ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report—2013; Focus Theme: Age

Lars H. Lund, MD, PhD, Leah B. Edwards, PhD, Anna Y. Kucheryavaya, MS, Anne I. Dipchand, MD, FRCPC, Christian Benden, MD, Jason D. Christie, MD, Fabienne Dobbels, PhD, Richard Kirk, MA, FRCP, FRCPCH, Axel O. Rahmel, MD, Roger D. Yusen, MD, MPH, and Josef Stehlik, MD, MPH; for the International Society for Heart and Lung Transplantation

From the ISHLT Transplant Registry, Dallas, Texas.

This 30th adult heart transplant report is based on data submitted on 110,486 heart transplants in recipients of all ages (including 99,008 adults) by 407 centers worldwide since 1982 through June 30, 2012, with follow-up until June 30, 2012. Summary data are provided for the entire cohort of patients, whereas a number of additional analyses focus on cohorts who received transplants more recently. Detailed data analyses can be viewed in the International Society for Heart and Lung Transplantation (ISHLT) Registry slide sets available online (www.ishlt.org/registries).

The report is divided into several sections:

1. Baseline donor, recipient, and transplant center demographics and characteristics;
2. Survival after heart transplantation according to donor and recipient characteristics;
3. Immunosuppression and allograft rejection;
4. Post-transplant morbidity and quality of life;
5. Multivariable analyses where the independent relationships between donor and recipient characteristics and post-transplant mortality and morbidity are examined; and—new for this year—
6. Focus theme, where donor age and recipient age are examined in detail.

In addition to the standard overview of donor and recipient characteristics and outcomes, this year's report and online slide set provide an in-depth analysis of age as a specific contemporary focus theme. Numerous analyses are presented that address demographic trends and the role of age in recipient and donor organ selection and their relationship to outcomes. The 6 sections are paralleled with additional and extended analyses presented in the online slide sets.

Statistical methods

Donor and recipient baseline demographics, characteristics, and immunosuppressive treatments, as well as outcomes in terms of mortality and causes of death, morbidity, hospitalization, and functional status and quality of life, are summarized using numbers and percentages or medians with 5^{th} and 95^{th} percentiles. Survival and event-free survival rates were calculated using the Kaplan-Meier method[1] and compared using pair-wise and overall log-rank tests. Adjustments for multiple comparisons were done using Scheffe's method. Many outcomes analyses are unadjusted and should thus be interpreted with caution. Multivariable analyses are presented in section 5 (multivariable analysis) and in the latter parts of section 6 (age analysis). Multivariable analyses were performed using Cox proportional hazard regression analysis.[2] Results of the multivariable analyses are reported as hazard ratios (HR) with corresponding 95% confidence intervals (CIs), and/or p-values. A HR significantly > 1 for a factor indicates that the factor is associated with an increased likelihood of the event occurring. Conversely, a HR < 1 indicates that the event is less likely to occur when that factor is present.

Reprint requests: Josef Stehlik, MD, MPH, University of Utah Health Sciences Center, Division of Cardiology, U.T.A.H. Cardiac Transplant Program, 50 N Medical Dr, 4A100 SOM, Salt Lake City, UT 84132. Telephone: 801-585-2340. Fax: 801-581-7735.

E-mail address: josef.stehlik@hsc.utah.edu

1053-2498/$ - see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.healun.2013.08.006

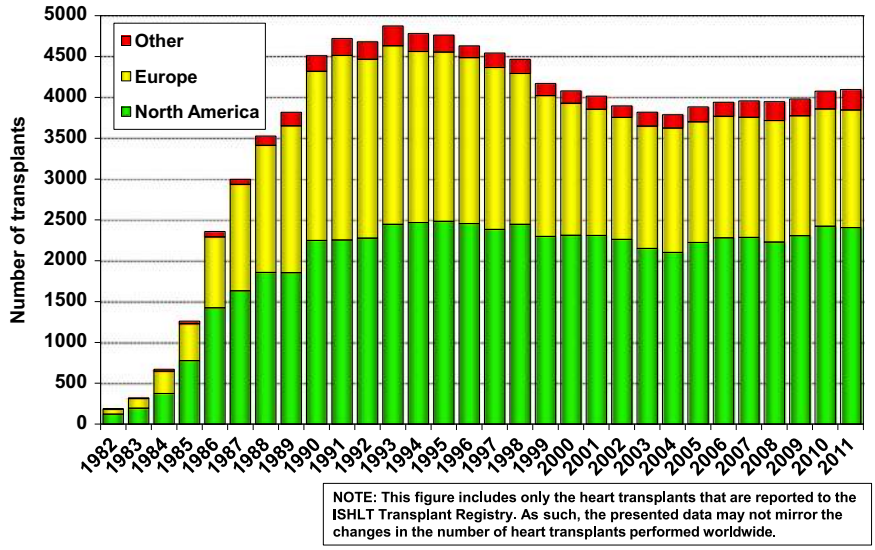

Figure 1 Number of heart transplants (all recipient ages) by year (1982–2011) and geographic region. ISHLT, International Society for Heart and Lung Transplantation.

For missing data in continuous data fields, multiple imputation was used.[3] 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 relative HR, 95% CIs, and *p*-values are obtained.

1. Heart transplant donor and recipient demographics and characteristics

Transplant volumes

A total of 4,096 heart transplants (including 3,529 adult) from 249 centers were performed in 2011 and reported to the ISHLT. After a decline between 1993 and 2004, the number of reported heart transplants remained stable for several years and now appears to be slowly increasing, particularly in North America and in other regions (Figure 1). The Registry captures an estimated 66% of worldwide heart transplants, and ascertaining whether these demographic trends are reflective of the overall worldwide heart transplant volume is difficult. The volume of transplants performed at different centers varies considerably (Figure 2). Most centers (78%) perform fewer than 20 heart

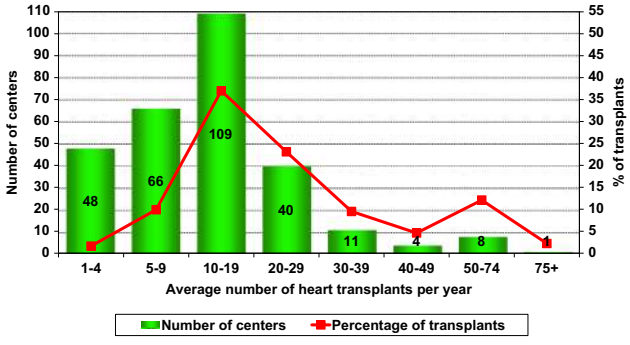

Figure 2 Average annual center heart transplant volume (all recipient ages) for transplants from 2006 to June 2012. Columns show the number of centers performing the number of transplants on the x-axis (eg, 109 centers perform 10–19 heart transplants per year) and the curves show the percentages of all transplants performed at centers performing the number of transplants listed on the x-axis (eg, 37% of all heart transplants are performed by the 109 centers).

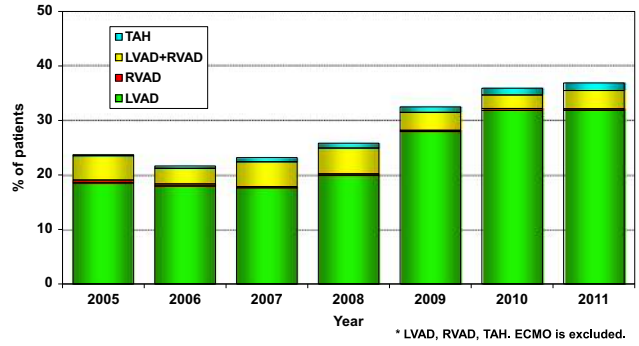

Figure 3 Percentage of adult recipients bridged with left ventricular assist device (LVAD), right ventricular assist device (RVAD), total artificial heart (TAH), or a combination of devices, over time.

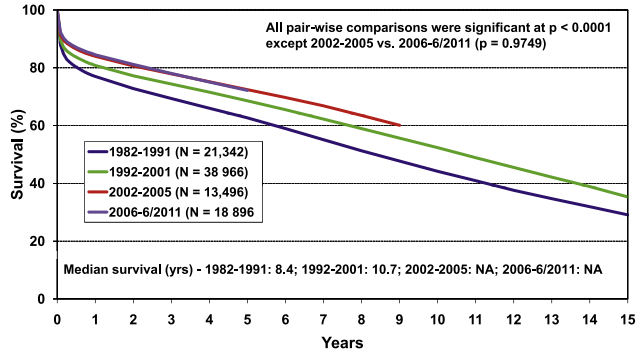

Figure 4 Kaplan-Meier long-term survival by era (adult recipients). NA, not applicable.

Table 1 Donor and Recipient Characteristics for Adult Heart Transplants

Variables[a]	1992–2000 (n = 37,146)	2001–2005 (n = 17,183)	2006–6/2012 (n = 22,318)	p-value
Age, years				
Recipient	54.0 (28.0–65.0)	54.0 (26.0–66.0)	54.0 (24.0–67.0)	<0.0001
Donor	31.0 (15.0–54.0)	33.0 (16.0–55.0)	34.0 (17.0–56.0)	<0.0001
Donor and recipient age difference, years	−19.0 (−44.0 to 7.0)	−17.0 (−43.0 to 10.0)	−16.0 (−43.0 to 12.0)	<0.0001
Recipient				
Weight, kg	75.0 (51.0–102.0)	77.6 (53.0–106.6)	79.4 (53.1–110.0)	<0.0001
Height, cm	173.0 (157.0–188.0)	174.0 (157.5–188.0)	175.0 (157.4–188.0)	0.0042
Body mass index, kg/m^2	22.7 (19.5–31.7)	24.2 (19.6–33.1)	24.4 (19.6–34.3)	<0.0001
Donor				
Weight, kg	75.0 (52.0–103.3)[b]	76.8 (55.0–108.8)	79.4 (56.7–113.0)	<0.0001
Height, cm	175.0 (155.0–188.0)[b]	175.3 (158.0–189.0)	175.0 (158.0–190.0)	<0.0001
Body mass index, kg/m^2	24.2 (18.8–32.9)[b]	24.8 (19.5–34.4)	25.5 (19.9–36.4)	<0.0001
Gender (male), %				
Recipient	81	78	76	<0.0001
Donor	68	69	69	0.1103
Male recipient/female donor, %	21	19	17	<0.0001
Female recipient/male donor, %	9.2	9.7	9.9	0.0055
Diabetes mellitus, %				
Recipient	13[b]	20	25	<0.0001
Donor	1.6[b]	2.0	3.0	<0.0001
Recipient, %				
Prior history of dialysis	3.0[b]	4.3	4.2	<0.0001
Amiodarone use (U.S. only)	22[b]	29	31	<0.0001
Cigarette history, %				
Recipient	…	47[c]	46	0.8536
Donor	38[b]	29	19	<0.0001
Hypertension, %				
Recipient	35[b]	38	45	<0.0001
Donor	11[b]	11	14	<0.0001
Recipient, %				
Prior cardiac surgery	…	39[c]	46	<0.0001
Peripheral vascular disease	3.8[b]	3.2	2.9	0.0002
Previous malignancy	3.3[b]	4.5	6.6	<0.0001
COPD	3.2[b]	3.2	4.3	<0.0001
Ischemic time, hours	2.9 (1.3–4.8)	3.1 (1.5–5.0)	3.3 (1.6–5.1)	<0.0001
Most recent PRA > 10%[d]				
Overall	7.7	8.9[e]	13.8[f]	<0.0001
Class I	…	…	14.4[g]	…
Class II	…	…	9.6[g]	…
Creatinine at transplant, mg/dl	1.2 (0.7–2.5)	1.2 (0.7–2.4)	1.2 (0.7–2.3)	<0.0001
Peripheral vascular resistance, Wood units	2.2 (0.4–6.1)[b]	2.0 (0.3–5.6)	2.1 (0.3–5.5)	<0.0001
HLA mismatches, %	4.3	4.4	3.8	
0–2	40	40	38	0.0003
3–4	55	55	58	
5–6	7.7	8.9[c]	14[d]	
Diagnosis, %				
Cardiomyopathy	46	48	54	<0.0001
Coronary artery disease	46	43	37	
Valvular	3.9	3.5	2.8	
Retransplant	1.9	2.2	2.5	
Congenital	1.8	2.7	2.9	
Other causes	0.4	0.6	0.9	
Donor cause of death, %				
Head trauma	46	55	46	<0.0001
Stroke	29	33	24	
Other	25	13	30	

Continued on page 954

Table 1 *(Continued)*

Variables[a]	1992–2000 (n = 37,146)	2001–2005 (n = 17,183)	2006–6/2012 (n = 22,318)	p-value
Pre-operative support (multiple items may be reported), %				
Hospitalized at time of transplant	61	48	44	<0.0001
On intravenous inotropes	56[b]	47	42	<0.0001
Left ventricular assist device	12[h]	17	28	<0.0001
Intra-aortic balloon pump	6.4	6.7	6.1	0.1650
Right ventricular assist device	...	5.0[i]	3.7	0.0055
Ventilator	3.3	3.2	2.7	0.0092
Total artificial heart	0.1[h]	0.1	1.0	<0.0001
ECMO	0.3[j]	0.5	1.1	<0.0001

COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; PRA, panel reactive antibody.
[a]Continuous factors are expressed as median (5th–95th percentiles).
[b]Based on April 1994–2000 transplants.
[c]Based on July 2004–2005 transplants
[d]PRA was collected as a single percentage outside of U.S. Until mid-2004, PRA was collected in U.S. as a single percentage. After this date, PRA was collected separately for class I and class II.
[e]Based on U.S. 2001–June 2004 transplants and non-U.S. 2001–2005 transplants.
[f]Based on non-U.S. transplants.
[g]Based on U.S. transplants.
[h]Based on November 1999–2000 transplants.
[i]Based on 2005 transplants.
[j]Based on May 1995–2000 transplants.

transplants per year and are responsible for 49% of all transplant volume.

Donor demographics

Donor demographics are presented in Table 1. In the most recent cohort, 69% of donors are male, and female donor-to-male recipient transplantation was less frequent than previously (17%). Donor diabetes mellitus (3.0%) and hypertension (14%) are rare but increasing. The leading cause of donor death is head trauma (46%). Donor age is addressed in detail in section 6.

Recipient demographics and characteristics

As shown in previous reports,[4,5] cardiomyopathy and coronary artery disease (CAD) are the leading underlying heart disease diagnoses, with the cardiomyopathy proportion increasing over time (Table 1). There are several changes over time that parallel changes in the overall population and/or appear to reflect a willingness to transplant higher risk patients. These include increases in retransplant and congenital heart disease, now approaching 3% of all transplants each, increasing proportions of sensitized recipients, and increasing comorbidity in the form of diabetes mellitus (25%), hypertension (45%), previous malignancy (6.6%), and previous cardiac surgery (46%; Table 1). Use of mechanical circulatory support (MCS) to bridge patients to transplant, predominantly with left ventricular assist devices (LVADs), continues to increase, and was 37% in 2011 (Figure 3).

2. Survival

For all 103,299 pediatric and adult heart transplants between 1982 and June 2011, 1-year survival is 81%, and 5-year survival is 69%, with median survival of 11 years for all and 13 years for those surviving the first year. We have previously reported that survival in adult heart transplant recipients has continued to improve over the years.[4] However, the most recent cohort of patients who received transplants in 2006 through June 2011 demonstrates survival similar to patients who received transplants in 2002 to 2005, with unadjusted 1-year survival of 84% (Figure 4). In patients surviving past 1 year after transplant, no significant improvement in survival was seen in the last cohort (2006 to June 2011) over 1-year survivors who received transplants in 1992 to 2001 and in 2002 to 2005. The estimated 5-year survival conditional on 1-year survival is 85% (online slide set). Section 5 (multivariable analyses) provides additional insights into survival after transplant in the most recent era.

Age is an important determinant of survival and is addressed in detail in the online slide set and in section 6 below. A heart disease diagnosis exerts time-dependent effects on post-transplant survival. One-year survival is highest in patients who receive transplants for cardiomyopathy and CAD and lowest in congenital heart disease, retransplant, and valvular cardiomyopathy (Figure 5A). However, long-term survival is highest in those who receive transplants for congenital heart disease and cardiomyopathy (Figure 5B). In patients who survive the first year after transplant, survival is highest in those who receive transplants for congenital heart disease (Figure 5C). Retransplant

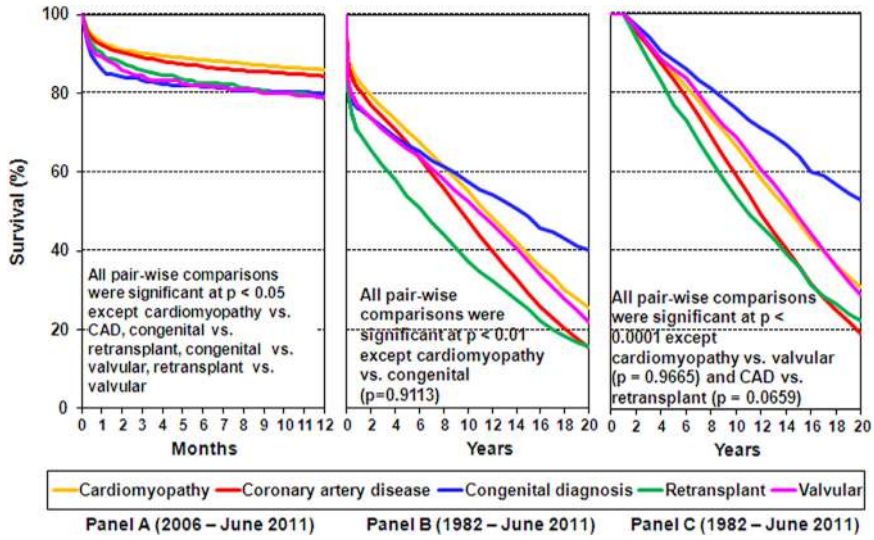

Figure 5 Kaplan-Meier (A) 1-year survival, (B) long-term survival, and (C) long-term survival conditional on survival to 1 year by diagnosis (adult recipients). Patients have different duration of follow-up and represent different cohorts. CAD, coronary artery disease.

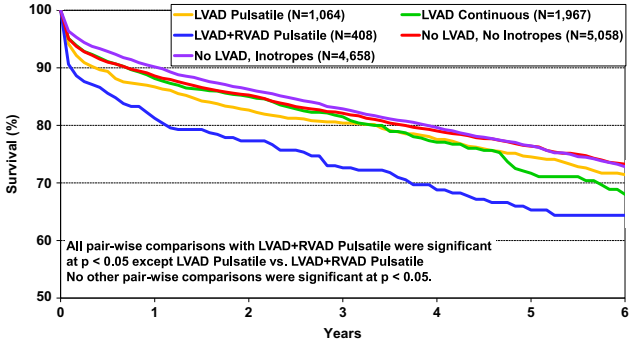

Figure 6 Kaplan-Meier intermediate-term survival by pre-transplant durable mechanical circulatory support use (adult recipients), transplants 2005–June 2011. LVAD, left ventricular assist device; RVAD, right ventricular assist device.

is associated with a distinctly worse prognosis, with 1-year survival of 70% compared with 83% for cardiomyopathy, for transplants since 1982.

LVAD use pre-transplant, potentially conferring worse post-transplant prognosis, appears less concerning in the era of modern continuous flow-devices, although the need for combined right ventricular assist device (RVAD) and LVAD remains associated with considerably worse post-transplant survival (Figure 6). Additional predictors of mortality are addressed in the online slides and section 5 (multivariable analyses).

Causes of death

The overall distribution of the leading causes of death has remained without major change since 1994, but the incidence of cause-specific mortality changes with time after transplant: in the first 3 years, graft failure and infection predominate, whereas after 3 to 5 years, malignancy, cardiac allograft vasculopathy (CAV), and renal failure become progressively more important. Acute rejection accounts for no more than 11% of deaths (in

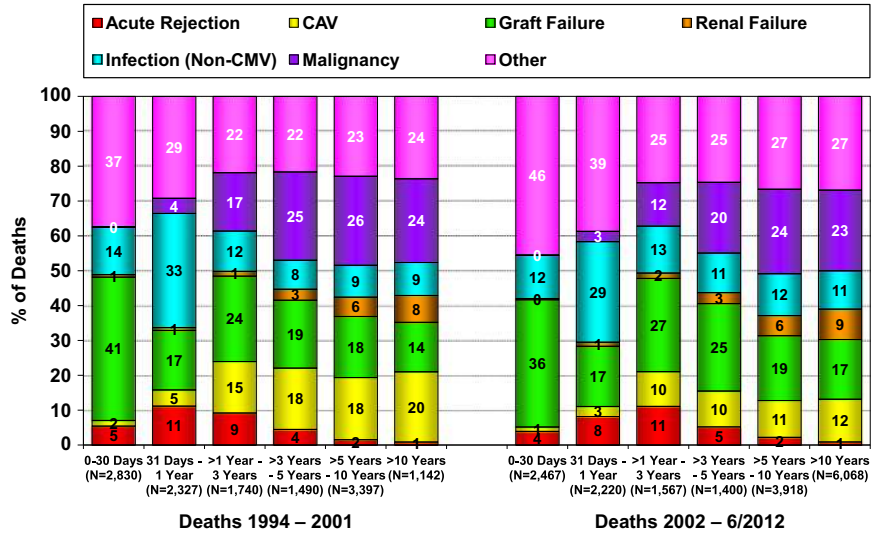

Figure 7 Contribution of causes of death by time of death and era (adult recipients), deaths 1994–June 2012. CAV, cardiac allograft vasculopathy.

Years 1 to 3), but acute and chronic immune injury are likely important contributors to graft failure, which remains a leading cause of death throughout follow-up (Figure 7).

3. Immunosuppression and rejection

Induction immunosuppression

The use of immunosuppressive induction is decreasing and was 47% overall in the first 6 months of 2012. Interleukin-2 receptor (IL-2R) antagonists had become the most frequently used induction agents, in 28% of all transplants, whereas polyclonal antilymphocytic antibodies were used in 19% and alemtuzumab in 1%. OKT3 is no longer available for clinical use in most countries.

Maintenance immunosuppression

There is a continued trend for use of tacrolimus as the preferred calcineurin inhibitor (81% at 1 year for January–June 2012 follow-up) and mycophenolate mofetil (MMF)/mycophenolic acid (MPA) as the preferred cell cycle inhibitor (85%). Compared with 2005, prednisone use is declining (66% at 1 year), and use of mammalian target of rapamycin (mTOR) inhibitors is steady (13%). Between Years 1 and 5 after transplant, the use of prednisone decreases and the use of mTOR inhibitors doubles.

Rejection

With improved immunosuppression, the incidence of any rejection between discharge and 1 year has decreased from 32% in 2004 to 25% in 2010. Furthermore, with the recognition that mild cellular rejection may not need acute treatment,[6] the incidence of treated rejection has decreased from 25% in 2004 to 14% in 2010 (Table 2). Survival in recipients with no rejection and in those with untreated rejection is similar. Survival in patients with treated rejection is worse, however, compared with both former groups (Figure 8). The Registry does not collect data on the type or severity of rejection; therefore analysis of the increasingly recognized antibody-mediated rejection cannot be performed, and the worse outcomes with treated rejection may be confounded by greater severity.

Table 2 Rejection Between Transplant Discharge and 1-Year Follow-up for Adult Heart Recipients

Transplant year	Rejection		No rejection	Total
	Treated	Untreated		
	No. (%)	No. (%)	No. (%)	No. (%)
2004	393 (25)	106 (7)	1,054 (68)	1,553 (100)
2005	380 (23)	96 (6)	1,181 (71)	1,657 (100)
2006	368 (21)	157 (9)	1,200 (70)	1,725 (100)
2007	312 (18)	199 (11)	1,229 (71)	1,740 (100)
2008	258 (16)	196 (12)	1,208 (73)	1,662 (100)
2009	278 (16)	242 (14)	1,212 (70)	1,732 (100)
2010	267 (14)	205 (11)	1,430 (75)	1,902 (100)

4. Post-transplant morbidity and functional status

Morbidity

Hypertension, hyperlipidemia, renal dysfunction, diabetes, and CAV are the most common post-transplant morbidities (Table 3). Of these, renal dysfunction and CAV, in addition to graft failure, infection, acute rejection, and malignancy, described above, are the important direct contributors to mortality.

In patients surviving to the respective follow-up, CAV affects 8% by Year 1, 30% by Year 5, and 50% by Year 10 after transplant. Renal dysfunction affects 26%, 52%, and 68% by Years 1, 5, and 10, respectively. Any malignancy affects 28%, skin malignancy affects 20%, and lymphoma affects 2% by 10 years after transplant. Rejection and infection are important contributors to hospitalization, but 56% of survivors are free from hospitalization during the first year after transplant and more than 70% between 2 and 3 years and between 4 and 5 years. The independent roles of post-transplant morbidities are examined in section 5: Multivariable analyses, and their relation to age in section 6: Age analyses.

Functional status

Compared with advanced heart disease before transplant, heart transplantation in appropriately selected candidates is associated with dramatic improvements in survival and quality of life.[7] The Registry data show that at 1 to 3 years after transplant, functional status remains very favorable, with the proportion of survivors capable of normal activity (Karnofsky score 80%–100%) approaching 90%. In this context, the extent of employment in heart transplant recipients appears disproportionately low, with 35% and 46% of recipients aged 25 to 60 years at the time of follow-up working at 1 and 3 years after transplant, respectively. It is possible that decisions regarding return to gainful employment in these patients may be influenced by factors beyond their functional status, such as employer-based health insurance eligibility and affordability.

5. Multivariable analyses

Unadjusted mortality and morbidity rates are described in the sections above. To determine the independent contributors to mortality and morbidity, we performed multivariable proportional hazards regression analyses for transplants that took place in more recent eras, using donor and recipient pre-transplant and recipient post-transplant characteristics as independent variables. Variables associated with risk of 1-, 5-, and 15-year mortality are reported in Table 4. Numerous additional multivariable data are shown in the online slide set, and the risk associated with age is addressed subsequently in section 6.

One-year mortality

For mortality up to 1 year, only pre-transplant data are considered. Important risk factors include congenital heart disease and retransplant, history of dialysis and transfusions, infection, ventilator support, and hospitalization before transplant (Table 4). In univariable analysis, male donor-to-female recipient transplants fared worse than other combinations, but in multivariable analysis, male recipients fared worse when receiving a female vs a male donor organ, suggesting a consequence of under-sizing. Several continuous variables were associated with essentially linear increases in risk, such as higher serum creatinine and bilirubin, percentage of class II panel reactive antibody, and lower donor/recipient ratio of body mass index. Other continuous variables exhibited U-shaped or non-linear patterns with higher risk at lower and higher recipient ages. Allograft ischemic time conferred increased risk only beyond 200 minutes.

Durable continuous-flow devices, total artificial heart, and temporary circulatory support, including extracorporeal membrane oxygenation (ECMO), are increasingly used and are associated with progressively increased risk. However, the multivariable analysis is based on data registered not at device implant but at the time of transplant, when organ failure (affecting the multivariable model) has often been reversed.[8] Patients supported by a device may still have more underlying morbidity and risk at the time of transplant; nevertheless, the model may not account for it. The effect of MCS on transplant candidacy and survival on the waiting list should also be considered, and this report alone should not guide decisions regarding pre-transplant MCS implantation.

The presented risk profiles also shed light on recent trends in survival. In univariable analysis (Figure 4), early survival improved up until the early 2000s but has remained unchanged thereafter. In multivariable analysis, more recent transplantation, in 2010 to 2011, is associated with lower risk, even compared with transplants performed as recently as 2008 (Table 4). Recipients with increasingly higher risk are receiving transplants (eg, age and comorbidity, section 1 above), and when this risk is adjusted for, even very recent years are associated with continued improved outcomes.

Five-year cumulative and conditional mortality

Risk factors for cumulative 5-year mortality are largely similar to those for short-term mortality but also include prior pregnancy and recipient morbidities that predispose to adverse outcomes in the longer-term, such as elevated body mass index and diabetes mellitus (Table 4). To separate causes of intermediate and early mortality, we also analyzed risk factors for 5-year mortality conditional on survival to 1 year, when numerous post-transplant variables are reported to the Registry (online slide set). Several pre-transplant risk factors are no longer significant, whereas several of the post-transplant factors now included in the model are important, including non-use of calcineurin and cell cycle inhibitors (possibly a marker of complications from these drugs), as well as rejection and dialysis before discharge.

Mortality at 10, 15, and 20 years

Detailed long-term mortality analyses are presented in the online slide set. Data collection in earlier eras was more limited, and fewer variables are included in the models. Risk factors from the 1990s may be different from those of recent years and less applicable to contemporary risk analysis.

With increasing time post-transplant, several general patterns emerge (Table 4 and online slide set). Some pre-transplant predictors, such as serum creatinine, remain but generally become less important. Consistent with the univariable analysis (Figure 5), retransplant remains an important predictor of long-term mortality, whereas congenital heart disease is no longer a risk factor in 15-year and 20-year mortality models. Gender mismatch, in both directions, and pregnancy are associated with increased

Table 3 Cumulative Morbidity Rates in Survivors of Adult Heart Transplants

		Within 1 Year	Total with known response	Within 5 Years	Total with known response	Within 10 Years	Total with known response
Follow-ups	Outcome	(%)	(No.)	(%)	(No.)	(%)	(No.)
January 1995–June 2012	Hypertension[a]	72	26,852	92	12,534	…	
	Renal dysfunction	26	29,301	52	14,680	68	4,879
	Abnormal creatinine ≤ 2.5 mg/dl	18		33		38	
	Creatinine > 2.5 mg/dl	6		15		20	
	Chronic dialysis	1.5		2.9		6.0	
	Renal transplant	0.3		1.2		3.6	
	Hyperlipidemia[a]	60	28,102	88	13,876	…	
	Diabetes[a]	26	29,289	38	14,470	…	
	CAV	8	26,480	30	10,651	50	2,815

CAV, Cardiac allograft vasculopathy.
[a]Data are not available 10 years post-transplant.

Table 4 Risk Factors for Mortality for Adult Heart Transplants

Model	Variable	No.	HR (95% CI)	*p*-value
1 year mortality, N = 10,473 (January 2006–June 2011)	Temporary circulatory support[a]	163	2.80 (2.04–3.83)	<0.0001
	Total artificial heart	98	2.26 (1.43–3.55)	0.0004
	Diagnosis: congenital vs cardiomyopathy	266	2.21 (1.62–3.02)	<0.0001
	Recipient history of dialysis	274	1.78 (1.39–2.28)	<0.0001
	Recipient on ventilator at time of transplant	302	1.66 (1.29–2.15)	0.0001
	Chronic pulsatile-flow device	952	1.56 (1.27–1.92)	<0.0001
	Chronic continuous-flow device	1,846	1.50 (1.24–1.81)	<0.0001
	Previous transplant	311	1.46 (1.08–1.96)	0.0125
	Male recipient/female donor vs male recipient/male donor	1,569	1.32 (1.12–1.55)	0.0009
	Recipient with infection requiring IV drug therapy ≤ 2 weeks before transplant	1,063	1.28 (1.08–1.52)	0.0043
	Previous transfusion	2,268	1.25 (1.08–1.45)	0.0034
	Not hospitalized just before transplant	5,742	0.87 (0.77–0.99)	0.0372
	Ventricular remodeling	1,835	0.80 (0.67–0.95)	0.0107
	Transplant year: 2006 vs 2010/2011	1,913	1.40 (1.17–1.68)	0.0002
	Transplant year: 2007 vs 2010/2011	1,882	1.32 (1.10–1.58)	0.0031
	Transplant year: 2008 vs 2010/2011	1,799	1.26 (1.05–1.51)	0.0146
	The continuous variables associated with increased or decreased risk of mortality were recipient age, recipient height, BMI ratio, donor age, transplant center volume, ischemia time, recipient pre-transplant bilirubin and creatinine, panel reactive antibody class II, and recipient systolic PAP.			
5-year mortality, N = 10,332 (January 2002–June 2007)	Temporary circulatory support[a]	160	2.23 (1.72–2.90)	<0.0001
	Total artificial heart	37	1.77 (1.01–3.08)	0.0442
	Continuous-flow device or VAD with type unknown	349	1.71 (1.16–2.52)	0.0065
	Recipient history of dialysis	326	1.70 (1.43–2.03)	<0.0001
	Diagnosis: congenital vs cardiomyopathy	284	1.46 (1.16–1.83)	0.0012
	Recipient on ventilator at time of transplant	301	1.37 (1.11–1.68)	0.0034
	Female recipient with prior pregnancy; male donor vs male recipient/male donor	752	1.33 (1.11–1.58)	0.0017
	Panel reactive antibody > 10%	685	1.25 (1.08–1.45)	0.0030
	Recipient hepatitis B core (+)	404	1.22 (1.01–1.47)	0.0388
	Recipient with infection requiring IV drug therapy ≤ 2 weeks before transplant	1,117	1.22 (1.08–1.37)	0.0018
	HLA mismatches at A locus (per locus), No.		1.18 (1.03–1.35)	0.0196
	0 A MM	677		
	1 A MM	4,910		
	2 A MM	4,745		
	Donor cause of death: anoxia vs head trauma	956	1.17 (1.02–1.33)	0.0243
	Recipient history of diabetes	2,275	1.15 (1.04–1.26)	0.0049
	Chronic pulsatile-flow device	1,730	1.15 (1.02–1.29)	0.0213
	Diagnosis: coronary artery disease vs cardiomyopathy	4,587	1.12 (1.02–1.23)	0.0206
	Ventricular remodeling	928	0.85 (0.73–0.99)	0.0415
	The continuous variables associated with increased or decreased risk of mortality were recipient age, recipient height, recipient BMI, donor age, donor BMI, transplant center volume, ischemia time, recipient pre-transplant bilirubin and creatinine, recipient PVR, and recipient diastolic PAP.			
15 year mortality, N = 11,055 (January 1992–June 1997)	Retransplant	268	1.67 (1.44–1.94)	<0.0001
	Diagnosis: not cardiomyopathy, coronary artery disease, congenital heart disease, valvular heart disease, or retransplant vs cardiomyopathy	73	1.66 (1.25–2.22)	0.0006
	On ventilator	338	1.33 (1.16–1.52)	<0.0001
	Recipient hepatitis B core (+)	265	1.27 (1.09–1.47)	0.0024
	Panel reactive antibody > 20%	534	1.21 (1.08–1.34)	0.0006
	Transplant year: 1992 vs 1996/1997	1,881	1.17 (1.08–1.27)	<0.0001
	Female recipient/male donor vs male recipient/male donor	1,218	1.16 (1.05–1.28)	0.0040
	On VAD at transplant	777	1.16 (1.05–1.27)	0.0039
	Diagnosis: coronary artery disease vs cardiomyopathy	5,506	1.15 (1.09–1.22)	<0.0001
	Transplant year: 1993 vs. 1996/1997	2,017	1.15 (1.06–1.24)	0.0005
	Male recipient/female donor vs. male recipient/male donor	2,260	1.14 (1.05–1.24)	0.0020
	2 mismatches at DR locus	6,774	1.11 (1.06–1.17)	<0.0001

Continued on page 959

Table 4 *(Continued)*

Model	Variable	No.	HR (95% CI)	*p*-value
	Transplant year: 1994 vs 1996/1997	2,072	1.08 (1.00–1.16)	0.0417
	The continuous variables associated with increased or decreased risk of mortality were recipient age, difference in recipient and donor age, recipient BMI, donor height, transplant center volume, ischemia time, and recipient pre-transplant creatinine,			

BMI, body mass index; CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio; IV, intravenous; PAP, pulmonary artery pressure; PVR, peripheral vascular resistance; VAD, ventricular assist device.

[a]Temporary circulatory support includes extracorporeal membrane oxygenation and temporary pulsatile flow devices.

risk, perhaps due to effects of both under-sizing (female donor/male recipient) and immune mechanisms (male donor/female recipient and prior pregnancy).

Morbidity

Because the complications and morbidities discussed in section 2 contribute to diminished quality of life and also generally contribute to mortality, assessing the predictors of post-transplant morbidity is of interest. The online slide set depicts risk factors for short-term and intermediate-term renal dysfunction, malignancy, and CAV.

6. 2013 report focus theme: Age

Numerous developments are making heart transplant recipient and donor age of particular contemporary interest. With improved heart failure care, there are more and older potential recipients, and centers are accepting higher-risk patients, both with regard to age and comorbidity. The rapid growth of LVAD use, including in elderly patients and as destination therapy,[9] also has implications for transplant recipient age and priority. With increasing organ shortage and with the use of formal or informal "alternate lists," centers are also accepting higher risk, particularly older, donors.

Age and all heart transplants

Recipient age has changed considerably between different eras (online slide set—overall heart transplants). The median age increased from 40 years in 1982 to 53 years in 1996, after which it remained fairly constant. Although the group aged 40 to 59 years remains the most common, the proportion of this group has declined at the expense of transplants taking place at the "extremes" of age. The 0- to 9-year age group increased from 5% to 8% between the 1982 to 1995 and 2006 to 2012 eras, the 60- to 69-year age group increased from 14% to 24%, and the 70 years and older age group increased from 0.2% to 1.3% of overall transplants (Figure 9).

Donor age has increased similarly, with the median age increasing from 22 to 32 years overall and to 43 years in Europe. The representation of youngest and oldest donors is increasing, with 7% of donors aged 0 to 9 years and 3% aged 60 years and older in 2011.

Age and adult heart transplant demographics and characteristics

Figures 10 and 11 depict geographic aspects of recipient and donor age. Among contemporary adult recipients, median age is 55 years in North America, 53 years in Europe, and 50 years in other regions. Ages 60 to 69 years and even 70 years and older account for a not inconsiderable proportion, representing respectively, 32% and 2% of adult recipients in North America (Figure 10). Donors are older in Europe, with a median age of 43 years, and most are aged 40 to 59 years, with as many as 5% in the group aged 60 years and older, compared with a median of 29 years, and most are in the group aged 18 to 39 years in North America (Figure 11).

Table 5 describes the different recipient age groups. The donor-recipient age difference is larger with increasing recipient age. Although male recipients predominate for all age groups, the percentage of male recipients increases with age.

The underlying heart disease diagnosis varies considerably with age. Cardiomyopathy is the major diagnosis up to age 59 years, but CAD predominates thereafter. Retransplantation is relatively uncommon in all ages. Transplantation for congenital heart disease accounts for 10% of transplants in the group aged 18 to 39 years and becomes uncommon in recipients aged 40 years older (Figure 12).

Older patients more commonly have a history of cardiac surgery and malignancy and worse renal function but are less frequently hospitalized or on inotropes at the time of transplant. Since 2006, the overall proportion with MCS (predominantly LVAD) has increased, and this increase has been more dramatic in the elderly: in 2006, 26% of those aged 18 to 39 years and 16% of those aged 60 to 69 years had pre-transplant MCS; in 2011, the figures were 33% and 38%, respectively. These changes may be related to the increasing frequency of bridge to candidacy scenarios, in turn possibly related to regulatory approval and increased acceptance of LVAD as destination therapy, particularly in North America.

Donor and recipient age and adult recipient survival

Increasing recipient age is associated with progressively worse survival in univariable analysis, in the overall cohort (Figure 13) and also in patients who received transplants more recently (online slide set). Similarly, increasing donor age is associated with progressively worse survival, particularly with donors aged 60 years and older. A greater negative donor–recipient age difference also conferred improved survival, primarily in the longer-term.

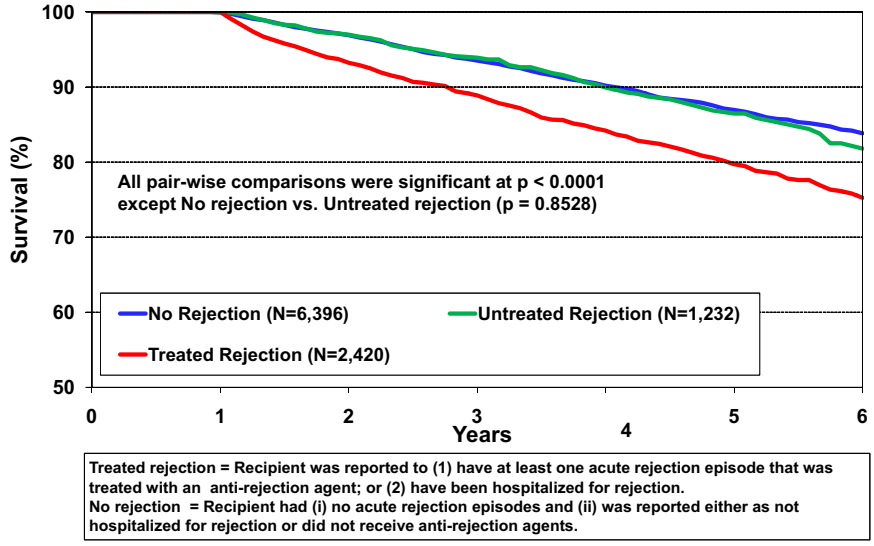

Figure 8 Kaplan-Meier intermediate-term survival, conditional on survival to 1 year, by rejection and treatment for rejection (adult recipients), 1-year follow-ups January 2005–June 2011.

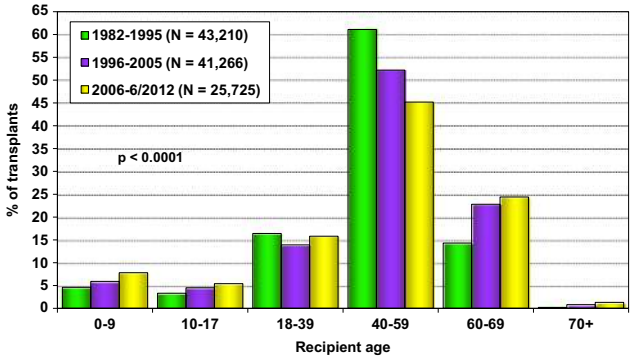

Figure 9 Recipient age by era (all recipient ages).

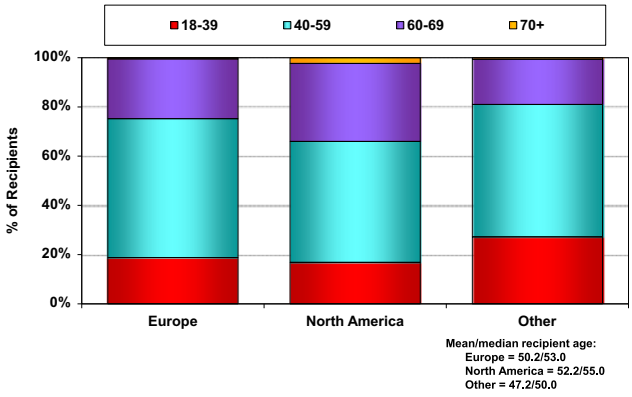

Figure 10 Recipient age by geographic region (adult recipients), transplants 2006–June 2012.

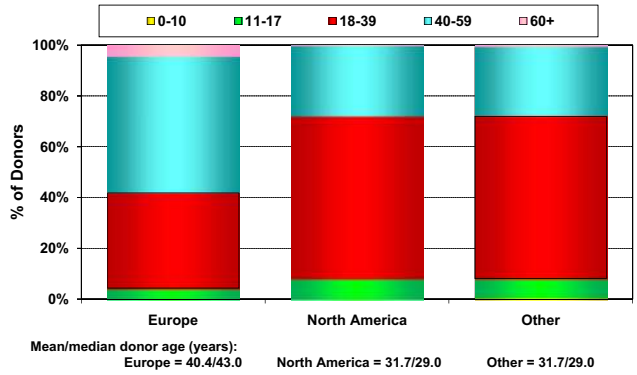

Figure 11 Donor age by geographic region (adult recipients), transplants 2006–June 2012.

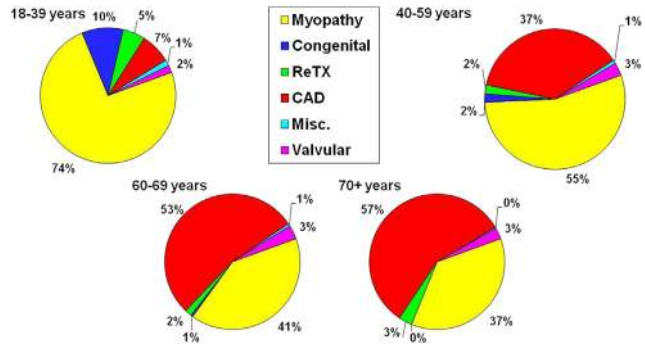

Figure 12 Recipient diagnosis by age (adult recipients), transplants 2006–June 2012. CAD, coronary artery disease; ReTX, repeat transplant.

Age and causes of death

The causes of death vary not only by time after transplant but also among different age groups (Table 6). Graft failure (likely often related to acute and chronic immune injury) is a dominant cause of death in all ages, but with increasing age, death from graft failure together with CAV and acute rejection become dramatically less common, whereas death from

Table 5 Donor and Recipient Characteristics by Recipient Age Group (Adult Heart Transplants: January 2006–June 2012)

	Recipient age group, years				
	18–39	40–59	60–69	≥70	
Variables[a]	(n = 4,053)	(n = 11,632)	(n = 6,287)	(n = 346)	p-value
Donor age, years	30.0 (16.0–53.0)	35.0 (17.0–56.0)	36.0 (17.0– 58.0)	36.0 (18.0– 59.0)	<0.0001
Donor and recipient age difference, years	2.0 (–18.0 to 25.0)	–17.0 (–37.0 to 7.0)	–28.0 (–47.0 to –5.0)	–35.0 (–53.0 to –13.0)	<0.0001
Body mass index, kg/m^2					
Recipient	22.6 (18.2– 34.3)	24.6 (20.1– 34.6)	25.0 (20.3– 33.7)	24.9 (20.1– 32.0)	<0.0001
Donor	24.8 (19.4– 35.9)	25.7 (20.0– 36.5)	25.7 (20.1– 36.6)	26.3 (21.0– 37.9)	<0.0001
Gender, % male					
Recipient	65	76	81	90	<0.0001
Donor	67	70	70	68	0.0153
Male recipient/female donor, %	14	16	19	26	<0.0001
Female recipient/male donor, %	15.4	9.7	7.1	3.8	<0.0001
Recipient, %					
Previous cardiac surgery	39	45	53	54	<0.0001
Previous malignancy	4.3	5.3	9.6	11.0	<0.0001
Creatinine at time of transplant, mg/dl	1.0 (0.6– 2.1)	1.2 (0.7– 2.4)	1.3 (0.8– 2.3)	1.3 (0.8–2.1)	<0.0001
Pulmonary vascular resistance, Wood units	2.0 (0.2– 5.6)	2.1 (0.3– 5.4)	2.1 (0.3– 5.4)	2.1 (0.3–5.8)	0.0505
Diagnosis, %					
Cardiomyopathy	74	55	40	37	< 0.0001
Coronary artery disease	7.3	37	53	57	
Valvular	1.7	3.0	3.3	2.6	
Retransplant	5.3	2.0	1.6	3.2	
Congenital	9.9	1.9	0.5	0.0	
Other causes	1.4	0.8	0.6	0.3	
Pre-operative support (multiple items may be reported), %					
Hospitalized at time of transplant	51	44	41	40	<0.0001
On intravenous inotropes	46	42	42	40	0.0083
Left ventricular assist device	30	30	27	18	<0.0001
Intra-aortic balloon pump	6.5	6.5	5.1	7.5	0.0214
Right ventricular assist device	5.7	4.0	2.3	1.3	<0.0001
Ventilator	3.5	2.7	2.3	3.7	0.0258
Total artificial heart	1.1	1.1	0.6	0.0	0.0140
ECMO	2.1	1.1	0.7	0.0	<0.0001

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio;
[a]Continuous factors are expressed as median (5th–95th percentiles).

non-lymphoma malignancy, renal failure, organ failure, and infection increases.

Recipient age, immunosuppression, and rejection

Use of induction therapy and the type of maintenance immunosuppression documented at the 1-year follow-up are generally similar between age groups. In contrast, any rejection (Figures 14 and 15) and treated rejection are progressively less common with increasing age. However, the higher risk of rejection associated with IL-2R antagonists compared with no induction in the overall cohort appears to be more pronounced in the elderly (Figure 14), and the relative benefit associated with tacrolimus vs cyclosporine in the overall cohort appears somewhat attenuated in the elderly (Figure 15).

Recipient age and post-transplant morbidity

The incidence of post-transplant severe renal dysfunction is less common in the group aged 18 to 39 years and is more frequent, and similar, in groups aged 40 years and older. Malignancy overall (Figure 16), but not lymphoma, increases considerably with increasing age. Although CAV is a less important cause of death in the elderly, its incidence is similar regardless of age (Figure 17), suggesting

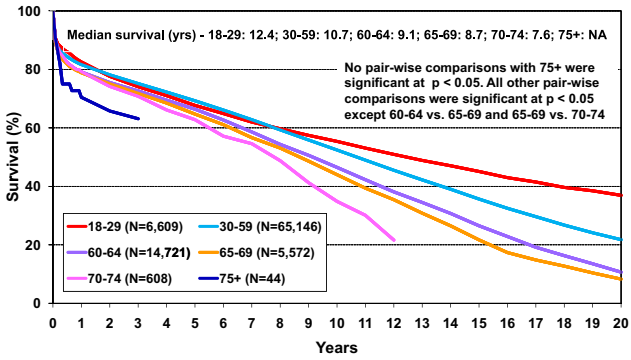

Figure 13 Kaplan-Meier long-term survival by recipient age (adult recipients), transplants 1982–June 2011. NA, not applicable.

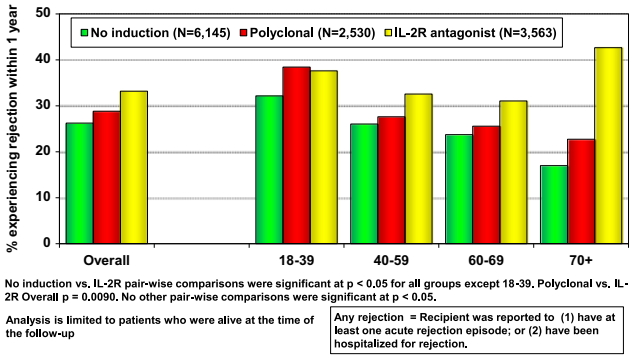

Figure 14 Percentage of recipients experiencing rejection between transplant discharge and 1-year follow-up, by type of induction immunosuppression, and age (adult recipients), follow-up 2005–June 2012. IL-2R, interleukin 2 receptor.

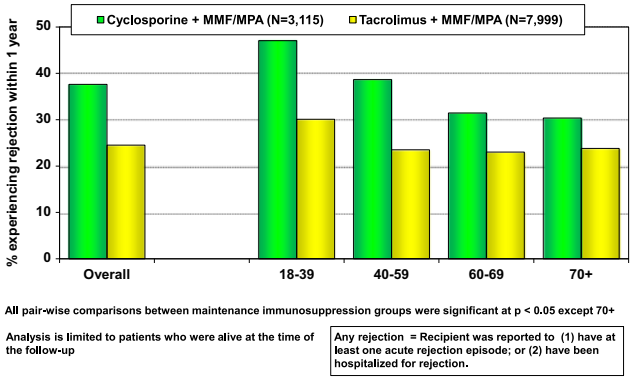

Figure 15 Percent of recipients experiencing rejection between transplant discharge and the 1-year follow-up, by type of maintenance immunosuppression and age (adult recipients), follow-up 2005–June 2012. MMF, mycophenolate mofetil; MPA, mycophenolic acid.

that other competing causes of death gain in importance with increasing age.

Recipient and donor age in multivariable analysis

The online slide set provides detailed results of the association between recipient and donor age and mortality during different periods of follow-up. Figures 18 and 19

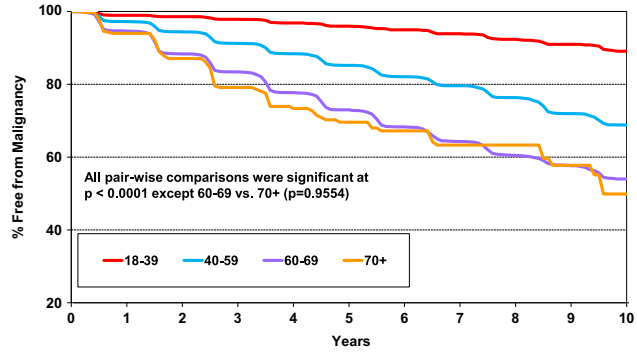

Figure 16 Freedom from malignancy by recipient age (adult recipients), transplants April 1994–June 2011.

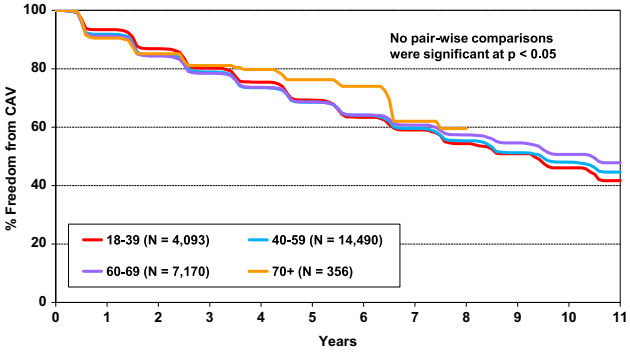

Figure 17 Freedom from cardiac allograft vasculopathy (CAV) by recipient age (adult recipients), transplants April 1994–June 2011.

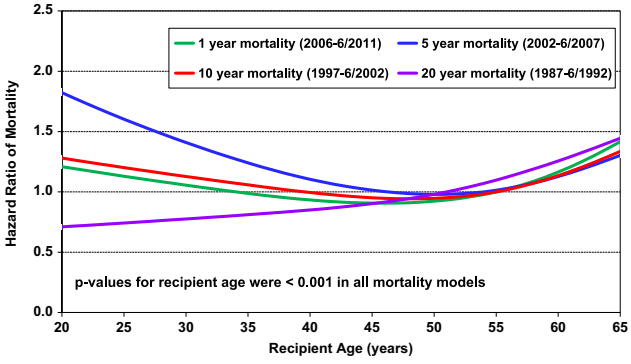

Figure 18 Hazard ratios for mortality by recipient age (adult recipients) from multivariable proportional hazards regression model. Recipients in the different follow-up analyses are from different cohorts.

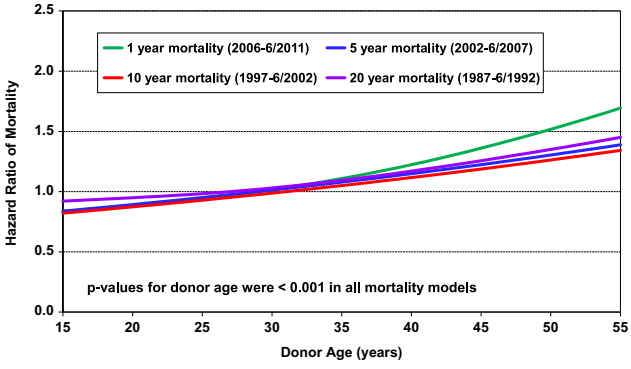

Figure 19 Hazard ratios for mortality by donor age (adult recipients) from multivariable proportional hazards regression models. Recipients in the different follow-up analyses are from different cohorts.

Table 6 Cause of Death for Adult Heart Transplant Recipients by Age Group (Deaths: January 1994–June 2012)

	Age group							
	18-39 years		40-59 years		60-69 years		≥70 years	
Cause of death	≤1 year (n = 1,388)	>1 year (n = 2,856)	≤1 year (n = 5,453)	>1 year (n = 12,967)	≤1 year (n = 2,886)	>1 year (n = 4,751)	≤1 year (n = 117)	>1 year (n = 148)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
CAV	45 (3.2)	578 (20)	154 (2.8)	1,833 (14)	47 (1.6)	393 (8.3)	3 (2.6)	9 (6.1)
Acute rejection	181 (13)	243 (8.5)	380 (7.0)	342 (2.6)	128 (4.4)	88 (1.9)	4 (3.4)	4 (2.7)
Lymphoma	8 (0.6)	88 (3.1)	34 (0.6)	437 (3.4)	17 (0.6)	144 (3.0)	0	0
Malignancy, other	9 (0.6)	186 (6.5)	63 (1.2)	2,588 (20)	41 (1.4)	1,163 (24)	2 (1.7)	37 (25)
CMV	7 (0.5)	2 (0.1)	32 (0.6)	18 (0.1)	15 (0.5)	10 (0.2)	0	0
Infection, non-CMV	189 (14)	201 (7.0)	1,139 (21)	1,418 (11)	733 (25)	613 (13)	31 (26)	18 (12)
Graft failure	455 (33)	879 (31)	1,572 (29)	2,422 (19)	786 (27)	687 (14)	30 (26)	22 (15)
Technical	77 (5.5)	29 (1.0)	254 (4.7)	162 (1.2)	118 (4.1)	33 (0.7)	5 (4.3)	6 (4.1)
Other	111 (8.0)	249 (8.7)	365 (6.7)	994 (7.7)	143 (5.0)	340 (7.2)	4 (3.4)	12 (8.1)
Multiple organ failure	169 (12)	171 (6.0)	914 (17)	901 (6.9)	517 (18)	412 (8.7)	26 (22)	13 (8.8)
Renal failure	6 (0.4)	79 (2.8)	40 (0.7)	746 (5.8)	26 (0.9)	333 (7.0)	2 (1.7)	12 (8.1)
Pulmonary	44 (3.2)	77 (2.7)	166 (3.0)	546 (4.2)	121 (4.2)	251 (5.3)	5 (4.3)	6 (4.1)
Cerebrovascular	87 (6.3)	74 (2.6)	340 (6.2)	560 (4.3)	194 (6.7)	284 (6.0)	5 (4.3)	9 (6.1)
Total deaths, No.	1,566	3,577	6,190	16,174	3,246	5,907	130	175

CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus.

attempt to combine these analyses but should be interpreted with caution because patients in the different follow-up analyses are from different eras, with different patient and treatment characteristics and different access to independent variables for adjustment.

Although the proportions of recipients in older adult age groups are increasing (Figure 9), the older adult age groups are also associated with higher post-transplant risk. Among adults, increasing recipient age throughout the age range was associated with higher mortality in univariable analysis (Figure 13), but the multivariable analysis found higher but also lower recipient ages were associated with higher short-term and intermediate-term survival (Figure 18). This suggests that young adult recipients have more favorable risk profiles in terms of known confounders that are adjusted for (eg, renal function) but higher risk in terms of confounders that are not captured by the Registry (possibly psychosocial and medication adherence limitations in young adults). Univariable and multivariable analyses consistently demonstrated higher mortality with higher donor age. The effect of donor age is most pronounced in the short-term (1-year post-transplant survival; Figure 19).

Conclusions

Thanks to the data reporting efforts of participating heart transplant centers worldwide, this report brings to the public comprehensive and current information regarding developments and challenges in adult heart transplantation. Developments that are notable in this report include a recovery and now a slow increase in the number or heart transplants reported to the Registry, increasing comorbidity and high-risk characteristics among recipients, and a continued increase in the use of MCS, especially in older recipients. There is decreasing use of induction immunosuppression and continued reductions in rejection and other post-transplant morbidities. Despite these improvements, the improvement in unadjusted short-term survival seen up to the early 2000s has leveled off, and long-term survival has not improved notably since reporting began in 1982. However, multivariable analyses show short-term and long-term survival has improved in more recent eras. This discrepancy suggests that care for and prognosis of heart transplant recipients continues to improve but is offset by acceptance of recipients and donors with increasingly higher risk characteristics.

The focus theme on age allows more detailed analysis of one aspect of this development. The proportion of older recipients, particularly aged 60 years and older, is increasing. Although increasing age is a strong independent risk factor for death at all points of follow-up, the complications and causes of death vary dramatically between different age groups. Little is known about age-related aspects of post-transplant outcomes, and generally, post-transplant care is currently not specifically adapted to age in adult heart transplantation. These observations suggest that post-transplant care, in particular immunosuppression, should be more individually tailored, especially with regard to age, and open up opportunities for research aimed at reducing age-specific adverse outcomes.

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.

References

1. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1957;53:457-81.
2. Cox D, Oakes D. Analysis of survival data. London: Chapman and Hall; 1984.
3. Harrell F Jr. Regression modeling strategies. Berlin: Springer; 2001.
4. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report—2012. J Heart Lung Transplant 2012;31:1052-64.
5. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-eighth adult heart transplant report—2011. J Heart Lung Transplant 2011;30:1078-94.
6. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24:1710-20.
7. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant 2006;25:1024-42.
8. Russell SD, Rogers JG, Milano CA, et al. Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. Circulation 2009;120:2352-7.
9. Kirklin JK, Naftel DC, Kormos RL, et al. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant 2013;32:141-56.