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Improved long-term survival in Dutch heart transplant patients despite increasing donor age: the Rotterdam experience

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Summary

Over the past decades donor and recipient characteristics and medical management of heart transplantation (HT) patients have changed markedly. We studied the impact of these changes on long-term clinical outcome. Data of all consecutive HT recipients in our center have been collected prospectively. Cohort A (n = 353) was defined as the adult pts transplanted between 1984 and 1999 and was compared with cohort B (n = 227) transplanted between 2000 and 2013. Compared with cohort A, recipients in cohort B had older donors (mean age 29 vs. 43 years, donors aged >50 year: 2% vs. 33%, respectively). Survival at 1 and 10 years in cohort A vs. B was 89% vs. 86% and 53% vs. 68%, respectively (P = 0.02). Cohort B pts were treated more often with tacrolimus-based immunosuppression (77% vs. 22%; P = <0.0001) and early statins post-HT (88% vs. 18%; P = 0.0001), while renal function was better conserved at 5 and 10 years (P = 0.001 and 0.02). Multivariate analysis showed significant reduction in 10-year mortality with tacrolimus-based immunosuppression (HR 0.27 and 95% CI 0.17–0.42), hypertension post-HT (HR 0.5, 95% CI 0.36–0.72), and revascularization (HR 0.28, 95% CI 0.15–0.52). In spite of the use of much older donors, the long-term outcome after HT has improved considerably in the last decade, probably due to the introduction of newer treatment modalities.

Background

Heart transplantation (HT) is the preferred treatment for patients with end-stage heart failure [1]. It prolongs life and improves its quality. Major limitations, however, are the shortage of suitable donor hearts and the relatively limited long-term survival after HT. According to the registry of the International Society for Heart and Lung Transplantation (ISHLT), the annual number of transplantations has stabilized around 4000 cases, worldwide (www.ishlt.org). Waiting lists are long, and sometimes patients have to wait for more than 2 years. In the ISHLT registry, the median donor age has gradually increased from 23 to 34 years over the past 30 years (www.ishlt.org). Median survival after HT is 11 years, while conditional survival on surviving the first year is 13 years. Short-term survival depends on the occurrence of early complications such as primary graft failure, right ventricular failure, acute rejection, and infection [2]. Side effects of the essential immunosuppressive therapy as well as allograft vasculopathy as a manifestation of vascular rejection have a major impact on long-term survival. Infections and malignancies are consequences of immunosuppression in general, whereas renal dysfunction and hypertension are side effects of the calcineurin inhibitors

cyclosporin and tacrolimus. Over the years, there has been a gradual and continuous improvement of long-term outcome after HT, mostly due to improvement in immunosuppressive therapy and the prevention, diagnosis, and treatment of complications [1–3].

In the Netherlands in particular, the increasing shortage of suitable donors has forced transplantation physicians to accept more risky and older donors, even beyond 55 years. The number of suitable donors from traffic accidents has shown a marked decrease, resulting in a larger proportion of older, more stroke-related donors, with a higher burden of atherosclerotic cardiovascular disease [4]. The latter may result in worsening of long-term outcome. On the other hand, newer immunosuppressive regimens have resulted in a lower incidence of side effects, less rejection episodes, and a lower risk of cardiac allograft vasculopathy [5]. Furthermore, the treatment of cardiac allograft vasculopathy has also improved due to the proactive application of revascularization procedures such as percutaneous coronary interventions and coronary artery bypass grafting [6].

The aim of this study was to investigate the long-term outcome of heart transplant recipients in the contemporary transplant and treatment era and to analyze the impact of the aging donor population, as well as of new treatment options.

Methods

Study design and patient population

Data of all HT patients who were transplanted in the Erasmus MC, Rotterdam, have been collected prospectively since the first transplantation in June 1984. We included all 580 adult (≥18 years) patients transplanted between 1984 and December 2013 in this study. Patients consented to use anonymized data for research purposes. The institutional review board of the Erasmus MC approved this study. Patients who were retransplanted were analyzed as new patients with the pretransplantation diagnosis 'failure of first graft'. A comparison was made between patients transplanted from 1984 up to and including 1999 (cohort A) and patients transplanted from 2000 up to December 2013 (cohort B). The definition of these cohorts was based on a combination of the following facts: Around the year 2000, the number of suitable donor hearts dropped despite the acceptance of older donors, newer immunosuppressants were introduced and statins were started early after HT irrespective of cholesterol levels.

Recipient selection

Patients suffering from end-stage heart disease despite optimal medical as well as interventional/or reparative surgical treatment were accepted on the Eurotransplant waiting list when absolute contraindications had been ruled out [2].

Donor selection

During the early years of the program, only hearts form donors under 36 years of age were accepted for transplantation. Later on, the upper age limit of donors gradually shifted to 65 years. This has been accompanied by more extensive screening of donor hearts, including echocardiography and in selected cases coronary angiography. At the one side, we decided to reject hearts with moderate to severe left ventricular hypertrophy (>14 mm), and at the other side, we no longer rejected older hearts solely on the presence of cardiovascular risk factors but postponed the decision about acceptance of the heart until after coronary arteriography. Donor hearts showing stenotic lesions of ≥50% in one or more coronary arteries have been excluded from transplantation. Transplant candidates with panel reactive antibodies of >5% were only transplanted after they tested negative in the cross-match with the allocated donor.

Transplant surgery

Almost all transplantations were performed according to the technique of Lower, using bi-atrial anastomoses [7]. Urgent HT refers to patients who deteriorated on the waiting list and were granted priority on the Eurotransplant waiting list. Ischemia time refers to the time from clamping the aorta of the donor during retrieval of the donor heart until removing the aortic clamp of the recipient after surgical completion of the transplantation.

Immunosuppression and rejection

Several regimens of induction therapy (intravenous anti-T-cell antibodies immediately after transplantation) have been used over time. In this study, we compared the use of induction therapy with no induction therapy at all. Maintenance immunosuppression has evolved over the last 30 years. The basic component has always been a calcineurin inhibitor. From 1984 to 1999, immunosuppression was cyclosporine based. Next to cyclosporine, prednisone was used. If two or more rejection episodes occurred, immunosuppression was complemented with azathioprine or mycophenolate mofetil (MMF). In 2000, the immunosuppression therapy changed to a tacrolimus-based scheme combined with prednisone and MMF. Acute rejection episodes were treated with pulsed high-dose methylprednisolone or, in case of steroid-resistant rejection, rabbit antithymocyte globulin (r-ATG).

Rejection surveillance was performed by routine endomyocardial biopsy (EMB) during the first year after transplantation. After the first year post-transplant, EMBs were only taken when rejection was suspected. Grading of the histological findings was by three consecutive systems: Billinghams' original criteria, the 1990 standard of grading from the ISHLT, and the revised 2005 standard of the ISHLT [8–11]. Treatment of cellular rejection was started whenever 'moderate rejection' or more, grade ≥3A (1990 grading) or grade ≥2R (revised 2005 grading), was diagnosed. Humoral rejection (later on antibody mediated rejection) was treated only in case of signs of graft failure in combination with histological and/or immunopathologic findings.

Infection prophylaxis and infection

Initially, cytomegalovirus (CMV) seronegative recipients of the heart from a CMV seropositive donor (i.e., CMV mismatch) received passive immunization with anti-CMV hyperimmunoglobulin during the first 72 days [12]. From 2003 on, oral valganciclovir was prophylactically administered for 6 months. In this study, we compared the number of patients with CMV mismatch and the occurrence of CMV disease between the two cohorts. Over the years, *Toxoplasma gondii* seronegative recipients of the heart of a Toxoplasma-seropositive donor were prophylactically treated with spiramycin, pyrimethamine alone or in combination with sulfadiazine, or cotrimoxazol, respectively.

Clinical course after transplantation

To monitor the clinical course after HT, data were collected on comorbidities, laboratory results and heart function. Exercise capacity at 1 year was determined by bicycle ergometry and was defined as percentage of the predicted capacity in a healthy population, adjusted for age, length, and weight. Hypertension after HT was considered to be present when patients received antihypertensive medication, which was usually started after repeated blood pressure measurements of >140/90 mm Hg. End-stage renal disease was defined as the need for renal replacement therapy (i.e., the start of either hemodialysis, peritoneal dialysis, or kidney transplantation).

Cardiac allograft vasculopathy

During the first year of the program, coronary arteriography (CAG) was performed annually. After the evaluation of our first 119 1-year survivors, however, CAG was performed 1 year after transplantation and only repeated annually if there was clear evidence of cardiac allograft vasculopathy [13]. In case of limited wall irregularities or normal coronary arteries, routine coronary angiography was postponed to the fourth year. From year 5 on, coronary angiography was performed only when annual surveillance myocardial perfusion imaging showed perfusion defects, the patient was symptomatic, showed signs of myocardial ischemia like electro-cardiographical alterations, and/or new wall motion abnormalities on echocardiography. Cardiac allograft vasculopathy was considered to be present when at least ISHLT cardiac allograft vasculopathy grade 1 was diagnosed by coronary angiography [13,14]. Myocardial infarction was diagnosed based on biomarkers, echocardiographic, scintigraphic, and/or electrocardiographic evidence according to the European Society of Cardiology guidelines at that time [15]. Since 1996, all patients, regardless of their lipid levels, were prescribed a statin, starting 1–2 weeks after transplantation [16].

Malignancies

All malignancies were noted and classified as skin cancer (which included melanoma), post-transplant lympho-proliferative disorder, lung cancer, or other.

Cause of death

Right ventricle failure due to pulmonary hypertension, primary graft failure, perioperative technical problems, and acute rejection in hospital was summarized as 'in hospital mortality'. Infections were classified as viral, bacterial, fungal, or parasitic. Vascular disease includes cerebrovascular, central aortic, or peripheral vessel pathology. Late cardiac mortality is defined as unexplained cardiac death. Coronary events are deaths caused by graft vascular disease proven by ECG, coronary angiogram, scintigraphy, or postmortem examination. Other modes of death were classified as malignancy, renal insufficiency, multi-organ failure, or unknown cause.

Statistical analysis

The data were analyzed using IBM SPSS STATISTICS version 22 (IBM Corp., New Orchard Road, Amonk, New York 10504, USA). All categorical data are presented as numbers with percentages. These variables were compared using the chi-square test. All continuous data are presented as mean ± standard deviation or median with interquartile range. An independent sample *t*-test was used to compare the continuous variables. Survival analysis was performed using the Kaplan–Meier method, and curves were compared with the log-rank test. Univariate analysis was performed by the Cox proportional hazards model. Significant results of univariate analysis (P value < 0.05) were included in a multivariate analysis to determine independent predictors of all-cause mortality.

Results

Cohort A included 353 patients with a median follow-up of 20 years. Cohort B includes 227 patients and had a median follow-up of 6.5 years. The clinical characteristics of these patients are listed in Table 1. The mean recipient age has not increased significantly, although more recipients in cohort B were over 60 years. More women were transplanted in the recent era and the original etiology of heart disease shifted from predominantly ischemic heart disease to cardiomyopathy. Diabetes mellitus was more often present prior to transplantation in cohort B.

Table 1. Clinical characteristics of all heart transplantation patients (n = 580).

	Cohort A 1984–1999 n = 353	Cohort B 2000–2013 n = 227	P value
Recipient			
Age (years; mean ± SD)	48 ± 10	50 ± 11	0.07
<39, *n* (%)	58 (16)	36 (16)	0.86
40–49, *n* (%)	107 (30)	60 (26)	0.31
50–59, *n* (%)	154 (44)	88 (39)	0.25
>60, *n* (%)	34 (10)	43 (19)	<0.0001
Female gender, *n* (%)	61 (17)	74 (33)	<0.0001
Pretransplantation diagnosis, *n* (%)			
Cardiomyopathy	133 (38)	123 (54)	<0.0001
Coronary artery disease	203 (58)	89 (39)	<0.0001
Valvular	11 (3)	5 (2)	0.51
Congenital	3 (1)	7 (3)	0.04
Retransplant	2 (1)	3 (1)	0.34
CMV mismatch, *n* (%)	69 (20)	56 (25)	0.14
Toxoplasmosis mismatch, *n* (%)	47 (13)	49 (22)	0.009
Serum creatinine pre-HT (μmol/l; mean ± SD)	121 ± 50	124 ± 42	0.53
Diabetes pre-HT, *n* (%)	12 (4)	21 (9)	0.004
Left ventricular assist device, *n* (%)		16 (7)	
Donor			
Age (years; mean ± SD)	29 ± 10	43 ± 13	<0.0001
<39, *n* (%)	286 (81)	73 (32)	<0.0001
40–49, *n* (%)	51 (14)	74 (33)	<0.0001
50–59, *n* (%)	8 (2)	62 (27)	<0.0001
>60, *n* (%)	0 (0)	13 (6)	<0.0001
Female gender, *n* (%)	143 (41)	131 (58)	<0.0001
Cause of death, *n* (%)			
Head trauma	161 (55)	64 (28)	<0.0001
Stroke	117 (40)	146 (65)	<0.0001
Other	14 (5)	16 (7)	0.10
Surgery			
Ischemia time (min; mean ± SD)	165 ± 38	192 ± 48	<0.0001
Rethoracotomy, *n* (%)	58 (16)	35 (15)	0.75
Prior cardiac surgery, *n* (%)	78 (22)	83 (37)	<0.0001
Urgent transplantation, *n* (%)	101 (29)	85 (37)	0.03
Days in ICU post-HT (median [IQR])	3 [3–4]	4 [3–8]	<0.0001
Days in hospital post-HT (median [IQR])	18 [16–29]	30 [23–41]	<0.0001
Immunosuppressive therapy			
Induction therapy, *n* (%)	242 (69)	205 (91)	<0.0001
Maintenance immunosuppression, *n* (%)			
Cyclosporine	262 (78)	47 (23)	<0.0001
Tacrolimus	73 (22)	156 (77)	<0.0001
+MMF	24 (7)	90 (44)	<0.0001
+Prednisone	310 (92)	167 (82)	<0.0001
+Azathioprine	85 (25)	0 (0)	<0.0001
Statins early post-HT, *n* (%)	65 (18)	198 (88)	<0.0001

SD, standard deviation; IQR, interquartile range; CMV, cytomegalovirus; ICU, intensive care unit; HT, heart transplantation; MMF, mycophenolate mofetil.

Donor characteristics

A major change in donor characteristics was noted. In cohort A, most donors were young men who died due to head trauma (traffic accident, etc.), whereas in cohort B, donors were much older (mean age 29 ± 10 vs. 43 ± 13 years) mostly female and the main cause of death was hemorrhagic stroke. The distribution of donor ages per year of transplantation is shown in Fig. 1.

Transplant surgery

Compared with cohort A, more patients in cohort B had had prior cardiac surgery (22 vs. 37%, $P < 0.0001$) and more transplantations were performed on an urgent basis (29% vs. 37%, $P = 0.03$). In cohort B, 16 (7%) patients were on LVAD as bridge to transplantation. The mean ischemia time was 27 min longer in cohort B and patients in cohort B stayed 1 day longer on the ICU ($P < 0.0001$) as well as 12 days longer in hospital ($P < 0.0001$; see also Table 1).

Immunosuppression and rejection

Induction therapy was used more often in cohort B (69% vs. 91%, $P < 0.0001$). Maintenance immunosuppression was mainly cyclosporin based (78%) in cohort A, combined with prednisone (92%) and/or azathioprine (25%). In cohort B, immunosuppression was mainly tacrolimus based (77%), often in combination with prednisone (82%), and/or MMF (44%). The incidence of rejection episodes after the first year was similar in both cohorts (Table 2), but in cohort A, more recurrent (>2) episodes of acute rejection occurred compared with cohort B (27% vs. 8%, $P < 0.0001$).

Infection

Both CMV serology donor–recipient mismatch and the occurrence of CMV disease were not significantly different between the two cohorts. Furthermore, we previously established that the *Toxoplasma gondii* sero-status was not associated with long-term survival after HT [17].

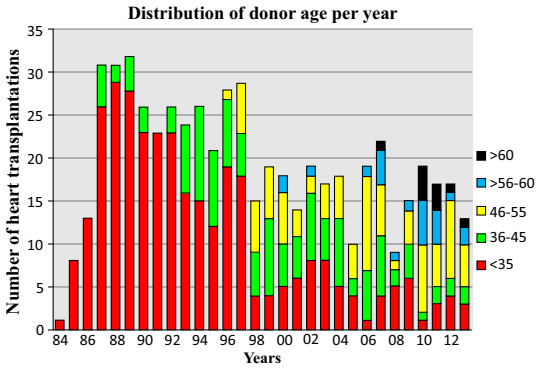

Figure 1 Distribution of donor age versus the year of transplantation.

Clinical course after transplantation

Left ventricular ejection fraction at 1 year was similar in both cohorts (Table 2). However, there was a modest decrease in exercise capacity at 1 year in cohort B (A vs. B: 77% vs. 71% $P = 0.002$).

Kidney function

Serum creatinine at 1 year did not differ between the two cohorts, but at 5- and 10-year renal function was substantially better in cohort B with creatinine levels of 128 and 131 μmol/l vs. 183 and 205 μmol/l, respectively ($P = 0.001$ and $P = 0.02$). In cohort A, significantly more patients (59; 17%) needed chronic dialysis, received a kidney transplant (9; 3%) within 10 years after HT versus eight patients (4%) and two patients (1%), respectively, in cohort B. The incidence of hypertension decreased from 80% to 48% ($P < 0.0001$), but the incidence of diabetes after transplantation increased from 21% to 32% ($P = 0.003$), along with the introduction of tacrolimus.

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy at 1 year, which is mostly donor related, was more often present in cohort B versus cohort A: 9% vs. 5% ($P = 0.04$), but at 4 years, there was no significant difference any more (Table 2.) After the demonstration of ischemia at annual scintigraphic follow-up or after electrocardiographic or clinical signs of ischemia or echocardiographic signs of graft failure between times, all significant (by eyeballing or with the help of fractional flow reserved measurement) lesions were treated. Throughout follow-up, 77 (22%) patients in cohort A had a myocardial infarction and 57 (16%) underwent at least one revascularization procedure. Twelve patients underwent balloon angioplasty, nine patients underwent bare-metal stenting, 37 drug-eluting stenting and one patient underwent both bare-metal and drug-eluting stenting. In cohort B, 8 (4%) patients had a myocardial infarction and 20 (9%) patients underwent at least one revascularization procedure. A comparison of the cohorts is hindered by the difference in follow-up duration. One patient underwent bare-metal stenting, 19 underwent drug-eluting stenting, and one patient underwent a CABG. Statins had been started early after transplantation in 88% of the cohort B patients compared with only 18% of the cohort A patients ($P < 0.0001$). Total cholesterol and triglyceride values were significantly lower in cohort B (Table 2).

Table 2. Clinical course after heart transplantation.

	Cohort A 1984–1999 *n* = 353	Cohort B 2000–2013 *n* = 227	*P* value
Acute rejection within 1st year, *n* (%)			
0 episodes	78 (23)	69 (34)	0.005
1 episode	106 (31)	76 (37)	0.14
2 or more episodes	161 (47)	61 (30)	<0.0001
Acute rejection after 1st year, *n* (%)			
1 or more episodes	63 (18)	26 (12)	0.07
CMV disease, *n* (%)	60 (17)	33 (19)	0.57
LV ejection fraction at 1 year (%; mean ± SD)	65 ± 9	64 ± 6	0.15
Exercise capacity at 1 year (%; mean ± SD)	77 ± 16	71 ± 18	0.002
Cholesterol at 1 year (mmol/l; mean ± SD)	7 ± 2	5 ± 1	<0.0001
Triglyceriden at 1 year (mmol/l; mean ± SD)	3 ± 1	2 ± 1	0.002
Serum creatinine at 1 year (μmol; mean ± SD)	143 ± 41	142 ± 111	0.94
Serum creatinine at 5 years (μmol; mean ± SD)	183 ± 169	128 ± 60	0.001
Serum creatinine at 10 years (μmol; mean ± SD)	205 ± 207	131 ± 49	0.02
Chronic dialysis, *n* (%)	78 (22)	10 (4)	<0.0001
Chronic dialysis within 10 years, *n* (%)	59 (17)	8 (4)	<0.0001
Kidney transplantation, *n* (%)	9 (3)	2 (1)	
Hypertension post-HT, *n* (%)	283 (80)	101 (48)	<0.0001
Diabetes post-HT, *n* (%)	73 (21)	71 (32)	0.003
CAV at 1 year, *n* (%)	14 (5)	16 (9)	0.04
CAV at 4 years, *n* (%)	51 (20)	28 (24)	0.33
Myocardial infarction, *n* (%)	77 (22)	8 (4)	
Myocardial revascularization, *n* (%)	57 (16)	20 (9)	
Malignancy, *n* (%)	117 (33)	27 (12)	
Skin	48 (41)	17 (63)	
PTLD	14 (12)	3 (11)	
Lung	18 (15)	1 (4)	
Other	37 (32)	6 (22)	

CMV, cytomegalovirus; LV, left ventricular; HT, heart transplantation; CAV, cardiac allograft vasculopathy; PTLD, post-transplant lymphoproliferative disorder. Comparisons between the two cohorts have not always been made because of the difference in follow-up time.

Malignancies

A comparison of the incidence of malignancies and other diseases in both cohorts is hampered by the different median follow-up times. The proportion of skin cancers, however, seems to be higher in cohort B. In the oldest cohort skin, cancers were the most frequent forms of malignant disease, followed by lung cancer and post-transplant lympho-proliferative disorder (Table 2).

Survival

The in-hospital mortality increased from 7% to 10% (albeit not statistically significant) in the recent cohort. Long-term cumulative survival of the two cohorts is shown in Fig. 2. In cohort A, 285 (81%) patients had died and in cohort B 58 (26%) patients had died. In cohort A, survival rates were 93%, 89%, 78% and 53% at 30 days, 1 year, 5 years, and 10 years, respectively. Cohort B showed survival rates of 90%, 86%, 81%, and 68% at 30 days, 1 year, 5 years, and 10 years, respectively. Kaplan–Meier analysis showed that long-term survival was significantly better in cohort B ($P = 0.02$). In patients who survived the first year after HT the 10-year survival rate increased markedly: The 10-year survival conditional on surviving the first year in cohort A was 60% vs. 80% in cohort B ($P < 0.0001$). The survival curve of cohort A shows a dent between 4 and 6 years. This is caused by the death of 30 patients between 4 and 6 years after transplantation, in whom graft vascular disease was the cause of death in 12 cases. In cohort B, only three patients died between 4 and 6 years until now, in one case because of graft vascular disease. The causes of death—in the first 10 years of follow-up—of the whole population are shown in Fig. 3, excluding the in-hospital mortality. The in-hospital mortality was increased from 7% to 10%, but was not statistically significant. The most notable mortality shift in the first 10 years in cohort A vs. B was the decrease in deaths due to coronary events (28% vs. 19%)

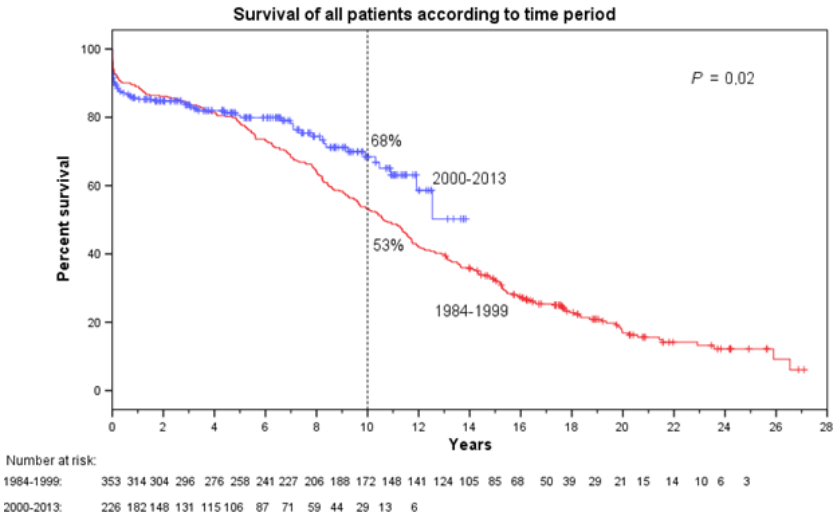

Figure 2 Kaplan–Meier cumulative survival according to time period 1984–1999 vs. 2000–2013.

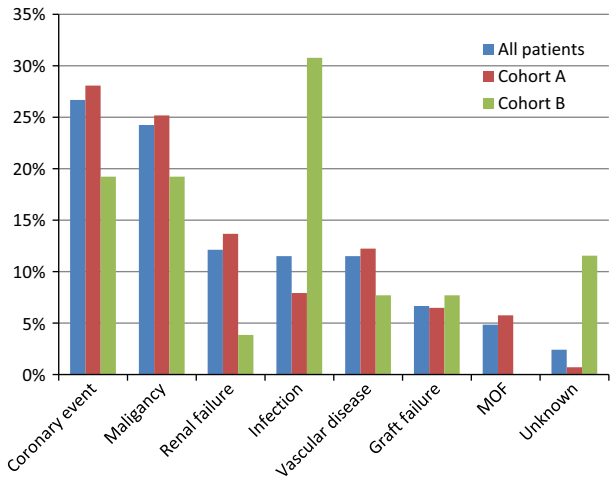

Figure 3 Causes of death (%; excluding the in-hospital mortality) of the whole cohort in the first 10 years of follow-up. MOF denotes multi-organ failure. $P = 0.001$ for infection and unknown case of death.

renal failure (14% vs. 4%) and sharp increase in deaths due to the infections (increase from 8% to 31%).

Univariate analysis was performed of the combined 580 patients to analyze the covariates of 10-year mortality (Table 3). Correlates for increased mortality at 10 years were cohort A vs. cohort B, recipient age, pretransplantation diagnosis of ischemic heart disease or failure of the first graft, treatment with cyclosporin instead of tacrolimus, serum creatinine at 1 and 5 years, chronic renal replacement therapy, cardiac allograft vasculopathy at 4 years, and post-transplant lymphoproliferative disorder.

Multivariate analysis of covariates of all patients for 10-year mortality showed improved long-term outcome significantly related to tacrolimus-based immunosuppression, treatment of hypertension post-HT, and myocardial revascularization (Table 4).

Discussion

In the present study, we showed significantly improved long-term survival after HT despite the use of older donor hearts and recipients with more comorbidity. In particular patients surviving the first year after HT have an excellent 10-year survival rate of 80% in the recent cohort as compared to a survival rate of 60% in the cohort that was transplanted between 1984 and 1999. This improvement seems due to a combination of newer immunosuppressive regimens, the early start of statins irrespective of cholesterol levels, extensive treatment of hypertension, and proactive revascularization for transplant vasculopathy. Although not proven by the multivariate analysis, the beneficial effects of the newer immunosuppressive regimes may be an important component of the excellent preservation of renal function due to far less prevalence of hypertension (from 80% in cohort A to 48% in cohort B), a known factor for the progression of chronic kidney diseases [18]. Also, in our cohort A, most of the patients on cyclosporin were basically on a double regimen (CsA + steroids). The addition of MMF to the calcineurin inhibitor-/steroid-based regimen made it also possible to safely accept lower calcineurin inhibitor whole blood concentrations already at the end of the first year, and this was associated with better renal function. However, we did not compare the exact levels of cyclosporin and tacrolimus because of the changes in laboratory methods and units used over the years. Beneficial effects of tacrolimus over cyclosporin for immunosuppression have been reported earlier [5,19]. The same holds true for the favorable effects of early statin therapy, which

Table 3. Univariate covariates of 10-year mortality in all patients.

	HR	95% CI	*P* value
Cohort A versus cohort B	1.42	1.04–1.94	0.03
Recipient			
Age (years)			
<39	1.00		0.11
40–49	1.73	1.06–2.82	0.03
49–59	2.03	1.28–3.22	0.003
>60	2.33	1.36–3.98	0.002
Female gender	0.76	0.54–1.08	0.12
Pretransplantation diagnosis			
Cardiomyopathy	0.57	0.43–0.78	<0.0001
Coronary artery disease	1.56	1.19–2.05	0.001
Valvular	1.72	0.91–3.25	0.09
Congenital	0.28	0.04–1.97	0.20
Retransplant	2.70	1.00–7.26	0.05
Prior cardiac surgery	1.21	0.90–1.64	0.20
Urgent transplantation	0.86	0.64–1.15	0.31
CMV mismatch	0.85	0.60–1.18	0.33
Toxoplasma mismatch	1.07	0.75–1.52	0.73
Serum creatinine pre-HT	1.00	1.00–1.01	0.14
Diabetes pre-HT	0.86	0.46–1.63	0.65
Donor			
Age (years)			
<39	1.00		0.11
40–49	0.76	0.53–1.10	0.15
50–59	1.19	0.76–1.87	0.15
>60	1.75	0.89–3.43	0.45
Female gender	0.97	0.75–1.27	0.85
Cause of death			
Head trauma	1.00	0.76–1.31	0.98
Stroke	0.89	0.68–1.16	0.39
Surgery			
Ischemia time	1.00	1.00–1.00	0.62
Days on ICU after HT	1.02	1.00–1.03	0.05
Days in hospital after HT	0.99	0.97–1.00	0.06
Immunosuppressive therapy			
Induction therapy	0.89	0.66–1.21	0.47
Maintenance immunosuppression			
Cyclosporine	3.17	2.19–4.60	<0.0001
Tacrolimus	0.31	0.20–0.47	<0.0001
MMF	0.74	0.48–1.13	0.16
Prednisone	2.55	1.35–4.82	<0.0001
Azathioprine	1.90	1.37–2.61	<0.0001
Statin treatment post-HT	0.43	0.32–0.59	<0.0001
Clinical course after HT			
Acute rejection within 1st year			
0 episodes	1.42	1.05–1.91	0.02
1 episode	0.93	0.69–1.25	0.62
2 or more episodes	0.81	0.609–1.07	0.14
Acute rejection after 1st year			
1 or more episodes	0.94	0.66–1.34	0.74
CMV disease	0.85	0.58–1.24	
LV ejection at 1 year	0.97	0.95–0.99	0.008
Cholesterol at 1 year	1.04	0.96–1.13	0.34
Triglycerides at 1 year	1.02	0.89–1.18	0.78
Serum creatinine at 1 year	1.00	1.00–1.00	0.002
Serum creatinine at 5 years	1.00	1.00–1.00	<0.0001
Hypertension post-HT	0.48	0.36–0.63	<0.0001
Chronic dialysis	1.01	0.72–1.42	0.94
Chronic dialysis within 10 years	1.52	1.08–2.12	0.02
Kidney transplantation	0.53	0.17–1.66	0.28
Diabetes post-HT	0.70	0.50–0.98	0.04
Pacemaker implantation post-HTX	0.98	0.97–1.00	0.05
CAV at 1 year	0.62	0.26–1.52	0.30
CAV at 4 years	2.05	1.34–3.14	0.001
Myocardial revascularization	0.26	0.15–0.47	<0.0001
Malignancy			
Skin	0.20	0.10–0.42	<0.0001
PTLD	4.32	2.24–8.34	<0.0001
Lung	1.99	0.99–4.00	0.05
Other	1.41	0.79–2.52	0.25

CMV, cytomegalovirus; LV, left ventricular; HT, heart transplantation; ICU, intensive care unit; CAV, cardiac allograft vasculopathy; PTLD, post-transplant lymphoproliferative disorder.

may reduce rejection incidence as well as cardiovascular events [16,20]. Furthermore, it has even been suggested that statins may be associated with lower incidence of post-transplantation malignancy [21]. Besides the effects of the early statins, a more aggressive approach to treat focal graft vascular disease by percutaneous intervention may have resulted in postponement of death by graft vascular disease. The influence of a more experienced transplant team is hard to measure.

Early hospital mortality, however, has increased from 7% to 10% (albeit not statistically significant) in the recent cohort. This increase can be related to donor as well as recipient characteristics. Prior cardiac surgery or an LVAD *in situ* complicate the transplant procedure and may prolong the ischemic time of the donor heart. Primary failure of the graft is more likely in the older donor, especially in case of longer ischemia times [22].

More recipients in the recent cohort were older than 60 years and were in critical condition as can be concluded from their urgent status on the waiting list. More patients received a heart from a donor older than 40 or even older than 60 years. These factors can also explain the lengthening of the stay in the ICU and in hospital after the HT.

The Rotterdam experience in global perspective

According to the data from the ISHLT registry, median survival after HT worldwide is 11 years with a median donor age of 34 years (www.ishlt.org). Although donor ages in Rotterdam are substantially higher, long-term survival after HT is at least comparable. Similarities between the Rotterdam cohorts and the ISHLT Registry are the proportional

Table 4. Multivariate covariates of 10-year mortality.

	HR	95% CI	*P* value
Cohort A versus cohort B	1.44	0.91–2.28	0.12
Tacrolimus-based immunosuppression	0.27	0.17–0.43	<0.0001
Hypertension post-HT	0.51	0.36–0.72	<0.0001
Myocardial revascularization	0.29	0.16–0.52	<0.0001

increase of cardiomyopathy as pretransplantation diagnosis and the use of mechanical circulatory support to bridge patients to transplantation. In contrast with the Rotterdam experience head trauma, worldwide still is the predominant donor cause of death. Finally, the impact of donor age on outcome has been analyzed in detail within the ISHLT Registry. This analysis strongly suggests that the increase in donor age is a causal factor in our observed increase in 30-day mortality [3].

A recent publication from the Nordic Thoracic Transplant Study Group showed that the long-term outcome of 2293 patients transplanted between 1983 and 2009 also improved over time [23]. In this Scandinavian experience, characteristics of HT recipients and donors showed a similar pattern as we observed. In particular pretransplantation diagnoses, the use of mechanical circulatory support, increase donor age (although only 38 years in their cohort) and ischemic time have a profound effect on clinical practice. In their multivariate analysis, they found recipient age, donor age, pretransplantation diagnosis (cardiomyopathy versus ischemic heart disease), and transplant era to be strongly related to long-term survival. These investigators omitted analysis of the effects of newer immunosuppressant's and early statin treatment [23]. In our analysis 10-year survival showed improved long-term outcome significantly related to tacrolimus-based immunosuppression, treatment of hypertension post-HT, and myocardial revascularization. This resulted in less death at 10 years follow-up due to decreased coronary arterial events, vascular disease, and end-stage renal disease in our cohorts treated from 2000 on. The down side is probably more deaths due to infections at long-term follow-up as well as an increase in the prevalence of diabetes mellitus.

Limitations of the study

The unequal follow-up period has to be taken into consideration, as the patients transplanted in cohort A have been followed for a maximum of 28 years and the patients of cohort B for a maximum of 13 years. Our study is a comparison of two nonrandomized, sequential cohorts of patients undergoing HT. Clinical characteristics of donors and recipients and multiple components of medical management have changed markedly over time. Our univariate and multivariate analysis allows us to describe associations, but do not prove cause and effect. Nevertheless, from a pathophysiologic perspective, it seems rational to assume that the improvements in pharmacological regimens do explain the observed improvement in outcome.

Implications

Our main findings, improved long-term survival despite older donor hearts in the current transplant era, have to be taken into account when discussing the long-term outcome after HT with potential heart transplant candidates. However, although the long-term outcome has improved, the early risks are not negligible. Compared with the history of advanced heart failure under conventional therapy, HT has a profound effect on mortality and quality of life if the recipient survives the first 30 days. But, availability of donor hearts remains the most important limitation, necessitating alternative management strategies for most patients with end-stage heart failure. The LVAD has become an essential bridge to transplantation for patients who are in danger of dying on the waiting list. Such mechanical circulatory support systems may also become a real alternative to transplantation in the near future [24–26].

In conclusion, in the present study, we show that in spite of use much older donors, the long-term outcome after HT in Rotterdam has improved considerably in the last decade, probably due to introduction of newer treatment modalities and proactive treatment of the complications.

Authorship

KC, AHMB designed the study; LZ, AC, AHMB, KC performed the study; AHMB, LZ, AC and OM collected the data; LZ, AC and RvD analyzed the data; LZ, AC, AHMB, KC wrote the paper; OB, DH and RT critically revised the reporting of the work. All authors contributed in writing the paper.

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