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REVIEW

Risk factors for cardiovascular disease in renal transplant recipients and strategies to minimize risk

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Summary

Cardiovascular disease is the leading cause of death following renal transplantation, and renal transplant patients have a greatly increased cardiac risk compared with the general population. Death with a functioning graft caused by cardiovascular disease also represents a substantial cause of graft loss. Decreased renal function in transplant recipients is a major contributor to increased cardiac risk, both as an independent risk factor and because of its negative effects on hypertension, anemia, left ventricular hypertrophy, and dyslipidemia. Graft loss and diabetes mellitus are also significant risk factors for cardiac death. Although critical for maintaining the transplanted organs, standard immunosuppressants have toxicities that exacerbate cardiac risk. Preservation of renal function, prevention of graft loss, and reductions in cardiovascular risk factors via improvements in both patient management and immunosuppressive therapies constitute critical strategies for optimizing patient and graft survival over the long term.

Introduction

Cardiovascular disease – including congestive heart failure, coronary artery disease, cerebrovascular disease, and peripheral vascular disease – is common in patients with end-stage renal disease (ESRD), and the risk of cardiac death in dialysis patients has been shown to be 10–20 times greater than that in the general population [1]. This increased risk is likely because of the presence of traditional cardiovascular risk factors: hypertension, hyperlipidemia, diabetes, physical inactivity, smoking, and older age, and is compounded by the presence of nontraditional risk factors related to poor kidney function: altered lipid and calcium-phosphate metabolism, hyperparathyroidism, homocysteinemia, microalbuminuria, chronic inflammation, anemia, and volume overload [2,3].

Kidney transplantation constitutes the standard care for patients with ESRD, as it significantly prolongs patient life, largely by halting the progression of cardiovascular disorders by improving renal function [4]. Renal transplant recipients have up to a 10-fold reduced rate of cardiac death compared with dialysis patients [1]. However, although the transplanted kidney imparts improved renal and cardiac benefits, renal function still remains lower than that of the normal population, and renal transplant recipients have up to 10 times the rate of cardiac death and 50 times the annual rate of fatal or nonfatal cardiovascular events as the general population (Fig. 1). Nearly 40% of patients have experienced a cardiovascular event at 36 months after renal transplantation [5,6], with congestive heart failure and coronary artery disease (myocardial infarction) being the most common events. Although transplantation reduces the risk of stroke [7], the prevalence of cerebrovascular events is still high in patients who have undergone renal transplantation, and the risk of cerebral hemorrhage is higher than in the general population [8]. Finally, although the incidence of peripheral arterial disease is lower in renal transplant recipients, *de novo* peripheral arterial disease increases the relative risk for death by almost twofold [9].

Furthermore, immunosuppressive regimens used to prevent graft rejection can actually undermine the benefits of the functioning organ. Standard immunosuppressant agents used in transplantation, namely calcineurin

inhibitors (CNIs) and corticosteroids, are nonselective drugs that affect signaling pathways in multiple cell types, leading to nephrotoxic, cardiovascular, and metabolic side-effects that contribute to increased cardiac risk in renal transplant recipients.

The complex interplay among renal function, additional cardiac risk factors, and immunosuppressant drugs culminates in elevated cardiac risk in renal transplant recipients (Fig. 2). This review discusses important risk factors for cardiovascular disease after renal transplantation, with a focus on decreased renal function. Strategies to minimize cardiac risk are also discussed.

Decreased renal function and cardiovascular risk

Decreased renal function is a strong risk factor for cardiac disease. In the nontransplant population, the degree of renal impairment correlates with the risk of cardiovascular mortality. Muntner *et al.* [10] calculated that the relative risk for cardiac death in patients with a glomerular filtration rate (GFR) <70 ml/min/1.73 m^2 was 1.68, compared with individuals with a normal GFR. In a separate study, each decrease in GFR of 5 ml/min/1.73 m^2 was associated with an increased relative risk of 1.26 for cardiovascular mortality [11].

Similarly, in kidney transplant patients, the quality of post-transplant renal function is significantly correlated with cardiac risk (Table 1). Patients with a low GFR (<44.8 ml/min/1.73 m^2) at 1 year post-transplant demonstrate substantially increased cardiac risks [12]. Meier-Kriesche *et al.* [13] found a strong dose-dependent association of serum creatinine at 1 year post-transplant with the risk and incidence of cardiovascular death. In another study, elevated post-transplant serum creatinine strongly correlated with major cardiac events and cardiac mortality [14]. A majority of renal transplant patients experience a progressive decline in graft function over time, which augments the degree of cardiac risk over a long-term [13].

Decreased renal function can cause and/or exacerbate hypertension, dyslipidemia, anemia, hyperglycemia, and left ventricular hypertrophy (LVH), all of which are well established risk factors for cardiovascular disease (Fig. 2) [2,15]. The effects of decreased renal function on these risk factors are detailed below.

It is difficult to separate the interrelated effects of renal dysfunction and hypertension. Renal dysfunction affects hypertension via volume expansion, sodium retention, increased circulating vasoactive substances, and effects on the sympathetic nervous and renin–angiotensin–aldosterone systems (RAAS) [2]. Increased blood pressure can then cause additional renal damage, which further reduces GFR, creating a negative cycle.

Decreased renal function and the uremic state can affect lipase function and increase insulin resistance, leading to hyperglycemia [15–17]. This can lead to reductions in high-density lipoprotein (HDL) cholesterol levels and hypertriglyceridemia, including an accumulation of partly metabolized triglyceride-rich particles. Patients with ESRD can have a highly abnormal, proatherogenic cholesterol

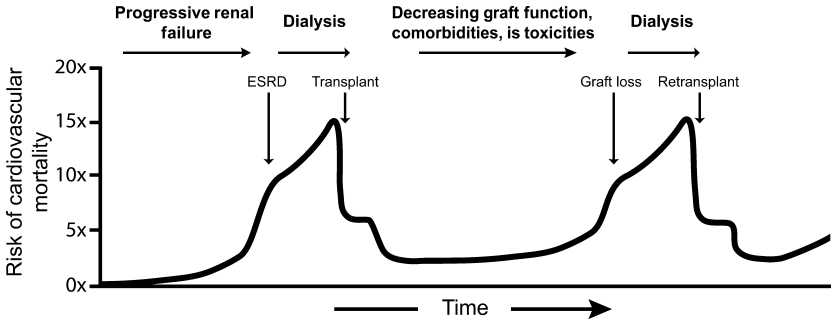

Figure 1 Risk of cardiovascular mortality over time among individuals with renal dysfunction, compared with the general population. Mortality rates because of cardiovascular disease are ~10–20 times higher in individuals with ESRD than in the general population [1]. The risk of cardiovascular mortality in ESRD patients increases with an increasing duration of dialysis before renal transplantation [13], reportedly ranging from 10 to 20 times higher among patients treated by dialysis compared with those in the general population [1]. The annual death rate from cardiovascular disease drops considerably after renal transplantation. The risk of cardiovascular death remains elevated in the immediate post-transplant period (0–3 months) [4], but thereafter, decreases to a level approximately twice that of the general population [1,3]. Following transplantation, several factors have the potential to increase cardiovascular risk over time, including decreased renal function, the presence of comorbidities (e.g. diabetes), and the effects of immunosuppressants (IS) on cardiovascular risk factors [3,13,22,45]. Graft loss with a return to dialysis is associated with a significant increase in cardiovascular mortality, to the same degree as that observed in ESRD patients [13]. Retransplantation has the potential to reduce cardiovascular risk yet again. Note: risk estimates are approximate; no units are given with regard to time because of extensive interpatient variability.

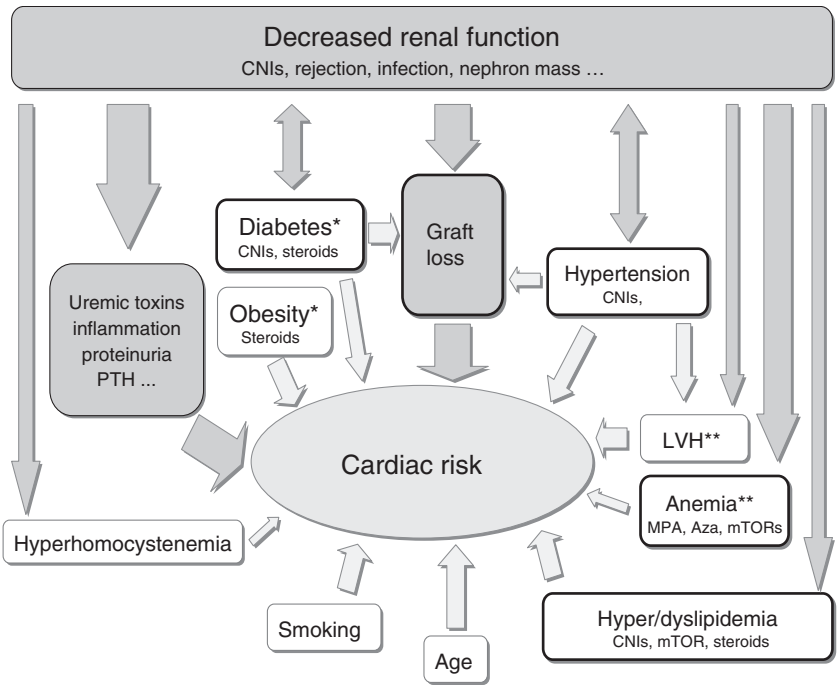

Figure 2 Interplay of decreased renal function, traditional and nontraditional risk factors, and immunosuppressants in the increased cardiovascular risk in renal transplant recipients. Several factors have the potential to increase cardiac risk in renal transplant recipients (white boxes). Two of these factors – hypertension and diabetes – also negatively affect renal function. Decreased renal function plays a central role in further increasing cardiac events post-transplant. It is an independent risk factor for cardiovascular disease [e.g. via the generation of uremic toxins, inflammation, proteinuria, and elevated PTH levels). Moreover, decreased renal function, along with diabetes and hypertension, negatively affect graft survival, which, in turn, contributes to increased cardiac risk. Immunosuppressants exacerbate cardiovascular risk via negative effects on renal function and numerous cardiac risk factors. The degree of cardiac risk imparted by each factor is represented by the size of the arrows. Major factors in graft loss – diabetes, hypertension, anemia, and dyslipidemia – are indicated in bold-face boxes. Single asterisks indicate that diabetes and obesity are frequently related to each other; double asterisks indicate that anemia and LVH are frequently related in kidney disease. Independently or in combination, these factors increase cardiac risk. AZA, azathioprine; CNIs, calcineurin inhibitors; LVH, left ventricular hypertrophy; MPA, mycophenolates; mTORs, mammalian target of rapamycin inhibitors; PTH, parathyroid hormone.

Table 1. Decreased renal function post-transplant is significantly associated with increased cardiac risk – Cox regression analyses.

Study	Renal function measure	RR (95% CI)	*P*-value
Abbott *et al.* [12]	GFR <44.8 ml/min/1.73 m^2 at 1 year	For ACS: 2.16 (1.39–3.35)	0.001
		For CHF: 2.95 (2.24–3.90)	<0.001
Meier-Kriesche *et al.* [13]	Serum creatinine at 1 year	For cardiovascular death:	
	• 1.5–1.6 mg/dl	1.19 (1.02–1.39)	0.025
	• 1.7–1.8 mg/dl	1.37 (1.16–1.62)	<0.001
	• 1.9–2.1 mg/dl	1.49 (1.25–1.76)	<0.001
	• 2.2–2.5 mg/dl	1.67 (1.38–3.03)	<0.001
	• 2.6–4.0 mg/dl	2.26 (1.85–2.75)	<0.001
Fellström *et al.* [14]	Creatinine increase per 100 μmol/l at any time	For MACE: 1.89 (1.42–2.55)	<0.0001
		For cardiac death: 2.94 (2.01–4.31)	<0.0001

ACS, acute coronary syndromes; CHF, congestive heart failure; CI, confidence interval; GFR, glomerular filtration rate; MACE, major adverse cardiac event; RR, relative risk.

subfraction profile, typified by small, dense low-density lipoprotein (LDL) particles. Lipid and apolipoprotein abnormalities increase in severity as renal function deteriorates.

Anemia is strongly associated with decreased renal function post-transplant via reduced erythropoietin synthesis [18]. The effect of anemia on cardiovascular risk is outlined in a subsequent section.

In addition to contributing to cardiovascular risk, renal functional deterioration is a prominent and obvious risk factor for graft loss. Hariharan *et al.* [19] showed that elevated serum creatinine at 1 year post-transplant and/or renal function decline during the previous 6 months increased the risk of graft loss. Similarly, grafts with poor functional recovery after acute rejection are at greater risk for later graft loss than grafts that return to baseline function [20].

Graft loss *per se* substantially increases the risk for major cardiac events. A long-term follow-up of the Assessment of LEscol in Renal Transplantation (ALERT) trial showed that after graft loss, the incidences of cardiac events were nearly doubled compared with recipients with a functioning graft [14]. In addition, an analysis of more than 58 000 patients in the US Renal Data System determined that the risk of post-transplant cardiovascular death was significantly increased at all time points after graft loss [13].

Diabetes and cardiovascular risk

Patients with pretransplant diabetes have a greatly increased cardiac risk, which is estimated to be 2–5 times greater than the risk in nondiabetic renal transplant patients [21,22]. The risk is similar for patients who develop new-onset diabetes after transplantation (NODAT). Patients with pretransplant diabetes had a hazard ratio (HR) of 1.13 for post-transplant myocardial infarction versus an HR of 1.60 for patients who developed NODAT [23].

New-onset diabetes after transplantation is a risk factor for renal graft dysfunction and loss. A prospective study showed that renal function was inferior at 5 years in patients with NODAT compared with those without. Despite similar patient survival at 12 years, graft survival was lower in patients with NODAT compared with nondiabetic patients (48% vs. 70%) [24].

Hypertension and cardiovascular risk

Hypertension is a well-known cause of cardiovascular disease in the general population [2]. In the transplant population, hypertension is common, affecting more than 70% of renal graft recipients, and post-transplant control of hypertension is poor [25]. High systolic blood pressure is independently associated with an increased risk of cardiovascular death in renal transplant patients, whereas lower blood pressure is associated with less cardiovascular death [26].

Hypertension may contribute to increased cardiovascular risk through graft loss. Hypertension at 1 year is a strong predictor of graft survival, even after controlling for renal function or previous acute rejections [25,26]. Kasiske *et al.* [25] found that each 10 mmHg increase in systolic blood pressure was independently associated with an increased risk of death-censored graft failure.

Dyslipidemia and cardiovascular risk

Dyslipidemia is common in renal transplant recipients, affecting up to 74% of patients [27]. Renal transplant recipients typically have increased levels of cholesterol (LDL and total), very low-density lipoprotein (VLDL), and triglycerides. HDL often remains at normal levels, but can be elevated as well.

In the normal population, elevated cholesterol increases the risk of cardiovascular events and deaths. Similarly, elevated total cholesterol is associated with an increased risk of ischemic heart disease in renal transplant patients [23]. The ALERT trial demonstrated that reducing cholesterol with fluvastatin significantly decreased the risk of major cardiac events [28].

In transplant recipients, dyslipidemia correlates with the development of atherosclerosis in nontransplant vessels, as well as in transplanted organs. Dyslipidemia may further contribute to chronic allograft dysfunction [29], and post-transplant hypercholesterolemia and hypertriglyceridemia are independent risk factors for graft loss [30,31].

Anemia and cardiovascular risk

Up to 48% of renal transplant recipients are anemic beyond 3 years post-transplant [32]. In patients with ESRD, anemia is a confirmed risk factor for LVH, and in dialysis patients, left ventricular cavity volume and functional status are strongly correlated with ischemic heart disease, cardiac failure, and death [33,34]. A retrospective analysis showed that 1-year post-transplant anemia was correlated with reduced long-term graft and patient survival [34].

Immunosuppression and cardiovascular risk

Effects on renal function

The majority of renal transplant patients are treated with CNIs, either cyclosporine (CsA) or tacrolimus. The nephrotoxic effects of CNIs are well established and are known to reduce graft function after renal transplantation [35]. The strong long-term nephrotoxic effects of CNIs are further exemplified by declining renal function in CNI-treated recipients of nonrenal grafts. Following 10 years of treatment with CNIs after heart or liver transplantation, approximately 5–10% of patients develop ESRD, and almost one-third experience poor renal function (GFR < 30 ml/min) [36].

Tacrolimus and CsA have similar overall nephrotoxic profiles. A study comparing patients treated with CsA versus tacrolimus found a high prevalence of chronic allograft nephropathy in both groups and similar histopathologic changes [37]. Despite similar histologic changes, renal function in some studies was marginally better preserved with tacrolimus compared with CsA, possibly owing to less vasoconstriction [35,38–40]. A meta-analysis comparing tacrolimus and CsA demonstrated overall similar renal function between the two agents [40] – findings that have since been corroborated by two large studies comparing both CNIs [41,42]. In contrast, better renal function was achieved with tacrolimus versus CsA in the Symphony study, most likely because of better rejection prophylaxis with tacrolimus [43]. However, higher exposure to mycophenolic acid – the primary active metabolite of mycophenolate mofetil (MMF) – which is correlated with therapeutic efficacy of MMF [44], might have contributed to these results.

Effects on diabetes

The risk of glucose metabolism disorders and NODAT is significantly increased with certain immunosuppressive drugs. Several immunosuppressants exert pathogenic effects on the physiology of glucose metabolism, resulting in deleterious effects on insulin secretion (tacrolimus, CsA, sirolimus) and insulin sensitivity (corticosteroids, tacrolimus) [45].

Corticosteroids increase the risk of glucose metabolism disorders and NODAT in a dose-dependent manner [46,47]. Steroids may enhance glucose production by the liver and decrease glucose uptake and glycogen synthesis in skeletal muscle cells, leading to insulin resistance and ultimately NODAT [48]. Steroid withdrawal can reduce the incidence of NODAT [49] and improve measures of insulin resistance [50]. Vincenti *et al.* [51] conducted the randomized FREEDOM study comparing three corticosteroid strategies: complete steroid avoidance, early steroid withdrawal on Day 7, and continued standard steroid therapy, all in combination with other immunosuppressants, including CsA. The incidence of NODAT was similar among all three groups at 1 year; however, fewer patients required antihyperglycemic agents in the corticosteroid-free group versus the standard-steroid group (4.5% vs. 14.7%). Woodle [52] published the largest ($N = 386$) and most rigorous study of steroid withdrawal that compared early corticosteroid withdrawal at Day 7 with continuous low-dose corticosteroid therapy. Both groups had similar long-term renal graft survival and function, although the withdrawal group had a 7.0% higher incidence of acute rejection. Of interest, a significant 7.9% reduction in the incidence of insulin-requiring (but not overall) NODAT was observed after steroid withdrawal versus low-dose steroid therapy. In sum, any steroid withdrawal or avoidance strategy will reduce the incidence and/or severity of NODAT, although the effect may be smaller than previously thought.

Calcineurin inhibitors are also associated with impaired glucose metabolism and NODAT [47,53]. Calcineurin signaling is critical for pancreatic cell growth and function. CsA reduces pancreatic beta cell volume, decreases insulin synthesis and secretion, and may alter glucagon production of pancreatic alpha cells [45,54]. Tacrolimus may cause insulin resistance, hyperinsulinemia, morphologic damage to beta cells, enhanced glucagon production, and impaired insulin synthesis and secretion [45,54]. Tacrolimus is more diabetogenic than CsA, perhaps because of a stronger reduction in insulin secretion [53]. A meta-analysis of 30 randomized controlled trials found that the relative risk of insulin-requiring diabetes mellitus at 1 year post-transplant was 1.86 with tacrolimus versus CsA [40].

It remains unclear whether sirolimus has diabetogenic properties and to what extent. There are reports that sirolimus is associated with diabetogenic risk [55], and mammalian target of rapamycin (mTOR) inhibitors have been shown to increase insulin resistance in *in vitro* and preclinical models [56,57]. However, data from prospective studies have not identified a strong association between mTOR inhibitor therapy and the development of NODAT, calling into question the overall diabetogenic effects of these agents [45,58,59].

Effects on hypertension

Immunosuppressive therapies are implicated in hypertension post-transplant. The incidence of hypertension increases with CNI therapy, from 42–60% with azathioprine to 63–78% with CsA at 1 year post-transplant. At 5 years post-transplant, 70–85% of CsA-treated patients have been reported to be hypertensive [60]. Although meta-analysis shows that tacrolimus causes similar rates of hypertension to CsA [40], tacrolimus appears to exert a slightly lesser hypertensive effect than CsA in some studies [38,61].

Effects on dyslipidemia

Alterations in the lipid levels of renal transplant recipients typically occur early post-transplant and are likely a consequence of immunosuppressant effects on lipid metabolism [62].

Steroids, especially in combination with CsA, are associated with increased total cholesterol, and a dose-dependent correlation between cholesterol levels and steroid

dose has been observed [62]. Steroids may affect lipid levels by altering the activity of acetyl-coenzyme A carboxylase, free fatty acid synthetase 3-hydroxy-3-methylglutaryl coenzyme A reductase, and lipoprotein lipase, resulting in increased levels of VLDL, total cholesterol, and triglycerides [45].

Early studies showed that CsA increased cholesterol levels by up to 45% by 3 months post-transplant [63]. CsA may affect cholesterol levels by reducing bile acid synthesis from cholesterol, which, in turn, may limit the clearance of circulating cholesterol via reduced transport to intestines. CsA increases circulating LDL cholesterol levels by reducing synthesis of the LDL receptor, and increases oxidation of LDL cholesterol, leading to larger circulating LDL particles and increased cardiac risk [45,54]. The effects of CsA on hepatic lipase and lipoprotein lipase activities may cause impaired clearance of VLDL and LDL cholesterol [64]. Tacrolimus appears to exert a lesser effect on lipid levels than CsA [38,40,61].

Hyperlipidemia is a significant side-effect of mTOR inhibitors and appears to be dose-dependent [65]. A review of multiple studies showed that approximately twice as many patients receiving mTOR inhibitors required lipid-lowering drugs than those patients not receiving these inhibitors [65]. Furthermore, sirolimus and everolimus exacerbated lipid levels when used in conjunction with CsA and steroids. As such, mTOR inhibitors may affect dyslipidemia differently depending on whether they are used alone, with steroids or CsA, or with tacrolimus [65]. The mechanisms underlying the affect of mTOR therapies on lipids remain unclear, but may include reduced catabolism of lipoproteins and/or increased production of triglycerides and secretion of VLDL. Also, sirolimus may interfere with insulin signaling, possibly disturbing lipid metabolism [65,66]. It remains unclear whether the mTOR inhibitor-induced dyslipemia is associated with an increased cardiovascular risk compared with other immunosuppressants. A large, randomized, controlled trial is needed to determine the effect of mTOR inhibitors on cardiovascular disease in renal transplant recipients and compare it with that of other immunosuppressants [65].

Effects on anemia

Anemia is a well-known side-effect of both azathioprine and MMF, resulting from impaired bone marrow function. Anemia is also associated with mTOR inhibitor use. In a direct comparison between sirolimus and MMF, anemia was significantly more prevalent with sirolimus use (57% vs. 31%) [67]. Potential mechanisms driving sirolimus-associated anemia include interference with erythropoietin receptor signaling, impaired erythroid cell proliferation, altered iron homeostasis, induction of an 'erythropoietin-resistant' state, and persistent inflammatory response.

Proteinuria and cardiovascular risk

Proteinuria is a significant risk factor for graft loss [68], cardiovascular events and death [69,70]. Even minor proteinuria is associated with poorer outcomes; early proteinuria is indicative of kidney injury [71], and microalbuminuria is associated with inflammatory markers, such as C-reactive protein (CRP) and cardiovascular risk factors [72]. Blockers of the RAAS-system effectively lower proteinuria, although their effect on graft outcome was unclear in retrospective studies [73,74]; prospective randomized trials are needed to show whether they have a beneficial effect [75,76]. The use of mTOR inhibitors is associated with a higher frequency of proteinuria [77]. At present, it remains unclear to what extent mTOR inhibitor-associated proteinuria is clinically relevant, and further research on the mechanisms and treatment is warranted [78].

Metabolic syndrome/elevated body mass index and cardiovascular risk

The metabolic syndrome, a known cardiovascular risk factor in renal transplant patients, is independently associated with impaired long-term renal graft function and is a prominent risk for graft failure, [79] and atherosclerotic events in this patient population [80]. Pretransplant obesity likely plays a predominant role in increasing cardiac risk, while post-transplant weight gain is a risk factor for graft loss [81]. Importantly, steroids contribute to weight gain post-transplantation, which may further aggravate insulin resistance and contribute to cardiac risk atherosclerotic events and graft loss [82].

Additional cardiovascular risk factors

Other factors associated with increased cardiac risk following renal transplantation include cigarette smoking, homocysteinemia, inflammation, endothelial dysfunction, and hyperparathyroidism [45,54].

Patients with chronic kidney disease (CKD), in particular patients with marked hyperparathyroidism, have a high prevalence of vascular calcification, a risk factor for cardiovascular disease that has been associated with coronary artery disease, stroke, and heart failure [83]. Although renal transplantation slows the progression of coronary calcification, it does not halt it [84].

Vascular inflammation is an important factor in the development of atherosclerosis, as illustrated by increased

numbers of post-transplant cardiovascular events in patients with elevated levels of CRP [85–87]. In other studies, high serum levels of CRP and hyperhomocysteinemia were found to be among the nontraditional factors contributing to the atherosclerotic events after transplantation and explaining a large amount of the excess risk of post-transplant diabetic patients [87]. Although traditional risk factors, which are represented by the Framingham risk score, have an excellent predictive value in low-risk renal transplant recipients, nontraditional cardiovascular risk factors, such as CRP as a marker for inflammation, greatly contribute to an increased incidence of ischemic heart disease in high-risk patients [87]. Markers of inflammation (such as IL-6 and CRP) are independently associated with major cardiovascular events and all-cause mortality after renal transplantation in a large prospective clinical trial [85]. Furthermore, a correlation has been established between post-transplant atherosclerotic events and Toll-like receptor-4 (TLR4) Asp299Gly polymorphism [87]. In the general population, such polymorphisms have been reported to be associated with a blunted immune response to microbial pathogens, as well as a decreased risk of atherosclerosis. However, although renal transplant recipients with TLR4 polymorphism have a lower risk of post-transplant atherosclerotic events and acute allograft rejection, they experience severe infectious episodes more frequently. These patients may benefit from a less-potent immunosuppressive regimen, along with increased preventative measures against infectious agents [87]. Results of a retrospective study suggest that MMF might be associated with less inflammation than other immunosuppressive therapies, with MMF use inversely correlating with CRP levels in renal transplant recipients [88]. However, a prospective study of the effects of MMF on cardiovascular risk factors such as CRP is needed.

Endothelial dysfunction is strongly associated with cardiovascular disease and outcome of patients with CKD [89]. It has been shown that endothelial function improves during the first month after transplantation, and that the degree of improvement correlates to inflammatory activity, e.g. reductions in circulating visfatin, adiponectin and CRP levels [90]. Furthermore, elevated plasma levels of asymmetric dimethylarginine, which are associated with endothelial dysfunction, are an independent risk factor for morbidity, mortality, and the deterioration of graft function in renal transplant recipients [91].

The retrospective Patient Outcomes in Renal Transplantation (PORT) study, based on data from 23 575 adult renal transplant patients, has recently shown that transplant-related risk factors, particularly those linked to graft function, explain much of the variation in coronary heart disease after renal transplantation [92]. Conversely, additional risk factors, such as hypertension, dyslipidemia, and cigarette smoking, add little additional predictive value [92].

Left ventricular hypertrophy and cardiovascular risk

Left ventricular hypertrophy may be considered either a risk factor for subsequent major cardiovascular events, or a cardiovascular disease itself. Although this is still a topic for debate, we consider LVH in this review as an independent risk factor for cardiac events [93]. LVH is present in 40–60% of renal transplant recipients, and its persistence in the first year after renal transplantation is associated with reduced patient survival [93]. LVH has also been shown to be the strongest predictor of all-cause mortality, together with diabetes [93].

Left ventricular hypertrophy is inversely correlated with renal function [33]. Improved renal function following renal transplantation ameliorates LVH; however, a degree of LVH is often still present in renal transplant recipients and may be exacerbated as graft function declines [94]. Renal dysfunction may increase LVH through hypertension, volume expansion, hyperparathyroidism, and/or altered calcium-phosphate homeostasis [95].

Preliminary results from a clinical trial examining the effects of conversion from CNI to sirolimus showed a significant regression of LVH in the majority of renal transplant patients at 1 year after conversion [96]. This regression in LVH occurs mainly by decreasing left ventricular wall thickness, which suggests a nonhemodynamic-effect mechanism of sirolimus of the left ventricular mass [96].

Strategies to minimize cardiovascular risk

Transplant physicians generally accept the inherent cardiovascular risk profile of the currently approved immunosuppressants because effective rejection prophylaxis and the restoration of renal function are the most important determinants of outcome. Current methods to reduce post-transplant cardiovascular risk are primarily reactive and include the use of antihypertensive medications, lipid-lowering medications, and lifestyle modification (e.g. exercise, smoking cessation). Although these have definite positive effects, new prophylactic approaches are needed. Given that renal function is an independent risk factor for cardiovascular disease and exacerbates other cardiac risk factors, strategies that preserve renal function may have a major impact on improving graft survival and reducing cardiac events post-transplant (Table 2).

Table 2. Predominantly reactive strategies for reducing cardiovascular risk in renal transplant recipients.

Strategy	Targeted outcomes
CNI minimization/elimination	Improved renal function Reduced graft loss Improved lipid profiles Reduced hypertension Reduced NODAT
Corticosteroid minimization/elimination	Improved lipid profiles Reduced NODAT
Statin therapy	Improved lipid profiles
Antihypertensive therapy with low-dose aspirin, ACE inhibitors/ARBs, and beta-blockers	Blood pressure normalization Reduced LVH Reduced proteinuria Improvements in coronary heart disease
Screening and treatment for NODAT	Reduced NODAT Improved glucose control
Routine screening for worsening coronary artery disease	Reduced risk for cardiac events
Erythropoietin therapy	Reduced anemia Possibly reduced LVH

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CNI, calcineurin inhibitor; LVH, left ventricular hypertrophy; NODAT, new-onset diabetes after transplantation.

CNI minimization or elimination

Because CNIs are nephrotoxic, strategies that minimize or eliminate CNI exposure may be instrumental for improving long-term outcomes in renal transplant recipients, as evidenced by the 20-year follow-up results from a multicenter trial conducted in Australia. In this study, patients with early CsA elimination who switched over to receive azathioprine and prednisolone, versus patients maintained on CsA, demonstrated superior long-term graft survival (14.8 vs. 12.5 years) and preservation of renal function throughout 20 years [97].

Three strategies for reducing long-term use of nephrotoxic CNIs are avoidance, conversion, and minimization. Complete CNI avoidance with a sirolimus-based regimen [43] and an MMF-based regimen [59] has failed, resulting in more complications, more graft rejections, and inferior renal function. Consequently, complete CNI avoidance with currently approved immunosuppressants may not be advisable. In contrast, compared with CsA, a belatacept-based, CNI-free regimen showed better renal function, less chronic allograft nephropathy, and improved cardiovascular (blood pressure and serum lipids) and metabolic (NODAT) outcomes at 1 year, with similar outcomes overall, despite a higher rejection rate [98,99].

As mentioned, another approach is to convert from a CNI-based regimen to a CNI-free regimen, similar to the approach taken in the long-term Australian study [97]. Studies show that conversion to MMF-based regimens results in higher rejection rates and inferior long-term outcomes when conversion is performed within 3 years of transplantation [100,101], whereas successful conversion to MMF and steroids has been reported in long-term transplant recipients with chronic kidney injury [102,103]. Initial studies evaluating mTOR inhibitor conversion show generally modest benefits regarding renal function (i.e. improved GFR at 1 year), but with variation seen across studies and patient subgroups [43,104,105]. Importantly, there are limited long-term data on these regimens, and they are inherently associated with mTOR inhibitor-associated toxicities [104,105]. Despite improving renal function, the late conversion approaches still are reactive, the optimal timing and drug doses remain unclear, and they rely on CNIs or mTOR inhibitors, which have negative effects on other cardiovascular risk factors. In the Symphony study, tacrolimus was associated with an elevated risk of NODAT, and sirolimus with hyperlipidemia and hypertriglycercidemia [43].

Despite a few successful avoidance and conversion studies, the transplant community continues to use CNIs as mainstay immunosuppressants, mainly because of fear of graft rejection and/or subclinical rejection. Thus, minimization strategies are attractive, and successful regimens have been described [106]. However, CNI levels considered to be 'minimal' vary considerably between centers, and the benefits of CNI minimization with regard to renal function improvement are uncertain [107]. Moreover, overall long-term outcomes remain unchanged despite a 20-year history of CNI-minimization attempts [108]. Thus, it appears that true minimization has not yet been achieved.

Developing non-nephrotoxic strategies that avoid or minimize CNIs to improve post-transplant renal function and, ultimately, longer term outcomes remains a key challenge. Thus far, these attempts, although promising, have not proven successful as the result of short-term toxicity or an increased risk of acute rejection without significant, reproducible improvements in renal function.

Steroid minimization or elimination

Steroid minimization and elimination regimens may reduce cardiovascular risk. The use of steroid-free immunosuppression in the USA has increased from 4% in 2000 to 32% in 2006, without an increased risk for adverse clinical outcomes and with a potentially lower incidence of NODAT [106]. In multiple studies, steroid reduction led to improvements in lipid levels, weight gain, and NODAT [49,52,109]. Current studies have clearly demonstrated equivalent survival, acceptable rejection risks, and clinical benefits following steroid minimization or

elimination, although the diabetogenic advantages of low-dose steroids are less than anticipated [52,109,110]. However, cessation of steroids also reduces other cardiovascular risk factors (e.g. blood pressure, lipids), as well as many other corticosteroid-associated side-effects.

When considering the use of steroid-free immunosuppression, pre-emptive NODAT management must balance the risk of NODAT against the risk of graft rejection on an individualized patient basis. Both acute rejection and NODAT are associated with an increased risk of graft loss by different mechanisms (death-censored graft loss and death with a functioning graft, respectively). The Diabetes Incidence after Renal Transplantation (DIRECT) study suggests that a preemptive CsA-based immunosuppressant regimen is preferable in *de novo* renal transplant recipients deemed to be at high risk for NODAT, with no disadvantage in short-term graft outcomes, although long-term data from this study are not available [42]. Given that NODAT is highly prevalent in tacrolimus-treated kidney transplant recipients and develops in up to 20% of previously nondiabetic patients, another potential strategy to reduce this traditional cardiovascular risk factor is to convert patients from tacrolimus to another immunosuppressant, such as CsA or an mTOR inhibitor [111]. Prospective randomized trials are underway to better define the risks associated with these strategies, which may be of limited value for glycemic control given that they may increase other cardiovascular risk factors such as lipids and blood pressure.

Classical intervention strategies

The KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend managing cardiovascular disease at least as intensively in renal transplant recipients as in the general population, with appropriate diagnostic tests and treatments [6]. In addition, based on current evidence, the guidelines suggest using low-dose aspirin (65–100 mg/day) in all patients with atherosclerotic CVD, unless there are contraindications (Grade 2B recommendation). Aspirin is safe in this patient population, and at least one retrospective observational study showed that its use was associated with better graft survival [112]. However, a randomized controlled trial is needed to determine the efficacy and safety of aspirin in renal transplant recipients.

Renin–angiotensin–aldosterone system blockade may improve cardiovascular prognosis in renal transplant recipients [6]. Data from nontransplant patients with CKD suggest that angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) may have beneficial effects on disease progression [113]. Randomized controlled trials performed to date in renal transplant recipients have not had sufficient statistical power to determine whether ACE-I or ARB therapy improves patient or graft survival [75,76]. Blockers of the RAAS decrease renal function, and a meta-analysis of randomized controlled trials comparing calcium channel blockers (CCB) and ACE-Is with placebo in renal transplant recipients suggest that CCBs might be the preferred first-line treatment in hypertension renal transplant recipients. Data on ACE-Is versus placebo were inconclusive for GFR and inconsistent for graft loss. However, compared with CCBs, ACE-Is decreased GFR. RAAS blockers are excellent blood pressure lowering drugs with good tolerability, and they are safe, with hyperkalemia and a decrease in hemoglobin being the most notable side-effects. Importantly, RAAS blockers may decrease LVH and decrease proteinuria in renal transplant recipients.

Other strategies

Independent of immunosuppression and classical intervention strategies, additional interventions have been proposed to help improve cardiovascular outcomes. These include lowering homocysteine levels with folate aggressive lipid-lowering strategies, mostly with statins, and optimal concomitant cardiovascular therapy with low-dose aspirin, ACE-Is, ARBs, or beta-blockers, when needed. Except for statin therapy [6,114,115], the benefits of these interventions have not been thoroughly evaluated in the transplant population or proved no benefit (FAVORIT-trial [116,117]). In the ALERT study, treatment with fluvastatin significantly lowered major cardiac events in renal transplant recipients; however, the effect was smaller than anticipated and of less importance compared with the effect of renal function [115].

Additional measures to improve cardiovascular outcomes include oral glucose tolerance tests to diagnose impaired glucose metabolism adequately, and strict glucose control to reduce the risks associated with hyperglycemia and NODAT [46]. Sharif *et al.* [118] demonstrated the benefits of aggressive lifestyle modification in attenuating abnormal glucose metabolism.

Erythropoietin therapy has been proposed to correct anemia in renal transplant patients, but the optimal hemoglobin threshold at which to implement such treatment to counterbalance costs and adverse outcomes, such as stroke and possibly death, remains undefined [32,60].

Screening for coronary artery disease by coronary angiography, usually pretransplant and especially in higher-risk patients, has been recommended [60], as it provides prognostic information, as well as information that could be used to limit access to transplantation [119]. However, the benefits of such a screening in identifying and treating coronary artery disease are still unclear [119]. Patients

with significant coronary artery disease who undergo revascularization procedures before or after renal transplant do not seem to have worse outcomes and may have a reduced incidence of cardiac events [120].

It has also been suggested that elevated troponin levels immediately pretransplant are strong and independent predictors of major adverse cardiac events in the immediate post-transplant period, especially in patients with cardiovascular history [121–123].

Conclusion

Renal transplant recipients are at high risk of cardiovascular disease because of (i) reduced renal function and the resulting effects on cardiovascular risk factors, and (ii) the toxicities of common immunosuppressants, which both reduce renal function and exacerbate cardiovascular risk directly. Preserving renal function post-transplant offers the greatest opportunity for reducing cardiac risk. New immunosuppressive therapies without renal and cardiovascular toxicities are needed to maximize patient and graft survival over the long-term.

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