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Systematic Literature Review

Economic Evaluations of Screening Programs for Chronic Kidney Disease: A Systematic Review

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ABSTRACT

Objectives: The aim of this review is to appraise and assimilate evidence from studies that have reported on the cost-effectiveness of screening programs for chronic kidney disease (CKD).

Methods: The study protocol was registered on International Prospective Register of Systematic Reviews (PROSPERO). The final search was conducted on 18 January 2023 using 7 databases. Screening of articles, data extraction, and quality assessment was performed by 2 independent reviewers. The ISPOR-AMCP-NPC checklist was used to assess the credibility of the included studies.

Results: From 4948 retrieved studies, a final total of 20 studies were included in the qualitative synthesis. Studies found that screening in diabetic populations was cost-effective (n = 8, 57%) or even cost-saving (n = 6, 43%). Four studies (67%) found that screening in hypertensive populations was also cost-effective. For the general population, findings were inconsistent across studies in which many found screening to be cost-effective (n = 11, 69%), some cost-saving (n = 2, 12%), and others not cost-effective (n = 3, 19%). The most influential parameters identified were prevalence of CKD and cost of screening.

Conclusions: Screening for CKD in patients with diabetes or hypertension is recommended from a cost-effectiveness point of view. For the general population, despite some inconsistent findings, the majority of studies demonstrated that screening in this population is cost-effective, depending mainly on the prevalence and the costs of screening. Healthcare decision makers need to consider the prevalence, stratification strategies, and advocate for lower screening costs to reduce the burden on healthcare budgets and to make screening even more favorable from the health-economic perspective.

Keywords: cost-effectiveness analysis, mass screening, renal insufficiency, systematic review.

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Introduction

Chronic kidney disease (CKD) is characterized by the presence of persistent abnormalities in the function or structure of a patient's kidney.[1] CKD can lead to kidney failure, a condition in which a patient will require kidney replacement therapy in the form of dialysis or kidney transplantation. Although CKD is not the most prevalent noncommunicable disease, the burden of CKD has a major impact on global health budgets, and CKD is a contributing risk factor for cardiovascular disease.[2] Additionally, CKD incrementally increases its economic burden over time because the direct and indirect costs for treatment will increase as the disease progresses. For many countries, the annual cost for kidney replacement therapy actually exceeds the per capita gross national income.[3,4]

Considering that CKD is almost asymptomatic until late stages,[5,6] and <5% of patients with early CKD report an awareness of their disease,[7] screening strategies may play a pivotal role in reducing the burden of CKD. Nonetheless, the US Preventive Services Task Force has stated that the risks and benefits for CKD screening in asymptomatic adults remains uncertain because the evidence available is still inadequate to unequivocally recommend screening.[8] Although no existing randomized clinical trials with sufficient time horizons have confirmed that screening for CKD can improve outcomes,[7] early detection by screening, followed by appropriate treatment may delay the progression of CKD.[9] Cost-effectiveness studies are therefore required to confirm that the benefits outweigh the potential financial burden associated with large-scale screening undertakings and before decision makers can be approached for the allocation of healthcare resources.[10]

A previous systematic review identified that, although screening for CKD was found to be cost-effective in high-risk patients, such as diabetics, screening in the general population has shown conflicting results across studies.[11] Therefore, assessing the cost-effectiveness of screening in the general population is crucial considering that only half of CKD and end-stage kidney disease

cases can be attributed to diabetes.[12] Furthermore, for patients with diabetes mellitus (DM), a recent study showed that CKD can still progress even in the absence of detectable urinary albumin excretion or microalbuminuria.[13] This illustrates the need for novel screening tests and corresponding cost-effectiveness evaluation. Notably, a strategy to increase cost-effectiveness for detecting patients with CKD has been suggested by developing stratification using a 2-step approach: provision of an initial score to stratify patients according to risk using a CKD database, followed by biochemical tests to confirm diagnosis.[14]

A comprehensive appraisal of all existing evidence regarding CKD screening programs is required to evaluate their cost-effectiveness. Therefore, the aim of this review is to appraise and assimilate evidence from studies that have reported on the cost-effectiveness of CKD screening programs and to evaluate parameters that influence cost-effectiveness.

Methods

This review was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA 2020) guideline.[15] The protocol of this review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) on February 28, 2021, with registration number CRD42021234039.

Eligibility Criteria

For inclusion, the following criteria had to be met by the study: (1) the population assessed had to be asymptomatic adult individuals and not already diagnosed with CKD, (2) the use of screening methods to detect people with CKD, (3) a full economic evaluation of the cost-effectiveness of CKD screening programs reporting an incremental cost-effectiveness ratio (ICER) of cost per quality-adjusted life-years (QALYs), life-years gained, or disutility-adjusted life-years averted had to be made, and (4) a comparison of strategies involving 1 or more types of screening with no screening or standard care strategies had to be made. Exclusion criteria prevented inclusion of studies that reported sole costs or outcomes, studies that appraised only cost per case identified, and any studies that reflected content of case reports, letters, editorials, abstracts/posters only, or systematic reviews. There was no restriction on publication period or language for the final review.

Information Sources and Search Strategy

To gather evidence, we searched for CKD screening cost-effectiveness studies from 7 different electronic bibliographic databases: PubMed, EMBASE, the Cochrane Library, Scopus, CINAHL, EconLit, and the NHS Economic Evaluation Database. We updated the search on 18 January 2023 and presented results based on this final search (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.003). We used a combination of 3 search terms: "chronic kidney disease," "screening," and "cost-effectiveness." We also included new potential biomarkers of CKD in our search terms. Citation checks were conducted by scanning the reference lists of the full-text articles.

Study Selection

From all databases, retrieved citations were entered into a reference manager, Mendeley, to identify duplicate articles. After removing duplications, the remaining citations were uploaded into Rayyan QCRI.[16] Two reviewers (M.R.R. and F.F.A.) independently screened each title and abstract and decided on the articles most applicable for further examination. Any disagreement between these 2 reviewers on study selection was resolved by consensus together with 2 other reviewers (C.B. and M.J.P.). Once complete, the selected articles were then searched for full-text and reviewed by the 2 reviewers (M.R.R. and F.F.A.) independently.

Data Extraction

A data extraction form was developed based on Wijnen et al[17] (2016). Two reviewers (M.R.R. and F.F.A.) independently conducted the data extraction of all articles in English. One article in German was extracted by 2 other reviewers (P.vD. and M.J.P.) independently. Any disagreement on data extraction was resolved by consensus with a third reviewer (C.B.).

Pre-planned subgroup analyses were performed according to screening method, study population, screening interval, and screening age. From the initial screening on the topic, we identified that screening programs for CKD were generally conducted in general, diabetic, and hypertension populations, which subsequently informed our stratification throughout the article. Costs derived from each study pertaining to annual screening costs, the cost for routine angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs), and costs for dialysis was converted to US dollars as of 2021 price levels.

The ICER as net costs per QALY was considered to ensure a generic uniform measure, optimally enabling comparison between studies. Based on the ICER value, screening strategies were classified into not cost-effective if the ICER value was higher than the cost-effectiveness threshold, cost-effective if the ICER value was lower than the cost-effectiveness threshold, and cost-saving if the ICER was negative because of negative incremental costs and positive incremental QALYs or health gains. The main focus was on what the authors of the publications themselves indicated as the "base-case analyses." Influential parameters were defined as those with a relevant impact on the ICER and identified based on the results of one-way sensitivity analysis as presented in the individual included studies.

Quality Assessment

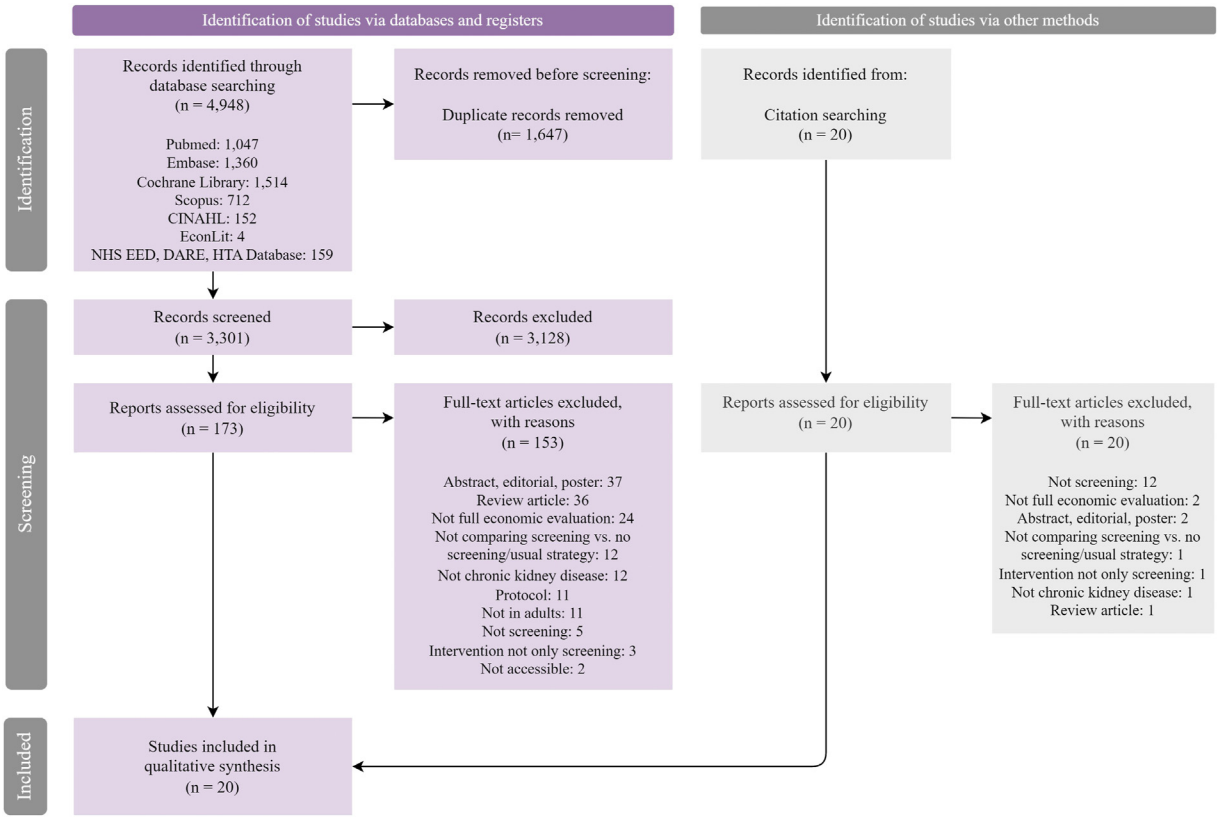
The ISPOR-AMCP-NPC checklist was used to assess the risk of bias and for quality assessment.[18] This instrument consists of 2 components "relevance" and "credibility." Considering that all included studies were relevant to the systematic review because they were selected using strict inclusion and exclusion criteria, only the credibility component was used to assess the risk of bias and quality of the included studies. Credibility of each study was appraised in accordance with 7 domains, namely, validation, bias because of study design, bias because of data source, appropriateness of model analysis, reporting bias, interpretation bias, and conflict of interest.[18] The risk of bias for each domain was rated "Low," "High," "Critical," or "Unclear."

Results

Search Results

The search strategy identified 4948 studies from 7 databases (Fig. 1). After removing duplicates, title and abstract screening was conducted on the remaining studies, and 173 studies were selected for full-text review. After performing citation checks, 20 articles were added for full-text review. A final total of 20 included studies underwent the data extraction process and were included in the qualitative synthesis. Nineteen studies reported in English (95%), whereas 1 study (5%) was written in the German language.[19]

Figure 1. Study selection process for this systematic review.



Settings and Population

Characteristics of the included studies are summarized in Table 1.[19-38] From the 20 studies, majority focused on the US (n = 6),[20,22,24,27,29,33] Germany (n = 3),[19,25,38] Canada (n = 2),[28,34] and Switzerland (n = 2).[21,30] The target population was the DM population in 40% of studies (n = 8),[19-21,23-25,32,35] the general population in 30% (n = 6),[22,26,31,33,34,37] and both general and targeted populations (DM and hypertension) in the remaining studies (n = 6).[27-30,36,38]

Screening and Follow-Up Treatment

Screening method was categorized based on initial screening method. Two studies reported on the cost-effectiveness of screening for kidney disease based on urinalysis alone, estimated glomerular filtration rate (eGFR) alone, and a combination of urinalysis and eGFR.[31,36] Accordingly, cost-effectiveness based on urinalysis was analyzed in 16 studies (67%),[19-27,29-32,35,36,38] eGFR in 4 studies (17%),[28,31,36,37] a combination of urinalysis and eGFR in 3 studies (12%),[31,34,36] and risk scoring as the first step of screening was analyzed in 1 study (4%).[33] After the initial screening, a confirmation test was carried out to clarify the results of initial screening.

An annual screening interval was evaluated in 12 studies (60%),[19,21-25,27,29-32,35] a 2-year screening interval in 3 studies,[33,36,38] and another 3 studies evaluated a 1-time screening without any repeated screening.[26,28,34] One study screened for twice a year,[20] whereas 1 remaining study did not clearly state a screening interval.[37]

In all studies, individuals with positive results at screening received follow-up treatment in the form of ACEI (enalapril, captopril, fosinopril, and ramipril) or ARB (irbesartan), except for 1 study that did not clearly state the treatment administered to individuals with positive results.[37] Presumably, ARB was prescribed when a patient was not able to tolerate the coughing or other side effects associated with ACEI treatment.

Types of Economic Evaluation

Table 2[19-38] summarizes the economic evaluation characteristics of the included studies. From the total 20 studies, 16 studies (80%) performed a cost-utility analysis (CUA),[22-25,27-38] whereas only 4 studies (20%) performed a cost-effectiveness analysis (CEA).[19-21,26] The study perspective was from the payer perspective in 15 studies (75%),[19,21,23-30,33-35,37,38] the societal perspective in 4 studies (20%),[22,31,32,36] and not clearly stated in 1 study (5%).[20] From the societal perspective, aside from incorporating direct medical costs, 2 studies also considered loss in productivity as an indirect cost,[22,31] whereas 2 other studies also included other nonmedical costs, such as transportation, food, and paid caregiver costs.[32,36]

Screening was modeled on a lifetime horizon (n = 18) except in 2 studies. From those, 1 study evaluated 8 years only because the study was developed based on 8-year trial data,[26] whereas the other did not clearly state the time horizon.[37]

Model Structure

The progression of CKD was modeled based on albuminuria or eGFR levels. When based on albuminuria, the progression was categorized with normoalbuminuria, microalbuminuria, and macroalbuminuria; whereas when based on eGFR, 5 stages were

Table 1. Detailed characteristics of included studies.

Study	Setting	Population	Initial screening	Confirmation test	Interval	Treatment
Siegel et al (1992)[20]	United States	T1D (aged 15 years)	Microalbuminuria	Microalbuminuria	Twice a year	ACEI (enalapril)
Gozzoli et al (2000)[19]	Germany	T2D (aged 69 years)	Microalbuminuria	Microalbuminuria	Annual	As program aimed at normalization of dietary protein intake and regulation of blood glucose, blood pressure, and blood lipids
Palmer et al (2000)[21]	Switzerland	T1D (aged 19 years)	Microalbuminuria	Microalbuminuria	Annual	ACEI (captopril)
Boulware et al (2003)[22]	United States	General population (aged 50 years)	Proteinuria	ACR and eGFR	Annual	ACEI or ARB
Palmer et al (2006)[23]	France	T2D and hypertension	Microalbuminuria	Microalbuminuria	Annual	ARB (irbesartan)
Palmer et al (2008)[24]	United States	T2D and hypertension	Microalbuminuria	Microalbuminuria	Annual	ARB (irbesartan)
Adarkwah and Gandjour (2010)[25]	Germany	T2D (aged 50 years)	Microalbuminuria	-	Annual	ACEI (ramipril) or ARB (irbesartan)
Boersma et al (2010)[26]	The Netherlands	General population	Microalbuminuria (UAC)	Microalbuminuria (UAE)	One-time	ACEI (fosinopril)
Hoerger et al (2010)[27]	United States	General population, DM, hypertension	Microalbuminuria	Microalbuminuria and eGFR	Annual	ACEI or ARB
Manns et al (2010)[28]	Canada	General population, DM, hypertension	eGFR	-	One-time	ACEI or ARB
Hoerger et al (2012)[29]	United States	General population, DM, hypertension (aged 50 years)	Microalbuminuria	Microalbuminuria and eGFR	Annual	ACEI or ARB
Kessler et al (2012)[30]	Switzerland	General population, DM and hypertension (aged 50 years)	Microalbuminuria	Microalbuminuria and eGFR	Annual	ACEI or ARB
Kondo et al (2012)[31]	Japan	General population (adults)	Proteinuria only, serum creatinine only or both	Physician visit	Annual	ACEI
Srisubat et al (2014)[32]	Thailand	T2D (aged 45 years)	Microalbuminuria	-	Annual	ACEI (enalapril)
Yarnoff et al (2017)[33]	United States	General population (age 30 years)	CKD risk score	ACR and eGFR	2 years	ACEI or ARB
Ferguson et al (2017)[34]	Canada	General population (adults)	Both eGFR and ACR	-	One-time	ACEI or ARB
Wu et al (2018)[35]	China	T2D (aged 51 years)	Microalbuminuria	Microalbuminuria	Annual	ACEI or ARB
Go et al (2019)[36]	Korea	General population, DM or hypertension (aged 40 years)	Urinalysis with dipstick alone, eGFR alone, or both	Physician visit	2 years	ACEI
Ravaghi et al (2019)[37]	Iran	General population (adults)	eGFR	Kidney ultrasonic	-	not stated
Kairys et al (2022)[38]	Germany	General population, DM or hypertension (aged 30 years)	Microalbuminuria (UAC)	Microalbuminuria (UAC)	2 years	ACEI or ARB

ACEI indicates angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; ARB, antagonist receptor blocker; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes; T2D, type 2 diabetes; UAC, urinary albumin-creatinine; UAE, urinary albumin excretion.

applied. Models considered that CKD was irreversible, except in 2 studies.[26,32] These 2 studies assumed that individuals with microalbuminuria could revert to the normoalbuminuria stage. This assumption was based on a trial.[26]

All models mainly assumed that treating with ACEI or ARB would decrease the number of patients with final stage of CKD and mortality. Only 1 study evaluated the cost-effectiveness of screening programs based on the combination of lifestyle interventions and medications, including ACEI treatment.[19] Aside from the abovementioned assumptions, 6 studies also incorporated the benefit of taking ACEI or ARB in preventing cardiovascular diseases, such as stroke and myocardial infarction in their models.[26,27,29,30,33,36] In all studies, the evaluation cycle was 1 year.

Input Parameters

The main input parameters of the included studies are presented in Table 3.[19-38] The highest prevalence of microalbuminuria was found in the DM population with hypertension at 29.9% to

Table 2. Detailed economic evaluations of included studies.

Study	Economic evaluation type	Model type	Time horizon	Perspective	Discount rate	One-way sensitivity analysis	Probabilistic sensitivity analysis	Scenario analysis
Siegel et al (1992)[20]	CEA	Semi-Markov model	Lifetime	Not stated	5% (costs)	Yes	No	No
Gozzoli et al (2000)[19]	CEA	Markov model	Lifetime	Payer	0% (costs and outcome)	Yes	No	No
Palmer et al (2000)[21]	CEA	Markov model	Lifetime	Payer	3-, 5- and 6% (costs and outcome)	Yes	No	No
Boulware et al (2003)[22]	CUA	Markov model	Lifetime	Societal	3% (costs and outcome)	Yes	No	Yes
Palmer et al (2006)[23]	CUA	Markov model	Lifetime	Payer	3% (costs and outcome)	Yes	No	Yes
Palmer et al (2008)[24]	CUA	Markov model	Lifetime	Payer	3% (costs and outcome)	Yes	Yes	Yes
Adarkwah and Gandjour (2010)[25]	CUA	Markov model	Lifetime	Payer	3% (costs and outcome)	Yes	Yes	No
Boersma et al (2010)[26]	CEA	Markov model	8 years	Payer	4% (costs) 1.5% (outcome)	Yes	Yes	Yes
Hoerger et al (2010)[27]	CUA	Microsimulation	Lifetime	Payer	3% (costs and outcome)	Yes	No	Yes
Manns et al (2010)[28]	CUA	Markov model	Lifetime	Payer	5% (costs and outcome)	Yes	Yes	Yes
Hoerger et al (2012)[29]	CUA	Microsimulation	Lifetime	Payer	3% (costs and outcome)	Yes	No	Yes
Kessler et al (2012)[30]	CUA	Microsimulation model	Lifetime	Payer	3% (costs and outcome)	Yes	Yes	Yes
Kondo et al (2012)[31]	CUA	Decision tree and Markov model	Lifetime	Societal	3% (costs and outcome)	Yes	No	Yes
Srisubat et al (2014)[32]	CUA	Markov model	Lifetime	Societal	3% (costs and outcome)	Yes	Yes	No
Yarnoff et al (2017)[33]	CUA	Microsimulation	Lifetime	Payer	3% (costs and outcome)	Yes	Yes	Yes
Ferguson et al (2017)[34]	CUA	Markov model	Lifetime	Payer	5% (costs and outcome)	Yes	Yes	Yes
Wu et al (2018)[35]	CUA	Decision tree and Markov model	Lifetime	Payer	5% (costs and outcome)	Yes	Yes	No
Go et al (2019)[36]	CUA	Markov model	Lifetime	Societal	5% (costs and outcome)	Yes	No	Yes
Ravaghi et al (2019)[37]	CUA	Markov model	Not stated	Payer	5% (costs and outcome)	Yes	No	No
Kairys et al (2022)[38]	CUA	Microsimulation	Lifetime	Payer	3.5% (costs and outcome)	Yes	Yes*	Yes

CEA indicates cost-effectiveness analysis; CUA, cost-utility analysis.
*Presenting 95% of confidence interval of the ICER but not presenting cost-effectiveness acceptability curve.

35.5%[23,24] followed by 18% to 30% in the DM population.[25,32,35] The prevalence of microalbuminuria in the general population was estimated between 6.3% to 8.9%,[19,26,27,29,30] except for African Americans at 14.3%.[29]

Prescribing ACEI or ARB for treatment after a positive screening for CKD was assumed beneficial because of the drugs' effectiveness in reducing the progression of CKD and mortality rate, as well as decreasing transition probabilities for progression. Concerning effectiveness on reducing the progression of CKD, the relative risk ranged from 55% to 70%, with most studies assuming a relative risk of 67%.[27,29,30,33,34,36,38] For reducing mortality, the relative risk was assumed to be between 60% and 93%, with the majority of studies using 77%.[22,27,29,30,33,34] The way in which the benefit of ACEI or ARB treatment in terms of transition probabilities modeled across studies varied to some degree; however, the main outcome for measurement was the slowing down of progression from microalbuminuria to macroalbuminuria, with most studies using 45%.[25,27,29,30,32,33,35,38]

Table 3. Main input parameters for the included studies.

Study	Prevalence of microalbuminuria (%)	Accuracy (%)		Relative risk of ACEI or ARB treatment (%)		
		Sensitivity	Specificity	Transition probabilities*	Mortality	Progression
Siegel et al (1992)[20]	-	-	-	50 (to ESKD)	-	-
Gozzoli et al (2000)[19]	18.8	-	-	-	-	-
Palmer et al (2000)[21]	-	-	-	50 (to ESKD)	-	55
Boulware et al (2003)[22]	Proteinuria: 0.19 (neither DM/HT) 1.2 (DM) 5.4 (HT)	76	79	-	77	70
Palmer et al (2006)[23]	35.5 (aged 20-49) 29.9 (aged ≥50)	70-97	71-98	30 (to early overt nephropathy)	-	-
Palmer et al (2008)[24]	35.5 (aged 20-49) 29.9 (aged ≥50)	70-97	71-98	30 (to early overt nephropathy)	-	56
Adarkwah and Gandjour (2010)[25]	18	100	81-98	45	-	-
Boersma et al (2010)[26]	8.9	-	-	-	60	-
Hoerger et al (2010)[27]	8.2 (general)	73	96	45	77	67
Manns et al (2010)[28]	Incidence of CKD 7.5 (DM, aged <65) 3.5 (non-DM, aged <65) 18.6 (DM, aged >65) 27.7 (non-DM, aged >65)	-	-	-	79	64
Hoerger et al (2012)[29]	14.3 (African American) 8.4 (non-African American)	76	96	45	77	67
Kessler et al (2012)[30]	6.3	73	96	45	77	67
Kondo et al (2012)[31]	5.45 (proteinuria)	76	79	58 (to ESKD)	-	58
Srisubat et al (2014)[32]	30	95	85	45	-	-
Yarnoff et al (2017)[33]	-	73	96	45	77	67
Ferguson et al (2017)[34]	-	-	-	-	77	67
Wu et al (2018)[35]	21.9	-	-	45	-	-
Go et al (2019)[36]	2.52 (stage 3) 0.75 (stage 4) 0.03 (stage 5)	31-36 (dipstick) 69-74 (eGFR)	95-98 (dipstick) 88-96 (eGFR)	-	93	67
Ravaghi et al (2019)[37]	15.14 (CKD)	-	-	-	-	-
Kairys et al (2022)[38]	Different based on age	87	88	45	79	67

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HT, hypertension.
*Transition from microalbuminuria to macroalbuminuria.
†ACEI.
‡ARB.

Some models also included adherence to better reflect the real situation, either in terms of adherence to screening, adherence to treatment, or even both. Health-related quality of life for people with dialysis ranged from 0.46 to 0.80, in which most of the studies applied 0.80.[27,29,30,33,37,38] Costs for screening, routine ACEI or ARB treatment, and cost for dialysis varied across studies. The range of costs for screening was vast, from $0.90 in Korea to $558.00 in Canada. The cost of screening identified by Ferguson et al[34] (2017) was $558.00 as screening was conducted in remote locations, with the cost including transportation and personnel requirements. For treatment costs, ARB treatment was always more costly than ACEI. Cost of dialysis ranged from $6856.00 in Thailand to $94 567.00 in the US.

Table 3. Continued

Adherence (%)		Utility	Costs (US$, 2021)		
Screening	Treatment	ESKD	Screening	ACEI/ ARB	ESKD
-	-	-	99.5	515	72 492
-	-	-	7.5	281	80 131
-	-	-	35.4	1083	78 009
75	75	0.70	5.4	585[†] 770[‡]	66 888
-	-	0.46	31.2	438	93 018
-	-	0.46	-	902	94 568
-	-	0.62	10.2	71[†] 534[‡]	70 865
implicit	implicit	-	10.2	115	
-	75	0.80	107.5	255[†] 642[‡]	80 586
50	75	0.64	47.4	373	63 418
-	75	0.80	107.5	255[†] 642[‡]	80 586
-	75	0.80	47.8	-	84,882
40	100	0.66	2.5 (dipstick) 1.3 (eGFR) 3.3 (both)	-	57,038
-	-	0.55	5.1	3	6856
-	75	0.80	99.3	237[†] 595[‡]	-
-	75	0.72	558	-	70,701
-	-	0.60	4.5	291	15 530
-	75	0.65	0.9 (dipstick) 1.2 (eGFR)	-	56,243
-	-	0.80	-	-	-
-	91	0.80	46.5	70.3	80 942

Sensitivity Analysis

A one-way sensitivity analysis was performed in 10 studies (50%),[19-23,27,29,31,36,37] and a combination of a one-way sensitivity analysis and a probabilistic sensitivity analysis were performed in the remaining 10 studies (50%).[24-26,28,30,32-35,38] Scenario analysis was performed to analyze the cost-effectiveness for different screening ages,[22-24,26,28,36] screening intervals,[22,27,29,30,33,36] screening methods,[31,36] (sub)populations,[22,27-30,36,38] proportion of home dialysis compared with in-center dialysis,[34] and variations of urine albumin-creatinine ratios or risk scores thresholds.[26,33]

Study Findings

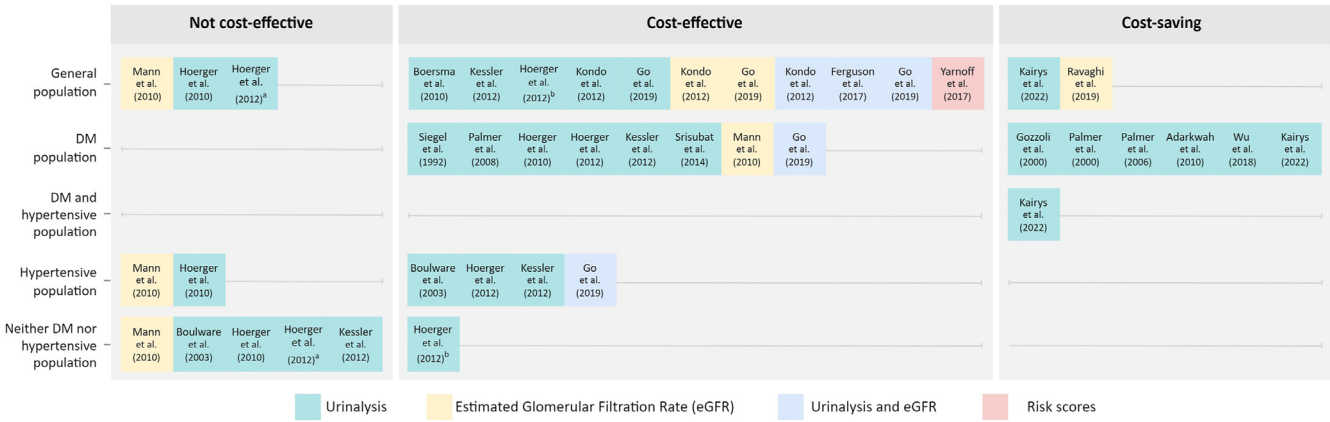
Table 4[19-38] details the ICER values of the included studies, whereas Figure 2 provides a summary. Screening strategies for the DM population was considered cost-effective in 8 studies (57%),[20,24,27-30,32,36] and even cost-saving in 6 studies (43%).[19,21,23,25,35,38] Screening by either by urinalysis,[19-21,23-25,27,29,30,32,35,38] eGFR,[28] or both[36] was not only recommended in the DM only population but also considered a cost-effective intervention across all studies, including for the hypertensive DM population (n = 1, 100%).[38]

Table 4. Incremental cost per LYG or QALY of included studies.

Study	Summary measure	Currency and year	Population (ICER)				Threshold
			General	DM	HT	Not DM-HT	
Urinalysis							
Siegel et al (1992)[20]	Cost per LYG	US$ (1991)	-	16 494	-	-	Not stated
Gozzoli et al (2000)[19]	Cost per LYG	DM (1999)	-	Cost-saving	-	-	*
Palmer et al (2000)[21]	Cost per LYG	CHF (1996)	-	−8286 (Cost-saving)	-	-	*
Boulware et al (2003)[22]	Cost per QALY	US$ (2002)	-	-	18,621	282 818†	50 000
Palmer et al (2006)[23]	Cost per QALY	€ (2002)	-	−16 593 (Cost-saving)	-	-	*
Palmer et al (2008)[24]	Cost per QALY	US$ (2000)	-	20 011	-	-	50 000
Adarkwah and Gandjour (2010)[25]	Cost per QALY	€ (2006)	-	−20 324 (Cost-saving)	-	-	*
Boersma et al (2010)[26]	Cost per LYG	€ (2008)	22 000	-	-	-	20 000, 50 000, and 80 000
Hoerger et al (2010)[27]	Cost per QALY	US$ (2006)	73 000†	21 000	55 000†	155 000†	50 000
Hoerger et al (2012)[29]	Cost per QALY	US$ (2006)	33 000‡ 81 000†,§	19 000‡ 43 000§	21 000‡ 40 000§	35 000‡ 106 000†,§	50 000
Kessler et al (2012)[30]	Cost per QALY	CHF (2010)	66 000	29 000	40 000	88 000†	71 000
Kondo et al (2012)[31]	Cost per QALY	US$ (2009)	12 660	-	-	-	128 000
Srisubat et al (2014)[32]	Cost per QALY	THB (2011)	-	3035	-	-	150 000
Wu et al (2018)[35]	Cost per QALY	US$ (2014)	-	−14 380 (Cost-saving)	-	-	*
Go et al (2019)[36]	Cost per QALY	US$ (2016)	65 003	-	-	-	50 000 (Korea) 80 000 (International)
Kairys et al (2022)[38]	Cost per QALY	€ (2016)	−6175 (Cost-saving)	−8500 (Cost-saving)	−12 582 (DM or HT, cost-saving)	-	*
eGFR							
Manns et al (2010)[28]	Cost per QALY	$C (2009)	104 900†	22 600	334 000†	1 411 100†	US$50 000
Kondo et al (2012)[31]	Cost per QALY	US$ (2009)	90 250	-	-	-	128 000
Ravaghi et al (2019)[37]	Cost per QALY	Rials (2017)	-277 686 954 (Cost-saving)	-	-	-	*
Go et al (2019)[36]	Cost per QALY	US$ (2016)	66 013	-	-	-	50 000 (Korea) 80 000 (International)
Urinalysis and eGFR							
Kondo et al (2012)[31]	Cost per QALY	US$ (2009)	91 505	-	-	-	128 000
Ferguson et al (2017)[34]	Cost per QALY	US$ (2013)	23 700	-	-	-	50 000
Go et al (2019)[36]	Cost per QALY	US$ (2016)	66 874	37 812	40 787	-	50 000 (Korea) 80 000 (International)
Risk scores							
Yarnoff et al (2017)[33]	Cost per QALY	US$ (2016)	19 116	-	-	-	50 000

DM indicates diabetes mellitus; eGFR, estimated glomerular filtration rate; HT, hypertension; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.
Cost-effectiveness threshold is
§African Americans.
‡Non-African Americans.
*ICER was cost-saving thus threshold was not necessary.
†Considered as not cost-effective interventions by the authors based on the applicable willingness to pay threshold.

Figure 2. Cost-effectiveness analysis results for the included studies based on initial screening method and target population.



a:among non-African Americans; b:among African Americans. DM indicates diabetes mellitus; eGFR, estimated glomerular filtration rate.

For other targeted screening, 4 studies (67%) concluded that screening in the hypertensive population was cost-effective,[22,29,30,36] whereas 2 studies (33%) concluded the opposite findings.[27,28] In contrast, the base-case analysis of screening in a population without DM or hypertension was reported as not cost-effective by all 4 studies.[22,27,28,30] There was only 1 study that considered it not cost-effective to screen non-African Americans but cost-effective for the African American population.[29]

For the general population, findings were contradictory across studies. Screening was considered cost-saving in 2 studies (12%),[37,38] cost-effective in 11 studies (69%),[26,29-31,33,34,36] and not cost-effective in 3 studies (19%)[27-29] (Fig. 2). Two studies reported that all scenario analysis by screening using urinalysis, eGFR, or both were cost-effective interventions.[31,36] Compared with the hypertension population, a screening strategy for the general population was less-cost-effective; however, screening in the DM population was more cost-effective than both strategies.[27-30,36,38]

Regarding one-way sensitivity analyses, some parameter estimates influenced the ICER value. Prevalence and incidence of CKD, including microalbuminuria or proteinuria incidence, was one of the most common influential parameters reported by 5 studies.[22,27,29,30,34] In terms of costs, costs of screening[20,27,30,32,34] and dialysis[20,25,34] were found to drive the ICER value significantly. Treatment adherence[22,27,29,34] and the effectiveness of CKD treatment in delaying CKD progression by prescribing ACEI or ARB[20,25,31,34,36] also appeared to substantially affect the ICER. Increasing the effectiveness of treatment would lead to screening programs becoming more cost-effective.

Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.003 shows studies that reported different scenarios of screening in terms of screening intervals and screening age. Longer duration screening intervals or less-frequent screening[22,27,29,30,33,36] and older starting age for screening[22,26,28,36] resulted in a lower ICER value. Boulware et al[22] (2003) found that although screening in a population without DM or hypertension was not cost-effective, screening those aged ≥60 years and using a 10-year screening interval was, in fact, cost-effective.

Quality Assessment

Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.003 presents a risk of bias summary for each study in accordance with the ISPOR-AMCP-NPC checklist, whereas Appendix Figure 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.003 shows the percentage of judgments in each domain. In addition, Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.08.003 combines details of the judgments and an appraisal of the risk of bias assessments.

Two domains with the highest risk of bias were that of data and validation. Bias in the data domain—the domain that refers to the source of input parameter estimates and from which three-quarters of the included studies (75%) were considered high risk, considering that almost of the input parameters were retrieved from selected literature and not from meta-analysis—might be attributed to the fact that studies derived data from clinical trial rather than from real-world settings, and the study may not have always limited data to only the country being researched. More than half of the included studies (55%) were classified high risk because these studies did not perform an external validation to judge the accuracy of the model or perform calibration to match the model output against published reports.

All studies performed a sensitivity analysis; however, 8 studies (40%) did not adequately examine the uncertainty of input parameters by using a probabilistic sensitivity analysis. In the reporting domain, 6 studies (30%) were marked high risk because of concerns regarding documentation and inadequacy in reporting so as to enable replication of the model. Additionally, concerns were marked in 5 studies (25%) that did not sufficiently declare a conflict of interest.

Discussion

Study Findings and Implications

This systematic review identified 20 studies that examine the economic evaluation of screening for CKD. All studies conducted in the DM population (type 1 or 2 DM) concluded that screening is cost-effective regardless of the screening method used (urinalysis alone, eGFR alone, or a combination of both). The high prevalence and rapid progression of CKD in this population makes screening more effective in preventing the need for and therefore avoiding the high costs associated with dialysis because of end-stage kidney disease. Screening for CKD in patients with hypertension is also likely to be cost-effective. These findings are in line with the previous review.[11]

For the general population, although 3 studies reported that screening was not recommended from an economic perspective,[27-29] most recent studies reported that screening was cost-effective.[31,33,34,36-38] Hoerger et al[27] (2010) found that screening in the general population was not cost-effective; however, halving the screening costs would reduce ICER enough to make it cost-effective. This study assumed relatively high screening costs because it included the cost of physician visits, whereas recent studies generally only included costs for laboratory testing and would assume that screening was part of routine care.[31,32,35,36] Another study revealed that screening in non-African Americans was not cost-effective because the prevalence of microalbuminuria in this population was only half that of African Americans.[29]

Prevalence plays as an important role in the cost-effectiveness of screening for CKD. In a population with high prevalence of CKD, screening will identify a high number of positive patients, thereby yielding a low number needed to screen (NNS) to detect 1 case.[39,40] Although the included studies did not report NNS, screening in populations with a high prevalence of CKD will generally result in low NNS and thus be cost-effective. Such populations might be diabetes populations rather than general populations, African Americans rather than non-African Americans, and older rather than younger populations. Only 2 studies found that screening in younger populations was more cost-effective than in older populations, which was based on an estimated higher prevalence of microalbuminuria in younger populations.[23,24]

Although screening in the US general population was estimated to be not cost-effective in earlier studies,[27,29] a more recent study by Yarnoff et al[33] (2017) found that screening was cost-effective. This study applied a 2-step approach in which a score was used to stratify the risk of CKD in the general population first, and those with a high risk would be screened using albuminuria. This strategy can be adapted to reduce the number of people requiring laboratory tests and specifically select those with prior elevated risk of CKD. In line with this argument, further stratification strategies can be formulated to increase screening cost-effectiveness, such as by using ethnicity[29] or age.[22-24,26,28,36] This stratification strategy was not reported in the previous review.[11]

WHO recommends that cost-effectiveness should be assessed from a societal perspective.[41] However, in this review, only 4 studies measured costs from this perspective, whereas the remaining studies modeled from a payer perspective. In a country where most patients with end-stage kidney disease are treated with hospital-based hemodialysis, nonmedical costs and loss of productivity should be seen as relevant for inclusion in models. Patients with hemodialysis need to be treated for 4 hours, 2 to 3 times a week in a hospital setting,[42] which results in a substantial financial burden for those patients and society.

Quality of Evidence

Data, validation, and analysis domains were identified as reflecting the highest risk of bias potential. Data used to build the model, for example, data used to determine transition probabilities or effectiveness of ACEI treatment, were potentially obtained from countries that might have different characteristics for determining prevalence of CKD, adherence, and mortality. Validation is required to ensure that models are accurate and is done by comparing a model's output with published reports.[18] Calibration may also be required if there are discrepancies, for example, calibration of the transition probabilities to match the incidence of end-stage kidney disease in the model output to national data.[29] However, more than half of the included studies did not report this external validation. In addition, probabilistic sensitivity analysis is required to assess the uncertainty of the input parameter estimates on the results. We recommend that future studies in this field include details on how the model was validated and to include proper sensitivity analysis to minimize bias and improve economic modeling accuracy.

Because ACEI and ARB treatments can also reduce the progression and complications of cardiovascular disease,[43] future studies should include these potential benefits in the model. Finally, a recent meta-analysis reported that combination of sodium-glucose cotransporter 2 (SGLT2) inhibitors and ACEI or ARB results in better clinical outcomes, including kidney parameters compared with ACEI or ARB alone in diabetic population.[44] However, our review did not find any evaluations on cost-effectiveness of screening programs using a combination of SGLT2 inhibitors and ACEI or ARB. Therefore, we encourage future studies to conduct such evaluations.

Strengths and Limitations

Although the previous review retrieved 9 articles until June 2012 using 4 databases,[11] our review retrieved 20 articles until January 2023 using 7 databases. In addition, we included studies not only in English but also in the German language.[19]

This review only included studies comparing screening with no screening strategies but excluded cost-effectiveness studies reporting on different screening methods compared with each other because these studies did not address the question whether decision makers should cover screening for CKD or not. In 2 of the included studies, aside from comparing screening with no screening, Kondo et al[31] (2012) and Go et al[36] (2019) also modeled screening in the general population using 3 screening methods, namely, urinalysis only, eGFR only, and a combination of both. In these 2 studies, the results indicate that screening is still cost-effective when using these methods, with urinalysis considered to be the most cost-effective, followed by eGFR, and then a combination of both. A final limitation is that because of the limited number of countries studied, applicability of the findings to other countries may come into question; therefore, further studies are needed to account for differences in healthcare systems.

Conclusions

Screening for CKD in patients with diabetes or hypertension is recommended from a cost-effectiveness point of view. For the general population, despite some inconsistent findings, the majority of studies demonstrated that screening in the general population is cost-effective, depending mainly on the prevalence of CKD and the costs of screening. Moreover, stratification based on CKD risk score, ethnicity, or age can be used to ensure general population screening is more cost-effective. Healthcare decision makers need to consider the prevalence of CKD and stratification and advocate for lower screening costs so as to reduce the burden on healthcare budgets, as well as make screening for the general population more favorable from a health-economic perspective.

Author Disclosures

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Supplemental Material

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