Post-Transplant Cardiovascular Disease

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Abstract
Cardiovascular disease remains a leading cause of death and morbidity in kidney transplant recipients and a common reason for post-transplant hospitalization. Several traditional and nontraditional cardiovascular risk factors exist, and many of them present pretransplant and worsened, in part, due to the addition of immunosuppression post-transplant. We discuss optimal strategies for identification and treatment of these risk factors, including the emerging role of sodium-glucose cotransporter 2 inhibitors in post-transplant diabetes and cardiovascular disease. We present common types of cardiovascular disease observed after kidney transplant, including coronary artery disease, heart failure, pulmonary hypertension, arrhythmia, and valvular disease. We also discuss screening, treatment, and prevention of post-transplant cardiac disease. We highlight areas of future research, including the need for goals and best medications for risk factors, the role of biomarkers, and the role of screening and intervention.

Introduction
Kidney transplantation is the preferred treatment for kidney failure, affording significant survival and quality of life advantages over long-term dialysis (1). This lower mortality is seen in populations with higher risk for cardiovascular disease at the time of transplant, including individuals with diabetes, older age, and obesity (2). Although short-term kidney graft and patient survival is excellent, long-term outcomes have been limited. Death with a functioning graft is the leading cause of graft loss in kidney transplant recipients, and a major cause of death is cardiovascular disease, accounting for about one third of known causes (3). Even though kidney transplantation reduces cardiovascular disease risk compared with staying on dialysis, kidney transplant recipients experience a higher risk of cardiovascular disease outcomes, including death, compared with the general population. These higher odds of cardiovascular death approach a 50-fold increase in patients in the fifth decade of life (4). In addition, cardiovascular disease is an increasingly common reason for post-transplant hospitalization, accounting for about 30% of these hospitalizations with an associated 4% mortality (5).

Cardiovascular Outcomes Post-Transplant
The spectrum of cardiovascular disease seen after kidney transplant includes coronary artery disease (CAD), heart failure, cardiac arrhythmias, and pulmonary hypertension. The risk for cardiovascular disease is affected by traditional and nontraditional cardiovascular disease risk factors, some of which are present prior to transplant and others that occur in the post-transplant period. The goal of this review is to elaborate on cardiovascular disease risk factors present after kidney transplant and their metabolic effect, their screening and prevention, and cardiovascular disease outcomes experienced by this population in the post-transplant period.

Cardiovascular Risk Factors
Kidney transplant recipients enter the post-transplant period with several preexisting cardiovascular disease risk factors, particularly hypertension and diabetes, which are highly prevalent in the CKD population and known to be associated with higher cardiovascular disease burden (6,7). These established risk factors include hypertension, tobacco use, dyslipidemia, and diabetes. In addition to these traditional cardiovascular disease risk factors, nontraditional risk factors, including some unique to the post-transplant state, also contribute to the higher cardiovascular disease burden. Patients with CKD experience several conditions to exacerbate vascular disease, including volume overload that may lead to left ventricular hypertrophy, anemia, and mineral bone disease (8,9).

Even though traditional cardiovascular disease risk factors are easily identified, studies have shown that control of these factors in kidney transplant recipients is often poor. For example, in a study by Kasiske et al. (10), only 56% of recipients had a systolic BP <140 mm Hg at 1 year. Another study found that a BP target of >130/80 mm Hg was not met in 69% of kidney transplant recipients, with uncontrolled hypertension (>140/90 mm Hg) observed in 44% on medications. In addition, 18% had borderline to elevated LDL, with 60% of those not treated (11). Furthermore, standard cardiovascular disease risk calculators may not be applicable to the kidney transplant population, and prior efforts made to construct relevant ones have not been widely adopted (12). The paragraphs below provide additional details of cardiovascular disease risk...
factors in relation to kidney transplant and strategies to modify them.

**Traditional Risk Factors**

**Hypertension.** The prevalence of post-transplant hypertension in the kidney transplant population is 80%–90% as observed in a retrospective cohort of 1666 kidney transplant recipients followed 5 years post-transplant (10). At 1 year, only 4% of recipients had normal BP without any use of antihypertensive medications. In this cohort, hypertension was independently associated with graft failure, death-censored graft failure, and death after adjusting for kidney function, acute rejection, and other transplant variables. For each 10-mm Hg higher systolic BP, the adjusted relative risk of death was 1.18 (95% confidence interval [95% CI], 1.12 to 1.23) (10). Similarly, in the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) cohort, a randomized control trial of 4110 stable kidney transplant recipients receiving a higher-versus-low-dose multivitamin of folic acid, vitamin B6, and vitamin B12 followed for 4 years, a follow-up study showed that each 20-mm Hg higher systolic BP was associated with a 32% higher risk of cardiovascular disease (hazard ratio [HR], 1.32; 95% CI, 1.19 to 1.46) (13). This study also showed that lower levels of diastolic BP (<70 mm Hg) were associated with higher risk of cardiovascular disease and death.

Despite the association of hypertension with worsened cardiovascular disease outcomes in kidney transplant recipients, the ideal BP target remains unknown, although experts often recommend <130/80 mm Hg (14,15). One retrospective study of 815 kidney transplant recipients stratified by mean office systolic BP values (<130, 130–139, or ≥140 mm Hg) showed a better composite graft and patient survival for a systolic BP <130 and 130–139 mm Hg compared with ≥140 mm Hg (P<0.001) with up to 120 months of follow-up (16). The best choice of antihypertensive medication is also unknown, although experts often recommend dihydropyridine calcium channel blockers for general use or angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) when proteinuria was independently associated with graft failure, death-censored graft failure, and death after adjusting for kidney function, acute rejection, and other transplant variables. For each 10-mm Hg higher systolic BP, the adjusted relative risk of death was 1.18 (95% confidence interval [95% CI], 1.12 to 1.23) (10). Similarly, in the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) cohort, a randomized control trial of 4110 stable kidney transplant recipients receiving a higher-versus-low-dose multivitamin of folic acid, vitamin B6, and vitamin B12 followed for 4 years, a follow-up study showed that each 20-mm Hg higher systolic BP was associated with a 32% higher risk of cardiovascular disease (hazard ratio [HR], 1.32; 95% CI, 1.19 to 1.46) (13). This study also showed that lower levels of diastolic BP (<70 mm Hg) were associated with higher risk of cardiovascular disease and death.

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**Tobacco.** Most kidney transplant centers do not require cessation of tobacco for kidney transplant listing, and the prevalence of tobacco users usually reflects that of the general population. Several studies support an association of ever tobacco use and worse graft and patient survival, with one study showing an adjusted HR of 1.60 (95% CI, 1.06 to 2.41) for mortality in ever smokers (19,20). One study that looked at incident smokers post-transplant reported that 5% of recipients become new smokers, and after excluding chronic obstructive pulmonary disease, adjusted higher risks of death-censored allograft loss (HR, 1.43; 95% CI, 1.16 to 1.76; P=0.001) and death (adjusted HR, 2.26; 95% CI, 1.91 to 2.66; P<0.001) were observed (21). Clearly, tobacco cessation should be encouraged pre- and postkidney transplant.

**Dyslipidemia.** Dyslipidemia is frequent post-transplant on the basis of common comorbid conditions like obesity, diabetes, and metabolic syndrome. Another risk factor is immunosuppression, including mammalian target of rapamycin (mTOR) inhibitors, calcineurin inhibitors (especially cyclosporin), and steroids. Treating dyslipidemia after kidney transplant is recommended. In the randomized control study Assessment of Lescol in Renal Transplantation (ALERT), 2106 kidney transplant recipients were randomized to fluvastatin versus placebo, with LDL lowered 32% in the statin group, but no difference was observed in the primary composite end point of adverse cardiac events after mean follow-up of 5.1 years (relative risk, 0.83; 95% CI, 0.64 to 1.06) (22). In a follow-up study with 2 more years of data, however, a 35% relative reduction in the risk of cardiac death or definite nonfatal myocardial infarction was observed (HR, 0.65; 95% CI, 0.48 to 0.88), supporting use of statins (23). Minimal data are available for the use of proprotein convertase subtilisin/kexin-9 inhibitors. The ideal LDL target is unknown, although Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest treating kidney transplant recipients with a statin regardless of LDL concentrations (24). It must be kept in mind the drug interaction of statin drugs with calcineurin inhibitors, particularly cyclosporin, when dosing these medications.

**Diabetes, Including Post-Transplant Diabetes.** Abnormalities in glucose metabolism are common post-transplant in patients without preexisting diabetes and represent a spectrum of disorders of impaired fasting glucose, impaired glucose tolerance, and post-transplant diabetes mellitus (25). Impaired fasting glucose is observed as early as the first week post-transplant in up to 45% of patients, whereas post-transplant diabetes develops in 16% at 1 year and 24% at 3 years (26,27). Diagnosis is made using American Diabetic Association guidelines, but post-transplant diabetes is recognized as a distinct form of type 2 diabetes caused by underlying insulin resistance combined with an insulin secretion defect (28). Given the many metabolic stressors immediately post-transplant affecting glucose, it is suggested that post-transplant diabetes should not be diagnosed until 46 days post-transplant (28). Post-transplant diabetes incidence has been declining over the past 10 years, although it remains a prevalent problem (29). The major consequence of abnormal glucose metabolism is higher risk of fatal and nonfatal cardiovascular disease events (26), with one study showing with an approximately three-fold higher risk of cardiac death or nonfatal acute myocardial infarction as compared with that in nondiabetic patients (HR, 3.27; 95% CI, 1.22 to 8.80; P=0.02) (30). Transplant recipients have fixed factors that increase their risk of post-transplant diabetes, including age >45 years, men, and Black or Hispanic heritage, but one modifiable factor, immunosuppression, plays a direct role in post-transplant diabetes through several mechanisms (31). Corticosteroids contribute to insulin resistance, and mTOR inhibitors decrease insulin sensitivity (32). Calcineurin inhibitors, especially tacrolimus, affect pancreatic β-cells and insulin secretion (33). Several studies have established tacrolimus as an independent risk factor for post-transplant diabetes in kidney transplant recipients, including a large retrospective study of 11,569 patients (27). A 6-month randomized, multicenter trial of 682 patients
showed that tacrolimus was significantly more likely than cyclosporin to cause post-transplant diabetes, with 34% of tacrolimus-treated patients developing impaired fasting glucose or post-transplant diabetes versus 26% of cyclosporin users (34). A separate study confirmed this finding even for patients where steroids were withdrawn on day 2 post-transplant (35). Increasing doses of tacrolimus (corrected by body weight) are independently associated with higher risk of post-transplant diabetes (36).

Treatment strategies for post-transplant diabetes include immunosuppression modification, lifestyle changes, and medications. Wissing et al. (37) showed in a randomized, prospective study that converting tacrolimus to cyclosporin use in kidney transplant recipients resulted in less need for diabetes treatment at 12 months, with 39% of patients in the cyclosporin group off glucose-lowering medication versus 13% of patients in the tacrolimus group (P=0.01). However, any change in immunosuppression must be balanced with whether it might increase the risk for rejection. Avoiding use of calcineurin inhibitors is another strategy, with a meta-analysis of trials using belatacept versus calcineurin inhibitors showing a lower odds of post-transplant diabetes at 12 months with belatacept (odds ratio, 0.43; 95% CI, 0.24 to 0.78) (38). Although it seems logical that steroid avoidance would be helpful, it has not been clearly shown that steroid avoidance improves post-transplant diabetes, and it might increase risk of rejection (39). A study by Sharif et al. (40) showed that an intensive lifestyle intervention in kidney transplant recipients with impaired fasting glucose led to 44% reverting to normal glucose metabolism as measured by oral glucose tolerance tests. For medications, hyperglycemia <45 days post-transplant is generally managed with insulin. After that, a combination of lifestyle changes, oral antiglycemic agents, and insulin is suggested (28).

The most used oral agents for post-transplant diabetes in kidney transplant recipients are the sulfonylureas and meglitinides, with metformin use frequently avoided due to safety concerns, although some promote its use (41). Newer oral agents have not been well studied in the kidney transplant population, but of interest are the inhibitors of sodium-glucose cotransporter 2 (SGLT2), which work by inhibiting glucose reabsorption at proximal renal tubules. SGLT2 inhibitors are associated with improved cardiovascular disease outcomes in patients with type 2 diabetes in randomized control trials (42–44). The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial specifically examined patients with type 2 diabetes and kidney dysfunction (eGFR of 30 to <90 ml/min per 1.73 m² body surface area and albuminuria), finding that the relative risk of the kidney-specific composite outcome was lower by 34% (HR, 0.66; 95% CI, 0.53 to 0.81; P<0.001) as well as lower risks of cardiovascular death, myocardial infarction, or stroke (HR, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (HR, 0.61; 95% CI, 0.47 to 0.80; P<0.001) (45). Given their mechanism of action, potential adverse events related to SGLT2 inhibitors include volume depletion and urinary tract infection, which are concerning for use in kidney transplant recipients where both conditions already commonly occur. The Empagliflozin in Post-Transplant Diabetes Mellitus pilot study from Vienna was the first study published on the use in kidney transplant recipients; a pilot study of 14 recipients examined glycemic control using empagliflozin in place of insulin, finding that empagliflozin monotherapy resulted in worse glucose control (46). A single-center, prospective, randomized, double-blind study of empagliflozin versus placebo in 49 kidney transplant recipients in Oslo showed improved hemoglobin A1C and body weight with no higher risk for adverse events (47). To date, additional small patient series using SGLT2 inhibitors in kidney transplant recipients have also shown that use of these medications may be safe, with a meta-analysis of eight studies including 132 patients reaching the same conclusion (48–50). However, studies are needed to confirm safety and to see if SGLT2 inhibitors reduce cardiovascular mortality and improve graft survival in this population.

**Nontraditional Risk Factors**

**Obesity.** The potentially protective effect of obesity seen on dialysis is lost with transplant. Obesity at the time of transplant is a unique risk factor in that it is independently associated with higher cardiovascular disease risk and death in kidney transplant recipients, but that it also contributes directly to several other cardiovascular disease risk factors (hypertension, post-transplant diabetes, dyslipidemia, metabolic syndrome, physical inactivity, and graft dysfunction), which likely compounds its effect on cardiovascular disease outcomes. In one study, each 5-unit higher body mass index was associated with a 25% higher risk of the cardiac composite (HR, 1.25; 95% CI, 1.07 to 1.47; P=0.005), largely driven by heart failure and atrial fibrillation (51). Additional weight gain post-transplant is also a problem, with an average weight gain of 5%–10% in the first 12 months (52). As such, weight gain prevention strategies should be prioritized. These include lifestyle changes, but increasingly, bariatric surgery is being used as a safe alternative in individuals with kidney disease as being abated. Turgeon et al. (53) showed in one study that patients undergoing bariatric surgery with CKD stages 3–5 had significantly more diabetes, hypertension, peripheral vascular disease, treated CAD, and prior strokes compared with those without CKD, but overall 30-day mortality was not significantly different, despite longer length of stay and higher percentage of return to the operating room in the CKD group. Another study of a larger population of patients undergoing bariatric surgery comparing groups of no CKD, CKD, and kidney failure showed higher mortality in the kidney failure group (odds ratio, 11.59; 95% CI, 6.71 to 20.04) but not the CKD group (odds ratio, 1.00; 95% CI, 0.32 to 3.11), although 30-day reoperation, readmission, and complication rate were higher in patients with CKD or kidney failure compared with those without (54). Pretransplant laparoscopic sleeve gastrectomy has shown to be safe and effective in providing weight loss, getting candidates on the kidney transplant waiting list, and decreasing comorbidities, including diabetes and hypertension, resulting in less delayed graft function and allograft dysfunction post-transplant compared with control groups (55,56). Similarly, individuals who undergo bariatric surgery after kidney transplant have been shown to have lower mortality, improved kidney function, and fewer obesity-related comorbidities compared with those who do not undergo surgery (57).

**Left Ventricular Hypertrophy.** In kidney transplant recipients, left ventricular hypertrophy prior to transplant
is associated with more cardiovascular disease. In a study of 1063 individuals with pretransplant echocardiography, left ventricular hypertrophy (HR, 1.58; 95% CI, 1.07 to 2.35, \( P=0.02 \)) and high relative wall thickness (HR, 1.44; 95% CI, 1.02 to 2.01, \( P=0.04 \)) were associated with cardiovascular disease events in a multivariable survival regression analysis independently of common pretransplant cardiovascular disease risk factors (58). Transplantation leads to regression in left ventricular hypertrophy, with one study showing a significant decrease in left ventricular mass index (\( P<0.001 \)) and left atrial volume index (\( P<0.001 \)), with a significant increase in ejection fraction (\( P=0.009 \)) over 24 months of follow-up (59). Improvement in left ventricular hypertrophy may lead to better post-transplant outcomes, as shown by Paoletti et al. (60) in a prospective observational extension of two randomized controlled trials where left ventricular hypertrophy regression (HR, 0.41; 95% CI, 0.22 to 0.79; \( P=0.01 \)) was protective from the cardiovascular end point and associated with improved cardiac event-free survival.

**Mineral Bone Disease, Inflammation, and Oxidative Stress.** Changes in the mineral bone metabolism seen in CKD have long been associated with adverse vascular health and higher cardiovascular disease risk (61). Hyperparathyroidism frequently persists after kidney transplant as tertiary hyperparathyroidism and may be associated with lower graft and patient survival (62). Pretransplant treatment with these options has not been shown to be associated with better long-term graft or patient survival (63,64). The best treatment option post-transplant, surgical parathyroidectomy versus use of calcimetics, is unknown, with one trial showing improved parathyroid hormone and calcium levels but no better long-term outcomes (65). However, a retrospective study from Sweden that included 156 kidney transplant recipients who underwent parathyroidectomy versus 736 matched control recipients who did not found lower risk of cardiovascular events in the parathyroidectomy group (HR, 0.53; 95% CI, 0.34 to 0.84) (66). Data on how tertiary hyperparathyroidism and its treatment affect cardiovascular outcomes after kidney transplant are needed.

Likewise, inflammation and oxidative stress are also associated with vascular disease and endothelial dysfunction in kidney disease, with C-reactive protein shown to be independently associated with cardiovascular disease and mortality in kidney transplant recipients (67). Post-transplant, with improvement in kidney function, several of these markers of inflammation change considerably, which may affect cardiovascular disease risk. Yilmaz et al. (68) showed that carotid intima media thickness improves significantly after kidney transplantation, with changes in C-reactive protein and fibroblast growth factor 23 the strongest independent correlates of carotid intima media thickness. Endothelial function improves rapidly following kidney transplantation, with this improvement maintained at 48 months (69).

**Immunosuppression.** Although current immunosuppression used in transplant has afforded excellent short-term outcomes, the off-target effects of these medications may contribute to cardiovascular disease risk as noted in the paragraphs above. These include increased hypertension (calcineurin inhibitors and steroids), dyslipidemia (steroids and mTOR inhibitors), post-transplant diabetes (calcineurin inhibitors, steroids, and mTOR inhibitors), and anemia (mycophenolate and azathioprine). Studies have examined if adjustment of immunosuppression regimens may improve cardiovascular disease risk factors, but often, one factor is helped at the exacerbation of another. For example, a meta-analysis looking at conversion studies from calcineurin inhibitors to mTOR inhibitors after kidney transplant found no changes in post-transplant diabetes risk but a significant increase in hypercholesterolemia (relative risk, 2.15; 95% CI, 1.35 to 3.41), acute rejection, proteinuria, and anemia (70). Belatacept, a costimulation blocker and one of the newer options for maintenance immunosuppression, may be beneficial in the context of cardiovascular risk. In a retrospective study of belatacept alone, belatacept and tacrolimus, or tacrolimus alone, the risk of post-transplant diabetes was lower with belatacept plus or minus tacrolimus versus tacrolimus alone (71). In the belatacept 5-year extension trial, belatacept was associated with fewer cardiac disorders (2%) than cyclosporin (12%) (72).

**Cardiovascular Disease in the Kidney Transplant Recipient**

**Coronary Artery Disease**

Considering the comorbidities of CKD and kidney failure, CAD is expected and prevalent among kidney transplant recipients. Screening and surveillance of kidney transplant candidates for CAD are standards of care at activation and during time spent on the waiting list (73). However, noninvasive cardiac stress testing may not be sufficiently accurate to exclude significant CAD in high-risk kidney transplant candidates (74). Only coronary angiography improves prediction of post-transplant mortality (75), but it is not routinely pursued due to concern about precipitating dialysis in predialysis kidney transplant candidates, especially those with a possible preemptive transplant from a living donor available. Coronary revascularization has not been shown to improve mortality or adverse cardiovascular outcomes in individuals with stable coronary disease and advanced CKD (76); the role of preoperative revascularization and the preferred method (percutaneous coronary intervention or coronary artery bypass grafting) are also unclear in kidney transplant recipients and, thus, are not currently recommended for asymptomatic patients (77). The outcomes of the CKD substudy of the Ischemia Trial also do not clearly support an initial invasive strategy relative to initial conservative management with medical therapy, and whether kidney transplant alters the course of coronary disease is not known (76).

The role of post-transplant risk stratification is even less clear. Mortality in kidney transplant recipients after hospitalization for acute coronary syndrome may be as high as 24% at 1 year to >45% at 4 years (78). Recipient characteristics associated with post-transplant myocardial infarction include older age, history of angina, peripheral vascular disease, dyslipidemia, and pretransplant myocardial infarction and arrhythmia (79). KDIGO guidelines suggest managing cardiovascular disease “at least as intensively in kidney transplant recipients as in the general population, with appropriate diagnostic tests and treatments” (80). Use of stress tests post-transplant for primary or secondary prevention is not established, but use of revascularization by coronary artery bypass grafting or percutaneous transluminal coronary angioplasty has been found to be effective in

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kidney transplant recipients and not associated with kidney allograft loss or allograft injury (81).

Measurement of biomarkers of cardiac ischemia both pre- and post-transplant may help with risk stratification. Elevated cardiac troponin T was found to be associated with higher risk of post-transplant death and major adverse cardiac events in high-risk patients at the Mayo Clinic (82). Troponin T levels that remained elevated after transplant (without normalization following restoration of normal kidney function from a healthy allograft) were found to be associated with high risk of death and cardiac events at up to 5 years follow-up.

Treatment of CAD has not been extensively studied exclusively in kidney transplant recipients. The ALERT trial demonstrated no difference in its primary end point (combined cardiovascular end point) but a favorable reduction in the separate outcomes of cardiac death and nonfatal myocardial infarction with fluvasatin therapy (22). Subsequent meta-analyses including ALERT suggested a likely benefit for statin use in reducing the outcome of major vascular event, coronary revascularization or stroke, and mortality. Overall, given the likely benefit and little harm, initiation and continuation of statin therapy in patients with functioning kidney transplants are recommended (83). The benefit of aspirin for primary prevention of CAD has not been studied in a randomized controlled trial of kidney transplant recipients. A secondary propensity score matching analysis of aspirin use in the FAVORIT trial showed no benefit from baseline aspirin use on cardiovascular disease or mortality outcomes (84). Given these limited data in general kidney transplant recipients, guidelines generally recommend aspirin use be considered in patients with diabetes or known atherosclerotic cardiovascular disease, unless contraindicated (80). KDIGO guidelines for treatment of triglycerides (often caused by immunosuppression) recommend primarily lifestyle modification, although fibric acid derivatives (i.e., ezetimibe; dose adjusted for kidney function) may be indicated for levels persistently >1000 mg/dl (24). Use of proprotein convertase subtilisin/kexin-9 inhibitors has not yet been established in kidney transplant recipients, although they seem to be safe in eGFR as low as 20 ml/ min per 1.73 m² (85).

Heart Failure

Heart failure is highly prevalent in patients with kidney failure, and heart failure is a leading cause of cardiovascular disease-related hospitalizations after kidney transplant (5). Although kidney transplant is associated with improvement in ejection fraction over time in most individuals (86), rates of de novo heart failure after transplant are as high as 10%–18% at 12 and 36 months, and de novo heart failure is independently associated with higher mortality and graft loss (87). Although improvement in left ventricular systolic and diastolic volumes and reduction in ventricular masses are also observed after transplant, the effects of the cardiorenal axis dysfunction pre- and post-transplant contribute to ongoing ventricular dilation, arrhythmia, and myocardial infarction in patients with heart failure (88). Prevalence of heart failure with preserved ejection fraction in kidney transplant recipients is not well known (89), but data using echocardiographic strain measurements suggest that subtle abnormalities in global longitudinal strain, a sensitive measure of left ventricular function, exist after transplant (mean follow-up time 338 days) even among individuals with normal left ventricular ejection fraction (90). Peritransplant reduction in global longitudinal strain may also be associated with higher risk of cardiovascular disease events or death after kidney transplant (91).

Evidence for screening and surveillance for heart failure in transplant candidates is limited, but KDIGO guidelines suggest that obtaining a screening echocardiogram is reasonable if symptoms of heart failure, history of cardiovascular disease, or hemodynamic instability on dialysis exists (89). Post-transplant de novo heart failure diagnosis should follow the approach in the general population, including evaluation for CAD. Risk stratification strategies using sensitive measures, like strain, may eventually be incorporated into clinical practice, although therapies for abnormal strain and heart failure with preserved ejection fraction do not yet exist outside preclinical studies. N-terminal prohormone B-type natriuretic peptide (NT-proBNP) measured pretransplant is independently associated with post-transplant mortality, whereas post-transplant NT-proBNP associates with left ventricular hypertrophy (92,93). Use of NT-proBNP to guide diagnosis or treatment of de novo heart failure post-transplant is not established.

Treatment of heart failure should be pursued as in the general population (89). Concern about hyperkalemia and reduction in eGFR often lead to withholding of otherwise beneficial treatments, and this is discouraged. Safety of the use of patiromer or sodium zirconium cyclosilicate to counteract hyperkalemia is unknown due to potential for reducing absorption of other medications, but evaluation of these strategies in conjunction with existing heart failure therapies should be pursued. Anemia is a risk factor for heart failure in the general population (94) and in kidney transplant recipients (87) in most studies, but treatment with erythropoieszis-stimulating agents for anemia in CKD has no role for prevention or treatment of heart failure (95). Although treatment of chronic heart failure and iron deficiency with or without anemia using parenteral iron improves symptoms, functional capacity, and quality of life, the specific use in kidney transplant recipients of parenteral iron or of hypoxia-inducible factor prolyl hydroxylase inhibitors has not been evaluated (89).

Pulmonary Hypertension

Pulmonary hypertension is present in up to 13%–33% of patients with CKD and kidney failure and develops as the result of several underlying factors common in CKD (96). The current World Health Organization (WHO) classification of pulmonary hypertension comprises five groups: group 1, pulmonary arterial hypertension; group 2, due to left heart disease; group 3, due to lung/respiratory disease; group 4, due to chronic pulmonary emboli; and group 5, due to unclear or multifactorial mechanisms or systemic diseases (96). Pulmonary hypertension (defined as a mean pulmonary artery pressure of $25 mm Hg at rest) may manifest in the kidney transplant recipient as a result of any one or more of these categories, but a specific consideration exists for kidney transplant recipients with high-flow arteriovenous fistulas previously used for dialysis. Compared with
patients with peritoneal dialysis or catheter-based dialysis, patients on hemodialysis with an arteriovenous fistula have higher prevalence of pulmonary hypertension (97).

Although right heart catheterization is the gold standard for diagnosis, transthoracic echocardiography is noninvasive, less expensive, and adequate to assess pulmonary pressures. Limitations of echocardiography-based diagnosis include dependence on patient volume status and image quality. Estimated pulmonary artery systolic pressure is an important metric that classifies severity of pulmonary hypertension as normal (<35 mm Hg), mild pulmonary hypertension (35–45 mm Hg), moderate (45–60 mm Hg), and severe (>60 mm Hg). Diagnosis and evaluation of pulmonary hypertension in kidney transplant candidates are important because pulmonary hypertension both is prevalent and likely has an independent effect on post-transplant outcomes. Following transplant, pulmonary hypertension may improve due to improvement in underlying heart failure and volume overload, but few studies have assessed post-transplant pulmonary hypertension prevalence, and none have assessed incidence. In patients with symptoms, echocardiography is a reasonable screening test. For patients with arteriovenous fistulas, assessing hemodynamics of the arteriovenous fistula in the resting state with the arteriovenous fistula occluded and not occluded is recommended to distinguish the relative contribution of the arteriovenous fistula to a high-flow state and elevated pulmonary pressures (96).

Evidence-based treatment of pulmonary hypertension in kidney transplant recipients is challenging due to exclusion of patients with kidney failure and kidney transplant recipients from clinical trials of pulmonary hypertension. In general, therapy on the basis of the pulmonary hypertension WHO group can be considered. Ligation of high-flow arteriovenous fistulas may lead to improvement of symptomatic pulmonary hypertension on the basis of small series (68,98).

Arrhythmia and Structural Heart Disease

Patients with CKD have a higher risk for both cardiac arrhythmias and sudden death due to electrolyte and volume disturbances, uremia, and abnormalities in myocardial structure and function. Atrial fibrillation is the most common arrhythmia in CKD. Preexisting atrial fibrillation is associated with higher mortality risk and graft failure after transplant (99), whereas post-transplant atrial fibrillation occurs in up to 7% by 35 months and is also associated with death (adjusted HR, 3.25; 95% CI, 2.92 to 3.63) and both death-censored and all-cause graft loss (adjusted HR, 2.88; 95% CI, 2.6 to 3.12) (100).

Age, men, White race, kidney failure caused by hypertension, and extended pretransplant dialysis duration are risk factors for post-transplant atrial fibrillation. As the age of kidney transplant recipients grows older, optimal risk stratification and prevention of atrial fibrillation and stroke will become increasingly important. Treatment with anticoagulation on the basis of stroke risk should be continued but poses challenges for drug interactions, and optimal use of new direct oral anticoagulants is uncertain in post-transplant patients (101). As use of novel direct oral anticoagulants rises, specific risks and benefits in kidney transplant recipients should be carefully observed.

Structural heart disease, particularly valvular disease, is common in CKD, and prevalence is higher with lower eGFR due to accelerated calcification and volume overload (101). Severe valvular disease is often a reason for the ineligibility of patients with kidney failure for kidney transplant, whereas severe heart failure with valve disease may be an indication for combined heart-kidney transplant (102). Whether kidney transplantation stabilizes disease progression is uncertain, although data suggest that hospitalizations for valvular disease are less frequent following kidney transplantation (102). Nevertheless, intervention for valvular disease in kidney transplant recipients is often required and commonly involves the aortic valve (103). Whether transcatheter aortic valve implantation is superior or noninferior to an open surgical approach is not certain in this population (104,105).

Special Populations

In studies comparing etiologies of kidney failure and associations with outcomes after kidney transplant, autosomal dominant polycystic kidney disease (ADPKD) is associated with better graft outcome overall but higher risk for metabolic complications (106). ADPKD is a nonmodifiable risk factor for post-transplant diabetes, which in turn, is a risk factor for cardiovascular complications (107). Death from cardiovascular disease is the leading cause of mortality relative to any other extra kidney manifestation of ADPKD (108). Cardiovascular disease is also the leading cause of death in patients with kidney failure across subtypes of glomerular disease (109). Although transplant improves the risk of cardiovascular disease death among patients with lupus nephritis relative to other waitlisted patients with lupus nephritis and kidney failure (110), cardiovascular disease is the most common cause of death in kidney transplant recipients with lupus nephritis (111). This is true for other subtypes of GN, including FSGS, membranous nephropathy, and membranoproliferative GN (111).

Prevention

As discussed above, aggressive management of preexisting cardiovascular disease is an important mainstay of preventing adverse cardiovascular disease outcomes, as kidney transplant recipients are undertreated with respect to cardiovascular risk factor modification (11). Because weight gain following transplant is a risk factor for adverse patient and graft outcomes, avoiding weight gain may be one method to prevent cardiovascular disease post-transplant, although this has not been proven prospectively (112). Belatacept may also provide a benefit to reduce cardiovascular disease risk after kidney transplant in eligible candidates via a lower risk of post-transplant diabetes (38).

Vascular arterial calcification is associated with cardiovascular and all-cause mortality in the general population and in kidney transplant recipients, and although progression of calcification appears to slow after transplant, it is not reversible (113). Methods to reduce and reverse the burden of arterial calcification are not yet available, although different immunosuppressive agents may differentially aggravate
vascular calcification (114). Other strategies to treat subclinical cardiovascular disease should be areas of focus for future research.

Preemptive Transplant
Preemptive transplant saves lives and is the basis for the “Transplant First” initiative in kidney failure care. Preemptive kidney transplantation is associated with improved allograft and patient survival (115). In a large study from France, preemptive kidney transplant was associated with a lower risk of graft failure than kidney transplant performed after initiation of dialysis, regardless of the duration of dialysis (even <6 months) (116). Identification of eligible living donors and reducing barriers to preemptive kidney transplant should be the focus for nephrologists and patients who are approaching KRT.

Future Directions and Conclusions
As in other areas of nephrology research, novel biomarkers of kidney injury have been evaluated as predictors of outcomes in kidney transplant, including graft loss (117) and cardiovascular outcomes (118). Although these biomarkers represent distinct kidney injury patterns from that of albuminuria, urine albumin-creatinine ratio remains one of the strongest predictors of allograft failure, cardiovascular disease events, and death (119).

Genetic risk may also be an important consideration for kidney transplant recipients. Associations between a genetic risk score comprising 27 single-nucleotide polymorphisms predictive of risk in the general population were analyzed in the ALERT trial. In analyses adjusted for cardiovascular risk factors, genetic risk score was significantly associated with major adverse cardiovascular event (HR, 1.81; 95% CI, 1.18 to 2.77, \( P = 0.006 \)) when comparing genetic high-risk patients (quartile 4) with genetic low-risk participants (quartile 1). Refining the score to better fit the transplant population may be feasible and incorporated in future clinical care (120).

As kidney transplantation continues to be the best option for patients requiring KRT, inclusion of kidney transplant recipients in cardiovascular disease trials will be important for improving outcomes in this population. Multidisciplinary clinical care models with an understanding of the risk of care fragmentation in cardiovascular disease management before and after kidney transplant should become standard (101).

In conclusion, several traditional and nontraditional cardiovascular risk factors have been identified in kidney transplant recipients, who experience a high burden of cardiovascular disease and related hospitalizations and death. Current management is largely on the basis of experience and expert transplant should be the focus for nephrologists and patients who are approaching KRT.
opinion. High-quality evidence is needed in this population to better understand risk and strategies to improve outcomes. On the basis of this review, it seems reasonable to target a systolic BP of <140 mm Hg, place kidney transplant recipients on a statin drug regardless of LDL unless a major contraindication is present, screen for and treat posttransplant diabetes, address weight gain and obesity with consideration of gastric bypass surgery for severe obesity, and individualize immunosuppression medication regimens. In addition, clinicians need to readily identify cardiovascular disease when present, working with a multidisciplinary team to provide comprehensive care. Treatment options are generally like what is used in the general population, with additional consideration of effect of kidney-specific factors, like arteriovenous fistula, on heart failure. Many opportunities for research are present (Figures 1 and 2, Table 1). Being more proactive regarding cardiovascular risk will hopefully lead to the better outcomes we desire for all our kidney transplant recipients.

Table 1. Immunosuppression and off-target effects on cardiovascular risk factors

<table>
<thead>
<tr>
<th>Immunosuppression Medication</th>
<th>Cardiovascular Risk Factor</th>
<th>Hypertension</th>
<th>Post-Transplant Diabetes Mellitus</th>
<th>Dyslipidemia</th>
<th>Mineral Bone Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

mTOR, mammalian target of rapamycin.

Disclosures

M. Park reports consultancy agreements with Abalone Bio and Acelink Therapeutics; receiving honoraria from Clarion, Deerfield, DRG, GLG, Grand Rounds, and the Healthcare Consultancy Group; other interest/relations with Kadmon as site primary investigator for a tesivatinib trial, with Reata as site primary investigator for A Trial of Bardoxolone Methyl in Patients With ADPKD-FALCON trial, and with Sano as site primary investigator for the Venglustat in Autosomal Dominant Polycystic Kidney Disease (SAVE-PKD) trial; and serving as an advisory board participant for Otsuka, Reata, and Sano. M. Park’s spouse reports ownership interest in Merck. The remaining author has nothing to disclose.

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References


conditions with a calcifying medium. *Ann Transplant* 23: 112–118, 2018


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