

Cardiothoracic Transplantation

Evolving trends in risk profiles and causes of death after heart transplantation: A ten-year multi-institutional study

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Background: As therapeutic options evolve for advanced heart failure, the appropriate role for cardiac transplantation will require survival analyses that reflect changing trends in causes of death and patient and institutional risk profiles. Results from multi-institutional studies could be used to monitor progress in individual centers.

Methods: Between 1990 and 1999, 7290 patients undergoing cardiac transplantation in 42 institutions entered a formal outcomes study. Changing survival, causes of death, and patient risk profiles were analyzed. Multivariable risk-factor equations were applied to a single institution (300 primary heart transplants) to examine differences in risk-adjusted expected versus observed actuarial outcomes over time.

Results: Overall survival in the 42 institutions improved during the decade ($P = .02$). One- and 3-year cardiac transplant research database survival was as follows: era 1 (1990-1992), 84% and 76%, respectively; era 2 (1993-1995), 85% and 79%, respectively; and era 3 (1996-1999), 85% and 79%, respectively. Causes of death changed over time. Pretransplantation risk profiles increased over time ($P = .0001$), with increases in reoperations, devices, diabetes, severely ill recipients, pulmonary vascular resistance, sensitization, ischemic times, donor age, and donor inotropic support. Three-year actuarial survival in a single institution was 3% less than risk-adjusted predicted survival in era 1, 1% higher than predicted in era 2, and 7% higher than predicted in era 3.

Conclusions: Survival after cardiac transplantation is gradually improving, despite increasing risk profiles. Further improvement requires periodic re-evaluation of risk profiles and causes of death to target areas of surveillance, therapy, and research. By using these methods, progress at individual institutions can be assessed in a time-related, risk-adjusted manner that also reflects changing institutional experience, expertise, or both.

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During the past 35 years of experience with human heart transplantation, many important advances have occurred that currently allow nearly routine early survival and a high probability of intermediate-term survival, yet still disappointing late survival after cardiac transplantation. The advances in donor heart preservation, new and evolving immunosuppressive modalities and strategies, and emerging potential therapies for chronic rejection (allograft vasculopathy) have drastically changed the expectations of patients undergoing heart transplantation and transplant physicians since the initial decade of experience in the late 1960s and 1970s. Despite substantial advances, patients undergoing transplantation continue to face the potential of death from 5 major causes: early graft failure, allograft rejection, infection, allograft vasculopathy, and malignancy.¹

Because of the ongoing donor shortages, the experience and level of expertise at individual institutions is variable and often limited by a small number of transplant procedures. Multi-institutional studies have emerged as an important method of understanding truths regarding outcomes in clinical cardiac transplantation through meaningful risk-factor analyses of a large patient population.

This 10-year multi-institutional analysis was undertaken to examine changes in causes of death and patient risk profiles over the most recent decade of cardiac transplantation.

Materials and Methods

Study Population

The cardiac transplant research database (CTRD) is a multi-institutional, prospective, event-driven database that began in January 1990. The focus of this database has been the identification of time-related frequency of and risk factors for major morbid events and mortality (both general and cause specific) after cardiac transplantation at Medicare-approved facilities in the United States. The study population includes 7290 patients undergoing cardiac transplantation at 42 institutions over a 10-year period (Appendix 1). All patients at participating institutions are included in the analysis, but some institutions participated in the database for a portion of the decade. Follow-up as of January 1, 2000, was complete on 93% of study patients.

Specific data are collected at the time of transplantation, at the time of occurrence of morbid or fatal events, and on a yearly basis. Data compiled included extensive donor and recipient demographic variables and data regarding rejection, infection, retransplantation, malignancy, and allograft vasculopathy.

Data entry, checking, and maintenance are based at the CTRD Coordinating Center at the University of Alabama at Birmingham (UAB). The primary end point of this study was death from all causes. Each study center independently verified the cause of death, which was subsequently also verified by the coordination and analysis center at UAB. In cases in which multiple causes contributed to the final fatal outcome, a primary cause of death was assigned. The primary cause of death (and not contributing causes) was analyzed in this study.

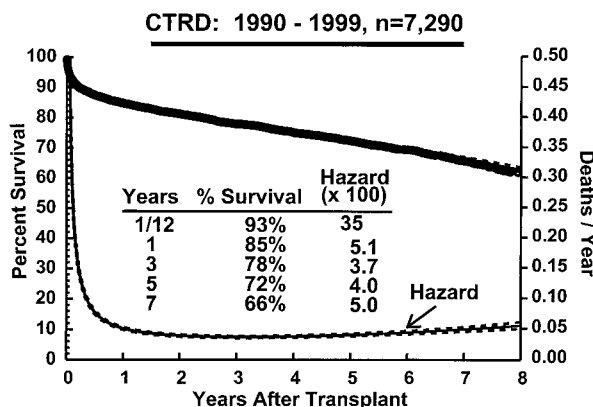


Figure 1. Actuarial and parametric survival after transplantation, including all patients during this 10-year experience. The lower curve represents the hazard function for death, with the units on the right-sided vertical axis.

TABLE 1. CTRD: 1990 to 2000—Time distributions of causes of death

Primary cause of death	Years after transplantation		
	<1 y (n [%] of 1076)	1-4 y (n [%] of 488)	5-10 y (n [%] of 300)
Early graft failure	217 (20)	0 (0)	0 (0)
Rejection	166 (15)	59 (12)	14 (5)
Infection	268 (25)	51 (10)	25 (8)
Nonspecific graft failure	57 (5)	38 (8)	7 (2)
Sudden	36 (3)	49 (10)	18 (6)
Neurologic	48 (4)	16 (3)	13 (4)
Malignancy	27 (3)	78 (16)	87 (29)
CAD	47 (4)	93 (19)	68 (23)
Other	210 (20)	104 (21)	68 (23)
Total	1076 (100)	488 (100)	300 (100)

Data Analysis

Standard time-related actuarial and parametric survival analyses in the hazard function domain were used to examine freedom from overall death and cause-specific mortality after transplantation.² The methods of competing outcomes analysis³ were used to examine the contribution from differing causes of death over time, both in relationship to the time after and the year of transplantation. Potential risk factors for death were examined by using multivariable hazard function analysis (Appendix 2). Risk factors were retained in the model if the *P* value was less than .05. The mortality observed in a specific institution (observed survival) was compared with the overall group performance by applying the risk-factor model to the specific patients within the single institution, and the expected survival at a specific time after transplantation was further adjusted by the era of transplantation within the decade of study.

Results

Survival

Among the 7290 patients undergoing cardiac transplantation between 1990 and 1999, 1-year survival was 85%,

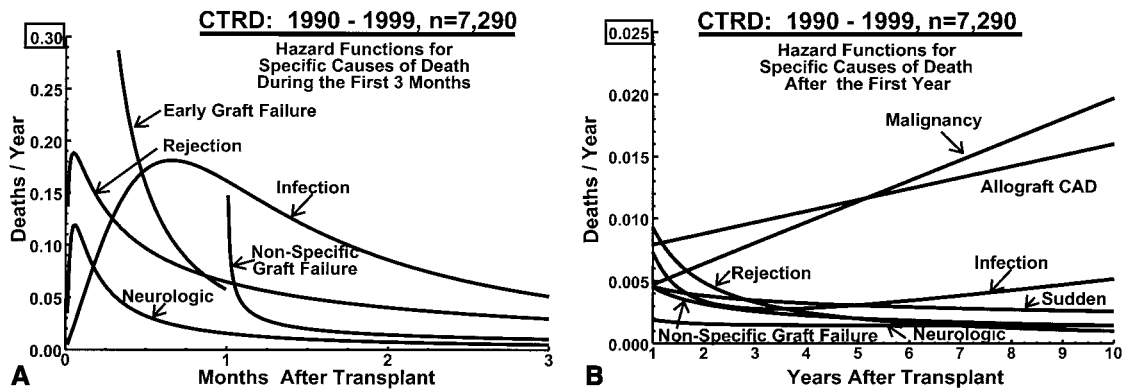


Figure 2. A, Hazard functions for the specific causes of death during the first 4 months after cardiac transplantation. B, Hazard functions for specific causes of death after the first year after cardiac transplantation. CAD, Coronary artery disease.

3-year survival was 78%, and 7-year survival was 66% (Figure 1). The hazard function for death was highest during the first 3 months and rapidly decreased thereafter, merging with a constant hazard function by 2 years. A late increasing hazard function was identified, with its effect becoming apparent after 6 years.

Causes of Death

The causes of death during this decade of experience according to the elapsed time after transplantation are listed in Table 1. During the first year, the major causes of death were early graft failure, infection, and rejection. Between 1 and 4 years, allograft vasculopathy was the major cause of death, followed by malignancy and rejection. After the fourth year, malignancy emerged as the leading cause of death. This evolution of likely causes of death related to evolving time after transplantation is reflected in the hazard functions for specific causes of death (Figure 2).

There was also a change in the proportion of patients who died from specific causes over the course of the study. The percentage of patients dying from early graft failure, malignancy, and infection within 3 years remained relatively constant over the decade. However, there was a progressive reduction in the likelihood of death from rejection and allograft vasculopathy during the first 3 years for patients transplanted during the latter part of the decade compared with those transplanted during earlier years (Figure 3).

Risk Factors for Mortality

The recipient and donor risk factors that were independent predictors of death in the early, constant, and late phases after cardiac transplantation are listed in Table 2. An earlier date of transplantation was an important additional risk factor for mortality in the constant phase, with a relative risk of 1.9 comparing 1992 with 1999.

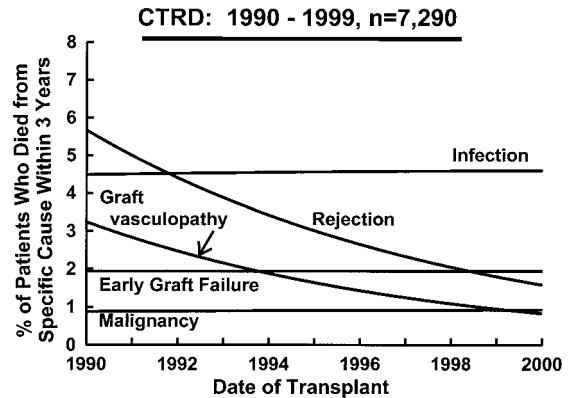


Figure 3. Proportion of patients who died from specific causes within the first 3 years after transplantation depicted by the year of transplantation (indicated along the horizontal axis). The proportion of patients dying from malignancy, early graft failure, and infection remained constant over the decade, whereas the proportion of patients dying from allograft vasculopathy and rejection within 3 years decreased during the decade experience.

Changing Risk Profiles Over Time

To evaluate the possibility that patients were either at lower or higher risk during the later period of this experience, the severity of the risk factors listed in Table 2 were profiled for 3 eras: 1990 through 1992 (1754 patients), 1993 through 1995 (2220 patients), and 1996 through 1999 (3316 patients) (Table 3). Note that patients transplanted were progressively more ill, as reflected by an increasing number of ventricular assist devices prior to transplantation and a greater proportion of status I patients at transplantation. The transplant operation was more often complicated during the later years, as reflected by more previous sternotomies and more ventricular assist devices at transplantation. The number of sensitized patients also grad-

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TABLE 2. Risk factors for death from any cause (CTRD: 1990-1999, n = 7290)

Risk factor	Early phase		Constant phase		Late phase	
	Relative risk	P value	Relative risk	P value	Relative risk	P value
Recipient						
Older age*	1.13	.008	1.41	.008		
Younger age†			1.94	.0002		
Black			2.02	<.001		
Obese recipient‡	2.35	.005				
Cachectic recipient§	2.5	.01				
Congenital cause	1.89	.002				
Noncongenital cause			3.76	.03		
Insulin-dependent diabetes			1.66	.0004		
Pulmonary disease	1.35	.03				
Peripheral vascular disease					11.3	.03
Herpes negative	1.29	.03				
Cigarette use within 6 mo			1.49	.0005		
Cocaine use			3	.0005		
Lower creatinine clearance at listing	1.28	.0006				
Higher serum creatinine at transplantation	1.43	<.0001	1.23	.01		
PAS-PCWP¶	1.4	.0005				
Mean RAP#	1.22	.01				
PRA >10	1.71	<.0001				
Previous sternotomy	1.44	<.0001				
>1 previous sternotomy	1.77	.03				
Ventilator	2.18	<.0001				
IABP	1.36	.01				
VAD, 14 d or less	1.86	.005				
Days on VAD**	1.29	.04				
Earlier date of transplantation††			1.91	<.0001		
Donor						
Older donor age§§	1.24	<.0001	1.23	<.0001		
Female	1.36	.0001				
Male			1.23	.03		
Abnormal echo	1.7	.01				
Diabetes			2.06	.01		
Longer ischemic time	1.7	<.0001				
Mismatch						
Recipient BMI-donor BMI (smaller donor, larger recipient)¶¶	1.49	.004				

PAS, Pulmonary artery systolic pressure; PCWP, mean pulmonary capillary wedge pressure; RAP, right atrial pressure; PRA, panel reactive antibody; IABP, intra-aortic balloon pump; VAD, ventricular assist device; BMI, body mass index.

*Relative risk compares age 50 years with age 60 years.

†Relative risk compares age 30 years with age 20 years.

‡Relative risk compares body mass index of 25 with body mass index of 30.

§Relative risk compares body mass index of 25 with body mass index of 15.

||Relative risk compares creatinine clearance of 100 with creatinine clearance of 50.

¶Relative risk compares serum creatinine level of 1.0 with serum creatinine level of 2.0.

#Relative risk compares systolic pulmonary gradient of 15 with systemic pulmonary gradient of 40.

**Relative risk compares right atrial pressure of 5 with right atrial pressure of 20.

††Relative risk compares days on vascular assist device of 30 with days on vascular assist device of 180

‡‡Relative risk compares transplant year of 1999 with transplant year of 1992.

§§Relative risk compares donor age of 25 years with donor age of 40 years.

|||Relative risk compares ischemic time of 180 with ischemic time of 300.

¶¶Relative risk compares body mass index difference of 10 with body mass index difference of 20.

ually increased. Donor age increased, ischemic time lengthened, and the percentage of donors receiving pres- sors increased during the decade.

Risk-adjusted Survival

The actuarial survival during each of these 3 time periods is depicted in Figure 4. Although the earlier period (1990-

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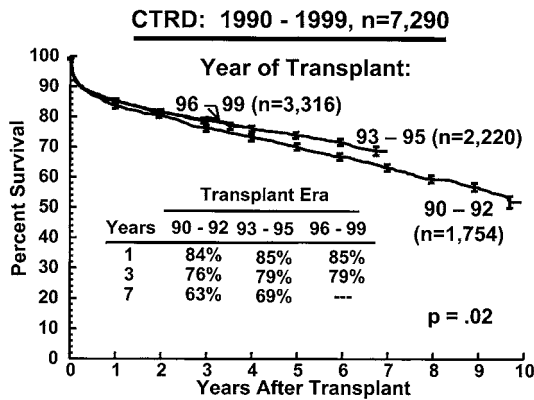


Figure 4. Actuarial survival after cardiac transplantation stratified by era of transplantation: 1990 through 1992, 1993 through 1995, and 1996 through 1999.

1992) showed a significant reduction in survival compared with that seen in later years, the magnitude of that difference was small. To further evaluate the adverse effect of increasing risk profiles (Table 3) on the one hand and the favorable effect of a later transplantation date (Table 2), a separate depiction was generated to indicate the magnitude of these effects. By solving the multivariable equations (Table 2) for the risk profile of patients and donors in 1990 and setting the date of transplantation as 1990, a 3-year survival of 76% (Figure 5, upper straight line) is projected over the decade, indicating the outcome if the risk profile remained stable and no institutional improvement occurred over time. The effect of a changing patient risk profile can be isolated and displayed by leaving the date of transplantation variable constant and calculating the risk-adjusted 3-year survival for the cohort of patients transplanted in each 6-month interval (Figure 5, bottom jagged curve). The difference between these curves at any time during the decade can be quantified as the risk-profile effect compared with patients transplanted in 1990.

The date of transplant as a separate risk factor revealed a progressive improvement in survival with increasing year of transplantation, likely indicating institutional or era improvements. This institutional-era effect is depicted in Figure 6. The lower curve once again reflects the 3-year survival for patients transplanted in 1990, assuming no effect of date of transplantation and no change in risk factors over the decade. The upper line depicts the improvement in survival over the decade when the risk profile is maintained at the 1990 level and only the date of transplantation variable changes. The area between the 2 curves indicates the isolated institutional-era effect (date of transplantation) on improved 3-year survival over the decade of experience.

The overall effect of these 2 factors (increasing risk

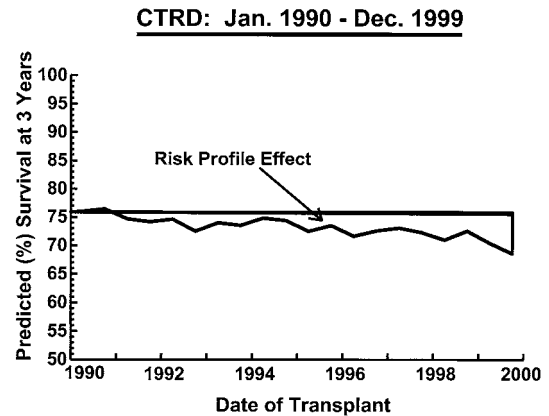


Figure 5. Risk-profile effect during the decade of transplantation. The upper solid curve indicates the 3-year survival for patients undergoing transplantation with a risk profile present in 1990 and with the variable "transplant date" set at 1990. The lower curve maintains the same transplantation date (1990) but demonstrates the effect of changing risk profile over the decade. The risk profile for patients in each 6-month interval are used to calculate the expected 3-year survival. Note that the effect of the changing risk profile is such that higher-risk patients were undergoing transplantation in later years of the experience.

profile and institutional-era effect) is depicted in Figure 7. Note that these 2 effects act in opposite directions; namely, the risk-profile effect (higher-risk patients later in decade) acts to decrease expected survival, whereas the institutional-era effect (improving outcome with later date of transplantation) acts to increase survival. The interaction of these 2 factors produces a slight progressive increase in 3-year survival over the course of the decade.

Application of Risk Profiles to Individual Institutions

The equations from the multivariable risk-factor analysis for CTRD were applied to a single institution (UAB) to examine differences in expected versus observed survival as a reflection of the date of transplantation (Figure 8). The 3 panels correspond to patients transplanted between 1990 and 1992, 1993 and 1995, and 1996 and 1999. Note that the UAB observed survival was less than the expected value (according to the CTRD risk-adjusted predictions) in 1990 through 1992 (Figure 8, A), and the observed and expected survivals were nearly superimposed for the experience between 1993 and 1995 (Figure 8, B). During the most recent 5-year experience, the UAB survival exceeded the risk-adjusted CTRD prediction (Figure 8, C).

This UAB institution-era effect is depicted in Figure 9 as the shaded area between the expected and observed curves. Thus in the early part of the decade, this single-institution experience reflected worse risk-adjusted survival than expected by the CTRD equation (negative institutional-era effect), but by the latter portion of the decade, the single-

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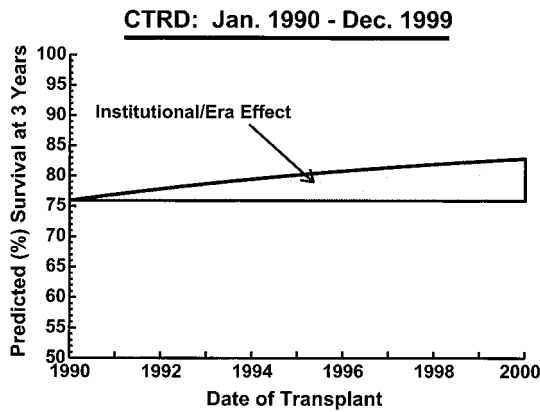


Figure 6. Institutional-era effect (date of transplantation effect). The lower solid curve is the same as the upper solid curve in Figure 5, indicating the date of transplantation as 1990 and a risk profile for 1990. The upper curve assumes a constant risk profile (1990 level) for patients operated on during the decade and demonstrates the effect of increasing date of transplant. The shaded area between the curves indicates the improvement in 3-year survival attributed to the institutional-era effect.

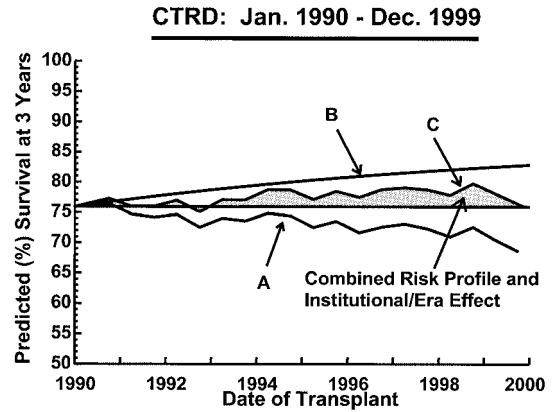


Figure 7. Combined risk profile and institutional-era effects. Figure 7 represents a composite of Figures 5 and 6, in which A is the isolated risk-profile effect (increasing risk factors), B indicates the isolated institutional-era effect, and C indicates the actuarial 3-year survival for patients transplanted in each 6-month interval over the decade, taking into account both increasing risk factors and the institutional-era effect. This results in a gradual increase in 3-year survival over the decade of experience.

TABLE 3. CTRD

	Year of transplantation			P value
	1990-1992 (n = 1754)	1993-1995 (n = 2220)	1996-1999 (n = 3316)	
Recipient				
Age (ys)	51.2	52.3	52.9	<.0001
Diabetes	13.0%	15.0%	19.0%	<.0001
Pulmonary resistance (units · m ²)	4.8	5.2	5.3	<.0001
PRA >10 (best)	2.7%	5.1%	6.2%	<.0001
PRA >10 (worst)	3.4%	6.0%	8.6%	<.0001
Previous sternotomy	38.0%	41.0%	46.0%	<.0001
IABP at transplant	8.7%	7.3%	4.9%	<.0001
VAD at transplant	3.0%	8.0%	18.0%	<.0001
Status 1 at transplant	45.0%	59.0%	72.0%	<.0001
Donor				
Age (y)	29.4	29.6	31.6	<.0001
Age >40 y	21.0%	24.0%	30.0%	<.0001
Ischemic time (min)	159	171	176	<.0001
Ischemic time >300 min	1.3%	2.4%	3.0%	.002
White	83.0%	78.0%	85.0%	<.0001
Black	10.0%	12.0%	12.0%	.08
On pressors	73.0%	83.0%	86.0%	<.0001

PRA, Panel-reactive antibody; IABP, intra-aortic balloon pump; VAD, ventricular assist device.

institution survival exceeded that predicted by the risk-factor equations (positive institutional-era effect).

Discussion

Study Limitations

Despite the obvious power of more than 7000 patients compromising the study group, the study is limited by the disadvantages of multi-institutional databases. Although the

event-driven design of this database is unique and rigorous in terms of follow-up and data checking, considerable interinstitutional differences exist. For example, a specific cause of death must be assigned by the investigators at each institution. Because of the frequent interaction between various morbid events contributing to a final fatal outcome, differences might exist as to the exact cause of death in a

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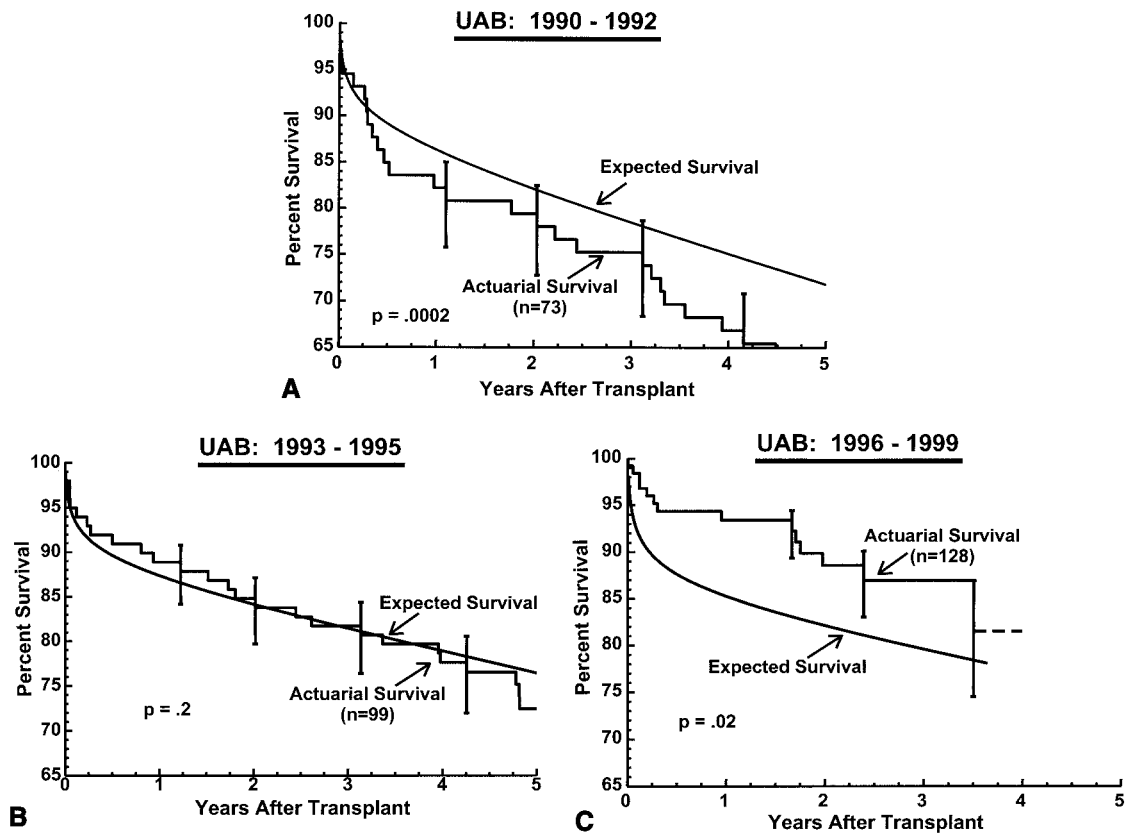


Figure 8. A, Actuarial survival (bottom curve) at UAB, 1990 through 1992. The upper curve represents the expected survival for UAB on the basis of risk adjustment according to the CTRD 10-year multivariable analysis. B, The same depiction as in A for the years 1993 through 1995. C, The same depiction as in A for the years 1996 through 1999.

given patient. For example, the assignment of rejection as an event and cause of death was frequently, but not uniformly, associated with clear evidence on endomyocardial biopsy or autopsy. Thus in the clinical practice of transplantation and in this study, some uncertainty frequently exists as to the diagnosis of allograft rejection in the setting of circulatory compromise. Infection is a frequent complication of aggressive immunosuppression in the setting of recurrent or severe rejection, further complicating the assignment of a primary cause of death in that setting. Other confounding issues include the differentiation of early graft failure from accelerated early rejection as a cause of death.

In any event-driven study of this magnitude, the possibility always exists of underreporting of events by individual institutions. In this study, however, death is the single end point that is most rigorously identified.

Causes of Death

It is of interest that allograft vasculopathy (transplant coronary artery disease) and malignancy emerge as the leading causes of death after the first several years after transplantation. It has long been the perception of many transplant

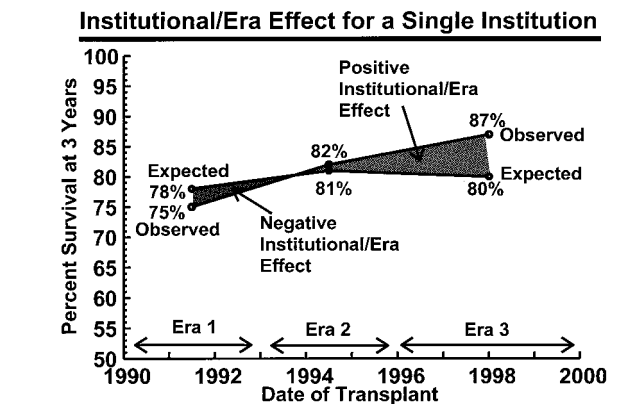


Figure 9. The expected versus observed survival at UAB for the 3 time periods depicted in Figure 8. The shaded area between the 2 curves represents the changing differences between observed and expected survival over time.

physicians that allograft vasculopathy will be the major factor that limits long-term survival. This study casts some doubt on that assertion, at least in the current era of immu-

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nosuppression. A review of Figure 2, *B*, indicates that although allograft vasculopathy provides the greatest hazard for death in the intermediate term (2-4 years after transplantation), malignancy emerges as the most likely cause of death after about 5 years. The ongoing and increasing risk of late fatal malignancy should be emphasized as longer-term survival becomes routine. Elimination of posttransplant risk factors for malignancy, such as continued smoking and appropriate surveillance protocols, are an increasingly important component of long-term care of transplant recipients.

The changing proportion of patients dying from various causes of death over the decade of this study provides important insights regarding the state of progress of transplantation therapy. Death from rejection and allograft vasculopathy (Figure 3) have decreased in frequency over the decade. This likely reflects advances in immunosuppressive modalities, both maintenance therapy and acute rejection treatments. A survival benefit has been suggested with mycophenolate compared with azathioprine,⁴ and many institutions currently routinely use mycophenolate as part of maintenance immunosuppression. Photopheresis^{5,6} has provided more successful treatment of recurrent rejection in the recent era, and plasmapheresis has evolved over the past decade into a near-routine component of therapy for rejection with hemodynamic compromise, a frequently lethal event.⁷

The reasons for decreasing mortality from allograft vasculopathy are unclear but might relate to more effective antirejection therapy, given the known relationship between frequent rejection and subsequent allograft vasculopathy.^{8,9} A greater emphasis on treatment of hyperlipidemia and other risk factors for generalized atherosclerosis might be having some (as yet unproven) beneficial effect.

The finding of the absence of decreasing early mortality from early graft failure, infection, and malignancy is disappointing and indicates that considerable work remains in the areas of improved donor heart preservation and early detection and treatment of malignancies and infections after transplantation.

Analysis of Survival

This study emphasizes that a simple actuarial depiction of survival in differing eras (Figure 4) often provides incomplete information. Proper multivariable risk-factor analyses play a critical role in identifying risk factors for adverse outcomes. This study further underscores the importance of examining changing risk profiles (the risk-profile effect) in comparing one era to another. Indeed, the findings in this study support the long-held clinical impression that patients undergoing transplantation have become progressively sicker over the past decade.

An additional institutional-era effect was identified that could not be explained by any other variables entered into

the risk-factor analysis. The finding that earlier transplantation date was a risk factor for mortality likely reflects increasing institutional expertise in many aspects of transplant care, as well as changing methods of immunosuppression and other scientific advancements, which are generally incorporated into most institutional transplant protocols. As seen in Figure 7, the improving institutional-era effect acted to overcome an increasing risk profile over the decade to produce the gradual slight overall improvement in survival.

This study also emphasizes the importance of examining individual institutional performance over time. The often-used expected versus observed survival at a given institution is typically based on risk-adjusted expected mortality on the basis of multi-institutional risk factors and is often reported by national agencies (eg, the United Network for Organ Sharing and insurance carriers). The depictions presented here provide the opportunity to graphically depict changing institutional factors over time compared with predicted national outcomes. In many cases it is the ability of the institution to make progress from within compared with national standards that is equally as important as their comparison with national standards at a single point in time.

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Appendix 1

CTRD Institutions

1. Abbott Northwestern Hospital
2. Albuquerque Presbyterian Hospital

3. Bowman Gray School of Medicine
4. Brigham and Women's Hospital
5. Cleveland Clinic Foundation
6. Downstate Heart Transplant Center
7. Emory University
8. University of Florida, Shands Hospital
9. Henry Ford Hospital
10. Hershey Medical Center
11. Indiana University Hospital
12. Johns Hopkins Hospital
13. Loyola University Medical Center
14. St Luke's Hospital
15. Medical College of Virginia
16. Massachusetts General Hospital
17. Methodist Hospital of Indiana
18. St Mary's Hospital, Mayo Clinic
19. Ochsner Clinic Transplant Program
20. Ohio State University, Cardiology
21. Rush Presbyterian-St Luke's Medical Center
22. Medical University of South Carolina, Charleston
23. Sharp Memorial
24. St Luke's Episcopal Hospital
25. Sentrara Norfolk Hospital
26. St Louis University
27. Tampa General Hospital
28. Baylor College of Medicine/The Methodist Hospital
29. Temple University School of Medicine
30. Tulane University
31. University of Alabama at Birmingham
32. University of California, Los Angeles
33. University of Cincinnati Medical Center
34. University of Iowa
35. University of Michigan Medical Center
36. University of Minnesota
37. University of Utah Health Sciences Center
38. University of Texas SW Medical Center
39. Hunter Holmes McGuire VA Medical Center
40. Vanderbilt University
41. Washington University Medical Center
42. Yale University School of Medicine

Appendix 2

Variables in the Multivariable Analysis for Death After Transplantation

Recipient demographic: age, sex, race, height, weight, body surface area

Donor: age, sex, race, height, weight, body surface area, blood type, ischemic time, cause of death, diabetes history, degree of inotropic support (mild [class 1] = dopamine, dobutamine, or both total dose of $<5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; moderate [class 2] = dopamine, dobutamine, or both total dose of $5\text{-}20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; severe [class 3] = dopamine, dobutamine, or both total dose $>20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) with or without additional pressor agents.

Recipient-donor mismatch variables: race, sex, blood type, HLA mismatches, weight, body surface area

Clinical variables: United Network for Organ Sharing status at listing, United Network for Organ Sharing status at transplantation, justification of status at transplantation (eg, inotropic drugs),

panel-reactive antibody closest to transplantation, cause of heart failure, diabetes diagnosis, peripheral vascular disease, amiodarone use, hyperlipidemia diagnosis, blood type, creatinine level at listing, creatinine level at transplantation, use of respirator at transplantation

Hemodynamic variables: right atrial mean pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, cardiac index, pulmonary vascular resistance

Surgical variables: previous sternotomy (number), type of transplantation (orthotopic versus heterotopic), date of transplantation

Discussion

Dr Eugene H. Blackstone (Cleveland, Ohio). Dr Kirklin, I applaud you on a decade of astonishing productivity of your visionary CTRD. This morning you have presented survival after cardiac transplantation in 3 novel and only loosely connected ways. Each is important, interesting, and in need of amplification.

First, you presented competing time-related hazards of various causes of death. These are reminiscent of those presented 20 years ago in heart valve replacement. I found risk of death from early and nonspecific graft failure a particularly interesting pair. Just as prosthetic valve endocarditis was once split arbitrarily into early and late prosthetic valve endocarditis, these 2 look like they belong together in a temporal continuum. However, the most important information is the marked decline in risk for some modes of death and relentless continuation of others. Yet calendar date of operation is terribly nonspecific.

Have you now returned to your database and analyzed those modes of death to identify specific management strategies and other factors associated with the declines? What makes other modes so immutable? Which is influenced by changing patient risk profile?

Second, you presented the effect of changing risk profiles across the decade. Your novel way of portraying the effect of changing risk profile is applicable to every area of cardiothoracic surgery. Instead of merely showing that patient profile is getting worse, you have provided a visually appealing and readily understood tool that neatly dissects changes in patient profile from temporal improvement and then shows the net result. My question is, how did you do that? I suspect your method is, or should be, an extension to the time domain of the risk-adjusted cumulative sum chart introduced by Tom Treasure for monitoring the quality of surgical programs. Again, have you suppressed the date of operation to identify treatment factors accounting for improvements?

Finally, you presented monitoring of long-term institutional quality. You have extended the medical report card concept into the arena of longitudinal patient care, but might there be more efficient ways to help institutions gain insight into why their programs have or have not improved? Perhaps if you used your risk model as a risk score and then analyzed each institution's data for residual risk, the result would be more helpful.

Dr Kirklin, I have read your article avidly, listened to your presentation eagerly, and now beg for more. Thank you and the Association for the opportunity to comment on the novel ideas you and your colleagues have introduced that are broadly applicable across cardiothoracic surgery.

Dr Kirklin. Thank you, Dr Blackstone, for your kind remarks. It is only fitting to pay tribute to Dr Blackstone and his major contributions in the science of outcomes research in cardiothoracic surgery, and certainly he has had a profound effect during his years at UAB in setting the foundation for many of these analyses that we have applied to cardiac transplantation.

With regard to the issue of a potential continuum between early graft failure and nonspecific graft failure, certainly that continuum is present and is true. However, there are situations like that for which we believe it is useful to categorize separately the event of early graft failure. There are causes of graft decline that occur later after transplantation in the setting of normal early function and that cannot be explained by rejection or allograft vasculopathy and remain an enigma. Therefore perhaps it is useful to categorize those separately.

Regarding the issue of date of transplantation as a variable; yes, it is very nonspecific, yet herein lies one of the difficulties of this type of analysis. Date of transplantation embodies not only increasing institutional experience and expertise but also new eras of immunosuppression, changing strategies and modalities of therapy, and so on. Unfortunately, some of these things actually occur after the transplantaion (*ie, the event when we either change modalities or introduce new immunosuppression*). That fact complicates an analysis such as this, which is a pretransplant risk-factor analysis. We are currently increasing our attention on variables and events that occur during the first year after transplantation. We can model predictions of later events from not only pretransplant variables but also variables that occur during the first year.

As regards those changes that are immutable, we were disappointed to find that the likelihood of dying from infection, early graft failure, and malignancy has not decreased during the decade. We do not believe they are immutable, but the emphasis in all

fields of transplantation has been on developing new immunosuppressive drugs and strategies, and therefore it is not surprising that rejection mortality has decreased. Its relationship to allograft vasculopathy is now increasingly clear, and a number of multivariable, multi-institutional studies have correlated rejection frequency and intensity with a higher probability of allograft vasculopathy. Perhaps that is one reason why total allograft vasculopathy is decreasing in the face of new immunosuppressive agents and an increasing emphasis on lipid therapy.

The risk-profile effect was calculated by looking specifically at each patient within each 6-month interval over the decade. Each of the patients had his or her cumulative hazard function calculated on the basis of risk profiles, and the average cumulative hazard was then translated into a survival curve to generate the predicted survival on the basis of those risk factors.

Finally, what might we do to help institutions better understand their report card? This is obviously an important yet sensitive issue. From an analytic point of view, in general, we apply an overall multivariable analysis model to an individual institution and then see what additional risk factors are identifiable in that institution. In addition, one could do a separate multivariable analysis if the volume was large enough in a given institution and compare, if you will, those risk factors overall.

It is important to remember that there are always dangers because of the fact that a small number of patients at a given institution might not allow a given risk factor to be unveiled. Also, if a given institution has a much higher-risk group of donors or recipients in a way that is not practiced by the overall community of transplantation, (eg, transplanting patients with a creatinine level of >3), you might not identify that as an overall risk factor, even though it might be present at a given institution. Thus it is important to look individually at factors with an institution before maligning it too much about less than expected outcome.