PATHOPHYSIOLOGY AND NATURAL HISTORY

VALVE REPLACEMENT

Death and other time-related events after valve replacement

EUGENE H. BLACKSTONE, M.D., AND JOHN W. KIRKLIN, M.D.

ABSTRACT  A total of 1533 patients received primary aortic and/or mitral valve replacement, with or without tricuspid valve surgery or other associated cardiac procedures, from January 1, 1975, to July 1, 1979. Actuarial survival at 5 years was 74%. The hazard function (instantaneous risk) of death was highest immediately after operation. Among the incremental risk factors for premature death from any cause were preoperative NYHA class, any valve lesion other than aortic stenosis, aortic cross-clamp time, and combined aortic and mitral valve replacement. Ten modes of death were identified, each with its unique hazard function and risk factors. The commonest mode was cardiac failure. Sudden death was the next commonest, and the early phase of its hazard function peaked about 3 weeks after operation. Seventy-five patients (6.7% of the 1533) had 103 valve reoperations in the follow-up period. Actuarial survival after reoperation was less than that after the primary operation; whether the reoperation was the first, second, or third was a risk factor. Actuarial freedom from prosthetic valve endocarditis (PVE) was 97% at 1 year, and that of periprosthetic leakage without evident infection was 98.8%; the hazard function for the event PVE had an early phase peaking at about 6 weeks and a constant low phase throughout, whereas that of periprosthetic leakage had a single early peaking phase. After reoperations, the actuarial freedom from PVE and periprosthetic leakage was less than that after the original operation. The risk factors for the development of periprosthetic leakage without evident infection were similar but not identical to those for PVE. Among patients receiving a bioprosthesis, 91% were free of bioprosthetic degeneration 5 years after operation. The hazard function was single and continuously rising, and young age and female gender were risk factors. Actuarial freedom from acute prosthetic thrombosis was 97.9% at 5 years. The single hazard function for this event peaked at 10 months. The risk of thrombosis was higher in female patients. The uses of this integrated study, and the inferences from it, are described.

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THE REPLACEMENT of diseased cardiac valves is an accepted form of treatment for many patients with valvular heart disease. The in-hospital mortality for most of these operations is now low but does not approach zero, and premature death and other unfavorable events continue to complicate the subsequent course of patients undergoing them. In-hospital and later death, as well as other events, have usually been addressed separately and as isolated complications, and the nature of their time-relatedness has been assessed.

We performed an integrated study of most of the time-related events that occur after valve replacement, dated from the time of operation and without the artificiality of separating them into those occurring in hospital and those occurring later. Methods specifically developed for the study of time-related events and their risk factors were used. The results can be used to develop inferences as to the current reasons for surgical failures and methods for neutralizing them and to evaluate results from different experiences.

Materials and methods

The study group consists of all patients undergoing primary cardiac valve replacement, with or without an associated cardiac procedure, between January 1, 1975, and July 1, 1979. Among the 1533 patients, 842 had aortic valve replacement, 478 had mitral valve replacement, and 213 had combined mitral and aortic valve replacement. Patients receiving valve replacement for mitral incompetence on the basis of ischemic heart disease were included. Patients who previously had replacement of a different valve or who underwent valve replacement in infancy or childhood (age less than 20 years) as part of the treatment for a congenital cardiac malformation were excluded. A few children receiving replacement for rheumatic valve disease were included. Associated surgical procedures included...
coronary artery bypass grafting (n = 412 patients), resection of left ventricular aneurysm (n = 13), resection of ascending aortic aneurysm (n = 82), tricuspid annuloplasty (n = 73), tricuspid replacement (n = 6), resection of subaortic stenosis (n = 13), repair of atrial septal defect (n = 6), and others (n = 6). Median age of the 1533 patients was 57 years (range 8 to 85 years); 70% were between 41 and 69 years of age and 95% were between 22 and 76 years.

The time-related events studied were death (considered to be premature in the context of a 5 year follow-up and an observed median survival of 8.6 years for male persons and 11.2 years for female persons aged 75 to 80 years in the 1976 U.S. Life Table), mode of death, reoperation on the valve originally replaced, and the valve complications of prosthetic valve endocarditis (PVE), periprosthetic leakage without evidence of PVE, bioprosthetic degeneration, and acute prosthetic thrombosis.

Information concerning early, in-hospital events was obtained from review of individual hospital charts and that concerning events occurring after hospital dismissal was obtained from personal evaluation of the patient at return visits and from replies to letters sent to the patients and their physicians. If the returned information was incomplete, it was completed by telephone calls to the patients and their physicians. The follow-up interval ended in January 1981 for patients with mitral valve replacement, in June 1981 for those with aortic valve replacement, and in November 1981 for those with combined aortic and mitral valve replacement. Only one of the 1533 patients was untraceable. The median follow-up period was 43 months.

The operations were done with simple hypothermic ischemic cardiac arrest until 1977 and with cold cardioplegic cardiac arrest thereafter. The Bjork-Shiley valve was the most commonly used mechanical prosthesis, with three patients receiving a Starr-Edwards prosthesis in the mitral position and two in the aortic position and one patient receiving a Lillehei-Kaster prosthesis in the aortic position. Both the Hancock (n = 241) and Carpentier-Edwards (n = 235) bioprostheses (porcine heterografts) were used; in addition, three patients received a porcine heterograft of unspecified type, and one patient received an aortic homograft for aortic valve replacement. Interrupted simple sutures of Dacron were most frequently used in suturing the prosthetic device in place, but interrupted pledged mattress sutures and, in the mitral position, continuous polypropylene sutures were used in many patients. Patients receiving Bjork-Shiley or other mechanical prostheses systematically received warfarin, beginning 48 hr after operation and to continue throughout life. Patients receiving bioprostheses usually were not given warfarin, even early after surgery. Prophylactic antibiotic treatment was given for 4 to 6 days early after surgery and was advised for later dental extractions, operations, and injuries but the details of compliance are not known. In most reoperations, the original prosthetic device was replaced. Repair rather than re-placement was done in one of the 42 operations for PVE and in 12 of the 37 for periprosthetic leakage without evident infection; thrombectomy rather than replacement was done in three of the 11 reoperations for acute thrombosis.

Among the 1533 patients, 67 (4.4%) died in the hospital after the operation; 271 patients (17.7%) died later. Also, 75 patients (4.9%) underwent 103 reoperations on the valves that had been replaced. Fifty-eight patients (3.8%) developed 65 episodes of PVE, and 31 (2.0%) developed 39 episodes of periprosthetic leakage without evident infection. Thirteen (2.9% of 446 patients receiving a bioprosthesis) developed bioprosthetic degeneration, and 19 (1.8% of the 1084 patients receiving a Bjork-Shiley prosthesis) developed acute thrombotic occlusion (one patient with a bioprosthesis developed this complication).

No attempt was made to separate the events into those occurring in-hospital (or within 30 days of operation) and those occurring later because of the artificiality imposed by such a strategy. Instead, all events were dated to the conclusion of cardiopulmonary bypass (no deaths occurred between the time patients were taken to the operating room and the start of cardiopulmonary bypass), which for convenience is referred to as the time of operation. The identification and classification of events, including modes of death, were done by the investigators after repeated detailed review of in-hospital and follow-up documents, some from hospitals elsewhere, and after personal telephone calls to patients, their families, and their physicians.

The mode of death (the category, syndrome, or pattern describing the subsystem failure or event that appeared to be associated with the death) was determined for each of the 298 patients who died after the original operation without reoperation; the 40 patients dying after reoperation were not included. Ten categories emerged: death with cardiac failure (acute, subacute, or chronic), sudden death (defined according to the Framingham study criteria of unexpected death without evidence of arrhythmia, occurring within an hour of the onset of symptoms), arrhythmic death (deaths, usually sudden, with documented life-threatening ventricular arrhythmias in close proximity to the death), death with documented uncontrolled and symptomatic infection (mediastinitis, blood stream or prosthetic infection), other cardiac deaths (delayed cardiac tamponade, death after a subsequent unrelated cardiac operation), death with postoperative hemorrhage, neurologic death, death with cancer, death with trauma, and death with other specific but miscellaneous modes (hepatitis, late acute or subacute pulmonary insufficiency, long-term drug and/or alcohol abuse, chronic renal failure, cirrhosis of the liver, diverticulitis with complications, systemic lupus erythematosus, massive hemoptysis of undetermined etiology, and after unrelated noncardiac surgery). There were no more than four patients in any one category of the miscellaneous modes. Assignment of mode of death was made independently by the two authors and was virtually self-evident and agreed upon in 271 patients. In 27 patients, the mode of death was either not agreed upon or undiscernible, and therefore no mode was assigned.

Reoperations refer to any subsequent operation on a prosthetic valve inserted at the original operation. Ten of the 75 first reoperations were performed in other institutions. The definitions of PVE with or without periprosthetic leakage used by Ivert et al. and that of periprosthetic leakage without evidence of PVE used by Dhasmana et al. were used, and these complications were included whether or not they led to reoperation. Bioprosthetic degeneration was considered as an event only when it became severe enough to cause reoperation or death (no instances of the latter occurred). Acute prosthetic thrombosis was considered as an event only under the same circumstances (11 required reoperation and nine caused death without reoperation).

A time-relatedness analysis was made for each event, starting with an actuarial analysis (Kaplan-Meier method) as a method of presenting the data in as direct a manner as possible. The degree of uncertainty in each actuarial analysis is expressed by the 70% confidence limits (CL) (corresponding to 1 SD). In some instances the actuarial analyses have been stratified, and the possibility was tested that differences between the stratified elements are due to chance. A parametric method was used to generate the hazard function, or the instantaneous risk of an event occurring in individuals not yet experiencing the event. The details of the method, the equations, and the shaping parameter estimates and risk factor coefficients for the hazard functions of each event are contained in appendices 1 and 2. These may be used to recalculate the various nomograms and may be compared with estimates made from a different data set. The hazard function is expressed as incidence of the event per
month (an arbitrarily selected unit of time). The hazard function analysis determines whether or not the risk is a constant one with time or whether it is in one or several phases. When there is more than one phase in the hazard function, the hazard function(s) that change(s) with time is (are) added to any constant hazard function that is present. Thus, when an early declining phase of increased risk and a constant phase are both present, the hazard function during the postoperative interval in which the early phase is present is the sum of both the early and constant hazard functions. The 70% confidence limits around the hazard function are presented to facilitate estimating the likelihood that differences are not due to chance. For some analyses, the parametric survivorship function has been used to calculate the probability of an event occurring within any time period. The survival and hazard functions are presented along with those of an age-race-sex–matched U.S. population, taken from the 1976 life tables.

Incremental risk factors (variables, either dichotomous or continuously variable, that are associated with increased risk in risk-containing situations) have been determined simultaneously for each phase of a hazard function by a multivariate step-wise elimination procedure, thus generating equations from which nomograms can be plotted and stratified. Variables were excluded when the p value for their association with an event was $\geq .1$. Risk factors for a constant phase pertain throughout the postoperative period, and in the case of more than one phase those for the changing (decreasing or increasing with time) early or late phase pertain only during the time of changing hazard function. The equations and coefficients of the parametric hazard and survivorship functions, and those of the multivariate equations are given in appendix 2.

The possible risk factors (dichotomous unless otherwise stated) analyzed for each time-related event, including the modes of death, after the original operation were age (years) at the time of operation; gender (male or female); race (white or black, in this study); pure incompetence vs pure stenosis vs mixed lesion at each valve; in the case of mitral incompetence, ischemic vs nonischemic origin; NYHA functional class (I through V, V indicating a state of shock requiring emergency operation); atrial fibrillation; native valve endocarditis; date of operation (years since January 1, 1975); cardiopulmonary bypass time (minutes); cardioplegia; in the case of cardioplegia, aortic cross-clamp (cardiac ischemic) time (minutes); valve replacement location (aortic, mitral, or both); tricuspid repair or replacement; concomitant coronary artery bypass grafting, resection of ascending aortic aneurysm, or other associated procedure; valve replacement device (mechanical vs bioprosthesis); and size of valve replacement device. Continuous variables were tested in the model both in their original units and in transformations to logarithmic and squared units, and that which fit the data best was selected. In addition, the potential interactions were examined between age and the valve replaced; NYHA functional class and valve replaced; and cardiac ischemic time (in the cardioplegic group) and NYHA functional class. Reoperation was not considered as a possible risk factor for death after the original valve operation because it too is an event after valve replacement.

In the case of events following one or more reoperations on the original valve replacement device, the risk factor analysis specific to each reoperation (i.e., the first reoperation, the second reoperation, etc.) included the same variables, except that "native valve endocarditis" was replaced by "prosthetic valve endocarditis." In addition, the reoperation number (first, second, third, or fourth reoperation) was entered as a possible risk factor, as was the indication for the reoperation (PVE, periprosthetic leakage in the absence of any evidence for PVE, bioprosthetic degeneration, and acute prosthetic thrombosis), and the procedure used at reoperation (replacement vs repair).

For events other than death following a given operation, the patient was censored at the time of another operation, if one occurred. In the case of the event death, no censoring was done at the time of any reoperation except in the analyses of modes of death.

Results

Premature death

Original valve replacement operation. Actuarial survival after the original valve replacement operation was 98.5% at 24 hr (CL 98.2% to 98.8%), 96.3% at 2 weeks (CL 95.8% to 96.8%), 87.3% at 1 year (CL 86.4% to 88.1%), and 73.6% at 5 years (CL 72.2% to 75.0%) (figure 1). The hazard function or instantaneous risk of death was highest immediately after operation, fell rapidly during the first postoperative month, and became a constant lower hazard phase by about 3 months after operation (figure 2).

Older age was an incremental risk factor for premature death in both the early phase ($p = .01$) and the constant phase ($p = .02$); the age effect is not very strong, however, since 5 year survival predicted from the multivariate equation (see appendixes 1 and 2) for aortic valve replacement during 60 min of aortic cross-
clamping with cold cardioplegia is 80% (CL 78% to 81%) for a 60-year-old man, whereas it is 75% (CL 72% to 77%) for a 75-year-old man. Black race was a risk factor in the constant phase (p < .0001). Only isolated aortic stenosis among the various valve lesions did not increase the risk of death in any phase. Aortic incompetence was a risk factor in the early phase (p = .003), as was mitral stenosis and/or incompetence (p < .0001). Ischemic mitral incompetence, with or without concomitant coronary artery bypass grafting, was a powerful risk factor in the constant phase (p = .003). Preoperative functional status (NYHA class) was a risk factor for premature death only in the early phase (p < .0001). Among the surgical variables, longer aortic cross-clamp time was a risk factor in the early phase (p < .0001), as was combined aortic and mitral valve replacement (p < .0001).

According to the parametric time-related risk factor analysis (see appendix 2), the predicted 2 week, 1 year, and 5 year survival of a patient 60 years of age undergoing isolated valve replacement for aortic stenosis is 99%, 94%, and 78%, respectively (table 1). The predicted 5 year survival is lower when (1) aortic valve replacement is combined with mitral valve replacement, (2) the aortic lesion is incompetence rather than stenosis, (3) the operation is isolated mitral valve replacement for stenosis or incompetence, and especially (4) the operation is for ischemic mitral incompetence (table 1). When the operation is aortic valve replacement for aortic stenosis and the conditions were the same as in table 1, the predicted 5 year survival, including in-hospital deaths, for patients in NYHA classes II, III, IV, and V before surgery was 82%, 80%, 75%, and 63%, respectively.

**Reoperation after valve replacement.** The actuarial survival after reoperation on the prosthetic valve previously inserted was 31% (CL 21% to 43%) at 3½ years (figure 1), considerably lower than that after the original valve replacement operation. The hazard function for death was different after reoperation in that the early phase was initially higher but dropped.

**TABLE 1**

<table>
<thead>
<tr>
<th>Valve lesions</th>
<th>Predicted survival</th>
<th>2 wk</th>
<th>CL</th>
<th>1 yr</th>
<th>CL</th>
<th>5 yr</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td></td>
<td>98.7</td>
<td>98.3–99.0</td>
<td>93.5</td>
<td>92.7–94.3</td>
<td>79.7</td>
<td>78.1–81.3</td>
</tr>
<tr>
<td>Aortic stenosis and mitral stenosis and/or incompetence</td>
<td></td>
<td>97.5</td>
<td>96.5–98.2</td>
<td>90.6</td>
<td>88.6–92.3</td>
<td>76.6</td>
<td>74.4–78.8</td>
</tr>
<tr>
<td>Aortic incompetence</td>
<td></td>
<td>97.2</td>
<td>96.3–97.9</td>
<td>89.9</td>
<td>88.0–91.6</td>
<td>75.9</td>
<td>73.7–78.0</td>
</tr>
<tr>
<td>Aortic incompetence and mitral stenosis or incompetence</td>
<td></td>
<td>94.5</td>
<td>92.6–95.9</td>
<td>83.8</td>
<td>80.0–86.9</td>
<td>69.5</td>
<td>65.7–73.1</td>
</tr>
<tr>
<td>Mitral stenosis and/or incompetence</td>
<td></td>
<td>95.7</td>
<td>94.7–86.5</td>
<td>86.4</td>
<td>84.4–88.3</td>
<td>72.3</td>
<td>70.0–74.5</td>
</tr>
<tr>
<td>Ischemic mitral incompetence</td>
<td></td>
<td>95.3</td>
<td>94.3–96.1</td>
<td>78.4</td>
<td>73.3–82.7</td>
<td>44.0</td>
<td>32–57</td>
</tr>
<tr>
<td>Total group (n = 1533)</td>
<td></td>
<td>95.8</td>
<td>95.3–96.2</td>
<td>87.2</td>
<td>86.3–87.9</td>
<td>73.9</td>
<td>72.7–75.2</td>
</tr>
</tbody>
</table>

CL = 70% confidence limits.

*Obtained by solution of the multivariate equation (see appendixes 1 and 2) for death in all modes. In solving for the predicted survivals for the individual valve lesions, NYHA functional class was set at III, age at 60 years, 15% of the patients black, and the aortic cross-clamp time (with cardioplegia) 60 min. Actuarial survival for the total group (n = 1533) for 5 years was 73.6% (CL 72.2% to 75.0%).
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more rapidly, essentially to disappear at about 2 weeks; the hazard function after this was a constant phase that was higher than that after primary valve replacement (figure 2).

There were fewer incremental risk factors for premature death after valve reoperations than after the original valve replacement operation. No demographic variables appeared. The number of the reoperation was a risk factor, the risk of death in the early phase increasing with each subsequent reoperation (p = .04). Among the valve lesions, only mitral valve disease (stenosis and/or incompetence) increased the risk, and that was in the constant phase (p = .0005). Higher NYHA functional class was a risk factor in the early phase (p = .04). Among the surgical variables, only use of a mechanical prosthesis (rather than a bioprosthesis or repair) was a risk factor, and then in the constant phase (p = .04).

According to the time-related risk factor analysis (see appendix 2), for a patient in NYHA class I the predicted 2 week survival after the original operation and that after the first reoperation are 99.7% (CL 99.6% to 99.8%) and 98.9% (CL 97.9% to 99.4%), respectively, and those for 5 years are 82% (CL 81% to 84%) and 46% (CL 35% to 58%), respectively. With more advanced preoperative disability and/or repeated reoperations, both early and late predicted survival are lower (table 2).

**Modes of death.** Ten modes of death after the original valve replacement operation were identified (table 3). The hazard functions for the various modes were highly variable (figure 3).

**Cardiac failure.** The commonest mode of death was cardiac failure (acute in 38 patients, subacute in 34, and chronic in 29). The median interval between operation and death was 3 days, 2.7 weeks, and 25 months, respectively, for the three subgroups. The instantaneous risk (hazard function) of death with cardiac failure in the early phase was highest immediately after operation and became a lower constant phase about 6 months after surgery.

The incremental risk factors for death with cardiac

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**TABLE 2**

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>Survival</th>
<th>Primary operation</th>
<th>Reoperation 1</th>
<th>Reoperation 2</th>
<th>Reoperation 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% (% )</td>
<td>% (% )</td>
<td>% (%)</td>
</tr>
<tr>
<td>I</td>
<td>2 wk</td>
<td>99.7 99.6-99.8</td>
<td>98.9 97.9-99.4</td>
<td>— B</td>
<td>— B</td>
</tr>
<tr>
<td></td>
<td>5 yr</td>
<td>82.3 80.6-83.9</td>
<td>46 35-58</td>
<td>— B</td>
<td>— B</td>
</tr>
<tr>
<td>II</td>
<td>2 wk</td>
<td>99.5 99.3-99.6</td>
<td>97.9 95.8-99.0</td>
<td>96.3 92.4-98.2</td>
<td>— B</td>
</tr>
<tr>
<td></td>
<td>5 yr</td>
<td>81.6 80.0-83.2</td>
<td>46 34-58</td>
<td>45 34-57</td>
<td>— B</td>
</tr>
<tr>
<td>III</td>
<td>2 wk</td>
<td>98.7 98.3-99.0</td>
<td>95.1 91.5-97.3</td>
<td>90.6 85.1-94.2</td>
<td>82 71-90</td>
</tr>
<tr>
<td></td>
<td>5 yr</td>
<td>79.7 78.1-81.3</td>
<td>44 34-56</td>
<td>42 32-54</td>
<td>38 28-50</td>
</tr>
<tr>
<td>IV</td>
<td>2 wk</td>
<td>96.6 95.5-97.5</td>
<td>88 83-91</td>
<td>77 71-82</td>
<td>61 47-74</td>
</tr>
<tr>
<td></td>
<td>5 yr</td>
<td>74.6 72.0-77.0</td>
<td>41 31-52</td>
<td>36 27-46</td>
<td>28 20-39</td>
</tr>
<tr>
<td>V</td>
<td>2 wk</td>
<td>91 88-94</td>
<td>71 62-78</td>
<td>53 42-64</td>
<td>35 21-52</td>
</tr>
<tr>
<td></td>
<td>5 yr</td>
<td>63 56-69</td>
<td>33 25-43</td>
<td>25 17-34</td>
<td>16 9-27</td>
</tr>
<tr>
<td>Mean NYHA</td>
<td>class</td>
<td>2.9(±0.71 SD)</td>
<td>3.7(±1.22 SD)</td>
<td>3.4(±1.29 SD)</td>
<td>3.6(±0.92 SD)</td>
</tr>
<tr>
<td></td>
<td>(n = 1533)</td>
<td>(n = 75)</td>
<td>(n = 18)</td>
<td>(n = 8)</td>
<td></td>
</tr>
</tbody>
</table>

CL = 70% confidence limits.

*The digital nomogram is a solution of the multivariate equation for death after the original valve replacement or valve re-replacement (see appendixes 1 and 2). In the solution of the equation, age was set at 60 years, mechanical prosthesis—yes, cardioplegia—yes, cross-clamp time 60 min, and 15% of the patients black.

*In the categories where no survival estimate is given, there were no examples in the data set and the estimate would be an extrapolation of the experience.
TABLE 3
Mode of death after the original valve replacement operation

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Modes of death</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cardiac failure</td>
<td>101</td>
</tr>
<tr>
<td>B</td>
<td>Sudden</td>
<td>62</td>
</tr>
<tr>
<td>C</td>
<td>Neurologic</td>
<td>27</td>
</tr>
<tr>
<td>D</td>
<td>Cancer</td>
<td>24</td>
</tr>
<tr>
<td>E</td>
<td>Hemorrhage</td>
<td>11</td>
</tr>
<tr>
<td>F</td>
<td>Infection</td>
<td>9</td>
</tr>
<tr>
<td>G</td>
<td>Arrhythmias</td>
<td>7</td>
</tr>
<tr>
<td>H</td>
<td>Other cardiac modes</td>
<td>7</td>
</tr>
<tr>
<td>I</td>
<td>Trauma</td>
<td>6</td>
</tr>
<tr>
<td>J</td>
<td>Miscellaneous</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>271</td>
</tr>
</tbody>
</table>

*In 27 additional patients a mode of death could not be agreed upon; their hazard function is depicted as K in figure 3. Seventy-five patients had reoperations, of whom 40 died after the first or subsequent operations and are not included in this analysis.

Symbols used in figure 3.

failure were similar to those for all deaths (table 4). Longer aortic cross-clamp time and increased preoperative functional disability only slightly increased predicted 2 week mortality after valve replacement for aortic stenosis, but both were associated with an evident increase in risk when the operation was for aortic incompetence, mitral valve disease, and particularly when it was a double valve replacement for aortic incompetence and mitral valve disease (figure 4).

Sudden death. Sudden death (62 events) was the next commonest mode of death (see table 3). Its hazard function peaked at about 3 weeks after operation and fell to become constant by about 8 months after surgery (see figure 3). The risk factors for sudden death included three variables (aortic incompetence, mitral valve stenosis and/or incompetence, and NYHA functional class), which were also risk factors for death with cardiac failure (table 5). Fifteen of the patients with sudden death had autopsy examination. In eight the prosthetic valve and the periprosthetic area appeared normal and no explanation was found for the death. Unexpectedly, there was extensive dehiscence of the valve in two patients, PVE with dehiscence in two, thrombosis of a Carpentier-Edwards bioprosthesis in one, and massive pulmonary embolization in two.

Neurologic. The hazard function for neurologic death (27 events) was constant and low across the time of this study (see figure 3). Older age at operation (p = .008) was the only risk factor. Autopsy was performed in four of the 27 patients and in all four there was evident intracranial disease (cerebral embolus in one, cerebral thrombosis in the bulbar area in one, multiple areas of cerebral hemorrhage in one, and diffuse brain necrosis in one. In addition, seven other patients with a neurologic mode of death had evidence of intracranial hemorrhage at the time of intracranial surgery or study by computed tomography.

Other modes of death. The hazard function for death with cancer was constant across time (see figure 3); only older age at operation (p = .07) was a risk factor. The hazard function of death with hemorrhage had a single phase and was highest immediately after operation and declined rapidly to essentially disappear after

![Figure 3](http://circ.ahajournals.org/)[Fig. 3](http://circ.ahajournals.org/) Nomogram of the hazard function of each mode of death after the original valve replacement. (See table 3 for meaning of symbols.) An age-sex-race–matched general population has an incidence of deaths/month of 0.001 across a 5 year period.

TABLE 4
Incremental risk factors for death with cardiac failure after original valve replacement operation (January 1975–July 1979; n = 1533, 101 events)

<table>
<thead>
<tr>
<th>Incremental risk factor</th>
<th>Time of influence (phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic variable</td>
<td></td>
</tr>
<tr>
<td>(Older) age (yr) at operation</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Black race</td>
<td>.004</td>
</tr>
<tr>
<td>Valve lesion</td>
<td></td>
</tr>
<tr>
<td>Aortic incompetence</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Mitral valve stenosis and/or incompetence</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Ischemic mitral incompetence</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>(Higher) NYHA functional class</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Surgical variables</td>
<td></td>
</tr>
<tr>
<td>Aortic cross-clamp time (min) in</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>cardioplogic group</td>
<td>.008</td>
</tr>
<tr>
<td>Tricuspid procedure</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>&gt;.1</td>
</tr>
</tbody>
</table>

In this and subsequent tables, p > .1 excludes the variable as a risk factor in that phase.
PATHOPHYSIOLOGY AND NATURAL HISTORY—VALVE REPLACEMENT

3 to 4 days. The incremental risk factors were higher NYHA functional class (p = .008), older age (p = .04), and duration of aortic cross-clamp time (p = .02). Among the nine patients dying with infection, only one, who died with septic shock and severe hyperthermia, had PVE. In seven patients extensive mediastinitis was the primary focus of infection. The ninth patient, a diabetic, had septic shock and fungal and bacterial infections of the blood stream and fungal native valve endocarditis before surgery; the patient died early after valve replacement and at autopsy had fungus (Candida) infection of many organs. The hazard function for death with arrhythmia (seven events) peaked at about 2 weeks after surgery and fell to a very low level within 6 months after operation. In only one of the patients (aortic valve replacement and coronary artery bypass grafting) with this mode of death was autopsy done; the grafts were open, the valve replacement area was normal, and no myocardial necrosis was found. The patient had documented ventricular tachyarrhythmia before death.

Reoperation. The actuarial incidence of reoperation after the original valve replacement was 2.5% (CL 2.2% to 3.0%) within 6 months, 4.3% (CL 3.8% to 4.8%) within 2 years, and 6.7% (CL 5.9% to 7.7%) within 5 years (figure 5). The hazard function for reoperation after the original operation had an early peak at about 3 months after operation, a rather rapid fall to a low and constant hazard function, and a rising third phase of hazard function beginning at about 3 years after surgery. The shape of the hazard function was different for mechanical valves and bioprostheses, with the late rise in hazard function characterizing only the latter (figure 6).

Thirty-four (45%; CL 39% to 52%) of 75 patients undergoing a first reoperation had PVE, in contrast to the original valve replacement operation in which 67 (4.4%; CL 3.8% to 5.0%) of the 1533 patients had
TABLE 5
Incremental risk factors for sudden death after original valve replacement operation (n = 1533, 62 events)

<table>
<thead>
<tr>
<th>Incremental risk factor</th>
<th>Time of influence (phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Throughout and constant (p value)</td>
</tr>
<tr>
<td>Demographic variable</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>.02</td>
</tr>
<tr>
<td>Valve lesions</td>
<td></td>
</tr>
<tr>
<td>Aortic incompetence</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>Mitral valve stenosis and/or incompetence</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>(Higher) NYHA functional class</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>Surgical variables</td>
<td></td>
</tr>
<tr>
<td>Use of bioprosthesis</td>
<td>.07</td>
</tr>
</tbody>
</table>

Although reoperation was not considered as a possible risk factor for death after the original operation, its occurrence in a patient increased the subsequent risk of death (see figure 1). If considered an additional “mode of death,” it would be the third most common (table 3).

PVE. The actuarial freedom from PVE after the original valve replacement operation was 97.0% (CL 96.5% to 97.4%) at 1 year and 95.6% (CL 95.0% to 96.2%) at 5 years after the original operation; it was lower after reoperations (figure 7). The hazard function for PVE peaked at 6 weeks after the original operation and then declined to a lower constant hazard function by about 6 months after surgery (figure 8). The early peak of the single hazard function after reoperations was higher than that after the original operation. The incremental risk factors were different for

FIGURE 5. Actuarial freedom from reoperation after the primary valve operation (n = 1533, 75 events) and after the first reoperation (18 events) and the second reoperation (eight events). The actuarial freedom from reoperation after the third reoperation (n = 8, two events) is 83% (CL 63% to 94%) at 6 months and 56% (CL 31% to 78%) at 2 years (not shown). After the fourth reoperation (n = 2) there were no further reoperations (not shown). p < .0001 for the difference between the original operation and the first reoperation; p = .12 for difference between the first and second reoperation.

FIGURE 6. Nomogram of the hazard function for reoperation for mechanical prostheses and bioprostheses, determined by separate analyses. In the hazard function for mechanical prostheses there is an early peaking phase and a constant phase: in that for bioprostheses there is an early peaking phase and a second rising late phase.

FIGURE 7. Actuarial freedom from PVE after the original valve replacement (54 events) and after reoperations. Note the expanded vertical axis. p < .0001 for difference between original operation and first reoperation (eight events); p = .4 for the difference between first and second reoperation (three events). PVE was not identified after the third or fourth reoperation.
PVE after the original operation compared with that after reoperations (table 6).

Periprosthetic leakage. Actuarial freedom from periprosthetic leakage without evident infection after the original valve replacement operation was 98.8% (CL 98.4% to 99.0%) at 1 year and 98.5% (CL 98.2% to 98.8%) at 5 years. Freedom from periprosthetic leakage was lower after reoperations (figure 9). The single phase hazard function for leakage after the original valve replacement operation peaked at about 2 months after operation and steadily declined thereafter; that after the re-replacement operations was high initially and declined slowly (figure 10). The incremental risk factors for periprosthetic leakage without evident infection after the original valve replacement (table 7) resembled but were not the same as those for PVE (see table 6). Among the 12 patients undergoing suture-repair of periprosthetic leakage without evident infection, only one redeveloped periprosthetic leakage without evident infection; two others subsequently had evident PVE.

The similarities between the two events, PVE and periprosthetic leakage without evident infection, are indicated by the similarity of their risk factors and by the similarity but not identity of their hazard functions (see figures 9 and 10). Also, the hazard function for periprosthetic leakage without evident infection was constant with time after reoperation for periprosthetic leakage, whereas it had a peak at 3 months after reoperation for PVE (figure 11A). The hazard functions for PVE after reoperation for periprosthetic leakage without evident infection and after reoperation for PVE

TABLE 6
Incremental risk factors for PVE after the original valve replacement operation (n = 1533, 54 events) and after reoperation (n = 103 reoperations in 75 patients, 11 events)

<table>
<thead>
<tr>
<th>Operation</th>
<th>Constant phase (p value)</th>
<th>Early phase (p value)</th>
<th>Single phase (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>&gt;.1</td>
<td>.01</td>
<td>.03</td>
</tr>
<tr>
<td>Black race</td>
<td>.01</td>
<td>.02</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>&gt;.1</td>
<td>&lt;.0001</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Surgical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical prosthesis</td>
<td>&gt;.1</td>
<td>.004</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Mitral replacement at original operation</td>
<td>&gt;.1</td>
<td>&gt;.1</td>
<td>.05</td>
</tr>
</tbody>
</table>
TABLE 7
Incremental risk factors for periprosthetic leakage without evident infection after the original valve replacement operation (n = 1533, 19 events) and after reoperation (n = 103, 20 events)

<table>
<thead>
<tr>
<th>Incremental risk factors</th>
<th>Operation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original valve replacement</td>
<td>Reoperation single phase</td>
<td>Reoperation single phase</td>
</tr>
<tr>
<td>Demographic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Younger) age at operation</td>
<td>.02</td>
<td>.1</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>.05</td>
<td>&gt;.1</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td>.05</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>.08</td>
<td>&gt;.1</td>
<td></td>
</tr>
<tr>
<td>Surgical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve replacement (isolated or combined)</td>
<td>.004</td>
<td>&gt;.1</td>
<td></td>
</tr>
<tr>
<td>Valve replacement rather than repair</td>
<td>NA</td>
<td>.08</td>
<td></td>
</tr>
</tbody>
</table>

NA = not applicable.

both peaked at about 6 weeks after surgery and gradually declined toward zero thereafter (figure 11, B).

Bioprosthetic degeneration. Actuarial freedom from bioprosthetic degeneration in patients receiving a porcine heterograft fell to 91% (CL 88% to 93%) by 5 years. The hazard function had a single rising phase (figure 12). Young age at the time of insertion of the bioprosthesis (p < .0001) and female gender (p = .02) were the risk factors for bioprosthetic degeneration. The predicted probability of important bioprosthetic degeneration within 5 years in persons aged 30 years at the time of insertion is 23% for women and 6% for men (figure 13).

Acute prosthetic thrombosis. Actuarial freedom from thrombosis after the original valve replacement was 97.9% (CL 97.4% to 98.4%) at 36 months among patients receiving the Bjork-Shiley prosthesis. The hazard function for acute thrombosis of Bjork-Shiley prostheses peaked at 10 months and declined nearly to zero by 6 years (figure 14). The single risk factor was female gender (p = .0006). There was no recurrence of the acute thrombosis in the three patients in whom simple thrombectomy, rather than valve replacement, was done.

Discussion
Special features of the study. The proportion of traced patients in this study is high (99.9%) and the follow-up sufficiently thorough that undetected events are unlikely. The concept of modes, or syndromes, of death (see definition under Materials and methods) has been used to avoid assignment of the cause of death, always a controversial matter. Assignment of a mode of death is not dependent on autopsy data, which are frequently missing, and generally not controversial (see Materials and methods) as compared with “cause of death.” Knowledge of the frequency and time-relatedness of the various modes of death, and of their specific risk factors, provides insight into the potential improvements that are most likely to reduce the overall inci-

FIGURE 11. Nomograms of the hazard function for periprosthetic leakage without evident infection (A) (n = 37) and PVE (B) (n = 42) after the primary valve replacement operation, determined separately for patients stratified according to two of the indications for reoperation.

FIGURE 12. Hazard function for bioprosthetic degeneration after the original valve replacement (n = 446). There is only a single phase.
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FIGURE 13. Nomogram of the estimated probability of bioprosthetic degeneration within 5 years of insertion, according to the patient’s sex and age at insertion.

dence of premature death in patients who have undergone valve replacement. The variability of the autopsy findings within one mode of death, however, indicates the need for caution in using this information.

The relative frequency with which events, including death, occur in the first few months after hospital dismissal makes it evident that the artificiality of emphasizing in-hospital deaths underestimates the incidence of early events. This has been avoided in this study by the use of a method that identifies differing risks across time by decomposing them into hazard phases, with their unique incremental risk factors.

Two important events have not been addressed by this study. One is thromboembolism and the other warfarin-related hemorrhage. There is a considerable degree of uncertainty in attributing death to either of these, but no doubt they have been the causes of some sudden and neurologic deaths.

A limitation of this study is that no prophylactic valve reoperations have been performed in these patients. In all likelihood, there is an overall lower incidence of death and other time-related untoward events after prophylactic valve reoperations than after those done for the indications present in this group of patients. However, the multivariate equation derived from the data in this study (see appendixes 1 and 2) can be used to estimate the probability of death (and other time-related events) in a specific patient after a valve reoperation done prophylactically and in anticipation of failure of a prosthetic valve. The NYHA functional class can be set for that patient, and in the case of most prophylactic operations it is I or II. The aortic cross-clamp time can be predicted with reasonable certainty by the surgeon. The other variables in the multivariate equation can also be set specifically for the patient at hand. Thereby the predicted 2 week or 5 year survival can be determined for the patient (as was done in table 2), and these can be compared with those of no reoperation.

The early and late survival probabilities of individual patients being considered for an original valve operation can also be estimated from the multivariate equations in a similar manner. These can be compared with the probability of survival with nonsurgical treatment, as an aid in making the decision about valve replacement.

The data and methodology can also be used to make valid comparisons with experiences in a different era in the same institution or in different institutions, a process that otherwise can be difficult because of potential differences in the age, functional status, and valve lesions of the patients (see appendix 3). Such comparisons can be useful in assessing progress, evaluating the quality of programs, and identifying means of improving results.

Premature death and its modes. The overall 5 year actuarial survival of about 75% is similar to that in previous reports.3-12 The inadequacy of using hospital survival figures as criteria of the early risks and result of a valve replacement operation is evident from the fact that the early phase of higher risk does not end with hospital dismissal or on postoperative day 30, but rather does not merge with a constant risk phase until about 3 months after operation.

It may be inferred from the data that improvement in survival after valve replacement operations could be achieved by reducing the incidence of deaths with cardiac failure and those that occur suddenly. The risk factors for these two most common modes of death suggest that they are associated with preoperatively important left ventricular secondary cardiomyopathy and dysfunction. The deaths in these modes that occur in the very early days after operation might be reduced

FIGURE 14. Nomogram of the hazard function for acute thrombosis of a Bjork-Shiley prosthesis after insertion at the original operation (n = 1084), 19 events). There is only a single phase in the hazard function.

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by better myocardial protection and a more efficient surgical technique with its shorter cross-clamp time (see figure 4). The deaths occurring later in the early phase and in the constant phase are unlikely to be improved by these measures and may be inevitable once the existing degree of ventricular disease has developed. Therefore, in the ongoing management of patients with valvular heart disease, the competing risks of continuation of the natural evolution of the ventricular disease (which appears to be particularly disadvantageous in the case of aortic incompetence and mitral valve disease) and those of prompt valve replacement must be repeatedly reconsidered. The adverse effect of ischemic mitral incompetence on late survival, also observed by Kay et al., 14 is no doubt related to its association with important ischemic cardiomyopathy, and once developed this probably has an immutable detrimental effect on late survival. Therefore its prevention is also to be stressed.

Although the event reoperation followed by death was not considered as a mode of death in a formal way (see table 3), it does account for 40 deaths (the third most common “mode”) among the original 1533 patients and does have an early phase of high risk after operation (see figure 2). Favorably influencing the risk factors for the indications for reoperation (PVE, periprosthetic leakage without evident infection, valve thrombosis, and bioprosthetic degeneration) would reduce the overall risk of premature death after valve replacement. PVE, usually with periprosthetic leakage, is often difficult to distinguish from periprosthetic leakage through evident infection. The similarities between the risk factors for PVE and those for periprosthetic leakage without evident infection, and the similarities between the hazard functions of these two events, suggest that some of the latter may in fact be instances of PVE. A precise surgical technique, scrupulous attention to the details of asepsis, and effective antibiotic prophylaxis are important in improving the overall results of primary valve replacement operations. Furthermore, the hairy chests of men may result in the presence of more skin bacteria at the time of operation than in women, and the reduction of the strength of male gender as a risk factor for these events may require improved methods of skin preparation for operation. The use of bioprostheses, including cryopreserved homografts in the aortic position, whenever there is native valve endocarditis or PVE could be expected to minimize these complications and thus the need for reoperation.3, 15

Because the increase in risk of premature death after valve replacement that is associated with older age is small, patients should not be advised against operation just because they are elderly. Neither should operation be advised prematurely, on the basis of advancing years. The association of black race with an increased hazard of premature death in the early phase of a number of modes may be related to the higher incidence of hypertension and left ventricular hypertrophy in blacks.

The study does not provide support for the preference of bioprostheses over mechanical valves, or vice versa, except when the operation is being done for native valve endocarditis (see above). Although bioprosthetic degeneration, a slow process in older male patients (see figure 13), may require reoperation, the risk of this is low when done while the patient’s functional status is good (see table 2). The relative rapidity of bioprosthetic degeneration in persons less than about 45 years old, and especially in women, cautions against the use of bioprostheses in such individuals.

Reoperation. There is a tendency to consider valve reoperation after an original valve replacement operation as a benign event, but this is not supported by this study. An increasing risk of complications after multiple valve reoperations has also been reported by Sandza et al. 17 This and the increased risks of death, reoperation, PVE, and periprosthetic leakage without evident infection after valve reoperations make it apparent that every effort should be made to make the first operation a lasting one.

PVE. Although PVE occurs uncommonly after an original valve replacement operation, it is a serious complication with a mortality of 63% in the patients in this series3 and a similar mortality in the experience of others. 18, 19 Its early peaking hazard phase is probably caused by organisms present in the patient’s valve area or introduced there at the time of operation, whereas its constant phase is probably related to transient bacteremias during which organisms lodge in the valve area.3 It is likely that the contention of Miller et al. 18 that the hazard of this event across time is constant resulted from their failure to decompose in detail the early period after operation.

Periprosthetic leakage without evident infection. In view of the data in this study, when the leakage is mild, nothing should be done surgically because the reoperation in this setting carries the same risks of untoward postoperative events as do other reoperations. When reoperation is indicated and there is no suggestion that PVE is present, the data support the use of repair of the leakage whenever possible, rather than re-replacement.

Bioprosthetic degeneration. The particular tendency of
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young patients to develop degeneration of porcine bioprostheses, previously reported by Magilligan et al., Dunn, Geha et al., Williams et al., and others is again emphasized by this study. The association of female gender with an increased risk of bioprosthetic degeneration has not been noted previously. The inference from these analyses is that currently available porcine bioprostheses should not be used, with rare exceptions, in women less than about 55 years of age and in men less than about 45 years of age.

Acute valve thrombosis. The early and transiently peaking hazard function of this low-frequency event in addition to the untoward events that tend to follow valve re-replacement suggest the advisability of declotting the prosthetic valve, rather than replacing it, whenever possible. This very important complication is not limited to the Bjork-Shiley valve, which was the type of mechanical device used nearly exclusively in the patients in this study, but was experienced by one patient in this series with a bioprosthesis, has been seen by us in one patient with a St. Jude Medical valve, and is reported by Miller et al. as occurring in patients receiving the Starr-Edwards Silastic ball valve mitral prosthesis.

We appreciate the cooperation of our surgical colleagues, Drs. R. B. Karp, N. T. Kouchoukos, A. D. Pacifico, G. L. Zorn, and J. K. Kirklin, for permitting us to include patients operated on by them in this study and for assisting us in the interpretation of the data. Drs. Joseph Defauw, Janardan Dhasmana, Torbjorn Ivert, Richard A. Reynolds, Ismail Sallam, Steven Westaby, and Frederick Wideman, as well as Robert Brown, Kathy Peterson, and Phyllis Smith, assisted in obtaining the follow-up data. Sandy O'Brien assisted in the preparation of the graphics. Drs. David Naftel and Malcolm Turner, Department of Biostatistics and Biomathematics, collaborated with us in the statistical work. Nancy Ferguson and Debbie Nuby contributed greatly in the formation of the tables and the typing and editing of the manuscript.

References


Appendix 1

Identification of the structure and risk factors of the time-related distribution of events

The parametric method is conceptualized in the cumulative hazard domain $\Lambda(t)$. Cumulative hazard is related to the survivorship function $S(t)$ by the expression:

$$S(t) = \exp \left[ -\Lambda(t) \right]$$

and to the hazard function $\lambda(t)$ by its first derivative with respect to time (exp is the base of the natural logarithms). The system considers up to three additive phases of hazard:

$$\Lambda(t) = \mu_1 G_1(t) + \mu_2 G_2(t) + \mu_3 G_3(t)$$
The $\mu$'s are scaling parameters and $G$'s are shaping parameters.

$$G_1(t) = \left[ 1 - \frac{m + m + 2m}{|m|} \right]^{-v|m|}$$  

represents early, decreasing risk (or a risk that rises transiently then declines). Based on the data in this study, its parameters and formula were simplified to:

$$G_1(t) = 1 \left( 1 + (p/t)^9 \right)^3, g_1(t) = G_1(v/t) \left[ 1 + (p/t)^9 \right]$$  

where $g_1(t)$ is the representation of $G_1(t)$ in the hazard domain, $p$ represents the half-time for early cumulative hazard, and $v$ determines the shape of the hazard function in the vicinity of time zero.

$$G_2(t) = t, g_2(t) = 1$$  

represents a constant hazard phase that is present throughout the experience.

$$G_3(t) = \left[ \exp \left( t / \beta_0 \right) \right]^{-v|m|}$$  

represents the increasing late phase of hazard. In this study, $\gamma = 2$ and $\eta = 1$ throughout, so only $\delta$ has been estimated, which corresponds to the time at which the hazard function begins to rise steeply. With these simplifications:

$$g_3(t) = 2t \left[ \exp \left( t / \beta_0 \right) \right] / \delta^2$$  

The scaling parameters were made parametric functions of concomitant information (possible risk factors):

$$\mu_1 = \ln \left[ 1 + \exp \left( \beta_1 \times 1 \right) \right]$$  

where $\ln$ is the natural logarithm and

$$\beta_1 \times 1 = \beta_0 + \beta_1 \times 1 + \beta_2 \times 2 + \cdots + \beta_k \times k$$  

that is, a linear regression model. Equation 8 is the logistic equation, expressed in cumulative hazard. The parametric scaling function for the constant and increasing hazard phases are log-linear (proportional hazards) regression models:

$$\mu_2 = \exp \left( \beta_2 \times 2 \right)$$  

and

$$\mu_3 = \exp \left( \beta_3 \times 3 \right)$$  

All parameters and regression coefficients were estimated simultaneously by the method of maximum likelihood. Structural parsimony of the model was determined by the likelihood ratio test. Asymptotic $p$ values for regression coefficients were based on the ratio of each coefficient to its standard deviation, and confidence limits for estimated functions were determined by the method of statistical differentials.

**Appendix 2**

**Parameter estimates and regression coefficients**

For each event analyzed, shaping parameter estimates and intercepts are given for the parametric estimates of events across time (hazard function and survivorship function); these plus regression coefficients are given from the multivariate analysis of the event. These are organized according to their time of influence on the hazard function: throughout and constant, early and decreasing, and late and increasing. For dichotomous variables, the presence of the stated factor takes on the value of 1, its absence 0; thus its coefficient is used when the factor is present and not used when it is absent. In the text, an average value for a dichotomous variable is used occasionally; in this case, that value is multiplied by the listed coefficient. For continuous variables, the units of the variable are multiplied by the coefficient in the equation.

1. **Death**

   **Parametric estimate.** Constant phase: intercept $-5.816$. Early phase: $p = 2.515$, $v = 0.533$, intercept $-1.852$.

   **Parametric multivariate estimates.** Constant phase: intercept $-6.802$, age 0.01531, black race 0.8899, ischemic mitral incompetence 1.271. Early phase: $p = 3.333$, $v = 0.5209$, intercept $-7.714$, age 0.2493, aortic incompetence 0.8924, mitral valve stenosis and/or incompetence $\times$ NYHA functional class (interaction term) 0.4602, NYHA functional class 1.100, cardiopulmonary $-1.901$, aortic cross-clamp time if cardiopulmonary was used 0.0284, combined mitral and aortic valve replacement 1.601, combined mitral and aortic valve replacement $\times$ aortic cross-clamp time (with cardiopulmonary) $-0.01384$.

2. **Death after first reoperation**

   **Parametric estimate.** Constant phase: intercept $-4.214$. Early phase: $p = 0.00182$, $v = 1.958$, intercept $-1.763$.

3. **Death after all reoperations**

   **Parametric estimate.** Constant phase: intercept $-3.862$. Early phase: $p = 0.003302$, $v = 1$, intercept $-1.483$.

   **Parametric multivariate estimates.** Constant phase: intercept $-5.516$, mitral valve stenosis and/or insufficiency at original operation 1.342, mechanical prosthesis 1.154. Early phase: intercept $-7.133$, reoperation number 0.7679, NYHA functional class 1.093.

4. **Death with cardiac failure**

   **Parametric estimate.** Constant phase: intercept $-7.291$. Early phase: $p = 0.3770$, $v = 0.5954$, intercept $-3.052$.

   **Parametric multivariate estimates.** Constant phase: intercept $-7.464$, black race 1.085, ischemic mitral incompetence 2.322. Early phase: $p = 0.3718$, $v = 0.6023$, intercept $-11.71$, age 0.04575, aortic incompetence 1.100, mitral valve stenosis and/or incompetence 1.946, NYHA functional class 1.290, cardiopulmonary $-2.235$, aortic cross-clamp time if cardiopulmonary was used 0.02101, tricuspid procedure 1.116, coronary artery bypass grafting 0.9684.

5. **Sudden death**


6. **Neurologic death**

   **Parametric estimate.** Constant phase: intercept $-7.630$.

7. **Death with cancer**

   **Parametric estimate.** Constant phase: intercept $-7.748$.

   **Parametric multivariate estimates.** Constant phase: intercept $-10.20$, age 0.04231.
(8) Death with hemorrhage

**Parametric estimate.** Early phase: \( \rho = 0.004278, v = 1.650, \) intercept \(-4.925.\)

**Parametric multivariate estimates.** Early phase: \( \rho = 0.004333, v = 1.648, \) intercept \(-13.07, \) age \(0.0651, \) NYHA functional class \(1.082, \) aortic cross-clamp time if cardioplegia was used \(0.01644.\)

(9) Death with infection

**Parametric estimate.** Early phase: \( \rho = 1.249, v = 2.900, \) intercept \(-5.066.\)

(10) Death with arrhythmias

**Parametric estimate.** Early phase: \( \rho = 1.538, v = 1.585, \) intercept \(-5.300.\)

(11) Death in other cardiac modes

**Parametric estimate.** Constant phase: intercept \(-8.980.\)

(12) Death with trauma

**Parametric estimate.** Constant phase: intercept \(-9.134.\)

(13) Death in miscellaneous modes

**Parametric estimate.** Constant phase: intercept \(-8.093.\)

(14) Death with uncertain modes

**Parametric estimate.** Early phase: \( \rho = 39.62, v = 1, \) intercept \(-3.173.\)

(15) Reoperation

**Parametric estimate.** Early phase: \( \rho = 4.522, v = 1.724, \) intercept \(-3.107.\) Increasing phase: \( \delta = 55.18, \) intercept \(-4.525.\)

(16) Reoperation for mechanical prostheses

**Parametric estimate.** Constant phase: intercept \(-9.520.\) Early phase: \( \rho = 5.097, v = 1.594, \) intercept \(-2.938.\)

(17) Reoperation for bioprostheses

**Parametric estimate.** Early phase: \( \rho = 3.847, v = 2.090, \) intercept \(-3.536.\) Increasing phase: \( \delta = 42.42, \) intercept \(-4.358.\)

(18) PVE after original operation

**Parametric estimate.** Constant phase: intercept \(-8.028.\) Early phase: \( \rho = 1.956, v = 2.056, \) intercept \(-3.648.\)

**Parametric multivariate estimates.** Constant phase: intercept \(-8.330, \) black race \(1.514.\) Early phase: \( \rho = 2.104, v = 2.073, \) intercept \(-7.098, \) males \(1.210, \) black race \(1.169, \) native valve endocarditis \(2.364, \) mechanical prosthesis \(1.816.\)

(19) PVE after all reoperations

**Parametric estimate.** Early phase: \( \rho = 1.940, v = 2.183, \) intercept \(-1.723.\)

**Parametric multivariate estimates.** Early phase: \( \rho = 2.049, v = 2.158, \) intercept \(-4.282, \) males \(2.490, \) mitral valve replacement at original operation \(1.457.\)

(20) Periprosthetic leakage after original operation

**Parametric estimate.** Early phase: \( \rho = 4.416, v = 1.613, \) intercept \(-4.239.\)

**Parametric multivariate estimates.** Early phase: \( 4.681, v = 1.595, \) intercept \(-4.520, \) age \(-0.03727, \) males \(1.076, \) black race \(1.033, \) native valve endocarditis \(1.128, \) mitral valve replacement (isolated or combined) \(1.700.\)

(21) Periprosthetic leakage after all reoperations

**Parametric estimate.** Early phase: \( \rho = 36.93, v = 1, \) intercept \(0.5335.\)

**Parametric multivariate estimates.** Constant phase: intercept \(-5.567, \) age \(-0.02448, \) black race \(1.383, \) valve replacement rather than repair \(1.804.\)

(22) PVE after reoperation when PVE was indication for reoperation

**Parametric estimate.** Early phase: \( \rho = 3.000, v = 1.661, \) intercept \(-1.071.\)

(23) Periprosthetic leakage after reoperation when PVE was indication for reoperation

**Parametric estimate.** Constant phase: intercept \(-4.562.\) Early phase: \( \rho = 3.645, v = 2.025, \) intercept \(-0.9921.\)

(24) PVE after reoperation when periprosthetic leakage was indication for reoperation

**Parametric estimate.** Early phase: \( \rho = 1.379, v = 3.257, \) intercept \(-1.816.\)

(25) Periprosthetic leakage when periprosthetic leakage was indication for reoperation

**Parametric estimate.** Constant phase: intercept \(-4.027.\)

(26) Bioprosthetic degeneration

**Parametric multivariate estimates.** Increasing phase: \( \delta = 45.22, \) intercept \(-4.127.\)

(27) Acute prosthetic thrombosis

**Parametric estimate.** Early phase: \( \rho = 18.33, v = 1.817, \) intercept \(-3.632.\)

**Parametric multivariate estimates.** Early phase: \( \rho = 18.94, v = 1.799, \) intercept \(-4.165, \) females (if mitral valve replacement) \(1.611.\)

**Appendix 3**

Comparison of differing experiences

A rigorous comparison of the results of different experiences requires the actual combination of the data sets; this is usually not feasible. Alternatively, the same multivariate analysis model can be fitted to differing experiences and the shaping and risk factor coefficients compared; this is also often not feasible. The approach most often possible is the application of the model from one study, such as that presented in appendixes 1 and 2, to the new experience in each of two ways. First, from the multivariate equation the expected incidence of an event (cumulative hazard function) can be calculated for each patient, with his specific incremental risk factors and his duration of follow-up. The summation of these individual cumulative hazard incidences totals the number of events expected in the total patient group. A chi-square test of the difference between the number of observed and expected events is then performed to determine whether that difference is greater than that expected by chance. This method gives an overall comparison of experiences.

Second, parametric survivorship functions, representing freedom from the event of interest, can be generated for each patient from the multivariate analysis. The average of these curves, with its confidence limit (a reasonable approximation to the expected curve for the given prevalence of risk factors) is compared with the observed actuarial estimate for the second group with its confidence limits.
Death and other time-related events after valve replacement.
E H Blackstone and J W Kirklin

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