CARDIOVASCULAR DISEASE IN KIDNEY TRANSPLANT RECIPIENTS

Bryce A. Kiberd, MD *

ABSTRACT

Cardiovascular disease is a major cause of morbidity and mortality after kidney transplantation. Effective prevention and management of cardiovascular disease in kidney transplant recipients are integral to increasing patient longevity and quality of life, in addition to improving graft survival. This article discusses cardiovascular disease and its management in kidney transplant recipients. The high prevalence of cardiovascular complications in kidney transplant recipients is explained by cardiovascular risk factors present before transplantation, in addition to the development of new risk factors and worsening of pre-existing risk factors after transplantation. Traditional independent risk factors for atherosclerotic cardiovascular disease include cigarette smoking, hypertension, dyslipidemia, male gender, diabetes mellitus, and advancing age. Kidney disease and kidney transplantation introduce additional cardiovascular risks that typically do not operate in the general population. For example, specific immunosuppressive drugs, graft dysfunction, and graft failure increase cardiovascular risk in the kidney transplant recipient. The management of cardiovascular risk in the kidney transplant recipient entails promotion of therapeutic lifestyle practices (eg, healthy diet, exercise, and avoidance of smoking), use of evidence-based pharmacotherapy, and strategies for optimizing provider and patient compliance. These strategies should be implemented before transplantation and should continue throughout the post-transplant course.


Introduction

Kidney transplantation is undertaken to improve the quality and length of life of individuals with end-stage kidney disease. Studies have shown that although transplantation improves life expectancy compared with dialysis, survival remains well below general population estimates. Approximately 50% of patients die with a functioning transplant, with approximately 50% of these deaths from cardiovascular disease or stroke. Cardiovascular mortality in the United States has been determined to be approximately 4.6 deaths per 1000 patient years in the kidney transplant population. Mortality rates from cardiovascular disease during the early perioperative period and much later at the time of graft failure are even higher.

Cardiovascular death rates underestimate the full impact of this disease process given the large number of nonfatal events—including acute myocardial infarction, cardiac arrhythmias, heart failure, and stroke—that impact quality of life. Incident dialysis patients have a high burden of cardiovascular disease before receiving a transplant. Even those patients without overt disease at transplantation often have been exposed for years to cardiovascular risk factors that place them at high risk for covert disease and subsequent events. Effective prevention and management of cardiovascular disease in kidney transplant recipients should begin during the pretransplant period and extend throughout the life of the recipient. This article discusses cardiovascular disease and its management in kidney transplant recipients.

Etiology of Cardiac Disease in Kidney Transplant Recipients

Cardiac disease in kidney transplant patients can be caused by disorders of coronary artery perfusion (ischemic heart disease) or by cardiomyopathy (alter-
ation in ventricular structure and function manifested as asymptomatic left ventricular hypertrophy or congestive heart failure.\textsuperscript{7} Perfusion disorders and cardiomyopathy share risk factors and often develop concurrently in individuals in the general population. Kidney disease poses unique hemodynamic challenges (eg, anemia, hypertension, and volume expansion) that can accelerate ventricular remodeling. Therefore, left ventricular disorders are sometimes observed in the absence of clinically evident ischemic heart disease.\textsuperscript{7}

**RISK FACTORS FOR CARDIOVASCULAR DISEASE IN KIDNEY TRANSPLANT RECIPIENTS**

Most research on risk factors for cardiovascular disease excludes patients with impaired kidney function. Additional research in transplant recipients is necessary before firm conclusions can be drawn about risk factors for cardiovascular disease and the effectiveness of strategies for modifying risk factors in the transplant population. However, data available to date suggest that cardiovascular risk factors established in the general population also operate in kidney transplant recipients.

**TRADITIONAL AND NOVEL RISK FACTORS**

Traditional independent risk factors for atherosclerotic cardiovascular disease include smoking, hypertension, elevated total cholesterol and low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein cholesterol, male gender, diabetes mellitus, and advancing age (Table 1).\textsuperscript{8,9} The problem of diabetes in the kidney transplant recipient is discussed in this monograph by Alan Wilkinson, MD. These same risk factors have been shown to predict subsequent events in the kidney transplant population.\textsuperscript{10}

A growing number of novel and potentially important biomarkers also contribute to the disease process or indicate impaired perfusion or function. For example, inflammatory biomarkers, such as elevated C-reactive protein, may be useful to stratify risk and may respond to intensified therapy.\textsuperscript{11} Table 1 shows a partial list of potential biomarkers. It is still under debate whether these biomarkers are independent and useful predictors of risk, even in the general population.\textsuperscript{12,13}

Predisposing risk factors such as obesity (Table 1) may also increase cardiovascular risk through traditional mechanisms (eg, insulin resistance and hypertension) or may be associated with other biomarkers, including those associated with inflammation.\textsuperscript{14} Cardiovascular risk increases continuously with longer duration, number, and severity of risk factors.\textsuperscript{15}

<table>
<thead>
<tr>
<th>Table 1. Cardiovascular Risk Factors</th>
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<tbody>
<tr>
<td><strong>Major Risk Factors for Coronary Heart Disease in ATP III Guidelines</strong></td>
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<tr>
<td>• Cigarette smoking</td>
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<tr>
<td>• Hypertension (ie, blood pressure &gt;140/90 mm Hg or on antihypertensive medication)</td>
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<tr>
<td>• High LDL cholesterol (ie, &gt;159 mg/dL)</td>
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<tr>
<td>• Low HDL cholesterol (ie, &lt;40 mg/dL)</td>
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<tr>
<td>• Family history of premature coronary heart disease (ie, &lt;55 years of age in male first-degree relative or &lt;65 years of age in female first-degree relative)</td>
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<tr>
<td>• Age (men 45 years and women 55 years)</td>
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<td>• Diabetes</td>
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<table>
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<tr>
<th><strong>Predisposing Risk Factors</strong></th>
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<tbody>
<tr>
<td>• Obesity (ie, body mass index &gt;30 kg/m²)</td>
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<tr>
<td>• Abdominal obesity (ie, waist circumference &gt;102 cm, or 40 in, for men and &gt;88 cm, or 35 in, for women)</td>
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<td>• Physical inactivity</td>
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<tr>
<td>• Family history of premature coronary heart disease</td>
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<tr>
<td>• Ethnic characteristics</td>
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<td>• Psychosocial factors</td>
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<table>
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<tr>
<th><strong>Nontraditional Biomarkers</strong></th>
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<tr>
<td>• Elevated serum triglycerides</td>
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<td>• Small LDL particles</td>
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<tr>
<td>• Elevated serum homocysteine</td>
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<tr>
<td>• Elevated serum lipoprotein(a)</td>
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<tr>
<td>• Prothrombotic factors (eg, fibrinogen)</td>
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<td>• Inflammatory markers (eg, C-reactive protein, IL-6, CMV)</td>
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<tr>
<td>• B-type natriuretic peptide/N-terminal pro-atrial natriuretic peptide,</td>
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<td>• Aldosterone</td>
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<table>
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<tr>
<th><strong>Risk Factors Associated with Kidney Disease or Transplant</strong></th>
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<tr>
<td>• Immunosuppressive agents</td>
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<td>• Graft failure</td>
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<tr>
<td>• Graft dysfunction (elevated homocysteinemia, proteinuria, predisposition to vascular calcification)</td>
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<tr>
<td>• Anemia</td>
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ATP = Adult Treatment Panel; CMV = cytomegalovirus; HDL = high-density lipoprotein; IL-6 = interleukin-6; LDL = low-density lipoprotein.

Data from Grundy et al\textsuperscript{10}; Ojo.\textsuperscript{14}
**Risk Factors Associated with Kidney Disease or Transplantation**

Kidney disease and kidney transplantation also introduce cardiovascular risks that typically do not operate in the general population (Table 1).16

**Immunosuppressive Drugs**

Specific immunosuppressive drugs used to prevent graft rejection affect cardiovascular risk in the kidney transplant recipient.2,3,4 The main immunosuppressive therapies used in kidney transplant recipients include corticosteroids, calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, the immunosuppressive antimitabolite azathioprine, the inosine monophosphate dehydrogenase inhibitor mycophenolate mofetil, and depleting and nondepleting antilymphocyte antibodies. Immunosuppressive therapies may increase cardiovascular risk partly through direct vascular effects, but their predominant effect is likely the exacerbation of other risk factors.7 The effects of immunosuppressive agents on traditional cardiovascular risk factors vary from drug to drug, even within a class of medication (eg, calcineurin inhibitors).

Corticosteroids and cyclosporine increase the risk of hyperlipidemia, hypertension, and diabetes mellitus.17,18 The calcineurin inhibitor tacrolimus seems to have little effect on blood pressure or blood lipids, but is associated with more diabetes mellitus post-transplantation than cyclosporine.7,19 An association between tacrolimus and post-transplantation diabetes was observed in a meta-analysis of 16 randomized studies on the incidence of diabetes in recipients of kidney, liver, or heart transplants.19 New-onset diabetes after transplantation was reported in 13.4% of patients. The incidence of new-onset diabetes was significantly higher with tacrolimus (9.8%) than cyclosporine (2.7%) among recipients of kidney transplants. mTOR inhibitors have been associated with hyperlipidemia. An association between sirolimus and hyperlipidemia was demonstrated by results of an open-label study conducted at 11 European centers.20

Hypercholesterolemia and hypertriglyceridemia were observed more frequently during the initial months after kidney transplantation in patients receiving corticosteroids, azathioprine, and sirolimus than in patients receiving corticosteroids, azathioprine, and cyclosporine. However, everolimus has been associated with less coronary artery disease in cardiac transplant recipients. This observation suggests that an overall protective vascular effect might occur despite worsening hyperlipidemia.21

In addition to exacerbating traditional risk factors, immunosuppressive therapy may be associated with other mechanisms that increase or even decrease cardiovascular risk. Azathioprine and mycophenolate mofetil have little effect on blood pressure or blood lipids. However, they can induce anemia, which can contribute to development of left ventricular hypertrophy.22 The association of depleting antilymphocyte antibody induction with higher cardiovascular death may be the result of confounding factors, the consequence of unknown direct or indirect cardiovascular effects.23 Most of the above medications increase the risk of cytomegalovirus (CMV) infections. Active CMV has been associated with increased cardiovascular events in the kidney transplant patient, and multiple infections have been implicated in the development of atherosclerosis.24 Conversely, one recent study reported lower C-reactive protein levels in kidney transplant patients treated with mycophenolate mofetil compared with those not on this medication, a finding suggesting a potential beneficial effect.25

**Graft Rejection**

Acute graft rejection also appears to be a cardiovascular risk factor in kidney transplant recipients. Post-transplant cardiovascular risk is directly related to the number of acute rejection episodes.26,27 The use of high doses of corticosteroids to manage acute graft rejection possibly accounts for this relationship. Poor kidney function from rejection also places the patient at risk for later graft failure and a return to dialysis. The return to dialysis is associated with a marked increase in mortality.5

**Graft Dysfunction**

Graft dysfunction can also increase cardiovascular risk. In the general population, poor kidney function is an independent risk factor for poor cardiovascular outcomes.28 Epidemiologic risk factors for cardiovascular disease and kidney disease are closely linked. For example, hypertension, a traditional risk factor, may result from poor graft function and may be associated with subsequent graft loss and cardiovascular death in the kidney transplant population.29,30 In one study, every 10-mm Hg increase in systolic blood pressure increased the risk of graft loss by 12% and death by 18%.31 In kidney transplant recipients, baseline kidney
allograft function as measured by serum creatinine was significantly associated with major cardiac adverse events, cardiac death, and all-cause mortality in patients receiving placebo in the randomized, double-blind, placebo-controlled Assessment of Lescol in Renal Transplantation (ALERT) study. The quartile of patients with a serum creatinine higher than 167 µmol/L (1.9 mg/dL) was at the greatest risk (Table 2). Proteinuria has been implicated as a risk factor for cardiovascular death and graft loss in kidney transplant recipients. Proteinuria is likely a marker for the presence of overt atherosclerotic burden, in addition to a marker and pathogenic mechanism for progressive kidney disease. In an analysis of data from 3365 kidney transplant recipients in the Spanish Chronic Allograft Nephropathy Study, approximately 15% of patients had post-transplantation proteinuria (>0.5 g/day). The main cause of death was vascular disease regardless of whether patients were proteinuric. However, proteinuric patients were particularly likely to die of vascular disease. The relative risk of death in proteinuric patients compared with nonproteinuric patients was 2.05 times higher at 0.5 to 1 g per day and 2.3 times higher at greater than 1 g per day. Even smaller degrees of proteinuria may be quite common and predictive of adverse events in patients with a functioning transplant. A recent European study found that microalbuminuria (30–299 mg/day) was present in approximately 40% of kidney transplant recipients in the program and was associated with marked increase in graft loss and patient death.

Likewise, graft dysfunction elevates the risk of hyperhomocysteinemia, which is implicated as a cardiovascular risk factor in the general population and in kidney transplant recipients. Homocysteine, an amino acid, can become elevated in the presence of insufficient amounts of folate, vitamin B12, and vitamin B6, which transform homocysteine to methionine and cysteine. Homocysteinemia is thought to increase cardiovascular risk by contributing to the development of atherosclerosis. In a study of 207 stable kidney transplant recipients followed for an average of 21.2 months, elevated fasting total homocysteine concentration was a strong, independent predictor of cardiovascular disease events including death. Risk of a cardiovascular event increased 6% for each µmol/L increase in homocysteine concentration.

One of the more interesting mechanisms of cardiovascular disease associated with reduced kidney dysfunction is vascular calcification. Among several proposed mechanisms, the association with elevated serum phosphorous is most intriguing. Poor kidney function limits the ability to excrete dietary phosphorous. Subsequent hyperphosphatemia acts as a signaling molecule with the ability to initiate phenotypic change in vascular smooth muscle cells to become osteoblast-like cells that can secrete and calcify matrix. Vascular calcification is associated with cardiac mortality in

<table>
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<tr>
<th>Table 2. Incidence of Endpoints Among 1052 Kidney Transplant Patients Treated with Placebo in the ALERT Study</th>
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<tr>
<td>Serum creatinine, µmol/L (mg/dL)</td>
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<tr>
<td>&lt;111</td>
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<tr>
<td>(1.26)</td>
</tr>
<tr>
<td>Major cardiac adverse event, % patients</td>
</tr>
<tr>
<td>Cardiac death, % patients</td>
</tr>
<tr>
<td>Noncardiovascular death, % patients</td>
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<tr>
<td>All-cause mortality, % patients</td>
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ALERT = Assessment of Lescol in Renal Transplantation.
Adapted with permission from Fellström et al. Transplantation. 2005;79:1160-1163.
patients with kidney dysfunction and may explain the unaccounted gap between observed and predicted events based on traditional risk factors alone.36

**ANEMIA**

Kidney dysfunction and some immunosuppressive therapies can cause anemia, which is associated with development of left ventricular hypertrophy—a risk factor for death and cardiovascular disease in the general population and in kidney dialysis patients. The relationship between anemia and left ventricular hypertrophy in kidney transplant recipients is demonstrated by a retrospective study in which left ventricular hypertrophy was defined using the Cornell electrocardiographic criteria.39 Anemia and diastolic blood pressure were independent risk factors for left ventricular mass between the first and fifth years after kidney transplantation.

With a prevalence of more than 30% in the kidney transplant population, anemia is a common complication of kidney transplantation and occurs out of proportion to the degree of kidney impairment.38,40,41 The multiple causes of anemia during the immediate and later post-transplant course include blood loss, low iron stores, medications (antiproliferative agents and angiotensin-converting enzyme [ACE] inhibitors), inflammation, and infections.42 Anemia in kidney transplant recipients is associated with increased mortality.43,44 Anemia is also an independent risk factor for death after an ischemic cardiovascular event in the general population.44

**MANAGEMENT OF CARDIOVASCULAR DISEASE IN THE KIDNEY TRANSPLANT RECIPIENT**

Strategies for management of cardiovascular disease have seldom been studied specifically in kidney transplant recipients. Although additional research is needed before firm conclusions can be drawn about the effectiveness of strategies for modifying risk factors in the kidney transplant population, data available to date suggest that management strategies established as effective in the general population can also be effective in kidney transplant recipients.

Control of risk factors through lifestyle changes or pharmacotherapy reduces the incidence of adverse cardiovascular outcomes, including myocardial infarction, stroke, heart failure, and death in the general population.45,46 For example, a 5-mm Hg decrease in blood pressure reduces the risk of myocardial infarction by 10% to 15%, and a 10% reduction in LDL-cholesterol reduces the risks of cardiovascular death by 10% and cardiovascular events by 25%. Benefits of risk-factor modification accrue in patients with established cardiovascular disease and in individuals without a history of cardiovascular events. Intervention aimed at multiple risk factors relative to a single risk factor confers synergistic benefits with respect to disease severity and clinical outcome. Therefore, cardiovascular risk factors should be assessed regularly, and intervention should target multiple factors.

The impact of this strategy is not inconsequential. In a medical decision analysis, modest reductions in blood pressure and hyperlipidemia with pharmacologic therapy in high-risk transplant recipients (diabetes mellitus, positive history of cardiovascular disease, or age >45) to the degree noted above was predicted to be very cost effective (<$25 000 per quality-adjusted life-year) and also predicted increases in patient survival and graft survival by as much as 2.0 and 1.7 years, respectively.39 Lower-risk patients also benefited, although the costs per benefit were higher and improvement in outcomes less. This study also examined the impact of reducing immunosuppressive therapies that were associated with increases in cardiovascular risk factors. Although this approach appeared promising, small increases in rejection rates could neutralize any benefit, especially in patients at low cardiovascular risk.

**LIFESTYLE MODIFICATION**

Lifestyle changes—including a healthy diet, weight reduction, exercise, and smoking cessation—can markedly influence many risk factors and remain the cornerstone of risk-factor modification. Therapeutic lifestyle changes aimed at controlling body weight can be particularly important: on average, kidney transplant recipients gain 22 to 30 pounds during the first year after transplantation.46 Smoking cessation is an area in which a dedicated clinic staff could have a significant impact. Smoking remains relatively prevalent (20%–25%) in the transplant population. Depending on the amount smoked, smokers are at a 30% higher risk of graft loss and 50% to 100% greater risk of a cardiovascular event. Many of the negative health effects of smoking dissipate after quitting for more than 5 years.47 Combined counseling and pharmacologic therapy appear to be superior to either strategy alone in the general population.48
MANAGING DYSLIPIDEMIA

Strategies for managing dyslipidemia in kidney transplant recipients include dietary modification, tailoring of the immunosuppressive regimen to minimize adverse blood-lipid effects, and administration of lipid-modifying agents, including statins, fibrates, and niacin. Bile acid sequestrants have also been used, although they can interfere with absorption of immunosuppressive agents. The National Kidney Foundation Working Group has issued recommendations on management of dyslipidemia in adult kidney transplant recipients (Table 3). These recommendations, consistent with the National Heart, Lung, and Blood Institute’s Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines, employ a treat-to-target approach. The recommendations specify that kidney transplant recipients should be considered a high-risk group with respect to lipid-lowering therapy and treatment goals.

Statin therapy, a foundation of management of dyslipidemia in kidney transplant recipients and in the general population, improved cardiovascular outcomes in kidney transplant recipients in the ALERT study. This randomized, double-blind, placebo-controlled trial followed kidney transplant recipients having baseline total cholesterol of 4.0 to 9.0 μmol/L (154.4–347.5 mg/dL). After a mean follow-up period of 5.1 years, LDL cholesterol concentrations were reduced by 32% in fluvastatin-treated patients (n = 1050) compared with placebo-treated patients (n = 1052). Fluvastatin compared with placebo statistically significantly reduced the risk of cardiac death or nonfatal myocardial infarction by 35%. However, the difference between fluvastatin and placebo was not statistically significant for the primary endpoint of a major cardiac adverse event, defined as cardiac death, nonfatal myocardial infarction, or coronary intervention procedure.

All patients who enrolled in the ALERT study were offered the option to receive open-label fluvastatin in a 2-year extension (n = 1652) of the double-blind trial. In patients who received fluvastatin during double-blind therapy, the percentage of patients who died or had myocardial infarction was reduced by 34% compared with placebo. This is consistent with previous studies showing the benefit of statin therapy in the general population.

### Table 3. Management of Dyslipidemia in Adult Kidney Transplant Recipients: National Kidney Foundation Working Group Guidelines

<table>
<thead>
<tr>
<th>Dyslipidemia</th>
<th>Goal</th>
<th>Initiate</th>
<th>Increase</th>
<th>Alternative</th>
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<tbody>
<tr>
<td>Triglycerides 500 mg/dL</td>
<td>Triglycerides &lt;500 mg/dL</td>
<td>Therapeutic lifestyle changes</td>
<td>Therapeutic lifestyle changes + fibrate or niacin</td>
<td>Fibrate or niacin</td>
</tr>
<tr>
<td>LDL 100–129 mg/dL</td>
<td>LDL &lt;100 mg/dL</td>
<td>Therapeutic lifestyle changes</td>
<td>Therapeutic lifestyle changes + low-dose statin</td>
<td>Bile acid sequestrant or niacin</td>
</tr>
<tr>
<td>LDL 130 mg/dL</td>
<td>LDL &lt;100 mg/dL</td>
<td>Therapeutic lifestyle changes</td>
<td>Therapeutic lifestyle changes + maximum-dose statin</td>
<td>Bile acid sequestrant or niacin</td>
</tr>
<tr>
<td>Triglycerides 200 mg/dL and non-HDL 130 mg/dL</td>
<td>Non-HDL &lt;130 mg/dL</td>
<td>Therapeutic lifestyle changes + low-dose statin</td>
<td>Therapeutic lifestyle changes + maximum-dose statin</td>
<td>Fibrate or niacin</td>
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HDL = high-density lipoprotein; LDL = low-density lipoprotein.
blind and open-label treatment periods compared with patients who were originally randomized to placebo, the risk of a major adverse cardiac event was reduced by 21%, and the risk of a cardiac death or definite nonfatal myocardial infarction was reduced by 29%. No differences between groups were observed for total mortality or incidence of graft loss. The authors concluded that the effects of fluvastatin in kidney transplant recipients are similar to those in other patient populations.\(^{60,61}\)

Since the National Kidney Foundation guidelines were written, even lower LDL targets (<80 mg/dL) have been advocated in higher-risk patients. High-dose atorvastatin (mean LDL 72.6 mg/mL) was associated with 30% fewer cardiovascular events compared with a lower dose (mean LDL 99.3 mg/dL) in a large study of high-risk patients.\(^{62}\) In addition, other therapies, including the cholesterol absorption inhibitor ezetimibe, may be used to achieve LDL targets.\(^{63}\) However, more information is needed before these approaches can be recommended in the kidney transplant population because drug interactions with calcineurin inhibitors may increase toxicity.

**MANAGING HYPERTENSION**

Strategies for managing hypertension, which affects an estimated 75% to 90% of kidney transplant recipients, include dietary modification, tailoring of the immunosuppressive regimen to minimize exposure, and administration of antihypertensive agents.\(^{16}\) The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines recommend a target of less than 130/80 mm Hg in patients with kidney disease as defined by an estimated glomerular filtration rate of less than 60 mL/min/1.73 m\(^2\) or the presence of albuminuria (>300 mg/d or 200 mg/g creatinine).\(^{64}\) A similar target is recommended for patients with diabetes mellitus. Most kidney transplant patients would fit under these special categories (presence of diabetes mellitus, proteinuria, or low glomerular filtration rate). In fact, the JNC 7 guidelines include kidney transplant recipients as a special population with a recommended blood pressure of less than 130/80 mm Hg.

Pharmacotherapies for managing hypertension in kidney transplant recipients include calcium channel antagonists, ACE inhibitors, angiotensin type II receptor antagonists, α blockers and β blockers, and diuretics. One class cannot be recommended over the others on the basis of the scant data available to date in the kidney transplant population. Calcium channel antagonists may be beneficial in counteracting arterial constriction caused by calcineurin inhibitors, and they potentially reduce calcineurin-inhibitor–associated nephrotoxicity.\(^5\) However, dihydropyridine calcium channel antagonists were associated with increased mortality in one study.\(^10\) ACE inhibitors and angiotensin type II receptor antagonists reduce proteinuria, in addition to reducing blood pressure in kidney transplant recipients.\(^16\) The additional benefits of these agents beyond their antihypertensive effect in kidney transplantation is yet to be defined.

Two large cohort studies differed in their conclusions on the benefits of these agents.\(^{65,66}\) A randomized, controlled trial is needed to determine whether there is added benefit. Given the likelihood of resistant hypertension from kidney dysfunction, obesity, older age, immunosuppressive agents, and diabetes mellitus in this population, several agents are required. For those with resistant hypertension, combining medications of different classes and with different mechanisms of action, including the use of diuretics, is likely required.\(^67\) One of the limitations of achieving cardiovascular risk reduction targets for hypertension and hyperlipidemia is the willingness of physicians to prescribe therapy.\(^68\) Clinical inertia (failure to add or intensify therapy) is probably an important problem in the kidney transplant population as it is in the general population.\(^69\)

**MANAGING DIABETES**

Strategies for managing post-transplant diabetes include judicious selection of immunosuppressive therapy, maintenance of a healthy body weight, regular physical activity, and pharmacologic and nonpharmacologic control of glycemia, hypertension, and dyslipidemia.

**BIOMARKER MANAGEMENT**

The benefit of therapy directed at biomarkers or other risk factors associated with cardiovascular risk is still unproven. Examples include specific treatment of proteinuria with ACE inhibitors, prevention of CMV infection with antiviral medication, treatment of anemia, reduction of C-reactive peptide with statins,
treatment of hyperphosphatemia in patients with poor graft function, and correction of homocysteinemia with folic acid and/or pyridoxine (vitamin B<sub>6</sub>). In a trial of 29 stable kidney transplant recipients, folic acid (5 mg/day) plus vitamin B<sub>6</sub> (0.4 mg/day) was associated with a 26.2% reduction versus placebo in fasting plasma total homocysteine concentrations. However, a small, randomized trial of cardiac transplant recipients showed no benefit of lowering homocysteinemia in the prevention of vasculopathy. But, studies of this size are underpowered to detect clinically relevant benefits and should not dissuade further study. A large trial in kidney transplant recipients is well under way. Until results of trials in the kidney transplant population are available, specific guidelines for treatment of anemia and hyperphosphatemia exist in the predialysis chronic kidney disease population and likely apply to the kidney transplant population. Adequate blood pressure and lipid control often requires ACE inhibitors and statin therapy. CMV infection prophylaxis in the early transplant period is becoming the more accepted practice.

**ASPIRIN**

Aspirin and other antiplatelet agents are important in the prevention of major cardiovascular events in high-risk patients in the general population. In a large meta-analysis of 287 studies involving 135,000 patients, absolute reductions in the risk of a serious vascular event were 36 per 1000 treated for 2 years among patients with previous myocardial infarction, 36 per 1000 treated for 2 years among those with previous stroke or transient ischemic attack, and 22 per 1000 treated for 2 years among other high-risk patients (including stable angina, peripheral arterial disease, and atrial fibrillation). In each of these categories, the absolute benefits substantially outweighed the absolute risks of major bleeding. Less is known about the benefits of aspirin in the kidney transplant population. To date, there is very little evidence of harm but some cohort evidence of benefit with less graft loss and death.

**CONCLUSIONS**

Kidney transplant recipients are at extremely high risk of adverse cardiovascular outcomes. Improvements in long-term outcomes after kidney transplantation depend on effective prevention and control of cardiovascular disease. The management of cardiovascular risk in the kidney transplant recipient includes preventive strategies such as promotion of therapeutic lifestyle practices (eg, healthy diet, exercise, and avoidance of smoking), evidence-based use of pharmacotherapy, and development of strategies for optimizing provider and patient compliance. Because of a paucity of research conducted on cardiovascular risk and risk management in kidney transplant recipients, cardiovascular assessment and treatment in this population are largely based on data from the general population. More research in kidney transplant recipients is warranted to better tailor risk evaluation and therapeutic approaches to the characteristics and needs of this patient population.

**REFERENCES**

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