AHA Science Advisory

Detection of Chronic Kidney Disease in Patients With or at Increased Risk of Cardiovascular Disease

A Science Advisory From the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group

Developed in Collaboration With the National Kidney Foundation

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Abstract*—**Chronic kidney disease (CKD) occurs commonly in patients with cardiovascular disease. In addition, CKD is a risk factor for the development and progression of cardiovascular disease. In this advisory, we present recommendations for the detection of CKD in patients with cardiovascular disease. CKD can be reliably detected with the combined use of the Modification of Diet in Renal Disease equation to estimate glomerular filtration rate and a sensitive test to detect microalbuminuria. All patients with cardiovascular disease should be screened for evidence of kidney disease with these two determinations. (Circulation*. 2006;114:1083-1087.)**

Key Words: AHA Scientific Statements ■ chronic kidney disease ■ albuminuria ■ risk factors

Recommendations

Class I

1. **The Modification of Diet in Renal Disease (MDRD) equation should be used to estimate glomerular filtration rate in adult patients with cardiovascular disease. Values <60 mL/min per 1.73 square meters body surface area should be regarded as abnormal**. ***(Level of Evidence: B)***

Class IIa

1. **The albumin-to-creatinine ratio should be used to screen for the presence of kidney damage in adult patients with cardiovascular disease. Values >30 mg albumin per 1 g creatinine should be regarded as abnormal.** ***(Level of Evidence: B)***
2. **All adult patients with cardiovascular disease should be screened for evidence of kidney disease with determinations of estimated glomerular filtration rate using the MDRD equation and albumin-to-creatinine ratio.** ***(Level of Evidence: C)***

It is estimated that up to 11% of adults in the United States have chronic kidney disease (CKD),[1] and the prevalence of CKD is even higher among patients with cardiovascular disease.[2] Additionally, CKD is a major and serious risk factor for cardiovascular disease.[2] Death from cardiovascular disease is 10 to 30 times higher in dialysis patients than in the general population. Recent studies have confirmed that even early CKD constitutes a significant risk factor for cardiovascular events and death.[3,4] In addition, CKD is a risk factor for recurrent cardiovascular events,[5] and proper management of cardiovascular disease is different and more complex in patients with CKD.[6] Finally, both the frequency of cardiovascular complications and the progression of CKD can be ameliorated in these patients by appropriate intervention. For all these reasons, healthcare providers should evaluate their patients for the presence of CKD as part of preventive care and treatment strategies.

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CKD is defined as structural or functional abnormalities of the kidney that persist for at least 3 months and are manifested by either kidney damage (most frequently detected as persistent albuminuria; >30 mg albumin/g creatinine) or a decreased glomerular filtration rate (GFR) (<60 mL/min per 1.73 m^2). Because techniques commonly used to estimate renal function often fail to detect patients with mild to moderate reduction in GFR and because screening for albuminuria is not consistently performed, CKD in many patients remains unidentified. Because a clinically useful method of accurately detecting CKD in patients is needed, this advisory will address currently available methods and make recommendations about the most appropriate screening tests for CKD.

The most accurate method to determine kidney function is a formal GFR measurement with iothalamate or similar markers. Such time-consuming tests are expensive, generally unsuitable for clinical practice, available in only a few centers, and certainly not cost-effective for CKD screening. Creatinine is a useful endogenous marker of renal filtration or GFR, but there are problems with the routine use of serum creatinine to estimate GFR. Inference of GFR from the serum creatinine level alone is complicated by the differing rates of creatinine production between persons, mainly because of variations in muscle mass. Women and the elderly often have deceptively low serum creatinine levels, despite substantial reductions in GFR. The inverse, nonlinear relation between serum creatinine level and GFR also clouds interpretation; healthcare providers often misinterpret small increases in creatinine as clinically insignificant. Currently, more suitable serum indicators of GFR are not available, although one possible exception to this is cystatin C.

Cystatin C is a serine protease inhibitor released at a relatively constant rate from all cells and is freely filtered by the glomerulus. Several studies have suggested that it may approximate GFR better than creatinine,[7–9] and a recent report has found that cystatin C levels better predict the development of congestive heart failure in elderly patients than do serum creatinine values.[10] However, cystatin C production may not remain completely constant, and factors other than kidney function may affect cystatin C levels, such as age, male sex, weight, height, cigarette smoking, serum C-reactive protein levels, steroid therapy, and rheumatoid arthritis.[11,12] Therefore, it is not certain that cystatin C has sufficient specificity to serve as a reliable indicator of GFR.

Traditionally, calculation of creatinine clearance from timed urine collections has been used for estimation of GFR. However, these timed urine collections are cumbersome and fraught with error, largely as a result of inaccurate urine collection.

Given the lack of accuracy of these methods, a more suitable screening test for GFR is needed. Fortunately, several validated estimation equations for GFR that use easily obtained clinical data and laboratory test results are available. These methods allow healthcare providers to diagnose CKD with greater accuracy. This advisory will describe these methods and their applicability to patients with cardiovascular disease.

TABLE 1. MDRD Study Equations for Calculating GFR

MDRD 1	$GFR = 170 \times [SCr]^{-0.999} \times [Age]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}] \times [BUN]^{-0.170} \times [Alb]^{0.318}$
MDRD 2 (Abbreviated)	$GFR = 186 \times [SCr]^{-1.154} \times [Age]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.21 \text{ if patient is black}]$

SCr indicates serum creatinine; BUN, blood urea nitrogen; and Alb, serum albumin.

This formula can be downloaded to a PDA by visiting http://www.kidney.org/professionals/kdoqi/cap.cfm.

Over the past decade, equations that estimate GFR on the basis of serum creatinine concentration and other easily obtainable patient data have been developed and validated. The widely used Cockcroft-Gault method uses serum creatinine, gender, age, and ideal weight.[13] However, weight measurements or estimations make calculation and reporting of Cockcroft-Gault results by laboratories problematic.

Other formulas have been validated that use data that are readily available to laboratories.[14–16] The formula developed from the Modification of Diet in Renal Disease (MDRD) study[14,15] is currently the best validated method to estimate GFR for adults in the typical office setting. There are 2 forms of this equation (Table 1). The original equation requires several laboratory tests in addition to the serum creatinine value, whereas the abbreviated MDRD study equation requires only demographic data plus the serum creatinine value. The abbreviated version appears to produce essentially similar results and is simpler.[17,18] It is important to note that GFR values derived from either form of the MDRD study equation can be automatically generated and placed in laboratory reports of any patient, because the age and gender information needed to make the calculation is generally included in the database on each patient. Because race is often not included in such databases, automatic reporting will include a comment asking the practitioner to multiply the calculated GFR by 1.21 for black patients.

Online calculators for the MDRD GFR equation are available from the National Kidney Foundation at www.kidney.org and from the National Kidney Disease Education Program (NKDEP) of the National Institutes of

TABLE 2. Screening for Chronic Kidney Disease[18,22–26]

1. Measure serum creatinine and calculate estimated GFR by the MDRD study equation (see Table 1). If estimated GFR is <60 mL/min per 1.73 m^2, repeat in 3 months.*
2. Obtain a random ("spot") urine for albumin-to-creatinine ratio determination. If albumin-to-creatinine is >30 mg albumin/g creatinine, repeat in 3 months.*
   - If either test is positive and persists for 3 months, the patient should be considered to have CKD. Appropriate evaluation and treatment should be undertaken as recommended in clinical practice guidelines.[23–26]
   - If tests are both negative, they should be repeated annually.
   - If estimated GFR is <30 mL/min per 1.73 m^2 or rapidly decreasing, or if urinary albumin-to-creatinine is >300 mg albumin/g creatinine, the patient should be referred to a nephrologist.

*If clinically indicated, repeat test sooner than 3 months as well as at 3-month mark.

Health at www.nkdep.nih.gov. The National Kidney Foundation and the American Society of Nephrology have joined with the NKDEP to educate healthcare providers about the need to routinely screen for CKD. In addition, these groups are encouraging laboratories to report estimated GFR using the MDRD formula along with serum creatinine to improve early detection of CKD.[19]

Although both forms of the MDRD study equation have been validated by other research groups for patients with significant reduction in GFR, their accuracy is reduced in persons with normal or only slightly diminished renal function. As screening tools, they can overestimate the number of patients with CKD,[17,18,20] and their accuracy in patients with cardiovascular disease has not been well substantiated. However, a study of patients with left ventricular dysfunction showed that a GFR $<$60 mL/min per 1.73 m^2, calculated by the MDRD study equation, remained an independent risk factor for death,[21] which suggests that the predictive value of the test was high. On balance, therefore, the MDRD study equation appears to accurately detect CKD in heart failure patients, including those with GFRs $<$60 mL/min per 1.73 m^2, and is likely to be applicable to patients with other cardiovascular diseases.

Albuminuria ($>$30 mg urinary albumin excretion per 24 hours) is associated with an increased risk for cardiovascular disease.[2,4] Spot urinary values $>$30 mg albumin/g creatinine are abnormal; repeated elevations of the urinary albumin-to-creatinine ratio over several months confirm increased cardiovascular risk and suggest the presence of CKD (Table 2). It should be noted that increased albuminuria may also reflect the presence of generalized endothelial dysfunction.[22,23] However, either condition is associated with increased cardiovascular risk. Therefore, screening for albuminuria should be included in the assessment of all patients. Urine albumin excretion of $<$300 mg/g creatinine is not reliably detectable with routine dipstick methods, so screening is best accomplished by determining the albumin-to-creatinine ratio on a spot urine specimen. Patients should be tested only when in stable condition without other acute complications, such as exacerbations of congestive heart failure, volume overload, and urinary tract infections, because these and other acute alterations are associated with transient increases in albumin excretion.[24] Finally, the sensitivity of this test may be reduced in patients who are already on angiotensin receptor blockade or angiotensin-converting enzyme inhibitor medications. Nonetheless, persistent albuminuria in that setting would likely reflect the presence of CKD. These urinary measurements have also been recommended as the standard of care by the National Kidney Foundation,[25–27] the American Diabetes Association,[24] and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[28] to screen for kidney disease.

Combined screening for microalbuminuria and estimation of GFR with the MDRD study equation are recommended for all adult patients with cardiovascular disease, including those with coronary artery disease or congestive heart failure as well as those with risk factors for CKD such as diabetes and hypertension, which are also risk factors for cardiovascular disease. Repeat screening at 3 months should be performed if either test is positive. If either test remains positive over at least a 3-month period, the patient should be considered to have CKD, and appropriate evaluation as to the cause of the CKD and appropriate treatment should be undertaken as noted in several published guidelines.[25–28]

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