AN ANALYSIS OF VALVE RE-REPLACEMENT AFTER AORTIC VALVE REPLACEMENT WITH BIOLOGIC DEVICES

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Biologic valve re-replacement was examined in a series of 1343 patients who underwent aortic valve replacement at The Prince Charles Hospital, Brisbane, with a cryopreserved or 4° C stored allograft valve or a xenograft valve. A parametric model approach was used to simultaneously model the competing risks of death without re-replacement and re-replacement before death. One hundred eleven patients underwent a first re-replacement for a variety of reasons (69 patients with xenograft valves, 28 patients with 4° C stored allograft valves, and 14 patients with cryopreserved allograft valves). By multivariable analysis younger age at operation was associated with xenograft, 4° C stored allograft, and cryopreserved allograft valve re-replacement. However, this effect was examined in the context of longer survival of younger patients, which increases their exposure to the risk of re-replacement as compared with that in older patients whose decreased survival reduced their probability of requiring valve re-replacement. In patients older than 60 years at the time of aortic valve replacement, the probability of re-replacement (for any reason) before death was similar for xenografts and cryopreserved allograft valves but higher for 4° C stored valves. However, in patients younger than 60 years, the probability of re-replacement at any time during the remainder of the life of the patient was lower with the cryopreserved allograft valve compared with the xenograft valve and 4° C stored allografts. (J Thorac Cardiovasc Surg 1997;113:311-8)

Biologic valve replacement devices (xenograft and allograft valves) have an important and complementary role in conjunction with mechanical valve devices in the treatment of valvular heart disease. Freedom from anticoagulant-related hemorrhage and a low incidence of thromboembolic events remain clear advantages of biologic valves over mechanical devices.[1] Furthermore, the allograft valve has an additional advantage over both xenograft and mechanical valves for aortic valve replacement in the setting of endocarditis with a lower probability of recurrent endocarditis.[2]

However, a clear disadvantage of biologic valves is their propensity for failure as a result of leaflet degeneration and mechanisms peculiar to allograft valves, including geometric distortion and changing mechanical properties of leaflets, specifically loss of radial extensibility of leaflets, which eventually results in central incompetence.[3]

The usual means of presenting time-related events (such as death and re-replacement) after valve replacement is by actuarial analysis of single events. However, many patients, particularly elderly patients, die before a biologic valve requires re-replacement. In the setting of competing risks (in this context, valve re-replacement before death and death before re-replacement), interpretation of the Kaplan-Meier curve is problematic.[4] In this case, the Kaplan-Meier curve for freedom from valve re-replacement is conditional that no patient dies because the censoring process is used at the time of

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Table I

Valve type used at primary valve replacement	*N*	*No. of first re-replacements*	*%*
Xenograft			
Carpentier-Edwards*	849	62	7.3
Hancock†	68	6	8.8
Xenotech‡	17	0	0
Medtronic Intact†	15	1	6.6
Ionescu-Shiley§	1	0	0
Subtotal	950	69	7.3
Cryopreserved allograft	299	14	4.7
4° C stored allograft	94	28	29.8
Subtotal	383	42	10.5
Total	1343	111	8.3

*Baxter Healthcare Corp., Edwards Division.
†Medtronic, Inc.
‡Medtronic Heart Valve Division, Irvine, Calif.
§Mallinckrodt Medical, Inc.

each death that occurs before re-replacement. Important information for the patient and the surgeon in deciding between a mechanical or biologic valve replacement device is the probability of re-replacement of a biologic valve before death, which takes into account the competing risks of death and re-replacement. Grunkemeier and colleagues[5] applied a "competing risk" analysis in a group of patients undergoing valve replacement with xenograft prostheses to determine both actuarial valve failure (conditional that no patient dies) and actual valve failure (probability of failure before death).

The purpose of this study was to analyze biologic valve re-replacement in a series of patients undergoing aortic valve replacement with cryopreserved and 4° C stored allograft valves and xenograft valves. The analysis was conducted in the "competing risk" domain to depict the unconditional probability (actual risk) of valve re-replacement before death after aortic valve replacement. The results of this analysis may provide information that could improve the precision with which a biologic valve replacement device and an individual patient are matched.

Patients and methods

The purpose of this retrospective observational study was to analyze the incidence and time relatedness of re-replacement of implanted biologic valves in the aortic position. The study group included patients who underwent aortic valve replacement (primary and subsequent valve replacements) with biologic valves, with or without concomitant procedures, at The Prince Charles Hospital between January 1, 1970, and January 31, 1990. The patient population was obtained from a previously published data set that examined survival after aortic valve replacement.[6] Patients who underwent concomitant mitral valve replacement were not included. Patients who received fascia lata and calf heterografts, which are now regarded as obsolete because of rapid failure, were not included. Patients who underwent an aortic valve replacement at another institution but subsequent aortic valve replacement at The Prince Charles Hospital were not included.

The study group comprised 1343 patients who underwent primary aortic valve replacement, of which 111 patients subsequently underwent a first re-replacement of the aortic valve prosthesis. Four of these patients underwent a second re-replacement but this second re-replacement was not considered in this analysis. At the initial aortic valve replacement, a xenograft valve was used in 950 patients, a 4° C stored allograft valve in 94 patients, and a cryopreserved allograft valve in 299 patients (Table I).

Of the 1343 patients who underwent primary aortic valve replacement, 1029 were male and 314 were female with an age range of 3.2 to 85 years (mean age of 57.3 years). The mean ages of patients receiving xenografts, cryopreserved allografts, and 4° C stored allografts were 60 years, 51.6 years, and 50 years, respectively. Of the 111 patients who underwent a first aortic valve re-replacement, 92 were male and 19 were female with an age range of 19 to 80 years (mean age of 53.9 years).

Operative technique. Aortic valve replacements were done with use of the usual methods of cardiopulmonary bypass. From 1970 to 1978, myocardial protection was provided by continuous coronary perfusion and from 1978 to 1990, by cold crystalloid cardioplegia with topical cooling.

Xenograft valves were implanted with use of an interrupted suture technique. Allograft valves were inserted by a variety of methods including the subcoronary and cylindrical techniques and as an aortic root replacement.[7] Xenograft valves were implanted from 1978 to 1990, 4° C stored allografts from 1969 to 1976, and cryopreserved allografts from 1975 to 1990.

Data collection and follow-up. A number of demographic, clinical, pathologic, and surgical variables were collected (Appendix A) by study of the patient hospital records and from collateral information provided by other hospitals and physicians. The data were collected by data managers and subsequently checked by the investigators before being entered into the database. Re-replacement of a previously implanted aortic valve and death were the end points of the study. Re-replacement of a valve device was undertaken because of leaflet failure caused by degeneration (xenografts and allografts) and changing mechanical properties of leaflets (allografts), geometric distortion (allografts), replacement valve endocarditis, miscellaneous technical reasons, and in the course of repair of an ascending aortic dissection. Re-replacement of a biologic valve during the repair of an acute or chronic ascending aortic dissection despite normal functioning of the valve occurred in five patients. One patient, who had previously undergone an aortic valve replacement with a xenograft valve, underwent cardiac transplantation 9 years later. The valve device was censored at the time of the transplantation.

Table II

Valve type used at primary valve replacement	*Reason for re-replacement*			
	Leaflet failure	*Replacement valve endocarditis*	*Other*	*Total*
Xenograft	53	10	6*	69
4° C stored allograft	24	3	1†	28
Cryopreserved allograft	2	6	6‡	14
Total				111

*Strut obstruction (1), ascending aortic graft infection (1), replacement during repair of ascending aortic dissection (4).

†Replacement during repair of ascending aortic dissection.

‡Dehiscence, paravalvular leak, geometric distortion.

Follow-up information was obtained from hospital records and by direct contact with the patient, family, cardiologist, and family physician. Follow-up was conducted through the months of May 1990 to February 1991 and the closing date for inclusion of events was February 22, 1991. Only one patient, who underwent aortic valve replacement with a xenograft prosthesis, was lost to follow-up. The number of patients followed up by time interval is outlined in Appendix Table II.

Data analysis. To estimate the probability of valve re-replacement before death, the competing risks of death and re-replacement were modeled in the hazard function domain. Details are provided in Appendix B. This method provides time-related estimates of the proportion of patients who will actually have a valve re-replaced. This approach can be conceptualized in terms of a cohort of patients that is followed up until each patient has either had a valve re-replaced or has died before valve re-replacement. At any time, one can calculate the proportion of patients that has had each event or is still free from both events. Ultimately, each patient will have one of the events and the proportion in each event group will become constant. The method also recognizes that the final proportion in each event group may well be a function of identifiable risk factors.

The analyses included estimates of the probability of re-replacement for any reason (leaflet failure, replacement valve endocarditis, and technical reasons) for xenograft valves and 4° C stored and cryopreserved allograft valves. Risk factors for re-replacement were sought by multivariable analysis using the method of maximum likelihood. A nomogram was derived for the relationship between probability of re-replacement for any reason before death and age at initial aortic valve replacement for xenografts and cryopreserved and 4° C stored allografts.

Results

A first valve re-replacement was done in 69 patients with a xenograft valve, 28 patients with a 4° C stored allograft valve, and 14 patients with a cryopreserved allograft valve. Valve re-replacement was done because of leaflet failure, replacement valve endocarditis, and a number of other miscellaneous causes (Table II). In the multivariable analysis only younger age at operation was found to be associated with increased probability of valve re-replacement.

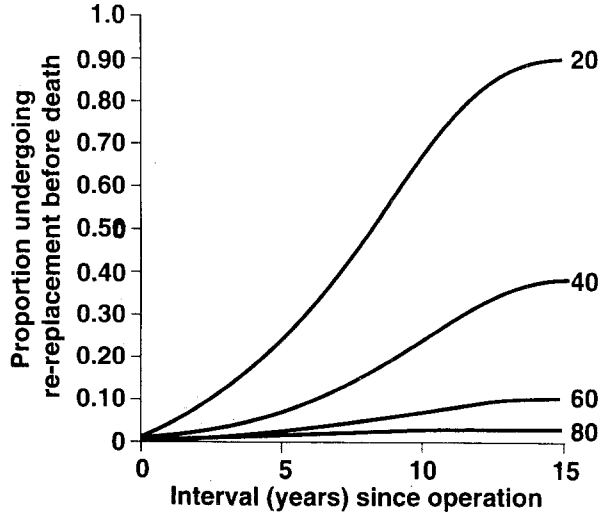

Fig. 1. Nomogram of the time-related proportion of patients with xenograft valves (950 patients, 53 re-replacements) who will actually require valve re-replacement for any reason before death according to the age of the patient. The *solid lines* are the parametric estimates.

Xenograft valve re-replacement. Fifty-three patients with xenograft valves underwent re-replacement for any reason. A nomogram of the time-related proportion of patients who will require re-replacement for any reason before death, stratified by age at operation, is depicted in Fig. 1. The asymptote of each curve represents the actual proportion of valves that will eventually require re-replacement before the death of the patients.

Re-replacement of 4° C stored allograft valves. Twenty-eight patients with 4° C stored allograft valves underwent re-replacement for any reason. The nomogram of the time-related proportion of patients who will require re-replacement for any reason before death, stratified by age at operation, is depicted in Fig. 2.

Cryopreserved allograft valve re-replacement. Fourteen patients with cryopreserved allograft valves underwent re-replacement for any reason. The nomogram of the time-related proportion of patients who will require re-replacement for any reason before death is depicted in Fig. 3.

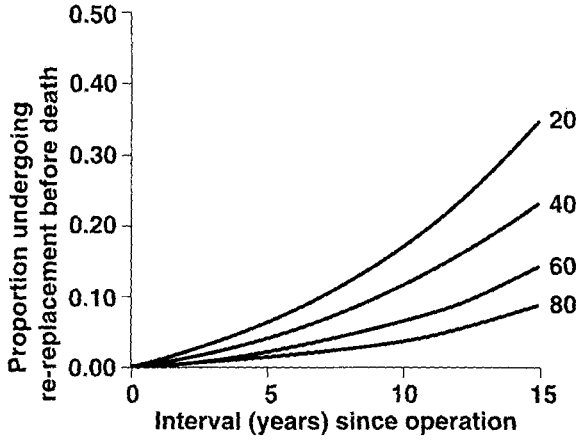

Fig. 2. Nomogram of the time-related proportion of patients with 4° C stored allograft valves (94 patients, 28 re-replacements) who will actually require valve re-replacement for any reason before death according to the age of the patient. The *solid lines* are the parametric estimates.

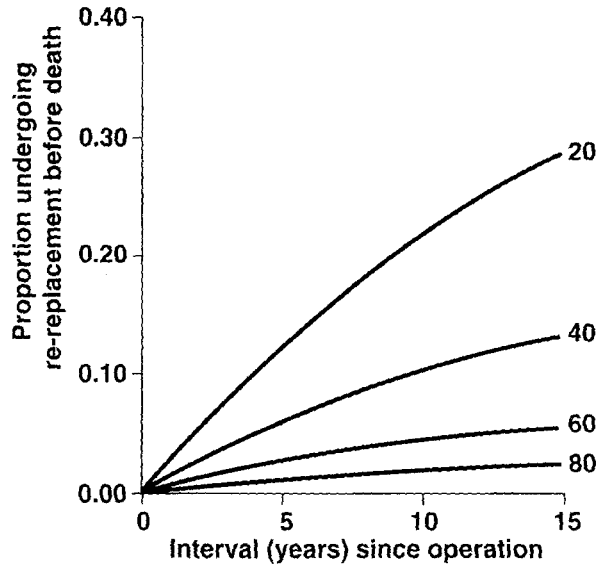

Fig. 3. Nomogram of the time-related proportion of patients with cryopreserved allograft valves (299 patients, 14 reoperations) who will actually require valve re-replacement for any reason before death according to the age of the patient. The *solid lines* are the parametric estimates.

Age-related re-replacement nomogram. The probability of re-replacement for any reason (leaflet failure, replacement valve endocarditis, and other reasons) before death for xenograft, 4° C stored, and cryopreserved allograft valves by age at operation is depicted in Fig. 4. One minus the probability of valve re-replacement before death is the probability of death before the valve requires re-replacement.

Discussion

When a cardiac surgeon and a patient are considering the choice of a valve device, the decision is partly influenced by an impression (in the surgeon's mind) of the likelihood that an implanted biologic valve will require re-replacement before the patient dies. This is, of course, particularly relevant in an elderly patient in whom, not infrequently, it is said that a biologic valve may "outlive" the patient. This process, which occurs informally, is taking into account in the decision the competing risks of death and re-replacement before death.

The Kaplan-Meier estimate of freedom from re-replacement (or other end point such as valve degeneration) assumes, because of the censoring process, that no patient dies and hence all patients will eventually require valve re-replacement. Consequently, the Kaplan-Meier estimate provides information regarding biologic valve durability and is a useful means to compare the durability of valve devices inasmuch as death is removed from the computation. Although this is important information, not only for valve manufacturers, but also for patients and surgeons, what is of more importance to the patient is the probability of requiring a valve re-replacement at some time during the remainder of his or her life. This information is not provided by the Kaplan-Meier estimate. Because death of the patient and re-replacement compete for the valve, both end points need to be solved for simultaneously.

The analytic tools to deal with multiple end points (competing risks) have been available for a long time. Grunkemeier and associates[5] proposed the term *actuarial* to describe the survivorship function (the usual Kaplan-Meier estimate) and the term *actual risk* to describe the competing risk depiction. Other terms that have been used to describe the actual risk include *cumulative incidence function*[8] *and cause-specific failure probability.*[9]

The competing risk analysis can be depicted either as the proportion free from re-replacement before death or, alternatively, as proportion undergoing re-replacement before death. In this study, the latter depiction was chosen. These curves, particularly those that portray proportion of patients who undergo re-replacement before death, have an unusual shape because they become asymptotic (as

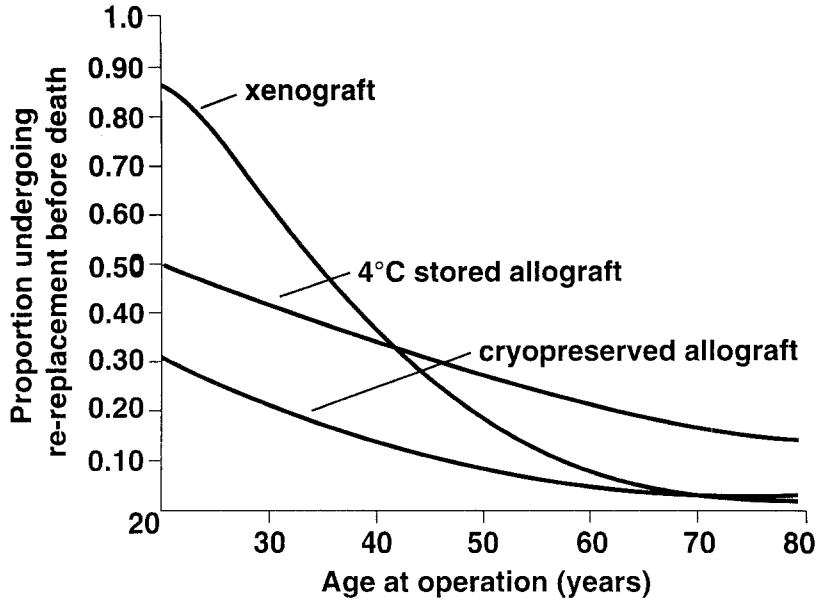

Fig. 4. Nomogram of the probability of re-replacement before death for any reason for patients with xenograft, 4° C stored, and cryopreserved allograft valves as a function of age at initial valve replacement. The *solid lines* are the parametric estimates.

time from operation increases, probability of re-replacement becomes constant). This is because the proportion of patients above the asymptotic part of the curve represents those who have died and hence the valve devices in those patients are no longer available for re-replacement. The competing risk plot for xenograft re-replacement (Fig. 1) has a clearly defined asymptote compared with the plots for 4° C stored allograft valve re-replacement (Fig. 2) and cryopreserved allograft valve replacement (Fig. 3). Competing risk is a process of assortment into events (in this case death and re-replacement). A clear asymptote for xenograft valves occurs at approximately 14 years, which means that after this time the assorting process has been completed and either death or re-replacement has occurred. However, there is no asymptote for 4° C stored and cryopreserved allograft valves, which indicates that the assorting process is still occurring at 15 years after operation. The estimates represented in the figures do not have confidence limits and hence carry some uncertainty.

In the multivariable analysis study, younger age at operation was found to be a risk factor for re-replacement of biologic valves. Previous studies by Magilligan and colleagues,[10] Jamieson and colleagues,[11] and Gallo, Nistal, and Artinano[12] demonstrated that younger age at operation was a risk factor for xenograft valve degeneration. Because these studies used the Kaplan-Meier estimate, censoring for death, younger age at operation reflected a biologic predisposition to tissue failure at younger age. However, in this study, by using a competing risk analysis, increased probability of re-replacement with younger age at operation reflects not only a biologic predisposition to leaflet failure, but also the fact that younger patients have a lower probability of dying than older patients and hence a higher probability of eventually requiring re-replacement. Similarly, when a competing risk analysis for re-replacement is applied to patients with allograft valves (4° C stored and cryopreserved), the effect of younger age at operation on the probability of re-replacement reflects the competing risk of death and re-replacement, as well as any biologic predisposition to leaflet failure.

The nomogram of the probability of undergoing a re-replacement sometime during the remainder of the patient's life, according to age at operation, is an important piece of information for a patient. This is depicted in Fig. 4 and provides this probability for xenograft, 4° C stored, and cryopreserved allografts. In terms of the proportion of patients who undergo re-replacement for any reason before death, cryopreserved allografts are superior to xenograft valves up until the age of approximately 60 years at the time of

operation. For a patient 20 years old at the time of operation who receives a cryopreserved allograft valve, over the remainder of the patient's lifetime there is a 30% predicted probability that a re-replacement of the valve will be required. If this patient were to receive a 4° C stored allograft valve (a valve that is still widely used), the predicted probability of a re-replacement during the remainder of the patient's life would be approximately 50%. If a xenograft valve were implanted in this patient, there would be an approximately 85% probability of requiring re-replacement before death. Beyond 60 years of age at operation, there appears to be no difference in the predicted probability of re-replacement before death in patients with xenograft valves compared with patients with cryopreserved allograft valves. Beyond the age of 40 years at operation, the predicted probability of re-replacement before death for a patient who receives a 4° C stored allograft valve is higher than that for patients who receive xenograft or cryopreserved allograft valves. In this study, failure of cryopreserved allograft valves caused by mechanical and technical reasons was an important reason for re-replacement. Allograft valve failure is a complex interplay between mechanisms such as leaflet degeneration, geometric distortion, changing mechanical properties of the leaflet tissue, and aortic root dilation. However, the current preference for the cylindrical or root replacement technique of allograft valve insertion as opposed to the subcoronary technique (the method most frequently used in this series) may reduce the probability of re-replacement by decreasing geometric distortion and hence improving leaflet coaptation. The efficacy of this strategy will require testing by repeating this study in the future.

Inferences

1. Younger age at operation is a risk factor for re-replacement of xenograft, 4° C stored, and cryopreserved allograft valves and this effect is a result of the competing risk of death and re-replacement, as well as a biologic predisposition to leaflet failure.
2. Competing risk analysis provides the actual probability of requiring a re-replacement during the remainder of the patient's life after aortic valve replacement. This is different information from that provided by the Kaplan-Meier estimate, which reflects valve durability.
3. In patients older than approximately 60 years at the time of aortic valve replacement, the probability of re-replacement (for any reason) before death is no different for xenografts and cryopreserved allograft valves. However, for patients younger than approximately 60 years, in terms of the probability of re-replacement before death, the cryopreserved allograft is superior to the xenograft and 4° C stored allograft valves.
4. In patients older than approximately 40 years, the probability of re-replacement before death remains higher with the 4° C stored allograft valve than with the xenograft or cryopreserved allograft valves.

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Appendixes

Appendix A: Variables entered into the multivariate models

Demographic variables. Age at operation; gender.

CLINICAL VARIABLES. New York Heart Association functional class immediately before operation (class V refers to shock); preoperative symptoms (angina, heart failure, syncope); significant lung disease and significant renal dysfunction; significant hepatic dysfunction; left ventricular dysfunction and atrial fibrillation; complete heart block; and aortic valve physiologic features (aortic stenosis, aortic regurgitation, mixed lesion).

Significant lung disease was defined as chronic limiting symptoms caused by lung disease with objective evidence on respiratory function tests, chest radiograph, and other tests. Significant renal dysfunction was defined as level of creatinine greater than or equal to 0.2 mmol/L or level of urea greater than or equal to 15 mmol/L, or both conditions. Significant hepatic dysfunction was defined as bilirubin level greater than or equal to 35 mmol/L. Left ventricular dysfunction was defined on the basis of echocardiogram, radionuclide scan, or left ventriculogram at cardiac catheterization. Ejection fraction was categorized as follows: normal, greater than 0.54; mild, 0.37 to 0.54; moderate, 0.20 to 0.37; and severe, less than 0.20. Fractional shortening was categorized as follows: normal, greater than 30%; mild, 20% to 30%; moderate, 10% to 20%; and severe, less than 10%.

PATHOLOGIC VARIABLES. Presence of coronary artery disease; aortic valve pathologic condition (rheumatic, calcareous aortic valve disease caused by a congenitally abnormal valve); calcareous aortic valve disease on a trileaflet valve; infective endocarditis, prosthetic valve dysfunction, aortic wall disease, or congenital valve disease (noncalcareous); and degree of left ventricular hypertrophy.

Calcareous aortic valve disease in a trileaflet valve was considered senile degenerative disease. Aortic wall disease was a pathologic condition of the aortic wall, including the aortic root, that resulted in dilation or dissection. For patients with endocarditis on a prosthetic valve or an abnormal valve (such as a rheumatic native valve) the pathologic condition was classified as endocarditis. The degree of left ventricular hypertrophy was defined as normal, mild, moderate, or severe (on the basis of the surgeon's intraoperative assessment).

SURGICAL VARIABLES. Date of operation; surgeon; cardiopulmonary bypass time; crossclamp time; use of cardioplegia; valve type; valve size; associated procedures; and completeness of revascularization for patients with coronary artery disease.

Appendix B

We let $S_1(t;x)$ and $f_1(t;x)$ denote the survival function and probability density function, respectively, where t denotes the time to death after the initial valve replacement operation for a patient age x (months) at the time of this operation. That is,

$$S_1(t;x) = pr\{T > t\} = \int_t^\infty f_1(u;x)du$$

where T is the random variable denoting time to death.

Concerning the other event of re-replacement, we let $S_2(t;x)$ and $f_2(t;x)$ denote the survival function and probability density function, respectively, for a patient age x at the time of initial operation, where t denotes the time to re-replacement in a hypothetical population for which there is no competing risk of death.

The survival function $S_i(t;x)$ is modeled as

$$S_i(t;x) = \exp[-e^x e^{\lambda_i}(e^{\beta_i t}-1)/\beta_i]$$

for i = 1, 2. The corresponding hazard function $h_i(t;x)$ is given by

$$h_i(t;x) = e^x h_{oi}(t)$$

where

$$h_{oi}(t) = e^{\lambda_i + \beta_i t}$$

is the hazard function for the Gompertz distribution. This effect of the age x of the patient at the time of the initial operation is modeled additively on the log scale of the baseline hazard function, which is taken to be of Gompertz form.

The survival functions $S_1(t;x)$ and $S_2(t;x)$ were fitted separately to the data, using the method of maximum likelihood where, in the estimation of the latter, a patient who died without a re-replacement was taken to be censored with respect to this event. The values of the parameter estimates are shown in Appendix Table I.

The cumulative incidence function $C_2(t;x)$ is defined as

$$C_2(t;x) = \int_0^t f_2(t;x)S_1(t;x)dt$$

It can be interpreted as the probability that a patient age x at the time of the initial operation will undergo a

Appendix Table I

	λ_i	β_i	γ_i
Xenograft valves			
$i = 1$	−11.3747	0.0462	−0.0026
	(0.3847)	(0.0026)	(0.0005)
$i = 2$	−4.7421	0.0206	0.0059
	(0.3035)	(0.0026)	(0.0007)
Cryopreserved allograft valves			
$i = 1$	−10.6683	0.0297	0.0027
	(1.630)	(0.0048)	(0.0022)
$i = 2$	−5.2656	−0.0020	−0.0034
	(1.1348)	(0.0084)	(0.0015)
4° C stored allograft valves			
$i = 1$	−16.6628	0.0598	0.0037
	(3.1028)	(0.0149)	(0.0016)
$i = 2$	−6.7309	0.0112	−0.0021
	(0.5609)	(0.0030)	(0.0007)

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Appendix Table II

Valve	*4° C stored allograft*	*Cryopreserved allograft*	*Xenograft*
0-5 yr	2	175	203
5-10 yr	9	46	501
10-15 yr	13	74	156
>15 yr	70	4	0
Total	94	299	950

re-replacement by time t afterward (and before the competing risk of death occurs). Thus the quantity

$$\pi_2(x) = C_2(\infty;x)$$

is the probability that a patient age x at the time of the initial operation will actually undergo a re-replacement before death.

Because the original data were no longer readily accessible, confidence intervals could not be presented.