Heart Valve Surgery

Preoperative Assessment and Clinical Outcome

LAILA HELLGREN
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Abstract

A more global analysis of the outcome of heart valve surgery is desirable to reflect the actual benefit for the patient. This thesis focuses on the preoperative assessment of the patient, and the outcome after surgery with regard to operative mortality, long-term survival, valve-related complications, and quality of life.

Magnetic resonance imaging and echocardiography were comparable in assessing severe mitral regurgitation, but did not agree in measuring regurgitant fraction. Natriuretic peptides correlated well to regurgitant fraction on magnetic resonance imaging and to PISA and vena contracta on echocardiography.

The risk of death, myocardial injury and postoperative heart failure after valve surgery has decreased over the last decade whereas the proportion older patients has increased.

Survival is reduced after mitral valve replacement in patients with severe symptoms whereas patients with less symptoms have excellent survival. Older patients are more often severely symptomatic at the time of mitral valve surgery.

Event-free survival is superior in patients with a mechanical prosthesis, but not influenced by valve type in older patients. A mechanical prosthesis is associated with a higher risk of bleeding < 5 years from surgery, especially in older patients; and a bioprosthesis is associated with a higher risk of thromboembolism > 5 years from surgery. Ageing with a mechanical prosthesis implied an increased risk for an adverse event; this was not true for bioprostheses.

Quality of life after complicated heart valve surgery resulted in reduced physical health but equal mental health compared to uncomplicated controls.

Keywords: Heart valve surgery, magnetic resonance imaging, echocardiography, operative mortality, survival, complications, quality of life

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List of Papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I  **Assessment of severe mitral regurgitation - relations between magnetic resonance imaging, echocardiography, and natriuretic peptides.**  
Hellgren L, Landelius J, Stridsberg M, Kvidal P, Ståhle E, Bjerner T.  
*Am J Cardiol.* In press.

II  **Improved results after heart valve surgery over the last decade.**  
Hellgren L, Kvidal P, Ståhle E.  

III  **Survival after mitral valve replacement – rationale for surgery before occurrence of severe symptoms**  
Hellgren L, Kvidal P, Hörte L-G, Krusemo U-B, Ståhle E.  

IV  **Mechanical versus biological prosthesis in relation to age - a study of 3,279 patients.**  
Hellgren L, Granath F, Ekbom A, Ståhle E.  
In progress.

V  **Quality of life after heart valve surgery with prolonged intensive care.**  
Hellgren L, Ståhle E.  
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### Abbreviations

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<tr>
<td>ANP</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
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<td>AVR</td>
<td>Aortic valve replacement</td>
</tr>
<tr>
<td>BNP</td>
<td>Brain natriuretic peptide</td>
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<tr>
<td>BP</td>
<td>Biological prosthesis</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
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<td>CAD</td>
<td>Coronary artery disease</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DVR</td>
<td>Double valve replacement</td>
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<td>EF</td>
<td>Ejection fraction</td>
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<tr>
<td>HAD</td>
<td>Hospital Anxiety and Depression (scale)</td>
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<td>HVR</td>
<td>Heart valve replacement</td>
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<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
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<td>LV</td>
<td>Left ventricular</td>
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<td>MCS</td>
<td>Mental component summary score</td>
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<tr>
<td>MS</td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>MR</td>
<td>Mitral regurgitation</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MVP</td>
<td>Mitral valvuloplasty</td>
</tr>
<tr>
<td>MVR</td>
<td>Mitral valve replacement</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Association Functional Heart Classification</td>
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<td>NHP</td>
<td>Nottingham Health Profile</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical component summary score</td>
</tr>
<tr>
<td>PISA</td>
<td>Proximal isovelocity surface area</td>
</tr>
<tr>
<td>% PY</td>
<td>Percent per year</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RH</td>
<td>Relative hazard</td>
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<tr>
<td>SVD</td>
<td>Structural valve deterioration</td>
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</table>
Introduction

The evaluation of the outcome of heart valve surgery has evolved over time into a systematised process [1,2,3]. There is now increasing awareness of the importance of endpoints other than operative mortality and survival in patients undergoing these surgical procedures. A more global analysis of the outcome of heart valve surgery would be desirable in order to more accurately elucidate the actual benefit for the patient. Thus, the spectrum of outcome measures should include assessment not only of the operative mortality and long-term survival, but also of the all-cause morbidity, postoperative functional capacity, and quality of life. These measures form a composite tool that should always be used when the results after heart valve surgery are to be evaluated.

It has been established that the results of heart valve surgery are not only dependent on the surgical procedure and type of prosthesis, but are also strongly associated with patient-related factors [4]. Any one population of patients referred for heart valve surgery has a complex constitution with considerable heterogeneity regarding risk factors, co-morbidity and age-span. Moreover, the timing of surgery among patients undergoing these operations varies considerably with the symptomatic panorama, which may extend from asymptomatic patients with left ventricular (LV) dysfunction to end-stage disease.

Thus, the evaluation of the outcome is a challenging procedure.

This thesis focuses on the outcome of heart valve surgery with regard to operative mortality, long-term survival, valve-related complications, and quality of life. Aspects of the preoperative assessment of the patient are also considered.
Background

Briefly regarding specific lesions

Aortic stenosis
When the aortic valve area is reduced to one fourth its normal (3-4cm²) size, changes in the circulation normally occur. The ACC/AHA committee has graded the degree of AS as mild (area>1.5cm²), moderate (area>1.0-1.5cm²), or severe (area<1.0cm²) [5]. Progression of the degree of aortic stenosis (AS) has been shown to be approximately 0.3m/s, 7 mmHg, or 0.1 cm² per year with great inter-individual variations. In general, severe stenosis has a mean transvalvular gradient > 50 mmHg if cardiac output is normal. After a long latent period, symptoms of dyspnea, angina or syncope develops.

Aortic regurgitation
Aortic regurgitation (AR) can be caused by abnormal valve leaflets or by enlarged aortic root. AR represents a condition of increased volume overload on the left ventricle which leads to a gradual increase in left ventricular dimensions. AR usually progresses slowly, with annual rate of symptom onset of 6% in those with end-systolic LV dimension of 40-49 mm. Asymptomatic patients with severe regurgitation and moderate ventricular enlargement, should be followed closely until they develop dyspnea or a decrease in exercise tolerance or approach the LV dimensional thresholds for surgery.

Mitral stenosis
The normal mitral valve is 4-5cm². Severe mitral stenosis (MS) is present when the area is reduced to ≤1.0cm² and the mean progression of the stenosis is approximately 0.3 cm² per year. Symptoms develops after a stable course in the early years and progressive acceleration later. Associated conditions such as atrial fibrillation or thromboembolic events are common. Catheter balloon commissurotomy, if not contraindicated, is the method of choice for correction.
Mitral regurgitation
Primary mitral regurgitation (MR) is caused by disease in any of the components of the mitral valve; the leaflets, chordae tendineae, the annulus or the papillary muscles. The most common cause is myxomatous degeneration of the valve. Secondary regurgitation occurs when the LV distorts an otherwise normal valve. The compensated phase may last for many years and ejection fraction is maintained >0.60. The progression of MR has recently been defined to approximately 7.5 ml per year for regurgitant volume and of 5.9 mm² per year for the effective regurgitant orifice. Symptoms include dyspnea and eventually development of atrial fibrillation and pulmonary hypertension.

Preoperative assessment

Symptoms
The decision to submit a patient to heart valve surgery is based on the presence of a severe lesion and, in the majority of cases, the presence or onset of symptoms [5,6,7,8,9]. However, if there is LV dysfunction, surgery can be performed in the asymptomatic stage [10]. The ACC/AHA guidelines for when to perform surgery are quite clear [5]. The indications for surgery are reviewed below:

Indications for aortic valve replacement (AVR) in severe aortic stenosis (AS):
- Symptoms
- Moderate AS + other heart surgery

- Asymptomatic patients with:
  - LV dysfunction
  - Abnormal response to exercise
  - Ventricular tachycardia
  - LV hypertrophy >15 mm
  - Valve area < 0.6 cm²

Indications for AVR in severe aortic regurgitation:
- Symptoms
- CCS class II or greater, with or without coronary artery disease

- Asymptomatic patients with:
  - LV dilatation
  - Severe LV dysfunction
Indications for mitral valve replacement (MVR) or repair in severe mitral stenosis:
- Symptoms
- Recurrent embolic episodes on adequate anticoagulation
- Severe pulmonary hypertension

Indications for MVR or repair in severe mitral regurgitation:
- Symptoms
- Asymptomatic patients with:
  - LV dysfunction
  - Atrial fibrillation and preserved LV function
  - Pulmonary hypertension
  - Reduced LV function and/or LV dilatation (chordal sparing)
  - Valve prolapse, and recurrent ventricular arrhythmias despite medical therapy

The golden standard for evaluation of the severity of a heart valve lesion is echocardiography. Is there a need for other diagnostic methods?

Diagnostic methods
Echocardiography is the method used for assessing the significance of valvular pathology. The heart valves can be analysed quickly and accurately through the use of Doppler ultrasound.

Stenotic lesions
In the patients with a stenotic lesion, the continuity equation approach with Doppler velocity-time integral data and the modified Bernoulli equation are methods used to estimate valve area and pressure gradients. These are reliable tools and many studies have demonstrated excellent concordance of echocardiographic and invasive catheter-based estimates of aortic valve area (AVA) and valve gradients [11-13]. Since echocardiography does not allow direct measurements of intravascular pressure, but permits several assump-
tions, the AVA and the gradients over the valve have to be assessed in combination. In patients with a low gradient and severe stenosis as judged by AVA, a dobutamine stress test can be useful to determine the presence of a fixed stenosis. If there is a discrepancy between clinical and echocardiographic data, catheterisation may be necessary to assess the haemodynamic severity of a stenosis.

As a non-invasive alternative, magnetic resonance imaging (MRI) has recently proved to be reliable and reproducible in assessing stenotic aortic valves [14,15]. The measurements of pressure gradients and valve dimensions on MRI are well in agreement with those found with echocardiography. Thus, regarding stenotic lesions, the arsenal of methods in clinical practice today might be considered sufficient for clinical demands.

Regurgitant lesions

In patients with regurgitant lesions, the presence of an abnormal jet on Doppler colour flow imaging indicates valvular regurgitation and provides semi-quantitative information about its severity. Although quantitative methods for assessing MR have been validated [16-19], the severity of regurgitation is still often assessed semiquantitatively on the basis of the size and the penetration of the regurgitant jet in the left atrium using Doppler colour flow mapping. Ideally the regurgitant stroke volume and regurgitant orifice area should be measured directly, but this has proved to be both technically demanding and tedious in clinical practice both with non-invasive and with invasive techniques. It can be difficult to obtain an accurate quantitative assessment of the regurgitation by echocardiography when measuring regurgitant volumes. It is established that measurements of LV volumes have the potential pitfall of underestimating the true LV volume and hence the severity of regurgitation [20].

In a recent study on patients with mitral regurgitation (MR) [21], it was concluded that quantitative grading of the lesion is a powerful predictor of the clinical outcome of asymptomatic MR. In that study, both the regurgitant volume and the regurgitant orifice predicted the outcome. This might lead to, as evidence accumulates, that these measures alone, without consideration of symptoms, might be sufficient to recommend the patient for surgery. Thus, demands for an accurate quantitative assessment of the regurgitation are becoming increasingly important.

In patients with regurgitant lesions and imaging difficulties at echocardiography and with no or unclear symptoms, there would seem to be a need for an alternative, reliable method for estimating the regurgitant fraction. MRI has been shown to be reliable in estimating ventricular volumes, function and mass; and might have a role in assessing mitral regurgitation in selected patients. However, for MRI to be applicable for evaluating regurgitant lesions in clinical practice, it must be comparable with echocardiography in
reliability, reproducibility and ease of use. Unfortunately, studies with comparisons of these two methods with regard to MR are sparse.

*Natriuretic peptides*

The concentrations of the natriuretic peptides BNP (brain natriuretic peptide) and ANP (atrial natriuretic peptide) are raised in patients with heart failure. These neurohormones are synthesized and secreted mainly from atrial ventricular myocardium and the stimulus for their release is wall distension and wall stress [22]. They are closely related to symptoms and have been recognised as markers for the diagnosis, severity and prognosis of heart failure. In general, the more severe the symptoms, the higher the plasma concentrations of these markers. In principle, therefore, the measurement of natriuretic peptides may aid decision-making in heart valve patients in clinical practice.

The potential of these markers as aids in the assessment of valve lesions has been investigated in several studies. In patients with AS, BNP is elevated with a correlation to severity and progression of disease [23-25]. Natriuretic peptides has also been shown to correlate with echocardiographic measures such as the transvalvular gradient and the LV-end systolic wall stress [26,27]. Moreover, one study showed higher levels of natriuretic peptides in AS patients with NYHA class II symptoms than those classified to NYHA class I [28]. These results suggest that the markers might be an aid in detecting early symptoms. Also, the peptides might be of use in unclear cases to discriminate between cardiac and non-cardiac symptoms, and have been shown to independently predict postoperative outcome with regard to survival, symptomatic status and LV function in patients with AS [29].

Regarding patients with MR, the investigations on its relation to natriuretic peptides are sparse. One study has shown that BNP is increased both in symptomatic and asymptomatic patients and its concentration varies widely [30]. Only one study has dealt with the relation between natriuretic peptides and MR severity. In that study, BNP and ANP was found to be positively correlated to regurgitant fraction, vena contracta width and LA dimensions as measured by echocardiography [31], suggesting that natriuretic peptide testing may add to the information obtained may aid in the assessment of MR patients. However, the relations of BNP and ANP to severity of MR on MRI and echocardiography have not been investigated.

The primary aim of study I (Paper I) was to compare MRI with echocardiography, and to examine their relation to natriuretic peptides in assessing severe mitral regurgitation.
One of the major issues for the patient undergoing heart valve surgery is the operative mortality. What rates have been reported and can the operative risk be predicted?

Operative mortality

Reported figures

The operative mortality is the most easily measured of the surgical outcomes. Mortality rates of 1 to 15% have been reported for heart valve surgery procedures, depending upon the patients’ age, burden of co-morbidity, valve position, and type of surgical procedure [32-38]. It is accepted that mitral valve surgery and multiple valve surgery have higher mortality rates than aortic valve surgery. It is also generally agreed that concomitant coronary artery bypass grafting (CABG) increases the early risk [39].

The large databases available today provide the most reliable figures regarding early results. The largest one, the STS National database (86,580 patients), reports early mortality rates, in the absence of coronary artery disease, of 4% for AVR, 6% for MVR, and 9.6% for multiple valves [40]. In the presence of coronary artery disease, these figures are 8%, 15% and 19%, respectively. The early mortality rate reported for mitral valve repair, 3%, is substantially lower than that for replacement. The United Kingdom Heart Valve Registry (UKHVR, 79,984 patients) reports a single valve mortality of 5.6% and double-valve mortality of 9.3%, figures in agreement with those of the STS database [41].

Elderly patients

The age of the patient population undergoing heart valve surgery is increasing [41,42]. It is established that the operative risk increases with advancing age [43,44]. However, there is an association between most risk factors and age, and according to most studies older patients both are more symptomatic and have higher co-morbidity [44,45]. In some studies, age itself has been
identified as a risk factor for operative mortality, whereas other authors have concluded that the increased co-morbidity in elderly patients, rather than age itself, is the reason for the increased risk. Although there are statistical models that can adjust for the effects of risk factors in older patients, this is a complex matter to sort out. In a recent study of 8,943 patients [46], the operative risk was found to increase with increasing age for both AVR and MVR, after adjustment for other risk factors. In that study the relative contribution of age as a risk factor for operative mortality was estimated to be approximately 20% (surgical priority 24-32%, NYHA 9-13%, conditions such as atrial fibrillation, diabetes and stroke 19-25%, valve versus repair 10%, and CABG 15%). Moreover, the UKHVR reports a mortality rate of 5% in patients <70 years and 7.9% in those >70 years for all HVR, but no risk factor analysis was made.

**Prediction of operative risk**

Great progress has been made regarding risk stratification in the practice of CABG. The quality assurance of valvular operations has lagged behind, partly because they require more time to amass adequate numbers of patients. However, in attempts to enable prediction of the operative outcome in the individual heart valve patient, much effort has recently been made to identify risk factors and to develop methods for risk modelling in these patients also. These studies are mainly based on the large data sets from the cardiac surgery registries of the New York State, the Society of Thoracic Surgery, the UKHVR database, and the EuroSCORE cardiac surgery database [39,46-50]. These registries have allowed identification of risk factors for early mortality after heart valve surgery, and are summarised below:

### New York State (14,190 patients 1995-1997)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AVR (OR)</th>
<th>MVR (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>8.7</td>
<td>9.2</td>
</tr>
<tr>
<td>LV heart failure</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.6</td>
<td>-</td>
</tr>
<tr>
<td>Dialysis</td>
<td>5.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>-</td>
<td>4.3</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>-</td>
<td>3.0</td>
</tr>
</tbody>
</table>

### Society of Thoracic Surgery (86,580 patients 1986-1995)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AVR (OR)</th>
<th>MVR (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvage status</td>
<td>7.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Dialysis</td>
<td>4.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Emergency status</td>
<td>3.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Reoperation</td>
<td>2.3</td>
<td>-</td>
</tr>
</tbody>
</table>
Northern New England (8,943 patients 1991-2001)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AVR (OR)</th>
<th>MVR (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High age</td>
<td>2.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Decreased renal function</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Emergency status</td>
<td>7.1</td>
<td>12.0</td>
</tr>
<tr>
<td>Advanced NYHA class</td>
<td>2.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>LV heart failure</td>
<td>2.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

EuroSCORE (19,030 patients September-November 1995)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HVR (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency status</td>
<td>2.8</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>3.8</td>
</tr>
<tr>
<td>Reoperation</td>
<td>2.6</td>
</tr>
<tr>
<td>LV EF &lt; 30%</td>
<td>2.5</td>
</tr>
</tbody>
</table>

None of the above mentioned databases identifies all risk factors, and, of course, the relative importance of each factor to overall outcome can not be inferred from these tables. Nevertheless, preoperative functional status, as reflected by NYHA class, and LV function are the most frequently cited risk factors for early mortality following valvular procedures.

**Trends in operative mortality and patient material**

There have been advances in the preoperative assessment, anaesthetic and operative techniques, and postoperative care in patients undergoing heart valve surgery. This has extended the range of patients that can be offered these procedures. Thus, trends for patients undergoing valve operations have reflected an increase in mean age and associated co-morbid risk factors [51]. One study on trends showed that despite an older age and a heavier burden of co-morbidity in valve patients, the early results were stable over the period 1988-1997 [45]. In another study, concerning AVR between the years 1990 and 2000, the early mortality was stable between three time periods (4.7%, 4.8% and 4.5%) but the early morbidity was decreased [42]. Studies on the trends of early mortality in relation to patient case-mix in heart valve surgery are relatively few. This is surprising, since the evaluation of early results and their trends is an essential component in ensuring the quality of the operative procedure.

The aim of study II (Paper II) was to investigate the time trends of the early results and of the clinical characteristics of patients undergoing heart valve surgery from 1990 to 1999 in our region.
Long-term survival after heart valve surgery is largely dependent on patient-related factors. What are these factors, and how do they influence survival?

Long-term survival

**Survival after aortic valve surgery**
Several studies have addressed the question of long-term survival AVR, and the mortality rates after 10 and 15 years are high [54-57]. Compared to patients with aortic regurgitation, patients with aortic stenosis show in general higher survival rates after surgery. Overall, after AVR, the 10-year survival rate is ≥ 60%, and the 15-year survival is ≥45%. The two extremes, patients <50 years of age and patients >70 years, have 10-year survival rates of approximately 88% and 45% respectively [58]. Studies have shown that one-half or more of late deaths are not related to the prosthesis but to associated cardiac abnormalities and other co-morbid conditions [59]. There is a relatively high incidence of late deaths from non-cardiac causes in older patients, whereas in younger patients the majority of deaths are cardiac or prosthesis-related. Thus, the late survival varies significantly in subgroups of patients. Risk factors for late mortality have included decade of age, LV dysfunction, heart failure, advanced NYHA class, concomitant CABG, valve regurgitation, co-morbidity such as renal failure, lung disease, hypertension, and diabetes [55-57].
In several studies, the relative survival rate after AVR (the survival rate compared to that in an age- and sex-matched cohort in the general population) has been used as a measure of the disease-specific excess mortality [60-62]. In the most recent of these analyses, advanced NYHA class, atrial fibrillation and regurgitant lesion were found to be associated with excess mortality [60]. Old age, on the contrary, was associated with excellent long-term survival, comparable to that in the general population. Consequently, AVR is usually not denied patients solely on the basis of high age.

**Survival after mitral valve surgery**
The survival rate is generally lower after MVR than after AVR [63]. Overall after MVR, the 10-year survival rate is approximately 55%, and the 15-year rate below 40%. The two extremes, patients <50 and patients >70 years, have 10-year survival rates of approximately 80% and 35%, respectively [59].
It is established that the most important predictor of long-term survival after MVR is preserved preoperative LV function [64-68]. In recent years, the increased feasibility of valve repair has led to improved survival rates in subgroups of patients in whom this procedure is an option [69,70]. In younger patients undergoing valve repair, the 10-year survival rate is approximately 80%, given that the preoperative LV function is preserved. Among patients with preoperative LV dysfunction, the 10-year survival rates after repair and replacement are comparable, at about 50%. Studies on risk factors for reduced long-term survival after MVR have established age, left atrial size, preoperative LV function, advanced NYHA class and presence of coronary artery disease as risk factors for reduced survival. There is only one available analysis of relative survival regarding MVR which yielded a 10-year relative survival rate at 65%, based on patients operated on in 1969-1983; no available analysis of subgroups was reported [61].

Furthermore, mitral valve surgery in older patients is a complex issue. The higher operative risks in older patients are of clinically significant magnitude. However, to what extent advanced age influences long-term survival after mitral valve surgery is not clearly established. Although age alone predicts survival, it has been shown that the expected survival in patients older than 75 years is not significantly reduced [65]. Moreover, mitral valve repair has not shown significant long-term survival benefit over replacement in older patients [70]. In summary, mitral valve surgery in older patients is a matter of some controversy partly due to the increased co-morbidity in this group. The actual relationships between the long-term outcome of mitral valve surgery, age, and symptoms have only been sparsely examined.

The aim of study III (Paper III) was to examine relative survival after MVR in relation to age and symptoms.

A valve replacement introduces the patient to a new disease process with the panorama of valve-related complications. The choice of the optimal heart valve prosthesis is still a matter of some controversy. Which is the most superior prosthesis in relation to age?
Prosthesis-related considerations

Selection of type of prosthesis and anticoagulation
To ensure a good and minimally complicated long-term prognosis, the choice of the optimal valve prosthesis is of the utmost importance for each patient. In the selection of the type of valve prosthesis, age is the single most determining factor. A mechanical valve is often the obvious choice in younger patients on account of its life-long durability, but a biological valve is preferred in older patients in view of their low rate of structural valve deterioration (SVD) and the advantage of avoiding oral anticoagulants in these patients. Moreover, a mechanical prosthesis implies life-long anticoagulant treatment, whereas among bioprosthetic recipients the need for such treatment varies. The recently published guidelines [71] for anticoagulation treatment in patients with heart valve prostheses are summarised below:

Mechanical heart valves
Life-long treatment with vitamin K antagonists
(low molecular weight heparin (LMWH) if vitamin K antagonists need to be discontinued)

<table>
<thead>
<tr>
<th>Valve type</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Jude bileaflet in aortic position</td>
<td>2.5 (range 2.0-3.0)</td>
</tr>
<tr>
<td>Carbomedics bileaflet in aortic position</td>
<td>2.5 (range 2.0-3.0)</td>
</tr>
<tr>
<td>Medtronic Hall tilting disc in aortic position</td>
<td>2.5 (range 2.0-3.0)</td>
</tr>
<tr>
<td>Caged ball or caged disc</td>
<td>3.0 (range 2.5-3.5)</td>
</tr>
<tr>
<td>Mechanical prosthesis + risk factors*</td>
<td>3.0 (range 2.5-3.5)+ aspirin</td>
</tr>
</tbody>
</table>

*Atrial fibrillation, low EF, myocardial infarction, large left atrium, endocardial damage, embolism despite therapeutic INR

Biological heart valves
Aspirin 75-100 mg/day in AVR with no risk factors
Vitamin K antagonists 3 months postoperatively in all MVR; and AVR with risk factors

<table>
<thead>
<tr>
<th>Long-term treatment</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm and no risk factors</td>
<td>Aspirin 75-100 mg/d</td>
</tr>
<tr>
<td>Risk factors *</td>
<td>2.5 (range 2.0-3.0)</td>
</tr>
</tbody>
</table>

*Atrial fibrillation, low EF, large left atrium, permanent pacemaker, history of systemic embolism, left atrial thrombus at surgery
Valve-related complications
Mechanical and biological valves are associated with different rates of complications in different subgroups of patients. In two large randomised trials these two prostheses have been compared regarding patient outcomes [59,72]:

**Edinburgh heart valve trial**
A total of 541 patients randomised between 1975 and 1979, with an average follow-up of 20 years. The major findings were:
1. Survival was better with a mechanical prosthesis
2. Bleeding was more common with mechanical valves.
3. Thromboembolism and endocarditis were equally common.

**The Veterans Affairs randomised trial**
A total of 574 patients were randomised between 1977 and 1982, with an average follow-up of 15 years. The major findings were:
1. Survival was better with mechanical valves in AVR but not in MVR.
2. Reoperation rate was higher after bioprosthetic AVR.
3. Bleeding was more common with mechanical valves.
4. Thromboembolism and endocarditis were equally common.

**Non-randomised trials**
In most studies addressing the issue of valve-related complications, patient characteristics at baseline have not been considered, and series of valves have been investigated after a relatively short follow-up time. Among these studies, complication rates for the same type of valve prosthesis have varied widely [73]. This has led to the realisation that valve-related complications are largely related to factors other than the type of valve prosthesis. From a review [74] of the long-term performance of heart valve substitutes (95 published studies of mechanical valves and 70 studies of biological valves), it was concluded that there is no significant difference among the various mechanical valves regarding thromboembolism, rate of thrombosis, bleeding, endocarditis, or leakage. This was also found true for the various bioprostheses. Concerning complication rates it was concluded that there is 1) a higher incidence of bleeding with mechanical prostheses, 2) a higher incidence rate of thromboembolism with mechanical prostheses and 3) a higher incidence of thromboembolism with valves in the mitral position than in the aortic position. These conclusions are essentially the same as those drawn from the two randomised trials and other observational studies [59,72,75,76].
**Valve thrombosis**
Prosthetic-valve thrombosis has a reported incidence of 0.1-5.7% per patient year [77,78]. The major contributing factors are inadequate anticoagulant therapy and mitral location of the prosthesis [79,80]. Valve thrombosis is equally common among mechanical and bioprosthetic recipients who are receiving adequate anticoagulant therapy [81]. Likewise, the incidence is similar with the various mechanical prosthesis, given equal anticoagulant therapy [76,80].

**Structural valve deterioration**
The risk of SVD with all currently used mechanical valves is very small, in fact almost non-existent. The rate of structural deterioration of biological valves is associated with the position of the valve and the patient’s age at operation [59,72,74]. In patients < 40 years of age, the SVD rate after AVR is ≥ 90%, as compared to ≤ 15% in patients older than 70 years, at 15 years [82]. Today, the SVD rate is believed to be lowest for the Carpentier-Edwards pericardial valve in the aortic position [74]. The conclusion can be drawn that the SVD rates of newer porcine valves are similar to those of older porcine valves [83].

**Special considerations in elderly patients**
Some studies have shown that older patients with mechanical valves have more bleeding events than younger patients [75]. The direct reason for this is somewhat unclear. However, it has been shown that old age is associated with high INR variability during anticoagulant treatment [84]. The same study concluded that INR variability is associated with reduced long-term survival both after AVR and MVR. Moreover, multiple co-morbidity is also of importance in increasing the risk of bleeding; and older patients have associated conditions to a larger extent than younger ones [85]. Moreover, the need for non-cardiac surgery is most certainly higher in older patients. The risk of valve thrombosis with interruption of anticoagulation treatment in patients with a mechanical prosthesis varied between 0-2% in AVR patients and 11-20% in MVR patients [76,86].

No study has addressed valve-related complications in a population-based manner with special focus on age and type of prosthesis.

The aim of study IV (Paper IV) was to compare valve-related morbidity between mechanical and biological prostheses in patients younger and older than 70 years on a population-based level.
It is established that heart valve surgery improves the functional capacity and quality of life of the patients without complications. What is known about the postoperative health status for patients with prolonged intensive care?

Quality of life

Quality of life (QoL) after heart valve surgery
Outcome results of heart valve surgery are traditionally evaluated in terms of operative mortality, morbidity and valve-related complications. Low rates of these adverse events are associated with favourable gains in the patient well being and functioning. However, there is now a recognition that these data alone provide incomplete measures of outcome [87]. The insights regarding the patients’ own perception of their health is becoming increasingly recognised as an important factor in the assessment of health outcomes.

QoL after heart valve surgery has been investigated in many studies but only few of them have had a prospective design [88-91]. It is generally accepted that the functional capacity and QoL improve after both AVR and MVR. In two prospective studies with follow-up times of 3 months and 12 months respectively, significant and overall improvement in QoL after valve replacement was found as measured by SF-36 [88,89]. With regard to mitral valve surgery, the improvement has been found to be greater among valve repair patients than among those undergoing valve replacement [92]. However, those undergoing replacement are also more likely to have advanced disease and to show less improvement in functional class postoperatively, and the results might therefore be difficult to interpret. Interestingly, neither old age nor ischaemic heart disease has been shown to influence the QoL negatively [93-95]. Further, although there may be an idea that bioprostheses might be associated with increased QoL because of the limited need for anticoagulation therapy, this has never been established in any study [96,97].

Previous studies on heart valve patients with complications have mainly been focused on rates of particular perioperative and postoperative complications and possible trends of improvements regarding these events. The QoL studies in patients with a complicated postoperative course after heart valve
surgery have included relatively few patients, with mixed populations of CABG and valve patients [98-102]. Many survivors of prolonged intensive care die soon after hospital discharge and many long term survivors have a poor functional state [103]. Hospital discharge alone is an incomplete measure of outcome in these patients. Therefore, longer follow-up of functional capacity and QoL is warranted.

No study has addressed the postoperative QoL and functional capacity in a homogeneous heart valve surgery population with a complicated postoperative course.

**The aim of study V (Paper V) was to examine the QoL and functional capacity in patients requiring prolonged intensive care after heart valve surgery.**
Aims of the thesis:

The specific questions to be answered by this thesis were:

- Is MRI comparable to echocardiography in assessing severe mitral regurgitation?

- Are natriuretic peptides positively correlated to the degree of mitral regurgitation as measured by MRI and echocardiography?

- Have the early results after heart valve surgery improved over the last decade?

- How does age and symptoms affect long-term survival after mitral valve surgery?

- Which valve prosthesis is optimal in relation to age with regard to valve-related complications?

- Is the quality of life reduced in heart valve surgery patients with a complicated postoperative course as compared to uncomplicated controls?
Material and methods

Study design and patients

All patients included in the present studies underwent heart valve surgery at the Department of Cardiothoracic Surgery at Uppsala University Hospital.

Study I
This was a prospective, descriptive study of the agreement between MRI and echocardiography, and of the relation of these two methods to natriuretic peptides, in patients with severe mitral regurgitation. A total of 18 consecutive patients accepted for mitral valve surgery entered the study from September 2004 to April 2005. There were 14 men (77%) and 4 women, mean age 66 years (32-73).

Study II
Study II was an in-hospital registry investigation of trends of early results and of the clinical characteristics of patients undergoing primary heart valve surgery. A total of 2,237 consecutive patients were included from January 1990 to December 1999. Of these, 1,746 (75%) had AVR, 432 (18%) had MVR, 78(3%) had double valve replacement (DVR) and 71(3%) had mitral valve repair. There were 1,427 men (61%) and 900 women, mean age 67 years (range 17-90).

Study III
This was an in-hospital registry investigation in which survival after mitral valve replacement was analysed. A total of 784 consecutive patients underwent primary MVR for mitral regurgitation (65%), mitral stenosis (16%) and combined lesions (19%) between January 1980 and December 2000. There were 379 men (48%) and 405 women mean age 63.5 years (22-81).

Study IV
In this population-based study an analysis was made of valve-related complications with a mechanical or a bioprosthesis occurring among all patients
undergoing primary heart valve replacements from January 1985 to December 2001. A total of 3,279 patients who were discharged alive after their heart valve surgery were followed up through the ICD system for classification of diseases. There were 1,973 men (60%) and 1,306 women, mean age 66 years (18-87). Mechanical prostheses were implanted in 2,176 patients (66%).

Study V
In a case-control quality of life survey, QoL was investigated in all patients suffering complications after heart valve surgery performed from January 1998 to December 2003. A total of 225 patients who were treated for ≥8 days at the intensive care unit (ICU) after AVR (69%), MVR (28%), and DVR (3%) were included. There were 86 men (64%) and 48 women, mean age 69 years (35-85). A control cohort matched for age, sex, surgical procedure and week of operation was created.

Data collection

Study protocol, study I
All 18 patients underwent MRI, transthoracic echocardiography and testing of natriuretic peptides the day prior to surgery.

Echocardiographic methods
All patients underwent echocardiographic and Doppler examination with use of a standard protocol. The examination was performed in accordance with the American Society of Echocardiography Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography [20].

Cardiac magnetic resonance imaging methods
All MR imaging was performed with a 1.5-T MR imaging system (Gyroscan Intera; Philips Medical Systems, Best, the Netherlands). Vector-ECG (with retrospective gating) was used for cardiac triggering. The cardiac function was examined with short and long axes views of the heart. The short axis images consisted of 8 mm thick slices with a slice gap of 2.5 mm. The number of slices was adjusted to cover the heart from apex to the atria with 18 phases / cardiac cycle. The long axis images consisted of 8 mm thick slices with a slice gap of 1.5 mm covering the heart with 60 phases / cardiac cycle.
Blood flow through the aorta was measured by a velocity encoded gradient echo sequence. One slice was acquired in the aorta during free breathing. The slice was planned in a frontal survey as a transverse slice perpendicular to the direction of aorta, corrected in the sagittal survey.

Left ventricular function and aortic flow was measured using a separate workstation (ViewForum, Philips Medical Systems, Best, the Netherlands). The following parameters were supplied by the software: left ventricular end-diastolic volume, left ventricular end-systolic volume and aortic flow.

The length and width of the left atrium was measured in the long axis 4-chamber images at end-systole. The time chosen was the time closest to the end-systolic time during the evaluation of the short axis images. The length was measured following a line from the middle of the mitral valve or the beginning of the mitral regurgitation, passing the centre of the atrium and to the dorsolateral wall of the left atria. The width was the longest perpendicular length to this line.

Mitral regurgitation was calculated by the following formulas:

\[
\text{Mitral regurgitation volume} = \text{Stroke volume} - \text{Aortic flow}
\]

\[
\text{Mitral regurgitation fraction} = \frac{\text{Mitral regurgitation volume}}{\text{Stroke volume}}
\]

**Measurement of natriuretic peptide levels**

Venous blood samples were taken in the morning of the day before surgery with the patient still resting. The samples were drawn into chilled vacutainers, placed immediately on ice, and centrifuged within 20 min at + 4 °C. The plasma was stored at −80 °C before being analysed for NT-proBNP and NT-proANP by established radioimmunoassays [104].

**Study protocol, studies II-V**

**Clinical data**

All clinical data were collected at a preoperative interview and stored in a computer. All patients in studies II, III and IV were analysed concerning the following variables: demographic variables, history of the disease, symptoms and clinical status, associated conditions, decreased renal function or any other serious diseases (e.g. malignancies), preoperative catheterization data, and characteristics of the surgical procedure. In study II, preoperative haemodynamics and perioperative myocardial injury were also included.

**Definition of NYHA functional classification**

NYHA classification of congestive heart failure was made on the basis of the clinical status of the patient at the preoperative interview: patients who suffered slight discomfort in their normal activity were allocated to NYHA class IIIA. Patients who managed only the lightest of activity without dis-
comfort were allocated to NYHA IIIB, and those confined to bed because of symptoms were assigned to NYHA IV [105].

**Classification of LV function**
LV function was classified as either normal, moderate dysfunction or severe dysfunction, on the basis of the ejection fraction. Ejection fraction values above 0.5 were considered to represent normal LV function, values between 0.50 and 0.35 moderate LV dysfunction, and values below 0.30 severe LV dysfunction.

**Follow-up and definitions of events**

**Follow-up (studies II-V)**

**Early and late death**
By use of two national registers, the Swedish Cause of Death Register and a continuously updated population register, all patients were assigned a date of death or identified as being alive at the closing date of the study.

**Hospital readmission (study IV)**
Hospital discharge after valve surgery was the starting point. Every death or hospital readmission due to a valve-related event was identified through computerised linkage to the National In-Patient Register (Centre of Epidemiology, National Board of Health and Welfare) [106]. In this register all hospital admissions in Sweden are recorded, and a primary diagnosis coded according to the International Classification of Diseases is assigned to every admission at discharge.

**Mortality (studies II-V)**
*Early mortality (operative mortality)* was defined as death from any cause within 30 days from surgery [3].
*Late mortality* was defined as death from any cause after 30 days from surgery [3].
Morbid events

**Valve-related morbidity (study IV)**
Embolic events, bleeding, prosthetic valve endocarditis, leak, valve thrombosis, and reoperation were defined according to the Guidelines for reporting Morbidity and Mortality after cardiac valvular operations [3].

**Postoperative complications (study II)**
In study II postoperative complications were defined as:
1) Heart failure defined as death within the first postoperative day due to heart failure; postoperative requirement of two or more inotropic drugs; failure to wean from cardiopulmonary bypass after prolonged reperfusion (over 45 min); or inadequate circulation later in the postoperative period. Inadequate circulation was defined as: mean arterial blood pressure (MAP) below 60 mmHg; poor peripheral perfusion as indicated by oliguria (less than 400 ml/24 h); mixed venous oxygen saturation below 60 %; or a cardiac index of less than 2 l/min/m².
2) Bleeding defined as excessive postoperative bleeding requiring reoperation.
3) Neurological complication defined as any neurological deficit occurring postoperatively with a corresponding cerebral lesion on computer tomography.

**Postoperative complications (study V)**
In study V postoperative complications were defined as:
1. Respiratory (mechanical ventilation for at least 48 h);
2. Cardiac (two or more inotropic drugs for at least 72 h or a need for an intra-aortic balloon pump postoperatively);
3. Renal (need for dialysis);
4. Gastrointestinal (parenteral feeding for at least 5 days);
5. Neurological (neurological deficit with corresponding lesion at computed tomography);
6. Sepsis (2 of 3 microbial blood cultures positive combined with fever/haemodynamic instability).

**Quality of life instruments (study V)**

**SF-36**
The SF-36 questionnaire is composed of 36 items, grouped into eight scales, which concern both physical and mental health and assess eight dimensions of QoL [107]. The raw subscale scores range from 0 to 100, where 0 represents the poorest state of health and 100 the best possible. Finally, the physi-
clinical component summary scores (PCS) and the mental component summary scores (MCS) are calculated to summarise the physical and mental state of health.

**Nottingham health profile (NHP)**
The NHP questionnaire consists of two parts, the first with 38 questions aggregated to six dimensions: energy, pain, emotional reaction, sleep, social isolation and physical mobility [108]. The patients are to give yes or no responses to each question. Each statement is weighted, and a score ranging from 0 to 100 is calculated for each dimension. A score of 0 means no problem in the dimension, and a score of 100 signifies maximal problems. Part two of the NHP lists seven activities of daily living that are affected negatively if the patient is in a poor state of health: occupation, housework, social life, family life, sex life, hobbies and holidays. These questions are also answered with yes or no responses. Question number 39 concerning occupation was excluded from the NHP questionnaire, since the majority of the patients in this study were not employed.

**Hospital Anxiety and Depression (HAD) scale**
The HAD scale is designed to measure anxiety and depression in somatically ill individuals [109]. The questionnaire contains 14 items for self-assessment on a scale of 0-3. Seven questions are related to anxiety and seven to depression, with a scale range of 0-21 for both variables. A score of 8 or more on each subscale represents “possible” psychiatric morbidity and a score of 11 or more represents “definite” clinical anxiety or depression.

**Specific questions**
In addition to the questionnaires, three questions were constructed. The patients were asked: 1) if they regretted undergoing heart valve surgery, 2) if they felt they had improved postoperatively the way they had expected, and 3) to grade their functional capacity according to the NYHA classification.

**Statistical methods**

**Study I**
Data are presented as mean (SD). Bland-Altman analysis was used to compare observations on echocardiography and MRI [110]. Spearman’s correlation coefficient was used for correlation. A two-tailed probability value of <0.05 was considered significant.
Study II
Logistic regression was used to identify risk factors for early outcome [111]. Interaction was tested for by introducing an interaction term. Two multivariate models were constructed: 1) preoperatively available risk factors and 2) preoperatively and perioperatively available risk factors. A risk score was calculated for each patient in both models. ROC curve graphs were constructed for validation of the two models [112]. The Cochran-Armitage Trend Test was used to detect trends [113].

Study III
Logistic regression was used to identify risk factors for early outcome. Student’s t test and one-way analysis of variance was used to compare differences in mean age among dichotomous and categorical variables. The Cochran-Armitage trend test was used to test for differences in distribution of risk factors in relation to NYHA class. Observed survival was calculated by the actuarial (life-table method) [114], and risk factors for reduced survival by analyses of the standard Cox proportional hazard model [115]. Relative survival was computed as the ratio of observed to expected survival (survival in a cohort in the general population matched for age, sex and intervention period) [116]. The observed/expected death ratio was calculated as the observed deaths in relation to the expected deaths (general population). Variables included into the logistic regression and Cox analyses are specified in paper III.

Study IV
Survival was determined by the Kaplan-Meier method and outcomes were compared using the log-rank method [117,118]. Incidence rates of complications were also calculated as linearised rates (percentage per year; % py), compared by the likelihood ratio test. The standard Cox proportional hazard model was used to identify risk factors for all time-related events, with relative hazards (RH) used as a measure of the relative risk. Separate models were estimated for 5-year periods after surgery (<5 years, 5-10 years, >10 years). Stratified regression was used to analyse interaction between type of prosthesis and age. An interaction term was introduced to test for interaction.

Study V
Data are presented as mean (SD). Baseline variables were compared using Student’s t test (means) and the chi-square test (proportions). The Mann-Whitney U-test was used to compare scores between groups. Change in NYHA class from before to after surgery was compared with McNemar’s test. Spearman’s correlation was used to test associations between NYHA class after surgery and reported scores. A two-tailed probability value of <0.05 was considered significant.
In studies I and V the SPSS statistical package 12.0 (SPSS Inc. Chicago) was used, and in studies II-IV the SAS 6.12 statistical program for PC (SAS Institute, Solna, Sweden).
Results

Preoperative assessment

Symptoms
The preoperative symptomatic status of the patients in all studies, as shown by NYHA class, is presented in Table 1. The distribution of patients between the different classes was relatively similar between studies. Study I had the largest proportion of NYHA class IIIB patients (61%), whereas study V (control cohort) had the largest proportion of patients in NYHA class II.

Table 1. Preoperative NYHA functional classification

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>IIIA</th>
<th>IIIB</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>-</td>
<td>5%</td>
<td>33%</td>
<td>61%</td>
<td>-</td>
</tr>
<tr>
<td>Study II</td>
<td>2%</td>
<td>10%</td>
<td>42%</td>
<td>40%</td>
<td>6%</td>
</tr>
<tr>
<td>Study III</td>
<td>&lt;1%</td>
<td>8%</td>
<td>37%</td>
<td>46%</td>
<td>9%</td>
</tr>
<tr>
<td>Study IV</td>
<td>1.3%</td>
<td>11%</td>
<td>42%</td>
<td>40%</td>
<td>5%</td>
</tr>
<tr>
<td>Study V, ICU</td>
<td>-</td>
<td>3%</td>
<td>43%</td>
<td>47%</td>
<td>7%</td>
</tr>
<tr>
<td>Study V, control</td>
<td>2%</td>
<td>20%</td>
<td>50%</td>
<td>27%</td>
<td>1%</td>
</tr>
</tbody>
</table>

MRI and echocardiography in patients with mitral regurgitation (study I)
Overall, MRI showed larger left ventricular volumes than did echocardiography (Table 2). The methods did not agree in the measurements of LV end-diastolic volume (LVEDV), with a mean difference of 74.7 ml. The agreement in aortic flow volume measurement was good, with a mean difference of 1.4 ml. Mean aortic flow volume with echocardiography was 76.9 (28.4) ml and with MRI 75.3 (20.0) ml.
For atrial size, MRI showed higher values than echocardiography. The agreement between the two methods was somewhat better for atrial width than for atrial depth, with mean differences of 6.1 and 12.3 mm respectively.
### Table 2. Echocardiographic and magnetic resonance imaging (MRI) measurements (mm ± SD) in the study population (n=18).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Echocardiography</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV</td>
<td>149.1 (43.7)</td>
<td>225.6 (54.4)</td>
</tr>
<tr>
<td>LVESV</td>
<td>55.2 (17.2)</td>
<td>66.4 (22.2)</td>
</tr>
<tr>
<td>Aortic flow</td>
<td>76.9 (28.4)</td>
<td>75.3 (20.0)</td>
</tr>
<tr>
<td>Atrial width</td>
<td>51.1 (15.2)</td>
<td>59.9 (11.2)</td>
</tr>
<tr>
<td>Atrial length</td>
<td>64.2 (8.1)</td>
<td>76.9 (9.7)</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>23.3 (13.8)</td>
<td>51.6 (12.5)</td>
</tr>
<tr>
<td>Vena contracta</td>
<td>9.6 (2.9)</td>
<td>-</td>
</tr>
<tr>
<td>PISA</td>
<td>5.5 (1.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, PISA = proximal isovelocity surface area.

The two methods were not in agreement in measurement of the regurgitant fraction. The mean difference was 27.5 (19) %, (p<0.0001) (Fig 1.).

**Figure 1.** Bland-Altman plot of agreement between MRI and echocardiography in measurements of regurgitant fraction (RF%) in patients with severe MR (n=18).
The mean regurgitant fraction was 51.7 (12.5)% with MRI and 23.4 (13.8)%
with echocardiography. Regurgitant fractions of over 40% were found in
2/18 (11%) patients with echocardiography but in 16/18 (88%) with MRI.

Natriuretic peptides
All 18 patients underwent preoperative measurement of natriuretic peptides
at rest. Mean NT-proANP was 1,033 (160) pmol/l and mean NT-proBNP was
368 (121) pmol/l.

Echocardiography and natriuretic peptides
The mean proximal isovelocity surface area (PISA) was 5.5 (1.0) mm and
correlated well to both NT-proANP (r=0.72, p<0.01) and NT-proBNP
(r=0.68, p<0.01). The mean vena contracta width was 9.6 (2.9) mm. There
was a significant correlation between vena contracta width and both NT-
proANP (r=0.69, p<0.001) and NT-proBNP (r=0.70, p=0.002) There was no
difference in the strength of the correlation of NT-ANP and NT-proBNP to
either PISA (p=0.77) or vena contracta width (p=0.34).

MRI and natriuretic peptides
The regurgitant fraction as measured by MRI correlated well to NT-proANP
(r=0.84, p<0.0001) and moderate to NT-proBNP (r=0.57, p=0.01); that is,
NT-proANP and NT-proBNP rose with increasing regurgitant fractions
(Figs. 2 and 3). NT-proANP correlated more strongly to regurgitant fraction
than NT-proBNP (p<0.01).

Figure 2. Correlation between regurgitant fraction (RF, %) on MRI and NT-proANP
in patients with severe mitral regurgitation (n=18).
Figure 3. Correlation between regurgitant fraction (RF, %) on MRI and NT-proBNP in patients with severe mitral regurgitation (n=18).

Operative mortality
The operative mortality found in all studies is presented in Table 3. The largest early mortality rate, 12%, was seen in the ICU cohort in study V, followed by 9.7% in the patients undergoing mitral valve surgery in study III. The lowest rate, 2.2%, was found in the control cohort in study V.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Operative mortality (%)</th>
<th>5-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>18</td>
<td>0%</td>
</tr>
<tr>
<td>Study II</td>
<td>2327</td>
<td>5.9%</td>
</tr>
<tr>
<td>Study III</td>
<td>784</td>
<td>9.7%</td>
</tr>
<tr>
<td>Study IV</td>
<td>3279</td>
<td>5.7%</td>
</tr>
<tr>
<td>Study V, ICU</td>
<td>225</td>
<td>12%</td>
</tr>
<tr>
<td>Study V, control</td>
<td>225</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Risk factors for operative mortality (studies II and III)
In study I, age over 70 years and advanced NYHA class increased the risk for early death, with OR 2.1 and 2.2 respectively among all heart valve surgery patients. There was a significant interaction effect between preoperative atrial fibrillation and type of valve procedure (p=0.002), atrial fibrillation
being a risk factor for early mortality only in AVR patients (OR=2.6). The strongest predictor was preoperative shock, with an OR of 3.5. Operative factors that increased the risk were aortic cross-clamp time over 150 min and by-pass time over 180 min, with ORs of 3.2 and 2.7 respectively.

In an alternative model based only on preoperatively available risk factors (operative variables excluded), the following risk factors gave independent prognostic information: advanced NYHA class, age >70 years, concomitant MVR, year of surgery, hypertension, atrial fibrillation, and decreased renal function.

Among the MVR patients in study III, advanced NYHA class and diabetic disease, but not age, were independent risk factors for early mortality.

Time trends (study II)
Study II showed a consistent decline in early mortality, in all valve groups, over the study period (OR=0.9 [0.87-0.94] for every year after 1990) (Fig.4). While there was a decrease in the incidence of perioperative myocardial injury and postoperative heart failure over the study period (p value for trend <0.001 for both complications), the incidence of other complications showed no such trend.

Figure 4. Time trend in early mortality during the study period 1990-1999. P value for trend: <0.001.
There was an increase in the proportion of patients older than 70 years of age. The annual number of procedures was constant over the study period.

The elderly

In study II, 49% of the total population were older than 70 years. Among those who died within 30 days after surgery, 67% were older than 70. Of the 455 patients who suffered postoperative heart failure, 282/455 (62%) were older than 70 years.

As depicted in Fig. 5, the majority (70%) of the patients over 70 years of age in study III were allocated to NYHA class IIIB or IV (p<0.001). Concomitant CABG and hypertension were also more frequent among older patients (p=0.02 and p<0.0001) (not shown).

**Figure 5.** The associations between age, NYHA class and other risk factors among patients undergoing mitral valve replacement (n=708). Presence of risk factors by NYHA classification.

Prognostic risk

In study II, a risk score for early mortality was calculated for each patient, using the model based on all available risk factors and the model based only on the preoperative risk factors. Patients were allocated either to a high-risk or a low-risk group. The sensitivity and specificity obtained by the two mod-
els were plotted in a ROC curve; and the area under the ROC curve was 0.77 for all available risk factors and 0.66 for the model based only on the preoperatively available risk factors. There was a significant difference between the two models (p<0.01).

In study V, there was no difference in preoperative EuroSCORE between the ICU cohort (median 6) and the control cohort (median 5), although the operative mortality rates were 12% and 2.2% respectively, (p=0.8).

Long-term survival

Observed survival
Overall, the cohort of 3,279 patients in study IV had a 5-year survival rate of 83% (Table 3). In MVR patients, the observed survival rates after 5, 10 and 15 years were 75%, 56% and 36% (Paper III). In mixed heart valve patients in study V, the 5-year survival rates of the ICU cohort and the control cohort were 68% and 85%, respectively.

In study IV, where patients with different valve prostheses of different ages were analysed, younger patients with a bioprosthesis had lower survival than young recipients of a mechanical prosthesis. In older patients, survival was equal between the two prosthesis groups.

Relative survival (study III)
After mitral valve surgery, the overall relative survival rates after 5, 10 and 15 years were 83%, 70% and 54% respectively. The patients in an advanced NYHA class, IIIB-IV, showed clear excess mortality, with a rate of 62% after 10 years, whereas patients with no or mild symptoms (NYHA class I-II) had excellent relative survival of approximately 90%, 5 to 15 years after surgery (Fig. 6).

Relative survival at 5 years was comparable in all age groups. The relative survival rates after 5 and 10 years were 80% and 62% respectively in patients in the highest age group (>70 years) and 83% and 78% in those in the youngest group (<50 years)(Fig. 7).
Figure 6. Relative survival after primary mitral valve replacement by preoperative NYHA functional class, (n=708) The numbers of patients at risk are given.

Figure 7. Relative survival after primary mitral valve replacement by age at operation, (n=708). The numbers of patients at risk are given.

Risk factors for reduced survival

In MVR patients in study III, male sex, high age, hypertension, congestive heart failure, concomitant CABG, and advanced NYHA class were independent predictors of reduced observed survival. The same risk factors that reduced observed survival also affected relative survival.
There were no significant interaction effects between type of valve lesion and different risk factors; that is, the identified risk factors and their effects were virtually the same in patients with mitral valve insufficiency, those with stenosis, and those with a combined lesion.

Observed and expected deaths (Paper III)

There were 308 observed late deaths during the follow-up period, Table 4. The expected number of deaths in a comparable cohort was 154. Among patients older than 70 years, there were 113 observed deaths, compared to 68 expected (O/E ratio 1.7). Also, in the youngest age group the observed number of deaths, 17, was higher than the expected 2 deaths, with an O/E death ratio death ratio of 7.8. Among patients in NYHA classes IIIB and IV, there were 182 observed deaths compared to 87 expected; and the corresponding figures for patients in less advanced NYHA classes (I and II) were 14 and 11 respectively.

In study IV on valve-related complications, there were 961 late deaths and 56% were cardiac, (non-prosthesis–related). Valve-related deaths accounted for 10 % of late deaths and 34% were non-cardiac.

Table 4. Observed number of deaths in the study cohort related to the expected number of deaths in a comparable cohort in the general population in follow-up years 1-15.

<table>
<thead>
<tr>
<th>Observed number of deaths</th>
<th>Expected number of deaths</th>
<th>Observed/expected death ratio (C.I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall late deaths</td>
<td>308</td>
<td>154</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>17</td>
<td>2.2</td>
</tr>
<tr>
<td>51-60</td>
<td>49</td>
<td>17</td>
</tr>
<tr>
<td>61-70</td>
<td>129</td>
<td>67</td>
</tr>
<tr>
<td>&gt;70</td>
<td>113</td>
<td>68</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>238</td>
<td>124</td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td>29</td>
</tr>
<tr>
<td>CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>177</td>
<td>95</td>
</tr>
<tr>
<td>Yes</td>
<td>131</td>
<td>59</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>IIIA</td>
<td>112</td>
<td>56</td>
</tr>
<tr>
<td>IIIB-IV</td>
<td>182</td>
<td>87</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>189</td>
<td>95</td>
</tr>
<tr>
<td>Yes</td>
<td>119</td>
<td>58</td>
</tr>
</tbody>
</table>

CHF= congestive heart failure, CABG=coronary artery bypass grafting
Complications

Postoperative complications (studies II and V)
In study II, 101/2,327 (4.3%) patients suffered a neurological complication postoperatively, and 35/2,327 (1.5%) needed reoperation because of sternal infection. The incidence of postoperative heart failure was 19.5% (455/2,327). In the AVR group it was 16 %, in the MVR group 31% and in the group with DVR 40%.

In the ICU cohort in study V, 127/134 (95%) had respiratory complications, 119/134 (89%) cardiac complications and 20/134 (15%) neurological complications.

Valve-related complications (study IV)

Thromboembolism
In all, 390 episodes of embolism were recorded in 301 patients (1.8% py). In 59 patients, more than one event occurred. The incidence of embolism was lower in patients with a mechanical prosthesis (248 events, 1.5% py) than in those with a bioprosthesis (142 events, 2.6% py; p<0.0001) and was not related to age, Table 5.

In multivariate analyses a mechanical prosthesis was found to decrease the risk of at least one thromboembolic event (RH= 0.5) in both age-groups

Bleeding
There were recordings of 328 episodes of bleeding in 212 patients (1.5% py). In 49 patients more than one episode of bleeding occurred. Bleeding was more common in patients with a mechanical prosthesis (271 bleeding episodes [1.7% py]) than in bioprosthesis recipients (57 episodes [1.1 % py]) (p=0.002). Among younger patients, bleeding was equally common in those with the two types of prosthesis (p=0.3). Older patients with a mechanical prosthesis had a higher incidence of bleeding (2.1 % py) as compared to younger ones (1.5% py; p < 0.001), whereas in bioprosthesis patients age was not related to the incidence of bleeding. Within the younger age group, increasing age was associated with an increased risk of bleeding, but within the older age group the risk of bleeding was constant with increasing age.

In patients over 70 years of age a mechanical prosthesis (RH = 1.9) and preoperative bleeding (RH = 4.4) increased the risk of bleeding.

Events in relation to time from surgery
The risk of thromboembolism during the first five years was comparable in patients with the two types of prosthesis. After five years patients with a
bioprosthesis were at higher risk of thromboembolism than those with a mechanical one. Regarding bleeding, the risk during the first five years was increased with a mechanical prosthesis. After five years, the risk of a bleeding event was comparable between the two types of prosthesis.

Other valve-related complications
In total, bacterial endocarditis occurred on 144 occasions in 88 patients, and more than once in 12 patients. Prosthetic-valve endocarditis was more common in patients with a bioprosthesis (44 events; 0.8% py) than in those with a mechanical prosthesis (79 events; 0.5% py) \( p=0.005 \). Mechanical complications occurred in 30 patients with a mechanical prosthesis and in 2 patients with a bioprosthesis. There were 38 reoperations for valve-related complications, 23 (0.15% py) in patients with a mechanical prosthesis and 15 (0.3% py) in patients with a bioprosthesis.

Table 5. Incidence (%/year [% py]) of prosthesis-related complications in 3,279 patients who underwent surgery from 1985-2001.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Mechanical prosthesis</th>
<th>Biological prosthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events % py</td>
<td>Events % py</td>
</tr>
<tr>
<td>All patients</td>
<td>( n=2,176 )</td>
<td>( n=1,103 )</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>248 1.5</td>
<td>142 2.6</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>271 1.7</td>
<td>57 1.1</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>79 0.5</td>
<td>44 0.8</td>
</tr>
<tr>
<td>Patients ≤70</td>
<td>( n=1,747 )</td>
<td>( n=173 )</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>190 1.5</td>
<td>21 2.8</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>200 1.5</td>
<td>8 1.0</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>61 0.5</td>
<td>11 1.4</td>
</tr>
<tr>
<td>Patients &gt;70</td>
<td>( n=547 )</td>
<td>( n=1031 )</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>58 1.7</td>
<td>121 2.6</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>71 2.1</td>
<td>49 1.1</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>15 0.5</td>
<td>31 0.7</td>
</tr>
</tbody>
</table>

Event-free survival
Patients below 70 years with a mechanical prosthesis had superior event-free survival as compared to young bioprosthesis recipients \( (p<0.0001) \). In the older group, event-free survival was equal in patients with the two types of prosthesis.
prosthesis (non-significant). There was a significant interaction between age and type of prosthesis (p<0.0001); a bioprosthesis was associated with impaired event-free survival, especially among younger patients.

In patients with a mechanical prosthesis the risk of an adverse event increased in relation to ageing, but in patients with a bioprosthesis there was no such increase in risk.

![Figure 8. Event-free survival in 3,279 patients who underwent heart valve surgery 1985-2001.](image)

**Quality of Life**

**Patients’ characteristics**

The response rate to the questionnaires was 87% in the ICU group and 94% in the control group. The mean age of both cohorts was 69 (35-85) years and 30% of the patients were older than 75 years. The patients in the ICU group were in a more advanced NYHA class preoperatively compared to the control group (p< 0.001). Also, impaired left ventricular function was more common in the ICU group (p=0.01). The mean follow-up time in both groups was 38.5(19.5) months.

**SF-36 scores**

The ICU study cohort had lower summary scores for physical health as compared to the control cohort (p<0.001) (Fig. 8). The ICU patients deviated from the control group in all of the eight subscales except one (role emotional). There was no difference in the mental summary scores between these two study groups (p=0.34).
Figure 9. SF-36 scores in the ICU study cohort (n=134) and in the control cohort (n=144). *Indicates a significant difference between ICU and control cohort.

(BP=bodily pain; GH=general health; MCS=mental summary score; MH=mental health; PCS=physical summary score; PF=physical function; RE=role emotional; RP=physical role function; SF=social function; VT=vitality)

Nottingham Health Profile scores
In the total NHP, the ICU study cohort showed more difficulties than the control cohort (p=0.002). The ICU patients reported higher scores (more difficulties) in all domains except emotional reactions and sleep in NHP part I. They also reported impairment in all daily activities, as measured in part II of the NHP.

Hospital Anxiety and Depression scale
There was no difference in anxiety (p=0.24) or depression (p=0.53) between the two cohorts.

Specific questions
No patient in the ICU cohort regretted undergoing heart valve surgery, whereas one patient in the control cohort reported such regret. There was no difference between the two groups in terms of subjective improvement as expected after surgery; such improvement was noted by 78% and 82% of the patients in the ICU and the control cohort respectively (p=0.42).
NYHA class before and after surgery

Preoperatively, there was a greater proportion of patients in NYHA class IIIB/IV in the ICU cohort than in the control cohort (p<0.001) (Fig. 9). Also, before surgery the control cohort had more patients in NYHA class II than did the ICU group (p<0.0001). After surgery, there was no difference between the two groups in the proportion of patients in NYHA class IIIB/IV (p=0.09), but patients in less advanced NYHA classes (I/II) were more common in the control group (p=0.01). Both groups improved by an average of one NYHA class with surgery.
Discussion

The preoperative assessment of the patient

The timing of surgery in relation to symptoms, are we operating late in the disease process?
The decision to submit a patient with a severe heart valve lesion to surgery is based, in the majority of cases, on the onset of symptoms. The symptomatic stage (NYHA class) is an indirect reflection of the severity of the disease in most patients. However, our studies, which can be considered to reflect the heart valve population to an adequate extent, represent a situation where the majority of the patients are in NYHA class IIIB. This is true for all populations of the present studies except for the control cohort in study V. This population, on the other hand, is selected on the basis of a totally uncomplicated postoperative course (<2 days of intensive care). Still, in these very selected patients, 30% are in NYHA class IIIB, and 50% are in class IIIA.
In study I, concerning MR patients operated on in the years 2004-2005, the proportion in NYHA class IIIB is as large as 61%. This must be considered to be too large a proportion in this subclass, since this population is relatively young and referred for elective mitral valve surgery, preferably valve repair. Inevitably, some patients will be submitted to surgery in the later phase of the disease process, but the goal must be to minimise this proportion of patients. In the view of the negative prognostic value of advanced symptoms, it is not advisable to delay surgery until NYHA classes IIIIB/IV. Although surgery can and is performed in end-stage disease, the prognosis for such patients is heavily reduced.

Moreover, at the other end of the spectrum, there is the aspect of patients’ delay. A successive deterioration in functional capacity is not always easily recognized by the patient. The onset of symptoms can be insidious, and the older patients may incorrectly ascribe a decrease in functional ability to other causes and unconsciously adapt to it. The physician caring for the patients should educate them about the significance of a decrease in exercise tolerance or any type of chest discomfort.
According to current guidelines for the management of valvular heart disease published in 1998, surgery for all lesions should be performed promptly after symptom onset. In view of our results, there is reason to believe that these recommendations are not strictly adhered to in clinical practice. In theory, clinical practice guidelines are developed in attempt to decrease the variability in the management of the patients. However, to this date there is no available tool for evaluating adherence to guidelines other than retrospective analyses. The lack of adherence to guidelines is known as a general problem in medicine and can partly be attributed to lack of familiarity with the recommendations in question [119]. Finally, the successful application of evidenced-based research to the actual treatment of the patients must be based on the supposition that practice guidelines do in fact guide practice.

Is there a need for other diagnostic methods? -the role of MRI

The symptomatic patient with a severe regurgitant lesion is not regarded as a great clinical dilemma. However, as the knowledge about silent LV dysfunction and its negative prognostic value increases, the demand for an accurate quantitative preoperative assessment of the lesion is becoming more important [21,120].

In study I, echocardiography correctly identified all patients as having severe MR with semiquantitative methods; whereas only 11% were quantitatively graded as severe MR (regurgitant fracture >40%). Although the value of exact quantification in routine practice may be disputed, it may be of particular importance in patients with a discrepancy between symptoms and severity of lesion on echocardiography. In patients with a suspected severe lesion, the need for an assessment that is more precise will in most cases only arise in the discussion of whether or not to perform surgery.

As MRI has entered the diagnostic arena, the imaging possibilities for the clinicians have increased. In study I, MRI and echocardiography were comparable in assessing severe MR, but not in measurement of regurgitant fraction. This is in agreement with an earlier study, which concluded that the difference between the two methods is greater in patients with severe MR as compared to patients with mild or moderate MR [121]. Furthermore, it is established that MRI is reliable in quantifying regurgitant lesions [122-124]. Since comparing two methods can be difficult, the introduction of a third method, in this case, natriuretic peptides might be useful. Consequently, increasing regurgitant fraction on MRI and increasing vena contracta and PISA on echocardiography correlated well to increasing levels of natriuretic peptides. These results speaks in favor of the peptides as a potential marker of surgical timing although their usefulness in clinical practice is still relatively unexplored.

In the present study, MRI added information to the clinical picture, such as the size of the regurgitant fraction, that was not as reliable or not available on echocardiography. We therefore believe that MRI has a role in the preop-
operative assessment of the patient with mitral regurgitation. For the patient, it is a more attractive option than the transoesophageal echocardiographic approach. Even though it might be premature to use MRI in routine practice, in patients with imaging problems on echocardiography or discordant clinical and echocardiographic data, it can definitely be of value.

Operative mortality

The complex changes in the patient population and the changes in the management of the patients in recent years makes the interpretation of trends in early results difficult. On the one hand there are the general improvements in the preoperative treatment, anaesthesia, surgical technique and postoperative care, and on the other hand there is the older valve population with increasing co-morbidity and coronary artery disease.

Reports regarding early results are often selected patients or case-series which should be viewed with care. Interestingly, a recent review of mortality studies after cardiac surgery suggests that published data tend to underestimate the risk of death and that caution should be exercised in interpreting results from small series, because selection bias and publication bias are more likely in these cases [125]. According to their analysis, most articles that reported operative mortality data below registry averages, where only in a minority of cases statistically different from registry figures.

Our results in patients undergoing mitral valve surgery, the operative mortality, 9.7%, must be considered somewhat high. However, 10% of this cohort includes NYHA class IV patients and almost 50% are patients in NYHA class IIIB. It is established that the preoperative symptomatic status of the patient affects both short- and long-term results. The uncomplicated cohort in study V showed excellent early results with a mortality rate of 2.2%, although 30% had mitral valve surgery and 35% had concomitant CABG. This cohort had the lowest proportion of patients with advanced symptoms, 28%, a fact that must at least partly have contributed to the excellent early results. The risk factors for early mortality found in study II were in conformity with those in earlier studies, that is, age > 70 years, advanced NYHA class, and in cases of AVR, atrial fibrillation. Interestingly, in study III, old age was not a risk factor in patients undergoing MVR when correction was made for other variables. The older patients in that study were more symptomatic and had higher co-morbidity.

In study II, in which two models were constructed, the one with only preoperative variables yielded more prognostic information. However, the practical value of this preoperative prognostic information in clinical work is limited and these assessments of the operative risk are simply estimates. This is reflected in study V, where the ICU cohort and the control cohort had comparable EuroSCOREs preoperatively but early mortality rates of 12% and
2.2%, respectively. This emphasises the fact that irrespective of the score, the outcome is somewhat unpredictable and in the individual patient it is always either one or zero. This aspect of all cardiac surgery underlines the importance of continuous quality assurance of the early results and efforts to improve them.

The usefulness of operative mortality as an outcome measure

Operative mortality is used by clinicians both as a benchmark measure for quality assurance and also when the risk-to-benefit ratio of the proposed procedure is discussed with the patient. Operative mortality remains a critical indicator of quality because it provides a measure of safety of a technique. However, although mortality is the most extreme adverse clinical endpoint, and easily measured, the use of operative mortality alone to evaluate the quality of the care has its limitations.

Most patients are aware of their dismal prognosis if they should choose not to be operated on. Regarding the aspect of survival, most patients are mainly focused on their chance of leaving the hospital alive after their valve replacement. However, the patient should also be enlightened of the fact that even though one survives the operation, the risk of dying in the first year is relatively high. It is known that the operative mortality rate in valve surgery is almost 60% of the 1-year mortality [126]. Most patients are normally unaware of, or do not consider, that if they survive the operation, the risk of dying the first postoperative year is not negligible. Most certainly the majority of the patients are unaware that more than 10% of the heart valve surgery population die within the first year, approximately 5% within 30 days of surgery and approximately 5% in the following 11 months. Therefore, operative mortality might not be optimal to use as an outcome statistic from the patient’s point of view. For most patients, one-year postoperative survival might represent a more meaningful extension of life compared with simply the chance of leaving the hospital alive after their valve replacement.

Long-term survival

In all studies the long-term survival was in accordance with that in earlier reports. In study IV, where subanalysis by age and type of prosthesis was performed, younger patients with a mechanical prosthesis showed superior survival, as compared to those receiving a bioprosthesis. On the contrary, the survival among older patients was not affected by the type of prosthesis.

The relative survival rate in MVR patients in study III is not encouraging, since there was a clear excess mortality, compared to the population in general. This was seen in all subgroups, although this was less pronounced in NYHA class II patients. Irrespective of age, the most important risk factor
for late mortality was the preoperative symptomatic status. Notably, the older patients were more symptomatic preoperatively. However, mitral valve surgery in the elderly is a complex issue that deserves special considerations. Although age was not a risk factor for operative death in study III, patients older than 75 years with need for mitral valve surgery generally have a very dismal prognosis both in the short and long term, and both with and without surgery. The selection of which old patients will or will not benefit from mitral surgery remains a challenge.

To aim for an earlier surgical approach in MVR patients, certain factors must be considered. The operative risk must be taken into consideration and the possibility of valve repair must be high. There is a window of opportunity for performing surgery when the risks of conservative management outweigh the risks of surgery and before the patient’s long-term postoperative survival is compromised. Based solely on the preoperative symptomatic status, the goal should be to operate on MVR patients somewhere in the transition between NYHA II and IIIA to be able to ensure the patient of the most optimal short- and long-term prognosis.

Early post operative complications

The improvements in perioperative myocardial injury and postoperative heart failure in study II are encouraging results. This is most certainly a reflection of improvements in factors related to the anaesthesia and the surgical procedure. The patients showed no tendency to be less symptomatic over the study period, although the occurrence of heart failure in relation to the surgical treatment might have decreased. Still, postoperative heart failure still occurs in as many as 30% of patients undergoing mitral valve surgery, again emphasising the vulnerability of this group. Thus, the preoperative condition of heart valve patients, especially those about to undergo mitral surgery, must be is optimised in attempts to reduce the incidence of postoperative heart failure.

Valve-related complications

Once surgery is performed, when valve repair is not feasible, the patient is put at a life-long risk for valve-related complications. In study IV the rate of these complications was examined. A mechanical prosthesis implied a higher risk of bleeding as compared to a bioprosthesis, especially in older patients. This is in agreement with earlier reports [59,72,74]. Furthermore, it is somewhat accepted that mechanical prostheses have a higher rate of prosthesis-related embolism than bioprostheses [59,72,74]. However, our results concluded the contrary. In our study, patients with a bioprosthesis had a higher incidence of thromboembolism than those with a
mechanical prosthesis. This was true for all age groups. The reason for the
contradictory result of our study is unclear. However, the risk of an overes-
timation of embolism must be considered small. If anything, it should be the
contrary, since all patients with an embolic event who did not require hospi-
tal admission were not registered. The possibility of under-reporting of em-olism in earlier studies must be considered. In most studies the details of
the follow-up are not very well described, and do most often consist of a
telephone call or a mailed questionnaire [72,74]. It has been shown that pa-
tients very easily forget to report events at interviews or in telephone calls.
No other study has used the ICD classification system to evaluate valve-
related complications. In previous studies the validity of the ICD classifica-
tion system has been found to be almost 90% [127]. The rate of false posi-
tive cases was approximately 5%, and the rate of false negatives was around
3%. Also, the rate of under-reporting has been established at around 1-2%.
However, if it was assumed that 10% of the diagnoses were misclassifica-
tions, our results would most probably not have been altered. The results
may be considered to be reliable, or at least not to imply a risk of overesti-
mating events. Thus, we believe that our results regarding valve-related
complications are valid.
The group of patients with a bioprosthesis might be undertreated with regard
to anticoagulation. Certainly, most patients develop risk factors that require
anticoagulation (stroke, LV dysfunction, atrial fibrillation) as their cardiac
condition worsens and perhaps this fact is not medically adjusted for with
time.
Moreover, the risk of events was time-related. The risk of bleeding was more
increased the first five years after surgery and the risk of a thromboembolic
event was more increased more than five years after surgery. Interestingly,
with a mechanical prosthesis, the risks for an adverse event increased with
increasing age, while this was not true for a bioprosthesis.
By tradition, technical surgical solutions are often searched for in order to
improve the long-term results for surgical patients, but in case of valve-
replacement surgery, ensuring a good anticoagulation control is likely to
have a great effect on survival. Physicians caring for patients with prosthetic
valves have a major responsibility to ensure that their patients receive the
best possible anticoagulation management.

The choice of the optimal prosthesis in relation to age

We speak in favour of using a bioprosthesis in older patients. This might
seem to be to prove the obvious. However, in most studies that are not se-
lected case-series, older patients still receive mechanical prostheses to a
great extent. For example, in the analysis of all heart valve operated patients
1985-2001 at our department, 40% of the patients older than 70 years re-
ceived a mechanical prosthesis for one reason or another. If an older patient
needs anticoagulant therapy for other indications such as atrial fibrillation, it
might still be preferable to insert a bioprosthetic valve. In any case, if a patient carries a mechanical there is no option to end the anticoagulant treatment if, for example, bleeding occurs. On the other hand, in a patient with a bioprosthesis one has the option of either initiate or terminate treatment if there are problems with embolism or bleeding.

Moreover, a recent study on life expectancy after valve replacement added some interesting information to the debate. They show that for a 65-year old man the life expectancy is 10.4 years after implantation with a mechanical valve and 10.7 years after a bioprosthesis. Event-free life expectancy was 7.7 and 8.4 years, respectively. They found that the age crossover points between the two valve types were 59 and 60 years. Consequently they suggest that the age threshold for implanting a bioprosthesis could be lowered further and thereby considered for patients under 65 years of age.

Moreover, with the assumption that the frequency of non-cardiac surgery increases with age, a patient with bioprosthetic valve will be more easily handled in such situations.

In certain circumstances, when a mechanical valve is chosen in older patients the anticoagulant treatment should be optimized. Certainly, it must be so that anticoagulation therapy has become more refined over the recent years [129-131], and that modern bleeding rates might hopefully be lower than those reported earlier. Although the only two randomised trials reported increased bleeding with mechanical prostheses it should be emphasized that they were conducted nearly thirty years ago and that caution should be made to extrapolate data from these two trials alone to modern practice.

Quality of life

Previously, the postoperative results focused mainly on the operative procedure, and the QoL of the patients undergoing heart valve surgery has only recently begun to gain attention.

From the patients’ point of view, the two major benefits of the operation are: 1) the likelihood of survival and 2) the improvement in functional status and quality of life. Studies have shown that most valve patients do improve both their QoL and their functional capacity with surgery. However, approximately 20% of the patients undergoing cardiac surgery do not benefit from the procedure with regard to QoL. This is in agreement with the results from study V, where 78% of the ICU cohort and 82% of the control cohort reported QoL improvement with surgery. Also, no patient in the ICU group and only one patient in the control cohort reported that they regretted having the operation. Thus, although approximately 20% of the patients did not experience an improvement, they did not regret undergoing surgery. Perhaps they were aware of the dismal prognosis associated with medically treated significant heart valve disease.
The ICU group of study V reported more physical difficulties in both SF-36 and NHP scores. However, there was no difference in anxiety or depression (HAD scale) or summarised mental health in the SF-36 between the two groups. This can be viewed from two perspectives. On the one hand, the least complicated patients are in no better mental health than the most complicated, which is somewhat surprising. On the other hand, the most complicated patients appear to be unaffected by the complex postoperative course. One would expect that the prolonged ICU stay might have had some mental sequelae, since this has been shown in earlier studies on such patients.

Traditionally, the postoperative mental health of surgical populations has not been considered to be “rocket science”, especially not by the surgeons themselves. However, as the horizon of outcome measures widens, studies regarding such outcomes are increasing. Recently it was shown that depression can predict mortality after valve surgery [132]. In that prospective study of 648 patients, depression was present in 30% of the patients at baseline and was an independent predictor of mortality. The authors suggest that depression screening should be incorporated into preoperative risk stratification and that treatment of depression might improve outcome.

Finally, it needs to be reemphasized that the QoL, functional status and mental health of the post surgical population seem to be essential pieces of the puzzle to ensure an optimal outcome.

Finally

To improve the overall results for the heart valve operated patient, the whole chain of management from the preoperative assessment to the optimising of anticoagulation control, must be taken into consideration. It is unlikely that improvements in one area, for example the operative procedure, will affect the wide spectrum of variables that determine the overall outcome for a patient. Our results show that areas of improvement of specific interest are to move closer perfection in the timing of surgery, and to aim for a reduction in valve-related complications. There are still some efforts to be made in order to improve the overall management of the heart valve patient.
Conclusions

- In patients with severe mitral regurgitation, MRI and echocardiography were comparable in assessing MR, but not in quantifying regurgitant fraction.

- NT-proANp and NT-proBNP correlated well to regurgitant fraction on MRI, and to vena contracta and PISA on echocardiography; and can therefore complement data obtained by imaging methods in patients with mitral regurgitation and imaging difficulties and/or diffuse symptoms.

- The risk of death, myocardial injury and postoperative heart failure early after heart valve surgery has decreased over the last decade. The proportion of patients over 70 years of age and of those with diabetes has increased whereas other risk factors have remained stable.

- Survival is reduced after mitral valve replacement in patients with severe preoperative symptoms, whereas patients with less severe symptoms have excellent survival. Older patients were more often severely symptomatic at the time of surgery.

- Event-free survival is superior in younger patients with a mechanical prosthesis, but is not influenced by valve type in older patients. Mechanical prostheses entail a higher incidence of bleeding, especially in older patients, whereas biological prostheses are associated with an increased risk of thromboembolism.

- Ageing with a mechanical prosthesis is associated with decreased event-free survival. This risk was not observed in patients with a bioprosthesis.

- Quality of life in terms of physical health in patients who required prolonged intensive care after heart valve surgery is reduced as compared to controls. Mental health is equivalent in the two groups.
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References


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