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Screening for Cardiovascular Disease in CKD: CON

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Introduction

Coronary artery disease is a leading cause of mortality in patients with chronic kidney disease (CKD) with the prevalence of coronary artery disease increasing dramatically as glomerular filtration rate (GFR) decreases below 60-75 ml/min/1.73 m$^2$. In the general population, screening for cardiovascular disease in asymptomatic patients requires testing for risk factors and risk assessment. In addition to traditional risk factors such as hypertension and diabetes mellitus, individuals with CKD are exposed to nontraditional risk factors such as anemia, inflammation and oxidative stress, change in mineral and bone disease homeostasis, and other factors that have been implicated in the pathogenesis of atherosclerosis and may increase the incidence of cardiovascular events.(1)

To help clinicians determine the potential need for cardiovascular interventions, The American Heart Association recommends performing a 10-year risk assessment such as the Framingham risk score (which includes age, sex, and blood pressure) to assess 10-year risk of cardiovascular disease beginning at age 40 and repeating every 5 years. The high incidence of cardiovascular morbidity and mortality in the setting of CKD along with the low utilization of coronary revascularization and standard medical therapies has generated interest in extending this concept to those with CKD and the idea that increased screening for and identification of coronary disease could reduce cardiovascular mortality in CKD—this perhaps accounts for the increasing use of cardiac stress testing in patients with CKD in contrast to decreasing utilization in individuals with preserved kidney function.(2) However, it is not clear that routine screening of patients with CKD for coronary disease is appropriate. This review will focus on the utilization of screening tests specifically for coronary artery disease in patients who are asymptomatic or have stable angina. Note that there are no current guidelines regarding the screening of other types of cardiovascular disease such as heart failure.

Screening for CAD in patients with CKD
Currently, the United States Preventive Services Taskforce (USPSTF) recommends against screening asymptomatic individuals at low risk (<10% at 10-years) of cardiovascular events with electrocardiography-based screening given the uncertain harms and low likelihood that screening will result in a change in risk management. The USPSTF makes no recommendations for individuals at intermediate risk based on a lack of sufficient evidence of benefit or harm.(3) Although these recommendations apply specifically to exercise-based electrocardiography, similar considerations apply to other screening modalities such as pharmacologic, nuclear stress-testing or coronary calcium CT scanning, which may be more widely utilized in the setting of CKD. On the basis of these recommendations, a predisposition against the routine screening of “low or moderate risk”, asymptomatic patients with CKD for CAD is prudent.

However, even in the absence of symptoms, individuals with CKD are likely to have moderate or high risks of cardiovascular events. Whether screening to identify revascularizable coronary disease is warranted in this scenario is, admittedly, a different question. Indeed, patients with CKD, particularly those of advance age or with diabetes, are likely to have significant CAD and might have enhanced benefits from the identification and treatment of sub-clinical lesions. Nevertheless, coronary intervention has not been shown to improve mortality and morbidity in most settings with the exception of left-main coronary disease. The International Study of Comparative Health Effectiveness (ISCHEMIA-CKD, NCT01985360) investigated whether there was any benefit of invasive therapy in patients with stable CAD and advanced CKD. Seven hundred and seventy seven patients with eGFR <30 ml/min/1.73 m$^2$ with moderate or severe ischemia were randomized to invasive treatment (either percutaneous coronary intervention or bypass surgery) or conservative treatment (medical therapy, smoking cession, and blood pressure and diabetes control). Death or nonfatal myocardial infarction occurred in 123 patients in the invasive-strategy group and 129 patients in the conservative group (1.01; 95% confidence interval, 0.79-1.29; p= 0.95). Furthermore, there were no substantial benefits with regard to
angina-related health status with the invasive approach compared with conservative therapy alone, and there was a higher incidence of death or initiation of dialysis in the invasive treatment group. (4) Of note, similar findings were previously documented in a general population study of individuals with stable coronary disease. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE trial) failed to show that percutaneous revascularization reduced the risk of death or nonfatal MI among patients with stable disease compared to medical therapy. (5) Both ISCHEMIA and COURAGE insinuate that medical therapy, which can be instituted without the benefit of screening tests, is non-inferior to revascularization-based therapy in the absence of symptoms not responsive to medical therapy. Formally testing the cost-effectiveness of universal prescription of CV medications to patients with CKD would be worthwhile. However, given that standard risk factors for CV disease such as hypertension, diabetes, and obesity are highly prevalent in the CKD population and that both reduced GFR and albuminuria are independently associated with increase CV risk, it is likely that even without confirmed evidence of CVD, most patients with CKD should be probably be placed on statins, antihypertensives, aspirin, and SGLT2 inhibitors to decrease the incidence of CVD events. Conversely, in the absence of clinical symptoms such as unstable angina or symptoms refractory to medical therapy, these studies suggest that there is little to be gained and potential for harm through routinely screening patients with CKD. Similarly, there are no recommended screening tests for asymptomatic congestive heart failure. Those who are at high risk, yet asymptomatic are usually treated with a combination of diet, exercise modifications, and medications such as statins and aspirin, and SGLT2 inhibitors in the absence of dedicated screening tests.

**CAD in Transplant Patients**

Screening for coronary disease in the context of pre-operative testing prior to kidney transplant merits specific consideration. A requirement for screening is mandated by many programs to prevent peri-operative myocardial infarction and in recognition that kidney recipients have an
increased risk of premature mortality due to cardiovascular disease compared with the general population even after transplantation. However, randomized trials in the general population failed to demonstrate improvements in peri-operative outcomes with a strategy of routine revascularization prior to high-risk (major vascular) surgery. Furthermore, a post-hoc analysis of the ISCHEMIA-CKD trial, did not identify differences in all-cause death or myocardial infarction (the primary outcomes) or secondary cardiovascular endpoints of the trial between invasive and non-invasive therapies in a sub-study including the 194 transplant-listed patients.

Potential for Harm
In addition to a lack of clear benefits, screening followed by the use of invasive revascularization procedures exposes individuals with CKD to risks of procedural complications that are much higher than those for individuals with preserved kidney function. In a study by Cooper, et.al, for example, worse kidney function was associated with increased risks of operative mortality as well as postoperative complications including stroke, reoperation, infection, prolonged ventilation, prolonged postoperative stay, and initiation of dialysis. Findings were similar in ISCHEMIA-CKD with markedly higher risk of stroke in the invasive strategy group compared with the medical therapy group (adjusted hazard ratio, 3.76; 95% CI, 1.52 to 9.32). Although randomized data on very high risk patients with CKD are lacking, the benefits of revascularization seem to be more apparent in the setting of CKD and presentation with unstable angina or myocardial infarction. Thus, in a recent retrospective study which compared the risks for kidney failure and death after treatment with percutaneous revascularization, coronary artery bypass surgery, and medical therapy, both surgical and percutaneous revascularization were associated with lower mortality than medical therapy. We note that the development of highly accurate, non-invasive screening tools such as biomarkers or cardiac PET, particularly if capable of identifying lesions associated with high risk and likely to respond
to intervention could change the risk calculus underlying our arguments. However, at the current time, no such tools are ready for prime time.

**Conclusion**

In summary, cardiovascular events remain the leading cause of death in CKD patients. Screening tests are meant to diagnose patients before developing symptoms and to prevent catastrophic events, but cannot be recommended when they fail to improve or actually worsen overall health status. Although screening for coronary disease may be beneficial for selected patients in the general population with preserved kidney function, this is not necessarily the case for patients with CKD. Although the likelihood of diagnosing cardiovascular disease in patients with CKD is very high, unless patients are symptomatic, medical therapy is likely to be non-inferior to invasive therapies and has the advantage of avoiding the significant risks of adverse outcomes including operative mortality, prolonged hospitalization, and initiation of dialysis generated by intervention. Thus, at the present time, the proposition that survival or quality of life can be improved by identifying and revascularizing coronary lesions that are either asymptomatic or readily treatable with medical therapy is at best unsupported for patients with CKD. We therefore recommended against routine screening for cardiovascular disease in the setting of CKD.
Disclosures

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Author Contributions

Giana Kristy Ramos: Conceptualization; Formal analysis; Writing - original draft; Writing - review and editing. David Charytan: Conceptualization; Formal analysis; Writing - original draft; Writing - review and editing.
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