Cardiovascular Disease in Transplant Recipients: Current and Future Treatment Strategies

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A cardiovascular disease event in a transplant recipient may be the result of a pretransplantation disease process, a direct effect of immunosuppressant medications, or the result of exposure to a variety of traditional and nontraditional risk factors after transplantation. Although the understanding of posttransplantation cardiovascular disease remains incomplete, there is evidence that the impact of posttransplantation cardiovascular disease has been decreased, through increased attention to this problem. In the absence of controlled studies to guide therapy, this review summarizes treatment of cardiovascular disease risk factors for which there is strong evidence of benefit in the nontransplantation setting, observational evidence of a similar risk in transplant recipients, and evidence that treatment can be safely administered to transplant recipients. Putative risk factors for posttransplantation cardiovascular disease for which the current level of evidence is insufficient to support specific treatment recommendations are also discussed. Potential new strategies to decrease the risk for cardiovascular disease events after transplantation in the future, including aggressive pretransplantation risk reduction, individualized treatments to prevent different types of cardiovascular disease, dedicated efforts to reduce cardiovascular disease events during transitions between dialysis and transplantation, and manipulation of immunosuppressant protocols, are also introduced.

Definitions and Approach

There are two major and overlapping categories of CVD: (1) Disorders of cardiovascular perfusion including atherosclerotic CVD (ischemic heart disease [IHD], cerebrovascular disease, and peripheral vascular disease) and (2) disorders of cardiac function including congestive heart failure (CHF) and left ventricular hypertrophy. Whereas some risk factors are unique to each type of CVD, many risk factors are common to the various types of CVD. Because our understanding of the relative contribution of individual risk factors to the different types of CVD is limited, no attempt to define specific treatment strategies for the different types of CVD is made in this review.

CVD Risk Factors for Which There Is an Evidentiary Basis for Treatment

Hypertension

Hypertension (HTN), defined as a systemic BP >140/90 (5), is prevalent in >70% of transplant recipients (6). HTN is a risk factor for allograft failure, death with a functioning allograft, atherosclerotic CVD, and disorders of cardiac function. The pathogenesis of HTN in transplant recipients is linked to pretransplant factors including pretransplant HTN, the type of primary kidney disease, and excess renin output from native kidneys. Posttransplantation factors include the quality of the donor organ, delayed graft function, acute rejection, transplant renal artery stenosis, the level of allograft function (GFR), chronic immune and nonimmune injury, recurrent or *de novo* glomerulonephritis in the allograft, and excessive weight gain (6,7). Both calcineurin inhibitors (CNI) and glucocorticoids contribute to HTN. HTN was significantly lower before the introduction of CNI (8,9). CNI cause *afferent* arteriolar vasoconstriction by sympathetic stimulation and by upregulation of the...
local renin-angiotensin-aldosterone system. (10,11) CNI also decrease vasodilator prostaglandins and nitric oxide and increase vasoconstrictor cytokines (12,13). Glucocorticoids contribute to HTN by causing sodium and water retention.

There are no randomized, controlled trials of antihypertensive drugs or optimal BP goals in transplant recipients. On the basis of large clinical trials in nontransplantation patients with and without kidney disease, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend BP goals of 125/75 mmHg for transplant recipients with proteinuria and 130/85 in the absence of proteinuria (14). Treatment should include nonpharmacologic interventions, but simultaneous initiation of nonpharmacologic and pharmacologic treatment should be considered when the BP is ≥15 mmHg higher than target (15). Weight reduction, exercise, and dietary sodium restriction are the main nonpharmacologic considerations (5). Pharmacologic management should consider the potential for drug interactions; drug efficacy; and coexisting factors, including diabetes, IHD, CHF, and proteinuria. Specific indications such as proteinuria or a preexisting history of CVD may warrant the use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), or β blockers as initial agents (16). Loop diuretics should be used in the presence of fluid retention and may be particularly useful in the early posttransplantation period or when allograft function is reduced.

Dihydropyridine calcium channel blockers (DHP-CCB) are widely used because they counteract the vasoconstrictive effects of CNI (17). DHP-CCB were unexpectedly associated with an increased risk for IHD in a single-center, retrospective analysis (4). The use of DHP-CCB in proteinuric patients with CKD is associated with an increased risk for kidney function decline and death unless used with ARB (18–20). The mechanism for the potential adverse effect of DHP-CCB is not clear, however; these drugs are associated with increased catecholamine levels (21). Of note, the long-term CVD risk in patients who were treated with DHP-CCB was similar to that in patients who were treated with ACEi and diuretics in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (22). Non-DHP-CCB are used frequently in the early posttransplantation period because they also prevent renal vasconstriction. CNI dosage reduction is required with the use of these agents. When used with ACEi, non-DHP-CCB have a synergistic antiproteinuric effect (23).

ACEi and ARB have well-documented antiproteinuric and cardioprotective effects. Use of these drugs may be complicated by hyperkalemia and anemia. A >30% reduction in kidney function should trigger suspicion of transplant renal artery stenosis (24–27). A recent systematic review concluded that ACEi and ARB were associated with a clinically significant reduction in proteinuria, GFR, and hematocrit, but there was insufficient evidence to determine the effect of these agents on patient or graft survival (28). A Canadian multicenter, randomized, controlled trial to determine the impact of ramipril on allograft function is ongoing (29).

**Dyslipidemia**

Dyslipidemia is present in 50 to 60% of kidney transplant recipients (30). Table 1 summarizes the current thresholds for the diagnosis of dyslipidemia as defined by the KDOQI guidelines (30). Dyslipidemia is strongly associated with atherosclerotic CVD in CKD and non-CKD populations (30,31).

Dyslipidemia is clearly linked to the use of corticosteroids, CNI, and sirolimus. Compared with cyclosporine, tacrolimus has been associated with better lipid profiles, whereas sirolimus has been associated with a greater incidence and severity of dyslipidemia. Other factors that contribute to dyslipidemia include weight gain, decreased kidney function, proteinuria, β blockers, and diuretics (32).

The KDOQI guidelines recommend that all adult and adolescent transplant recipients be tested for dyslipidemia (complete fasting lipid profile including total cholesterol, LDL, HDL, and triglycerides) (30). Testing should be done when patients are stable after transplantation and at least annually thereafter. In addition, testing should be done 2 to 3 mo after a change in immunosuppressant medications or conditions that are known to cause dyslipidemia (e.g., change in proteinuria or GFR).

The Assessment of Lescol in Renal Transplantation (ALERT) study randomly assigned 2102 prevalent transplant recipients with total cholesterol 4.0 to 9.0 mmol/L to fluvastatin 40 to 80 mg/d versus placebo (33). Fluvastatin lowered LDL cholesterol by 32%. The primary composite end point (cardiac death, nonfatal myocardial infarction, or coronary revascularization) was not different between the treatment and control groups; however, there was a significant difference in cardiac death and nonfatal myocardial infarction. Further analyses demonstrated that earlier initiation of therapy resulted in a greater reduction in CVD events. Patients who enrolled in ALERT within the first 4 yr of transplantation had a 64% risk reduction compared with 19% in patients who received a transplant ≥10 yr before enrollment.

Key differences between the KDOQI recommendations for treatment of dyslipidemia in transplant recipients (30) and the Adult Treatment Panel III (ATP III) (31) guidelines written for the general population are the inclusion of transplant recipients in the highest risk category for treatment, the requirement for at least annual evaluation for dyslipidemia (versus every 5 yr in ATP III), initiation of pharmacologic treatment at lower thresholds (drug therapy to treat an LDL of 100 to 129 mg/dl after 3 mo of lifestyle and dietary modifications), the use of statins as

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<th>Table 1. Definition of dyslipidemia in adult kidney transplant recipients</th>
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<td>Dyslipidemia (mg/dl)</td>
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<td>TG ≥500</td>
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<td>LDL 100 to 129</td>
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*aAdapted from reference (30). To convert mg/dl to mmol/L, multiply triglycerides by 0.01129 and cholesterol by 0.02586. TG, triglycerides.
the initial pharmacologic treatment, and recommendations for
patients who are younger than 20 yr (there is no recommenda-
tion for treatment of patients who are younger than 20 yr in
ATP III).

The use of statins in the presence of CNI can lead to a
significant increase in statin blood levels and increased risk for
rhabdomyolysis. Recommended dosages specific for transplant
recipients are available (30), and monitoring of creatinine phos-
phokinase levels may be prudent. Bile acid sequestrants may
interfere with absorption of immunosuppressant drugs. When
used, these drugs should be taken 1 h before or 4 h after a CNI.
Ezetimibe blocks intestinal absorption of dietary cholesterol
and is a useful adjuvant to statin therapy. No reports of inter-
actions between ezetimibe, CNI, or sirolimus have been pub-
lished.

New-Onset Diabetes
The reported incidence of new-onset diabetes (NOD) is highly
variable and may be related to the variable criteria used define
NOD in the literature. Despite the probable high incidence of
NOD, patients may not be routinely screened and the incidence
of NOD may be underestimated. Similar to mature-onset dia-
betes in the nontransplantation setting, patients who develop
NOD can have glucose intolerance and may be asymptomatic
for years before diagnosis. NOD may not be permanent, and
glucose abnormalities may normalize without treatment,
thereby making the condition difficult to diagnose. NOD seems
to develop in two patterns: It either appears abruptly during
the first 6 mo after transplantation or slowly develops over
years (coincident with aging). For example, in a study of >2000
transplant recipients, the cumulative incidence of NOD was
5.9% at 6 mo and 7.1, 10.4, 13.2, 20.5, and 29.8% at 1, 3, 5, 10, and
15 yrs.

NOD has been associated with both allograft loss and death
with a functioning allograft (35,36). A number of studies have
shown that patients who develop NOD have a two to three
times increased risk for fatal and nonfatal CVD events (37,38).
Risk factors for development of NOD include transplantation
from a deceased donor, older age, male gender, family history
of diabetes, black race, Hispanic ethnicity, obesity, posttrans-
plantation weight gain, hypertriglyceridemia, low HDL, hyper-
tension, hyperuricemia, hepatitis C infection, CNI, glucocorti-
coids, and possibly sirolimus (36,39,40). Tacrolimus is
associated with an increased risk for NOD compared with
cyclosporine, and this risk may be magnified in black patients
(41).

Published guidelines recommend that NOD be defined ac-

tording to current American Diabetes Association and World
Health Organization criteria (42). A complete history to identify
risk factors for NOD before transplantation should be per-
formed and used to individualize therapy to reduce the risk for
NOD. Patients should also be screened for metabolic syndrome
before transplantation (increased waist circumference, hyper-
triglyceridemia, low HDL, BP >130/85, and serum glucose of
at least 110 mg/dl or 6.1 mmol) because this syndrome is
associated with an increased risk for diabetes and CVD. Fasting
plasma glucose should be monitored routinely after transplan-
tation according to the following schedule: At least weekly
during the first posttransplantation month; at 3, 6, and 12 mo;
and then annually. Plasma glucose should also be randomly
monitored at regular intervals. Oral glucose tolerance tests may
be more predictive of CVD events than fasting plasma glucose,
particularly in patients with impaired glucose tolerance. The
2003 international consensus guidelines recommend a stepwise
approach to treatment unless patients develop symptomatic
hyperglycemia or ketosis, in which case insulin monotherapy is
required (42). The first step is nonpharmacologic therapy in-
cluding lifestyle modification and patient education. In patients
who require pharmacologic therapy, monotherapy with an oral
agent (α-glucoside reductase inhibitor, biguanides, meglitin-
ides, sulfonylureas, and thiazolidinediones) is recommended.
The choice of agent depends on individual patient needs, co-
morbid conditions, and safety considerations. In patients with
impaired kidney function, the risk for lactic acidosis with met-
formin and for hypoglycemia with sulfonylureas are important
considerations. Elderly patients may be at increased risk for
hypoglycemia and should be treated initially with lower dos-
ages of oral agents. Patients whose NOD does not respond to
oral monotherapy can be treated with combined use of oral
agents; no one combination of medications is more efficacious,
and combinations should be tailored to individual patient
needs. Failure of combination therapy requires insulin therapy,
either alone or with combined use of oral agents. Co-adminis-
tration of rosiglitazone and insulin is not recommended. Pa-

tients who require insulin should be referred to an endocrinol-
ogist.

Cigarette Smoking
Smoking clearly increases the risk for CVD death in kidney
transplant recipients, and there is evidence that the smoking-
related risk for death dissipates 5 yr after smoking cessation
(43). Transplantation represents an opportunity to initiate
smoking cessation successfully. The combined use of pharma-
cologic and nonpharmacologic strategies may be most effective,
and there are no significant interactions between the commonly
used drugs for smoking cessation and immunosuppressant
medications.

Obesity
Obesity is a frequent posttransplantation complication. An
analysis of US Renal Data System data showed that a surprising
60% of American transplant recipients between 1987 and 2001
were overweight or obese at the time of transplantation (44).
Obesity is an established risk factor for atherosclerotic heart
disease, and obesity increases the risk for diabetes, dyslipide-
mia, and hypertension. The risk for obesity is increased in
steroid-treated patients. Removal of dietary restrictions after
transplantation and physical inactivity are other important con-

tributors to posttransplantation obesity.

Management of posttransplantation obesity includes lifestyle
and dietary modifications. Rapid steroid elimination or steroid
avoidance protocols are associated with a lower incidence of
obesity (45,46). The benefit of late steroid withdrawal (>3 mo
after transplantation) on weight gain is less clear (47). The
potential benefit of steroid reduction or withdrawal must be balanced against the risk for allograft rejection. There is limited experience with pharmacologic agents to promote weight loss in transplant recipients. The published experience with bariatric surgery in transplant recipients is limited; both gastric bypass surgery (48) and laparoscopic gastric banding (49) have been used to treat obesity in transplant recipients.

CVD Risk Factors for Which There Is Insufficient Evidence for Treatment

Proteinuria
Proteinuria is prevalent in 20 to 40% of transplant recipients (50,51). The evidence to treat proteinuria specifically to reduce CVD risk is lacking. Proteinuria is believed to be a marker of endothelial dysfunction, and there are ample observational data showing that proteinuria is clearly associated with an increased risk for CVD in transplant and nontransplant patients (51–53); however, there are limited data from controlled studies demonstrating that treatment of proteinuria decreases the risk for CVD (54). Controlled trials in the nontransplantation setting clearly demonstrate that proteinuria reduction is renoprotective; therefore, there is a stronger rationale to treat proteinuria to preserve allograft function. To date, no controlled trials in transplant recipients have demonstrated that proteinuria reduction preserves allograft function.

Anemia
The recent KDOQI guidelines on anemia management contain a dedicated discussion of posttransplantation anemia (55). Although anemia is associated with CVD in both transplant and nontransplant patients (56–58), there is no clear evidence that correction of anemia reduces the risk for CVD events. The main proven benefit of anemia treatment with erythropoiesis-stimulating agents in dialysis-treated and non–dialysis-treated patients with CKD is avoidance of transfusions and improved quality of life (59). There are no controlled studies demonstrating improvement in CVD, quality of life, or the need for transfusions in transplant recipients. Prospective interventional studies are needed to define the benefits of anemia treatment on posttransplantation CVD and other clinically meaningful outcomes.

Hyperhomocysteinemia
Several studies have documented that hyperhomocysteinemia is an independent risk factor for CVD in transplant recipients (60). Controlled trials in the nontransplantation setting have shown no benefit to treatment of hyperhomocysteinemia (61). Results of the ongoing Folic Acid for Vascular Outcome Reduction in Renal Transplantation (FAVORIT) study will provide definitive evidence regarding the benefit of treatment in transplant recipients (62).

C-Reactive Protein
An elevated concentration of C-reactive protein (CRP) is independently associated with increased risk for CVD events in transplant recipients (63). This finding is consistent with studies in the general population demonstrating an association between CRP and ischemic heart disease. CRP levels were lowered with the use of statins, and this reduction in CRP was associated with a reduced risk for CVD independent of the lipid-lowering effect (64). Further studies are warranted to determine the role of targeted therapies to lower the levels of inflammatory markers to reduce CVD risk.

Future Strategies to Decrease the Risk for CVD Events after Transplantation

This remainder of this review focuses on new potential strategies to decrease the risk for CVD events after transplantation.

Aggressive Pretransplantation Management of CVD
The concept that posttransplantation CVD is in part due to pretransplantation exposures has gained momentum with the inclusion of kidney transplant recipients in the CKD classification (65,66). This issue has significant therapeutic implications. If pretransplantation exposures portend an increased risk for CVD after transplantation, then a paradigm shift in our current waiting list management strategy would be indicated to minimize the impact of uremia in the setting of increased waiting times for transplantation. Our current waiting list management strategies are focused on identifying and excluding from transplantation patients who are at high risk for posttransplantation complications or who develop contraindications to transplantation, and are not necessarily focused on prevention of CVD.

There is evidence to suggest that pretransplantation exposures have a significant impact on posttransplantation CVD risk. A number of observational studies have demonstrated that patients with either no or short durations of dialysis exposure before transplantation have a lower risk for death than patients with longer durations of pretransplantation dialysis exposure (67–70); however, these observations may be confounded by the fact that patients who are likely to do well after transplantation may also be more likely to obtain transplants more rapidly. For example, patients with strong social supports, favorable sociodemographic characteristics, and predialysis nephrology care may be more likely to receive preemptive transplants and to pursue transplantation as a treatment option (68,71–73).

In contrast, findings from other studies have shown that the rates of death and nonfatal CVD events decrease dramatically after transplantation and that this change seems to occur in patients with both short and long durations of pretransplantation dialysis exposure. One study demonstrated that transplantation seems to halt the progression of CVD (74). Another study demonstrated relatively similar death rates after transplantation among patients who received transplants with waiting times of <12, 12 to 24, and 24 to 36 mo duration (75). These findings are particularly noteworthy, because the death rate among transplant candidates who remained on the waiting list increased dramatically with waiting time.

For better understanding of the impact of pretransplantation exposures on posttransplantation outcomes, a better method to determine the pretransplantation CVD burden is needed. The duration of pretransplantation dialysis exposure is likely a poor indicator of the pretransplantation CVD burden. Patients who
receive a transplant after long durations of dialysis exposure may represent a surviving population who have a low burden of CVD because they are biologically protected from developing disease for reasons that we do not understand. Similarly, reliance on a history of overt clinical events (e.g., myocardial infarction, stroke, CHF) before transplantation is likely inadequate if the physiologic changes that occur with uremia do not result in overt clinical events before transplantation. A number of studies have shown that physiologic abnormalities such as coronary calcification, left ventricular hypertrophy, impaired arterial compliance, abnormalities of diurnal BP rhythm, elevated markers of oxidative stress, systemic inflammation, and endothelial dysfunction (63,76–82) are prevalent in kidney transplant recipients. Further studies to determine the natural history of these abnormalities after transplantation and their association with posttransplantation events are needed.

Develop Specific Treatment Strategies for Different Types of CVD
As discussed previously, our understanding of the risk factors that contribute to the different forms of CVD is limited. Recent analyses from the US Renal Data System demonstrated significant differences in the risk for specific CVD events after transplantation (Figure 1) (83). For example, the rates of myocardial infarction and cerebrovascular disease seem to be only minimally increased in transplant recipients compared with Medicare recipients without a known diagnosis of CKD (Figure 1). In contrast, the rates of CHF and peripheral vascular disease were higher in transplant recipients (Figure 1). These findings are consistent with observations from a retrospective study of more than 600 Canadian transplant recipients that found the incidence of CHF to be significantly higher than that in the Framingham cohort, whereas the incidence of IHD was not different from that in Framingham, leading the authors to conclude that transplantation should be considered a “state of accelerated heart failure” (56). The observations clearly suggest the need to identify patients who are at risk for specific types of CVD and to identify unique disease-specific risk factors for therapeutic intervention.

Intensified Surveillance and Risk Reduction during Transitions between Dialysis and Transplantation
Recent publications have emphasized that there seems to be a distinct time course during which CVD events develop after transplantation (84,85). Most fatal CVD events are clustered around the time of transplantation and during the return to dialysis after transplant failure (Figure 2). Between these transition periods, CVD events seem to be relatively infrequent and slowly progressive over time. These findings suggest the need for well-defined prophylactic strategies during these high-risk transition periods. Research is needed to understand better the mechanisms underlying the high CVD event rates during transitions between dialysis and transplantation. Increased inflammation during the peritransplantation period may lead to an increase in atherosclerotic disease events during this time. Alternatively, peritransplantation events may be related to rapid administration of large volumes of fluid to patients with abnormal ventricular function. Similarly, the high mortality in patients with transplant failure may in part be related to graft loss’s being a proximal event in the disease course of a dying patient. Alternatively, other mechanisms, such as sepsis, may precipitate CVD events in patients with transplant failure (86).

Figure 1. Cardiovascular disease event rates in adult dialysis (n = 191,278), transplant (n = 22,673), chronic kidney disease (CKD; n = 44,941), and non-CKD (n = 1378,122) Medicare-insured prevalent patients on January 1, 2002. Rates are adjusted for gender, race, and diabetes status. Adapted from reference (83), with permission.

Individualized Use of Immunosuppressant Medications and Immunosuppressant Withdrawal Strategies
Immunosuppressant medications have variable effects on the incidence and severity of different CVD risk factors. This suggests that individualized use of immunosuppressant medications in patients may be useful in minimizing CVD risk. For example, patients who are at high risk for NOD could be identified before transplantation and treated with cyclosporine rather than tacrolimus or with a rapid steroid elimination protocol. There are a number of considerations with this approach. We do not have a clear understanding of the net impact of different immunosuppressant medications on CVD. Specifically, we do not know the relative importance of different CVD risk factors (e.g., is NOD more important than dyslipidemia?); neither do we understand all of the mechanisms by which immunosuppressant medications may increase CVD risk. To date, there is no clear evidence
that any one immunosuppressant medication provides a survival advantage over another. Similarly, the metabolic benefits of rapid steroid elimination or CNI avoidance/reduction protocols must be weighed against the increased risk for acute rejection and uncertainty about the long-term safety of these regimens. Nonetheless, the increased availability of new immunosuppressant agents provides an important new opportunity to decrease CVD risk and should be further developed. New trials testing these strategies should use standardized methods and definitions to permit assessment of all relevant CVD risk factors. For example, diabetes should be defined using standardized criteria, and kidney function should be measured or estimated by an agreed-on standard method. Further long-term outcomes from these trials should be provided to determine the safety of these approaches.

Conclusions

Although we lack complete understanding of posttransplantation CVD, there is evidence that we have decreased the impact of CVD on transplant outcomes through increased attention to risk factor reduction. There is sufficient evidence to recommend aggressive treatment of traditional CVD risk factors (hyper tension, dyslipidemia, diabetes, smoking, and obesity). There is less evidence to support treatment of nontraditional CVD risk factors, including anemia, hyperhomocysteinemia, and CRP. New strategies that may decrease posttransplantation CVD in the future include aggressive management of CVD risk factors before transplantation, identification of patients who are at risk for different types of CVD and treatment of unique disease-specific risk factors, increased attention to CVD risk reduction during transitions between dialysis and transplantation, and individualized use of immunosuppressant medications in patients with different CVD risk profiles or reduced exposure to immunosuppressant medications with the use of minimization or avoidance protocols.

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Disclosures

None.

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