Prognosis after Aortic Valve Replacement with Mechanical Valves and Bioprostheses

Use of Meta-analysis and Microsimulation

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Prognosis after Aortic Valve Replacement with Mechanical Valves and Bioprostheses

Use of Meta-analysis and Microsimulation

Prognose na aortaklepvervanging met mechanoprothesen en bioprothesen

Gebruik van meta-analyse en microsimulatie

Thesis

to obtain the degree of Doctor from the
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by

John Premlal Ashok Puvimanasinghe
born in Colombo, Sri Lanka

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“The more alternatives, the more difficult the choice” (Abbe’ D’ Allanival)

To the memory of my late father

Contents

Introduction and Methodology

1. Introduction

1.1. The normal aortic root and aortic valve

The aortic root forms the first part of the aorta and extends from the insertion of the aortic annulus in the left ventricular myocardium to the sino-tubular junction. It comprises the aortic valve leaflets, the walls of the aortic sinuses and the inter-leaflet triangles respectively. Described by Zimmerman in 1969 as 'a crownlike formation of collagenous tissue' [1], the annulus of the aortic root is a complex circular shaped structure which provides attachment to the valve leaflets. Distal to the leaflet attachments are the three aortic sinuses (sinuses of Valsalva), which bulge out of the aortic root, two of them giving rise to the right and left coronary arteries. The borderline between the thinner wall of the sinuses and the more distal arterial wall forms the sino-tubular junction [2].

The normal aortic valve is composed of three half-moon-shaped leaflets, each of which is attached to the aortic wall just beneath one of the three aortic sinuses. The aortic valve leaflets corresponding to the coronary arteries are termed the right and left leaflets while the third is the non-coronary leaflet. A fibrous skeleton supports the aortic valve, which is in continuity with the anterior leaflet of the mitral valve and the membranous interventricular septum. The valve leaflets consist of fibrous tissue and are lined with endothelium. The free edge of the leaflet is of tougher consistency than the rest of the structure. At the midpoint of the free edge of each leaflet is a fibrous nodule, the nodule of Arantius. During ventricular systole, the valve leaflets open towards the aortic wall and in diastole they meet at the central nodules of Arantius [3,4] (Figure 1).

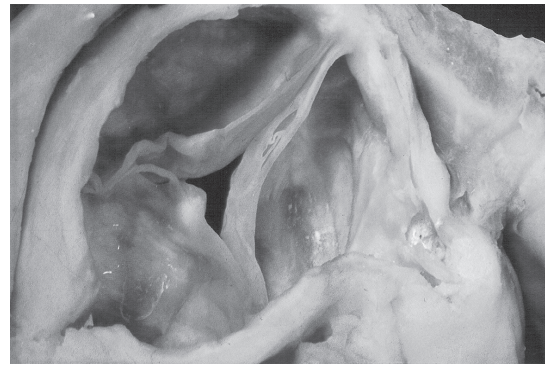

Figure 1. The normal aortic valve as seen from the aortic aspect. The fibrous nodules are seen to meet centrally in diastole. The coronary arteries are at the lower right and left of the figure.

1.2. Dysfunction of the aortic valve

Pathological lesions of the aortic valve can result in obstruction of blood flow from the left ventricle to the aorta during systole (aortic stenosis), a leakage of the valve backward into the left ventricle during diastole (aortic regurgitation) or a combination of both.

1.2.1. Aortic stenosis

Aortic stenosis is mostly related to calcific, rheumatic and degenerative valves [5]. Calcific aortic stenosis may occur secondary on a congenitally abnormal valve. Most often, the congenital anomaly is a bicuspid valve that occurs in 1-2% of the general population and predisposes to calcific stenosis of the valve commonly in the fifth and sixth decades of life [6] (Figure 2). Calcification of the valve progresses with advancing age and results in significant stenosis, presenting as a bulky cauliflower-like mass involving both leaflets.

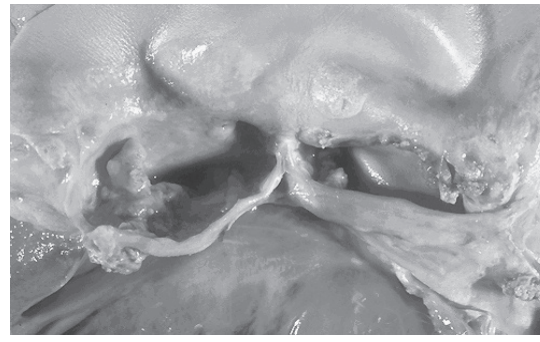

Figure 2. A congenital bicuspid valve showing nodules of calcification on either valve surface. The valve has been opened with the aortic outflow above and the ventricular myocardium below.

Rheumatic aortic stenosis usually follows a previous history of rheumatic fever, although other unrecognized inflammatory processes may also play a role. The affected valves display a prominent fibrous thickening with fusion of one or two commissures. Although the incidence of rheumatic aortic disease has declined in the West, it is still considered to be the major etiological factor in other parts of the world [7]. Degenerative (atherosclerotic) aortic stenosis is related to an atheromatous process in the valve and is common in patients over 65-years of age. Its prevalence has been shown to increase with advancing age [4,8].

1.2.2. Aortic regurgitation

The etiological factors underlying aortic regurgitation overlap considerably with that of aortic stenosis and hence mixed aortic valve disease is a frequent finding in many patients. Apart from bicuspid aortic valve disease, rheumatic valve disease and degenerative valve disease that may cause aortic regurgitation, annulo-aortic ectasia can produce incompetence of varying degrees. Annulo-aortic ectasia is defined as abnormal dilatation of the aortic valve annulus and aortic root, most commonly due to cystic medial necrosis of the aortic wall. This process begins in the sinuses of Valsalva and extends with time to involve the proximal ascending aorta resulting in progressive aortic regurgitation. Other causes of aortic regurgitation include native valve endocarditis and myxoid degeneration of the aortic valve respectively [4,8]. Rheumatoid arthritis, ankylosing spondylitis, syphilitic aortitis and other disease processes have also been associated with aortic regurgitation [9]. Most of these lesions

result in chronic aortic regurgitation with a prolonged asymptomatic phase. However, other lesions such as endocarditis and aortic dissection often produce acute aortic regurgitation.

1.2.3. Aortic regurgitation with concomitant aortic root disease

Disease of the aortic root, such as in Marfan Syndrome, dissection, cystic medial necrosis of the aortic wall and chronic dilatation caused by hypertension, is commonly associated with aortic regurgitation [9]. Aortic regurgitation in these patients, at least initially, is mainly or entirely due to the aortic root disease per se with the aortic valve leaflets often being normal for age.

1.2.4. Mixed valve disease

Mixed valve disease is a concurrence of stenosis and regurgitation at a single valve and / or the involvement of multiple valves. The combination of aortic stenosis and aortic regurgitation is common with a large proportion of patients with calcific aortic stenosis having some degree of aortic regurgitation. A more balanced degree of aortic stenosis and regurgitation is less common. Rheumatic heart disease is a common cause of multiple valvular lesions [10].

1.3. Surgery for aortic valve disease

1.3.1. Aortic stenosis

1.3.1.1. Aortic valve replacement (AVR) – Aortic valve replacement is the only effective treatment for severe aortic stenosis in adults. However, the optimal timing for surgery in asymptomatic patients remains unclear. Aortic stenosis is graded as severe when the aortic valve area is smaller than 1 cm^2 [9]. When the aortic stenosis is severe and the cardiac output is normal, the mean aortic transvalvular pressure gradient usually exceeds 50 mm Hg. Others define severe aortic stenosis as the aortic valve area index being less than 0.4 to 0.6 cm^2/m^2 [11].

At present, there are no European or Dutch guidelines in the field of valvular heart disease [12]. The working group on valvular heart disease of the European Society of Cardiology is yet to release their recommendations in this respect. The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly developed guidelines to assist

physicians in the management of selected cardio-vascular disorders and in the selection of certain cardio-vascular procedures, including selection of a valve prosthesis [9]. They have issued the following recommendations for AVR in patients with aortic stenosis.

Definite indications for AVR

- Patients who have severe aortic valve stenosis and present with one or more of its classic symptoms, for example, angina, syncope or dyspnoea.
- Patients with severe aortic valve stenosis who require coronary artery bypass surgery (CABG), surgery of the aorta or surgery for other heart valves.

Possible indications for AVR

- Patients with moderate aortic stenosis who require coronary artery bypass surgery (CABG), surgery of the aorta or surgery for other heart valves.
- Asymptomatic patients with severe aortic stenosis with an ejection fraction of less than 0.5 or an abnormal response to exercise such as hypotension.

As given in the above guidelines, AVR is indicated in symptomatic patients with severe aortic stenosis. However, patients with low-gradient aortic stenosis need to be considered carefully. These may be patients with a low cardiac output and can present with only modest transvalvular pressure gradients, often less than 30 mm Hg. In patients with low cardiac output, it may be difficult to distinguish those with severe aortic stenosis from those with only mild to moderate aortic stenosis, respectively. In the former, the stenotic lesion contributes to the decreased ejection fraction while in the latter, primary contractile failure is the primary cause. In both situations, the low flow rate and the low transvalvular gradient may result in the calculated aortic valve area meeting the criteria of severe aortic stenosis. While surgery is indicated in those with severe aortic disease, even in the presence of low output, it is not indicated in patients without anatomically severe aortic stenosis [9,13].

The indications and timing of surgery in asymptomatic patients with severe aortic stenosis is still debated. The reluctance for surgery in the background of appreciable long-term morbidity and mortality after valve replacement has to be weighed against the possibility of development of irreversible myocardial depression during the asymptomatic stage. The ACC / AHA guidelines attempt to identify high-risk groups among these patients and have identified

those with left ventricular systolic dysfunction and those with abnormal response to exercise, as possibly requiring surgery. However, such a high-risk group is rarely asymptomatic. Although an increased incidence of sudden death has been associated with asymptomatic, severe stenotic patients, the guidelines do not recommend AVR for such patients without any other concomitant finding [9,14].

1.3.1.2. Surgical valvotomy – Although the most appropriate treatment remains controversial, open surgical valvotomy under cardio-pulmonary bypass is considered a realistic approach for the management of aortic stenosis in neonates, infants and children in many centers [15]. Taking into account the possibility of the need for a future valve replacement in these patients, the goal of surgical valvotomy is to delay AVR until the child grows sufficiently to accommodate a larger valve size. In surgical valvotomy, the leaflets of the fused valves are surgically separated to within 1mm of the aortic valve, with an aim to increase the valve opening.

1.3.1.3. Percutaneous balloon aortic valvuloplasty – A less invasive option to surgical valvotomy is percutaneous balloon aortic valvuloplasty. This is a catheterization procedure in which a deflated valvuloplasty balloon is introduced percutaneously into the femoral artery and positioned across the stenotic aortic valve, which is then inflated to decrease the severity of the stenosis. Although this procedure has been shown to be efficacious in children and adolescents with obstruction due to fusion of the commissures, it is of limited value in adults. While early symptomatic relief is usually seen after the procedure, restenosis and clinical deterioration has been reported in most patients within one year. Therefore, in adults, balloon aortic valvotomy is considered only as a palliative procedure to subsequent aortic valve replacement in those patients who are considered high surgical risk candidates or who cannot be considered for surgery [9,16,17].

1.3.2. Aortic regurgitation

1.3.2.1. Aortic valve replacement - Aortic valve replacement is recommended only in severe aortic regurgitation. Severe aortic regurgitation has been defined as clinical and Doppler evidence of severe regurgitation together with dilatation of the left ventricular cavity[9]. While early surgery is indicated for acute severe aortic regurgitation due to infective

endocarditis or aortic dissection, the timing of AVR in chronic aortic regurgitation depends on many factors. Compensatory hypertrophy of the left ventricular musculature that accompanies chronic aortic regurgitation permits the ventricle to maintain a normal ejection fraction. During this compensated phase, which may last for decades, patients remain asymptomatic. The transition to reversible left ventricular dysfunction and then to irreversible dysfunction represents a continuum and is variably associated with the onset of clinical symptoms. The ACC / AHA has issued the following guidelines for AVR in patients with severe aortic regurgitation[9];

Definite indications for AVR

(a) For patients with normal left ventricular function (normal left ventricular function has been defined as an ejection fraction ≥ 0.50 at rest) and;
- New York Heart Association (NYHA) functional class III or IV symptoms.
- NYHA functional class II symptoms and progressive ventricular dilatation or diminishing ejection fraction, on serial studies.
- Canadian Heart Association functional classes II to IV angina pectoris.

(b) For patients with left ventricular dysfunction, with or without symptoms.

(c) For patients requiring coronary artery bypass surgery, surgery of the aorta or of other valves

Possible indications for AVR

(a) For patients with normal left ventricular function and;
- NYHA functional class II symptoms
- Asymptomatic, but with severe left ventricular dilatation (defined as an end-diastolic dimension > 75mm or end-systolic dimension >55mm).

AVR for asymptomatic patients with chronic severe aortic regurgitation remains controversial. However, in such cases, valve replacement is indicated in the presence of left ventricular dysfunction [18]. Even in the presence of normal left ventricular systolic function, valve replacement is indicated for severe left ventricular dilatation [19].

1.3.3. Aortic regurgitation with concomitant aortic root disease

Although there is still no agreement on the optimal treatment for these patients, conventional surgical treatment is to replace the entire aortic root and valve with a composite valve graft ("CVG") which incorporates a mechanical valve (http://www.marfan.org).

Another surgical option is a valve-sparing operation, whereby the aortic root is stabilized with a Dacron graft with preservation of the native aortic valve. Two main types of valve-sparing operations have been described. Sir Magdi Yacoub introduced the aortic root 'remodeling' procedure in 1979 [20] while the aortic root 're-implantation' procedure was popularized by Tirone David in 1988 [21]. Although valve-sparing operations were initially performed only on patients with a normal aortic valve, the procedure has been now extended to those with prolapse of a valve cusp and bicuspid aortic valves respectively [20,22]. However, a "CVG" is recommended in the case of friable or abnormal aortic leaflets and in severe aortic root dilatation [9].

The aortic root wrapping procedure or 'aortoplasty', where AVR is accompanied by a tailoring of the ascending aorta to a smaller size, is less frequently performed at present.

1.3.4. Mixed valve disease

The relative severity, chronicity and order of development respectively of the individual lesions usually determine the clinical presentation and natural history of mixed valve lesions. In the aortic valve, when either the stenosis or regurgitation is mild, the case presentation will be similar to that of the predominant lesion. However, in more balanced cases, the clinical course appears to be that of aortic stenosis. The ACC / AHA have not developed any specific guidelines for the management of mixed valve disease. Hence, each case needs to be considered individually and the management based on the hemodynamic derangement, left ventricular function and probable benefits of medical versus surgical therapy [9,10].

1.4. Range and choice of valve prostheses for aortic valve replacement

Charles Hufnagel, professor of surgical research at the Georgetown University Medical Center, clinically introduced a ball valve into the descending aorta for the treatment of aortic insufficiency. The outer casing and ball of his aortic valve was made of methyl methacrylate (Perspex), which was known to inhibit the coagulation of blood[23,24] (Figure 3).

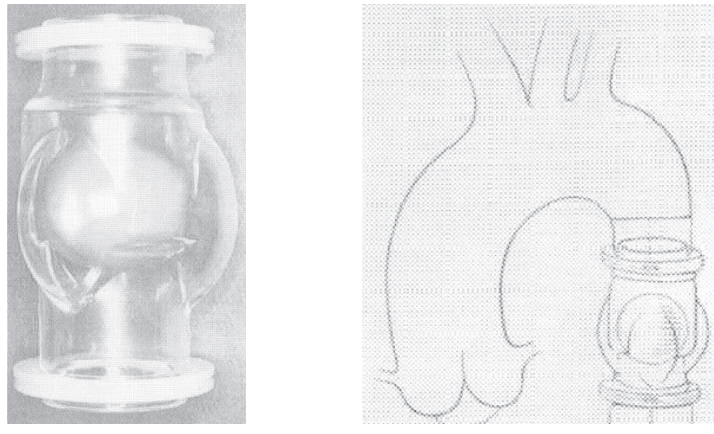

Figure 3. The ball valve used by Hufnagel and an illustration depicting the placement of the valve in the descending aorta.

Since this pioneering effort in 1952, substantial progress has been made in the development of valvular substitutes with more than 80 models of prosthetic heart valves being developed and implanted[25]. Valve prostheses are now placed in the anatomic position, with several types of valve prostheses available for aortic valve replacement. These valve prostheses can be classified into two broad categories according to the origin of their occluding mechanism:

1. Mechanical prostheses
2. Biological prostheses

The choice of particular valve prosthesis for a given patient depends on multiple factors that are related to the patient, physician and the prostheses. These factors include patient age, concomitant disease, pre-operative atrial fibrillation, preference and experience of the attending surgeon, need for and risk associated with anti-coagulation and size of the aortic

orifice respectively. Given the complexity and limited knowledge on many of these factors, the choice of valve prosthesis often involves a subjective judgement. In this background, the ACC / AHA have also developed guidelines to assist physicians in the selection of a valve prosthesis [9]. These practice guidelines are based on previous clinical experience and the consensus opinion of experts in the related fields. However, the guidelines only provide major criteria for choice of a valve and do not provide patient-specific recommendations.

1.4.1. Mechanical prostheses – some examples and the ACC / AHA guidelines for their use

The first aortic valve replacement with an intra-cardiac mechanical prosthesis, which led to long-term survivors, was performed in 1960. Since this pioneering effort by Harken [26], the mechanical valve has become the most popular prosthesis for aortic valve replacement in many countries [27] (http://www.sts.org). Mechanical valves are classified according to their structure as caged-ball, single-tilting-disk or bileaflet-tilting-disk valves (Figure 4). The Starr-Edwards caged-ball valve has been available since the 1960's and comprises a silastic ball, which rests on the sewing ring when closed and moves forward into the cage when the valve opens [28,29]. The single-disk valves, for example, the Bjork-Shiley prosthesis and the Medtronic-Hall prosthesis, contain a disk that tilts between two struts of the orifice housing. Some models of the ill-fated and much publicized Bjork-Shiley valve were prone to fracture of one of its supporting struts [30], and are no longer manufactured.

Figure 4. Mechanical valves: a. Starr-Edwards cage-ball valve, b. Bjork-Shiley mono-leaflet valve and c. St. Jude Medical bileaflet valve.

The most popular of the mechanical valves at present are the bileaflet valves, of which the St. Jude Medical valve and the Carbomedics valve are widely implanted [28,31]. Both these devices are implanted within the aortic annulus. The two semi-circular leaflets of the bileaflet valve are connected to the housing by a butterfly hinge mechanism and swing apart during opening of the valve creating three outflow tracts, one central and two peripheral respectively [25,28,29]. In contrast to the configuration of the latter, the Carbomedics Top Hat (Sulzer Carbomedics, Austin, TX) bileaflet aortic valve that was introduced in 1993, has a unique supra-annular design with all its components incorporated within the aortic sinuses.

The choice of a mechanical valve has its advantages and disadvantages. These valves are durable, with minimal loss of structural integrity, and consequently have lower re-operation rates than other valve types [32]. The negative attributes are due to the higher risk of valvular thrombosis and thrombo-embolism associated with the mechanical valves, which in turn necessitates long-term anti-coagulant therapy with the concomitant risk of bleeding [9,33]. Another potential disadvantage of mechanical valves is due to the sound caused by the closure of the valve. However, the response of the patient to the valve sound depends on various physiological and psychological factors and this has been shown to differ among patients and with different mechanical valve types [34,35].

The indications for implantation of a mechanical valve in the aortic position according to the ACC / AHA guidelines [9] are as follows:

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 who require warfarin therapy due to the presence of risk factors of thrombo-embolism such as atrial fibrillation, severe left ventricular dysfunction, previous thrombo-embolism and hypercoagulable conditions.
5. Patients ≤ 65 years. (This age limit is based on the major reduction in rate of structural valvular deterioration in bioprosthesis after age 65 and the increased risk of bleeding in this group.)

1.4.2. Biological prostheses – some examples and the ACC / AHA guidelines for their use

The biological prostheses include a wide variety of devices. Included within this broad category are the bioprostheses, a term which is used for valves with non-viable tissue of biological origin. The bioprostheses include the heterografts, composed of porcine or bovine tissue and the allografts, which are preserved human aortic valves.

1.4.2.1. Allograft (homograft or donor) valves - Pioneered by Donald Ross in 1962 [36], the first biological valves used successfully for aortic valve replacement were the allografts. The allografts are valves that are transplanted from a human donor. Although fresh valves were implanted initially, logistical considerations led to the evolution of various preservation techniques. Cryopreservation, which permits indefinite storage, has enhanced the availability of this valve type. In recent years the complete allograft aortic root is implanted as a functional unit with concomitant re-implantation of the coronary arteries [37].

1.4.2.2. Autograft valves – Described by Ross in 1967 [38], the autograft is a translocation of the pulmonary valve to the aortic position to replace the diseased aortic valve. Following on the subcoronary and intra-aortic cylinder autograft techniques, the modified Ross procedure was introduced in 1986, whereby the aortic root was replaced with the pulmonary root, with re-implantation of the coronary arteries [39]. An International Registry of the Ross Procedure (http://www.rossregistry.com) was established in 1993, to evaluate the clinical outcomes of these procedures worldwide.

The pulmonary autograft has shown promising results in both children [40] and in adults [41,42]. It brings with it the likelihood of greater durability than other biological valves and the property of further growth of the valve when implanted in childhood. The modified Ross procedure, by using the pulmonary valve in its own functional unit to replace the aortic root, avoids anatomic malpositioning of the valves and reduces the risk of paravalvular leakage [41]. However, the suitability of the pulmonary autograft for aortic root replacement in patients with Marfan's Syndrome, juvenile rheumatoid arthritis and acute rheumatic fever is debated[41]. The demonstrated increase in the autograft annulus and sinus diameters after aortic root replacement [43], may also predispose to subsequent aortic regurgitation.

1.4.2.3. Autologous pericardial valves – In this innovative valve concept developed recently, a kit is used to fabricate a frame-mounted valve from the patient's own pericardium, in the surgical theater. However, no large series are available as yet for proper evaluation of these valves.

1.4.2.4. Heterograft (or xenograft) valves - Heterograft bioprostheses are valves transplanted from another species (porcine) or one that is manufactured from tissues of another species (bovine pericardium). The initial bioprostheses were mounted on stents to which the leaflets and sewing ring were attached but subsequently stentless valves, which are sewn in free hand, have been developed (Figure 5).

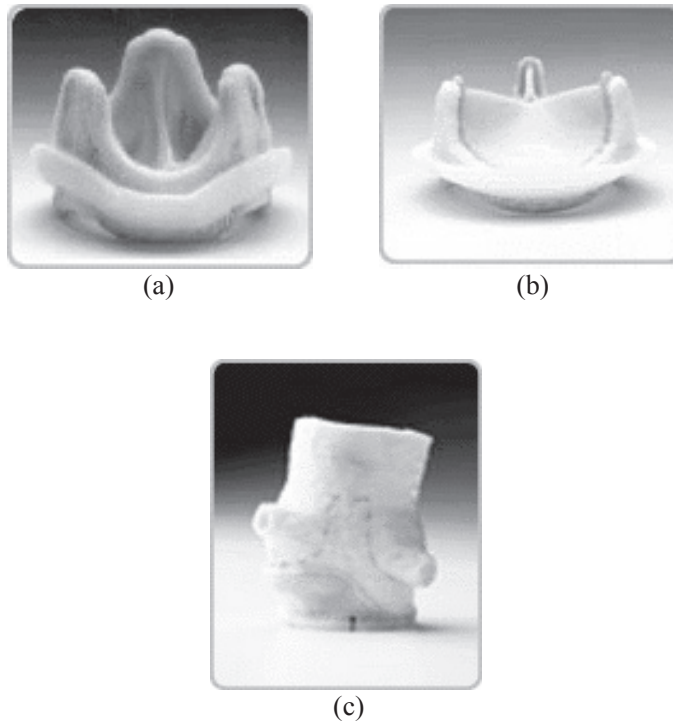

Figure 5. Heterograft bioprostheses: (a) stented porcine bioprosthesis, (b) pericardial bovine bioprosthesis and (c) stentless porcine bioprosthesis

Stented porcine heterograft valves – The stented porcine bioprostheses have been widely used for aortic valve replacement since the early seventies when the first-generation prostheses became commercially available. The Hancock standard prosthesis (Medtronic Inc. Irvine, CA) was introduced in 1971 and the Carpentier-Edwards standard prosthesis (Baxter Healthcare Corp., Edwards CVS Division, Irvine, CA) in 1975 [33,44]. Both these prostheses have an intra-annular configuration and are treated with glutaraldehyde, a substance used for fixing and preserving prosthetic heart valves. The standard porcine bioprosthesis incorporates a muscular ridge at the base of the right leaflet, which may impede hemodynamics by reducing the effective orifice area. With a view to improving the functional effective orifice area, the composite Hancock modified orifice prosthesis was introduced in 1977. This fabrication process eliminated the obstructive septal ridge by substituting the septal leaflet with a non-septal leaflet obtained from a second porcine valve [45,46]. The second-generation valves, the Hancock II and the Carpentier-Edwards supra-annular prostheses, were introduced in the early eighties with the aim of reducing structural valvular deterioration and improving hemodynamic performance. Their leaflets are fixed with glutaraldehyde at low pressure and are treated with surfactant agents to retard calcification. As opposed to the first-generation valves, the second-generation valves are implanted above the aortic annulus but are sutured to it [47,48]. Although widely used in Europe and Canada, the second-generation valves are currently not available in the USA.

Stented bovine pericardial heterograft valves – Rather than being harvested directly, as are the previously described porcine valves, the bovine pericardial valves are fabricated using bovine pericardium, which is sewn into a valvular configuration on a stented frame. This permits more symmetrical and complete opening of the valve with resultant better hemodynamics. Theoretically, greater durability can be expected too, as the fabrication process provides an opportunity to allow extra tissue for eventual shrinkage and a higher percentage of collagen to be cross-linked during fixation. The Ionescu-Shiley valve (Shiley, Inc, Irvine, CA), the first commercially available pericardial valve, was withdrawn in 1988 due to a high incidence of SVD [49]. The second-generation Carpentier-Edwards pericardial bioprosthesis, which received FDA approval in 1991, is widely implanted in many centers at present. It incorporates a sophisticated method of mounting the leaflets on the stent and

thereby obviates the need of stitches passing through the leaflets, a possibly negative feature of the pioneer valve in this class [50,51].

Stentless porcine heterograft valves – In addition to being associated with a less than desirable hemodynamic performance, accelerated fatigue tests have revealed that the artificial stent of the stented heterografts constitutes a major factor responsible for stress on the biological component of the valve. The stent results in suboptimal valve geometry and maldistribution of stress on the leaflets, which is related to the long-term durability of the valve. Accordingly, it was postulated that the natural aortic root could serve as the most efficient stent. The structure of the natural aortic root is such that it dissipates mechanical stress during leaflet closure, reducing the stress on the leaflets, which would translate to enhanced durability [52,53]. With this knowledge, Tirone David in 1988, developed a stentless porcine bioprosthesis, the Toronto SPV valve (St Jude Medical, MN, USA) [54,55]. The inflow tract of this glutaraldehyde-preserved valve is supported by Dacron cloth and it is inserted by a subcoronary implantation technique. Other devices in this category include the Freestyle valve (Medtronic, MN, USA), supplied as the intact porcine aortic root with ligated coronary arteries, which can be implanted using either subcoronary, inclusion root or freestanding root replacement techniques respectively.

The principle advantage of implantation of a bioprosthesis is related to its lack of thrombogeneity. The low risk of thrombo-embolism obviates the need for long-term anti-coagulation in most patients, which consequently results in a lower incidence of hemorrhagic events. The advantage of a bioprosthesis is somewhat mitigated in patients who already require anti-coagulation therapy, for example in those with atrial fibrillation or those with a mechanical valve in another position. The main disadvantage associated with the bioprostheses is their propensity to undergo structural valvular deterioration, which often necessitates re-operation. This is especially pronounced in the younger patients. However, new techniques being employed to minimize valvular stress and retard the calcification process could diminish the risk of valvular deterioration [9,33,56].

The indications for implantation of a bioprosthesis in the aortic position according to the ACC / AHA guidelines [9] are as follows:

1. Patients who cannot or will not take anti-coagulation therapy.
2. Patients ≥ 65 years who require aortic valve replacement, who do not have the risk factors for thrombo-embolism such as atrial fibrillation, severe left ventricular dysfunction, previous thrombo-embolism and hypercoagulable conditions.
3. Patients considered having possible compliance problems with anti-coagulation therapy.

1.5. Outcomes after aortic valve replacement

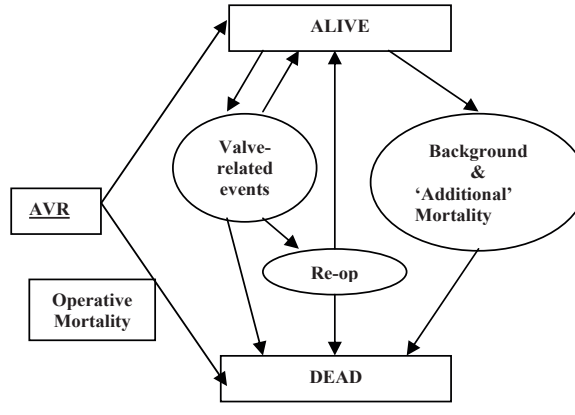

Figure 6. Outcomes after aortic valve replacement.

Figure 6 depicts in general the possible outcomes after aortic valve replacement.

1.5.1 Operative mortality

Following aortic valve replacement, a patient can either die due to the operative procedure *per se*, or can remain alive. Operative (thirty-day) mortality is defined as death within 30 days of operation regardless of the patient's geographic location [57]. According to the Society of Thoracic Surgeons National Cardiac Surgery Database, operative mortality due to isolated aortic valve replacement was about 3% in 2001/ 2002 (http://www.sts.org). This is similar to estimates by Lytle and colleagues, who over a decade ago estimated an operative mortality varying between 2 and 5% [58]. Many factors have been associated with an increased risk of

operative mortality in isolated AVR. Some of these risk factors are age, female gender, diabetes, renal failure, emergency status, previous operation, advanced pre-operative NYHA class, lower cardiac index, concomitant coronary artery bypass grafting and longer aortic crossclamp and cardiopulmonary bypass time respectively [59,60].

The long-term outcome of a patient who remains alive after the operation depends on valve-related and non-valve-related events and mortality.

1.5.2. Valve-related events and sequelae

A patient who survives the operation is at risk of developing specific valve-related events during his or her remaining lifetime. These valve-related events are:

1. Structural valvular deterioration
2. Nonstructural dysfunction
3. Valve thrombosis
4. Embolism
5. Bleeding events and
6. Valvular endocarditis

With the objective of standardizing the reporting of outcomes after valve operations, the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity of the American Association of Thoracic Surgery and the Society of Thoracic Surgeons published guidelines in 1988 [61]. These guidelines were designed to facilitate comparison of outcomes between different surgeons and centers, whose experience may differ, for example, according to the patient cohort, period of surgery and materials and techniques used respectively. In 1996, these guidelines were reviewed in order to update and clarify definitions and to consider other recommendations [57]. The Edmund's guidelines, as they are known, are now widely used in reporting outcomes after valve surgery and have been used throughout this thesis. Hence, a summary of the definitions of the valve-related events and their consequences, as per the updated guidelines, is given on the following page.

Definitions of valve-related events

1. Structural valvular deterioration – Any change in function or deterioration (a decrease of one New York Heart Association functional class or more) of an operated valve due to an intrinsic abnormality, which causes stenosis or regurgitation. Changes intrinsic to the valve include wear, fracture, poppet escape, calcification, leaflet tear stent creep and suture line disruption of the components of the operated valve. The definition excludes changes due to infection or thrombosis.
2. Nonstructural dysfunction (NSD) – Any abnormality that is not intrinsic to the valve per se, which causes stenosis or regurgitation. Examples for this include entrapment of pannus, tissue or suture; paravalvular leak; inappropriate sizing or positioning; residual leak and clinically important hemolytic anemia. This definition also excludes changes due to infection and thrombosis.
3. Valve thrombosis – Any thrombus, in the absence of infection, which is attached to or near an operated valve that occludes part of the blood flow path or that interferes with function of the valve.
4. Embolism – Any embolic event that occurs, in the absence of infection, after the immediate peri-operative period. This could be either a neurologic or peripheral embolic event. A neurologic event includes any new, temporary or permanent focal or global neurologic deficit. A peripheral embolic event is due to an embolus that produces symptoms from obstruction of a peripheral (non-cerebral) artery.
5. Valvular endocarditis – Any infection involving an operated valve diagnosed by customary clinical criteria.
6. Bleeding event – Formerly classified as anti-coagulant hemorrhage, a bleeding event is an episode of major internal or external bleeding that causes death, hospitalization, permanent injury or requires transfusion. This definition applies to all patients, irrespective of anti-coagulation status.

As mentioned previously, the higher risk of valvular thrombosis and thrombo-embolism associated with the mechanical valves necessitates long-term anti-coagulant therapy. The intensity of anti-coagulation was previously measured with the prothrombin time test. However, the International Normalized Ratio (INR) was introduced in the mid 1980's, which enables the expression of anti-coagulation intensity in standardized terms. It is the method of

international communication on the subject at present. High anti-coagulation variability has been identified as an important independent risk factor for reduced survival after AVR with a mechanical valve [62].

Definitions of the sequelae of valve-related events

Re-operation – Any operation that repairs, alters or replaces a previously operated valve.

Valve-related mortality – Death due to any of the six valve-related events or due to re-operation of an operated valve. Sudden, unexplained, unexpected deaths (SUUD) of patients with an operated valve are included in the category.

Cardiac death – All deaths due to cardiac causes and include valve-related deaths and non-valve-related cardiac deaths. Examples for the latter include congestive cardiac failure, acute myocardial infarction and fatal arrhythmias.

Permanent valve-related impairment – Any permanent neurological or other functional deficit caused by the six valve-related events or by re-operation.

1.5.3. Non-valve-related events and mortality

The mortality experience of the general population has been termed the 'background mortality', and will be identified as such throughout this thesis. The mortality hazard function of a patient who survives aortic valve replacement is greater than the mortality hazard function of an age-race-sex matched person in the general population [63]. In other words, patients do not achieve a normalized survival pattern after AVR, illustrating the palliative nature of the procedure. Relative survival is a measure of the excess mortality in patients and is calculated by relating the observed survival to that expected in the general population. Lindblom and colleagues demonstrated that the relative survival of patients was much lower than the actuarial freedom from valve-related death [64]. This points to an increased incidence of 'intercurrent disease' in patients after AVR, which component we have termed 'additional mortality'. Hence, the excess mortality in the AVR patient, compared to a matched person in the general population, is due to valve-related mortality and an 'additional mortality' component. The cause of this 'additional mortality' is largely unknown and is probably related to the increased occurrence rates of cardiac death and sudden unexplained and unexpected deaths seen in patients after AVR [64]. It may be due to valve disease, impaired function and morphology of the left ventricle including cardiomyopathy and factors

introduced by the prosthetic device [65,66]. Another probable component of 'additional mortality' is the underreporting of valve-related events [65]. In general, most late deaths after valve replacement are unrelated to the specific replacement device while cardiac failure and myocardial infarction have been identified as the commonest modes of death [8,64].

1.5.4. Factors affecting long-term outcome after AVR

Apart from the prosthesis-related factors mentioned above, multiple other patient- and surgery-related factors could affect the long-term outcome after AVR [8,60,62,66-69]. Some of these factors are enumerated below:

- Demographic
  - Older age
  - Male sex
  - Black race
- Clinical
  - Higher pre-operative NYHA functional class
  - Pre-operative atrial fibrillation and non-sinus rhythm
  - Pure aortic regurgitation
  - Hypertension
  - Diabetes mellitus
  - Renal failure
- Surgery-related
  - Longer cardiopulmonary bypass time
- Morphological
  - Previous myocardial infarction
  - Left ventricular structure and functional abnormality
  - Previous aortic valve surgery
  - Coronary artery disease (CAD)

The ACC / AHA task force recommends concomitant coronary artery bypass grafting (CABG) for patients undergoing AVR in whom there is significant CAD. However, there is some uncertainty as to whether coronary re-vascularization of patients with CAD undergoing AVR leads to a long-term survival similar to that of patients without CAD requiring AVR [70].

Nunley *et al*. reported that [71] patients who had AVR with concomitant CABG had similar survival to those without CAD, who had isolated AVR. Conversely, other studies have shown that patients, who had concomitant CABG, still had survival rates inferior to those without CAD who underwent AVR [63,72].

1.6. Assessment of long-term outcome after AVR

Many reports have been published up to now documenting and comparing long-term outcomes after AVR with different prostheses, patient groups, surgical techniques and from different time periods and institutions. This published clinical experience provides much information on outcome after aortic valve replacement. Considering the varied and multiple characteristics of an individual patient, it is likely that one or another valve type would have a clear advantage over the others. Given the multitude of available data, the hesitancy of surgical groups over the years in recommending one valve type over another indicate however that there is no clear consensus as per valve choice for the individual patient.

Factors that influence the outcome of a patient group can be identified by the application of the numerous parametric and semi-parametric models for risk factor assessment. The univariate Weibull and Gompertz models and the multivariate Cox proportional hazards model are examples for those commonly used in the literature [73]. By inserting an individual patient's risk factors into the equations of these risk models, one could predict his or her long-term outcomes. Although feasible this not easy as it would require integration of inter-related, time- and event-dependent factors that play a role in that specific outcome. In this background, the microsimulation methodology provides a useful adjunct to standard statistical methods in providing further insight into the outcomes after AVR, which together with clinical judgement and other traditional forms of assessment, will aid in the choice of a valvular prosthesis for the individual patient. This thesis is an attempt to further develop the microsimulation methodology and will focus on mechanical valves and bioprostheses, which account for the majority of implants in AVR.

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1.7. Objectives of this thesis

General Objective – To determine the outcomes of patients after aortic valve replacement with mechanical valves and bioprostheses in order to assist in the selection of a valve type for a given patient.

Specific Objectives

- To further improve the microsimulation methodology to enable objective ascertainment of outcomes after valve replacement
- To use microsimulation to determine the prognosis of patients after aortic valve replacement with bioprostheses and to compare one another
- To use microsimulation to determine the prognosis of patients after aortic valve replacement with mechanical valves
- To provide evidence based estimates to assist in the choice of a mechanical valve or a bioprosthesis for the individual patient.
- To study the effect of coronary artery bypass grafting (CABG) on the outcomes after aortic valve replacement and in the choice of a valve type.

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2. Clinical Decision Analysis and Microsimulation Methodology

2.1. Clinical Decision Analysis

'Decisions have to be made and if they are not made actively, they will be made by default'.
Milton C. Weinstein, Henry J. Kaiser Professor of Health Policy and Management and Biostatistics, Harvard School of Public Health.

Some clinical decisions are straightforward. Many others are more complex and involve consideration and balancing of risks, benefits and costs of the various options, available scientific evidence, patient preferences and the reconciliation of the physician's intuition with rational analysis. Hence, uncertainty about the preferred course of action often prevails in clinical decisions. Clinical decision analysis is a systematic, quantitative technique for evaluating the relative value of alternative options in surgical and health care decision problems [1]. One of the pioneering articles on medical decision-making, written by Ledley and Lusted, was published in Science in 1959 [2]. Although initially developed as a method of assisting physicians in the care of the individual patient, clinical decision analysis is at present also used in the development of management policies for groups of patients and economic evaluations. This technique envisages enhanced, rational clinical decisions and better communication on clinical problems [1,3,4].

The process of clinical decision analysis can be briefly summarized by the following five steps [1,3]:

1. Identifying and bounding the problem – This consists of making the main issue explicit and breaking the problem down into its component parts.
2. Structuring the problem – This is usually done by constructing a decision tree or another appropriate decision model, which depict the components of the decision problem, including for example, the alternative treatment options and possible outcomes.
3. Parameterization of the decision model or 'input' – This entails filling in the constructed model with the probabilities of occurrence of the possible outcomes. Literature review, including meta-analysis, primary data and expert opinion are the sources for this data. A 'quality of life factor' or value could be incorporated into the outcome, whereby patient preferences are also considered [5].

4. Analyzing the model –This involves calculating and synthesizing the risks and benefits of the alternative treatment options. The calculated so-called "expected utility" or value for each alternative helps identify the optimal decision.
5. Sensitivity analysis – This is done to assess the stability of the conclusions of the analysis to the uncertainties in the assumptions made.

We will describe 3 decision models, first the simple decision tree and subsequently the more complex Markov model and the microsimulation model, and their appropriateness in analyzing the clinical decision of choosing an optimum prosthesis for aortic valve replacement. The microsimulation methodology, which is used in this thesis, is described in greater detail.

2.1.1. Decision trees

A decision tree is the fundamental graphical tool of decision analysis. It is a representation of all possible options in a clinical problem and the outcomes that may follow each option. By explicit structuring, a decision tree helps clarify and delineate complex clinical problems [1].

A decision tree consists of nodes and branches and is built conventionally from left to right. There are 3 kinds of nodes, decision nodes, chance nodes and terminal nodes. Of these, a decision node, depicted as a square, identifies the point at which a decision is made and is under control of the decision-maker. The branches of the decision node represent the available options to the problem. Chance nodes, depicted as circles, represent points where the consequences of the initial decision may occur. The numbers under the branches spreading from a chance node indicate the probability of occurrence of these consequences. At any given chance node, the sum of the probabilities sum up to 100%. At the end of each branch of the tree is a terminal node, customarily depicted as a rectangle, which represents the outcome or endpoint.[1,3,5].

A basic decision tree for analyzing the choice of a valve prosthesis for aortic valve replacement, for example in a 65-year-old male, is given in figure 1.

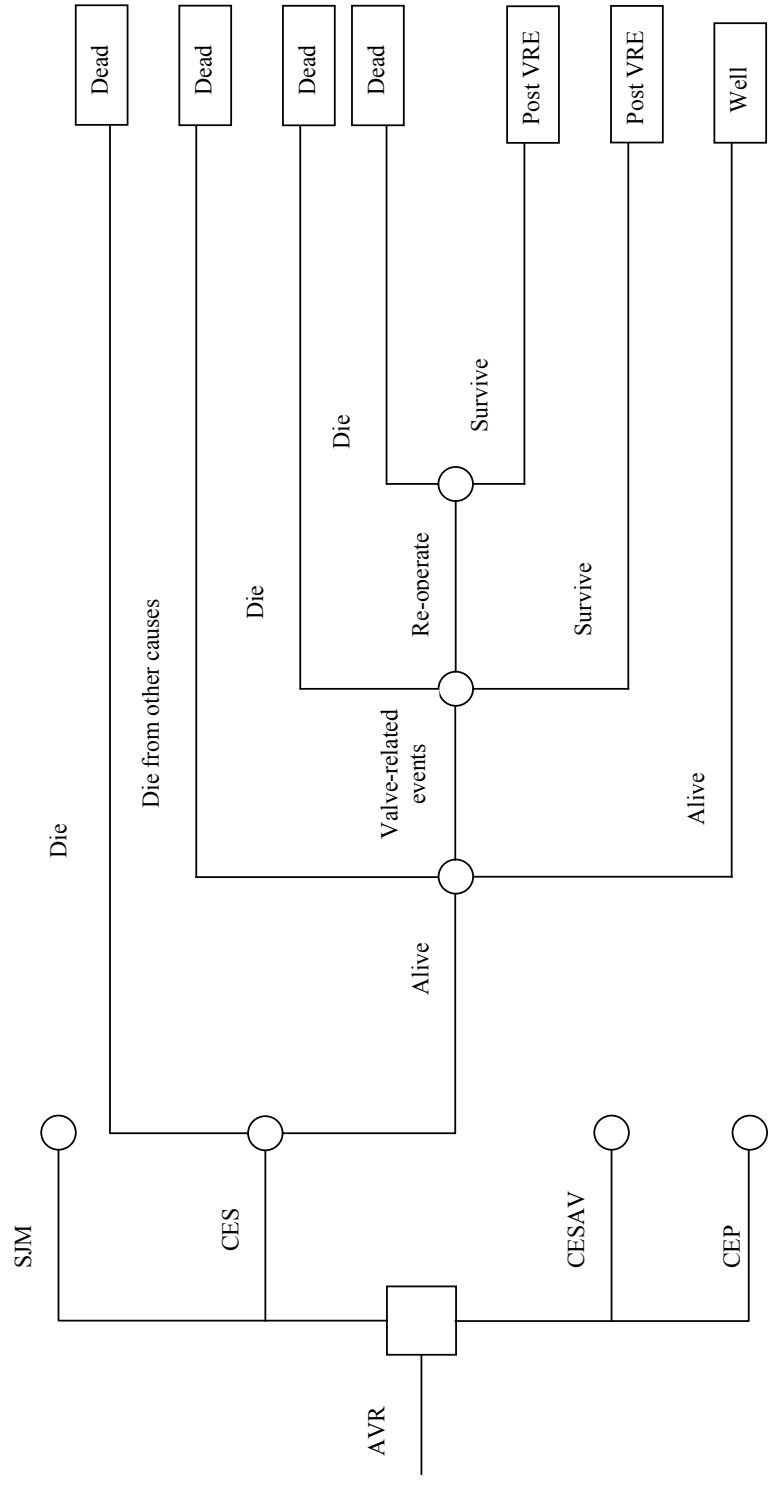


Figure 1. A partial decision tree for AVR depicting the possible consequences and outcomes after implantation of a CES valve. The tree structure has been elaborated for CES. A similar structure will also apply for the other valve types, although the probabilities may differ.

[SJM = St. Jude Mechanical valve, CES = Carpentier-Edwards standard bioprosthesis, CESAV = Carpentier-Edwards supra-annular bioprosthesis, CEP = Carpentier-Edwards pericardial bioprosthesis, VRE = valve related event]

The tree starts with a decision node indicating the choice of a prosthesis from a selected range of prostheses. After implantation, the initial chance node indicates the chance of either dying or remaining alive due to the operative procedure. A patient who survives the operation can remain alive without experiencing a valve-related event, may experience a valve-related event or could die of other causes. Those who experience a valve-related event can die, be re-operated or could survive and remain alive. By parameterizing such a decision tree, one may envisage analysis of the AVR decision problem [6].

A decision tree representation is useful for decision problems with limited recursion and a limited time period. However, following AVR, valve-related events could occur repeatedly over the lifetime of the patient. Life spans of the patients vary, but conventional decision trees usually require stipulation of a fixed time horizon. Further, the probabilities of occurrence of valve-related events vary with patient age and time since the operation. Although decision trees could be expanded to overcome some of these drawbacks, they then become 'bushy' and unmanageable. Hence, although it provides a structure to analyze the AVR decision problem, the complexity of the clinical decision deems the decision tree inadequate for that purpose [1,6].

2.1.2. Markov models

Markov models become useful in clinical decision analysis when the decision problem involves changing risks over time, when the timing of an event is important and when events may occur repeatedly over a long time horizon. The Markov model, named after Professor Andrei A. Markov of St. Petersburg University, Russia (1886), is a state-transition model in which uncertain events are modeled as transitions between defined health states [1,4]. An example of a Markov model, with hypothetical probabilities, as applied to the AVR decision problem is depicted in figure 2.

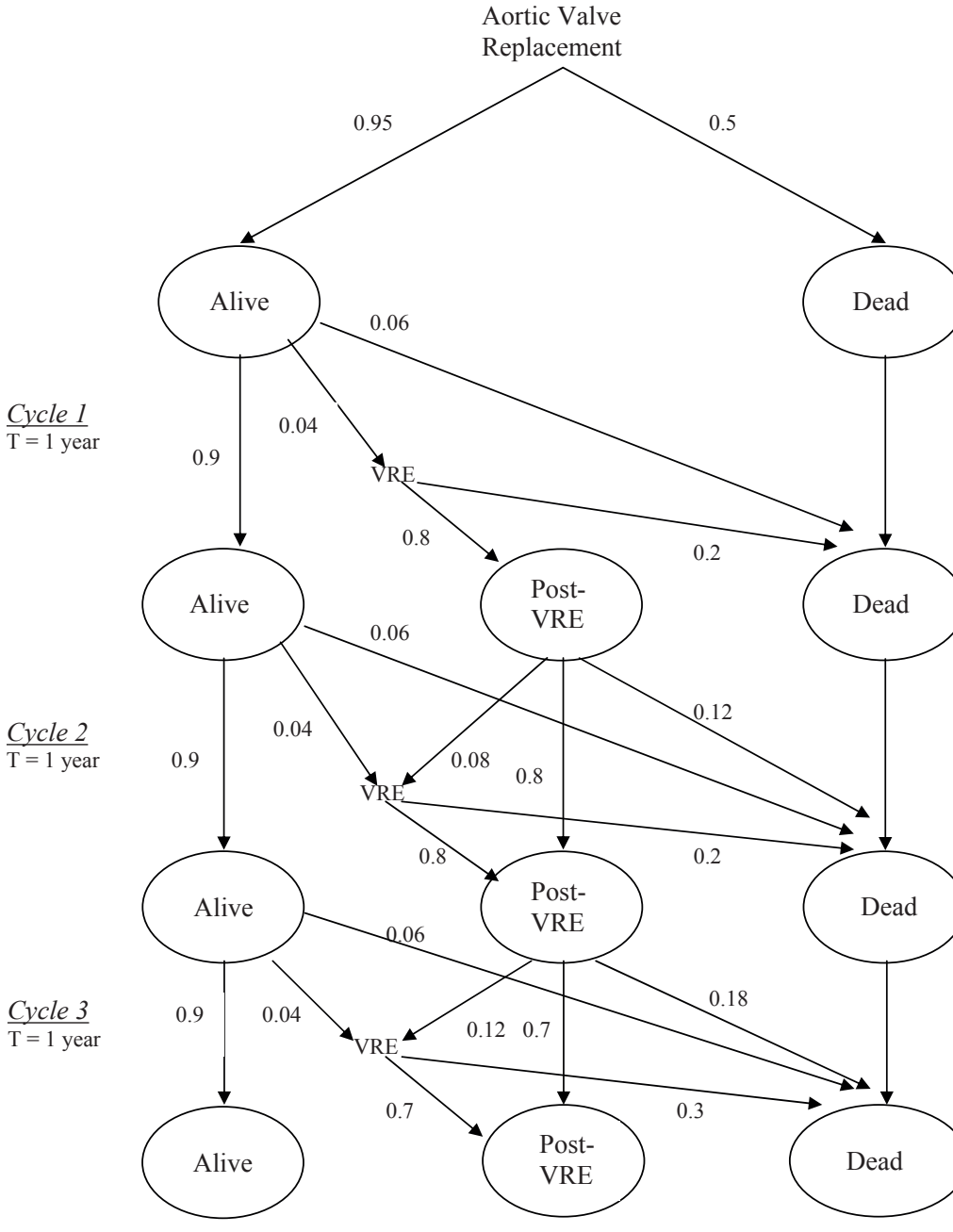


Figure 2. A diagram of a Markov state-transition model for the aortic valve replacement clinical decision problem depicting the health states and hypothetical transition probabilities. [VRE = valve-related event, Post VRE = post valve-related event health state]

The representation of a clinical decision problem by a Markov model entails 4 main steps, as described briefly herewith [1,3,4,6];

1. Initially, the various health states through which the patients may pass are determined. A health state reflects the status in which hypothetical patients reside in between cycles of the model. These health states are mutually exclusive and collectively exhaustive. In the AVR decision analysis, the health states determined were Alive, Post valve-related event (Post-VRE) and Dead respectively. Next, events of interest, for example valve-related events are modeled as transitions between the health states.
2. The time horizon of the analysis is then divided into appropriate time intervals, referred to as cycles. The length of a cycle is the time that elapses between successive evaluations of outcome. The length of a cycle could vary (month, year) and is chosen to reflect the frequency of events that were modeled as transitions and the availability of data respectively.
3. During each cycle, a probability exists of the patient passing from one health state to another. These probabilities are called transition probabilities. They are estimated by methods mentioned previously under 2.1. The transition probabilities could be constant in every cycle (a stationary Markov model) or may vary from cycle to cycle, the latter being more common in most health situations.
4. Finally, the outcome (life expectancy) is determined for the alternative procedures. The methods used for this calculation are not within the scope of the thesis.

At the onset of simulations, an arbitrary hypothetical cohort of identical patients resides in one or more of the defined health states. As simulation proceeds, groups of patients undergo transition to other health states according to the transition probabilities. The simulation continues for a period of time stipulated by the analyst. During this process the model keeps track of the 'value' accumulated by the starting cohort of patients and then calculates an average life expectancy [4].

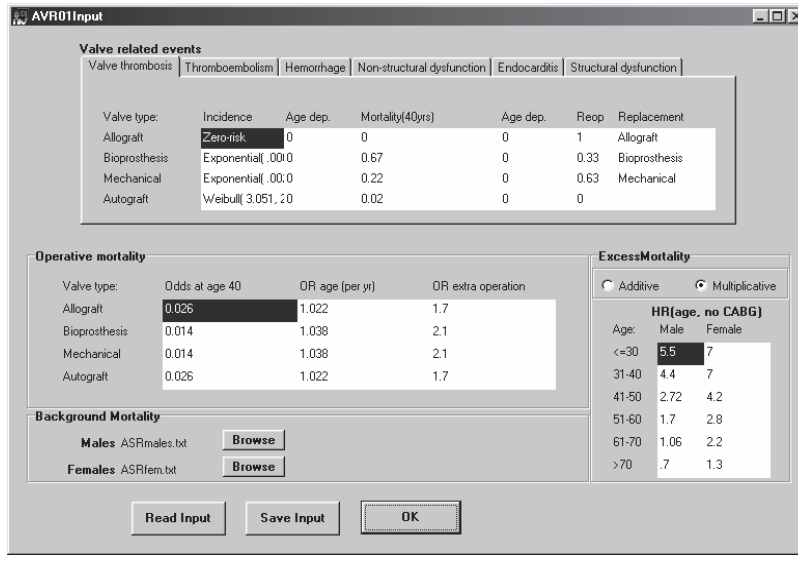
The Markov process is commonly represented graphically. By convention, health states are depicted as ovals and the cycles are defined on the left of the graph. Time runs downward on the graph. The transition probabilities are indicated besides each transition arrow in the diagram. As depicted in figure 2, the Markov model permits valve-related events to occur

repeatedly over time. The model also allows changing probabilities of events over time, which is of importance when modeling, for example, structural valvular deterioration and hemorrhage [1,5,6].

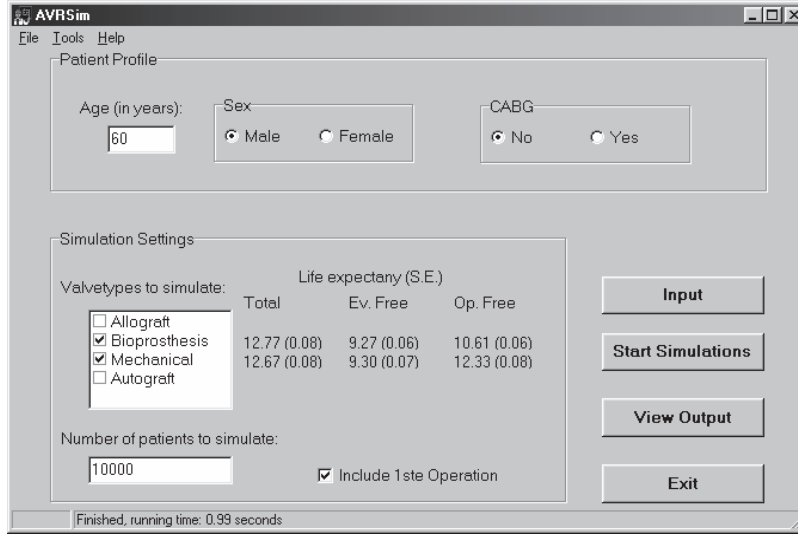
A limitation of the Markov model in analyzing the AVR decision problem is its 'lack of memory' of previous health states. This is known as the Markovian property, which states that the prognosis of the patient depends only on the current health state of the patient and not on the history of prior states. For example, if the patient currently resides in a specific Post-VRE health state, his or her transition probabilities would not be affected by whether he / she had already spent several cycles in that state or had reached that state for the first time. Hence, the Markov model assumes that patients in a particular state are homogenous. This is not in accordance with most clinical situations, including after AVR, where patient prognosis depends among other factors on co-morbid conditions and previous disease status respectively. However, this shortcoming can be overcome to some degree by incorporating additional states (tunnel states) into the model, but at the expense of increasing the complexity of its structure [1,5].

2.2. The microsimulation methodology

Microsimulation, a technique developed in the field of operational research, has since been used to model disease screening programs [7,8] and in health economics [9]. In contrast to Markov models, which simulate the outcome of large cohorts of patients, microsimulation directly simulates the life histories of individual patients. This is done by aging the individual, modeling progression of the disease and by updating the individual's disease status, as he or she passes through the model. Instead of dividing the time horizon into cycles during which events may occur or not, as done in the Markov models, microsimulation uses the probability distributions of time-to-events. The time-to-events for each individual patient are obtained by computer generated random numbers. This process of drawing numbers resembles a casino game, hence the name Monte Carlo Simulation after the casinos in Monte Carlo, Monaco [1,10]. The structure of the microsimulation model as applied to the AVR decision problem and the advantages and disadvantages of the model are described in chapter 3. The interfaces of the model are depicted in figure 3.



(A)



(B)

Figure 3. The interfaces of the microsimulation model. (A). Data input interface of the model (B). Output interface of the model. Details of patient profile are also entered here.

2.2.1. Parameters and assumptions of the microsimulation model

2.2.1.1. Background mortality – The mortality of a patient who survives the AVR procedure is greater than that of a matched individual in the general population [11]. The mortality of such a patient comprises three components, namely the background mortality, mortality due to valve-related events and an 'additional mortality'. The mortality experience of the general population, to which the patient belongs, is called the background mortality. The background mortality was incorporated into the microsimulation model by means of life tables of the relevant populations. In this thesis, American and Dutch life tables were used to incorporate the background mortality.

2.2.1.2. 'Additional mortality' – The excess mortality of an AVR patient, in relation to a matched individual in the general population, is due to valve-related events and an 'additional mortality' component respectively. This 'additional mortality' may be due to the underlying pathological process of the diseased valve, left ventricular residual hypertrophy and functional abnormality and to the valve replacement procedure per se [12,13]. It may in part be explained by the increased cardiac deaths and sudden unexplained unexpected deaths (SUUD's) experienced by AVR patients [6]. However, the 'additional mortality' is not clearly defined and estimated at present. Hence, we estimated age- and sex-specific hazard ratios to represent its effect. This was done by approximating age- and sex- specific survival curves produced by the model, which contained the background mortality and mortality due to valve-related events, to the corresponding empirical curves obtained from the literature, which contained all three components of patient mortality. For example, hazard ratios of 2.9, 1.8, 1.2 and 0.8 were estimated for male patients aged 45, 55, 65 and 75 years respectively.

The 'additional mortality' after AVR could be either 'additive' or multiplicative'. Birkmeyer and colleagues [14], who applied a Markov state-transition model to the AVR decision problem, were of the opinion that this additional mortality was solely determined by coronary artery disease and hence assumed an 'additive' effect. They added an excess mortality of 1.2% yearly to the life table estimates of the US general population. Kvidal and colleagues [11], who investigated the excess mortality of patients after heart valve replacement, described an increasing excess hazard with advancing age and a decrease with advancing age at valve implantation. This suggests a 'multiplicative' excess hazard. We used the latter as a structural

assumption of the model throughout this thesis. Note that both 'additive' and 'multiplicative' assumptions can be incorporated into the microsimulation model.

2.2.1.3. Operative mortality – The risk of operative mortality in AVR depends on many factors. These include the type of prosthesis, age of the patient, elective or urgent status, etiology of valve lesion, concomitant procedures and re-operation respectively [15]. Data on AVR from the Society of Thoracic Surgeons (STS) National Cardiac Surgery database in the USA depicts the increasing risk of operative mortality with advancing patient age (http://www.sts.org). These data also describe an increasing risk of operative mortality with re-operation. The microsimulation model allows for modeling of an increasing operative mortality with advancing age of valve implantation and with re-operation. We assumed an operative mortality of 1.5% for a 40-year-old male increasing with odds ratios of 1.022 per year for age and 1.7 for every re-operation. With incorporation of CABG into the model, an analysis of the STS database was used to estimate the operative mortality for the model [15]. For a 65-year-old male for example, the operative mortality was 5.2% and 3.3% respectively, with and without CABG.

2.2.1.4. Valve-related events – In order to carry out simulations, the appropriate probability distributions need to be specified [10]. The following distributions were modeled for the valve-related events that a patient may experience after AVR with either a mechanical valve or a bioprosthesis respectively;

a. **Zero risk** – This implies no risk of the event occurring.
   - The mechanical valves in theory have a zero risk of structural valvular deterioration (SVD) and were so modeled. Although the Bjork-Shiley valve was shown to have a risk of strut failure [16], it is no longer in production and was not included in this thesis.

b. **Exponential distribution** – The exponential distribution describes a constant risk of an event over time. The annual risk of the event is usually given as the linearized annual occurrence rate (LOR) [17].
   - Valve thrombosis, thrombo-embolism and NSD, in both mechanical and tissue valves, were modeled with exponential distributions throughout this thesis. It is likely that the risk of valve thrombosis and thrombo-embolism is somewhat elevated during the first few days and months after AVR, prior to full endothelialization of the valve and

optimum anti-coagulation [18,19]. However, the assumption of a constant hazard is considered an acceptable approximation [17].

- Comparing different time periods of implantation, a significant decrease in early prosthetic valve endocarditis has been described in recent years. This indicates a more or less constant hazard over time [20]. Hence, an exponential curve was used to model endocarditis in some studies included in this thesis.
- Because of the increased risk of valve thrombosis during the first three months after AVR with a bioprosthesis, oral anti-coagulation with warfarin is recommended during the initial period, which is associated with an increased risk of hemorrhage [18]. This risk is minimized by the exclusive use of aspirin in some centers [19]. Further, the majority of patients do not require long-term anti-coagulation after implantation of a bioprosthesis [21,22]. Therefore, assuming a constant risk over time, hemorrhage after AVR with a bioprosthesis was modeled exponentially.

c. **Two-period exponential distribution** – This describes an increased hazard during a pre-defined period immediately after AVR, followed by a constant baseline hazard.
   - Some studies show an increased hazard followed by a constant hazard for prosthetic valve endocarditis [20]. Hence, this complication has been modeled using a two-period exponential distribution, in some component studies of this thesis.

d. **Weibull distribution** – This is a generalization of the exponential distribution, which incorporates an additional shape parameter to reflect changing risks over time [23].
   - SVD is a drawback in bioprostheses. The risk of SVD in a bioprosthesis increases with the time elapsed since implantation and decreases with implantation age. It has been previously demonstrated that the Weibull distribution is efficient in summarizing SVD in bioprostheses [24,25] and hence, was used to model SVD.

e. **Gompertz distribution** – This describes an exponentially increasing risk over time.
   - All patients receiving a mechanical valve require long-term oral anti-coagulation with warfarin, which as mentioned, is associated with an increased risk of hemorrhage. The intensity of oral anti-coagulation is measured by the International Normalized Ratio (INR), which is the universal scale for reporting prothrombin time results [26]. A study conducted at the Leiden Thrombosis Service, Leiden, The Netherlands, on the frequency of major bleeding complications determined age and INR as the most important and consistent risk factors for anti-coagulant-related hemorrhage [27]. We

used data from this study to construct a Gompertz distribution to model hemorrhage after AVR with mechanical valves.

The consequences of valve-related events (re-operation, death) are incorporated into the model as risks. In the event of re-operation, the model allows specification of the replacement valve type. In case of SVD in a bioprosthesis, a mechanical valve was specified as the replacement device.

2.2.2. Parameterization of valve-related events in the microsimulation model

In order to simulate the life histories of patients after AVR, the model requires data 'input' on the valve-related events and their consequences experienced by patients after AVR. This information was obtained by systematic literature reviews coupled with meta-analysis and from primary data respectively.

2.2.2.1. Literature review and meta-analysis – Meta-analysis is of published data, also termed type II meta-analysis, was used throughout this thesis. Type II meta-analysis can be done on published data without the consent and cooperation of the respective authors [28]. However, many of the authors of the selected publications were contacted for further information and clarifications. The basic procedure employed in this thesis to review the literature and select publications for the meta-analysis is described herewith.

A comprehensive literature search of the Medline database was conducted using the PubMed search interface. The need for the most recent studies, adequate numbers of publications and the requirement for the use of standardized criteria for event assessment dictated the time span for this search. The MeSH terms and the text words required for the Medline search were ascertained by review of previous publications and from expert opinion. The results of the search were screened by their titles and abstracts, for those that described outcomes after AVR with the relevant prosthesis. Further, the references in the identified publications were cross-checked for other potentially relevant studies.

Given several studies of a particular prosthesis, one might expect similar complication rates, which do not vary significantly from one another. However, since these studies differ in their designs, patient populations, data collection methods and definitions of variables, considerable variations in outcome are seen. It is emphasized that pooled estimates should not be calculated in case of considerable heterogeneity between studies [17,28]. In order to obtain a similar group of studies, several criteria were applied to the selected publications. Further, studies not adhering to the Edmund's criteria were excluded. Following this process of elimination, possible heterogeneity in the remaining publications was investigated by means of sensitivity analysis. This finally resulted in a group of similar publications, which were then scrutinized in detail for data required for calculating the input parameters of the microsimulation model.

When a constant hazard over time was assumed for a valve-related event, weighted mean linearized rates were computed by summing all events and dividing by the sum of all the follow-up years. Pooling of individual time-to-event curves was performed for endocarditis and SVD [29]. This was done as follows: The selected curves were scanned and enlarged in a graphical computer package. The heights of the curves were measured at each year. Next, the corresponding survival probabilities and their complimentary log-log transformations were calculated. These transformed probabilities were pooled with weighting according to the estimated number of patients at risk at each year. Re-transformation of the weighted-pooled estimate resulted in the summary curve. Two-period exponential curves and Weibull distributions were fitted to the summary curves in order to calculate the respective parameters, which were used in the microsimulation model. Combined mortality and re-operation after event were also calculated.

2.2.2.2. Primary data – The following data sets were used to directly calculate the parameters of the respective Weibull distributions for the Carpentier-Edwards pericardial bioprostheses and Carpentier-Edwards supra annular bioprostheses respectively.

(a). Carpentier-Edwards pericardial bioprostheses

- Source - Edwards Lifesciences, LLC, Irvine, CA, USA.
- Number of patients - 267
- Period during which valves were implanted – 1981 through 1984

- Follow-up period – 18 years

(b). Carpentier-Edwards supra annular bioprostheses

- Source – Dr. W.R.E. Jamieson, University of British Columbia, Vancouver, Canada.
- Number of patients – 1823
- Period during which valves were implanted – 1982 through 1999
- Follow-up period – 20 years

2.2.3. Validation of microsimulation model outputs

To verify the validity of its calculations, the microsimulation model was run for patients of different ages and sex, receiving a particular valve type. The actuarial survival curves produced by the model were then compared with the corresponding curves obtained from the literature and with those obtained from primary data. The goodness of correspondence was visualized.

2.2.4. Sensitivity analysis

Sensitivity analysis is defined as a test of the stability of the conclusions of an analysis over a range of structural assumption, probability estimates or outcome values [1]. In one-way sensitivity analysis the value of one probability is varied while the others are kept constant. One-way sensitivity analysis was conducted in this thesis, whereby the uncertain variables were varied over a plausible range (for example, 95% confidence interval) and the model outputs were re-calculated. In a clinical decision analysis, for example in the choice of a valve for a given patient, if the result of the sensitivity analysis does not have an impact on the decision, the precise value of the parameter is irrelevant. However, if the decision does change, it then warrants further study on the precise value of the parameter [1].

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3. Simulation Models to Predict Outcome after Aortic Valve Replacement

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3.1. Introduction

Which valve substitute would you prefer to implant in a 63-year-old male patient? And which valve substitute would in your opinion be best for a 36-year old woman? It can be quite complicated to predict prognosis after implantation of a certain aortic valve substitute in the individual patient who requires aortic valve replacement. Multiple interrelated factors (patient-, physician-, and prosthesis-related) affect outcome after aortic valve replacement. Published clinical experiences provide information on outcome after aortic valve replacement on a group level. By applying standard parametric and semi-parametric models for risk factor assessment, it is possible to identify factors that may influence long-term outcome in that particular patient group. One can translate this to the outcome in the individual patient by inserting his or her risk factors into the equation for the model. Although feasible, it is often not an easy task as it necessitates integration of information on many interrelated factors that simultaneously play a role. Simulation techniques may provide in this respect a useful adjunct to standard methods, since they allow modeling of complex outcome paths resulting from many simultaneous risks.

Recently, several authors reported on the use of simulation techniques to predict outcome after aortic valve replacement and to support prosthetic valve choice[1-4]. These studies employ a complex and mostly unknown methodology, and are therefore often difficult to interpret. This report focuses on the microsimulation method that is used in this thesis and describes the background and structure of the aortic valve replacement model, illustrates the steps that are taken during one simulation cycle and highlights the advantages and disadvantages of the use of this methodology.

3.2. Background and structure of the microsimulation model

Simulation methodologies emerged from the field of operational research. The best known example of a simulation program is the flight simulator used in the aviation industry to simulate flights and train pilots.

The 2 types of simulation models that are currently used to model outcome after aortic valve replacement are the Markov state-transition model and the microsimulation model. Both models are state-transition models and based on the same principle: patients who undergo aortic valve replacement can enter a number of discrete health states over time, and transition occurs from one health state to another according to transition probabilities. Although the basic assumptions of the Markov and the microsimulation model are similar, there are a few important differences between the models: using the Markov model a virtual population is followed over time (at population or 'macro' level), while the microsimulation model allows simulation of the life histories of individual patients (at patient or 'micro' level). Also, in the Markov model time is divided into intervals during which events may or may not occur, with microsimulation the time to next event is estimated based on the probability distribution of that event. Finally, the Markov model has no memory, i.e. it assumes that subjects in a particular state are a homogeneous group without variability, while microsimulation allows adjusting of hazards for the individual patient depending on prior events (for example increasing operative mortality with each reoperation).

To date, microsimulation techniques have been used sporadically in clinical medicine studies. A PubMed search for the term "microsimulation" dated July 6 2002 resulted in 63 publications that are mainly related to health economics, for example the cost-effectiveness of screening programs. A schematic representation of the basic principle of the microsimulation model is given in Figure 1. After aortic valve replacement the patient can either die as a result of the procedure or stay alive. If the patient stays alive, he or she is at risk for developing valve-related events for the remainder of life. If the patient experiences a valve-related event, he or she may die due to the event (immediately or as a result of reoperation) or stay alive (with or without reoperation). Eventually the patient will either die of valve-related causes or due to other mortality. "Other mortality" includes first of all the mortality that is observed in the general population, and in addition excess mortality that is observed in patients after aortic valve replacement in comparison to the general population and which cannot be explained by valve-related events[5-7]. Important

causes of this excess mortality are largely unknown but are most likely due to increased occurrence rates of cardiac death and sudden unexplained and unexpected death in patients after aortic valve replacement compared to the general population. Underreporting of valve-related events is probably also a component of excess mortality.

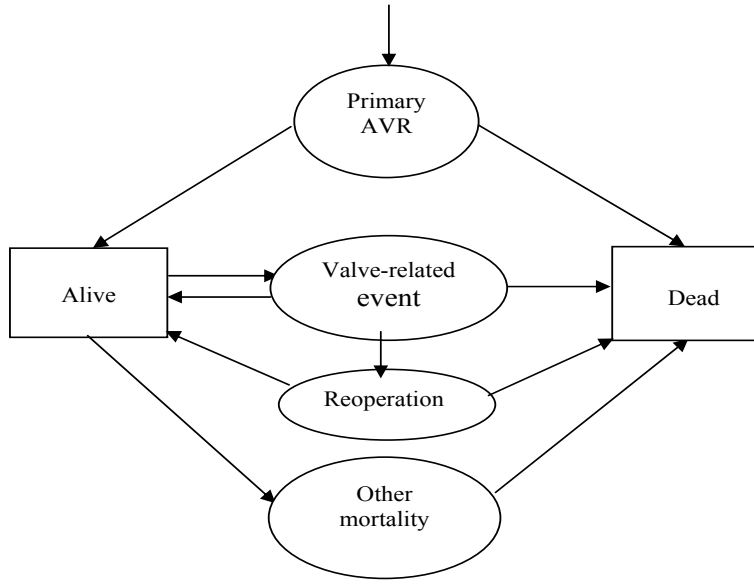


Figure 1. Schematic representation of different health states of a patient after aortic valve replacement as implemented in the microsimulation model.

The microsimulation model is comparable to a flight simulator in the aviation industry: a flight simulator simulates flights of a particular airplane on a particular route, taking in to account several conditions like the type of weather and possible chances of malfunction of parts of the plane. Microsimulation simulates the lives of particular patients after aortic valve replacement with a particular valve, taking in to account several valve-related events that may occur during a particular remaining life expectancy. If microsimulation of a particular patient is repeated several times, a 'virtual' patient population is created, consisting of patients with identical characteristics and with all possible outcomes after aortic valve replacement one can think of. This is the main power of microsimulation: It actually simulates individual life histories of numerous (for example 10,000) virtual patients with the same characteristics, allowing insight into all probable outcomes after aortic valve replacement for that particular patient and the importance of the individual

valve-related events. From this large dataset with identical patients the average prognosis of an individual patient with those characteristics can be calculated.

In order to make predictions using microsimulation it is necessary to obtain real-life estimates of the occurrence of valve-related events after aortic valve replacement and the effect they have on prognosis. In other words, the limited clinical evidence from real-life practice is used to feed the model with information on outcome after aortic valve replacement. Currently, the aortic valve replacement microsimulation model is fed by pooled complication rates from systematic literature reviews and primary data on outcome after aortic valve replacement.

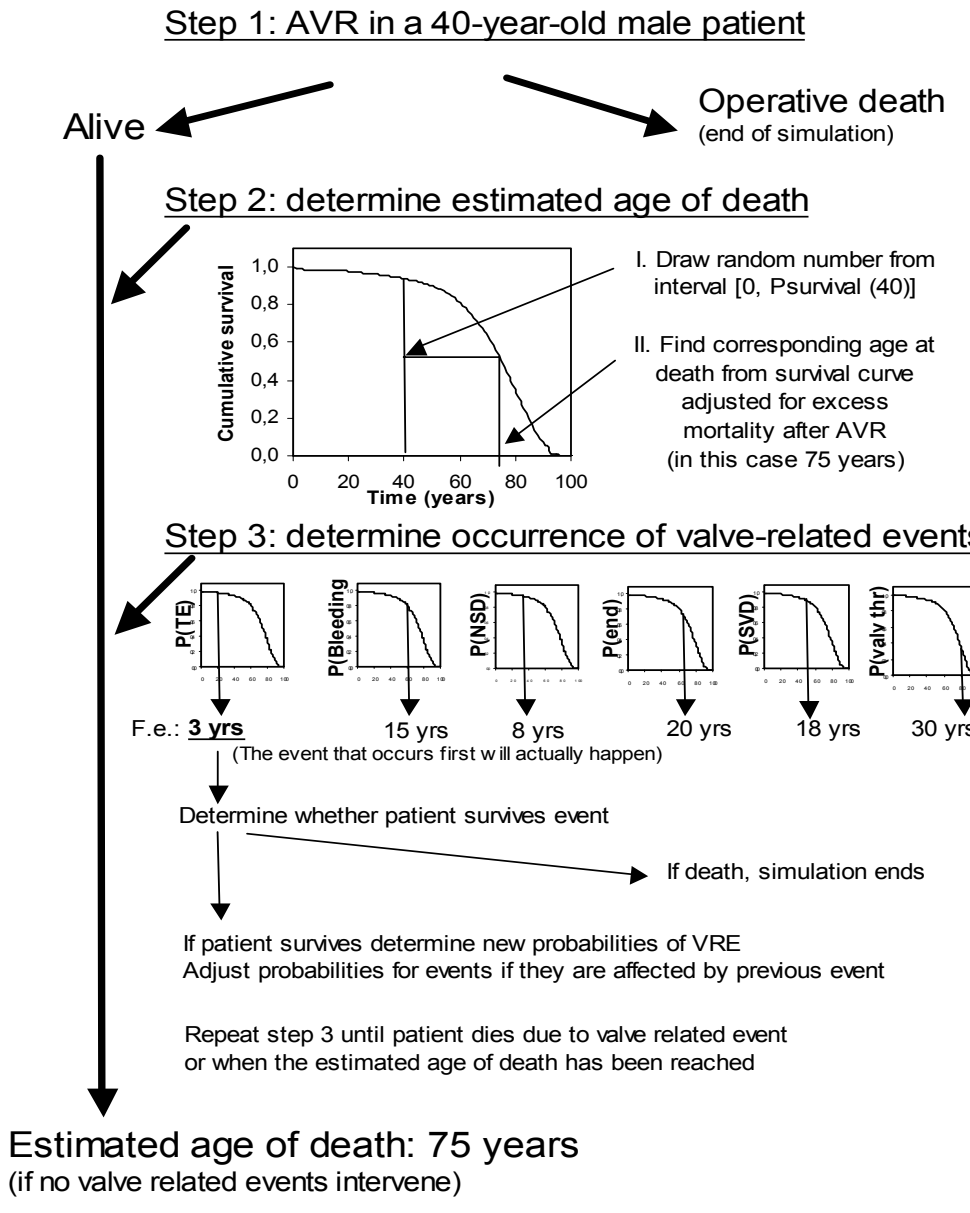
3.3. Microsimulation step-by step

Figure 2 represents the microsimulation of one life history of a 40-year-old male individual in a population of 40-year-old males requiring aortic valve replacement. A number of steps can be discriminated:

Step 1. First, it is randomly determined whether the patient will survive the operation. Operative mortality is dependent on the age of the patient and of the valve type that is implanted. Let's assume that the patient survives the operation. Next, the real microsimulation process begins.

Step 2. From the general population life table for 40-year-old males the age of death is randomly drawn and adjusted for excess mortality after aortic valve replacement by applying an age- and gender-specific hazard ratio to the general population life table. The random draw in this example results in death at the age of 75, if no valve related events interfere.

Step 3. Next, for all valve-related events the virtual age at which they will take place is calculated by randomly drawing the age at which each valve related event would take place from the distribution of the duration until each valve related event, starting at the time of primary valve surgery. This distribution can be based on linearized occurrence rates but also on hazard estimates that change over time (for example, the hazard for structural valve deterioration of tissue valves increases with time). The valve-related event with the earliest age of occurrence is considered to be the first event that really happens. The probability of immediate mortality due to the event is used to randomly determine whether the patient will die of the event or not. In the first case the simulation of this patient ends, in the latter case the simulation goes on and the time to the next event is determined.



Step 4: repeat Step 1-3 many times to create simulated population

Figure 2. Illustration of steps taken during one microsimulation cycle.

(P(TE), P(NSD), P(end), P(SVD), P(valv. thr) = freedom from thrombo-embolism, non-structural dysfunction, endocarditis, structural valvular deterioration and valve thrombosis respectively. VRE = valve related events.)

If the distributions of time until events are affected by the event that just occurred, new random times until event are drawn from the adapted distributions. Again the event with the earliest time of occurrence will be the one that really occurs. This process continues until the patient either dies from a valve-related event, or the estimated age of death has been reached, which is 75 years in this example. Of note, it is very well possible that the patient dies without experiencing valve-related events.

Step 4. This simulation cycle is repeated for a large number of random 40-year-old male patients (for example 10,000 or 100,000), and thus a virtual population of 40-year-old males with all possible outcomes after aortic valve replacement is created. From this population average estimates of outcome can be calculated, for example event-free life expectancy, total life expectancy, and lifetime event risk.

The more patients are simulated, the more precise the estimates of outcome become since random noise disappears. This phenomenon is also illustrated in Figure 3, which shows a known distribution, in this example an exponential distribution for mortality with a hazard of 3% per year (dotted line). From this known distribution 4 random samples of time to death are drawn, with sample sizes of 5, 15, 35 and 100 patients. The Figure shows that by increasing the sample size of random draws the empirical distribution function will more and more approach the true distribution function.

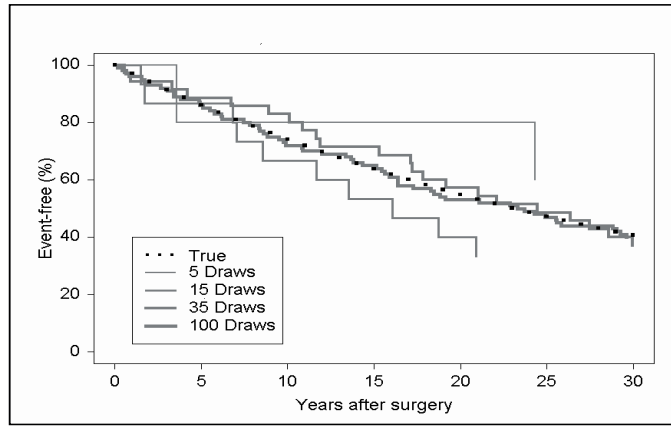


Figure 3. Example of four random draws (n = 5, 15, 35 and 100) from a known distribution, illustrating that by increasing the sample size the estimates of outcome become more precise. Increasing widths of the solid lines indicates the increasing sample sizes and the true underlying distribution is depicted by the dotted line.

3.4. Advantages and disadvantages of microsimulation

The example in Figure 2 showed that microsimulation is not only capable of (1) taking in account life expectancy of the patient, (2) changing hazards over time and (3) allowing events to occur repeatedly over time, but also of (4) adjusting hazards depending on events that occurred in the past. In addition, it allows detailed insight into the life history of each virtual patient, including the duration of the event-free period, the total number of years lived and the numbers of each of the events per patient. Standard statistical techniques for outcome analysis also address each of these issues, individually. The added value of microsimulation is that it integrates these multiple, complex and interrelated factors that determine outcome after aortic valve replacement.

Three major disadvantages of the microsimulation model are (1) that it is a simplification of real life, (2) it requires several assumptions regarding mortality after aortic valve replacement and the occurrence of valve-related events, and (3) it is limited by the quality of the input.

By structuring the clinical problem, simplification of reality can not be avoided. To date, the microsimulation model only considers age and gender when calculating prognosis, while a number of other factors are also important determinants of outcome, for example the need for concomitant coronary artery surgery, etiology of the aortic valve disease, heart rhythm and left ventricular function. Therefore, it is yet unable to make predictions taking in account all these important additional risk factors. These risk factors should, and ultimately will, be integrated into the microsimulation model to give more precise patient-specific estimates. However, by enabling us to make age-and gender-specific estimates of outcome, the microsimulation model is already helping us to get some rudimentary insights into overall patient prognosis.

Several assumptions are necessary when using microsimulation. First of all an excess mortality hazard after aortic valve replacement is assumed. As explained above this is done because the additional mortality that is observed after aortic valve replacement can only in part be explained by valve-related events. The causes of this additional mortality are probably related to the heart valve disease, associated with myocardial muscle abnormalities, and increased risk of heart rhythm disturbances. Future research should be aimed at improving knowledge on these causes of excess mortality. Also, several assumptions are made with regard to the occurrence of valve related events. For example

the hazard for thrombo-embolism is constant with time and patient age, while in fact there is evidence that with age this hazard increases. However, this hazard also increases in the general population and is therefore implemented in the background mortality of the model that is based on the general population. Further studies are necessary to study the true relation between thrombo-embolism, time and patient age.

The quality of the input of the model is the third potential limitation to a microsimulation model. Since most of the input of the model is currently obtained from pooled reported clinical evidence, the quality of the input may be adversely affected by heterogeneity between the studies and publication bias. Also, the estimated hazards obtained from current clinical evidence that are entered into the aortic valve replacement microsimulation model all carry some uncertainty. For example, the structural valve failure hazard for bioprostheses and allografts varies with patient age. Empirical data on this subject are scarce and have a limited follow-up. This results in a considerable degree of uncertainty regarding this parameter. By means of sensitivity analysis one can investigate the magnitude of the effect that this uncertainty may have on the outcome of the microsimulation model.

3.5. Conclusion

Is microsimulation a valid tool for prediction of outcome after aortic valve replacement? The methodology is only as good as the assumptions that define the model, and the available reported evidence from which the parameters of the model are estimated. An advantage of this method is that it is easy to change the input of the model as new evidence on outcomes after aortic valve replacement becomes available. Ideally, this methodology could eventually be individualized to the patient sitting across the table in the doctor's office deciding what the most appropriate valve substitute is in his or her particular clinical situation. Microsimulation and associated simulation techniques have the potential to become an additional dynamic source of insight into the prognosis after aortic valve replacement.

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Prognosis after Aortic Valve Replacement with Mechanical Valves and Bioprostheses

4. Prognosis after Aortic Valve Replacement with a Bioprosthesis: Predictions based on Meta-analysis and Microsimulation

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Key words: heart diseases, surgery, valves, meta-analysis, prognosis, survival.

Abstract

Background: Bioprostheses are widely used as an aortic valve substitute, but knowledge on prognosis is still incomplete. The purpose of this study was to provide insight into the age-related life expectancy and actual risks of re-operation and valve-related events of patients following aortic valve replacement with a porcine bioprosthesis.

Methods and Results: We conducted a meta-analysis of nine selected reports on stented porcine bioprostheses, including 5837 patients with a total follow-up of 31,874 patient years. The annual rates of valve thrombosis, thrombo-embolism, hemorrhage and non-structural dysfunction were 0.03%, 0.87%, 0.38% and 0.38% respectively. The annual rate of endocarditis was estimated at 0.68% for after 6 months of implantation, and 5 times as high during the first 6 months. Structural valve deterioration was described with a Weibull model, incorporating lower risks for older patients. These estimates were used to parameterize, calibrate and validate a mathematical micro-simulation model. The model was used to predict life expectancy and actual risks of re-operation and valve-related events following implantation for patients of different ages. For a 65-year-old male, these figures were 11.3 years, 28% and 47% respectively.

Conclusions: The combination of meta-analysis with micro-simulation enabled a detailed insight into the prognosis following aortic valve replacement with a bioprosthesis for patients of different ages. This information will be useful for patient counseling and clinical decision making. It also could serve as a baseline for the evaluation of newer valve types.

4.1. Introduction

Nearly 40 years after the pioneering efforts of Starr and Edwards in heart valve replacement, a wide variety of mechanical, bioprosthetic and human tissue prostheses are now available for clinical use. Mechanical valves have a greater durability and consequently lower re-operation rates. However, they are associated with a greater risk of thrombo-embolism, which necessitates regular anticoagulation with the concomitant risk of hemorrhage. In contrast, bioprostheses have a low thrombogeneity, which in most patients obviates the need for regular anticoagulation and consequently reduces hemorrhagic accidents. However, the main factor limiting their use is the propensity to undergo tissue degeneration, often necessitating re-operation. Human tissue valves have a relatively low rate of thrombo-embolism and endocarditis. However, the long-term incidence of structural valve deterioration (SVD) of these valves is uncertain, and human valves are scarce [1-3].

With the aging of the general population, the number of elderly patients requiring aortic valve replacement has increased rapidly during recent years. Hence, the choice and long-term performance of a valve prosthesis is of paramount importance. Currently, bioprostheses are recommended for elderly patients, who do not have risk factors for thrombo-embolism. These valves may also be used in younger patients presenting with a contra-indication to long-term anticoagulation [3].

Because of the limited life expectancy (LE) of elderly patients, the benefits of avoiding anticoagulation may outweigh the disadvantages of a possible re-operation, i.e. the valve will probably outlive the patient. However, in younger patients, a re-operation will be frequent, and re-operation-free LE and event-free LE are important considerations in decision making on implantation.

The purpose of this study was to provide insight into the prognosis of patients of different ages, following implantation with a stented porcine bioprosthesis. We hereto incorporated data from various smaller clinical studies in a mathematical micro-simulation model.

4.2. Methods

Meta-analysis

Literature Search - We conducted a literature search of the PubMed and MEDLINE databases for the period January 1990 to December 1999. The terms used for the search were both MESH terms and the text words "heart valve prostheses", "aortic valve" or "bioprostheses" in combination with "porcine", "stented", "Hancock", "Carpentier-Edwards" or "modified orifice". The search was limited to "human" and to the English language. We then screened the titles and the abstracts of the remaining studies in order to select those, which examined the valve-related events, outcomes and/or survival of patients following aortic valve replacement with a bioprosthetic valve. Reports that considered stentless and pericardial valves were excluded during this process. The references in the reports were cross-checked for other potentially relevant studies. This resulted in 53 published reports.

We stipulated 5 criteria to obtain a group of similar studies.

1) Studies which described one or more of the following stented porcine bioprostheses: Carpentier-Edwards standard and Carpentier-Edwards supra-annular valves (Baxter Healthcare Corp., Santa Ana, CA), Hancock standard, Hancock modified orifice and Hancock II valves (Medtronic Inc., Minneapolis, MN).
2) Isolated valve implantation in the aortic position.
3) Valves of size 19 mm or more implanted in patients over 15 years of age.
4) Valve-related events defined according to the standard definitions published in 1988 [4] and 1996 [5]. Valve-related events included valve thrombosis, thrombo-embolism, hemorrhage, endocarditis, non-structural dysfunction and SVD respectively. For this analysis, we only included studies, which contained data on at least one of these valve-related events.
5) No duplicate publication or overlapping patient population.

Following these criteria, 44 studies were excluded, leaving 9 studies for the analysis [6-14].

Data extraction and analysis - We reviewed the nine reports to obtain the input data required for the micro-simulation model. The annual hazards of valve thrombosis, thrombo-embolism, hemorrhage and non-structural dysfunction were assumed to be constant over time. Hence, combined estimates of the linearized occurrence rates for these events were calculated as the ratio of the sums of the number of events and patient years of follow-up in the individual reports. The combined mortality and re-operation rates following an event were similarly calculated.

Pooling of time-to-event curves was performed for survival, freedom from endocarditis and structural valve deterioration (SVD). Published curves were scanned and enlarged in a graphical computer package. The heights of these curves were measured at each year, and corresponding survival probabilities were calculated with their complementary log-log transformations. These transformed probabilities were pooled with weighting according to the estimated number of patients at risk at each year, and transformed back to obtain a summary curve [15]. Homogeneity of the curves was assessed graphically and judged satisfactory.

The risk of endocarditis was assumed to take 2 phases of constant hazard, with a hazard during the first 6 months greater than the subsequent period. Therefore, we fitted a two-period exponential model on the pooled freedom from endocarditis curve, which was based on three reports [7, 10, 13]. The risk of SVD depended on the time that elapsed since valve replacement and the age of the patient at implantation. A Weibull model described this relationship [16, 17]. This model is a generalization of the exponential distribution to accommodate a changing risk over time. The shape parameter of the Weibull model was estimated from the average freedom from SVD curve, which was pooled from four reports [7, 8, 12, 13]. The age effect was incorporated in the scale parameter of the Weibull model, based on one study [12].

Microsimulation model

Parameters in the model - We used the estimates from the meta-analysis to parameterize a previously developed micro-simulation model (Figure 1) [18]. The model incorporates SVD (age-dependent), other valve-related events (valve thrombosis, thrombo-embolism, hemorrhage, endocarditis, non-structural dysfunction), and the background mortality of aortic valve recipients ("non-valve-related deaths"). The simulation model calculates

patient survival rates by super-imposing the mortality associated with valve-related events on a background mortality. The background mortality may well exceed that of the general population, due to the aortic valve disease as such, cardiomyopathy and the valve replacement procedure [19-21]. Therefore, hazard ratios were applied to the age-specific survival rates of the Dutch population, to calibrate the model outputs with the age-specific survival curves obtained from the literature [12]. Operative mortality was estimated as 1.5% for a 40-year-old man, increasing with odds ratios of 1.022 for age (per year) and 1.7 for every re-operation.

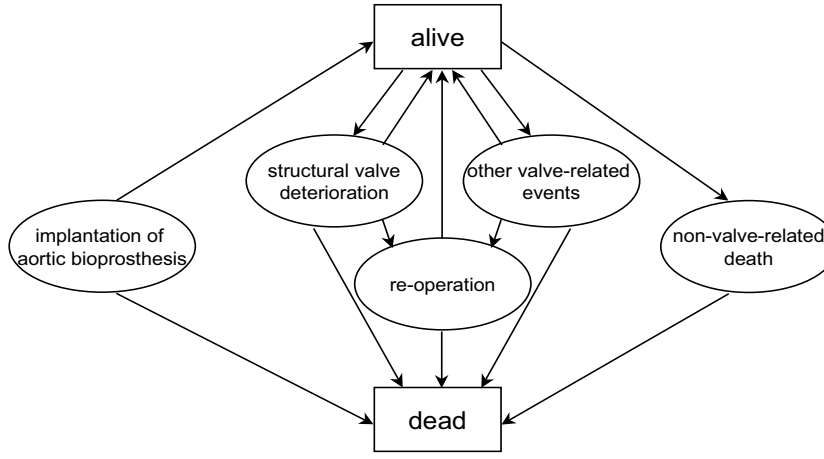

Figure 1. Structure of the microsimulation model. After implantation of a bioprosthesis, valve-related events can occur, which can lead to re-operation and mortality. Non-valve-related death indicates background mortality.

Evaluation and validation - Micro-simulation is a type of Monte Carlo simulation [17]. For our evaluations, 10,000 virtual life histories were randomly drawn. The age at death, occurrence of events and re-operation were registered for each simulated patient. This enabled us to calculate the LE, event-free LE and re-operation-free LE, as well as actual risks of valve-related events and reoperation, for a patient of a given age and gender. The model output was validated against the pooled survival curve, as obtained from three reports [8, 10, 12].

Sensitivity analyses - We performed one-way sensitivity analyses to investigate the effect of uncertainty in the parameter estimates. When we varied the estimates of valve-related events according to their 95% confidence intervals, we found only very small variations in the event-free LE. We therefore defined larger ranges for the valve-related events, i.e. from half to double the baseline parameter values. The mortality hazard ratio was assumed to exceed 1, i.e. that the mortality was at least at the level of the general population.

4.3. Results

Literature Search - The nine selected reports contained data on 5837 bioprosthetic valve recipients with a total follow-up of 31,874 patient years (Table 1) [6-14]. The majority of patients were male and the mean age of the population was 64.6 years, although differences between the component studies were noted. Most patients were in New York Heart Association class III or IV (on average 71%), and a coronary artery bypass graft was present in around one-third (on average 36%).

Study (Ref. No.)	Patients (n)	Males n (%)	Mean age (SD)	Age range (years)	Follow-up (pt-years)	Pre-op NYHA^{+} (%)	CABG n (%)
1 (12)	1108	546 (49)	74 (8)	24-91	4735	749 (68)	*
2 (13)	429	309 (72)	64(12)	18+	3000	*	152 (35)
3 (6)	843	490 (58)	69 (*)	16-91	5093	704 (84)	365 (43)
4 (14)	1594	1124 (71)	60 (15)	16-94	10212	908 (57)	545 (34)
5 (9)	536	391 (73)	64 (12)	18-86	2276	393 (73)	213 (40)
6 (15)	165	116 (70)	67 (9)	27-87	551	127 (77)	32 (19)
7 (16)	571	*	59 (*)	15-85	3375	531 (93)	*
8 (17)	196	163 (83)	48 (12)	17-70	1368	167 (85)	*
9 (8)	395	245 (62)	65	22-84	1264	*	122 (31)
Total	5837	3384 (64)	64.6	15-94	31,874	3579 (71)	1429 (36)

Pt-years = patient-years, pre-op = pre-operative, NYHA = New York Heart Association and CABG = coronary artery bypass grafting.
$^{+}$ Pre-operative NYHA classes III and IV, * data not available.

Table 1. Characteristics of the nine studies selected for meta-analysis

Data extraction and analysis - A summary of the meta-analysis is given in table 2. Adequate data on valve thrombosis were available in only 4 reports [7, 9, 11, 13], which yielded 3 events from 9925 patient years of follow-up. Two of these patients died giving a death rate of 67% for this rare event. Assuming a constant hazard, a linearized occurrence rate was calculated for each of four types of valve complications, of which thrombo-embolism was the highest with 0.87% per patient year. The incidence of endocarditis was estimated as 0.68% per patient year after the first 6 months after valve replacement and 3.4% per patient year before that, i.e. 5 times as high.

Valve-related events	Events (n)	LOR	Outcome		Freedom from Event	
			Death Rate	Re-op Rate	At 5 years (%)	At 10 Years (%)
Valve thrombosis	3	0.030	0.67	0.33	99.8	99.7
Thrombo-embolism	277	0.869	0.19	0	95.7	91.6
Haemorrhage	113	0.382	0.21	0	98.1	96.2
Endocarditis	167	3.4/0.68*	0.34	0.55	96.0 #	92.4 #
NSD	94	0.384	0.05	0.52	98.1	96.2
SVD	352	+	0.10	0.84	99.4 #	85.2 #

LOR = linearized occurrence rates (per 100 patient-years), pt-year = patient-year, Re-op = re-operation, NSD = non-structural dysfunction, SVD = structural valvular deterioration.
* A two-period exponential model was constructed for risk during and after the first six months after implantation.
+ A Weibull model was constructed incorporating age dependency.
# Percentages from summary survival curves.

Table 2. Summary of meta-analysis.

A Weibull model, as shown in Figure 2, estimated the average incidence of SVD. The formula for the freedom from SVD was;

$$S(t) = e^{-(t/\sigma)^{\wedge}\beta},$$

where S(t) indicated the probability of being free from SVD at time *t*, and σ and β the scale and shape parameters in the Weibull model respectively. The value of σ depended on age: $\sigma = e^{2.11 + 0.0112\ age}$, and the value of β was 3.49. With these parameters, the median time till SVD was 17.1 years for a 65-year-old patient.

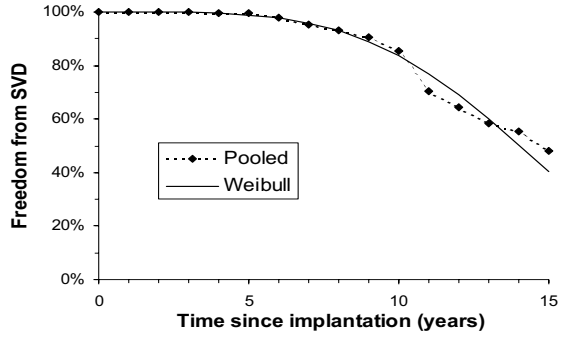

Figure 2. Average freedom from SVD as estimated from literature (pooled) and with the Weibull model.

Model calibration - The simulation model was calibrated by comparing survival curves produced by the model (for both males and females of varying ages) with empirical survival curves of the corresponding age ranges [12]. Hazard ratios of 8.0, 3.6, 1.5, 1.1 and 1.0 were found adequate for the background mortality in males of age 35, 45, 55, 65 and 75 years respectively.

Model validation - An overall impression of the validity of the model was obtained by comparison of expected and observed overall survival. The observed survival was obtained by pooling the curves from three reports, where the mean age was 61.5 years [8, 10, 12]. The expected survival was calculated with the model for male and female patients aged 62 years. These curves closely approximated the pooled survival curve (Figure 3A).

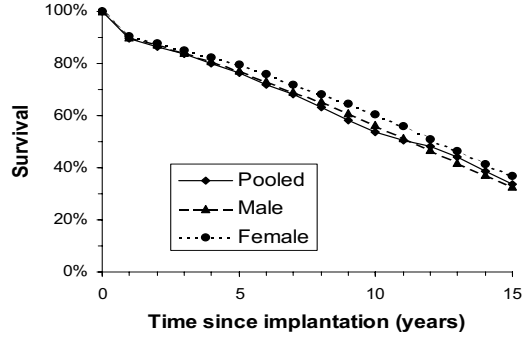

Figure 3A. Survival after implantation of a stented porcine bioprosthesis – Pooled estimate from the literature (pooled) and predicted survival for a 62-year-old man and woman according to microsimulation model.

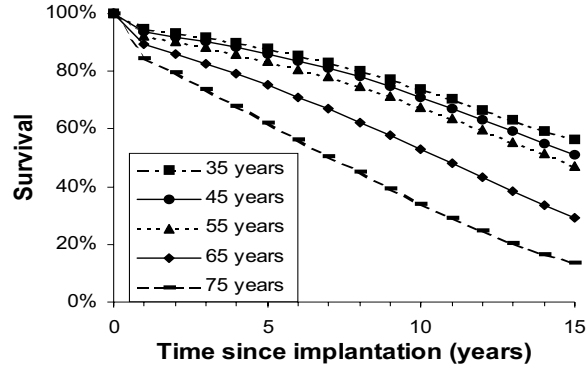

Figure 3B. Survival after implantation of a stented porcine bioprosthesis – predicted survival for men of different ages.

Age-specific results - Survival curves were estimated for males of different ages at implantation of the valve (Figure 3B). The area under each survival curve equals the life expectancy (LE). The LE decreases with advancing age, i.e. from 17.1 to 7.2 years for males aged 35 to 75 years. The re-operation-free LE and event-free LE show a remarkable pattern: an increase to age 55 followed by a decrease (Figure 4). The increase is caused by the age-dependency of the SVD risk (decreasing with age), while the eventual decrease is caused by the dominating effect of background mortality at older age. For a 65-year-old male, the LE, re-operation-free LE and event-free LE were 11.3, 9.5 and 8.4 years, respectively.

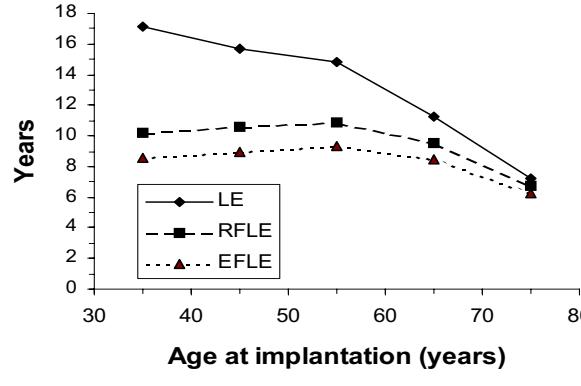

Figure 4. Life expectancy (LE), re-operation-free life expectancy (RFLE) and event-free life expectancy (EFLE) for men of different ages.

We further calculated the actual lifetime risk of a re-operation or a valve-related event following aortic valve replacement. The lower this risk, the better is the prognosis. As shown in Figure 5, the probability of ever undergoing a re-operation or suffering from a valve-related event rapidly decreases with the age at implantation, from 63% and 83% at 35 years to 11% and 24% respectively at 75 years.

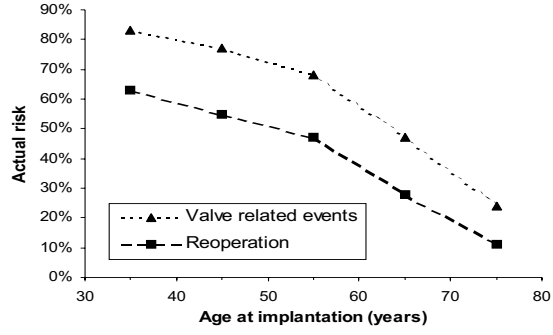

Figure 5. Lifetime risk (actual risk) of re-operation and valve-related events for men of different ages**.**

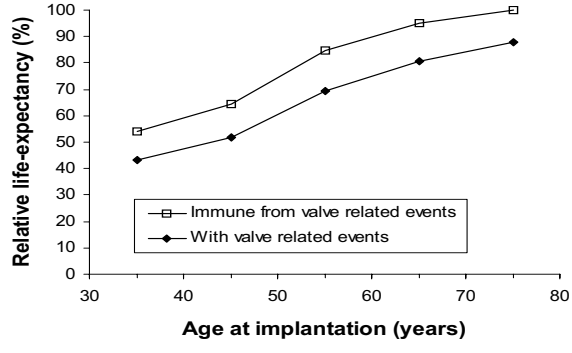

Figure 6. Life expectancy for men with aortic valve disease relative to that of men in the general population for different ages.

Furthermore, we compared the LE of male bioprosthesis recipients with the LE of males in the general Dutch population. The relative LE increased with the age of valve replacement (Figure 6). We also estimated the relative LE of a hypothetical valve recipient, were he immune to valve-related events. Hereto, the relevant parameters in the model were set to zero. This enabled us to quantify the impact of the increased background mortality. This impact was large for young patients (e.g. 46% for 35-year-old males), and decreased to 0% for 75-year-old males, corresponding to the decrease in

hazard ratio to 1. The difference between the curves in Figure 6 represents the loss in LE due to the occurrence of valve-related events. This relative difference was approximately 12% for all ages. On an absolute scale, the difference decreases with age.

Sensitivity analyses - The event-free LE of a 65-year-old male patient is shown in Table 3 for extreme values of the valve-related events, while other parameters are kept at baseline values. Changes in the SVD risk had the largest influence. A doubling of the median failure time would increase the event-free LE by 1.5 years (from 8.4 to 9.9 years) and a halving would reduce the event-free LE by 2.8 years (from 8.4 to 5.6 years, Table 3). Further, increasing the hazard ratio associated with the background mortality from 1.1 to 1.5 resulted in an event-free LE of 7.6 instead of 8.4 years.

Parameter	Baseline estimate *	Plausible range +		Event free LE (years)	
		Favorable	Unfavorable	Favorable	Unfavorable
Valve thrombosis	0.03	0.015	0.06	8.45	8.43
Thrombo-embolism	0.87	0.43	1.74	8.67	8.02
Hemorrhage	0.38	0.19	0.76	8.54	8.24
Endocarditis	0.68	0.34	1.36	8.66	8.05
NSD	0.38	0.19	0.77	8.53	8.25
SVD	17.1 #	34.2 #	8.5 #	9.89	5.57
Hazard ratio	1.1	1	1.5	8.66	7.66

NSD = non structural dysfunction, SVD = structural valvular deterioration
* The event-free life expectancy was 8.44 years in the baseline analysis.
+ The plausible range was defined by halving and doubling of the baseline estimate.
# Median time to SVD according to the Weibull model.

Table 3. Summary of sensitivity analysis.

4.4. Discussion

We used a meta-analysis of empirical data and a mathematical micro-simulation model to predict the life expectancy (LE) and actual lifetime risk of re-operation and valve-related events for patients following implantation with a stented porcine bioprosthesis. The micro-simulation model generates the life histories of a large number of virtual patients. Compared to standard statistical methods, the added value of modeling is that it provides detailed insights into the occurrence of valve-related and non-valve-related events. For a 65-year-old male for example, the model predicted a LE of 11.3 years and a life-time risk of re-operation and a valve-related event of 28% and 47% respectively, following implantation with a bioprosthesis. Such information will be useful for patient counseling and for the surgeon and patient in decision making. We envisage presenting an user-friendly version of the model on the internet in the near future, which could serve as a bedside tool to the surgeon. The model results may also serve as a baseline for the evaluation of newer valve types.

We chose 5 types of stented porcine bioprostheses, both first and second generation, which were not markedly different from one another. The Hancock standard prosthesis and the Carpentier-Edwards standard prosthesis, two of the initial stented, porcine valves, were introduced in the early 1970's [2, 22]. The composite Hancock modified orifice prosthesis was designed to improve hemodynamic performance, by substituting the septal leaflet with a non-septal leaflet from a second porcine valve [6, 23]. In contrast to the above, the second generation Carpentier-Edwards supra-annular bioprosthesis and the Hancock II bioprosthesis were introduced in the 1980's and incorporated several considered improvements, including a supra-annular configuration, to maximize the effective orifice of the prosthesis [7, 8].

Similarities in the performance of these valve types have been documented in the literature. A randomized prospective comparison of the Hancock standard and the Carpentier-Edwards standard valves showed no clear difference in durability or other valve-related complications after 10 years [22]. Also, no important differences were found in durability or other valve-related complications between the Hancock modified orifice valve and the 2 standard valve types [23]. The 2nd generation porcine bioprostheses (Carpentier-Edwards supra-annular, Hancock II) were designed to improve clinical performance by reducing the incidence of SVD. However, Jamieson and others failed to

demonstrate clinically relevant differences with regard to the freedom from SVD between the Carpentier-Edwards standard and Carpentier-Edwards supra-annular valves, except for the 21-40 age group [24]. The risk of valve-related complications with the Hancock II prosthesis has been reported to be similar with the previously mentioned valve types [25, 26]. We note however that the limited improvement in durability of the 2nd generation valves could be related to enhanced surveillance and early intervention.

Ideally, for the application of simulation methodology, a sufficiently comprehensive "super-data-set" should be analyzed [19]. Such a data set should contain detailed information on patients who underwent aortic valve replacement, have complete and long-term follow-up for all patients, and consider all relevant valve-related events. However, no such databases are available as yet, although reports on larger series with long-term follow-up have become more frequent [27, 28]. We pooled the results of selected reports, which satisfied strict criteria, and calculated quantitative estimates for the parameters of interest (Table 2). An advantage of pooling was that the estimates represented the experience of many institutions with possibly slightly varying patient populations. Single center results may be less generalizable due to typical patient populations and unique surgical practices.

Standard actuarial statistical techniques (e.g. Kaplan-Meier) have been used in many studies to assess the survival of patients and the performance of valve prostheses, while "actual" analysis has recently gained interest [29]. For survival, the actuarial and actual methods provide identical estimates. However, when the actuarial method is applied to non-fatal complications, such as SVD, the risk described is that which patients would experience provided they were immortal. Patients with valve disease have relatively high annual risks of death. Hence, a more relevant estimate of valve failure is the actual percentage of patients who will experience an event before they die [27, 29, 30]. The simulation model provides estimates of the actual risk of re-operation and of valve-related events, according to age (Figure 5). This information is more meaningful than actuarial risks, or actual risks for "average" patients. We note that the estimates by Grunkemeier and colleagues [29] for the actual risk of ever experiencing a SVD (20% for the age group 70-73 years and 40% for the 59-63 age group) were rather similar to our model estimates (18% for 71-year-old and 42% for 61-year-old males respectively).

The micro-simulation model calculates patient survival rates by super-imposing the mortality associated with valve-related events on a background mortality rate. The background mortality is the non-valve-related mortality of the valve recipients. It was previously assumed that in the absence of morbid valve events, the patients would follow the trajectory of the general population [18]. This assumption may not be tenable, since valve disease, cardiomyopathy, and the valve replacement procedure per se, may cause higher non-valve-related mortality than noted in the general population [19-21]. By applying age-specific hazard ratios to the age-specific survival curves of the general population, we aimed to obtain a more accurate prediction of patient prognosis. For young patients, the increase in background mortality was substantial compared to the general population (e.g. a 36% lower LE for a 45-year-old male).

Limitations of our micro-simulation model included that certain structural assumptions had to be made. For example, a constant hazard was assumed for valve thrombosis, thrombo-embolism, hemorrhage and non-structural dysfunction, where in fact, these hazards may be time and age-dependent. Further, endocarditis risk was assumed to be piecewise constant before and after 6 months of follow-up, and SVD risk was described with a Weibull model. Further studies need to address these assumptions. Furthermore, survivals after aortic valve replacement will not only depend on age and gender, but also on many risk factors, including pre-operative NYHA class and the presence of coronary heart disease.

In addition to structural assumptions, uncertainty existed in parameter values due to small or moderate numbers of events. The time to SVD was the most important factor for the event-free LE. This is of interest in assessing the value of newer bioprostheses, e.g. stentless types [31, 32]. When more data become available on such valves, these can easily be included in our model to quantify the impact on patient prognosis. Further, a change in background mortality resulted in a marked variation in the LE. This illustrates the need for incorporation of more detailed information on the clinical characteristics of the patients into the model. Also, updating of the model with the growing experience with bioprostheses is essential to provide valid estimates of prognosis in the future.

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5. Prognosis after Aortic Valve Replacement with the Carpentier-Edwards Pericardial Valve

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Key words: Aortic valve replacement, bioprostheses, prognostic modeling

Abstract

Background: The second-generation pericardial valves have excellent hemodynamic function, but knowledge on long term outcome after implantation is still incomplete. This study aimed at providing insight into the age-related life expectancy, event-free life expectancy and lifetime risks of valve-related events after aortic valve replacement (AVR) with the Carpentier-Edwards pericardial valve.

Methods: We conducted a meta-analysis of 8 published reports of AVR with Carpentier-Edwards pericardial valves (2685 patients, 12,250 patient-years) to estimate hazards of valve-related events. Structural valvular deterioration (SVD) was described by age dependent Weibull curves. The parameters of the Weibull curves were calculated using a data set of 267 patients who were implanted with the Carpentier-Edwards pericardial valve and who formed part of the original four-center clinical investigation conducted for the US Food and Drug Administration. These estimates were used to parameterize a micro-simulation model, which was used to calculate the outcomes of patients of different ages after AVR. The model estimates of survival were validated using data sets from Portland, USA.

Results: The Weibull model estimated median time to re-operation for SVD ranging from 18.1 years for a 55-year-old male to 23.2 years for a 75-year-old male. For a 65-year-old male, for example, microsimulation calculated a life expectancy and event-free life expectancy of 10.8 and 9.1 years respectively. The lifetime risk of at least one valve-related

event was 38% and that of re-operation due to SVD 17% respectively for this 65-year-old male. The model estimates of survival showed good agreement with the Portland data.

Conclusions*:* The use of microsimulation provides detailed insight into outcomes after AVR with Carpentier-Edwards pericardial valves. This information can be used to compare the valve performance with that of other bioprostheses and can help in the choice of a valve prosthesis for the individual patient.

5.1. Introduction

Stented bovine pericardial bioprosthetic heart valves, which offer an alternative to the glutaraldehyde-treated porcine valves, have been used for aortic valve replacement (AVR) for over 30 years. After disappointing results with the first-generation Ionescu-Shiley valve (Shiley, Inc., Irvine, CA) [1,2], the second-generation Carpentier-Edwards (Perimount) pericardial bioprosthesis (Edwards Lifesciences LLC, Irvine, CA) was introduced in 1982 and obtained US Food and Drug Administration (FDA) approval in 1991. It is currently the most widely used pericardial valve worldwide and the only pericardial valve approved by the FDA[3].

Compared with its predecessors, the Carpentier-Edwards pericardial valve incorporates significant design modifications including improved tissue fixation and a sophisticated method of mounting leaflets on a flexible elgiloy metal stent [4]. This has resulted in the reported excellent hemodynamics and durability of the valve [5,6]. However, knowledge on the long-term outcome of patients after valve replacement with Carpentier-Edwards pericardial valves and the lifetime risk of valve-related events, is still incomplete. This information would be useful for comparison of the Carpentier-Edwards pericardial valve with other bioprostheses, especially the more commonly used porcine valves, and in the choice of a valve for the individual patient.

We combined a meta-analysis and other data with microsimulation to provide insight into the age-related life expectancy and lifetime risks of valve-related events after AVR with the Carpentier-Edwards pericardial valve.

5.2. Methods

Meta-Analysis

We conducted a literature search of the Medline database using the PubMed interface for the period January 1995 to December 2002, to identify reports that examined the outcomes of patients after AVR with the Carpentier-Edwards pericardial valve. The text words used for the search were 'Carpentier-Edwards' and the terms 'bioprosthesis' and 'tissue heart valves' in combination with 'bovine' and 'pericardial' respectively. The titles and abstracts of the search results were screened for reports that contained data on valve-related events, their consequences and long-term survival of patients after AVR. The references in these reports were cross-checked for other potentially relevant studies, which finally resulted in 30 published reports.

We then applied six criteria to these reports in order to obtain a similar group of studies. These criteria were: (1) Valve sizes 19-31 mm, not focussing on a particular size or range; (2) Patients >15 years of age, not focussing on a particular age group; (3) Predominantly first time AVR; (4) AVR with or without coronary artery bypass grafting (CABG), excluding other valve replacements; (5) Predominantly patients who do not require long-term anti-coagulation; and (6) No overlapping patient populations. This excluded 22 reports, leaving 8 reports for further analysis [6-13]. Valve-related events in these reports were defined according to the guidelines of Edmunds and colleagues [14,15]. The 8 reports were reviewed in detail to obtain data required for calculation of the input parameters of the microsimulation model.

Assuming a constant hazard over time, weighted mean estimates of linearized annual occurrence rates were calculated for valve thrombosis, thrombo-embolism, hemorrhage and non-structural dysfunction respectively. The risk of endocarditis was assumed to take 2 phases of constant hazard, the hazard within six months of implantation greater than in the subsequent period. Hence, a 2-period exponential model was fitted to the pooled freedom-from-endocarditis curve obtained by combining the individual curves in the selected reports[16]. The combined mortality and re-operation rates were also calculated.

Analysis of SVD

The risk of SVD in a bioprosthesis depends on the age of the patient at implantation and on the time elapsed since valve replacement. The risk decreases with implantation age but increases with time since implantation. We used an age-dependent Weibull model to describe this relationship [17,18]. The Weibull formula for the freedom from SVD is:

$$S(t) = e^{-(t/\sigma)^{\wedge}\beta},$$

where S(t) indicates the freedom from SVD at time t while σ and β denote the scale and shape parameters of the model. The shape parameter reflects the changing risk of SVD over time. We used a data set of 267 patients, implanted with Carpentier-Edwards pericardial prostheses between 1981 and 1984, to calculate the parameters of the Weibull model. The mean age of the patients at implantation was 65 ± 12 years, 64% were men and the follow-up extended to 18 years. These patients formed part of the original four-center pre-marketing clinical investigation conducted for the US FDA.

Microsimulation model

The microsimulation model is a computer application that simulates the life of a patient after AVR with a particular valve, taking into account morbidity and mortality events that the patient may experience. The mortality of a patient is composed of the mortality experience of the general population, mortality due to valve-related events and an 'additional mortality' component that is associated with underlying valve pathology, left ventricular function and valve replacement procedure respectively [19].

The mortality experience of the general population was incorporated into the model by means of the life table of the relevant population, American males in this analysis. Mortality due to valve-related events was incorporated using the data obtained from the meta-analysis. We previously estimated age- and sex-specific hazard ratios to represent the effect of 'additional mortality'. They were 2.9, 1.8, 1.2 and 0.8 for male patients aged 45, 55, 65 and 75 years respectively [20]. Operative mortality was estimated at 1.5% for a 40-year-old patient, increasing with odds ratios of 1.022 per additional year of age and 1.7 per re-operation. The model calculates patient outcomes after AVR by superimposing the morbidity and mortality estimates of valve-related events on the other two mortality components. In principle, the model can be applied for any valve type and for a patient of either sex. For this analysis, the

model was used to calculate outcomes of male patients after AVR with the Carpentier-Edwards pericardial valve. A detailed account of the microsimulation structure and methodology has been given previously [21 22].

Validation

To assess the validity of the microsimulation model calculations against the 'true life' outcomes of patients undergoing AVR, we compared the age- and sex-specific survival calculations of the microsimulation model with the corresponding Portland experience with Carpentier-Edwards pericardial valves. The Portland pericardial data, from the Providence Health System, Portland, Oregon, USA, contains 1021 patients who were implanted with the prosthesis between 1991 and 2002. The mean age of the patients was 74.3 years. We also compared the age- and sex-specific model outputs with the Portland 25-year follow-up data on patients who underwent AVR with the Carpentier-Edwards 'standard' bioprosthesis [23].

Sensitivity Analysis

To investigate the effect of uncertainty in the parameter estimates, we performed a one-way sensitivity analysis. This was done by varying each individual parameter, while keeping the other estimates fixed. Variation of the estimates of valve-related events by their 95% confidence intervals yielded only very small changes in the long-term outcomes. Therefore for this analysis, we defined larger ranges by increasing and decreasing the baseline estimates by 25%. A plausible range was also considered for the hazard ratio representing the additional mortality component.

5.3. Results

Meta-Analysis

The 8 reports selected for the meta-analysis comprised 2685 Carpentier-Edwards pericardial valve recipients and 12,250 patient-years of follow-up respectively. Sixty-two percent of the patients were male and the mean age at implantation was 67 years. Concomitant CABG was performed on about 30% of the patients, although differences between the component studies were noted. The pooled incidence of valve-related events and their outcomes are given in table 1. As depicted in this table, thrombo-embolism occurred with an annual incidence of 1.35% per patient-year while the incidence of endocarditis was 1.76% per patient-year in the first 6-months after implantation, decreasing three-fold in the subsequent period.

Valve-related events	Events (n)	Hazard Rate (LOR)	Outcome	
			Death Rate	Re-operation Rate
Valve thrombosis	2	0.03	0.50	0.50
Thrombo-embolism	166	1.35	0.23	0
Hemorrhage	53	0.43	0.41	0
Endocarditis	70	1.76 / 0.54 *	0.38	0.17
Non-structural dysfunction	4	0.13	0	0.50
Structural valvular deterioration	55	+	0.09	0.85

* A 2-period exponential model was constructed for the risk of endocarditis during and after the first six months after aortic valve replacement.
+ An age dependent Weibull model was constructed using the original pre-marketing clinical investigation data set.

Table 1. Pooled incidence of valve-related events and their outcomes after aortic valve replacement with Carpentier-Edwards pericardial valves.

SVD

The value of the scale (σ) parameter of the Weibull model, fitted to represent SVD in the pericardial valves, depends on age: $\sigma = e^{2.31 + 0.0124 * age}$. The shape parameter ($\beta$) = 3.76. With these parameters, the median time to re-operation due to SVD in the pericardial valves was 18.1, 20.5 and 23.2 years respectively for 55-, 65-, and 75-year male patients.

Microsimulation model output

The microsimulation model calculated actuarial patient survival, re-operation-free survival and event-free survival of male patients of different ages at valve implantation. The areas under the respective curves give the LE, re-operation-free life expectancy (RFLE) and the event-free life expectancy (EFLE). For a 65-year-old male patient for example, the LE was 10.8 years, RFLE was 10.0 years and the EFLE 9.1 years respectively after implantation with

a Carpentier-Edwards pericardial valve. The LE, RFLE and EFLE for men at different ages of valve implantation are given in figure 1.

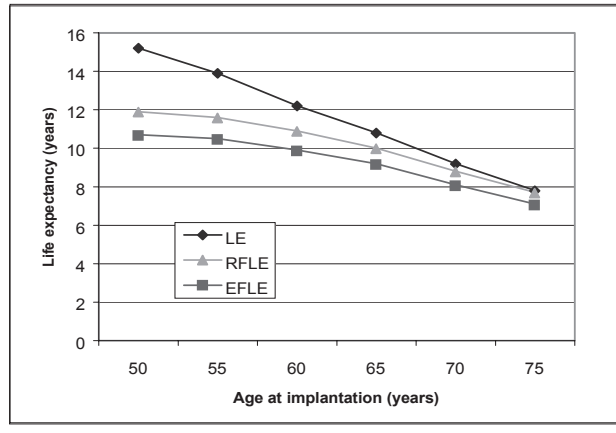

Figure 1. Life expectancy (LE), re-operation-free life expectancy (RFLE) and event-free life expectancy (EFLE) for men after aortic valve replacement with Carpentier-Edwards pericardial valves.

The microsimulation model also calculates the 'actual' or lifetime risks of valve-related events and re-operation after valve implantation (Figure 2). The lifetime risk of a re-operation due to SVD reduced with advancing age of implantation and was 17% and 5% respectively for 65- and 75-year-old males.

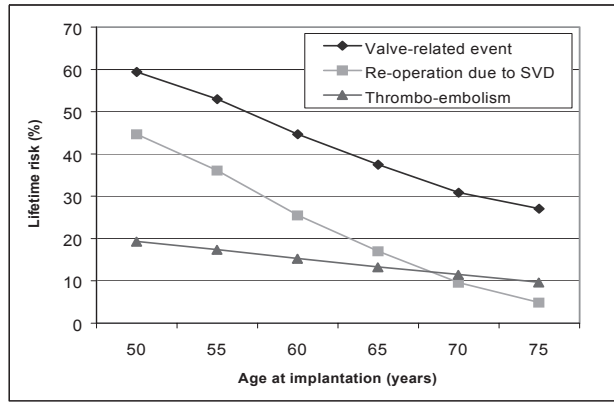

Figure 2. Lifetime risk of at least one valve-related event, re-operation due to structural valvular deterioration and thrombo-embolism for males after aortic valve replacement.

We further compared the LE of male patients who received Carpentier-Edwards prostheses with that of corresponding males of the general American population. As depicted in figure 3, the relative LE increased with advancing age of implantation, from 61% at 50-years to about 95% for a 75-year patient. The relative LE of a hypothetical valve recipient who was immune from valve-related events was also analyzed. It too increased with advancing age of implantation and was >100% that of a person in the general population at 75-years. The difference between the 2 curves represents the mortality associated with valve-related events. The difference between the curve for the hypothetical patient and the general population standard (i.e. 100%) represents the 'additional mortality' component, which was incorporated into the microsimulation model by way of hazard ratios.

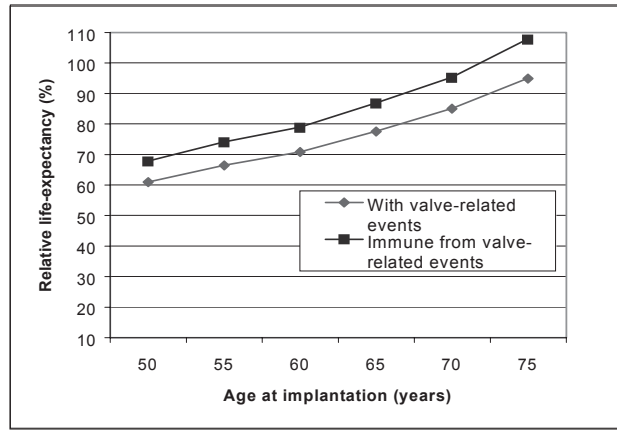

Figure 3. Life expectancy of men after aortic valve replacement relative to that of men in the general population.

Validation

The actuarial 7-year survival of (60-69)-year-old males in the Portland pericardial data, who survived the AVR procedure, was 69%. The corresponding microsimulation estimate for a 65-year-old male was 68%. The actuarial 8-year survival of (70-79)-year-old males was 54%, compared with the 8-year estimate of 47% calculated by the microsimulation model. The small numbers at risk and the absence of events precluded comparison up to 10-years and in the (50-59)-year-old age group respectively. Further, the survival outputs of the microsimulation model for males of different ages compared favorably with the

corresponding curves of the Carpentier-Edwards 'standard' Portland experience, through 25-years post-implantation (Figure 4).

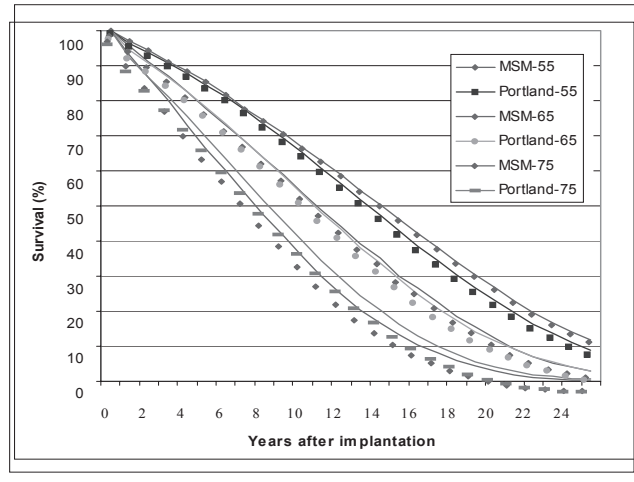

Figure 4. Comparison of microsimulation model outputs and corresponding Portland Carpentier-Edwards standard valve survival for 55-, 65- and 75-year-old males after isolated aortic valve replacement.

Sensitivity Analysis

The LE and EFLE of a 65-year-old male patient, on individually increasing and decreasing the baseline valve-related event estimates by 25%, are given in table 2. Variation in the median time to SVD and the hazard ratio representing 'additional mortality' had the most effect on the life expectancies.

5.4. Discussion

The pericardial bioprostheses, which have been in use for over 30 years [4], are considered an important alternative to the porcine valves. The pericardial bioprostheses are fabricated using bovine pericardium, which is sewn into a valvular configuration on a stented frame. The first commercially available pericardial valve, the Ionescu-Shiley valve (Shiley, Inc, Irvine, CA), was abandoned in 1988 due to a high incidence of valvular deterioration characterized by leaflet tears and valve incompetence [2,24]. Of the second-generation pericardial valves, the Carpentier-Edwards pericardial valve has shown better results than the other valve in its class, the Pericarbon pericardial bioprosthesis (Sorin Biomedica, Italy) [8].

Parameter	Baseline Estimate	Plausible Range *		Life Expectancy (years)		Event-free Life Expectancy (years)	
		Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable
Valve Thrombosis	0.03	0.02	0.04	10.8	10.8	9.1	9.1
Thrombo-Embolism	1.35	1.01	1.69	10.9	10.7	9.3	8.9
Hemorrhage	0.43	0.32	0.54	10.9	10.7	9.2	9.0
Endocarditis	1.76 / 0.54	1.32 / 0.41	2.2 / 0.68	10.8	10.7	9.2	9.0
Non-structural Dysfunction	0.13	0.10	0.16	10.8	10.8	9.1	9.1
S.V.D. +	20.5 years	25.6 years	15.4 years	10.9	10.6	9.4	8.4
Additional Mortality (Hazard ratio)	1.2	1.1	1.3	11.2	10.4	9.4	8.8

* The plausible range was estimated by increasing and decreasing the baseline estimates by 25% (except for the hazard ratio).
+ Median time to structural valvular deterioration.

[The Life Expectancy and Event-free life Expectancy were 10.8 and 9.1 years for a 65-year-old male patient.]

Table 2. Summary of sensitivity analysis for a 65-year-old male patient after aortic valve replacement.

The Carpentier-Edwards pericardial valve, which received FDA approval in 1991 and is widely implanted in many centers at present, was chosen to represent the pericardial valves in this analysis. We used a microsimulation model to provide insight into the age- and sex-related life expectancy and lifetime risks of valve-related events after AVR with this valve. Simulation techniques, by modeling complex outcome paths that result from many competing risks, provide a useful adjunct to standard statistical methods in calculating the outcomes of patients after AVR. Data required to parameterize the microsimulation model were obtained by two methods. Estimates of the occurrence of valve-related events were obtained by a meta-analysis of published reports. An advantage of pooling data was that it represented the experience of many centers. SVD was incorporated into the microsimulation model by age-dependent Weibull curves. Grunkemeier and colleagues have shown that the Weibull distribution was efficient in summarizing SVD in biological valves. However, they stressed that at least 12 years of follow-up was needed to provide reliable estimates [25]. We used data on the Carpentier-Edwards pericardial valve, with an 18-year follow-up, to calculate the Weibull parameters. Accordingly, the median time to re-operation due to SVD for 55-, 65- and 75-year-old males implanted with pericardial valves was 18.1, 20.5 and 23.2 years respectively. These estimates may be used to compare the durability of pericardial valves with the porcine valves and with newer bioprostheses.

The LE, RFLE and EFLE for males of different ages as estimated by the microsimulation model, is depicted in figure 1. Mortality of an AVR patient, who survives the operation, is greater than that of a matched person in the general population. This excess mortality is due to valve-related mortality and an 'additional mortality'. The 'additional mortality', which may be related to underlying valve pathology, left ventricular residual hypertrophy and functional abnormality and the valve replacement procedure, is not clearly defined and estimated at present. Hence, we had previously estimated age- and sex-specific hazard ratios to represent the effect of additional mortality in the model, using data from a follow-up study on stented porcine bioprostheses [26]. Kvidal and colleagues, who investigated the excess mortality after heart valve replacement, described an increasing excess hazard during follow-up and a decreasing excess hazard with advancing age of implantation [27]. This supports a 'multiplicative' excess mortality, which was a structural assumption in our model. The use of an 'additive' model may increase LE estimates, especially in patients under 70 [28,29].

The possibility that 'additional mortality' may vary with different valve types and valve sizes, necessitating different hazard ratios to represent 'additional mortality', has not been addressed by us at present. In this regard, the Carpentier-Edwards pericardial valve has been shown to be less obstructive in the aortic position than the Carpentier-Edwards standard and supra annular valves [5,30]. This may translate to greater and more rapid regression of left ventricular hypertrophy after AVR with a pericardial valve [31], thus conferring a higher survival benefit than presently calculated by the microsimulation model. Hence, we have used sensitivity analysis to underscore the importance of excess mortality on the outcomes of patients after AVR. The effect on LE and EFLE of a 65-year-old male, caused by lowering of the hazard ratio, is given in table 2.

Actuarial analysis is commonly used for the analysis of valve-related events that are not necessarily fatal. Such analysis describes the risk for patients provided they were immortal. Hence, actuarial analysis overestimates the risk of SVD, this error being magnified with increasing age. A more relevant estimate is the cumulative incidence, termed 'actual' analysis, which calculates the percentage of patients who will experience an event before they die [32,33]. It provides a better estimate of the durability of a bioprosthesis, especially in the elderly. The microsimulation model calculates the 'actual' life time risk of valve-related events. For a 65- and 75-year-old male for example, the life time risk of re-operation due to SVD is 17% and 5% respectively.

The American College of Cardiology / American Heart Association (ACC / AHA) guidelines for the management of patients with valvular heart disease recommends a bioprosthesis for those above 65-years, based on the major reduction in SVD and increased risk of hemorrhage in this age group [34]. Birkmeyer and colleagues, who used a Markov state-transition model to simulate the outcomes after AVR with a mechanical valve, calculated a 20% or more life time risk of hemorrhage in a 65-year-old patient [28]. Considering our model calculation for the life time risk of re-operation, a lowering of the 65-year age threshold for implantation of a pericardial valve may be considered, especially in younger patients whose life expectancy is reduced by concomitant disease.

Limitations of this study included certain structural assumptions in the microsimulation model and the uncertainty associated with the input parameters. For example, a constant hazard was assumed for valve thrombosis, thrombo-embolism, hemorrhage and non- structural dysfunction. However, these hazards may vary with increasing age and age at implantation. Based on a previous study [35], we assumed endocarditis to take 2 phases of constant risk, the initial risk up to 6 months after implantation, greater than in the subsequent period. However, comparisons of different time periods of implantation have shown a significant decline in early prosthetic endocarditis in recent years [36]. Many other patient- and surgery-related factors have been shown to influence overall survival after AVR [37-40]. However at present, the model calculates outcome for an average risk profile only. The moderate numbers of events for some valve-related events and possible publication bias give a degree of uncertainty to the input parameters of the model.

In conclusion, we have described the use of microsimulation in providing detailed insight into outcomes after AVR with the Carpentier-Edwards pericardial valve. This information can be useful for patient counseling and in selecting the optimal valve prosthesis for a given patient.

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6. Comparison of Carpentier-Edwards Pericardial and Supraannular Bioprostheses in Aortic Valve Replacement

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Key words: Aortic valve replacement, bioprostheses, prognostic modeling

Abstract

Objective: Technological innovations have resulted in improved hemodynamics and greater durability of the second-generation Carpentier-Edwards pericardial and supraannular bioprostheses. However, knowledge on long-term outcome of patients implanted with these valves is limited. This study aimed at calculating and comparing the long-term outcomes after AVR with the Carpentier-Edwards pericardial and supraannular porcine bioprostheses using microsimulation.

Methods: We conducted a meta-analysis of published results of AVR with Carpentier-Edwards pericardial valves (2685 patients, 12,250 patient-years) and supraannular valves (3796 patients, 20,127 patient-years) to estimate the occurrence rates of valve-related events. Long follow-up data sets were used to construct age-dependent Weibull curves that described their structural valvular deterioration (SVD). The estimates were entered into a microsimulation model, which was used to calculate the outcomes of patients after AVR.

Results: For example, for a 65-year-old male, median time to SVD was 20.1 and 22.2 years for the pericardial and supraannular valves. Life expectancy was 10.8 and 10.9 years and event-free life expectancy 9.0 and 8.8 years respectively. Lifetime risk of re-operation due to SVD was 18.3% and 14.0% respectively.

Conclusions: The microsimulation methodology provides insight into prognosis after AVR with the Carpentier-Edwards pericardial and supraannular valves. Both valve types perform satisfactorily, especially in elderly patients, and show no appreciable difference in long-term outcomes when implanted in the aortic position.

6.1. Introduction

Stented bovine pericardial and porcine bioprostheses have been used for aortic valve replacement (AVR) since the early 1970's when their first-generation prostheses became commercially available. The second-generation of these valves were introduced in the early eighties with the aim of reducing structural valvular deterioration (SVD) and improving hemodynamic performance. The Carpentier-Edwards (Perimount) pericardial (Edwards Lifesciences LLC, Irvine, CA) and the Carpentier-Edwards supraannular (CE-SAV) (Baxter Healthcare Corp, Irvine, CA) bioprostheses were the initial second-generation valves introduced in their respective categories, and are implanted in many centers at present [1,2].

Compared with its predecessor, the first-generation Ionescu-Shiley valve (Shiley, Inc., Irvine, CA) [3], the Carpentier-Edwards pericardial valve incorporates significant design modifications including improved tissue fixation and a sophisticated method of leaflet mounting [4]. This permits more symmetrical opening of the valve resulting in better hemodynamics [5]. In contrast to the first-generation porcine valves, the Carpentier-Edwards supraannular valve has its tissue fixed at 2mm Hg and has a supra-annular configuration to maximize the effective orifice of the prosthesis [1]. Although these technological innovations have resulted in improved hemodynamics and greater durability, knowledge on important end points and long-term outcome of patients is still incomplete. Such information would be useful in complementing the available data, comparing the two valve types and in the optimal choice of a valve for a given patient.

We used meta-analysis and multi-center data on SVD to feed a microsimulation model, which was then used to provide insight into the age-related life expectancy and life time risks of valve-related events for patients after AVR and thereby compare the second-generation Carpentier-Edwards pericardial and porcine valves respectively.

6.2. Methods

Systematic literature review and meta-analysis

We conducted a Medline search using the PubMed search interface in order to identify reports that examined the outcomes of patients who received the Carpentier-Edwards pericardial and supraannular valves for AVR. The search was limited to the English language and to the publication period January 1, 1995 through 31 December 2002. The text word 'Carpentier-Edwards' and the terms 'bioprosthesis' and 'tissue heart valve' in combination with 'bovine', 'pericardial' and with 'porcine', 'supraannular' respectively were used for the search. Abstracts of reports obtained from the search were screened for those that contained information on valve-related events, their sequelae and long-term survival of patients after AVR. This resulted in 30 published reports on the Carpentier-Edwards pericardial valve and 18 reports on the supraannular valve respectively.

We then applied several criteria to these selected reports with a view to obtaining a similar group of studies for each valve type. These criteria were: (1) Valve sizes 19-31 mm, not focussing on a particular size or range; (2) Patients >15 years of age, not focussing on a particular age group; (3) Predominantly first time AVR; (4) AVR with or without coronary artery bypass grafting (CABG), excluding other valve replacements; and (5) Predominantly patients who did not require long-term anti-coagulation. Valve-related events in these reports were defined according to the guidelines of Edmunds and colleagues [6,7]. Reports with overlapping patient populations were excluded. This resulted in a selection of 8 reports on the pericardial valves [2,8-14] and 5 on the supraannular valves [15-19] respectively, the contents of which were then reviewed in detail to obtain data required for calculation of the occurrence rates of valve-related events.

Assuming constant hazards over time, weighted mean estimates of linearized annual occurrence rates were computed for the valve-related events other than SVD. The combined mortality and re-operation rates due to the valve-related events were also calculated.

Analysis of SVD

The risk of SVD in a bioprosthesis increases with the time elapsed since implantation and decreases with implantation age of the patient. The Weibull distribution [20] has been shown to be efficient in summarizing SVD in bioprostheses [21] and hence an age-dependent Weibull

model was used for this purpose. The Weibull model was constructed on Egret windows version 2.0.1 (Cytel Software Corp.). Further details on the construction of the Weibull model is given in the appendix.

Microsimulation model

The microsimulation model is a computer application designed to simulate the remaining lifetime of a patient after AVR with a given valve type, taking into account the risk of experiencing valve-related events and mortality. The mortality of a patient after AVR is composed of the mortality of the general population (background mortality), mortality due to valve-related events and an 'additional mortality' component. The latter may be associated with underlying valve pathology, left ventricular function and the valve replacement procedure respectively [22,23]. This 'additional mortality' component has not been quantified in the literature as yet and hence, was incorporated into the model by way of hazard ratios. The mortality due to valve-related events and the 'additional mortality' constitute the excess mortality experienced by patients after AVR.

Repeated simulations by the model of a particular patient results in a 'virtual' patient population, consisting of patients with identical characteristics and all possible outcomes which may occur after AVR. From this large simulated data set of identical patients (for example, 10,000), the model calculates the average outcome for that particular individual. In principle, the model can be applied for any valve type and for patients of either sex and any given age. In this analysis, the model was used to calculate outcomes of male patients who received the Carpentier-Edwards pericardial and supraannular valves for AVR at different implantation ages. Real-life estimates of the occurrence of valve-related events after AVR, obtained from the meta-analysis and from Weibull analysis of individual patient data for SVD, were used as input for the model. A detailed account of the microsimulation methodology has been published previously [24,25].

Validation

How valid are the model predictions? In order to verify the validity of its calculations, we compared the age- and sex-specific survival calculations of the microsimulation model for the Carpentier-Edwards pericardial valve with the corresponding Portland experience with the same valve. The latter did not constitute part of the model input. The Portland pericardial

data, from the Providence Health System, Portland, Oregon, USA, contains 1021 patients who received the prosthesis between 1991 and 2002. The mean age of the patients was 74.3 years. We also compared the age- and sex-specific model estimates of survival for the porcine valve with the Portland 25-year follow-up survival data on patients who underwent AVR with the Carpentier-Edwards 'standard' bioprosthesis [26].

Sensitivity Analysis

How precise are the model predictions? A one-way sensitivity analysis was performed to investigate the effect of uncertainty in the parameter estimates. In one-way sensitivity analysis, a single parameter is varied while the others are kept constant. Since variation of the estimates of valve-related events by their 95% confidence intervals yielded negligible changes in the long-term outcomes, we increased and decreased the baseline values by 25% for this analysis. The hazard ratios representing the 'additional' mortality were also systematically varied.

6.3. Results

Meta-Analysis

The 8 reports selected for meta-analysis of the Carpentier-Edwards pericardial valve comprised 2685 patients and a total follow-up of 12,250 patient-years. The 5 reports on the Carpentier-Edwards supraannular valve included 3796 valve recipients and 20,127 patient-years of follow-up. The mean ages of the two cumulative populations were 66.9 and 69.8 years. Approximately 62% of patients in both groups were males. The pooled incidence of valve-related events and their outcomes for both the pericardial and supraannular group are given in table 1. Thrombo-embolism was the most frequent event to occur in both valve types, giving hazard rates of 1.35% and 1.76% per 100 patient years respectively.

Analysis of SVD

According to the Weibull model, the median time to re-operation due to SVD in the pericardial valves were 17.1 (15.7 – 18.7), 19.9 (18.0 – 21.9) and 23.0 (20.5 – 25.9) years for 55-, 65-, and 75-year male patients. The estimates for the supraannular valves were 19.0 (17.9 – 20.1), 22.0 (20.3 – 23.8) and 25.5 (22.9 – 28.4) respectively.

Valve-related events	Events (number)		Hazard rate (per 100 pt-years)		Outcome			
					Death rate		Re-operation rate	
	CEP	CESA	CEP	CESA	CEP	CESA	CEP	CESA
Valve thrombosis	2	1	0.03	0.02	0.5	0	0.5	1
Thrombo-embolism	166	355	1.35	1.76	0.23	0.33	0	0
Hemorrhage	53	92	0.43	0.46	0.41	0.18	0	0
Endocarditis	70	79	0.62	0.39	0.38	0.25	0.17	0.35
Non-structural dysfunction	4	46	0.13	0.61	0	0	0.5	0.28
Structural valvular deterioration	55	173	#	#	0.09	0	0.85	0.72

Weibull models incorporating age dependency were constructed from primary data sets.

Table 1. Pooled incidence of valve-related events and their outcomes after aortic valve replacement with Carpentier-Edwards pericardial (CEP) and Carpentier-Edwards supra-annular (CESA) bioprostheses.

Microsimulation model calculations

The microsimulation model calculates total life expectancy (LE), event-free life expectancy (EFLE) and re-operation-free life expectancy (RFLE) after AVR for male and female patients of a given age. We give the results for male patients in this analysis. For a 65-year-old male patient for example, LE was 10.8 and 10.9 years; RFLE was 9.9 and 10.1 years and the EFLE 9.0 and 8.8 years respectively after implantation with the Carpentier-Edwards pericardial and supraannular valves. The LE, RFLE and EFLE after AVR at different ages of valve implantation, for both valves, are given in figure 1.

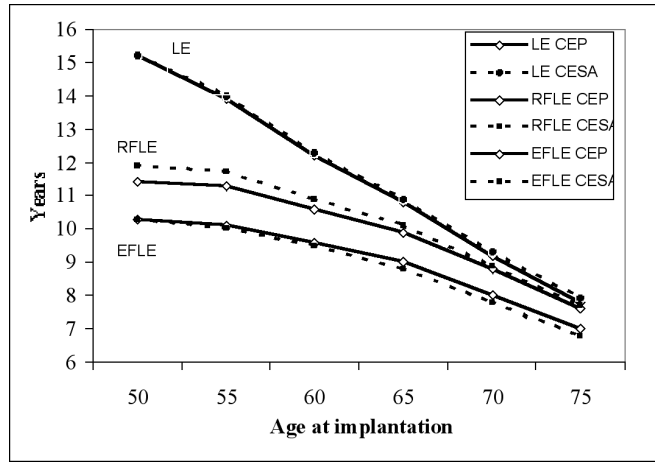


Figure 1. Life expectancy (LE), re-operation-free life expectancy (RFLE) and event–free life expectancy (EFLE) after aortic valve replacement with Carpentier-Edwards pericardial (CEP) and supraannular (CESA) valves.

The microsimulation model also calculates the cumulative incidence or lifetime risk of valve-related events and re-operation after valve implantation ('actual' analysis). The lifetime risk of a re-operation due to SVD was 18.3% and 14.0% for a 65-year-old male and 5.4% and 3.8% for a 75-year-old male respectively after AVR with pericardial and supraannular valves (Figure 2).

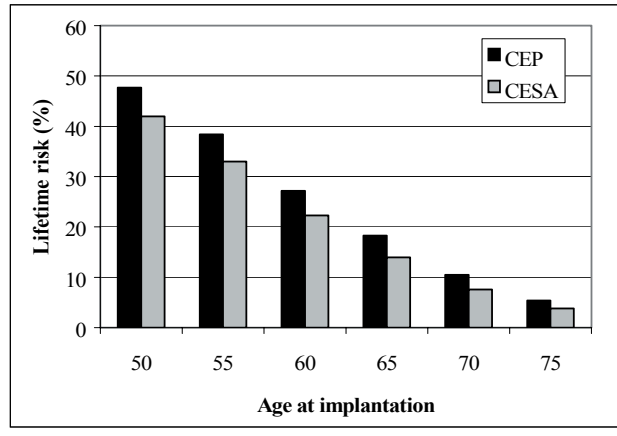
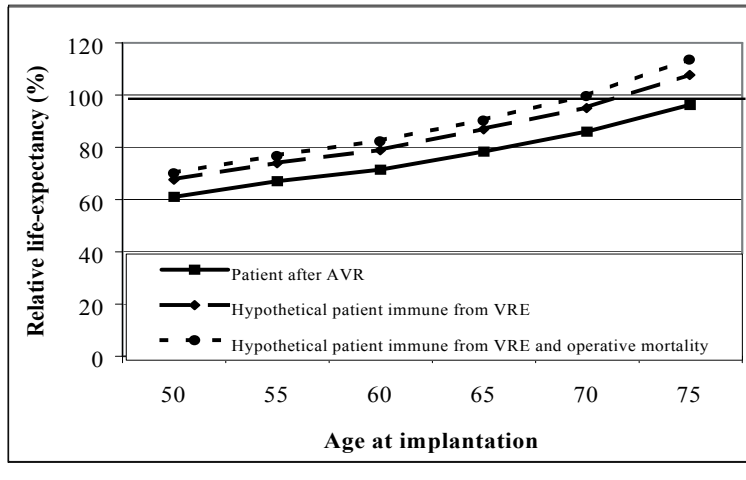


Figure 2. Lifetime risk of re-operation due to structural valvular deterioration after aortic valve replacement with the Carpentier-Edwards pericardial (CEP) and supraannular (CESA) valves at different ages of implantation.

We further compared the LE of patients who received the two types of prostheses with that of age-matched males of the general American population. As the LE was similar between the two valve types, we depict this comparison using only the supraannular valve (Figure 3).



AVR = aortic valve replacement, VRE = valve-related events

Figure 3. Life expectancy of men after aortic valve replacement with the Carpentier-Edwards supraannular valve relative to that of men in the general population.

It is seen that relative LE increased with advancing age of implantation, from about 60% at 50-years to nearly 100% for a 75-year patient. The relative LE's of hypothetical patients who were immune from valve-related events and operative mortality were also analyzed. These showed similar trends of increase with advancing age of implantation and was >100% that of a person in the general population at 75-years. The difference between the LE curve and the other two hypothetical curves represents the mortality associated with valve-related events and the operative procedure. The difference between curve for the hypothetical patient immune from valve-related events and operative mortality and the general population standard (i.e. 100%) represents the 'additional mortality' component.

Validation

We compared microsimulation model survival outputs with the corresponding Gompertz model-derived survival estimates of the Portland Carpentier-Edwards pericardial data. For 55-65-, and 75-year-old male patients, for example, the 10-year survival estimates were 64.1% and 63.7%, 51.2% and 48.9% and 33.1% and 32.3% respectively. Further, the survival outputs of the microsimulation model for patients of different ages receiving the Carpentier-Edwards supraannular valve compared favorably with the corresponding curves of the Carpentier-Edwards 'standard' Portland experience, through 25-years post-implantation (Figure 4).

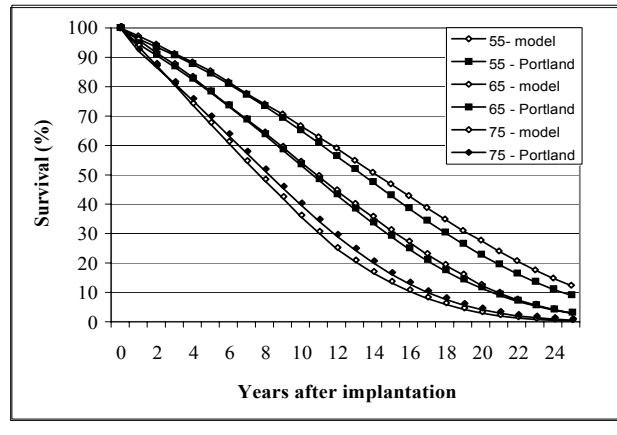


Figure 4. Comparison of microsimulation model survival output for Carpentier-Edwards supraannular valve and corresponding Portland Carpentier-Edwards standard valve survival for 55-, 65- and 75-year-old males after aortic valve replacement.

Parameter*	Plausible range for hazard rates [+] (per 100 pt-years)				Event-free life expectancy (EFLE) in years			
	CEP		CESA		CEP		CESA	
	Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable
Valve thrombosis	0.02	0.04	0.015	0.025	9.0	9.0	8.8	8.8
Thrombo-embolism	1.01	1.69	1.32	2.2	9.2	8.8	9.0	8.5
Hemorrhage	0.32	0.54	0.35	0.58	9.1	8.9	8.9	8.7
Endocarditis	0.47	0.78	0.29	0.49	9.1	8.9	8.8	8.7
NSD	0.10	0.16	0.46	0.76	9.0	9.0	8.9	8.7
[#]SVD (95% CI)	22.0 years	18.1 years	23.9 years	20.4 years	9.2	8.8	8.9	8.6
SVD (25% change)	25.1 years	15.1 years	27.7 years	16.7 years	9.4	8.3	9.0	8.2
Hazard Ratio	1.1	1.3	1.1	1.3	9.3	8.7	9.1	8.5
Hazard Ratio	1.0	1.4	1.0	1.4	9.6	8.5	9.3	8.3

CEP = Carpentier-Edwards pericardial valve, CESA = Carpentier-Edwards supraannular valve. The EFLE for a 65-year-old male patient after aortic valve replacement with CEP and CESA was 9.0 and 8.8 years respectively with the baseline hazard rates.

* Baseline values of the valve-related events are given in Table 1. The baseline median time to SVD was 20.1 and 22.2 years for CEP and CESA. The Hazard Ratio was 1.2 for a 65-year-old male patient.

[+] The plausible range was estimated by increasing and decreasing the baseline values by 25%. The 95% confidence interval was also used for structural valvular deterioration (SVD). Possible values were selected for the hazard ratio.

[#] Median time to SVD.

Table 2. Summary of sensitivity analysis for a 65-year-old male patient after aortic valve replacement.

Sensitivity Analysis

The effect on LE and EFLE of a 65-year-old male on individually increasing and decreasing the baseline valve-related event estimates is given in table 2. The most prominent effect on LE and EFLE was achieved by variation in the estimates of SVD. Variation in the 'additional mortality' estimate is also shown to have an appreciable effect on the life expectancies of a patient.

6.4. Discussion

In comparison to the mechanical prostheses, the bioprostheses are less thrombogenic, obviating the need in general for long-term anti-coagulation [27,28]. However, their propensity to undergo SVD [29] and concern regarding the comparative obstructive nature of the valves [30] limited their use. The second-generation pericardial and porcine valves were developed in the early eighties to improve durability and enhance hemodynamic function. Although previous studies have described and compared the outcomes after implantation with both valves [31], knowledge on long-term patient prognosis is still incomplete. We combined a systematic literature review, meta-analysis and separate data on SVD with microsimulation to calculate life expectancy and lifetime risk of re-operation for patients receiving these two valve types. This information would be useful for supporting prosthetic valve choice and in the management of individual patients after AVR.

Estimates of valve-related events required to parameterize the model were obtained by meta-analyses of selected reports. An advantage of pooling data was that it represented the experience of many centers. The risk of SVD after valve replacement is not constant but depends on the age of implantation and the time elapsed since the operation. Kaplan-Meier curves are usually used to describe this changing risk [32]. Grunkemeier and colleagues demonstrated that the Weibull curve was efficient in summarizing SVD in biological valves [21]. However, they suggested that at least 12 years of follow-up were needed to produce reliable estimates. We used primary data on the Carpentier-Edwards pericardial and supraannular valves, with over 18-years of follow-up, to calculate the respective Weibull parameters. Although the estimates of median time to re-operation calculated from the fitted Weibull distributions favor the supraannular valves, they were implanted on average in older patients (69.8 years versus 66.9 years). As there is a tendency for enhanced durability in older patients [21], these results do not permit us to conclude on the superior durability of either valve

type. Jamieson and colleagues who compared their experience in Vancouver on the Carpentier-Edwards pericardial and supraannular valves found no significant difference in the actuarial freedom from SVD between the two groups. While the overall actual freedom from SVD favored the pericardial valves (93.5 +/- 1.5 versus 89 +/- 1.0), there was negligible difference between the (61-70) and > 70 years age groups [31].

Microsimulation, by modeling multiple factors and complex outcome pathways that simultaneously determine outcome after AVR, provides a useful adjunct to the standard statistical methods used in the literature for calculating the prognosis of patients. The model calculates patient outcomes by superimposing the morbidity and mortality associated with valve-related events on the other components of mortality experienced by the patient [24]. Considering the many patient- and surgery-related factors that might affect valve durability and long-term survival [31,33,34], an attempt to directly compare pericardial and supraannular valves may be misleading. However, such concerns are reduced by use of the microsimulation model, which permits comparison of the individual valve type per se, assuming a uniform underlying mortality.

The Kaplan-Meier (actuarial) analysis was originally designed to describe the freedom from death. As previously indicated, this method has been extended to summarize complications such as SVD which are not necessarily fatal. In the latter instance, it describes the risk of SVD for the patient based on the assumption of immortality. However in reality, death occurring before implanted valve failure acts as a competing risk, resulting in an over-estimation of the actual risk of SVD. This error is magnified with advancing age of implantation and serves to underestimate the benefits of biological valve replacement. Conversely, cumulative incidence or 'actual' analysis considers the competing risk of death and calculates the percentage of patients who will experience an event before they die. It provides a better estimate of the durability of a bioprosthesis, especially in the elderly [32,35-37]. The microsimulation model calculates the lifetime risk of SVD and of other valve-related events. For a 65-year-old male for example, the life time risk of re-operation due to SVD is 18.3% and 14% after AVR with the Carpentier-Edwards pericardial and supraannular valves (Figure 2). The risk is further reduced for a 75-year-old male, estimated at 5.4% and 3.8% respectively. This information is useful in deciding on an age cut-off point for the choice of a mechanical valve or bioprosthesis.

The LE, RFLE and EFLE for males of different ages as estimated by the microsimulation model, is depicted in figure 1. The point estimates for LE and EFLE for both valve types, at various ages of implantation do not show appreciable difference. Kvidal and colleagues [38], who investigated the excess mortality after heart valve replacement, described an increasing excess hazard during follow-up and a decreasing excess hazard with advancing age of implantation. This supports a 'multiplicative' excess mortality, which was a structural assumption in our model. The alternative assumption of an 'additive' excess mortality may increase LE estimates, especially in patients under 70 [39,40]. RFLE is shown to be higher in the supraannular valves, which is explained by the higher median time to SVD of these valves.

The improvement of hemodynamics after AVR is related to normalization of left ventricular mass and function [41]. This in turn may reduce 'additional' mortality of a patient [22,23]. We have not yet addressed the possibility that 'additional mortality' may vary with different valve types and valve sizes, necessitating the use of different hazard ratios. In this context, the Carpentier-Edwards pericardial valve has been shown to be less obstructive in the aortic position than the Carpentier-Edwards supraannular valve [30]. This could translate to greater and more rapid regression of left ventricular hypertrophy after AVR with a pericardial valve conferring a higher survival benefit than presently calculated by the microsimulation model. We have used sensitivity analysis to underscore the importance of the 'additional mortality' factor on the outcomes of patients after AVR (Table 2).

Limitations of this methodology included certain structural assumptions in the microsimulation model and the uncertainty associated with the input parameters. For example, a constant hazard was assumed for valve-related events other than SVD. However, these hazards may vary with increasing age and age at implantation. Although we previously assumed endocarditis to take 2 phases of risk, comparisons of different calendar periods of implantation have shown a significant decline in early prosthetic endocarditis in recent years [42]. The model's user-friendly input interface permits addition and change of data when required. Many other patient- and surgery-related factors have been shown to influence overall survival after AVR [33,34]. However at present, the model calculates outcome for an average risk profile only. We have subsequently added coronary artery bypass grafting (CABG) to the model [43]. The moderate numbers of events for some valve-related events and possible publication bias give a degree of uncertainty to the input parameters of the model.

We hope to extend the microsimulation model with probabilistic sensitivity analysis, which is a more robust technique to analyze the uncertainty of the input variables.

In conclusion, we have described the use of the microsimulation methodology in providing insight into prognosis after AVR with the Carpentier-Edwards pericardial and supraannular valves. Both valve types perform satisfactorily, especially in the elderly patient, while no appreciable difference in long-term outcomes was apparent between either valve type when implanted in the aortic position.

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Appendix

Analysis of SVD

The Weibull formula for the freedom from SVD is:

$S(t) = \exp. - ((t / \sigma)^{\beta})$,

Where S (t) indicates the freedom from SVD at time t while σ and β denote the scale and shape parameters of the model. The scale parameter incorporates the age dependency of the Weibull model while the shape parameter reflects the changing risk of SVD over time [20].

We used data on 267 patients, implanted with Carpentier-Edwards pericardial valve between 1981 and 1984, to directly calculate the parameters of the Weibull model for the pericardial valves. These patients formed part of the original four-center pre-marketing clinical investigation conducted for the US Food and Drug Administration. The mean age of the patients at implantation was 65 ± 12 years, 64% were men and the follow-up extended to 18 years. For the Carpentier-Edwards supra-annular valve we used data on 1847 operations that were conducted between 1981 and 1999 at the University of British Columbia, Vancouver, Canada. The mean age of the population was 68.9 ± 10.9 years and follow-up extended up to 20-years.

A difference in median time to re-operation due to SVD between the 2 valve types could result from a difference in the age dependencies of the respective Weibull models. To examine the significance of a possible difference in the age effects, we combined the two data sets and estimated an overall Weibull model with factors for valve type, age dependency and their interaction. According to the overall Weibull model, there was no significant difference in the age dependency and shape parameters of the two Weibull models [age dependency = 0.015, shape parameter (β) = 3.419]. However, the intercepts of the scale parameters were significantly different between the two valve types. The scale parameters (σ) of the respective Weibull models were as follows;

Pericardial valve = exp. (2.133 + 0.015 * age)

Supraannular valve = exp. (2.235 + 0.015 * age)

These parameters were used to calculate the median time to re-operation due to SVD of both valve types. The parameters were also used to parameterize the microsimulation model.

As the pericardial valves were implanted during the period 1981 to 1984 and the supraannular valves from 1981 through 1999, we also examined the possibility of whether the more recent operations of the porcine valve were related to greater durability. Extension of the Weibull curve with a factor for the year of operation was not significant, indicating an absence of a period effect.

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7. Prognosis after Aortic Valve Replacement with St. Jude Medical Bileaflet Prostheses: Impact on Outcome of Varying Thrombo-Embolic and Bleeding Hazards

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Key words: Aortic valve replacement, bleeding, mechanical valves, prognostic modeling, thrombo-embolism.

Abstract

Aims: Prognosis after aortic valve replacement (AVR) with mechanical prostheses depends on multiple inter-related factors. Investigation of these factors is complicated by limited knowledge on outcome after AVR, and by the varying therapeutic International Normalized Ratio (INR) ranges employed worldwide. Meta-analysis was combined with microsimulation to calculate evidence-based age-specific outcome after AVR with St. Jude Medical (SJM) prostheses (St. Jude Medical Inc., St. Paul, MN, U.S.A.).

Methods and Results: Eight studies were included in a meta-analysis of published results of primary isolated AVR with SJM prostheses (2,986 patients, 16,163 patient years) to estimate the hazards of postoperative valve-related events. Using microsimulation, calculated life expectancy and event-free life expectancy was 22 and 16 years in 35-year-old, and 7 and 5 years in 75-year-old males. Calculated lifetime risk of experiencing thrombo-embolic or bleeding events was 22 and 15% in 35-year-old, and 7 and 37% in 75-year-old males. Varying thrombo-embolic and bleeding hazards resulted in considerable shifts in lifetime risks and deaths associated with these events.

Conclusion: Meta-analysis combined with microsimulation provides a powerful tool for reliable estimates of longterm prognosis and allows detailed insight into the occurrence of valve-related events. Thrombo-embolism and bleeding occur frequently after AVR with

mechanical prostheses and have an important impact on survival. Optimal INR control is therefore of utmost importance.

7.1. Introduction

Prognosis after aortic valve replacement depends on multiple inter-related factors associated with the patient, the medical center, and the type of prosthesis used[1]. Mechanical valves are designed to last a lifetime, but are thrombogenic. Therefore all patients require coumarin derivate therapy, which carries an increased risk of bleeding. It is important to achieve optimal anticoagulation, in which the incidence of thrombo-embolism and bleeding are minimized. The optimal therapeutic International Normalized Ratio (INR) range is still under discussion, however[2].

There is limited knowledge on outcome with regard to thrombo-embolic and bleeding complications following aortic valve replacement with a mechanical prosthesis. Most reported series are small with a short follow-up. Few randomized trials exist.[3, 4] Also, reported incidence of complications with the same valve and between different valve types varies considerably[1]. This can be explained by the different therapeutic INR ranges employed in the individual studies, the different means of reporting (e.g. with regard to definition and collection of outcome measures), the prosthetic valves used, patients' ability to manage their INR, and the inter-individual variance in predisposition to thrombo-embolism and bleeding.

We combined meta-analysis and microsimulation to study prognosis after aortic valve replacement with the St. Jude Medical (SJM) bileaflet prosthesis, and in particular we investigated the effect on long-term outcome of varying thrombo-embolic and bleeding hazards.

7.2. Methods

Meta-analysis.

Literature Search. We conducted a literature search of the PubMed and Medline databases for the period January 1990 to June 2000. The terms used for the search were both MESH terms and the text words "heart valve prostheses", "aortic valve" or "mechanical valve" in combination with "St. Jude". The search was limited to "humans" and to the English language literature. The references in the reports were cross-checked for other potentially relevant studies.

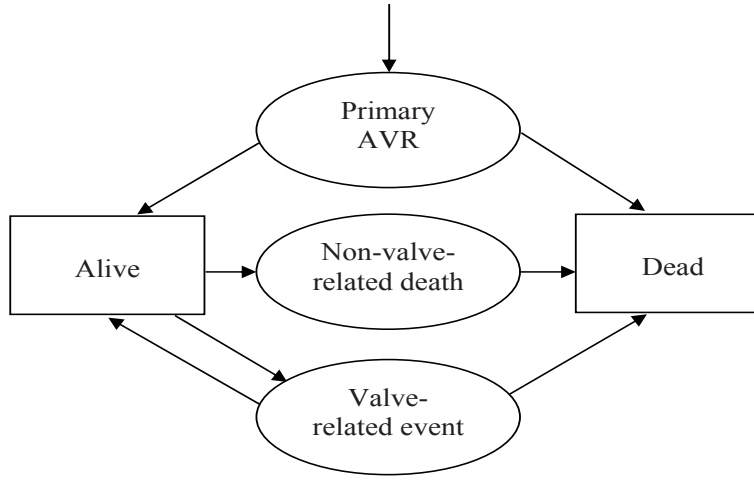
Seven criteria were stipulated to obtain a homogenous group of studies:

1) Studies that considered SJM mechanical prostheses.
2) Patient age ≥ 10 years at the time of operation. Reports that considered special age groups were omitted.
3) Isolated aortic valve replacement with or without coronary artery bypass grafting and with or without valve repair procedures. If replacement of other valves occurred in the studies, they were excluded.
4) Mainly first-time aortic valve replacement. Studies were excluded if more than 10% of patients had had previous aortic valve replacement or other cardiac operations.
5) Valve size 19-33 mm. Studies focusing on specific valve sizes were omitted.
6) Valve-related events defined according to the standard definitions published in 1988[5] and 1996[6].
7) INR range 1.8-4.5.

Data extraction and analysis. The selected published papers were carefully reviewed and patient characteristics and results of each study were tabulated in a spreadsheet. Events and outcomes in all studies were defined according to Edmund's guidelines [6]. Heterogeneity among the various studies was investigated by means of sensitivity analyses. Mantel-Haenszel-weighted pooling was used to obtain combined estimates of linearized annual thrombo-embolic and bleeding event rates. A combined estimate of the other valve-related event rates was obtained by means of simple pooling, because of the low number of events. The mortality associated with the individual valve-related events was also estimated.

Microsimulation model

The basic assumption of the simulation model is that a disease follows a course in time that can be adequately characterized by a number of discrete states. After aortic valve replacement, the patient can either die as a result of the procedure or continue to live. If the patient lives then he or she remains at risk of developing valve-related events for the rest of his or her life. Eventually the patient will die of either valve-related or non-valve-related causes. A schematic representation of these health states and events is given in Figure 1.



AVR = aortic valve replacement

Figure 1. Schematic representation of different health states of a patient after aortic valve replacement as implemented in the microsimulation model.

On the basis of microsimulation, or Monte Carlo type simulation conclusions can be drawn for a specific patient profile (e.g. 40-year-old males) by performing calculations of random individual life histories of patients. These calculations are repeated a number of times, thus producing a simulated or 'virtual' closed cohort of patients with similar characteristics. From this cohort, the mean outcome can be calculated and detailed insight can be obtained into the factors that affect the outcome. An attractive feature of microsimulation is that it has a memory, for example, it can adjust operative mortality, taking into account whether the individual patient has had previous aortic valve replacements.

The information on outcome after aortic valve replacement with the SJM prosthesis from the meta-analysis was entered into the microsimulation model. Details on the input of the microsimulation model are presented in the Appendix. A total of 10,000 'virtual' life histories were calculated for males at different ages (35, 45, 55, 65 and 75 years) by randomly drawing the age of death from the Dutch general population life table. Because there is a higher mortality rate among patients after aortic valve replacement compared to the general population that cannot be solely attributed to valve-related events[7, 8], we multiplied the age- and gender-specific mortality hazard of the general population with an age- and gender-related hazard for excess mortality, based on previous work[9-12] (see

Appendix). In the study it is also assumed that operative mortality increases with age. Operative mortality also increased with each reoperation. We employed an early increased hazard for endocarditis. The bleeding hazard derived from the meta-analysis increased with age. The bleeding hazard was 0.23% per patient-year in patients aged 35 years, 1.58% per patient-year in patient aged 60 years and 4.9% per patient-year in patients aged 75 years[13]. Mortality related to bleeding also increased with age. Bleeding-related mortality rates were 4% at age 35 years, 10% at age 60 years and 17% at age 75 years[14, 15].

For male patients at 5 different ages (35, 45, 55, 65 and 75 years) life expectancy, reoperation-free life expectancy, event-free life expectancy and actual lifetime risks for the various valve-related events were calculated. In addition, by doubling and halving the hazard rate of thrombo-embolic and bleeding events (sensitivity analysis), the effect of these events on lifetime risks and mortality was investigated.

Validation of the model was done by comparing its outcome with the long-term outcome of aortic valve replacement patients in a large dataset from Portland, Oregon, USA[12], as previously described [10].

7.3. Results

Meta-analysis.

The literature search identified 67 reported studies. After applying the selection criteria, 8 papers remained[16-23] and are shown in Table 1. The pooled population comprised 2,986 patients and a total follow-up of 16,163 patient-years. Mean age was 59 years and the ratio of males-to-females was 1.6. The pooled estimates of the linearized rates of valve-related events and their associated mortality are shown in Table 2. The most frequently occurring valve-related events were bleeding (1.58% per patient-year) with an estimated 10% risk of mortality: and thrombo-embolism (1.15% per patient-year) with an estimated 7% risk of mortality. Endocarditis was less frequently reported (0.45% per patient-year), but carried a considerable mortality risk of 36%.

Study characteristics	References							
	21	**22**	**19**	**23**	**16**	**18**	**20**	**17**
First author	Peterseim	Smith	Lund	Zellner	Arom	Khan	Myken	Horstkotte
Year of publication	1999	1993	2000	1999	1994	1994	1995	1993
Type of study	Retrosp	Retrosp	Retrosp	Prosp	Retrosp	Retrosp	Prosp	Prosp
No. of patients (N)	412	351	694	418	363	471	73	204
Mean age (yrs)	62	54	58	55	65	65	65	52
Male/female ratio	1.4	1.9	1.6	2.3	1.3	1.4	1.1	1.2
Follow-up (pt-yrs)	1800	1640	4502	2376	1255	2096	525	1969

Retrosp = retrospective study; Prosp = prospective study; pt-yrs = patient-years.

Table 1. Overview of the eight selected reports in the meta-analysis of St. Jude Medical aortic valve prostheses

Valve-related events	Pooled hazard rate (LOR: % per patient-year)*	Pooled estimate of lethality (%)
Valve thrombosis	0.08	25
Thrombo-embolism	1.15	7
Bleeding	1.58	10
Endocarditis	0.45	36
Non-structural valve failure	0.42	2
Structural valve failure	0.00	Not applicable

* Linearized annual occurrence rate (% per patient-year).

Table 2. Pooled hazard rate of valve-related events and their lethality after aortic valve replacement with a St. Jude Medical bileaflet prosthesis according to the meta-analysis.

Microsimulation.

Overall life expectancy, re-operation-free life expectancy and event-free life expectancy are shown in Figure 2 for male patients of various ages. Lifetime risks of the various valve-related events are displayed in Figure 3, again for male patients of various ages. Figure 4 illustrates the impact of varying the hazard of thrombo-embolism (figure 4a) and bleeding (figure 4b) on lifetime risks and mortality associated with these events.

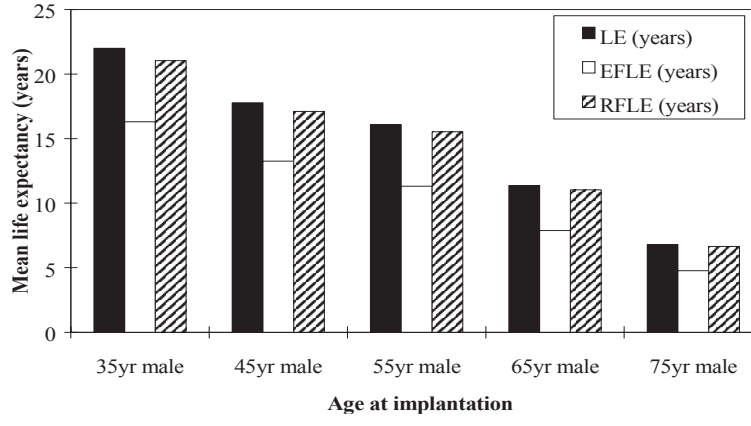


Figure 2. Mean life expectancy (LE), event-free life expectancy (EFLE) and re-operation-free life expectancy (RFLE) after aortic valve replacement with a St. Jude Medical bileaflet prosthesis for males at different ages.

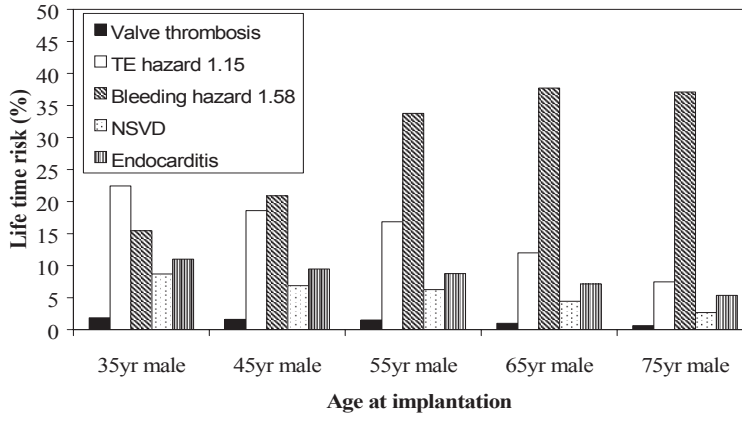


Figure 3. Lifetime risks of valve thrombosis, thrombo-embolism (TE), bleeding, non-structural valve dysfunction (NSVD) and endocarditis for male patients at different ages.

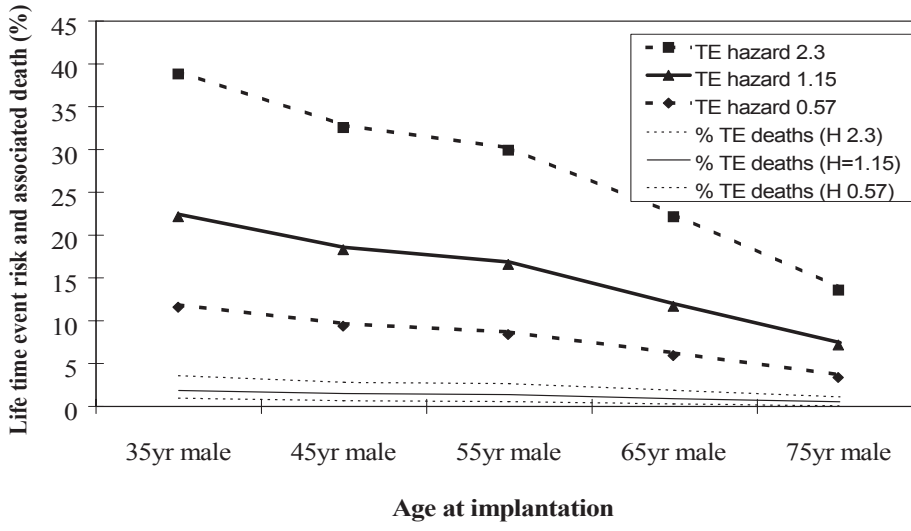


Figure 4a. Lifetime risk of at least one thrombo-embolic (TE) episode and associated mortality according to varying hazards (0.57, 1.15 and 2.3) for male patients at different ages.

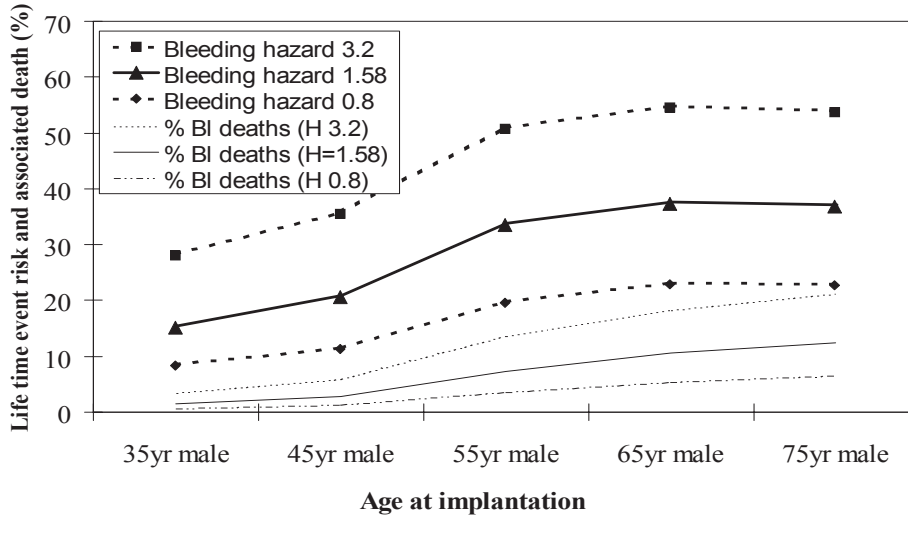


Figure 4b. Lifetime risk of at least one bleeding (Bl) episode and associated mortality according to varying bleeding hazards (0.8, 1.58 and 3.2) for male patients at different ages.

Validation showed that the outcome of the microsimulation model agreed well with the dataset from Portland[10, 12] for all age groups. For example, the calculated cumulative survival at 10 years postoperative for 45 and 65 year old patients was 77% and 55% according to the microsimulation model, compared to 77% and 58% respectively in the Portland dataset.

7.4. Discussion

Major thrombo-embolism and bleeding occur frequently after aortic valve replacement with a mechanical prosthesis and have a significant impact on prognosis. By lowering the thrombo-embolic and bleeding hazards, a major reduction in the occurrence of these events and their associated mortality can be achieved. It is therefore of the utmost importance to gain a better knowledge of the optimal INR range and to keep patients within this range.

Multiple interrelated factors (patient-, physician-, and prosthesis-related factors) affect outcome after aortic valve replacement. Published clinical experiences provide information on outcome after aortic valve replacement on a group level. By applying standard statistical techniques to assess risk factors (e.g. log-rank tests and the Cox proportional hazards model), it is possible to identify factors that may impact on the long-term outcome in a particular patient group. It is difficult to apply such analysis to the individual patient, however. In addition, in most reported series, the follow-up time is limited. This results in a considerable degree of uncertainty regarding long-term outcomes, and prompted us to develop a method to provide insight into the impact of risk factors on the individual patient (age- and sex-specific) and to assess the long-term outcome more accurately. The present study shows that the combined use of meta-analysis and microsimulation is a powerful tool with which to calculate reliable estimates of long-term prognosis after aortic valve replacement with the SJM mechanical prosthesis. It is a good option in the absence of a 'super dataset'[7]. In addition, it allows detailed insight into the occurrence of events that affect patient survival.

Bleeding and thrombo-embolism both play a major role in the life of patients after aortic valve replacement with a mechanical valve, and represent an important cause of death and disability. Based on the estimates from the meta-analysis, the microsimulation model calculated that the lifetime risk of at least one thrombo-embolic event varies from 8% in a 75-year-old to 22% in a person aged 35 years: for bleeding those risks were 37% and 16%

respectively. It should be noted that these risks are additive, which means that, for example, the combined lifetime risk of experiencing at least one thrombo-embolic or bleeding event is 49% in a 65-year-old patient, and that 12% of all deaths in 65-year-old patients are associated with these events.

Thrombo-embolic complications play an important role especially in younger patients, who have a relatively long life expectancy. On the other hand, bleeding complications gain significance as the patient grows older because of higher annual occurrence rates and increased associated mortality. By lowering the thrombo-embolic and bleeding hazards, a substantial reduction in the occurrence of those events can be achieved. New randomized trials[3] are therefore needed, in order to gain the necessary information regarding the desired therapeutic INR range in individual patients. Also, self-management of oral anticoagulant therapy represents an important improvement in our ability to maintain such an INR range in the individual patient[24]. Both will hopefully result in lower thrombo-embolic and bleeding hazards, and minimize the risks of experiencing these events after aortic valve replacement with mechanical prostheses.

The methods employed in the present study have their limitations. Using meta-analysis implies a combination of data from different sources that may not be comparable. Heterogeneity was minimized by employing strict selection criteria . The limitations of the microsimulation model necessitated certain structural assumptions. For example, a constant hazard was assumed for valve thrombosis, thrombo-embolism, and non-structural dysfunction, although these hazards may in fact be dependent on time since operation and age. Furthermore, endocarditis risk was assumed to be constant before and after 6 months of follow-up. Further studies are necessary to address these assumptions. Another issue concerns the excess mortality that was built into the model. These age- and sex-related multiplicative hazard ratios were obtained from previous work on survival after implantation with mechanical mono-leaflet prostheses and stented bioprostheses[9, 11]. We previously validated our excess mortality estimates using the Portland dataset and found good agreement[10, 12]. Therefore, although these patient populations may differ from the population under consideration, we are confident that the present analysis reflects the real-life situation adequately. Finally, survival after aortic valve replacement not only depends on age and sex, but also on many risk factors, including pre-operative New York Heart Association class and the presence of a coronary heart disease[8, 25]. These factors were not taken into account in the microsimulation model. In the present study we only considered

male patients for the purpose of illustration. However, the model is also capable of calculating life expectancy for female patients.

We are currently expanding the microsimulation model to cover other valve types[10, 11] and alternative surgical strategies like aortic valve repair, in order to provide an objective evidence-based clinical decision support system for clinicians who have to select a prosthetic aortic valve for an individual patient. This requires continuous refinement and regular updates on the input of the model as more experience is gained with the different types of aortic valve substitutes to provide valid estimates of prognosis for patients in the future.

Appendix: Input microsimulation model

Operative mortality

At age 40 years operative mortality is 2.7% and increases with age (odds ratio (OR) 1.034 per year) and with each re-operation (odds ratio 2.165)

Valve related events

For valve thrombosis: Linearized annual occurrence rate (LOR) 0.08% per patient year, mortality rate 25% and reoperation rate 50%.

For thrombo-embolism: LOR 1.15% per patient year and mortality rate 7%.

For bleeding: Gompertz distribution (gamma = 0.076; lambda = -8.71), mortality rate increasing with age (OR 1.0345 per year).

For endocarditis: Two-period risk (LOR 6.6 in the first 6 months and LOR 0.4 thereafter), mortality rate 36% and re-operation rate is 44%.

For non-structural valve failure: LOR 0.42% per patient-year, mortality rate 2% and reoperation rate 41%.

For structural valve failure: LOR 0.0% and mortality not applicable.

Excess mortality

See appendix table 1 on the next page.

Age (years)	HR Males	HR Females
25	8	7
35	6	7
45	3.6	4.2
55	1.5	2.8
65	1.1	2.2
75	1	1.3

HR = hazard ratio

Appendix table 1. Hazard ratios applied to the age- and sex-matched Dutch population life tables in order to approximate mortality of patients after aortic valve replacement.

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8. Comparison of Outcomes after Aortic Valve Replacement with a Mechanical Valve or a Bioprosthesis using Microsimulation

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Key words: aortic valve replacement, prognostic modeling, microsimulation, mechanical valves, bioprostheses, bileaflet, stented.

Abstract

Background – Mechanical valves and bioprostheses are widely used for aortic valve replacement (AVR). Although previous randomized studies indicate that there is no important difference in outcome after implantation with either valve type, insight into the outcomes after AVR is incomplete. The purpose of this study was to predict age- and gender-specific outcomes of patients after AVR with bileaflet mechanical valves and stented porcine bioprostheses and to provide evidence-based support for the choice of prosthesis.

Methods – Meta-analysis of published results of primary AVR with bileaflet mechanical prostheses (9 reports, 4274 patients and 25,726 patient-years) and stented porcine bioprostheses (13 reports, 9007 patients and 54,151 patient-years) was used to estimate the annual risks of post-operative valve-related events and their outcomes. These estimates were entered into a microsimulation model, which was then used to calculate age- and gender-specific outcomes of patients after AVR.

Results – The life expectancy (LE) and event-free life expectancy (EFLE) for a 65-year-old male, for example, after implantation with a mechanical valve and a bioprosthesis was 10.4

and 10.7 years and 7.7 and 8.4 years respectively. The lifetime risk of at least one valve-related event for a mechanical valve was 48% compared with 44% for a bioprosthesis. When LE and EFLE was considered, the age crossover point between the two valve types was 59 and 60 years respectively.

Conclusions - Meta-analysis based microsimulation provide an insight into the long-term outcomes of patients after AVR and suggest the currently recommended age threshold for implanting a bioprosthesis could be lowered further.

8.1. Introduction

Mechanical valves and bioprostheses are common valve types used in aortic valve replacement (AVR) [1, 2]. However, both are known to have inherent advantages and disadvantages. Mechanical valves, for example, offer long-term durability, but are thrombogenic necessitating lifelong anti-coagulation that carries an increased risk of hemorrhage. In contrast, bioprostheses are less thrombogenic, which in most patients obviates the need for long-term anti-coagulant agents. However their propensity to undergo structural valvular deterioration (SVD) limits their durability [3]. The risk of hemorrhage with mechanical valves and the risk of SVD in bioprostheses are age dependent, the first increasing and the latter decreasing with advancing age [4, 5]. Consequently, the choice between a mechanical valve and a bioprosthesis for a given patient undergoing AVR involves a balance between the risks and benefits of each valve type. Thus, knowledge of the outcomes after AVR for each valve type could assist the surgeon in his/ her choice of valve. Microsimulation and associated simulation techniques are capable of providing insight into outcomes after AVR. We therefore combined meta-analyses of several clinical studies with microsimulation to study the outcomes of patients after AVR with bileaflet mechanical valves and stented porcine bioprostheses respectively.

8.2. Methods

Meta-analysis

We conducted a literature search of the Medline database using the PubMed search interface, to identify reports which considered St. Jude Medical (SJM) bileaflet valves, models ‘standard’ and ‘hemodynamic plus’ (St. Jude Medical Inc., MN, USA) and one or more of the following stented porcine bioprostheses: Carpentier-Edwards ‘standard’ and ‘supra-annular’ valves (Baxter Healthcare Corp., CA, USA) or Hancock ‘standard’, ‘modified orifice’ and

'Hancock II' valves (Medtronic Inc., MN, USA). The MeSH terms in combination with the text words "St. Jude" for the mechanical valves and "stented", "Hancock", "Carpentier-Edwards" or "modified orifice" for the bioprostheses respectively was used for the search. The search was limited to the period January 1990 to October 2001 and to the English language. The title and abstracts of the studies obtained were screened for those that examined outcomes following AVR. References in these reports were cross-checked for other relevant studies. This resulted in 76 published reports for mechanical valves and 68 for bioprostheses respectively. The following criteria for each valve type was then stipulated in order to obtain homogenous groups of studies:

- Valves 19-33 mm in size, not focussing on a particular size or range.
- Patients > 15 years of age. Mean age of the study populations' ≥ 50 years.
- Predominantly first time AVR (> 90%).
- AVR with or without concomitant coronary artery bypass grafting (CABG) or any other valve repair procedure, but excluding other valve replacements.
- Valve-related events ascertained according to standard definitions published in 1988 [6] and 1996 [7].
- For mechanical valves: International Normalized Ratio (I.N.R.) between 1.8 and 4.5.

Studies that had overlapping patient populations were excluded. Finally, nine reports on St. Jude Medical mechanical valves [4, 8-15] and 13 reports on stented porcine bioprostheses [8, 16-27] were selected. Heterogeneity in the selected publications was investigated by means of sensitivity analysis. Morbidity and mortality data on valve-related events was obtained from these selected reports (see appendix).

Microsimulation

The data on valve-related events obtained from the meta-analysis were entered into a microsimulation model. The microsimulation model is a computer application that simulates the remaining lifetime of a given patient, taking into account all morbidity and mortality events and sequences of events that the patient might experience after AVR. The basic structure of the model is depicted in figure 1.

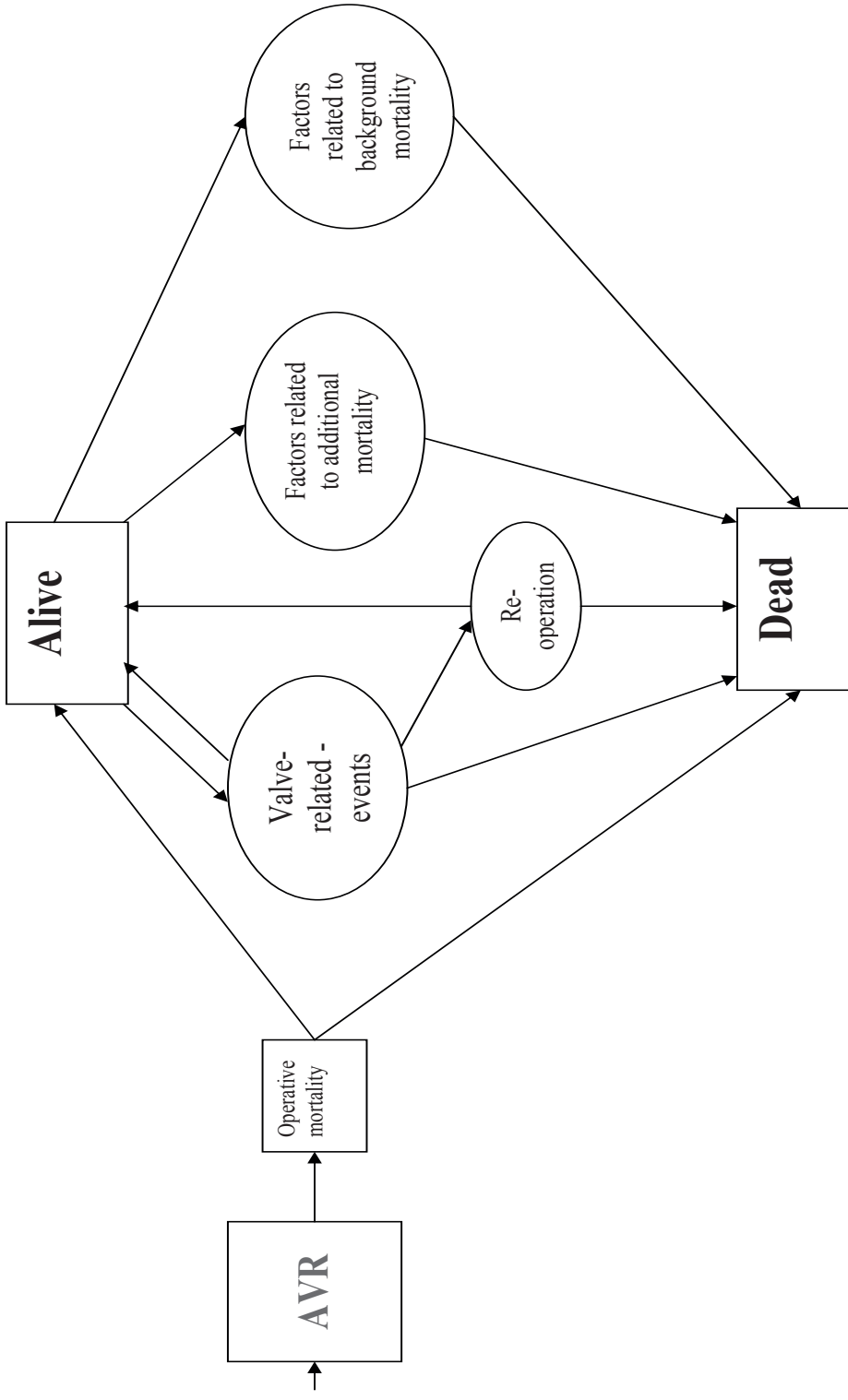

Figure 1. Basic structure of the microsimulation model

The microsimulation model assumes that, following AVR, a patient follows a course over time that can be adequately characterized by a number of discrete states. After AVR, the patient can either die, as a result of the operation, or can remain alive. The mortality of a patient who remains alive after AVR, is greater than that of a matched individual in the general population. This extra or excess mortality in the patient, compared to a matched person in the general population, is due to valve-related events and to 'additional mortality' that is associated with the underlying valve pathology, left ventricular function and the valve replacement procedure per se [28].

The model incorporates the mortality experience of the general population, called the background mortality, by means of life tables of the relevant population (ex: American males). Mortality due to valve-related events is incorporated using the data obtained from the meta-analysis. The 'additional mortality' experienced by AVR patients is not clearly defined and estimated at present. Thus, we estimated age- and sex-specific hazard ratios to represent the effect of the 'additional mortality'. This was done by approximating age- and sex-specific survival curves produced by the model, which contained the background mortality and mortality due to valve-related events, to the corresponding empirical curves obtained from the literature [20], which contained all three components of mortality. Consequently, hazard ratios of 2.9, 1.8, 1.2 and 0.8 were estimated for male patients' aged 45, 55, 65 and 75 years respectively.

The model calculates patient outcomes by superimposing the morbidity and mortality estimates of valve-related events, on the background mortality and additional mortality incorporated in the model. Ten thousand simulations of a given patient create a 'virtual' patient population, i.e. a cohort of patients with identical characteristics but with all possible outcomes after AVR. From this large cohort of identical patients, the model calculates the average life expectancies and lifetime risks of valve-related events for that given patient. A detailed account of the microsimulation structure and methodology has been given previously[29].

Validation

To assess the agreement between age- and sex-specific model calculations and the corresponding true-life experience of AVR patients, the results of the model were compared with the long-term outcomes of patients in large data sets from Portland, Oregon, USA [30] and the United Kingdom Heart Valve Registry (UKHVR), UK [31]. The Portland data set, from St. Vincent Heart Institute, Portland, USA, contains 30 years of follow-up data on patients who underwent AVR with the Starr-Edwards mechanical prosthesis and the Carpentier-Edwards 'standard' bioprosthesis and includes data on age, gender and CABG. The UKHVR, which is based at the Hammersmith Hospital, London, UK, is a computerized database that prospectively collects data on heart valve replacement surgery carried out in all cardiac centers throughout the UK. The data includes certain pre-operative, implant and post-operative data matched against individual patient demographics. All patients are followed-up via the national agencies responsible for registering all deaths of UK nationals. The 15-year follow-up data on bileaflet mechanical valves and stented porcine bioprostheses were used for the validation.

Sensitivity analysis

A one-way sensitivity analysis was conducted to investigate the effect of uncertainty in the parameter estimates. Variation of the estimates of the valve-related events by their 95% confidence intervals resulted in very small variations of the life expectancies. Hence we defined larger ranges by increasing and decreasing the baseline estimates by 25%. For SVD, the median time to SVD was varied by 10%.

8.3. Results

Meta-analysis

The nine selected reports on St. Jude Medical mechanical valves comprised 4274 patients and a total follow-up of 25,726 patient-years. The 13 reports on stented porcine bioprostheses included 9007 valve recipients and 54,151 patient-years of follow-up. The mean age was 59.1 and 65.4 years respectively. Approximately 65% of patients in both groups were males (Tables 1 & 2). The incidence of valve-related events and their outcomes are given in Table 3. The most frequent events were thrombo-embolism and hemorrhage in the mechanical valves and thrombo-embolism and SVD in the bioprostheses.

Study Characteristic	Reference number									
	8	9	10	11	4	12	13	14	15	Total
Type of study	RS	RS	RS	PS	RS	PS	RS	RS	RS	
Patients, n	412	351	694	418	666	204	178	773	578	4274
% Males	59	72*	62	70	60	46*	63	69	+	64
Mean age	62	54	58	55	66	52*	51	57	59*	59
Follow-up (patient-years)	1800*	1640	4502	2376	3881	1969	699	6419	2441	25726
% Concomitant CABG	42	22	24	27	50	+	7	9*	17	30

* Approximate figures, + data not available

RS = retrospective study, PS = prospective study

Table 1. Characteristics of the nine reports selected for the meta-analysis of St. Jude Medical aortic valve prostheses.

Study Characteristics	Reference number													
	16	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**8**	**24**	**25**	**26**	**27**	**Total**
Type of study	PS	+	PS	RS	RS	PS	RS	RS	RS	RS	RS	RS	+	
Patients, n	843	395	1108	165	1594	670	136	281	429	573	1823	561	429	9007
% Males	58	62	49	70	71	75	85	62	72	+	+	70	73	65
Mean age	69	66	74	67	60	65	50	75	64	59	69	72	64	65
Follow-up (patient-years)	5093	1264	4735	551	10212	4813	1496	937	3000	5187	12640	1792	2431	54151
% Concomitant CABG	43	31	+	19	34	43	7	+	35	+	42	39	34	37

+ Data not available

RS = retrospective study, PS = prospective study

Table 2. Characteristics of the 13 reports selected for the meta-analysis of the stented porcine bioprostheses.

Valve-related events	Events (n)		LOR (per 100 patient-years)		Outcome			
					Death Rate		Re-operation rate	
	Mech	Bio	Mech	Bio	Mech	Bio	Mech	Bio
Valve thrombosis	39	2	0.16	0.01	0.22	0.67	0.63	0.33
Thrombo-embolism	419	717	1.6	1.3	0.17	0.18	0	0.01
Hemorrhage	419	189	1.6*	0.4	0.14	0.2	0	0
Endocarditis	89	240	3.9/0.66+	3.2/0.48+	0.43	0.36	0.53	0.5
Non-structural dysfunction	70	91	0.29	0.3	0.04	0	0.37	0.43
Structural valvular deterioration	0	469	0	#	0	0.12	0	0.75

*A Gompertz model was constructed

+ A two-period exponential model was constructed for risk during and after the first six months after implantation.

A Weibull model was constructed incorporating age dependency.

LOR = Linearized occurrence rate or hazard, Mech = mechanical valve, Bio = bioprosthesis

Table 3. Pooled incidence of valve-related events and their outcomes after aortic valve replacement with a mechanical valve and a bioprosthesis

Microsimulation

The microsimulation model calculates total life expectancy (LE) and event-free life expectancy (EFLE) following AVR with mechanical valves and bioprostheses for patients of either sex and of different ages. We give the results for male patients. For a 65-year-old male patient for example, LE was 10.4 and 10.7 years and EFLE was 7.7 and 8.4 years respectively after implantation with a mechanical valve and a bioprosthesis. The comparisons of LE and EFLE are depicted in Fig 2. When considering LE and EFLE, the age crossover points between the two valve types were 59 and 60 years respectively.

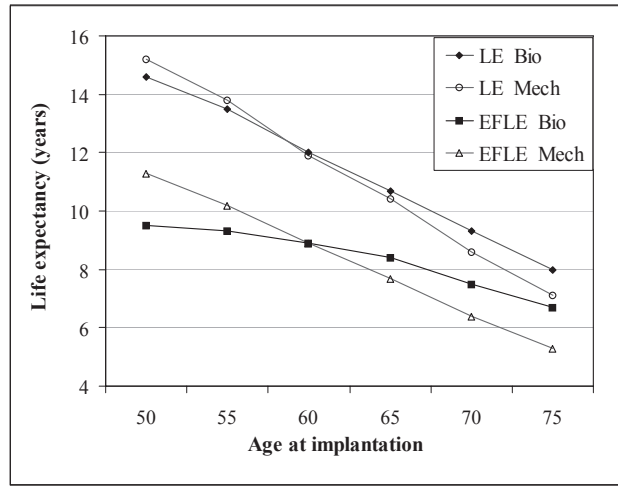

Figure 2. Comparison of life expectancy and event-free life expectancy in males after aortic valve replacement with mechanical valves and bioprostheses.

The lifetime risks of the more frequently occurring valve-related events are depicted in figures 3a and 3b. As seen in figure 3a, the lifetime risk of SVD following a bioprosthesis, reduces with advancing age at implantation, and is about 10% for a 75 year old patient. For the mechanical valves, the decreasing risk of thrombo-embolism with advancing age at implantation, concomitant on a decreasing life expectancy, is opposed by an increasing risk of hemorrhage (Fig. 3b). When considering the lifetime risk of experiencing at least one valve-related event, the age crossover point for AVR was 63 years.

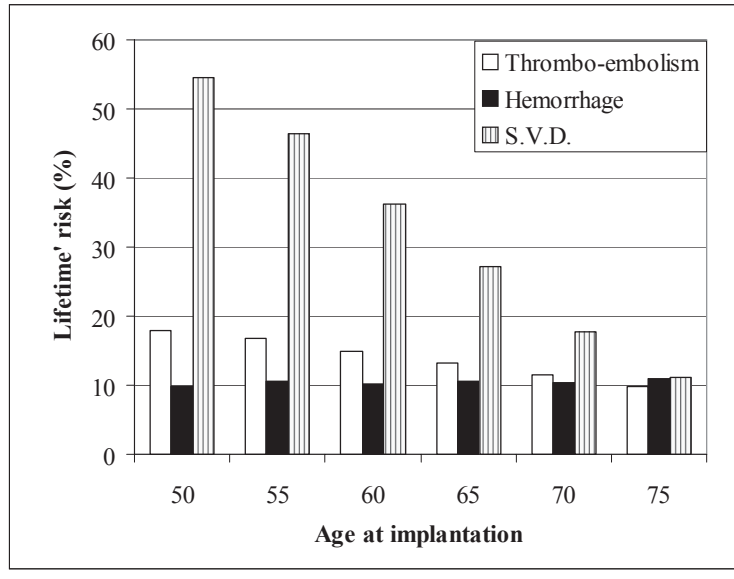

Figure 3a. Lifetime risks of thrombo-embolism, hemorrhage and structural valvular deterioration following aortic valve replacement with bioprostheses in males of different ages.

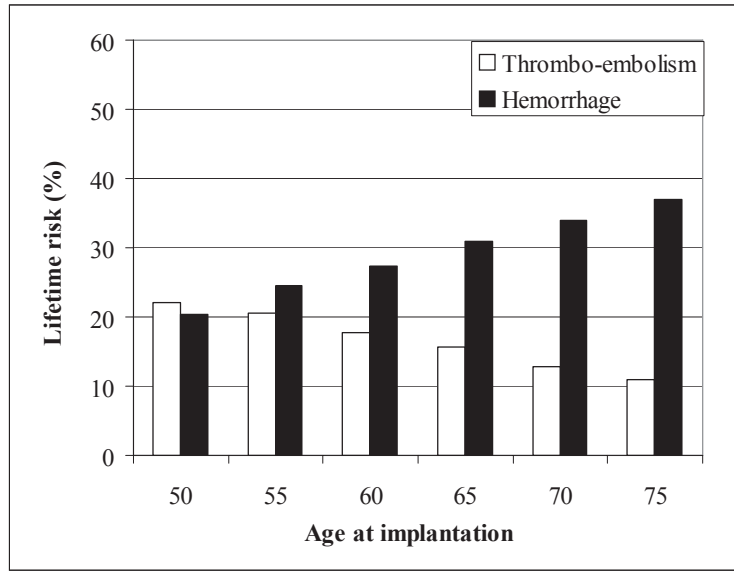

Figure 3b. Lifetime risks of thrombo-embolism and hemorrhage following aortic valve replacement with mechanical valves in males of different ages.

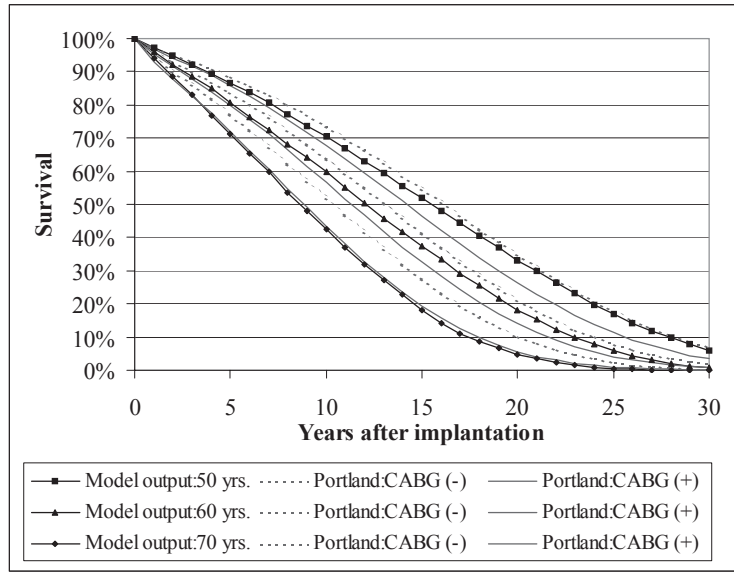

Figure 4a. Comparison of microsimulation model output and corresponding Portland data for 50-, 60- and 70-year-old males after aortic valve replacement with mechanical valves.

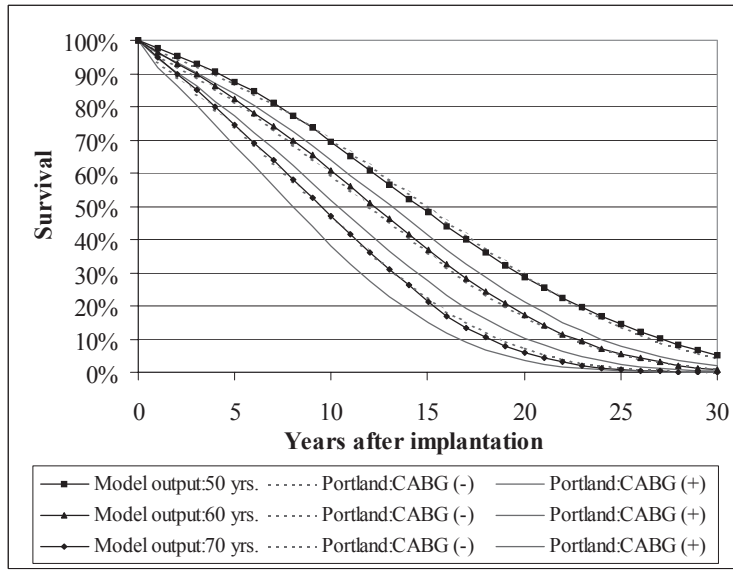

Figure 4b. Comparison of microsimulation model output and corresponding Portland data for 50-, 60- and 70-year-old males after aortic valve replacement with bioprostheses.

Validation

The results from our model for males of different ages and for both valve types were compared with the corresponding long-term survival data from Portland, Oregon [30]. The overall agreement was favorable (Figures 4a & 4b). Applying the United Kingdom background mortality estimates, we also compared model outputs with the 15-year experience of the UKHVR [31]. Interestingly, the UK patients appeared to have a better survival. For example, when the model output for a 62-year-old male who received a bioprosthesis was compared to a similar group of (60-65)-year-old patients in the UKHVR, the 15-year survival calculated by the model was 36% as compared to 47% (40%-53%) in the UKHVR.

Sensitivity analysis

The EFLE for a 60-year-old male patient and the corresponding age crossover point between the two valve types, for extreme values of some selected valve-related events, is given in table 4. A change in the risk of SVD was shown to have the largest influence on EFLE and the age crossover point.

8.4. Discussion

Simulation methodologies are widely used in operations research and management science [32]. A well-known example of a simulation program is the flight simulator in the aviation industry. Although not commonly used in clinical medicine, simulation models have been used previously to determine the prognosis of patients after AVR [33, 34]. We have designed a microsimulation model, which calculates the outcomes of patients after AVR. Compared to standard statistical techniques, the added value of microsimulation is that it allows modeling of complex outcome pathways resulting from the many simultaneous risks and provides detailed insight into the outcomes of patients following valve replacement, deducible to the individual patient. The structure of the model incorporates a schematic representation of the lives of AVR patients (Fig. 1) and in principle, the model can be applied to any valve type. For this analysis, data from meta-analysis of published reports were incorporated into the model to predict the outcomes of patients after AVR with bileaflet mechanical valves and stented porcine bioprostheses respectively.

Parameter and (valve type)	Baseline Estimate	Plausible Range *		Event-free Life Expectancy (years) +		Age Crossover Point #	
		Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable
Thrombo-embolism (Mech.)	1.6	1.2	2	9.1	8.6	62	58
Thrombo-embolism (Bio.)	1.3	1	1.6	9.1	8.7	59	61
Hemorrhage (Mech.) ~	1.3	1	1.7	9.2	8.5	62	58
Endocarditis (Mech.)	0.7	0.5	0.9	9	8.7	61	59
S.V.D. (Bio.)	16 years	17.6 years	14.4 years	9.2	8.5	57	63

* The plausible range was defined by increasing or decreasing the baseline estimates for thrombo-embolism, hemorrhage and endocarditis by 25%. For SVD, the median time to SVD was varied by 10%.

\+ The event-free life expectancy (EFLE) calculated by the model was 8.9 years for a 60-year-old male with baseline estimates.

\# The age crossover point between mechanical valves and bioprostheses was 60 years for EFLE at baseline analysis.

~ Data from another study (5) was used to model hemorrhage in mechanical valves. The baseline risk was varied for this analysis.

Mech. = mechanical valve, Bio. = bioprosthesis, SVD = structural valvular deterioration.

Table 4. Summary of one-way sensitivity analysis

Ideally for simulation methodology, a comprehensive data set should be available. This data set should contain detailed information on a wide range of patients, including data on all valve-related events and long-term follow-up. However, such a database is hard to assimilate and is not available at present. Hence, we pooled empirical data and quantified estimates required to parameterize the model. An advantage of pooling data was that it represented the experience of many institutions and countries and thereby enhanced generalizability of the results. We selected the St. Jude Medical valve, a bileaflet low-profile prosthesis, to represent the mechanical valves. It is one of the most commonly implanted mechanical prostheses at present [1]. We further selected five types of stented porcine bioprostheses, both first and second generation, to represent the bioprostheses. No overt differences in the performance of these valves have been documented in the literature [35-38].

The actuarial method and the Kaplan-Meier analysis are commonly used in many studies to estimate the survival of patients after AVR. However, when applied to non-fatal complications such as SVD, the risk described is that which patients would experience provided they were immortal and answers the hypothetical question "what is the risk of the event if no patient ever died?" A more relevant estimate is the actual percentage of patients who will experience an event before they die. Estimation of the cumulative incidence, termed 'actual' analysis in cardiac literature has recently gained interest [39]. This method modifies the survival estimate to exclude future events attributed to already dead patients and answers the question "what is the lifetime risk of the event?" The microsimulation model provides estimates of the lifetime risk of valve-related events (Fig. 3a & 3b). Thus, for example, a 65-year-old male would have a 48% risk of experiencing at least one valve-related event if he had a mechanical valve replacement compared to 44% if he had a bioprosthesis. The age crossover point was 63 years. As depicted in figures 3a and 3b, the crossover point in overall valve complications follows the increasing risk of hemorrhage with advancing age of implantation in mechanical valves, balanced against the decreasing risk of SVD with advancing age in bioprostheses.

The model predicted a LE of 10.4 and 10.8 years respectively for a 65-year-old male following implantation with a mechanical valve and a stented bioprosthesis. Considering LE, the age crossover point between either valve type was 59 years. This result concurs well with the results of Birkmeyer and colleagues [33] who used a Markov state-transition model to

simulate the prognosis of AVR patients. They obtained a crossover point of 60 years. The microsimulation model also calculates the EFLE after AVR. For the 65-year-old male patient for example, the model predicted an EFLE of 7.7 and 8.4 years respectively, for mechanical valves and bioprostheses. Considering EFLE, the age crossover point between either valve type was 60 years.

Results from previous randomized studies [40, 41] and another long-term prospective study [4] indicate that there is no significant difference in outcome after implantation with mechanical valves and bioprostheses. The American College of Cardiology and the American Heart Association guidelines [3] recommend a bioprosthesis for patients ≥ 65 years of age, who do not have risk factors for thrombo-embolism, based on the reduced risk of SVD and the increasing risk of hemorrhage above this age. Our results suggest that, contrary to current recommendation, a bioprosthesis can be considered for patients under 65 years of age. New strategies being developed to retard mineralization of xenograft valves [2], with hopefully a concomitant reduction in SVD risk, would further support reduction of the 65-year-old threshold. Nevertheless, patient-related factors including individual hazards for valve-related events (for example, increased risk of bleeding), patient preference, type of surgery and health care delivery factors also need to be considered in the decision making process for valve choice in the individual patient [42]. The long-term results for mechanical valves and bioprostheses, calculated using our model, agreed with the corresponding long-term follow-up data from Portland, USA [30] (Figures 4a and 4b). However, for most age groups, the UK patients [31] appeared to have a somewhat better survival than the model results and US patients. The smaller number of patients in the UK data during the latter part of follow-up might account for this discrepancy. If systematically different criteria (New York Heart Association (NYHA) class, timing of surgery etc.) were used in the selection of patients in the UK as compared to the US, the 'additional mortality' (see appendix) of UK patients could differ from their counterparts in the US. The 'additional mortality' inherent in AVR patients is incorporated into the model by means of age-specific hazard ratios and hence different hazard ratios may be required to model the UK patients.

Limitations of the model included certain structural adjustments made with respect to the valve-related events. For example, valve thrombosis, thrombo-embolism and non-structural

dysfunction (NSD) was assumed to carry constant hazards. The risk of endocarditis was assumed to be constant during the early and late phases. These hazards may in fact be time- and age-dependant, and hence, further knowledge is necessary to address these assumptions. Survival after AVR has also been shown to depend on pre-operative cardiac rhythm, type of valve lesion, concomitant CABG and NYHA functional status [43]. Although the model incorporates these factors non-specifically by means of hazard ratios, the model cannot determine the individual influence of these factors on overall survival. At present, the model can only predict outcome for an average risk profile. However, we are currently incorporating CABG into the model. Ultimately, we envisage the introduction of a user-friendly microsimulation model on the Internet, which could be used as a bedside tool by the cardiologist or surgeon. This microsimulation methodology could also find application in other fields of medicine.

In conclusion, we have described the use of microsimulation to provide insight into age- and gender-specific long-term outcomes after AVR. We suggest the currently recommended age threshold for implanting a bioprosthesis could be lowered further.

Appendix

Input microsimulation model

Valve-related events

The annual hazards of valve thrombosis, thrombo-embolism and non-structural dysfunction (NSD) were considered to be constant over time. Weighted pooling was used to obtain combined estimates of the linearized annual occurrence rates (LOR) for these events. The estimates for endocarditis, and for SVD in bioprostheses were obtained by pooling the respective freedom-from-event curves [44]. The risk of endocarditis was assumed to take 2 phases of constant hazard, with the hazard during the first 6 months greater than the subsequent period. Therefore, we fitted 2-period exponential models to the pooled freedom-from-endocarditis curves of the 2 valve types.

The risk of SVD in bioprostheses depends on the time that elapsed since valve replacement and the age of the patient at implantation. This relationship is well described by a Weibull

model[45]. The Weibull model is a generalization of the exponential distribution, which incorporates an additional shape parameter. The shape parameter reflects the changing risk of SVD over time. We estimated the shape parameter from the pooled freedom from SVD curve and calculated the age effect from another selected study [20]. The formula for freedom from SVD is:

$$S(t)= e^{-(t/\sigma)^{\wedge}\beta},$$

where S(t) indicates the probability of remaining free from SVD at time t while σ and β denote the scale and shape parameter of the model. The value of σ depends on age: $\sigma = e^{2.21 + 0.0112 * age}$ while $\beta = 3.35$. With these parameters, the median time to SVD was 15.1, 16.8 and 18.8 years respectively for 55-, 65- and 75-year male patients. As per meta-analysis, a zero risk of SVD was assigned for the mechanical valves.

Incorporating data from a previous study [5], hemorrhage after AVR with mechanical valves was modeled using the Gompertz distribution, which takes into account the exponentially increasing hazard of that event with patient age. Mortality and re-operation rates associated with individual valve-related events was also estimated (Table 3).

Operative mortality

Operative mortality was estimated at 1.5% for a 40-year-old male patient, increasing with odds ratios of 1.022 per year and 1.7 with every re-operation.

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9. Decision-Making in Aortic Valve Replacement: Bileaflet Mechanical Valves versus Stented Bioprostheses

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Key words: aortic valve replacement, prosthetic valve choice, mechanical versus Bioprostheses, microsimulation, clinical decision support system.

Abstract

Background: Valve prosthesis selection for patients who require aortic valve replacement is dependent on several interrelated factors. Often, more than one valve type seems suitable for the individual patient, and selection of a valve type may be difficult.

Methods: The application of an evidence-based microsimulation model as an objective tool to support the choice between a bileaflet mechanical prosthesis and a stented bioprosthesis in the individual patient is described. In addition, a pilot study investigating the effect of knowledge gained by this microsimulation model on prosthetic valve choice by cardio-thoracic surgeons and cardiologists is presented for 2 hypothetical patients.

Results: After implantation with a mechanical valve bleeding and thrombo-embolism are common, especially in the elderly. After implantation with a bioprosthesis re-operation for structural failure is the most important valve-related complication, especially in younger patients. Life expectancy after aortic valve replacement is markedly reduced compared to the general Dutch age-matched population, regardless of the valve type implanted. In the pilot study knowledge gained by the microsimulation model caused a shift in the preference towards a mechanical prosthesis in clinical experts.

Conclusion: Microsimulation incorporating current epidemiological data provides an objective tool to estimate prognosis for individual patients after aortic valve replacement with different valve prostheses. It may develop towards a useful clinical decision support system for valve prosthesis selection.

9.1. Introduction

Prognosis after aortic valve replacement (AVR) depends on multiple interrelated factors associated with the patient, the medical center and the type of prosthesis used[1]. Given the number and complexity of factors that affect outcome after AVR, it can be difficult to make an objective selection of the preferred valve substitute in the individual patient. The application of an evidence-based microsimulation model to predict age- and gender-specific outcome after AVR is illustrated for two commonly used prosthetic valve types, bileaflet mechanical valves and stented porcine bioprostheses. In addition, a pilot study was conducted to investigate the effect of presenting the microsimulation model to cardio-thoracic surgeons and cardiologists on their preference for a particular valve substitute, in 2 hypothetical patients.

9.2. Methods

Meta-analysis and microsimulation.

Meta-analyses were previously performed in order to obtain evidence on the outcome of patients after AVR with bileaflet mechanical valves (St Jude Medical) and stented porcine bioprostheses (Carpentier Edwards Standard or supra-annular, Hancock Standard, modified orifice or II) [2,3]. The pooled reported estimates of operative mortality, valve-related events and their consequences (death, re-operation) were entered into a microsimulation model [4].

The basic assumption of a microsimulation model is that a disease follows a course in time that can be adequately characterized by a number of discrete states and the events that cause a change of state. After aortic valve replacement, the patient can either die as a result of the procedure or stay alive. If the patient stays alive, he or she remains at risk of developing valve-related events for the rest of his or her life. Eventually this patient will die of either valve-related or non-valve-related causes.

From microsimulation or Monte Carlo-type simulation, conclusions can be drawn for a specific patient profile (for example, a 65-year old male) by performing calculations of random individual life histories of a large number of ‘cloned’ patients. These calculations are repeated a number of times, thus producing a simulated or ‘virtual’ closed cohort of patients with identical characteristics. From this cohort, the mean outcome can be calculated and detailed insight can be obtained into the factors that affect the outcome. An attractive feature of microsimulation is that it has a memory. For example, it can adjust

operative mortality, taking into account whether the individual patient has had previous aortic valve replacements.

The information from the meta-analyses on outcome after aortic valve replacement with bileaflet mechanical valves and stented bioprostheses was entered into the microsimulation model. Details on the input of the microsimulation model can be found in the Appendix. Ten thousand life histories were calculated for males at different ages (55, 65, 75 years) by randomly drawing the age of death from the Dutch general population life table. A higher mortality rate has been seen among patients after aortic valve replacement compared to the general population, which cannot solely be attributed to valve-related events[5,6]. Hence, we multiplied the age- and gender-specific mortality hazard of the general population with an age- and gender-related hazard for excess mortality, based on previous work[3,7-9](see Appendix). In this study it was also assumed that operative mortality increased with age and with each re-operation. An early increased hazard for endocarditis was employed. After implantation with a mechanical valve, the bleeding hazard derived from the meta-analysis increased with age, resulting in bleeding hazards ranging from 0.23% per patient year in patients aged 35, 1.58% per patient year in patient aged 60, to 4.9% per patient year in patients aged 75[10]. Mortality related to bleeding increased with age, resulting in bleeding-related annual mortality rates varying from 4% at age 35, 10% at age 60, to 17% at age 75[11,12]. After implantation with a bioprosthesis, the occurrence of structural valve failure derived from the meta-analysis was fitted into a Weibull model, which is a generalization of the exponential distribution that accommodates a changing risk over time [13]. The Weibull model has been used previously to describe structural valve failure in biological valves, where the risk of structural valve failure increases with time [14,15].

For male patients at 3 different ages (55, 65 and 75 years) life expectancy, event-free life expectancy and actual lifetime risk of the various valve-related events by valve prosthesis types were calculated. To explore the influence of variation in parameter estimates a sensitivity analysis was performed. Hereto, we doubled and halved the hazard rate of bleeding events after implantation with a mechanical prosthesis. The effect of these events on lifetime risks of experiencing valve-related events was investigated. Finally, relative life expectancy after aortic valve replacement compared to the general age- and gender-matched population was calculated, and the impact of valve-related events on the reduction of relative life expectancy was assessed.

Validation of the model was done by comparing its outcome with the long-term outcome of aortic valve replacement patients in a large dataset from Portland, Oregon, USA[7], as previously described [9].

Pilot study

During the joint meeting of the Netherlands Society of Cardiology and the Netherlands Association for Cardio-Thoracic Surgery in The Hague, the Netherlands on 26 April 2002, a session on prosthetic valve choice in aortic valve replacement was organized. Preceding the lecture on meta-analysis and microsimulation based estimates of outcome after AVR with a stented bioprosthesis or a bileaflet mechanical valve, the participants were asked to choose either a mechanical valve or a bioprosthesis for 2 hypothetical patients:

CASE 1: A 66-year-old male, retired with active lifestyle, presents with asymptomatic aortic valve stenosis (gradient 120 mm Hg), no coronary artery disease, normal left ventricular function, no concomitant morbidity. In case of mechanical prosthesis, this patient wants to self-monitor the INR, which is associated with low thrombo-embolic and bleeding risks.

CASE 2: A 60-year-old female presents with dyspnoea on exertion caused by severe aortic regurgitation after an episode of endocarditis. Left ventricular function is normal-impaired; there is no coronary artery disease. The patient has non-insulin-dependent diabetes mellitus that is difficult to control (compliance problem?). This patient is therefore at an increased risk of thrombo-embolism, bleeding and endocarditis.

The choice options were as follows:
1=definitely mechanical valve, 2=probably mechanical valve, 3=no preference, 4=probably stented bioprosthesis, 5=definitely stented bioprosthesis.

After the lecture the audience was confronted with the same two cases and with the evidence-based estimates of life expectancy of the two cases according to the microsimulation model. The audience was asked again to choose the preferred valve type for the 2 hypothetical cases. To investigate the effect of the presentation on prosthetic valve preference in the two hypothetical cases the Wilcoxon matched pairs signed ranks test was employed. SPSS 10.0 for Windows (SPSS, Chicago, Ill, USA) was used for all analyses.

9.3. Results

Meta-analysis and microsimulation

An overview of the estimated occurrence of valve-related events after implantation with a bileaflet mechanical valve or a stented bioprosthesis from the meta-analyses is displayed in Table 1. Figure 1 shows the age-dependent estimates of freedom from structural valve failure after implantation of a stented bioprosthesis derived from the meta-analysis. Conditional on survival, median time to structural valve failure was 13.8, 15.4, and 17.3 years for patients aged 55, 65 and 75 years respectively at the time of implantation.

	Mechanical valve	**Stented bioprosthesis**
	LOR (lethality)	**LOR (lethality)**
Valve thrombosis	0.08%/yr (25%)	0.03%/yr (67%)
Thrombo-embolism	1.15%/yr (7%)	0.90%/yr (19%)
Bleeding	1.58%/yr (10%)*	0.38%/yr (21%)
Endocarditis	0.45%/yr (36%)	0.68%/yr (34%)
Non-structural valve failure	0.42%/yr (2%)	0.38%/yr (5%)
Structural valve failure	0.00%/yr (NA)	Weibull function

LOR = linearized annual occurrence rates, NA = not applicable.

* In the microsimulation model an age-dependent incidence was used (see Appendix).

Table 1. Estimated occurrence of valve-related events and associated lethality by valve prosthesis type.

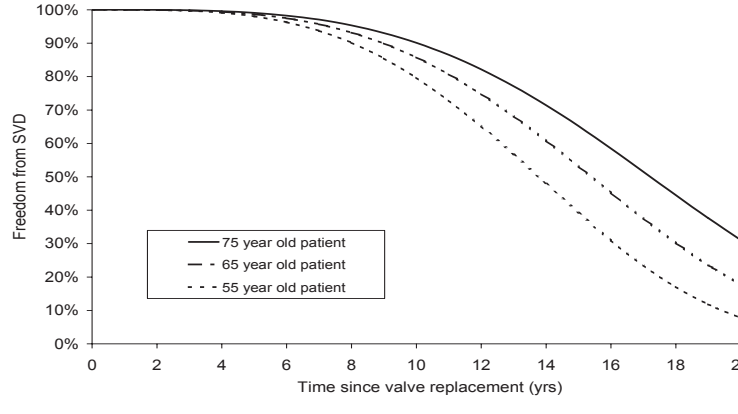


Figure 1. Meta-analysis based Weibull function describing the actuarial freedom from structural valve failure after implantation of a stented bioprosthesis for patients aged 55, 65 and 75 years at the time of implantation.

Figure 2 displays the calculate mean life expectancy and event-free life expectancy after AVR with a bileaflet valve or a bioprosthesis according to the microsimulation model for male patients aged 55 to 75 years.

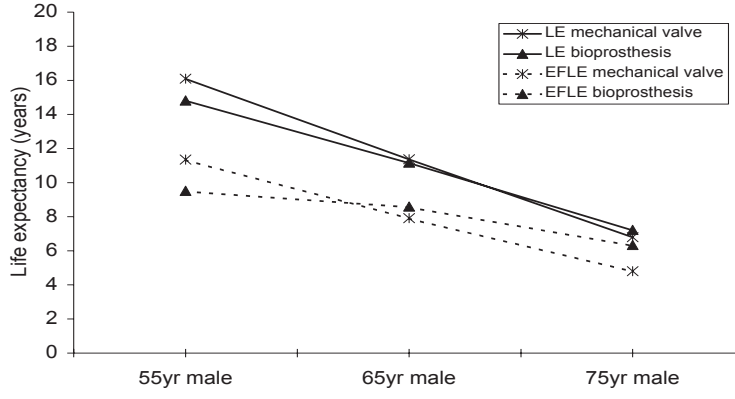


Figure 2. Calculated life expectancy and event-free life expectancy after AVR with a bileaflet valve or a bioprosthesis according to the microsimulation model.

In Figure 3, the life time risk of experiencing at least 1 valve related event by valve prosthesis type is shown for male patients aged 55, 65 and 75 years. After implantation with a mechanical valve the valve-related events that the patient encounters are mainly bleeding and thrombo-embolism, while after implantation with a bioprosthesis structural valve failure is the most common valve-related event.

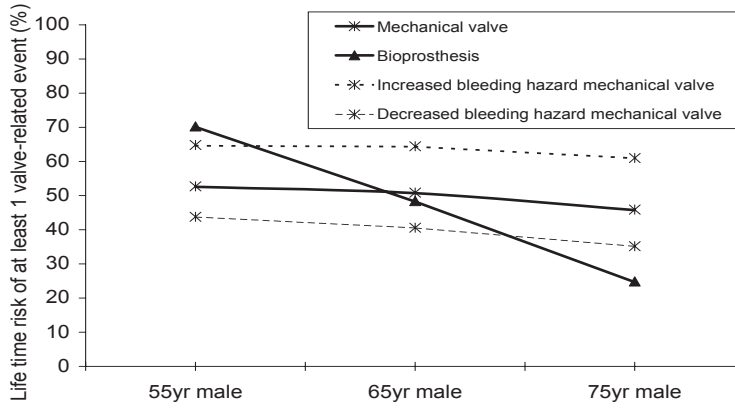


Figure 3. Lifetime risk of experiencing at least one valve-related event by valve prosthesis type for male patients aged 55, 65 and 75 years.

The age threshold for implantation of either valve type is approximately 63 years. The interrupted lines in Figure 3 represent the effect of doubling and halving the hazard rates of bleeding events on lifetime risks of valve-related events after implantation with a bileaflet mechanical prosthesis. In case of a twofold increased bleeding hazard the age threshold for implantation of either valve type is approximately 58 years, while this is approximately 69 years for a twofold decreased bleeding hazard. Figure 4 shows the relative life expectancy of patients after AVR with a bileaflet mechanical valve and stented bioprosthesis compared to the age- and gender-matched general Dutch population. In addition, the relative life expectancy of the hypothetical case of no valve related events, i.e. after implantation with the perfect valve substitute is shown. The relative life expectancy after implantation with a bileaflet mechanical valve, a stented bioprosthesis and the perfect valve substitute ranged from 75%, 69% and 81% respectively for a 55-year-old male patient, to 82%, 87% and 93% respectively for a 75-year-old patient.

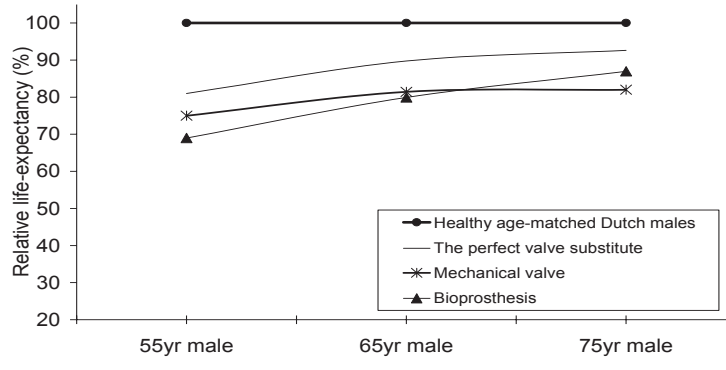
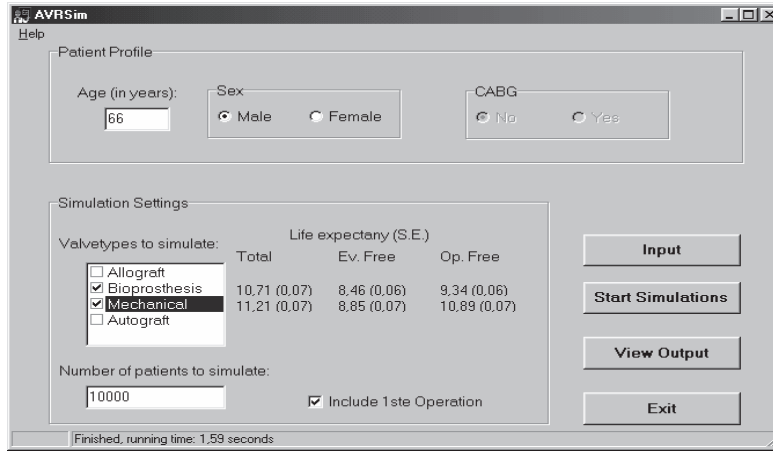


Figure 4. Relative life expectancy of patients after AVR compared with the age- and gender-matched general Dutch population.

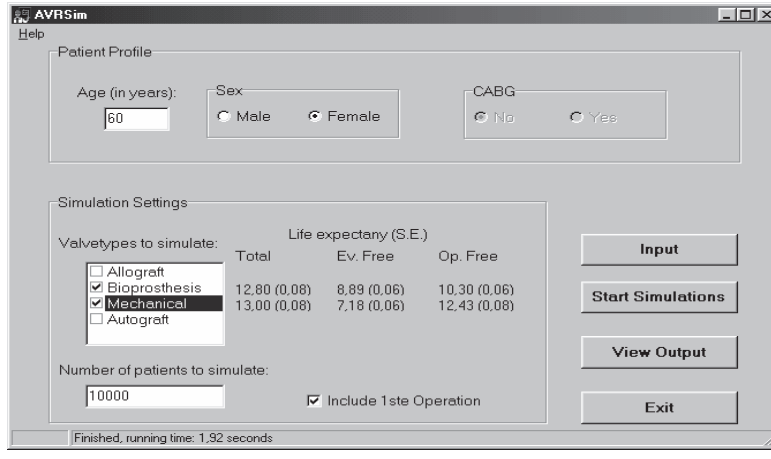
Pilot study

Figure 5 shows the evidence-based microsimulation estimates of prognosis after aortic valve replacement with both valve prostheses in the 2 hypothetical cases. Of the 80 questionnaires that were distributed among the attendants of the meeting, only 31 were returned. Of these 31, 24 were completed in a correct manner (in 7 only the initial 2 questions were answered).

Case 1



Case 2



Case 1 – Total life expectancy, event-free life expectancy and re-operation-free life expectancy are in favor of a mechanical prosthesis.

Case 2 – Total life expectancy and re-operation-free life expectancy are better with a mechanical prosthesis but event-free life expectancy is better with a bioprosthesis.

Figure 5. Calculated outcome after AVR by prosthesis type according to the microsimulation model.

For case 1 the initial preference was approximately 50% mechanical prosthesis and 50% bioprosthesis. After the presentation of the microsimulation model there was a significant shift in prosthetic valve preference towards a mechanical prosthesis (Wilcoxon matched pairs signed ranks test Z=-2.45; p=0.014). For case 2 the initial preference was clearly in favor of a bioprosthesis. After the presentation of the microsimulation model no

significant change in valve preference was evident (Wilcoxon signed ranks test Z=-1.42; p=0.15) although a trend towards preference for a mechanical prosthesis was observed. Table 2 given below represents the distribution of the answers to the questionnaire.

	Case 1	Case 1 revised	Case 2	Case 2 revised
Definitely mechanical valve	4	10	1	3
Preferably mechanical valve	7	2	1	6
No preference	1	5	5	1
Preferably bioprosthesis	5	2	9	4
Definitely bioprosthesis	7	5	8	10

Table 2. Distribution of the answers to the questionnaire (n = 24).

9.4. Discussion

Many interrelated factors play a role in the prognosis of patients after AVR and it may therefore be hard to select the preferred aortic valve substitute in the individual patient. Knowledge on outcome after AVR is limited, with regard to both the length of follow-up and number of patients, and clinical results are usually reported on a group level, which may be hard to translate to the individual patient.

This study shows that based on pooled evidence from clinical practice, microsimulation offers an objective tool to support the decision for a particular aortic valve substitute in the individual patient by providing age- and gender-specific estimates of outcome after AVR with stented bioprostheses and bileaflet mechanical valves. It is also a flexible tool, because it allows insight into the effect of variation of the hazard rates of the different valve-related events.

In addition, from a scientific point of view, microsimulation is useful for obtaining improved knowledge on the outcome after AVR. Microsimulation allows determination of the impact of the different factors that cause the reduced life expectancy in patients after AVR compared to the general population. Knowledge of these factors can be used to optimize treatment strategies and eventually improve outcome.

This study focused on the choice between a bileaflet mechanical prosthesis and a stented bioprosthesis. After implantation with a mechanical valve, bleeding and thrombo-embolism are common, especially in the elderly. On the other hand, after implantation with a bioprosthesis, reoperation for structural failure is the most important valve-related complication, especially in younger patients. The age threshold for implanting either valve type is approximately 63 years when comparing the lifetime risks of experiencing at least one valve-related event. This is in good agreement with the general recommendations of the American Heart Association and American College of Cardiology[16]. However, this age threshold varies considerably depending on the bleeding hazard, illustrating the impact of individual patient characteristics and showing that general recommendations do not always apply to the individual patient.

Life expectancy after aortic valve replacement is markedly reduced compared to the general Dutch age-matched population, regardless of the valve type implanted. The observed reduction in life expectancy can only in part be explained by the occurrence of valve-related events and is more pronounced in the younger age groups. One can currently only speculate on the other possible causes of excess mortality after aortic valve replacement. Sudden unexpected unexplained death and cardiac death related to valve disease and cardiomyopathy appear to be the most likely causes, but extensive further research is required[5,6]. With increasing age, valve-related events become more important causes of mortality[11,12]. Especially in these older patient groups optimal selection of a valve prosthesis becomes increasingly important.

The pilot study described in this paper showed that presentation of the microsimulation model might cause a shift in a clinical expert's preference for a prosthetic valve for a particular patient. It should be noted that the shift seen in this pilot study, although in one case statistically significant, was modest. The reasons for this shift in preference were not documented, and should be investigated in future studies on this subject. An important goal of the microsimulation model is to provide the clinician with evidence-based objective insight into the impact of several factors on outcome after aortic valve replacement. After using the microsimulation model several times, the clinician will have enhanced insight into the determinants of outcome after aortic valve replacement, which will facilitate the objective selection of the best type of valve for the individual patient.

Limitations of the data from the literature necessitated certain structural assumptions. For example, a constant hazard was assumed for several valve-related events, although these hazards may in fact be dependent on time and age. Another issue concerns the excess mortality that was built in the model. The age- and gender-related multiplicative hazard ratios were obtained from previous work on survival after implantation with mechanical mono-leaflet prostheses and stented bioprostheses[3,8]. We validated our excess mortality estimates using the Portland dataset and found good agreement[7,9]. Therefore we are confident that it is a good reflection of reality. Finally, survival after AVR not only depends on age and gender, but also on many risk factors, including pre-operative NYHA class and the presence of a coronary heart disease[6,17]. These factors were not taken into account in the microsimulation model. In this study we only considered male patients for the purpose of illustration. However, the model is also capable of calculating life expectancy for female patients.

In conclusion, microsimulation allows for age- and gender-specific calculation of life expectancy, event-free life expectancy and life time risks of the occurrence of valve-related events after aortic valve replacement with both types of valve. It is both a useful clinical decision support system for valve prosthesis selection and a promising tool to study factors that determine outcome after aortic valve replacement.

Acknowledgements

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Appendix

Input microsimulation model

Operative mortality

2.7% at age 40, increasing with age (OR 1.034 per year) and with each reoperation (OR 2.165)

Valve-related events after AVR with a bileaflet mechanical prosthesis

Valve thrombosis: Linearized annual occurrence rate (LOR) 0.08% per patient year, mortality rate 25%, reoperation rate 50%; thrombo-embolism: LOR 1.15% per patient year, mortality rate 7%; bleeding: Gompertz distribution (gamma = 0.076; lambda = -8.71), mortality rate increasing with age (OR 1.0345 per year); endocarditis: 2-period risk (LOR 6.6 in the first 6 months, thereafter LOR 0.4), mortality rate 36%, reoperation rate 44%; non-structural valve failure: LOR 0.42% per patient year, mortality rate 2%, reoperation rate 41%; structural valve failure: LOR 0.0%, mortality N/A.

Valve-related events after AVR with a stented bioprosthesis

Valve thrombosis: LOR 0.03% per patient year, mortality rate 67%, reoperation rate 33%; thrombo-embolism: LOR 0.90% per patient year, mortality rate 19%; bleeding: LOR 0.38% per patient year, mortality rate at age 40 = 14% and increasing with age (OR 1.0345 per year); endocarditis: 2-period risk (LOR 3.4 in the first 6 months, thereafter LOR 0.68), mortality rate 34%, reoperation rate 56%; non-structural valve failure: LOR 0.38% per patient year, mortality rate 5%, reoperation rate 52%; structural valve failure: Weibull distribution $S(t) = e^{-(t/\sigma)^{\wedge}\beta}$, where S(t) indicates the probability of being free from structural valve failure at time t, and σ and β indicate the scale and shape parameters of the Weibull model. The value of σ depended on age: $\sigma = e^{2.11+0.0112*age}$, and the value of β was 3.49, mortality rate = re-operation mortality rate.

Excess mortality

Age (years)	HR Males	HR Females
55	1.5	2.8
65	1.1	2.2
75	1	1.3

Appendix table 1. Hazard ratios for mortality for selected age groups compared with the general Dutch population.

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10. Choice of a Mechanical Valve or a Bioprosthesis for AVR: ` Does CABG Matter?

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Key words: aortic valve replacement, CABG, prognostic modeling, mechanical valves, bioprostheses.

Abstract

Background: Mechanical valves and bioprostheses are the commonly used devices in aortic valve replacement (AVR). Many patients with valvular disease also require concomitant coronary artery bypass grafting (CABG). We used a microsimulation model to provide insight into the outcomes of patients after AVR with mechanical valves and stented bioprostheses, with and without CABG, and to determine the age-thresholds or age crossover points in outcomes between the two valve types.

Methods: We conducted a meta-analysis of published results after primary AVR with bileaflet mechanical prostheses (9 reports, 4274 patients, 25,726 patient-years) and stented porcine bioprostheses (13 reports, 9007 patients, 54,151 patient-years) to estimate risks of valve-related events. A hazard ratio of 1.3 was used to incorporate the effect of CABG on long-term survival. Estimates were entered into a microsimulation model, which was then used to predict the outcomes of patients after AVR, with and without CABG. The model calculations were validated using a large data set from Portland, USA.

Results: For a 65-year-old male without CABG, the life expectancy (LE) was 11.2 and 11.6 years and the event-free life expectancy (EFLE) 8.2 and 8.9 years respectively after implantation with mechanical valves and bioprostheses. The lifetime risk of at least one

valve-related event was 51% and 47% respectively. The age crossover point between the two valve types, considering the above outcome parameters, was 59, 60 and 63 years respectively. CABG reduced LE and consequently EFLE and lifetime risk of an event, but only minimally influenced the patient age crossover points. The model calculations showed good agreement with the Portland data.

Conclusions: The currently recommended patient age for using a bioprosthesis (65-years) could be lowered further, irrespective of concomitant CABG. The trade-off between the reduced risks of bioprosthetic failure and of hemorrhage in mechanical valves, resulting from a lower life expectancy, minimized the effect of CABG on the age crossover points between the two valve types.

10.1. Introduction

Despite new procedures and advances in the design and construction of prosthetic heart valves, mechanical valves and xenograft bioprosthetic valves remain the two most commonly used devices in aortic valve replacement (AVR) [1]. Both mechanical valves and bioprostheses have their inherent advantages and disadvantages [2] and the choice between these devices for an individual patient remains difficult. The choice may be further complicated by the presence of coronary artery disease (CAD), which is a common finding in patients with valvular disease [3]. The American College of Cardiology / American Heart Association (ACC/AHA) task force recommends coronary artery bypass grafting (CABG) in the presence of significant CAD in patients requiring AVR [3]. Insight into the outcomes of patients after AVR will help in the selection of the optimal prosthesis. We combined meta-analysis of published data and other data sources with microsimulation, to provide insight into the outcomes of patients after AVR with bileaflet mechanical valves and stented porcine bioprostheses respectively with and without concomitant CABG. The age crossover points in outcomes between the two valve types were also estimated.

10.2. Methods

Selection of reports for meta-analysis

We conducted a literature search of the Medline database using the PubMed search interface for the period January 1990 to October 2001 in order to estimate the hazards of post-operative valve-related events and their outcomes. The St. Jude Medical (SJM) bileaflet valves, models 'standard' and 'hemodynamic plus' (St. Jude Medical Inc., MN, USA) were selected to

represent the mechanical valves. The bioprostheses were represented by 1 or more of the following stented porcine bioprostheses: Carpentier-Edwards 'standard' and 'supra-annular' valves (Baxter Healthcare Corp., CA, USA) and Hancock 'standard', 'modified orifice' and 'Hancock II' valves (Medtronic Inc., MN, USA). The MeSH terms in combination with the text words "St. Jude" for the mechanical valves and "stented", "Hancock", "Carpentier-Edwards" or "modified orifice" for the bioprostheses respectively were used for the search, which was limited to the English language. The titles and abstracts of these reports were screened for those that examined outcomes following AVR, which were selected and perused. References in these reports were cross-checked for other potentially relevant studies. This resulted in 76 published reports for mechanical valves and 68 for bioprostheses respectively. We then stipulated the following criteria for each valve type in order to obtain relatively homogenous groups of studies:

- Valves 19-33 mm in size, not focussing on a particular size or range.
- Patients > 15 years of age, not focussing on a particular age group. Mean age of the study population 50 years and above.
- Predominantly first time AVR (> 90%).
- AVR with or without CABG or any other valve repair procedure, but excluding other valve replacements.
- Valve-related events ascertained according to standard definitions published in 1988 [4] and 1996 [5].
- For mechanical valves: Intended therapeutic level of anti-coagulant intensity measured by International Normalized Ratio (I.N.R.) and between 1.8 and 4.5.

Studies that had overlapping patient populations were excluded. Finally, 9 reports on St. Jude Medical mechanical valves and 13 reports on stented porcine bioprostheses was selected (see Appendix A). The authors of some of the selected papers were contacted for clarifications and additional information.

Estimation of model parameters and assumptions made

Data required to parameterize the micro-simulation model was obtained from the results of the meta-analysis (Table 1) and from other data sources [6-8].

Valve-related event	Events (n)		LOR (per 100 patient-years)		Outcome			
					Death Rate		Re-operation rate	
	Mech	Bio	Mech	Bio	Mech	Bio	Mech	Bio
Valve thrombosis	39	2	0.16	0.01	0.22	0.67*	0.63	0.33*
Thrombo-embolism	419	717	1.6	1.3	0.17	0.18	0	0.01
Hemorrhage	419	189	1.6[+]	0.4	0.14	0.2	0	0
Endocarditis	89	240	3.9/ 0.66[#]	3.2/ 0.48[#]	0.43	0.36	0.53	0.5
N.S.D.	70	91	0.29	0.3	0.04	0	0.37	0.43
S.V.D.	0	469	0	1.2[$]	0	0.12[@]	0	0.75[@]

LOR = linearized occurrence rates (hazards), Mech = mechanical valves, Bio = bioprostheses, N.S.D. = non-structural dysfunction, S.V.D. = structural valvular deterioration.

[*] Due to the small number of events, re-operation rate was obtained from another study [13].

[+] A Gompertz distribution was used, incorporating data from another study [6].

[$] A Weibull model was constructed incorporating age dependency.

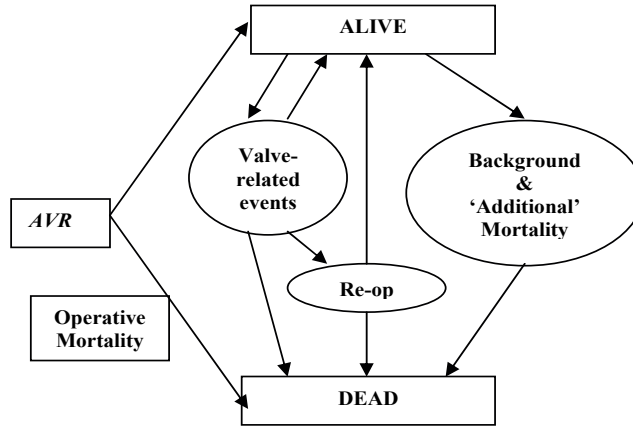
[@] For SVD in a bioprosthesis, the table does not indicate the fate of 13%. This represents the patients who had a SVD but neither died, nor were re-operated.

Table 1. Pooled incidence of valve-related events and their outcomes after aortic valve replacement with mechanical valves and bioprostheses.

The annual hazards of valve thrombosis, thrombo-embolism and non-structural dysfunction (NSD) were considered to be constant. Weighted pooling was used to calculate the linearized annual occurrence rates (LOR) for these events. The risk of endocarditis was assumed to take 2 phases of constant hazard, with the hazard during the first 6 months greater than the subsequent period. Therefore, we fitted 2-period exponential models to the pooled freedom-from-endocarditis curves of the 2 valve types. Taking into account the increasing hazard with age, hemorrhage after AVR with a mechanical valve was modeled using the Gompertz distribution, incorporating data from another study [6]. The risk of structural valvular deterioration (SVD) in a bioprosthesis depends on the age of the patient at valve implantation and the time elapsed since valve replacement. This relationship is well described by a Weibull distribution [9]. The Weibull distribution is a generalization of the exponential curve that

accommodates the increasing risk of SVD over time. We estimated the shape parameter of the Weibull model from the pooled freedom from SVD curves obtained from the selected reports and calculated the age effect from another selected study [10]. Mortality and re-operation rates associated with individual valve-related events were also estimated.

As depicted in figure 1, there are three components of mortality in patients who survive AVR, namely the background mortality, mortality due to valve-related events and 'additional mortality'.



Re-op = re-operation

Figure 1. Basic structure of the microsimulation model.

The microsimulation model incorporates the mortality experience of the general population, the so-called background mortality, by means of life tables of the relevant population (for example American males). The mortality of a patient, who remains alive after AVR, is greater than that of a matched individual in the general population. This excess mortality in the patient, compared to a matched person in the general population, is due to the mortality caused by valve-related events and to 'additional mortality' that may be associated with the underlying valve pathology, left ventricular function and the valve replacement procedure per se [11]. The 'additional mortality' component is not clearly defined and estimated at present. Therefore, we calculated age- and sex-specific hazard ratios to represent this effect in the model. This was done by approximating age- and sex-specific survival curves obtained from

the microsimulation model, which contained the background mortality and mortality due to valve-related events, to the corresponding 'true' survival curves obtained from the literature, which contained all 3 components of mortality. Hazard ratios of 2.9, 1.8, 1.2 and 0.8 were calculated for male patients' aged 45, 55, 65 and 75 years respectively. Further, a hazard ratio of 1.3 was incorporated into the microsimulation model to represent a patient who required concomitant CABG [7]. Results obtained from analysis of the Society of Thoracic Surgeons (STS) National Cardiac Surgery Database [8] was used to estimate operative mortality in the model. For a 65-year-old patient for example, the operative mortality was 5.2% and 3.3% respectively, with and without concomitant CABG.

Microsimulation

The microsimulation model is a computer application that simulates the remaining lifetime of a patient after AVR, taking into account all morbidity and mortality events that the patient might experience. The basic structure of the model is depicted in figure 1. In principle, the model can be applied for any valve type and for either sex. For this analysis the model was used to predict the life expectancy (LE), event-free life expectancy (EFLE) and lifetime risks of valve-related events for male patients undergoing AVR with bileaflet mechanical valves and stented porcine bioprostheses, with or without concomitant CABG.

The model simulates the lifetime of a patient, with given characteristics, by aging the individual and updating the status of the individual with the incidence of various valve-related events that may occur. The valve-related events are simulated by random draws from distributions describing the probability of an event. The model calculates patient outcome by superimposing the occurrence and mortality estimates of valve-related events, on the background mortality and 'additional mortality' incorporated in the model. Ten thousand simulations of any given patient create a 'virtual' patient population, i.e. a cohort of patients with identical characteristics but with many random outcomes after AVR. The number of simulations conducted was chosen arbitrarily, but was the same for each combination of risk factors. From this large cohort of identical patients, the model calculates the average life expectancies and lifetime risks of valve-related events for that given patient.

Validation

To assess the agreement between age-specific model outputs and the corresponding true life experience of AVR patients, we compared the model outputs with the long-term outcomes of patients in a large data set from Portland, Oregon, USA [12]. The Portland data set, from Providence Health System, Portland, USA, contains 25 years of follow-up data on patients who underwent AVR with the Starr-Edwards mechanical prosthesis and the Carpentier-Edwards 'standard' bioprosthesis and includes data on age, gender and concomitant CABG.

10.3. Results

Meta-analysis

The 9 reports selected on St. Jude mechanical aortic valves contained 4274 patients undergoing AVR with a cumulative follow-up of 25,726 patient-years. Males accounted for 64% of the patients and the mean age of the population was 59 years. Thirty percent of the patients had concomitant CABG. The 13 reports on stented porcine bioprostheses consisted of 9007 patients, with 65% males, and had a follow-up of 54,151 patient-years. The mean age was 65 years and 37% had concomitant coronary re-vascularization.

Model parameters and assumptions

The risks of the valve-related events and their outcomes, obtained from the meta-analysis, are given in Table 1. A Gompertz model estimated the increasing hazard of hemorrhage with advancing age associated with the mechanical valves. The lambda and gamma parameters of this model were –8.874 and 0.076 respectively. The average incidence of SVD in a bioprosthesis was estimated using a Weibull model (Figure 2). The probability of remaining free from SVD at time t (St) is given by the formula:

$$S(t)= e^{-(t/\sigma)^{\beta}}$$

where σ and β denote the scale and shape parameter of the model. The value of σ depends on age: $\sigma = e^{2.21 + 0.0112 * age}$ while $\beta = 3.35$. The estimated median time to SVD was 15.1, 16.8 and 18.8 years respectively for 55-, 65- and 75-year male patients.

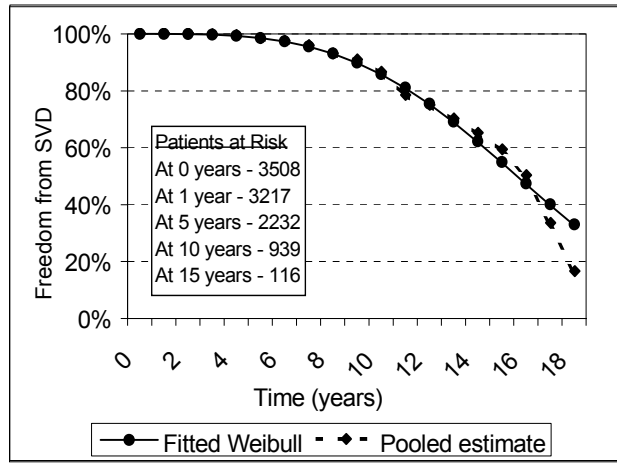


Figure 2. Average freedom from structural valvular deterioration estimated from the literature (pooled) and with the Weibull model.

Microsimulation

Figure 3A shows the calculated LE and EFLE for male patients of different ages after implantation with a mechanical valve and a bioprosthesis respectively, without concomitant CABG.

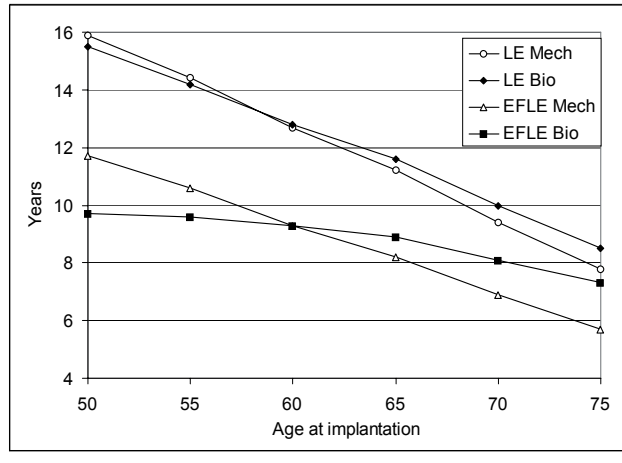


Figure 3A. Comparison of life expectancy and event-free life expectancy in males after aortic valve replacement with mechanical valves and bioprostheses, without concomitant CABG.

For a 65-year-old patient for example, the LE was 11.2 and 11.6 years while the EFLE was 8.2 and 8.9 years respectively. Considering LE and EFLE, the age crossover point between the two valve types was 59 and 60 years respectively. At implantation ages below the age crossover point, mechanical valves had a better outcome than the bioprostheses, whereas above the crossover point the bioprostheses performed better. Concomitant CABG resulted in a decrease of LE and EFLE. For the 65-year-old patient the LE was 9.9 and 10.2 years and EFLE was 7.4 and 8.1 years respectively after implantation with a mechanical valve and a bioprosthesis. The age crossover points were 58 and 59 years considering the LE and EFLE respectively (Figure 3B).

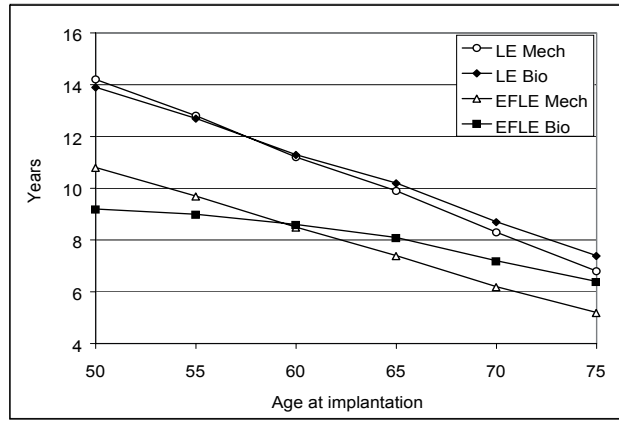


Figure 3B. Comparison of life expectancy and event-free life expectancy in males after aortic valve replacement with mechanical valves and bioprostheses, with concomitant CABG.

We also estimated the lifetime risks of valve-related events following implantation of both valve types. The lifetime risk of SVD with a bioprosthesis was seen to decrease with advancing age of valve implantation, consequent to a decrease in LE. For a 75-year-old patient with and without CABG for example, the risk was 8.9% and 12.4% respectively. Conversely, advancing age of implantation of a mechanical valve was associated with a greater risk of hemorrhage. For a 75-year-old patient with and without CABG, this risk was 35.5% and 41.2% respectively (Figure 4). The risk of thrombo-embolism reduced with advancing age of implantation for both valve types. When considering the lifetime risk of any valve-related event, the age crossover point between the two valve types was 63 years for a patient without CABG. It was 62 years when the patient required coronary re-vascularization.

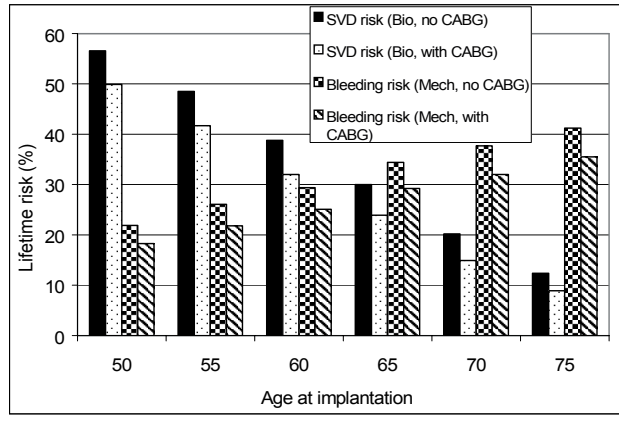


Figure 4. Lifetime risk of structural valvular deterioration with bioprostheses and the lifetime risk of hemorrhage with mechanical valves respectively after aortic valve replacement with and without concomitant CABG.

Validation

We compared the microsimulation model outputs for male patients of varying ages, who had undergone AVR with and without concomitant CABG, with the corresponding long-term data from Portland, Oregon, USA [12]. Although the model predicted slightly higher survival for bioprostheses in most age groups, there was reasonably good agreement with the Portland data (Figures 5 & 6).

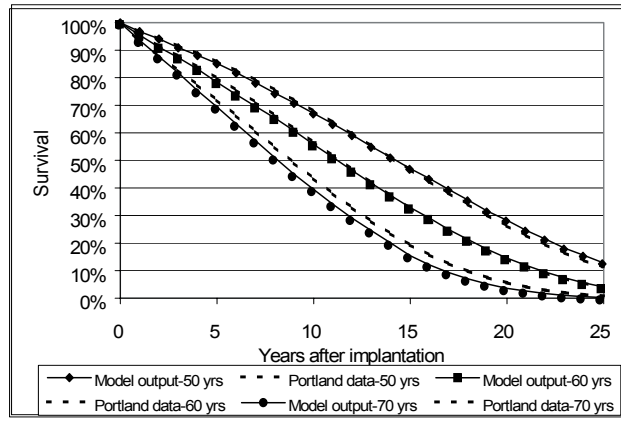


Figure 5. Comparison of microsimulation model output and corresponding Portland data for 50-, 60- and 70-year-old males after aortic valve replacement with a mechanical valve and concomitant CABG.

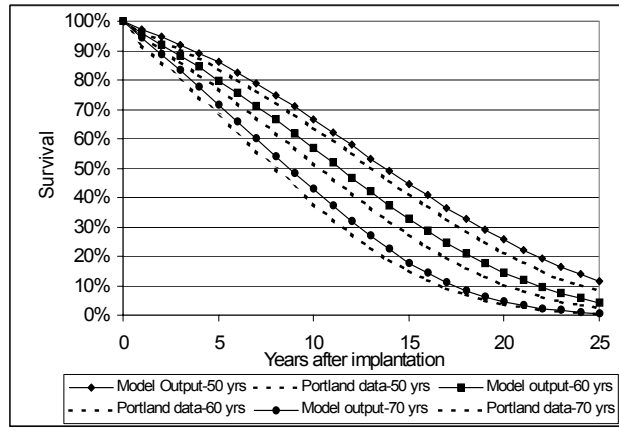


Figure 6. Comparison of microsimulation model output and corresponding Portland data for 50-, 60- and 70-year-old males after aortic valve replacement with a bioprosthesis and concomitant CABG.

10.4. Discussion

Simulation techniques, by allowing modeling of complex outcome paths resulting from many simultaneous risks, provide a useful adjunct to standard statistical methods in predicting outcomes of individual patients after AVR. These models have been used previously to predict outcome after AVR and to support prosthetic valve choice [13,14]. Birkmeyer and colleagues [14] used a Markov state-transmission model to simulate the prognosis after AVR. Although the Markov model and microsimulation have similar assumptions, they encompass important differences between them. The Markov model follows a virtual population over time and has no 'memory', which translates to the assumption that subjects in a particular state are a homogenous group. In microsimulation, individual life histories are simulated. Further, it permits adjusting of hazards for the individual patient depending on prior events, thereby accommodating the variability with groups of subjects' [15]. We used the microsimulation model to predict, for a 65-year-old male without CABG, a LE of 11.2 and 11.6 years and an EFLE of 8.2 and 8.9 years respectively after implantation with a mechanical valve and a bioprosthesis. Considering LE, the age crossover point between either valve type was 59 years. This concurs well with the results of Birkmeyer and colleagues who obtained a similar LE for 60-year-old patients receiving mechanical valves and bioprostheses [14]. CABG resulted in a decrease in the age crossover point to 58 years.

The actuarial method and the Kaplan-Meier analysis are commonly used in studies to estimate survival of patients after AVR. However, when applied to a non-fatal event such as SVD, it estimates the freedom from event by censoring patients who had not yet experienced that event, including those who had died and will therefore never experience it. Consequently, Kaplan Meier analysis estimates a higher percentage of events than will actually occur. An alternative method, the 'actual' analysis (cumulative incidence) modifies this estimate to exclude future events attributed to already deceased persons and answers the more pertinent question, "what is the lifetime risk of the event?" [16]. The microsimulation model provides estimates of the lifetime risk of each of the valve-related events and the overall risk of an event, following AVR. For the 65-year-old patient, the overall lifetime risk of any event was 51% and 47% respectively for a mechanical valve and a bioprosthesis.

There is uncertainty as to whether coronary re-vascularization of patients with CAD undergoing AVR leads to a long-term survival similar to that of patients without CAD requiring AVR [17]. The influence of concomitant CABG on long-term survival is complex and theoretically can be viewed in two aspects [18]. Concomitant CABG may be associated with increased long-term survival compared to those who had mild coronary disease, that did not require re-vascularization at the time of surgery, whose atherosclerotic disease progressed subsequently. Further, patients having concomitant CAD have less severe aortic valve disease in general. These factors may lend support to the view that concomitant CABG returns those patients with concomitant aortic valve disease and CAD to a prognostic curve determined by the valvular disease. Nunley and colleagues [19] found that patients who had AVR with concomitant CABG had similar survival to those without CAD, who had isolated AVR. Conversely, it has been postulated that patients who had concomitant CABG had atherosclerotic disease that increased the risk even after CABG, compared to those who only required AVR. Studies have shown that patients, who had concomitant CABG, still had survival rates inferior to those without CAD who underwent AVR [7,20]. Assuming the latter possibility, we incorporated a hazard ratio of 1.3 to the survival curve estimates of patients to represent those who had concomitant CABG. This hazard ratio was in good agreement with the Portland data [12].

Does CABG matter in the choice of a valve for AVR? The main difference in outcomes between the two valve types is due to the high risk of hemorrhage in the mechanical valves and the high risk of SVD in the bioprosthesis. The lifetime risk of hemorrhage with mechanical valves and SVD with bioprostheses, for patients with different implantation ages are given in figure 4. It shows that the age cross-over point in overall valve complications follows the increasing risk of hemorrhage in mechanical valves and decreasing risk of SVD in the bioprostheses, with advancing age of implantation. Considering the overall risk of any valve-related event, the age crossover point was 63 years. Concomitant CABG results in a reduced LE compared to those who only require AVR (Figure 3A and 3B). In a patient with concomitant CABG, the trade-off between the reduced risks of SVD and hemorrhage resultant from a lowered LE, minimizes the effect of CABG on the age crossover point, which was then 62 years.

The American College of Cardiology and the American Heart Association guidelines [3] recommend a bioprosthesis for patients => 65 years of age, who do not have risk factors for thrombo-embolism, based on the reduced risk of SVD and the increasing risk of hemorrhage at this age. Considering the patient age crossover points calculated by our model for total LE, EFLE and the lifetime risk of a valve-related event, we suggest that a bioprosthesis may be considered for patients under 65 years of age. New strategies being developed to retard mineralization of xenograft valves and evidence that pericardial aortic valves have a better durability than porcine valves further support reduction of the 65-year-old limit. However, our suggestion needs to be considered in the context of the narrow age difference between the LE for both valve types (Figures 3A & 3B) and the present inability of the microsimulation model to estimate the uncertainty of the input data. The influence of age on the risk of anticoagulation-related bleeding is disputed in the literature [6,21]. We assumed an exponentially increasing risk of hemorrhage with advancing age for the mechanical valves, based on a large study that assessed the risk of bleeding complications in patients treated with oral anti-coagulants [6]. However, an alternative assumption of a constant hazard for hemorrhage or consideration of anti-coagulation strategies which aim for lower INR ranges, will push the age crossover point towards the 65-year limit. When considering the lifetime risk of a valve-related event, equal weight was given to the severity and outcomes of all events. Patient preference is also important in clinical decisions about valve prostheses.

Limitations of the model include certain structural and parameter uncertainties respectively. Several assumptions were necessary in structuring the microsimulation model. For example, valve thrombosis, thrombo-embolism and NSD were assumed to carry constant hazards. These events may have an increased hazard during the early period (<30 days), but was not incorporated into the model. The risk of endocarditis was assumed to be greater during the first 6-months than the subsequent period, but was assumed to be constant during these 2 phases. These hazards may in fact be time- and age-dependant, and hence, further knowledge is necessary to address these assumptions. Further, an 'additional mortality' after AVR has been incorporated into the model by means of hazard ratios. As previously described, this was necessitated by the observation that the excess mortality in patients after AVR, compared to the general population, can only in part be explained by valve-related events. We used one set of hazard ratios to represent this 'additional mortality'. The possibility that 'additional mortality' varies according to valve type, operative procedure and cross-clamp time needs also to be considered further. Parameter uncertainties relate to the quality of the input of the model. The estimated hazards obtained from clinical literature, which are used to parameterize the model carry some uncertainty.

Survival after AVR has also been shown to depend on pre-operative cardiac rhythm, type of valve lesion and New York Heart Association (NYHA) functional status. Although the model incorporates these factors non-specifically by means of the hazard ratios, the model cannot determine the individual influence of these factors on overall survival. At present, the model can only predict outcome for an average risk profile.

In conclusion, we have described the combination of meta-analysis and microsimulation to provide insight into age- and gender-specific long-term prognosis after AVR, with and without concomitant CABG. Based on the age crossover points for patient outcomes between the two valve types, we suggest that the currently recommended age for implanting a bioprosthesis could be lowered further, irrespective of concomitant coronary re-vascularization.

Acknowledgements

The authors acknowledge Dr. Tirone David, Dr. Steven Khan and Dr. Jose Bernal for providing additional information on their publications.

Appendix A

The 9 reports selected on St. Jude mechanical valves are as follows:

1. Khan SS et al. J Thorac Cardiovasc Surg. 2001;122:257-69.
2. Peterseim DS et al. J Thorac Cardiovasc Surg. 1999;117:890-7.
3. Smith JA et al. Circulation. 1993;88:II49-54.
4. Lund O et al. Ann Thorac Surg. 2000;69:1459-65.
5. Zellner JL et al. Ann Thorac Surg. 1999;68:1210-8.
6. Horstkotte D et al. J Heart Valve Dis. 1993;2:291-301.
7. Aoyagi S et al. J Thorac Cardiovasc Surg. 1994;108:1021-9.
8. Baudet EM et al. J Thorac Cardiovasc Surg. 1995;109:858-70.
9. Ibrahim M et al. J Thorac Cardiovasc Surg. 1994;108:221-30.

The 13 reports selected on stented porcine bioprostheses are as follows:

1. Peterseim DS et al. J Thorac Cardiovasc Surg. 1999;117:890-7.
2. Cohn LH et al. Ann Thorac Surg. 1998;66:S30-4.
3. Wilson ES et al. J Heart Valve Dis. 1996;5:40-4.
4. Logeais Y et al. Ann Thorac Surg. 1999;68:421-5.
5. Hurle A et al. J Heart Valve Dis. 1998;7:331-5.
6. Fann JI et al. Ann Thorac Surg 1996;62(5):1301-11; discussion 1311-2.
7. David TE et al. J Thorac Cardiovasc Surg. 2001;121:268-278.
8. Bernal JM et al. Ann Thorac Surg. 1995;60:S248-52.
9. Westaby S et al. Ann Thorac Surg. 2000;70:785-90; discussion 790-1.
10. Jamieson WR et al. Ann Thorac Surg. 1995;60:999-1006; discussion 1007.
11. Jamieson WR et al. Ann Thorac Surg. 2001;71:S224-7.
12. Orszulak TA et al. Ann Thorac Surg. 1995;59:462-8.
13. Akins CW et al. Circulation. 1990;82:IV65-74.

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3. ACC/AHA 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 (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol* 1998;32(5):1486-588.
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5. Edmunds LH, Jr., Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *Eur J Cardiothorac Surg* 1996;10(9):812-6.
6. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Assessment of a bleeding risk index in two cohorts of patients treated with oral anticoagulants. *Thromb Haemost* 1996;76(1):12-6.
7. 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.
8. Jamieson WR, Edwards FH, Schwartz M, Bero JW, Clark RE, Grover FL. Risk stratification for cardiac valve replacement. National Cardiac Surgery Database. Database Committee of The Society of Thoracic Surgeons. *Ann Thorac Surg* 1999;67(4):943-51.
9. Grunkemeier GL, Bodnar E. Comparative assessment of bioprosthesis durability in the aortic position. *J Heart Valve Dis* 1995;4(1):49-55.
10. Fann JI, Miller DC, Moore KA, et al. Twenty-year clinical experience with porcine bioprostheses. *Ann Thorac Surg* 1996;62(5):1301-11; discussion 1311-2.
11. Blackstone EH. The choice of a prosthetic heart valve: how shall patient-specific recommendations be made? *J Heart Valve Dis* 1998;7(1):1-3.
12. Grunkemeier GL, Chandler JG, Miller DC, Jamieson WR, Starr A. Utilization of manufacturers' implant card data to estimate heart valve failure. *J Heart Valve Dis* 1993;2(5):493-503.
13. Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, et al. Prognosis after aortic valve replacement with a bioprosthesis : predictions based on meta-analysis and microsimulation. *Circulation* 2001;103(11):1535-41.
14. Birkmeyer NJO, Birkmeyer JD, Tosteson ANA, Grunkemeier GL, Marrin CA, O'Connor GT. Prosthetic valve type for patients undergoing aortic valve replacement: a decision analysis. *Ann Thorac Surg* 2000;70:1946-52.
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20. Cohn LH, Allred EN, DiSesa VJ, Sawtelle K, Shemin RJ, Collins JJ, Jr. Early and late risk of aortic valve replacement. A 12 year concomitant comparison of the porcine bioprosthetic and tilting disc prosthetic aortic valves. *J Thorac Cardiovasc Surg* 1984;88(5 Pt 1):695-705.

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General Discussion

11. Discussion and Future Direction

This thesis attempts to further develop and use the microsimulation methodology to determine the long-term outcomes of patients after aortic valve replacement (AVR) with mechanical valves and bioprostheses. It is envisaged that this methodology, an alternative to standard statistical techniques, will provide the cardiologist, cardiac surgeon and the patient evidence-based support in the optimal choice of valve prosthesis. De Kruyk and colleagues[1] at the Erasmus University, Rotterdam, The Netherlands, pioneered the use of a microsimulation model to support decision-making in AVR nearly half a decade ago. Subsequently, Takkenberg and co-workers[2] of the same institution used the methodology to ascertain outcomes of patients after AVR with allografts and autografts. This thesis describes improvements to the microsimulation model including the expansion of the model with coronary bypass grafting (CABG) and recalculation of hazard ratios representing the 'additional mortality' component and provides insight into the long-term outcomes of patients implanted with bioprostheses and mechanical valves respectively. The research utilized data and expertise from many international centers in an attempt to generalize the results to all patients after AVR.

The findings, merits and demerits of the component studies included in this thesis have been discussed in the respective manuscripts. In this section, I will briefly re-examine and discuss the salient aspects of the microsimulation model and related methods, the model results in respect of mechanical valve and bioprosthetic AVR and finally comment on possible future directions to this research methodology.

11.1. The microsimulation model

The microsimulation model described in this thesis is a computer application that simulates the remaining lifetime of a given patient after AVR. The model incorporates real-life clinical data of patients and takes into account all morbidity and mortality events that such a patient might experience in its calculation. In principle, the model can be used for any valve type and for either sex.

The microsimulation technique provides a useful adjunct to the standard parametric and semi-parametric models commonly employed in the cardiac literature by facilitating the modeling of complex outcome pathways that could occur after AVR and by extrapolating the limited available clinical data. This additional information on the long-term outcomes after AVR would be useful in evaluating the performance of different valve types. The microsimulation model calculates patient prognosis by superimposing the morbidity and mortality associated with valve-related events on the other components of mortality experienced by the patient. Apart from the prosthesis-related factors, many patient- and surgery-related factors have also been identified that influence the long-term survival after AVR [3,4]. Therefore, an attempt to directly compare two valve types would be misleading. The use of microsimulation reduces such concern by permitting the comparison of the individual valve type per se, superimposed on a uniform underlying mortality.

The microsimulation model was initially developed to calculate outcomes for a patient with a given age and sex profile. However as mentioned, many other factors including concomitant coronary artery bypass grafting (CABG) have been shown to affect the long-term outcome after AVR [3,5,6]. The influence of concomitant CABG on long-term survival after AVR is complex and has been postulated variously. Although Nunley and colleagues reported that those undergoing concomitant CABG had a similar survival to those requiring only AVR [7], other reports have shown that the initial group of patients still had a somewhat inferior survival [8]. Assuming the latter possibility, we modified the simulation programme and the model interface in order to include CABG in the patient profile used for predictions. The incorporation of other important risk factors such as left ventricular function, etiology of aortic valve disease and pre-operative heart rhythm would be required to give more patient-specific estimates.

It was previously assumed that in the absence of morbid valve-related events, patients after AVR would follow the survival trajectory of comparable persons in the general population [1]. Blackstone in his critique of the de Kruyk paper, pointed out that this might not be tenable as valve disease, cardiomyopathy and the valve replacement procedure per se result in an additional non-valve-related mortality, compared to the general population [9]. We have coined the term ‘additional mortality’ to represent this component of mortality associated with AVR.

The increased occurrence rates of cardiac death and sudden unexplained and unexpected deaths (SUUD) seen in patients after AVR [10] and under-reporting of valve-related events [9] may also contribute to this 'additional mortality' which has not been quantified as yet in the literature. We applied age- and sex-specific hazard ratios to the corresponding survival curves of the general population to represent this 'additional mortality'. These estimates were calculated on long-term results of the first generation Carpentier-Edwards standard bioprosthesis [11]. We have not yet addressed the possibility that the 'additional mortality' may vary with different valve types, necessitating the use of different hazard ratios. The improvement of hemodynamics after AVR is related to normalization of left ventricular mass and function [12], which in turn may reduce 'additional mortality' after AVR. In this context, the second-generation bioprostheses have been shown to be less obstructive in the aortic position than the Carpentier-Edwards standard bioprosthesis [13]. This could translate to greater regression of left ventricular hypertrophy after AVR with the second-generation bioprostheses and confer a higher survival benefit than presently calculated by our model.

11.2. Some other methodological considerations

Real-life estimates of the occurrence of valve-related events are required to parameterize the microsimulation model. Ideally, a sufficiently comprehensive 'super data set' should be analyzed for this purpose. Such a data set should contain a detailed profile of the patients who underwent AVR, consider all valve-related events and their sequelae and have complete and long-term follow-up for all patients [9]. Although large series with long-term follow-up have been reported recently for some valve types [14,15], they may not be sufficiently comprehensive to provide data for parameterization of the microsimulation model. We therefore pooled the results of published studies in order to calculate the quantitative estimates of the parameters of interest.

Meta-analysis of published data, known as type II meta-analysis, can be performed without the consent and cooperation of the respective authors [16]. However, most of the authors of the selected reports were contacted for further information and clarifications. Pooling served to increase the number of patients and events and represented the experience of many institutions. A single- center result may be less generalizable due to the typical patient profile and unique surgical practices. Selection bias is a potential disadvantage of using published

reports [17]. Such reports are more likely to contain a relatively better result than those that remain unpublished. Heterogeneity between the studies selected for pooling is another disadvantage, and is likely given the variations in study design, patient population and data collection methods. It has been emphasized that data should not be pooled in case of considerable heterogeneity between studies[16,18]. We applied several criteria to a primary selection of suitable clinical reports in order to obtain a similar group of studies. Possible heterogeneity in the remaining publications was further examined by means of sensitivity analysis. The timing and design of studies could also influence its results. For example, a retrospective study could be assumed to contain lower estimates for valve-related events in comparison to prospective studies [19]. The majority of reports selected for pooling in the various manuscripts of this thesis contained a predominance of retrospective studies, which mirrors the publications in this field. Hence, some of the estimates of the valve-related events could be an underestimation of reality.

To assess the validity of the model calculations, we compared the age- and sex-specific model estimates of survival with the corresponding survival curves obtained from the literature and with those obtained from primary data. Although the comparisons were generally favorable, it was less so for the 70-year-old and older patients undergoing AVR. Patients who undergo an operation in this age group do not strictly represent the average patient in this age group who actually requires AVR. Such patients represent a selection of relatively 'healthier' patients with a relatively better life expectancy. Conversely, with the advances in surgical techniques and peri-operative myocardial protection, relatively older and higher-risk patients are now considered for valve replacement [20,21]. The microsimulation model was calibrated using data from a previous study [11]. Systematic variations in the patient profile, especially in the older age groups, could explain these differences between model output and comparison data.

The assumptions required to parameterize the model and the paucity of data in certain instances could result in a degree of uncertainty in parameter estimates. Hence, in order to assess the precision of the model calculations, we conducted one-way sensitivity analyses in this thesis. As variation of the estimates of valve-related events by their 95% confidence limits yielded negligible changes in the long-term outcomes, we also increased and decreased the baseline values by 25%. The hazard ratios representing the 'additional mortality' was also

varied within a plausible range. The most prominent effect on long-term outcomes was achieved by variation in the SVD estimates for bioprostheses and hemorrhage for the mechanical valves respectively. This highlights the importance of the assumptions and quality of data with respect to SVD and hemorrhage respectively when calculating long-term outcomes and deciding on an age cut-off point between the two valve types. Variations in the 'additional mortality' estimates were also shown to have appreciable effect on long-term outcome. The need for further knowledge and more specific quantification of this parameter has been discussed previously.

11.3. Some aspects on the results of bioprosthetic and mechanical valve implantation

In our initial attempt to calculate the prognosis of patients after AVR with a bioprostheses, we used data from both first- and second-generation valves to parameterize the microsimulation model [22]. Similarities in the performance of these two valve types have been documented in the literature [23-25] and hence, our endeavor of predicting for a bioprosthesis in general. The second-generation Carpentier-Edwards pericardial and supraannular valves were introduced in the early 1980's to enhance durability and have been shown to have better hemodynamics compared to the earlier generation valves [13]. Although previous studies have compared the outcome after implantation with both valves [26], knowledge on long-term outcome is still incomplete and hence our analyses using the microsimulation model. These two valve types are implanted in this institution and are the choice for the elderly in many institutions [27,28].

SVD is a serious disadvantage which undermines the attractiveness of bioprostheses and usually necessitates re-operation [29]. The risk of SVD after valve implantation depends on the age of the patient at implantation and on the time that has elapsed since the operation. Kaplan-Meier curves have been used in the literature to describe this changing risk over time [30]. Grunkemeier and colleagues subsequently demonstrated that the Weibull curve was efficient for summarizing SVD in biological valves, provided that at least 12 years follow-up was available [31]. The Weibull curve is a generalization of the exponential distribution, which incorporates an additional shape parameter, the latter reflecting the changing risk of SVD over time [32]. We used primary data on Carpentier-Edwards pericardial and supraannular valves, with over 18-years of follow-up, to calculate the respective Weibull parameters. Using these parameters, the calculated median time to SVD appeared to marginally favor the supraannular

valves. However, a tendency for greater valve durability has been described in older patients. As the supraannular patients were older than the pericardial patients in general (69.8 years versus 66.9 years) we prefer not to conclude on the superior durability of either valve.

The Kaplan-Meier and the actuarial method are commonly used to estimate the survival of patients after AVR. These methods have been extended to summarize complications such as SVD which are not necessarily fatal [30]. In the latter instance, the actuarial method estimates the freedom from event by also censoring patients who had died and will therefore never experience the event. It therefore describes the risk of SVD for the patient based on the assumption of immortality, resulting in an over-estimation of the actual risk of SVD. This error is magnified with advancing age of implantation and serves to underestimate the benefits of biological valve replacement. In reality, death occurring before implanted valve failure acts as a competing risk. An alternative method, the cumulative incidence or 'actual' analysis considers the competing risk of death and calculates the percentage of patients who will experience an event before they die. It answers the more pertinent question, "what is the lifetime risk of the event?" [30,33,34]. The microsimulation model calculates the lifetime risk of SVD and of other valve-related events. For a 65-year-old male for example, the life time risk of re-operation due to SVD was 18.3% and 14% after AVR with the Carpentier-Edwards pericardial and supraannular valves. The risk was further reduced for a 75-year-old male, calculated by the model at 5.4% and 3.8% respectively. The 'actual' analysis provides a more appropriate estimate of the durability of a bioprosthesis, especially in the elderly.

In the comparison of the Carpentier-Edwards pericardial and supraannular bioprostheses, the point estimates for life expectancy and event-free life expectancy for both valve types at various ages of valve implantation did not show appreciable difference. The relatively better hemodynamics of the Carpentier-Edwards pericardial valve could translate to greater and more rapid regression of the left ventricle, conferring a higher survival benefit than computed by the microsimulation model. As previously discussed, we have not yet addressed the possibility that 'additional mortality' may vary with different valve types, valve sizes and operative procedures.

We selected the St. Jude Medical valve, a bileaflet prosthesis, to represent the mechanical valves in this thesis. It is one of the most commonly implanted mechanical prostheses at present [35,36]. Mechanical valves are associated with a high risk of thrombo-embolism, which necessitates regular anti-coagulation. However, lifetime anti-coagulation is associated with an increased risk of hemorrhage, which together with thrombo-embolism constitute the majority of adverse effects related to the mechanical valves [37,38]. While the range of optimal INR for mechanical valves is still debated [39,40], the association between 'achieved' INR and hemorrhage [41] and high INR variability and reduced survival after AVR have been described[42]. Van der Meer and colleagues who analyzed the bleeding complications of two large cohorts of patients treated by the Leiden Thrombosis Service, Leiden, The Netherlands, identified advancing age and 'achieved' INR as the most important risk factors for hemorrhage after mechanical valve implantation [43]. The target INR range at their Center was 3.6 – 4.8 during the period of the study and the authors used a novel method in calculating the achieved INR of their patients [44]. We used data from this study to construct a Gompertz distribution to describe the risk of hemorrhage, the parameters of which were used to parameterize the microsimulation model. The variability in target INR levels at different institutions and the difficulty in precisely assessing the patient's 'achieved' INR may reduce the generalizability of the van der Meer results and consequently, the overall results of the microsimulation model. We require more specific data to improve the predictions of the microsimulation model.

What is the age cut-off point between bioprostheses and mechanical valves in aortic valve replacement? The American College of Cardiology and the American Heart Association guidelines recommend a bioprosthesis for patients 65 years and older, who do not have risk factors for thrombo-embolism [38]. However our model calculations suggest that the cut-off point could be further reduced, with a bioprosthesis being considered for patients less than 65 years of age. These results concur well with that of Birkmeyer and colleagues who used a Markov model for their analysis [45]. However, our results should be considered in the context of the narrow age difference in life expectancy estimates between the two valve types and the present inability of the model to provide uncertainty estimates. Alternative assumptions on the hazards of hemorrhage after mechanical valve implantation and consideration of anti-coagulation strategies which aim at lower target INR ranges will push the age cut-off point

towards the 65-year limit while new strategies being developed to retard mineralization of bioprostheses [46] will have the opposite effect.

We also analyzed the effect of concomitant CABG on the age cut-off point between bioprostheses and mechanical valves. CABG resulted in a reduced life expectancy compared to those who only required AVR. In a patient who requires concomitant CABG, the trade-off between the reduced risk of SVD with a bioprosthesis and the reduced risk of hemorrhage with a mechanical valve, resultant from a lowered life expectancy, minimized the effect of CABG.

11.4. Future direction

Dr. "Bones" McCoy of the popular science fiction Star Trek uses a probe to instantly determine the problem and damage experienced by a colleague. Similarly, a futuristic apparatus that would identify the perfect valve substitute for a patient and the ideal timing for implantation may be proposed. The development of the microsimulation model is an initial step in that direction. Many new areas of research have emerged with the development of the microsimulation methodology over the past few years. I briefly describe below some of these research areas and possible expansions of this methodology, ideas that I have developed in consultation with colleagues of the Departments of Cardio-Thoracic Surgery, Cardiology and Public Health of the Erasmus MC, Rotterdam.

11.4.1. Further improvements to the microsimulation methodology.

- *Estimation of input parameter uncertainty* – Although the model input carries a certain degree of uncertainty, this is not expressed at present in the model output. Probabilistic sensitivity analysis (second order microsimulation model) is a technique to analyze the uncertainty of the variables in the microsimulation model. In this technique, all input variables (for example, valve thrombosis, thrombo-embolism etc.) are modeled with the probability distributions of their values. For each simulation of the model, a value from the probability distribution of each input variable is chosen at random and a corresponding model output calculated. A large number of such simulations yield a distribution of possible model outcomes. This provides a measure of the uncertainty of the model results associated with probabilistic nature of the input variables [47].

- *Identification of causes and quantification of 'additional mortality'* - The 'additional mortality' component of extra mortality after AVR remains a 'black-box' in the model. Identification of the exact determinants of 'additional mortality' and quantification of its impact, by different valve types, would further improve the validity of the model calculations.
- *Inclusion of other determinants of survival after AVR* – Apart from those already incorporated in to the model, other factors such as NYHA functional class, pre-operative heart rhythm, etiology of valve disease and other concomitant disease also determine the prognosis after AVR [3,4,48]. These factors need to be integrated into the model.
- *Further refinement of model parameters* – Hemorrhage constitutes an important valve-related event after implantation with a mechanical valve. As previously discussed, the target INR level, achieved INR and INR variability are related to the incidence of hemorrhage and late survival [41,42] and need to be accounted in the model calculations. The model interface should provide the user with an option of selecting one of many INR ranges [39,40] as found appropriate. This would require more extensive data sets containing the necessary variables for calculation of the model's input parameters. Thrombo-embolism is another valve-related event that requires more specific input. The risk of thrombo-embolism after valve implantation has been shown to depend on the intensity of anticoagulation [49] and on many individual risk factors. Butchart and colleagues have developed a scoring system based on certain blood tests and clinical risk factors, which they claim accurately predicts the risk of thrombo-embolism [50]. They showed that the total number of positive risk factors effectively stratified patients into different long-term risk groups with varying hazard rates, which they estimated. Incorporation of such a tool within the microsimulation model would further individualize the model calculations.
- *Estimation of prognosis after AVR with other valve types and procedures* – This would include, for example, stentless valves [51], newer third-generation valves [52] and valve-sparing operations [53] respectively.
- *Incorporation of other quality of life aspects in to model* – Patient perceptions also play a role in valve choice. In this respect, quality-adjusted life years (QALY's) could form an end-point in the model calculations. The patient's perception of valve sound [54] and anxiety of a possible re-operation are some aspects which could be considered.

11.4.2. Expansion of microsimulation methodology to other areas of cardiac / cardiovascular disease and development of an overall Cardiac Procedure Decision Support System

Cardiac Surgeons and Cardiologists working on cardiac procedures other than AVR may also benefit from a clinical decision support tool. Different support tools applied to different research questions in cardiology could form an overall Cardiac Procedure Decision Support System at Erasmus MC. Some cardiac procedures that might benefit from a decision support tool are listed below.

- *Mitral valve replacement (MVR) and mitral valve repair* - In the choice between a mechanical valve and a bioprosthesis, the ACC / AHA recommend an age cut-off point of 70 years [38]. Similar to AVR, given the many valve types and surgical procedures available for MVR, a decision support tool would be of relevance. Further, the choice between MVR and valve repair is also debatable in certain patients [55], which could be supported by clinical decision analysis.
- *Progression of coronary atherosclerosis and prediction of acute myocardial infarction* – Boersma and colleagues of the Department of Cardiology, Erasmus MC, Rotterdam, have researched extensively on the natural course of atherosclerosis and on risk factors of coronary artery disease [56]. Their interest in utilizing microsimulation to model the progression of atherosclerosis and predict myocardial infarction augurs well for the expansion of the methodology to other branches of cardiology.
- *Optimization of the treatment of coronary artery disease (CAD)* – The advent and claimed effectiveness of the new drug-eluting stents as therapeutic alternatives to CABG [57] have generated interest on the ideal intervention in coronary disease [58,59]. Simulation models may be useful in predicting the long-term outcomes with either intervention and in the choice of intervention for a given patient. The availability of 25-year follow-up data on coronary re-vascularization at this institute [60] would be useful in this endeavor.
- *Optimized management of ventricular septal defect (VSD) in infancy and childhood* – Ventricular septal defect is the most common congenital intra-cardiac defect of clinical importance. The indication for surgery and the type of surgical procedure is dependant on many factors [61]. Here too, microsimulation could play a role as a decision support tool.

11.4.3. Enhanced accessibility and usage of the microsimulation model

- *Introduction of an user-friendly version of the microsimulation model on the Internet* – An Internet application of the microsimulation model would increase its accessibility. Comments and criticisms by its users would also serve as a stimulus for further development of the methodology. Although an initial version of the model is currently available on the Internet, an updated version with user instructions has been planned for the future.
- *Incorporation of user-friendly software* – The microsimulation model has been constructed using Delphi, a Pascal-based programming language. The complexity of this programming language requires statistical expertise to alter or add parameters, which is a drawback to the user-friendliness of the model. In this respect, the possibility of utilizing other user-friendly software, (for example, Excel) should be examined.
- *Integration of the microsimulation model and a future Cardiac Procedure Decision Support System into the proposed Cardiology Information System* – Current advances in information technology (IT) permits the integration of many different data systems, which would support data exchange. Of relevance in the field of cardiology, the proposed Cardiology Information System [62] would enable the physician to access at his or her table a host of patient-related and background information. This would include patient-specific clinical and diagnostic information from hospital information systems, background educational material (books and journals), relevant guidelines and survey and registry data. The inclusion of a decision support system into this network would further enhance the benefit to the physician.

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Appendices

Summary

Aortic valve replacement (AVR) is a surgical procedure aimed at replacing a diseased aortic valve with a prosthetic device. The prognosis of a patient after AVR depends on many inter-related factors. The objective of this thesis was to further develop and utilize the microsimulation methodology to determine the prognosis of patients after AVR with mechanical valves and bioprostheses, which in turn could assist in the optimal choice of a valve prosthesis for a given patient.

Chapter 1 provides an introduction to AVR with brief descriptions of the normal aortic valve, dysfunction of the valve and indications for surgery, and an overview of the types of prostheses available for implantation. Further, possible patient outcomes after AVR and factors affecting long-term outcome are described. Finally, explaining the rationale of this pursuit, the objectives of the thesis are enumerated.

Chapter 2 introduces clinical decision analysis and describes the appropriateness of 3 decision models in analyzing the clinical decision on the choice of valve prosthesis in AVR. The decision tree, the fundamental graphical tool of decision analysis, provides a structure to analyze the problem. However, the complexity of the problem makes the decision tree inappropriate for the purpose. The Markov model is then described, which shows the different health states that the patient could be in. A limitation of the Markov model is its 'lack of memory' of previous health states, thereby assuming that patients in a particular state are homogenous. An introduction to the third alternative decision model, the microsimulation model is provided in this chapter. The parameters of the model, assumptions made and data required to parameterize the model are further described.

Chapter 3 involves a detailed description of the microsimulation model, which was developed to predict outcomes of a patient after aortic valve replacement. The microsimulation model simulates the life of a given patient after implantation with a particular valve by taking in to account the remaining life expectancy and the valve-related events that could occur in that patient. Repeating the simulation of the life of this patient many times creates a 'virtual' population consisting of patients with identical initial characteristics, but with all possible outcomes after AVR. This enables the calculation of the average prognosis

of the given patient. The steps involved in a simulation cycle are described and graphically depicted while the relationship between the number of simulations and the precision of the model outcome is highlighted. Finally, the advantages and disadvantages of the microsimulation methodology are discussed.

Chapter 4 describes the use of meta-analysis and microsimulation to predict the outcomes of patients after AVR with a bioprosthesis. Five types of stented porcine bioprostheses, both first- and second-generation, were selected to represent the bioprostheses in this analysis. Data required to parameterize the model was obtained by meta-analysis. The 9 reports selected for the meta-analysis included 5837 patients and 31,874 patient-years of follow-up. Combined estimates of the linearized occurrence rates (LOR) were calculated for some of the valve-related events. Pooling of time to event curves of different studies were used to calculate the hazards of endocarditis and structural valvular deterioration (SVD), the former being described by a two-period exponential model and the latter by a Weibull curve. The microsimulation model calculated the life expectancy and lifetime risk of re-operation after AVR for patients of different ages and sex profiles.

Chapter 5 consists of a description of the use of the microsimulation model to determine the long-term outcome of patients after implantation with the Carpentier-Edwards bovine pericardial valve. A meta-analysis of 8 selected reports (2685 patients and 12,250 patient-years) on patients implanted with this valve was used to estimate the hazard rates of valve-related events. Eighteen-year follow-up data on 267 patients implanted with the Carpentier-Edwards pericardial valve between 1981 through 1984 was used to calculate the parameters of the age-dependent Weibull curve, which described SVD. According to the Weibull parameters, the median time to re-operation due to SVD, for a 65-year-old male, was 20.5 years. Microsimulation calculated for this patient a life expectancy of 10.5 years and a lifetime risk re-operation due to SVD of 17%. Validation of the model survival outputs with external data showed favorable agreement.

Chapter 6 calculates and compares the long-term outcomes of patients after AVR with the second-generation Carpentier-Edwards bovine pericardial and porcine supraannular bioprostheses. Although shown to have improved hemodynamics and enhanced durability, knowledge on the long-term outcomes of these valve types are limited. Meta-analyses of

published results of AVR with the pericardial valves (2685 patients and 12, 250 patient-years) and supraannular valves (3796 patients and 20,127 patient-years) were used to estimate the occurrence rates of valve-related events. Long-term follow-up data sets were used to generate age-dependant Weibull curves that described SVD. According to these parameters, the median time to SVD for a 65-year-old male was 20.1 and 22.2 years for the pericardial and supraannular valves. These estimates were used to parameterize the microsimulation model, which calculated the outcomes of patients of different ages. According to the model results, both valve types were shown to perform satisfactorily, especially in the elderly patient, while no appreciable difference in long-term outcome was apparent between patients having either valve type.

Chapter 7 constitutes a study on the prognosis after AVR with St. Jude Medical bileaflet prostheses, one of the most commonly implanted mechanical valves at present. A meta-analysis was conducted on published results of AVR with this prosthesis (2986 patients and 16,163 patient-years) to estimate post-operative valve-related events. A Gompertz model was used to represent the increasing hazard of bleeding with advancing patient age. Microsimulation calculated the life expectancies of patients and provided insight into lifetime risks of valve-related events. The lifetime risk of at least one thrombo-embolic episode reduced from 22% in a 35-year old male to 7% in a 75-year-old patient. Conversely, the lifetime risk of post-implantation bleeding increased from 15% to 37% respectively underscoring the importance of these two valve-related events in mechanical valve implantation.

Chapter 8 compares the prognosis of patients after AVR with bileaflet mechanical valves with stented porcine valves and attempts to provide evidence-based support for the choice of a prosthesis for a given patient. Meta-analysis of published results of AVR with mechanical prostheses (9 reports, 4274 patients and 25,726 patient-years) and stented bioprostheses (13 reports, 9007 patients and 54,151 patient-years) was used to estimate the annual risks of valve-related events and their outcomes. For a 65-year-old male for example, the model calculated a life expectancy of 10.4 and 10.7 years after implantation with mechanical valves and bioprostheses respectively. Although the ACC / AHA recommends a bioprosthesis for patients 65-years and older, the model results suggest a further lowering of this age-cut off point.

Chapter 9 investigates the effect of knowledge gained by the model on prosthetic valve choice. For this purpose, a pilot study was carried out among cardiologists and cardiac surgeons attending a conference session on prosthetic valve choice. Results of the study showed a shift in preference after observing the model results, implying the possible impact of decision support tool on valve choice.

Chapter 10 describes the incorporation of coronary artery bypass surgery (CABG) in to the structure of the microsimulation model and its effect on the prognosis of patients after AVR. The model was used to provide insight into the outcomes of patients after AVR with mechanical valves and stented bioprostheses, with and without CABG, and to determine the age cut-off point in outcomes between the two valve types. CABG reduced life expectancy and consequently the life time risks of valve-related events. However, the trade-off between the reduced risks of bioprosthetic failure and hemorrhage in mechanical valves minimized the effect of CABG on the age cut-off point between the two valve types.

Chapter 11 embodies the general discussion of this thesis. In this section, the salient aspects of the microsimulation methodology and the model results for AVR with mechanical valves and bioprostheses are discussed. Some ideas and suggestions on the possible future direction of this methodology conclude this section.

Samenvatting

Aortaklepvervanging (AVR) is een chirurgische procedure waarbij de zieke aortaklep vervangen wordt door een klepprothese. Vele onderling samenhangende factoren bepalen de prognose van een patiënt na aortaklepvervanging. Doel van dit proefschrift is het verder ontwikkelen en toepassen van de microsimulatie-methodologie om zo de prognose van patiënten na aortaklepvervanging met mechanische en biologische prothesen te bepalen. Dit zou de optimale keuze voor een bepaald type klepprothese kunnen ondersteunen.

Hoofdstuk 1 geeft een introductie over het onderwerp AVR met korte beschrijvingen van de normale aortaklep, de pathofysiologie van de kleppen, de indicaties voor AVR en beschrijft de verschillende types klepprothesen die beschikbaar zijn voor AVR. Daarnaast worden mogelijke uitkomsten van patiënten na AVR beschreven en de factoren die van invloed zijn op lange termijn prognose. Tot slot wordt het doel van dit proefschrift beschreven en worden de daaruit voortvloeiende onderzoeksvragen opgesomd.

Hoofdstuk 2 geeft een introductie tot de klinische besliskunde en beschrijft de geschiktheid van een drietal besliskundige modellen voor de analyse van de klinische beslissing voor een bepaald type klepprothese bij AVR. De beslisboom, de fundamentele grafische methode van de besliskunde, biedt een structuur om het probleem te analyseren. Echter, door de complexiteit van het AVR klepkeuze probleem is de beslisboom niet geschikt voor dit doel. Het Markov model wordt vervolgens beschreven. Dit model toont in detail de verschillende stappen van het klinisch-besliskundig probleem, waaronder de verschillende gezondheidstoestanden waarin een patiënt zich na AVR kan bevinden. Een beperking van het Markov model is dat het geen geheugen heeft voor eerdere gezondheidstoestanden. Het Markov model gaat er vanuit dat patiënten die zich in een bepaalde gezondheidstoestand bevinden een homogene populatie vormen. Een derde alternatief is een microsimulatiemodel, zoals dat in dit proefschrift gebruikt wordt. De parameters van het model, de aannames die gemaakt zijn bij het construeren van het model, en de gegevens die nodig waren om het model te parametriseren (van de benodigde informatie over prognose na AVR te voorzien) worden verder beschreven.

Hoofdstuk 3 beschrijft het microsimulatiemodel dat ontwikkeld is om de prognose van patiënten na AVR te schatten. Het microsimulatiemodel simuleert aselect het leven van een bepaalde patiënt na implantatie met een bepaald type klepprothese, waarbij rekening

wordt gehouden met de resterende levensverwachting van die bepaalde patiënt en de klepgerelateerde complicaties die op kunnen treden. Door de simulatie van deze patiënt vele malen te herhalen, wordt een "virtuele" populatie gegenereerd die bestaat uit een groot aantal patiënten met identieke eigenschappen, maar met alle mogelijke uitkomsten na AVR. Dit maakt het mogelijk om voor deze patiënt de gemiddelde prognose te berekenen. De verschillende stappen waaruit een microsimulatie-cyclus bestaat worden beschreven en grafisch weergegeven. Daarnaast wordt de relatie tussen het aantal simulaties en de precisie van de uitkomsten van het model kort uiteengezet. Tot slot worden de voor- en nadelen van de microsimulatie-methodologie beschreven.

Hoofdstuk 4 beschrijft het gebruik van meta-analyse en microsimulatie om de prognose van patiënten na AVR met een bioprothese te voorspellen. Vijf types gestente bioprothesen, zowel eerste als tweede generatie, werden geselecteerd voor de meta-analyse. Hazard-ratio's werden berekend om de "additionele mortaliteit" van de extra sterfte onder patiënten na AVR weer te geven. De benodigde gegevens voor de parametrisering van het model werden verkregen door meta-analyse van bovengenoemde kleptypen. De 9 publicaties die werden geselecteerd voor de meta-analyse bevatten 5.837 patiënten en 31.874 patiëntenjaren aan follow-up. Gecombineerde schattingen van “linearised occurrence rates” (LOR) werden berekend voor de meeste klepprelateerde gebeurtenisen. Om het risico op endocarditis en structureel klepfalen ('slijtage van de klep') te berekenen, werden de grafieken uit de verschillende studies samengevoegd. Endocarditis werd beschreven als een risico met 2 fasen (een vroege fase met een hoog constant risico en een late fase met een laag constant risico), structureel klepfalen werd beschreven door een Weibull-functie. Het microsimulatiemodel berekende de levensverwachting en het risico om gedurende de rest van het leven opnieuw geopereerd te worden na AVR voor patiënten van verschillende leeftijden en geslacht.

Hoofdstuk 5 beschrijft het gebruik van meta-analyse en microsimulatie om de prognose van patiënten na AVR met een Carpentier-Edwards bovine pericardklep te voorspellen. Een meta-analyse van 8 publicaties (2.685 patiënten en 12.250 patiëntenjaren) over patiënten met deze prothese werd gebruikt om het vóórkomen van klepgerelateerde complicaties te schatten. Gegevens over 18 jaar follow-up van 267 patiënten die een Carpentier-Edwards bovine pericardklep kregen tussen 1981 en 1984 werden gebruikt om een leeftijdsspecifieke Weibull-functie te construeren voor de beschrijving van klepfalen. Volgens deze Weibull-functie wordt de mediane tijd tot reoperatie als gevolg van

klepfalen geschat op 20.5 jaar voor een 65-jarige man. Het microsimulatiemodel berekende voor deze patiënt een levensverwachting van 10.5 jaar en een risico om gedurende de rest van het leven gereopereerd te worden in verband met klepfalen van 17%. Validatie van de door het model geschatte overleving met externe gegevens liet een goede overeenkomst zien.

Hoofdstuk 6 berekent en vergelijkt de lange termijn prognose van patiënten na AVR met de tweede generatie Carpentier-Edwards bovine pericardkleppen en supra-annulaire varkenskleppen. Alhoewel is aangetoond dat deze kleptypen geassocieerd zijn met een verbeterde hemodynamiek en duurzaamheid is er slechts weinig bekend over de lange termijn resultaten met deze kleptypen. Meta-analyse van publicaties over patiënten met bovine pericardkleppen (2.685 patiënten en 12.250 patiëntenjaren) en supra-annulaire varkenskleppen (3.796 patiënten en 20.127 patiëntenjaren) werden gebruikt om het voorkomen van klepgerelateerde complicaties te schatten. Lange termijn follow-up datasets werden gebruikt om een leeftijdsspecifieke Weibull-functie te construeren om klepfalen te beschrijven. Volgens deze Weibull-functie werd de mediane tijd tot reoperatie als gevolg van klepfalen voor een 65-jarige man geschat op 20.1 jaar en 22.2 jaar voor respectievelijk de bovine pericardklep en de supra-annulaire varkensklep. Deze schattingen werden gebruikt voor de parametrisering van het microsimulatiemodel, waarna het model de prognose van patiënten met verschillende leeftijden berekende. Volgens de berekeningen van het model functioneerden beide klepprothesen goed, met name in oudere patiënten. Er waren geen belangrijke verschillen met betrekking tot lange termijn prognose van oudere patiënten met een van deze twee kleptypen.

Hoofdstuk 7 is een studie over de prognose van patiënten na AVR met een St. Jude Medical bileaflet klep, een wereldwijd zeer frequent geïmplanteerde mechanoprothese. Een meta-analyse van publicaties (2.986 patiënten en 16.163 patiëntenjaren) over patiënten met deze prothese werd gebruikt om het voorkomen van klepgerelateerde complicaties te schatten. Een Gompertz model werd gebruikt om het met de leeftijd van de patiënt toenemende bloedingsrisico te schatten. Het microsimulatiemodel berekende de levensverwachting van patiënten met verschillende leeftijden en het risico om gedurende de rest van het leven klepgerelateerde complicaties te krijgen. Het risico om gedurende de rest van het leven ten minste één thrombo-embolische complicatie te krijgen nam af van 22% voor een 35-jarige tot 7% voor een 75-jarige patiënt. Omgekeerd nam het bloedingsrisico toe van 15% voor een 35-jarige tot 37% voor een 75-jarige patiënt. Deze

bevindingen tonen dat bloeding en thrombo-embolie belangrijke complicaties vormen na implantatie van een mechanoprothese, maar een geheel verschillende relatie met de leeftijd van de patient hebben.

Hoofdstuk 8 vergelijkt prognose van patiënten na implantatie met een St. Jude Medical bileaflet mechanoprothese versus een gestente bioprothese. Er wordt getracht om "evidence-based" ondersteuning te geven bij de keuze voor een prothese bij patiënten met verschillende leeftijden. Meta-analyses van 9 publicaties over resultaten met de St. Jude Medical bileaflet mechanoprothese (4.274 patiënten en 25.726 patiëntenjaren) en 13 publicaties over gestente bioprothesen (9.007 patiënten en 54.151 patiëntenjaren) werden gebruikt om de jaarlijkse risico's voor het krijgen van een klepgerelateerde complicatie en de gevolgen daarvan te schatten. Het microsimulatiemodel berekende bijvoorbeeld voor een 65-jarige patiënt een levensverwachting van 10.4 na implantatie met een mechanoprothese en 10.7 jaar met een gestente bioprothese. Alhoewel de Amerikaanse cardiologenverenigingen (ACC en AHA) een bioprothese aanraden voor patiënten van 65 jaar en ouder, zou volgens de berekeningen van het microsimulatiemodel deze leeftijdsgrens verlaagd kunnen worden.

Hoofdstuk 9 poogt het effect van het gebruik van het microsimulatiemodel door cardiologen en hartchirurgen op klepkeuze te onderzoeken. Aan de bezoekers van een klepkeuze-sessie tijdens een Nederlands congres voor cardiologen en hartchirurgen werd gevraagd voor 2 patiënten een klepkeuze te maken tussen een bioprothese en een mechanoprothese. Daarna werd met het microsimulatiemodel uitgerekend wat de prognose van deze 2 patiënten was na implantatie met een bioprothese en een mechanoprothese, en werd het publiek opnieuw gevraagd hun voorkeur voor een bepaalde prothese te noteren. Er was een verschuiving in de preferentie voor een bepaald kleptype zichtbaar hetgeen suggereert dat het microsimulatiemodel een nuttige ondersteuning kan bieden bij klepkeuze.

Hoofdstuk 10 beschrijft de toevoeging van coronairchirurgie (CABG) als patiënteneigenschap aan de structuur van het microsimulatiemodel en onderzoekt het effect dat CABG heeft op de prognose van patiënten na AVR. Dit microsimulatiemodel werd gebruikt om het effect van CABG op de prognose van patiënten na AVR met een mechanoprothese of een gestente bioprothese te bestuderen, en te bepalen of het al dan niet ondergaan van CABG ten tijde van AVR van invloed is op de leeftijdsgrens voor het

implanteren van een mechanoprothese of een bioprothese. Het ondergaan van CABG tijdens AVR resulteerde in een verkorte levensverwachting en als gevolg daarvan lagere risico's om gedurende de rest van het leven klepgerelateerde complicaties te krijgen. Er was opmerkelijk genoeg geen belangrijk effect van CABG op de leeftijdsgrens voor het implanteren van een bepaalde klep. Dit kwam doordat zowel de kans op klepfalen bij patiënten met een bioprothese als de kans op bloedingen en thrombo-embolische complicaties bij patiënten met een mechanoprothese afnam.

Hoofdstuk 11, de algemene discussie**,** bespreekt de belangrijkste aspecten van de microsimulatiemethodologie en bevat een discussie van de resultaten van het microsimulatiemodel over de prognose na AVR met mechanoprothesen en bioprothesen. Enkele ideeën en suggesties voor mogelijke toekomstige toepassingen van deze nieuwe en veelbelovende methodologie ter ondersteuning van klinisch besliskundige problemen besluiten dit hoofdstuk.

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Publications and Presentations

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Puvimanasinghe JPA, Takkenberg JJM, Eijkemans MJC, Steyerberg EW, Herwerden LA van, Jamieson WRE, Grunkemeier GL, Habbema JDF, Bogers AJJC. Comparison of Carpentier-Edwards pericardial and supraannular bioprostheses in aortic valve replacement. Submitted.

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Comparison of Carpentier-Edwards pericardial and porcine bioprostheses in aortic valve replacement. 13th World Congress of the International Society of Cardio-Thoracic Surgeons. San Diego, California, USA. November 2003.

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Prognosis following aortic valves replacement with a mechanical valve and a bioprosthesis. Annual Sessions of the Society of Medical Decision-Making. Cincinnati, Ohio, USA. September 2000.

Curriculum Vitae

The author of this Ph.D. thesis was born in Colombo, Sri Lanka, on the 6th of July 1962. Following early education at Hampden Guerney School, London, UK, he joined St. Joseph's College, Colombo, Sri Lanka, where he completed his Ordinary Level and Advanced Level examinations. He studied medicine at the North Colombo Medical College, Ragama, Sri Lanka and obtained the degree of Bachelor of Medicine and Bachelor of Surgery (MBBS) in 1991. Following a stint as a non-commissioned medical officer in the Sri Lankan Army, he joined the Ministry of Health of Sri Lanka and completed his internship at the Base Hospital, Kegalle, Sri Lanka. In 1993, he was appointed as the Medical Officer of Health (MOH) of the Arachchikattuwa health area in the Puttalam district of Sri Lanka, and was subsequently appointed as the Divisional Director of Health Services of that area.

In 1995, in pursuit of post-graduate education, the author joined the Department of Community Medicine of the Faculty of Medicine, University of Colombo and obtained the M.Sc. in Community Medicine in 1996 and the doctorate in Community Medicine (MD) in 1998 respectively from the Postgraduate Institute of Medicine, Sri Lanka. During this period, he attended the three-month Field Epidemiology Training Programme (FETP) conducted by the National Institute of Communicable Diseases, India in collaboration with the World Health Organization (WHO), in Delhi, India. Following his post-graduate studies, he was appointed as the Regional Epidemiologist of the Kalutara district, Sri Lanka. In mid 1999, the author joined the Netherlands Institute for Health Sciences (NIHES) of the Erasmus University in Rotterdam and completed the M.Sc. degree in clinical epidemiology. On his return to Sri Lanka, he was appointed to the central Epidemiological Unit, Ministry of Health, Colombo, as an Epidemiologist and was subsequently board-certified as a consultant. Returning to the Netherlands in July 2001, he joined the Erasmus MC in Rotterdam, and has been jointly attached to the Department of Cardio-Thoracic Surgery and the Department of Public Health, where he works on an international collaborative research project on aortic valve replacement.

The author is married to Shyami, lawyer, formerly Senior Lecturer, University of Colombo, and presently a Ph.D. scholar in The Hague. He has two children - Amadhya Marishque aged 6 years and Apeksha Marize aged 10 months.

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