The Prognostic Value of MPI in CKD: Can we do better?

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with chronic kidney disease (CKD).¹ Mortality from CVD progressively increases with worsening severity of CKD, despite adjustment for confounders.^{2,3} The prevalence of coronary artery disease (CAD) is more than two-fold greater among patients with CKD than those with normal kidney function. This is likely a result of a combination of traditional risk factors, such as diabetes and hypertension, and non-traditional risk factors, such as oxidative stress and chronic inflammation. Thus, patients with CKD more frequently undergo revascularization procedures. Among Medicare beneficiaries, patients with CKD have a higher prevalence of percutaneous coronary intervention and coronary artery bypass grafting. Expectedly, these patients have a lower adjusted survival probability when stratified by CKD stage.⁴ Therefore, clinicians have long attempted to risk stratify patients with kidney disease. Risk stratification based on clinical variables alone, such as the Framingham risk score, has shown poor predictive accuracy for cardiovascular events in this population.⁵ Therefore, although clinical variables are used as the first step in defining risk, further stratification is often based on non-invasive or invasive imaging.⁶ Stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is the most commonly used non-invasive testing modality in patients with CKD. The

sensitivity and specificity of MPI is lower in patients with CKD than the general population,⁷ which may impact the prognostic utility of MPI in this population. Although there is plethora of retrospective, single-center data demonstrating the prognostic utility of SPECT MPI,^{8,9} a few studies have failed to demonstrate statistically significant results.

In this issue of the Journal, Cantoni, Green and colleagues performed an updated systematic review and a comprehensive meta-analysis looking at the prognostic significance of SPECT MPI in patients with kidney disease.¹⁰ They summarized data from 16 studies (11 stage IV–V, 3 stage III–V, and 2 stage I–V), encompassing a total of 7834 CKD patients undergoing either pharmacological or exercise stress testing. The summary effect size was quantitatively presented as hazard ratios (HR). Although only studies that had a sample size of > 100 patients and reported adjusted or unadjusted HRs were included, the statistical analysis is sound and appropriate. The primary outcome was the occurrence of adverse events, including death, myocardial infarction (MI), late coronary revascularization, stroke, heart failure, or acute coronary syndrome. A secondary analysis was performed for hard events of cardiac death or MI. Expectedly, this meta-analysis affirmed the prognostic value of SPECT MPI in patients with CKD, with a pooled HR for adverse events of 2.02 (95% CI 1.68–2.42). The pooled HR for hard events (cardiac death or MI) was 2.36 (95% CI 1.77–3.13). The meta-regression analysis showed an association between HR for adverse events and age, hypertension and smoking.

Generally, meta-analyses are performed to analyze cumulative data from several studies and calculate a more precise pooled effect size, taking into account the heterogeneity between studies. In the present report, there was little doubt about the prognostic value of MPI in patients with CKD, as most individual studies reported statistically significant results. The rare exceptions of negative studies were generally

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underpowered but reported HRs that are similar to positive studies. This meta-analysis further supports the mounting evidence showing that an abnormal SPECT MPI carries significant prognostic implications in patients with CKD. More importantly, this meta-analysis provides us with more precise effect size of an abnormal MPI in this population. Patients with an abnormal scan have approximately twice the hazard of an adverse event when compared to those with a normal scan. This increase in risk is clearly statistically significant, but how valuable is it clinically? Can we do better? An abnormal MPI scan predicts increased event rates, but how well does a normal scan predict low risk in this population? First, a HR of 2, although significant, is slightly lower than the prevailing MPI literature in the general population where an abnormal MPI has been reported to be associated with larger effect size of a multi-fold increase in risk.^{11,12} Second, the effect size alone does not reveal the absolute risk, and certainly does not inform us of the risk associated with a normal scan. Our team has previously reported annualized event rates of all-cause death at 5.2 % and death/MI at 6.2% among ESRD patients with a normal SPECT MPI.⁹ These unacceptably high rates of adverse events in CKD patients with a “normal scan” undermines the premise of risk stratification in this high-risk population. Microvascular disease from capillary rarefaction of the microvascular circulation leading to myocardial injury may explain these poor outcomes in patients with CKD.¹³ Additionally, high prevalence of atherosclerotic risk factors, chronic inflammation, diffuse CAD, and comorbid cardiovascular diseases, all contribute to worse outcomes even among those with normal SPECT MPI. Hence, MPI alone, which is best suited to assess discrete obstructive epicardial coronary stenoses, would miss the adjunctive prognostication that can be provided by assessing the microvascular flow and other ancillary findings.

Positron emission tomography (PET) appears to be a promising modality for refining risk stratification in this population. The most prominent advantage of PET is the ability to perform dynamic acquisition, allowing for quantitative measurements of absolute myocardial blood flow (MBF) at rest and stress and coronary flow reserve (CFR). Global CFR integrates the hemodynamic effects of epicardial stenosis, diffuse atherosclerosis, and microvascular dysfunction. In a study of 168 ESRD patients, Shah and colleagues reported a higher all-cause mortality among patients with a reduced PET-measured global CFR of ≤ 1.4 compared with those with a CFR > 1.4 . Global CFR was identified as an independent predictor of all-cause mortality in a multivariate model.¹⁴ Similarly, Charytan et al. demonstrated that CFR can reclassify risk across the spectrum of CKD and ESRD,

and those with normal CFR were at a low risk, comparable to those without CKD.¹⁵

In addition to CFR, other complimentary imaging such as coronary calcium quantification may provide an additional opportunity to enhance risk prediction. It is well established that abnormalities of mineral metabolism and renal osteodystrophy predispose patients with CKD to vascular calcifications. Patients with CKD on dialysis have 2- to 5-fold more coronary artery calcification (CAC) than age-matched individuals with angiographically proven coronary artery disease.¹⁶ This process starts early, with calcifications noted even in adolescents and young adults.¹⁷ Chen et al. showed that CAC improves risk prediction over conventional and novel cardiovascular disease risk factors in patients with CKD.¹⁸ Winther et al. showed favorable risk stratification using CAC score and coronary CT angiography; however, the risk of further decline in kidney function by iodinated contrast limits the use of coronary CTA in this patient group.¹⁹ There is limited data on prognostication by combining CAC score and MPI findings in patients undergoing PET/CT or SPECT/Imaging. This would be particularly promising, given the growing use of these technologies.^{20,21}

Furthermore, incorporating ancillary stress MPI data with perfusion findings can further improve prognostication. In a study by Gomez et al., integrating heart rate response (HRR) to vasodilator stress with SPECT MPI finding can refine risk assessment in patients with ESRD. HRR was defined as (peak HR – resting HR)/resting HR.^{22,23} The authors demonstrated that patients with normal HRR ($\geq 28\%$) and normal MPI represent a low-risk group (2.8% annualized risk of cardiac death or MI), whereas subjects with normal MPI and abnormal HRR were at elevated risk (6.6%), and those with abnormal MPI and abnormal HRR were at very high risk (9.5%).²⁴ Additionally, ischemic electrocardiographic changes, particularly among patients with normal MPI, have been shown to provide an incremental prognostic value.^{25,26} Finally, left ventricular dyssynchrony, which may be the earliest marker in the ischemic cascade,²⁷ can be a useful tool in risk stratification in patients with CKD.

Patients with CKD, including ESRD, represent a unique population affected by an exceptionally high burden of cardiovascular disease. Between the lack of randomized trial data to optimize management decisions and “oligo-symptomatic” clinical presentations affecting timely diagnosis, the academic community should continue to focus on pre-emptive screening and disease modification. This risk stratification becomes even more meaningful in patients who are considered for kidney transplantation, where limited number of donor organs demands rigorous screening in an effort to minimize peri

and post-transplant cardiac events. While there is no doubt that abnormal MPI equals worse outcomes, the limitations lie in patients with normal MPI scans, where adverse events remain high. The available evidence is clear; perfusion data alone is insufficient to adequately risk stratify these patients. We must and can do better! This requires us to look beyond MPI data. Incorporating ancillary data readily available from stress MPI, CAC quantification, and PET-derived CFR measurement is crucial for improving risk prediction. Future research should focus on using imaging data to guide management and modify risk, which remains the holy grail of prognostication in this and every other population.

Disclosure

The authors have indicated that they have no financial conflict of interest.

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