 2004; 44(5):1142-1143; author reply 1144-1145.
42. Wong V, Cheng CH, Chan KC. Fetal and neonatal outcome of exposure to anticoagulants during pregnancy. Am J Med Genet 1993; 45(1):17-21.
43. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 2000; 160(2):191-196.
44. Porter GF, Skillington PD, Bjorksten AR, Morgan JG, Yapanis AG, Grigg LE. Exercise hemodynamic performance of the pulmonary autograft following the Ross procedure. J Heart Valve Dis 1999; 8(5):516-521.
45. David TE, Armstrong S, Maganti M. Hancock II bioprosthesis for aortic valve replacement: the gold standard of bioprosthetic valves durability? Ann Thorac Surg 2010; 90(3):775-781.
46. Valfre C, Ius P, Minniti G, Salvador L, Bottio T, Cesari F, Rizzoli G, Gerosa G. The fate of Hancock II porcine valve recipients 25 years after implant. Eur J Cardiothorac Surg 2010; 38(2):141-146.
47. El-Hamamsy I, Clark L, Stevens LM, Sarang Z, Melina G, Takkenberg JJ, Yacoub MH. Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial. J Am Coll Cardiol 2010; 55(4):368-376.

Chapter 14

Does Pregnancy Influence the Durability of Human Aortic Valve Substitutes?



Bardia Arabkhani, Helena J. Heuvelman, Ad J.J.C. Bogers, M. Mostafa Mokhles, Jolien W. Roos-Hesselink, Johanna J.M. Takkenberg

J Am Coll Cardiol. 2012;60:1991-2

To the Editor,

There is insufficient published evidence about the potential degenerative effects of pregnancy on the homograft and pulmonary autograft in the aortic position. To assess the association between pregnancy and accelerated degeneration of human aortic valve substitutes, we conducted a retrospective analysis of a prospective cohort study of female patients who received a human tissue valve in the aortic position at our institution.

All patients who have received a homograft or autograft in the aortic position in our center since 1987 are enrolled in an ongoing prospective follow-up study (1). Patients undergo annual clinical follow-up and biennial standardized serial echocardiography (aortic gradient [V_{max}]), aortic regurgitation (AoI), and annular and sinotubular junction diameter (AD and STJ). We identified 108 female patients who underwent 59 homograft and 49 autograft procedures, and who were ≤50 years old at the time of surgery and at least 16 years old at the time of study (age 29 ± 13 years). Informed consent was obtained from the patients to interview them (December 2010) for additional information on pregnancy and cardiac status (institutional review board number 2010–272).

Freestanding root replacement with reimplantation of the coronary arteries was performed in most patients. Fifteen homograft patients underwent a subcoronary homograft implantation, and 2 autograft patients had an inclusion cylinder aortic root replacement.

Outcome was reported according to the 2008 American Association of Thoracic Surgery/European Association of Cardio-Thoracic Surgery/Society of Thoracic Surgeons guidelines for reporting mortality and morbidity after cardiac valve interventions. Mixed-effects models were used to assess changes in echocardiographic measurements over time while accounting for within-patient correlation between repeated follow-up measurements (2). Total follow-up was 1,448 patient years and 99% complete. Ninety-nine patients had ≥1 echocardiographic examinations (median 6; range 1 to 11).

Thirty-one patients (13 homografts and 18 autografts) experienced 55 pregnancies, including 48 completed pregnancies, 4 elective abortions for noncardiac reasons, and 3 miscarriages. Homograft recipients without pregnancies were older than homograft recipients who became pregnant (35 vs. 28 years; p=0.02). There were no other differences in patient characteristics between homograft and autograft patients without pregnancies and those who became pregnant.

During follow-up, 9 homograft patients and 4 autograft patients died. Fifteen-year survival in homograft patients was 80.0 ± 7.3% for patients without pregnancies and 100% for patients with pregnancies; in autograft patients, this was 94.1 ± 4.0% for patients without pregnancies and 94.4 ± 5.4% for patients with pregnancies (p = NS).

Fifteen homograft patients required reoperation for a calcified and degenerated homograft; 2 additional homograft patients were reoperated for paravalvular leak. Twelve

autograft patients were reoperated for neoaortic regurgitation and dilation of the neoaortic root, including 11 autograft replacements and 1 valve-sparing aortic root replacement (Yacoub procedure). Freedom from aortic valve reoperation at 15 years was 63% (95% confidence interval [CI]: 57% to 69%) in homograft patients; in autograft patients, this was 75% (95% CI: 63% to 87%). Freedom from reoperation was comparable between patients who experienced pregnancy and those who did not, in both homograft and autograft recipients (p = NS).

Figure 1 shows progression of V_{max}, STJ diameter, AD, and AoI over time. Pregnancy was not associated with changes in V_{max} over time, STJ diameter over time, AD over time, or AoI grade over time for either valve type.

Pregnancy is known to produce significant hemodynamic changes, with an increase in heart rate, plasma volume, and cardiac output (3). This may impose a burden on biological valve substitutes, accelerating degeneration. However, we found that pregnancy was not associated with either homograft or pulmonary autograft valve reoperation and echocardiographic valve function over time. This is in concordance with previous, but very limited, evidence (4 and 5).

The question remains as to what the best valve substitute choice is for young female patients who require aortic valve replacement, and who may contemplate pregnancy. Bioprosthetic valves are an option, but valvular deterioration seems to accelerate during pregnancy (6). Mechanical prostheses are far from ideal during pregnancy because of

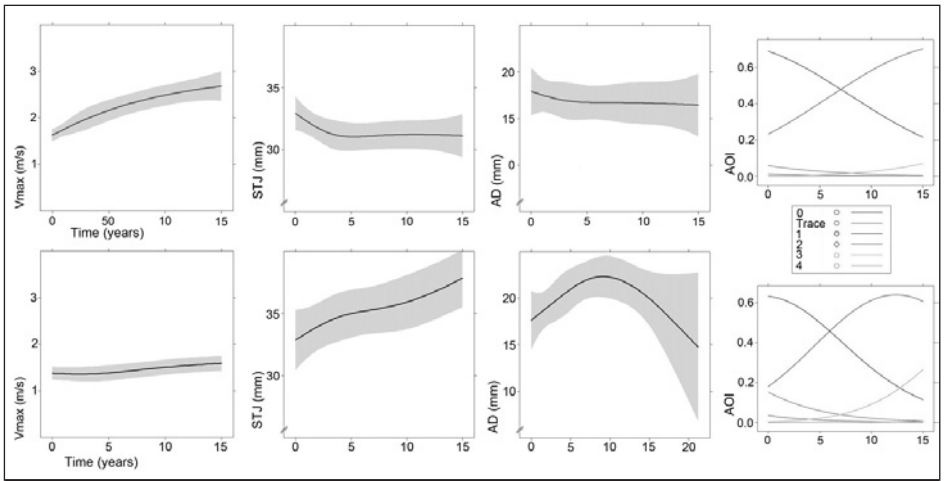


Figure 1. Vmax, STJ Diameter, AD, and AoI Marginal Probability of AoI Grade Over Time
(Top row) Homograft models. (Bottom row) Autograft models. (Shaded grey areas) 95% confidence intervals. AD , annulus diameter; AoI, aortic regurgitation; STJ, sinotubular junction; Vmax, peak velocity.

anticoagulation therapy-related complications, although in some patients mechanical valves are the only option. Human tissue valves do not require anticoagulation therapy and have good hemodynamic performance, but homografts—in contrast to autografts—do not increase in size with the growing child. In addition, autografts have a superior hemodynamic profile (7), which particularly during pregnancy has potential beneficial effects on cardiac function. In contrast, neoaortic root dilation and neoaortic regurgitation cause an increased need for reoperation (8).

Because human tissue valve durability is not influenced by pregnancy, it offers an attractive biological option for aortic valve replacement in young female patients. Young female patients who (may) contemplate pregnancy should consider human tissue valves as a suitable aortic valve substitute.

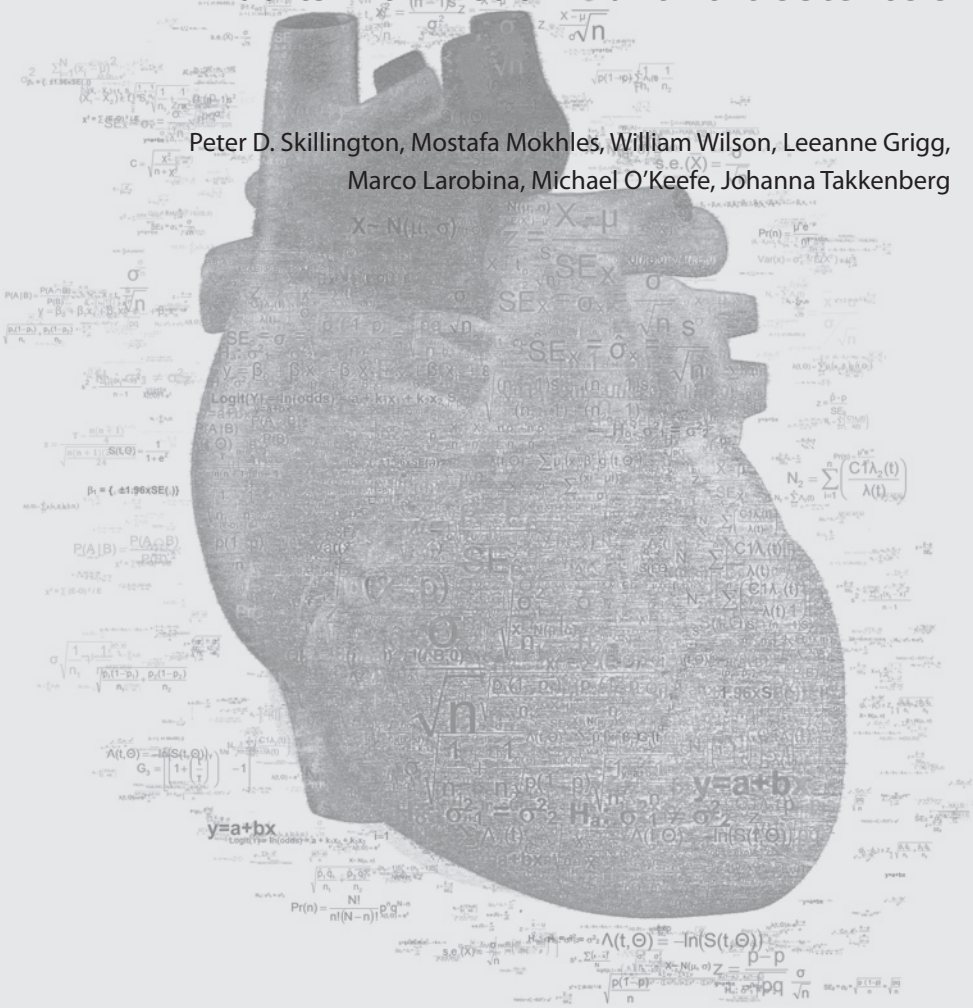
REFERENCES

1. Takkenberg JJ, van Herwerden LA, Galema TW, Bekkers JA, Kleyburg-Linkers VE, Eijkemans MJ, Bogers AJ. Serial echocardiographic assessment of neo-aortic regurgitation and root dimensions after the modified Ross procedure. J Heart Valve Dis 2006;15:100–6; discussion 106–7.
2. Verbeke G Molenberghs G. Linear Mixed Models for Longitudinal Data. New York, NY: Springer, 2009.
3. Stout KK, Otto CM. Pregnancy in women with valvular heart disease. Heart 2007;93:552– 8.
4. North RA, Sadler L, Stewart AW, McCowan LME, Kerr AR, White HD. Long-term survival and valve-related complications in young women with cardiac valve replacements. Circulation 1999;99: 2669 –76.
5. Dore A, Somerville J. Pregnancy in patients with pulmonary autograft valve replacement. Eur Heart J 1997;18:1659–62.
6. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. Circulation 2003;107:1240–6.
7. El-Hamamsy I, Eryigit Z, Stevens L-M, Sarang Z, George R, Clark L, Melina G, Takkenberg JM, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 2010;376: 524–31.
8. Takkenberg JJM, Klieverik LMA, Schoof PH, van Suylen RJ, van Herwerden LA, Zondervan PE, Roos-Hesselink JW, Eijkemans MJ, Yacoub MH, Bogers AJ. The Ross procedure: a systematic review and meta-analysis. Circulation 2009:119: 222–8.

Chapter 15

Inclusion Cylinder Method for Aortic Valve Replacement Utilising the Ross Operation in Adults with Predominant Aortic Stenosis

Peter D. Skillington, Mostafa Mokhles, William Wilson, Leeanne Grigg, Marco Larobina, Michael O'Keefe, Johanna Takkenberg



Submitted

ABSTRACT

Aim

To report our experience with the Ross operation in patients with predominant aortic stenosis (AS) using an inclusion cylinder (IC) method.

Methods and Results

Out of 324 adults undergoing a Ross operation, 204 patients of mean age of 41.3 years (limits 16 – 62) underwent this procedure for either AS or mixed AS and regurgitation (AS/AR) between October, 1992 and February, 2012, implanting the PA with an IC method. Clinical follow up and serial echo data for this group is 97% complete with late mortality follow up 99% complete. There has been zero (0%) early mortality, and late survival at 15 years is 98% (96%, 100%). Only one re-operation on the aortic valve for progressive aortic regurgitation (AR) has been required with freedom from re-operation on the aortic valve at 15 years being 99% (96%, 100%). The freedom from all re-operations on the aortic and pulmonary valves at 15 years is 97% (94%, 100%). Echo analysis at the most recent study shows that 98% have nil, trivial or mild AR. Aortic root size has remained stable, shown by long term (15 year) echo follow up.

Conclusions

In an experience spanning 19 years, the Ross operation used for predominant AS using the IC method described, results in 99% freedom from re-operation on the aortic valve at 15 years, better than any other tissue or mechanical valve. For adults under 65 years without significant co-morbidities who present with predominant AS, the pulmonary autograft inserted with this technique gives excellent results.

INTRODUCTION

For younger adult patients requiring AVR, the Ross procedure has many proven benefits in comparison to other valve substitutes, including absence of need for oral anticoagulation drugs, i.e. Coumadin, better durability than other tissue valve alternatives (1-4), excellent haemodynamic function (5), improved exercise tolerance (6), and possibly improved long term survival (2, 7, 8).

However, its use has been restricted to relatively small numbers of centres with sufficient expertise to achieve good results (9-11), and most long term results thus far reporting on implantation of the PA by an unsupported root replacement method, have shown increasing risk of regurgitation of the PA in the second decade, leading to aortic valve re-operation being required (12-14). Also, the freestanding root replacement method for PA implantation has shown significant increases in aortic root size (15) with time. The risk for aortic valve re-operation increases when the indication for surgery has been a patient presenting with AR, male gender, and in younger patients presenting with rheumatic valve disease (10, 12). In addition, the pulmonary valve allograft inserted into the right ventricular outflow tract provides an additional hazard for valve-related complications (12, 13).

With regard to more recent techniques to improve the PA durability, these mainly have utilised either wrapping the autograft with prosthetic materials to prevent the development of later aneurysmal enlargement of the neo-aortic root, thus helping preventing late AR, or inserting the PA inside a Dacron graft (16-18). Both of these measures have insufficient follow up duration to determine their success, and involve insertion of significant amounts of prosthetic material, which is against the Ross principle and which may place more strain on the neo-aortic valve leaflets over time as they open and close within a more rigid aortic root. Alternatively, subcoronary implantation of the PA has been proven durable in one particular centre in Germany, but is technically challenging (9).

The IC method used in this series involves insertion of the PA inside the patient's aortic root, giving it autologous support without need for excessive prosthetic material. This IC method (19, 20) is conceptually different to the technique usually referred to when describing an IC technique (21, 22), and is the first long term study reported of any IC method involving more than 100 patients and allowing for estimates of outcome far into the second postoperative decade. Patients with predominant aortic stenosis are the focus of this report.

METHODS

Between October, 1992 and February, 2012, 324 patients underwent AVR utilising the Ross procedure. Of these, in 217 the indication for surgery was predominant AS (either pure AS, or mixed AS/AR). The remaining 107 patients presented with pure AR. Of 217 with predominant AS, 13 patients had the PA inserted using other known techniques (7 root replacements, one subcoronary technique, and in 5, the PA was inserted inside a Valsava dacron graft). For the purposes of this study, the remaining 204 patients with predominant AS who had the PA inserted using an IC method were analysed. The Ethics Committee at the Royal Melbourne Hospital approved the study of these patients and each individual patient gave informed consent for participation in this study.

The demographics of the patients operated on as well as concomitant procedures performed can be seen in Table 1. All operations were performed via median sternotomy using cardiopulmonary bypass, aortic cross-clamping and a combination of antegrade and retrograde cardioplegia for myocardial protection. The technique has previously been described (19, 20), with the sequence of events being:

- Aortic transection and excision of the aortic valve, vertical extension of incision into the non-coronary sinus.
- Narrowing of the aortic root if required to allow for aortic valve/pulmonary valve size mismatch, using quadrangular or wedge excision of the non-coronary sinus. If either the aortic annulus or sinotubular junction diameter exceeds 34 mm, this would contra-indicate use of the inclusion cylinder method because of excessive pulmonary valve/aortic valve mismatch.
- Narrowing and stabilisation of the aortic annulus, if required, using partial circumference external Dacron ring.
- Marking of neocommissural points around the aortic annulus.
- Excision of pulmonary autograft root and insertion of a Cryopreserved pulmonary allograft. These were used exclusively, sourced from tissue banks within Australia.
- Insertion of the PA into aortic root using interrupted 4/0 Prolene sutures at the level of the annulus.
- Detachment of coronary ostial buttons, which are brought inside the aortic root and anastomosed to holes created in the pulmonary autograft root.
- Closure of aortic root with direct suture in non-coronary sinus region, enclosing the PA cylinder.
- Distal anastomosis of the PA to patient's native ascending aorta or if the ascending aorta replaced, to the lower end of the Dacron graft used.
- De-airing, removal of aortic cross-clamp and weaning from bypass.

· Check left ventricular (LV) function and aortic valve function with transoesophageal echo (TEE).

There have been some minor changes in technique since the previously described method (19). The distal autograft to ascending aortic anastomosis now includes the lower aortic root remnant only in the region immediately cephalad to the left coronary ostium. Please see Figure 1 showing the completed IC method.

All patients have been followed up with review by surgeon and/or cardiologist yearly and echocardiograms have been obtained before hospital discharge and 6 - 12 months after surgery, thereafter every second year. The following echocardiographic measures were assessed: aortic and pulmonary valve function and aortic root size by maximal aortic sinus diameter (mm).

Table 1. Patient Demographics and Concomitant Procedures.

No. of Patients		**204**
Age	Mean	41.3 years
	Limits	16 – 62 years
Gender	Male	127 (62%)
	Female	77 (38%)
Aortic Valve Lesion	AS	137 (67%)
	AS / AR	67 (33%)
Bicuspid Valve Aetiology		193 (94.6%)
NYHA Class	I	24 (12%)
	II	134 (67%)
	III	44 (22%)
	IV	2 (1%)
Previous Heart Surgery		22 (11%)
	Aortic Valve Repair	14 (6.9%)
	AVR	7 (3.4%)
	Other Heart Surgery	1 (0.5%)
Concomitant Procedures		90 (44%)
	Ascending Aorta	77 (38%)
	- Replacement	31 (15.2)
	- Tailoring Aortoplasty	46 (22.5)
	Subaortic Resection	3 (1.5%)
	CABG	3 (1.5%)
	ASD/PFO	2 (1%)
	Miscellaneous	5 (2.5%)

AS, Aortic Valve Stenosis; AR, Aortic Valve Regurgitation; AVR, Aortic Valve Replacement; CABG, Coronary Artery Bypass Graft Surgery; ASD, Atrial Septal Defect

Statistical Analyses

Continuous variables are displayed as mean (SD), discrete variables as counts and proportions. Kaplan-Meier analysis was done to study time-related events such as death and re-operation. In order to calculate 95% confidence limits, the standard error of the estimate of the survival curve was estimated using Greenwood's formula (23).

Analyses of the 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 analyzed longitudinally for change in percentages of patients in each regurgitation grade across time. A non-linear cumulative logit mixed model (24, 25) was used to resolve a number of time phases on cumulative odds domain to form a temporal decomposition model and to estimate the shaping parameters at each phase. Longitudinal cumulative logistic mixed model (26, 27) for repeated measurements (SAS® PROC NLMIXED) was used to implement the temporal decomposition model and to estimate the patient-specific probabilities for being in each conduit regurgitation grade. These patient-specific estimates were then averaged to obtain the percentages of patients (prevalence) in each grade.

Continuous echocardiographic measurement

To assess the temporal trend of conduit gradient over time after surgery, follow-up transthoracic echo-cardiographic measurements were analyzed longitudinally for change in mean response across time (28). A non-linear longitudinal mixed model regression (26, 29) (SAS® PROC NLMIXED) was used to analyze these continuous repeated measurements.

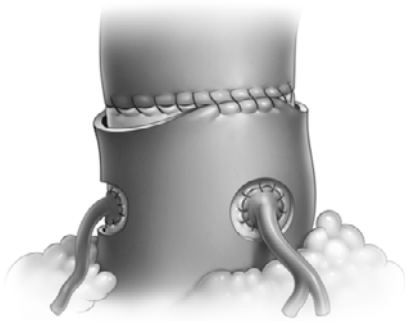


Figure 1. Completed inclusion cylinder method – diagram of aortic root with coronary ostia anastomosed to PA root.

Variable selection and risk factor analyses

Patient characteristics, conduit properties and procedure related variables were screened for association with postoperative autograft regurgitation, mean and peak autograft gradient, pulmonary allograft regurgitation, and mean pulmonary allograft gradient. In addition, year of surgery (calculated as time interval between first and last surgical procedure) and various transformations (e.g. inverse, natural logarithm) of the available continuous variables were also screened as potential risk factors.

Variable selection, with a P value criterion for retention of variables in the model of 0.05, utilized bootstrap bagging (bootstrap aggregation) (26, 30). This was a four-step process. First, a patient was randomly selected from the original data set to begin a new data set. The original data set continued to be sampled until the new data set was 100% the size of the original. Second, risk factors were identified using automated forward stepwise selection. Third, results of the variable selection were stored. These three steps were repeated 1000 times. Finally, the frequency of occurrence of variables related to group membership was ascertained and indicated the reliability of each variable (aggregation step). All variables with bootstrap reliability of 50% or greater were retained in the guided analysis.

Because of the limited capability of PROC NLMIXED to explore multivariable relations, we initially screened the variables using ordinary multivariable linear regression (PROC REG SAS) and the assumption of independence of observations with liberal entry criteria (0.2) and stay criteria (0.12). This analysis was performed simply to identify possible candidates for our repeated measurements model. These candidates and their transformations, if any, were entered at once into our model, and then eliminated one by one until all variables remaining had a P value of 0.05 or less. Parametric estimates of continuous postoperative echocardiography measurements are accompanied by asymmetric 95% confidence limits, comparable to ± 2 SE, obtained by a bootstrap percentile method (31). All statistical tests with a p-value of 0.05 or lower were considered significant. The longitudinal analyses of echocardiographic data were performed using SAS9.2 (SAS®, Cary, N.C.).

The deadline for data capture was 15th February, 2012.

RESULTS

Early and late mortality

There have been no early deaths either in hospital or within 30 days post-operative. The 204 surviving patients have been followed up, with only 7 patients lost to late follow up, i.e. 97% complete clinical follow up. An Australian Death Index search confirms that 6 of these patients are alive. The remaining patient lives overseas in Asia and last contact was 6 years after surgery. Thus late mortality follow up is 99% complete. As can

be seen from Figure 2a, 15 year survival is 98% (96%, 100%), with only 3 late deaths, all from malignant neoplastic disease (i.e. non-cardiac), occurring at 3, 5 and 10 years post-operatively. Mean late follow up time is 7.84 years (0.1 – 17.8 years), and encompasses 1576 patient years.

In-hospital complications

Early complications after surgery occurred in 50 patients and included the following: acute renal failure defined as doubling of serum creatinine (none required haemofiltration or dialysis) 3 (1.5%), bleeding requiring return to operating theatre 3 (1.5%), late pericardial effusion requiring drainage 2 (1%), atrial arrhythmias 23 (11%), ventricular arrhythmias 1 (0.5%), pneumothorax 2 (1%), acute myocardial infarction 1 (0.5%), low cardiac output syndrome 1 (0.5%), and deep sternal wound infection 1 (0.5%). There were no cases of post-operative CVA or TIA, respiratory or multisystem failure.

Late re-operation on aortic and pulmonary valves

(a) Neo-aortic valve for progressive AR. One patient developed moderate aortic regurgitation 3 years following surgery, and this resulted in symptomatic, enlarging left ventricular dimensions, leading to re-do AVR at 7 years. The freedom from re-operation on the neo-aortic valve for this problem can be seen in Figure 2b, which reveals 99% (96%, 100%) freedom at 15 years post-operatively.

(b) Endocarditis of aortic and pulmonary valves (3 patients). There was one case of aortic valve endocarditis, one case of pulmonary valve endocarditis, and one case of both aortic and pulmonary valve endocarditis occurring at 3, 7 and 9 years post-operatively. All three cases underwent re-operation successfully. Except for the case of lone endocarditis affecting the aortic valve in which the infection was peri-aortic and the pulmonary autograft valve preserved (as it was functioning normally), the other three infected valves (in 2 patients) required replacement. The cumulative incidence of endocarditis is 0.19%/pt/yr of follow up.

(c) Pulmonary valve for structural valve degeneration: there have been no re-operations necessary for this complication. Thus the freedom from all re-operations on aortic and pulmonary valves (see Figure 2c) is 97% (94%, 100%) at 15 years.

Late non-aortic or pulmonary valve cardiac re-operations

During the period prior to 1997, bicuspid aortic valve related aortopathy was not fully appreciated as an entity that could lead to later further dilatation of the mid ascending aorta. Four patients operated on between 1992 -1996 (inclusive) exhibited mild enlargement of the mid ascending aorta (maximum 4.5 cm. diameter). In these patients, none of whom underwent a procedure on the ascending aorta at their initial surgery, progressive later enlargement of the ascending aorta was noted, without any change in

aortic root size or aortic valve function. In each case, the ascending aorta was replaced electively once the ascending aortic diameter exceeded 5.0 cm. diameter. Two of these cases required hemi-arch replacement as well, and in the other two cases, near total arch replacement was required. These secondary operations were performed 7, 11, 12 and 15 years respectively after the primary operation. None of these cases required further

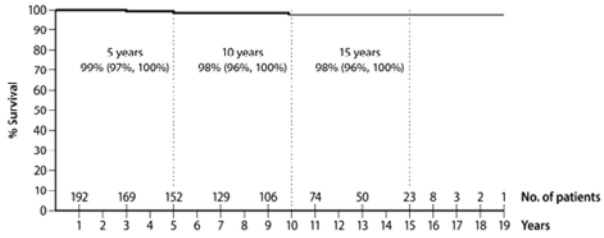


Figure 2a. Actuarial survival of entire cohort of 204 patients presenting with predominant AS (Kaplan-Meier).

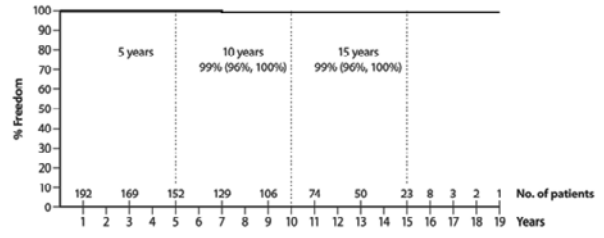


Figure 2b. Percent freedom from re-operation on the aortic valve in patients presenting with predominant AS (Kaplan-Meier).

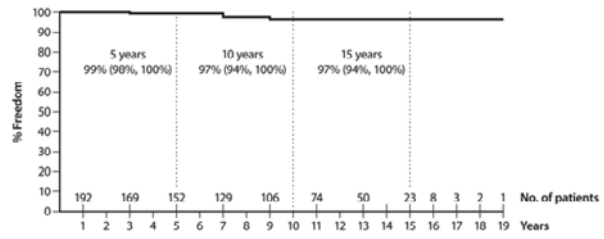


Figure 2c. Percent freedom from re-operation on both aortic and pulmonary valves for patients presenting with predominant AS (Kaplan-Meier).

surgery to either the aortic or pulmonary valves. Thus, these cases were not considered to be in the category of re-operations on either aortic or pulmonary valves. In addition, a further 5th patient developed severe mitral valve regurgitation two years after surgery, and required a mitral valve replacement using a mechanical prosthesis.

Late echo-doppler data

(a) Aortic valve function: Echocardiographic follow-up on autograft regurgitation. Regurgitation was graded as 0 for no regurgitation, 1+ trivial, 2+ mild, 3+ for moderate, and 4+ for severe. Because of low frequency (2 patients with a total of 7 observations) in grade 3+ this grade was collapsed together with 2+ and is treated as one category. None of the patients had 4+ AR. As can be seen in Figure 3a there is no general trend for increasing severity of post-operative AR over time. Mean aortic valve (autograft) gradients are between 4-5 mmHg, with no change over time (see Figure 3b).

(b) Aortic root size: The maximum aortic root diameter has been assessed, with measurements in mm. The assessments have been performed before surgery, one week after surgery, at one year post-operative, and then second yearly intervals. Because echocardiograms are performed every second year routinely, after three years, results for year 4, 5 post-operative, are included under 5 years, etc. As can be seen from Figure 4, mean aortic root size, as measured by maximum aortic size diameter increases very slowly with time. The mean pre-operative diameter is 33 (28, 38) mm and this increases to 35 (32, 38) mm at 15 years post-operative. This equates to 0.13mm increase in aortic root size per year, i.e. minimal increase in aortic size over time.

(c) Pulmonary valve function: The mean late pulmonary valve gradient, measured by Doppler study is 10 mmHg (limits 2 – 44). There are 6 patients with mean gradient between 20 to 30 mmHg, and 3 where this gradient exceeds 30 mmHg, i.e. only 4.4% in excess of 20 mmHg. Analysis of patients with pulmonary valve gradients in excess of 20 mmHg mean, shows that these gradients have appeared between 6 – 18 months after surgery, and then plateaued without further elevation over time. Right ventricular size, function and wall thickness have remained normal in these patients. Please see Figure 5a for the temporal change in pre-operative pulmonary valve gradient with time. Risk factors associated with increased post-operative pulmonary allograft gradient can be seen in Table 2. In summary, older recipient age, male patient gender, and earlier year of surgery were found to be associated with higher pulmonary allograft gradient during follow-up of patients after the Ross procedure. Older donor age, on the other hand, was associated with a lower allograft gradient. However, older donor age was found to be associated with an increased risk of higher PR (Table 3). The temporal trend in pulmonary valve regurgitation grade can be seen in Figure 5b.

NYHA Class: 99% are NYHA Class I, at most recent evaluation, 1% in NYHA Class II.

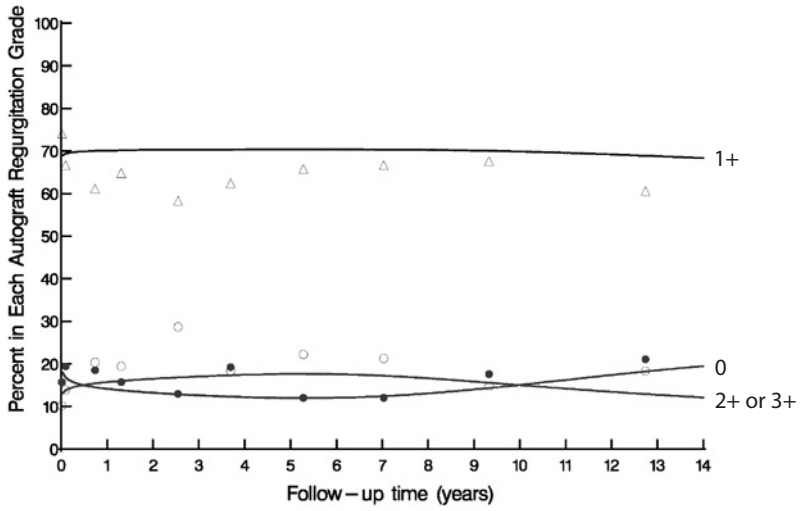


Figure 3a. Temporal trend of aortic regurgitation after the Ross procedure. Solid lines represent percentage of patients (mean effect) in each grade at various time points. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting. Aortic regurgitation was graded as 0 for no regurgitation, 1+ trivial, 2+ mild, 3+ for moderate, and 4+ for severe. Because of low frequency (2 patients with a total of 7 observations) in grade 3+ this grade was collapsed together with 2+ and is treated as one category. None of the patients had 4+ AR.

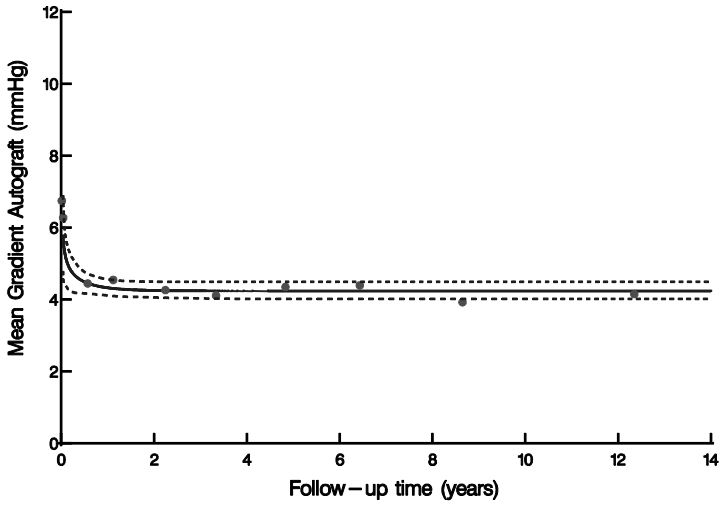


Figure 3b. Solid lines are parametric estimates of mean autograft gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

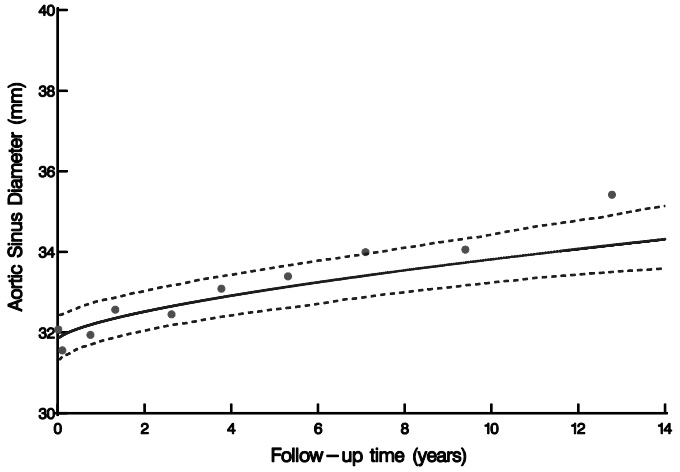


Figure 4. Temporal trend of echo derived maximum aortic root size, as assessed by maximum aortic sinus diameter (mm.). Solid lines are parametric estimates of mean aortic sinus diameter from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, 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.

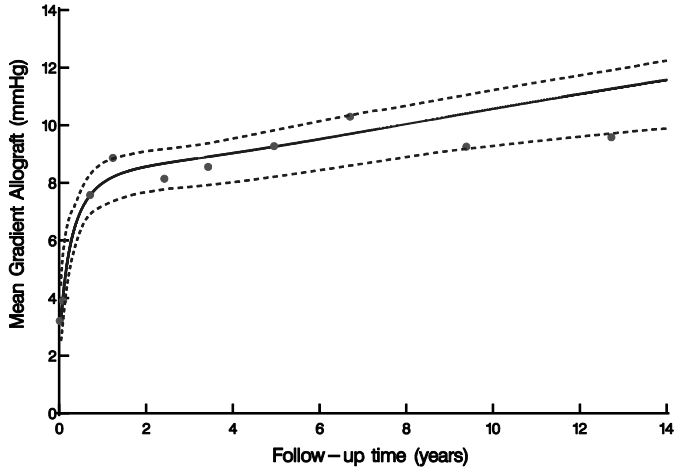


Figure 5a. Solid lines are parametric estimates of pulmonary allograft gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting. Pulmonary allograft regurgitation (PR) was graded as 0 for no regurgitation, 1+ trivial, 2+ mild, 3+ for moderate, and 4+ for severe. Because of low frequency (9 patients with a total of 14 observations) in grade 3+ this grade was collapsed together with 2+ and is treated as one category. None of the patients had 4+ PR.

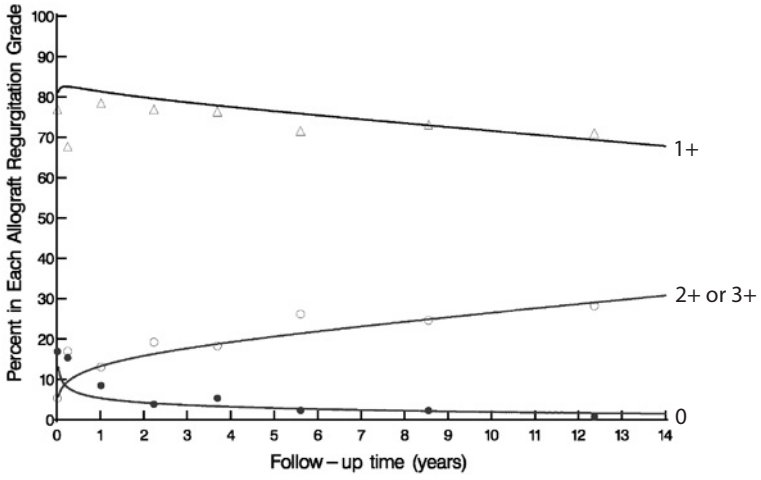


Figure 5b. Temporal trend of pulmonary allograft regurgitation after the procedure. Solid lines represent percentage of patients (mean effect) in each grade at various time points. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

Table 2. Pre-OP Risk factors associated with post-op pulmonary allograft gradient.

Factor	Estimate ± SE	P	Reliability
Recipient age*	0.0254±0.0070	0.0004	100
Male patient gender	0.0934±0.0207	<.0001	82.9
Donor age#	-0.1040±0.0293	0.0005	100
Timing/period of surgery^	0.1618±0.0319	<.0001	89.1

*During bootstrap analyses inverse of age was found to be most reliable and this variable was used in the multivariate analyses. #During bootstrap analyses the natural logarithm of donor age was found to be most reliable and this variable was used in the multivariate analyses. ^During bootstrap analyses the natural logarithm of 'timing of surgery' was found to be most reliable and this variable was used in the multivariate analyses

Table 3. Pre-OP Risk factors associated with post-op pulmonary allograft regurgitation.

Factor	Estimate ± SE	P	Reliability
Donor age*	0.7521±0.2840	0.0088	96.9

*During bootstrap analyses inverse of donor age was found to be most reliable and this variable was used in the multivariate analyses

DISCUSSION

This is the first report of a large and long-term experience with the Ross procedure employing an inclusion cylinder technique, with results extending far into the second post-operative decade. It shows that the use of this surgical technique in patients with predominant aortic stenosis provides a durable solution that is far superior to any other surgical technique and any other biological or mechanical valve substitute. Originally described as a method for implantation of the PA or an aortic allograft, the author has modified the technique (19) in order to retain the root replacement principle which ensures early neo-aortic valve competence.

With this technique, the patient's aortic root, rather than being discarded or substituted by prosthetic material to wrap around the PA, is retained as an autologous support around the autograft, the main advantage being to prevent its later enlargement which has been shown to lead to neo-aortic root aneurysm, and also, in an unsupported root replacement, to progressive aortic regurgitation, the main reason for late left-sided re-operation after the Ross procedure (13). The method employed is different to previous descriptions of the inclusion cylinder or intra-aortic implant techniques.

Late echo-Doppler assessment in this series shows that the IC method used limits expansion of the autograft root, with only 2 mm increase in maximum diameter during 15 years of follow up. There have been no cases of neo-aortic root aneurysmal enlargement noted in the follow up period either. This would appear to be the reason for excellent late results with this technique, with only one re-operation being necessary for progressive AR or structural valve degeneration of the autograft, leading to 15 year freedom from re-do AVR for this problem, of 99% (96%, 100%), as well as trivial incidence of moderate or greater late AR shown in 2 (1%) patients only, during the follow up period.

Late survival in this series is excellent also, with only 3 late deaths 98% (96%, 100%) survival at 15 years, none of which are cardiac related, all due to cancer. Many late deaths after tissue AVR have been shown in various series to be due to cardiac causes including heart failure, arrhythmias, re-operation and endocarditis. By minimising late aortic valve dysfunction and re-operation, presumably this should improve survival. It has been shown that in particular younger adult patients who undergo aortic valve replacement, there is a considerable excess mortality compared to the general population (32). This observation is not confirmed in our experience with the Ross procedure where we observe a late survival comparable to the general age and gender matched population.

Endocarditis remains an infrequent, although serious hazard for all patients undergoing AVR (16, 33, 34), regardless of the prosthesis used. In this series, there have been 3 patients who developed this complication, either on the aortic or pulmonary valves, or on both. Thus, the cumulative incidence of endocarditis in the patients with predomi-

nant AS is 0.19%/pt/yr, which is less than the overall rate of prosthetic valve endocarditis associated with other bioprostheses and mechanical valve prostheses (33-35).

The pulmonary valve replacement (PVR) remains the Achilles' heel of the Ross procedure. A proportion of patients after PVR with a pulmonary allograft (the PVR of choice in the Ross procedure) develop stenosis of the pulmonary allograft, probably of immunological or inflammatory basis. In this series, six of 204 patients have mean pulmonary valve (PV) gradients between 20 and 30 mmHg, and two between 30 and 40 mmHg. One patient was found to have an allograft gradient of 44mmHg two years postoperative, unfortunately this patient was lost to follow up. No patients have required re-intervention for this problem with the threshold for re-operation being the development of a mean PV gradient in excess of 40 mmHg, development of right ventricular enlargement or hypertrophy or development of symptoms. There is a slight trend for increasing pulmonary allograft regurgitation with time. It is highly probable that some patients will require re-operation on the PV in the future. Options will include percutaneous PVR or surgical PVR. If surgical PVR is required, it can be performed with cardiopulmonary bypass support, although without the need for aortic cross-clamping, with the heart continuing to beat throughout the procedure. This minimizes mortality and morbidity, if required in the future.

Thus, the freedom from all surgical re-interventions on either the aortic and pulmonary valves in this series of 204 patients presented, utilising the IC method is 97% (94%, 100%) at 15 years. This is better than many series of mechanical AVR patients (33-35), with the latter group not infrequently requiring late re-operation for issues such as prosthetic valve endocarditis, pannus obstruction and paravalvular leak.

Of course, the freedom from re-operation on the neo-aortic valve in this series will require further study, and it is assumed that some degree of valve degeneration could be expected after 15 years even if the pulmonary autograft valve remains viable, with no leaflet degeneration. Of course, Ross operation recipients have an advantage vs. mechanical valve subjects in that patients undergoing a Ross operation do not require anticoagulation with Coumadin and have better haemodynamic performance of the aortic valve than mechanical valve recipients (5).

Important limitations of this study include the fact that not all patients who are referred for a Ross procedure, ultimately have this operation performed. The reasons for exclusion include older age and excessive co-morbidities (especially in patients in their late 50s and 60s), because of the increased operation risk that would entail, patients with Marfan's syndrome and other connective tissue disorders, patients with more than minor coronary artery disease or mitral valve disease. Also patients with excessively dilated aortic roots. As mentioned in the methods section, if either the patient's aortic annulus or sinotubular junction exceeds 34 mm diameter, a Ross operation utilising the inclusion cylinder method described is not appropriate because of excessive pulmonary

valve/aortic valve size mismatch. The author would still manage a number of these cases by utilising the Ross principle, inserting the pulmonary autograft inside a Valsava dacron graft. Approximately 2% to 3% of patients have a structurally abnormal pulmonary valve, precluding a Ross operation. It is estimated that approximately 10% of all patients referred for a Ross procedure do not have a Ross utilising an inclusion cylinder method. However, if one looks at younger patients under the age of 50 years, the exclusion rate would fall to less than 5%.

In summary, long term follow up extending to 19 years in adult patients having a Ross operation for predominant aortic stenosis using an IC method, shows excellent patient survival and outstanding autograft durability. Enclosing the pulmonary autograft root in the patient's own aortic root provides autologous support for the autograft and has been shown to prevent late enlargement of the neo-aortic root with very low rate of late progressive AR, such that only 1 re-operation has been required for this problem, and with the remaining patients showing stable aortic valve function at late echo-Doppler assessment. In young adult patients with predominant AS who require AVR, the option of a Ross procedure employing the IC method should be considered in a centre of expertise that is successful in applying this method.

ACKNOWLEDGEMENTS

The authors would like to thank Tonia Iacuone for assistance with retrieval of references and typing of the manuscript. Also Mardi Malone for assistance with submission of the manuscript.

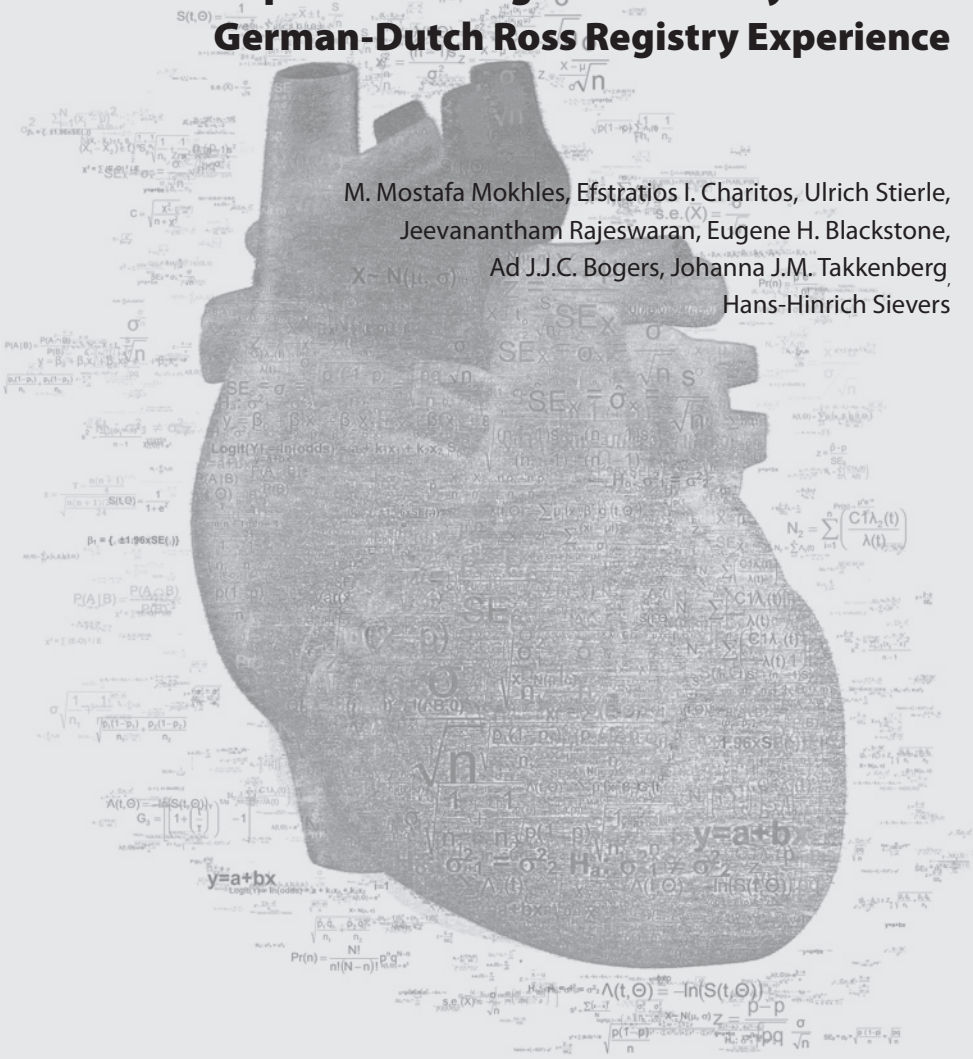
REFERENCES

1. Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, Steyerberg EW, van Herwerden LA, Grunkemeier GL, Habbema JD, Bogers AJ. Prognosis after aortic valve replacement with the Carpentier-Edwards pericardial valve: use of microsimulation. Ann Thorac Surg 2005; 80(3):825-831.
2. El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G, Takkenberg JJ, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 2010; 376(9740):524-531.
3. David TE, Puschmann R, Ivanov J, Bos J, Armstrong S, Feindel CM, Scully HE. Aortic valve replacement with stentless and stented porcine valves: a case-match study. J Thorac Cardiovasc Surg 1998; 116(2):236-241.
4. O'Brien MF, Stafford EG, Gardner MA, Pohlner PG, Tesar PJ, Cochrane AD, Mau TK, Gall KL, Smith SE. Allograft aortic valve replacement: long-term follow-up. Ann Thorac Surg 1995; 60(2 Suppl):S65-70.
5. Oury JH, Doty DB, Oswalt JD, Knapp JF, Mackey SK, Duran CM. Cardiopulmonary response to maximal exercise in young athletes following the Ross procedure. Ann Thorac Surg 1998; 66(6 Suppl):S153-154.
6. Porter GF, Skillington PD, Bjorksten AR, Morgan JG, Yapanis AG, Grigg LE. Exercise hemodynamic performance of the pulmonary autograft following the Ross procedure. J Heart Valve Dis 1999; 8(5):516-521.
7. Yacoub MH, Klieverik LM, Melina G, Edwards SE, Sarathchandra P, Bogers AJ, Squarcia U, Sani G, van Herwerden LA, Takkenberg JJ. An evaluation of the Ross operation in adults. J Heart Valve Dis 2006; 15(4):531-539.
8. Brown JW, Ruzmetov M, Shahriari A, Rodefeld MD, Mahomed Y, Turrentine MW. Midterm results of Ross aortic valve replacement: a single-institution experience. Ann Thorac Surg 2009; 88(2):601-607; discussion 607-608.
9. Sievers HH, Hanke T, Stierle U, Bechtel MF, Graf B, Robinson DR, Ross DN. A critical reappraisal of the Ross operation: renaissance of the subcoronary implantation technique? Circulation 2006; 114(1 Suppl):I504-511.
10. David TE, Woo A, Armstrong S, Maganti M. When is the Ross operation a good option to treat aortic valve disease? J Thorac Cardiovasc Surg 2010; 139(1):68-73; discussion 73-65.
11. Sievers HH, Stierle U, Charitos EI, Hanke T, Gorski A, Misfeld M, Bechtel M. Fourteen years' experience with 501 subcoronary Ross procedures: surgical details and results. J Thorac Cardiovasc Surg 2010; 140(4):816-822, 822 e811-815.
12. Elkins RC, Thompson DM, Lane MM, Elkins CC, Peyton MD. Ross operation: 16-year experience. J Thorac Cardiovasc Surg 2008; 136(3):623-630, 630 e621-625.
13. Klieverik LM, Takkenberg JJ, Bekkers JA, Roos-Hesselink JW, Witsenburg M, Bogers AJ. The Ross operation: a Trojan horse? Eur Heart J 2007; 28(16):1993-2000.
14. Frigiola A, Ranucci M, Carlucci C, Giamberti A, Abella R, Di Donato M. The Ross procedure in adults: long-term follow-up and echocardiographic changes leading to pulmonary autograft reoperation. Ann Thorac Surg 2008; 86(2):482-489.
15. Hanke T, Stierle U, Boehm JO, Botha CA, Matthias Bechtel JF, Erasmi A, Misfeld M, Hemmer W, Rein JG, Robinson DR, Lange R, Horer J, Moritz A, Ozaslan F, Wahlers T, Franke UF, Hetzer R, Hubler M, Ziemer G, Graf B, Ross DN, Sievers HH, German Ross R. Autograft regurgitation and aortic root dimensions after the Ross procedure: the German Ross Registry experience. Circulation 2007; 116(11 Suppl):I251-258.

16. Juthier F, Banfi C, Vincentelli A, Ennezat PV, Le Tourneau T, Pincon C, Prat A. Modified Ross operation with reinforcement of the pulmonary autograft: Six-year results. J Thorac Cardiovasc Surg 2010; 139(6):1420-1423.
17. Slater M, Shen I, Welke K, Komanapalli C, Ungerleider R. Modification to the Ross procedure to prevent autograft dilatation. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2005:181-184.
18. Koul B, Al-Rashidi F, Bhat M, Meurling C. A modified Ross operation to prevent pulmonary autograft dilatation. Eur J Cardiothorac Surg 2007; 31(1):127-128.
19. Skillington PD, Fuller JA, Grigg LE, Yapanis AG, Porter GF. Ross procedure. Inserting the autograft using a fully supported root replacement method; techniques and results. J Heart Valve Dis 1999; 8(6):593-600.
20. Skillington PD, Grigg LE. Insertion of the pulmonary autograft as an inclusion cylinder--modifications to existing techniques. J Heart Valve Dis 1995; 4(4):374-378.
21. Elkins RC, Santangelo K, Stelzer P, Randolph JD, Knott-Craig CJ. Pulmonary autograft replacement of the aortic valve: an evolution of technique. J Card Surg 1992; 7(2):108-116.
22. Pacifico AD, Kirklin JK, McGiffin DC, Matter GJ, Nanda NC, Diethelm AG. The Ross operation--early echocardiographic comparison of different operative techniques. J Heart Valve Dis 1994; 3(4):365-370.
23. Collett D. Modelling Survival Data in Medical Research, Chapman and Hall, London, 1994;22-26.
24. Blackstone EH, Rajeswaran J., A non-linear cumulative logit mixed model with time varying phases and coefficients, Conference proceedings, XXIII International Biometric Conference, Montreal, Canada 2006
25. Gillinov AM, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik JF, Svensson LG, Cosgrove DM, Hill KM, Gonzalez-Stawinski GV, Marrouche N, Natale A. Surgical ablation of atrial fibrillation with bipolar radiofrequency as the primary modality. J Thorac Cardiovasc Surg 2005; 129(6):1322-1329.
26. Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. J Thorac Cardiovasc Surg 2001; 122(3):430-439.
27. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of longitudinal data. 2nd ed. New York: Oxford University Press, 2002
28. Mason DP, Rajeswaran J, Murthy SC, McNeill AM, Budev MM, Mehta AC, Pettersson GB, Blackstone EH. Spirometry after transplantation: how much better are two lungs than one? Ann Thorac Surg 2008; 85(4):1193-1201, 1201 e1191-1192.
29. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of longitudinal data. 2nd ed. New York: Oxford University Press, 2002.
30. Breiman L. Bagging predictors. Machine Learning. 1996;24:123-140.
31. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman and Hall/CRC; 1998.
32. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. J Am Coll Cardiol 2000; 35(3):747-756.
33. Zellner JL, Kratz JM, Crumbley AJ, 3rd, Stroud MR, Bradley SM, Sade RM, Crawford FA, Jr. Long-term experience with the St. Jude Medical valve prosthesis. Ann Thorac Surg 1999; 68(4):1210-1218.
34. Butchart EG, Li HH, Payne N, Buchan K, Grunkemeier GL. Twenty years' experience with the Medtronic Hall valve. J Thorac Cardiovasc Surg 2001; 121(6):1090-1100.
35. Lund O, Nielsen SL, Arildsen H, Ilkjaer LB, Pilegaard HK. Standard aortic St. Jude valve at 18 years: performance profile and determinants of outcome. Ann Thorac Surg 2000; 69(5):1459-1465.

Chapter 16

The Faith of Pulmonary Conduit after the Ross Operation: Longitudinal analysis of the German-Dutch Ross Registry Experience



M. Mostafa Mokhles, Efstratios I. Charitos, Ulrich Stierle, Jeevanantham Rajeswaran, Eugene H. Blackstone, Ad J.J.C. Bogers, Johanna J.M. Takkenberg, Hans-Hinrich Sievers

Heart, in press

ABSTRACT

Objective: To assess the allograft function over time after the Ross procedure.
Design: Prospective multi-center 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 Ross patients, 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 4.7mmHg at 1 month to 10mmHg by 14 years, while peak gradient increased from 8.4mmHg to 18.5mmHg.

Smaller conduit diameter, male patient gender, younger patient age, younger donor age, and use of bioprosthesis were associated with a significantly higher mean and peak gradient.

During follow-up 76 re-interventions were required on the pulmonary conduit in 67 patients. Freedom from pulmonary conduit re-intervention or dysfunction was 90.6% (87.7–93.6%) and 79.5% (75.2–84.0%) at 15 years, respectively.
Conclusions: Echocardiographic follow-up of pulmonary conduits shows outstanding conduit durability. Clinically important conduit regurgitation and stenosis is 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 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's crucial for more comprehensive judgment of this operation since this procedure results in treatment of a single aortic valve disease with a two valve procedure subsequently placing two valves at risk for 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. This knowledge can potentially lead to a 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 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 only in few reports with small patient numbers (3, 9-11). The natural dynamics of conduit stenosis and/or regurgitation are poorly understood.

In the present multi-center study the availability of large number of patients and systematically collected echocardiographic records, and the use of sophisticated statistical methods offer the unique opportunity to extensively study the pulmonary conduit function over time in Ross patients and to the explore potential risk factors associated with poor performance of the pulmonary conduits.

METHODS

Study population

Data from 2038 patients who underwent a Ross operation between November 1988 and September 2011 were collected and analyzed from the German-Dutch Ross Registry database. All patients aged ≥ 16 years (n=1775) were subject of this 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 center (Clinical trial ID NCT 00708409).

Table 1. Baseline patient characteristics.

Characteristic	Patient cohort (n=1775)	
	Data avalaible n(%)*	No. (%) or Mean ± SD
Demography		
Age (y)	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 hemodynamics	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 24h		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 (e.g. 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 (e.g. heart block, pacemaker)		6 (0.34)
Left Ventricular Function	1189 (67)	
Ejection Fraction ≥ 50 %		1051 (88)
Ejection Fraction 26 – 49 %		134 (11)
Ejection Fraction ≤ 25 %		4 (0.34)
Ejection Fraction (continuous, %)	1276 (72)	63.5 ± 11.3

**Number of patients from whom data is available.*

Surgical technique

The surgical technique was determined by the responsible surgeon at each center. Details of the operative technique have been described elsewhere (6, 7). Perioperative and pulmonary 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 vast 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.

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 color flow Doppler echocardiography, analogous to the semi quantitative 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 tiny regurgitation jet in early diastole near the detection limit was included in the analyses as grade 0.5. Because of low frequency of patients in grade 4 (n=7), this grade was collapsed with grade 3 and treated as one category. Since this is a multi-center study, the final decision of regurgitation grading was left to the decision of the attenting echocardiographer. Maximum velocities across the pulmonary conduit were obtained by continuous Doppler in the basal short axis. Pressure gradients across the right ventricular outflow tract were calculated by the modified Bernoulli equation.

The prospective echocardiographic database was frozen on November 1st 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). The number of patients and echocardiographic measurements available for analyses at each follow-up point are shown in Table 3. Based on the distribution of the echocardiographic measurements, we can reliably assess overall temporal trend up to 14 years postoperatively.

A total of 6950 standardized echocardiographic measurements were analyzed. 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 e.g. did not reach 12 months postoperative follow-up at the time of database freeze, lost to follow-up) (Figure 1).

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).

Table 2. Perioperative characteristics.

Characteristic	Patient cohort (n=1775)	
	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)
Aorta Ascendens and or Arch reconstruction	1775 (100)	601 (34)
Specific surgical adjustments of the allograft#	1775 (100)	215 (12)

CABG, *Coronary Artery Bypass Grafting*; *Number of patients from whom data is 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.

Statistical Analyses

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

Table 3. Number of patients with echocardiograms available at and beyond various time points, and number of echocardiograms available for analysis.

Time	Regurgitation		Mean gradient		Peak gradient	
	# of Patients	# of Echoes	# of Patients	# of Echoes	# of Patients	# of Echoes
> 0	1516	6784	1320	5523	1442	6253
≥ 6 Months	1456	6194	1261	5103	1389	5767
≥ 1 Year	1379	5644	1193	4669	1315	5266
≥ 3 Years	1135	4192	986	3515	1081	3933
≥ 5 Years	907	3003	793	2536	875	2832
≥ 7 Years	683	1978	591	1680	657	1873
≥ 10 Years	375	845	324	724	364	797
≥ 12 Years	212	408	185	360	203	386
≥ 14 Years	89	155	79	136	84	143

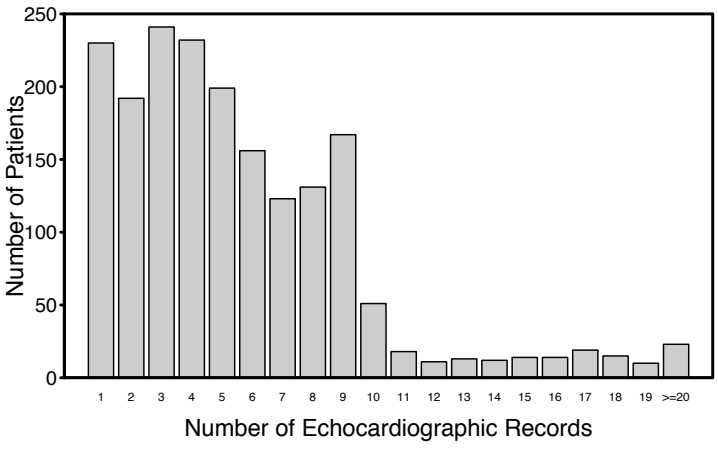


Figure 1. Number of echoes available per patient.

Analyses of clinical data

Actuarial estimates of freedom from conduit reintervention and conduit failure were accomplished with Kaplan-Meier methods (SPSS 11.0 for Windows, SPSS Inc., Chicago, Ill.). The indications for reintervention were clinically overt right heart failure, medically intractable infective endocarditis or maximal pressure gradients across the right ventricular outflow tract 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 mmHg or regurgitation grade III or IV.

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 analyzed longitudinally for change in percentages of patients in each aortic regurgitation grades 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 echo-cardiographic measurements were analyzed longitudinally for change in mean response across time (15). A non-linear longitudinal mixed model regression (16, 17) (SAS® PROC NLMIXED) was used to analyze these continuous repeated measurements.

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 utilized 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 statistical 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 SAS9.1 (SAS® , Cary, N.C.).

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 7 reinterventions. Pulmonary conduit endocarditis was present in 16 reinterventions.

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

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 6 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 99.2–99.9%), 95.5% at 10 years (95% CI 94.1–97.0%), and 91.4% at 15 years (95% CI 88.5–94.3%). Freedom from pulmonary conduit failure was 98.4% at 1 year (95% CI 97.8–99.0%), 88.4% at 10 years (95% CI 86.4–90.5%), and 78.1% at 15 years (95% CI 74.6–83.1%).

With regard to bioprostheses, during follow-up 13 reinterventions (8 explants, 5 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 1 reinterventions. Pulmonary conduit endocarditis was present in 2 reinterventions. In patients with bioprostheses freedom from reintervention was 98.2% at 1 year (95% CI 95.8–100.0%) and 85.4% at 10 years (95% CI 78.0–93.6%). Freedom from dysfunction was 91.4% at 1 year (95% CI 86.8–96.2%) and 66.8% at 5 years (95% CI 55.3–80.6).

Pulmonary conduit Regurgitation with Time

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.

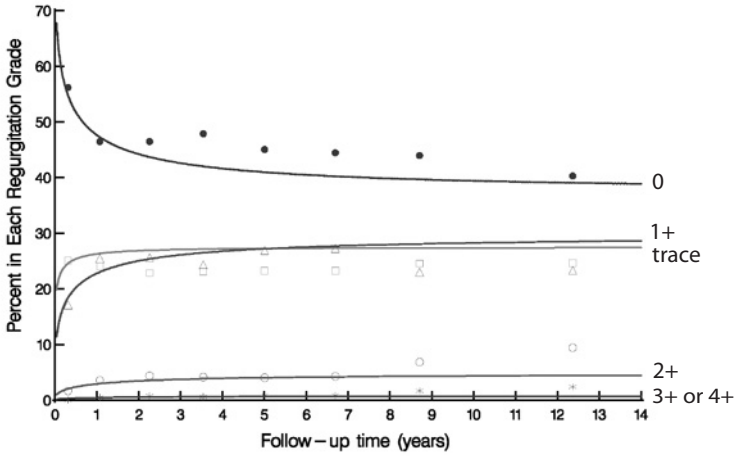


Figure 2(a). Temporal trend of pulmonary regurgitation grade after the Ross procedure. Solid lines represent percentage of patients (mean effect) in each grade at various time points. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

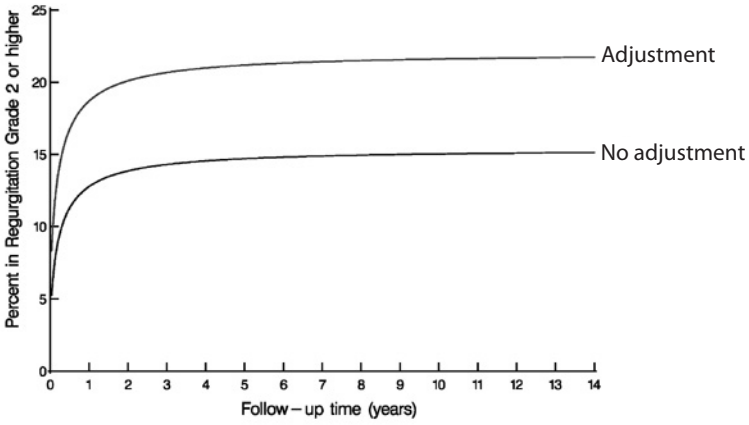


Figure 2(b). Predicted percentages of patients in regurgitation grade 2 or higher stratified by specific surgical adjustments of the allograft. The nomogram was solved for patients with high risk profile with the following values for variables in the model: Type of prosthesis = allograft, antibiotic treatment of the allograft = yes, female donor gender, female recipient gender, absence of sclerosis or fibrosis, and absence of fenestrations.

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 2(a))

The risk factors associated with a greater risk of higher pulmonary conduit regurgitation grade are shown in Table 4. 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 higher risk of higher pulmonary conduit regurgitation grade. In addition, the use of allograft (as compared to 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 2(b)).

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).

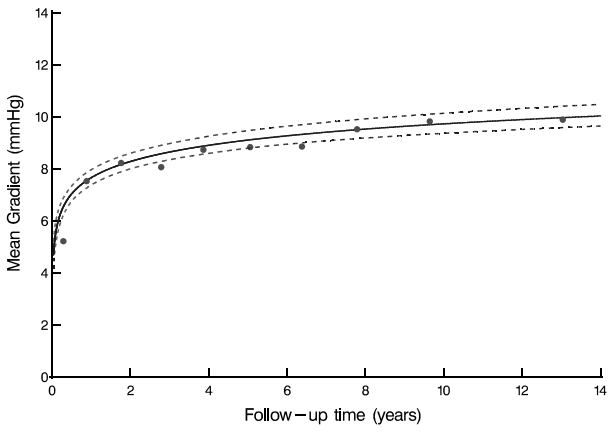


Figure 3. Solid lines are parametric estimates of mean gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

Table 4. Risk factors associated with increased likelihood of higher conduit regurgitation grade and increased mean/peak conduit gradient.

Factor	Estimate ± SE	*P*	*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	<.001	89.3
Risk factors related to allografts only			
Surgical adjustment of the allograft	0.64 ± 0.20	0.001	100
Antibiotic treatment of the allograft	1.01 ± 0.23	<.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	<.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	<.001	95
Younger patient age*	- 0.16 ± 0.02	<.001	100
Use of bioprosthesis (as compared to allograft)	0.21 ± 0.04	<.001	96
Smaller conduit diameter†	- 0.27 ± 0.06	<.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	<.001	98
Use of bioprosthesis (as compared to allograft)	0.81 ± 0.17	0.002	76
Younger patient age*	- 0.75 ± 0.08	<.001	100
Male patient gender	0.41 ± 0.05	<.001	59
Recent date of surgery§	0.16 ± 0.08	0.039	73
Interrupted proximal sutureline	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	<.001	100

*[Patient age / 40], †[Conduit diameter /25], ‡[Donor age /47], §[Interval first-last surgery in database/15]

Pulmonary Conduit Obstruction with Time

Mean pulmonary conduit gradient

Mean pulmonary conduit gradient increased from about 4.7 mmHg at 1 month to about 10 mmHg by 14 years after the procedure (Figure 3). 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 ($p<0.001$) and the use of smaller conduit diameters ($p<0.001$) were correlated with a higher mean pulmonary conduit gradient. Furthermore, the use of bioprosthesis (as compared to allografts) ($p<0.001$) appeared to be associated with higher pulmonary conduit gradient.

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.

Peak pulmonary conduit gradient

Peak pulmonary conduit gradient appears to be slightly increased from about 8.4 mmHg at 1 month to about 18.5 mmHg by 14 years after the procedure (Figures 4(a)). 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 4(b)) and the use of bioprosthesis (as compared to allograft) ($p<0.001$) (Figure 4(b)) were associated with a significantly higher peak pulmonary conduit gradient after 14 years of follow-up. Figure 4b 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 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 bioprosthesis is correlated with a higher gradient compared to the use of allografts, independent of how old the patient is at the time of z (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 interrupted suturline (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 right ventricular outflow tract 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.

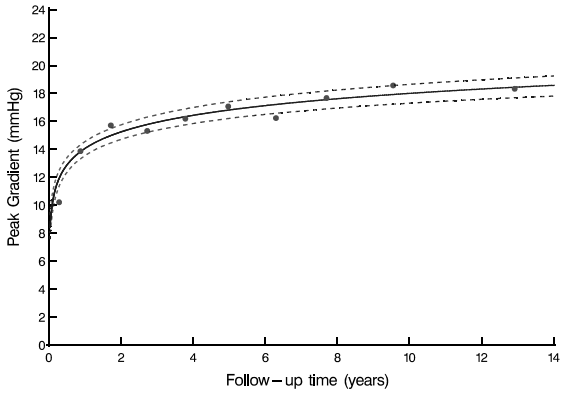


Figure 4(a). Solid lines are parametric estimates of peak gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

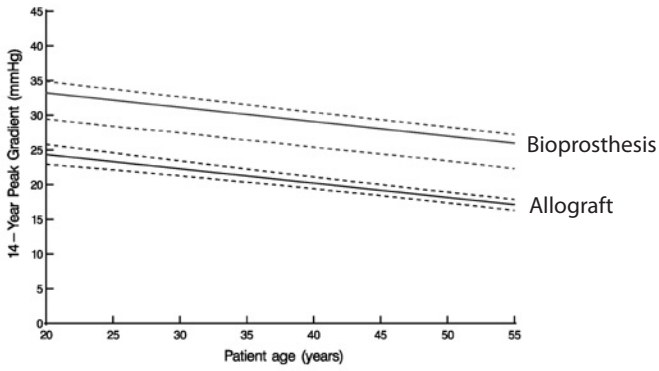


Figure 4(b). 14-Year predicted peak gradient by age, stratified by type of prosthesis used. The nomogram was solved for the following values for variables in the model: Mean conduit diameter (25 mm), continuous proximal sutureline, allograft harvested from non-heart beating donor, male patient gender, and mean donor age (47 years).

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 less than 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 follow-up of the Ross patients.

The use of allografts in the reconstruction of the right ventricular outflow tract 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 preparation and storage of this valves, have led to the use of bioprostheses as a suitable alternatives. Some studies investigating hard clinical end-points showed comparable intermediate results between allograft and bioprosthesis (19, 20), while other reported a significantly higher risk of reintervention for bioprosthetic valves as compared to allografts (21). The results of the present study show that the use of bioprosthetic valves is correlated with significantly higher mean and peak gradient 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, 22). We observed a clear age-dependent association between donor age and mean/peak allograft gradient: the younger the donor allograft, the higher allograft mean and peak gradient. This is in accordance to communications in the literature which reported on the entire age range from infants to adults (23). 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 amounts of viable cells with pronounced immunogenic properties (23).

The effect of conduit diameter on valve failure has been extensively studied, but no generally accepted consensus has been reached (24, 25). Previous reports have shown that smaller conduit diameter is associated with limited longevity while others did not find any relation between absolute allograft diameter and its longevity (26-28). 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 immunological 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 hemodynamics (11).

Shrinkage of the allograft was pronounced in the proximal annulus area (29), suggesting that implantation of a glutaraldehyde fixated pericardial strip after donor muscle resection might reduce allograft annulus shrinkage with a hemodynamic 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 modeled results.

A more recent year of operation was correlated with a significantly higher peak conduit gradient. This finding has also been previously reported by other investigators (22).

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(30), other investigators were not able to find any association at all (31-33). 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 hemodynamic 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 homograft 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 of reoperation) have to be reported, but also the number of conduits at risk with an expected high failure rate in the longer term. An almost linear increase of the mean transvalvular gradient occurred within the first two years and flattened out in a steady state afterwards. In contrast, a small gradual increase in conduit regurgitation with 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 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 right ventricular outflow tract substitute so far, due to the lacking scientific evaluation with respect to large patient cohorts and mid-term or even long term observation.

Strengths and Limitations

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

One of the major strengths of the present study is 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 generalisability of the results presented. Furthermore, the statistical analysis of serial echocardiographic data in the previously mentioned studies is often performed by means of the Kaplan-Meier method. However, this method considers follow-up time as a continuous variable while echo data are usually available within a certain time frame and are often incomplete in one or more time frames. In addition it considers valve dysfunction as an irreversible endpoint, while severity of regurgitation is often variable over time. Furthermore, only a snapshot image of valve function is expressed by this approach (34). 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 visualize the temporal trend of each conduit regurgitation grade over time during follow up which enables the clinicians to exactly determine how conduit regurgitation develops over time after valve implantation. These methods are superior to dichotomizing outcomes and analyzing them with actuarial methods as if they were events, such as freedom from grade 1+ or 3+ conduit regurgitation after valve surgery (35, 36). Modeling of the temporal trend and identifying factors that influence this temporal trend can be of particular importance since it can help the clinicians understand how a certain process changes over time and thus can contribute to a better

patient management (e.g. by determining which patients should be monitored more closely by their physicians and at which time interval).

The current study presents several limitations. The mean echocardiographic follow-up time is 5.5 ± 4.2 years. Furthermore, a slow-going hemodynamic deterioration of the right ventricular outflow tract conduit is well compensated clinically for a long time. Therefore, long-term studies are necessary. As with all multi-centre echocardiographic follow-up studies, a bias cannot be excluded and may have influenced the results. The lack of an echo core lab 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 it.

Conclusions

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

ACKNOWLEDGEMENT

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.

REFERENCES

1. Luciani GB, Favaro A, Casali G, Santini F, Mazzucco A. Ross operation in the young: a ten-year experience. Ann Thorac Surg 2005; 80(6):2271-2277.
2. El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G, Takkenberg JJ, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 2010; 376(9740):524-531.
3. Mokhles MM, Rizopoulos D, Andrinopoulou ER, Bekkers JA, Roos-Hesselink JW, Lesaffre E, Bogers AJ, Takkenberg JJ. Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure: insights from the Rotterdam Prospective Cohort Study. Eur Heart J 2012; 33(17):2213-2224.
4. Skillington PD, Mokhles MM, Takkenberg JJ, O'Keefe M, Grigg L, Wilson W, Larobina M, Tatoulis J. Twenty-Year Analysis of Autologous Support of the Pulmonary Autograft in the Ross Procedure. Ann Thorac Surg 2013.
5. Sievers HH, Hanke T, Stierle U, Bechtel MF, Graf B, Robinson DR, Ross DN. A critical reappraisal of the Ross operation: renaissance of the subcoronary implantation technique? Circulation 2006; 114(1 Suppl):I504-511.
6. Hanke T, Stierle U, Boehm JO, Botha CA, Matthias Bechtel JF, Erasmi A, Misfeld M, Hemmer W, Rein JG, Robinson DR, Lange R, Horer J, Moritz A, Ozaslan F, Wahlers T, Franke UF, Hetzer R, Hubler M, Ziemer G, Graf B, Ross DN, Sievers HH, German Ross R. Autograft regurgitation and aortic root dimensions after the Ross procedure: the German Ross Registry experience. Circulation 2007; 116(11 Suppl):I251-258.
7. Takkenberg JJ, van Herwerden LA, Galema TW, Bekkers JA, Kleyburg-Linkers VE, Eijkemans MJ, Bogers AJ. Serial echocardiographic assessment of neo-aortic regurgitation and root dimensions after the modified Ross procedure. J Heart Valve Dis 2006; 15(1):100-106; discussion 106-107.
8. Yacoub MH, Klieverik LM, Melina G, Edwards SE, Sarathchandra P, Bogers AJ, Squarcia U, Sani G, van Herwerden LA, Takkenberg JJ. An evaluation of the Ross operation in adults. J Heart Valve Dis 2006; 15(4):531-539.
9. Kouchoukos NT, Masetti P, Nickerson NJ, Castner CF, Shannon WD, Davila-Roman VG. The Ross procedure: long-term clinical and echocardiographic follow-up. Ann Thorac Surg 2004; 78(3):773-781; discussion 773-781.
10. Elkins RC. The Ross operation: a 12-year experience. Ann Thorac Surg 1999; 68(3 Suppl):S14-18.
11. Carr-White GS, Kilner PJ, Hon JK, Rutledge T, Edwards S, Burman ED, Pennell DJ, Yacoub MH. Incidence, location, pathology, and significance of pulmonary homograft stenosis after the Ross operation. Circulation 2001; 104(12 Suppl 1):I16-20.
12. Perry GJ, Helmcke F, Nanda NC, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. J Am Coll Cardiol 1987; 9(4):952-959.
13. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008; 135(4):732-738.
14. Efron, B and Tibshirani, R.J., An introduction to the bootstrap, New York, Chapman and Hall/CRC, 1998.
15. Mason DP, Rajeswaran J, Murthy SC, McNeill AM, Budev MM, Mehta AC, Pettersson GB, Blackstone EH. Spirometry after transplantation: how much better are two lungs than one? Ann Thorac Surg 2008; 85(4):1193-1201, 1201 e1191-1192.

16. Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. J Thorac Cardiovasc Surg 2001; 122(3):430-439.
17. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of longitudinal data. 2nd ed. New York: Oxford University Press, 2002.
18. Breiman L. Bagging predictors. Machine Learning. 1996;24:123-140.
19. Novick WM, Anic D, Lora Solf A, Arboleda Torres M, Nino De Guzman Leon I, Reid RW, Di Sessa TG. Medtronic Freestyle valve for right ventricular reconstruction in pediatric Ross operations. Ann Thorac Surg 2004; 77(5):1711-1716.
20. Bilal MS, Aydemir NA, Cine N, Turan T, Yildiz Y, Yalcin Y, Celebi A. Intermediate-term results of Medtronic freestyle valve for right ventricular outflow tract reconstruction in the Ross procedure. J Heart Valve Dis 2006; 15(5):696-701.
21. Miskovic A, Monsefi N, Doss M, Ozaslan F, Karimian A, Moritz A. Comparison between homografts and Freestyle(R) bioprosthesis for right ventricular outflow tract replacement in Ross procedures. Eur J Cardiothorac Surg 2012.
22. Niwaya K, Knott-Craig CJ, Lane MM, Chandrasekaren K, Overholt ED, Elkins RC. Cryopreserved homograft valves in the pulmonary position: risk analysis for intermediate-term failure. J Thorac Cardiovasc Surg 1999; 117(1):141-146; discussion 146-147.
23. Feier H, Collart F, Ghez O, Riberi A, Caus T, Kreitmann B, Metras D. Risk factors, dynamics, and cutoff values for homograft stenosis after the Ross procedure. Ann Thorac Surg 2005; 79(5):1669-1675; discussion 1675.
24. Raanani E, Yau TM, David TE, Dellgren G, Sonnenberg BD, Omran A. Risk factors for late pulmonary homograft stenosis after the Ross procedure. Ann Thorac Surg 2000; 70(6):1953-1957.
25. Askovich B, Hawkins JA, Sower CT, Minich LL, Tani LY, Stoddard G, Puchalski MD. Right ventricle-to-pulmonary artery conduit longevity: is it related to allograft size? Ann Thorac Surg 2007; 84(3):907-911; discussion 911-902.
26. Tatebe S, Nagakura S, Boyle EM, Jr., Duncan BW. Right ventricle to pulmonary artery reconstruction using a valved homograft. Circ J 2003; 67(11):906-912.
27. Forbess JM, Shah AS, St Louis JD, Jaggers JJ, Ungerleider RM. Cryopreserved homografts in the pulmonary position: determinants of durability. Ann Thorac Surg 2001; 71(1):54-59; discussion 59-60.
28. Perron J, Moran AM, Gauvreau K, del Nido PJ, Mayer JE, Jr., Jonas RA. Valved homograft conduit repair of the right heart in early infancy. Ann Thorac Surg 1999; 68(2):542-548.
29. Bechtel JF, Gellissen J, Erasmi AW, Petersen M, Hiob A, Stierle U, Sievers HH. Mid-term findings on echocardiography and computed tomography after RVOT-reconstruction: comparison of decellularized (SynerGraft) and conventional allografts. Eur J Cardiothorac Surg 2005; 27(3):410-415; discussion 415.
30. Christenson JT, Sierra J, Colina Manzano NE, Jolou J, Beghetti M, Kalangos A. Homografts and xenografts for right ventricular outflow tract reconstruction: long-term results. Ann Thorac Surg 2010; 90(4):1287-1293.
31. Jashari R, Daenen W, Meyns B, Vanderkelen A. Is ABO group incompatibility really the reason of accelerated failure of cryopreserved allografts in very young patients?--Echography assessment of the European Homograft Bank (EHB) cryopreserved allografts used for reconstruction of the right ventricular outflow tract. Cell Tissue Bank 2004; 5(4):253-259.
32. Lange R, Weipert J, Homann M, Mendler N, Paek SU, Holper K, Meisner H. Performance of allografts and xenografts for right ventricular outflow tract reconstruction. Ann Thorac Surg 2001; 71(5 Suppl):S365-367.

33. Mokhles MM, van den Bogaerdt AJ, Takkenberg JJ, Bogers AJ. Right ventricular outflow tract reconstruction: the impact of allograft characteristics. Ann Thorac Surg 2011; 91(6):2025.
34. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 2008; 85(4):1490-1495.
35. Murashita T, Kubota T, Kamikubo Y, Shiiya N, Yasuda K. Long-term results of aortic valve regurgitation after repair of ruptured sinus of valsalva aneurysm. Ann Thorac Surg 2002; 73(5):1466-1471.
36. Losay J, Touchot A, Capderou A, Piot JD, Belli E, Planche C, Serraf A. Aortic valve regurgitation after arterial switch operation for transposition of the great arteries: incidence, risk factors, and outcome. J Am Coll Cardiol 2006; 47(10):2057-2062.
37. Rubin D.B., Multiple Imputation for Non-response in Surveys, Wiley: New York, 1997.
38. Blackstone EH, Rajeswaran J., A non-linear cumulative logit mixed model with time varying phases and coefficients, Conference proceedings, XXIII International Biometric Conference, Montreal, Canada 2006.
39. Gillinov AM, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik JF, Svensson LG, Cosgrove DM, Hill KM, Gonzalez-Stawinski GV, Marrouche N, Natale A. Surgical ablation of atrial fibrillation with bipolar radiofrequency as the primary modality. J Thorac Cardiovasc Surg 2005; 129(6):1322-1329.
40. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of longitudinal data. 2nd ed. New York: Oxford University Press, 2002.
41. Breiman L. Bagging predictors. Machine Learning. 1996;24:123-140.
42. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman and Hall/CRC; 1998.

LIST OF ABBREVIATIONS

CABG	Coronary Artery Bypass Graft
NYHA	New York Heart Association Functional Classification
SD	Standard Deviation
SE	Standard Error
VSD	Ventricular Septal Defect

APPENDIX: DETAILS OF STATISTICAL ANALYSES

Missing values

In the present study, some variables have missing values. We have used multiple imputation (37) using Markov Chain Monte Carlo technique to impute the missing values. We have used 5-fold multiple imputation using PROC MI (SAS v9.1, Cary, N.C.). In multivariate modeling, for each imputed complete dataset, we have estimated the regression coefficients and their variance-covariance matrix. Then following Rubin (16), we have combined the estimates from the 5 models. This was implemented using PROC MIANALYZE.

Analyses of categorical echocardiographic measurement

A non-linear cumulative logit mixed model(38, 39) was used to resolve a number of time phases on cumulative odds domain to form a temporal decomposition model and to estimate the shaping parameters at each phase. Longitudinal cumulative logistic mixed model(16, 40) for repeated measurements (SAS® PROC NLMIXED) was used to implement the temporal decomposition model and to estimate the patient-specific probabilities for being in each conduit regurgitation grade. These patient-specific estimates were then averaged to obtain the percentages of patients (prevalence) in each grade.

Variable selection and risk factor analyses

Variable selection, with a P value criterion for retention of variables in the model of .05, utilized bootstrap bagging (bootstrap aggregation) (16, 41). This was a four-step process. First, a patient was randomly selected from the original data set to begin a new data set. The original data set continued to be sampled until the new data set was 100% the size of the original. Second, risk factors were identified using automated forward stepwise selection. Third, results of the variable selection were stored. These three steps were repeated 1000 times. Finally, the frequency of occurrence of variables related to group membership was ascertained and indicated the reliability of each variable (aggregation step). All variables with bootstrap reliability of 50% or greater were retained in the guided analysis.

Because of the limited capability of PROC NLMIXED to explore multivariable relations, we initially screened the variables using ordinary multivariable linear regression (PROC REG SAS) and the assumption of independence of observations with liberal entry criteria (0.2) and stay criteria (0.12). This analysis was performed simply to identify possible candidates for our repeated measurements model. These candidates and their transformations, if any, were entered at once into our model, and then eliminated one by one until all variables remaining had a P value of 0.05 or less. Parametric estimates of continuous

postoperative echocardiography measurements are accompanied by asymmetric 95% confidence limits, comparable to ± 2 SE, obtained by a bootstrap percentile method (42).

REFERENCES APPENDIX STATISTICAL ANALYSES DETAILS

1. Rubin D.B., Multiple Imputation for Non-response in Surveys, Wiley: New York, 1997.
2. Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. J Thorac Cardiovasc Surg 2001; 122(3):430-439.
3. Blackstone EH, Rajeswaran J., A non-linear cumulative logit mixed model with time varying phases and coefficients, Conference proceedings, XXIII International Biometric Conference, Montreal, Canada 2006.
4. Gillinov AM, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik JF, Svensson LG, Cosgrove DM, Hill KM, Gonzalez-Stawinski GV, Marrouche N, Natale A. Surgical ablation of atrial fibrillation with bipolar radiofrequency as the primary modality. J Thorac Cardiovasc Surg 2005; 129(6):1322-1329.
5. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of longitudinal data. 2nd ed. New York: Oxford University Press, 2002.
6. Breiman L. Bagging predictors. Machine Learning. 1996;24:123-140.
7. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman and Hall/CRC; 1998.

APPENDIX: PARTICIPATING CENTERS ROSS REGISTRY

University of Luebeck, Department of Cardiac and Thoracic Vascular Surgery, Luebeck, Germany, Registry Site
Thorsten Hanke, MD
J.F Matthias Bechtel, MD
Armin Gorski, MD

Erasmus University Medical Center, Department of Cardiothoracic Surgery, Rotterdam, The Netherlands
Ad JJC Bogers, MD PhD
Johanna JM Takkenberg, MD PhD

Sana Herzchirurgische Klinik, Stuttgart, Germany
Wolfgang Hemmer

Herzzentrum Bodensee, Konstanz, Germany
Cornelius A. Botha, MD

Robert-Bosch-Hospital, Stuttgart, Germany
Ulrich F. W. Franke, MD
Marc Albert, MD

University Wuerzburg, Department of Cardiothoracic Surgery, Wuerzburg, Germany
Armin Gorski, MD

University Heart Center Hamburg, Hamburg, Germany
Siegmar Sachweh, MD
Arlindo Riso, MD

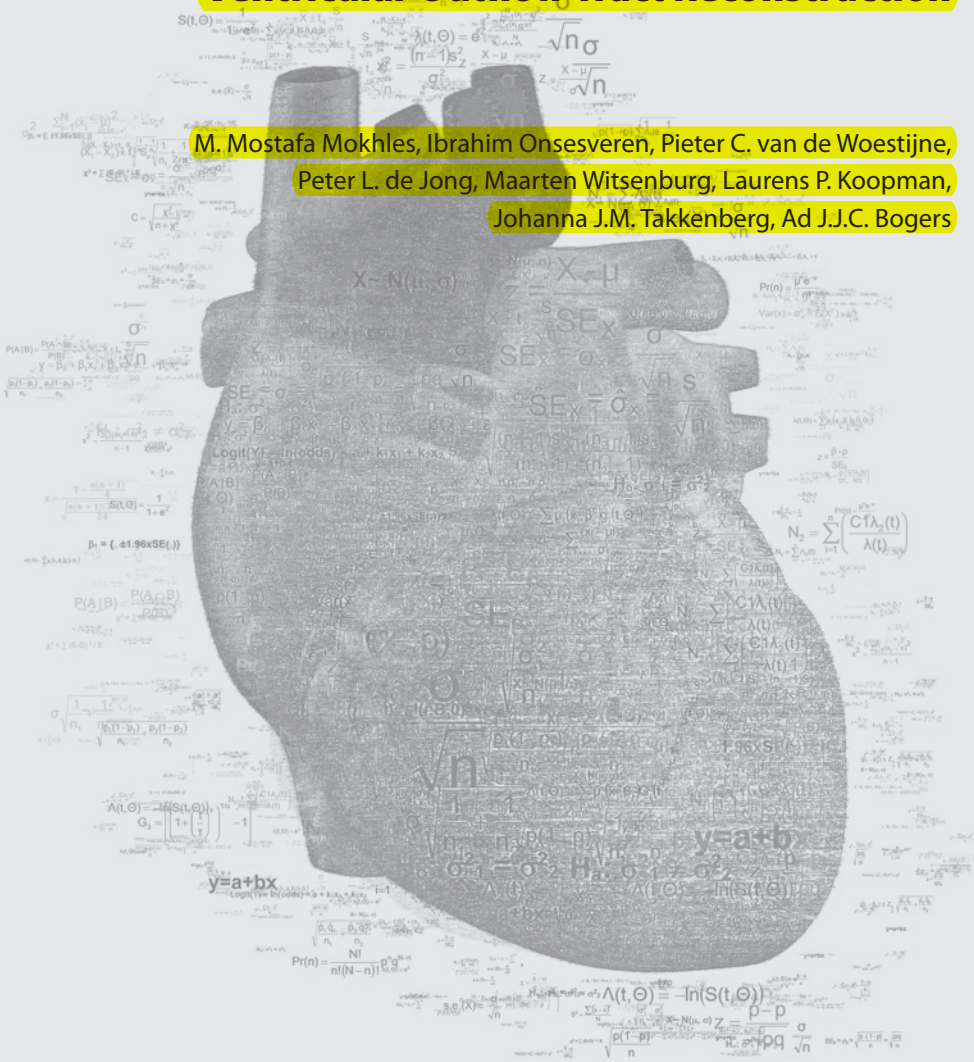
Johann-Wolfgang-Goethe-University, Frankfurt/Main, Germany
Anton Moritz, MD

German Heart Center, Berlin, Germany
Roland Hetzer, MD PhD

Chapter 17

Allograft Conduit Function over Time after Right Ventricular Outflow Tract Reconstruction

M. Mostafa Mokhles, Ibrahim Onsesveren, Pieter C. van de Woestijne, Peter L. de Jong, Maarten Witsenburg, Laurens P. Koopman, Johanna J.M. Takkenberg, Ad J.J.C. Bogers

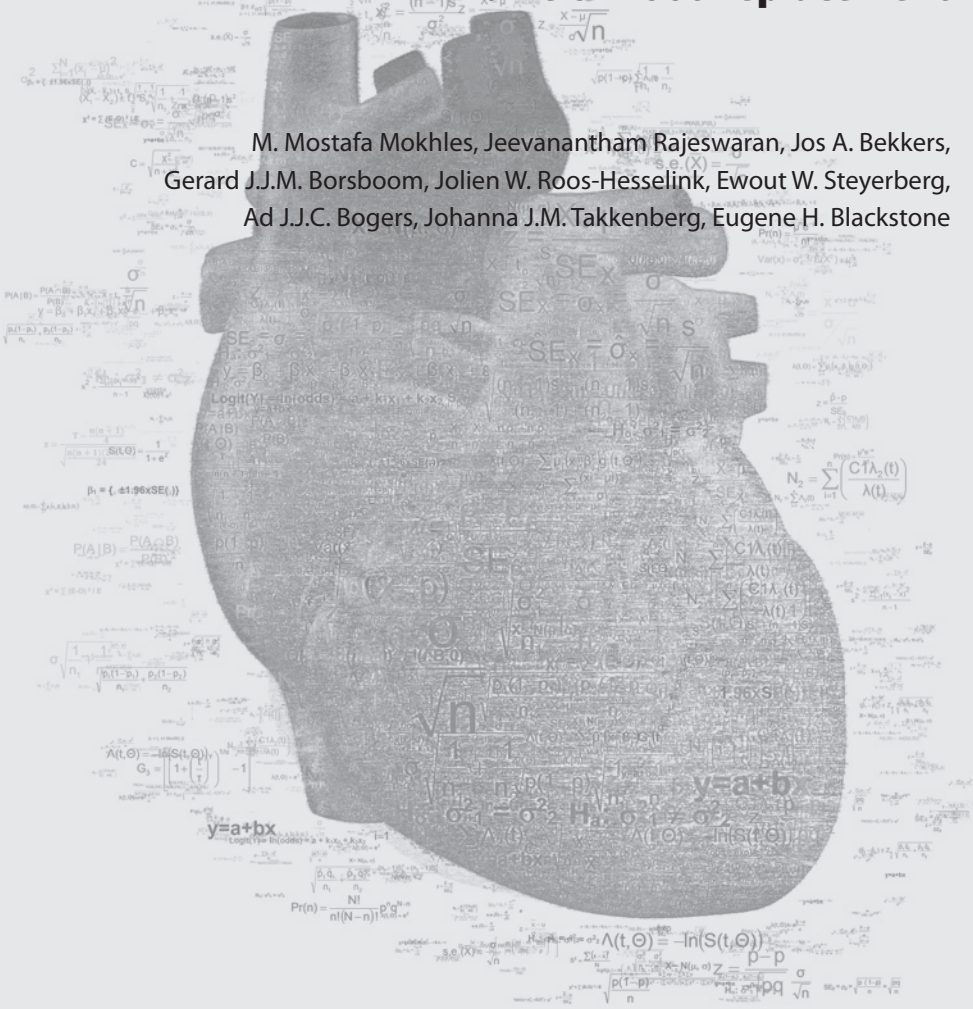


Submitted

Chapter 18

Capturing Echocardiographic Allograft Valve Function over Time after Allograft Aortic Valve or Root Replacement

M. Mostafa Mokhles, Jeevanantham Rajeswaran, Jos A. Bekkers, Gerard J.J.M. Borsboom, Jolien W. Roos-Hesselink, Ewout W. Steyerberg, Ad J.J.C. Bogers, Johanna J.M. Takkenberg, Eugene H. Blackstone



Submitted

ABSTRACT

Objective

This study describes echocardiographic allograft valve function over time in a cohort of patients who were prospectively followed after allograft aortic valve or root replacement, illustrating the use of longitudinal data analysis for assessing valve function over time.

Methods

Serial, standardized echocardiographic measurements of aortic regurgitation, aortic gradient, annulus diameter, left ventricular outflow tract (LVOT) diameter and aortic diameter in 301 hospital survivors (mean age 46 years; range 16-83) after allograft aortic valve (N=77) or root replacement (N=224) were analyzed using non-linear longitudinal models. The association between temporal allograft valve function patterns, patient age and surgical technique was studied.

Results

Aortic regurgitation increased over time. At 15 years 41% of patients had at least moderate AR. Younger patient age and subcoronary implantation technique were associated with increased aortic regurgitation. Aortic gradient increased over time (from 9.4 mmHg at 6 months to 21.3 mmHg at 15 years); both initial and increase in aortic gradient were greater in younger patients and after subcoronary implantation technique. Annulus diameter slightly increased (from 21.9 mm at 6 months to 22.4 mm at 15 years) while aortic diameter slightly decreased over time (from 34.3 mm at 6 months to 32.7 mm at 15 years). LVOT diameter remained constant at 22 mm. Younger patients in the subcoronary implantation group had a larger annulus diameter.

Conclusions

Both aortic regurgitation and stenosis increase over time after allograft aortic valve or root replacement. Younger patient age and use of the subcoronary implantation technique are associated with increased regurgitation and stenosis. The use of non-linear longitudinal models allows for an insightful analysis of allograft valve function over time.

INTRODUCTION

Allografts have been used for the replacement of the diseased aortic valve for over 5 decades (1). Initially thought to be superior to xenografts, today there is increasing evidence that allograft durability is comparable to other biological valve substitutes (2, 3). Nowadays their application is mainly in patients with complex cardiac and aortic root pathology in the setting of an active endocarditis.

The assessment of allograft valve performance over time is, however, difficult. Echocardiographic measurements obtained over time after allograft implantation are usually dichotomized by using time-to-event methods and are reported as, for example, freedom from aortic regurgitation grade 1+ or 3+ at a certain follow-up time (4, 5). Dichotomization of longitudinal data is however often inappropriate as it leads to loss of information and incorrect statistical inferences. The 2008 guidelines for reporting mortality and morbidity after cardiac valvular interventions (6) propose the use of longitudinal data analysis for series of assessments like repeated echocardiographic measurements of valve function to estimate it's average temporal pattern and variability in a group of patients. Repeated measurement data have several important characteristics that are taken into account by longitudinal analyses methods but which are not taken into account by time-to-event methods.

The aim of this study is to describe echocardiographic allograft valve function over time in a prospective cohort of patients who underwent allograft aortic valve or root replacement. This will be done by employing and illustrating the use of advanced longitudinal data analysis techniques.

PATIENTS AND METHODS

Patients

Between April 1987 and September 2010 a total of 347 patients underwent 356 aortic valve or root replacement with an allograft in Erasmus MC, Rotterdam, The Netherlands (Table 1). After these 356 procedures, 301 hospital survivors had one or more standardized echocardiographic examinations. The small number of patients with repeat operations (n=9) were considered as independent patients since the primary focus of this study was allograft valve function over time. Approval from the Institutional Review Board (IRB number EMC00-813) was obtained for this prospective follow-up study and all patients provided informed consent. The clinical outcome of the total cohort was previously reported (3).

Table 1. Baseline characteristics of patients used for clinical follow-up (=total cohort) and for echocardiographic follow-up (=echo cohort).

Characteristic	Total cohort (n=356)		Echo cohort (n=301)		Subcoronary (S) (n=77/301)	Root Replacement (R) (n=224/301)	S vs. R
	n(%)*	No. (%) or Mean ± SD	n(%)*	No. (%) or Mean ± SD	No. (%) or Mean ± SD	No. (%) or Mean ± SD	p-value
Demography							
Age (y)	356 (100)	44.4 ± 16.4	301 (100)	45.6 ± 14.5	46 ± 14.1	45.4 ± 14.7	0.9
Gender	356 (100)		301 (100)				0.88
Male		251 (71)		217 (72)	55 (71)	162 (72)	
Female		105 (29)		84 (28)	22 (29)	62 (28)	
BSA (m^2)	356 (100)	1.89 ± 0.26	301 (100)	1.93 ± 0.2	1.91 ± 0.19	1.94 ± 0.2	0.5
Creatinin (µmol/L)	354 (99)	103 ± 85.2	300 (100)	97.8 ± 62.4	109 ± 101	93.8 ± 41.5	0.033
Symptoms							
NYHA functional class	355 (100)		300 (100)				<0.001
I		92 (26)		83 (28)	11 (14)	72 (32)	
II		95 (27)		81 (27)	21 (27)	60 (27)	
III		105 (30)		89 (30)	38 (49)	51 (23)	
IV		63 (18)		47 (16)	7 (9.1)	40 (18)	
Timing of surgery	354 (99)		299 (99)				0.007
Surgery within 24h		39 (11)		30 (10)	2 (2.6)	28 (13)	
Surgery within the same hospitalization		101 (29)		84 (28)	17 (22)	67 (30)	
Elective surgery		214 (60)		185 (62)	58 (75)	127(57)	
Ventilation support	356 (100)	21 (5.9)	301 (100)	14 (4.7)	0 (0)	14 (6.3)	0.025
Aortic valve	355 (100)		289 (96)				0.092
Pure aortic stenosis		68 (19.2)		59 (20)	21 (27)	38 (17)	

Table 1. (Continued).

Characteristic	Total cohort (n=356)		Echo cohort (n=301)		Subcoronary (S) (n=77/301)	Root Replacement (R) (n=224/301)	S vs. R
	n(%)*	No. (%) or Mean ± SD	n(%)*	No. (%) or Mean ± SD	No. (%) or Mean ± SD	No. (%) or Mean ± SD	p-value
Pure aortic regurgitation		206 (58.0)		175 (58)	43 (56)	132 (59)	
Mixed aortic regurgitation/stenosis		65 (18.3)		55 (18)	13 (17)	42 (19)	
Non-cardiac comorbidity							
DM	356 (100)	12 (3.4)	301 (100)	8 (2.7)	3 (3.9)	5 (2.2)	0.43
Hypertension	356 (100)	51 (14)	301 (100)	40 (13)	10 (13)	30 (13)	0.93
Renal Disease	353 (99)	12 (3.4)	298 (99)	5 (1.7)	3 (3.9)	2 (0.9)	0.078
CVA	356 (100)	19 (5.3)	301 (100)	16 (5.3)	7 (9.1)	9 (4)	0.087
Rhythm	354 (99)		300 (100)				0.4
Sinus rhythm		326 (92)		284 (95)	71 (92)	213 (96)	
Atrial fibrillation		11 (3.1)		6 (2)	2 (2.6)	4 (1.8)	
Heart block		9 (2.5)		7 (2.3)	2 (2.6)	5 (2.2)	
Other rhythm		8 (2.3)		3 (1)	2 (2.6)	1 (0.45)	
Left Ventricular Function	348 (98)		298 (99)				0.54
Good		260 (75)		222 (74)	59 (77)	163 (74)	
Impaired		64 (18)		55 (18)	14 (18)	41 (19)	
Moderate		7 (2)		6 (2)	0 (0)	6 (2.7)	
Poor		17 (4.9)		15 (5)	4 (5.2)	11 (5)	

*Number of patients from whom data is available

Surgical procedures

Surgical procedures were performed through a median sternotomy on cardiopulmonary bypass with moderate hypothermia (Table 2). Crystalloid cardioplegia and topical cooling were used for myocardial protection. Deep hypothermia and circulatory arrest were used in 32 patients with ascending aorta or arch pathology. Early in our experience the subcoronary technique was used; since 1998, root replacement has become the technique of choice. Of the 356 procedures, subcoronary allograft implantation was done in 94 patients (7) and root replacement was performed as a freestanding root with reimplantation of the coronary arteries in 262 patients. From these patients one or more standardized echocardiographic examination was available for 77 patients with subcoronary allograft implantation technique and for 224 patients with root replacement technique.

Clinical Follow up

All patients who receive a human tissue valve in Erasmus MC are enrolled in an ongoing prospective follow-up study. They are followed systematically and actively through direct annual patient contact by telephone. Clinical follow-up was based on the data obtained from the total cohort of 356 aortic valve or root replacement that were performed during the study period.

Valve-related complications and their consequences were defined according to the 2008 guidelines for reporting morbidity and mortality after cardiac valvular operations (6) after confirmation of the event by the patient's treating physician. The database was frozen on September 30, 2010. Clinical follow-up was 95% complete (the ratio of total observed person time to potential person time of follow-up to the closing date of the study) (8). The mean clinical follow-up duration was 10.8 years (median 10.8 years; range 0-23.9 years), with a total follow-up of 3842 patient years.

Echocardiographic follow-up

Serial, standardized echocardiography is done in our center in all patients age 16 years and older who received human tissue valves since 1987. Postoperative echocardiographic examinations were scheduled at 6 months, at 1 year and thereafter once every 2 years (9).

Of the 356 aortic valve or root replacements that were performed during the study period, 301 hospital survivors had one or more standardized echocardiographic examinations. The analyses of echocardiographic valve function over time were based on these 301 patients. Preoperative characteristics of these "Echo cohort" patients are displayed in Table 1. A total of 1765 echocardiographic records were available for 301 patients. The mean echocardiographic follow-up was 5.6 years (median 4.9 years, and range: 1 week- 17 years) with 5% of the records collected after 15 years.

Postoperative transthoracic echocardiographic records were utilized to assess hemodynamic stability of the prosthesis. The severity of aortic stenosis (mmHg) and aortic regurgitation were estimated according the guidelines (10, 11). Aortic regurgitation was graded as 0 for no regurgitation, 1+ for mild, 2+ for moderate, 3+ for moderately severe, and 4+ for severe. Because of low frequency in grade 4+, this grade was collapsed together with 3+ and is treated as one category. Also, annulus diameter (mm), LVOT diameter (mm) and aortic diameter at the sinotubular junction (mm) were recorded with the "leading-edge to leading-edge" method (12). At least one echocardiographic follow-up was obtained in 95% of eligible patients (301/318; 318 = 352 minus 5 patients who are still younger than 16 years minus 25 patients who died in hospital or within the first 6 postoperative months minus 4 patients who had not yet reached the 6 month postoperative point in time). Reasons for not participating in the remaining 5% of eligible patients were emigration, refusal, and bad quality of echo measurements (usually due to obesity).

The echocardiographic examinations were initially performed with different echocardiographic equipment. Since January 1993 all examinations are performed by two experienced technicians.

Statistical analyses

All the analyses were performed using SAS9.1 (SAS® , Cary, N.C.) and some plots were created using S-Plus6.2 (Insightful corporation, Lucent Technologies Inc. Palo Alto, CA, USA) statistical software.

Analyses of clinical data

Presentation

Continuous variables are summarized as mean ± standard deviation, and comparison was done using the unpaired T-test unless the data were not normally distributed (Kolmogorov-Smirnov test); in these instances we used the Mann-Whitney U-test for comparison. Categorical data are presented as proportions, and comparison was done using the Chi-Square test or the Fisher Exact test where appropriate. All tests were 2-sided, with an α-level of 0.05.

Survival analyses

Overall nonparametric survival estimates were obtained by the method of Kaplan and Meier. A parametric method was used to resolve the number of phases of instantaneous risk of death (hazard function) and to estimate the shaping parameters (13). To identify risk factors for death, multivariable analyses were performed in the multi-phase hazard function domain.

Table 2. Perioperative characteristics of patients used for clinical follow-up (=total cohort) and for echocardiographic follow-up (=echo cohort).

Characteristic	Total cohort (n=356)		Echo cohort (n=301)		Subcoronary (S) (n=77/301)	Root Replacement (R) (n=224/301)	S vs. R
	n(%)*	No. (%) or Mean ± SD	n(%)*	No. (%) or Mean ± SD	p-value	No. (%) or Mean ± SD	p-value
Female donor gender	345 (97)	130 (38)	294 (98)	109 (37)	24 (32)	85 (39)	0.34
Allograft diameter	353 (99)	22.7 ± 2.05	300 (100)	22.7 ± 1.92	23.3 ± 2.13	22.5 ± 1.82	0.007
Procedure							
Perfusion Time	355 (99)	197 ± 77.6	300 (100)	194 ± 76.8	177 ± 41.7	200 ± 85	0.21
Cross clamp time	355 (99)	141 ± 57.8	300 (100)	141 ± 58.7	134 ± 31.7	143 ± 65.4	0.77
Circulatory Arrest	353 (99)	3.55 ± 14.5	300 (100)	3.79 ± 15.2	0 ± 0	5.1 ± 17.4	<0.001
Type of allograft implanted	355 (100)		300 (100)				.31
Aortic		297		298 (99%)	76 (99)	222 (99)	
Pulmonary		6		2 (1%)	1 (1)	1 (1)	
Allograft preservation method	356 (100)		301 (100)				.1
Cryopreserved		349 (98)		298 (99)	75 (97.4)	223 (99.6)	
Fresh		7 (2)		3 (1)	2 (2.6)	1 (0.4)	
Concomitant procedures			299 (99)				<0.001
CABG	354 (99)	34 (9.6)		30 (10)	10 (13)	20 (9)	
Mitral valve surgery	354 (99)	25 (7.1)		17 (5.7)	7 (9.1)	10 (4.5)	
Extended root surgery	354 (99)	48 (14)		44 (15)	0 (0)	44 (20)	
Other Procedures	354 (99)	65 (18)		50 (17)	7 (9.1)	43 (19)	
Rhythm at discharge	345 (97)		300 (100)				0.16
Sinus rhythm		305 (88)		276 (92)	68 (88)	208 (93)	
Atrial fibrillation		11 (3.2)		11 (3.7)	5 (6.5)	6 (2.7)	

Table 2. (Continued).

Characteristic	Total cohort (n=356)		Echo cohort (n=301)		Subcoronary (S) (n=77/301)	Root Replacement (R) (n=224/301)	S vs. R
	n(%)*	No. (%) or Mean ± SD	n(%)*	No. (%) or Mean ± SD	p-value	No. (%) or Mean ± SD	p-value
Heart block		12 (3.5)		10 (3.3)	2 (2.6)	8 (3.6)	
Other rhythm		6 (1.7)		3 (1)	2 (2.6)	1 (0.45)	
Complications							
Postoperative bleeding	347 (97)	46 (13)	301 (100)	36 (12)	11 (14)	25 (11)	0.47
Postoperative pacemaker	346 (97)	16 (4.6)	301 (100)	9 (3)	2 (2.6)	7 (3.1)	0.81

*Number of patients from whom data is available.

In the multivariable analysis, factors modulating both hazard phases were considered simultaneously. Early risk factors are those found to increase the area beneath the early decreasing hazard phase, and late risk factors are those that increase the level of underlying increasing hazard. Within each hazard phase, we assume proportional hazards, but because the two hazard phases are operative across all time, this produces overall a non-proportional hazard model. Such a model is particularly appropriate for strongly time-varying hazard, as is evident for these events.

Reoperation analyses

Reoperation and multivariable analyses of patients who underwent reoperation were performed in a similar method used to study survival.

Competing outcomes

The earliest occurrence after aortic allograft surgery of one of the mutually exclusive outcomes (assumed absorbing states) was identified: 1). reoperation, 2). death before reoperation. The common interval of the analysis was either interval between date of reoperation and earliest occurrence of one of these outcomes, or the duration to last follow-up date of being alive without any reoperation. Freedom from each event was then estimated by the non-parametric product limit method (14).

Variances of the estimates were based on Greenwood formula (15). The instantaneous risk (hazard function) for each competing event was estimated by a parametric method (16). Consequences of the independent transition rates (hazard functions) from the category "alive, at risk" into the event categories were calculated by integrating the parametric equations (17).

Analyses of echocardiographic data

Categorical echocardiographic measurement

To assess the temporal trend of likelihood of AR grades over time after surgery, follow-up transthoracic echocardiograms were analyzed longitudinally for percentages of patients in each aortic regurgitation grade across time. A non-linear cumulative logit mixed model(18, 19) was used to resolve a number of time phases on cumulative odds domain to form a temporal decomposition model and to estimate the shaping parameters at each phase. A longitudinal cumulative logistic mixed model (20, 21) for repeated measurements (SAS® PROC NLMIXED) was used to implement the temporal decomposition model and to estimate the patient-specific probabilities for being in each AR grade. These patient-specific estimates were then averaged to obtain the percentages of patients (prevalence) in each grade.

Continuous echocardiographic measurement

To assess the temporal trend of aortic valve gradient, annulus diameter, aortic diameter, and LVOT diameter over time after surgery, follow-up transthoracic echo-cardiographic measurements were analyzed longitudinally for change in mean response across time (22). A non-linear longitudinal mixed model regression (20, 23) (SAS® PROC NLMIXED) was used to analyze these continuous repeated measurements.

Variable selection and risk factor analyses

Baseline characteristics (Table 1) and perioperative characteristics (Table 2) were screened for association with death, reoperation, postoperative aortic regurgitation, aortic gradient, annulus diameter, LVOT diameter and aortic diameter. In addition, year of surgery was also included in the model as a potential risk factor.

Variable selection, with a P value criterion for retention of variables in the model of .05, utilized bootstrap bagging (bootstrap aggregation) (20, 24). This was a four-step process. First, a patient was randomly selected from the original data set to begin a new data set. The original data set continued to be sampled until the new data set was 100% the size of the original. Second, risk factors were identified using automated forward stepwise selection. Third, results of the variable selection were stored. These three steps were repeated 1000 times. Finally, the frequency of occurrence of variables related to group membership was ascertained and indicated the reliability of each variable (aggregation step). All variables with bootstrap reliability of 50% or greater were retained in the guided analysis.

Because of the limited capability of PROC NLMIXED to explore multivariable relations, we initially screened the variables using ordinary multivariable linear regression (PROC REG SAS) and the assumption of independence of observations with liberal entry criteria (0.2) and stay criteria (0.12). This analysis was performed simply to identify possible candidates for our repeated measurements model. These candidates and their transformations, if any, were entered at once into our model, and then eliminated one by one until all variables remaining had a P value of 0.05 or less. Parametric estimates of continuous postoperative echocardiography measurements are accompanied by asymmetric 95% confidence limits, comparable to ± 2 SE, obtained by a bootstrap percentile method (25).

RESULTS

Peri-operative details

Table 2 displays peri-operative details. There were 4 patients (all root replacements) who required coronary artery bypass grafting due to problems related to the reinsertion of the coronary arteries. The detailed causes were as follows: In one patient the left coronary artery button was too small, causing coronary ostium stenosis. Another

patient had annular calcifications extending up to the right coronary ostium that was very thin-layered and ruptured after reimplantation. A third patient experienced right ventricular dysfunction due to kinking of the reimplanted right coronary artery. Finally, in one patient the coronary artery buttons were very big, probably causing malperfusion of both the right and left coronary artery. Hospital mortality was 5.9% (21 out of 356 surgical procedures).

Clinical follow-up

During follow-up another 79 patients died (2.1%/patient year): 28 were not valve related and non-cardiac, 16 were not valve-related cardiac, 23 were valve-related (15 sudden unexpected unexplained deaths, 1 intracranial bleeding, 4 endocarditis, and 3 deaths due to structural valve deterioration (1 after reoperation and 2 due to heart failure), and the cause of death was unknown in 12 patients. The overall parametric estimates of survival at 1 year, 5 years, 10 years and 15 years were 93%, 86%, 78%, and 65% respectively (Figure 1a and 1b). Risk factors associated with early and late death are shown in Table 3.

During follow-up, 103 patients required a reoperation, of which 81 were done for structural valve deterioration, 18 for non-structural valve failure, and 4 for allograft endocarditis. After taking the competing occurrence of death into account, the overall parametric estimates of freedom from reoperation at 1 year, 5 years, 10 years and 15 years were 97%, 92%, 80%, and 56% respectively (Figure 1a and 1b). Risk factors associated with early and late reoperation are shown in Table 3.

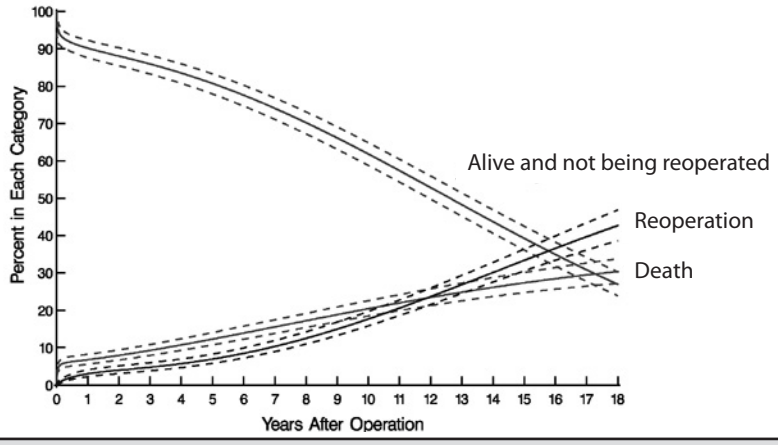


Figure 1(a). Competing risks of outcomes. Prevalence (parametric estimates with non-parametric points) of death and reoperation at each moment in time of patients in each of 3 mutually exclusive categories in the overall group. Each symbol represents a death or reoperation positioned on the vertical axis by the nonparametric Kaplan-Meier estimator, error bars are asymmetric 95% confidence limits (equivalent to ±2 standard error). Solid lines are parametric estimates enclosed within 95% confidence limits.

Echocardiographic follow-up

Aortic Regurgitation

A total of 1728 echocardiographic measurements of aortic regurgitation in 300 patients were available; 37 patients had 1 or more echocardiographic measurements of aortic

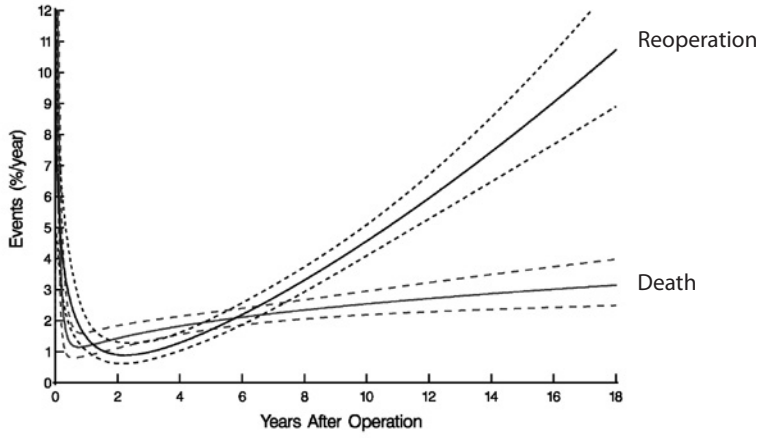


Figure 1(b). Instantaneous risks of death and reoperation (hazard function). Solid lines are parametric estimates enclosed within 95% confidence limits.

Table 3. Incremental risk factors for death and reoperation after aortic valve implantation.

Death	Coefficient ± SD	P-Value	Reliability* (%)
Early hazard phase			
Age#	1.85± 0.48	0.0001	76
History of endocarditis	1.58 ± 0.60	0.0092	63
Renal disease	2.82 ± 0.60	<.0001	91
Late hazard phase			
Age#	1.33 ± 0.21	<.0001	100
Renal disease	0.48 ± 0.26	0.041	59
Reoperation	**Coefficient ± SD**	**P-Value**	**Reliability* (%)**
Early hazard phase			
Early date of surgery†	-0.97 ± 0.25	<.0001	55
Renal disease	2.21 ± 0.65	0.001	66
Late hazard phase			
Age	-0.05 ± 0.01	<.0001	100
Aorta ascendens aneurysm	0.91 ± 0.26	0.001	66

*Percentage of occurrence out of 1000 bootstrapped models; #Exp[age/50], exponential transformation; †Log (time interval interval [Date of surgery – 1 / 3/ 1987])

regurgitation beyond 15 years.

Temporal trend analyses yielded only one phase. Figure 2(a) shows the_temporal change in the percentages of patients in each AR grades over time. Percentage of patients in each grade of AR has changed significantly over time. While the percentage of patients with AR grade 0 decreased sharply from 38% at 6 month to 20% by 15 years after the procedure and percentage of patients with grade 1+ remained the same at about 40% during the same time period, percentage of patients with grade 2+ increased sharply from 19% to 31%. Percentage of patients with grade 3+/4+ increased gradually from 3.6% to 10% during the same time period.

Subcoronary implantation group was associated with higher post-op AR grade than the root replacement group (p=0.0001) (Figure 2(b)). The potential risk factors associated with AR grade over time are shown in Table 4. Younger age was associated with higher grade of post-op AR (p=0.0007) and the effect is significantly large in the subcoronary group (Figure 2(c)). Furthermore, endocarditis seems to be associated with lower likelihood of postoperative AR grade (p=0.0250).

Aortic gradient

A total of 1609 echocardiographic measurements of aortic gradient in 292 patients were available; 34 patients had 1 or more echocardiographic measurements of aortic gradient beyond 15 years.

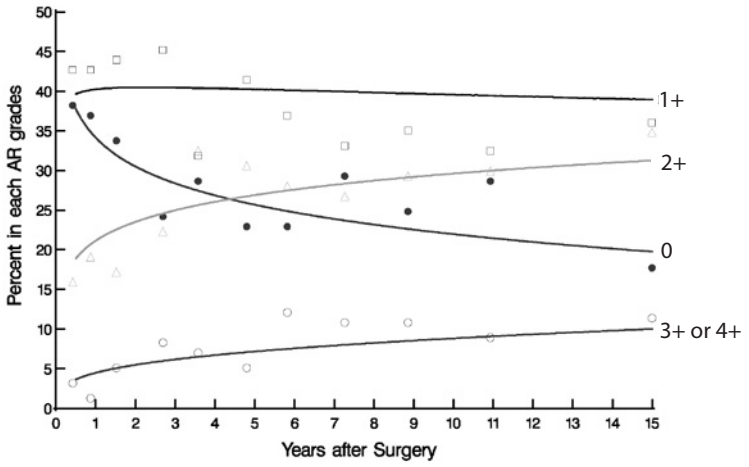


Figure 2(a). Temporal trend of aortic regurgitation (AR) after the procedure. Solid lines represent percentage of patients (mean effect) in each grade at various time points. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

Temporal trend analyses yielded only one phase. Aortic gradient appears to be increasing from 9.4mmHg at 6 months to 21.3mmHg by 15 years after the procedure (Figures 3(a)).

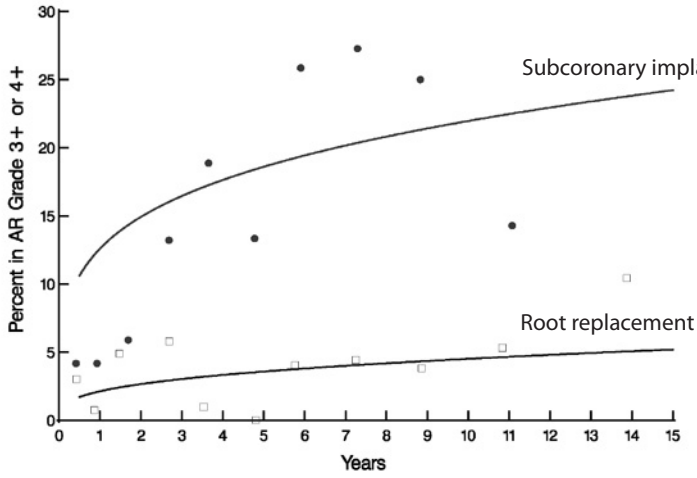


Figure 2(b). Predicted percentages of patients in AR grade 3+/4+ stratified by operative technique. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

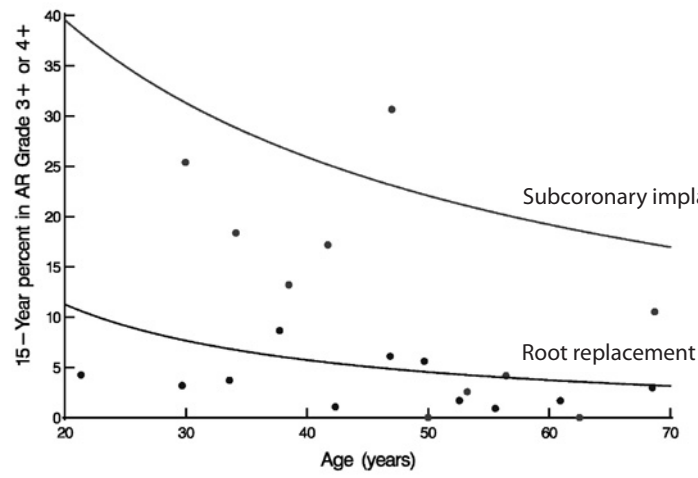


Figure 2(c). 15-Year Predicted percentages of patients in AR grade 3+/4+ by age, stratified by operative technique. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

Subcoronary implantation group appears to be associated with higher aortic gradient than the root replacement group (p= 0.0005). Younger age appears to be associated with higher aortic gradient (p=<0.0001) (Figure 3(b)). Male donor gender (P=0.0015) and concomitant mitral valve surgery (P=0.0011) were associated with higher aortic gradient during follow-up. The potential risk factors associated with aortic gradient over time are shown in Table 4.

Annulus diameter

A total of 1445 echocardiographic measurements of annulus diameter in 284 patients were available; 31 patients had 1 or more echocardiographic measurements of annulus diameter beyond 15 years.

Table 4. Preoperative risk factors associated with postoperative longitudinal echocardiographic measurement (results from the multivariate analyses).

Echocardiographic Measurement	Factor	Estimate ± SE	P	Reliability* (%)
Aortic Regurgitation	Younger age#	-1.44± 0.42	0.0007	90.0
	Subcoronary AVR (vs. Root Replacement)	2.48 ± 0.33	<.0001	100
	Endocarditis	-0.70 ± 0.31	0.0250	73.2
Aortic Gradient	Male donor	0.17 ± 0.05	0.0015	98.0
	Subcoronary AVR (vs. Root Replacement)	0.21 ± 0.06	0.0005	100
	Younger age	-0.01 ± 0.00	<.0001	93.5
	Concomitant mitral valve surgery	0.25 ± 0.12	0.0445	91.5
Annulus Diameter	Larger allograft diameter	0.03 ± 0.01	<.0001	96.7
	Male donor	0.05 ± 0.02	0.0047	52.8
	Male recepient	0.09 ± 0.02	<.0001	58.3
	Root Replacement AVR (vs. Subcoronary)	0.07 ± 0.02	<.0001	65.2
LVOT Diameter	Male gender	0.10 ± 0.02	<.0001	84.2
	Aortic annulus aneurysm	0.08 ± 0.03	0.0011	82.1
	Tricuspid vs bicuspid aortic valve	0.08 ± 0.03	0.0011	67.3
	Smaller allograft diameter	-0.04 ± 0.02	0.0123	59.4
Aortic Diameter	Male donor gender	0.07 ± 0.01	<.0001	99.3
	Calcified aortic annulus	0.04 ± 0.02	0.0061	94.6
	Preoperative aortic regurgitation	0.05 ± 0.01	<.0001	78.8
	Male patient gender	0.09 ± 0.01	<.0001	65.7
	Elective surgery	0.03 ± 0.01	0.0106	99.3
	Concomitant mitral valve surgery	-0.05 ± 0.03	0.0496	61.3

*Percentage of occurrence out of 1000 bootstrapped models; #Log[age], logarithmic transformation

Temporal trend analyses yielded only one phase. Annulus diameter increased from 21.9mm at 6 months to 22.4mm by 15 years after the procedure. This increase was statistically not significant (P=0.5460) (Figures 4(a)).

There appears to be a procedure effect on the annulus diameter. Root replacement technique appears to be associated with larger annulus diameter (P<.0001) (Figure 4(b)).

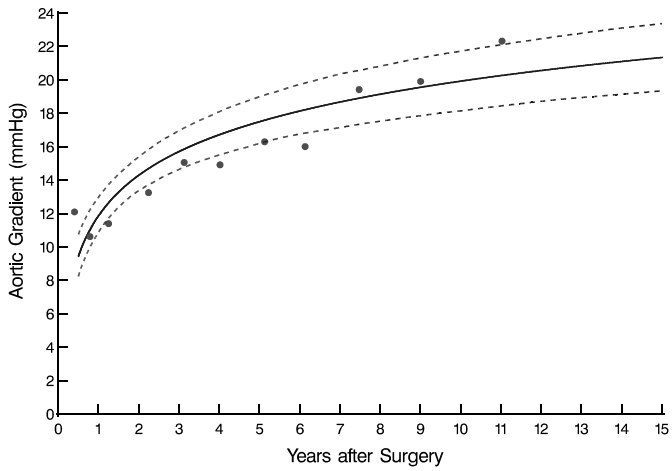


Figure 3(a). Solid lines are parametric estimates of mean aortic gradient from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

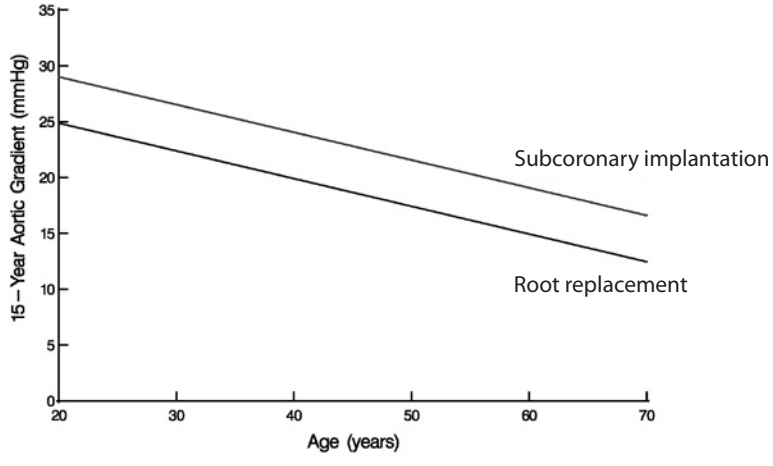


Figure 3(b). 15-Year Predicted mean aortic gradient by age, stratified by operative techniques.

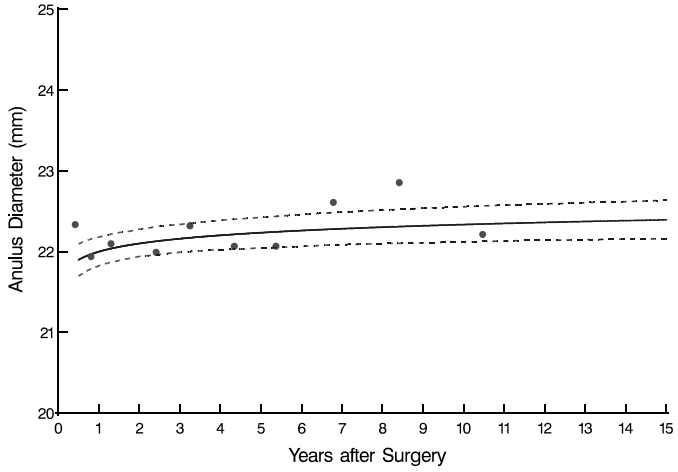


Figure 4(a). Solid lines are parametric estimates of mean annulus diameter from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

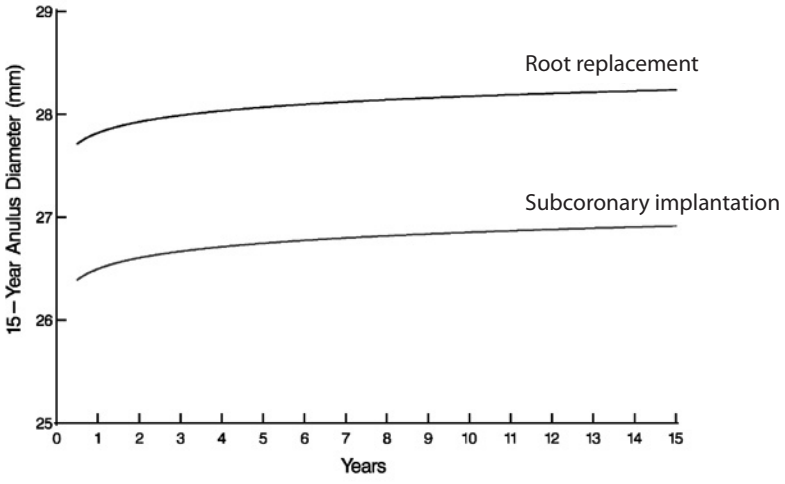


Figure 4(b). 15-Year Predicted mean of annulus diameter, stratified by operative technique.

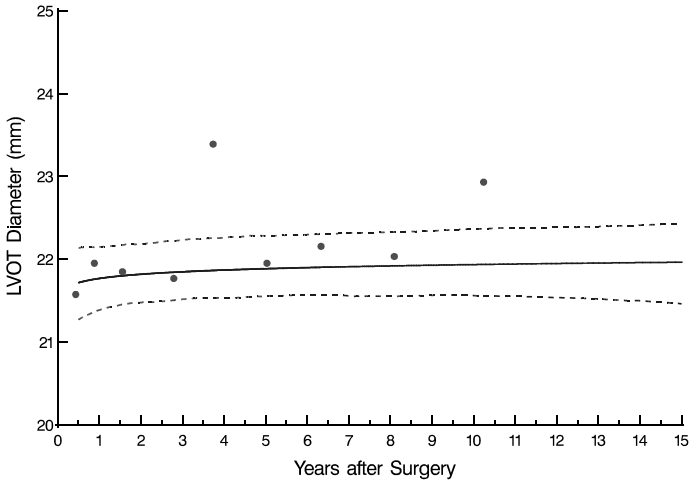


Figure 5. Solid lines are parametric estimates of mean LVOT diameter from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

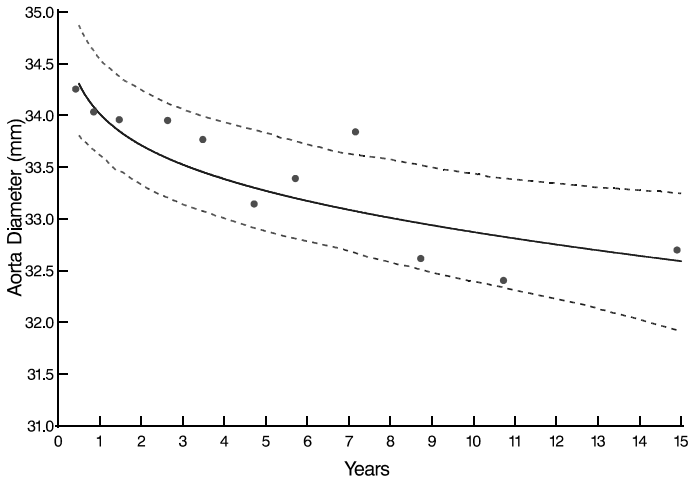


Figure 6. Solid lines are parametric estimates of mean aortic diameter from non-linear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 SD. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented here just to verify the model fitting.

Male donor gender (p<0.0047), male patient gender (p<0.0001) and higher allograft diameter (p<0.0001) were associated with larger annulus diameter during follow-up. The potential risk factors associated with annulus diameter over time are shown in Table 4.

LVOT diameter

A total of 1463 echocardiographic measurements of annulus diameter in 286 patients were available; 32 patients had 1 or more echocardiographic measurements of annulus diameter beyond 15 years.

Temporal trend analyses yielded only one phase. No significant change in the LVOT diameter was observed (p=0.6582) with a diameter of about 21.8mm at 6 months and 22.0mm at 15 years after the procedure (Figure 5).

Male donor gender (p<0.0001), Aortic annulus aneurysm (p=0.0011) and tricuspid aortic valve (p=0.0011) were associated with larger LVOT diameter during follow-up. Larger allograft diameter was associated with larger LVOT diameter during follow-up. The potential risk factors associated with LVOT diameter over time are shown in Table 4.

Aortic diameter

A total of 1603 echocardiographic measurements of aortic diameter in 294 patients were available; 34 patients had 1 or more echocardiographic measurements of aortic diameter beyond 15 years.

Temporal trend analyses yielded only one phase. Aortic diameter appears to decrease slightly from 34.3mm at 6 months to 32.7mm by 12 years after the procedure. Even though the decrease is statistically significant (p<0.0001), it may not be clinically significant (Figure 6).

Male donor gender (p<0.0001), calcified aortic annulus (p=0.0061), preoperative AR (p<0.0001), male patient gender (p<0.0001) and elective surgery (p=0.0106) were associated with larger aortic diameter during follow-up. Concomitant mitral valve surgery (p=0.0496) was associated with smaller aortic diameter during follow-up. The potential risk factors associated with aortic diameter over time are shown in Table 4.

DISCUSSION

This study describes echocardiographic allograft valve function over time in a cohort of patients who were followed prospectively after allograft aortic valve or root replacement, illustrating the use of longitudinal data analysis for the assessment of valve function over time.

Clinical outcomes

In our patient population, patient survival was 68% after 15 years of follow-up. Freedom from reoperation was 56% after same time period. These results are comparable to other series that report survival and freedom from reoperation after allograft aortic valve and root replacement (26-30).

Echocardiographic outcomes

Among patients that underwent allograft aortic valve or root replacement 41% had 2+ or higher AR after 15 years of follow-up. In patients in whom the complete aortic root was implanted instead of the aortic valve in the subcoronary position, the risk of higher AR grade was considerably lower during follow-up. Furthermore, we observed more often higher AR grades during follow-up in younger patients. Although it has been shown previously that younger patients are at higher risk of aortic allograft degeneration (31), the results of our longitudinal echocardiographic study show that younger patients are especially at risk for valve degeneration when the subcoronary implantation technique is used to implant the allograft.

The aortic gradient increased during follow-up from 9.4 mmHg at 6 months to 21.3 mmHg at 15 years. Comparable with AR, the severity of aortic gradient during follow-up was primarily influenced by younger patient age and the use of subcoronary implantation technique. Furthermore, male donor gender was found to be significantly correlated with higher aortic gradient during follow-up which confirms the results of previous studies where it has been shown that immunological reaction might be (partly) responsible for valve failure (32).

We have not observed major changes in the annulus diameter, LVOT diameter and aortic diameter during follow-up.

The results of our longitudinal data analyses of echocardiographic valve function over time indicate that both younger patient age and subcoronary implantation technique are important risk factors of allograft degeneration. This is in accordance with previous studies that investigated the clinical outcomes of patients with aortic allograft (31, 33-35).

Methodology

The described methodology for the analyses of echocardiographic data was applied in the present study because of several reasons.

Longitudinal analyses versus time-to-event analyses

The assessment of allograft valve performance (and other valve substitutes) is complicated by several factors. First of all, valves are implanted in patients, who themselves have a limited survival. This creates a situation in which the risk of patient death competes

with valve durability. Second, valve failure is a continuous process, not a hard end point. Time-to-event analysis is therefore inappropriate when assessing echocardiographic valve function, since it considers time of follow-up as a continuous variable while echo data are usually available within a certain time frame and are often incomplete in one or more time frames. In addition, it considers valve dysfunction as an irreversible endpoint, while severity of valve dysfunction (for example aortic regurgitation) is often variable over time. Third, the means by which echocardiographic follow-up is obtained may influence the results: opportunistic versus standardized follow-up, experience of the observer, and intervals between measurements may all cause bias. Finally, allograft dysfunction may present in different ways: through regurgitation, stenosis or a combination, further complicating valve performance analysis. The challenge in analyzing longitudinal data is, therefore, estimating the average pattern of outcome over time and its variability in the group of patients. In addition, this average must take several sampling characteristics into account (e.g. censoring by death, unequal number of observations per patient, different follow-up intervals between observations).

In the present study, non-linear longitudinal analysis techniques were used to model the trend of various echocardiographic measurements over time after the procedure. This enabled us in turn to visualize the temporal trend of, for example, each aortic regurgitation grade over time during follow up. Clinicians can use such methods/graphs to determine how for example aortic regurgitation on average develops over time after aortic allograft implantation. From a statistical perspective, the employed methods are superior and more informative compared to the methods where repeated outcomes are dichotomized and analyzed with actuarial methods as if they were events, such as freedom from grade 1+ or 3+ aortic regurgitation after aortic valve surgery (4, 5). Assessing the trend of outcomes of interest and identifying factors that influence these outcomes over time can be of particular importance since it can help the clinicians understand how a certain process changes over time and thus can contribute to a better patient management (e.g. by determining which patients should be monitored more closely by their physicians and at which time interval).

Although the use of time-to-event methods is less time and effort consuming, these methods have major limitations that may result in loss of information and wrong statistical inferences which can lead to inadequate conclusions, depending on the type of research question investigated. Researchers should, therefore, be encouraged in taking into account the important characteristics of longitudinally collected data when choosing the method of data analysis.

The methods applied in present study versus other typical longitudinal analyses methods

Several longitudinal analyses methods exist. Both linear and non-linear structures can be used to analyze longitudinal data. In linear methods, the degree of the outcome (y)

is determined by the degree of the input (x), which can be written as a y=ax+b equation. An important characteristic of linear methods is proportionality since there is a straight-line relationship between the input value and the outcome. Therefore, the behavior of linear methods can be fully predicted. However, the cardiovascular system is a complex mechanical, chemical, and hemodynamic system in which the processes are often related via a variety of mechanisms. Therefore, these processes are often non-linearly structured (36-38). Since the principle of proportionality may not be valid, using linear methods may mean simplification of the real process and therefore inaccurate results and inferences. For example, the analyses of our study shows that aortic gradient is non-linearly shaped. During follow-up, the increase in aortic gradient mainly occurred in the first 5 years after the surgery. If we had modeled the aortic gradient as a linear process we would not be able to see the difference between how the aortic gradient increased before and after this 5 year period. We emphasize that not the data but the model determines the shape of the relationship between the input and the outcome. However, further validation is necessary to confirm whether the non-linear pattern is indeed the better description of aortic gradient measurements.

The statistical methods that we applied are also able to simultaneously model the risk factors for each time phase, while in case when one has to use the usual longitudinal methods to identify time-dependent risk factors several transformations of time along with their interaction effects are needed in the equation. In the latter scenario, it would be very difficult for the model to handle 40 or 50 covariates and the combination of them with different transformations of time and the interpretation of such model would be difficult. The statistical technique that has been illustrated in this study is able to explicitly model the non-linear trend and divides it in different overlapping time phases, which in turn enable us to simultaneously identify risk factors that are of particular importance shortly after the procedure and those that are of particular importance on the long-term.

The approach of longitudinal data analyses that is used in the present study is also proposed by the 2008 guidelines for reporting mortality and morbidity after cardiac valvular interventions (6).

Conclusions

Both aortic regurgitation and stenosis increase over time after allograft aortic valve or root replacement, and are the most important cause for allograft failure. Younger patient age and use of the subcoronary implantation technique are associated with increased regurgitation and stenosis. The analysis of allograft valve function is complex, and requires advanced longitudinal models for adequate statistical analysis.

REFERENCES

1. Ross DN. Homograft replacement of the aortic valve. Lancet 1962; 2(7254):487.
2. Smedira NG, Blackstone EH, Roselli EE, Laffey CC, Cosgrove DM. Are allografts the biologic valve of choice for aortic valve replacement in nonelderly patients? Comparison of explantation for structural valve deterioration of allograft and pericardial prostheses. J Thorac Cardiovasc Surg 2006; 131(3):558-564 e554.
3. Takkenberg JJ, Klieverik LM, Bekkers JA, Kappetein AP, Roos JW, Eijkemans MJ, Bogers AJ. Allografts for aortic valve or root replacement: insights from an 18-year single-center prospective follow-up study. Eur J Cardiothorac Surg 2007; 31(5):851-859.
4. Murashita T, Kubota T, Kamikubo Y, Shiiya N, Yasuda K. Long-term results of aortic valve regurgitation after repair of ruptured sinus of valsalva aneurysm. Ann Thorac Surg 2002; 73(5):1466-1471.
5. Losay J, Touchot A, Capderou A, Piot JD, Belli E, Planche C, Serraf A. Aortic valve regurgitation after arterial switch operation for transposition of the great arteries: incidence, risk factors, and outcome. J Am Coll Cardiol 2006; 47(10):2057-2062.
6. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008; 135(4):732-738.
7. Ross D. Technique of aortic valve replacement with a homograft: orthotopic replacement. Ann Thorac Surg 1991; 52(1):154-156.
8. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet 2002; 359(9314):1309-1310.
9. Willems TP, Takkenberg JJ, Steyerberg EW, Kleyburg-Linkers VE, Roelandt JR, Bos E, van Herwerden LA. Human tissue valves in aortic position: determinants of reoperation and valve regurgitation. Circulation 2001; 103(11):1515-1521.
10. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quinones M, American Society of E, European Association of E. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009; 22(1):1-23; quiz 101-102.
11. Lancellotti P, Tribouilloy C, Hagendorff A, Moura L, Popescu BA, Agricola E, Monin JL, Pierard LA, Badano L, Zamorano JL, European Association of E. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). Eur J Echocardiogr 2010; 11(3):223-244.
12. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing G, American Society of Echocardiography's G, Standards C, European Association of E. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18(12):1440-1463.
13. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. J Am Stat Assn. 1986;81:615-24.
14. Andersen PK, Borgan O, Gill RD, Keiding N, Statistical models based on counting processes. Chapter 4. Nonparametric estimation. New York: Springer-Verlag, 1993: 176-331.

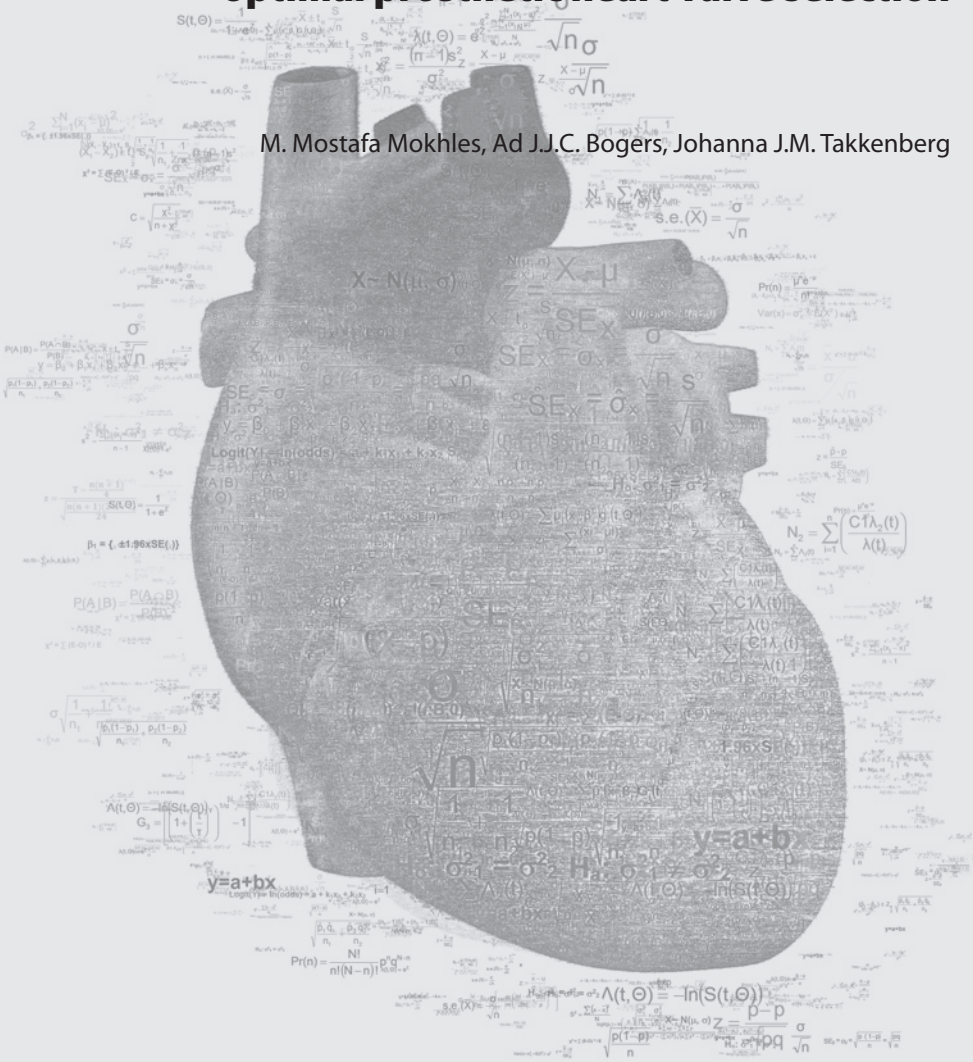
15. Andersen PK, Borgan O, Gill RD, Keiding N, Statistical models based on counting processes. Chapter 4. Nonparametric estimation. New York: Springer-Verlag, 1993: 176-331.
16. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. J Am Stat Assn. 1986;81:615-24.
17. Blackstone EH, Lytle BW. Competing risks after coronary bypass surgery: the influence of death on reintervention. J Thorac Cardiovasc Surg 2000; 119(6):1221-1230.
18. Blackstone EH, Rajeswaran J., A non-linear cumulative logit mixed model with time varying phases and coefficients, Conference proceedings, XXIII International Biometric Conference, Montreal, Canada 2006.
19. Gillinov AM, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik JF, Svensson LG, Cosgrove DM, Hill KM, Gonzalez-Stawinski GV, Marrouche N, Natale A. Surgical ablation of atrial fibrillation with bipolar radiofrequency as the primary modality. J Thorac Cardiovasc Surg 2005; 129(6):1322-1329.
20. Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. J Thorac Cardiovasc Surg 2001; 122(3):430-439.
21. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of longitudinal data. 2nd ed. New York: Oxford University Press, 2002.
22. Mason DP, Rajeswaran J, Murthy SC, McNeill AM, Budev MM, Mehta AC, Pettersson GB, Blackstone EH. Spirometry after transplantation: how much better are two lungs than one? Ann Thorac Surg 2008; 85(4):1193-1201, 1201 e1191-1192.
23. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of longitudinal data. 2nd ed. New York: Oxford University Press, 2002.
24. Breiman L. Bagging predictors. Machine Learning 1996; 24:123-140.
25. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman and Hall/CRC; 1998.
26. Dagenais F, Cartier P, Voisine P, Desaulniers D, Perron J, Baillot R, Raymond G, Metras J, Doyle D, Mathieu P. Which biologic valve should we select for the 45- to 65-year-old age group requiring aortic valve replacement? J Thorac Cardiovasc Surg 2005; 129(5):1041-1049.
27. Knott-Craig CJ, Elkins RC, Santangelo KL, McCue C, Lane MM. Aortic valve replacement: comparison of late survival between autografts and homografts. Ann Thorac Surg 2000; 69(5):1327-1332.
28. Lund O, Chandrasekaran V, Grocott-Mason R, Elwidaa H, Mazhar R, Khaghani A, Mitchell A, Ilsley C, Yacoub MH. Primary aortic valve replacement with allografts over twenty-five years: valve-related and procedure-related determinants of outcome. J Thorac Cardiovasc Surg 1999; 117(1):77-90; discussion 90-71.
29. O'Brien MF, Harrocks S, Stafford EG, Gardner MA, Pohlner PG, Tesar PJ, Stephens F. The homograft aortic valve: a 29-year, 99.3% follow up of 1,022 valve replacements. J Heart Valve Dis 2001; 10(3):334-344; discussion 335.
30. Dossche KM, de la Riviere AB, Morshuis WJ, Schepens MA, Defauw JJ, Ernst SM. Cryopreserved aortic allografts for aortic root reconstruction: a single institution's experience. Ann Thorac Surg 1999; 67(6):1617-1622.
31. Yacoub M, Rasmi NR, Sundt TM, Lund O, Boyland E, Radley-Smith R, Khaghani A, Mitchell A. Fourteen-year experience with homovital homografts for aortic valve replacement. J Thorac Cardiovasc Surg 1995; 110(1):186-193; discussion 193-184.
32. Grunkemeier GL, Bodnar E. Comparison of structural valve failure among different 'models' of homograft valves. J Heart Valve Dis 1994; 3(5):556-560.

33. O'Brien MF, Stafford EG, Gardner MA, Pohlner PG, Tesar PJ, Cochrane AD, Mau TK, Gall KL, Smith SE. Allograft aortic valve replacement: long-term follow-up. Ann Thorac Surg 1995; 60(2 Suppl):S65-70.
34. Rubay JE, Raphael D, Sluysmans T, Vanoverschelde JL, Robert A, Schoevaerdts JC, Marchandise B, Dion RA. Aortic valve replacement with allograft/autograft: subcoronary versus intraluminal cylinder or root. Ann Thorac Surg 1995; 60(2 Suppl):S78-82.
35. Willems TP, van Herwerden LA, Taams MA, Kleyburg-Linker VE, Roelandt JR, Bos E. Aortic allograft implantation techniques: pathomorphology and regurgitant jet patterns by Doppler echocardiographic studies. Ann Thorac Surg 1998; 66(2):412-416.
36. Elbert T, Ray WJ, Kowalik ZJ, Skinner JE, Graf KE, Birbaumer N. Chaos and physiology: deterministic chaos in excitable cell assemblies. Physiol Rev 1994; 74(1):1-47.
37. Sugihara G, Allan W, Sobel D, Allan KD. Nonlinear control of heart rate variability in human infants. Proc Natl Acad Sci U S A 1996; 93(6):2608-2613.
38. Scher AM, Young AC. Nonlinearity in the control of blood pressure and heart rate. Ann N Y Acad Sci 1969; 156(2):722-730.

Chapter 19

Informed patient preferences are key to optimal prosthetic heart valve selection

M. Mostafa Mokhles, Ad J.J.C. Bogers, Johanna J.M. Takkenberg



Circulation. 2011;124:e897

To the Editor,

Drs Huang and Rahimtoola (1) presented an interesting clinician update discussing several factors that have to be taken into consideration in choosing a prosthetic heart valve. However, the authors' considerations for prosthetic heart valve selection are, in our opinion, not complete and deserve further discussion.

With respect to section on biological valves that need additional aortic root replacement: the Ross procedure and stentless xenograft valve implantation can also be performed successfully and durably using the subcoronary implantation technique, which do not necessitate root replacement. These techniques can also provide patients with a hemodynamically superior valve substitute (2, 3).

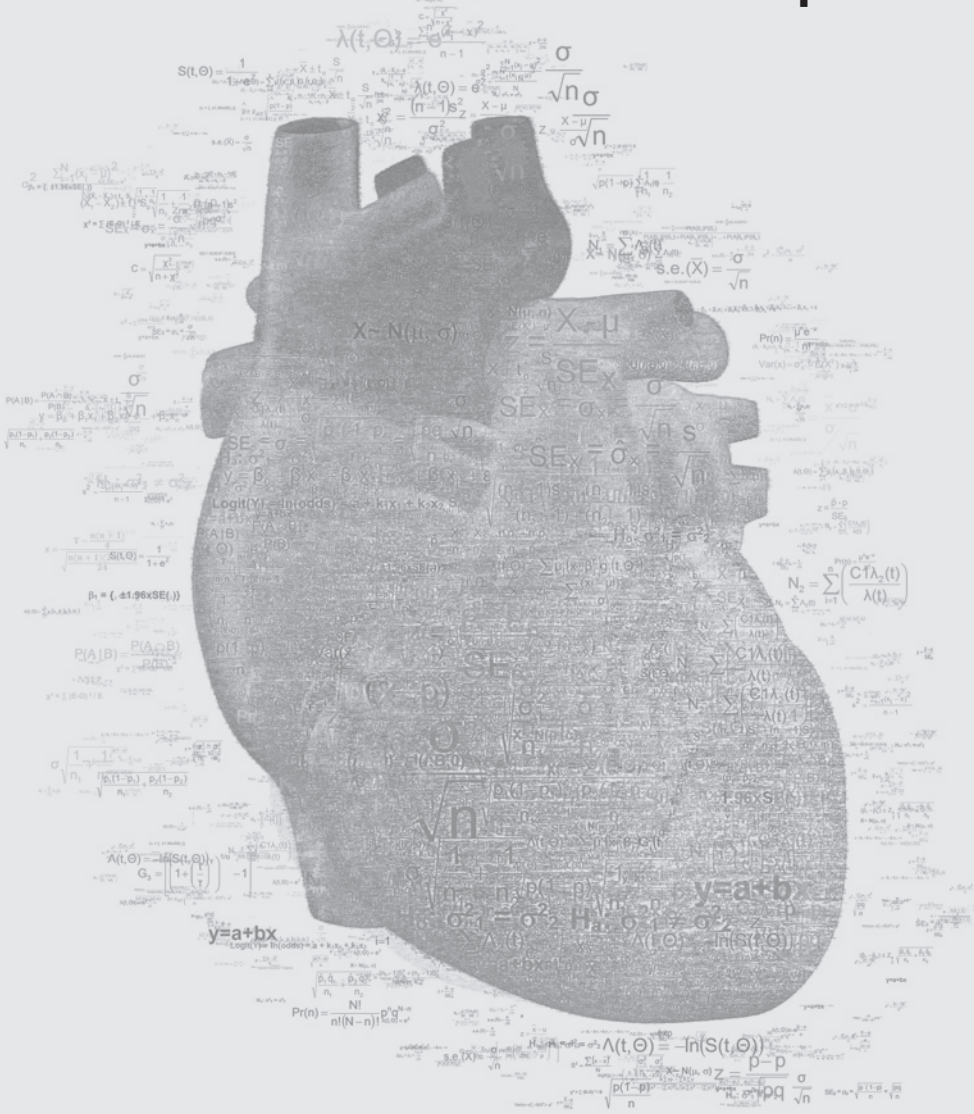
However, the main point we would like to address concerns the position of the patient in the selection of the most appropriate prosthesis. The factors that the authors discuss are mainly related to clinical status and patient characteristics, while patient preferences are also important in choosing the most appropriate prosthesis. The patient that served as an example in the clinician update was a 55-year-old interventional cardiologist, a highly educated individual who through his extensive experience in the field of cardiology was clearly able to by himself make an informed decision according to his values and preferences in life. However, the average patient who faces this difficult decision is less well educated and has no knowledge of heart valves. There are many replacement options, uncertain outcomes, and benefits and harms in choosing a particular prosthetic heart valve, especially in patients who are middle-aged and in whom life expectancy is comparable between mechanical and bioprosthetic heart valve substitutes (4). Therefore, there is no single 'best choice' in selecting a prosthetic valve for an individual patient since all these factors can be valued differently by individual patients: a patient may very well prefer a 60% life time risk of a reoperation with a bioprosthesis over a 20% life-time risk of a major TE or bleeding with a mechanical valve, or vice versa, depending on his or her preferences. Although doctors are the ones responsible for applying evidence-based medicine, patients should be informed adequately and according to their educational background and next be able to discuss their preferences with their doctors. The concept of shared-decision making recognizes the importance of having patients and doctors work together in the selection of most appropriate treatment option. Using this concept, well-informed patients and doctors can determine which option best matches what is most important to patients. This approach will not only result in providing evidence-based care, but also in providing patient-centered care. We plead for a patient-centered approach that incorporates evidence on outcome with different therapeutic strategies with preferences of the informed patient. In this respect in Table 1 of the clinician update the item "patient's wishes and expectations" should be on top of the list, and renamed "informed patient's wishes and expectations".

REFERENCES

1. Huang J and Rahimtoola SH. Prosthetic Heart Valve. Circulation 2006;123:2602-2605.
2. Lehmann S, Walther T, Kempfert J, Leontjev S, Rastan A, Falk V, Mohr FW. Stentless versus conventional xenograft aortic valve replacement: midterm results of a prospectively randomized trial. Ann Thorac Surg 2007; 84(2):467-472.
3. Sievers HH, Stierle U, Charitos EI, Hanke T, Gorski A, Misfeld M, Bechtel M. Fourteen years' experience with 501 subcoronary Ross procedures: surgical details and results. J Thorac Cardiovasc Surg 2010; 140(4):816-822, 822 e811-815.
4. Stoica S, Goldsmith K, Demiris N, Punjabi P, Berg G, Sharples L, Large S. Microsimulation and clinical outcomes analysis support a lower age threshold for use of biological valves. Heart 2010; 96(21):1730-1736.

Chapter 20

General Discussion and Future Perspectives



GENERAL DISCUSSION

The aim of this thesis was to illustrate the use of innovative statistical methods for the assessment of patient outcome and heart valve function after aortic- and/or pulmonary valve replacement. This final chapter discusses the results in a broader context and presents implications for clinical practice and further research. Firstly, the prognosis of patients undergoing heart valve replacement will be discussed. Secondly, the implications that innovative statistical methods have in the assessment of valve function over time after cardiac surgery will be delineated. Thirdly, innovative statistical methods which enable us to combine patient outcome, valve durability and valve function over time will be discussed. Finally, the clinical implications of the results presented in this thesis and future prospects will be proposed.

Patient outcome after aortic and pulmonary valve replacement

Survival after aortic and/or pulmonary valve replacement

The evaluation of our data on the use of allografts and autografts in the aortic position, and allografts in the pulmonary position showed satisfactory results with regard to both early and late patient mortality. Several studies presented in this thesis showed that long-term patient survival after the autograft procedure is relatively good in contemporary practice and in the first postoperative decade even comparable with the general population, a finding that is in accordance with data reported by several other investigators (1-3). However, this thesis also illustrates that although long-term mortality rates of autograft patients are relatively low and comparable with that of the general population in the first decade, the survival rate of these patients shows a decline in the second postoperative decade compared with the general population. This observation indicates the importance of careful monitoring of autograft patients, especially in the second decade after the initial autograft operation when the need for autograft reintervention is increasing. The autograft procedure is considered to be the only procedure being capable of providing patients a survival rate that is comparable to the general age- and gender-matched population (4). However, it remains unclear whether this excellent survival is a consequence of the autograft attributes (5) or the careful selection of patients for the Ross procedure (6). In this thesis an attempt was made to find an answer to this puzzling and clinically important question by performing a propensity score matched study that assessed late survival in young adult patients after a Ross operation versus mechanical aortic valve replacement with optimal anticoagulation self-management. The results of this study suggest that survival of mechanical valve patients, with highly specialized anticoagulation-self-management, is comparable to autograft patients. This is a clini-

cally relevant observation since the choice for particular valve prosthesis for aortic valve replacement in young adults has an important impact on the lives of these patients.

The long-term results after pulmonary valve replacement with an allograft conduit are being presented in several chapters of this thesis. The survival of patients after pulmonary valve replacement with an allograft conduit is good and in our center even slightly better than those reported by other centers (7-11). These results suggest that RVOT reconstruction with an allograft conduit can be performed with low operative mortality (12-14). Quality of life has emerged as an increasingly important outcome parameter for several reasons: it provides a precise indicator of overall health status of the individual patient and higher quality of life is associated with improved disease specific prognosis and also with increased survival (15, 16). This thesis describes the results of a cross sectional assessment of the quality of life of patients receiving an allograft for the reconstruction of RVOT (**Chapter 2**). Although the overall perceived quality of life was good in this patient population, the quality of life of young adult patients after pulmonary valve replacement with an allograft was impaired on subscale 'physical functioning'. Furthermore, this patient group has an impaired score on the 'general health' subscale, indicating that they evaluate their overall health to be lower than in the general population. It was interesting to see that with increasing age the perceived quality of life was more in accordance with the quality of life of the general Dutch population. This can be caused by the fact that older patients are physically less active and, therefore, are less impaired in their functioning.

Freedom from events after aortic and/or pulmonary valve replacement

The assessment of echocardiographic function of allografts over time showed that durability of allografts in the aortic position is limited and the majority of patients will require a re-operation later in life. Almost half of the patients have moderate or severe aortic regurgitation (AR) after 15 years of follow-up.

With regard to autografts in the aortic position, an increasing rate of reoperation in the second postoperative decade was noticed. The main cause for the reoperation is the progressive dilatation of the autograft root, often combined with autograft valve insufficiency, necessitating reoperation (2, 17-20). Due to this dilatation, coaptation of the cusps is lost and AR occurs. The exact cause of autograft root dilatation is unknown. It is speculated that several factor may contribute to dilatation of the aortic root. Younger patient age (21), congenital aortic valve disease (22), rheumatic valve disease (23), and preoperative AR (24) and dilatation (21) are the most commonly reported patient-related determinants of limited durability of the autograft valve. Furthermore, due to significantly increased mechanical stress postoperatively hypertension may potentially have a negative effect on autograft durability (25, 26). In a recent publication, Mookhoek and colleagues reported that explanted failed autografts consistently show fibrous

hyperplasia of the ventricularis and cellular and extracellular matrix characteristics of active remodeling which in the long-term can result in failure of the pulmonary autograft valve (27).

Progressive allograft dysfunction with increasing patient follow-up can be expected after implantation of an allograft at the pulmonary position. Longitudinal analyses of echocardiographic allograft function over time shows that that both pulmonary conduit pressure gradient and pulmonary conduit regurgitation grade increases over time. In patients with congenital heart disease, progressive allograft conduit regurgitation and stenosis can be expected after RVOT reconstruction, especially at the end of the first decade after the initial procedure. In patients who underwent the autograft procedure, the pulmonary conduit pressure gradient and pulmonary conduit regurgitation grade increases predominantly within the first two postoperative years. However, clinically important pulmonary conduit regurgitation is rare in adult patients after the autograft procedure. This indicates that the outcome of patients with congenital heart defects in need of allograft conduit for RVOT reconstruction differs from those that received an allograft as part of the autograft procedure.

Clinical factors influencing patient outcome

The different studies in this thesis show that patient outcome is strongly influenced by specific clinical factors. Significant differences were found in patients who received an allograft in the aortic position concerning the mode of implantation. In patients in whom the complete aortic root was implanted instead of the aortic valve in the subcoronary position, the risk of higher AR grade was considerably lower during follow-up. These observations were also reported by several other investigators (28-31). However, next to the implantation mode, there are several other factors that potentially influence patient and valve outcome after allograft aortic valve replacement. This thesis shows that younger patient age is correlated with an accelerated allograft failure, an observation which has also been reported in several other studies examining the clinical outcome of allografts in the aortic position (32-34). Furthermore, immunological rejection, allograft donor characteristics, the use of pulmonary allografts and mechanical stress are also correlated with failure of the allograft in the aortic position (35, 36). The cause of allograft failure in the aortic position seems, therefore, to be complex and multifactorial.

With regard to the autograft procedure, outcome varies considerably between different centers (1) and surgical techniques employed and by individual variation of the application of the root replacement technique (1-4, 37). The autograft was originally implanted by Donald Ross using the subcoronary implantation technique. However, other methods have been developed for the implantation of the autograft in the aortic

position. The other two often employed methods are the implantation of the autograft using the freestanding root replacement technique with re-implantation of the coronary arteries (using a variety of surgical techniques) and the insertion of the autograft using the inclusion cylinder technique. In our institution, the root replacement technique was mainly used. A recent publication from the German-Dutch Ross registry showed, however, better patient and autograft outcomes using the subcoronary implantation technique (38). Although it should be noted that this technique can only be applied in patients with isolated valve disease and has its technical limitations. The third method often used for autograft implantation, called inclusion cylinder technique (39), was also evaluated in this thesis. We have observed excellent patient survival and outstanding autograft durability with this method, especially in patients operated for predominant aortic stenosis. The use of this surgical technique in patients with predominant aortic stenosis may provide a durable solution with better results as compared to other surgical techniques and other biological or mechanical valve substitutes. In contrast to the root replacement technique, no cases of neo-aortic root aneurysmal enlargement were noted during the follow-up of patient in whom the inclusion cylinder technique was employed. Particularly the variant of the inclusion cylinder technique which incorporates autologous support of the pulmonary autograft seems to lead to excellent durability with very low re-operation rates and near perfect long term aortic valve function as determined by echocardiography (**Chapter 6**). This is an encouraging observation as it may improve the outcomes of patients undergoing the autograft procedure. However in the younger pediatric age group this method cannot be applied because of limited size of the aorta, while in older children and adults a size mismatch between the aorta and pulmonary artery also may prohibit this technique.

Furthermore, a more recent finding is that the presence of preoperative aortic regurgitation seems to be a strong predictor of autograft failure (24, 31-33), which would make this procedure less suitable for patients presenting with pure aortic regurgitation.

Young female patients in need of aortic valve replacement and who (may) contemplate pregnancy require special attention. Although these patients would benefit from the longevity of mechanical valves, the use of anticoagulant medication creates additional risks during pregnancy for both the mother and the fetus. As previously mentioned, warfarin use can result in complications during pregnancy (40, 41). Pregnancy is a hypercoagulable state, and pregnant women with a mechanical prosthesis are at increased risk for thrombo-embolic complications (42, 43). The other potential option of for aortic valve replacement in patients with a pregnancy wish would be the bioprosthetic valve. These valves are, however, associated with accelerated deterioration during pregnancy, leading to higher rates of reoperation, morbidity and mortality (44-46). Finally, human tissue valves can also be an option for young females who need to undergo aortic valve

replacement but want to become pregnant in the future. Since pregnancy leads to significant hemodynamic (e.g. increase plasma volume and cardiac output) and hormonal changes, it has been suggested that these alterations during pregnancy can negatively affect a human valve substitute like allograft or autograft (47-50). Due to insufficient published evidence on the possible degenerative effects of pregnancy on the allograft and pulmonary autograft in aortic position (44), the potential association between pregnancy and accelerated degeneration of human aortic valve substitutes in young female patients was investigated in this thesis. A considerable proportion of female patients became pregnant during the study period. No association was observed between pregnancy and human tissue valve substitute durability and function. These results are encouraging since human tissue valves seem to be a very attractive alternative for aortic valve replacement in female patients who are planning to become pregnant in the near future and want to avoid the negative effect of anticoagulation medication which inherent to mechanical prosthesis implantation. This choice should, however, be made in the awareness that human tissue valve are less durable than mechanical valves and the risk of reoperation later in life is, therefore, potentially higher. Young female patients in need of aortic valve replacement and with pregnancy wish should be well informed about the risk and benefits of the available valve substitutes and the decision of which prosthesis is the most suitable one should be a shared decision of both the doctor and the patient.

During the past decades the prognosis of infective endocarditis (IE) improved considerably and the disease is no longer by definition fatal (51, 52). However, IE still remains a serious condition characterized by high morbidity and mortality (53, 54). In **Chapter 7**, the long-term outcome of patients after the diagnosis of IE is described. Although the overall long-term survival after diagnosis of IE is relatively low, considerable difference were observed between the long-term survival of patients with IE and the survival of age and gender matched general population. The discrepancy in survival rates between patients with IE and the general Dutch population also remained considerable after the exclusion of in-hospital mortality. It has been suggested that surgical intervention may contribute to a better patient outcome (55-57). The European Society of Cardiology guidelines recommend performing surgery in order to avoid progressive heart failure, irreversible structural damage caused by severe infection and to prevent systemic embolism (58). The results of a systematic review and meta-analyses, described in **Chapter 8**, showed that in-hospital mortality results are either in favor of surgical therapy over medical therapy or there is no statistically significant difference. The long-term survival of patients operated for infective endocarditis is described in **Chapter 11**. Although hospital mortality is considerable for patients who are surgically treated for IE in our institution, those patients who survive the immediate post-operative period after the diagnosis of IE seem to have a good prognosis. With increasing follow-up time, the

survival of hospital survivors becomes comparable with that of the general population. Advancement in the medical treatment, diagnostic tools, development of guidelines, and better timing of surgery may have contributed to these improved results. Although these results are based on patients with IE who were selected to undergo surgery and, therefore, could be subject to selection bias, they do indicate that IE is a potentially curable disease if surgical cure is achieved. Surgical intervention needs, therefore, to be considered early in the process of the disease in order to improve the outcome of these patients. Future studies with larger sample size are needed to further confirm these results. In addition, while the original EuroSCORE seems to be no longer able to accurately predict the risk of in-hospital mortality for the overall group of patients undergoing cardiac surgery, it seems that EuroSCORE might be very well of use in more complex pathologies like IE. Both the additive EuroSCORE model and the logistic EuroSCORE model were able to accurately predict the risk of in-hospital mortality in surgically treated IE patients. These results suggest that the EuroSCORE is still applicable as a predictive model in a selected subgroup of high-risk patients (59).

The concept of patient-prosthesis mismatch (PPM) was introduced by Rahimtoola in 1978 (60). PPM is used to describe a condition in which the effective orifice area (EOA) of the implanted prosthesis may be inadequate for the patient's body size which can result in in continuous left ventricular outflow tract obstruction. The potential negative effect of PPM on transvalvular gradients and left ventricular mass regression has been shown in several studies (61-63). However, contradicting results have been published with regard to potential negative effect of PPM on patient survival (64, 65). The results of a systematic review and meta-analyses that assessed the effect of PPM on patient survival are described in **Chapter 9**, which shows a significant reduction in overall and cardiac-related long-term survival for patients with PPM after aortic valve replacement. Moreover, this association increases with PPM severity and appears constant over time. This clinically important observation should encourage surgeons to avoid PPM, especially in younger patients who often receive a mechanical valve and PPM, therefore, may have a higher negative impact on their survival.

The studies presented in this thesis found several potential risk factors for accelerated allograft failure in the RVOT position. Younger patient age was found to be an independent risk factor for accelerated allograft failure. A plausible explanation for this observation is the fact that the heart will outgrow the allograft after a few years, resulting in the need for reoperation. To prevent this some authors advise using an allograft with a relatively large diameter (66). However, implanting too large an allograft entails a risk for compression or kinking of the allograft. Furthermore, the use of aortic allograft (as compared to pulmonary allografts) is also correlated with allograft failure. The finding

that aortic allografts are more prone to failure, have also been reported in several other studies (7, 8, 11, 67). It has been postulated that a lower content of elastic tissue and a lower amount of total calcium in the wall of the pulmonary allograft in comparison to the aortic allograft can be responsible for this difference (68). It has also been suggested that ABO blood group incompatibility can have a negative impact on the durability of allograft conduits and on the reoperation rate. **Chapter 4** shows that blood group compatibility and assignment of quality codes do not have an impact on allograft durability after pulmonary valve replacement with a donor allograft.

Statistical methods used for the assessment of patient outcome

In this thesis several novel statistical methods were used for the assessment of patient outcome after aortic and pulmonary valve replacement. These methods will be briefly discussed here.

Propensity Score analyses

The propensity score was defined by Rosenbaum and Rubin and reflects the probability of treatment assignment conditional on observed baseline characteristics (69) (70, 71). The propensity score is a balancing score which means that conditional on the propensity score, the distribution of measured baseline variables is similar between the treatment and control group.

In contrast to randomized clinical trials, investigators have no control over the treatment assignment in observational studies. Propensity score can, therefore, be used to reduce the potential bias in estimated effects obtained from observational studies. Most widely used propensity-score methods are covariate adjustment using the propensity score, propensity score matching and stratification of the study population based on the propensity score (72).

The application of both propensity score adjustment and propensity score matching is illustrated in **Chapter 10**, where it is shown that without using the propensity score method it would not be possible to compare late survival between young adults undergoing an autograft procedure and young adults receiving a mechanical prosthesis. Autograft patients were for example on average seven years younger, had more often aortic valve stenosis and had better physical condition compared to patients that received a mechanical prosthesis. Patients that received a mechanical prosthesis had more often diabetes, hypertension, and next to aortic valve disease also other cardiac conditions requiring concomitant cardiac surgery. All these differences have an important impact on late survival in these patient groups (73-75). The additional advantage of calculating the propensity scores for the different group of patients is that it elegantly can illustrate the strict selection of patients for a particular procedure.

Although the propensity score method offers an elegant solution for reducing bias in observational studies, the main limitation of this method is that the propensity score can only make a balance based on registered or measured baseline characteristics between treated and untreated subjects. Hence, it is theoretically possible that there are important unregistered or unmeasured characteristics for which the matched groups are not balanced. These unmeasured baseline characteristics and subsequently unbalanced propensity score can result in biased estimation of the true treatment effect and, therefore, wrong conclusions.

Matching patient survival

The analyses of outcome of patients after a certain treatment can be relatively easy. However, putting these results into a perspective is much more difficult. The evaluation of long-term survival of patients can be difficult to interpret since several other causes of death compete with those that are a direct consequence of the disease or treatment studied. This is particularly the case when the study population consists of elderly patients. Therefore, in order to be able to correctly assess the degree of mortality in a certain patient population it is important to compare the mortality of this group with that of a reference group.

The method of 'relative survival' was introduced by Ederer et al. in 1961 (76). Relative survival is defined as the ratio between observed cumulative survival rate in a group of patients during a specified follow-up period, and the expected cumulative survival rate in a reference population. The relative survival can be estimated by using the national life table for individuals from general population while matching by age, gender, the calendar year in which the patient was followed within the study and, when possible, race. This method has been used in **Chapter 11** to evaluate the long-term mortality of patients with infective endocarditis who undergo operation in relation to the age-matched and gender-matched general population. Using this method, we were able to illustrate that, although hospital mortality is considerable for patients that were operated for infective endocarditis in our institution, those patients who survived the immediate postoperative period after the diagnosis of infective endocarditis had a survival rate similar to the age- and gender-matched general population.

The main advantage of the 'relative survival' method is that it provides a measure of excess mortality observed in a group of patients even when the exact causes of death are not known. Since relative survival provides clinically important information, the comparison of patient survival with that of general population should be performed in each clinical study that assesses the (long-term) patient survival in order to make a distinction between mortality as a direct consequence of the disease or treatment and mortality due to all other causes. Patient survival should be matched with survival of the general population based on age, gender, follow-up period, and (whenever possible)

race and socio-economic status. In addition, because of the exponential relationship between increasing patient age and mortality hazard, it is important that the relative survival of the patients is calculated based on the individual patient age and not the average age of the entire patient population.

Multiple imputation of missing values

Missing values are commonly encountered in observational studies and can result in major issues with regard to obtaining valid estimates. Since several types of analyses require complete data, researchers often decide to delete observations with missing values. This approach, however, does not only result in loss of data and power reduction, but can also result in obtaining biases estimates (77). The other approach is to impute missing values in order to avoid deleting incomplete observations. Although several alternatives exist for imputing missing values, the method of multiple imputation has shown in simulation studies to result in estimates which are efficient and valid (78). The application of multiple imputation method is illustrated in **Chapters 16 and 17**. Multiple imputation uses existing values of other variables to predict the missing values of the variable of interest. The process of imputing the missing values is performed several times which ultimately results in multiple imputed data sets (hence the term "multiple imputation"). Each of these imputed datasets is then used for statistical analyses producing multiple analysis results. Then following Rubin (79), the results of multiple analyses are combined to an overall analyses. An important advantage of multiple imputation is that it accounts for missing data by restoring not only the natural variability in the missing data, but also by incorporating the uncertainty caused by estimating missing data. This uncertainty is taken into account because the multiple imputation procedure replaces each missing value with a set of plausible values, and not with just a single value for each missing value, resulting in statistically valid inferences that adequately reflect the uncertainty caused by missing values. The method of multiple imputation is not often applied in cardiovascular surgical community or even the medical community. Not only this method requires theoretical knowledge but also advanced statistical software in order to perform the analyses. However, this method does offer the researchers an important tool for dealing with missing values and should therefore be more often applied in medical research, especially since the additional value of this method has been proven in several studies (80, 81). Although imputation technique offer good solutions of the missing data problem, it is still important that researchers explicitly indicate which variables had missing data and how much of the data was missing.

Variable Selection using bootstrap

The selection of a correct set of variables is an important part of the process of identifying independent risk factors associated with an outcome. Researchers often use

automated methods like forward selection, backward elimination and stepwise regression in order to identify potential risk factors associated with a certain outcome or in order to construct a parsimonious regression model. However, it has been shown that the application of these type of methods can result in suboptimal models (82, 83). These suboptimal models can be the consequence of omitting an important predictor, resulting in biased predictions, or selecting certain variables which are wrongly identified as an independent predictor of the outcome of interest. In addition, it has been shown that the application of these types of methods can result in models which are unstable and not reproducible (84). **Chapters 15-18** illustrate the use of bootstrap method for the selection of potential variables for the multivariable model. Instead of making predictions from a single model fit to the observed data, bootstrap samples are taken of the data, then the model is fit to each sample, and finally predictions are averaged over all of the fitted models to get the bagged prediction. Bootstrap bagging, although demanding huge amounts of computer cycles, removes much of the human arbitrariness from multivariable analysis and provides an important statistic: a measure of reliability of a risk factor. Bootstrap bagging provides a balance between selecting risk factors that are not reliable (type I error) and overlooking variables that are reliable (type II error). It has been shown that the use of bootstrap with automated selection methods results in models with excellent performance which are superior in predictive accuracy as compared to models applying Aikaike's Information Criterion, Schwartz's Bayesian Information Criterion or cross-validation (85). Within the cardiovascular surgical community, the bootstrap method has been particularly applied by dr Eugene Blackstone (86, 87). However, the application of this method should be encouraged more widely as it can provide an additional value of correctly identifying potential risk factors associated with an outcome.

Assessment of (allograft) valve function over time

The assessment of valve performance is complicated by several factors. First of all, valves are implanted in patients, who themselves have a limited survival. This creates a situation in which the risk of patient death competes with valve durability. Secondly, valve failure is a continuous process, not a hard end point. Time-to-event analysis is therefore inappropriate when assessing echocardiographic valve function, since it considers time of follow-up as a continuous variable while echo data are usually available within a certain time frame and are often incomplete in one or more time frames. In addition, it considers valve dysfunction as an irreversible endpoint, while severity of valve dysfunction (for example aortic/pulmonary regurgitation) is often variable over time. Thirdly, the means by which echocardiographic follow-up is obtained may influence the results: opportunistic versus standardized follow-up, experience of the observer, and intervals between measurements may all cause bias. Finally, allograft dysfunction may present in

different ways: through regurgitation, stenosis or a combination, further complicating valve performance analysis.

The challenge in analyzing longitudinal data is, therefore, estimating the average pattern of outcome over time and its variability in the group of patients. In addition, this average must take several sampling characteristics into account (e.g. censoring by death, unequal number of observations per patient, different follow-up intervals between observations). In contrast to time-to-event methods, linear and non-linear longitudinal models are able to adequately deal with these important characteristics of longitudinal data (88).

The 2008 guidelines for reporting mortality and morbidity after cardiac valvular interventions (88) propose the use of longitudinal data analysis for series of assessments like repeated echocardiographic measurements of valve function to estimate it's average temporal pattern and variability in a group of patients. The application of linear and non-linear longitudinal methods enables the researchers to model the trend of various repeatedly collected data such as echocardiographic measurements over time after allograft implantation. Using these methods it is possible to visualize the temporal trend of, for example, each aortic regurgitation grade over time during follow up. Clinicians can use such temporal trends to determine on average how for example aortic regurgitation develops over time after aortic allograft implantation. From statistical perspective, these types of methods are superior and more informative compared to the methods where repeated outcomes are dichotomized and analyzed with actuarial methods as if they were events, such as freedom from grade 1+ or 3+ aortic regurgitation after aortic valve surgery (89, 90). Assessing the trend of outcomes of interest and identifying factors that influence these outcomes over time can be of particular importance since it can help the clinicians understand how a certain process changes over time and thus can contribute to a better patient management (e.g. by determining which patients should be monitored more closely by their physicians and at which time interval).

Several methods for longitudinal analyses exist. Both linear and non-linear structures can be used to analyze longitudinal data. In linear methods, the degree of the outcome (y) is determined by the degree of the input (x), which can be written as a $y=ax+b$ equation. An important characteristic of linear methods is proportionality since there is a straight-line relationship between the input value and the outcome. Therefore, the behavior of linear methods can be fully predicted. In non-linear methods, the model uses parameters that are allowed to vary. Therefore, the assumption of proportionality is absent in non-linear models and the behavior of such model cannot be fully predicted. The cardiovascular system is a complex mechanical, chemical, and hemodynamic system in which the processes are often related via a variety of mechanisms. Therefore, these processes are often non-linearly structured (91-93). Since the principle of proportionality may not be valid, using linear methods may result in simplification of the real process

and therefore inaccurate results and inferences. On the other hand, the application of non-linear models is relatively time-consuming and more advanced.

Both the linear and non-linear methods are more advanced and time consuming compared to application of for example actuarial methods for the analyses of serial data. However, these methods are more reliable and reproducible, and can be done using standard available software. Currently, it is not entirely clear whether the non-linear pattern indeed results in better description of echocardiographic (allograft) valve function over time and further validation is necessary to confirm whether linear models are also suitable for the analyses of echocardiographic valve function over time.

Combining patient outcome and valve outcome and function

Patients are at risk of several types of events during follow-up after a certain treatment and they may experience a certain event which is not the one of interest but which does alter the probability of experiencing the event of interest. The situation where the occurrence of one event competes with the occurrence of the other events is described as competing risks analyses. The application of competing risks analyses is illustrated in **Chapter 18** where the competing risks of reoperation and death before reoperation are evaluated.

Actuarial methods like the Kaplan-Meier method assume that only one type of event of interest occurs and provide rate estimates for a certain event without taking into account the potential presence of other competing risks. As for many other diseases and treatments, taking into account competing risks can be important for the correct assessment of patient and prosthesis outcome after heart valve replacement. The application of actuarial methods in case of an allograft will answer the question of how high the the time-varying failure rate of the allograft is, while the application of competing risks analyses will answer the question of how likely the probability of allograft failure is while the recipient of this allograft is still alive. The assessment of the latter question does not only require the estimation of the intrinsic probability of allograft failure, but also the likelihood that the patient will still be alive in order to experience the allograft failure. Analyzing and evaluating each event separately in a certain patient population can result in misleading conclusions. This is because not taking into account competing events, while they are present, will result in an overestimation of the cumulative incidences, particularly in the context of the Kaplan-Meier method. Researcher should be encouraged to present both the results of the the event of interest and the results of competing risks in order to being able to objectively assess the outcome of patients.

Over the last two decades an increased attention has been given to combining longitudinal data with time-to-event data. This approach is called joint-modeling and enables us to investigate for example in which degree serial echocardiographic measurements (or certain biomarkers) are capable of predicting events (e.g. death or reoperation) that

patients might experience after a certain treatment (94-96). Several well established classical models exist for the separate analyses of longitudinal data and time-to-event data. However, these classical models do not consider dependencies between these two different data types (longitudinal data and time-to-event data) which can lead to inefficient or biased results when the longitudinal data is correlated with time-to-event data. In case where these two types of data are correlated, the application of joint modeling is more appropriate. In joint-modeling, typically a mixed-effects model is used for the longitudinal data and a Cox model for the survival data in order to build a single model where dependency and association between these types of data is taken into account (97). This approach can ultimately lead to a less biased and more efficient identification of potential prognostic factors of a certain outcome (97). The problem with the application of joint modeling is currently the complexity of the analyses and lack of appropriate software. It can be expected, however, that this issues will become less important when freely available and easy applicable software will become more readily available.

Future perspectives

The ideal substitute for the diseased aortic valve is yet to be found. While currently several types of prosthesis exist, they all have one or more properties (e.g. hemodynamics, durability, thrombogenicity) limiting their use in clinical practice. The development of novel techniques in aortic valve replacement may contribute to the search of the ideal prosthesis for the individual patients. Although on-pump aortic valve replacement still remains the procedure of choice, it can be expected that less invasive approaches currently used in surgical high-risk patients (e.g. percutaneous aortic valve replacement) may become a serious alternative for a certain group of patients. Furthermore, while prosthesis implantation offers an elegant solution for the native valve disease, the patients face the consequences of prosthetic valve disease during the remaining years of their lives. Particularly young adult patients are at risk of several repeat valve replacements because of the failing prosthesis. Consideration of risk factors associated with prosthesis failure can considerably improve the outcome of patients after heart valve prosthesis implantation. The application of modern and novel statistical techniques can significantly contribute to a better risk factor assessment and outcome modeling of patients undergoing cardiac surgery. In this regard, it is important that researchers and clinicians are encouraged to educate themselves in these techniques and apply them whenever there are more appropriate than conventional statistical methods.

Although allografts are currently the preferred type of conduit for pulmonary valve replacement and most experience has been acquired with these allografts, other options will probably become more established in basic clinical care. Pulmonary valve replacement using percutaneous approach is a very promising technique from which many patients may benefit without undergoing multiple redo surgeries (98). Most pa-

tients with an indication for pulmonary valve replacement have undergone at least one surgical procedure and will need to undergo one or more redo valve replacements in the future. The introduction of new minimally invasive techniques can further improve the survival and quality of life of this group of patients. It's inevitable that minimally invasive procedures will be further developed. However, it remains uncertain whether these techniques can replace conventional methods on short term since an important aspect of these new developments is the durability of the prosthesis (99). Long-term follow-up studies have to prove whether the performance of these novel devices is comparable with the allografts. Furthermore, associated lesions (e.g. tricuspid regurgitation, residual ventricular septal defects, branch pulmonary artery stenosis) in patients with congenital heart disease in whom the pulmonary valve needs to be replaced cannot be neglected when deciding between the conventional surgical approach, percutaneous approach, and other minimally invasive alternatives.

Currently, there is no evidence-based consensus on optimal timing for (redo) valve replacement in (young adult) patients with human tissue prosthesis in the aortic or pulmonary valve position (e.g. patients with congenital heart disease and autograft patients). In order to determine the optimal timing of prosthesis replacement in a particular patient population, ideally all patients should be followed over time until everybody has died and all events (not only the first) that took place over time should be analyzed. Furthermore, this should be combined with periodically assessed prosthesis (dys)function over time. In real life, the former is usually not a realistic option and the latter is difficult to achieve since there is no statistical test at this moment which combines clinical outcome with longitudinal prosthesis (dys)function (e.g. echocardiographic outcome). Our future studies will explore the feasibility to statistically combine clinical outcomes (discrete endpoints like death and reoperation) with longitudinal echocardiographic outcome (point estimates of continuous data gathered over time). This statistical method may significantly contribute to the decision of what optimal timing of aortic or pulmonary valve replacement is for a single patient with particular risk factors combined with echocardiographic valve (dys)function at that particular time. Furthermore, this type of statistical method can take into account the morbidity and mortality that the patient may experience according to predefined estimates of operative mortality, event occurrence and their consequences (death or reoperation), the probability of dying of other non-valve-related causes, risk factors responsible for valve dysfunction or event, and echocardiographic measurements of pulmonary valve (dys)function. Development of a clinical decision support tool that takes into account the estimated clinical outcome of the patient and the estimated echocardiographic progression of valve failure will enable clinicians to predict the pattern of further functional deterioration of allografts and to determine, evidence-based, the optimal timing of aortic or pulmonary valve replacement.

Advances in medical science have resulted in having many replacement options for patients in need of heart valve replacement. Although the application of evidence based medicine in some instances clearly indicates which treatment option is the best for a particular patient, often there are several reasonable options available which are all associated with uncertain outcomes, benefits and harms. With regard to heart valve replacement, this is for example the case in patients who are middle-aged and in whom life expectancy is comparable between mechanical and bioprosthetic heart valve substitutes (100). For these patients there is no single 'best choice' in selecting a prosthetic valve since patients may very well prefer a 60% life time risk of a reoperation with a bioprosthesis over a 20% life-time risk of a major thromboembolic event or bleeding with a mechanical valve, or vice versa, depending on his or her preferences. Although patient-centered care and shared decision making has gained increased awareness among the healthcare community, it still remains elusive to many health care providers. Evidence-based individualized shared decision making should, therefore, be more widely adopted in routine clinical practice by informing patients adequately and according to their educational background and by enabling patients to discuss their preferences with their doctors. In order for shared decision making to become part of mainstream clinical practice it is important to develop and implement decision aids (e.g. prognostic models) which can be used to provide evidence based information to doctors and patients in a balanced manner about the benefits and harms of different treatment options (101). Furthermore, future physicians should not only be educated in knowing the outcomes of different treatment options but should also be able to adequately inform their patients about these outcomes in the context of patient's educational background and patients preferences towards the pros and cons of the available treatment options. Shared decision making may also contribute to a reduction of health care costs. We live in an era where the growth in health care expenditures and changes in the current economic environment have made the cost of health care a major policy priority. Health care is no longer by definition financed based on the number of procedures performed (quantity), but more often based on the quality of care that is provided to patients. Involving patients in treatment decision making processes can increase patient's perceived quality of care. In addition, it has been shown that shared decision making can also contribute to cost reduction since patients may choose less costly alternative as treatment than their doctors initially would (102, 103).

Concluding remarks

This thesis provides further knowledge about the outcome of patients undergoing aortic or pulmonary valve replacement. The different studies presented show that, although patients undergoing aortic or pulmonary valve replacement with human tissue valves have a good late survival probability which is in most instances comparable with the

general population, an increasing rate of valve failure can be expected in the second post-operative decade. These results underline the importance of careful monitoring of patients after heart valve replacement irrespective of the type of surgical technique applied. This thesis also illustrates that the application of novel statistical methods can contribute to a better understanding of patient and valve outcome after heart valve replacement procedures and can help clinicians to better tailor surgical treatment and improve the outcome of their patients.

REFERENCES

1. El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G, Takkenberg JJ, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 2010; 376(9740):524-531.
2. Klieverik LM, Takkenberg JJ, Bekkers JA, Roos-Hesselink JW, Witsenburg M, Bogers AJ. The Ross operation: a Trojan horse? Eur Heart J 2007; 28(16):1993-2000.
3. Sievers HH, Stierle U, Charitos EI, Hanke T, Misfeld M, Matthias Bechtel JF, Gorski A, Franke UF, Graf B, Robinson DR, Bogers AJ, Dodge-Khatami A, Boehm JO, Rein JG, Botha CA, Lange R, Hoerer J, Moritz A, Wahlers T, Breuer M, Ferrari-Kuehne K, Hetzer R, Huebler M, Ziemer G, Takkenberg JJ, Hemmer W. Major adverse cardiac and cerebrovascular events after the Ross procedure: a report from the German-Dutch Ross Registry. Circulation 2010; 122(11 Suppl):S216-223.
4. Takkenberg JJ, Klieverik LM, Schoof PH, van Suylen RJ, van Herwerden LA, Zondervan PE, Roos-Hesselink JW, Eijkemans MJ, Yacoub MH, Bogers AJ. The Ross procedure: a systematic review and meta-analysis. Circulation 2009; 119(2):222-228.
5. El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G, Takkenberg JJ, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet; 376(9740):524-531.
6. Klieverik LM, Noorlander M, Takkenberg JJ, Kappetein AP, Bekkers JA, van Herwerden LA, Bogers AJ. Outcome after aortic valve replacement in young adults: is patient profile more important than prosthesis type? J Heart Valve Dis 2006; 15(4):479-487; discussion 487.
7. Tweddell JS, Pelech AN, Frommelt PC, Mussatto KA, Wyman JD, Fedderly RT, Berger S, Frommelt MA, Lewis DA, Friedberg DZ, Thomas JP, Jr., Sachdeva R, Litwin SB. Factors affecting longevity of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease. Circulation 2000; 102(19 Suppl 3):III130-135.
8. Bando K, Danielson GK, Schaff HV, Mair DD, Julsrud PR, Puga FJ. Outcome of pulmonary and aortic homografts for right ventricular outflow tract reconstruction. J Thorac Cardiovasc Surg 1995; 109(3):509-517; discussion 517-508.
9. Hawkins JA, Bailey WW, Dillon T, Schwartz DC. Midterm results with cryopreserved allograft valved conduits from the right ventricle to the pulmonary arteries. J Thorac Cardiovasc Surg 1992; 104(4):910-916.
10. Brown JW, Ruzmetov M, Rodefeld MD, Vijay P, Turrentine MW. Right ventricular outflow tract reconstruction with an allograft conduit in non-ross patients: risk factors for allograft dysfunction and failure. Ann Thorac Surg 2005; 80(2):655-663; discussion 663-654.
11. Gerestein CG, Takkenberg JJ, Oei FB, Cromme-Dijkhuis AH, Spitaels SE, van Herwerden LA, Steyerberg EW, Bogers AJ. Right ventricular outflow tract reconstruction with an allograft conduit. Ann Thorac Surg 2001; 71(3):911-917; discussion 917-918.
12. Vliegen HW, van Straten A, de Roos A, Roest AA, Schoof PH, Zwinderman AH, Ottenkamp J, van der Wall EE, Hazekamp MG. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of fallot. Circulation 2002; 106(13):1703-1707.
13. Bove EL, Kavey RE, Byrum CJ, Sondheimer HM, Blackman MS, Thomas FD. Improved right ventricular function following late pulmonary valve replacement for residual pulmonary insufficiency or stenosis. J Thorac Cardiovasc Surg 1985; 90(1):50-55.

14. d'Udekem Y, Rubay J, Shango-Lody P, Ovaert C, Vliers A, Caliteaux M, Sluysmans T. Late homograft valve insertion after transannular patch repair of tetralogy of Fallot. J Heart Valve Dis 1998; 7(4):450-454.
15. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995; 41(10):1403-1409.
16. Koch CG, Li L, Lauer M, Sabik J, Starr NJ, Blackstone EH. Effect of functional health-related quality of life on long-term survival after cardiac surgery. Circulation 2007; 115(6):692-699.
17. Kouchoukos NT, Masetti P, Nickerson NJ, Castner CF, Shannon WD, Davila-Roman VG. The Ross procedure: long-term clinical and echocardiographic follow-up. Ann Thorac Surg 2004; 78(3):773-781; discussion 773-781.
18. Luciani GB, Casali G, Favaro A, Prioli MA, Barozzi L, Santini F, Mazzucco A. Fate of the aortic root late after Ross operation. Circulation 2003; 108 Suppl 1:II61-67.
19. Stulak JM, Burkhart HM, Sundt TM, 3rd, Connolly HM, Suri RM, Schaff HV, Dearani JA. Spectrum and outcome of reoperations after the Ross procedure. Circulation 2010; 122(12):1153-1158.
20. Bekkers JA, Klieverik LM, Raap GB, Takkenberg JJ, Bogers AJ. Aortic root reoperations after pulmonary autograft implantation. J Thorac Cardiovasc Surg 2010; 140(6 Suppl):S58-63; discussion S86-91.
21. Luciani GB, Favaro A, Casali G, Santini F, Mazzucco A. Ross operation in the young: a ten-year experience. Ann Thorac Surg 2005; 80(6):2271-2277.
22. Settepani F, Kaya A, Morshuis WJ, Schepens MA, Heijmen RH, Dossche KM. The Ross operation: an evaluation of a single institution's experience. Ann Thorac Surg 2005; 79(2):499-504.
23. Sampath Kumar A, Talwar S, Saxena A, Singh R. Ross procedure in rheumatic aortic valve disease. Eur J Cardiothorac Surg 2006; 29(2):156-161.
24. Laudito A, Brook MM, Suleman S, Bleiweis MS, Thompson LD, Hanley FL, Reddy VM. The Ross procedure in children and young adults: a word of caution. J Thorac Cardiovasc Surg 2001; 122(1):147-153.
25. Carr-White GS, Afoke A, Birks EJ, Hughes S, O'Halloran A, Glennen S, Edwards S, Eastwood M, Yacoub MH. Aortic root characteristics of human pulmonary autografts. Circulation 2000; 102(19 Suppl 3):III15-21.
26. Yacoub MH, Klieverik LM, Melina G, Edwards SE, Sarathchandra P, Bogers AJ, Squarcia U, Sani G, van Herwerden LA, Takkenberg JJ. An evaluation of the Ross operation in adults. J Heart Valve Dis 2006; 15(4):531-539.
27. Mookhoek A, de Heer E, Bogers AJ, Takkenberg JJ, Schoof PH. Pulmonary autograft valve explants show typical degeneration. J Thorac Cardiovasc Surg 2010; 139(6):1416-1419.
28. Yacoub M, Rasmi NR, Sundt TM, Lund O, Boyland E, Radley-Smith R, Khaghani A, Mitchell A. Fourteen-year experience with homovital homografts for aortic valve replacement. J Thorac Cardiovasc Surg 1995; 110(1):186-193; discussion 193-184.
29. O'Brien MF, Stafford EG, Gardner MA, Pohlner PG, Tesar PJ, Cochrane AD, Mau TK, Gall KL, Smith SE. Allograft aortic valve replacement: long-term follow-up. Ann Thorac Surg 1995; 60(2 Suppl):S65-70.
30. Rubay JE, Raphael D, Sluysmans T, Vanoverschelde JL, Robert A, Schoevaerdts JC, Marchandise B, Dion RA. Aortic valve replacement with allograft/autograft: subcoronary versus intraluminal cylinder or root. Ann Thorac Surg 1995; 60(2 Suppl):S78-82.
31. Willems TP, van Herwerden LA, Taams MA, Kleyburg-Linker VE, Roelandt JR, Bos E. Aortic allograft implantation techniques: pathomorphology and regurgitant jet patterns by Doppler echocardiographic studies. Ann Thorac Surg 1998; 66(2):412-416.

32. Lund O, Chandrasekaran V, Grocott-Mason R, Elwidaa H, Mazhar R, Khaghani A, Mitchell A, Ilsley C, Yacoub MH. Primary aortic valve replacement with allografts over twenty-five years: valve-related and procedure-related determinants of outcome. J Thorac Cardiovasc Surg 1999; 117(1):77-90; discussion 90-71.
33. Smedira NG, Blackstone EH, Roselli EE, Laffey CC, Cosgrove DM. Are allografts the biologic valve of choice for aortic valve replacement in nonelderly patients? Comparison of explantation for structural valve deterioration of allograft and pericardial prostheses. J Thorac Cardiovasc Surg 2006; 131(3):558-564 e554.
34. Takkenberg JJ, Klieverik LM, Bekkers JA, Kappetein AP, Roos JW, Eijkemans MJ, Bogers AJ. Allografts for aortic valve or root replacement: insights from an 18-year single-center prospective follow-up study. Eur J Cardiothorac Surg 2007; 31(5):851-859.
35. Takkenberg JJ, van Herwerden LA, Eijkemans MJ, Bekkers JA, Bogers AJ. Evolution of allograft aortic valve replacement over 13 years: results of 275 procedures. Eur J Cardiothorac Surg 2002; 21(4):683-691; discussion 691.
36. Green MK, Walsh MD, Dare A, Hogan PG, Zhao XM, Frazer IH, Bansal AS, O'Brien MF. Histologic and immunohistochemical responses after aortic valve allografts in the rat. Ann Thorac Surg 1998; 66(6 Suppl):S216-220.
37. Elkins RC, Thompson DM, Lane MM, Elkins CC, Peyton MD. Ross operation: 16-year experience. J Thorac Cardiovasc Surg 2008; 136(3):623-630, 630 e621-625.
38. Charitos EI, Stierle U, Hanke T, Schmidtke C, Sievers HH, Richardt D. Long-term results of 203 young and middle-aged patients with more than 10 years of follow-up after the original subcoronary ross operation. Ann Thorac Surg 2012; 93(2):495-502.
39. Skillington PD, Fuller JA, Grigg LE, Yapanis AG, Porter GF. Ross procedure. Inserting the autograft using a fully supported root replacement method; techniques and results. J Heart Valve Dis 1999; 8(6):593-600.
40. Wong V, Cheng CH, Chan KC. Fetal and neonatal outcome of exposure to anticoagulants during pregnancy. Am J Med Genet 1993; 45(1):17-21.
41. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 2000; 160(2):191-196.
42. North RA, Sadler L, Stewart AW, McCowan LM, Kerr AR, White HD. Long-term survival and valve-related complications in young women with cardiac valve replacements. Circulation 1999; 99(20):2669-2676.
43. Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 1980; 68(1):122-140.
44. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. Br Heart J 1994; 71(2):196-201.
45. Nishida H, Takahara Y, Takeuchi S, Mogi K, Murayama H. Long-term evaluation of bovine pericardial bioprostheses in young women: influence of pregnancy. Jpn J Thorac Cardiovasc Surg 2005; 53(10):557-561.
46. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. Circulation 2003; 107(9):1240-1246.
47. Stout KK, Otto CM. Pregnancy in women with valvular heart disease. Heart 2007; 93(5):552-558.
48. Reimold SC, Rutherford JD. Clinical practice. Valvular heart disease in pregnancy. N Engl J Med 2003; 349(1):52-59.
49. Thorne SA. Pregnancy in heart disease. Heart 2004; 90(4):450-456.

50. Fliegner D, Schubert C, Penkalla A, Witt H, Kararigas G, Dworatzek E, Staub E, Martus P, Ruiz Noppinger P, Kintscher U, Gustafsson JA, Regitz-Zagrosek V. Female sex and estrogen receptor-beta attenuate cardiac remodeling and apoptosis in pressure overload. Am J Physiol Regul Integr Comp Physiol 2010; 298(6):R1597-1606.
51. Lowes JA, Hamer J, Williams G, Houang E, Tabaqchali S, Shaw EJ, Hill IM, Rees GM. 10 Years of infective endocarditis at St. Bartholomew's Hospital: analysis of clinical features and treatment in relation to prognosis and mortality. Lancet 1980; 1(8160):133-136.
52. McCartney AC. Changing trends in infective endocarditis. J Clin Pathol 1992; 45(11):945-948.
53. Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, Casalta JP, Danchin N, Delahaye F, Etienne J, Le Moing V, Leport C, Mainardi JL, Ruimy R, Vandenesch F. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA 2002; 288(1):75-81.
54. Cabell CH, Jollis JG, Peterson GE, Corey GR, Anderson DJ, Sexton DJ, Woods CW, Reller LB, Ryan T, Fowler VG, Jr. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 2002; 162(1):90-94.
55. Croft CH, Woodward W, Elliott A, Commerford PJ, Barnard CN, Beck W. Analysis of surgical versus medical therapy in active complicated native valve infective endocarditis. Am J Cardiol 1983; 51(10):1650-1655.
56. Vikram HR, Buenconsejo J, Hasbun R, Quagliarello VJ. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. JAMA 2003; 290(24):3207-3214.
57. Lalani T, Cabell CH, Benjamin DK, Lasca O, Naber C, Fowler VG, Jr., Corey GR, Chu VH, Fenely M, Pachirat O, Tan RS, Watkin R, Ionac A, Moreno A, Mestres CA, Casabe J, Chipigina N, Eisen DP, Spelman D, Delahaye F, Peterson G, Olaison L, Wang A. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation; 121(8):1005-1013.
58. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Muller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009; 30(19):2369-2413.
59. Mestres CA, Castro MA, Bernabeu E, Josa M, Cartana R, Pomar JL, Miro JM, Mulet J, Hospital Clinico Endocarditis Study G. Preoperative risk stratification in infective endocarditis. Does the EuroSCORE model work? Preliminary results. Eur J Cardiothorac Surg 2007; 32(2):281-285.
60. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. Circulation 1978; 58(1):20-24.
61. Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: definition, clinical impact, and prevention. Heart 2006; 92(8):1022-1029.
62. Del Rizzo DF, Abdoh A, Cartier P, Doty D, Westaby S. Factors affecting left ventricular mass regression after aortic valve replacement with stentless valves. Semin Thorac Cardiovasc Surg 1999; 11(4 Suppl 1):114-120.
63. Pibarot P, Dumesnil JG, Lemieux M, Cartier P, Metras J, Durand LG. Impact of prosthesis-patient mismatch on hemodynamic and symptomatic status, morbidity and mortality after aortic valve replacement with a bioprosthetic heart valve. J Heart Valve Dis 1998; 7(2):211-218.

64. Blackstone EH, Cosgrove DM, Jamieson WR, Birkmeyer NJ, Lemmer JH, Jr., Miller DC, Butchart EG, Rizzoli G, Yacoub M, Chai A. Prosthesis size and long-term survival after aortic valve replacement. J Thorac Cardiovasc Surg 2003; 126(3):783-796.
65. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. J Am Coll Cardiol 2000; 36(4):1131-1141.
66. Tam RK, Tolan MJ, Zamvar VY, Slavik Z, Pickering R, Keeton BR, Salmon AP, Webber SA, Tsang V, Lamb RK, et al. Use of larger sized aortic homograft conduits in right ventricular outflow tract reconstruction. J Heart Valve Dis 1995; 4(6):660-664.
67. Albert JD, Bishop DA, Fullerton DA, Campbell DN, Clarke DR. Conduit reconstruction of the right ventricular outflow tract. Lessons learned in a twelve-year experience. J Thorac Cardiovasc Surg 1993; 106(2):228-235; discussion 235-226.
68. Livi U, Abdulla AK, Parker R, Olsen EJ, Ross DN. Viability and morphology of aortic and pulmonary homografts. A comparative study. J Thorac Cardiovasc Surg 1987; 93(5):755-760.
69. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
70. Rubin DB. Using propensity score to help design observational studies: application to the tobacco litigation. Health Services and Outcomes Research Methodology 2001;2:169–188.
71. Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg 2002; 123(1):8-15.
72. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Stat Med 2008; 27(12):2037-2049.
73. Tjang YS, van Hees Y, Korfer R, Grobbee DE, van der Heijden GJ. Predictors of mortality after aortic valve replacement. Eur J Cardiothorac Surg 2007; 32(3):469-474.
74. Toumpoulis IK, Chamogeorgakis TP, Angouras DC, Swistel DG, Anagnostopoulos CE, Rokkas CK. Independent predictors for early and long-term mortality after heart valve surgery. J Heart Valve Dis 2008; 17(5):548-556.
75. Hannan EL, Samadashvili Z, Lahey SJ, Smith CR, Culliford AT, Higgins RS, Gold JP, Jones RH. Aortic valve replacement for patients with severe aortic stenosis: risk factors and their impact on 30-month mortality. Ann Thorac Surg 2009; 87(6):1741-1749.
76. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961; 6:101-121.
77. Demissie S, LaValley MP, Horton NJ, Glynn RJ, Cupples LA. Bias due to missing exposure data using complete-case analysis in the proportional hazards regression model. Stat Med 2003; 22(4):545-557.
78. Little RJA, Rubin DB. Statistical analysis with missing data. New York, NY: John Wiley & Sons, Inc, 1987
79. Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. J Thorac Cardiovasc Surg 2001; 122(3):430-439.
80. Twisk J, de Vente W. Attrition in longitudinal studies. How to deal with missing data. J Clin Epidemiol 2002; 55(4):329-337.
81. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995; 142(12):1255-1264.
82. Derkson S, Keselman HJ. Backward, forward and stepwise automated subset selection algorithms: frequency of obtaining authentic and noise variables. Br J Math Stat Psychol 1992;45:265e82.
83. Murtaugh PA. Methods of variable selection in regression modeling. Commun StatdSimul Comput 1998;27:711e34.

84. Austin PC, Tu JV. Automated variable selection methods for logistic regression produced unstable models for predicting acute myocardial infarction mortality. J Clin Epidemiol 2004; 57(11):1138-1146.
85. Austin PC, Tu JV. Bootstrap methods for developing predictive models in cardiovascular research. Am Stat 2004;58:131e7.
86. Mihaljevic T, Pattakos G, Gillinov AM, Bajwa G, Planinc M, Williams SJ, Blackstone EH. Robotic Posterior Mitral Leaflet Repair: Neochordal Versus Resectional Techniques. Ann Thorac Surg 2012.
87. Pattakos G, Koch CG, Brizzio ME, Batizy LH, Sabik JF, 3rd, Blackstone EH, Lauer MS. Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. Arch Intern Med 2012; 172(15):1154-1160.
88. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJ, David TE, Butchart EG, Adams DH, Shahian DM, Hagl S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008; 135(4):732-738.
89. Murashita T, Kubota T, Kamikubo Y, Shiiya N, Yasuda K. Long-term results of aortic valve regurgitation after repair of ruptured sinus of valsalva aneurysm. Ann Thorac Surg 2002; 73(5):1466-1471.
90. Losay J, Touchot A, Capderou A, Piot JD, Belli E, Planche C, Serraf A. Aortic valve regurgitation after arterial switch operation for transposition of the great arteries: incidence, risk factors, and outcome. J Am Coll Cardiol 2006; 47(10):2057-2062.
91. Elbert T, Ray WJ, Kowalik ZJ, Skinner JE, Graf KE, Birbaumer N. Chaos and physiology: deterministic chaos in excitable cell assemblies. Physiol Rev 1994; 74(1):1-47.
92. Sugihara G, Allan W, Sobel D, Allan KD. Nonlinear control of heart rate variability in human infants. Proc Natl Acad Sci U S A 1996; 93(6):2608-2613.
93. Scher AM, Young AC. Nonlinearity in the control of blood pressure and heart rate. Ann N Y Acad Sci 1969; 156(2):722-730.
94. Andrinopoulou ER, Rizopoulos D, Jin R, Bogers AJ, Lesaffre E, Takkenberg JJ. An introduction to mixed models and joint modeling: analysis of valve function over time. Ann Thorac Surg 2012; 93(6):1765-1772.
95. Henderson R, Diggle P, Dobson A. Joint modelling of longitudinal measurements and event time data. Biostatistics 2000; 1(4):465-480.
96. Wulfsohn MS, Tsiatis AA. A joint model for survival and longitudinal data measured with error. Biometrics 1997; 53(1):330-339.
97. Ibrahim JG, Chu H, Chen LM. Basic concepts and methods for joint models of longitudinal and survival data. J Clin Oncol 2010; 28(16):2796-2801.
98. Bonhoeffer P, Boudjemline Y, Saliba Z, Merckx J, Aggoun Y, Bonnet D, Acar P, Le Bidois J, Sidi D, Kachaner J. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 2000; 356(9239):1403-1405.
99. Eicken A, Ewert P, Hager A, Peters B, Fratz S, Kuehne T, Busch R, Hess J, Berger F. Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients. Eur Heart J 2011; 32(10):1260-1265.
100. Stoica S, Goldsmith K, Demiris N, Punjabi P, Berg G, Sharples L, Large S. Microsimulation and clinical outcomes analysis support a lower age threshold for use of biological valves. Heart 2010; 96(21):1730-1736.
101. Breslin M, Mullan RJ, Montori VM. The design of a decision aid about diabetes medications for use during the consultation with patients with type 2 diabetes. Patient Educ Couns 2008; 73(3):465-472.

102. Arterburn D, Wellman R, Westbrook E, Rutter C, Ross T, McCulloch D, Handley M, Jung C. Introducing decision aids at Group Health was linked to sharply lower hip and knee surgery rates and costs. Health Aff (Millwood) 2012; 31(9):2094-2104.
103. Oshima Lee E, Emanuel EJ. Shared decision making to improve care and reduce costs. N Engl J Med 2013; 368(1):6-8.

Chapter 21

Summary

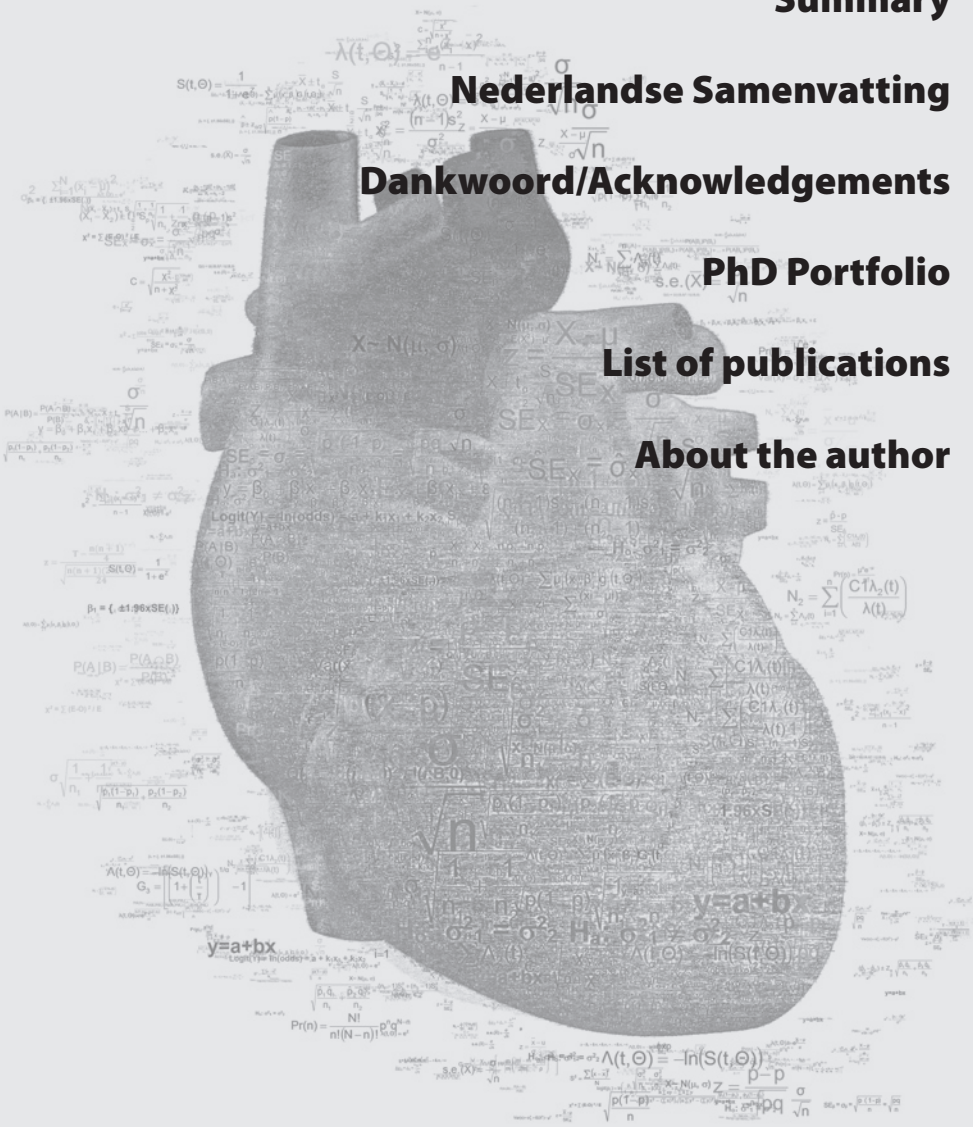
Nederlandse Samenvatting

Dankwoord/Acknowledgements

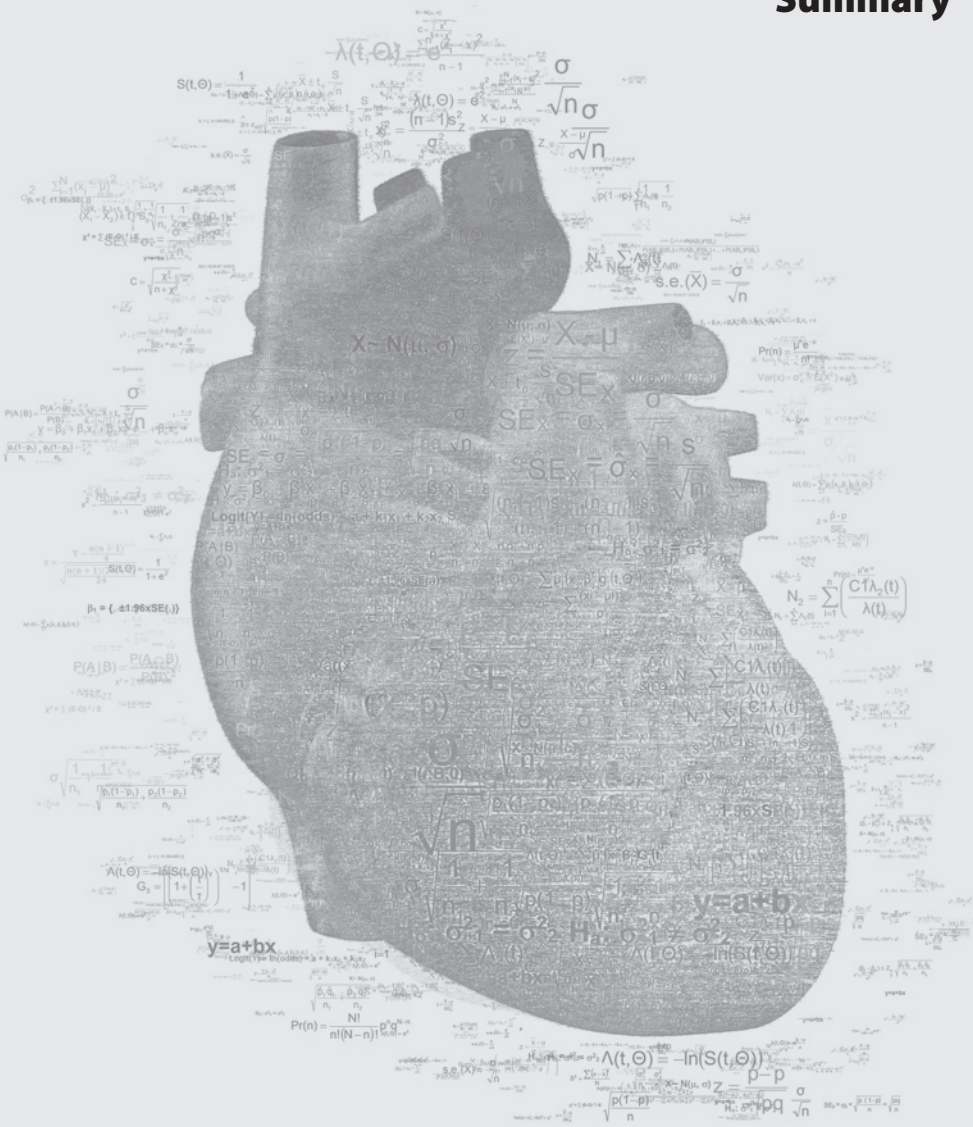
PhD Portfolio

List of publications

About the author



Summary



Chapter 1 gives a general introduction to the topics studied in this thesis. The aims of our studies are presented and an outline of this thesis is given.

Chapter 2 describes the Rotterdam long-term experience with the use of allograft conduits for reconstruction of the right ventricular outflow tract in congenital heart malformations and autograft procedures. The results of this study show that this procedure can be performed with good patient survival (93% at 10 years and 88% at 15 years), acceptable long-term allograft durability (89% at 10 years and 81% at 15 years) and good perceived quality of life.

Chapter 3 concerns the long-term experience with the use of allograft conduits for right ventricular outflow tract reconstruction after correction of tetralogy of Fallot in our institution. Allograft implantation after previous tetralogy of Fallot repair can be performed with low risk and a low reintervention rate (freedom from allograft replacement was 83% at 10 years and 70% at 15 years). The results of allograft durability are acceptable at long-term follow-up (freedom from any valve related event was 80% at 10 years and 67% at 15 years). Functional improvement after allograft implantation in patients with a previous correction of tetralogy of Fallot is good, even after a relatively long period of follow-up. However, there is concern about the long-term patient survival (80% at 15 years) and the occurrence of heart failure as a cause of late mortality.

Chapter 4 describes the impact of ABO blood group compatibility and assignment of quality codes on the reoperation rate of allograft conduits used for right ventricular outflow tract reconstruction. In our experience blood group compatibility and assignment of quality codes do not have an impact on allograft durability.

Chapter 5 is a letter to the editor underlining the importance of using correct statistical methods and having an appropriate number of subjects being at risk in order to achieve reliable estimates of the 3 major functions (survival, probability density, hazard) and to ensure that the standard error of the survival estimate is less than 10%.

Chapter 6 describes the long-term results of autologous support of the pulmonary autograft in the Ross procedure. This study shows that application of a variant of the inclusion cylinder technique, whereby the aortic root size was adjusted to match the pulmonary autograft, leads to excellent results in the groups of patients presenting with aortic stenosis and mixed aortic stenosis/regurgitation, and good results for those presenting with pure aortic regurgitation.

Chapter 7 describes the long-term survival of patients with infective endocarditis. This study shows that despite diagnostic and therapeutic advances, infective endocarditis is associated with a high long-term mortality. Compared to the general Dutch population, the survival of patients with infective endocarditis was significantly lower. Even in the event of infective endocarditis being cured, the survival of these patients may be diminished compared to that of the general population. Hence, a careful follow up of these patients is warranted.

Chapter 8 presents a systematic literature review that was undertaken to assess the timing of surgery in the treatment of infective endocarditis. Although endocarditis has been extensively described over the last decades and treatment with surgery is established for certain indications associated with improved survival, surgical treatment of prosthetic valve endocarditis carries quite a high mortality and requires close follow-up due to a continued postoperative risk of heart failure, renal failure, recurrent endocarditis and neurologic disorders. The selection of patients who benefit most from valve replacement is becoming more transparent, but treatment often remains biased because of several reasons (e.g. surgeon preferences, cardiologist preferences, referral patterns, institutional policies). A large number of ongoing studies and randomized trials will produce stronger evidence.

Chapter 9 describes the results of a systematic review and meta-analysis of observational studies assessing the impact of prosthesis–patient mismatch on long-term survival after aortic valve replacement. Prosthesis–patient mismatch was associated with an increase in all-cause and cardiac-related mortality over long-term follow-up, in particular in younger patients and those receiving a mechanical prosthesis. Current efforts to prevent prosthesis–patient mismatch should therefore receive more emphasis and widespread acceptance to improve long-term survival after aortic valve replacement.

Chapter 10 concerns 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. In comparable patients with isolated aortic valve disease, 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.

Chapter 11 describes the long-term mortality of patients with surgically treated infective endocarditis in relation to the age-matched and gender-matched general population. Although mortality of infective endocarditis patients who have undergone operation remains considerable during the immediate postoperative period, the mortality of hospital survivors is, with increasing follow-up time, comparable with the general population.

Chapter 12 describes the long-term allograft function after surgical procedures in which a standard or bicuspidalized homograft was used in the right ventricle-pulmonary artery position in infants younger than 12 months, including patients with a Ross or extended Ross procedure. The results of this study show that when properly sized cryopreserved homografts for placement in the right ventricle-pulmonary artery position in Ross, Konno—Ross, and other procedures in infants under the age of 1 year are not readily available, bicuspidalized homografts provide an acceptable alternative.

Chapter 13 describes the long-term results of our ongoing prospective cohort of autograft recipients. We observed good late survival in patients undergoing autograft procedure without reinforcement techniques (90% at 18 years). However, over half of the autografts failed prior to the end of the second decade. The reoperation rate and the results of echocardiographic measurements over time underline the importance of careful monitoring especially in the second decade after the initial autograft operation and in particular in patients with pre-operative aortic regurgitation.

Chapter 14 describes the influence of pregnancy on durability of homografts and pulmonary autografts. This study shows that pregnancy is not associated with impaired durability of human tissue valve substitutes. Thus, young female patients who are planning to start a family may consider human tissue valves as a suitable aortic valve substitute, although at the cost of a reoperation later in life.

Chapter 15 details the Melbourne experience with the Ross operation in patients with predominant aortic stenosis using an inclusion cylinder method. In an experience spanning 19 years, the Ross operation used for predominant aortic stenosis using the inclusion cylinder method described, results in 99% freedom from re-operation on the aortic valve at 15 years, better than any other tissue or mechanical valve. For adults under 65 years without significant co-morbidities who present with predominant aortic stenosis, the pulmonary autograft inserted with this technique gives excellent results.

Chapter 16 describes the pulmonary conduit function over time in Ross patients using sophisticated statistical methods. Echocardiographic follow-up of pulmonary conduits

shows outstanding conduit durability. Clinical important pulmonary conduit regurgitation is rare in adult patients after the Ross operation. Conduit obstruction of potential clinical impact occurs in a minority of patients. While conduit pressure gradient development occurs predominantly during the first two years postoperatively, conduit regurgitation increases gradually across time yet clinically insignificant on average.

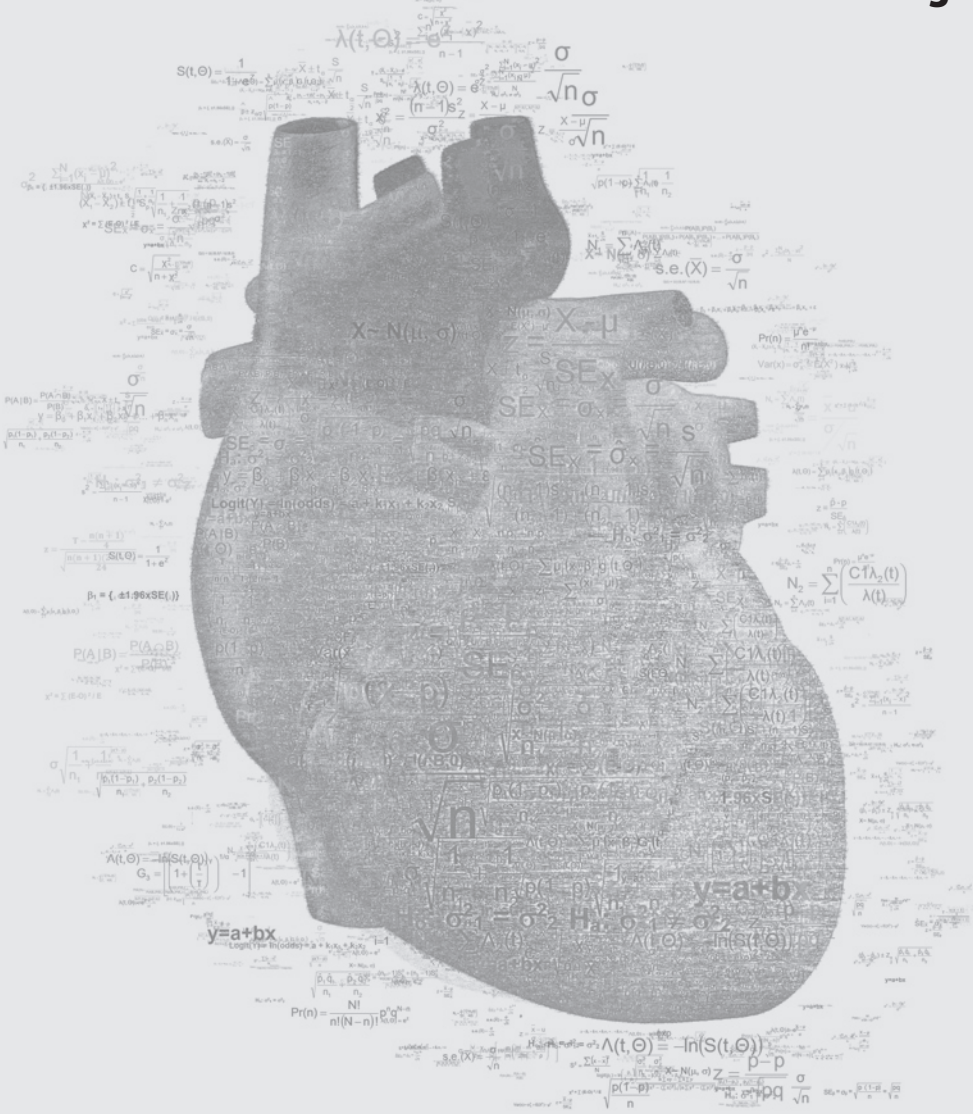
Chapter 17 describes the echocardiographic allograft valve function over time in a cohort of patients that underwent right ventricular outflow tract reconstruction with an allograft conduit. Although the allograft valve function over time is acceptable, progressive allograft conduit regurgitation and stenosis can be expected in the second decade after right ventricular outflow tract reconstruction with an allograft, in particular when implanted in the extra-anatomic position.

Chapter 18 describes echocardiographic allograft valve function over time in a cohort of patients who were prospectively followed after allograft aortic valve or root replacement, illustrating the use of longitudinal data analysis for assessing valve function over time. Both aortic regurgitation and stenosis increase over time after allograft aortic valve or root replacement. Younger patient age and use of the subcoronary implantation technique are associated with increased regurgitation and stenosis. The use of non-linear longitudinal models allows for a useful analysis of allograft valve function over time.

Chapter 19 is a letter to the editor underlining the importance of involving the patients in the selection of most appropriate treatment option. Although patient-centered care and shared decision making has gained increased awareness among the healthcare community, it still remains elusive to many health care providers. Evidence-based individualized shared decision making should, therefore, be more widely adopted in routine clinical practice by informing patients adequately and according to their educational background and by enabling patients to discuss their preferences with their doctors.

In **Chapter 20**, the general discussion, the results that were presented in this thesis are discussed and the research questions that were posed in Chapter 1 are answered.

Nederlandse Samenvatting



In **Hoofdstuk 1**, de algemene introductie, wordt de achtergrond van het onderzoek beschreven en worden het doel en de onderzoeksvragen uiteengezet.

Hoofdstuk 2 beschrijft de ervaring met het gebruik van donorkleppen bij patiënten met een aangeboren afwijking van de pulmonaalklep en bij patiënten die de autograft procedure hebben ondergaan. De resultaten van deze studie laten zien dat deze patiënten een goede overleving hebben van 93% na 10 jaar en 88% na 15 jaar. De duurzaamheid van de donorkleppen kan als acceptabel worden beschouwd met een vrijheid van heroperatie van 89% na 10 jaar en 81% na 15 jaar. Tevens geven deze patiënten aan dat ze een goede kwaliteit van leven hebben met weinig beperkingen bij het uitvoeren van dagelijkse bezigheden.

Hoofdstuk 3 betreft de lange termijn resultaten van het gebruik van donorkleppen op de pulmonaalklep positie na eerdere reconstructie in verband met tetralogie van Fallot. Het implanteren van donorkleppen bij deze patiënten kan plaats vinden met een laag operatief risico. Het risico van heroperatie op de lange termijn is relatief laag met een vrijheid van reoperatie van 83% na 10 jaar en 70% na 15 jaar. De duurzaamheid van de donorkleppen bij deze groep patiënten is tevens acceptabel. Echter, gezien de relatief lage overleving van 80% na 15 jaar waarbij hartfalen relatief frequent de doodoorzaak was dienen deze patiënten nauwgezet vervolgd te worden.

Hoofdstuk 4 beschrijft het verband tussen ABO bloedgroep incompatibiliteit en het toekennen van kwaliteitscodes enerzijds, en de duurzaamheid van donorkleppen op de pulmonaalklep positie anderzijds. De analyses van onze ervaring laten zien dat er geen significant verband is tussen ABO bloedgroep incompatibiliteit en de duurzaamheid van de donorkleppen. Tevens werd er geen verband gevonden tussen het toekennen van kwaliteitscodes bij het prepareren van donorkleppen en de duurzaamheid van deze kleppen na implantatie.

Hoofdstuk 5 is een brief aan de editor waarin het belang van het toepassen van de juiste statistische methodes bij het analyseren van de data wordt benadrukt.

Hoofdstuk 6 betreft de lange termijn resultaten van de pulmonalis autograft in patiënten die de Ross procedure hebben ondergaan en waarbij er additionele technieken zijn gebruikt om de pulmonalis autograft extra te ondersteunen. Deze studie toont aan dat het aanpassen van de aortawortel aan de grootte van de pulmonalis autograft tot een uitstekende duurzaamheid van de deze kleppen leidt bij patiënten die zich voornamelijk presenteren met een aorta stenose of een combinatie van zowel aorta stenose en aorta insufficiëntie.

Hoofdstuk 7 beschrijft de lange termijn overleving van patiënten met een infectieuze endocarditis. Ondanks de ontwikkelingen op het gebied van diagnostiek en therapie, blijft infectieuze endocarditis een ziekte welke gepaard gaat met een relatief hoge mortaliteit. Vergeleken met de overleving van de algemene Nederlandse bevolking was de overleving van deze groep patiënten aanzienlijk lager. Zelfs in het geval men geneest van deze ziekte, blijft de overleving nog steeds significant lager vergeleken met voor een leeftijd en geslacht gecorrigeerde overleving van een persoon in de algemene Nederlandse bevolking. Deze patiënten dienen dan ook nauwgezet vervolgd te worden.

Hoofdstuk 8 betreft een literatuurstudie naar het optimale tijdstip van chirurgie bij patiënten met infectieuze endocarditis. Hoewel er afgelopen decennia vele studies zijn gepubliceerd met betrekking tot de behandeling van patiënten met infectieuze endocarditis, blijft cardiochirurgie bij deze groep patiënten nog steeds gepaard gaan met een relatief hoge mortaliteit en dienen deze patiënten postoperatief zeer nauwlettend gecontroleerd te worden in verband met complicaties. Naarmate de tijd vordert wordt het steeds duidelijker welke subgroepen patiënten met infectieuze endocarditis in potentie het meest van chirurgische interventies profiteren, maar duidelijke indicaties voor chirurgie zijn er op dit moment niet mede gezien de persoonlijke voorkeuren van de afzonderlijke chirurgen, afzonderlijke cardiologen en institutionele richtlijnen. Op dit moment worden verschillende gerandomiseerde studies uitgevoerd welke meer duidelijkheid zullen verschaffen over de vraag welke patiënten met infectieuze endocarditis het meest van chirurgische interventies zullen profiteren.

Hoofdstuk 9 beschrijft de resultaten van een literatuurstudie en meta-analyse van observationele studies met betrekking tot de invloed van 'kunstklep-patiënt-mismatch' op de lange termijn overleving van patiënten die een aortaklepvervanging ondergaan. De resultaten van de deze studie tonen aan dat het bestaan van 'kunstklep-patiënt-mismatch' gepaard gaat met een verhoogde kans op algehele- en cardiale mortaliteit wanneer patiënten gedurende een lange tijd vervolgd worden, met name als het gaat om relatief jonge patiënten en patiënten die een mechanische kunstklep krijgen. Het fenomeen van 'kunstklep-patiënt-mismatch' dient dan ook meer aandacht te krijgen van de artsen om de overleving van de patiënten na een aortaklepvervanging verder te verbeteren.

Hoofdstuk 10 betreft de resultaten van een studie waarin de overleving van jongvolwassen patiënten die een Ross procedure hebben ondergaan vergeleken is met de overleving van patiënten die een mechanische aortaklep vervanging hebben ondergaan waarbij men streefde naar een optimale antistollingstherapie. De resultaten van deze studie tonen aan dat Ross procedure geen overlevingsvoordeel biedt wanneer er

gekeken wordt naar vergelijkbare patiënten die een mechanische aortaklepvervanging hebben ondergaan met een optimale antistollingsbehandeling. De overleving van deze beide groepen jongvolwassen patiënten is vergelijkbaar met een voor leeftijd en geslacht gecorrigeerde overleving van de algemene bevolking.

Hoofdstuk 11 beschrijft de lange termijn overleving van patiënten die een operatie hebben ondergaan in verband met infectieuze endocarditis. Patiënten met infectieuze endocarditis die een klepoperatie ondergaan lopen een aanzienlijk sterfterisico tijdens de direct postoperatieve periode. Patiënten die het eerste jaar overleven hebben echter dezelfde overlevingskansen als gezonde mensen.

Hoofdstuk 12 beschrijft de resultaten van gebicuspidaliseerde kleppen welke geïmplanteerd zijn op de pulmonaalklep positie. Deze studie toont aan dat deze in grootte gereduceerde donorkleppen een goed alternatief kunnen zijn bij patiënten jonger dan 1 jaar indien er een tekort is aan donorkleppen met een kleine diameter.

Hoofdstuk 13 betreft de lange termijn resultaten van de pulmonalis autograft operatie. Hoewel de overleving van de patiënten uitstekend is (90% na 18 jaar), is de levensduur van de kleppen beperkt en dient de helft van deze kleppen opnieuw vervangen te worden voor het eind van de tweede decade na de operatie. Deze resultaten benadrukken het belang van het feit dat deze patiënten nauwgezet gecontroleerd dienen te worden, voornamelijk in de tweede decade na de initiële operatie en met name bij patiënten die geopereerd zijn in verband met aortaklep insufficiëntie.

Hoofdstuk 14 beschrijft de invloed van zwangerschap op de duurzaamheid van donorhartkleppen. De resultaten van deze studie tonen aan dat zwangerschap geen negatieve invloed heeft op de duurzaamheid van donorkleppen. Donorkleppen kunnen dan ook als een goed alternatief beschouwd worden bij vrouwelijke patiënten die een hartklepvervanging moeten ondergaan en voornemens zijn zwanger te worden na de operatie.

Hoofdstuk 15 rapporteert de ervaringen van de cardiochirurgen in Melbourne met de Ross procedure bij patiënten die geopereerd zijn in verband met voornamelijk aorta stenose en waarbij een speciale techniek (inclusion cylinder method) is gebruikt voor het implanteren van de pulmonalis autograft. De resultaten van deze studie tonen aan dat deze techniek gepaard gaat met uitstekende uitkomsten waarbij de vrijheid van reoperatie 99% was na 15 jaar. Deze techniek dient dan ook sterk in overweging genomen te worden bij patiënten jonger dan 65 jaar met weinig co-morbiditeit die zich met voornamelijk aorta stenose presenteren.

Hoofdstuk 16 beschrijft de functie van de pulmonalis allograft in Ross patiënten door gebruik te maken van geavanceerde statistische methoden. De analyses van de echocardiografische data van deze allografts tonen aan dat deze kleppen een uitstekende duurzaamheid hebben. Klinisch revelante allograft insufficiëntie komt zelden voor bij volwassen patiënten die een Ross procedure hebben ondergaan. Klinisch relevante stenose van de allograft wordt voornamelijk in de eerste twee postoperatieve jaren gezien en treedt alleen bij een zeer klein aantal patiënten op.

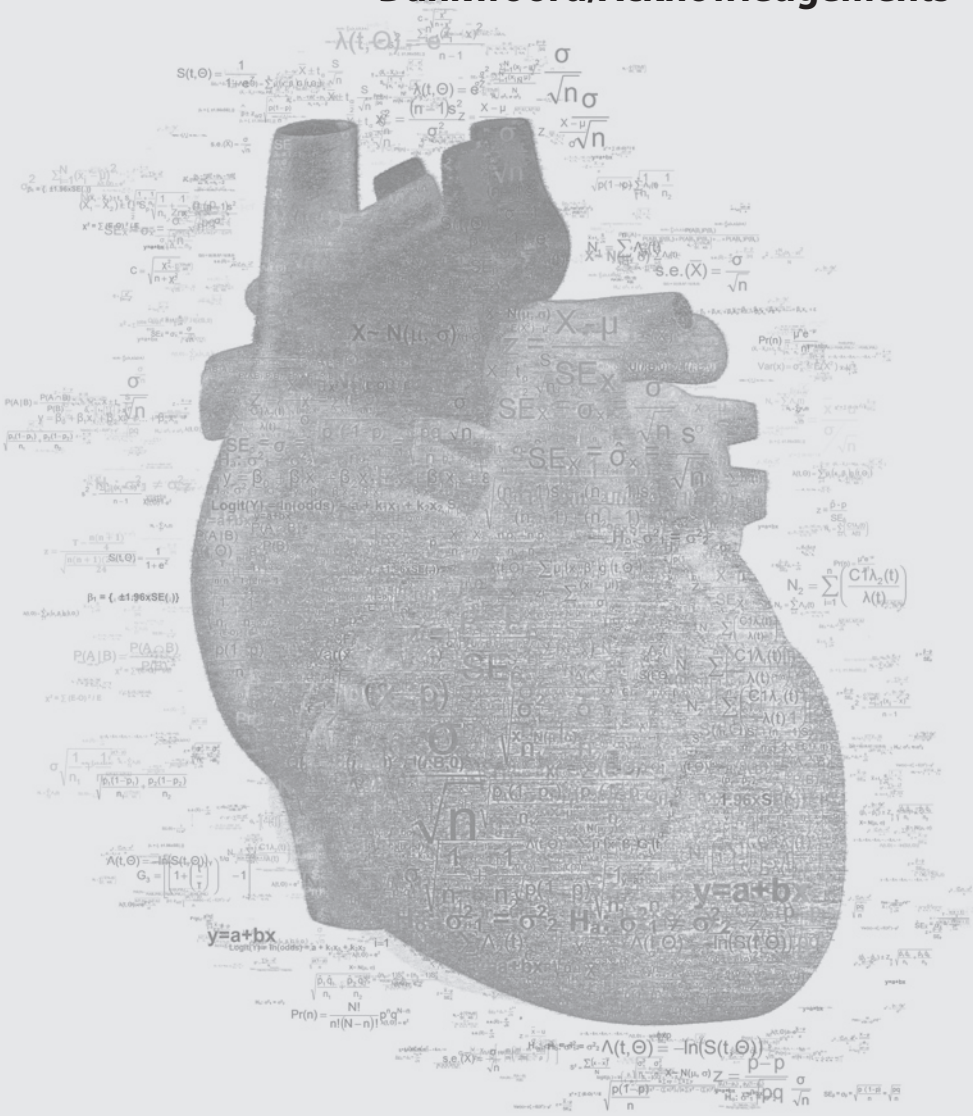
Hoofdstuk 17 beschrijft de functie van de allografts in de loop van de tijd na de operatie bij patiënten die een pulmonaalklepvervanging hebben ondergaan. Hoewel het analyseren van de echocardiografische data aantoont dat de duurzaamheid van deze donorkleppen acceptabel is, wordt een progressieve toename van klepinsufficiëntie en klepstenose gezien in de tweede decade na de initiële operatie. Deze toename van klepinsufficiëntie en klepstenose wordt vaker gezien wanneer de donorklep geïmplanteerd is in de extra-anatomische positie.

Hoofdstuk 18 beschrijft de echocardiografische functie van de allografts na een aortaklep- of aortawortelvervanging waarbij innovatieve statistische methodes worden geïllustreerd die gebruikt kunnen worden voor het bepalen van klepfunctie in de loop van de tijd na een hartklepvervanging. Zowel insufficiëntie als stenose van de allografts wordt na een aortaklep- of aortawortelvervanging steeds vaker gezien naarmate de tijd vordert. Het gebruik van innovatieve statistische methodes, zoals longitudinale methodes, kan zeer behulpzaam zijn bij het bepalen van de klepfunctie in de loop van de tijd na een hartklepoperatie.

Hoofdstuk 19 is een brief aan de editor waarin het belang van het betrekken van patiënten bij het vaststellen van beleid benadrukt wordt. Hoewel een aantal artsen de benadering van gezamenlijke besluitvorming hebben geaccepteerd, zijn er ook relatief veel artsen die patiënten niet op deze manier benaderen en betrekken bij het vaststellen van het beleid rondom medische behandelingen. Binnen de klinische praktijk dienen de artsen vaker te streven naar een gezamenlijke besluitvorming waarbij de patiënten niet alleen geïnformeerd dienen te worden over de beschikbaar alternatieven, maar waarbij er ook rekening gehouden wordt met het kennisniveau van de patiënten zodat ze in staat gesteld worden om adequaat mee te discussiëren over de keuze van behandeling.

Hoofdstuk 20 bevat de algemene discussie, worden de bevindingen die zijn beschreven in dit proefschrift bediscussieerd en worden de onderzoeksvragen die geformuleerd zijn in hoofdstuk 1 beantwoord.

Dankwoord/Acknowledgements



Graag besluit ik mijn proefschrift met het bedanken van iedereen zonder wiens hulp, steun en bijdrage dit proefschrift niet tot stand was gekomen. Een aantal van hen wil ik hier in het bijzonder noemen.

Allereerst mijn promotor prof.dr. Ad Bogers. Beste professor Bogers, op het moment dat ik me als tweedejaars geneeskunde student bij u meldde met de vraag of ik wellicht kon helpen bij een onderzoeksproject had ik nooit durven dromen dat u vervolgens zoveel kansen en mogelijkheden voor mij zou creëren. Ik ben u veel dank verschuldigd, niet alleen voor het feit dat u voor mij werkelijk altijd de ideale omstandigheden creëerde om het maximale uit mijn promotietijd te halen, maar ook omdat u mij de kans gaf om gedurende mijn promotieonderzoek ook mijn rechtenopleiding te voltooien. Ik heb ontzettend veel respect voor hoe u in staat bent om onderzoek te combineren met klinische werkzaamheden. Iedere keer weer stond ik versteld van de snelheid en deskundigheid waarmee u de manuscripten becommentarieerde. Het was en is een groot voorrecht om van u te mogen leren en door u begeleid te worden.

Mijn promotor prof.dr. Takkenberg. Beste Hanneke, ontzettend veel dank voor je geweldige begeleiding. Je bent altijd enthousiast, stimulerend en inspirerend. Je hebt ontzettend veel kansen voor me gecreëerd en dankzij jou heb ik het maximale uit mijn promotietijd kunnen halen. Iedere keer als ik ergens op vast liep hoefde ik alleen maar even jouw kamer binnen te lopen en te vragen hoe jij erover dacht, en het probleem was meteen opgelost. Het is echt uitzonderlijk hoe goed jij je onderzoekers kan begeleiden. Met jouw geweldige contactuele eigenschappen heb je een enorm internationaal netwerk opgebouwd waarvan je ook mij hebt laten profiteren. Heel veel dank hiervoor. Ik vind het een eer om bij je te promoveren.

Dear dr Blackstone, thank you so much for giving me the opportunity to spend one year as a research fellow at your department. During our first meeting you immediately made me feel welcome and I will never forget our weekly meetings. It was such an honor for me to learn so much from you and I am deeply honored that you will be a member of my PhD committee.

Jeevanantham Rajeswaran. Dear Rajes, I cannot thank you enough for your supervision and indispensable guidance. Arezo and I were very fortunate to get to know Melissa, you and the kids. Thank you for all you have taught me. I will be looking forward to any next opportunity to work with you again.

De leden van de kleine commissie, prof.dr. Klautz, prof.dr. Roos-Hesselink en prof.dr. Steyerberg, dank voor uw bereidheid om dit proefschrift op zijn wetenschappelijke

waarde te beoordelen en voor uw deelname in de kleine commissie. Prof.dr. Helbing, dank voor uw bereidheid om als opponent deel te nemen in de grote commissie.

I would like to take this opportunity to also thank prof. Sievers, prof. Stierle, dr Skillington and Efstratios Charitos for their indispensable contribution to different manuscripts in this thesis.

Graag wil ik hierbij ook alle auteurs bedanken voor hun onmisbare bijdrage aan verschillende manuscripten. In het bijzonder Jos Bekkers, Peter de Jong, prof. Roos-Hesselink, Maarten Witsenburg en Pieter van de Woestijne.

Collega promovendi Stuart Head, Nelleke Korteland, Aart Mookhoek en Ruben Osnabrugge, dank voor de gezelligheid en vele leerzame discussies. Ik wens jullie heel veel succes met jullie onderzoeken en verdere carrière!

Heel veel dank aan alle thoraxchirurgen, (oud) arts-assistenten, datamanagers, onderzoekscoördinatoren en de medewerkers van het secretariaat van de afdeling Thoraxchirurgie. In het bijzonder Annet Damhuis bij wie ik altijd met allerlei soorten vragen terecht kon.

Mijn familie en vrienden ben ik erg dankbaar voor hun steun en begrip.

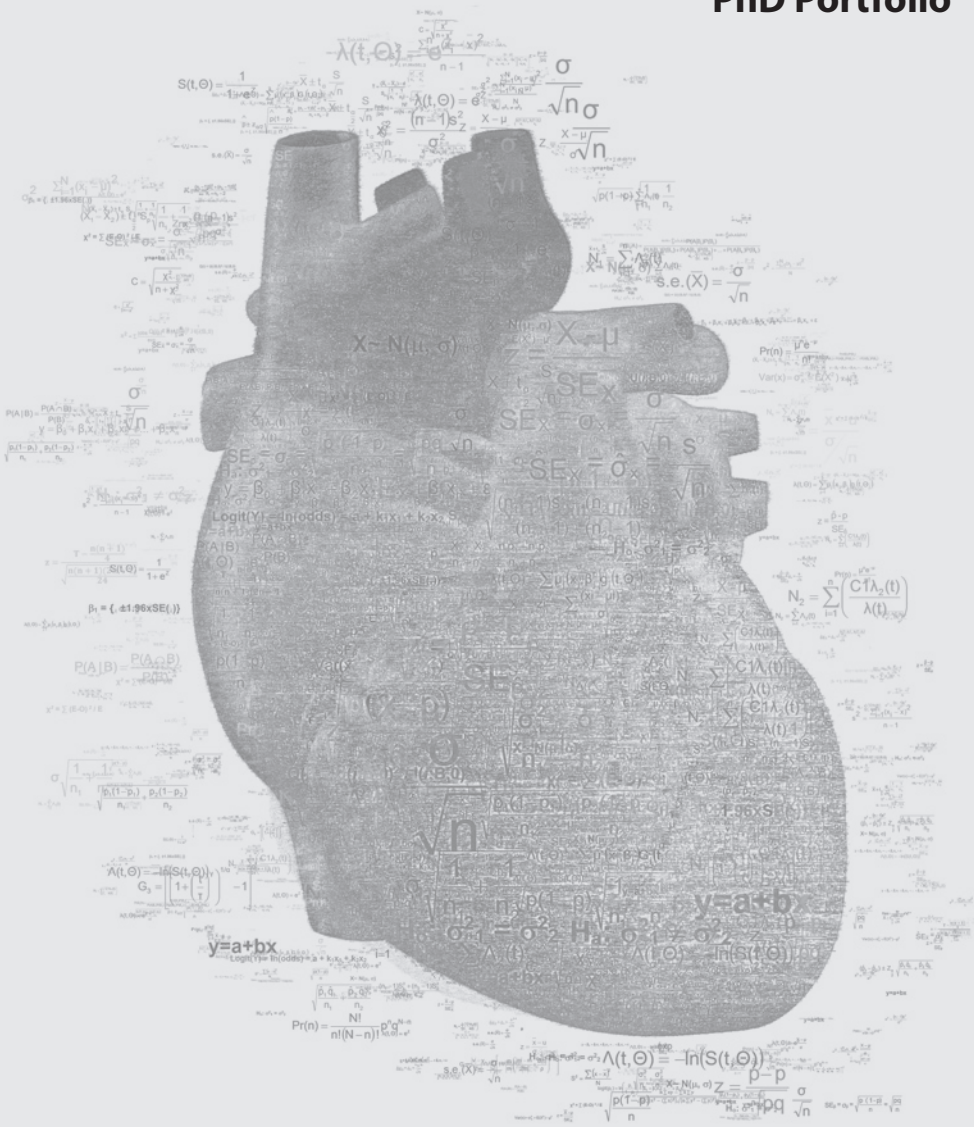
Abdel, Alijan, Burcu, David en Willem. Dank voor jullie belangstelling, support, bemoediging, en bovenal geweldige vriendschap. Ik kan me geen betere vrienden wensen. David, ik vind het geweldig dat je hebt kunnen regelen dat je bij de verdediging van mijn proefschrift aanwezig kunt zijn! Mijn paranimfen Abdel en Alijan, ik ben er trots op dat jullie mijn paranimfen zijn en naast me willen staan op de 18de!

Lieve mama en papa, alles wat jullie hadden opgebouwd hebben jullie achtergelaten om jullie kinderen een betere toekomst te geven. Dat motiveert mij enorm om altijd mijn best te blijven doen. Ik heb alles wat ik heb bereikt en zal bereiken aan jullie te danken. Jullie onvoorwaardelijke steun en liefde is overweldigend. Dank voor alles!

Mijn lieve zusjes Palwasha en Sahar. Het is niet in woorden uit te drukken hoe trots ik op jullie ben, trots op hoe jullie als persoon zijn, maar ook op wat jullie hebben bereikt en zullen bereiken. Ook dank voor het feit dat jullie altijd voor me klaar staan en me overal bij willen helpen.

Lieve Arezo, mijn allergrootste schat. Mijn laatste woorden zijn uiteraard voor jou. Heel veel dank voor je liefde, vertrouwen, geduld en de steun.

PhD Portfolio



Name PhD student:	M.M. Mokhles
Erasmus MC department:	Cardiothoracic Surgery
Research school:	Cardiovascular Research School (COEUR)
PhD period:	September 2009 - October 2012
Title thesis:	Innovative modeling of outcome in cardiac surgery
Promotors:	Prof.dr. A.J.J.C. Bogers
	Prof.dr. J.J.M. Takkenberg
Date defense thesis:	December 18, 2013

ACADEMIC EDUCATION

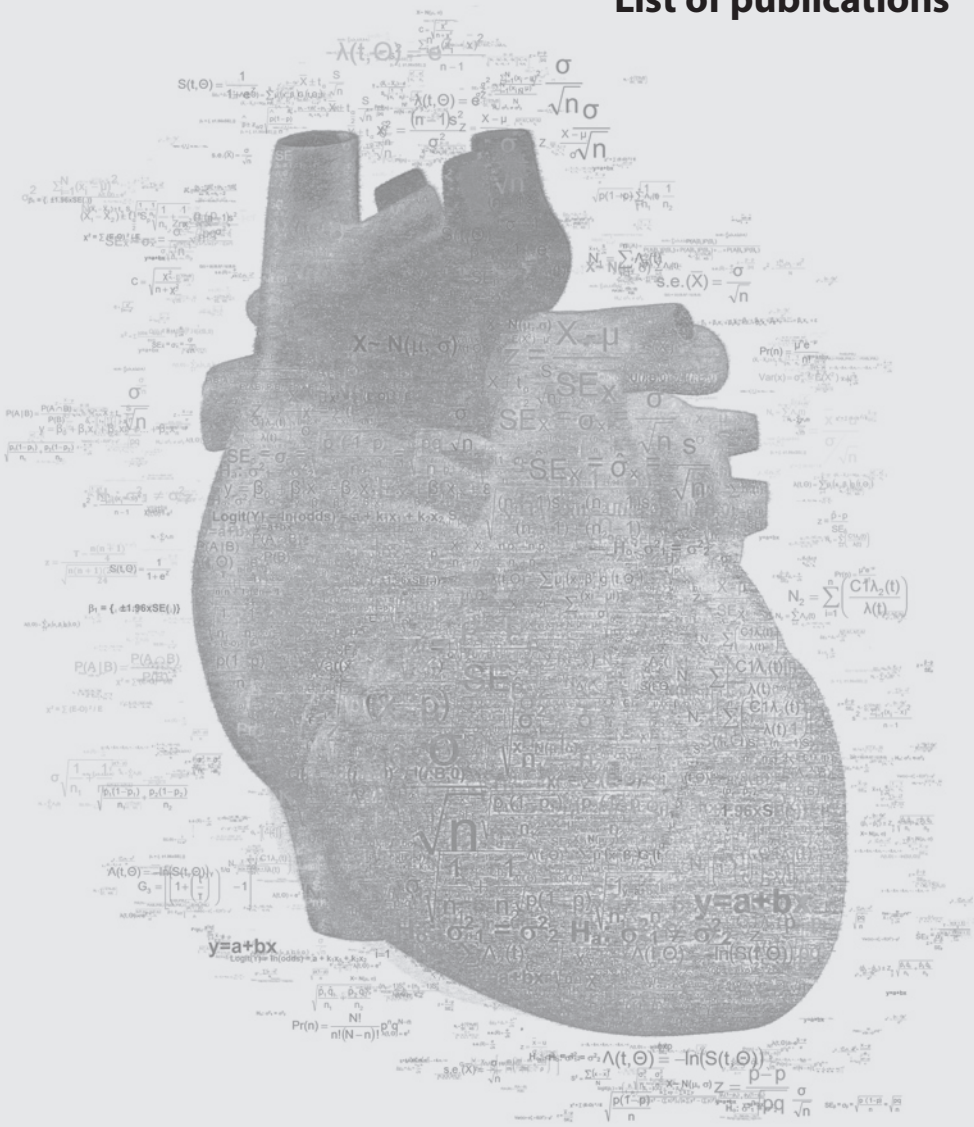
2010-2010	Master of Laws (LLM), EUR, Rotterdam, The Netherlands
2010	Bachelor of Laws (LLB), Utrecht University, Utrecht, The Netherlands
2007-2010	MSc in Clinical Research, NIHES, Rotterdam, The Netherlands
2007	Erasmus Honours Program, EUR, Rotterdam, The Netherlands
2005-2009	Doctorate in Medicine, Erasmus MC, Rotterdam, The Netherlands

PhD Training	Year	Workload
Oral presentations		
· Does the Ross procedure carry a survival advantage over mechanical aortic valve replacement in young adult patients? (SHVD, New-York)	2010	0.6
· Survival comparison between the Ross procedure and mechanical valve replacement in young adult patients (NVT, Utrecht)	2010	0.6
· Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit (EACTS, Geneva)	2011	0.6
· Patient outcome and autograft durability in the second postoperative decade after the Ross procedure: Insights from the Rotterdam prospective cohort study (WCC, Dubai)	2012	0.6
· Longitudinal Data Analysis of Echocardiographic Allograft Valve Function (AHA, Los Angeles)	2012	0.6
· Pulmonary conduit function after the Ross Operation: Longitudinal analysis of the German-Dutch Ross Registry (WCPCCS, Cape Town)	2013	0.6
· Allograft Conduit Function over Time after Right Ventricular Outflow Tract Reconstruction (SHVD, Venice)	2013	0.6
Poster presentations		
· Risk of heart failure with dopamine agonist use in Parkinson's disease (ESC, Stockholm)	2010	0.6
· Gender Differences and Early Outcome aftee Coronary Artery Bypass Graft Surgery (ESC, Paris)	2011	0.6

In-depth courses		
· Introduction to Management of Health Care Organizations, Harvard School of Public Health, Boston, USA	2009	2.0
· Measuring and Analyzing the Outcomes of Health Care, Harvard School of Public Health, Boston, USA	2009	2.0
· Peripheral and Intracranial Obstructive Vascular Disease COEUR, Rotterdam, The Netherlands	2009	1.5
· Congenital Heart Disease, COEUR, Rotterdam, The Netherlands	2009	1.5
· COEUR research seminar and lectures	2009-2012	3.0
· Repeated Measurements in Clinical Studies NIHES, Rotterdam, The Netherlands	2010	1.9
Teaching		
· Supervising 2nd year medical students in writing a systematic review, Erasmus MC, Rotterdam, The Netherlands	2010	0.6
· Supervising 3rd year medical students in writing a systematic review, Erasmus MC, Rotterdam, The Netherlands	2011	0.6
· Lectures minor congenital heart disease	2012	0.6
International conferences		
· Ross Summit (Atlanta, USA)	2009	0.9
· Annual joint scientific meeting of het Heart Valve Society of America and the Society of Heart Valve Disease (New York, USA)	2010	1.5
· European Society of Cardiology Congress (Stockholm, Sweden)	2010	1.5
· European Association of Cardio Thoracic Surgery Annual Meeting (Geneva, Switzerland)	2011	1.5
· European Society of Cardiology Congress (Paris, France)	2011	1.5
· EACTS & AEPC Course: "Right Ventricle Outflow Tract Management" from Neonates to Adults: An Interdisciplinary View (Mallorca, Spain)	2011	1.2
· World Congress of Cardiology (Dubai, UAE)	2012	1.5
· Research Day Cleveland Clinic (Cleveland, USA)	2012	0.3
· American Heart Association Scientific Sessions (Los Angeles, USA)	2012	1.5
· World Congress Paediatric Cardiology & Cardiac Surgery (Cape Town, South Africa)	2013	1.5
· Annual joint scientific meeting of het Heart Valve Society of America and the Society of Heart Valve Disease (Venice, Italy)	2013	1.5
· European Association of Cardio Thoracic Surgery Annual Meeting (Vienna, Austria)	2013	1.5
Meetings		
· Scientific Advisory Board meeting of the dopamine agonist study (Naples, Italy)	2009	1.0
· Meetings of the Dutch Association for Thoracic Surgery	2009-2011	2.0
· Scientific meetings department of Cardiothoracic Surgery Erasmus MC, Rotterdam, The Netherlands	2009-2013	4.0
· Scientific meetings department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Ohio, USA	2011-2012	2.0

Peer Reviewer International Scientific Journals		
· The Annals of Thoracic Surgery	2010-…	2.0
· The Journal of Heart Valve Disease	2010-…	0.5
· European Journal of Cardiothoracic Surgery	2010-…	0.5
· The Archives of Internal Medicine	2011-…	0.5
· Clinical Infectious Disease	2011-…	0.5
· The Journal of Cardiovascular Surgery	2011-…	0.5
Total Workload (ECTS)		**48.5**

List of publications



1. **Mokhles MM**, Körtke H, Stierle U, Wagner O, Charitos EI, Bogers AJ, Gummert J, Sievers HH, Takkenberg JJ. Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. Circulation. 2011 Jan 4;123(1):31-8.

2. **Mokhles MM**, Ciampichetti I, Head SJ, Takkenberg JJ, Bogers AJ. Survival of surgically treated infective endocarditis: a comparison with the general Dutch population. Ann Thorac Surg. 2011 May;91(5):1407-12.

3. **Mokhles MM**, van den Bogaerdt AJ, Takkenberg JJ, Bogers AJ. Right ventricular outflow tract reconstruction: the impact of allograft characteristics. Ann Thorac Surg. 2011 Jun;91(6):2025.

4. van de Woestijne PC, **Mokhles MM**, de Jong PL, Witsenburg M, Takkenberg JJ, Bogers AJ. Right ventricular outflow tract reconstruction with an allograft conduit in patients after tetralogy of Fallot correction: long-term follow-up. Ann Thorac Surg. 2011 Jul;92(1):161-6.

5. **Mokhles MM**, van de Woestijne PC, de Jong PL, Witsenburg M, Roos-Hesselink JW, Takkenberg JJ, Bogers AJ. Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. Eur J Cardiothorac Surg. 2011 Sep;40(3):571-8.

6. **Mokhles MM**, Bogers AJ, Takkenberg JJ. No Ross operation for patients with aortic regurgitation? Ann Thorac Surg. 2011 Sep;92(3):1156-7; author reply 1157.

7. Bramer S, **Mokhles MM**, Takkenberg JJ, Bogers AJ. Long-term outcome of right ventricular outflow tract reconstruction with bicuspidalized homografts. Eur J Cardiothorac Surg. 2011 Dec;40(6):1392-5.

8. Head SJ, **Mokhles MM**, Osnabrugge RL, Bogers AJ, Kappetein AP. Surgery in current therapy for infective endocarditis. Vasc Health Risk Manag. 2011;7:255-63.

9. **Mokhles MM**, Bogers AJ, Takkenberg JJ. Letter by Mokhles et al regarding article, "Prosthetic heart valve". Circulation. 2011 Dec 13;124(24):e897; author reply e898.

10. **Mokhles MM**, Ciampichetti I, van Domburg R, Cheng JM, Bogers AJ, Witsenburg M. Infective endocarditis in a tertiary referral hospital: long-term follow up. J Heart Valve Dis. 2012 Jan;21(1):118-24.

11. **Mokhles MM**, Takkenberg JJ. Invited commentary. Ann Thorac Surg. 2012 Jan;93(1):57-8.

12. Trifirò G, **Mokhles MM**, Dieleman JP, van Soest EM, Verhamme K, Mazzaglia G, Herings R, de Luise C, Ross D, Brusselle G, Colao A, Haverkamp W, Schade R, van Camp G, Zanettini R, Sturkenboom MC. Risk of cardiac valve regurgitation with dopamine agonist use in Parkinson's disease and hyperprolactinaemia: a multi-country, nested case-control study. Drug Saf. 2012 Feb 1;35(2):159-71.

13. Head SJ, **Mokhles MM**, Kappetein AP. Invited commentary. Ann Thorac Surg. 2012 Feb;93(2):530.

14. **Mokhles MM**, Trifirò G, Dieleman JP, Haag MD, van Soest EM, Verhamme KM, Mazzaglia G, Herings R, Luise Cd, Ross D, Brusselle G, Colao A, Haverkamp W, Schade R, Camp Gv, Zanettini R, Sturkenboom MC. The risk of new onset heart failure associated with dopamine agonist use in Parkinson's disease. Pharmacol Res. 2012 Mar;65(3):358-64.

15. Head SJ, **Mokhles MM**, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, Bogers AJ, Kappetein AP. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. Eur Heart J. 2012 Jun;33(12):1518-29.

16. Verberkmoes NJ, **Mokhles MM**, Bramer S, van Straten AH, Ter Woorst JF, Maessen JG, Berreklouw E. Long-Term Clinical Outcome of the Symmetry Aortic Connector System in Off-Pump Coronary Artery Bypass Grafting. Thorac Cardiovasc Surg. 2012 Jun 8.

17. **Mokhles MM**. Invited commentary. Ann Thorac Surg. 2012 Sep;94(3):725.

18. **Mokhles MM**, Rizopoulos D, Andrinopoulou ER, Bekkers JA, Roos-Hesselink JW, Lesaffre E, Bogers AJ, Takkenberg JJ. Autograft and pulmonary allograft performance in the second post-operative decade after the Ross procedure: insights from the Rotterdam Prospective Cohort Study. Eur Heart J. 2012 Sep;33(17):2213-24.

19. Arabkhani B, Heuvelman HJ, Bogers AJ, **Mokhles MM**, Roos-Hesselink JW, Takkenberg JJ. Does pregnancy influence the durability of human aortic valve substitutes? J Am Coll Cardiol. 2012 Nov 6;60(19):1991-2.

20. Verberkmoes NJ, **Mokhles MM**, Bramer S, Van Straten AH, Ter Woorst JF, Maessen JG, Berreklouw E. Clinical outcome of the PAS-Port® proximal anastomosis system in off-pump coronary artery bypass grafting in 201 patients. J Cardiovasc Surg (Torino). 2012 Nov 9.

21. Skillington PD, **Mokhles MM**, Takkenberg JJM, O'Keefe M, Grigg L, Wilson W, Larobina M, Tatoulis J. Twenty-Year Analysis of Autologous Support of the Pulmonary Autograft in the Ross Procedure (Accepted for publication in Annals of Thoracic Surgery).

22. **Mokhles MM**, Rajeswaran J, Bekkers JA, Borsboom GJJM, Roos-Hesselink JW, Steyerberg EW, Bogers AJJC, Takkenberg JJM, Blackstone EH. Capturing Echocardiographic Allograft Valve Function over Time after Allograft Aortic Valve or Root Replacement (submitted).

23. **Mokhles MM**, Charitos EI, Stierle U, Rajeswaran J, Blackstone EH, Bogers AJJC, Takkenberg JJM, Sievers HH. Pulmonary Conduit Function after the Ross Operation: Longitudinal analysis of the German-Dutch Ross Registry Experience (Heart, in press).

24. Skillington PD, **Mokhles MM**, Takkenberg JJM, Wilson W, Grigg L, Larobina M, O'Keefe M. Inclusion Cylinder Method for Aortic Valve Replacement Utilising the Ross Operation in Adults with Predominant Aortic Stenosis – 99% Freedom from Re-operation on the Aortic Valve at 15 Years (submitted).

25. Henrichs J, **Mokhles MM**, Utens EM, Ciampichetti J, Bogers AJ, Cheng JM, van Domburg R, Witsenburg M. Health-Related Quality of Life in Long-term Survivors of Infective Endocarditis: Associations with Comorbid Conditions and Complications (submitted).

26. **Mokhles MM**, Onsesveren I, de Jong PL, Witsenburg M, Takkenberg JJM, Bogers AJJC. Allograft Conduit Function over Time after Right Ventricular Outflow Tract Reconstruction (submitted).

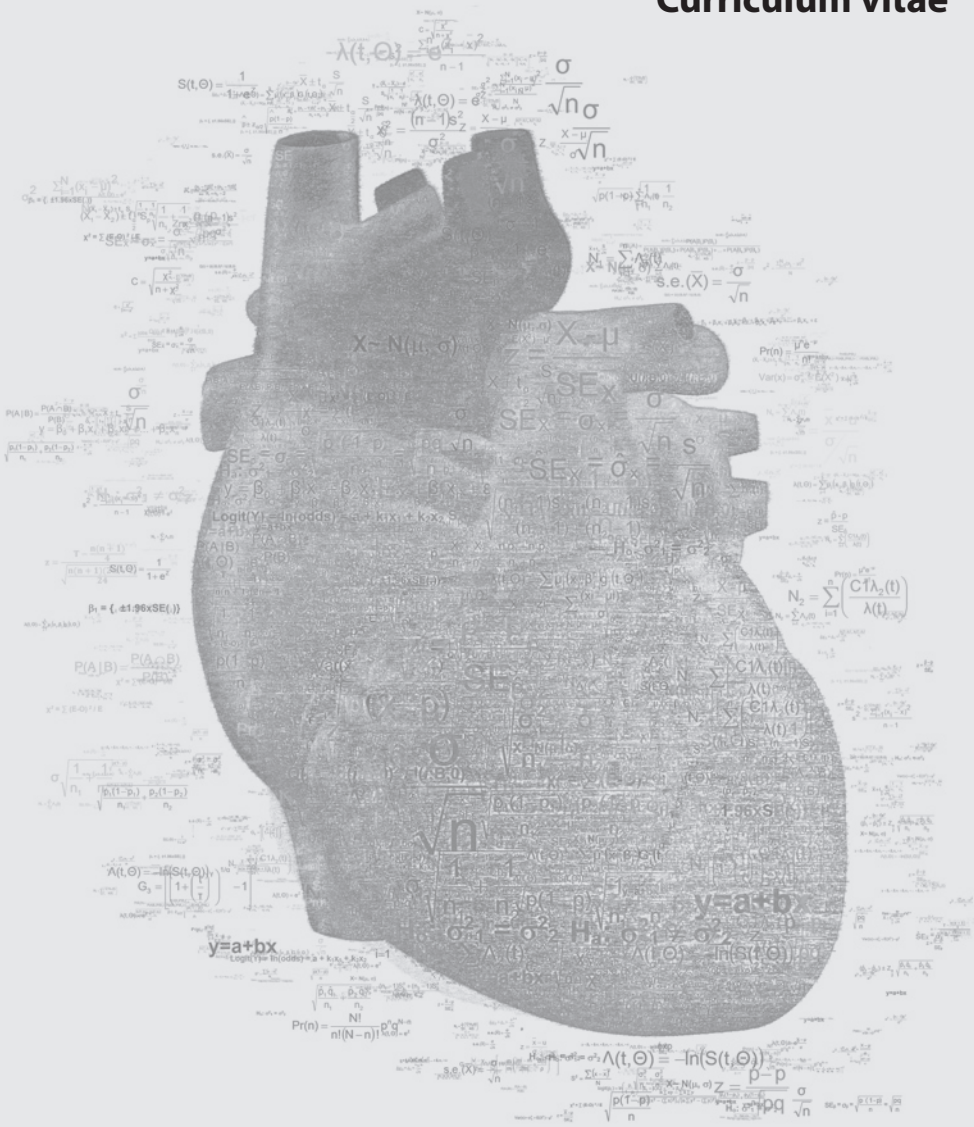
27. da Costa FDA, Takkenberg JJM, Fornazari D, Filho EMB, Colatusso C, **Mokhles MM**, da Costa ABBA, Sagrado AG, de Aragon Ferreira AD, Fernandes T, Lopes SV. Long-term results (18 years) of the Ross Operation - a single institutional experience (submitted).

28. De Jonge M, Van Boxtel A, Van Straten AHM, **Mokhles MM**, Bramer S, Berreklouw E. Myocardial damage in coronary artery bypass surgery: a propensity score matched comparison between blood and crystalloid cardioplegia (submitted).

Book chapter

MM Mokhles, JJM Takkenberg. "Current treatment of aortic regurgitation". Chapter 12: Long-term results of aortic valve surgery (p. 114-125). Editor: Schäfers, Hans-Joachim. 1st edition - Bremen: UNI-MED Verlag AG, 2013. ISBN 978-3-8374-1406-6. ISBN 978-1-84815-196-3.

Curriculum vitae



Mostafa Mokhles was born on May 15th, 1985 in Kabul, Afghanistan. At the age of 13 he moved together with his parents and 2 sisters to The Netherlands as political refugees. After graduating from secondary school (Gymnasium, Nature & Health, Openbaar Zeister Lyceum, Zeist), he started Medical school in 2005 at the Erasmus University Rotterdam. During the second year, he started doing research at the department of Cardiothoracic Surgery (supervisors: prof. dr A.J.J.C. Bogers and prof. dr J.J.M. Takkenberg). In 2007, Mostafa was among the top 10% of medical students and was selected to participate in a special program for medical students organized by the Netherlands' Institute of Health Sciences (NIHES). This program enabled him to combine Medical school with the Master of Science in Clinical Research program. During this program he received his initial training in epidemiology, part of which was spent at the Harvard School of Public Health in Boston, Massachusetts, USA during the Sixteenth Annual Summer Session. In 2007 he successfully participated in the Erasmus University Honours Program, an interdisciplinary academic training program to explore the boundaries of science together with students from other disciplines. Furthermore, he was one of the founding editors of the Erasmus Journal of Medicine (EJM), a journal that aims to stimulate scientific development of medical students.

After obtaining his MSc degree in Medicine in 2009, he was awarded with the prestigious Mosaic grant from the Netherlands Organization for Scientific Research for four year doctoral research. With this grant he started his PhD research in September 2009 at the department of Cardiothoracic Surgery, Erasmus University Medical Center, under supervision of prof. dr A.J.J.C. Bogers and prof. dr J.J.M. Takkenberg, which resulted in this thesis.

In 2010 he graduated cum laude from the MSc in Clinical Research at the Netherlands Institute of Health Sciences. Parallel to Medical school and his PhD research, Mostafa also attended the Law school. In 2010 he obtained his Bachelor of Laws degree at the University of Utrecht and in 2011 his Master of Laws degree in Health Law at the Erasmus University Rotterdam.

During the opening of the academic year of the Erasmus University Rotterdam in 2011, he was awarded with the prestigious Professor Lambers Prize, which is each year presented to one excellent student who has at least two master's degrees obtained at different faculties.

Between September 2011 and October 2012, he worked as a research fellow at the departments of Quantitative Health Sciences and Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio, USA, where he acquired knowledge about the application of several novel statistical methods under the supervision of dr Eugene Blackstone.

In November 2012 he started with his medical internships, which he expects to complete in September 2014.

Financial support for the publication of this thesis was generously provided by
Abn Amro, AtriCure, Cardialysis, Chipsoft BV, Edwards Lifesciences, Erasmus Universiteit, JenaValve, Johnson&Johnson Medical, Krijnen Medical Innovations, Maquet Netherlands, Pfizer, QP&S, Sorin Group Nederland, St Jude Medical Netherlands, Stichting Hartekind, Takeda, Thoraxcentrum Research BV and Vascutec Nederland