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Key Points:

Abstract:

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Screening for Cardiovascular Disease in CKD: PRO

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Introduction

In nephrology practice, we often encounter patients with chronic kidney disease (CKD) experiencing a multitude of adverse health effects arising from cardiovascular diseases (CVD): coronary artery disease (CAD), peripheral vascular disease (PVD), 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. The conundrum faced by practicing nephrologists is that given CKD is now considered an ASCVD (atherosclerotic CVD) risk equivalent, why screen and not just treat all CKD patients 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 – should be undertaken in patients with CKD for the following reasons. First, all CKD patients with the same glomerular filtration rate (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 non-diabetic etiology of CKD, such as autosomal dominant polycystic kidney disease (ADPKD). Second, all CKD patients that are undergoing evaluation for kidney transplantation should be screened in order to address peri-operative risk. Third, treating all CKD patients with evidence-based CVD interventions derived in the general population – i.e., aspirin, statins, and revascularization, to name a few – 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 CKD patients, 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 (cTn), elevated N-terminal brain natriuretic peptide (NT-pro-BNP) and BNP are associated with higher left ventricular mass index (LVMI), CVD events, and death in CKD patients. Blood levels of cardiac troponins (cTn) and NT-pro-BNP/BNP are chronically elevated in >80% of asymptomatic individuals with advanced CKD, and 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. However, it remains unclear whether such cardiac evaluation in response to elevated cardiac biomarkers would improve outcomes for asymptomatic CKD patients.

A normal EKG is usually reassuring; an abnormal one, a fairly common occurrence in CKD patients, requires comparison to previous ones to determine clinical relevance. Routine exercise stress testing is seldom performed in CKD patients due to a higher prevalence of abnormal baseline EKGs, as well as mobility problems. Transthoracic echocardiography is the first choice for assessing anatomic and functional abnormalities affecting the LVMI, valves, and left ventricular ejection fraction (LVEF) 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 CKD patients who screen positive, especially in those with a GFR <30 ml/min/1.73m$^2$. The ISCHEMIA-CKD trial randomly assigned CKD patients 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. Early invasive strategy reduced the composite of death or AMI, 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 multi-vessel CAD, and is limited in individuals who develop collaterals in chronic occlusive CAD. For these complex anatomic abnormalities, coronary artery bypass graft is recommended only in the setting of AMI, and its benefits remain unclear in asymptomatic CKD patients.

Although the measurement of the ankle brachial index (ABI) is a simple and inexpensive test for PVD screening, this index is often falsely elevated in patients with CKD due to vascular calcifications. Although there are no studies to show ABI screening improves limb survival for these patients, ABI is widely used in clinical practice to screen asymptomatic individuals with an abnormal examination and is often supplemented with CT angiography prior to 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.

**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 CKD patient population.
Overall, among asymptomatic individuals \textit{without} CKD, existing data support assessing risk with an ASCVD calculator first to determine the presence of risk factors for future ASCVD events.\textsuperscript{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 anti-hypertensive medications, statins, and aspirin as variables. The 10-year ASCVD risk is then calculated and categorized into low risk (<5\%), borderline risk (5\% to <7.5\%), intermediate risk (\geq 7.5\% 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 abovementioned risk assessment is recommended every 4-6 years, as compared to annual assessment for individuals 40-75 years old.

Until more data become available, we suggest the use of the abovementioned approaches to risk-stratify asymptomatic CKD patients without known CVD, as shown in \textbf{Figure 2}, at least once so that individualized management plans can be formulated. For those who qualify for screening using the algorithm in \textbf{Figure 2}, identification of anatomic and functional cardiac abnormalities should be undertaken. In the setting of work-up 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, e.g., with history of diabetes or CAD (Table and Figure 2).\textsuperscript{9}

\textbf{Monitor progression of CVD}

There are no data to support monitoring levels of circulating cardiac biomarkers or repeating cardiac imaging or stress testing toascertain CVD progression in asymptomatic patients with CKD.\textsuperscript{4} We suggest individualized monitoring of patients for response to any CVD interventions that are implemented, as well as 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 CKD patients, although evidence to support screening is scarce in asymptomatic CKD individuals. 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) CKD patients in anticipation for kidney transplant listing; (2) asymptomatic patients with a eGFR of <60, given advanced CKD is an ASCVD risk equivalent; (3) asymptomatic patients with a eGFR ≥60 mL/min/1.73 m² who have ASCVD risk scores >20%, presence of ASCVD risk enhancers, or those with ASCVD scores between ≥7.5-20% with coronary calcium scores of ≥100 units (Figure 2).
DISCLOSURES
S. Hedayati reports the following: Honoraria: American College of Physicians for participation in Nephrology MKSAP, American Society of Nephrology Post-Graduate Education Program; Scientific Advisor or Membership: American Heart Association, study sections, ACP, MKSAP Nephrology Committee. The remaining authors have nothing to disclose.

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The content of this article reflects the personal experience and views of the author(s) 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 author(s).

AUTHOR CONTRIBUTIONS
Nishank Jain: Writing - original draft. Meredith McAdams: Writing - review and editing. S Susan Hedayati: Conceptualization; Writing - original draft; Writing - review and editing.
REFERENCES


Table. Recommendations for Cardiovascular Screening in Asymptomatic Patients with Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDOQI&lt;sup&gt;1&lt;/sup&gt;</td>
<td>A baseline electrocardiogram should be obtained at dialysis initiation.</td>
</tr>
<tr>
<td></td>
<td>An echocardiogram should be obtained after achieving dry weight and at 3-year intervals thereafter.</td>
</tr>
<tr>
<td></td>
<td>A clinical examination should be performed at dialysis initiation and imaging (ABI or CTA lower extremities) only obtained for those with an abnormal examination.</td>
</tr>
<tr>
<td>KDIGO&lt;sup&gt;5&lt;/sup&gt;</td>
<td>CKD patients should be regularly examined for signs of PVD and be considered for usual approaches to therapy. Regular podiatry care should be offered to diabetic CKD patients.</td>
</tr>
<tr>
<td></td>
<td>Serum concentrations of BNP/NT-proBNP and cardiac troponins should be interpreted with caution and in relation to GFR.</td>
</tr>
<tr>
<td>KDIGO&lt;sup&gt;10&lt;/sup&gt;</td>
<td>All candidates being considered for kidney transplant should be evaluated for cardiac disease with history, physical examination, and EKG.</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic CKD candidates with poor functional capacity or individuals at risk for ASCVD (e.g., history of diabetes or CAD) should undergo non-invasive screening and be evaluated by a cardiologist.</td>
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<td></td>
<td>Asymptomatic dialysis-dependent candidates should undergo echocardiography to evaluate for pulmonary hypertension.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
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<tr>
<td></td>
<td>Asymptomatic candidates who screen positive on ABI should undergo non-contrasted CT of the abdomen and pelvis.</td>
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<tr>
<td></td>
<td>Asymptomatic candidates don’t need to be screened for CBVD. Candidates with ADPKD could be screened for intracranial aneurysms if there is a family history of subarachnoid bleeds.</td>
</tr>
<tr>
<td>ESC/ACC&lt;sup&gt;2,6&lt;/sup&gt;</td>
<td>ASCVD risk should be routinely assessed in individuals 40-75 years old.</td>
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<td></td>
<td>Assessment of ASCVD risk for individuals 20-39 years old should be performed every 4-6 years.</td>
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<td></td>
<td>Coronary calcium scores are useful in ruling out CAD in patients at intermediate risk (≥7.5% to &lt;20% 10-year ASCVD risk).</td>
</tr>
<tr>
<td></td>
<td>Use of cardiac biomarkers to screen asymptomatic individuals with CKD is not recommended.</td>
</tr>
</tbody>
</table>

Figure Legends

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

**Figure 2.** Algorithm for ASCVD screening in asymptomatic patients with CKD but without known CVD. ASCVD, atherosclerotic cardiovascular disease; CAC, coronary calcium scores; eGFR, estimated glomerular filtration rate (units, mL/min/1.73 m²). ASCVD risk enhancers include family history of premature ASCVD (males, age <55 years; females, age <65 years), primary hypercholesterolemia, metabolic syndrome, chronic inflammatory conditions, premature menopause (before age 40 years) or history of preeclampsia, high risk race, and persistently elevated triglycerides ≥175 mg/dL.
Valvular heart disease
Aortic stenosis, mitral regurgitation

Coronary artery disease
Medial thickening with smaller luminal area
Extensively calcified fibroatheromatous plaques

Microvascular disease
Extensive arteriolar wall thickening with capillary rarefaction
Ischemia despite normal coronaries and predisposition to vasoconstriction due to endothelial dysfunction

Dysrhythmias
Atrial fibrillation
Sudden cardiac death

Cerebrovascular disease
Ischemic stroke from intimal calcifications
Hemorrhagic stroke from medial calcifications
Small vessel disease including white matter rarefaction
Cerebral microbleeds 5-10 mm in size, and microinfarcts,
White matter or global atrophy, increased perivascular spaces

Uremic cardiomyopathy
Left ventricular hypertrophy
Left ventricular systolic and/or diastolic dysfunction
Subclinical cardiomyopathy with normal left ventricular ejection fraction

Vascular calcification
Patchy calcification of intima close to atherosclerotic lipid deposits
Monkeberg’s medial calcific sclerosis with arterial stiffness
Increase in pulse pressure and left ventricular hypertrophy especially seen in diabetics

Peripheral vascular disease
Intermittent claudication, pain, ulceration, and gangrene

Figure 1
Figure 2. Algorithm for ASCVD Screening in Asymptomatic Patients with CKD

Candidate for kidney transplant listing

- No
  - eGFR ≥60
    - 10-year ASCVD score <7.5%, or no ASCVD risk enhancer
      - Monitor for symptoms or eGFR decline
      - No
    - 10-year ASCVD score ≥7.5-20%
      - Coronary artery calcification score ≥100
      - Yes
  - eGFR <60
    - Screen
    - Yes
    - 10-year ASCVD risk >20% or presence of ASCVD risk enhancer