

Better Management Needed to Lower Cardiovascular Risks After Kidney Transplant

By Daniel M. Keller

Even with protocols in place to improve compliance, many kidney transplant patients did not achieve risk factor targets for cardiovascular disease, a leading cause of graft failure and of death after transplantation, according to study results presented at the American Transplant Congress in Philadelphia in early May. But as time went on after transplantation, the modifiable risk factors of hypertension, hyperlipidemia, and diabetes mellitus could become better controlled, said lead author Rakesh Kumar, MD, of the State University of New York at Buffalo.

Although advances in immunosuppressive therapy can prevent immune-mediated damage to transplanted kidneys and improve short-term allograft survival, the same factors that increase cardiovascular risk—hypertension, dyslipidemia, and diabetes—also affect the function and survival of grafts. Cardiovascular disease in itself accounts for up to 25 percent of patient deaths in the long term.

In this single-center retrospective chart review study performed at the university-affiliated Erie County Medical Center Kidney-Pancreas Transplant Unit, the researchers assessed blood pressure and levels of LDL cholesterol and hemoglobin A1c (HbA1c) annually, starting 1 year after transplant. Data were collected for 1–5 years (2005–2009) depending on the date of the transplant.

Uncontrolled blood pressure was defined as readings above 130/80 mm Hg on three or more occasions over 5 years. The results

were compared with the Kidney Disease: Improving Global Outcomes (KDIGO) recommended guidelines of blood pressure no greater than 130/80 mm Hg, LDL cholesterol less than or equal to 100 mg/dL, and HbA1c less than or equal to 7.5 percent. The immunosuppressive regimen was alemtuzumab induction with tacrolimus and mycophenolate maintenance.

The 128 patients (44 women) in the study had a mean age of 51 years; 6 percent were white, 44 percent had a history of diabetes, 83 percent had dyslipidemia at the time of the study, and 96 percent were hypertensive. Thirty-four percent were taking three or more antihypertensive medications.

Results

In general, blood pressure appeared to improve over time. One year after transplantation, 41 percent of patients had controlled hypertension. “After 5 years of transplant, 55 percent of patients had blood pressure less than 130/80,” Kumar reported. “There was a greater decline in eGFR [estimated glomerular filtration rate] among patients with uncontrolled hypertension compared with patients with controlled hypertension, although it did not reach a significant level.”

At 1 and 5 years, eGFR was 59.2 and 55.1 mL/min, respectively, among patients with controlled hypertension and 52.9 and 45.3 mL/min, respectively, for patients with uncontrolled hypertension. At 1 year, 76 percent of 106 patients had an LDL cholesterol reading at or below 100 mg/dL, and

at 5 years, the figure was 91 percent of 12 patients. Seventy percent of 78 patients had HbA1c levels at or below the desired level of 7.5 percent at 1 year, and by 5 years the figure increased to 81 percent of 9 patients for whom there was a reading. Kumar summarized his findings, saying that hypertension was the most prevalent cardiovascular risk factor in this cohort of renal transplant patients and that eGFR declined faster in the presence of uncontrolled blood pressure. Some patients were fairly refractory to the multiple antihypertensive therapies prescribed. “Forty percent of patients with uncontrolled hypertension and 35 percent of patients with controlled hypertension were on three or more antihypertensive medications,” Kumar said.

Although compliance with KDIGO guidelines for blood pressure, LDL cholesterol, and HbA1c improved over time, a substantial proportion of transplant recipients missed some of the routine screenings for cardiovascular risk factors, and 30–60 percent of patients failed to reach risk factor goals in the first year after transplant. “Evidence-based guidelines alone were insufficient to uniformly drive ideal care,” Kumar concluded, and he said that better strategies are needed to meet treatment objectives.

Session moderator Vinay Nair, DO, a transplant nephrologist at Mt. Sinai Medical School in New York, told *ASN Kidney News* that continued improvement in KDIGO parameters over the years would not be expected. “If anything, when you go further

years you’d expect some graft deterioration. It’s very common with transplantation,” he said. “A lower GFR should mean worse blood pressure control if anything. So it is a little bit surprising” that blood pressure control improved over time but that eGFR was declining.

He agreed that better strategies are needed if outcomes are to improve, but that first it is important to know how well patients do with chronic kidney disease but without transplantation, and how the general population compares. He asked that if patients who have received transplants are doing worse, “are we as transplant nephrologists not doing a good enough job, or it is something with the medications that makes them harder to treat and control?”

Nair also noted Kumar’s statement that calcium channel blockers were the majority of first-line antihypertensive medications used for the study patients. However, “JNC 7 [Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7] suggests that the first medication is a diuretic. We’re often, initially at least, reluctant to give diuretics because of rises and falls in creatinine, or ACE [angiotensin converting enzyme] inhibitors,” Nair explained. He said that clinicians have historically tended to prescribe calcium channel blockers because some previous data suggested that they may reverse the effects of calcineurin inhibitors on blood pressure, but more recent data have called that idea into question. ●

Chronic Opioid Use Before Kidney Transplant Shortens Graft Survival

Chronic use of opioids (COU) before kidney transplantation may be associated with an increased risk of early graft loss and higher mortality after transplant, according to a retrospective study from the University of Michigan presented at the American Transplant Congress in Philadelphia in May.

Of the 1064 adult patients who received a kidney graft at the university between 2004 and 2008, 42.5 percent reported that they had chronic pain and 10.2 percent reported that they had used opioids on a chronic basis before their transplants. The patients were followed up until the end of 2010. These figures are in line with published reports showing that 50 percent of patients with ESRD report some degree of chronic pain, and 5–36 percent use opioid analgesics on a chronic basis, said Fidel Barrantes, MD, clinical transplant fellow at the University of Michigan. Barrantes spoke at the session Painful Consequences: Chronic Use of Prescription Opioids Is Associated with Adverse Kidney Transplant Outcomes.

“Four types of opioids were used in more than 90 percent of this population,” Barrantes reported. Forty-four percent used hydrocodone, 17 percent propoxyphene, 15

percent oxycodone, and 14 percent tramadol. The most common pain was neuropathic (53 percent of patients), followed by limb pain (39 percent), lower back (16 percent), headache, abdominal, and other pains.

The COU group, comprising 108 patients, had more African Americans than did the non-COU group (25 percent versus 17.5 percent, respectively) and had more comorbidities, double the rate of alcohol abuse (18.5 percent versus 9.9 percent), more illicit drug abuse (20.4 percent versus 11.1 percent), a more positive psychiatric history (51.9 percent versus 27.8 percent), and three times the rate of use of nonopioid analgesics (26.9 percent versus 8.2 percent).

The non-COU group included more employed patients (44.1 percent versus 18.5 percent) and more patients with private insurance (43.8 percent versus 30.6 percent).

The two groups did not differ significantly in terms of age (approximately 50 years), gender (approximately 60 percent male), body mass index (approximately 28.5 kg/m²), proportion with diabetes, or length of time receiving dialysis.

“Pretransplant chronic opioid use is associated with worse patient survival at 1, 3, and 5 years,” Barrantes said, with significant

differences in survival between the COU and non-COU groups at 3 and 5 years. The death rates at 3 years were 18 percent for the COU group and 7.5 percent for the non-COU group. At 5 years, death rates were 21 percent versus 12 percent, respectively (p = 0.026).

Reported chronic opioid use before transplant was associated with a 66 percent increased risk of death after transplant, according to a multivariate model. This risk was higher than even for the presence of diabetes before transplant, which conferred a 42 percent increased risk. Receipt of a kidney from a living donor lowered the risk of death after transplant by half.

Graft loss was significantly increased by COU only at the 1-year point in comparison with the non-COU group (5.5 percent versus 1.5 percent, respectively). At 3 years, graft loss was in the range of 4.5–6.5 percent and was around 7–7.5 percent at 5 years. These latter differences were not statistically significant between the COU and non-COU groups.

In the first year after transplant, COU emerged as the major predictor of graft loss. When compared with non-COU, COU conferred almost a threefold increased risk of graft loss (hazard ratio = 2.90). Current

smoking was associated with a more than twofold increased risk (hazard ratio = 2.63).

A much smaller study by Walczak and colleagues also presented at the conference again showed that cigarette smoking (n = 9) was associated with a nonsignificant trend toward lower graft survival at 3 and 5 years after transplant, as was alcohol use.

Barrantes noted that his study was retrospective, depended on self-reported use of pain medication, and lacked information on opioid use after transplant—all limitations of the study.

Speaking with *ASN Kidney News*, he said that because the study was retrospective and based on self-reports, it was impossible to discern the reasons for opioid use, leaving open the possibility that patients used the drugs to treat painful conditions, such as diabetes or vascular conditions, that in themselves could affect patient or graft survival.

Barrantes cautioned that the study should not be interpreted to disqualify COU patients from consideration for transplants. However, clinicians should be vigilant to identify such patients and to target them for follow-up by social workers and possibly psychologists, particularly in the first year after transplant. ●