Long-term follow-up of morbidity and mortality after aortic valve replacement with a mechanical valve prosthesis

P. Kvidal¹, R. Bergström², T. Malm³ and E. Ståhle⁴

¹Departments of Cardiology and ⁴Thoracic and Cardiovascular Surgery, University Hospital, Uppsala, Sweden, ²Department of Thoracic and Cardiovascular Surgery, University Hospital, Lund, Sweden; ³Department of Statistics, University of Uppsala, Uppsala, Sweden

Aims The aim of this study was to determine the incidence of valve-related complications in patients with a mechanical aortic valve prosthesis and to identify risk factors for an adverse outcome.

Methods and Results In the 424 patients, event-free survival rates 5 and 10 years after aortic valve replacement were 62% and 37%, respectively. The linearized incidence of thromboembolic events was 4.4% per patient-year, and of anticoagulant-related haemorrhage 8.5% per patient-year. Advanced NYHA functional class, atrial fibrillation, pure aortic regurgitation and thromboembolism prior to surgery decreased event-free survival. A history of pre-operative thromboembolism increased the risk for a first embolic event after aortic valve replacement (relative hazard [RH] 3.2), but was even more strongly associated with the risk for repeated events (≥2 events, RH 5.4). After each thromboembolic episode that occurred, the risk for a subsequent one was increased. The risk for at least one, and up to three or more haemorrhages was increased in patients with a pre-operative history of bleeding (RH 3.3–5.1) and of atrial fibrillation (RH 1.8–3.9). The risk for a subsequent event was increased by a history of repeated haemorrhages, a short interval since previous bleeding, and high age.

Conclusions There were few factors strongly related to valve related morbidity. However, previous bleedings and previous thromboembolism were powerful risk factors for repeated events.

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Key Words: Heart valve replacement, aortic valve, mechanical valve prosthesis, Björk-Shiley Monostrut, Edwards Duromedics, long-term follow-up, prospective.

See page 1032 for the Editorial comment on this article

Introduction

The timing of surgery in patients with heart valve disease is still a matter of controversy¹–⁶. Many recent studies have confirmed that marked symptomatic deterioration implies an increased early and long-term risk and that excellent survival is achieved for patients in functional class II of the New York Heart Association (NYHA)⁷. Some authors therefore advocate earlier surgical intervention¹,²,⁵. However, a number of considerations, besides the expected excellent relative survival, must be taken into account in the management of patients with no or minimal symptoms. Even though the operative mortality and morbidity are low in patients in NYHA classes I and II, they are still not negligible, considering that a negative outcome will affect a more or less asymptomatic individual with at least some years of intact quality of life ahead. Further, early surgery exposes the patient to a number of extra years with a risk of valve-related mortality and morbidity. A number of patient- and disease-related factors will influence the morbidity associated with the prosthetic valve. In the majority of patients undergoing surgery a mechanical prosthesis is the valve substitute of first choice⁸.

Moreover, a substantial problem is that a considerable proportion of the patients sustain not only one but several episodes of particular complications⁹–¹¹. In these reports the second or further repeated thromboembolic events constituted 28% to 31% of all the documented episodes.

The present study is a prospective and careful documentation of morbidity and mortality during a 10-year period after aortic valve replacement among 424 patients who received mechanical valve prostheses.
Methods

Patients

From October 1983–May 1988, 943 patients underwent heart valve replacement at the Department of Thoracic and Cardiovascular Surgery of the University Hospital, Uppsala, Sweden. Of these operations 649 were isolated aortic valve procedures, and in 519 of those cases a mechanical prosthesis was used. Of the 519 patients, 424 (82%) were enrolled in a prospective randomized study undertaken with the primary aim of carrying out a long-term follow-up of the morbidity and mortality associated with two mechanical prostheses, namely the Björk-Shiley Monostrut (n=213) and the Edwards Duromedics (n=211). A secondary aim was to compare the performance of these two valves, the Björk-Shiley Monostrut prosthesis representing the single tilting disc, and the Edwards Duromedics prosthesis representing the bileaflet model. These 424 patients constituted the basis of the present report. Ninety-five patients, not included in the study, were given a St. Jude bileaflet (n=78) or a Björk-Shiley Monostrut (n=17) by reason of the personal preference of the surgeon.

Of the 424 studied patients, 316 (74%) were men (mean age 58.5 years, range 11–76) and 108 (26%) were women (mean age 60±4 years, range 22–77). One hundred and forty-four patients (34%) underwent concomitant coronary artery bypass grafting (CABG). Pre-operative coronary angiography was performed in 83% and echocardiography in 91% of the patients. In 239 (56%) patients the left ventricular function was good, 158 (37%) had moderate dysfunction and 27 (7%) patients had severe left ventricular dysfunction. Fifty patients had a history including myocardial infarction, 32 infectious endocarditis and 29 patients had experienced episodes of heart failure. Twenty-six patients had diabetic disease.

All operations were performed with a uniform standard technique. Our policy at the time was to recommend a bioprosthesis to patients aged 70 years or more. However, the type and trademark of the prosthesis were left to the discretion of each surgeon. In the 424 patients of the present study, the decision concerning their inclusion was made by the surgeon in the operating room, after pre-operative approval by the patient. The surgeon then randomized the patient to receive either an Edwards Duromedics or a Björk-Shiley Monostrut prosthesis.

Anticoagulation and antiplatelet therapy

The patients were prescribed life-long treatment with oral anticoagulants. The therapeutic range of prothrombin complex (factors II, VII and X) is 10% to 20%, corresponding to an International Normalized Ratio (INR) of 2.5 to 4.3. Different thromboplastins have been used for tests in controlling anticoagulant therapy, but most laboratories, including the laboratory at the Uppsala University Hospital, initially applied the Thrombotest® (Nycomed, Oslo, Norway). Subsequently the Prothrombin complex® test (Nycomed, Oslo, Norway) was introduced and this gradually replaced the Thrombotest®. These tests produce results for an anticoagulant measurement as a percentage of the normal. In the present studies the figures were converted to the corresponding INR. Dipyridamole was recommended in all patients (100 mg four times daily). The treatment was instituted immediately after the surgical procedure.

Data collection, follow-up and outcome events

Regular follow-up examinations were carried out 1, 3, 5 and 10 years after the valve replacement. A unique 10-digit national registration number is allocated to every Swedish citizen. All patients were followed up with respect to survival by computerized linkage to two national registers, namely the Swedish Cause of Death Register and a continuously updated population register. By use of these combined registers, all patients could be assigned a date of death or identified as being alive. The last follow-up according to survival was on 31 December 1997. The 1-year follow-up included a recording of the patient’s history and physical examination by both a cardiac surgeon and a cardiologist. Follow-ups after 3, 5, and 10 years were performed by written questionnaires. All data concerning suspected events of morbidity were collected from hospital records. In all deceased patients autopsy reports and death certificates were also collected. For definitions of morbidity and mortality the Guidelines recommended by the Council of The Society of Thoracic Surgeons were considered[12].

The total duration of follow-up in the 424 patients comprised 3873 patient-years (range 0–13.9 years, median 10.3 years). No patient was lost to follow-up. The 1, 3, 5 and 10-year follow-ups comprised 100, 95, 95 and 100% of the patients, respectively, but for the missing patients data were obtained from records of the local hospitals.

Statistical methods

Early mortality (death from any cause within 30 days postoperatively)

For identification of factors related to the early outcome, logistic regression analysis[19] was performed. The odds ratio (OR) from this analysis was used as a measure of the relative risk.

Long-term morbidity and mortality

The probability of freedom from the first event (with death and valve-related complication used as endpoints) was calculated by the actuarial (life-table) method. Analyses of factors related to outcome were
based on the standard Cox proportional hazards model\cite{15}. For analyses of overall and event-free survival, a modified version of the Cox model was also employed. As the basic models used imply the assumption that the relative hazards are constant over time, separate models were estimated for follow-up years 0–5 years and ≥ 5 years. Further, the standard Cox model was used for analysis of the interaction between risk factors and type of lesion (i.e. pure regurgitation vs stenotic or combined lesion).

Linearized rates\cite{12,15} of thromboembolism and haemorrhages represent the sum of events per patient-year, presented as the average rates with 95% confidence intervals\cite{15} over the total follow-up period, by follow-up year and by calendar year.

Analyses of repeated events of thromboembolism and haemorrhages were performed by two different approaches\cite{15}.

**Analyses of a specified number of episodes of a particular complication.** In order to assess the risk for a specified number of episodes of a particular complication, each event (each of one or more, two or more or three or more events) was defined as a separate, terminating, time-related event, each with a starting time at the original valve replacement and censored by death, valve removal or attainment of the end of the patients’ study period. Using this approach, actuarial freedom from one or more, two or more and three or more episodes of thromboembolism or haemorrhage after aortic valve replacement could be depicted as a function of time after operation and of associated risk factors.

**Analyses of the overall risk for an episode of a particular complication and the risk for a subsequent event in the subset of patients who had already experienced at least one such event.** In order to assess the risk and to identify and evaluate risk factors for any event, and the conditional risk for a new event given the occurrence of a previous one, a new data set was constructed, consisting of: (a) the original cohort of patients, with the starting time set to the time of valve replacement, (b) the patients experiencing a first event with the time zero set to the time of the occurrence of the first event, and (c) the patients experiencing a second event with the time zero set to the time of the second event; (d) this adjustment is then repeated for the patients experiencing a following event with the starting time re-set to the time of each preceding event. Thus a database consisting of 592 situations with risk for thromboembolism and 744 situations with risk for haemorrhage was constructed. Patients who suffered a lethal event and died within one day from the onset of that event were not at risk for a subsequent event. This augmented data set became the basis of a multivariate analysis, and the number of previous thromboembolic or haemorrhagic events and the interval since the last event were also considered in the risk factor analyses. The actuarial curves for thromboembolism and anticoagulant-related haemorrhage for the augmented data set were calculated by the actuarial (life-table) method.

Uni- and multivariate analyses of factors related to outcome were based on the standard Cox proportional hazards model and applied in the above-described settings. The explanatory variables were used in dichotomous, categorical or categorized form and were analysed as a set of k-1 dummy variables, where k is the number of categories, one of the categories serving as reference. The reference categories were chosen so as to include a sufficient number of patients. In the multivariate analyses the variables were used in the form with the best discriminatory power. The relative hazard (RH=exp[β1]) was used as a measure of the risk of a negative outcome in different categories, where β1 is the basic parameter in the Cox model.

All statistical calculations were performed with the SAS 6.12 statistical procedure (SAS Institute).

The following variables were entered into the analysis: demographic variables (age at operation, sex), history of the disease (previous myocardial infarction, previous thromboembolic episode), symptoms and clinical status (left heart failure, the modified NYHA functional class\cite{16}, pre-operative heart rhythm [sinus rhythm, atrial fibrillation, or other], infectious endocarditis), associated conditions (pre-operative renal dysfunction [defined as pre-operative serum creatinine >125 μmol.1⁻¹], pre-operative catheterization data (concomitant coronary artery disease [i.e. at least one major vessel with a stenosis of 50% or more], left ventricular function, type of lesion), and characteristics of the surgical procedure (concomitant CABG, trademark of the mechanical valve), information concerning previous thromboembolic episodes (number of previous episodes, nature of immediately previous episode [transient ischaemic attack], INR level in relation to previous episode (<2.1), time interval since immediately previous episode), and information concerning previous haemorrhagic episodes (number of previous haemorrhages, time interval since immediately previous episode of haemorrhage).

### Results

**Early outcome**

Seventeen patients (4-0%) died within the first post-operative month. The causes of early death are given in Table 1. Pre-operative atrial fibrillation (OR=11.7, 95% confidence interval (CI=5.6–24.6), and type of mechanical valve (Edwards Duromedics OR=0.3, 95% CI=0.08–0.8), were the only factors that influenced early mortality independently.

Valve-related morbidity that occurred within 30 days comprised 10 patients who developed thromboembolism, three patients with an anticoagulant-related haemorrhage, and two patients who were submitted to early reoperation because of periprosthetic leakage and peroperative injury to the right coronary artery, respectively.
Overall mortality (based on all deaths)  
(Fig. 1, Table 1)

The overall observed survival rates after 3, 5 and 10 years were 92%, 88% and 70%, respectively. At the close of the study, a total of 166 patients had died. The causes of death (Table 1) were ascertained at autopsy in 72 of these cases (43%) at study end. In line with the definitions, 13 patients with sudden death without autopsy were included in the group of valve-related complications and thereby valve-related deaths. Cardiac causes and/or valve dysfunction were found in 47% of the deaths, and heart failure as the primary cause in 17%.

Event-free survival (Fig. 1, Table 2)

Three hundred and four patients died or had a valve-related complication. The event-free survival rates

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**Table 1 Causes of death**

<table>
<thead>
<tr>
<th>(a) Early deaths (within 30 days after surgery)</th>
<th>Cause</th>
<th>No.</th>
<th>No. with autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac non-valve-related</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve-related</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular thrombosis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Various</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) Late deaths (more than 30 days after surgery)</th>
<th>Cause</th>
<th>No.</th>
<th>%</th>
<th>No. with autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac non-valve-related</td>
<td>57</td>
<td>38.3</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>22</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>19</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden death, cardiac</td>
<td>16</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve-related</td>
<td>57</td>
<td>38.3</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>21</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained sudden death</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periprosthetic leakage with heart failure</td>
<td>6</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular thrombosis</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural prosthetic failure</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>5</td>
<td>3.4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total cardiovascular and/or valve-related deaths</td>
<td>119</td>
<td>79.9</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>21</td>
<td>14.1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Various (e.g. infection)</td>
<td>9</td>
<td>6.0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total of all late deaths</td>
<td>149</td>
<td>100</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

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Eur Heart J, Vol. 21, issue 13, July 2000
after 3, 5 and 10 years were 72%, 62% and 37%, respectively

Thromboembolism (Figs 2–5, Table 2)

There were 171 thromboembolic events in 96 patients, consisting of 96 transitory attacks, 54 minor strokes and 21 major strokes, of which 10 were lethal. Thirty-two patients had two or more thromboembolic events. In addition, there were three cases of valve thrombosis, and in line with the above definition of thromboembolism, these were not included under that heading. The valve thrombosis resulted in death in two patients. The overall linearized rate of thromboembolism was 4.4% per patient-year and the linearized rates by follow-up year and calendar year are depicted in Figs 2 and 3.

Actuarial freedom from a specified number of episodes of thromboembolism after aortic valve replacement with a mechanical valve prosthesis is depicted in Fig. 4.

After surgery the 5-year estimated freedom from the first thromboembolic event was 84%, after a first event the 5-year estimated freedom from a second event was 65%, and after two or more events the 5-year estimated freedom from a new event was 30% (Fig. 5).

Anticoagulant-related haemorrhage (Figs 2, 3, 6 and 7, Table 2)

After surgery, 329 episodes of non-trivial bleeding were observed in 164 patients. Twenty-three patients (0.59%
per patient-year) suffered a lethal haemorrhage, in 15 (65%) of whom it was intracerebral. Twenty-five per cent (82/329) of the bleedings were of nasal origin. In 80% of the events the haemorrhage was of non-traumatic cause, in 8% it was connected with surgery and in 12% it was explained by other trauma. Sixty patients suffered two or more haemorrhages.

The average linearized rate of haemorrhage among all patients was 8.5% per patient-year and is presented by follow-up and calendar year in Figs 2 and 3.

Actuarial freedom from a specified number of episodes of haemorrhage after aortic valve replacement is depicted in Fig. 6.

After surgery the 5-year estimated freedom from a first haemorrhage was 80%, and after a first haemorrhage the 5-year estimated freedom from a second event was 56%. Following two or more events the estimated freedom from a new event was 37% after 5 years (Fig. 7).

Structural valve dysfunction (Table 2)

Two patients with an Edwards Duromedics prosthesis had a leaflet escape. In both cases autopsy revealed that one of the two leaflets had broken. Two patients with an Edwards Duromedics prosthesis and one patient with
seemed to be associated with deaths occurring within the NYHA comitant CABG, pre-operative atrial fibrillation, and Advanced NYHA functional class, higher age, concomitant aortic regurgitation were independent risk factors for overall mortality (based on all deaths) (Tables 3 and 4).

The results are specified in Table 2.

## Risk factor analysis

### Overall mortality (based on all deaths) (Tables 3 and 4)

Advanced NYHA functional class, higher age, concomitant CABG, pre-operative atrial fibrillation, and pure aortic regurgitation were independent risk factors in the Cox model (Table 3). The results from the modified Cox model are presented in Table 4. NYHA functional class and pre-operative atrial fibrillation seemed to be associated with deaths occurring within the first 5 years postoperatively, but had little impact on deaths occurring more than 5 years after surgery. The Duromedics valve prosthesis was associated with a somewhat lower risk more than 5 years after surgery.

### Event-free survival (Tables 3 and 4)

Advanced NYHA class, pre-operative atrial fibrillation, a pre-surgical episode of thromboembolism and pre-operative renal insufficiency were independent risk factors for events occurring within 5 years. Only pure aortic regurgitation was a significant ($P=0.04$) risk factor for valve-related complications or deaths occurring more than 5 years after surgery, and this risk factor was weak (RH 1.5).

### Interaction analysis

Concomitant coronary artery disease with grafting influenced survival only in patients with a stenotic or mixed lesion (RH=1.9; 95% CI=1.3–2.6 for stenotic or mixed lesion, RH 0.9; 95% CI=0.4–1.7 for pure regurgitation). There were no significant interaction effects between type of lesion and risk factors for event-free survival.

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**Table 3** Results of multivariate analyses of the influence of pre-operative patient characteristics on overall and event-free survival, using the Cox regression model and a stepwise approach

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>Event-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>51</td>
</tr>
<tr>
<td>IIIA</td>
<td>167</td>
</tr>
<tr>
<td>IIIB</td>
<td>182</td>
</tr>
<tr>
<td>IV</td>
<td>24</td>
</tr>
<tr>
<td>Lesion</td>
<td></td>
</tr>
<tr>
<td>AS/mixed</td>
<td>313</td>
</tr>
<tr>
<td>AR</td>
<td>111</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>376</td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>280</td>
</tr>
<tr>
<td>Yes</td>
<td>144</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>65</td>
</tr>
<tr>
<td>50–59</td>
<td>109</td>
</tr>
<tr>
<td>60–69</td>
<td>216</td>
</tr>
<tr>
<td>≥70</td>
<td>34</td>
</tr>
<tr>
<td>Prosthesis</td>
<td></td>
</tr>
<tr>
<td>BSM</td>
<td>213</td>
</tr>
<tr>
<td>DM</td>
<td>211</td>
</tr>
<tr>
<td>Thromboemboli</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>384</td>
</tr>
<tr>
<td>Yes</td>
<td>40</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>411</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
</tr>
</tbody>
</table>

RH=relative hazard; CI=confidence interval; NYHA=New York Heart Association; AS=aortic stenosis; AR=aortic regurgitation; CABG=coronary artery bypass grafting; BSM=Björk-Shiley Monostrut; DM=Edwards Duromedics.

a Björk-Shiley Monostrut had a valve thrombosis. Finally, in one patient with a Björk-Shiley Monostrut a prosthetic leakage due to suture trap occurred.

### Valve-related complications

The results are specified in Table 2.
on pre-operative patient characteristics

Analyses of overall and event-free survival using a modified Cox regression model on pre-operative patient characteristics

**Table 4** Comparison of relative hazards at different time intervals. Based on analyses of overall and event-free survival using a modified Cox regression model on pre-operative patient characteristics

(a) Overall survival

<table>
<thead>
<tr>
<th></th>
<th>0–5 years after surgery</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Dead</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>51</td>
<td>1</td>
</tr>
<tr>
<td>IIIA</td>
<td>167</td>
<td>22</td>
</tr>
<tr>
<td>IIIb</td>
<td>182</td>
<td>30</td>
</tr>
<tr>
<td>IV</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Lesion</td>
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<td></td>
</tr>
<tr>
<td>AS/mixed</td>
<td>313</td>
<td>40</td>
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<tr>
<td>AR</td>
<td>111</td>
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<td>Atrial fibrillation</td>
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<tr>
<td>No</td>
<td>376</td>
<td>41</td>
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<td>Yes</td>
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<td>CABG</td>
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<tr>
<td>No</td>
<td>280</td>
<td>32</td>
</tr>
<tr>
<td>Yes</td>
<td>144</td>
<td>28</td>
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<tr>
<td>Age, years</td>
<td></td>
<td></td>
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<tr>
<td>&lt;50</td>
<td>65</td>
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<td>50–59</td>
<td>109</td>
<td>14</td>
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<tr>
<td>60–69</td>
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<td>≥70</td>
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<td>Prosthesis</td>
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<td>213</td>
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<tr>
<td>DM</td>
<td>211</td>
<td>30</td>
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</tbody>
</table>

(b) Event-free survival

<table>
<thead>
<tr>
<th></th>
<th>0–5 years after surgery</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Events</td>
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<tr>
<td>NYHA</td>
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<td></td>
</tr>
<tr>
<td>I–II</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>IIIA</td>
<td>167</td>
<td>68</td>
</tr>
<tr>
<td>IIIb</td>
<td>182</td>
<td>88</td>
</tr>
<tr>
<td>IV</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS/mixed</td>
<td>313</td>
<td>131</td>
</tr>
<tr>
<td>AR</td>
<td>111</td>
<td>53</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>376</td>
<td>151</td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>411</td>
<td>173</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Thromboemboli</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>384</td>
<td>158</td>
</tr>
<tr>
<td>Yes</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

RH = relative hazard; CI = confidence interval; NYHA = New York Heart Association; AS = aortic stenosis; AR = aortic regurgitation; CABG = coronary artery bypass grafting; BSM = Bjork-Shiley Monostrut; DM = Edwards Duromedics.

**Thromboembolism (Tables 5 and 6)**

A pre-operative history of thromboembolism was a strong risk factor for any specified number of thromboembolic events after aortic valve replacement and became progressively more important with increasing numbers of events (Table 5). Pre-operative renal dysfunction was a risk factor for the first thromboembolic event.

**Anticoagulant-related haemorrhage (Tables 5 and 6)**

The number of previous events and a pre-operative history of a thromboembolic episode were independent risk factors for the occurrence of a subsequent thromboembolic event (Table 6).

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Among the 32 patients with repeated events of thromboembolism, nine had antiplatelet therapy reinforced, three by re-introduction of dipyridamole and six by addition of aspirin. In another six patients dipyridamole was actually withdrawn.

### Discussion

This study was carried out as a prospective and careful follow-up and revealed that mechanical aortic prostheses are associated with substantial morbidity and mortality. In order to be representative of patients with aortic valve disease, the studied patients should ideally be unselected. During the study period, all patients with significant aortic valve disease, within a defined population, were referred to our clinic for surgery, which meant that selection was minimized. However, the study was not strictly population-based, since the patients were not consecutive but consisted of 82% of such patients operated on during the defined time period. This study is one of the few prospective long-term studies\(^9,17,18\) in the sense of data collection, which is the method recommended in the guidelines for achieving more realistic morbidity figures.

There are numerous papers\(^8\) reporting on the performance of available prostheses of different trademarks. A major problem in the interpretation of these studies is the inconsistency in the definitions used for reporting morbid events\(^8,9\). In spite of the accepted Guidelines\(^12\) recommended by all journals, many investigators do not follow the proposed principles.

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**Table 5** Risk factors for a specified number of episodes of thromboembolism or haemorrhage in the multivariate Cox regression model

<table>
<thead>
<tr>
<th>Patients</th>
<th>Patients experiencing ≥1 event</th>
<th>≥2 events</th>
<th>≥3 events</th>
</tr>
</thead>
<tbody>
<tr>
<td>at risk no.</td>
<td>RH (95% CI)</td>
<td>no.</td>
<td>RH (95% CI)</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboemboli before AVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>384</td>
<td>78</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>40</td>
<td>18</td>
<td>3.2 (1.9-5.4)</td>
</tr>
<tr>
<td>Pre-operative renal dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>411</td>
<td>91</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>5</td>
<td>3.0 (1.2-7.4)</td>
</tr>
<tr>
<td>Haemorrhagic events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage before AVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>413</td>
<td>155</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>9</td>
<td>3.3 (1.7-6.6)</td>
</tr>
<tr>
<td>Atrial fibrillation before AVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>376</td>
<td>146</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>18</td>
<td>1.8 (1.1-2.2)</td>
</tr>
<tr>
<td>Renal dysfunction before AVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>411</td>
<td>155</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>9</td>
<td>4.6 (2.3-9.1)</td>
</tr>
</tbody>
</table>

RH=relative hazard; CI=confidence interval; AVR=aortic valve replacement.
Table 6  Factors that influenced the risk for any and a subsequent thromboembolic and haemorrhagic event in the multivariate Cox regression model. Analyses of 592 situations with a risk for a thromboembolus based on 171 thromboembolic episodes, and 744 situations with a risk for a haemorrhage based on 329 haemorrhagic episodes in 424 patients

<table>
<thead>
<tr>
<th>Thromboembolic events</th>
<th>Subsequent events (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events (n=592)</td>
<td></td>
</tr>
<tr>
<td>No. of previous thromboemboli after AVR</td>
<td>RH (95% CI)</td>
</tr>
<tr>
<td>0</td>
<td>424 96 1 0 (reference)</td>
</tr>
<tr>
<td>1</td>
<td>95 32 2 1 (4.3-1.1)</td>
</tr>
<tr>
<td>2</td>
<td>31 16 3 6 (2.1-6.3)</td>
</tr>
<tr>
<td>3</td>
<td>16 9 4 6 (2.3-9.2)</td>
</tr>
<tr>
<td>≥4</td>
<td>26 18 7 6 (4.5-13.3)</td>
</tr>
</tbody>
</table>

| Pre-operative thromboembolism |                          |
| No                      | 506 123 1 0 (reference)  |
| Yes                     | 86 48 2 4 (1.7-3.5)       |

<table>
<thead>
<tr>
<th>Haemorrhagic events</th>
<th>Subsequent events (n=320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events (n=744)</td>
<td></td>
</tr>
<tr>
<td>No. of previous haemorrhages after AVR</td>
<td>RH (95% CI)</td>
</tr>
<tr>
<td>0</td>
<td>424 164 1 0 (reference)</td>
</tr>
<tr>
<td>1</td>
<td>157 60 1 8 (1.4-2.5)</td>
</tr>
<tr>
<td>2</td>
<td>32 26 3 3 (2.2-4.9)</td>
</tr>
<tr>
<td>≥3</td>
<td>72 52 8 1 (5.7-11.7)</td>
</tr>
</tbody>
</table>

| Pre-operative history of haemorrhage |                          |
| No                    | 702 296 1 0 (reference)  |
| Yes                   | 42 33 2 3 (1.6-3.4)      |

| Atrial fibrillation before AVR |                          |
| No                    | 632 263 1 0 (reference)  |
| Yes                   | 112 66 1 4 (1.0-1.9)     |

| Inter-event interval, years |                          |
| Linear                 | 0.9 (0.8-1.0)            |

| Age at surgery, years |                          |
| <50                   | 34 9 1 0 (reference)     |
| 50-<60                | 62 27 1 8 (0.9-4.3)      |
| 60-<70                | 205 117 2 4 (1.3-5.3)    |
| ≥70                   | 19 12 3 7 (1.7-10.0)     |

1Situation with risk; RH=relative hazard; CI=confidence interval; AVR=aortic valve replacement; 2Every year in the time interval since the previous event implies a reduction in RH by 0.9.

Horstkotte[19] suggests that all studies reporting an annual incidence of thromboembolic plus bleeding complications of less than 2.0% per year lack proper follow-up techniques, as not even the background incidence of such complications in the general populations will have been detected. Furthermore, most reports on follow-up of morbidity associated with mechanical aortic prostheses provide insufficient information on the length of follow-up per patient to allow an evaluation of the risk for repeated morbid events. In our study, all surviving patients were followed up for a minimum of 9 years, which means that the present study may provide a representative picture of the long-term incidence of thromboembolism and haemorrhages.

The incidence of thromboembolism in this study (4.4% per patient-year) was higher than that reported from many other studies[8], but comparable with the figures in some reports. Horstkotte[9] found a linearized incidence of late thromboembolic events of 4.2% per patient-year for the St. Jude medical prostheses in the aortic position. In a recent study[10] excellent performance was achieved with the CarboMedics prosthetic valve, with an incidence of major thromboembolism of 0.9% per patient-year. However, according to the recommended guidelines not only major but also minor and transient thromboembolic events should be reported. The incidence of major thromboembolic episodes in the present study was 0.5% per patient-year, but transient episodes...
constituted 56% of all thromboembolic events. This further illustrates how the definition used will inevitably influence the result and how a careful follow-up will reveal a higher incidence of adverse events.

This study underlines the chronic nature of thromboembolism in patients with mechanical heart valves. Recurrent morbid events constitute an important clinical problem in patients with mechanical heart valves, both in respect to potential physical consequences for the individual patients and to the amount of health care involved. Twenty-one per cent of the patients in the present study had at least two episodes of thromboembolism and/or at least two episodes of haemorrhage. Furthermore, 63% of all the thromboembolic episodes (107/171) and 68% of all the haemorrhages (225/329) after surgery occurred in patients who sustained more than one episode of the complication.

Our results illustrate the strong impact of previously experienced thromboembolism on the risk for a new event and in order to reduce the risk for repeated thromboembolism a number of factors need to be considered in relation to a thromboembolic event:

First, was the INR not within the therapeutic range? The present study has confirmed that a high proportion (53%) of the INR values were outside the therapeutic range in association with the first incidence of thromboembolism[20,21]. At regular follow-ups after 1 and 10 years, 38% and 32% of the INR values were outside the intended target range. This emphasizes that the quality of management of anticoagulation can still be improved. However, data on the percentage time within the target range would permit a more accurate assessment of compliance. This requires repeated measurements of anticoagulation in individual patients. The patients with thromboembolic events were receiving anticoagulation therapy of the same degree of intensity as the event-free patients at the 1-year and 10-year follow-up, indicating that they did not belong to a notoriously non-compliant group of patients.

Second, is the therapeutic range adequate? During the study period the therapeutic range recommended for many patients, including patients with previous thromboembolism, was changed to a less intensive regimen over time. The majority of those patients were free from haemorrhages and thus there must have been other explanations. Probably the altered target limits resulted from the increasing data supporting regimens of lower intensity[23,24]. The recommendation in the recently published American guidelines[25] favours a target INR of between 2–0 and 3-0 for bileaflet valves, but of 2-5 to 3-5 for other disc valves. The European guidelines from 1995[26], however, recommended a target INR of 2-5–3-0 for the second generation of mechanical valve prostheses in the aortic position, including the St. Jude (bileaflet valve) and Medtronic Hall/Björk-Shiley Monostrut (tilting disc valves). The target limits in the present study were similar for the patients with Edwards Duromedics and Björk-Shiley Monostrut throughout the study, and there was no difference between them in the incidence of thromboembolism or haemorrhage. The guidelines[25,26] also recommend adjustment of the therapeutic range in patients with risk factors for thromboembolism. The patients with previous thromboembolism at the 10-year follow-up in the present study had received instructions concerning the target INR similar to those in patients without such a risk factor.

Third, will the addition of antithrombotic drugs be appropriate? Beneficial effects of adding low-dose aspirin to warfarin treatment for prevention of thromboembolism have been reported[27,28]. Turpie et al.[29] found a significant reduction of the incidence of death, non-fatal thromboembolism or haemorrhage from 9-9% per year with warfarin alone to 3-9% per year with the addition of low-dose aspirin. The group of patients treated with aspirin showed not only a reduced frequency of thromboembolism, but also a reduction in non-embolic vascular events. The guidelines[25] cited above have adopted the recommendation to add 80–100 mg of aspirin daily.
especially in patients with previous thromboembolic events, evidence of vascular disease or a hypercoagulable status, despite a minor increase in the frequency of haemorrhage. Despite repeated events of thromboembolism in 32 patients in this study, only six of them received concomitant treatment with aspirin. This further emphasizes the need for improvement of the quality of anticoagulant treatment in patients with artificial heart valves. We are unable to determine whether the supplementary action of dipyridamole is effective or not. A meta-analysis of the randomized trials on this subject has shown a 56% reduction of fatal and non-fatal thromboembolic events in the group of patients with combined warfarin and dipyridamole treatment. Others claim that there is an insufficient amount of data to support a preference for dipyridamole over low doses of aspirin.

The most frequent valve-related complication was haemorrhage, which occurred at a rate of 8-5% per patient-year. Haemorrhage also contributed to 38% of all valve-related mortality. Thus, warfarin-related haemorrhage was the major contributor to valve-related morbidity and mortality in this study. Our figure is comparable to the 6-6% per patient-year reported by Horstkotte et al. However, in many other studies substantially lower incidence rates have been found. One probable explanation for the observed high incidence of haemorrhage might be the careful prospective search for such events. Significantly more patients were out of the therapeutic range for anticoagulation in connection with the event, compared with the results at the regular follow-up. However, the bleeders, as a group, showed the same degree of anticoagulation at follow-up as the haemorrhage-free patients. The median INR values at follow-ups correspond to a moderately high level of anticoagulation (INR 2.5 to 3.0). We cannot exclude, however, the possibility that inappropriately high or fluctuating levels of anticoagulation in individual patients might have contributed. The concomitant use of dipyridamole has been shown not to increase the frequency of bleeding, but the possibility of other drug interactions was not studied in the present investigation.

In this study atrial fibrillation was a risk factor for haemorrhage. However, we found no evidence that patients with atrial fibrillation received more intensive anticoagulation therapy. A small group of patients, 2.6% (11/424), reported haemorrhages prior to valve replacement. These patients accounted for 10% of the bleedings after surgery. The patients at highest risk for a haemorrhagic episode were those patients who had already sustained at least one haemorrhage after the aortic valve replacement. These represented 39% (164/424) of the study population.

One of the ultimate challenges in the anticoagulation treatment must be a combined history of both bleeding and thromboembolism. In our study 46 patients had this experience. They accounted for 33% of all haemorrhages (109/329) and 39% of all episodes of thromboembolism (66/171). In this group, the margins of adjustments in the therapy are probably reduced. Harenberg et al. reported good results with low-molecular-weight heparin as a substitute for warfarin in a cohort of patients with bleeding problems, which may be an alternative in selected patients.

Symptoms widely accepted as indications for timing of surgery were closely related to overall survival, but were not strong risk factors for event-free survival. In fact, few factors were strongly related to the risk for valve-related complications. Although a previous episode of thromboembolism and pre-operative renal dysfunction increased the risk for thromboembolism, haemorrhage and valve-related morbidity or mortality, few patients had these features. The majority of valve-related complications occurred in patients without these risk factors. In patients operated on in NYHA I or II, the event-free survival rates after 5 and 10 years were 76% and 49%, respectively. However, only 51 patients were in functional class I or II and caution must be observed in the interpretation of these results. Lethal valve-related complications occurred in five of these patients, corresponding to 50% of all deaths. Valve-related complications do occur in NYHA I and II, and functional class was not a strong predictor of such complications in this series of patients.

The change in risk factor influence over time, as indicated by the modified Cox model, suggests that for mortality beyond 5 years all relative hazards except that for trademark of the prosthesis are reduced. The increased risk associated with pre-operatively identified risk factors was most apparent during the first 5 years after surgery, and we have little knowledge about what factors influence very late mortality. The same interpretation could be applied to the event-free survival, when almost all risk factors are neutralized more than 5 years after surgery.

Conclusions

The present study underlines the substantial morbidity and mortality still associated with mechanical heart valves. The most powerful risk factor for both thromboembolism and haemorrhage is a history of previous events, and the risk increases after each new event. Repeated events as confirmed in this study constitute a considerable clinical problem. This should have implications for the management of anticoagulation and use of low-dose aspirin. The results strongly indicate that greater effort should be made to sharpen the surveillance of anticoagulation therapy in patients with artificial heart valves.

Most of the patients considered for a mechanical valve prosthesis in the aortic position are expected to survive beyond a 5- to 10-year period after surgery. However, this study has highlighted the lack of knowledge in the evaluation of the factors influencing the very late survival.

Financial support was provided by the Swedish Heart and Lung Foundation.
References


