The Paucity of Evidence Supporting Screening for Stages 1–3 CKD in Asymptomatic Patients with or without Risk Factors

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Abstract

The American College of Physicians recently published a guideline on screening for CKD that recommends against screening for CKD in asymptomatic adults without risk factors. The generally accepted criteria for population-based screening for disease state that screening should improve important clinical outcomes while limiting harms for those individuals screened. However, CKD screening does not meet these criteria. There is currently no evidence evaluating or demonstrating benefits for providing early treatment for patients identified *via* screening who do not have risk factors. On the other hand, harms are associated with the screening and include false-positive results, unnecessary testing and treatment, and disease labeling.

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Introduction

The American College of Physicians (ACP) recently published a guideline on screening for CKD that states the following: "ACP recommends against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease. (Grade: weak recommendation, low-quality evidence)" and "ACP recommends against testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor or an angiotensin II–receptor blocker. (Grade: weak recommendation, low-quality evidence)" (1). In addition, under the area of inconclusive evidence, the guideline states that "Although there are known risk factors for CKD (diabetes, hypertension, and cardiovascular disease), ACP found the current evidence insufficient to evaluate the benefits and harms of screening for CKD in asymptomatic adults with CKD risk factors." At first glance, CKD screening appears to be a wise health care choice. CKD is a major health problem resulting in considerable medical morbidity and health care costs. More than 90% of patients with CKD have early stage disease (stages 1–3) and most are asymptomatic. In a majority of patients, CKD risk factors are easily identifiable and include diabetes and hypertension. Other risk factors include older age, obesity, family history, and ethnicity (African American, Native American, or Hispanic). Screening tests are inexpensive and readily available. These include the urine test to measure albuminuria, the spot urine test using either the albumin-specific dipstick or albumin-to-creatinine ratio, and the blood test for serum creatinine to estimate GFR. A closer look at the evidence used to develop a clinical guideline that meets the appropriate quality standards (2) and the principals behind high-value screening decisions, however, indicates that the current evidence does not support mass CKD screening in asymptomatic adults without risk factors or testing for proteinuria in adults with diabetes who are currently taking an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB).

Screening Principles

Unlike case finding, disease management, or diagnosis in symptomatic individuals, screening identifies, *via* testing, people with no signs or symptoms of a disease who may be at an increased risk of the disease (3) and for whom intervention may not otherwise be indicated. Thus, the intent of CKD screening is the early identification of patients with asymptomatic CKD in order to initiate an intervention that can prevent or delay progression to a symptomatic stage (*e.g.*, ESRD). Among the fundamental clinical criteria that define a successful screening program (4), the most important is that detection and treatment of individuals with asymptomatic disease should improve health outcomes compared with deferring treatment until symptomatic disease has developed. In the case of CKD, there is no current evidence showing benefit of early detection and treatment.

The burden of proof for the value of mass screening is higher than it is for testing symptomatic patients because screening involves harms and costs associated with a large number of asymptomatic individuals with the hope of affording later benefits to a small minority. Although CKD is highly prevalent in the general population in the United States (11%), the prevalence is markedly lower in adults aged <50 years and in adults without major risk factors such as diabetes and hypertension (5). Because screening is applied to large, asymptomatic populations with lower pretest probability of disease compared with diagnostic testing, even

small costs and risks are amplified. Even if we presume that affected individuals found by screening may benefit, that benefit must be compared with the possible harms and costs across the screened population.

Among screening tests, albuminuria is commonly associated with false positive results, particularly with one-time testing (5). This can lead to erroneous disease labeling and subsequently unnecessary, ineffective, and harmful therapy. The natural history of early asymptomatic CKD is typically very favorable in the absence of interventions, yet most patients may undergo treatment (5). Therefore, there is considerable overdiagnosis and overtreatment with no conclusive evidence of benefit. Importantly, treatment options and goals for individuals with hypertension or diabetes plus early stage CKD are similar to those without CKD. There is no high-quality evidence showing that screen-detected early stage CKD independently alters management decisions or outcomes, including mortality, quality of life, and progression to ESRD. In addition, there are no randomized controlled trial (RCT) data demonstrating that primary prevention of cardiovascular disease should be more vigorously undertaken in patients with early stage CKD than in those without CKD, including early initiation of statins or lower LDL goals. Such studies are needed.

Screening in the General Population without Any Risk Factors

No randomized trials have assessed the benefits and harms of screening and treatment for stages 1–3 CKD. Observational data are insufficient to assess screening and treatment effectiveness. Thus, the ACP used an indirect chain of evidence to derive its recommendations. Although tests to detect microalbuminuria and measure serum creatinine–derived eGFR are readily available in primary care settings, no studies have evaluated their sensitivity or specificity for screening in the general population. Although these tests have acceptable accuracy (1), they also are associated with frequent false-positive results (estimated to be 13%–18%) and considerable test-retest variability (especially albuminuria testing). This is particularly relevant because many CKD disease classification and management decisions in daily clinical practice are based on one-time testing (6–8). This variability is likely to lead to widespread inappropriate diagnosis and treatment. Furthermore, the known natural history of CKD and limited evidence of any plausible incremental effectiveness of interventions suggest that the number to screen over a ≥10-year period to possibly prevent one case of ESRD would be very large and would result in frequent screening and treatment harms and high health care costs. Even if we identify patients at risk of ESRD using these laboratory tests, there is no evidence that early treatment of screen-detected CKD is associated with any improved health outcomes in asymptomatic patients without risk factors (1,9). However, harms and costs exist, including false-positive results (6–8), disease labeling, overdiagnosis, unnecessary testing, and unnecessary treatment (7,8).

Screening in Patients with Risk Factors

Diabetes and hypertension are well established risk factors for CKD. The current evidence is insufficient to assess the balance of benefits and harms of screening for CKD in asymptomatic adults with risk factors. Case-finding and disease management strategies include periodic assessment of serum creatinine levels in patients taking ACEIs and ARBs to evaluate for drug-related adverse effects on creatinine, and thus fall outside the realm of screening. Furthermore, treatment with ACEIs and ARBs, lipid-lowering agents, and diet modification is already indicated in the large majority patients with diabetes and hypertension. In patients with early stage CKD and macroalbuminuria (microalbuminuria is 30–299 mg/g; macroalbuminuria is >300 mg/g), ACEIs (19 RCTs) and ARBs (5 RCTs) had no effect on reducing the risk of mortality but did reduce ESRD risk (5). The absolute effect was small and there was no benefit of ACEIs or ARBs in patients with only microalbuminuria or impaired GFR. The evidence showed that there is no consistent difference in clinical outcomes between patients with stages 1–3 CKD with more versus less intensive therapy (5).

Evidence indicates that the majority of patients with early stage CKD have hypertension, diabetes, and/or cardiovascular disease and that these risk factors are already being addressed. We agree that treatments in patients with existing diabetes, hypertension, or cardiovascular disease are effective in slowing or preventing ESRD progression and reducing cardiovascular and all-cause morbidity and mortality. Evidence does not show incremental benefit of monitoring patients, altering type or dose of therapy, or aiming for different intermediate targets (*e.g.*, BP, glycohemoglobin) based on CKD status among individuals already taking appropriate medications (as noted above, exceptions include periodic assessment of serum creatinine in patients taking ACEIs and ARBs to evaluate for a drug-related adverse effect on creatinine). There is no evidence that proteinuria levels positively affect treatment decisions or improve patient outcomes, although they may provide prognostic value. In addition, low-quality evidence showed no improvement of clinical outcomes with the use of interventions designed to reduce proteinuria levels. Although evidence does not support CKD screening in patients with or without risk factors the ACP focused its screening recommendation on individuals with no known risk factors. The ACP's recommendation on proteinuria testing pertains to patients with diabetes already taking an ACEI or ARB.

Costs Related to a Screening Program

It is frequently observed that screening for CKD is relatively inexpensive. However, this does not account for costs associated with follow-up evaluation of abnormal results, unnecessary treatment that has no beneficial effect on clinical outcomes, and complications and adverse effects of treatment. The overused screening interventions and the downstream costs make up a considerable portion of unnecessary health care costs (10). A careful assessment of benefits, harms, and costs of a screening test to determine its value is critical to preserving quality of care while reducing costs. More judicious use of such tests will improve quality and reflect responsible awareness of costs. A high-value screening test provides health benefits that demonstrably outweigh its costs and/or harms. By contrast, screening for CKD exemplifies a low-value intervention: Our discernment is blunted because the screening tests themselves are inexpensive; however, screening has little or no proven net benefit.

Conclusion

Evidence currently does not demonstrate that CKD screening in asymptomatic adults without risk factors and testing for proteinuria in adults with or without diabetes who are currently taking an ACEI or ARB improves health outcomes or would positively affect treatment decisions. Rather, there is substantial evidence that it results in harms and costs. We believe that the burden of proof lies on showing any benefit of early screening on clinical outcomes of a patient before implementing any screening program, rather than after implementing a screening program. The evidence of potential benefits or harms should be clearly demonstrated in the literature before adopting screening programs. The current evidence is not convincing to argue for population-based CKD screening, particularly in light of no evidence that knowing early CKD status will affect treatment decisions or alter health outcomes in high-risk populations who are already taking medications. There is no evidence showing any clinical benefit of screening for CKD in adults without risk factors or those patients who are already taking ACEIs or ARBs (other than periodic monitoring of serum creatinine to evaluate for adverse treatment effects). Screening tests have costs, including downstream costs, labeling, overdiagnosis, and overtreatment, which may lead to difficulty in absenteeism from insurance or more costly insurance. Therefore, the ACP recommends against screening for CKD in asymptomatic adults without risk factors and against testing for proteinuria in adults with or without diabetes who are currently taking an ACEI or ARB. The current evidence is insufficient to recommend screening for CKD in adults with risk factors such as diabetes, hypertension, or cardiovascular disease. There is no evidence of benefit from reduced risk for ESRD with ACEI and ARB monotherapy in patients with CKD and macroalbuminuria. We encourage randomized screening trials to address these important evidence gaps.

We recognize that physicians who work daily with people approaching ESRD and on dialysis have the best interest of patients at heart when they recommend screening healthy populations for CKD. However, it is increasingly appreciated that in the consensus opinion of experts, so-called "eminence-based medicine" does not reliably align with recommendations resulting from rigorous and disciplined assessment of scientific literature (2,11). In addition to the ACP, other evidence-based organizations (*e.g.*, the US Preventive Services Task Force, Royal College of Physicians, and Kidney Disease Improving Global Outcomes) have also recommended against screening in patients with no risk factors or found insufficient evidence for or against screening (9,12,13).

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