Long-Term Relative Survival Rates After Heart Valve Replacement

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The calculation and comparison of relative survival rates after interventional studies is a method that permits correction for important demographic variables, thereby adjusting for the "background mortality" in the general population. Long-term relative survival rates were analyzed in a consecutive series of 2,805 Swedish patients who, on the basis of clinical symptoms, underwent aortic valve replacement (n = 1,741), mitral valve replacement (n = 792) and double (aortic plus mitral) valve replacement (n = 272) between 1969 and 1983. The follow-up period, which closed August 1, 1985, included 100% of patients and covered 16,822 patient-years. Autopsy was performed in 75% of all deaths.

The results underscore previously well known differences between the long-term survival after aortic valve replacement and mitral or double valve replacement, whereas no differences were noted between mitral and double valve replacement. Within the subgroup undergoing aortic valve replacement, analysis of relative survival rates disclosed a highly significant (p < 0.001) difference between patients operated on for aortic stenosis and those operated on for aortic regurgitation, representing a mortality rate more than twice as high in the latter group. This difference was of much lesser magnitude when analyzed in the standard (actuarial) way. With a low (<2.5%) operative mortality rate for patients undergoing isolated elective aortic valve replacement in the current era and with an acceptable incidence of late valve-related death (5.2% at 10 years), these results may justify aortic valve replacement earlier in the course of chronic aortic regurgitation to prevent irreversible myocardial damage.

Patients ≥65 years of age who underwent aortic valve replacement for pure aortic stenosis achieved a normalized survival pattern from the second postoperative year on, and had a "cure" rate of 94%, which, however, is partly related to preoperative patient selection.

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increased "intercurrent mortality" among these patients and whether it could be linked to prosthesis-related factors or to an increased number of deaths from myocardial causes.

Methods

Study patients. Between January 1969 and July 1983, 2,884 patients underwent aortic or mitral valve replacement, or both, at this institution. Fifty-six foreign patients who stayed in Sweden for only a short period after the operation were excluded because expected survival was calculated on the basis of Swedish inhabitants (see later). Furthermore, 23 children and teenagers who underwent valve replacement as part of the treatment for complex congenital malformations were excluded. The remaining 2,805 patients formed the basis of this study. There were 1,741 aortic valve replacements, 792 mitral valve replacements and 272 double (aortic plus mitral) valve replacements. Some patient characteristics are listed in Table 1, and the age distribution is illustrated in Figure 1.

Operative and postoperative management. Standard cardiopulmonary bypass equipment and moderate perfusion hypothermia (25° to 32°C) were employed. Cardioplegia was routinely used since 1978. All but one patient received Björk-Shiley tilting disc valves (15,16). All valves were implanted with interrupted sutures. Reheparinization was started as soon as the chest tubes were removed. Oral anticoagulants with an intention of life-long treatment and Thrombotest (Thrombotest, Nyegaard, Oslo, Norway) values between 6% and 15% were prescribed for all patients undergoing mitral or double valve replacement and for most patients after aortic valve replacement (8,16). All survivors received antibiotic prophylaxis for 2 to 3 months postoperatively.

Follow-up and data collection. Our methods of data collection have been outlined previously (8,15-17). Follow-up study was achieved by means of telephone calls or postal questionnaires, or both. All patients were followed up to August 1, 1985. The follow-up study was 100% and covered 16,822 patient-years. The mean follow-up time was 6.4 years for operative (30 days) survivors and 7.1 years (range 2.1 to 16.6) for current survivors. Fifty-four percent of the patients were followed up >5 years, 18% >10 years and 2% >15 years.

Assignment of cause of death. Cause of death was assigned according to autopsy reports, which were available in 638 (75%) of 856 deaths. In cases lacking an autopsy, we scrutinized hospital records in search for valve-related complications.
Valve-related death. The following causes of death were considered valve-related: embolism, valve thrombosis, anticoagulant-related hemorrhage, mechanical failure, prosthetic valve endocarditis and noninfectious periprosthetic leakage (15,16). All fatal strokes were considered either as embolism or as anticoagulant-related bleeding, and thus in all cases were regarded as valve-related death. Any death occurring during or within 30 days of a reoperation for a valve-related complication was considered valve related.

Cardiac but not valve-related death. Patients who died from congestive heart failure without signs of prosthetic malfunction, patients who died from myocardial infarction without evidence of embolism and patients who died from documented arrhythmias were considered to have died a cardiac but not valve-related death.

Sudden unexplained death. Patients unexpectedly found dead, patients who died suddenly within a matter of minutes and patients who died within 48 h after the sudden onset of symptoms compatible with severe left ventricular failure but without an autopsy were considered to have died a sudden unexplained death. (The probability that sudden unexplained deaths are caused by valve-related complications was explored in a previous study [17].)

Other causes of death. All other causes of death (for example, trauma, cancer, infection) were grouped together as “other.”

Statistical methods. Actuarial curves describing observed survival ($O(s)$) and freedom from valve-related death were constructed and compared using standard formulas (2,18,19).

The expected survival ($E(s)$) was calculated in an “exact” way (11) from Swedish life tables with a specially designed computer software program.* Briefly, this program assigns a separate “control group” for every patient in the study group. This control group consists of all Swedish inhabitants of the same gender and age as the patient and alive at the time of operation. The expected survival for this control group was then retrieved from computer-based life tables (“Statistics Sweden”) that cover the entire Swedish population (because >50% of our patients were referred from outside Stockholm, we used life tables for Sweden rather than for Stockholm only). All these individually based expected survival curves were then weighted to a composite survival curve that represented all patients (Fig. 2). Because of the age heterogeneity in the patient cohort (Fig. 1), a successive rejuvenation process due to a higher mortality rate among older patients may be present (14). To correct for this and to avoid overestimating the relative survival rate, the control groups that represented patients who died during the follow-up period were withdrawn from the calculations of $E(s)$ at the year of the respective patient’s death. Because the calculations of $E(s)$ are based on the entire Swedish population, the errors of sampling do not apply and no standard errors are provided for $E(s)$. The relative survival rate is calculated as $O(s)/E(s)$.

Presentation and interpretation of relative survival rates. The relative survival rates are calculated with successively longer time intervals, all of which start at the time of operation. If the study group eventually achieves a normalized survival pattern, this is represented by a constant relative survival rate from that time on. The fraction surviving until this normalized survival is reached is, therefore, subject only to the normal risk of dying and can be considered as “cured” from a statistical point of view. If, on the other hand, there is an increased risk of death in the study group throughout the study period, this will be represented by a continuously decreasing relative survival rate.

In studies of survival after treatment for cancer, relative survival rates are sometimes compared with the actuarial

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*Further details of this program are available from the authors.

Figure 2. Observed survival ($O(s)$) among 2,805 patients undergoing aortic or mitral valve replacement, or both. The expected survival rate ($E(s)$) line represents the experienced survival in a gender- age- and year of operation-matched control group. The vertical bar indicates the 95% confidence limits (95CL). PAT = patient; POST-OP = postoperatively.
survival in the study group, but with all noncancer deaths regarded as withdrawals (13). Both types of survival analysis represent methods to correct for intercurrent disease. If the relative survival rate is lower than this cancer survival rate, this can be interpreted as an increased incidence of intercurrent disease in the study group. When considering survival after valve replacement, these patients are exposed to a number of new potential causes of death, such as prosthetic dysfunction, thromboembolism and anticoagulant-related bleeding. Our patients can, therefore, be considered to have traded acquired valvular disease for prosthetic valvular disease (9), the risks of which are not negligible. In analogy with cancer survival and to assess the incidence of intercurrent disease among patients with artificial heart valves, we compared the relative survival rates with the actuarial freedom from valve-related death.

Illustrations of actuarial or relative survival are graphically presented with logarithmic y axis because this facilitates a visual comparison between different curves (that is, subgroups with equal hazard rate during a specified time interval have parallel survival curves). Actuarial and relative survival rates as well as binomial proportions are presented together with their 95% confidence limits.

### Results

#### Overall survival.

Of the 2,805 patients operated on, 156 (5.6%, 95% confidence limits 4.7% to 6.4%) died within 30 days of surgery and 700 (25%) died later during the follow-up period. An autopsy was performed in 638 (75%) of these deaths. One hundred fifty-six (18%, 95% confidence limits 16% to 21%) of these deaths were considered valve related (Fig. 3). The incidence of valve-related death among various subgroups of patients is illustrated and compared in Table 2. The actuarial survival for all patients was 77%, 63% and 48% at 5, 10 and 15 years after operation, respectively (Fig. 2). Ten year actuarial survival rate was significantly higher among patients who underwent aortic valve replacement (66%, 95% confidence limits 63% to 69%) than among those undergoing mitral or double valve replacement (58%, 95% confidence limits 54% to 63%, and 57%, 95% confidence limits 50% to 65%, respectively). Furthermore, patients

### Table 2. Incidence of Valve-Related Mortality in 2,805 Patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Linearized Rate (events/100 patient years)</th>
<th>Actuarial incidence (%)</th>
<th>Significance at 10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 2,805)</td>
<td>0.9 ± 0.1</td>
<td>5.3 (4.4–6.2)</td>
<td>7.4 (6.2–8.6)</td>
</tr>
<tr>
<td>AVR</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All (n = 1,741)</td>
<td>0.7 ± 0.1</td>
<td>3.7 (2.8–4.6)</td>
<td>5.7 (4.3–7.2)</td>
</tr>
<tr>
<td>For AS (n = 845)</td>
<td>0.7 ± 0.1</td>
<td>3.4 (2.1–4.7)</td>
<td>5.7 (3.5–7.8)</td>
</tr>
<tr>
<td>For AI (n = 397)</td>
<td>0.8 ± 0.2</td>
<td>4.3 (2.1–6.5)</td>
<td>5.2 (2.7–7.7)</td>
</tr>
<tr>
<td>MVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n = 792)</td>
<td>1.3 ± 0.2</td>
<td>8.2 (6.1–10.3)</td>
<td>10.1 (7.5–12.7)</td>
</tr>
<tr>
<td>For MS (n = 183)</td>
<td>1.2 ± 0.3</td>
<td>7.9 (5.6–12.1)</td>
<td>8.8 (4.2–13.3)</td>
</tr>
<tr>
<td>For MI (n = 303)</td>
<td>1.4 ± 0.3</td>
<td>11.1 (4.4–10.9)</td>
<td>9.9 (5.4–14.5)</td>
</tr>
<tr>
<td>DVR (n = 272)</td>
<td>1.3 ± 0.3</td>
<td>7.2 (3.6–10.7)</td>
<td>9.9 (5.3–14.6)</td>
</tr>
</tbody>
</table>

| Data in parentheses represent 95% confidence limits. AI = aortic insufficiency; AS = aortic stenosis; MI = mitral insufficiency; MS = mitral stenosis; other abbreviations as in Table 1. |
undergoing aortic or mitral valve replacement for pure regurgitant lesions had a significantly increased mortality rate than patients operated on because of pure stenotic lesions (Table 3).

**Relative survival.** When calculating relative survival, the differences among some of the subgroups became even more pronounced. The relative survival rate did not differ between patients undergoing mitral or double valve replacement, but in both patient groups the rate was significantly (p < 0.01) lower than that for patients undergoing aortic valve replacement (Fig. 4). This increased mortality rate among patients with mitral or double valve replacement persisted throughout the follow-up period.

**Figure 4.** Relative survival rates among patients undergoing aortic (AVR) (solid line, n = 1741), mitral (MVR) (dashed line, n = 792) and double (DVR), (dash-dot line, n = 272) valve replacement. Note different truncation of the y axis in this and subsequent figures. **Vertical bars** indicate 95% confidence limits. POST-OP = postoperatively.

The relative survival rate in patients with aortic regurgitation was significantly (p < 0.001, Fig. 5) lower than in patients with aortic stenosis and represented a more than doubled mortality rate. This increased mortality rate was observed (Fig. 5) until the fifth postoperative year, after which time the relative survival curves became parallel.

**Figure 5.** Relative survival rates for patients operated on for pure aortic stenosis (AS, n = 845) or pure aortic insufficiency (AI, n = 397). **Vertical bars** indicate 95% confidence limits. POST-OP = postoperatively.

The relative survival rate was significantly lower than the actuarial freedom from valve-related death among patients undergoing aortic, mitral or double valve replacement (Fig. 8).

**Time-frame analysis (Table 4).** Because a major change in surgical treatment was introduced in 1978 (that is, the routine use of cardioplegia), relative survival analyses were performed with patients being stratified according to time frame (patients operated on during 1969 to 1977 versus patients operated on during 1978 to 1983). The only statis-

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### Table 3. Actuarial Survival at 10 Years in 2,805 Patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 1,741)</td>
<td>65.8 (62.8–68.8)</td>
</tr>
<tr>
<td>For AS (n = 845)</td>
<td>68.3 (63.8–72.8)</td>
</tr>
<tr>
<td>For AI (n = 397)</td>
<td>59.4 (53.6–65.2)</td>
</tr>
<tr>
<td>All (n = 792)</td>
<td>58.2 (53.8–62.6)</td>
</tr>
<tr>
<td>For MS (n = 183)</td>
<td>65.4 (56.1–74.7)</td>
</tr>
<tr>
<td>For MI (n = 303)</td>
<td>53.1 (45.9–60.3)</td>
</tr>
<tr>
<td>DVR (n = 272)</td>
<td>57.3 (49.8–64.8)</td>
</tr>
</tbody>
</table>

Data in parentheses represent 95% confidence limits. Abbreviations as in Tables 1 and 2.
Figure 6. Relative survival rates for patients undergoing valve replacement for pure mitral stenosis (MS, n = 183) or pure mitral insufficiency (MI, n = 303). Vertical bars indicate 95% confidence limits. POST-OP = postoperatively.

Figure 8. Actuarial freedom from valve-related mortality and relative survival rates among patients undergoing aortic (AVR) or mitral (MVR) valve replacement. Vertical bars indicate 95% confidence limits. POST-OP = postoperatively.

A statistically significant difference found was an improved survival rate in the latter era for patients undergoing aortic valve replacement. This difference was of much lesser magnitude when only patients <65 years old were considered. No time frame-dependent differences were noted for patients undergoing mitral or double valve replacement.

**Discussion**

Limitations of the present study. Two major arguments have been raised against the appropriateness of comparing postoperative survival with survival in a general population (20). The first is that calculations of expected survival are based on the unverified assumption that the survival in the

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Relative Survival (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td></td>
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</tr>
<tr>
<td>Early (n = 778)</td>
<td>83.9 (80.9–87.0)</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Late (n = 963)</td>
<td>89.9 (86.9–92.9)</td>
<td></td>
</tr>
<tr>
<td>AVR &lt;65 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (n = 675)</td>
<td>84.1 (80.9–87.2)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Late (n = 583)</td>
<td>88.2 (84.7–91.6)</td>
<td></td>
</tr>
<tr>
<td>MVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (n = 397)</td>
<td>75.3 (70.7–79.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Late (n = 395)</td>
<td>79.6 (74.5–84.5)</td>
<td></td>
</tr>
<tr>
<td>DVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (n = 125)</td>
<td>74.9 (66.5–83.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Late (n = 147)</td>
<td>75.4 (66.8–84.1)</td>
<td></td>
</tr>
</tbody>
</table>

Data in parentheses represent 95% confidence limits. Abbreviations as in Tables 1 and 2.
general population is unaffected by deaths related to the disease under study. This argument may be relevant in studies of ischemic heart disease, but because of its relative rarity, valvular heart disease influences survival in the general population only marginally. The second argument is that the populations may not be matched socioeconomically. This argument seems less valid in Sweden where the availability of surgical treatment is mainly unrelated to socioeconomic factors.

**Experiences from the present study.** Valve replacement is the treatment of choice for most significant valve lesions. Hemodynamic improvement has been documented by several postoperative catheterization studies (21–23), especially in patients undergoing surgery for stenotic lesions. In comparison with historic series (24,25), the superiority over medical treatment seems firmly established. This is especially true for patients with aortic stenosis, for which a 50% mortality rate within 2 years after the onset of symptoms has been reported with medical treatment alone (24). Yet, the present study has clearly demonstrated the inability to “cure” these patients, except in the subgroup of old (≥65 years) patients undergoing aortic valve replacement for pure aortic stenosis. Even this concept of “cure” can be disputed because these older patients represent a selected group, with an underrepresentation of other serious disorders that are otherwise common in this age group (26). It must nevertheless be considered gratifying to observe a 94% “cure” rate and a normalized survival pattern in this group of patients whose disease has a very serious outcome without surgery.

The identical relative survival rate after mitral and double valve replacement (Fig. 4) implies that the longer cross-clamp time and the presence of two prostheses did not affect the late results adversely.

The finding in all patient groups that the relative survival rate was much lower than the actuarial freedom from valve-related death (Fig. 8) indicates that the inability to achieve a “cured” group was not primarily linked to the incidence of valve-related complications, but rather to the incidence of “intercurrent disease.” Because the fraction of noncardiac deaths was low (17%) (Fig. 3), this increased incidence of intercurrent disease was mainly related to a high incidence of deaths attributable to myocardial factors.

**Future improvements.** Further improvements in survival after valve replacement may be achieved in at least three different ways: 1) by improved surgical treatment (defined broadly, including overall perioperative management); 2) by improved prosthetic heart valves; and 3) by improved preoperative myocardial function (that is, a changed referral pattern).

So-called improvements in the surgical treatment are constantly introduced, but their effects on long-term survival are seldom documented. Ferruzzi et al. (5) recently studied the long-term survival after mitral valve replacement during two different time frames. Contrary to current beliefs, they found that results analyzed in a multivariate fashion remained unchanged during the latter era. This is corroborated by our findings of small or nonexisting differences when relative survival was analyzed in relation to time frame (Table 4). The only improvement observed in the most recent era was among patients undergoing aortic valve replacement. This was, however, mainly related to an increased number of old patients having aortic valve replacement (39% were ≥65 years in the latter era compared with 13% before 1978). With a normalized relative survival rate among patients in this age group (Fig. 7), a higher relative survival rate must be expected in the entire aortic valve replacement group after 1977.

New heart valves are also introduced, each of which is assigned various advantages in terms of improved hemodynamic performance or decreased incidence of valve-related complications. Only long-term follow-up studies can prove whether one valve is superior to another, and in the absence of well controlled randomized trials, comparisons among different prostheses can, at best, only be guiding. Even if further improvements in the design of prosthetic valves are likely, the chance that this will more than marginally improve long-term survival seems small.

The third possibility for achieving improved results would be to operate on patients in a less advanced state of the disease. The patients in this series were all accepted for valve replacement on the basis of symptoms. The poor results obtained among patients with aortic regurgitation as compared with patients with aortic stenosis are well known from several previous studies (6,7,10) which, however, did not correct for major variations in demographic variables. Despite an equal incidence of valve-related death (Table 2), patients with aortic regurgitation had a more than doubled mortality rate when relative survival rates were considered (Fig. 5). Several authors (27–29) have claimed that asymptomatic patients with severe aortic regurgitation should be recommended for surgery on the basis of noninvasively detected signs of left ventricular dysfunction. Concerned by the high incidence of sudden unexpected death among asymptomatic patients with depressed left ventricular function and encouraged by the low operative mortality rate and improved long-term survival rate among patients operated on early in the course of chronic aortic regurgitation, Turina et al. (30) currently recommend surgery even in the absence of symptoms in patients with signs of depressed left ventricular function. With a current early mortality rate in the range of 1% to 2.5% (8,16,30) for patients undergoing isolated elective aortic valve replacement, and with a yearly incidence of late valve-related death of 0.7 ± 0.1% (actuarially 3.7% at 5 years and 5.7% at 10 years, Table 2) (16), it would probably be justified to operate on patients with chronic aortic regurgitation earlier to lower the late mortality rate. Mitral valve replacement carries a significantly higher early mortality rate and an almost doubled incidence of late
valve-related death (Table 2) (9,10,15), and more liberal indications for this procedure seem less warranted.

Conclusions

1. Most subgroups of patients did not achieve a normalized survival pattern after valve replacement, a finding that illustrates the palliative rather than the curative effect of surgery. The increased mortality rate after valve replacement seems mainly linked to an increased number of cardiac but not valve-related deaths. 2. This increased late mortality rate was especially marked among patients operated on because of aortic regurgitation and among patients undergoing mitral or double valve replacement. 3. Patients aged ≥65 years who underwent valve replacement for aortic stenosis can, from a statistical point of view, be considered "cured" if they survive the first postoperative year. 4. Our data support the idea of earlier referral to surgery for patients with chronic aortic regurgitation. 5. Analysis of relative survival rates provide a meaningful way to compare results among different patient groups. It takes into account variations in important demographic variables, thereby correcting for the "background" mortality.

References