Going beyond the obvious: Predicting cardiac events in renal disease

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As a medical community, we have known about the adverse implication of renal disease to overall human health for many years. However, the fate of patients with renal disease changed dramatically in the 1960s, with the advent of the Teflon shunt. The Teflon shunt allowed repeated access to patient's blood, and thus hemodialysis was born. The 1960s were groundbreaking for renal health as advances in technology allowed renal disease to emerge as a chronic, rather than a life-threatening, condition. Kidney Disease Outcomes Quality Initiative published the first official guidelines in 1997, and in 2002, the landmark guideline established the five stages of kidney disease. Fifteen years since, we continue to refine our knowledge of the chronic kidney disease (CKD) patient population, specifically focusing on the impact of CKD in forecasting adverse cardiovascular (CV) events.

The recent work by Ahmed et al provides us with the framework to risk stratify the chronic renal disease patient population for development of cardiovascular disease. Using SPECT-MPI imaging, the authors related the total perfusion deficit (TPD) to development of cardiac death and non-fatal myocardial infarction in a group of patients with CKD, stratified by severity of renal impairment. Slomka et al. first introduced TPD as an unbiased quantitative perfusion parameter, which represents both the severity and extent of a defect when compared to the normal database.[1] In the study by Ahmed et al., 11, 518 patients were evaluated, with a mean age of 64.6 ± 12.3 years, of which 51.7% were males and 39.4% were of black ethnicity. These patients were referred for clinically indicated SPECT-MPI imaging for evaluation of the extent of known coronary artery disease, or for the diagnosis of suspected coronary artery disease. Of the 11,518 patients, 46.7% had GFR of 60-89 ml/min/1.73 m^2, signifying no clinically relevant renal impairment.

Hypertension, prior myocardial infarction, prior revascularization including percutaneous coronary intervention and coronary artery bypass graft, dyslipidemia, diabetes mellitus, family history of coronary artery disease, and smoking were prevalent amongst the patients included in the study. These patients were followed for over 5 years, with cardiac death and myocardial infarction reported as primary outcomes.

Several interesting conclusions emerge from the study. First, across the spectrum of the renal function impairment, SPECT-MPI offered robust risk stratification for cardiac death, independently and incrementally to the traditional CV risk factors (Figure 1). As seen in Figure 1, normal SPECT-MPI resulted in favorable prognosis, although the rate of events increased across continuum of worsening renal function. Thus, while it is safe to say that in patients with mild-to-moderate renal impairment normal SPECT-MPI resulted in 1-2% annual event rates, this number doubled to 4% in the group with end-stage renal disease.

Additionally, CKD was an independent predictor of worse outcomes in a setting of even mild ischemia (defined as SSS >/= 4, Figure 2). When the multivariable models were adjusted for the SPECT-MPI findings, in addition to the traditional CV risk factors, SSS remained an independent predictor of cardiac death and myocardial infarction (Figure 3), resulting in net

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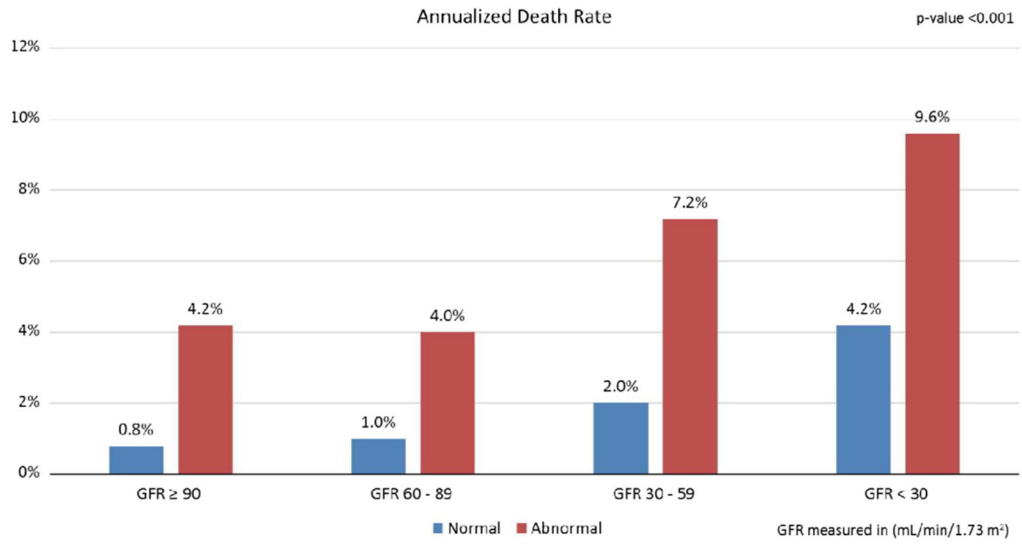

Figure 1. Annualized death rate for myocardial perfusion imaging results across stages of renal function.

reclassification of 25% and 28% of low and intermediate risk patients into a higher risk category. The extent of ischemia was independently associated with prognosis, with SSS $\geq$ 4 and SSS $\geq$ 10 resulting in 110% and 150% increase, respectively, in cardiac events.

Some notable limitations exist in this study. There were selection bias, inherent in a retrospective study design, documentation bias, Berkson's bias, and diagnostic suspicion bias. Furthermore, within the realm of chronic kidney disease, end-stage renal disease patients were underrepresented in this study.

Ahmed et al. work significantly adds to the emerging body of evidence to risk stratify patients with CKD. Yoda et al. identified SSS, estimated glomerular filtration rate, and left ventricular systolic function as

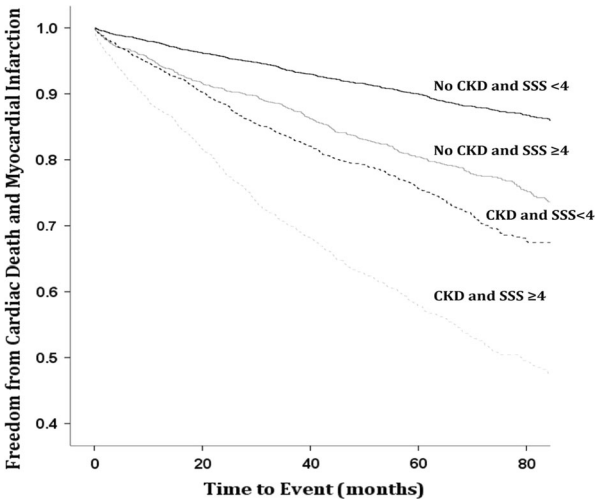

Figure 2. Risk stratification according to CKD and SSS.

significant predictors of adverse cardiac events in patients with CKD without coronary artery disease.[2] Furthermore, they found patients with CKD and SSS $\geq$ 10 had an annual death rate of 5.1%, compared to 0.8% in non CKD patients with SSS $<$ 9. This finding appears similar to the results yielded in the current investigation.

For a physician, SPECT-MPI continues to be a well-validated tool to assess cardiovascular risk in CKD patients beyond clinical predictors. SPECT-MPI offers physiologic data in addition to anatomic data that allow lesions to be appropriately treated in the cardiac catheterization lab and prevents interventions on lesions that are not physiologically relevant. This is especially important to patients with less than end-stage impairment in renal function as it may deteriorate into end-stage range due to the contrast induced nephropathy. Additionally, SPECT-MPI, as an initial approach for low-to-intermediate risk group patients with CKD, retains a powerful prognostic utility for forecasting event rates based on normal vs. abnormal perfusion. However, several abnormalities prevalent in patients with CKD, and specifically end-stage renal disease patients, may limit the predictive accuracy of SPECT-MPI.[3] For instance, poor endothelial function and the presence of impaired coronary flow reserve is known to exist in diabetic patients, which may decrease the sensitivity of vasodilator stress testing. Furthermore, existence of structural heart disease can limit the diagnostic sensitivity by missing small perfusion defects.

Since 1960s, our understanding of CKD and risk stratification for cardiovascular disease has advanced tremendously. However, this patient population continues to be underrepresented in the cardiac studies; many excluding patients with moderate-to-severe renal

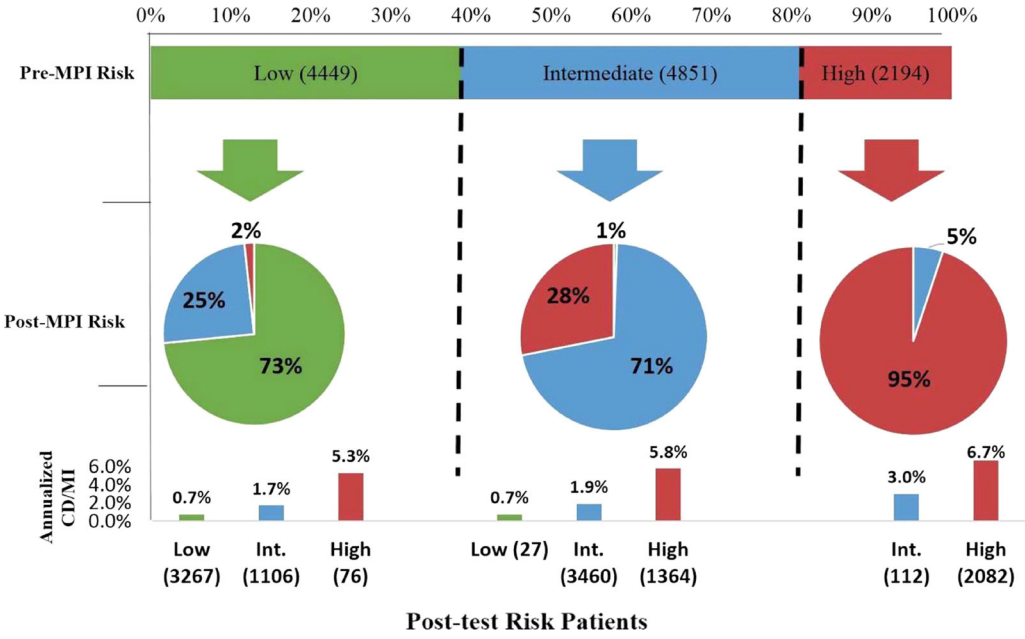

Figure 3. Risk reclassification of cardiovascular death and myocardial infarction in chronic kidney disease patient.

impairments. Thus, study by Ahmed et al. is noteworthy as it fills the gap in our understanding of this challenging patient population cardiac risk stratification. Through development of better non-invasive risk stratification approaches, we as physicians can treat CKD patients in a timely manner, through appropriate referral for invasive procedures such as coronary angiography, surgical interventions, and focus resources to prevent the progression of disease process. As we continue to bridge the gap in our knowledge, identifying molecular underpinnings of atherosclerosis, such as endothelial disruption, activation of renin-angiotensin system, oxidative stress, elevated levels of asymmetric dimethylarginine, continuous active inflammation, and circulating cytokines associated with renal impairment, we continue to build on the foundation of clinical and imaging framework of risk stratification.

Disclosure

No conflicts to disclose.

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