Cardiac Events After Kidney Transplantation According to Pretransplantation Coronary Artery Disease and Coronary Revascularization Status

R. Felix[d], T. Saparia[d], R. Hirose[a], L. Almers[b], Q. Chau[d], T. Jonelis[d], S. Zheng[c], and J. Zaroff[b,*]

[a]Division of Transplant Surgery, University of California, San Francisco, California; [b]Division of Research and [c]Nephrology Department, Kaiser Oakland Medical Center, Oakland, California; and [d]Cardiology and Nephrology Departments, Kaiser San Francisco Medical Center, San Francisco, California

ABSTRACT

Objectives. The aims of this study were to compare the rates of cardiovascular events among renal transplant recipients according to pre-transplantation coronary artery disease (CAD) and revascularization status and to describe the coronary angiographic findings in patients with post-transplantation events.

Methods. This was a retrospective cohort study of patients who had coronary angiography within 2 years before kidney transplantation. The predictor variables were pre-transplantation CAD and coronary revascularization. The primary outcome was a composite of cardiovascular mortality, acute coronary syndrome, and post-transplantation revascularization.

Results. The study included 403 patients. Pre-transplantation CAD was present in 73%, and 22% were revascularized. During a follow-up period of 5.6 years, the primary outcome occurred in 5% of the subjects without CAD, in 23% of those with CAD and no revascularization, and in 26% of those with CAD and revascularization (CAD hazard ratio [HR], 4.39 [$P = .002$]; revascularization HR, 1.27 [$P = .36$]). Thirty-five patients had a primary outcome and repeated coronary angiography, which demonstrated progression of previously nonsevere disease in the majority of cases.

Conclusions. Adverse cardiovascular outcomes are common after renal transplantation and are associated with pre-transplantation CAD of any severity. Secondary prevention of CAD events should be a high priority in the management of this high-risk population.

CORONARY ARTERY DISEASE (CAD) is highly prevalent in patients with renal insufficiency and end-stage renal disease [1–3], and CAD is also a common cause of death in patients after renal transplantation (RT) [3–7]. Given the high morbidity and mortality associated with CAD in post-transplantation patients, it is routine practice to screen for CAD as part of the evaluation for kidney allograft transplantation [8]. However, the role of coronary angiography and revascularization in this process remains controversial [9–11]. In those patients that are proven to have severe or flow-limiting CAD lesions, the data showing benefit of performing pre-transplantation coronary revascularization are sparse [12–14]. It is known that patients undergoing revascularization with renal disease have relatively high rates of periprocedural complications, including death and higher restenosis rates [12,15–17]. The 1st objective of the present study was to compare the rates of short (30-day) and long-term adverse cardiovascular (CV) events among renal transplant recipients according to pre-transplantation CAD and coronary revascularization status (aim 1). The second objective was to describe the coronary pathophysiology identified during coronary angiography performed after renal transplantation in patients with adverse events (aim 2).

MATERIALS AND METHODS
Patient Selection

This was a retrospective cohort study using Kaiser Permanente Northern California (KPNC) databases followed by review of the medical records of identified patients. KPNC is an integrated health care system that provides comprehensive medical services to >3.2 million members in northern California, serving ∼30% of the general population in that region. The sociodemographic characteristics of the members are generally representative of the underlying population [18,19].

KPNC members with a diagnostic code indicating a history of RT occurring from 1998 to 2011 were included in the study if they were ≥18 years old at the time of RT, were KPNC members for ≥2 years before and after RT, and underwent a cardiac catheterization with coronary angiography within 2 years before RT. The only study exclusion criterion was a history of combined heart-kidney transplantation. The study was approved by the KPNC Institutional Review Board.

Clinical Indications for Pre-Transplant Coronary Angiography

KPNC patients with end-stage renal disease were managed by Permanente Medical Group nephrologists before and after renal transplantation, with the exception of the 1st 90 postoperative days, when management was directed by University of California San Francisco (UCSF) or University of California Davis (UCD) transplant teams. Decisions about listing for transplantation and the need for pre-transplantation coronary angiography were made by local the transplant centers (UCSF or UCD). The UCSF pre-transplantation CV work-up guidelines require electrocardiography for all patients and may require echocardiography and/or a pharmacologic stress test, depending on clinical factors such as age, diabetes, and hypertension. Coronary angiography was required for nondiabetics when echocardiography showed a focal wall motion abnormality or a left ventricular ejection fraction <35% or if a pharmacologic stress test was abnormal. For patients with type I diabetes <25 years or type II <10 years without a history of atherosclerosis, coronary angiography was required when either echocardiography or stress test was abnormal (as above). For patients with diabetes of longer duration, coronary angiography was recommended for all patients on dialysis and for nondialysis patients with abnormal echocardiography or stress test (as above). Coronary revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was required before transplantation for any severe coronary stenosis. The guidelines left the decision about bare metal versus drug-eluting stents to the discretion of the interventional cardiologist. UCD used similar guidelines.

Predictor Variables: CAD and Revascularization Status

The presence of CAD was defined as an International Classification of Diseases (ICD-9) code for CAD associated with a KPNC clinical encounter (hospitalization, office visit, or procedure) within 1 year before RT. Pre-transplantation coronary revascularization was defined as PCI or CABG performed within 2 years before transplantation.

Outcome Variables

The primary outcome measure was a composite of CV mortality, acute coronary syndrome (ACS), and coronary revascularization occurring after renal transplantation during the time period of 1998–2012. The secondary outcomes included the components of the primary outcome, all-cause mortality, incident heart failure (HF; newly coded after transplantation), and incident angina. The outcomes were initially identified by database programming with the use of ICD-9 codes. However, all outcomes identified by database programming were adjudicated by chart review, and only those events confirmed by chart review and occurring after RT were included in the analysis. For all primary outcomes, the chart review included an assessment of whether or not the patient was taking aspirin, statin, and/or beta-blocker at the time of the event.

For all mortality outcomes, the cause of death was reported after chart review and categorized as CV, non-CV, or indeterminate (owing to lack of data) with the use of published definitions [20–22]. For comparison, the mortality rate and causes of death for the RT population that did not receive cardiac catheterization was also reported.

Demographic and Clinical Covariates of Interest

Covariate data was imported from KPNC databases with the use of ICD-9 codes for comorbid conditions. These data included age at the time of transplantation, sex, race/ethnicity, pre-transplantation CV risk factors (diabetes mellitus, hypertension, and hyperlipidemia coded within 1 year before transplantation), and treatment with statin or beta-blocker, defined as a dispensed supply of ≥90 days' worth of medication within 60 days before or after transplantation. To validate the statin and beta-blocker programming data, a random series of 40 patient charts were reviewed to confirm that the medication was purchased by the patients. Aspirin use is not reliably determined by database programming owing to its nonprescription status, so aspirin status also was assessed in the 40-patient chart review. Steroid dose was not used as a covariate, but both UCSF and UCD transplant centers start with high-dose solumedrol (500 mg) or prednisone (250 mg) and taper over time to a long-term prednisone dose of 5 mg/d in the UCSF protocol and 0–5 mg/d in the UCD protocol, depending on immunologic risk factors.

Aim 2: Comparison of Pre- and Post-Transplantation Coronary Angiographic Findings

Those aim 1 cohort subjects who met the additional inclusion criterion of cardiac catheterization with coronary angiography occurring any time after renal transplantation were eligible for the aim 2 cohort. Detailed chart review was performed by study investigators for all aim 2 cases, including review of the pre- and post-transplantation catheterization reports and, whenever possible, the angiographic images. Only those cases with available reports and/or images for both cardiac catheterizations were included in the analysis. The goal of the angiographic chart review was to categorize the findings of each post-transplantation coronary angiogram as either without significant angiographic change (no new flow-limiting lesions) or having ≥1 new severe (flow-limiting, ≥70%) lesion. The severe lesions were further categorized as a newly severe CAD lesion, in-stent restenosis, in-stent thrombosis, or CABG graft stenosis.

Statistical Analysis

For comparison purposes, the cohort was divided according to the 2 predictor variables of interest: pre-transplantation CAD and pre-transplantation revascularization. Therefore, the 3 comparison groups were no CAD, CAD without revascularization, and CAD with revascularization. The demographic and clinical characteristics were compared among the 3 groups by means of analysis of