Chronic kidney disease and risk for coronary events: Value of myocardial perfusion imaging

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The risk of all-cause mortality, cardiac mortality, and prevalence of cardiovascular disease rises significantly in proportion to the decrement in renal function as measured by the eGFR.[1-3] The cardiac event rate rises significantly once the eGFR falls below 60/mL/min/m^2. Chronic kidney disease (CKD) patients have more than a 10- to 20-fold increased risk of cardiac death compared with age- and gender-matched subjects without CKD.[4] Many patients with CKD die from cardiovascular causes before they require dialysis. For patients with Stage 5 CKD, cardiovascular mortality is 10-30 times higher than in the general population. The 2-year mortality rate after an acute myocardial infarction in patients with Stage 5 CKD is estimated to be 50%. For patients with Stages 3 to 4 CKD, the majority die of cardiovascular causes before they develop end-stage renal disease (ESRD). Diabetic patients with CKD have a higher cardiac event rate than nondiabetic patients with CKD.

Approximately one-half of the patients on hemodialysis who have significant CAD have no symptoms such as chest pain. CKD patients have a high mortality after primary PCI for an acute ST-elevation myocardial infarction.[5] The in-hospital mortality was 29% in this study for patients with severe renal dysfunction.

In addition to the traditional risk factors associated with CAD, patients with CKD also exhibit marked endothelial dysfunction, abnormal coronary flow reserve, low grade inflammation, markers of oxidative stress, accelerated vascular calcification, activation of the renin-angiotensin system, anemia and vitamin D deficiency.

With such a high prevalence of CAD and cardiovascular events in patients with CKD, nephrologists usually refer CKD patients for either stress MPI or stress echocardiography, or refer them directly for cardiac catheterization in order to identify those with CAD. The rationale for such testing is the notion that revascularization may improve outcomes. This screening is deemed particularly relevant for patients going on hemodialysis and listed for renal transplantation. Patients manifesting abnormal perfusion on stress imaging prior to renal transplantation have a worse event-free survival after transplant.[6,7] Knowledge of presence of CAD or inducible ischemia may also prompt more aggressive anti-ischemic therapy and CAD risk factor modification. The problem with pursuing an invasive screening strategy at the outset is that many ESRD patients have diffuse CAD but may not be manifesting ischemia. It has been known for some time that many stenoses that are intermediate in severity (50%-70%) are associated with normal fractional flow reserve and PCI is not effective in improving outcomes.

Several studies published in recent years lend support to the value of stress MPI for risk stratifying patients with CKD. Hakeem et al[8] stratified patients according to both the eGFR and the summed stress score (SSS), which is a semiquantitative measure of the extent and severity of stress MPI defects. They found a substantial increase in cardiac death once the eGFR fell below 60 and the SSS exceeded 8.0. The annual rate of all-cause mortality and subsequent nonfatal myocardial infarction was also significantly higher in patients with an eGRF of <60 and SPECT perfusion defects compared patients with an eGFR of ≥60 who had perfusion defects. The annual cardiac death rate more than doubled in the patients with more severe renal dysfunction who had defects (9.5% vs 4%). In contrast, the annual cardiac death rate was only 0.8% in patients with an eGFR of ≥60 and normal SPECT MPI studies.

In a subsequent study by Hakeem et al,[9] patients with CKD were divided between those with and without diabetes. As expected, the patients with the combination of CKD and diabetes had the highest cardiac event rate compared to those with CKD alone, diabetes alone, or the absence of both. Furthermore, the annual cardiac death rate was 16.8% for patients with CKD+ diabetes who had a SSS >8 and 5.4% for such patients with an SSS of 4-8. This is compared to an annual death rate of 6% and 2.4%, respectively, for patients with diabetes and patients with no CKD.

Venkataraman et al[10] showed that the larger the defect size on vasodilator stress MPI, the worse the prognosis for patients on hemodialysis. Risk stratification was better achieved employing defect size as the variable compared to extent of anatomic CAD as determined on coronary angiography. The event rate of patients with no significant coronary stenoses was

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similar to the event rate for patients with one- and two-vessel disease. The dialysis patients with 3-vessel disease had a worse outcome than the other groups. Patients with an LVEF of ≤40% had even a worse outcome with moderate or severe perfusion defects than patients with an LVEF of >40%. One reason for better discrimination of high, intermediate, and low risk with MPI compared to the anatomic stratification into 0-, 1-. 2-, and 3-vessel disease is the observation that CKD patients with perfusion defects on SPECT, with insignificant CAD on angiography, have a substantially higher cardiac event rate than non-CKD patients with insignificant CAD.[11] This may reflect the endothelial dysfunction in CKD patients with even mild coronary atherosclerosis as seen on catheterization.

Thus, these studies suggest that stress MPI can identify high-risk CKD patients and the greater the perfusion abnormalities and the greater the renal dysfunction the higher the risk of cardiac complications. Patients with CKD+ diabetes with moderate or large perfusion defects are at the highest risk for future cardiac events. The noninvasive MPI approach appears to yield better risk stratification in asymptomatic CKD patients than direct referral to coronary angiography. The latter, as the first test for risk assessment, poses a risk with contrast administration for those ESRD patients not yet on dialysis. What is yet to be determined with clinical research studies is whether revascularization improves outcomes in such patients with advanced CKD who have ischemic defects on MPI. No randomized studies have been performed comparing medical therapy to revascularization in patients with advanced CKD. In fact, in-hospital and 1-year mortality is quite high for patients with a significant decrement in eGFR who receive drug-eluting stents.[12] This is an area where more clinical trials are warranted. Suffice it to say that CKD Stage 4 or 5 patients, particularly with diabetes and other CAD risk factors, are among the highest risk patients for cardiovascular mortality, and the question of whether noninvasive risk assessment as with MPI can impact on prognosis is not yet answered. Whether knowledge of the presence of asymptomatic CAD and ischemia with MPI truly impacts outcomes with revascularization vs medical therapy is yet to be determined.

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