CHAPTER I

GENERAL INTRODUCTION

For patients with aortic valve disease requiring surgical treatment several options are available. In some instances the valve can be repaired, however replacement of the valve is usually necessary. Valve repair is only an option in carefully selected patients with aortic regurgitation or aortic stenosis in whom the valve is not calcified. It should be noted that long-term results are limited at this time.

The aortic valve can be replaced by 4 major types of prosthetic valves:

1. Mechanical prosthesis
2. Bioprosthesis
3. Allograft
4. Autograft

The choice for a particular aortic valve prosthesis is influenced by several inter-related factors such as patient age, concomitant disease (for instance coronary artery disease or mitral valve disease), atrial fibrillation, the center's experience with implantation of a prosthesis, and preference of the referring cardiologist, attending surgeon and the patient. Often, more than one type of prosthesis seems suitable for the individual patient, whereby the decision for a particular prosthesis is made rather arbitrarily.

Unfortunately, there are no European or Dutch guidelines to support the choice for a particular aortic valve prosthesis. The working group on valvular heart disease of the European Society of Cardiology has not yet released recommendations or guidelines in this respect, and within the European Association for Cardio-thoracic Surgery no committee or working group that addresses this issue exists. However, in 1998 the American College of Cardiology/American Heart Association (ACC/AHA) Committee on Management of Patients with Valvular heart Disease published an ACC/AHA Task force Report with guidelines for the management of patients with valvular heart disease[1]. These guidelines were developed to improve the effectiveness of care, optimize patient outcomes, and favorably impact the overall cost of care by focusing resources on the most effective strategies. Although these guidelines provide translucent and detailed recommendations regarding the timing of aortic valve replacement, only major criteria for valve selection are given. This again confirms that the choice of an aortic valvular prosthesis is complex and needs to be tailored to the individual patient. With the current knowledge on outcome of patients after aortic valve replacement with different types of prosthesis, no specific recommendations can be given. This is especially true for the allograft and autograft, since no long-term outcome is yet available from clinical practice.

This thesis will focus primarily on the choice for an autograft or an allograft in aortic valve replacement. The methodology of microsimulation will be introduced, and applied to the problem of choosing the 'right' aortic valve substitute for the individual patient. Evidence-driven microsimulation aims to provide objective, reliable and valid estimates of long-term outcome after aortic valve replacement with a particular prosthesis in the individual patient. It could therefore be useful in clinical practice to support the decision for a therapeutic strategy.

I-1. Outline of this thesis

The goal of this thesis is to develop an objective and valid methodology to support the choice for a particular aortic valve substitute in the individual patient, with a primary focus on autografts and allografts. In order to do so the following research questions will be answered:

1. What are the aortic valve substitute *options*?
2. What clinical decision *analysis tool* is suitable to structure the clinical problem?
3. What is the *clinical experience* with aortic valve replacement using allografts and autografts?
4. What are the surgical options in *children* with aortic valve disease?
5. What is the evidence-based calculated prognosis after *autograft* aortic root replacement in adults?
6. What is the evidence-based calculated prognosis after aortic root replacement with cryopreserved *allografts* in adults?
7. How does *outcome* after autograft aortic root replacement compare to outcome after aortic root replacement with a cryopreserved allograft in adults?
8. How does outcome after autograft or allograft aortic root replacement compare to outcome after aortic valve replacement with *mechanical valves or bioprostheses*?
9. Can patient-specific *recommendations* be made with regard to the preferred valve substitute in patients requiring aortic valve replacement, based on the methodology described in this thesis?

I-2. Prosthetic valve choices in aortic valve replacement

Since the first orthotopic aortic valve replacement in 1960[2], several types of aortic valve substitutes have been developed. Below, the 4 major types of heart valves will be briefly described.

I-2-1. Mechanical prostheses

Mechanical valves have been used over three decades for the replacement of the aortic valve. In 1960 the first aortic valve replacement with an intracardiac mechanical valve was performed by Harken[2]. Since then, the mechanical valve has become worldwide the most commonly used aortic valve substitute. Of the 9.095 isolated aortic valve replacements performed in the United States in 1997, 49% was done using a mechanical prosthesis (http://www.sts.org).

Mechanical valves are primarily composed of metal or carbon alloys and can be classified according to their structure as caged-ball, single tilting disc, and bileaflet tilting disk (Figure I-1a-c)[3]. Currently, the most commonly used type of mechanical valve is the bileaflet tilting disk.

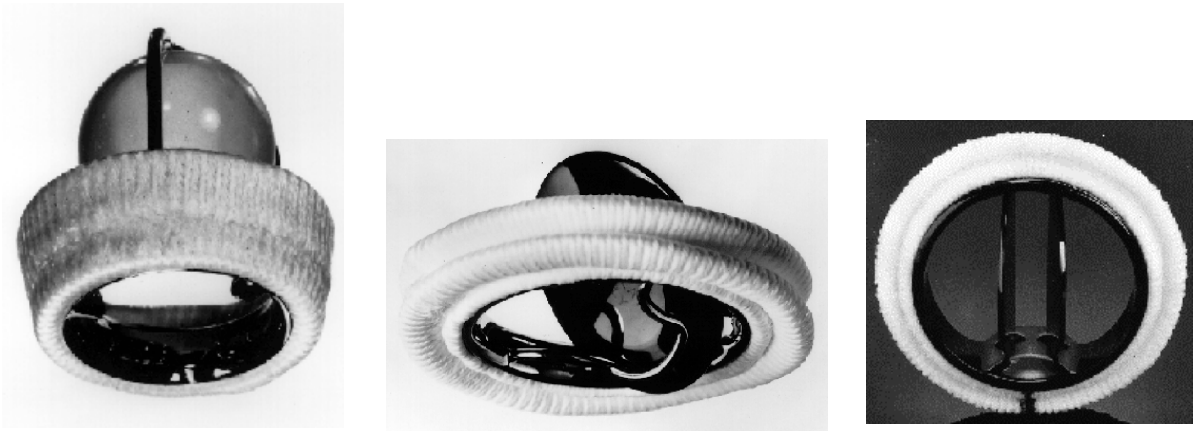

Figure I-1. a: Starr-Edwards cage-ball valve; b: Bjork-Shiley monoleaflet valve; c: St Jude Medical bileaflet valve

The main advantage of mechanical valves is their durability. They are designed to outlive the patient and most mechanical valves last at least 15-30 years[3,4].

Disadvantages of mechanical valves are their thrombogenicity, suboptimal hemodynamic profile, increased risk of endocarditis and a high sound level.

Because of the thrombogenicity of mechanical valves patients require lifelong high-intensity oral anticoagulant therapy (coumarin derivates). This is to prevent thrombo-embolic complications but is associated with an increased risk of bleeding complications. To maintain an optimal level of anticoagulation patients need to be closely monitored and a target INR (International Normalized Ratio) of 3.0-4.0 is recommended[5]. Coumarin therapy is

contraindicated during the first 13 weeks of pregnancy because of its teratogenous side effects.

The hemodynamic profile of a mechanical prosthesis is inferior to that of the native valve, with a smaller effective orifice area[3], and results in less regression of left ventricular hypertrophy when compared to patients who receive an allograft[6].

Prosthetic valve endocarditis occurs in 3-6 percent of patients and is associated with considerable mortality: mortality from early (<60 days after valve replacement) prosthetic valve endocarditis is 30-80 percent, late mortality is 20-40 percent[3].

A final potential disadvantage of a mechanical prosthesis, that is often underestimated, is the high sound level. Although some patients experience the sound of the valve as comforting, others are seriously bothered by the noise and occasionally this may result in elective explantation of the valve[7-9].

ACC/AHA recommendations for valve replacement with a mechanical prosthesis[1]:

1. Patients with expected long life spans.
2. Patients with a mechanical prosthetic valve already in place in a different position than the valve to be replaced.
3. Patients in renal failure, on hemodialysis, or with hypercalcemia.
4. Patients requiring warfarin therapy because of risk factors for thrombo-embolism (atrial fibrillation, severe LV dysfunction, previous thrombo-embolism, hypercoagulable condition).
5. Patients ≤65 years for AVR and ≤70 years for MVR. The age limit is based on the major reduction in rate of structural bioprosthetic valve deterioration after age 65 and the increased risk of bleeding in this group.

For patients who require re-reoperation for a thrombosed biologic valve the benefits of a mechanical prosthesis are less well established.

I-2-2. Bioprostheses

Bioprostheses are valve substitutes made out of animal tissues. Best known are the porcine bioprostheses, however bovine pericardial valves are also frequently used. Examples of bioprostheses are displayed in Figure I-2.

In 1971 stented porcine bioprostheses became commercially available. These prostheses have intra-annular configurations with tissue fixation using glutaraldehyde at approximately 60 mmHg pressure. In the early 80's a surfactant was added against

glutaraldehyde resistant microorganisms. In 1992 stentless bioprostheses became available, with the potential advantage of better hemodynamics due to decreased pressure gradients. Bioprostheses are frequently used as an aortic valve substitute: of the 9.095 isolated aortic valve replacements performed in the United States in 1997, almost 41% was done using a bioprosthesis. In 1992 this was only 30%, so an increase in popularity is evident in recent years (http://www.sts.org).

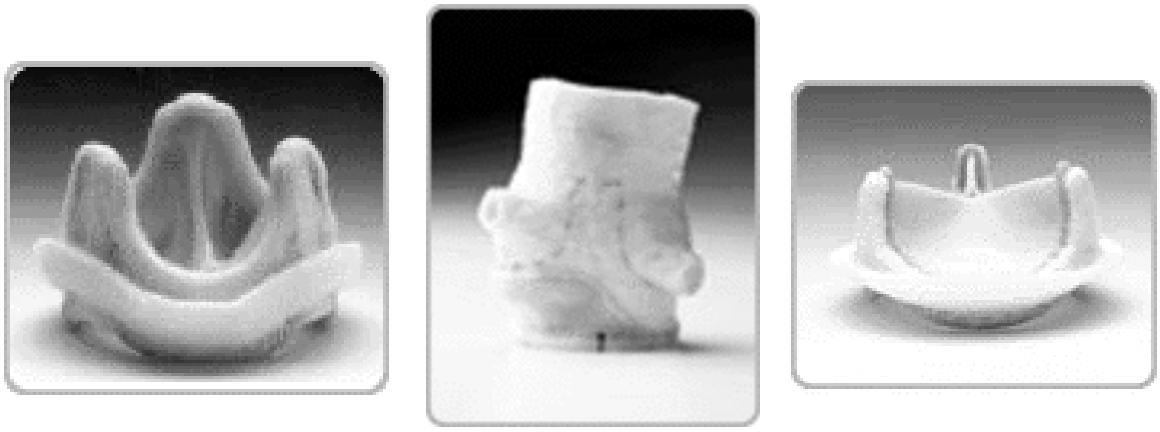

Figure I-2.a: Stented porcine bioprosthesis; b: Stentless porcine bioprosthesis; c: pericardial bovine bioprosthesis.

Advantages of bioprostheses are lower thrombogenicity compared to mechanical prostheses and no need for anti-thrombotic therapy. The rate of structural valvular deterioration is less than 10% for patients aged 65 and older.

On the other hand bioprostheses have an increased rate of structural valvular deterioration for patients younger than 65, and especially in patients younger than 50 years. For patients who require anti-thrombotic therapy for any reason, like atrial fibrillation or a mechanical prosthesis in another position, the advantages of a biological valve are reduced substantially.

ACC/AHA recommendations for valve replacement with a bioprosthesis[1]:

1. Patients who cannot or will not take warfarin therapy.
2. Patients ≥65 years needing AVR who do not have risk factors for thrombo-embolism (atrial fibrillation, severe LV dysfunction, previous thrombo-embolism, hypercoagulable condition). The age limit is based on the major reduction in rate of structural bioprosthetic valve deterioration after age 65 and the increased risk of bleeding in this group.

3. Patients considered to have possible compliance problems with warfarin therapy.
4. For patients who require re-reoperation for a thrombosed mechanical valve the benefits of a bioprosthesis are less well established.

Also, for patients < 65 years the benefits of a bioprosthesis are less well established. In patients with a small aortic valve annulus that will not permit use of an adequately sized valve (≥ 23 mm), consideration should be given to aortic root/annular enlargement.

I-2-3. Allografts

Allografts, also known as homografts or donor valves, have been used for replacement of the aortic valve since 1962. It was Ross who first described the orthotopic replacement of the aortic valve with an allograft [10]. Several changes have taken place over the years with the use of allografts. Initially, fresh valves were used. However, because of logistic reasons (limited maintainability), other preservation techniques like chemical and antibiotic sterilization and in more recent years cryopreservation evolved. Nowadays, cryopreservation is the most commonly used preservation technique. Another important change over time is the surgical technique used to implant the allograft in aortic position. Initially, the subcoronary or freehand implantation technique was used. With this technique, only the allograft cusps were implanted. In recent years the root replacement technique, where the complete allograft aortic root is implanted as a functional unit, is most commonly used. In comparison with the subcoronary implantation technique, donor-recipient mismatch becomes less important, it is associated with less initial echocardiographic aortic regurgitation and less technical failure, but requires reimplantation of the coronary arteries [11,12]. In Figure I-3 a cryopreserved aortic root with arch is displayed.

Figure I-3. Cryopreserved allograft root with arch.

Compared to the frequent use of mechanical valves and bioprostheses, allografts are implanted in a limited number of patients: only 2.5% of the isolated aortic valve replacements that took place in the United States in 1997 were done using an allograft (http://www.sts.org).

Advantages of the allograft are low thrombo-embolic event rates, the avoidance of lifelong anticoagulant therapy and possibly the risk of prosthetic valve endocarditis is reduced.

Disadvantages of the allograft are the limited availability, the surgical skill required to implant the valve and the unknown long-term incidence of structural valvular deterioration. There is experimental evidence for immune mediated structural valvular deterioration [13] and in allograft recipients donor-specific cytotoxic T-lymphocytes have been found [14]. Another possible indication that structural valvular deterioration is at least in part immune mediated, is the fact that younger patient age is associated with increased risk for structural valvular deterioration [15].

The ACC/AHA guidelines[1] give no specific recommendations for the use of allografts. Allograft roots are often used in patients with acute endocarditis and in patients with aortic root disease. Women who are contemplating pregnancy should preferably receive an allograft or an autograft (provided the necessary skill and experience are present), since mechanical valves require anti-thrombotic therapy (complications to patients and/or fetus) and bioprostheses have a relatively higher rate of early structural valvular deterioration in pregnant women. Exceptions are women who require warfarin for another reason, but only when the mechanical valve does not require a higher INR level [1]. In patients with a small aortic valve annulus that will not permit use of an adequately sized valve (≥ 23 mm), consideration should be given to the use of an allograft.

I-2-4. Autografts

Ross was also the first to describe the use of the pulmonary autograft in aortic valve replacement in 1967 [16]. The patient's pulmonary valve is used to replace the diseased aortic valve and an allograft valve or bioprosthesis is implanted in pulmonary position. Originally, the autograft was implanted using the subcoronary implantation technique. In 1986 autograft aortic root replacement with reimplantation of the coronary arteries, also known as the modified Ross procedure, was introduced [17]. A schematic representation of the modified Ross procedure is displayed in Figure I-4. In 1993, the International Registry of the Ross Procedure was established to investigate worldwide longitudinal clinical outcome [18]. According to this registry the number of Ross procedures performed continues to grow rapidly: in 1996 over

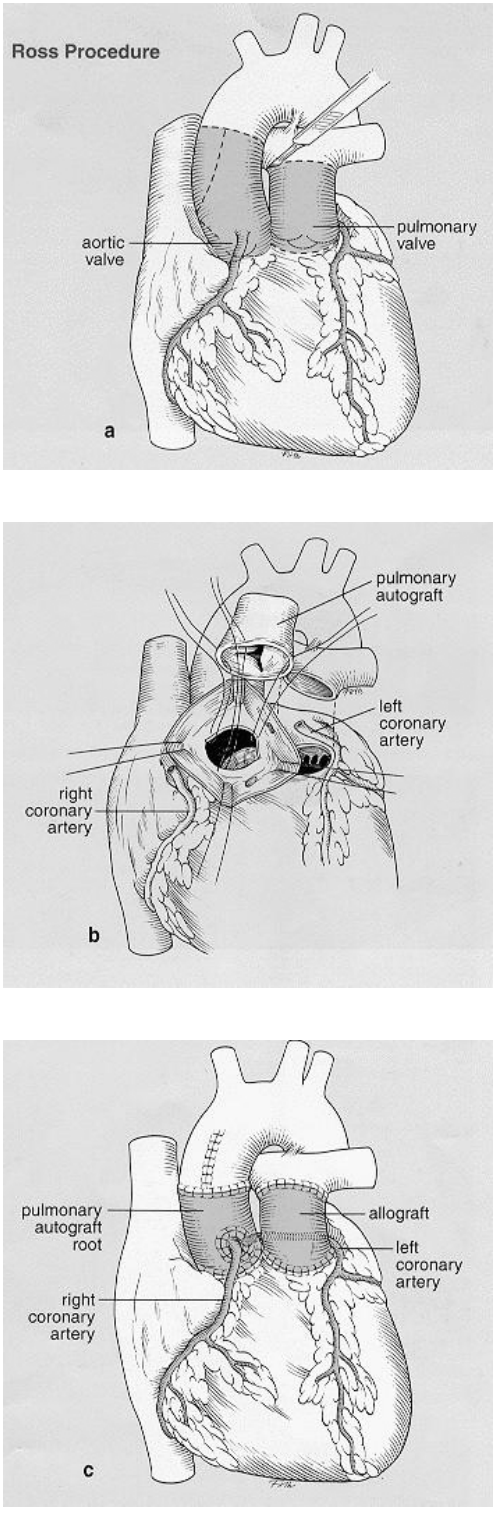

Figure I-4 A schematic representation of the modified Ross procedure.

550 Ross procedures were performed (www.rossregistry.com). However, compared to bioprostheses and mechanical prostheses, autografts are used sporadically.

Advantages of the autograft are the use of the patient's own tissue, thereby avoiding potential immune-mediated structural valve deterioration and life-long anti-thrombotic therapy, and possibly a reduction of the risk of prosthetic valve endocarditis.

An important disadvantage of the autograft procedure is the extent of the operation and the surgical skill that is required: it is a complicated procedure requiring replacement of two valves. Long-term prognosis is therefore affected not only by complications related to the autograft but also by complications related to the valve substitute that is implanted in the right ventricular outflow tract.

In addition, long-term durability of the autograft is yet unknown. Recently, some concern has been risen regarding progressive dilatation of autograft roots [19-22]. A valved conduit that was designed to function in the low pressure environment of the right ventricular outflow tract, may theoretically experience hemodynamic challenges in the high pressure left ventricular outflow tract. Therefore, the autograft is contra-indicated in patients with connective tissue diseases. This may also apply to patients with bicuspid valve disease. These patients have more severe degenerative changes in the media of the ascending aorta and main pulmonary artery than patients with tricuspid aortic valve disease, and are therefore possibly at a higher risk for progressive dilatation [20].

The ACC/AHA guidelines[1] give no specific recommendations for the use of autografts. Usually, the autograft procedure is performed in children and young adults. In children the dilatation or so-called 'growth potential' of the autograft is advantageous, since the pulmonary autograft 'grows' with the child and reoperation for relative stenosis of the valve substitute can be avoided. Also, women who are contemplating pregnancy may benefit from an autograft (provided the necessary skill and experience are applied), since mechanical valves require anti-thrombotic therapy (complications to patients and/or fetus) and bioprostheses have a relatively higher rate of early structural valvular deterioration in pregnant women. Exceptions are women who require warfarin for another reason, but only when the mechanical valve does not require a higher INR level [1]. In patients with a small aortic valve annulus that will not permit use of an adequately sized valve (≥ 23 mm), consideration should be given to the use of an autograft.

I-3. Monitoring valve performance over time

In order to assess valve performance over time, several factors should be taken into consideration. As discussed above, each valve type has different advantages and disadvantages. Structural and non-structural valve deterioration, valve thrombosis, thrombo-embolism, bleeding, prosthetic valve endocarditis, are all important factors to consider when studying valve performance over time.

In 1988 the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity of The American Association for Thoracic Surgery and the Society of Thoracic Surgeons first published Guidelines for reporting morbidity and mortality after cardiac valvular operations[23,24] (also known as Edmunds' Guidelines). This was done in order to facilitate the analysis and reporting of results of operations on diseased cardiac valves. These guidelines were designed to facilitate comparisons between the experience of different surgeons who treat different cohorts of patients at different times with different techniques and materials.

In 1996 these guidelines were updated and clarified[24-27]. Since Edmunds' Guidelines will be applied throughout this thesis, a summary of the definitions for morbidity and mortality after cardiac valvular operations from the updated Edmunds' Guidelines will be given below.

Mortality

Thirty-day mortality. Death within 30 days of operation regardless of the patient's geographic location.

Hospital mortality. Death within any time interval after operation if the patient is not discharged from the hospital.

Definitions of morbidity

Structural valvular deterioration (SVD). Any change in function (a decrease of one NYHA functional class or more) of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation. Exclusive of thrombosis and infection.

Nonstructural dysfunction (NSD). Any abnormality resulting in stenosis or regurgitation at the operated valve that is not intrinsic to the valve itself. Exclusive of thrombosis and infection.

Valve thrombosis. Any thrombus, in the absence of infection, attached to or near an operated valve that occludes part of the blood flow path or that interferes with function of the valve.

Embolism. Any embolic event that occurs in the absence of infection after the immediate peri-operative period. A distinction can be made between neurologic and peripheral embolic

events. A neurologic embolic event includes any new, temporary or permanent, focal or global neurologic deficit, while a peripheral embolic event produces symptoms from complete or partial obstruction of a peripheral (non-cerebral) artery.

Bleeding event. Any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury or necessitates transfusion

Operated valvular endocarditis. Any infection involving an operated valve based on customary clinical criteria.

Consequences of morbid events

Reoperation. Any operation that repairs, alters, or replaces a previously operated valve.

Valve-related mortality. Death caused by SVD, NSD, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or death related to reoperation of an operated valve. Includes sudden unexpected , unexplained death. Excludes deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves.

Sudden, unexplained, unexpected death (SUUD). The cause of these deaths is unknown and the relationship to an operated valve is also unknown. Therefore, these deaths should be reported as a separate category of valve-related mortality.

Cardiac death. All deaths resulting from cardiac causes, including valve-related deaths (including SUUD) and non-valve related cardiac deaths.

Total deaths. All deaths resulting from any cause after a valve operation.

Permanent valve-related impairment. Any permanent neurologic or other functional deficit caused by SVD, NSD, valve thrombosis, thrombotic embolism, bleeding event, operated valvular endocarditis, or reoperation.

I-4. Selecting an aortic valve substitute

In conclusion, although several prosthetic valve options exist in aortic valve replacement, the perfect valve substitute has yet to be found. Weighing the advantages and disadvantages of the available aortic valve substitute options in the individual patient can be very difficult, given the substantial number of inter-related factors that play a role in the decision for an aortic valve substitute.

Edmunds' Guidelines provide an important tool to systematically assess the valve-related events that are encountered during the course of time after implantation of a valve substitute[1]. Nowadays, it is common to report results according to these guidelines, allowing better comparison between reported series.

Most reported series are small, which makes it hard to estimate the impact on prognosis of the pros and cons of the different aortic valve substitutes. For allografts and autografts, the fact that no long-term experience is available yet introduces an additional uncertainty in predicting outcome of the individual patient.

The lack of sufficient size and duration of the reported experiences with allograft and autograft aortic root replacement has led to the introduction of the combined methodology of meta-analysis and microsimulation that is employed throughout this thesis.

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