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The Decomposition of Time-Varying Hazard Into Phases, Each Incorporating a Separate Stream of Concomitant Information

EUGENE H. BLACKSTONE, DAVID C. NAFTEL, and MALCOLM E. TURNER, JR.*

The hazard function of time-related events, such as death or reoperation following heart valve replacement, often is time-varying in a structured fashion, as is the influence of risk factors associated with the events. A completely parametric system is presented for the decomposition of time-varying patterns of risk into additive, overlapping phases, descriptively labeled as early, constant-hazard, and late. Each phase is shaped by a different generic function of time constituting a family of nested equations and is scaled by a separate logit-linear or log-linear function of concomitant information. Model building uses maximum likelihood estimation. The resulting parametric equations permit hazard function, survivorship function, and probability estimates and their confidence limits to be portrayed and adjusted for concomitant information. These provide a comprehensive analysis of time-related events from which inferences may be drawn to improve, for example, the management of patients with valvar heart disease.

KEY WORDS: Survival analysis; Parametric analysis; Hazard function; Cumulative hazard; Mixture distributions; Censored data; Logistic regression; Risk factors.

1. INTRODUCTION

Death and other time-related events following a major surgical intervention or acute illness often are distributed in a highly structured, time-varying pattern. Risk is high immediately, falls rapidly to a much lower level, and later rises [see particularly the analysis of death after heart valve replacement (Miller et al. 1983), the multi-institutional analysis of death after admission to coronary care units for acute myocardial infarction (Gilpin, Koziol, Madsen, Henning, and Ross 1983), and the analysis of death after coronary artery bypass grafting (Kirklin, Blackstone, and Rogers 1985)]. The influence of risk factors associated with these events also varies in accordance with this pattern.

In this article a completely parametric system is presented for modeling the structure of the time-related distribution of such events, based on the decomposition of the pattern of time-varying risk into a small number of phases. Risk factors are identified that are specific for each phase. The resulting model may be used to portray the relation between risk factors and time-related events in a way that facilitates the process of drawing useful inferences from clinical experiences. Certain time-related events after heart valve replacement are used to illustrate the method.

2. TIME-RELATED EVENTS AFTER HEART VALVE REPLACEMENT

Following surgery to replace one or more diseased heart valves, several time-related events may occur, including death, reoperation, prosthesis failure, or infection of the prosthesis. Progress in minimizing or preventing these events requires knowledge of their time of occurrence and of their associated, time-specific risk factors.

To study valve-related events, follow-up information was obtained concerning the 1,533 patients undergoing their first heart valve replacement at our institution between January 1, 1975 and July 1, 1979 (Blackstone and Kirklin 1985; Ivert et al. 1984). All but one patient was traced beyond hospital discharge. The median follow-up interval was 43 months.

Patterns of the distribution in time of various postoperative events varied widely. For example, the nonparametric product–limit *survival* estimates (Kaplan and Meier 1958) show that death occurs at a rapid rate immediately after operation (Fig. 1A). This early high-risk phase extends several months beyond surgery before merging into a phase of lower risk. The risk of valve *reoperation* appears to have a phase of transiently higher risk beginning soon after operation, and this phase merges into one of modestly accelerating risk after 3 to 4 years (Fig. 1B). In contrast, reoperation for *degeneration* of the biological valve prosthesis used in some of the patients appears to have a single phase of late accelerated risk (Fig. 1C). These differences in time-related risk pattern are most meaningfully portrayed by the hazard function. Its nonparametric estimation, however, is unstable.

Patterns of the distribution in time of valve-related events are often described in terms of "early" and "late" phases (e.g., hospital or 30-day mortality vs. later mortality). The concept is useful because not only the risk itself, but also the risk factors associated with the events, differ early and later after surgery. Although it is convenient to analyze

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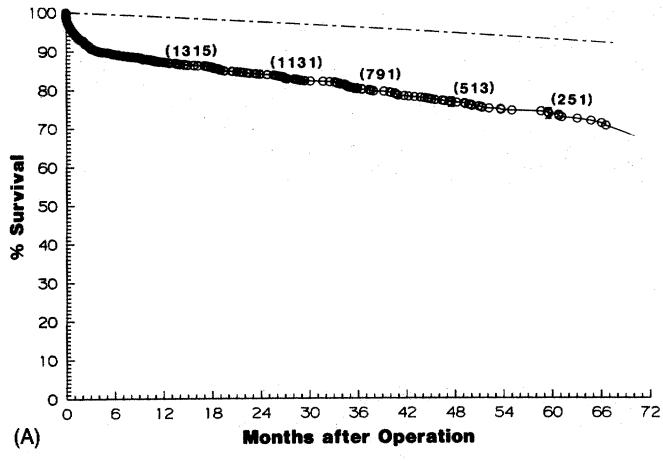
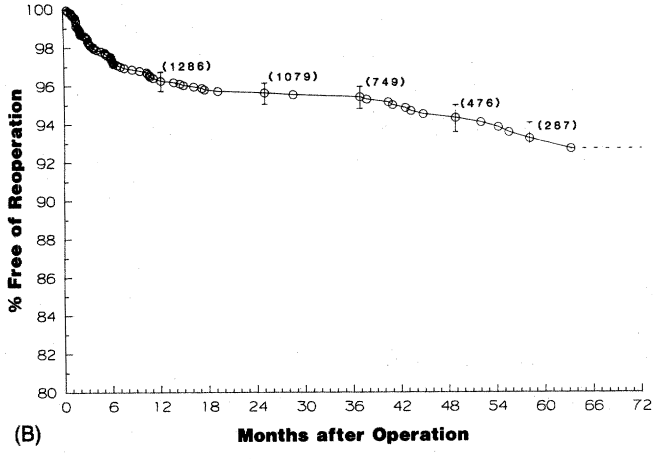




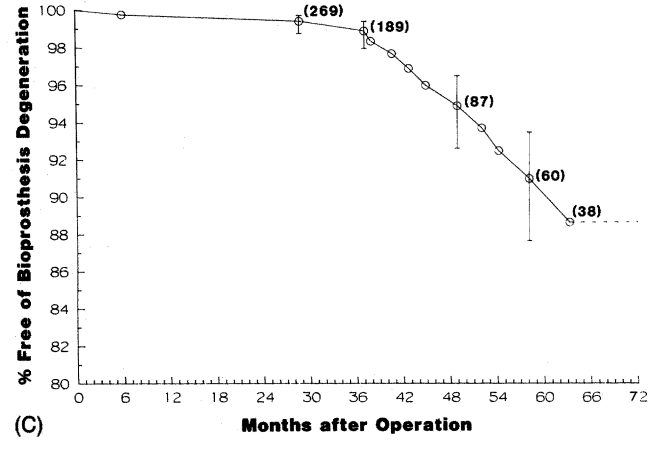


Figure 1. Time-related Events After Heart Valve Replacement (1975–July 1979; n = 1,533). The circles represent product–limit estimates at the time of each event; the vertical bars represent 68% confidence limits, equivalent to one standard deviation; the numbers in parentheses represent patients traced beyond that time; and the horizontal dashed line represents traced event-free patients, except that one reoperation for bioprosthesis degeneration at 75 months postoperatively is not depicted. (A) Survival, accompanied by an age-race-gender matched population life table (dash-dot-dash line) for informal comparison. (B) Valve reoperation. (C) Reoperation for bioprosthesis degeneration among 446 patients with such prostheses. Note that the vertical scale has been expanded greatly in B and C.

these separate time frames, the distinction between phases is not sharp, as Figure 1 demonstrates. Thus a method is needed for a comprehensive analysis of time-related events, which begins at the point of entry into the study, extends throughout the period of observation, and simultaneously decomposes risk into meaningful phases and identifies the risk factors specific for each phase.

3. DESCRIPTION OF MULTIPLE–PHASE PARAMETRIC MODEL

Decomposition into phases of time-varying risk is accomplished by a parametric modeling system that is conceptualized in terms of the cumulative hazard function $\Lambda(t)$. Multiple overlapping phases of risk are considered to be additive, with each phase individually shaped by a function of time $G(t, \boldsymbol{\Theta})$ and scaled by a function of concomitant information $\mu(\mathbf{x}, \boldsymbol{\beta})$, as follows:

$$\Lambda(t, \mathbf{x}) = \sum_{j=1}^{k} \mu_j(\mathbf{x}_j, \boldsymbol{\beta}_j) \cdot G_j(t, \boldsymbol{\Theta}_j). \quad (1)$$

This article presents a model for decomposition of $\Lambda(t)$ into as many as three phases, descriptively labeled as an early phase ($j = 1$) immediately following $t = 0$, a constant-hazard phase ($j = 2$) of linearly increasing $\Lambda(t)$, and a late phase ($j = 3$) of accelerating risk. Each phase is defined for $0 \leq t < \infty$, although the effects of each are more prominent at one time than another (Fig. 2). Shaping and scaling parametric functions were chosen, which can be expressed in closed form in all survival function domains.

3.1 Early Phase

The *generic shaping function* for the early phase ($j = 1$) is based on the family of equations described originally as models of cumulative mortality by Hazelrig, Turner, and Blackstone (1982) and further generalized in Turner, Hazelrig, and Blackstone (1982), as follows:

$$G_1(t, \boldsymbol{\Theta}_1) = \frac{|\nu| - \nu}{2|\nu|} + \frac{\nu}{|\nu|}\left[1 + \frac{m}{|m|}\left(\frac{|m| - m}{2|m|} + B(t)\right)^{-1/\nu}\right]^{-1/m}. \quad (2)$$

This generic equation simplifies to three forms, depending on the signs of ν and m, fulfilling the criteria that $G_1(0, \boldsymbol{\Theta}_1) = 0$ and $\lim t \to \infty\ G_1(t, \boldsymbol{\Theta}_1) = 1$:

$$G_1(t, \boldsymbol{\Theta}_1) = [1 + B(t)^{-1/\nu}]^{-1/m}, \qquad m > 0, \nu > 0, \quad (3)$$

$$G_1(t, \boldsymbol{\Theta}_1) = [1 - (1 + B(t))^{-1/\nu}]^{-1/m}, \qquad m < 0, \nu > 0, \quad (4)$$

and

$$G_1(t, \boldsymbol{\Theta}_1) = 1 - [1 + B(t)^{-1/\nu}]^{-1/m}, \qquad m > 0, \nu < 0, \quad (5)$$

where $B(t) = [\exp(\delta t) - 1]/(\delta\rho)$, $\delta > 0$, $\rho > 0$. These models may be simplified further to a number of three-, two-, and one-parameter models, including the limiting

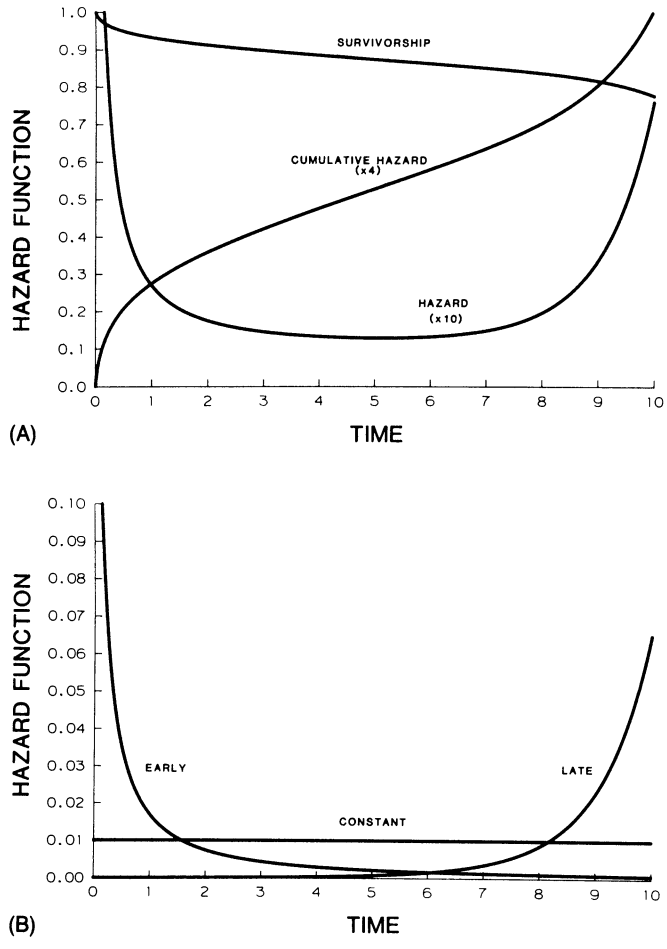


Figure 2. Interrelationship Among Functions Describing Time-Related Events. These are typical of the patterns observed following heart operations. (A) The pattern of the survivorship function is made apparent by the cumulative hazard function, which initially rises rapidly, then merges with a constantly rising phase, and finally accelerates. The corresponding hazard function is infinite at time zero, rapidly falls to a low level, then rises steeply. (B) Decomposition into separate but overlapping phases of hazard that, when added, constitute the hazard function depicted in A. Its phases are labeled early, constant, and late to denote the times at which the influence of each is dominant. The parameter values used to generate these curves were $\rho = .6$, $\nu = 1.4$, $\delta = 0$, $m = 1$, $\tau = 4.5$, $\gamma = 2$, $\delta = 0$, $\eta = 1$, $\mu_1 = .1$, $\mu_2 = .01$, and $\mu_3 = 4.4 \times 10^{-4}$.

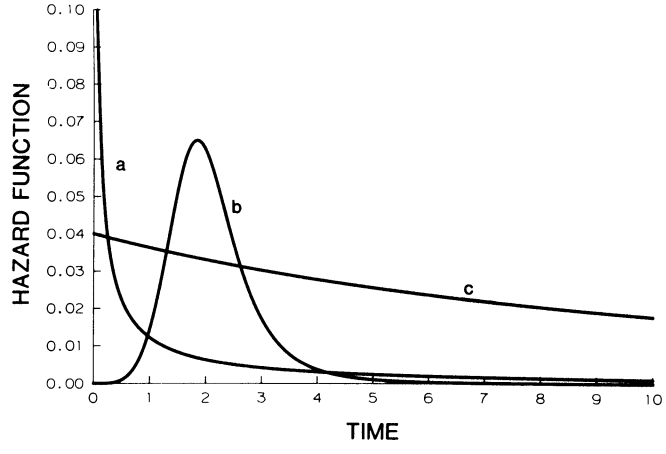


Figure 3. Typical Forms of Hazard Function [$\lambda(t)$] Generated by the Early-Phase Generic Equation. In all cases $\delta = 0$ and $m = 1$. In (a) $\rho = 2$, $\nu = 2$, and $\mu_1 = .1$; in (b) $\rho = 2$, $\nu = .2$, and $\mu_1 = .1$; in (c) $\rho = 20$, $\nu = 1$, and $\mu_1 = .8$. Notice that $\lambda(t)$ may approach infinity as time approaches 0 as in (a) ($m\nu > 1$); it may begin at 0, slowly rise, then peak and fall as in (b) ($m\nu < 1$); or it may begin at a finite value and fall as in (c) ($m\nu = 1$).

forms when δ, ν, or $m = 0$. In this way, a family of nested functions having a wide range of shapes is provided (Naftel 1978) (Fig. 3).

The shaping parameters have useful interpretations. The half time $t_{1/2}$ for early cumulative hazard is related to ρ. Thus for Equation (3), with $\delta = 0$,

$$\rho = t_{1/2}(2^m - 1)^{\nu}.$$

The shape of the hazard function $\dot{G}_1(t, \boldsymbol{\Theta}_1)$ as $t \to 0$ is determined by the relationship of ν to m (Fig. 3). For Equation (3) $\lim_{t\to 0} \dot{G}_1(t, \boldsymbol{\Theta}_1) = \infty$ when $m\nu > 1$, $\dot{G}_1(0, \boldsymbol{\Theta}_1) = 1/\rho$ when $m\nu = 1$.

The *scaling parametric function* $\mu_1(\mathbf{x}_1, \boldsymbol{\beta}_1)$ is related to the area beneath the hazard function of the early risk phase between $t = 0$ and infinity, although the contribution to early risk rapidly becomes vanishingly small. Thus $1 - \exp[-\mu_1(\boldsymbol{\beta}_1'\mathbf{x}_1)]$ is the probability $P_\infty(\mathbf{x}_1, \boldsymbol{\beta}_1)$ of an early event. This suggested that the scaling parametric function be logit-linear in probability, as follows:

$$\mu_1(\mathbf{x}_1, \boldsymbol{\beta}_1) = \ln[1 + \exp(\boldsymbol{\beta}_1'\mathbf{x}_1)] \tag{6}$$

and

$$P_\infty(\mathbf{x}_1, \boldsymbol{\beta}_1) = 1/[1 + \exp(-\boldsymbol{\beta}_1'\mathbf{x}_1)]. \tag{7}$$

Alternatively, the simpler log-linear form may be used.

3.2 Constant-Hazard Phase

For the constant-hazard phase ($j = 2$), the *shaping function* $G_2(t, \boldsymbol{\Theta}_2) = t$ and $\dot{G}_2(t, \boldsymbol{\Theta}_2) = 1$. The *scaling parametric function* $\mu_2(\mathbf{x}_2, \boldsymbol{\beta}_2)$ is the level of constant hazard; it is modeled as a log-linear function (proportional hazard) of concomitant information: $\mu_2(\mathbf{x}_2, \boldsymbol{\beta}_2) = \exp(\boldsymbol{\beta}_2'\mathbf{x}_2)$.

3.3 Late Phase

The *generic shaping* function for the late phase ($j = 3$) is

$$G_3(t, \boldsymbol{\Theta}_3) = [(1 + (t/\tau)^{\gamma})^{1/\alpha} - 1]^{\eta}, \tag{8}$$

where $\tau > 0$, $\gamma > 0$, $\alpha \geq 0$, $\eta > 0$, $\gamma\eta \geq 2$, and $\gamma\eta/\alpha \geq 2$. $G_3(t, \boldsymbol{\Theta}_3)$ constitutes a hierarchical family of increasing functions of time with $\lim_{t\to 0}\dot{G}_3(t, \boldsymbol{\Theta}_3) = 0$. The model can be simplified to a limiting exponential form when α is 0. The late hazard function component can vary from an apparent delay before accelerating to a linear increase (Fig. 4). The *scaling parametric function* $\mu_3(\mathbf{x}_3, \boldsymbol{\beta}_3)$ is modeled as a log-linear function of concomitant information: $\mu_3(\mathbf{x}_3, \boldsymbol{\beta}_3) = \exp(\boldsymbol{\beta}_3'\mathbf{x}_3)$.

4. ESTIMATION

Shaping parameters and concomitant information coefficients are estimated by the method of maximum likelihood. The likelihood function is generalized for any combination of longitudinal-censored, cross-sectional-censored,

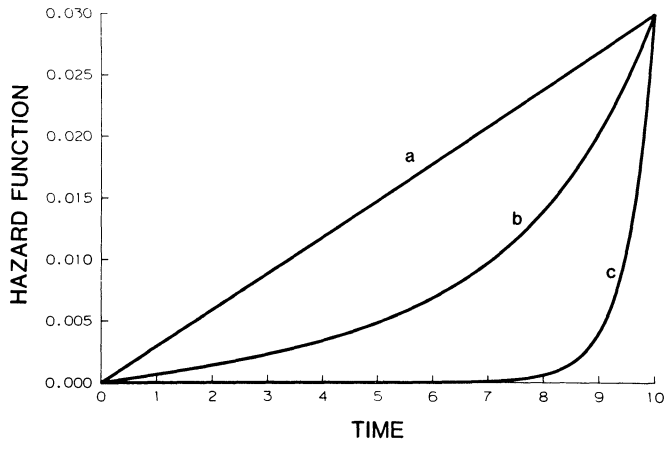


Figure 4. Typical Forms of Hazard Function [$\lambda(t)$] Generated by the Late-Phase Generic Equation. In all cases, $\gamma = 2$, $\alpha = 0$, and $\eta = 1$. In (a) $\tau = 892$ and $\mu_3 = 9.9$; in (b) $\tau = 8$ and $\mu_3 = .022$; in (c) $\tau = 3$ and $\mu_3 = 6.8 \times 10^{-7}$. Notice that $\lambda(t)$ may increase linearly as in a Rayleigh (a), it may curve sharply upward after a prolonged period of imperceptible rise (c); or it may take on an intermediate form (b).

and interval-censored data (Hazelrig et al. 1982) and is expressed as counts of uncensored and censored observations when more than one observation occurs at a specific time (Breslow 1974). It is usefully formulated in terms of $\Lambda(t)$ and the hazard function [$\lambda(t)$] rather than the more complex expressions of the density and survivorship [$S(t)$] functions (Bradley 1982). All shaping parameters are transformed to an unbounded scale for use with unconstrained optimization algorithms. Initial parameter estimates are obtained by inspection of the nonparametric estimate of $\Lambda(t)$ (Nelson 1969, 1972), whereas initial starting values of zero are adequate for the concomitant information coefficients.

Asymptotic variance and covariance estimates are calculated by using second partial derivatives of the likelihood function or by the method of finite-difference derivatives (Dennis and Schnabel 1983, pp. 77–80). Tests of hypotheses concerning the parameters are based on the asymptotic normality of the maximum likelihood estimates (Nelson 1982, pp. 356–358). Confidence limits for predictions derived from the model are estimated by using the method of statistical differentials (see Ku 1966). For these, a separate formulation of the confidence limits for $\lambda(t)$ and $S(t)$, transformed in each case to an unbounded scale, has been used: the logarithmic transformation for $\lambda(t)$ and the logit transformation for $S(t)$.

5. IMPLEMENTATION

This multiple-phase parametric system for decomposition of time-varying risk has been used in a procedure interfaced to SAS (and available from the authors) to analyze more than 200 data sets ranging in size from 12 to 4,000 observations with up to 99% censoring. The number of phases resolved has been as few as one and as many as three (e.g., Kirklin et al. 1985). Initially, the nonparametric estimate of $\Lambda(t)$ is helpful in indicating structure in the distribution of events, such as the presence of an early phase, a linearly increasing phase (representing constant hazard), and an accelerated-hazard late phase. The specific phases necessary for adequate decomposition of the structure, however, are determined by the likelihood ratio test for a model with a phase included and with it excluded.

The next conceptual step, although performed in conjunction with the process of resolving phases, is the selection of the most parsimonious mathematical form of the generic shaping functions. The likelihood ratio test is used for selection of simpler family members. This process provides a form of goodness-of-fit test within the constraints of the general parametric model. Using a stepwise strategy of working from fewer phases toward a larger number and from a simple family member toward the more complex aids the estimation process.

6. APPLICATION TO TIME-RELATED EVENTS AFTER VALVE REPLACEMENT

The parametric system is illustrated by its application to several time-related events following heart valve replacement, some of which are depicted in Figure 1. The complete data set is available from the authors upon request, and the medical inferences derived from its analysis are presented in Blackstone and Kirklin (1985).

6.1 Reoperation

The nonparametric estimate of $\Lambda(t)$ for reoperation following heart valve replacement reveals at least two phases (Fig. 5). The parametric system resolved an early phase (simplified to two shaping parameters) and a late phase (simplified to a single shaping parameter) as adequate for the decomposition of the time-related pattern of reoperation. The resulting parametric estimate of $\Lambda(t)$ and its confidence limits are shown superimposed on the nonparametric estimates in Figure 5. Visually, the two independent estimates, and even the width of their asymptotic confidence limits are quite similar. Nevertheless, a systematic difference is evident beyond about 48 months. This difference may be due to the well-recognized overesti-

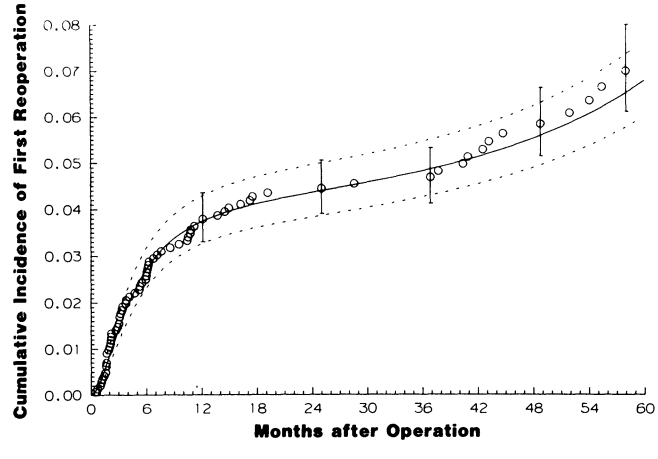
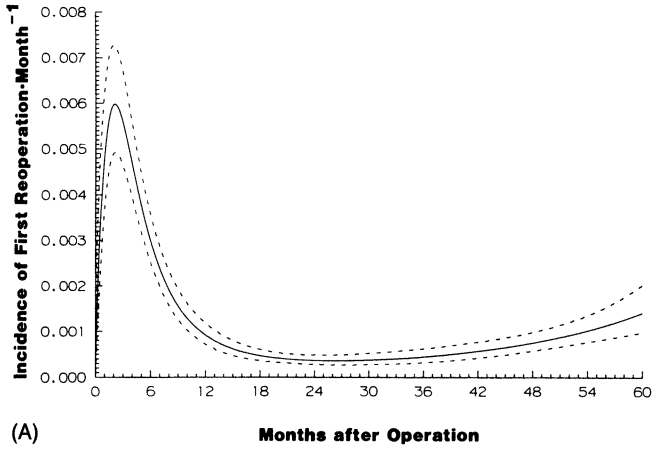
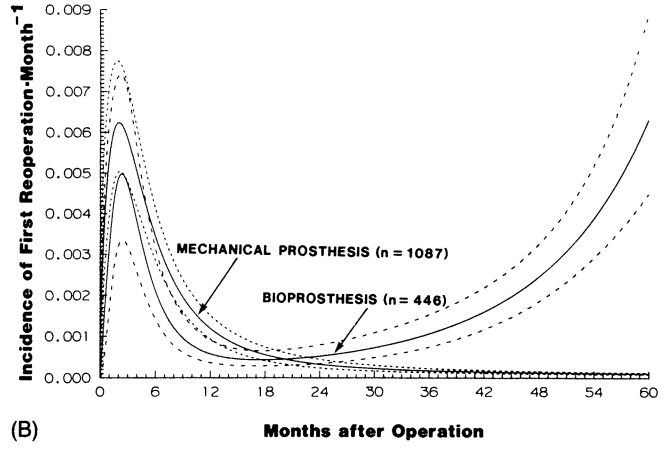


Figure 5. Cumulative Hazard Function for Valve Reoperation. The nonparametric estimates were calculated as minus the logarithm of the product–limit estimates in Figure 1B. Superimposed is the independent maximum likelihood estimate of $\Lambda(t)$ from the multiple-phase parametric system. The dashed lines enclose the 68% confidence limits of the parametric estimates.





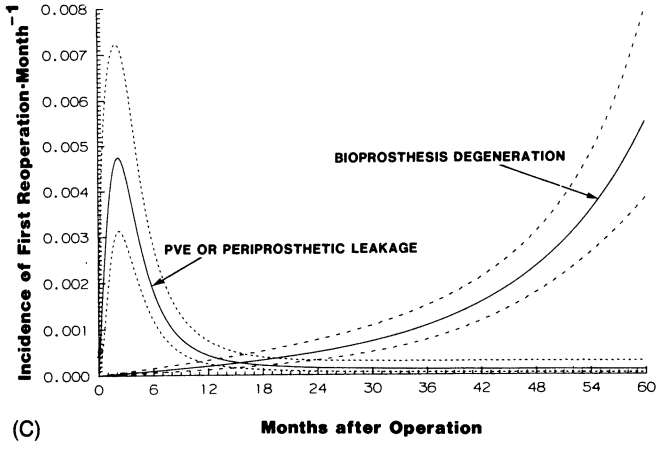


Figure 6. Hazard Functions for Reoperation After Heart Valve Replacement. The dashed lines enclose the 68% confidence limits of the parametric estimates. (A) Hazard function for reoperation showing two phases, early and late. (B) Hazard functions derived by stratifying the data set into those patients receiving a mechanical prosthesis (n = 1,087) and those receiving a porcine heterograft bioprosthesis (n = 446). (C) Analysis of the 446 patients receiving bioprostheses according to the competing risks of indication for reoperation.

mation of $\Lambda(t)$ by the nonparametric method (Cox and Oakes 1984, pp. 56–57), particularly when the censoring rate is high.

Interpretation of the structure of the two-phase hazard function for reoperation (Fig. 6A) was sought by stratifying the patients according to type of prosthesis used: mechanical (n = 1,087) or biological (n = 448). Separate analyses of each strata revealed a similar early hazard phase but a dissimilar later hazard pattern (Fig. 6B); namely, the accelerated hazard phase occurred only in the patients receiving a biological prosthesis, within the time frame of observation. Among the 448 patients with a bioprosthesis, a competing-risks analysis of indication for reoperation was then performed: an analysis of the event *reoperation for infection or leakage* and an analysis of *reoperation for bioprosthesis degeneration.* The resulting hazard functions (Fig. 6C) demonstrate that infection of the prosthetic valve or leakage around its perimeter account for the early transient phase and that reoperation for bioprosthesis degeneration accounts for the accelerated phase.

6.2 Reoperation for Bioprosthesis Degeneration

Risk factors for reoperation for bioprosthesis degeneration were identified by both standard Cox regression and the completely parametric system. A large number of demographic, clinical status, valve lesion, and surgical variables was entered into the analyses, and both revealed the same risk factors: younger age at operation and female gender (Table 1). Estimates of the strength and significance level of each factor were similar. An advantage of the parametric system is that the risk of bioprosthesis degeneration may be portrayed graphically, adjusting for the effects of these risk factors (Fig. 7). Such a portrayal is valuable in several ways: it is useful in the decision-making process in which the relative advantages and disadvantages of a mechanical versus a biological prosthesis are weighed for a given patient; it stimulates research to discover the cause for the observation of accelerated degeneration in younger patients and in females; and it forms the basis for later comparison with proposed improved devices.

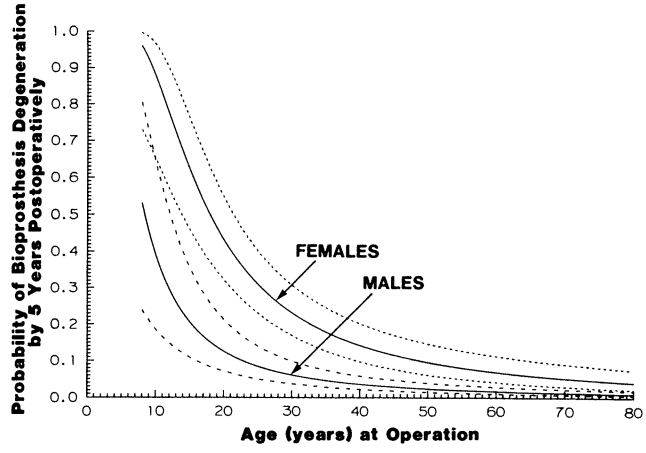


Figure 7. Probability of Reoperation for Bioprosthesis Degeneration Within 5 Years According to Age at Operation and Gender. These estimates are derived from the analysis presented in Table 2. This equation was solved for S(60 months) and is presented as 1 − S(t).

Table 1. Incremental Risk Factors for Bioprosthesis Degeneration After Heart Valve Replacement (1975–July 1979; n = 446, 13 events)

Incremental risk factor	Late phase		Cox regression	
	Coefficient ± SD	p Value	Coefficient ± SD	p Value
Demographic variables				
(Younger) age at operation (ln years)	−1.9 ± .47	<.0001	−1.8 ± .47	.0002
Females	1.4 ± .64	.02	1.6 ± .67	.02
Intercept	1.5 ± 1.75			

NOTE: SD is standard deviation and ln is logarithm. The shaping parameters are $\tau = 40 \pm 6.3$, $\gamma = 2$, $\alpha = 0$, and $\eta = 1$. In this and subsequent tables the risk factors have not been standardized. Thus the intercept merely adjusts for the average value of the risk factors and does not in itself depict a hazard rate.

6.3 Infection of the Prosthetic Valve

Prosthetic valve endocarditis (PVE) occurred in 54 of the 1,533 patients during the period of observation. The multiple-phase parametric system was used to establish the structure of $\lambda(t)$ for this event (Ivert et al. 1984). Until this analysis, PVE had been classified as early or late depending on whether it occurred within or beyond 60 days of valve replacement. Although $\lambda(t)$ peaks within 60 days, the early transient phase merges with a constant phase only after about 12 months. This is accompanied by a change in hazard function pattern for the major groups of responsible microorganisms (see Ivert et al. 1984, fig. 5).

In Ivert et al. (1984), a Cox regression analysis was employed to identify risk factors for PVE. We have reanalyzed these data to determine the risk factors according to hazard phase. Several factors were identified for early phase risk, all identical to those identified by Cox regression (Table 2). One factor was found for the constant phase. Except for black race, all early hazard phase regression coefficients are systematically larger than the corresponding Cox regression coefficients; their standard deviations are also larger. These observations may reflect the more specific focus of the parametric system on the risk factors for the events within a particular phase. The one exception, black race, is a risk factor for both phases at about the same strength. The overall Cox coefficient lies between these two values.

The influence of one factor, native valve endocarditis, is of particular interest. In Figure 8A are depicted the product–limit estimates of PVE with the patients stratified according to the presence or absence of preoperative native valve endocarditis. Although the difference in freedom from PVE is striking between these two groups, the hazard functions (Figure 8B) reveal the correctness of the visual impression that the difference in incidence is confined to the transient early phase. An overall analysis, such as by a Cox regression analysis across the entire observation period, would not reveal that the influence of this risk factor, and of most of the other risk factors, sharply declines and disappears after a very few months. Thus the underlying hazard function for PVE is not modified proportionally over all time by the risk factors.

6.4 Death

Among the 1,533 patients, 338 died during the observation period, including deaths in the operating room, in-hospital deaths during the postoperative period, and those after hospital dismissal (Fig. 1A). The data supported decomposition of the distribution of deaths into two phases: early and constant hazard (Fig. 9). The highest risk is immediately after the operation, but the early phase is not over by the time of hospital dismissal. Rather, it slowly falls over a period of months to a constant. Thus a conventional analysis of hospital deaths (or those within 30 days) underestimates the early risk of the operation.

Incremental risk factors for death were identified from among 55 possible risk factors and interaction terms considered (Table 3). The table illustrates that both different

Table 2. Incremental Risk Factors for PVE After Heart Valve Replacement (1975–July 1979; n = 1,533, 54 events)

Incremental risk factor	Early		Constant		Cox regression	
	Coefficient ± SD	p Value	Coefficient ± SD	p Value	Coefficient ± SD	p Value
Demographic variables						
Males	1.2 ± .53	.02	—	—	.7 ± .33	.03
Black race	1.2 ± .50	.02	1.5 ± .57	.008	1.3 ± .33	.0001
Clinical variable						
Native valve endocarditis	2.4 ± .48	<.0001	—	—	1.8 ± .38	<.0001
Surgical variables						
Cardiopulmonary bypass time (min)	.007 ± .0043	.10	—	—	.006 ± .0033	.07
Mechanical prosthesis	1.8 ± .63	.004	—	—	1.1 ± .38	.004
Intercepts	−7.1 ± .93		−8.3 ± .34			

NOTE: SD is standard deviation. The shaping parameters are $\hat{\rho} = 2.0$ (CL, 1.7–2.4), $\hat{\nu} = .48$ (CL, .40–.58), $\delta = 0$, and $m = 1$, where CL = confidence limits are equivalent to ±1 SD.

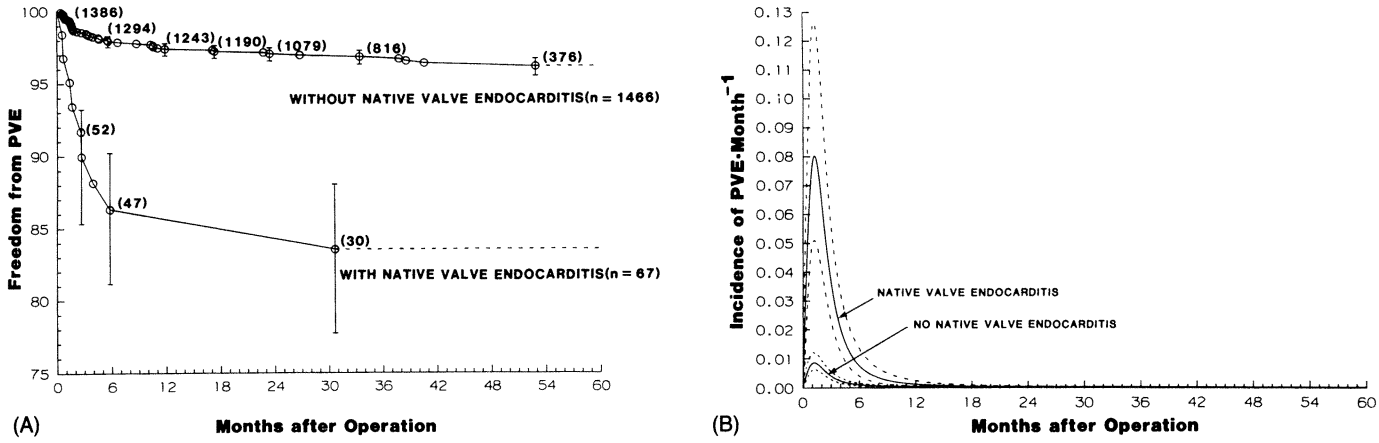


Figure 8. Prosthetic Valve Endocarditis (PVE) After Valve Replacement. (A) Product–limit estimates shown for patients stratified according to the presence or absence of preoperative native valve endocarditis. (B) Corresponding parametric hazard functions.

and common factors were found for each phase. To understand better the influence of one risk factor on survival, the parametric equation represented by Table 3 was used to estimate $\lambda(t)$ and $S(t)$ for various levels of functional disability, holding all other factors constant (Fig. 10). They demonstrate the recognized clinical observation that the more ill the patient before surgery, the greater the risk and the longer the protraction of early-phase deaths. Selecting one specific time point to perform a separate analysis of early risk would, then, tend to underestimate the seriousness of the higher levels of functional disability.

7. DISCUSSION

7.1 Decomposition of Time-Varying Risks

Decomposition of time-varying patterns of risks into phases dates at least to Pearl and Miner (1935). The present work belongs to that class of mixture distribution models that are continuous in all survival domains and whose phases have physical interpretation (Bailey, Homer, and Summe 1977; Bradley 1982; Bradley, Bradley, and Naftel 1984; Heligman and Pollard 1980; Siler 1979; Taulbee 1979). The description of the various phases differs from the specific

Table 3. Incremental Risk Factors for Death After Heart Valve Replacement (1975–July 1979; n = 1,533, 338 events)

	Hazard phase			
	Early		Constant	
Incremental risk factor	Coefficient ± SD	p Value	Coefficient ± SD	p Value
Demographic variables				
(Older) age (years) at operation	.026 ± .0104	.01	.014 ± .0068	.04
Males	—	—	.34 ± .188	.07
Black race	—	—	.9 ± .22	.0001
Clinical variables				
(Higher) NYHA functional class	.96 ± .194	<.0001	.27 ± .136	.05
NYHA × mitral valve replacement (interaction)	.42 ± .092	<.0001	—	
Valve lesion variables				
Aortic incompetence with no or mild stenosis	.9 ± .30	.003	—	—
Nonischemic mitral incompetence with no or mild stenosis	—	—	.4 ± .24	.08
Ischemic mitral incompetence	—	—	1.2 ± .40	.002
Surgical variables				
Combined mitral and aortic valve replacement	1.5 ± .37	<.0001	—	—
Use of cardioplegia	−1.8 ± .48	.0002	—	—
Aortic cross-clamp time (min) in cardioplegia group	.028 ± .0057	<.0001	—	—
Cross-clamp time × combined mitral and aortic valve replacement in cardioplegia group (interaction)	−.014 ± .0057	.02	—	—
Use of mechanical prosthesis	.5 ± .30	.13	—	—
Intercepts	−7.8 ± .92		−7.8 ± .48	

NOTE: SD is standard deviation, NYHA is the New York Heart Association. A dash indicates that the variable does not appear in that phase ($p \geq .2$). The shaping parameters are $\hat{p} = 2.0$ (CL, 1.1–3.5), $\hat{v} = 1.8$ (CL, 1.6–2.0), $\delta = 0$, and $m = 1$, where CL = confidence limits are equivalent to ±1 SD.

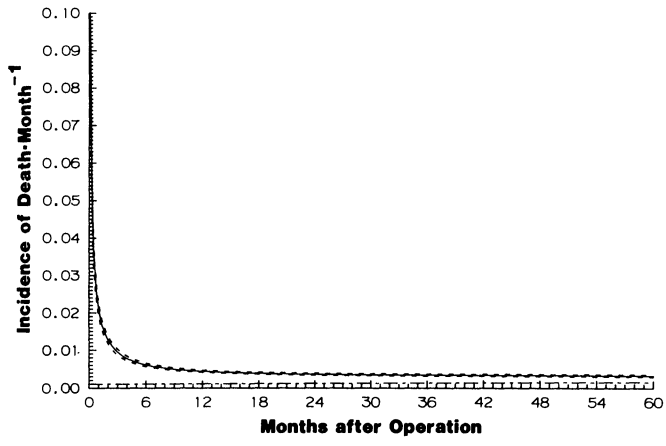


Figure 9. Hazard Function for Death After Valve Replacement. The hazard function for a matched general population is indicated by the dash-dot-dash line.

application: infant mortality, adult mortality, and senescence, or burn-in, random failure, and wear-out. They all permit portrayal of the underlying hazard function, which is important in drawing inferences about the pattern of risk. Experience with time-related events arising in various clinical situations, however, indicated that the available models lacked robustness in describing adequately the variety of structure encountered within the risk phases, particularly within the early hazard phase.

Our interactions with the work of Bradley (1982) lead us to recognize that the shaping functions for early-phase risk used and cited by her were scaled cumulative distribution models that belonged to the generic family of survival distributions described previously by Hazelrig et al. (1982). These provided a flexible, hierarchical system of well-behaved mathematical functions for the fitting of the early phase of risk. A similarly flexible generic function was developed for the late hazard phase that is a broad generalization of the Weibull model.

Integration of these generic functions into a complete multiple-phase system was facilitated by conceptualizing the model in $\Lambda(t)$, since (a) the number and shape of the individual phases can be visualized in the nonparametric estimates of $\Lambda(t)$, (b) initial parametric estimates can be obtained from the nonparametric estimates of $\Lambda(t)$, and (c) the mathematical functions of $\Lambda(t)$ are easily transformed or differentiated into all survival domains.

7.2 Resolution of Phases

The statistical resolution of a particular phase in the decomposition process is dependent on the relationships among (a) the underlying structure of the distribution of events, (b) the duration of follow-up, and (c) the unique form of the phase-specific shaping equation. For a phase to be resolved, it must predominate during some period of the follow-up (as in Fig. 2B). For example, if a late phase is not prominent until 10 years and the duration of follow-up is 5 years, the late phase will not be resolved. Similarly, if both an early and constant phase exist but the early phase is protracted to the end of follow-up so that

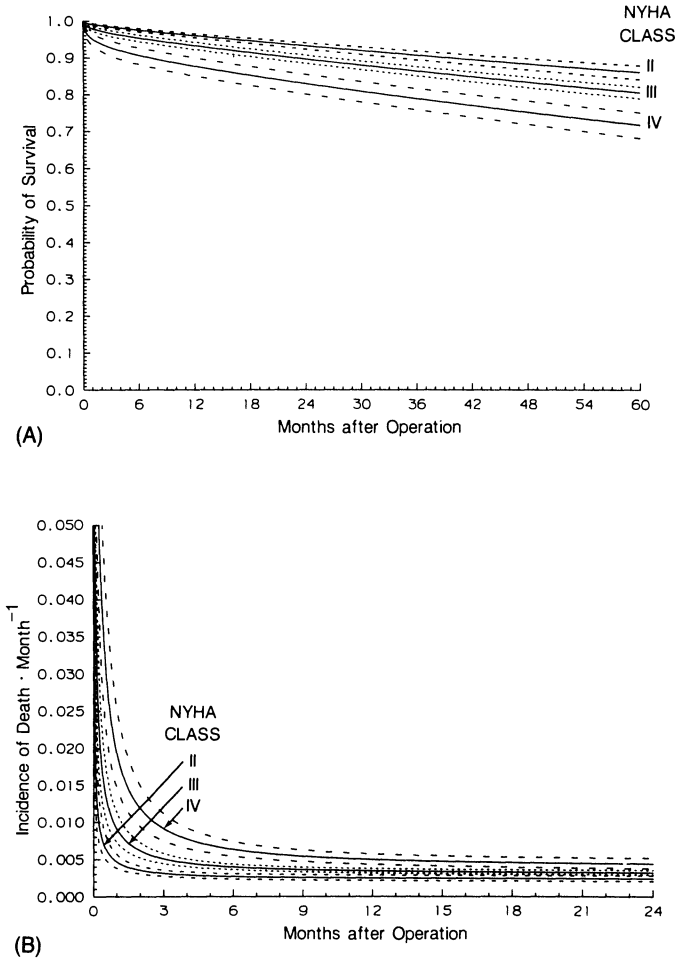


Figure 10. Parametric Survivorship and Hazard Functions According to Increasing Preoperative Level of Functional Disability (NYHA Class). Estimates were generated for patients having aortic stenosis with typical characteristics (age 57, 76% males, 10% blacks, 60 minutes of cross-clamp time, and mechanical valve used). (A) Parametric survivorship functions on a 0–60-month time scale. (B) Corresponding hazard functions on a 0–24-month time scale.

the constant phase never predominates, then resolution of the constant-hazard phase may not be possible. If there is no discernible transient increase in the incidence of events near time 0, then an early phase cannot be resolved. These limitations in resolving phases are those imposed by the data and by the principle of statistical parsimony. It is thus advisable not to extrapolate beyond the limits of follow-up observation. Finally, each phase is modeled with a different mathematical form for the different time frames to aid in resolving the phases. As an example, Table 4 contains the correlations among the parameter estimates displayed in Table 2. The small degree of correlation between the estimates in the two phases is an indication of good resolution of at least these two phases.

7.3 Tractability in Estimation

Although without concomitant information the complete three-phase model contains 11 parameters (8 shaping and 3 scaling), the actual estimation of the subset of parameters necessary for a good fit to the data has been surprisingly

Table 4. Correlation Matrix for the Analysis of Prosthetic Valve Endocarditis Presented in Table 2

	Hazard phase									
	Early								Constant	
	E1	E2	EO	Male	Black	Native valve endocarditis	Cardiopulmonary bypass time	Mechanical	CO	Black
E1	1	−.44	.05	.07	.12	−.02	−.10	.03	−.23	−.04
E2		1	−.10	−.04	−.07	.06	.11	.01	.26	.00
EO			1	−.51	−.33	−.38	−.43	−.72	−.16	.06
Male				1	.11	.03	−.11	.10	.05	−.07
Black					1	.01	.03	.26	.05	−.21
Native valve endocarditis						1	.17	.28	.07	.02
Cardiopulmonary bypass time							1	.01	.09	.01
Mechanical								1	.05	−.02
CO									1	−.54
Black										1

NOTE: E1 and E2 are reparameterizations of ρ and ν to an unbounded scale, and EO and CO are the intercept terms for early and constant-hazard phases, respectively. Risk factors have not been standardized, giving rise to a high degree of correlation between them and their respective intercept terms.

easy. Some of the reasons for this tractability may relate, first, to the choice of model functions for which there exists only one maximum in the likelihood function with respect to each parameter. Second, the complete model provides an extremely flexible family of models, making it robust. The decomposition into phases, however, permits the model for any one phase to take on the simplest form required by the data within the family of functions for that phase. This results in parsimony both of model structure and number of parameters to be estimated. Thus a particular analysis rarely requires the estimation of more than four shaping parameters: for example, ρ and ν with $\delta = 0$ and $m = 1$ or $m = 0$ in the early phase and τ and γ with $\eta = 2$ and $\gamma\eta/\alpha = 2$ in the late phase. This is a small number of parameters to be estimated relative to the amount of information available. Third, the form of the model is such that one scaling parameter may be estimated directly rather than iteratively. This has two salutary effects: the iterative process is of order one less than the number of parameters to be estimated, and the model is always restrained during optimization to predict the observed number of events no matter the current value of the shaping parameters.

7.4 Concomitant Information

Having developed a robust system for the decomposition of time-related patterns of risk, it was imperative to incorporate the analysis of risk factors into each phase. We have previously presented a parametric analysis in which a separate stream of concomitant information was incorporated into each parameter (Hazelrig et al. 1982), as have Bailey et al. (1977). Experience in fitting data stratified according to risk factors, however, indicates that the shaping parameters are far less sensitive to concomitant information than are the scaling parameters. The present scheme thus restricts concomitant information to the scaling parameters for each phase, a limitation that makes the model mathematically and computationally more tractable and that appears to minimize correlation between the multiple streams of risk factors (Table 4).

The form chosen for the parametric scaling functions of concomitant information was based in part on the desire to maintain an unbounded scale. Others have employed a log-linear model (Cox 1972), as was done for the constant-hazard and late phases. The parametric scaling function for the early phase, however, might appropriately be logit-linear in $S(t)$, since the early-phase scaling parameter represents the asymptotic limit of early cumulative risk and thus the probability of an early event. This form for the scaling parametric function links the system with logistic regression (Walker and Duncan 1967) and permits graphical expression of results in terms of the "probability of an early event."

Risk factor coefficients from multiple-phase analyses have been similar numerically to those obtained from separate analyses of hospital events using logistic regression and of late events using Cox regression (Blackstone and Kirklin 1986).

7.5 Significance of the Methodology to Valve Replacement

The current approach to analysis of early events after valve replacement is to employ logistic regression analysis of risk factors for in-hospital events, with graphic portrayal of the probability of an event as a function of risk factors (Czer et al. 1984; Miller et al. 1984a; Penta, Qureshi, Radley-Smith, and Yacoub 1984). When hospital mortality rates were higher, these analyses and presentations of early-phase risk were valuable in clinical decision making and in programming research and development efforts to improve the immediate postoperative results. As progress has been made, the risk of in-hospital mortality has become quite low, but deaths and other events extending into the first few months after operation are now a challenge, as those occurring some months and years later have always been. Currently, posthospitalization "late" valve-related events are described increasingly in terms of linearized hazard rates (Feigl and Zelen 1965; Grunkemeier, Thomas, and Starr 1977), but it is recognized that the rates are rarely constant (CASS Principal Investigators and Their Associates 1983; Miller et al. 1983; Miller et al. 1984b). Cox

regression is generally performed to identify risk factors over the duration of posthospitalization follow-up (Baughman, Kallman, Yurchak, Daggett, and Buckley 1984; Grunkemeier et al. 1980; Louagie et al. 1984; Penta et al. 1984). Single variable stratified nonparametric actuarial curves are used to illustrate some of the risk factors.

What has been lacking is a comprehensive analysis that begins with valve replacement and longitudinally extends for the entire duration of patient follow-up. The present method permits just such an analysis. Its essential feature is the formal parametric decomposition of time-related events into component phases, needed for time-specific risk factor identification.

The concept of incorporating simultaneous multiple streams of concomitant information into the analysis is emphasized, since the influence of a particular risk factor may change with time. It is of importance, for example, for the physician and surgeon who are advising a male patient with acute native valve endocarditis to know that such a patient is particularly susceptible to the early development of an infection on his prosthetic valve. From the analysis presented, strong consideration should be given to recommending use of a biological prosthesis, despite its propensity to degeneration, and perhaps use of extended antibiotic prophylaxis for a few months. But he can also be advised that, after about a year, he is expected to have as low a risk of infection as a patient undergoing routine valve replacement under more favorable circumstances.

The application illustrates the parsimony of this comprehensive method of data analysis and its capacity to yield relevant and clinically useful information.

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