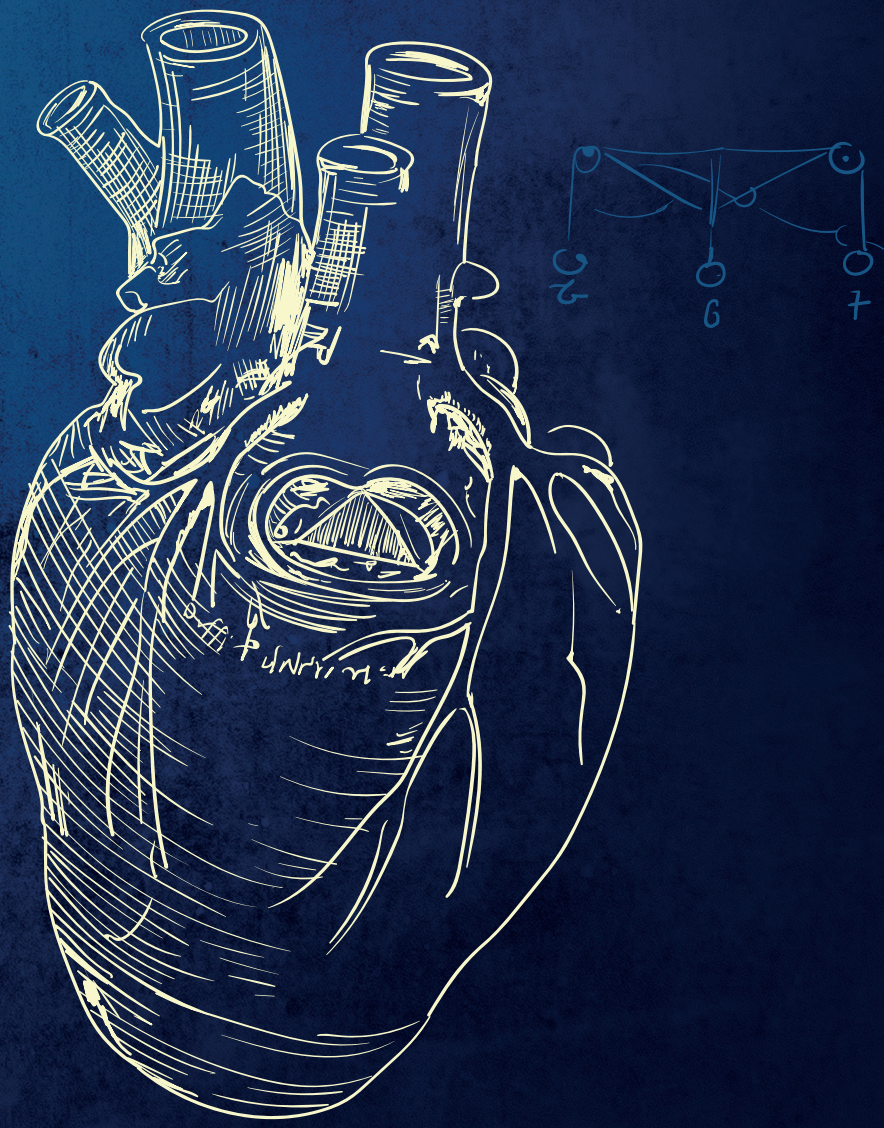
SURGICAL STRATEGY AND CLINICAL OUTCOME

in patients with Aortic Root Disease



BARDYA ARABKHANI

SURGICAL STRATEGY AND CLINICAL OUTCOME

in patients with Aortic Root Disease

BARDYA ARABKHANI

COLOFON

Cover & layout design:	Design Your Thesis, www.designyourthesis.com
Printing:	Ridderprint, www.ridderprint.nl
ISBN:	978-94-6299-617-5

SURGICAL STRATEGY AND CLINICAL OUTCOME IN PATIENTS WITH AORTIC ROOT DISEASE

CHIRURGISCHE STRATEGIE EN KLINISCHE UITKOMST IN PATIËNTEN MET AORTAWORTEL PATHOLOGIE

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr. H.A.P. Pols
en volgens besluit van het college voor Promoties
De openbare verdediging zal plaatsvinden op
28 juni 2017 om 15:30

door

Bardya Arabkhani
Geboren te Teheran, Iran

Erasmus University Rotterdam

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

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

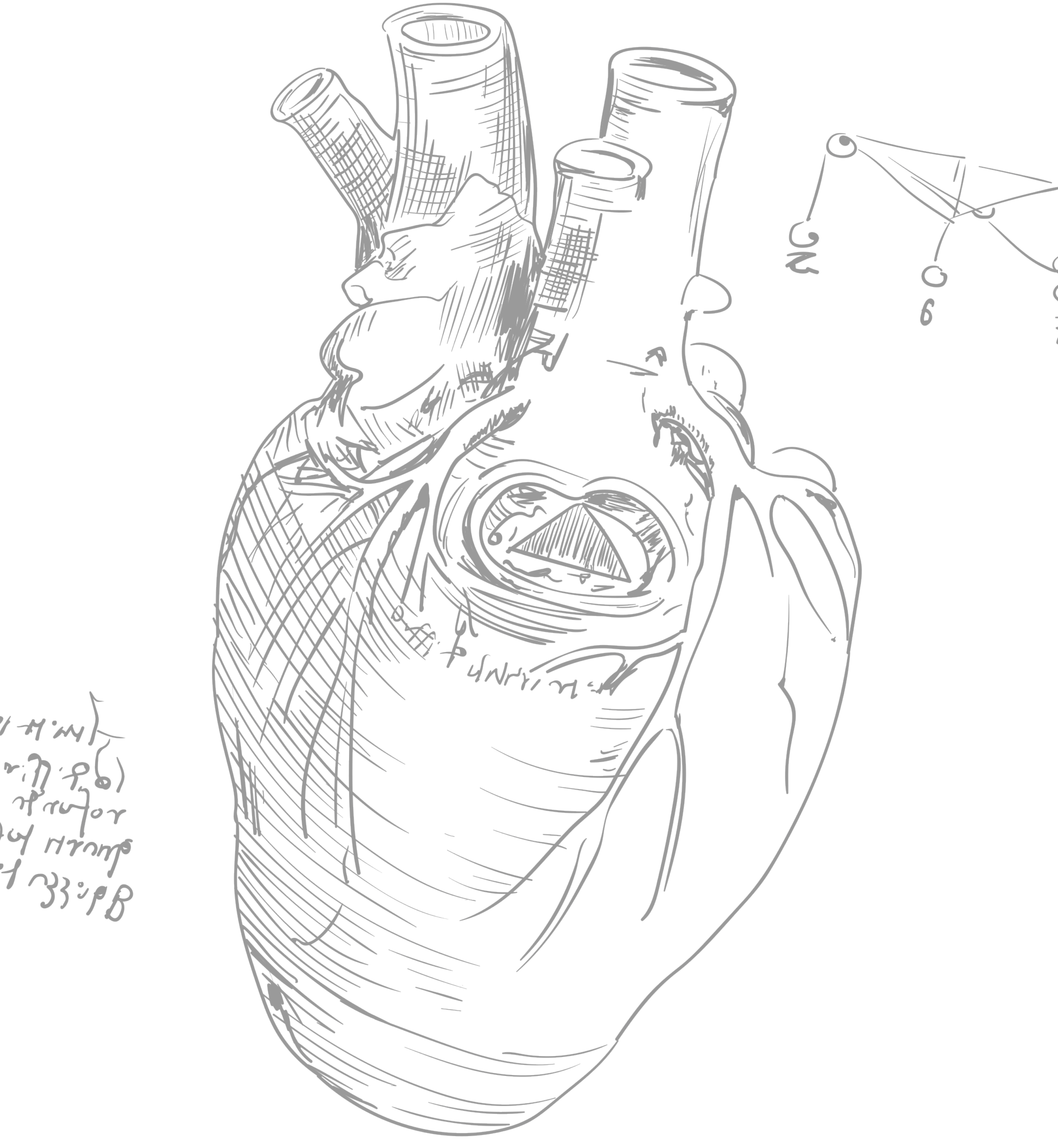
Voor mijn ouders

Yek chand be koodaki be ostaad shodim
Yek chand be ostadi khod shaad shodim
Payan sokhan sheno ke ma ra che rasid
Az khaak bar-amadim o bar baad shodim

With them the Seed of Wisdom did I sow,
And with my own hand labour'd it to grow:
And this was all the Harvest that I reap'd —
From the Water I came, and like Wind I go

Omar Khayyam

TABLE OF CONTENTS



Chapter 1

Introduction

There are several surgical techniques and various valve prostheses available for the treatment of diseased aortic valve and root. The decision-making on the most suitable treatment strategy is a challenging and dynamic process. It depends not only on the technical complexity of the surgical treatment, but on specific characteristics and preferences of the individual patient as well. This thesis intends to evaluate these issues and addresses the surgical options currently available.

THE AORTIC ROOT

The aortic root consists of the three leaflets that form the aortic valve, sinuses of Valsalva. The line of closure of the valve is just below the free edge. At the center of the free edge a nodular thickening is present, called the nodule of Arantius. The root also includes the left and the right ostium from where the coronary arteries arise, as well the three commissures (i.e. areas where attachments of two adjacent cusps meet). The normal aortic valve contains three cusps and corresponding sinuses of Valsalva (the aortic sinuses). The aortic valve is in continuity with the anterior leaflet of the mitral valve and the membranous septum, where it is a fibrous layer. The junction where the aortic root continues into the tubular aorta is known as the sinotubular junction.

The aortic valve has a passive movement mechanism, unlike the atrioventricular valves. During closure this mechanism ideally prevents backflow of blood by aligning the cusps accurately, withstanding systemic blood pressures. The components of the aortic root provide the ability for the valve to close during the diastole and to open during the systole, thus taking part in the hemodynamic changes of the cardiac cycle.

Any change in the aortic root that may cause dysfunctional opening of the aortic valve (in case of aortic stenosis) and/or closure (in aortic regurgitation) may cause symptoms and may be associated with decreased survival, increased morbidity and decreased quality of life for the patients involved.

Aortic valve and root disease

Aortic valve dysfunction includes aortic stenosis and aortic regurgitation.

The etiology of aortic stenosis may be subdivided three categories:
1) congenital aortic disease, like bicuspid aortic valves, which is associated with a higher calcification rate [1], 2) degenerative (calcific) aortic valves, and 3) rheumatic valve disease, which is less frequent in the developed countries nowadays. The prevalence of aortic stenosis varies from 0.2 percent at 50 to 59 years, to 1.3 percent at 60 to 69, 3.9 percent at 70 to 79 years, and 9.8 percent at ages 80 to 89 years [2]. The progression of aortic stenosis is associated with symptoms of dyspnea on exertion or mostly with exercise intolerance, exertional dizziness and/or syncope, and exertional angina pectoris. Aortic valve stenosis is the most common heart valve disease with an increasing incidence with age, which has a great impact on our health and health care. Patients with symptomatic severe aortic stenosis who have not been treated surgically, or, in selected patients, percutaneously, have a poor prognosis, with reduced survival [3-5]. Thus, surgical treatment of aortic stenosis is recommended in patients with severe, symptomatic aortic stenosis, by European and U.S. guideline on valvular heart disease [6, 7]. Percutaneous treatment with valve implantation is rapidly developing [8].

Aortic regurgitation of the aortic valve is less common and may or may not be due to a dilated aortic root. Aortic regurgitation accounts for approximately 10% of aortic valve surgery and occurs typically at a younger age than aortic stenosis. The etiology of aortic regurgitation is more diverse : 1. congenital disease (bicuspid valves), 2. perforation due to (infective) endocarditis, 3. rheumatic disease, 4. root aneurysm (idiopathic or associated with connective tissue disease) with deformation of the symmetrical hanging points of the valve, and 5. (acute) dissection of the ascending aorta. While sudden aortic regurgitation is associated with acute ascending dissection and endocarditis of the aortic valve, the more common causes of isolated aortic regurgitation are congenital, bicuspid valves and aortic root aneurysm. Patients may not have any symptoms at the beginning of aortic regurgitation, but often progressively experience shortness of breath, dyspnea on exercise, chronic chest pain, and syncope. The natural history of aortic regurgitation depends predominantly on the severity of regurgitation [9]. After onset of symptoms in acute severe aortic regurgitation, first year survival is only about 10 to 30 percent [10], and could be higher in endocarditis and acute dissection patients. Therefore, guidelines on valvular heart disease recommend surgical treatment in case of severe, symptomatic aortic regurgitation, and in case of aortic root aneurysm with a root diameter above

55mm in most connective tissue disease and bicuspid aortic valves, or above 50mm with additional risk factors (e.g., family history of aortic dissection or aortic growth rate ≥0.5 cm per year). In addition, replacement of the ascending aorta of 45mm or greater is reasonable in asymptomatic patients with bicuspid aortic valve undergoing aortic valve surgery [11]. Additionally, patients with connective tissue disease (e.g. Marfan syndrome) with risk factors like; family history of aortic dissection and/or aortic size increase .2 mm/year, severe AR or mitral regurgitation, desire of pregnancy; have a lower threshold (≥45mm) in favor of operation [6, 7].

Treatment of aortic root disease

There are several surgical options to treat aortic valve or root aneurysm. Depending on the presence and extent of aortic root dilatation (like in connective tissue disease or in bicuspid aortic valves), the valve can be replaced with or without aortic root replacement. Valve replacement may be performed with either a mechanical or biological valve substitute. In case of aortic root replacement the "gold standard" has been composite valve replacement (the Bentall procedure; i.e. tube graft with mechanical valve prosthesis) [12]. Biological valve substitutes include stented and stentless bioprostheses, allografts (i.e. aortic root replacement by a human donor aortic root) [13], and the pulmonary autograft procedure (i.e. Ross procedure; replacement of the aortic root with patients' own pulmonary valve and implantation of a biological conduit in pulmonary position) [14]. In addition, in case of aortic regurgitation with or without root aneurysm, aortic valve repair or a valve sparing aortic root replacement is possible, where the patients native valve is preserved and a (partial) prosthetic tube graft replaces the aortic root [15, 16]. Young female patients with a child wish require special attention, since the type of therapy used in these patients is associated with both mother and fetal outcome [17], as the physiological adaptations to pregnancy influence the cardiac function and clinical status (e.g., an increased risk of thrombo-embolism and alternated pharmacokinetics with increased intravascular blood volume). In addition, in the last decade transcatheter aortic valve implantation (TAVI) has become available as an alternative to surgical aortic valve replacement (SAVR). TAVI was intended for those patients who are not surgical candidates due to comorbidity [18, 19] and frailty, but, at present TAVI is associated with a relatively higher incidence of valve related complications than conventional surgical valve replacement [20]. However, the use of TAVI is expected to increase in the next years as indications for the use of this therapeutic strategy widen [21]. Chapter 2 will discuss the surgical options for aortic valve and root disease in further detail.

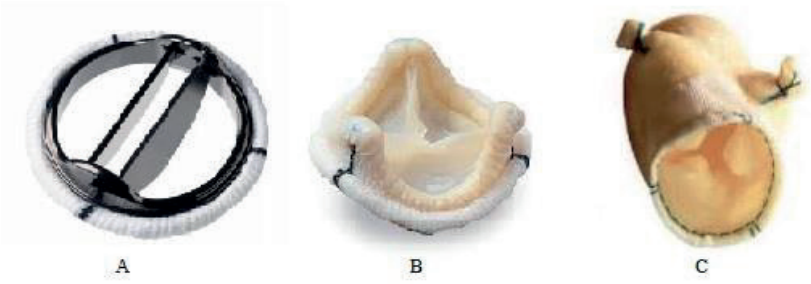


FIGURE 1. Different types of valve prosthesis. A: Mechanical valve; B: Stented bio-prosthesis; C: Stentless bio-prosthesis

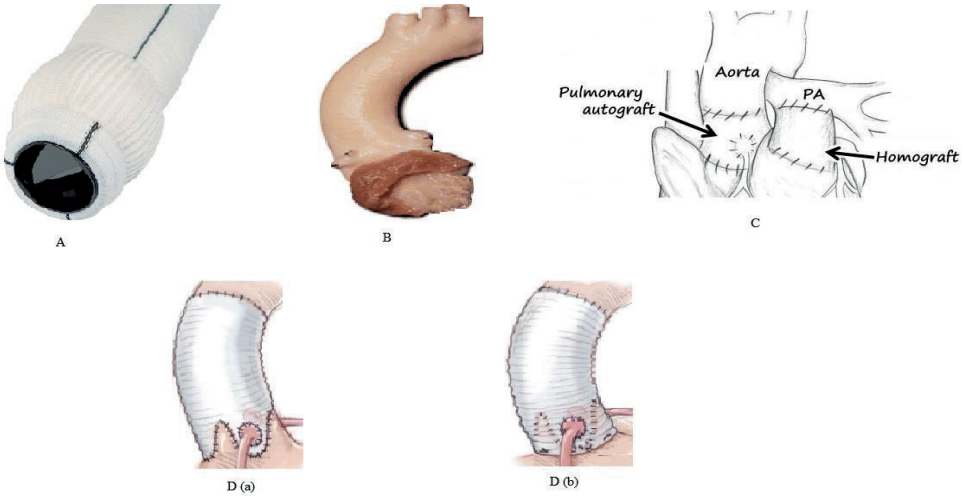


FIGURE 2. Different prosthesis/techniques for aortic root replacement. A: Bentall (mechanical) valve prosthesis; B: Allograft; C: Pulmonary autograft (Ross); D: Valve sparing root replacement (a: Yacoub procedure; b: David procedure)

Quality of life after aortic valve surgery and choice of surgical treatment

Apart from clinical results, an important outcome after aortic valve surgery is patient quality of life. In this regard a technically well performed operation is a prerequisite for good outcome. However, individual patient-preference and specific life expectation after aortic valve surgery must be taken into account while choosing the optimal treatment. It is obvious that a young patient with contraindication for anticoagulation therapy is not a good

candidate for mechanical valve prosthesis. Nevertheless, relatively young patients with a very active lifestyle may have a better quality of life with a biological valve, although at cost of a reoperation later in life [22]. An important tool for measuring quality of life experienced by patients is the Short Form Health Survey (SF-36) questionnaire, where both physical and mental health of patients is assessed and may be compared to the general population [23]. Evidence on quality of life after aortic valve and root surgery may help the clinicians and patients to further tailor an individual treatment to the individual patient taking into account clinical outcome as well as patient preference. Quality of life after aortic valve surgery is addressed in Chapter 11.

Objectives of this thesis

This thesis aims to provide insight into clinical outcome after surgery on the aortic valve and root for a variety of indications (valve stenosis, regurgitation, infective endocarditis, root aneurysm). Early and late clinical outcome, as well as quality of life will be addressed, with special attention to young adult patients after aortic valve or root surgery. Various types of surgical treatment; valve replacement with biological and mechanical prosthesis, and valve sparing root replacement techniques will be presented. Moreover, echocardiographic parameters and patient characteristics associated with valve related outcome are investigated. In addition, quality of life after aortic valve or root surgery and decision making and patient selection is addressed.

OUTLINE

Chapter 2 provides an overview of indications for surgery in aortic regurgitation, surgical options, and subsequent outcomes after aortic valve repair and replacement.

In **Chapter 3** a systematic review of literature and a meta-analysis was performed to outline the occurrence rate of valve related outcome after composite valve replacement in patients with aortic root disease.

Chapter 4 is a systematic review and microsimulation after mechanical aortic valve replacement in young adolescents estimating the occurrence rate of valve related outcome in time.

In **Chapter 5** a systematic review of literature and a meta-analysis was undertaken on outcome after valve sparing aortic root replacement (both David and Yacoub procedure) in relatively young patients, presenting an overview and testing surgical technique as well as variables associated with valve related outcome.

In **Chapter 6** a systematic review and meta-analysis with microsimulation modeling provides an overview on outcome after aortic root replacement with biological valve prosthesis in elderly.

Chapter 7 provides insight into long-term outcome after aortic valve replacement with allografts in a prospective single center study and studies potential echocardiographic factors for the prediction of reoperation and death in a joint model.

In **Chapter 8** and **Chapter 9** the use of allografts in the setting of pregnancy is studied: Chapter 8 studies the association between pregnancy and allograft durability while chapter 9 addresses challenges and complications that heart valve recipients may experience during pregnancy.

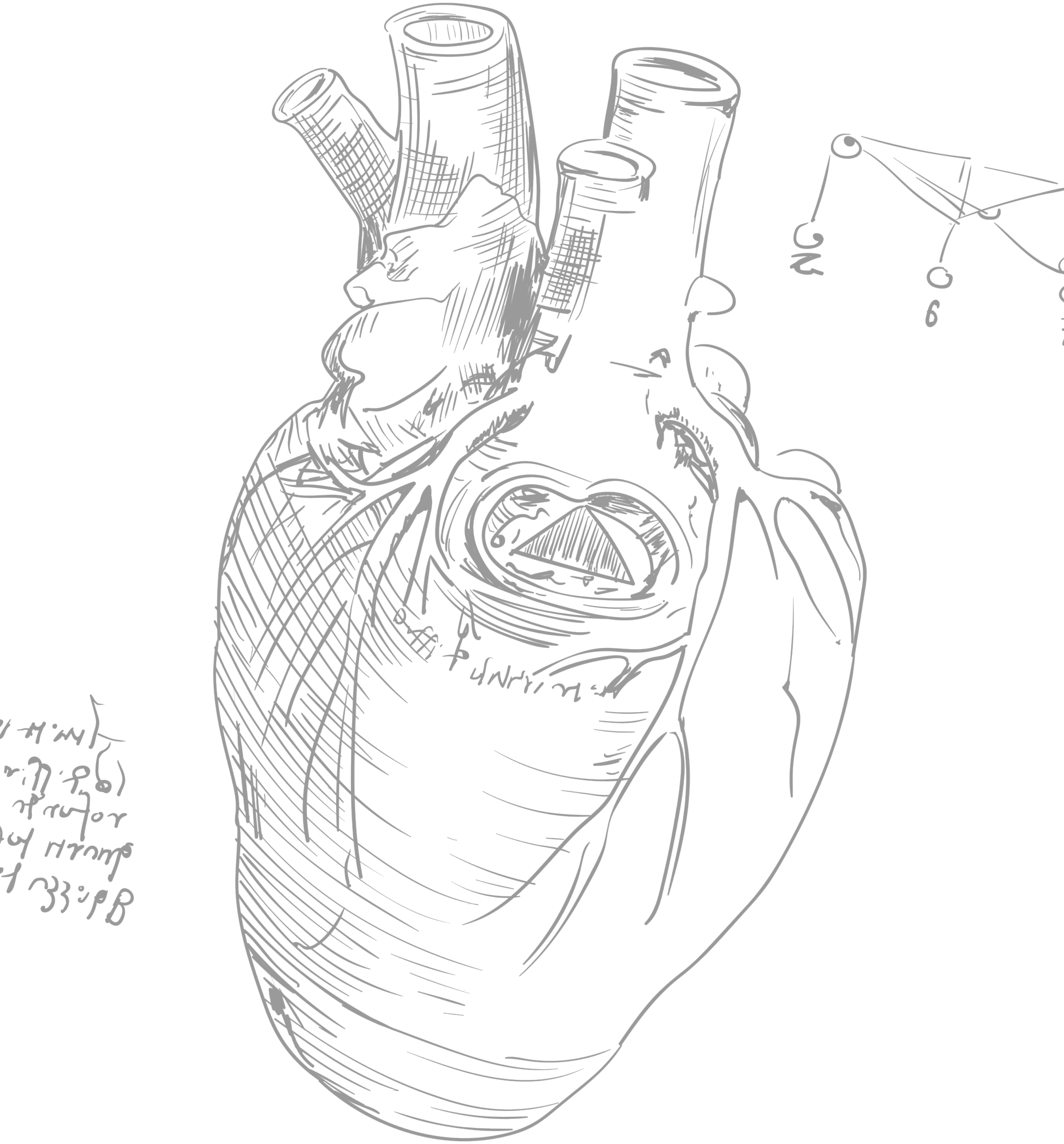
Chapter 10 describes the difference between conservative treatment and surgery regarding symptomatic patients with severe aortic stenosis and timing of the operation.

Chapter 11 describes early and late outcome (reimplantation technique), echocardiographic changes in valve function during follow-up, and the reported quality of life after valve sparing aortic root replacement.

REFERENCES

1. Sabet, H.Y., et al., *Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases.* Mayo Clin Proc, 1999. 74(1): p. 14-26.
2. Eveborn, G.W., et al., *The evolving epidemiology of valvular aortic stenosis. the Tromso study.* Heart, 2013. 99(6): p. 396-400.
3. Schwarz, F., et al., *The effect of aortic valve replacement on survival.* Circulation, 1982. 66(5): p. 1105-10.
4. Chizner, M.A., D.L. Pearle, and A.C. deLeon, Jr., *The natural history of aortic stenosis in adults.* Am Heart J, 1980. 99(4): p. 419-24.
5. Ross, J., Jr. and E. Braunwald, *Aortic stenosis.* Circulation, 1968. 38(1 Suppl): p. 61-7.
6. Vahanian, A. and B. Iung, *The new ESC/EACTS guidelines on the management of valvular heart disease.* Arch Cardiovasc Dis, 2012. 105(10): p. 465-7.
7. Nishimura, R.A., et al., *2014 AHA/ACC guideline 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.* J Am Coll Cardiol, 2014. 63(22): p. e57-185.
8. Di Piazza, M., et al., *[TAVI in degenerative aortic stenosis treatment: state of the art and future perspectives].* Recenti Prog Med, 2014. 105(2): p. 63-7.
9. Hegglin, R., H. Scheu, and M. Rothlin, *Aortic insufficiency.* Circulation, 1968. 38(1 Suppl): p. 77-92.
10. Kirklin/Barrat-Boyes., *Cardiac surgery. Third edition.* 2003.
11. Hiratzka, L.F., et al., *Surgery for Aortic Dilatation in Patients With Bicuspid Aortic Valves: A Statement of Clarification From the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* J Am Coll Cardiol, 2016. 67(6): p. 724-31.
12. Bentall, H. and A. De Bono, *A technique for complete replacement of the ascending aorta.* Thorax, 1968. 23(4): p. 338-9.
13. Ross, D. and M.H. Yacoub, *Homograft replacement of the aortic valve. A critical review.* Prog Cardiovasc Dis, 1969. 11(4): p. 275-93.
14. Ross, D.N., *Replacement of aortic and mitral valves with a pulmonary autograft.* Lancet, 1967. 2(7523): p. 956-8.
15. David, T.E. and C.M. Feindel, *An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta.* J Thorac Cardiovasc Surg, 1992. 103(4): p. 617-21; discussion 622.
16. Sarsam, M.A. and M. Yacoub, *Remodeling of the aortic valve anulus.* J Thorac Cardiovasc Surg, 1993. 105(3): p. 435-8.

17. European Society of, G., et al., *ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC).* Eur Heart J, 2011. 32(24): p. 3147-97.
18. Vahanian, A., D. Himbert, and E. Brochet, *Transcatheter valve implantation for patients with aortic stenosis.* Heart, 2010. 96(22): p. 1849-56.
19. Leon, M.B., et al., *Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery.* N Engl J Med, 2010. 363(17): p. 1597-607.
20. Van Mieghem, N.M., et al., *Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation.* Am J Cardiol, 2012. 110(9): p. 1361-7.
21. Vahanian, A., et al., *Transcatheter aortic valve implantation: our vision of the future.* Arch Cardiovasc Dis, 2012. 105(3): p. 181-6.
22. Aicher, D., et al., *Quality of life after aortic valve surgery: replacement versus reconstruction.* J Thorac Cardiovasc Surg, 2011. 142(2): p. e19-24.
23. Ware, J.E., Jr. and B. Gandek, *Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project.* J Clin Epidemiol, 1998. 51(11): p. 903-12.



Chapter 2

The long term results of aortic valve repair and replacement (Chapter 10, pages 473-491, from "Aortic Regurgitation")

B. Arabkhani , J.J.M. Takkenberg

Vojáček J., Žáček P. and Dominik J., October 2016, Aortic Regurgitation, Skladem, Czech Republic, GRADA (ISBN: 978-80-247-5685-1)

INTRODUCTION

The gold standard for surgical treatment of aortic regurgitation is aortic valve or root replacement with either a mechanical or biological valve substitute. However, in the past decades several surgical approaches aimed at preserving the aortic valve have been introduced, and gain popularity. This chapter aims to describe the long-term results of aortic valve repair and replacement in the setting of aortic regurgitation. In order to adequately understand long-term results of aortic valve repair it is important to realize that patient outcome after surgical treatment of aortic regurgitation is determined by patient related factors, timing of surgery and procedural factors which are often interrelated. This makes prognostication challenging. Nevertheless in this chapter we attempt to take all these factors into account in describing indications for surgery, surgical options, and subsequent outcomes after aortic valve repair and replacement.

Indications for surgery in aortic regurgitation

According to 2012 ESC/EACTS guidelines on the management of valvular heart disease all patients with severe aortic regurgitation who are experiencing symptoms have an indication for aortic valve surgery, as do asymptomatic patients with a resting LVEF < 50% and patients who require CABG or surgery of the ascending aorta or another valve. In addition, surgery should be considered in asymptomatic patients with a resting EF > 50% with severe LV dilatation [1]. The 2014 AHA/ACC guidelines for the management of patients with valvular heart disease echo most of these recommendations, and add that surgery is reasonable in patients with moderate aortic regurgitation while undergoing surgery on the ascending aorta, CABG, or mitral valve surgery [2]

According to the ESC/EACTS guidelines in Marfan patients with a a maximal ascending aorta diameter ≥ 50 mm, regardless of the severity of aortic valve regurgitation, surgery is indicated with. Surgery should be considered in patients who have aortic root disease with maximal ascending aortic diameter of ≥45 mm for patients with Marfan syndrome with risk factors (family history of aortic dissection and/or aortic size increase .2 mm/year, severe AR or mitral regurgitation, desire of pregnancy), ≥50 mm for patients with bicuspid valve with risk factor (coarctation of the aorta, systemic hypertension, family history of dissection or increase in aortic diameter .2 mm/year), and ≥55 mm for other patients. The AHA/ACC guidelines slightly deviate from the European guidelines regarding intervention in patients with bicuspid valve and ascending aortic dilatation by stating that an operative

intervention to repair the aortic sinuses or replace the ascending aorta is indicated in patients with a bicuspid aortic valve if the diameter of the aortic sinuses or ascending aorta is greater than 5.5 cm. In addition, they state that an operative intervention to repair the aortic sinuses or replace the ascending aorta is reasonable in patients with bicuspid aortic valves if the diameter of the aortic sinuses or ascending aorta is greater than 5.0 cm and a risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥0.5 cm per year), and that replacement of the ascending aorta is reasonable in patients with a bicuspid aortic valve who are undergoing aortic valve surgery because of severe AS or AR if the diameter of the ascending aorta is greater than 4.5 cm.

Surgical options

There are several surgical options to treat AR. The gold standard is valve replacement with or without aortic root replacement, depending on the presence and extent of aortic root dilatation. Valve replacement can be done with either a mechanical or biological valve substitute. Biological valve substitutes include stented and stentless bioprostheses, homografts, and the Ross procedure. In addition, AR can be treated by repairing the valve or by valve sparing aortic root replacement. All surgical options carry a number of advantages and disadvantages that are detailed in Table 1. Both the European and the US guidelines state that when it comes to choosing any of these options, this should be a shared decision-making process that accounts for the patient's values and preferences, with full disclosure of the indications for and risks of anticoagulant therapy and the potential need for and risk of reoperation [1, 2].

Mechanical valve prostheses

Since the first successful mechanical valve (i.e. the so called caged-ball valves) was designed in the mid-1960s by pioneers M. Lowell Edwards and Albert Starr [3, 4] tremendous improvements have been made in the design of mechanical valves. Nowadays the most popular mechanical valve prostheses are bileaflet mechanical valves. The main advantage of mechanical valve prostheses is their outstanding durability, and therefore low -although not absent- risk of reoperation. On the downside, because of the increased thrombogenicity of mechanical valve prostheses life-long use of anti-coagulation therapy is necessary in order to prevent valve thrombosis and other thromboembolic events. Anticoagulation therapy is associated with an increased bleeding risk, and currently available anticoagulants require frequent monitoring of the level of anticoagulation and

if necessary adjustment of anticoagulation dose. Another feature of mechanical valve prostheses is the characteristic ticking closing sound of the valve that may be heard by the patient and/or others. This sound can be perceived anywhere between very positive ("knowing that the valve is working well") and very negative ("the sound is driving me crazy"). When aortic valve regurgitation and aortic root dilatation are both present, the "gold standard" surgical treatment is composite valve graft replacement, better known as the Bentall procedure that involves complete replacement of the aortic valve and ascending aorta with a tube graft containing a mechanical valve prosthesis [5, 6]. It is also possible to use a bioprosthesis when performing a Bentall procedure, the so-called bio-Bentall procedure.

TABLE 1. Surgical options for the treatment of AR: advantages and disadvantages

	Mechanical prostheses	**Stented bioprostheses**	**Stentless bioprostheses**	**Homografts**	**Ross Procedure**	**Valve repair or preservation**
Specific surgical expertise required	-	-	+/-	+	++	++
Durability	Excellent	Limited	Limited	Limited	Limited	Limited
AC required?	Yes	No	No	No	No	No
Valve sound	Yes	No	No	No	No	No
Hemodynamics	Adequate	Adequate	Good	Good	Excellent	Excellent

According to current ESC/EACTS guidelines on the management of valvular heart disease, a mechanical valve prosthesis is recommended according to the desire of the informed patient and if there are no contraindications for long-term anticoagulation, in patients at risk of accelerated structural valve deterioration (SVD) or those already on anticoagulation therapy as a result of having a mechanical prosthesis in another valve position. A mechanical prosthesis should be considered in patients aged younger than 60 years, in patients with a reasonable life expectancy for whom future redo valve surgery would be of high risk. Finally, a mechanical prosthesis may be considered in patients already on long-term anticoagulation due to high risk of thromboembolism [1]. The US AHA/ACC guidelines are in agreement with the European guidelines.

Biological valve substitutes

Biological valve substitutes include stented and stentless bioprostheses, homografts, and the Ross procedure. The main advantage of biological valve substitutes as depicted in Table 1 is their absent need for anticoagulation therapy and thus the avoidance of bleeding complications associated with anticoagulant use. On the downside, all biological valves have a limited durability that may necessitate a re-intervention later in life. Nowadays biological valves are increasingly being used in patients under the age of 65 years. In 2004, 30% of patients aged 60-65 years who underwent AVR in the United Kingdom received a biological valve; this has increased to 60% in 2008 and this number is increasing [7, 8].

Stented bioprostheses are the most commonly used biological valve substitutes. This prosthesis type is composed of a sewing ring and an artificial frame in which porcine, bovine or equine pericardial leaflets are suspended. The prosthesis is relatively easy to implant and since its introduction in 1965 by Carpentier et al [9], it is widely used in mainly older adults [10].

Stentless bioprostheses form good alternative to stented bioprostheses as they have better hemodynamics and may also be used to replace the aortic root. They are especially useful in patients with a relatively small aortic annulus to avoid prosthesis-patient mismatch as stentless bioprostheses have a larger effective orifice area (EOA) which provides lower transvalvular gradients resulting in improved reduction of left ventricular hypertrophy [11]. However, a disadvantage of stentless bioprostheses is that they require some surgical expertise and are more time-consuming to implant.

Homografts or human donor valves were introduced in the early 1980's a good alternative for bioprostheses, expecting they would have better hemodynamics, increase infection resistance and superior durability compared to bioprostheses. Due to their favorable tissue characteristics they can be either implanted using a subcoronary technique, replacing only the valve, or as a root replacement. In more recent years it has become apparent that homograft durability is comparable to bioprostheses [12]. This, and the fact that homografts are not readily available "of the shelf", has resulted in that nowadays homografts account for less than 1% of AVRs and are used almost exclusively in case of active endocarditis with complex root pathology [13], where excess homograft tissue can be used to repair tissue defects caused by endocarditis.

Pulmonary autograft valve replacement, better known as the Ross procedure, was introduced by Donald Ross in 1967 and entails replacement of the diseased aortic valve by the patient's own pulmonary valve with concomitant pulmonary valve replacement usually with a homograft or bovine jugular vein [14]. Being the only living biological valve substitute it has become an alternative option for aortic valve replacement in children and young adult patients [14-16]. As with other biological valves, the advantage of the autografts lies in the absent need for anticoagulation therapy and the related complications. In addition, the hemodynamic performance of pulmonary autograft valves is superior to other biological and mechanical valve substitutes, and in the growing child the autograft increases in size proportional to the growth of the child [17]. On the downside, the Ross procedure is a complex procedure that should only be performed by trained surgeons in specialized centers. In addition, when performed as a root replacement the neo-aortic root tends to dilate over time with an increasing need for reintervention in the second postoperative decade. Finally, the valve substitute in pulmonary position may degenerate and require reintervention, although less common in adults [18]. The Ross procedure is discussed more comprehensively in a dedicated chapter in this book.

According to the European ECS/EACTS guidelines a bioprosthesis is recommended according to the desire of the informed patient, when good quality anticoagulation is unlikely (compliance problems; not readily available) or contraindicated because of high bleeding risk (prior major bleed; comorbidities; unwillingness; compliance problems; lifestyle; occupation), and for reoperation for mechanical valve thrombosis despite good long-term anticoagulant control. In addition, a bioprosthesis should be considered in patients for whom future redo valve surgery would be at low risk, in young women contemplating pregnancy, and in patients aged >65 years or those with life expectancy lower than the presumed durability of the bioprosthesis. The AHA/ACC guidelines agree mostly, and add that a bioprosthesis is reasonable in patients >70 yrs, and both a mechanical and bioprosthesis are reasonable between ages 60-70 years [2].

The ESC/EACTS guidelines do not give specific recommendations for the use of homografts but state that, although under debate, the main indication for homografts is acute infective endocarditis with perivalvular lesions [1]. With regard to the Ross procedure the ESC/EACTS guidelines do not give specific recommendations either, but the AHA/ACC guidelines recommend that replacement of the aortic valve by a pulmonary autograft valve, when performed by an experienced surgeon, may be considered in young patients when VKA anticoagulation is contraindicated or undesirable. [1, 2].

Aortic valve repair and valve preserving aortic root replacement

Although outcome after AVR has improved over the past decades, the concerns about prosthetic valve-related complications such as SVD, thromboembolism and valve thrombosis, bleeding, and endocarditis remain. In this light several reconstructive methods have been developed to treat AR and/or preserve the aortic valve in the setting of aortic root dilatation, mainly based on repairing the native aortic valve, and/or sparing the valve while replacing or stabilizing the other components of the aortic root [19-21]. These different surgical techniques are discussed extensively in other chapters of this book.

As with biological prostheses, the main advantages of aortic valve repair and valve preserving aortic root replacement are the absent need for anticoagulation. In addition, hemodynamic function is excellent. On the downside, specific surgical expertise is required as these procedures are technically more demanding compared to standard aortic valve replacement. Also, durability is limited, and patients may need a reoperation later in life. Neither the ESC/EACTS not the AHA/ACC guidelines provide recommendations for the reconstructive methods that have been developed to treat AR and/or preserve the aortic valve in the setting of aortic root dilatation

Reported outcome after aortic valve replacement and valve repair

In order to adequately understand long-term results of aortic valve replacement and repair it is important to realize that patient outcome after surgical treatment of aortic regurgitation is not only determined by valve replacement or repair approach but also by patient related factors, timing of surgery and procedural factors which are often interrelated. This makes prognostication challenging.

Patient related factors that play a prominent role in the outcome after aortic valve surgery include patient age, preoperative NYHA class, hemodynamic diagnosis, the need for concomitant CABG, and heart rhythm. In the landmark paper by Kvidal et al. [22] it was shown that although *older* patient age seems to be associated with increased observed late mortality, *younger* patient age is associated with increased relative late mortality compared to the age-matched population: in AVR patients younger than 50 years observed mortality was 4.5 times higher than would be expected in the age-matched general population, while AVR patients over the age of 70 years showed a life expectancy comparable to the general population. These observations can be explained by the more severe phenotype of valve disease in younger patients, and at the same time by the more

stringent selection that takes place for AVR in the elderly. The same paper showed that a higher preoperative NYHA class, the presence of atrial fibrillation, and the hemodynamic diagnosis of aortic regurgitation versus aortic stenosis were all important determinants of increased late mortality. It should be noted that survival after aortic valve replacement in non-elderly adult patients has improved significantly over the past few decades [23], and this also applies to patients with aortic regurgitation, even for those with severe left ventricular dysfunction [24].

Timing of surgery is another crucial determinant of both early and late outcome after aortic valve surgery. Patients who present urgently and patients who present late in their disease process do worse than elective patients with relatively early symptoms and signs of disease. The question is: how early should we treat? Earlier surgery on the one hand will deal with some of the patient related factors mentioned above. However, on the other hand all surgery carries early operative risks, and in the setting of aortic valve surgery late (prosthetic) valve related complications. *Procedural factors* may also have an impact on outcome after aortic valve surgery: for example concomitant cardiac surgery carries a higher operative risk than isolated aortic valve surgery, while the need for multiple valve surgery and/or CABG will increase both early and late morbidity and mortality.

Outcome after valve replacement and repair is defined by the 2008 AATS/STS/EACTS guidelines for reporting morbidity and mortality after cardiac valvular interventions [25]. These guidelines help us to uniformly report on outcome after valve surgery and provide us a tool to compare the results after valve surgery in a structural manner.

Reported outcomes after mechanical valve implantation and Bentall procedure

Early mortality after mechanical AVR is on average below 2% in non-elderly adults [26] while early mortality after a mechanical Bentall procedure is considerably higher, on average 6% [27]. In patients after mechanical valve AVR reported annual occurrence rates of major bleeding, thromboembolism, and valve thrombosis are 1.6%, 1.6% and 0.16% per patient-year respectively; endocarditis rates are 3.9% per patient-year in the first 6 postoperative months and 0.66% per patient-year after the first 6 postoperative months; reoperation rates (due to non-structural valve deterioration) are 0.29% per patient-year [26]. Using microsimulation these annual occurrence rates can be translated to life time risks of complications for patients of different ages. These life time risks for the most commonly occurring complications after mechanical AVR, bleeding and thrombo-

embolism, are detailed in Figure 1. This Figure illustrates that although annual occurrence rates appear low, they translate to considerable lifetime risks of bleeding and thrombo-embolism.

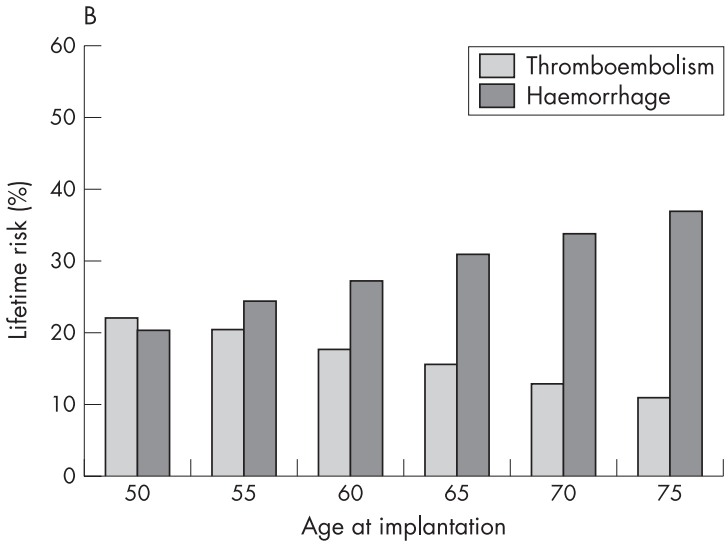


FIGURE 1. Lifetime risk of major bleeding and thrombo-embolism after mechanical aortic valve replacement for different patient ages at the time of valve implantation (From Puvimanasinghe et al. Heart, 2004) [26]

In patients after the Bentall procedure an average aortic root reoperation rate of 0.46% per patient-year and an aortic valve reoperation rate of 0.30% per patient-year is reported. Reported bleeding and thrombo-embolic event rates are 0.64%, and 0.77% per patient-year respectively, while endocarditis rates are 0.39%, [27]. Although bleeding and thrombo-embolic event rates appear lower after Bentall compared with mechanical AVR, a direct comparison of the groups is hampered by differences in patient age, etiology, and by potential bias caused by the predominantly retrospective study designs of the reports that were combined to obtain these estimates. Nevertheless, bleeding and thrombo-embolism also represent the most common complications after the Bentall procedure, and result in considerable lifetime risks of major bleeding and thrombo-embolism for these predominantly young adult patients.

Reported outcomes after stented bioprosthetic aortic valve replacement

As would be expected, compared to mechanical prostheses reported major bleeding event rates are lower (although not absent) after stented bioprosthetic valve implantation, but interestingly thrombo-embolic event rates appear comparable at first sight. A systematic review of reported outcome after AVR with two common stented bioprostheses (Carpentier Edwards (CE) pericardial and supra-annular bioprostheses) report major bleeding event rates of 0.43 and 0.46% per patient year respectively, major thrombo-embolic event rates of 1.35 and 1.76% per patient-year and valve thrombosis event rates of 0.03 and 0.02%/ patient year respectively. When interpreting these event rates one should realize that bioprosthetic valve recipients are on average approximately 15 year older compared to mechanical valve recipients, more often have atrial fibrillation requiring anticoagulation, and a higher baseline bleeding and thrombo-embolic event hazard as this is observed to increase with age in the general population. Endocarditis and reoperation rates for non-structural valve failure are reportedly 0.62 and 0.39%/patient year and 0.13 and 0.61%/ patient year respectively for CE pericardial and supra-annular bioprostheses. SVD is the major downside of stented bioprostheses; it cannot simply be depicted in an annual event rate as the hazard of SVD increased with the time since the operation and is inversely related to patient age at the time of operation: in particular younger patients have a very high lifetime risk of reoperation for SVD which can be explained by the fact that they live longer than older patients but also by the observation that older patients are less likely to be referred for redo surgery. Figure 2 illustrates the lifetime risks of reoperation for SVD for male stented bioprosthetic valve recipients of different ages at implantation.

Reported outcomes after stentless bioprosthesis aortic valve replacement

SVD of stentless bioprostheses is age-dependent and comparable to stented aortic bioprostheses, as depicted in Figure 3. Estimated annual occurrence rates of major bleeding, thrombo-embolism and valve thrombosis for one of the most commonly used stentless bioprostheses (Medtronic Freestyle stentless bioprosthesis) are 0.28%, 2.9% and 0.04% per patient year respectively, while endocarditis and reoperation for non-structural valve failure have an annual hazard of 0.45% and 0.28% per patient year [28].

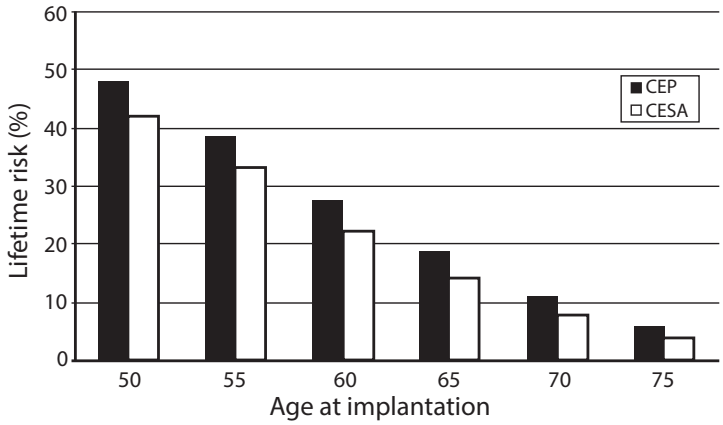


FIGURE 2. Lifetime risk of reoperation for SVD with CE pericardial (CEP) and supra-annular bioprostheses (CESA) for male patients of different ages at implantation.

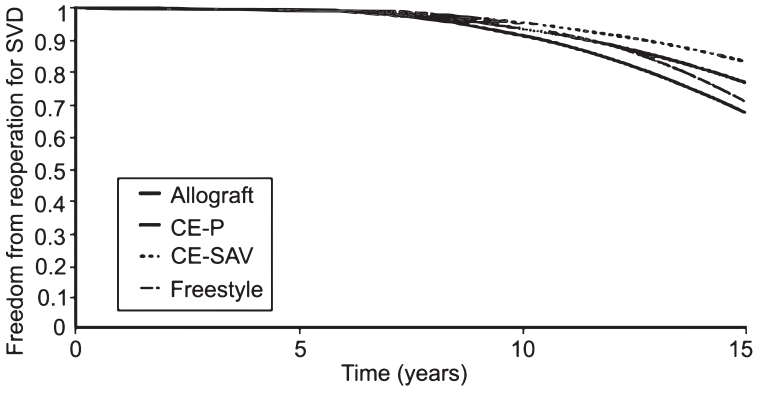


FIGURE 3. Weibull estimates of freedom from reoperation for SVD for a 65-year-old male after implantation with an allograft valve, a Carpentier Edwards pericardial valve, a Carpentier Edwards supra-annular valve or a stentless Freestyle valve (From Kappetein et al. Interact Cardiovasc Thorac Surg., 2006) [28].

Reported outcomes after homograft aortic valve and root replacement

The latest report of the Rotterdam prospective cohort study [13] shows an early mortality of 5.8% after homograft implantation in 353 patients with a mean age of 45 years. This is considerably higher than in standard aortic valve replacement with mechanical or bioprosthetic valves, but can be explained by the high proportion of complex patients (endocarditis, aneurysm, dissection, often urgent operations). Estimated annual occurrence rates of major bleeding, thrombo-embolism and valve thrombosis are reportedly 0.1%, 0.5% and 0% per patient year respectively, while endocarditis rates of 0.33% per patient year illustrate the resistance of homografts to infection. The SVD pattern of homografts appears comparable to stented and stentless bioprostheses, as illustrated in Figure 3, and younger patient age is associated with a shorter time to reoperation for SVD. However, the only randomized controlled trial comparing homografts with Freestyle stentless bioprostheses shows significantly less progressive aortic valve dysfunction and reoperations with the Freestyle valve [30].

Reported outcomes after the Ross procedure

Although initially there was concern about high early operative mortality after the Ross procedure, several short and mid-term studies have proven that in experienced hands in dedicated centers this procedure can be performed with low operative risk and survival rates comparable to the general population [31-33]. A comprehensive systematic review (12 observational studies in 1749 adult patients, mean age ranging from 28-51 years) showed an early mortality risk of 3.04% and a late mortality rate of 0.48% per year[34]. The excellent observed survival rates may be explained by the excellent hemodynamic characteristics of the only living valve substitute available today [33]. On the other hand, there is also evidence that through optimization of anticoagulation management in mechanical valve prosthesis recipients, a survival pattern comparable to Ross patients can be achieved [35]. Freedom from autograft reoperation has been reported to range between 69% and 99% after 10 to 13 years of follow-up, depending on which surgical technique has been used[31, 33, 36, 37]. The results of the comprehensive systematic review showed a linearized rate of 1.15%/patient year for structural and nonstructural autograft failure leading to reoperation [34]. Application of proven durable autograft implantation techniques are crucial for the durability results after the Ross procedure. In addition, patient characteristics may also play a role: younger patient age [32], congenital aortic valve disease [38], rheumatic valve disease[39], and preoperative AR [40] and dilatation [32] are the most commonly reported patient-related determinants of durability

of the autograft valve. However, even if the durability of autografts is less in patients with preoperative AR, the decision whether to perform the Ross procedures depends also on technical considerations and informed patient preferences, and the option of the Ross procedure should not upfront be discarded [41]. Freedom from pulmonary allograft reoperation is reported to range between 87% and 96% after 10 to 13 years of follow-up [31, 33]. The pooled structural or non-structural pulmonary allograft failure has been shown to be 0.91% per year [34]. Autograft endocarditis occurs with a rate of 0.32% per year, ranging between 0.04% and 0.70% between different studies [34]. Pulmonary allograft endocarditis has been reported to range between 0.04% and 0.69% per year for different studies with a pooled estimate of 0.32% per year [34].

Further details on the autograft operation is given elsewhere in this book.

Reported outcomes after valve sparing aortic root replacement

A recently published systematic review and meta-analyses of 31 articles published between 2000 and 2014 on valve sparing aortic root replacement [42] showed a pooled early mortality of 2%, and a late mortality rate of 1.53% per patient-year. Additionally a reoperation rate of 1.32% per patient-year was reported. Thromboembolism and hemorrhagic event rates were estimated to be 0.23% and 0.41% per patient-year, respectively. Reported pooled endocarditis rates were 0.21% per patient-year. Importantly, preoperative severe aortic valve regurgitation showed a trend toward higher reoperation rates, while remodeling and reimplantation techniques show comparable survival and valve durability results. Obviously, given the limited follow-up duration of studies in this review, these results can only be applied to the first postoperative decade, and longer follow-up studies are needed to assess durability in the longer term.

Another systematic review (11 publications) in 1385 Marfan patients that compared total root replacement with valve sparing root replacement, has shown a reintervention rate of 0.3%/year versus 1.3%/year while thromboembolic events rate was 0.7%/year versus 0.3%/y, respectively. Among patients undergoing valve sparing aortic root replacement, the reimplantation technique was associated with a reduced rate of reintervention compared with the remodeling technique (0.7%/year vs 2.4%/year) [43].

Aortic valve preservation and repair in the setting of acute type A dissection has been nicely summarized in a systematic review of 19 observational studies concerning 2402 patients (median age 59 years) with a median follow-up of 4.1 years. AV resuspension

was performed in 95% of the patients and the remainder underwent valve-sparing root replacement. Pooled early mortality rate was expectedly considerable, 18.7%, as was the late mortality rate of 4.7%/pt-yr. Aortic valve reintervention rate was 2.1%/year. The composite rate of thromboembolism and bleeding was 1.4%/year [44].

Reported outcomes after aortic valve repair

Aortic valve repair is currently in transition from surgical improvisation to a reproducible operation and an option for many patients with aortic regurgitation [45]. It is therefore not surprising that reports on outcomes are small, of limited follow-up duration and usually concern specific patient subcategories and varying surgical repair techniques. A few reports are worth mentioning.

A large series from Germany reports on 640 patients undergoing aortic valve repair for regurgitation of a unicuspid, bicuspid, tricuspid or quadricuspid aortic valve. The mechanism of regurgitation included prolapse, cusp retraction, and/or root dilatation. Treatment consisted of cusp repair (n=529), root repair (n=323) or a combination of both (n=208). Hospital mortality was 3.4% in the total patient cohort and 0.8% for isolated aortic valve repair. Thrombo-embolism rate was 0.2% per patient year, endocarditis rates 0.16%per patient year. Freedom from re-operation at 10 years was 81% in bicuspid and 93% in tricuspid aortic valves ($p<0.001$), showing an impaired durability in bicuspid versus tricuspid valves [46]. This case series nevertheless nicely shows that reconstructive surgery of the aortic valve is feasible with low mortality in many individuals with aortic regurgitation.

A more recent report from the same group that focused on bicuspid aortic valve repair it was shown that preservation of the bicuspid aortic valve results in good long-term stability of the repaired valves, and that the negative impact of a dilated atrioventricular junction can be reduced by suture annuloplasty [47]. This group has also shown that in patients with a unicuspid aortic valve the concept of valve bicuspidization and root remodeling can be applied with satisfactory hemodynamic results [48].

Finally, a multicenter European collaboration recently showed that neo-aortic valve sparing reoperations after the Ross procedure may be performed with limited early morbidity and mortality in most patients. This approach provides patients with the continued benefit of a functioning autograft valve. However, the need for reintervention after valve-sparing

reoperation is common in the first 2 postoperative years in patients with isolated and/or severe autograft regurgitation; careful consideration of the surgical approach in these patients is warranted [49].

The observed lack of standardization in data reporting concerning outcomes after valve sparing aortic root replacement, and the sparsity of available outcome data after aortic valve repair have led to an international prospective multicenter registry for aortic valve-sparing/repair and replacement surgical procedures called AVIATOR (www.heartvalvesociety.org). AVIATOR aims to provide sufficient patient numbers to address key epidemiological and therapeutic issues and standardize indications for surgery as well as the place of repair versus replacement in aortic valve surgery.

Quality of life after aortic valve surgery

The main goal of aortic valve surgery is not only optimizing clinical outcomes but also patient quality of life. It is therefore important in choosing a particular surgical strategy to consider the available evidence on quality of life after aortic valve surgery. Koch et al showed an improved quality of life after aortic valve surgery in particular in patients with an impaired quality of life before surgery. Interestingly, patients with relatively high preoperative quality of life had little quality of life to gain after surgery, and more importantly: a lot to lose [46, 50]. Quality of life may differ between the different valve surgery options: Ruel et al observed in young adult patients with mechanical valve substitutes a lower physical capacity; a higher prevalence of disability; and poorer disease perception compared to bioprosthetic valve recipients [51]. In their landmark study concerning mechanical valve recipients, Ross procedure patients and patients who underwent aortic valve repair, Aicher et al have demonstrated that Ross procedure patients and aortic valve repair patients have better physical functioning, general health and mental health, and less cardiac anxiety compared to mechanical valve recipients [52]. These observations underline the importance of considering patient preferences and quality of life when choosing a surgical strategy.

Selecting the optimal treatment for the individual patient with AR

Unfortunately, the ideal non-thrombogenic, infection-resistant, living autologous valve substitute with excellent hemodynamics and an unlimited durability is not yet available. In real life, the available aortic valve substitutes are associated with one or

more disadvantages. Valve repair or preservation offers an attractive biological solution in selected patients with aortic regurgitation and/or aortic root disease, but also have limitations as detailed above.

In selecting the optimal treatment for the individual patient one needs to consider evidence on outcome after the different available treatment options, individual patient characteristics, and importantly informed patient preferences. The choice between a mechanical or a biological surgical strategy is ideally driven by the anticipated valve-related morbidity of each strategy, and patient valuation of this morbidity: some patients may highly value a life without anticoagulation therapy, while others may wish to avoid a potential reoperation due to valve failure at any cost. The failure to consider patient preferences may negatively affect patient quality of life. Of course, there are patients in whom objective assessment of their clinical condition leaves little room for alternative treatment strategies. However, in the majority of patients there are multiple options that should ideally be discussed with the patient, informing the patient and allowing the patient to participate in the decision. Ideally, a choice is made in a process of shared decision making that allows patients to be informed about their options, weigh these options in their own context, invited them to participate in decision making, and finally come to a decision together with their treating physician [53].

The continuous improvement of heart valve prostheses and aortic valve repair and valve sparing aortic root replacement techniques will certainly help to optimize patient outcome after aortic valve surgery. In particular for patients with aortic regurgitation the recently established international AVIATOR registry (www.heartvalvesociety.org) that aims to collect and share real life data on the characteristics and outcomes of valve preserving and valve replacement strategies in the setting of aortic regurgitation and/or aortic root dilatation, will provide an important knowledge platform concerning optimal individualized patient tailored surgical strategies to treat aortic regurgitation.

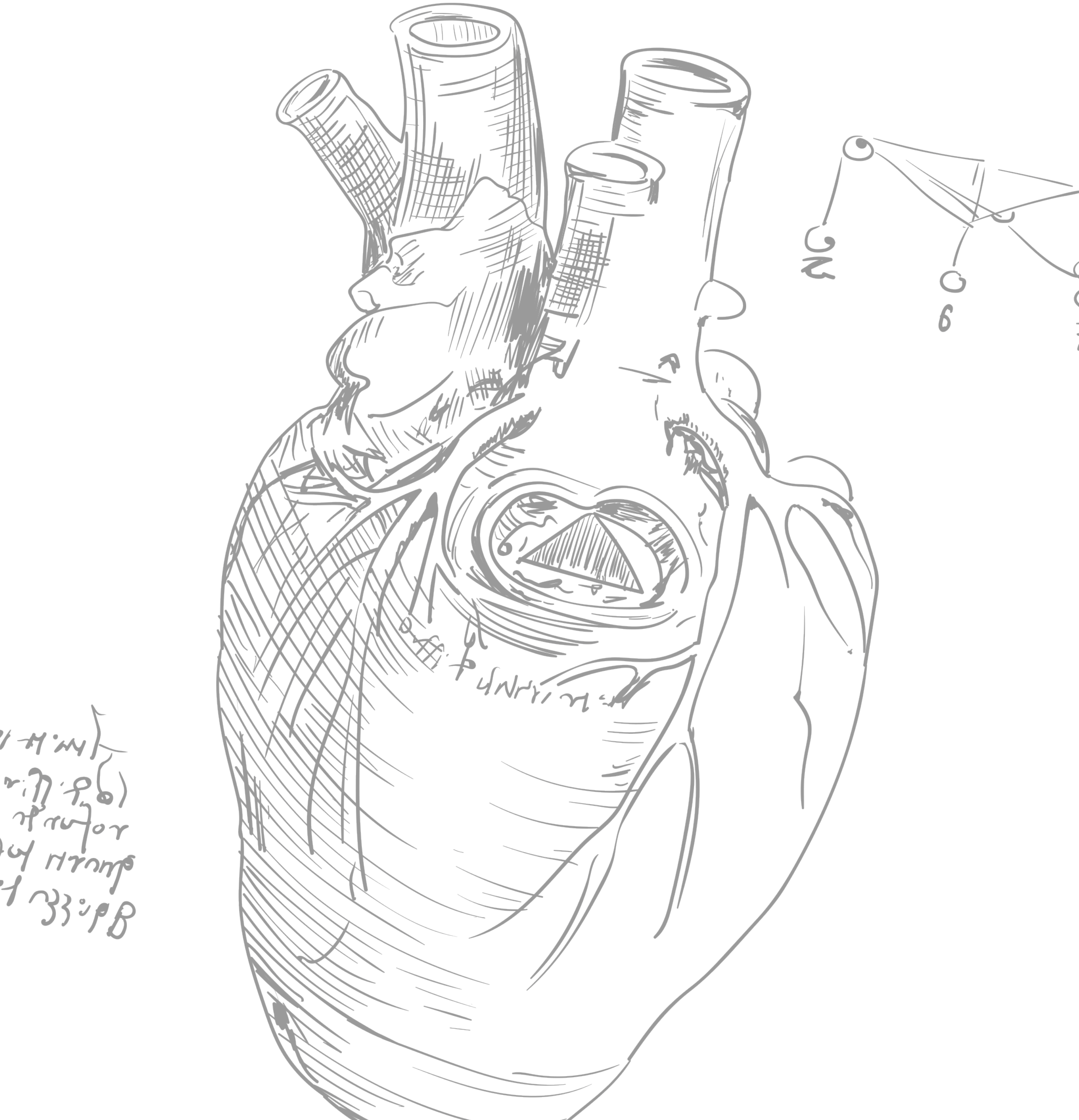
REFERENCES

1. Vahanian, A. and B. Iung, *The new ESC/EACTS guidelines on the management of valvular heart disease.* Arch Cardiovasc Dis, 2012. 105(10): p. 465-7.
2. Nishimura, R.A., et al., *2014 AHA/ACC guideline 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.* J Am Coll Cardiol, 2014. 63(22): p. e57-185.
3. Lewis, R.P., et al., *Aortic valve replacement with the Starr-Edwards ball-valve prosthesis. Indications and results.* Am Heart J, 1966. 71(4): p. 549-63.
4. Bristow, J.D., et al., *Clinical and Hemodynamic Results of Aortic Valvular Replacement with a Ball-Valve Prosthesis.* Circulation, 1964. 29: p. SUPPL:36-46.
5. Bentall, H. and A. De Bono, *A technique for complete replacement of the ascending aorta.* Thorax, 1968. 23(4): p. 338-9.
6. Kouchoukos, N.T. and R.B. Karp, *Resection of ascending aortic aneurysm and replacement of aortic valve.* J Thorac Cardiovasc Surg, 1981. 81(1): p. 142-3.
7. Bridgewater B, K.R., Walton P., *Sixth National Adult Cardiac Surgical Database Report Demonstrating quality.* 2008.
8. Stamou, S.C., et al., *Aortic root surgery in the United States: a report from the Society of Thoracic Surgeons database.* J Thorac Cardiovasc Surg, 2015. 149(1): p. 116-22 e4.
9. Carpentier, A., et al., *Biological factors affecting long-term results of valvular heterografts.* J Thorac Cardiovasc Surg, 1969. 58(4): p. 467-83.
10. Carpentier, A., *From valvular xenograft to valvular bioprosthesis (1965-1977).* Med Instrum, 1977. 11(2): p. 98-101.
11. Dunning, J., et al., *Stentless vs. stented aortic valve bioprostheses: a prospective randomized controlled trial.* Eur Heart J, 2007. 28(19): p. 2369-74.
12. Smedira, N.G., et al., *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): p. 558-564 e4.
13. Bardia Arabkhani MD, M.J.A.B.M., PhD[1]; Eleni-Rosalina Andrinopoulou PhD[1]; Jolien W. Roos-Hesselink[1], MD, PhD; Johanna JM Takkenberg MD, PhD[1]; Ad JJC Bogers MD, PhD[1], *Allografts in aortic position: insights from a 27-year single-center prospective study.* Journal of Thoracic and CardioVascular Surgery (Submitted), 2015.
14. Ross, D.N., *Replacement of aortic and mitral valves with a pulmonary autograft.* Lancet, 1967. 2(7523): p. 956-8.
15. Ross, D., M. Jackson, and J. Davies, *The pulmonary autograft--a permanent aortic valve.* Eur J Cardiothorac Surg, 1992. 6(3): p. 113-6; discussion 117.
16. Kouchoukos, N.T., et al., *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): p. 1-6.

17. Yacoub, M.H., et al., *An evaluation of the Ross operation in adults.* J Heart Valve Dis, 2006. 15(4): p. 531-9.
18. Mokhles, M.M., et al., *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): p. 2213-24.
19. Cabrol, C., et al., *[Treatment of aortic insufficiency by means of aortic annuloplasty].* Arch Mal Coeur Vaiss, 1966. 59(9): p. 1305-12.
20. Haydar, H.S., et al., *Valve repair for aortic insufficiency: surgical classification and techniques.* Eur J Cardiothorac Surg, 1997. 11(2): p. 258-65.
21. Cosgrove, D.M., et al., *Valvuloplasty for aortic insufficiency.* J Thorac Cardiovasc Surg, 1991. 102(4): p. 571-6; discussion 576-7.
22. Kvidal, P., et al., *Observed and relative survival after aortic valve replacement.* J Am Coll Cardiol, 2000. 35(3): p. 747-56.
23. Ruel, M., et al., *Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age.* Circulation, 2007. 116(11 Suppl): p. I294-300.
24. Bhudia, S.K., et al., *Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction.* J Am Coll Cardiol, 2007. 49(13): p. 1465-71.
25. Akins, C.W., et al., *Guidelines for reporting mortality and morbidity after cardiac valve interventions.* Ann Thorac Surg, 2008. 85(4): p. 1490-5.
26. Puvimanasinghe, J.P., et al., *Comparison of outcomes after aortic valve replacement with a mechanical valve or a bioprosthesis using microsimulation.* Heart, 2004. 90(10): p. 1172-8.
27. Aart Mookhoek MD, N.M.K., Bardia Arabkhani MD, Isabelle Di Centa MD, Emmanuel Lansac MD, PhD, Jos A Bekkers MD, PhD, Ad JJC Bogers MD, PhD, Johanna JM Takkenberg MD PhD, *Bentall Procedure: a Systematic Review and Meta-Analysis.* The Annals of Thoracic Surgery, 2016, article in press.
28. Kappetein AP1, T.J., Puvimanasinghe JP, Jamieson WR, Eijkemans M, Bogers AJ., *Does the type of biological valve affect patient outcome?* Interact Cardiovasc Thorac Surg, 2006. 5 (4): p. 398-402.
29. Lehmann, S., et al., *Ten-year follow up after prospectively randomized evaluation of stentless versus conventional xenograft aortic valve replacement.* J Heart Valve Dis, 2011. 20(6): p. 681-7.
30. El-Hamamsy, I., et al., *Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial.* J Am Coll Cardiol, 2010. 55(4): p. 368-76.
31. Klieverik, L.M., et al., *The Ross operation: a Trojan horse?* Eur Heart J, 2007. 28(16): p. 1993-2000.
32. Luciani, G.B., et al., *Ross operation in the young: a ten-year experience.* Ann Thorac Surg, 2005. 80(6): p. 2271-7.
33. El-Hamamsy, I., et al., *Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial.* Lancet, 2010. 376(9740): p. 524-31.

34. Takkenberg, J.J., et al., *The Ross procedure: a systematic review and meta-analysis.* Circulation, 2009. 119(2): p. 222-8.
35. Mokhles, M.M., et al., *Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study.* Circulation, 2011. 123(1): p. 31-8.
36. Sievers, H.H., et al., *Major adverse cardiac and cerebrovascular events after the Ross procedure: a report from the German-Dutch Ross Registry.* Circulation, 2010. 122(11 Suppl): p. S216-23.
37. Elkins, R.C., et al., *Ross operation: 16-year experience.* J Thorac Cardiovasc Surg, 2008. 136(3): p. 623-30, 630 e1-5.
38. Settepani, F., et al., *The Ross operation: an evaluation of a single institution's experience.* Ann Thorac Surg, 2005. 79(2): p. 499-504.
39. Sampath Kumar, A., et al., *Ross procedure in rheumatic aortic valve disease.* Eur J Cardiothorac Surg, 2006. 29(2): p. 156-61.
40. Laudito, A., et al., *The Ross procedure in children and young adults: a word of caution.* J Thorac Cardiovasc Surg, 2001. 122(1): p. 147-53.
41. Mokhles, M.M., A.J. Bogers, and J.J. Takkenberg, *No Ross operation for patients with aortic regurgitation?* Ann Thorac Surg, 2011. 92(3): p. 1156-7; author reply 1157.
42. Arabkhani, B., et al., *Reported Outcome After Valve-Sparing Aortic Root Replacement for Aortic Root Aneurysm: A Systematic Review and Meta-Analysis.* Ann Thorac Surg, 2015. 100 (3): p. 1126-31.
43. Benedetto, U., et al., *Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis.* Heart, 2011. 97(12): p. 955-8.
44. Saczkowski, R., et al., *Aortic valve preservation and repair in acute Type A aortic dissection.* Eur J Cardiothorac Surg, 2014. 45(6): p. e220-6.
45. Schafers, A.a., *Aortic Valve Repair—Current Status, Indications, and Outcomes.* Semin Thorac Cardiovasc Surg, 2012. Volume 24(Issue 3): p. Pages 195–201.
46. Diana Aichera, R.F., Svetlana Rodionychevaa, Kathrin Schmidta, Frank Langera and Hans-Joachim Schäfers, *Aortic valve repair leads to a low incidence of valve-related complications.* European Journal Cardio-Thoracic Surgery, 2009. 37(1): p. 127-132.
47. Aicher D1, S.U., Schmied W, Kunihara T, Tochii M, Schäfers HJ., *Early results with annular support in reconstruction of the bicuspid aortic valve.* JTCVS, 2013. 145(3): p. S30–S34.
48. Franciulli, M., et al., *Root remodeling and aortic valve repair for unicuspid aortic valve.* Ann Thorac Surg, 2014. 98(3): p. 823-9.
49. Mookhoek, A., et al., *European multicenter experience with valve-sparing reoperations after the Ross procedure.* J Thorac Cardiovasc Surg, 2015. 150(5): p. 1132-7.
50. Koch, C.G., et al., *Impact of prosthesis-patient size on functional recovery after aortic valve replacement.* Circulation, 2005. 111(24): p. 3221-9.

51. Ruel, M., et al., *Long-term outcomes of valve replacement with modern prostheses in young adults.* Eur J Cardiothorac Surg, 2005. 27(3): p. 425-33; discussion 433.
52. Aicher, D., et al., *Quality of life after aortic valve surgery: replacement versus reconstruction.* J Thorac Cardiovasc Surg, 2011. 142(2): p. e19-24.
53. Korteland NM1, B.F., van Hout FM3, Kluin J2, Klautz RJ3, Bogers AJ1, Takkenberg JJ1., *Prosthetic aortic valve selection: current patient experience, preferences and knowledge.* Open Heart, 2015. 2(1).



Chapter 3

Bentall Procedure: a Systematic Review and Meta-Analysis

Aart Mookhoek, Nelleke M Korteland, Bardia Arabkhani, Isabelle Di Centa, Emmanuel Lansac, Jos A Bekkers, Ad JJC Bogers, Johanna JM Takkenberg

Ann Thorac Surg. 2016 May;101(5):1684-9. doi: 10.1016/j.athoracsur.2015.10.090. Epub 2016 Feb 6.

ABSTRACT

Background. The Bentall procedure is considered the gold standard in treatment of patients requiring aortic root replacement. An up-to-date overview of outcome following the Bentall procedure is lacking.

Methods. We conducted a systematic review and meta-analysis of characteristics of and long-term outcome after the Bentall procedure with a mechanical valve prosthesis. Pooling was performed using the inverse variance method within a random-effect model. Outcome events are reported as linearized occurrence rates (percentage per patient year) with 95% confidence intervals.

Results. In total, 46 studies with 7629 patients (mean age 50 years, 76% males) were selected. Pooled early mortality was 6% (422 patients). During a mean follow-up of 6 years (49,175 patient years), the annual linearized occurrence rate for late mortality was 2.02% (1.77% - 2.31%; 892 patients), for aortic root reoperation 0.46% (0.36% - 0.59%), for hemorrhage 0.64% (0.47% - 0.87%), for thromboemboli 0.77% (0.60% - 1.00%), for endocarditis 0.39% (0.33% - 0.46%) and for major adverse valve-related events 2.66% (2.17% - 3.24%). Operations performed in more recent years were associated with lower rates of aortic root reoperation (beta = -0.452, P=0.015).

Conclusion. This systematic review illustrates that rates of aortic root reoperation after the Bentall procedure have decreased over the years. However, late mortality, major bleeding and thromboembolic complications remain a concern. This report may be used to benchmark the potential therapeutic benefit of novel surgical approaches, such as valve-sparing aortic root replacement.

INTRODUCTION

The Bentall procedure is considered the gold standard in treatment of patients requiring aortic root replacement. Since its introduction, novel surgical techniques and approaches have changed the Bentall procedure considerably [1]. While the original procedure was associated with a high incidence of coronary button complications, several modifications have been proposed to tackle this problem [2, 3]. The vast majority of Bentall procedures concerns replacement of the aortic root with a mechanical valved conduit. The use of a mechanical valve provides a durable solution, but requires life-long anticoagulation associated with increased bleeding risk.

Surprisingly, an up-to-date overview of outcome following the Bentall procedure is lacking, as most reports are single center and usually concern limited numbers of patients. Pooling data from the literature will allow individual centers or surgeons to benchmark their experience. More importantly, it is key to allow for assessment of the potential therapeutic benefit of novel techniques such as valve-sparing aortic root replacement [4]. This study comprises a systematic review and meta-analysis of published evidence on characteristics of and outcome after the Bentall procedure using a mechanical valve prosthesis.

METHODS

Search Strategy

On July 20th 2015, a systematic literature search was conducted in Embase, MEDLINE, The Cochrane Collaboration and Web of Science (Appendix 1). All studies published from January 1998 onwards were screened by two independent reviewers (AM and NMK) using the following inclusion criteria: morbidity and mortality after the Bentall procedure with a mechanical valve prosthesis, cohorts ≥ 30 patients and mean age ≥ 18 years. Exclusion criteria were: studies limited to patients with acute type A aortic dissection, studies limited to reoperations or to patients receiving a biological valve prosthesis, studies with mean follow < 4 years and studies reporting state of the art, case reports, experimental studies and reviews. In case of multiple publications on the same patient cohort, the most recent and complete study was selected. All selected studies were cross-referenced to identify additional publications. In case of disagreement between the reviewers about inclusion of a publication, consensus was reached.

Data Extraction

Data extraction was performed in duplicate with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) by two of the authors (AM and NMK) according to the guidelines for reporting mortality and morbidity after cardiac valve interventions [5]. Events were not included in our database when adherence to the reporting guidelines could not be ascertained. For each article with missing information on important variables, the corresponding author was requested to provide the missing data. An overview of extracted variables is presented in Appendix 2.

Data Analysis

Data analysis was performed with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) and IBM SPSS version 21.0 (IBM, Somers, NY, USA). Reported study characteristics are quoted as mean ± standard deviation for continuous variables and percentages for discrete variables. To study the association between surgical period and outcome after the Bentall procedure, the continuous variable "surgical period" was defined as the year of first patient inclusion in each cohort.

Outcome events are reported as linearized occurrence rates (percentage per patient year). The rate for each event, calculated by dividing the number of events by the total follow-up in patient years, was calculated for each individual study and then pooled on a logarithmic scale using the inverse variance method within a random-effect model. When a certain event did not occur in an individual study, we set the number of events to 0.5 to allow for inclusion of the study in pooling of the linearized occurrence rate for that particular event. When a certain event was not reported according to the guidelines for reporting mortality and morbidity after cardiac valve interventions (5) in an individual study, this study was excluded from the analysis of that particular event.

To assess the association of five variables (age, surgical period, proportion of patients with Marfan's disease, proportion of patients with acute type A aortic dissection, proportion of patients receiving a mechanical valve prosthesis with the Bentall procedure) with four important outcome events (late mortality, reoperation, major bleeding, major adverse valve-related events), linear regression was performed with correction for age as a possible confounder. Regression analysis was weighted by study size according to the inverse variance method. To better characterize the patient population with Marfan's disease or other connective tissue disorders, Pearson's correlation coefficient was calculated to

analyze whether the proportion of patients with connective tissue disorder was correlated to age, proportion of patients with acute type A aortic dissection or proportion of patients receiving a mechanical valve prosthesis with the Bentall procedure.

Statistical heterogeneity between studies was assessed for each outcome event using the I^2 test. Publication bias was assessed for each outcome event by inspection of Funnel plots.

RESULTS

The systematic literature search identified 1,403 articles. Figure 1 illustrates the selection process that resulted in the inclusion of 46 articles in the systematic review and meta-analysis. Missing data was provided by the authors of the article by Van Duffel *et al* [6]. Characteristics of the included studies are summarized in Appendix 3 [2, 6-50].

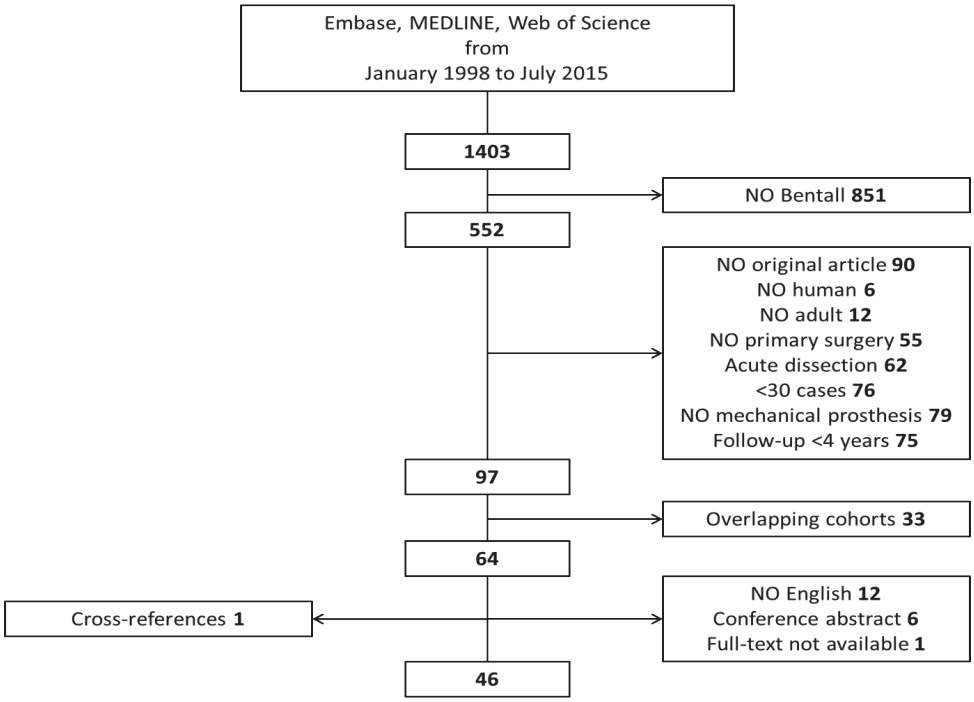


FIGURE 1. Flowchart of systematic literature search.

Pooled pre-operative and peri-operative characteristics are displayed in Table 1. Early mortality occurred in 422 patients (pooled early mortality 5.6%), there was no trend toward reduced operative mortality in more recent years. The article by Milano *et al*. was not included in this analysis because it only concerned hospital survivors [30].

TABLE 1. Pooled pre-operative and peri-operative characteristics

Variable		Pooled data	Range	Included studies (N)
Total patient number		**7629**	40 - 675	46
Surgical period		**1968 - 2012**		45
Mean age		**49.8 years**	29 – 65 years	44
Gender	Male	**76.3%**	55 – 91%	45
Comorbidity	Connective tissue disease	**22.6%**	0 – 100%	38
	Bicuspid aortic valve	**24.9%**	4 – 100%	17
Prior surgery	Cardiac	**16.2%**	1 – 37%	22
	Aortic valve	**11.8%**	0 – 30%	14
Other indications *	Acute type A dissection	**15.3%**	0 – 39%	43
	Active endocarditis	**2.0%**	0 – 15%	25
Emergency surgery		**15.8%**	0 – 43%	35
Other surgery types †	Homograft	**0.4%**	0 – 5%	43
	Valve-sparing	**2.2%**	0 – 27%	45
	Other	**0.9%**	0 – 41%	45
Valve type	Mechanical	**93.2%**	43 – 100%	40
	Biological	**6.8%**	0 – 57%	40
Reexploration for bleeding		**6.7%**	0 – 23%	28
Concomitant	Aortic hemiarch repair	**11.6%**	0 – 39%	28
	Aortic arch repair	**5.9%**	0 – 18%	26
	CABG	**11.9%**	0 – 31%	36
	Mitral valve surgery	**6.1%**	0 – 18%	36
Early mortality		**5.6%**	1 – 20%	46
Causes of early mortality ‡	Low cardiac output	**29.4%**		
	Hemorrhage	**8.5%**		
	Multiorgan failure	**7.8%**		
	Myocardial infarction	**5.9%**		
	Cardiac arrhythmias	**5.7%**		
	Unknown / unreported	**20.4%**		

CABG indicates coronary artery bypass grafting. * majority of patients underwent Bentall procedure for aortic root aneurysm with or without aortic valve insufficiency; † majority of patients received Bentall procedure; ‡ major causes of early mortality.

Mean follow-up after the Bentall procedure was 6.4 years (range 3.0 – 10.4 years) resulting in a total of 49,175 patient years. From four articles, it proved impossible to ascertain the exact number of late deaths [8, 20, 36, 45]. Although unknown or unreported in 47.9% of cases, the main causes of late mortality were low cardiac output (9.9%), distal aortic dissection or rupture (8.9%), hemorrhage (4.1%), stroke (3.8%), endocarditis (3.7%), cardiac arrhythmias (3.3%), other cardiac-related deaths (9.6%) and other non cardiac-related deaths (8.9%). The linearized occurrence rates of late mortality, reoperation on the aortic root, hemorrhage, thromboembolism, endocarditis and major adverse valve-related events are presented along with a measure of statistical heterogeneity in Table 2 and Appendix 4.

TABLE 2. Linearized occurrence rates of late outcome events

Pooled late outcome events	LOR + 95% CI	Heterogeneity (I^2)	Included studies (N)	Events (N)	Patient years (N)
Late mortality *	**2.02** (1.77 – 2.31)	70.60	42	892	41803
Valve-related mortality	**0.46** (0.36 – 0.59)	49.49	43	172	42845
Root reoperation †	**0.46** (0.36 – 0.59)	50.79	40	161	37231
Valve reoperation	**0.30** (0.22 – 0.41)	37.27	35	87	32423
Hemorrhage	**0.64** (0.47 – 0.87)	67.91	31	174	29234
Thromboembolism	**0.77** (0.60 – 1.00)	72.08	30	291	36318
Endocarditis	**0.39** (0.33 – 0.46)	0.00	31	125	35638
MAVRE	**2.66** (2.17 – 3.24)	79.35	20	531	19839

*Including valve-related mortality. † Including valve reoperation. LOR indicates linearized occurrence rates; CI, confidence interval; MAVRE, major adverse valve-related events.

The proportion of patients with a connective tissue disorder was correlated with age (coefficient -0.671, P<0.001), proportion of patients with a BAV (coefficient -0.482, P=0.069) and proportion of patients with acute aortic dissection (coefficient 0.370, P=0.024).

A more recent surgical period was associated with a decreased hazard of reoperation on the aortic root (beta = -0.452, P=0.015). Use of a mechanical valve prosthesis was also associated with a decreased hazard of reoperation on the aortic root (beta = -0.425, P=0.011). The other analyses did not show significant associations.

Inspection of funnel plots revealed asymmetry, with smaller studies showing consistently lower event rates than studies with large patient numbers.

Comment

This systematic review offers cardiologists and cardiac surgeons a unique and up-to-date overview of long-term outcome following the Bentall procedure. We have shown that surgical centers worldwide have performed the Bentall procedure in a highly heterogeneous patient population with respect to patient age, indication for surgery, comorbidities and concomitant procedures. This is corroborated by the demonstration of substantial statistical heterogeneity.

The findings of the systematic review and meta-analysis, which represent the real-world experience with the Bentall procedure, may be used by individual surgeons or surgical centers to benchmark their experience with the procedure. In addition, the meta-analysis will allow comparison of the gold standard in aortic root aneurysm surgery with novel therapeutic approaches such as valve-sparing aortic root replacement and personalized external aortic root support (PEARS) [51].

In the Society of Thoracic Surgeons database, early mortality in adult patients receiving root reconstruction with a valved conduit, including patients with acute endocarditis and those operated non-electively, operated between 2000 and 2011 was 8.9% [52]. Therefore, our finding of pooled early mortality of 5.6% appears excellent, especially when taking into account that many of our patients were operated several decades ago. However, while the Society of Thoracic Surgeons database represents daily clinical practice, our finding of pooled early mortality may have been influenced by publication bias and/or selective outcome reporting.

Given the mean age and comorbidities of the patient population, pooled late mortality is acceptable. The reported incidence of both major bleeding and thromboembolic complications is substantial accounting for a combined cumulative incidence of 14.1% at ten years. The reported low incidence of prosthetic valve endocarditis following the Bentall procedure is encouraging. However, major adverse valve-related events are common after the Bentall procedure with a cumulative incidence of 26.6% at ten years. Despite the lower linearized occurrence rates of reoperation in patients operated in more recent years, no such trend is apparent for late mortality, major bleeding, thromboembolic complications and endocarditis. Major bleeding and thromboembolic complications are strongly correlated with use of oral anticoagulation and mechanical valve implantation, respectively. Therefore, it may prudent to advise a different surgical approach in selected patients.

In this systematic review and meta-analysis, patients with Marfan's disease or other connective tissue disorders were on average younger and more often presented with acute aortic dissection. Interestingly, hazards of late mortality, reoperation, major bleeding and major adverse valve-related events were not associated with the presence of connective tissue disease. Five studies in this systematic review focused specifically on aortic root surgery in patients with connective tissue disease [7, 10, 15, 20, 53]. The pooled linearized occurrence event rates from these studies were comparable to the rates reported in Table 2, except for reoperation (1.01% versus 0.46% per year). In contrast, in a meta-analysis from Benedetto *et al*. focusing on Marfan's disease, the linearized occurrence rate for reoperation after the Bentall procedure is reported as 0,3% per year [54]. Our reported high reoperation rate in the studies focused on connective tissue disease can be attributed to poor results from one study with an estimated freedom from reoperation of only 67.1% at ten years. This study was not included in the meta-analysis from Benedetto *et al*. [15].

According to the recent American Heart Association / American College of Cardiology valvular heart disease guidelines, a mechanical valve prosthesis is not recommended in patients in whom use of oral anticoagulation is either contraindicated or not desired [55]. For instance, use of oral anticoagulation may not be desired in women who may wish to become pregnant in the future or in high performance athletes. In this meta-analysis, no association was shown between implantation of a mechanical valve prosthesis and occurrence of major valve-related events, including major bleeding and thromboembolic complications. Implantation of a mechanical valve prosthesis was associated with lower hazard of reoperation. In one study included in this meta-analysis with 57% of patients receiving a biological valve substitute, the authors described a higher freedom from thromboembolic complications at ten years in these patients [40]. Interestingly, the majority of manuscripts included in this meta-analysis that reported on a substantial proportion of patients (>10%) receiving a biological valve substitute did not analyze the association between the choice of valve substitute and outcome measures. The only other study to do so, showed similar late survival in both groups [6].

The guidelines also state that choice of both valve intervention and prosthesis type should be an informed, shared decision. This is especially important in aortic valve disease, as the choice between available options is often highly value-sensitive. Therefore, patients and surgeons should discuss and explore all available options, including implantation of a bioprosthesis, valve-sparing aortic root replacement and perhaps even considering novel therapeutic approaches in selected patients such as PEARS [51].

In this light, we compared our findings to those from a systematic review and meta-analysis on outcome after valve-sparing aortic root replacement published by Arabkhani et al. [56]. Pooled data from 4,777 patients with a follow-up of 21,716 patient years show that reinterventions are more common after valve-sparing aortic root replacement than after the Bentall procedure. Interestingly, rates of early and late mortality as well as late hemorrhage and thromboembolic complications were substantially lower after valve-sparing aortic root replacement. Patient characteristics, such as age at the time of operation, proportion of patients with connective tissue disease and aortic arch repair were similar between the two studies. However, differences in surgical era between the studies may explain why differences in early and late mortality were so striking. Nonetheless, the comparison clearly illustrates that valve-sparing aortic root replacement offers a great promise for the future.

To improve decision making, detailed and up-to-date information on long-term outcome of the available techniques is required. In this light, we strongly support projects such as the recently initiated AVIATOR registry; a prospective international registry of patients undergoing surgery, including the Bentall procedure and valve-sparing root replacement, for ascending aorta aneurysm and/or isolated aortic regurgitation.

Limitations

Statistical heterogeneity limits application of our findings for use in individual patients and precluded use of meta-regression. Heterogeneity is likely the result of large diversity in patient characteristics as well as the large time period in which surgery was performed.

When interpreting the findings, it is important to realize that the presented pooled outcome measures may underestimate the actual occurrence of late mortality and morbidity following the Bentall procedure as most included studies were of a retrospective nature. In addition, publication bias may have contributed to lower mean linearized occurrence rates.

Several studies included in the systematic review did not adhere to the available guidelines on reporting after heart valve interventions [5]. Therefore, it was not always possible to extract (reliable) information on the important outcome measures.

Lack of access to individual patient data precluded use of more robust outcome measures than the linearized occurrence rate. The main concern with linearized occurrence rates is that many biological events occur in a non-linear fashion.

CONCLUSIONS

Published experience with the Bentall procedure with a mechanical valve prosthesis is extensive in a diverse patient population. Over the years, rates of aortic root reoperation have decreased. However, rates of late mortality, major bleeding and thromboembolic complications, associated with the use of a mechanical valve prosthesis, remain a concern. In this light, we encourage using this report as a benchmark to assess the potential therapeutic benefit of novel surgical approaches, such as valve-sparing aortic root replacement.

REFERENCES

1. Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. Thorax. 1968;23(4):338-9.
2. Aomi S, Nakajima M, Nonoyama M, et al. Aortic root replacement using composite valve graft in patients with aortic valve disease and aneurysm of the ascending aorta: Twenty years' experience of late results. Artif Organs. 2002;26(5):467-73.
3. Girardi LN. Composite Root Replacement with a Mechanical Conduit. Oper Tech Thorac Cardiovasc Surg. 2008;13(3):148-60.
4. David TE, Armstrong S, Manlhiot C, McCrindle BW, Feindel CM. Long-term results of aortic root repair using the reimplantation technique. J Thorac Cardiovasc Surg. 2013;145(3 Suppl):S22-5.
5. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg. 2008;85(4):1490-5.
6. Van Duffel DV, Van Gemert RV, Starinieri P, et al. Elective reconstruction of the ascending aorta for aneurismal disease restores normal life expectancy. An analysis of risk factors for early and late mortality. Acta Cardiol. 2013;68(4):349-53.
7. Alexiou C, Langley SM, Charlesworth P, Haw MP, Livesey SA, Monro JL. Aortic root replacement in patients with Marfan's syndrome: The Southampton experience. Ann Thorac Surg. 2001;72(5):1502-7.
8. Brandt M, Abdelkerim S, Clemm S, Boning A, Cremer J. Composite valve graft versus separate aortic valve and ascending aortic replacement. Cardiology. 2004;102(3):156-9.
9. Byrne JG, Gudbjartsson T, Karavas AN, et al. Biological vs. mechanical aortic root replacement. European Journal of Cardio-Thoracic Surgery. 2003;23(3):305-10.
10. Carrel T, Beyeler L, Schnyder A, et al. Reoperations and late adverse outcome in Marfan patients following cardiovascular surgery. European Journal of Cardio-Thoracic Surgery. 2004;25(5):671-5.
11. Caynak B, Sagbas E, Onan B, et al. Comparison of three different surgical methods in aortic root aneurysms: Long-term results. J Card Surg. 2009;24(6):710-5.
12. Dunne B, Marr T, Andrews D, Larbalestier R, Edwards M, Merry C. Aortic root replacement for ascending aortic disease: A 10 year review. Heart Lung Circul. 2013;22(2):81-7.
13. Etz CD, Bischoff MS, Bodian C, et al. The Bentall procedure: Is it the gold standard? A series of 597 consecutive cases. J Thorac Cardiovasc Surg. 2010;140(6 SUPPL.):S64-S70.
14. Etz CD, Girrbach FF, von Aspern K, et al. Longevity after aortic root replacement: is the mechanically valved conduit really the gold standard for quinquagenarians? Circulation. 2013;128(11 Suppl 1):S253-62.
15. Gao L, Zhou X, Zhang L, et al. Factors influencing prognosis in patients with Marfan syndrome after aortic surgery. J Cardiothorac Vasc Anesth. 2011;25(4):625-31.

16. Gelsomino S, Masullo G, Morocutti G, et al. Sixteen-year results of composite aortic root replacement for non-dissecting chronic aortic aneurysms. Ital Heart J. 2003;4(7):454-9.
17. Girdauskas E, Rouman M, Borger MA, Kuntze T. Comparison of aortic media changes in patients with bicuspid aortic valve stenosis versus bicuspid valve insufficiency and proximal aortic aneurysm. Interact Cardiovasc Thorac Surg. 2013;17(6):931-6.
18. Gott VL, Greene PS, Alejo DE, et al. Replacement of the aortic root in patients with Marfan's syndrome. N Engl J Med. 1999;340(17):1307-13.
19. Joo HC, Chang BC, Youn YN, Yoo KJ, Lee S. Clinical experience with the Bentall procedure: 28 years. Yonsei Med J. 2012;53(5):915-23.
20. Karck M, Kallenbach K, Hagl C, et al. Aortic root surgery in Marfan syndrome: Comparison of aortic valve-sparing reimplantation versus composite grafting. J Thorac Cardiovasc Surg. 2004;127(2):391-8.
21. Kim TS, Na CY, Oh SS, Kim JH. Long-term mortality and morbidity after button bentall operation. J Card Surg. 2013;28(3):280-4.
22. Kindo M, Billaud P, Gerelli S, Levy F, Mazzucotelli JP, Eisenmann B. Twenty-seven-year experience with composite valve graft replacement of the aortic root. J Heart Valve Dis. 2007;16(4):370-7.
23. Lim JY, Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Surgical Management of Aortic Root Dilatation with Advanced Aortic Regurgitation: Bentall Operation versus Valve-sparing Procedure. Korean j thorac cardiovasc surg. 2012;45(3):141-7.
24. Luciani GB, Casali G, Barozzi L, Mazzucco A. Aortic root replacement with the carboseal composite graft: 7-year experience with the first 100 implants. Annals of Thoracic Surgery. 1999;68(6):2258-62.
25. Malashenkov AI, Rusanov NI, Muratov RM, et al. Eight years clinical experience with the replacement of the ascending aorta using composite xenopericardial conduit. Eur J Cardio-thorac Surg. 2000;18(2):168-73.
26. Mataraci I, Polat A, Kiran B, et al. Long-Term Results of Aortic Root Replacement: 15 Years' Experience. Ann Thorac Surg. 2009;87(6):1783-8.
27. Maureira P, Vanhuyse F, Martin C, et al. Modified bentall procedure using two short grafts for coronary reimplantation: Long-term results. Ann Thorac Surg. 2012;93(2):443-9.
28. Mazzola A, Di Mauro M, Pellone F, et al. Freestyle aortic root bioprosthesis is a suitable alternative for aortic root replacement in elderly patients: a propensity score study. Ann Thorac Surg. 2012;94(4):1185-90.
29. Meharwal ZS, Khanna SN, Choudhary A, Misha M, Mehta Y, Trehan N. Ascending aortic aneurysm resection: 15 year's experience. Asian Cardiovasc Thorac Ann. 2006;14(4):300-5.
30. Milano AD, Pratali S, Mecozzi G, et al. Fate of coronary ostial anastomoses after the modified Bentall procedure. The Annals of thoracic surgery. 2003;75(6):1797-801.
31. Mingke D, Dresler C, Stone CD, Borst HG. Composite graft replacement of the aortic root in 335 patients with aneurysm or dissection. Thoracic and Cardiovascular Surgeon. 1998;46(1):12-9.

32. Nakahira A, Shibata T, Sasaki Y, et al. Outcome After the Modified Bentall Technique With a Long Interposed Graft to the Left Coronary Artery. Ann Thorac Surg. 2009;87(1):109-15.
33. Nardi P, Pellegrino A, Russo M, Saitto G, Bertoldo F, Chiariello L. Midterm results of different surgical techniques to replace dilated ascending aorta associated with bicuspid aortic valve disease. Ann Thorac Surg. 2013;96(5):1648-54.
34. Pacini D, Pantaleo A, Berretta P, et al. Long term results of aortic valve and root replacement in 1045 patients over thirty-three years. A single-centre experience. Circulation. 2011;124(21).
35. Panos A, Amahzoune B, Robin J, Champsaur G, Ninet J. Influence of technique of coronary artery implantation on long-term results in composite aortic root replacement. Ann Thorac Surg. 2001;72(5):1497-501.
36. Prifti E, Bonacchi M, Frati G, et al. Early and long-term outcome in patients undergoing aortic root replacement with composite graft according to the Bentall's technique. Eur J Cardio-thorac Surg. 2002;21(1):15-21.
37. Radu NC, Kirsch EWM, Hillion ML, Lagneou F, Drouet L, Loisance D. Embolic and bleeding events after modified Bentall procedure in selected patients. Heart. 2007;93(1):107-12.
38. Ruvolo G, Fattouch K, Sinatra R, et al. Factors influencing immediate and long-term results after button's technique. J Cardiovasc Surg. 2002;43(3):337-43.
39. Schachner T, Vertacnik K, Nagiller J, Laufer G, Bonatti J. Factors associated with mortality and long time survival in patients undergoing modified Bentall operations. J Cardiovasc Surg. 2005;46(5):449-55.
40. Sioris T, David TE, Ivanov J, Armstrong S, Feindel CM. Clinical outcomes after separate and composite replacement of the aortic valve and ascending aorta. J Thorac Cardiovasc Surg. 2004;128(2):260-5.
41. Sokullu O, Sanioglu S, Orhan G, et al. New use of Teflon to reduce bleeding: In modified Bentall operation. Tex Heart Inst J. 2008;35(2):147-51.
42. Tabayashi K, Fukujyu T, Turu Y, et al. Replacement of the ascending aorta and aortic valve with a composite graft: operative and long-term results. Tohoku J Exp Med. 1998;184(4):257-66.
43. Tamura K, Arai H, Kawaguchi S, et al. Long-term results of modified bentall procedure using flanged composite aortic prosthesis. Ann Thorac Cardiovasc Surg. 2013;19(2):126-30.
44. Tsunekawa T, Ogino H, Matsuda H, et al. Composite Valve Graft Replacement of the Aortic Root: Twenty-Seven Years of Experience at One Japanese Center. Ann Thorac Surg. 2008;86(5):1510-7.
45. van Putte BP, Ozturk S, Siddiqi S, Schepens MA, Heijmen RH, Morshuis WJ. Early and late outcome after aortic root replacement with a mechanical valve prosthesis in a series of 528 patients. Ann Thorac Surg. 2012;93(2):503-9.
46. Zafar MA, Farkas EA, Javier A, Anderson M, Gilani O, Elefteriades JA. Are Thromboembolic and Bleeding Complications a Drawback for Composite Aortic Root Replacement? Annals of Thoracic Surgery. 2012;94(3):737-43.

47. Zehr KJ, Orszulak TA, Mullany CJ, et al. Surgery for aneurysms of the aortic root - A 30-year experience. Circulation. 2004;110(11):1364-71.
48. Nishida T, Sonoda H, Oishi Y, et al. More than 20-year experience of Bentall operation with mechanical prostheses for chronic aortic root aneurysm. Gen Thorac Cardiovasc Surg. 2014;63(2):78-85.
49. Varrica A, Satriano A, de Vincentiis C, et al. Bentall operation in 375 patients: long-term results and predictors of death. J Heart Valve Dis. 2014;23(1):127-34.
50. Vendramin I, Meneguzzi M, Sponga S, et al. Bicuspid aortic valve disease and ascending aortic aneurysm: should an aortic root replacement be mandatory?dagger. Eur J Cardiothorac Surg. 2015.
51. Treasure T, Takkenberg JJ, Golesworthy T, et al. Personalised external aortic root support (PEARS) in Marfan syndrome: analysis of 1-9 year outcomes by intention-to-treat in a cohort of the first 30 consecutive patients to receive a novel tissue and valve-conserving procedure, compared with the published results of aortic root replacement. Heart. 2014;100(12):969-75.
52. Caceres M, Ma Y, Rankin JS, et al. Evolving Practice Trends of Aortic Root Surgery in North America. Ann Thorac Surg. 2014.
53. Mingke D, Dresler C, Pethig K, Heinemann M, Borst HG. Surgical treatment of Marfan patients with aneurysms and dissection of the proximal aorta. J Cardiovasc Surg. 1998;39(1):65-74.
54. Benedetto U, Melina G, Takkenberg JJ, Roscitano A, Angeloni E, Sinatra R. Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis. Heart. 2011;97(12):955-8.
55. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(23):2440-92.
56. Arabkhani B, Mookhoek A, Di Centa I, et al. Reported Outcome After Valve-Sparing Aortic Root Replacement for Aortic Root Aneurysm: A Systematic Review and Meta-Analysis. Ann Thorac Surg. 2015.

APPENDIX 1

Embase

(bentall:ab,ti OR (((‘aorta valve’/de OR ‘aorta valve replacement’/de OR ‘aorta valve prosthesis’/de OR ‘aorta valve disease’/exp OR (aort* NEAR/3 valv*):ab,ti) AND (‘aorta root’/de OR ‘aortic root surgery’/de OR (aort* NEAR/3 root*):ab,ti) AND (‘ascending aorta’/de OR ‘ascending aorta surgery’/de OR (ascend* NEAR/3 aort*):ab,ti)) AND (surgery/exp OR surgery:lnk OR (surg* OR graft* OR homograft* OR replace* OR composit* OR operat* OR postoperat*):ab,ti))) AND (survival/exp OR mortality/exp OR (surviv* OR mortal* OR ‘death rate’):ab,ti) NOT (‘case report’/de OR (‘case report’):ab,ti)

MEDLINE

(bentall.ab,ti. OR ((("aortic valve"/ OR (aort* ADJ3 valv*).ab,ti.) AND ((aort* ADJ3 root*).ab,ti.) AND ((ascend* ADJ3 aort*).ab,ti.)) AND ("Surgical Procedures, Operative"/ OR surgery.xs. OR (surg* OR graft* OR homograft* OR replace* OR composit* OR operat* OR postoperat*).ab,ti.))) AND (survival/ OR exp mortality/ OR mortality.xs. OR (surviv* OR mortal* OR "death rate").ab,ti.) NOT ("case reports".pt. OR ("case report").ab,ti.)

PubMed as supplied by publisher

(bentall[tiab] OR ((((aort*[tiab] AND valv*[tiab])) AND ((aort*[tiab] AND root*[tiab])) AND ((ascend*[tiab] AND aort*[tiab])))) AND ((surg*[tiab] OR graft*[tiab] OR homograft*[tiab] OR replace*[tiab] OR composit*[tiab] OR operat*[tiab] OR postoperat*[tiab]))))) AND ((surviv*[tiab] OR mortal*[tiab] OR death rate*[tiab])) NOT (case reports[pt] OR (case report[tiab])) AND publisher[sb]

The Cochrane Collaboration

(bentall:ab,ti OR ((((aort* NEAR/3 valv*):ab,ti) AND ((aort* NEAR/3 root*):ab,ti) AND ((ascend* NEAR/3 aort*):ab,ti)) AND ((surg* OR graft* OR homograft* OR replace* OR composit* OR operat* OR postoperat*):ab,ti))) AND ((surviv* OR mortal* OR ‘death rate’):ab,ti) NOT ((‘case report’):ab,ti)

Web of Science

TS=((bentall OR ((((aort* NEAR/3 valv*)) AND ((aort* NEAR/3 root*)) AND ((ascend* NEAR/3 aort*))) AND ((surg* OR graft* OR homograft* OR replace* OR composit* OR operat* OR postoperat*)))) AND ((surviv* OR mortal* OR "death rate")) NOT (("case report")))

APPENDIX 2

Variables	Description
First author	
Publication Year	
Journal	
Country	Country where patients were operated in
Operative period	
Patient Number	
Follow-up	Mean in years; calculated from median and interquartile range when mean was not given
Age	Mean in years; calculated from median and interquartile range when mean was not given
Sex	
CTD	
BAV	
Prior cardiac surgery	
Prior aortic valve surgery	
Acute type A dissection	As indication for Bentall procedure
Acute infective endocarditis	As indication for Bentall procedure
Emergency surgery	Within 24 hours after diagnosis
Homograft surgery	Patients with non-Bentall procedures
Valve-sparing surgery	Patients with non-Bentall procedures
Other surgery	Patients with non-Bentall procedures
Mechanical prosthesis	Valve choice for Bentall procedure
Bioprosthesis	Valve choice for Bentall procedure
Aortic hemiarch repair	
Aortic arch repair	
CABG	
Mitral valve surgery	
Reexploration for bleeding	In-hospital or within 30 days post-operatively
Early mortality	In-hospital mortality and 30 days mortality
Late mortality	According to guidelines (5)
Root reoperation	According to guidelines (5)
Hemorrhage	According to guidelines (5)
Thromboembolism	According to guidelines (5)
Endocarditis	According to guidelines (5)
MAVRE	Composite of late valve-related mortality, reoperation, hemorrhage, thromboembolism and endocarditis

CTD indicates connective disease; BAV, bicuspid aortic valve; CABG, coronary artery bypass grafting; MAVRE, major adverse valve-related events.

APPENDIX 3

First author	Publication year	Country	Operative period	Patients (N)	Mean age (years)	Sex (% female)	Mean follow-up (years)
Mingke	1998	Germany	1979-1996	79	33,8	30%	5,7
Tabayashi	1998	Japan	1974-1995	49	48,1		5,6
Gott	1999	United States	1968-1996	675	34	30%	6,7
Luciani	1999	Italy		190	54,5	22%	5,5
Malashenkov	2000	Russia	1989-1999	144	38,7	27%	4,3
Alexiou	2001	United Kingdom	1972-1998	65	41,7	37%	8
Panos	2001	France	1985-1999	150	55	21%	5,9
Aomi	2002	Japan	1980-1999	193	43,2	34%	5,8
Prifti	2002	Italy	1989-2000	212	56	26%	4,9
Ruvolo	2002	Italy	1989-1999	105	55,1	21%	4,3
Byrne	2003	United States	1992-2001	85		21%	4
Gelsomino	2003	Italy	1986-2002	45	58,7	16%	7,3
Milano*	2003	Italy	1993-1999	71	63	18%	4,1
Pacini	2003	Italy	1978-2001	274	53,5	20%	5,2
Brandt	2004	Germany	1981-2000	84	52,2	20%	10,4
Carrel	2004	Switzerland	1990-2003	71	29	45%	5,2
Karck	2004	Germany	1979-2012	74	35	34%	9,5
Sioris	2004	Canada	1990-2001	452	52,2	23%	4,4
Zehr	2004	United States	1971-2000	203	53	25%	7,3
Schachner	2005	Austria	1986-2002	74	48	18%	4,1
Meharwal	2006	India	1989-2004	148	46,2	12%	8,5
Kindo	2007	France	1975-2002	162	51,3	19%	6,1

Radu	2007	France	1993-2003	100	51	13%	4,4
Sokullu	2008	Turkey	2000-2006	44	53,4	16%	4,8
Tsunekawa	2008	Japan	1978-2005	273	47,5	34%	8,8
Caynak	2009	Turkey	1997-2007	54	57,9	11%	5
Mataraci	2009	Turkey	1993-2008	254	48,3	19%	6,3
Nakahira	2009	Japan	1992-2007	40	54,7	20%	5,7
Etz	2010	United States	1995-2008	290	51,3	20%	8,2
Gao	2011	China	1984-2008	125		25%	4
Joo	2012	Korea	1982-2010	218	44,4	31%	9
Lim	2012	Korea	1999-2009	72	49	38%	4,9
Maureira	2012	France	1995-2009	153	57	14%	5,8
Mazzola	2012	Italy	2001-2010	106	56	12%	4,5
Van Putte	2012	The Netherlands	1974-2008	528	53,8	24%	9
Zafar	2012	United States	1995-2011	242	52,8	19%	4,7
Dunne	2013	Australia	1999-2009	89	54	21%	5,6
Etz	2013	United States	1998-2011	448	52,8	21%	5,8
Girdauskas	2013	Germany	1995-2005	79	52,3	19%	9,1
Kim	2013	Korea	1997-2010	195	50,5	29%	
Nardi	2013	Italy	2005-2011	46	51	11%	4,2
Tamura	2013	Japan	1984-2010	73	52,7	34%	7
Van Duffel	2013	Belgium	1988-2012	72	64,8	36%	5,4
Varrica	2014	Italy	90-07	375	57,2	21%	8,2
Nishida	2015	Japan	75-13	71	50,1	18%	9,4
Vendramin	2015	Italy	94-10	77	55,7	9%	8,8

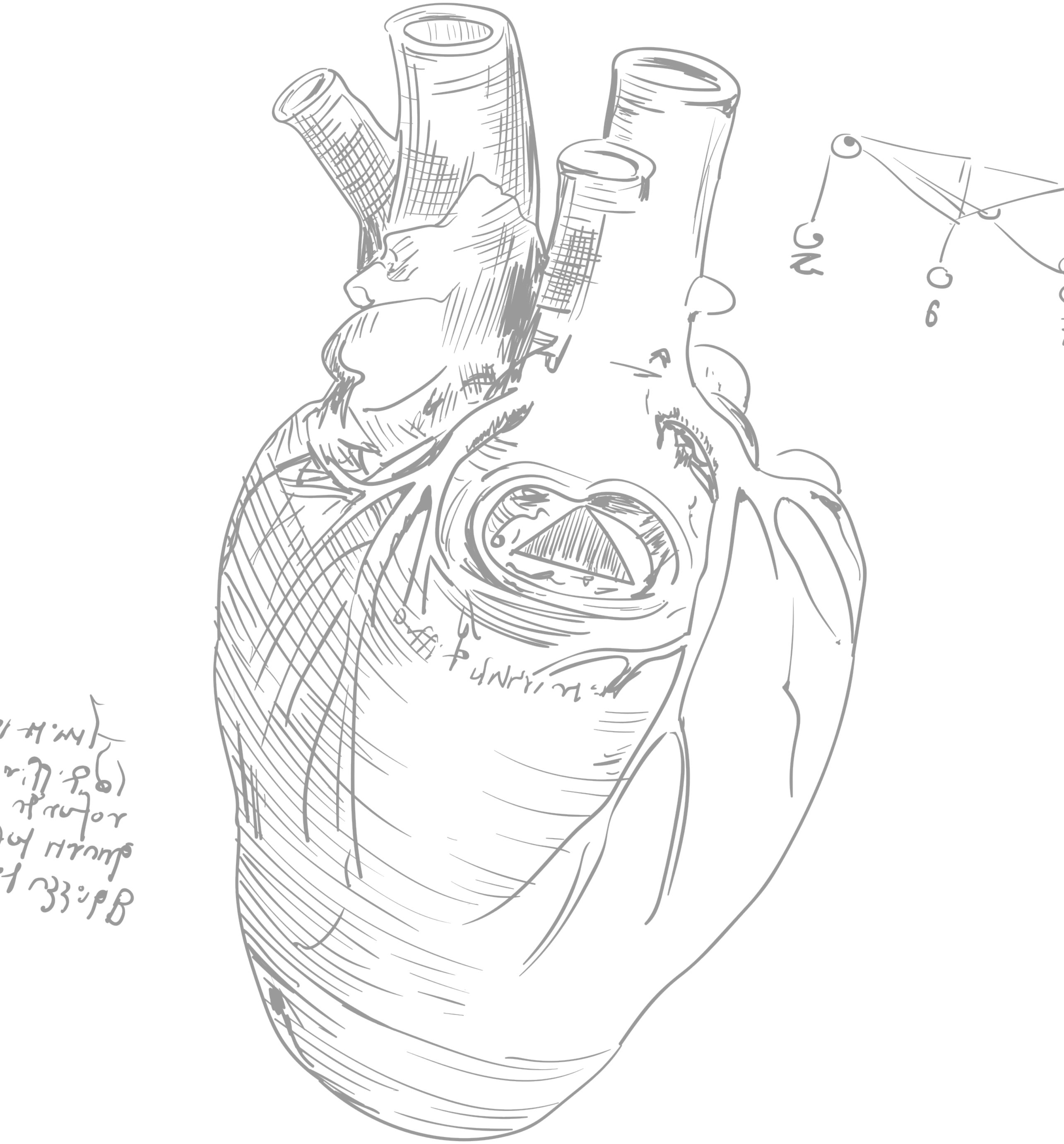
* Not included in analysis of early mortality, only patients who survived to discharge from hospital were included.

APPENDIX 4

First author	Publication year	Late mortality % / year	Root reoperation % / year	Hemorrhage % / year	Thromboembolism % / year	Endocarditis % / year	MAVRE % / year
Mingke	1998	2,23	0,89	0,45		0,45	
Tabayashi	1998	2,19			2,55		
Gott	1999	2,52			0,60	0,53	
Luciani	1999	0,94	0,31	0,31	0,16	0,16	0,63
Malashenkov	2000	1,96	0,49				
Alexiou	2001	2,89	0,39	0,96	0,96	0,19	2,89
Panos	2001	1,13	0,57				
Aomi	2002	2,31	0,35		1,42		
Prifti	2002					0,48	
Ruvolo	2002	2,72	1,02	0,34	0,34	0,68	3,06
Byrne	2003	2,94	0,59	0,59	0,59	0,59	2,35
Gelsomino	2003	1,30	0,22	0,11		0,43	
Milano	2003	1,72	0,17				
Pacini	2003	3,98	0,42	0,91	0,63	0,35	3,84
Brandt	2004		0,06				
Carrel	2004	0,81	0,81				
Karck	2004		0,85	1,71	0,71		
Sioris	2004	2,26	0,55	1,01	1,26	0,40	3,82
Zehr	2004	2,36	1,21	0,27	0,54	0,13	2,90
Schachner	2005	1,85	0,37	0,18	0,18	0,37	0,74
Meharwal	2006	1,43	0,24				
Kindo	2007	4,47	0,51	1,32	1,02	0,30	4,37

Radu	2007	2,75	0,11	2,29	3,21	0,11	5,95
Sokullu	2008	0,47	0,24				
Tsunekawa	2008	1,87	1,00	0,58	0,33	0,41	2,90
Caynak	2009	1,12	0,37			0,37	
Mataraci	2009	0,44	0,03	0,13	0,03	0,19	0,50
Nakahira	2009	2,19		0,44		1,32	
Etz	2010	2,12	0,09				
Gao	2011	2,03	2,03	0,20		0,20	
Joo	2012	2,19	0,10	0,41		0,15	
Lim	2012	1,42	0,28	1,13	0,14	0,14	1,70
Maureira	2012	2,43	0,21	1,27	0,42	0,21	3,07
Mazzola	2012	1,66	0,10	0,10	0,62		
Van Putte	2012				1,62	0,42	
Zafar	2012	1,69		0,89	1,07	0,27	
Dunne	2013	1,01	0,10			0,40	
Etz	2013	3,62	0,54	0,19	0,77		
Girdauskas	2013	1,74	0,58	0,14	0,87	0,58	3,19
Kim	2013	1,27	0,17	1,87	0,59	0,25	3,23
Nardi	2013	1,57	0,26	0,52	0,52	0,52	1,57
Tamura	2013	2,36	0,20	0,10	0,10		
Van Duffel	2013	1,80	0,13	0,52	0,26		
Varrica	2014	3,30	0,15	1,20	0,75	0,30	3,15
Nishida	2015	2,23	0,15	0,07	0,07	0,15	1,04
Vendramin	2015	1,04	0,42	0,02	0,59	0,29	1,56

Linearized occurrence rates of late outcome events. MAVRE indicates major adverse valve-related events



CHAPTER 4

Mechanical aortic valve replacement in non-elderly adults: meta-analysis and Microsimulation

Nelleke M. Korteland; Jonathan R.G. Etnel; Bardia Arabkhani; M. Mostafa Mokhles; Arezo Mohamad; Jolien W. Roos-Hesselink; Ad J.J.C. Bogers; Johanna J.M. Takkenberg

European Heart Journal, article in Press

ABSTRACT

Aims. To support decision-making regarding prosthetic valve selection in non-elderly adults, we aim to provide a detailed overview of outcome after contemporary mechanical aortic valve replacement (AVR).

Methods and Results. A systematic review was conducted for papers reporting clinical outcome after AVR with bileaflet mechanical valves with a mean patient age ≥18 and ≤55 years, published between 1/1/1995 and 31/12/2015. Through meta-analysis outcomes were pooled and entered into a microsimulation model to calculate (event-free) life expectancy and lifetime event risk.

Twenty-nine publications, encompassing a total of 5728 patients with 32515 patient-years of follow-up (pooled mean follow-up: 5.7 years), were included. Pooled mean age at surgery was 48.0 years. Pooled early mortality risk was 3.15%(95%CI:2.37-4.23), late mortality rate was 1.55%/year(95%CI:1.25-1.92); 38.7% of late deaths were valve-related. Pooled thromboembolism rate was 0.90%/year(95%CI:0.68-1.21), major bleeding 0.85%/year(95%CI:0.65-1.12), nonstructural valve dysfunction 0.39%/year(95%CI:0.21-0.76), endocarditis 0.41%/year(95%CI:0.29-0.57), valve thrombosis 0.14%/year(95%CI:0.08-0.25), structural valve deterioration 0.00%/year(zero events observed), and reintervention 0.51%/year(95%CI:0.37-0.71), mostly due to nonstructural valve dysfunction and endocarditis. For a 45-year-old, for example, this translated to an estimated life expectancy of 19 years (general population: 34 years) and lifetime risks of thromboembolism, bleeding and reintervention of 18%, 15% and 10%, respectively.

Conclusions. This study demonstrates that outcome after mechanical AVR in non-elderly adults is characterized by suboptimal survival and considerable lifetime risk of anticoagulation-related complications, but also reoperation. Non-elderly adult patients who are facing prosthetic valve selection are entitled to conveyance of evidence-based estimates of the risks and benefits of both mechanical and biological valve options in a shared decision-making process.

INTRODUCTION

Aortic valve replacement (AVR) is the most widely used surgical treatment for aortic valve disease in non-elderly adults. When valve repair is not possible, two types of valve substitutes are available: mechanical and biological valves. The primary advantage of mechanical valves is their durability. They do, however, require lifelong anticoagulation due to their increased thrombogenicity, which gives rise to a substantial risk of thromboembolic and bleeding complications that may have an important impact on quality of life.[1] Furthermore, patients are faced with the hassle of INR regulation, the valve sound and, in the case of a woman with pregnancy wishes, the hazards of anticoagulation during pregnancy. Biological valves do not require long-term anticoagulation unless another indication is present. However, they are subject to valve deterioration over time and young patients, in particular, may require a reoperation later in life.[2]

Since all currently available valve substitutes have important limitations, younger patients who require AVR are facing a difficult choice. A mechanical valve is often recommended in non-elderly adult patients due to the lower, though not absent, rate of reoperation compared with biological valves. Subsequently, most non-elderly adult patients will face a lifelong risk of bleeding and thromboembolic events after their mechanical AVR. To improve decision-making with regard to prosthetic valve selection in non-elderly adults, detailed and up-to-date information on mechanical valve-related mortality and morbidity is required. To gain insight in morbidity and mortality after contemporary mechanical AVR in non-elderly adults, we aim to provide an overview of published evidence by conducting a systematic review and meta-analysis of reported outcome. Furthermore, we aim to estimate age-specific life expectancy and lifetime risk of valve-related events with the use of a microsimulation model based on the results of our meta-analysis.

METHODS

This systematic review was conducted according to the PRISMA guidelines.[3] This study was approved by the institutional review board and informed consent was waived (MEC-2015-170).

Literature search

On December 7, 2015, a systematic literature search was conducted in Embase, MEDLINE, The Cochrane Collaboration and Web of Science by a biomedical information specialist (Supplement 1). All studies were screened by two independent reviewers (NMK, JRGE). Studies reporting survival after contemporary AVR with a mechanical valve in patients with a mean age ≥18 and ≤55 years published in English after 1/1/1995 were considered for inclusion. Studies were included if >90% of the cohort received bileaflet prostheses. Studies limited to patients with preexisting comorbidities or patients with a history of previous AVR were excluded. Studies with a study size ≤20 patients or focusing only on certain prosthetic valve sizes or multiple valve replacement were also excluded.

In case of overlapping study populations, only the most recent or most complete study was included. In case of disagreement between the reviewers, a consensus was negotiated.

In case a full text publication was not available or information was missing the author was contacted by e-mail.

Data Extraction

Microsoft Office Excel (details in Supplement 5) was used for data extraction. The same pair of reviewers (NMK, JRGE) extracted the data independently. After data extraction, each reviewer verified the other reviewer's data entries. Recorded study characteristics, baseline patient and operative characteristics and outcome events are listed in Supplement 5. Morbidity and mortality were documented according to the guidelines.[4] Early outcome events were defined as occurring within the first 30 postoperative days, regardless of the patient's location, and late outcome events were defined as occurring after the first 30 postoperative days. If the total follow-up was not reported, it was calculated by multiplying the number of patients with the mean follow-up of that study.

Meta-analysis

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as counts and percentages. Linearized event occurrence rates are presented as percentages per year.

Pooled baseline patient characteristics were calculated with the use of sample size weighting. Early mortality risk and linearized occurrence rates of late mortality, reoperations and complications after AVR were calculated and pooled with the use of inverse variance weighting on a logarithmic scale, as the Shapiro-Wilk test revealed a significantly skewed distribution among the included studies in the majority of outcome measures. Inverse variance weighting was conducted according to the number of patients for early mortality and according to the number of patient-years of follow-up for late events. In case a particular event was reported not to occur in an individual study, then for the purpose of inverse variance weighting it was assumed that 0.5 patient experienced that event. A random-effects model was used to estimate pooled effects.

The Cochran Q statistic and the I^2 test were used to assess heterogeneity. Potential causes of heterogeneity were explored by investigating the effect of year of first inclusion, mean follow-up duration, case mix and study design (retrospective versus prospective/randomized controlled trial) by means of univariable random-effects meta-regression. Funnel plots were used to investigate publication bias. To investigate the potential influence of publication bias on pooled outcome, sensitivity analyses were conducted by temporarily excluding the smallest quartile (by sample size) of included studies. Statistical analyses were performed in Microsoft Office Excel, IBM SPSS Statistics and R (software details are listed in Supplement 5).

Microsimulation

A microsimulation model based on the pooled outcome estimates of our meta-analysis was used to calculate age-specific life expectancy and lifetime risk of valve-related morbidity.[5,6] The microsimulation model iteratively simulates individual patient lives after surgery, taking into account the morbidity and mortality events that the patient may experience. The simulated individual patient life histories are then aggregated to obtain estimates of population level outcome. The mortality of a patient is composed of the background mortality of the general population, operative mortality, mortality due

to valve-related events and an additional excess mortality component that is not a direct result of valve-related events, but is associated with underlying valve pathology, left ventricular function and other associated pathology.

The operative mortality risk, the occurrence rate of each valve-related event and the risk of mortality and reintervention as a direct result of each of these valve-related events were obtained from our meta-analysis. The occurrence rates of all events were assumed to be linear and non-age-dependent. The hazard ratios of the additional excess mortality not directly resulting from valve-related events have been previously estimated.[6] For patients aged 25, 35, 45 and 55, these hazard ratios were 5.5, 4.4, 2.9 and 1.8 for males and 7.0, 7.0, 4.2 and 2.8 for females, respectively. The background mortality of the general population was obtained from the 1996 United States Life Tables, as 1996 was the pooled median year of intervention (assuming a constant incidence rate over time in each study) and the majority of the included study population originated from, or was comparable to the United States population.[7]

To obtain age-specific estimates of life expectancy and lifetime risk of valve-related morbidity, the microsimulation model was run for the ages 25, 35, 45 and 55 years for 10,000 iterations each and separately for males and females. The age-specific outcomes of both genders were then pooled at the male/female ratio obtained from our meta-analysis (72.0% male).

For the purposes of internal validation, the model was additionally run for 10,000 iterations at the pooled mean age (48 years) and pooled male/female ratio of the included studies (72.0% male). The actuarial survival curve obtained from this model was then plotted against the pooled overall mortality observed in our meta-analysis.

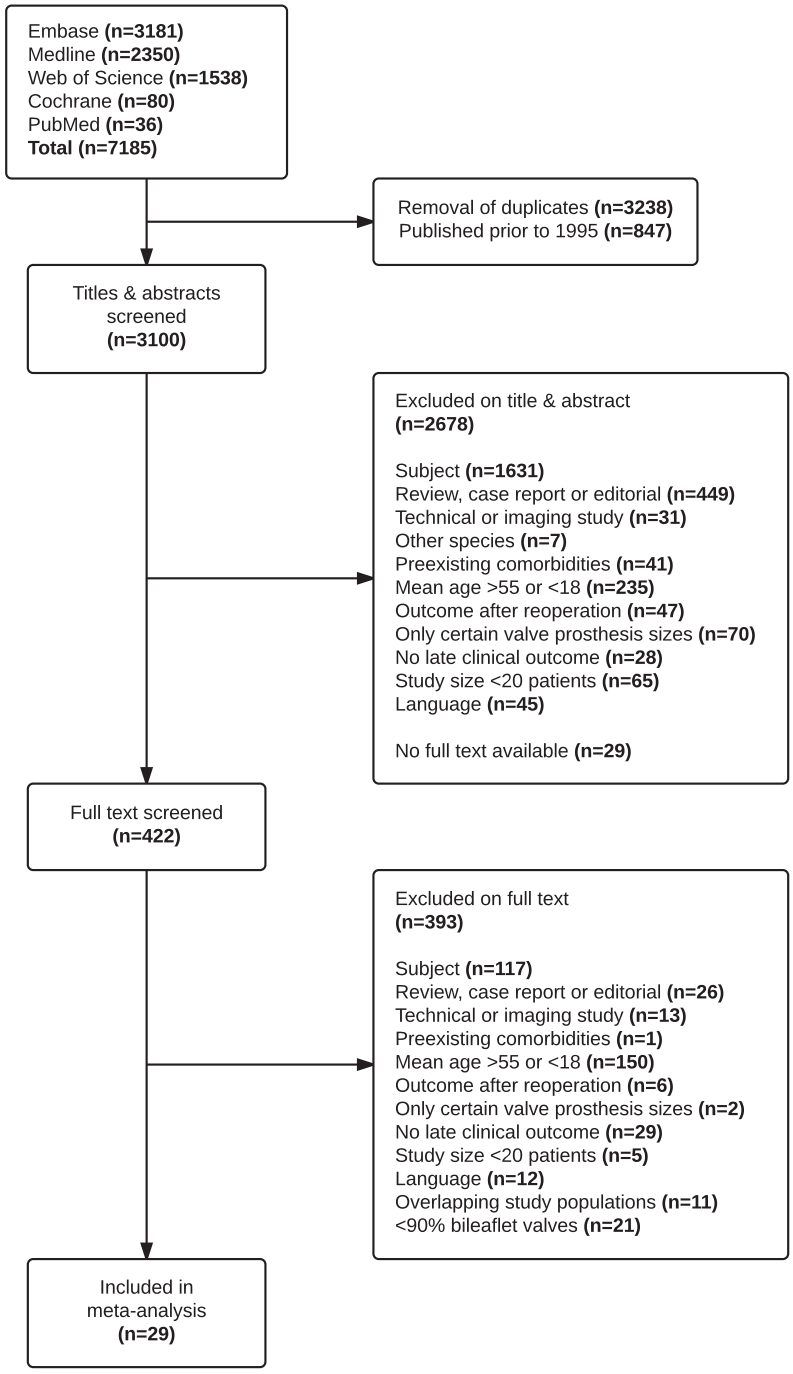


FIGURE 1. Flowchart of systematic literature search.

RESULTS

The systematic literature search identified 3100 publications, of which 29 were included in the meta-analysis, encompassing a total of 5728 patients with 32515 patient-years of follow-up (pooled mean follow-up: 5.7 years) (Figure 1). Supplement 2 represents the characteristics of the included studies (references listed in Supplement 6). Pooled baseline patient characteristics are shown in Table 1.

Pooled risks of early mortality and early complications and pooled linearized occurrence rates of late mortality and late morbid events are presented in Table 2 (individual study estimates are presented in Supplement 3).

TABLE 1. Pooled pre-operative and peri-operative characteristics.

Variable		Pooled data	Range	Included studies (N)
Total number of patients		5728	20–865	29
Mean age (years)		48.0	33.0–54.9	29
Gender	Male	72.0%	50.0–91.0%	23
Etiology	Degenerative	21.5%	0.0–78.0%	12
	Endocarditis	10.0%	0.0–100%	19
	Rheumatic	36.4%	0.0–77.8%	12
	Congenital	16.5%	0.0–57.0%	10
	Prosthetic valve dysfunction	3.8%	0.0–22.0%	14
	Other/unknown	11.7%	0.0–66.0%	13
Aortic valve hemodynamics	Stenosis	43.5%	0.0–100%	13
	Regurgitation	40.4%	0.0–70.0%	13
	Combined	16.2%	0.0–30.0%	12
Bicuspid aortic valve		24.5%	1.4–100%	4
Previous cardiac intervention		8.4%	0.0–26.0%	13
Emergency surgery		3.4%	0.0–35.0%	10
Prosthetic valve type	Bileaflet	99.9%	96.5–100%	29
	Tilting-disc	0.1%	0.0–3.5%	29
	Caged-ball	0.0%	0.0–0.0%	29
Concomitant procedures		22.2%	0.0–52.2%	11
	CABG	7.1%	0.0–17.5%	21
	Aortic surgery	8.6%	0.0–33.0%	11
	Multiple valve replacement	2.6%	0.0–24.6%	17

CABG=coronary artery bypass grafting.

TABLE 2. Pooled risk of early outcome events and linearized occurrence rates of late outcome events obtained from the meta-analysis.

Outcome events	Overall		
	Pooled estimate	Heterogeneity*	Included studies (N)
Early(<30 days)			
Early mortality(%)	3.15(2.37-4.21)	I^2=70%(p<0.001)	25
Re-exploration for bleeding(%)	5.15(2.57-11.81)	I^2=87%(p<0.001)	7
Pacemaker implantation(%)	3.53(2.47-5.05)	I^2=20%(p=0.289)	4
Deep sternal infection/mediastinitis(%)	2.48(1.56-3.94)	I^2=0%(p=0.409)	5
Endocarditis(%)	0.43(0.16-1.13)	I^2=0%(p=0.853)	7
Stroke(%)	1.55(0.98-2.46)	I^2=15%(p=0.312)	8
Transient ischemic attack(%)	0.81(0.38-1.72)	I^2=1%(p=0.400)	5
Myocardial infarction(%)	0.87(0.40-1.87)	I^2=0%(p=0.687)	5
Valve thrombosis(%)	0.30(0.09-1.05)	I^2=0%(p=0.782)	5
Peripheral bleeding(%)	0.41(0.15-1.09)	I^2=0%(p=0.756)	7
Late(>30 days)			
Late mortality(%/year)	1.55(1.25-1.92)~	I^2=83%(p<0.001)	29
-Cardiac death(%/year)	0.95(0.71-1.27)	I^2=70%(p<0.001)	22
-Valve-related death(%/year)	0.60(0.44-0.81)	I^2=64%(p<0.001)	24
-SUD(%/year)	0.37(0.26-0.54)	I^2=47%(p=0.011)	19
Reintervention(%/year)	0.51(0.37-0.71)	I^2=47%(p=0.011)	20
Thromboembolism(%/year)	0.90(0.68-1.21)#	I^2=79%(p<0.001)	25
Valve thrombosis(%/year)	0.14(0.08-0.25)	I^2=62%(p<0.001)	18
Bleeding(%/year)	0.85(0.65-1.12)#	I^2=67%(p<0.001)	26
SVD(%/year)	0.00†	-	15
NSVD(%/year)	0.39(0.21-0.76)	I^2=83%(p<0.001)	17
Endocarditis(%/year)	0.41(0.29-0.57)	I^2=34%(p=0.072)	19

*The reported p-values are the p-values of Cochran's Q test for heterogeneity. †There were zero events of SVD in the 15 studies that reported this outcome. The background mortality rate in the age- and gender-matched United States general population for the pooled year of surgery and length of follow-up of our cohort was 0.55%/year. #The background rates of thromboembolism and bleeding events in the age- and gender-matched general population were 0.12%/year and 0.03%/year, respectively (based on the Oxford Vascular Study[28]). Pooled estimates presented as "percentage (95% confidence interval)". SUD=sudden, unexplained death;SVD=structural valve deterioration;NSVD=nonstructural valve dysfunction.

Microsimulation-based age-specific estimates of (event-free) life expectancy and lifetime risk of valve-related morbidity are shown in Figure 2. The microsimulation model calibrated well with the pooled mortality observed in our meta-analysis over the first postoperative decade (Supplement 7). For a 45-year-old, for example, microsimulation-based estimated life expectancy was 19 years (general population: 34 years) and lifetime risks of thromboembolism, bleeding and reintervention were 18%, 15% and 10%, respectively.

The funnel plots showed evidence of possible publication bias in early mortality, late mortality, thromboembolism, and bleeding (Supplement 8). Sensitivity analyses showed that this potential publication bias did not substantially influence our pooled outcomes, as pooled outcomes remained largely unchanged after temporary exclusion of the smallest quartile of studies (before vs. after exclusion: early mortality [3.15% vs. 3.03%], late mortality [1.55%/year vs. 1.55%/year], thromboembolism [0.90%/year vs. 0.88%/year], bleeding rates [0.85%/year vs. 0.87%/year]).

Heterogeneity

There was substantial heterogeneity in early mortality, re-exploration for bleeding and all late outcome measures with the exception of structural valve deterioration (SVD) and endocarditis. Univariable random-effects meta-regression (Supplement 4) showed that studies with a longer mean follow-up reported lower early mortality ($p<0.001$), lower reintervention rates ($p=0.010$) and lower bleeding rates ($p=0.042$), although follow-up duration was moderately negatively correlated with concomitant CABG ($r=-0.37$) and earlier year of first inclusion ($r=-0.31$).

Etiology was another important factor associated with heterogeneity as a higher proportion of preoperative endocarditis appeared to be correlated with higher rates of late mortality ($p=0.008$) and NSVD ($p=0.002$), while a higher proportion of rheumatic etiology was associated with lower rates of NSVD ($p=0.004$). Bleeding and nonstructural valve dysfunction (NSVD) rates were higher in cohorts with a higher proportion of aortic stenosis (bleeding $p=0.026$; NSVD $p<0.001$) and, consequently, a lower proportion of aortic regurgitation (bleeding $p=0.003$; NSVD $p<0.001$), although there was a moderate-to-strong negative correlation between preoperative aortic valve stenosis (as opposed to regurgitation) and etiology (endocarditis $r=-0.71$; rheumatic $r=-0.37$). Lastly, higher proportions of emergency surgeries ($p=0.007$) and concomitant CABG ($p=0.046$) were associated with higher rates of NSVD and a higher proportion of concomitant procedures was associated with higher reported early mortality risk ($p=0.045$). We were unable to

find any explanatory variables for the heterogeneity in thromboembolism and valve thrombosis rates. Differences in study design, year of first inclusion and previous cardiac interventions were not associated with heterogeneity in any of the outcome measures. Meta-regression was not conducted for re-exploration for bleeding due to limited sample size.

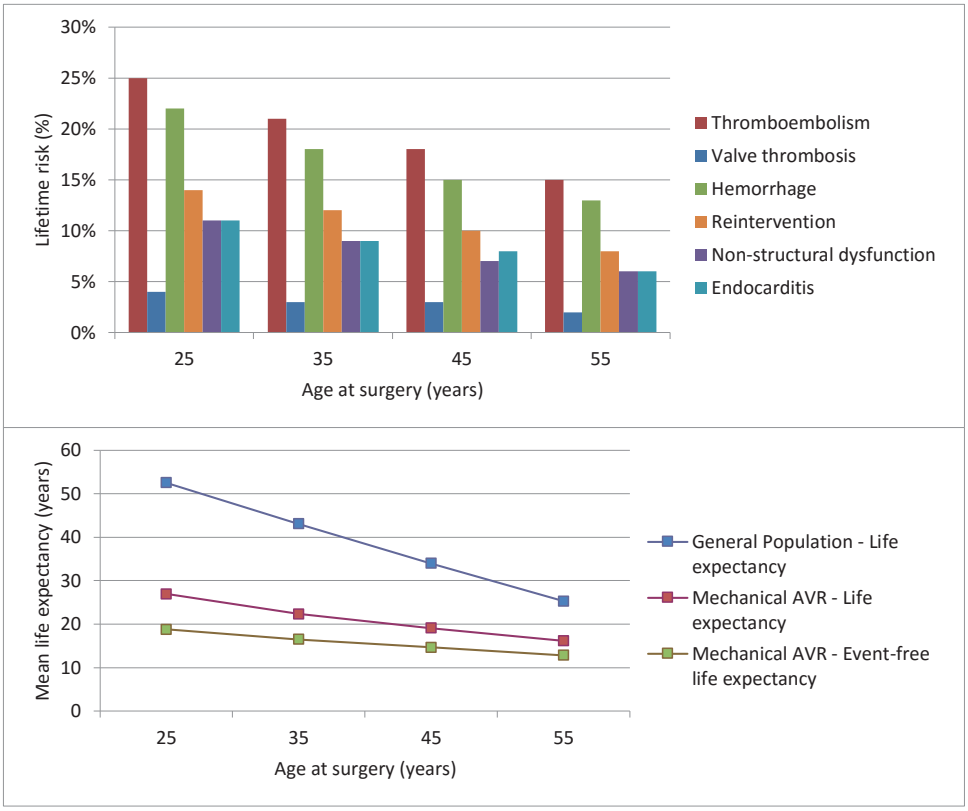


FIGURE 2. Microsimulation-based age-specific life expectancy and lifetime risk of valve-related morbidity. AVR=aortic valve replacement.

DISCUSSION

This study offers an overview of reported mortality and morbidity after single mechanical AVR in non-elderly adult patients and microsimulation-based age-specific estimates of expected lifetime outcome. It confirms the excellent long-term durability of mechanical valves in these patients, but also underlines the substantial late cardiovascular death and anticoagulation-related complication hazards after mechanical AVR. Although no cases of SVD were observed after contemporary AVR with currently available mechanical valves, microsimulation revealed a considerable lifetime risk of reintervention in this subgroup that ranged from 15% for patients aged 25 years at surgery to 8% for 55-year-olds, mostly due to NSVD and endocarditis. Most notably however, the combined lifetime risk of thromboembolism, valve thrombosis and bleeding ranged from 53% for patients aged 25 years at surgery to 30% for 55-year-olds. Life expectancy is substantially impaired in these patients compared with the general population and about 40% of deaths are valve-related.

Mortality

Elective, isolated mechanical AVR has been previously shown to be associated with significant excess mortality when compared with the general age-matched population.[8] In our meta-analysis we found a 3.15% early mortality risk and a substantial late mortality rate of 1.55%/year in patients with a pooled mean age of 48.0 years at the time of surgery. Microsimulation-based mean life expectancy after contemporary mechanical AVR ranged from 28 years for patients aged 25 years at surgery to 16 years for 55-year-olds, which is little over half the life expectancy of the age-matched general population. When taking the absent risk of SVD and subsequent reintervention associated with contemporary mechanical AVR into account, this mortality rate appears to be relatively high in comparison with other valve substitutes in non-elderly adults, such as the Ross procedure, which has been reported to be associated with lower late mortality in non-elderly adults compared with our pooled results after contemporary mechanical AVR (0.64%/year vs. 1.55%/year), while early mortality risk was comparable (3.24% vs. 3.15%).[9] Prosthetic valve-associated hemodynamic factors, such as prosthesis-patient mismatch, may play a role in this observed excess mortality.[10,11] Furthermore, the higher mortality after mechanical AVR may be attributable in part to the required anticoagulation treatment. In this regard, optimization of the anticoagulation therapy after mechanical AVR may offer a survival benefit in these patients. This is supported by a recent study by Mokhles et

al., which found that, with optimal self-management anticoagulation, mechanical AVR offers excellent late survival, comparable to the general age-matched population and to patients undergoing the Ross procedure.[12]

The survival differences between mechanical valves and other valve substitutes may be further explained by possible differences in patient characteristics, surgical technique and concomitant procedures performed at the time of AVR. Rheumatic valve disease being the most common etiology in present study (34% of our patients) may represent evidence of this possible selection bias.

Thromboembolism and bleeding

Present study underlines the burden of thromboembolism and bleeding after mechanical AVR in non-elderly patients as approximately half of patients aged 25 and 1 out of 3 patients aged 55 at the time of surgery are estimated to experience thromboembolism, valve thrombosis or bleeding events during their lifetime. This is most likely an underestimate as the included studies were largely retrospective in design, which may have given rise to recall bias. Anticoagulation related complications remain an important limitation of mechanical valve prostheses, especially in the young patients in which they are generally used, as there are serious implications for life-, career- and pregnancy-planning in these patients. However, optimizations of the required anticoagulation therapy such as self-management and lower dosing may be promising methods of reducing complication rates after mechanical AVR. There is increasing evidence that patients with contemporary mechanical valves and no comorbidities may be safely managed at a lower INR than currently recommended, subsequently reducing bleeding complications without increasing the risk of thromboembolic events.[13-15] Furthermore, advances in the design of mechanical valves may lead to reduced thrombogenicity. Mechanical valves specifically designed with this in mind have emerged, one of which has recently received FDA-approval for anticoagulation management at a lower INR than recommended by the guidelines.[15] Nevertheless, we did not find any evidence in this systematic review that thromboembolism and bleeding hazard has decreased in more recent years.

Pharmacological advances that provide more stable INR management may further reduce complication rates as studies have shown that, in patients treated with currently available anticoagulants, 25% of periodically measured INR values lie outside of the target range.[13]

Reintervention, (N)SVD and Endocarditis

Our results underline excellent long-term durability as the main advantage of mechanical valves, with negligible SVD rates. Although SVD remains a rare complication in mechanical valve recipients, depending on age at surgery, approximately 8%-15% of patients require reintervention during their lifetime, mostly due to NSVD (pannus formation, paravalvular leakage, etc.), valve thrombosis or prosthetic valve endocarditis. Although this risk of reintervention is very low compared with other valve substitutes in non-elderly adults, it is not absent and should always be taken into consideration and discussed with the patient when prosthetic valve selection is addressed.

Prosthetic valve selection

In prosthetic valve selection, mechanical valve-associated thromboembolism and bleeding risk is generally weighed against the risk of SVD and subsequent reintervention associated with biological valve substitutes. In non-elderly patients a mechanical valve is often recommended due to the limited durability of biological alternatives. However, the durability of modern bioprostheses is improving. These improvements as well as improved outcomes in reoperative aortic valve surgery and the prospect of transcatheter valve-in-valve replacement of failing bioprostheses has led to an increase in their use in younger patients.[16-21] Additionally, the Ross procedure represents another valuable option in these patients that avoids the need for long-term anticoagulation and provides superior long-term survival, excellent hemodynamic performance and a low risk of endocarditis in selected patients when performed in centers of expertise. Due to the continued improvements in bioprosthetic AVR and the option of the Ross procedure, the substantial risk of mechanical valve-related complications, as delineated by our results, will become more prominent in the process of prosthetic valve selection. Furthermore, although the risk of reintervention after mechanical AVR is low, it is certainly not absent and should also be taken into consideration in the process of prosthetic valve selection. This also applies to the risk of thromboembolism and bleeding after AVR with biological alternatives. Besides clinical factors, the benefits and limitations of each option have substantial implications for life-, career- and pregnancy planning in these patients. Therefore, conveyance of patient-tailored evidence-based risks and benefits of both mechanical and biological valve options in a shared decision-making process is of great importance.[2,22] Innovative solutions such as patient information portals and decision aids may prove useful in this setting.[23]

Heterogeneity

Although heterogeneity was considerable in our meta-analysis and may have potentially influenced the results, we pursued a thorough examination of possible sources of heterogeneity. Etiology and concomitant procedures appear to be important factors of influence on the reported outcomes, which is in line with expectations based on the literature.[24,25] Furthermore, we found aortic regurgitation vs. stenosis to be associated with more favorable reported outcome with regard to bleeding and NSVD rates, while regurgitation has been previously described to be associated with less favorable outcome. [24] This discrepancy may be explained by the strong correlation we found in our meta-regression between aortic valve hemodynamics and etiology (studies with a higher proportion of stenosis had lower proportions of endocarditis and rheumatic etiology), which may have confounded the results.

Lastly, although there were no consistent evidence thereof in our analyses, the year of operation, ranging from 1977-2014 among the included studies, may still have affected the results, as case-mix may have changed over the years and evolution of operative techniques may have led to lower operative risk.

Although this observed heterogeneity might have introduced uncertainty in our meta-analysis, with the use of a random-effects model, this uncertainty is incorporated in the reported pooled outcome estimates.

The asymmetry we found in our funnel plots may represent evidence of possible publication bias. However, assessment of publication bias in absolute risk outcomes, as were all of our outcomes, is associated with substantial methodological limitations which may in itself give rise to funnel plot asymmetry.[26] Our funnel plots should therefore be interpreted with caution. Although a conclusive investigation of publication bias may not be possible, our sensitivity analyses show that any potential publication bias did not substantially influence our pooled outcomes.

Limitations

The present study is a systematic review and meta-analysis of observational studies, most of which are retrospective in design. As such, the inherent limitations of meta-analyses and combining data from retrospective observational studies should be taken into consideration.[27] Selection bias may have affected the observed outcomes, as unpublished data, abstracts and presentations were not included. Among the included studies, baseline

and surgical characteristics were not reported in sufficient detail and consistently enough for us to fully account for all baseline covariates in our meta-analyses. Direct comparisons with alternative valve prostheses is hampered by the lack of published comparative data. Setting a time limit to systematic literature searches may introduce potential bias, but we chose to do so in our aim to provide an overview of contemporary outcome. Finally, there are some limitations to the microsimulation model that should be taken into account. The relationship of the occurrence rates of valve-related events after mechanical AVR with age, follow-up duration and history of previous valve-related events remains poorly defined and could, thus, not be incorporated into our microsimulation model. Uncertainty in the parameters within the model (second order uncertainty) was also not incorporated in our microsimulation model. The model requires assumptions to be made about the evolution of event occurrence rates beyond the observed follow-up period, which may have introduced uncertainty. Our United States general population-based background mortality estimate should be regarded as merely a reference point, as it may not be an ideal reflection of the general population mortality of the different countries that are represented in the individual studies in the review.

CONCLUSIONS

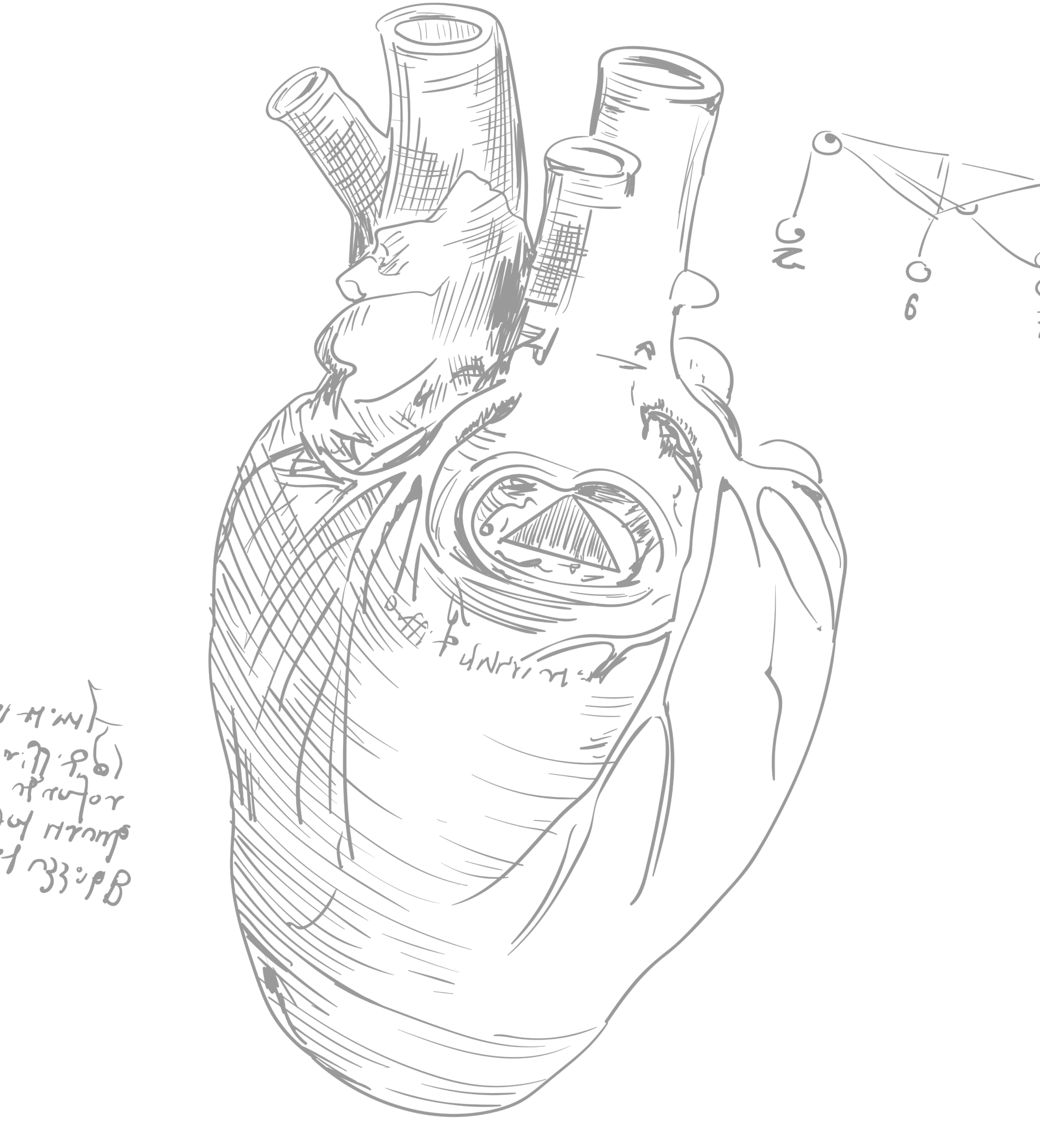
This review shows that the use of mechanical valves in non-elderly adult patients is associated with substantial excess mortality over time and considerable lifetime risk of anticoagulation-related complications, but also reoperation. This confirms the fact that non-elderly adult patients who require AVR are facing a difficult choice between mechanical and biological valves and, therefore, conveyance of patient-tailored evidence-based risks and benefits of both mechanical and biological valve options in a shared decision-making process is of great importance in the setting of prosthetic valve selection.

REFERENCES

1. Aicher D, Holz A, Feldner S, Kollner V, Schafers HJ. Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg 2011;142(2):e19-24.
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD, Members AATF. 2014 AHA/ACC Guideline 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. Circulation 2014;129(23):e521-643.
3. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine 2009;6(7):e1000097.
4. 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, Councils of the American Association for Thoracic S, Society of Thoracic S, European Assoication for Cardio-Thoracic S, Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve M. Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg 2008;135(4):732-8.
5. Takkenberg JJ, Puvimanasinghe JP, Grunkemeier GL. Simulation models to predict outcome after aortic valve replacement. Ann Thorac Surg 2003;75(5):1372-6.
6. Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, Steyerberg EW, van Herwerden LA, Grunkemeier GL, Habbema JD, Bogers AJ. Choice of a mechanical valve or a bioprosthesis for AVR: does CABG matter? Eur J Cardiothorac Surg 2003;23(5):688-95; discussion 695.
7. Anderson RN, National Center for Health Statistics (U.S.). *Method for constructing complete annual U.S. life tables*. Hyattsville, Md.: U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 1999.
8. Bouhout I, Stevens LM, Mazine A, Poirier N, Cartier R, Demers P, El-Hamamsy I. Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults. J Thorac Cardiovasc Surg 2013.
9. 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):222-8.
10. 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):1131-41.
11. 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;33(12):1518-29.

12. Mokhles MM, Kortke H, Stierle U, Wagner O, Charitos EI, Bogers AJJC, Gummert J, Sievers HH, Takkenberg JJM. Survival comparison of the ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: Propensity-matched cohort study. Circulation 2011;123(1):31-38.
13. 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.
14. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, De Santo L, De Feo M, Amarelli C, Sasso FC, Salvatore T, Ellison GM, Indolfi C, Cotrufo M, Nappi G. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: Results from the "IOWERING-IT" Trial. Am Heart J 2010;160(1):171-178.
15. Puskas J, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, Fermin L, McGrath M, Kong B, Hughes C, Sethi G, Wait M, Martin T, Graeve A. Reduced anticoagulation after mechanical aortic valve replacement: Interim results from the Prospective Randomized On-X Valve Anticoagulation Clinical Trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg 2014;147(4):1202-1211.E1202.
16. Ruel M, Chan V, Bedard P, Kulik A, Ressler L, Lam BK, Rubens FD, Goldstein W, Hendry PJ, Masters RG, Mesana TG. Very long-term survival implications of heart valve replacement with tissue versus mechanical prostheses in adults <60 years of age. Circulation 2007;116(11 SUPPL. 1):I294-I300.
17. Niclauss L, Von Segesser LK, Ferrari E. Aortic biological valve prosthesis in patients younger than 65 years of age: Transition to a flexible age limit? Interact Cardiovasc Thorac Surg 2013;16(4):501-508.
18. Une D, Ruel M, David TE. Twenty-year durability of the aortic Hancock II bioprosthesis in young patients: is it durable enough? Eur J Cardiothorac Surg 2014;46(5):825-30.
19. Potter DD, Sundt TM, 3rd, Zehr KJ, Dearani JA, Daly RC, Mullany CJ, McGregor CG, Puga FJ, Schaff HV, Orszulak TA. Operative risk of reoperative aortic valve replacement. J Thorac Cardiovasc Surg 2005;129(1):94-103.
20. Davierwala PM, Borger MA, David TE, Rao V, Maganti M, Yau TM. Reoperation is not an independent predictor of mortality during aortic valve surgery. J Thorac Cardiovasc Surg 2006;131(2):329-35.
21. Bourguignon T, El Khoury R, Candolfi P, Loardi C, Mirza A, Boulanger-Lothion J, Bouquiaux-Stablo-Duncan AL, Espitalier F, Marchand M, Aupart M. Very Long-Term Outcomes of the Carpentier-Edwards Perimount Aortic Valve in Patients Aged 60 or Younger. Ann Thorac Surg 2015;100(3):853-9.

22. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33(19):2451-96.
23. Stacey D, Legare F, Col NF, Bennett CL, Barry MJ, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L, Wu JH. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014;1:CD001431.
24. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. J Am Coll Cardiol 2000;35(3):747-56.
25. Klieverik LMA, Noorlander M, Takkenberg JJM, Kappentein AP, Bekkers JA, Herwerden LAV, Bogers AJJ. 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.
26. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001;54(10):1046-55.
27. Ioannidis JP, Lau J. Pooling research results: benefits and limitations of meta-analysis. The Joint Commission journal on quality improvement 1999;25(9):462-9.
28. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JN, Bull LM, Welch SJ, Cuthbertson FC, Binney LE, Gutnikov SA, Anslow P, Banning AP, Mant D, Mehta Z, Oxford Vascular S. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet 2005;366(9499):1773-83.



CHAPTER 5

Reported Outcome After Valve-Sparing Aortic Root Replacement for Aortic Root Aneurysm: A Systematic Review and Meta-Analysis

Arabkhani B, Mookhoek A, Di Centa I, Lansac E, Bekkers JA,
De Lind Van Wijngaarden R, Bogers AJ, Takkenberg JJ

Ann Thorac Surg. 2015 Sep;100(3):1126-31

ABSTRACT

Background. Valve-sparing aortic root techniques have progressively gained ground in the treatment of aortic root aneurysm and aortic insufficiency. By avoiding anticoagulation therapy it offers a good alternative to composite graft replacement. This systematic review describes the reported outcome of valve-sparing aortic root replacement focusing on the remodeling and reimplantation technique.

Methods. A systematic literature search on characteristics of and outcome after valve-sparing aortic root replacement revealed 1.659 articles. Inclusion criteria: focus on valve-sparing aortic root replacement in adults with aortic root aneurysm, presenting survival data, including at least 30 patients. Data were pooled by inverse variance weighting and analyzed by linear regression.

Results. Of 1.659 articles published between 01/01/2000 and 01/01/2014, 31 were included (N = 4.777 patients). Mean age at operation was 51 ± 14.7 years, 14% had bicuspid aortic valve. The reimplantation technique was used in 72%, remodeling in 27% (1% other). No clinical advantage in terms of survival and reoperation of one technique over the other was found. Cusp repair was performed in 33%. Pooled early mortality was 2% (N=103). During follow-up (21.716 patient-years), 262 patients died (survival 92%) and 228 (5%) were reoperated, mainly valve replacement. Major adverse valve related events was low (1.66% patient-years). Preoperative severe aortic valve regurgitation showed a trend toward higher reoperation rate.

Conclusions. Remodeling and reimplantation techniques show comparable survival and valve durability results providing a valid alternative to composite valve replacement. The heterogeneity in data underlines the need for a collaborative effort to standardize outcome reporting.

INTRODUCTION

There are no comprehensive recommendations in the literature regarding the surgical treatment of aortic root aneurysms other than that it should be concentrated in those centers with proven expertise with the procedure[1]. Various valve sparing aortic root replacement techniques have been developed in the last decades to preserve the native aortic valve and to avoid anticoagulation therapy, as is needed with the standard composite aortic root replacement (Bentall procedure) [2]. The two most widely used techniques are the remodeling and the reimplantation technique. In the Yacoub procedure, the aortic root is reduced and neo-sinuses of Valsalva are created using synthetic tube graft, thereby producing a nearly physiological reconstruction of the aortic root. However, the aortic annulus remains untreated [3]. The David procedure (the most widely used reimplantation technique) involves reimplantation of the aortic valve within a synthetic tube, whereby the sino-tubular junction as well as the annulus are reduced but includes the interleaflet triangles thus impairing root expansibility and possibly valve dynamics [4]. Over the years numerous modifications to these techniques have been described, such as a standardized and physiological approach of valve sparing procedure with the association of a remodeling root reconstruction to an aortic ring annuloplasty in order to combine advantages of both original techniques [5-7].

To contribute to the debate on which type of valve surgery is most appropriate in patients with aortic root aneurysms, we conducted a systematic review of observational reports on characteristics of, and mortality and morbidity after valve sparing aortic root replacement (VSARR), and explored factors potentially influencing outcome.

METHODS

This systematic review and meta-analysis was conducted using the guidelines of the Meta-analysis Of Observational Studies in Epidemiology, proposed by Stroup et al. [8].

Search Strategy

On 10 January 2014, a search was executed in Embase, MEDLINE, Cochrane database and Web of Science (Appendix 1). All studies published from 1 January 2000 to 10 January 2014 were screened by two reviewers (BA and AM) using the following inclusion criteria: reporting on mortality and morbidity after VSARR, study size N≥ 30 patients, mean age ≥

18 years. Exclusion criteria were: solely acute aortic dissections, more than 50% children included, studies reporting state of the art, case reports, experimental studies and reviews. In case of disagreement, studies were assessed by a third, independent reviewer (RLW) and agreement was negotiated. In case of multiple publications on the same patient cohort, the most complete study in terms of outcome with the greatest number of patients included was selected. All selected studies were used for cross-referencing.

Data Extraction

Microsoft Office Excel (Microsoft, l. Redmond, Washington) was used for data extraction. Data extraction was performed in duplicate by two of the authors (BA and AM).

Outcome events in individual studies were registered according to the 2008 American Association for Thoracic Surgery/Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery guidelines for reporting mortality and morbidity after cardiac valve interventions[9]. Events were not included in our database when adherence to the reporting guidelines could not be ascertained. For each article with missing information on important variables, the corresponding author was requested to provide the missing data. An overview of extracted variables is presented in Appendix 2 [5, 10-39].

Statistical Analysis

Data analysis was performed with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) and IBM SPSS version 21.0 (IBM, Somers, NY, USA). Linearized occurrence rates of valve-related complications were calculated as number of events divided by number of patient-years for each study and pooled on a logarithmic scale with the use of the inverse variance method in a random-effect model, to minimize the variance of the weighted average. Each random variable is weighted in inverse proportion to its variance. Reported study characteristics are quoted as mean ± standard deviation for continuous variables and percentages for discrete variables. Baseline characteristics are reported as means. For dichotomous or ordinal outcomes, individual and pooled statistics were calculated as occurrence rates and 95% CI. When the total number of patient-years was not reported, it was calculated by multiplying number of patients with mean follow-up. In case a certain event did not occur in an individual study, then we assumed that 0.5 events occurred for that particular outcome, to allow calculation of pooled occurrence rates. When a particular event was not reported in a study, this study was excluded from the analysis of that particular event.

Subgroup analyses of outcome were performed for surgical technique (reimplantation versus remodeling), preoperative AR severity, bicuspid valve disease, connective tissue disease and cusp repair. To assess the association of these variables with late mortality and reoperation, linear regression was performed with correction for age as a possible confounder. Regression analysis was weighted by study size according to the inverse variance method.

Heterogeneity between the studies was assessed with the use of the I^2 test in Excel. Funnels plots were used to study publication bias.

RESULTS

Study characteristics and outcome

The initial literature search yielded 1.659 publications. The selection procedure of this systematic review is depicted in Figure 1. A total of 31 studies were included in this systematic review with a total number of 4.777 patients and 21.716 patient-years. An overview of the included publications and study characteristics is given in Appendix 3.

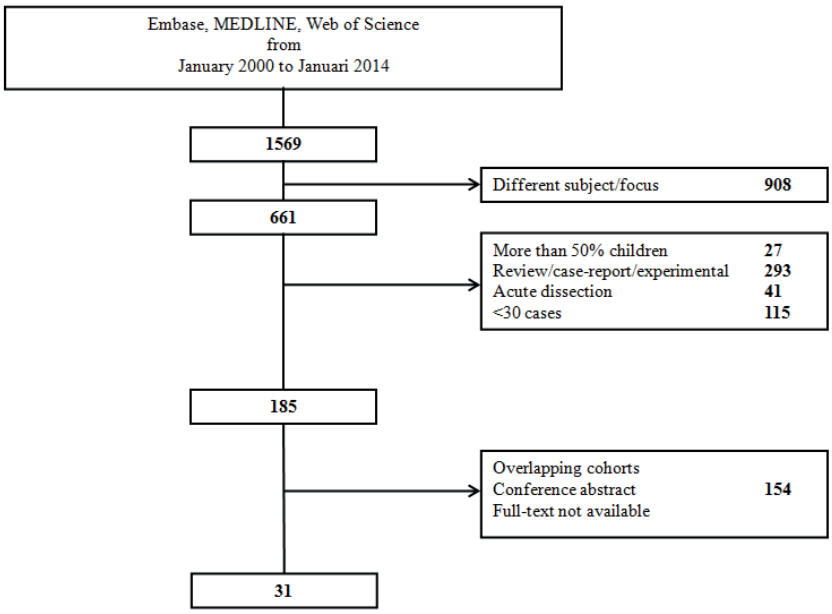


FIGURE 1. Selection procedure.

Pooled pre-operative and peri-operative characteristics are displayed in Table 1. Early mortality occurred in 103 patients (pooled early mortality 2.2%).

Mean follow-up after VSARR was 4.4 years (range 1.5-13.2 years). Late mortality occurred in 262 cases and was unknown or unreported in 19% of deaths. The main causes of late mortality were non-cardiac (39%). Cardiac valve-related and cardiac non-valve related death occurred in 37% and 5% of deaths respectively.

TABLE 1. Pooled pre-operative and peri-operative characteristics.

Variable		Pooled data	Range	Included studies (N)
Total patient number		**4.777**	32 - 430	31
Surgical period		**1988 - 2012**		31
Mean age		**51.0 years**	29 – 63 years	30
Gender	Male	**71.0%**	57 – 85%	30
Comorbidity	Connective tissue disease	**23.9%**	0 – 100%	35
	Severe aortic regurgitation	**46.1%**	6.4 – 100%	25
	Bicuspid aortic valve	**14.1%**	0 – 33%	28
Prior surgery	Cardiac	**4.49%**	2 – 12%	14
Other indications	Acute type A dissection	**10.5%**	0 – 33%	28
Reexploration for bleeding		**6.4%**	0 – 23%	27
Concomitant	Aortic (hemi)arch repair	**22.1%**	0 – 68%	26
	Cusp repair†	**33.2%**	0 – 76%	30
	CABG	**9.1%**	0 – 19%	25
	Mitral valve surgery	**5.3%**	0 – 12%	25
Extracorporeal circulation	Time in minutes	**157**	66-281	22
Aortic cross-clamping	Time in minutes	**122**	36-223	22
Early mortality		**2.2%**	0 – 7%	31
Causes of early mortality ‡	Low cardiac output	**29.6%**	0 – 60%	
	Hemorrhage	**1.0%**	0 – 33%	
	Multiorgan failure	**12.6%**	0 – 40%	
	Stroke	**1.0%**	0 – 25%	
	Unknown / unreported	**55.8%**		

CABG indicates coronary artery bypass grafting; † Peroperative cusp repair in order to tailor the aortic valve; ‡ major causes of early mortality.

Pooled outcome

The linearized occurrence rates of late mortality, reoperation on the aortic root, hemorrhage, thromboembolism, endocarditis and major adverse valve-related events are presented along with a measure of statistical heterogeneity in Table 2 and Appendix 3.

TABLE 2. Linearized occurrence rates of late outcome events.

Pooled late outcome events	LOR + 95% CI*	Heterogeneity (I^2)	Included studies (N)	Events (N)	Patient years (N)
Late mortality	1.53 (1.19 – 1.96)	82.6	31	262	21274
Reoperation on aortic valve	1.32 (1.0 – 1.74)	72.3	31	228	21274
Hemorrhage	0.23 (0.13 – 0.42)	78.7	26	15	19158
Thromboembolism	0.41 (0.22 – 0.77)	27.6	26	42	19158
Endocarditis	0.23 (0.11 – 0.51)	0.00	30	29	20930
MAVRE	1.66 (1.24 – 2.23)	100	20	300	19158

LOR indicates linearized occurrence rates; CI, confidence interval; MAVRE, major adverse valve-related events.

Publication Bias

Analysis of the funnel plots revealed evidence of underreporting of late mortality in studies with smaller patient numbers. For other parameters, no evidence of publication bias was found.

Subgroup Analyses

A total of 12 studies reported using both the remodeling and the reimplantation technique. Four studies reported using solely the remodeling technique and 15 studies solely the reimplantation technique. Data about severity of post-procedural AR was mentioned in 9 studies and further specified in AR grade II or more in 6 of these studies, with a total of 41 patients (3.5% of these studies). Additionally, there were no data regarding leaflet heights and coaptation surfaces of the repaired valves.

Surgical technique was not associated with higher survival or reoperation rates. Figure 2 represents the association between preoperative AR severity and reoperation hazard based on pooled LOR. Correcting for age we found a trend (p = 0.07) toward preoperative severe AR being associated with a higher reoperation risk. Other analyses did not show any significant associations. No other factors were found to be associated with survival and/or reoperation rates.

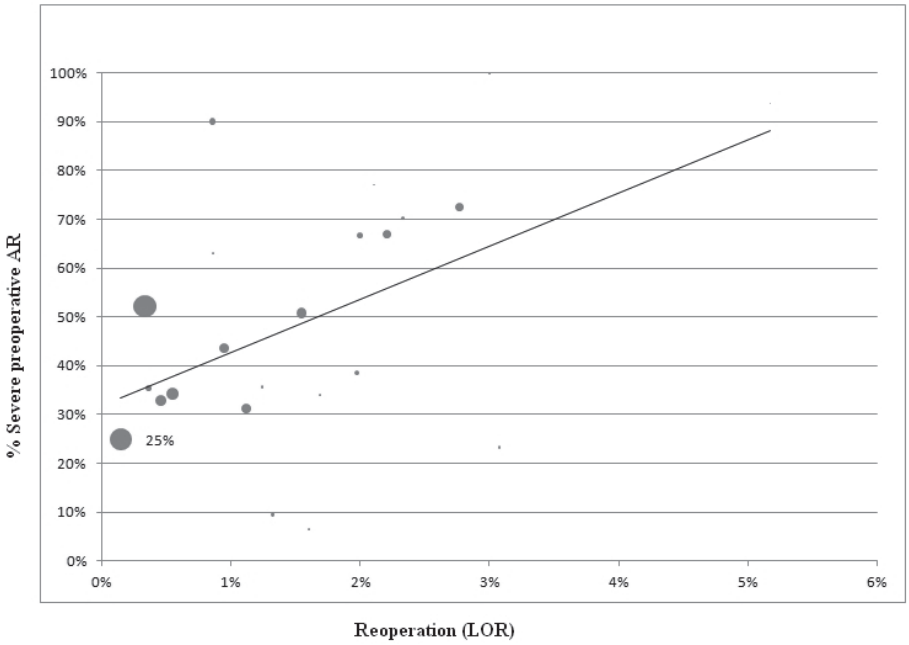


FIGURE 2. Association of reoperation rate and preoperative severe AR, based on LOR's.

Dots represent studies (the larger the study the greater the dots), p-value is derived from regression analysis (according to the weighted, inverse variance method).

COMMENT

This systematic review and meta-analysis gives an overview of published contemporary evidence on characteristics and outcome after valve sparing aortic root replacement. It shows acceptable outcomes in terms of survival and freedom from both reoperation and valve-related events in the first 5 postoperative years, regardless of the surgical technique

employed (remodeling or reimplantation). Moreover, it illustrates that current evidence is fragmented and heterogeneous, and does not allow for furthermore exploration of potential determinants of outcome.

Early and late outcomes

The observed pooled early and late mortality in this systematic review is low. Additionally, there is a low incidence of thromboembolism, endocarditis and hemorrhagic events after valve sparing aortic root replacement. Previous reports, including a less exhaustive review conducted by Rahnavardi et al. [40], confirm our observation of low early mortality and 4 year reoperation hazard, and that bicuspid aortic valves are not associated with a significant higher reoperation rate. The rate of bicuspid repair is low (14%) in this meta-analysis, as confirmed by Badiu et al. that BAV is not associated with a higher reoperation hazard, but there is a trend toward higher reoperation hazard for patients with preoperative severe AR [17]. Only 9 studies in our systematic review describe their direct postoperative echocardiographic aortic valve regurgitation data. Thus, based on our systematic review it is not possible to make assumptions about the association between direct postoperative AR and reoperation hazard. Although there are no large reports on VSARR and cusp prolapse, a report by Schäfers et al. emphasized that symmetric cusp prolapse should be corrected during VSARR to avoid AR by the measurement of cusp effective Height using a dedicated caliper [41]. This was confirmed by Lansac et al. defining the absence of cusp effective height resuspension as an independent risk factor for AR grade 2 or higher and for reoperation [21]. There were no reports about leaflet heights and cusp anatomy, therefore we are not able to test any assumption about their possible association with reoperation or other valve-related complications. Of course, given the limited follow-up duration of most studies in this review, the reported late outcomes cannot be extended beyond the first postoperative decade.

Surgical technique: remodeling versus reimplantation

No clinical advantages in terms of survival and reoperation of one technique over the other is evident from our meta-analysis of the literature. Although the remodeling technique provides physiological cusp movements within the three reconstructed neo sinuses, thus preserving root expansibility through the interleaflet triangles, it does not address annulus dilation which has been identify as a risk factor of failure (>25-28mm) [7-8, 13-15]. The reimplantation procedure as an inclusion technique performs a subvalvular annuloplasty through the proximal suture of the graft but withdraws the sinuses of

Valsalva and includes the interleaflet triangles within the non-compliant prosthesis, thus impairing root dynamics [8, 14]. Therefore, since annulus dilation has been identified as a risk factor for repair failure for dystrophic aortic roots with bicuspid and tricuspid valves, there is a consensus among authors to favor valve sparing root replacement providing an aortic annuloplasty through either a proximal suture using the reimplantation technique or an annuloplasty ring device in combination with the remodeling technique.

VSARR versus Bentall

VSARR offers patients with aneurysms of the ascending aorta several advantages over composite graft replacement (Bentall), such as no need for oral anticoagulation, thereby avoiding increased bleeding risk, INR monitoring, and lifestyle adjustments (e.g. sports, alcohol intake etc.). In addition, there is evidence that patients receiving a VSARR may experience a better overall quality of life compared to patients with a mechanical valve [42]. On the downside, after VSARR more reoperations are expected compared to the Bentall procedure.

Although the Bentall procedure yields a lower risk of reoperation, especially in longer follow up, there is a lower hemorrhagic risk and thromboembolism seems to occur less often in patients receiving a VSARR because of anti-coagulation therapy needed after the Bentall [43, 44]. This is particularly important in patients with an active lifestyle as well as in female patients with the desire of a pregnancy after the operation [45, 46]. Patient characteristics, such as age at the time of operation, proportion of patients with connective tissue disease and aortic arch repair are similar between the two studies.

Need for standardized data

Given the observed heterogeneity, it is obvious from this systematic review that there is a need for uniform standardized reporting of VSARR procedures and their outcomes. Also, there is a need for collaboration between centers in their reporting of VSARR procedures, as it will accelerate our knowledge building of this complex surgical procedure and its outcomes. Within the Heart Valve Society the AVIATOR registry was initiated: a multicenter, prospective registration with the goal to combine forces and share experience in order to advance knowledge in the field of surgical treatment of patients with aortic root dilatation and/or aortic valve regurgitation (www.researchonline.org/link/study/aviator). This initiative will hopefully provide an evidence base to tailor the most suitable surgical treatment, such as valve sparing procedures, to the individual patient.

Limitations

The available guidelines on reporting after heart valve interventions were not applied in several studies included in our systematic review and may have resulted in misinterpretation of the available data. It is obvious that the included studies represent a heterogeneous population of patients in their thirties through sixties, with varying aortic aneurysm, bicuspid valve, and aortic regurgitation prevalence. These patients of various cohorts were operated between 1988 and 2011, spanning over 20 years. In this light, the observed outcomes should be weighted carefully. Additionally, the limited follow up duration of the included studies does not allow for conclusions beyond the first five postoperative years.

The pooled linearized occurrence rates for reoperation and mortality data were based on heterogeneous data, under the linearity assumption, and should be treated with considerable caution. We included only studies with cohorts greater than 30 patients were included and in addition, where available, selecting the largest series of published data from a center was included, thus selecting more experienced surgeons and centers. This may have led to selection bias.

Finally, due to the retrospective nature of the available and included studies, underreporting of – in particular nonfatal – events is likely.

CONCLUSION

Valve sparing aortic root replacement is an acceptable option for the treatment of aortic root aneurysm, with or without aortic regurgitation, especially in young active patients, and patients in whom anticoagulation therapy is less desirable due to lifestyle or medical history. Severe preoperative aortic valve regurgitation is associated with a trend towards a higher reoperation rate. Therefore, in order to improve the results, valve sparing aortic root replacement would benefit from a technical standardization that resuspends cusp effective height and reduces the dilated aortic annulus (either by an annuloplasty device in case of remodeling or a proximal suture when using the reimplantation technique) and restores proper valve coaptation. The observed lack of standardization in data reporting has led to the proposition of an international prospective multicenter registry for aortic valve sparing/repair and replacement surgery (AVIATOR registry). In addition, the most suitable surgical procedure should be determined on an individual basis, also taking into account patient preference.

REFERENCES

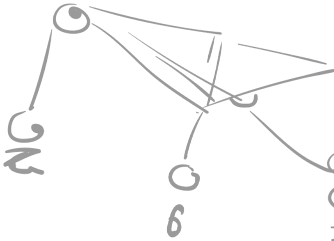
1. Nishimura, R.A., et al., *2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol, 2014.
2. Bentall, H. and A. De Bono, *A technique for complete replacement of the ascending aorta.* Thorax, 1968. 23(4): p. 338-9.
3. Sarsam, M.A. and M. Yacoub, *Remodeling of the aortic valve anulus.* J THORAC CARDIOVASC SURG, 1993. 105(3): p. 435-8.
4. David, T.E. and C.M. Feindel, *An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta.* J THORAC CARDIOVASC SURG, 1992. 103(4): p. 617-21; discussion 622.
5. Lansac, E., et al., *Aortic prosthetic ring annuloplasty: a useful adjunct to a standardized aortic valve-sparing procedure?* Eur J Cardiothorac Surg, 2006. 29(4): p. 537-44.
6. El Arid, J.M., et al., *A Technique to Facilitate the Native Valve Reimplantation During the David Procedure.* J Card Surg, 2014.
7. Hechadi, J., et al., *Modified valve-sparing reimplantation technique for para-commissural coronary ostia.* Eur J Cardiothorac Surg, 2014. 45(5): p. 937-8.
8. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.* JAMA, 2000. 283(15): p. 2008-12.
9. Akins, C.W., et al., *Guidelines for reporting mortality and morbidity after cardiac valve interventions.* Ann Thorac Surg, 2008. 85(4): p. 1490-5.
10. Bassano, C., et al., *Mid-term follow-up of aortic root remodelling compared to Bentall operation.* Eur J Cardiothorac Surg, 2001. 19(5): p. 601-5.
11. Kallenbach, K., et al., *Decade of aortic valve sparing reimplantation: are we pushing the limits too far?* Circulation, 2005. 112(9 Suppl): p. I253-9.
12. Pacini, D., et al., *Early results of valve-sparing reimplantation procedure using the Valsalva conduit: a multicenter study.* Ann Thorac Surg, 2006. 82(3): p. 865-71; discussion 871-2.
13. Erasmi, A.W., et al., *Remodeling or reimplantation for valve-sparing aortic root surgery?* Ann Thorac Surg, 2007. 83(2): p. S752-6; discussion S785-90.
14. Segal, B., et al., *Prevalence, severity, and predictors of fatigue in subjects with primary Sjogren's syndrome.* Arthritis Rheum, 2008. 59(12): p. 1780-7.
15. de Kerchove, L., et al., *Effects of preoperative aortic insufficiency on outcome after aortic valve-sparing surgery.* Circulation, 2009. 120(11 Suppl): p. S120-6.
16. Nagamani, S.C., et al., *Interstitial deletion of 6q25.2-q25.3: a novel microdeletion syndrome associated with microcephaly, developmental delay, dysmorphic features and hearing loss.* Eur J Hum Genet, 2009. 17(5): p. 573-81.

17. Badiu, C.C., et al., *Should root replacement with aortic valve-sparing be offered to patients with bicuspid valves or severe aortic regurgitation?* Eur J Cardiothorac Surg, 2010. 38(5): p. 515-22.
18. David, T.E., M. Maganti, and S. Armstrong, *Aortic root aneurysm: principles of repair and long-term follow-up.* J Thorac Cardiovasc Surg, 2010. 140(6 Suppl): p. S14-9; discussion S45-51.
19. Ruggero De Paulis, M., a Raffaele Scaffa, MD,a Saverio Nardella, MD,a Daniele Maselli, MD,a, M. Luca Weltert, a Fabio Bertoldo, MD,b Davide Pacini, MD,c Fabrizio Settepani, MD,d, and M. Giuseppe Tarelli, d Roberto Gallotti, MD,d Roberto Di Bartolomeo, MD,c and Luigi Chiariello, MD, *Use of the Valsalva graft and long-term follow-up.* The Journal of Thoracic and Cardiovascular Surgery 2010. 140(6S).
20. Dias, R.R., et al., *Aortic root reconstruction through valve-sparing operation: critical analysis of 11 years of follow-up.* Rev Bras Cir Cardiovasc, 2010. 25(1): p. 66-72.
21. Lansac, E., et al., *An aortic ring: From physiologic reconstruction of the root to a standardized approach for aortic valve repair.* J Thorac Cardiovasc Surg, 2010. 140(6 SUPPL.): p. S28-S35.
22. Matalanis, G., W.Y. Shi, and P.A. Hayward, *Correction of leaflet prolapse extends the spectrum of patients suitable for valve-sparing aortic root replacement.* Eur J Cardiothorac Surg, 2010. 37(6): p. 1311-6.
23. Bakhtiary, F., et al., *Long-term results and cusp dynamics after aortic valve resuspension for aortic root aneurysms.* Ann Thorac Surg, 2011. 91(2): p. 478-484.
24. Berutti, T.W., et al., *Promoting adherence to ventilator management and ventilator weaning protocols.* AMIA Annu Symp Proc, 2008: p. 877.
25. Matsoukas, K., et al., *Expanding DISCERN to create a tool for assessing the quality of Web-based health information resources.* AMIA Annu Symp Proc, 2008: p. 1048.
26. Pacini, D., L. Di Marco, and R. Di Bartolomeo, *Methods of cerebral protection in surgery of the thoracic aorta.* Expert Rev Cardiovasc Ther, 2006. 4(1): p. 71-82.
27. Kunihara, T., et al., *Preoperative aortic root geometry and postoperative cusp configuration primarily determine long-term outcome after valve-preserving aortic root repair.* J Thorac Cardiovasc Surg, 2012. 143(6): p. 1389-1395.
28. Teichmann, S. and N.H. Patel, *Genomes and evolution: multidimensional approaches to understanding diversity.* Curr Opin Genet Dev, 2008. 18(6): p. 469-71.
29. Leshnower, B.G., et al., *Expanding the indications for the David V aortic root replacement: early results.* J Thorac Cardiovasc Surg, 2012. 143(4): p. 879-84.
30. Patel, E.H., et al., *Rhamnose catabolism in Bacteroides thetaiotaomicron is controlled by the positive transcriptional regulator RhaR.* Res Microbiol, 2008. 159(9-10): p. 678-84.
31. Malvindi, P.G., et al., *Bicuspidy does not affect reoperation risk following aortic valve reimplantation.* Interact Cardiovasc Thorac Surg, 2012. 14(6): p. 717-720.
32. Jones, D.M., et al., *The hepatitis C virus NS4B protein can trans-complement viral RNA replication and modulates production of infectious virus.* J Virol, 2009. 83(5): p. 2163-77.

33. Urbanski, P.P., et al., *Valve-sparing aortic root repair without down-sizing of the annulus.* J Thorac Cardiovasc Surg, 2012. 143(2): p. 294-302.
34. David, T.E., et al., *Long-term results of aortic root repair using the reimplantation technique.* J THORAC CARDIOVASC SURG, 2013. 145(3 Suppl): p. S22-5.
35. Forteza, A., et al., *Should aortic valve reimplantation be offered to patients with a large aorto-ventricular junction?* Eur J Cardio-thorac Surg, 2013. 43(5): p. e130-e135.
36. Visser, N., C.N. McGhee, and D.V. Patel, *Laser-scanning in vivo confocal microscopy reveals two morphologically distinct populations of stromal nerves in normal human corneas.* Br J Ophthalmol, 2009. 93(4): p. 506-9.
37. Escobar Kvitting, J.P., et al., *David valve-sparing aortic root replacement: Equivalent mid-term outcome for different valve types with or without connective tissue disorder.* J Thorac Cardiovasc Surg, 2013. 145(1): p. 117-127.e115.
38. Liebrich, M., et al., *Aortic valve-sparing reimplantation technique (David-procedure) in different pathologies: Long-term clinical and echocardiographic follow-up in 170 patients. A single-center experience.* Thorac Cardiovasc Surg, 2011. 59.
39. Ustinov, A.V., et al., *Reactive trityl derivatives: stabilised carbocation mass-tags for life sciences applications.* Org Biomol Chem, 2008. 6(24): p. 4593-608.
40. Bolderman, R.W., et al., *Atrium-targeted drug delivery through an amiodarone-eluting bilayered patch.* J Thorac Cardiovasc Surg, 2010. 140(4): p. 904-10.
41. Schafers, H.J., D. Aicher, and F. Langer, *Correction of leaflet prolapse in valve-preserving aortic replacement: Pushing the limits?* Ann Thorac Surg, 2002. 74(5): p. S1762-S1764.
42. Aicher, D., et al., *Quality of life after aortic valve surgery: replacement versus reconstruction.* J Thorac Cardiovasc Surg, 2011. 142(2): p. e19-24.
43. Tourmousoglou, C. and C. Rokkas, *Is aortic valve-sparing operation or replacement with a composite graft the best option for aortic root and ascending aortic aneurysm?* Interact Cardiovasc Thorac Surg, 2009. 8(1): p. 134-47.
44. Lim, J.Y., et al., *Surgical Management of Aortic Root Dilatation with Advanced Aortic Regurgitation: Bentall Operation versus Valve-sparing Procedure.* Korean J Thorac Cardiovasc Surg, 2012. 45(3): p. 141-7.
45. Erie, E.A., et al., *Corneal subbasal nerve density: a comparison of two confocal microscopes.* Eye Contact Lens, 2008. 34(6): p. 322-5.
46. Babington, L. and B. Patel, *Understanding child feeding practices of Vietnamese mothers.* MCN Am J Matern Child Nurs, 2008. 33(6): p. 376-81.

ABBREVIATIONS

AR	=	Aortic Regurgitation
AS	=	Aortic Stenosis
CTD	=	Connective Tissue Disease
BAV	=	Bicuspid Aortic Valve
MAVRE	=	Major Adverse Valve Related Events
TE	=	Thromboembolism
VSARR	=	Valve Sparing Aortic Root Replacement
LOR	=	Linearized occurrence rates



Chapter 6

Bioprosthetic aortic root replacement: A Meta-Analysis and Microsimulation model

Bardia Arabkhani, Jonathan RG Etnel, Mirjam t'Mannetje, Richard van Valen, Tanja van Essen, Emmanuel Lansac, Rob de Lind van Wijngaarden, Isabelle Di Centa, Ad JJC Bogers, Johanna JM Takkenberg

Submitted

ABSTRACT

Background. For middle-aged patients, aortic root replacement with biological valve prostheses offers a good alternative to the "gold standard" mechanical Bentall-procedure, avoiding anticoagulation therapy. Evidence on outcome after bioprosthetic aortic root replacement remains limited and fragmented.

Methods. A systematic literature search on this subject revealed 2,105 publications between January 2000 and July 2016. Inclusion criteria: aortic root replacement in adults with root aneurysm, presenting survival, and ≥50 patients. Data were pooled by inverse-variance weighting and entered into a microsimulation model to calculate lifetime event-risk and (event-free) life expectancy.

Results. Of 2,105 publications, 29 were included (N = 4,623 patients, 74% stentless valves). Mean age at operation was 65.9 years (68% male), 14% had prior cardiac surgery. Pooled early mortality was 5.9% (N= 220: 95% CI: 4.7-7.3%). During follow-up (mean 4.1 years, total 18,675 patient-years), 742 patients died (4.6%/patient-year) and 140 were reoperated (0.7%/patient-year). Linearized-occurrence-rates for thromboembolism, endocarditis, and hemorrhagic events were 1.4%/patient-year, 1.0%/patient-year and 0.6%/patient-year, respectively. Estimated life-time event risk of bleeding and thromboembolism were 21% and 8%, respectively.

Conclusions. The meta-analysis and microsimulation model suggest acceptable results in terms of freedom from reintervention and valve-related events after bioprosthetic aortic root replacement, regardless of the prosthesis type (stented or stentless). The relatively high thromboembolic event hazard may be explained by older patient age. The age threshold for bioprosthetic root replacement remains debatable, as prosthetic valve selection is value-sensitive. The observed heterogeneity among studies underlines the need for international collaboration to obtain reliable data on the characteristics and outcomes after bioprosthetic aortic root replacement.

INTRODUCTION

There are several surgical techniques to treat aortic root aneurysm when the valve is not eligible for sparing or repair procedure. In younger patients, i.e. patients under the age of 60-65 [2], mechanical composite valve replacement (the "Bentall" procedure(1)) is a widely used prosthesis, due to its long-term durability (2). In older patients, aortic root replacement with biological valve prosthesis is more common, because reoperations are less prominent because of the shorter life expectancy and because of avoiding the higher anticoagulation-related hemorrhagic complication rate associated with mechanical valve implantation. While structural valve deterioration (SVD) is associated with higher reintervention risk in younger patients (3, 4), there are no large, long follow-up studies presenting outcome after bioprosthetic aortic root replacement in middle-aged patients, and most published studies have limited follow-up duration which is a limitation for the interpretation of the results, in particular regarding SVD and reoperation hazard (5). Nevertheless, biological valve prostheses are increasingly implanted in middle-aged patients. Another topic of debate remains the most appropriate type of biological valve prosthesis (i.e. stented or stentless) in patients with aortic valve and root disease (6). Although stentless valves may have better hemodynamics, advantages in terms of patient survival and long-term durability have not yet been demonstrated (7). To assess the current body of evidence on bioprosthetic aortic root replacement we conducted a systematic review of observational reports on patient characteristics and outcome valve related morbidity, mortality and reintervention rates after bioprosthetic aortic root replacement with stented or stentless prostheses, and explored potential determinants of outcome.

MATERIAL AND METHODS

Search Strategy

On 30 July 2016, a systematic literature search was conducted in MEDLINE, Embase, The Cochrane Collaboration and Web of Science, and Google Scholar (Appendix 1). Studies published from January 2000 onwards were screened by three independent reviewers (BA, MM, RvV) using the following inclusion criteria: reporting morbidity and mortality after bioprosthetic aortic root replacement with stentless or stented prosthesis, cohorts ≥ 50 patients (in order to prevent including early experience reports highlighting the learning curve), and mean age at surgery ≥ 18 years. Exclusion criteria were: > 50% acute

type A aortic dissection included, studies limited to reintervention or to patients receiving a mechanical valve prosthesis (i.e. Bentall-procedure), studies reporting only on early results, > 10% use of subcoronary technique, > 50% children included (aged <18 years), and state of the art publications, case reports, experimental studies and reviews. In case the same cohort was published more than once, the most complete publication was selected. All included studies were cross-referenced to identify additional publications. In case of disagreement, studies were assessed by another, independent reviewer (RLW) and agreement was negotiated until consensus was reached.

Data Extraction

Data extraction was performed in duplicate with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) by two of the authors (BA and JE) according to the guidelines for reporting mortality and morbidity after cardiac valve interventions (8). Events were not included in our database when adherence to the reporting guidelines could not be ascertained. For each article with missing information on important variables, the corresponding author was requested to provide the missing data. An overview of extracted variables is presented in Appendix 2.

Data Analysis

Data analysis was performed with Microsoft Excel (Microsoft Office 2010, Microsoft, Redmond, WA, USA) and IBM SPSS version 21.0 (IBM, Somers, NY, USA) and in the R statistical software (version 3.1.0. R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the metafor package. Pooled baseline patient characteristics were calculated with the use of sample size weighting. Early mortality and linearized occurrence rates of late valve-related complications were pooled on a logarithmic scale with the use of inverse variance weighting in a random-effects model. Reported study characteristics and pre- and peri-operative patient characteristics are presented as mean ± standard deviation for continuous variables and percentages for discrete variables. For outcome variables, individual and pooled statistics are presented as linearized occurrence rates and 95% confidence interval (CI). In studies where median and ranges instead of mean and variance were reported, the method described by Hozo et al. (9) was used to calculate the mean. In case of absence of total number of patient-years, this was calculated by multiplying the number of patients with the mean follow-up duration in years. In case a certain event did not occur in an individual study, we assumed that 0.5 events occurred for that particular outcome for the purpose of inverse variance weighting. When a particular event was not

reported in a study, this study was excluded from the analysis of that particular event.

For late mortality and reintervention, subgroup analyses were performed stratifying the root replacement by prosthesis type (stented vs. stentless), follow-up duration (individual study mean follow-up less than pooled mean follow-up versus individual study mean follow-up more than pooled mean follow-up), and age at surgery. To assess the association of these variables with late mortality and reintervention rates, linear regression analyses were performed with weighting the studies according to the inverse variance of the occurrence rate. Heterogeneity between the studies was assessed using the I^2 test. Funnels plots were used to investigate publication bias. This systematic review and meta-analysis was conducted according to the PRISMA guidelines (10).

Microsimulation

In order to estimate the age-specific life expectancy and an additional lifetime risk of valve-related morbidity, a microsimulation model was used based on the pooled outcome estimates of our meta-analysis.

Microsimulation model: the concept

The microsimulation model is a computer application that simulates the life of a patient after aortic valve replacement, taking into account the morbidity and mortality events that the patient could experience. The calculated mortality of a patient is composed of the background mortality of the general population, operative mortality, mortality due to valve-related events and an additional "excess mortality". This so called excess mortality in the patient compared to a matched person in the general population reflects mortality associated with the underlying left ventricular function, valve pathology, and the root replacement procedure.

All pooled and weighted occurrence rates of (operative) mortality risk, the occurrence rate of valve-related events together with the risk of mortality and reintervention directly due to valve-related events were obtained from the meta-analysis. The occurrence rates of all events were assumed to be linear and non-age-dependent. The hazard ratios of the additional excess mortality not directly resulting from valve-related events have been previously estimated (11). A more detailed account of the microsimulation and the methodology has been supplied previously (12).

For patients aged 61-70 and > 70 years, these "excess mortality" hazard ratios were 1.2 and 0.8 for males and 2.2 and 1.3 for females, respectively. The background mortality of the general population was obtained from the 2004 United States Life Tables, as 2004 was the pooled median year of intervention, assuming a constant incidence rate over time in each study (13).

To obtain age-specific estimates of life expectancy and lifetime risk of valve-related morbidity, the microsimulation model was run for the ages of 60, 65 and 70 years for 10,000 iterations each and separately for males and females. The age-specific outcomes of both genders were then pooled at the male/female ratio obtained from our meta-analysis. For the internal validation of the model, we performed an additional run for 10,000 iterations at the pooled mean age (65.9 years) and male/female ratio (67.6%) of the meta-analysis. The actuarial survival obtained from the microsimulation model for these data was then plotted against the pooled (overall) mortality observed in the meta-analysis.

RESULTS

Study and baseline patient characteristics

The initial literature search exposed 2,105 publications. The selection procedure is illustrated in Figure 1. Cross-referencing did not result in additional papers. A total of 29 studies were finally included in this systematic review with a total number of 4,623 patients, a mean follow-p of 4.1 yea rs (range 1-10 years), and a total follow-up of 17,725 patient-years.

Of these root replacements 26% were with stented and 74% with stentless valve prostheses. In one of the studies the implantation period was missing, which was provided by the authors (14). This study by Melina et al. was also the only prospective randomized trial; all others were retrospective, observational studies. Excluding this study from the analysis did not result in any inference and therefore this study was included in the analysis. Appendix 3 shows an overview of the included publications and study characteristics. Pooled pre- and peri-operative characteristics are presented in Table 1.

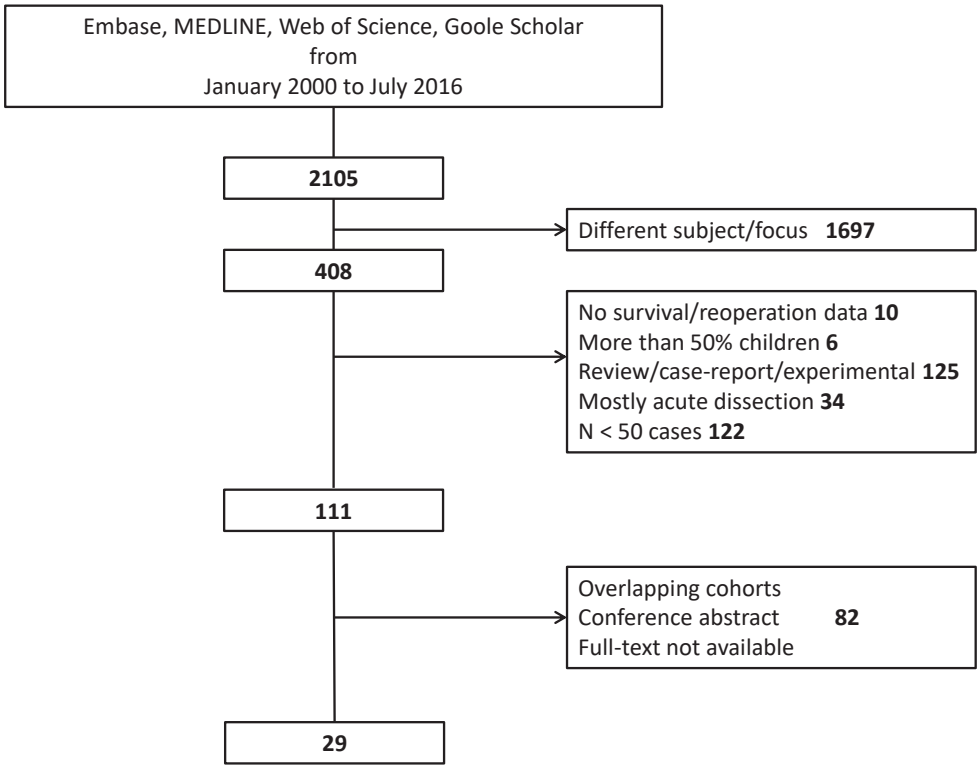


FIGURE 1. Flowchart of systematic search and included articles.

TABLE 1. Pooled pre-operative and peri-operative characteristics.

Variable		Pooled data	Range	Included studies (N)
Total patient number		4623	50 - 421	29
Surgical period		1992 - 2014		28
Mean age		**64.2 years**	47 – 73 years	28
Gender	Male	**67.6%**	30 – 85%	29
Etiology	Valve pathology			17
	Aortic stenosis	**49.8%**	3 – 100%	
	Aortic regurgitation	**37.7%**	0 – 92%	
	Stenosis & regurgitation	17.9%		
	Connective tissue disease	**2.9%**	0 – 32%	12
	Bicuspid aortic valve	28.0%	0 – 42.6%	14
Prior surgery	Cardiac	**14.2%**	0 – 39%	22
Other indications	Acute type A dissection	**7.2%**	0 – 24%	19
	Acute endocarditis	**9.1%**	1 – 11%	8
Valve type	Stentless	**99.7%**	95 – 100%	21
	Stented	**92.8%**	84 – 100%	5
	Mixed	**50%**	50 – 50%	2
Concomitant procedures	Aortic hemiarch repair	**18.2%**	0 – 44%	19
	Aortic arch repair	**5.9%**	3 – 21%	19
	CABG	**28.9%**	0 – 44%	19
	Mitral valve surgery	**3.3%**	0 – 17%	19
Reexploration for bleeding		**10.8%**	1 – 28%	14
Early mortality		5.9%	0 – 16%	29
Causes of early mortality *	*Low cardiac output*	**22.7%**	1 – 44%	
	Multi-organ failure *Hemorrhage*	**18.1%** **7.5%**	13 – 100% 0 – 13%	
	Sepsis *Myocardial infarction*	**5.0%** **4.0%**	6 – 25% 0 – 100%	
	Unknown / unreported	**9.6%**	10 – 55%	

CABG indicates coronary artery bypass grafting. * major causes of early mortality. Data indicate the pooled mean % of occurrence and the pooled range of occurrence. Included studies are publications reporting on the specific characteristic. The percentages mentioned are means of the reported variables in the studies that provided these variable numbers. The range indicates the lowest and the highest reported % of that specific variable within all studies, and N indicates the number of studies reporting on that specific variable.

Pooled outcome

Early (30 day) mortality occurred in 220 patients, corresponding to a weighted early mortality of 5.9% (95% CI: 4.7 – 7.3%). The linearized occurrence rates of mortality, reintervention on the aortic root, hemorrhage, thromboembolism, endocarditis and major adverse valve-related events are presented along with a measure of statistical heterogeneity in Table 2.

TABLE 2. Linearized occurrence rates of late outcome events.

Pooled late outcome events	LOR (%/yr) + 95% CI*	Heterogeneity (I^2)	Included studies (N)	Events (N)	Patient years of follow-up (N)
Late mortality	**4.61** (3.98 – 5.36)	71	29	742	18675
Root reintervention	**0.72** (0.47 – 1.10)	73	29	140	118675
Hemorrhage	**0.56** (0.33 – 0.94)	68	24	75	13743
Thromboembolism	**1.41** (0.96 – 2.06)	73	24	141	13911
Endocarditis	**1.00** (0.69 – 1.44)	69	26	134	15694
SVD*	**0.32** (0.16 – 0.62)	76	25	63	14405
NSVD*	**0.21** (0.13 – 0.35)	49	23	15	12438

LOR indicates linearized occurrence rates; CI, confidence interval; SVD, structural valve degeneration; MAVRE, major adverse valve-related events.* not all (N)SVD led to reintervention

Late mortality occurred in 742 patients (4.6%/patient-year); in 41% the cause was unknown or not reported. The main causes of late mortality were cardiac (52%). Cardiac valve-related and cardiac non valve-related death occurred in 51% and 49% of all cardiac deaths, respectively.

Publication Bias

Analysis of the funnel plots revealed evidence of underreporting of late mortality, reintervention on the aortic root, and thromboembolism in studies with smaller patient numbers. For other variables, no evidence of publication bias was found (Appendix 3).

Subgroup Analyses

A total of 21 studies reported using solely a biological valve-containing vascular prosthesis (14-34), of which 14 studies with Freestyle bioprosthesis, 2 studies solely Bio-Valsalva prosthesis, 2 Shelhigh bioconduit, 1 Edwards S prima Plus, 2 with mixed stentless prosthesis. In and one study the type of the biological valve was unspecified (35). Two

studies included both stentless and stented bioprostheses (36, 37). Four studies used (nearly) exclusively self-made aortic root prosthesis using a stented bioprosthesis (38-41). No associations were found between late mortality or reintervention and the type of prosthesis used. Moreover, mean follow-up time, age at operation, with a sub-analysis of studies with a mean follow-up of more than 4.1 years versus less than 4.1 years, and use of the Freestyle bioprosthesis were not associated with mortality or reintervention. Of 8 studies that explicitly tested age as a potential predictor for reoperation, 3 found an association between younger age and reoperation hazard.

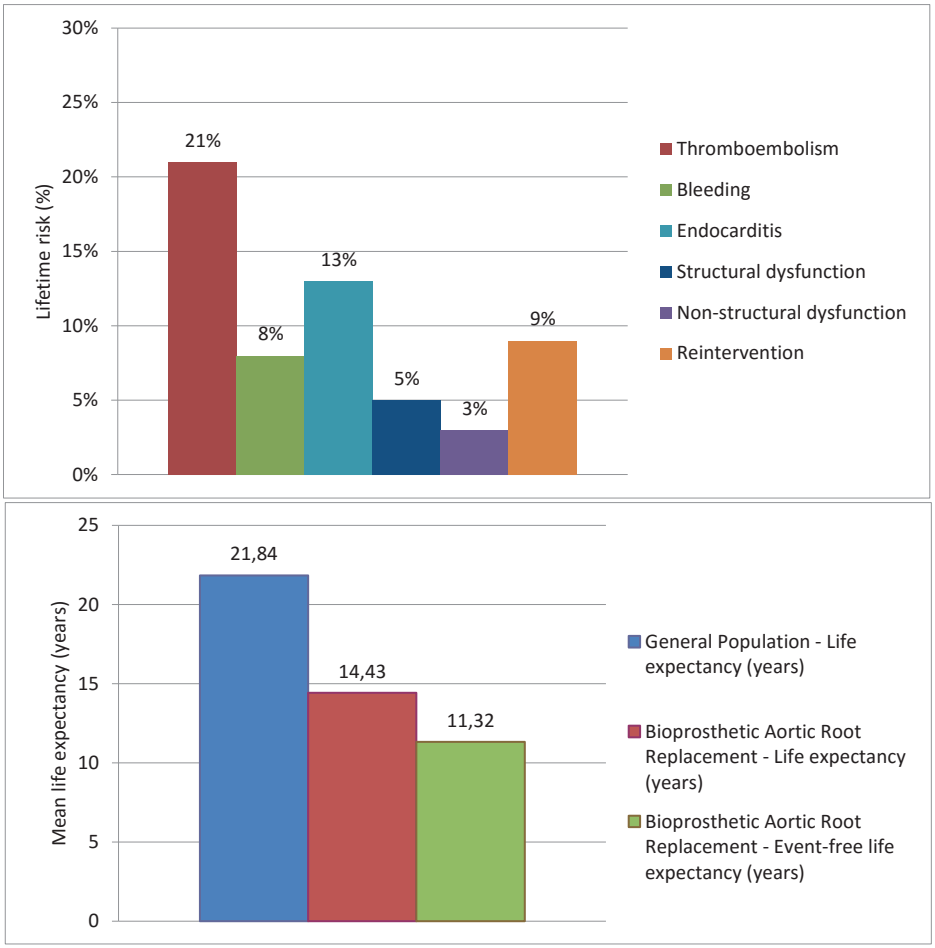


FIGURE 2. Microsimulation-based life expectancy and lifetime risk of valve-related morbidity for 60, 65 and 70 years old patients.

Microsimulation-based estimates of (event-free) life expectancy and lifetime risk of valve-related morbidity for 60, 65 and 70 years old patients are shown in Figure 2. The microsimulation model calibration with the pooled mortality is shown is Appendix 4.

COMMENT

This systematic review and meta-analysis provides an overview of contemporary published evidence on outcome after aortic root replacement with biological valve prostheses. It shows acceptable outcomes in terms of patient survival and freedom from reintervention irrespective of the type of valve prosthesis used (stented or stentless). Although stentless valves may have better hemodynamics (6), no improvement in terms of patient survival or long-term durability were observed in this review. In addition, thromboembolic events occur relatively frequently. The observed heterogeneity of the compiled outcome data does not allow for accurate exploration of potential risk factors associated with outcome.

Early outcome

The observed pooled early mortality was 5.9%. This is in accordance with earlier published review on aortic root replacement with the Freestyle prosthesis (4.5 to 5.3%) and in the recent report of the Society of Thoracic Surgeons database from the U.S. that estimates early mortality after bioprosthetic aortic root replacement to be 6.2% (42, 43). Early mortality was mainly due to low cardiac output (22.7%) and multi-organ failure (18.1%). Although surgical indication was endocarditis in 9.2% of patients and type A aortic dissection in 7.2%, no further details on early mortality in these subgroups could be extracted from the individual studies. Thus further inferences on comorbidity and early mortality were not possible. Additionally, there was a 1.8% risk of re-exploration for excessive bleeding or cardiac tamponade. The 16 studies that reported on re-exploration for bleeding and tamponade did not assess potential risk factors for this complication, and did not specify the postoperative anticoagulation regime, which precluded any further inferences.

Late mortality and reintervention outcome

There was a high mortality rate of 4.6%/pt-year for a pooled mean age of 65.9 years in our meta-analysis, which is higher than the general population mortality. Translated to our microsimulation-based life expectancy, there is a life expectancy of 14.3 year for a 60 year old patient receiving a bioprosthetic root replacement, while there is a

life expectancy of 22.5 years for the 60 year old U.S. "healthy" population (13). From previous research there is evidence of significant "excess mortality" in (elective) isolated aortic valve replacement and in case of prosthesis-patient mismatch, compared to the age-matched general population (44). Additionally, patients in this meta-analysis were diagnosed with a diseased aortic root as well, with some 13% suffering from a dissection of the root and/or connective tissue disease, which are conditions that may have an effect on patient survival due to complication other than valve-related events. Nevertheless, the calibration of the microsimulation model seems to underestimate the mortality hazard over time (appendix 4). This could be explained by the excess mortality data that was based on data from studies in de 1990's which may not be representative for our patients and this underestimation of the "excess mortality" probably led to overestimating the life time event risks observed. More accurate data on more recent mortality in the general population will probably lead to better calibration of our data.

Our microsimulation model shows a life time reintervention risk of 9% for a patients older than 60 years, which is comparable to previous predictions on biological aortic valve prostheses (3). From the literature it is known that younger patient age is associated with higher reintervention hazard after aortic valve replacement, especially in patients younger than 60 years old, mainly due to higher, progressive SVD in these younger patients (3, 45). However, we could not confirm this association between age and reintervention hazard. Notably, mean age at inclusion in the individual studies was higher than 60 years, except for 2 studies (Desai et al.[18] and LeMaire et al.[14]), which may explain this discordance in findings between younger age and reintervention outcome. Although, LeMaire et al. with a mean age at inclusion of 55 years reported lower reintervention hazard (0.23%/pt-year) compared to Desai et al. (2.72%/pt-year), with a mean age of 47 at inclusion [14, 18]. Moreover, out of 8 studies that explicitly tested association between age and reintervention, 3 found indeed that older age is associated with lower reintervention hazard. More studies on bioprosthetic aortic root replacement in younger patients are needed in order to investigate this presumed association.

Thromboembolic events

In this study, there is a high incidence of thromboembolic events, with a life time risk of TE more than >20%, after bioprosthetic aortic root replacement. The data in our meta-analysis on TE events are not comprehensive, thus the impact of the TE and e.g. discriminating

between TIA and disabling ischemic CVA is not possible. However, a previous systematic review and microsimulation study on aortic valve replacement with isolated biological (stented) valve, published by Puvimanasinghe et al. (3), report similar TE event rates (1.4%/patient-year). Additionally, the incidence of a thromboembolic event is known to increase with age (46, 47) and this may, at least partly, explain the high incidence of thromboembolic events in these patients with a pooled mean age of 65.9 years.

Subsequently the question arises whether there may be a difference with patients receiving a mechanical valve prosthesis. Although comparing patients receiving biological aortic valve prostheses and mechanical valve prostheses is hampered by the differences in patient characteristics, mainly due to the younger age in patient receiving mechanical valves; a recently published systematic review and meta-analysis on Bentall procedure in patients with mean age of 50 years, shows lower thromboembolic event rates (0.77%/patient-year) (48). Anticoagulation therapy that is required after mechanical valve implantation in these patients may also play a protective role in prevention of thromboembolic events, as TE events occur irrespective of the aortic valve replacement due to the aging process and higher atrial fibrillation incidence in the older population (47).

According to the current US and European guidelines on the management of valvular heart disease antiplatelet therapy is reasonable/may be considered for the first 3 months after biological valve replacement (2, 49). Additionally, the European guidelines state that the need for a 3 months postoperative period of anticoagulation therapy has been challenged in patients with bioprostheses, with the use of low-dose aspirin being favored as an alternative. According to our findings, with high incidence rate of TE events, it is questionable whether the proposed anticoagulation therapy is appropriate in patient receiving a bioprosthetic aortic root replacement. Further studies are needed to determine the most optimal anticoagulation therapy after biological aortic valve replacement.

Endocarditis

Although the rate of endocarditis after bioprosthetic aortic root replacement varies widely in the literature (50), our findings are comparable to a systematic review and microsimulation study on biological (stented) aortic valve replacement by Puvimanasinghe et al. [3]. Additionally, in our systematic review there are 3 large studies with an endocarditis rate of >2.8%/patient-year (22, 26, 51), with all 3 including only stentless valve prostheses. However, these studies included a relatively high proportion of patients with active

endocarditis which may explain the higher re-endocarditis rate. Moreover, we did not find an association between the type of prostheses used (stentless or stented valves) and endocarditis, neither is there to our knowledge any association reported in the literature. Hence, both stented and stentless bioprosthetic valve prostheses are good alternatives to be used in case of endocarditis. Notably, the severity of endocarditis was not included in the analysis.

The place of bioprosthetic aortic root replacement on the surgical menu

There is no perfect valve substitute for the individual patient with aortic valve or root disease as all valve prostheses are associated with certain valve-related events of varying nature. Careful weighting of the advantages and disadvantages of biological and mechanical valve substitutes tailored to the patient's unique clinical characteristics as well as patient preference, is the current golden standard. Interestingly, there is a trend toward using a biological valve in younger patients than recommended in the mentioned guidelines (5, 52). Although evidence is lacking, perhaps this is emerging due to the potential prospect of transcatheter valve-in-valve therapy in younger patients. However, it remains debatable which option is the most appropriate for the individual patient.

According to the ESC/EACTS guidelines on valvular heart disease, age limits contain an arbitrary element, and the choice of prostheses type should be individualized in a joint decision between the informed patient, cardiologist and surgeon. Although SVD is known to occur earlier in younger patients (53), mechanical valve prostheses are not desirable in all young patients. Moreover, quality of life and patient preferences must also be taken into account when choosing the most suitable valve prosthesis. Briefly, these relatively young patients (below 60-65) with a life expectancy exceeding the mean durability of a bioprosthetic valve should be aware of the prospect and risks of a reintervention later in life, but also the profits gained for not receiving a mechanical valve prostheses (e.g. avoid the use of anticoagulation therapy). Nevertheless, as individual patient norms, values and goals in life vary widely, the decision for a particular valve prosthesis should be individualized in a shared decision making process, and together with surgical experience, the most suitable surgical approach should be determined (2, 49). Our systematic review adds to the body of evidence by showing in a middle-aged patient population undergoing bioprosthetic ARR acceptable reintervention rates and valve-related event occurrence.

Limitations

This is a systematic review and meta-analysis of retrospective observational studies. Hence, inherent (known) limitations of a meta-analysis of this type should be taken into consideration (54) Furthermore, recall bias inherent to the retrospective design of all but one study and publication bias may have affected the observed outcome. In addition, the included studies represent a heterogeneous population of patients with differing patient characteristics between these populations, with patients operated in different era spanning over 20 years, and considering improvements in anticoagulation strategies, medical management of valvular heart disease and surgical techniques over the past decades, which may have influenced outcome. Moreover, a lack of uniform data reporting as proposed by the guidelines (8) may have influenced the uniformity of the pooled data.

The pooled late outcome estimates are based on the linearity assumption, while occurrence of outcome events may not be linear in nature. However, due to the lack of randomized trials where homogeneous data are present, this meta-analysis was performed to provide an overview of published outcomes after bioprosthetic aortic root replacement.

CONCLUSION

This systematic review and meta-analysis provides an overview of contemporary outcome after bioprosthetic aortic root replacement and demonstrates acceptable outcome in terms of survival and freedom from reintervention, irrespective of the type of valve prosthesis used (stented or stentless). Thromboembolic events occur relatively frequent and may reflect the higher thromboembolic risk in the middle aged and older patients. Given the observed heterogeneity of the pooled study results, in-depth analysis of potential risk factors remains challenging. It requires a collective international effort such as the recently started AVIATOR registry (55) employing uniform data definitions and high quality data collection, to push forward the knowledge on outcomes and provide clues toward optimization of treatment selection for patients requiring aortic root replacement.

REFERENCES

1. Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. Thorax 1968;23(4):338-339.
2. Vahanian A, Alfieri O, Andreotti F et al. Guidelines on the management of valvular heart disease (version 2012): The joint task force on the management of valvular heart disease of the european society of cardiology (esc) and the european association for cardio-thoracic surgery (eacts). European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2012;42(4):S1-44.
3. Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ et al. Prognosis after aortic valve replacement with the carpentier-edwards pericardial valve: Use of microsimulation. The Annals of thoracic surgery 2005;80(3):825-831.
4. Johnston DR, Soltesz EG, Vakil N et al. Long-term durability of bioprosthetic aortic valves: Implications from 12,569 implants. The Annals of thoracic surgery 2015;99(4):1239-1247.
5. Dunning J, Gao H, Chambers J et al. Aortic valve surgery: Marked increases in volume and significant decreases in mechanical valve use--an analysis of 41,227 patients over 5 years from the society for cardiothoracic surgery in great britain and ireland national database. The Journal of thoracic and cardiovascular surgery 2011;142(4):776-782 e773.
6. de Kerchove L, Glineur D, El Khoury G, Noirhomme P. Stentless valves for aortic valve replacement: Where do we stand? Curr Opin Cardiol 2007;22(2):96-103.
7. Dunning J, Graham RJ, Thambyrajah J, Stewart MJ, Kendall SW, Hunter S. Stentless vs. Stented aortic valve bioprostheses: A prospective randomized controlled trial. European heart journal 2007;28(19):2369-2374.
8. Akins CW, Miller DC, Turina MI et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. The Annals of thoracic surgery 2008;85(4):1490-1495.
9. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC medical research methodology 2005;5:13.
10. Beller EM, Glasziou PP, Altman DG et al. Prisma for abstracts: Reporting systematic reviews in journal and conference abstracts. PLoS medicine 2013;10(4):e1001419.
11. Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ et al. Choice of a mechanical valve or a bioprosthesis for avr: Does cabg matter? European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2003;23(5):688-695; discussion 695.
12. Takkenberg JJ, Puvimanasinghe JP, Grunkemeier GL. Simulation models to predict outcome after aortic valve replacement. The Annals of thoracic surgery 2003;75(5):1372-1376.
13. Arias E. United states life tables, 2004. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System 2007;56(9):1-39.

14. Melina G, De Robertis F, Gaer JA, Amrani M, Khaghani A, Yacoub MH. Mid-term pattern of survival, hemodynamic performance and rate of complications after medtronic freestyle versus homograft full aortic root replacement: Results from a prospective randomized trial. The Journal of heart valve disease 2004;13(6):972-975; discussion 975-976.
15. Kon ND, Riley RD, Adair SM, Kitzman DW, Cordell AR. Eight-year results of aortic root replacement with the freestyle stentless porcine aortic root bioprosthesis. The Annals of thoracic surgery 2002;73(6):1817-1821.
16. Auriemma S, D'Onofrio A, Brunelli M et al. Long-term results of aortic valve replacement with edwards prima plus stentless bioprosthesis: Eleven years' follow up. The Journal of heart valve disease 2006;15(5):691-695.
17. Dapunt OE, Easo J, Holzl PP et al. Stentless full root bioprosthesis in surgery for complex aortic valve-ascending aortic disease: A single center experience of over 300 patients. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2008;33(4):554-559.
18. LeMaire SA, Green SY, Sharma K et al. Aortic root replacement with stentless porcine xenografts: Early and late outcomes in 132 patients. Annals of Thoracic Surgery 2009;87(2):503-513.
19. Zannis K, Deux JF, Tzvetkov B et al. Composite freestyle stentless xenograft with dacron graft extension for ascending aortic replacement. The Annals of thoracic surgery 2009;87(6):1789-1794.
20. Baraki H, Al Ahmad A, Sarikouch S et al. The first fifty consecutive bentall operations with a prefabricated tissue-valved aortic conduit: A single-center experience. Journal of Heart Valve Disease 2010;19(3):286-291.
21. El-Hamamsy I, Clark L, Stevens LM et al. Late outcomes following freestyle versus homograft aortic root replacement. Results from a prospective randomized trial. Journal of the American College of Cardiology 2010;55(4):368-376.
22. Desai ND, McCarthy F, Moser W et al. Durability of porcine bioroots in younger patients with aortic root pathology: A propensity-matched comparison with composite mechanical roots. The Annals of thoracic surgery 2011;92(6):2054-2061.
23. Ennker IC, Albert A, Dalladaku F, Rosendahl U, Ennker J, Florath I. Midterm outcome after aortic root replacement with stentless porcine bioprostheses. Eur J Cardio-thorac Surg 2011;40(2):429-434.
24. Galinanes M, Meduoye A, Ferreira I, Sosnowski A. Totally biological composite aortic stentless valved conduit for aortic root replacement: 10-year experience. Journal of cardiothoracic surgery 2011;6:86.
25. Kaya A, Heijmen RH, Kelder JC, Schepens MA, Morshuis WJ. Stentless biological valved conduit for aortic root replacement: Initial experience with the shelhigh bioconduit model nr-2000c. The Journal of thoracic and cardiovascular surgery 2011;141(5):1157-1162.

26. Kaya A, Heijmen RH, Kelder JC, Morshuis WJ. First 102 patients with the biovalsalva conduit for aortic root replacement. The Annals of thoracic surgery 2012;94(1):72-77.
27. Lehr EJ, Wang PZT, Oreopoulos A, Kanji H, Norris C, MacArthur R. Midterm outcomes and quality of life of aortic root replacement: Mechanical vs biological conduits. Can J Cardiol 2011;27(2):262.e215-262.e220.
28. Pagni S, Slater AD, Trivedi JR et al. Proximal thoracic aortic replacement for aneurysmal disease using the freestyle stentless bioprosthesis: A 10-year experience. Annals of Thoracic Surgery 2011;92(3):873-879.
29. Bach DS, Kon ND. Long-term clinical outcomes 15 years after aortic valve replacement with the freestyle stentless aortic bioprosthesis. The Annals of thoracic surgery 2014;97(2):544-551.
30. Meszaros K, Liniger S, Czerny M et al. Mid-term results of aortic root replacement using a self-assembled biological composite graft. Interactive cardiovascular and thoracic surgery 2014.
31. Mohammadi S, Kalavrouziotis D, Voisine P et al. Bioprosthetic valve durability after stentless aortic valve replacement: The effect of implantation technique. The Annals of thoracic surgery 2014;97(6):2011-2018.
32. Benetis R, Bolys R, Jakuska P et al. Long-term clinical and hemodynamic outcomes after operations on aortic root using stentless aortic valves. Exp Clin Cardiol 2014;20(7):307-327.
33. Sherrah AG, Jeremy RW, Puranik R et al. Long term outcomes following freestyle stentless aortic bioprosthesis implantation: An australian experience. Heart, lung & circulation 2016;25(1):82-88.
34. Sahin A, Muggler O, Sromicki J et al. Long-term follow-up after aortic root replacement with the shelhigh(r) biological valved conduit: A word of caution! European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2016.
35. Svensson LG, Pillai ST, Rajeswaran J et al. Long-term survival, valve durability, and reoperation for 4 aortic root procedures combined with ascending aorta replacement. The Journal of thoracic and cardiovascular surgery 2016;151(3):764-771 e761-764.
36. Yang JA, Neely RC, Stewart AS. Modified bentall procedure with composite biologic grafts. Journal of cardiac surgery 2013;28(6):731-735.
37. Gleason TG, David TE, Coselli JS, Hammon Jr JW, Bavaria JE. St. Jude medical toronto biologic aortic root prosthesis: Early fda phase ii ide study results. The Annals of thoracic surgery 2004;78(3):786-793.
38. Etz CD, Bischoff MS, Bodian C et al. The bentall procedure: Is it the gold standard? A series of 597 consecutive cases. The Journal of thoracic and cardiovascular surgery 2010;140(6 Suppl):S64-70; discussion S86-91.
39. Mazzola A, Di Mauro M, Pellone F et al. Freestyle aortic root bioprosthesis is a suitable alternative for aortic root replacement in elderly patients: A propensity score study. The Annals of thoracic surgery 2012;94(4):1185-1190.

40. Badiu CC, Deutsch MA, Bleiziffer S et al. Early hemodynamic performance of the biovalsalva valved conduit after aortic root replacement. The Journal of heart valve disease 2014;23(1):97-104.
41. Urbanski PP, Dinstak W, Rents W, Heinz N, Diegeler A. Long-term results after aortic root replacement using self-assembled valve composite grafts in patients with small aortic annulus. Interactive cardiovascular and thoracic surgery 2014;18(2):159-163.
42. Sherrah AG, Edelman JJ, Thomas SR et al. The freestyle aortic bioprosthesis: A systematic review. Heart, lung & circulation 2014;23(12):1110-1117.
43. Stamou SC, Williams ML, Gunn TM, Hagberg RC, Lobdell KW, Kouchoukos NT. Aortic root surgery in the united states: A report from the society of thoracic surgeons database. The Journal of thoracic and cardiovascular surgery 2015;149(1):116-122 e114.
44. Head SJ, Mokhles MM, Osnabrugge RL et al. 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. European heart journal 2012;33(12):1518-1529.
45. Chan V, Malas T, Lapierre H et al. Reoperation of left heart valve bioprostheses according to age at implantation. Circulation 2011;124(11 Suppl):S75-80.
46. Yiin GS, Howard DP, Paul NL et al. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: A population-based study. Circulation 2014;130(15):1236-1244.
47. Rothwell PM, Coull AJ, Giles MF et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in oxfordshire, uk from 1981 to 2004 (oxford vascular study). Lancet 2004;363(9425):1925-1933.
48. Mookhoek A, Korteland NM, Arabkhani B et al. Bentall procedure: A systematic review and meta-analysis. The Annals of thoracic surgery 2016.
49. Nishimura RA, Otto CM, Bonow RO et al. 2014 aha/acc guideline 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. Journal of the American College of Cardiology 2014;63(22):e57-185.
50. Sherrah AG, Edelman JJB, Thomas SR et al. The freestyle aortic bioprosthesis: A systematic review. Heart Lung Circul 2014.
51. Dapunt OE, Easo J, Holzl PPF et al. Stentless full root bioprosthesis in surgery for complex aortic valve-ascending aortic disease: A single center experience of over 300 patients. European Journal of Cardio-Thoracic Surgery 2008;33(4):554-558.
52. Head SJ, Kappetein AP. Aortic valve replacement in younger adults: A biological valve is not the logical choice. European heart journal 2015.

53. Bourguignon T, Bouquiaux-Stablo AL, Candolfi P et al. Very long-term outcomes of the carpentier-edwards perimount valve in aortic position. The Annals of thoracic surgery 2015;99(3):831-837.
54. Ioannidis JP, Lau J. Pooling research results: Benefits and limitations of meta-analysis. The Joint Commission journal on quality improvement 1999;25(9):462-469.
55. 2014 The aviator registry database: An overview of the intentions and goals of this collaborative working group on aortic valve and root treatment. Available.

APPENDIX 1

Embase

((bio* NEAR/3 (bentall* OR valsalva*)) OR biobentall* OR Biovalsalva* OR (Freestyle NEAR/3 (bioprosthe* OR 'aortic valve' OR 'aortic valves' OR 'aorta valve' OR 'aorta valves' OR xenograft OR 'aortic root' OR 'aortic roots' OR 'aorta root' OR 'aorta roots'))):ab,ti OR ('aorta valve prosthesis'/de OR 'aorta valve replacement'/de OR 'aorta valve'/de OR (aort* NEAR/3 valve*):ab,ti) AND ('aorta root'/de OR 'aortic root surgery'/de OR (aort* NEAR/3 root*):ab,ti) AND ('aorta valve prosthesis'/de OR 'aorta valve replacement'/de OR 'aortic root surgery'/de OR 'aorta valve prosthesis'/exp OR ((root* OR valve* OR aort*) NEAR/3 (replace* OR conduit* OR prosthe* OR bioprosthe*)):ab,ti) AND (bioprosthesis/de OR 'heart valve bioprosthesis'/exp OR xenograft/de OR (freestyle* OR bioprosth* OR biologic* OR (bio NEXT/1 prosth*) OR porcine* OR xenograft* OR (xeno* NEXT/1 (graft* OR transplant*)) OR xenotransplant* OR 'Tissue-valved'):ab,ti) NOT ('mitral valve'/de OR 'Ross procedure'/de OR (mitral OR (Ross NEXT/1 (procedure* OR operat*)) OR (pulmonar* NEXT/1 autograft*)):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Conference Paper]/lim OR [Editorial]/lim)

Medline (OvidSP)

((bio* ADJ3 (bentall* OR valsalva*)) OR biobentall* OR Biovalsalva* OR (Freestyle ADJ3 (bioprosthe* OR "aortic valve" OR "aortic valves" OR "aorta valve" OR "aorta valves" OR xenograft OR "aortic root" OR "aortic roots" OR "aorta root" OR "aorta roots"))).ab,ti. OR ("aortic valve"/ OR (aort* ADJ3 valve*).ab,ti.) AND ((aort* ADJ3 root*).ab,ti.) AND ("Heart Valve Prosthesis"/ OR "Heart Valve Prosthesis Implantation"/ OR ((root* OR valve* OR aort*) ADJ3 (replace* OR conduit* OR prosthe* OR bioprosthe*)).ab,ti.) AND (bioprosthesis/ OR (freestyle* OR bioprosth* OR biologic* OR (bio ADJ prosth*) OR porcine* OR xenograft* OR (xeno* ADJ (graft* OR transplant*)) OR xenotransplant* OR "Tissue-valved").ab,ti.) NOT ("mitral valve"/ OR (mitral OR (Ross ADJ (procedure* OR operat*)) OR (pulmonar* ADJ autograft*)).ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Cochrane

((bio* NEAR/3 (bentall* OR valsalva*)) OR biobentall* OR Biovalsalva* OR (Freestyle NEAR/3 (bioprosthe* OR 'aortic valve' OR 'aortic valves' OR 'aorta valve' OR 'aorta valves' OR xenograft OR 'aortic root' OR 'aortic roots' OR 'aorta root' OR 'aorta roots'))):ab,ti OR ((aort* NEAR/3 valve*):ab,ti) AND ((aort* NEAR/3 root*):ab,ti) AND (((root* OR valve* OR aort*) NEAR/3 (replace* OR conduit* OR prosthe* OR bioprosthe*)):ab,ti) AND ((freestyle* OR bioprosth* OR biologic* OR (bio NEXT/1

prosth*) OR porcine* OR xenograft* OR (xeno* NEXT/1 (graft* OR transplant*)) OR xenotransplant* OR 'Tissue-valved'):ab,ti) NOT ((mitral OR (Ross NEXT/1 (procedure* OR operat*)) OR (pulmonar* NEXT/1 autograft*)):ab,ti)

Web-of-science

TS=(((bio* NEAR/3 (bentall* OR valsalva*)) OR biobentall* OR Biovalsalva* OR (Freestyle NEAR/3 (bioprosthe* OR "aortic valve" OR "aortic valves" OR "aorta valve" OR "aorta valves" OR xenograft OR "aortic root" OR "aortic roots" OR "aorta root" OR "aorta roots"))) OR ((aort* NEAR/3 valve*)) AND ((aort* NEAR/3 root*)) AND (((root* OR valve* OR aort*) NEAR/3 (replace* OR conduit* OR prosthe* OR bioprosthe*))) AND ((freestyle* OR bioprosth* OR biologic* OR (bio NEAR/1 prosth*) OR porcine* OR xenograft* OR (xeno* NEAR/1 (graft* OR transplant*)) OR xenotransplant* OR "Tissue-valved")) NOT ((mitral OR (Ross NEAR/1 (procedure* OR operat*)) OR (pulmonar* NEAR/1 autograft*)))) AND DT=(Article)

Scopus

TITLE-ABS-KEY(((bio* W/3 (bentall* OR valsalva*)) OR biobentall* OR Biovalsalva* OR (Freestyle W/3 (bioprosthe* OR "aortic valve" OR "aortic valves" OR "aorta valve" OR "aorta valves" OR xenograft OR "aortic root" OR "aortic roots" OR "aorta root" OR "aorta roots"))) OR ((aort* W/3 valve*)) AND ((aort* W/3 root*)) AND (((root* OR valve* OR aort*) W/3 (replace* OR conduit* OR prosthe* OR bioprosthe*))) AND ((freestyle* OR bioprosth* OR biologic* OR (bio W/1 prosth*) OR porcine* OR xenograft* OR (xeno* W/1 (graft* OR transplant*)) OR xenotransplant* OR "Tissue-valved")) AND NOT ((mitral OR (Ross W/1 (procedure* OR operat*)) OR (pulmonar* W/1 autograft*)))) AND DOCTYPE(ar)

PubMed publihser

((bio*[tiab] AND (bentall*[tiab] OR valsalva*[tiab])) OR biobentall*[tiab] OR Biovalsalva*[tiab] OR (Freestyle AND (bioprosthe*[tiab] OR aortic valve*[tiab] OR aorta valve*[tiab]OR xenograft OR aortic root*[tiab] OR aorta root*[tiab]))) OR ((aort*[tiab] AND valve*[tiab])) AND ((aort*[tiab] AND root*[tiab])) AND (((root*[tiab] OR valve*[tiab] OR aort*[tiab]) AND (replace*[tiab] OR conduit*[tiab] OR prosthe*[tiab] OR bioprosthe*[tiab]))) AND ((freestyle*[tiab] OR bioprosth*[tiab] OR biologic*[tiab] OR bio prosth*[tiab] OR porcine*[tiab] OR xenograft*[tiab] OR xeno graft*[tiab] OR xeno transplant*[tiab] OR xenotransplant*[tiab] OR Tissue-valved*[tiab])) NOT ((mitral[tiab] OR Ross procedure*[tiab] OR ross operat*[tiab] OR pulmonary autograft*[tiab])) AND publisher[sb]

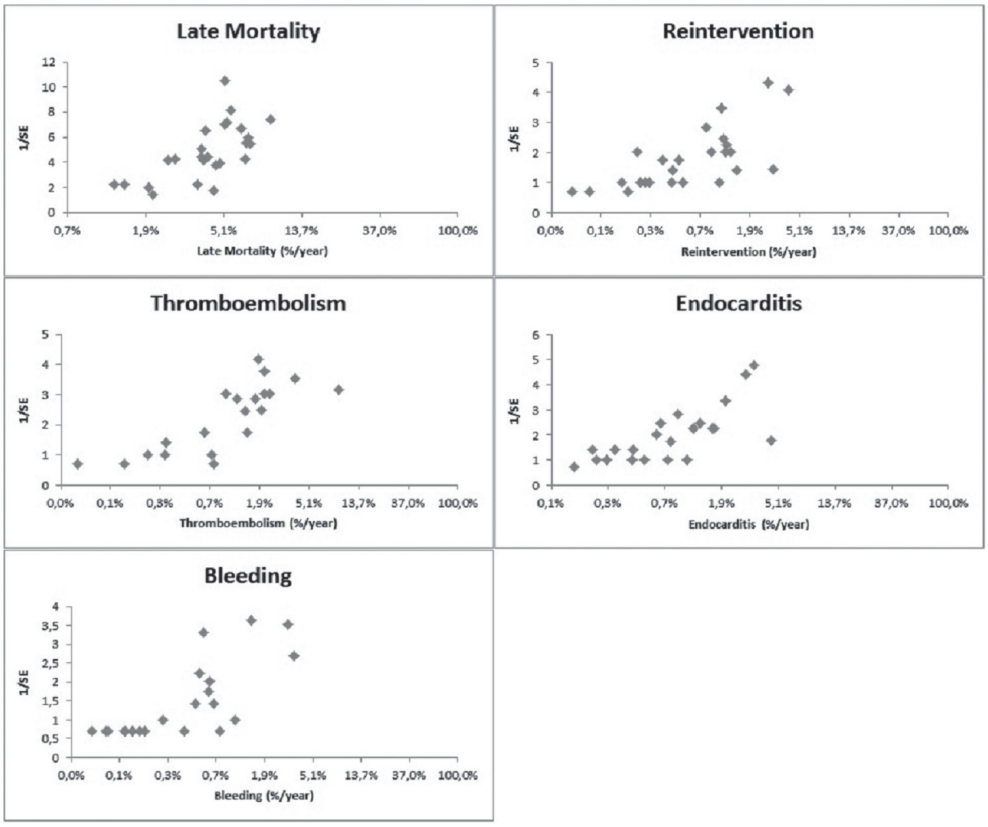
APPENDIX 2

Study characteristics of included publications

First Author	Publi-cation Year	Implantation Period	Patients (N)	Mean Age (yrs)	Type of prosthesis	Mean FU (yrs)	BAV (%)	AD (%)	CTD (%)
Kon	2002	1992-1997	104	72	Stentless	6	-	-	-
Gleason	2004	2001-2003	176	63	Mixed	1	37	8	12
Melina	2004	1993-2003	80	66	Stentless	4	-	-	-
Auriemma	2006	1993-2004	318	69	Stentless	3	-	20	-
Dapunt	2008	1999-2007	317	70.2	Stentless	2	-	14	-
LeMaire	2009	2001-2007	132	54.8	Stentless	3	34	10	20
Zannis	2009	1997-2008	55	71	Stentless	2	18	9	-
Baraki	2010	2007-2009	50	65	Stentless	8	-	4	-
El- Hamamsy	2010	1997-2005	90	66	Stentless	7	-	-	-
Etz	2010	1995-2008	307	71	Stented	7	27	48	1
Desai	2011	1997-2007	138	47,4	Stentless	5	-	8	-
Ennker	2011	1996-2007	301	72	Stentless	10	-	-	-
Galinanes	2011	1999-2008	67	67.9	Stentless	7	-	9	-
Kaya	2011	1998-2007	175	71.1	Stentless	3	9	11	3
Lehr	2011	1998-2007	93	60.9	Stentless	3	-	11	5
Pagni	2011	1998-2009	170	67.4	Stentless	3	21	9	-
Kaya	2012	2008-2011	102	70.9	Stentless	1	16	4	2
Mazzola	2012	2001-2010	79	73	Stented	4	18	0	0
Yang	2013	2004-2010	150	66.3	Mixed	1	-	-	1
Bach	2014	1992-1997	178	71.7	Stentless	6	-	-	-
Badiu	2014	2000-2011	91	65	Stented	4	-	22	2
Benetis	2014	1997-2012	51	72.5	Stentless	5	12	-	-
Meszaros	2014	2005-2011	201	66	Stentless	2	0	21	0
Mohammadi	2014	1993-2013	101	65.2	Stentless	10	43	0	0
Urbanski	2015	1998-2008	79	-	Stented	6	-	1	-
Sherrah	2015	2004-2014	237	63.2	Stentless	2	-	9	-
Sahin	2016	2001-2005	63	62	Stentless	10	-	-	-
Svensson	2016	1995-2011	297	66	Unspecified	6	24	-	-
Gaudino	2016	1997-2014	421	63.3	Stented	2	52	0	3.1

AD = Acute Dissection, BAV = Bicuspid Aortic Valve, CTD = Connective Tissue Disease, FU = Follow-up

APPENDIX 3

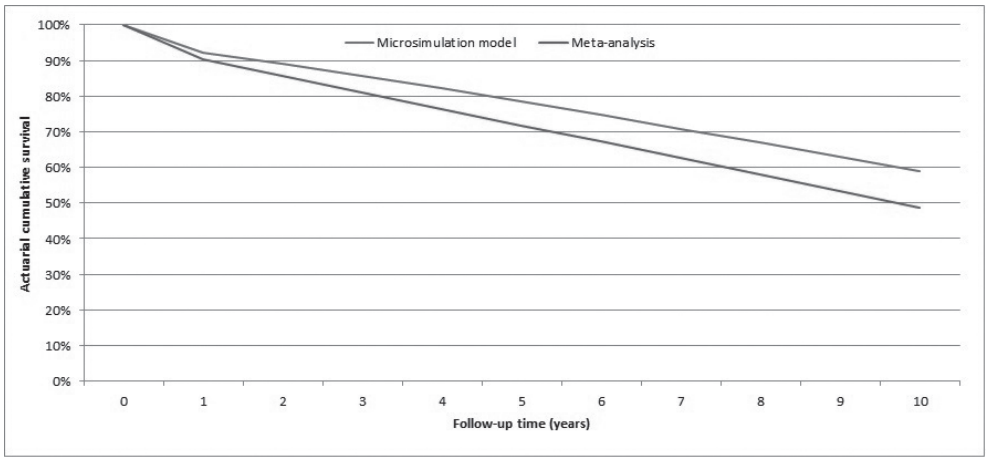


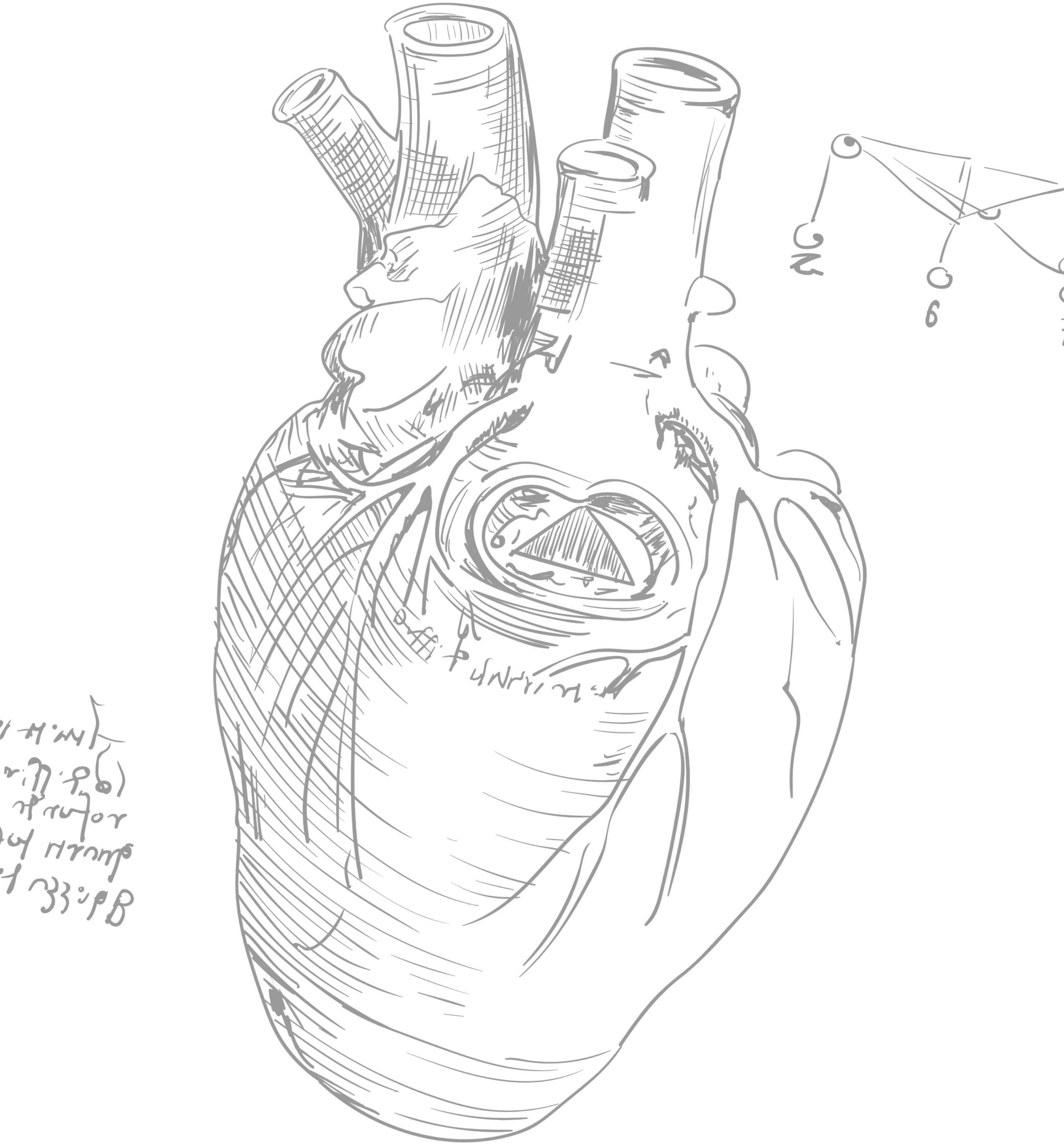
Funnel plots for estimating publication bias.

SE = standard error.

APPENDIX 4

The actuarial survival curve obtained from the microsimulation model run for 10,000 iterations at the pooled mean age (66 years) and male/female ratio (67.6% male) observed in the meta-analysis compared to the pooled overall mortality observed in the meta-analysis.





Chapter 7

Allografts in aortic position: Insights from a 27-year, single-center prospective study

Arabkhani B, Bekkers JA, Andrinopoulou ER, Roos-Hesselink JW, Takkenberg JJ, Bogers AJ

J Thorac Cardiovasc Surg. 2016 Dec;152(6):1572-1579

ABSTRACT

Objective. Over the past decades the indication for allograft implantation in aortic position has evolved. The purpose of this study is to report long-term survival, allograft durability, and potential risk factors.

Methods. Between 1987 and 2010, 353 patients underwent aortic valve replacements using allograft (92 subcoronary, 261 root replacement; 98% aortic allografts). Patient characteristics, survival, valve durability, and valve-related events were analyzed. Additionally, patients were followed with standardized echocardiography. A joint modeling approach was used to detect the effect of (echocardiographic) variables on mortality and reoperation hazard.

Results. Mean age was 45 years (range 1 month to 84 years); 71% males. Etiology: endocarditis 32% (active 22%), congenital 31%, degenerative 9%, aneurysm/dissection 12%, rheumatic 6%, and prosthetic valve failure 10%. Hospital mortality: 5.9% (N = 21). During follow-up (mean 12 years, range 0-24, 99% complete), 113 patients died. Twenty-year cumulative survival was 41% (95% CI: 32-50). Valve-related reoperations occurred in 117 patients: 100 SVD, 9 NSVD, and 8 endocarditis. Competing-risk analysis predicted that at 20 years 31% died, and 30% were alive without reoperation. Younger patient-age was associated with increased reoperation. During follow-up left ventricular dilatation and severe aortic regurgitation were associated with mortality (p= 0.006 and 0.005 respectively), and ≥ grade 3 aortic regurgitation during follow-up was associated with reoperation risk (p= 0.001).

Conclusions. After almost 3 decades of experience with allografts in aortic position, the indication for use has become selective, mainly because of progressive SVD over time. In case of complex aortic root pathology and active endocarditis allografts may still be useful.

Ultramini abstract. Allografts have excellent clinical results in the first postoperative decade. However, from the second postoperative decade SVD becomes more apparent and a reoperation hazard will increase. Infective endocarditis (reinfection) hazard after allograft implantation is low. Allograft may be used in case of endocarditis and complex aortic root pathology.

INTRODUCTION

The indication for implantation of allografts in aortic position has changed over the last decades. Initially allografts were regarded as a good alternative to biological and mechanical valve substitutes because of the excellent hemodynamics, low thrombo-embolic complications, good resistance to endocarditis, and no need for anticoagulation therapy. In addition, aortic allografts were found very useful in complex aortic root pathology with aortic annular destruction because of the flexible allograft tissue properties that allow for reconstruction of destructed tissue. However, the durability of the allografts showed to be limited and age dependent and the advantages of the allografts must be weighed against the risk of a possible reoperation due to structural valve deterioration (SVD) over time [1, 2].

In 1987 we started a prospective cohort study in our institution, using cryopreserved allografts for aortic valve and root disease. The allografts were used as a simple valve substitute, using a sub-coronary implantation technique, as well as full root replacement with reimplantation of the coronary arteries. Our earlier reports described the mid-term clinical outcome [3-5]. After almost 3 decades we are now able to present the long-term results of this prospective cohort. Comparable long-term follow-up has not frequently been reported on. The aim of our study is to describe the long term clinical outcome after aortic valve and/or root replacement with allografts. In addition, the associations of several echocardiographic variables with survival and reintervention on implanted allograft are displayed.

MATERIALS AND METHODS

Between April 1987 and March 2013, 353 consecutive patients underwent allograft aortic valve or root replacement at Erasmus University Medical Center. All patients receiving an allograft in the aortic position are part of this prospective follow up study in our center [3, 6]. Institutional Review Board approval was obtained for this study (MEC 12-477), and informed consent was waived.

Operation technique

Cardiopulmonary bypass with moderate hypothermia was used in all surgical procedures. Crystalloid cardioplegia and topical cooling were used for myocardial protection. In addition, deep hypothermia and circulatory arrest were used in 37 patients with ascending aorta and/or arch pathology. Initially the subcoronary technique was the

preferred technique for aortic valve replacement, while from 1998 the root replacement technique was performed (Appendix 1). A subcoronary technique was initially performed with scalloping of the sinuses of Valsalva (N=32), while later on the non-coronary cusp was preserved (N=63). Root replacement was performed as a freestanding root with reimplantation of the coronary arteries.

Follow-up

All patients who received an allograft (98% aortic) at Erasmus University Medical Center were followed up prospectively through their visits to their cardiologist and by annual telephone interviews. Additionally, echocardiographic follow-up was obtained at 6 months, 1 year postoperative, and thereafter biennially by means of serial standardized echocardiography. Valve-related events were registered according to the 2008 American Association for Thoracic Surgery/Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery guidelines for reporting mortality and morbidity after cardiac valve interventions [7]. The study database was frozen on December 31, 2014. Follow-up was 98% completed: eight patients were lost to follow-up because of emigration.

Statistical methods

Continuous data are presented as means (standard deviation; range). Comparison between groups was performed using the unpaired t-test unless data were not normally distributed (Mann-Whitney U-test in these cases). Categorical data are presented as proportions. Comparison was done by chi-square test or the Fisher-exact test, where appropriate. The study started at the time of allograft implantation and ended at the time of event (death/reoperation) or at the last follow-up date. Univariable logistic regression analysis was used to study potential variables affecting early mortality (hospital and/or 30 day mortality).The Cox proportional hazards model was used for univariable analyses of time-related events. Survival was analyzed using the Kaplan-Meier method (Appendix 2). Survival and freedom from overall re-operation were presented using the cumulative incidence function, from a competing risk analysis. Tests were performed two-sided and a p-value of 0.05 was considered statistically significant. Variables that were tested as potential risk factors for hospital mortality, late mortality, and reoperation are displayed in Appendix 3. For the analyses mentioned above, Statistical Package for Social Sciences (SPSS) 21.0 for Windows statistical software (SPSS, Chicago, IL, USA) was used. Advanced statistical linear mixed-effects model was used to assess changes in echocardiographic measurements of hemodynamic variables while accounting for the correlation between

repeated measurements in each patient. Residuals plot was used to test the assumption of homoscedasticity in the model. Details of how the mixed-effects models were built are presented in Appendix 4. Furthermore, joint models of longitudinal and survival data were used to test whether echocardiographic variables were associated with survival or reoperation hazard. Specifically, this approach accounts for the biological variation in repeated (echocardiographic) measured variables within patients [8]. The association of the following variables (which are of clinical interest) with survival and reoperation were tested: LVEDD (in mm), LEVSD (in mm), STJ (in mm), Annulus diameter (in mm), Aortic regurgitation (grade), and Aortic gradient (in mmHg). For the advanced joint modeling R (version 3.1.3, available at: www.r-project.org) was used. A more detailed specification of the mixed-effects model and the joint model together with the syntax is provided in Appendix 4.

RESULTS

The mean follow-up was 11.5 years (range 0-24.5 years), with a total follow-up of 4188 patient years. There were several differences in characteristics between the subcoronary implantation and the full root replacement recipients. Table 1 displays patient characteristics and the preoperative data. Coronary artery bypass grafting (CABG) due to complications related to reimplantation of the coronary arteries was necessary in six patients, of which two subsequently died.

Indication for allograft implantation

The indication for implantation of an allograft has changed over the years. Between 1987 and 2005 334 patients received an allograft in aortic position. The etiology of disease was: 33% endocarditis; 23% prosthetic valve/allograft failure; 24% bicuspid valve disease; 7% rheumatic disease; 8% senile valve dysfunction; and 6% congenital disease. Between 2006 and 2014 the etiology of disease was (N= 26): 41% bicuspid valve disease; 35% endocarditis; 12% senile valve dysfunction; *8%* prosthetic valve/allograft failure; 4% rheumatic disease. Figure 1 displays the etiology of disease, thus indication for allograft implantation over the years. Allograft characteristics are displayed in appendix 5.

TABLE 1. Patient characteristics and perioperative data.

	All patients (N= 353)	Subcor technique (N = 92)	Root replacement (N = 261)
Mean age (yrs (SD; range))	45 (16; 0.1-84)	46 (16; 14-84)	44 (17; 0.1-77)
Male	72%	75%	71%
Creatinin (µmol/l; (SD; range))	102 (85; 22-930)	113 (107; 48-930)	99 (76; 22-900) [a]
Prior cardiac surgery	26.3% (N = 93)	17.4% (N = 16)	29.5% (N = 77)
Hypertension	14.0 % (N = 49)	14.1% (N = 13)	13.8% (N = 36)
Ischemic heart disease	8,5% (N = 30)	10.8% (N = 10)	7.6% (N = 20)
Connective tissue disease	5% (N = 18)	0	6.8% (N = 18) [a]
Diabetes mellitus	3.4% (N = 12)	4.3% (N = 4)	3.0% (N = 8)
Prior CVA	5,1% (N = 18)	8.6% (N = 8)	3.8% (N = 10)
Ventilation support	5,9% (N = 21)	0	8% (N = 21) [a]
Urgent operation (< 24 h)	11% (N = 39)	2.1% (N = 2)	14.2% (N = 37) [a]
Diagnosis			
Aortic valve regurgitation (AR)	79.4% (N = 201)	56.7% (N = 52)	57.1% (N = 149)
Aortic valve stenosis (AS)	18.4 % (N = 65)	27.2% (N = 25)	15.3% (N = 40)
Combined AR + AS	17.5% (N = 62)	16.1% (N = 15)	18.0% (N = 47)
Other	6.2% (N = 22)	0	8.4% (N = 22)
Etiology			
Endocarditis	32.5% (N = 115)	33.6% (N = 31)	32.2% (N = 84)
Active	N = 80	N = 13	N = 67
Congenital (incl. bicuspid*)	31.1% (N = 111)	32.6 % (N = 30)	30.0% (N = 81)
Degenerative	8.8% (N = 31)	11.9% (N = 11)	7.6% (N = 20)
Aneurysm	7.1% (N= 25)	0	9.5% (N = 25) [a]
Rheumatic	6.2% (N = 22)	15.2% (N = 14)	3.1% (N = 8)
Dissection	5.1% (N = 18)	0	6.9% (N = 18)
Other (prosthetic valves)	7.9% (N = 28)	6.5% (N = 6)	8.4% (N = 22)
Systolic LVF			
Good	74.2% (N = 267)	78.9% (N = 75)	72.5% (N = 192)
Impaired	18.3% (N = 66)	16.8% (N =16)	18.9% (N = 50)
Moderate/Severe	6.6% (N = 24)	4.3% (N = 4)	7.5% (N = 20)
Preoperative NYHA class			
I	25.8% (N = 92)	12,6% (N= 12)	30.5% (N = 80)
II	26.9% (N = 96)	27.4% (N = 26)	26.7% (N = 70)
III	29.7% (N = 106)	48.4% (N = 46)	22.9% (N = 60)
IV	17.7% (N = 63)	11.6% (N = 11)	19.8% (N = 52)

Perioperative characteristics Valve requiring operation			
Bicuspid	36% (N = 130)	44% (N = 42)	33% (N = 88)
Tricuspid	48% (N = 174)	47% (N = 45)	49% (N = 129)
Quadricuspid	1% (N = 2)	0	1% (N = 2)
Prosthesis	12% (n = 44)	4% (N = 4)	15% (N = 40) [a]
Allograft	1% (N = 4)	3% (N = 3)	1% (N = 3)
Concomitant procedures	51% (N = 184)	32% (N =30)	58% (N = 154) [a]
Aortic cross clamp time min (SD; range)	142 (58; 0 - 357)	132 (30; 79 - 248)	145 (65; 0 - 357)
Perfusion time min (SD; range)	198 (78; 79 -589)	176 (40; 116 - 316)	206 (86; 79 - 589)
Circulatory arrest (N = 35) min (SD; range)	4 (14; 0 - 163)	0	5 (17; 0 - 163)
Procedure related CABG	2% (N = 6)	0	2% (N = 6)
Bleeding requiring reoperation	13% (N = 47)	14% (N = 13)	13% (N = 34)
Permanent pacemaker	4% (N = 16)	4% (N = 4)	5% (N = 12)
Perioperative CVA	3% (N = 11)	3% (N = 3)	3% (N = 8)
Early mortality (< 30 days)	5.9% (N = 21)	4.3% (N = 4)	6.5% (N = 17)

[a] Statistical significant difference between the 2 groups (unpaired t-test or Mann–Whitney U-test)
*Endocarditis excluded

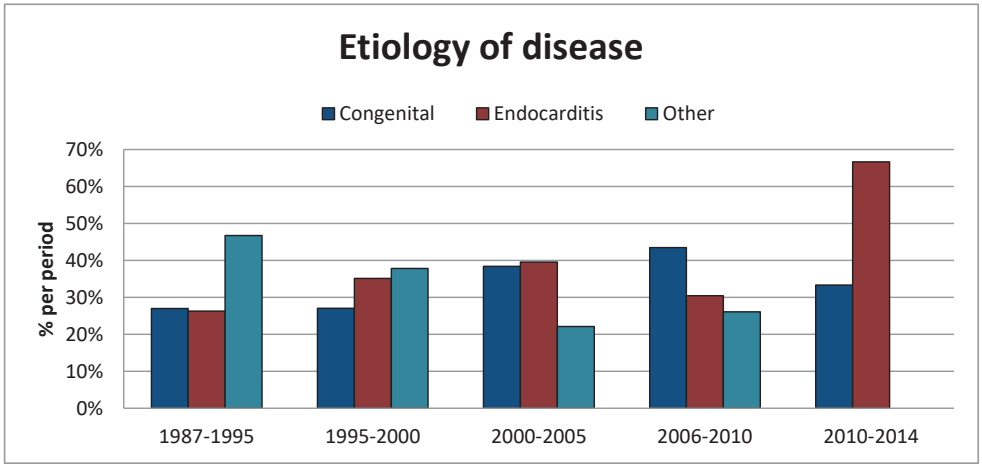


FIGURE 1. Evolution of indication for allograft implantation over the years.

Early mortality and morbidity

Operative mortality concerned six patients. This was attributed to persistent massive bleeding in three patients (one had an active endocarditis with abscesses, one with an acute dissection, and one patient who underwent a reoperation for paravalvular leakage of a mechanical valve), left ventricular failure in two patients (one patient with an active prosthetic-valve endocarditis and one patient with acute endocarditis including a fistula to the left atrium), and finally one patient who died during a salvage procedure of a prosthetic aortic valve endocarditis with extensive tissue destruction of the left ventricular outflow tract and proximal ascending aorta with abscesses. Another 15 patients died within 30 days postoperative or during the same hospitalization. The causes of death were registered as cardiac and not valve-related in 10 patients. Three valve-related early deaths concerned two patients who died of a major intracerebral bleeding and one patient with a myocardial infarction caused by kinking of the reimplanted right coronary artery. Another patient had an acute endocarditis and died as a result of a stroke caused by septic emboli, and finally one patient who was operated on because of an active endocarditis of a biological valve substitute who developed multi-organ failure and died. Early mortality was 5.8%.

In six patients additional CABG for complications related to reimplantation of the coronary arteries was necessary, of which two subsequently died. In one patient, coronary orifice stenosis occurred because the left coronary artery button was too small. Another patient had annular calcifications extending up to the right coronary ostium that was qualitatively poor and ruptured after reimplantation. A third patient had an active bioprosthetic endocarditis with abscesses, and after reimplantation the edematous right coronary artery (RCA) button ruptured. Two other patients experienced right ventricular dysfunction due to kinking of the reimplanted RCA. In another patient, the coronary artery buttons were large, possibly causing malperfusion of the right and left coronary artery.

Late survival

During follow-up another 113 patients died. There were 72 non-valve-related deaths. In addition, 42 patients died from a valve related cause: 26 patients died sudden, unexpected, and unexplained; 5 patients died from a major bleeding (3 of them were on anticoagulation therapy because of atrial fibrillation in 2, and a mechanical mitral valve prosthesis in 1 patient); 4 patients who had structural (allograft) valve deterioration died of heart failure; 3 patients died due to endocarditis; another patient died after a CVA. The

cause of death could not be retrieved in 3 patients. Cumulative survival (including early mortality) was 98.20% (95% CI 96-99%) at 1 year, 87.5% (95% CI 83-90%) at 10 years, and 40.0% (95% CI 32-49%) at 20 years respectively. Figure 2 shows the KM-curve of cumulative late survival, including early mortality.

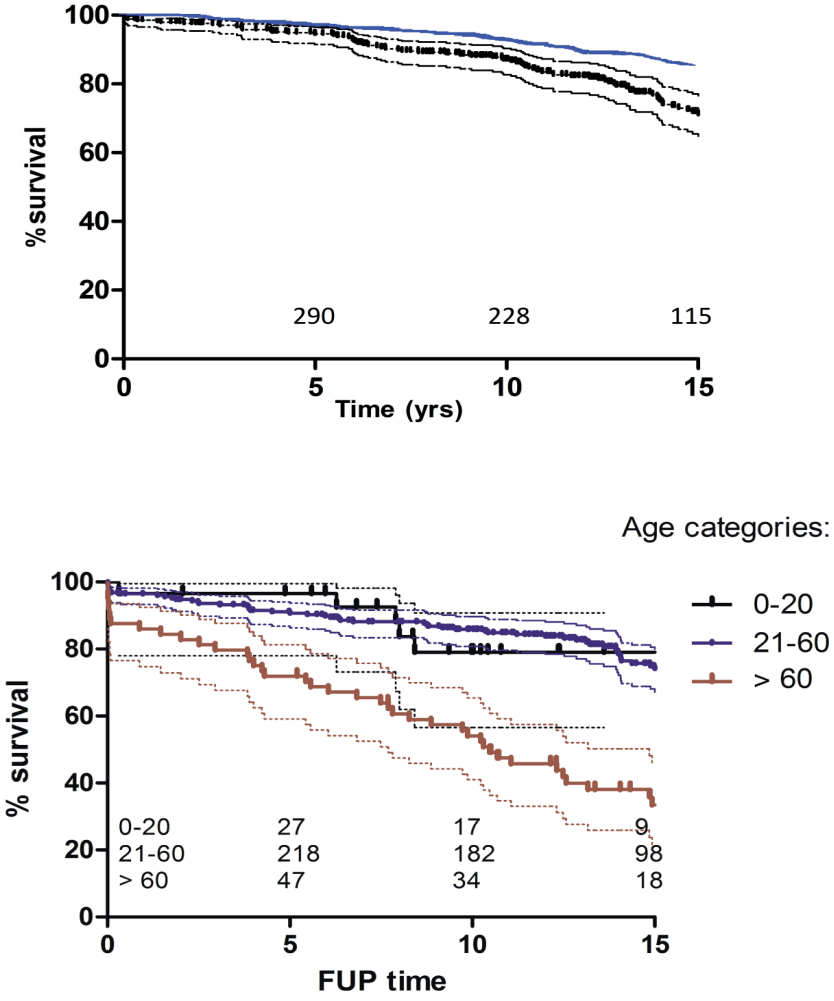


FIGURE 2. Top) Cumulative survival (all patients) including 95% CI. Blue line indicates general Dutch population (mean age 45 years). **Under)** Survival by subgroup. Upper-line indicates patients aged 0 to 20 years; Middle-line indicates patients aged from 21 to 60 years; lower-line indicates patients aged 61 and older.

Patients were subsequently subdivided in 3 age categories:
1) 0 to 20 years at operation, 2) 21 to 60 years at operation, and 3) 61 and older. Patients in the latter category have a significant worse survival compared to other categories. Additionally, multivariable (independent) predictors of late mortality in our Cox model were: patient age at operation (HR 1.06, 95% CI 1.03-1.08; $p < 0.001$) and preoperative ventilation support (HR 2.58, 95% CI 1.20-5.32; $p = 0.01$).

Competing risk for death or subsequent reoperation

A total of 110 patients were reoperated because of an allograft related cause. Reason for reoperation was SVD in 93 patients, non-structural valve deterioration (NSVD) in 9 patients, and endocarditis in 8 patients. The allograft was replaced by a mechanical valve substitute in 62 patients, a composite valve replacement (Bentall) in 31 patients, allograft in 3 patients, autograft in 4 patients, stented bioprosthesis in 12 patients, and TAVI in 2 patients. In one patient the allograft could be saved by removal of a vegetation from the proximal anastomosis of the allograft 3 weeks after the initial operation because of active endocarditis. Ten years later this allograft was replaced with a mechanical valve. In another patient a false aneurysm of the allograft was closed operatively. Finally, in another patient a fistula from the allograft towards the right atrium was closed. Reoperation mortality was 3.9%. During follow-up 99 patients died without a reoperation and 104 were reoperated who were still alive at last follow-up date. Competing-risks analysis predicted that after 20 years from initial allograft implantation, 31% had died without a reoperation, 39% underwent a reoperation, and 30% remained alive without reoperation (Figure 3).

Valve related complications

Structural and non-structural valve deterioration

A total of 98 patients experienced SVD. Replacement of the allograft due to SVD was performed in 100 patients. The other 4 patients died due to structural valve deterioration while being treated medically. Structural valve deterioration was mainly due to the calcification of the aortic (allograft) root in the second decade of follow-up. The progression of aortic gradient in time is displayed in Figure 4.

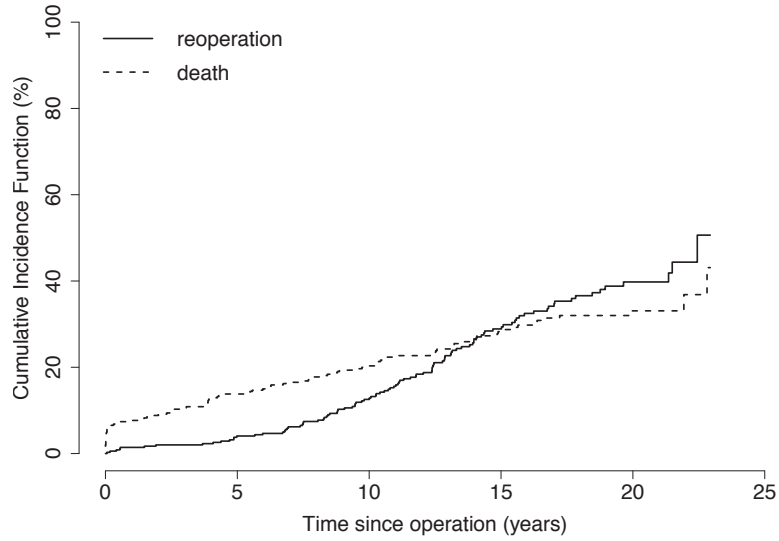


FIGURE 3. Competing-risks analysis for subsequent reoperation on the allograft or death.

All patients were included at the time of initial allograft implantation (n = 353) and could transition to either death or a subsequent reoperation on the allograft.

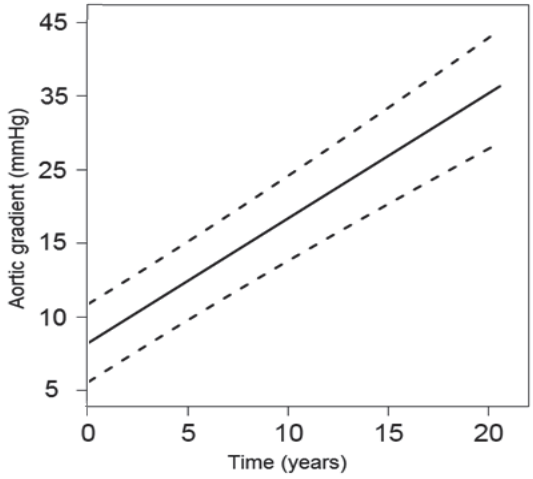


FIGURE 4. Progression of aortic gradient over time.

The dashed-lines denote 95% confidence intervals.

Non-structural valve deterioration occurred in 9 patients, and it was mainly due to (paravalvular) leakage as a result of technical error in patients who received an allograft using the subcoronary implantation technique.

Endocarditis

There were 14 cases of endocarditis. Endocarditis was the reason for reoperation on the allograft in 8 patients. In addition, 3 other patients were diagnosed with endocarditis, 2 of them were treated medically without the need of reoperation and 1 patient was a drug user who could not be operated because of brain abscesses and was treated medically and died eventually. As described in the late survival section above, 3 other patients died from endocarditis. Reoccurrence of endocarditis occurred in 6 patients. In 4 of these patients there was an active endocarditis noticed at the operation time of allograft implantation.

Other valve-related complications

During follow-up 20 cerebrovascular events were registered, one patient died because of a CVA, as described above. Besides the five lethal bleedings described earlier, there was another (non-lethal) major bleeding.

Echocardiographic variables

A subset of 308 patients was followed by means of standardized echocardiography with a mean of 6 echocardiograms (range 1-13). Variables in the joint model predicting higher hazard of mortality were: severe (grade 3 and/or 4) aortic regurgitation (HR 1.06, CI (1.0-1.1); p = 0.03) and enlargement of left ventricle end systolic dimension (HR 1.05, CI (1.01-1.09); p = 0.007). Variables predicting (joint model) a higher reoperation hazard were: progression of the gradient over the allograft (HR 1.40, CI (1.13-1.76); p = 0.001); progression of allograft valve regurgitation (HR 1.05, CI (1.01–1.09); p = 0.005), and increase in aortic annulus diameter (HR 2.33, CI (0.99-5.88); p = 0.053).

There is a progression of aortic valve (i.e. allograft) regurgitation (Appendix 6). Largely patients with grade 1 AR progress to grade 2 AR over time. Mixed effect modeling reveals the following predictors to be correlated with progression of regurgitation over the aortic allograft: time from operation (p = < 0.001), subcoronary technique (p = < 0.001), and active endocarditis (p = 0.02).

DISCUSSION

After almost three decades we observe good long-term outcome after allograft implantation with regard to mortality and occurrence of thromboembolic and hemorrhagic events. However, the risk of a reoperation due to SVD in the second decade after allograft implantation is increased. Furthermore, survival and freedom from reoperation is roughly comparable to other biological valve substitutes [9]. Despite a decrease of implantation of allografts in aortic position over the years, use in selected cases of active aortic root endocarditis and complex aortic root pathology may still be useful.

In the 80's an enthusiasm existed for the use of allografts for aortic valve or root replacement as a superior durability of human tissue valves compared to bioprostheses was envisioned. However, with time it became evident that allograft durability was not better, but more or less comparable to bioprostheses and inferior to mechanical prosthesis [9, 10]. This is reflected in the current ESC/EACTS guidelines for the management of patients with valvular heart disease that have no specific recommendations in favor of allografts for aortic valve replacement, except for active endocarditis with perivalvular lesions [11].

Survival and reoperation

Our findings regarding patient survival and reoperation rates show good results even after 3 decades of follow-up, with median survival of around 20 years. Patient survival is comparable to patients after a biological valve in aortic position; however there seems to be a slightly higher hazard of reoperation in allografts. This was also shown in a clinical trial by El-Hamamsy et al. comparing allografts to freestyle biological valve substitute [10]. Of note, the patient characteristics in El Hamamsy's study differed from ours, as there were just a few patients with endocarditis as etiology of disease in their randomized control trial. Valve related event occurrence such as SVD and reoperation hazard is comparable with earlier reports [12, 13]. Additionally, another option for the treatment of aortic valve disease, especially at younger age, is the Ross procedure. Some great results have been achieved, with freedom from reoperation of about 90% to 99% at 15 years of follow-up [14, 15]. However, these results have only been achieved in slightly different patients groups and in highly specialized centers.

SVD and mode of failure

Early valve failure occurred mainly in the subcoronary implanted allografts in the first few years after implantation, and was mainly due to technical errors during the implantation. The suboptimal results of the subcoronary implantation technique were noticed and therefore we started to use the subcoronary technique less frequently and stopped using it after 1998. If one disregards the early technical failures in the subcoronary allografts, then the pattern of SVD is comparable to root replacement allografts in the first postoperative decade [12]. In the second postoperative decade it appears that subcoronary implants have a slightly better SVD pattern compared to root replacement allografts, but the low number of patients still at risk at that point in time prohibits any firm conclusions. In long-term follow-up the main reason for reoperation was SVD in most cases. SVD is known to be the main cause of allograft failure [1, 3]. During reoperation we noticed that in most cases the allograft sinuses of Valsalva were calcified, with or without fenestration/rupture of the valve leaflets, causing valvular stenosis and/or regurgitation. Although we know from the literature that a reoperation after allograft implantation can be challenging and associated with higher hazards of less favorable outcome [1, 16], hospital mortality was relatively low in our patients, as described by Bekkers et al. earlier [5]. Notably, almost all reoperations were performed by one the same surgeon and this expert experience could be of influence in obtaining these excellent results. Additionally, our rigorous follow-up regimen with annual clinical and biennial echocardiographic standardized follow-up allowed us to detect allograft failure early on and carefully plan for an elective reoperation in most cases.

Other valve related complications

The occurrence of endocarditis was low, as expected, and the main indication for allograft use nowadays [17, 18]. In addition, the reoccurrence of endocarditis in patients who had received an allograft because of infective endocarditis was low. This should be taken into consideration when looking for a suitable valve substitute to treat an infective endocarditis in aortic position, especially with complex aortic root pathology with abscesses and/or fistula formation around the root. In these cases it may be difficult to use the Bentall prosthesis to cover the entire aortic root without leaving behind cavities and is an allograft a good alternative.

Thromboembolic event occurrence was uncommon, highly favorable in comparison with mechanical valve prostheses [19], and comparable to biological valve prosthesis [4, 10, 20], and underlines once more the advantages of biological valve substitutes in this regard.

Hemorrhagic events occurred in only five patients of whom 3 were on anticoagulation therapy: two patients because of atrial fibrillation, and one due to earlier implanted mitral valve prosthesis. The avoidance of anticoagulation therapy in allograft aortic valve or root replacement is particularly important for patients with an active lifestyle as well as in female patients who have a desire of future pregnancy, especially given the notion that pregnancy is not associated with allograft failure [21].

Echocardiographic outcome

We found that enlargement of left ventricle end systolic dimension and progression of aortic (allograft) regurgitation is associated with a higher mortality hazard probably due to less favorable hemodynamics. Additionally an increase in aortic annulus diameter; progression of the gradient over the allograft, and progression of allograft regurgitation is associated with a higher reoperation hazard. This information should help to be able to intervene earlier in the process in order to adjust treatment where possible, and to help evaluate the patients at risk more accurately and maybe more frequently, certainly in the second decade after allograft implantation where SVD play a significant role. The challenging goal is still to find out which specific dynamic variables and variations are associated with worse outcome, and what exactly the timing for (surgical) intervention must be.

To estimate the association between a single measure and time to event, standard statistical tools such as Cox regression are applicable. However, when it comes to the analysis of repeated measurements in relation to time-to-event, the Cox model including time-dependent covariates, has been widely used. However, problems arise from the fact that repeated measurements may contain biological variation which is not taken into account by the time-dependent (covariates) Cox model. The problem with ignoring this biologic variation and using the time-dependent covariates Cox model is that derived results may be substantially biased. Therefore the joint model for longitudinal and survival data have been proposed. Despite the appropriateness of these models, there are some disadvantages. The joint models of longitudinal and survival data are not easily applicable by any physician since a level of expertise in programming may be required. The complexity of analyses of SVD and risk factors related to an increased risk of SVD is

addressed recently by Blackstone [22], and the importance and usefulness of such models have been demonstrated [23, 24]. More recently there are more statistical tools available as the joint modeling approach for the prognostic evaluation of serial biomarkers [25], and specifically the concept of joint modeling of longitudinal and survival data in repeated valve function measurements after implantation of an allograft is introduced by Andrinopoulou et al. in 2012 [8]. The translation of the longitudinal data to a predictive-model using thesestatistical tools should allow us to understand the association between the serial measured parameters influencing SVD (i.e. aortic gradient, aortic regurgitaion, verntricul dimentions etc.), and important clinical endpoints such as survival and reoperation.

Limitations

Our study concerns a single-center experience with a heterogeneous etiology of disease, with a relatively large proportion of patients with endocarditis, and furthermore significant differences between patients receiving allografts as a subcoronary implant comparing to recipients with full root replacement. This may lead to interpretations that are not necessarily applicable to other patient cohorts.

CONCLUSION

Implantation of an allograft in aortic position is associated with low valve-related events peri-operatively. From this prospective observational cohort study that spans almost 30 years it becomes evident that although allograft aortic valve or root replacement yields excellent clinical results in the first postoperative decade, in the second postoperative decade a structural valve deterioration pattern that resembles bioprostheses becomes apparent. Reoperation on degenerated allografts proofs challenging but can be managed well through systematic clinical and echocardiographic follow-up and careful planning of elective reoperation. In selected patients, especially those less favorable for anticoagulation therapy, and patients with active endocarditis with complex aortic root pathology, allografts may still be considered, accepting an increased life-time risk of reoperation.

REFERENCES

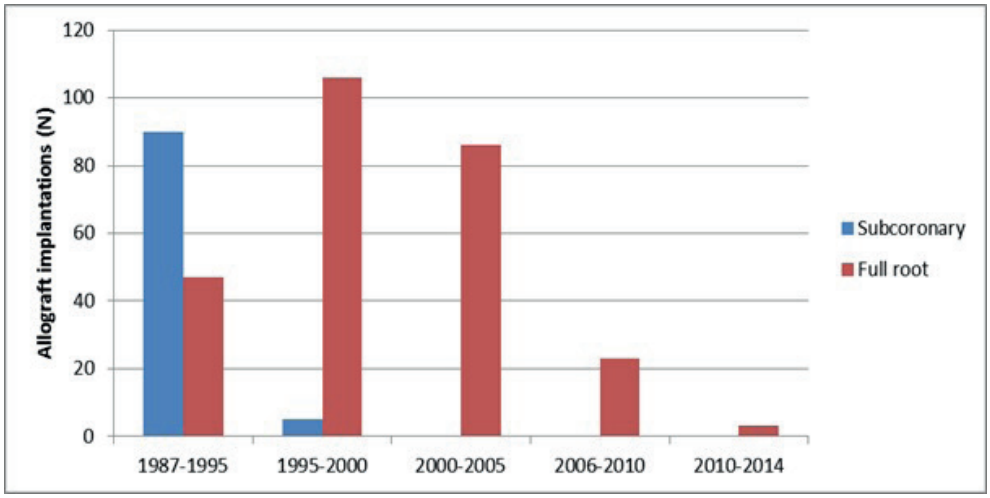
1. Nowicki, E.R., et al., *Aortic allograft valve reoperation: surgical challenges and patient risks.* Ann Thorac Surg, 2008. 86(3): p. 761-768 e2.
2. Takkenberg, J.J., et al., *Prognosis after aortic root replacement with cryopreserved allografts in adults.* Ann Thorac Surg, 2003. 75(5): p. 1482-9.
3. Takkenberg, J.J., et al., *Evolution of allograft aortic valve replacement over 13 years: results of 275 procedures.* Eur J Cardiothorac Surg, 2002. 21(4): p. 683-91; discussion 691.
4. Takkenberg, J.J., et al., *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): p. 851-9.
5. Bekkers, J.A., et al., *Re-operations for aortic allograft root failure: experience from a 21-year single-center prospective follow-up study.* Eur J Cardiothorac Surg, 2011. 40(1): p. 35-42.
6. Takkenberg, J.J., et al., *Serial echocardiographic assessment of neo-aortic regurgitation and root dimensions after the modified Ross procedure.* J Heart Valve Dis, 2006. 15(1): p. 100-6; discussion 106-7.
7. Akins, C.W., et al., *Guidelines for reporting mortality and morbidity after cardiac valve interventions.* Ann Thorac Surg, 2008. 85(4): p. 1490-5.
8. Andrinopoulou, E.R., et al., *An introduction to mixed models and joint modeling: analysis of valve function over time.* Ann Thorac Surg, 2012. 93(6): p. 1765-72.
9. Smedira, N.G., et al., *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): p. 558-564 e4.
10. El-Hamamsy, I., et al., *Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial.* J Am Coll Cardiol, 2010. 55(4): p. 368-76.
11. Vahanian, A., et al., *Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS).* Eur J Cardiothorac Surg, 2012. 42(4): p. S1-44.
12. Lund, O., et al., *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): p. 77-90; discussion 90-1.
13. O'Brien, M.F., et al., *The homograft aortic valve: a 29-year, 99.3% follow up of 1,022 valve replacements.* J Heart Valve Dis, 2001. 10(3): p. 334-44; discussion 335.
14. Skillington, P.D., et al., *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.* Glob Cardiol Sci Pract, 2013. 2013(4): p. 383-94.
15. da Costa, F.D., et al., *Long-term results of the Ross operation: an 18-year single institutional experience.* Eur J Cardiothorac Surg, 2014. 46(3): p. 415-22; discussion 422.

16. Joudinaud, T.M., et al., *Redo aortic root surgery for failure of an aortic homograft is a major technical challenge.* Eur J Cardiothorac Surg, 2008. 33(6): p. 989-94.
17. Habib, G., 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). 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): p. 2369-413.
18. Byrne, J.G., et al., *Surgical management of endocarditis: the society of thoracic surgeons clinical practice guideline.* Ann Thorac Surg, 2011. 91(6): p. 2012-9.
19. Cannegieter, S.C., F.R. Rosendaal, and E. Briet, *Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses.* Circulation, 1994. 89(2): p. 635-41.
20. Rahimtoola, S.H., *Choice of prosthetic heart valve for adult patients.* J Am Coll Cardiol, 2003. 41(6): p. 893-904.
21. Arabkhani, B., et al., *Does pregnancy influence the durability of human aortic valve substitutes?* J Am Coll Cardiol, 2012. 60(19): p. 1991-2.
22. Blackstone, E.H., *Of SOLOs and ensembles.* J Thorac Cardiovasc Surg, 2015. 150(1): p. 10-1.
23. Mokhles, M.M., et al., *Capturing echocardiographic allograft valve function over time after allograft aortic valve or root replacement.* J Thorac Cardiovasc Surg, 2014. 148(5): p. 1921-1928 e3.
24. Blackstone, E.H., *Breaking down barriers: helpful breakthrough statistical methods you need to understand better.* J Thorac Cardiovasc Surg, 2001. 122(3): p. 430-9.
25. Rizopoulos, D., *Joint Models for Longitudinal and Time-to-Event Data with Applications in R.* Chapman and Hall/CRC Biostatistics Series, Boca Raton., 2012.

ABBREVIATIONS

LVED	=	Left Ventricular End Diastolic Diameter
LEVSD	=	Left Ventricular End Systolic Diameter
STJ	=	Sinotubular Junction
CABG	=	Coronary Artery Bypass Grafting
TAVI	=	Transcatheter Aortic Valve Implantation
SVD	=	Structural Valve Deterioration
NSVD	=	Non Structural Valve Deterioration

APPENDIX 1



Number of allografts and the surgical technique used for implantation by year of operation.

APPENDIX 2

Potential urivariable risk factors for increased early and late mortality.

Variable	HR	95% CI	P-value
Early mortality			
Age	1.1	1.0-1.1	< 0.001
Active Endocarditis	3.8	1.6-9.2	0.003
Severe renal disease	13.7	3.9-47.8	< 0.001
Ventilation support	5.5	3.8-16.8	0.003
Preop non-SR	2.1	1.3-3.3	0.002
Surgical procedure	2.7	1.7-4.6	0.002
Late mortality			
Age	1.05	1.04-1.07	< 0.001
Active Endocarditis	2.05	1.38-3.06	< 0.001
Hypertension	2.39	1.56-3.68	< 0.001
Severe renal disease	3.61	1.75-7.45	0.001
Ventilation support	3.06	1.71-5.48	< 0.001
Preop non-SR	1.65	1.32-2.08	< 0.001
Surgical procedure	1.11	1.04-1.18	0.001
Urgency	2.88	1.75-4.75	< 0.001

APPENDIX 3

Variables that were tested (univariable) as potential risk factors for hospital mortality, late mortality, and re-operation.

Variable	**Specification**
Patient age	Continuous variable (years)
Gender	
Preoperative ventilation support	
Preoperative abnormal cardiac rhythm	Any rhythm other that sinus rhythm
Preoperative renal function	Creatinine, continuous (mmol/l)
Severe renal disease requiring either dialysis or transplantation	
Prior cardiac surgery	
Marfan disease	
Ischemic heart disease	
Etiology of heart valve disease	
Preoperative hypertension	
Systolic left ventricular function	Good/ impaired/ moderate/ bad
Pior cerebrovascular accident (CVA)	
Preoperative New York Heart Association (NYHA) class	From I to IV
Emergency of the procedure	
Cardiopulmonary bypass time	Continuous (minutes)
Hemodynamic diagnosis*	
Allograft diameter*	Continuous (mm)

* Exclusively for re-operation

APPENDIX 4

Statistical model building for mixed-effects models:

Likelihood ratio test was used for the fixed part and the mixture distribution of chi-square for the random part. We used linear time for Aortic gradient (p-value = 0.9302), Annulus diameter (p-value = 0.1391) and nonlinear for Left Ventricle End Systolic (LVES) diameter (p-value < 0.0001) for the fixed and the random effects. For the ordinal longitudinal outcome linearity was assumed due to convergence problems. Furthermore, we used clinically relevant baseline covariates in the fixed part, namely for LVES, Aortic gradient and Annulus diameter we included: Sex, left ventricle function, Hypertension, Etiology of disease and patient age at operation. For AR we included Sex, LVfunction, Hypertension, Diagnosis and Etiology. Finally, no serial correlation term in the residual errors was assumed since it could result in estimation problems.

Specification of mixed-effects models and joint models of longitudinal and survival data

Let T_i^* denote the true failure time for the i-th individual (i = 1,…, n), and d C_i the censoring time, then $T_i = \min(T_i^*, C_i)$ represents the observed failure time for the i-th patient. Moreover, $\delta_i = 0,1$ is the event indicator where 0 indicates censoring.

For the longitudinal part, we let y_i consist of longitudinal responses that may be obtained at different time points t_{ij} and have length n_i.To describe the subject-specific evolutions over time of the longitudinal outcome we utilize a linear mixed-effects model. Specifically, it takes the form,

$$y_i(t) = f_i(t) + \varepsilon_i = \chi^T{}_i(t)\beta + z^T{}_i(t)b_i = \varepsilon_i,$$

where $\chi_i(t)$ denotes the design vector for the fixed effects regression coefficients β and $z_i(t)$ the design vector for the random effects b_i.

Finally, we assume that a normal distribution for the random effects describes the evolution of the longitudinal outcomes, i.e.,

$$b_i \sim N(0, \sigma_b),$$

Where σ_b is the variance of the random intercept.

For the survival process we have:

$h_i(t,\theta_s) = h_0(t)e^{\{\gamma^T\omega_i+\alpha f_i(t)\}}$,

where θ_s is the parameter vector for the survival outcomes, ω_i is a vector of baseline covariates with a corresponding vector of regression coefficients γ, and α denotes the strength of association between the longitudinal and survival outcomes. Moreover, a Weibull baseline hazard $h_0(t) = \psi t^{\psi-1}$ was assumed.

Syntax for one joint model

Variable notation in the model:
Gender(male of female) = Sex
Left ventricle function = LVfunction
Patient age at operation = ptageatok
Hypertension = Hypertension
Etiology of disease = Etiology
Echotime =' time of echocardiogram
Annulusdiameter = diameter of annulus
MaxOfFUP = maximum follow-up time
Active.endocarditis = Active endocarditis
VentilationSupport = Ventilation support
Type.of.operation = subcoronary or full root
Urgency.code.for.operation = Urgent (<24hours), within the same hospitalization or elective
FUPreop = follow-up time for reoperation
Reop = reoperation

```
library(JM)
fm1 <- lme(Annulusdiameter ~ echotime + Sex + LVfunction + Hypertension + Etiology
    + ptageatok.x, data = data, na.action = na.exclude, random = ~ echotime | IDnr)

coxFit.avD. <- coxph(Surv(MaxOfFUP, LastOfDeath.) ~ Active.endocarditis + Hypertension
    + VentilationSupport + Type.of.operation + Urgency.code.for.operation, data =
    data.id, x = TRUE)
```

```
coxFit.avR. <- coxph(Surv(FUPreop, Reop) ~  Hypertension +  Etiology + Sex + LVfunction
      , data = data.id, x = TRUE)

jointFit.avD <- jointModel(fm1, coxFit.avD., timeVar = "echotime", method = "piecewise-
      PH-aGH", verbose = TRUE, iter.EM = 80) summary(jointFit.avD)

jointFit.avR <- jointModel(fm1, coxFit.avR., timeVar = "echotime", method = "piecewise-
      PH-aGH", verbose = TRUE, iter.EM = 80) summary(jointFit.avR)
```

Additional software package

Joint modeling of longitudinal and survival data; Package: JM (version: 0.8-3)

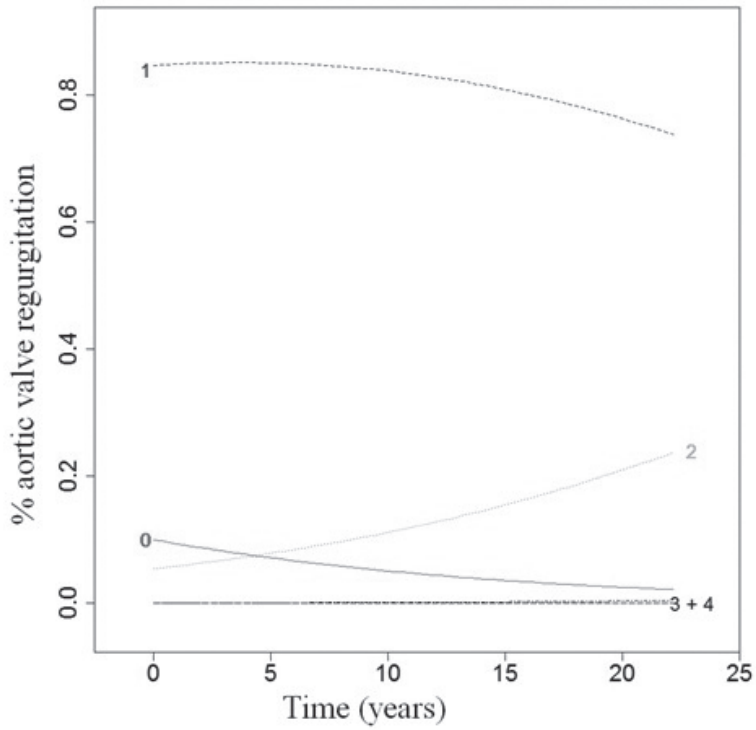
APPENDIX 5

Allograft statistics.

	All patients (N= 353)	SC technique (N = 92)	Root replacement (N = 261)
Type of allograft			
Aortic	98% (N = 348)	95% (N = 88)	>99% (N =260)
Pulmonary	2% (N = 5)	5% (N = 4)	<1% (N = 1)
Allograft size (mm) Mean (SD; range)	22.7 (2.1; 14 – 30)	23.3 (2.4; 19 – 30)	22.4 (1.9; 14 – 28) [a]
≤ 24 mm	84%	70%	89%
≥ 24 mm	16%	30%	11%
Donor age (years) Mean (SD; range)	40 (13; 8 – 62)	36 (13; 12 – 60)	42 (13; 8 – 62) [a]
Preservation method			
Cryopreserved	98%	94%	>99%
Fresh	2%	6%	<1%

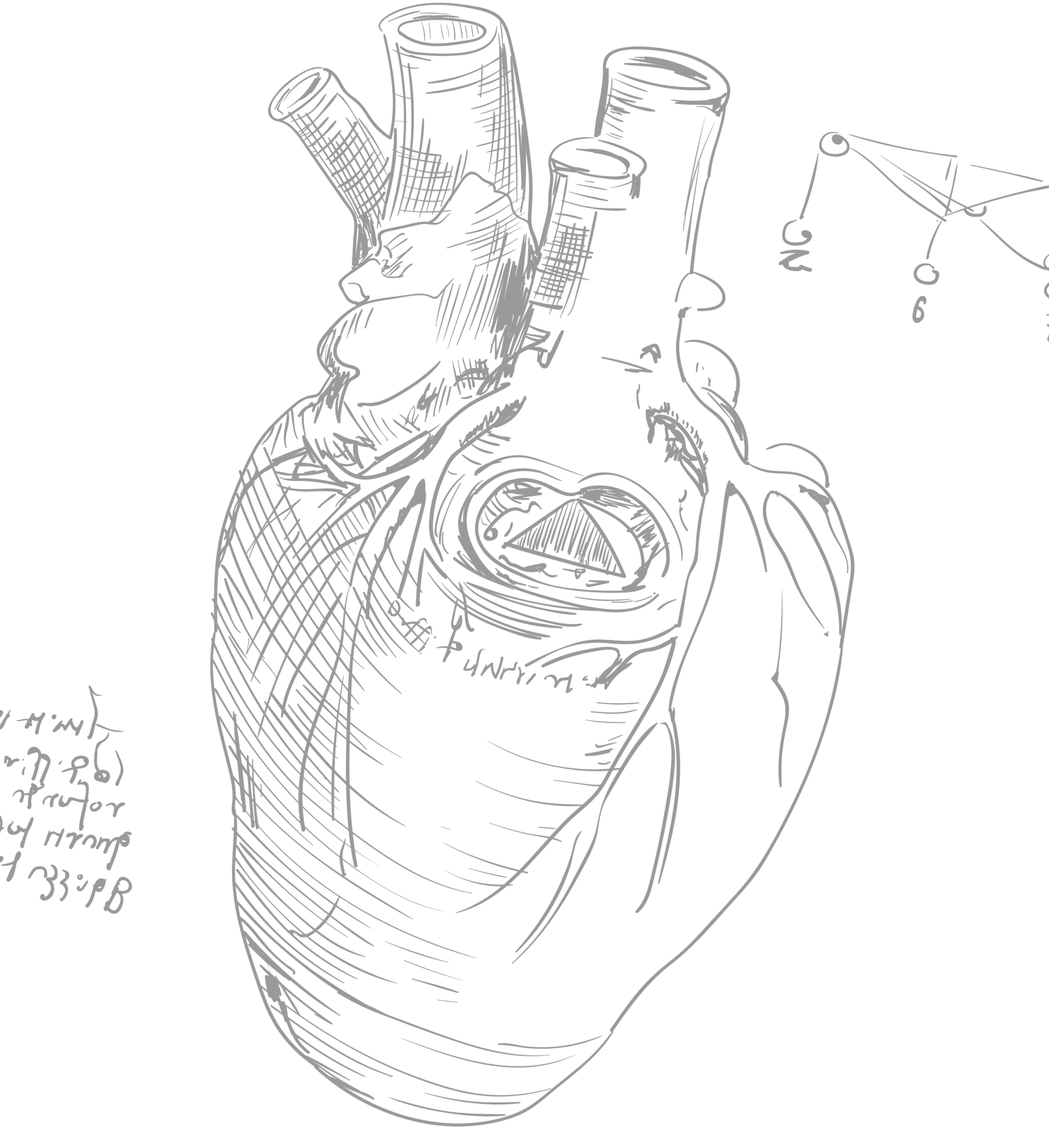
[a] Statistical significant difference between the 2 groups (unpaired t-test or Mann–Whitney U-test)

APPENDIX 6



Progression of AR grade during years.

A mixed effect model was used to predict variables associated with progression of AR grade. Blue line indicates grade 0 AR, red line grade 1 AR, green line grade 2 AR, black lines grade 3 and 4 AR.



Chapter 8

Pregnancy outcomes in women with aortic valve substitutes

Heuvelman HJ, Arabkhani B, Cornette JM, Pieper PG,
Bogers AJ, Takkenberg JJ, Roos-Hesselink JW

Am J Cardiol. 2013 Feb 1;111(3):382-7

ABSTRACT

Young women who require aortic valve replacement (AVR) need information on the potential cardiac and obstetric complications of pregnancy for the different available valve substitutes. We therefore assessed pregnancy outcome in women who received an autograft, homograft, or mechanical valve in the aortic position. Women who were pregnant after surviving AVR in our institution between 1987 and 2011 were included. Information on cardiac status and pregnancy outcome was obtained through hospital medical records and by means of an extensive patient questionnaire. Forty women experienced 67 pregnancies of which 55 (82%) completed pregnancies, 6 (9%) miscarriages, and 6 (9%) terminations of pregnancy. Eighteen (45%) women had a pulmonary autograft, 13 (32%) a homograft, and 9 (23%) a mechanical valve. Mean age at first pregnancy was 30.0 ± 5.7 years. There was no maternal mortality, but 1 fetal death (1.8%) and 1 neonatal death (1.8%) occurred. Maternal cardiac complications occurred in 13% and obstetric complications in 38% of the completed pregnancies. Heart failure (9%), arrhythmias (7%), hypertension-related disorders (7%), preterm delivery (24%), and small for gestational age infants (15%) were most often encountered. Mechanical valve recipients had the highest incidence of both cardiac and obstetric complications. In conclusion, pregnancy-associated complications after AVR were common and human tissue valves should be considered in the discussion for the optimal aortic valve substitute in a young female. However, careful obstetric monitoring is mandatory.

When a young woman requires aortic valve replacement (AVR), it is important to incorporate reliable information on potential pregnancy complications and pregnancy outcome when considering the available surgical options. In mechanical valve recipients, complications due to anticoagulation therapy represent a threat for both mother and her unborn child.[1-3] Accelerated valve dysfunction due to degeneration may be a point of concern in biological valve substitutes although more recent studies report that pregnancy does not increase structural deterioration or reduce survival.[4-6] There is limited evidence available on the rate of cardiac and obstetric complications in young women who become pregnant after AVR. Most available information concerns mechanical –mainly mitral- valve recipients and shows increased risks of anticoagulation-related complications and increased maternal and fetal mortality and morbidity.[1, 2, 5, 7-10] Also for human tissue valve recipients, reports on pregnancy related outcomes are scarce.[5, 10-12] In this perspective, the aim of the present study was to determine the occurrence of cardiac and obstetric complications in women who experienced a pregnancy after implantation an autograft, homograft, or mechanical valve in the aortic position in our institution.

METHODS

Women who were pregnant after surviving an AVR with a pulmonary autograft, a homograft, or a mechanical valve prosthesis in the Erasmus University Medical Center, were aged 50 years or younger at time of surgery, were operated between April 1987 and January 2011, and were at least 16 years at the last clinical follow-up, were invited to participate. The study protocol was approved by the Institutional Review Board (MEC 2010-272) and informed consent was obtained. All patients who receive a human tissue valve substitute in our institution are followed prospectively (MEC 2000-813). Eligible patients were identified through our prospective cohort study of human tissue valve recipients and through our departmental patient information system.[13, 14]

Information on pregnancy and cardiac status of the patients until January 1st, 2011 was obtained through hospital medical records and structured patient questionnaire that was conducted between December 1st 2010 and September 1st, 2011. We collected data on underlying valve etiology at last surgery, hemodynamic diagnosis, previous surgical/ interventional procedures, age at surgery, type (and size) of aortic valve substitute, concomitant procedures, time from surgery to first pregnancy, age at conception, and preconceptional systolic left ventricular function (LVF), maximum aortic jet velocity (Vmax), and peak pulmonary artery pressure (PAP).

Pregnancy was defined as positive HCG test or obstetric ultrasound. Miscarriage was defined as spontaneous loss of pregnancy <20 weeks of gestation. Information about each completed pregnancy (duration >20 weeks of gestation) included: New York Heart Association (NYHA) functional class, medication, physical examination, pregnancy duration, mode of delivery. For each baby, gender, birth weight, and APGAR score was registered.

Registered cardiac complications were: arrhythmia (symptomatic sustained documented arrhythmia), heart failure (requiring treatment), persistent NYHA functional class deterioration (≥1 year postpartum), syncope, thrombo-embolic complications, aortic dissection, and/or endocarditis. Obstetric complications included: pregnancy-induced hypertension (PIH; de novo onset of hypertension after ≥20 weeks of gestation), preeclampsia (hypertension and proteinuria), eclampsia (preeclampsia with grand mal seizures), Hemolysis Elevated Liver Enzymes Low Platelets (HELLP) syndrome, preterm premature rupture of membranes (membrane rupture <37 weeks gestation), premature labor (spontaneous onset of labor <37 weeks gestation), postpartum hemorrhage (>1000 ml), placental abruption, premature delivery (<37 weeks of gestation), small-for-gestational-age (birth weight <10th percentile), fetal death (≥20 weeks of gestation), and neonatal death (<30 days postpartum).[15] The incidence of complications and mode of delivery in this study was compared to data derived from the 2008 Dutch Perinatal Registry. In this registry, maternal and fetal data of all deliveries occurring in the Netherlands are recorded (about 180,000; 96% complete). It included both home as well as hospital deliveries and contained information on the presence of cardiovascular disease in the mother (no further specification) and neonatal congenital defects (cardiac 0.41%; non-cardiac 2.38%).[16]

Anticoagulation therapy administered in our institution to mechanical valve recipients was according to our local protocol and initiated in close collaboration with the hematologist.[17] As soon as pregnancy was confirmed, acenocoumarol was changed to a weight adjusted therapeutic dose of low molecular weight heparin (LMWH) until the end of the first trimester and when necessary monitored with anti-Xa levels. Acenocoumarol was then restarted until 36 weeks of gestation. Hereafter a therapeutic dose of LMWH was given until spontaneous onset of labor or the day before induction of labor or elective cesarean section. After delivery, LMWH was initiated again, along with acenocoumarol until 2 consecutive appropriate INR levels were reached.

TABLE 1. Patient characteristics of the 40 women who experienced ≥1 pregnancy after aortic valve replacement.

Variable	All (n=40)	Autograft (n=18)	Homograft (n=13)	MP (n=9)	P-value
Intervention/surgery before AVR					
0	23 (58%)	10 (56%)	9 (69%)	4 (44%)	.46
1	8 (20%)	2 (11%)	4 (31%)	2 (22%)	.46
> 1	9 (23%)	6 (33%)	0	3 (33%)	.07
Diagnosis					
Aortic stenosis	15 (38%)	10 (56%)	4 (31%)	0	**.02**
Aortic regurgitation	13 (33%)	3 (17%)	6 (46%)	5 (55%)	.10
Mixed	12 (30%)	5 (28%)	3 (23%)	4 (44%)	.61
Etiology					
Congenital	26 (65%)	16 (89%)	8 (62%)	2 (22%)	**<.01**
Rheumatic	12 (30%)	2 (11%)	4 (31%)	6 (67%)	**.01**
Aneurysm/Dissection	2 (5%)	0	1 (8%)	1 (11%)	.49
Age at last surgery (years)	25.4 ± 7.7	21.5 ± 6.6	26.9 ± 5.0	31.2 ± 9.0	**<.01**
Concomitant procedures					
None	28 (70%)	16 (89%)	8 (62%)	4 (44%)	**.04**
Coronary bypass	3 (8%)	1 (6%)	0	2 (22%)	.23
Mitral valve surgery	6 (15%)	0	3 (23%)	3 (33%)	**.04**
Size prosthesis (mm)	-	-	22 (21-22)	21 (21-23)	
Time surgery-1stpregnancy (years)*	3.1 (1.6-6.1)	5.5 (1.8-9.4)	2.3 (1.4-4.6)	2.1 (1.5-4.6)	.14
Total number of pregnancies	67	33	22	12	.39
1	40 (60%)	18 (55%)	13 (59%)	9 (75%)	.46
2	20 (30%)	11 (33%)	6 (27%)	3 (25%)	.83
3	7 (10%)	4 (12%)	3 (14%)	0	.46
Pregnancy age (years)*					
1st (n=40)	30.0 ± 5.7	27.0 ± 4.1	30.2 ± 4.6	35.7 ± 5.9	**<.01**
2nd (n=20)	30.9 ± 4.7	30.0 ± 3.9	31.9 ± 5.0	32.1 ± 8.0	.75
3rd (n=7)	32.1 ± 5.5	32.7 ± 7.0	31.3 ± 4.0	-	.86
LVF preconceptional (n=66)					
Good	64%	61%	77%	50%	.18
Moderate	36%	39%	23%	50%	.18
PAP preconceptional (mmHg) (n=62)	6 (3-15)	13 (9-18)	3 (2-3)	4 (1-11)	**<.01**

Vmax preconceptional (m/s)*					
1st pregnancy (n=38)	1.78 ± 0.69	1.36 ± 0.42	1.85 ± 0.60	2.60 ± 0.55	**<.01**
2nd pregnancy (n=19)	1.70 ± 0.54	1.41 ± 0.46	2.01 ± 0.36	2.23 ± 0.38	**.01**
3rd pregnancy (n=7)	1.83 ± 0.80	1.41 ± 0.48	2.39 ± 0.87	-	.23
Completed pregnancies	55 (82%)	28 (85%)	20 (91%)	7 (58%)	.05
Miscarriage	6 (9%)	3 (9%)	0	3 (25%)	.05
Termination pregnancy	6 (9%)	2 (6%)	2 (9%)	2 (17%)	.64
Social reasons	4 (6%)	2 (6%)	2 (9%)	0	.70
Maternal cardiac indication	1 (1%)	0	0	1 (17%)	.18
Fetal spina bifida	1 (1%)	0	0	1 (8%)	.18

MP = mechanical aortic valve prosthesis, n = number of patients, AVR = aortic valve replacement, LVF = systolic left ventricular function, PAP = peak pulmonary artery pressure, * = all 67 pregnancies, including miscarriages and terminations. Data are presented as number of patients (%), unless indicated otherwise. Continuous variables are presented as mean ± standard deviation or as median with interquartile range.

Normality of the distribution of continuous data was tested with the Kolmogorov-Smirnov test with Lilliefors correction. Continuous data are displayed as means with standard deviations or in case of a skewed distribution, as medians with interquartile ranges and were compared using the one-way analysis of variance test or the Kruskal-Wallis test. Discrete data are presented as absolute numbers and percentages and compared using the Pearson's Chi-Square test or Fisher's exact test.

Univariable logistic regression analysis was performed to identify possible factors associated with the incidence of pregnancy-related complications. Missing values were imputed by the mean. Age at surgery, maternal age at first pregnancy, valve type, time from surgery until first pregnancy, duration of pregnancy, caesarean section, preconceptional LVF, Vmax, and PAP were considered as co-variables in the univariable model for cardiac and obstetric events. For comparison of the event incidence with the general Dutch population the Chi squared test was used. All statistical tests were two-sided and a p-value ≤ 0.05 was considered significant. For data analysis SPSS 17.0 for Windows (SPSS, Chicago, Illinois) was used.

RESULTS

Forty patients experienced at least 1 pregnancy after AVR in our institution (Table 1). There were 67 singleton pregnancies in these 40 women. Fifty-five pregnancies continued beyond 20 weeks (47% males) in 35 women. All 6 spontaneous miscarriages were <14 weeks of gestation. Six pregnancies were terminated (Table 1). The only termination of pregnancy for maternal cardiac reason was performed in a mechanical valve recipient with pulmonary hypertension, tricuspid insufficiency, and moderate stenosis of the mechanical prosthesis in aortic position of 3.3 m/s. One termination was performed in a fetus with spina bifida. There were no acenocoumarol associated embryopathies. Table 2 displays the mode of delivery for the 55 completed pregnancies differentiated by type of valve substitute; Figure 1 illustrates the modes of delivery in comparison to the Dutch general population. There was no maternal mortality.

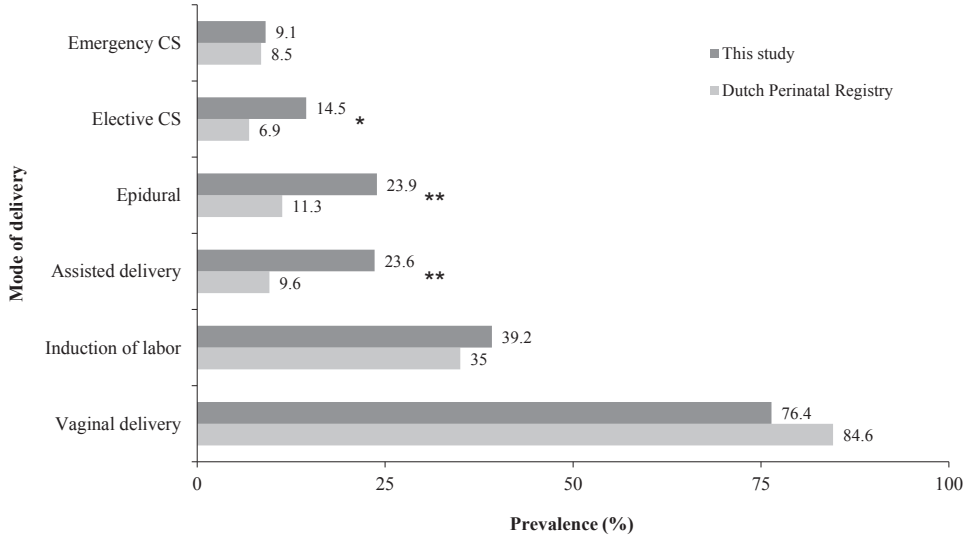


FIGURE 1. Mode of delivery of the 55 completed pregnancies compared to the Dutch Perinatal Registry.
CS = cesarean section.

Heart failure was the most common cardiac complication with a persistent NYHA deterioration in 3 patients (Table 2). One mechanical valve recipient with permanent atrial fibrillation developed prosthetic valve thrombosis and subsequent heart failure

at 33 weeks gestation. Anticoagulation was converted to intravenous heparin and the woman underwent a caesarean section at 36 weeks. A girl of 2,150 g was born. Five weeks later she underwent a re-AVR with another mechanical valve.

The most common obstetric complications concerned hypertension-related disorders, preterm delivery, and small-for-gestational-age infants (Table 3; Figure 2). Five of the 13 pregnancies which ended prematurely were induced before 37 weeks for cardiac indication: congestive heart failure in 2 patients (1 mechanical valve prosthesis; 1 pulmonary autograft), prosthetic valve thrombosis (mechanical valve prosthesis), Marfan syndrome (homograft), and dilated aortic root with aortic and pulmonary regurgitation (pulmonary autograft).

TABLE 2. Mode of delivery of the 55 completed pregnancies in 35 women who underwent aortic valve replacement

Variable	All (n=55)	Autograft (n=28)	Homograft (n=20)	MP (n=7)	P-value
Vaginal delivery*	42 (76%)	19 (68%)	17 (85%)	6 (86%)	.32
Spontaneous	11 (20%)	3 (11%)	5 (25%)	3 (43%)	.25
Assisted delivery	13 (24%)	7 (25%)	5 (25%)	1 (14%)	.67
Epidural anesthesia	11 (20%)	4 (14%)	5 (25%)	2 (29%)	.80
Induction of labour	20 (36%)	11 (39%)	7 (35%)	2 (29%)	.53
Elective caesarean section	8 (15%)	5 (18%)	2 (10%)	1 (14%)	.89
Maternal cardiovascular risk	5 (9%)	3 (11%)	2 (10%)	0	.72
Prosthetic valve thrombosis	1 (2%)	0	0	1 (14%)	.13
Fetal presentation	1 (2%)	1 (4%)	0	0	1.00
Fetopelvic disproportion	1 (2%)	1 (4%)	0	0	1.00
Emergency caesarean section	5 (9%)	4 (14%)	1 (5%)	0	.42
Fetal distress	2 (4%)	1 (4%)	1 (5%)	0	1.00
Placental abruption	1 (2%)	1 (4%)	0	0	1.00
Fetopelvic disproportion	2 (4%)	2 (7%)	0	0	.62

MP = mechanical valve prosthesis, n = number of pregnancies, fetal distress = decelerations on cardiotocography, * = overlapping categories.

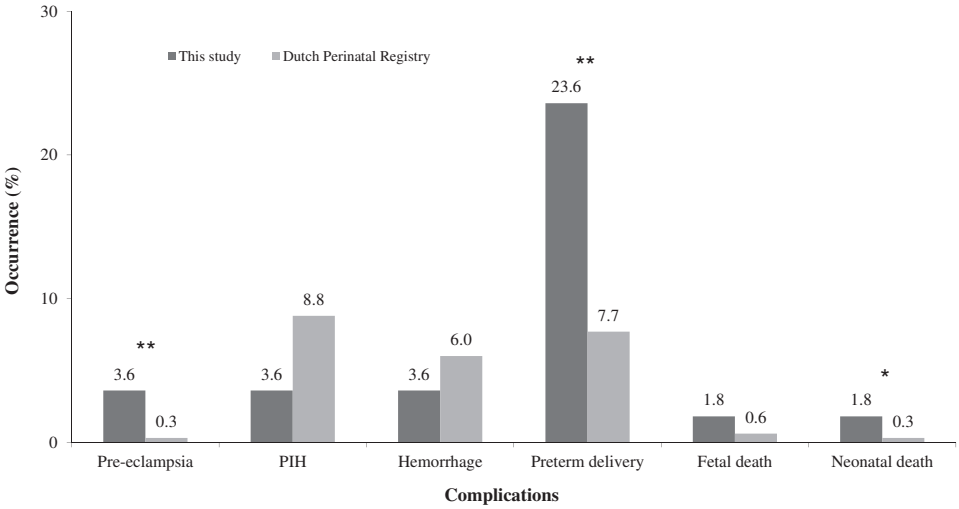


FIGURE 2. Incidence of obstetric and perinatal complications of the 55 completed pregnancies compared to the Dutch Perinatal Registry.16 PIH = Pregnancy induced hypertension.

There was 1 fetal death in a mechanical valve recipient at 20 weeks and 4 days which presented with absent heart rate, growth restriction, and fetal hydrops on ultrasound. A macerated male infant (190 gram) with a placenta of 30 gram was born. Fetal autopsy was declined by the parents. Placental pathology showed severe placental insufficiency. One postnatal death occurred in a pulmonary autograft recipient who was on oral anticoagulation therapy because of a protein C deficiency and prior deep venous thrombosis. At 19 weeks, she had preterm premature rupture of membranes and fetal growth restriction. Despite the poor prognosis the woman opted for expectant management. At 30 weeks, she spontaneously delivered a 600 g boy who died on the first postnatal day due to lung hypoplasia.

No potential predictors of cardiac complications could be identified. Obstetric complications were more common in patients with cardiac complications during pregnancy (OR 13.2; 95% CI 1.5-119.5; p=0.02). There was no correlation between preconceptional Vmax over the aortic valve and birth weight (r -0.01; p=0.95).

Two women with a completed pregnancy were not treated according to the current ESC guidelines for the use of anticoagulation in pregnant mechanical valve patients.[17] One patient received an insufficient dose of oral anticoagulation therapy and developed

a prosthetic valve thrombosis. The other patient was treated with a combination of acenocoumarol and LMWH until a healthy girl was born by spontaneous vaginal delivery at 40 weeks.

TABLE 3. Outcome of the 55 completed pregnancies in 35 women who underwent aortic valve replacement.

Variable	All (n=55)	Autograft (n=28)	Homograft (n=20)	MP (n=7)	P-value
Pregnancy duration (weeks)	38 (36-40)	38 (35-40)	39 (38-40)	36 (31-39)	.20
Birth weight (kg) (n=54)	3.0 (2.5-3.3)	3.0 (2.4-3.3)	3.1 (2.9-3.3)	2.7 (1.9-3.0)	.11
Birth weight percentile (n=54)*	31 (14-54)	30 (11-54)	34 (21-54)	16 (11-80)	.47
APGAR score ≥8 at 5 minutes	94%	96%	95%	86%	.55
Cardiac complications**	7 (13%)	4 (14%)	1 (5%)	2 (29%)	.21
Heart failure	5 (9%)	2 (7%)	1 (5%)	2 (29%)	.20
Supraventricular arrhtymias	4 (7%)	1 (4%)	1 (5%)	2 (29%)	.09
Persistent NYHA deterioration	3 (5%)	1 (4%)	1 (5%)	1 (14%)	.71
Valve thrombosis	1 (2%)	0	0	1 (14%)	.13
Obstetric complications**	21 (38%)	11 (39%)	6 (30%)	4 (57%)	.50
Hypertension related disorders	4 (7%)	0	4 (20%)	0	**.02**
PIH	2 (4%)	0	2 (10%)	0	.14
Preeclampsia	2 (4%)	0	2 (10%)	0	.14
Premature labor	4 (7%)	3 (11%)	0	1 (14%)	.33
PPRoM	3 (5%)	3 (11%)	0	0	.26
Placental abruption	1 (2%)	1 (4%)	0	0	1.00
Preterm delivery	13 (24%)	8 (29%)	2 (10%)	3 (43%)	.14
Spontaneous	5 (9%)	4 (14%)	0	1 (14%)	.24
Cardiac maternal indication	5 (9%)	2 (7%)	1 (5%)	2 (29%)	.20
Obstetric indication	3 (5%)	2 (7%)	1 (5%)	0	1.00
Small for gestational age	8 (15%)	5 (18%)	3 (15%)	0	.67
Fetal death	1 (2%)	0	0	1 (14%)	.13
Postpartum hemorrhage	2 (4%)	2 (7%)	0	0	.36
Postpartum blood loss (ml)	300 (200-425)	300 (200-650)	350 (300-400)	200 (200-500)	.48
Neonatal death	1 (2%)	1 (4%)	0	0	1.00

MP = mechanical aortic valve prosthesis, n = number of pregnancies, APGAR = appearance, pulse, grimace, activity, respiration, NYHA = New York Heart, Classification, PIH = pregnancy induced hypertension, PPRoM = preterm premature rupture of membranes, * = adjusted for gestational age, fetal sex, and parity, ** = overlapping categories. Data are presented as number of pregnancies (%) and continuous variables are presented as median with interquartile ranges.

DISCUSSION

Pregnancy in patients after AVR with a human tissue valve or a mechanical valve substitute was associated with serious maternal cardiac and obstetric complications in half of the patients in our study. However, all patients survived pregnancy. Human tissue valve recipients had a lower incidence of cardiac maternal and obstetric complications than patients with mechanical valve prostheses. Mechanical valve recipients were at risk for miscarriage, supraventricular arrhythmias, heart failure, and preterm delivery.

Pregnancy elicits major hemodynamic changes.[18, 19] In addition, pregnancy induces alterations in the maternal coagulation cascade which makes it difficult to provide sufficient anticoagulation therapy in mechanical valve recipients and is therefore associated with maternal morbidity and mortality.[1, 9, 10] However, more intensive anticoagulation may lead to hemorrhage. A recent review of maternal mortality considers care as suboptimal when there has been inappropriate management of anticoagulation, which can contribute to maternal cardiac death.[20] A Danish cohort study describes 2 maternal deaths in 107 mechanical valve recipients of which 1 was anticoagulation related.[1] The mechanical valve patient in our cohort who developed a prosthetic valve thrombosis failed to comply with het anticoagulation therapy leading to inadequate anticoagulation. While appropriate dosing of oral anticoagulation can be challenging in pregnancy, patient compliance has also to be taken into account.

Another important cardiac complication in our study population was symptomatic heart failure during pregnancy which occurred in 5 patients, of whom 3 experienced a persistent New York Heart Association (NYHA) deterioration after 1 year. Heart failure is described as a serious complication in pregnant patients who underwent prior valve replacement;[1, 21-23] it was the cause of maternal death,[1] but also an indication for termination of pregnancy.[22] Two of the 5 patients with heart failure in our study were advised against pregnancy prior to conception; both had persistent NYHA deterioration after pregnancy. Although preconceptional counseling has the intention to reduce the risk on severe maternal cardiac events during pregnancy, it is the patient and her family who finally decides to pursue or decline a pregnancy based on the informed wishes and expectations.

In the present study, hypertensive related disorders occurred significantly more often in homograft recipients. Of the reports on pregnancy outcomes in homograft patients,[2, 10, 21, 24, 25] only 1 study describes a case of pre-eclampsia.[24] The aortic gradient increases

significantly in homograft patients during pregnancy, but this is also seen in mechanical valve recipients,[21] and probably reflects the increased cardiac output (increased stroke volume) and decrease in systemic vascular resistance. Unfortunately, we could not identify a specific reason for the increase in hypertensive related disorders among homograft patients.

Almost all newborns of mechanical recipients were vaginally delivered without excessive maternal hemorrhage during labor or caesarean section (Figure 2). The Danish cohort on the other hand reports a postpartum bleeding incidence of 12% and reported 1 fatal bleeding.[1] This underlines the importance of careful anticoagulation monitoring during delivery. Our study illustrates that through careful anticoagulation monitoring during delivery it is possible for mechanical valve recipients to deliver a baby without extensive bleeding.

There was 1 fetal death and 1 postnatal death, both in patients on oral anticoagulation therapy. Although the risks appears to be decreasing in the last few decades, mechanical valve recipients still have up to 9% fetal death risk.[1, 9, 26] Perinatal death risk is reported to be up to 6% in mechanical valve recipients,[9, 26, 27] and up to 8% in the mostly small cohorts of human tissue valve recipients.[10-12, 21, 24, 25] Dore and Somerville report 1 perinatal death among 14 pregnancies in pulmonary autograft patients, although not directly related to cardiac reasons.[11]

Preterm delivery occurred more often (24%) in our study population as compared to the general Dutch population, especially in mechanical valve recipients. This high rate of preterm delivery was also found in the Danish cohort which found a rate of 49%.[1] Of the 13 cases of preterm delivery in the current study, 8 were induced on medical indication of which 5 due to cardiac reasons. As preterm delivery is the leading cause of infant mortality and morbidity, it is crucial to understand which risk factors are associated with preterm delivery.[28] Maybe the treating physicians are too cautious with this particular patient group and therefore it is mainly a 'doctors decision' to intervene earlier as compared to the normal Dutch population. Maybe with good advice how to guide the anticoagulant management during delivery (new ESC guidelines) and some reinsurance, based on our findings, less preterm deliveries can be reached for.

Counseling of young female patients who require AVR and may contemplate pregnancy, requires a multidisciplinary discussion including several important issues. These patients should be individually informed about the (dis)advantages of the different available

valve substitutes and corresponding potential pregnancy-associated maternal and fetal complications.[3] The high incidence of preterm delivery and valve thrombosis in mechanical valve recipients illustrates that these valves are far from ideal in patients during pregnancy. On the other hand, the curious finding of a high incidence of hypertension related disorders in homograft recipients calls for further studies and indeed careful monitoring of the last stage of pregnancy in this patient group. Although human tissue valves needs careful obstetric monitoring, they provide female patients a biological solution that eliminates the daily burden of anticoagulation, in particular during pregnancy, and their durability is not influenced by pregnancy.[29] Therefore, human tissue valves should be considered as aortic valve substitute of choice in young patients with severe aortic valve disease who are planning to start a family.

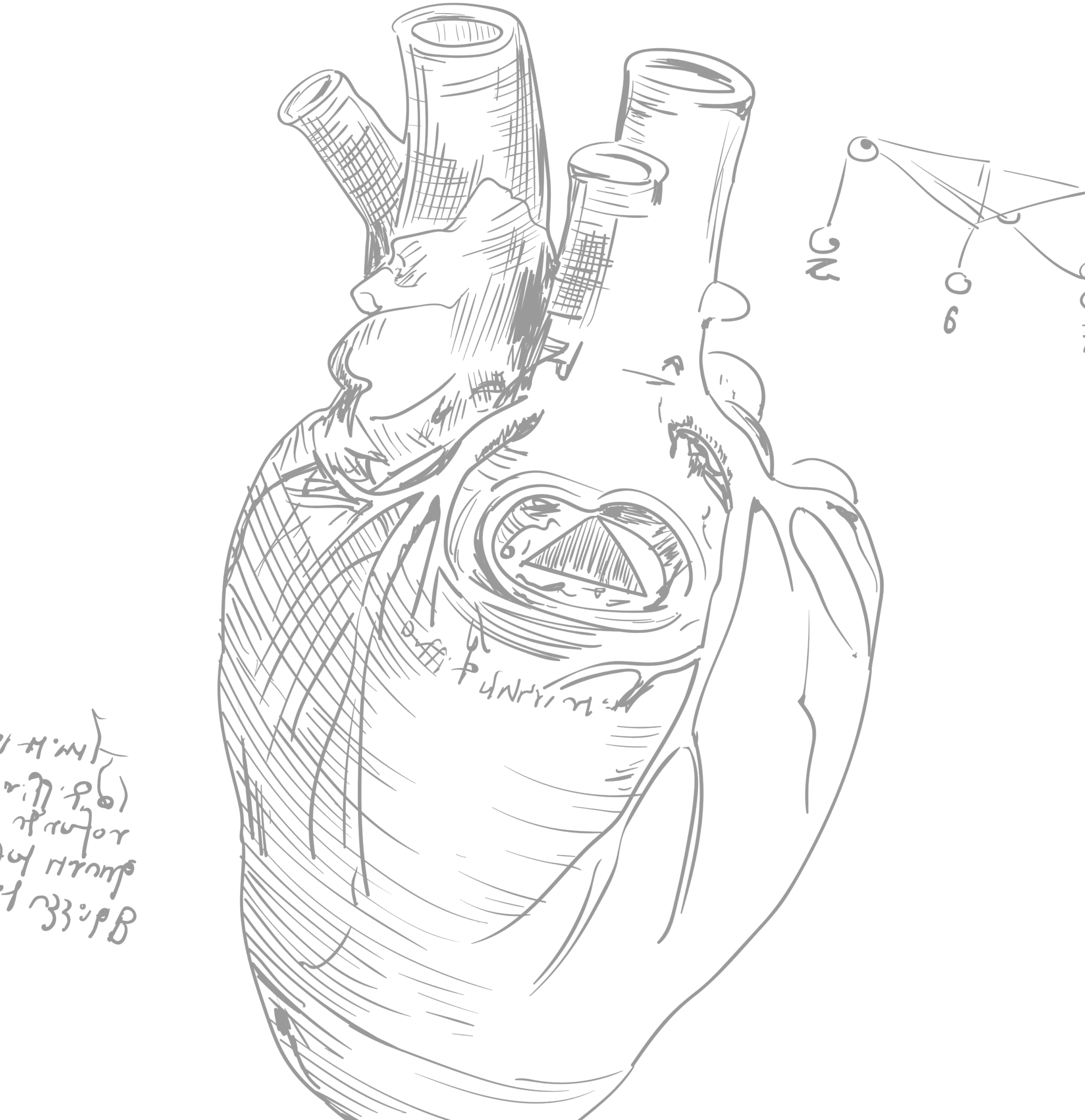
As in most studies on this topic, patient numbers in the present study are relatively small and treatment took place in a tertiary hospital which necessitates careful interpretation of the results.

REFERENCES

1. Sillesen M, Hjortdal V, Vejlstrup N, Sorensen K. Pregnancy with prosthetic heart valves - 30 years' nationwide experience in Denmark. *Eur J Cardiothorac Surg* 2011;40:448-454.
2. Mihaljevic T, Paul S, Leacche M, Rawn JD, Cohn LH, Byrne JG. Valve replacement in women of childbearing age: influences on mother, fetus and neonate. *J Heart Valve Dis* 2005;14:151-157.
3. Pieper PG, Balci A, Van Dijk AP. Pregnancy in women with prosthetic heart valves. *Neth Heart J* 2008;16:406-411.
4. Jamieson WR. Modern cardiac valve devices--bioprostheses and mechanical prostheses: state of the art. *J Card Surg* 1993;8:89-98.
5. 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;99:2669-2676.
6. Avila WS, Rossi EG, Grinberg M, Ramires JA. Influence of pregnancy after bioprosthetic valve replacement in young women: a prospective five-year study. *J Heart Valve Dis* 2002;11:864-869.
7. Suri V, Sawhney H, Vasishta K, Renuka T, Grover A. Pregnancy following cardiac valve replacement surgery. *Int J Gynaecol Obstet* 1999;64:239-246.
8. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000;160:191-196.
9. Yinon Y, Siu SC, Warshafsky C, Maxwell C, McLeod A, Colman JM, Sermer M, Silversides CK. Use of low molecular weight heparin in pregnant women with mechanical heart valves. *Am J Cardiol* 2009;104:1259-1263.
10. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *BJOG* 2000;107:245-253.
11. Dore A, Somerville J. Pregnancy in patients with pulmonary autograft valve replacement. *Eur Heart J* 1997;18:1659-1662.
12. Yap SC, Drenthen W, Pieper PG, Moons P, Mulder BJ, Klieverik LM, Vliegen HW, van Dijk AP, Meijboom FJ, Roos-Hesselink JW, investigators Z. Outcome of pregnancy in women after pulmonary autograft valve replacement for congenital aortic valve disease. *J Heart Valve Dis* 2007;16:398-403.
13. Bekkers JA, Klieverik LM, Raap GB, Takkenberg JJ, Bogers AJ. Re-operations for aortic allograft root failure: experience from a 21-year single-center prospective follow-up study. *Eur J Cardiothorac Surg* 2011;40:35-42.
14. Klieverik LM, Takkenberg JJ, Bekkers JA, Roos-Hesselink JW, Witsenburg M, Bogers AJ. The Ross operation: a Trojan horse? *Eur Heart J* 2007;28:1993-2000.

15. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hyperten Pregnancy* 2001;20:9-14.
16. The Netherlands Perinatal Registry. Perinatal care in the Netherlands 2008. Utrecht, The Netherlands Perinatal Registry, 2011.
17. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, Bax J, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Aguiar C, Al-Attar N, Garcia AA, Antoniou A, Coman I, Elkayam U, Gomez-Sanchez MA, Gotcheva N, Hilfiker-Kleiner D, Kiss RG, Kitsiou A, Konings KT, Lip GY, Manolis A, Mebaaza A, Mintale I, Morice MC, Mulder BJ, Pasquet A, Price S, Priori SG, Salvador MJ, Shotan A, Silversides CK, Skouby SO, Stein JI, Tornos P, Vejlstrup N, Walker F, Warnes C. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:3147-3197.
18. Elkayam U, Bitar F. Valvular heart disease and pregnancy: part II: prosthetic valves. *J Am Coll Cardiol* 2005;46:403-410.
19. Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart* 2007;93:552-558.
20. (CMACE). CfMaCE. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011;118:1-203.
21. Lesniak-Sobelga A, Tracz W, KostKiewicz M, Podolec P, Pasowicz M. Clinical and echocardiographic assessment of pregnant women with valvular heart diseases--maternal and fetal outcome. *Int J Cardiol* 2004;94:15-23.
22. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J* 1994;71:196-201.
23. Born D, Martinez EE, Almeida PA, Santos DV, Carvalho AC, Moron AF, Miyasaki CH, Moraes SD, Ambrose JA. Pregnancy in patients with prosthetic heart valves: the effects of anticoagulation on mother, fetus, and neonate. *Am Heart J* 1992;124:413-417.
24. Denbow CE, Matadial L, Sivapragasam S, Spencer H. Pregnancy in patients after homograft cardiac valve replacement. *Chest* 1983;83:540-542.
25. Cleuziou J, Horer J, Kaemmerer H, Teodorowicz A, Kasnar-Samprec J, Schreiber C, Lange R. Pregnancy does not accelerate biological valve degeneration. *Int J Cardiol* 2010;145:418-421.
26. McLintock C, McCowan LM, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. *BJOG* 2009;116:1585-1592.

27. Bian C, Wei Q, Liu X. Influence of heart-valve replacement of warfarin anticoagulant therapy on perinatal outcomes. *Arch Gynecol Obstet* 2011;285:347-351.
28. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75-84.
29. Arabkhani B, Heuvelman HJ, Bogers AJJC, Mokhles MM, Roos-Hesselink JW, Takkenberg JJM. Does pregnancy influence the durability of human aortic valve substitutes? *J Am Coll Cardiol* 2012; DOI 10.1016/j.jacc.2012.06.055.



Chapter 9

Does pregnancy influence the durability of human aortic valve substitutes?

Arabkhani B, Heuvelman HJ, Bogers AJ, Mokhles MM, Roos-Hesselink JW, Takkenberg JJ

J Am Coll Cardiol. 2012 Nov 6;60(19):1991-2

There is insufficient published evidence about the potential degenerative effects of pregnancy on the homograft and pulmonary autograft in 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 aortic position at our institution.

Patients

All patients who receive a homograft or autograft in 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 standardised serial echocardiography (aortic gradient (Vmax), aortic regurgitation (AoI), annular and sinotubular junction diameter (AD and STJ). We identified 108 female patients who underwent 59 homograft and 49 autograft procedures, and were 50 years or younger at time of surgery and at least 16 years old at the time of study (mean age 29 years; SD 13). 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 an inclusion cylinder aortic root replacement.

Outcome was reported according to the 2008 AATS/EACTS/STS 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 or more echocardiographic examinations (median 6; range 1-11).

Thirty-one patients (13 homograft and 18 autograft) experienced 55 pregnancies, including 48 completed pregnancies, 4 elective abortions for non-cardiac reasons and 3 miscarriages. Homograft recipients without pregnancies were older than homograft recipients who became pregnant (35 versus 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 neo-aortic regurgitation and dilatation of the neo aortic root, including eleven autograft replacements and one valve sparing aortic root replacement (Yacoub procedure). Freedom from aortic valve reoperation at 15 years was 63% (95%CI: 57-69%) in homograft patients; in autograft patients 75% (95%CI: 63-87%). 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 Vmax, STJ diameter, AD and AoI over time. Pregnancy was not associated with changes in Vmax over time, STJ diameter over time, AD over time or AoI grade over time for either valve type.

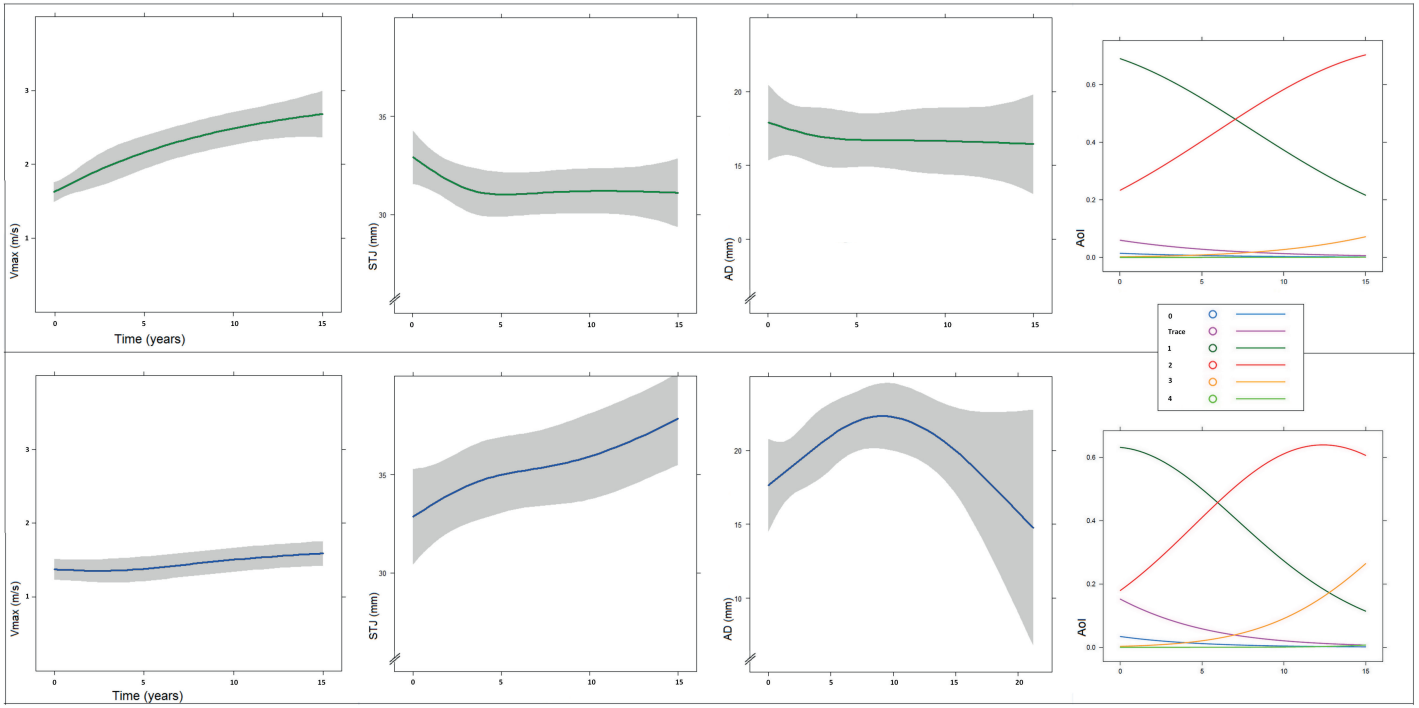


FIGURE 1. From left to right: Peak velocity (Vmax), Sinotubular junction (STJ) diameter, Anulus diameter (AD) and Aortic regurgitation (AoI) marginal probability of AoI grade; over time. Upper row concerns homograft models. Lower row concerns autograft models.

Shaded grey areas: 95% CI.

DISCUSSION

Pregnancy is known to provide 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 (4,5).

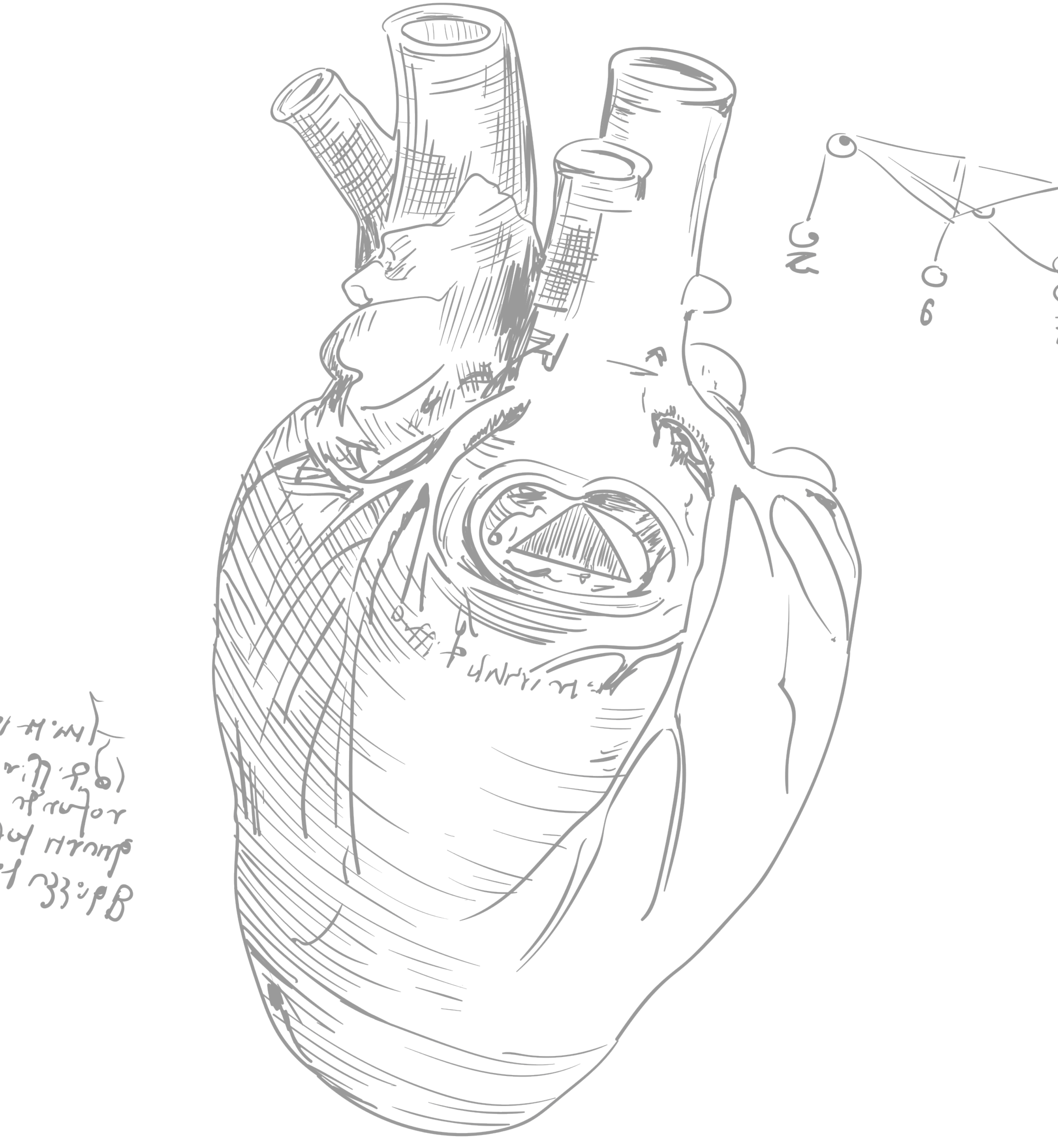
The question remains what the best valve substitute choice is for young female patients who require aortic valve replacement, and who may contemplate pregnancy. Bioprosthetic valves are an option, but valvular deterioration seems to be accelerated during pregnancy (6). Mechanical prostheses are far from ideal during pregnancy because of 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 haemodynamic 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 in particular during pregnancy has potential beneficial effects on cardiac function. On the other hand, neo-aortic root dilatation and neo-aortic regurgitation cause an increased need for reoperation (8).

CONCLUSION

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 Jan;15(1):100-6; discussion 106-7.
2. Verbeke G & Molenberghs G. 2009. Linear Mixed Models for Longitudinal Data. New York. Springer.
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;2669-2676.
5. A. Dore and J. Somerville. Pregnancy in patients with pulmonary autograft valve Replacement. European Heart Journal (1997) 18, 1659-1662.
6. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. Circulation 2003;107:1240–6.
7. Ismail El-Hamamsy, Zeynep Eryigit, Louis-Mathieu Stevens, Zubair Sarang, Robert George, Lucy Clark, Giovanni Melina, Johanna JM Takkenberg and Magdi H Yacoub. 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 (2010).
8. Johanna J.M. Takkenberg, Loes M.A. Klieverik, Paul H. Schoof, Robert-Jan van Suylen, Lex A. van Herwerden, Pieter E. Zondervan, Jolien W. Roos-Hesselink, Marinus J.C. Eijkemans, Magdi H. Yacoub, Ad J.J.C. Bogers. The Ross Procedure: A Systematic Review and Meta-Analysis. Circulation 2009, 119:222-228.



Chapter 10

Therapeutic decisions for patients with symptomatic severe aortic stenosis: room for improvement?

van Geldorp MW, van Gameren M, Kappetein AP, Arabkhani B,
de Groot-de Laat LE, Takkenberg JJ, Bogers AJ

Eur J Cardiothorac Surg. 2009 Jun;35(6):953-7; discussion 957

ABSTRACT

Objective. Symptomatic severe aortic stenosis is an indication for aortic valve replacement. Some patients are denied intervention. This study provides insight into the proportion of conservatively treated patients and into the reasons why conservative treatment is chosen.

Methods. Of a patient cohort presenting with severe aortic stenosis between 2004 and 2007, medical records were retrospectively analyzed. Only symptomatic patients (n=179) were included. We studied their characteristics, treatment decisions and survival.

Results. Mean age was 71 years, 50% were male. During follow-up (mean 17 months, 99% complete) 76 (42%) patients were scheduled for surgical treatment (63 conventional valve replacement, 10 transcatheter, 1 heart transplantation, 2 waiting list) versus 101 (56%) who received medical treatment. Reasons for medical treatment were: perceived high operative risk (34%), symptoms regarded mild (19%), stenosis perceived non-severe (14%) and patient preference (9%). In 5% the decision was pending at the time of the analysis and in 20% the reason was other/unclear. Mean age of the surgical group was 68 versus 73 years for medically treated patients (p=0.004). Predicted mortality (EuroSCORE) was 7.8% versus 11.3% (p=0.006). During follow-up 12 patients died in the surgical group (no 30-day operative mortality), versus 28 in the medical group. Two-year survival was 90% versus 69%.

Conclusions. A large proportion (56%) of symptomatic patients does not undergo aortic valve replacement. Often operative risk is estimated (too) high or hemodynamic severity and symptomatic status are misclassified. Interdisciplinary team discussions between cardiologists and surgeons should be encouraged to optimize patient selection for surgery.

INTRODUCTION

The prevalence of aortic stenosis increases with age to up to 8% in the elderly [1]. Meanwhile the Western population increases to age during the last decades and this trend is expected to continue [2]. Therefore aortic stenosis constitutes a growing health burden.

While the treatment of asymptomatic patients with severe aortic stenosis remains debatable, both European and American guidelines on the management of valvular heart disease recommend that symptomatic patients have aortic valve replacement [3,4]. This recommendation is not only based on the survival advantage that can be expected after surgery but also on the improvement in functional class, even in elderly patients [3-5].

Recent literature suggests that a considerable proportion (33-60%) of patients with symptomatic severe aortic stenosis does not receive aortic valve replacement (AVR) [6-9]. We sought to confirm that many symptomatic patients remain unoperated and were interested in the reasons and the consequences of the decision to operate or not. The goal of our study was therefore to gain insight into decision making and survival in patients with severe symptomatic aortic stenosis.

METHODS

Study design and data collection

A retrospective search in the echocardiography database of our department revealed 115 patients with severe aortic stenosis. An additional 140 patients were recruited from the echocardiography laboratories in the outpatient cardiology clinics of 7 hospitals in the Rotterdam region. All echocardiograms were made between October 2004 and December 2007. Patients had at least one of the following inclusion criteria: aortic valve area < 1.0 cm^2, maximum aortic jet velocity > 4.0 m/s, peak aortic gradient > 64 mmHg or mean aortic gradient > 40 mmHg. To avoid missing low-output aortic stenosis, patients were also included if the ratio between the velocity time integral over the aortic valve and the left ventricular outflow tract was > 4.0.

Information was gathered on medical history, cardiovascular risk factors and symptomatic status at the time of the echocardiogram. Asymptomatic patients were excluded from the eventual analysis. For all symptomatic patients, anticipated operative risk was calculated using the logistic EuroSCORE risk model (www.euroscore.org).

Treatment strategies and their reasons were retrieved from notes in the patients' medical charts. Reasons for 'conservative/medical treatment' were classified in 6 main categories: 1) anticipated high operative risk (including advanced age or left ventricular dysfunction); 2) only mild symptoms; 3) stenosis non-severe; 4) patient preference; 5) decision not final yet; 6) other, including 'reason unclear'.

The study protocol was approved by the institutional review board, patient informed consent was waived (MEC 06-066, MEC 08-022). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Study population

Of the 255 patients that were initially identified, 73 asymptomatic patients were excluded plus 3 patients of whom symptomatic status could not be retrieved, leaving 179 symptomatic patients in the study cohort. Mean age was 71 years, 50% were male.

TABLE 1. Patient characteristics

Patient characteristics	AVR n= 76	Conservative n= 101
Age (mean ± SD in years)	67.9 ± 12.4	73.3 ± 12.3
Male (%)	49	51
Follow-up (mean ± SD in months)	20.3 ± 11.8	15.1 ± 11.5
Echocardiographic parameters (mean ± SD)		
Maximal transaortic velocity (m/s)	4.4 ± 0.8	4.0 ± 0.8
Peak gradient (in mmHg)	82 ± 32	66 ± 26
AV/LVOT VTI ratio	4.9 ± 1.8	5.0 ± 2.3
Aortic Valve Area (cm^2)	0.68 ± 0.24	0.71 ± 0.26
NYHA class (%)		
II	42.1	54.5
III	38.2	34.7
IV	13.2	8.9
Missing	6.6	2.0
Left Ventricular Function (%)		
Good/impaired (EF >50%)	56.6	57.4
Moderate (EF 30-50%)	38.2	30.7
Poor (EF <30%)	2.6	7.9
Missing	1.3	4.0
Logistic EuroSCORE (mean ± SD)	7.8 ± 7.9	11.3 ± 9.6

During follow-up (mean 17 months, median 13.6, range 0.1-40) 76 patients (42%) underwent AVR or were scheduled for surgery (Figure 1). There were 63 conventional aortic valve replacements, 9 percutaneous and 1 transapical valve implantations. Two patients were on a waiting list for AVR and 1 patient required a heart transplantation during follow-up. Medical treatment was given in 101 patients (56%). Two patients were lost to follow-up (99% completeness). Mean age of the surgical group was 68 versus 73 years for the medically treated patients (P=0.004). Predicted operative mortality according to the logistic EuroSCORE was 7.8% versus 11.3% (P=0.009). More patient characteristics are given in Table 1.

Statistical Analysis

Continuous data are presented as mean ± 1 standard deviation, and median. Categorical data are presented as proportions. Chi-square testing was used for comparison of categorical variables. Continuous variables were compared using the Student's t-test. A p-value < 0.05 was considered significant. Survival curves were estimated by the Kaplan-Meier method. Differences in survival were not statistically assessed. Statistical analyses were performed with SPSS for Windows (release 15.0; SPSS Inc, Chicago, Illinois).

RESULTS

There was no 30-day mortality. During follow-up 12 patients died in the surgical group, versus 28 patients in the medical group. One- and two-year survival was respectively 93% and 90% for the AVR group and for the conservative group 77% and 69% (Figure 1).

Reasons for choosing non-surgical treatment were: operative risk deemed 'too high' (34%), symptoms regarded as 'mild' (19%), stenosis regarded as 'non-severe' (14%) and patient preference (9%). In 5% the decision to operate was still under consideration by cardiologist and/or patient. In 20 patients (20%) the reason behind decision making could not be retrieved accurately. Of the latter 20 patients, 11 were in NYHA class II, 6 were in NYHA III and 3 were in NYHA class IV.

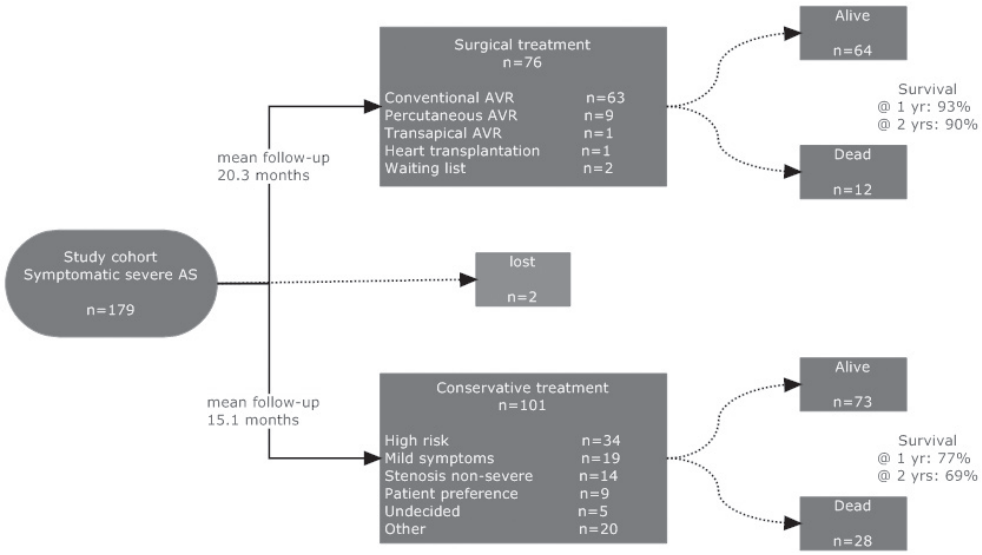


FIGURE 1. Flow chart of main results.

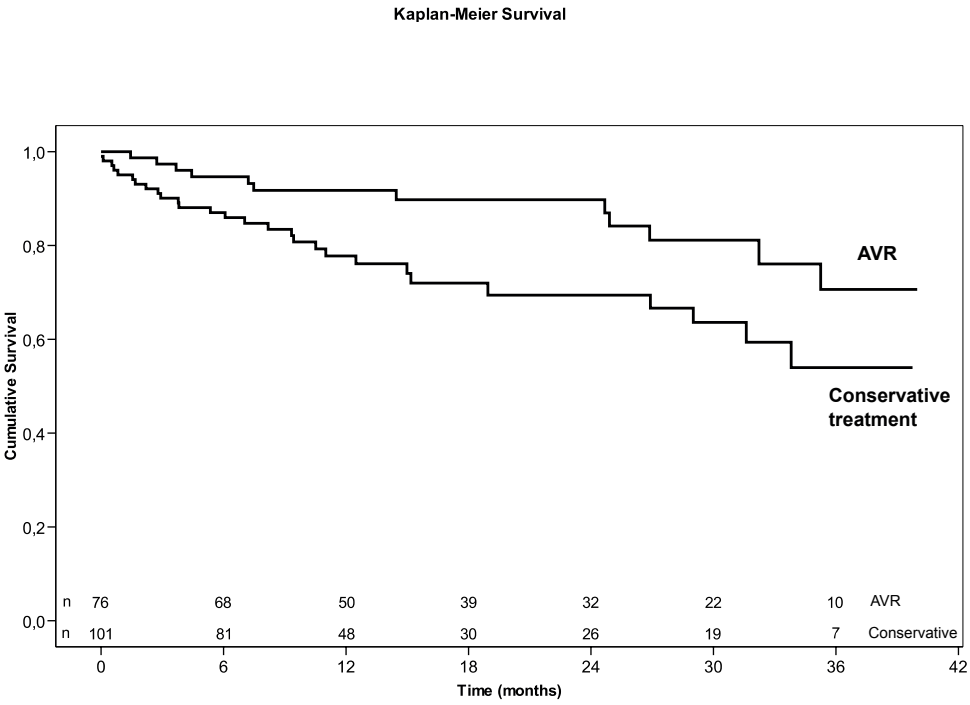


FIGURE 2. Kaplan Meier survival for the conservatively treated group and the AVR group.

Of the 34 patients in whom the reason not to operate was 'high risk', the mean age was 75.7 years and the mean EuroSCORE was 11.6%. Eight of them had a history of malignancy or active malignancy (six of these patients eventually died during follow up). Eighteen patients had a EuroSCORE <10% and only 9 of the 34 patients in whom the operative risk was deemed too high had a EuroSCORE > 15%.

DISCUSSION

Although treatment consensus seems to exist on symptomatic patients with severe aortic stenosis, it is not uncommon to diverge from these guidelines [6,8-10]. Advanced age and left ventricular dysfunction are known reasons to deny surgery in a symptomatic patient [6,11]. Instead of using patient characteristics to predict whether a patient gets AVR or not, our study was designed to investigate the decision making. Therefore it provides a different perspective: in our cohort an overestimation of operative risk, underestimation of symptoms and misclassification of hemodynamic severity are common causes why symptomatic patients are denied AVR. Furthermore, we found that survival of the conservative group is not as pessimistic as reported by others [12,13].

'Overestimation' of operative risk?

In a third of the patients who were treated conservatively, an anticipated high operative risk was the main reason not to go for AVR. This subgroup had a mean age of only 76 years, and only 9 of the 34 patients had a EuroSCORE > 15%. Perhaps it is even more important that more than half (18 patients) had a relatively low operative risk with a EuroSCORE <10%.

From literature it is known that remission of symptoms after starting medical treatment can be a reason to stay conservative and that patients who are treated conservatively are generally older and more often have impaired left ventricular function than surgically treated patients [6,7]. Yet, both remission of symptoms, advanced age and depressed left ventricular function are debatable reasons not to operate on a symptomatic patient. Even elderly patients can be operated upon with acceptable morbidity and mortality, and can expect a considerable quality of life [5,11].

Note that 10 patients in the AVR group underwent a minimally invasive valve replacement. They were deemed not amendable for surgery. This indicates that even in a region with a tertiary center that uses new percutaneous and transapical techniques to replace the aortic valve, the majority of patients are treated conservatively.

Eight patients had either a malignancy in medical history or an active malignancy, risk factors which are not taken into account by the EuroSCORE. Another issue with risk models is that they do not score characteristics such as 'vitality' or 'biological age'. Furthermore there is a large variability between different risk models, and the one most commonly used (EuroSCORE) seems to overestimate the actual operative risk most [14]. Perhaps this adds to the large variance in treatment advise that exists among cardiologists which was already found by Bouma et al [7].

Underestimation of symptoms?

Due to inactivity or gradual adjustment of daily activities to developing symptoms, patients with aortic stenosis often do not acknowledge the presence of symptoms or attribute them to the ageing process. Exercise testing is recommended in asymptomatic patients with aortic stenosis in order to exclude symptoms with more certainty [15-17], and up to 37% of patients previously considered asymptomatic have limiting symptoms when they are tested [17]. According to the European Heart Survey exercise testing is highly underused [3,18]. This could lead to an underestimation of the proportion of symptomatic patients treated medically that was reported by others and in the current study [6,8-10].

In this study, the classical aortic stenosis symptoms such as dyspnea, syncope or angina were documented for several patients but regarded as 'mild' or non-debilitating. Having only 'mild' symptoms does not exclude a patient from being an AVR candidate [3,4]. It is furthermore known that even íf symptoms are recognized, the resulting functional disability is often underestimated by physicians [19]. Symptomatic patients with severe aortic stenosis from our cohort suffer from both physical and emotional impairment hampering normal daily activities (unpublished data). These are clear reasons to assess symptomatic status accurately, and to reconsider a conservative approach when symptoms are present.

Underestimation of hemodynamic severity

As much as 14% of the symptomatic patients who were denied surgery were not referred because the stenosis was classified *'non-severe'* by the treating cardiologist during the initial assessment. According to the guidelines they should however have been classified as severe [3,4]. Since only patients with a *severe* stenosis are recommended to have surgery, these misclassified patients are at increased risk of left ventricular deterioration and sudden death [20].

Even if the stenosis severity is only just below the 'severe' threshold, it can be disputed that 'watchful waiting' is the best treatment. Peak aortic gradient increases 10-15 mmHg/year and aortic valve area decreases 0.1-0.12 cm^2/year [21-23]. Given these progression rates, borderline patients will enter the 'severe' category within a few months or at most a year later. Meanwhile left ventricular function will only get worse.

Survival in the conservative and in the surgical group

Survival in the medically treated group cannot easily be compared with the surgically treated group because the patients have quite different characteristics, which could account for a large part of the difference in survival. It is therefore questionable if, and to what extent, the survival of the total study group would have improved supposed more patients would have had aortic valve replacement.

From the survival curve of the non-AVR group it can be seen that a decline in survival already occurs in the first year after the echocardiogram (Figure 2). Still, survival in the conservative group is not as bad as expected based on previous reports [12,13,20]. Perhaps improvement in medical treatment over the past years plays a role, but survival in the conservative group highly depends on referral strategy as well; if more high risk patients are operated upon, the patients with a really bad prognosis are left for conservative treatment, resulting in low survival in this category. Therefore the relatively 'good' prognosis of our medically treated group could be a reflection of the conservative approach of the cardiologists in our region.

Because of its dependence on referral, 'natural history' of aortic stenosis is very difficult to study. If one would like to gain a clear view on 'natural history', theoretically all eligible patients should be excluded from having AVR, or they should be randomised to receive either surgical or conservative treatment. In practice this would be impossible and ethically incorrect.

Future prospects

Microsimulation methods can accurately estimate life-expectancy for patients after AVR [24,25], but have yet to be developed for patients who are treated conservatively. Our department intends to develop these models, but this requires large datasets with extensive numbers of variables and some patient factors, such as vitality, will be difficult to grasp in a model.

CONCLUSION

A considerable proportion of patients with symptomatic severe aortic stenosis is not referred for surgery although theoretically they have an indication for aortic valve replacement. Often operative risk is estimated (too) high, and misclassification of both hemodynamic severity and symptomatic status occurs frequently.

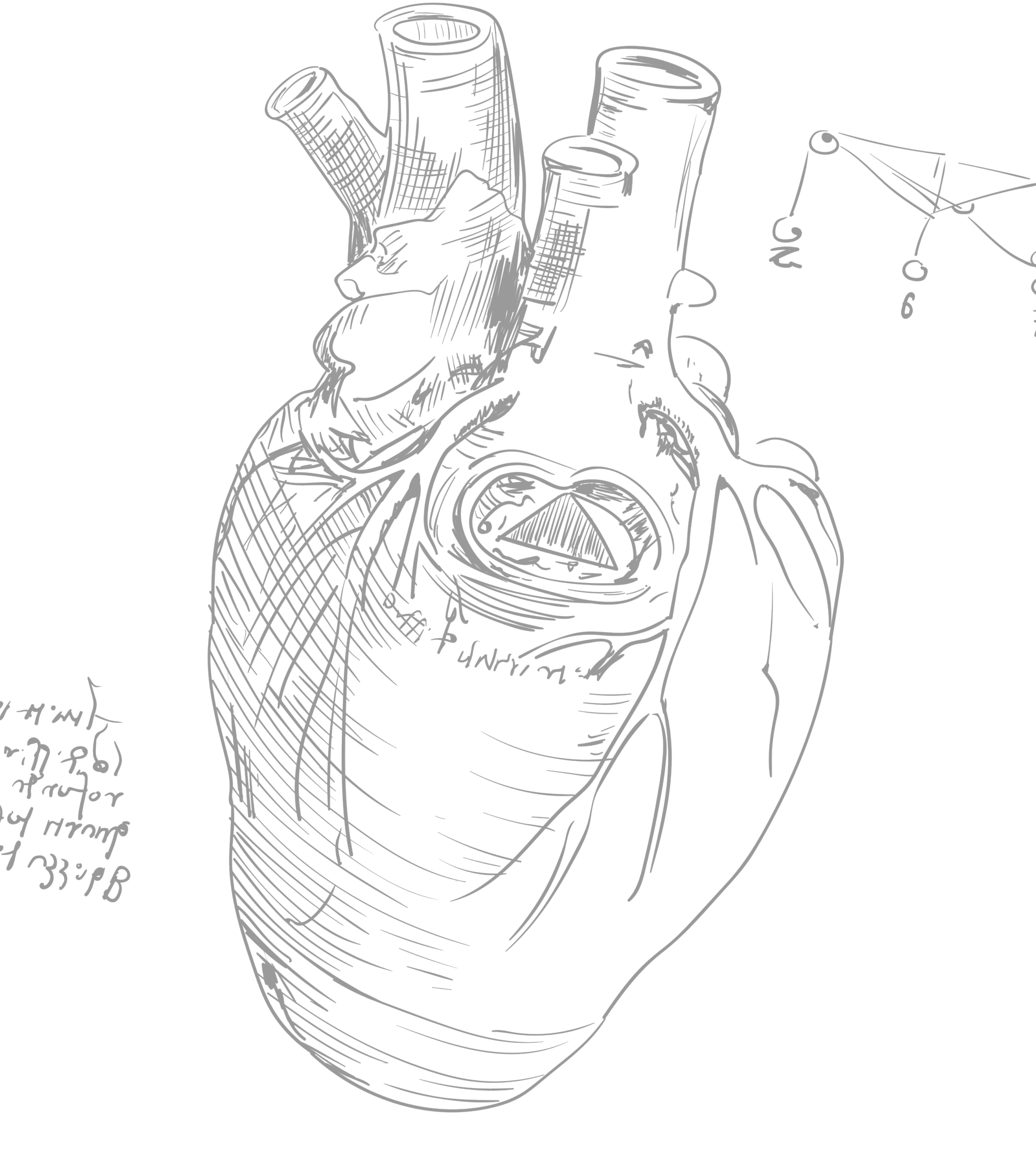
Most patients who were treated conservatively were simply not *referred* to a surgical department. Referral to surgical departments should be encouraged in order to have more interdisciplinary team discussions between cardiologists and surgeons. Hopefully, this will result in better patient selection for surgery, possibly resulting in better survival of patients with severe symptomatic aortic stenosis.

REFERENCES

1. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am Coll Cardiol 1993;21:1220-5.
2. Devision UNP. World Population Prospects: The 2006 Revision Population Database, 2006.
3. Bonow RO, Carabello BA, Kanu C, de Leon AC, Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. 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): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation 2006;114:e84-231.
4. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28:230-68.
5. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: Results from a cohort of 277 patients aged > or =80 years. Eur J Cardiothorac Surg 2006;30:722-7.
6. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohlke-Barwolf C, Boersma E, Ravaud P, Vahanian A. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J 2005;26:2714-20.
7. Bouma BJ, van der Meulen JH, van den Brink RB, Arnold AE, Smidts A, Teunter LH, Lie KI, Tijssen JG. Variability in treatment advice for elderly patients with aortic stenosis: a nationwide survey in The Netherlands. Heart 2001;85:196-201.
8. Charlson E, Legedza AT, Hamel MB. Decision-making and outcomes in severe symptomatic aortic stenosis. J Heart Valve Dis 2006;15:312-21.
9. Bach DS, Cimino N, Deeb GM. Unoperated patients with severe aortic stenosis. J Am Coll Cardiol 2007;50:2018-9.
10. Bouma BJ, van Den Brink RB, van Der Meulen JH, Verheul HA, Cheriex EC, Hamer HP, Dekker E, Lie KI, Tijssen JG. To operate or not on elderly patients with aortic stenosis: the decision and its consequences. Heart 1999;82:143-8.
11. Bouma BJ, van den Brink RB, Zwinderman K, Cheriex EC, Hamer HH, Lie KI, Tijssen JG. Which elderly patients with severe aortic stenosis benefit from surgical treatment? An aid to clinical decision making. J Heart Valve Dis 2004;13:374-81.

12. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. Eur Heart J 1988;9 Suppl E:57-64.
13. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. Ann Thorac Surg 2006;82:2116-22.
14. Dewey TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 2008;135:180-7.
15. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Jr., Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC, Jr. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002;106:1883-92.
16. Bonow RO, Carabello B, de Leon AC, Edmunds LH, Jr., Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O'Gara PT, O'Rourke RA, Rahimtoola SH, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A, Jr., Gibbons RJ, Russell RO, Ryan TJ, Smith SC, Jr. ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease. Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). J Heart Valve Dis 1998;7:672-707.
17. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J 2005;26:1309-13.
18. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231-43.
19. Calkins DR, Rubenstein LV, Cleary PD, Davies AR, Jette AM, Fink A, Kosecoff J, Young RT, Brook RH, Delbanco TL. Failure of physicians to recognize functional disability in ambulatory patients. Ann Intern Med 1991;114:451-4.
20. Chizner MA, Pearle DL, deLeon AC, Jr. The natural history of aortic stenosis in adults. Am Heart J 1980;99:419-24.
21. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation 1997;95:2262-70.
22. Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. J Am Coll Cardiol 1989;13:545-50.
23. Faggiano P, Ghizzoni G, Sorgato A, Sabatini T, Simoncelli U, Gardini A, Rusconi C. Rate of progression of valvular aortic stenosis in adults. Am J Cardiol 1992;70:229-33.

24. Takkenberg JJ, Puvimanasinghe JP, Grunkemeier GL. Simulation models to predict outcome after aortic valve replacement. Ann Thorac Surg 2003;75:1372-6.
25. van Geldorp MW, Jamieson WR, Kappetein AP, Puvimanasinghe JP, Eijkemans MJ, Grunkemeier GL, Takkenberg JJ, Bogers AJ. Usefulness of microsimulation to translate valve performance into patient outcome: patient prognosis after aortic valve replacement with the Carpentier-Edwards supra-annular valve. J Thorac Cardiovasc Surg 2007;134:702-9.



Chapter 11

Outcome and Quality of Life After Valve Sparing Aortic Root Reimplantation (David Procedure): A Single-Center Study

B Arabkhani, CM Kievit, WG Morshuis, ML Geleijnse,
JJM Takkenberg, AJJC Bogers, JA Bekkers

Submitted

ABSTRACT

Objective. Valve-sparing aortic root replacement has gained popularity for treating aortic root aneurysm. This study aims to report on valve-related outcome and quality of life after valve sparing aortic root reimplantation.

Methods. Between 2001 and 2014, 41 consecutive patients underwent valve-sparing aortic root reimplantation. Patient characteristics, survival, freedom from reoperation and valve-related events were analyzed. Standardized echocardiography was performed comparing preoperative and last follow-up measurements. Health-related QoL was explored by means of SF-36 forms and compared to the aged-matched Dutch population.

Results. Median age was 39 (range 18-65) years (78% male). Etiology was connective-tissue-disease (51%), idiopathic aortic aneurysm (32%), and aortic root dilatation after Ross-procedure (17%). During follow-up (mean 5.1 years; range 0.4 to 13.9; 100% complete), one patient died. Freedom from reoperation after 8 years was 78% (95% CI 60-90%) for all patients and 88% (95% CI 67-96%) excluding post Ross-procedure patients. All reoperations were because of aortic regurgitation. Ross-procedure (HR 8.5; 95% CI 1.9-38.5; p = 0.005), greater sinotubular-junction diameter (HR 1.6; 95% CI 1.0-2.6; p = 0.04), and annulus diameter (HR 1.2; 95% CI 1.0-1.6; p = 0.06), were associated with reoperation. Only 2 valve-related (thrombo-embolic) events occurred. Quality of life was comparable to the general age-matched Dutch population.

Conclusions. In our experience, valve-sparing aortic root replacement using the reimplantation technique provides excellent clinical outcome and quality of life in the first postoperative decade. However, despite low valve-related complication rates, there is a hazard of reoperation due to progressive valve regurgitation, particularly in patients after the Ross-procedure.

INTRODUCTION

Since the introduction of the composite aortic root replacement [1], this has been the "gold standard" treatment for aortic root aneurysm. Alternatively biological valve prostheses are available. However, both are associated with valve-related complications.

Valve sparing aortic root replacement (VSARR) techniques are gaining popularity as an alternative treatment for aortic root aneurysm, with or without aortic regurgitation, in the absence of calcification, preserving the native aortic valve, avoiding anticoagulation therapy and the risk of biological valve deterioration. The most frequently used techniques are remodeling (Yacoub) [2] and reimplantation (David) of the aortic root within a prosthetic conduit [3].

Good durability results of the repaired valves are reported from experienced centers. However, these results may contain a positive publication bias. Consequently, there are no clear recommendations in the current guidelines regarding valve-sparing techniques [4]. The main concern remains the probability of valve failure and need for reoperation. Moreover, there are only a few studies presenting the quality of life after VSARR. In this light we conducted this study to report on clinical outcome and quality of life after valve sparing aortic root replacement using the David procedure [3], and to investigate potential risk factors leading to VSARR failure.

MATERIALS AND METHODS

From January 2002 to September 2014, forty-one consecutive patients underwent VSARR using the David reimplantation procedure [3] at the Department of Cardiothoracic Surgery of the Erasmus MC, Rotterdam. Institutional Review Board approval was obtained for this study (MEC 14-518), and informed consent was obtained. The medical records of all patients were reviewed. Patient characteristics and echocardiographic data were collected and are displayed in Table 1. Perioperative characteristics are displayed in Table 2.

Valve-related events were registered according to the 2008 American Association for Thoracic Surgery/Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery guidelines for reporting mortality and morbidity after cardiac valve interventions [5].

All patients who were not reoperated on the aortic valve after VSARR were invited for a standardized echocardiographic follow-up, and a Short Form-36 health related quality of life questionnaire. For all other patients the first preoperative and the latest available echocardiogram before reoperation or death was obtained and analyzed in a structural manner.

TABLE 1. Patient characteristics.

Patient characteristics	**Total cohort (N = 41)**
Age (SD; range) yrs	39,1 (15; 16 - 65)
Female (n, %)	9 (22%)
Prior cardiac surgery (n, %)	8 (19.5%)
Ross operation	7 (17.1)%
VSD closure	1 (2.4%)
Hypertension (n, %)	10 (24.4%)
Mean Creatin level µmol/L (range)	67 (42 -92)
Etiology (N; %)	
Connective tissue disease	21 (51)
Marfan Syndrome	11
SMAD 3 mutation	9
Loeys- Dietz Syndrome	1
Post Ross operation	7 (17)
Idiopathic	13 (32)
Aortic valve regurgitation	
No/Trace	27 (65.9%)
Mild	6 (14.6%)
Moderate	2 (4.9%)
Severe	6 (14.6%)
Aneurysm diameter (mean; SD)	48 (10.2) mm
Systolic LVF (N; %)	
Good	33 (81)
Impaired	8 (19)
Moderate/Severe	0

Echocardiography

All echocardiographic measurements were conducted and reported according to standardized echocardiogram based on criteria of the AVIATOR registry workgroup [5]. All echocardiographic images were evaluated by a cardio-thoracic and cardiology resident. In case of doubt a senior cardiologist was consulted. Furthermore, preoperative and perioperative parameters were analyzed in order to find potential risk factors for repair failure and reoperation. For all patients data on AR preoperatively and at last follow-up was available. However, for 12 patients there were no complete or only postoperative in-hospital echocardiograms, which were excluded from the analysis of other echocardiographic parameters. Appendix 1 shows a detailed description of echocardiographic measurements.

TABLE 2. Perioperative characteristics.

Characteristics	Total cohort (N = 41)
Concomitant procedure (N)	8
CABG	2
MVP	2
Hemiarch aortic replacement	3
VSD closure	1
PVR	1
Aortic cross clamp time (min (SD; range)	159 (25,8 (123-227))
Perfusion time (min (SD; range)	199 (13 (138 - 307)
Circulatory arrest (min (SD; range) (N = 3)	14 (4 (12 - 19)
Bleeding requiring reoperation	5 (12,2%)
Rhytm disturbance postoperative	6 (14,6%)
Supraventricular	6 (100%)
Ventricular	0
Permanent pacemaker	1 (2,4%)
CVA	0

CABG: Coronary artery bypass grafting; MVP: mitral valve plasty; VSD: ventricular septal defect; PVR pulmonary valve replacement.

Quality of life

The Dutch version of the SF-36 was used to evaluate the health-related quality of life. This questionnaire contains questions clustered into 8 domains: physical functioning, role limitations due to physical health problems, general health perceptions, bodily pain, vitality, social functioning, role limitations due to emotional problems, and general mental health. These questions are summarized to form 2 components, namely Physical Component Scale (PCS) and Mental Component Scale (MCS). The scales are from 0 to 100 and are obtained by summing the items together within a domain. Thereafter the scores are divided by the range of scores and transformed into the scale. The mean score of both components is 50 with a standard deviation of 10. Higher scores represent better health status [6]. The study by Aaronson et al. was used to compare QoL between the general Dutch population and the study population [7].

Surgical technique

All patients were operated through a median sternotomy, using cardiopulmonary bypass and St. Thomas cardioplegia. All dilated sinus of Valsalva tissue was resected leaving a 2 to 3 mm rim of aortic tissue distal of the aortic valve attachment. The coronary buttons were dissected and were mobilized. Graft size was measured by a Hegar sizer at the level of the ventriculo-aortic junction, adding 2-3 mm in diameter for the appropriate size. Reimplantation of the aortic valve was performed by anchoring the aortic annulus and subcommissural triangles inside a tubular graft. Horizontal (Prolene 4-0) sutures were placed circumferentially in the left ventricular outflow tract, at the level of the nadir, except in the region of the perimembranous septum, and used to attach the proximal end of the vascular prosthesis. In most patients a Vascutek Valsalva vascular prosthesis (Terumo, Ann Arbor, MI) was used. Subsequently the residual aortic rim was sutured to the prosthesis with a running Prolene 4-0 suture (Ethicon, Inc., Somerville, NJ) and coronary buttons were reimplanted. From 2013 onward we used the caliper cusp measurement instrument introduced by Schäfers in order to asses optimal coaptation height of the aortic valve leaflets [8]. In 2 patients an additional plication of the coronary cusps was performed. Three patients were operated under deep hypothermic cardiac arrest with an open distal anastomosis.

Statistical Analysis

Continuous variables are displayed by the mean and standard deviation and by the median and range where appropriate. The distribution of the continuous variables was tested by Kolmogorov-Smirnov test. Categorical variables are displayed as counts and percentages. The Mann-Whitney U-test (for categorical variables) or unpaired t-test (for continuous variables) was used to compare unpaired groups.

The one-sample t-test was used to compare health-related QoL between the study population and the general Dutch population mean. To compare preoperative to postoperative echocardiographic measurements the paired-sample T-test and the Wilcoxon signed-rank test (continuous parameters) or Mc Nemar's test (binominal parameters), and Marginal Homogeneity test (ordinal parameters) was used. A Cox-regression model was used to test for variables associated with reoperation hazard; multivariable analyses was not performed (low number of events). All tests were 2-sided, and a p-value of 0.05 or less was considered statistically significant. Patient survival and freedom from reoperation were analyzed using the Kaplan-Meier method. The statistical analyses were performed using IBM-SPSS 21 (IBM Corp., Armonk, NY). Graphs were constructed using GraphPad Prism 5.0 (San Diego, CA, USA).

RESULTS

The mean clinical follow-up was 5.1 years (SD 3.1 years; range 0.4-13.9 years) 100 % completed, containing a total of 297 patient-years. Mean time to last follow-up echocardiogram was 3.6 years (SD 2.6 years; range 0.5-10.1 years), 90% complete.

Early mortality and morbidity

There were no early deaths. Coronary artery bypass grafting (CABG) due to complications related to reimplantation of the coronary artery with kinking of the RCA was necessary in one patient. One patient was diagnosed a post-operative third-degree AV-block and received a permanent pace-maker during the hospital stay. Another 5 patients had re-sternotomy because of hemorrhage or tamponade.

Late survival

One patient, a 22-year old man with Marfan's syndrome, died suddenly 4 months after surgery. A post-mortem CT-scan showed asphyxia, probably related to aspiration of blood. The aortic valve and root appeared to be as expected after a David procedure. Overall cumulative survival at 10 years of follow-up was 98% (95% CI 93-100%).

Reoperation

Six patients were reoperated on the aortic root (2.4 %/patient year) due to severe AR and one because of moderate to severe AR with symptoms. Reason for reoperation was structural valve deterioration (SVD). Four of these patients had undergone VSARR because of aortic root dilatation after a Ross procedure, and three for Marfan's syndrome. In all reoperated patients the aortic root was replaced using the composite valve replacement technique (Bentall). There was no reoperation mortality. Cumulative freedom from reoperation on the aortic root was 98% (95% CI 82-99%) at 1 year, and 78% (95% CI 59-89%) at 8 years; and 88% (95% CI 78-99%) when excluding (seven) patients with congenital heart disease and Ross procedure in the past. Figure 1 displays the Kaplan-Meier-curve of freedom from reoperation. Additionally, one of the first operated patients, a 16 year old male with Loeys-Dietz syndrome, was reoperated within 2 weeks after the operation because of severe mitral regurgitation. The fixation sutures in the left ventricular outflow tract had perforated the base of the anterior mitral valve leaflet. The mitral valve was repaired using an autologous pericardial patch. At last follow-up echocardiogram (4 years) there was no sign of mitral or aortic regurgitation.

VSARR after Ross-procedure was associated with higher reoperation hazard in our Cox regression model (HR 8.5, 95% CI 1.9-38.5; $p = 0.005$). Additionally, preoperative STJ diameter and annulus diameter were associated with higher reoperation hazard (HR 1.6, 95% CI 1.0-2.6; $p = 0.043$ and HR 1.2, 95% CI 1.0-1.6; $p = 0.056$ respectively). Detailed information of variables tested is displayed in Appendix 2.

Valve related complications

There were seven cases of SVD due to prolapse of the leaflets and sagging of the commissures, as described above (LOR 2.4% per patient-year). Another 2 patients were diagnosed with a thromboembolic event (LOR 0.7% per patient-year; one case of TIA and one lung embolism). Both patients were diagnosed with aneurysms-osteoarthritis syndrome (SMAD3 mutation) [9], one of whom with

multiple aneurysms and TIA in the past treated with coiling of cerebral arteries. There were no hemorrhagic events, no endocarditis and no non-structural valve deterioration during follow-up. Figure 2 demonstrates follow-up AR in 2 groups; patients with pre-operative AR grade 0 and 1 and patients with grade 2 or greater.

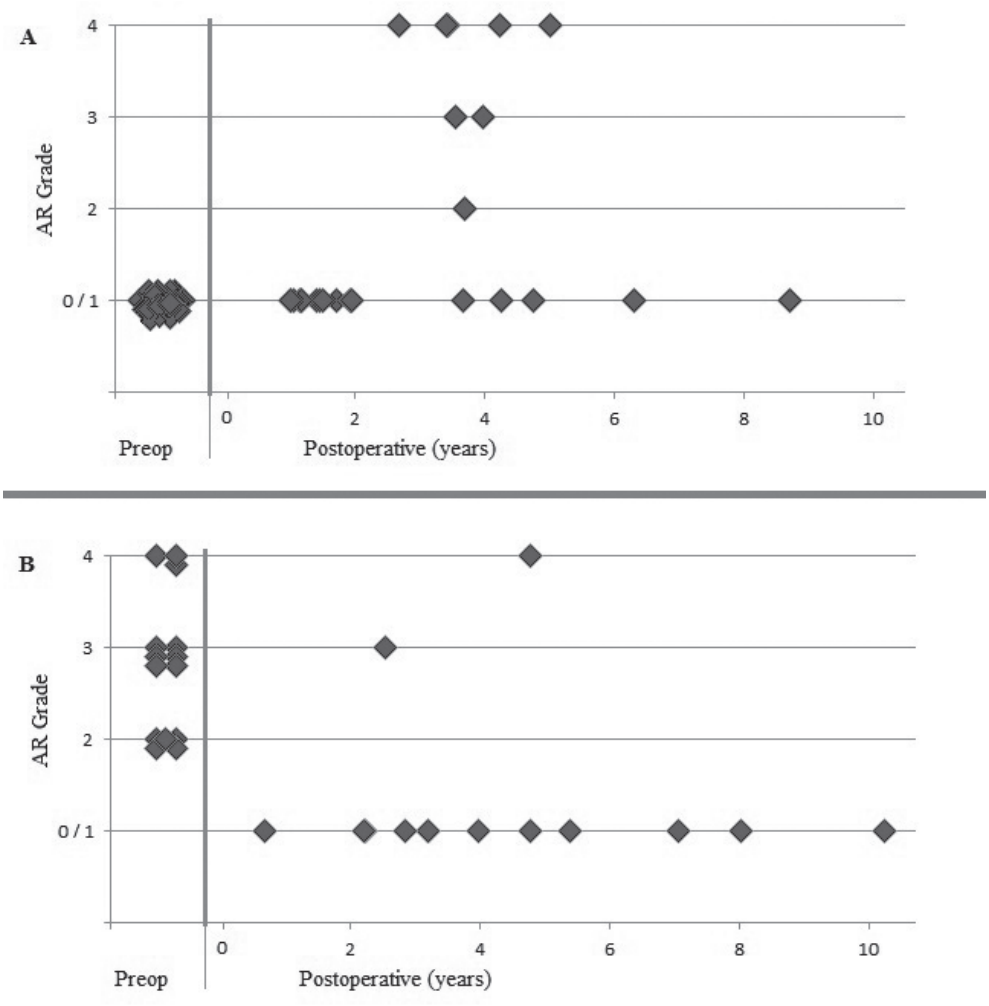


FIGURE 2. Aortic regurgitation preoperative compared to last follow-up. A: Patients with preoperative AR grade 0 or 1. B: Patients with preoperative AR grade 2 or higher.

TABLE 3. Echocardiographic parameters preoperative compared to last follow-up.

Parameter	Preop	Last FUP	P-value
AR			
Trace/mild	80%	83%	0,7
Moderate/severe	20%	17%	
LVEDD (mm)	53,8	53,7	0,9
LVESD (mm)	36	35,3	0,7
Coaptation height (mm)	11,3	9,9	0,3
Annulus diameter (mm)	26,1	22,4	0,001
Mean gradient (mmHg)	1,1	0,8	0,3
LVF			
Good	81%	82%	0,6
Impaired	19%	18%	

Echocardiographic parameters

Four of the 33 invited patients had no or only postoperative in-hospital echocardiograms, which were excluded from the analysis. Therefore 29 patients had structural echocardiogram measurements. Mean time to last follow-up echocardiogram was 3.6 years (SD 2.6; range 0.5-10.1 years). During this follow-up time we found no significant change in LVESD and LVESD. Coaptation height of the leaflets increased from 8.1 mm to 11.5 mm and annulus diameter decreased from 26.1 to 22.4 mm. Moreover, there was no change in LVF comparing preoperative to last follow-up values. Table 3 displays a comparison of echocardiographic parameters measurements preoperative to last follow-up.

Quality of life

The SF-36 quality of life questionnaire was completed by 21 patients. Of the 33 invited patients, 5 were not available for the follow-up questionnaire due to missing contact information or mental disease, and another 7 did not fill in the questionnaire after several requests, despite initial agreement. The SF-36 showed a quality of life comparable to the general age-matched Dutch population, displayed in Figure 3. Remarkably, 'emotional role functioning' and 'bodily pain' were experienced better in our study population compared to the general Dutch population, while "physical functioning" was worse.

Additionally, aggregated composite Mental component and Physical component scores were 50.1 and 53.7. None of the tests mentioned above were statistically significant. Moreover, we excluded 3 patients (2 diagnosed with aneurysms-osteoarthritis syndrome and 1 with Marfan's syndrome) who recently had operations and disabilities clearly linked to their disease (i.e. abdominal aneurysm surgery, coiling of cerebral artery and TIA, and thromboses and osteoporosis with musculoskeletal symptoms). If we would not have exclude these 3 patients there would still be no significant difference between our study population and the general Dutch population, although there would be no better quality of life in aggregated composite mental component.

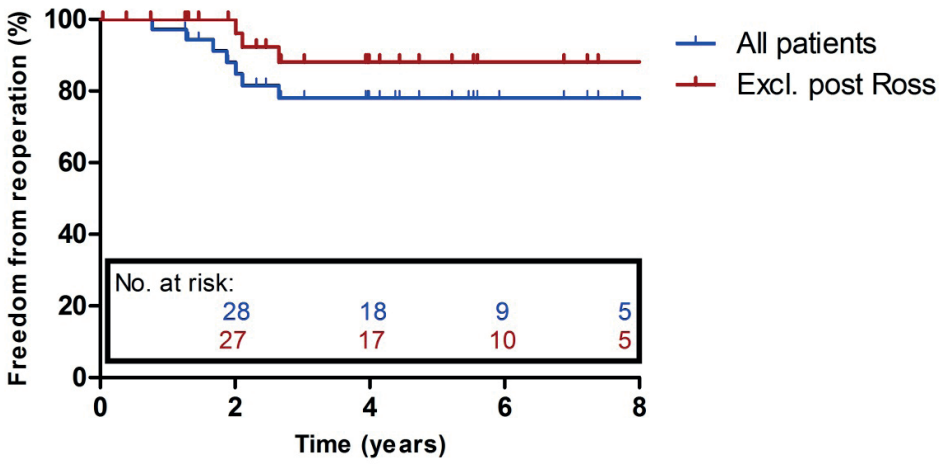


FIGURE 1. Freedom from reoperation. Blue indicates all patients included. Red indicates patients with Ross-procedure in the past excluded.

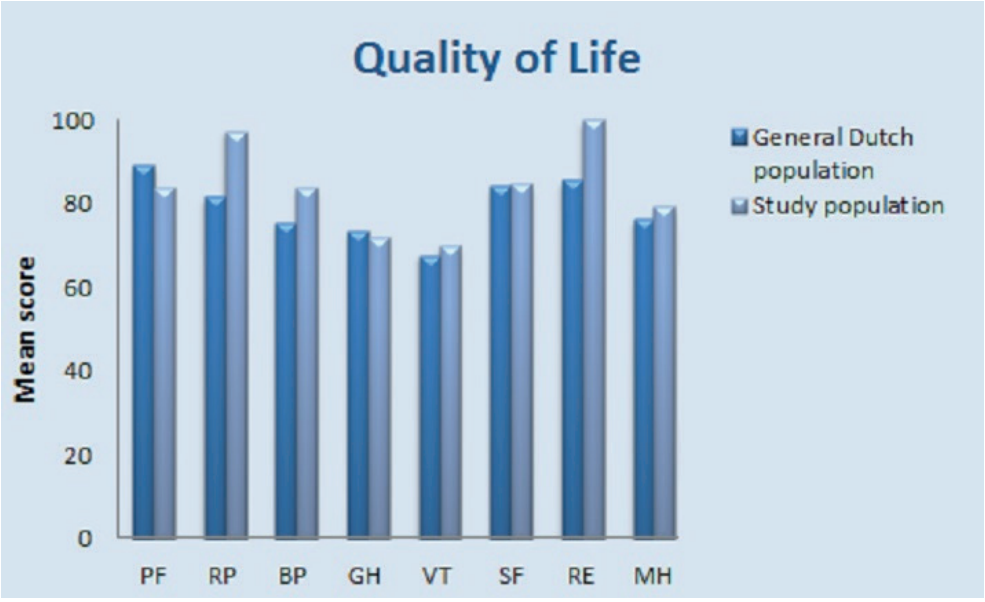


FIGURE 3. Quality of life compared to age-matched general Dutch population.

PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health; PC: physical component score; MC: mental component score

DISCUSSION

Our study shows excellent midterm survival after valve sparing aortic root replacement using the David technique. In addition, valve-related events other than structural valve deterioration are rare. Taking into account the quality of life comparable to the general population after VSARR and the great hemodynamic results, the reimplantation technique (David procedure) is a good alternative to composite valve replacement and biological valve prosthesis for the treatment of aortic root aneurysm, with or without aortic regurgitation. However, there is a reoperation hazard due to aortic regurgitation and in our experience in all cases within 3 years of operation, which indicates non-optimal surgical results in specific patients, more specifically in patients with a Ross-procedure in the past. According to the European and US guidelines on valvular heart disease VSARR should only be considered in experienced centers [4, 10]. Our experience may encourage "smaller" centers to use the valve sparing techniques with good results, at least in younger patients who lead an active life and will preferably avoid anticoagulation therapy.

Survival

Both early as well as late survival are excellent in this study population. There were no early deaths and only one patient died after the operation and probably not related to the aortic root surgery. Cumulative survival is comparable or even better than most published studies by greater centers, although the mean age was slightly higher in these studies (range from 45 to 51years), and data was from non-homogeneous cohorts [11-13]and this could (partly) explain the better survival.

Reoperation

Out of the seven patients who were reoperated due to progression of aortic regurgitation there were 4 patients with congenital aortic heart disease who had a pulmonary autograft operation (Ross-procedure) in the past. Ishizaka and colleagues [14] published good results in 4 patients, without any reoperations after reimplantation technique in patients post Ross operation. However, mean follow-up was shorter than 1 year and the results may differ after longer follow-up. Another study from an experienced center in Brussels by De Kerchove et al. containing 26 patients after Ross operation who received a VSARR on the autograft shows similar results to our study, with cusp repair as a risk factor for higher reoperation rates [15]. Finally, a multicenter retrospective cohort study in 86 patients requiring VSARR after Ross-procedure shows a freedom from reintervention of 76% (95% confidence interval: 57%-87%) at 8 years, with even higher reoperation hazard in patients with isolated and/or severe autograft regurgitation [16]. In our experience patients requiring a VSARR of the autograft after Ross-procedure are associated with high reoperation rates thus consequently we would not recommend using VSARR technique in these patients. When excluding post Ross-procedure patients, the freedom from reoperation is almost 90% after 8 years, which is in agreement with the rate of reoperation found in a large systematic review on VSARR by our research group [17]. Moreover, in comparison to a larger cohort published by David and colleagues, with more than 300 patients included with (mean follow-up of 7 years), there was a freedom from reoperation of 94% [18], suggesting achievable excellent results, at least in specific patients and by experienced surgeons.

Mode of failure

Reoperation was due to progression of aortic regurgitation in all cases and occurred within 3 years after the valve sparing operation, indicating less optimal technical results. It is assumed that an early postoperative AR grade II or greater is associated with reoperation hazard [12], therefore only a postoperative AR grade I or less was accepted in our study. However, in these seven reoperated patients there was a rapid progression. Main reason of valve failure was prolapse of the cusps, with retraction of one or more commissures in all cases. In valve-sparing procedures, reduction of the dilated STJ and annulus brings the leaflets inward and thereby increases their coaptation, but alternately it may also lower the level of coaptation. As a consequence the coaptation height may drop extremely. This is especially the case in elongated free margins of the leaflets as well as in extended reduction of STJ [19, 20]. The lowered coaptation height

is associated with an increased hazard of progressive AR resulting in reoperation, as shown by Pethig et al. [21]. Additional cusp repair might alleviate this prolapse [8]. Additionally, new onset of valve prolapse after graft implantation may be due to modification of the valve geometry while reattaching the commissures into the graft. Also the size of the tube-graft may play a role in postoperative AR. Several measuring formulas have been proposed, but there is no consensus about standardized implementation of these methods [22-24]. De Kerchove et al. [12] suggest that downsizing of the graft is probably worse than oversizing, especially when the leaflets are large. In our study patients with Ross-procedure in the past had relatively larger annulus diameters. Three of the four patients reoperated after initial valve-sparing procedure had an annulus diameter of ≥29 mm and received a tubular prosthesis of smaller size. According to the reports mentioned above this may have played a role in the progression of AR and consequently resulted in a reoperation. However, more data is needed to confirm these results.

Moreover, in the first 20 patients operated, five were reoperated during follow-up (mean follow-up time to reoperation 6.0 years), while in the last 21 patients, only 2 patients were reoperated (mean follow-up time to reoperation 2.4 years). Most reoperations occurred at approximately 3 years. Hence, learning curve may have influenced the results, but this difference could also be due to a difference in follow-up time.

Furthermore, the absence of sinuses is believed to cause change in the mobility characteristics of the cusps, which may induce thickening and rolling of the free margins of the leaflets [25].

Echocardiographic outcome

From our echocardiographic measurements we conclude that hemodynamics of the valve and the left ventricle are excellent, with a very low gradient over the aortic valve (mean gradient < 1mmHg) and no deterioration of left ventricular function. Additionally, we found a small reduction in de end diastolic and end systolic left ventricle dimensions assuming remodeling of the left ventricle after valve-sparing surgery. Although the reduction was trivial and not statistically significant in our study, others have shown left ventricular remodeling and improvement after valve sparing aortic root replacement [26, 27]. However, we had no patients with severe or moderate left ventricular dysfunction. Out of 8 patients with preoperative mild left ventricular dysfunction, 2 patients improved to good LVF and 6 remained the same. Left ventricular remodeling may be of more hemodynamic importance in patients with preoperative severe ventricular dysfunction.

Four of the seven patients reoperated due to progressive AR where patients who had VSARR after Ross operation. In other patients there was no or trivial AR at last follow-up. This suggests that when properly performed in adequately selected patients, there is no or very low progression of AR. The challenge is to find preoperatively risk factors indicating early failure in patients in order to have durable valve repair. We expect that the AVIATOR registry will provide these answers in the coming years [5].

Quality of life

The quality of life has been an actual issue in medicine in the last few years. To our belief there are no large studies describing quality of life after valve sparing aortic root replacement. A study by Aicher and colleagues comparing Ross operation, Bentall, and valve sparing technique, shows a better QoL in patients with valve sparing procedures, although not statistically significant. Notably, in this study patients with mechanical valve prosthesis feared a valve failure significantly more than valve repair patients [28]. Additionally, another study published by Franke et al. investigating the difference in QoL between patients after valve sparing reimplantation technique and the Bentall operation, shows also better quality of life in the valve sparing patients. Our results are in concordance with the mentioned studies and accentuate the arguments in favor to perform valve sparing root replacement.

The fact that mental health was experienced slightly better (although not statistically) than the general Dutch population is probably due to the coping mechanism of patients. A substantial part of the patients were diagnosed a connective tissue disease without

hemodynamic consequences at the moment of surgery, however knowing that they are potentially at risk of an acute medical emergency, like acute dissection. Hence, after the operation patients may feel released from those feelings and may experience life more positive, and this might lead to a better reported mental health status.

Limitations

As this was a single-center study, with a small number of participants, non-participating patients and no long-term follow-up, we are not able to discriminate for survival, valve durability, and quality of life for subgroups. In addition, statistical techniques to test possible factors associated with outcome are limited and may not find any association in these relatively small numbers. Moreover, we were not able to include all patients for the quality of life analysis, which may have led to less adequate interpretation of these data.

CONCLUSION

This study shows that valve-sparing aortic root replacement with the reimplantation (David) technique for patients with aortic regurgitation and/or root aneurysm is safe, has satisfactory midterm valve durability with a low occurrence rate of valve-related events, and provides good hemodynamics. Additionally, there is a good quality of life that is comparable to the general Dutch population. Additionally, valve-sparing aortic root replacement in patients after Ross-procedure is associated with a higher reoperation risk.

REFERENCES

[1] Bentall H, De Bono A. *A technique for complete replacement of the ascending aorta*. Thorax 1968;23:338-9.

[2] Sarsam MA, Yacoub M. *Remodeling of the aortic valve anulus*. The Journal of thoracic and cardiovascular surgery 1993;105:435-8.

[3] David TE, Feindel CM. *An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta*. J THORAC CARDIOVASC SURG 1992;103:617-21; discussion 22.

[4] Vahanian A, Iung B. *The new ESC/EACTS guidelines on the management of valvular heart disease*. Archives of cardiovascular diseases 2012;105:465-7.

[5] *The AVIATOR working group.* http://heartvalvesociety.org/working-groups.cgi date last accessed: 2 February 2017).

[6] Ware JE, Jr., Sherbourne CD. *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection*. Medical care 1992;30:473-83.

[7] Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R *et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations*. Journal of clinical epidemiology 1998;51:1055-68.

[8] Schafers HJ, Bierbach B, Aicher D. *A new approach to the assessment of aortic cusp geometry*. The Journal of thoracic and cardiovascular surgery 2006;132:436-8.

[9] van de Laar IM, Oldenburg RA, Pals G, Roos-Hesselink JW, de Graaf BM, Verhagen JM *et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis*. Nature genetics 2011;43:121-6.

[10] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA *et al. 2014 AHA/ACC Guideline 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*. Circulation 2014;129:e521-643.

[11] David TE, Feindel CM, Webb GD, Colman JM, Armstrong S, Maganti M. *Aortic valve preservation in patients with aortic root aneurysm: results of the reimplantation technique*. Ann Thorac Surg 2007;83:S732-5; discussion S85-90.

[12] de Kerchove L, Boodhwani M, Glineur D, Poncelet A, Verhelst R, Astarci P *et al. Effects of preoperative aortic insufficiency on outcome after aortic valve-sparing surgery*. Circulation 2009;120:S120-6.

[13] Badiu CC, Eichinger W, Bleiziffer S, Hermes G, Hettich I, Krane M *et al. Should root replacement with aortic valve-sparing be offered to patients with bicuspid valves or severe aortic regurgitation?* European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2010;38:515-22.

[14] Ishizaka T, Devaney EJ, Ramsburgh SR, Suzuki T, Ohye RG, Bove EL. *Valve sparing aortic root replacement for dilatation of the pulmonary autograft and aortic regurgitation after the Ross procedure*. Ann Thorac Surg 2003;75:1518-22.

[15] de Kerchove L, Boodhwani M, Etienne PY, Poncelet A, Glineur D, Noirhomme P *et al. Preservation of the pulmonary autograft after failure of the Ross procedure*. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2010;38:326-32.

[16] Mookhoek A, de Kerchove L, El Khoury G, Weimar T, Luciani GB, Mazzucco A *et al. European multicenter experience with valve-sparing reoperations after the Ross procedure*. The Journal of thoracic and cardiovascular surgery 2015;150:1132-7.

[17] Arabkhani B, Mookhoek A, Di Centa I, Lansac E, Bekkers JA, De Lind Van Wijngaarden R *et al. Reported Outcome After Valve-Sparing Aortic Root Replacement for Aortic Root Aneurysm: A Systematic Review and Meta-Analysis*. Ann Thorac Surg 2015;100:1126-31.

[18] Garrido-Olivares L, Maganti M, Armstrong S, David TE. *Clinical outcomes of aortic root replacement after previous aortic root replacement*. The Journal of thoracic and cardiovascular surgery 2013;146:611-15.

[19] Babin-Ebell J, De Vivo F, Vogt PR, Roth P. *Impact of graft size and resuspension level of the commissures on aortic insufficiency after reimplantation of the aortic valve*. The Thoracic and cardiovascular surgeon 2007;55:351-4.

[20] Maselli D, De Paulis R, Scaffa R, Weltert L, Bellisario A, Salica A *et al. Sinotubular junction size affects aortic root geometry and aortic valve function in the aortic valve reimplantation procedure: an in vitro study using the Valsalva graft*. Ann Thorac Surg 2007;84:1214-8.

[21] Pethig K, Milz A, Hagl C, Harringer W, Haverich A. *Aortic valve reimplantation in ascending aortic aneurysm: risk factors for early valve failure*. Ann Thorac Surg 2002;73:29-33.

[22] Beyersdorf F, Rylski B. *Current state of the reimplantation technique (DAVID Operation): surgical details and results*. HSR proceedings in intensive care & cardiovascular anesthesia 2012;4:73-6.

[23] David TE, Feindel CM, Bos J. *Repair of the aortic valve in patients with aortic insufficiency and aortic root aneurysm*. The Journal of thoracic and cardiovascular surgery 1995;109:345-51; discussion 51-2.

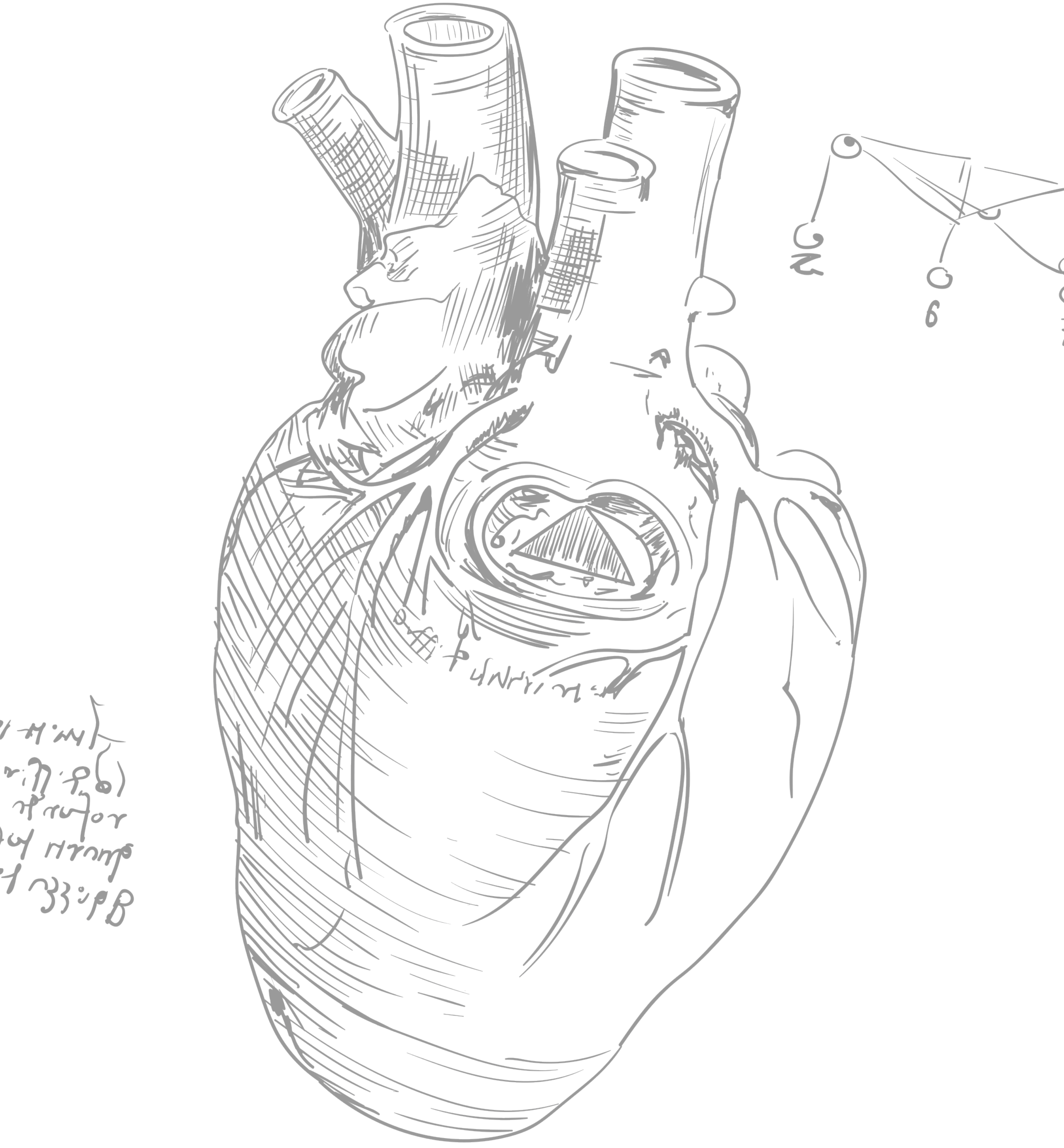
[24] Regeer MV, Versteegh MI, Klautz RJ, Schalij MJ, Bax JJ, Ajmone Marsan N *et al. Transthoracic echocardiography for selection of tubular graft size in David reimplantation technique*. Interactive cardiovascular and thoracic surgery 2015;21:459-64.

[25] Leyh RG, Schmidtke C, Sievers HH, Yacoub MH. *Opening and closing characteristics of the aortic valve after different types of valve-preserving surgery*. Circulation 1999;100:2153-60.

[26] Leshnower BG, Guyton RA, McPherson L, Kilgo PD, Chen EP. *Improved left ventricular function and remodeling after the david v for significant aortic insufficiency*. Ann Thorac Surg 2013;96:2090-4.

[27] Kortekaas KA, Hoogslag GE, de Boer RA, Dokter MM, Versteegh MI, Braun J *et al. Galectin-3 and left ventricular reverse remodelling after surgical mitral valve repair*. European journal of heart failure 2013;15:1011-8.

[28] Aicher D, Holz A, Feldner S, Kollner V, Schafers HJ. *Quality of life after aortic valve surgery: replacement versus reconstruction*. The Journal of thoracic and cardiovascular surgery 2011;142:e19-24.



Chapter 12

General Discussion
and Future Perspectives

GENERAL DISCUSSION

The aim of this thesis was to provide an overview of clinical outcome after surgical treatment of aortic valve and/or root disease, and to put this into a broader perspective taking into account patient characteristics, quality of life and patient preference. This chapter attempts to put the research questions posed in the introduction section and the findings of the presented studies in this thesis into the perspective of treatment of patients with aortic valve and/or root disease and in particular optimal selection of surgical treatment for the individual patient. Additionally, it provides recommendations with regard to optimization of treatment selection and future research.

Indications for surgery in aortic valve and root disease

Aortic valve or root surgery concerns surgical therapy for individual patients with a wide variety of diagnoses, such as aortic valve stenosis, isolated aortic valve regurgitation, or combined stenosis and regurgitation, with or without aortic root aneurysm, and isolated aortic root (ascending aortic) aneurysm needing aortic root replacement in order to prevent dilation of sinus of Valsalva and thus aortic regurgitation or aortic dissection [1]. Aortic valve stenosis is predominantly a degenerative disease that occurs mainly in elderly in the western population [2], while aortic regurgitation is, in developed countries, most often due to aortic root dilation, bicuspid aortic valve disease, and calcific valve disease (stenosis) [3] and occurs in relatively younger patients.

According to the 2012 European ESC/EACTS guidelines on the management of valvular heart disease [4] all symptomatic patients with severe aortic stenosis (AS) and impaired left ventricular function, or patients with severe AS undergoing CABG, surgery of the ascending aorta or another valve, have an indication for aortic valve replacement (AVR). AVR is also recommended in asymptomatic patients with abnormal exercise test showing symptoms (clearly related to AS) on exercise. The same is recommended according to the US AHA/ACC 2014 guidelines on the management of patients with valvular heart disease [5] (level of recommendation: Class I for both guidelines).

In addition, the ESC/EACTS guidelines report that AVR should be considered in asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure and in patients with moderate AS undergoing coronary bypass or other valve surgery. The AHA/ACC guidelines find AVR reasonable in these same patients, with the same level of recommendation (both Class IIa).

The same ESC/EACTS and AHA/ACC guidelines state that patients with severe aortic regurgitation who are experiencing symptoms, have an indication for aortic valve surgery, as do asymptomatic patients with a resting LVEF < 50% and patients who require CABG or surgery of the ascending aorta or another valve. In addition, surgery should be considered/ is reasonable in asymptomatic patients with resting ejection fraction more than 50% with severe LV dilatation.

Additionally, in the ESC/EACTS guidelines surgery of the ascending aorta (root) is indicated when the diameter of the dilated ascending aorta exceeds 50 mm in patients with Marfan syndrome, regardless of the severity of AR. Surgery should be considered all patients when the ascending aortic diameter exceeds 55 mm; in patients with Marfan syndrome with additional risk factors (i.e. family history of aortic dissection and/or aortic size increase .2 mm/year, severe AR or mitral regurgitation, desire of pregnancy), and in patients with a bicuspid aortic valve (BAV) with an aortic diameter of greater than 50 mm with additional risk factor (i.e. coarctation of the aorta, systemic hypertension, and family history of dissection or increase in aortic diameter 2 mm/year).

The latest AHA/ACC guidelines (2014) are less specified regarding aortic dilatation and have no recommendations regarding aortic dilatation and connective tissue disease. Different from the European ESC/EACTS guidelines regarding intervention in patients with bicuspid valve and ascending aortic dilatation, the U.S AHA/ACC guidelines recommend surgical treatment of the ascending aorta in bicuspid artic valves when ascending artic diameter greater than 55 mm. Additionally, surgical treatment is reported to be reasonable in BAV patients with ascending aorta of ≥ 50 mm and a risk factor for dissection, and in those undergoing aortic valve surgery because of severe AS or AR if the diameter of the ascending aorta is greater than 45 mm (Chapter 2).

Treatment options

Several surgical options to treat aortic valve and root disease are available. At present the "gold standard" is valve replacement with or without aortic root replacement, depending on the presence and extent of aortic root dilatation. Valve replacement can be done with either a mechanical or biological valve substitute. Biological valve substitutes include stented and stentless bioprostheses, allografts, and the pulmonary autograft (Ross) procedure. Additionally, isolated aortic regurgitation can be treated by isolated valve repair while aortic root aneurysm can be treated by valve sparing aortic root replacement. All surgical options carry a number of advantages and disadvantages.

According to current European ESC/EACTS guidelines on the management of valvular heart disease, a mechanical valve prosthesis is recommended according to the desire of the informed patient, without contraindications for anticoagulation therapy, in patients at risk of accelerated structural valve deterioration (aged < 40 years) or those already on anticoagulation therapy. Below the age of 60, and in patients with a reasonable life expectancy for whom future redo valve surgery would be of high risk a mechanical valve should be considered. A mechanical prosthesis may be considered in patients already on long-term anticoagulation therapy due to high risk of thromboembolism. A bioprosthesis is recommended according to the desire of the informed patient and when good quality anticoagulation is unlikely or contraindicated because of high bleeding risk, and for reoperation for mechanical valve thrombosis despite good long-term anticoagulant control. Additionally, the same guidelines report that a bioprosthesis should be considered in young women contemplating pregnancy and in patients for whom future redo valve surgery would be at low risk, and in those aged 65 or older. Main difference with the AHA/ACC guidelines is that in the latter a bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contra-indicated, cannot be managed appropriately, or is not desired, and that a biological valve is reasonable in patients aged 70 and older.

The main advantage of mechanical valve prostheses is their outstanding durability, and therefore low risk of reoperation. On the downside, because of the increased thrombogenicity of mechanical valve prostheses, life-long use of anti-coagulation therapy is required. Anticoagulation therapy is associated with an increased bleeding risk. The currently available anticoagulants require frequent monitoring of the level of anticoagulation and may impose a burden on patient compliance. Chapter 4 describes the excellent long-term durability of mechanical prostheses in young adult patients after aortic valve replacement. Nevertheless, a substantial proportion of patients experience valve-related morbidity (mainly anticoagulation-related but also reoperations) and a life expectancy that is severely impaired compared to the general population, as evidenced by the microsimulation analyses. In case of aortic root dilatation with aortic valve disease (e.g. connective tissue disease or degenerative aortic aneurysm), the "gold standard" surgical treatment has been composite valve graft replacement (better known as the Bentall procedure) since its introduction in 1968 [6]. This procedure shows the same mechanical valve related complications as the isolated mechanical valve replacement,

and equally depends on anticoagulation therapy. However, early mortality is higher after the Bentall procedure which may be due to the higher complexity of the surgery and due to concomitant disease (e.g. connective tissue disease, other congenital disease).

In Chapter 3, we found a pooled early mortality of 6% and late mortality rate of 2.02% per patient-year, an average aortic root reoperation rate of 0.46% per patient-year and an aortic valve reoperation rate of 0.30% per patient-year after the Bentall procedure. Bleeding and thrombo-embolic event rates were 0.64%, and 0.77% per patient-year respectively, and endocarditis rate of 0.39%. This highlights that although the Bentall procedure remains an utmost valuable treatment for the diseased aortic root, the late mortality, major bleeding and thromboembolic complications, but also reoperation remain a concern. In many, certainly younger patients without contraindications for anticoagulation therapy, the Bentall procedure remains an adequate treatment. Nonetheless, its advantages and disadvantages should be taken into account and discussed with patients during the decision-making process of prosthetic heart valve selection.

The main advantage of biological valve substitutes is their absent need for anticoagulation therapy and thus the avoidance of bleeding complications associated with anticoagulant use. On the downside, all biological valves have a limited durability, mainly due to structural valve degeneration, that may necessitate a re-intervention, usually in de second decade after the initial valve replacement. The ESC/EACTS guidelines describe a grey area of ages 60 to 65 years, where both mechanical and biological valves should be considered, taking into account not only patient age, but also patient characteristics and preference. The AHA/ACC guidelines report both mechanical and biological valves to be reasonable options in patients aged 60 to 70 years. Interestingly, in recent years biological valves are increasingly implanted in patients under the age of 60-65 years. For example, the percentage of patients aged 60 to 65 receiving a biological valve in the United Kingdom has doubled from 30% in 2004 to 60% in 2010, and this number is still increasing, also in the US [7, 8], while for patients aged 50 to 69 in Sweden, this percentage has grown from 17% in the period of 1997-2002 to 65% in 2009-2013[9].

Stented bioprostheses are the most commonly used biological valve substitutes. Stentless xenograft bioprostheses are an alternative to stented bioprostheses. They claim to show better hemodynamics and may also be used to replace the aortic root. Especially in patients with a relatively small aortic annulus, stentless valves are useful in order to avoid prosthesis-patient mismatch as stentless bioprostheses have a larger effective orifice area which provides lower transvalvular gradients [10]. Stentless biologic valves

can be implanted using different techniques: the subcoronary implantation technique or aortic root replacement. The subcoronary technique has the main advantage of avoiding the manipulation of and the need to reimplant the coronary ostia as is the case with the root replacement techniques, a technique that leads to a more complex operation with longer cross-clamp times in comparison to stented valve prostheses. The disadvantages of the subcoronary technique could be difficulties occurring in patients with a small aortic annulus and calcified aortic root, and the risk of valve insufficiency by changing the shape of the stentless valve prosthesis.

The current ESC/EACTS guidelines report that biological valves should be considered in patients aged greater than 65 years, when life expectancy is lower than the presumed durability of the bioprosthesis, in young women contemplating pregnancy, in patients for whom future redo valve surgery would be at low risk, and in patients with contraindication for anticoagulation therapy [4]. Notably, in the past decade progressively more centers are implanting biological aortic valve prosthesis in younger patients (younger than 60 years) [11] Although there is an accelerated rate of structural valve deterioration in younger patients [12], especially younger patients may put a greater value on living without the burden of anticoagulation for 1-2 decades at the cost of a reoperation than facing this burden of anticoagulation. Another argument to use a biological valve in younger patients is the potential prospect of transcatheter aortic valve implantation that could in due time be used as a valve in valve in biological valve prostheses. However, this argument cannot be supported by evidence as there are no data available on outcomes in young patients with biological valves who have been consequently treated with valve-in-valve implantation [13]. Nonetheless, given the value-sensitive nature of the choice between a mechanical or a biological valve it still remains debatable which valve substitute to choose for the individual patient and there seems no single right answer at this point in time.

Allografts are another option to treat the diseased aortic valve and/or root. Chapter 7 presents a long-term follow-up, prospective cohort study of patients with aortic valve disease who have been treated with allografts. It shows good results and low reoperation rate after complex endocarditis, although the subcoronary implantation of allografts is associated with higher reoperation rates, possibly due to technical errors. The use of allografts in general has decreased enormously in the last decades. The ESC/EACTS guidelines on management of valvular heart disease mention that allografts are used in less than 1% of the patient population undergoing aortic valve surgery and the main indication for their, although under debate, is acute infective endocarditis with perivalvular

lesions. Nevertheless, a randomized prospective trial showed comparable results in terms of survival and recurrence of endocarditis, but a higher reoperation rate in comparison with Freestyle® aortic root prosthesis [14]. Interestingly, in the 2014 AHA/ACC guidelines there is no indication reported for allografts in the aortic position. Given the restricted availability of allografts and easily available stentless bioprostheses with possibly superior durability, it is most probable that the end of an era for the implantation of allografts in the aortic position has come.

Pulmonary autograft valve replacement, better known as the Ross procedure, is yet another (stentless) human aortic valve substitute, where the patient's own pulmonary valve is used to replace the diseased aortic valve, with concomitant pulmonary valve replacement commonly with an allograft. This procedure is mainly used in children and young adults, because the pulmonary autograft increase in diameter along with somatic growth in children. The pulmonary autograft operation can be performed with low mortality and valve related events, and provides excellent hemodynamics. Nonetheless, it is well established that autograft function may deteriorate over time resulting in a reoperation and valve replacement [15-17].

There are several techniques to perform a pulmonary autograft procedure: Subcoronary implantation, full root, and the root inclusion method. Although the subcoronary technique was the initial method described for this procedure and is a more accepted approach for isolated aortic valve replacement the full root replacement technique is nowadays the most commonly used technique to perform the Ross procedure. Sievers and colleagues reported excellent hemodynamics and freedom from any valve-related intervention of 95% in the first decade after the subcoronary Ross implantation [18] , while Skillington et al. reported a freedom from reoperation of 99% after 15 years using the inclusion cylinder method [19]. Additionally, Charitos et al. reported on the value of autograft reinforcement to preserve function after the Ross procedure, with a freedom from reoperation of 94% after 10 years follow-up. Longer follow-up points at a further decline in autograft function and an increased number of reoperations. Additionally, a previous randomized controlled trial, including patients between 18 and 69 years with aortic valve/root disease, demonstrated beneficial survival outcome and reoperation rates in patients after the Ross procedure over allograft [20]. Nevertheless, even in these patients there is the problem of neo-aortic root dilatation and (as a consequence) aortic valve regurgitation, demanding a reoperation in the second , or following, decade after the initial surgery [21, 22]. The Ross procedure remains a complicated procedure

that needs special expertise. Technical errors relating to prosthesis sizing and failure to achieve appropriate geometry within the aortic root resulting in early valve failure and the pulmonary valve allograft inserted into the right ventricular outflow tract that may provide additional hazard for valve-related complications, are amongst reasons why this procedure is not used in a broader range [15]. Both ESC/EACTS and AHA/ACC guidelines report that candidates for the Ross procedures should be referred to centers that are experienced and successful in performing this operation.

Although outcome after aortic valve replacement has improved over the past decades, the concerns about prosthetic valve-related complications remain. In this light several surgical strategies to repair or spare the aortic valve have been developed in the setting of aortic regurgitation and/or aortic root dilatation. Chapter 5 describes pooled outcomes after valve sparing aortic root replacement for aortic aneurysm using both remodeling better known as Yacoub procedure [23] and reimplantation -better known as David procedure- [24], and shows no difference in outcome between these techniques, at least when annuloplasty with the use of a ring is added in the remodeling technique. On the downside, specific surgical expertise is required as these procedures are technically really demanding. Moreover, durability is limited, and patients may need a reoperation later in life. However, specialized centers have published excellent results with a freedom from reoperation of more than 90% in the first decade after valve-sparing root replacement [25-27]. This could be explained partly by better patient selection, and partly by an experienced team, but the role of patient characteristics need to be further explored. There is a need for large studies containing homogeneous data for the analysis of potential risk factors associated with reoperation hazard and valve related events, in order to select patients with specific clinical and valve characteristics that may have a beneficial influence on these outcomes. Currently, initiatives like the AVIATOR registry, an international multi-center prospective registry where all consecutive potentially repairable aortic valves will be included, regardless of whether the valve is replaced or repaired/spared, can contribute to optimizing surgical treatment selection [33]. A main challenge remains patient selection. For example, in case of a 75 year old patient with aortic root disease, it is less attractive to perform a valve sparing operation, while a biological alternative will adequately help the patient with a much lower chance of reoperation on the aortic valve. On the other hand, a 35 year old patient, without any contraindications for anticoagulation therapy, and for whom a lower chance of being reoperated on the aortic valve (e.g. due to SVD, a common valve-related event especially in young patients) is more important, a mechanical valve substitute would probably be a more adequate treatment.

There are also no specific recommendations on valve-sparing root replacement except for that it should be performed in specialized centers. A classification system comparable to Carpenter's mitral valve disease could help standardize the valve sparing technique. Although several propositions on this theme have been made [28, 29], there is still not an accepted classification that is systematically used worldwide.

Pregnancy and outcome after aortic valve surgery

In case of women with the (potential) desire to become pregnant, there is no ideal prosthetic valve. Mechanical valve prostheses have an excellent hemodynamic performance and long-term durability, but there is a need for anticoagulation therapy with the risk of increased fetal and maternal morbidity and mortality [30]. On the other hand, biological valve prostheses also provide good hemodynamics and do not require anticoagulation therapy. However, especially in young patients, there seems to be a high risk of structural valve deterioration [1]. There is conflicting evidence as to whether or not pregnancy accelerates bioprosthetic degeneration [21]. Another option, especially in younger women, is the human tissue valve (i.e. Ross procedure and allografts). The Ross procedure is associated with good hemodynamics and there is no need for anticoagulation therapy, as described earlier. However, few data are available about pregnancy in women who have undergone aortic valve surgery [31].

During pregnancy there are several physiological changes in the female body, for example increased blood volume, heart rate (hence cardiac output), and hypercoagulability, that may influence durability of prosthetic heart valves [21, 32, 33]. Additionally, uterine contractions, pain, stress and exertion, all impose an extra demand on the cardiovascular system [34]. According to the ESC Guidelines on the management of cardiovascular diseases during pregnancy [35], in female patients who are contemplating pregnancy, a biological valve prosthesis may be considered. Nonetheless, the choice for the valve prosthesis should be based on patient preference, after informing the patient with features of both mechanical and biological valves. In addition, women with a dilated aortic root are at higher risk of aortic dissection or rupture due to elevated pressure in the aorta and should be monitored carefully, and in women with a bicuspid aortic valve and an aortic diameter of 50 mm or greater, surgical treatment should be considered. However, some recent studies failed to confirm this association [2, 32]. The question remains what the best surgical treatment is in these young female patients with the desire to become pregnant.

Chapters 8 and 9 describe the clinical outcome of mother and newborn after aortic valve replacement. Although there is an excellent survival, maternal complications like heart failure and arrhythmias occurred frequently in these young female patients. Additionally, obstetric complications like pre-term delivery, newborns small for gestational age, and hypertension related complications (e.g. pre-eclampsia) occurred during pregnancy. Both maternal and obstetric complications were more common in patients with mechanical valve substitutes, and this may be due to the volume overload during pregnancy and the hemodynamic consequences. Nonetheless, it is hard to monitor and determine the optimal anticoagulation therapy during pregnancy because of the altered coagulation state during pregnancy, which could be of influence on the thromboembolic event risk, thus with survival of mother and child [33]. Therefore, management of labor, delivery, and post-partum surveillance require specific expertise and should take place by a specialized team, in experienced maternal–fetal centers [36-38]. Furthermore, Chapter 8 describes that human aortic valve substitutes do not hemodynamically deteriorate during pregnancy. In particular, echocardiographic measurements on aortic regurgitation, ventricular dimensions and gradient over the human tissue valve (both pulmonary auto graft and allograft) show no deterioration during pregnancy. Human tissue valves shows good performance throughout pregnancy and are recommendable in young female patients with valvular aortic disease. We found no difference in outcome between allograft and pulmonary autograft (Ross procedure) recipients. However, only 31 patients became pregnant, and this may have limited the power to identify differences in outcome.

In summary, it is evident that in young women who have the (potential) desire to become pregnant, individual counseling and weighting of obstetric complications with respect to maternal outcome is challenging. Thus young female patients with potential pregnancy desire should be carefully informed about the available types of valve substitutes and their cons and pros. In the process of choosing the most suitable valve for the individual patient, the doctor should inform the patient on the different features of mechanical valves (with relatively higher pregnancy related complications, but lower chance of reoperation), and biological valve substitutes (with lower complication rates during pregnancy, but at the potential cost of a reoperation later in life). Since there is no ideal valve prosthesis and several types of prostheses described above have both advantages and disadvantages that may play a different role in every individual patient, patients should actively participate in this shared decision making process, in order to optimally tailor treatment.

Quality of life after aortic valve surgery

The main goal of aortic valve surgery, whether replacement of the valve with a biological or mechanical valve substitute or sparing the valve, is not only optimizing clinical outcomes but also to improve patient quality of life. Therefore it is highly recommendable that during the decision-making on a particular surgical strategy to consider the available evidence on quality of life after aortic valve surgery. Quality of life after aortic valve surgery improves in particular in patients with an impaired quality of life before surgery. Interestingly, patients with a relatively high preoperative quality of life have little to gain after surgery, but potentially a lot to lose [39, 40]. Although evidence is scarce on specific treatment options, an observational study in young adult patients showed a lower physical capacity in patients with mechanical valve substitutes, a higher prevalence of disability, and poorer disease perception compared to bioprosthetic valve recipients [41]. Another observational cohort study demonstrated that patients after aortic valve repair and Ross procedure show better physical functioning, general health and mental health, and surprisingly less cardiac anxiety compared to mechanical valve recipients. [42]. Chapter 11 describes a single center study of relatively young patients after valve-sparing aortic root replacement with besides excellent survival and few valve related complications a quality of life that is comparable to the Dutch general population, and specifically a very good mental health. It may be that preservation of the patient's own valve has (positively) influenced the mental health, but of course this is a non-comparative study and a cause-effect relationship cannot be determined. Although the results of this study were not compared to patients with other types of surgical treatment, these findings do add evidence to the data already published regarding quality of life after valve sparing treatments, namely that the majority of patients have a good quality of life. Although valve-sparing techniques may be applicable only in a limited proportion of patients with aortic root disease, and there is a relatively higher chance of reintervention compared to composite ARR, the process of decision making concerning the most suitable surgical treatment should also take into consideration patient's quality of life. Where one patient may live happier not risking a higher chance of reoperation after the initial treatment, another patient may be willing to take the "chance" and live as long as possible without the burden of anticoagulation therapy, although (possibly) at cost of a reoperation later in life.

Optimal treatment choice

The most important insight that this thesis provides is perhaps that there is no single perfect surgical strategy for the treatment of the diseased aortic valve and root. It is far more important to choose a tailored treatment that is safe and effective for the patient, and that will fit the patient's needs, values and expectations. In order for patients to participate in this decision making process, there needs to be sufficient information available about the different aspects of the several available treatments. Tools like websites with specific treatment information and (web)applications may be helpful. After gaining this information, there should be enough time for the patient to evaluate the consequences of different treatment options in their own context and to discuss this with their physician in order to reach an optimal tailored decision shared by the patient and physician.

CONCLUSION

In summary, from this thesis a number of insights emerged:
There is no perfect valve prosthesis for the treatment of aortic valve and root disease. Mechanical valve prostheses have a lower reintervention rates, however, late mortality, major bleeding, and thromboembolic complications remain a concern. On the other hand, biological valve substitutes are associated with relatively higher structural valve deterioration and thrombo-embolism, although other valve related events (like hemorrhagic events) are less frequent. In isolated aortic regurgitation or aortic root aneurysm, valve sparing root replacement techniques show good survival and low valve related event occurrence, but hazard of reoperation later in life should be considered carefully. Hence, choosing the optimal treatment for aortic root disease remains a patient tailored procedure, taken into surgeons experience and patients preferences.

There is no association between pregnancy and deterioration of human tissue valves (autografts and allografts). Human tissue valves may be considered as a good alternative to mechanical valves in young female patients contemplating a pregnancy. On the other hand, cardiac; obstetric; and prenatal complications are frequent in female with aortic prostheses, especially with mechanical valves.

Quality of life is as good as the general population after valve-sparing root replacement in young adults with aortic valve and root disease. However, valve-sparing root replacement is only applicable in patients with aortic regurgitation and/or root dilatation. Thus, in other

etiologies (e.g. aortic stenosis) the choice of a mechanical or biological valve remains arbitral and should take into account clinical outcome and the individual expectations of patients.

PROSPECTS AND RECOMMENDATIONS

The need for standardization in aortic valve repair: AVIATOR

The guidelines currently available for patients with aortic valve regurgitation and/or ascending aortic aneurysm are based on (single- center) studies with small number of patients, with a limited follow-up duration. The aortic valve repair working group within Heart Valve Society has therefore initiated the international prospective multicenter registry (AVIATOR) in 2013. It is a multicenter, prospective registration with the goal of combining forces and sharing experience to advance knowledge in the field of surgical treatment of patients with aortic root dilatation and/or aortic valve regurgitation, and on the determinants of outcome. By combining surgical experience from multiple centers, and applying uniform definitions of echocardiography data and outcome parameters, there will be a base to provide an evidence based treatment and to standardize the most suitable surgical technique (repair versus replacement) in aortic valve surgery.

Minimal invasive/transcatheter aortic valve replacement therapy

Since the introduction of transcatheter aortic valve implantation (TAVI) in 2002 [33], the treatment of aortic stenosis has changed. While medical therapy with or without balloon aortic valvuloplasty was for long the only option for inoperable patients, recently TAVI has become a widely accepted treatment for these patients and merged even as an alternative for high-risk and intermediate-risk operable patients. Currently, surgical aortic valve replacement (SAVR) remains the "gold standard" for patients at low risk. However, as there are comparable results between TAVI and SAVR in the high-risk population, there is a trend towards TAVI even in intermediate-risk patients in anticipation of the results of randomized trials in that population (PARTNER trial and SURTAVI trial). Nevertheless, questions still remain regarding TAVI involving paravalvular leak, pacemaker requirements, stroke, and durability that remain to be answered before TAVI can routinely be performed in a broader, lower risk population. These complications are less frequent in surgical aortic valve replacement, both mechanical and biological. Although, improvements in patient

selection, imaging, and devices have decreased the incidence of paravalvular leak and vascular complications, the longer term durability of TAVI devices and a role for post-procedure antithrombotic management remain unanswered.

Hence, until these questions are answered, we should be careful not to rush into less acceptable complication risks in intermediate risk patients. Long-term outcome of the Partner II trial and the SURTAVI trial should give us answers to, at least part, of these questions. In addition, in selected patients with calcified aortic root and small aortic annular diameter, other surgical options, like sutureless aortic valve prostheses, may be valuable [43-45].

Tissue engineering

Another, experimental, treatment option for the diseased aortic valve is a tissue engineered aortic valve. First of all a sufficient extracellular matrix, the so-called scaffold, is needed to utilize a three-dimensional structure in order to create a tissue engineered valve. These scaffolds are made out of polymers in general or out of decellularized allo- or xenogenic materials. The goal of aortic valve tissue engineering is to regenerate a functional structure (i.e. the new valve to be) containing endothelial and interstitial cells capable of continuously remodeling the extracellular matrix that functions structurally and biomechanically as a valve leaflet. Despite an exciting potential for tissue engineered heart valves, significant technical barriers should be overcome before widespread clinical application can be proposed [46]. Nonetheless, there are several experimental studies performed on tissue engineered valves implanted in the aortic position, and these data support the feasibility to implant these valves, into the systemic circulation. Although the first clinical results are promising [47, 48], long-term results must be awaited before tissue engineered valve become a real, widespread option in the treatment of aortic valve disease [49].

Patient involvement, quality of life and decision support

The selection of the most suitable valve substitute for aortic valve replacement is a complex procedure that should be as individualized as possible and should take into account patient preference and lifestyle. Different life goals and patient characteristics may play an important role in which valve prosthesis will turn out to be the most appropriate one. In an era where patients are more aware of the several choices and are easily truly or falsely informed e.g. (through internet) about the (dis)advantages of several types of prosthetic

valves, physicians must try to provide the information that is needed in order to be able for patients to choose a prosthesis that will be safe and match to their wishes and lifestyle. Interestingly, cardiologist and cardiothoracic surgeons seem to have different views on which valve prosthesis (mechanical or biological) is more appropriate for their patients, with cardiologist tending more towards mechanical and surgeons toward biological valve substitute, and patient may be less involved in this process [50]. The next step in providing patients the most suitable valve substitute is to develop a shared-decision tool which provides the information needed for the patients to choose the most optimal valve prosthesis suitable to their lifestyle and expectations. Currently our department intends to develop such tools; i.e. an online decision-making models where patient can fill in questionnaires about their wishes and their life-style, which will raise awareness on pros and cons of the available valve prosthesis. This way, both patient and physician are actively involved in this process and patients' compliance to medical treatment regarding their prosthetic valve may increase. Moreover, the quality of life in the several treatment options (valve-sparing, mechanical and biological) may be a tool that can be used to answer these questions. A prospective randomized trial on the quality of life, including these treatment options in comparable patient populations should give us more insights on patient preference adding another tool to use when informing patients about their surgical options and choosing the most suitable option for the individual patient.

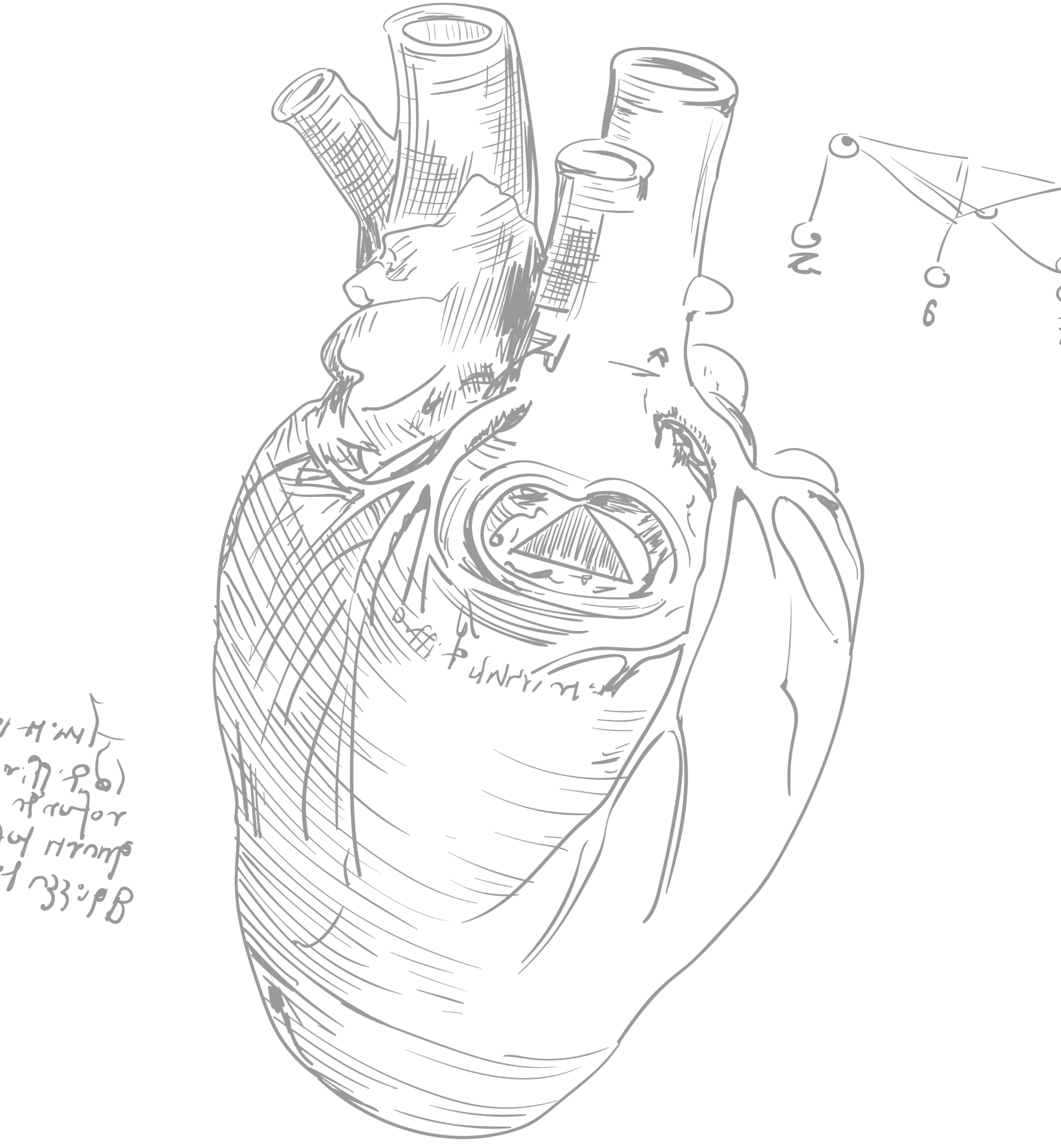
REFERENCES

1. Hung, L. and S.H. Rahimtoola, Prosthetic heart valves and pregnancy. Circulation, 2003. 107(9): p. 1240-6.
2. Cleuziou, J., et al., Pregnancy does not accelerate biological valve degeneration. Int J Cardiol, 2010. 145(3): p. 418-21.
3. Cleuziou, J., et al., Aortic root replacement with re-implantation technique in an infant with Loeys-Dietz syndrome and a bicuspid aortic valve. Pediatr Cardiol, 2010. 31(1): p. 117-9.
4. Vahanian, A. and B. Iung, The new ESC/EACTS guidelines on the management of valvular heart disease. Arch Cardiovasc Dis, 2012. 105(10): p. 465-7.
5. Nishimura, R.A., et al., 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 2014. 63(22): p. 2438-88.
6. Bentall, H. and A. De Bono, A technique for complete replacement of the ascending aorta. Thorax, 1968. 23(4): p. 338-9.
7. Stamou, S.C., et al., Aortic root surgery in the United States: a report from the Society of Thoracic Surgeons database. J Thorac Cardiovasc Surg, 2015. 149(1): p. 116-22 e4.
8. Bridgewater B, K.R., Walton P., Sixth National Adult Cardiac Surgical Database Report Demonstrating quality. 2008.
9. Wyland, J. and D. Krulak, U.S. navy diver/aviator/skydiver with AGE from a previously unknown PFO. Undersea Hyperb Med, 2005. 32(2): p. 129-33.
10. Dunning, J., et al., Stentless vs. stented aortic valve bioprostheses: a prospective randomized controlled trial. Eur Heart J, 2007. 28(19): p. 2369-74.
11. Dunning, J., et al., Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use--an analysis of 41,227 patients over 5 years from the Society for Cardiothoracic Surgery in Great Britain and Ireland National database. J Thorac Cardiovasc Surg, 2011. 142(4): p. 776-782 e3.
12. Bourguignon, T., et al., Very long-term outcomes of the Carpentier-Edwards Perimount valve in aortic position. Ann Thorac Surg, 2015. 99(3): p. 831-7.
13. Head, S.J. and A.P. Kappetein, Aortic valve replacement in younger adults: a biological valve is not the logical choice. Eur Heart J, 2015.
14. El-Hamamsy, I., et al., Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial. J Am Coll Cardiol, 2010. 55(4): p. 368-76.
15. Elkins, R.C., et al., Ross operation: 16-year experience. J Thorac Cardiovasc Surg, 2008. 136(3): p. 623-30, 630 e1-5.
16. Luciani, G.B., et al., Fate of the aortic root late after Ross operation. Circulation, 2003. 108 Suppl 1: p. II61-7.

17. Klieverik, L.M., et al., The Ross operation: a Trojan horse? Eur Heart J, 2007. 28(16): p. 1993-2000.
18. Sievers, H.H., et al., A critical reappraisal of the Ross operation: renaissance of the subcoronary implantation technique? Circulation, 2006. 114(1 Suppl): p. I504-11.
19. Skillington, P.D., et al., 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. Glob Cardiol Sci Pract, 2013. 2013(4): p. 383-94.
20. El-Hamamsy, I., et al., Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet, 2010. 376(9740): p. 524-31.
21. Mokhles, M.M., et al., 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): p. 2213-24.
22. Aljassim, O., et al., Dilatation of the pulmonary autograft and native aorta after the Ross procedure: a comprehensive echocardiographic study. J Thorac Cardiovasc Surg, 2011. 142(3): p. 634-40, 640 e1.
23. Sarsam, M.A. and M. Yacoub, Remodeling of the aortic valve anulus. J Thorac Cardiovasc Surg, 1993. 105(3): p. 435-8.
24. David, T.E. and C.M. Feindel, An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. J Thorac Cardiovasc Surg, 1992. 103(4): p. 617-21; discussion 622.
25. Boodhwani, M. and G. El Khoury, Aortic valve repair: indications and outcomes. Curr Cardiol Rep, 2014. 16(6): p. 490.
26. David, T.E., et al., Aortic valve preservation in patients with aortic root aneurysm: results of the reimplantation technique. Ann Thorac Surg, 2007. 83(2): p. S732-5; discussion S785-90.
27. Lansac, E., et al., Aortic prosthetic ring annuloplasty: a useful adjunct to a standardized aortic valve-sparing procedure? Eur J Cardiothorac Surg, 2006. 29(4): p. 537-44.
28. Lansac, E., et al., An aortic ring: from physiologic reconstruction of the root to a standardized approach for aortic valve repair. J Thorac Cardiovasc Surg, 2010. 140(6 Suppl): p. S28-35; discussion S45-51.
29. Boodhwani, M., et al., Repair-oriented classification of aortic insufficiency: impact on surgical techniques and clinical outcomes. J Thorac Cardiovasc Surg, 2009. 137(2): p. 286-94.
30. Abadi, S., A. Einarson, and G. Koren, Use of warfarin during pregnancy. Can Fam Physician, 2002. 48: p. 695-7.
31. Yap, S.C., et al., Outcome of pregnancy in women after pulmonary autograft valve replacement for congenital aortic valve disease. J Heart Valve Dis, 2007. 16(4): p. 398-403.
32. El, S.F., et al., Pregnancy has no effect on the rate of structural deterioration of bioprosthetic valves: long-term 18-year follow up results. J Heart Valve Dis, 2005. 14(4): p. 481-5.

33. Royse, C., et al., Assessment of thoracic aortic atheroma by echocardiography: a new classification and estimation of risk of dislodging atheroma during three surgical techniques. Ann Thorac Cardiovasc Surg, 1998. 4(2): p. 72-7.
34. Haydar, H.S., et al., Valve repair for aortic insufficiency: surgical classification and techniques. Eur J Cardiothorac Surg, 1997. 11(2): p. 258-65.
35. European Society of, G., et al., ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J, 2011. 32(24): p. 3147-97.
36. Warnes, C.A., et al., ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). Circulation, 2008. 118(23): p. 2395-451.
37. Bonow, R.O., 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 Society of Thoracic Surgeons. Circulation, 2008. 118(15): p. e523-661.
38. Stout, K., Pregnancy in women with congenital heart disease: the importance of evaluation and counselling. Heart, 2005. 91(6): p. 713-4.
39. Koch, C.G., et al., Effect of functional health-related quality of life on long-term survival after cardiac surgery. Circulation, 2007. 115(6): p. 692-9.
40. Aicher, D., H.V. Groesdonk, and H.J. Schafers, [Quality in aortic valve replacement--how good have hybrid valves have to be?]. Dtsch Med Wochenschr, 2009. 134 Suppl 6: p. S200-2.
41. Ruel, M., et al., Long-term outcomes of valve replacement with modern prostheses in young adults. Eur J Cardiothorac Surg, 2005. 27(3): p. 425-33; discussion 433.
42. Aicher, D., et al., Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg, 2011. 142(2): p. e19-24.
43. Kang, S., et al., Measuring the cumulative effect of G force on aviator neck pain. Aviat Space Environ Med, 2011. 82(11): p. 1042-8.
44. Franzos, M.A., et al., Alcohol abuse or dependence in the military aviator: guidance for the non-flight surgeon. Mil Med, 2012. 177(10): p. 1191-5.
45. Demetriades, A.K., From encephalitis lethargica to cerebral cytoarchitectonics: the polymath talent of Constantin von Economo (1876-1931), pioneer neuroanatomist, neurophysiologist and military aviator. Scott Med J, 2012. 57(4): p. 232-6.

46. Mendelson, K. and F.J. Schoen, Heart valve tissue engineering: concepts, approaches, progress, and challenges. Ann Biomed Eng, 2006. 34(12): p. 1799-819.
47. Butcher, J.T., et al., Unique morphology and focal adhesion development of valvular endothelial cells in static and fluid flow environments. Arterioscler Thromb Vasc Biol, 2004. 24(8): p. 1429-34.
48. Emmert, M.Y., et al., Transcatheter aortic valve implantation using anatomically oriented, marrow stromal cell-based, stented, tissue-engineered heart valves: technical considerations and implications for translational cell-based heart valve concepts. Eur J Cardiothorac Surg, 2014. 45(1): p. 61-8.
49. Dohmen, P.M., Tissue engineered aortic valve. HSR Proc Intensive Care Cardiovasc Anesth, 2012. 4(2): p. 89-93.
50. Korteland, N.M., et al., Cardiologist and cardiac surgeon view on decision-making in prosthetic aortic valve selection: does profession matter? Neth Heart J, 2014. 22(7-8): p. 336-43.



Chapter 13

Summary / Samenvatting

Acknowledgements / Dankwoord

PhD Portfolio

List of Publications

About the author

SUMMARY

Chapter 1
Presentation of the introduction, the hypotheses and outline of this thesis. Aortic valve disease is the most common valvular heart disease in the developed countries. The aim of this thesis is to explore the various surgical techniques and several valve prostheses currently available for the treatment of diseased aortic valve and root, and to expand the current knowledge on patient outcome after aortic valve/root operation in terms of survival and quality of life.

Chapter 2
A book chapter that illustrates an overview of indications for surgery in aortic regurgitation, surgical options, and subsequent outcomes after aortic valve repair and valve replacement.

Chapter 3
A systematic review of literature and a meta-analysis that outlines the hazard of valve related outcome after composite valve replacement (Bentall) in patients with aortic root disease. Aortic root reoperation after the Bentall procedure has decreased over the years. However, valve related events such as late mortality, major bleeding, and thromboembolic complications remain a concern.

Chapter 4 is a systematic review and microsimulation after mechanical aortic valve replacement in young adolescents estimating the occurrence rate of valve related outcome in time. This study shows that mechanical valves in non-elderly adult patients is associated with substantial excess mortality over time and considerable lifetime risk of anticoagulation-related complications, and also reoperation. Hence, there is no prefect valve prosthesis for non-elderly patients and shared decision-making process is of great importance in the setting of prosthetic valve selection.

In **Chapter 5** a systematic review of literature and a meta-analysis was undertaken on outcome after valve sparing aortic root replacement in relatively young patients, presenting an overview and testing surgical technique as well as variables associated with valve related outcome. Both remodeling and reimplantation techniques show good survival and valve durability results, and low valve-related events, providing a valid alternative to composite valve replacement.

In **Chapter 6** a meta-analysis and microsimulation model provides an overview on outcome after bioprosthetic aortic root replacement in middle-aged patients, showing acceptable results in terms of freedom from reintervention and valve-related events after bioprosthetic aortic root replacement, regardless of the prosthesis type (stented or stentless). There was a relatively high thromboembolic event hazard that may (partly) be explained by older patient age.

Chapter 7 provides insight into long-term outcome after aortic valve replacement with allografts in a prospective single center study and studies potential echocardiographic factors for the prediction of reoperation and death in a joint model. The indication for use of allografts in aortic position has become selective, mainly because of progressive structural valve deterioration over time. In case of complex aortic root pathology and active endocarditis allografts may still be useful.

Chapter 8 addresses the results of maternal, cardiac and obstetric complications in 67 pregnancies in 40 women who have undergone an aortic valve replacement in the past with a mechanical valve or a human donor valve (allograft or Ross procedure). Maternal and obstetric complications occurred in respectively 13% and 38% patients, however, mainly in patients with mechanical valve prosthesis. For young female patients with aortic valve disease who are planning to become pregnant, human donor valves should to be considered as a valuable option. Nevertheless careful obstetric monitoring remains very important in these patients. In **Chapter 9** the impact of pregnancy on durability of human donor valves in young women is examined. Pregnancy is not associated with prosthetic valve durability. Therefore, the human donor valve should be considered as a suitable valve prosthesis in young female patients who desire a pregnancy in the future.

Chapter 10

This chapter describes the difference between conservative treatment and surgery regarding symptomatic patients with severe aortic stenosis and timing of the operation, and deals with this discrepancy by studying the reasons why more than half of the patients studied, received medical treatment instead of surgery. Operative risk, hemodynamic severity and symptomatic status appear to be misclassified frequently leading to an (surgical) under treatment.

Chapter 11 describes early and late outcome after valve sparing aortic root replacement (David procedure), echocardiographic changes in valve function during follow-up, and the reported quality of life after valve sparing aortic root replacement. There was an

excellent clinical outcome and quality of life in the first postoperative decade. However, despite very low valve-related complication rates, there is a hazard of reoperation due to progressive valve regurgitation, particularly in patients after the Ross-procedure.

Chapter 12

This chapter outlines the general discussion, conclusion and recommendations following from this thesis. It provides an overview of clinical outcome after surgical treatment of aortic valve and/or root disease, in a broader perspective taking into account patient characteristics, quality of life and patient preference. There are several surgical solutions for the diseased aortic valve and root (mechanical and biological prosthesis, and valve-sparing root replacement), however all these options have their advantages and disadvantages. International collaboration on data-gathering and follow-up of patients with aortic root disease should help us find the most suitable treatment for specific patients. Hence, patients' preference should be taken into account to improve decision making and to choose the most appropriate treatment for the individual patient.

SAMENVATTING

Hoofdstuk 1
Dit hoofdstuk omvat de introductie, de hypothesen en de hoofdlijnen van dit proefschrift. Aortaklep ziekte is de meest voorkomende hartklepafwijkingen in de ontwikkelde landen. Het doel van dit proefschrift is om de verschillende chirurgische technieken en verschillende klepprothesen die momenteel beschikbaar zijn voor de behandeling van de aangedane aortaklep en de aortawortel te belichten en bij te dragen aan de huidige kennis over de uitkomsten na aortaklep en/of aortawortel operatie, in termen van overleving en kwaliteit van leven.

Hoofdstuk 2
Een hoofdstuk uit een boek over aortaklepinsufficiëntie dat een overzicht geeft over indicaties voor operatieve behandeling van aortaklepinsufficiëntie, verschillende chirurgische opties en de daaropvolgende resultaten na aortaklep reparatie en aortaklepvervanging.

Hoofdstuk 3 betreft een systematische review van de literatuur en een meta-analyse die de klepgerelateerde uitkomst na aortawortelvervanging met een (mechanische) klephoudende vaatprothese (Bentall) bij patiënten met aortawortel ziekte schetst. Reoperaties aan de aortawortel na de Bentall procedure zijn afgenomen in de loop der jaren. Echter, klepgerelateerde complicaties zoals late mortaliteit, grote bloedingen, en trombo-embolische complicaties blijven een punt van zorg.

Hoofdstuk 4 is een systematische review van de literatuur en microsimulatie na mechanische aortaklepvervanging bij jonge patiënten die het optreden van de klepgerelateerde uitkomsten voorspelt. Deze studie toont aan dat de mechanische klepprotheses in deze groep patiënten geassocieerd is met een aanzienlijke "oversterfte" en een aanzienlijk risico op het krijgen van anticoagulantia-gerelateerde complicaties, maar ook kans op reoperatie. Er is dus geen prefect klepprothese voor jonge patiënten en een gezamenlijke besluitvorming over het type klepprothese (mechanisch danwel biologisch) is derhalve van groot belang.

In **hoofdstuk 5** wordt een systematische review van de literatuur en een meta-analyse uitgevoerd die een overzicht en de uitkomsten na een klepsparende aortawortelvervanging in relatief jonge patiënten weergeeft. Tevens worden verschillende chirurgische technieken en variabelen die mogelijk invloed hebben op de uitkomst na klepsarende

aortawortelvervanging getest. Zowel de "remodeling" als de "reimplantatie" techniek laten een goede overleving van patiënten en duurzaame klepreparatie zien met weinig klepgerelateerde complicaties, wat een goed alternatief kan zijn voor mechanische klepvervanging (Bentall) in deze patiënten.

In **hoofdstuk 6** wordt middels een meta-analyse en microsimulatie model een overzicht gegeven van de uitkomsten na aortawortelvervanging met een biologische prothese bij patiënten van middelbare leeftijd, wat aanvaardbare resultaten laat zien met betrekking tot de kans op een reinterventie en klepgerelateerde complicaties, ongeacht het type prothese dat is gebruikt (gestente of stentloze). Er was een relatief hoog risico op tromboembolische complicaties die (deels) verklaard kan worden door de hogere leeftijd van de patiënten.

Hoofdstuk 7 geeft inzicht in de lange termijn resultaten na aortaklepvervanging met 'allogratfs" in een prospectieve, "single-center" studie. Tevens worden echocardiografische parameters onderzocht die de kans op een reoperatie en sterfte voorspellen in een zogenoemde "joint-model". De indicatie voor het gebruik van allografts in de aorta positie is minder en selectiever geworden, vooral als gevolg van progressieve, structurele klepdegeneratie. In geval van complexe aortawortel pathologie en actieve endocarditis kan een allograft wel uitkomst bieden.

Hoofdstuk 8 adressert de uitkomst van maternale, cardiale en obstetrische complicaties in 67 zwangerschappen bij 40 vrouwen die een aortaklepvervanging hebben ondergaan met een mechanische klep of een humane donorklep (allograft of een Ross operatie). Maternale en obstetrische complicaties kwamen in respectievelijk 13% en 38%, doch met name patiënten met een mechanische klepprothese ondervonden deze complicaties. Voor jonge vrouwen met een aortaklepaandoening die een zwangerschapswens hebben dienen humane donorkleppen ook als een optie te worden beschouwd. Desalniettemin blijven zorgvuldige verloskundige controles erg belangrijk in deze patiënten. In **hoofdstuk 9** wordt het effect van zwangerschap op de duurzaamheid van humane donorkleppen in jonge vrouwen onderzocht. Zwangerschap was niet geassocieerd met de duurzaamheid van deze donorkleppen. Derhalve dient de humane donorklep overwogen te worden bij de jonge vrouwelijke patiënten met een aortaklepaandoening, die een zwangerschapswens hebben.

Hoofdstuk 10 beschrijft het verschil tussen een conservatieve behandeling en chirurgie met betrekking tot symptomatische patiënten met ernstige aortaklepstenose en de timing van de operatie. Tevens behandelt dit hoofdstuk deze discrepantie door de redenen te bestuderen waarom meer dan de helft van deze onderzochte patiënten een mecicamenteuze behandeling kregen in plaats van een operatie. Operatierisico, hemodynamische ernst van klepstenose en symptomatische status van de patient lijken vaak ten onrechte te leiden tot een (chirurgische) onder behandeling.

Hoofdstuk 11 beschrijft de vroege en late uitkomsten na klepsparende aortawortelvervanging (David procedure), echocardiografische veranderingen van de klep tijdens de follow-up en de kwaliteit van leven na klepsparende aortawortelvervanging. Er was sprake van een uitstekende overleving en kwaliteit van het leven in de eerste postoperatieve decennium. Desalniettemin, ondanks zeer lage klepgerelateerde complicaties, is er een reële kans op een reoperatie door progressieve aortaklepregurgitatie, vooral bij patiënten na de Ross-procedure.

Hoofdstuk 12

In dit hoofdstuk wordt de algemene discussie, conclusie en aanbevelingen naar aanleiding van dit proefschrift beschreven. Het geeft een overzicht van de klinische uitkomst na de chirurgische behandeling van aortaklep en/of aortawortel ziekte, in een breder perspectief, rekening houdend met karakteristieken en voorkeuren van de patiënt, en kwaliteit van leven. Er zijn verscheidene chirurgische behandelingen voor de zieke aortaklep en/of aortwortel (mechanische prothesen, biologische prothesen en klep-sparende wortel vervanging), maar al deze opties kennen hun voor-en nadelen. Internationale samenwerking op het gebied van dataregistratie en follow-up van patiënten met aortawortel ziekte kunnen ons helpen om de meest geschikte behandeling voor specifieke patiënten te vinden. Daarom dient de voorkeur van patiënten in acht te worden genomen ten tijde van de besluitvorming omtrent het type prothese en behandeling, om zo de meest geschikte behandeling voor de individuele patiënt te bewerkstelligen.

DANKWOORD / ACKNOWLEDGEMENTS

Het voltooien van dit proefschrift is mede te danken aan de inspanning en steun van een groot aantal mensen. Graag wil ik dan ook van de gelegenheid gebruik maken om een woord van dank uit te spreken, omdat zonder hun bijdrage dit proefschrift nooit tot stand zou zijn gekomen.

Allereerst mijn promotor prof.dr. Bogers. Beste professor Bogers, de afgelopen jaren heeft u mij de mogelijkheid geboden om mij te kunnen ontwikkelen als wetenschapper en als medicus op uw afdeling. De wetenschappelijke deskundigheid en de snelheid waarmee u de manuscripten van waardevol commentaar heeft voorzien zijn belangrijke bouwstenen geweest voor dit proefschrift. Tevens voel ik mij bevoorrecht dat ik getuige heb mogen zijn van uw chirurgische vaardigheden in de operatiekamer. De beheersing en kalmte waarmee u opereert zijn exceptioneel. Het is een zeer waardevolle ervaring geweest en mijn grote dank hiervoor.

Mijn promotor prof.dr. Takkenberg. Beste Hanneke, woorden schieten tekort om het belang van jouw aandeel in dit proefschrift en mijn dankbaarheid daarvoor te beschrijven. Je bent een uitzonderlijk inspirerende vrouw die de gave heeft om het beste in de onderzoekers naar boven te halen. Met een zorgvuldige deskundigheid en een aangename persoonlijkheid heb je een enorm internationaal netwerk van vooraanstaande mensen opgebouwd, waarin je een zeer gerespecteerd lid bent. Desalniettemin heb je ook alle aandacht en steun voor enthousiaste, beginnende onderzoekers die nog dwalen en enige sturing behoeven. Daarnaast heb je ook oog voor de mens achter de wetenschapper. Het is oprecht een voorrecht om jouw promovendus te zijn geweest. Dank ook voor je begrip en steun in tijden van moeilijke (persoonlijke) omstandigheden. Ik heb heel veel van je geleerd en hoop dat ook in de toekomst te kunnen blijven doen.

De leden van de "kleine commissie". Beste prof.dr. Klautz, ik ben zeer trots dat u deel uit wilt maken van deze commissie, daarmee is deze mijlpaal extra bijzonder geworden. Graag wil ik u ook bedanken voor uw vertrouwen in mij en dat ik onderdeel mag zijn van uw team. Het is werkelijk bewonderenswaardig om te zien hoe u zowel op organisatorisch vlak als in de operatiekamer excelleert. Ik hoop nog zoveel mogelijk van u te kunnen leren de komende jaren. Beste prof.dr. Steyerberg, veel dank dat u tijd hebt willen vrijmaken om dit proefschrift te beoordelen en plaats te nemen in deze commissie. Nu u ook in Leiden gevestigd bent, hoop ik in de toekomst een beroep te mogen doen op uw expertise. Beste

prof.dr. Roos-Hesselink. Beste Jolien, jouw deskundige visie en betrokkenheid hebben geresulteerd in een paar mooie publicaties. Heel hartelijk dank voor de zeer prettige samenwerking en voor alle steun. Het is een eer dat je in deze commissie hebt willen plaatsnemen.

Beste dr. Bekkers, het completeren van dit proefschrift was erg moeilijk, zo niet onmogelijk, geweest zonder uw steun. Graag wil ik u bedanken voor de tijd en energie die u heeft gestoken in mij en in dit proefschrift. Wat mij ook altijd bij zal blijven zijn de serene rust en de volledige beheersing waarmee u opereert, het is bijzonder inspirerend en leerzaam geweest. Het feit dat u bereid bent om deel uit te maken van de grote commissie maakt deze dag compleet. Beste prof.dr. Deckers, veel dank voor uw bereidheid om deel uit te maken van deze commissie en dank ook voor de fijne begeleiding in de allereerste fase van de Master of Science (NIHES) opleiding.

Beste prof.dr. Kappetein, beste Arie Pieter. Ik herinner me de bijzondere zaterdag dat ik als eerstejaars student mee mocht lopen op de afdeling en uiteindelijk ook op OK. Het maakte zoveel indruk dat ik meteen verkocht was. Kort daarna volgde de introductie in de wetenschapswereld van thoraxchirurgie. Daar is ook de basis gelegd voor dit proefschrift. Mijn grote dank hiervoor.

Uiteraard mag dr. van Geldorp hier zeker niet ontbreken. Beste Martijn, de eerste stappen in de richting van dit proefschrift zijn aan jou te danken. Jouw enorme gedrevenheid en werklust (zelfs kerstavond was niet ongelegen om het cardiologie archief in te duiken) heeft mij gestimuleerd om verder te gaan in de wetenschap. Dank voor de fijne begeleiding en alle wijze raad.

Beste dr. Heuvelman, beste Helena. Hartelijk dank voor de begeleiding en het helpen opzetten van mijn eerste echte onderzoeksproject. Het heeft heel wat mooi herinneringen opgeleverd, refererend aan onze bel avonden voor de DIAMOND studie. Heel veel succes en gezondheid gewenst voor jou en je gezin.

Mijn paranimfen. Beste Aria, broertje, vriend, reisgenoot in het avontuur dat ons meegenomen en gemaakt heeft. Door jouw onvoorwaardelijke steun en liefde, zeker in de “grijze” periode, heb ik me altijd sterk en onoverwinnelijk gevoeld. Ik benijd jouw evenwichtige kijk op het leven en de rust die je uitstraalt in alles wat je doet. Je bent in alle opzichten de broer en vriend die ik me kan wensen. We zijn onlosmakelijk met elkaar verbonden en dat koester ik ten zeerste. Het maakt mij ontzettend trots dat je op dit

bijzondere moment aan mijn zijde staat en wederom mijn steunpilaar bent. Mijn eeuwige dank voor alles! Uiteraard mag Sofie hier ook niet ontbreken. Ik denk dat ik namens de hele familie spreek als ik zeg dat jouw aanwezigheid een verrijking is, in de breedste zin des woords, voor ons allemaal. Ik ben erg blij met onze band en hoop dat het alleen maar sterker wordt.

Beste Bob (matti), zoals we dat vaker tegen elkaar zeggen als we oude herinneringen ophalen, wie had na onze eerste ontmoeting tijdens de Eurekaweek gedacht dat deze onbeschrijfelijk prachtige vriendschap op ons te wachten stond. Ik prijs me erg gelukkig dat ik het voorrecht heb gehad om jou op deze manier te leren kennen. Je bent een van de weinige mensen die ik blind vertrouw en de meest attente persoon die ik ken. Daarnaast beschik je over een intellect en intelligentie waar geen superlatief de omvang ervan, ook maar bij benadering, recht aan doet. Ik heb inmiddels heel veel mooie herinneringen mogen maken met jou en hoop dat in de toekomst te kunnen multipliceren.

Alle onderzoekers en vrienden waarmee ik heb mogen brainstormen en waar ik ontzettend veel van geleerd heb. Aart, Nelleke, Sahar, Simone, Gerdien en Elrozy; dank voor jullie hulp en de gezelligheid. Ik zal de ochtenden missen waarop ik, na een "zware nachtdienst", kwam klagen op de onderzoekskamer. Jonathan, ik zal niet refereren aan een bepaald congres, maar het schijnt dat er beelden van te vinden zijn...;). Dank voor je waardevolle hulp! Stuart en Ruben, wanneer lanceren we die app waarmee we wereldfaam verwerven? Mostafa, veel dank voor je hulp en voor de wijze raad (en nee, ik heb het niet over Monaco). Ik waardeer het enorm! Natuurlijke mogen hier Anton en Adriaan niet ontbreken (zegt Flavio Briatore genoeg?). Ik kijk erg uit naar onze toekomstige samenkomsten! Sabrina (Jeopardy partner!), dank voor je hulp en support.

Ook wil ik graag Liesbeth en Usha bedanken voor hun hulp en ondersteuning de afgelopen jaren. En uiteraard Marlies, bedankt voor alle steun.

I would like to take this opportunity to kindly thank dr. Lansac for his indispensable contribution and help in several projects. I hope to continue working with you in the future.

Mijn opleider Michel Versteegh (werkelijk een alleskunner), maar uiteraard ook de mede-opleiders die, ondanks de werkdruk die soms met dit prachtige vak gepaard gaat, er altijd naar streven om hun vakkundigheid en kennis over te dragen aan de assistenten: Jerry Braun, Meindert Palmen, Arend de Weger, Thomas van Brakel, Rob de Lind van

Wijngaarden en Martin de Jonge. Vanzelfsprekend ook de congenitaal chirurgen Mark Hazekamp, Dave Koolbergen, Vlado Sojak en Jolanda Kluin. Ik kan me goed voorstellen dat het opleiden van assistenten bepaald geen sinecure is. Hartelijk dank voor jullie geduld en het vertrouwen. Het is een eer om dit vak van jullie te mogen leren.

Alle stafleden en assistenten (AIOS en ANIOS), NP's, PA's en alle andere collegae uit Rotterdam en Leiden waarmee ik zeer prettig heb samengewerkt, hartelijk dank voor jullie steun.

Afzal, onze vriendschap gaat "way back". Al vanaf het begin van de studie ben je mijn steun en toeverlaat geweest. Uiteraard mag Delal hier ook niet ontbreken. Dank voor jullie steun en voor deze dierbare vriendschap. Het betekent veel voor me. Ali, jouw ambitieuze instelling en gedrevenheid hebben mij altijd erg geïnspireerd. Ik weet dat ik altijd op je kan rekenen en waardeer je betrokkenheid enorm (damet garm). Bedankt voor alles.

Lieve familie (Kioumars, Elly & Mo, Frank & Ingrid, Payam & Freek, Aram & Michael, Nika, Kia, Sadaf, Roya en Celina), jullie hebben mij altijd erg gestimuleerd en gesteund in alles wat ik doe. Dank voor jullie onvoorwaardelijke en onmisbare support!

Lieve papa en mama, heel vaak heb ik mij afgevraagd hoe ontzettend moeilijk het leven voor jullie geweest moet zijn. Dat je, als gevolg van het nastreven van je idealen en een betere toekomst voor ons, alles achter moet laten en ergens, in een ver en onbekend land, helemaal opnieuw moet beginnen. Met veel bewondering en respect kijk ik naar de manier waarop jullie omgaan met deze "nieuwe situatie". Hoe jullie je aangepast hebben getuigt van een onbeschrijfelijke kracht. Jullie hebben er alles aan gedaan om het leven zo mooi en aangenaam mogelijk te maken voor Aria en mij, en daarbij hebben jullie jezelf volledig weggecijferd. Er zijn geen woorden die de lading kunnen dekken voor mijn dank voor de onvoorwaardelijke liefde en steun die jullie mij hebben gegeven. Lieve baba en maman, zonder jullie was het nooit gelukt. Dank voor alles!

Lieve Carina, ik weet niet waar ik moet beginnen. We hebben al zo ongelooflijk veel meegemaakt. Je bent een bijzonder sterke vrouw die, ondanks de tegenslagen die soms op het levenspad verschijnen, nooit opgeeft en vol overtuiging, bijna altijd met succes, voor je doel blijft vechten. Je hebt een zeer sterke wil en een onvoorstelbare gedrevenheid in alles wat je doet, maar tegelijkertijd ben je erg zorgzaam en ontzettend lief voor iedereen die je dierbaar is. Ik realiseer me heel goed dat mijn baan en dit proefschrift ook een behoorlijke impact hebben gehad op jouw (ons) leven, maar jij doet er alles aan om

dat zo aangenaam en zo makkelijk mogelijk te maken. Je bent een prachtige vrouw en een onwaarschijnlijk geweldige moeder, en ik houd heel veel van je. Zonder jou was het zeker niet gelukt. Bedankt voor de onvoorwaardelijke steun en liefde!

Lieve Dante, prachtige zoon. Je bent nu nog te jong om te beseffen dat jouw aanwezigheid en lieve lach het leven een stuk mooier maakt. Ik ben trots op je en houd ontzettend veel van je!

PHD PORTFOLIO

Name PhD student:	B. Arabkhani
Erasmus MC department:	Cardiothoracic Surgery
Research school:	Cardiovascular research School (COEUR)
PhD Period:	June 2014 – May 2017
Title thesis:	Surgical Strategy and Clinical Outcome in Patients with Aortic Root Disease
Promotors:	Prof. Dr. AJ.J.C. Bogers Prof. Dr. J.J.M. Takkenberg
Date define thesis:	June 28, 2017

Academic education

2005 – 2006 Biomedical science, Utrecht University, Utrecht, The Netherlands
2006 – 2010 Doctorate in Medicine, Erasmus MC, Rotterdam, The Netherlands
2008 – 2011 MSc in Clinical Research, NIHES, Rotterdam, The Netherlands

PhD training	Year	Workload
Oral presentations		
Operation outcome, valve durability and quality of life after valve sparing aortic root reimplantation (David procedure): a single-center study (NVT, Utrecht)	2015	0.6
Allografts In Aortic Position: Insights From A 27-year Single-center Prospective Study (NVT, Utrecht)	2015	0.6
Allografts In Aortic Position: Insights From A 27-year Single-center Prospective Study (HVS, Monaco)	2015	0.6
Reported outcome after valve sparing aortic root replacement for aortic root aneurysm: a systematic review and meta-analysis (NVT, Utrecht)	2014	0.6
Valve Sparing Aortic Root Replacement for Aortic Aneurysm: A Systematic Review and Meta-Analysis. (Antalya, Turkey)	2014	0.6
Does pregnancy influence the durability of human aortic valve substitutes? (HVS, New York)	2012	0.6
Poster presentations		
Bioprosthetic Aortic root replacement: A meta-analysis and microsimulation model (HVS, Monte Carlo)	2017	0.6

PhD training	Year	Workload
Teaching		
Surgical anatomy lessons	2014 - 2015	4.0
COEUR Course Congenital Heart Disease	2017	0.6
In-depth courses		
Good Clinical Practice (eGCP) for medical devices	2014	4.0
Methods of Public Health Research, Harvard School of Public Health, Boston, USA	2010	2.0
Methods of Health Services Research, Harvard School of Public Health, Boston, USA	2010	2.0
COEUR research seminar and lectures	2009 - 2012	3.0
Repeated Measurements in Clinical Studies NIHES, Rotterdam, The Netherlands	2010	1,9
International conferences		
Annual joint scientific meeting of the Heart Valve Society of America and the Society of Heart Valve Disease (New York, USA)	2012	1.5
European Association of Cardio Thoracic Surgery Annual Meeting (Amsterdam, The Netherlands)	2015	1.5
Inaugural scientific meeting of the Heart Valve Society (Monte Carlo, Monaco)	2015	1.5
European Association of Cardio Thoracic Surgery Annual Meeting (Barcelona, Spain)	2016	1.5
Annual joint scientific meeting of the Heart Valve Society (Monte Carlo, Monaco)	2017	1.5
Meetings		
Meetings of the Dutch Association for Thoracic Surgery	2010 - 2016	4.0
Scientific meetings department of Cardiothoracic Surgery Erasmus MC, Rotterdam, The Netherlands	2009 - 2013	4.0
Aortasymposium: "Aortapathologie – Te nauw of te wijd?	2015	1.5

PhD training	Year	Workload
Peer Reviewer International Scientific Journals		
Bio Med Central (Cardiovascular Disorders) Journal	2015	0.5
American Journal of Cardiology	2016	0.5
International Journal of Clinical Cardiology	2016	1.0
AORTA Journal	2016	0.5

Total workload	**41.2**

LIST OF PUBLICATIONS

Van Geldorp MW, van Gameren M, Kappetein AP, **Arabkhani B**, de Groot-de Laat LE, Takkenberg JJ, Bogers AJ. Therapeutic decisions for patients with symptomatic severe aortic stenosis: room for improvement? Eur J Cardiothorac Surg. 2009 Jun;35(6):953-7; discussion 957

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

Heuvelman HJ, **Arabkhani B**, Cornette JM, Pieper PG, Bogers AJ, Takkenberg JJ, Roos-Hesselink JW. Pregnancy outcomes in women with aortic valve substitutes. Am J Cardiol. 2013 Feb 1;111(3):382-7

Arabkhani B, Mookhoek A, Di Centa I, Lansac E, Bekkers JA, De Lind Van Wijngaarden R, Bogers AJ, Takkenberg JJ. Reported Outcome After Valve-Sparing Aortic Root Replacement for Aortic Root Aneurysm: A Systematic Review and Meta-Analysis. Ann Thorac Surg. 2015 Sep;100(3):1126-31

Aart Mookhoek, Nelleke M Korteland, **Bardia Arabkhani**, Isabelle Di Centa, Emmanuel Lansac, Jos A Bekkers, Ad JJC Bogers, Johanna JM Takkenberg. Bentall Procedure: a Systematic Review and Meta-Analysis. Ann Thorac Surg. 2016 May;101(5):1684-9

Arabkhani B, Bekkers JA, Andrinopoulou ER, Roos-Hesselink JW, Takkenberg JJ, Bogers AJ. Allografts in aortic position: Insights from a 27-year, single-center prospective study. J Thorac Cardiovasc Surg. 2016 Dec;152(6):1572-1579

Nelleke M. Korteland; Jonathan R.G. Etnel; **Bardia Arabkhani**; M. Mostafa Mokhles; Arezo Mohamad; Jolien W. Roos-Hesselink; Ad J.J.C. Bogers; Johanna J.M. Takkenberg. Mechanical aortic valve replacement in non-elderly adults: meta-analysis and microsimulation. Accepted for publication (European Heart Journal, 2017)

Bardia Arabkhani, Jonathan RG Etnel, Mirjam t'Mannetje, Richard van Valen, Tanja van Essen, Emmanuel Lansac, Rob de Lind van Wijngaarden, Isabelle Di Centa, Ad JJC Bogers, Johanna JM Takkenberg. Bioprosthetic aortic root replacement: A Meta-Analysis and Microsimulation model. Submitted

B Arabkhani, CM Kievit, WG Morshuis, ML Geleijnse, JJM Takkenberg, AJJC Bogers, JA Bekkers.Outcome and Quality of Life After Valve Sparing Aortic Root Reimplantation (David Procedure): A Single-Center Study. Submitted

Anton Tomšič, **Bardia Arabkhani**, Jan W. Schoones, Thomas J. van Brakel, Johanna J.M. Takkenberg, Robert J.M. Klautz, Meindert Palmen. Outcome reporting of surgical treatment for degenerative mitral valve disease: a systematic review and critical appraisal. Submitted

Book Chapter

B. Arabkhani, J.J.M. Takkenberg. "Aortic Regurgitation". Chapter 10: The long term results of aortic valve repair and replacement (p. 473 - 491). Editors: Vojáček J., Žáček P. and Dominik J., October 2016, Skladem, Czech Republic, GRADA (ISBN: 978-80-247-5685-1)

ABOUT THE AUTHOR

Bardia Arabkhani was born on June 18th, 1983 in Teheran, Iran. At the age of 12 he moved together with his parents and brother to The Netherlands, as political refugees. After 5.5 years, the family was granted the Dutch citizenship. After graduating from secondary school (Nature&Health, CSG Johannes Calvijn, Rotterdam) he started Medical school in 2006 at the Erasmus University Rotterdam. At the end of the first year, he started cooperating in a research project at the department of Cardiothoracic Surgery where he was introduced into scientific research. In 2007, Bardia was among the top 10% of medical students and was selected to participate in a special international scientific 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, participating in several research projects under supervision of prof.dr. Takkenberg. In 2011 he graduated from the MSc in Clinical Research at the Netherlands Institute of Health Sciences, and started his medical internship. Bardia was graduated from Medical School in June 2013. After his graduation he started as resident at the department of Cardiothoracic Surgery at the Erasmus Medical Center, and parallel to his residency he started a PhD project under supervision of prof. dr A.J.J.C. Bogers and prof. dr J.J.M. Takkenberg, which resulted in this thesis. In July 2015 Bardia moved to Leiden University Medical Center (LUMC) to start as resident at the Department of Cardiothoracic Surgery, and currently he is in training to become a cardiothoracic surgeon.

The financial support for the publication of this thesis by the following companies is gratefully acknowledged: Abbott Netherlands, Cardialysis, Chipsoft BV, Edwards Lifesciences, Erasmus Universiteit, Krijnen Medical Innovations, Maquet Netherlands, QP&S, Sanofi and Thoraxcentrum Research BV.

ISBN 978-1-4028-9462-7

Publication data: Library of Congress Cataloging-in-Publication Data
Names: Hollowell, Rebecca, author. | Illustrations by Mara Kessler
Title: The Quiet Orchard
Description: First edition. | Includes bibliographical references and index.
Subjects: Orchards—Maintenance and repair—Juvenile literature. | Pruning—Juvenile literature.
Classification: LCC SB355.H65 2021 | DDC 634.1—dc23

Printed in Malaysia

First Edition

10 9 8 7 6 5 4 3 2 1