AORTIC STENOSIS IN ADULTS

Natural history, treatment and outcome

Helena J. Heuvelman

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NATURAL HISTORY, TREATMENT AND OUTCOME

HELENA J. HEUVELMAN

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Voor Marinus

Friends are as important as achievement. Another is that teamwork is the one key to success and that selfishness only makes a man small...

Sherpa Tenzing, 1914-1986

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Be less curious about people and more curious about ideas.

M.S. Sklodowska-Curie

1

GENERAL INTRODUCTION AND OUTLINE OF THESIS

PREFACE

This thesis concerns aortic stenosis (AS) in contemporary clinical practice. First, an introduction will be given to provide background information on the normal aortic valve, and thereafter on the incidence, disease spectrum, diagnosis, treatment, and prognosis of AS disease. Second, the aim of the thesis and the research questions addressed in this thesis will be formulated. Finally, an overview of the thesis contents will be provided.

THE NORMAL AORTIC VALVE

The formation of the aortic valve starts already at week 4 of gestation and its development is part of a complex process. A non-diseased aortic valve consists of 3 leaflets (tricuspid) which smoothly move in a one-way direction during contractions of the heart[1,2] (Figure 1). During systole, the left ventricle (LV) contracts and increases pressure in the LV which results in an opening of the aortic valve leaflets allowing blood flow from the LV into the aorta, the largest artery in the body. When systole ends, the pressure will rapidly decrease which allows the aortic pressure to close the aortic valve and blood flow from the left atrium into the LV.

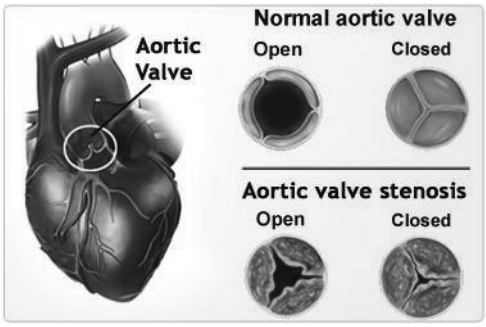

Figure 1. Normal and stenosed aortic valve.

AORTIC STENOSIS: PREVALENCE AND DISEASE SPECTRUM

AS disease is common and its prevalence increases with age up to 5% among people aged over 75 years.[3] Within 40 years, in 2052, the estimated world population will have increased to 9.3 billion of whom at least 280 million inhabitants will have AS disease that requires treatment.[3,4] AS disease will constitute a major worldwide health issue.[5] Etiologically, the distinction can be made between calcific, congenital, and rheumatic AS.

Calcific AS

Calcific AS is a common progressive valvular disorder among elderly people in industrialized countries and represents a major public-health problem for ageing societies.[3,4] Up to 3% of the elderly aged 75 years and older have calcific AS while aortic sclerosis, the preceding stage of calcific AS, is prevalent in almost 30% of the adults aged over 65 years.[3,6-8] Calcific AS counts for 50 to 80% of native valvular heart disease and has a male predominance.[9-11]

The pathway of calcific AS disease is complex and appears to be an actively regulated disease process which comprises varying disease stages from initial alterations in the cell biology of the leaflets to end-stage calcification.[12,13] The stenosis of the calcific tricuspid aortic valve is located at valvular level (Figure 1). The progressive valvular calcification (Figure 2) causes a gradually decreasing leaflet opening to which the LV responds with hypertrophy. However, this compensatory mechanism fails as systolic LV dysfunction starts to develop, and the final stage of AS disease is entered. In this stage, most patients become symptomatic which marks a critical point in the course of AS disease since prognosis worsens dramatically.[14] When angina and heart failure develop, life expectancy is limited to a maximum of 5 years.[15] In asymptomatic patients with severe AS, the course of AS disease is more difficult to predict and requires careful monitoring due to the progressive nature of AS disease and the risk of sudden death which is approximately 1% per year.[14,16]

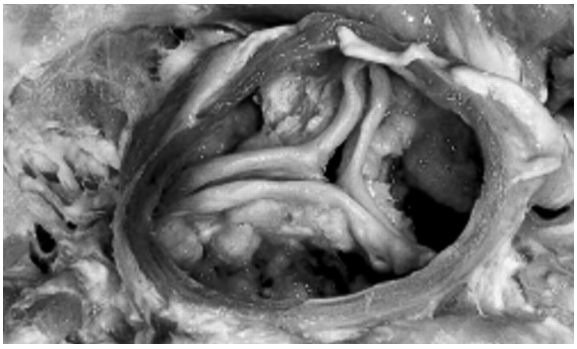

Figure 2. Calcific aortic valve stenosis.

Congenital AS

Congenital AS contributes importantly to the growing population of young adults with congenital heart disease (CHD) who have survived childhood (the so-called Grown-Up Congenital Heart (GUCH) patients) and increases the impact of valvular heart disease on global disease burden.[17,18] The estimated worldwide prevalence of adult CHD for the year 2000 was 0.28% of whom half suffered from moderate to truly complex CHD.[18,19] A bicuspid aortic valve, the most common cause of

congenital valvular AS (Figure 3), is present in 1 to 2% of the general population and counts for 5 to 40% of native AS disease.[11,20-23] Although much less prevalent, also unicuspid and quadricuspid aortic valves exist in the disease spectrum of congenital AS.[1]

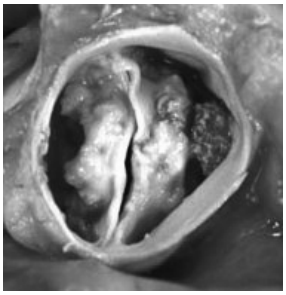

Figure 3. Severely calcified bicuspid aortic valve.

Bicuspid AS is characterized by a varying disease presentation ranging from severe valvular AS in utero to asymptomatic disease in the elderly.[21] The presence of congenital AS in infancy is often due to commissural fusion and marks more severe disease with poor outcomes.[21] Over 80% of the children with initially mild AS disease progress to more severe AS disease during a 30-year follow-up period.[24] In adults, congenital AS is often due to leaflet calcification comparable to tricuspid aortic valve calcification, except that calcification is often already present at an average age of 40 years and requires earlier intervention.[9,10,21,25]

Although less prevalent, the disease spectrum of congenital AS also includes subvalvular and supravalvular AS disease.

Subvalvular AS counts for up to 30% of the pediatric LV outflow tract obstructions and usually presents after the first year of life.[26-28] The disease has two pathological presentations; the focal, discrete membrane form (so-called discrete subaortic stenosis (DSS)) which is most often encountered (90%) with a prevalence of 6.5% among adults with CHD, and the diffuse muscular narrowing form (with varying forms of tunnel stenosis and hypertrophic obstructive cardiomyopathy (HOCM)) which is associated with more severe AS.[29-31] DSS is known for its unpredictable and progressive course during childhood due to the increasing obstruction of the LV outflow tract over time and severity of aortic regurgitation.[30,32] It also may be part of complex multilevel and obstructive lesions; it is often associated with ventricular septal defects, coarctation of the aorta, and in almost one-fourth of the patients accompanied with a bicuspid aortic valve.[30] Although studies concerning children, who survived CHD into adulthood, are now emerging, evidence about DSS evolution over time in adult patients, is limited.

Supravalvular AS is a rare (1/20,000 to 1/50,000) congenital anomaly of the aortic root, often associated with the Williams-Beuren syndrome, a genetic deficiency in elastin production, which is characterized by mental retardation, elfin face, and hoarse voice production.[30,33,34] The phenotype of this disease is may vary from the discrete form which is characterized by a ring-like thickening at the sinotubular junction which occur in 75% of the patients with supravalvular AS, to the diffuse form which involves thickening and hypoplasia of the complete ascending aorta, sometimes including the pulmonary arterial system as well, and turns out a complex disease to manage.[33] Both disease entities require intervention at childhood age due to the consequence of LV outflow tract obstruction and because both are commonly associated with other pathology like subvalvular AS, bicuspid aortic valve, tricuspid aortic dysplastic thickening, pulmonary stenosis, and coronary stenosis and ischemia.[30,35-37]

Since congenital AS encloses a wide disease spectrum with an increasing number of GUCH patients and longitudinal studies are lacking, it is difficult to provide detailed information about the prognosis of congenital AS disease. In the Netherlands, in 2009 only 1% of all cardiovascular deaths was due to CHD.[38] Asymptomatic adults with a bicuspid aortic valve have the same life expectancy compared to the general population.[39,40] On the other hand, when heart failure develops, the prognosis of patients with severe symptomatic AS disease without intervention is shortened to 2 or 3 years.[12] In case of concomitant aortic root or ascending aorta dilatation in patients with a bicuspid valve, patients could die of a dissection or ruptured aneurysm.[21,30]

Rheumatic AS

Finally, rheumatic AS disease in the developing regions of the world and in indigenous populations in developed countries, contributes further to the incidence and burden of heart disease.[41] While rheumatic heart disease has an estimated prevalence range from 15.6 to 19.6 million cases worldwide, rheumatic AS seems a less common cause of isolated AS with an estimated prevalence of 2 to 11% of the native valvular heart diseases.[10,11,42,43]

Rheumatic AS (Figure 4) is preceded by (acute) rheumatic fever, which is a constellation of symptoms based on an abnormal autoimmune response following a group A streptococcal infection.[44,45] Over one-third of the patients with rheumatic fever presents with carditis encompassing varying disease stages from valvulitis to myocarditis to pericarditis which can result in irreversible valve damage and heart failure.[43,44] Although isolated rheumatic AS is rare as it is almost always accompanied by mitral valve disease and aortic regurgitation, chronic progression can lead to fusion of the commissures of the aortic valve with scarring and eventual calcifica-

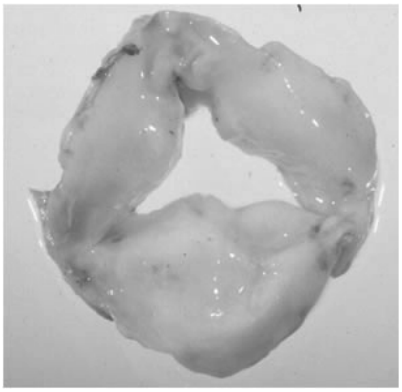

Figure 4. Post-rheumatic aortic valve.

tion of the cusps.[45,46] Unfortunately, many patients present too late and severe heart failure with myocardial dilatation and dysfunction will ultimately lead to the death of these patients. The estimated annual number of deaths from rheumatic heart disease for the year 2000 was 332,000 worldwide and it remains a major cause of cardiovascular death of children and young adults in developing countries.[43,44,47,48]

AORTIC STENOSIS: DIAGNOSIS

The clinical presentation of patients with AS disease depends on the underlying etiology, the severity of stenosis, severity of calcification, LV function, and concomitant other disease.[12] Calcific AS often presents at the age of 60 years and beyond, congenital AS often firstly presents at childhood and young adult age, and rheumatic AS presentation varies from the age of 20 to 50 years.[44]

History taking

History taking shows that exertional shortness of breath is the most common feature of AS disease at presentation, but angina, dizziness, and/or syncope could also exist. It is not uncommon that asymptomatic patients present themselves with a murmur which was identified during a regular medical check-up. In an emergency setting, acute heart failure, an embolic event such as transient ischemic attack or cerebrovascular accident, infective endocarditis, or arrhythmia could be the first presentation of AS disease. If young patients present with AS disease, it is important to investigate the occurrence of AS disease in their relatives because of the familial clustering and high heritability of bicuspid aortic valve disease.[49] Finally, a history of rheumatic fever may suspect for rheumatic etiology of AS disease.

Physical examination

Physical examination reveals a systolic crescendo-decrescendo murmur along the left sternal border which radiates into the carotid arteries which is characteristic for AS.[12] The intensity of the murmur does not correspond with the severity of AS disease, but the duration of the murmur increases as AS becomes more severe. In some patients, the murmur is 'missed'; in obese patients and patients with lung disease where the murmur is muffled, and in patients with LV dysfunction where the murmur is blunted.[50] Patients with AS disease are classified into the New York Heart Association to provide insight into their exercise tolerance. When severe AS is present and the left part of the heart could not compensate any longer, left heart failure starts to develop from LV hypertrophy to dilatation in the final stage, resulting in pulmonary edema and severe respiratory distress. If also the right side of the heart is involved, edema of the lower limbs (or sacral edema if bedridden), nycturia, ascites, hepatomegaly, and increased central venous pressure appear.

Additional examination

Additional examination may consist of electrocardiography, chest radiography, echocardiography, exercise testing, and cardiac catheterization.

On *electrocardiography,* LV hypertrophy accompanied by secondary repolarization abnormalities occur in 85% of the patients with severe AS.[12] Easy to obtain and at a relatively low cost, the absence of hypertrophy, conduction abnormalities such as left and right bundle branch block, atrial enlargement, atrial fibrillation (in patients with hypertension and in the elderly), prior myocardial infarction, and ischemia on electrocardiography provides useful negative information.[14]

As cardiomegaly is a late feature in AS disease, cardiac size is often normal on *chest radiography*, except the rounding of the LV border and apex due to hypertrophy.[12] This examination also provides information about cardiac calcification, and the pulmonary and systemic venous pressure.[14] In patients with a bicuspid aortic valve, the ascending aorta may dilate whereas in advanced heart failure, dilatation of the right atrium and ventricle may occur.[12]

According to the American College of Cardiology, the American Heart Association (ACC/AHA), the European Society of Cardiology, and the European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines for the management of patients with valvular heart disease, the (final) hemodynamic diagnosis of AS is made by echocardiography (Figure 5).[14,51] The severity of AS is defined as: Mild (aortic valve area >1.5 cm^2, aortic jet velocity < 3.0 m/s, or mean aortic gradient < 25 mmHg), moderate (aortic valve area 1.0-1.5 cm^2, aortic jet velocity 3.0-4.0 m/s, or mean aortic gradient 25-40 mmHg), or severe (aortic valve area < 1.0 cm^2, aortic jet velocity >4.0 m/s, or mean aortic gradient >40 mmHg).[14]

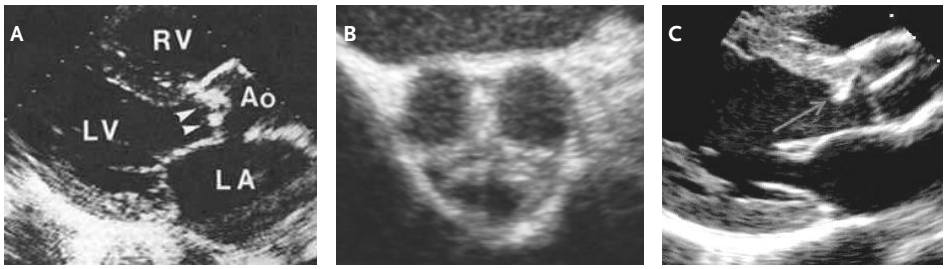

Figure 5. A and B. Severe aortic valve stenosis. Ao = aortic valve, LV = left ventricle, LA = left atrium, RV = right ventricle, **c.** Discrete subaortic stenosis, arrow = subaortic membrane.

The use of echocardiography in AS disease decreased the number of invasive cardiac catheterizations performed for measuring and monitoring hemodynamic AS severity.[12] Two-dimensional echocardiography often differentiated between a tri-leaflet or bicuspid morphology and shows valve calcification varying from focal areas of valve thickening to heavily calcified and thickened leaflets with limited reduction and a small aortic valve area.[12,13]

In addition to conventional echocardiography, one could approach AS disease severity in another way by estimating the LV response to the chronic overload as LV dysfunction is the main adverse physiological consequence of AS disease.[12,52,53] In this regard left ventricular twisting and the presence of strain (as a marker for subendocardial ischemia) may be better derivatives of systolic LV function and detect LV dysfunction earlier in order to optimize the timing of aortic valve intervention.[54,55]

Exercise testing is preserved for patients in which it is difficult to distinguish the origin of their symptoms.[14,52] Although a proven safety record even in asymptomatic patients with severe AS, this test is not often used in clinical practice.[11]

Cardiac catheterization is performed when there is a discrepancy between the clinical and echocardiography findings and provides additional information about the presence and severity of AS disease.[14] Compared to the above described examinations, cardiac catheterization is an invasive examination and therefore only preserved for specific indications. For example, when a patient presents with shortness of breath and angina, a cardiac catheterization will be applied to determine whether concomitant coronary artery disease is involved as well. The outcome of the cardiac catheterization will have different implications for the treatment of this particular patient.

Finally, a more recent, additional approach is to either screen for or monitor calcific AS disease with the use of *biomarkers*. N-terminal pro-brain natriuretic peptide (NT-proBNP) is released from the myocardium in response to pressure and volume overload.[56] Although biomarkers are subject of investigation in many

studies, data on the capacity of NT-proBNP to mark the progression of AS disease in (a)symptomatic patients, are scarce.[7,57]

AORTIC STENOSIS: TODAY'S TREATMENT OPTIONS

There are several treatment options for AS disease.[14,51] Asymptomatic patients with mild to moderate AS disease are treated conservatively and carefully monitored over time and treated conservatively while aortic valve replacement (AVR) is indicated (Class I, level of evidence B) for symptomatic patients with severe AS according to the ACC/AHA and ESC/EACTS guidelines for the management of patients with valvular heart disease.[14,51]

There are different options for invasive treatment of AS: aortic valvuloplasty, aortic valve replacement with a prosthesis (mechanical or bioprosthetic) or human valve substitute (autograft or homograft), or transcatheter bioprosthetic valve implantation.

In the Netherlands, from 2007 to 2010, of the 63,601 open heart procedures performed in adults, 16,662 (26.4%) consisted of aortic valve surgery with an operative mortality of 4.4%.[58] Of the 16,662 aortic valve procedures, 7,372 (11.7%) were isolated AVRs with an operative mortality of 2.6 %.[58] Reports published in 2010 by the European Association for Cardio-Thoracic Surgery and in 2009 by the Society of Thoracic Surgeons' database, established in the USA, reported a consistent operative mortality.[59,60] Worldwide, from 1997 to 2006, an estimated 200,000 patients underwent AVR each year.[61-63]

The following paragraphs outline the main invasive treatment options for severe AS.

Aortic valvuloplasty

Since several decades, surgical aortic valvuloplasty (mostly valvulotomy, sometimes repair) is performed in neonates, children, and youngsters to treat critical congenital AS and a known complication of this technique is residual stenosis.[64-66] The introduction of the transcatheter balloon aortic dilatation in the 1980s started the debate about the value of the balloon aortic valvuloplasty as compared to the surgical valvuloplasty. Since neonates, the most affected patients in the spectrum congenital AS, have similar 5-year survival rates after both techniques, the discussion focused on intervention-free survival.[67,68] Compared to surgical valvuloplasty, balloon dilation is associated with progressive aortic regurgitation which necessitates earlier intervention.[68,69] However, surgical and balloon valvuloplasty are both capable of delaying the need for childhood aortic valve replacement.[67-70] In adults,

balloon aortic valvuloplasty may be performed as bridge to open heart surgery or applied as palliative care, but today, these patients usually undergo transcatheter aortic valve implantation.[71,72]

Bioprosthesis and mechanical valve prosthesis

In contemporary clinical practice, bioprostheses (also called xenografts or heterografts) are most frequently used to replace the diseased native aortic valve.[14] Almost a decade ago, the European Heart Survey reported that of adult patients with AS (54% aged 70 years or older) who underwent AVR in 2001, 49% received a mechanical valve prosthesis and 50% a bioprosthesis.[11] However, more recently, The Society of Thoracic Surgeons' database showed a dramatic shift toward the use of bioprostheses from 44% in 1997 to 78% in 2006 corresponding with a concomitant decrease in the use of mechanical valve prostheses.[62] This trend was confirmed by data from US Department of Health and Human Services which contain information on approximately 8 million hospital stays each year, and more recently by the Fourth Adult Cardiac Surgical Database Report 2010 and the Dutch cardiac surgery registry.[60,73-75]

Bioprostheses most often are stented, but stentless types are available. Bioprostheses are usually composed of porcine valve or bovine pericardial tissue (Figure 6a). They are easily available, have a low thrombogenicity and do not require lifelong anticoagulation therapy whereas the over the years decreasing hemodynamic performance and limited durability are the main disadvantages.[14]

Mechanical valve prostheses nowadays are usually bi-leaflet valve prostheses (Figure 6b) which are easily implanted, readily available, and have the major advantage of lifelong durability.[14] Unfortunately, the increased thrombogenicity of these valves necessitate lifelong anticoagulation therapy which is associated with an increased hazard of bleeding.[14,76] This may require lifestyle adjustments (with regard to for instance: sports, food, and alcohol intake), and in addition young

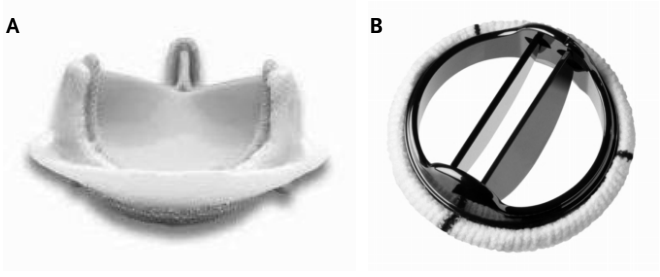

Figure 6 A. Pericardial bovine bioprosthesis. **b.** Mechanical valve prosthesis.

women who may contemplate pregnancy should be aware of the potential risks of anticoagulation therapy during pregnancy.

The choice for a particular aortic valve prosthesis depends not only on research evidence (compliance with clinical guidelines) and clinical-technical considerations, but also on informed patient preference.[61,62] The ESC/EATCS guidelines for the management of patients with valvular heart disease recommend a mechanical prosthesis 1) according to informed patient preference in patients without contra-indications for long-term anticoagulation, 2) in patients at risk of accelerated structural valve deterioration, and 3) in patients already on anticoagulation as a result of having a another mechanical prosthesis (all Class I, level of evidence C).[51] In addition, mechanical prostheses should be considered in patients <60 years of age and those with a reasonable life expectancy, for whom future redo valve surgery would be at high risk (Class IIa, level of evidence C), and may be considered in patients already on long-term anticoagulation due to high risk of thrombo-embolism (Class IIb, level of evidence C).[51]

Bioprostheses are recommended 1) according to the desire of the informed patients, 2) when good quality anticoagulation is unlikely or contraindicated, and 3) for reoperation for mechanical valve thrombosis despite good long-term anticoagulant control (all Class I, level of evidence C).[51] In addition, bioprostheses should be considered 1) in patients for whom future redo valve surgery would be at low risk, 2) in young women contemplating pregnancy, and 3) in patients >65 years of age (all Class IIa, level of evidence C).[51] Sometimes, younger patients prefer a bioprosthesis at the cost of a reoperation later in life to avoid the burden of anticoagulation, or the noisy 'clicking' sound of a mechanical valve prosthesis.

Homograft aortic valve replacement and pulmonary autograft procedure

Homografts and pulmonary autografts are mainly implanted in young patients with CHD such as congenital AS with or without concomitant other aortic valvular (regurgitation) or root disease.

From 2006 until 2009, of the adult patients with AS and/or aortic regurgitation, *homografts* count for 0.4 to 1.1% of the isolated AVRs.[11,60,62,77] This human tissue valve consists of an aortic valve, root, and part of the aortic arch, and can be implanted subcoronary or as complete root which is the preferred technique in case of endocarditis with excessive tissue damage. Advantages are the excellent hemodynamics and low thrombogenicity which makes anticoagulation therapy redundant. Because homografts are donated postmortem or retrieved from heart transplant recipients with native healthy aortic valves, availability is limited. Graft calcification and infection are the main problems and often necessitates a reoperation later in life.[78] Compared to porcine and pericardial bioprostheses, actual risk on homograft

reoperation is comparable, but when compared to the stentless porcine aortic root, homografts show higher calcification scores, more valve dysfunction, and need more reoperations.[79-81] Currently the main indication for the use of a homograft in aortic position is active endocarditis with extensive tissue damage.

Pulmonary autografts (so-called Ross procedure) were introduced in 1967 by Donald Ross and count for 0.3 to 0.4% of the isolated AVRs of AS patients with or without aortic regurgitation.[11,60,62,82] This human valve substitute provides the potential for neo-aortic root diameter increase along with somatic growth, excellent hemodynamic performance, low risk on endocarditis, and low thrombogenicity and therefore avoidance of anticoagulation therapy.[83-85] It is currently the only available living valve substitute. On the downside, it is technically demanding and creates double-valve disease by replacing the patient's aortic valve the patient's own pulmonary valve and implanting a pulmonary homograft, bovine jugular vein, or other valve substitute in pulmonary position.[85-87] However, a major disadvantage of pulmonary autografts that are implanted using the unsupported freestanding root replacement technique is the progressive neo-aortic root dilation and concomitant aortic regurgitation, which necessitates redo surgery usually in the second postoperative decade.[85,86,88,89] In addition, a valve substitute in pulmonary position may also require re-intervention usually due to calcification.

A recent randomized controlled trial compared outcomes of pulmonary autografts and homografts and showed that long-term outcomes of the pulmonary autografts are superior to those of the homografts both with regard to survival and the need for reoperations.[90]

Transcatheter aortic valve implantation

As we face a growing elderly population with multiple co-morbidities and a limited life-span, not every symptomatic patient is a candidate for open-heart surgery or desires open-heart surgery. Transcatheter aortic valve implantation (TAVI) was introduced 10 years ago for the high-risk patients who were not surgical candidates.[91,92] In the past decade, TAVI has been performed in over 50,000 patients worldwide and the use of TAVI is expect to increase even more in the next years.[93]

In TAVI, the aortic valve prosthesis is retrogradely inserted into the body by the transfemoral, transiliac, transsubclavian, transaxillary arterial or aortic approach, or antegradely by applying the transapical approach. Positioning of the prosthesis at the level of the aortic valve and deploying it, must be adequately precise in order to reduce the risk on acute myocardial ischemia or acute mitral dysfunction.[94]

The advantage of TAVI is that it is a less invasive procedure compared to AVR because it does not require entry into the chest cavity (with the exception of the transapical approach) or use of cardiopulmonary bypass, with high post-procedural

immediate success rates are achieved, good initial hemodynamic valve function is good (severe aortic regurgitation is uncommon), a shorter hospital stay, and a faster and less complicated recovery as compared to surgical AVR.[95,96] On the contrary, early outcomes (30 day results) raise concerns about vascular injury, stroke, and paravalvular regurgitation.[96,97] In addition, long-term longitudinal data to evaluate the valve durability and safety are lacking. Until now, taking into account the high-risk patient profiles, satisfactory hemodynamic and functional results are achieved up to 5 years post procedure.[98] With the ongoing improvements of transcatheter valve systems and implantation techniques, optimized multidisciplinary collaboration with formally trained experienced physicians, and refined patient selection including factors as frailty, TAVI becomes an appealing future option for a broader range of patients.[97,99,100]

Enucleation and myectomy in patients with discrete subaortic stenosis

For patients with DSS, different surgical strategies exist which can be performed early in the disease or later on when there is a severe obstruction of the LV outflow tract.[101] Enucleation of the subvalvular fibrous or fibromuscular membrane or collar is performed, and in case of severe hypertrophy of the interventricular septum, a myectomy could be added to the surgical procedure. However, performing a myectomy is still a matter of debate among clinicians. Although adequate surgical excision, obstruction may reappear and aortic regurgitation could be progressive and subsequently urge reoperation.[102] Data on postoperative outcome in adult DSS are limited. Patients with discrete and tunnel subvalvular AS had a 40-year survival of 94% and 84%, respectively, including hospital mortality.[103]

AORTIC STENOSIS: PATIENT PROGNOSIS

The prognosis of patients with severe aortic stenosis is determined by a multitude of interrelated factors that will be discussed extensively in this thesis, in the setting of natural history, current clinical practice, and for specific subgroups such as patients with DSS and female patients of childbearing age. Not only will this thesis focus on determinants of clinical outcome but also on quality of life.

Clinical outcome is measured in patient survival and freedom of complications which preferably should be reported uniformly and transparent. Clinical outcome after a heart valve procedure is reported according to the guidelines for reporting mortality and morbidity after cardiac valve interventions.[104] Generally, survival is determined by the number of all patients dying during the first 30 days postoperatively (operative or hospital mortality), and the number of patients dying during follow-up.

Survival can be reported as percentage or as an annual rate. Causes of death can be further specified in all-cause, cardiac, valve-related, or sudden unexplained death.[104]

Another measure to assess clinical outcome is freedom from complications. Like mortality, complications should be defined uniformly and transparent and, after a cardiac procedure, reported according to the current guidelines.[104] Valve-related complications that may occur over time after a cardiac procedure are defined as structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding events, operated valve endocarditis, and their consequences, such as death and reoperation.[104]

Another measure of patient outcome is quality of life. The increase in life-expectancy has resulted in a growing population of elderly AS patients with a limited life span for which quality of life becomes important. Improvement in quality of life through a reduction in symptoms and a better physical function is therefore the main goal of valvular surgery in these elderly patients with AS.[94] Quality of life, a measure of individual disease burden, is defined as the quality of life experienced by the patient at a particular moment in time and assessed with a questionnaire such as the Short Form-36® Health Survey (SF-36) questionnaire or its modifications.[105] Evidence on quality of life in patients with AS who are treated conservatively or surgically is limited.

One special aspect associated with patient prognosis concerns pregnancy: up to 4% of the pregnancies in industrialized countries are complicated by cardiovascular disease and this number still increases.[106] The number of young patients who had valve surgery and want to start a family afterwards, has increased. In clinical practice, the treating physician has to be aware that treatment concern not only the mother, but the fetus as well. A therapy which is favorable for the mother, could be unfavorable for the fetus, sometimes even cause the death of the fetus, and vice versa.[106] However, knowledge on pregnancy outcomes in patients who underwent prior aortic valve surgery is not only important prior to conception, but already preoperatively when choosing the type of aortic valve substitute.

AIM OF THIS THESIS

The aim of this thesis is to provide insight in several aspects of the natural history, treatment, and prognosis of adult patients with AS.

The following research questions are addressed:

1. What is the clinical course of severe AS disease in contemporary clinical practice? (With specific attention for new diagnostic markers, for quality of life and for DSS.)
2. What challenges do young females with prosthetic heart valves encounter during pregnancy? (With specific attention for human tissue valve substitute durability.)

OUTLINE OF THIS THESIS

Chapters 2, **3**, and **4** describe the natural history of (elderly) patients with calcific AS and the results of a meta-analysis on AS progression. In addition, **Chapter 5** describes the potential predictors for progression of AS disease using mixed-effects analysis of longitudinal data of a cohort with severe AS patients.

To gain insights into the association between (mechanical) LV aspects and AS disease, **Chapter 6** describes the rotation parameters of the LV in a large cohort of patients with severe AS, compared to age-matched healthy controls, whereas **Chapter 7** illustrates the association between electrocardiographic strain and systolic longitudinal shortening of the LV in patients with AS.

Chapter 8 describes the 2-year clinical course of a prospective cohort of symptomatic and asymptomatic patients with severe AS in the wider Rotterdam area**,** while **Chapters 9** and **10** describe the quality of life of these patients during the 2-year follow-up period and in particular the association between AVR and quality of life in symptomatic patients.

Chapter 11 concerns a multicenter study that recorded the natural history of DSS in adults, while **Chapter 12** describes the surgical outcome of DSS in a large multicenter cohort study.

Chapter 13 describes the pregnancy outcomes of patients who underwent aortic valve or root replacement with a homograft, a pulmonary autograft, or a mechanical valve prosthesis. Finally, **Chapter 14** describes of the clinical course of female patients who received a homograft or pulmonary autograft in aortic position, and assesses the potential association between pregnancy and accelerated degeneration of the human aortic tissue valves.

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For NASA, space is still a high priority.

D. Quayle

2

NATURAL HISTORY OF AORTIC VALVE STENOSIS

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CARDIAC VALVULAR MEDICINE, SPRINGER 2012

INTRODUCTION

Aortic valve stenosis (AS) is the most common heart valve disease in the world, with a prevalence up to 3% of adults over the age of 75 years.[1] One-third of US adults ≥65 years has aortic valve sclerosis and of these at least one-third will develop some degree of AS within 5 years.[2,3] The natural history, diagnosis, and cellular mechanisms of this disease process have evolved over the past several decades. Over the last 10 years, the scientific progress in the field of calcific aortic valve stenosis has increased exponentially. A critical discovery in our understanding of calcification as the end-stage pathogenesis of a congenital bicuspid or tricuspid aortic valve is the osteogenic process.[4-6]

Progressive calcification of the leaflets usually leads to severe narrowing of the aortic valve orifice and fibrosis of the left ventricular wall, finally resulting in left ventricular outflow tract obstruction and severe aortic stenosis. After a prolonged asymptomatic period with low morbidity and mortality, the development of the classic triad of symptoms including: angina, syncope, or heart failure marks the critical point in the natural history of aortic valve disease. AS is a progressive disease and without intervening treatment associated with high morbidity and mortality rates within a few years of diagnosis.[7] Survival declines when a patient with AS develops angina or syncope, and is even more limited when the patient develops congestive heart failure. Because AS is a disease of the elderly, it can be difficult to distinguish the gradual decrease in physical functioning attributed to advanced age and multiple co-morbidities such as frailty, lung disease, neurological disease, and symptoms from the worsening AS disease. It is not uncommon that patients will lower their activity level below their symptom threshold, to accommodate to the progressive left ventricular outflow tract obstruction. This chapter will outline the studies in the field of diagnosis and the impact of the evolving science of clinical risk factors for calcific aortic valve disease.

Patients with mild to severe asymptomatic AS are monitored until the development of symptoms. Sudden death is a rare event with an occurrence of 1% per year without preceding symptoms.[8] If symptomatic severe AS is present, according to the present ACC/AHA and ESC guidelines, aortic valve replacement is indicated.[9-10] An evolving option in the twenty-first century for patients who are not candidates for surgery, is the transcatheter aortic valve implantation which is performed in specific patient populations in Europe and US. In an effort to assess AS severity and progression for the individual adult patient, it is important to consider the changing basic concept of AS disease, current knowledge about AS progression, and insight in the factors associated with AS progression. These topics will be described in the following paragraphs of this chapter.

HISTORICAL PERSPECTIVE OF AS DISEASE

Early reports on the natural history of AS are based on post-mortem studies, invasive cardiac catheterization studies, and Doppler echocardiography. Historically, symptomatic AS was seen as a passive degenerative disease and associated with a significant risk (>15%) of sudden death while asymptomatic AS reportedly had a risk of sudden death of 3-5%.[11] According to the post mortem studies from the period 1930-1950, the time from symptom onset until death was on average less than 5 years for patients with angina and only 2 years for patients with heart failure as shown in Figure 1. With the development of cardiac catheterization in the 1930s, hemodynamic assessment of AS severity became possible. Although the published catheterization studies in patients with AS often consist of small study populations, they provide the first quantitative data of AS progression over time.[12] In the late 1980s, the non-invasive Doppler echocardiography technique became available and offered an opportunity for longitudinal studies regarding AS disease and progression. These studies provide further information for the understanding of this complex disease process via non-invasive imaging.

On July 13, 1912, Theodore Tuffier, a French surgeon, performed the first successful closed heart surgery in a young patient with severe AS by digitally invaginating the aortic wall into the aortic valve orifice to dilate the stenosed valve.[13] Several different invasive approaches to palliate severe AS followed with poor outcomes.[14] The first aortic valve replacements were performed with an caged-ball valve prosthesis in the

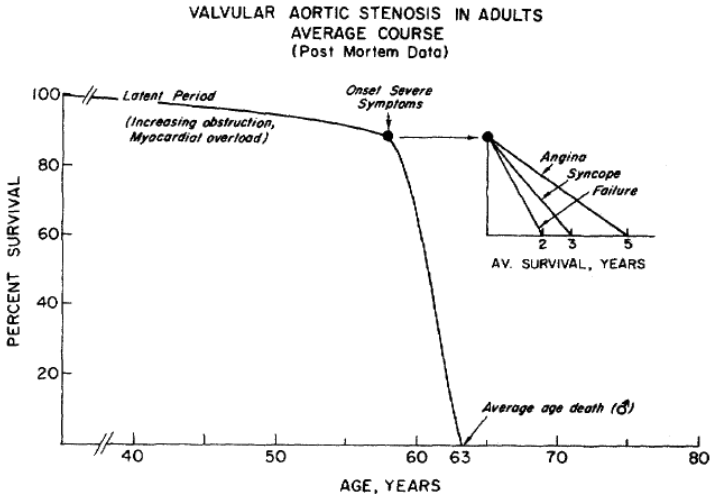

Figure 1. Average course of valvular aortic stenosis in adults. Data assembled from post-mortem studies (reprinted with permission).

1960s and were accompanied by mortality rates ranging from 25% to 50%, but over time, mortality rates decreased considerably, even for complex aortic valve procedures.[15] The introduction of cardiopulmonary bypass in the 1950s and cardioplegia in the mid 1960s was associated with the continuous improvements in operative techniques and postoperative care. The development of new valve substitutes, such as bioprosthetic valves, are important developments which have resulted in the extremely low morbidity and mortality that is observed in contemporary clinical practice.

In more recent years, the concept that AS is passive and degenerative is not valid anymore. It is now proven that AS represents a more active regulated disease process characterized by lipoprotein deposition, active leaflet calcification, and chronic inflammation for which medical treatment possibly could play a role.[16-18] The understanding of this biologic process may offer an opportunity to treat AS with medications, in order to prevent, reverse or slow down the disease as more scientific studies in this field are performed.

WHAT IS KNOWN ABOUT AS PROGRESSION?

There are several studies investigating AS progression and its potential determinants, however, due to small sample size, non-randomized retrospective study design, heterogenic study populations, large variability in AS progression estimates, and limited follow-up duration, it has been difficult in the past to draw general conclusions. A meta-analysis on the diagnostic studies in cardiac catheterization and echocardiography demonstrates the differences in these diagnostic approaches, and the challenges that are present in following the natural history of this disease by echo and cardiac catheterization data.

Figure 2 shows progression of AS measured by cardiac catheterization according to nine published reports from the 1970s and 1980s, describing the course of AS disease over time in patients with a mean age of 55 years (range 37-61 years) of whom 75% males.[19-27] The studies include predominantly male patients with ages ranging from 40 to 60 years with mostly non-severe AS who underwent serial measurements for clinical reasons, for example for the evaluation of a systolic murmur. Progression of AS disease, as measured by the aortic valve area calculated with the Gorlin formula and the peak-to-peak aortic gradient, shows a large variability in the progression rates between studies. Annual reductions of the aortic valve area vary from 0.03 to 0.24 cm^2/year and annual increase in aortic peak-to-peak gradients ranging from 2 to 11 mmHg/year.

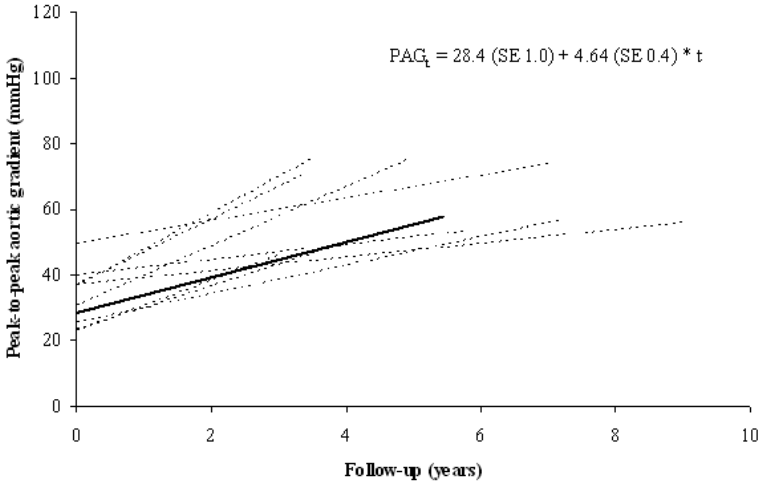

Figure 2. AS progression in cardiac catheterization studies. AS = aortic valve stenosis, PAG_t = peak-to-peak aortic gradient at time t, SE = standard error, t = time. Interrupted lines = individual study estimates, solid line = pooled estimate.

Figure 3 displays echocardiographic AS progression from a systematic review and meta-analysis of observational reports published between 1989 and 2009.[28] The results of this analysis demonstrate a similar large variability in AS progression rates compared to cardiac catheterization studies. Annual reductions in aortic valve area vary from 0.04 to 0.22 cm^2/year. There is an annual increase in maximum aortic jet velocity ranging from 0.06 to 0.40 m/s/year. The annual increase in peak and mean aortic gradient varying from 2 to 15 and from 2 to 8 mmHg respectively.[28] This meta-analysis for catheterization and echo variability demonstrates further understanding into the complex assessment of the hemodynamic parameters, which reflects most probably institutional variability in measurements and differences in patients' clinical risk factors. Assessing the degree of stenosis, hemodynamic severity, and anatomic criteria for TAVI is also evolving quickly and the results of this meta-analysis will help to further understand this process.

In addition to the measures above, assessing the amount of aortic valve calcification can also be used to monitor AS severity and progression. This has been measured in a few studies in which different methods were employed to assess aortic calcification, often without a reference test to quantify the extent of aortic valve calcification and the timing to progression.[29-32] This textbook will provide an overview for why these differences may exist which include risk factors, diagnostic techniques, and understanding the variable stages of this disease by assessing the calcification in the overall outcome of this patient population.

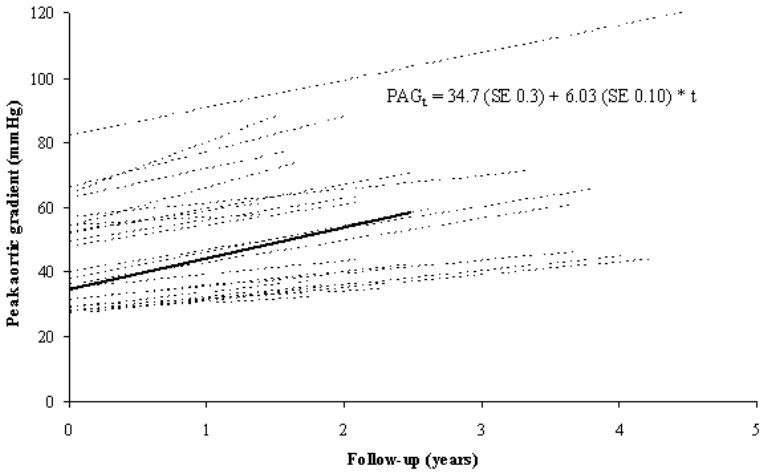

Figure 3. AS progression in observational studies. AS = aortic valve stenosis, PAG_t = Peak aortic gradient at time t, SE = standard error, t = time. Interrupted lines = individual study estimates, solid line = pooled estimate (reprinted with permission)[28].

FACTORS ASSOCIATED WITH AS PROGRESSION AND CLINICAL OUTCOME

Many factors are reportedly potentially associated with faster AS progression and/or impaired clinical outcome of AS disease: advanced patient age, male gender, obesity, smoking, hypertension, diabetes, coronary artery disease, chronic obstructive lung disease, severe pulmonary hypertension, significant aortic valve calcification, a higher maximum aortic jet velocity at baseline and faster progression rate, decreased aortic valve area, left ventricular dysfunction, aortic regurgitation, impaired functional status, abnormal exercise response on exercise testing, inactivity, elevated levels of serum cholesterol, calcium, creatinine, C-reactive protein, and natriuretic peptides, osteoporosis treatment, chronic renal failure, and hemodialysis.[8,30,33-51]

As the basic concept of AS disease as a passive degenerative disease is now a concept of the past, and we are moving to the notion that it represents an active disease process with many similarities to atherosclerosis, the interest in potential medical treatments of AS disease is growing. The recent Working group of the National Heart Lung and Blood Institute/NIH, has defined the concept that calcific AS is not a passive degenerative process but an active biology.[16] In this respect, five randomized controlled trials on AS progression were developed to determine whether statins could reduce AS progression in adult patients with AS.[32,52-55] These

statin trials provide invaluable information into future trial design and also the effects of statins on the progression of AS in vastly different patient populations. The TASS trial, the SALTIRE trial, the large SEAS trial, and the ASTRONOMER trial included patients with mild to severe AS, a mean age varying from 54 to 70 years with predominantly male patients and show an annual decrease in aortic valve area ranging from 0.03 to 0.08 cm^2/year, an annual increase in maximum aortic jet velocity of 0.15 to 0.20 m/s/year, an annual increase in peak aortic gradient of 2 to 7 mmHg/year, and an annual increase in mean aortic gradient of 1 to 4 mmHg/year and showed no significantly reduction in AS progression in patients receiving lipid-lowering therapy, in this range of patient population.[28,32,52-54] Figure 4 displays the echocardiographic AS progression from a systematic review and meta-analysis of these published randomized controlled statin trials between 2005 and 2010.[28] Again there is some variability in the echo results as shown in Figure 4, but not as significant as the progression study analysis in Figure 2 and 3. Recently, the hypothesis of lipid-lowering therapy on AS progression was tested in a congenital AS patient population, entitled the PROCAS trial. This trial included 63 patients with an age range of 18 to 45 years and no decrease in AS progression in patients randomized to rosuvastatin 10 mg for the duration of the trial.[55] The results of these randomized trials can be possibly attributed to trial design, timing of treatment, and level of LDL lowering. Earlier initiation of therapy may be the key to success in the future clinical trials to treat this disease. The only study to demonstrate the

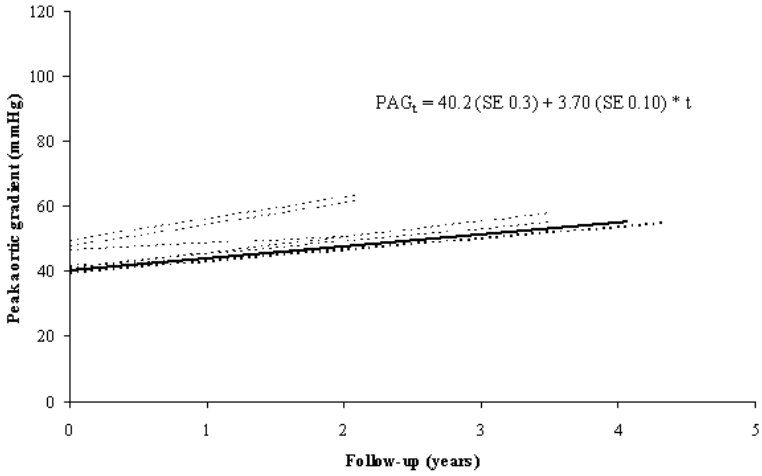

Figure 4. AS progression in randomized controlled trials. AS = aortic valve stenosis, PAG_t = Peak aortic gradient at time t, SE = standard error, t = time. Interrupted lines = individual study estimates, solid line = pooled estimate (reprinted with permission)[28].

positive effects of a statin in the treatment of calcific aortic valve disease is the RAAVE trial, Rosuvastatin Affecting Aortic Valve Endothelium in aortic stenosis.[56] This open label hypothesis driven study demonstrating slowing of progression of AS using Rosuvastatin 10 mg a day by measuring aortic valve area, mean gradient, and peak jet velocity. The retrospective and prospective studies and animal models are providing the foundation for the treatment of this disease in the future.

Several observational studies suggest that in particular age, baseline severity of AS disease, and aortic valve morphology like calcification and the presence of a bicuspid valve, may affect AS progression rate.[8,33,45] The ASTRONOMER trial sub-study identified aortic valve calcification as an independent factor associated with a faster AS progression after correcting for age, baseline AS severity, and tricuspid aortic valve morphology.[52] It represents more severe and aggressive disease in bicuspid patients as compared to tricuspid patients, and therefore alerts the physician to careful clinical decision making for patients with bicuspid aortic valve disease.

These studies illustrate a wide variation in the observed progression of AS over time. As compared to observational studies, randomized controlled trials show smaller AS progression estimates which may be explained by selection bias and different echocardiographic methods employed to monitor AS disease. Our observations of AS progression are biased in many ways. Another recent report shows that the hemodynamic criteria for AS severity are applied inconsistently for grading AS, even in patients with normal left ventricular function.[57] If AS severity is assessed using the aortic valve area method, more patients are classified as having severe AS compared to AS assessment with the mean aortic pressure or maximum aortic jet velocity method. These observations call for a universal classification of AS severity, in order to optimize uniformity in assessment of AS disease. This textbook of valvular medicine provides further understanding into establishing criteria to include these novel findings and clinical risk factors for this disease process.

CONCLUSIONS

This chapter aimed to provide insight in the natural history of AS over time and the complex nature of AS disease, especially to identify factors associated with AS progression and clinical outcome of AS disease in the aging population. We are only starting to understand the mechanisms underlying AS disease, and its complexity. From basic science to applied clinical studies, there are so many aspects of AS disease, which are under intense investigation. For example, there is increasing evidence that genetics may play a role in bicuspid valve disease and the calcification of the tricuspid aortic valve.[16] Improved insights into genetic factors associated

with AS disease may help clinicians to better diagnose and treat our patients. On a more general note, the emerging knowledge of the mechanisms underlying AS disease may provide us with drugs that prevent, reverse or slow down AS disease. Also, the tremendous development of different non-invasive imaging techniques will help clinicians better diagnose disease severity, provided that a universal classification of AS severity is achieved. Biomarkers that are at the horizon may also help prognostication.

Using the information obtained from emerging knowledge, the next step is to integrate this knowledge into clinical decision tools that can provide evidence-based estimates of outcome for individual patients, allowing optimal individualized treatment in the natural history of AS.

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007's Profound state of health may be due, at least in part, to compliant bartenders.

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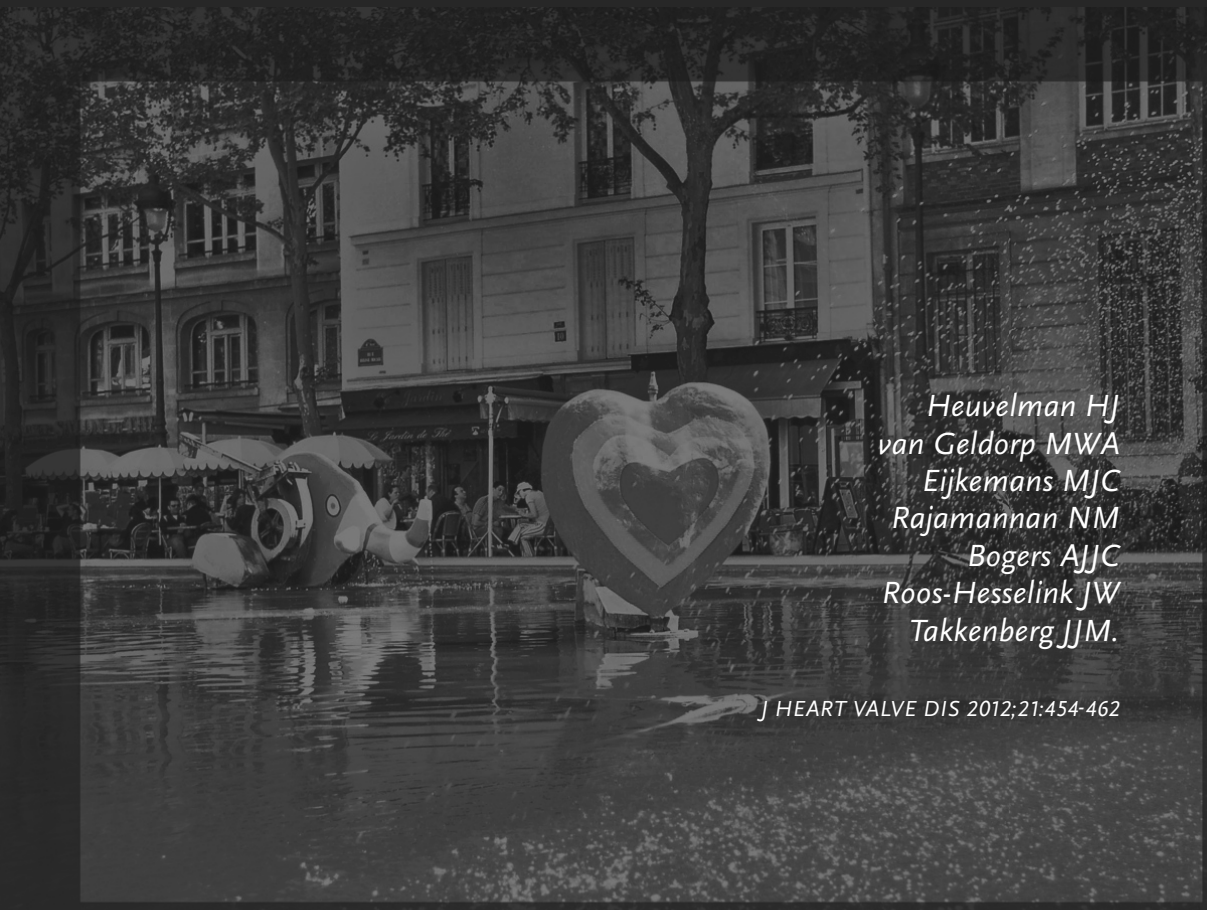
Progression of aortic valve stenosis in adults: A systematic review



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van Geldorp MWA
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Takkenberg JJM.

J HEART VALVE DIS 2012;21:454-462

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 controlled 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.

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 controlled 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 I). 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]

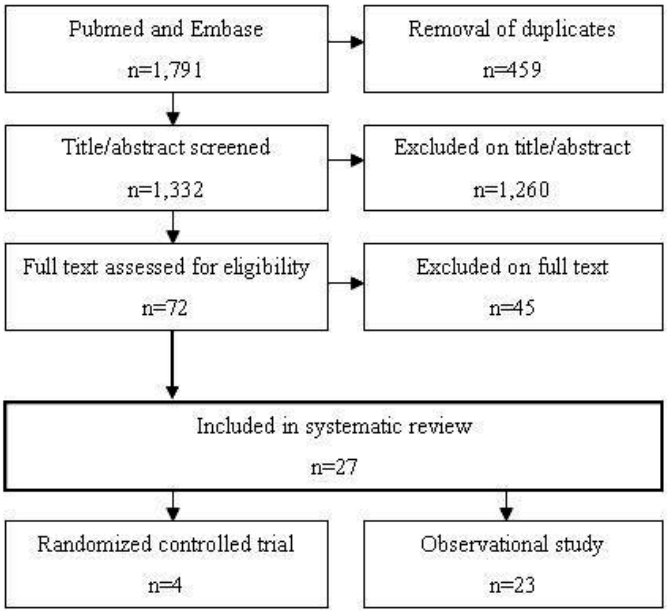

Figure 1. Flowchart of the search.

Table 1: 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 ≥2.5 m/s
		78	68	72	25	28	27	69	5	6	1.02	0.08	3.45	0.20	49.5	6.56			Vmax ≥2.5 m/s
Dichtl et al. (19)	2008	23	64.2	65	24	17	-	39	4	-	-	-	-	-	46.5	2.1	29.2	1.05	MAG ≥15 mmHg, Vmax ≥2.0 m/s
		24	69.7	54	24	4	-	58	21	-	-	-	-	-	41.1	2.8	25.6	2.15	MAG ≥15 mmHg, Vmax ≥2.0 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 2: 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 ≥16 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 ≥2.5 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 cm^2
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 cm^2
Ngo et al. (27)	2001	87	70.8	83	30	-	49	-	-	-	-	-	-	-	-	31.4	6.3	-	-	Vmax ≥ 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 cm^2
		117	67	45	21	15	44	-	63	20	-	1.2	0.11	-	-	29	4.57	15	3.43	AVA 1.0-1.8 cm^2
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 ≥10 mmHg, AVA ≤2 cm^2
		118	78	51	44	11	26	57	64	24	-	1.2	0.09	3.0	0.25	36	6.77	22	4.64	MAG ≥10 mmHg, AVA ≤2 cm^2
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 ≥3 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 cm^2

Table 2: 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 cm^2
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 cm^2
		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 cm^2
Mohler et al. (18)	2007	39	69.5	72	12	0	28	-	72	18	-	1.13	0.08	-	-	-	-	-	-	AVA 0.7-2.0 cm^2
		22	63.9	67	12	0	9	-	32	14	-	1.22	0.04	-	-	-	-	-	-	AVA 0.7-2.0 cm^2
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.*

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 ($p < 0.00001$).

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.

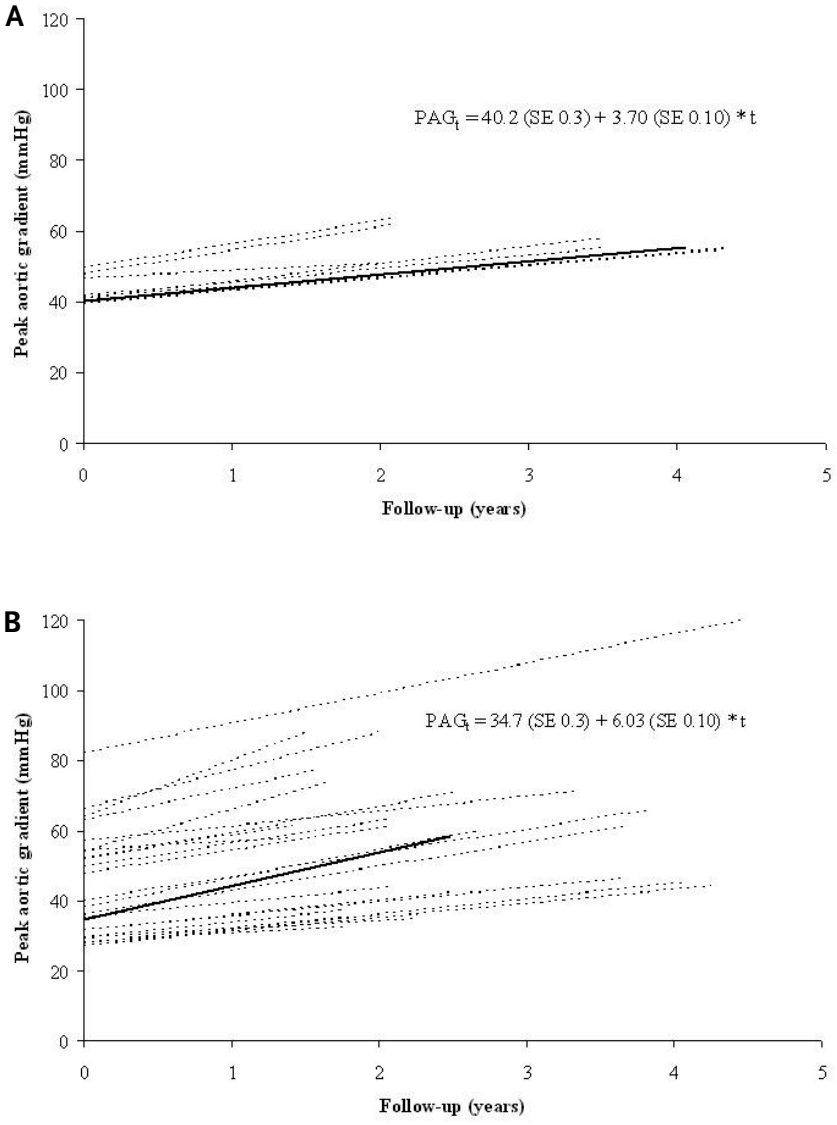

Figure 2a. Aortic valve stenosis (AS) progression in randomized controlled trials. **b.** AS progression in observational studies. PAG = peak aortic gradient at time t; SE = standard error; t = time. Dotted lines indicate individual study estimates; solid lines indicate pooled estimates.

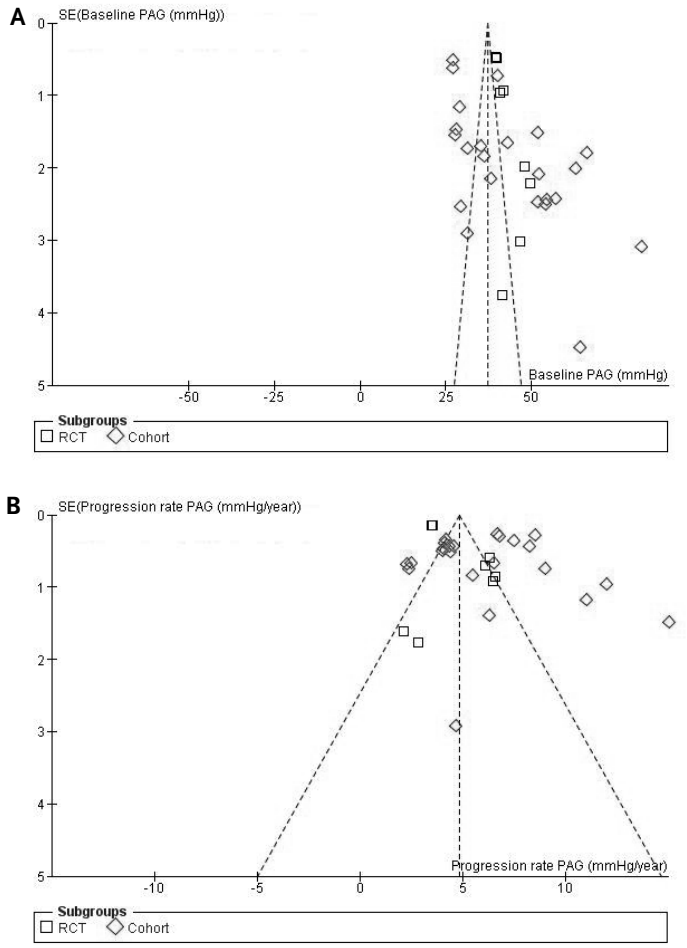

Figure 3a. Funnel plot of baseline peak aortic gradient (PAG, mmHg) in randomized controlled trials and observational studies. **b.** Funnel plot of AS progression in randomized controlled trials and observational studies. SE = standard error. The funnel indicates 95% confidence intervals.

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.

In 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:

$4*Vmax^2$

Progression rate peak aortic gradient (PAG):

$$\text{Progression rate}_i = \left(\frac{PAG_{final} - PAG_{baseline}}{} \right) / \text{follow-up}_i$$

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 = $1/\sqrt{(\Sigma \text{weights})}$

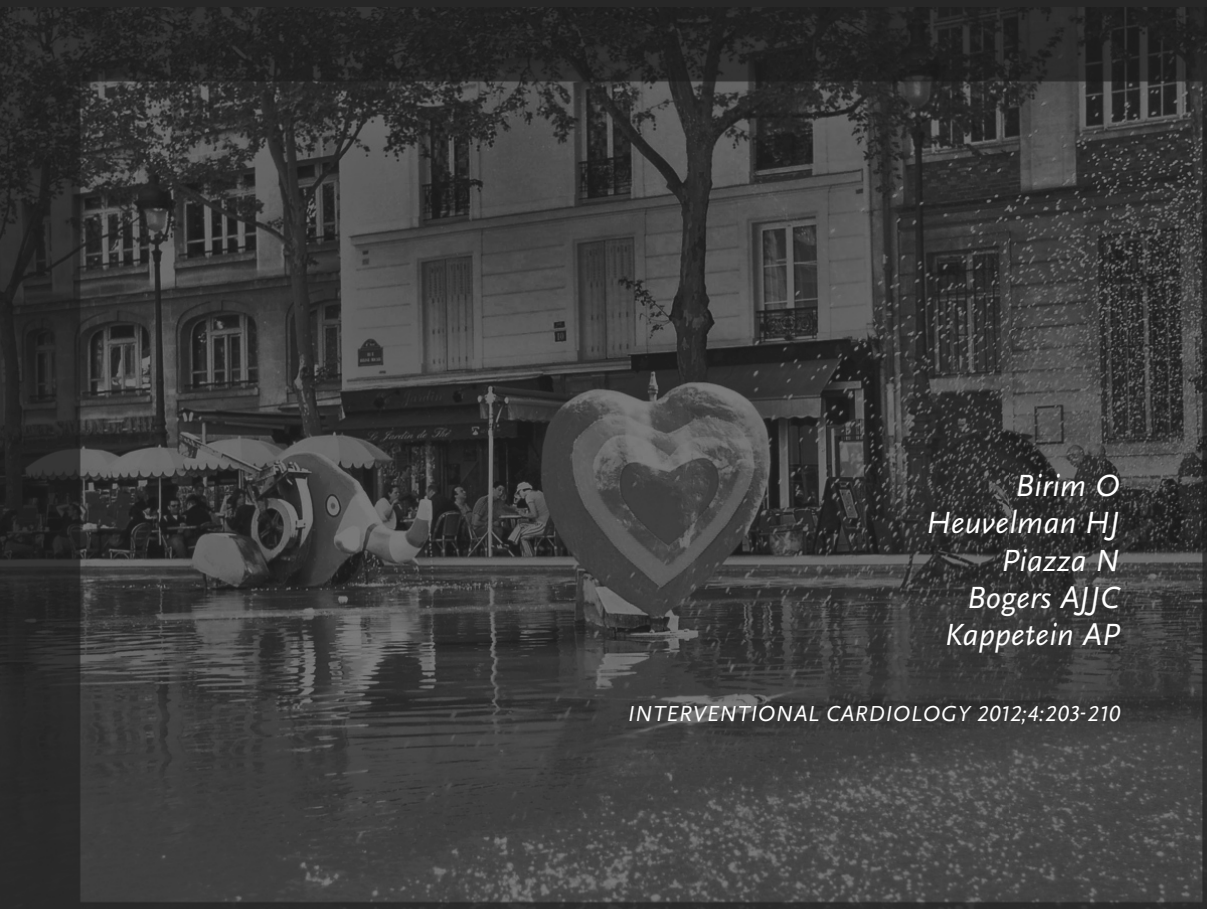
95% CI = pooled mean ± 1.96*pooled standard error

Bescheidenheid is een vorm van intelligentie.

E.M. Beunder

4

What do we know about the natural history of severe symptomatic aortic valve stenosis?



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ABSTRACT

Aortic valve stenosis (AS) is increasingly observed in the clinic. Although at present surgical valve replacement is the gold standard in patients with severe symptomatic AS, elderly patients experience higher morbidity and mortality compared with younger patients. The emergence of transcatheter aortic valve implantation offers an alternative for high-risk or inoperable patients. However, mortality and morbidity is high and long-term outcome, particularly with respect to device durability, are not yet available. The life expectancy of patients with severe symptomatic AS who are not operated upon is reduced. Most of the reported data, however, date back to the presurgical and precatheterization era. The aim of this article is to outline the evidence of natural history with medical treatment to assist in optimal clinical decision-making in the high-risk elderly population with severe symptomatic AS.

After hypertension and coronary artery disease, aortic valve stenosis (AS) is the most frequent cardiovascular disease. AS is increasingly observed in octogenarians and even in nonagenarians. The prevalence of AS is currently reported to be 2.5% at the age of 75 years and almost 8% at 85 years.[1]

Angina pectoris, syncope and congestive heart failure are the classic manifestations of severe AS. However, severe asymptomatic AS may manifest clinically in earlier stages with more subtle symptoms, such as decrease in exercise tolerance, fatigue or exertional dyspnea. The onset of symptoms is a critical point for making treatment decisions. It has been reported that only 50% of patients who present with angina survive for 5 years or more, whereas the average survival is 3 years for patients who present with syncope and 2 years in patients with congestive heart failure.[2]

At present, surgical aortic valve replacement is the gold standard for treatment of severe symptomatic AS and numerous reports document the safety and efficacy of this approach even in elderly patients. However, elderly patients experience higher morbidity and mortality compared with younger patients, with mortality rates ranging from 5.7% to 13% (Table 1).[3-9] Although consensus exists regarding the utility of aortic valve replacement for severe symptomatic AS, the decision to offer surgery to the elderly high-risk population is much more complex. Some patients are physically unfit for surgery, or surgery is denied because of a treatment preference of either the patient or the physician. Certain comorbid factors, such as preoperative cerebrovascular accident, respiratory insufficiency, renal failure and reduced left ventricular function, are independent predictors of in-hospital mortality in octogenarians.[3,5,6]

At present, patients who are high-risk candidates for surgical valve replacement may be offered transcatheter aortic valve implantation (TAVI). Although promising, periprocedural complications and mortality rate are significant (Table 2). The

Table 1. Outcome of surgical aortic valve replacement in octogenarians

Author	No. of patients	Patient characteristics	Mortality	Morbidity			5-year survival
				CVA	MI	Respiratory failure	
Thourani (2008) [3]	88	≥ 80 years (Isolated AVR)	5.7%	3%	0%	-	61%
De Vincentiis (2008) [5]	345	≥ 80 years (70% CABG)	7.5%	-	-	5%	61%
Filsoufi (2008) [6]	231	≥ 80 years (48% CABG)	5.2%	4%	1%	13%	66%
Melby (2007) [7]	245	≥ 80 years (57% CABG)	9.0%	3%	1%	22%	56%
Kolh (2007) [8]	220	≥ 80 years (26% CABG)	13.0%	2%	4%	21%	75%
Bose (2007) [4]	68	≥ 80 years (46% CABG)	13.0%	3%	-	-	78% at 2 years
Chiappini (2004) [9]	115	≥ 80 years (38% CABG)	8.5%	1%	4%	5%	69%

CVA = cerebrovascular accident, MI = myocardial infarction.

Table 2. Studies of the natural history of symptomatic patients with severe aortic valve stenosis

Author, year	Period of study	Design	No. of patients	Age (years)	Survival (years)	Definition severe stenosis
Bergeron (1954) [10]	1943 - 1952	Retrospective Autopsy	82	Mean: 69	Angina: 3 year 45% 5 year 15% Syncope: 3 year 45% 5 year 25% CHF: 3 year 35% 5 year 10%	Aortic valve admitting at most the tip of a finger
Mitchell (1954) [11]	1913 - 1952	Retrospective Autopsy/ Follow-up	122	Mean: 65	Angina: mean 4.1 Syncope: mean 3.0 CHF: mean 2.0	Clinical findings or autopsy
Olesen (1958) [29]	1933 - 1949	Retrospective Autopsy/ Follow-up	42	Mean: 53	Angina: mean 4.7 Syncope: mean 3.2	Clinical findings or autopsy
Anderson (1961) [38]	-	Retrospective Autopsy	49	Mean: 63	Angina: mean 3.5 CHF: mean 2.2	Not described
Takeda (1963) [27]	1948 - 1959	Retrospective Follow-up	60	Mean: 57	Overall: mean 6.1 Angina: mean 6.3 Syncope: mean 6.4 CHF: mean 3.6	Not described
Ross (1968) [2]	Review 1968	Retrospective Autopsy	-	Not described	Angina: mean 5.0 Syncope: mean 3.0 CHF: mean 2.0	Not described
Frank (1973) [12]	1954 - ...	Retrospective Follow-up	15	Range: 32 - 59	Overall: 3 year 64% 5 year 48%	Aortic valve area index ≤ 0.7 cm^2 or maximum peak gradient ≥ 50 mmHg
Chizner (1980) [13]	1966 - 1971	Retrospective Follow-up	23	Mean: 56	Overall: 3 year 43% 5 year 36%	Aortic valve area ≤ 1.1 cm^2 or maximum peak gradient ≥ 40 mmHg
Schwarz (1982) [30]	1975 - 1980	Retrospective Follow-up	19	Mean: 56	Overall: 3 year 21%	Clinical findings and maximum peak gradient ≥ 45 mmHg
O'Keefe (1987) [31]	1978 - 1985	Retrospective Follow-up	50	Mean: 77	Overall: 1 year 57% 2 year 37% 3 year 25%	Clinical findings
Horstkotte (1988) [16]	1968 - 1976	Retrospective Follow-up	35	Not described	Angina: mean 4.5 Syncope: mean 2.6 CHF: mean 1.0	Aortic valve area ≤ 0.8 cm^2

Table 2. Studies of the natural history of symptomatic patients with severe aortic valve stenosis (Cont.)

Iivanainen (1996) [17]	1990 - 1991	Retrospective Follow-up	13	Range: 75 - 86	Overall: 4 year 24%	Aortic valve area ≤ 0.8 cm² and velocity ratio ≤ 0.35 (ratio of the peak outflow tract velocity to the peak transvalvular velocity)
Bouma (1) (2004) [18]	1991 - 1994	Retrospective Follow-up	157	Range: 70 - 93	Overall: 1 year 60% 5 year 28%	Aortic valve area ≤ 1.0 cm² or maximum peak gradient ≥ 50 mmHg
Iung (2005) [23]	2001	Retrospective Follow-up	72	Mean: 82	Overall: 1 year 85%	Aortic valve area index ≤ 0.6 cm²/m² or mean gradient ≥ 50 mmHg
Charlson (2006) [39]	1995 - 1997	Retrospective Follow-up	75	Mean: 85	Overall: 1 year 55% 3 year 23% 5 year 15%	Aortic valve area ≤ 0.8 cm² or mean gradient ≥ 50 mmHg
Varadarajan (2006) [19]	1993 - 2003	Retrospective Follow-up	453	Mean: 75	Overall: 1 year 62% 5 year 32% 10 year 18%	Aortic valve area ≤ 0.8 cm²
van Geldorp (2009) [20]	2004 - 2007	Retrospective Follow-up	101	Mean: 73	Overall: 1 year: 77% 2 year: 69%	Aortic valve area < 1.0 cm² or maximum aortic jet velocity >4.0 m/s or peak aortic gradient >64 mmHg or mean aortic gradient >40 mmHg
Bakaeen (2010) [40]	1997 - 2008	Retrospective Follow-up	140	Mean: 76	Overall: 1 year 65% 3 year 29% 5 year 16%	Aortic valve area < 1.0 cm²

prognosis is influenced by increased age (patient's life expectancy) and various comorbidities. In this setting, the cardiologist and surgeons have to balance the mortality and morbidity associated with surgery or TAVI against the expected duration and quality of life with medical treatment, as life expectancy of elderly people is short, regardless of whether or not the patient has severe symptomatic AS (Figure 1). The benefit of surgery or alternative treatment methods such as TAVI is uncertain because the majority of information about the outcome of medical treatment dates back to the presurgical and precatheterization era.[2] Therefore, the aim of this article is to outline the evidence of natural history with medical treatment to assist in optimal clinical decision-making in the high-risk elderly population with severe symptomatic AS.

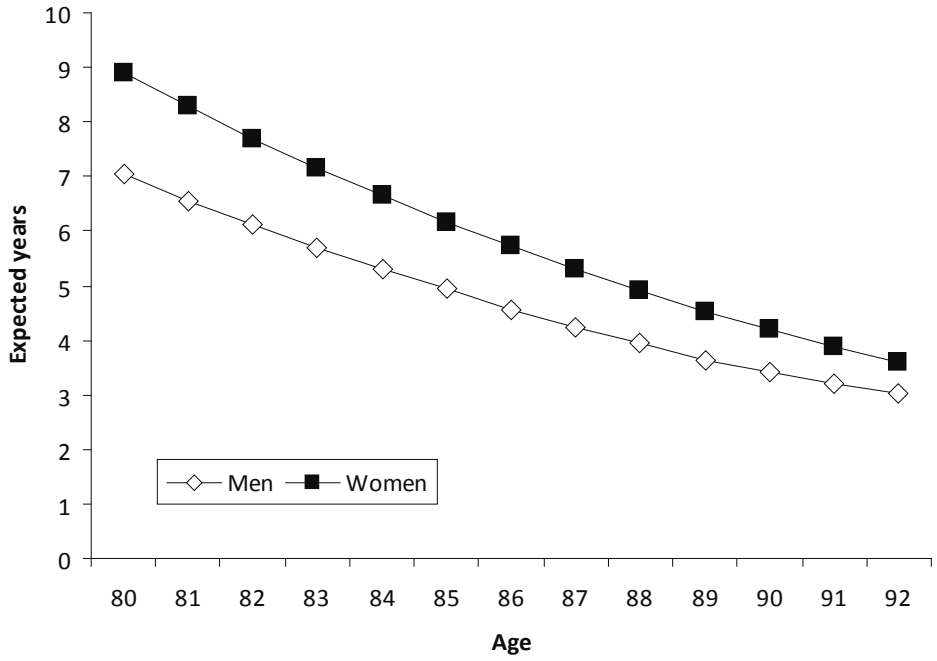

Figure 1. Expected gender-specific survival for octogenarians.

NATURAL HISTORY: THE EVIDENCE

The first report presenting survival data of patients treated conservatively for severe symptomatic AS was published in 1954. Bergeron et al. described the natural history outcome of 82 patients, mean age 69 years, with severe symptomatic AS who had been followed up over an 11-year period.[10] All patients were examined at necropsy

at which severe AS was described as "an aortic valve admitting at most the tip of a finger". In their analysis, 3-year survival was 45% in patients presenting with angina, 45% in patients with syncope and 35% in patients with congestive heart failure (Table 2). In line with these observations, the next important contribution to the understanding of the natural history of severe symptomatic AS was also in 1954 by Mitchell et al..[11] Over a 39-year period, they investigated the natural history outcome in 122 patients with severe symptomatic AS. Aortic stenosis was proven at autopsy, or the diagnosis was made clinically and verified by the demonstration of calcium in the region of the aortic valve by x-ray and fluoroscopic study. Mean survival in patients presenting with angina, syncope and congestive heart failure was 4.1, 3.0 and 2.0 years, respectively.

In 1968, still before the era of hemodynamic assessment of AS severity, Ross and Braunwald summarized data from seven postmortem studies on the natural history of severe symptomatic AS.[2] Most of these studies were retrospective and published before 1955. Based on their analysis, they observed that the average life expectancy after the onset of angina pectoris, syncope and congestive heart failure was 5, 3 and 2 years, respectively. Ever since, these data have become commonly used to describe the natural history of severe symptomatic AS.

In the decade after this report, two studies assessed the hemodynamic consequence of valvular obstruction in severe symptomatic patients with AS.[12,13] In a report by Frank et al. comprising 15 patients, the 5- and 10-year survival rates were 48 and 10%, respectively.[12] Among the 23 patients reported by Chizner et al., 26% were deceased 1 year after the onset of symptoms and 64% by 5 years.[13] Not surprisingly, a prospective study examining the natural history of severe symptomatic AS has not been conducted since the introduction of aortic valve replacement. Because of the limited number of patients who were not operated for severe symptomatic AS, some studies retrospectively identified the natural history of patients who refused or were denied aortic valve replacement.[12-17] The natural history of this small subset of highly selected patients probably does not represent the natural history of all patients with severe symptomatic AS.

In 2004, Bouma et al. reported on a cohort of 280 elderly patients with severe symptomatic AS of which 120 were operated upon and 160 were treated conservatively.[18] The overall 1-year survival of these 160 patients was 60% and the 5-year survival was 28%. They found no difference in survival among patients ≥80 years with severe symptomatic AS and without cardiac comorbidity. One of the most recent series was published by Varadarajan et al. in 2006.[19] In this study, the authors screened their echocardiographic database over a 10-year period for patients with severe AS (Doppler estimated aortic valve area (AVA) of 0.8 cm^2 or less). Seven hundred and forty patients were identified, of whom 453 had no aortic valve re-

placement through follow-up. These patients had a 1-, 5- and 10-year survival of 62, 32 and 18%, respectively. In a recent series, van Geldorp et al. also screened the Erasmus MC echocardiographic database over a 3.5-year period for patients with severe symptomatic AS.[20] One hundred and seventy-seven patients were identified, of whom 101 were treated conservatively. These patients had a 1- and 2-year survival of 77 and 69%, respectively.

The most recent series was published in 2010 by Rajani et al..[21] The authors published a series of 85 patients who were screened for TAVI. Of these patients, 38 received TAVI and 47 patients (55%) were managed medically as these patients were deemed not suitable for a TAVI procedure. Survival was better for the TAVI group compared with the medically managed group. However, as medically treated patients were deemed not suitable for TAVI, these results are biased owing to selection bias.

DISCUSSION

Successful cardiac surgical therapy in the octogenarians and nonagenarians is increasingly performed and the number of procedures will increase even further over the coming years as healthcare in general improves and the population ages. Despite the high risk, surgical valve replacement is still the gold standard in those patients who are medically fit and have severe symptomatic AS. The decision to proceed with aortic valve replacement depends on many factors, including the patient's wishes and expectations. However, some patients are at high-risk due to several reasons and some will refuse surgery, even with a clear understanding of the risks and benefits.

The development of TAVI offers a viable option for patients at high surgical risk. Recent studies have highlighted the underuse of aortic valve replacement ranging from 30 to 60% of elderly patients with severe symptomatic AS.[22,23] As a result of the emergence of TAVI, some high-risk patients are now being referred because the strategy of the cardiologists is changing. The feasibility and immediate efficacy of the percutaneous devices have been demonstrated, while its long-term outcomes, particularly with respect to device durability, remains to be proven. However, the rates of serious periprocedural complications and major adverse cardiac and cerebrovascular events rates within 30 days are of concern and need further improvement.[24-26]

The hand drawn survival figure, based on data from seven postmortem studies on natural history of AS, published by Ross and Braunwald in 1968 is still being used in current clinical practice as the accepted clinical view regarding the natural history

of severe symptomatic AS.[2] However, the natural history studies described in this article have significant limitations when extrapolating findings to current clinical decision-making. Studies in which prognosis is based only on postmortem cases are biased, because prognosis will appear better if living patients with symptoms are also included. For example, Takeda et al. reported an average survival of 4.4, 3.8 and 2.8 years after angina, syncope and congestive heart failure, respectively.[27] However, they excluded living patients in their calculation. If living patients were included, mean survival calculations would be 6.3, 6.4 and 3.6 years after angina, syncope and congestive heart failure, respectively.

A problem that has arisen in clinical practise is the definition of 'severe' AS. Over recent years, echocardiography has evolved to become the major tool for evaluating patients with valvular AS. At present, severe AS is defined by the American College of Cardiology/American Heart Association Practice Guidelines as an AVA less than 1.0 cm^2, mean gradient greater than 40 mm Hg or jet velocity greater than 4.0 m/s.[28] In the past, the severity of AS was based on clinical examination.[11,27,29-31] As cardiac catheterization evolved and provided an objective measurement of the severity of AS by means of the AVA, the criterion for severe AS was first set as an AVA less than 0.7 cm^2 .[32] However, the precise hemodynamic criterion for 'severe' AS has varied in the past (Table 3). As a consequence, the validity (patient generalizability) of earlier studies must be questioned.

Table 3. Success and outcome of transcatheter aortic valve implantation

Author	No. of patients	Approach	Procedure success	30-day mortality	30-day MACCE
Edwards-Sapien valve					
Cribier (2006) [24]	34	Antegrade Retrograde	74%	17%	26%
Webb (2006) [41]	18	Retrograde	78%	11%	-
Webb (2007) [42]	50	Retrograde	86%	12%	16%
Global update: Eltchaninoff (2008) [43]	>270	Retrograde	86%	12%	-
Ye (2009) [25]	26	Transapical	100%	23%	31%
Thomas (SOURCE Registry) (2010) [44]	1038	Transfemoral Transapical	94%	9%	30%
Walther (2007) [45]	59	Transapical	90%	14%	-
Core valve					
Grube (2006) [26]	25	Retrograde	84%	20%	32%
Grube (2007) [46]	86	Retrograde	88%	12%	22%
Global update: Grube (2008) [47]	175	Retrograde	92%	15%	-

MACCE = major adverse cardiac and cerebrovascular events.

Coronary angiography was not performed in most of the published series, although the presence of coronary artery disease is clearly a major risk factor for mortality. In a study by Turina et. al., 50% of patients with severe symptomatic AS with additional coronary artery disease died within the first year of follow-up, while only 16% of patients without coronary artery disease died.[33] Therefore, survival and symptoms may even be improved if medically treated patients undergo percutaneous coronary intervention of significant coronary lesions.

Furthermore, treatment decisions made in the past differ greatly from those of today. For example, today an impaired left ventricular function would be an indication for operation,[34] whereas in the past it would be considered a relative contraindication. In addition, the aetiology of AS and the characteristics of the patient population have changed markedly during the past decades, and it can be questioned whether the course of AS in middle-aged patients of the 1960s should guide the management of today's octogenarians and nonagenarians with severe symptomatic AS.

Moreover, studies have involved few elderly patients and have reported on combined end points (e.g., a combination of death and cardiac surgery), which makes their results difficult to interpret.[16,35,36]

Important 1-year data of the randomized trial in the USA, PARTNER-US, in which TAVI is compared with standard therapy in a group of patients unsuitable for surgical aortic valve replacement have recently been published.[37] At 1 year, the rate of death was 31% with TAVI, as compared with 50% with standard therapy ($p<0.001$). However, the incidence of major strokes at 30 days (5.0 vs. 1.1%; $p=0.06$) and major vascular complications (16.2 vs. 1.1%; $p<0.001$) was higher with TAVI as compared with standard therapy. These data must be interpret with caution as patients in the TAVI group compared with the standard therapy group had a significantly lower incidence of prognostic factors which have an effect on outcome, such as a lower EuroSCORE, lower rate of chronic obstructive pulmonary disease and lower rate of atrial fibrillation. Moreover, only 12% of those patients considered not be suitable candidates for surgery were considered suitable for TAVI and underwent randomization. An important issue in the future will be the cost-benefit of TAVI versus medical therapy, since after 1 year 31% of the TAVI patients are death and 20% have severe symptoms (New York Heart Association Class 3 or 4), resulting in a 1-year asymptomatic or mild symptomatic survival of only 50%. Nevertheless, recently Reynolds et al. showed that among selected inoperable patients with severe symptomastic AS, compared with standard therapy, TAVI resulted in significant improvements in health-related quality of life.[38]

Management decision in elderly high-risk patients with severe symptomatic AS must be taken thoughtfully and should be made on an individual basis, taking into

account patients' life expectancy and quality of life, patients' wishes and cardiac and non-cardiac comorbid factors. Once coronary disease, other valvular heart disease, neurological deficits, renal failure and other comorbidities are added to the clinical setting, outcome worsens and these factors must be taken into consideration when deciding whether to correct AS in elderly patients. As life expectancy in the octogenarian is short and the main aim in the elderly is to improve quality of life rather than to increase the duration of life, surgeons and cardiologists have to question whether they do their patients a favour or a disservice with the chosen therapy. Based on the available data, TAVI promises significantly improved 1-year survival when compared with medical management. Nevertheless, the technology of TAVI is still in its infancy and rigorous evaluation of transcatheter technology with adequate follow-up is needed. In addition, the natural history of medically managed patients with severe symptomatic AS in the modern era is still unclear, as most published data is outdated or biased. In this regard, much remains to be learned about the current natural history of severe symptomatic AS, especially in high-risk elderly patients.

FUTURE PERSPECTIVE

At present, surgical aortic valve replacement is still the gold standard for treatment of severe symptomatic AS. However, TAVI has been proven to be a feasible treatment option to treat high-risk inoperable elderly patients with severe symptomatic AS. An assessment of the durability and long-term clinical safety and effectiveness of the bioprosthetic valves will require more prolonged follow-up of patients who participate in clinical trials of TAVI.

The key issue in the future is to adequately select those elderly patients who will benefit from TAVI and select those who will benefit from medical treatment. For example, treatment options could be different in an 85-year-old patients with severe AS, mild angina and comorbidity (medical treatment could be a better option) compared with an 85-year-old patients with severe AS, congestive heart failure and no further comorbidity (TAVI could be a better option). Additional randomized trials on specific patient populations with certain symptoms and comorbidity is necessary to determine the best treatment option in those groups of patients. In addition, a clinical course of patients who are denied TAVI (which was 88% in the PARTNER-US trial) should be documented.

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EXECUTIVE SUMMARY

- Surgical aortic valve replacement is still the gold standard for treatment of severe symptomatic aortic valve stenosis.
- Patients who are inoperable of high-risk candidates may be offered transcatheter aortic valve implantation.
- The feasibility and immediate efficacy of transcateheter aortic valve implantation has been demonstrated, while its long-term outcome, particularly with respect to device durability, remains to be proven.
- The majority of published series describing the natural history of severe symptomatic aortic valve stenosis are biased because most reported series are post-mortem studies and date back to the presurgical and precatheterization era, or are biased due to highly selected patient populations.
- The first randomized trial (PARTNER-US) comparing transcatheter aortic valve implantation with medical therapy in a group of inoperable patients with severe symptomatic aortic valve stenosis clearly demonstrates an improved 1-year survival in the transcatheter group. However, data cannot be extrsapolated to all inoperable patients since the study population was higly selected (only 12% of inoperable patients were included in the study).
- The natural history of medically treated patients with severe symptomatic aortic valve stenosis in the modern era is still unclear. Additional randomized trials in specific patient populations with certain symptoms and comorbidity is necessary. The clinical course of patients who are denied transcatheter aortic valve implantation should be documented.

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What is a scientist after all? It is a curious man looking through a keyhole, the keyhole of nature, trying to know what's going on.

J.Y. Cousteau

5

Predictors for hemodynamic progression of adult severe aortic valve stenosis

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SUBMITTED

Als je de beperkingen kent,
kun je daarbinnen onbeperkt te werk gaan.

J.A. Deelder

6

Left ventricular twist and untwist in aortic stenosis

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ABSTRACT

Background

To optimally exploit the potential added diagnostic and prognostic value of new left ventricular (LV) deformation parameters, better understanding of LV mechanics in aortic stenosis (AS) is warranted. We sought to determine a broad spectrum of LV rotation parameters in AS patients and age-matched healthy controls, in order to gain insight into the mechanical properties of the LV in AS.

Methods

The study comprised 48 AS patients with an aortic valve area <2.0 cm^2 and LV ejection fraction >50%, and 24 healthy – for age and gender matched – control subjects.

LV peak systolic rotation (Rot_{max}), LV peak systolic twist ($Twist_{max}$), untwisting rate (*mean* diastolic untwisting velocity from $Twist_{max}$ to mitral valve opening), *peak* diastolic untwisting velocity, and *time-to-peak* diastolic untwisting velocity were determined by speckle tracking echocardiography.

Results

AS patients had normal basal Rot_{max} and increased apical Rot_{max}, resulting in increased $Twist_{max}$ (13.4 ± 4.0° versus 11.4 ± 2.7°, P <0.05). Apical Rot_{max} and $Twist_{max}$ correlated significantly to echo-Doppler indicators of AS severity. Time-to-peak diastolic untwisting velocity was increased (20 ± 10 % versus 15 ± 9 %, P <0.05) and untwisting rate was decreased (-38 ± 21°/s versus -50 ± 28°/s, P <0.01) in AS patients.

Conclusions

$Twist_{max}$ increases proportionally to the severity of AS, which might serve as a compensatory mechanism to maintain systolic LV function. LV diastolic untwisting is delayed and the untwisting rate is reduced in AS.

INTRODUCTION

The timing of aortic valve replacement in patients with severe aortic stenosis (AS) is based on symptoms and left ventricular (LV) ejection fraction.[1] Newer LV deformation parameters, such as strain and rotation, may serve as better estimates of LV function.[2] However, to optimally exploit the added value of these new parameters, better understanding of LV mechanics in AS is warranted. In previous tagged magnetic resonance imaging (MRI) studies changes in LV rotation parameters in AS patients have been described.[3-6] However, these studies were limited by small numbers of patients[3-6] and not for age matched control subjects.[4-6] Since LV rotation parameters are known to be influenced by age,[7,8] this latter is a serious limitation. Speckle tracking echocardiography (STE) is a new imaging modality that is able to assess LV rotation.[9,10] The purpose of the current study was to determine a broad spectrum of LV rotation parameters in a large group of AS patients compared to age-matched healthy controls, in order to gain insight into the mechanical properties of the LV in AS. In addition, LV rotation parameters were correlated to echocardiographic indicators of AS severity.

METHODS

Study participants

The study population consisted of 46 consecutive patients (mean age 65 ± 14 years, 26 men) referred for echocardiography because of a murmur or follow-up of known AS, in sinus rhythm, with an aortic valve area <2.0 cm^2, normal LV ejection fraction (>50%), and good echocardiographic image quality that allowed for complete segmental assessment of LV rotation at both the basal and apical LV level, and without moderate to severe mitral regurgitation. During the enrolment of these 46 patients, 26 other patients (36%) were excluded because of suboptimal echocardiographic image quality not fulfilling this criterion or the presence of atrial fibrillation. Of the 46 included patients, 33 (72%) were symptomatic (dyspnoea in 23 (50%), angina in 12 (26%), and collapse in 1 (2%)). Mild mitral regurgitation was present in 14 patients (30%). The AS patients were compared to 23 healthy – for age and gender matched – control subjects in sinus rhythm, without hypertension, diabetes, or regular use of medication for cardiovascular disease, and with normal left atrial dimensions, LV dimensions, LV ejection fraction and LV diastolic function for age (in elderly subjects >60 years an impaired relaxation pattern (grade 1 diastolic dysfunction, defined as: E/A ratio <0.75 and E-wave velocity deceleration time >240 ms) was not considered abnormal). Control subjects were recruited from our

department (personnel) or were family members or friends. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's review board and all subjects gave informed consent.

Echocardiography

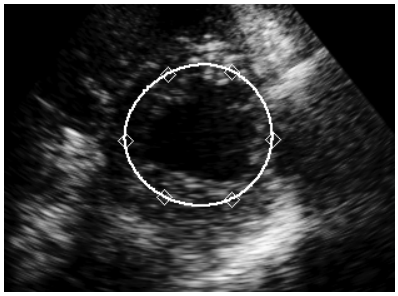
Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (iE33, Philips, Best, The Netherlands), equipped with a broadband (1-5 MHz) S5-1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz). All echocardiographic measurements were averaged from three heartbeats. From the M-mode recordings the following data were acquired: left atrial size, LV end-diastolic anteroseptal and inferolateral wall thickness, and LV end-diastolic and end-systolic dimension. LV mass was assessed with the two-dimensional area–length method.[11] LV ejection fraction was calculated from LV volumes by the modified biplane Simpson rule in accordance with the guidelines.[11] From the mitral-inflow pattern, peak early (E) and late (A) filling velocities, E/A ratio, and E-velocity deceleration time were measured. Tissue Doppler was applied end-expiratory in the pulsed-wave Doppler mode at the level of the inferoseptal side of the mitral annulus from an apical 4-chamber view. To acquire the highest wall tissue velocities, the angle between the Doppler beam and the longitudinal motion of the investigated structure was adjusted to a minimal level. The spectral pulsed-wave Doppler velocity range was adjusted to obtain an appropriate scale. The timing of the beginning and ending of the isovolumic relaxation time were determined using pulsed wave Doppler. Aortic valve areas were calculated by the continuity equation and also indexed by body surface areas, calculated using the Mosteller formula.[12] The severity of aortic and mitral regurgitation was determined according to the guidelines.[13]

To optimize STE, images were obtained at a frame rate of 60 to 80 frames/s. Parasternal short-axis images at the LV basal level (showing the tips of the mitral valve leaflets) with the cross section as circular as possible were obtained from the standard parasternal position, defined as the long-axis position in which the LV and aorta were most in-line with the mitral valve tips in the middle of the sector. To obtain a short-axis image at the LV apical level (just proximal to the level with end-systolic LV luminal obliteration) the transducer was positioned 1 or 2 intercostal spaces more caudal as previously described by us.[14] From each short-axis image, three consecutive end-expiratory cardiac cycles were acquired and transferred to a QLAB workstation (Philips, Best, The Netherlands) for off-line analysis.

Speckle tracking analysis

Analysis of the datasets was performed using QLAB Advanced Quantification Software version 6.0 (Philips, Best, The Netherlands), which was recently validated against MRI for assessment of LV twist.[10] To assess LV rotation, six tracking points were placed manually (after gain correction) on the mid-myocardium on an end-diastolic frame in each parasternal short-axis image. Tracking points were separated about 60° from each other and placed on 1 (30°, anteroseptal insertion into the LV of the right ventricle), 3 (90°), 5 (150°), 7 (210°), 9 (270°, inferoseptal insertion into the LV of the right ventricle), and 11 (330°) o'clock to fit the total LV circumference (Figure 1).

Data were exported to a spreadsheet program (Excel, Microsoft Corporation, Redmond, WA) to determine LV peak systolic rotation during ejection (Rot_{max}), time to Rot_{max} (from R wave to Rot_{max}), instantaneous LV peak systolic twist ($Twist_{max}$, defined as the maximal value of instantaneous apical systolic rotation – basal systolic rotation), time to $Twist_{max}$ (from R wave to $Twist_{max}$), and LV untwisting at 5%, 10%, 15%, and 50% of diastole. The *degree of untwisting* was expressed as a percentage of maximum systolic twist: untwisting = ($Twist_{max}$ – $Twist_t$)/ $Twist_{max}$ x 100%, where $Twist_t$ is twist at time t. Furthermore, *peak* systolic rotation velocity



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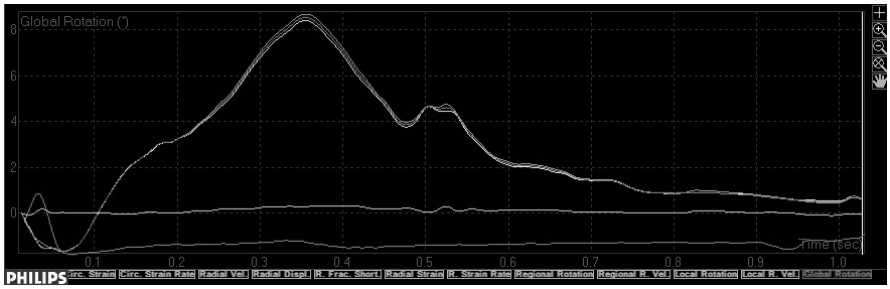

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Figure 1a. Positioning of the tracking points at the left ventricular apical level. **b.** Left ventricular rotation–time curve (x-axis: time in ms; y-axis: left ventricular apical rotation in degrees). The grey line represents left ventricular apical rotation (peak systolic rotation 8.2°), and the white line recruitment, which was not activated in this example. The electrocardiogram is displayed at the bottom.

and *peak* diastolic de-rotation velocity, *peak* systolic twist velocity and *peak* diastolic untwist velocity, and the timing of these parameters were assessed. Normalized velocities were determined by correcting for Rot_{max} or $Twist_{max}$. Finally, untwisting rate was defined as the *mean* diastolic untwisting velocity from peak systolic twist to mitral valve opening and calculated as: (twist at mitral valve opening – peak systolic twist) / time interval from peak systolic twist to mitral valve opening. To adjust for intra- and intersubject differences in heart rate, the time sequence of systolic and diastolic events was normalized to the percentage of systolic and diastolic duration, respectively. End-systole was defined as the point of aortic valve closure. In each study it was verified that heart rate for the cardiac cycle in which the timing of aortic valve closure was assessed, was the same as the cardiac cycle used for analysis of LV rotation parameters.

Statistical Analysis

Matching of controls and AS patients was achieved by randomly matching each control with two AS patients with the same sex and age ± 5 years. Measurements are presented as mean ± SD. Variables were compared using Student's *t* test, or Chi-square test when appropriate. Kolmogorov-Smirnov test with Lilliefors significance correction was used for testing normality of distribution. The homogeneity of variance in the data for AS patients and control subjects was checked with Levene's test. Relations between parameters were assessed using Pearson's and Spearman's test for parametric and nonparametric correlations. A P value <.05 was considered statistically significant. Intraobserver and interobserver variability for LV twist in our center are 6% ± 6% and 9% ± 5%, respectively.[15]

RESULTS

Characteristics of the study population

In Table 1, the clinical and echocardiographic characteristics of the study population are shown. On average, AS was moderate-to-severe with a mean jet velocity of 3.9 ± 0.9 m/s, a mean gradient of 41 ± 20 mmHg, an aortic valve area of 1.0 ± 0.5 cm^2, and an aortic valve area indexed by body surface area of 0.45 ± 0.27 cm^2/m^2. Heart rate, left atrial size and LV mass were increased in AS patients as compared to control subjects. E-wave and A-wave velocities, the E-wave velocity deceleration time, and the E/Em ratio were increased in AS patients as well, whereas the E/A ratio was comparable.

Table 1. Clinical and echocardiographic characteristics of the study population

	Control subjects (n = 23)	**Aortic stenosis patients** (n = 46)	**p-value**
Clinical characteristics			
Age, year	61 ± 7	65 ± 14	0.117
Male, n (%)	12 (54)	25 (54)	0.330
Heart rate, beats/minute	60 ± 11	67 ± 11	0.015
Hypertension, n (%)	0	9 (20)	0.054
Diabetes, n (%)	0	5 (11)	0.245
Coronary artery disease, n (%)	0	18 (39)	0.002
Echocardiographic characteristics			
Left atrial size, cm	3.8 ± 0.5	4.4 ± 0.9	0.004
Left ventricular mass, g	162 ± 54	236 ± 112	0.004
Left ventricular ejection fraction, %	60 ± 8	56 ± 8	0.054
E, cm/s	60 ± 11	81 ± 30	0.002
A, cm/s	69 ± 17	89 ± 30	<0.001
E/A ratio	1.1 ± 0.3	1.0 ± 0.5	0.381
Deceleration time, ms	185 ± 29	239 ± 85	0.004
Em septal, cm/s	8.0 ± 1.9	5.3 ± 2.5	<0.001
E/Em ratio	8.4 ± 2.2	17.4 ± 9.4	<0.001
Aortic valve			
Velocity, m/s	1.3 ± 0.3	3.9 ± 0.9	<0.001
Mean gradient, mmHg	4 ± 2	41 ± 20	<0.001
Valve area, cm^2	3.0 ± 0.4	1.0 ± 0.5	<0.001
Valve area indexed by BSA, cm^2/m^2	1.60 ± 0.23	0.45 ± 0.27	<0.001
Regurgitation grade (1-4), mean	0.0 ± 0.0	1.1 ± 0.9	<0.001

E = peak early phase filling velocity, A = peak atrial phase filling velocity, Em = peak early diastolic wave velocity, BSA = body surface area. Values are means ± SD.

Systolic LV rotation parameters

AS patients had normal basal Rot_{max}, and increased apical Rot_{max}, resulting in increased $Twist_{max}$ (Figure 2). Apical peak systolic rotation velocity and peak systolic twist velocity were increased in AS patients, although these differences were lost when the velocities were normalized for apical Rot_{max} and $Twist_{max}$, respectively. The time-to-peak systolic twist velocity was decreased in AS patients (Table 2).

Diastolic LV rotation parameters

AS patients had decreased untwisting at 10% and 15% of diastole. Furthermore, AS patients had normal basal peak diastolic de-rotation velocity, and increased apical

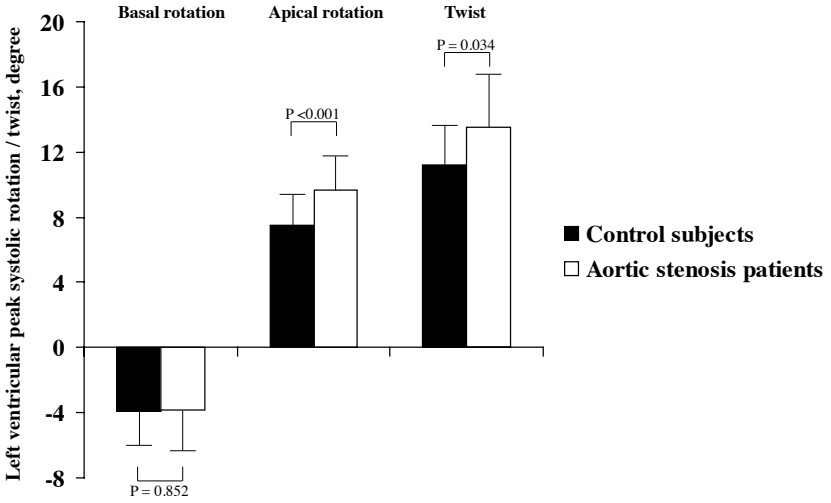

Figure 2. Peak systolic left ventricular rotation and twist.

peak diastolic de-rotation velocity, resulting in increased peak diastolic untwisting velocity. However, again these differences were lost when apical peak diastolic de-rotation velocity and peak diastolic untwisting velocity were normalized for apical Rot_{max} and $Twist_{max}$, respectively. The time-to-peak apical diastolic de-rotation velocity and time-to-peak diastolic untwisting velocity were increased in AS patients. Untwisting rate was decreased in AS patients (Table 3).

Relations of LV rotation parameters to echocardiographic indicators of AS severity

Apical Rot_{max} and $Twist_{max}$ correlated positively to aortic valve jet velocity (R^2 = 0.22, and R^2 = 0.21, respectively, both P = 0.006) and mean gradient (R^2 = 0.19, and R^2 = 0.20, respectively, both P = 0.005), negatively to aortic valve area (R^2 = 0.30, and R^2 = 0.27, respectively, both P <0.001), and aortic valve area indexed by body surface area (R^2 = 0.34, and R^2 = 0.30, respectively, both P <0.001) (Figure 3). To investigate the influence of the bimodally distributed patients group (relatively many patients had either severe or very mild AS) on these correlations, a separate analysis was performed in AS patients with an aortic valve area <1.5 cm^2. In this subgroup, all relationships remained identifiable (apical Rot_{max} and $Twist_{max}$ correlated positively to aortic valve jet velocity (R^2 = 0.14, P = 0.01 and R^2 = 0.13, P = 0.02, respectively) and mean gradient (both R^2 = 0.12, P = 0.02), negatively to aortic valve area (R^2 = 0.20, P = 0.006 and R^2 = 0.17, P = 0.008), and aortic valve area indexed by body surface area (R^2 = 0.20 and R^2 = 0.19, both P = 0.006)). The only velocity parameter that was related to echocardiographic indicators of AS severity,

Table 2. Systolic left ventricular rotation parameters in aortic stenosis patients and control subjects

	Control subjects (n = 23)	**Aortic stenosis patients** (n = 46)	**p-value**
Left ventricular basal level			
Rot_{max}, degree	-3.9 ± 1.6	-3.8 ± 2.3	0.852
Peak systolic rotation velocity, degree/sec	-42 ± 10	-46 ± 15	0.252
Normalized peak systolic rotation velocity, sec^{-1}	11.4 ± 2.4	10.7 ± 5.0	0.528
Time to Rot_{max}, %	94 ± 12	92 ± 12	0.516
Time-to-peak systolic rotation velocity, %	47 ± 10	46 ± 18	0.805
Left ventricular apical level			
Rot_{max}, degree	7.5 ± 2.2	9.7 ± 2.5	<0.001
Peak systolic rotation velocity, degree/sec	52 ± 11	67 ± 18	<0.001
Normalized peak systolic rotation velocity, sec^{-1}	7.9 ± 3.0	7.4 ± 3.2	0.535
Time to Rot_{max}, %	95 ± 5	95 ± 8	1.000
Time-to-peak systolic rotation velocity, %	51 ± 14	47 ± 18	0.354
Left ventricular twist			
$Twist_{max}$, degree	11.4 ± 2.7	13.4 ± 4.0	0.034
Peak systolic twist velocity, degree/sec	69 ± 17	81 ± 22	0.025
Normalized peak systolic twist velocity, sec^{-1}	6.4 ± 1.0	6.7 ± 1.7	0.438
Time to $Twist_{max}$, %	96 ± 5	97 ± 6	0.494
Time-to-peak systolic twist velocity, %	56 ± 11	45 ± 14	0.002

Normalized rotation and twist velocities adjusted for Rot_{max} and $Twist_{max}$, respectively. Time to peak as a percentage of duration of systole. Rot_{max} = left ventricular peak systolic rotation during ejection, $Twist_{max}$ = instantaneous left ventricular peak systolic twist. Values are means ± SD.

was the time-to-peak apical de-rotation velocity (positively to aortic valve jet velocity (R^2 = 0.24, P = 0.008), and aortic valve mean gradient (R^2 = 0.18, P = 0.02), and negatively to aortic valve area (R^2 = 0.20, P = 0.007) and aortic valve area indexed by body surface area (R^2 = 0.22, P = 0.009)). LV mass was not related to any of the LV rotation parameters.

Mutual relations of LV rotation parameters

Basal and apical Rot_{max} correlated positively to basal (R^2 = 0.61, P <0.001) and apical (R^2 = 0.46, P <0.001) peak systolic rotation velocity, respectively, and to basal (R^2 = 0.34, P = 0.003) and apical (R^2 = 0.24, P <0.009) peak diastolic de-rotation velocity, respectively. $Twist_{max}$ correlated positively to peak systolic twist velocity (R^2 = 0.63, P <0.001) and peak diastolic untwisting velocity (R^2 = 0.45, P <0.001).

Table 3. Diastolic left ventricular rotation parameters in aortic stenosis patients and control subjects

	Control subjects (n = 23)	Aortic stenosis patients (n = 46)	p-value
Left ventricular basal level			
Peak diastolic de-rotation velocity, degree/sec	50 ± 13	56 ± 19	0.178
Normalized peak diastolic de-rotation velocity, sec^{-1}	-12.6 ± 4.3	-12.5 ± 10.3	0.965
Time-to-peak diastolic de-rotation velocity, %	17 ± 11	23 ± 14	0.077
Left ventricular apical level			
Peak diastolic de-rotation velocity, degree/sec	-62 ± 23	-81 ± 26	0.004
Normalized peak diastolic de-rotation velocity, sec^{-1}	-9.1 ± 3.6	-9.4 ± 5.2	0.805
Time-to-peak diastolic de-rotation velocity, %	11 ± 7	22 ± 13	<0.001
Left ventricular untwist			
Untwisting at 5% of diastole, %	14 ± 6	12 ± 8	0.294
Untwisting at 10% of diastole, %	30 ± 13	22 ± 15	0.033
Untwisting at 15% of diastole, %	43 ± 17	32 ± 18	0.017
Untwisting at 50% of diastole, %	70 ± 10	68 ± 14	0.544
Peak diastolic untwisting velocity, degree/sec	-89 ± 22	-103 ± 27	0.035
Normalized peak diastolic untwisting velocity, sec^{-1}	-8.7 ± 2.4	-8.3 ± 2.9	0.570
Time-to-peak diastolic untwisting velocity, %	15 ± 9	20 ± 10	0.042
Untwisting rate, degree/sec	-50 ± 27	-37 ± 21	0.031

Normalized de-rotation and untwist velocities adjusted for Rot_{max} and $Twist_{max}$, respectively. Time-to-peak as a percentage of the duration of diastole. Values are means ± SD.

DISCUSSION

This study sought to assess a broad spectrum of LV rotation parameters in a large group of AS patients compared to age-matched healthy controls and to correlate these parameters to echocardiographic indicators of AS severity. The main findings of this study are, 1) $Twist_{max}$ is increased in AS, driven by increased apical Rot_{max}, 2) this increased $Twist_{max}$ may facilitate maintenance of peak diastolic untwisting velocity, although overall untwisting is delayed and untwisting rate is decreased, and 3) apical Rot_{max} and $Twist_{max}$ are related to the severity of AS.

Systolic LV rotation in AS

LV twist is caused by the dynamic interaction between oppositely oriented subepicardial and subendocardial myocardial fibre helices and has an important role in LV ejection.[16] The direction of LV twist is governed by the subepicardial fibres, mainly owing to their longer arm of movement.[17] Subendocardial ischemia has long been recognized as an early sign of myocardial suffering from pressure overload caused by AS.[18,19] Apical Rot_{max} and $Twist_{max}$ were increased in AS patients, possibly because

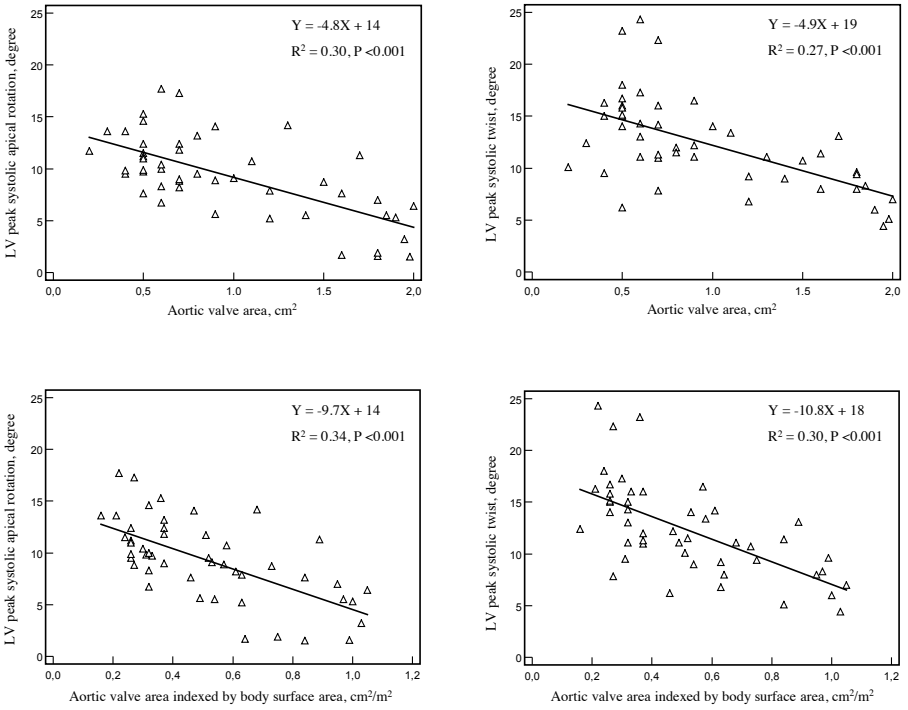

Figure 3. Linear regressions between aortic valve area and aortic valve area indexed by body surface area and left ventricular peak systolic apical rotation and twist.

subendocardial ischemia diminishes the counteraction of the subendocardial myofibres. Another potential mechanism may be LV hypertrophy with an increased arm of force over which the subepicardial fibres work, although LV mass was not related to any of the LV rotation parameters in the current study. Nevertheless, both mechanisms may be expected to lead to increased basal Rot_{max} as well, supported by findings in a previous study in which increased basal Rot_{max} was found in hypertrophic cardiomyopathy patients.[20] The lack of increased basal Rot_{max} in the current study may be explained by stiffening of the atrioventricular valvular plane that might prevent basal Rot_{max} to increase.

The current study is the first to relate LV rotation parameters to echocardiographic indicators of AS severity. Apical Rot_{max} and $Twist_{max}$ correlated positively to aortic valve jet velocity and mean gradient, and negatively to aortic valve area and aortic valve area indexed by body surface area. This underlines the potential role of subendocardial ischemia as the cause of increased apical Rot_{max} and $Twist_{max}$ in AS since the severity of subendocardial ischemia is known to be related to the severity of AS.[21] We have previously shown that septal and lateral mitral annular velocities

are reduced in patients with severe AS and normal LV ejection fraction.[22] Increased $Twist_{max}$ may serve as a compensatory mechanism to balance loss of LV myocardial contraction in other directions due to subendocardial ischemia. LV apical rotation, and in particular changes within one patient, may therefore provide an easy assessable marker of subendocardial ischemia. However, before large-scale clinical studies will be started, the relation between increased $Twist_{max}$ and subendocardial ischemia should be investigated in more detail, perhaps by using more objective measures of subendocardial ischemia, such as provided by contrast perfusion echocardiography.

In previous tagged MRI studies increased $Twist_{max}$ in AS patients has also been described.[3-6] However, these studies were limited by small numbers of patients[3-6] and not for age-matched control subjects.[4-6] It is well known that LV rotation parameters are influenced by age,[7,8] so this latter is a serious limitation not present in our study. In other small tagged MRI studies, LV rotation parameters before and after aortic valve replacement were investigated.[23,24] Sandstede et al.[23] found that the compensating increased $Twist_{max}$ in AS patients declined with increasing LV hypertrophy and dilatation, and that aortic valve replacement led to normalization of $Twist_{max}$. The former may be a surprising finding since increasing LV hypertrophy would be expected to be accompanied by increasing subendocardial ischemia and a larger difference in lever arms between the subendocardial and subepicardial fibres, leading to a further increase in $Twist_{max}$. Sandstede et al. explained their finding by suggesting a reverse mechanism in which a smaller degree of compensating increased $Twist_{max}$ might result in more LV hypertrophy and dilatation. Biederman et al.[24] investigated the role of coronary artery disease and found that independent of the presence of concomitant coronary artery disease, $Twist_{max}$ decreased after aortic valve replacement. Finally, Tzemos et al.[25] studied women with congenital aortic stenosis and found that $Twist_{max}$ was increased in this population as well. Furthermore, during pregnancy, LV twist further increased in the antepartum period, except in those women who experienced functional deterioration requiring urgent aortic balloon valvuloplasty.

Diastolic LV rotation in AS

The LV myocardium adapts to increased pressure overload due to AS by hypertrophy of individual myocytes. In addition, this pathological hypertrophy is accompanied by interstitial and perivascular fibrosis, and thickening of the media of intramyocardial coronary arteries.[26] Each of these factors in turn contributes to diastolic dysfunction commonly seen in AS patients.[27,28] In our study, LV untwist was delayed and the untwisting rate was reduced.

Normally, over 40% of diastolic LV untwisting has been completed after the first 15% of diastole, which contributes to the large pressure decrease during the isovolumic relaxation phase.[29,30] This early, rapid LV untwisting process may be supported by *active* and *passive* mechanisms. There is a temporal dispersion in endocardial and epicardial repolarization, with in early diastole still depolarized endocardial fibres (as opposite to the already repolarized epicardial fibres) that may *actively* untwist the LV (normally the action of these fibres are, as mentioned in the previous section, overruled by the epicardial fibres). However, the effective force of contraction of myocardial fibres is expected to be minimal during this part of the cardiac cycle. Nevertheless, dissimilarities of apparent stiffness of the endocardium and epicardium caused by differences in breakdown of actin-myosin cross-bridges may be of influence. Furthermore, high levels of stored potential energy from the active systolic twist are transformed into kinetic energy, adding a *passive* component to rapid early diastolic untwisting.[31] Subendocardial ischemia in AS patients may lead to loss of the *active* part of diastolic untwisting and the relaxation abnormality seen in AS patients may further compromise LV untwisting, evidenced by delayed and reduced early (and thus overall) LV untwisting. Surprisingly, peak diastolic untwisting velocity was higher in AS patients. This may be explained by the increased potential energy stored in the more twisted LV that will be released after all. This may lead to increased, but delayed, peak diastolic untwisting velocity, that may serve as a compensatory mechanism to help LV filling.

Conclusions

$Twist_{max}$ is increased in AS patients, proportionally to the severity of LV outflow obstruction. This increased $Twist_{max}$ might serve as a compensatory mechanism to maintain systolic function in the pressure overloaded LV. Conversely, LV untwist is delayed and the untwisting rate is reduced. However, the increase in $Twist_{max}$ may cause an (although delayed) increase in peak diastolic untwisting velocity that may partially compensate for the decrease in untwisting rate.

Acknowledgements

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.[32]

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De uitdrukking “het gaat als een trein” heeft door de NS een geheel andere betekenis gekregen.

L. van Erp

7

Association between electrocardiographic strain, angina and systolic left ventricular longitudinal velocities in patients with severe aortic valve stenosis

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Bashir AH
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Galema TW
Geleijnse ML

SUBMITTED

Wie gelijk heeft, hoeft niet te schreeuwen.

M. Schönherr

8

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

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NETH HEART J 2012;20:487-493

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, brain natriuretic peptide (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 optimisation 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 European Society of Cardiology and American College of Cardiology/American Heart Association 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) ≤1 cm^2, peak transaortic jet velocity (Vmax) ≥4 m/s, or aortic valve / left ventricular outflow tract velocity time integral ratio ≥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 test-

ing 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, AVAi (indexed by body surface area), left ventricular ejection fraction, left ventricular hypertrophy (on electrocardiography), ischaemia (on electrocardiography), and aortic and mitral regurgitation ≥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 ≥2 mm (N=10), no increase blood pressure (N=2), collapse (N=1), angina (N=1), and

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 (cm^2)	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%).

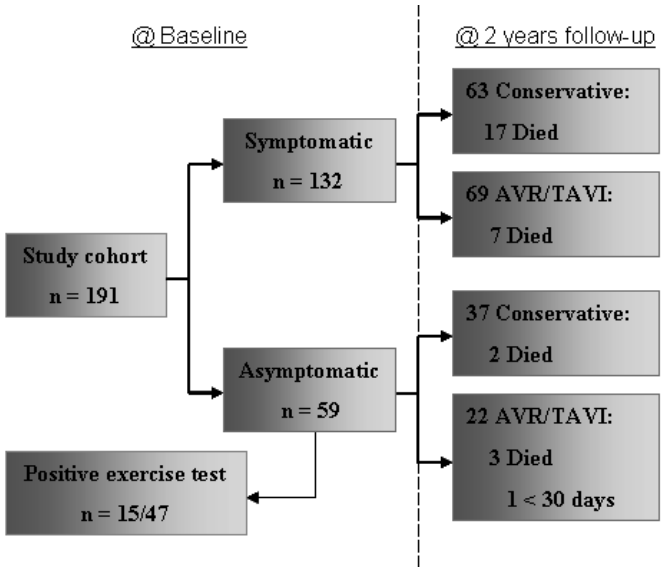

Figure 1. Flowchart of patient distribution during the study.

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.

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

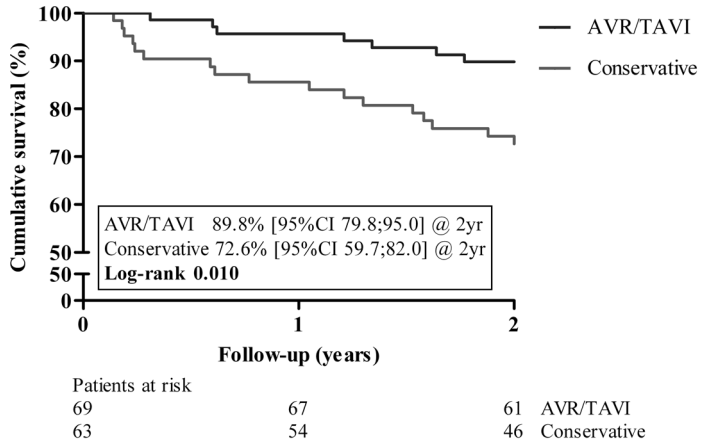

Figure 2. Patient survival for symptomatic patients differentiated by treatment strategy.

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).

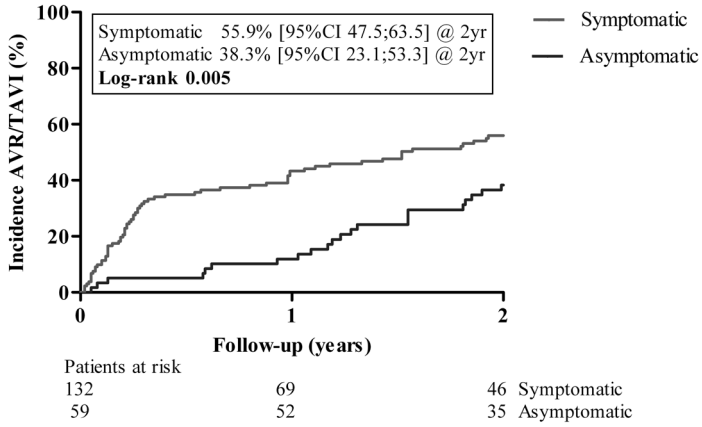

Figure 3. Cumulative incidence of AVR/TAVI differentiated by symptom status.

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 with 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%).

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.

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 underutilised and the true number of symptomatic patients may be much higher than is currently observed.[17]

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 with 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 treat-

ment.[18] 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.[19,20] 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.[21]

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.[22] Although treatment strategy may not affect survival, it does influence quality of life[23].In elderly patients with severe AS, quality of life should play a key role in optimising 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 with 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.[24] 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 AS and the need for stringent and frequent watchful waiting.

A systematic evidence-based multidisciplinary team approach is recommended to optimise treatment selection for symptomatic patients with severe AS. There is an urgent need to optimise 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.

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Conflict of interest

None declared.

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APPENDIX

Definitions

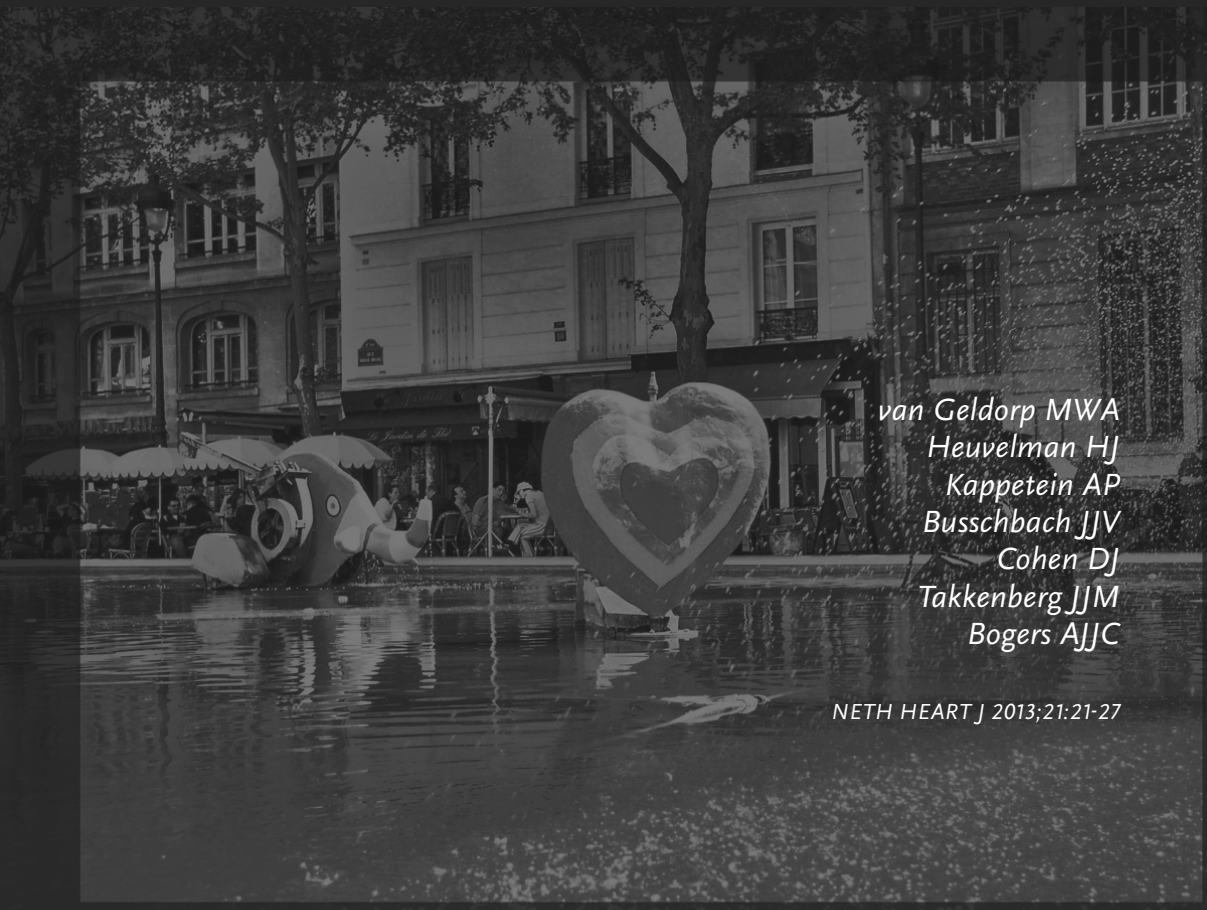
- *Body surface area*: calculated with DuBois and DuBois formula.
- *Carotid disease*: stenosis >50%, or previous or planned surgery.
- *Chronic obstructive pulmonary disease*: diagnosis previously made by physician, or receiving bronchodilators.
- *Congestive heart failure*: hospital stay with clinical 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.

Let's go!

Y.A. Gagarin

9

Quality of life among patients with severe aortic stenosis



van Geldorp MWA
Heuvelman HJ
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Busschbach JJV
Cohen DJ
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Bogers AJJC

NETH HEART J 2013;21:21-27

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, hypothesising 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 with 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 well-being. There was no relation between degree of stenosis and physical or mental health scores.

Conclusions

Both physical and emotional problems have a 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 and represents a growing health problem. Medical therapy does not slow the progression of severe aortic stenosis nor has it proven to reduce major adverse cardiac events, the only effective treatment is replacement of the aortic valve.[1-3] Surgical techniques and postoperative care have improved over the years and even patients with advanced age and comorbidities can be operated relatively safely.[4,5] Recently, the indications of transcatheter valve implantations have been evaluated, which now form a treatment option in patients with high operative risk.[6,7]

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.[6,8,9] Nonetheless, several studies show that for various reasons many patients who have an indication for aortic valve replacement are denied surgery.[10-13]

Although some literature is available on the functional status and quality of life (QoL) of (elderly) patients after AVR, more high-quality studies are needed.[14,15] Even less is known about the QoL of patients in whom the decision to operate is yet to be considered. 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 QoL, the impact of symptoms on daily life and the resulting disease burden remain unknown. The New York Heart Association (NYHA) classification is a functional measurement of physical performance or pain. It does not take social and emotional aspects into account and only roughly reflects one's current health status but certainly not one's desired health status or disease burden. Furthermore, physicians sometimes fail to recognize the functional disability of their patients.[16] An underestimation by the treating physician of the impact of symptoms on a patient's QoL might be one of the reasons why so many symptomatic patients with severe aortic stenosis are not referred for surgery. If these patients indeed present with a low QoL and better evidence about this burden of disease could be presented, there would be an additional argument to follow the clinical guidelines more strictly.

This paper presents the results of the Short Form-36v2™ Health Survey (SF-36v2™) in patients with severe aortic stenosis compared with 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 QoL 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.

METHODS

Patients

This study is part of a recently published multicentre prospective cohort study among patients with severe aortic stenosis in the Rotterdam area (the Netherlands) between July 2006 and April 2009.[17] In short, patients with severe aortic stenosis were recruited from the echocardiography laboratories of the outpatient clinics of seven local hospitals and all consecutive patients who provided written informed consent 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).

Methods

Patients were invited for a personal assessment by the principal investigators (MvG, HH). This assessment included an echocardiogram according to a specific study protocol focused on the aortic valve, recording of patient characteristics, NYHA class, medication and a calculation of anticipated operative mortality -for descriptive purposes only- using both the EuroSCORE model and the STS risk model (www.euroscore.org, www.sts.org). While establishing NYHA class, the investigators were blinded for the results of the health survey.

The QoL assessment was made by means of the SF-36v2™ Health Survey according to the instructions given by Ware et al. regarding data collection, scoring, interpretation and validation.[18] To allow for comparison of burden between the study patients and the general population we used the paper presented by Aaronson et al. in 1998.[19] They took a sample of the general Dutch population, subdivided in different age-categories and generated normative SF-36® Health Survey data for use in the Netherlands. Our study population was therefore subdivided in the same age categories.

The SF-36v2™ Health Survey is an evolution of the SF-36® Health Survey and 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: the 'Physical-' and 'Mental Component Summary'. The raw SF-36 scores given by Aaronson et al. are converted into a norm-based score from 0 to 100 in which 50 represents the mean score of the general population and 10 points on the scale correspond to 1 standard deviation (SD).[19]

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)

Statistical analyses

For the statistical analyses SPSS 13.0.1 software was used (SPSS Inc. 2001). Continuous variables are displayed as means ± SD 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

We identified 459 patients with severe aortic stenosis; 268 of these patients (mean age 76±14 years) 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). A total of 191 patients (mean age 70.6 years) agreed to participate. Table 1 shows their characteristics.

Figures 1a, b and c display the results for the symptomatic patients versus the general Dutch population in three age groups. In each age category almost all health domains were scored significantly lower than the general Dutch population except 'Bodily Pain'. More importantly, in most health domains the differences compared to the general population were considerable. Table 2 gives the exact norm-based scores and standard deviations of each group compared with the general Dutch population.

Figure 2 shows that QoL 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 versus 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 large.

Echocardiographic measurements indicating stenosis severity were not related to either physical or mental health scores (data not shown).

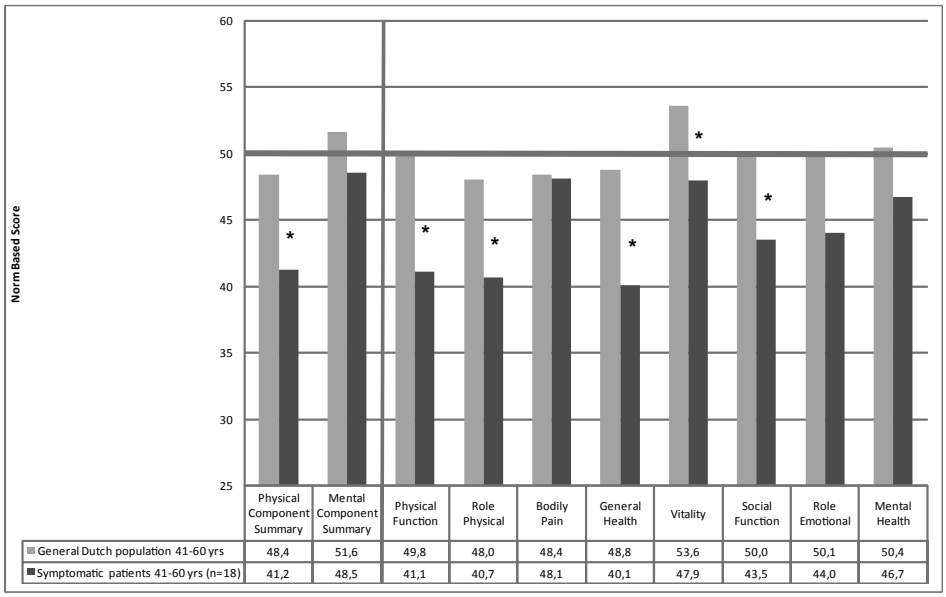


Figure 1a. Quality of life of symptomatic patients with severe aortic stenosis (AS) aged 41-60 years (n=18) versus the general Dutch population aged 41-60 years. * p<0.05

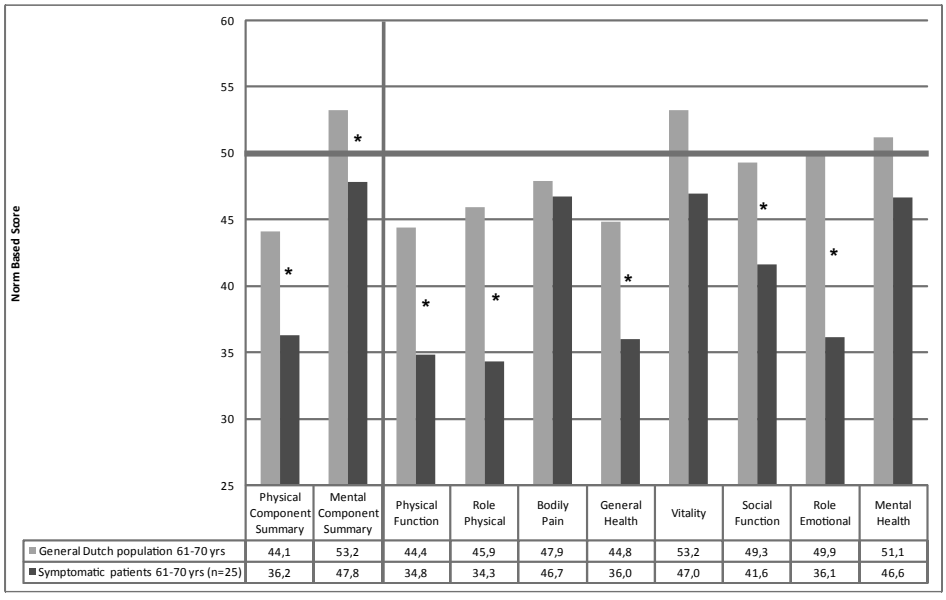


Figure 1b. Quality of life of symptomatic patients with severe aortic stenosis (AS) aged 61-70 years (n=25) versus the general Dutch population aged 61-70 years. * p<0.05

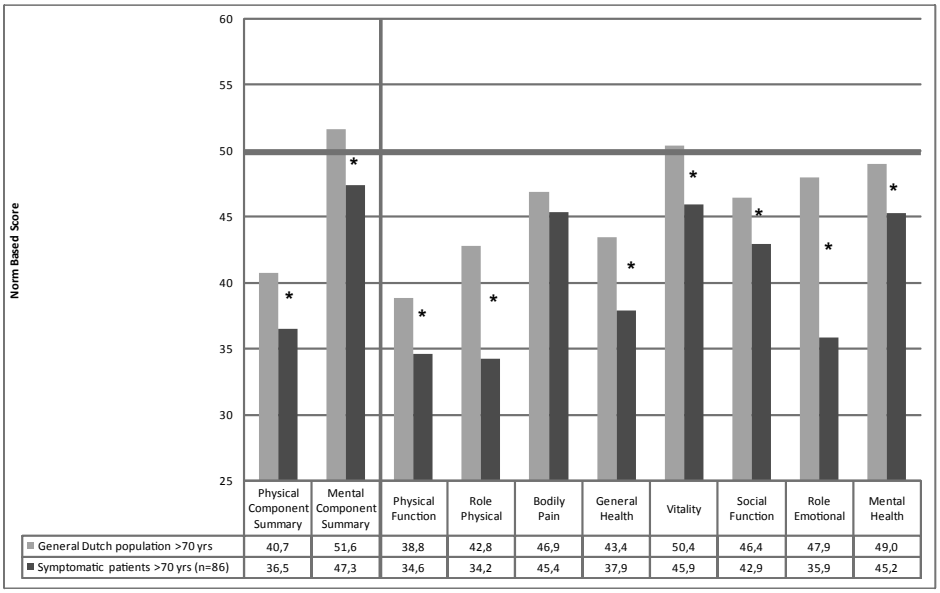
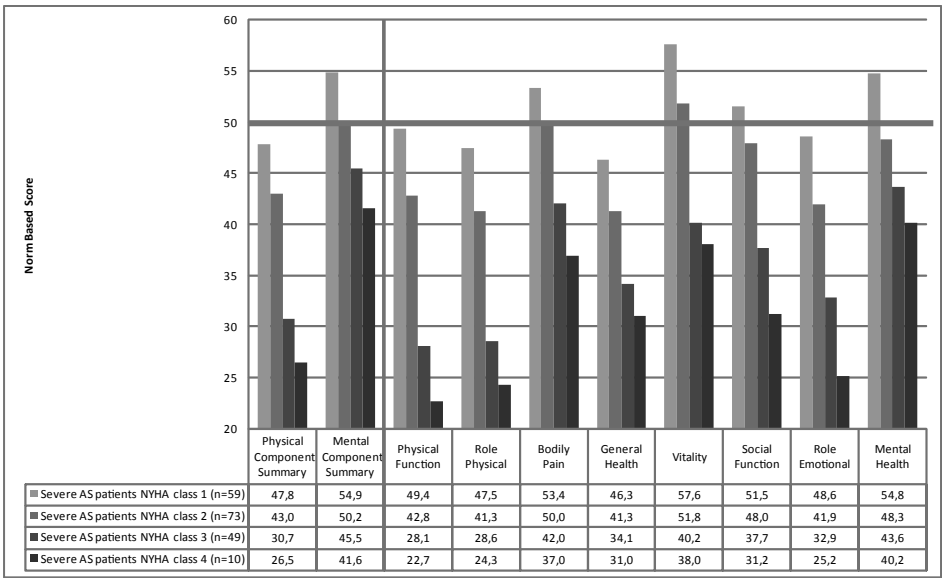


Figure 1c. Quality of life of symptomatic patients with severe aortic stenosis (AS) aged >70 years (n=86) versus the general Dutch population aged >70 years.* p<0.05

Table 2. 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 [19].



	Physical Component Summary	Mental Component Summary	Physical Function	Role Physical	Bodily Pain	General Health	Vitality	Social Function	Role Emotional	Mental Health
Severe AS patients NYHA class 1 (n=59)	47,8	54,9	49,4	47,5	53,4	46,3	57,6	51,5	48,6	54,8
Severe AS patients NYHA class 2 (n=73)	43,0	50,2	42,8	41,3	50,0	41,3	51,8	48,0	41,9	48,3
Severe AS patients NYHA class 3 (n=49)	30,7	45,5	28,1	28,6	42,0	34,1	40,2	37,7	32,9	43,6
Severe AS patients NYHA class 4 (n=10)	26,5	41,6	22,7	24,3	37,0	31,0	38,0	31,2	25,2	40,2

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

DISCUSSION

Interpretation and discussion of main results

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 between the general population and the symptomatic patients are large and remain significant for most health domains across all three age groups we studied.

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. The low scores on the 'Role Physical' domain indicate that patients do have severe physical constraints by dyspnea or fatigue.

Not only the physical domains but also the mental health scores show large differences compared with 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 affecting daily activities. Also the 'Social Function', 'Vitality' and 'General Health' scores indicate patients lack energy and have a negative view on their health, hampering social contact.

There was no relation between stenosis severity and physical or mental QoL in our patient cohort. Thus, whenever the aortic stenosis is above the 'severe' threshold,

'objective' measures of valve function do not correlate to disease burden. Since we only studied the 'severe' category, a relation between disease burden and stenosis severity in mild or moderate aortic stenosis 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). Although asymptomatic patients have a normal health perception, patients in NYHA class II -thus having only 'mild' symptoms- clearly experience a lower QoL. 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 QoL in this patient population.

Policy implication

AVR is recommended both by American and European guidelines in symptomatic patients with severe aortic stenosis because even elderly patients can be operated on with acceptable risks and can expect improvement in functional class and survival compared to non-operated patients.[4-6,8,9,14,20-22] Still, 30 to 60% of them do not undergo AVR.[10,12,20,23,24] Exercise testing is highly underused and downgraded from a class 2a to a 2b recommendation in the ACC/AHA guidelines although it is reported to elicit symptoms in approximately 37% of patients with aortic stenosis who were previously regarded as 'asymptomatic'.[8,25,26] Therefore, the proportion of patients who would deserve operative treatment could even be underestimated. Years ago it has already been shown that doctors have difficulty to recognize functional disability in patients -not so much the symptoms themselves- and one could speculate this is even more true for emotional impairment.[16] 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 represents another cause to underestimate the need for treatment. Given the highly conservative approach towards patients with 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. Although some retrospective studies report on functional status and QoL in patients after AVR, they are often troubled by several limitations.[5,14,15,27] Furthermore, these studies used patients with aortic stenosis who were referred (selected) for surgery. The effect of AVR on QoL among patients with severe aortic stenosis is discussed in the companion paper.[28] Importantly, in our current study we focussed not on the QoL of AVR selected patients before or after surgery, but on the quality of life when the decision to operate or not is yet to be made. Therefore these results can also be used for decision making in the individual patient. A patient could fill in a survey -online or on paper

(www.qualitymetric.com)- and the cardiologist or heart team could then compare these results with the general population or with similar patients (Figure 2), and use this information in deciding whether or not to advise AVR.

Limitations

Although enrolment from the outpatient cardiology echocardiography departments was encouraged, some patients may not have been identified and also 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. This problem may be improved by easier, but often less specific, surveys, such as the EuroQOL survey (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: even minor symptoms have major impact on patient well-being and result in a strongly impaired QoL compared to the general population. Not only do 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 AVR 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 both physically and mentally. Using the SF-36v2™ Health Survey together with this study, an individual patient's QoL 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.

Acknowledgments

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Medisch Centrum Rijnmond Zuid, Rotterdam; and Erasmus University Medical Center, Rotterdam.

Disclosures

None of the authors have any competing interests.

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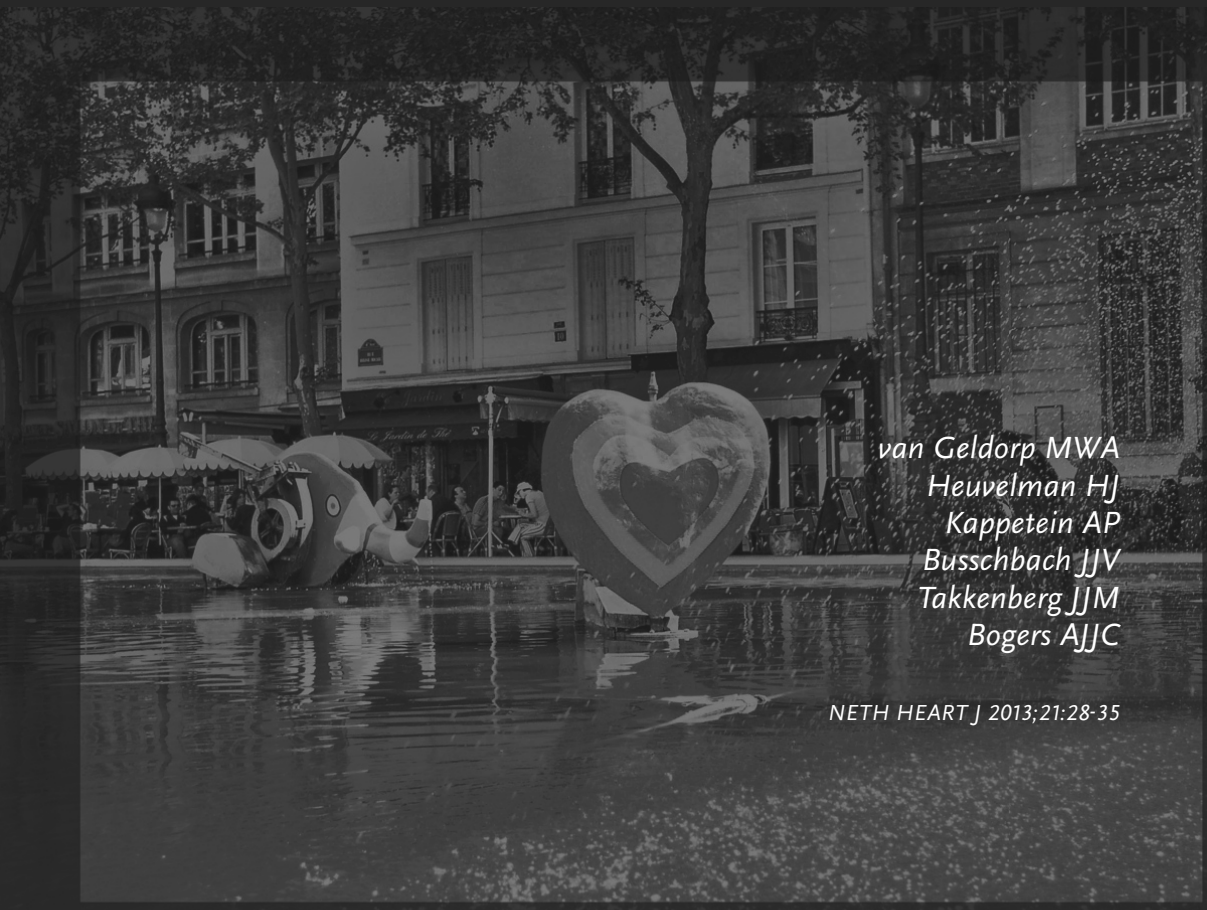
Wer nicht rackert, verdummt!

A.D. Merkel

10

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



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NETH HEART J 2013;21:28-35

ABSTRACT

Objective

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 aortic valve replacement relative to conservative treatment.

Methods

This observational study followed 132 symptomatic patients with severe aortic stenosis who were subjected to an SF-36v2™ Health Survey.

Results

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

Conclusions

Aortic valve replacement improves physical quality of life, general health and vitality in patients with symptomatic severe aortic stenosis. Besides having a low life expectancy, conservatively treated patients experience deterioration of physical quality of life. Health surveys such as the SF-36v2™ can be valuable tools in monitoring the burden of disease for an individual patient and offer additional help in treatment decisions.

INTRODUCTION

Prognosis of symptomatic patients with severe aortic stenosis (AS) is poor when treated conservatively, and according to the American College of Cardiology/ American Heart Association and European Society of Cardiology guidelines patients should be referred for aortic valve replacement (AVR) without delay when they become symptomatic.[1-3] However, in daily practice many symptomatic patients do not receive operative treatment.[4-6] Underestimation of disease burden and the effect of AVR on quality of life (QoL) could in part be responsible for the observed under-treatment, yet there is hardly any literature on this subject.[7]

Previously we compared the QoL of patients with severe AS to the general age-matched population and found it is much lower in symptomatic patients: even 'mild' symptoms result in both physical and emotional problems which have a major impact on normal daily life and social functioning.[8] 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 QoL of conservatively treated patients during follow-up. This is a novel approach compared to other studies, which only describe subgroups of patients selected for surgery.[9-11]

METHODS

Patients

This study is part of a recently published multicentre prospective cohort study among patients with severe AS in the Rotterdam area (the Netherlands) between July 2006 and April 2009.[12] Patients with severe AS were recruited from the outpatient clinics of seven local hospitals and were invited to our hospital for several clinical investigations, an echocardiogram and a QoL assessment. 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).

After the baseline measurements, patients were followed to register treatment selection, major adverse cardiac events, QoL and survival. Since the design of this study was strictly observational, the investigators did not interfere with treatment selection. Follow-up of the entire patient cohort continued until May 1st 2011.

The current study concerns only the QoL of the symptomatic patients. For observational and analysis purposes we registered symptomatic patients into two groups: an AVR group and a conservatively/medically treated group. Medically treated patients were re-invited to our hospital after six, 12 and 24 months. Patients

who were referred for AVR (by their treating cardiologist) were re-invited only once, 1 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). In the patients who crossed to the AVR group, the measurements of earlier 'conservative' visits were carried forward as 'pre-AVR measurements'. By doing so all AVR patients had recent pre-operative QoL data, instead of data collected at the start of the study.

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 and widely used questionnaire originating from the Medical Outcomes Study.[13] 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: the 'Physical-' and 'Mental Component Summary'.

Comparing QoL 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 refused to participate in a certain time interval –either in the AVR or in the conservative group- were withdrawn.

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 (SD). If data were not normally distributed the median and interquartile ranges are given. Categorical variables are displayed as percentages.

Previously, Dutch norms have been established by Aaronson et al. using the first version of the SF-36 Health Survey.[14] To allow for useful comparison these raw SF-36 scores have been transformed to norm-based scores from 0 to 100 in which 50 represents the mean score of the general population and 10 points on the scale

correspond to 1 SD.[15,16] A detailed explanation regarding data collection, scoring, interpretation and validation of the SF-36v2™ is given by Ware et al.[15]

Paired t-test analyses were used to compare QoL 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. Because the distinction between the two 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.

RESULTS

Of 191 participating patients with severe AS, 132 were symptomatic and formed the current study group (flowchart is given in Figure 1, baseline characteristics in Table 1).

The baseline QoL 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 QoL in both groups was much worse over almost all health domains compared to the general age-matched Dutch population.

Conservative group

Initially 84 symptomatic patients were treated medically. In this group 15 patients died during a mean follow-up of 18 months. 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 and 30 after two years of conservative treatment. Kaplan-Meier survival in the conservative group was 85% at 1 year and 72% at 2 years.

In medically treated patients physical health worsened significantly (Figure 3b). 'Bodily Pain', 'General Health', 'Vitality' and 'Social Function' only showed a tendency to worsen yet not significant and 'Mental Health' remained stable.

AVR patients

Initially 48 patients were referred for AVR within 6 months and during follow-up another 22 patients (Figure 1). 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 1 year.

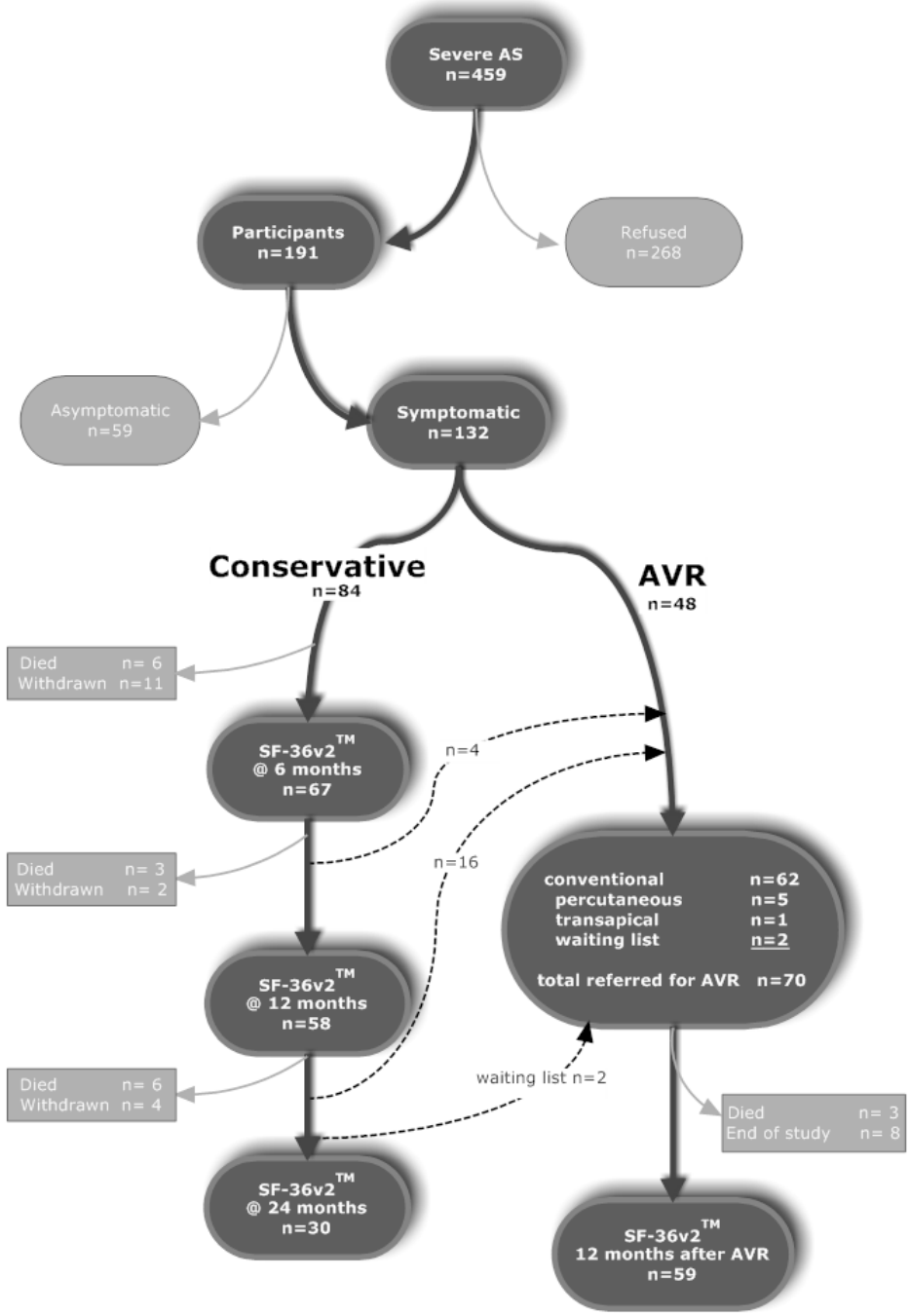


Figure 1. Flow chart.

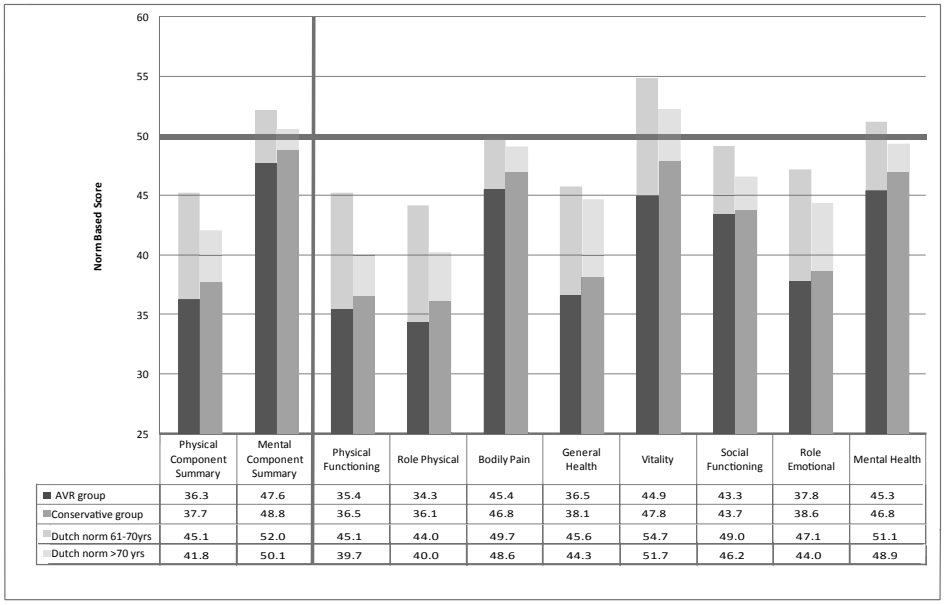
Table 1. Patient characteristics

	Conservative (n=84)	**AVR** (n=70)
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		
Aortic jet velocity V_{max} (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)
Aortic Valve Area (cm^2)	0.76 (± 0.25)	0.74 (± 0.31)
Aortic valve/Left ventricular outflow tract velocity time integral ratio	4.5 (± 1.4)	4.7 (± 1.7)
Ejection Fraction (%)	52.2 (± 12.8)	48.3 (± 11.5)
Medical history (%)		
Smoking (current or past)	60.0	53.0
Diabetes Mellitus	18.8	15.1
Renal failure / dialysis	11.8 / 2.4	6.1 / 0
Hypertension	60.0	43.9
Dyslipidaemia	51.8	48.5
Chronic Obstructive Pulmonary Disease	20.0	19.7
Cerebro Vascular Accident (infarction/bleeding)	4.7	7.6
Open Heart Surgery previously	7.1	6.1

Not only the physical QoL components improved, but also 'Vitality' and 'General Health' were significantly better than pre-operatively and approached the scores of the general Dutch population (Figure 4).

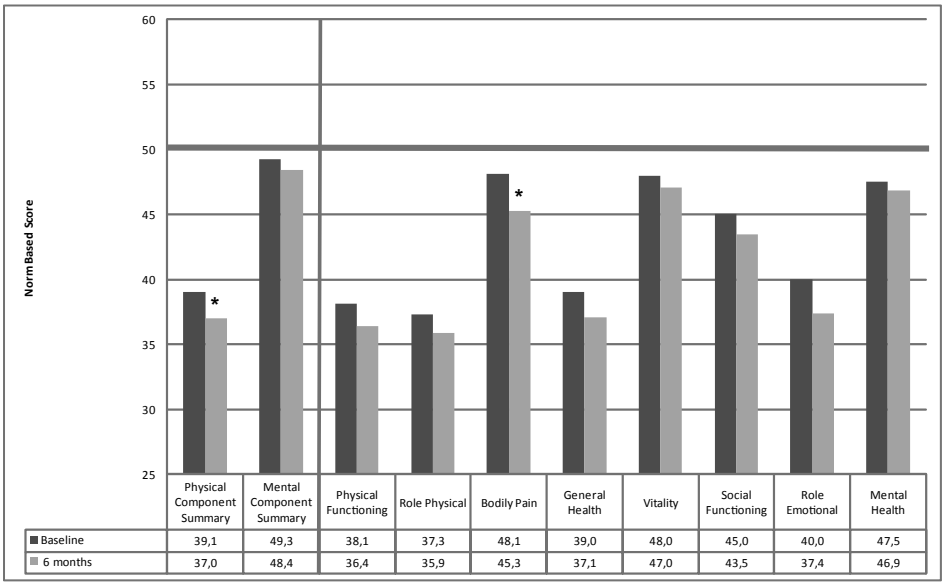
DISCUSSION

Quality of life in symptomatic patients with severe AS is lower in almost all health domains than in the age-matched general Dutch population, both in patients selected for surgery as well as in conservatively treated patients. In a previous paper



	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

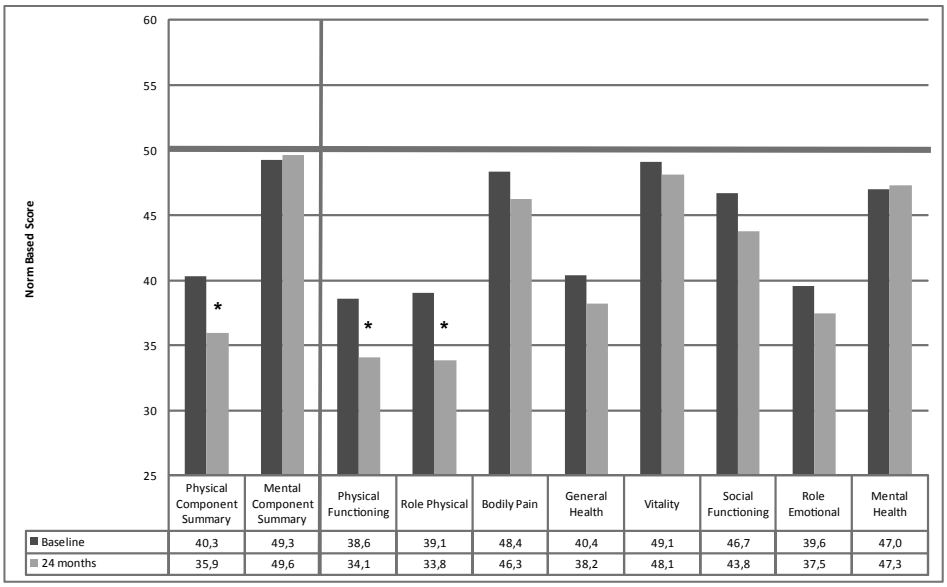
Figure 2. Baseline quality of life of AVR and conservative groups versus general Dutch population.



	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

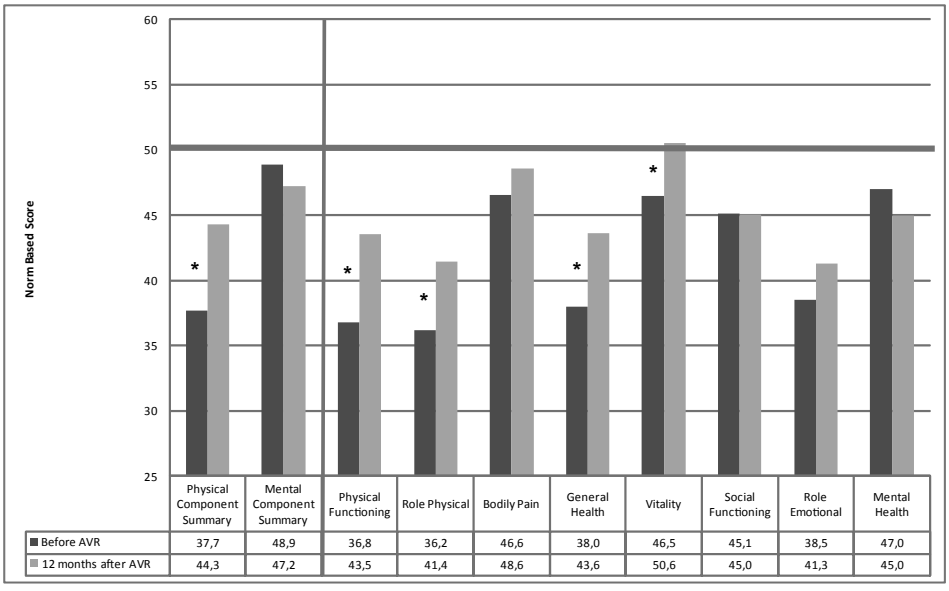
Figure 3a. Quality of life of conservative group: baseline versus 6 months.



	Physical Component Summary	Mental Component Summary	Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health
Baseline	40,3	49,3	38,6	39,1	48,4	40,4	49,1	46,7	39,6	47,0
24 months	35,9	49,6	34,1	33,8	46,3	38,2	48,1	43,8	37,5	47,3

* p< 0.05

Figure 3b. Quality of life of conservative group: baseline versus 24 months.



	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. Quality of life of AVR group: baseline versus 12 months.

we also showed a clear association between New York Heart Association (NYHA) class and the SF-36v2™ outcomes.[8]

Conservative group

The conservatively treated patients who survived two years showed a slight deterioration of their physical health status after 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.[17,18] However, besides a higher mortality also the number of patients who were not capable to complete the subsequent questionnaires is larger in the conservative group compared with the AVR group. The baseline QoL of these withdrawn patients was lower than that of the rest of the group (data not shown). Therefore the observed QoL in our study overestimates the real QoL over time in the total conservative group.

AVR group

Although patients in the conservative group are older, the QoL 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 1 year follow-up showed a markedly improved QoL after 1 year compared with 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 1 year after AVR would be enough to eliminate most direct postoperative 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 form the basis of this observation and whether this could be explained by the operation or postoperative recovery remains speculative.

Implications

Whether the improved QoL in operated patients can be extrapolated to the total symptomatic population with severe AS still remains a matter of debate. The gain of surgery in the operated group might be higher than it would be in patients who are currently treated conservatively. In reality, some (elderly) patients are not surgical candidates or simply refuse to be operated upon. From these data it cannot be determined how the outcomes, both in terms of survival and QoL, would have been supposed all patients would have had AVR. Therefore projection of the study results to the entire symptomatic patient population is only speculative.

One could argue that current treatment selection seems good: in selected patients, QoL generally improves after AVR. Compared with other reports the observed mortality in the conservative group is less high and the presented QoL outcomes in the surviving patients show only a slowly and borderline significant worsening over time.[17,18] On the other hand these findings could be a reflection of a somewhat conservative approach among the studied population.

Timing of surgery in patients with AS is an important and continuing issue of debate. An underestimation of the impact of symptoms on a patient's QoL might be one of the reasons why many symptomatic patients with severe AS are not referred for surgery. Based on our previous study and the current paper, we argue in favour of using QoL survey's in the pre-operative assessment when the choice between surgery or conservative treatment has to be made.[8]

Literature

Although other studies describe QoL in cardiac surgery patients,[9-11,19-24] 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) AS and in whom the decision to operate or not is yet to be made. Most studies we found did not study QoL in patients with AS, but QoL in patients with AS who were referred (selected) for surgery. Some of them describe QoL only in long-term survivors after intervention and do not have a baseline (pre-operative) value. Such analyses constitute a selection bias in which only the healthier patients are subjected to a survey: 'survival of the fittest'.[7,19,20,22,24]

Some studies only concern selective subgroups, others use NYHA classifications as a raw reflection of QoL rather than objective health surveys.[19,23,24] The SF-36v2™ Health Survey describes multiple physical and emotional aspects and is therefore a better and more objective reflection of one's (desired) health status than the NYHA classification.

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, resulting in substantial number of patients denying participation because of perceived high burden. 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 QoL impairment in the total patient population with symptomatic severe aortic stenosis.

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

CONCLUSIONS

AVR offers improved quality of life in selected symptomatic patients with severe AS. 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 in contrast to conservatively treated patients.

Besides considering life-expectancy and anticipated risks with either conservative or operative treatment, QoL should be taken into account when making treatment decisions in patients with severe AS. 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 this decision.

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Disclosures

The authors have no disclosures to make.

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Common sense in an uncommon degree is what the world calls wisdom.

S.T. Coleridge

11

Natural history of discrete subaortic stenosis in adults: A multicenter study

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ABSTRACT

Aims

DSS is often diagnosed early in life and known for its sometimes rapid hemodynamic progression in childhood and strong association with AR. However, data about the evolution of DSS in adulthood are scarce. Therefore we aimed to evaluate the natural history of discrete subaortic stenosis (DSS), and identify risk factors for progression of DSS, aortic regurgitation (AR) and intervention-free survival.

Methods and Results

Conservatively managed adult DSS patients were included in this retrospective multicentre cohort study. Mixed-effects and joint models were used to assess progression of DSS and AR, and intervention-free survival.

Longitudinal natural history data were available for 149 patients (age 20 (IQR 18-34) years, 48% male). Sixty patients (40.3%) had associated congenital heart defects (CHD). Median follow-up duration was 6.3 (IQR 3.0-12.4) years. Baseline peak left ventricular outflow tract (LVOT) gradient was 32.3±17.0 mmHg and increased with 0.8±0.1 mmHg/year. While baseline LVOT gradient (p=0.891) or age (p=0.421) did not influence progression rate, presence of associated CHD was associated with faster progression (p=0.005). Mild AR was common (58%), but did not significantly progress over time (p=0.701). Median intervention-free survival was 16 years and associated with baseline LVOT gradient (HR=3.9 (95%CI 2.0-7.6)), DSS progression (HR=2.6 (95%CI 2.0-3.5)) and AR (HR=6.4 (95%CI 2.6-15.6)).

Conclusions

In contrast to children, DSS progresses slowly in adulthood. In particular patients with associated CHD are at risk for faster progression and should be monitored cautiously. DSS progression is not influenced by baseline LVOT gradient or age. Mild AR is common, but nonprogressive over time.

INTRODUCTION

Fibromuscular discrete subaortic stenosis (DSS) is often diagnosed early in life and notable for its unpredictable, but sometimes rapid hemodynamic progression during childhood.[1-4] Aortic regurgitation (AR) is present in 30-80% of patients and thought to develop secondary to aortic valve damage caused by the high velocity subvalvular jet.[1-11] In children, natural history is well established and several predictors for hemodynamic progression have been identified such as younger age or a higher gradient at diagnosis.[1,12-14] Despite the fact that DSS is a relatively frequent abnormality (6.5%) in adults with congenital heart defects (CHD), data about DSS in adulthood are scarce.[7,8,15-18] In contrast to infants and children, adults with DSS seem to have a slower progression rate.[7] However, there is a lack in studies focusing on the elucidation of factors that predict DSS or AR progression in adults. Therefore, the main purpose of this study was to evaluate the natural history of DSS in a large cohort of adults and identify risk factors for DSS progression, AR progression, and the need for surgery.

METHODS

All adult patients (18 years or older) with a pre-existing diagnosis of fibromuscular DSS seen between January 1980 and October 2011 at the Congenital Cardiac Centre for Adults of one of the participating centres (Erasmus University Medical Centre, Rotterdam, The Netherlands; University Hospital Gasthuisberg, Leuven, Belgium; Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Toronto Congenital Cardiac Centre for Adults located at Peter Munk Cardiac Centre, Toronto, Canada) were evaluated for eligibility. Fibromuscular DSS was defined as: 'encirclement of the left ventricular outflow tract (LVOT) by a membrane or short-segment stenosis consisting of fibrous or fibromuscular tissue'. Eligible patients were selected from the CONCOR database,[19] the Dutch registry for adult patients with CHD, and the Leuven and Toronto database for adults with CHD.

Exclusion criteria were: prior surgical resection of subaortic tissue, lack of serial echocardiographic examinations, predominant dynamic subaortic obstruction due to hypertrophic cardiomyopathy, subvalvular obstruction caused by accessory mitral valve tissue or the support system of mitral valve prosthesis, complex LVOT obstruction (tunnel-like subaortic narrowing), concomitant moderate-to-severe valvular aortic stenosis, transposition of the great arteries, or univentricular connections. This retrospective study was approved by the institutional review board and ethical committee of the participating centres. Informed consent was waived.

Demographic, clinical, and surgical data were obtained from medical charts and electronic health records. All available transthoracic echocardiograms, electrocardiograms and exercise tests were collected. Baseline was defined as entry of the study (first available echocardiogram in adulthood). Follow-up was defined as the time between the first and last available echocardiogram. Peak systolic instantaneous LVOT gradient was derived from the continuous wave Doppler LVOT peak flow velocity from the apical three- or five-chamber views. The degree of AR was graded by experienced echocardiographers and cardiologists as mild, moderate, or severe.[20] Left ventricular (LV) mass was calculated using the modified Devereux formula.[21] The aorto-septal angle was measured in the parasternal long-axis view at end-diastole, as previously described.[22,23]

Statistical analysis

The Statistical Package for Social Sciences, version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for descriptive data analysis. Normally distributed continuous variables were summarized using the mean ± standard deviation (SD). Non-normally distributed continuous variables were summarized using the median and interquartile range (IQR). Categorical variables were summarized using the frequency and percentage. Group differences in baseline variables were assessed using the 2-sample t test, chi-square test, or Mann-Whitney U test. All statistical tests were 2-sided; a p-value <0.05 was considered statistically significant.

For advanced statistical analyses of the longitudinal and survival data, the R statistical software (version 2.15.0, available at: www.r-project.org) was used. To assess changes in echocardiographic measurements over time while accounting mfor the correlation between repeated follow-up measurements in each patient, mixed-effects models analyses were used. In particular, for the LVOT gradient progression rate a linear mixed-effects model was used, whereas for AR progression a mixed-effects continuation ratio model was employed.[24] The following factors were included in the models as covariates: age at baseline, age at diagnosis, gender, prior intracardiac surgery, additional CHDs, baseline LVOT gradient (< or ≥50 mmHg), aortic valve morphology, LV mass, ventricular septal defect (VSD), AR, aorto-septal angle, and smoking. For each of the covariates in the model, its main effect and interaction with time was added, allowing for different average longitudinal evolutions per covariate. Residual plots were used to validate the models' assumption, and when appropriate, transformations of the outcome variables were used in the analysis. Furthermore, to account for missing covariate data a multiple imputation approach was used. Wald tests were used to assess which prognostic factors were most associated with the progression of LVOT gradient and AR.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan-Meier method. Survival of DSS patients was compared to the expected survival of the normal Dutch population.[25] Patients were censored at end of follow-up or classified as event (surgery for DSS or death). A penalized likelihood approach was employed for the Cox regression model with baseline data, to account for the low number of events compared to the number of covariates. A joint modelling approach and time-dependent Cox model were respectively used to investigate the effect of LVOT gradient and AR on the hazard ratio (HR).[26]

RESULTS

Out of 427 identified patients with fibromuscular DSS, longitudinal natural history data were available for 149 patients (Figure 1). Baseline characteristics are summarized in Table 1. Sixty patients (40.3%) had associated CHD (Table 1). Median

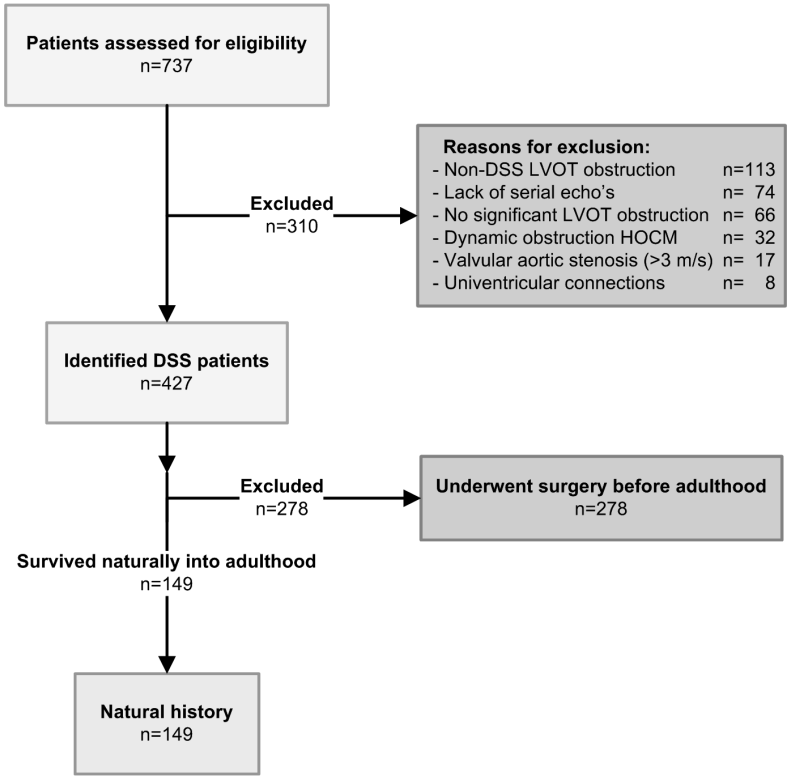

Figure 1. Flowchart of patient inclusion. DSS = discrete subaortic stenosis, HOCM = hypertrophic obstructive cardiomyopathy, LVOT = left ventricular outflow tract.

Table 1. Baseline characteristics

	Discrete subaortic stenosis patients (n=149)	**Intervention-free survival group** (n=106)	**Patients with an event (surgery or death)** (n=43)	**p-value**
Male	72 (48.3)	52 (49.1)	20 (46.5)	0.778
Age at baseline, years	20.4 (17.6-33.8)	20.2 (17.5-33.6)	20.5 (17.8-34.2)	0.701
Age at DSS diagnosis, years	17.0 (7.5-30.5)	18.8 (7.4-31.8)	16.7 (5.9-29.0)	0.810
Body mass index, kg/m^2	25.4 ± 5.5	25.8 ± 6.1	24.6 ± 3.9	0.251
Systolic blood pressure, mmHg	125.6 ± 16.6	125.9 ± 16.6	125.1 ± 16.6	0.787
Diastolic blood pressure, mmHg	74.9 ± 10.3	75.5 ± 10.2	73.5 ± 10.6	0.282
Peak systolic instantaneous LVOT gradient, mmHg	32.3 ± 17.0	28.4 ± 14.1	41.9 ± 19.9	< 0.001
≤30 mmHg	76 (51.0)	64 (60.4)	12 (27.9)	<0.001
30-50 mmHg	51 (34.2)	33 (31.1)	18 (41.9)	
≥50 mmHg	22 (14.8)	9 (8.5)	13 (30.2)	
Aortic regurgitation				
None / trivial	57 (38.3)	44 (41.5)	13 (30.2)	0.085
Mild	86 (57.8)	61 (57.5)	25 (58.1)	
Moderate	5 (3.4)	1 (9.4)	4 (9.3)	
Severe	1 (0.7)	0 (0.0)	1 (2.3)	
Associated CHD / repaired *				
None	89 (59.7)	63 (59.4)	26 (60.5)	0.961
Ventricular septal defect	24 (16.1) / 7 (4.7)	17 (16.0) / 5 (4.7)	7 (16.3) / 2 (4.7)	0.971
Atrial septal defect	11 (7.4) / 6 (4.0)	9 (8.5) / 5 (4.7)	2 (4.7) / 1 (2.3)	0.417
Valvular aortic stenosis (< 3 m/s)	7 (4.7) / 0 (0.0)	2 (1.9) / 0 (0.0)	5 (11.6) / 0 (0.0)	0.011
Coarctation of the aorta	15 (10.1) / 6 (4.0)	10 (9.4) / 4 (3.8)	5 (11.6) / 2 (4.7)	0.687
Persistent ductus arteriosus	6 (4.0) / 4 (2.7)	4 (3.8) / 3 (2.8)	2 (4.7) / 1 (2.3)	0.805
Shone's complex	2 (1.3) / 0 (0.0)	0 (0.0) / 0 (0.0)	2 (4.7) / 0 (0.0)	0.025
Aorto-septal angle, ° #	138.2 ± 16.2	138.8 ± 16.8	133.6 ± 11.0	0.423
Left atrial diameter, mm	36.6 ± 8.4	35.9 ± 7.7	40.1 ± 10.8	0.058
Indexed for BSA, mm/m^2	20.1 ± 5.2	19.5 ± 4.8	22.6 ± 6.4	0.028
LV mass, gram	174.0 ± 65.0	164.9 ± 55.8	215.6 ± 86.8	0.003
Indexed for BSA, gram/m^2	94.6 ± 35.1	88.6 ± 27.9	121.5 ± 49.8	<0.001
LVOT diameter, mm	16.5 ± 3.3	16.4 ± 3.4	17.0 ± 3.0	0.640
LV end-diastolic diameter, mm (IQR)	46.8 ± 6.7 (41.0 ± 51.0)	46.1 ± 6.2 (40.0-50.0)	50.1 ± 8.0 (46.5-56.3)	0.059
Indexed for BSA, mm/m^2	25.8 ± 4.3	25.2 ± 3.9	28.4 ± 5.3	0.004
LV end-systolic diameter, mm (IQR)	28.3 ± 5.6 (25.0 ± 32.0)	27.8 ± 5.3 (24.3-31.0)	30.6 ± 6.8 (24.8-35.0)	0.053
Indexed for BSA, mm/m^2	15.6 ± 3.5	15.2 ± 3.1	17.4 ± 4.6	0.013
Fractional shortening, %	39.7 ± 7.2	39.8 ± 7.1	38.9 ± 7.9	0.641
Maximum exercise capacity, % from norm	86.3 ± 22.3	86.6 ± 21.8	85.8 ± 23.4	0.256
Sinus rhythm	146 (98.0)	104 (98.1)	42 (97.7)	0.283

Table 1. Baseline characteristics (Continued)

Heart frequency, beats per minute	71.9 ± 14.5	72.5 ± 14.6	70.3 ± 14.5	0.487
QRS duration, ms	101.8 ± 20.8	98.7 ± 17.5	110.8 ± 26.6	0.005
PR time, ms	154.6 ± 34.3	153.6 ± 35.8	157.0 ± 30.3	0.640
NYHA class I	144 (96.6)	104 (98.1)	40 (93.0)	0.118
Smoking				
Never	112 (75.2)	84 (79.2)	28 (65.1)	0.323
Former	11 (7.4)	6 (5.7)	5 (11.6)	
Current	26 (17.4)	16 (15.1)	10 (23.3)	

BSA = body surface area, CHD = congenital heart defects, DSS = discrete subaortic stenosis, IQR = interquartile range, LV = left ventricular, LVOT = left ventricular outflow tract, NYHA = New York Heart Association.

*Diagnoses are not mutually exclusive (one patient could have multiple associated CHD).

This variable was only available for 82 patients.

Values are expressed as n(%), median (IQR) or mean ± SD.

follow-up duration was 6.3 (IQR 3.0-12.4) years, yielding a total of 1191 patient-years. On average 2.7 ± 0.9 (range 2-9) echocardiographic studies were available for each patient.

Progression of LVOT gradient over time

Peak systolic instantaneous LVOT gradient was 32.3 ± 17.0 mmHg at baseline and linearly increased over time with a rate of 0.8 ± 0.1 mmHg per year. Six patients demonstrated a progression rate >5 mmHg/year. The presence of an associated CHD was associated with faster progression of the LVOT gradient (p=0.005; Figure 2), in particular a VSD (p=0.035). The LVOT gradient progression rate was not influenced by age at baseline (p=0.421), age at time of diagnosis (p=0.273), gender (p=0.960), prior intracardiac surgery (p=0.162), baseline LVOT gradient ≥50 mmHg (p=0.891; Figure 2), current smoking (p=0.282), or aortic valve morphology (p=0.240) (see Supplementary material online, Table S1).

Progression of AR over time

A LVOT gradient ≥50 mmHg (p=0.007) was independently associated with a higher probability of having AR (see Supplementary material online, Table S2). Although Figure 3 demonstrates that over 10 years time the probability of not having AR decreases from approximately 40% to approximately 20%, progression to moderate-to-severe AR was rare. Overall, AR severity did not significantly progress over time (p=0.747). A baseline peak LVOT gradient ≥50 mmHg did not influence the progression of AR (p=0.999).There were no factors significantly associated with progression from mild to moderate-to-severe AR (see Supplementary material online, Table S2).

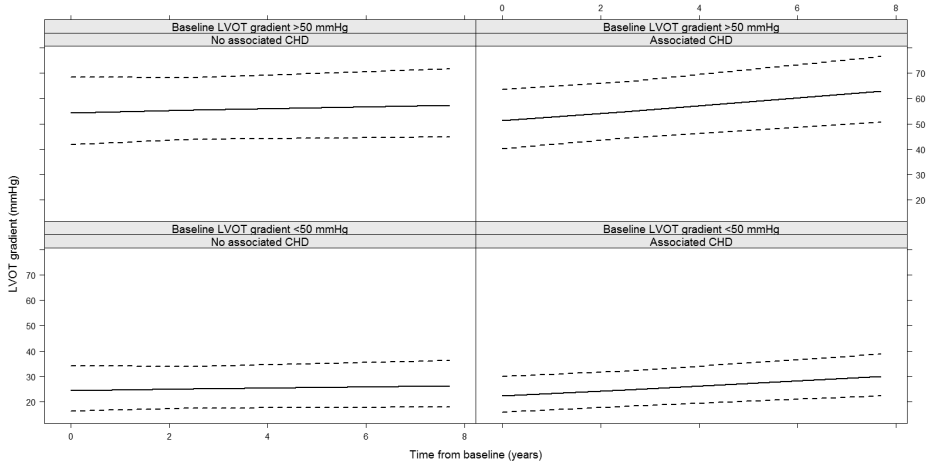

Figure 2. Evolution of discrete subaortic stenosis over time. Progression of the left ventricular outflow tract gradient over time by the baseline left ventricular outflow tract gradient (<50 and ≥50 mmHg; p = 0.891) and by the presence or absence of an associated congenital heart defect (p = 0.005). The dashed lines denote 95% confidence intervals. LVOT = left ventricular outflow tract, CHD = congenital heart defect.

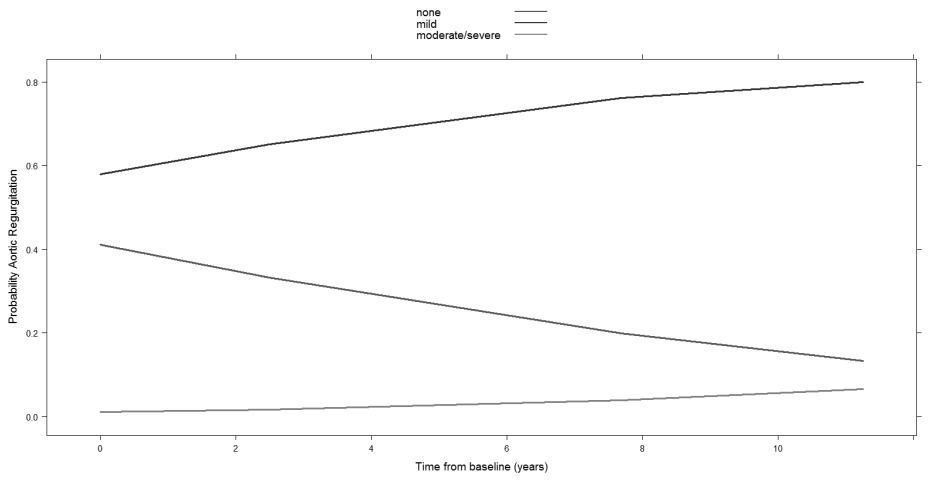

Figure 3. Evolution of aortic regurgitation over time. No significant progression the severity of in aortic regurgitation over time (p = 0.747).

Clinical outcome

Two patients died suddenly 4 and 16 years after entry in the study (37 and 39 years old, LVOT gradients before death 63 and 85 mmHg, respectively, no associated CHD, no left ventricular hypertrophy). The cause of death was unknown in both

patients (no autopsy). The cumulative survival was 94% at 20 years (0.17% per patient-year; Figure 4a). One patient was successfully resuscitated after an episode of ventricular fibrillation (36 years old, LVOT gradient before event 49 mmHg, associated repaired VSD and left ventricular hypertrophy). Two patients (22-year old male and 52-year-old female, LVOT gradient 21 and 64 mmHg, respectively, both

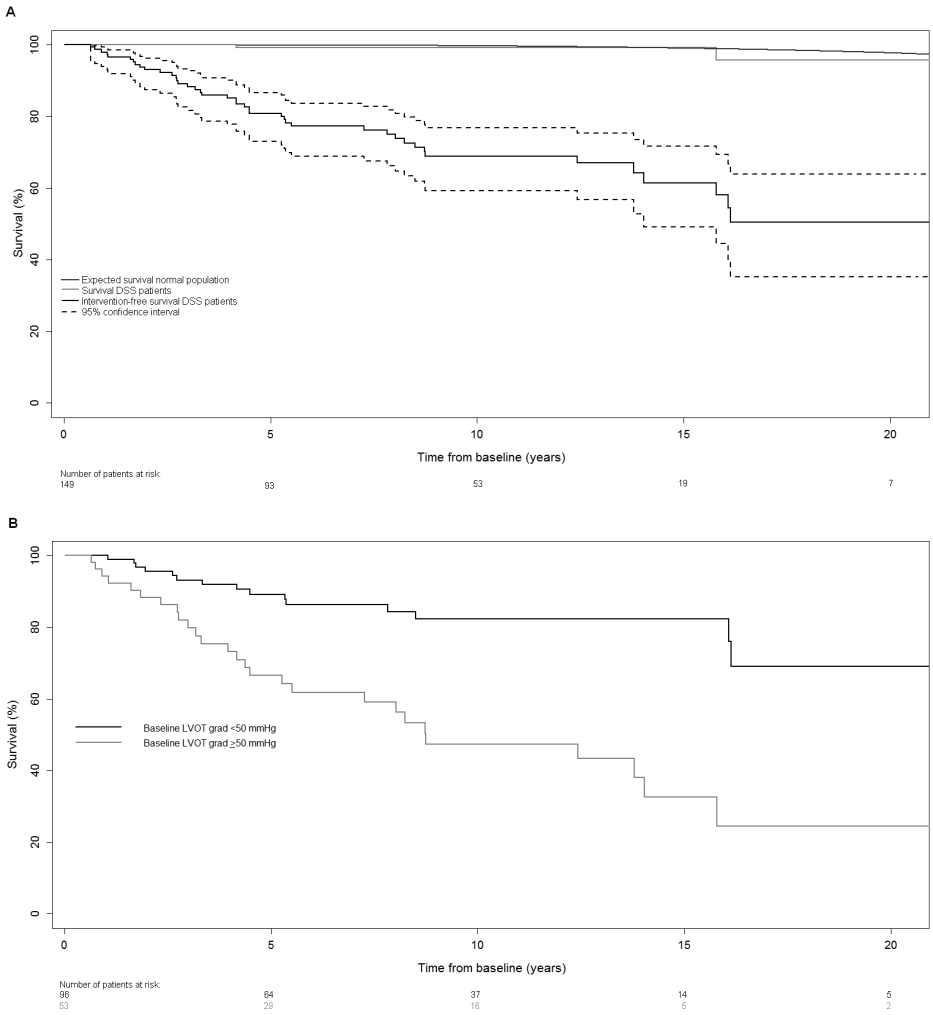

Figure 4. Kaplan–Meier plots. **a.** Cumulative Kaplan–Meier survival and intervention-free survival for discrete subaortic stenosis patients and expected survival for the normal Dutch population. **b.** Cumulative Kaplan–Meier intervention-free survival for discrete subaortic stenosis patients with a baseline peak systolic instantaneous left ventricular outflow tract gradient <50 mmHg compared with ≥50 mmHg (p <0.001). DSS = discrete subaortic stenosis, LVOT = left ventricular outflow tract.

had an associated unrepaired VSD and mild AR) had an episode of endocarditis (0.17% per patient-year).

During follow-up 41 patients required surgery for DSS according to the clinical practice guidelines (5.9% per patient-year). Median intervention-free survival was 16 years (Figure 4a). The mean age at time of DSS surgery was 35.1 ± 14.0 years. The pre-operative LVOT gradient was 75.3 ± 3.6 mmHg and 17 of the 41 patients (41.5%) had moderate-to-severe AR. Type of DSS surgery was enucleation in 20 patients (48.8%) and enucleation with additional myectomy in 21 patients (51.2%). Nineteen patients (46.3%) underwent concomitant surgery: aortic valve replacement or repair (n=16) or VSD closure (n=3). Post-operative complications included bleeding requiring rethoracotomy (n=1), atrial fibrillation (n=4), complete AV block requiring permanent pacemaker implantation (n=3), and heart failure (n=1).

Independent predictors for impaired intervention-free survival were the baseline LVOT gradient ≥50 mmHg (HR 3.9 (95%CI 2.0-7.6); Figure 4b), LVOT gradient progression over time (HR 2.6 (95%CI 2.0-3.5)) and moderate-to-severe AR (HR 6.4 (95%CI 2.6-15.6)) (see Supplementary material online, Table S3).

DISCUSSION

This study is the first large longitudinal study focusing on the natural course of DSS over time and risk factors influencing clinical outcome in adult patients. Given the scarcity of data about the natural evolution of DSS in adults, these results will contribute to our understanding of the clinical course of DSS in adulthood and guide clinical management.

Progression of DSS

Interestingly, the present study demonstrates that DSS in adulthood progresses very slowly, with less than 1 mmHg gradient increase per year. These results confirm the findings of a series published by Oliver et al. that showed a similar slow progression rate in only 25 patients with sequential echocardiographic studies.[7] Remarkably, the slow progression rate along several decades in adults contrasts to the progressive nature of DSS described in children.[1-4] This phenomenon might be explained by the fact that adults who survived into adulthood without an intervention compile a highly selected subgroup and represent a mild phenotype within the spectrum of DSS.

The study by Oliver et al. suggested that age influences DSS evolution, since they found significant correlations between age and LVOT gradient and progression.[7] To evaluate if age was not only correlated but could actually significantly predict

DSS disease progression, we explored age as a covariate in longitudinal echocardiographic models in this large population. However, neither age at study baseline nor age at time of diagnosis significantly influenced LVOT progression over time. Furthermore, in contrast to paediatric populations, we did not find an association between DSS severity at baseline and the progression rate in adults who naturally survived into adulthood.[1,12-14] Thus, patients with LVOT gradients ≥50 mmHg were not at risk for faster progression of the LVOT obstruction.

With respect to the prevalence of associated CHD, our population was comparable to those described in other studies.[7,8,15] Notably, the presence of an associated CHD, particularly a VSD, was the only independent predictor for DSS progression. Many previous studies have tried to elucidate the poorly understood aetiology of DSS.[3,27,28] It has been demonstrated that abnormal geometric arrangements in the LVOT, such as steepened aorto-septal angle, malaligned VSD and mitral-aortic separation, may induce increased shear stress.[22,23,29-31] Cellular flow studies have shown that increased shear stress triggers growth factors and cellular proliferation, eventually stimulating development of the subaortic membrane and progression of the LVOT obstruction.[11] Our findings suggest that adult DSS patients with associated CHD and those without additional CHD compile two different subgroups within the DSS spectrum. We hypothesize that the presence of associated CHD, particularly a VSD, causes more abnormal hemodynamic forces at the LVOT level, which could be caused either by the CHD itself or by prior intracardiac surgery for that defect. The abnormal hemodynamic forces might cause increased shear stress, thereby evoking a more intense response on a cellular level and faster progression of the LVOT obstruction. We tried to elucidate whether the aorto-septal angle influenced LVOT progression over time, but unfortunately there were too many missing values for this covariate. Future rheological studies in adult DSS patients are certainly warranted to test this hypothesis.

Aortic regurgitation

The most commonly described hemodynamic sequel in DSS patients is AR, which is thought to evolve secondary to the high velocity subvalvular jet produced by the LVOT obstruction.[5-11] In an attempt to prevent damage to the aortic valve, early surgical resection of the subaortic membrane has been advocated.[32,33] However, Oliver et al. demonstrated in 25 adults that AR is common, and usually mild, and nonprogressive over time.[7] Similarly, our study clearly showed that AR is only haemodynamically relevant (moderate-to-severe) in a minority of patients although mild AR is found in the majority of adult DSS patients. More importantly, while approximately 20% of patients developed mild AR during the study period, progression to moderate-to-severe is rare. In the total group, the AR progression was not

statistically significant and we could not identify a subgroup of patients at higher risk for progression. Therefore, the fear of development of progressive AR seems to be overestimated and early surgical repair of DSS in adult patients with a low LVOT gradient and no/mild AR is not justified.

Survival

Overall, the cumulative 20-year survival of patients with DSS is comparable with the survival of the age-matched normal Dutch population.[25] Since the life expectancy of Canada, the Netherlands and Belgium is comparable; this probably does not influence our survival results at young adult age.[34] However, the rate of (near) sudden death (0.17-0.25% per patient-year) in our study of young adult patients with DSS is worrisome. This seems to be higher than the generally estimated 0.09% per patient-year in adult patients with any type of CHD.[35,36] Moreover, it represents a 30-125 times increased risk of sudden death compared to the general population with a similar age range.[37-41] Unfortunately the absolute number of events was too small to identify any risk factors for sudden death in patients with DSS.

Clinical implications

DSS progresses very slowly in adulthood; however, patients with associated congenital lesions, particularly a VSD, are at risk for faster disease progression and should be monitored cautiously. Furthermore, this large study shows that AR is usually mild and does not progress over time; thereby rejecting the hypothesis that early repair is required to prevent development of progressive AR.

According to the present study, prophylactic surgery in asymptomatic adult DSS patients is not indicated solely to prevent rapid progression of the LVOT obstruction or progressive AR. Our data do not support the current North American guidelines that state that surgical intervention should be recommended in any DSS patient with a peak LVOT gradient ≥50 mmHg, but are more in line with the European and Canadian guidelines.[42-44] However, the timing of surgical intervention is a highly complex issue compiling various factors in an individual patient based approach: the peak LVOT gradient, progression rate of the LVOT gradient, severity and progression of AR, presence of associated CHD, LV diameter and function, and risk of sudden death. Postponing surgery to higher LVOT gradients might increase the chance of requirement of concomitant aortic valve repair or replacement and increase the risk of sudden death. On the other hand, up till now it is unclear whether surgery will prevent or at least minimize the risk of sudden death. Unfortunately, the optimal timing of surgical intervention in adult patients with DSS cannot yet be derived from the present study.

Since endocarditis only occurred in two patients with a concomitant unrepaired VSD, it is likely that these cases were related to the unrepaired VSD rather than DSS. Thus, the risk of endocarditis in patients with isolated DSS seems to be low and endocarditis prophylaxis should only be indicated in high risk patients.[44]

Since the LVOT gradient progression is generally slow and AR is usually mild, echocardiographic follow-up can probably be limited to 3-5-year intervals for the majority of patients. However, for patients with associated congenital lesions (particularly a VSD), peak LVOT gradient ≥50 mmHg, or moderate-to-severe AR more frequent echocardiographic follow-up evaluations seem reasonable, for example every 1-2 years.

Study limitations

This retrospective study inheriting all limitations of a retrospective study design included patients monitored in adult congenital clinics at tertiary care centre, and therefore referral bias may exist. Inclusion of deceased patients from the databases limited survival bias. Unfortunately, some echocardiographic parameters could not be retrieved for all patients, but this was dealt with by using the multiple imputation approach for missing values. The fact that echocardiography was not performed precisely every year, was accounted for by the use of mixed-effects models that take different lengths of follow-up into account. Furthermore, by using the joint modelling approach we allowed for the dependency and association between the longitudinal echocardiographic data and survival data. Finally, we have to acknowledge that the median follow-up duration of 6.3 years was relatively short. For definitive conclusions regarding the long-term outcome of DSS in adulthood, a longer follow-up period is required.

CONCLUSIONS

Conservatively (non-surgically) managed DSS progresses slowly in adulthood, though patients with associated congenital lesions, especially a VSD, are at risk for faster DSS progression and should be monitored cautiously. Baseline LVOT gradient does not influence DSS progression over time, and thus should not be used as sole indication to proceed to surgery. AR is usually mild and does not progress over time, indicating that prophylactic surgery to prevent AR progression is not justified.

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Conflict of interest

D.vd.L. is an Erasmus University Rotterdam Prof. Bruins grant recipient, Rotterdam, The Netherlands. D.R. is an Erasmus University Rotterdam Fellowship recipient, Rotterdam, the Netherlands.

Supplementary material

Supplementary material is available at European Heart Journal online: www.eurheartj.oxfordjournals.org.

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Werken en feesten vormt schoone geesten.

J. Westerdijk

12

Surgical outcome of discrete subaortic stenosis in adults: A multicenter study

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ABSTRACT

Background

DSS is notable for its unpredictable hemodynamic progression in childhood and high reoperation rate; however, data about adulthood are scarce.

Methods and results

Adult patients who previously underwent surgery for DSS were included in this retrospective multicenter cohort study. Mixed-effects and joint models were used to assess postoperative progression of discrete subaortic stenosis and aortic regurgitation, as well as reoperation.

A total of 313 patients at 4 centers were included (age at baseline, 20.2 years (25th–75th percentile, 18.4–31.0 years), 52% male). Median follow-up duration was 12.9 years (25th–75th percentile, 6.2–20.1 years), yielding 5617 patient-years. The peak instantaneous left ventricular outflow tract gradient decreased from 75.7 ± 28.0 mmHg preoperatively to 15.1 ± 14.1 mmHg postoperatively ($p<0.001$) and thereafter increased over time at a rate of 1.31 ± 0.16 mmHg/y ($p=0.001$). Mild aortic regurgitation was present in 68%, but generally did not progress over time ($p=0.76$). A preoperative left ventricular outflow tract gradient ≥80 mmHg was a predictor for progression to moderate aortic regurgitation postoperatively. Eighty patients required at least one reoperation (1.8% per patient-year). Predictors for re-operation included female gender (hazard ratio, 1.53; 95% confidence interval, 1.02-2.30) and left ventricular outflow tract gradient progression (hazard ratio, 1.45; 95% confidence interval, 1.31–1.62). Additional myectomy did not reduce the risk for reoperation ($p=0.92$), but significantly increased the risk of a complete heart block requiring pacemaker implantation (8.1% versus 1.7%; $p=0.005$).

Conclusions

Survival is excellent after surgery for discrete subaortic stenosis; however, reoperation for recurrent discrete subaortic stenosis is not uncommon. Over time, the left ventricular outflow tract gradient slowly increases and mild aortic regurgitation is common, although generally nonprogressive over time. Myectomy does not show additional advantages and as it is associated with an increased risk of complete heart block, it should not be performed routinely.

INTRODUCTION

Discrete subaortic stenosis (DSS) is notable for its unpredictable and sometimes rapid hemodynamic progression in childhood and its association with aortic regurgitation (AR), which is found in 30 to 80% of patients.[1-7] Different strategies exist for the timing of surgical treatment, ranging from early (mild to moderate obstruction) to late (severe or symptomatic) repair. Early repair has been advocated to prevent aortic valve damage and thus AR progression.[5-12] Nevertheless, it remains unclear whether surgery can actually alter the course of progressive AR. Furthermore, surgery is associated with a high recurrence risk and need for reoperation (8-34%).[12-18] A major factor in DSS recurrence is believed to be inadequate relief of the obstruction.19 Therefore some groups advocate concomitant selective myectomy to achieve complete relief of the left ventricular outflow obstruction (LVOT) obstruction[8,18-21] whereas others have reported that the addition of myectomy does not reduce the number of recurrences.[16,17,22-27]

Although postoperative outcome and risk factors for reoperation in children are well established, postoperative data for the adult population are limited.[15,27,28] Therefore, the aim of this study was to identify risk factors for postoperative DSS recurrence, AR progression and reoperation in a large cohort of adult patients who previously underwent surgical treatment for DSS.

METHODS

All adult patients who previously underwent surgery for fibromuscular DSS and were seen between January 1980 and October 2011 at the Congenital Cardiac Center for Adults of one of the participating centers (Erasmus University Medical Center, Rotterdam, and Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; University Hospital Gasthuisberg, Leuven, Belgium; and Toronto Congenital Cardiac Centre for Adults located at Peter Munk Cardiac Centre, Toronto, Canada) were evaluated for eligibility for this study.

Fibromuscular DSS was defined as a complete or incomplete encirclement of the LVOT by a membrane or short-segment stenosis consisting of fibrous or fibromuscular tissue. The baseline of this study was defined as time of first adult outpatient clinic visit. Eligible patients were selected from the CONgenital CORvitia (CONCOR) database (the Dutch registry for adult patients with congenital heart disease (CHD))[29] and from the Leuven and Toronto local database for adults with CHD. Although all patients followed in Congenital Cardiac Centers for Adults were ≥17 years old, the first surgery for DSS could have been performed in childhood. Ex-

clusion criteria were: lack of serial echocardiograms, non-DSS causes for subaortic obstruction (tunnel-like subaortic narrowing, hypertrophic cardiomyopathy, accessory mitral valve tissue, or mitral valve prosthesis), concomitant moderate-to-severe valvular aortic stenosis, transposition of the great arteries, and univentricular connections. This retrospective study was approved by the institutional review board and ethical committee of participating centers. Informed consent was waived.

Demographic, clinical, and surgical data were obtained from medical charts and electronic health records. All available transthoracic echocardiograms, ECGs, and exercise tests were collected. Peak systolic instantaneous LVOT gradient was derived from the continuous-wave Doppler LVOT peak flow velocity. The degree of AR was graded by experienced echocardiographers and cardiologists as mild, moderate, or severe.[30] Left ventricular mass was calculated using the modified-Devereux-formula.[31] In the parasternal long-axis view at end-diastole, we measured the aorto-septal angle, which is the angle formed by the plane of the ventricular septum and the ascending aorta, as previously described.[32,33]

Statistical analysis

The Statistical Package for Social Sciences, version 19.0 (SPSS, Inc, Chicago, IL) was used for descriptive data-analysis. Continuous variables were summarized using the mean±SD or median and 25^{th} and 75^{th} percentile. Categorical variables were summarized by use of frequency and percentage. The paired t-test, paired Wilcoxon, and McNemar tests were used to compare preoperative and postoperative measurements. All statistical tests with a p-value <0.05 were considered significant.

For advanced statistical analyses of the longitudinal and survival data, the R statistical software (version 2.15.0; www.r-project.org) was used. To assess changes in echocardiographic measurements over time while accounting for the correlation between repeated follow-up measurements in each patient, mixed-effects models analyses were used. In particular, for the postoperative LVOT gradient progression rate, a linear mixed-effects model was used, whereas for postoperative AR progression a mixed-effects continuation ratio model was used.[34] To allow flexibility in the modeling of the patientspecific longitudinal trajectories, we used natural cubic splines of time in the specification of the mixed-effects models, in both the fixed- and random-effect parts of the models. The following variables were included in the models as covariates: age at the time of surgery, age at diagnosis, gender, preoperative peak instantaneous LVOT gradient, difference between preoperative and postoperative gradient (delta), type of surgery (isolated enucleation or additional myectomy), associated CHD, and smoking. For each of the covariates in the model, its main effect and interaction with time was added, allowing for different average longitudinal evolutions per covariate. Residual plots were used to validate

the model assumptions, and when appropriate, transformations of the outcome variables were used in the analysis. Furthermore, to account for missing covariate data, a multiple imputation approach was used for the preoperative and postoperative LVOT gradient covariates (missing for 42 patients). Five generations of complete data sets were realized. Wald tests were used to assess which prognostic factors were most associated with the progression of peak instantaneous LVOT gradient and AR.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan-Meier method. Survival of DSS patients was compared to the expected survival of the age-matched normal Dutch population.[35] Patients were censored at end of follow-up or classified as event (surgery for DSS or death). A penalized likelihood approach was employed for the Cox regression model with baseline data, to account for the low number of events compared to the number of covariates. A joint longitudinal and survival model and the timedependent Cox model were used to investigate the effect of peak instantaneous LVOT gradient and AR, respectively, on the hazard ratio for intervention-free survival.[36]

RESULTS

A total of 737 patients were assessed for eligibility to participate in this study. Inclusion criteria were met by 313 patients. A total of 424 patients were excluded, mainly due to LVOT obstruction resulting from another cause (n=145), no history of DSS surgery (n=149), or lack of serial echocardiography examinations (n=74).

Baseline characteristics of the 313 patients are summarized in Table 1. Of the 313 patients, 163 patients (52.1%) had ≥1 associated CHD. Baseline LVOT diameter was 14.5 ± 3.8 mm in women and 15.7 ± 4.2 mm in men (p=0.19). Follow-up ranged from 1 to 31 years (median, 12.9 years; 25th–75th percentile, 6.2–20.1 years), yielding a total of 5617 patient-years. On average, 2.3 ± 1.4 (minimum, 2; maximum, 8) echocardiographic studies were available for each patient.

Operative outcomes

The 313 included patients underwent a total of 412 operations for DSS. The peak instantaneous LVOT gradient decreased from 75.7 ± 28.0 mmHg pre-operatively to 15.1 ± 14.1 mmHg postoperatively (p<0.001). The LVOT diameter increased from 14.5 ± 3.8 mm to 19.0 ± 3.7 mm (p<0.001). In 251 patients (61%), the first surgery was performed in childhood (mean age, 12.9 ± 6.7 years). Table 2 shows the surgical details, including concomitant surgery and postoperative complications. In those patients who did not undergo concomitant aortic valve repair or replacement

Table 1. Baseline characteristics

	Operated DSS patients
Male	163 (52.1)
Age at baseline, years	20.2 (18.4-31.0)
Age at DSS diagnosis, years	8.0 (4.0-15.0)
Body surface area, m^2	1.8 ± 0.2
Body mass index, kg/m^2	25.9 ± 5.4
Systolic blood pressure, mmHg	125.6 ± 19.4
Diastolic blood pressure, mmHg	72.6 ± 10.9
Associated CHD anomalies; previously repaired *	
None	150 (47.9)
Ventricular septal defect	72 (23.0); 15 (4.8)
Atrial septal defect	18 (5.8); 4 (1.3)
Valvular aortic stenosis	29 (9.3); 2 (0.6)
Coarctation of the aorta	48 (15.3); 10 (3.2)
Persistent ductus arteriosus	20 (6.4); 8 (2.6)
Shone complex	10 (3.2); 0 (0.0)
Aortoseptal angle, °	124.7 ± 15.9
Left atrial diameter, mm (indexed for BSA, mm/m^2)	42.4 ± 11.7 (22.8 ± 5.3)
Left ventricular mass, gram (indexed for BSA, mm/m^2)	222.0 ± 86.3 (120.1 ± 42.8)
LV end-diastolic diameter, mm (indexed for BSA, mm/m^2)	49.1 ± 7.5 (27.1 ± 4.4)
LV end-systolic diameter, mm (indexed for BSA, mm/m^2)	29.5 ± 7.4 (16.3 ± 4.3)
LV fractional shortening, %	40.3 ± 9.0
E/A ratio	1.5 ± 0.6
E/E' ratio	11.9 ± 6.0
Maximum exercise capacity, % from norm	82.1 ± 20.4
Sinus rhythm	295 (94.2)
Heart frequency, beats per minute	72.5 ± 14.5
QRS duration, ms	114.9 ± 28.9
PR time, ms	160.5 ± 30.9
NYHA class I	290 (92.9)
Smoking	
Never	211 (67.4)
Former	26 (8.3)
Current	64 (20.4)
Unknown	12 (3.8)

BSA = body surface area, CHD = congenital heart disease, DSS = discrete subaortic stenosis, LV = left ventricular, LVOT = left ventricular outflow tract, NYHA = New York Heart Association.
* Diagnoses are not mutually exclusive.
Values are n(%), median (IQR) or mean ± SD.

during surgery for DSS, the severity of AR was unchanged postoperatively (p=0.60). Seventeen patients (4.4%) suffered from a complete heart block postoperatively, requiring pacemaker implantation. Patients who underwent an additional myectomy more frequently developed a complete heart block than patients who underwent isolated enucleation (respectively 8.1% versus 1.7%; p=0.005).

Mortality and morbidity

One death occurred within 30 days after surgery for DSS resulting from heart failure. Ten patients (mean age, 49.1 ± 16.5 years) died during follow-up (0.18% per patient-year; Figure 1a). Five deaths were for cardiac reasons (4 heart failure and 1 septic shock after endocarditis). In 2 patients the cause of death was metastasized cancer. Three patients died suddenly during follow-up (unknown cause of death, no autopsy; age 19, 30, and 48 years old; all had an LVOT gradient <30 mmHg at last follow-up visit, 2 had an associated ventricular septal defect, no left ventricular hypertrophy). The cumulative survival of DSS patients after surgery was 97% at 20 years.

During follow-up 34 patients (age, 29.9 ± 15.1 years) were hospitalized for various reasons (0.61% per patient-year): heart failure (n=13), endocarditis (n=12), ventricular fibrillation followed by successful resuscitation (n=2), cardioversion for atrial fibrillation (n=5), stroke (n=1), and pericarditis (n=1).

Reoperations

During follow-up, 80 patients (25.6%) underwent at least 1 reoperation for recurrent DSS; 19 of these patients required a third operation (reoperation rate 1.76% per patient-year; Table 2). The mean time interval between initial operation and reoperation was 12.0 ± 7.6 years. Median intervention-free survival was 17 years (Figure 1a). Independent predictors for impaired intervention-free survival were female sex (hazard ratio, 1.531; 95% confidence interval, 1.018–2.302; Figure 1b), peak instantaneous LVOT gradient progression over time (hazard ratio, 1.454; 95% confidence interval, 1.308–1.616), preoperative peak instantaneous LVOT gradient ≥80 mm Hg (hazard ratio, 1.016; 95% confidence interval, 1.004–1.028), and difference between preoperative and postoperative peak instantaneous LVOT gradients (hazard ratio, 1.021; 95% confidence interval, 1.007–1.035; Table I in the online-only Data Supplement).

Recurrence of LVOT gradient postoperatively

Postoperative peak instantaneous LVOT gradient was 15.1 ± 14.1 mmHg, which linearly increased over time at a rate of 1.31 ± 0.16 mmHg per year (p=0.001). Independent risk factors for faster postoperative peak instantaneous LVOT gradient pro-

Table 2. Surgical details for 412 DSS operations

	First operation (n=313)	Second operation (n=80)	Third operation (n=19)
Age at time of surgery, years	17.1 ± 14.9	22.9 ± 13.9	32.1 ± 10.4
Pre-operative peak LVOT gradient, mmHg	74.7 ± 28.9*	79.3 ± 22.2	76.6 ± 36.3
Postoperative peak LVOT gradient, mmHg	14.6 ± 13.8*	17.6 ± 16.2	10.9 ± 9.2
Pre-operative aortic regurgitation			
None	84 (26.8)	15 (18.8)	1 (5.3)
Mild	173 (55.3)	26 (32.5)	5 (26.3)
Moderate	44 (14.1)	15 (18.8)	4 (21.0)
Severe	12 (3.8)	24 (30.0)	9 (47.4)
Postoperative aortic regurgitation			
None	87 (27.8)	18 (22.5)	5 (26.3)
Mild	208 (66.4)	59 (73.8)	13 (68.4)
Moderate	18 (5.8)	3 (3.8)	1 (5.3)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Type of surgery			
Isolated enucleation	189 (60.4)	31 (38.8)	8 (42.1)
Additional myectomy	122 (39)	43 (53.8)	9 (47.4)
Unknown	2 (0.6)	6 (7.5)	2 (10.5)
Concomitant surgery †	8 (2.5)	7 (8.8)	2 (10.5)
Aortic valve bioprosthesis	10 (3.2)	12 (15.1)	8 (42.1)
Aortic valve mechanical prosthesis	18 (5.8)	7 (8.8)	2 (10.5)
Aortic valve repair	2 (0.6)	12 (15.0)	2 (10.5)
Ross procedure	4 (1.3)	0 (0.0)	0 (0.0)
Coarctation repair	3 (1.0)	1 (1.3)	1 (5.3)
Supravalvular aortic repair	9 (2.9)	0 (0.0)	0 (0.0)
Persistent ductus arteriosus ligation	8 (2.5)	3 (3.8)	0 (0.0)
Mitral valve replacement or repair	46 (14.7)	1 (1.3)	0 (0.0)
Ventricular septal defect closure	6 (1.9)	0 (0.0)	0 (0.0)
Atrial septal defect closure			
Postoperative complications †			
New left bundle branch block	36 (3.2)	8 (10)	0 (0.0)
New right bundle branch block	33 (3.2)	3 (3.8)	1 (5.3)
New complete heart block requiring pacemaker	12 (3.8)	3 (3.8)	2 (10.5)
Atrial fibrillation	6 (1.9)	2 (2.5)	2 (10.5)
Heart failure	3 (1.0)	1 (1.3)	0 (0.0)
Mortality	1 (0.3)	0 (0.0)	0 (0.0)
Neurological complication (stroke or neuropathy)	1 (0.3)	2 (2.5)	0 (0.0)

DSS = discrete subaortic stenosis, LVOT = left ventricular outflow tract obstruction.
*Only available for 298 patients.
† Overlapping categories.
Values are n(%) or mean ± SD.

gression were increased age at the time of DSS diagnosis (p=0.048) and female sex (p=0.059 for trend; Figure 2). A higher preoperative LVOT gradient was associated with an overall higher residual postoperative peak instantaneous LVOT gradient (p<0.001) but did not significantly influence the postoperative peak instantaneous LVOT gradient progression rate (p=0.74). Peak instantaneous LVOT gradient progression rate was not influenced by type of surgery (enucleation with or without myectomy; p=0.85), age at the time of surgery (p=0.21), presence of associated CHD (p=0.12), or smoking (p=0.24; Table II in the onlineonly Data Supplement).

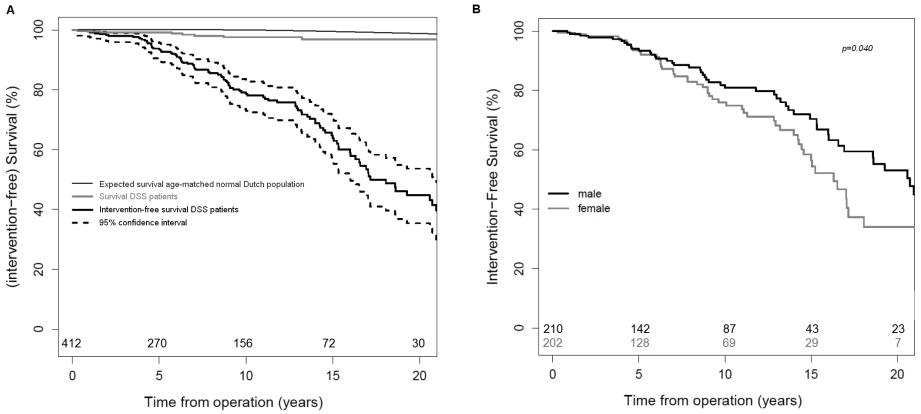

Figure 1. Kaplan-Meier plots. **a.** Survival and intervention-free survival for patients with discrete subaortic stenosis (DSS) and expected survival for the normal age-matched Dutch population. **b.** By sex.

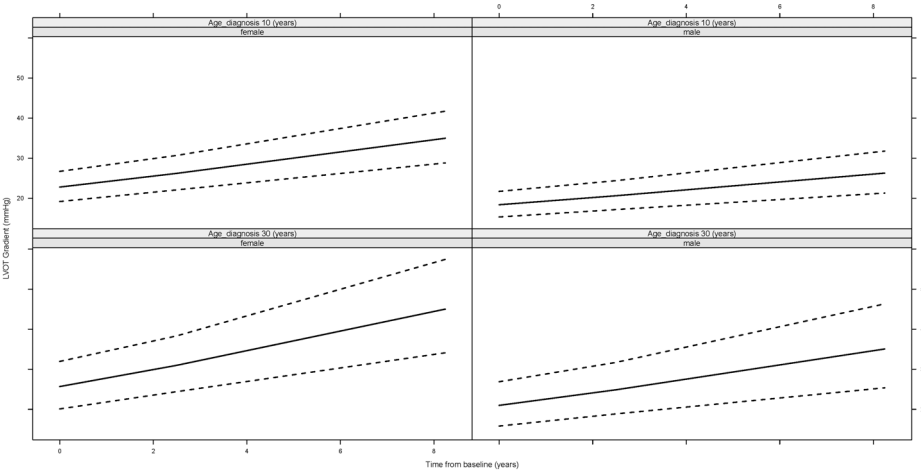

Figure 2. Discrete subaortic stenosis over time. Evolution of discrete subaortic stenosis over time postoperatively by age at time of diagnosis (p = 0.048) and sex (p =0.059). LVOT = left ventricular outflow tract.

Progression of AR postoperatively

Immediately postoperatively, mild AR was present in 68% of patients and moderate AR in 5%; no patients exhibited severe AR. Over time, AR severity did not significantly progress in the total study population (p=0.76; Figure 3). However, approximately 10% of patients progressed from having no AR to mild AR, and another 10% of patients developed moderate AR during the first 8 years after surgery (Figure 3). None of the patients progressed to severe AR. A preoperative peak instantaneous LVOT gradient ≥80 mmHg was an independent risk factor for development of moderate AR postoperatively (p=0.008; Figure 4). We could not identify any other factor that was significantly associated with postoperative development of mild AR or progressive AR (Table III in the online-only Data Supplement).

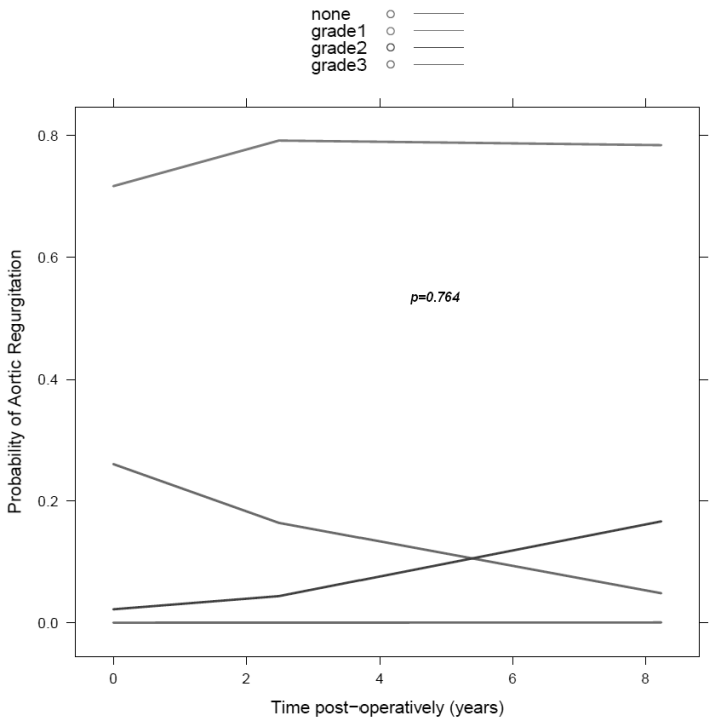

Figure 3. Aortic regurgitation over time. Probability of postoperative aortic regurgitation over time.

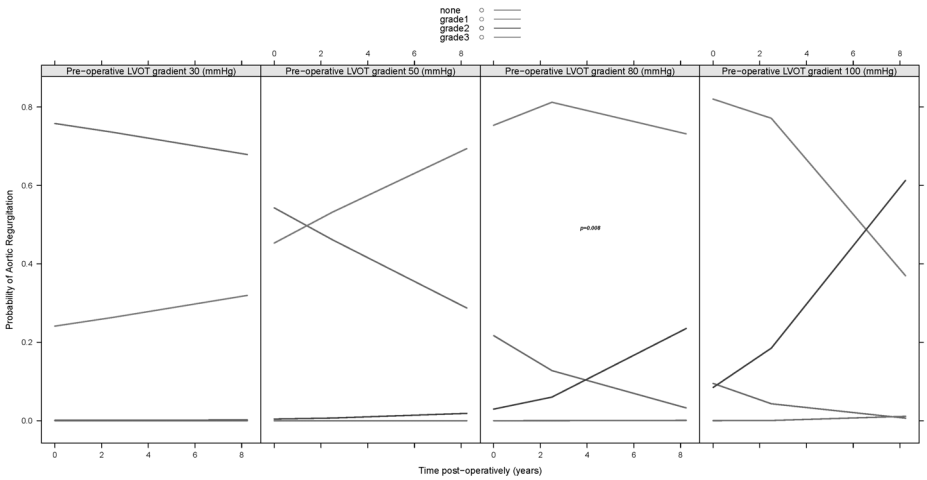

Figure 4. Preoperative left ventricular outflow tract (LVOT) gradient vs postoperative aortic regurgitation. Association between various levels of preoperative peak LVOT gradient and probability of postoperative aortic regurgitation progression over time.

DISCUSSION

In this multicenter study, we have analyzed data on a large cohort of adult patients who underwent surgical DSS resection with 13 years postoperative follow-up (range, 1-31 years) to determine predictors for DSS recurrence, AR worsening, and re-operation. The results of the present study may be the basis for modification of the current strategies for management of DSS patients.

DSS recurrence and reoperations

In the total study population, postoperatively, the peak instantaneous LVOT gradient increased slowly but significantly over time at 1.3 mmHg/year. This finding confirms a smaller study that previously reported a slight increase in postoperative gradient at late follow-up.[27] Surprisingly, increased age at the time of diagnosis (>30 years old) was a risk factor for faster postoperative LVOT gradient progression. This phenomenon might be explained by the fact that when DSS was discovered late in adulthood, patients were more likely to present with symptoms and thus might be in an advanced stage of the disease. Another hypothesis is that aging itself is related to faster postoperative progression.

In this study we used reoperation as an objective clinically relevant outcome, rather than recurrence only because of the lack of a universal definition for recurrence. We do acknowledge that the indication for reoperation is also not concrete and universal. Our reoperation rate for recurrent DSS (1.8% per patient-year) was

comparable to two other adult surgical series, which reported reoperation rates of 0.5% and 2.6% per patient-year.[15,27] As reported in several studies in children with DSS, a higher peak instantaneous gradient across the LVOT at the final preoperative echocardiogram was an independent predictor for reoperation in our adult patient population.[10,12,16,17,24] Testing various cutoff points, we found that a peak instantaneous LVOT gradient ≥80 mmHg is most predictive for the need of reoperation. In addition, incomplete removal of the LVOT obstruction, reflected in a smaller difference between preoperative and postoperative gradients, was found to be a risk factor for reoperation. This has previously been demonstrated in several previous studies.[12,15,20,22,26,37] Furthermore, as expected, LVOT gradient progression postoperatively is a strong predictor for reoperation. In addition to the echocardiographic parameters to monitor and predict LVOT gradient progression, perhaps biomarkers might be useful to identify those with more rapidly progressing disease. Further research in this area is warranted.

Surprisingly, women carry a 1.5-times elevated risk for reoperation compared to men. In addition, female patients tended to have a more rapid postoperative LVOT gradient progression rate than male patients. These sex differences in reoperation or recurrence risk have not been reported previously. This phenomenon might be explained by the fact that women are likely to have a smaller LVOT. In our cohort the LVOT diameter tended to be smaller in women compared to men, although not statistically significant. Perhaps pregnancy might have been a confounding factor, but unfortunately we did not collect information about pregnancies during follow-up, and there is a lack of studies investigating the consequences of pregnancy in DSS patients. Furthermore, transcriptional regulation of genes related to myocardial hypertrophy and fibrosis might be sex dependent, as has been shown after aortic valve replacement for valvular aortic stenosis.[38] Pathophysiological studies are required to explore the underlying mechanisms for these sex differences.

Isolated enucleation versus additional myectomy

Several hypotheses regarding DSS recurrence have been proposed. Recurrence may result from regeneration of tissue from the same region or from scar formation in the subvalvular area during healing.[19,39] Furthermore, turbulence due to incomplete removal of the LVOT obstruction has been postulated to promote fibrosis and subsequent restenosis.[12] Although some previous studies have suggested that additional myectomy during the first operation reduces the incidence of recurrence, other authors have questioned this finding.[8,16-27] Our results do not support the benefit of additional myectomy for either the risk of reoperation or LVOT gradient progression rate postoperatively. A tradeoff when performing aggressive surgical resection to potentially lower the recurrence rate is the risk of a complete atrioventricular block,

which was significantly higher in the patients who underwent additional myectomy compared to those who underwent isolated enucleation (8% versus 2%). In previous studies the risk of a postoperative complete atrioventricular block is typically 1% to 5%, however this might be up to 14% when a more aggressive surgical approach is performed.[6,7,12,17,20] Of course, the results of a myectomy and risk of heart block are operator dependent, but this study included patients from four different centers over a time span of 30 years, making it impossible to study this factor adequately. Therefore, from our study we conclude that an additional myectomy may be justified when a substantial degree of septal hypertrophy is detected but should be discouraged in most patients.

AR after DSS surgery

Although most DSS patients exhibited mild (non hemodynamically relevant) AR both preoperatively and postoperatively, our study shows that in most patients AR is not progressive over time. Approximately 10% of patients who did not have AR before surgery, however, developed mild AR relatively shortly after surgery. Furthermore, another 10% of patients progressed from mild to moderate AR, but progression to severe AR was very rare. We identified a preoperative peak instantaneous LVOT gradient ≥80 mmHg as a risk factor for progressive AR after surgery. Previous studies in children with DSS have also demonstrated the association between a high preoperative LVOT gradient and progressive AR postoperatively.[40,41] In order to prevent progressive AR postoperatively, it may be wise to reoperate before the peak LVOT gradient reaches 80 mmHg. In conclusion, we agree with the statement made by Stassano et al. that resection of the subaortic membrane cannot improve AR, but we disagree with their suggestion that resection can entirely "stabilize" the grade of regurgitation.[27]

Clinical implications

Postoperative long-term survival after surgical treatment of DSS is excellent and comparable to that of the normal population. However, the rate of reoperation is considerable (approximately 2%/year), and given the excellent survival of these young adult patients, most patients will require a reoperation for recurrent DSS at some point in their lifetime. Postoperatively, the peak instantaneous LVOT gradient progresses slowly but steadily over time in adults. Therefore, lifelong regular follow-up, including echocardiography, is required after surgery. However, because the LVOT progression is generally slow, follow-up can probably be limited to 2- to 4-year intervals in most patients. Women and patients >30 years old at time of diagnosis are at risk for faster LVOT gradient progression after surgery and should thus be monitored more frequently. Of course, patients with decreased LV function

or severe/progressive AR should also be followed more frequently. Additional myectomy did not reduce DSS recurrence or reoperation risk and significantly increased the risk of a complete heart block. Therefore, myectomy should not be encouraged in most patients and should only be performed in case of marked LV hypertrophy. Postoperative AR is common but generally mild and non-progressive over time in most patients. Patients with a preoperative Doppler derived peak instantaneous LVOT gradient ≥80 mmHg, however, are at increased risk for development of moderate AR, but progression to severe AR is rare.

Study limitations

Several limitations of this study merit attention. This retrospective study included patients monitored in adult congenital clinics; therefore, referral bias may exist. One of the major study limitations was the fact that indications for (re)operation were not standardized because of the multicenter approach and broad time period. By using prospective databases to identify eligible patients and therefore also including deceased patients, we aimed to limit survival bias. Unfortunately, some echocardiographic parameters could not be retrieved for all patients, but this was dealt with through the use of the multiple imputation approach for missing values. The fact that echocardiography was not performed precisely every year was accounted for by the use of mixed-effects models that take different lengths of follow-up into account. Furthermore, by using the joint modeling approach, we allowed for the dependency and association between the longitudinal echocardiographic data and survival data. Ideally, our findings need to be validated by a large prospective cohort study.

The current European Society of Cardiology and American College of Cardiology/American Heart Association guidelines for adults with CHD do not provide specific recommendationsfor reinterventions in DSS patients.[42,43] The Canadian guidelines state that a peak instantaneous LVOT gradient >50 mmHg is an indication for reoperation when patients have symptoms.[44] The timing of reoperation is a highly complex issue that should take various factors into account: the peak LVOT gradient, progression rate of the LVOT gradient, severity and progression of AR, left ventricular volume and function, presence of (exercised-induced) symptoms, and risk of sudden death. Unfortunately, the optimal timing of reoperation, when all these factors are combined, in adult patients with DSS cannot yet be derived from the present study.

Conclusions

Although survival is excellent after surgery for DSS, most patients will require a reoperation for recurrent DSS at some point during their lifetime. Postoperatively,

the LVOT gradient progresses slowly and mild AR is common but nonprogressive over time in most patients. Myectomy should not be performed routinely because it does not reduce the risk of recurrence or reoperation and increases the risk of a complete heart block.

Clinical Perspective

Discrete subaortic stenosis is a narrowing of the left ventricular outflow tract just beneath the aortic valve. In childhood, discrete subaortic stenosis is known for its unpredictable and sometimes rapid hemodynamic progression. Furthermore, aortic regurgitation is present in 30% to 80% of patients. Because reoperation rates have been reported to be high (8%–34%), there is ongoing debate about the timing of surgical intervention and type of surgery. This is the first large study to evaluate the surgical outcome in adult patients. In contrast to children, the left ventricular outflow tract gradients in adults progress slowly. Mild aortic regurgitation is common but nonprogressive over time in the majority of patients. Patients with a preoperative peak left ventricular outflow tract gradient ≥80 mm Hg, however, are at risk for progression to moderate aortic regurgitation. Survival after surgery for discrete subaortic stenosis is excellent, with survival rates comparable to those of the normal population. The reoperation rate in young adult patients, however, is high (2%/year). Given the excellent survival in this young patient population, most patients face a reoperation for recurrent discrete subaortic stenosis throughout their lifetime. Additional myectomy does not reduce the risk for reoperation but significantly increases the risk of a complete heart block requiring pacemaker implantation. Therefore, myectomy should not be performed routinely.

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Disclosures

None.

Supplementary material

Supplementary material can be found online at: www.circ.ahajournals.org.

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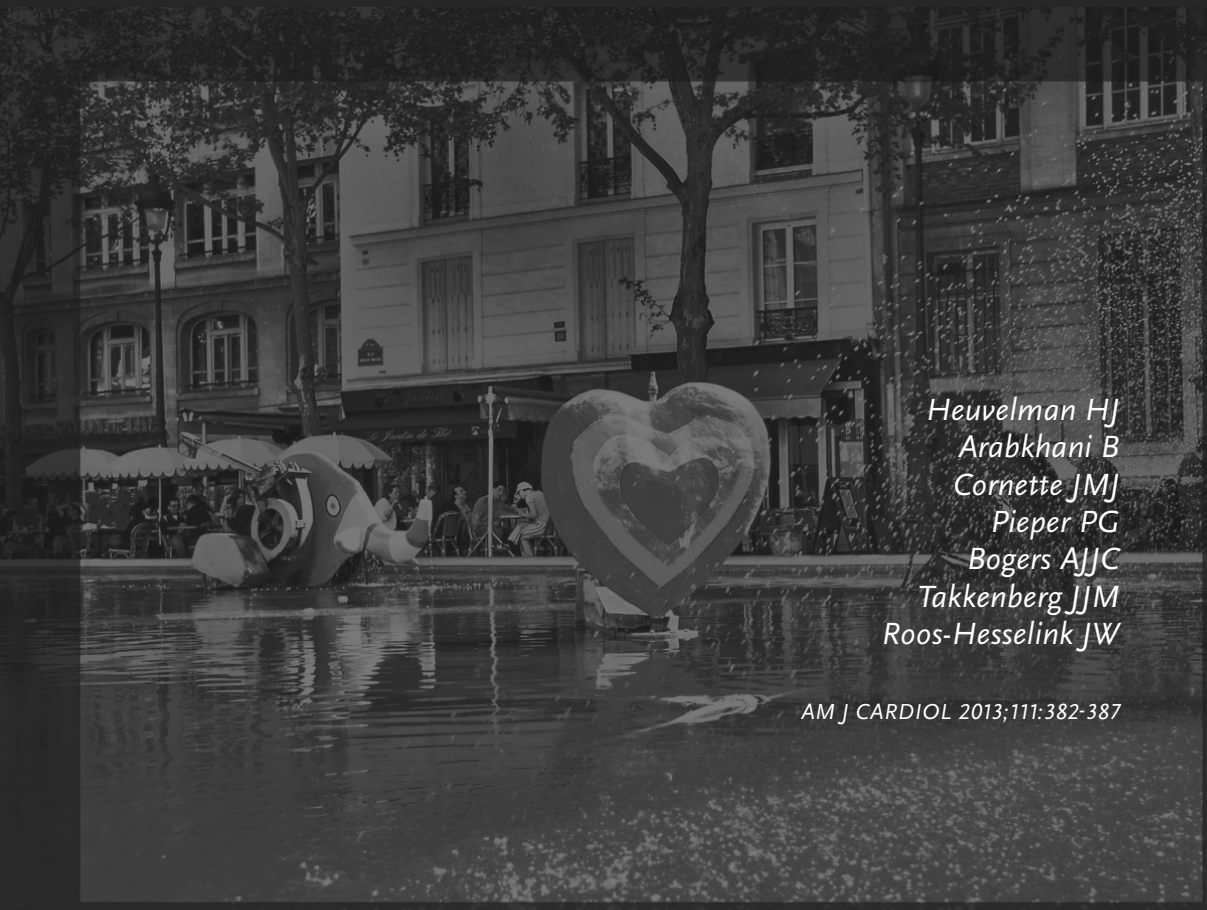
It is the brain, the little gray cells on which one must rely. One must seek the truth within, not without.

H. Poirot

13

Pregnancy outcomes in women with aortic valve substitutes



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ABSTRACT

Young women who require aortic valve replacement need information on the potential cardiac and obstetric complications of pregnancy for the different available valve substitutes. We, therefore, assessed the pregnancy outcomes in women who had received an autograft, homograft, or mechanical valve in the aortic position.

Women who were pregnant after surviving AVR at our institution from 1987 to 2011 were included. Information on cardiac status and pregnancy outcome was obtained through hospital medical records and by an extensive patient questionnaire.

A total of 40 women experienced 67 pregnancies of which 55 (82%) were completed pregnancies, 6 (9%) were miscarriages, and 6 (9%) were terminated. Of the 40 women, 18 (45%) women had a pulmonary autograft, 13 (32%) a homograft, and 9 (23%) a mechanical valve. The mean age at the first pregnancy was 30.0 ± 5.7 years. No maternal mortality but 1 fetal death (1.8%) and 1 neonatal death (1.8%) occurred. Maternal cardiac complications occurred in 13% and obstetric complications in 38% of the completed pregnancies. Heart failure (9%), arrhythmias (7%), hypertension-related disorders (7%), preterm delivery (24%), and small for gestational age infants (15%) were most often encountered. Mechanical valve recipients had the highest incidence of both cardiac and obstetric complications.

In conclusion, pregnancy-associated complications after AVR were common, and human tissue valves should be considered in the discussion for the optimal aortic valve substitute in a young woman. However, careful obstetric monitoring is mandatory.

INTRODUCTION

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

METHODS

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

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

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

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

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

The normality of the distribution of continuous data was tested with the Kolmogorov-Smirnov test with Lilliefors' correction. Continuous data are displayed as the mean ± SD or in case of a skewed distribution, as the median and interquartile range and were compared using the one-way analysis of variance test or the Krus-

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

	All	Autograft	Homograft	MP	p-value
Variable	(n=40)	(n=18)	(n=13)	(n=9)	
Intervention/surgery before AVR					
0	23 (58%)	10 (56%)	9 (69%)	4 (44%)	.46
1	8 (20%)	2 (11%)	4 (31%)	2 (22%)	.46
>1	9 (23%)	6 (33%)	0	3 (33%)	.07
Diagnosis					
Aortic stenosis	15 (38%)	10 (56%)	4 (31%)	0	**.02**
Aortic regurgitation	13 (33%)	3 (17%)	6 (46%)	5 (55%)	.10
Mixed	12 (30%)	5 (28%)	3 (23%)	4 (44%)	.61
Etiology					
Congenital	26 (65%)	16 (89%)	8 (62%)	2 (22%)	**<.01**
Rheumatic	12 (30%)	2 (11%)	4 (31%)	6 (67%)	**.01**
Aneurysm/Dissection	2 (5%)	0	1 (8%)	1 (11%)	.49
Age at last surgery (years)	25.4 ± 7.7	21.5 ± 6.6	26.9 ± 5.0	31.2 ± 9.0	**<.01**
Concomitant procedures					
None	28 (70%)	16 (89%)	8 (62%)	4 (44%)	**.04**
Coronary bypass	3 (8%)	1 (6%)	0	2 (22%)	.23
Mitral valve surgery	6 (15%)	0	3 (23%)	3 (33%)	**.04**
Size prosthesis (mm)	-	-	22 (21-22)	21 (21-23)	
Time surgery-1stpregnancy (years)*	3.1 (1.6-6.1)	5.5 (1.8-9.4)	2.3 (1.4-4.6)	2.1 (1.5-4.6)	.14
Total number of pregnancies	67	33	22	12	.39
1	40 (60%)	18 (55%)	13 (59%)	9 (75%)	.46
2	20 (30%)	11 (33%)	6 (27%)	3 (25%)	.83
3	7 (10%)	4 (12%)	3 (14%)	0	.46
Pregnancy age (years)*					
1st (n=40)	30.0 ± 5.7	27.0 ± 4.1	30.2 ± 4.6	35.7 ± 5.9	**<.01**
2nd (n=20)	30.9 ± 4.7	30.0 ± 3.9	31.9 ± 5.0	32.1 ± 8.0	.75
3rd (n=7)	32.1 ± 5.5	32.7 ± 7.0	31.3 ± 4.0	-	.86
LVF preconceptional (n=66)					
Good	64%	61%	77%	50%	.18
Moderate	36%	39%	23%	50%	.18
PAP preconceptional (mmHg) (n=62)	6 (3-15)	13 (9-18)	3 (2-3)	4 (1-11)	**<.01**
Vmax preconceptional (m/s)*					
1st pregnancy (n=38)	1.78 ± 0.69	1.36 ± 0.42	1.85 ± 0.60	2.60 ± 0.55	**<.01**
2nd pregnancy (n=19)	1.70 ± 0.54	1.41 ± 0.46	2.01 ± 0.36	2.23 ± 0.38	**.01**
3rd pregnancy (n=7)	1.83 ± 0.80	1.41 ± 0.48	2.39 ± 0.87	-	.23
Completed pregnancies	55 (82%)	28 (85%)	20 (91%)	7 (58%)	.05

Table 1. Patient characteristics of the 40 women who experienced ≥1 pregnancy after aortic valve replacement (Continued)

Miscarriage	6 (9%)	3 (9%)	0	3 (25%)	.05
Termination pregnancy	6 (9%)	2 (6%)	2 (9%)	2 (17%)	.64
Social reasons	4 (6%)	2 (6%)	2 (9%)	0	.70
Maternal cardiac indication	1 (1%)	0	0	1 (17%)	.18
Fetal spina bifida	1 (1%)	0	0	1 (8%)	.18

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

kal-Wallis test. Discrete data are presented as absolute numbers and percentages and compared using the Pearson's chi-square test or Fisher's exact test.

Univariate logistic regression analysis was performed to identify possible factors associated with the incidence of pregnancy-related complications. Missing values were imputed by the mean. Age at surgery, maternal age at first pregnancy, valve type, interval from surgery to first pregnancy, duration of pregnancy, cesarean section, pre-conceptional left ventricular function, maximum aortic jet velocity, and pulmonary artery pressure were considered as covariables in the univariate model for cardiac and obstetric events. For comparison of the event incidence with the general Dutch population the chi-square test was used. All statistical tests were 2-sided and a p-value ≤0.05 was considered significant. For data analysis SPSS, version 17.0, for Windows (SPSS, Chicago, Illinois) was used.

RESULTS

A total of 40 patients experienced ≥1 pregnancy after AVR in our institution (Table 1), with 67 singleton pregnancies. Of these 67 pregnancies, 55 continued >20 weeks (47% male infants) in 35 women. All 6 spontaneous miscarriages were <14 weeks of gestation. Six pregnancies were terminated (Table 1). The only termination of pregnancy for maternal cardiac reason was performed in a mechanical valve recipient with pulmonary hypertension, tricuspid insufficiency, and moderate stenosis of the mechanical prosthesis in aortic position of 3.3 m/s. One termination was performed in a fetus with spina bifida. No acenocoumarol-associated embryopathies developed. The mode of delivery for the 55 completed pregnancies, differentiated by type of valve substitute, is listed in Table 2. Figure 1 illustrates the modes of delivery compared to the Dutch general population. No maternal mortality occurred.

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

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

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

Heart failure was the most common cardiac complication, with persistent NYHA deterioration in 3 patients (Table 3). One mechanical valve recipient with permanent atrial fibrillation developed prosthetic valve thrombosis and subsequent heart failure at 33 weeks' gestation. Anticoagulation was converted to intravenous heparin, and the woman underwent caesarean section at 36 weeks. A female infant of 2,150 g was born. Five weeks later, she underwent repeat AVR with another mechanical valve.

The most common obstetric complications concerned hypertension-related disorders, preterm delivery, and small-for-gestational-age infants (Table 3 and Figure 2). Of the 13 pregnancies that ended prematurely, 5 were induced before 37 weeks because of cardiac indication: congestive heart failure in 2 patients (1 mechanical valve prosthesis, 1 pulmonary autograft), prosthetic valve thrombosis (mechanical valve prosthesis), Marfan syndrome (homograft), and dilated aortic root with aortic and pulmonary regurgitation (pulmonary autograft).

One fetal death occurred in a mechanical valve recipient at 20 weeks and 4 days that presented with an absent heart rate, growth restriction, and fetal hydrops on ultrasonography. A macerated male infant (190 gram) with a placenta of 30 gram was born. Fetal autopsy was declined by the parents. Placental pathologic examination showed severe placental insufficiency. One postnatal death occurred in a pulmonary

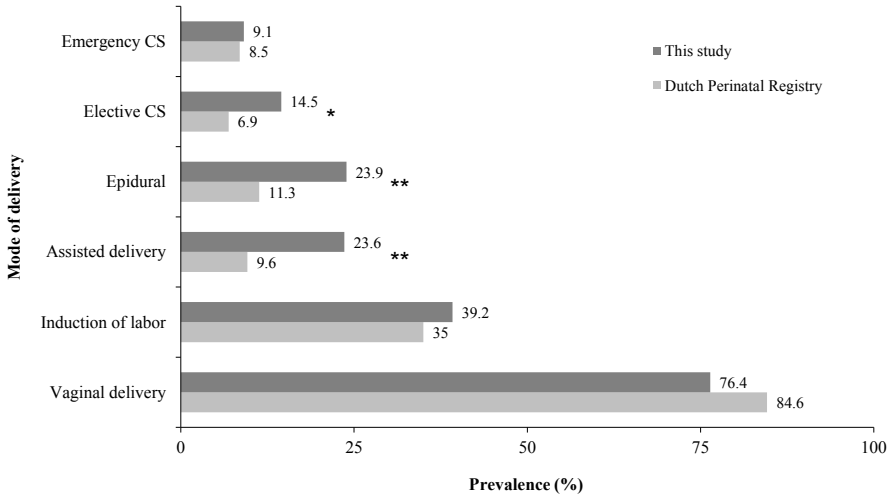

Figure 1. Mode of delivery of 55 completed pregnancies compared to Dutch Perinatal Registry. CS = caesarean section.

autograft recipient who was on oral anticoagulation therapy because of a protein C deficiency and previous deep venous thrombosis. At 19 weeks, she experienced preterm premature rupture of the membranes and fetal growth restriction. Despite the poor prognosis, the woman chose expectant management. At 30 weeks, she spontaneously delivered a 600-g boy who died on the first postnatal day from lung hypoplasia.

No potential predictors of cardiac complications could be identified. Obstetric complications were more common in patients with cardiac complications during pregnancy (odds ratio 13.2, 95% confidence interval 1.5 to 119.5; p = 0.02). No correlation was found between the preconceptional maximum aortic jet velocity over the aortic valve and the birth weight (r -0.01; p = 0.95).

Two women with a completed pregnancy were not treated according to the current European Society of Cardiology guidelines for the use of anticoagulation in pregnant mechanical valve patients.[17] One patient received an insufficient dose of oral anticoagulation therapy and developed a prosthetic valve thrombosis. The other patient was treated with a combination of acenocoumarol and LMWH until a healthy female infant was born by spontaneous vaginal delivery at 40 weeks' gestation.

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

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

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

DISCUSSION

Pregnancy in patients after AVR with a human tissue valve or a mechanical valve substitute was associated with serious maternal cardiac and obstetric complications in half of the patients in our study. However, all patients survived pregnancy. Human tissue valve recipients had a lower incidence of cardiac maternal and obstetric

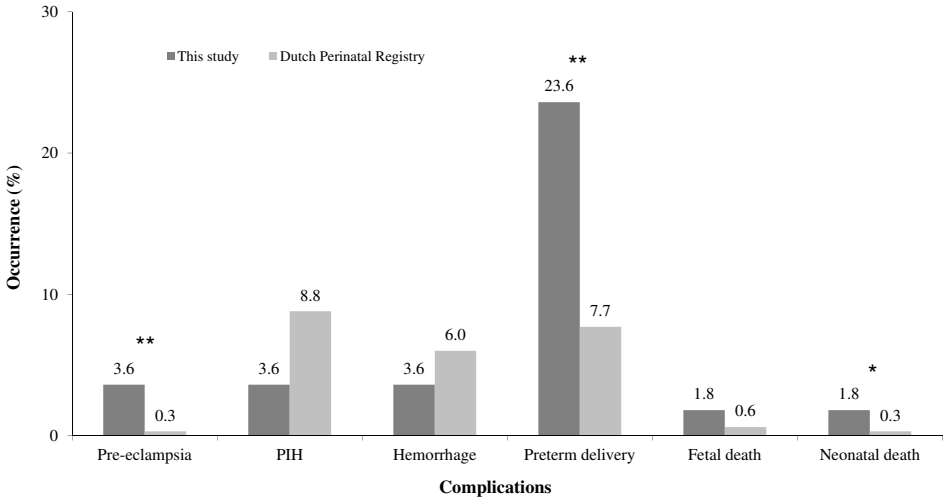

Figure 2. Incidence of obstetric and perinatal complications of 55 completed pregnancies compared to Dutch Perinatal Registry[16]. PIH = pregnancy-induced hypertension.

complications than did patients with mechanical valve prostheses. The mechanical valve recipients were at risk of miscarriage, supraventricular arrhythmias, heart failure, and preterm delivery.

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

Another important cardiac complication in our study population was symptomatic heart failure during pregnancy, occurring in 5 patients, of whom 3 experienced persistent NYHA deterioration after 1 year. Heart failure is a serious complication in pregnant patients who have undergone previous valve replacement.[1,21-23] It has been the cause of maternal death[1], but also been an indication for pregnancy termination.[22] Of the 5 patients with heart failure in our study, 2 were advised against pregnancy prior to conception; both had persistent NYHA deterioration after pregnancy.

Although preconceptional counseling includes the intention to reduce the risk on severe maternal cardiac events during pregnancy, it is the patient and her family who finally decides to pursue or decline a pregnancy according to their informed wishes and expectations.

In the present study, hypertension-related disorders occurred significantly more often in homograft recipients. Of the reports on pregnancy outcomes in homograft patients[2,10,21,24,25], only 1 study has described a case of preeclampsia.[24] The aortic gradient increases significantly in homograft patients during pregnancy, but this is also seen in mechanical valve recipients[21] and probably reflects the increased cardiac output (increased stroke volume) and decrease in systemic vascular resistance. However, we could not identify a specific reason for the increase in hypertension-related disorders among the homograft patients.

Almost all newborns of mechanical recipients were delivered vaginally, without excessive maternal hemorrhage during labor or cesarean section (Figure 2). The Danish cohort, however, reported a postpartum bleeding incidence of 12% and 1 fatal bleeding episode.[1] This underlines the importance of careful anticoagulation monitoring during delivery. Our study has illustrated that through careful anticoagulation monitoring during delivery, it is possible for mechanical valve recipients to deliver an infant without extensive bleeding.

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

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

The counseling of young female patients who require AVR and might contemplate pregnancy requires a multidisciplinary discussion that includes several important issues. These patients should be individually informed about the advantegs and disadvantages of the different available valve substitutes and corresponding potential pregnancy-associated maternal and fetal complications.[3] The high incidence of preterm delivery and valve thrombosis in mechanical valve recipients illustrates that these valves are far from ideal for patients during pregnancy. However, the curious finding of a high incidence of hypertension-related disorders in homograft recipients requires additional studies and careful monitoring of the last stage of pregnancy in this patient group. Although human tissue valves needs careful obstetric monitoring, they provide female patients with a biological solution that eliminates the daily burden of anticoagulation, in particular during pregnancy, and their durability is not influenced by pregnancy.[29] Therefore, human tissue valves should be considered as aortic valve substitute of choice for young patients with severe aortic valve disease who are planning to become pregnant.

Just as with most studies on this topic, the patient numbers in the present study were relatively small, and treatment occurred at a tertiary hospital, necessitating careful interpretation of the results.

Disclosures

The authors have no conflicts of interest to disclose.

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Flying might be not all plain sailing, but the fun of it is worth the price.

A. Earhart

14

Does pregnancy influence the durability of human aortic valve substitutes?

Arabkhani B
Heuvelman HJ
Bogers AJJC
Mokhles MM
Roos-Hesselink JW
Takkenberg JJM

J AM COLL CARDIOL. 2012;60:1991-1992

TO THE EDITOR

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

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

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

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

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

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

for patients without pregnancies and 94.4 ± 5.4% for patients with pregnancies (p = NS).

Fifteen homograft patients required reoperation for a calcified and degenerated homograft; 2 additional homograft patients were reoperated for paravalvular leak. Twelve autograft patients were reoperated for neoaortic regurgitation and dilatation of the neoaortic root, including 11 autograft replacements and 1 valve-sparing aortic root replacement (Yacoub procedure). Freedom from aortic valve reoperation at 15 years was 63% (95% confidence interval (CI): 57 to 69%) in homograft patients; in autograft patients, this was 75% (95% CI: 63 to 87%). Freedom from reoperation was comparable between patients who experienced pregnancy and those who did not, in both homograft and autograft recipients (p = NS).

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

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

The question remains as to what the best valve substitute choice is for young female patients who require aortic valve replacement, and who may contemplate pregnancy. Bioprosthetic valves are an option, but valvular deterioration seems to accelerate during pregnancy.[6] Mechanical prostheses are far from ideal during pregnancy because of anticoagulation therapy-related complications, although in some patients mechanical valves are the only option. Human tissue valves do not require anticoagulation therapy and have good haemodynamic performance, but homografts –in contrast to autografts- do not increase in size with the growing child. In addition, autografts have a superior hemodynamic profile,[7] which particularly during pregnancy has potential beneficial effects on cardiac function. In contrast, neoaortic root dilatation and neoaortic regurgitation cause an increased need for reoperation.[8]

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

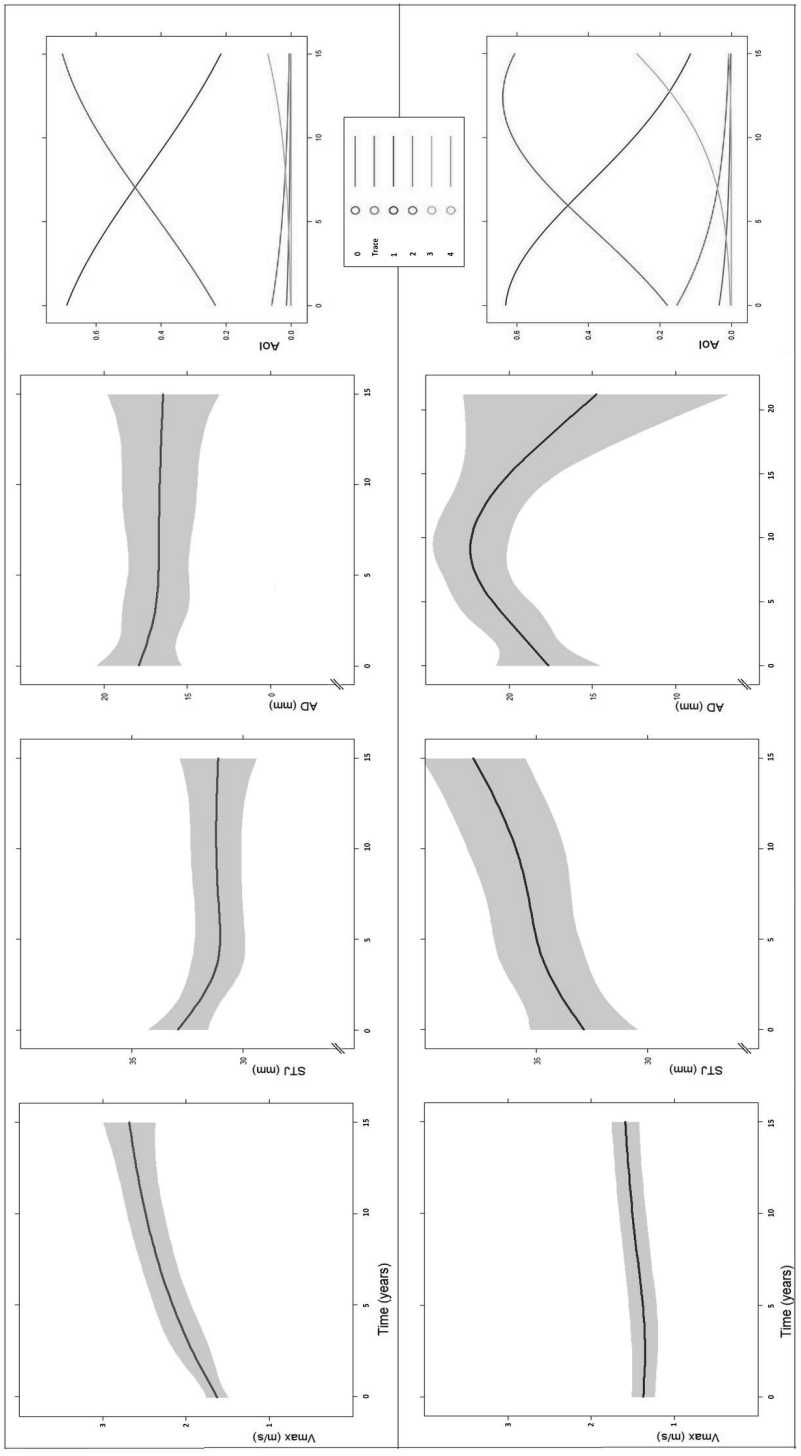

Figure 1. Vmax, STJ diameter, AD, and AoI marginal probability of AoI grade over time. **Top row** Homografts models. **Bottom row** Autograft models. **Shared grey areas** 95% confidence intervals. AD = annulus diameter, AoI = aortic regurgitation, STJ = sinotubular junction, Vmax = peak velocity.

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Wenn du nicht irrst, kommst du nicht zu Verstand.

J.W. von Goethe

15

General discussion

INTRODUCTION

The aim of this thesis was to provide insight in the natural history, treatment, and prognosis of adult patients with aortic stenosis (AS). From the studies included in this thesis several observations emerged, illustrating the complexity of AS and the challenges it poses in current clinical practice.

This chapter will address the research questions that were formulated and discuss how the insights obtained from this thesis may help treating physicians to optimize clinical decision-making with respect to the diagnostic process, treatment strategy, and monitoring patients with AS disease. Finally, prospects and recommendations for future research will be presented.

WHAT IS THE NATURAL COURSE OF AS DISEASE?

Progression of valvular AS disease is very heterogeneous as evidenced from the cardiac catheterization and echocardiographic studies that are described in Chapter 2, 3, and 4. This heterogeneity may be explained by several factors: patient characteristics, different methods of measuring AS severity, and by the heterogeneous course of AS disease itself.

Older age is associated with an increased prevalence of AS disease.[1] In patients with normal or sclerotic valves (mean age >70 years), advanced age has been reported a significant predictor for progression to AS.[2] This thesis showed that in patients with moderate to severe AS, older age was associated with a lower rate of AS progression. Lower AS progression estimates may be caused by age-dependent inflammatory and atherosclerotic pathways underlying AS pathophysiology.[3-7] However, by using mixed model analysis in Chapter 5 in which information about baseline aortic valve area was included, age was no longer a predictor for AS progression rate. An explanation for this could be the limited follow-up duration of the study population included in the mixed model analysis which allowed only minor progression over time. To rule out this shortcoming, a longer follow-up period is needed.

Cardiovascular co-morbidities seem to be associated with a lower AS progression rate. As the pathway of AS disease also involves atherosclerotic characteristics, one would expect the opposite: a faster AS progression rate in patients with cardiovascular co-morbidities.[8,9] A possible explanation is that the presence of co-morbidities may urge treating physicians to more frequent patient monitoring and therefore earlier detection of AS disease, which in general is accompanied by lower aortic gradients. As a lower baseline peak aortic gradient is associated with a lower AS pro-

gression rate compared to patients with a higher baseline gradient, this may cause lower AS progression estimates in patients with cardiovascular co-morbidities.[10]

Several classifications are used for defining AS severity as described in Chapter 2, 3, and 5. Although aortic valve area (AVA), maximum aortic jet velocity (Vmax), mean and peak aortic gradient (MAG, PAG) are recommended by the current American and European guidelines for the management of valvular heart disease,[11,12] these criteria have shown to be inconsistent in patients with AS disease, even in patients with a normal left ventricular (LV) function.[13,14] Using AVA will overestimate AS severity as compared with Vmax and MAG, and this overestimation is only partly due to reduced stroke volume. A uniform classification of AS disease worldwide would greatly improve the comparability of available reports and allowed enhanced estimation of AS progression.

As aortic valve calcification is identified as one of the few known predictors for AS progression, there is need for a universal method to measure aortic valve calcification.[15,16] Unfortunately, this is not the case and a wide range of tests are used to assess aortic valve calcification, employing transthoracic and transoesophageal echocardiography, computed tomography, or magnetic resonance imaging.[17-19] The development of an imaging modality that allows measurement of all aspects of calcification from early sclerosis to advanced calcific thickening of the leaflets, would greatly enhance assessment of AS severity and patient prognosis.

Our attempts to capture the natural history of aortic stenosis undoubtedly have been influenced by study design and several types of bias. In general, patient selection in randomized controlled trials is subject to more strict inclusion criteria as compared to observational studies.[20] In addition, observational studies are more prone to publication bias as compared to randomized controlled trials.[21] Even a meta-analysis that carries one of the highest levels of evidence if properly performed, may induce bias by including only published studies, arbitrarily determined cut-off values of continuous values and proportions, data-driven subgroup analysis, using different outcomes measures (single or composite endpoint), and inadequate control of all confounding factors due to the often incomplete adjustment of confounding factors in observational studies.[22] In an ideal world one would like to prospectively study all patients with AS in a uniform manner and at pre-specified intervals. This can only be achieved through agreement on the definitions of AS severity, standardization of methods to measure AS severity, and the initiation of large international consortia that collaborate to further unveil the natural history of AS and its determinants.

WHAT IS THE ADDED VALUE OF DIFFERENT DIAGNOSTIC MARKERS FOR AS?

In severe AS, subendocardial fibrosis may develop. As a result, subendocardial ischemia may occur, with associated increased morbidity and mortality.[23] Therefore, subendocardial ischemia should be diagnosed and monitored properly. There are several manifestations of subendocardial ischemia: the presence of angina, electrocardiographic strain pattern, and changing echocardiographic LV deformation parameters.

In patients with AS disease, LV geometry changes by the increased LV load in order to preserve normal ejection fraction despite depressed LV myocardial systolic function.[24,25] LV deformation parameters such as rotation, shortening, and strain, provide a direct measure of myocardial deformation which enables assessment of LV myocardial systolic function.[26-30] LV twist, the measure of instantaneous apical-basal systolic rotation resulting from the dynamic interaction of counteracting muscle fibres arranged in subendocardial and subepicardial spiral loops, increases proportionally to AS severity and might serve as a compensatory mechanism to maintain systolic function in patients with severe AS as described in Chapter 6. LV hypertrophy contributes to LV diastolic dysfunction and is associated with a delayed LV untwist and reduced untwisting rate.[31-33] However, the observation in this thesis that peak diastolic untwisting velocity is higher in AS patients as compared to age-matched healthy controls, needs further exploration. Serial echocardiographic data are needed to reveal the longitudinal course of LV twisting and rotation and its diagnostic value in monitoring AS disease.

In addition, this thesis shows that electrocardiographic strain, defined as ST-segment depression, is associated with impaired systolic LV longitudinal velocities in patients with severe AS and normal LV function without coronary artery disease or left bundle branch block as described in Chapter 7. In patients with asymptomatic AS, electrocardiographic strain was independently predictive of a poor prognosis such as a 3.1-fold higher risk of (in-study) myocardial infarction.[34] In patients with AS, echocardiographic strain is reportedly associated with higher LV mass, concentric LV geometry, and more severe AS, and has incremental prognostic value over traditional risk markers including hemodynamic severity, symptom class, and LV ejection fraction.[30,35] Evidence about the diagnostic value of electrocardiographic strain is scarce and needs to be further explored in larger studies with longitudinal data and compared to echocardiographic strain studies.

WHAT IS THE CLINICAL COURSE OF SEVERE AS DISEASE IN CONTEMPORARY CLINICAL PRACTICE?

The current American and European guidelines for the management of valvular heart disease state that a symptomatic patient with severe AS has an indication for aortic valve replascement (AVR).[11,12] In the absence of serious co-morbidities, AVR is indicated in symptomatic patient with severe AS and should be performed promptly after onset of symptoms.[11,12] However, half of the patients in the AVARIJN study did not undergo AVR or transcatheter aortic valve implantation (TAVI) as described in Chapter 8.

Several possible explanations for a conservative treatment strategy in these patients are already reported: high anticipated operative risk, presence of serious co-morbidities, misclassification of AS severity and symptoms, and patient preferences.[36] In addition, age-related factors like frailty may play a role when selecting a treatment strategy. These are currently not taken into account in surgical risk scores but may be of great value in improving the performance of surgical risk models for elderly patients with severe symptomatic AS. Referral to a multidisciplinary heart team is encouraged, since it allows for a guidelines-driven team approach that formally includes patients' preferences to achieve optimal evidence-based and well informed decisions for symptomatic patients.[37,38]

Nowadays, as described in Chapter 4, TAVI is emerging for candidates who cannot undergo surgery for symptomatic severe AS.[39] Not all patients want to be treated despite a clear understanding of the individual risks and benefits which takes into account patient wishes, life expectancy, quality of life, cardiac and non-cardiac co-morbidities. Future studies are needed to identify those patients who in fact will benefit from TAVI and those who will take advantage of conservative treatment. One of the major challenges in the next few years is to determine a better balance between undertreatment and overtreatment of AS: while some patients are currently denied invasive treatment and the prospect of a better quality of life, the suffering of other patients –usually those at the end of their life- may be unnecessarily prolonged by invasive treatment of AS.

Chapter 8 of this thesis showed that three asymptomatic patients with severe AS disease in the AVARIJN cohort underwent aortic valve surgery. Performing an AVR in asymptomatic patients and more specifically the time of this intervention, remains a matter of controversy.[12] Morbidity and mortality due to the procedure itself plus long-term mortality and morbidity due to valve-related complications have to be balanced against potential benefits such as a decreased risk of sudden cardiac death and LV dysfunction. Although the number of prognostic markers is growing, critical appraisal of these markers in asymptomatic patients with severe

AS still shows difficulty to identify which markers adequately predict a high risk of sudden death.[40] A recent decision-analytic study showed that immediate surgery, as compared to watchful waiting, in asymptomatic severe AS does not improve outcomes unless the risk of sudden death pre-AVR and heart failure postoperative are higher than currently reported.[41] These results support the current American and European guidelines for the management of valvular heart disease of frequent clinical follow-up.[11,12]

HOW DOES AS TREATMENT IN CONTEMPORARY PRACTICE AFFECT QUALITY OF LIFE?

Given their limited lifespan, quality of life becomes an important measure of disease burden and outcome in elderly patients. Regardless of treatment strategy, AVARIJN patients with severe symptomatic AS had an impaired quality of life as compared to asymptomatic patients with severe AS and as compared to the general population as described in Chapter 9. Regardless of age, both physical and mental components are significant lower in symptomatic patients. This indicates that patients in each health domain aged from 40 years to over 70 years suffer equally from severely impaired quality of life due to severe AS disease.

Even patients with only mild symptoms experience a lower quality of life compared to asymptomatic patients or the general population. With increasing severity of symptoms, both mental and physical quality of life decrease and correspond to the severity of symptoms according to the New York Heart Association classification. This indicates that the SF-36v2 is a valid tool to measure quality of life in this population.

Quality of life in surviving AVR patients improves in most health domains while symptomatic patients who were treated conservatively –for example due to advanced age or co-morbidities- were left with a clearly impaired quality of life. Especially these conservatively treated symptomatic patients should be referred for the multidisciplinary heart team because it has been shown that they may potentially benefit from TAVI.[42] As life expectancy is increasing and hardly any evidence about quality of life in patients with severe AS is available, the information on quality of life from AVARIJN is important and can be applied for individual shared decision-making purposes, since most patients can be operated with acceptable risks of morbidity and mortality nowadays.

The 'watchful waiting' strategy in asymptomatic AVARIJN patients proved to be right at first presentation as they had the same quality of life as compared to the general population. However, as a substantial part became symptomatic within 2

years, the debate about preventive early (surgical) intervention in asymptomatic patients with severe AS is on-going.[41] Future, randomised controlled trials with a longer follow-up are required to reveal the potential benefit of early AVR or TAVI by preventing an increase in disease burden.

WHAT IS THE NATURAL HISTORY AND SIRGUCAL OUTCOME OF DISCRETE SUBAORTIC STENOSIS IN ADULT PATIENTS?

In the spectrum of AS disease, discrete subaortic stenosis (DSS) is part of congenital subvalvular AS disease which represents a small and very specific patient population. Compared to childhood DSS, adult DSS progresses slowly as described in Chapter 11.[43,44] An explanation for this may be that adult patients with conservatively treated DSS represent a mild phenotype in the spectrum of DSS. However, the observed faster progression of patients with concomitant other congenital heart disease (CHD) needs further exploration to test the hypothesis whether CHD itself, the concomitant prior cardiac surgery, or other factors are associated with this faster progression.

The current indication for surgery is mainly based on DSS severity and prevention of progressive aortic regurgitation.[45-47] This thesis showed that initial severity of DSS is not associated with DSS progression over time which is another contrast to the existing paediatric studies.[44,48,49] Also aortic regurgitation does not significantly progress over time.[50] Given this information, the current indication for DSS surgery according to the American guidelines seems too aggressive by applying the cut-off value of 50 mmHg for the left ventricular outflow tract (LVOT) peak gradient and may need a revision.[45]

In our study concerning the surgical outcome of DSS in adults, the re-operation rate for DSS was 1.8% per patient-year (Chapter 12) and comparable to other large series.[51,52] Although this rate appears to be low, given the excellent survival of patients after DSS surgery, a majority will require a reoperation for recurrent DSS later in life. Postoperative mild aortic regurgitation is common, but not progressive. Surprisingly, older age at the time of DSS diagnosis is a strong predictor for an increasing postoperative LVOT gradient which may be explained by aging itself or the fact that when DSS is discovered late in adulthood, patients might be in an advanced stage of the disease. As expected, progression of the postoperative LVOT gradient and incomplete removal of the LVOT obstruction are risk factors for re-operation. Curiously, female gender is a strong predictor for re-operation for DSS too, possibly due to hormonal and/or genetic changes and future studies have to explore the pathophysiological background of this gender difference further.[53,54]

With regard to myectomy, several hypotheses for recurrence of DSS exist55 and evidence about the value of an additional myectomy to decrease DSS recurrence is conflicting.[52,56-61] Chapter 12 showed that myectomy was of no additional value with regard to preventing reoperations and did not decrease postoperative LVOT gradient progression rate. In addition, myectomy was associated with an increase in complete AV-block. Given these observations, additional myectomy should not be performed routinely.

CHOICE FOR AORTIC VALVE SUNSTITUTE IN YOUNG FEMALE PATIENTS WITH AS

When a young female patient requires aortic valve replacement, she needs to be counselled on the advantages and disadvantages of each available valve substitute including the potential pregnancy-associated complications accompanying these valve substitutes. Evidence on these clinically relevant issues is scarce.

Pregnancy itself induces several alterations in the maternal body such as an increase in blood volume, cardiac output, and heart rate, a decrease in systemic vascular resistance, and alterations in the coagulation cascade which result in hypercoagulability.[62-64] Chapter 13 of this thesis described that, although survival is excellent, pregnancy after AVR with a human tissue valve or mechanical prosthesis is associated with serious maternal cardiac, obstetric, or perinatal complications in 50% of the patient population. Especially mechanical valve recipients are at risk for maternal cardiac and perinatal complications. Heart failure and arrhythmias were reported relatively common in mechanical valve recipients and may be related to the increased hemodynamic forces on the static mechanical valve prosthesis during pregnancy and labour. Additionally, it is difficult to provide adequate anti-coagulation therapy in mechanical valve recipients due to the altered coagulation cascade which indirectly may contribute to maternal morbidity and even mortality.[64] In contrast, surprisingly, almost all newborns of mechanical valve recipients were delivered without excessive maternal haemorrhage during labour or caesarean section despite anticoagulation therapy. A limitation of the study in Chapter 13 is the lack of an (universal) anticoagulation protocol because most patients became pregnant before the introduction of the recent European Society of Cardiology (ESC) guidelines on the management of cardiovascular disease during pregnancy.[65] The clinical implementation of these current ESC guidelines results hopefully in a decrease of anticoagulation associated complications. Finally, preterm delivery was a common complication regardless of the implanted valve substitute, but especially in mechanical valve recipients. As preterm delivery is the leading cause of infant

morbidity and mortality, it is important to understand the underlying mechanism and to attempt -if possible- to reduce iatrogenic induced preterm deliveries.[66] In this study, induced preterm deliveries were mostly performed because of maternal cardiac reasons. Possibly, the multidisciplinary team of treating physicians is over-cautious with this particular patient group and therefore intervenes earlier.

Given our observations on pregnancy after AVR, for young female patients who may contemplate pregnancy, human tissue valves seem the favourable aortic valve substitutes with excellent hemodynamic performance and absent need for anticoagulation therapy although careful obstetric monitoring is necessitated and valve durability is limited.[67] Nevertheless, pregnancy may potentially affect human tissue valve durability. Evidence about pregnancy-associated valve degeneration of bioprosthesis remains conflicting. Biological valve prosthesis have been reported to degenerate faster during or shortly after pregnancy[68] while more recent studies showed no long term pregnancy-associated degeneration of bioprosthesis.[69,70] Chapter 14 of this thesis showed that the durability of pulmonary autografts and homografts is not influenced by pregnancy as measured by the need for homograft or pulmonary autograft valve reoperation and echocardiographic valve function over time. A recent randomized controlled trial showed that pulmonary autograft implantation is superior over homograft implantation with regard to patient survival and valve durability.[67] However, the problem of neo-aortic root dilatation and regurgitation which necessitates a reoperation later in life, has still to be solved.[67,71,72] Individual counseling of young female patients who require AVR should include information on the (dis)advantages of the different available valve substitutes, the corresponding potential pregnancy-associated maternal and fetal complications, and the risk of a reoperation later during life. These (surgical) aspects as well as informed patient preferences are the basis for informed shared decision making to select the most appropriate aortic valve substitute in the individual patient.

CONCLUSIONS

In conclusion, several important insights emerge from this thesis:

1. The heterogeneous natural history of AS disease demands careful monitoring of patients with (a)symptomatic AS disease, employing uniform standardized diagnostic criteria for assessment and description of AS disease severity.
2. LV systolic deformation parameters should be considered as additional, early markers of subendocardial ischemia since they add additional information above the standard echocardiographic parameters in contemporary practice which may allow earlier diagnosis of LV dysfunction.

3. The observation that many symptomatic patients with severe AS are not referred for evaluation for invasive treatment, emphasizes the need for a systematic evidence-based multidisciplinary team approach to optimise individual treatment selection.
4. Patients with symptomatic AS disease have a markedly reduced quality of life. Aortic valve replacement in patients with symptomatic AS disease is associated with a marked improvement of quality of life.
5. Isolated DSS progresses slowly in adulthood.
6. Surgery for DSS shows excellent long-term results and is postoperatively accompanied by mild aortic regurgitation and slowly increasing LVOT gradient. Myectomy should be only performed in case of marked septal hypertrophy and re-operation is indicated when the peak LVOT gradient approaches 80 mmHg.
7. Cardiac maternal, obstetric, and perinatal complications are common in young female patients with aortic valve substitutes, especially in mechanical valve recipients.
8. There is no association between pregnancy and the durability of pulmonary autografts and aortic homografts as measured by valve function and dimensions, and the need for re-operation. Human valve substitutes therefore offer young female patients who require aortic valve or root replacement a good biological solution.

CLINICAL IMPLICATIONS, RECOMMENDATIONS AND PROSPECTS

The knowledge emerging from this thesis may be helpful in clinical practice in several ways.

This thesis emphasizes both the heterogeneous nature of AS disease and the varying methods to assess AS disease and intensifies the call for uniform and careful monitoring of patients. Not only patients, but also clinicians and scientists will greatly benefit from uniform and careful monitoring, since it allows for standardization of clinical care and the potential to better compare outcome reports between institutions. National and international registries may also play an important role in this regard.

In an effort to identify potential genetic, anatomic (echocardiographic), and clinical predictors for the onset of AS disease and its progression, several aspects should be highlighted. First, long-term serial echocardiographic studies are needed which by using LV deformation parameters in combination with electrocardiographic strain, identify patients with subendocardial ischemia and may help clinicians to optimize the timing of (surgical) aortic valve intervention. Second, an

international tissue bank of aortic valves (and roots) donated by patients of all ages would greatly enhance basic biological research of the aortic valves. As biomarkers emerge on the horizon and their added value is investigated for the different diseases in AS spectrum, it is likely that this research accelerates the identification of potential, new predictors for faster disease progression. It is also expected that tissue engineered heart valves may help in providing the ultimate living and durable aortic valve substitute and potentially decrease the use of mechanical devices which require life-long anticoagulation therapy.

The observation that a substantial part of the symptomatic patients with severe AS disease does not undergo aortic valve (surgical) intervention will hopefully encourage physicians to refer patients for multidisciplinary heart team discussion to offer each patient an objective patient tailored and individualised treatment advice. Also the finding that symptomatic patients with severe AS disease have a markedly decreased quality of life which improves after (surgical) intervention, hopefully stimulates physicians to take quality of life into account when considering the different treatment options and furthermore, as potential tool to optimize the timing of treatment.

In case of present concomitant other CHD in patients with DSS, treating physicians should be alert of potentially faster DSS progression with necessitates cautious patient monitoring. DSS severity should not be used as only criterion for intensifying surveillance or performing surgery. In addition, on the basis of expected progressive aortic regurgitation in adult patients with conservatively treated DSS, prophylactic surgery to prevent future valve damage seems not justified. Given this information, the current indication for DSS surgery can be seen as aggressive in applying the cut-off of 50 mmHg for the LVOT peak gradient as formulated in the American guidelines and may need a revision. Additional myectomy for DSS should be considered very carefully and seems only justified in patients with clear septal hypertrophy.

Finally, the high occurrence of pregnancy-associated complications in female AVR patients should be confirmed by larger cohort studies, preferable in a large international registry setting to ascertain sufficient numbers which include all currently available aortic valve prostheses.

As pregnancy-associated complications are common, careful and frequent monitoring during pregnancy and postnatal period by a multidisciplinary team is recommended.

Information on the occurrence of pregnancy- and prosthetic valve-associated complications should be part of preconceptional counselling as well as part of the consultations during pregnancy. In addition, since pregnancy is not associated with human tissue valve durability, pulmonary autografts and aortic homografts provide

a suitable biological valve substitute in young female patients who need an AVR and (may) contemplate pregnancy, at the cost of a reoperation later in life. Also here, informed patient preferences should be part of the shared decision making process aiming for the most suitable treatment for the individual patient.

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Van de maan af gezien zijn we allen even groot.

Multatuli

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Summary

This thesis provides an insight in several aspects of the natural history, the different treatment options, and prognosis of adult patients with aortic stenosis (AS).

Chapter 1 describes the prevalence of aortic stenosis, the disease spectrum, the way in which it is diagnosed, today's treatment options, and patient prognosis including pregnancy. Aortic stenosis is a common disease among elderly, the prevalence of this disease increases with age up to 5% among people aged over 75 years. Within 38 years, in 2052, the estimated world population will have increased to 9.3 billion of whom at least 280 million inhabitants will have AS disease that requires treatment.

Chapter 2 and 3 focus on the progression of AS disease and the factors potentially associated with AS progression and clinical outcome. In addition, chapter 2 also provides a historical perspective of AS disease.

In literature, AS progression rates varies widely in usually small study populations. Therefore, chapter 3 presents a systematic literature review on the rate of AS progression in adults patients. The meta-analysis showed a pooled annual progression rate of the peak aortic gradient of 3.7 mmHg/year in randomised controlled trials and 6.0 mmHg/year in observational studies. Due to the heterogeneous nature of AS disease, the various methods of monitoring and individual patient factors, optimal and uniform monitoring of AS disease is needed to ultimately assist in tailoring the best treatment for the individual patient.

Chapter 4 emphasizes the course of severe AS disease in symptomatic patients who underwent medical treatment, open heart surgery or transcatheter aortic valve implantation. In general, elderly patients have an increased morbidity and mortality after a surgical or transcatheter intervention as compared with younger patients. Therefore, management decisions in elderly high-risk patients with severe symptomatic AS should be made individually and based on patients' life expectancy and quality of life, patients' wishes, and comorbidities. Medical treatment could be a better option in a 85-year old patient with severe AS, mild angina and co-morbidities as compared to a 85-year old patient with severe AS, congestive heart failure and no further co-morbidity.

Chapter 5 evaluates progression of AS disease and potential predictors for AS progression with a mixed-model analysis of serial echocardiographic aortic valve area measurements in 186 patients in the multicenter prospective AVARIJN cohort study. Analysis of AS progression is usually done with standard statistical methods which introduce bias. Therefore, the more advanced mixed-model analysis was selected for these study. On average, AVA decreased -0.034cm^2/year in adult patients

with severe aortic stenosis. In particular older female patients with severe AS who present with a relatively large AVA have the highest rates of AS disease progression, over a 2 year time period.

Chapter 6 presents a broad spectrum of left ventricular (LV) rotation parameters to understand the mechanical properties of the LV in AS disease in patients with an aortic valve area <2.0 cm^2 and LV ejection fraction >50%. The results were compared to age-matched healthy control patients. The LV peak systolic twist increases in patients with AS disease and was proportionally to the severity of LV outflow obstruction. This might serve as a compensatory mechanism to maintain systolic LV function in the pressure overloaded LV. Diastolic untwisting rate was decreased in patients with AS.

Chapter 7 provides insight in the association between LV longitudinal velocities, a marker for subendocardial ischemia, and electrocardiographic ST-segment depression (strain) in 122 patients with severe AS with or without angina. Patients with strain had lower mean and septal systolic mitral annular velocities and a higher LV mass. Electrocardiographic strain was a predictor for lower LV velocities and could be a potential tool for identifying patients at risk for sudden cardiac death in patients with severe AS.

Chapter 8, 9 and 10 describe the AVARIJN study, a multicenter prospective cohort study which included 191 patients with severe AS in the Rotterdam area.

Chapter 8 analyzes the treatment strategy and survival by assessing clinical and echocardiographic assessments at baseline, 6, 12 and 24 months. The 2-year cumulative incidence of aortic valve replacement or transcatheter aortic valve implantation was 56% in symptomatic patients. In particularly, elderly symptomatic patients with co-morbidities did not undergo invasive treatment. The 2-year survival of these symptomatic surgical treated patients was 90% as compared to 73% of the symptomatic conservatively treated patients. In addition, 68% of the asymptomatic patients became symptomatic during the 2-year follow-up period, illustrating the progressive nature of AS that demands watchful waiting.

Chapter 9 provides insight in the quality of life of both symptomatic and asymptomatic AVARIJN patients by assessing the SF-36v2 Health Survey at baseline, 6, 12 and 24 months. It It turned out that even minor symptoms have major impact on patient well-being and result in a strongly impaired quality of life as compared to the general age-matched Dutch population. The quantification of this burden by using the SF-36v2 can assist in tailoring the best individual treatment.

Chapter 10 focuses further on the quality of life in symptomatic AVARIJN patients who were treated either conservatively or surgical. After aortic valve replacement, patients experience a better physical quality of life, but also general health perception, vitality and emotional aspects improve to the level of the general age-matched Dutch population. In conservatively treated symptomatic patients who survive the long term, especially physical quality of life worsens over time.

Chapter 11 and 12 describe the course and outcome of patients with discrete subaortic stenosis (DSS) who were treated conservatively or previously underwent surgery.

Chapter 11 evaluates the natural history of 149 conservatively treated DSS patients and identified risk factors for progression of DSS, aortic regurgitation (AR) and intervention-free survival. The median age was 20 years and median follow-up was 6.3 years. The baseline peak LV outflow tract (LVOT) gradient was 32 mmHg and progresses slowly into adulthood with 0.8 mmHg/year. Not baseline LVOT gradient or age, but presence of associated congenital heart disease (CHD) was associated with a faster DSS progression. Therefore, these patients should be monitored cautiously. Mild AR was common, but did not evidently progress over time. The median intervention-free survival was 16 years and was associated with baseline LVOT gradient, DSS progression and AR.

Chapter 12 presents the surgical outcome of 313 adult patients who previously underwent surgery for DSS. The mean age at baseline was 20 years and median follow-up was 13 years. The peak instantaneous LVOT gradient decreased from 76 mmHg preoperatively to 15 postoperatively and thereafter increased over time with a rate of 1.3 mmHg/year. Mild regurgitation was common, but did not evidently progress over time. Eighty percent required at least 1 re-operation and this risk was not reduced by additional myectomy. Predictors for reoperation were female sex and progression of the LVOT gradient.

Although survival is excellent after DSS surgery, progression of the LVOT gradient postoperatively is slow, and mild AR is common, reoperation for recurrent DSS is not uncommon. Due to the increased risk of complete heart block, additional myectomy should not be performed routinely.

Chapter 13 and 14 presents the results of the DIAMOND study, a single-center retrospective cohort study which assessed pregnancy outcomes in patients who previously underwent AVR and evaluate the potential influence of pregnancy on the durability of human tissue valve substitutes.

Chapter 13 provides insight in the 67 pregnancy outcomes of 40 women who had received an pulmonary autograft, homograft, or mechanical valve in aortic

position in the Erasmus University Medical Center from 1987 to 2011. Mean age at first pregnancy was 30 years and 55 pregnancies were completed. There was no maternal mortality, but 1 fetal death and 1 neonatal death. Maternal cardiac complications occurred in 13% and obstetric complications in 38% of the completed pregnancies and emphasized careful obstetric monitoring. Especially mechanical valve recipients experienced the greatest incidence of both cardiac and obstetric complications. In the discussion for the optimal aortic valve substitute in a young woman, human tissue valves should be considered.

Chapter 14 shows that pregnancy did not influence the durability of human aortic valve substitutes in 108 women who underwent 59 homograft and 49 pulmonary autograft procedures. Homograft recipient without pregnancies were older than homograft recipients who became pregnant. There were no other differences in patient characteristics and freedom of reoperation between the pregnant and non-pregnant women in both valve groups. Pregnancy was not associated with changes in aortic gradient, AR, annular and sinotubular junction diameter for either valve substitute. Therefore, human tissue valves should be considered as a suitable aortic valve substitute in young patients who (may) contemplate pregnancy.

Chapter 15 provides a general discussion, conclusions, clinical implications, recommendations and prospects emerging from this thesis. To optimize management of (female) patients with (severe) AS, several fields should be of interest for patients, physicians, and scientists.

Regarding the diagnostic field, a uniform classification and assessment of AS worldwide would allow for enhanced estimation of AS progression, identify predictors for this progression and enhance comparability of outcome reports. Potential new diagnostic (bio)markers could also help the diagnostic process. However, both need to be validated in longitudinal serial (echocardiographic) AS studies or registries. An international tissue bank of aortic valves (and roots) would greatly enhance biological research of aortic valves.

In the field of treatment and prognosis, available treatment options should be individually weighed and selected for each patient including preoperative risk factors, surgical aspects, prognosis including improvement of experienced quality of life, and informed patient preferences.

The high occurrence of pregnancy-associated complications demand larger cohort studies to confirm these results. Nevertheless, objective and comprehensible information on the (dis)advantages of each aortic valve substitute including pregnancy-associated complications should be part of the preconceptional counselling of young women who require aortic valve replacement as well as part of the consultation during pregnancy.

I don’t believe medical discoveries are doing much to advance human life. As fast as we create ways to extend it we are inventing ways to shorten it.

C.N. Barnard

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Samenvatting

Dit proefschrift biedt inzicht in enkele aspecten van het natuurlijk beloop, de verschillende behandelmogelijkheden en de prognose van volwassen patiënten met ernstige aortaklepstenose (AS).

Hoofdstuk 1 beschrijft de prevalentie van AS, het ziektespectrum, de manier waarop dit wordt gediagnosticeerd en de prognose van patiënten inclusief zwangerschap. AS is een veelvoorkomende ziekte onder ouderen; de prevalentie van deze ziekte loopt op tot 5% van de mensen ouder dan 75 jaar. De verwachting is dat binnen 38 jaar, in 2052, de wereldpopulatie toeneemt naar 9.3 miljard waarvan tenminste 280 miljoen mensen een ernstige AS zullen hebben waarvoor zij moeten worden behandeld.

Hoofdstuk 2 en 3 richten zich op de progressie van de ziekte AS en de factoren die mogelijk van invloed zijn op AS progressie en klinische uitkomst. Aanvullend beschrijft hoofdstuk 2 de ziekte AS in historisch perspectief.

In de literatuur varieert de toename in AS progressie fors in de vaak kleine studiepopulaties. Daarom beschrijft hoofdstuk 3 een systematische literatuur review over de toename in AS progressie in volwassen patiënten. De meta-analyse toont een gepoolde jaarlijkse progressie van de maximale aortagradiënt van 3.7 mmHg/jaar in gerandomiseerde gecontroleerde trials en 6.0 mmHg/jaar in observationele studies. Vanwege het heterogene beloop van de ziekte AS en de verschillende methoden van monitoren en individuele patiëntfactoren, is optimale en uniforme monitoring van de ziekte AS nodig om uiteindelijk te helpen bij de bepaling van de beste behandeling voor de individuele patiënt.

Hoofdstuk 4 benadrukt het beloop van ernstige AS in symptomatische patiënten die medicamenteuze behandeling, open hart chirurgie of transcutane aortaklep implantatie ondergaan. In het algemeen hebben oudere patiënten een hogere morbiditeit en mortaliteit na een chirurgische of transcutane interventie vergeleken met jongere patiënten. Dit is de reden dat een behandelbeslissing in oudere, hoog-risico patiënten met ernstige symptomatische AS individueel gemaakt moet worden en gebaseerd moet zijn op de levensverwachting, kwaliteit van leven, wensen en comorbiditeiten van de patiënt. Medicamenteuze behandeling kan een betere optie zijn voor 85-jarige patiënt met ernstige AS, milde angina en comorbiditeiten, terwijl een 85-jarige patiënt met ernstige AS en hartfalen zonder comorbiditeiten waarschijnlijk meer gebaat is bij een invasieve behandeling.

Hoofdstuk 5 evalueert AS progressie en potentiële predictoren voor deze progressie met een mixed-model analyse van seriële echometingen van het aortaklepoppervlak

in 186 patiënten in de multicenter prospectieve AVARIJN cohort studie. Analyse van AS progressie wordt meest verricht met standaard statistische methoden welke bias introduceren, derhalve werd gekozen voor de meer geavanceerde mixed-model analyse in deze studie. In volwassen patiënten met ernstige AS nam het aortaklepoppervlak gemiddeld met 0.034cm^2/jaar af. In het bijzonder oudere vrouwelijke patiënten met ernstige AS die zich presenteren met een relatief groot aortaklepoppervlak, hebben de snelste ziekteprogressie gemeten over een periode van 2 jaar.

Hoofdstuk 6 presenteert een breed spectrum aan linker ventrikel (LV) rotatie parameters om inzicht te krijgen in de mechanische eigenschappen van het LV in AS in patiënten met een aortaklepoppervlak <2.0 cm^2 en LV ejectiefractie >50%. De resultaten werden vergeleken met gezonde, leeftijd-gematchte controle patiënten. De LV systolische 'twist' nam toe in patiënten met AS en was proportioneel aan de ernst van de LV outflow obstructie. Mogelijk dient dit als compensatiemechanisme om zodoende de systolische LV functie in de door druk overbelaste LV te handhaven. Diastolische 'untwisting' snelheid was afgenomen in patiënten met AS.

Hoofdstuk 7 geeft inzicht in de associatie tussen longitudinale snelheden van het LV, een marker voor sub-endocardiale ischemie, en elektrocardiografische ST-segment depressie (strain) in 122 patiënten met ernstige AS, met of zonder angina. Patiënten met strain hadden een lagere gemiddelde en septale systolische mitraalannulus snelheid en een hogere LV massa.

Electrocardiografische strain was een predictor voor lagere LV snelheden en kan een mogelijke middel zijn voor identificatie van patiënten met ernstige AS die een verhoogd risico lopen op plotse hartdood.

Hoofdstuk 8, 9 en 10 beschrijven de AVARIJN studie, een multicenter prospectieve cohort studie waarin 191 werden geïncludeerd met ernstige AS in de regio van Rotterdam.

Hoofdstuk 8 analyseert de behandelstrategie en overleving met behulp van klinische en echocardiografische metingen bij patiënten-inclusie in de studie en daarna op 6, 12 en 24 maanden. De cumulatieve 2-jaars incidentie van aortaklepvervanging en transcutane aortaklepimplantatie was 56% in symptomatische patiënten. In het bijzonder oudere symptomatische patiënten met comorbiditeiten ondergingen een conservatieve behandeling. De 2-jaars overleving van deze symptomatische, chirurgisch behandelde patiënten was 90% vergeleken met 73% van de conservatief behandelde symptomatische patiënten. Aanvullende bleek dat 68% van de asymptomatische patiënten symptomatisch werden gedurende de 2 jaar

follow-up. Dit illustreert het progressieve beloop van AS dat 'watchful waiting' vereist.

Hoofdstuk 9 biedt inzicht in de kwaliteit van leven in zowel symptomatische als wel asymptomatische AVARIJN patiënten door middel van de SF-36v2 Health Survey afgenomen bij patiënten-inclusie in de studie en daarna op 6, 12 en 24 maanden. Het bleek dat zelf minimale symptomen een grote invloed hebben op het welzijn van patiënten en resulteren in een sterk verminderde kwaliteit van leven wanneer vergeleken met de algemene, leeftijd-gematchte Nederlandse bevolking. De kwantificatie van deze (gezondheids)belasting door middel van de SF-36v2 kan bijdragen bij het bepalen van de beste individuele behandeling.

Hoofdstuk 10 gaat dieper in op de kwaliteit van leven in symptomatische AVARIJN patiënten welke conservatief of chirurgisch werden behandeld. Patiënten ervaren na een aortaklepvervanging een betere fysieke kwaliteit van leven, maar ook verbeteren het algemene gezondheidsbesef, vitaliteit en emotionele aspecten tot het niveau van de algemene, leeftijd-gematchte Nederlandse bevolking. In de conservatief behandelde symptomatische patiënten die overleefden was het voornamelijk de fysieke kwaliteit van leven die afnam over tijd.

Hoofdstuk 11 en 12 beschrijven het beloop en de uitkomst van patiënten met discrete subaortale stenose (DSS), in een multicenter setting, welke conservatief dan wel chirurgisch waren behandeld.

Hoofdstuk 11 evalueert het natuurlijk beloop van 149 conservatief behandelde DSS patiënten en identificeert risicofactoren voor DSS progressie, aortaklep regurgitatie en interventie-vrije overleving. De mediane leeftijd was 20 jaar en de mediane follow-up was 6.3 jaar. De baseline piek linker ventrikel outflow tract (LVOT) gradiënt was 32 mmHg en nam langzaam toe met 0.8 mmHg/jaar. Niet de baseline LVOT gradiënt of leeftijd waren geassocieerd met een snellere DSS progressie, maar de aanwezigheid van een geassocieerde congenitale hartaandoening. Om deze reden dienen deze patiënten zorgvuldig gevolgd te worden. Milde AR kwam vaak voor, maar toonde geen evidente progressie over tijd. De mediane interventievrije overleving was 16 jaar en was geassocieerd met baseline LVOT gradiënt, DSS progressie en AR.

Hoofdstuk 12 presenteert de chirurgische uitkomst van 313 volwassen patiënten die eerder DSS chirurgie hadden ondergaan. De gemiddelde leeftijd bij aanvang van de studie was 20 jaar en de mediane follow-up was 13 jaar. De piek 'instantaneous' LVOT gradiënt reduceerde van 76 mmHg preoperatief naar 15 postoperatief en nam daarna met een snelheid van gemiddeld 1.3 mmHg/jaar toe.

Milde regurgitatie kwam vaak voor, maar toonde geen evidente progressie over tijd. Tachtig procent had tenminste 1 reoperatie nodig en het risico hierop werd

niet gereduceerd door een additionele myectomie. Predictoren voor een reoperatie waren vrouwelijk geslacht en progressie van de LVOT gradiënt. Alhoewel de overleving na DSS chirurgie excellent was, progressie van de LVOT gradiënt postoperatief langzaam was en milde regurgitatie vaak voorkwam, bleek reoperatie voor recidief DSS niet ongewoon. Vanwege het risico op een totaal hartblok dient een additionele myectomie niet routinematig uitgevoerd te worden.

Hoofdstuk 13 en 14 tonen de resultaten van de DIAMOND studie, een singlecenter retrospectieve cohort studie die de uitkomsten van zwangerschap in patiënten die een aortaklepvervanging hadden ondergaan evalueert alsmede de potentiële invloed van zwangerschap op de duurzaamheid van humane weefselkleppen.

Hoofdstuk 13 biedt inzage in de uitkomsten van 67 zwangerschappen van 40 vrouwen die een pulmonale autograft, homograft of mechanische klep in aorta positie hadden ontvangen in het Erasmus Universitair Medisch Centrum van 1987 tot 2011. De gemiddelde leeftijd tijdens de eerste zwangerschap was 30 jaar en 55 zwangerschappen waren voldragen. Er was geen maternale mortaliteit, maar wel 1 foetale dood en 1 neonataal overlijden. Maternale cardiale complicaties kwamen voor bij 13% en obstetrische complicaties bij 38% van de voldragen zwangerschappen en benadrukt een zorgvuldige obstetrische monitoring. Met name mechanische kleppatiënten ondervonden de meeste cardiale en obstetrische complicaties. In de discussie omtrent de optimale aortaklepvervanger voor jonge vrouwen dienen humane weefselkleppen overwogen te worden.

Hoofdstuk 14 toont dat de duurzaamheid van humane aortaklepvervangers niet beïnvloed werd door zwangerschap in 108 vrouwen die 59 homograft en 49 pulmonale autograft procedures ondergingen. Homograft patiënten zonder zwangerschap waren ouder dan homograft patiënten die wel zwanger werden. Er waren geen andere verschillen in patiënt kenmerken en vrijheid van reoperatie tussen zwangere vrouwen en niet zwangere vrouwen in beide klepgroepen. Zwangerschap was niet geassocieerd met veranderingen in aortagradiënt, aorta regurgitatie, diameter van annulaire en sinotubulaire overgang voor elke van de klepvervangers.

Een humane weefselklep dient derhalve overwogen te worden als een geschikte aortaklep substituut in jonge patiënten die een zwangerschap overwegen.

Hoofdstuk 15 beschrijft de algemene discussie, conclusies, klinische implicaties, aanbevelingen en prospectus voortkomend uit dit proefschrift. In het optimaliseren van de behandelstrategie van (vrouwelijke) patiënten met (ernstige) AS kunnen diverse aspecten interessant zijn voor patiënten, dokters en wetenschappers.

Inzake het diagnostisch veld, een uniforme classificatie en beoordeling van AS wereldwijd zou de bepaling van AS progressie kunnen optimaliseren, predictoren

voor deze progressie identificeren en de vergelijkbaarheid van studie uitkomsten verbeteren.

Potentieel nieuwe diagnostische (bio)markers kunnen ook een bijdragen leveren aan het diagnostisch proces. Niettemin dienen beide gevalideerd te worden in longitudinale seriële (echocardiografische) studies of registraties. Een internationale weefselbank van aortakleppen (en wortels) zou een grote aanwinst zijn voor het experimenteel onderzoek van aortakleppen.

Op het gebied van behandeling en prognose dienen diverse behandelopties op individuele basis gewogen en geselecteerd te worden voor elke patiënt inclusief de preoperatieve risicofactoren, chirurgische aspecten, prognose inclusief verbetering van de ervaren kwaliteit van leven en 'informed patient preferences'.

Het hoge percentage van zwangerschap-geassocieerde complicaties vraagt om grote cohortstudies om de in dit proefschrift beschreven bevindingen te kunnen bevestigen. Desniettemin dient het objectief en in begrijpelijke taal informeren van de patiënt over de voor- en nadelen van de verschillende aortaklepsubstituten, inclusief zwangerschaps-geassocieerde complicaties, onderdeel te zijn van de pre-conceptionele counseling van jonge vrouwen die een aortaklepvervanging nodig hebben, alsmede onderdeel van de consulten tijdens de zwangerschap.

Friends applaud, the comedy is over.

L. van Beethoven

Dankwoord
Curriculum vitae
Portfolio
Publications
Abbreviations

DANKWOORD

Dit proefschrift, een trots eindresultaat van mijn promotieonderzoek, heeft mij geleerd dat doorzettingsvermogen en samenwerking de key issues zijn in het onderzoeksbestaan.

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volume van onze zoons! Ik hoop van harte dat we nog lang van elkaar, Koenraad en Jan-Wycherd mogen genieten.

Koenraad, mama's grote letterboek is af (je kan dit inmiddels al een beetje lezen); nu kunnen we eindelijk samen op strooptocht met onze jongensclub!

Jan-Wycherd, je krijgt er nog niet veel van mee, maar papierscheuren kan je als de beste, zo ook uit mama's boek...

CURRICULUM VITAE

Helena J. Heuvelman was born in The Netherlands. After graduating high school, she started her training as operating theatre nurse in 1996 in the IJsselland Hospital, Capelle aan den IJssel. After graduating in 1999, she worked in the Medical Center Rotterdam Zuid, location Zuider in which she first meet the field of Cardio-Thoracic Surgery by assisting coronary artery bypass grafting procedures. The author then started her medical training at the University of Utrecht and worked at the Department of Cardio-Thoracic and Vascular Surgery of the University Medical Center of Utrecht. She started her scientific career as medical student by writing a systematic review under supervision of prof.dr. J.J.M. Takkenberg (Cardio-Thoracic Surgery) en prof.dr. J.W. Roos-Hesselink (Cardiology) of the Erasmus University Medical Center in Rotterdam. After graduating medical school in 2008, the author started her PhD training in Rotterdam in the field of aortic valvular stenosis under supervision of prof.dr. A.J.J.C. Bogers (Head Department of Cardio-Thoracic Surgery) and prof.dr. J.J.M. Takkenberg. She took over and completed the AVARIJN study from dr. M.W.A. van Geldorp and designed, continued and completed the DIAMOND study. The author also worked together with dr. N.M. Rajamannan of the Northwestern University Feinberg School of Medicine, National Institute of Heallth and Mayo Clinic, on the subject of the progression of aortic valvular stenosis. This subject was also her master thesis of the Master of Clinical Health Sciences with subspecialisation in Clinical Epidemiology, obtained in 2009 at the Netherlands Institute of Health Sciences (prof. dr. A. Hofman, Science director NIHES).

In 2012, the author worked as resident on the Emergency Department of the Amsterdam Medical Center. In April 2013, she started as resident-in-training Insurance Medicine under supervision of drs. R.W. van Hes and will continue this training in spring 2015 at The Netherlands School of Public & Occupational Health in Utrecht.

Last, but not least, the author is married to Marinus and mother of two wonderful sons: Koenraad and Jan-Wycherd.

PORTFOLIO

Name PhD student	: Helena J. Heuvelman
Department	: Cardio-Thoracic Surgery
Research School	: COEUR
PhD period	: 2008-2014
Promotor	: Prof.dr. A.J.J.C. Bogers
Copromotor	: Prof.dr. J.J.M. Takkenberg

PhD training	Year	Workload (ECTS)
Research skills		
- Master in Health Sciences, specialisation of Clinical Epidemiology	2004-2009	30.4
- BROK course	Nov 2008	0.9
- BROK re-registration	Sep 2014	0.1
- Regression analysis for Clinicians	Jan 2009	1.9
- CPO course	Feb 10th 2009	0.3
- Biomedical English Writing and Communication	Apr-Jul 2009	4.0
- Repeated Measurements	Feb-Mar 2011	1.4
In-depth courses		
- Arrythmia Research Methodology (COEUR)	Jan 2009	1.5
- Congenital Heart Disease (COEUR)	Feb 2009	1.5
- Peripheral and Intracranial Obstructive Vascular Disease (COEUR)	Apr 2009	1.5
- Pathophysiology of ischemic heart disease (COEUR)	Feb 2012	1.5
Presentations		
- Aortic valve stenosis in Rijnmond (2nd Nursing Symposium Thoraxcenter Erasmus MC)	May 2009	0.6
- Aortic valve progression: A systematic review (Joint Meeting SHVD & HVSA)	Jun 2009	0.6
- Progression of aortic valve stenosis in elderly patients: timing and choice of treatment (COEUR)	May 2010	0.6
- Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: Insights from the AVARIJN study (Joint Meeting SHVD & HVSA)	June 2011	0.3
- Does pregnancy influence the durability of human aortic valve substitutes? (Joint Meeting SHVD & HVSA)	April 2012	0.6
- Pregnancy outcomes of women with aortic valve substitutes (Joint Meeting SHVD & HVSA)	April 2012	0.6

International conferences		
- 5th Biennial Meeting - The Society for Heart Valve Disease - Berlin	Jun 2009	1.2
- 7th Biennial Meeting - The Society for Heart Valve Disease - Barcelona	Jun 2011	1.2
- 8th Biennial Meeting - The Society for Heart Valve Disease – New York	Apr 2012	1.2
Seminars and workshops		
- Gene and cell based therapies of cerebro and cardiovascular disease (COEUR)	Nov 2008	0.4
- Imaging of carotid bifurcation atherosclerosis. Improving insight and foresight by using biomechanics (COEUR)	Dec 2008	0.4
- Hypertension (COEUR)	Mar 2009	0.4
- Young investigators seminar (NIHES)	Apr 2009	0.4
- New developments in percutaneous revascularisation (COEUR)	Apr 2009	0.4
- Neo-angiogenesis as a treatment of myocardial ischemia (COEUR)	May 2009	0.4
- Vascular imaging: Atherosclerosis and biomechanics (COEUR)	June 2010	0.4
- Coarctation of the aorta (COEUR)	Nov 2010	0.4
Other		
- Meetings of the Dutch Association for Thoracic Surgery	2008-2012	0.9
- COEUR Annual PhD-day	2010-2012	0.9
Teaching activities	**Year**	**Workload (ECTS)**
Lecturing		
- Introduction in Evidence Based Medicine for 2nd year medical students	2009-2010	0.6
- Supervising/coaching 4th year medical students during research project	2009-2012	2.0
- Minor Congenital Heart Disease	2010-2011	1.8
Supervising Master's theses		
- Long term outcome of aortic valve replacement in young females & influence of pregnancy on durability (MSc Clinical Research)	2010-2013	4.0
Reviewer for:		
- American Journal of Cardiology	2009-2014	1.0

PUBLICATIONS

Van der Linde D, Roos-Hesselink JW, Rizopoulos D, Heuvelman HJ, Budts W, van Dijk AP, Witsenburg M, Yap SC, Oxenius A, Silversides CK, Oechslin EN, Bogers AJ, Takkenberg JJ. Surgical outcome of discrete subaortic stenosis in adults: a multicenter study. Circulation 2013;127:1184-1191.

Van Dalen BM, Tzikas A, Soliman OI, Heuvelman HJ, Vletter WB, Ten Cate FJ, Geleijnse ML. Assessment of subendocardial contractile function in aortic stenosis: a study using speckle tracking echocardiography. Echocardiography 2013;30:293-300.

Van der Linde D, Takkenberg JJ, Rizopoulos D, Heuvelman HJ, Budts W, van Dijk AP, Witsenburg M, Yap SC, Bogers AJ, Silversides CK, Oechslin EN, Roos-Hesselink JW. Natural history of discrete subaortic stenosisin adults: a multicentre study. Eur Heart J 2013;34:1548-1556.

Van Geldorp MW, Heuvelman HJ, Kappetein AP, Busschbach JJ, Takkenberg JJ, Bogers AJ. The effect of aortic valve replacement on quality of life in symptomatic patients with severe aortic stenosis. Neth Heart J 2013;21:28-35.

Van Geldorp MW, Heuvelman HJ, Kappetein AP, Busschbach JJ, Cohen DJ, Takkenberg JJ, Bogers AJ. Quality of life among patients with severe aortic stenosis. Neth Heart J 2013;21:21-27.

Heuvelman HJ, Arabkhani B, Cornette JM, Pieper PG, Bogers AJ, Takkenberg JJ, Roos-Hesselink JW. Pregnancy outcomes in women with aortic valve substitutes. Am J Cardiol 2013;111:382-387.

Arabkhani B, Heuvelman HJ, Bogers AJ, Mokhles MM, Roos-Hesselink JW, Takkenberg JJ. Does pregnancy influence the durability of human aortic valve substitutes? J Am Coll Cardiol 2012;60:1991-1992.

Heuvelman HJ, van Geldorp MW, Eijkemans MJ, Rajamannan NM, Bogers AJ, Roos-Hesselink JW, Takkenberg JJ. Progression of aortic valve stenosis in adults: a systematic review. J Heart Valve Dis 2012;21:454-462.

Heuvelman HJ, van Geldorp MW, Kappetein AP, Geleijnse ML, Galema TW, Bogers AJ, Takkenberg JJ. Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study. Neth Heart J 2012;20:487-493.

Van Dalen BM, Tzikas A, Soliman OI, Kauer F, Heuvelman HJ, Vletter WB, ten Cate FJ, Geleijnse ML. Left ventricular twist and untwist in aortic stenosis. Int J Cardiol 2011;148:319-324.

ABBREVATIONS

ACC	American College of cardiology
AD	Annular diameter
AHA	American Heart Association
AoI	Aortic regurgitation
AR	Aortic regurgitation
AS	Aortic stenosis
AVA	Aortic valve area
AVR	Aortic valve replacement
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAVS	Calcific aortic valve stenosis
CHD	Congenital heart disease
DSS	Discrete subaortic stenosis
EACTS	European Association of Cardio-Thoracic Surgery
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation
GUCH	Grown-Up Congenital Heart
HOCM	Hypertrophic obstructive cardiomyopathy
HR	Hazard ratio
IQR	Interquartile range
LDL	Low density lipoprotein
LV	Left ventricular / ventricle
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MAG	Mean aortic gradient
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAG	Peak aortic gradient
QoL	Quality of life
RCT	Randomized controlled trial
Rot_{max}	Left ventricular peak systolic rotation during ejection
SE	Standard error
SF-36v2™	Short Form 36 version 2
STE	Speckle tracking echocardiography
STJ	Sinotubular junction
STS	Society of Thoracic Surgery

TAVI	Transcatheter aortic valve implantation
$Twist_{max}$	Instantaneous left ventricular peak systolic twist
Vmax	Transaortic peak velocity
VSD	Ventricular septal defect

...Still another is that no man, on a mountain or elsewhere, gets more out of anything than he puts into it. If it is a discredit to me that I was a step behind Hillary, then I must live with that discredit. But I do not think it was that....

Sherpa Tenzing, 1914-1986