

NEPHROLOGY

Rounds®

Cardiovascular Risk In Adult Kidney Transplant Patients

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More than 140,000 patients are living with a functioning kidney transplant in the United States. Although kidney transplantation confers relatively longer survival compared with any of the dialysis modalities, the life expectancy of kidney transplant recipients (KTRs) remains lower than that of the age- and sex-matched general population.¹ Cardiovascular (CV) disease is the single leading cause of death in KTRs and the majority of functioning transplants are lost due to the recipient's death. Thus, primary prevention, early detection, and secondary prevention of CV disease in KTRs could be instrumental in further improving the outcomes of these patients. This issue of *Nephrology Rounds* reviews the evidence on individual CV risk factors and potential treatment interventions in KTRs.

While determinants of CV risk in the general population have been studied for several decades, predominantly with the use of large prospective studies such as the Framingham Study cohort, the importance of impaired kidney function as a CV risk factor has only recently been recognized.² Further, the best prevention and treatment for the CV epidemic in patients with advanced kidney disease remains unclear. The evidence supporting standards of CV prevention and care in the general population has been derived from randomized controlled trials that systematically excluded patients with advanced chronic kidney disease (CKD), including KTRs. While some physicians have proposed that KTRs are similar to patients with CKD, there are at least 3 important reasons why this may not be the case: the presence of immunosuppressant therapy, the altered inflammatory milieu, and the past history of prolonged maintenance dialysis therapy in most KTRs.

Estimating cardiovascular risk in kidney transplant patients

Wilson and colleagues used the Framingham Study cohort to establish a formula that gives a reliable estimation of a person's future risk of CV disease.³ In its original form, the estimation equation incorporated information on age, gender, blood pressure (BP), total-cholesterol, low-density lipoprotein (LDL)-cholesterol, diabetes, and smoking history. Kasiske and colleagues used this formula to estimate CV risk in 1,124 KTRs and compared the estimate with event rates that were actually observed in that cohort.⁴ Figure 1 impressively illustrates that the Framingham risk score underestimates CV risk in these patients. Only younger patients, who lacked other major CV risk factors, had observed rates of events that matched the calculated expectation.⁴ This landmark observation raises several important questions: Is the risk associated with some of the established factors amplified in KTRs? Is the excess CV mortality attributable to a greater prevalence of certain novel CV risk factors that are not included in the Framingham risk score (eg, C-reactive protein [CRP], homocysteine, or anemia)? Finally, are there other risk factors involved that are specific to kidney transplantation, such as disturbances in calcium-phosphorus metabolism, certain immunosuppressive drugs, and the altered inflammatory milieu? The following discussion explores these questions.

Traditional cardiovascular risk factors

As mentioned above, Kasiske et al compared the relative risk associated with the Framingham risk score factors in the general population and a cohort of KTRs.⁴ Technically, most associations were nonsignificant, but with a simple examination of the best estimates of association, they found that age, gender, BP, and cholesterol levels appeared to have similar associations with CV risk. In contrast, the risk from smoking and diabetes was considerably greater in KTRs compared with the general population. In the general population, diabetes increased the risk by 1.5 in men and 1.8 in women; in KTRs, the corresponding relative risks were 2.8 and 5.4, respectively. Similarly, smoking conferred a 70% greater CV risk in men, but smoking

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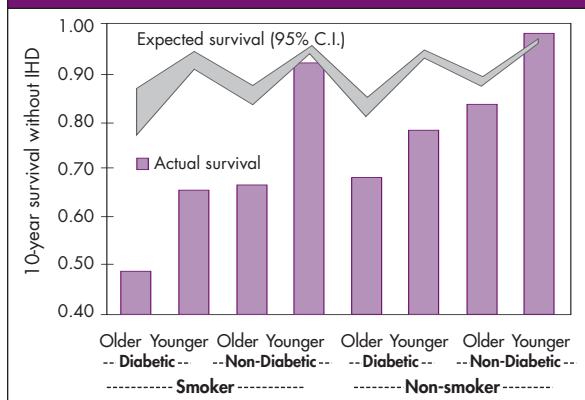
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Figure 1: Observed and expected risks for ischemic heart disease (IHD) after renal transplantation.⁴



The vertical bars indicate actuarial survival free of IHD after 10-yr of follow-up monitoring (11 yrs after renal transplantation). The shaded areas above the vertical bars are 95% confidence intervals (CI) for the calculated 10-yr IHD risk from the Framingham Heart Study. With permission from LWW.⁴

doubled the risk in male KTRs (risk increased by 100%). For women, the corresponding numbers were 30% (general population) and 80% (KTRs), respectively.⁴

What interventions do we have in our repertoire to modify the CV risk derived from these traditional factors? Age and gender are clearly nonmodifiable and, certainly, no further evidence is needed to support the huge importance of smoking cessation counseling in any patient, especially KTRs, who are at substantially increased CV risk from smoking.⁵

The spectrum of diabetes mellitus

The importance of tight glycemic control has been impressively demonstrated in the Dialysis Complications and Control Trial.⁶ Although conducted in patients with type 1 diabetes, this trial has clear implications for the care of patients with type 2 diabetes. While adequate control and monitoring of KTRs with preexisting diabetes are clearly relevant, prevention of a new occurrence of diabetes after kidney transplantation appears even more important. New-onset diabetes after transplantation (NODAT) may affect as many as 25% of patients within 3 years of transplantation;⁷ therefore, it has become an important concern in the transplant population. NODAT appears predominantly related to 2 distinct factors: weight gain after transplantation and use of immunosuppressive drugs that impair glucose tolerance (eg, corticosteroids or tacrolimus). Hjelmsaeth and colleagues prospectively studied 201 consecutive KTRs for 3 months after transplantation and examined the association between the absence of diabetes, diabetes at transplantation, and NODAT and the risk of cardiac events.⁸ They found that patients with pretransplant diabetes experienced 5 times the mortality of patients who were free from diabetes, but patients with NODAT also experienced a 3-fold increase in the rate of major cardiac events.⁸ Cosio and colleagues further refined this observation by studying 490 patients who were free from diabetes at transplantation and stratifying them by the presence of posttransplant impaired glucose tolerance or overt NODAT.⁹ They found that there was a steady increase in CV risk with increasing fasting glucose impairment and the

risk was greatest in patients who developed posttransplant overt diabetes mellitus.⁹ Thus, even early indicators of impaired glucose tolerance are important risk factors of future CV risk and should be treated seriously. The risk of NODAT, particularly, is driven by the use of corticosteroids as part of the immunosuppressant regimen. As a result, efforts to reduce corticosteroid dosages or eliminate these medications altogether have been implemented. Indeed, prednisone withdrawal had a favorable effect on glucose tolerance.¹⁰ Numerous projects are currently underway to better define the relationship between immunosuppressant choice and patterns of CV risk factors, including NODAT, but long-term studies are needed to define the actual benefits of specific regimens in terms of reduced CV risks.

Dyslipidemias

Disturbances in lipoprotein patterns are common in KTRs and it is speculated that dyslipidemias may contribute to the increased mortality and CV risk in these patients. However, studies evaluating these associations have demonstrated heterogeneous results. Roodnat studied 676 prevalent KTRs with a functioning graft at 1 year and found that higher serum cholesterol levels were associated with greater all-cause mortality.¹¹ Booth et al described a similar association between pretransplant total cholesterol concentrations and mortality.¹² In contrast, Cardinal and colleagues found no associations between pretransplant cholesterol or triglyceride concentrations and patient survival in elderly KTRs in Quebec.¹³ Finally, the aforementioned study by Kasiske et al and another study of 730 KTRs in Austria detected no significant associations between total cholesterol, high-density lipoprotein (HDL)-, or LDL-cholesterol and all-cause mortality in prevalent KTRs.^{4,14} Fortunately, a large, randomized trial of lipid-lowering therapy in a KTR population — the Assessment of LEscol in Renal Transplantation (ALERT) trial — was conducted to settle this issue.¹⁵ In several European centers, 2,102 KTRs with total cholesterol concentrations between 4–9 mmol/L were recruited and randomly allocated to receiving 40 mg of fluvastatin or placebo. Patients were followed for >5 years to the occurrence of major adverse cardiac events (primary endpoint was the earliest of cardiac death, non-fatal myocardial infarction [MI], or coronary revascularization procedure). Unfortunately, the trial failed to detect a difference between the randomized treatment and the primary study endpoint ($p=0.13$).¹⁵ Secondary analyses, however, revealed significant reductions in the rates of cardiac death ($p=0.03$), definite MI ($p=0.05$), and the combination of these ($p=0.005$), while there was no effect on the rate of coronary revascularization. Due to the ambiguity of the study results, enrolled patients were offered to continue the study and patients in both randomization groups were offered open-label fluvastatin, 80 mg.¹⁶ The results from this ALERT Extension study were finally significant; after 6.7 years of follow-up, on average, patients originally randomized to fluvastatin experienced a 21% reduction in the risk of the primary study endpoint compared with those in the original placebo arm ($p=0.036$).¹⁶

While ALERT established the efficacy of fluvastatin treatment for the reduction of CV risk in KTRs, several important questions remain. Is there a class effect among statins? Should statins be used for secondary prevention only, or rather, for all patients independent of their history

Table 1: Recommended daily statin dose ranges¹⁸

Statin	Level of glomerular filtration rate (in mL/min/1.73m ²)		
	≥30	<30 or dialysis	With cyclosporine
Atorvastatin	10-80 mg	10-80 mg	10-40 mg
Fluvastatin	20-80 mg	10-40 mg	10-40 mg
Lovastatin	20-80 mg	10-40 mg	10-40 mg
Pravastatin	20-40 mg	20-40 mg	20-40 mg
Simvastatin	20-80 mg	10-40 mg	10-40 mg

of CV events? What should be the lipoprotein targets? Most of these questions remain unanswered.

The assumption of a statin class effect regarding efficacy seems reasonable; however, statins do differ with regard to their safety, especially when considering drug-drug interactions with certain immunosuppressant medications. Statins that are metabolized by cytochrome P450 (CYP) 3A4, ie, lovastatin, simvastatin, and atorvastatin (but not fluvastatin and pravastatin), may be subject to decreased metabolism in the presence of calcineurin inhibitors.¹⁷ The ALERT trial demonstrated the exquisite safety profile of fluvastatin specifically in KTRs;¹⁵ as a result, it is suggested that fluvastatin be regarded the standard statin in this specific population, or at least in those KTRs whose immunosuppression includes a calcineurin inhibitor. Clinical guidelines recommend that all KTRs be treated to reach an LDL-cholesterol concentration < 100 mg/dL, and no differentiation is made regarding primary or secondary prevention.¹⁸ It is also recommended that statin dosages be reduced in KTRs whose estimated glomerular filtration rate (GFR) is <30 or if cyclosporine is part of the concurrent regimen. These dosing recommendations are summarized in Table 1.¹⁸

Blood pressure

Elevated BP is an important CV risk factor in the general population and this relationship appears to hold in the kidney transplant population as well. Mean arterial pressure seems to be the most meaningful measurement and has shown an association with greater CV risk in KTRs; for each 10 mm Hg increase in mean arterial BP, the CV risk increased by 25%.¹⁹ In addition, greater pulse pressure (defined as the difference between systolic and diastolic BP) carries an independent direct association with all-cause mortality.^{19,20} Several studies have highlighted that as many as half of prevalent KTRs have a BP that exceeds 140 mm Hg systolic and/or 90 mm Hg diastolic, despite prescriptions for at least 2 different BP medications.¹⁹ This is an even greater concern, since these patients are considered at particular risk and the 7th Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a target BP in patients with kidney disease (presumably including transplant recipients) of ≤ 130/80 mm Hg.²¹ This discrepancy highlights the considerable efforts that are necessary to improve BP control in KTRs to recommended targets. After all, elevated BP does not only increase these patients' CV risk, but it also greatly jeopardizes the function of their kidney allograft.^{19,22} The question of whether certain classes

of antihypertensives are preferred in KTRs remains unresolved. Specifically, the question whether angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) should be preferentially used in these patients has been rather hotly debated. Heinze et al studied all incident KTRs at the University of Vienna over more than a decade and ascertained medication use from the claims files of Austrian sickness funds. Using several analytical approaches, they found that use of ACEIs or ARBs was associated with a substantial decrease of approximately 43% in mortality risk. More recently, Opelz et al used a large registry of KTRs whose medications were determined by facility questionnaires and they failed to detect a difference in mortality between users and nonusers of these drugs. Both studies have certain methodological shortcomings that make a definitive assessment of the benefits of ACEIs and ARBs in these patients difficult, especially since ACEIs and ARBs may behave differently in KTRs due to the denervated state of the transplanted kidney. Although a randomized trial would be highly desirable to settle this issue, I am personally skeptical that it will ever be conducted. Perhaps more important than the specific choice of antihypertensive is the particular attention that we practitioners need to direct towards educating our patients about the risks associated with suboptimal control of BP and investigating our patients' adherence to prescribed regimens at every single encounter.

Obesity

While obesity is an important CV risk factor in the general population, the relationship between body mass index (BMI) and several outcomes, including CV events, is U-shaped in KTRs; ie, both underweight and obese patients experience greater CV event rates compared to those with normal BMI.²³ Since high BMI is correlated with diabetes, high BP and plasma lipids,²⁴ some, but not all of the excess risk in obese patients is likely attributable to the unfavorable patterns of these and other risk factors. Although dietary intervention has been shown to reduce the extent of the typical posttransplant weight gain,²⁵ I am unaware of any lifestyle intervention studies that demonstrate definitive reductions of long-term CV risk in KTRs.

Novel cardiovascular risk factors

In recent years, several additional CV risk factors have been proposed and tested. The following section will consider those supported by the best evidence and appearing to have the greatest clinical relevance: kidney function, C-reactive protein, homocysteine, and anemia.

Kidney (transplant) function

Only very recently was kidney function recognized as an important determinant of CV outcomes in the general population² and, as well, for prognosis after CV events.²⁶ In KTRs, recent work confirmed that reduced transplant function was also associated with the risk of MI and CV death in the ALERT study cohort.²⁷ Using the overall US transplant population, Meier-Kriesche et al demonstrated that the risk of CV death increased with decreasing transplant function; for example, compared to KTRs who had a serum creatinine of ≤1.2 mg/dL at 1-year after transplantation, those with a creatinine of 1.5 to 1.69 had a 19%

increased CV risk, and a creatinine level between 2.6 and 4.0 mg/dL conferred greater than twice the risk (2.26).²⁸ In otherwise similar patients, those patients who lost their allograft had an even more pronounced CV risk compared with those whose graft retained its function.²⁷ These data underscore, once again, the paramount importance of maintaining graft function in regard to other patient outcomes.

C-reactive protein

C-reactive protein (CRP) is an acute phase protein that has long been used for the detection and monitoring of infectious or inflammatory diseases and disorders. More recently, through the pivotal work of Paul Ridker and his colleagues at Brigham and Women's Hospital (BWH), CRP has been established as a prominent predictor of CV risk.²⁹ Only a few studies have investigated CRP as a risk factor in KTRs and most used CRP concentrations measured prior to transplantation. Since it is unclear how pretransplant and posttransplant CRP concentrations may relate, it appears important to determine this association in prevalent KTRs and to use CRP levels that are unaffected by the changes of the early posttransplant period. In a small study, Ducloux et al found an association between CRP and CV outcomes: those KTRs whose CRP was in the highest quartile (>5.2 mg/L) had 2.6-times the risk compared to those in the lowest quartile (<2.1 mg/L).³⁰ Similarly, our group found that KTRs with a CRP ≥ 5 mg/L had a 53% increased mortality risk compared with those patients whose CRP was <5 mg/L.³¹ In more recently presented work, however, we found evidence that the association between CRP and mortality in KTRs might not be as linear as has been shown in the general population.³² Patients with very low CRP concentrations (ie, <0.06 mg/L) also experienced an increased mortality compared to patients with only slightly higher concentrations (0.06–1.26 mg/L).³³ While CRP is a useful indicator of CV risk in KTRs, no interventions targeting elevated CRP have been studied in this specific population. It is possible that the beneficial effect of aspirin on CV risk is attributable to its anti-inflammatory properties, which are also reflected in lower CRP concentrations.²⁹ Currently, statins are being investigated for the indication of elevated CRP in individuals with normal lipid levels in the general population; the results from these large trials are still pending.

Homocysteine

Homocysteine is an amino acid and hyperhomocysteinemia is present in the majority of KTRs; in one study, three-quarters of prevalent KTRs had an elevated fasting total homocysteine (>12 $\mu\text{mol/L}$).³⁴ Homocysteine concentrations are directly associated with increased CV risk in the general population,³⁵ as well as in patients with diabetes or in the elderly. Similar associations were recently demonstrated in KTRs, both for CV outcomes and for all-cause mortality.^{30,34} To date, it is unclear whether these associations are actually causal or whether elevated homocysteine is a

casual bystander in patients with higher CV risk. Although vitamin supplementation has been shown to reduce homocysteine concentrations in several patient groups, including KTRs, it is unclear whether this intervention would actually reduce CV risk. To date, trials in the general population have been inconclusive, but large trials, including the NIH-funded Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) study, are currently underway to answer this question in the kidney transplant population. At this point, it is not recommended to measure homocysteine concentrations in KTRs and no evidence supports the long-term efficacy of homocysteine-lowering therapy, such as high-dose vitamin supplementation.

Anemia

Anemia has been investigated with great interest and intensity in the dialysis population; however, studies of the prevalence and clinical relevance of posttransplant anemia were scarce until the beginning of the new millennium. Several studies have since described the prevalence of anemia in a considerable proportion of KTRs. Nevertheless, this body of literature is difficult to interpret because the definitions of anemia used in these studies vary greatly. As a byproduct of these investigations, it was also determined that only a fraction of KTRs received erythropoiesis-stimulating agents (ESA) even if their hemoglobin or hematocrit concentrations were quite low. At BWH, approximately 42% of KTRs whose hematocrit was <30% received ESA,³⁶ with near identical findings (40%) at the institution across town, the New England Medical Center.³⁷ There, 25% of KTRs with a hematocrit <33% received ESA, which corresponds nicely with the 27% of patients with hemoglobin concentrations <11 g/dL in Ottawa, Canada.³⁸ While some have claimed that these findings indicate undertreatment of anemia in KTRs, initially, two questions should be raised: first, is anemia actually associated with CV outcomes in KTRs, and second, can ESA treatment reduce the rates of hard study endpoints in these patients? Surprisingly, little evidence is available to clarify these issues.

Rigatto et al assembled a retrospective cohort of 638 incident KTRs who were free from CV disease at 1-year after transplantation; the outcomes for the study were *de novo* CV disease, *de novo* congestive heart disease, and mortality. After multivariate analyses, lower hemoglobin concentrations were associated with an increased risk in all 3 outcomes, but due to the relatively small number of outcomes, only limited adjustments for confounding were possible and most CV risk factors mentioned in the present review were unavailable in that study.³⁹ In contrast, other studies with more extensive controls for confounding have failed to detect an independent association between hemoglobin concentrations and mortality.^{40,41} Thus, the importance of anemia as a risk factor in KTRs and the putative efficacy of ESA in improving outcomes in KTRs remains unclear. Several studies are currently underway or in the planning stages and will provide sorely needed evidence in the years to come.

Table 2: Recommended interventions for cardiovascular risk factors		
Cardiovascular risk factor	Intervention	Comments
Diabetes, preexisting	Control of glycemia, proteinuria, blood pressure; ACE-inhibitors or ARBs preferred	Extrapolation from general population
Diabetes, new onset after transplantation (NODAT)	Screen regularly for impaired glucose tolerance, limit weight gain after transplantation, minimize/avoid corticosteroids, tacrolimus	
Hypertension	Strict blood pressure control, target <130/80 mmHg	Preferred agents unknown. Personally, I would use ACE-inhibitors or ARBs in all patients, but definitively in patients with reduced systolic or diastolic left ventricular function, after myocardial infarction, or (pre-) diabetes (extrapolation from general population).
Dyslipidemias	Statins, target LDL-cholesterol <100 mg/dL	Caveat: interactions between calcineurin inhibitors and cytochrome P450 (CYP) 3A4-metabolized statins (lovastatin, simvastatin, and atorvastatin)
Obesity	Prevent weight gain, reduce excess weight	Inform patients early that they will likely struggle with weight gain after transplantation. Provide a support network of affiliated professions to avoid weight gain in the first place, which will yield indirect benefits in terms of other risk factors (lipids, diabetes, blood pressure)
Smoking	Ask your patients! Smoking cessation	
C-reactive protein	N.A.	It also does not make much sense to even measure these parameters solely with the intention to better assess cardiovascular risk. Remember, nearly all KTRs are at high cardiovascular risk.
Homocysteine	N.A. (no proven benefit of high-dose vitamin supplementation)	
Anemia	Erythropoiesis-stimulating agents, especially in symptomatic patients, optimal target hemoglobin concentrations are unknown	In light of recent trial evidence, it appears to be prudent to take a rather conservative route. Personally, I would not treat patients beyond 12 g/dL.

Several observational studies have failed to find an association between ESA treatment and CV outcomes in KTRs;⁴² one study found a nonsignificant trend towards greater mortality in ESA-treated patients.⁴⁰ The recently published findings of increased CV risk in patients with CKD, who were treated to a relatively higher target hemoglobin concentration (13.3 g/dL) compared with patients treated towards a lower target (11.8 g/dL), are alarming and should promote a conservative approach to using ESA in KTRs as well, until solid trial evidence becomes available.⁴³ Personally, I believe that a hemoglobin concentration of 12 g/dL is the highest target currently justified, given the most recent data.

Other hypothetical risk factors

Several other CV risk factors have been proposed; some factors have been established in the general population or in patients with CKD. The most relevant ones for the KTRs population are probably serum concentrations of calcium and phosphorus and their product, parathyroid hormone, and vitamin D. These are of particular interest because treatments are available and several studies are currently underway. It is beyond the scope of this publication to review the evidence on differences in CV risk profiles or the effects on outcomes with different immunosuppressive drugs or regimens. As with anemia, practitioners should be cautious in interpreting the evidence provided and ascertain that indications for treatment are driven by

science rather than marketing messages, since the safety of our patients is the greatest concern.

Summary

Kidney transplant recipients are at great CV risk and several established and novel risk factors are highly prevalent in this population. Only a few interventions have been tested specifically in these patients, requiring that results be extrapolated from findings in the general population. Since this may not be an entirely valid approach, prospective trials in the KTR population specifically, need to clarify these issues. Table 2 summarizes my current recommendations after reviewing the existing literature. While a daunting task in its complexity, successful and comprehensive management of CV risk in KTRs, whether in primary or secondary prevention, may remove a major barrier to further improving the outcomes of our transplant patients.

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