EDITORIAL

Perioperative cardiac risk assessment in kidney transplantation: It's time to search for a new gold standard

Yasmeen Golzar, MD,[a] and Rami Doukky, MD, MSc, MBA, FASNC[a,b]

[a] Division of Cardiology, Cook County Health, Chicago, IL
[b] Division of Cardiology, Rush University Medical Center, Chicago, IL

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Increased cardiac risk associated with advanced chronic kidney disease (CKD) poses a particular challenge when evaluating candidates for renal transplantation. The incidence of myocardial infarction (MI) in renal transplant candidates is considerable, ranging 8.7%-16.7% by 3 years after transplant listing and 4.7%-11.1% after transplantation.[1] Alarmingly, almost half of the deaths that occur within 30 days after kidney transplantation are due to MI.[2] With little data to help guide cardiac risk stratification and even fewer tools to mitigate that risk, not only do transplant teams have to contend with a challenging peri-transplant period, they must also grapple with how to ethically, yet prudently allocate scarce donor organs in an extraordinarily high-risk patient population.

Identifying reliable methods to assess cardiac risk is the first step in working toward effectively decreasing peri-transplant cardiac event rates. Unfortunately, guideline-based risk assessment tools used in the general population do not perform well when applied to this uniquely high-risk patient population.[3,4] While current perioperative guidelines rely on symptom-limited exercise capacity to guide risk stratification, the majority of end-stage renal disease (ESRD) patients who have significant coronary artery disease (CAD) do not display typical symptoms.[9] Hence, the 2012 American Heart Association (AHA)/American College of Cardiology (ACC) consensus statement on cardiac disease evaluation and management among kidney and liver transplantation candidates veers away from standard practice by proposing the use of non-invasive CAD surveillance in *asymptomatic* patients with three or more pre-defined risk factors (age > 60 years, hypertension, diabetes, cardiovascular disease, dyslipidemia, smoking, dialysis > 1 year, and left ventricular hypertrophy).[3,4] Whether this screening approach improves patient survival or transplant outcomes is yet to be determined.[4]

Without strong evidence to guide this practice, the question remains: Does an aggressive approach to stress testing asymptomatic kidney transplant candidates truly help to identify occult, high risk, and (ideally) modifiable CAD to drive down perioperative cardiac event rates, or does it just drive away potential transplant candidates by unreasonably delaying or excluding those who have an abnormal non-invasive test? Part of the answer lies in the diagnostic and prognostic performance of available non-invasive imaging tools. Stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is the most commonly used stress testing modality in CKD patients. Along with its prognostic value being well established in this patient population,[5–8] several studies specifically evaluating the prognostic utility of stress SPECT-MPI in renal transplant candidates have shown that an abnormal MPI is a predictor of adverse cardiac events.[9,10] However, data from mostly small, single-site studies suggest that the diagnostic performance of SPECT-MPI in this patient population may be less reliable.

In this issue of the Journal, Kelderman et al. present an updated comprehensive meta-analysis assessing the diagnostic accuracy of SPECT-MPI for detection of significant CAD in patients being evaluated for kidney transplantation.[11] They analyzed data from 13 studies, including a total of 1245 SPECT scans compared to the

''gold standard'' of invasive coronary angiography. SPECT-MPI studies, including the use of variable radioisotopes and acquisition protocols, were designated as abnormal based on the presence of fixed or reversible perfusion defects or the calculated summed stress score. The presence of CAD had variable definitions based on percentage of stenosis of epicardial coronary arteries (five studies used $\geq$ 50% stenosis, six studies used $\geq$ 70% stenosis, and two studies used a combination of $\geq$ 50% and $\geq$ 70% stenosis). Pooled results showed that SPECT-MPI had a sensitivity of 66% and specificity of 75%. These findings led the authors to conclude that SPECT-MPI has only moderate diagnostic accuracy in candidates being evaluated for kidney transplantation.[11]

Despite the variability in radioisotopes, SPECT-MPI protocols, and angiographic definitions of CAD used in the included studies, this meta-analysis offers a valuable re-examination of the limited diagnostic utility of SPECT-MPI in renal transplant candidates. Even with the inclusion of more contemporary studies, the authors' findings are very similar to previously published pooled results which delineate the suboptimal diagnostic performance of SPECT-MPI in detecting significant macrovascular CAD in kidney transplant candidates.[3,9,12]

In acknowledging the limitation of using a functional imaging test against the anatomic ''gold standard'' of coronary angiography as inherently problematic, the authors touch on an important point. Our current risk stratification strategies rely primarily on the premise of detecting and intervening on high-risk macrovascular CAD. Given our burgeoning understanding that the presence of myocardial ischemia and anatomic macrovascular CAD are not mutually inclusive, this unidimensional approach to perioperative risk assessment is worthy of re-examination.

Ultimately, the value of a preoperative risk assessment and disease detection tool is in its ability to (1) accurately predict perioperative outcomes, and (2) diagnose risk-modifying disease, the treatment of which can be used to improve survival. On both fronts, coronary angiography is an imperfect ''gold standard.'' Angiographically defined coronary stenosis has not been shown to be a reliable prognostic tool, having variable correlation with subsequent clinical events in renal transplant candidates. While some observational studies have reported worse outcomes in patients with angiographic CAD, others have shown that this increased risk only exists in specific patient populations such as those with proximal CAD or with nondiabetic kidney failure. Furthermore, recent studies have found no correlation between the presence of significant CAD on angiography and patient survival.[13]

The fact that macrovascular CAD is not a reliable predictor of cardiac event rates reflects the complex and multifactorial mechanism of perioperative MI. While patients with significant macrovascular CAD are at higher risk of perioperative MI by the mechanism of demand ischemia, the phenomenon of plaque rupture is unpredictable and most often occurs in non-flow limiting coronary lesions which would go undetected in stress testing and would not warrant intervention even if detected on coronary angiography. Moreover, patients with advanced kidney disease have impaired coronary microcirculation and decreased coronary flow reserve.[3] In the perioperative period, impaired coronary flow dynamics likely contribute to the high risk of ischemic events seen in renal transplant patients, even in the absence of macrovascular CAD.

Positron emission tomography (PET), with its ability to assess myocardial blood flow and coronary flow reserve, is a promising non-invasive tool which is able to integrate the hemodynamic effects of epicardial coronary stenosis and microvascular dysfunction.[14] Though PET-MPI has not been studied specifically in renal transplant candidates, it has been shown to be an effective prognostic tool in CKD and ESRD patients as an independent and incremental predictor of adverse cardiac outcomes.[14,15] Future research is needed to better understand the potential role of PET-MPI in the cardiac evaluation of renal transplant candidates. However, no matter how well-performing a prognostic device may be, risk stratification strategies will only function to be exclusionary tools unless they are coupled with effective risk reduction strategies, of which we have very few. With a new ''gold standard,'' it is imperative that we simultaneously work toward effective interventions that will help improve peri-transplant outcomes. Only then, will we truly be able to better serve this high-risk patient population.

Disclosures

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