Stress myocardial perfusion imaging vs. stress echocardiography for risk stratification of kidney transplant candidates: Does it even matter?

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Cardiovascular disease (CVD), rather than end-stage kidney disease (ESRD), is the leading cause of death in patients with chronic kidney disease (CKD), accounting for nearly 50% of all deaths.^{1,2} In the USA, there are over 100,000 patients awaiting kidney transplant and close to 3000 patients are added to the waiting list every month.³ With such a high prevalence of CVD in CKD patients and limited number of donor kidneys, several professional societies provide recommendations for cardiac assessment of patients undergoing kidney transplantation in an effort to optimize peri-transplant outcomes. While management of patients with symptomatic coronary artery disease (CAD) is generally well defined, the management and outcome implications of pre-operative cardiac testing in asymptomatic ESRD patients are unclear. The 2014 ACC/AHA peri-operative cardiovascular evaluation guidelines for non-cardiac surgery are not intended for patients undergoing solid organ transplant evaluation.⁴ ESRD patients have a significantly higher prevalence of CAD (up to 53%) in comparison to non-ESRD patients.⁵ Additionally, cardiac risk assessment of kidney transplant candidates extends beyond the peri-operative period and demands long-term cardiac risk stratification to ensure proper organ allocation to a host with a favorable long-term prognosis.

It is accepted that CAD surveillance using noninvasive stress testing may be considered in asymptomatic kidney transplantation candidates with no active cardiac conditions based on the presence of multiple CAD risk factors regardless of functional status.^{6,7} The modality of stress testing with either stress echocardiography or stress radionuclide myocardial perfusion imaging (MPI) is left at the discretion of the provider and the expertise of the transplant center. While the sensitivity and specificity of noninvasive stress testing is lower in patients with ESRD compared to the general population, there had been no head-to-head comparisons between different testing modalities in this population. However, the published data suggest a comparable diagnostic accuracy between SPECT MPI and dobutamine stress echocardiography (DSE). The literature provides even less insight into the comparative prognostic utility of these tests.^{8,9}

In this issue of the journal, Bautz et al directly compared, in the same patients, the prognostic utility of SPECT MPI and DSE in 229 kidney transplant candidates who underwent both tests within 1 month.¹⁰ The primary endpoint was a composite of nonfatal myocardial infarction (MI) or all-cause death and the secondary endpoint was a composite of nonfatal and fatal MI or coronary revascularization (not triggered by baseline MPI or DSE). The threshold for an abnormal MPI scan (SSS ≥ 1) was lower than the traditional cut-off (SSS ≥ 4) commonly used in the literature. Abnormal MPI or abnormal DSE were observed in 15.7% and 16.2% of subjects, respectively. MPI and DSE showed good overall agreement in 88.6% of cases at rest (rest perfusion/rest regional wall motion abnormalities [RWMA]) and 80% at stress (stress perfusion/stress RWMA). Contradictory results were noted in 9% of resting images and 14% of stress images. The study was not designed or powered to evaluate the diagnostic accuracy of either modality.

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The primary (nonfatal MI or all-cause death) and secondary (fatal/nonfatal MI or coronary revascularization) endpoints were observed in 70 (30.6%) and 24 (10.5%) patients. Abnormal MPI was associated with a statistically significant increase in the primary endpoint (adjusted hazard ratio [HR] 1.77; 95% confidence interval [CI] 1.02–3.08; $P = .043$), whereas abnormal DSE was not associated with a statistically significant increase (adjusted HR 1.36; 95%CI 0.78–2.37; $P = \text{NS}$). On the other hand, both abnormal MPI (adjusted HR 3.21; 95%CI 1.35–7.61; $P = .008$) and abnormal DSE (adjusted HR 2.67; 95%CI 1.15–6.20; $P = .022$) were associated with a statistically significant increase in the secondary endpoint. Combining the two imaging modalities only modestly improved the prognostic value for the primary (adjusted HR 1.92; 95%CI 1.17–3.17; $P = .01$) and secondary (adjusted HR 3.45; 95%CI 1.49–8.01; $P = .04$) endpoints. It is interesting to note that the effect size (HR) of abnormal stress MPI seems to be numerically greater than DSE. A greater HR may suggest that stress MPI is more effective than DSE in risk stratification. It is unclear whether this observation is statistically significant, as interaction analysis between the stress modality and the study finding (normal vs. abnormal) was not performed. However, noting a substantial overlap between confidence intervals suggests that there is no significant interaction.

Patients who underwent kidney transplant during the follow-up had lower incidence of the primary (21.9% vs. 54.2%) and secondary (8.9% vs. 13.3%) endpoints. However, these differences were not statistically significant when kidney transplant was used as a time-dependent exposure.

We commend the authors for performing this first of its kind study, wherein all patients underwent both MPI and DSE within 1 month. The results of this study confirmed an existing consensus that both abnormal stress MPI and DSE can predict adverse cardiac events in ESRD patients undergoing kidney transplant evaluation. The study informs us that there is no additive value for performing both stress testing modalities in these patients. Although it was not demonstrated statistically, the study suggests that SPECT MPI appears to outperform DSE in prognostication. This observation can be explained by the ischemic cascade physiology. It is established that myocardial perfusion abnormality occurs at lower threshold of ischemia than RWMA (more sensitive). Thus, MPI may have better identified patients at risk. Larger studies are needed to further investigate this observation.

While Inflammation and oxidative stress with CKD have been linked to the pathogenesis of plaque formation and plaque rupture leading to acute MI,¹¹ heart failure remains the most common manifestation of CVD

in this population.¹² Besides the increased prevalence of traditional risk factors,¹³ non-traditional risk factors, such as vascular calcifications,^{14,15} circulating proinflammatory mediators,^{16,17} and pathological myocardial fibrosis leading to hypertrophy (uremic cardiomyopathy)¹⁸ contribute significantly to cardiovascular risk and mortality in these patients. CAD remains one part of this puzzle and we may be too focused on identifying CAD. Although there are certain scenarios where identifying severe and extensive CAD in asymptomatic ESRD patients may have important implications on outcome and management, there is no proven benefit of routine revascularization in CKD patients.¹⁹ Importantly, identifying ESRD patients with unacceptably high CVD risk and limited life expectancy would be crucial in determining eligibility for kidney transplantation and better allocate scarce donor organs.

Reflex coronary revascularization in asymptomatic patients with abnormal stress test is not the standard of care in general population and we believe this should not be the case in kidney transplant candidates either. Optimizing medical management of CAD and heart failure remains the mainstay of management in these patients. Undoubtedly, pre-operative stress testing has shown prognostic value in ESRD patients undergoing transplant evaluation. However, it is still unclear how to use this prognostic information in decision-making. While we improve the management of traditional risk factors and aim for early kidney transplant, additional research is needed to find ways to incorporate this prognostic information into patient management to achieve the eventual goal of improving outcomes. Realizing this goal requires large-scale comparative outcome studies and randomized clinical trials addressing the value of medical therapy and coronary revascularization in patients undergoing kidney transplantation.

Disclosure

None.

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