Actuarial versus actual risk of porcine structural valve deterioration

Actuarial analysis, using nonparametric (e.g., life table or Kaplan-Meier) or parametric (statistical modeling) methods, is used to describe and compare survival probabilities by allowing for partial survival times (censoring). Although devised to describe freedom from death, this method has been extended to nonfatal complications, such as freedom from tissue valve failure. However, the risk described for nonfatal events is that which a patient would experience *provided he were immortal*. And patients with valve disease have a relatively high risk of dying, generating the question: "What is the chance the valve will fail before the patient dies?" To answer this more practical (for individual patient management and population resource allocation) question requires an estimate of what we call *actual* failure, that is, the percentage of patients whose valve will *actually* fail before they die. This risk is less than the risk which the usual *actuarial* curve describes. This difference increases with patient age, because older patients have a lower risk of tissue failure and a higher risk of death than younger patients. (J THORAC CARDIOVASC SURG 1994;108:709-18)

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Actuarial analysis has been used for the evaluation of heart valve results for almost 30 years¹ and is considered the standard for reporting time-related results.² We use this word to refer to the usual analysis of single end point, grouped interval data by the life table method³ or individual patient data by the Kaplan-Meier product-limit method.⁴ The actuarial event-free (survival) curve for a nonfatal event, such as structural valve deterioration (SVD) of porcine valves, estimates the event-free proba-

bility for a population in which death has been eliminated. This overestimates the percentage of valves that will *actually* fail, because many patients die before the valve fails. What is of greater interest for advising patients, or for expense planning for a population, is the risk of SVD occurring *before death*. There is no consensus on the name for this risk in the statistical literature; *cumulative incidence* is commonly used, but we also refer to this as *actual* risk.

We⁵ previously used SVD results based on a visual fit of points from published curves to illustrate this concept. In the present report we use individual porcine valve follow-up data from two centers to fit models for *actual* and *actuarial* SVD; to incorporate the risk factors age, gender, and position; and to compare these parametric models with nonparametric fits.

Patients and methods

Patients. A total of 4910 Hancock and Carpentier-Edwards porcine valves (Hancock valves, Medtronic, Inc., Minneapolis, Minn.; Carpentier-Edwards valves, Baxter Healthcare Corp.,

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Table I. Summary of patients by center and valve position*

	Vancouver		Stanford	
	Aortic	Mitral	Aortic	Mitral
Implant survivors	1435	1162	1350	948
Age (yr)				
Mean	62	59	60	58
Range	21-87	20-84	20-94	20-85
Male gender (%)	72	36	70	43
Implant year				
1975-1979	287	234	631	408
1980-1984	657	567	498	300
1985-1988	491	361	221	140
Valve model				
CE standard	544	451	344	113
CE SAV	891	711	0	0
CE LP	0	0	0	102
Hancock standard	0	0	492	669
Hancock MO	0	0	513	64
Valve size* (mm)				
19-23	606	6	573	0
25-27	572	369	621	53
29-35	119	615	155	894

CE, Carpentier-Edwards; SAV, supraannular valve; LP, low profile; MO, modified orifice.

*Valve position and size missing for some valves.

Table II. Summary of follow-up information by center and valve position

	Vancouver		Stanford	
	Aortic	Mitral	Aortic	Mitral
Follow-up (yr)				
Mean	5.7	5.5	6.6	6.4
Total	8154	6389	8973	6094
Maximum	14.7	13.8	14.6	15.0
Events (No.)				
Fatal SVD	6	17	22	23
Nonfatal SVD	66	116	127	139
Non-SVD death	272	285	446	346

Edwards Div., Santa Ana, Calif.) from two centers, including all operative survivors of isolated (nonmultiple) porcine valve replacement during 1975 to 1988, were available for analysis (Table I). These valves combined for 29,610 patient-years of follow-up, with a maximum of 15.0 years (Table II). Follow-up completeness, defined as a known date of death or explantation, or contact from 1988 through 1990, was 94%. Among these isolated valves, there were 516 cases of SVD (68 fatal) and 1349 deaths not related to SVD (Table II). In addition, 164 patients with double valve replacement (Table III) were used to compare their observed SVD experience with that predicted from the risk of their two separate valves.

Methods. We determine separate parametric actuarial models for (1) SVD and (2) patient survival and (3) combine them to determine a parametric equation for *actual* SVD. For all three of these models, we use nonparametric methods for comparison.

Actuarial SVD. Nonparametric actuarial SVD-free curves were constructed by the Kaplan-Meier method.⁴ For paramet-

ric analysis, we fit several probability functions commonly used in reliability analysis (including exponential, Weibull, Rayleigh, gamma, normal, and lognormal), evaluating the fits according to values of the likelihood function and visual comparison of fitted and empirical event-free and cumulative hazard function curves. The Weibull distribution, which is widely used to describe wear-out or fatigue failure data,⁶ was chosen to model actuarial SVD.

Risk factors considered for the regression model were patient age and gender; valve position, size, and model; and year of implantation (several interaction terms were also considered during the model fitting). The maximum likelihood method was used to simultaneously estimate the shape parameter of the Weibull distribution and the coefficients of the risk factors that determine its scale parameter.⁷

The parametric event-free percentage for a subgroup at a given postoperative time was computed by exponentiating the negative of the cumulative hazard, which is computed as the integral of the mean hazard, based on the regression model, up

Fig. 1. Actuarial freedom from SVD for two porcine heart valve series and the corresponding cumulative incidence of (actual) SVD. The Vancouver series is entirely Carpentier-Edwards valves, and the Stanford series is predominantly Hancock valves. The nonparametric (Kaplan-Meier) SVD-free curves are remarkably similar for these two series of isolated valve replacements performed from 1975 to 1988. The *actual* incidence curves describe a lower percentage of SVD than the actuarial curves would imply.

Table III. Summary of patients having double valve replacement

Patients	164
Age (yr)	
Mean	58.7
Range	18-84
Male gender (%)	40
Implant years	
75-79	14
80-84	90
85-90	60
Follow-up (yr)	
Mean	5.3
Total	865
Maximum	13.7
Events (No.)	
Fatal SVD	5
Nonfatal SVD	17
Non-SVD death	142

until that time. The mean hazard at each point is taken as the mean for all valves still potentially at risk (at that postoperative time), rather than the mean of all valves entering the series.⁸

Double valve replacement data were not used to estimate the regression models. To see if the risk for an individual valve is changed in the double valve replacement environment, we computed the individual risk for each patient having double valve replacement based on the Weibull regression model for each valve separately, assuming the two valves would fail indepen-

Table IV. Results of Weibull regression model for SVD

	Coefficient $\pm$ SE	p Value
AGE*	-0.358 $\pm$ 0.033	<0.0001
Mitral	0.538 $\pm$ 0.089	<0.0001
Constant	-9.92 $\pm$ 0.237	<0.0001
Shape	3.48 $\pm$ 0.100	<0.0001

SE, Standard error.
*AGE = (age - 60)/10.

dently (i.e., added the individual risks, which is equivalent to multiplying the individual SVD-free curves), and compared this predicted risk with the nonparametric actuarial SVD-free curve for the patients having double valve replacement.

Actuarial patient survival. Nonparametric actuarial survival curves were constructed by the Kaplan-Meier method.⁴ Parametric estimation of late survival used a regression model from a previous study,⁹ based on the Gompertz distribution, which is widely used for survival, especially in older populations.¹⁰ SVD-related deaths were excluded (censored) in the survival analysis, to estimate patient survival in the absence of valve failure. Less than 5% of late deaths were associated with SVD (see Table II).

Actual SVD. Nonparametric estimation of *actual* SVD involves a summation,^{11,12} and the parametric model involves a counterpart to this sum (i.e., mathematical integration of the models for actuarial SVD and patient survival).¹³ Methods for obtaining standard error and confidence interval estimates for these functions have been described for nonparametric^{11,12} and parametric¹³ estimates but are not implemented here. Our pur-

Fig. 2. Actuarial freedom from SVD by age group for isolated valve replacement; nonparametric Kaplan-Meier curves (*jagged lines*) and Weibull model (*smooth curves*).

Fig. 3. Actuarial freedom from SVD by valve position for isolated valve replacement; nonparametric Kaplan-Meier curves (*jagged lines*) and Weibull model (*smooth curves*).

pose is to describe this concept rather than make statistical comparisons; because of the large sample size, however, confidence intervals would be rather narrow.

Results

Nonparametric actuarial SVD-free curves (Fig. 1, *top*) and cumulative incidence curves (Fig. 1, *bottom*) were both remarkably similar for the two centers. At 14 years,

the actuarial SVD-free probabilities are 50% to 58%, whereas the cumulative incidence of SVD is only about 30%.

Actuarial SVD. Individual (univariate) significant risk factors for SVD were young age, large valve size, female gender, and mitral position. Mitral position was a significant risk factor when considered alone, second in

Fig. 4. Actuarial freedom from SVD for double valve replacement; nonparametric Kaplan-Meier curves (*jagged lines*) and Weibull model (*smooth curves*). The Weibull model used separate regression equations for the potential SVD risk of each valve, assuming an additive risk of SVD for the two valves.

Fig. 5. Patient survival by age group, excluding SVD-related deaths, for isolated valve replacement. Actuarial curves (*jagged lines*) and Gompertz model (*smooth curves*) based on a previously developed model (see text).

importance only to age, but lost significance after valve size and gender entered the model. Even though size and sex together appeared more important statistically than position, we used position in the model (Table IV) because it is known beforehand, whereas size is not, and position has more often been found to influence SVD by other studies.

The Weibull shape parameter from the overall regression model was 3.5 (Table IV), and it was similar for various subsets. The Weibull model approximated the observed data when stratified by age group (Fig. 2) and position (Fig. 3).

Double valve replacement. The risk of SVD occurring in patients requiring double valve replacement could be

Fig. 6. Cumulative incidence of SVD by age group, for isolated valve replacement. Nonparametric curves (*jagged lines*) and parametric model (*smooth curves*).

Fig. 7. Example of cumulative incidence of SVD, based on the parametric model, for a female patient having mitral valve replacement according to her age at implantation. The probability that the valve will ever need replacement (i.e., fail before the patient dies) is indicated by the *solid symbols* at the ends of the curves.

calculated by addition of the risks of each individual valve (Fig. 4). Thus the risk for a valve to fail does not seem to be influenced by the existence of a companion valve in the same patient.

Patient survival. The previously developed Gompertz model for survival included valve size. To avoid using size

(for the reasons stated earlier), we set the size variable equal to the mean size of the combined series (26.8 mm). This model still described the survival of the valve population by age group fairly well (Fig. 5).

Actual SVD. Nonparametric estimates were calculated for each age group and compared with parametric

Fig. 8. Nomogram for the probability of ever experiencing re-replacement for SVD according to age at implantation, gender, and valve position. These probabilities are strongly related to age at implantation, and less affected by valve position and patient gender. The various ages for the female patient with mitral replacement in Fig. 7 are indicated by the *solid symbols*.

models that used the mean values for the risk factors in each age group (Fig. 6). Parametric estimates for various ages of a female patient with mitral valve replacement are shown in Fig. 7. The curves level off after about 20 years; thus the solid symbols at the end of the lines represent the percentage of valves that will ever fail (before the patient dies). Fig. 8 contains a nomogram of the percentage of patients estimated to ever experience SVD, for various subgroups and for ages 30 to 80 at implantation, based on cumulative incidence curves similar to Fig. 7. The solid symbols from Fig. 7 have been superimposed onto Fig. 8.

Discussion

Actuarial risk of death. If a series is followed up until all patients have died, then the percentage who have died at any given postoperative year can be given directly. However, in the usual *ongoing* series this simple percentage would underestimate the probability of death, because many patients are still alive at the time of reporting. Actuarial methods precisely accommodate the partial follow-up times of these patients, referred to as *censored* observations. If patients who are censored proceed on with the same risk of death as those who were not censored, then the *actuarial method provides estimates of percent dead (or alive) at each year as if censoring were removed*, that is, all patients had been followed up until death.

Actuarial risk of nonfatal events. The actuarial

method is also used for nonfatal events, such as SVD, by including death as an additional censoring mechanism (Appendix A). This assumes that those who die are only temporarily suspended from the calculation and will continue on to experience the same SVD risk as their fellows. Thus, provided this assumption is true, this method *yields estimates of percent SVD at each year as if death never occurs*. This may be regarded as the intrinsic risk of the nonfatal event, but this risk does not have a direct interpretation for a patient.

Actual risk of nonfatal events. Of more direct clinical relevance is the percent experiencing SVD, *given that death does intervene*. This statistic is more useful for describing the outcome for an individual patient and for anticipating the future flow of returning patients for health care planning purposes.¹³ Increased patient age has a doubly important effect on *actual* SVD, decreasing the actuarial (intrinsic) risk of the event (see Fig. 5) while increasing the risk of the competing event death (see Fig. 2).

Features of parametric models. We have used a parametric approach, based on separate models for (the actuarial risk of) SVD and death, to estimate *actual* SVD. Parametric estimation results in an equation that describes the entire experience over time, given a relatively few number of parameters; usually a constant (intercept), a shaping parameter, and some coefficients for the risk factors that constitute the scaling factor of the

chosen statistical distribution (Appendix B). Parametric models provide smooth estimates that more realistically portray the continuity of nature, rather than the irregularities of one particular data set.¹⁷ Using such models, one can compute the entire event-free curve for a given set of risk factors, even beyond the maximum observation time, and compute summary statistics such as mean and median survival times. This enables us to extrapolate the *actual* SVD curves beyond the 15 years of observation, to the point where they level off and thus estimate the percent of patients who will *ever* actually experience SVD (before death), as in Fig. 7. Of course the results from such extrapolations must be interpreted cautiously because they depend on assumptions regarding the distribution and risk factors of the model.

Risk factors for SVD. The regression models for actuarial SVD and death in this study were based on a limited number of risk factors. Our risk factors for SVD agree with the findings of others. Jones and associates¹⁸ performed a Cox regression of the effect of age on SVD which, according to their graphs, agrees remarkably well with the results of the present study. Other studies have shown the continuous effect of age¹⁹⁻²¹ and the effect of valve position¹⁹⁻²² on the actuarial risk of SVD.

However, these models could be expanded by incorporating other potential risk factors for SVD (activity level, renal and hepatic function, anticoagulation, etc.) and late death (valve lesion, functional class, concomitant coronary bypass, etc.). Another set of factors associated with SVD could be porcine factors. Unlike mechanical valves, in which units of the same model may be considered almost identical, tissue valves possess inherent biologic variation because of donor and perhaps manufacturing factors. When tissue valves of the same type are tested in vitro under identical conditions, there is a wide variation in times to failure,^{23,24} and in 24 patients who received sequential porcine valves, the second seemed to fare better than the first.²⁵

Conclusion

This article has two themes. A minor theme is that the Weibull distribution seems to fit the actuarial SVD curves for porcine valves, thus allowing (cautious) extrapolation beyond observed experience. The major theme is that the usual actuarial curves do not provide the most meaningful percentages of SVD, as far as patient prognosis is concerned. The first finding (combined with a previously developed model for patient survival) allows us to use parametric methods for the second; that is, to project (extrapolate) the percentage of patients who will *ever* experience SVD. One could use the nomogram in Fig. 8 to determine lower age bounds for the use of porcine

valves, depending on the eventual risk of replacement one wished to tolerate. For example, a risk of 20% of ever experiencing SVD (lowest horizontal grid line) corresponds to a minimum age of 70 to 73 years; a risk of 40% corresponds to ages 59 to 63 years.

The present study used series that include the earliest use of first-generation porcine valves. With current application, the overall results can be expected to be better because of refinements in the newer generations of porcine and pericardial valves and better refined criteria for selecting which patients receive a bioprosthesis.

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Appendixes

Appendix A: Basic survivorship functions.

Single end point. When time-related events are being evaluated statistically, a usual construct is the random variable T , which is the time to the event or end point. For example, in a clinical series, T_{death} is the time (from operation) to death. It can be characterized by any of a number of equivalent mathematical functions. The most fundamental is the cumulative distribution function:

$$F(t) = \text{prob}(T_{\text{death}} \leq t)$$

the probability that death occurs before time t . In clinical

description, its complement, the familiar survival function, is more often used:

$$S(t) = 1 - F(t) = \text{prob}(T_{\text{death}} > t)$$

the probability of survival to time t . These two functions add to unity for every time t .

There are other useful representations for computing and representing risk, such as the density function $f(t) = F'(t)$, which is the mathematical derivative of $F(t)$ with respect to time, and the hazard function $h(t) = f(t)/S(t)$, which measures the instantaneous risk given survival to time t . But the survival and distribution functions are both expressed as cumulative probabilities and are easier to interpret, to appreciate the risk of an outcome, such as the chance of living until (or dying before) 5 years, 10 years, and so on.

Multiple end points—actuarial. When the lifetime of a prosthetic valve is being considered, two (or more) risks compete as end points: failure of the valve (our primary concern here) and death of the patient, either of which will terminate its functioning. These events are associated with two times: T_{SVD} and T_{death} .

The usual actuarial curve is derived with the assumption that death and SVD are statistically independent events. The distribution function is as follows:

$$F_{\text{SVD}}(t) = \text{prob}(T_{\text{SVD}} \leq t \text{ and } T_{\text{death}} = \text{infinite}),$$

the probability the valve has failed by time t , with death removed as a risk. The survival function can be written as follows:

$$S_{\text{SVD}}(t) = \text{prob}(T_{\text{SVD}} > t \text{ and } T_{\text{death}} = \text{infinite})$$

that is, the probability the valve has not failed by time t , with death removed as a risk. The assumption of independence is not true in this situation, because those at higher risk for death are at lower risk for SVD.

Multiple endpoints—actual. When the presence of death is acknowledged, there are two “distribution” functions:

$$\text{prob}(T_{\text{death}} < t \text{ and } T_{\text{death}} < T_{\text{SVD}}) \quad (1)$$

that is, the probability the patient died before t and before the valve (would have) failed. This might be called a success of valve selection;

$$\text{prob}(T_{\text{SVD}} \leq t \text{ and } T_{\text{SVD}} < T_{\text{death}}) \quad (2)$$

that is, the probability the valve failed before t and (obviously) before the patient died. This might be called a failure of valve selection. It measures the probability of SVD in the situation where death is acting. It is not a true distribution function because it is always less than one. In the statistical literature, the terms *absolute risk*,¹³ *crude incidence*,^{11, 16} *cause-specific failure*,¹² and *cumulative incidence*^{12, 14-16} have been used to describe functions, probabilities, and curves associated with this concept. The term *actual risk* is one we have introduced to refer to this concept, in phonetic contradistinction to the term *actuarial*. To emphasize that it is not an accepted statistical term, we have used parentheses or italics throughout the text.

The survival function which, with the two cumulative incidence functions described earlier adds to unity at every time t , is as follows:

$$S_{\text{both}}(t) = \text{prob}(T_{\text{SVD}} > t \text{ and } T_{\text{death}} > t)$$

that is, the probability the valve has not failed and the patient has not died (the patient is alive with a functioning valve).

Appendix B: Parametric and nonparametric formulas. In

this section, bold symbols ($\mathbf{x}, \mathbf{y}$) are used to indicate one or more risk factors. A general formula for a parametric event-free percentage at time t for a patient with risk factor(s) $\mathbf{x}$ is the exponential function of the negative of the cumulative hazard:

$$S(t|\mathbf{x}) = \exp(-R(\mathbf{x}) \cdot H(t))$$

The cumulative hazard above is itself the product of two functions: a common *shaping* function $H(t)$, from a basic family of distributions, and a patient-specific *scaling* function $R(\mathbf{x})$, which incorporates risk factor(s) into the model. For technical reasons, $R(\mathbf{x})$ is usually an exponential function of the risk factors. For example, with two factors $x_1 = \text{AGE}$ and $x_2 = \text{MITRAL}$:

$$R(\mathbf{x}) = R(x_1, x_2) = \exp(B_0 + B_1 \cdot \text{AGE} + B_2 \cdot \text{MITRAL})$$

where AGE is in years (or a transformation thereof) and MITRAL equals 1 for yes and 0 for no. The coefficients (B 's) are estimated from the data.

Actuarial SVD. The Weibull distribution used to model SVD has a cumulative hazard of the form:

$$(R \cdot t)^A = R^A \cdot t^A$$

where the superscript indicates exponentiation. A is the shape parameter (aging factor) and R is the scale parameter. In the regression model, R^A is replaced by $R(\mathbf{x})$, a function of the risk factors $\mathbf{x}$, and the actuarial SVD-free function becomes:

$$S_{\text{SVD}}(t|\mathbf{x}) = \exp(-R(\mathbf{x}) \cdot t^A)$$

Patient survival. The Gompertz distribution used for late death has a cumulative hazard of the form:

$$R \cdot (\exp(A \cdot t) - 1)$$

where A is a shape parameter and R is a scale parameter. In the regression model, R is replaced by a function $R(\mathbf{y})$ of the risk factors, and the patient survival function is as follows:

$$S_{\text{dead}}(t|\mathbf{y}) = \exp(-R(\mathbf{y}) \cdot (\exp(A \cdot t) - 1))$$

Actual SVD. The nonparametric, cumulative incidence function for SVD (see Fig. 6) at postimplantation time T is a sum, for all failure times $t_i < T$:

$$\sum_{t_i \leq T} S_{\text{BOTH}}(t_{i-1}) \cdot \frac{d_i}{n_i}$$

where $S_{\text{BOTH}}(t_i)$ is the nonparametric (Kaplan-Meier) estimate of freedom from both SVD and death at time t_i , and d_i and n_i are the numbers of SVD events and remaining valves at time t_i , respectively. This summand is the product of the percent of (the original number of) valves still functioning at time t_i and the percent failing at that time and is thus an estimate of the percent of the original valves failing at that time. Summing this over all times up to T provides an estimate of the percent of valves (actually) experiencing SVD by time T .

The parametric expression for the actual SVD percentage at T years (Figs. 6 to 8) for a patient with risk factors $\mathbf{x}$ for SVD and $\mathbf{y}$ for death is as follows:

$$\int_{t=0}^T S_{\text{SVD}}(t|\mathbf{x}) \cdot S_{\text{death}}(t|\mathbf{y}) \cdot h_{\text{SVD}}(t|\mathbf{x}) dt$$

where h_{SVD} represents the instantaneous hazard function for SVD. This is the parametric counterpart to the previous formula, with summation replaced by integration and the overall survival function written as the product of the two survival functions for SVD and death. (There is a small omission here, because a third possible end point, nonfatal non-SVD valve explants, has been ignored; if incorporated, it would slightly lower the estimate of actual SVD.) Because the expressions inside the integral sign can be computed out to any time T , we can let T approach infinity (20 or so years, really) to estimate the percentage of patients who will ever experience SVD.