Cardiovascular risk factors in renal transplantation—current controversies

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Abstract
Cardiovascular diseases are more common in renal transplant recipients than in the general population, and a number of ‘traditional’ risk factors, such as smoking, diabetes mellitus and dyslipidaemia, are known to be associated with an increased risk. However, concentrating solely on these risk factors can lead to an underestimation of the true risk in this patient population, because other factors such as C-reactive protein and homocysteine levels are also associated with cardiovascular morbidity and mortality. Renal insufficiency also appears to be a key cardiovascular risk factor in the general population, with increasing proteinuria and decreasing glomerular filtration rate related to increased risk. In renal transplant recipients, a high proportion of whom have some renal insufficiency, the role of graft dysfunction in cardiovascular risk is controversial. While some studies have shown no correlation between graft dysfunction and congestive heart failure or ischaemic heart disease, registry data suggest that increased post-transplant serum creatinine levels are strongly associated with cardiovascular risk. This is believed to be the result of cardiovascular disease developing in the pre-transplantation period, as renal transplantation has been shown significantly to improve cardiovascular risk. As such, renal transplant recipients should be routinely screened for cardiovascular disease pre-transplantation, and immunosuppressive therapy should be tailored to minimize further risk. Different immunosuppressive agents, such as corticosteroids and calcineurin inhibitors, are associated with different exposure to cardiovascular risk, and studies involving withdrawal of these agents have generally shown improvement in parameters such as blood pressure and dyslipidaemia. However, these benefits are often associated with an increased incidence of acute rejection, although overall graft loss and mortality rates are not affected. Further studies are required to determine optimal regimens for minimizing cardiovascular risk in renal transplant recipients.

Keywords: cardiovascular disease; graft function; renal transplantation; traditional and non-traditional risk factors

Introduction

Patients with chronic kidney disease (CKD) are known to be at greatly increased risk of cardiovascular morbidity and mortality, with the prevalences of coronary artery disease and left ventricular hypertrophy as high as 40 and 75%, respectively, in dialysis patients [1]. Moreover, it is now becoming accepted that transplant recipients are also at high risk of cardiovascular disease compared with the general population. In a French study of post-transplant hyperlipidaemia, the incidence of myocardial infarction in renal transplant recipients ranged from 8.1/1000 patient-years in men aged 35–44 years to 15.5/1000 patient-years in those aged 55–65 years, compared with 1.3/1000 and 7.5/1000 patient-years in the general population [2]. Similar results were observed in a Spanish study, in which the overall incidence of myocardial infarction in renal transplant recipients ranged from 8.1/1000 patient-years in men aged 35–44 years to 15.5/1000 patient-years in those aged 55–65 years, compared with 1.3/1000 and 7.5/1000 patient-years in the general population [2]. Similar results were observed in a Spanish study, in which the overall incidence of myocardial infarction in renal transplant recipients was 7.4/1000 patient-years (prevalence: 3.4%), while the incidence and prevalence of ischaemic heart disease were 10.5/1000 patients-years and 5.3%, respectively [3]; these prevalences are substantially higher than those of myocardial infarction (1.35%) and coronary event rates (2.1%) in the general male Spanish population. In addition, transplant recipients also have an increased incidence of atherosclerotic plaques and other vascular alterations compared with the general population [4–6]. This high prevalence of cardiovascular disease leads to a substantial increase in cardiovascular mortality in transplant recipients, particularly in those ≤65 years of age (Figure 1) [1].
The role of traditional and non-traditional risk factors

Traditional risk factors for cardiovascular disease, such as smoking, diabetes mellitus and hypercholesterolaemia, are well known to increase the risk of cardiovascular disease in otherwise healthy individuals, and studies have now shown that these factors can also increase the risk of ischaemic heart disease in renal transplant recipients. Indeed, transplant recipients have been shown to have increases in a number of traditional risk factors (Table 1) [7–10], with studies showing that these risk factors can predict the incidence of ischaemic heart disease. For example, a retrospective study of 638 renal transplant recipients showed that older age, diabetes mellitus, male gender, anaemia and hypertension were dominant risk factors in the development of congestive heart failure and ischaemic heart disease [11], and an analysis of registry data in the USA showed that older age and co-morbidities such as diabetes mellitus, angina or peripheral vascular disease were important risk factors for post-transplant myocardial infarction [12]. However, traditional risk factors do not fully predict the incidence of cardiovascular disease in renal transplant recipients [10,13]. In a retrospective analysis of 1500 transplant patients, calculations of risk based on equations from the Framingham Heart Study (FHS) were significant predictors of ischaemic heart disease ($P < 0.001$), but tended to underestimate the actual risk [10]. This was largely related to differences in the risk associated with diabetes mellitus. In the FHS, diabetes increased the risk of ischaemic heart disease in men by 53%, compared with an almost 3-fold increase in renal transplant recipients ($P < 0.05$), while in women the increase in the risk of ischaemic heart disease was 82% compared with a 5-fold increase in renal transplant recipients ($P < 0.05$). Furthermore, having two or more episodes of acute rejection in the first year post-transplant was also associated with a subsequent risk of ischaemic heart disease. In addition, the analysis showed that cigarette smoking had a significantly greater association with ischaemic heart disease in male renal transplant recipients than observed in the FHS ($P < 0.05$) [10].

In recent years, a number of non-traditional risk factors have been identified that could play an important role in cardiovascular risk in transplant patients. In a prospective study in 344 renal transplant recipients, a C-reactive protein (CRP) level $\geq 0.52$ mg/dl (relative risk 2.78; $P = 0.007$) and a homocysteine level $\geq 20.8$ mmol/l (relative risk 4.19; $P = 0.008$) were significantly predictive of increased risk [13]. Overall, the FHS equation was a good predictor of cardiovascular events in low-risk patients (observed vs expected incidences, 0.6% vs 0.51%) but underestimated events in high-risk patients (6.4% vs 2.8%). In a second prospective study in 438 renal transplant recipients, an increased CRP level ($\geq 0.5$ mg/dl) was associated with a 53% increase in mortality ($P = 0.04$) compared with those with a lower level, and a body mass index $> 30$ kg/m$^2$ was also associated with a significant increase in mortality (hazard ratio, 2.67; $P = 0.005$) [14].

Graft function and cardiovascular disease

There is currently an increasing body of evidence to suggest that renal insufficiency itself is a risk factor for cardiovascular disease. A US study in 8786 individuals from a national database showed that mortality rates increase with increasing proteinuria and decreasing glomerular filtration rate (GFR) [15]. Cardiovascular disease-related mortality rates increased from

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>General population %</th>
<th>CAPD %</th>
<th>Haemodialysis %</th>
<th>Renal transplant recipients %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>21–26</td>
<td>50</td>
<td>80</td>
<td>70–85</td>
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<tr>
<td>Smoking</td>
<td>25.7</td>
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<td>24.7</td>
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<tr>
<td>Total cholesterol $&gt; 240$ mg/dl</td>
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<td>25</td>
<td>20</td>
<td>60</td>
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<tr>
<td>LDL cholesterol $&gt; 130$ mg/dl</td>
<td>40</td>
<td>45</td>
<td>30</td>
<td>60</td>
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<tr>
<td>HDL cholesterol $&lt; 35$ mg/dl</td>
<td>15</td>
<td>20</td>
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<tr>
<td>Lp(a) $&gt; 30$ mg/dl</td>
<td>15</td>
<td>50</td>
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CAPD = Continuous ambulatory peritoneal dialysis; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a)
6.2 deaths/1000 person-years in patients with a urinary protein level <30 mg/dl to 37.2 deaths/1000 person-years among those with a urinary protein level ≥300 mg/dl. Similar results were seen with regard to GFR, with mortality rates varying from 4.1 deaths/1000 person-years in those with a GFR ≥90 ml/min to 20.5 deaths/1000 person-years among participants with a GFR <70 ml/min. After adjusting for confounding variables, there was a significant trend towards increased all-cause mortality and cardiovascular disease-related mortality with increasing proteinuria (P < 0.001 and P = 0.02, respectively) and decreasing GFR (both P < 0.001) [15].

CKD of stage 3 or greater (GFR <60 ml/min/1.73 m²) is present in more than 60% of renal transplant recipients [16], and the effect of graft dysfunction on cardiovascular risk is currently a topic of some controversy. For example, in a retrospective analysis of a cohort of 638 renal transplant recipients, graft dysfunction was not predictive of either congestive heart failure or ischaemic heart disease, although acute allograft rejection was a significant predictor of ischaemic heart disease [11]. Conversely, analysis of data from 58,900 patients in the US Renal Data System (USRDS) registry showed that serum creatinine levels at 1 year after transplantation were strongly associated with the risk of cardiovascular death, with a significant, progressive increase in risk above a serum creatinine level of 1.5 mg/dl (Figure 2) [17]. Data from the Assessment of Lescol in Renal Transplantation (ALERT) study also show an increase in cardiac death, non-cardiovascular death, all-cause mortality and major adverse cardiac events (MACE) with increasing serum creatinine, particularly in patients with a creatinine level >200 µmol/l (2.3 mg/dl; P < 0.0001) (Figure 3) [18]. However, it is important to remember that the patients in these studies had been on dialysis for a considerable period of time before receiving a kidney transplant, and thus the subsequent cardiovascular risk may have been influenced by the effects of CKD and dialysis. Indeed, studies have shown that kidney transplantation can halt the progression of cardiovascular disease. An analysis of 60,141 renal transplant recipients from the USRDS registry compared with 66,813 patients awaiting a kidney transplant showed that rates of cardiovascular death peaked during the first 3 months after transplantation and then subsequently decreased in patients with a functioning graft [19]. In patients awaiting transplantation, the incidence of cardiovascular disease increased sharply with duration on the waiting list.

Routine screening of cardiovascular disease in renal transplant recipients is controversial among cardiologists. Although it is acknowledged that pre-transplant information on the cardiovascular profile of renal transplant recipients is useful in determining the ideal immunosuppressive regimen to minimize the risk of cardiovascular events in these patients, many of the techniques currently used to perform these analyses, such as coronary angiography, are invasive and costly, and, in many cases, underestimate the diagnosis of cardiovascular disease. However, many nephrologists continue to advocate that pre-transplant screening for cardiovascular disease should be an integral part of assessing patient history in renal transplant recipients.

**Cardiovascular risk—what is the ideal immunosuppressive regimen?**

Any immunosuppressive regimen is a balance between maximizing graft survival while minimizing biopsy-proven acute rejection (BPAR), nephrotoxicity, cardiovascular risk and other adverse events. Corticosteroids and calcineurin inhibitors (CNIs) in particular have a range of potential effects on cardiovascular risk [10], including increases in the risk...
and severity of hypertension, lipid abnormalities and diabetes mellitus. Since increased episodes of acute rejection are also a risk factor for cardiovascular disease [10], immunosuppressive regimens should also control for the incidence of BPAR. In a meta-analysis of six steroid-withdrawal studies involving patients receiving mycophenolate mofetil (MMF), either with ciclosporin (CsA) or tacrolimus, there was a significant reduction in serum cholesterol levels when prednisone was withdrawn from the treatment regimen \((P < 0.0001)\) [20]. However, steroid withdrawal was associated with a significant increase in the risk of acute rejection (risk ratio, 2.28; \(P < 0.00001\)), although there was no increase in the risk of graft failure (relative risk, 0.73).

Low-dose CNI regimens have also been assessed in a number of studies. In a 5-year, prospective study, 170 renal transplant recipients were randomized to either continuing maintenance immunosuppression with MMF, CsA and steroids, or to having their CsA dose gradually tapered over a 12 week period [21]. At 5 years, seven patients in the withdrawal group had experienced acute rejection, compared with one in the CsA group \((P = 0.0283)\). While there was no significant difference in graft loss between the two groups, three of six graft losses in the CsA group were the result of chronic rejection, compared with all nine graft losses in the withdrawal group. No differences in blood pressure or cholesterol levels between groups were observed at 5 years [21]. The role of the proliferation signal inhibitors (PSIs)/mammalian target of rapamycin (mTOR) inhibitors everolimus and sirolimus on cardiovascular risk has not been widely assessed. Comparison of renal transplant recipients in our centre receiving everolimus and CsA \((n = 15)\) or MMF and tacrolimus \((n = 15)\) showed that although the FHS score was lower for the everolimus–CsA group at 1 year post-transplant \((7.5 \text{ vs } 11.7\%\), respectively), by 3 years post-transplant it had risen to 10.1%. In contrast, the FHS score for the MMF–tacrolimus group had remained relatively constant, rising to 12.7% (R. Marcen, personal communication). Furthermore, everolimus is associated with an increased incidence of hyperlipidaemia in de novo renal transplant recipients when compared with MMF [22]. This is reflected in these analyses through the higher statin use in the everolimus–CsA group \((26.7 \text{ vs } 73.0\%\); \(P = 0.03)\). Any dyslipidaemia observed in renal transplant patients following treatment with PSIs should be balanced by benefits to cardiovascular risk factors. For example, analysis of six studies in which the CNI was withdrawn from sirolimus-based therapy showed an improvement in graft function \((P < 0.00001)\) and a significant reduction in hypertension \((P = 0.0006)\) in patients receiving sirolimus alone, with no significant differences in total cholesterol levels or triglycerides between the groups. However, there was a trend towards higher statin use in the withdrawal group [23]. CNI withdrawal was associated with an increased risk of acute rejection \((P = 0.002)\); however, there was no overall difference in graft loss or death after 1 year [23]. Four-year analysis of an early CNI withdrawal study with sirolimus has also reported a significant reduction in hypertension in patients receiving maintenance therapy with sirolimus and steroids compared to those receiving sirolimus, steroids and CsA \((P < 0.05)\). However there was little difference in the number of deaths due to cardiovascular events between the two groups \((3.7\% \text{ vs } 1.9\% \text{ for sirolimus-steroid-CsA and sirolimus-steroid groups respectively}) [24]. Furthermore, 5-year analysis confirms the improvement in hypertension in patients on sirolimus monotherapy whilst demonstrating similar lipid profiles between the two groups [25]. With regard to cardiovascular risk, changing the CNI appears to have benefits for traditional, although not for non-traditional, risk factors. For example, a study in 124 maintenance renal transplant recipients, randomized to continue CsA therapy or switch to tacrolimus, showed a significant reduction in FHS risk score after 2 years in those switched to tacrolimus \((P < 0.05)\) [26]. In a small-scale, open-label study, a range of risk factors was assessed in 22 patients with serum cholesterol levels >5.18 mmol/l switched from CsA to tacrolimus [27]. Six months after conversion, significant improvements in serum fibrinogen, total cholesterol and low-density lipoprotein (LDL) cholesterol were observed \((P < 0.001)\), although there were no significant differences in high-density lipoprotein cholesterol, triglycerides, homocysteine, CRP, haemoglobin A1c, blood pressure or requirement for anti-hypertensive medications [27].

### Managing cardiovascular risk in transplant recipients

Numerous interventions are now known to have important benefits for cardiovascular risk in the general population, and it seems likely that these will translate into similar benefits for transplant recipients. Lifestyle changes are often an important first step; giving up smoking has been shown to eliminate one-third of the excess risk of heart disease within 2 years of stopping in middle-aged women [28]. Based on results from trials of angiotensin-converting enzyme inhibitors and calcium antagonists, control of hypertension can lead to reductions in the incidence of stroke, coronary heart disease and MACE by 20–30%, particularly with more intensive therapy [29]. Treatment of hypercholesterolaemia with statins is now widely accepted as an important part of cardiovascular risk management, and the benefits of these agents have been confirmed in a number of large-scale studies. The UK Heart Protection Study enrolled 20 536 adults with occlusive arterial disease or diabetes mellitus into a randomized, placebo-controlled study of simvastatin, showing that statin use could reduce the incidence of myocardial infarction, stroke and revascularization by around 25\% \((P < 0.0001)\) [30]. Similar results were observed
in 19,342 patients with hypertension and at least three other cardiovascular risk factors randomized to atorvastatin or placebo in addition to one of two anti-hypertensive medications [31]. After a median follow-up of 3.3 years, patients in the atorvastatin group had a significantly lower incidence of stroke ($P = 0.024$) and cardiovascular and coronary events ($P = 0.0005$). The benefits of statin therapy on cardiovascular risk have also been demonstrated in renal transplant recipients. In the ALERT study in 2102 transplant recipients, although risk reduction for the primary endpoint (first occurrence of MACE) was not significant ($P = 0.139$) [32], fluvastatin therapy was associated with a 33% reduction in cardiac death and non-fatal myocardial infarction compared with placebo ($P = 0.005$) [33]. In the 2 year extension period of the ALERT study, mean LDL cholesterol was reduced by 36% following the introduction of fluvastatin in patients previously randomized to the placebo group. Similarly, the incidence of first MACE, the primary end point, was not statistically significant at 21% lower in the fluvastatin group compared with the placebo group ($P = 0.036$) [34]. Further analysis of the reduction in risk of cardiac death or definite non-fatal myocardial infarction, the secondary end points, seen at the end of follow-up should be considered when generating a hypothesis.

Conclusions

Renal transplant patients are at increased risk of cardiovascular complications that cannot be fully explained by traditional risk factors. Studies have suggested that non-traditional risk factors such as CRP and homocysteine, as well as graft dysfunction, could contribute to the increased level of risk. As such, the FHS equations are not sufficiently robust for analysing the risk of cardiovascular mortality in the renal transplant population, and an adapted analysis should be formulated. Choice of immunosuppressant may be of particular importance in renal transplant recipients at a high risk of cardiovascular disease, and choice of regimen should be tailored to balance hyperlipidaemia with positive benefits such as a reduction in hypertension and BPAR. To this end, assessing cardiovascular risk should be integral in determining patient history prior to transplantation, to ensure that the risks of cardiovascular disease are minimized in patients with pre-existing cardiovascular disease. Studies are now required to determine the optimal immunosuppressive regimens for minimizing cardiovascular risk in transplant recipients.

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References


25. Morales JM, Hartmann A, Arns W et al. Similar lipid profile but improved long-term outcomes with sirolimus (SRL) after cyclosporine (CsA) withdrawal compared to SRL with continuous CsA. Presented at World Transplant Congress, Boston, July 2006.


