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Cardiac Stress Testing in Patients With Chronic Kidney Disease

Cardiovascular disease (CVD) is a major cause of morbidity and mortality among patients with chronic kidney disease (CKD),[1] whether or not other risk factors for heart disease are present.[2] Even patients with early-stage or mild kidney disease have a higher risk of CVD and heart disease-related death vs the general population.[2] Therefore, it is recommended that healthcare providers routinely evaluate their patients with CKD for signs and symptoms of CVD to assess risk and initiate appropriate management.[3]

STAGES OF CHRONIC KIDNEY DISEASE

Chronic renal insufficiency is the stage of chronic renal disease in which damage to the kidney has impaired renal function, but systemic manifestations are minimal. Because most patients with renal insufficiency are asymptomatic, the disease is usually detected because serum creatinine is slightly elevated. In chronic renal failure, renal dysfunction has progressed to a level that results in systemic manifestations including a rise in blood concentration of urea, creatinine, and phosphate, which are all normally eliminated by the kidneys. Most patients with chronic renal failure progress to end-stage renal disease (ESRD). Diabetes mellitus is the primary cause of ESRD, which also has risk factors for CVD including obesity, hypertension, and abnormal cholesterol levels. ESRD is generally irreversible and requires dialysis or kidney transplantation to sustain life.[4]

The severity of CKD is based on several factors, one of which is the ability of the glomerular capillaries to filter fluid from the blood. As nephrons begin to be lost in stage 1 CKD, the kidney initially compensates by increasing the glomerular filtration rate (GFR). However, the continued loss of nephrons (<60 mL/min/1.73 m^2) eventually overwhelms the compensatory mechanism and GFR declines in stages 2 through 4. When GFR drops below 15 mL/min/1.73 m^2, the patient has reached stage 5 CKD, or end-stage renal disease, in which the kidney has failed and dialysis is necessary, Table 1.[3]

CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is the leading cause of death in patients with CKD prior to progression to end-stage renal disease (ESRD),[3] which indicates that even early CKD is a significant risk factor for cardiovascular events and death. The prevalence of hypertension among patients with CKD ranges from 60% to 100%.[5] Elevated total cholesterol is found in 30% of CKD patients without nephrotic syndrome and 90% of CKD patients with nephrotic syndrome, vs 20% of the general population.[5]

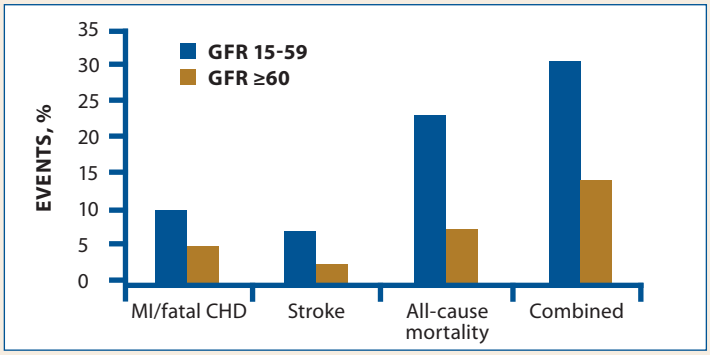
CVD—including coronary heart disease, cerebrovascular disease, peripheral vascular disease, and congestive heart failure—may be both a cause and a complication of CKD.[3,6] For example, congestive heart failure can lead to renal failure. Likewise, severe hypertension can lead to extensive, and rapidly progressing, renal damage.[4] Conversely, electrolyte imbalances caused by renal disease can lead to cardiac arrhythmias. Renal disease can also lead to hyperlipidemia as a result of increased synthesis and decreased clearance of lipoproteins from the body during nephrotic syndrome. These patients typically have increased levels of low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) with little change in high-density lipoproteins (HDL). These consequences of renal disease are significant risk factors for atherosclerosis and the development of CAD.[4]

Table 2 shows the pooled results from 4 publicly available, community-based longitudinal studies representing a population of more than 22,000 patients who were followed for an average of 99 months.[7]

Table 1. CKD Stages Based on GFR

STAGE	DESCRIPTION	GFR (mL/min/1.73 m^2)
1	Kidney damage with mildly normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 (or dialysis)

Table 2. CKD and CVD



The fully adjusted hazard ratio was significantly higher for patients with CKD (defined in this study as a GFR 15-59 mL/min/1.73 m^2) as compared with those without CKD (defined as a GFR ≥60 mL/min/1.73 m^2). Thus, chronic kidney disease was found to be a risk factor for all-cause mortality and cardiovascular events in the general population.

Based on the results of studies like this one, current guidelines recommend that all patients with CKD be considered at high risk for cardiovascular disease, whether or not other CVD risk factors are present.[3] Compared with CVD in the general population, CVD in patients with CKD has:[8]

- Earlier onset
- More rapid progression
- Stronger association with calcification
- Increased vascular stiffness
- Resistance to lipid-lowering properties of statins
- Increased complications with revascularization
- Higher rates of sudden death

Therefore, detection and management of CVD should be a standard component of care for all patients with CKD.[9]

CARDIAC RISK ASSESSMENT

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) evidence-based guidelines state that all patients with CKD (defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months) should be considered in the "highest risk group" for subsequent CVD events and should undergo assessment for traditional and CKD-related CVD risk factors, as listed in Table 3.

The KDOQI guidelines state that "risk factor reduction is likely to be effective in reducing morbidity and mortality due to cardiovascular disease in patients with chronic kidney disease."[3] Early detection and intervention may prevent or delay cardiovascular adverse events[9] and potentially improve outcomes for this high-risk patient population.[10]

CARDIAC STRESS IMAGING IN PATIENTS WITH CKD

Detecting the extent and severity of myocardial ischemia provides useful information for the risk stratification and management of patients with varying degrees of renal dysfunction.[11]

Exercise electrocardiographic (ECG) testing and exercise stress testing are often limited by the inability of patients with CKD to achieve peak exercise capacity. ECG may be uninterpretable in many cases because of the potential for exercise-induced hypotension and the presence of left ventricular hypertrophy in this patient population.[10] Likewise, coronary angiography is often contraindicated in patients with renal failure because of the risk of contrast nephropathy.[6] Therefore, in patients with CKD, pharmacologic stress myocardial perfusion imaging (MPI) is often required.[12]

Table 3. CVD Risk Factors

TRADITIONAL CVD RISK FACTORS	ADDITIONAL CKD-RELATED CVD RISK FACTORS
• Older age	• Type of CKD
• Male gender	• Decreased GFR
• White race	• Proteinuria
• Hypertension	• Renin-angiotensin system activity
• Elevated LDL cholesterol	• Extracellular fluid volume overload
• Decreased HDL cholesterol	• Abnormal calcium and phosphorus metabolism
• Diabetes mellitus	• Dyslipidemia
• Tobacco use	• Anemia
• Physical inactivity	• Malnutrition
• Menopause	• Inflammation
• Psychosocial stress	• Infection
• Family history of CVD	• Thrombogenic factors
	• Oxidative stress
	• Elevated homocysteine
	• Uremic toxins

Adapted from National Kidney Foundation, *Am J Kidney Dis*. 2002;39:S1-S266.

CONCLUSIONS

CVD is prevalent in patients with CKD and is the leading cause of death, regardless of the stage of kidney disease.[2] All patients with CKD are at the "highest risk" for CVD according to the National Kidney Foundation KDOQI evidence-based clinical practice guidelines.[3] In addition, the KDOQI guidelines recommend that all patients with CKD undergo routine assessment for CVD because regular screening may help identify CKD patients who would benefit from interventions to reduce CVD risk.[3] Radionuclide MPI for patients who have CKD and either known or suspected CAD may help predict adverse cardiac outcomes and provide appropriate management to reduce cardiac risks in this patient population.[10,11]

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