Nephrol Dial Transplant (2007) 22: 1383–1389
doi:10.1093/ndt/gfl811
Advance Access publication 31 January 2007

Original Article

NDT
Nephrology Dialysis Transplantation

Poor prognosis of heart transplant patients with end-stage renal failure

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Abstract

Background. Chronic kidney disease (CKD) and end-stage renal failure (ESRF) are major complications after a heart transplant. The aim of this study is to compare survival in heart transplant (HT) *vs* non-heart transplant (non-HT) patients starting dialysis.

Methods. Survival was studied among the 539 newly dialysed patients between 1 January 1995 and 31 December 2005 in our Department. All patients were prospectively followed from the date of first dialysis up to death or 31 December 2005. Multivariate survival analysis adjusted on baseline characteristics was performed with the Cox model.

Results. There were 21 HT patients and they were younger than non-HT patients at first dialysis: 58.6 ± 11.6 *vs* 63.0 ± 16.2 years ($P = 0.09$). Calcineurin inhibitor nephrotoxicity was the main cause of ESRF in HT patients (47.6%). Crude 1, 3 and 5-year survival rates in HT and in non-HT patients were as follows: 76.2%, 57.1%, 28.6% and 79.1%, 58.7%, 46.7% ($P = 0.2$). The adjusted hazard ratio of death in HT *vs* non-HT patients was 2.27 [1.33–3.87], $P = 0.003$. Sudden death was the main cause of death in HT patients, in 33.3% *vs* 10.4% in non-HT patients ($P = 0.01$). Five HT patients benefited from renal transplant. They were all alive at the end of the study period, while one patient among the 16 remaining on dialysis survived.

Conclusion. HT patients with CKD who reached ESRF have a poor outcome after starting dialysis in comparison with other ESRF patients. Improvement in renal function management in the case of CKD is needed in these patients and non-nephrotoxic immunosuppressive regimens have to be evaluated. Renal transplant should be the ESRF treatment of choice in HT patients.

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Keywords: dialysis; end-stage renal failure; heart transplant; renal transplant; survival

Introduction

Chronic kidney disease (CKD) is one of the most important complications in heart transplant (HT) recipients [1]. Using the American Scientific Registry of Transplant Recipients, Ojo *et al*. [2] described in 2003 the natural history of renal failure in HT recipients, that the cumulative 5-year risk of developing CKD, defined as a glomerular filtration rate (GFR) $< 30\,\text{ml/min/1.73}\,\text{m}^2$ of body surface area, was 10.9%. At least 3 to 10% of HT recipients reached end-stage renal failure (ESRF) requiring chronic renal replacement therapy (RRT) during the 10-year post-transplant period [2–6].

Actually, HT recipients are at high risk of CKD because they carry cardiovascular risk factors and specific risk factors associated with renal impairment [1–3]. Risk factors for kidney injury in this population were identified both from single-centre or registry-based studies [1–12]: pretransplant GFR, post-operative acute renal failure, recipient age, presence of diabetes mellitus, hypertension and/or dyslipidaemia, smoking, hepatitis C infection and treatment with calcineurin inhibitors (CNI).

CNI that had made solid organ transplantation successful is paradoxically one of the most important aetiologic factors of CKD in HT patients [1–3]. Myers *et al*. [13,14] first reported in 1984 renal injury associated with cyclosporin A (CsA) immunosuppressive treatment.

Renal impairment and ESRF associated with HT result in an excessive risk of mortality in HT patients [1–3,9,15]. However no conclusive studies compared survival after dialysis onset in HT patients *vs* non-heart transplant (non-HT) patients [15–17].

The aim of our study is to determine if being heart transplanted is a risk factor for death after first dialysis in comparison with non-HT patients.

Materials and methods

Study design

The study design of this comparison of survival in HT patients *vs* non-HT patients entering dialysis was retrospective. With data from a previous explanatory study performed in our Department in an 8-year period [9] and using the approach of Schoenfeld and Richter [18], we were able to calculate sample sizes needed in the present study. When α risk is 0.05, study power is 0.8, hazard ratio (HR) of death between HT patients and non-HT patients is 2.2, median survival in control group (non-HT patients) is 4 years, time of recruitment is 10 years, mean follow-up time is 5 years, and ratio of non-HT patients to HT patients is 25, then sample size of HT patients cohort has to be 20.

About 50 patients per year started dialysis in our department. With an average of two HT patients staring dialysis per year, we defined a study period of 10 plus 1 years with a follow-up period of 0–11 years to respect sample size specifications.

Patients

All patients who started chronic dialysis between 1 January 1995 and 31 December 2005 in the Department of Nephrology, Dialysis and Renal Transplantation of the Lyon-Sud Academic Hospital in France were included. Patients temporarily dialysed for acute renal failure with renal function recovery were excluded. ESRF patients who benefited from pre-emptive renal transplant during this period (2 HT patients and 21 non HT patients) were excluded.

The study population consisted of 539 incident dialysed patients including 21 HT patients.

Origin of the follow-up time and study period

Patients were prospectively included at dialysis onset, i.e. haemodialysis (HD) or peritoneal dialysis (PD). The study period ended on 31 December 2005.

Studied parameters

Age, gender, date of first dialysis, original nephropathy, comorbid conditions at time of first dialysis and modality of dialysis were prospectively collected.

Modality of dialysis was the one used 3 months after the first dialysis, or the one at dialysis initiation if death occurred before the fourth month.

Original nephropathy included diabetic nephropathy, vascular nephropathy, primary and secondary glomerulonephritis (except diabetic nephropathy), polycystic kidney disease, chronic tubulo-interstitial nephritis, malformative uropathy, other causes and unknown cause.

Comorbid conditions at first dialysis included type 1 diabetes, type 2 diabetes, arterial hypertension (blood pressure >140/90 mmHg or anti-hypertensive medications), peripheral vascular disease (defined as a clinical claudication and/or a peripheral amputation and/or a peripheral artery stenosis >50%), coronary disease (angina, myocardial infarction), congestive heart failure (acute pulmonary oedema and/or left-ventricular ejection fraction <50% over an echocardiograph), cerebrovascular accident, heart transplantation, malignancy, alcohol addiction, hepatitis B or C virus infection, hepatic insufficiency (defined as a coagulation factor V < 50%), liver transplantation, HIV infection, and respiratory insufficiency (defined as need of chronic oxygenotherapy or mechanic ventilation).

Follow-up

Patients were prospectively followed-up up to death or up to 31 December 2005. Follow-up was performed with the ESRF patient registry of our Department and with the Renal Epidemiology and Information Network (REIN) registry [19]. Registration on a renal transplant waiting list was recorded. Transplanted patients were followed-up with the database of the Agence de la Biomédecine (named CRISTAL). Ten patients were lost to follow-up (1.8%) because they moved out of Rhône-Alpes region. No HT patient was lost to follow-up.

Study endpoint was death of any cause. Causes of death were pooled in six categories: sudden death, cardiovascular (myocardial infarction, cerebrovascular accident, heart failure, peripheral vascular disease), infection, malignancy, and other known and unknown causes.

Statistical analyses

Analyses included the following: (i) Descriptive analysis of patient characteristics and comorbid conditions in HT patients and non-HT patients at first dialysis; (ii) Univariate comparison of survival and causes of death; (iii) Multivariate survival analyses.

When appropriate, univariate comparisons in case-mix and tabulation were done with χ^2 test or Fisher's exact test for category variables and with Student's t-test for continuous variables. Kaplan–Meier non-parametric survival curves and Log Rank test were used to compare survival in HT and non-HT patients (univariate analysis).

In multivariate analyses, Cox proportional hazards model was used to identify patient conditions which have independent effects on probability of death after first dialysis and to quantify their size effects [20]. Study start was the date of first dialysis. The endpoint was death of any cause. Patients who benefited from renal transplantation were not right-censored in the analysis at the date of transplantation. Heart transplant state was the parameter of interest in the Cox model. Age, gender, nephropathy, comorbidities at first dialysis (as described earlier, if comorbidity was present in more than 5 patients in our cohort) and registration on a renal transplant waiting list were introduced in the model. Analysis was stratified on five periods of first dialysis (1995–96, 1997–98, 1999–2000, 2001–02, and 2003–05).

Age was modelled as continuous variable in a first model and as a polynomial variable (age, age^2 and age^3) in a second model to take into account, by both manners, the effect of age on adjusted HRs of death in other variables.

Step-by-step analysis was done with both backward and forward entrance of variables in order to analyse interactions between variables.

The validity hypothesis of the Cox model (proportional HR) was checked by the test based on Shoenfeld's residuals [21]. When a variable did not respect HR proportionality in Cox regression, we compared results of the model without the variable and the model with variable in order to observe modifications in HRs of other variables.

All statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (© 1988–2001 Insightful Corp).

Results

Baseline characteristics

Baseline characteristics of the 539 incident dialysed patients are presented in Table 1 in the HT patient group and in the non-HT patient group. There were 21 HT patients in this cohort. Over the same period of time (1995–2005), 483 heart transplantations were performed in the Department of Heart Transplant of the Hospices Civils de Lyon. Clinical characteristics of HT patients with chronic kidney disease referred to our Department of Nephrology were described elsewhere [9].

In HT patients, causes of cardiac transplantation were ischaemic cardiomyopathy in 16 (76.2%) and dilated cardiomyopathy in 5 (23.8%). Mean time between cardiac transplantation and first dialysis was 9.1 ± 3.1 years with a median time of 9.1 years.

Patient characteristics and comorbid conditions were not equally balanced between groups. HT patients were younger ($P = 0.09$) and sex ratio was 9.5 *vs* 1.6 in non-HT patients ($P = 0.01$). Chronic tubulo-interstitial nephritis (CTIN) was over-represented in HT patients, 47.6% *vs* 6.0% in non-HT patients ($P < 0.0001$). In HT patients, CTIN was related to CNI nephrotoxicity. Type 2 diabetes and cardiovascular diseases were equally represented in both groups. No HT patient presented HBV, HCV or HIV infection, nor hepatic failure and liver transplantation.

HT patients were significantly more often treated by HD as first dialysis modality, as compared to the non-HT patient group (90.5% *vs* 66%, $P = 0.03$).

Outcome: univariate analyses

Survival assessed by Kaplan–Meier method is presented in Figure 1. HR of death in HT patients *vs* non-HT patients was 1.4 with a 95% confidence interval (95% CI) of 0.8–2.3. In univariate analysis, Log-Rank test didn't show any significant difference in survival between the two groups ($P = 0.2$). Median survival time was 33.5 months in HT patients and 50.8 months in non-HT patients.

Registration on a renal transplant waiting list was completed for 5 HT patients (23.8%) and 148 non-HT patients (28.5%), $P = 0.64$. The main reasons for renal

Table 1. Baseline characteristics of the study population at first dialysis

	HT patients ($n = 21$)	Non-HT patients ($n = 518$)
Age at ESRF: mean ± SD (years)	58.6 ± 11.6	63.0 ± 16.2
Median age at ESRF (years)	58.0	66.0
Men	19 (90.5%)	319 (61.6%)*
Original nephropathy (number, %)		
Vascular nephropathy	5 (23.8%)	120 (23.1%)
Diabetic nephropathy	0 (0.0%)	118 (22.8%)
Primary and secondary glomerulonephritis[a]	4 (19.1%)	74 (14.3%)
Polycystic kidney disease	0 (0.0%)	25 (4.8%)
Chronic tubulo-interstitial nephritis	10 (47.6%)	31 (6.0%)*
Malformative uropathy	0 (0.0%)	14 (2.7%)
Other	0 (0.0%)	59 (11.4%)
Unknown	2 (9.5%)	77 (14.9%)
Comorbidity at first dialysis (number, %)		
Type 1 diabetes	0 (0.0%)	17 (3.3%)
Type 2 diabetes	6 (28.6%)	162 (31.3%)
Arterial hypertension	20 (95.2%)	406 (78.4%)
Peripheral vascular disease	5 (23.8%)	105 (20.3%)
Coronaropathy	6 (28.6%)	134 (25.9%)
Congestive heart failure	7 (33.3%)	111 (21.4%)
Cerebrovascular accident	4 (19.1%)	67 (12.9%)
Malignancy	4 (19.1%)	76 (14.7%)
HBV infection	0 (0.0%)	12 (2.3%)
HCV infection	0 (0.0%)	15 (2.9%)
Hepatic failure	0 (0.0%)	23 (4.4%)
Liver transplantation	0 (0.0%)	9 (1.7%)
HIV infection	0 (0.0%)	6 (1.1%)
Chronic respiratory disease	1 (4.8%)	35 (6.7%)
First dialysis modality (number, %)		
Hemodialysis	19 (90.5%)	342 (66.0%)*
Peritoneal dialysis	2 (9.5%)	176 (34.0%)*

[a]Diabetic nephropathy was excluded from secondary glomerulonephritis.
*Comparison between HT and non-HT patients: $P < 0.05$.

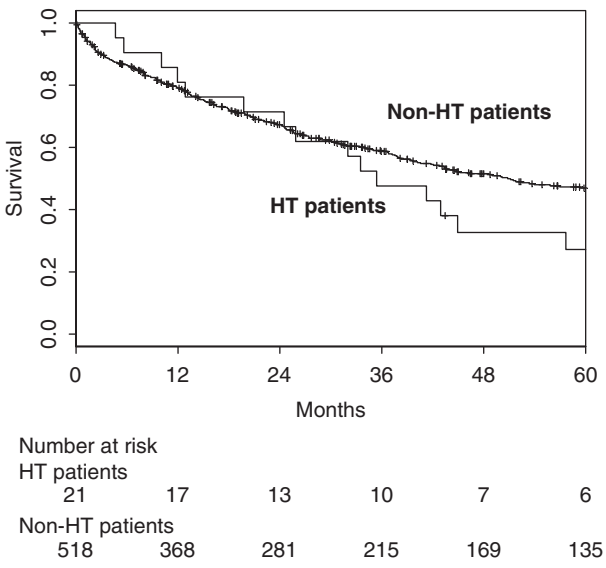

Fig. 1. Kaplan–Meier survival curves in HT patients ($n = 21$) and in non-HT patients ($n = 518$). HR: 1.4 (0.80–2.30), $P = 0.20$, univariate analysis. +: right-censored patients.

transplant contraindication in HT patients were age >70 years in three, neoplasm in four, congestive heart failure in six without indication of a second heart transplantation, and diabetes associated with at least two cardiovascular diseases in three.

Renal transplantation was performed in equivalent rates between the groups during the study period, i.e. in 5 HT patients (23.8%) and in 110 non-HT patients (21.2%).

In the HT patient group, only six patients were alive at the end of the study period, including the five renal transplanted patients. Among them, one benefited from a second heart transplantation with concomitant renal transplantation.

Living HT patients were significantly younger than dead HT patients at first dialysis, 50.1 ± 12.1 years *vs* 62.0 ± 9.9 ($P = 0.048$). They did not present peripheral vascular disease or malignancy at first dialysis.

In the HT patient group, patients contraindicated for renal transplantation ($n = 16$) presented a survival rate at 1, 3 and 5 years after first dialysis of 75%, 31.2% and 6.2%, respectively.

Causes of death

In the HT patients, causes of death were as follows: sudden death in five (33.3%), cardiovascular in three (20%), malignancy in three (20.0%) and unknown in four (26.7%). In non-HT patients, causes of death were the following: sudden death in 27 (10.4%), cardiovascular in 68 (26.2%), infection in 26 (10.0%), malignancy in 20 (7.7%), other known causes in 70 (26.9%) and unknown in 49 (18.8%).

Sudden death and malignancy were significantly over-represented as cause of death in HT patients in comparison with non-HT patients in this cohort ($P = 0.01$). We did not observe death from infectious causes in HT patients.

Survival: multivariate analyses

Because there was no significant difference in survival between HT and non-HT patients in univariate analysis, we first performed survival comparison between these groups with adjustment on age and sex. Actually, HT patients were younger than non-HT patients and sex ratios were different in these groups (Table 1 as well.). These variables are strongly associated with death and especially age may be a confounder in univariate analysis comparing survival in HT and non-HT patients. At this first step, HT was associated with a significant worse prognosis in dialysis: the age and sex adjusted HR of death in HT patients *vs* non-HT patients was 1.84 with a 95% CI of 1.10–3.06, $P = 0.02$ (result did not change if age was introduced as a polynomial in Cox regression).

Because HT was significantly associated with death in this first analysis, we conducted multivariate analysis adjusted on all baseline conditions as described in 'Materials and methods' section. Table 2 shows results of this multivariate analysis. The presented model included age as continuous variable. No change in results was observed with age introduced as polynomial. Original nephropathies were not included in the final model because of colinearity between some nephropathies and comorbid conditions (diabetes and diabetic nephropathy, cardiovascular diseases and vascular nephropathy). The first modality of dialysis variable did not have valid proportionality in HR and was not included in the final model. HRs of other variables were not modified when this variable was introduced in the Cox model.

Table 2. Adjusted HR of death and 95% CI

	HR	95% CI	*P*
Heart transplant	2.27	1.33–3.87	0.003
Age at first ESRF (+1 year)	1.05	1.04–1.07	<0.0001
Men versus women	1.06	0.82–1.37	0.65
Type 1 diabetes	1.67	0.77–3.61	0.19
Type 2 diabetes	1.12	0.85–1.46	0.42
Coronary disease	1.00	0.76–1.32	1.00
Congestive heart failure	1.47	1.10–1.96	0.009
Peripheral vascular disease	1.28	0.96–1.71	0.09
Cerebrovascular accident	1.35	0.97–1.89	0.08
Malignancy	1.03	0.76–1.40	0.86
HBV infection	1.09	0.44–2.70	0.85
HCV infection	1.78	0.84–3.77	0.13
Chronic hepatic insufficiency	2.14	1.10–4.14	0.02
Liver transplant	0.99	0.31–3.16	0.99
HIV infection	2.14	0.62–7.42	0.23
Chronic respiratory insufficiency	1.18	0.72–1.94	0.50
Registration on renal transplant waiting list	0.34	0.22–0.51	<0.0001

In this final model (Table 2), HT was significantly associated with death. Adjusted HR of death in comparison with non-HT was 2.27 with a 95%CI of 1.33–3.87 ($P = 0.003$). The following other conditions were associated with survival in this ESRF patient cohort: age, congestive heart failure, hepatic insufficiency and being registered on a renal transplant waiting list. Liver transplantation was not associated with outcome (adjusted HR: 0.99 (0.31–3.16), $P = 0.99$).

Discussion

This study demonstrates that heart transplantation is associated with a poor outcome in patients starting dialysis. To the best of our knowledge, no direct survival comparison with adjustment on baseline patients' characteristics at first dialysis is available in the literature [4,15–17]. Our study confirms trends observed in previous non-adjusted analyses both in the United Kingdom [16] and in the USA [17].

The strengths of our study are the exhaustiveness of this single-centre cohort concerning ESRF patients starting dialysis with a very low rate of loss to follow-up (1.8% of the patients), the prospective recording of the analysed data and the homogeneity of the recorded data. This HT patient cohort starting dialysis ($n = 21$) is larger than the ones of previously

published series [4,15–17]. Patient characteristics and survival in the whole cohort were comparable with data observed in the French REIN registry and in the Lorraine region in France [19,22]. Survival in HT patients of our cohort was consistent with survival of HT patients in previously published studies [4,15–17]. Those make acceptable generalization of the results of this single-centre study.

We do not include in the analysis patients who benefited from pre-emptive renal transplant as first RRT modality because they constituted a sub-group of ESRF patients with particular conditions and outcomes. In this survival analysis, patients who benefited from renal transplant were not censored at the date of transplant: the study explored survival in patients starting dialysis and then included the natural history of RRT modality management.

In unadjusted comparison, survival seemed equal in HT and in non-HT patients. Adjustment on age and sex underlined the dark prognosis of HT patients starting dialysis. The effect of being heart transplanted on survival in dialysis remained significant after adjustment on baseline patient characteristics. Probability of death after first dialysis was more than 2-fold superior in HT patients than in non-HT patients.

We introduced in regression model the variable 'being registered on renal transplant waiting list' to assess whether age and comorbid conditions, such as cardiovascular diseases and diabetes, influenced patient death or prevented patients from being waitlisted and transplanted. Not introducing this variable in the regression model only slightly influenced the HR of death in HT patients *vs* non-HT patients; 2.05 (1.22–3.44) with $P = 0.007$ [*vs* 2.27 (1.33–3.87), $P = 0.003$]. In this model (without the variable 'being registered on renal transplant waiting list'), new conditions significantly associated with death after first dialysis were type 1 diabetes, peripheral vascular disease and hepatitis C virus infection. This suggests that these last conditions were significant for not being registered on a renal transplant waiting list.

Rates of registration on renal transplant waiting list, rates of renal transplantation, and medical reasons for renal transplant contraindication did not differ in HT patients and in non-HT patients and from contraindication reasons in the general dialysed population [23].

In these HT patients, links between cardiovascular risk factors, heart failure, CKD, dialysis and accelerated atherosclerosis, are hypotheses to explain excess of death in HT patients starting dialysis beyond the role of immunosuppressive regimen [1,3,8,15–17]. It is remarkable that liver transplantation did not modify outcome in dialysis in this study.

In this cohort, ischaemic heart disease was the main cause of heart failure leading to cardiac transplantation, in about 75% of the patients. This confirms the high risk of CKD and ESRF in patients with ischaemic heart disease prior to HT that is a condition associated with ischaemic nephropathy [11]. Cardiovascular diseases and type 2 diabetes as comorbid conditions at first dialysis were equally balanced between HT and non-HT patients. Sudden death was the main cause of death in HT patients, in a significantly higher rate than in non-HT patients. HT patients contraindicated for renal transplantation presented an abysmal prognosis after first dialysis. Only one non-renal transplanted HT patient among 16 HT patients was living 5 years after first dialysis. On the other hand, HT patients selected for renal transplantation presented a higher survival rate related to their younger age and best clinical condition.

These results suggest that mechanisms beyond classical cardiovascular risk factor may be involved and/or accelerated in HT patients by ESRF treatment [8] and that transplanted myocardium may be particularly sensitive to rapid changes in ionic serum concentrations (as kalaemia) and to modifications of fluid overloads between dialysis sessions, especially in patients treated by HD. Accelerated coronary atherosclerosis, plaque rupture and uraemic cardiomyopathy could explain fatal cardiac events in this population [8]. Prospective studies focused on progression of coronary artery disease should be designed to confirm its role in mortality in HT patients undergoing dialysis therapy.

The challenge is then to improve prognosis of HT patients with CKD and ESRF. In our center, we previously observed that HT patients were late in being referred to nephrologist consultation, with an average serum creatinine of 261.5 ± 99 μmol/l and an average GFR of 32 ± 15 ml/min (Cockcroft and Gault formula) [9]. Moreover, progression from CKD to ESRF depended on renal function impairment at the first nephrologist visit [9]. Preventive measures to delay progression of renal dysfunction should be instituted at an early stage of CKD [22], when GFR is over 60 ml/min, i.e. when serum creatinine reached 137 μmol/l in men and 104 μmol/l in women [24]. Kidney protection includes [25] diet, blood-pressure and proteinuria control, use of ACE inhibitor, blood-glucose control in diabetes mellitus, dyslipidaemia treatment and smoking cessation. Control of cardiovascular risk is the cornerstone of CKD patient care. This should be applied to HT patients who are at high risk of CKD [1–3].

But one factor is specific of solid organ transplant patients as HT patients: CNI nephrotoxicity [1–3]. CsA is involved both in aetiology and in progression of CKD in these patients [1–14]. Available data comparing nephrotoxicity of CsA and tacrolimus (Tac) are contradictory [26,27]. No randomized trial is available in this field of clinical research. Similar toxicity profiles of CsA and Tac suggest that CNI-free immunosuppressive regimens are one of the keys of renal function management in HT patients [1,3]. Recent studies with mycophenolate mofetil (MMF) and sirolimus provided substantial optimistic data. In a controlled but non-randomized study, improvement in renal function was observed in HT patients in which CsA dosage was reduced after introduction of MMF, with a reduction of at least 20% of serum

creatinine in 35% of the patients in this arm [28]. Reports of a switch from CNI to MMF and sirolimus as CNI-free immunosuppressive regimen showed significant improvement in renal function without a serious adverse event, especially acute rejection [29,30]. Meiser B *et al*. [31] published in 2005 results of a pilot study where eight HT *de novo* recipients were treated with MMF, sirolimus and corticosteroids without any CNI [31]. Low rejection rate and no renal impairment were observed in a follow-up of 3–12 months after cardiac transplantation.

Our study confirms that renal transplantation is the RRT modality of choice in these ESRF patients [32]. No death was observed in HT patients who benefited from renal transplant in this cohort. Renal transplanted HT patients were clearly selected on comorbid conditions that explain in part a better survival than in non-renal transplant patients. Renal transplantation is associated with a better control of cardiovascular risk factors than dialysis therapy [33]. This decreases risk for fatal cardiovascular events, the major cause of mortality in HT patients [1,3].

Our study should be interpreted in light of few limitations. The factors of death related to being on dialysis, such as inflammation and nutritional parameters, or dialysis dose were not available for analysis. Nevertheless, age seems to be the principal confounding factor to compare survival in HT patients and in non-HT patients reaching ESRF. Adjustment on comorbid conditions and registration on a renal transplant waiting list *vs* adjustment on age and sex alone modified HR of death in HT patients *vs* non-HT in the same proportion as the adjustment on age and sex alone *vs* crude survival comparison did. Despite the fact that this study is observational by nature, and has to be interpreted with limitations of such studies, we can emphasize the strength of the association between being heart transplanted and death after first dialysis.

In conclusion, this study underlines the poor prognosis of HT patients starting dialysis in comparison with non-HT patients. It confirms that ESRF is a major complication of cardiac transplantation. CNI-free immunosuppression regimens with m-TOR inhibitors and MMF have to be studied in large randomized trials in order to assess their efficacy and safety in cardiac transplantation. Referral to nephrologists is recommended at an early stage of CKD, when GFR reaches 60 ml/min/1.73m^2, in order to slow down progression of renal dysfunction. Renal transplant has to be proposed as an RRT modality as early as possible in the case of the absence of medical contraindication, due to maximal gain of life expectancy associated with renal transplant in this population [32–34].

Acknowledgements. We acknowledge the contribution of Mrs A. Merono and Mrs A. Mourgues for data management of REIN Rhône – Alpes Registry.

Conflict of interest statement. None declared.

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Received for publication: 28.9.06
Accepted in revised form: 12.12.06