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Editorial Comment

EDITORIAL COMMENT

Cost-effectiveness of screening for chronic kidney disease: existing evidence and knowledge gaps

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ABSTRACT

It is well known that the worldwide prevalence of chronic kidney disease (CKD) has risen to over 10% of the general population during the past decades. Patients with CKD are at increased risk of both kidney failure and cardiovascular disease (CVD), posing a substantial health challenge. Therefore, screening for CKD is warranted to identify and treat patients early to prevent progression and complications. In this issue of the Journal, Yeo and colleagues provide an updated systematic review of the cost-effectiveness of screening for CKD in the general adult population. They show that screening for CKD in high-risk populations is cost-effective and that there is limited evidence for screening the general population. It should be noted that most studies they discuss do not consider the benefit of screening to prevent CVD in addition to preventing kidney failure, the treatment effect of novel therapeutic agents such as SGLT2 inhibitors, and the possibility of screening in a home-based setting. These three aspects will likely improve the cost-effectiveness of CKD screening, making it feasible to move towards general population screening for CKD.

Keywords: albuminuria, chronic kidney disease, cost-effectiveness, eGFR, screening

INTRODUCTION

Over the past decades, the prevalence of chronic kidney disease (CKD) has rapidly increased to over 10% of the general population worldwide, affecting around 850 million individuals [1]. Moreover, CKD is expected to become the fifth global cause of death in 2040. The prevalence of CKD is higher among older individuals, women, and those with a lower socioeconomic status. The burden of CKD is especially higher in low- and middle-income countries. It is well known that the risks associated with CKD are not only the incidence of kidney failure with a need for dialysis or kidney transplantation but also the occurrence of cardiovascular disease (CVD). Even the earliest stages of CKD are associated with an increased risk of CVD [2]. Thereby, CKD represents a significant health and economic burden, reducing life expectancy, diminishing quality of life, and increasing healthcare expenses. Early identification is required to allow sufficient time for appropriate preventive interventions. Therefore, screening for CKD is a critical factor in preventing progressive kidney function decline and CVD.

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HOW TO EVALUATE THE EFFECTIVENESS OF CKD SCREENING

In 2019, Kidney Disease: Improving Global Outcomes (KDIGO) held a controversies conference where CKD was evaluated as a screening target using the World Health Organization (WHO) principles of screening for disease (Table 1) [3–5]. The conference attendants agreed that screening for CKD generally complies with all the WHO principles of screening. In short, CKD is an important health problem with a latent asymptomatic phase. Accurate and low-cost diagnostic tests and effective treatments with few side effects are available. Additionally, the economic burden of CKD was identified as an essential additional principle for early CKD screening and treatment [3]. It is estimated that in Europe, costs related to CKD and kidney failure are more than €140 billion per year. In the United States (US), Medicare spending is estimated at around US$130 billion [6, 7].

To evaluate whether CKD screening strategies lead to efficient use of healthcare resources and support their implementation in healthcare systems, economic evaluations of such programs are performed to assess their cost-effectiveness. In this issue of *Clinical Kidney Journal*, Yeo *et al*. provide an up-to-date systematic review of cost-effectiveness analyses of CKD screening strategies in the general adult population [8]. Below, we address several issues that are relevant to make CKD screening (cost-) effective.

WHICH TEST SHOULD BE USED IN CKD SCREENING?

The diagnosis of CKD is based on the measurement of the estimated glomerular filtration rate (eGFR) and albuminuria to assess kidney function and the presence of kidney damage, respectively [9]. In their systematic review, Yeo *et al*. included 21 studies, of which the majority investigated screening for albuminuria ($n = 13$), and fewer studies investigated screening for estimated glomerular filtration rate (eGFR) ($n = 3$) or both ($n = 3$) [8]. Traditionally, eGFR is the most commonly used marker to detect CKD. Although strongly related to the progression of CKD and kidney outcomes, eGFR is known as a late marker rather than an early marker of CKD. Additionally, it can be questioned which eGFR threshold to use for screening. The risk for kidney outcomes is substantially higher at an eGFR of < 45 compared to <60 ml/min/1.73 m^2, but this relatively low <45 ml/min/1.73 m^2 threshold leaves less room for preventive treatment [10]. Measuring the eGFR can also be considered invasive because it necessitates a venipuncture. Moreover, it is relatively costly, requiring a visit to a healthcare provider. More recently, attention has been directed towards screening for albuminuria. Albuminuria, defined by the urinary albumin-to-creatinine ratio (UACR), generally increases before eGFR declines. It defines, therefore, the early stages of CKD. Albuminuria is now recognized as the strongest risk predictor for progressive CKD and among the strongest predictors for CVD [9–12]. Additionally, albuminuria serves as a target for intervention, and albuminuria levels have the ability to improve when treatment is initiated (in contrast to eGFR). In a large meta-analysis, reducing albuminuria was strongly correlated with a reduction in CKD progression [13]. Compared to eGFR measurements, the UACR has the advantage that it can be assessed non-invasively, at lower costs, without the need for a healthcare provider visit. Therefore, albuminuria may be a more suitable target for identifying people within a CKD screening program than the eGFR.

Table 1: World Health Organization (WHO) Wilson & Jungner's principles of screening for disease.

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic phase.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including a diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuous process and not a 'once and for all' project.

Adapted from Wilson *et al*. [4, 5].

WHO SHOULD BE SCREENED FOR CKD: HIGH-RISK POPULATIONS ONLY?

The KDIGO conference participants concluded that efforts for CKD screening should initially be aimed at individuals with established CKD risk factors such as hypertension, diabetes, or cardiovascular disease because the prevalence of CKD is higher in such individuals [3]. In their review, Yeo *et al*. identified 13 studies examining CKD screening targeted to such high-risk populations [8]. From those studies, they conclude that CKD screening is especially cost-effective in patients with diabetes at a median incremental cost-effectiveness ratio (ICER) of US$27 471 (range US$113–US$42 359) and in patients with hypertension at a median ICER of US$53 531 (range US$28 351–US$424 191). Of note, the authors applied a predefined willingness-to-pay threshold of US$50 000 per quality of life year (QALY) gained for screening to be cost-effective, although the actual threshold applied per country differs. In the Netherlands and the United Kingdom respectively, ICERs of €20 000 and £20 000–£30 000 are accepted for implementing preventive programs, whereas in the US, thresholds of US$100 000 and US$150 000 are applied [14–16]. Remarkably, CKD screening appears more cost-effective in middle-income countries than in high-income countries. Yeo *et al*. did not identify any studies performed in low-income countries [8]. Thus, screening of those at high risk of CKD can be recommended based on available evidence.

WHO SHOULD BE SCREENED FOR CKD: THE GENERAL POPULATION?

It has been argued that screening the general population for CKD could offer the most comprehensive approach [3, 17]. This is especially true because the implementation of screening in high-risk groups in clinical practice is unsatisfactory. Several publications showed that the percentage of individuals with diabetes, and especially individuals with hypertension, screened according to the recommendation in guidelines is low [18, 19]. Targeted high-risk screening also excludes those yet to be identified as being at high risk, i.e. individuals with diabetes or hypertension that are not yet known to have diabetes or hypertension. Since the 2019 KDIGO conference, evidence and guidelines have emerged that acknowledge the importance of

screening the general population. In 2021, the European Society of Cardiology (ESC) published updated guidelines on CVD prevention in clinical practice. It proposed that, as a first step in strategies to prevent CVD, individuals should be categorized into those with atherosclerotic CVD, diabetes, or specific risk factors such as familial hypercholesterolemia or CKD [20]. This guideline advocates the inclusion of eGFR and albuminuria in an individual's initial cardiovascular risk assessment. Thus, measurement of CKD variables should not be done in high-risk patients only but all individuals, independent of their diabetes and hypertension status. This notion is supported by the recent efforts to incorporate eGFR and albuminuria in the Systematic Coronary Risk Estimation 2 (SCORE2) risk prediction algorithms used in the 2021 ESC CVD prevention guideline. Adding these CKD measures markedly improved CVD risk prediction in the general adult population [21].

Until now, the cost-effectiveness of screening the general population has been questioned. The results of Yeo *et al*. show widely varying ICERs ranging from US$661 to US$430 595 per QALY from studies investigating screening of the general adult population [8]. As noted by Yeo *et al*., we believe three factors strongly influenced these results. First, screening at home will be less costly than screening in a healthcare setting. Second, benefits associated with screening and early prevention should not only focus on kidney-related outcomes, but also on cardiovascular disease. Third, and lastly, the availability of novel kidney and cardiovascular protective treatments should be considered. When these factors, described in more detail below, are addressed in cost-effectiveness analyses, the cost-effectiveness of general population screening may be more beneficial.

IN WHICH SETTING IS CKD SCREENING TO BE PERFORMED?

Fifteen out of 21 studies analysed by Yeo *et al*. modeled screening for CKD as performed by a primary care provider [8]. Compared to such a screening approach, a home-based screening approach would avoid the costs of a visit to the primary care provider for many individuals. The authors identified one study that applied a home-based screening for albuminuria and two that applied a home-based albuminuria pre-screening, followed by an elaborate risk factor assessment in primary care [8, 22–24]. The first setting appeared to be even cost-saving (saving US$2 884 per patient per lifetime). The latter two studies found home-based albuminuria screening with a subsequent elaborate screening to be cost-effective at US$29 112 and US$38 372 per life year gained. Compared to the ICERs mentioned in the sections above, these results indicate that home-based screening instead of screening by primary care providers could positively impact the cost-effectiveness of CKD screening.

WHICH CLINICAL OUTCOMES ARE TO BE CONSIDERED?

Most studies included in the presented systematic review modeled only benefits to be obtained by preventing the progression of kidney disease towards kidney failure. However, when screening the general population, most patients with moderately increased albuminuria or mildly decreased kidney function will rarely experience kidney failure. In contrast, many will experience a cardiovascular event [2]. These patients would benefit from the start of preventive treatments, such as blood pressure control and renin-angiotensin system (RAS) inhibitors, which generally are both kidney protective and cardioprotective [25]. Including cardiovascular outcomes in cost-effectiveness models is, therefore, necessary to accurately assess the cost-effectiveness of CKD screening. Subsequently, it likely would improve cost-effectiveness by preventing more clinical outcomes.

WHICH TREATMENTS ARE TO BE CONSIDERED?

As Yeo *et al*. correctly point out, the studies in their systematic review only included the beneficial effect of RAS inhibition [8]. However, treatment options for CKD patients have significantly improved in the last decade. Glucagon-like peptide-1 (GLP1) analogues, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and nonsteroidal mineralocorticoid receptor antagonists (MRAs) have shown to be kidney- and cardioprotective on top of standard blood pressure control and RAS inhibition [25, 26]. Future cost-effectiveness analyses should therefore incorporate the beneficial effect of these novel therapeutic agents. This is supported by Yeo *et al*.'s review, which identified treatment effectiveness as one of the leading influential parameters in cost-effectiveness studies [8]. This notion is reinforced by the work of Cusick *et al*. In a publication in the *Annals of Internal Medicine*, they recently assessed the cost-effectiveness of population-wide albuminuria screening, adding SGLT2 inhibition to their analysis [27]. Screening the general population at the age of 55 and subsequently treating individuals identified with CKD with conventional therapy and SGLT2 inhibition was cost-effective in the US at an ICER of US$86 300 per QALY. Unfortunately, no benefits on cardiovascular outcomes were considered in this analysis [28]. If these benefits were included, the cost-effectiveness of screening would likely be further enhanced, but these results are nonetheless promising.

REMAINING KNOWLEDGE GAPS

Despite the thorough analysis of Yeo *et al*., several important questions still need to be answered before systematic general population screening can be introduced. First, what should be the optimal testing interval, and is this interval similar for everyone? Should the interval, for instance, be shorter in individuals near the cut-off defining abnormal albuminuria or kidney function? Second, what age groups should be screened? It is expected that the prevalence of CKD in younger individuals is lower. On the other hand, in younger individuals, the early start of preventive measures could have more impact than in older individuals, from a lifetime perspective. Eventually, the applied screening strategy must be tailored to a country's resources and income. This review highlights the necessity for further efforts to investigate the cost-effectiveness of CKD screening to improve kidney health worldwide.

CONCLUSION

The systematic review by Yeo *et al*. shows that, at present, there is abundant evidence for the cost-effectiveness of screening high-risk individuals. Evidence for screening the general population is more limited, and the studies that have been published suggest that this approach is not cost-effective in most cases. However, the cost-effectiveness of general population screening will be far more beneficial when considering the benefits of screening in a home-based setting instead of a primary care

provider setting, when cardiovascular outcomes are adequately considered, and when novel therapeutic interventions are taken into consideration. We are currently investigating the cost-effectiveness of a formal home-based general population albuminuria screening program that we recently published in *The Lancet* [29]. The preliminary results of this analysis, in which we also consider cardiovascular benefits and the application of novel kidney- and cardioprotective treatments, suggest that home-based general population screening is cost-effective in the Netherlands.

CONFLICT OF INTEREST STATEMENT

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