Screening for Cardiovascular Disease in CKD: PRO

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KIDNEY360 3: 1831–1835, 2022. doi: https://doi.org/10.34067/KID.0005012021

Introduction

In nephrology practice, we often encounter patients with CKD experiencing a multitude of adverse health effects arising from cardiovascular diseases (CVD): coronary artery disease (CAD), peripheral vascular disease, cerebrovascular disease, dysrhythmias, cardiomyopathy, and valvular heart disease (Figure 1). Not surprisingly, CVD is the leading cause of death in such patients, and some clinical practice guidelines recommend that all patients with CKD, regardless of symptoms, be evaluated for CVD (1). The conundrum faced by practicing nephrologists is that given CKD is now considered an atherosclerotic CVD (ASCVD) risk equivalent (2,3), why screen and not just treat all patients with CKD with available evidence-based CVD treatments?

Screening is defined as a process to detect risk factors (primary prevention) or occult pathologies (secondary prevention), so that early detection would lead to prompt and efficacious intervention, alter the natural history of a disease process, and improve outcomes. We, therefore, argue that screening for CVD that includes diagnosis, risk stratification, identification of those who may benefit from early intervention, and monitoring response to interventions (4) should be undertaken in patients with CKD for the following reasons. First, all patients with CKD with the same GFR may not have the same risk in the absence of diabetes mellitus or other ASCVD risk enhancers, and risk is likely lower in patients with nondiabetic etiology of CKD, such as autosomal dominant polycystic kidney disease (5). Second, all patients with CKD who are undergoing evaluation for kidney transplantation should be screened in order to address perioperative risk. Third, treating all patients with CKD with evidence-based CVD interventions derived in the general population (e.g., aspirin, statins, and revascularization) may not be without risk. Herein, we review the existing data and the rationale for risk stratification and screening of asymptomatic individuals and monitoring progression of CVD. It should be emphasized that most of the existing recommendations are based on extrapolation or an absence of data, given that patients with CKD, particularly those with advanced CKD, were excluded from most studies that inform evidence-based CVD screening guidelines.

Risk Stratification and Screening of CVD in Asymptomatic Individuals

There is scarce evidence to support screening of asymptomatic patients with CKD, and specific recommendations from most guidelines are lacking. Detectable cardiac troponins, elevated N-terminal brain natriuretic peptide (BNP), and BNP are associated with higher left ventricular mass index, CVD events, and death in patients with CKD (4). Blood levels of cardiac troponins and N-terminal BNP/BNP are chronically elevated in >80% of asymptomatic individuals with advanced CKD, and the presence of abnormal levels does not trigger a spate of investigations for further risk stratification in asymptomatic individuals with CKD. In the non-CKD population, screening of asymptomatic patients at risk for heart failure with annual measurements of blood BNP levels, followed by echocardiographic and cardiology evaluations among those with BNP levels ≥50 pg/ml, was shown to reduce incident heart failure or left ventricular systolic dysfunction (6). However, it remains unclear whether such cardiac evaluation in response to elevated cardiac biomarkers would improve outcomes for asymptomatic patients with CKD.

A normal electrocardiogram (EKG) is usually reassuring; an abnormal one, a fairly common occurrence in patients with CKD, requires comparison with previous ones to determine clinical relevance. Routine exercise stress testing is seldom performed in patients with CKD due to a higher prevalence of abnormal baseline EKGs and mobility problems. Transthoracic echocardiography is the first choice for assessing anatomic and functional abnormalities affecting the left ventricular mass index, valves, and left ventricular ejection fraction and evaluating for wall motion abnormalities. Further testing using a stress myocardial perfusion scan achieved by drugs or exercise should be considered in those who have an abnormal echocardiogram.

Early invasive strategies are poorly utilized in patients with CKD who screen positive, especially in those with a GFR <30 ml/min per 1.73 m². The ISCHEMIA-CKD trial randomly assigned patients with CKD with stable CAD but with evidence of moderate or severe ischemia on stress testing to initial invasive strategy consisting of coronary angiography and revascularization or to medical management (7). Early invasive strategy reduced the composite of...
death or acute myocardial infarction but was associated with higher incidences of stroke or dialysis initiation and no difference in symptom/angina-free health status. Stress testing may fail to detect significant functional CVD, resulting in global ischemia in those with multivessel CAD, and is limited in individuals who develop collaterals in chronic occlusive CAD (8). For these complex anatomic abnormalities, coronary artery bypass graft is recommended only in the setting of acute myocardial infarction, and its benefits remain unclear in asymptomatic patients with CKD.

**Figure 1.** Cardiovascular disease manifestations in patients with CKD.

**Figure 2.** Algorithm for ASCVD screening in asymptomatic patients with CKD but without known cardiovascular disease. ASCVD, atherosclerotic cardiovascular disease; CAC, coronary calcium scores. ASCVD risk enhancers include family history of premature ASCVD (men, age <55 years; women, age <65 years), primary hypercholesterolemia, metabolic syndrome, chronic inflammatory conditions, premature menopause (before 40 years of age) or history of preeclampsia, high-risk race, and persistently elevated triglycerides $\geq 175$ mg/dl.
Table 1. Recommendations for cardiovascular screening in asymptomatic patients with CKD

| Source | Recommendations |
|--------|-----------------|
| KDOQI (1) | A baseline electrocardiogram should be obtained at dialysis initiation. An echocardiogram should be obtained after achieving dry weight and at 3-year intervals thereafter. A clinical examination should be performed at dialysis initiation and imaging (ABI or CTA lower extremities) only obtained for those with an abnormal examination. |
| KDIGO (5) | Patients with CKD should be regularly examined for signs of PVD and be considered for usual approaches to therapy. Regular podiatry care should be offered to diabetic patients with CKD. Serum concentrations of BNP/NT-proBNP and cardiac troponins should be interpreted with caution and in relation to GFR. |
| KDIGO (9) (transplant) | All candidates being considered for kidney transplant should be evaluated for cardiac disease with history, physical examination, and EKG. Asymptomatic CKD candidates with poor functional capacity or individuals at risk for ASCVD (e.g., history of diabetes or CAD) should undergo noninvasive screening and be evaluated by a cardiologist. Asymptomatic dialysis-dependent candidates should undergo echocardiography to evaluate for pulmonary hypertension. All candidates should be evaluated by history and physical examination for presence and severity of PVD. Asymptomatic individuals should undergo non-invasive testing (e.g., ABI) if they have an abnormal exam. Asymptomatic candidates who screen positive on ABI should undergo a noncontrast CT scan of the abdomen and pelvis. Asymptomatic candidates do not need to be screened for CBVD. Candidates with ADPKD could be screened for intracranial aneurysms if there is a family history of subarachnoid bleeds. |
| ESC/ACC (2,6) | ASCVD risk should be routinely assessed in individuals 40–75 years old. Assessment of ASCVD risk for individuals 20–39 years old should be performed every 4–6 years. Coronary calcium scores are useful in ruling out CAD in patients at intermediate risk ($\geq 8\%$ to $<20\%$ 10-year ASCVD risk). Use of cardiac biomarkers to screen asymptomatic individuals with CKD is not recommended. |

ABI, ankle brachial index; ACC, American College of Cardiology; ADPKD, autosomal dominant polycystic kidney disease; ASCVD, atherosclerotic cardiovascular disease; BNP, brain natriuretic peptide; CAD, coronary artery disease; CBVD, cerebrovascular disease; CT, computed tomography; CTA, computed tomography angiogram; EKG, electrocardiogram; ESC, European Society of Cardiology; KDOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease: Improving Global Outcomes; PVD, peripheral vascular disease.

Although the measurement of the ankle brachial index (ABI) is a simple and inexpensive test for peripheral vascular disease screening, this index is often falsely elevated in patients with CKD due to vascular calcifications (1). There are no studies to show ABI screening improves limb survival for these patients (1), but ABI is widely used in clinical practice to screen asymptomatic individuals with an abnormal examination and is often supplemented with computed tomography angiography before peripheral revascularization. Finally, although carotid Doppler and brain imaging are used to diagnose disease in symptomatic individuals, these tests are rarely used to screen asymptomatic individuals (4).

Use of ASCVD Risk Calculator

Despite a lack of clear and consistent evidence to support screening for CVD in asymptomatic patients with CKD, data suggest that screening for CVD and early disease in asymptomatic individuals without CKD is meaningful and allows the implementation of interventions that would change outcomes. We suggest that these data be extrapolated to patients with CKD until more direct evidence becomes available in the population of patients with CKD. Overall, among asymptomatic individuals without CKD, existing data support assessing risk with an ASCVD calculator first to determine the presence of risk factors for future ASCVD events (3,8). The ASCVD risk calculator uses age, sex, race, blood pressure readings, cholesterol readings, presence of diabetes mellitus, smoking status, receipt of treatment with antihypertensive medications, statins, and aspirin as variables. The 10-year ASCVD risk is then calculated and categorized into low risk ($<5\%$), borderline risk (5% to $<8\%$), intermediate risk ($\geq 8\%$ to $<20\%$), or high risk ($\geq 20\%$). For individuals with borderline and intermediate risks, ASCVD risk enhancers are further used to revise the risk estimates. For younger individuals who are 20–39 years old, the aforementioned risk assessment is recommended every 4–6 years, as compared with annual assessment for individuals 40–75 years old.

Until more data become available, we suggest the use of these approaches to risk stratify asymptomatic patients with CKD without known CVD, as shown in Figure 2, at least once so that individualized management plans can be formulated. For those who qualify for screening using the algorithm in Figure 2, identification of anatomic and functional cardiac abnormalities should be undertaken. In the
setting of workup for kidney transplantation listing, every patient would get evaluated with an EKG, echocardiography, and ABI, and the decision to screen with noninvasive stress testing is based on the presence of poor functional capacity or recommended for individuals at risk for ASCVD, for example those with a history of diabetes or CAD (Table 1 and Figure 2) (9).

**Monitor Progression of CVD**

There are no data to support monitoring levels of circulating cardiac biomarkers or repeating cardiac imaging or stress testing to ascertain CVD progression in asymptomatic patients with CKD (4). We suggest individualized monitoring of patients for response to any CVD interventions that are implemented, and periodic assessment for any ensuing adverse events.

**Conclusion**

In summary, it is important to diagnose CVD early so that existing interventions can be deployed to modify risk factors in the management of certain patients with CKD, although evidence to support screening is scarce in asymptomatic individuals with CKD. This area is ripe for research, as is identification of novel CVD biomarkers and imaging modalities, specifically in the CKD population. Until more data become available, we recommend screening (1) patients with CKD in anticipation for kidney transplant listing; (2) asymptomatic patients with an eGFR of <60 ml/min per 1.73 m^2^, given advanced CKD is an ASCVD risk equivalent; (3) asymptomatic patients with an eGFR ≥60 ml/min per 1.73 m^2^ who have ASCVD risk scores ≥20%, presence of ASCVD risk enhancers, or those with ASCVD scores between ≥8% and 20% with coronary calcium scores of ≥100 units (Figure 2).

**Disclosures**

S.S. Hedayati reports honoraria from the American College of Physicians for participation in Nephrology MKSAP, American Society of Nephrology Post-Graduate Education Program, and is a scientific advisor for the American Heart Association, study sections, ACP, MKSAP Nephrology Committee. All remaining authors have nothing to disclose.

**Funding**

Support was provided by the American Society of Nephrology (ASN) Foundation for Kidney Research and the Data Scholar Award (NJ) from the Translational Research Institute (grant TL1 TR003109) through the National Center for Advancing Translational Sciences of the National Institutes of Health. M. McAdams is supported by training grant ST32DK007257-38 from the National Institutes of Diabetes and Digestive and Kidney Diseases. S.S. Hedayati is supported by the Yin Quan-Yuen Distinguished Professorship in Nephrology at the University of Texas Southwestern Medical Center, Dallas, Texas.

**Acknowledgments**

The content of this article reflects the personal experience and views of the authors and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the authors.

**Author Contributions**

S.S. Hedayati was responsible for the conceptualization; S.S. Hedayati and N. Jain wrote the original draft of the manuscript; and S.S. Hedayati and M. McAdams reviewed and edited the manuscript.

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**Received:** July 30, 2021 **Accepted:** November 30, 2021

See related debate, “Screening for Cardiovascular Disease in CKD: CON,” and commentary, “Screening for Cardiovascular Disease in CKD: COMMENTARY,” on pages 1836-1838 and 1839-1841, respectively.