Martijn van Geldorp

SEVERE AORTIC STENOSIS

DIAGNOSIS, TREATMENT AND PROGNOSIS

Severe Aortic Stenosis:
diagnosis, treatment and prognosis

Martijn van Geldorp

The financial support for the publication of this thesis by the following companies is gratefully acknowledged:

ESJ Accountants & Belastingadviseurs
Erpa B.V. specialisten in Porsche 911-912
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Krijnen Medical Innovations B.V.
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Johnson & Johnson Medical B.V.
Thoraxcentrum Research B.V. Erasmus Medisch Centrum
Stichting R&D Cardio Pulmonale Chirurgie Catharina Ziekenhuis
Pa en Ma van Geldorp

ISBN: 978-94-6169-334-1

Layout and printing by Optima Grafische Communicatie, Rotterdam, The Netherlands

Cover design: M.W.A. van Geldorp, detail of exhaust valve of a 2.2 litre 6-cylinder boxer engine

Severe Aortic Stenosis:
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Ernstige aortaklepstenose:
diagnose, behandeling en prognose

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 20 februari 2013 om 11.30 uur

door

Martijn Willem Albertus van Geldorp

geboren te Utrecht

PROMOTIECOMMISSIE

Promotoren:	Prof.dr. J.J.M. Takkenberg
	Prof.dr. A.P. Kappetein
Overige leden:	Prof.dr. A.J.J.C. Bogers
	Prof.dr. F. Zijlstra
	Prof.dr.ir. H.A. van Swieten
	Prof.dr. P.P.T. de Jaegere

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

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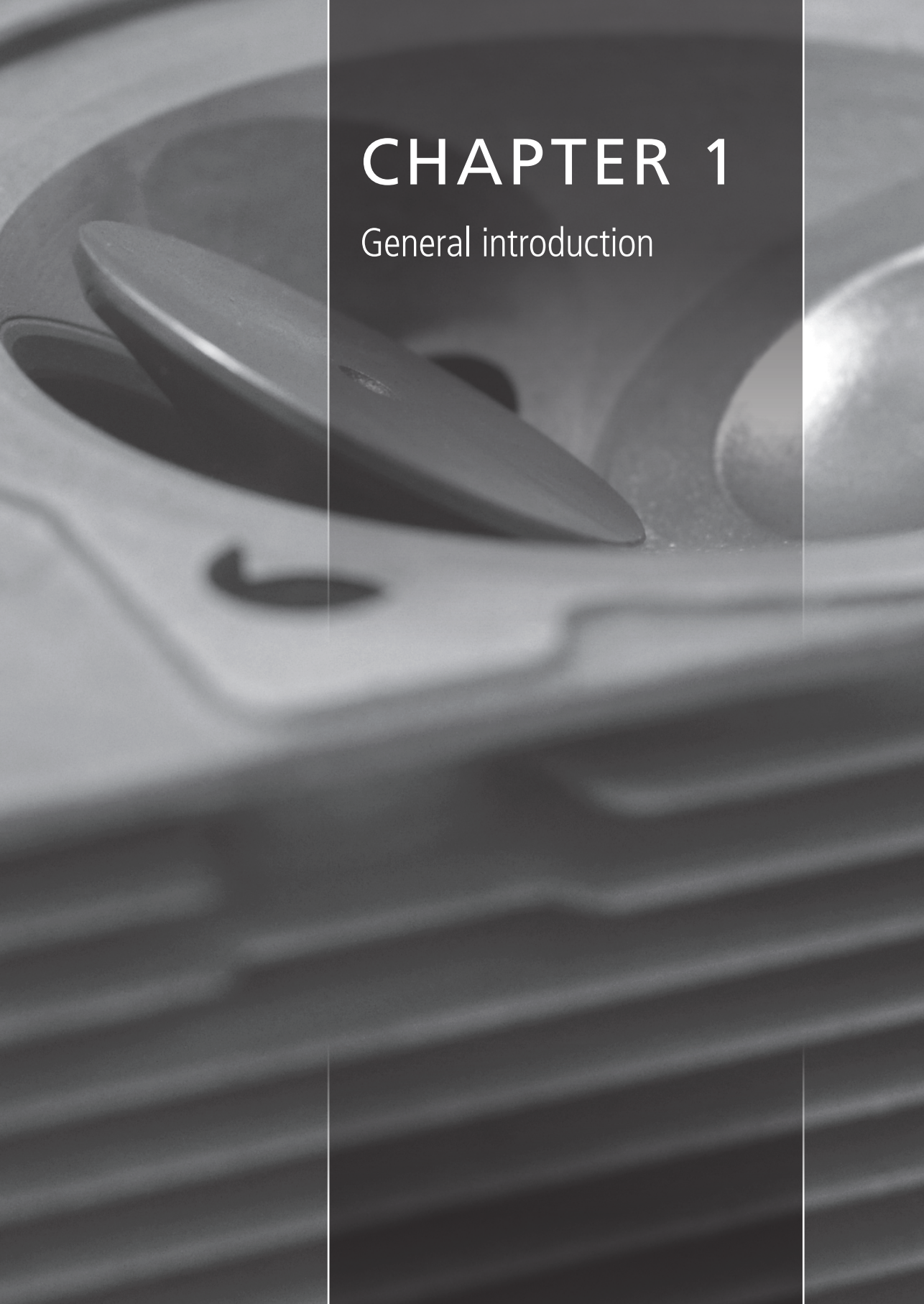

CHAPTER 1

General introduction

INTRODUCTION

Degenerative aortic stenosis is the most common valvular heart disease in developed countries. The prevalence of severe aortic stenosis increases with age from 1% in people below 65 years of age to nearly 6% in people over the age of 85.[1-2] Since the population life expectancy continues to expand, severe aortic stenosis represents a growing health problem: the global annual need for aortic valve replacement (AVR) is expected to triple to approximately 850,000 by the year 2050.[3]

According to the guidelines of the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC) for the management of patients with valvular heart disease, symptomatic patients with severe aortic stenosis require AVR because prognosis is poor when treated conservatively:[4-5] after onset of angina average life-expectancy is reported to be 4.5 years, after syncope 2.6 years and after heart failure less than one year.[6] Besides this dismal prognosis, not much is known about the burden of disease of symptomatic patients during these final years of life. Surgical aortic valve replacement (AVR) with either a mechanical or biological prosthesis is the treatment of choice because it offers good long-term results even in elderly patients.[7-10] However, up to 60% of symptomatic patients are denied AVR because of advanced age or severe co-morbidity.[11-14] Furthermore, the proportion of symptomatic patients is likely to be underestimated: up to 37% of the patients who claim to be asymptomatic, experience limiting symptoms when an exercise test is performed.[15]

In truly asymptomatic patients AVR is not recommended since the risk of surgical intervention may be higher than the risks of medical treatment.[4] In contrast, recent reports document a dismal prognosis in asymptomatic severe aortic stenosis, suggesting that diastolic dysfunction, interstitial fibrosis and secondary pulmonary hypertension already exist before symptoms occur, implying the threshold for performing AVR should be lowered to asymptomatic patients.[5, 14, 16] Altogether it would be useful to have a better indicator of disease-severity, to be able to identify those who are at risk of rapid clinical deterioration and to determine the optimal threshold for AVR. Ideally this cut-off point would be just before irreversible left ventricular dysfunction occurs.

Implantation of a prosthetic aortic valve by transcatheter techniques has emerged in recent years. The Thoraxcentre of the Erasmus Medical Center pioneered these techniques. They were the first to perform a successful transcatheter aortic valve implantation (TAVI) in the Netherlands in 2005. This technique was designed to relieve the stenosis with minimal surgical trauma in order to improve postoperative outcome especially in patients with severe comorbidity and in the frail elderly. Now that even these patients with a relatively short life-expectancy can be offered treatment, new societal issues are being raised concerning the increase of health care costs and the urgent need for its containment. In order to guide this political debate, several medical issues should be elucidated: we have

to gain more insight in the disease burden and life expectancy of the elderly patient with severe aortic stenosis when treated medically, in the choice of a surgical or transcatheter replacement, and in the expected benefit –both in terms of survival ánd quality of life- after either treatment option.

THESIS OBJECTIVES

The goal of this thesis is to explore the current treatment options, treatment utilization and prognosis of elderly patients with aortic valve stenosis. The following research questions were posed:

1. What is the current knowledge of aortic stenosis, and how does the disease progress with time?
2. What are the main therapeutic choices for patients with severe aortic stenosis, what are the options for replacement of the aortic valve in middle aged and elderly patients, and how can we compare patient outcome after implantation with several available devices?
3. In contemporary clinical practice, how are patients with severe AS treated? What are reasons for non-referral to surgical treatment, what are the determinants of treatment selection and how do they affect prognosis in terms of survival and quality of life?

OUTLINE

Chapter 2 is a review of the clinical presentation of a patient with aortic stenosis and of the causes and pathology of the diseased aortic valve. It also discusses current diagnostic tools and treatment options.

In **chapter 3** a systematic review of literature was undertaken to estimate the rate of progression of aortic stenosis in adult patients.

The departments of Cardiothoracic Surgery and Public Health in the Erasmus Medical Center in Rotterdam (the Netherlands) in collaboration with the University of British Columbia, Vancouver (Canada) developed microsimulation models to simulate outcome of patients who underwent aortic valve replacement. **Chapter 4** gives insight into the microsimulation methodology, its advantages and disadvantages, and how it can assist in counseling a patient when choosing between different types of valve prostheses.

In **chapter 5** the microsimulation model was used to study age- and gender-specific life expectancy, event-free life expectancy and reoperation-free life expectancy after aortic valve replacement with either a mechanical- or biologic valve prosthesis.

Chapter 6 presents how to use microsimulation to compare patient outcome after AVR with several valve substitutes: stented- and stentless bioprostheses, allografts and autografts.

Chapter 7 describes the difference between the ACC/AHA and the ESC guidelines and what takes place in daily practice with regards to the management of symptomatic patients with severe aortic stenosis. We studied treatment decisions in 179 symptomatic patients and documented the reasons why so many patients did not receive the indicated surgical treatment.

Based on the paper presented in Chapter 7, a letter to the editor was written with a short discussion on the role of statins in the treatment of patients with aortic stenosis.[17] Our reply constitutes **Chapter 8**.

Chapter 9 elaborates on the **A**ortic **VA**lve **RIJN**mond study: a multi-center prospective observational cohort study among patients with severe aortic stenosis in the outpatient cardiology clinics of the Rotterdam Rijnmond region (The Netherlands). The primary goals were to study determinants of treatment selection and patient outcome. Patients were followed over a time-period of two years and subjected to several clinical assessments.

In **Chapter 10** the SF-36v2 Health Survey was used to assess the quality of life of all symptomatic and asymptomatic patients in the AVARIJN cohort and this was compared to the general age-matched Dutch population.

Chapter 11 sequels the previous chapter and describes the quality of life of the symptomatic patients during follow-up: it compares the quality of life after AVR to the quality of life of conservatively treated patients.

In **Chapter 12** recent or ongoing multi-center randomized trials are discussed that explore the safety, benefits, (dis-) advantages and cost-aspects of the new TAVI technology compared to the conventional AVR in order to define the indication of either technique.

Chapter 13 provides the general discussion with conclusions and recommendations following from this thesis.

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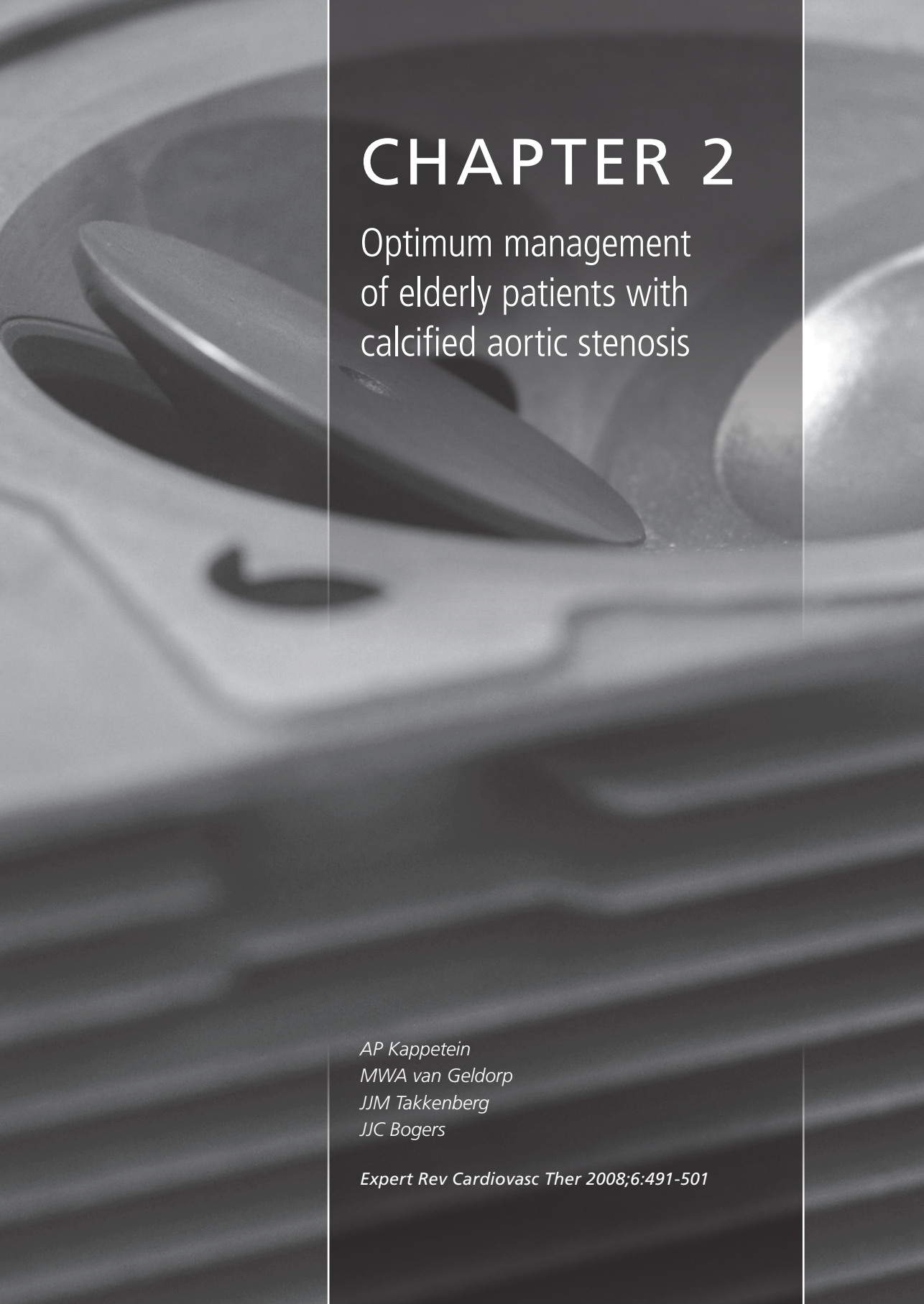

CHAPTER 2

Optimum management of elderly patients with calcified aortic stenosis

AP Kappetein
MWA van Geldorp
JJM Takkenberg
JJC Bogers

Expert Rev Cardiovasc Ther 2008;6:491-501

ABSTRACT

Increased life expectancy has led to a growing elderly population frequently presenting with aortic stenosis. This review focuses on the pathogenesis of calcific aortic stenosis, diagnosis, and possible ways to halt progression to severe symptomatic aortic stenosis, methods of assessing symptoms and severity, and modalities and timing of aortic valve replacement. At present the treatment of aortic stenosis for the majority of patients is surgical, and any patient with symptomatic severe aortic stenosis should be considered for aortic valve replacement (AVR). This article also discusses the role of emerging techniques of closed heart valve implantation either transfemoral or transapical and which patients might be candidates for these new approaches to the treatment of aortic stenosis in the elderly population.

INTRODUCTION

The prevalence of aortic valve stenosis (AS) increases with age and as a result of the advancing age of the general population an increasing number of elderly patients are presenting with symptomatic valve disease.[1] The prevalence of AS is 2.5% at the age of 75 years and almost 8% at 85 years.[1] Calcific aortic stenosis is due to an active chronic disease, starting with thickening and calcification of valve cusps, termed aortic sclerosis. In the beginning aortic sclerosis is without haemodynamic consequences but slowly it may progress towards heavily calcified stiff cusps, aortic valve stenosis, with restricted leaflet opening with obstruction to left ventricular outflow.

Cause

A bicuspid aortic valve is the most common cause of aortic stenosis in patients under age 65 while in patients over 65 years of age the most common cause is so called "senile calcific aortic stenosis." Although bicuspid valves usually do not impede blood flow when the patients are young, they do not open as widely as normal valves with three cusps. Therefore, blood flow across the bicuspid valves is more turbulent, causing increased wear and tear on the valve leaflets. Over time, excessive wear and tear leads to calcification, scarring, and reduced mobility of the valve leaflet. Senile calcific aortic stenosis results from destruction of protein collagen of the valve leaflets and calcium is deposited on the leaflets. Turbulence across the valve increases causing scarring, thickening, and stenosis of the valve once valve leaflet mobility is reduced by calcification.

Rheumatic fever is a condition resulting from untreated infection by group A streptococcal bacteria. Damage to valve leaflets from rheumatic fever causes increased turbulence across the valve and more damage. The narrowing from rheumatic fever occurs from the fusion (melting together) of the edges (commissures) of the valve leaflets.

Pathology

Histopathologically, sclerosis of the aortic valve is defined as fibrous thickening and calcification of the valve cusps. In the past it was thought that aortic valve sclerosis was caused by passive calcium precipitation within the aortic valve leaflets. However, there is increasing evidence that the development and progression of calcific aortic stenosis may be triggered by underlying genetic and cardiovascular risk factors. These risk factors are frequent in the elderly and include smoking, hypertension, hyperlipidaemia, lipoprotein(a) levels, higher body mass index and diabetes.[2] The accumulation of macrophages and lymphocytes observed in stenotic valves indicates that calcific aortic stenosis might be based on a chronic inflammatory process.[3] The angiotensin-converting enzyme cascade also works locally within the aortic leaflet, causing fibroblasts within the fibrosa layer to differentiate into myofibroblasts wherein the angiotensin I receptor is highly expressed. The

myofibroblast plays a central role in the process because it is believed to differentiate into an osteoblast-like cell phenotype, which in turn promotes deposition of calcified nodules and bone formation.[4]

The progression from aortic sclerosis, which can already easily be detected by echocardiography or computed tomography, to haemodynamically severe aortic stenosis is variable and may take many years. Although aortic sclerosis is clinically asymptomatic, its presence is associated with a 40% increase in the risk of myocardial infarction and a 50% increase in the risk of cardiovascular death in patients with no preexisting diagnosis of coronary artery disease.[5]

Clinical presentation

The three classical symptoms of aortic stenosis are dyspnoea, angina, and syncope. Chest pain is the first symptom in one–third of patients and eventually occurs in one–half of patients with aortic stenosis. Angina often occurs without any underlying narrowing of the coronary arteries. The thickened heart muscle must pump against high pressure to push blood through the narrowed aortic valve. This increases heart muscle oxygen demand in excess of the supply delivered in the blood, causing chest pain. Syncope related to aortic stenosis is usually associated with exertion or excitement. These conditions cause vasodilatation. In aortic stenosis, the heart is unable to increase output to compensate for the drop in blood pressure. Therefore, blood flow to the brain is decreased, causing fainting. The average life expectancy is less than three years after the onset of chest pain or syncope symptoms. Symptoms of pulmonary oedema and syncope are late manifestations of the disease process, and prompt treatment is necessary. It reflects the heart muscle's failure to compensate for the extreme pressure load of aortic stenosis. Without treatment, the average life expectancy after the onset of heart failure due to aortic stenosis is between six to 24 months.[6]

Many patients will not report overt symptoms but might instead simply notice a decrease in exercise tolerance without a distinct limiting symptom. This exercise intolerance can often be misinterpreted as "due to aging" but is in fact symptomatic aortic stenosis. Patients become symptomatic when the degree of outflow obstruction prevents an adequate increase in cardiac output with exertion. Some patients develop clear symptoms with obstruction that traditionally has not been considered important, while others remain asymptomatic with apparently severe obstruction. A difficult clinical problem is the patient who has symptoms compatible with aortic stenosis but has outflow obstruction that traditionally would be considered only moderate. In this situation it can be difficult to separate symptoms caused by outflow obstruction from symptoms caused by other comorbidity. Exercise testing can be helpful in providing an objective measure of exercise tolerance and in documenting the hemodynamic response to exercise in these patients.[7]

DIAGNOSIS

Echocardiography

Echocardiography is the clinical standard for evaluation of adults with suspected or known valvular aortic stenosis. Anatomic images show the aetiology of aortic stenosis, level of obstruction, valve calcification, leaflet motion, and aortic root anatomy. Obstruction at the aortic valve level increases left ventricular afterload, resulting in increased wall thickness and early diastolic dysfunction. Echocardiography also evaluates the left ventricular function, wall thickness, and other hemodynamic consequences of aortic stenosis.[8] Basic hemodynamic parameters include the velocity of blood flow through the narrowed aortic valve, the mean pressure gradient between the left ventricle and aorta, and the cross-sectional area of valve opening. In humans, the normal aortic valve area (AVA) is 3.0 to 4.0 cm^2. As AS develops, little gradient is present until the orifice area becomes less than half of normal. The relationship of gradient to orifice area is best described by the Gorlin formula: gradient = CO^2/AVA^2 where CO = cardiac output and AVA = aortic valve area. AVA can be calculated from data obtained by cardiac catheterization and by Doppler echocardiography. By cardiac catheterization the actual stroke volume is used in the calculation of AVA, thus, accounting for the variable of changes in flow affecting the gradient.[9] Calculation of AVA by Doppler echocardiography can be obtained by dividing the flow measured in the left ventricular outflow tract (LVOT) by transvalvular velocity. Difficulties in measuring LVOT diameter and velocity precisely at the same level as well as the simplifying assumption of a flat flow profile and circular shape for the LVOT may cause inaccuracies. This is known to result in an erroneously low calculated AVA in a significant percentage of patients.[9-10]

Table 1. Criteria for grading the severity of Aortic Stenosis

Aortic Stenosis	Jet velocity (m per second)	Mean gradient (mm Hg)	AVA (cm2)	AVA index (cm2/m2)
Mild	< 3.0	< 25	> 1.5	>0.9
Moderate	3.0 – 4.0	25 - 40	> 1.0 to 1.5	>0.6 to 0.9
Severe	> 4.0	> 40	≤ 1.0	≤ 0.6

Stress echocardiography

When stenosis is severe and cardiac output is normal, the mean transvalvular pressure gradient is generally greater than 40 mm Hg. However, when cardiac output is low, severe stenosis may be present with a lower transvalvular gradient and velocity. Stress echocardiography using low dose dobutamine may be helpful in patients with low-flow/low-gradient aortic valve stenosis (AS) and left ventricular (LV) dysfunction to determine the transvalvular pressure gradient and to calculate valve area during a baseline state and

again during dobutamine stress, to distinguish whether stenosis is severe or only moderate in severity. Patients who do not have true anatomically severe stenosis will exhibit an increase in the valve area and little change in gradient during an increase in stroke volume. Patients with severe AS will have a fixed valve area with an increase in stroke volume and an increase in gradient. These patients are likely to respond favourably to surgery. Patients failing to show an increase in stroke volume with dobutamine, referred to as "lack of contractile reserve," may have a superimposed and separate myocardial disease process such as cardiomyopathy, ischemia, or fibrosis in which myocardial function is abnormal. These patients have an increased operative risk, symptomatic status does not always improve, and ejection fraction remains depressed after valve replacement surgery.[11-12]

Coronary angiography

Coronary angiography is routinely performed before aortic valve surgery because of the high prevalence of coronary disease in elderly patients so that bypass grafting can be performed at the time of valve replacement or percutaneous coronary intervention (PCI) before the surgical intervention takes place.

Multislice CT-scan

The role of new imaging modalities as multislice Computed Tomography (MS-CT) at present is limited. At the present time quantification of calcification can be used in research studies of treatment that is hypothesized to interfere with the progression of AS. In clinical practice, however, echocardiography remains the preferred method for detection and quantification of AS. In patients with inadequate and inconclusive echocardiograms, MS-CT may serve as an alternative to obtain aortic valve area. However, the evaluation will remain incomplete as the method does not yield additional haemodynamic information such as transvalvular pressure gradients, presence of regurgitation and additional valve disease, and pulmonary artery pressure. Finally, MS-CT with a specific angiographic protocol, may gain a role for the pre-operative exclusion of coronary artery disease but so far only in patients with low likelihood of atherosclerosis.[13]

Brainnatriuretic peptide

Brainnatriuretic peptide (BNP) is a more objective marker in patients with unclear complaints and has a progressive association with the severity of AS and left ventricular dysfunction. Asymptomatic patients with more haemodynamically significant AS had higher serum BNP levels, which suggest that BNP may represent a marker of disease severity and may potentially serve to discriminate between normal exercise tolerance and true early symptoms of heart failure. Postoperative survival also seems to be related with BNP.[14-16]

TREATMENT

Medical therapy

Aortic stenosis is an actively regulated inflammatory process and given the clinical association of calcific AS with hyperlipidaemia and coronary artery disease, hopes are high that the cause of calcific AS might be modifiable by medical therapy. Targeted drug therapy to prevent the progression of calcific aortic valve disease should be based on the knowledge of risk factors and the molecular pathogenesis of the disease.

Statins may lower lipid levels and reducing systemic inflammation and thereby influence the pathogenesis of calcification in patients with AS. Several retrospective studies have provided evidence that statins slow the hemodynamic progression of AS.[17-20] The prospective, randomized clinical SALTIRE trial of 155 patients showed that, although atorvastatin 80 mg daily more than halved serum LDL cholesterol concentrations, it did not halt the progression or induce regression of the valve disease process as measured by echocardiography or CT-scan.[21] A possible explanation is that patients with aortic velocities below 2.5 m/s were excluded from the SALTIRE trial, and intervening at this earlier stage of the disease process may have been more beneficial. The results of the studies on statin therapy in patients with aortic sclerosis are eagerly awaited, and research on other drugs is likely to follow.[22]

Recent findings raise the possibility that aortic valve calcium accumulation might slow by inhibiting angiotensin-converting enzyme (ACE) and mediate the fibrous thickening of the valve.[23] However, ACE inhibition did not appear to slow the progression of AS in a clinical study, nevertheless this does not preclude the presence of ACE inhibiting effects at the valvular level, which may reduce aortic valve calcium accumulation. It might be that the initiation of ACE inhibition therapy at an earlier stage of disease and longer treatment intervals may have positive effects on disease progression.[17]

Risk analysis and patients denied surgery

Although healthy elderly patients can be treated safely with good outcomes, additional risk factors may account for increased perioperative morbidity and mortality. Decision-making is particularly complex in older patients who represent a heterogeneous population, with more advanced and diffuse cardiovascular disease with higher co-morbidity resulting in a wide range of operative risk, as well as life expectancy. Elderly patients with symptoms due to severe AS, normal coronary arteries, and preserved left ventricular function can expect a better outcome than those with coronary artery disease or left ventricular dysfunction. Cardiac related factors that may further increase operative risk are pulmonary hypertension and previous cardiac surgery. Non-cardiac related factors that carry a greater risk of disabling complications and prolonged hospital stay are cerebrovascular and peripheral vascular disease, diabetes, respiratory dysfunction and renal failure. Advanced cancer and permanent neurological defects as a result of stroke or dementia make cardiac surgery

improper. Patients in a poor condition often do not return to an active existence because the presence of other comorbidities play an important role in their physical condition.

There is no perfect method for weighing all of the relevant factors and identifying specifically high- and low-risk elderly patients, but this risk can be estimated using various scoring systems e.g. the EuroSCORE or the STS risk calculator.[24-25] A more specific risk score developed to predict outcome for cardiac valve surgery is the New York state score.[26] However, decision-making should rely not only on estimation of operative risk, but also on estimation of the risk–benefit ratio, requiring outcome after surgery to be compared with spontaneous evolution. Biological ageing is quite heterogeneous and precise algorithms should be replaced by integrative individualized management. Microsimulation allows modeling of complex outcome paths resulting from many simultaneous risks and might be a valuable tool to estimate patients' individual outcome after valve replacement.[27] The most difficult aspects of decision making are choosing the appropriate timing of surgery and the necessity of whether or not to perform combined valve and coronary procedures.[9] The statistical risk may be somewhat higher than the effective risk in experienced hands and individual and sometimes challenging decisions based on the surgeons' skill and experience in the postoperative care of complex patients are required.

Many patients with severe AS do not undergo surgery because of excessive risk, advanced age, or preference. Recent studies have highlighted the underuse of AVR ranging from 30% - 60% of elderly patients with severe, symptomatic AS.[6,28-30] Older age and left ventricular dysfunction are the most striking characteristics of patients who are denied surgery, whereas in some reports selection on basis of comorbidity played a less important role.[28] Congestive heart failure and left ventricular dysfunction are strong predictors of poor outcome in non-operated patients with AS.[6] Many physicians are unaware that elderly patients with AS and impaired left ventricular function are the most likely to benefit from relief of outflow obstruction.[11]

Medical therapy for the inoperable patient

If a patient is deemed inoperable limited medical therapies are available to lessen symptoms. Patients with evidence of pulmonary congestion can benefit from cautious treatment with digitalis, diuretics, and ACE inhibitors. In patients with acute pulmonary oedema due to AS, nitroprusside infusion may be used to reduce congestion and improve left ventricular performance.[31-32] Such therapy should be performed under the guidance of invasive hemodynamic monitoring. Excessive preload reduction can reduce cardiac output and lower systemic arterial pressure; patients with severe AS are especially subject to this untoward effect due to a small hypertrophied ventricle. Digitalis should be reserved for patients with depressed systolic function or atrial fibrillation.[31-32]

Balloon valvuloplasty

Percutaneous balloon aortic valvuloplasty is a procedure in which a balloon is placed across a stenotic valve and inflated to decrease the severity of AS. This procedure has been proposed as an alternative to operation in the treatment of high risk, elderly patients. It can also be used as a bridge to surgery in haemodynamically unstable patients. Hospital mortality ranges from 3% to 13% and hospital morbidity from 10% to 25%.[33] Despite a relatively modest improvement in valve function, most often there is a degree of functional improvement of short duration however immediate restenosis (within 72 h) occurred in 25% of patients and 66% had restenosis within 6 months. The acute aortic insufficiency that may occur after balloon valvuloplasty may also impair a hemodynamic improvement. Long-term survival after balloon aortic valvuloplasty is also poor with 1- and 3-year survival rates of 55% and 23%, respectively.[34] Therefore, in adults with AS, balloon valvuloplasty is not a substitute for AVR. However, through improved knowledge and refined transcatheter device developments it might be that balloon valvuloplasty nowadays yields better outcome and perhaps the procedure is an alternative for the increasing numbers of high risk surgical candidates in the expanding very elderly population that mandate less invasive methods.[35]

Aortic valve surgery

The natural prognosis of severe AS is poor with 90% of patients presenting with angina and syncope dying within 3 years.[36] Symptomatic AS is therefore the definitive indication for surgery, in which valve replacement can both reduce symptoms and extend life.

Choice of prosthesis

There is no perfect heart valve substitute. Mechanical valves have the advantage of structural stability but all require long-term anticoagulation. Bioprostheses are less thrombogenic and do not require anticoagulation but have the disadvantage of being subject to structural valve deterioration over time. Both types of valves have suboptimal haemodynamics and present a risk to infection. There is no survival difference between mechanical and biological valves and the choice between the two types of valves should primarily be determined by assessing the risk of anticoagulation related bleeding versus the risk of structural valve deterioration.[37]

Besides structural valve deterioration the disadvantages of stented heterografts are imperfect hemodynamic performance, prosthetic valve endocarditis, and a low (0.7% per year) risk of thromboembolism. Bovine pericardial valves appear to have a low rate of structural valve deterioration with an 18-year actuarial freedom from reoperation of 76%, and freedom from valve failure of 85% among patients undergoing primary AVR at an age greater than 60 years.[38] Structural deterioration of tissue valves is limited in the elderly population and the risk of a bleeding event due to anticoagulation in case of a mechanical valve is considerable and outweighs the risk of structural valve failure. Besides the differ-

ences in prosthesis one should take into account that the life expectancy of a patient who survives an AVR is less than that of a matched person in the general population.[39] Even the life expectancy of a hypothetical patient who is immune from valve-related events and from operative mortality is lower than that of the general population. This excess mortality is due to valve related mortality and an additional mortality. The additional mortality might be related to underlying valve pathology, left ventricular residual hypertrophy and functional abnormality and the valve replacement procedure itself. On the basis of these considerations, most patients over 60-65 years of age receive a bioprosthesis. Type of bioprosthesis does not seem to influence patient outcome.[40]

Stentless valves are constructed from porcine aortic valves and do not have a prosthetic sewing ring, allowing for larger valves to be implanted with presumably better hemodynamic performance than if a stented bioprosthesis is used. The disadvantage is that their implantation is more complex than that for stented valves. Retrospective data suggest excellent survival with this type of bioprosthesis but it is unclear whether this is due to the hemodynamic benefits of the valve or to patient selection.[39] A stentless allograft might be a good choice for patients with small aortic root sizes at risk for patient-prosthesis mismatch.

PROGNOSIS

Hospital morbidity and mortality after surgery

Complication rates are higher in the elderly but not per se higher compared to the younger population. It seems that an operation is relatively safe and has little increased risk over younger age groups if the patient is operated upon in a stable condition and not in an urgent or emergent situation and the patient does not have major comorbidities.[41] Identified risk factors for hospital mortality are previous coronary bypass operation, impaired renal function, age, left ventricular dysfunction, previous stroke and a history of myocardial infarction. NYHA classification was not an independent risk factor for operative mortality for patients aged 80 years and older.[42-43] Postoperative complications in elderly patients occur frequently and involve renal failure (6-12%), arrhythmias (25-45%), permanent stroke (2-4%), respiratory complications resulting in prolonged ventilation (21-27%), or reoperation for bleeding (4-9%).[42,44]

In patients over the age of 70 years the operative mortality ranges from 2%-6%,[6,45] while 30-day mortality rates for octogenarians are approximately 8% to 20%, with lower mortality for isolated aortic valve surgery (6%) and higher mortality for multiple valve, and valve plus coronary artery bypass graft operations.[42,44] Postoperative complications that account for hospital mortality are renal dysfunction and stroke.

Late survival

Elderly patients have acceptable late outcome after AVR. Survival rates in octogenarians of 82-85% at 1 year, 70-81% at 3 years, and 55-73% at 5 years have been achieved at different centers.[41,42,44] Preoperative risk factors for late mortality in octogenarians include female sex, congestive heart failure, recent myocardial infarction, cerebrovascular disease, peripheral vascular disease, respiratory disease, diabetes, and chronic renal impairment.[46] Postoperative complications as renal failure and permanent stroke are also strong predictors for poor long-term survival.[42] Valve replacement for AS offers the best treatment option in elderly patients to ensure an acceptable late outcome. Comparing a surgically and medically treated group of patients over 70 years, survival during the first six months in both groups decreased to about 85%. However at three years the survival in the surgical group was 80% whereas the survival in the medical group continued in a steep decline to 49%.[6]

Quality of life

Although valve surgery will be undertaken in select elderly patients for potential survival benefit, the main goal of cardiac valve surgery in this population is improvement in quality of life through reduction of symptoms and better physical function. This improvement comes at some cost, however. In addition to the risk of perioperative death, the morbidity rate is considerable and the hospital length of stay prolonged. Improvement in NYHA functional class however is substantial and similar to NYHA class among the general elderly population.[47] In a series of operated octogenarians ninety percent of long-term survivors were in New York Heart Association class I or II.[48]

Quality of life (QOL) as assessed with SF-36 scores in operated patients is equal to or better than that of the general elderly population.[41] Intriguingly age alone is not a strong predictor of QOL improvement after surgery. The magnitude of improvement in mental health is similar in elderly and younger patients.[49] At more than 2 years follow-up 68-85% of survivors are living at home and more than 90% of the long-term survivors believed in retrospect that having decided to have cardiac surgery after age 80 years had been a good choice.[44,50]

Concomitant surgical procedures

There is convincing histopathologic and clinical data suggesting that calcific valve disease is an active disease process akin to atherosclerosis with lipoprotein deposition, chronic inflammation, and active leaflet calcification. The overlap in the clinical factors associated with calcific valve disease and atherosclerosis and the correlation between the severity of coronary artery and aortic valve calcification provide further support for a shared disease process. About 35 percent of octogenarians with AS have clinically significant luminal

narrowing on coronary angiography[51] which must be considered in the evaluation of symptoms.

Previous investigators have found that the performance of concomitant surgical procedures exposes elderly patients to higher early mortality of up to 24%[44] while others found that concomitant Coronary Artery Bypass grafting (CABG) improved operative and long-term survival in patients operated over 80 years of age.[42] Myocardial revascularization however, should be performed at the time of AVR in all patients in whom a significant coronary stenosis coexist regardless of the presence or absence of angina.[52]

Vice versa, patients presenting with coronary disease may also have aortic valve disease. If AS is severe, AVR should be performed in conjunction with CABG surgery. There is controversy, however, over the appropriate care of asymptomatic patients with mild or moderate stenosis. If no intervention is done at the time of CABG, AS symptoms may develop, necessitating a second open-heart procedure (AVR), with additional technical challenges and complications. Conversely, an initial CABG/AVR increases the initial operative risk and exposes patients to potential long-term valve-related complications of 2%-6% per year. Clinical factors as severity and rate of progression of AS, patient life expectancy, and probability of valve- or operative-related complications, must be considered in making this decision.[53] Only about 12% of patients with mild AS will have developed severe AS in 10 years.[54] For patients under age 70 years, an AVR for mild AS is preferred if the peak valve gradient is >25 to 30 mm Hg. For older patients, the threshold increases by 1 to 2 mm Hg/year, so that an 85-year-old patient undergoing CABG should have AVR only if the gradient exceeds 50 mm Hg

Concomitant mitral regurgitation (MR) is found in as many as 78% of patients being evaluated for AVR.[55] It has been suggested that MR occurs as a consequence of altered ventricular performance associated with AS and will improve after isolated AVR. However other reports have shown that MR improved only in 45% of the patients and in 55% it remained unchanged or deteriorated.[55] It seems that patients who undergo AVR and have a preoperative mitral regurgitation ≥2+ have a higher risk of congestive heart failure which is an independent risk factor for late postoperative death.[56] What remains to be determined however, is whether a more aggressive approach to mitral valve repair results in improved long-term outcome and outweighs the potential morbidity and mortality of an added procedure in high-risk patients.

Reoperation

An increasing number of patients have been followed with moderate AS after another heart operation. Many patients requiring AVR have had prior coronary artery bypass grafting and return with severe AS. Especially in the setting of a patent internal mammary artery graft this poses a high risk because of potential damage to the internal mammary artery and poor myocardial protection in the LAD territory.[57] Mortality rate ranges from 6-18%.[58]

Life expectancy of patients with heart valve replacement also increases and approximately 10% of patients who were between 60 and 70 years old at the time of their first operation will need replacement of their prosthetic valve in the ninth decade of their life. A cardiac redo procedure has a higher hospital mortality of approximately 5-15% but survival at 3 years is the same as octogenarians who had their first AVR.[59-60] Increased risk of reoperation is due to sternal reentry complications, inconsistent myocardial protection, emboli originating from old grafts and aorta, comorbidities leading to diminished reserve of subsystems and tissue fragility.[61]

This feasibility of an elective hybrid approach of combining minimally invasive AVR for aortic valve disease with PCI in combination of a drug-eluting stent for coronary artery stenosis produced satisfactory outcomes and suggests an alternative treatment for high-risk patients with AS and coronary artery disease.[62]

Transcatheter valve implantation

Many patients with severe AS do not undergo surgery because of excessive risk, advanced age, or preference. Prognosis with medical management is poor and percutaneous alternatives to surgery have been limited to balloon valvuloplasty with only transient modest improvement and is reserved for palliation only. The disappointing results of balloon valvuloplasty have led to investigation of the possibility of percutaneous placement of prosthetic aortic valves. The development of a technique for percutaneous valve implantation in the aortic position poses a challenge because of the high hemodynamic stresses and the proximity of both the mitral valve and coronary artery orifices. The positioning of the implanted valve must be extremely precise, as malposition of the prosthesis in either direction could result in severe acute mitral dysfunction or acute myocardial ischemia.

Antegrade technique

The first percutaneous valve implantations were implanted using the antegrade approach.[63] This approach requires femoral venous access, a transseptal puncture, dilation of the atrial septum and passage of a flotation balloon through the mitral valve. The passage of large diameter catheters through the mitral valve produces temporary mitral insufficiency, and mitral injury may occur. Acute mitral insufficiency after injury of the mitral chordae carries a high mortality rate in this procedure. Hemodynamic instability has been characteristic of the antegrade technique, and acute procedural mortality is a concern.[63]

Retrograde technique

The technical complexity and associated risks of the antegrade approach enabled the development of the percutaneous retrograde transfemoral implantation of aortic prosthetic valves.[64-65] During this procedure first a valvuloplasty is performed and a large sheath is introduced to a position beyond the iliac arteries into the aorta. Next a steerable deflection

Figure 1. The Edwards Sapien® Valve

Figure 2. The stent of the Corevalve prosthesis

catheter is inserted which actively directs the prosthesis through the aorta. The prosthesis is then positioned coaxial with the calcified native valve leaflets and during rapid right ventricular pacing the stent-deployment balloon is rapidly inflated and then deflated. Vascular trauma accounted for 50% of the mortality in the initial series reported by Webb et al.[64] This procedure can also be achieved in a true percutaneous way without a surgical exposure and closure of the femoral vessels.[66] Currently two devices are under clinical investigation: the Edwards Sapien® heart valve (Figure 1) and the CoreValve® (Figure 2) self-expandable aortic implant. The Sapien® heart valve is fabricated from three equal sections of bovine pericardium affixed to a stainless steel expandable stent and comes in two sizes (23 mm and 26mm). The femoral introductory sheaths that are used have an internal diameter of 22F and 24F respectively. The CoreValve revalving system® contains a porcine bioprosthesis within a nitinol frame which is introduced through an 18F sheath. Both valves are also under investigation for transapical implantation (see below).

Transapical valve implantation

Another route for a closed heart valve procedure, which obviates vascular trauma, is the implantation of an aortic valve prosthesis through the apex of the left ventricle without sternotomy and the use of cardiopulmonary bypass.[64] The apex of the left ventricle is in direct line with the aortic valve, and is crossed in an antegrade fashion in the direction of blood flow. This permits a shorter and stiffer delivery system that allows easier and more precise positioning and placement. After an anterolateral incision of the thoracic wall, the pericardium over the apex of the left ventricle is identified and opened. Temporary epicardial ventricular pacing wires are placed on the left ventricle. Sutures with pledgets are placed into the myocardium and after puncture of the apex a sheath is introduced into the left ventricle. A wire is placed through the sheath into the aorta. After balloon valvuloplasty (see Figure 3), the prosthesis, balloon for valve expansion, and steerable catheter are passed over the previously placed wire and introduced as a unit through the sheath. After positioning of the valve, rapid pacing is started and the balloon is inflated and the valve deployed. Subsequently wire and sheath are removed and the apex is closed. This transapical procedure might be better suited for patients with small femoral or iliac arteries, tortuosity of the vessels or atheroma. Technical difficulties may occur in case of fragile tissue of the apex, especially in elderly patients.[64,67]

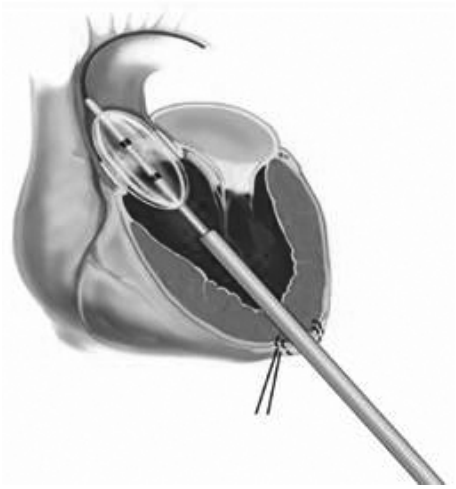

Figure 3. Transapical balloon valvuloplasty

Valve-in-a-valve concept

Patients may suffer xenograft degeneration requiring reoperation. The risk of reoperative surgery may be increased, because of advanced age, additional risk factors, and an increased technical difficulty caused by adhesions. A transcatheter implantation of a sutureless stent-fixed xenograft into a conventional bioprosthesis on the beating heart using a minimally invasive transapical approach has been demonstrated in a pig model. This new valve in a valve procedure may lead to a significantly decreased risk for reoperative valve replacement surgery.[68]

Many critical questions towards percutaneous or transapical aortic valve implantation remain unanswered, including the durability of these devices and the potential adverse effects they may have on subsequent heart valve surgery. Risk for paravalvular leakage probably is the biggest issue at present but also the size of the catheters that are needed and the trauma to the femoral vessels and also valve embolization is a potential risk. Therefore, one cannot justify the use of these experimental technologies in patients for whom published guideline indications do not exist or in situations of prophylactic therapy until data on safety and effectiveness are gathered from well-designed clinical trials.

CONCLUSION

Cardiac surgical therapy in the elderly is increasing and will increase even further in the coming years as healthcare in general improves and the numbers of elderly patients requiring AVR increases. Symptom control is greatly improved following aortic valve surgery in seriously compromised patients compared with patients on continued medical treatment.

In the absence of severe comorbidities, octogenarian patients can undergo AVR with low morbidity and mortality, provided the elderly patient is operated upon in stable condition. A non-elective operation, a preoperative NYHA class III or preoperative intubation, and end-stage organ failure significantly increase the risks of surgery. Conventional surgery remains the gold standard for the treatment of patients with significant aortic valve disease. Surgical consultation is recommended in nearly all patients with symptomatic severe AS. Some elderly patients will refuse surgery, even with a clear understanding of the risks and benefits. Other elderly patients have mental status alterations or physical limitations that markedly reduce the potential benefits of valve replacement. Clinical decision making in the elderly patient is based on assessment of the severity of AS, a complete medical history, evaluation of comorbid conditions, and a full discussion with the patient and family. The use of percutaneous valve replacement not requiring cardiopulmonary bypass is still being evaluated, but these procedures will be applied increasingly in the coming years.

Expert commentary

For patients with aortic valve disease there is no effective medical therapy and balloon valvotomy is not an acceptable alternative to surgery. Despite the fact that surgical valve replacement carries an important operative morbidity and mortality in elderly patients, AVR must therefore be considered in patients who have symptoms caused by aortic stenosis. There is increased operative risk with aortic valve replacement (AVR), but there also is reduced life expectancy without surgery and more important decreased quality of life. Unfortunately, there are no widely available alternatives to open surgery.

Percutaneous aortic valvuloplasty inhabits a small niche in stabilizing critically ill patients prior to surgery, but its offspring, percutaneously placed valves, have demonstrated short-term benefits in patients deemed inoperable by multiple surgical teams. Their long-term benefits and results in the hands of others is still unknown. Surgically implanted prosthetic valves are the dominant therapy, with tissue valves traditionally reserved for patients over 65 years of age.

Five year view

In light of the heavy calcification present at the time that many patients seek medical attention for AS, it seems very unlikely that drug therapy will play a role in established symptomatic AS. However, there is continued interest in statin and angiotensin-converting enzyme inhibitor therapy to slow the progression of mild and moderate AS. Aortic balloon valvuloplasty is a generally unsatisfying procedure, and will continue to play a very limited role in treatment. For the next 5 years, percutaneously implanted aortic valves will be reserved for situations in patients too ill to survive technically successful surgery. Percutaneous valve ablation techniques and filters avoiding systemic embolization during percutaneous valve implantation will lower the risks of the procedure.

Owing to its excellent long-term results with minimal mortality, AVR with a prosthetic valve using a median sternotomy will continue to be the mainstay of therapy for AS. At present there are no safe alternatives to warfarin, the active lifestyles of aging baby boomers and growing confidence in pericardial valves all favour the increasing use of tissue prostheses.

Key issues

- The numbers of elderly patients requiring AVR will increase further in the coming years.
- Clinical decision making in the elderly patient is based on assessment of the severity of aortic stenosis, a complete medical history, evaluation of comorbidities, and a full discussion with the patient and family.
- Improvement in the quality of life is the main goal in aortic valve replacement in the elderly.
- The use of percutaneous aortic valve replacement in the elderly patients will increase in the coming years.

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CHAPTER 3

Progression of aortic valve stenosis in adults: a systematic review

HJ Heuvelman
MWA van Geldorp
MJC Eijkemans
NM Rajamannan
AJJC Bogers
JW Roos-Hesselink
JJM Takkenberg

J Heart Valve Dis 2012;21:454-62

ABSTRACT

Background and aim of the study

Published reports on the progression of aortic valve stenosis (AS) over time are usually small, with widely varying AS progression rate estimates. Reliable estimates of AS progression are important for surveillance scheduling and optimal timing of surgical or interventional treatment. This systematic review presents an overview of published evidence on AS progression over time in adult patients with AS.

Methods

A systematic review using PubMed and Embase was performed to assess AS progression over time in adult patients with AS measured by echocardiography. A total of 27 reports (15 prospective, 12 retrospective, total 4,921 patients, pooled age 69 years) was included in which the baseline and progression rates of the hemodynamic variables were pooled. Subgroup analyses were performed to investigate factors associated with AS progression and sources of heterogeneity.

Results

Pooled annual AS progression was 3.70 mmHg per year (SE = 0.10) for randomized clinical trials, and 6.03 mmHg per year (SE = 0.10) for observational studies. A large variability in observed AS progression was found between studies, as well as a wide variety of methods employed to measure AS.

Conclusion

The observed large individual variability in measuring AS progression among the selected studies calls for the implementation of a universal method of AS assessment. This will facilitate an insight into the determinants of AS progression and allow for an evidence-based tailoring of treatment.

BACKGROUND AND AIM OF THE STUDY

Aortic valve stenosis (AS) is a common disease among the elderly, with a prevalence of 1-3% among American adults aged ≥65 years.[1-5] In the same age group, the prevalence of aortic valve sclerosis is 25-29%, with 16% of cases deteriorating to AS within seven years.[2,3,6] Mortality for patients with severe symptomatic AS is 56-83% within five to seven years after diagnosis.[7]

According to the present American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines, aortic valve replacement is indicated in symptomatic patients with severe AS, whereas the indication remains debatable in asymptomatic patients with severe AS.[8,9] Asymptomatic patients with mild to severe AS are monitored over time.[8,9] In the past, several small studies have been conducted to investigate AS progression and its potential determinants although, due to their small sample size, it is difficult to draw general conclusions. Thus, a systematic review and meta-analysis of available echocardiographic information on AS progression would allow for an improved insight into AS progression and its potential determinants. This may ultimately provide important clues for treatment optimization.

The aim of the present systematic literature review was to provide an overview of the published evidence on the progression of AS in adult patients, as measured using echocardiography.

MATERIALS AND METHODS

Search strategy

A literature search using the PubMed and Embase databases, with the key words 'aortic stenosis' and 'progression', and their synonyms, was performed on July 20th, 2010. The search was limited to English-language publications, human adults aged ≥18 years, and published between January 1st, 1989 and July 20th, 2010. Any duplicates were filtered out. All titles and abstracts were screened for study design (prospective and retrospective observational studies or randomized clinical trials; RCTs) and study population (patients with AS with none or only mild aortic regurgitation, who were not initially selected for coronary artery bypass grafting; CABG). A second independent reviewer (M. van G.) assessed whether the inclusions and exclusions had been performed correctly. In case of any disagreement, an agreement was negotiated. The references of selected reports were crosschecked for other relevant studies. Authors were contacted when a publication could not be obtained, or when not all required information could be retrieved from a publication.

Data extraction

The selected reports were reviewed and the patient characteristics and outcome variables tabulated using MS Excel for Windows and Review manager (version 5.0; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). The following patient characteristics were registered: gender (male), age (years), peak aortic gradient (PAG; mmHg), mean aortic gradient (MAG; mmHg), aortic jet velocity (V_{max}, m/s), aortic valve area (AVA, cm^2), left ventricular ejection fraction (%), aortic valve calcification, prevalence of coronary artery disease (CAD), current smoking, hypertension, hyperlipidemia, and diabetes. Typically, CAD was defined as prior percutaneous transluminal coronary angioplasty, CABG or (symptoms of) myocardial infarction, and obstruction of the coronary arteries (i.e. stenosis ≥70%). Hyperlipidemia was defined as (a history of) hypercholesterolemia or hyperlipidemia.

Hemodynamic echocardiographic variables were registered according to the ACC/AHA guidelines for the clinical application of echocardiography.[10] Outcome variables included baseline AVA, PAG, V_{max}, and MAG, annual decrease in AVA, and annual increase in PAG, V_{max}, and MAG.

For studies that compared statin users with non-statin users, these two subgroups were considered as separate study populations because overall estimates of the total study population were unavailable.[11-20]

Statistical analysis

The initial AS, as measured by PAG, MAG, V_{max}, and AVA, and AS progression rate were pooled using the inverse variance method. If only V_{max} was reported, the simplified Bernoulli equation was used to calculate the PAG (see Appendix). The AS progression rates were assumed constant over time, and annual AS progression rates were calculated using the formula described in Appendix I. Studies were divided by study design, namely RCTs versus observational studies. Heterogeneity among the studies was explored by the Q and I^2-statistic, and by funnel plots. A subgroup analysis was carried out among observational studies to study factors that were potentially associated with the progression rate of PAG, employing cut-off points for classical risk factors. In the subgroup analyses, the following subgroups were compared: studies with mean age ≥70 years versus <70 years, with a mean CAD prevalence of ≥50% versus <50%, with a mean hypertension prevalence of ≥50% versus <50%, with a mean hyperlipidemia prevalence of ≥50% versus <50%, with a mean smoking prevalence of ≥25% versus <25%, with a mean diabetes prevalence of ≥20% versus <20%, and with a mean PAG ≥40 mmHg versus <40 mmHg. Any missing values in the independent variables were excluded test-by-test. All statistical analyses were performed using Review manager 5.0 and SPPS 15.0 (SPSS, Chicago, IL, USA).

RESULTS

Search results

The search identified a total of 1,332 publications (Fig. 1). In addition, 1,305 reports were excluded, including those in which no serial hemodynamic measurements were described (n = 364 studies), patients underwent (percutaneous) aortic valve replacement, (balloon) valvuloplasty or revascularization (elective or percutaneous cardiac intervention) during hemodynamic measurements (n = 232, 100, and 6, respectively), age <18 years (n = 142), specific patient subgroups (n = 93), case reports (n = 108), reviews, letters or editorials (n = 72), focus on biological features of AS (n = 46), patients with low-gradient AS, poor left ventricular function (left ventricular ejection fraction ≤30%) or congestive heart failure (n = 42), patients with concomitant valve pathology or root dissection (n = 61), supravalvular or subvalvular AS (n = 25), experimental studies (n = 8), or focus on aortic sclerosis (n = 6). Finally, 27 Doppler echocardiography reports were used for the review.[11-37] From these studies, eight study populations were obtained from four RCT reports,[15,16,19,20] and 29 study populations from 23 observational study reports.[11-14,17,18,21-37]

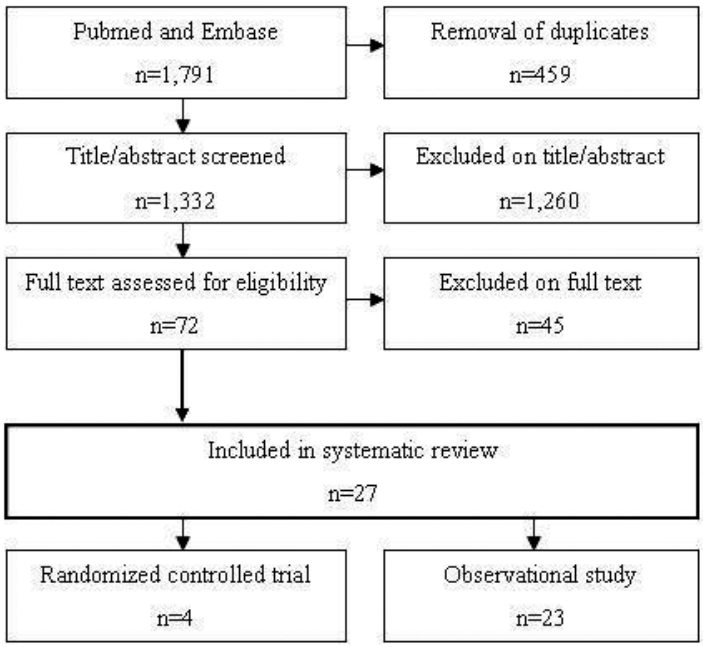

Figure 1: Flowchart of the search.

Study characteristics

The eight study populations derived from the four RCTs (see Table I) included a total of 2,344 patients with a mean age of 67 years at inclusion (range: 58 to 70 years), and 62% of these patients (age range: 54 to 72 years) were male. The mean follow up period was 49 months; hence, the total follow up was 9,506 patient-years (pt-yr).

The 29 study populations derived from the 23 observational studies (see Table II) included a total of 2,577 patients with a mean age of 71 years at inclusion (range: 58 to 78 years), and 83% of these patients (age range: 33 to 99 years) were male. The mean follow up time was 30 months, and the total follow up 6,399 pt-yr. In total, there were 15 prospective and 14 retrospective cohorts.

Study outcome

The echocardiographic hemodynamic variables of the RCTs and observational studies are shown in Tables I and II, respectively. Details of individual studies and pooled AS progression over time are shown in Figure 2a and b.

Heterogeneity, subgroup analyses, and publication bias

Heterogeneity and subgroup analyses

Significant heterogeneity was observed for all hemodynamic outcomes (see Tables I and II). Subgroup analyses of the observational studies showed that studies with a mean patient age ≥70 years had a slower AS progression rate compared to those with a mean patient age <70 years ($p < 0.00001$). Studies with a higher smoking prevalence had a faster AS progression rate compared to those with a lower smoking prevalence ($p < 0.00001$).

Studies with a higher CAD prevalence had a slower progression rate compared to those with a lower CAD prevalence ($p < 0.00001$); the same effect was apparent for the variables hypertension and diabetes, in which the high prevalence groups had a slower progression rate ($p < 0.00001$).

Studies with a higher mean baseline PAG showed a faster AS progression rate compared to those with a lower mean baseline PAG ($p < 0.00001$).

Table I: Patient characteristics of patients included in randomized controlled trials concerning AS progression

Author(s)	PY	N	Age	Male	FU	Smok	CAD	HT	D	HL	AVA	ΔAVA	Vmax	ΔVmax	PAG	ΔPAG	MAG	ΔMAG	AS at inclusion defined as
Cowell et al. (15)	2005	77	68	68	25	27	23	62	4	10	1.03	0.08	3.39	0.20	47.8	6.48	-	-	Vmax ³2.5 m/s
		78	68	72	25	28	27	69	5	6	1.02	0.08	3.45	0.20	49.5	6.56			Vmax ³2.5 m/s
Dichtl et al. (19)	2008	23	64.2	65	24	17	-	39	4	-	-	-	-	-	46.5	2.1	29.2	1.05	MAG ³15 mmHg, Vmax ³2.0 m/s
		24	69.7	54	24	4	-	58	21	-	-	-	-	-	41.1	2.8	25.6	2.15	MAG ³15 mmHg, Vmax ³2.0 m/s
Rossebo et al. (20)	2008	944	67.7	62	52	20	-	52	-	-	1.29	0.03	3.09	0.15	39.3	3.49	22.2	2.7	Vmax 2.5-4.0 m/s
		929	67.4	61	52	18	-	51	-	-	1.27	0.03	3.10	0.16	39.6	3.55	22.5	2.8	Vmax 2.5-4.0 m/s
Chan et al. (16)	2010	134	58	60.5	42	11.2	-	-	-	-	1.49	0.07	-	-	40.8	6.3	22.5	3.8	Vmax 2.5-4.0 m/s
		135	57.9	63	42	10.4	-	-	-	-	1.56	0.08	-	-	41.6	6.1	23.1	3.9	Vmax 2.5-4.0 m/s
Total		2,344																	
Mean*			67	62	49	18	25	53	5	8	1.27	0.03	3.11	0.15	40.2	3.70	22.5	2.75	
SD			4.7	5.4	12.7	8.3	2.8	10.3	8.3	2.8	0.22	0.03	0.04	0.003	4.0	1.86	2.8	1.07	
Q			-	-	-	-	-	-	-	-	94.2	47.7	37.1	429.7	44.7	55.1	14.0	440.7	
I2 (%)			-	-	-	-	-	-	-	-	95	90	92	99	84	87	64	99	

*, Pooled mean.

Empty fields indicate that data were not mentioned in the text.

Δ: Annual progression; Age: Mean age (years); AS: Aortic valve stenosis; AVA: Aortic valve area (cm2); CAD: Coronary artery disease (%); D: Diabetes (%); FU: Mean follow up (months); HL: Hyperlipidemia (%); HT: Hypertension (%); MAG: Mean aortic gradient (mmHg); Male: Male patients (%); N: number of patients included; PAG: Peak aortic gradient (mmHg); PY: Publication year; Q: Q-statistic; I2: I2- statistic; SD: Standard deviation; Smok: Current smoking (%); Vmax: Maximum aortic jet velocity (m/s).

Table II: Patient characteristics of patients included in observational studies concerning AS progression

Author(s)	PY	N	Age	Male	FU	Smok	CAD	EF	HT	D	HL	AVA	ΔAVA	Vmax	ΔVmax	PAG	ΔPAG	MAG	ΔMAG	AS at inclusion defined as
Otto et al. (30)	1989	42	66	-	20	-	-	-	-	-	-	0.96	0.07	3.7	0.36	54	12	35	8	NS
Roger et al. (33)	1990	112	69	63	25	-	51	63	-	-	-	-	-	2.9	0.23	35	4.11	-	-	NS
Faggiano et al. (24)	1992	45	72	47	18	-	-	-	-	-	-	0.75	0.10	4.0	0.40	64	15	-	-	Vmax £2 m/s
Peter et al. (32)	1993	49	58	59	32	-	20	-	20	-	-	-	-	-	-	38	8.25	-	-	Max gradient ³16 mmHg
Otto et al. (29)	1997	123	63	70	30	11	50	51	34	6	-	1.3	0.12	3.6	0.32	51.8	7.49	29	7	Vmax ³2.5 m/s
Bahler et al. (23)	1999	91	68	33	22	32	48	53	68	42	-	1.24	0.04	2.64	0.19	27.6	4.36	15.8	2.79	AVA £2 cm2
Palta et al. (31)	2000	170	71	78	23	38	-	55	60	22	-	1.17	0.10	-	-	-	-	20	3.65	Any degree of AS
Nassimiha et al. (26)	2001	225	76	41	29	-	-	-	-	-	-	1.08	0.08	-	-	-	-	-	-	AVA 0.75-1.49 cm2
Ngo et al. (27)	2001	87	70.8	83	30	-	49	-	-	-	-	-	-	-	-	31.4	6.3	-	-	Vmax ³ 2 m/s
Novaro et al. (12)	2001	57	71	42	21	16	89	-	81	35	-	1.2	0.06	-	-	28	2.29	15	1.71	AVA 1.0-1.8 cm2
		117	67	45	21	15	44	-	63	20	-	1.2	0.11	-	-	29	4.57	15	3.43	AVA 1.0-1.8 cm2
Bellamy et al. (13)	2002	38	73	55	44	13	63	56	71	24	-	1.32	0.04	2.8	0.16	31.4	4.06	18	2.45	MAG ³10 mmHg, AVA £2 cm2
		118	78	51	44	11	26	57	64	24	-	1.2	0.09	3.0	0.25	36	6.77	22	4.64	MAG ³10 mmHg, AVA £2 cm2
Rosenhek et al. (21)	2004	176	58	59	46	-	33	-	41	21	34	-	-	3.13	0.24	40.0	6.68	-	-	Vmax 2.5-3.9 m/s
Rosenhek et al. (11)	2004	50	72	34	24	-	60	-	86	21	100	0.84	0.08	4.08	0.10	66	11	42	8	Vmax >2.5 m/s
		161	69	56	24	-	29	-	78	20	40			3.92	0.39	-	-	-	-	Vmax >2.5 m/s
Yilmaz et al. (35)	2004	42	60	67	54	52	38	-	36	12	-	-	-	-	-	82	8.5	-	-	Isolated AS, referred for AVS
Antonini-Canterin et al. (14)	2005	95	69	62	51	3	73	56	63	28	95	-	-	2.6	0.15	27	4	-	-	Vmax 1.5-3.9 m/s
		95	68	62	49	1	19	57	57	13	12			2.6	0.15	27	4.41	-	-	Vmax 1.5-3.9 m/s
Ohara et al. (28)	2005	82	73	35	40	-	-	40	-	27	41	0.9	0.06	3.7	0.15	57	4.2	-	-	Vmax ³3 m/s
Briand et al. (37)	2006	105	69	62	28	-	-	-	81	31	64	1.08	0.1	3.2	0.19	43	5.5	25	3.5	AVA £1.5 cm2

Table II: Patient characteristics of patients included in observational studies concerning AS progression (continued)

Author(s)	PY	N	Age	Male	FU	Smok	CAD	EF	HT	D	HL	AVA	ΔAVA	Vmax	ΔVmax	PAG	ΔPAG	MAG	ΔMAG	AS at inclusion defined as
Sánchez et al. (34)	2006	43	73	70	6	-	-	-	-	-	-	1.25	0.10	3.6	0.16	51.8	4.66	-	-	NS
Kume et al. (25)	2007	41	75	54	27	-	34	65	66	34	46	1.40	0.07	2.7	0.11	29.2	2.48	-	-	AVA 1.0-2.0 cm2
Moura et al. (17)	2007	61	73.4	34	17	-	-	54	7	4	-	1.22	0.04	3.65	0.06	54.3	2.40	34.9	2.96	AVA 1.0-1.5 cm2
		60	73.9	60	17	-	-	56	5	2	-	1.24	0.09	3.62	0.17	52.1	6.49	34.7	4.02	AVA 1.0-1.5 cm2
Mohler et al. (18)	2007	39	69.5	72	12	0	28	-	72	18	-	1.13	0.08	-	-	-	-	-	-	AVA 0.7-2.0 cm2
		22	63.9	67	12	0	9	-	32	14	-	1.22	0.04	-	-	-	-	-	-	AVA 0.7-2.0 cm2
Stewart et al. (22)	2008	65	67	77	19	-	-	-	-	-	-	0.94	0.15	3.96	0.27	62.7	9.01	-	-	Vmax >3.0 m/s
Kamalesh et al. (36)	2009	166	70	99	30	31	-	-	-	-	-	1.45	0.22	-	-	-	-	-	-	All degrees of AS
Total	2,577																			
Mean*		71	83	30	8	42	55	50	14	96	0.87	0.09	3.32	0.20	34.7	6.03	22.0	3.56		
SD	51.5	5.0	16.1	12.4	16.4	20.4	6.2	24.6	10.5	30.4	0.18	0.04	0.52	0.10	15.4	3.23	9.3	2.15		
Q		-	-	-	-	-	-	-	-	-	2,264.1	115.3	7,032.8	156.9	1,770.7	441.9	673.7	164.7		
I2 (%)		-	-	-	-	-	-	-	-	-	99	83	100	89	99	95	98	93		

**, Pooled mean.*

Empty fields indicate that data were not mentioned in the text.

EF: Left ventricular ejection fraction (%). Other abbreviations as for Table I.

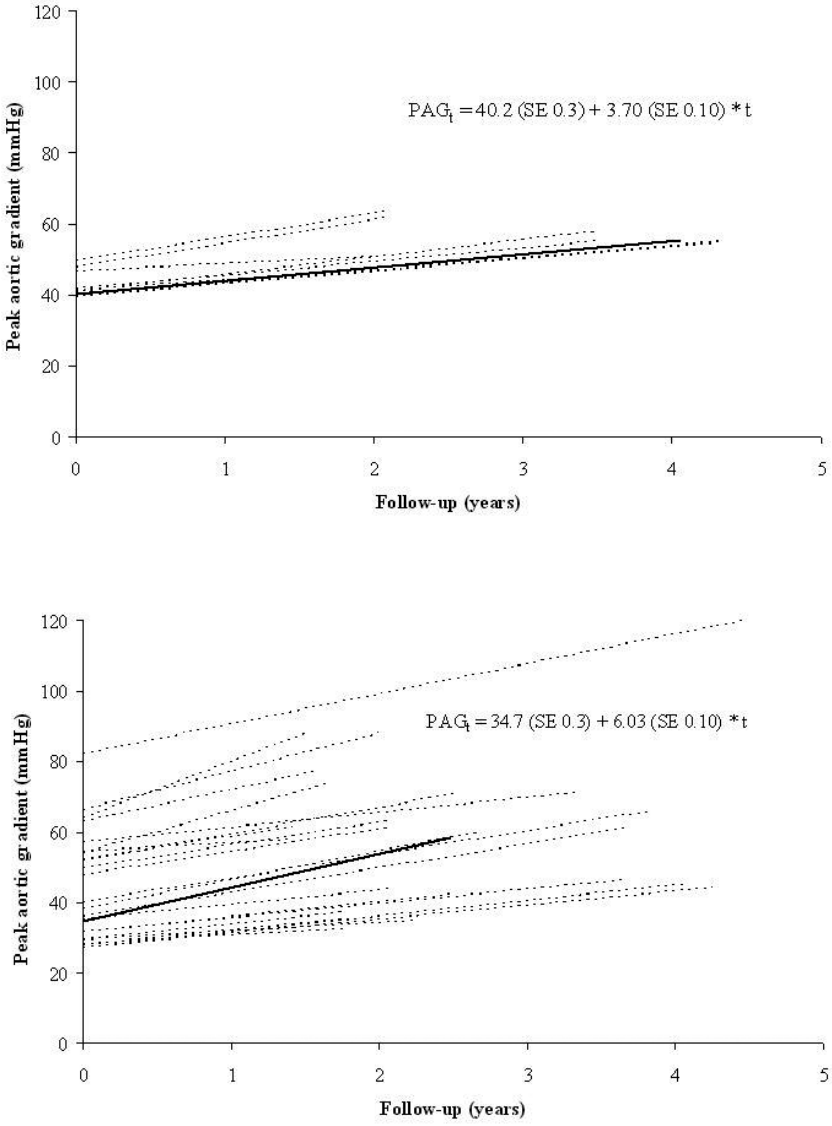

Figure 2: a) Aortic valve stenosis (AS) progression in randomized clinical trials. b) AS progression in observational studies. PAGt: Peak aortic gradient at time t; SE: Standard error; t: Time. Dotted lines indicate individual study estimates; solid lines indicate pooled estimates.

Publication bias

The funnel plot for baseline PAG was asymmetric. Smaller studies showed higher estimates of baseline PAG compared to larger studies (Fig. 3a), while the funnel plot for progression rate showed outliers in both small and large studies (Fig. 3b). Age, smoking, CAD, hyperlipidemia, hypertension, diabetes, and baseline PAG were each considered as potential determinants for the large variability of both funnel plots, though none was detected.

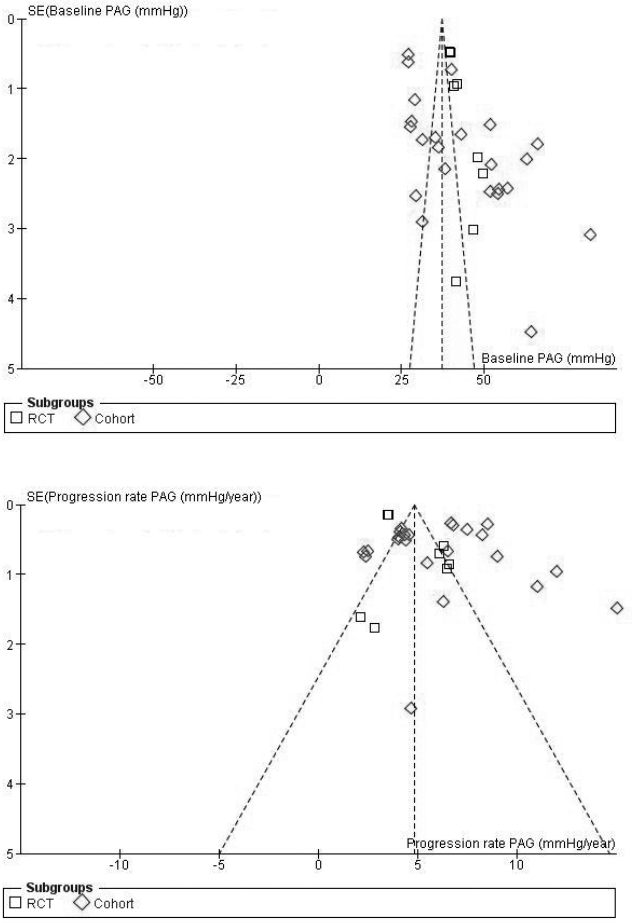

Figure 3: a) Funnel plot of baseline peak aortic gradient (PAG, mmHg) in randomized clinical trials and observational studies. b) Funnel plot of AS progression in randomized clinical trials and observational studies. SE: Standard error. The funnel indicates 95% confidence intervals.

DISCUSSION

This review is the first to compile, systematically and as a comprehensive overview, the available evidence published during the past two decades relating to AS progression in adults. Clearly, the main findings were the wide variability in observed AS progression between studies, and the wide variety of methods used to measure AS. Furthermore, the review findings have confirmed that AS progression is faster in those patients who have more severe AS at baseline.

Patient factors associated with AS progression

Although heterogeneity was considerable in this meta-analysis and may potentially lead to inaccurate results, a thorough examination of possible sources of heterogeneity was pursued. Consequently, patient age, CAD, hypertension, diabetes, and smoking were found to be potentially associated with AS progression. Most of these patient factors are in some way inter-related, and it is beyond the scope of this review to attempt to disentangle their potential individual role in AS progression. However, these observations may form the basis for future studies that focus on dissecting the determinants of AS progression.

Older patient age, which is thought to be the most important risk factor for the prevalence of AS,[3] was in the present subgroup analysis associated with a slower annual AS progression. Potential explanations for this may lie in age-dependent inflammatory and atherosclerotic pathways underlying AS pathogenesis,[38,39] or the fact that the elderly patients - who typically have multiple comorbidities - are monitored more carefully or have a higher death rate, which may have influenced the serial AS measurements. Nevertheless, these are all highly speculative suggestions that are yet to be confirmed.

In the present review, smoking was found to be associated with a faster annual AS progression. A potential explanation for this may be found in the Cardiovascular Health Study, which showed that in elderly patients smoking was associated with a 35% higher risk for degenerative aortic valve disease.[3] However, in another case-matched study of patients with severe AS, smoking was found to be significantly associated with the presence of CAD, but was not more prevalent among patients with severe AS when compared to a control population without AS.[40] These conflicting results highlight the need for further exploration of the potential association between smoking and the progression of AS.

AS measurement methods

The present review confirmed the current use of several different classifications of AS severity, with guidelines employing AVA, V_{max}, and MAG for grading AS.[9] However, Minners and colleagues showed these criteria to be inconsistent, even in patients with a normal left ventricular systolic function.[41] In the present review, PAG was used to measure AS progression because this was the method most often used in the studies. Nonetheless, a

universal classification of AS severity would greatly enhance the comparability of different reports and allow an enhanced estimation of AS progression.

In addition, a wide range of tests was employed to estimate aortic valve calcification, though without any reference test to quantify the extent of calcification. Although determined in only a few of the studies reviewed, aortic valve calcification was identified on several occasions as a strong predictor for AS severity and outcome, and described a close association with AS severity.[42-44] Unfortunately, pooling of the data from calcification studies was not possible because of the varying assessment methods employed.

Study design

The meta-analysis of RCTs demonstrated smaller AS progression estimates compared to the observational studies. This may be explained by differences in patient selection and monitoring methods over time.

Study limitations

The main limitation was that most of the included studies were retrospective, heterogenic, non-randomized and small, with a limited follow up duration and without registration of drug therapy. In addition, compared to RCTs, observational studies are more prone to publication bias.[45]

The primary aim of this systematic review was to provide an overview of AS progression, and for the subsequent subgroup analyses to provoke discussion. However, spurious results may emerge from the meta-analysis of observational data and must therefore be reproduced to be convincing. The included patients underwent serial measurements, which are most likely more frequently performed in more severe cases of AS. Attention was not focused on concomitant cardiac (valve) diseases, and this may have influenced the results. The reasons for patient referral (CAD or AS) were not retrievable, and may have hampered any analysis of the association between CAD and AS. Finally, disease severity at baseline potentially introduces bias. Most variables employed in this systematic review were continuous, for which different methods of analysis and cut-off points were used, leading to a potential bias of the results obtained.

CONCLUSION

The present systematic review was the first to include all published echocardiography data on AS progression in adult patients with the condition. The results demonstrated a wide variability in observed AS progression which was, most likely, due to the heterogeneous nature of AS and the various methods used for its monitoring. Indeed, an optimal and uniform monitoring of AS severity is the key to a better understanding of AS progression

in adult patients, and these issues should be addressed in future clinical practice guidelines for the diagnosis and management of patients with this condition. This will eventually allow for a better assessment of the potential determinants of AS, the development of clinical decision tools that can predict disease progression, potential measures to reduce AS progression, and will ultimately also assist in an evidence-based tailoring of treatment for individual patients.

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APPENDIX

Statistical formula used for the different calculations

Simplified Bernoulli equation: $4 \times V_{max}^{2}$

Progression rate peak aortic gradient (PAG):

Progression rate$_i$ = (PAG$_{final}$ - PAG$_{baseline}$)/Follow up$_i$

The 95% confidence intervals (CI) of the individual studies:

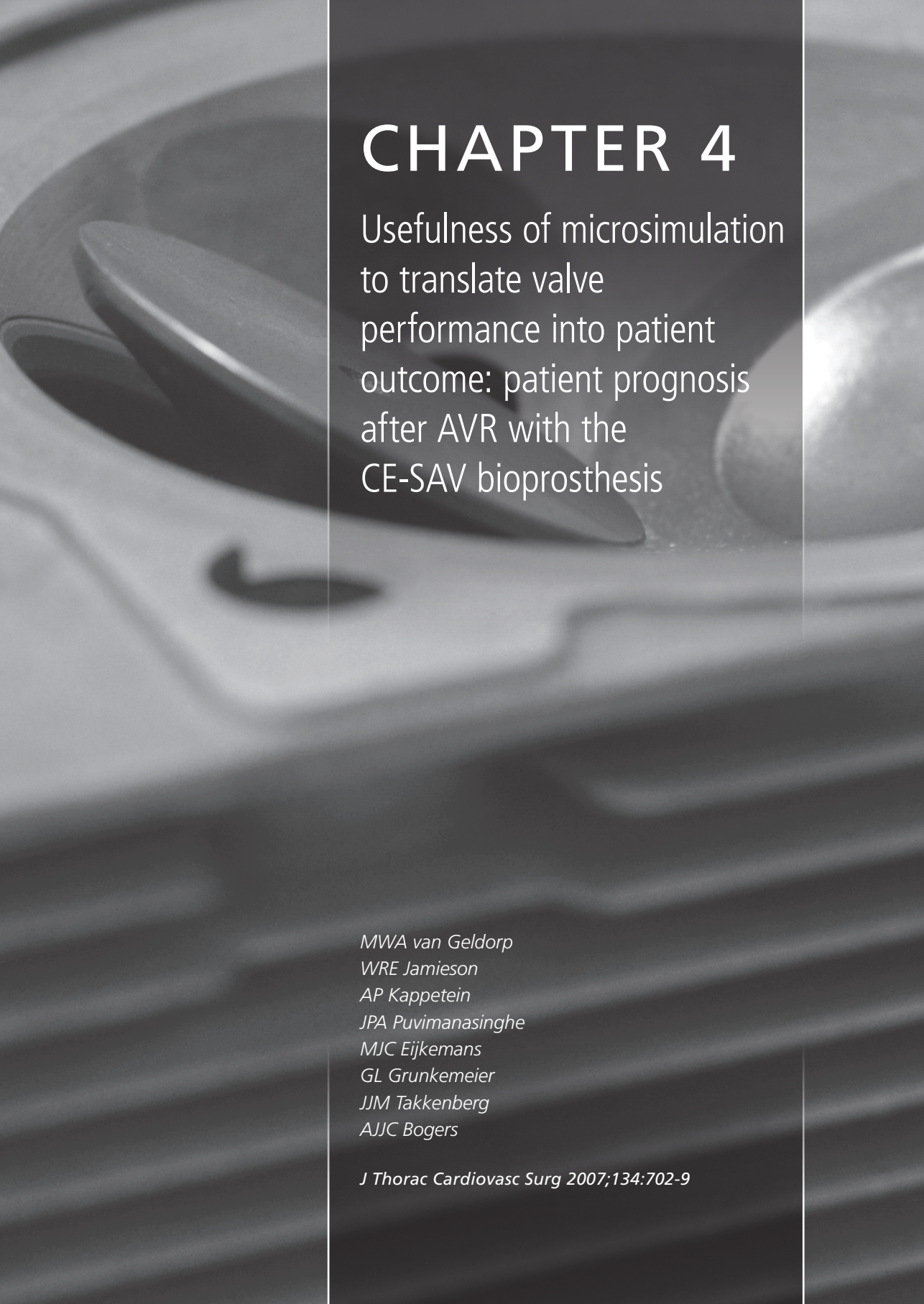
95% CI = pooled mean ± $t_{\alpha,df=n-1}$ × standard error, with $\alpha = 0.05$ (if $n < 30$ patients).

95% CI = pooled mean ± 1.96 × standard error (if $n \geq 30$ patients)

The 95% confidence intervals (CI) of the pooled outcomes:

Pooled standard error = 1/√(åweights).

95% CI = pooled mean ± 1.96*pooled standard error.



CHAPTER 4

Usefulness of microsimulation to translate valve performance into patient outcome: patient prognosis after AVR with the CE-SAV bioprosthesis

MWA van Geldorp
WRE Jamieson
AP Kappetein
JPA Puvimanasinghe
MJC Eijkemans
GL Grunkemeier
JJM Takkenberg
AJJC Bogers

J Thorac Cardiovasc Surg 2007;134:702-9

ABSTRACT

Objective

Numerous reports have been published documenting the results of aortic valve replacement (AVR). It is often not easy to translate these valve outcomes into the actual consequences for the patient. We previously developed an alternative method to study outcome after AVR that allows direct estimation of patient outcome after AVR: microsimulation modeling. The goal of this article is to provide insight into microsimulation methodology and to give an overview of the advantages and disadvantages of simulation methods (in particular microsimulation) in comparison with standard methods of outcome analysis.

Methods

Using a primary dataset containing 1847 patients and 14,429 patient-years, advantages and disadvantages of standard methods of outcome analysis are discussed, and the potential role of microsimulation is illustrated by means of a step-by-step explanation of building, testing and using such a model.

Results

Total life expectancy, event-free life expectancy, and reoperation-free life expectancy for a 65-year-old male patient were 10.6 years, 9.2 years, and 9.8 years, respectively. Lifetime risk of reoperation due to structural valve deterioration was 13.3%.

Conclusions

Microsimulation is capable of providing accurate estimates of age-related life expectancy and lifetime risk of reoperation for patients who underwent aortic valve replacement with the Carpentier-Edwards supra-annular valve. It provides a useful tool to facilitate and optimize the choice for a specific heart valve prosthesis in a particular patient.

INTRODUCTION

Numerous reports have been published documenting the results of aortic valve replacement (AVR) with different types of valve prosthesis. In most reports emphasis is on the performance of the various prosthetic valves, as measured by the occurrence rates of valve-related complications and their consequences, and time-to-event analyses. This is a valid approach but limited by several methodological issues,[1] and it is often not easy to translate these valve outcomes into the actual consequences for the patient who requires AVR.

We have previously developed an alternative method to study outcome after AVR that allows direct estimation of patient outcome after AVR: microsimulation.[2] This method solves most of the methodological limitations of standard outcomes analyses, but does have several limitations of its own.

The goal of this article is to provide insight into microsimulation methodology and to give an overview of the advantages and disadvantages of microsimulation compared to standard methods of outcome analysis. This will be done using primary data on outcome after AVR with the Carpentier-Edwards supra-annular valve (CE-SAV) prosthesis from a large single center in Canada.[3] The following issues will be addressed:

1. Using the primary dataset on outcome after AVR with CE-SAV prosthesis we will discuss the advantages and disadvantages of standard methods of outcome analysis.
2. The information from this primary dataset will then be used to estimate patient outcome with a microsimulation model, illustrating step by step the construction and testing of a microsimulation model and its potential advantages and disadvantages.

MATERIALS AND METHODS

Description dataset

For this study a primary dataset containing 1847 AVR procedures with the CE-SAV device was used to estimate the parameters of the Weibull distributions.[3] These operations were conducted from February 1982 through December 1999 at the affiliated teaching hospitals of the University of British Columbia in Canada, namely, St. Paul's Hospital, Vancouver General Hospital and the Royal Columbian Hospital.

The characteristics of the complete dataset (n=1847) are summarized in Table 1. To calculate the input of the microsimulation model 85 aortic valve re-replacements were excluded, resulting in 1762 remaining primary AVR's (see Table 1 for characteristics). Details of the occurrence of valve related events, and the associated mortality of these primary AVR's are given in Table 2. Valve-related events were defined according to the Society of Thoracic Surgeons / American Association for Thoracic Surgery Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations[4] with 2 modifications: transient

Table 1: Dataset summary

	Total dataset	Only primary AVR included
Number of procedures	1847	1762
Follow-up:		
Total follow-up (patientyears)	14,429	13,849
Mean follow-up time (years)	7.8	7.9
Range (years)	0-20.6	0-20.6
Male (%)	69.1	68.7
Mean age (years)	69.0	69.4
Operative mortality	5.3	5.0
Outcome:		
Valve Related Morbidity #	311	292
Valve Related Mortality	158	154
Valve Related Reoperations	161	148
Valve Related Events	469	446

Valve Related Morbidity is defined as 'non-fatal Valve Related Event', thus including non-fatal reoperations

Table 2: Occurrence rates of valve related events and the associated reoperation and mortality rates for 1762 primary AVR procedures with the CE-SAV.

Event	Occurrence	Linearized Occurrence Rate	Number of reoperations	Proportion reoperated (%)	Number of fatalities	Proportion fatalities (%)	Proportion fatalities if not reoperated (%)
Hemorrhage	72	0.52	0	0	23	31.9	31.9
Non-Structural Dysfunction	33	0.24	29	87.9	3	9.1	50.0
Prosthetic Valve Endocarditis	46	0.33	17	37.0	19	41.3	62.1
Structural Valve Deterioration #.	118	Weibull	98	83.1	26*	22.0	100.0
Thrombo-Embolism	155	1.12	0	0	65	41.9	41.9
Valve Thrombosis	4	0.03	4	100.0	0	0	Not applicable

Structural valve deterioration was confirmed at reoperation or autopsy

* 6 patients died at reoperation for SVD, 20 patients were not reoperated but died with SVD confirmed at autopsy

ischemic attacks were not counted as neurologic events (in order to avoid recall bias), and structural valve deterioration (SVD) was only included if diagnosed either at reoperation or autopsy.

Slight differences in reporting numbers of valve related events between this paper and the earlier report of essentially the same dataset[3] can be explained by the use in the present study of a subset of 1762 patients, and by differences in definition of 'SVD'.

Standard methods of outcome analysis

The Kaplan-Meier (KM) and the actuarial method are commonly used time-to-event models to estimate the survival of patients after AVR. The distribution of the time-to-death for currently alive patients is assumed to follow the pattern of those who have already died. These methods have now been extended to summarize valve-related events such as SVD that are not necessarily fatal. In Figure 1 the cumulative ("actuarial") risk of reoperation for SVD calculated by using the KM method (the complement of cumulative freedom from reoperation for SVD) is displayed for the CE-SAV dataset. For estimating the life-time risk of non-fatal events the KM and actuarial methods assume non-informative censoring: they assume the risk of dying and the risk of developing SVD are independent, which in fact is not true (patients with high risk of death have lower risk of SVD, and patients with low risk of death have a higher risk of having SVD at some time in their lives). The KM and actuarial methods therefore estimate the freedom from SVD by also censoring patients who have not yet experienced the event, including those who have died and will therefore never have the event. In doing so they describe the risk of SVD for the patient based on

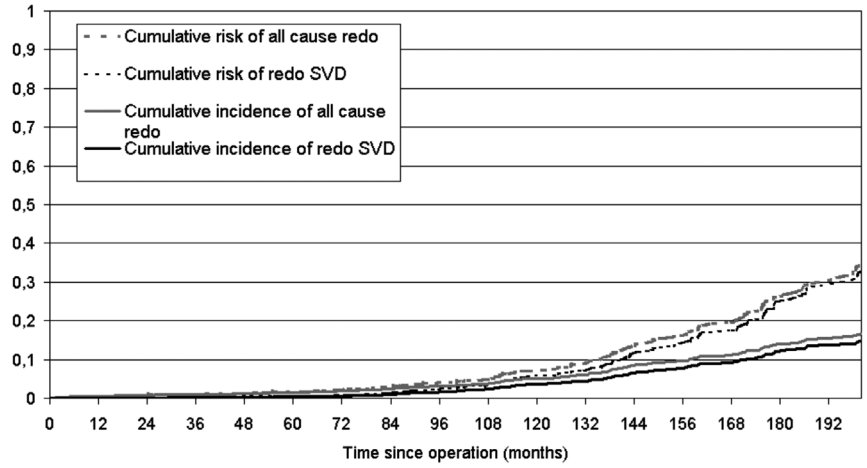


Figure 1: Cumulative incidence of reoperation and cumulative risk (equivalent of '1 minus freedom from reoperation') of all cause reoperation and reoperation due to SVD for patients in the CE-SAV dataset

the assumption of immortality, resulting in a higher probability of SVD than the patient in reality has. This effect is magnified with advancing age of valve implantation and could serve to underestimate the benefits of biological valve implantation. So, although the KM and actuarial methods are perfectly capable of analyzing fatal events, for describing competing events their value is dubious because in clinical medicine the assumption of non-informative censoring can often not be guaranteed.

One of the alternate methods of summarizing complications that are not necessarily fatal such as SVD is the cumulative incidence or "actual" analysis.[5,6] This method takes into consideration the competing risk of death, it excludes future events attributed to already deceased patients, and therefore calculates the percentage of patients who will experience an event before they die, answering the more pertinent question of the lifetime risk of the event.[1,7-9] As is shown in Figure 1, the cumulative "actuarial" risk of reoperation for SVD (7.0% at 15 years) is higher than the "actual" patient risk of reoperation for SVD (4.3% at 15 years).

The guidelines for reporting morbidity and mortality after cardiac valve operations have also incorporated the actual method.[4] Except for the cumulative incidence estimation, competing risk analyses in general do have the disadvantage of assuming that the competing events are independent. However, occurrence of an event (or reintervention) may alter the subsequent survival time, and alter the risk of reoccurrence of the event.

An advantage of the KM method and the cumulative incidence method is that they can be performed using standard statistical software, and that they give a valid general impression of outcome in patient populations after valve replacement. However, there are several limitations to these methods. In both KM and cumulative incidence analysis, an event can only occur once in the same patient. After the occurrence of an event, the patient is excluded from the analysis. Furthermore, although the KM and cumulative incidence analyses permit any hazard function while the parametric exponential method requires a constant hazard, neither of these models take into account that event risk may change over time, and may change after occurrence of events.

Simulation methods

If one would like to obtain optimal insight into outcome after valve replacement in a particular population, ideally all patients should be followed over time until everybody has died and all events (not only the first) that took place over time should be analyzed. In real life, the former is usually not a realistic option and the latter is difficult and time-consuming to achieve using standard methods of outcome analysis. Simulation methods offer a complementary tool to standard methods of outcome analysis by simulating the lives of virtual patients until death and taking into account all complications that may occur over time (including repeating events and changing hazards over time, with the occurrence of prior events, or both).

The two types of simulation models that have been used to model patient outcomes after AVR are the Markov state-transition model and the microsimulation model.[2,10] The Markov model creates a virtual population of patients that is followed over different time intervals until all patients have died. At each time interval, a transition from one health state to the other can occur, depending on predefined operative mortality estimates, occurrence rates of valve-related events and their consequences (death or reoperation) and the probability of dying of other non-valve-related causes. Events can occur repeatedly over time, hazards can change with each time interval, but it is hard to change hazards following the occurrence of an event using a Markov model.

A microsimulation model is a computer model that simulates a representative population, but at the level of the individual: the 'micro' level. The remaining life (until death) of a single patient with a particular age and sex after AVR with a given valve type is simulated. It takes into account the morbidity and mortality that the patient may experience according to predefined estimates of operative mortality, event occurrence and their consequences (death or reoperation), and the probability of dying of other non-valve-related causes. By repeating this simulation multiple times (eg, 10,000 times) a virtual patient population is generated, consisting of identical patients with all possible outcomes after AVR. A detailed account of the microsimulation structure and methodology has been given previously.[2,11]

We used the AVR microsimulation model, designed at our institution, to provide insight into the age- and sex-related life expectancy and lifetime risks of valve-related events after AVR with the CE-SAV bioprosthesis because it has several advantages over the Markov model. First, the microsimulation model allows simulation of the individual life histories of patients, starting directly after AVR and ending with the death of the patient (follow-up does not end at the event), rather than following a virtual population over time. By simulating multiple times the lives of identical virtual patients, all possible competing events that may occur during the remainder of life, and the time to occurrence of these events can be studied. Then, using this virtual closed cohort dataset, the average prognosis (including the lifetime risk of SVD and of other valve-related events) of an individual patient with these characteristics can be calculated. Furthermore, unlike the Markov model in which time is divided in intervals during which an event may or may not occur, the micosimulation model estimates the time to the next event based on the occurrence probability of that event. Finally, the microsimulation model allows for adjustment of event occurrence rates with time or based on the occurrence of prior events: eg, operative mortality increases with age and with each successive reoperation.

Building a microsimulation model

Figure 2 shows the general structure of the microsimulation model including and itemizing the information that is needed to start building the model:

1. Operative mortality estimates

To obtain accurate (and age-related) estimations of operative mortality after AVR, these parameters were estimated using data derived from an earlier meta-analysis containing 5837 patients with a total follow-up of 31,874 patient-years.[11] Operative mortality was estimated as 2.6% for a 40-year old man, increasing with an odds ratio of 1.034 for age (per year). For a 69-year-old man, operative mortality would be 6.6%. The real operative mortality derived from the CE-SAV dataset for primary AVR (mean age 69 years) was 5.0%.

2. Estimates of occurrence rates of valve related events

The estimates of occurrence rates of valve-related events are derived from the primary dataset described earlier (primary AVR patients only), and are depicted in Table 2. Assuming a constant hazard over time, weighted mean estimates of linearized annual occurrence rates were calculated for valve thrombosis, thrombo-embolism, endocarditis and

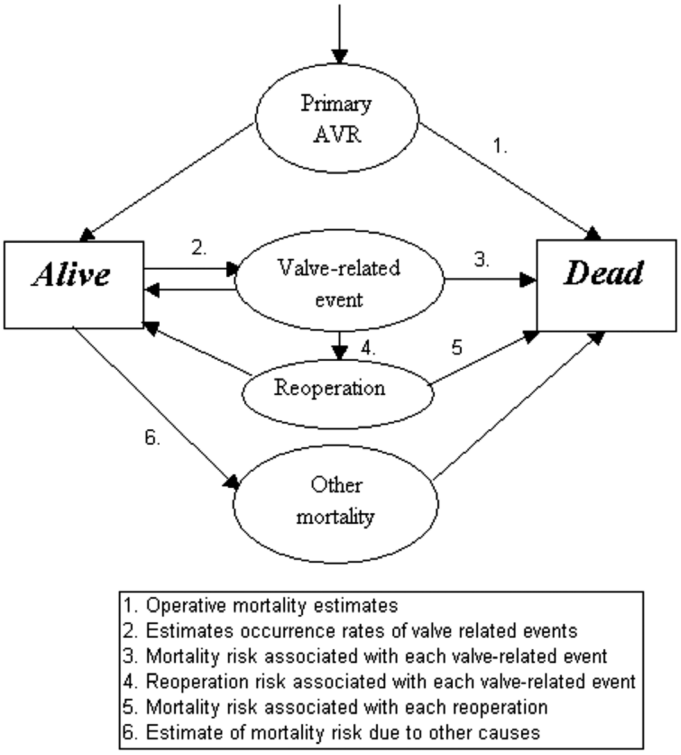


Figure 2: General structure of the microsimulation model

non-structural dysfunction respectively. The occurrence of hemorrhage was modeled as an age-dependent hazard of 0.076 with an age-dependent mortality of 0.034.[12]

A reoperation because of SVD is more relevant to the patient than the occurrence of SVD without consequences.[7] Furthermore, the onset and severity of structural valve deterioration is difficult to measure. Hence, SVD was defined as 'reoperation due to SVD' or 'SVD confirmed by means of autopsy'. The cumulative risk of SVD in a bioprosthesis decreases with increasing age of the patient at valve implantation and increases sub-exponentially with elapsing time since implantation.[13] Grunkemeier and colleagues have shown that the Weibull distribution, a generalization of the exponential distribution, was efficient in summarizing SVD in biological valves.[14,15] However, they stressed that at least 12 years of follow-up are needed to provide reliable estimates.[14] We used primary data on the CE-SAV, with a 20-year follow-up, as described in the previous section, to calculate the parameters of the Weibull distributions.[3] The value of the scale (σ) parameter of the Weibull model, fitted to represent SVD depends on age: $\sigma = e^{2.2240 + 0.0154 * age}$. The shape parameter ($\beta$) was estimated at 3.316. With the resulting age-dependent Weibull distributions for reoperation due to SVD, median time to reoperation due to SVD in the supra-annular valves was 19.2 (18.0 – 20.5), 22.4 (20.5 – 24.6) and 26.2 (23.1 – 29.7) respectively for 55-, 65-, and 75-year-old male patients.

3. Mortality risk associated with each valve related event

The estimates of mortality risk associated with each valve-related event are derived from the primary dataset described earlier and are depicted in Table 2.

4. Reoperation risk associated with each valve related event

The estimates of reoperation risk associated with each valve-related event are derived from the primary dataset described earlier and are depicted in Table 2.

5. Mortality risk associated with each reoperation

The estimates of reoperative mortality risk were also obtained from the previous meta-analysis discussed above.[11] For each first and following reoperation in a single patient, the operative mortality of 1.5% was increased with an odds ratio of 1.7. The mean age of the reoperated patients in the CE-SAV dataset was 53 years, so the expected reoperative mortality in the dataset would be $2.6\%+1.034^{(53-40)}+1.7=5.9\%$. Again this reoperative mortality was comparable to the observed reoperative mortality in the CE-SAV dataset, which was 5.4%.

6. Estimate of mortality risk due to other causes (mortality risk of general population plus 'excess mortality')

The mortality of a patient after valve replacement is composed of the mortality of the general population, the operative mortality, the valve-related mortality, and an excess mortality. This excess mortality cannot be explained by valve-related events, but is due to mortality associated with underlying valve pathology, left ventricular function, increased occurrence of sudden unexplained unexpected cardiac death, and the underreporting of

valve-related events respectively.[16-18] The model calculates patient outcomes by superimposing the morbidity and mortality estimates of valve-related events on the other components of patient mortality.

The mortality of the general population was incorporated into the model by means of the life table of the relevant age and gender matched population, American males in this analysis.[19] The excess mortality, not accounted for by the valve-related events, was represented by age- and sex-specific hazard ratios. These hazard ratios have previously been estimated by approximating age- and sex-specific survival curves produced by the model, which contained background morbidity and mortality caused by valve-related events, to the corresponding empirical curves obtained from data on stented porcine bioprostheses which contained all three components of patient mortality.[20,21] The hazard ratios were 2.9, 1.8, 1.2 and 0.8 for male patients aged 45, 55, 65 and 75 years respectively.[16] The life expectancy (LE) of a 65-year-old patient, for example, was estimated at 10.6 years. This corresponds to a 10- year survival of 50%, which is comparable to survival in other reports.[22-24] However, it is in contrast to a LE of 13.8 years for a 65-year-old male in the relevant general population, which translates to a 78% relative LE for the patient. The relative LE of a 65-year-old hypothetical patient who is immune from valve-related events and from operative mortality was about 90%. In the latter instance, the excess mortality of the patient may be related to underlying valve pathology, left ventricular residual hypertrophy and functional abnormality

Kvidal and colleagues, who investigated this excess mortality after heart valve replacement, described an increasing excess hazard during follow-up and a decreasing excess hazard with advancing age of implantation.[17] This supports a 'multiplicative' excess mortality, which was a structural assumption in our model. The use of an 'additive' model may overestimate LE estimates, especially in patients younger than 70 years.

Running a microsimulation model

By repeatedly simulating individual life histories of male patients aged 55, 65 and 75 years a total of 10,000 times, the microsimulation model calculated actuarial patient survival, reoperation-free survival and event-free survival of male patients of different ages at valve implantation. The areas under the respective curves represent life expectancy (LE), reoperation-free life expectancy (RFLE) and event-free life expectancy (EFLE). LE, RFLE and EFLE for men at different ages of valve implantation are given in Figure 3.

The microsimulation model also calculated the 'actual' or lifetime risks of valve-related events and SVD after valve implantation. The risk of SVD reduced with advancing age of implantation, namely 31.8%, 13.3% and 3.6% respectively for 55-, 65- and 75-year-old males. The lifetime risk of having at least one event also decreased with increasing implantation age.

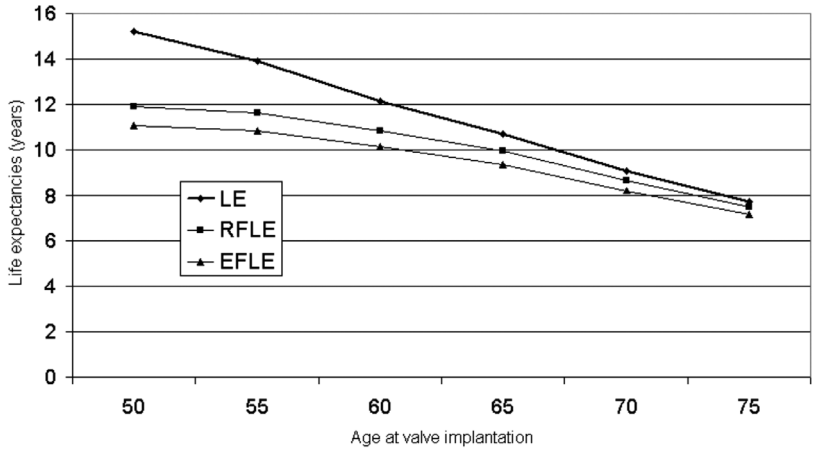
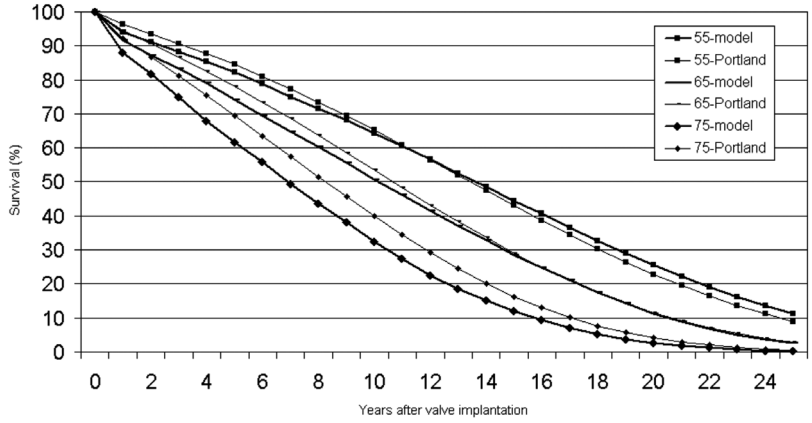


Figure 3: Life Expectancy, Event-Free Life Expectancy and Reoperation-Free Life Expectancy for men at different ages of valve implantation

Testing a microsimulation model

Validation

There are 2 types of validation: internal and external validation. Internal validation tests whether the results of the microsimulation model correspond to the outcome in the dataset from which the model was derived. For example, observed survival in the CE-SAV



E-Figure 1: External validation: microsimulation calculated survival compared to observed survival (Portland dataset)

dataset was 27% at 15 years, while this was 21% using the microsimulation model for a 69-year-old patient (mean age of CE-SAV population). Furthermore, observed "actual" freedom from all cause reoperation in the dataset was 86% at 15 years, while this was 82% for a 69 year-old patient by using microsimulation.

External validation tests whether a model also performs satisfactorily for patients other than the ones from whose data the model was derived. E-Figure 1 displays the age- and sex-specific survival results of the model with corresponding survival curves for the Carpentier-Edwards standard bioprosthesis (Edwards Lifesciences LLC, Irvine, Calif). This dataset was obtained from the Providence Health System in Portland, Oregon.[25] The survival outputs of the microsimulation model for 55- and 65-year old male patients compared favorably with the corresponding curves of the Carpentier-Edwards 'standard' Portland experience, through 25-years post-implantation: the 10-year-survival of a 55- and 65-year-old male patient was respectively 64% and 50% in the model versus 65% and 53% in the Portland dataset. However, the model showed a slight overestimation of mortality for 75-year-old males compared to the Portland dataset: the 10-year-survival was 32% in the model versus 40% in the Portland dataset. Patients who undergo an operation in this age group do not strictly represent the average patient in this age group who actually requires AVR. In fact they represent a selection of relatively healthier patients with a relatively better life expectancy. Systematic variations in the patient profile, too, especially in the older age groups, might result in these differences between model output and comparison data.

Sensitivity analysis

The effect of uncertainty in the parameter estimates of the model, such as variability across subgroups, can be investigated by means of sensitivity analysis. In one-way sensitivity analysis the value of one probability is varied while others are kept constant to test the stability of the analysis' conclusions and to test whether the outcome might change depending on the characteristics of the subgroup.[26] It ignores interactions between different parameters, and can therefore underestimate the level of uncertainty. Multivariate sensitivity analysis would be preferred, but then also the distributions of the parameters have to be known, which in our study is not yet possible. For this reason we performed one-way sensitivity analysis, and variation of the estimates by their 95% confidence intervals yielded only very small changes in the long-term outcomes. Therefore we defined larger ranges by increasing and decreasing the baseline estimates by 25%. The resulting life expectancy and event-free life expectancy of a 65-year-old male patient, for a plausible range of valve-related events and additional mortality, is given in Table 3. It shows that variation in the hazard ratio representing 'excess mortality' had the most pronounced effect on both LE and EFLE, and it underscores the importance of the excess mortality on the outcomes of patients after AVR.

Table 3: Summary of sensitivity analysis for a 65 year-old male patient after AVR with the CE-SAV

Parameter	Baseline Estimate	Plausible Range *		Life Expectancy (years)		Event-free Life Expectancy (years)		Reoperation-free Life Expectancy (years)	
		Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable
Hemorrhage	0.52	0.39	0.65	10.7	10.4	9.3	9.1	9.9	9.8
Non-Structural Dysfunction	0.24	0.18	0.30	10.6	10.6	9.3	9.2	9.9	9.8
Prosthetic Valve Endocarditis	0.33	0.25	0.42	10.6	10.5	9.3	9.2	9.9	9.8
Structural Valve Deterioration +.	22.4	28.0	16.8	10.8	10.6	9.7	8.7	10.3	9.2
Thrombo-Embolism	1.12	0.84	1.40	10.7	10.5	9.4	9.1	9.9	9.7
Valve Thrombosis	0.03	0.02	0.04	10.6	10.6	9.2	9.2	9.8	9.8
Excess Mortality (Hazard ratio)	1.2	0.9	1.5	12.0	9.5	10.2	8.4	10.9	9.0

** The baseline estimates were increased and decreased by 25% to estimate the plausible range.*

+ Median time to reoperation due to structural valve deterioration.

DISCUSSION

Microsimulation has several important limitations. First, microsimulation is a simplification of reality, just like any other model. Adding more variables will result in more patient-specific outcome estimates, and will bring the model closer to reality. We intend to study the effect of parameters like left ventricular function, cardiac rhythm and renal function etc. However, it is very difficult to derive the necessary data from published studies: more high quality primary datasets are needed for this refinement of the microsimulation model. In addition, currently the microsimulation model uses point estimates of the occurrence rates of valve-related events, ignoring the variation in these estimates. We are currently developing a new extension of the microsimulation model that allows entering not only point estimates of the occurrence rates of valve-related events but also the distribution

of these estimates. Furthermore, in the model we assume (by definition) all patients with SVD either have a reoperation or die, while in reality a proportion of patients with SVD, particularly the elderly, will not receive a reoperation and will die of other causes. Therefore the model will slightly overestimate the risk of reoperation for SVD, especially in the higher age group.

Second, the current simulation model is based on certain structural assumptions regarding mortality and morbidity after AVR. For example, a constant hazard was assumed for the valve-related events other than SVD. Certain hazards of complications, such as hazard of bleeding, will not be constant over time, but will increase with advancing age, or have a phase with high risk and a lower-risk phase such as endocarditis. Therefore, in our model there is an age-dependent risk and age-dependent mortality for 'bleeding'. The model does not have a 2-period risk for endocarditis, because we do not have access yet to primary datasets to support these changing hazards over time. Furthermore, sudden unexpected unexplained death is incorporated in the 'excess mortality' because gaining insight into this determinant remains difficult.[27]

The third limitation is the fact that the quality of the model, as in any model, is directly dependent on the quality of the input. Especially for input in simulation models, high quality data are essential. Most of the model-input is obtained from meta-analysis of earlier published studies, largely with a retrospective design, which are generally known to underestimate the incidence of (valve-related) events. Furthermore heterogeneity between the studies and possible publication bias can diminish the quality of the model-input.

Finally, another disadvantage is the fact that the microsimulation software is not yet available in standard statistical software packages. However, the computer program along with an extensive manual to get started with microsimulation is available at www.cardiothoracicresearch.nl .

CONCLUSIONS

This study aimed to provide insight into microsimulation methodology and to give an overview of the advantages and disadvantages of simulation methods (in particular microsimulation) in comparison to standard methods of outcome analysis. It showed, using a large existing dataset,[3] that microsimulation is capable of translating valve performance into patient outcome by providing age-related life expectancy and risk of reoperation for patients who underwent AVR with the CE-SAV bioprosthesis. These estimates of patient outcome may be used to compare the patient lifetime risk of reoperation with the CE-SAV bioprosthesis with the pericardial valves and with newer bioprostheses in a comparable patient population.

This study also showed that microsimulation has several disadvantages and limitations that need to be considered carefully and dealt with systematically when attempting to perform simulation studies.

In conclusion microsimulation can be a quick, accurate and useful tool to assess patient outcome after AVR with a specific prosthetic heart valve. Outcomes after implantation of different prosthetic heart valves can easily be compared, in order to facilitate and optimize the choice of specific heart valve prosthesis for both physician and patient.

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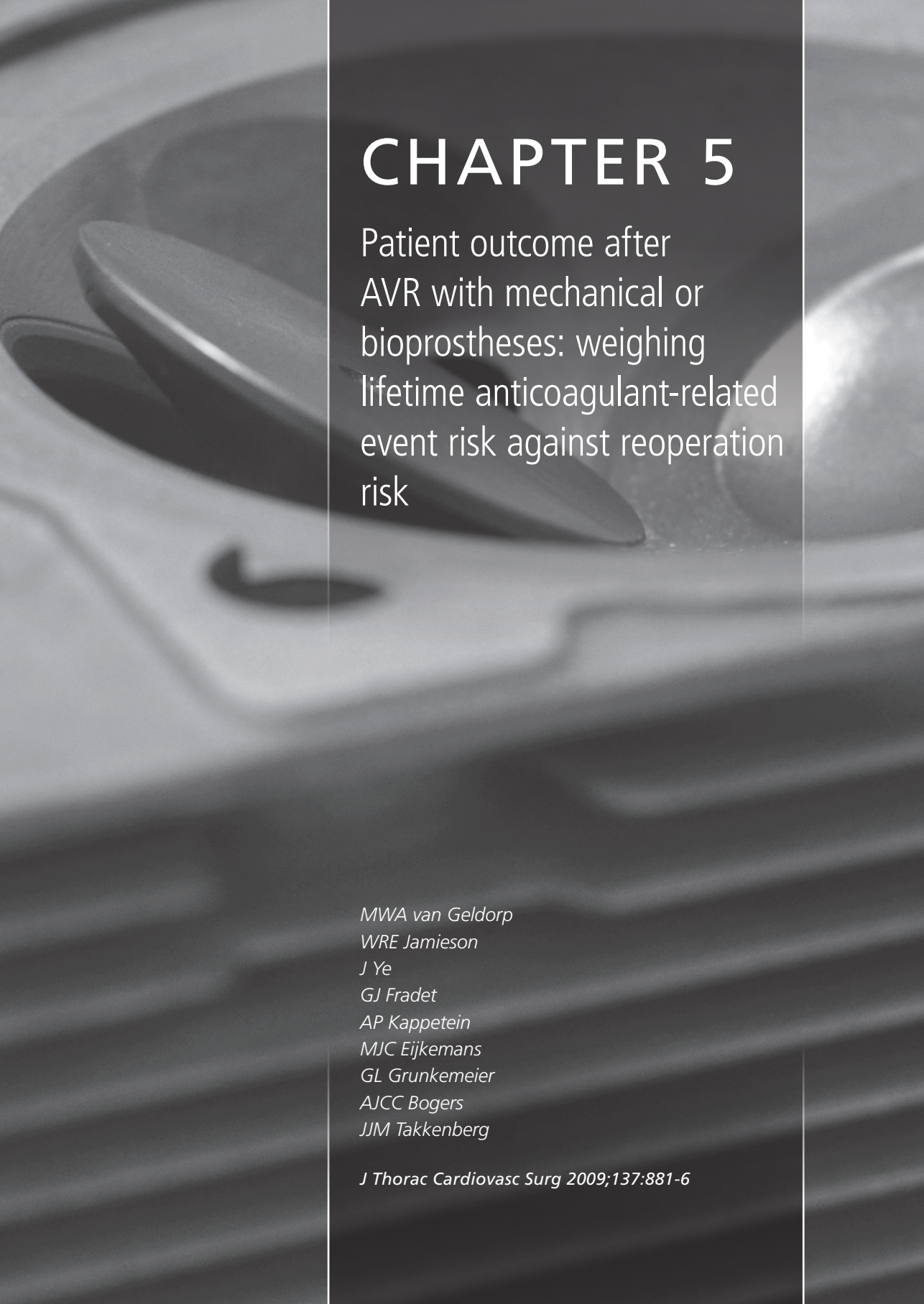

CHAPTER 5

Patient outcome after AVR with mechanical or bioprostheses: weighing lifetime anticoagulant-related event risk against reoperation risk

MWA van Geldorp
WRE Jamieson
J Ye
GJ Fradet
AP Kappetein
MJC Eijkemans
GL Grunkemeier
AJCC Bogers
JJM Takkenberg

J Thorac Cardiovasc Surg 2009;137:881-6

ABSTRACT

Objective

Although results of aortic valve replacement with different valve prostheses are well documented in terms of survival, risks of (valve related) events are less well explored.

Methods

We used a dataset of 3934 patients who had aortic valve replacement with either a bioprosthesis (73%) or a mechanical prosthesis (27%) between 1982-2003 to simulate outcome of patients after aortic valve replacement with either valve type. Using microsimulation we compared total age and gender-specific life-expectancy, event-free life-expectancy, reoperation-free life-expectancy, and lifetime risks of reoperation and valve related events for both valve types.

Results

Total follow-up was 26,467 patient-years. Mean follow-up was 6.1 years in the biological and 8.5 years in the mechanical arm. Mean age at implantation was 70 and 58 years for bioprostheses and mechanical prostheses respectively, and percentage of concomitant CABG 47% and 28%. For a 60-year-old male, simulated life expectancy in years for biological versus mechanical prostheses was 11.9 versus 12.2, event-free life expectancy 9.8 versus 9.3 and reoperation-free life expectancy 10.5 versus 11.9 Lifetime risk of reoperation was 25% versus 3%. Lifetime risk of bleeding was 12% versus 41%.

Conclusions

Even for patients aged 60, event-free life expectancy is better with a bioprosthesis: although the chance of reoperation is higher, the lifetime risk of bleeding is much lower compared to a mechanical prosthesis. Comparing lifetime event risks between different types of valve prostheses provides more insight into patient outcome after AVR, and can help in patient selection and counselling.

INTRODUCTION

Biological and mechanical valve prostheses are the most commonly used valve substitutes for replacement of the native aortic valve. Each valve type has its own advantages and drawbacks. The risk of reoperation for structural valve deterioration (SVD) in patients with a biological valve increases with time and decreases with advancing age. In contrast, patients with a mechanical prosthesis need lifelong anticoagulation and the risk of bleeding events increases with advancing age.

Outcome after aortic valve replacement (AVR) with either valve type is well documented in literature. These results are mostly described in terms of cumulative survival, freedom from events and reoperation, and linearized occurrence rates of valve-related complications and their consequences. A patient's lifetime risk of having a (valve-related) event after AVR is less well explored. Estimations of survival and valve related event risk for an individual patient after AVR are difficult to determine using standard time-to-event analyses.[1] Nevertheless, these parameters are important in counselling a patient.

The goal of this study was to calculate detailed and age-specific patient outcome after aortic valve replacement with mechanical prostheses and bioprostheses by using microsimulation.

METHODS

Patients

Previously a report on a large single-center dataset on outcome after AVR from Vancouver, Canada, was published using standard methods of data-analysis.[2] For the input of the microsimulation model we used essentially the same primary dataset, but excluded reoperations and operations with concomitant procedures other than CABG, leaving 3934 primary AVR procedures. Table 1 summarizes the dataset.

Methods

To simulate the lives of patients after AVR a microsimulation model was used. A microsimulation model is a computer model that simulates a representative population at the individual patient-level. This simulation model offers a complementary tool to standard methods of outcome analysis by simulating the lives of virtual patients until death and taking into account all complications that may occur over time (including repeating events, changing hazards over time and/or with the occurrence of prior events). It can provide insight into age- and sex-specific life expectancy and gives detailed information on the life time risk of valve-related events. Detailed descriptions on how to construct, test and run

this model, have previously been published.[3-5] The model can be downloaded from www.cardiothoracicresearch.nl.

Table 1: Summary dataset description

	Bioprosthesis	Mechanical prosthesis
Number of patients	2860	1074
Percentage of total dataset	72.7	27.3
Follow-up (patient-years)	17,352	9,115
Mean follow-up (years)	6.1	8.5
Mean age (years)	70.0	57.6
Male (%)	65.7	71.4
Coronary Artery Bypass Grafting (%)	47.3	27.7
Atrial Fibrillation (%)	7.0	9.7
Prosthesis brands (%)		
Carpentier-Edwards Supra-Annular Valve porcine	56.5	0
Carpentier-Edwards Perimount pericardial	23.0	0
Medtronic Mosaic porcine	20.5	0
St. Jude Medical	0	53.3
Carbo Medics	0	46.7

Model input

The data needed to run the microsimulation model comprise: 1. occurrence of valve-related events and their outcome, 2. operative and reoperative mortality, 3. background mortality of the general population, and 4. excess mortality. Valve related events were defined in accordance with the guidelines. [6]

1. Using the Vancouver dataset we calculated occurrence rates of valve related events and their outcome (e.g. death, reoperation), results are given in the appendix (Table 2). For most events, linearized occurrence rates were calculated, but for the occurrence of structural valve deterioration (SVD) a Weibull function was constructed. For bleeding we assumed an age-dependent incidence and -mortality. See details in the paragraphs below.

The cumulative risk of SVD in a bioprosthesis decreases with increasing age of the patient at valve implantation and increases sub-exponentially with time elapsed since implantation.[7] Grunkemeier and colleagues have shown that the Weibull distribution, a generalization of the exponential distribution, is efficient in summarizing SVD in biological valves.[8, 9] The formula for the hazard of SVD is: $h(t) = e^{-(t/\vartheta\hat{}\sigma}$. Based on the Vancouver dataset we estimated the parameters of this distribution. The value of the scale (σ) parameter of

the Weibull model, fitted to represent SVD and depending on age: $\sigma = e^{2.209 + 0.0153 * age}$. The shape parameter (β), which reflects the changing risk over time, was estimated at 3.211.

The incidence risk of bleeding increases with advancing age, especially in patients with a mechanical valve who need life-long anticoagulation. The occurrence of bleeding in the biological group was modelled as an age-dependent hazard of 0.076 with an age-dependent mortality of 0.0345.[10] For the mechanical group, a Gompertz distribution was used (α=0.076; β=-8.71).[11]

Because the risk of prosthetic valve endocarditis early after valve replacement is higher than later on, for prosthetic valve endocarditis two phases of constant risks were used. The linearized occurrence rate of the first phase, until 6 months after AVR, has an odds ratio of 5.8 for mechanical and 6.7 for bioprostheses compared to the second phase. These numbers are obtained from an earlier meta-analysis.[12] The linearized occurrence rate of the second period was derived from the Vancouver dataset.

2. Operative mortality was calculated as 2.7% for a 40-year-old man, increasing with an odds ratio of 1.034 for age (per year),[11] this corresponds to a 5.0% mortality for a 60-year-old man. For each reoperation an additional odds ratio of 1.7 was used.[4, 12-14] This odds ratio corresponds with the odds ratio of 1.6 that the STS risk calculator and also Rankin et al. use to calculate the risk of primary versus secondary AVR.[15, 16]

3. The background mortality, which is the mortality experienced by the normal population, is the equivalent of the life expectancy in the normal population. This was calculated using age- and sex matched American life tables derived from the Vital statistics of the US 1992, from the 'Centers for Disease Control and Prevention' and the 'National Center for Health Statistics'.[17] The life expectancy curves of the normal American, British Columbian and United Kingdom male populations are given in Figure 1.[17-19] This figure also displays the microsimulation calculated life-expectancy after AVR.

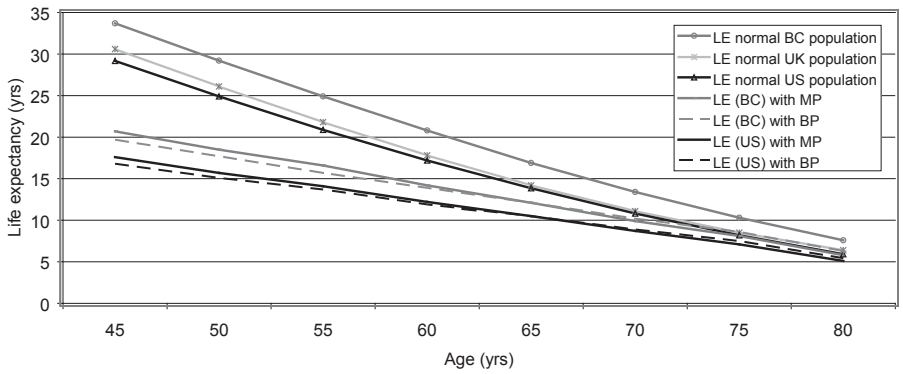

Figure 1: Life expectancy (LE) in men of different ages in British Columbia, Canada (BC), the United Kingdom (UK) and the United States (US) versus life expectancy after aortic valve replacement in British Columbian and United States patients.

4. The excess mortality is the mortality difference between the general population and patient population that cannot be accounted for by valve related events, but can be ascribed to increased occurrence of sudden death, underreporting of valve related events and underlying pathology such as left ventricular hypertrophy.[13,20] The hazard ratios after AVR are previously estimated as 2.9; 1.8; 1.2 and 0.8 for male patients aged 45, 55, 65 and 75 years respectively.[12]

Model validation

To assess the validity of the microsimulation model predictions, the microsimulation calculated survival for both patients with mechanical and biological prostheses was compared with the observed survival in the Vancouver dataset (internal validation). For external validation of the biological valve simulations a dataset from Portland, Oregon, was used.[21] The simulations of the mechanical valves were validated by comparison with a dataset on mechanical valve patients of the United Kingdom Heart Valve Registry.[22]

Sensitivity analysis

One-way sensitivity analysis was performed to study the effect of changing one of the input-parameters on model outcome (e.g. life expectancy, event-free life expectancy, reoperation-free life expectancy, and lifetime risk of events). The baseline estimates of the valve related events were varied by 25 percent to obtain favorable and unfavorable outcomes for a 60-year-old male after AVR.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

As shown in Figure 1, life expectancy after AVR is comparable for bioprostheses and mechanical prostheses for patients among all studied ages. Also, life expectancy after AVR is substantially lower than the life expectancy of the general population, especially in the younger age groups. Life expectancy of the normal population differs between different countries (Canada>United Kingdom>USA).[17-19] The differences in life expectancy between these countries disappear with increasing age.

In patients with bioprostheses the lifetime risk of reoperation is higher than in patients with mechanical valves, but in patients with mechanical prostheses the anticoagulation related bleeding risk is much higher, as seen in Figure 2. The risk of a bleeding event in the bio-group is not absent but about 12% in a 60-year-old male, neither is the lifetime risk of reoperation absent in the mechanical group which is about 3% in a 60-year-old male.

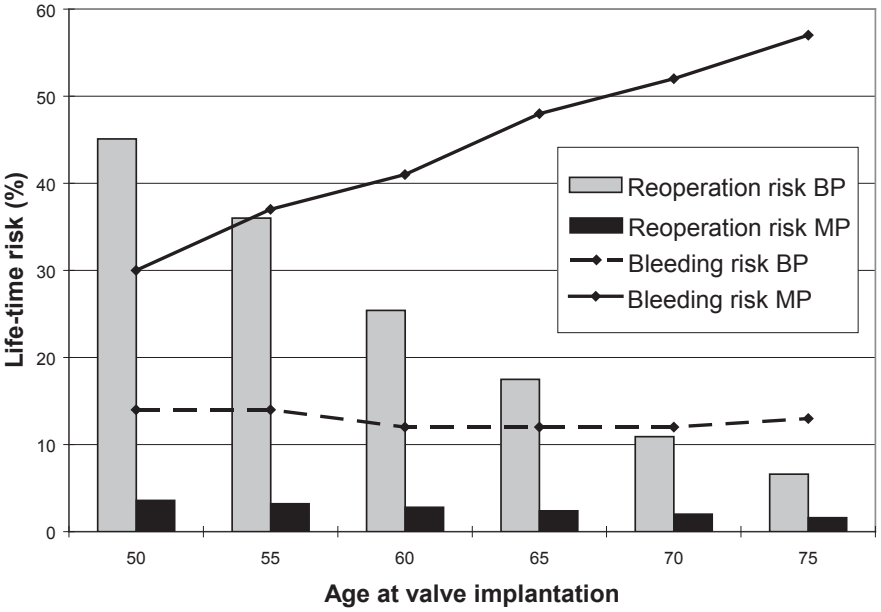

Figure 2: Lifetime risks of reoperation and bleeding after aortic valve replacement with mechanical and bioprostheses.

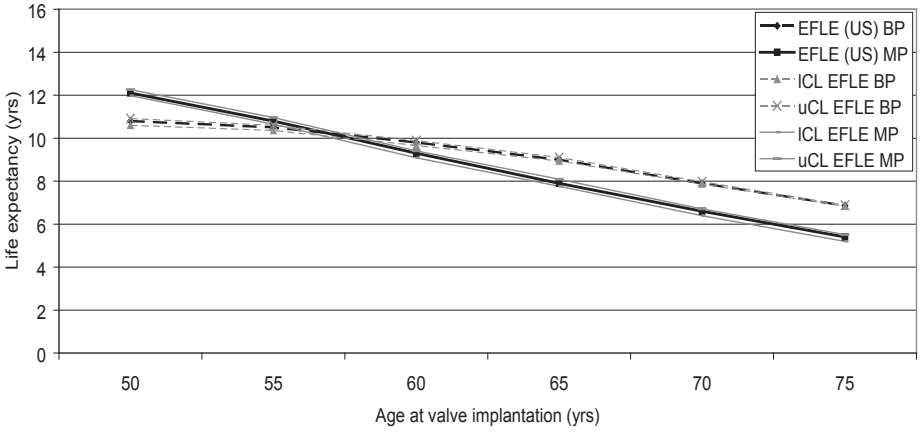

Figure 3: Event-free life expectancy (with 68% confidence limits in grey) after aortic valve replacement with mechanical and bioprostheses in the the United States (US) population. lCL=lower confidence limit, uCL=upper confidence limit.

For patients over 60 years of age, event-free life expectancy is better with a bioprosthesis (Figure 3), mainly because lifetime bleeding risk is lower. As shown in Figure 2, at age 60, the bleeding risk in patients with a mechanical prosthesis is already higher than the reoperation risk would be if a patient of the same age received a bioprosthesis. However, in the Vancouver dataset, the observed mortality after a bleeding event was 22%. In contrast the mortality after a reoperation for SVD (n=137) was 7.3%. The mean age of this patient group was 54 years.

Internal validation

E-Figure 1a of the appendix presents the overall observed survival for both patients with bioprostheses and mechanical prostheses in the Vancouver dataset versus the simulated survival of male patients with a bioprosthesis aged 70 and patients with a mechanical prosthesis aged 58 yrs. These are the mean ages of the respective groups. E-Figures 1b and 1c present the internal validation subdivided for each age group for biological and mechanical valves respectively. While validation appears adequate for the average patient in the dataset, a systematic underestimation of survival was observed in the simulated survival output, in particular in the older mechanical valve patient subgroups.

External Validation

E-Figure 2a of the appendix depicts the external validation of survival of bioprosthesis patients, and E-Figure 2b describes the external validation of survival of patients with mechanical prostheses.

Sensitivity analyses

E-Table 2a and 2b of the appendix show the summary of the one-way sensitivity analysis for the bioprosthesis and the mechanical prosthesis respectively. Variation of the input parameters of the model yielded only relatively small changes in the output, except for changes in the hazard ratios for excess mortality, and to a lesser extent changes in median time-to-SVD.

DISCUSSION

The estimates of lifetime patient risk of non-fatal events are obtained using cumulative incidence analysis. Sometimes Kaplan-Meier analysis is incorrectly used for this purpose. The issue of appropriate use of actuarial (Kaplan Meier) and actual analysis has been highlighted in several previous publications.[23,24] For the present paper the differences in results with either analysis are illustrated in E-Figure 4 of the appendix. Actuarial analysis of all-cause reoperation in the Vancouver bio-group would give a cumulative risk estimate

of 30% at 15 years, clearly higher than the cumulative incidence ('actual') value which is 16% at 15 years.

Total life expectancy after aortic valve replacement is not much different whether the patient gets a mechanical valve or a bioprosthesis. Because reoperation-free life expectancy, event-free life expectancy and lifetime event risks do differ between both patient groups, these are more important factors in choosing which valve substitute should be implanted in a particular patient.

For patients after age 60, event-free life expectancy is better with a bioprosthesis, mainly because the risk of bleeding with a bioprosthesis is much lower compared to a mechanical valve. Of course this is at the cost of the higher risk of a reoperation for structural valve deterioration (SVD). However, the lifetime risk of a reoperation for a 60-year-old man in whom a biological valve is implanted is only 25% (risk of reoperation due to SVD is 22%), so three quarters of the 60-year-olds will never experience a reoperation. The lifetime risk of a bleeding event when the same patient would have a mechanical valve implanted, is as high as 41%. The overall observed mortality of a bleeding event in the Vancouver dataset was 22%, which implies that these bleedings are life-threatening events. In contrast, the mortality risk after reoperation for SVD was 7.3% in this dataset, certainly not negligible but far lower than the mortality of bleeding. This is in accordance with an earlier report on the same dataset.[25]

As can be seen in Table 1, coronary artery disease (CAD) occurs more frequently in the bioprosthesis group, probably because the mean age is higher. Previous publications have shown that performing additional CABG does not have a significant impact on the crossing points of the life-expectancy and event-free life-expectancy curves.[26] Patients who have CAD have a shorter life expectancy than those without CAD. Due to this shorter life expectancy both the lifetime risk of a reoperation in the bioprosthesis group and the lifetime risk of bleeding and thrombo-embolic events in the mechanical group is lower compared to patients without CAD. The end result is that the age cut-off point at which a bioprosthesis is preferable over a mechanical prosthesis doesn't change and therefore it does not affect prosthetic valve selection.

The ACC/AHA guidelines generally recommend implantation of a bioprosthesis for patients older than 65 years.[27] Guided by the simulation-data presented in this study, patients in younger age groups, even around 60 years of age, may benefit more from a biological than a mechanical prosthesis. This is in correspondence with the report by Chan et al. based on standard analysis of the same patient population.[2] Newer biological prostheses may show even more reduction in the need for reoperation for SVD, and thus lower the threshold for implantation of a bioprosthesis even more.

To reduce bleeding complications more emphasis should be put on new anticoagulation strategies, new mechanical valve prostheses that require lower INR target rate, or simply by lowering the age threshold for implantation of a bioprosthesis. The negative

aspect of lowering this threshold is that not only more but also older patients will require a reoperation. This of course may increase the reoperative mortality. On the other hand, new less invasive techniques to replace the aortic valve are rapidly emerging in cardio-thoracic fields. The first reports on percutaneous and transapical approaches to replace the aortic valve are promising and their use is expected to rise.[28,29] Although experience with these techniques is yet rather limited and each approach seems to have its own advantages and disadvantages, their potential is not limited to treat native aortic valve disease. Most likely these techniques are also applicable to replace deteriorated biological prostheses, the 'valve-in-valve' concept.[30] This could reduce operative morbidity and mortality in high risk subsets of patients, and may therefore offer a solution for the treatment of elderly patients who experience SVD. In contrast, at the moment it appears that the awareness of surgeons that structural valve deterioration may occur after implantation of a biological valve is far greater than the awareness of the incidence and impact of bleeding events after implantation of a mechanical valve. This gap in knowledge may affect the valve selection process.

Limitations

Microsimulation is capable of quite accurate and precise simulations, as long as the input of the model is based on significantly large and, more importantly, high quality datasets. The quality of the model output is directly dependent on the quality of the input. The data to feed microsimulation models are usually derived from historical cohorts with a considerable follow-up, and may not necessarily be applicable to 21st century practice. For instance, the mean age of the reoperated patients is quite low, which implies the patients were very young when they received their biological valve, reflecting surgical practice in the eighties of the previous century. Nowadays only few young patients get a bioprosthesis. Also, the age-specific operative mortality estimates by the model are based on previous meta-analyses performed several years ago, and at the moment these estimates seem high. Perhaps new estimates should be established, although the effect of operative mortality on long-term outcome and life expectancy is only small, as can be seen in the sensitivity analyses (Tables 3a and 3b of the appendix). Further it can be argued that current valve prostheses have the same occurrence rates as prosthetic valves that were implanted in the past. Possibly nowadays these are lower. Despite this drawback, the Vancouver database consists of high quality data on an extensive number of patients who were interviewed by annual telephone calls and whose medical records (including echocardiograms) were reviewed to check if any events had occurred. In doing so it is likely that not many events have been missed.

More high-quality datasets are needed to incorporate other variables than only age and sex. Other determinants of life expectancy after AVR are coexisting coronary artery disease, left ventricular-, pulmonary- and renal function or other co-morbid conditions such as

malignancies or neurological diseases. When these parameters would be taken into account, the model would represent survival much more tailored to the individual patient.

For now we can only perform one-way sensitivity analysis. It would be better to check the results in simulated outcome when the distributions of the input parameters are known. In this matter work is in progress.

Microsimulation models are not yet widely known and used in the cardio-thoracic fields, and are not available in standard statistical software packages yet. The model described in this paper is available by downloading the program along with instructions at www.cardiothoracicresearch.nl.

CONCLUSION

Based on the Vancouver dataset it seems that even for patients aged 60 requiring AVR, implantation of a bioprosthesis generally may be considered superior over a mechanical prosthesis. The risk of bleeding with a bioprosthesis is not absent, but compared to mechanical valves the risk-reduction of bleeding that can be achieved with bioprostheses outweighs the increased risk associated with structural valve deterioration.

Comparing lifetime event risks between different types of valve prostheses provides more insight into patient outcome after AVR, and can help in patient selection and counselling. When combined with careful assessment of individual patient preferences this will provide a new key to optimized informed decision making.

Disclosures

Dr. Jamieson received grants in aid to facilitate the research data used in this manuscript. Dr. Fradet is a consultant for Medtronic and member of the advisory board of Biotronic and Bayer. The other authors have nothing to disclose.

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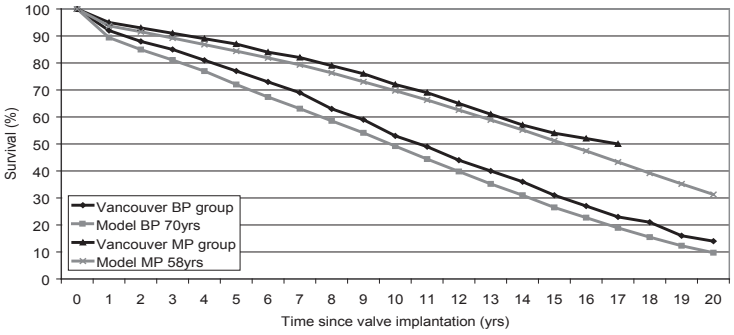
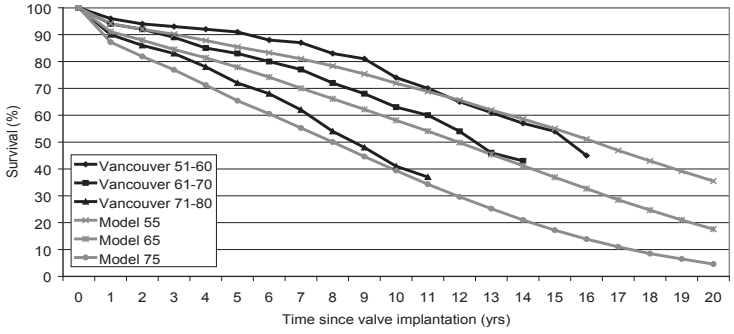
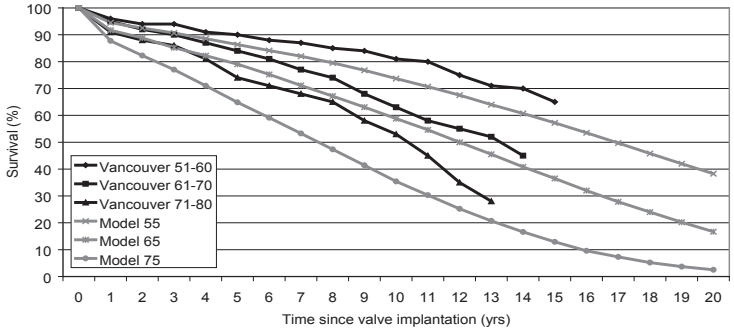
APPENDIX

Internal validation The overall survival that was calculated by the model showed a slightly worse survival for both prosthesis groups than observed in the Vancouver dataset (E-Figure 1a). When this dataset is split by different age groups the differences between simulated and observed survival increase, especially in the older ages and more in the mechanical group than in the biological group (E-Figures 1b and 1c). Apparently the excess mortality is lower in the Vancouver dataset than it is in our model. An explanation may be that the microsimulation model predicts life expectancy 'a priori' in a random patient, only knowing age and sex. The assumption is made that the excess mortality is equal for both patients who receive mechanical or bioprostheses. However, in clinical practice other patient-characteristics are also taken into account in the valve selection process; patients with a better life expectancy are more likely to receive a mechanical valve, while patients with a decreased life expectancy are more likely to receive a bioprosthesis. This patient selection process is probably responsible for the differences between observed and simulated survival.

External validation Although simulated survival after AVR with a bioprosthesis corresponded quite nicely with the Portland dataset (E-Figure 2a), the simulated survival for the mechanical prostheses was again lower than the observed survival in the UK Heart Valve Registry (E-Figure 2b). The differences between the curves are considerable. Several factors can be responsible for this. First, patient selection is probably different among different medical centers, countries and continents. Second, prosthesis types and brands will differ between medical centers, only it is questionable whether this factor contributes much to the observed survival differences. Third, background mortality is different between different countries. This clearly influences life expectancy after AVR, as is shown in Figure 1. However, difference in background mortality has hardly any influence on the point of indifference for the event-free life expectancy curves for both prostheses. To show this we simulated patients after AVR using both background mortalities from the United States, and from British Columbia, Canada. The effect on event-free life expectancy is displayed in E-Figure 3a. The curves will only shift upwards or downwards, but the age cut-off point at which a bioprosthesis is preferable over a mechanical prosthesis remains the same. This





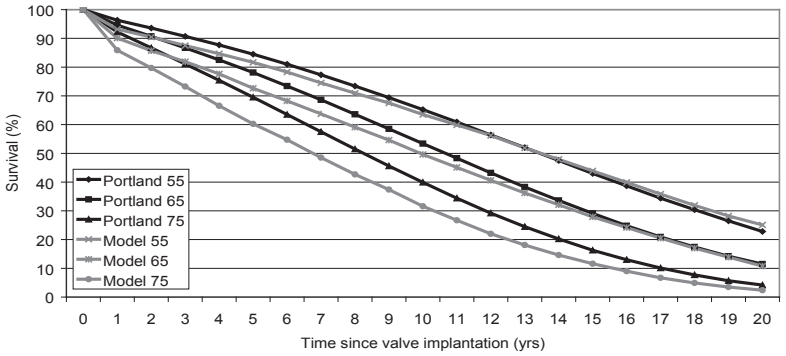


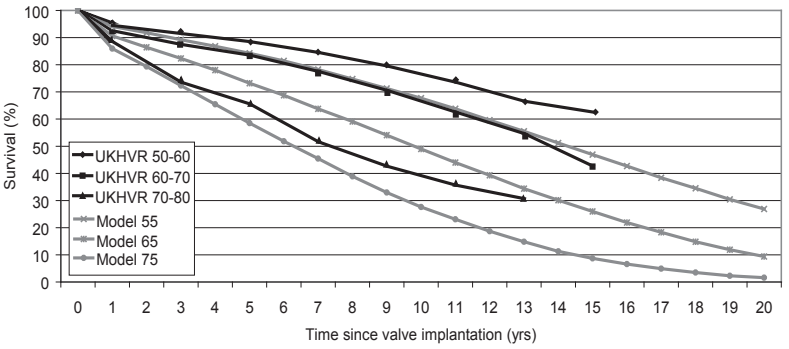
E-Figure 1: Internal validation.

a: simulated survival of 58-year-old mechanical- and 70-year-old bioprosthesis patients versus total observed survival in the bio- and mechanical prosthesis group of the Vancouver dataset.

b: simulated survival of 55-, 65- and 75-year-old male patients with a bioprosthesis versus the bioprosthesis group of the Vancouver dataset, subdivided in age categories.

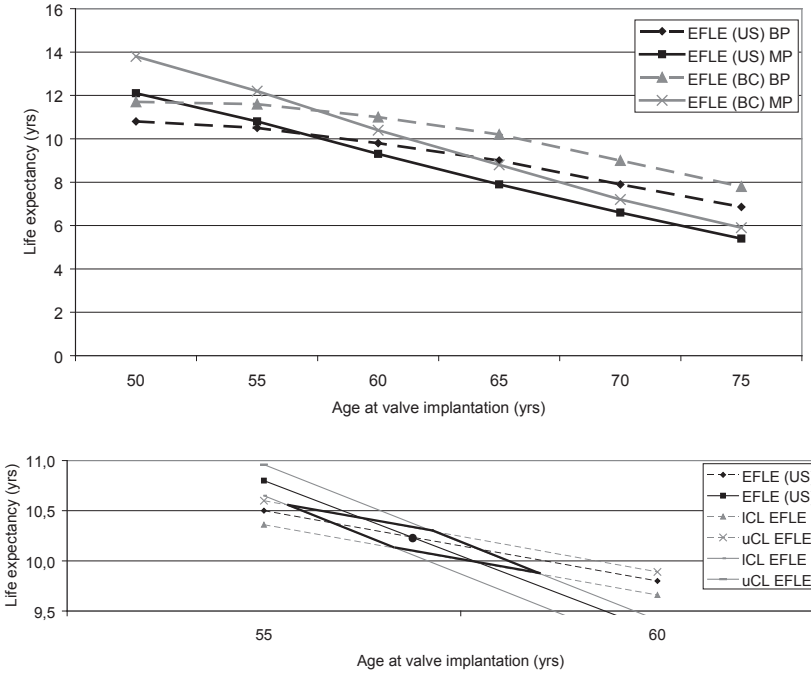
c: simulated survival of 55-, 65- and 75-year-old male patients with a mechanical prosthesis versus the mechanical prosthesis group of the Vancouver dataset, subdivided in age categories.



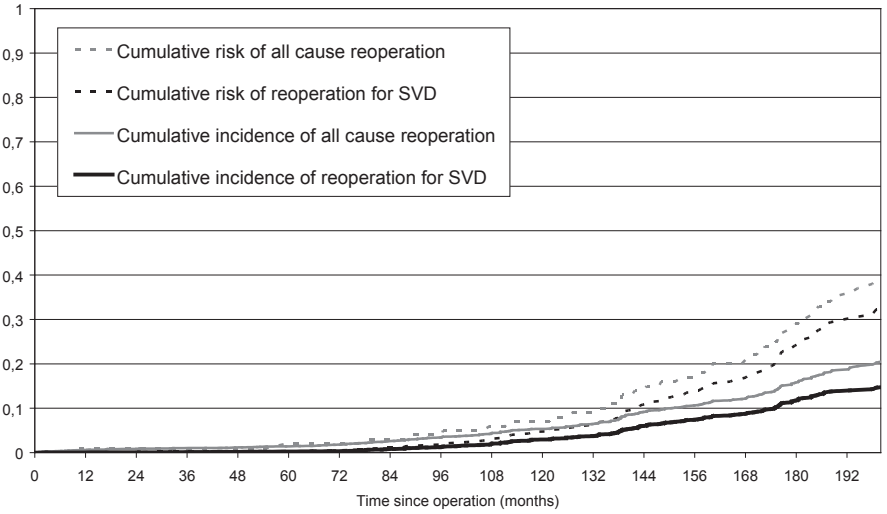


E-Figure 2: External validation.
a: Simulated survival of 55-, 65- and 75-year-old male patients with a bioprosthesis versus the observed survival in the Portland dataset, subdivided in age categories.
b: Simulated survival of 55-, 65- and 75-year-old male patients with a mechanical prosthesis versus the observed survival in the United Kingdom Heart Valve Registry (UKHVR) mechanical dataset, subdivided in age categories.

finding implies that the conclusions drawn from this article would remain the same for British Columbian patients or patients from other Western countries such as the United Kingdom. E-Figure 3b is a detail of Figure 3 and E-Figure 3a and displays the crossing point of the event-free life expectancy curves. The 68% confidence limits around the event-free life expectancy curves of the mechanical and the bioprosthesis group are also given The crossing 68% confidence limits demarcate the area in which the real crossing point of the event-free life expectancy curves lies (with a 95% certainty).



E-Figure 3: Event-free life expectancy (EFLE) for men at different ages of valve implantation.
a: EFLE for men with a mechanical valve (solid lines) versus a bioprosthesis (dotted lines). Black lines represent the United States population, grey lines represent the population in British Columbia, Canada. Background mortality changes among different populations, which has an effect on absolute EFLE, but hardly any effect on the age cut-off point at which a bioprosthesis is preferable over a mechanical prosthesis.
b: Detail of Figure 3 and E-Figure 3a. The crossing points of the 68% confidence limits around the EFLE curves demarcate the area in which the real EFLE age cut-off point lies (with a 95% certainty). lCL=lower confidence limit, uCL=upper confidence limit.



E-Figure 4: Actual versus actuarial analysis of all cause reoperation and reoperation for structural valve deterioration (SVD) in the biological group of the Vancouver dataset.

E-Table 1: Input microsimulation model, directly derived from dataset Vancouver.

Valve related event	n		Linearized Occurrence Rate *		Fatalities if no reoperation †		Mortality Rate		Number of Reoperations		Reoperation Rate ‡	
	BP §	MP ||	BP (17352 pt- yrs)	MP (9115 pt-yrs)	BP	MP	BP	MP	BP	MP	BP	MP
Bleeding	92	202	0.53	Gompertz	34	33	0.37	0.16	0	0	0	0
Non-Structural Dysfunction	40	41	0.23	0.45	2	4	0.05	0.10	35	16	0.92	0.43
Prosthetic Valve Endocarditis (Late)	53 (46)	16 (7)	2-Period (0.29)	2-Period (0.082)	18	1	0.34	0.06	20	9	0.57	0.60
Structural Valve Deterioration #	137	0	Weibull	0	0	NA	0	NA	137	NA	1.0	NA
Thrombo-Embolism	219	121	1.26	1.33	72	28	0.33	0.23	0	0	0	0
Valve Thrombosis	7	5	0.04	0.06	0	1	0	0.20	7	2	1.0	0.50
Sudden Unexpected Unexplained Death **	15	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	585	392			126	67			199	27		

* Linearized occurrence rate: number of events per 100 patient-years

† Number of fatalities if no reoperation was performed (either because patient died before or after decision-making not to operate)

‡ Proportion that was reoperated after surviving the event in the first place (no. reoperations / (no. events – no. fatalities))

§ Bioprosthesis

|| Mechanical prosthesis

Structural Valve Deterioration (SVD) was defined as 'reoperation due to SVD' and has therefore no direct fatalities.

** The cases of sudden unexpected unexplained death were entered into the model as part of the 'excess mortality'

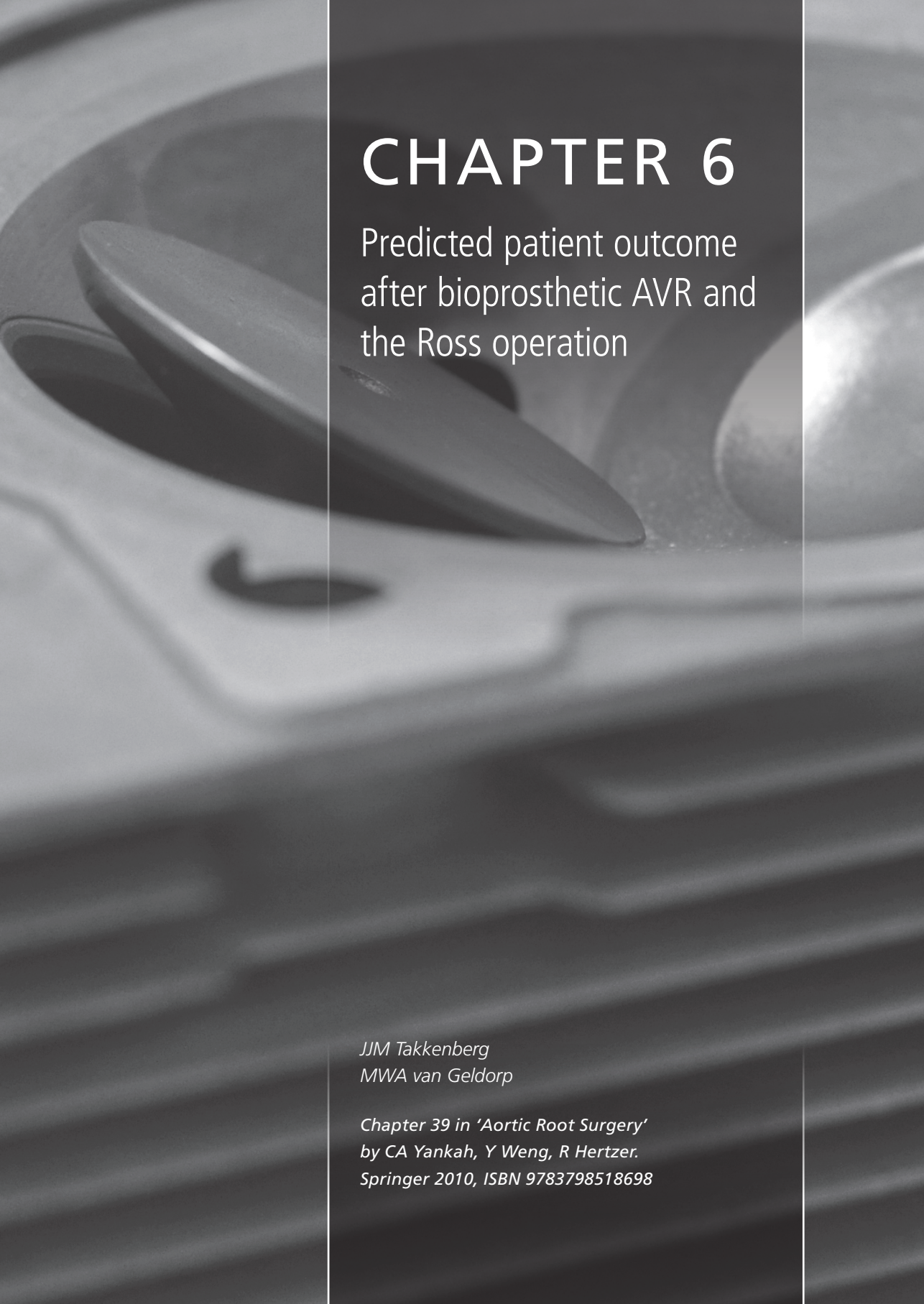
E-Table 2a: Sensitivity analysis for a 60-year-old American male after AVR with a bioprosthesis

	INPUT			OUTPUT					
	Linearized Occurrence Rate			**Life Expectancy**		**Event-free Life Expectancy**		**Reoperation-free Life Expectancy**	
Valve related event	(baseline)	minus 25% (favorable)	plus 25% (unfavorable)	Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable
Bleeding	0.53	0.40	0.66	12.1	11.9	9.9	9.7	10.6	10.5
Non-Structural Dysfunction	0.23	0.17	0.29	12.1	12.1	9.9	9.8	10.7	10.6
Prosthetic Valve Endocarditis	0.29	0.22	0.36	12.2	12.1	9.9	9.8	10.7	10.6
Structural Valve Deterioration*	22.0	27.5	16.5	10.6	10.3	9.3	8.4	10.0	8.9
Thrombo-Embolism	1.26	0.95	1.58	12.2	12.0	10.1	9.6	10.7	10.6
Valve Thrombosis	0.04	0.03	0.05	12.1	12.1	9.9	9.9	10.7	10.6
Operative mortality	5.0 %	3.8%	6.3%	12.1	11.8	9.9	9.6	10.7	10.4
Hazard ratio	1.2	0.9	1.5	12.9	11.3	10.3	9.4	11.2	10.1

*Median time to SVD is 22.0 years

E-Table 2b: Sensitivity analysis for a 60-year-old American male after AVR with a mechanical prosthesis

	INPUT			OUTPUT					
	Linearized Occurrence Rate			**Life Expectancy**		**Event-free Life Expectancy**		**Reoperation-free Life Expectancy**	
Valve related event	(baseline)	minus 25% (favorable)	plus 25% (unfavorable)	Favorable	Unfavorable	Favorable	Unfavorable	Favorable	Unfavorable
Bleeding	Gompertz			12.9	8.7	11.0	4.1	12.6	8.5
Non-Structural Dysfunction	0.45	0.34	0.56	12.2	12.2	9.3	9.2	12.0	11.9
Prosthstic Valve Endocarditis	0.08	0.06	1.0	12.2	12.2	9.3	9.2	12.0	11.9
Structural Valve Deterioration	NA	NA	NA	NA	NA	NA	NA	NA	NA
Thrombo-Embolism	1.33	1.00	1.66	12.3	12.1	9.5	9.1	12.0	11.9
Valve Thrombosis	0.06	0.04	0.07	12.2	12.2	9.3	9.3	12.0	11.9
Operative Mortality	5.0%	3.8%	6.3%	12.1	11.8	9.9	9.6	10.7	10.4
Hazard ratio	1.2	0.9	1.5	12.9	11.4	9.7	8.8	12.7	11.2



CHAPTER 6

Predicted patient outcome after bioprosthetic AVR and the Ross operation

JJM Takkenberg
MWA van Geldorp

Chapter 39 in 'Aortic Root Surgery'
by CA Yankah, Y Weng, R Hertzer.
Springer 2010, ISBN 9783798518698

DETERMINANTS OF SURVIVAL AFTER AVR

Multiple interrelated factors (patient-, physician-, and prosthesis-related) affect patient survival after aortic valve replacement. Every aortic valve re-placement is associated with a risk of death due to the surgical procedure. This risk may vary with the type of prosthesis that is implanted, and obviously increases with patient age and with each reoperation. In addition, the etiology of the valve lesion, concomitant procedures, and other well known risk factors may also affect operative mortality. Late survival of patients after aortic valve replacement differs considerably from survival of age-matched individuals in the general population. Figure 1 shows that life expectancy of male patients after aortic valve replacement is significantly reduced compared to the age-matched population life expectancy. This difference in life expectancy is particularly evident in young adult patients. Operative mortality and the occurrence of valve-related events[1] *(valve-related mortality)* can only in part explain this difference, as is illustrated in Figure 1 by the life expectancy of a patient who receives the – thus far hypothetical – perfect valve substitute, i.e., a valve substitute that has no associated valve-related complications. The remaining loss in life expectancy compared to the general population is depicted by the term *excess mortality*.

For older patients after aortic valve replacement, survival is only slightly worse than observed survival in the general population. This is most likely due to the selection process that takes place prior to aortic valve replacement: recent studies have shown that a considerable proportion of older patients who require aortic valve replacement according to the current guidelines[4,18] do not undergo surgery.[3,5,7]

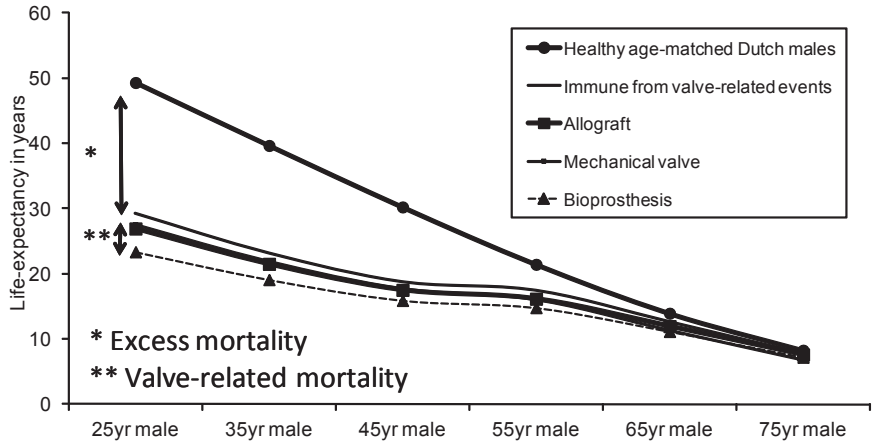


Figure 1: Absolute life expectancy (years) after aortic valve replacement with stented bioprostheses, mechanical prostheses and allografts compared to the age-matched Dutch population. Hypothetical immunity from valve-related events is depicted by the uninterrupted solid line just above the life expectancy estimates of the different prosthetic valve types

What are the causes of *excess mortality* after aortic valve replacement? Aortic valve disease is not limited to the aortic valve itself: it affects the entire heart. One can imagine that the strain posed on the myocardium by aortic valve disease will result in damage of the myocardium. Therefore, cardiac death is more common in patients with heart valve disease compared to the general population. Also, sudden unexplained unexpected death is probably more common in the former group. These may partly explain the observed differences in mortality. A landmark study by Kvidal et al.[12] investigated factors associated with *observed and relative survival* in a large patient cohort after aortic valve replacement. Risk factors associated with increased *observed* late mortality after aortic valve replacement included older patient age, pure aortic regurgitation, preoperative atrial fibrillation, advanced New York Heart Association class, and the presence of coronary artery disease. Interestingly, *relative* late survival (the ratio of observed late deaths in aortic valve replacement patients and expected deaths in the general age-matched population) was significantly greater in younger adult patients compared to older patients confirming the findings depicted in Figure 1. In addition, pure aortic regurgitation, preoperative atrial fibrillation, and advanced New York Heart Association class were important factors associated with increased *relative* survival.

After AVR, life expectancy, total event-free life expectancy and reoperation-free life expectancy are highly dependent on the mortality in the general (reference/source) population. This 'background mortality' differs between countries and is different over time periods (life expectancy around the world has increased dramatically during in recent decades). Figure 2 illustrates that even between developed countries, there are marked differences in population mortality that complicate the comparison of survival after aortic valve replacement between those countries. As can be seen in Figure 2, the life expectancy of, for example, a 60-year-old individual in the Canadian population is approximately 21 years, about 4 years longer compared to a 60-year-old in the US population. This will result in a 2–3 year difference in life expectancy after aortic valve replacement between patients residing in Canada versus the US and may have implications for valve selection. The observed differences in general population mortality and their effect on survival after aortic valve replacement complicate the comparison of outcome after aortic valve replacement with different valve substitutes, and it therefore remains a challenge to study the possible survival advantage of certain biological valve substitutes (stentless bioprostheses and the Ross procedure). The following paragraphs provide an overview of reported patient outcome with different biological valve substitutes.

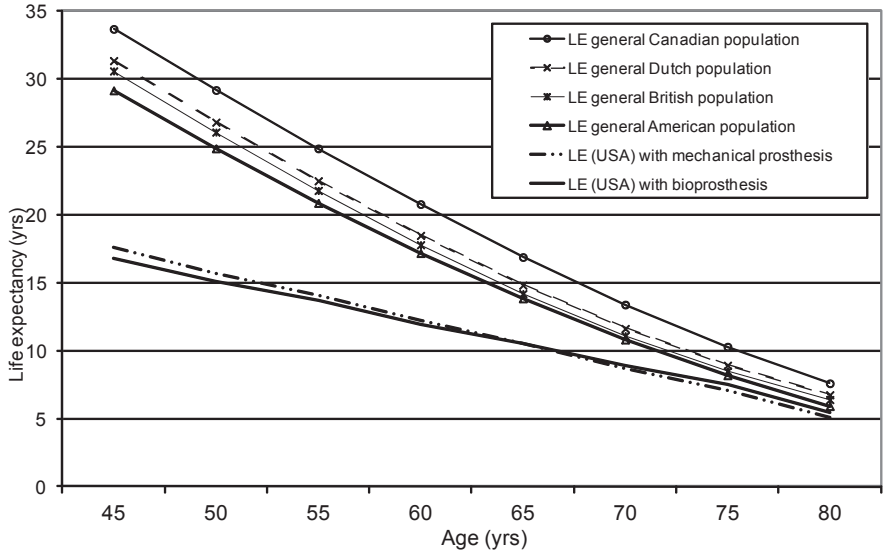


Figure 2: Life expectancies for men in several general populations and life expectancy after implantation of a prosthetic aortic valve. Reprinted with permission from [20]; © American Association for Thoracic Surgery

PREDICTED PATIENT OUTCOME AFTER AVR

A microsimulation model was designed at Erasmus University Medical Center, Rotterdam, The Netherlands, to predict specific outcome of patients after AVR.[17] This computer model simulates a representative population at the individual patient level and offers a complementary tool to standard (e.g., Kaplan-Meier) methods of outcome analysis: it simulates the lives of virtual patients until death and takes into account all complications that may occur over time. The model can provide insight into age-and sexspecific life expectancy, event-free and reoperation-free life expectancy, and provides detailed information on the lifetime risk of valve-related events. Detailed descriptions on how to construct, test, and run this model have been published.[14,19] The model including detailed instructions for use can be downloaded at *www.cardiothoracicresearch.nl*.

For conventional aortic valve surgery, one can choose between mechanical prostheses, biological stented or stentless prostheses, autografts and allo-(or homo-) grafts. The mechanical prosthesis has the major advantage of great durability and virtually zero technical valve failures. However, to prevent valve thrombosis and thromboembolism, lifelong coumadin anticoagulation is absolutely necessary. Unfortunately, this results in a higher bleeding risk, especially in the elderly. Limited availability of coumadin therapy and ap-

propriate INR control in poorly developed countries result in a contraindication for the use of a mechanical prosthesis.

The main advantage of biological prostheses including allografts and autografts lies in the fact that there is no need for long-term anticoagulation, and the risk of bleeding approximates that of the normal population. The major downside of these biological valve types is structural deterioration of the valve apparatus which can lead to either regurgitation or stenosis of the valve leaflets, or root dilatation in case of autografts. This process of structural valve deterioration (SVD) increases with advancing time after implantation, decreases with age, and often – and in particular in younger adult patients and children – necessitates a reoperation.

In the following sections, microsimulation will be used to calculate patient outcome after aortic valve replacement with different biological valve substitutes.

Stented bioprostheses

Stented bioprostheses are the most commonly used biological valve substitutes. This prosthesis type is composed of a sewing ring and an artificial frame in which three porcine, bovine or equine pericardial leaflets are suspended. The prosthesis is relatively easy to implant and since it has been widely used large numbers of studies with long-term follow-up are available.

As mentioned before, the major downside of a (stented) bioprosthesis is the risk of SVD. This risk decreases as life-expectancy decreases (patients die before SVD develops). Therefore, current guidelines state that a bioprosthesis is generally preferable in patients over 65 years (without another indication for anticoagulation such as atrial fibrillation).[4] However, from our microsimulation studies and the work of Jamieson and others,[6] it seems this age-threshold could be lowered to around 60 years: compared with mechanical valves, around this age the risk reduction of bleeding that can be achieved with a bioprosthesis outweighs the increased risk associated with SVD. This results in a better event-free life expectancy, although total life expectancy after AVR remains comparable for mechanical and bioprosthesis patients. For a 60-year-old man, simulated life expectancy in years for biological versus mechanical prostheses was 11.9 versus 12.2, event-free life expectancy was 9.8 versus 9.3, and reoperation-free life expectancy was 10.5 versus 11.9. Lifetime risk of reoperation was 25% versus 3%. Lifetime risk of bleeding was 12% versus 41%.[20]

Stentless bioprostheses

One of the downsides of the stented bioprosthesis is the relative obstruction that remains after the native valve has been replaced. This is caused by the valve opening, the sewing ring and its frame and could cause a ‘patient-prosthesis mismatch’ especially when the surgeon is forced to use a prosthesis of the smaller sizes (diameter 17–21 mm). Stentless bioprostheses have a larger effective orifice area (EOA) which provides lower transval-

vular gradients, better hemodynamics and, therefore, more reduction of left ventricular hypertrophy. Furthermore, some consider stentless bioprostheses to be more durable than conventional stented bioprostheses, all contributing to a possible survival advantage. A disadvantage is they are more difficult and time-consuming to implant. A recent randomized trial comparing 96 patients who received a stented bioprosthesis versus 127 patients who received a stentless bioprosthesis showed that there was a late survival advantage for stentless valve recipients.[13] However, no causeeffect relationship between lower transvalvular pressure gradients and improved survival was found, and the need for additional trials studying this subject remains.

Microsimulation studies of the Medtronic stentless Freestyle valve predicted for a 65-year-old male a life expectancy of 13.1 years, which is close to that of the general population. The reoperation-free life expectancy was 11.2 years and the event-free life expectancy was 8.4 years.[8]

Allografts

The human donor valve (allograft) has excellent hemodynamics, low occurrence of thromboembolic events and endocarditis, and does not require anticoagulation. It is most often used in aortic root disease or destructive endocarditis, because it has redundant tissue attached and provides more possibilities for reconstructive surgery than bio-or mechanical prostheses. On the other hand, the allograft is not an 'off the shelf' item and requires special preparation, storage, and considerable surgical skills. The number of studies on long-term allograft outcome is limited and affected by a considerable amount of bias/selection, since it is mostly used in a highly selected patient group. Microsimulation enabled multiple studies to be combined and predicted for a 65-year-old male a life expectancy of 12 years, a reoperation-free life expectancy of 10 years, and an event-free life expectancy of 9.7 years.[15]

Finally, a microsimulation study that compared outcome after aortic valve replacement with either stented bioprostheses (Carpentier-Edwards supraannular and pericardial), stentless bioprostheses, or cryopreserved allografts showed that when assuming uniform patient characteristics and excess mortality, the difference in performance between the four biological valve types is small.[9] Patient selection and the timing of operation may explain most of the observed differences in prognosis after aortic valve re-placement with biological prostheses.

PREDICTED PATIENT OUTCOME AFTER THE ROSS OPERATION IN YOUNG ADULTS

The Ross operation or autograft procedure is mainly performed in children and young adult patients. In this operation, the patient's pulmonary valve is used to replace the aortic valve either as a subcoronary implantation or as a full aortic root replacement, while the pulmonary valve is replaced with an alternative prosthesis, usually a pulmonary homograft. The potential advantages of the autograft or Ross procedure are the use of the patient's own living valve with favorable hemodynamic characteristics, low endocarditis risk, low thrombogenicity, avoidance of anticoagulant therapy, and autograft size increase in children. However, the Ross procedure is a technically demanding operation and both the autograft in aortic position and the valve substitute in the right ventricular outflow tract may develop structural failure over time. The Ross operation has been performed in small numbers, and long-term follow-up studies have been inconsistent, which makes analysis of long-term advantages and disadvantages difficult.

Although survival of young adult patients after this procedure is almost uniformly excellent and comparable with the general population, autograft durability is in some centers clearly superior to other biological valve conduits, while other centers report worrisome autograft reoperation rates. It remains unclear why these results diverge so much. A very recent systematic review and meta-analysis of reported outcome after the Ross procedure[16] shows that in young adult patients (mean age 39 years; range 11–71 years) the late survival pattern runs parallel to the general age-matched population (Figure 3). Early pooled mortality was 3.24% (95% CI 1.47– 6.58%), while the late mortality rate was 0.64%/patient

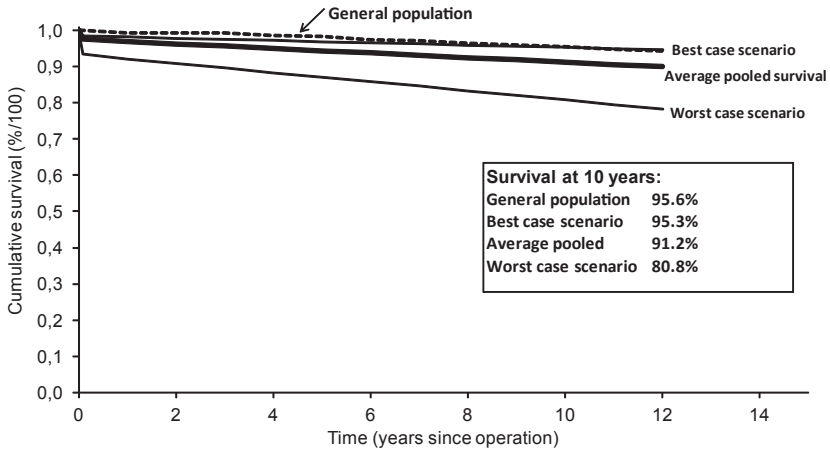


Figure 3: Cumulative survival after the Ross procedure in young adult patients

year (95% CI 0.32– 1.26%/patient year). Figure 3 illustrates pooled estimated survival after the Ross operation in adults including 95% confidence intervals (best and worst case scenario). The review also illustrates that although the occurrence rates of most valve-related complications are very low, the durability results of in particular the pulmonary autograft diverge considerably, especially 10 years postoperatively (95% CI for freedom from autograft failure at 10 years 86–96%). The question remains whether it is possible to optimize autograft durability through better patient selection, more optimal application of the root replacement technique, and perhaps postoperative antihypertensive treatment.

Remarkable is the excellent reported survival after the Ross operation in young adult patients, which appears to run parallel to the general population. This is in contradiction to the observed impaired *relative* survival in young adult patients after aortic valve replacement that was discussed in the first section of this chapter. It seems that *excess mortality* is virtually absent in patients after the Ross operation, and some authors suggest that this excellent survival advantage may be caused by the fact that the autograft provides a living and hemodynamically superior valve substitute. An update of the ongoing randomized trial in the United Kingdom (Harefield) between allograft and autograft aortic root replacement (personal communication) suggests indeed that autograft patients have superior survival compared to patients who receive an allograft.[2] On the other hand, the Ross operation is performed in a select group of patients, and their characteristics may also explain the observed survival pattern. For example, a single center observational study by Klieverik et al.[11] in young adult patients who underwent aortic valve replacement found that in a univariable Cox regression model for late survival the Ross procedure appeared to carry a survival advantage over allografts and mechanical prostheses. However, in a multivariable Cox regression model that also included preoperative renal impairment, preoperative impaired left ventricular function, concomitant mitral valve surgery, prior aortic valve surgery and patient age, the factor implanted valve substitute was no longer of influence on late survival. Another study by Klieverik et al.[10] that compared outcome after allograft or autograft aortic root replacement in young adult patients with congenital aortic valve disease showed no difference in survival between the two groups. These observations suggest that patient characteristics are important determinants of late survival and that the implanted valve type is of minor importance.

SUMMARY AND CONCLUSIONS

Late patient survival after aortic valve replacement is impaired compared to the general population. This difference can only in part be explained by the occurrence of valve-related complications. In particular in younger adult patients there is a considerable amount of

excess mortality that is due to patient-related factors. Regional differences in population mortality hamper studies on survival after aortic valve replacement and should be taken into account when assessing evidence on outcome after aortic valve replacement.

Microsimulation studies show that patient outcome after implantation of stented and stentless bioprostheses or cryopreserved allografts is acceptable and that differences in patient outcomes are most likely explained by patient selection and the timing of operation, rather than differences in the performance of these valve substitutes.

The pulmonary autograft appears to be the only biological valve substitute that carries a survival advantage. However, this survival advantage may very well be caused by patient selection. A randomized trial or a propensity score matching study of young adult patients who received either an autograft, allograft or mechanical prosthesis will elucidate whether there truly is a survival advantage. Durability of the autograft varies widely between reported series and may be optimized through better patient selection, more optimal application of the root replacement technique, and perhaps postoperative antihypertensive treatment.

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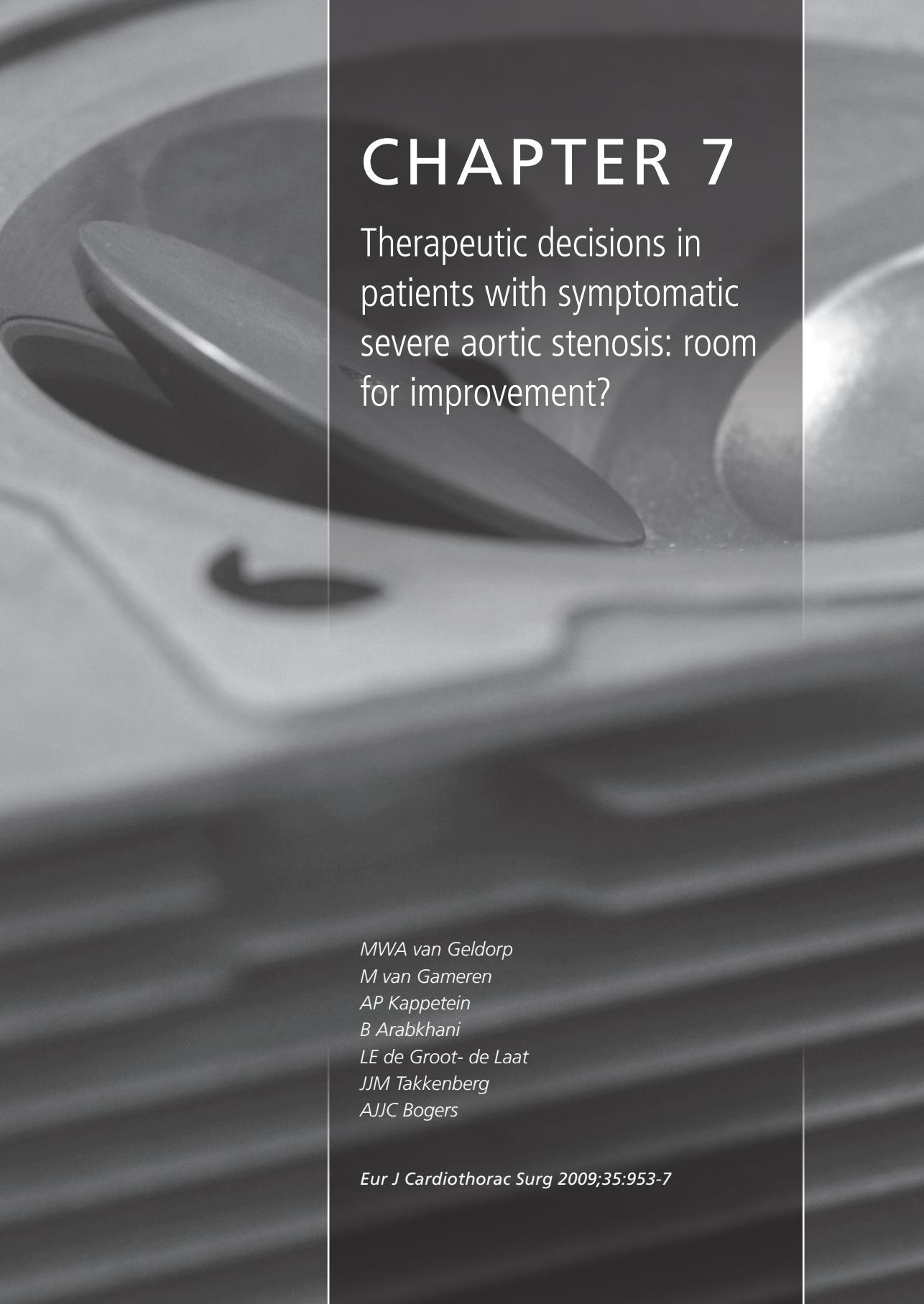

CHAPTER 7

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

MWA van Geldorp
M van Gameren
AP Kappetein
B Arabkhani
LE de Groot- de Laat
JJM Takkenberg
AJJC Bogers

Eur J Cardiothorac Surg 2009;35:953-7

ABSTRACT

Objective

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

Methods

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

Results

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

Conclusions

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

INTRODUCTION

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

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

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

METHODS

Study design and data collection

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

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

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

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

Study population

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

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

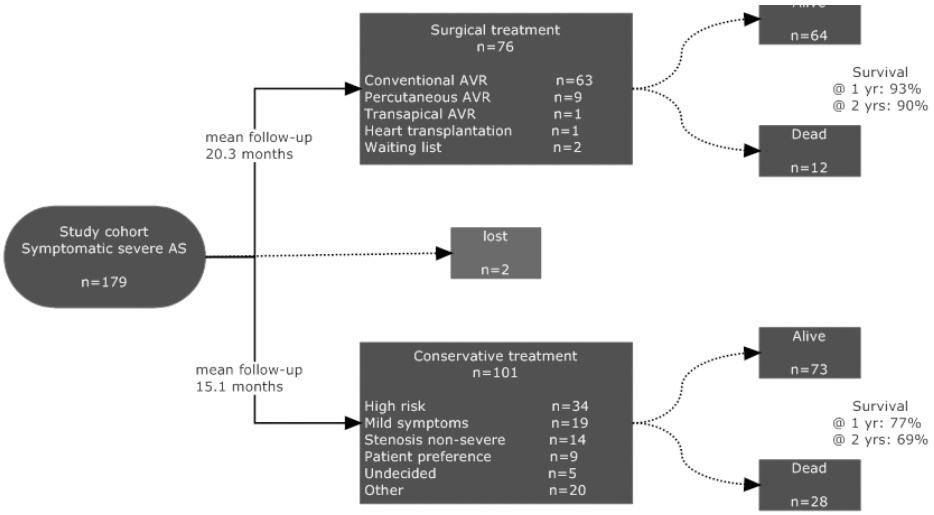

Figure 1: Flow chart of main results.

Table 1: Patient characteristics

Patient characteristics	AVR n= 76	Conservative n= 101
Age (mean ± SD in years)	67.9 ± 12.4	73.3 ± 12.3
Male (%)	49	51
Follow-up (mean ± SD in months)	20.3 ± 11.8	15.1 ± 11.5
Echocardiographic parameters (mean ± SD)		
Maximal transaortic velocity (m/s)	4.4 ± 0.8	4.0 ± 0.8
Peak gradient (in mmHg)	82 ± 32	66 ± 26
AV/LVOT VTI ratio	4.9 ± 1.8	5.0 ± 2.3
Aortic Valve Area (cm2)	0.68 ± 0.24	0.71 ± 0.26
NYHA class (%)		
II	42.1	54.5
III	38.2	34.7
IV	13.2	8.9
Missing	6.6	2.0
Left Ventricular Function (%)		
Good/impaired (EF >50%)	56.6	57.4
Moderate (EF 30-50%)	38.2	30.7
Poor (EF <30%)	2.6	7.9
Missing	1.3	4.0
Logistic EuroSCORE (mean ± SD)	7.8 ± 7.9	11.3 ± 9.6

Statistical analysis

Continuous data are presented as mean ± 1 standard deviation, and median. Categorical data are presented as proportions.

Chi-square testing was used for comparison of categorical variables. Continuous variables were compared using the Student's t-test. A p-value < 0.05 was considered significant.

Survival curves were estimated by the Kaplan-Meier method. Differences in survival were not statistically assessed.

Statistical analyses were performed with SPSS for Windows (release 15.0; SPSS Inc, Chicago, Illinois).

RESULTS

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

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

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

DISCUSSION

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

'Overestimation' of operative risk?

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

From literature it is known that remission of symptoms after starting medical treatment can be a reason to stay conservative and that patients who are treated conservatively are generally older and more often have impaired left ventricular function than surgically

treated patients.[6,7] Yet, both remission of symptoms, advanced age and depressed left ventricular function are debatable reasons not to operate on a symptomatic patient. Even elderly patients can be operated upon with acceptable morbidity and mortality, and can expect a considerable quality of life.[5,11]

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

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

'Underestimation' of symptoms?

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

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

'Underestimation' of hemodynamic severity

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

these misclassified patients are at increased risk of left ventricular deterioration and sudden death.[20]

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

Survival in the conservative and in the surgical group

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

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

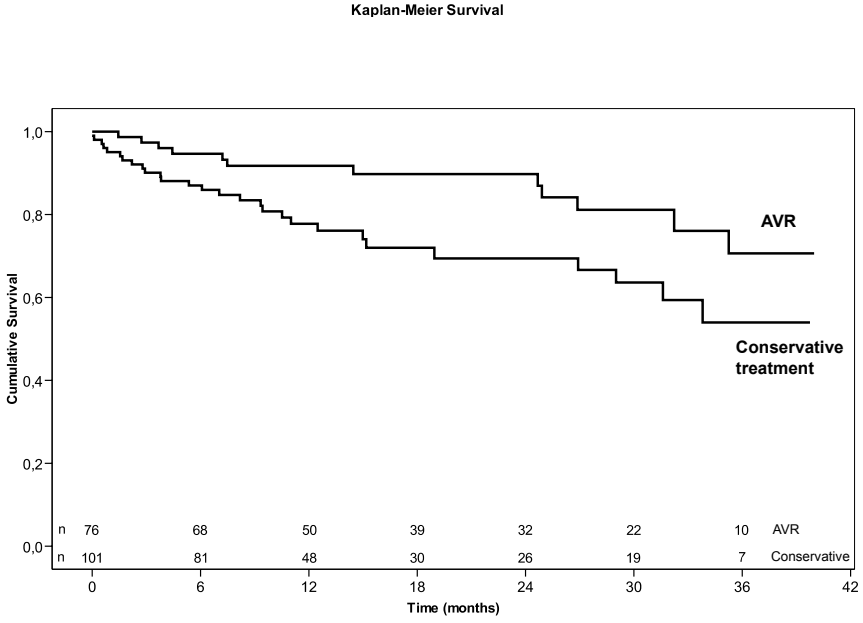

Figure 2: Kaplan Meier survival for the conservatively treated group and the AVR group.

ment, resulting in low survival in this category. Therefore the relatively 'good' prognosis of our medically treated group could be a reflection of the conservative approach of the cardiologists in our region.

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

Future prospects

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

CONCLUSION

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

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

Disclosures

None

Acknowledgements

The authors would like to thank the patients, cardiologists, echo laboratory workers and secretaries of the following participating hospitals for their kind cooperation.

- Havenziekenhuis, Rotterdam
- St. Franciscus Gasthuis, Rotterdam
- IJsselland Ziekenhuis, Capelle aan den IJssel
- Vlietland Ziekenhuis, Vlaardingen
- Albert Schweitzer Ziekenhuis, Dordrecht
- Medisch Centrum Rijnmond Zuid, Rotterdam
- Erasmus University Medical Center, Rotterdam

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CHAPTER 8

Reply to Paraskevas 'Prescribing statins in aortic stenosis, little to lose, much to gain'

MWA van Geldorp
JJM Takkenberg

Letter to the editor, Eur J Cardiothorac Surg 2010;37:497-9

In reaction to 'Prescribing statins in aortic stenosis: Little to lose, much to gain' [1], we would like to provide the readership of this journal with some additional information concerning statin use — or underuse — in our study population.

In our observational prospective cohort study, we described treatment strategies in symptomatic patients with severe aortic stenosis in the Rotterdam area, the Netherlands.[2] In the patients observed, the so-called medical or conservative treatment was mostly aimed at relief of symptoms by diuretics, treatment of atrial fibrillation and systemic or pulmonary hypertension. To prevent endocarditis, all patients were treated with prophylactic antibacterial treatment before starting non-sterile surgical procedures.

Approximately only half of the patients received lipidlowering drugs: 54% of the 76 patients in the aortic valve replacement (AVR) group and 47% of the 101 patients in the 'medical/conservative' group.

Although we only documented drug prescriptions and have not studied why certain patients received statins (and why many did not), we doubt statin usage was aimed at slowing the progression of aortic stenosis. It is more likely statins were prescribed for (cardio-) vascular co-morbidity or dyslipidaemia.

Statins may interfere with the progression of aortic stenosis, but to what degree and until which disease stage remains uncertain and has yet to be established in larger prospective series. Dr Paraskevas refers to a cohort study in which statins slowed the haemodynamic progression in patients with asymptomatic moderate-to-severe aortic stenosis,[1] others reported no clear effect on the progression of moderate-to-severe aortic stenosis in a recent randomized trial.[3] Further, the SEAS trial he refers to, concerned patients with asymptomatic mild-to-moderate aortic stenosis.[1,4] In his comprehensive review, Dr Paraskevas concludes statins improve cardiovascular outcomes in surgical patients (either coronary artery bypass graft (CABG) or patients who need valve replacement or other thoracic surgery).[5] However, it remains to be seen whether statin therapy is useful in the cohort we studied: the symptomatic patient with severe aortic stenosis in whom the decision to operate or not is yet to be made. Although interesting, this will be difficult to study because co-morbidities, age, the advanced state of the valve stenosis and treatment selection probably play a major role in clinical outcome.

On the other hand, of course, one could also argue there is not much to lose. Since we have no hard data of our own to either support or reject this statement, we leave this subject open for debate. Nevertheless, we are grateful for Dr Paraskevas' enthusiastic comments and discussion.[1]

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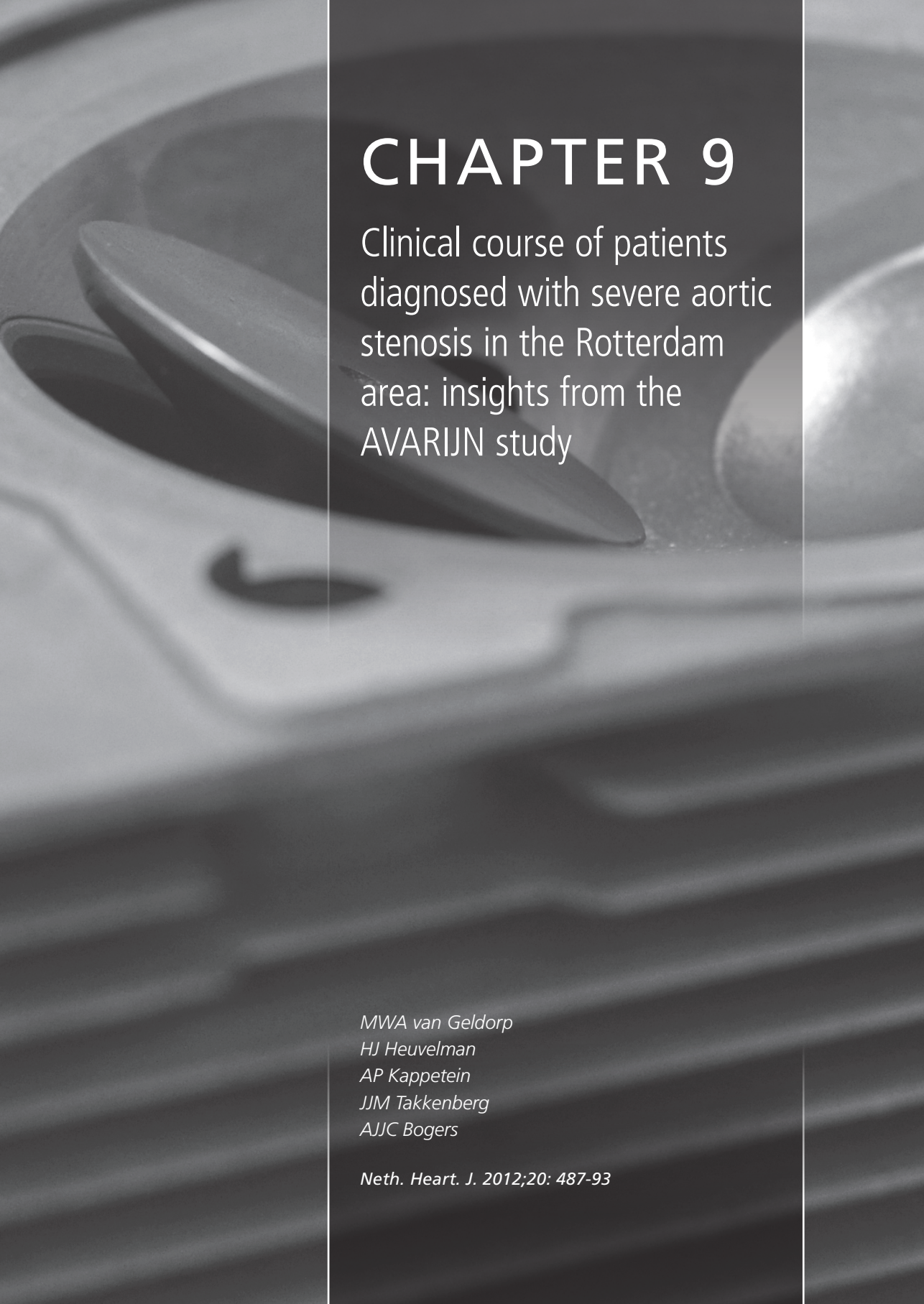

CHAPTER 9

Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study

MWA van Geldorp
HJ Heuvelman
AP Kappetein
JJM Takkenberg
AJJC Bogers

Neth. Heart. J. 2012;20: 487-93

ABSTRACT

Objective

To prospectively evaluate the clinical course of patients with severe aortic stenosis (AS) and identify factors associated with treatment selection and patient outcome.

Methods

Patients diagnosed with severe AS in the Rotterdam area were included between June 2006 and May 2009. Patient characteristics, echocardiogram, NT-proBNP, and treatment strategy were assessed at baseline, and after 6, 12, and 24 months. Endpoints were aortic valve replacement (AVR) / transcatheter aortic valve implantation (TAVI) and death.

Results

The study population comprised 191 patients, 132 were symptomatic and 59 asymptomatic at study entry. Two-year cumulative survival of symptomatic patients was 89.8% (95% CI 79.8-95.0%) after AVR/TAVI and 72.6% (95% CI 59.7-82.0%) with conservative treatment. Two-year cumulative survival of asymptomatic patients was 91.5% (95% CI 80.8-96.4%). Two-year cumulative incidence of AVR/TAVI was 55.9% (95% CI 47.5-63.5%) in symptomatic patients. Sixty-eight percent of asymptomatic patients developed symptoms, median time to symptoms was 13 months; AVR/TAVI cumulative incidence was 38.3% (95% CI 23.1-53.3%). Elderly symptomatic patients with multiple comorbidities were more likely to receive conservative treatment.

Conclusions

In contemporary Dutch practice many symptomatic patients do not receive invasive treatment of severe AS. Two-thirds of asymptomatic patients develop symptoms within 2 years, illustrating the progressive nature of severe AS. Treatment optimization may be achieved through careful individualised assessment in a multidisciplinary setting.

INTRODUCTION

The prevalence of calcified aortic stenosis (AS) increases with the ageing of the population, and represents a growing health burden.[1,2] According to the current ESC and ACC/AHA guidelines, aortic valve replacement (AVR) is indicated in patients with severe symptomatic AS.[3,4] Even elderly patients with multiple comorbidities are usually eligible for AVR, and if surgery is not an option, transcatheter aortic valve implantation (TAVI) is often feasible.[5,6] Nevertheless, at least one third of patients with symptomatic AS do not undergo AVR although they have a clear indication.[7-10] Advanced age, poor left ventricular function, and comorbidities are common reasons for non-referral for AVR.[8-9,11-13]

The aim of this study was to prospectively evaluate the clinical course of patients with severe AS in contemporary Dutch practice and identify factors associated with treatment selection and patient outcome. This information may facilitate treatment optimisation.

METHODS

Patient population

The Aortic Valve RIJNmond (AVARIJN) Study is a multicentre prospective cohort study of patients diagnosed with severe AS in seven Cardiology clinics in the wider Rijnmond area between June 2006 and May 2009. Patients 18 years and older were included if they met one of the following echocardiographic criteria: aortic valve area (AVA) $\leq$ 1 cm^2, peak transaortic jet velocity (Vmax) $\geq$ 4 m/s, or aortic valve / left ventricular outflow tract velocity time integral ratio $\geq$ 4. The study protocol was approved by the medical ethics committee of Erasmus University Medical Center (MEC 2006-066); all patients provided written informed consent.

Patient characteristics, i.e. medical history, cardiovascular risk factors, symptomatic status defined as presence of dyspnoea, angina, and/or syncope at study entry,[3,4] echocardiographic data including Vmax, peak and mean aortic gradient, AVA, left ventricular ejection fraction, and low-flow/low-gradient AS (mean aortic gradient < 30 mmHg and an AVA < 1.0 cm^2), brain natriuretic peptide (NT-proBNP), and treatment strategy (conservative or either AVR or TAVI) were assessed at baseline, and after 6, 12, and 24 months. Expected operative risk was calculated using the logistic EuroSCORE and the Society of Thoracic Surgeons' risk model (www.euroscore.org; www.sts.org). Asymptomatic patients were invited for exercise testing at baseline; a positive exercise test outcome was defined according to the ACC/AHA guidelines.[14] Patients with a positive test stayed in the asymptomatic group.

Treatment strategies were retrieved from the patients' medical charts. Study endpoints were AVR or TAVI and all-cause death, which were documented using the hospital information systems or information obtained through the treating physicians.

Statistical analysis

Continuous data are presented as mean (SD) or median (interquartile range) and for comparison between groups the unpaired t-test or Mann-Whitney U test was used. Categorical data are presented as counts and proportions, and comparison was done with the Chi-square test.

Kaplan-Meier analysis was used to assess patient survival and cumulative incidence of AVR/TAVI. Patient follow-up started at enrolment and ended at time of death (event), completion of study, or when the patient was lost to follow-up (censoring).

Logistic regression was used to evaluate the association between baseline characteristics and conservative treatment strategy. Cox proportional hazards analysis was used to analyse time-related events. Missing values were imputed by the mean. Univariable predictors with a p-value ≤ 0.05 were entered into the multivariable model using the enter method. In case of correlation between potential predictors, the potential predictor that was considered clinically most relevant was selected for the multivariable model. Age, male gender, smoking, hypertension, diabetes, dyslipidaemia, chronic obstructive pulmonary disease, carotid disease, stroke, peripheral arterial disease, previous myocardial infarction, coronary artery disease, renal failure, symptomatic status, body mass index, body surface area, systolic and diastolic blood pressure, NT-proBNP, Vmax, AVA_i (indexed by body surface area), left ventricular ejection fraction, left ventricular hypertrophy (on electrocardiography), ischaemia (on electrocardiography), and aortic and mitral regurgitation $\geq$ grade II were considered as co-variables in the models (definitions in the Appendix). All statistical tests were two-sided and a p-value ≤ 0.05 was considered significant. Statistical analyses were performed using SPSS for Windows, version 15 (SPSS Inc, Chicago, Illinois) and GraphPad Prism 5 for Windows (GraphPad Software, San Diego, California).

RESULTS

The study population consisted of 191 patients with severe AS, of whom 132 were symptomatic and 59 were asymptomatic at study entry (Table 1).

Forty-seven of the 59 patients who were asymptomatic underwent an exercise test at baseline. Of these 47 patients, 15 (32%) tested positive (ST depression $\geq$ 2 mm (N=10), no increase blood pressure (N=2), collapse (N=1), angina (N=1), and dyspnoea (N=2)), 25 (53%) patients tested negative, and in 7 (15%) patients the test was inconclusive. Twelve patients were unable to perform the exercise test due to impaired mobility, logistic reasons, or refusal.

Figure 1 displays the flow chart of patients during the study. Completeness of follow-up was 99%; 2 patients had emigrated.

Table 1 Patient characteristics at baseline differentiated by symptomatic status

	All N=191	Symptomatic N=132	Asymptomatic N=59	P-value
Age (yrs)	72.6 (63.7-78.6)	74.0 (64.4-79.2)	69.9 (61.6-76.4)	0.034
Male gender (%)	62	56	76	0.008
Previous valve surgery (%)	1	2	0	0.343
Previous CABG (%)	6	8	3	0.272
Smoking (%)	61	56	71	0.049
Hypertension (%)	52	54	49	0.554
Diabetes (%)	20	19	22	0.622
Dyslipidemia (%)	49	49	47	0.820
COPD (%)	17	20	10	0.083
PAD (%)	13	15	7	0.108
History of MI (%)	13	15	8	0.207
Stroke (%)	19	18	20	0.725
Vmax (m/s)	4.3 ± 0.8	4.3 ± 0.8	4.2 ± 0.7	0.693
AVA (cm2)	0.74 (0.59-0.91)	0.72 (0.54-0.85)	0.80 (0.63-0.96)	0.026
LVEF (%)	61 ± 7	61 ± 7	62 ± 6	0.129
Low flow/low gradient AS (%)	13	15	8	0.207
AR grade ≥ II (%)	17	18	14	0.494
MR grade ≥ II (%)	11	15	4	0.025
LVH (%)	27	28	24	0.445
NT-proBNP (pmol/l)	50 (22-153)	89 (29-180)	31 (13-74)	<0.001
Logistic EuroSCORE (%)	5.4 (3.1-8.2)	6.2 (3.9-9.6)	4.0 (2.1-6.9)	<0.001
STS score (%)	4.5 (2.8-7.6)	5.1 (3.3-8.0)	3.8 (2.0-6.0)	0.002

CABG = coronary artery bypass graft, COPD = chronic obstructive pulmonary disease, PAD = peripheral arterial disease, MI = myocardial infarction, Vmax = peak transaortic jet velocity, AVA = aortic valve area, LVEF = left ventricular ejection fraction, AS = aortic stenosis, AR = aortic regurgitation, MR = mitral regurgitation, LVH = left ventricular hypertrophy, NT-proBNP = N-terminal pro-brain natriuretic peptide,
STS = Society of Thoracic Surgeons. Normal distributed variables: mean ± standard deviation; skewed distributed variables: median (interquartile range 25 and 75%).

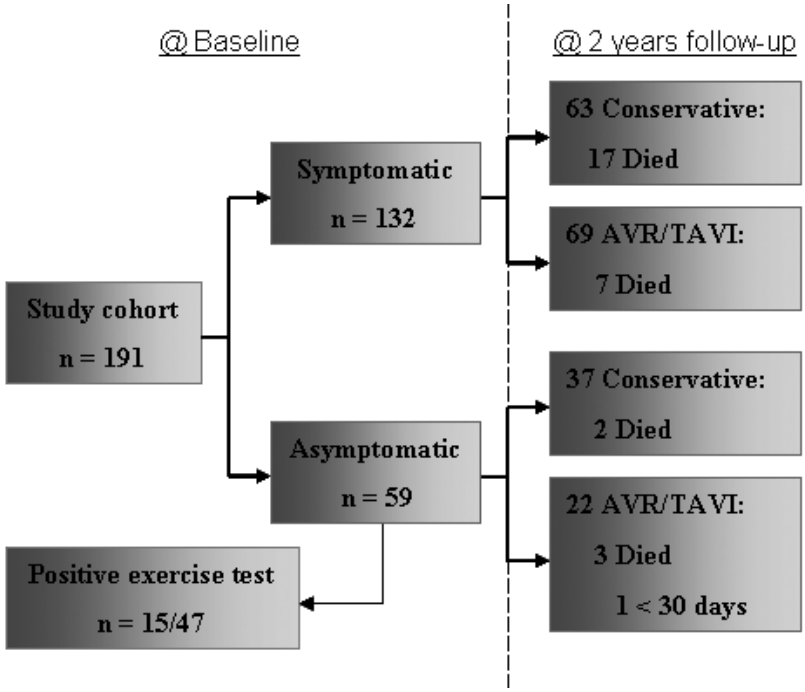

Figure 1: Flowchart of patient distribution during the study

Clinical course of symptomatic patients

Of the 132 symptomatic patients at baseline, 24 patients (18%) died during follow-up of whom 7 patients after AVR/TAVI due to: pneumonia (N=3), sudden unexpected unexplained death (N=1), subdural haematoma (N=1), mediastinitis (N=1), and unknown reason (N=1). Causes of death in the non-operated patients were congestive heart failure (N=11), sudden unexpected unexplained death (N=3), ruptured abdominal aortic aneurysm (N=1), pneumonia (N=1), and intestinal bleeding (N=1).

Sixty-four patients (48%) underwent AVR, 5 (4%) TAVI, and 63 (48%) were treated conservatively (Figure 1). Reasons for TAVI were informed patient preference in 1 patient (age 53 years) and inoperability due to comorbidities in the other 4 patients (age >70 years).

Overall cumulative survival at 2 years was 81.7% (73.9-87.3%). For patients receiving AVR/TAVI, 2-year cumulative survival was 89.8% (95% CI 79.8-95.0%) and for patients who were treated conservatively 72.6% (95% CI 59.7-82.0%) (Figure 2). Older patient age (HR 1.05; 95% CI 1.001-1.101; p=0.046), previous myocardial infarction (HR 2.75; 95% CI 1.14-6.60; p=0.024), and a higher baseline NT-proBNP (HR 1.002; 95% CI 1.001-1.003; p<0.001) were independently associated with increased mortality rates. Although in the univariable model AVR/TAVI was associated with decreased mortality rates (HR 0.30; 95% CI 0.13-0.67; p=0.004), in the multivariable model it was no longer a significant factor (HR 0.69; 95% CI 0.27-1.75; p=0.430).

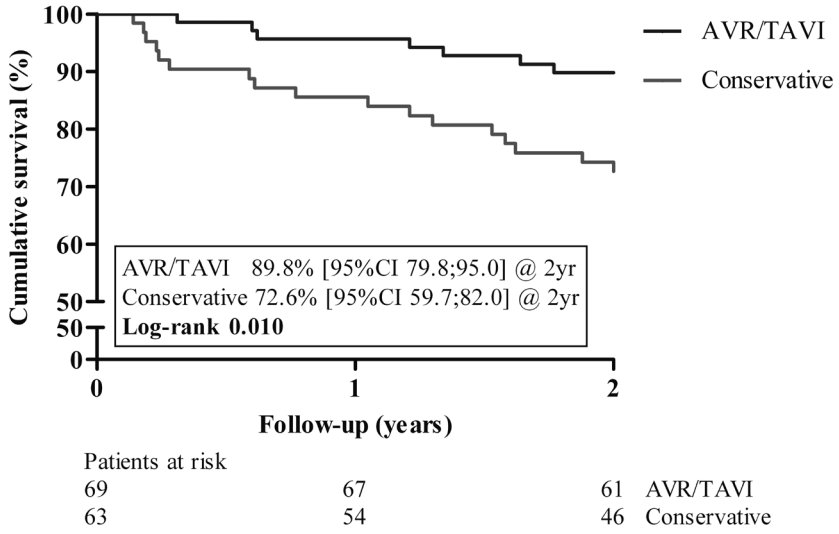

Figure 2: Patient survival for symptomatic patients differentiated by treatment strategy

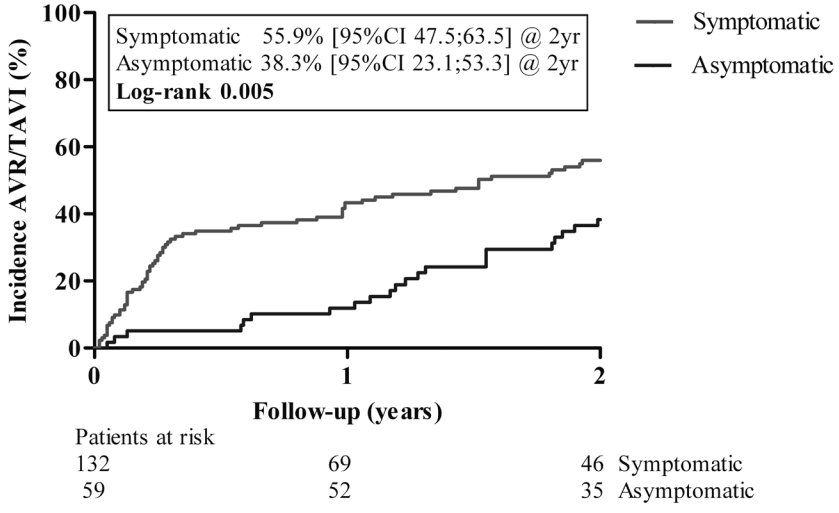

Figure 3: Cumulative incidence of AVR/TAVI differentiated by symptomatic status

Table 2 Logistic regression analysis for conservative treatment in symptomatic patients at baseline

	Odds ratio			
	Univariable	**p-value**	**Multivariable***	**P-value**
Age (yrs)	1.09 (1.05-1.14)	<0.001	1.10 (1.04-1.15)	0.001
PAD (%)	8.77 (2.42-31.25)	0.001	10.99 (2.32-52.63)	0.003
Vmax (m/s)	0.37 (0.22-0.63)	<0.001	0.46 (0.25-0.85)	0.013
Previous MI (%)	5.95 (1.87-18.87)	0.003	5.26 (1.30-21.28)	0.020
Hypertension (%)	3.21 (1.56-6.58)	0.002	2.72 (1.11-6.67)	0.029
MR (%)	2.93 (1.04-8.26)	0.042	0.64 (0.17-2.34)	0.495
Low flow/low gradient AS (%)**	3.23 (1.15-9.01)	0.025		
EuroSCORE (%)**	1.11 (1.04-1.19)	0.002		

PAD = peripheral arterial disease, Vmax = peak transaortic jet velocity, MI = myocardial infarction, MR = mitral regurgitation, AS = aortic valve stenosis, () = 95% confidence interval. Univariable p-values ≤ 0.05 were included in multivariable model. * Enter method. **Low flow/low gradient AS and EuroSCORE were highly correlated with ≥ 1 other co-variables and not entered in multivariable model.

Cumulative incidence of AVR/TAVI at 2 years was 55.9% (95% CI 47.5-63.5%) (Figure 3). Factors associated with a conservative treatment strategy are displayed in Table 2. Logistic EuroSCORE in symptomatic patients was 5.1% for those who underwent AVR/TAVI and 7.2% for symptomatic patients who were treated conservatively (p<0.001). Low-flow/low-gradient AS was more common in symptomatic patients who were conservatively treated compared to those who underwent AVR/TAVI (22% versus 9%; p=0.013).

Clinical course of asymptomatic patients

Of the 59 asymptomatic patients at baseline, 5 patients died during follow-up. Three patients died after AVR due to congestive heart failure (N=2: 1 < 30 days postoperative) and malignancy (N=1). One patient died of a pulmonary embolism and 1 patient died of unknown cause.

Forty patients (68%) became symptomatic, median time to symptom development was 13 months (range 1-24 months); 19 underwent AVR. In addition, 3 asymptomatic patients underwent AVR for rapidly progressing very severe AS (n=2) and 1 for subvalvular AS with a gradient of 61 mmHg.

Overall cumulative survival at 2 years was 91.5% (80.8-96.4%). Of the 19 patients who became symptomatic and underwent AVR/TAVI, 2-year cumulative survival was 89.5% (95% CI 64.1-97.3%). For the 21 patients who became symptomatic during follow-up but were treated conservatively, survival was 90.5% (95% CI 67.0-97.5%), for the 16 patients who remained asymptomatic and were treated conservatively 100%, and for the 3 patients who remained asymptomatic but nevertheless underwent AVR, survival was 66.7% (95% CI 5.4-94.5%).

Symptom development rate was faster in patients with a higher Vmax at baseline (HR 2.06; 95% CI 1.29-3.27; p=0.002), those with CAD (HR 4.73; 95% CI 1.20-18.73; p=0.027), and prior myocardial infarction (HR 3.47; 95% CI 1.14-10.54; p=0.028).

Cumulative incidence of AVR/TAVI at 2 years was 38.3% (95% CI 23.1-53.3%) (Figure 3).

DISCUSSION

This study reflects current clinical practice for adult patients with severe AS in several ways. First, a significant proportion of asymptomatic patients have a positive exercise test, underlining the importance of exercise testing in asymptomatic severe AS patients. Secondly, a considerable proportion of symptomatic patients do not undergo AVR/TAVI. In particular, elderly symptomatic patients with multiple comorbidities and a relatively low peak transaortic gradient are not likely to undergo AVR, and have a poor survival. Finally, the majority of asymptomatic patients become symptomatic over a 2-year period of time. This illustrates the progressive nature of severe AS and the need for careful and frequent 'watchful waiting' if a conservative strategy in the asymptomatic patients is pursued.

Challenges at diagnosis

A significant proportion of asymptomatic patients have a positive exercise test.[13,15] The gradual decrease in physical functioning in the elderly can be attributed to advanced age, multiple comorbidities or to the worsening of AS, which might sometimes be difficult to differentiate. If it is not clear whether a patient with severe AS is symptomatic, exercise testing and/or measuring BNP can play an important role.[16] Unfortunately, the European Heart Survey shows that exercise testing is underutilized and the true number of symptomatic patients may be much higher than is currently observed.[18]

Symptomatic patients

This study shows that symptomatic patients are usually older, more often female, and have more severe AS, more often concomitant mitral regurgitation, a higher NT-proBNP, and higher surgical risk scores compared to asymptomatic patients. Almost half of the symptomatic patients at study entry, as well as half of the asymptomatic patients who develop symptoms, are treated conservatively. Confirming previous reports, in particular older patients with a lower Vmax and multiple comorbidities are more likely to be treated conservatively.[8,12-13] Low-flow/low-gradient AS may possibly explain the association between lower Vmax and conservative treatment.[19] Although a higher EuroSCORE is associated with conservative treatment, the average EuroSCORE of conservatively treated patients in our study was only 7.2%. However, EuroSCORE and other operative risk stratification models

do not consider patient factors related to ageing, such as frailty, which become increasingly important in determining short- and long-term outcome with advancing age.[20-21] In this respect, there is a need for risk stratification models that better fit this elderly population.

We previously showed that important reasons for conservative treatment of symptomatic AS patients include misclassification of AS severity and symptoms, overestimation of operative risk, and patient preferences.[13] Given the survival benefit of TAVI for inoperable patients,[10] patients with severe symptomatic AS should be referred for multidisciplinary heart team discussion to assess individual feasibility of invasive treatment approaches.[22]

Although survival appears better in symptomatic patients who undergo AVR/TAVI versus those treated conservatively, this survival benefit disappears when corrected for patient age, NT-proBNP, and previous myocardial infarction. This suggests that patient survival is mainly driven by patient characteristics and to a lesser extent by treatment strategy. Our finding that NT-proBNP is associated with increased mortality confirms a previous report.[23] Although treatment strategy may not affect survival, it does influence quality of life.[24] In elderly patients with severe AS, quality of life should play a key role in optimizing treatment strategies. With the steadily increasing application of TAVI it is expected that more elderly symptomatic AS patients will receive invasive treatment, and hopefully an improved quality of life.

Asymptomatic patients

Asymptomatic severe AS has a progressive course, evidenced by the fact that no less than two-thirds of asymptomatic patients in our study became symptomatic within 2 years. This is higher compared to a previous report in which only one third became symptomatic and may be explained by the higher prevalence of classical risk factors, more left ventricular hypertrophy, and smaller aortic valve areas in our study patients.[25] AS severity was predictive of symptom development in our study, and underlines the importance of frequent monitoring of asymptomatic patients with more severe AS. Of all asymptomatic patients who became symptomatic, less than half undergo invasive treatment, while there are also a few patients who remain asymptomatic, but actually receive AVR. This illustrates the ongoing debate on the timing of AVR in asymptomatic patients with very severe AS.

Limitations

Some elderly patients refused participation which has undoubtedly resulted in a selection bias toward younger patients with milder symptoms and less comorbidity. The 15 patients who tested positive during exercise testing remained assigned to the asymptomatic group during data analysis. Exercise test results were sent to the treating cardiologists and may have influenced treatment strategy.

CONCLUSIONS

In contemporary practice in the Rotterdam Rijnmond area nearly half of the patients with symptomatic severe AS, in particular elderly patients with multiple comorbidities, do not undergo invasive treatment. In addition, our observation that more that two-thirds of asymptomatic patients develop symptoms during a two-year period underlines the progressive nature of severe aortic stenosis and the need for stringent and frequent watchful waiting.

A systematic evidence-based multidisciplinary team approach is recommended to optimize treatment selection for symptomatic patients with severe AS. There is an urgent need to optimize patient treatment strategy by taking into account clinical factors related to AS and comorbidities, costs and benefits of treatment strategies, patient preferences, quality of life, and anticipated life expectancy.

Acknowledgements

The authors would like to thank the patients and colleagues of the participating hospitals for their enthusiastic collaboration: Albert Schweitzer Hospital, Erasmus University Medical Center, Havenziekenhuis, Maasstad Hospital, Sint Franciscus Gasthuis, Vlietland Hospital, and IJsselland Hospital.

H. Heuvelman and M. van Geldorp contributed equally to this manuscript.

Conflict of interest

None declared.

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APPENDIX: DEFINITIONS

Body surface area: calculated with DuBois and DuBois formula.

Carotid disease: stenosis >50%, or previous or planned surgery.

Chronic obstructive pulmonary disease: diagnosis previously made by physician, or receiving bronchodilators.

Congestive heart failure: hospital stay with clinical sign(s) of congestive heart failure.

Coronary artery disease: >50% stenosis in at least one coronary artery proved by coronary angiography, or previously coronary artery bypass grafting.

Diabetes: diagnosis previously made by physician, or receiving blood glucose lowering medication.

Dyslipidemia: diagnosis previously made by physician, or receiving lipid lowering medication.

Hypertension: diagnosis previously made by physician, or known blood pressure of ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on at least two measurements, or receiving blood pressure lowering medication.

Ischemia: ST-depression ≥ 1 mm at J+60 ms in at least two electrocardiographic leads.

Left ventricular hypertrophy: S in V1 plus R in V5/V6 > 35 mm, R in V6 > R in V5, R in I and/or aVL > 12 mm on electrocardiography at J+60 ms.

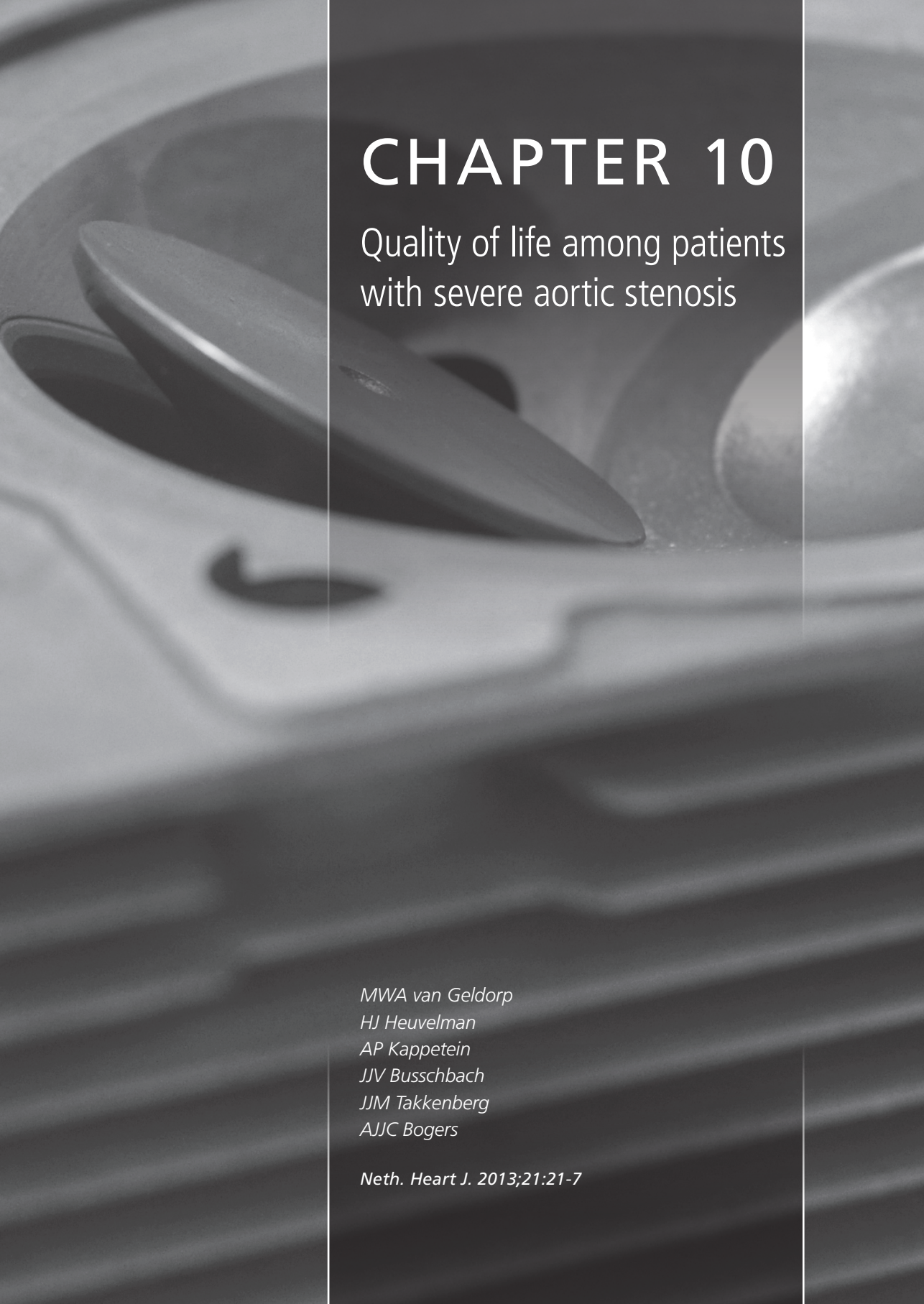
Myocardial infarction: diagnosis previously made by physician.

Peripheral arterial disease: claudication, or previous or planned surgery of the lower limbs.

Renal failure: diagnosis previously made by physician or creatinin ≥ 200 μmol/L.

Smoking: smoking cigarette or cigar during ≥ 5 years in the past.

Stroke: diagnosis 'transient ischemic attack' or 'cerebrovascular accident' previously made by physician, or neurological disease severely affecting ambulation or day-to-day functioning.



CHAPTER 10

Quality of life among patients with severe aortic stenosis

MWA van Geldorp
HJ Heuvelman
AP Kappetein
JJV Busschbach
JJM Takkenberg
AJJC Bogers

Neth. Heart J. 2013;21:21-7

ABSTRACT

Background

The disease burden of patients with severe aortic stenosis is not often explored, while the incidence is increasing and many patients who have an indication for aortic valve replacement are not referred for surgery. We studied the quality of life of 191 patients with severe aortic stenosis, hypothesizing that symptomatic patients have a far worse quality of life than the general population, which could enforce the indication for surgery.

Methods

The SF-36v2 Health Survey was completed by 191 consecutive patients with symptomatic or asymptomatic severe aortic stenosis.

Results

Asymptomatic patients (n=59) had health scores comparable to the general Dutch population but symptomatic patients (n=132) scored significantly lower across different age categories. Physical functioning, general health and vitality were impaired, as well as social functioning and emotional wellbeing. There was no relation between degree of stenosis and physical or mental health scores.

Conclusions

Both physical and emotional problems have major impact on normal daily life and social functioning of symptomatic patients with severe aortic stenosis, regardless of age. If the aortic stenosis is above the 'severe' threshold, the degree of stenosis does not predict disease burden. These results encourage to reconsider a conservative approach in symptomatic patients with severe aortic stenosis.

Using the SF-36v2 Health Survey together with this study, an individual patient's quality of life profile can be assessed and compared with the patient group or with the general population. This can assist in decision making for the individual patient.

INTRODUCTION

Degenerative aortic stenosis is the most common valvular heart disease in developed countries. The prevalence of aortic stenosis increases with age to about 8% in patients over 85 years of age.[1-2] With the aging of the general population, aortic stenosis represents a growing health problem.

Medical therapy does not slow the progression of aortic stenosis nor has it proven to reduce major adverse cardiac event rates.[3-5] The only effective treatment of severe stenosis is replacement of the aortic valve. Surgical techniques and postoperative care have improved over the years and even patients with advanced age and comorbidities can be operated relatively safely.[6-7] Recently transcatheter valve implantation has been introduced, which might be a treatment option in patients with high operative risk.[8]

The guidelines of both the American Heart Association / American College of Cardiology and the European Society of Cardiology on the management of patients with valvular heart disease, recommend prompt aortic valve replacement (AVR) once symptoms occur in patients with severe aortic stenosis.[9-10] Nonetheless, recent studies show that many patients who have a clear indication for aortic valve replacement are denied surgery.[11-13] Reasons to choose for conservative treatment are often advanced age, poor left ventricular function or otherwise high operative risk.[11-12] Moreover, in a significant number of cases the operative risk is overestimated or hemodynamic severity and symptomatic status are misclassified.[14]

Physicians frequently fail to recognize the functional disability of their patients, especially the full impact and resulting disease burden of certain symptoms are not always appreciated.[15] Classical symptoms of aortic stenosis are dyspnea, angina and syncope, and although the severity of symptoms can be used as a rough surrogate for the quality of life, the impact of symptoms on daily life remains unknown. The NYHA classification is a functional measurement of physical performance or pain, and roughly reflects one's *current* health status but certainly not one's *desired* health status or disease burden. Especially the social and emotional aspects are underreported and not taken into account in the New York Heart Association (NYHA) classification. An underestimation by the treating physician of the impact of symptoms on a patient's quality of life might be one of the reasons why so many symptomatic patients with severe aortic stenosis are not referred for surgery. Some literature is available on the functional status and quality of life of (elderly) patients *after* AVR,[16] but very little is known about the quality of life of patients in whom the decision to operate is yet to be considered. If these patients indeed present themselves with a low quality of life and better evidence about this burden of disease could be presented, one would have an additional argument to follow the clinical guidelines more strictly. The trade-off between anticipated operative risk and expected benefit for the patient after AVR should not solely be based on survival advantages, but also on gain in quality of life.

This paper presents the results of the Short Form-36v2™ Health Survey (SF-36v2™) in patients with severe aortic stenosis compared to the general population in order to investigate if, and to what extent, patients experience impairment of their daily life. We hypothesized that in symptomatic patients quality of life is far worse than in the general population, both in younger and elderly patients, which could enforce the indication for surgery. Further we hypothesized that echocardiographic parameters are not good indicators of disease burden, at least not in our patient group in whom the degree of stenosis is *severe* 'per inclusionem'.

METHODS

Patients

This study is part of a larger multi-center prospective cohort study in the Rotterdam area (the Netherlands) between July 2006 and April 2009 among patients with severe aortic stenosis. Patients were recruited from the echocardiography laboratories of the outpatient clinics of seven local hospitals if they had a severely stenosed native aortic valve and at least one of the following echocardiographic criteria were met: aortic valve area $\leq$ 1 cm^2, maximal trans aortic jet velocity $\geq$ 4 m/s, peak aortic gradient $\geq$ 64 mmHg, aortic valve / left ventricular outflow tract velocity time integral ratio $\geq$ 4. All consecutive patients who met these criteria and who agreed to participate were included, regardless of whether they were referred for surgery or not. The study protocol was approved by the institutional ethical committee (MEC 2006-066) and all patients provided written informed consent.

Methods

All consecutive patients who complied to the criteria mentioned above were contacted by telephone and invited for a personal baseline study visit. At this visit each patient's functional class was assessed by the principal investigator using the functional classification according to the New York Heart Association. Based on patient characteristics and medical history an anticipated operative mortality was calculated -for descriptive purposes only- using both the EuroSCORE model and the STS risk model (www.euroscore.org , www.sts.org). We also made an echocardiogram according to a specific study protocol, focused on the aortic valve.

The quality of life assessment was made by means of the SF-36v2™ Health Survey. According to the guidelines given by Ware et al. this questionnaire was sent to the patient and completed at home before each study-visit.[17] While establishing NYHA class, the investigator was blinded to the results of the health survey.

To allow for comparison of burden between our study patients and the general population we used the paper presented by Aaronson et al in 1998.[18] They took a sample of the

general Dutch population, consisting of 1742 people (56% male, mean age 47.6 years), subdivided in different age-categories and presented their quality of life outcomes as measured by the SF-36 Health Survey to generate normative data for use in the Netherlands. Our study population was therefore subdivided in the same age-categories.

The SF-36v2™ Health Survey is a modification of the original Short Form-36® Health Survey developed from the Medical Outcomes Study.[19] The questionnaire consists of 36 scale rated health-related questions, grouped into eight multi-item domains which are not disease-specific and which measure functioning in different aspects of daily life: *'Physical Functioning'*, physical health related to age- and role-specific activities termed *'Role-Physical'*, *'Bodily Pain'*, *'General Health'*, *'Vitality'*, *'Social Functioning'*, personal feelings of performance in age- and role-specific activities termed *'Role-Emotional'*, and *'Mental Health'*. The eight domains form two main components according to physical and mental health. The 'Physical Functioning', 'Role Physical' and 'Bodily Pain' domains contribute most to the scoring of the *'Physical Component Summary'* measure. The 'Mental Health', 'Role Emotional', and 'Social Functioning' domains contribute most to the scoring of the *'Mental Component Summary'* measure.

The raw SF-36 scores given by Aaronson et al are linearly and step-wise converted to a norm-based score from 0-100 in which 50 represents the mean score of the general population in the United States and 10 points on the scale correspond to 1 standard deviation.[18] When comparing group-data to the norm, a difference of more than 3 points on this norm-based scale (corresponding to a difference of 0.3 SD) indicates a significant difference from normal, while 8 points or more indicate a large difference [17, 20]. A detailed explanation regarding data collection, scoring, interpretation and validation of the SF-36v2™ is given by Ware et al.[17]

Statistical analyses

For the statistical analyses SPSS 13.0.1 software was used (SPSS Inc. 2001). Continuous variables are displayed as means ± standard deviation if normally distributed, skewed distributed variables as median with interquartile range. Categorical variables are displayed as proportions. One-sided Student's T tests were used for comparisons of health scores of patient groups to the general population. A p-value below 0.05 was considered significant.

RESULTS

Between July 2006 and April 2009 a total of 459 patients with severe aortic stenosis were identified, informed by the principal investigator and invited to participate. 268 patients (mean age 76±14 years) could not be examined because they declined participation (n=185), had an operation scheduled (n=65) or died (n=18) before they could participate

in the study. Reasons to refuse participation were most often high age and severe disability resulting in personal logistic problems or perceived high burden (data not shown).

One-hundred-ninety-one patients (mean age 70.6 years) agreed to participate. E-Table 1 shows their characteristics. Fifty-nine patients were asymptomatic, 73 were in NYHA class II, 49 in NYHA class III and 10 in NYHA class IV.

E-Table 1: Patient characteristics

Patient characteristics	**Total patient group**	**Symptomatic patients**
	N=191	N=132
Age (median, interquartile range, in years)	72.6 (63.7-78.6)	74.0 (64.4-79.2)
Age category		
≤40	4 (2%)	3 (2%)
41-60	28 (15%)	18 (14%)
61-70	44 (23%)	25 (19%)
>70	115 (60%)	86 (65%)
Male sex	119 (62%)	75 (57%)
NYHA class		
I	59 (31%)	Not applicable
II	73 (38%)	73 (55%)
III	49 (26%)	49 (37%)
IV	10 (5%)	10 (8%)
Sort of symptom (%)		
Only dyspnea		46.2
Only angina		4.5
Only syncope		3.8
Combination		45.5
Cardiovascular history (%)		
Diabetes Mellitus	20	19
Hypertension	52	54
Dyslipidaemia	49	49
Chronic obstructive pulmonary disease	17	20
Renal failure	7	9
Peripheral vascular disease	13	15
Cerebro vascular accident (residual neurological deficit)	19	18
Previous coronary artery bypass grafting	6	8
Logistic EuroSCORE (median, interquartile range)	5.4 (3.1-8.2)	6.2 (3.9-9.6)
STS score (median, interquartile range)	4.5 (2.8-7.6)	5.1 (3.3-8.0)

Figures 1a, b and c display the results for the symptomatic patients versus the general Dutch population in three age groups: age 41 to 60 years (n=18); age 61 to 70 years (n=25); age over 70 years (n=86). In each age category almost all health domains were scored significantly lower than the general Dutch population except 'Bodily Pain'. The 'Mental Component Summary' in the younger patient group (age 41-60 years) was also comparable to the general population. More importantly, in most health domains the differences compared to the general population were considerable especially in the 61-70 years age group. E-Table 2 gives the exact norm-based scores and standard deviations of each group compared to the general Dutch population.

Figure 2 shows that quality of life outcomes in all domains are related to the NYHA classification. *Asymptomatic* patients showed a trend towards high scores in most domains compared to the general population, certainly given the higher mean age of the patients (71 vs 47 yrs). Patients in NYHA class II had lower scores on the 'Physical Function', 'Role Physical', 'General Health' and 'Role Emotional' scales. Patients in NYHA class III and IV had lower scores on all scales, and the differences compared with the general population were considerable.

Echocardiographic measurements indicating stenosis severity –such as aortic valve area and maximal aortic jet velocity- were not related to either physical or mental health scores (data not shown).

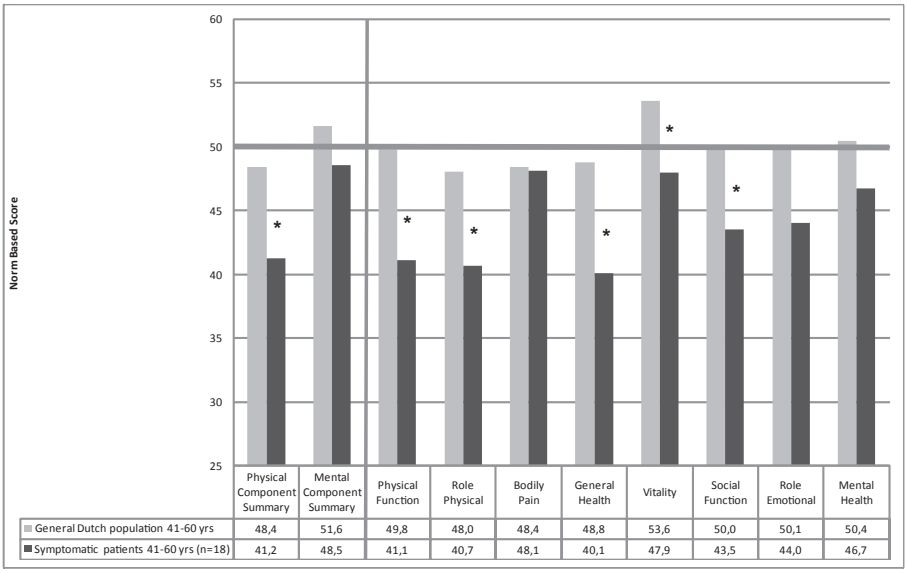
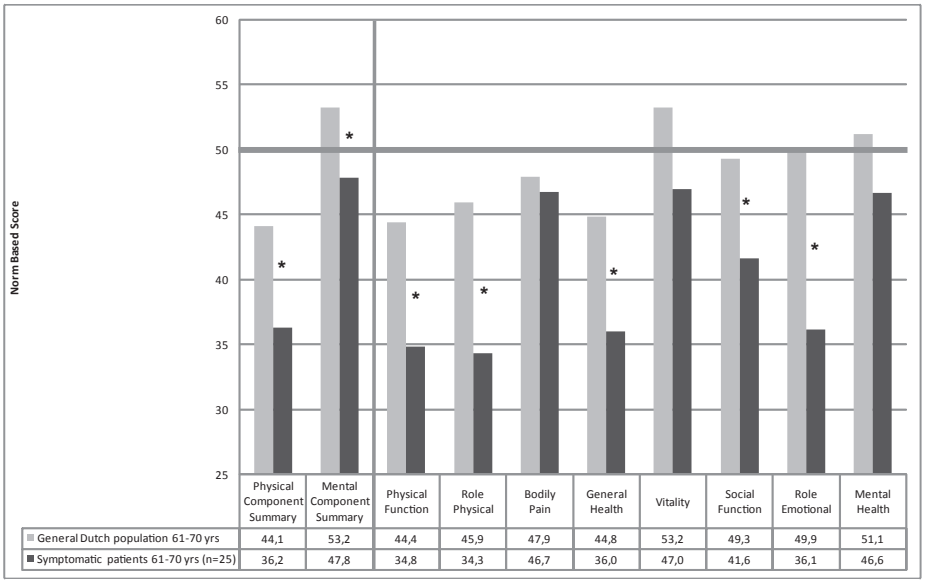


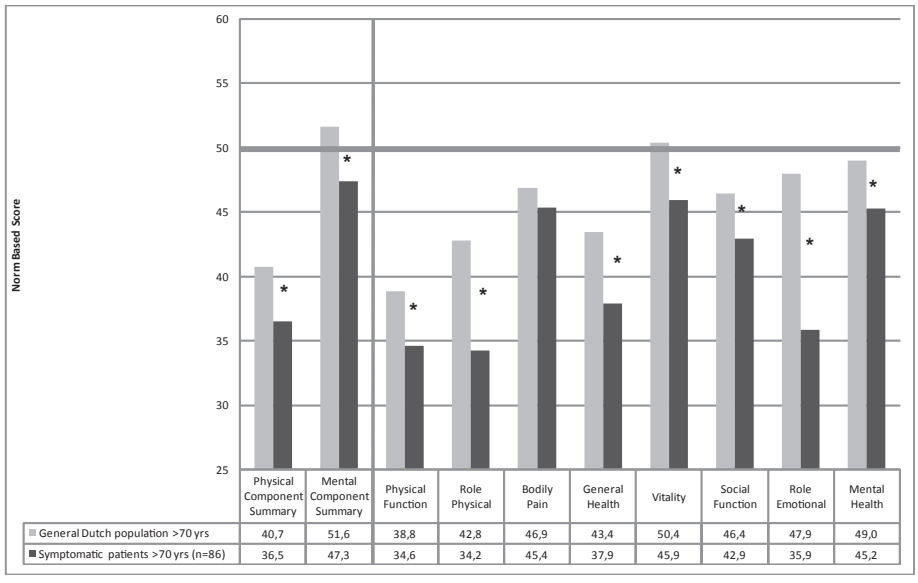
Figure 1a: Quality of life of symptomatic patients with severe aortic stenosis (AS) aged 41-60 years (n=18) versus the general Dutch population aged 41-60 years.
* p<0.05



	Physical Component Summary	Mental Component Summary	Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health
General Dutch population 61-70 yrs	44,1	53,2	44,4	45,9	47,9	44,8	53,2	49,3	49,9	51,1
Symptomatic patients 61-70 yrs (n=25)	36,2	47,8	34,8	34,3	46,7	36,0	47,0	41,6	36,1	46,6

* p< 0.05

Figure 1b: Quality of life of symptomatic patients with severe aortic stenosis (AS) aged 61-70 years (n=25) versus the general Dutch population aged 61-70 years.
* p<0.05



	Physical Component Summary	Mental Component Summary	Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health
General Dutch population >70 yrs	40,7	51,6	38,8	42,8	46,9	43,4	50,4	46,4	47,9	49,0
Symptomatic patients >70 yrs (n=86)	36,5	47,3	34,6	34,2	45,4	37,9	45,9	42,9	35,9	45,2

* p< 0.05

Figure 1c: Quality of life of symptomatic patients with severe aortic stenosis (AS) aged >70 years (n=86) versus the general Dutch population aged >70 years.
* p<0.05

E-Table 2: Exact norm-based scores of symptomatic patients with severe aortic stenosis and the general Dutch population

Health Domain	Norm-Based Score Symptomatic patients with severe aortic stenosis			Norm-Based Score General Dutch population *		
	41-60 yrs n=18	61-70 yrs n=25	>70 yrs n=86	41-60 yrs	61-70 yrs	>70 yrs
Physical Component Summary	41.2 ± 9.9	36.2 ± 9.7	36.5 ± 9.8	48.4	44.1	40.7
Mental Component Summary	48.5 ± 9.9	47.8 ± 10.2	47.3 ± 12.7	51.6	53.2	51.6
Physical Function	41.1 ± 10.1	34.8 ± 10.1	34.6 ± 11.6	49.8	44.4	38.8
Role Physical	40.7 ± 10.5	34.3 ± 10.9	34.2 ± 11.1	48.0	45.9	42.8
Bodily Pain	48.1 ± 10.8	46.7 ± 12.3	45.4 ± 12.3	48.4	47.9	46.9
General Health	40.1 ± 8.1	36.0 ± 8.6	37.9 ± 9.0	48.8	44.8	43.4
Vitality	47.9 ± 10.2	47.0 ± 9.7	45.9 ± 12.1	53.6	53.2	50.4
Social Function	43.5 ± 10.6	41.6 ± 12.1	42.9 ± 13.7	50.0	49.3	46.4
Role Emotional	44.0 ± 13.9	36.1 ± 15.0	35.9 ± 15.3	50.1	49.9	47.9
Mental Health	46.7 ± 9.8	46.6 ± 11.1	45.2 ± 14.4	50.4	51.1	49.0

* Norm-Based Score calculated based on the paper by Aaronson et al [18]

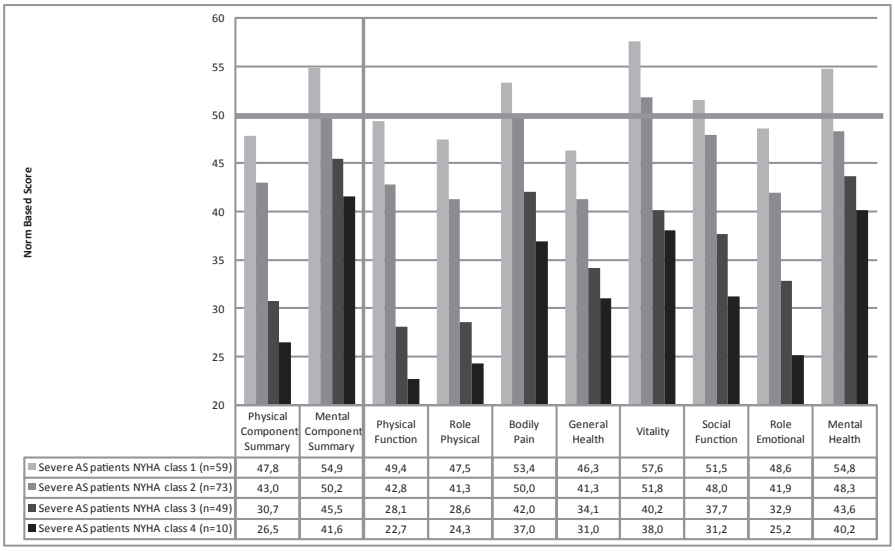


Figure 2: Quality of life of patients with severe aortic stenosis (AS) according to symptomatic status.

DISCUSSION

Interpretation and discussion of main results

This study confirms the obvious finding that the quality of life decreases with increasing age both in the general population and in the symptomatic severe AS patients (Figures 1a, b and c). However, the key point is that the differences in quality of life between the general population and the symptomatic patients are large and remain significant for most health domains across all three age groups we studied. This indicates that patients in each age category suffer equally from severely impaired quality of life.

While angina is one of the classical symptoms of aortic stenosis, it is notable that 'Bodily Pain' was scored almost normal, suggesting that pain itself only plays a modest role. This is confirmed by the anamnesis in which over 90% of the symptomatic patients complained of dyspnea or a combination of dyspnea and angina or syncope (Table 1). The low scores on the 'Role Physical' domain indicate that patients do have severe physical constraints by dyspnea and that this affects daily life to great extent.

Not only the physical domains but also the mental health scores show large differences compared to normal. Figure 1b and 1c show that among patients aged over 60 years, the largest difference with the general population is observed in the 'Role Emotional' scale, meaning patients suffer from anxiety or a depressed state of mind which affects daily activities. Also 'Social Function' is lower than normal. Apparently complaints are hampering patients in their social contacts e.g. visiting friends and relatives. Finally, the low 'Vitality' and 'General Health' scores indicate patients have lack of energy and a negative general view on their health.

There was no relation between stenosis severity and physical or mental quality of life in our patient cohort. Thus, whenever the aortic stenosis is above the 'severe' threshold, "objective" measures of aortic valve function do not correlate to functional status: the degree of stenosis does not predict disease burden. This is important to realize and relevant for clinical practice. However, we only studied the 'severe' category, therefore a relation between disease burden and stenosis severity in the whole patient population with either mild, moderate or severe aortic stenosis certainly cannot be ruled out.

We did demonstrate that scores of the SF-36v2™ correspond well with the severity of symptoms according to NYHA classification (Figure 2). Asymptomatic patients don't seem to have a worse health perception than the general population, especially on the mental part of the survey. Importantly, even patients in NYHA class II -thus having only 'mild' symptoms- experience clearly lower quality of life than asymptomatic patients or the general population. With the increase of the severity of the symptoms, scores are lower on both the physical and mental part of the survey. This is what one would expect and indicates that the SF-36v2™ is a valid measure of the quality of life in this patient population.

Policy implication

As stated in the introduction, both American and European guidelines recommend AVR in symptomatic patients with severe aortic stenosis.[9-10] Even elderly patients can be operated with acceptable risks of morbidity and mortality nowadays. They can expect improvement in functional class and prolonged survival compared to non-operated patients, and AVR is cost-effective.[6-7, 16, 21-23] Still, 30 to 60% of (elderly) symptomatic patients with severe aortic stenosis do not undergo AVR.[11, 21, 24-25] Exercise testing is reported to elicit symptoms in approximately 37% of all cardiac patients who were previously regarded 'asymptomatic'.[26] However, although earlier advocated in asymptomatic aortic stenosis patients, exercise testing remains highly underused and shifted from a class 2a to a 2b recommendation in the ACC/AHA guidelines.[9, 27] Therefore the proportion of patients who would deserve operative treatment could even be underestimated.

There is a large variability between different risk models in cardiac surgery, and the one most commonly used (EuroSCORE) seems to overestimate the actual operative risk for AVR most.[28] Perhaps this adds to the large variance in treatment advise that exists among cardiologists already found by Bouma et al.[12] Previously we reported that part of the non-referral observed in current clinical practice is caused by patient refusal, by an overestimation of the anticipated operative risk and by misclassification of hemodynamic severity and symptomatic status.[14] Years ago it has already been shown that doctors have difficulty to recognize functional disability in patients[15] -not so much the symptoms themselves- and one could speculate this is even more true for emotional impairment. Although we are unable to draw any conclusions based on the results of the current study, one could hypothesize that underestimating the *impact* of symptoms or NYHA-class represents another cause to underestimate the need for treatment. Given the highly conservative approach of many cardiologists concerning symptomatic severe aortic stenosis, we feel that this burden should receive more attention.

Quality of life is of utmost importance for a patient, yet there is hardly any literature on this subject in patients with severe aortic stenosis. Some retrospective studies report on functional status and quality of life in patients *after* AVR: quality of life is supposed to be comparable to the normal population, and the major part of long-term survivors reported to be happy with the decision to be operated upon.[7, 16, 29] In such studies all patients that did not survive on the long term cannot be included, while these are the most likely to have had a low quality of life before their death. Furthermore, these studies did not study quality of life in patients with aortic stenosis, but quality of life in patients with aortic stenosis *who were referred (selected) for surgery*. In our study we focussed not on the quality of life of –AVR selected- patients *before* or *after* AVR, but on the quality of life when the decision to operate or not is yet to be made. Therefore our results not only reflect the physical and mental state of the total patient group, but can also be used for decision making in the individual patient. A patient could fill in a questionnaire -online or on paper- prior to his or

hers doctor visit (www.qualitymetric.com). The cardiologist could then compare the results of the patient with the results of the general population, or with the results of similar patients (Figure 2a,b,c), and use this information in deciding whether or not to send the patient for AVR.

Limitations

The study group described in this paper is a selected cohort. Although enrolment from the outpatient cardiology echocardiography departments was encouraged, some patients may not have been identified. We attempted to enrol every patient but were not able to do so because a substantial number of patients declined participation. Mostly these patients were the elderly, or the more sick patients for whom an extra study-trip to the hospital was unfeasible. Therefore it is likely that we even underestimated the magnitude of quality of life impairment in the total patient population with symptomatic severe aortic stenosis and are only able to present the tip of the iceberg.

A limitation of using the SF-36v2™ survey could be the number of questions. A minority of patients has difficulty answering the questions, mostly because they are somewhat time-consuming, and sometimes because the questions are regarded as 'annoying' or 'confronting'. Other useful -but often less specific- surveys have been developed, such as the EuroQOL survey, which contains only five questions and is therefore easier and faster to answer for the patient, and easier to analyze and interpret for the doctor (www.euroqol.org).

CONCLUSIONS

Our results encourage to reconsider a conservative approach in symptomatic patients with severe aortic stenosis. If the aortic stenosis is above the 'severe' threshold, the degree of stenosis does not predict disease burden. This study provides a quantification of this burden, especially in symptomatic patients with severe aortic stenosis: even minor symptoms have major impact on patient well-being and result in a strongly impaired quality of life compared to the general population. Not only physical complaints affect daily life to a great extent, patients also suffer from emotional problems hampering normal daily activities and social functioning. When considering to send a patient for aortic valve replacement or to treat conservatively, one should not only consider the operative risks and the lifespan gained after AVR, but also the current state of the patient including his or hers physical and mental quality of life. A good way of doing this is by standardized surveys like the SF-36v2™. Using the SF-36v2™ Health Survey together with this study, an individual patient's quality of life profile can be assessed and compared with the patient group or with the general population. This can assist in decision making for the individual patient.

Disclosures

None of the authors has any competing interests.

Acknowledgements

The authors would like to thank the patients, cardiologists, echo laboratory workers and secretaries of the participating hospitals for their kind cooperation.

Participating hospitals are:

- Havenziekenhuis, Rotterdam
- St. Franciscus Gasthuis, Rotterdam
- IJsselland Ziekenhuis, Capelle aan den IJssel
- Vlietland Ziekenhuis, Vlaardingen
- Albert Schweitzer Ziekenhuis, Dordrecht
- Medisch Centrum Rijnmond Zuid, Rotterdam
- Erasmus University Medical Center, Rotterdam

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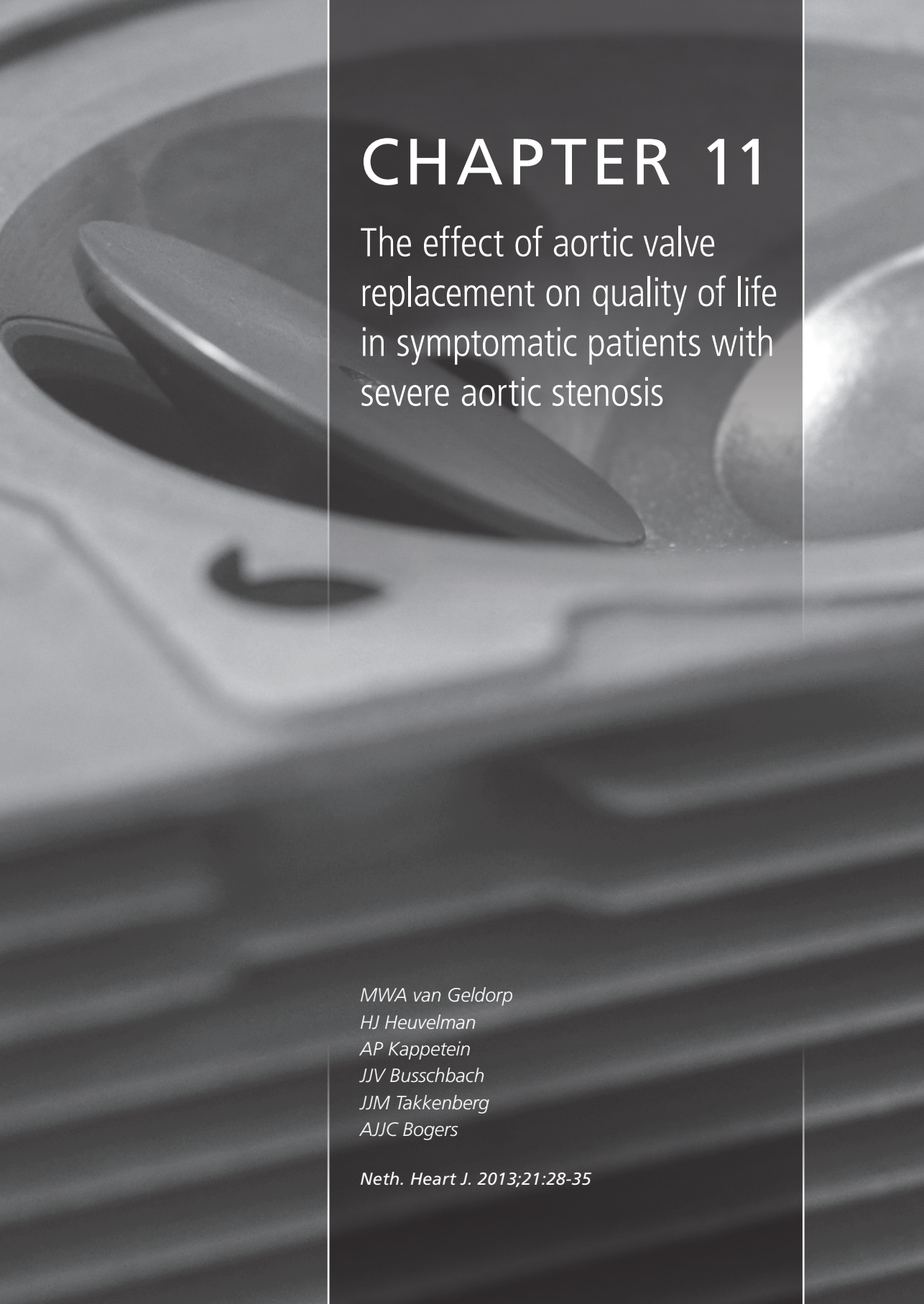


CHAPTER 11

The effect of aortic valve replacement on quality of life in symptomatic patients with severe aortic stenosis

MWA van Geldorp
HJ Heuvelman
AP Kappetein
JJV Busschbach
JJM Takkenberg
AJJC Bogers

Neth. Heart J. 2013;21:28-35

ABSTRACT

Background

Although symptomatic patients with severe aortic stenosis have a high disease burden and guidelines recommend aortic valve replacement, many are treated conservatively. This study describes to what extent quality of life is changed by AVR relative to conservative treatment.

Methods

This observational study followed 132 symptomatic patients who were subjected to a SF-36v2™ Health Survey. If patients were treated medically the survey was repeated 6, 12 and 24 months after baseline; if they underwent aortic valve replacement, the survey was repeated 12 months after surgery.

Results

At baseline 84 patients were treated conservatively, 48 were referred for AVR. In the conservative group 15 patients died during a mean follow-up of 18 months (Kaplan Meier survival was 85% and 72% at 1 and 2 years respectively) and 22 patients crossed over to the AVR group. Of the resulting 70 patients in the AVR group 3 patients died during a mean follow-up 11 months (survival 95% at 1 year). Physical functioning, vitality and general health improved significantly one year after AVR and emotional role showed a tendency toward improvement. In conservatively treated patients physical quality of life deteriorated significantly over time while general health, vitality and social functioning showed a declining trend. Mental health remained stable in both groups.

Conclusions

AVR improves physical quality of life and vitality in patients with symptomatic severe AS, most evident in the physical health components, but also present in general health and vitality. Besides having a low life expectancy, conservatively treated patients experience deterioration of physical quality of life.

INTRODUCTION

Degenerative aortic stenosis (AS) is the most common valvular heart disease in developed countries. Aortic valve calcification increases with age and the prevalence of aortic stenosis increases concomitantly. Because the Western population continues to age, aortic stenosis constitutes a growing health burden.[1]

The classical and most frequent symptoms of aortic stenosis are angina, syncope and dyspnea. Prognosis of symptomatic patients is poor when treated conservatively, and according to the ACC/AHA and ESC guidelines patients should be referred for aortic valve replacement (AVR) without delay when they become symptomatic.[2-3] However, in daily practice many symptomatic patients with severe aortic stenosis do not receive operative treatment.[4-6] Underestimation of disease burden and the effect of AVR on quality of life could in part be responsible for the observed under-treatment, yet there is hardly any literature on this subject. Therefore it is important to investigate the quality of life of patients with severe AS and the outcome after surgical versus conservative treatment.

Previously we compared the quality of life of symptomatic patients with severe AS to the general age-matched population and found it is much lower: even mild symptoms result in both physical and emotional problems which have a major impact on normal daily life and social functioning.[7] The objective of our current study is to investigate if -and to what extent- AVR improves this disease burden, and to compare these outcomes with the quality of life of the conservatively treated patients during follow-up. This is a novel approach compared to other studies, which only describe subgroups of patients selected for surgery.[8-10]

METHODS

Patients

Patients with severe aortic stenosis were recruited from the outpatient clinics of 7 hospitals in the Rotterdam region in the Netherlands from July 2006 until April 2009. Patients were included if one of the following echocardiographic criteria for severe aortic stenosis were met: aortic valve area ≤ 1 cm^2, maximal trans aortic jet velocity ≥ 4 m/s, peak aortic gradient ≥ 64 mmHg, aortic valve / left ventricular outflow tract velocity time integral ratio ≥ 4.

The current study is part of a larger prospective observational cohort study in which patients who fulfilled the described criteria were invited to our hospital for several clinical investigations and a quality of life assessment. Patients were categorized according to New York Heart Association (NYHA) classification by the investigators and relevant medical history was documented. Based on patient characteristics and medical history -and for descriptive purposes only- an anticipated operative mortality was calculated using the

EuroSCORE model (www.euroscore.org). This paper focuses on the on the quality of life, measured by the SF-36v2™ Health Survey at different points in time, of the symptomatic subgroup of the described population with severe aortic stenosis.

After the baseline measurements, patients were followed to register treatment selection, major adverse cardiac events and survival. Since the design of this study was strictly observational, the investigators did not interfere with treatment selection. For observational and analysis purposes we divided patients into 2 groups: an AVR group and a conservatively/medically treated group. Unless they had AVR or died in the meanwhile, medically treated patients were re-invited to our hospital after 6, 12 and 24 months to be examined again. Patients who were referred for AVR (by their treating cardiologist) were re-invited only once, namely one year after AVR. Patients who were initially treated conservatively but referred for AVR later on, were accounted for in the conservative group and crossed over to the AVR group at the time of operation (and therefore accounted for in both groups). Because the distinction between both groups is based on selection, we deliberately chose not to compare baseline characteristics or survival between both groups and therefore no p-values or log-rank tests are given. In the patients who crossed to the AVR group, all measurements of the last 'conservative' visit (both of the SF-36v2™ Health Survey and echocardiography data) were carried forward as 'pre-AVR measurements'. By doing so all AVR patients had recent pre-operative data, instead of data collected at the start of the study. Follow-up of the entire patient cohort continued until May 1st 2011.

AVR patients generally had conventional AVR through a median sternotomy using extra corporal circulation, cold crystalloid cardioplegia and mild hypothermia. A minority of AVR patients had a percutaneous valve implantation, using the retrograde transfemoral approach and a Core Valve® device. Transapical valve implantations were performed through a small intercostal incision. All procedures were performed electively.

The study protocol was approved by the institutional ethical committee (MEC 2006-066) and all patients provided written informed consent.

Quality of life measurement

The SF-36v2™ Health Survey is a validated, well accepted and widely used questionnaire originating from the Medical Outcomes Study.[11] The survey consists of 36 multiple-choice health-related questions, grouped into eight multi-item domains measuring quality in different aspects of daily life: *'Physical Functioning'*, physical health related to age- and role-specific activities termed *'Role-Physical'*, *'Bodily Pain'*, *'General Health'*, *'Vitality'*, *'Social Functioning'*, personal feelings of performance in age- and role-specific activities termed *'Role-Emotional'*, and *'Mental Health'*.

The eight domains form two main components according to physical and mental health. The *'Physical Functioning'*, *'Role Physical'* and *'Bodily Pain'* domains contribute most to the scoring of the 'Physical Component Summary' measure, but also a little -negatively- to

the 'Mental Component Summary'. The *'Mental Health'*, *'Role Emotional'*, and *'Social Functioning'* domains contribute most to the scoring of the 'Mental Component Summary' measure, and a little –also negatively- to the 'Physical Component Summary'.

Comparing quality of life results of (long-term) survivors with the results of all patients alive at baseline, constitutes a bias since a selection of the healthier patients takes place over time. Therefore patients who died or denied participation in a certain time-interval –either in the AVR or in the conservative group- were withdrawn for comparisons of health survey results over that time-interval.

Statistics

For the statistical analyses SPSS 17.0 software was used (SPSS Inc.). Continuous variables with a normal distribution are displayed as means ± standard deviation. If data were not normally distributed the median and interquartile range are given. Categorical variables are displayed as percentages.

Raw SF-36v2™ scores are linearly and step-wise converted to a norm-based score from 0-100 in which 50 represents the mean score of the general population in the United States and 10 points on the scale correspond to 1 standard deviation. When comparing group-data to the norm or to other groups, a difference of more than 3 points on this norm-based scale (corresponding to a difference of 0.3 SD) is generally considered significant, while 8 points or more indicate the difference between the groups is large.[12-13] A detailed explanation regarding data collection, scoring, interpretation and validation of the SF-36v2™ is given by Ware et al.[12] Previously Dutch norms have been established by Aaronson et al.[14] by using the first version of the SF-36 Health Survey. Their scores are raw SF-36 scores and have been transformed to norm-based-scores to allow for useful comparison in this paper.

Paired t-test analyses were used to compare quality of life outcomes between different points in time within each group. P values lower than 0.05 were considered statistically significant.

Survival was explored using Kaplan Meier analysis in patients who had AVR during follow-up and separately in conservatively treated patients.

RESULTS

Details on categorisation of patients and follow-up are displayed in the flow chart (Figure 1). Of all 191 participating patients with severe aortic stenosis, the symptomatic patients (n=132) formed the current study group. At baseline, 84 of them were treated conservatively and 48 were referred for AVR. Their baseline characteristics are given in Table 1.

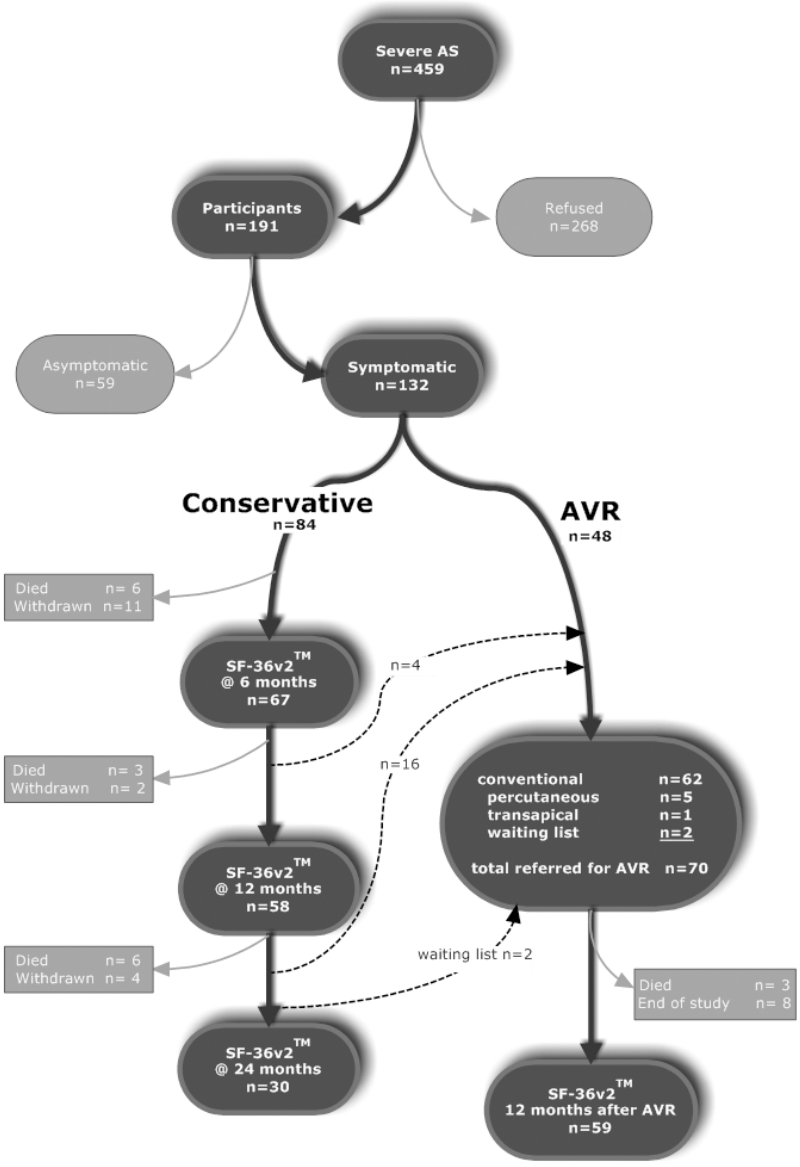


Figure 1: Flow Chart

Table 1: Patient characteristics

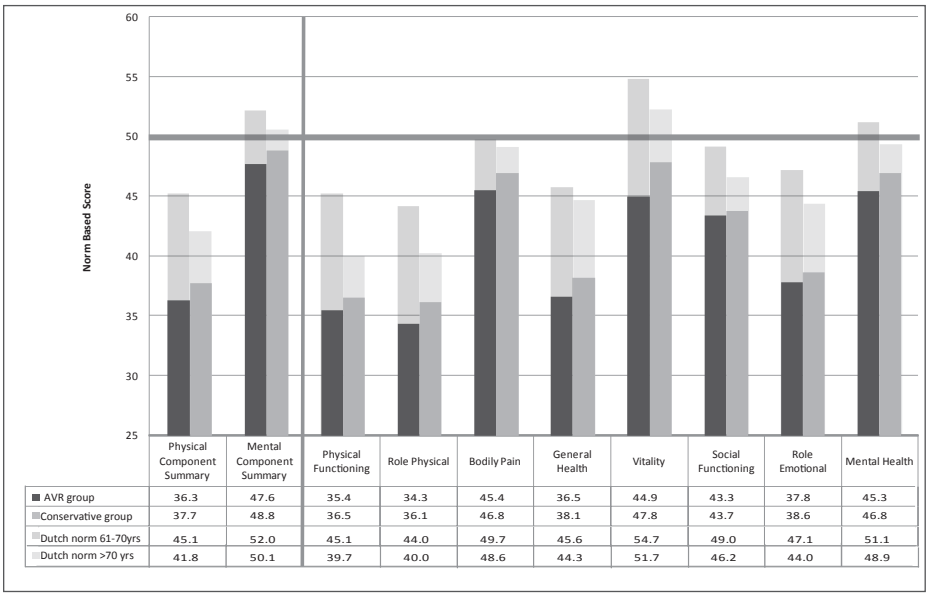
	Conservative (n=84)	AVR (n=70)
Mean follow-up (months)	19.6 (± 10.1)	22.2 (± 10.7)
Mean age (years)	73.2 (± 10.9)	67.8 (± 12.2)
Male gender (%)	61	49
NYHA class (%)		
II	62	45
III	32	45
IV	6	9
Mean NYHA class	2.4 (± 0.6)	2.6 (± 0.7)
Logistic EuroSCORE	8.2 (± 6.3)	6.0 (± 6.0)
Echocardiography		
Vmax (m/s)	4.1 (± 0.7)	4.6 (± 0.8)
Peak gradient (mmHg)	68.0 (± 23.7)	88.3 (± 32.5)
Mean gradient (mmHg)	38.5 (± 13.6)	50.8 (± 20.1)
AVA (cm2)	0.76 (± 0.25)	0.74 (± 0.31)
AV/LVOT VTI ratio	4.5 (± 1.4)	4.7 (± 1.7)
EF (%)	52.2 (± 12.8)	48.3 (± 11.5)
Medical history (%)		
Smoking (current or past)	60.0	53.0
DM	18.8	15.1
Renal failure / dialysis	11.8 / 2.4	6.1 / 0
Hypertension	60.0	43.9
Dyslipidaemia	51.8	48.5
COPD	20.0	19.7
CVA (infarction/bleeding)	4.7	7.6
OHO in past	7.1	6.1

The baseline quality of life in the AVR group was slightly worse over all health domains compared to the baseline of the conservative group (Figure 2). Figure 2 also shows that quality of life in both groups was much worse over all health domains compared to the general age-matched Dutch population, except for 'Bodily pain' (data presented previously [7]).

Conservative group

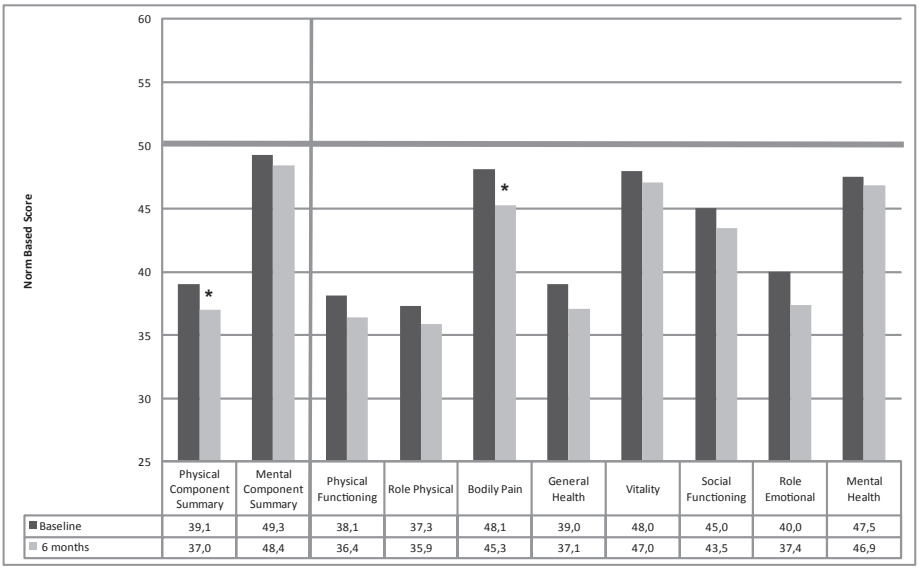
Of the study cohort, 84 symptomatic patients were initially treated medically. In this group 15 patients died during a mean follow-up of 18 months, of whom nine died within one year. A total of 22 patients were referred for AVR after initial conservative treatment, therefore these patients crossed over to the AVR group (Figure 1). Sixty-seven patients completed the SF-36v2™ Health Survey after 6 months, 58 after one year and 30 after two years of conservative treatment. Kaplan-Meier survival in the conservative group was 85% at one year and 72% at two years.

In medically treated patients who survived and were able to complete the follow-up questionnaires, the quality of life remained virtually unchanged across all health domains



	Physical Component Summary	Mental Component Summary	Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health
AVR group	36.3	47.6	35.4	34.3	45.4	36.5	44.9	43.3	37.8	45.3
Conservative group	37.7	48.8	36.5	36.1	46.8	38.1	47.8	43.7	38.6	46.8
Dutch norm 61-70yrs	45.1	52.0	45.1	44.0	49.7	45.6	54.7	49.0	47.1	51.1
Dutch norm >70 yrs	41.8	50.1	39.7	40.0	48.6	44.3	51.7	46.2	44.0	48.9

Figure 2: Baseline QoL vs general population



	Physical Component Summary	Mental Component Summary	Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health
Baseline	39,1	49,3	38,1	37,3	48,1	39,0	48,0	45,0	40,0	47,5
6 months	37,0	48,4	36,4	35,9	45,3	37,1	47,0	43,5	37,4	46,9

* p< 0.05

Figure 3a: QOL of conservative group, baseline vs 6 months

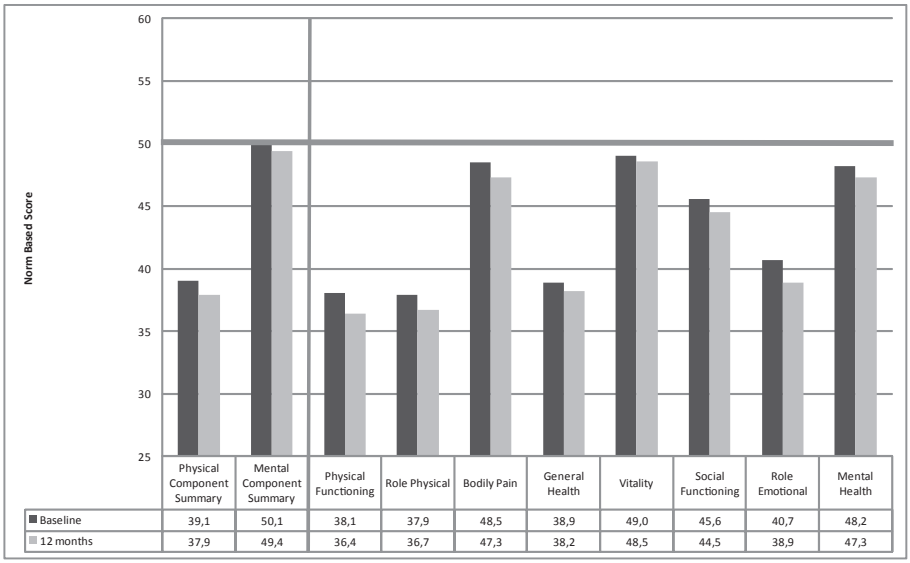


Figure 3b: QOL of conservative group, baseline vs 12 months

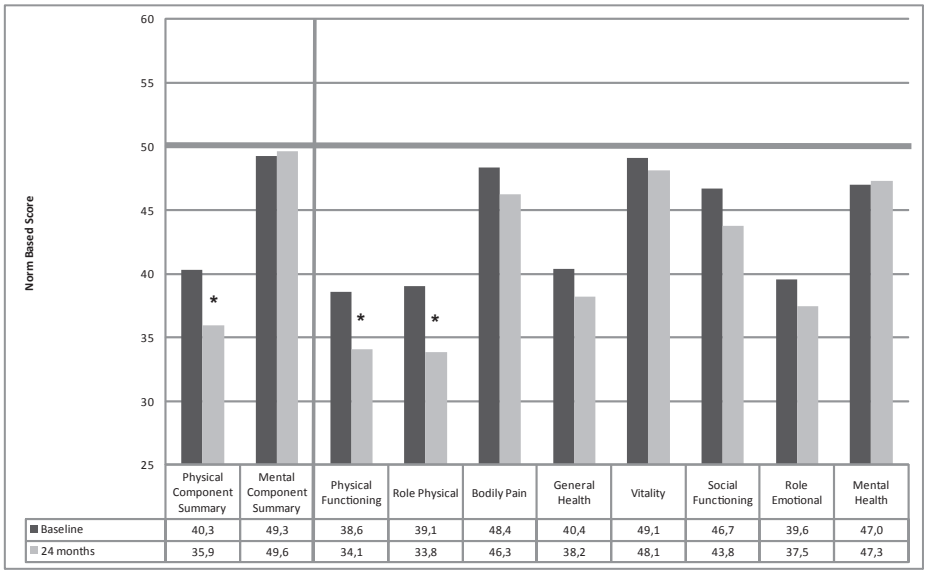


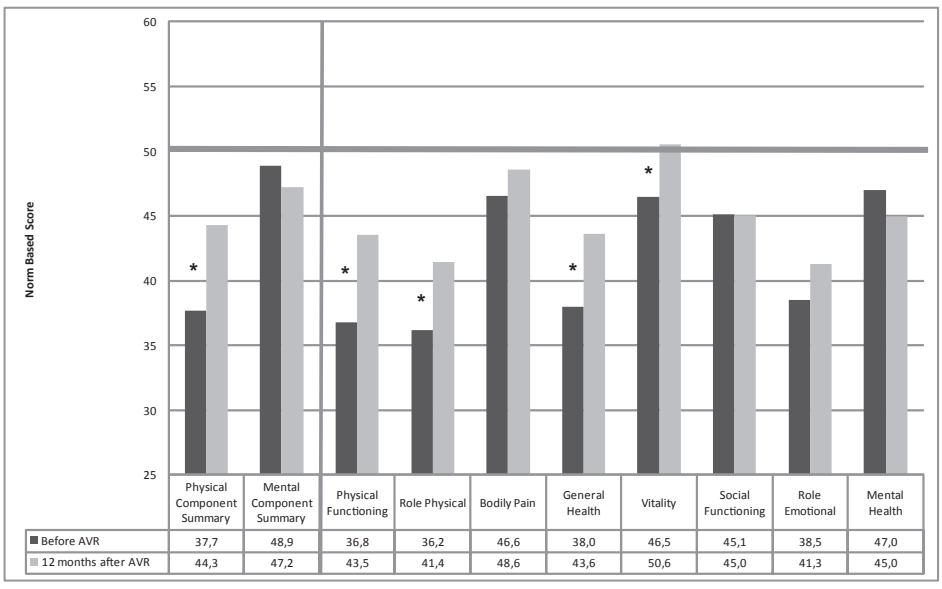
Figure 3c: QOL of conservative group, baseline vs 24 months

until one year after baseline visit (please see Figure 3a and b). The 30 patients who reached two years of follow-up and were able and willing to complete a survey at that time, showed worsening of their physical health outcomes. The 'Physical Component Summary' is significantly worse after two years compared to the baseline value. The physical subscales 'Physical Functioning', 'Role Physical', are significantly worse but 'Bodily Pain', 'General Health', 'Vitality' and 'Social Function' only show a tendency to worsen yet not significant with these small numbers of patients. 'Mental Health' remains stable (Figure 3c).

AVR patients

Initially 48 patients were referred for AVR within six months, during follow-up another 22 patients who were initially treated conservatively were referred for AVR (Figure 1). Sixty-two patients had conventional AVR, five had a percutaneous and one patient had a transapical valve implantation. Thirty-day mortality was zero but three patients died within one year after AVR. The mean follow-up in the AVR group was 11 months. Kaplan-Meier survival was 95% at one year. Fifty-nine patients completed the survey one year after AVR (Figure 1).

Quality of life in surviving AVR patients improves in most health domains (Figure 4). Especially the physical components have improved, as reflected by the 'Physical Component Summary' but also *'Vitality'* and *'General Health'* scales are significantly better than preoperatively. *'Physical functioning'*, *'Bodily pain'*, *'General health'* and *'Vitality'* approach



	Physical Component Summary	Mental Component Summary	Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health
Before AVR	37,7	48,9	36,8	36,2	46,6	38,0	46,5	45,1	38,5	47,0
12 months after AVR	44,3	47,2	43,5	41,4	48,6	43,6	50,6	45,0	41,3	45,0

* p< 0.05

Figure 4: QOL of AVR group, before vs 12 months after AVR

the scores of the general age-matched Dutch population. The *'Role Emotional'* scale shows a trend towards improvement yet not significant, *'Mental Health'* and *'Social Functioning'* remained unchanged.

DISCUSSION

Quality of life in symptomatic patients with severe aortic stenosis is lower in almost all health domains than in the age-matched general Dutch population, both in patients selected for surgery as well as conservatively treated patients. This has been discussed more elaborately in a previous paper, in which we also showed a clear association between NYHA class and the SF-36v2™ outcomes.[7]

Conservative group

The conservatively treated patients who survived 2 years showed a slight deterioration of their physical health status after one and two years. Yet the degree of deterioration seems to be less than what might be expected based on the low life expectancy of symptomatic AS patients reported in literature.[15-16] However, besides a higher mortality also the number of patients that were not capable to complete the subsequent questionnaires is larger in the conservative group compared to the AVR group. The baseline quality of life of these withdrawn patients was lower than that of the rest of the group (data not shown). Therefore the observed quality of life in our study overestimates the real quality of life over time in the total conservative group.

AVR group

Although patients in the conservative group are older, the quality of life of the AVR patients seems slightly lower at baseline (Figure 2). This is a reflection of clinical practice in which patients with severe symptoms are more likely to be referred for surgery than the ones who have only mild symptoms.

The patients who had AVR and were alive at one year follow-up, showed a markedly improved quality of life after one year compared to pre-operatively, except in *'Mental Health'*. The improvement is quite large in the physical domains, and -although not significant- a positive trend is clearly visible in the *'Bodily Pain'* and *'Role Emotional'* scales.

We assumed a period of one year after AVR would be enough to eliminate most direct postoperative emotional problems, and assumed a relatively stable health after that period. It is interesting to see that 'Mental health' does not improve after AVR, and remains much lower than in the age-matched general population. Whether concentration, memory, emotional or other cognitive problems are at the basis of this observation, and whether this could be explained by the operation or postoperative recovery remains only speculative.

Implications

Patients who are selected for AVR have a (non-significant) lower baseline quality of life as measured by the SF-36v2™, a higher NYHA classification and a lower risk score than conservatively treated patients. Therefore the gain of surgery in the former group might be higher than it would be in patients who are currently treated conservatively. Colak et al. described that high-risk cardiac surgery patients (predominantly CABG) have a lower pre-operative quality of life and greater improvement after surgery than low-risk patients.[17] At first sight this seems in contrast with our findings, however it is important to realize that Colak's patients –although high risk- were already accepted for surgery.

Whether the improved quality of life in operated patients can be extrapolated to the total symptomatic population with severe aortic stenosis remains yet a matter of debate. From these data it cannot be determined how the outcomes, both in terms of survival and quality of life, would have been supposed *all* patients would have had AVR. Such a scenario probably results in lower survival and lower quality of life than is currently observed in the AVR group one year postoperatively, but it could show improved overall survival and improved quality of life in the total group of symptomatic AS patients. In reality, some (elderly) patients are not surgical candidates or simply refuse to be operated upon. Therefore projection of the study results to the entire symptomatic patient population is only speculative.

On the other hand one could argue that current treatment selection seems good: in the patients who were selected for AVR, the quality of life improves over several domains after AVR. Compared to other reports in literature the observed mortality in the conservative group is low and the presented quality of life outcomes in the surviving patients show only a slowly and borderline significant deteriorating quality of life over time.[15-16]

Timing of surgery in patients with aortic stenosis is an important and continuing issue of debate. An underestimation by the treating physician of the impact of symptoms on a patient's quality of life might be one of the reasons why so many symptomatic patients with severe aortic stenosis are not referred for surgery. Based on our previous study and the current paper, we argue in favour of using quality of life survey's in the pre-operative assessment when the choice between surgery or conservative treatment has to be made.[6,7]

Literature

Although other studies describe quality of life in cardiac surgery patients,[8-10, 18-23] quality of life studies by objective survey's such as the SF-36v2™ have -to our knowledge- not been performed in patients who have (symptomatic) aortic valve disease and in whom the decision to operate or not is yet to be made. Most studies we found did not study quality of life in patients with aortic stenosis, but quality of life in patients with aortic stenosis *who were referred (selected) for surgery.* Some of them describe quality of life only in long-term survivors after intervention and do not have a baseline (pre-operative) value.[18-19] In such

designs all patients that did not survive on the long term can obviously not be included, while these are the most likely to have had a low quality of life before their death.

Some studies use NYHA classifications as raw reflection of quality of life rather than objective health survey's, other studies only concern selective subgroups.[18, 22-23] The NYHA classification is a functional measurement of physical performance or pain, and roughly reflects one's *current* health status but certainly not one's *desired* health status or disease burden. Especially the social and emotional aspects are underreported and not taken into account in the New York Heart Association (NYHA) classification. In contrast, the SF-36v2™ Health Survey is an objective and validated questionnaire, available in multiple languages and widely used. It describes multiple physical and emotional domains (not just Physical Component Summary and Mental Component Summary) and is therefore a better and more objective reflection of one's health status than simply using the NYHA classification.

Perhaps most important, comparison of quality of life in long-term survivors with the general age-matched population might be interesting,[18-19, 21, 23] but is not entirely fair since the patients who have deceased were more likely to have had a lower quality of life before death. Such analyses constitute a selection bias in which only the healthier patients are subjected to a survey (survival of the fittest).

Limitations

For adequate functional and echocardiographic assessment we believed it to be necessary to invite the patients to our hospital each time a quality of life assessment was done. We attempted to enrol every identified patient but were not able to do so because a substantial number of patients denied participation because of perceived high burden of the extra study hospital visits. Often these were the elderly, more sick patients for whom an extra study-trip to the hospital was unfeasible. Therefore it is likely that we underestimated the magnitude of quality of life impairment in the total patient population with symptomatic severe aortic stenosis.

We described only the symptomatic subgroup of patients with severe aortic stenosis. In doing so we described patients with one primary aetiology -severe aortic valve stenosis- and therefore our results may not be applicable to patients with a different primary disease.

An obvious limitation is the fact that some of the patients –and most likely those with low quality of life- die or refuse further cooperation over time which precludes further observations.

CONCLUSIONS

AVR offers improved quality of life in selected symptomatic patients with severe aortic stenosis. The beneficial effect is most evident in the physical components, but also general health perception, vitality and emotional aspects improve after AVR to the level of the general age-matched population. Mental health remained one year after AVR. In conservatively treated patients who survive on the long term, especially the physical quality of life worsens over time.

Besides considering life-expectancy and risks with either conservative or operative treatment, quality of life should be taken into account when making treatment decisions in patients with severe aortic stenosis. A health survey like the SF-36v2™ could be a valuable tool in monitoring the burden of disease for an individual patient and offer additional help in decision making. Whenever the health survey shows a large deviation from normal or signs of increasing disease burden, one should consider an interventional conservative approach.

Disclosures

The authors have no disclosures to make.

Acknowledgements

The authors would like to thank the patients, cardiologists, echo laboratory workers and secretaries of the participating hospitals for their kind cooperation.

Participating hospitals are:

- Havenziekenhuis, Rotterdam
- St. Franciscus Gasthuis, Rotterdam
- IJsselland Ziekenhuis, Capelle aan den IJssel
- Vlietland Ziekenhuis, Vlaardingen
- Albert Schweitzer Ziekenhuis, Dordrecht
- Medisch Centrum Rijnmond Zuid, Rotterdam
- Erasmus University Medical Center, Rotterdam

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CHAPTER 12

The evolution of advanced techniques for the management of symptomatic aortic stenosis in the elderly population: conventional surgical management vs transcatheter valve implantation

M Jahangiri
AP Kappetein
MWA van Geldorp
AJJC Bogers

J R Coll Physicians Edinb 2010;40:323-7

INTRODUCTION

The shifting age demographic of the adult population has affected every area of contemporary medical and surgical practice. Many more people are living well, not just into their 70s but into their 80s and beyond. Their expectations of treatment for every illness have shifted markedly upwards at the same time. Despite the decline in cases of rheumatic fever in Westernised populations in recent times, the ageing population has led to no decline in the prevalence of valvular aortic stenosis. This is now realised to be an active pro-inflammatory disease, rather than a degenerative process. Thus the condition has remained in the mainstream and continues to be responsible for considerable morbidity, hospitalisation and mortality among the elderly and very elderly.

Management has always been based on the triage of cases for direct intervention to the valve by surgery. Just as expectations have risen from patients, the techniques, application and monitoring of cardiac surgery have also made huge strides forward to meet this aspiration. More and more, surgeons are routinely asked to consider procedures in frailer, more elderly patients with more severe disease and co-morbidity. Managing the stenosis is rarely the only issue confronting the operating surgeon. Attempts to provide alternatives to open valve replacement surgery on cardiopulmonary bypass have now emerged. These are based around the transcutaneous placement of a valve prosthesis. While these technologies were initially highly selective in their application, they have now reached a stage to be compared with contemporary standards of cardiac surgical practice. In this debate we have invited two international experts from the fields of cardiac surgery (Professor Jahangiri) and interventional cardiology (Professor Kappetein and colleagues) to take deliberately opposing positions on the evolving management of valvular aortic stenosis in the very elderly. We have asked them to try to consider the strengths of each route. Both approaches provide options for patients that only a few years ago might have been regarded as essentially untreatable.

TAVI AND SURGERY IN HIGH-RISK AORTIC VALVE PATIENTS

M Jahangiri

With the advent of transcatheter aortic valve implantation (TAVI) and its recent expansion,[1,2] the number of patients being referred for the management of aortic valve (AV) disease has increased. It is also perceived that the less invasive TAVI is associated with better outcomes. Previously medically managed patients with AV disease are now being referred for intervention. A European heart survey on valvular heart disease showed that 33% of patients with severe symptomatic aortic stenosis (AS) did not undergo surgery.[3] Other surveys have shown that approximately half of patients with severe AS did not undergo surgery, where the operative risks were thought to be 5-I2%.[4] This may be due to a lack of knowledge of referring physicians about surgical risk scoring and the results of surgery. Bach and colleagues reported that among 30 patients who were thought to have prohibitive risks for surgery, calculated operative risk was less than 5% in II and less than I0% in I7 of them and only half were evaluated by surgeons.[4]

The advent of TAVI has created a resurgence of interest in the multidisciplinary meeting as a process. There are several reports of outcome of patients who have undergone TAVI.[2,5]

The risk of aortic valve replacement (AVR) in octogenarians is reported to be approximately 5-8%.[6] In the national database of cardiac surgery over a six-year period, this figure was approximately 5.5%, with the overall risk of stroke less than 2%.[1 2]

To this date, data from various registries from both the UK and other surveys within Europe[7] show comparable mortality and length of hospital stay for both TAVI and surgical AVR. However, the risk of stroke in TAVI (6-8%) is significantly higher than in patients undergoing surgical AVR (2%). In a recent study, cerebral ischaemia was assessed by neurological testing and serial cerebral diffusion-weighted magnetic resonance imaging in patients who underwent TAVI compared with AVR.[8] The authors detected clinically silent new foci of restricted diffusion on magnetic resonance imaging in 84% of TAVI patients with a multiple dispersed pattern suggesting cerebral embolisation. This may be due to the showering of emboli from the aorta, particularly the arch, or the dislodgement of aortic leaflet plaques. If emboli from the arch play a more significant role, it may be that transapical delivery systems potentially reduce the risks of embolisation. Some have suggested the use of distal protection devices to prevent emboli reaching the brain.[9] However, the potential benefits of these future devices have to be balanced against their own invasiveness, prolongation of the procedure and existing results of surgery.

Furthermore, the need for pacemaker implantation following TAVI, especially with some of the devices, such as CoreValve, is as high as 25% in the TAVI population, compared with nearly zero in surgical patients. Additionally, up to half of TAVI patients develop mild to moderate aortic regurgitation following the procedure.[7,9]

Although data from registries are not randomised and therefore subject to the inherent deficiencies of non-randomised studies, they reflect 'real-world' practice. Some of the data from the 'real-world' practice include outcomes of all high-risk patients discussed at multidisciplinary meetings for consideration of TAVI. There are as yet no randomised studies to compare the outcome of patients undergoing surgical AVR and TAVI, particularly the quality of life following treatment. The results of the PARTNER trial in the US, a large randomised trial comparing TAVI with surgical AVR in patients suitable for both, are pending.

The new techniques of surgery, including mini-AVR and sutureless valves, deserve attention. The mini-AVR is performed via a limited sternotomy or a small right-sided lateral thoracotomy. Several large studies have shown excellent outcomes, especially shorter time to extubation and improved pulmonary function.[10] The future sutureless valves will also allow shorter cross clamp and cardiopulmonary bypass times.

An expanding and promising use of TAVI is in patients with previous cardiac surgery, be it coronary artery bypass graft or valvular heart surgery where there are patent grafts or a malfunctioning tissue prosthesis present, the so-called valve-in-valve procedure. The risk of re-do surgery, particularly in the elderly, in this cohort can be high. However, the age of the patient and complexity of the operation should be weighed against the potential durability and complications of the transcatheter valve. The notion that all patients who have undergone previous cardiac surgery no longer qualify for re-do operations is not correct.

Transcatheter AV implantation is a promising and important development in the field of cardiovascular intervention. However, its current reported mortality, significantly higher stroke rate, mild to moderate aortic regurgitation and a high rate of pacemaker implantation should be considered before its wider application, especially to a younger population. This is particularly important considering the very good results of surgery in the UK for AV disease. Furthermore, the referring physicians should be made aware of the current very good results of surgery in the elderly.

Transcatheter AV implantation is a promising development. Its use must be considered in the setting of a multidisciplinary meeting where interventional and non-interventional cardiologists and cardiac surgeons are present.

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THE EVOLUTION OF ADVANCED TECHNIQUES FOR MANAGEMENT OF SYMPTOMATIC AORTIC STENOSIS IN THE ELDERLY POPULATION. PROMISING RESULTS WITH TRANSCATHETER VALVE IMPLANTATION, BUT MORE DATA ARE NEEDED

A. Pieter Kappetein, Martijn W.A. van Geldorp, Ad J.J.C. Bogers

Aortic valve stenosis (AS) is the most frequent valvular heart disease in the adult population in developed countries affecting approximately 2 to 4% of people over 65 years of age[1 2]. Increased life expectancy has resulted in a growing elderly population and, consequently, an increase in the number of patients with aortic valve disease. This results in approximately 3 million people with AS in Europe alone. One in five will eventually progress to symptomatic AS representing 600,000 patients.

Once symptoms appear, the prognosis is very poor. Median survival averages only 2-5 years after symptom onset of angina, syncope and heart failure.[3] Medical therapy is unlikely to modify the course of the disease, especially once symptoms or left ventricular dysfunction become manifest. Balloon aortic valvuloplasty has only a limited role in the treatment of AS, as the results are not long-lasting.[4] Surgical aortic valve replacement (AVR) is the reference treatment and guidelines on valvular heart disease stress the need for surgical aortic valve replacement (SAVR) once symptoms develop or in case of impaired LV function (Level of evidence grade 1).[5 6]

Despite these well-established guidelines, one in every three patients with symptomatic AS is not offered surgery mostly because of age, left ventricular dysfunction and co-morbidities.[7 8] Elderly patients and patients suffering from severe co-morbidities face higher operative risks and this definitely underscores an unmet clinical need. Undoubtedly this reality and patients' and physicians' preferences for lesser invasive strategies have fuelled the on-going interest in developing minimally invasive therapies. Minimised access AVR was established, which decreased surgical trauma, but still required extracorporeal circulation with its associated complications.

Transcatheter aortic valve implantation (TAVI) met the need for a less-invasive solution to treat severe aortic stenosis in the high-risk elderly population, in whom few options were available. Feasibility studies validated the proof of concept.[9 10] There are now 2 different TAVI systems clinically available with CE mark approval since 2007, Edwards SAPIEN valve (Edwards Life Sciences, Irvine) and CoreValve (Medtronic, Minneapolis). Numerous single-centre and multi-centre observational registries followed with dazzling speed suggesting the safety and efficacy of the TAVI technology.[11 12]

The availability of both trans-femoral and transapical approaches increased the number of those patients, in comparison with the use of the trans-femoral approach alone. Although the mortality rate with TAVI was higher in earlier reports, the 30-day mortality of around 8% in patients with high or prohibitive operative risk appears promising and resembles

short-term outcome in high-risk cohorts in the surgical literature.[13-16] The SOURCE registry, which has the largest patient population reported a 30 day mortality of 8.5%, with respective mortality rates of 6.3% and 10.3% in the transfemoral and transapical groups.[17]

Numerous studies have documented a dramatic reduction in the left ventricle–aortic gradient and a marked increase in the valve area. On the basis of postoperative echocardiograms, the effective orifice area of the transcatheter prosthesis is as good as, if not better than, that of valves placed in open surgery.[17] The only concern is a higher incidence of paravalvular leakage. A less than grade 2+ regurgitation seems to be well tolerated without heart failure or hemolysis, but the long-term effect remains unclear.

This innovation in cardiovascular therapeutics has been a collaborative effort by both interventional cardiologists and surgeons and has resulted in a rapid acceptance of TAVI in Europe. The TAVI technology comes with its own complications: vascular injury, stroke, cardiac injury, malposition, coronary obstruction, cardiac perforation, aortic regurgitation and heart block. The non-uniformity in presenting respective data makes comparison of results from different centres hazardous and impractical.[18] The Valvular Academic Research Consortium, a FDA approved collaboration between academic research organizations and professional societies in the United States and Europe is an initiative to generate a consensus statement on TAVI related definitions aiming to create order and uniformity making data more prone to analysis and comparison.

Technical refinements and commercial entrepreneurship have made the technology accessible to many centres worldwide. This might pose future implications especially in the current era where randomized trials with TAVI are strikingly lacking.

Randomized controlled trials comparing TAVI with SAVR with longer follow-up are the next step and will help to better define the safety and durability, and subsequently, indications of the technique, and the respective places of transfemoral and transapical approaches.

The ongoing PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial) in the United States is the first to randomize patients. In Cohort B inoperable patients are randomized to TAVI or medical therapy whereas in Cohort A patients with high operative risk are randomized to SAVR or TAVI. The trial completed its randomization early 2009. One-year outcome results will be reported in the forthcoming months. By study design, findings will only apply to this highly selected patient cohort representing only a fraction of the global AS burden.

For a new technology to be accepted as a new asset in the armamentarium for treating symptomatic AS several essential questions need to be answered: does the technology work? Which patients are likely to benefit (patient selection)? How does this new strategy compare with the alternatives? And what's the cost of the intervention? The proof of concept has been validated. The innovative less invasive transcatheter strategy should be at least as effective but safer than traditional SAVR or have proof of superiority for both safety and efficacy compared to medical therapy.

While anticipating the results of the Partner US trial, over 18000 patients worldwide have been treated with TAVI by May 2010. Currently, TAV is restricted to elderly patients who are considered at very high risk for conventional surgery but unavoidably, with increased operator experience and access to the device, physicians will shift their attention to younger patients with a less pronounced operative risk. Similar to what happened in the coronary revascularization arena[19] the blending of surgical and interventional expertise has created unique interdisciplinary dynamics reinforcing these new endeavours and paving the way for a randomized trial comparing TAVI with SAVR in a surgical moderate to high-risk patient population.

In high-risk patients, TAVI meets the criteria of ease of insertion, safety, and excellent orifice area but for lower risk patients a new randomized trial is necessary. The objective of the so called SURTAVI trial is to assess whether in patients with symptomatic severe aortic stenosis and at intermediate risk, Transcatheter Aortic Valve Implantation (TAVI) is non-inferior to Surgical Aortic Valve Replacement (SAVR) with respect to the event free survival time of the combined endpoint of all-cause mortality and stroke at a median follow-up duration of 2 years. Ultimately these patients need to be followed for a longer time to determine long-term durability of these valves.

Secondary objective is to compare patients with symptomatic severe aortic stenosis and at intermediate risk treated with TAVI to SAVR with respect to quality of life, clinical benefit, and health economics.

The interdisciplinary approach with cooperation between surgeons, cardiologists, and anaesthesiologists, the so-called Heart Team, is crucial in this trial. This team will decide whether patients with intermediate risk can be randomized. If in opinion of the heart team the surgical risk is deemed low, the patient will be operated. In case the interdisciplinary team judges the risk too high for surgery the patient will receive TAVI and for those patients where there is doubt which treatment offers the best outcome the patient will be randomized. This SURTAVI trial is likely to start in 2011.

Theoretical benefits of these transcatheter instrumentations in a beating heart avoiding the need of musculoskeletal incisions, cardioplegic arrest, aortic cross clamping, full cardiopulmonary bypass (including subsequent LV septal motion abnormality) seem evident. Ultimately the cost-effectiveness will determine whether the new treatment strategy is a valid option to be considered for reimbursement by governmental health institutions. The price–tag of the device is essential and will ideally cover the company's capital investment made during research and development. The cost-effectiveness relationship will only become favourable once competitive companies enter the market and introduce alternative devices at lower prices. Randomized trials that address these issues are needed now.

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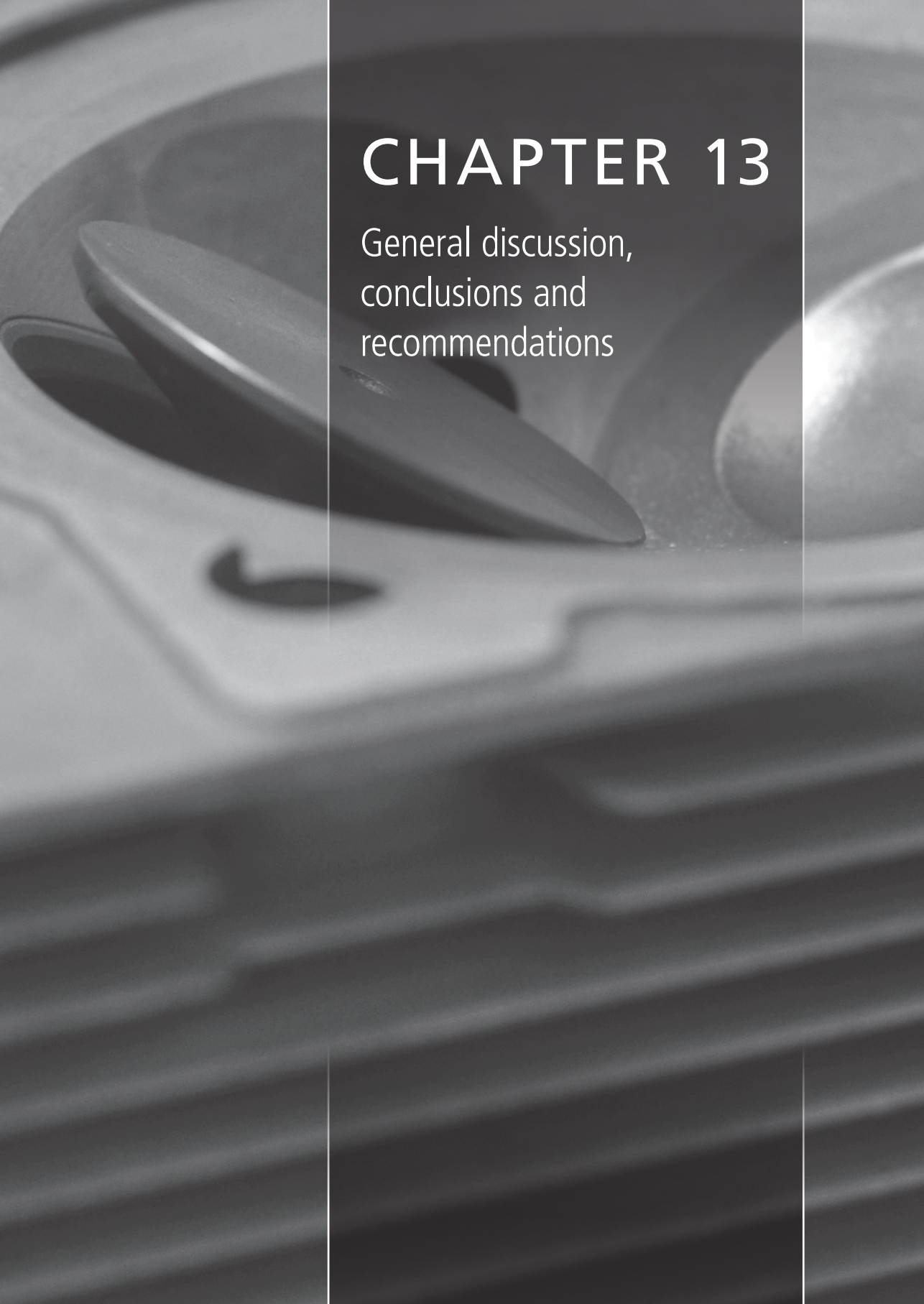

CHAPTER 13

General discussion, conclusions and recommendations

ABSTRACT

This thesis describes the current knowledge on the pathology and progression of aortic stenosis, the clinical presentation of patients with this disease and the currently available treatment options. One could call this widely used approach "the doctor perspective".

Perhaps more important, this thesis intends to highlight aortic stenosis from another point of view: "the patient perspective". Whenever a patient is confronted with the decision to perform surgical aortic valve replacement, often the choice between a mechanical or biological valve prosthesis remains a difficult issue. Use of the microsimulation methodology as presented in this thesis facilitates patient counseling by providing more -and for the patient understandable- insight in (event-free) life expectancy after AVR with a certain prosthesis. Besides exploring prognosis in terms of quantity of life, quality of life of patients with severe aortic stenosis was studied over time, both for surgically and medically treated patients. When studying treatment utilization we observed that many patients are not offered surgical treatment although new techniques to correct aortic stenosis are rapidly emerging. By identifying several modifiable determinants of treatment utilization, we hope that eventually more patients are offered some form of treatment or at least are well informed about their options.

The next section discusses in more detail the research questions as they were posed in the introduction, and provides general conclusions and recommendations for future research.

'NATURAL HISTORY' OF AORTIC STENOSIS

Aortic stenosis (AS) is the most common valvular heart disease in developed countries. Nowadays its cause is mostly degenerative, and while aortic valve calcification increases with age, the prevalence of severe aortic stenosis increases concomitantly. Prevalence estimates range from 1% in people below the age of 65 years, to 2-3% in those aged 75-85 years and to nearly 6% in people who are over 85 years.[1-2]

In the past, many papers have attempted to describe the 'natural history' of aortic stenosis,[3-9] something that might have been possible five decades ago when treatment options were very limited. Nowadays 'natural history' of a disease like aortic stenosis is virtually impossible to study because all kinds of decision or selection processes and interventions should be taken into account. If one would like to gain an unbiased view on 'natural history', theoretically all eligible patients should be excluded from an intervention, or they should be randomized to either the intervention or conservative treatment. Of course in practice this would be impossible and ethically incorrect.

In Chapter 3 we systematically reviewed all available literature on the progression of aortic stenosis. Of over 1300 hits in the first search, we finally retrieved 27 papers describing aortic stenosis progression rate as observed with Doppler echocardiography, and performed a meta-analysis. We found a striking variability both in observed stenosis-severity and stenosis-progression and also in the parameters that were used to record this severity or progression. Most often peak aortic gradient was used as primary parameter. Measured by peak aortic gradient, pooled annual AS progression was 3.7 mmHg/year as reported by randomized clinical trials (RCTs) and 6.0 mmHg/year in observational studies. Whether the true rate of progression is somewhere in between remains unsure, and probably it is not constant over time.[10] The finding that the rate of progression was higher in studies that concerned patients with more severe initial stenosis complies with this theory. Also other patient-related factors seem to play a role in the progression of aortic stenosis, therefore the rate of progression is largely dependent on the patient-population being studied.[2] The systematic review did bring an important point to attention, namely the need to establish consensus about reporting aortic stenosis severity. This will remain a difficult issue since jet velocities or pressure gradients –either peak or mean aortic gradient- are the parameters most widely reported although they are subjective to left ventricular function. In these cases the use of velocity-time-integral ratios would provide more accurate and uniform parameters. The degree of valvular calcification and inflammation also play a role in AS progression, but are currently difficult to measure. Recent promising studies have shown that positron emission tomography could fill this gap by offering reproducible measures of both valve inflammation and calcification.[11-12]

THERAPEUTIC OPTIONS FOR PATIENTS WITH SEVERE AORTIC STENOSIS

The ACC/AHA and the ESC guidelines for the management of patients with valvular heart disease recommend medical therapy and close monitoring of all patients with truly asymptomatic severe aortic stenosis with at least one new echocardiogram annually to prevent deterioration of the left ventricle. The guidelines also present clear consensus to treat symptomatic patients with severe aortic stenosis with a replacement of the aortic valve (Class 1, level of evidence B).[13-14]

Medical therapy

Anti-hypertensive medication, beta blockers and diuretics can help to relieve symptoms of congestive heart failure resulting from aortic stenosis but do not act on the valve pathology itself. Lipid lowering drugs are the only drugs reported to have a beneficial effect on the progression of aortic stenosis but their usefulness remains subject of much debate.

The cohort studies we used for our meta-analysis in Chapter 3 showed a trend toward a slower progression rate in patients who received statins. This slower progression rate is confirmed by a meta-analysis of mainly observational studies showing statins are likely to delay the progression of aortic stenosis.[15] However, several randomized clinical trials failed to demonstrate a difference in progression between the experimental and control arms: the SALTIRE trial (Scottish Aortic stenosis and Lipid lowering Trial, Impact on REgression) showed that intensive lipid-lowering therapy did not halt progression and did not induce regression of aortic stenosis.[16] The TASS (Tyrolean Aortic Stenosis Study) trial did not support the concept that atorvastatin slows down progression.[17-18] Recently, the ASTRONOMER (Aortic STenosis pRogressiON Observation: Measuring the Effects of Rosuvastatin) trial showed no reduction in progression in patients with mild to moderate aortic stenosis who received rosuvasatin daily.[19] Furthermore, there was no reduction in composite endpoint of combined aortic valve and ischemic events in patients with *asymptomatic mild-to-moderate* aortic stenosis according to the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial.[20]

As a reaction on the study presented in Chapter 7, Dr. Paraskevas wrote a letter to the editor of the European Journal Cardio-thoracic Surgery,[21] in which he advocates the use of statins in patients with aortic stenosis. In this letter he refers to a cohort study in which statins slowed the hemodynamic progression in patients with *asymptomatic moderate to severe* aortic stenosis.[22] Further he stresses in an earlier review that statins improve cardiovascular outcomes in *surgical* patients (either CABG or patients who need valve replacement or other thoracic surgery).[23] Both patient categories are different from the one we studied, namely a cohort of patients with severe aortic stenosis who are not (yet) selected for surgery. Although statins may interfere with the progression of aortic stenosis, it remains uncertain to what degree, in which patients and until what disease stage. Recent positron emission tomography studies have confirmed that in the aortic

valve inflammatory features are increased in mild to moderate aortic stenosis, but that inflammation has largely disappeared in severe cases.[11-12] Whether statin therapy is useful in the patient with *severe* aortic stenosis is therefore doubtful and has yet to be established in larger prospective series.[24-25] Probably comorbidity, old age, the advanced state of the valve stenosis and the possible indication for surgical treatment play a major role in this patient population and prohibit effective studies to either prove or reject a beneficial effect of lipid lowering drugs.

Conventional options for valve replacement

In 1952 the first aortic valve prosthesis was implanted by Hufnagel in the descending aorta to correct aortic regurgitation.[26] In the meanwhile extracorporeal circulation was developed and shortly thereafter orthotopic aortic valve replacement became common practice. In more recent years improvements in myocardial protection, cardiac anesthesia and postoperative care have led to increased willingness of surgeons to operate on elderly and high risk patients. Nowadays operative results are acceptable even in octogenarians, with an operative mortality of around 8% for single AVR.[27] Operative mortality in middle-aged otherwise healthy patients is approximately only 1%.[28]

Several types of valve prostheses are available, each having their own advantages and limitations. Most frequently used are the mechanical and the biological prosthesis. Mechanical prostheses have a long lasting durability but necessitate anticoagulation to prevent valve thrombosis and thrombo-embolic complications, leading to increased risk of bleeding. Bioprostheses do not require long-term anticoagulation but are subject to structural valve deterioration which increases the risk of reoperation. Valve related events which can occur with either prosthesis are paravalvular leakage, prosthetic valve endocarditis, prosthetic valve thrombosis and thrombo-embolic events. Overall, the occurrence of prosthetic valve-related morbidity and mortality together is around 3-4% per year.[13] The choice between a mechanical or biological valve prosthesis remains a difficult issue: patient age, comorbidity, additional anti-coagulant indications and patient preference can all play a role in this choice, let alone developments in surgical or transcatheter techniques and valve substitutes. In any case, accurate patient assessment is necessary to optimize patient selection for (surgical) treatment, and patient perspectives should be taken into account in this process. If indeed the decision for AVR has been made, microsimulation can help in individual decision making for a particular valve prosthesis.

Microsimulation models to study patient outcome after AVR were previously developed by Takkenberg and Puvimanasinghe some years ago.[29-36] Microsimulation appears difficult to grasp and is not yet commonly used in the fields of cardio-thoracic surgery, therefore an extensive introduction is given in Chapter 4.[37] The model described in this thesis is available by downloading the program along with instructions at www.cardiothoracicresearch.nl. Microsimulation provides accurate estimates of age-related life expectancy and lifetime

event risks after AVR with a particular valve prosthesis, based on systematically accumulated published evidence or primary datasets.

A reoperation for structural valve deterioration of a bioprosthesis can pose a serious challenge for both patient and surgeon. On the other hand, since patient monitoring is largely done by the referring cardiologist, a cardiac surgeon is hardly ever confronted to a patient with a major cerebro-vascular accident in the long-term postoperative period after mechanical valve implantation. Experiences with such reoperations or lack of personal experience with anti-coagulant related major bleedings could therefore influence a surgeon's counseling in future patients. Using microsimulation, lifetime event risks between different types of valve prostheses can easily and quickly be compared, providing more insight into patient outcome after AVR. This not only helps in patient selection but also facilitates patient counseling and when combined with individual informed patient preferences, it improves optimized informed decision making for specific heart valve prosthesis in a particular patient. The challenge remains to effectively translate the evidence-based estimates from microsimulation models to the doctor and the patient who are facing the decision between an mechanical or biological valve prosthesis. Implementation of microsimulation estimates in patient decision aids, employing non-numerical visualization of risks rather than providing percentages, may facilitate this transfer of knowledge.[38]

Based on the Vancouver dataset provided by Dr. Jamieson we have shown that life-expectancy after AVR is quite similar for patients who have a mechanical prosthesis implanted compared to patients with a biological prosthesis, at least for patients aged between 45 and 80 years. Stoica et al took the microsimulation method to the next level by adding confidence limits to their point estimates for (event-free) life-expectancy, and came to the similar conclusions: life-expectancy is similar for patients with biological compared to mechanical valve prostheses, and even event-free life-expectancy is comparable.[39] The difference lies in the nature of the valve-related events. For patients over the age of 60, implantation of a bioprosthesis generally can be considered a good option. The risk of bleeding with a bioprosthesis is not absent, but compared to mechanical valves the risk-reduction of bleeding that can be achieved by avoiding coumadins outweighs the increased risk associated with the feared structural valve deterioration. If these results were to be followed, the current age-threshold for implantation of a bioprosthesis could thus be lowered from 65 to 60 years. The negative aspect of lowering this threshold is that not only more but also older patients will require a reoperation in the future, which could increase re-operative mortality. On the other hand, the emerging TAVI technique may offer a solution in patients with high re-operative risk: the 'valve-in-valve' concept has already shown to be effective to substitute deteriorated biological prostheses in a few cases.[40-41] Of note, long-term durability of the TAVI procedure has not yet been established, and therefore a durability comparison between surgical bioprostheses and 'TAVI bioprostheses' is not yet possible. Quality of life after cardiac surgery in general and especially after AVR

is yet relatively unexplored. High-quality studies on quality of life after AVR with either valve prosthesis are urgently needed in the near future to shed some extra light on this issue in order to optimize patient information.[42] Altogether, since there is no clear survival advantage between the two prosthesis types, the choice should be driven by shared decision making based on individual patient preferences.[38]

TREATMENT OF SEVERE AORTIC STENOSIS IN CONTEMPORARY DAILY PRACTICE

Like stated before, the ACC/AHA and the ESC guidelines for the management of patients with valvular heart disease recommend prompt aortic valve replacement as soon as a patient with severe aortic stenosis becomes symptomatic. Remission of symptoms after starting medical treatment, advanced age and depressed left ventricular function are known, yet debatable, reasons to deny surgery in a symptomatic patient.[43-45]

In contemporary practice cardiac surgeons are more willing to operate on elderly patients with associated morbidities than a few decades ago. Progress in operative and postoperative care which have led to decreased mortality and morbidity (especially in the high-risk patients), form the basis of this shift. Especially since TAVI became available in clinical practice, surgeons and interventional cardiologists feel they deny AVR only in a minority of patients. Therefore it is surprising to find several articles reporting that up to 60% of symptomatic patients with severe aortic stenosis do not undergo AVR.[44, 46-49] In the studies presented in this thesis we found similar results, implying that even in a region with a highly specialized tertiary center where new percutaneous and transapical valve implantation techniques were being implemented, more than half of the patients are not treated by aortic valve implantation or replacement.[49] Most of these patients were simply not referred for invasive treatment. In chapter 7 we studied *why* so many patients are not referred by their cardiologists and found four main reasons for the non-referral of symptomatic patients: preference of the patient (reported in 9% of cases), perceived high operative risk (34%), underestimation of hemodynamic severity (14%) and underestimation of symptoms (19%). These reasons will be discussed in more detail in the following paragraphs.

Patient preference

One of the reasons to choose for conservative treatment instead of AVR was patient preference. Of course, ultimately the patient should be the one to make the final informed decision whether to agree with an operation or not. However, one can imagine patient preference for a certain treatment is largely dependent on the doctor providing the information.[38, 50] Cardiologists and surgeons often rely on different information sources and can

have different opinions about operative risk and expected benefit after treatment.[51] The surgical team should at least be involved not only in decision-making, but also in supplying information to the patient about risks and expected benefits of surgical procedures. Ideally, a multidisciplinary team approach is used, the patient is provided with comprehensible objective information on the benefits and risks of the different treatment strategies and given time to explore the options in his/her own context.[52] Patient decision aids may be of help for these potentially value-sensitive decisions.

Perceived high operative risk

Of the patients with perceived high operative risk as described in Chapter 7, more than half had a relatively low estimated operative risk with a logistic EuroSCORE below 10%. Similar findings were reported by other groups who confirm this mismatch between perceived and calculated operative risk, raising the question that possibly many patients are wrongly denied AVR.[44, 46-47, 53] Apart from this mismatch also truly high risk patients should at least be considered for surgery since these are the ones most likely to benefit from valve replacement once they have overcome these risks. This is also known as the risk-treatment paradox [54-55].

An important issue with current risk models is that characteristics such as 'vitality', 'frailty' or 'biological age' are difficult to measure and incorporate in a risk model. Furthermore there are many risk models available and there is a large variability between the different models, in model output and even in definition of 'operative mortality'.[28, 56-58] For valve surgery patients, the EuroSCORE risk model –which is the one most commonly used in the Netherlands- overestimates the current actual operative risk greatly.[59] Recently, a new version of this risk model has been released: the EuroSCORE II.[60] It has been recalibrated, contains new risk factors, while the weight of the established risk factors has been reassessed. Factors related to ageing and frailty have not been added. The applicability of this new model to the elderly patient population with severe AS has to be evaluated in the upcoming period. Another approach that may more adequately describe contemporary outcome in elderly patients and other heart surgery subgroups would be to model outcome dynamically, using contemporary large data registries representing current clinical practice. Then a systematic approach can be applied with contemporary modeling methods that employ advanced estimation and validation techniques such as penalization and bootstrapping. These systems should be dynamic both with regard to the weight (and type) of co-variables and with regard to the calibration of outcomes.[61]

Most medically treated patients are not referred to a surgical department and therefore do not undergo a full clinical assessment of e.g. pulmonary function, presence of coronary or peripheral artery disease or pulmonary hypertension. It is questionable if one can make a clear judgment about operative risk and the possible benefits a patient would have from treatment when these issues are not addressed.

The majority of publications on operative risk-modeling in cardio-thoracic surgery is written by surgeons and is published in cardiac surgery journals. Since not every cardiologist has expertise with operative risk assessment, referral of any patient with severe valve pathology to an expert 'heart team' or 'heart valve team' seems to be a better option. This 'heart valve team' should ideally include a cardiologist, interventional cardiologist, cardiac surgeon, and a specialized anesthesiologist to check the indication and discuss all possible treatment options with their associated risks. Even the family physician could be consulted. In case of doubt, e.g. about vitality, the patient could be invited to the outpatient clinic to be examined, both by the surgical team and also by other specialists like a geriatrician. For the patient this would be the opportunity to be informed about benefits and risks of the different treatment options, to discuss these options and finally make a well-informed decision.[52] Such a patient centered team approach would promote evidence-based medicine and well-informed decision making.[38, 54]

Underestimation of hemodynamic severity

As much as 14% of symptomatic patients (Chapter 7) who were not referred for surgery were classified as having a *'non-severe'* stenosis by the treating cardiologist, although the echocardiographic parameters clearly complied to a severe valve stenosis. These patients are at risk of left ventricular deterioration and sudden death.[3, 6] Even if the stenosis severity is only just below the 'severe' threshold, it can be disputed whether 'watchful waiting' is the best treatment. Although in our meta-analysis in Chapter 3 the progression rate of 3.7-6.0 mmHg/year in terms of peak aortic gradient appears to be lower than previously anticipated,[62-64] the rate of progression was higher in patients having more severe stenosis. Borderline patients will therefore enter the 'severe stenosis' category within a short period of time. Meanwhile the left ventricle is at risk for hypertrophy and deterioration, resulting in more severe symptoms, worse quality of life and increased risk of sudden death. Since long-term outcome after AVR is worse when left ventricular hypertrophy is more outspoken, in particular these 'borderline' patients should be monitored frequently and once AS becomes severe, referred promptly for surgery.[65]

Underestimation of symptoms

We reviewed all cardiology chart documentation on our study patients and often found descriptions of the classical aortic stenosis symptoms such as dyspnea yet described as 'mild' or non-debilitating. In 19% of symptomatic patients this was the main reason not to refer to surgery. Apart from the fact that having only 'mild' symptoms does not exclude a patient from being an AVR candidate,[13-14, 66] the patient's functional disability is often underestimated by physicians [67] and disease burden is high, even in NYHA class 2 patients (as is discussed in one of the next sections and also in Chapter 10 and 11).

CHALLENGES AT TREATMENT SELECTION AND THEIR EFFECT ON OUTCOME

In order to gain more insight into factors related to treatment selection and their effect on clinical outcome in patients with severe aortic stenosis, we designed the **A**ortic **VA**lve **RIJN**mond study (Chapter 9). Grossly, treatment selection in this patient population is based on the presence of symptoms that can be attributed to the aortic stenosis. What seems like a clear distinction at first glance appears to be a remarkably difficult issue: which patient is symptomatic and who is not? Often, as the stenosis gradually progresses, patients attribute symptoms to co-morbidities or the ageing process, introducing both patient- and doctor delay once symptoms become more clear. Exercise testing used to be recommended in asymptomatic patients with severe aortic stenosis in order to exclude symptoms with more certainty.[68-70] Up to 37% of previously considered 'asymptomatic' patients have limiting symptoms or signs when they are tested.[69] Yet exercise testing remains highly underused -also in the Rotterdam region- and shifted from a Class 2a to a 2b recommendation in the latest ACC/AHA guidelines.[13, 71] If physically possible, we performed exercise testing in the asymptomatic part of the AVARIJN cohort and found similar results: one-third of the patients has blood-pressure drops, significant ST-segment changes or limiting symptoms such as severe dyspnea, angina or near-syncope when tested (Chapter 9). Therefore the underuse of exercise testing could lead to an underestimation of the true proportion of symptomatic patients leading to an even greater number of patients treated medically than as reported by others and by ourselves.[44, 46-48] This implies that we are only observing the tip of the iceberg and even more patients could be eligible for aortic valve replacement or TAVI.

Factors associated with therapeutic strategy

Two-thirds of the AVARIJN patients reported to be symptomatic and in this group we studied the factors that were related to treatment strategy by multivariable analysis. Age, peripheral arterial disease, previous myocardial infarction and hypertension were associated with a conservative policy, stenosis severity was related to operative treatment. This confirms earlier reports of years ago that many of these factors form debatable reasons for either surgical or conservative treatment and illustrates the urgent need for an evidence-based multi-disciplinary team approach.[44-46, 48, 52]

Prognosis

A decline in survival in medically treated symptomatic patients already occurred in the first year after inclusion.[49, 72] Still, survival in the conservative group is with 73% at 2 years not as bad as expected based on previous reports by others.[3, 5, 73] Although survival appears to be better in symptomatic patients who undergo AVR/TAVI versus those treated conservatively, the survival benefit disappears when corrected for age and several comor-

bidities. This suggests that patient survival is mainly driven by patient characteristics and to a lesser extent by treatment strategy. On the other hand, the relatively 'good' prognosis of our medically treated group could be a reflection of the conservative approach of the cardiologists in our region because this group also contains misclassified 'asymptomatic' and misclassified 'high risk' patients. Further the AVARIJN cohort represents another tip of an iceberg: the included patients are a selected sample from a larger population; many potential AVARIJN candidates refused to participate in the study because of old age and multiple comorbidities. Therefore, the patients included in AVARIJN represent most likely a relatively "healthy" subgroup of patients with severe AS.

As expected, the asymptomatic patients had a far better prognosis in terms of survival: 92% were still alive at 2 years. On the other hand, as much as 68% became symptomatic with a median time to symptom development of 13 months, only 38% had valve replacement. This stresses the progressive nature of the disease at this stage and at least urges the need of close follow-up or perhaps even a shift to a more aggressive treatment policy.[65]

Quality of life

The study presented in chapter 10 shows that asymptomatic patients from the AVARIJN cohort seem to have a similar health perception compared to the general population. Symptomatic patients however, suffer from both severe physical and emotional impairment hampering normal daily life.[74] The differences in health perception of symptomatic patients compared with the age-matched Dutch population are large across most health domains. Further there was no association between stenosis severity and physical or mental quality of life in our patient cohort. Thus, whenever the aortic stenosis is above the 'severe' threshold, "objective" measures of aortic valve function do not correlate to functional status: the degree of stenosis does not predict disease burden. This is important to realize and relevant for clinical practice. However, we only studied the 'severe' category: an association between disease burden and stenosis severity in the whole patient population with either mild, moderate or severe aortic stenosis certainly cannot be ruled out.

Elderly patients can expect a good quality of life after surgery,[9, 43] but these results should be placed into perspective: most studies describe quality of life in those selected patients with aortic stenosis *who were referred for surgery.*[75-83] Some of these studies even lack a baseline (pre-operative) quality of life measurement and only describe quality of life in long-term survivors after intervention.[76-77] These issues have also been addressed by Noyez and colleagues in a recent paper.[42] They performed a meta-analysis of multiple studies on quality of life, often found shortcomings in methodology and came up with several recommendations in order to stimulate and improve future research on this subject. The quality of life study that is described in Chapter 11 was undertaken in patients in whom the decision to operate or not still had to be made, and we repeated the measurements over time, both in medically and surgically treated patients. AVR indeed offers improved

quality of life in –for surgery selected- symptomatic patients.[84] The beneficial effect is not only evident in the physical component of the SF-36v2™ Health Survey, also general health perception, vitality and emotional aspects improve to the level of the general age-matched population.

Besides considering life-expectancy and risks with either conservative or operative treatment, the possible gain in quality of life should be an important consideration when assessing symptomatic status, and might be a reason to reconsider a conservative approach when only 'mild' symptoms are present. Standardized surveys like the SF-36v2™ should be added to the armamentarium of the cardiologist as a simple diagnostic tool in order to aid decision making. The cardiologist –or preferably: the 'heart team'- could then compare the results of the patient with the quality of life of the general population, or with the results of similar patients from our cohort, and use this information to reconsider or confirm a conservative approach.

Whether the improved quality of life of the operated patients can be extrapolated to the total patient population with symptomatic severe aortic stenosis remains yet a matter of debate. From the data presented in Chapter 11 it cannot be determined how the outcomes, both in terms of survival and quality of life, would have been when *all* patients would have had AVR. Such a scenario probably results in lower survival and lower quality of life than is currently observed in the AVR group, but it could show improved overall survival and quality of life in the total group of patients with symptomatic aortic stenosis. In reality, some (elderly) patients are simply not surgical candidates or refuse to be operated upon.

Using surveys like the SF-36v2 Health Survey during follow-up of -either medically or surgically treated- patients still leaves a problem to be solved: all patients who have died cannot be taken into account. In order to do so, another type of analysis can be used. The EuroQOL is a simple survey containing only five questions with three possible answers each.[84-86] Analysis of this survey can determine the number of 'quality adjusted life years (QALY's)': the number of life years gained by a certain therapy corrected for the quality of life. Insurance companies use this information and reimbursement policies are often based on this type of analysis. For the AVARIJN cohort we have all these data since we subjected the patients not only to the SF-36v2, but also to the EuroQOL survey. These data will be studied and used for cost-effectiveness studies in the near future.

Limitations of the AVARIJN study

The AVARIJN study group described in this thesis is a selected cohort. Although enrolment from the outpatient cardiology echocardiography departments was encouraged, some patients may not have been identified. We attempted to enroll every patient but were not able to do so because a substantial number of patients denied participation: of the 459 patients we invited, only 191 agreed to participate. Also a few patients who initially consented denied participation during follow-up.[72] Often these patients were the elderly,

or the more sick patients for whom an extra study-trip to the hospital was unfeasible. Therefore we have a less representative patient population than we initially hoped for. It is likely that this leads to an underestimation of the proportion of symptomatic patients which in turn leads to an underestimation of the real undertreatment. Also this would lead to an underestimation of the magnitude of quality of life impairment, and a too optimistic view on prognosis in conservatively treated patients.

NEW DEVELOPMENTS IN THE MANAGEMENT OF PATIENTS WITH SEVERE AORTIC STENOSIS

Since aortic stenosis nowadays has a mainly degenerative origin, it is clear that it is becoming an increasingly important health problem in developed countries. As the life expectancy of the population continues to increase, concomitantly the number of chronically ill patients increases, as a result the need for valve replacement is expected to triple by the year 2050.[85] Not only is the number of patients with aortic stenosis still increasing, also the proportion of patients that is eligible for surgical valve replacement or transcatheter valve implantation will increase. So will the costs per patient, especially with the latter technique which currently still is very expensive. In contrast, it is expected that from 2025 onward the number of people working in healthcare will only decrease. These prospects not only pose a medical problem, but also tremendous financial and social challenges, calling for an efficient healthcare system. It is in this light that the Dutch government has introduced a new cost-system for hospitals in 2012 (http://www.rijksoverheid.nl/documenten-en-publicaties#ref-minvws). This new cost-system aims to guarantee sustainable healthcare while keeping costs contained at the same time. No longer will hospital budgets be determined by the number of treatments provided, but by the quality of treatment. Therefore new developments in treatment will have to meet high standards, not only in medical efficiency but also in terms of efficacy and effectiveness. Intensive research and publication of treatment results, as well as transparency to society will play a key role to get reimbursement.

Transcatheter Aortic Valve Implantation (TAVI)

Many patients in the AVARIJN cohort followed with great interest the news concerning the implementation of the new TAVI technology in the Erasmus Medical Center. Even elderly patients were often well informed by (local) media, family and friends and were enthusiastic for the less invasive procedure. Yet medical information was strikingly lacking at that time: the indications for the TAVI technique, the disadvantages such as peripheral vascular complications, cerebral embolism, paravalvular leakage, conduction disorders and the uncertain long-term durability were not yet clearly documented.

We encountered many possible candidates for TAVI in the AVARIJN cohort, some of whom were previously treated conservatively and were only referred to our department after the introduction of the TAVI technique. Interestingly, the majority of these patients underwent surgical AVR, and only a few were treated with TAVI. New treatment options thus have led to increased patient referral and caution is advised not to bypass the 'heart team'. Initially, the TAVI procedure was reserved for the very high risk patient who was rejected for conventional AVR. With time the indications for this lesser invasive technique are steadily shifted to younger patients with lower operative risk while the long-term durability of the TAVI technology is still not established. The SOURCE registry has the largest patient population until now and shows a total 30-day mortality of no less than 8.5%, with respective mortality rates of 6.3% and 10.3% in the transfemoral and transapical groups.[88] This observation underlines that TAVI is not without considerable risk for early mortality.

Fortunately a number of randomized clinical trials are ongoing in order to clarify the indications for either the surgical or percutaneous technique. The PARTNER trial (Placement of AoRtic TraNscathetER valve trial) allocated patients in two cohorts: in cohort A high risk patients were randomized to either surgical valve replacement or TAVI, in cohort B inoperable patients were randomized to TAVI or conservative treatment.[86] In the PARTNER A cohort TAVI was associated with more vascular and cerebral complications, but atrial fibrillation and postoperative bleeding were more common after surgical AVR. The TAVI procedure was associated with increased paravalvular regurgitation, but its clinical importance remains yet unexplored. The main finding was that the TAVI procedure had similar mortality as AVR after one year and was therefore found to be 'non-inferior' to AVR in high risk operable patients with severe AS, at least in the short term. The B cohort showed a lower mortality in the patients treated with TAVI compared to conservative treatment at the expense of a higher incidence of stroke and vascular complications. The SURTAVI and PARTNER II trials have recently been designed to randomize intermediate risk patients to TAVI or surgical AVR.[90-91] It is important to await the results of these trials before further lowering the indications for this new and promising transcatheter technology.

Advances in surgical aortic valve replacement

Several different approaches have been used in order to avoid median sternotomy, trying to retaining thoracic stability in order to reduce wound associated morbidity and mortality and to improve cosmetic results. Some of the possibilities are a reversed "C" ministernotomy, a right anterior minithoracotomy, or a "J" shaped incision.[92-95] Most of these techniques are feasible and safe, some studies suggest improved pulmonary function, a faster recovery, less complications and less chest pain resulting in more patient satisfaction, less rehabilitation and less costs.[87 97-99] Others find no difference, except for the better cosmetic result.[100-101]

An interesting new technique to replace the diseased native aortic valve is introduced by Berreklouw and colleagues.[102-103] In order to reduce cross-clamp time and cardio pulmonary bypass time, they developed a Nitinol ring to attach contemporary and FDA approved prostheses -both biological and mechanical - without sutures in the aortic position after surgical excision of the native aortic valve. This concept is proven to be feasible in experimental animal settings and could have several advantages over the TAVI technique, such as reduction in conduction abnormalities, coronary obstruction, paravalvular regurgitation, mitral valve damage and cerebral complications. A major advantage is the fact that also mechanical valves can be implanted. Hopefully the concept proves to reduce operative mortality associated with long cross-clamp times in multiple valve procedures and facilitate the conventional or ministernotomy AVR.

New anticoagulant therapy

For many years Vitamin K antagonists have been the anticoagulants of choice in preventing thrombo-embolic events after AVR with a mechanical prosthesis. Their unpredictable and highly variable response, narrow therapeutic window and extensive drug interactions make dose management complex but also very important since 60% of all anti-coagulation related complications occur when the INR is out of the therapeutic range.[104] In the Netherlands, self control programs have been shown to be effective in maintaining the therapeutic range compared to the conventional control by the Thrombosis Service and it results in improved quality of life.[88]

Recently new anticoagulant drugs have entered the market of which Dabigatran seems most promising. This thrombin inhibitor is short acting, has few side-effects and can be used without monitoring. Recent trials showed that in the treatment of atrial fibrillation Dabigatran has similar rates of stroke and systemic embolisation compared to Warfarin but with a lower rate of major bleeding.[106-107] If also anti-coagulant related bleeding complications after mechanical valve surgery could be reduced in combination with improved drug management, a new era in favor of the mechanical valve could start. Theoretically this could widen the indications for conventional, minimal invasive and sutureless mechanical AVR at the expense of bioprostheses or TAVI.

CONCLUSIONS AND RECOMMENDATIONS

With regard to the 'natural history' of aortic stenosis this thesis has added the observation that pooled annual increase in peak aortic gradient is highly variable and estimated to be somewhere between 3.7 and 6.0 mmHg/year. There is a large variability both in observed stenosis-severity and –progression, most likely the rate of progression is largely dependent on the patient-population being studied. Assessment of valvular calcification

and inflammation by (PET-)CT may have additional value in identifying fast progression of aortic stenosis. Further, the parameters that were used to display stenosis severity or progression are highly variable. More uniformity in these parameters would be helpful for a better comparison between different studies and a better estimate of the 'true' rate of progression.

This thesis applied microsimulation to compare patient outcomes after implantation of biological versus mechanical valve substitutes. It was demonstrated that using microsimulation, lifetime event risks between different types of valve prostheses can easily and quickly be compared, providing more insight into the different events that patients encounter in life after AVR. Such information not only helps in treatment selection but can also improve patient counseling when the microsimulation interface would be used embedded in a patient decision aid in face-to-face contact with the patient in the out-patient clinic setting. It improves visualization of the advantages and disadvantages of the different prosthesis options and thereby optimizes informed decision making when combined with individual patient preferences.

Important insights were obtained in this thesis from the research that concerned the treatment of severe aortic stenosis in contemporary practice. In more than half of the symptomatic patients the current clinical practice guidelines are not followed and patients are not treated by valve replacement. This seems a remarkably high proportion. Patient preferences play an important role, but also other more debatable issues such as perceived high operative risk, underestimation of hemodynamic severity and underestimation of symptoms. Multivariate analysis further showed age, peripheral arterial disease, previous myocardial infarction and hypertension to be associated to a conservative policy, stenosis severity was related to operative treatment. In order to optimize patient and treatment selection any patient with severe valve pathology should be referred to a 'heart team' or 'heart valve team'. This 'heart valve team' should ideally include a cardiologist, interventional cardiologist, cardiac surgeon and specialized anesthesiologist, to check the indication and discuss all possible treatment options with their associated risks. Such team effort could eliminate inappropriate 'competition' between surgical, transcatheter or conservative strategies. Standardized surveys like the SF-36v2™ should be added to the standard armamentarium of the cardiologist and the 'heart team' as a simple diagnostic tool in order to aid decision making. In case of doubt about vitality, frailty or other issues, the patient should be examined in the outpatient clinic by members of the heart team. Last but certainly not least: the patient should be centered in informed decision making.

The general conclusion following from this thesis is that there is a lot to gain in the management of patients with severe aortic stenosis. Progress can be made in the areas of diagnosis, treatment selection and treatment utilization. Both doctors and patients should and can be better informed about prognosis after each treatment modality, also in terms of quality of life. This will improve decision making especially when the patient is

placed right in the center of this evidence-based multi-disciplinary process. As long as the life-expectancy of the general population continues to rise and medical options to halt or prevent aortic stenosis are lacking, surgical and transcatheter technical developments and their indications will continue to expand provided reimbursement by society. Optimization of treatment decision making starts with an evidence-based patient-centered team approach that considers not only morbidity and mortality, but also patient benefits and societal costs.

Future research

Since at least part of the symptoms associated with severe AS are more likely to be caused by the effects on systolic and diastolic left ventricular function rather than by the stenosis itself, it is important to gain more insight into left ventricular function. Tissue Doppler Imaging is an ultrasound technique that measures left ventricular wall motion and provides objective means to quantify global and regional left and right ventricular function even before the occurrence of (subjective) symptoms.[89] We are currently analyzing all AVARIJN echocardiograms in order to investigate whether it is useful to add Tissue Doppler Imaging to the standard echocardiographic evaluation.

Several studies found that B-type natriuretic peptides (BNP) are useful in discriminating cardiac versus non-cardiac dyspnea, is related to the severity and progression of aortic stenosis, related to symptom development and accurate in discriminating symptomatic and asymptomatic patients, and predictive of patient outcome.[109-114] We have saved serum samples of all AVARIJN patients at each study-visit and will study whether the assessment of Nt-proBNP indeed has predictive value in the AVARIJN cohort, and whether it should be added to the standard clinical evaluation of the patient with severe aortic stenosis.

Microsimulation methods are obviously also applicable for other diseases, e.g. they could also be developed for patients who are treated conservatively. The development of prognostic models that weigh not only the pros and cons of AVR related to mortality, but also related to quality of life, are the next step towards optimized decision making whether to operate or not on a patient with severe aortic stenosis. Our department intends to develop these models, although this requires large datasets with extensive numbers of variables and some patient factors, such as vitality, are hard to measure and will therefore be difficult to grasp in a model. In addition we intend to build evidence-based patient decision aids that in an objective and comprehensible manner inform patients of the benefits and risks of different treatment options, and allow patients to weigh these options in their own personal context, in order to facilitate objective evidence-based shared decision making.

Since even patients with 'mild' symptoms clearly suffer from both severe physical and emotional impairment, we recommend assessing quality of life in patients with severe aortic valve pathology. We intend to develop a Dutch online tool to measure quality of life –related to the general population, and the patient population- resulting in only very

little extra work for a cardiologist or heart team. Further we plan to study whether quality of life measurements can predict hospital (re)admissions and survival, like it can in other heart diseases.[115-116]

Eventually reimbursement policies will largely determine whether new treatment modalities such as the TAVI technique will be used on a large scale. Therefore it is important to evaluate and compare the costs and benefits of all available treatment options. We are currently working on a cost-effectiveness study using the EuroQOL method in order to evaluate the efficacy of conservative treatment compared to conventional AVR in the AVARIJN cohort. The next step would be to compare the efficacy of surgical AVR (currently the 'gold standard') to the TAVI technique.

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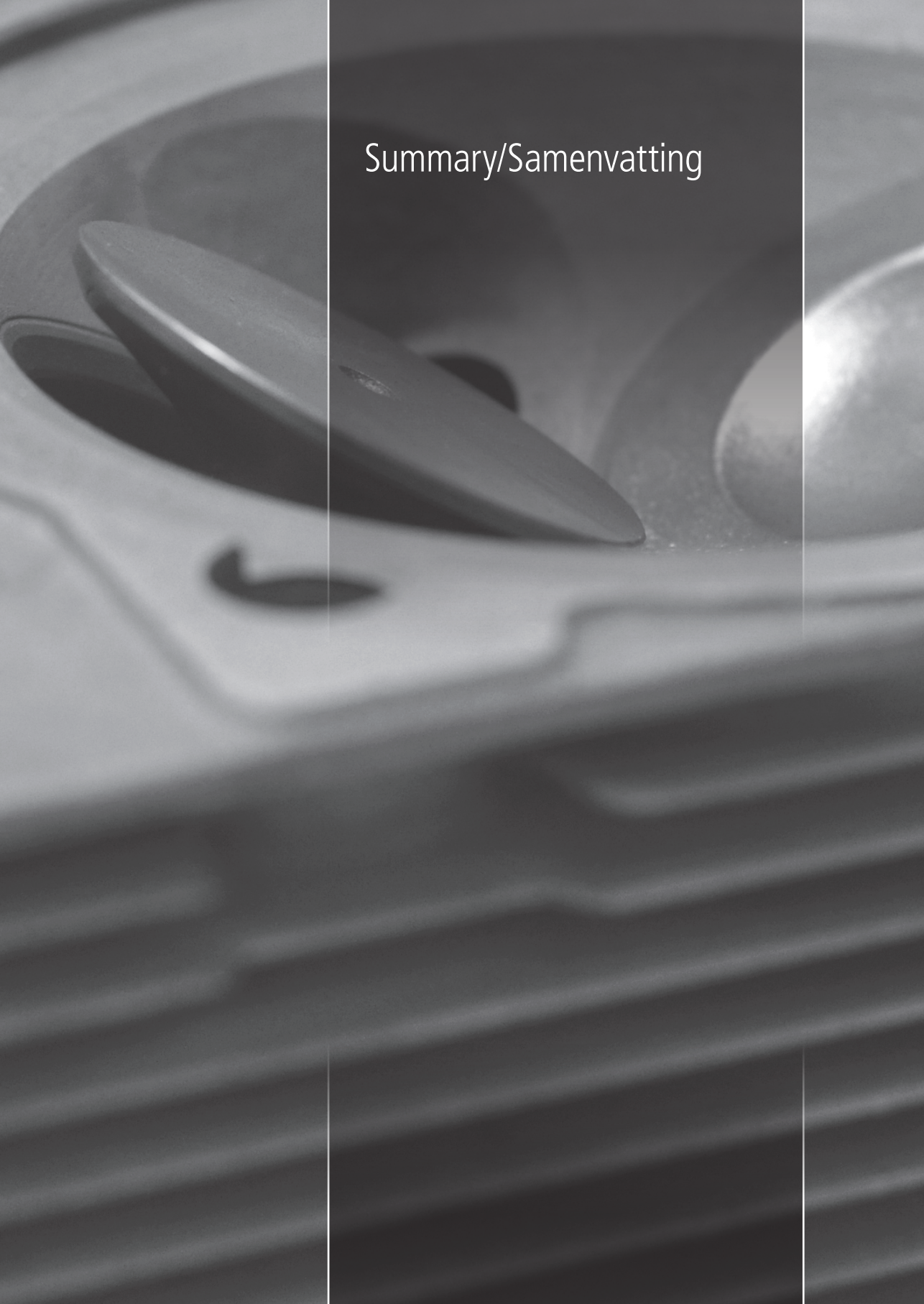

Summary/Samenvatting

Summary

Chapter 1 presents the introduction, the hypotheses and outline of this thesis. Degenerative aortic stenosis is the most common valvular heart disease in developed countries. The aim of this thesis is to explore and expand the current knowledge of severe aortic stenosis concerning diagnosis, treatment and prognosis. Disease progression, utilization of different treatment options and their effect on prognosis were studied, both in terms of survival and quality of life.

Chapter 2 provides a general overview of knowledge on patients with aortic stenosis. The causes and pathology of aortic valve stenosis, the clinical presentation of a patient and also current diagnostic tools and treatment options are discussed. Although new techniques to correct degenerative aortic stenosis are upcoming, surgical aortic valve replacement is the current gold standard, and so it will be in the next few years.

The **3rd chapter** presents a systematic literature review that was undertaken to establish the rate of progression of aortic stenosis in adult patients. From the meta-analysis comprising 27 papers, a large variability in reported progression rates was found. Further, different studies used different parameters to report this progression. Mostly used was peak aortic gradient. Pooled annual progression in peak aortic gradient was 3.7 mmHg/year as reported by clinical trials randomizing between statin and non-statin users, and 6.0 mmHg/year in observational studies. Progression rate appeared to be higher in patients with a more severe aortic stenosis, as is reported by others. Since patient-related factors and timing of the first measurement play a role in establishing a progression rate, this rate is largely dependent on the patient-population being studied.

Chapter 4 explains how the microsimulation methodology can be used as a prognostic tool to estimate age- and gender-specific life-expectancy after AVR. The advantages and limitations are discussed extensively in this chapter. The microsimulation model can help in patient selection for AVR and facilitate patient counseling when choosing between a bioprosthesis and mechanical prosthesis or even other types of valve prostheses. Thereby it improves optimized informed decision making for a specific heart valve prosthesis in a particular patient especially when combined with individual patient preferences.

In the **5th chapter** the microsimulation model was used to study age- and gender-specific life expectancy, event-free life expectancy and reoperation-free life expectancy after aortic valve replacement with either a mechanical- or biologic valve prosthesis. For patients over 60 years, the risk of bleeding with a bioprosthesis is not absent, but compared to mechanical valves the risk-reduction of bleeding that can be achieved by avoiding coumadins

outweighs the increased risk associated with reoperations for the feared structural valve deterioration.

Chapter 6 is a book chapter that illustrates how microsimulation can be used to compare patient outcome after AVR with several valve substitutes: stented- and stentless bioprostheses, allografts and autografts. Patient outcome after implantation of stented and stentless bioprostheses or cryopreserved allografts appears to be acceptable and differences in patient outcomes are mostly explained by patient selection and the timing of operation, rather than differences in the performance of these valve substitutes.

In the last decade several papers report a striking discrepancy between the guidelines -either by the ACC/AHA and the ESC- and daily practice concerning the management of symptomatic patients with severe aortic stenosis: many patients do not receive the recommended surgical treatment. **Chapter 7** deals with this discrepancy by studying the reasons why 56% of the 179 patients studied, received medical treatment during an 18 month follow-up. Operative risk, hemodynamic severity and symptomatic status appear to be misclassified frequently leading to an undertreatment of this patient category.

On account of the paper presented in Chapter 7, Dr. Paraskevas wrote a letter to the editor of the European Journal of Cardio-thoracic Surgery in which he shortly discusses the role of statins in the treatment of patients with aortic stenosis. After reviewing available literature on this subject we replied in **Chapter 8** that although statins may interfere with the progression of aortic stenosis, it remains uncertain to what degree, in which patients and until what disease stage. Statin therapy is probably not useful in the cohort we studied: the patient with *severe* aortic stenosis. Comorbidity, high age, the advanced state of the valve stenosis and the possible indication for surgical treatment play a major role in this patient population and prohibit effective studies to either prove or reject this hypothesis.

Chapter 9 provides the objectives, design and early results of the AVARIJN study: a multi-center prospective observational study among 191 patients with severe aortic stenosis in the Rotterdam region (the Netherlands). Patients were followed for 2 years and received clinical and echocardiographic assessments at different time intervals. In this chapter an overview of patient characteristics relative to treatment strategy is given and survival is analyzed by using uni- and multivariable Cox regression and Kaplan-Meier analyses. Symptomatic conservatively treated patients had a survival of approximately 73% at 2 years. Two-thirds of asymptomatic patients developed symptoms during this 2-year period underlining the progressive nature of aortic stenosis and the need for frequent 'watchful waiting'.

In order to assess the quality of life of both symptomatic and asymptomatic patients with severe aortic stenosis the AVARIJN study patients were subjected to the SF-36v2 Health Survey at each study visit. **Chapter 10** discusses the results of these health questionnaires: quality of life among symptomatic patients with severe aortic stenosis is severely impaired compared to the general age-matched Dutch population, both on the physical and on the

emotional level. The study provides a quantification of this burden and it illustrates how the SF-36v2™ Health Survey can assist in decision making for the individual patient

Chapter 11 elaborates further on the quality of life of symptomatic patients with severe aortic stenosis, and shows the results during follow-up either with medical treatment or after AVR. AVR improves not only physical quality of life, but also general health perception, vitality and social function. Besides a low life expectancy, conservatively treated symptomatic patients experience severe physical deterioration emphasizing their need for treatment. Therefore quality of life should be taken into account when making treatment decisions in patients with severe AS.

Chapter 12 gives a glance at the evolving aspects of treatment elderly or high risk patients with (severe) aortic stenosis. Several multi-center randomized trials are ongoing or have recently been performed, exploring safety, benefits, limitations and cost-aspects of the new TAVI technique compared to the conventional surgical aortic valve replacement. The main finding of the PARNTER trial was that the TAVI procedure had similar mortality as AVR after one year and was therefore found to be 'non-inferior' to AVR in high risk operable patients with severe AS, at least in the short term. The SURTAVI trial has recently been designed to randomize intermediate risk patients to TAVI or surgical AVR. It is important to await the results of this trial before further lowering the indications for this new and promising transcatheter technology.

Chapter 13 provides a general discussion, conclusion and recommendations following from this thesis. There is a lot to gain in the management of patients with severe aortic stenosis. Progress can be made in the areas of diagnosis, treatment selection and treatment utilization. Both doctors and patients should and can be better informed about prognosis after each treatment modality, also in terms of quality of life. This will improve decision making especially when the patient is placed right in the center of this evidence-based multi-disciplinary process.

Samenvatting

Hoofdstuk 1 bevat de introductie, de hypotheses en een algemene uiteenzetting van dit proefschift. Aortaklepstenose is de meest voorkomende hartklepziekte in de westerse wereld. Het doel van dit proefschrift is om de huidige kennis over patiënten met ernstige aortaklepstenose te onderzoeken en uit te breiden wat betreft diagnose, behandeling en prognose. Daartoe werd onder andere de progressie van aortklepstenose bestudeerd evenals het gebruik van de verschillende behandelmogelijkheden en hun effect op prognose, zowel wat betreft levensduur als kwaliteit van leven.

Hoofdstuk 2 verschaft een algemeen overzicht van de huidige kennis over patiënten met aortaklepstenose. De onderliggende oorzaken en pathologie van aortaklepstenose, de klinische presentatie van een patiënt, gangbare diagnostische methoden en behandelopties worden in dit hoofdstuk besproken. Hoewel in hoog tempo nieuwe technieken worden ontwikkeld om aortaklepstenose te behandelen, is de chirurgische aortaklepvervanging tot op heden de gouden standaard. Waarschijnlijk blijft dat zo in de nabije toekomst.

Het **derde hoofdstuk** bestaat uit een systematische review van de literatuur die uitgevoerd werd om de mate van progressie van aortaklepstenose bij volwassenen te onderzoeken. Uit de meta-analyse van 27 studies viel op dat er een grote variabiliteit in gerapporteerde progressie bestond. Ook gebruikten verschillende studies verschillende parameters om de progressie te meten. Gepoolde progressie in piek gradiënt over de aortaklep was 3,7 mmHg per jaar in studies die randomiseerden tussen statine gebruikers en patiënten die geen statine gebruikten. Uit observationele studies kwam een gepoolde progressie van 6,0 mmHg per jaar. Verder bleek de progressie hoger bij patiënten met een ernstiger stenose als uitgangspunt. Omdat patiëntgerelateerde factoren en timing van de eerste meting een rol spelen bij de mate van progressie is deze mate dus voor een groot deel afhankelijk van de bestudeerde populatie.

Hoofdstuk 4 toont hoe microsimulatie gebruikt kan worden als hulpmiddel om geslacht- en leeftijdspecifieke levensverwachting na aortaklepvervanging te schatten. De methodologie wordt stap voor stap uitgelegd en de voor- en nadelen komen uitvoerig aan bod. Het model verschaft inzicht in de levensverwachting na aortaklepvervanging met een bepaalde klepprothese en in de mogelijke complicaties op de lange termijn. Daarmee kan het helpen bij de keuze tussen de diverse typen klepprothesen bij de individuele patiënt en kan het bovendien de patiëntvoorlichting verduidelijken.

In **hoofdstuk 5** wordt het microsimulatie model gebruikt om geslacht- en leeftijdspecieke levensverwachting, event-vrije levensverwachting en reoperatie-vrije levensverwachting

na aortaklepvervanging met mechanische of biologische klepprothese te bestuderen. De levensverwachting blijkt vergelijkbaar, maar de event-vrije levensverwachting is hoger na implantatie van een bioprothese voor patiënten vanaf een leeftijd van 60 jaar. Doordat na implantatie van een bioprothese op lange termijn geen (coumarine) antistolling noodzakelijk is -in tegenstelling tot de mechanische prothese- weegt de risicoreductie op antistolling gerelateerde bloedingen op tegen de hogere kans op reoperaties wegens klepdegeneratie.

Hoofdstuk 6 is een hoofdstuk in het boek 'Aortic Root Surgery' dat illustreert hoe met behulp van microsimulatie de resultaten na aortaklepvervanging met diverse types prothesen zoals gestente en stentloze bioprothesen, allografts en autografts vergeleken kunnen worden. De levensverwachting op de lange termijn is voor patiënten na klepvervanging lager vergeleken met de algemene bevolking en dit verschil kan niet alleen verklaard worden door klepgerelateerde complicaties. Waarschijnlijk is vooral bij jonge patiënten een groter deel bepaald door patiëntgerelateerde factoren. Ook lijken de patiënt uitkomsten voor de verschillende kleptypes vergelijkbaar en meer bepaald te worden door patiëntfactoren dan door verschillen in de klepprotheses zelf.

In de laatste jaren zijn er diverse publicaties verschenen die een grote discrepantie aangeven tussen heersende richtlijnen voor de behandeling van symptomatische patiënten met ernstige aortaklepstenose en de dagelijkse praktijk: veel patiënten krijgen niet de aanbevolen (minimaal invasieve) chirurgische behandeling. In **hoofdstuk 7** is gezocht naar de redenen waarom meer dan de helft van de bestudeerde 179 symptomatische patiënten niet chirurgisch werden behandeld gedurende een follow-up van anderhalf jaar. Vaak bleek het operatierisico te worden overschat; hemodynamische ernst van de stenose en symptomatologie werden regelmatig onvoldoende ernstig bevonden om tot chirurgie over te gaan.

Naar aanleiding van de publicatie die werd beschreven in hoofdstuk 7, schreef dr. Paraskevas een brief naar de editor van 'the European Journal of Cardio-thoracic Surgery' waarin hij de rol van statines in de behandeling van patiënten met aortaklepstenose wilde benadrukken. Na literatuur onderzoek op dit gebied te hebben gedaan hebben wij een antwoord geschreven naar de editor, dit is **hoofdstuk 8**. Hoewel statines waarschijnlijk de progressie van aortaklepstenose vertragen is het onduidelijk in welke mate, bij welke patiënten en tot welke gradatie van stenose. In de patiënten groep waarop dit proefschrift betrekking heeft, namelijk patiënten met een ernstige stenose, heeft behandeling met statines waarschijnlijk weinig meerwaarde, althans om de progressie te vertragen. Comorbiditeit, hoge leeftijd en de vergevorderde staat van stenose met daarbij de mogelijke indicatie tot chirurgie spelen een grote rol en bemoeilijken onderzoek naar de rol van statines in deze patiëntpopulatie.

Hoofdstuk 9 beschrijft de doelen, de opzet en de vroege resultaten van de AVARIJN (Aortic VAlve RIJNmond) studie: een multi-center observationele studie onder 191 patiënten met ernstige aortaklep stenose in de regio Rotterdam Rijnmond. Deze patiënten werden

gedurende twee jaar gevolgd waarbij klinische en echocardiografische onderzoeken op diverse tijdsintervallen werden verricht. In dit hoofdstuk worden patiënt karakteristieken gerelateerd aan behandelstrategie en wordt overleving geanalyseerd met behulp van Cox regressie en Kaplan-Meier analyses. Symptomatische patiënten die conservatief werden behandeld hadden een overleving van ongeveer 73% na twee jaar. Twee-derde deel van de asymptomatische patiënten ontwikkelde klachten in deze periode van twee jaar hetgeen het pogressieve karakter van deze ziekte toont en de noodzaak tot frequente en nauwkeurige follow-up bekrachtigt.

Om de kwaliteit van leven te onderzoeken bij symptomatische en bij asymptomatische patiënten met ernstige aortaklepstenose, werden alle patiënten van de AVARIJN studie bij ieder studie bezoek gevraagd een SF-36v2™ gezondheid vragenlijst in te vullen. **Hoofdstuk 10** bespreekt de resultaten van deze vragenlijsten: de kwaliteit van leven bij symptomatische patiënten blijkt ernstig beperkt ten opzichte van de algehele bevolking, zowel fysiek als geestelijk. Deze studie verschaft inzicht in de ziektelast die veel patiënten ervaren en toont tevens de meerwaarde van een dergelijke survey bij het uitstippelen van een behandelplan voor een individuele patiënt.

Hoofdstuk 11 gaat verder in op de kwaliteit van leven van symptomatische patiënten met ernstige aortaklepstenose en toont de resultaten gedurende follow-up na conservatieve behandeling en na aortaklepvervanging. Aortaklepvervanging blijkt niet alleen de fysieke kwaliteit van leven te verbeteren, maar ook de algehele gezondheidperceptie, vitaliteit en sociale interactie. Naast een lagere levensverwachting blijken conservatief behandelde patiënten forse fysieke achteruitgang door te maken, hetgeen de noodzaak onderstreept chirurgische behandeling te overwegen. Gezien deze bevindingen is het belangrijk naast de levensverwachting ook de kwaliteit van leven bewust mee te nemen in de overwegingen op het moment dat er beslissingen over de behandeling moeten worden genomen.

Hoofdstuk 12 bespreekt de snel evoluerende rol van nieuwe behandelmodaliteiten voor aortaklepstenose bij oudere patiënten of patiënten met een hoog operatie risico. Recent zijn meerdere multi-center gerandomiseerde trials uitgevoerd of nog gaande om de veiligheid, de voor- en nadelen en het kostenaspect van de transcatheter techieken te vergelijken met conventionele aortaklepvervanging. De voornaamste bevinding van de PARTNER trial was dat TAVI (transcatheter aortic valve implantation) 'non-inferior' is bij operabele hoog risico patiënten omdat na TAVI de 1-jaars mortaliteit vergelijkbaar was met die na chirurgische aortaklep vervanging. De recent opgestarte SURTAVI trial randomiseert patiënten met een matig hoog operatie risico voor TAVI dan wel chirurgische aortaklepvervanging. De resultaten van deze trial zullen moeten worden afgewacht alvorens de indicaties van de veel belovende TAVI procedure verder te verlagen.

Hoofdstuk 13 bevat de algemene discussie, conclusie en aanbevelingen die volgen uit dit proefschrift. Er kan op allerlei terreinen nog winst worden geboekt in de behandeling van patiënten met ernstige aortaklepstenose. Zo zou in de nabije toekomst zowel

dokter als patiënt beter geïnformeerd moeten zijn over de prognose na de verschillende behandelmodaliteiten, zowel wat betreft levensverwachting als kwaliteit van leven. Dit zal de besluitvorming omtrent de behandeling ten goede komen, vooral wanneer de patiënt centraal wordt geplaatst in dit evidence-based multi-disciplinaire proces.

Dankwoord
Curriculum Vitae
PhD portfolio
List of publications
Abbreviations
Trials
Websites

Dankwoord

Allereerst wil ik alle **patiënten en hun familieleden** bedanken voor hun bereidwilligheid, tijd en moeite om de onderzoekingen te ondergaan. Dit terwijl voor velen een tripje buiten de deur een aanzienlijke lichamelijke, geestelijke en logistieke inspanning vergde.

Sommige patiënten kan ik helaas niet meer persoonlijk bedanken. Mijn dank wil ik dan ook uitspreken aan hun nabestaanden. Hopelijk biedt dit proefschrift een tastbare herinnering dat hun inspanningen niet voor niets zijn geweest.

Professor Bogers, hartelijk dank voor de begeleiding in de afgelopen jaren. U was er altijd voor een helder overleg en een stappenplan voor de toekomst. Het gezag en de rust die u daarbij uitstraalde is indrukwekkend en blijkt zich niet alleen te beperken tot dit soort vergaderingen of patiënten besprekingen. Onlangs heb ik die haast serene rust ook in de operatiekamer mogen ervaren, gecombineerd met uw chirurgische vaardigheden verheft dit uw operaties tot ware kunst. En mócht plan A of B niet lukken, is er altijd nog een plan C t/m F om een probleem op te lossen. Dit is waar ik het meest van heb geleerd. Mijn grote dank hiervoor.

Professor Takkenberg, beste Hanneke, je bent gepromoveerd. Niet alleen op de auto- en allografts, maar ook van co-promotor tot mijn promotor! Dank voor de vele uren begeleiding tijdens korte werkonderbrekingen die je voor me inruimde. We hebben optimaal gebruik gemaakt van moderne media als telefoon, e-mail, msn en skype. Ook tijdens je verblijf in de USA en later tijdens de meest onzekere periode in je bestaan bleef je op deze manier bereikbaar voor een vraag of methodologisch probleem. Je betrokkenheid en aanwezigheid bij de diverse presentaties in binnen- en buitenland heb ik altijd zeer gewaardeerd. Dankjewel!

Professor Kappetein, beste Arie Pieter. Nog zo'n duizendpoot, maar dan anders: het is werkelijk ongelooflijk hoe je al je werkzaamheden op de verschillende continenten weet te combineren. Volgens mij breng je meer tijd door in het vliegtuig dan ik in de auto! Vaak zat je in een spagaat tussen internationale vergaderingen en de lokale problematiek van deze onderzoeker. Je kritische en heldere analyses van diverse artikelen hebben me dikwijls verrast en soms verbaasd. Ik ben blij dat we er goed uitgekomen zijn en ben zeer dankbaar jou als begeleider te hebben gehad.

Professor Van Swieten, ik ben er trots op dat u in 'mijn' promotiecommissie hebt willen plaatsnemen om dit onderzoek te beoordelen. U hebt aan de basis gestaan van mijn carrière en tevens vormde u de stimulus dit promotieonderzoek te starten. Ik heb nog nooit ergens zo veel geleerd als in mijn eerste tijd, in het Antonius Ziekenhuis. Vooral

leerde u mij goed en kritisch na te denken, goed naar patiënten te luisteren en hen te observeren. En verder om allerlei diagnostiek, technieken en meningen van anderen -en van mijzelf- kritisch tegen het licht te houden. Daar probeer ik me nog steeds in te trainen. Elk detail telt.

Professor Zijlstra en **professor De Jaegere,** hartelijk dank voor uw aandeel in deze promotiecommissie en de tijd en moeite die u beiden hebt genomen om dit proefschrift te onderwerpen aan een kritische blik. Uw beider cardiologische visie op dit proefschrift is voor mij zeer belangrijk aangezien een groot deel van het onderzoek zich bevindt op cardiologisch vlak, echter verricht vanuit cardio-chirurgisch perspectief. Ik ben benieuwd naar uw mening!

Professor Jamieson, thank you for your excellent dataset and even more for your enthusiasm, your ideas and your support that have helped me working on the micro-simulation papers, Chapters 4 and 5 of this book. The trip to Canada was a great way to join business with pleasure, although I didn't get to see much of Vancouver: the weather prohibited vision of more than a few meters but the snow was great!

Helena Heuvelman, dank voor het voortzetten van de AVARIJN studie. Het was niet altijd gemakkelijk maar mede dankzij jouw zorgvuldigheid en toewijding kon de studie en daarmee dit proefschrift goed worden afgerond. Hopelijk bevalt je nieuwe carrière en zal jouw boekwerk snel volgen! Heel veel succes!

Tjebbe Galema en **Marcel Geleijnse** ben ik dank verschuldigd voor hun cardiologische advies over de opzet en uitvoering van de AVARIJN studie en voor hun visie op individuele patiënten en echo's.

Verder wil ik voor het kostenloos mogelijk maken van de AVARIJN studie de **Cardiologen, echolaboranten** en **andere medewerkers** van de volgende deelnemende centra in de regio bedanken voor hun medewerking: **Erasmus MC, St. Franciscus Gasthuis, Vlietland Ziekenhuis, IJsselland Ziekenhuis, Albert Schweitzer Ziekenhuis, Maasstad Ziekenhuis** en het **Haven Ziekenhuis**.

Yusuf Karamermer wil ik bedanken voor zijn inzet veel van de AVARIJN echo's mede te beoordelen en mee op jacht te gaan naar nieuwe patiënten. Je was teleurgesteld in je baan destijds, ik hoop dat je nu op een meer comfortabele plek zit en wens je alle succes in je carrière!

Liz van der Velden, zoveel patiënten waren enthousiast over alle aandacht en tijd die je hen schonk. Ze kennen je nu nog precies! Mede namens hen bedankt voor al je goede zorgen! Verder dank ik **Marijke Rozema, Angelique Venema, Els Berenschot** en **Liesbeth Duininck** voor de ondersteuning van de diverse studies en voor de vragen die jullie steeds weer bereid waren te beantwoorden. Natuurlijk ben ik ook **Annet Damhuis** veel dank verschuldigd voor het regelen van diverse afspraken in de drukke agenda's van de hoge heren en dame.

Loes Klieverik en **Menno van Gameren**, collega onderzoekers destijds, bedankt voor de broodnodige afwisseling tijdens lange dagen onderzoek. Jullie hebben het toch wat sneller klaar gespeeld. Menno dank ik daarnaast voor het onderhouden van de monteurs- en plaatwerkers vaardigheden: rijdt de Mini eigenlijk nog? Loes, het weekendje New York was gezellig, wanneer delen we nog eens een kamertje?

Mijn opleider **Dr. Berreklouw,** mede-opleiders **Bart van Straten, Joost ter Woorst, Erwin Tan, Ted Elenbaas** en **Ibrahim Özdemir**. Het moeten werken met assistenten valt natuurlijk niet mee, zeker niet als ze ook nog eens bijdehand zijn. Ik geniet van de vele zaken die ik van jullie leer, vooral in de operatiekamer, maar ook daarbuiten. Dank voor het beantwoorden van de vragen die ik jullie stel, het geduld dat jullie betrachten en het vertrouwen dat er in mij gesteld wordt.

Mede-assistenten **Niels Verberkmoes**, **Martin de Jonge** en **Astrid van Boxtel**, oud assistenten **Sander Bramer**, **Bart Koene, Mohamed Soliman** en **Suzanne Kats** en verder alle **ANIOS** en **nurse practitioners** die het dagelijkse werk veraangenamen bedank ik voor de gezelligheid, voor de collegialiteit en voor het uitwisselen van de vele ervaringen.

Dr. G.A.P. Nieuwenhuijzen dank ik voor een zeer goede start van de opleiding door een gedegen introductie in de algemene chirurgie. Grard, je bent een zeer betrokken, correcte en enthousiaste opleider die assistenten mogelijkheden en tijd biedt voor andere zaken dan alleen het assistentschap: voor wetenschap kon ik tijd inruimen, mits dat niet ten koste ging van de sociale interactie met de groep. Een betere opleider kon die groep zich niet wensen denk ik. Hartelijk bedankt!

Dr. L.K.J. de Hondt dank ik voor de persoonlijke begeleiding in de laatste maanden.

Heren van de jaarclub, **Mark van Nijnatten, Ewoudt van de Garde, Ton Bosshardt, Haye Strikwerda, Mark van der Lubbe, Boudewijn Wilmink** en **Frido Oei**, de bijnamen laat ik hier maar even achterwege.. Jaartje ’96 blijft toch het mooiste jaar: peren en presteren moeten hand in hand... Die balans wil ik weer herstellen, bovendien heeft de Utregse horeca het zwaar zonder ons. Ook een clubweekend in een stad als Madrid overslaan zal me niet snel meer gebeuren. Dank voor de onsterfelijke vriendschap!

Een aantal andere vrienden wil ik nog expliciet noemen: **Wouter Eikelboom,** Wout, van al m’n vrienden ken ik jou het langst, we hebben nog samen in de box gelegen. De vriendschap is me dierbaar en ik ben dankbaar dat dit al die jaren heeft stand gehouden ondanks onze verschillende levens. **Michiel Toxopeus**, Tox, op jou kan ik terugvallen wanneer dat nodig is en dat is een fijne gedachte. Mijn dank hiervoor is groot. **Michael Dijkstra**, Mich, ook jij bent een trouwe vriend op wie ik kan bouwen, en het komt goed uit dat je veel meer gastronomisch ingesteld bent dan ik. Dank voor de vele mooie avondjes thuis en in de diverse Utrechtse etablissementen.

Pap en mam, zonder jullie had ik het al meer dan eens niet gered en zonder jullie was dit promotie-onderzoek een paar jaar geleden gestrand. Dank voor het zitvlees dat jullie me al vroeg hebben laten kweken, ik heb het nodig gehad. Nog veel belangrijker is jullie

onvoorwaardelijke steun op velerlei vlakken, jullie niet-aflatende liefde en altijd aanwezige gastvrijheid. Dank voor de uitdagingen en de mogelijkheden die ik altijd van jullie heb gekregen, daarom zijn jullie ook op financieel vlak eigenlijk de hoofdsponsor van deze productie (en toch sta je dan onderaan het sponsorlijstje..). Pap, dank je voor het kritisch beoordelen van de eerdere papers, voor de inhoudelijke discussies en het uitwisselen van ervaringen. Dat je je taak om dit boekwerk nog eens kritisch na te lopen zo serieus nam, gaf me veel rust. Dankjewel!

Zusjes Irene en Marie-Sophie, **Miep** en **Ietje**. Tja Ietje, was ik toch nog eerder paranimf bij jou dan jij bij mij. Dat had ik eigenlijk op de middelbare school al moeten weten. Ik vind het prachtig om te zien hoe je je sindsdien hebt ontwikkeld, zowel in je werkzame bestaan als in je persoonlijke leven. Je hebt genoten van je jaar in Frankrijk en ik hoop van harte dat je die levensstijl blijft nastreven! Miepie, je bent een kanjer en een lief zusje. Hard wanneer dat moet, zacht wanneer het kan. Binnen enkele jaren run jij je eigen bedrijf of heb je er al een paar overgenomen, dat weet ik zeker. Dank je voor je genegenheid, voor je enthousiasme en natuurlijk voor al je kledingadviezen.

Lieve **Ingrid,** je hebt al je principes aan de kant gezet en vervolgens heb ik hart gebroken. Dat, en de manier waarop, spijt me zeer. Ik hoop m'n leven inmiddels beter op orde te hebben en in de toekomst niet meer gevangen te zitten in tweestrijd. Ik heb het te weinig laten blijken, maar je hebt met je vrolijkheid en genegenheid veel meer voor me betekend dan je denkt. Dankjewel.

Lieve **Annebeth**, ons zeilbootje is uiteindelijk toch vast komen te zitten en helaas niet vanwege het rietzeilen; dat hebben we te weinig gedaan. Ik realiseer me dat mijn werk, dit proefschrift en mijn karakter een grote wissel hebben getrokken op ons bestaan. Wat heb jij het zwaar gehad met mij. Ik hoop van harte dat we beiden ons geluk weer kunnen hervinden, in elk geval verdien je dat want je bent een mooi mens, een lieve vriendin en een geweldige moeder!

Lieve **Dries,** jij bent het mooiste ventje dat ik me kan voorstellen, een leuker zoontje had ik me niet kunnen wensen! Bijna altijd ben je vrolijk, uitdagend en leergierig. Als er al wat nukkigheid naar boven komt blijkt steevast dat er onvoldoende is voldaan aan basale levensbehoeften als tijdige slaap en voeding. Je bent een pienter, lief en zachtaardig mannetje. Verder ben je ontzettend gezellig met andere 'kleuters' van uiteenlopende leeftijden, hoewel je ook een eigen willetje hebt dat je altijd krachtig zult verdedigen. Je hebt humor blijkend uit de grappen die je maakt en je kletst de hele dag door, "Oh, waarom?" blijven hierbij de kernwoorden. Met je grote opmerkzaamheid en onstilbare nieuwsgierigheid wil je werkelijk alles tot in detail weten. In jou herken ik veel van mezelf en gelukkig veel ook niet. Je bent een verrijking van mijn leven, dankjewel!

Curriculum Vitae

The author was born in Utrecht, the Netherlands, on June 25th 1978. In 1996 he graduated from high school, 'Stedelijk Gymnasium Bredanum' and started his medical training at the State University Utrecht. The senior internship was done at the department of cardio-thoracic surgery of the Antonius Hospital Nieuwegein (prof.dr.ir. H.A. van Swieten) where he started working as a resident -not in training- after his graduation in April 2004. Here he obtained his first clinical experience and basic operative skills. The first serious scientific contributions were made during his Ph.D. training which was started in October 2005 under supervision of prof.dr. A.J.J.C. Bogers, prof.dr. J.J.M. Takkenberg and prof.dr. A.P. Kappetein of the department of cardio-thoracic surgery of the Erasmus University Medical Center. Designing and running the AVARIJN study as well as work on micro-simulation in collaboration with Dr. Jamieson (University of British Columbia, Vancouver, Canada) formed the basis of this thesis. In the summer of 2008 a master in Clinical Epidemiology was obtained at the Netherlands Institute for Health Sciences (NIHES, prof.dr. A. Hofman). In October 2008 he started as a resident at the department of cardio-thoracic surgery of the Catharina Hospital in Eindhoven, and from March 2009 he is in training to become a cardio-thoracic surgeon. The first two years consisted of training in general surgery (dr. G.A.P. Nieuwenhuijzen), the remaining years of training in cardio-thoracic surgery are supervised by dr. E. Berreklouw.

PhD Portfolio

Name PhD student:	M.W.A. van Geldorp
Erasmus MC Department:	Cardio-thoracic Surgery
Research School:	COEUR
PhD period:	2005-2012
Promotores:	Prof.dr. J.J.M. Takkenberg
	Prof.dr. A.P. Kappetein

PhD Training	Year	Workload
Education		
· Master 'Clinical Epidemiology' at the Netherlands Institute for Health Sciences (NIHES)	2007-2008	70
· Erasmus Winter Programme (NIHES)	2006	4.5
Oral presentations		
· Patient outcome after AVR with mechanical or bioprostheses: weighing lifetime anticoagulant related event risk against reoperation risk (SHVD, New-York)	2007	0.6
· Symptomatic severe aortic stenosis-Therapeutic decisions and consequences in 179 patients (1st prize NVT, Utrecht)	2008	0.6
· Symptomatic severe aortic stenosis-Therapeutic decisions and consequences in 179 patients (EACTS, Lisbon)	2007	0.6
· Quality of life of patients with symptomatic severe aortic stenosis (NVT, Utrecht)	2008	0.6
· Exercise testing in severe aortic stenosis reveals symptoms in one-third of previously presumed 'asymptomatic' patients (NVT, Leiden)	2008	0.6
· Exercise testing in severe aortic stenosis reveals symptoms in one-third of previously presumed 'asymptomatic' patients (SHVD, Berlin)	2009	0.6
· Clinical course of patients diagnosed with severe aortic stenosis: insights from the AVARIJN study (SHVD, Barcelona)	2011	0.6
· Quality of life of patients with severe aortic stenosis (SHVD, Barcelona)	2011	0.6
· Paraprosthetic regurgitation after surgical aortic valve replacement (NVT, Utrecht)	2011	0.6
Poster presentations		
· Patient outcome after AVR with mechanical or bioprostheses: weighing lifetime anticoagulant related event risk against reoperation risk (1st prize poster NVT, Amsterdam)	2007	0.6
· AVR improves quality of life in selected symptomatic patients with severe aortic stenosis (SHVD, Barcelona)	2011	0.6
Coeur courses		
· Cardiovascular imaging and diagnostics	2006	1.5
· Congenital heart disease	2006	1.5
· Vascular medicine	2007	2
· Arrhythmia-research methodology	2007	1.5
· Peripheral and intracranial aneurysmal diseases	2008	1.5
Coeur seminars and workshops		
· Electrophysiology	2006	0.4
· Pulmonary circulation	2007	0.4
· Tetralogy of Fallot	2008	0.4
· Percutaneous aortic valve implantation	2009	0.4

International conferences

· European Association of Cardio Thoracic Surgery annual meeting (Stockholm)	2006	1.5
· ´At the heart of evolution, evolving scenarios in aortic valve surgery´ (Amsterdam)	2007	0.3
· Society for Heart Valve Disease biennial meeting (New-York)	2007	1.5
· European Association of Cardio Thoracic Surgery annual meeting (Lisbon)	2008	1.5
· Society for Heart Valve Disease 5th biennial meeting (Berlin)	2009	1.5
· Society for Heart Valve Disease 6th biennial meeting (Barcelona)	2011	1.5

National and local conferences

· Meetings of the Dutch Association for Thoracic Surgery	2004-2012	3.5
· Meetings of the 'Cardiologen Club Rijnmond'	2005-2008	0.5
· Cardiology and Vascular Medicine, update and perspective (Rotterdam)	2006	1
· Local conferences	2004-2012	4.5

List of publications

PAPERS

MWA van Geldorp, WRE Jamieson, AP Kappetein, JPA Puvimanasinghe, MJC Eijkemans, GL Grunkemeier, JJM Takkenberg, AJJC Bogers. Usefulness of microsimulation to translate valve performance into patient outcome: patient prognosis after AVR with the CE-SAV bioprosthesis. *J Thorac Cardiovasc Surg 2007;134:702-9.*

AP Kappetein, **MWA van Geldorp**, JJM Takkenberg, AJJC Bogers: Optimum management of elderly patients with calcified aortic stenosis. *Expert Rev Cardiovasc Ther 2008;6:491-501*

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MWA van Geldorp, M van Gameren, AP Kappetein, B Arabkhani, LE de Groot- de Laat, JJM Takkenberg, AJJC Bogers: Therapeutic decisions in patients with symptomatic severe aortic stenosis: room for improvement? *Eur J Cardiothorac Surg 2009;35:953-7.*

MWA van Geldorp, JJM Takkenberg, AJJC Bogers, AP Kappetein: New trends and developments in patients with severe aortic stenosis: towards optimal treatment? *European Cardiology, Touch briefings 2009, 81-4*

M Jahangiri, AP Kappetein, **MWA van Geldorp**, AJJC Bogers. The evolution of advanced techniques for the management of symptomatic aortic stenosis in the elderly population: conventional surgical management vs transcatheter valve implantation. *J R Coll Physicians Edinb 2010;40:323-7.*

MWA van Geldorp, HJ Heuvelman, AP Kappetein, ML Geleijnse, TW Galema, AJJC Bogers, JJM Takkenberg. Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study. *Neth Heart J. 2012 Aug 3. Neth. Heart. J. 2012;20: 487-93*

MWA van Geldorp, AP Kappetein, JJV Busschbach, JJM Takkenberg, AJJC Bogers. Quality of life among patients with severe aortic stenosis. *Neth. Heart J. 2013;21:21-7*

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HJ Heuvelman, **MWA van Geldorp**, MJC Eijkemans, NM Rajamannan, AJJC Bogers, JW Roos-Hesselink, JJM Takkenberg. Progression of aortic valve stenosis in adults: A systematic review *J Heart Valve Dis 2012;21:454-62*

BMJA Koene, AHM van Straten, **MWA van Geldorp**, FJ ter Woorst, ThWO Elenbaas, MA Soliman Hamad. Can the EuroSCORE Predict Midterm Survival After Aortic Valve Replacement? *J Cardiothorac Vasc Anesth. 2012 Aug;26(4):617-23. Epub 2012 Mar 8.*

S. Bramer, FJ ter Woorst, **MWA van Geldorp**, KC van den Broek, JG Maessen, E Berreklouw, AHM van Straten. Does new-onset postoperative atrial fibrillation after coronary artery bypass grafting affect postoperative quality of life? J Thorac Cardiovasc Surg. 2012 Jul 25. *[Epub ahead of print]*

LETTER

MWA van Geldorp, JJM Takkenberg. Reply to Paraskevas 'Prescribing statins in aortic stenosis, little to lose, much to gain', *Eur J Cardiothorac Surg 2010;37:497-9.*

BOOK CHAPTERS

MWA van Geldorp, MAAM Schepens. Pijn op de borst: type A aorta dissectie; Chapter 12 (p159-73) 'Probleem georiënteerd denken in de cardiologie', G.K. Hovingh, G.A. Somsen, *De Tijdstroom 2007, ISBN 9789058981080*

JJM Takkenberg, **MWA van Geldorp**. Predicted patient outcome after bioprosthetic AVR and the Ross operation. *Chapter 39, Aortic Root Surgery, CA Yankah, Y Weng, R Hertzer. Springer 2010, ISBN 9783798518698*

List of Abbreviations

Abbreviation	Explanation	Website
ACC	American College of Cardiology	www.acc.org
ACE	Angiotensin Converting Enzyme	
AHA	American Heart Association	www.heart.org
AS	Aortic Stenosis	
AV	Aortic Valve	
AVA	Aortic Valve Area	
AVR	Aortic Valve Replacement	
BNP	Brain Natriuretic Peptide	
BP	Bioprosthesis	
CABG	Coronary Artery Bypass Grafting	
CAD	Coronary Artery Disease	
CE-SAV	Carpentier Edwards Supra-Annular Valve	
CI	Confidence Interval	
CT	Computed Tomography	
EF	Ejection Fraction	
EFLE	Event-Free Life Expectancy	
EOA	Effective Orifice Area	
EuroQol	European Quality of life group	www.euroqol.org
ESC	European Society of Cardiology	www.escardio.org
EuroSCORE	European System for Cardiac Operative Risk Evaluation	www.euroscore.org
HR	Hazard Ratio	
KM	Kaplan Meier	
LAD	Left Anterior Descending artery	
lCL	Lower Confidence Limit	
LE	Life Expectancy	
LVEF	Left Ventricular Ejection Fraction	
LVOT	Left Ventricular Outflow Tract	
MAG	Mean Aortic Gradient	
MP	Mechanical Prosthesis	
MR	Mitral Regurgitation	
MS	Micro-Simulation	www.cardiothoracicresearch.nl
MS-CT	Multi-Slice Computed Tomography	

Nt-proBNP	N-terminal prohormone Brain Natriuretic Peptide	
NYHA	New-York Heart Association	
PAG	Peak Aortic Gradient	
PCI	Percutaneous Coronary Intervention	
PET	Positron Emission Tomography	
QALY	Quality Adjusted Life Year	
QOL	Quality Of Life	
RCT	Randomized Clinical Trial	
RFLE	Reoperation-Free Life Expectancy	
SAVR	Surgical Aortic Valve Replacement	
SD	Standard Deviation	
SF-36v2	Short-Form 36 version 2	www.sf-36.org
STS	Society of Thoracic Surgery	www.sts.org
SVD	Structural Valve Deterioration	
TAVI	Transcatheter Aortic Valve Implantation	
uCL	Upper Confidence Limit	
Vmax	Maximum trans aortic jet velocity	
VRE	Valve Related Event	
VTI	Velocity Time Integral	

Trials

Acronym	Explanation	Website
ASTRONOMER	Aortic STenosis pRogressiON Observation Measuring the Effects of Rosuvastatin	www.clinicaltrials.gov/ct2/show/NCT00800800
AVARIJN	Aortic VAlve RIJNmond	
PARTNER	Placement of AoRtic TraNscathetER valve trial	www.clinicaltrials.gov/ct2/show/NCT00530894
RAAVE	Rosuvastatin Affecting Aortic Valve Endothelium	www.clinicaltrials.gov/ct2/show/NCT00114491
SALTIRE	Scottish Aortic stenosis and Lipid lowering Trial, Impact on REgression	
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis	
SOURCE	SAPIEN XT™ Aortic Bioprosthesis Multi-region Outcome Registry	www.clinicaltrials.gov/ct2/show/NCT01238497
SURTAVI	Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement	www.clinicaltrials.gov/ct2/show/NCT01586910
TASS	Tyrolean Aortic Stenosis Study	

Websites

Aortaklep stenose	www.aortaklep.nl
American Association for Thoracic Surgery	www.aats.org
American College of Cardiology	www.acc.org
American Heart Association	www.heart.org
American Thoracic Society	www.thoracic.org
AVR Microsimulatie model	www.cardiothoracicresearch.nl
Cardio-thoracic Surgery Network	www.ctsnet.org
Centers for Disease Control and Prevention	www.cdc.gov
Centraal Bureau voor Statistiek	www.cbs.nl
Clinical trials	www.clinicaltrials.gov
Erasmus MC	www.erasmusmc.nl
European Society of Cardiology	www.escardio.org
European Society of Cardio-Thoracic Surgery	www.eacts.org
European System for Cardiac Operative Risk Evaluation	www.euroscore.org
EuroQol	www.euroqol.org
International Society for Heart & Lung Transplantation	www.ishlt.org
International Society for Minimally Invasive Cardiothoracic Surgery	www.ismics.org
Ministerie van Volksgezondheid, Welzijn en Sport	www.rijksoverheid.nl/ministeries/vws#ref-minvws
Nederlandse Vereniging voor Cardiologie	www.nvvc.nl
Nederlandse Vereniging voor Thoraxchirurgie	www.nvtnet.nl
Short-Form 36TM Health Survey	www.sf-36.org en www.qualitymetric.com
Society for Heart Valve Disease	www.shvd.org
Society of Thoracic Surgery	www.sts.org
Statistics Canada	www.statcan.gc.ca
United Kingdom National Statistics	www.statistics.gov.uk