Cardiovascular risk assessment with regadenoson SPECT MPI in patients with end-stage renal disease is safe, effective, and well tolerated: Does it matter?

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Patients with chronic kidney disease (CKD) constitute a special population that carries substantial risks of developing cardiovascular disease and complications of diagnostic and prognostic evaluation. Glomerular filtration rate (GFR) is inversely related to the rate of cardiovascular events, and patients with end-stage renal disease (ESRD) carry more than three times the risk of suffering a cardiovascular event compared with patients who have normal GFR.[1] In recognition of this risk of excess morbidity and mortality of cardiovascular disease in this special population, the American College of Cardiology and the American Heart Association recommend considering CKD, a coronary heart disease risk equivalent.[2] Diagnostic and prognostic assessments of patients with CKD pose serious potential safety concerns associated with the unique pathophysiology of CKD, including increased risk of iodinated contrast-induced nephropathy associated with invasive or CT coronary angiography, and nephrogenic systemic fibrosis with gadolinium cardiac magnetic resonance imaging.[3] In patients with ESRD, mineralocorticoid excess, disordered bone and mineral metabolism, uremia, hyperhomocysteinemia, anemia, oxidative stress, inflammation, elevated norepinephrine and endothelin-1 levels cause vasoconstriction, frequent diabetes mellitus, depressed circulating endothelial progenitor cells (EPCs) for vascular repair, and enhanced vascular calcification which may predispose to the serious health risks of contrast exposure for diagnostic cardiac CT and MRI testing.[4] The excess clinical cardiovascular morbidity and mortality, the diagnostic and prognostic evaluation risks, and the complex pathophysiologic metabolic, inflammatory, hormonal, and hematologic insults of patients with CKD including ESRD are compounded by underrepresentation in cohort studies validating methods for assessing cardiovascular disease in this special population.[5]

Pooled data from the ASSUAGE and ASSUAGE-CKD trials represent the largest prospective study of the use of regadenoson-stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in patients with CKD including ESRD and have established the safety and tolerability of regadenoson vasodilator stress SPECT imaging in this high-risk population. A remarkable finding of the ASSUAGE trial has been the high degree of patient satisfaction associated with routine reversal of regadenoson with aminophylline, with 91% patients receiving aminophylline reversal indicating they would definitely or probably be willing to repeat the test.[6] Prior to the ASSUAGE-CKD Trial, safety concerns existed for the potential of serious adverse events associated with reduced excretion, enhanced exposure, and toxicity of regadenoson. These concerns seemed justified on the basis of the triphasic half life of regadenoson with a 2-hour terminal elimination phase of regadenoson and

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with urinary elimination of 57% of administered regadenoson as unchanged drug.[7] Indeed, patients with CKD and ESRD demonstrate reduced clearance of regadenoson and are exposed to the regadenoson for a longer periods of time which likely explains the finding of greater prevalence of headaches and minor gastrointestinal adverse effects including diarrhea and abdominal discomfort which were substantially reduced with prophylactic administration of aminophylline, which competitively inhibits A2a receptor activation and associated coronary vasodilation compared to placebo-treated patients.[6,8] In the ASSUAGE-CKD trial, routine standardized administration of intravenous 75 mg aminophylline 90 s post-radioisotope injection in all patients with severe CKD substantially reduced the frequency of any prespecified adverse event, diarrhea and headache, and severity of the adverse effects associated with regadenoson-stress and was better tolerated in the aminophylline group without changing the ischemic burden. [9] Thus, with prompt routine reversal of regadenoson with administration of aminophylline, regadenoson vasodilator SPECT MPI is safe and well tolerated in patients with ESRD without increased risk of serious adverse events.

Beyond safety and tolerability of regadenoson SPECT MPI demonstrated in the ASSAUAGE and ASSUAGE-CKD trials, in the current study, Doukky et al. report that regadenoson-stress SPECT MPI with 99mTc-tetrofosmin provides significant prognostic value in patients with ESRD, defined as GFR <15 mL/min/1.73 m^2 or renal dialysis therapy.[10] The investigators analyzed 303 patients who were followed for approximately 3 years. Adjusting for clinical covariates, abnormal regadenoson-stress MPI (SSS $\geq$4) was associated with increased risk of the composite of cardiac death or MI (23.9% vs 14.4%; HR 1.88; CI 1.04–3.41; $P = .037$) and the composite of cardiac death, MI, or late cardiac revascularization (27.3% vs 16.7%; HR 1.80; CI 1.03–3.14; $P = .039$). Adjusting for clinical covariates, regadenoson-induced myocardial ischemia (SDS $\geq$2) was associated with increased rate of the composite endpoint of cardiac death, MI, or late cardiac revascularization (33.3% vs 16.9%; HR 1.97; CI 1.19–3.27; $P = .008$).

Predictably, a stepwise increase in the risk of adverse cardiac events, commensurate with the extent and severity of perfusion abnormality, was observed. Regadenoson SPECT MPI added incremental prognostic value above and beyond traditional risk factors. The prognostic value of regadenoson-stress MPI was consistent irrespective of LV ejection fraction, LV end-diastolic volume, and LV mass, meaning that results of regadenoson SPECT MPI evaluation can be added to existing tools for risk assessment to quantify more precisely risk of cardiovascular morbidity and mortality in patients with ESRD. While the twofold increase in risk assessment in this study is less than may have been predicted based on extensive literature of risk assessment with SPECT MPI, the investigators offer two important observations about their study population which may explain this modest magnitude of incremental risk assessment: (1) the study population is predominantly ESRD patients without ischemic symptoms who are undergoing CAD surveillance as part of kidney transplant evaluation; and (2) due to ESRD, all patients are at increased risk irrespective of MPI finding.[11,12] Additional factors may include (3) diffuse microvascular dysfunction associated with ESRD may have further reduced the discriminative prognostic capacity of semi-quantitative regional regadenoson SPECT MPI; and (4) underestimation of vasodilator stress induced ischemia with diffuse intermediate stenotic coronary plaque associated with reduced tracer extraction of Tc99m-tetrofosmin compared to Tc-99m-sestamibi.[13]

An important limitation of the study addressed by the authors is that their investigation is a single-center study, and validation of these results is warranted in order to conclude that the results are generalizable to the ESRD population. Second, many of the included patients were undergoing evaluation for renal transplantation and could therefore be considered ''healthier'' ESRD patients. However, risk stratification for patients awaiting renal transplantation is important clinically and represents a unique advantage of safety, tolerability, and effectiveness of regadenoson SPECT MPI. Remarkably, the investigators report an expected and troublesome observation: ESRD patients with normal SPECT MPI have a relatively high event rate of cardiac death or MI: 4.9% per year, a rate that exceeds that of many other patient populations.

The very high hard cardiac event rate in ESRD patients with non-ischemic MPI studies gives us pause to reflect and consider the value of this testing approach. Does a modest incremental twofold risk assessment of cardiovascular morbidity, mortality, and need for revascularization matter in a special population that carries a high risk of events in the lower risk cohort that requires intensive ongoing therapy? In short, yes it matters. Renal transplantation is associated with superior quality of life and enhanced survival compared to patients who remain on the waiting list.[14,15] Sadly, the supply of kidney donors falls far short of demand for patients with CKD and ESRD who are candidates for kidney transplant surgery. In societies where donors for renal transplantation are in short supply and renal transplantation programs are under public and regulatory scrutiny and funding pressure to optimize outcomes of

renal transplantation, safe, effective, and well tolerated risk stratification with regadenoson SPECT MPI can be predicted to continue to grow. Beyond this foreseeable need to optimize success of renal transplantation programs and enhance quality and quantity of life of patients with ESRD, monitoring the effectiveness of CV risk reduction associated with innovative dialysis strategies and medical therapies directed at correcting the complex pathophysiology of CKD and ESRD provides promising opportunities for further research. While semi-quantitative assessment of SPECT MPI is an extensively validated risk factor in studies of prognostication, studies of quantitative coronary flow reserve assessment with cardiac PET MPI by Murthy, Ziadi, and Taqueti have been shown to reclassify risk in more than one-third of patients and optimize cardiac risk stratification.[16–19] Semi-quantitative assessment of regional myocardial perfusion with SPECT MPI and quantitative assessment of global myocardial flow reserve with PET MPI using regadenoson vasodilator stress and rapid routine reversal with aminophylline in patients with ESRD may be expected to provide the most effective, safest, and best tolerated means of identifying the lowest risk patients whose best chance of survival with renal transplantation can be optimally identified.

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