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Original Article

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Renal transplant dysfunction—importance quantified in comparison with traditional risk factors for cardiovascular disease and mortality

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Abstract

Background. Renal transplant recipients (RTR) mainly die of premature cardiovascular disease. Traditional cardiovascular disease risk factors are prevalent in RTR. Additionally, non-traditional risk factors seem to contribute to the high risk. The impact of renal dysfunction was compared with traditional risk factors for cardiovascular morbidity and mortality in 1052 placebo-treated patients of the ALERT trial.

Methods. All patients were on cyclosporine-based immunosuppressive therapy, follow-up was 5–6 years and captured endpoints included cardiac death, non-cardiovascular death, all-cause mortality, major adverse cardiac event (MACE), non-fatal myocardial infarction (MI) and stroke.

Results. A calculated 84 μmol/l increase in serum creatinine was needed to double the risk for cardiac death, an increase of 104 μmol/l to double the risk for non-cardiovascular death and an increase of 92 μmol/l to double the risk for all-cause mortality. MACE risk was doubled if serum creatinine was elevated by 141 μmol/l, age was increased by 23 years, or LDL-cholesterol by 2 mmol/l. Diabetes increased the incidences of cardiac death, all-cause mortality, MACE, stroke and non-fatal MI. A serum creatinine increase of ~130 μmol/l, or ~20 years increase in age was calculated as similar in risk for cardiac death, all-cause mortality and MACE, and comparable to risk of diabetes in RTR.

Conclusion. An increase in serum creatinine of 80–100 μmol/l doubles the risk for cardiac death, non-cardiovascular death and all-cause mortality in RTR. An increase of 130 μmol/l in serum creatinine or ~20 years increase in age is comparable to risk of diabetes.

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Introduction

Renal transplant recipients (RTR) mainly die of premature cardiovascular disease (CVD) [1]. Traditional CVD risk factors are highly prevalent in RTR and immunosuppression may induce or aggravate hypertension, diabetes and hyperlipidaemia [2,3]. Prior to transplantation, these patients have mostly been exposed to uraemia-specific non-traditional risk factors such as increased oxidative stress, chronic inflammation, hyperhomocysteinaemia, malnutrition, calcium–phosphate imbalance and volume overload [4]. The intermediate endpoint for CVD, left ventricular hypertrophy (LVH), has been described in 50–70% of RTR and has been used as part of a prognostic index for mortality in these patients [4,5].

Ducloux *et al.* [6] showed that Framingham risk model underestimated CVD risk in the RTR and hypertension was not associated with coronary heart disease risk. We recently demonstrated that in RTR every 100 μmol/l (~1.13 mg/dl) increase in baseline serum creatinine increased the risk for cardiac death, non-cardiovascular death, all-cause mortality and major adverse cardiac event (MACE). The influence of serum creatinine on the risk increment remained significant after adjustment for other risk factors [7]. To study the importance of renal transplant dysfunction in CVD and mortality risk further, we have set renal transplant dysfunction into the perspective of traditional risk factors. Calculating risk factor increases needed to achieve certain risks enabled us to compare the impact of renal transplant dysfunction with traditional risk factors.

Methods

The Assessment of Lescol in Renal Transplantation (ALERT) trial was an investigator-initiated and investigator-led, randomized, double-blind, parallel group study designed to investigate the effects of fluvastatin on cardiac and renal endpoints in RTR. The ALERT study design, baseline data and outcomes have been previously published [8,9].

Participants

Adult RTR were recruited from nephrology and transplant clinics in Belgium, Denmark, Finland, Norway, Sweden, Switzerland, the UK and Canada. The patients had received renal or combined renal and pancreas transplants >6 months prior to randomization. All patients were on cyclosporine-based immunosuppression, but no one received statins prior to inclusion. Total fasting cholesterol ranged from 4–9 mmol/l (4–7 mmol/l for those with previous cardiac event). Patients, who had had an acute rejection episode in the last 3 months, or who had a predicted life expectancy of <1 year were excluded. The recorded endpoints included cardiac death, non-cardiovascular mortality, all-cause mortality, non-fatal myocardial infarction (MI), stroke and MACE (defined as cardiac death, non-fatal MI or coronary revascularization procedure). Single event per patient was accounted for. The critical events committee (CEC) consisted of two nephrologists and two cardiologists who were unaware of treatment assignment. All endpoints were adjudicated by the CEC and classified after agreement by consensus majority vote [9]. The present analysis was performed in 1052 patients in the placebo arm of the study only, because this was considered to be the 'cleanest' approach, preferable to including and adjusting for the treatment arm. The study adhered to the International Conference on Harmonisation Guidelines and for good clinical practice and was done in accordance with the Declaration of Helsinki. All participants provided written informed consent, and the Ethics Committee at each participating centre approved the trial.

Statistical analysis

The statistical analysis plan of the main study has been described previously [9]. Univariate and multivariate Cox proportional hazards models were used to analyse the impact of serum creatinine, low density lipoprotein (LDL)-cholesterol, age and the presence of diabetes on predefined endpoints. Risk ratio (RR) was calculated per 100 μmol/l (~1.13 mg/dl) increment in serum creatinine, per 1 mmol/l increment in LDL-cholesterol, and per 1 year increment in age. Diabetes was accounted for as a binary variable. A large number of potential risk factors were analysed for each outcome before stepwise selection of variables, using *P*-values of 0.1 for inclusion, was applied in the multivariate model. The potential risk factors were age, diabetes, previous transplant rejection, smoking, previous coronary heart disease, cerebrovascular disease, peripheral vascular disease, LVH, number of transplants, LDL-cholesterol, high density lipoprotein (HDL)-cholesterol, polycystic kidney disease, serum creatinine, systolic blood pressure, pulse pressure, HLA-DR mismatch, body mass index, proteinuria, time on dialysis prior to transplantation and time since transplantation. The multivariate models referred to include only variables selected by the stepwise procedure. Between-group differences were assessed with χ^2. Logistic regression models were used to calculate the probabilities of experiencing events at continuous risk factor levels. The increments needed to achieve certain risks were calculated using the estimated relative risk from the univariate model and obtaining the increment needed as the value of the independent variable resulting in a doubling of the relative risk or in relative risk corresponding to diabetes mellitus. All analyses were performed using the SAS statistics package (SAS Institute, Cary, NC). $P < 0.05$ was regarded significant.

Results

Between June 1996 and October 1997, 2102 patients were recruited to the ALERT trial, of whom, 1052 were randomly assigned to the placebo arm and followed for 5–6 years. During that time there was a 'drop-in' rate of 14% for statin use in this arm of the study, compared with 7% in the active treatment (fluvastatin 40–80 mg) arm, mainly occurring late in the study. The patients in the placebo arm of the study experienced 54 cardiac deaths. In addition, there were 66 patients with definite MI and 65 patients died of non-cardiovascular causes. The baseline demographic and clinical characteristics for the placebo group are presented in Table 1.

Risk factor analyses

Risk-factor analyses of baseline serum creatinine, age, diabetes, and LDL-cholesterol concentrations were performed. Diabetes mellitus was a significant risk factor for cardiac death, all-cause mortality, MACE, non-fatal MI and stroke, both in univariate and multivariate models. Diabetes did not increase the RR for non-cardiovascular death (Figure 1). Every 1 year increase in age resulted in RR increments for cardiac death, non-cardiovascular death, all-cause mortality, MACE, non-fatal MI, and stroke. Multivariate analyses confirmed the independence of age as risk factor for these endpoints (Table 2). Every 1 mmol/l increase in baseline LDL-cholesterol was associated with increments in MACE and non-fatal MI risks in univariate and multivariate models (Table 2). Using logistic regression models, the probabilities of reaching endpoints at different risk factor levels could be estimated (Figure 2).

Doubling of risk

We calculated the estimated increments needed in serum creatinine, age and LDL-cholesterol to double the RR for predefined endpoints This provided an interesting comparison of risk factors, e.g. the risk of cardiac death was doubled if serum creatinine increased

Table 1. Baseline demographic and clinical characteristics of the placebo group (*n* (%) or mean ± SD)

Demographic and clinical characteristics	Placebo ($n = 1052$)
Age, years	50.0 ± 11.0
Male	686 (65.2%)
Diastolic blood pressure, mmHg	85.6 ± 10.0
Systolic blood pressure, mmHg	144.0 ± 19.1
Body mass index, kg/m^2	25.8 ± 4.6
LDL-cholesterol, mmol/l (mg/dl)	4.1 ± 1.0 (159 ± 39)
HDL-cholesterol, mmol/l (mg/dl)	1.4 ± 0.4 (54 ± 15)
Triglycerides, mmol/l (mg/dl)	2.2 ± 1.5 (196 ± 134)
Serum creatinine, μmol/l (mg/dl)	142 ± 51(1.58 ± 0.58)
Diabetes mellitus*	199 (19%)
Time taking for renal replacement therapy, months	89 ± 58
Time on dialysis prior to transplantation, months	28 ± 42
First transplantation	900 (85.6%)
Type of last transplant: cadaveric donor	822 (78.1%)
Hypertension	777 (73.9%)
Current smoker	185 (17.6%)
History of angina pectoris	77 (7.3%)
Previous myocardial infarction	34 (3.2%)
History of cerebrovascular disease	60 (5.7%)
History of peripheral vascular disease	78 (7.4%)
Known family history of coronary heart disease	124 (11.8%)
Concomitant immunosuppressive therapy**	680 (64.6%)
Azathioprine	848 (80.6%)
Prednisolone	10 (1.0%)
Cyclophosphamide	159 (15.1%)
Mycophenolate mofetil	224 (21.3%)
Other	
Concomitant cardiovascular medication**	999 (95%)
Any cardiovascular drug	353 (33.6%)
Acetylsalicylic acid	26 (2.5%)
Dipyridamole	94 (8.9%)
Coumarin or warfarin	627 (59.6%)
β-Blockers	738 (70.2%)
Calcium antagonists	529 (50.3%)
ACE inhibitors or AIIRA	573 (54.5%)
Diuretics	170 (16.2%)
α-Blockers	373 (35.5%)
Other	

From reference [7], with permission from Blackwell Publishing.
ACE, angiotensin-converting enzyme, AIIRA, angiotensin-II-receptor blocker.
*Includes pre-existing diabetes mellitus and post-transplantation diabetes mellitus.
**Taken at least once during study.

by 84 μmol/l (≈1.0 mg/dl), or age increased by 14 years. Non-cardiovascular death risk doubled with 104 μmol/l increase in serum creatinine, or with every 10 years increase in age. All-cause mortality risk doubled with either 92 μmol/l increment in baseline serum creatinine, or with increase by 12 years in age. An estimated age increment of 23 years, LDL-cholesterol increment of 2 mmol/l or 141 μmol/l increment in serum creatinine were associated with doubling the risk for MACE. To double the RR for non-fatal MI in RTR, 23 years increment in age or 2.0 mmol/l increment in LDL-cholesterol was needed. The risk of stroke was doubled with 14 years increment in age (Table 3).

Diabetes as risk factor

Comparing diabetic and non-diabetic RTR, it was found that non-diabetic patients had a cardiac death rate of 4% and diabetic patients 10.1% ($P = 0.0004$) during the 5-year follow-up. The all-cause mortality rate was 10.4% for non-diabetic patients and 24.6% for diabetic patients ($P < 0.0001$). Non-fatal MI rate was 5.3% for non-diabetic and 11.1% for diabetic RTR ($P = 0.0026$); the stroke rate was 2.5% for non-diabetic patients, while it was 12.1% for diabetic patients ($P < 0.0001$). The corresponding figures for MACE were 11.3% and 19.1%, respectively ($P = 0.0028$) (Figure 1).

Diabetes vs other risk factors

The estimated increments needed in risk factors that are continuous variables to correspond to the risk associated with diabetes mellitus for different endpoints were also calculated. It was revealed that in order to correspond to risk for cardiac death in diabetic

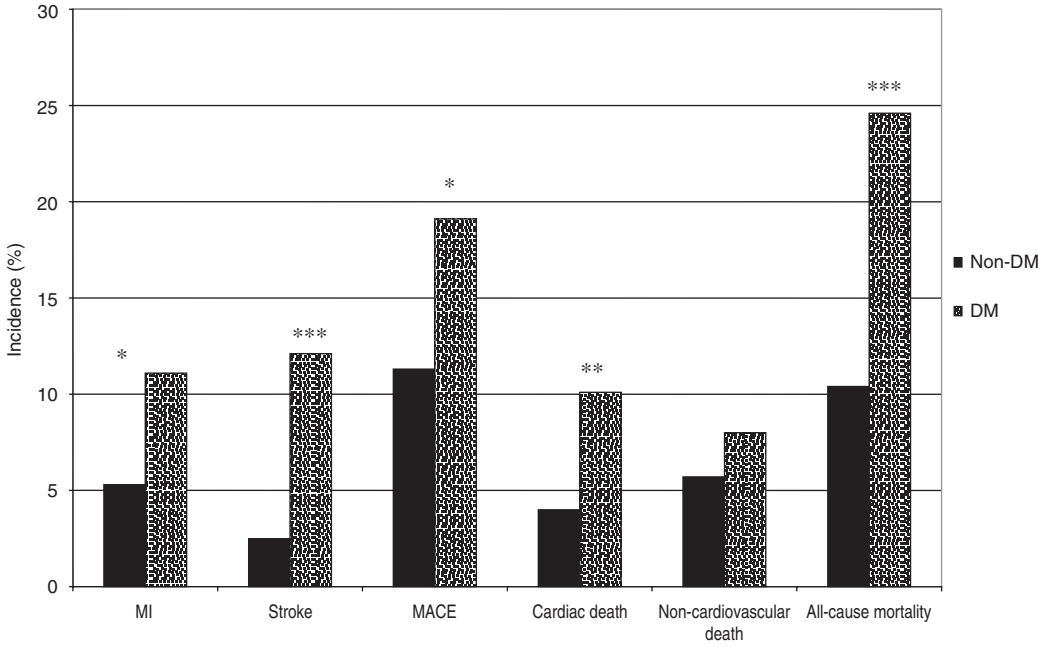


Fig. 1. Endpoint incidences in non-diabetic ($n = 853$) and diabetic ($n = 199$) renal transplant recipients. *$P < 0.003$; **$P < 0.0005$ ***$P < 0.0001$.

RTR (RR = 2.82), an estimated 125 μmol/l increase in serum creatinine or 21 years increase in age would be needed. The all-cause mortality risk in diabetes mellitus (RR = 2.61) corresponded to a baseline serum creatinine increase of 128 μmol/l or an age increase of 16 years in a non-diabetic RTR. To equal the RR of diabetic patients for non-fatal MI (RR = 2.41), an estimated increase in age of 30 years or increase in LDL-cholesterol by 2.6 mmol/l was needed. A diabetic RTR had a stroke risk (RR = 5.43) which corresponded to that of a 35 year older non-diabetic RTR. The MACE risk of the diabetic RTR (RR = 1.93) was achieved if a non-diabetic RTR had a baseline serum creatinine increase of 135 μmol/l, was 22 years older or had a LDL-cholesterol increase of 1.9 mmol/l (Table 4).

Discussion

In the ALERT trial, fluvastatin treatment reduced the risk for cardiac death and non-fatal MI, but had no effect on renal endpoints in RTR [9,10]. Analyses in the placebo arm of the trial revealed that renal dysfunction was an independent risk factor for cardiac death, non-cardiovascular death, all-cause mortality, MACE and graft loss [7,11,12]. Increased age was associated with mortality and cardiovascular morbidity risk, LDL-cholesterol was a risk factor for MACE and non-fatal MI, and diabetes was associated with increased risk of cardiac death, all-cause mortality, MACE, non-fatal MI and stroke [13].

Doubling of risk

Calculating the estimated increments needed in baseline serum creatinine, age and LDL-cholesterol to double the risk for the captured endpoints, set the relative influence of these risk factors into a new perspective, and to our knowledge, no similar comparisons of risk factors has been made previously. Surprisingly, only a moderate degree of renal transplant dysfunction doubled CVD and mortality risk, similar to the impact of increased age or LDL-cholesterol. Therefore, the prominence of renal dysfunction as a risk factor in comparison with age and LDL-cholesterol is not to be underrated in RTR.

Diabetes

Diabetes mellitus as pre-existing disease or post-transplant complication has a negative impact on patient and renal graft survival [14,15]. In the present study, diabetes mellitus was associated with an increased risk for non-fatal MI, stroke, MACE, cardiac death and all-cause mortality, but not for non-cardiovascular mortality. We also calculated the estimated increments needed in creatinine, age and LDL-cholesterol to equal the risk by diabetes mellitus. Only a moderate degree of renal dysfunction led to a risk of cardiac death, MACE and all-cause mortality which was comparable to diabetes mellitus. However, because CVD risk factors occur simultaneously, the assessed total risk should be based on their co-existence as well.

Table 2. Univariate and multivariate relative risks (95% confidence intervals) for the given increases in risk factors at baseline

	Creatinine increase by 100 µmol/l		Age increase by 1 year		LDL-cholesterol increase by 1 mmol/l		Presence of diabetes mellitus (binary)	
	Uni	Multi	Uni	Multi	Uni	Multi	Uni	Multi
MACE	1.63 (1.23–2.17)	1.9 (1.42–2.55)	1.03 (1.02–1.05)	1.03 (1.01–1.05)	1.41 (1.20–1.66)	1.35 (1.14–1.60)	1.93 (1.32–2.81)	1.96 (1.31–2.93)
	$P = 0.0007$	$P < 0.0001$	$P < 0.0001$	$P = 0.0004$	$P < 0.0001$	$P = 0.0004$	$P = 0.0007$	$P = 0.0010$
Cardiac death	2.29 (1.58–3.32)	2.94 (2.01–4.31)	1.05 (1.02–1.08)	1.059 (1.03–1.09)	1.28 (0.99–1.65)	–	2.82 (1.62–4.91)	2.97 (1.65–5.36)
	$P < 0.0001$	$P < 0.0001$	$P = 0.0001$	$P < 0.0001$	$P = 0.0607$		$P = 0.0002$	$P = 0.0003$
Non-fatal MI	1.12 (0.69–1.83)	–	1.02 (1.00–1.05)	1.03 (1.00–1.05)	1.41 (1.12–1.77)	1.36 (1.06–1.74)	2.41 (1.44–4.02)	2.17 (1.25–3.79)
	$P = 0.6426$		$P = 0.0351$	$P = 0.0414$	$P = 0.0038$	$P = 0.0141$	$P = 0.0008$	$P = 0.0063$
Stroke	1.30 (0.75–2.25)	–	1.05 (1.02–1.08)	1.05 (1.02–1.09)	1.12 (0.83–1.51)	–	5.43 (3.02–9.76)	4.75 (2.63–8.61)
	$P = 0.355$		$P = 0.0002$	$P = 0.0006$	$P = 0.4618$		$P < 0.0001$	$P < 0.0001$
Non-cardiovascular death	1.95 (1.34–2.83)	2.3 (1.54–3.43)	1.07 (1.04–1.10)	1.08 (1.05–1.12)	0.99 (0.77–1.27)	–	1.53 (0.87–2.70)	–
	$P = 0.0005$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P = 0.9124$		$P = 0.1380$	
All-cause mortality	2.12 (1.66–2.7)	2.50 (1.9–3.29)	1.06 (1.04–1.08)	1.08 (1.06–1.1)	1.10 (0.93–1.3)	–	2.61 (1.84–3.70)	2.4 (1.58–3.66)
	$P = 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P = 0.2752$		$P < 0.0001$	$P < 0.0001$

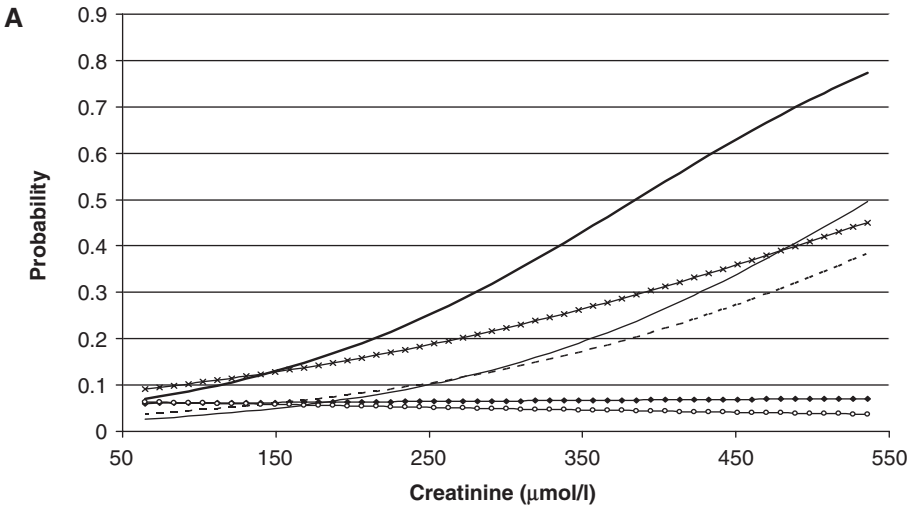
Renal dysfunction

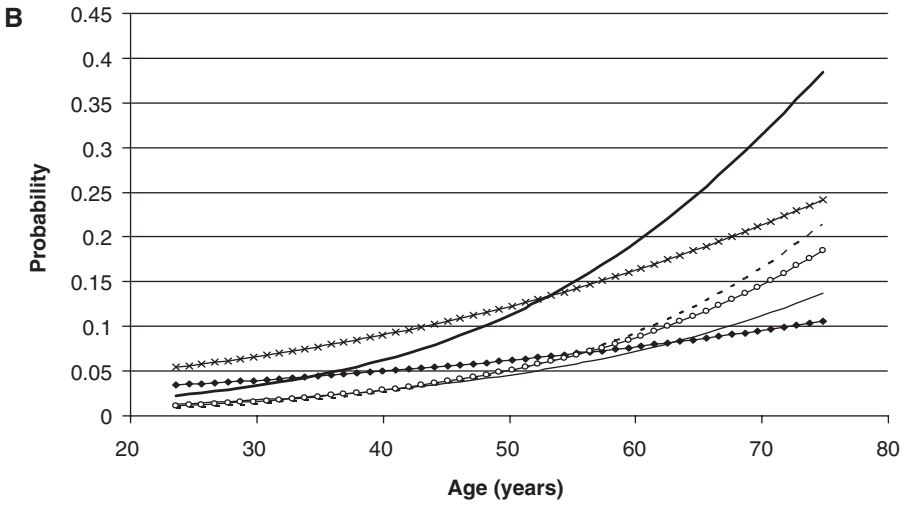
Even minute renal dysfunction in other populations has been associated with increased mortality and cardiovascular risk [16]. The CVD risk has been shown to increase progressively with deteriorating glomerular filtration rate and is increased significantly by the time serum creatinine is elevated [16]. The study does not reveal the mechanisms by which renal dysfunction contributes to the increased risk. In RTR, non-traditional risk factors such as inflammation, oxidative stress, hyperhomocysteinaemia, endothelial dysfunction and arterial stiffness may have greater than estimated influence on CVD and mortality. Ducloux *et al*. [6] have demonstrated that high C-reactive protein and homocysteine are associated with increased coronary heart disease risk in RTR. In RTR, serum creatinine has a strong association with graft failure, which is associated with increased cardiac death and all-cause mortality [11,17]. In our study population, graft loss increased the incidences of non-fatal MI, MACE, non-cardiovascular death and all-cause mortality [7].

Cardiac mortality patterns in renal patients differs from the general population with the predominance of sudden cardiac death explained by the high prevalence of uraemic cardiomyopathy, and the resultant predisposition to spontaneous arrhythmia [18,19]. In the present study, LDL-cholesterol was associated with increased risk for MACE and non-fatal MI, but not for cardiac death. On the other hand, serum creatinine was associated with cardiac death and MACE risk, but not with the risk of non-fatal MI alone [7,13].

To further establish renal dysfunction as a risk factor for mortality and cardiovascular complications, interventional studies are needed. Immunosuppressive therapy constitutes a prevailing toxic burden on the kidney transplant, and in patients who undergo other organ transplantation impairment of native healthy kidney function has been observed during calcineurin-inhibitor-based immunosuppression [20]. Although corticosteroids are not considered nephrotoxic, they adversely affect CVD risk factors such as hypertension, hyperlipidaemia and diabetes. In the ALERT trial, hypertension and diabetes were also associated with the risk for renal endpoints [11]. Therefore, cardiovascular outcomes in patients on different immunosuppressive regimens should be compared. It could be assumed that the use of a less nephrotoxic immunosuppressive regimen led to reduced mortality.

In conclusion, renal transplant dysfunction is a strong and independent risk factor for CVD and mortality, and comparable with traditional risk factors such as diabetes mellitus, age and LDL-cholesterol. An estimated increase in serum creatinine by 80–100 µmol/l doubles the risk for cardiac death, non-cardiovascular death and all-cause mortality in RTR. An increase by 130 µmol/l in serum creatinine or 20 years increase in age results in cardiac death, all-cause mortality and MACE risk comparable with diabetes in RTR.





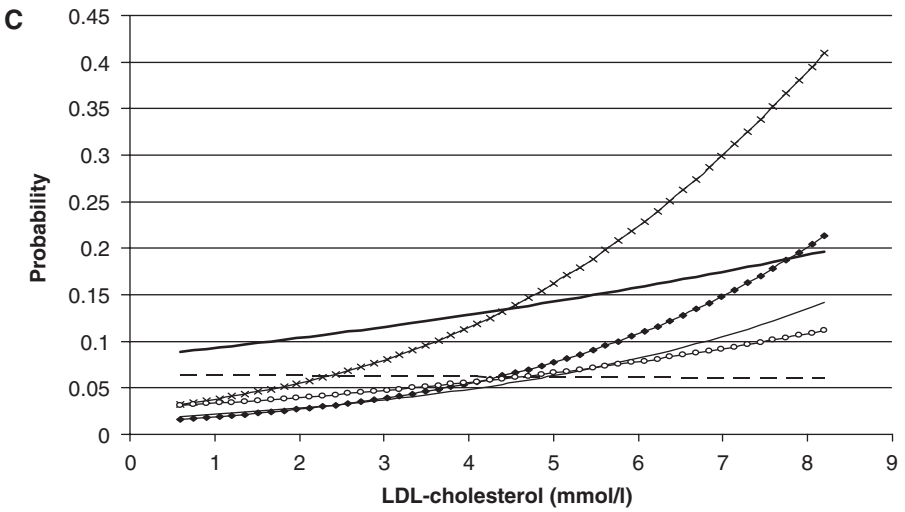


Fig. 2. (A) Endpoint probabilities at baseline creatinine levels. From reference [7] with permission from Blackwell Publishing. (▬) All-cause mortality ($P < 0.0001$) (——) Cardiac death ($P < 0.0001$) (- - -) Non-cardiovascular death ($P = 0.0005$) (—X—) MACE ($P = 0.0007$) (—◆—) Non-fatal MI (NS) (—○—) Stroke (NS). **(B)** Endpoint probabilities at baseline age. (▬) All-cause mortality ($P < 0.0001$) (——) Cardiac death ($P < 0.0001$) (- - -) Non-cardiovascular death ($P = 0.0001$) (—X—) MACE ($P = 0.0001$) (—◆—) Non-fatal MI ($P = 0.0351$) (—○—) Stroke ($P = 0.0002$). **(C)** Endpoint probabilities at baseline LDL-cholesterol levels. (▬) All-cause mortality (NS) (——) Cardiac death (NS) (- - -) Non-cardiovascular death (NS) (—X—) MACE ($P < 0.0001$) (—◆—) Non-fatal MI ($P = 0.0038$) (—○—) Stroke (NS). All *P*-values have been calculated by univariate Cox regression analysis.

Table 3. Increments needed in risk factors to double the risk in renal transplant recipients

	Cardiac death	Non-cardiovascular death	All-cause mortality	MACE	Non-fatal MI	Stroke
Creatinine (μmol/l)	84	104	92	141	–	–
Age (years)	14	10	12	23	23	14
LDL-cholesterol (mmol/l)	–	–	–	2.0	2.0	–

Table 4. Increments needed in risk factors to equal the risk in diabetic renal transplant recipients

RR in diabetes	Cardiac death 2.82	All-cause mortality 2.61	MACE 1.93	Non-fatal MI 2.41	Stroke 5.43
Creatinine (μmol/l)	125	128	135	–	–
Age (years)	21	16	22	30	35
LDL-cholesterol (mmol/l)	–	-–	1.9	2.6	–

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