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Long-term evolution, secular trends, and risk factors of renal dysfunction following cardiac transplantation

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Summary

Recent reports suggest that individuals who underwent heart transplantation in the last decade have improved post-transplant kidney function. The objectives of this retrospective study were to describe the incidence and to identify fixed and time-dependent predictors of renal dysfunction in cardiac recipients transplanted over a 25-year period (1983–2008). To illustrate temporal trends, patients (n = 306) were divided into five groups based on year of transplantation. The primary endpoint was the estimated glomerular filtration rate (eGFR) at year 1. Secondary endpoints were time to moderate (eGFR <60 ml/min/1.73 m^2) and severe renal dysfunction (eGFR <30 ml/min/1.73 m^2). Risk factor analyses relied on multivariable regression models. Kidney function was mildly impaired before transplant (median eGFR=61.0 ml/min/1.73 m^2), improved at discharge (eGFR=72.3 ml/min/1.73 m^2; $P < 0.001$), decreased considerably in the first year (eGFR = 54.7 ml/min/1.73 m^2; $P < 0.001$), and deteriorated less rapidly thereafter. At year 1, 2004–2008 recipients exhibited a higher eGFR compared with all other patients ($P < 0.001$). Factors independently associated with eGFR at year 1 and with moderate and severe renal dysfunction included age, gender, pretransplant eGFR, blood pressure, glycemia, and use of prednisone ($P < 0.05$). In summary, kidney function worsens constantly up to two decades after cardiac transplantation, with the greatest decline occurring in the first year. Corticosteroid minimization and treatment of modifiable risk factors (hypertension, diabetes) may minimize renal deterioration.

Introduction

Chronic renal dysfunction is highly prevalent in the heart transplant population, resulting in significant morbidity and mortality [1–3]. Many groups have studied the evolution of kidney impairment following cardiac transplantation, but there are only very limited data regarding the changes in renal function and the risk factors for chronic kidney disease beyond the first 10 years post-transplant [4–7].

Calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, are a leading cause of renal impairment after heart transplant [8,9]. Although a growing number of cardiac recipients have additional characteristics that might

increase their risk of kidney dysfunction (e.g., greater age, hypertension, diabetes), recent reports reveal that patients who underwent heart transplantation in the last decade have improved post-transplant renal function compared to those transplanted before 2003 [3]. To clarify these observations and to provide new insights on recipients' very long-term renal function (up to two decades post-transplant), we have initiated a project whose objectives were to describe the incidence and secular trends of chronic renal dysfunction and to identify its risk factors in heart transplant patients. Most publications have so far focused on baseline or fixed post-transplant features when investigating predictors of kidney impairment. Hence, the impact of temporal changes in several of these factors remains uncertain, which is why we have used time-dependent covariates in our analyses, along with traditional peritransplant variables.

Materials and methods

Study design

We conducted a retrospective cohort study of patients who received a first heart transplant at the Montreal Heart Institute (Canada) between 1983 and 2008 and were discharged alive. For convenience, we illustrated the trends over the years by dividing the subjects into five groups based on their year of transplantation (1983–1988, 1989–1993, 1994–1998, 1999–2003, and 2004–2008). Patients from the first four eras were also combined (1983–2003) in select analyses to allow comparison with 2004–2008 recipients. Clinical data were obtained from a computerized database and a retrospective chart review, and were collected before heart transplant, at hospital discharge, 1, 2, and 3 months following the intervention, and then every 3 months for up to 26 years. The last follow-up date was December 31, 2010. This study was approved by the Montreal Heart Institute Scientific and Ethics Committees.

Study endpoints

The primary endpoint was the estimated glomerular filtration rate (eGFR) 1 year post-transplant, as calculated by the Modification of Diet in Renal Disease abbreviated formula [10]. Secondary endpoints were the time to moderate renal dysfunction [first eGFR < 60 ml/min/1.73 m^2; stage 3 of the National Kidney Foundation (NKF) classification] and the time to severe renal dysfunction (first eGFR < 30 ml/min/1.73 m^2; NKF stage 4) [11].

Statistical analyses

We used descriptive statistics [median (25th; 75th percentiles) for continuous data, counts, and percentages for categorical variables] to depict recipients' and donors' characteristics. Normality was assessed with a Shapiro–Wilk test. Intergroup comparisons involving all five groups and comparisons between 2004–2008 and 1983–2003 recipients were carried out using appropriate tests (chi-square test, Fisher's exact test, Kruskal–Wallis test, Mann–Whitney U-test). We also performed paired-sample Wilcoxon tests to compare patients' eGFR at different time points.

Factors potentially associated with eGFR 1 year post-transplant were investigated with a multivariable linear regression model. The covariates we analyzed included recipients' characteristics at baseline (e.g., age, sex, diagnosis, comorbidities) and at year 1 (e.g., immunosuppressants, blood pressure, glycemia), as well as donors' characteristics (e.g., age, sex). The effect of cyclosporine doses and tacrolimus concentrations was evaluated in two separate submodels containing only patients who were treated with either medication. Covariates associated with impaired renal function in univariable analyses ($P < 0.15$) were included in the multivariable model.

We built Kaplan–Meier curves to illustrate the time to moderate and severe renal dysfunction. Individuals with censored data included those experiencing death, transfer to another hospital during follow-up, end of follow-up, second heart transplant, kidney transplant, or nephrectomy. Multivariable Cox proportional hazard regression models were created to test the association between the time to moderate or severe renal dysfunction and numerous factors, consisting of baseline recipients' and donors' characteristics (fixed covariates) as well as time-dependent variables. The latter were used to evaluate the relationship between factors whose values can change over time (e.g., use of a drug, blood pressure, glycemia) and the endpoint of interest [12]. Covariates were included in multivariable models (relying on a stepwise approach) if they presented a univariable P value < 0.05. Statistical analyses were performed using (i) SAS 9.2 and 9.3 (Cary, NC, USA), (ii) SPSS Statistics 20.0.0 (Armonk, NY, USA), (iii) NCSS 07.1.15 (Kaysville, UT, USA), and (iv) GraphPad Prism 5.02 (San Diego, CA, USA). All tests were two-sided at a 5% level of significance.

Results

Pretransplant recipients' and donors' characteristics according to era of transplant

The study included 306 patients (Fig. 1). Table 1 summarizes pretransplant recipients' and donors' characteristics. Comparison of patients transplanted between 1983 and 2003 with those from the 2004–2008 era revealed that the latter received hearts from older donors ($P = 0.014$). Also, the distribution of disease etiology leading to the need for cardiac transplantation was significantly different

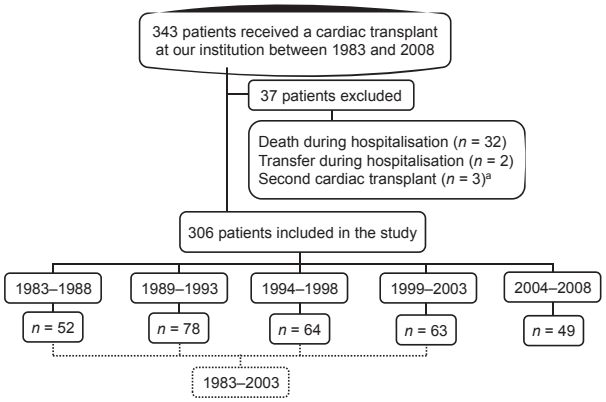


Figure 1 Patients' selection. [a]The three excluded patients with a second cardiac transplant had previously received a first heart transplantation in another hospital.

($P = 0.006$), with apparently fewer patients being transplanted because of ischemic heart disease in the most recent cohort. However, no difference in pretransplant eGFR was observed neither between the five groups ($P = 0.200$) nor between the 2004–2008 and 1983–2003 recipients ($P = 0.142$).

Evolution of post-transplant renal function in all recipients

The median time of follow-up for the entire cohort of patients was 10.2 (5.3; 15.3) years. The evolution of recipients' renal function up to 20 years after transplantation is presented in Fig. 2. The first 5 years post-transplant are reproduced in Fig. 3a to illustrate more clearly the immediate changes in kidney function. These figures demonstrate that renal function was mildly impaired prior to transplant [median eGFR: 61.0 (50.5; 70.8) ml/min/1.73 m^2], but improved significantly [median eGFR: 72.3 (58.2; 88.2)ml/min/1.73 m^2; $P < 0.001$ versus pretransplant] at hospital discharge [median duration of post-transplant hospitalization: 18.0 (15.0; 24.0) days]. They also show that the greatest decline in kidney function occurred in the first year post-transplant [median eGFR: 54.7 (43.5; 67.9) ml/min/1.73 m^2; $P < 0.001$ at year 1 versus pretransplant and discharge]. Following year 1, recipients' renal function continued to deteriorate ($P < 0.005$ at years 2, 3, 4, 5, 10, 15, and 20 versus pretransplant, discharge and year 1), albeit less rapidly. Ten years after transplantation, 77.1% of the 157 patients had moderate renal dysfunction (NKF stage 3) or worse (eGFR < 60 ml/min/1.73 m^2), and 12.1% had severe renal dysfunction (NKF stage 4) or worse (eGFR < 30 ml/min/1.73 m^2). Twenty years post-transplant, 90.9% of the 22 recipients had an eGFR < 60 ml/min/1.73 m^2, and 13.6% had an eGFR < 30 ml/min/1.73 m^2. During the study period, 20 patients (6.5%) required chronic dialysis [median time of initiation: 13.1 (9.2; 15.3) years] and 4 (1.3%) received a kidney transplant, 4.7, 12.6, 12.9, and 14.7 years, respectively, following their heart transplantation.

Evolution of post-transplant renal function according to era of transplant

Figure 3b depicts renal function within the first 5 years post-transplant for the five groups of recipients. Intergroup comparisons revealed that eGFRs differed significantly between groups at discharge, at 3, 6, and 9 months, as well as 1, 2, 3, and 4 years after transplantation ($P < 0.05$). Further analyses combining patients transplanted before 2004 in a single group (1983–2003) showed that 2004–2008 and 1983–2003 recipients presented a similar eGFR at discharge ($P = 0.520$), whereas the former had a higher eGFR at 3 ($P = 0.001$), 6 ($P < 0.001$), and 9 months ($P < 0.001$), as well as 1 ($P < 0.001$), 2 ($P = 0.003$), and 3 years post-transplant ($P = 0.005$). From the fourth year post-transplant, this difference in renal function was no longer detectable ($P = 0.389$ at year 4, and $P = 0.600$ at year 5).

Recipients' characteristics at year 1 according to era of transplant

Table 2 presents recipients' clinical parameters, immunosuppressive regimens, and additional medication at year 1. Several characteristics differed significantly between 2004–2008 and 1983–2003 recipients. Most importantly, 2004–2008 patients exhibited lower systolic and diastolic blood pressure ($P < 0.001$), lower LDL and total cholesterol levels ($P < 0.001$), and lower tacrolimus doses and levels ($P = 0.020$ and $P < 0.001$, respectively) as well as a less frequent use of prednisone ($P < 0.001$) compared with 1983–2003 recipients. In addition, treatment with tacrolimus ($P < 0.001$) and mycophenolate mofetil (MMF; $P < 0.001$) was more common in 2004–2008 recipients.

Independent risk factors for reduced eGFR at year 1

Table 3 provides the results of the multivariable linear regression model for risk factors for reduced eGFR 1 year post-transplant. Increased age, female gender, lower pretransplant eGFR, elevated systolic blood pressure, and use of prednisone correlated significantly with a reduced eGFR at year 1 ($P < 0.005$). The adjusted R^2 for this model was 0.39, indicating that variability within these five factors explained 39% of the overall variability in eGFR. Despite a univariable P value < 0.15, the era of transplantation was not identified as an independent predictor of eGFR after adjusting for other variables. Neither cyclosporine doses

Table 1. Pretransplant clinical characteristics of cardiac recipients and donors.

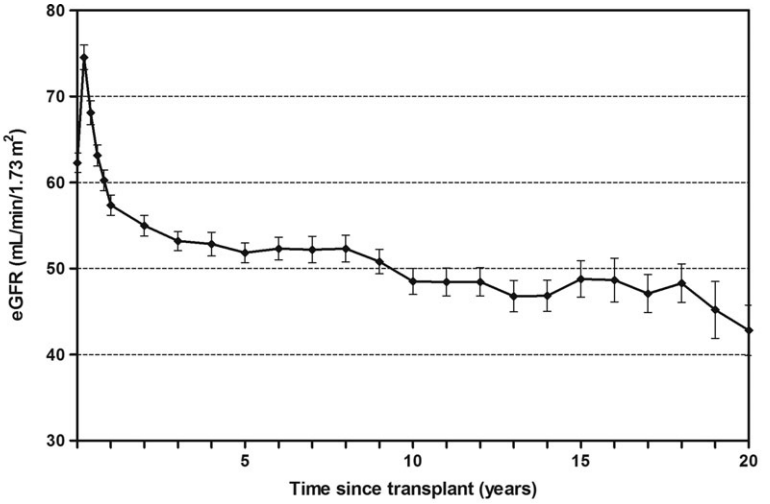
							P value	
	All (n = 306)	1983–1988 (n = 52)	1989–1993 (n = 78)	1994–1998 (n = 64)	1999–2003 (n = 63)	2004–2008 (n = 49)	Intergroup comparison	2004–2008 versus 1983–2003
Recipients								
Demographics								
Age at transplant (years)*	48.9 (41.6; 55.6)	47.0 (40.9; 51.0)	47.9 (41.6; 52.9)	52.6 (40.9; 57.2)	52.0 (43.4; 58.9)	50.0 (37.4; 56.4)	0.025	0.709
Male gender, *n* (%)	244 (79.7)	46 (88.5)	65 (83.3)	49 (76.6)	49 (77.8)	35 (71.4)	0.221	0.114
Disease etiology								
Ischemic heart disease, *n* (%)	154 (50.3)	35 (67.3)	43 (55.1)	29 (45.3)	31 (49.2)	16 (32.7)	0.002	0.006
Dilated cardiomyopathy, *n* (%)	78 (25.5)	7 (13.5)	23 (29.5)	23 (35.9)	12 (19.0)	13 (26.5)		
Other, *n* (%)	74 (24.2)	10 (19.2)	12 (15.4)	12 (18.8)	20 (31.7)	20 (40.8)		
Comorbidities								
Diabetes, *n* (%)	29 (9.5)	2 (3.8)	10 (12.8)	10 (15.6)	2 (3.2)	5 (10.2)	0.069	0.850
Hypertension, *n* (%)	52 (17.0)	7 (13.5)	11 (14.1)	12 (18.8)	13 (20.6)	9 (18.4)	0.787	0.780
eGFR (ml/min/1.73 m^2)†	61.0 (50.5; 70.8)	62.2 (47.7; 76.7)	60.9 (53.8; 67.9)	57.2 (47.1; 66.7)	61.4 (48.2; 75.0)	63.7 (52.6; 77.6)	0.200	0.142
Pretransplant support								
Inotropes, *n* (%)	113 (36.9)	17 (32.7)	26 (33.3)	22 (34.4)	27 (42.9)	21 (42.9)	0.609	0.348
IABP, *n* (%)	35 (11.4)	5 (9.6)	9 (11.5)	5 (7.8)	8 (12.7)	8 (16.3)	0.689	0.241
MCS, *n* (%)	25 (8.2)	1 (1.9)	0 (0)	2 (3.1)	16 (25.4)	6 (12.2)	<0.001	0.256
Donors								
Demographics								
Age (years)	30.0 (19.0; 40.3)	25.0 (18.0; 31.0)	28.0 (19.0; 37.0)	31.5 (20.0; 40.8)	36.0 (20.0; 46.0)	34.0 (22.0; 50.0)	<0.001	0.014
Male gender, *n* (%)	204 (66.7)	39 (75.0)	53 (67.9)	41 (64.1)	38 (60.3)	33 (67.3)	0.553	0.912
Cause of death								
Road accident, *n* (%)	110 (35.9)	26 (50.0)	37 (47.4)	21 (32.8)	13 (20.6)	13 (26.5)	0.014	0.060
Head trauma, *n* (%)	36 (11.8)	3 (5.8)	9 (11.5)	7 (10.9)	9 (14.3)	8 (16.3)		
Cerebral hemorrhage, *n* (%)	112 (36.6)	17 (32.7)	22 (28.2)	29 (45.3)	29 (46.0)	15 (30.6)		
Other, *n* (%)	48 (15.7)	6 (11.5)	10 (12.8)	7 (10.9)	12 (19.0)	13 (26.5)		

eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support.
*Continuous data are presented as median (25th; 75th percentiles).
†Data are missing for 12 patients.

nor tacrolimus concentrations were associated with eGFR in their respective submodel.

Factors influencing the time to moderate and severe renal dysfunction

Figure 4a and b shows the time to moderate (first eGFR < 60 ml/min/1.73 m^2) and severe renal dysfunction (first eGFR < 30 ml/min/1.73 m^2) in patients with a discharge eGFR ≥ 60 and ≥ 30 ml/min/1.73 m^2, respectively. The cumulative probability of developing moderate renal dysfunction within 15 years post-transplant was 96.1%, whereas the cumulative probability of developing severe renal dysfunction within the same period of time was 47.4%. Table 4 summarizes the findings of the multivariable Cox proportional hazard regression models investigating factors possibly influencing the time to moderate and severe renal dysfunction. The development of moderate renal dysfunction was significantly associated with increased age, female gender, longer post-transplant hospitalization, higher glycemia during follow-up, and use of sirolimus, ezetimibe, or loop diuretics after transplantation ($P < 0.05$). In contrast, treatment with MMF or mycophenolate sodium instead of azathioprine or no antimetabolite agent was correlated with a reduced risk of moderate renal dysfunction ($P < 0.001$). Borderline risk factors ($0.05 < P < 0.10$) possibly associated with a decline in renal function were lower pretransplant eGFR, pretransplant



# of subjects	306[a]	286	231	157	78	22
% of subjects[b]						
with eGFR<60	60.5		73.2	77.1	78.2	90.9
with eGFR<30	5.2		6.9	12.1	12.8	13.6

Figure 2 Recipients' renal function up to 20 years after cardiac transplantation. Renal function was mildly impaired prior to transplant, improved at hospital discharge ($P < 0.001$ versus pretransplant), decreased considerably during the first year ($P < 0.001$ at year 1 versus pretransplant and discharge), and then continued to deteriorate up to 20 years after heart transplantation ($P < 0.005$ at years 2, 3, 4, 5, 10, 15, and 20 versus pretransplant, discharge and year 1), albeit less rapidly. Data in the graph are presented as mean ± standard error of the mean (SEM). [a]Data pertaining to pretransplant eGFR are missing for 12 patients. [b]These percentages represent the prevalence of moderate renal dysfunction (NKF stage 3) or worse (eGFR <60 ml/min/1.73 m^2) at 1, 5, 10, 15, and 20 years post-transplant, as well as the prevalence of severe renal dysfunction (NKF stage 4) or worse (eGFR <30 ml/min/1.73 m^2) at the same time points. eGFR, estimated glomerular filtration rate; NKF, National Kidney Foundation.

hypertension, and use of potassium-sparing diuretics during follow-up. Significant predictors of severe renal dysfunction were increased age, female gender, lower pretransplant eGFR, longer hospitalization and use of prednisone, loop diuretics, or potassium-sparing diuretics during follow-up ($P < 0.05$). Borderline results ($0.05 < P < 0.10$) included pretransplant hypertension and inotropic support in the immediate pretransplant period. Again, the era of transplantation was not an independent predictor of the time to moderate and severe renal dysfunction.

Discussion

Our study indicates that renal function deteriorates constantly up to 20 years after cardiac transplantation, with the greatest decline occurring in the first year. To the best of our knowledge, this is one of the first publications reporting such long-term longitudinal data on eGFR in heart transplant recipients. Moreover, we have identified and validated several risk factors of kidney dysfunction. Time-dependent analyses, which took advantage of the important amount of information collected throughout the years, led to the discovery of additional modulators of renal dysfunction mainly related to patients' medication. Our findings might eventually help to predict the risk of renal insufficiency in cardiac recipients, but could also become valuable when designing prevention strategies to preserve renal function. Specifically, our results suggest that corticosteroid weaning and a stricter control of blood pressure and glycemia may be interesting interventions to study in order to limit the post-transplant deterioration of kidney function.

The characterization of renal impairment in our cohort of patients definitely adds to the existing literature because it extends the observation period beyond two decades post-transplant. Previous publications have only rarely presented follow-up data on kidney function more than 10 years after cardiac transplant [4–7]. We have demonstrated that the cumulative probabilities of developing moderate (96.1% at 15 years) or severe renal dysfunction (47.4% at 15 years) are excessively high after the first decade post-transplant. In addition, our data revealed that a significant proportion of patients (6.5%) require chronic dialysis at some point following cardiac transplant. Our investigation has also provided new evidence regarding the very short-term variations in renal function after heart transplantation. Indeed, while many centers have reported a marked worsening of kidney function in the first year post-transplant, with a slower decline thereafter [6,13–16], very few groups have illustrated the progression of renal function in cardiac recipients from the pretransplant period to the first few

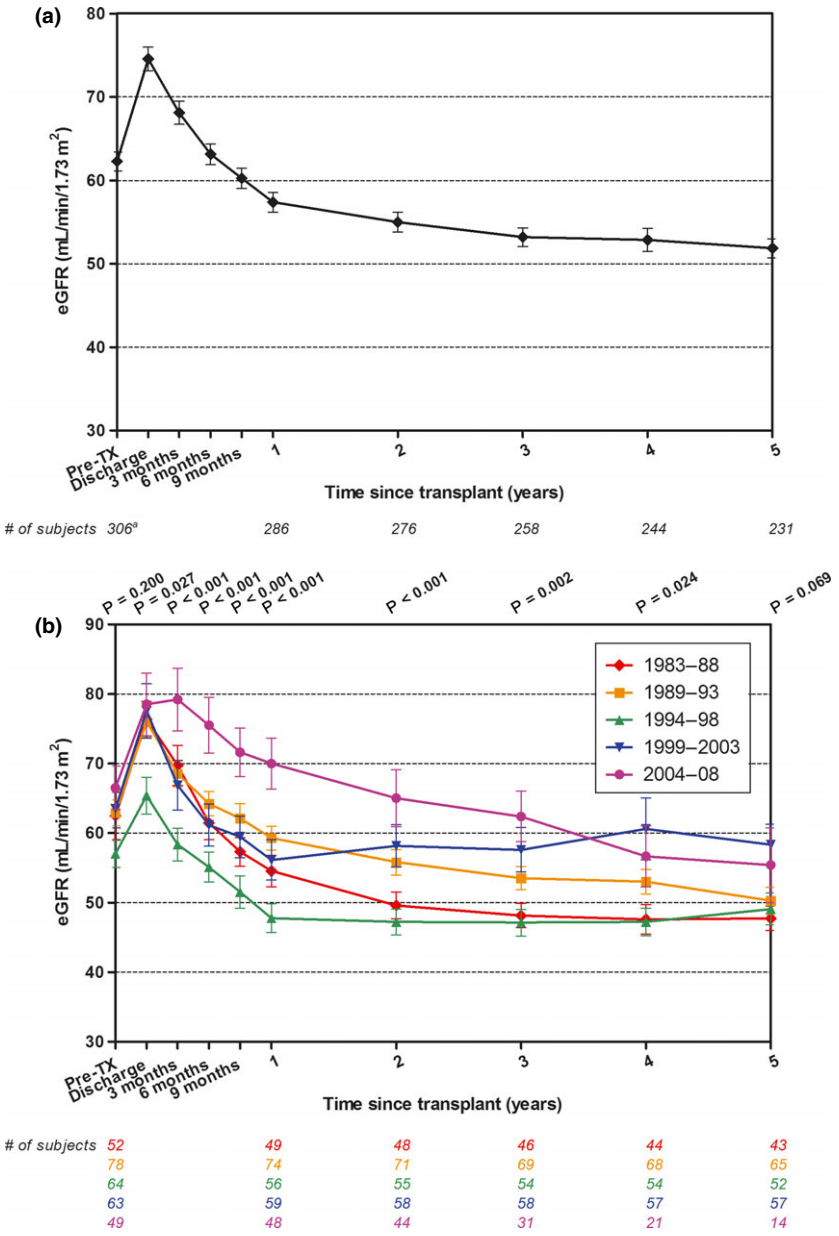


Figure 3 Recipients' renal function up to 5 years after cardiac transplantation. (a) This graph reproduces the evolution of renal function in the first 5 years post-transplant in the entire cohort of patients. (b) This graph is similar to 3a, but data have been divided according to the five eras of transplantation. Intergroup comparisons revealed that eGFRs were similar between groups prior to transplant ($P = 0.200$), but differed significantly at discharge, at 3, 6, and 9 months, as well as 1, 2, 3, and 4 years after transplantation ($P < 0.05$). Data in the graphs are presented as mean ± standard error of the mean (SEM). [a]Data pertaining to pretransplant eGFR are missing for 12 patients. eGFR, estimated glomerular filtration rate; Pre-TX, pre-transplant.

days or weeks following the procedure [13,17,18]. We have shown that kidney function is significantly improved at discharge when compared with pretransplant values. This finding highlights the need for early interventions to sustain the initial recovery in renal function so to prevent its rapid deterioration in the following year.

Our analyses are consistent with recent data showing that patients who underwent cardiac transplantation in the last decade have better post-transplant renal function than those transplanted before 2003 [3]. Here, we have demonstrated that despite similar pretransplant kidney function, 2004–2008 recipients exhibit a significantly higher eGFR as

Table 2. Clinical characteristics of recipients 1 year after cardiac transplantation.

	All (n = 286)	1983–1988 (n = 49)	1989–1993 (n = 74)	1994–1998 (n = 56)	1999–2003 (n = 59)	2004–2008 (n = 48)	P value: Intergroup comparison	P value: 2004–2008 versus 1983–2003
Clinical parameters								
SBP (mmHg)*	130.0 (120.0; 140.0)	140.0 (130.0; 150.0)	133.0 (128.8; 140.0)	130.0 (126.5; 150.0)	120.0 (120.0; 140.0)	122.0 (110.0; 133.5)	<0.001	<0.001
DBP (mmHg)	88.0 (80.0; 95.0)	95.0 (80.0; 100.0)	90.0 (80.0; 100.0)	90.0 (80.0; 100.0)	80.0 (70.0; 90.0)	80.0 (70.0; 84.0)	<0.001	<0.001
Glycemia (mM)	5.3 (4.8; 6.1)	5.5 (5.0; 6.3)	5.4 (4.7; 6.3)	5.4 (4.8; 6.3)	5.2 (4.8; 5.8)	5.3 (4.9; 5.9)	0.232	0.778
Total cholesterol (mM)	5.3 (4.5; 6.5)	6.9 (5.8; 7.9)	5.9 (5.2; 6.8)	5.5 (4.8; 6.6)	4.8 (4.0; 5.4)	3.5 (2.9; 4.5)	<0.001	<0.001
HDL cholesterol (mM)	1.2 (0.9; 1.4)	1.2 (0.9; 1.4)	1.2 (0.9; 1.5)	1.2 (0.9; 1.5)	1.1 (1.0; 1.3)	1.0 (0.8; 1.2)	0.027	0.001
LDL cholesterol (mM)	3.1 (2.4; 4.1)	4.5 (3.7; 5.1)	3.7 (3.1; 4.6)	3.4 (2.7; 4.0)	2.6 (2.1; 2.9)	1.8 (1.3; 2.5)	<0.001	<0.001
Triglycerides (mM)	1.7 (1.3; 2.4)	1.8 (1.3; 3.3)	1.6 (1.2; 2.2)	2.0 (1.4; 2.8)	1.7 (1.3; 2.6)	1.5 (1.0; 1.9)	<0.001	0.001
Immunosuppressant use								
Cyclosporine, n (%)	210 (73.4)	49 (100.0)	74 (100.0)	48 (85.7)	30 (50.8)	9 (18.8)	<0.001	<0.001
Tacrolimus, n (%)	73 (25.5)	0 (0)	0 (0)	8 (14.3)	28 (47.5)	37 (77.1)	<0.001	<0.001
MMF, n (%)	108 (37.8)	0 (0)	0 (0)	19 (33.9)	51 (86.4)	38 (79.2)	<0.001	<0.001
Mycophenolate sodium, n (%)	9 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)	9 (18.8)	<0.001	<0.001
Azathioprine, n (%)	121 (42.3)	28 (57.1)	61 (82.4)	31 (55.4)	1 (1.7)	0 (0)	<0.001	<0.001
Sirolimus, n (%)	8 (2.8)	0 (0)	0 (0)	0 (0)	4 (6.8)	4 (8.3)	0.007	0.011
Prednisone, n (%)	221 (77.3)	49 (100.0)	74 (100.0)	54 (96.4)	30 (50.8)	14 (29.2)	<0.001	<0.001
Immunosuppressant doses†								
Cyclosporine (mg/day)	300.0 (250.0; 400.0)	350.0 (300.0; 450.0)	300.0 (275.0; 400.0)	275.0 (250.0; 375.0)	225.0 (200.0; 281.3)	250.0 (212.5; 337.5)	<0.001	0.071
Tacrolimus (mg/day)	5.0 (3.5; 7.0)			4.5 (4.0; 7.5)	6.0 (4.0; 8.0)	4.0 (3.0; 6.0)	0.047	0.020
MMF (mg/day)	2000.0 (1500.0; 2250.0)			2000.0 (2000.0; 2000.0)	2000.0 (1500.0; 2000.0)	2000.0 (1500.0; 3000.0)	0.420	0.331
Mycophenolate sodium (mg/day)	1440.0 (720.0; 1440.0)					1440.0 (720.0; 1440.0)	N/A	N/A
Azathioprine (mg/day)	100.0 (50.0; 150.0)	112.5 (81.3; 150.0)	100.0 (50.0; 150.0)	75.0 (25.0; 125.0)	25.0		0.027	N/A
Sirolimus (mg/day)	2.0 (1.1; 2.4)				1.8 (1.1; 2.4)	2.0 (1.3; 2.4)	0.765	0.765
Prednisone (mg/day)	6.0 (5.0; 10.0)	12.0 (10.0; 15.0)	7.0 (5.0; 10.0)	5.0 (3.9; 6.0)	5.0 (4.8; 7.5)	5.0 (5.0; 5.0)	<0.001	0.004
Immunosuppressant trough concentrations‡								
Cyclosporine (µg/l)§	211.0 (142.3; 272.8)	123.0 (102.0; 162.0)	212.5 (177.3; 282.8)	266.0 (219.3; 297.5)	229.5 (143.5; 277.8)	209.0 (140.5; 245.0)	<0.001	0.632
Tacrolimus (µg/l)	10.0 (7.0; 13.0)			14.0 (13.3; 17.8)	11.0 (9.0; 14.0)	8.0 (6.0; 10.5)	<0.001	<0.001

Table 2. continued

	All (n = 286)	1983–1988 (n = 49)	1989–1993 (n = 74)	1994–1998 (n = 56)	1999–2003 (n = 59)	2004–2008 (n = 48)	*P* value	
							Intergroup comparison	2004–2008 versus 1983–2003
MPA (mg/l)	3.0 (2.2; 4.5)				3.3 (2.3; 4.2)	2.6 (2.1; 4.5)	0.474	0.474
Sirolimus (μg/l)	9.3 (6.5; 13.0)				8.0 (7.0; 11.4)	10.5 (5.0; 17.8)	0.827	0.827
Additional medication								
Antihypertensive agent, *n* (%)¶	240 (84.2)**	44 (89.8)	55 (75.3)**	53 (94.6)	54 (91.5)	34 (70.8)	0.001	0.005
ACEI/ARA, *n* (%)	142 (49.8)**	31 (63.3)	26 (35.6)**	34 (60.7)	30 (50.8)	21 (43.8)	0.012	0.356
Statin, *n* (%)	128 (44.8)	3 (6.1)	9 (12.2)	26 (46.4)	46 (78.0)	44 (91.7)	<0.001	<0.001
Fibrate, *n* (%)	3 (1.0)	2 (4.1)	1 (1.4)	0 (0)	0 (0)	0 (0)	0.189	1.000
Ezetimibe, *n* (%)	5 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	5 (10.4)	<0.001	<0.001
Anticoagulant, *n* (%)	15 (5.2)	2 (4.1)	1 (1.4)	1 (1.8)	2 (3.4)	9 (18.8)	<0.001	<0.001
Acetylsalicylic acid, *n* (%)	61 (21.4)**	7 (14.3)	15 (20.3)	4 (7.3)**	10 (16.9)	25 (52.1)	<0.001	<0.001
Oral hypoglycemic agent, *n* (%)	20 (7.0)	4 (8.2)	4 (5.4)	5 (8.9)	3 (5.1)	4 (8.3)	0.882	0.755
Insulin, *n* (%)	14 (4.9)	1 (2.0)	8 (10.8)	3 (5.4)	0 (0)	2 (4.2)	0.049	1.000
Loop diuretic, *n* (%)	145 (50.7)	35 (71.4)	42 (56.8)	39 (69.6)	17 (28.8)	12 (25.0)	<0.001	<0.001
Thiazide diuretic, *n* (%)	27 (9.4)	6 (12.2)	1 (1.4)	5 (8.9)	12 (20.3)	3 (6.3)	0.005	0.589
Potassium-sparing diuretic, *n* (%)††	15 (5.2)	2 (4.1)	2 (2.7)	1 (1.8)	7 (11.9)	3 (6.3)	0.101	0.723

ACEI, angiotensin-converting enzyme inhibitor; ARA, angiotensin II type 1 receptor antagonist; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; N/A, not applicable; SBP, systolic blood pressure.

*Continuous data are presented as median (25th; 75th percentiles).

†These results only include patients receiving the studied medication.

‡These results only include patients receiving the studied medication and for whom blood concentrations were measured.

§Before January 29, 1991: plasma/serum concentrations; after January 29, 1991: whole blood concentrations.

¶Antihypertensive agents include drugs such as ACEIs, ARAs, renin inhibitors, β-blockers, calcium channel blockers, central-acting agents, and α_1-adrenergic blockers, but they exclude diuretics.

**Data are missing for one patient.

††Potassium-sparing diuretics include spironolactone, eplerenone, triamterene, and amiloride.

Table 3. Independent risk factors for reduced eGFR 1 year after cardiac transplantation in the multivariable model.

	1 year post-transplant	
	Parameter estimate	*P* value in multivariable analysis
Recipient baseline characteristics*		
Age at transplant	−0.55	<0.001
Female gender	−8.25	0.001
Pretransplant eGFR	0.33	<0.001
Recipient characteristics at year 1†		
Systolic blood pressure	−0.20	0.003
Prednisone use	−7.06	0.003

ACEI, angiotensin-converting enzyme inhibitor; ARA, angiotensin II type 1 receptor antagonist; BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.
*We tested the following baseline variables: age, gender, reason for transplant, pretransplant BMI, pretransplant diabetes, pretransplant hypertension, pretransplant eGFR, inotropes, intra-aortic balloon pump, mechanical circulatory support, ischemic time, pre- and postoperative LVEF, antibody induction therapy, duration of post-transplant hospitalization, group (era of transplantation), donor's age, donor's gender, donor's cause of death.
†We tested the following variables at year 1: BMI, systolic and diastolic blood pressure, heart rate, white blood cell count, platelet count, glycemia, total cholesterol, HDL, LDL, triglycerides, number of coronary angiographies in the first year, calcineurin inhibitor, antimetabolite, sirolimus, prednisone, prednisone dose, antihypertensive agent, ACEI/ARA, statin, fibrate, ezetimibe, anticoagulant, acetylsalicylic acid, oral hypoglycemic agent, insulin, loop diuretic, thiazide diuretic, potassium-sparing diuretic, cyclosporine doses (submodel analysis), tacrolimus concentrations (submodel analysis).

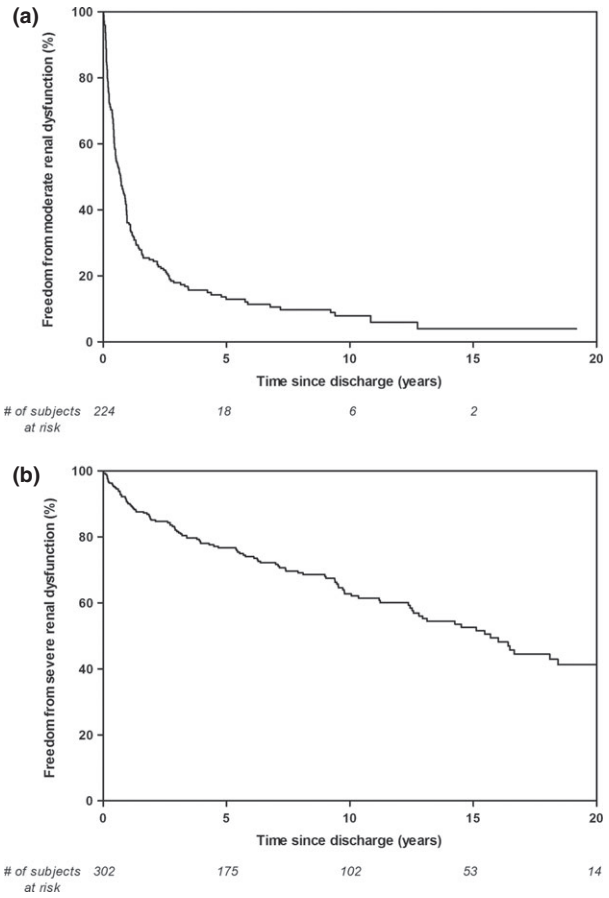


Figure 4 Time to moderate (first eGFR <60 ml/min/1.73 m^2) and severe renal dysfunction (first eGFR <30 ml/min/1.73 m^2). (a) Kaplan–Meier curve for freedom from moderate renal dysfunction (eGFR <60 ml/min/1.73 m^2) in patients with an eGFR ≥ 60 ml/min/1.73 m^2 at discharge (n = 224). (b) Kaplan–Meier curve for freedom from severe renal dysfunction (eGFR <30 mL/min/1.73 m^2) in patients with an eGFR ≥ 30 ml/min/1.73 m^2 at discharge (n = 302). eGFR, estimated glomerular filtration rate.

early as 3 months and up to 3 years post-transplant in comparison with individuals transplanted before 2004. This difference in renal function was no longer significant starting from the fourth year post-transplant. This could be attributable to the low number of patients in the 2004–2008 group at year 4 (n = 21) and year 5 (n = 14). At least one other publication has reported that patients transplanted more recently were at decreased risk of chronic kidney disease [19]. Nonetheless, our subsequent risk factor analyses revealed that the era of transplantation was not an independent predictor of worsening renal function, suggesting that the improvement detected in 2004–2008 recipients was most likely due to changes over time in recipient selection, immunosuppressive regimens, and post-transplant management. Results from our between-era investigations indicated that a better control of blood pressure and cholesterol in the 2004–2008 era, a lower exposition to tacrolimus (lower doses and concentrations compared to previous groups) as well as the changes in the use of different immunosuppressants (prednisone, tacrolimus, and MMF), may have contributed to this observation. However, as discussed below, only some of these factors (hypertension, prednisone, and MMF) were independently correlated with renal function in multivariable models. In accordance with previously published data which are either inconclusive or conflicting, dyslipidemia [6,13–15,20–22] and tacrolimus (in terms of use versus cyclosporine, doses, and concentrations) [1,3,6,19,23–33] were not identified as important modulators of renal insufficiency in our study.

Our multivariable linear regression model allowed us to validate that significant predictors of deteriorating eGFR at year 1 include increased age [1,3,4,13–16,18,19,22,23,34,35], female gender [1,3,15,16,18,19,23,34,35], elevated blood pressure [1,4,5,34–36], and impaired pretransplant renal function [1,3,4,6,13,15,17–20,22,23], all of which have

Table 4. Factors influencing the time to moderate and severe renal dysfunction in multivariable models.

	Time to moderate renal dysfunction (first eGFR <60 ml/min/1.73 m^2)		Time to severe renal dysfunction (first eGFR <30 ml/min/1.73 m^2)	
	Hazard ratio*	*P* value in multivariable analysis	Hazard ratio	*P* value in multivariable analysis
Baseline (fixed) variables†				
Age at transplant	1.04 (1.02; 1.06)	<0.001	1.03 (1.01; 1.06)	0.010
Female gender	1.79 (1.30; 2.47)	<0.001	1.82 (1.18; 2.81)	0.007
Pretransplant eGFR	0.99 (0.99; 1.00)	0.099	0.98 (0.97; 0.99)	0.004
Pretransplant hypertension	1.35 (0.97; 1.89)	0.079	1.56 (0.97; 2.49)	0.065
Use of positive inotropes at transplant	N/A‡	N/A	0.68 (0.44; 1.06)	0.087
Duration of hospitalization after transplant	1.01 (1.00; 1.02)	0.020	1.01 (1.00; 1.02)	0.023
Time-dependent variables§				
Glycemia	1.07 (1.01; 1.12)	0.014	N/A	N/A
Antimetabolite use (MMF or mycophenolate sodium versus azathioprine or none)	0.59 (0.45; 0.78)	<0.001	N/A	N/A
Sirolimus use	1.98 (1.26; 3.12)	0.003	N/A	N/A
Prednisone use	N/A	N/A	1.90 (1.15; 3.16)	0.013
Ezetimibe use	1.48 (1.00; 2.19)	0.048	N/A	N/A
Loop diuretic use	1.38 (1.03; 1.87)	0.033	1.61 (1.05; 2.46)	0.029
Potassium-sparing diuretic use	1.64 (0.98; 2.73)	0.060	3.56 (1.91; 6.62)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARA, angiotensin II type 1 receptor antagonist; BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MMF, mycophenolate mofetil; N/A, not applicable.

*Hazard ratios are presented as HR (95% confidence interval).

†We tested the following baseline (fixed) variables: age, gender, reason for transplant, pretransplant BMI, pretransplant diabetes, pretransplant hypertension, pretransplant eGFR, inotropes, intra-aortic balloon pump, mechanical circulatory support, ischemic time, pre- and postoperative LVEF, antibody induction therapy, duration of post-transplant hospitalization, group (era of transplantation), donor's age, donor's gender, donor's cause of death.

‡Covariates with "N/A" were not significant at the univariable level and hence were not considered in the multivariable models.

§We tested the following time-dependent variables: BMI, systolic and diastolic blood pressure, heart rate, white blood cell count, platelet count, glycemia, antimetabolite, sirolimus, prednisone, prednisone dose, antihypertensive agent, ACEI/ARA, statin, fibrate, ezetimibe, anticoagulant, acetylsalicylic acid, oral hypoglycemic agent, insulin, loop diuretic, thiazide diuretic, potassium-sparing diuretic.

already been associated in the literature with an increased risk of renal dysfunction after heart transplantation. Data linking female gender to renal deterioration after cardiac transplant are fairly consistent, but they might seem contradictory to what is described in the general population in which men are usually thought to be more susceptible to renal dysfunction [37]. No clear explanation for this discrepancy has been proposed in the heart transplant literature. Furthermore, our results emphasize that adequate blood pressure control, fundamental to patient care in chronic kidney disease [38], might be a key element to reduce the risk of kidney dysfunction in cardiac recipients. The use of prednisone at year 1 also appears to have a detrimental influence on post-transplant renal outcomes. Corticosteroids' numerous adverse effects (e.g., hypertension and diabetes) [39] could indeed aggravate kidney dysfunction. This hypothesis is coherent with our observation that both elevated blood pressure and hyperglycemia are independent risk factors for renal impairment. Current guidelines state that corticosteroid minimization or withdrawal should be attempted in pediatric heart transplant patients to avoid hypertension and subsequent chronic kidney disease [39]. Although the concept of early corticosteroid weaning is well established in adult recipients, strong data concerning its positive impact on renal function are still lacking [39]. Finally, as many other groups [5–7,13,16,32], we have not found cyclosporine doses or tacrolimus concentrations to be correlated with reduced eGFR in our submodel analyses. A potential justification is that neither doses nor trough levels correlate perfectly with real CNI exposure, especially in the case of cyclosporine [8]. In addition, recent data suggest that the role of direct CNI toxicity in postheart transplant renal dysfunction might be overestimated in some instances [40].

Further investigations using multivariable Cox proportional hazard regression models confirmed that increased age, female gender, and lower pretransplant eGFR had an unfavorable impact on the evolution of post-transplant renal function, and these baseline factors being associated with moderate and severe renal dysfunction. Hypertension

was a borderline predictor of kidney impairment in both models. Other fixed covariates with a possible effect on renal function were length of hospitalization and pretransplant inotropes. We are aware of a single publication reporting that prolonged postoperative intensive care unit stay was associated with renal dysfunction at 2 years [22]. The influence of inotropes on post-transplant kidney function has been evaluated in a number of studies, but conclusions are inconsistent [16,20,36,41].

We have also identified several time-dependent variables potentially correlated with moderate or severe renal dysfunction. Hyperglycemia, whose harmful structural changes in the kidney are thoroughly documented [42], is widely discussed in earlier publications, albeit with varying results [1,3–6,13–16,19–23,34,35,41,43]. Given its beneficial effects on renal deterioration in patients with diabetes [38], adequate glycemic control appears to be an important goal to achieve in cardiac recipients as well. Prednisone and sirolimus were also associated with renal impairment in our study, whereas MMF or mycophenolate sodium had a protective effect on kidney function. In light of sirolimus' established benefits as a CNI withdrawal strategy [44,45], our observation was most likely related to an increased use of mTOR inhibitors in those who experienced more advanced renal dysfunction while receiving cyclosporine or tacrolimus and were then switched to sirolimus to minimize further kidney damage. Our findings regarding MMF are consistent with CNI minimization studies reporting improvements in heart transplant patients' renal function when comparing MMF to azathioprine [44,45].

Other drugs correlated with moderate or severe renal dysfunction were loop diuretics, potassium-sparing diuretics, and ezetimibe. Despite their well-known deleterious impact on renal function [46], loop diuretics are the agents of choice in chronic kidney disease patients [47]. Thus, whether their use is a cause or a consequence of renal dysfunction is unclear. Similar uncertainty accompanies our finding that potassium-sparing diuretics are associated with worsening renal function, particularly in view of the existing data suggesting that spironolactone could protect against cyclosporine nephrotoxicity [48–50]. Our results may have been affected by the low number of patients receiving one of these agents after transplantation (5.2% at year 1) and by the fact that we combined aldosterone receptor antagonists (spironolactone and eplerenone) and other potassium-sparing diuretics (triamterene and amiloride) in a single category. One report showed that ezetimibe could increase cyclosporine concentrations in healthy subjects [51], but most studies found no signs of decreased renal function in cardiac recipients using both drugs [52–56]. Our observation perhaps reflects the presence of more advanced comorbidities in individuals receiving ezetimibe, which may in fact be responsible for their increased risk of kidney dysfunction. Moreover, this finding should be interpreted with caution given that few patients received ezetimibe following transplantation (1.7% at year 1 [all in the 2004–2008 group because ezetimibe's approval was only obtained in 2003 in Canada]).

Our results revealed that variability within the five risk factors for reduced eGFR at year 1 explains approximately 40% of the overall variability in renal function. Therefore, other predictors of worsening kidney function in heart transplant patients remain to be identified. Pharmacogenomic investigations could eventually help to bridge this gap [8,57], several groups having discovered genetic variants potentially increasing the risk of CNI nephrotoxicity [21,34,35,58–60].

The major strengths of our study are its extended follow-up (up to 26 years after transplant), its time-dependent analyses, and its comprehensive assessment of possible risk factors for post-transplant renal dysfunction. Limitations include its retrospective design, as well as the statistical restrictions preventing the evaluation of 1) CNI doses and concentrations in the general model at year 1 (because of missing values for either cyclosporine or tacrolimus), and 2) CNI use (cyclosporine versus tacrolimus versus none) as a time-dependent variable in the Cox proportional hazard regression models. Also, cyclosporine concentrations could not be analyzed because measurement methods (plasma/serum versus whole blood) changed during the study period. Finally, although 157 patients had a minimum follow-up of 10 years in our study, the number of recipients with a 20-year follow-up was limited ($n = 22$).

In summary, the initial improvement in kidney function following heart transplantation and its rapid decline and constant deterioration thereafter emphasize the need for early interventions aiming to prevent renal failure in cardiac recipients. Given our finding that the use of prednisone negatively impacts patients' kidney function, corticosteroid weaning could be considered in select individuals to limit renal damage in the long term. Furthermore, our results suggest that a more aggressive treatment of comorbidities such as hypertension and diabetes may minimize kidney impairment. Data from randomized controlled trials are necessary to validate the benefits of these interventions and to identify the best treatment targets (e.g., for blood pressure) as well as the most efficacious pharmacological agents (e.g., antihypertensive agents, hypoglycemic agents) in the heart transplant population.

Authorship

SdD, MW and KL: designed the study. KL: collected the data. AM and KL: analyzed and interpreted the data. KL and SdD: wrote the article. MW, MC, AM, NR, ML and AD: critically reviewed and approved the article.

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