Cardiovascular Risk in Renal Transplantation

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Abstract

Renal transplant patients suffer from a higher risk of cardiovascular morbidity and mortality. The risk-factor spectrum is different from the general population; several risk factors are transplantation specific, and to a large extent dependent on the immunosuppressive drugs used to prevent rejection. Due to the complexity of the risk factors, the variable impact of each factor on different cardiovascular outcomes and the inter-relationships between risk factors, it is difficult to judge the overall cardiovascular risk in a single renal transplant patient. In this paper we review risk-factor data from the literature, limited to single risk factors and their impact on single cardiovascular outcomes. We believe that a cardiovascular risk calculator specific to the renal transplant population, which takes into account all the important risk factors for a cardiovascular event, based upon a high quality database such as the ALERT data set, may provide a solid guidance to means to assess the overall cardiovascular risk in renal transplant recipients. **(Trends in Transplant. 2008;2:62-8)**

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Introduction

Patient and graft survival following renal transplantation have improved progressively over the last few decades, largely as a consequence of improved immunosuppressive agents. One result of the effective prevention of acute rejection episodes, however, is the emergence of long-term problems in renal transplantation, including graft failure due to chronic allograph nephropathy (CAN) and premature patient death[1-3].

Mortality after renal transplantation is mainly due to cardiovascular disease (CVD), infections, and malignancies. In most countries that have active renal transplant programs, CVD are the predominant cause of premature death[4]. An exception may be Australia, where malignancy (skin malignancies in particular) has been reported to be the dominating cause of patient death in some years. However, CVD recently surpassed it as the leading cause of death. Although cardiovascular (CV) mortality is increased in renal transplant recipients (RTR) (3-5-times that of the general population), it is still significantly lower than in dialysis patients[4,5], where mortality rates are 10-100-fold higher than the general population. The CV complications that affect RTR include myocardial infarction, left ventricular hypertrophy**,** heart failure, sudden (presumed arrhythmic) cardiac death, stroke, and peripheral vascular disease. These different manifestations of CVD in RTR differ from the general population, both in their prevalence and the relationship between CV risk factors and individual events.

The spectrum of risk factors in RTR includes traditional risk factors (found in the general population) such as age, smoking, male gender, hyperlipidemia, hypertension, diabetes, and preexisting CVD[3]. However, there are also risk factors that are transplantation-specific, such as the impact of immunosuppressive treatment on the CV risk, and the differing impact of individual agents on conventional CV risk factors[6,7]. Previously treated acute rejection episodes, graft loss, return to dialysis treatment, and the overall duration of renal replacement therapy (RRT) have also been identified as CV risk factors in RTR.

A useful way of classifying risk factors is to divide them into modifiable and non-modifiable risk factors, which gives direction to treatment or prevention of CV events in this population. A further important aspect in the assessment of CV risk is the interaction or co- variation between risk factors, as well as difficulties in comparing the relative influence of one risk factor versus another for future CV events. These problems encouraged us to develop a cardiovascular risk calculator based on the placebo group in the ALERT trial and comparable to the Framingham model used in the general population[8]. In the present review we will discuss some of the reported risk factors, how they are interrelated, and what may be done to reduce the influence of respective risk factors.

Age and gender

Age and gender are clearly non-modifiable risk factors in the general population; age also seems to be an independent, non-modifiable risk factor for all CV events that occur in a renal transplant population[9]. In our experience, female gender has a hazard ratio of 0.75 with regard to both myocardial infarction and cardiac death, but no impact on non-CV death. Advanced age, on the other hand, was a significant risk factor for CV and non-CV death (HR: 1.27-1.95/decade). Older age was also a significant risk factor for the occurrence of stroke during the follow-up for the ALERT trial (unpublished results).

Time on renal replacement therapy

Time on RRT has been implicated as a CV risk factor following renal transplantation[10]. This relationship has been suggested to be related to remodeling of the vascular wall in uremic patients undergoing dialysis treatment. However, in the ALERT trial we could not show that time on RRT was related to either the frequency or incidence of nonfatal myocardial infarction or cardiac death[9]. Although total time on RRT was a significant risk factor (HR: 1.06 per annum; $p < 0.004$) for non-cardiac death in a univariate analysis, in a multi-

variate analysis of risk factors of non-cardiac death, time on RRT did not emerge as a significant factor. Thus, in our understanding, there is still an uncertainty as to whether time on RRT has any influence on cardiac or non-cardiac causes of death in RTR, on whether it is possible to "write off" risk accumulated on dialysis in those patients who survive to get a successful transplant.

Preexisting cardiovascular disease

Several studies have reported that preexisting coronary heart disease (CHD) has a strong impact up on subsequent development of cardiac or coronary events after renal transplantation[2,9,11,12]. In the ALERT trial, preexisting coronary artery disease (CAD) was associated with a hazard ratio of > 3 for nonfatal myocardial infarction or cardiac death during follow-up. Prior cerebral vascular events were also independent risk factors for subsequent ischemic events. Thus, previous CVD must be recognized as a strong and important, albeit non-modifiable, risk factor for a variety of posttransplant CVD events (Table 1).

Diabetes mellitus

Diabetes mellitus (DM) is a well-documented risk factor for several types of CV events in the general population[9,13,14]; a relationship that appears to hold in RTR. Since DM is the fastest growing cause of end-stage renal disease, we foresee an associated increase in posttransplant CV events. Furthermore, there is an increasing incidence of posttransplant diabetes mellitus (PTDM), partly due to the use of calcineurin inhibitors (specifically tacrolimus) and corticosteroid treatment in the prevention of rejection[13,15]. Posttransplant DM has comparable impact as a posttransplant CV risk factor to DM prior to renal transplantation, and is potentially reversible or preventable[15]. According to figures from U.S. Renal Data System (USRDS), the prevalence of PTDM one year after transplantation is 20-25% in adults, and three years following transplantation a prevalence of 30% PTDM has been reported. Similar findings are reported in pediatric transplant recipients, although the rate is lower (e.g. 10% at three years). In the ALERT trial, PTDM or preexisting DM were strong independent risk factors for posttransplant, nonfatal myocardial infarction (HR: 2.41), for cardiac death (HR: 2.82), and also for stroke (both hemorrhagic and ischemic; HR: 3.9 and 4.5, respectively[9,14]. This translates into an overall significant risk for all causes of mortality (HR: 2.40; $p < 0.001$), attributable to DM, despite the fact that non-cardiac deaths were not dependent on DM. Thus, it is of great importance to prevent the development of end-stage renal disease in patients with DM and to consider non-diabetogenic immunosuppressive regimens where a patient is at risk or shows signs of PTDM.

Metabolic syndrome

Metabolic syndrome is associated with increased risk of CV events in the general population. In the ALERT trial we identified metabolic syndrome according to the Adult Treatment Panel III 2001 definition (except that BMI ≤ 30 was used instead of waist circumference). Where three out of five of the criteria were fulfilled (BMI ≤ 30, triglycerides ≤ 1.7, HDL-cholesterol < 1.03 in males or < 1.29 in females, systolic blood pressure > 130 or diastolic blood pressure > 85 and glucose ≤ 110 mg/dl) in nondiabetic patients, then individuals were classified as having metabolic syndrome. In patients with metabolic syndrome (498 of 1,718), 40% suffered a major adverse cardiac event (MACE), compared to 28% in patients without metabolic syndrome ($p < 0.001$). Moreover, acute myocardial infarction and cardiac death were significantly more common during the follow-up in patients with metabolic syndrome compared to those without (42 vs. 28%; $p < 0.006$) and cardiac death was also significantly more common (47 vs. 28%; $p \leq 0.001$). These are preliminary data which will be further analyzed with regard to which components of metabolic syndrome are more important than others, and the extent to which this classification adds to the risk attributable to conventional risk factors such as hyperlipidemia and obesity.

Lipid abnormalities

In the general population, hypocholesterolemia (specifically elevated LDL cholesterol and low

Table 1. Semiquantitative summary of risk factors versus cardiovascular disease events in renal transplant patients

Risk factors	Nonfatal myocardial infarction	Cardiac death	MACE	Ischemic stroke	Hemorrhagic stroke	All cause mortality
Age	+	+	+	+	0	+
Previous CVD	+	+	+	?	?	+
LVH	0	+	+	0	+	+
DM	+	+	+	+	+	+
Metab. Syndr.	+	+	+	?	?	+
Hyperlipidemia	+	+	+	0	0	0
Hypertension	0	0	0	0	+	0
Renal dysfunction	0	+	+	+	0	+

MACE: major adverse cardiac events; CVD: cardiovascular disease; LVH: left ventricular hypertrophy: DM: diabetes mellitus; +: positive risk factor; 0: neutral as risk factor.

HDL cholesterol) is associated with increased CV risk. Although the literature in RTR[16,17] is less clear, recent large studies[6] tend to support an adverse effect of hyperlipidemia on CVD and suggest that previous negative studies (e.g. Kasiske, et al.[3] 1996) may be a consequence of pooling CV endpoints with disparate determinants. *Post-hoc* analyses of the ALERT trial[9,11,12] demonstrated that total cholesterol and LDL cholesterol were significant risk factors for nonfatal myocardial infarction, but had less impact on cardiac death or stroke. In contrast, lipid abnormalities were not related to non-CV deaths. In a multivariate analysis, elevated LDL cholesterol value was an independent risk factor both for MACE and nonfatal myocardial infarction, with a hazard ratio of 1.35 per mmol/l increase in LDL cholesterol. Conversely, the risk of stroke was not related to LDL cholesterol values at baseline. Thus, in summary, LDL cholesterol is a risk factor for ischemic coronary events rather than other CV events, and it is ischemic coronary events that are modifiable by lipid lowering in this population.

Hypertension

Hypertension is a well-documented CV risk factor in the general population. However, the situation is not as clear in a renal transplant population. Hypertension is more prevalent in transplant patients compared with the general population (2-4-fold). In contrast to hyperlipidemia, hypertension did not seem to be a risk factor for nonfatal myocardial infarction in the ALERT trial, but systolic blood pressure and pulse pressure[9] were determinants of stroke (HR: 1.34/10 mm hg) and cardiac death. The relationship with cardiac death is likely to be linked to left ventricular hypertrophy, associated fibrosis, and the development of arrhythmias. The differential effect of hypertension and hyperlipidemia on specific CV events in this population is an important observation with implications for risk management. Thus, hypertension is a risk factor for stroke and cardiac death in renal transplant patients, whereas the principal risk factor for myocardial infarction is hyperlipidemia.

Renal transplant dysfunction and graft loss

Reduced renal function has been reported in several investigations to be strongly related to CVD in the general population[18,19]. This is true both in individuals with only a small reduction of renal function[19], as well as those patients on dialysis treatment[5]. In the latter group, it is well established that the rate of CVD is extremely high, disproportionately so in younger patients[8]. The spectrum of risk factors for CV complications of renal insufficiency may differ from the situation in a non-renal population[20]. For example, total cholesterol has even been shown to be inversely re-

lated to CVD in patients on maintenance hemodialysis. In contrast, systemic inflammation, reflected by increased C-reactive protein or interleukin-6 levels is also strongly associated with cardiovascular risk in patients with renal insufficiency[21]. The CVD in renal insufficiency is also characterized by an excessive calcification of small and large arteries, in particular coronary arteries, rather than simple atheromatous CAD. This is due to calcium, phosphate and parathyroid hormone abnormalities, as well as inadequate synthesis and levels of calcification inhibitors such as fetuin and N-methylpurine-DNA glycosylase (MPG)[22]. Due to the high quality of data in the ALERT trial we were able to analyze the relationship between moderate renal dysfunction at baseline and the different CV events that were captured during the follow-up[23]. Similar data have been presented from registry studies made on USRDS data[24].

We demonstrated that renal dysfunction, assessed by increased creatinine levels at baseline, was a significant and independent risk factor both for MACE, cardiac death and all-cause mortality (HR: 1.9-2.9 per 100 umol/l creatine; $p < 0.0001$). In a recent as yet unpublished analysis it seems that renal dysfunction is an independent risk factor for ischemic rather than hemorrhagic stroke. However, renal dysfunction was not a risk factor with regard to nonfatal myocardial infarction. There seems to be a threshold serum creatinine level of 200 umol/l, above which the risk of cardiac death (and all cause mortality) was tripled[12]. In a subsequent analysis[14], the relative importance of increased creatinine levels was compared to the relative risk in diabetes for cardiac death, MACE, and all-cause mortality. It could be shown that serum creatinine levels of 125-135 umol/l confer the same CV risk as DM for MACE, cardiac death and all-cause mortality. Furthermore, severe dysfunction as a consequence of graft loss was associated with a doubling of the risk of myocardial infarction, MACE, and all-cause mortality compared to patients with a functioning graft[23].

Taken together, the importance of renal dysfunction as a risk factor for MACE, cardiac death, and all-cause mortality cannot be underestimated. Transplant function should be considered a modifiable CV risk factor in this population that not only impacts on the risk for graft loss[15], but also on patient survival.

Immunosuppressive agents

The various immunosuppressive agents that are used in renal transplantation have been documented to have an impact on conventional CV risk factors. The effects are upon blood pressure**,** lipoprotein profile, diabetes, hypertension and renal dysfunction hyperlipidemia, and also on graft function and PTDM. The effects on blood pressure**,** lipoprotein profile and diabetes differ between the various agents used in organ transplantation (Table 2). It has been well documented that calcineurin inhibitors (CNI), including both cyclosporin and tacrolimus, interfere with lipid metabolism and also contribute to resistant hypertension. Whether there is a difference between cyclosporin and tacrolimus is a matter of debate[25-27]. It has been claimed that the effects on lipid metabolism and hypertension may be more evident with cyclosporin than tacrolimus, although there are no reports linking these effects on risk factors to “hard” outcome variables such as CV events. The mechanism by which CNI affect lipid metabolism has been reported be mainly due to interference with LDL-receptor sensitivity and impaired activity of lipoprotein lipase[28]**.** Calcineurin inhibitors may also cause hypertension by sodium and water retention, vasoconstriction in the vascular wall, and possibly sympathetic activation[29]. It has also been claimed that long-term use of CNI may have an adverse effect on endothelial function, possibly related to the influence by CNI on glucose metabolism. In fact, both tacrolimus and cyclosporine contribute to an increased incidence of PTDM[30]. The cause of DM in CNI-treated individuals may be due to an effect on insulin release together with insulin resistance. The dependence of insulin release on FK binding-protein 12 probably explains the observation that tacrolimus causes more PTDM than cyclosporin, and tacrolimus use was clearly shown to impair insulin secretion in the DIRECT study. However, the extent to which

Table 2. Semiquantitative estimation of influence by immunosuppressive agents on cardiovascular risk factors in renal transplantation

Drug/Agent	Hypertension	Hyperlipidemia	Diabetes	Renal dysfunction
Cyclosporine	+ +	+ +	+	+
Tacrolimus	+	+	+ +	+
Sirolimus /Everolimus	0	+ + +	0	0
Corticosteroids	+	+ +	+ + +	0
Mycophenolate mofetil	0	0	0	0
Monoclonal Ab	0	0	0	0

0: neutral effect; +, ++, +++: degree of enhanced effect.

differences in PTDM translate into worse long-term CV outcome is less clear. Corticosteroids are also used in almost all patients undergoing organ transplantation. Corticosteroids are known to induce peripheral insulin resistance and subsequently type II-like DM. Corticosteroids also cause dyslipidemia, principally increased levels of VLDL triglycerides and increased LDL cholesterol. However, corticosteroids increase all cholesterol subfractions, a phenomenon most clearly seen in the early post-transplant period (SOLAR study). Corticosteroids also cause hypertension through salt and water retention and enhanced receptor function, the pattern of hypertension and hyperlipidemia being akin to that seen in Cushing's syndrome[31].

Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus and everolimus are both documented to cause hypercholesterolemia and hypertriglyceremia. This is strongly dose-dependent and is less of a clinical problem at current dosage levels[32-34]. The pattern of dyslipidemia is also atypical with a disproportionate effect on HDL such that the overall pattern, together with the antiproliferative effects of vascular cells, may be cardioprotective (as it is in experimental animals[35]). The mTOR inhibitors appear to have little effect on blood pressure or PTDM and do not cause nephrotoxicity. However, any long-term effects on CV events remain to be established.

Other immunosuppressive agents such as mycophenolate mofetil and monoclonal antibodies directed towards CD20 and CD25, and monoclonal antibodies directed against receptors of the co-stimulatory pathway of T-cell activation (Belatacept), all seem to be neutral with regard to CV risk factors.

In summary, CNI, mTOR inhibitors and corticosteroids all seem to have an adverse influence on CV risk factors, whereas other immunosuppressive agents used in organ transplantation seem to be neutral. However, to the best of our knowledge there are no data to show that these adverse effects on risk factors actually translate into an increased incidence of "hard" CV events or CVD, although modification of immunosuppression is one option when managing CV risk in RTR.

Cardiovascular risk calculator

The Framingham risk factor model used in the general population is not applicable in a renal transplant population, since their risk factor profile (and the impact of risk factors on CV events) is different, and there are risk factors which are transplantation specific. For that reason we are developing a risk calculator, similar to the Framingham model, but targeting RTR and based upon the high quality data set from the ALERT trial. This work is ongoing, but may offer a way of identifying specific risk in individual patients and optimizing treatment, both conventional CV treatment and CV modification of immunosuppression, to prevent future events.

In summary, RTR suffer from a higher risk of CVD and mortality. The spectrum of risk fac-

tors is different from the general population. Several risk factors are transplantation-specific and, to a large extent, dependent on the drugs used to prevent allograft rejection. Due to the complexity of the risk factors, the differential impact of each factor, the co-variability between risk factors and the differences of risk factors for different CV manifestations, it is difficult to judge the risk in a single renal transplant patient. We believe that a risk calculator which takes into account all the important risk factors for CV events, based upon a high quality database such as the ALERT data set, may be invaluable when trying to assess and manage the overall CV risk in a renal transplant patient.

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