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The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Heart Transplant Report—2011

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This Twenty-eighth Report of the International Society for Heart and Lung Transplantation (ISHLT) Transplant Registry is based on data submitted by participating transplant centers worldwide. A total of 388 heart transplant centers have contributed information to the Registry. This year we have also achieved another important milestone: the 100,000th heart transplant recipient was registered in the database.

This report reviews important statistics for the entire cohort of patients registered in the database. However, similar to prior reports,[1–5] many of the more detailed analyses will focus on recent transplant recipients, exploring information relevant to contemporary heart transplantation practice. The first part of the report reviews important donor, recipient, and medical center demographics. The second part provides an overview of immunosuppressive therapies used after transplantation. The third part examines survival, mortality risk factors, and causes of death after adult heart transplantation. The last section focuses on quality of life after transplant.

Statistical methods

Recipient and donor demographics, immunosuppressive treatments, morbidity, hospitalization, causes of death, and functional status are summarized using percentages or median with 5th and 95th percentile, as appropriate.

Survival rates were calculated using the Kaplan-Meier method[6] and compared using the log-rank test. Multivariable analyses were performed using Cox proportional hazard regression analysis.[7] Results of the multivariable analyses are reported as relative risk (RR) with 95% confidence intervals (CI) and/or a corresponding *p*-value. A RR significantly exceeding 1.0 indicates that the factor examined is associated with an increased likelihood of occurrence of the event of interest (eg, death, rejection, etc). Conversely, a RR significantly below 1.0 indicates that the event is less likely to occur when that factor is present.

Multiple imputation was used to handle missing information for continuous data fields, such as ischemia time and donor age.[8] This method produces an estimated value for the missing value based on the other characteristics of the patient, donor, and/or transplant. The algorithm is performed multiple times, producing new estimates for the missing information. Models are fit on each imputed data set and then combined to produce a final set of estimates from which the RR estimates and *p*-values are obtained.

Heart transplant demographics

Transplant volumes

After a transient peak in the number of heart transplants reported to the Registry in the mid-1990s, the number of reported heart transplants has remained essentially stable. In the last decade, between 3,600 and 3,850 heart transplants have been registered every year (Figure 1). We believe this represents approximately 66% of the heart transplant procedures performed worldwide.[6]

There are significant differences in the number of transplants being performed among the centers participating in the Registry. The typical center performs between 10 and 19 transplants every year; 39% of centers fall into this category

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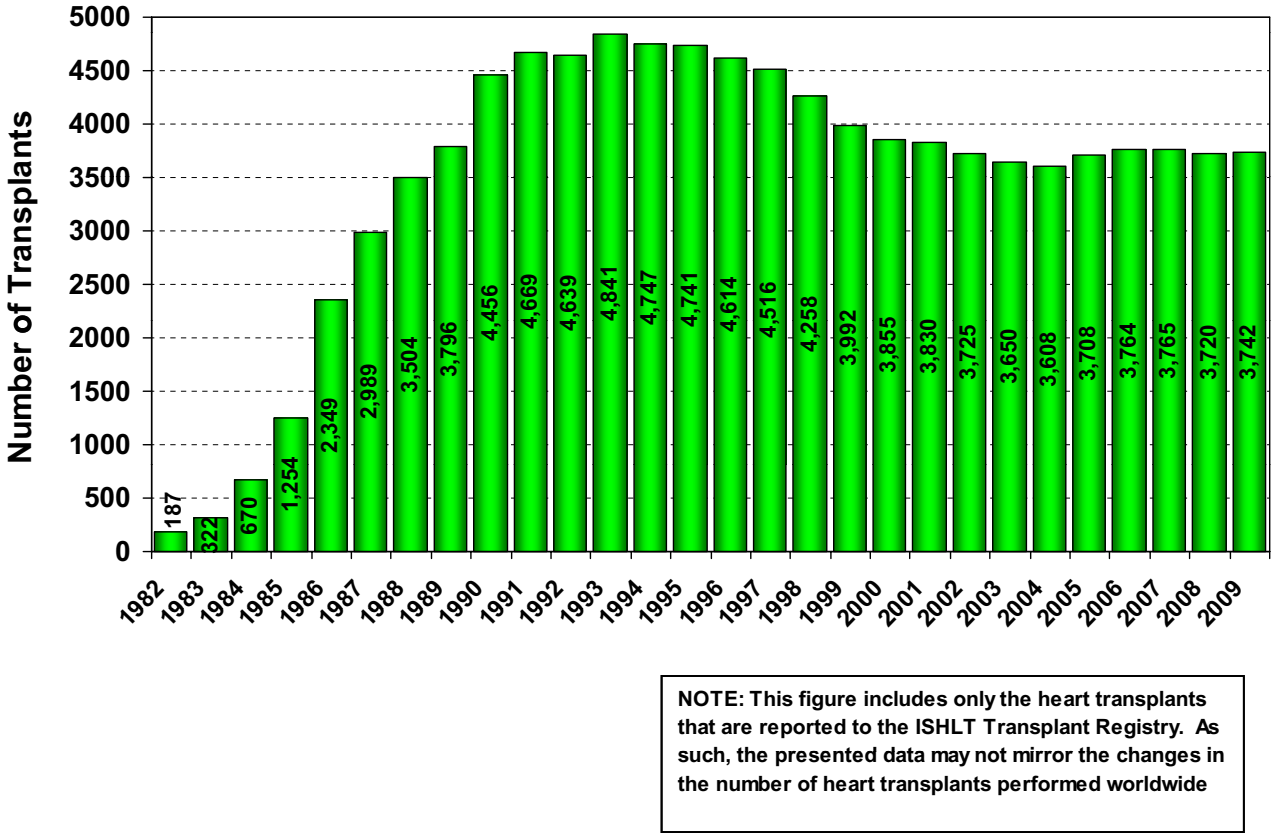

Figure 1 Number of heart transplant procedures reported to the Registry by year. Note: This figure includes only the heart transplants that are reported to the International Society for Heart and Lung Transplantation Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.

and perform approximately 33% of all transplants. Smaller centers that perform fewer than 10 transplants per year represent a similar number of centers (40%) and perform 13% of transplants. Finally, 21% of centers perform more than 20 transplants per year and are responsible for half of all transplants.

Recipient demographics

In the last 5 years (January 2005 to June 2010), non-ischemic cardiomyopathy was the leading cause of heart disease for adult heart transplant recipients (53.3% of the recipients), ischemic cardiomyopathy was the second most frequent diagnosis (37.7%), followed by adult congenital heart disease (2.9%), valvular heart disease (2.7%), and repeat transplantation (2.6%). A small number of patients with other diagnoses accounted for the remaining 0.8% of transplants (Figure 2).

The distribution of the leading diagnoses for which heart transplant is performed has shifted significantly over time. Ischemic cardiomyopathy accounted for more than 50% of all the transplants in the late 1980s, whereas non-ischemic cardiomyopathy has now become the leading indication (Figure 3). This gradual change toward transplantation for non-ischemic cardiomyopathy has been consistent over the past several years and is seen across the different geographic locations.[9] It is likely that decreasing prevalence of nicotine use, new therapies for ischemic heart disease, and particularly, additional treatment options provided by the evolving field of mechanical circulatory support have influenced the selection of patients for transplantation.

The median age of an adult heart transplant recipient is 54 years and has not changed significantly over time. The actual age distribution of transplant recipients did change, however, as a higher proportion of patients in their 60s and 70s have received a heart transplant during the last decade (Figure 4).

It is interesting to compare recipient demographics during the past decade with characteristics of recipients who received transplants a decade earlier (Table 1). The proportion of female recipients has increased a few percentage points and is now 22.8%. The proportion of recipients with certain comorbidities at time of transplant continues to increase: 23% have diabetes mellitus, and 41% have hypertension. Despite the increasing proportion of patients receiving allografts for non-ischemic cardiomyopathy, the number of recipients with previous cardiac surgery (43%) remains high. The proportion of patients who are sensitized to human leukocyte antigens (HLA) has also increased, and 12% of patients now have a serum panel reactive antibody (PRA) level higher than 10%. Median allograft ischemic time has also increased, and is 3.0 ± 1.5 hours in the most recent era.

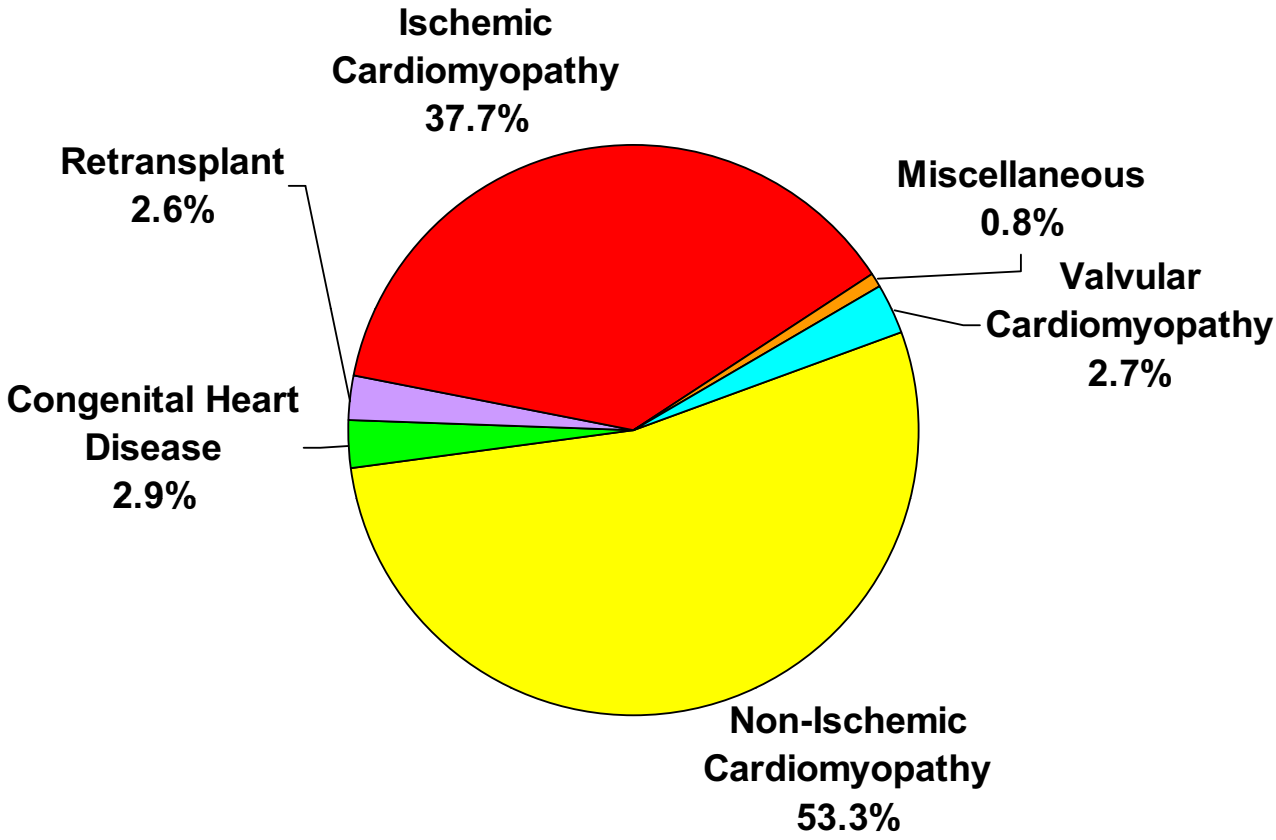

Figure 2 Etiology of heart disease preceding heart transplant in adults for transplants that occurred from January 2005 through June 2010.

Compared with a decade ago, the number of patients bridged to transplant with mechanical circulatory support devices has increased dramatically. In the period between January 2002 and June 2010, 19% of recipients had left ventricular assist devices (LVAD). In 2009, the proportion of patients who were bridged to transplant with mechanical circulatory support exceeded 30% for the first time (Figure 5). Between 2005 and 2009, 3% to 5% of recipients had right ventricular assist device (RVAD) at the time of transplant (RVAD only, or RVAD and LVAD).

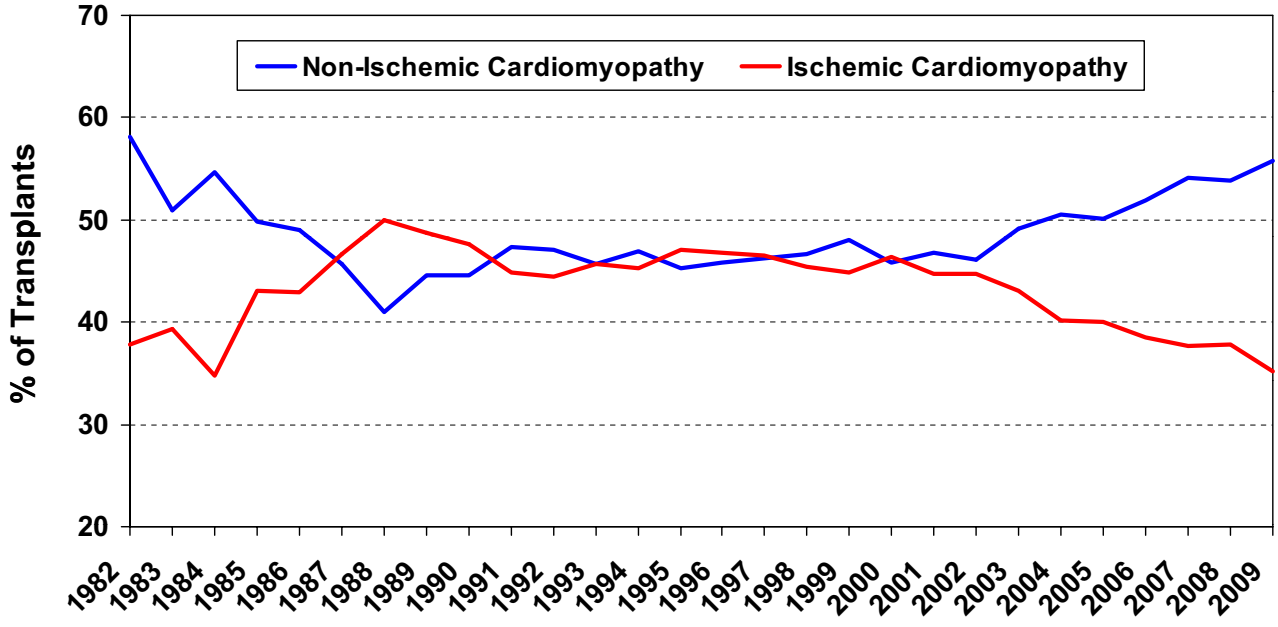

Figure 3 Non-ischemic cardiomyopathy vs ischemic cardiomyopathy diagnosis in adult heart transplant recipients.

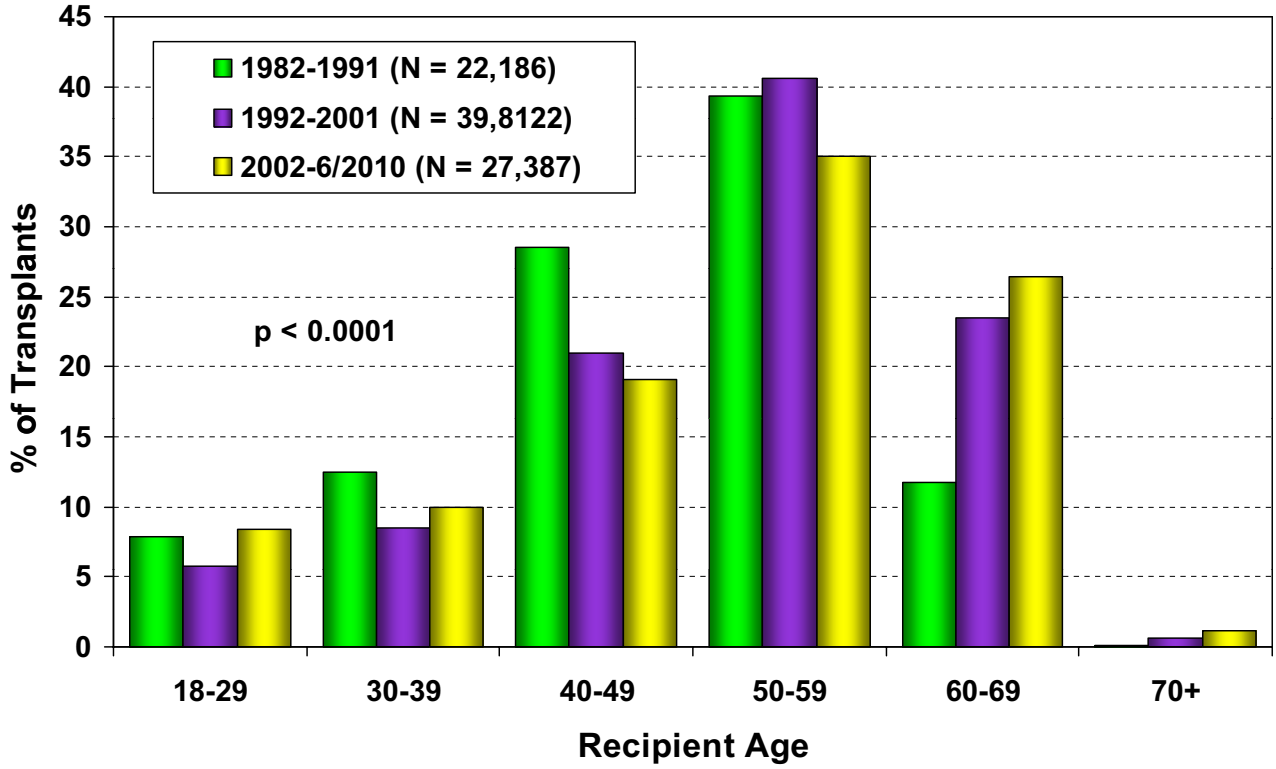

Figure 4 Age at transplant in adult heart transplant recipients, distribution by era.

In summary, the typical recent heart allograft recipient continues to have a higher number of characteristics at time of transplant that might be associated with post-transplant risk of morbidity and death than an average recipient who underwent transplantation in previous eras.

Donor demographics

The median donor age in 2009 was 35 years, which has increased from 27 years in 1990. In 2009, 14% of donors were aged 50 to 60 years, compared with 4% of donors in this age category in 1990. Use of allografts from donors aged 60 years or older remains unusual, but the number of donors in this age category has also been slowly rising: individuals in this age group were donors for 76 transplants (2%) in 2009. There are substantial geographic variations in the use of older donors; in Europe, 22% of donors are 50 years or older, a much higher proportion than in other locations (Figure 6). It is possible that shorter distances between donor and recipient hospitals, the mode of allocation, or other factors that result in shorter allograft ischemic times in Europe (Figure 7) facilitate transplantation of organs from older donors. Additional donor characteristics are presented in Table 2.

Combined organ transplantation

The number of simultaneous combined organ transplants has been gradually increasing; however, the absolute number of these transplants remains low (Figure 8). During the last 5 years, the Registry received reports of 334 heart-kidney, 51 heart-liver, 4 heart-kidney-liver, and 2 heart-kidney-pancreas transplants. Heart-lung transplants are not included in this figure.

Immunosuppression

Immunosuppressive induction therapy continues to be used frequently. In the first 6 months of 2010, 52% of patients received immunosuppressive induction (Figure 9). Interleukin-2 receptor (IL-2R) antagonists were used in 30% of patients, polyclonal anti-lymphocytic antibodies were used in 20%, and induction with alemtuzumab was used in 3% of patients. Use of OKT3 has become negligible. Interestingly, there are marked geographic variations in the use of immunosuppressive induction therapy. In Europe, induction therapy is used in 76% of patients, and polyclonal anti-lymphocytic antibodies are the preferred induction agents. In North America, induction therapy is used in 51% of patients and is more evenly split between IL-2R antagonists and polyclonal antibodies (Figure 10).

Significant changes have also occurred during the past 10 years in the use of maintenance immunosuppression therapy. Immunosuppressive therapy used at 1 year after transplant in 3 groups of patients who received allografts at different times during the last 10 years is shown in Figure 11. Tacrolimus is now the dominant calcineurin inhibitor, and its use increased from 23% in 2000 to 73% in 2009 through June 2010. The use of cyclosporine has decreased below 20%. Mycophenolate mofetil (MMF)/

Table 1 Recipient Characteristics at the Time of Transplant for Two Eras: 1992 Through 2001 and 2002 Through June 2010[g]

Variable[a]	1992–2001 (n = 39,812)	2002–June 2010 (n = 27,387)	p-value
Pre-transplant diagnosis			<0.0001
Ischemic cardiomyopathy	45.7	39.5	
Non-ischemic cardiomyopathy	46.4	51.6	
Valvular cardiomyopathy	3.7	3.0	
Retransplant	1.9	2.4	
Congenital heart disease	1.9	2.8	
Other causes	0.4	0.7	
Age, years	54.0 ± 11.0 (28.0–65.0)	54.0 ± 12.4 (25.0–67.0)	0.5756
Female sex	19.5	22.8	<0.0001
Weight, kg	75.0 ± 16.7 (51.7–102.1)	78.0 ± 17.2 (53.0–108.8)	<0.0001
Height, cm	173.0 ± 11.3 (157.0–188.0)	175.0 ± 10.7 (157.5–188.0)	<0.0001
Body mass index, kg/m^2	25.0 ± 4.3 (18.9–32.8)	25.8 ± 4.7 (19.2–34.4)	<0.0001
History of cigarette use	. . .[b]	46.9[b]	. . .
Comorbidities			
Diabetes mellitus	14.5[b]	22.7	<0.0001
Hypertension	34.6[b]	40.9	<0.0001
Peripheral vascular disease	3.9[b]	3.0	<0.0001
Chronic obstructive pulmonary disease	3.2[b]	3.6	0.0601
Prior malignancy	3.5[b]	5.3	<0.0001
Prior cardiac surgery	. . .[b]	43.0[b]	. . .
Serum creatinine (mg/dl)	1.2 ± 9.7 (0.7–2.5)	1.2 ± 0.9 (0.7–2.3)	0.0001
Pulmonary vascular resistance (WU)	2.1 ± 2.2 (0.4–6.0)[c]	2.1 ± 2.0 (0.3–5.6)	<0.0001
Panel reactive antibody > 10%[d]			
Overall (US 1992–6/2004, non-US 1992–6/2010)	7.8	9.2	0.0016
Class I (US 6/2004–6/2010)		13.3	
Class II (US 6/2004–6/2010)		9.0	
Hospitalized at time of transplant	58.7	46.0	<0.0001
Mechanical ventilation	3.5	3.0	0.0065
Pre-op inotropic/circulatory support			
Intravenous inotropes	55.3[b]	44.8	<0.0001
Intra-aortic balloon pump	6.7	6.7	0.7815
Left ventricular assist device	1.7[d]	19.0	<0.0001
Right ventricular assist device	. . .	4.1[f]	. . .
Total artificial heart	0.1[d]	0.5	<0.0001
Extracorporeal membrane oxygenation	0.3[e]	0.8	<0.0001
Donor/recipient HLA mismatches			0.0003
0–2	4.8	4.2	
3–4	41.6	40.4	
5–6	53.6	55.4	
Allograft ischemic time, hours	2.6 ± 1.5 (0.0–4.6)	3.0 ± 1.5 (0.0–5.0)	<0.0001

HLA, human leukocyte antigen; US, United States; WU, Woods units.

[a]Data are expressed as median ± standard deviation (5th–95th percentiles) or percentages.

[b]Data available for 7/2004–6/2010 transplants.

[c]Data available for 4/1994–2001 transplants.

[d]Until mid-2004, panel reactive antibody was collected in the US as a single percentage. After this date, panel reactive antibody was collected separately for class I and class II antibodies.

[e]Data available for 11/1999–2001 transplants.

[f]Data available for 4/1995–2001 transplants.

[g]Based on 2005–6/2010 transplants.

mycophenolic acid (MPA) were used in 85% of patients in 2009 to June 2010, and azathioprine in only 3%. The use of sirolimus peaked at 15% in 2003. The 2 clinically used mammalian target of rapamycin (mTOR) inhibitors—sirolimus and everolimus—were used in 8% of patients in 2009 through June 2010. Most patients also remain on prednisone therapy. However, the proportion of patients weaned from prednisone within 1 year of transplant has increased: Specifically, in 2000, only 6% of patients had been weaned from prednisone at 1 year after transplant compared with 20% not taking prednisone at 1 year after transplant in 2009 through June 2010.

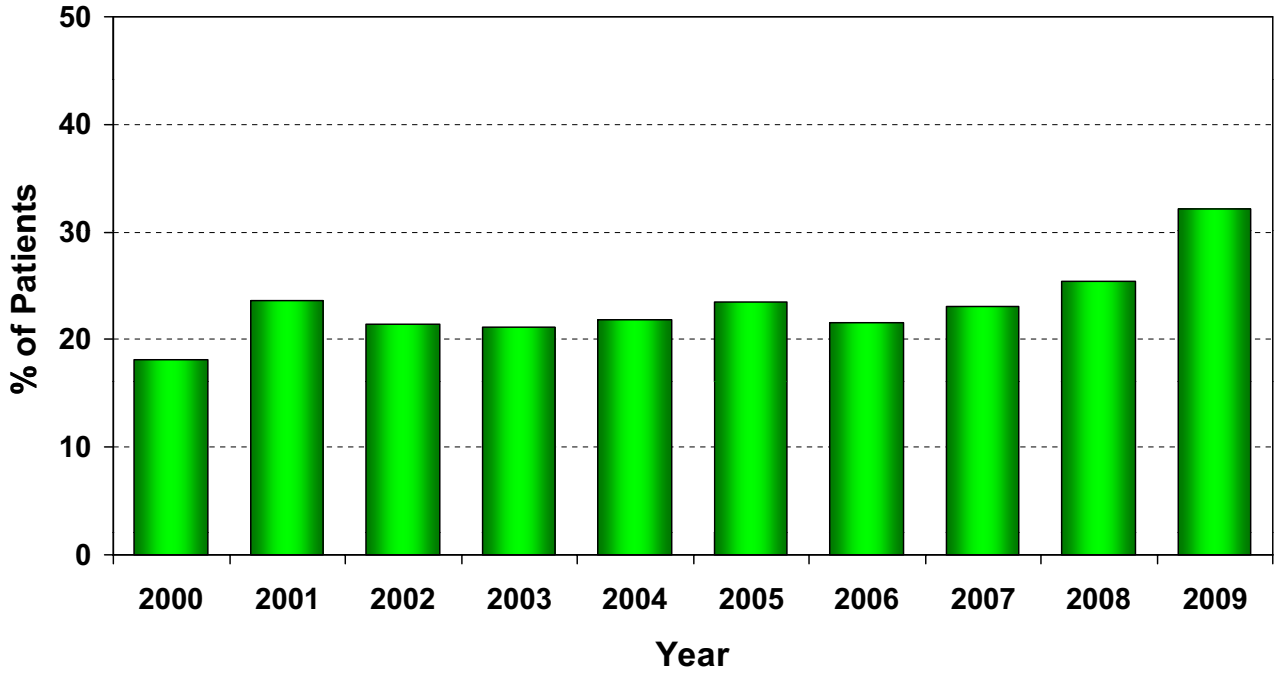

Figure 5 Adult patients bridged to heart transplantation with mechanical circulatory support by left ventricular assist device (LVAD), right ventricular assist device (RVAD) or biventricular support (LVAD + RVAD, total artificial heart).

Among patients reaching 5-year follow-up between January 2007 and June 2010, 49% had been weaned from prednisone.[9]

Post-transplant outcomes

Survival

The median survival or half-life (the time at which 50% of transplant recipients remain alive) is 11 years for the entire cohort of adult and pediatric heart recipients who received allografts since the initiation of the Registry in 1982. For adult and pediatric patients surviving to 1 year after transplant, the median survival has reached 14 years. Almost 100 patients have now lived past 25 years since their transplant procedure.

Post-transplant survival of adult heart transplant recipients continues to improve (Figure 12A). The first year after transplant continues to represent the period with the highest risk of death. Reduction in mortality during this critical period is mostly responsible for the improved survival seen after heart transplantation in the more recent eras. The mortality rate beyond 1 year after transplant has improved only marginally for patients who received allografts after 1992, and there has been no statistically significant improvement in the past 2 decades (Figure 12B). This fairly constant mortality rate of approximately 3 to 4 percentage points per year is higher than that of a general population and it is therefore reasonable to hypothesize that further improvements in post-transplant survival are likely to result from interventions aimed at the processes responsible for this long-term mortality.

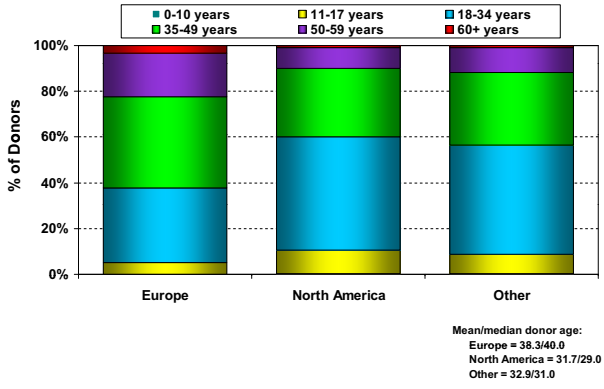

Figure 6 Donor age distribution by geographic location for adult heart transplants that occurred from January 2000 through June 2010. Mean/median donor age: Europe = 38.3/40.0; North America = 31.7/29.0; other = 32.9/31.0.

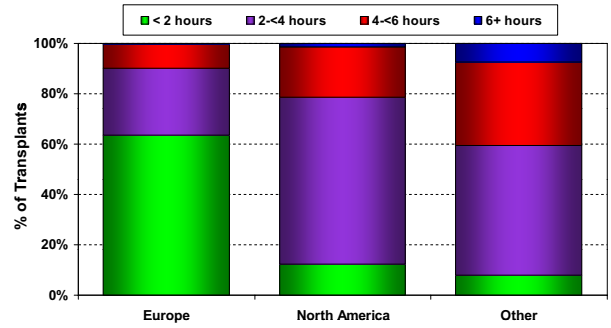

Figure 7 Allograft ischemic time distribution in different geographic locations for adult heart transplants from January 2000 through June 2010.

Table 2 Donor Characteristics at the Time of Transplant for Two Eras: 1992 Through 2001 and 2002 Through June 2010

Donor variable[a]	1992–2001 (n = 39,812)	2002–June 2010 (n = 27,387)	p-value
Cause of death			<0.0001
Head trauma	45.7	50.2	
Stroke	28.5	28.8	
Other	25.8	21.1	
Age, years	31.0 ± 12.8 (15.0–54.0)	34.0 ± 13.1 (16.0–56.0)	<0.0001
Female sex	31.6	30.5	0.0030
Weight, kg	75.0 ± 17.6 (52.0–103.9)[b]	78.0 ± 17.1 (55.6–110.0)	<0.0001
Height, cm	175.0 ± 18.9 (155.0–188.0)[b]	175.0 ± 10.3 (159.0–190.0)	<0.0001
Body mass index, kg/m^2	24.2 ± 4.5 (18.8–33.0)[b]	25.2 ± 4.9 (19.7–35.4)	<0.0001
History of cigarette use	37.5[b]	23.6	<0.0001
History of hypertension	10.8[b]	12.4	<0.0001

[a]Data are expressed as median ± standard deviation (5th–95th percentiles) or percentages.
[b]Data are available for April 1994–2001 transplants.

Additional analyses available in the online Registry data set[9] explore survival in different recipient age groups as well as in patients stratified by etiology of heart disease leading to the need of transplant. Overall, these analyses show that the improvement in survival has been realized across all recipient ages and across the different heart disease categories. The more recent cohort of patients who received allografts between January 2002 and June 2009 demonstrates smaller differences in survival as a function of recipient age: the survival of patients aged 30 to 39 years is not statistically different from those aged 40 to 49 or 50 to 59 years. Although the survival of the other age groups—18 to 29, 60 to 69, and ≥ 70 years—is statistically worse than in the former 3 age groups, these differences are less pronounced than in previous eras.

The etiology of heart disease leading to transplantation remains an important predictor of survival, even in the more recent cohort of patients underwent transplantation between January 2002 and June 2009 (Figure 13). Those who undergo transplantation for non-ischemic cardiomyopathy have the best survival, followed by those with ischemic cardiomyopathy. Survival of patients who receive allografts because of congenital heart disease, valvular cardiomyopathy, and those in need of retransplant is inferior to the former 2 groups, with the survival differences again being limited to the first post-transplant year.[9]

A number of analyses exploring the effect of bridging to transplantation with mechanical assist devices on post-transplant survival are presented in the online Registry data set.[9] A survival analysis that included patients who received allografts between January 2002 and June 2009 demonstrated that patients bridged with both pulsatile-flow and continuous-flow LVADs had worse post-transplant survival than patients who did not require an LVAD bridge to transplant. The excess mortality appeared to be limited to the first 6 months after transplant, with 6-month survivors having

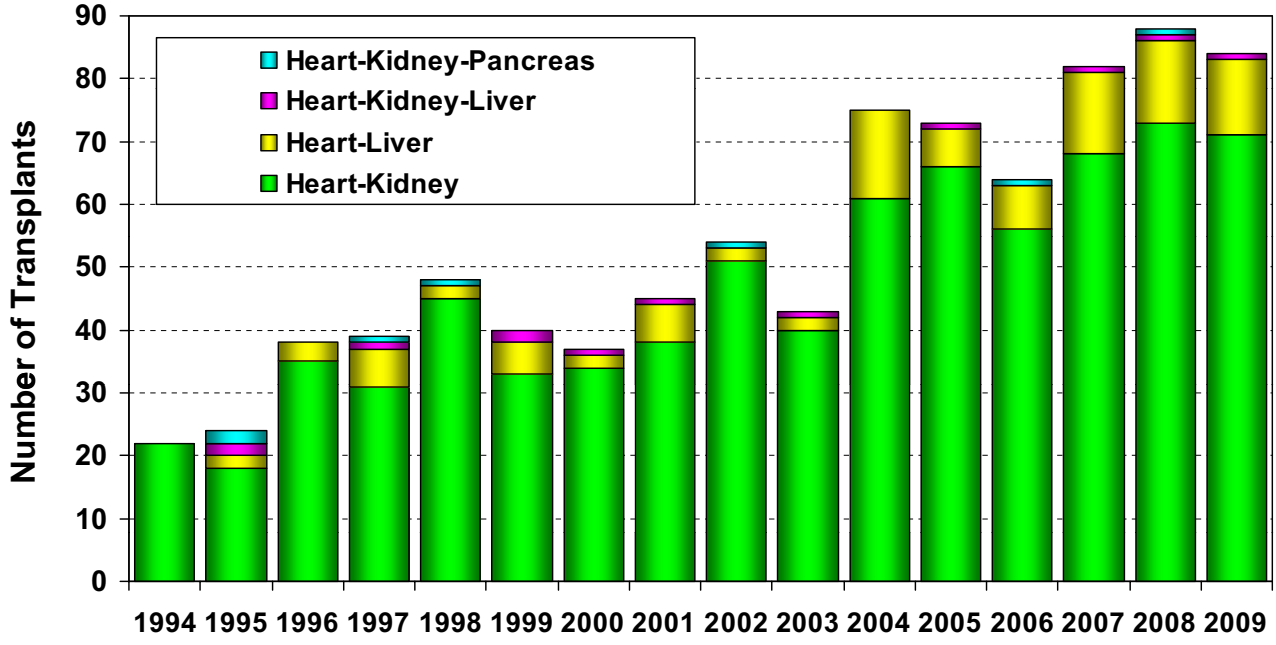

Figure 8 Combined heart and other solid-organ transplants in adults (excluding heart-lung transplants).

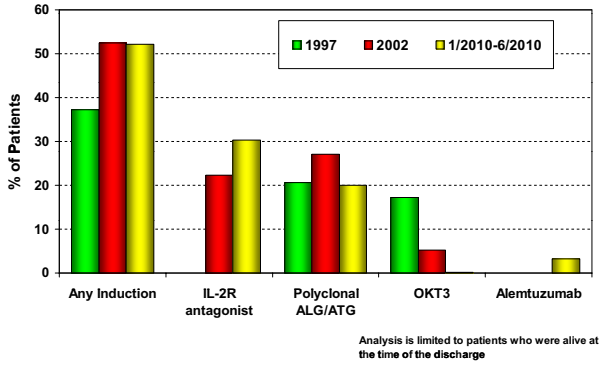

Figure 9 Immunosuppressive induction therapy for adult heart transplant recipients from 1997, 2002, and January through June 2010. IL, interleukin; ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin. Analysis is limited to patients who were alive at the time of the discharge.

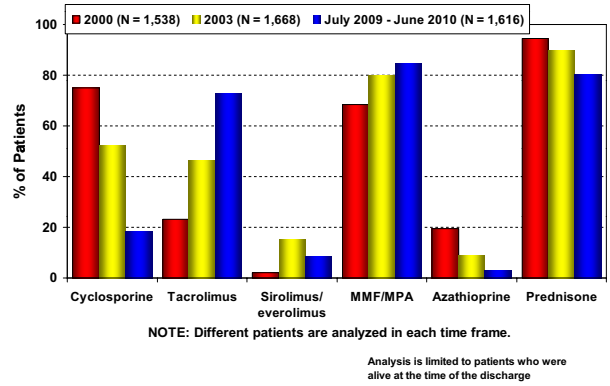

Figure 11 Maintenance immunosuppressive agents at 1 year after transplant for adult heart recipients. One year follow-up reported for 2000, 2003, and July 2009 to June 2010. MMF, mycophenolate mofetil; MPA, mycophenolic acid. Note: Different patients are analyzed in each time frame. Analysis is limited to patients who were alive at the time of the discharge.

equivalent survival to up to 7 years after transplant. An analysis that focused on the most recent cohort of patients—those who received allografts between July 2004 and June 2009—showed that there was no longer a statistically significant difference in survival of patients bridged with pulsatile-flow or continuous-flow VADs compared with patients not requiring LVAD bridging. Patients requiring a bridge with biventricular pulsatile support, however, had markedly increased mortality, with a 1-year survival of 79% and 5-year survival of 62% (Figure 14).

Mortality

Risk factors for 1-year mortality. We performed a multivariable analysis using a proportional hazards model to analyze risk factors for mortality at 1 year after transplant in contemporary patients who underwent transplantation between January 2004 and June 2009 (Table 3). Categoric risk factors are ordered by strength of their association with mortality (RR). The number of patients with the particular characteristic is also listed along with each of the variables to provide further insight into the clinical relevance of the individual factors. Continuous risk factors are also considered, and a set of graphs in the online Registry slide set describes RRs associated with the different values of the continuous variables.[8]

Donor characteristics associated with 1-year post-transplant survival include donor age, donor weight, and anoxia as donor cause of death. Allograft ischemic time also remains a strong predictor of 1-year mortality (Figure 15). The remaining predictors of 1-year mortality are recipient characteristics and transplant center volume. Need for temporary mechanical support before transplant markedly increases the risk of 1-year mortality: the RR is 3.32 for extracorporeal membrane oxygenation (ECMO) and Abiomed BVS (Abiomed Inc, Danvers, MA) temporary support ($p < 0.0001$), and 2.1 for temporary continuous-flow LVAD support ($p = 0.02$). The need for bridging with total artificial heart also represents a risk for 1-year mortality (RR, 1.82; $p = 0.04$). Although need for a bridge with long-term continuous-flow or pulsatile-flow VAD in a recent cohort of patients was not associated with increased mortality in the univariable survival analysis described above, adjustment in this multivariable model did attribute excess risk of 1-year mortality for chronic continuous-flow VAD (RR, 1.48; $p < 0.01$) and pulsatile-flow VAD (RR, 1.34; $p \leq 0.01$).

Whether the multivariable model is more accurate in determining the risk of a mechanical assist device than a univariable survival analysis requires careful consideration. This is because the multivariable adjustment uses variables recorded at the time of transplant rather than when the assist device is implanted because recipient characteristics may be altered by the LVAD placement, and finally, because the characteristics used in the multivariable adjustment may be correlated with mechanical assist use. Regardless of the statistical method used, however, the need for LVAD bridging with long-term devices appears to confer a lower risk of post-transplant death in patients who receive transplants in more recent years compared with a more remote experience. Also, it is important to remember that our analyses examine

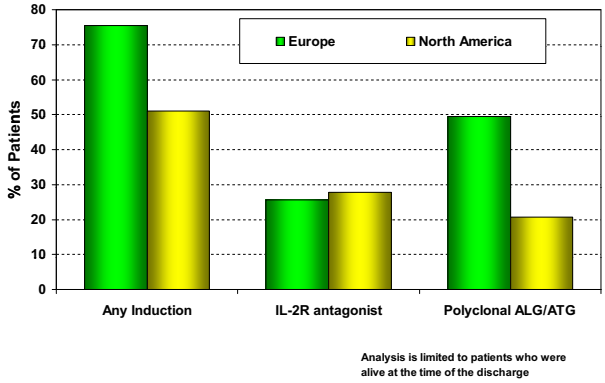

Figure 10 Immunosuppressive induction therapy for adult heart transplant recipients by geographic location for transplants from January 2002 through June 2010. IL, interleukin; ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin. Analysis is limited to patients who were alive at the time of the discharge.

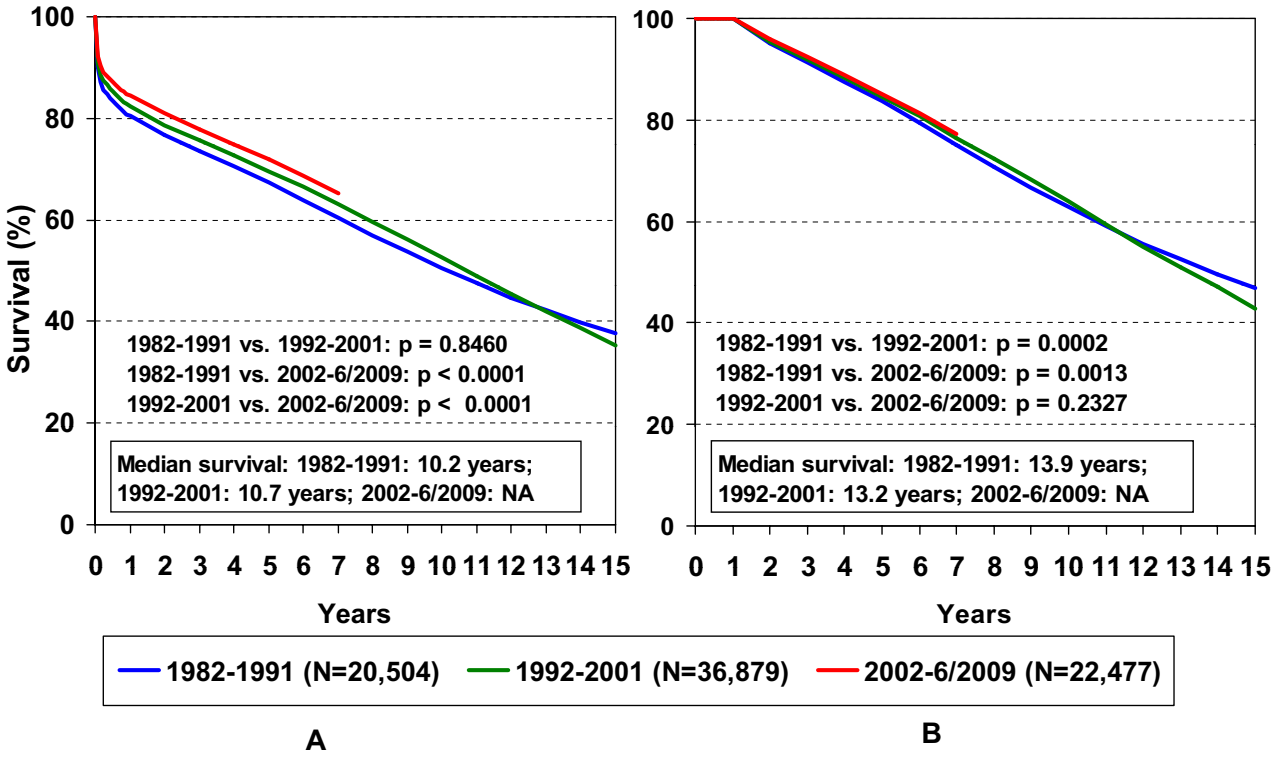

Figure 12 (A) Survival and (B) survival conditional on surviving to 1 year after transplant for adult heart transplants performed between January 1982 and June 2009, stratified by era of transplant.

post-transplant survival, and that the effect of VAD use during the pre-transplant period cannot be assessed with this data set.

Additional recipient characteristics associated with increased risk of 1-year mortality are recipient age, congenital and ischemic etiology of cardiomyopathy, previous heart transplant, and the presence of certain comorbidities, such us history of dialysis, elevated serum creatinine and bilirubin, allosensitization, and others (Table 3).

Risk factors for 5-year mortality. We used multivariable analysis to examine risk factors for 5-year mortality in patients who underwent transplantation between January 2000 and June 2005. Many of the 5-year mortality risk factors identified are similar to those affecting 1-year post-transplant survival (detailed data included in the online Registry slide set[9]). Recipient history of pregnancy (RR, 1.26; $p < 0.01$), recipient hepatitis B core positive serology (RR, 1.25; $p = 0.02$), higher number of mismatches at A locus (RR, 1.24; $p < 0.01$), inpatient status at time of transplant (RR, 1.13; $p < 0.01$), recipient history of diabetes (RR, 1.17; $p \leq 0.01$), and female allograft allocation to a male recipient (RR, 1.13; $p = 0.03$) were additional clinical variables associated with 5-year mortality but not affecting 1-year survival.

Using data of the same patient cohort, we also performed a multivariable analysis of 5-year survival, conditional on survival to 1 year after transplant. This approach allowed us to separate factors associated with the high hazard of death during the first year after transplant from factors responsible for a more long-term mortality risk. In addition to the factors identified in the 1-year and 5-year multivariable

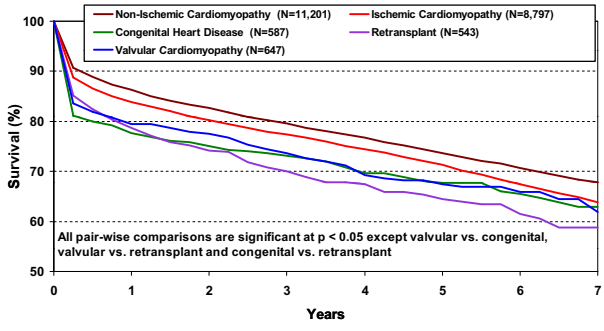

Figure 13 Survival for adult heart transplant recipients by diagnosis for transplants from January 2002 through June 2009.

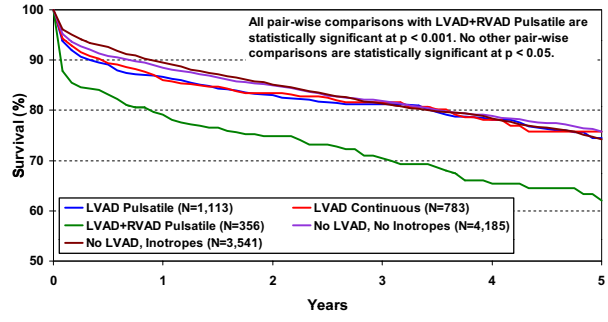

Figure 14 Survival of adult heart transplant recipients by ventricular assist device (VAD) usage for transplants occurring from July 2004 through June 2009) LVAD, left VAD; RVAD, right VAD.

Table 3 Risk Factors for Death Within 1 Year of Transplant for Transplants From January 2004 Through June 2009 ($N = 10,271$)

Variable	No.	RR (95% CI)	*p*-value
Categoric variables			
Temporary circulatory support[a]	180	3.32 (2.46–4.48)	<0.0001
Diagnosis: congenital vs non-ischemic cardiomyopathy	271	2.23 (1.67–2.97)	<0.0001
Temporary continuous-flow device	31	2.10 (1.12–3.92)	0.0204
Total artificial heart	58	1.82 (1.04–3.20)	0.0365
Recipient history of dialysis	256	1.72 (1.35–2.19)	<.0001
Recipient supported by ventilator at time of transplant	285	1.59 (1.22–2.07)	0.0006
Previous transplant	298	1.51 (1.14–2.01)	0.0046
Chronic continuous-flow device	731	1.48 (1.18–1.87)	0.0008
Chronic pulsatile-flow device	1,401	1.34 (1.11–1.62)	0.0022
Prior transfusion	2,056	1.26 (1.08–1.46)	0.0032
Recipient infection requiring IV drug therapy ≤ 2 weeks pre-transplant	1,021	1.23 (1.03–1.46)	0.019
Donor cause of death: anoxia vs head trauma	1,146	1.22 (1.02–1.45)	0.0275
Diagnosis: coronary artery disease vs cardiomyopathy	4,257	1.19 (1.04–1.36)	0.0126
Balloon pump	578	0.71 (0.55–0.91)	0.0062
Continuous variables			
Recipient age			<0.0001
Recipient height			<0.0001
Recipient weight			0.0064
Donor age			<0.0001
Donor weight			0.0147
Transplant center volume			0.0378
Allograft ischemic time			<0.0001
Serum bilirubin			<0.0001
Serum creatinine			<0.0001
Panel reactive antibody			0.0203
Pulmonary capillary wedge pressure			0.0075
Pulmonary vascular resistance			0.0067

CI, confidence interval; IV, intravenous; RR, relative risk.
[a]Includes extra-corporeal membrane oxygenation and Abiomed BVS. There were too few temporary continuous-flow devices to analyze.

models, risk factors for 5-year mortality in patients surviving to 1 year after transplant were dialysis or infection after transplant, rejection during the first post-transplant year, and lack of immunosuppression therapy with a combination of at least 2 of the following classes: cell cycle inhibitors, calcineurin inhibitors, and mTOR inhibitors (Table 4).

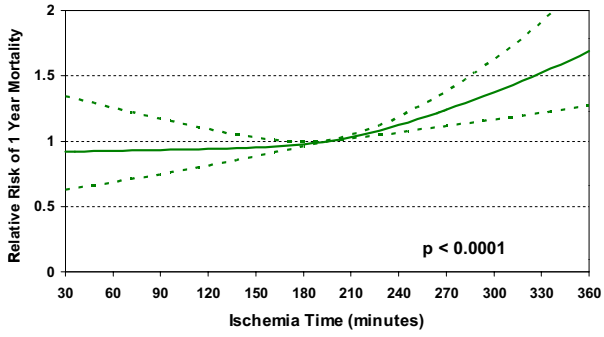

Figure 15 Allograft ischemic time and relative risk of mortality at 1 year after transplant for the era January 2004 through June 2009.

Risk factors for 10-, 15- and 20-year mortality. Patients included in the analysis for death at 10, 15, and 20 years received allografts in 1995 to June 2000, 1990 to June 1995, and between 1985 and 1990, respectively. Generalizing these results to the care of the patients receiving allografts today must be done with caution because many processes of care have changed since the studied patients underwent transplantation. In addition, the variables collected in the earlier eras were less comprehensive than today, and some mortality risk factors may therefore not have been identified in our analysis. Despite these limitations, we believe these data provide important insights into the factors favorable to long-term survival after heart transplantation.

A number of factors predictive of 10-year mortality are similar to those predictive of 1-year and 5-year mortality

Table 4 Risk Factors for Death Within 5 Years of Transplant, Conditional on Survival to 1 Year For Transplants Performed January 2000 Through June 2005 ($N = 9,189$)

Variable	No.	RR (95% CI)	*p*-value
Categoric variables			
No cell cycle inhibitor or mTOR inhibitor at 1 year post-transplant	768	1.60 (1.32–1.94)	<0.0001
Rejection between discharge and 1 year	2,675	1.53 (1.36–1.72)	<0.0001
HLA mismatches at A locus (per mismatch)		1.41 (1.17–1.71)	0.0003
0A	559		
1A	4,664		
2A	3,966		
Recipient history of dialysis before transplant	214	1.41 (1.05–1.89)	0.0242
Dialysis after transplant	511	1.35 (1.09–1.67)	0.0052
Recipient hepatitis B core (+)	333	1.34 (1.04–1.73)	0.0221
Prior pregnancy	1,304	1.27 (1.01–1.60)	0.0445
Recipient history of diabetes	1,786	1.26 (1.10–1.44)	0.0007
Treated for infection after transplant	1,916	1.25 (1.09–1.42)	0.0010
Diagnosis: coronary artery disease vs cardiomyopathy	4,257	1.22 (1.07–1.40)	0.0025
Rejection before discharge	1,433	1.16 (1.01–1.34)	0.0416
Hospitalized (including intensive care unit) at transplant	4,390	1.13 (1.01–1.27)	0.0327
Chronic pulsatile-flow device	1,487	0.85 (0.72–0.99)	0.0391
Continuous variables			
Recipient age			<0.0001
Recipient body mass index			0.0368
Donor age			<0.0001
Pulmonary vascular resistance			0.0124
Serum creatinine at transplant			0.0039

CI, confidence interval; mTOR, mammalian target of rapamycin; RR, relative risk.

(Table 5). In addition, donor history of hypertension and need for inotrope use in a recipient at the time of transplant also confer a modestly increased risk of death at 10 years after transplant.

A sufficient number of patients have now survived more than 20 years after transplant to allow for a robust mortality analysis. The results of a multivariable analysis of 15-year mortality, which included 10,342 recipients who received allografts between 1990 and June 1995, and the analysis of 20-year mortality, which included 13,578 patients who received allografts between 1985 and June 1990, are presented in Table 5. In addition to transplant year, etiology of heart disease leading to transplantation influences 20-year survival. Specifically, patients receiving re-transplant and those receiving transplant for ischemic heart disease or valvular heart disease have a lower likelihood of survival past 20 years after transplant compared with patients who receive an allograft for non-ischemic cardiomyopathy (RR, 3.18, 1.38, and 1.11, respectively). Women also have a somewhat higher risk of death compared with their male counterparts (RR, 1.11, $p < 0.01$). Younger donor age, younger recipient age, lower allograft ischemic time, and higher center volume are additional factors associated with long-term survival.

Many risk factors for 1-, 5-, 10-, and 15-year mortality have been observed in transplantation cohorts from different eras. However, the RR of death associated with some of these characteristics has changed significantly over the years. There are also a number of other clinical variables that no longer have an association with death. In this context, it is important to note that evolving clinical practice has major effects on the effect of risk factors on post-transplant survival. Organ allocation is not a random process, and identification of risk factors through analyses such as these hopefully results in modification of clinical practice. Targeted allocation decisions made by transplant clinicians intend to mitigate the risks associated with certain characteristics on post-transplant survival. Advances in post-transplant therapies also influence the long-term outcome. As a result, characteristics such as recipient sex, recipient history of malignancy, or donor-recipient cytomegalovirus mismatch appear to have much less effect on long-term survival in patients who received allografts recently compared with patients who underwent transplantation more than a decade ago.

Causes of death

As discussed, the first year after transplantation represents a period of high mortality risk for heart transplant recipients. Graft failure, infection, multiple organ failure, and rejection are the leading causes of death during this period (Figure 16). Past 1 year after transplant, the risk of mortality remains fairly constant and higher than that of a general population. Better understanding of the processes responsible for death during this period may help in defining treatment approaches that could lead to improved long-term survival. Figure 16 shows the relative incidence of the leading causes of death during 15 years after transplant. These data are based on cause of death information in

Table 5 Risk Factors for Mortality Within 10, 15 and 20 Years of Transplant

Variable	No.	RR (95% CI)	p-value
Predictors of 10-year mortality: transplant era 7/1995–6/2000	11,861		
Categoric variables			
Repeat transplant	288	1.56 (1.32–1.84)	<0.0001
Recipient on dialysis	213	1.49 (1.24–1.78)	<0.0001
Ventilator support at time of transplant	365	1.36 (1.17–1.59)	<0.0001
Panel reactive antibody > 20%	601	1.28 (1.14–1.44)	<0.0001
Diagnosis: coronary artery disease vs cardiomyopathy	5,997	1.24 (1.16–1.32)	<0.0001
Recipient history of diabetes	1,863	1.23 (1.15–1.33)	<0.0001
Recipient infection requiring IV drug therapy ≤ 2 weeks pre-transplant	949	1.23 (1.12–1.36)	<0.0001
Year of transplant: 1995 vs 1999/2000	2,125	1.21 (1.11–1.31)	<0.0001
Female recipient/male donor vs male recipient/male donor	1,265	1.19 (1.06–1.33)	0.0021
Receiving ventricular assist device support at time of transplant	1,355	1.19 (1.09–1.30)	0.0001
Year of transplant: 1996 vs 1999/2000	2,143	1.15 (1.06–1.26)	0.0008
Mismatches at B locus (per mismatch)		1.13 (1.01–1.27)	0.0356
0B	241		
1B	2,760		
2B	8,860		
Donor history of hypertension	1,275	1.12 (1.02–1.22)	0.0150
Inotropes at time of transplant	6,210	1.07 (1.01–1.13)	0.0288
Continuous variables			
Recipient age			<0.0001
Recipient weight			<0.0001
Recipient height			0.0011
Donor age			<0.0001
Allograft ischemic time			<0.0001
Serum creatinine at transplant			<0.0001
Serum bilirubin at transplant			0.0012
Transplant center volume			<0.0001
Predictors of 15-year mortality: transplant era 1/1990–6/1995	10,342		
Categoric variables			
Retransplant	266	2.13 (1.82–2.48)	<0.0001
Ventilator support	306	1.38 (1.18–1.62)	<0.0001
Number of HLA mismatches at the DR locus		1.35 (1.23–1.49)	<0.0001
0 DR	573		
1 DR	5,327		
2 DR	4,442		
Recipient hepatitis B core (+)	197	1.35 (1.12–1.63)	0.002
Male recipient/female donor vs male recipient/male donor	2,075	1.17 (1.06–1.29)	0.0018
Transplant year: 1991 vs 1994/1995	1,842	1.12 (1.02–1.22)	0.0155
Transplant year: 1992 vs 1994/1995	1,881	1.12 (1.02–1.22)	0.0192
Diagnosis: coronary artery disease vs cardiomyopathy	5,087	1.11 (1.04–1.19)	0.0023
Continuous variables			
Recipient age			<0.0001
Donor age			<0.0001
Recipient weight			0.0077
Recipient height			<0.0001
Recipient serum creatinine			<0.0001
Allograft ischemic time			0.0001
Panel reactive antibody			0.0087

Continued on page 1090.

Table 5 Continued from page 1089.

Variable	No.	RR (95% CI)	p-value
Predictors of 20-year mortality: transplant era 1/1985–6/1990	13,578		
Categoric variables			
Retransplant	253	3.18 (2.75–3.68)	<0.0001
Transplant year: 1985 vs 1989/1990	1,057	1.61 (1.47–1.76)	<0.0001
Diagnosis: coronary artery disease vs cardiomyopathy	2,910	1.38 (1.25–1.52)	<0.0001
Transplant year: 1986 vs 1988/1990	2,003	1.18 (1.11–1.25)	<0.0001
Transplant year: 1987 vs 1988/1990	2,565	1.17 (1.08–1.26)	0.0001
Female recipient	2,170	1.11 (1.04–1.20)	0.0032
Diagnosis: valvular heart disease vs cardiomyopathy	563	1.11 (1.04–1.19)	0.0024
Continuous variables			
Recipient age			<0.0001
Donor age			<0.0001
Allograft ischemic time			0.0134
Center volume			<0.0001

CI, confidence interval; HLA, human leukocyte antigen; IV, intravenous; RR, relative risk.

patients who died between January 2000 and June 2010. Between 1 and 3 years after transplant, acute rejection is responsible for 9% of deaths. Past 3 years after transplant, death as a result of acute rejection becomes unusual. Infection is a frequent cause of death between 1 and 3 years after transplant, being responsible for approximately 30% of deaths, and remains an important cause of death past 3 years after transplant. Approximately 20% of deaths past 1 year after transplant are due to "graft failure." This descriptive diagnosis is used when the exact cause of heart failure is not known, which to some degree reflects the lack of our full understanding of chronic graft injury. Past 1 year after transplant, graft failure likely results from processes such as antibody-mediated rejection and cardiac allograft vasculopathy (CAV). The proportion of deaths confirmed to be caused by CAV is approximately 10% between 1 and 3 years after transplant, with increases further in subsequent years. Another prominent diagnosis leading to death is malignancy, responsible for 11% of deaths between 1 and 3 years after transplant, and becoming the most likely cause of death after 5 years post-transplant. Renal failure also becomes a frequent cause of death, accounting for 8% of deaths past 10 years after transplant. The distribution of the less frequent diagnoses leading to death is further explored in the online Registry data set.[9]

It is evident that deaths from what could be considered a result of over-immunosuppression (infection, malignancy) and deaths from what could be interpreted as ineffective

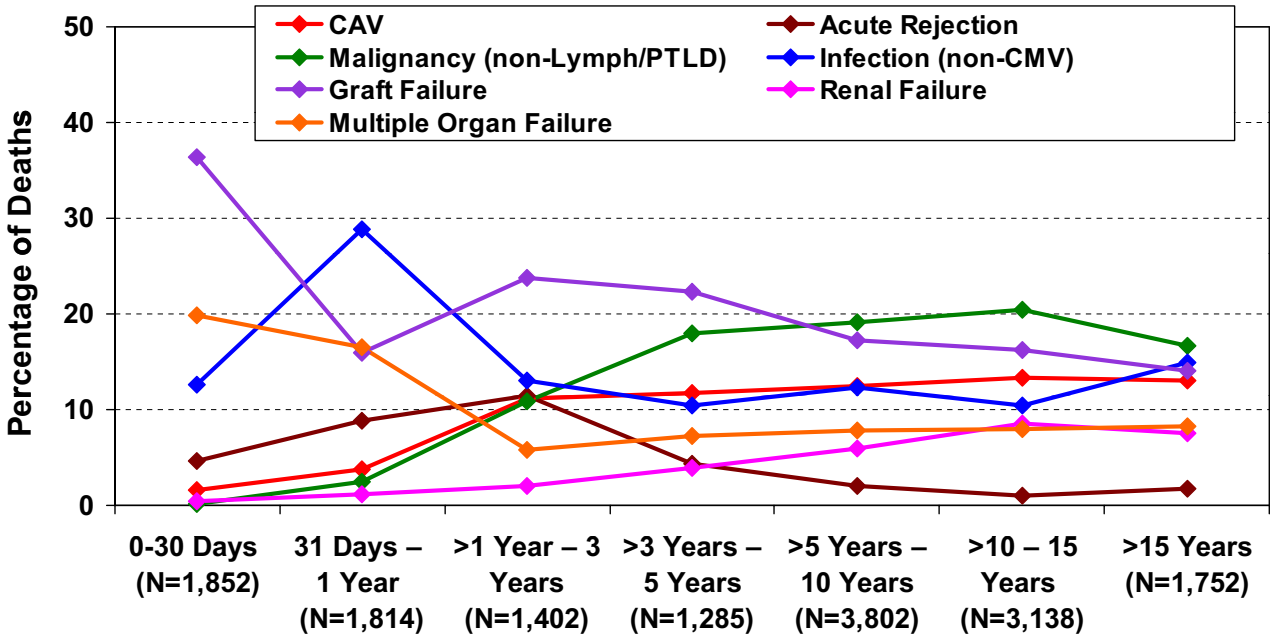

Figure 16 Relative incidences of the leading causes of post-transplant death in adult heart allograft recipients from January 2000 through June 2010. CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; PTLD, post-transplant lymphoproliferative disorder.

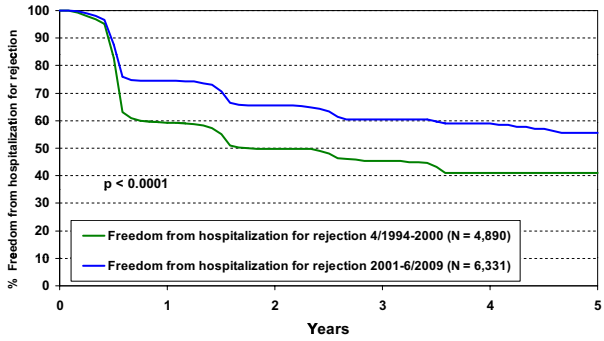

Figure 17 Freedom from hospitalization for rejection for adult heart transplant recipients by era for transplants from April 1994 through June 2009.

immunosuppression (rejection, CAV, late graft failure) are both prominent causes of death. It is conceivable that approaches able to quantify individual recipient risk for certain clinical events, such as rejection or infection, could allow us to make targeted adjustments to immunosuppressive strategy aimed at decreasing patient morbidity and, ultimately, increasing survival. Of course, the efficacy of such approaches needs rigorous testing.

Post-transplant morbidity

Acute allograft rejection

Interpretation of allograft rejection data needs to take into account certain limitations. The Registry has collected information on the incidence of rejection requiring hospitalization since 1994. Since 2004, more detailed rejection data are available, including information on whether the rejection episode was confirmed with a myocardial biopsy specimen and whether an additional anti-rejection agent was used to treat the rejection episode. In addition, we are not able to distinguish between cellular and antibody-mediated rejection.

The incidence of rejection requiring a hospitalization has significantly decreased. Among patients who underwent transplant between April 1994 and 2000, the need for hospitalization for treatment of rejection within 1 and 5 years after transplant was 41% and 59%, respectively. In a more recent cohort of who received allografts between 2001 and June 2009, hospitalization for rejection treatment occurred in 26% of patients within 1 year and in 44% of patients within 5 years after transplant (Figure 17).

In a cohort of patients who underwent transplant between July 2004 and June 2010, younger recipients were at a higher risk of rejection. Similarly, female recipients had a higher risk of rejection than male recipients.[9]

There are also differences in the risk of rejection as it relates to the immunosuppressive therapy used. Data regarding the effect of immunosuppressive therapies on the risk of rejection have to be interpreted with caution because their use is often tailored to the risk of rejection in an individual patient. Nevertheless, overall, patients treated with tacrolimus in combination with MMF/MPA had a lower incidence of rejection than those who received cyclosporine, and this finding was consistent across a wide range of patient demographics.[9] Patients receiving immunosuppressive induction therapy also had a higher risk of rejection between discharge and 1 year after transplant compared with patients not receiving induction therapy—31% in polyclonal antibody induction, 35% in IL-2R antagonist induction, and 28% in no induction ($p < 0.05$). However, this difference may have resulted from selective use of immunosuppressive agents in patients with a known elevated risk of rejection.

Patients who required treatment for acute rejection in the first year after transplant, and survived until 1 year after transplant, still had a worse long-term survival than those who did not have rejection during the first post-transplant year (78% vs 87% at 5 years, respectively; $p < 0.001$).

Cardiac allograft vasculopathy

CAV is responsible for a significant proportion of deaths after transplant, and its contribution to mortality increases with time from transplant (Figure 16). There has been a small decrease of approximately 2 to 4 percentage points in the cumulative incidence of CAV in patients who underwent transplant between 2001 and June 2009 compared with those between April 1994 and 2000 ($p < 0.0001$, Figure 18). Despite this improvement, the prevalence of CAV remains high—20% at 3 years, 30% at 5 years, and 45% at 8 years after transplant.

We also performed a multivariable analysis that explored risk factors for developing CAV within 8 years of transplant, including patients who received allografts between 1998 and June 2002 (Table 6). The characteristics that affect the risk of CAV development include a number of donor characteristics, recipient characteristics, and use of certain medications after transplant. Donor characteristics associated with CAV risk include higher age, male sex, higher body surface area, history of hypertension, history of infection, and cause of death. Recipient characteristics associated with CAV include history of ischemic heart disease, VAD implant before transplant, and history of infection. Immu-

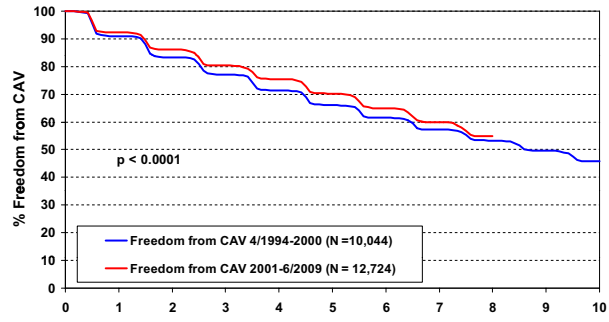

Figure 18 Freedom from cardiac allograft vasculopathy for adult heart recipients for transplants done from April 1994 through June 2009. CAV, cardiac allograft vasculopathy.

Table 6 Risk Factors for Cardiac Allograft Vasculopathy Development Within 8 Years of Transplant, Conditional on Survival to Transplant Discharge for Transplants Performed From January 1998 Through June 2002 ($N = 6,264$)

Variable	No.	RR (95% CI)	*p*-value
Categoric variables			
Donor cause of death: head trauma vs anoxia	2,402	1.31 (1.06–1.61)	0.0113
Use of azathioprine at discharge vs MMF/MPA	1,542	1.29 (1.14–1.45)	<0.0001
Induction with OKT3	630	1.21 (1.04–1.39)	0.0116
Male donor	4,771	1.19 (1.06–1.35)	0.0049
Recipient infection requiring IV antibiotics ≤2 weeks pre-transplant	525	1.19 (1.02–1.40)	0.0307
Donor history of hypertension	666	1.18 (1.02–1.36)	0.0234
Diagnosis: coronary artery disease vs cardiomyopathy	3,086	1.16 (1.05–1.29)	0.0052
Donor clinical infection	1,202	1.16 (1.03–1.30)	0.0113
Use of cyclosporine A at discharge vs tacrolimus	5,047	1.16 (1.00–1.34)	0.0482
Number of mismatches at A locus		0.86 (0.74–1.00)	0.047
0A	399		
1A	3,147		
2A	2,718		
Induction with polyclonal agent	1,163	0.85 (0.74–0.97)	0.0176
Recipient supported with ventricular assist device at transplant	1,031	0.82 (0.72–0.95)	0.006
Continuous variables			
Recipient age			0.0005
Donor age			<0.0001
Donor body surface area			0.0428
Transplant center volume			0.0078

CI, confidence interval; IV, intravenous; MMF, mycophenolate mofetil; MPA, mycophenolic acid; RR, relative risk.

nosuppression use before discharge—use of azathioprine rather than MMF/MPA, use of cyclosporine rather than tacrolimus, and use of OKT3 for induction therapy—also increase the risk of CAV.

Renal failure

As is shown in the survival analyses earlier in this report, renal dysfunction, both at the time of transplant and in the first post-transplant year, is strongly associated with short-term and long-term mortality after transplant. Nephrotoxic effects of commonly used immunosuppressive medications are widely credited with chronic progressive compromise in renal function in many patients after transplantation. Diabetes mellitus and hypertension, comorbidities frequently seen in heart transplant recipients, also contribute to loss of renal function.

Although renal dysfunction after transplant still represents a major problem, there has been a clinically significant improvement in freedom from severe renal insufficiency (serum creatinine > 2.5 mg/dl, need for dialysis or kidney transplant) in more recent transplant recipients (2001 to June 2009) compared with earlier recipients (April 1994 to 2000)—93% vs 89% at 1 year and 83% vs 73% at 5 years, respectively ($p < 0.0001$). Whether this recent improvement in renal function will translate to improved long-term post-transplant survival remains to be seen.

To better describe factors that predispose heart transplant recipients to renal dysfunction, we examined risk factors for development of early renal dysfunction (severe renal dysfunction developing within 1 year of transplant) in a multivariable analysis. The results of this multivariable model are presented in Table 7, with additional graphic information for the continuous variables available in the online slide set.[9]

Malignancy

The need for long-term immunosuppressive therapy is believed to be the main reason why solid-organ transplant recipients are at higher risk for developing malignancy than the general population. By 15 years after transplant, close to 50% of heart transplant recipients are diagnosed with some form of malignancy. Skin cancer is the most frequent and has been diagnosed in 29% of heart transplant recipients by 15 years after transplant. By 15 years after transplant, non-skin malignancies, which are usually associated with less benign outcome than skin cancer, are seen in 18% of heart

Table 7 Risk Factors for Developing Renal Dysfunction Within 1 Year for Patients In Transplant Era January 2003 Through June 2009 Conditional on Survival to Transplant Discharge ($N = 9,916$)[a]

Variable	No.	RR (95% CI)	p-value
Categoric variables			
Dialysis before discharge	531	3.75 (3.01–4.67)	<0.0001
Chronic continuous-flow device	639	1.63 (1.18–2.25)	0.0032
Transplant year: 2003 vs 2008/2009	1,412	1.51 (1.14–1.99)	0.0036
Infection requiring IV antibiotics ≤ 2 weeks pre-transplant	929	1.46 (1.13–1.89)	0.0034
Female recipient	2,335	1.43 (1.10–1.86)	0.0069
Rejection before discharge	1,059	1.35 (1.05–1.74)	0.0188
Interleukin-2R antagonist used for induction	2,876	1.25 (1.04–1.49)	0.0148
Donor CMV+/recipient CMV–	2,097	1.24 (1.01–1.51)	0.0367
Tacrolimus at discharge	5,529	0.75 (0.63–0.90)	0.0023
Continuous variables			
Recipient age			0.0014
Recipient creatinine			<0.0001
Recipient weight			0.0215
Pulmonary artery systolic pressure			0.0165

CI, confidence interval; CMV, cytomegalovirus; IV, intravenous; RR, relative risk.
[a]Limited to recipients without severe renal dysfunction (serum creatinine > 2.5 mg/dl, need for dialysis or kidney transplant) pre-transplant.

transplant recipients, and lymphoproliferative malignancies are seen in 6%. Other common malignancies include prostate cancer, various forms of adenocarcinoma; lung, bladder, renal, breast, and colon cancer; and Kaposi sarcoma. The incidence of cancer appears to increase gradually, without a clear threshold effect of time since transplant. Mortality related to cancer becomes prominent past 3 years after transplant (Figure 16).

We examined freedom from malignancy among patients who received allografts between April 1994 and 2000 and those between 2001 and June 2009. Among the more recent cohort, there appears to be a significant increase in freedom from malignancy—75% vs 81% at 7 years after transplant ($p < 0.001$). This improvement is seen across the examined malignancy diagnoses of skin cancer, lymphoma, and other non-skin cancer.

Whether different rates of cancer are seen with different immunosuppressive therapies was examined in a cohort of patients who underwent transplant between 2000 and June 2010. At 7 years after transplant, patients treated with a combination of cyclosporine and azathioprine had a lower freedom from any malignancy (75%, $p < 0.001$) than those treated with cyclosporine and MMF/MPA (79%) or tacrolimus and MMF/MPA (81%; Figure 19).

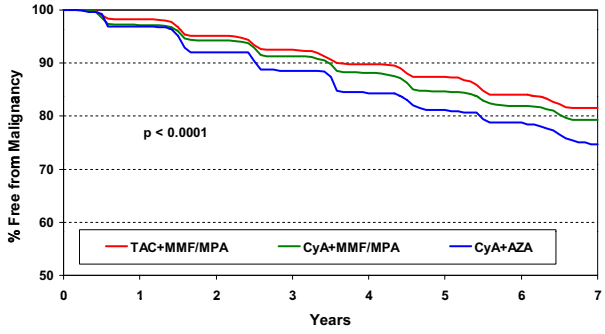

Figure 19 Freedom from malignancy by maintenance immunosuppression combinations at discharge, conditional to survival to 14 days, for transplants done from January 2000 through June 2009. AZA, azathioprine; CyA, cyclosporine A; MMF, mycophenolate mofetil; MPA, mycophenolic acid. TAC, tacrolimus.

Other morbidities

Hypertension after heart transplant is highly prevalent: 75% of recipients between 2000 and June 2005 who survived to 5 years were treated for hypertension at 1 year after transplant, and 90% at 5 years after transplant. The prevalence of hyperlipidemia is similarly high—73% at 1 year and 91% at 5 years after transplant. Diabetes mellitus is present in 28% of recipients at 1 year and in 40% at 5 years after transplant. The high incidence of these comorbidities is a result of higher-risk recipients, described in more detail above, and the adverse effect profile of many of the key immunosuppressive medications used today.

Hospitalization and functional status

The expected survival of the appropriate patient with stage D heart failure is greatly improved through heart transplantation.[10] This dramatic change in expected survival is paralleled by improvement of quality of life and restoration of active lifestyle in most heart transplant recipients. In the first years after heart transplant, approximately 75% of recipients report having a normal healthy lifestyle or only few disease symptoms, an additional 15% participate in normal activities with some difficulty, and less than 10% report a higher degree of limitations.[9] Heart transplant recipients

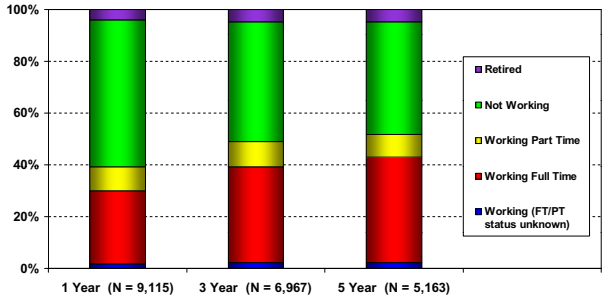

Figure 20 Full-time (FT) and part-time (PT) employment status of surviving adult heart transplant recipients aged 20-55 years at follow-up for the era January 1995 through June 2010.

nevertheless remain under close medical follow-up and can expect to be hospitalized relatively frequently: 45% of recipients are hospitalized in the first post-transplant year and 20% to 25% of recipients are hospitalized every year thereafter. Of note, these data include hospitalizations for any reason, including admissions for unrelated ailments or planned admissions for annual examinations, which is standard practice in some participating centers.

Many patients return to work after transplant. Among recipients aged 25 to 55 years old, approximately 50% were employed 5 years after transplantation (Figure 20). On the basis of the functional data reviewed above, it is apparent that additional recipients could return to the workplace; however, the structure of disability benefits and health insurance considerations may represent a barrier in this process.

Conclusions

The commitment of national transplant registries as well as individual transplant centers ensures that the ISHLT Registry continues to be current and relevant to today's clinical care. This year's report illustrates many of the changes transplant clinicians are faced with in their practice. Patients awaiting heart transplantation, in addition to having advanced heart disease, also have an increasing number of comorbidities that need to be considered at the time of transplantation. The use of mechanical assist support has become dominant—every third transplant in 2009 was done in a VAD-bridged patient. This, of course, has important implications for processes of care in patients with advanced heart failure as well as for organ allocation decisions. Survival after transplant is respectable and continues to improve in the first post-transplant year. Relatively modest but consistent reductions in the incidence of CAV, renal dysfunction, and malignancy after transplant provide a roadmap toward possible improvements in survival past 1 year after transplant.

Disclosure statement

All relevant disclosures for the Registry Director, Executive Committee Members and authors are on file with the ISHLT and can be made available for review by contacting the Executive Director of the ISHLT. All of the figures and tables from this report, and a more comprehensive set of Registry slides are available at www.ishlt.org/registries/.

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