

# Twenty-Five Years of Heart Transplantation at Papworth Hospital: Changes in Factors Influencing Short- and Long-Term Patient Survival Over Time

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**Abstract:** 25 years of heart transplantation data were used to identify factors associated with patient survival and investigate changes over time. Analysis was performed across 5 time eras – pre-triple therapy, post-triple therapy to 1990 and the remaining 15 years through 2005 divided into 3 groups of 5 years each. Both short- and long-term survival improved with the advent of triple therapy, but remained unchanged from the early 1990's. Mean donor and recipient age, proportion of female donors and recipients, transplants with two human leucocyte antigen (HLA)-DR mismatches, ischaemic and cardiopulmonary bypass times (CPB) have increased, while rates of rejection and infection have decreased over time. Female donor and recipient diagnosis were independent predictors of short-term mortality. Older age, recipient diagnosis, 2 or more early rejection episodes and number of HLA-A mismatches were independent predictors of mortality in the long-term. Survival rates after heart transplantation improved with advances in patient care, but have remained static since, during which time there have been increases in risk factors and use of more marginal donors.

**Key Words:** Heart transplantation, changes over time, survival analysis.

## INTRODUCTION

Heart transplantation is a well-established treatment for heart failure [1]. The first heart transplant at our institution was performed in 1979, and the procedure has been routinely done for more than twenty-five years.

The main cause of early mortality after transplant is graft failure [1]. Mortality a year or more after transplant is mostly due to cardiac allograft vasculopathy (CAV) [1], which is thought mainly to result from chronic rejection. Modifications of , and additions to, immunosuppression therapy over time have helped to delay and minimize rejection [2-4]. Since the introduction of cyclosporine in 1982, and of triple therapy (cyclosporine, azathioprine and prednisone administered with antithymocyte globulin [ATG]) in 1986, survival after heart transplantation has improved elsewhere [2-5] and at our institution [6]. Advances in donor organ preservation and diagnosis of rejection have also occurred [7]. The International Society for Heart and Lung Transplantation (ISHLT) report that survival has improved in each 5 year period after 1982-1988, although most of this improvement can be attributed to better early post-operative (6-12 month) survival [1].

Risk factors that have been reported to affect survival after heart transplantation include: donor and recipient age, sex, and cytomegalovirus (CMV) status, recipient diagnosis,

donor organ ischaemic time, human leucocyte antigen (HLA) mismatches, donor cause of death, episodes of infection and acute rejection and being on ventricular assist device (VAD) support [1,6;8-20]. A few studies have looked at changes in risk factors over time, and have identified increases in donor and recipient age, female recipients, ischaemic times, and illness and pre-operative inotropic and mechanical support in recipients [1,9;21-23]. These findings indicate that heart transplantation has been performed with more donors and recipients at higher risk (marginal donors and recipients) over time. The concomitant decrease in donors over time [24-28] has led to the use of hearts from borderline donors [22]. It is difficult to delineate the effect more marginal donors and recipients have on survival after heart transplantation when there have been concurrent improvements in donor management and post-transplant treatment [7,29-31].

Studies that have looked at changes in risk factors affecting survival after heart transplantation over time have not combined the use of extensive multiple covariate analyses, survival conditional on surviving the early post-transplant period and a time period as long as 25 years. Using such techniques, this study aims to assess changes in risk factors for survival, and operative and post-operative characteristics, over time and their influence upon survival after heart transplantation. The study was done in particular to see if there were any changes in the impacts of known risk factors and to see whether increases in risk factors in donors and recipients over time had a detrimental effect upon survival. Such information may be useful for centres with shorter follow-up times.

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## METHODS

### Subjects

Between 1979 and December, 2005, there were 1048 first adult heart transplants (97.8% of all heart recipients) during this period. Donors and recipients were matched on ABO blood type and height. Most transplants were performed using the bi-atrial technique [32]. In the mid-1990's, a donor management and resuscitation protocol was implemented at our institution to increase the donor pool [33,34]. This protocol includes full invasive haemodynamic monitoring to assess function and application of optimized treatment for the donor heart based upon the results of monitoring. Donors are started on thyroxine and vasopressin infusion and blood sugar levels of the donor are carefully monitored and maintained. Recipients are consented for use of their routinely gathered data for research upon acceptance to the heart transplantation waiting list, so patients were not further consented for use of their information in this study.

### Variable Definitions

Short-term survival was defined as patient survival to 3 months post-transplant. Long-term survival was defined as patient survival past 3 months post-transplant. Survival times were calculated from transplantation to death or censoring at 31/12/2005. CMV status was paired as follows: donor negative/recipient negative (D-/R-), donor negative/recipient positive (D-/R+), donor positive/recipient negative (D+/R-), and donor positive/recipient positive (D+/R+). For some analyses, ischaemic and cardiopulmonary bypass (CPB) times were grouped into quartiles. Rejection was defined as grade 3 or above or grade 2 with haemodynamic compromise requiring treatment. Infection was documented when an organism was identified in association with clinical evidence of sepsis.

### Statistical Analysis

Analysis was performed across 5 eras: pre-triple therapy (1979-03/1986), and 4 triple therapy eras: 04/1986-1990; 1991-1995; 1996-2000; 2001-2005. The eras were constructed to separate out the pre-triple therapy era, where outcomes might be expected to be different from those that followed, with the remaining years divided into 5-year time periods, providing groups of a sufficient size for analysis, while attempting to ensure consistency in outcomes within a given era. Changes in recipient and donor characteristics and operative factors were assessed over time using Mantel-Haenszel test for trend for categorical variables, ANOVA or Kruskal-Wallis tests for continuous variables, the log rank test for trend for long-term survival and Poisson regression and likelihood ratio tests for rejection and infection rates. Time at risk of rejection/infection was calculated as the time between transplantation and death or censoring at 31/12/2005.

Logistic and Cox proportional hazards regression models were used to explore the relationships between short- and long-term patient survival, respectively, and the following potential explanatory variables: donor and recipient age, sex and CMV status, recipient diagnosis, donor cause of death, and human leukocyte antigen (HLA) mismatches, while adjusting for transplant era. Rejection and infection episodes in

the first three months post-transplant were also included as potential explanatory variables in the analysis of long-term survival. Variables that were not considered for logistic or Cox proportional hazards models are shown in the tables as NC (not considered). Variables that were considered for these analyses, but were not in the final models are shown in the tables as dashes (---). As the time eras served as a proxy for changes over time, including immunosuppression treatment, no further adjustment for type of treatment was made. Backwards stepwise regression methods were used. Variables significant at the  $p < 0.2$  level in univariate analysis were included in the initial multiple model. The likelihood ratio test was used to determine which variables to remove at each iteration. The variable with the largest p-value was removed and this was repeated until those remaining in the model were significant at  $p \leq 0.1$ . For the modeling, the significance level used was 0.1. Any variables listed above that were not significant at this level were tested in the final model to see if they were significant at  $p \leq 0.1$ . This level was used in order to ensure that all potentially important covariates were included in the models. For the other analyses, a significance level of 0.05 was used.

## RESULTS

Of the 1048 patients undergoing heart transplantation, 23 had a second heart transplant and one had a third transplant in this period. The number of heart transplants peaked in 1987/1988 and then declined.

The most common causes of death within 3 months of transplant were infection (28.8%), acute rejection (19.9%, though only 4 patients since 1991), donor organ failure (16.4%) and cerebrovascular accident (6.8%). After 3 months, patients most commonly died from CAV (18.5%), malignancies (7.3%) and infection (4.2%).

### Changes Over Time

Changes over time in pre-transplantation risk factors are shown in Table 1 and changes in operative factors and outcomes including survival are shown in Table 2. Mean recipient age increased over the first two eras, then has remained steady since ( $p < 0.001$ ). Mean donor age and ischaemic times have increased ( $p < 0.001$ ). There was also a higher proportion of female donors ( $p = 0.022$ ), female recipients ( $p < 0.001$ ) and transplants with two HLA-DR mismatches over time ( $p = 0.015$ ). A smaller proportion of ischaemic heart disease (IHD) diagnoses was seen in the most recent era and transplants in patients with rarer conditions increased in the 1996 to 2000 era, with this increase maintained in the 2001-2005 era ( $p < 0.001$ ). The proportion of donors that died from trauma decreased with a concomitant increase in donors that died from stroke, although these changes did not reach significance. In the last two eras, transplants were performed in recipients using VAD support; most of these were in the most recent era. The proportion of transplants with CMV mismatches and two mismatches at the HLA-A and -B loci have not changed significantly over time. CPB and ventilation times have increased ( $p < 0.001$ ), while stay in ITU varied without any monotonic pattern ( $p < 0.001$ ). Short-term survival increased with the advent of triple therapy and again in the next era ( $p = 0.002$ ). Long-term survival in 3-month survivors also improved with triple therapy from 88.7% to

**Table 1. Changes in Characteristics of Heart Transplants Over Five Eras**

Factor	Pre-TT	TT-1990	1991-1995	1996-2000	2001-2005	p-Value
Number of transplants	150	259	236	220	183	
R age, mean (SD)	40.0 (9.6)	46.6 (11.1)	49.0 (9.8)	49.3 (10.3)	46.8 (13.1)	<0.001 <sup>1</sup>
R sex, n (%) female	14 (9.3)	35 (13.5)	34 (14.4)	40 (18.2)	42 (23.0)	<0.001 <sup>2</sup>
R diagnosis, n (%) IHD	71 (47.3)	149 (57.5)	118 (50.0)	105 (47.7)	57 (31.1)	<0.001 <sup>2</sup>
n (%) dilated CM	71 (47.3)	102 (39.4)	104 (44.1)	83 (37.7)	96 (52.5)	
n (%) other	8 (5.3)	8 (3.1)	14 (5.9)	32 (14.5)	30 (16.4)	
VAD support n (%) yes	0	0	0	7 (3.2)	27 (14.8)	ND
D age, mean (SD)	24.6 (7.6)	28.4 (10.6)	34.2 (12.2)	35.5 (13.1)	37.8 (12.8)	<0.001 <sup>1</sup>
D sex, n (%) female	32 (21.3)	80 (30.9)	84 (35.7)	80 (36.4)	59 (32.2)	0.022 <sup>2</sup>
D cause of death, n (%) stroke	59 (39.3)	84 (34.9)	96 (48.0)	116 (58.3)	99 (55.6)	0.90 <sup>2</sup>
n (%) trauma	74 (49.3)	125 (51.9)	82 (41.0)	62 (31.2)	56 (31.5)	
n (%) other	17 (11.3)	32 (13.3)	22 (11.0)	21 (10.6)	23 (12.9)	
Mean mins ischaemic time (SD)	160.3 (32.2)	165.1 (41.9)	186.0 (64.0)	195.3 (52.4)	217.8 (54.6)	<0.001 <sup>1</sup>
CMV mismatches, n (%) D+/R-	16 (12.9)	47 (18.2)	44 (18.6)	45 (20.5)	29 (16.4)	0.42 <sup>2</sup>
HLA-A mismatches, n (%) 0-1	83 (57.2)	160 (64.5)	83 (57.6)	135 (63.7)	98 (56.3)	0.68 <sup>2</sup>
n (%) 2	62 (42.8)	88 (35.5)	61 (42.4)	77 (36.3)	76 (43.7)	
HLA-B mismatches, n (%) 0-1	63 (43.4)	110 (44.4)	60 (41.7)	89 (42.0)	72 (41.4)	0.55 <sup>2</sup>
n (%) 2	82 (56.6)	138 (55.6)	84 (58.3)	123 (58.0)	102 (58.6)	
HLA-DR mismatches, n (%) 0-1	70 (61.4)	141 (58.3)	82 (57.7)	108 (50.9)	86 (50.0)	0.015 <sup>2</sup>
n (%) 2	44 (38.6)	101 (41.7)	60 (42.3)	104 (49.1)	86 (50.0)	

<sup>1</sup>ANOVA p-value, <sup>2</sup>Mantel-Haenszel test for trend p-value, R=recipient, D=donor, TT = triple therapy, SD=standard deviation, IHD=ischemic heart disease, CM=cardiomyopathy, VAD=ventricular assist device. ND=not calculated as not available for all eras.

**Table 2. Changes in Operative Factors and Outcomes after Heart Transplantation Over Five Eras**

Factor	Pre-TT	TT-1990	1991-1995	1996-2000	2001-2005	p-Value
Number of transplants	150	259	236	220	183	
Median mins CPB time (IQR)	94 (27)	84 (30)	102 (33)	114 (40)	122 (54)	<0.001 <sup>1</sup>
Median hrs ventilation (IQR)	7.0 (5.8)	10.0 (6.0)	7.0 (3.3)	9.0 (6.0)	12.0 (17.0)	<0.001 <sup>1</sup>
Median days in ITU (IQR)	6.5 (5.0)	3.0 (2.0)	2.0 (1.0)	1.0 (1.0)	3.0 (5.0)	<0.001 <sup>1</sup>
3-month survival n, % alive	115 (76.7)	220 (84.9)	211 (89.4)	192 (87.3)	164 (89.6)	0.002 <sup>2</sup>
Survival conditional on 3-month survival at 1 year	88.7	94.1	95.3	93.2	94.5	0.001 <sup>3</sup>
Survival conditional on 3-month survival at 5 years	73.0	77.7	84.4	84.4	---	
Rejection episodes within 3mo, n (%) 0	31 (20.7)	72 (27.8)	80 (33.9)	86 (39.1)	115 (62.8)	<0.001 <sup>2</sup>
n (%) 1	60 (40.0)	91 (35.1)	79 (33.5)	65 (29.5)	46 (25.1)	
n (%) 2 or more	59 (39.3)	96 (37.1)	77 (32.6)	69 (31.4)	22 (12.0)	
Infection episodes within 3mo, n (%) 0	69 (46.0)	162 (62.5)	149 (63.1)	151 (68.6)	162 (88.5)	<0.001 <sup>2</sup>
n (%) 1	52 (34.7)	58 (22.4)	69 (29.2)	45 (20.5)	14 (7.7)	
n (%) 2 or more	29 (19.3)	39 (15.1)	18 (7.6)	24 (10.9)	7 (3.8)	

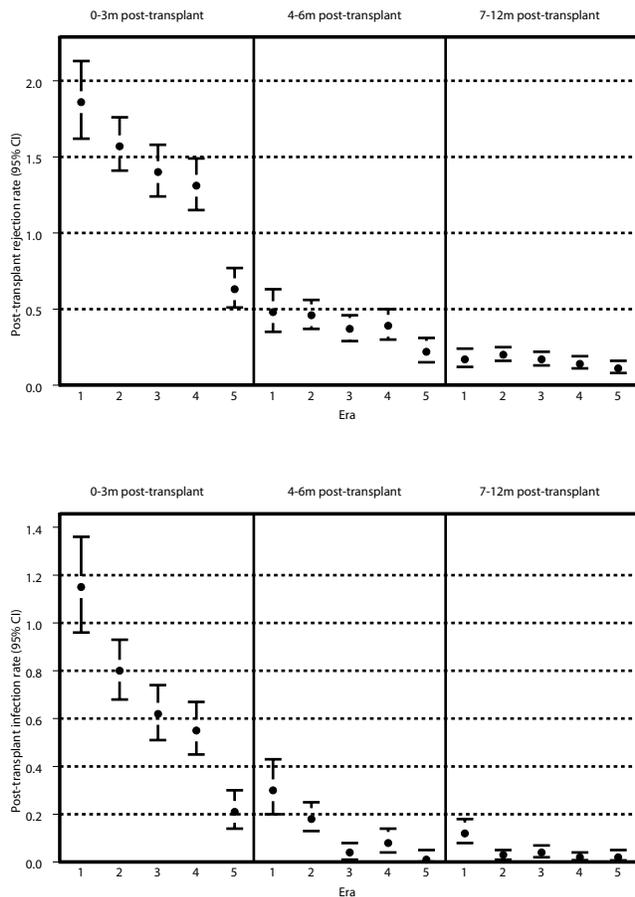
<sup>1</sup>Kruskal-Wallis p-value, <sup>2</sup>Mantel-Haenszel test for trend p-value, <sup>3</sup>Log-rank test for trend p-value, TT = triple therapy, CPB=cardiopulmonary bypass, IQR=interquartile range.

94.1% at 1 year (p=0.001). However, both short- and long-term survival remain unchanged from the early 1990's to date. The proportion of patients with two or more rejection

and infection episodes within 3 months of transplantation has decreased over time (p<0.001).

### Infection and Rejection Rates

Treated rejection rates have decreased over time early after transplantation (Fig. 1,  $p < 0.001$ ), and between 4 to 6 months post-transplantation ( $p = 0.006$ ). Infection rates have decreased over time in all 3 month periods post-transplantation up to 1 year (Fig. 1,  $p < 0.001$ ). Between 7 and 12 months post-transplantation, there was a decrease in infection rates from pre-triple therapy to the first triple therapy era, which has been maintained in subsequent eras.



**Fig. (1).** Post-transplant rejection and infection rates per 100 patient days.

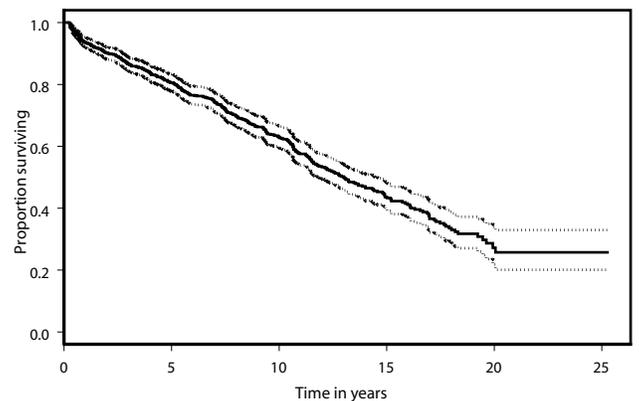
### Short-Term Survival

Results are summarized in Table 3. Transplant recipients in the pre-triple therapy era were more likely to die within 3 months than those in the most recent era. Female recipients, and those with female donors, were more likely to die in the short-term. In general, greater CPB times increased the likelihood that an individual died early. Recipients with a diagnosis of IHD, or with other diagnoses were more likely to die within 3 months than people with dilated cardiomyopathy (CM). Receiving a heart from a CMV positive donor, especially when the recipient was CMV negative, was related to death early after transplantation. There was a weak relationship between longer ischaemic times and dying within 3 months, although this was not significant in the presence of other variables. Recipient and donor age, HLA mismatches and donor cause of death were not associated with short-term mortality in this study.

Multiple logistic regression analysis showed that donor sex and recipient diagnosis were the strongest predictors of short-term mortality when adjusting for transplant era (Table 3).

### Long-Term Survival

Survival (including the first three months post-transplantation) for the cohort of transplant recipients after 1, 5, 10 and 20 years were 80.5%, 69.3%, 54.1% and 23.4%. The same figures for transplant recipients conditional on surviving 3 months were 93.6%, 80.5%, 62.9% and 27.2% (Fig. 2). The median survival time from first transplant for this subgroup was 13.0 years (95% CI, 11.7 – 14.3).



**Fig. (2).** Survival from 1st transplant by year in recipients surviving for 3 months.

Results of the Cox regression analysis are summarized in Table 4. Older recipients and recipients of organs from older donors had poorer long-term survival. Longer ventilation time and IHD diagnosis were also significantly associated with poorer long-term survival. Having one HLA-A mismatch was weakly associated with better long-term survival when compared to having no mismatches, although this did not reach significance. Recipients of hearts from CMV positive donors fared worse than those receiving hearts from CMV negative donors, particularly CMV negative recipients. Recipient sex, donor sex, ischaemic time, CPB time, HLA-B or -DR mismatches and donor cause of death were not associated with long-term survival.

Multiple Cox regression analysis indicated that recipient age, diagnosis, number of rejection episodes and number of HLA-A mismatches were the strongest predictors of long-term survival when adjusting for transplantation era (Table 4).

### DISCUSSION

The existence of more than 25 years of heart transplantation experience provided an opportunity both to observe changes in patient care over time and to update our knowledge of the characteristics of recipients and donors and how these affect outcomes. This is particularly important in light of the shortage of donors in order to determine the effect of expansion of donor selection criteria and improvements in treatment over time on recipient outcomes.

**Table 3. Relationship between Pre-Transplant and Operative Characteristics and Short-Term (3 Month) Mortality**

Risk Factor	Died n=146	Survived n=902	OR Adjusted for Era (95% CI)	OR Multiple <sup>1</sup> (95% CI)
Time period, n (%) 1 <sup>st</sup> era	35 (24.0)	115 (12.7)	2.63 (1.43, 4.82)	2.95 (1.58, 5.52)
n (%) 2 <sup>nd</sup> era	39 (26.7)	220 (24.4)	1.53 (0.85, 2.75)	1.55 (0.84, 2.83)
n (%) 3 <sup>rd</sup> era	25 (17.1)	211 (23.4)	1.02 (0.54, 1.92)	1.00 (0.52, 1.90)
n (%) 4 <sup>th</sup> era	28 (19.2)	192 (21.3)	1.26 (0.68, 2.34)	1.16 (0.62, 2.17)
ref=5 <sup>th</sup> era				
Mean R age (SD) (OR for 10y)	47.1 (11.5)	46.8 (11.2)	1.13 (0.95, 1.34)	---
R sex, n (%) female	30 (20.5)	135 (15.0)	1.63 (1.04, 2.55)	---
ref=male				
R diagnosis, n (%) IHD	79 (54.1)	421 (46.7)	1.51 (1.02, 2.22)	1.57 (1.07, 2.32)
n (%) other	17 (11.6)	75 (8.3)	2.08 (1.12, 3.87)	2.08 (1.11, 3.87)
ref= dilated CM				
Mean D age (SD) (OR for 10y)	32.4 (12.2)	32.3 (12.5)	1.13 (0.97, 1.33)	---
D sex, n (%) female	63 (43.2)	272 (30.2)	1.93 (1.34, 2.78)	1.97 (1.36, 2.85)
ref=male				
D cause of death				
n (%) trauma	55 (39.9)	344 (41.4)	0.85 (0.57, 1.26)	---
n (%) other	16 (11.6)	99 (11.9)	0.90 (0.50, 1.63)	---
ref=stroke				
Ischaemic time				
n (%) 149-180 m	43 (30.1)	218 (24.5)	1.24 (0.76, 2.03)	---
n (%) 181-219 m	25 (17.5)	229 (25.7)	0.78 (0.45, 1.36)	---
n (%) 220-393 m	40 (28.0)	216 (24.2)	1.71 (0.99, 2.93)	---
ref=18-148 m				
Paired CMV status				
n (%) D+/R-	31 (23.3)	150 (17.0)	2.11 (1.16, 3.83)	---
n (%) D+/R+	42 (31.6)	237 (26.9)	1.75 (1.00, 3.07)	---
n (%) D-/R+	39 (29.3)	285 (32.3)	1.35 (0.77, 2.37)	---
ref=D-/R-				
HLA-A locus mismatches				
n (%) 1	63 (47.4)	393 (49.7)	0.83 (0.46, 1.51)	---
n (%) 2	54 (40.6)	310 (39.2)	0.92 (0.50, 1.69)	---
ref=0				
HLA-B locus mismatches				
n (%) 1	44 (33.1)	301 (38.1)	1.27 (0.47, 3.38)	---
n (%) 2	84 (63.2)	445 (56.3)	1.66 (0.64, 4.34)	---
ref=0				
HLA-DR locus mismatches				
n (%) 1	51 (42.1)	372 (48.9)	0.58 (0.29, 1.16)	---
n (%) 2	58 (47.9)	337 (44.3)	0.76 (0.38, 1.51)	---
ref=0				
CPB time, n (%) 86-102 m	39 (30.0)	209 (23.9)	1.93 (1.11, 3.33)	NC
n (%) 103-125 m	22 (16.9)	222 (25.4)	1.21 (0.64, 2.26)	
n (%) 126-207 m	43 (33.1)	202 (23.1)	2.95 (1.67, 5.23)	
ref= 25-85 m				

<sup>1</sup>OR adjusted for all variables in final model, R=recipient, D=donor, OR=odds ratio, SD=standard deviation, IHD=ischaemic heart disease, CM=cardiomyopathy, CPB=cardiopulmonary bypass, NC = not considered for multiple models, --- = considered but not in final model.

**Table 4. Relationship between Pre-Transplant and Operative Characteristics and Long-Term Survival**

Risk Factor	Deaths n=390	Survivors n=512	HR Adjusted for era (95% CI)	HR Multiple <sup>1</sup> (95% CI)
Time period, n (%) 1 <sup>st</sup> era	95 (24.4)	20 (3.9)	1.44 (0.85, 2.46)	1.78 (1.00, 3.19)
n (%) 2 <sup>nd</sup> era	141 (36.2)	79 (15.4)	1.01 (0.60, 1.70)	1.02 (0.58, 1.79)
n (%) 3 <sup>rd</sup> era	88 (22.6)	123 (24.0)	0.80 (0.47, 1.37)	0.76 (0.42, 1.38)
n (%) 4 <sup>th</sup> era	48 (12.3)	144 (28.1)	0.81 (0.47, 1.42)	0.77 (0.43, 1.39)
ref=5 <sup>th</sup> era				
Mean R age (HR for 10y)	46.8 (10.6)	46.7 (11.6)	1.27 (1.14, 1.41)	1.26 (1.11, 1.43)
R sex, n (%) female	42 (10.8)	93 (18.2)	0.80 (0.58, 1.10)	---
ref=male				
Recipient diagnosis, n (%) IHD	220 (56.4)	201 (39.3)	1.50 (1.22, 1.85)	1.30 (1.02, 1.65)
n (%) other	22 (5.6)	53 (10.4)	1.04 (0.66, 1.63)	1.05 (0.64, 1.73)
ref= dilated CM				
D age, n (%) 21-30 y	105 (27.0)	134 (26.2)	1.05 (0.79, 1.39)	---
n (%) 31-40 y	91 (23.4)	107 (20.9)	1.51 (1.13, 2.02)	---
n (%) 41-50 y	79 (20.3)	105 (20.5)	1.55 (1.13, 2.13)	---
n (%) 51 y+	20 (5.1)	57 (11.2)	1.44 (0.86, 2.40)	---
ref=0-20 y				
Dsex, n (%) female	104 (26.7)	168 (32.8)	0.93 (0.74, 1.17)	---
ref=male				
Donor cause of death, n (%) trauma	161 (44.8)	183 (38.9)	0.88 (0.71, 1.10)	---
n (%) other	39 (10.9)	60 (12.7)	0.89 (0.62, 1.26)	---
ref=stroke				
Ischaemic time, n (%) 149-180m	108 (28.1)	110 (21.7)	1.08 (0.83, 1.40)	---
n (%) 181-219m	104 (27.1)	125 (24.7)	1.25 (0.95, 1.63)	---
n (%) 220-393m	58 (15.1)	158 (31.2)	1.00 (0.72, 1.40)	---
ref=18-148 m				
Paired CMV status, n (%) D+/R-	69 (18.4)	81 (16.0)	1.47 (1.06, 2.04)	---
n (%) D+/R+	114 (30.3)	123 (24.4)	1.33 (1.00, 1.78)	---
n (%) D-/R+	115 (30.6)	170 (33.7)	1.12 (0.84, 1.50)	---
ref=D-/R-				
HLA-A locus mismatches, n (%) 1	159 (46.8)	234 (52.0)	0.77 (0.53, 1.13)	0.83 (0.56, 1.22)
n (%) 2	149 (43.8)	161 (35.8)	1.02 (0.70, 1.50)	1.07 (0.73, 1.57)
ref=0				
HLA-B locus mismatches, n (%) 1	127 (37.4)	174 (38.7)	1.01 (0.63, 1.60)	---
n (%) 2	192 (56.5)	253 (56.2)	1.05 (0.67, 1.65)	---
ref=0				
HLA-DR locus mismatches, n (%) 1	156 (48.6)	216 (49.1)	1.08 (0.69, 1.71)	---
n (%) 2	144 (44.9)	193 (43.9)	1.24 (0.78, 1.97)	---
ref=0				
Rejection episodes within 3mo, n (%) 1	124 (31.8)	182 (35.5)	0.82 (0.64, 1.07)	0.94 (0.71, 1.24)
n (%) 2 or more	153 (39.2)	139 (27.1)	1.15 (0.90, 1.47)	1.32 (1.01, 1.73)
ref=0				
Infection episodes within 3mo, n (%) 1	104 (26.7)	108 (21.1)	0.94 (0.74, 1.19)	---
n (%) 2 or more	54 (13.8)	36 (7.0)	1.32 (0.97, 1.78)	---
ref=0				
Median mins CPB (IQR) (HR for 30m)	96.0 (35.0)	107.0 (41.8)	1.07 (0.98, 1.16)	NC
Median hrs ventilation (IQR) (HR per hr)	8.0 (6.0)	9.0 (8.0)	1.01 (1.00, 1.01)	NC

<sup>1</sup>HR adjusted for all variables in final model, R=recipient, D=donor, HR=hazard ratio, IHD=ischaemic heart disease, CM=cardiomyopathy, CPB=cardiopulmonary bypass, IQR=interquartile range, NC = not considered for multiple models, --- = considered but not in final model.

At our institution, overall patient survival after heart transplantation was similar to that seen by others [1,12,17, 19,21-23,35], as were trends in early mortality over time [21]. Despite improvement with the advent of triple therapy, survival has remained static in subsequent time periods. The number of heart transplants performed at our institution per year has generally declined after 1988. This stems from less availability of donor organs [24-28], probably due in part to the passing of seatbelt legislation in the late 1980s and again in the late 1990s, reflected by fewer donors dying from trauma, and improvements in treatment for stroke. As might be expected, fewer donors and the implementation of the marginal donor resuscitation protocol (see Methods - Subjects section) led to the use of more marginal donors, who were older, more likely to be female and had longer cold ischaemic times in more recent eras. Longer ischaemic times have resulted from fewer domino transplants and more out-of-zone donors [36]. Transplants were also performed in recipients with more risk factors; over time recipients were older, more often female, had rarer conditions and were more often using VADs, the latter indicating that some recipients may have been less well acutely, but were stabilized. Similar trends have been seen by others [1,22]. Operations at our institution have become more complex over time with longer CPB and ventilation times. Use of marginal donors and more complex operations in marginal recipients could explain why survival rates have not appreciably improved over time. We did not, however, see a decrease in either short- or long-term survival. Heart transplantation has been shown to be beneficial in the case of high risk recipients and marginal donors [37]. A U.S. study showed improved survival over time despite increasing risk factors for transplantation [22]. Advances in immunosuppression and management of infection and rejection, reflected in these findings by decreasing rejection and infection rates over time, may have counterbalanced the increased risks.

Donor gender and recipient diagnosis predicted early mortality; recipients of hearts from female donors or with rarer diagnoses had nearly two times the odds of early death. Others have also found donor gender to be a predictor of early mortality [12,22] and an association between female donor and worse graft survival [38]. Female recipient also predicted an increased risk of death in the short term. Female recipients most often get female hearts because of size-matching of donor and recipient. Hearts from females tend to be smaller and to generally have a lower power output, which could affect early outcomes. Another possible reason for the risk of early death could be the association of hearts from female donors with early death from acute rejection [6,10]. While they were related to short-term survival, donor and recipient gender were not important predictors of long-term survival, which has been seen by others [10,35,39,40]. Recipient characteristics were important for long-term survival; the hazard of death for recipients increased 1.3 times for every 10 year increment of age and recipients with IHD diagnosis had 1.3 times the hazard of dying compared to those with dilated CM. This suggests that recipient age and diagnosis should continue to be considered when deciding on suitability for transplant. It has, however, been shown that many older recipients have good outcomes [41-43]. The effect of HLA-A mismatches is not clear and it is likely that acute rejection episodes provide a more direct measure of the

effect of tissue mismatch on survival. A detrimental effect of no mismatches on longer term graft survival has been noted before [18]. Rejection remains an important contributor to mortality in the long-term. Although the proportion of recipients having 2 or more rejection episodes within 3 months of transplantation has decreased significantly over time, multiple early rejection episodes increased the risk of death in the long-term, possibly due to acute rejection episodes predisposing these patients to CAV [44]. There is a continued need to understand the mechanisms of rejection and to improve its treatment.

Some characteristics were associated with survival in univariate, but not multiple variable analyses. This does not necessarily mean that these variables are not important predictors of survival in the context of changes over time and variables such as age, gender and diagnosis which are related; multiple variable analysis identifies the most powerful variables and the variables with independent associations with the outcome. For example, CMV matching status was associated with short- and long-term survival in univariate, but not multiple variable analyses. CMV prophylaxis has changed over time; initially none was available, then intravenous prophylaxis with ganciclovir was introduced in 1992 [45], followed by effective oral therapies [46]. Such improvements in CMV prophylaxis and, in common with all infections, decreasing CMV infection over time (data not shown) may explain the weaker effect of donor/recipient CMV mismatch on survival. Donor age was also associated with long-term survival in univariate, but not multiple variable analyses. The effect of donor age on long-term survival found here is consistent with the association between donor age and the onset of CAV, likely due to older donors having the potential to carry pre-existing coronary disease [47].

Although mean donor organ ischaemic time has increased over time, and had a weak association with short-term mortality, it was not an independent predictor of short- or long-term survival in this study. There was some evidence in our study that patients with the longest ischaemic times had poorer short-term survival than those with the shortest when taking era into account, however, this effect did not remain when donor sex and recipient diagnosis were included. A UK study of first adult heart transplants also found an association with short-term mortality in a univariate analysis [36]. Some groups have found a relationship between ischaemic time and 1 year mortality in studies of larger numbers of patients [1,22], but there does not seem to be a relationship with long-term survival [1,12,22]. Smaller studies such as ours have less power to detect differences in ischaemic time. It may also be that improvements in donor management have partly overcome increasing ischaemic times. In addition, the effect of ischaemic time is difficult to separate from other risk factors because the transplant decision is multifactorial.

In conclusion, the early increase in survival after cardiac transplantation due to improved immunosuppression and patient care has been maintained but has not increased further. Likely causes are increasing numbers of marginal donors (as a result of the shortage of ideal donors) and higher-risk recipients. Heart transplantation is an extremely effective therapy for patients with end-stage heart disease and strategies to maintain and encourage organ donation are important.

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