Management of Cardiovascular Disease in Renal Transplant Recipients

Anushree C. Shirali and Margaret J. Bia
Division of Nephrology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

Cardiovascular disease is a major cause of graft loss and the leading cause of death in renal transplant recipients. Although there are robust data on the frequency of risk factors and their contributions to cardiovascular disease in this population, few trials have demonstrated the benefit of modifying these risk factors to reduce cardiovascular events. Nevertheless, it is widely accepted that the clinical acumen filtered through the best available studies in the general population be used to treat individual renal transplant recipients given their high cardiovascular mortality. Transplant task forces and the Kidney Disease Outcomes Quality Initiative have created guidelines for this purpose. This review examines the data available for prevention and treatment of major risk factors contributing to cardiovascular disease in renal transplant recipients. The contribution of immunosuppressive agents to each risk factor and the evidence to support lifestyle modification as well as drug therapy are examined. Reducing cardiovascular risk factors requires an integrative approach that is best accomplished by a team of health care professionals. It creates a significant challenge but one that must be met if allograft survival is to improve.

Published online ahead of print. Publication date available at www.cjasn.org.

Kidney transplantation is the renal replacement therapy of choice for most patients with ESRD, not only improving quality of life but also offering extended life expectancy compared with dialysis (1,2). Immunosuppressive therapies have significantly improved allograft outcomes, yet, for many patients, the advantages of renal transplantation do not result in a normal life span. Compared with the general population, renal transplant recipients (RTR) are at higher risk for morbidity and mortality, largely as a result of cardiovascular disease (CVD) (3). Although CV mortality is improved in transplant recipients compared with those on dialysis (4), it remains a prominent problem. In fact, death with a functioning kidney is a major reason for graft loss in the transplant population, with CVD being the leading cause of death with a functioning graft (5). Despite the magnitude of the problem, there is a paucity of direct evidence in kidney transplant patients regarding prevention and treatment of CVD. Patients with chronic kidney disease (CKD) are not well represented in randomized, controlled trials (RCT) involving CVD. Patients with proteinuria.

CVD: Epidemiology and Risk Factors

By 36 mo after transplantation, nearly 40% of patients have experienced a CV-related event (7). Although acute myocardial infarction occurs after transplantation, especially in the elderly and patients with diabetes (8), CV events related to congestive heart failure (CHF) are more common (7). Indeed, after infection, CHF is the most common cause of hospital admissions after renal transplantation (7). Clearly, management of CVD after transplantation should include modifying risk factors that contribute to CHF as well as ischemic heart disease.

Table 1 lists the predisposing factors for CVD after transplantation. Traditional risk factors for CVD in the general population remain relevant for transplant recipients (9–11). Some of these, such as diabetes and hypertension, are likely to be pre-existing conditions, although, along with other diseases, particularly hyperlipidemia and anemia, they can also arise de novo from the unintended effects of immunosuppression (12).

There is now general consensus that worsening kidney function is also an independent risk factor for cardiac disease. Although renal replacement by transplantation can abrogate that effect (13), allograft dysfunction is still an important risk factor for all-cause and CV mortality (10,14). In addition, proteinuria itself is a risk factor for CVD. Fernando-Fresneda et al. (15) found in a single-center retrospective analysis that transplant recipients with proteinuria carry a relative risk of 2.45 for development of CVD when compared with patients without proteinuria.

Markers of inflammation, such as hyperhomocysteinemia, C-reactive protein (CRP), and advanced glycation end products, are independently linked to CVD in some studies of RTR (16,17). Their particular role in contributing to CVD in RTR is still under intense study, and an in-depth analysis of these novel risk factors is beyond the scope of this article. In this review, we focus on the major risk factors. We examine the role of immunosuppressive drugs and review the consequences of altering or discontinuing the drug on major CV risk factors. We
also review the data supporting lifestyle modifications as well as drug therapy for preventing and treating the major risk factors.

**Obesity**

Now a global public health epidemic, obesity is also affecting the RTR population. Obesity can be stratified according to body mass index (kg/m²): Overweight (25 to 29.9), obese (30 to 34.9), and morbidly obese (≥35). Increasing numbers of obese and overweight patients are now presenting for transplant than ever before (18), and there is further weight gain after transplantation (19). Recent data from a contemporary cohort of the United Network for Organ Sharing database indicated that 50% of transplant patients could be classified as obese or morbidly obese (20). Obesity can predispose to insulin resistance, diabetes, ischemic heart disease, and reduced graft survival (9,21,22).

Obesity in transplant patients is also being increasingly recognized in the context of the metabolic syndrome, which is defined in Table 2. When examined at 6 yr after transplantation, up to 63% of RTR meet the criteria for metabolic syndrome, with an associated decrease in kidney allograft survival (23) and increased number of CVD events (24).

**Role of Immunosuppressive Agents**

Although the use of steroids clearly plays a role (22), improvement in appetite and freedom from dialysis-related dietary restrictions also contribute to posttransplantation weight gain. In reports of steroid-avoidance protocols, small decreases in weight gain after transplantation were noticed in some (25) but not all (26) studies. In a carefully controlled study, Painter et al. (27) reported that neither weight nor body fat composition was different at 1 yr in patients in a steroid-avoidance protocol versus those who were maintained on steroids. These findings are consistent with the fact that obesity precedes transplantation in many patients (18,22). Thus, although steroids can stimulate appetite and are blamed for obesity by both patients and physicians, there is not convincing evidence that steroid-free regimens should be used specifically to avoid posttransplantation weight gain.

**Lifestyle Modification for Prevention and Control of Obesity**

It is well appreciated that diet and exercise form the backbone of lifestyle changes needed to achieve and support sustained weight loss. Van den Ham et al. (28) found that physical activity was more important than steroid dosage in posttransplantation weight gain. Dietary counseling needs to be incorporated into routine visits. Although patient motivation drives adherence to both diet and exercise, weight loss programs can help patients achieve weight loss goals. Of the major commercial weight loss programs in the United States, Weight Watchers (WW) has performed two RCT with long-term follow-up documenting sustained weight loss (29). In a large prospective trial in the general population that compared WW with other popular programs such as Atkins, Zone, and Ornish, equal efficacy was...
demonstrated in obtaining modest weight loss and reducing CV risk factors, but the Atkins and Ornish groups sustained higher dropout rates (30). Furthermore, the higher protein intake (Ornish and Atkins) and high fat intake (Atkins) diets may not be advisable in RTR. Thus, weight loss programs that are moderate in both their dietary composition and their message should be supported. It should be noted that with a doctor’s prescription for weight loss, initial registration for WW and other weight loss programs may be waived. In addition, the use of weight loss programs can qualify for federal income tax deduction (31).

Drug Therapy

Effective drug therapy for obesity is limited, partly because of the complex pathogenesis. Orlistat is a pancreatic lipase inhibitor that blocks fat absorption. It is modestly effective in promoting weight loss when compared with placebo in nontransplant patients (32). No similar studies exist for RTR, but there are case reports of subtherapeutic calcineurin inhibitor (CNI) levels in patients who used orlistat (33). Physicians should be mindful of its potential use among patients, especially because orlistat recently became available without a prescription. Antidepressants may be useful for depressed patients who have an emotional component of weight gain, particularly selective serotonin reuptake inhibitors such as fluoxetine and sertraline, which, unlike other antidepressants, are less likely to cause weight gain. St. John’s wort, an herbal preparation used as part of an alternative prescription for depression, decreases CNI levels by potent cytochrome P450 induction. Transplant patients should be cautioned against its use, because it has been linked to acute rejection episodes (34).

Smoking

Tobacco use, which occurs in approximately 25% of RTR, is an independent risk factor for CVD and confers a 30% risk for graft loss as a result of premature CVD (35,36). In fact, smoking has been demonstrated to be a risk for death with a functioning graft as great as that due to diabetes (37). This risk can be reversed with smoking cessation. RTR who stopped smoking >5 yr before transplantation had a 34% risk reduction in CV events (35). Thus, the commitment to modify this risk factor needs to begin long before transplantation.

Counseling and Group Therapy

The most successful approaches to smoking cessation involve both pharmacologic therapy (usually nicotine replacement therapy [NRT]) and sustained behavioral therapy (counseling) (38). The important role of the physician in this process needs to be emphasized. Unfortunately, evidence reveals that only 20% of physicians reportedly provide antismoking advice during an office visit (39). Physicians should intervene during the pretransplantation evaluation visit by providing resources for tobacco cessation.

Drug Therapy

Long-term smoking is a sign of chemical dependence on nicotine, providing the rationale for NRT as pharmacologic therapy. Several modalities exist, including transdermal patches, gum, and inhalers, with all displaying nearly equal efficacy (40). Published studies in the nontransplant literature report that tobacco users are 1.5 to 2.5 times more likely to quit with NRT compared with placebo, but success rates depend on a supportive environment (40). Although no data are yet available in RTR with the use of varenicline (Chantix; Pfizer, New York, NY), a partial agonist that selectively binds nicotinic acetylcholine receptors (41), we have used it safely in several patients. Varenicline is cleared by the kidney, and prescribing information suggests dosage reduction for patients with creatinine clearance <30 ml/min (42).

Hyperlipidemia

Hypercholesterolemia and hypertriglyceridemia have prevalence rates of 40 and 60%, respectively, among RTR (43). In addition to increasing risk for CVD, hyperlipidemia has been associated with reduced renal allograft survival (44). The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) has published extensive guidelines on managing dyslipidemias in kidney recipients (43). On the basis of the Adult Treatment Panel III (ATP III) classification, the working group considered RTR in the highest CVD risk category and suggested goal lipid levels accordingly (43). Goals for therapy are outlined in Figure 1 and include both lifestyle modifications and drug therapy. In RTR, a goal of LDL <100 mg/dl is recommended, but in transplant patients with diabetes or previous CVD, one could justify an LDL goal of <70 mg/dl, which has been shown to be even more protective in preventing cardiac events in non-RTR (45).

Role of Immunosuppressive Agents

Steroids, even at maintenance dosages, contribute to hyperlipidemia in RTR (46), and improved lipid profiles have been reported in most steroid-free or steroid-withdrawal studies (25,47). Risk for acute rejection with late steroid withdrawal and lack of long-term follow-up in steroid-avoidance trials suggest the need for caution in choosing a steroid-free regimen to improve lipid profile. Cyclosporine and tacrolimus both can

Figure 1. Management of dyslipidemias in renal transplant recipients. HbA1c, glycosylated hemoglobin; LFTs, liver function tests; TG, triglycerides; TSH, thyroxin-stimulating hormone. Reprinted with permission from reference (131).
contribute to hyperlipidemia, but cyclosporine has a greater effect (48). In fact, switching from cyclosporine to tacrolimus to improve hyperlipidemia, especially in a patient who is intolerant to statin therapy, can significantly improve levels of cholesterol and LDL (49). Sirolimus has the greatest effect on lipid profiles and elevates both cholesterol and triglycerides in a dosage-dependent manner (50,51). Because of the antiproliferative effect of sirolimus on the vascular endothelium, some have postulated that elevated lipid levels are not as much of a risk in patients who take sirolimus, with some clinical data to support this hypothesis (52). The antimetabolite immunosuppressants, namely mycophenolate mofetil and azathioprine, are not associated with de novo development of dyslipidemias.

Lifestyle Modification: Diet
Lifestyle modifications presented in the National Cholesterol Education Project Plan III (NCEP III) are appropriate goals for transplant patients and include diet, weight reduction, and increased physical activity (53). Diet composition should contain <200 mg/d cholesterol, <7% saturated fat, plant sterols (2 g/d), and increased soluble fiber (10 to 25 g/d) (53). Trans fats should also be avoided. Although benefits in lipid profile in RTR have been demonstrated in small studies (54,55), most transplant patients need drug therapy to reach lipid profile goals.

Drug Therapy
Many RCT in nontransplant patients have demonstrated the CV risk reduction achieved in lowering levels of cholesterol (56). In RTR, the Assessment of Lescol in Renal Transplantation (ALERT) trial investigated the benefit of statins in lowering lipid levels by randomly assigning 2102 patients to fluvastatin (40 to 80 mg) or placebo (11). Fluvastatin was safe and effective in lowering LDL levels in renal transplant patients (11). Although the study was not adequately powered to detect a significant reduction in the primary end point of cardiac events, the investigators demonstrated 35% reduction in the secondary end points of cardiac death and nonfatal myocardial infarction in the statin group (11). An extension phase of the trial in which all patients were offered open-label fluvastatin (80 mg) therapy resulted in a significant reduction in the composite cardiac end point, including cardiac events, in patients who were treated with statin versus the original placebo cohort (57). Post hoc analysis of the ALERT data also suggested that early initiation of lipid therapy provided the greatest benefit (58). Despite statistical concerns, the ALERT study is the only RCT to date to support aggressive treatment of hyperlipidemia in RTR. Benefits of statin use may extend beyond lipid control, including decreased proteinuria (59), decreased CRP (60), and a decrease in interstitial fibrosis in transplant protocol biopsies (61).

Drugs that treat hyperlipidemia are listed in Table 3. Among different statins, atorvastatin is the most potent and along with pravastatin and fluvastatin does not need dosage adjustment for renal insufficiency. Most statins are metabolized by the same cytochrome P450 system (CP3A4) as cyclosporine, leading to an accumulation of the former in plasma and resulting in a greater frequency of rhabdomyolysis (62). Data on tacrolimus are sparse, although pharmacokinetic studies in a limited number of patients on concomitant atorvastatin and tacrolimus therapy did not show a significant interaction between the two (63). Fluvastatin is metabolized by CP2C9, whereas pravastatin metabolism relies on sulfation; therefore, both should theoretically be safer to use (43,64). The potential for rhabdomyolysis also increases as the lipophilicity of the compound increases, because the more lipid-soluble statins are more likely to deposit in extrahepatic tissues and cause toxicity (65). Among statins in current use, simvastatin and lovastatin are the most lipophilic compounds, whereas atorvastatin and fluvastatin are less so and pravastatin is hydrophilic (65). In considering these differences among statins, fluvastatin, pravastatin, and atorvastatin seem to have a more favorable safety profile over simvastatin and lovastatin. To our knowledge, there are no head-to-head safety comparisons among statins in RTR. In heart transplant patients who received cyclosporine, a higher incidence of rhabdomyolysis was seen in patients who were randomly assigned to simvastatin versus pravastatin (66); therefore, only low dosing of simvastatin and lovastatin (10- and 20-mg maximum doses, respectively) is recommended for this population (67). K/DOQI guidelines do not exclude any statin from use after renal transplantation but suggest decreasing maximum dosing of all statins in patients who are on cyclosporine or tacrolimus (43). Choice of statin is also influenced by insurance restrictions. If maximal statin dosages are not sufficient, then combination therapy with ezetimibe has been shown to be safe and effective in lowering LDL levels in a limited number of RTR (68,69), with no adverse effect on kidney function or drug interaction reported to date. Ezetimibe is available as mono-

Table 3. Classes of lipid-lowering drugs and their effects

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>LDL Cholesterol</th>
<th>HDL Cholesterol</th>
<th>Triglycerides</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (HMG-CoA reductase inhibitors, e.g., atorvastatin)</td>
<td>↓ ↓ ↓</td>
<td>↑</td>
<td>↓ ↓</td>
<td>Rhabdomyolysis, myositis, elevated LFT, increased levels with CNI use</td>
</tr>
<tr>
<td>Fibrates (e.g., gemfibrozil)</td>
<td>↓ ↓</td>
<td>↑ ↑</td>
<td>↓ ↓</td>
<td>Elevated creatinine, erectile dysfunction</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>↓ ↓</td>
<td>↔</td>
<td>↓ ↓</td>
<td>Interferes with absorption of CNI, GI distress</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓ ↓</td>
<td>↑ ↑</td>
<td>↔</td>
<td>Flushes, hyperglycemia</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor (e.g., ezetimibe)</td>
<td>↓ ↓</td>
<td>↔</td>
<td>↔</td>
<td>GI distress</td>
</tr>
</tbody>
</table>

*CNI, calcineurin inhibitor; GI, gastrointestinal; HMG-CoA, hepatic hydroxymethyl glutaryl-CoA; LFT, liver function tests.

*Elevated creatinine is less likely with gemfibrozil than other fibrates (43,64,130).
therapy or in combination with simvastatin [Vytorn; Merck (Whitehouse Station, NJ)/Schering-Plough (Kenilworth, NJ)]; however, as detailed previously, given the greater potential for rhabdomyolysis as a result of the interaction between cyclosporine and simvastatin, cautious use and close monitoring are especially advised in RTR on this combination therapy. Caution is also to be noted with the use of Vytorn in view of the recent announcement by the company of an increase in vascular plaques noted with this combination drug (www.merck.com/newsroom/press_releases/product/2008_0114.html) (accessed January 17, 2008).

Managing triglycerides can be a challenge, especially for some patients who are taking sirolimus. Increased risk for rhabdomyolysis has been associated with fibrate therapy for hypertriglyceridemia, especially with concurrent use of statins (67). Fibrates may also cause elevations in serum creatinine, especially in cyclosporine-treated patients (43). Of the fibrates available, gemfibrozil has less of an effect on kidney function in such patients and is preferred (43,70). Nicotinic acid (niacin) can cause glucose intolerance and may not be suitable for certain patients. Bile acid sequestrants are not recommended for RTR because they can interfere with absorption of immunosuppressants (43). Fish oil therapy may be used for patients who are intolerant of conventional therapies but is not likely to be effective monotherapy. A recent meta-analysis of omega-3 use after renal transplantation demonstrated only modest triglyceride lowering and no decrease in CV mortality (71).

Hypertension
Hypertension after renal transplantation is defined according to criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, and Evaluation of High Blood Pressure (JNC VII) as systolic BP (SBP) >140 mmHg or diastolic BP (DBP) >90 mmHg (72). Given this definition, 75 to 90% of kidney transplant patients have hypertension (73), a figure that has changed little in recent years. In a large cohort (29,751 patients) in the Collaborative Transplant Study, Opelz et al. (74) reported that up to 55% of kidney transplant patients did not reach the goal for BP control. Each 10-mmHg incremental rise in SBP independently increases the risk for death and death-censored graft failure in RTR by 18 and 17%, respectively (75). Hypertension is also associated with poor long-term graft survival (76). K/DOQI guidelines suggest goal BP ≤130/80 mmHg for all RTR with decreased targets considered appropriate for patients with proteinuria (77). European best practice guidelines specify BP <125/75 mmHg in patients with proteinuria (78).

Role of Immunosuppressive Agents
The CNI (cyclosporine more than tacrolimus) contribute to hypertension via vasoconstriction and salt retention (73), and improvement in hypertension has been reported when dosage is reduced or the drug is eliminated (79–81). Mechanisms by which steroids contribute to hypertension include salt retention, weight gain, and mineralocorticoid effect. Improvement in hypertension has been reported in steroid-withdrawal and steroid-avoidance trials (25,26).

Lifestyle Modification for BP Control
Lifestyle modification for hypertension control includes diet and exercise. Nontransplant patients who followed the Dietary Approaches to Stop Hypertension (DASH) diet were demonstrated to have a decrease in SBP (11.4 mmHg) and DBP (5.5 mmHg) (82). This diet, which features a high intake of fruits and vegetables and a low intake of fats, is now recommended for all patients with hypertension by national guidelines, including JNC VII (72). The new DASH diet recommends a sodium intake of 1600 mg/d (72). Unfortunately, despite its proven efficacy, evidence suggests that the DASH diet is seldom followed. In a study of 4386 hypertensive patients, Mitka (83) reported that only 22% of patients were following this diet.

Drug Therapy
No single class of antihypertensive agents has proved to be superior for all RTR, and the choice depends on the particular patient. The use of calcium channel blockers (CCB) is popular as first-line therapy (75), because they are often used to counteract the vasoconstrictive effects of cyclosporine as well as posttransplantation hyperuricemia (84). In studies in which improved allograft function has been reported with the use of dihydroxypiridine (DHP) CCB compared with angiotensin-converting enzyme inhibitors (ACEI) (85,86), the results are likely explained by the hemodynamic effects of ACEI to decrease GFR and may not represent an advantage for long-term survival. There are some concerns about the use of CCB. In a retrospective, single-center analysis, Kasiske et al. (9) found that DHP CCB imposed a relative risk of 2.26 for major ischemic heart disease events, independent of other variables, including BP. Furthermore, there is a greater risk for proteinuria with these agents compared with ACEI in nontransplant patients with CKD (87,88). Edema can be a major problem with the use of dihydropyridine (DHP) CCB compared with angiotensin-converting enzyme inhibitors (ACEI) in RTR, and the non-DHP CCB can delay metabolism and elevate the levels of cyclosporine and tacrolimus (75). Classes of drugs to be used are listed in Table 4.

The use of ACEI and angiotensin II receptor blockers (ARB) in RTR is more widespread now than in the past. The cardioprotective and renoprotective effects of renin-angiotensin system blockade in the general population and in patients with CKD make the use of these agents attractive in the RTR population; however, limited prospective data in the transplant population confirm these benefits. Regarding cardioprotection, Middvedt et al. (89) found equal benefits of lisinopril and nifedipine in reducing left ventricular mass index after transplantation. This trial was not powered to study CV events or mortality. Regarding renoprotection, data compiled from many studies document decreased proteinuria in RTR with the use of ACEI. In a meta-analysis of the use of ACE/ARB in >1500 RTR who were enrolled in RCT, Hiremath et al. (90) reported a 0.47-g/d reduction in proteinuria. Although caution has been advised in using these agents too early after transplantation, we (91) and others (92) have reported no deleterious effect of these drugs on GFR when used in the early posttransplantation period. Whether these agents are renoprotective aside from improving proteinuria, as they are in patients with CKD, is controversial. In one report involving 2031 RTR from a single...
Table 4. Classes of antihypertensive agents commonly used in RTRa

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diuretics</th>
<th>CCB</th>
<th>ACEI/ARB</th>
<th>β Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected examples</td>
<td>Loop: furosemide</td>
<td>Non-DHP: diltiazem, verapamil</td>
<td>ACEI: lisinopril</td>
<td>Selective: lopressor</td>
</tr>
<tr>
<td>Considerations for initiating use in RTR</td>
<td>Thiazide: HCTZ</td>
<td>DHP: amlodipine, nilodenpine</td>
<td>ARB: losartan</td>
<td>Nonselective: carvedilol</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Volume overload</td>
<td>Minimizes CNI vasoconstriction</td>
<td>Proteinuria, CHF, LVH</td>
<td>Preferred in patients with known IHD</td>
</tr>
<tr>
<td>Interactions with immunosuppressive drugs</td>
<td>Volume depletion, ED Edema with DHP</td>
<td>Elevated K+, anemia, elevated creatinine</td>
<td>Elevated K+, anemia, elevated creatinine</td>
<td>Bradycardia, ED</td>
</tr>
</tbody>
</table>

aACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHF, congestive heart failure; DHP, dihydropyridine; ED, erectile dysfunction; HCTZ, hydrochlorothiazide; IHD, ischemic heart disease; LVH, left ventricular hypertrophy; RTR, renal transplant recipients.

center, improvement in 10-yr actual patient survival (74 versus 53%; P = 0.002) and graft survival (59 versus 41%; P < 0.001) was reported in patients who were versus were not on ACEI/ARB therapy (93). Shortly thereafter, in another report involving 17,209 RTR in the Collaborative Transplant Study, no benefit on ACEI or ARB use could be demonstrated (74). Adverse effects such as anemia, hyperkalemia, and decrease in GFR must be monitored with patients who are taking these agents. Because the combination of afferent arteriolar vasoconstriction from CNI and efferent arteriolar vasodilation as a result of renin-angiotensin system blockade can predispose to acute kidney injury, we routinely advise our patients to discontinue their ACEI or ARB therapy (93). Shortly thereafter, in another report involving 17,209 RTR in the Collaborative Transplant Study, no benefit on ACEI or ARB use could be demonstrated (74). Adverse effects such as anemia, hyperkalemia, and decrease in GFR must be monitored with patients who are taking these agents. Because the combination of afferent arteriolar vasoconstriction from CNI and efferent arteriolar vasodilation as a result of renin-angiotensin system blockade can predispose to acute kidney injury, we routinely advise our patients to discontinue their ACEI or ARB therapy (93).

Diabetes

With the increasing incidence of diabetes in the ESRD population, >20% of recent transplant recipients have existing disease at the time of transplantation (97). The rate of new-onset diabetes after transplantation (NODAT) is also on the rise, with prevalence in a contemporary US Renal Data System cohort estimated at 9.1, 16.1, and 24% at 3, 12, and 36 mo after transplantation, respectively (98). Obesity, hepatitis C infection, black and Hispanic ancestry, and older recipient age are associated with NODAT (98). In addition, there is appreciation that the increasing prevalence of metabolic syndrome after renal transplantation independently predicts development of NODAT (99,100). RTR with NODAT have as high a risk for CVD as patients with diabetes before transplantation (101). RTR with impaired fasting hyperglycemia also experience a higher risk for death from CVD (101).

Prevalence rates have varied in previous reports because of varying definitions of diabetes. In 2003, the transplant community issued international consensus guidelines (ICG) that suggested that screening for NODAT be based on the American Diabetes Association criteria for diagnosing diabetes (102,103). The American Diabetes Association issued revised criteria in 2003 (104), which are detailed in Table 5. Screening by fasting plasma glucose is recommended in all RTR weekly in the first month after transplantation, then at the 3-, 6-, and 12-mo visits. All abnormal values should be confirmed with testing on a separate day. Although screening with the more sensitive glucose tolerance testing has been advocated in certain at-risk populations (105,106), fasting glucose is still used in most transplant centers.

The ICG recommend that glycemic control in established diabetes be based on glycosylated hemoglobin (HbA1c) ≤6.5% and fasting plasma glucose 90 to 130 mg/dl (102,103). K/DOQI guidelines are similar, except that HbA1c <7% is considered acceptable (107). Testing for HbA1c is not recommended in first 3 mo after transplantation (102,103). Glycemic control may be

Table 5. Current definition of glucose intolerance and diabetes (99)a

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fasting Glucose</th>
<th>Random Glucose</th>
<th>2-H GTTb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100 mg/dl</td>
<td>N/A</td>
<td>&lt;140 mg/dl</td>
</tr>
<tr>
<td>Impaired</td>
<td>100 to 125 mg/dl</td>
<td>N/A</td>
<td>140 to 199 mg/dl</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥126 mg/dl</td>
<td>≥200 mg/dl</td>
<td>≥200 mg/dl</td>
</tr>
</tbody>
</table>

aGTT, glucose tolerance test.
bDefined as the serum glucose obtained 2 h after a 75-g glucose load.
difficult for patients to achieve but is an essential part of reducing adverse outcomes. In non-RTR, a 1% drop in HbA1c decreases CV mortality by 15 to 20% (108).

**Role of Immunosuppressive Agents**

Prednisone and the CNI (tacrolimus more than cyclosporine) contribute to glucose intolerance and NODAT (98,109,110). Steroids are a known cause of insulin resistance, and the CNI impair insulin secretion. The tendency for a greater prevalence of diabetes with tacrolimus versus cyclosporine is diminished with steroid-free protocols and with the lower dosages of tacrolimus being used today (25,106,111–114). Although higher dosages of steroids clearly lead to more diabetes, Midvedt et al. (115) could demonstrate no difference in insulin sensitivity between 5 mg of prednisone and a prednisone-free protocol. Sirolimus does not have a marked effect on glucose metabolism, but a decrease in insulin sensitivity has been reported (116), as well as a worsening of glucose tolerance when sirolimus is added to a calcineurin-based protocol (117). Again, caution is advised in considering modifying immunosuppression to improve glucose tolerance because of the risk for rejection.

**Lifestyle Modification for Prevention and Treatment of NODAT**

There is strong evidence in non-RTR that lifestyle modification through weight loss and exercise for overweight individuals can prevent diabetes more dramatically and in a more sustained manner than any pharmacologic agent (118–120). In a recent study of patients with overt diabetes, the combination of weight resistance training and aerobic exercise (30 min three times weekly) was more effective than either alone in leading to a 1% decrease in HbA1c (121). Although there is no direct evidence in RTR, it seems logical to assume that lifestyle modification would play an important role in the treatment and prevention of diabetes in this population as well.

In addition to lifestyle modification, stepwise initiation of oral monotherapy, oral combination therapy, and/or insulin therapy may be required to maintain targets for glycemic control. The choice of initial oral therapy depends on patient characteristics and physician preference, because no RCT are available to compare drug classes in RTR. Recent K/DOQI guidelines (107) addressed drug therapy for diabetes in patients with CKD, which are also appropriate for RTR. The classes of drugs are detailed in Table 6. The risk for hypoglycemia is highest with insulin and insulin secretagogues such as sulfonylureas and is potentiated with renal insufficiency. Thus, drugs that have hepatic clearance are preferred over those that have renal clearance. Meglitinides are reasonable to consider. They also enhance insulin secretion but are less hypoglycemic. In many cases, combination therapy is needed, and it is logical to use drugs that increase both insulin availability and insulin sensitivity.

**Table 6. Classes of drugs used to treat diabetes in RTR (102)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosing Recommendations</th>
<th>Adverse Effects/Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation sulfonylureas</td>
<td>Glipizide</td>
<td>Preferred agent</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride</td>
<td>Begin with low dosage</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>None</td>
<td>Volume retention/edema, CHF</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Repaglinide</td>
<td>Preferred agent</td>
<td>Levels may be increased</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td>Renally cleared; begin with low dosage</td>
<td>with statin/fibrate use</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Not recommended, especially with reduced GFR</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Not recommended with creatinine ≥2.0 mg/dl</td>
<td>Gl distress</td>
</tr>
<tr>
<td>GLP-1 (incretin mimic)</td>
<td>Exenatide</td>
<td>None</td>
<td>No published data on interactions</td>
</tr>
<tr>
<td>DPP-IV inhibitor</td>
<td>Sitagliptin</td>
<td>Reduce dosage: 50% for GFR 30 to 50% 75% for GFR &lt;30</td>
<td>No published data on interactions</td>
</tr>
<tr>
<td>Insulin</td>
<td>Rapid acting: regular, lispro, aspart</td>
<td>None</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Intermediate acting: NPH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long acting: glargine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*DPP-IV, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide-1; NPH, neutral protamine Hagedorn.*
Recent data from nontransplant patients attributed increased incidence of CV-related death to use of one of the thiazolidinediones, rosiglitazone (122). Recently, however, a meta-demonstrated that this is not a class effect, because patients who were taking another thiazolidinedione, pioglitazone, in fact had decreased CV-related events and mortality (123). Although the pioglitazone-treated patients had an increased incidence of heart failure, this did not result in increased mortality. In light of these findings, it seems safe to continue therapy with pioglitazone.

Metformin belongs to the biguanide class of drugs, but its use in renal transplantation has been limited because of its association with lactic acidosis, especially in renal insufficiency and CHF (124). The literature, however, suggests that the incidence of metformin-associated lactic acidosis, even with renal insufficiency, is rare (124). Although this drug is usually avoided in RTR, it may be reasonable to challenge this belief in RTR with preserved renal function.

There are other agents, currently in use and on the horizon, which may also be of use in transplant patients. α-Glucosidase inhibitors reduce hyperglycemia by blocking intestinal uptake of carbohydrates. To date, no interactions with immunosuppressive drugs have been reported, although renal impairment with creatinine ≥2 mg/dl and gastrointestinal adverse effects limit its use. Newer drugs include the glucagon-like peptide-1 receptor agonists such as exenatide (Byetta; Eli Lilly, Indianapolis, IN) and the dipeptidyl peptidase IV inhibitors such sitagliptin (Januvia; Merck, Whitehouse Station, NJ), which may be promising agents for the future.

Insulin therapy is required in up to 40% of RTR (125). The ICG recommend referral to an endocrinologist once this is needed (102), although earlier referral should be considered for all patients who are not achieving target glucose levels. Different preparations of insulin are available, and they are chosen according to desired effect and half-life. Insulin glargine is relatively newer among the agents currently in use, and because it does not reach peak levels in serum, it has the advantage of providing basal insulin coverage.

There is a significant body of evidence from retrospective studies in non-RTR that ACEI and ARB are effective at preventing diabetes (126). Statin drugs improve insulin sensitivity and in studies in non-RTR that ACEI and ARB are effective at preventing diabetes. To date, no interactions with immunosuppressive drugs have been reported, although renal impairment with creatinine ≥2 mg/dl and gastrointestinal adverse effects limit its use. Newer drugs include the glucagon-like peptide-1 receptor agonists such as exenatide (Byetta; Eli Lilly, Indianapolis, IN) and the dipeptidyl peptidase IV inhibitors such sitagliptin (Januvia; Merck, Whitehouse Station, NJ), which may be promising agents for the future.

Insulin therapy is required in up to 40% of RTR (125). The ICG recommend referral to an endocrinologist once this is needed (102), although earlier referral should be considered for all patients who are not achieving target glucose levels. Different preparations of insulin are available, and they are chosen according to desired effect and half-life. Insulin glargine is relatively newer among the agents currently in use, and because it does not reach peak levels in serum, it has the advantage of providing basal insulin coverage.

There is a significant body of evidence from retrospective studies in non-RTR that ACEI and ARB are effective at preventing diabetes (126). In a retrospective study of 300 RTR, Prasad et al. (127) reported a 70% reduction in the incidence of diabetes with statin use. These data suggest additional benefit with the use of these agents in RTR.

Other Risk Factors
Anemia occurs in 20 to 60% of RTR (128) and contributes to left ventricular hypertrophy and CHF (129). Factors that contribute to posttransplantation anemia, such as iron deficiency, erythropoietin deficiency, infections, and drugs (ACEI, ARB, sirolimus, and mycophenolate mofetil), must be evaluated. Preventing worsening of renal function, which increases risk for CVD, must also be addressed in the care of RTR. Further discussion of these factors is beyond the scope of this article.

Considerations for Aspirin Therapy in the Management of CVD
Aspirin therapy has been found to be beneficial after myocardial infarction even in patients who have CKD and may have uremic platelet dysfunction (130). In a single retrospective study in RTR, aspirin therapy was demonstrated by multivariate analysis to be associated with improved allograft function and survival (131). Current guidelines recommend the use of aspirin, 65 to 325 mg/d, for primary and secondary prevention in RTR with ischemic heart disease, diabetes, or other high risk factors for CVD (132). It remains to be proved whether all RTR should take aspirin for CVD prevention. The cardioprotective effect of aspirin is limited mainly by the risk for serious gastrointestinal bleeding, a risk that may be higher in RTR (133). If aspirin is to be used in all RTR, then it would seem prudent to recommend the use of low-dosage aspirin.

Summary of CV Effects of Immunosuppressive Drugs
An overall summary of the effects of immunosuppressive drugs on CVD risk factors is depicted in Table 7. Improvement in diabetes, lipid profile, and hypertension can be expected with steroid reduction and avoidance; however, it may be too early to advocate for the use of steroid-free protocols in all patients to improve CVD risk because the long-term effects on allograft survival remain unknown. It is reasonable to switch a patient from cyclosporine to tacrolimus to improve lipid profile, especially in a patient who is intolerant to statin therapy. Switching patients from tacrolimus to cyclosporine to improve glucose control has been met with mixed results. Despite the poorer glucose tolerance with tacrolimus, it has a better CV risk profile compared with cyclosporine because of improved BP control, lipid profile, kidney function, and long-term graft survival (12,48,134). Eliminating sirolimus because of uncontrolled lipids will improve the hyperlipidemia but may subject the patient to the nephrotoxicity of a CNI if it is initiated or re-

<p>| Table 7. Immunosuppressive drugs and their effect on major CV risk factorsa |
|-----------------------------------------|----------------|----------------|---------------|---------------|----------------|---------------|</p>
<table>
<thead>
<tr>
<th>Effect</th>
<th>Prednisone</th>
<th>CsA</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
<th>MMF, Aza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>←</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Hypertension</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Diabetes</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>←</td>
<td>←</td>
</tr>
</tbody>
</table>

aAza, azathioprine; CsA, cyclosporine; MMF, mycophenolate mofetil.
started. Of course, switching the type or dosage of any immunosuppressive agent can be associated with the risk for acute rejection.

Future Directions

We need immunosuppressive drugs that are equally as potent as current drugs but with less CV risk. Furthermore, we need trials specifically in RTR that address whether interventions to reduce each risk factor leads to a reduction in CV mortality. Future research should also be directed at ways to implement these interventions. The use of more combination drugs should be examined. Such drugs could reduce the pill burden, reduce the insurance copay burden, and improve patient compliance (135). Novel use of medical teams, consisting of nurses, nutritionists, and exercise experts in addition to the physician, to educate the patient and evaluate progress should be explored. Consideration should be given to educating transplant physicians and nurses in the skill of counseling for motivational change because this method of counseling has been shown to be the most successful in effecting changes in patient behavior (136,137). Lastly, it is clear that patients need to become more empowered to assume responsibility for their care and their risks. Practices such as monitoring and recording BP and blood glucose levels at home have long been in place. These functions could be expanded to have the patient carry a CV risk profile data sheet on which the value for each risk factor being measured could be recorded. A member of the transplant team could review the information during clinic visits, thereby encouraging the patients to follow and understand their own progress. Addressing the challenges on all of these levels is needed if true progress is to be achieved.

Conclusions

A summary of factors associated with CV risk and their management is depicted in Figure 2. Although there is good evidence documenting the high incidence of CVD in RTR and the risk factors involved, only one trial (the ALERT study) has addressed whether reduction in these risk factors improves patient or allograft survival; therefore, most recommendations for prevention and treatment are extracted from studies in the CKD and general populations. Individual task forces in the transplant community and K/DOQI offer guidelines for identifying and managing these risks, as detailed in this review. Managing CVD after renal transplantation is a big challenge but one that must be met if allograft survival and patient survival is to improve.

Disclosures

None.

References

10. Meier-Kriesche HU, Baliga R, Kaplan B: Decreased renal


34. Ernst E: St john’s wort supplements endanger the success of organ transplantation. *Arch Surg* 137: 316–319, 2002


41. Jorenby D, Hays JT, Rigotti N, Azoulay S, Watsky E, Williams K, Billing C, Gong J, Reeves K, for the Varenicline Phase 3 Study Group: Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smok-
ing cessation: A randomized controlled trial. JAMA 296: 56–63, 2006
44. Wissing KM, Abramowicz D, Broeders N, Vereerstraeten P: Hypercholesterolemia is associated with increased kidney graft loss caused by chronic rejection in male patients with previous acute rejection. Transplantation 70: 464–472, 2000
69. Puthenparampil JJ, Keough-Ryan T, Kiberd M, Lawen J, Kiberd BA: Treatment of hypercholesterolemia with
enzyme inhibitor or angiotensin II type 1 receptor antagonistic therapy is associated with prolonged patient and graft survival after renal transplantation. J Am Soc Nephrol 17: 889–899, 2006
95. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA 288: 2981–2997, 2002


