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Key Points:

Abstract:

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Screening for Cardiovascular Disease in CKD: Commentary

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with chronic kidney disease (CKD), with the probability of developing coronary artery disease (CAD) increasing as the estimated glomerular filtration rate (eGFR) falls below 60 ml/min/1.73 m$^2$. The decision to screen asymptomatic patients with CKD for CVD, however, remains controversial. In this commentary we focus on screening for CAD, rather than all forms of CVD, as including all other types of vascular disease—such as peripheral arterial disease and carotid arterial disease—is beyond the scope of this debate. We acknowledge that the authors Jain, McAdams and Hedayati (PRO argument) discuss risk assessment as well as screening for obstructive CAD using imaging and stress tests, while authors Ramos and Charytan (CON argument) only discuss screening for obstructive CAD. In the following, we briefly discuss risk assessment but focus most of our discussion on screening for obstructive CAD.

On the PRO side, Jain, McAdams and Hedayati suggest that risk assessment for the non-CKD patient population should be extrapolated to patients with CKD. They present recommendations from the 2019 ACC/AHA guidelines on primary prevention of cardiovascular disease, which support performing risk assessment of all asymptomatic individuals by use of the Atherosclerotic Cardiovascular Disease (ASCVD) risk calculator. This calculator serves as a guide toward encouraging primary preventative measures, such as blood pressure (BP) control, initiation of statin therapy, and other lifestyle measures to help reduce the risks of future CAD. For asymptomatic individuals with 10-year ASCVD risk scores of borderline or intermediate risk (between 5 and 20%), the guidelines suggest consideration of a computed tomography (CT) scan to assess the burden of coronary artery calcification (CAC) to determine whether a statin should be initiated or not; for high risk scores >20%, they recommend initiation of statins regardless. We agree with the general concept of risk assessment in patients with CKD, and support the KDIGO lipid guidelines which state that the vast majority of patients with CKD and above the age of 50 years are at high risk for CAD and should take statins. We also agree with tight BP control, healthy diet, and improved glycemic control, as outlined in the KDIGO CKD guidelines. We would, however, not recommend screening asymptomatic patients with CKD, irrespective of their ASCVD risk score, with cardiac CT scans to assess CAC. The reasoning for this includes the following: 1) as above, we are of the
belief that irrespective of the exact ASCVD score, traditional CVD risk factors should be aggressively managed and statins incorporated into routine care in the majority of patients; 2) we are not aware any evidence that data on CAC would change management; and 3) while CAC has been associated with cardiovascular mortality among patients with CKD, it is less clear the degree with which it is associated with obstructive CAD lesions as in the non-CKD population, as well as the contribution of CKD associated mineral and bone disease (CKD-MBD) to this calcification. Jain et al also raise the concern that medical management for presumed CAD, without a screening test, could have potential risks in some individuals. While this concern is theoretically valid on an individual level, we are not aware of evidence of significant risks on aggregate with medical management of traditional CVD risk factors.

On the CON side, Ramos and Charytan focus their commentary on screening for the presence of obstructive CAD. They argue that there are a lack of data to support screening asymptomatic patients with CKD for CAD, and instead that focus should be placed on optimizing medical management regardless of documented CAD or not. They present data from the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease (ISCHEMIA-CKD) trial where 777 asymptomatic patients with eGFR <30 ml/min/1.73 m² with moderate or severe ischemia were randomized to invasive treatment or to conservative medical therapy, and no difference in the primary outcome of death or nonfatal myocardial infarction was noted. In addition, they point out that there was a significantly higher risk of stroke in the invasive arm of ISCHEMIA-CKD, compared with the medical arm. Other studies have shown not only risks associated with revascularization such as acute kidney injury, but also risks associated with invasive diagnostic testing, including exposure to intravenous contrast and access site complications. With this imbalance of potential peri-procedural risks of harm and lack of clear benefit to invasive revascularization for stable CAD among patients with CKD, we agree that asymptomatic patients with CKD should not be screened for CAD. Ramos and Charytan also highlight that the United States Preventative Services Taskforce (USPSTF) recommends against screening for CAD among asymptomatic patients at low risk; for intermediate risk patients, the USPSTF makes no recommendation citing lack of evidence.
While there have been no randomized controlled studies to evaluate screening for CAD among asymptomatic patients with CKD, it may be possible to extrapolate from a randomized trial conducted among asymptomatic patients with type 2 diabetes, another high cardiac-risk patient population. In the Detection of Ischemia in Asymptomatic Diabetes (DIAD) study, 1123 patients with type 2 diabetes were randomized 1:1 to screening with an adenosine-stress radionuclide myocardial perfusion imaging test or not. In the screening arm, 83 patients were found to have a perfusion defect (33 of whom had a moderate or large defect), and 25 of whom underwent revascularization; in the no-screening arm, 3 patients underwent revascularization. Overall, there were 15 nonfatal myocardial infarctions or cardiac deaths in the screening arm, and 17 nonfatal myocardial infarctions or cardiac deaths in the non-screening arm over a mean follow-up of 4.8 years (HR 0.88 [0.44, 1.88]). While the overall low rate of cardiac events could raise concerns regarding lack of adequate statistical power, there was no overt suggestion to benefit with screening. It is also notable that in this trial, the mean low-density lipoprotein level was 114 mg/dl and systolic BP around 130 mm Hg. The lower-than-expected cardiac event rates could potentially be reflective of overall medical management that was incorporated into both arms of the study, although this was not directly evaluated.

One of the key factors in this debate is that screening modalities for obstructive CAD have lower sensitivity and specificity among patients with CKD (Table 1). However, even if prediction of a high-risk lesion were to be significantly improved, trials like ISCHEMIA-CKD have not shown any benefit of an invasive strategy.

While we do not recommend universal screening for obstructive CAD in asymptomatic patients with CKD, we acknowledge that kidney transplant candidates are a unique CKD patient population where more careful consideration may be required because of the high stakes involved. One can argue that the scarcity of available organs, which is out of proportion to the immense pool of patients in need of an organ, leads to a societal obligation for careful risk assessment as to who may benefit from the donated organ. The on-going Canadian-Australasian Randomized Trial of Screening Kidney Transplant Recipients for Coronary Artery Disease (CARSK; NCT03674307), designed to test whether eliminating
asymptomatic CAD screening tests after activation on the transplant waitlist is non-inferior to screening at regular intervals, will add to this area of controversy.\textsuperscript{13}

Future research directions include but are not limited to: development of risk equations incorporating albuminuria and eGFR as well as novel CKD-related factors to better define the risk of obstructive CAD and CAD prognosis throughout the age spectrum of CKD; improved understanding of the pathophysiology of CAD, particularly the contributions of calcification, inflammation and senescence to atherosclerotic lesions; investigation of novel screening modalities for predicting high risk obstructive CAD; and ultimately trials of screening of higher risk asymptomatic individuals with clinical CAD as the outcome.

In summary, traditional risk factors for CVD should be treated aggressively in the CKD patient population. We would not, however, recommend screening asymptomatic patients with CKD (outside of the transplant candidate) because currently used non-invasive tests have lower sensitivity and specificity for detecting obstructive CAD, screening may lead to invasive diagnostic testing with its associated risks, and trials comparing invasive revascularization versus conservative medical management in patients with known ischemia have not shown any benefit.
Disclosures:

M. Sarnak reports the following: Consultancy: Akebia. On the Steering Committee of a trial. Funds come to the Division of Nephrology; Cardurian. Consultant; Research Funding: NIH; and Advisory or Leadership Role: Served as a consultant for Cardurian in the last 24 months. W. McCallum has nothing to disclose.

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Table 1. Summary of select non-invasive screening tests with their limitations in CKD

| Screening Test                      | Requirements or limitations                                      | Sensitivity and Specificity to detect anatomic obstructive CAD lesions          |
|-------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------|
| **Static Imaging Modalities**       |                                                                  |                                                                                  |
| Coronary artery calcium scoring     | Multi-detector CT scanner or electron beam CT scanner             | For a stenosis >50% (threshold of CAC score of 400 HU):\(^{14}\)               |
|                                     |                                                                  | Sensitivity: 67% (47%, 83%)                                                    |
|                                     |                                                                  | Specificity: 77% (68%, 84%)                                                   |
| Coronary CT angiography             | Requires intravenous contrast                                     | For a stenosis >50%:\(^{14}\)                                                 |
|                                     |                                                                  | Sensitivity: 93% (78%, 99%)                                                   |
|                                     |                                                                  | Specificity: 63% (53%, 72%)                                                   |
| **Functional Imaging Modalities**   |                                                                  |                                                                                  |
| Exercise EKG stress test            | Requires ability to exercise to ≥5 Mets, with an interpretable EKG | *For a stenosis >70%:\(^{11}\)                                                 |
|                                     |                                                                  | Sensitivity: 36% (21%, 54%)                                                   |
|                                     |                                                                  | Specificity: 91% (83%, 96%)                                                   |
| Stress echocardiogram               | Pharmacologic agents can have risk of hypotension, arrhythmias   | For stenosis >70%:\(^{11}\)                                                 |
|                                     |                                                                  | Sensitivity: 79% (67%, 88%)                                                   |
|                                     |                                                                  | Specificity: 89% (81%, 94%)                                                   |
| SPECT myocardial perfusion test     | Same as above                                                    | For a stenosis >50%:\(^{14}\)                                                 |
|                                     |                                                                  | Sensitivity: 53% (34%, 72%)                                                   |
|                                     |                                                                  | Specificity: 82% (73%, 88%)                                                   |

Abbreviations: CAC: coronary artery calcium; CT: computed tomography; HU: Hounsfield units; SPECT: single photon emission computed tomography

*Data from only 1 study