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REVIEW

Cardiovascular morbidity and mortality after kidney transplantation

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Summary

Kidney transplantation is the optimal treatment for patients with end stage renal disease (ESRD) who would otherwise require dialysis. Patients with ESRD are at dramatically increased cardiovascular (CV) risk compared with the general population. As well as improving quality of life, successful transplantation accords major benefits by reducing CV risk in these patients. Worldwide, cardiovascular disease remains the leading cause of death with a functioning graft and therefore is a leading cause of graft failure. This review focuses on the mechanisms underpinning excess CV morbidity and mortality and current evidence for improving CV risk in kidney transplant recipients. Conventional CV risk factors such as hypertension, diabetes mellitus, dyslipidaemia and pre-existing ischaemic heart disease are all highly prevalent in this group. In addition, kidney transplant recipients exhibit a number of risk factors associated with pre-existing renal disease. Furthermore, complications specific to transplantation may ensue including reduced graft function, side effects of immunosuppression and post-transplantation diabetes mellitus. Strategies to improve CV outcomes post-transplantation may include pharmacological intervention including lipid-lowering or antihypertensive therapy, optimization of graft function, lifestyle intervention and personalizing immunosuppression to the individual patients risk profile.

Background

Transplantation confers the highest survival benefit among all the different renal replacement therapies. Multiple studies have shown that patient survival is better with renal transplantation than with maintenance dialysis after an increased risk of death in the early period after transplantation [1–5]. This is true for patient groups who are otherwise at increased cardiovascular (CV) risk including diabetics, African Americans, all age groups [3], obese patients [6], as well as recipients of marginal kidneys [7–9] and following repeat renal transplantation after failed primary transplantation [10,11]. Although long-term allograft survival has improved, death with a functioning graft remains the leading cause of late renal allograft loss [12,13]. Cardiovascular disease (CVD) persists as the leading cause of premature death in most kidney transplant registries [14].

Knowledge of the incidence, risk factors and the natural history of CVD in renal transplantation derives from registry data, observational population-based studies, clinical trials and extrapolation from studies on nontransplant cohorts. This review focuses on describing the nature of CVD in renal transplant recipients (RTR), including dissecting the various components, which combine as the syndrome of CVD in RTR. We highlight evidence-based treatments for reducing CV risk where this exists.

Epidemiology of CVD in kidney transplantation

Cardiovascular disease mortality in haemodialysis (HD) patients is 10–20 times greater than in the general population [15]. RTR have lower risk for CVD than patients who remain on the transplant waiting list, but higher CVD risk when compared with the general population [16], particularly those aged 25–55 years who have substantially more CVD mortality than their age-, gender- and race-matched nondialysis counterparts. Registry data show that cardiac disease is the cause of death for 18–30% of prevalent transplant patients [17,18]. Recent UK Registry data of 566 deaths (3.0%) within the first year post-transplant (from 19 103 kidney transplants performed over an 11-year period) demonstrate that whilst infection was the single leading cause of death (21.6% of deaths) in the first year post-transplant, CV events combined with cerebrovascular disease accounted for the greatest proportion of deaths at 22.9% [19]. With longer follow-up, CVD continues to accumulate and accounts for 31% of deaths with a functioning graft in the 2013 United States Renal Data System (USRDS) Report [17].

Clinical aspects of CVD in kidney transplantation

In the general population, CVD predominantly relates to underlying coronary artery atherosclerosis and is associated with conventional CV risk factors such as hypertension, dyslipidaemia, diabetes, cigarette smoking and family history. This paradigm does not hold true for patients with end stage renal disease (ESRD) where sudden, presumed arrhythmic, cardiac death rather than myocardial infarction (MI) is the predominant mode of CV mortality. The paradox of reverse epidemiology is acknowledged in patients with ESRD on dialysis where J-shaped (rather than linear) relationships are seen between blood pressure (BP) [20], cholesterol [21] and body mass index [22] and mortality risk. Following successful transplantation patients with ESRD have more conventional relationships between CV risk factors and outcome, as illustrated recently by *post hoc* analysis of the folic acid for Vascular Outcome Reduction in Transplantation [23] [23] trial [24], where there was a linear relationship between increasing systolic BP and mortality. Although more conventional relationships between CVD and risk factors evolve post-transplantation, legacy of time spent on dialysis remains. Along with diabetes and age, evidence of left ventricular (LV) hypertrophy with 'strain' on the ECG, often associated with longstanding ESRD was associated with increased risk of cardiac death in the Assessment of Lescol in Renal Transplantation (ALERT) trial [25].

Whilst the relationship between risk factors and CV events reverts towards the general population, the outcomes following a CV event in RTR are not comparable with the general population. In the ALERT study [26], there was a similar rate of fatal and nonfatal CV events to other randomized controlled trials (RCT) of lipid-lowering therapy (WOSCOPS [27] and 4S [28]). In nontransplant populations, nonfatal CV events are more common than fatal events. Therefore in RTR, risk of CVD is increased and there is a high prevalence of CV risk factors. There are dichotomous patterns of CVD in RTR, including both atheromatous coronary artery disease (CAD) as seen in the general population and sudden cardiac death as observed in dialysis patients. When they occur, CV events are more likely to be fatal than in the general population.

Coronary artery disease

Coronary artery disease influences listing for transplantation. At the time of transplantation, prior MI suggesting occlusive CAD is reported in 2.6% of transplant recipients in the UK [19]. Estimating prevalence of nonocclusive coronary artery atherosclerosis prior to transplantation is more difficult as most reports favour only performing coronary angiography in higher risk transplant candidates (e.g. over aged 50, diabetes mellitus, prior MI). Nonetheless, it appears that coronary artery atheroma is present in approximately 50% of higher risk transplant candidates [29]. Performing unselected coronary angiography appears to lead to low rates of coronary intervention in renal transplant candidates and is unlikely to be a useful strategy for risk reduction pretransplantation [30,31].

Once transplanted, prevalent CVD accumulates and was reported in 20% (14% previous MI or CAD) of participants at study entry in the FAVORIT trial [32] compared with 11.5% (4.7% previous MI, 6.8% revascularization procedure) of participants in the observational PORT study [33]. US data [17] show that hospitalizations for coronary atherosclerosis increase from 5.5% in year one to 9% in year two. Lentine *et al.* [34] concluded that post-transplantation MI is common, affecting approximately 11.1% of patients by 3 years post-transplantation, and that much of this risk is experienced early, within the first 6 months of transplantation. MI risk was linked with modifiable factors, including delayed graft function, post-transplantation diabetes and graft failure, and in turn, occurrence of MI predicted graft failure and death. Additionally, *post hoc* analyses of the ALERT trial [25] demonstrated that, determinants of nonfatal MI in RTR include total cholesterol level, prior CAD and previous acute rejection. Combined, these data suggest that whilst RTR share common risk factors with the general population for CAD and MI post-transplantation; there are further graft-specific aspects to post-transplant CAD.

Congestive heart failure

Congestive heart failure (CHF) and renal dysfunction form a 'vicious circle' that augur poor prognosis. At commencement of dialysis, up to 70% of patients with ESRD may have abnormal cardiac structure or function [35]. Transplantation may decrease the risk for CHF specifically compared with dialysis therapy [36]. However, CHF remains a clinical concern after transplantation. Wali *et al.* [37] showed an improvement of LV systolic function in more than 86% of patients following kidney transplantation which was associated with an improvement in NYHA functional status in more than two-thirds of patients. Duration of dialysis therapy before transplantation was the only factor that predicted normalization of LV systolic dysfunction. Lentine *et al.* [38] examined incidence of *de novo* CHF in 27 011 transplant recipients. Cumulative incidences of CHF were 10.2% and 18.3% at 1 and 3 years post-transplantation and beyond the early post-transplantation period, incidence of new onset CHF decreased progressively to less than the incidence in transplant candidates (18.3% vs. 32.3% at 3 years). US data [17] show that CV hospitalizations due to CHF rise from 21% in the first post-transplant year to 25% in the second year.

Arrhythmia

Despite the high incidence of sudden cardiac death, surprisingly little is known about arrhythmias in RTR. This reflects the difficulty in capturing short-lived arrhythmic episodes in asymptomatic patients. Using 24-h ECG monitoring, RTR have been shown to have higher rates of ventricular arrhythmia, usually ventricular extra systoles, compared with patients with mild chronic kidney disease (CKD) [39]. Ventricular repolarization is also abnormal, usually due to underlying left ventricular hypertrophy (LVH). Whilst ventricular arrhythmia when sustained is life-threatening, atrial arrhythmia, in particular atrial fibrillation and flutter are relatively common (6.4% of US transplant recipients [40]), and confers increased risk of ischaemic stroke. Patients with atrial fibrillation are likely to be older and have greater comorbidity burden [40]. There are no specific guidelines or studies to inform therapeutic strategies in RTR with atrial fibrillation.

Risk factors for development of CVD in kidney transplantation

The burden of CVD in RTR is not entirely explained by traditional risk factors such as hypertension, dyslipidaemia and diabetes [16]. Other factors may be involved, particularly those that influence systemic inflammation including graft rejection, infection and use of immunosuppressive medications (Fig. 1) [13,41].

Standard CVD risk calculators for the general population are poorly predictive in RTR. Soveri *et al.* [42] developed a formula for 7-year CVD and mortality risk calculation for prevalent RTR using models with different variables including age, CAD, diabetes, low-density lipoprotein (LDL), creatinine, number of transplants, time on renal replacement therapy and smoking (http://www.anst.uu.se/insov254/calculator/). Carpenter *et al.* [32] demonstrated that traditional CVD risk factors are inadequately managed in RTR. Using baseline data from the FAVORIT study, they showed that almost a third of the patients did not meet BP target of <130/80 mmHg, one to five had borderline or elevated LDL cholesterol and a third of the participants with prevalent CVD were not using an antiplatelet agent for secondary prevention.

Hypertension

Hypertension is common after kidney transplantation and is present in 50% to 90% of RTR [43,44]. Multiple factors induce susceptibility to high BP after transplantation including recipient, donor and transplant factors, immunotherapy, transplant dysfunction, renal artery stenosis and obstruction [45]. Hypertension is a leading cause for both decline in graft function and development of CVD [13,16,41,46]. The influence of BP on long-term kidney graft outcomes was demonstrated in the Collaborative Transplant Study (CTS) [47]. Increased BP at different time intervals post-transplantation was associated with late graft failure. Subsequent studies [43,48] showed that this strong, graded relationship between post-transplant BP and renal allograft failure was independent of acute rejection and baseline renal function, thus suggesting that progressive renal dysfunction was the result of elevated BP (Table 1).

Blood pressure control in RTR is particularly challenging. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [49] recommend a BP target of ≤130/80 mmHg irrespectively of level of proteinuria. This is based on data from patient subgroups in the general population rather than data in RTR. Retrospective data [50] showed that systolic BP of ≤140 mm Hg at 3 years after transplantation is associated with improved graft survival and reduced CV mortality at 10 years, and this effect remained even after lowering systolic BP several years post-transplantation.

Vasoconstriction is the dominant mechanism by which calcineurin inhibitors (CNI) induce acute nephrotoxicity and hypertension, thus, dihydropyridine calcium channel blockers (CCB) are an attractive option at least for the early management of hypertension after transplant. The beneficial effect of CCB on kidney function, compared with either

Table 1. Modifiable risk factors for post-transplant cardiovascular disease and strategies to address.

Modifiable risk factors for post-transplant CVD	Pretransplant hazard	Post-transplant exacerbation	Potential strategies to address	Rationale	Studies
Hypertension	Recipient, donor and transplant factors	Immunotherapy, transplant dysfunction and renal artery stenosis	Target BP ≤130/80, avoid ACEi/ARB within the first 3 months post-transplantation, consider in the long-term especially if persistent albuminuria, LVH or other indications	No evidence for benefit of any particular antihypertensive agent	Small RCT [51–54,57,59] Observational data [43,46–48,50]
Post-transplantation diabetes mellitus	African American or American Hispanic ethnicity and obesity	Immunotherapy, HLA mismatch, viral infections	Target HbA1c 7.0–7.5%, early basal insulin, incretin-based therapy, steroid reduction or withdrawal, switch from tacrolimus to CsA	Chances of reversing or ameliorating PTDM may be improved by early detection and intervention	Small RCT [115,116] Observational data [75,78,79]
Left ventricular hypertrophy	Hypertension, aortic valve calcification, anaemia, dialysis and AVF flow	Immunotherapy	ACEi, CsA, mTOR inhibitors	Regression of LVH with BP decrease, other mechanisms independent of haemodynamic effects on BP	Small RCT [90,91,93]
Dyslipidaemia	Pretransplant lipid abnormalities	Hyperlipemic effect of immunotherapy	Statins, replace CsA by tacrolimus, avoid sirolimus, low dose prednisolone	Statins improve CV outcomes, no benefit in overall mortality, remarkably safe	ALERT [26,66] *Post hoc* analyses [67,68]
Renal impairment	Previous graft loss and transplant factors	CNI nephrotoxicity, AR episodes and proteinuria	Optimization of graft function, CNI minimization to achieve adequate IS	Mild renal insufficiency is associated with adverse CV outcomes	*Post hoc* analyses [25,82] Observational data [81]
Calcineurin inhibitors	Transplant factors	Nephrotoxic, PTDM, Hypertension, Dyslipidaemia	CNI dose reduction after the first 3 months, conversion from CNI to mTOR inhibitors 3–6 months post-transplant is relatively safe	CNI withdrawal leads to increased acute rejection	RCT [96,100]
Corticosteroids	Diabetes and race	PTDM, Hypertension, Dyslipidaemia	Low dose steroids in the long-term, discontinuation could be attempted in patients at increased CV risk with low immunological risk and stable allograft function	No clear benefit for improved patient or graft outcomes after early or late discontinuation of steroids	Short- and medium-term RCT [117–121]
Other CV risk factors	Smoking, obesity, low physical activity, anaemia	Immunotherapy, systemic inflammation	Quit smoking, diet, correction of anaemia	Unclear benefits of exercise and vitamins	RCT [111] Observational data [102,106,108] Extrapolation from studies in the general population [103]

AR, acute rejection; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; AVF, arteriovenous fistula; CVD, cardiovascular disease; BP, blood pressure; CsA, cyclosporine; IS, immunosuppression; HLA, human leucocyte antigen; mTOR, mammalian target of rapamycin; LVH, left ventricular hypertrophy; RTR, renal transplant recipients; RCT, randomized controlled trials; PTDM, post-transplantation diabetes mellitus.

placebo or angiotensin converting enzyme inhibitors (ACEi), was shown in short-term RCT [51–54] although effects of CCB on long-term kidney function in CNI-treated RTR have been reported with variable efficacy [55–57]. A recent meta-analysis of RCT [58] indicated that use of CCB, versus placebo or no treatment (plus additional agents in either arm, as needed) was associated with 25% lower rate of graft loss and higher glomerular filtration rate (GFR) and in direct comparison with ACEi, CCB significantly improved GFR by approximately 12 ml/min.

Angiotensin converting enzyme inhibitors may reverse post-transplant erythrocytosis, decrease proteinuria and have a theoretical effect in mitigating antibody-mediated rejection mediated by antibody to AT1 receptor. In a RCT of RTR with LVH [59], patients administered ACEi had significantly better general and CV outcome after 10-year follow-up, suggesting that the effect by renin-angiotensin-system (RAS) blockade on clinical outcome can only be observed with longer follow-up. Another RCT that was adequately powered to assess hard outcomes in comparison between RAS blockade and placebo in RTR [60] was prematurely discontinued after 2 years because the incidence of events was considerably lower than expected in both arms of the study.

Finally, two recent meta-analyses [61,62] pointed out advantages of adopting CCB for BP control in RTR because RAS blockers are associated with progressive worsening of renal graft function without benefit in CV risk. Patients on ACEi or angiotensin receptor blockers (ARB) had a decrease in GFR (5.8 ml/min), lower haematocrit (3.5% translating to haemoglobin lowering of approximately 1.2 g/dl) and reduction in proteinuria [61]. The rate of CV death was similar in patients who received ACEi/ARB therapy or other antihypertensive treatment overall and in subpopulations of patients known to be at high CV risk [62].

Dyslipidaemia

Almost half of the RTR have LDL cholesterol levels >2.6 mmol/L, and 41% are on statin treatment 6 months post-transplantation [63]. Dyslipidaemia is common after transplantation, partly due to the hyperlipidaemic effect of corticosteroids, cyclosporine, tacrolimus and mammalian target of rapamycin (mTOR) inhibitors. In the CONVERT trial [64], conversion from cyclosporine or tacrolimus to rapamycin was associated with higher prevalence of hypertriglyceridemia (54% vs. 26%) and hypercholesterolaemia (42% vs. 12%) by month 24, even in the context of more common use of lipid-lowering therapy (78% vs. 55%). On the contrary, converting from cyclosporine to tacrolimus may provide significant benefits in serum lipid levels [65].

The Assessment of Lescol in Renal Transplantation (ALERT) trial [26] was the first large study to address cardiac and renal outcomes in transplantation. Treatment with fluvastatin (40–80 mg) failed to reach statistical significance in the primary composite end points (major adverse cardiac events defined as cardiac death, nonfatal MI and coronary intervention) despite 32% lowering of LDL cholesterol during a mean follow-up of 5.1 years. On the 'hard' CV endpoints, treatment with fluvastatin demonstrated a reduction of 38, 32 and 35% in the risk of cardiac death, nonfatal MI and in the cumulative incidence of cardiac death or first nonfatal MI, respectively. Nonetheless, a 2-year extension to the original study [66] demonstrated significant long-term benefits in the primary composite outcome. *Post hoc* analyses of the ALERT study demonstrated that early initiation of lipid-lowering therapy had a more favourable effect on cardiac events than late intervention [67] and lowering of LDL cholesterol by 39 mg/dL reduced cardiac death or MI by approximately 30% [68].

Long-term treatment with fluvastatin was well tolerated and had no harmful effects on renal function. This was opposed with previous reports [69] highlighting increased risk of myopathy and rhabdomyolysis, especially when co-administered with cyclosporine, which often results in several-fold increase in statin blood level.

Additionally, a Cochrane meta-analysis of 22 studies [70] including 3465 RTR confirmed the CV benefits of statins. The 2013 KDIGO guidelines [71] suggest initial evaluation of all transplant patients with a lipid profile, without follow-up lipid levels for the majority of patients as the indication for treatment is the higher CV risk, rather than LDL concentration.

Post-transplantation diabetes mellitus

Post-transplantation diabetes mellitus (PTDM) is increasing in incidence and is a major challenge following solid organ transplantation [72,73]. Approximately one-third of nondiabetic kidney transplant recipients develop persistently impaired glucose metabolism by 6 months post-transplantation [74]. At 3 years, the cumulative incidence of post-transplant diabetes amongst RTR is between 24.0% and 42.0% [17,75]. Risk factors for PTDM include age, obesity, African American race and Hispanic ethnicity, family history and impaired glucose tolerance [76]. In addition, risk factors that are unique to transplantation include immunosuppressive agents, HLA mismatch, donor gender, type of underlying renal disease and viral infections (HCV and CMV) [76,77]. Both PTDM and impaired glucose tolerance [65] confer a higher risk of developing CVD. The increased relative risk for death from CVD ranges from 1.5 to 3 among those who develop PTDM versus those without diabetes [75,78]. In a cohort study of 37 448 RTR [79], pre-existing diabetes was associated with higher CV and

overall mortality compared with PTDM, at least shortly after transplantation.

Renal impairment

Reduced kidney function is a risk factor for CVD in the general population, in part reflecting the close association of CVD risk factors and GFR. Population data [80] suggest that even minor kidney dysfunction is associated with increased CV risk (Fig. 1). The relationship of GFR with CVD risk in transplant recipients may differ following transplantation, because the level of GFR may no longer reflect lifelong exposure to CVD risk factors [13]. A *post hoc* analysis of 1052 participants in the ALERT Study [25] showed that renal dysfunction was associated with fatal CVD. Mild renal insufficiency was independently associated with increased risk of acute coronary syndromes and CHF [81], and 15% higher risk of CVD and death for each 5 ml/min/1.73 m^2 lower estimated glomerular filtration rate (eGFR) (at levels below 45 ml/min/1.73 m^2) [82].

Left ventricular hypertrophy

Left ventricular hypertrophy is present in 50–70% of patients following renal transplantation [16] and is a significant risk factor for CHF and death in RTR [83]. Correction of the uraemic state by transplantation leads to a fall in LV mass with echocardiographic examination [84,85] although when LV mass was measured by the more accurate cardiac magnetic resonance [86], renal transplantation was not associated with significant regression of LV mass suggesting that improvement in fluid balance leads to apparent improvement in LV mass.

Left ventricular hypertrophy is primarily an adaptive response to volume and pressure overload with the aim of minimizing ventricular wall stress. Multiple risk factors contribute to LVH development including age, hypertension, hypercholesterolaemia, tobacco smoking, obesity or diabetes, as well as transplant-specific risk factors including anaemia, the arteriovenous fistula flow and immunosuppressive therapy [87]. Resistance to LV outflow produced by aortic valve calcification during dialysis [88], anaemia and high BP [89] appear to be leading contributors to development, progression and persistence of LVH in RTR. ACEi are effective in reversing LVH persisting despite successful renal transplantation, probably by reducing BP [90] but also through mechanisms that are at least partially independent of hemodynamic effects on BP [91]. In one study [91], ACEi were effective in regressing post-transplantation LVH only in patients on cyclosporine therapy,

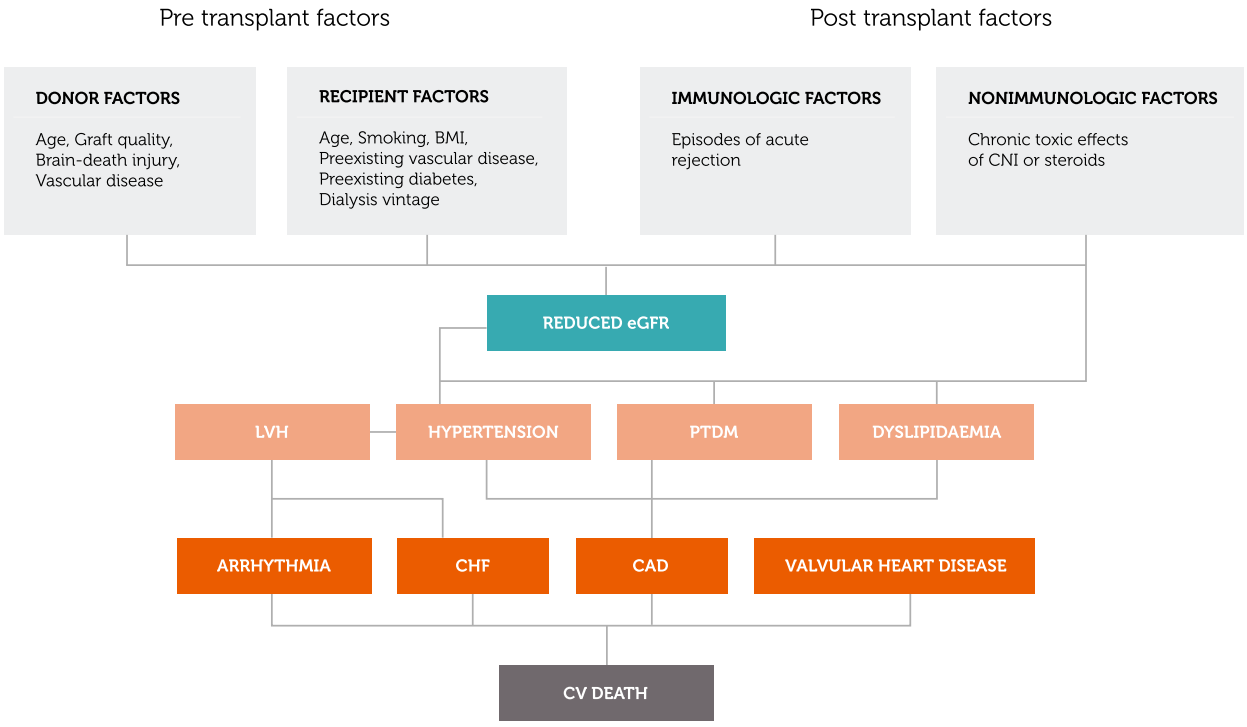

Figure 1 Pre- and post-transplant factors conferring increased cardiovascular risk after kidney transplantation. BMI, body mass index; CNI, calcineurin inhibitors; CHF, congestive heart failure; CAD, coronary artery disease; CyA, cyclosporine; CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; PTDM, post-transplantation diabetes mellitus.

perhaps because of an interaction effect between the two treatments. This indicates that immunosuppressive agents might modulate the effect of antihypertensive therapy on the LV mass of RTR.

The mTOR inhibitors play a role in regulating cell growth and may be a therapeutic tool to regress established cardiac hypertrophy. In two small studies, both sirolimus [92] and everolimus [93] regressed LVH in RTR regardless of BP changes, mainly by decreasing LV wall thickness, suggesting nonhemodynamic effect mechanisms of mTOR inhibitors on LV mass.

Effects of immunosuppression on CV risk

Corticosteroids

Corticosteroids have been a cornerstone of transplant immunosuppression for over 50 years, both as maintenance immunosuppression and for treatment of acute rejection. However, adverse effects of corticosteroids, mainly CV, have led to attempts to find maintenance immunosuppression regimens that do not include corticosteroids. Different protocols have been developed including 'steroid-free' protocols which do not use steroids as initial or maintenance immunosuppression, 'steroid avoidance' protocols in which steroids are initially used and are then withdrawn during the first week after transplantation, and 'steroid withdrawal' protocols in which steroids are discontinued weeks to months after transplantation.

Cardiovascular risk in RTR varies with comorbidities such as pre-existing metabolic syndrome, race and age and in addition, many of the adverse effects attributed to corticosteroids were observed with high doses. Whether the low doses commonly used for maintenance immunosuppression are associated with major adverse effects is less clear and is difficult to dissociate the CV profile of steroids from other factors, such as underlying renal function and CNI use.

Calcineurin inhibitors

Calcineurin inhibitors-sparing maintenance immunosuppression regimens have been applied to help maintain the balance between allograft survival and nephrotoxicity. CNI raise arterial BP in transplant recipients by several mechanisms, including arteriolar vasoconstriction, activation of the renin-angiotensin system, direct effects on juxtaglomerular cells and increased tubular sodium reabsorption [94,95]. The beneficial effects of late CNI withdrawal on ambulatory BP were documented in a recently published RCT of 119 stable RTR on a triple-drug regimen [96].

Complete CNI withdrawal after the initial period of high immunological risk is attractive; however, this has been associated with an increased incidence of late acute rejection and a possible reduction in long-term allograft survival [97]. Trials that explored the switching from CNI to mTOR inhibitors 3–6 months post-transplant [98–100] have shown the relative safety of this approach with improvement in renal function and BP despite increased risk of acute rejection.

Lifestyle and other CV risk factors in kidney transplant recipients

Cigarette smoking increases the risk for graft failure [101,102], ischaemic heart disease [102] and CHF [38] in RTR. Prevalence of cigarette smoking at time of transplantation varies between 25% and 50% [101,102]. In smoking RTR, graft failure is largely due to death with a functioning graft [102] and having quit smoking more than 5 years before transplantation reduced the relative risk of graft failure by 34% [102]. In the general population, there is strong evidence that screening patients for tobacco use and implementing prevention and treatment measures are effective. Guidelines suggest that the same approach should be applied for the RTR [103,104].

Obesity among transplant recipients is associated with the metabolic syndrome, which is present in two-thirds of RTR at 6 years post-transplant [105]. Registry data show that obesity is associated with adverse CV outcomes including increased risk of cardiac death [106] CHF [81] and atrial fibrillation [107]. Lifestyle changes based in diet and exercise, with dietary counselling as needed, are first-line strategies to achieve normal body weight among obese RTR. There is a paucity of data on the safety and efficacy of post-transplantation gastric banding or bypass surgery in ameliorating comorbid conditions such as hypertension, diabetes mellitus and dyslipidaemia.

Although low physical activity is strongly associated with increased risk for CV and all-cause mortality in RTR [108], the effect of exercise training in the CV risk profiles of RTR is unclear. A recent meta-analysis of exercise training in solid organ transplant recipients [109] (including two RCT with 164 RTR) showed no significant improvements in exercise capacity or CV risk factors such as incidence of PTDM, indicating that exercise training is a promising but unproven intervention for improving the CV outcomes in RTR.

Homocysteine is implicated to be an atherogenic amino acid, and fasting hyperhomocysteinaemia has been shown to be an independent predictor of CV events among RTR [110]. However, in the Folic Acid for Vascular Outcome Reduction in Transplantation [23] trial [111], lowering homocysteine levels has not been shown to decrease CV risk among 4110 RTR treated with vitamin B6 and vitamin B12 and with either high or low dose folic acid, despite the fact that homocysteine was effectively lowered with high dose folic acid.

Multiple other nontraditional risk factors have been associated with increased CV risk in various studies including anaemia, dialysis vintage prior to transplantation, elevated levels of lipoprotein a, elevated C-reactive protein and interleukin-6 levels [46,112–114].

Conclusions

Renal transplantation is the single most effective intervention for reducing CV risk in appropriately selected patients with ESRD. Nonetheless, CVD is common and is the leading cause of death with a functioning graft and hence graft loss. Strategies targeting modifiable conventional CV risk factors (diabetes, hypertension, dyslipidaemia and lifestyle) are crucial to reducing post-transplant CVD. However, further strategies to address transplant-specific CV risk factors should also be employed. These should include optimization of renal function, limiting risk of rejection, avoidance of PTDM and anticipation of CV side effects of immunosuppression. Further studies are required to address how each of these strategies is tailored to the requirements of the individual patient and graft.

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