

Population based screening for chronic kidney disease: cost effectiveness study

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ABSTRACT

Objective To determine the cost effectiveness of one-off population based screening for chronic kidney disease based on estimated glomerular filtration rate.

Design Cost utility analysis of screening with estimated glomerular filtration rate alone compared with no screening (with allowance for incidental finding of cases of chronic kidney disease). Analyses were stratified by age, diabetes, and the presence or absence of proteinuria. Scenario and sensitivity analyses, including probabilistic sensitivity analysis, were performed. Costs were estimated in all adults and in subgroups defined by age, diabetes, and hypertension.

Setting Publicly funded Canadian healthcare system.

Participants Large population based laboratory cohort used to estimate mortality rates and incidence of end stage renal disease for patients with chronic kidney disease over a five year follow-up period. Patients had not previously undergone assessment of glomerular filtration rate.

Main outcome measures Lifetime costs, end stage renal disease, quality adjusted life years (QALYs) gained, and incremental cost per QALY gained.

Results Compared with no screening, population based screening for chronic kidney disease was associated with an incremental cost of \$C463 (Canadian dollars in 2009; equivalent to about £275, €308, US \$382) and a gain of 0.0044 QALYs per patient overall, representing a cost per QALY gained of \$C104 900. In a cohort of 100 000 people, screening for chronic kidney disease would be expected to reduce the number of people who develop end stage renal disease over their lifetime from 675 to 657. In subgroups of people with and without diabetes, the cost per QALY gained was \$C22 600 and \$C572 000, respectively. In a cohort of 100 000 people with diabetes, screening would be expected to reduce the number of people who develop end stage renal disease over their lifetime from 1796 to 1741. In people without diabetes with and without hypertension, the cost per QALY gained was \$C334 000 and \$C1 411 100, respectively.

Conclusions Population based screening for chronic kidney disease with assessment of estimated glomerular filtration rate is not cost effective overall or in subgroups of people with hypertension or older people. Targeted

screening of people with diabetes is associated with a cost per QALY that is similar to that accepted in other interventions funded by public healthcare systems.

INTRODUCTION

End stage renal disease and its precursor chronic kidney disease are emerging public health problems because of their associated adverse clinical outcomes, poor quality of life, and high healthcare costs. Given that chronic kidney disease (defined as glomerular filtration rate below 60 ml/min/1.73 m²) is often not detected until it is advanced, screening programmes using blood or urine tests have been recommended.¹⁻³ With population based screening, however, there are potential benefits (such as early identification and treatment of affected patients) and drawbacks (such as identification of patients with only mild disease, in whom additional treatment might not be warranted).⁴

Several studies have examined the effectiveness of screening for chronic kidney disease with estimated glomerular filtration rate or urinalysis.⁵⁻⁹ Previous studies of screening in high risk groups have found that it would identify one person with disease for every three to six people screened,⁵⁻¹⁰ whereas population based screening would detect one for every 16-21 people screened.^{10 11} Existing cost effectiveness studies have examined screening only with urinalysis.^{12 13} As only 26% and 3% of North Americans with glomerular filtration rate <30 ml/min/1.73 m², and 30-60 ml/min/1.73 m², respectively, have macroalbuminuria on urinalysis, this form of screening would be expected to miss a considerable proportion of people with chronic kidney disease.¹⁰

While clinical practice guidelines for chronic kidney disease from the National Kidney Foundation/Kidney Dialysis Outcomes Quality Initiative have recommended targeted screening of high risk patients, including those with diabetes or hypertension and aged >60,¹⁴ others have suggested a population based approach.^{4 15 16} The International Federation of Kidney Foundations recently surveyed its 28 member nations on the existence of screening programmes for chronic kidney disease, and 24 reported some form of screening activity.¹⁷ While most programmes entailed

Table 1 | Baseline characteristics of patient cohort from Alberta Kidney Disease Network. Figures are numbers (percentages) of patients unless otherwise specified

	Overall (n=290 613)	People with diabetes (n=30 277)	People without diabetes (n=260 336)
Mean (SD) age (years)	55 (18)	64 (14)	54 (18)
Aged ≥65	90 090 (31)	15 139 (50)	75 497 (29)
Women	168 555 (58)	14 533 (48)	153 598 (59)
CKD (estimated GFR in ml/min/1.73 m ²):			
None (≥60)	235 160 (81)	19 788 (65)	215 372 (83)
Stage 3 (30-59.9)	51 591 (18)	9162 (30)	42 429 (16)
Stage 4 (15-29.9)	2962 (1)	1000 (3)	1962 (1)
Stage 5 (<15)	900 (0)	327 (1)	573 (0)
Determination of proteinuria*	12 754/55 453 (23)	9021/10 489 (86)	7644/44 964 (17)
Presence of proteinuria*†	893/12 754 (7)	812/9021 (9)	459/7644 (6)
Comorbidity (%)*:			
Myocardial infarction	4658/55 453 (8)	1704/10 489 (16)	2954/44 964 (7)
Peripheral vascular disease	2462/55 453 (4)	909/10 489 (9)	1553/44 964 (3)
Cerebrovascular disease	3295/55 453 (6)	1035/10 489 (10)	2260/44 964 (5)
Median (IQR) Charlson comorbidity score*	0 (0-1)	1 (0-3)	0 (0-0)

CKD=chronic kidney disease; GFR=glomerular filtration rate; IQR=interquartile range.
*Patients with CKD stage 3-5 only
†Among people with CKD (GFR <60 ml/min/1.73 m²), proteinuria defined as present if urine dipstick was > trace or urine protein:creatinine ratio >23 mg/mmol (>200 mg/g).¹⁹

screening for disease among high risk groups, including those with hypertension, diabetes, and a family history of chronic kidney disease and older people, a few countries, including Hong Kong, Japan, and the Netherlands, have active population based screening programmes. Given the current interest in screening, as well as the controversy concerning its optimal use, we assessed the cost effectiveness of population based screening for chronic kidney disease based on estimated glomerular filtration rate alone (compared with no screening) in all adults and in subgroups of people defined by age, diabetes, and hypertension.

METHODS

Overview and validation

We carried out an incremental cost utility analysis of one-off screening for chronic kidney disease with estimated glomerular filtration rate compared with no

screening in adults with no previous assessment of glomerular filtration rate. The box shows a high level overview of the modelling process.

In the base case analysis we used the perspective of the publicly funded healthcare system. Health benefits were measured in cases of end stage renal disease prevented and quality adjusted life years (QALYs) gained over a lifetime. We also assessed the incremental cost associated with screening for chronic kidney disease and measured the incremental cost per QALY gained. Costs and benefits were discounted at 5% annually. All costs were inflated to 2009 Canadian dollars (1 \$C=£0.59=€0.67=US \$0.83) by using the Canadian healthcare consumer price index.

Computer simulation model

We constructed a Markov model using decision analysis software (TreeAge Pro Suite 2007, Williamstown, MA) in accordance with existing guidelines for economic evaluation.¹⁹ Base case analyses were performed with Markov cohort simulation with transitions modelled on an annual basis, though we used first order Monte Carlo simulation to determine the incidence of end stage renal disease over time. We considered several health states in both the screening and no screening strategies, including people without chronic kidney disease, those with non-dialysis chronic kidney disease, patients receiving dialysis, and patients with a functioning transplant.

Model validity was established,²⁰ including internal validation with primary clinical data (R² between model outcomes and primary data was >0.97 for both end stage renal disease and mortality at five years) and external validity by comparing with other published reports.^{21 22} Among patients with chronic kidney disease, mortality and end stage renal disease was 24% and 2.7% at five years and 71% and 4.1% at 20 years, respectively. Several models were evaluated, and, given the excellent performance of all models, we used the simplest and most transparent model, where chronic kidney disease is represented as one health state (as opposed to modelling patients with varying severity of chronic kidney disease as three separate disease states¹), in accordance with optimal modelling guidelines.²⁰ Additional benefits of modelling with only one health state is that it offers increased flexibility to incorporate estimates of benefit (that is, relative risk for end stage renal disease and death) as reported in clinical trials, compared with models that use several distinct stages of chronic kidney disease based on severity of disease.

Data inputs

We based the prevalence of non-dialysis chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m²) on the results of the National Health and Nutrition Examination Survey III, a representative survey of the North American population stratified by age and the presence of diabetes.¹⁰ In the survey, conducted by the National Center for Health Statistics in the United States, data (including estimated

Overview of analysis

- The prevalence of undiagnosed chronic kidney disease in different subgroups of patients stratified by age (<65 or ≥65) and diabetes was determined from a North American population based survey¹⁰
- The natural course of chronic kidney disease was then determined within the Alberta Kidney Disease Network,¹⁸ a large population based laboratory cohort of patients, with mortality rates and incidence of end stage renal disease estimated over a five year follow-up period
- Screening for chronic kidney disease would be expected to identify patients with no previous diagnosis who could then receive angiotensin blockade
- The relative risks of end stage renal disease and death associated with angiotensin blockade were taken from high quality published meta-analyses
- This information was combined with decision analysis to examine the long term outcomes and costs for a strategy of screening for chronic kidney disease and subsequent management of patients compared with no screening (disease undiagnosed and untreated until detected incidentally during routine care)

Table 2 | Annual probability of end stage renal disease and mortality in people with chronic kidney disease in Alberta Kidney Disease Patient cohort, stratified by diabetes and presence of proteinuria*

Variables	Without diabetes (n=44 964)		With diabetes (n=10 489)	
	No proteinuria	Proteinuria	No proteinuria	Proteinuria
End stage renal disease				
Age <65:				
Year 1	0.0037	0.0523	0.0049	0.0547
Year 2	0.0024	0.0380	0.0013	0.0608
Year 3	0.0011	0.0336	0.0045	0.0630
Year 4	0.0031	0.0296	0.0053	0.0703
Year 5	0.0014	0.0340	0.0083	0.0597
Age ≥65:				
Year 1	0.0011	0.0274	0.0029	0.0377
Year 2	0.0015	0.0243	0.0015	0.0340
Year 3	0.0008	0.0158	0.0027	0.0193
Year 4	0.0022	0.0235	0.0023	0.0232
Year 5	0.0015	0.0255	0.0018	0.0306
Mortality				
Age <65:				
Year 1	0.0024	0.0182	0.0122	0.0369
Year 2	0.0054	0.0299	0.0186	0.0478
Year 3	0.0116	0.0222	0.0240	0.0243
Year 4	0.0115	0.0288	0.0234	0.0690
Year 5	0.0136	0.0194	0.0361	0.0409
Year 6-10†	0.008	0.028	0.0258	0.0559
Year 11-15†	0.012	0.045	0.0252	0.0523
Year 16-20†	0.015	0.044	0.0321	0.0550
Year 21-25†	0.019	0.053	0.0405	0.0632
Year 26-30†	0.027	0.069	0.0465	0.0954
Year 31-35†	0.032	0.053	0.0591	0.0912
Year 36-40†	0.053	0.093	0.0742	0.1249
Year 41-45†	0.066	0.131	0.0993	0.0999
Year 46-50†	0.052	0.135	0.1459	0.1973
Age ≥65:				
Year 1	0.0124	0.0570	0.0258	0.0640
Year 2	0.0208	0.0759	0.0483	0.0883
Year 3	0.0288	0.0842	0.0528	0.0889
Year 4	0.0363	0.0907	0.0613	0.1019
Year 5	0.0438	0.0962	0.0638	0.0937
Year 6-10†	0.030	0.079	0.0545	0.0841
Year 11-15†	0.042	0.110	0.0646	0.1237
Year 16-20†	0.061	0.165	0.0940	0.1165
Year 21-25†	0.079	0.129	0.1095	0.1559

*Incidence of proteinuria at age <65 was 0.20 in those without diabetes and 0.32 in those with diabetes and 0.16 and 0.22, respectively, at age ≥65.¹⁰

†Based on probability of mortality observed in progressively older patients. For example, mean age of patients <65 was 55, and mortality over first five years for this cohort is reported per year by using full cohort. Mortality for years 6-10 estimated on mortality observed for patients with mean age 60 (range 57-63) within each of four diabetes/proteinuria subgroups, while mortality for years 11-15 was based on mortality observed for patients with mean age 65 (63-68) within each of four diabetes/proteinuria subgroups.

glomerular filtration rate) were collected with rigorous methods according to standardised protocols.²³

We also used data from the Alberta Kidney Disease Network,¹⁸ a repository of laboratory data for routinely collected tests (including estimated glomerular filtration rate) for the entire province of Alberta, Canada. Patients in the laboratory repository are linked to provincial healthcare programmes, which care for all

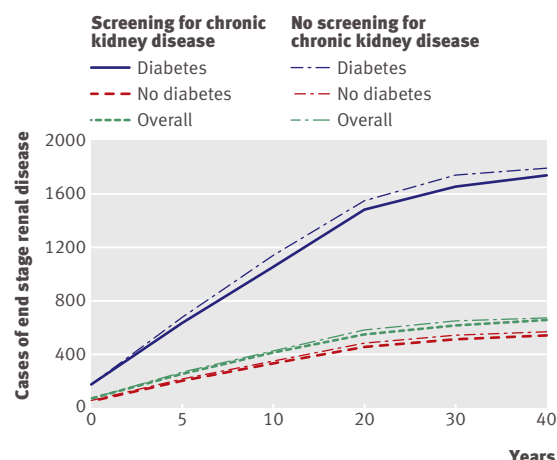


Fig 1 | Impact of screening for chronic kidney disease in cohort of 100 000 people on number of cases of end stage renal disease overall and for people with and without diabetes

dialysis and transplant patients,²⁴ and to provincial administrative data (using the unique provincial health number) to obtain demographic information (including death) and details regarding use of healthcare resources (physician claims, admission to hospital, and use of prescription drugs (for people aged ≥65)).¹⁸

Data from the network enabled us to estimate the annual incidence of end stage renal disease and death in a cohort of Albertans receiving routine care between May 2002 and December 2007 (table 1). The initial and subsequent glomerular filtration rate for these patients was estimated with an equation from the Four Variable Modification of Diet in Renal Disease Study,²⁵ with the baseline rate being defined by the mean estimated rate of all measurements during the first year. Diabetes mellitus was identified from hospital discharge records and physicians' claims,²⁶ and other chronic medical conditions were identified with validated algorithms.^{27 28} Proteinuria was defined as more than trace on a urine dipstick or if the urine protein:creatinine ratio was >23 mg/mmol (>200 mg/g).¹⁸

The cohort included 290 613 individuals, of whom 55 453 had chronic kidney disease and 30 277 had diabetes. All participants were followed to ascertain the incidence of death, end stage renal disease, and renal replacement therapy until 31 December 2007. Annual rates of these outcomes (stratified by age, presence of diabetes and presence of proteinuria) were estimated for up to five years after the index measurement of glomerular filtration rate, with censoring at end stage renal disease, death, or 31 December 2007 (table 2 and table 3).

Mortality

For people without chronic kidney disease, age dependent population mortality rates were estimated from observed rates for Canadians.²⁹ For people with chronic kidney disease, mortality rates were based on the annual rate observed within the Alberta Kidney

Disease Network cohort after the initial assessment of estimated glomerular filtration rate. We accounted for age related increases in mortality in those with chronic kidney disease based on the observed mortality rates for patients in different age groups in the network (table 2 and table 3).

Adherence with screening and incidental case finding

We assumed that 50% of people would agree to screening, which requires venipuncture.³⁰ As estimation of glomerular filtration rate can also occur during routine care, irrespective of screening, we assumed that a proportion of unscreened people would undergo such assessment each year. Using data from the network (to determine the number of people undergoing their first creatinine measurements each year) and the 2006 Canadian census (to define the total Alberta population³¹), we estimated the annual likelihood of undergoing incidental screening for chronic kidney disease in this previously unscreened population.

Diagnostic investigation for people in whom screening identified chronic kidney disease

We assumed that all people with newly diagnosed chronic kidney disease would undergo evaluation by a nephrologist, including a standard laboratory investigation (table 4). This assumption was tested in a sensitivity analysis, in which we assumed that only 20% of patients were assessed by a nephrologist with the remainder managed by a primary care physician. Consistent with previous surveys of physicians,^{12 32} we also assumed that a kidney biopsy would be done in 5% and 20% of people with incident chronic kidney disease with and without diabetes.

Effectiveness of angiotensin blockade for people with chronic kidney disease

The benefit of screening for chronic kidney disease is assumed to be the detection of previously undiagnosed

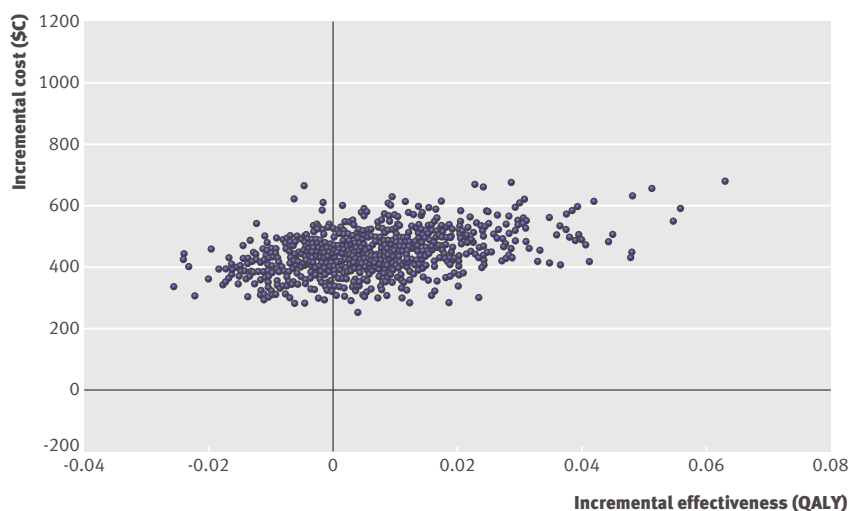


Fig 2 Incremental cost effectiveness of population based screening for chronic kidney disease compared with no screening overall

Table 3 Annual probabilities of events in people with end stage renal disease

Variables	Probability
Annual mortality on dialysis (95% CI)	
Age <65	0.077 (0.072 to 0.083) ⁴³
Age ≥65	0.212 (0.202 to 0.223) ⁴³
Annual mortality for patients with functioning transplant*	
Age <65:	
Year 1	0.012
Year 2	0.007
Year 3	0.001
Year 4	0.007
Year 5	0.003
Age ≥65:	
Year 1	0.071
Year 2	0.051
Year 3	0.054
Year 4	0.043
Year 5	0.030
Initial probability of treatment being dialysis (rather than transplant) after developing end stage renal disease*	
Age <65	0.854
Age ≥65	0.989
Subsequent annual probability of transplant for dialysis patients*	
Age <65	0.108
Age ≥65	0.008
Annual probability of transplant failure requiring return to dialysis (95% CI)	
All	0.04 (0 to 0.1) ⁶²

*From Alberta Kidney Disease Network cohort.

disease, enabling appropriate assessment and management. While detection of previously undiagnosed disease or undiagnosed severe glomerulonephritis requiring immunosuppression is possible, nearly all people detected by screening would have stage 3 chronic kidney disease unrelated to glomerulonephritis¹⁰; as such, management would focus on control of blood pressure through the use of angiotensin blockade, particularly in people with proteinuria.³³⁻³⁵ While it is possible that people with chronic kidney disease identified by screening would already be receiving angiotensin blockade, given that the target population consisted of people in whom glomerular filtration rate had not previously been measured, we assumed that this would not be the case.

We assumed that people found to have chronic kidney disease would receive an ACE (angiotensin converting enzyme) inhibitor or angiotensin blocker (if tolerated), with a target blood pressure of <130/80 mm Hg. We based the effectiveness of angiotensin blockade by conducting a focused literature search that identified relevant high quality meta-analyses and randomised trials in people with chronic kidney disease.³³⁻³⁵⁻⁴² As the effectiveness of angiotensin blockade at reducing end stage renal disease and death varies by diabetes and proteinuria status, we estimated the relative risk for these outcomes separately in these four subgroups (table 4).

Table 4 | Additional clinical information required for base case analysis. Data shown with 95% confidence intervals when available

Variables	Mean base case estimate overall (95% CI)	Base case estimate in people with CKD	
		Without diabetes	With diabetes
Proportion of general population aged <65	0.629 ³¹	—	—
Proportion of general population with diabetes:			
Age <65	0.044 ⁶¹	—	—
Age ≥65	0.183 ⁶¹	—	—
Incidence of CKD in general population:			
Age <65		0.035 ¹⁰	0.075 ¹⁰
Age ≥65		0.186 ¹⁰	0.277 ¹⁰
Proportion of patients identified as having CKD in whom kidney biopsy is undertaken	—	0.20 ³²	0.051
Adherent with screening	0.50 (0.25 to 0.75) ³⁰	—	—
Utility (range 0–1):			
People with CKD	0.85 (0.55 to 0.9) ⁶³	—	—
Age <65 on dialysis	0.639 (0.45 to 0.7) ^{47 64}	—	—
Age ≥65 on dialysis	0.572 (0.55 to 0.8)	—	—
Patients with functioning transplant	0.816 (0.65 to 0.9) ^{45 64}	—	—
Relative risks associated with angiotensin blockade in patients with CKD:			
ESRD in people with proteinuria	—	0.59 (0.37 to 0.94)* ³⁹	0.64 (0.4 to 1.03) ³⁵
ESRD in people without proteinuria	—	1.01 (0.44 to 2.32) ³⁹	1.00 (0.67 to 2.30) ^{35 37 65}
Death in people with proteinuria	—	1.00 (0.55 to 2.93)* ³⁸	0.79 (0.63 to 0.99) ³⁵
Death in people without proteinuria	—	1.00 (0.36 to 2.17) ³⁸	0.84 (0.75 to 0.95)† ^{37 65}
Annual discount rate:			
Costs	0.05 (0 to 0.06) ¹⁹	—	—
Utilities	0.05 (0 to 0.06) ¹⁹	—	—

CKD=chronic kidney disease; ESRD=end stage renal disease.

*While Jafar et al.³⁹ and Giatras et al.³⁸ both present data from Angiotensin Converting Enzyme Inhibition and Progressive Renal Disease Study Group, who analysed patient level data from 10 and 11 randomised trials, respectively, comparing ACE inhibitors in patients without diabetes with CKD, data from Jafar et al is used for ESRD as it reports data stratified by proteinuria, while data from Giatras et al is used for mortality as they conducted analyses with and without including study of Maschio et al.,⁶⁶ a small randomised controlled trial reporting relative risk of mortality of 7.55 (95% CI 0.95 to 60.0) associated with use of ACE inhibitor, which was thought implausible. Data from Giatras et al excluding this trial showed no significant difference in relative risk of mortality associated with use of ACE inhibitors.

†While Strippoli et al.³⁵ presented relative risk of ESRD in patients with diabetes and CKD, most patients had nephropathy and baseline proteinuria. As such, relative risk of ESRD and mortality for patients with diabetes and proteinuria was estimated from Strippoli et al.,³⁵ while relative risk of ESRD and mortality for patients with diabetes without proteinuria was estimated from microHOPE study,³⁷ which excluded patients with overt nephropathy.

Costs related to screening

For people without chronic kidney disease, screening included a visit to a primary care physician and measurement of glomerular filtration rate, at a cost of about \$C48 (table 5). In patients found to have chronic kidney disease, the cost of screening was about \$C83, accounting for an additional follow-up visit to a physician.

Costs related to managing chronic kidney disease with and without dialysis

The cost of managing people with chronic kidney disease was assumed to be the incremental costs resulting from a new diagnosis, including those of nephrologist care, the requirement for angiotensin blockade, and laboratory monitoring (table 5). As admission to hospital in patients with stage 3–5 non-dialysis chronic kidney disease is usually because of comorbidity and because randomised trials of management of chronic kidney disease have not shown that interventions prevent admissions, we did not include the cost of admissions in our analysis. The annual cost of dialysis was estimated at \$C64 218, assuming that nearly 81% of

people were treated in haemodialysis centres.^{43 44} The cost of transplantation was estimated at \$C84 531 for year one and \$C35 545 for subsequent years.⁴⁵

Valuing health benefits

Health benefits were measured in cases of end stage renal disease prevented and QALYs gained. We did not assume any difference in utility estimates for “diagnosed” and “undiagnosed” chronic kidney disease, as studies of antihypertensive therapy (the only additional treatment in people with diagnosed chronic kidney disease) suggest no significant impact on quality of life.⁴⁶ We estimated utilities for relevant health states (dialysis and transplantation) based on contemporary Canadian studies.^{45 47}

Sensitivity and scenario analyses

Sensitivity and scenario analyses were performed to determine the impact of uncertainty on the results of the model by varying all key parameters through plausible ranges. We conducted an additional scenario analysis examining the cost effectiveness of screening in

Table 5 | Average cost of care associated with managing patients with newly diagnosed chronic kidney disease (CKD) Figures are \$C, 2009

Costs with source	Cost estimate by CKD stage* (GFR)		
	Stage 3 (30-60 ml/min)	Stage 4 (15-30 ml/min)	Stage 5 (<15 ml/min)
Cost of screening (Alberta Schedule of Medical Benefits):			
People found to have CKD		83	
People without CKD		48	
Specialist visits for people found to have CKD (Alberta Schedule of Medical Benefits)†:			
Year 1	226	226	302
Years 2 and on	189	189	302
Testing for people with CKD:			
Urine studies ^{44,‡} :			
Year 1	130	130	130
Years 2 and on	109	109	109
Haematology and serology ^{44,§} :			
Year 1	129	180	326
Years 2 and on	108	158	304
Radiological studies (year 1) ⁴⁴ :			
Renal ultrasonography ⁴⁴		325	
Biopsy/pathology (year 1):			
Renal biopsy (when indicated) ^{44,¶}		538	
Medications for people with known CKD (all years):			
ACE inhibitor ^{67,**}	378	378	378
Additional anti-hypertensives ^{67,††}	857	857	857
Mean cost of erythropoietin stimulating agent (ESA) for people with known CKD receiving ESA ^{68,‡‡}		2668/patient	
Multidisciplinary CKD clinics ^{69,70,§§}		1590/patient	

CKD=chronic kidney disease; GFR=glomerular filtration rate.

*Total annual cost of managing patients with CKD (GFR <60 ml/min) based on proportion of patients with CKD stages 3, 4, and 5 (see table 1) and relative cost of managing patients with stages 3, 4, and 5.

†Assumes that patients with stages 3 and 4 CKD are seen annually, while patients with non-dialysis stage 5 CKD are seen every four months.

‡Assumes that urine protein:creatinine ratio is monitored every 3 months, with urine protein electrophoresis conducted once in year 1 only.

§Assumes that complete blood count, electrolytes, serum phosphate, calcium, and albumin are measured every 3, 2, and 1 months for patients with stages 3, 4, and 5 CKD, respectively, with serum protein electrophoresis being conducted once in year 1 only.

¶Only 20%, and 5% of people without and with diabetes require biopsy.^{12,32}

**Assumes that 75%⁶⁹ of people are treated with ACE inhibitor (generic ramipril \$0.63/day), and 25% with angiotensin blockers (irbesartan \$1.21/day) plus appropriate pharmacist prescribing fees.

††On average, people also receive calcium channel blocker and diuretic (Barrett et al, personal communication) at combined cost of \$2.04/day, plus appropriate pharmacist prescribing fees.

‡‡Assumes 2.6%, 11.6%, and 39.4% of people with stage 3, 4, and non-dialysis stage 5 CKD are taking ESA,⁶⁸ and based on average dose of 3351 units/week⁶⁸ (\$15.31/1000 units).

§§Assumes that 2.7% of all people with GFR <60 ml/min/1.73 m² are managed in multidisciplinary CKD clinic.⁶⁹

people without diabetes but with known hypertension, reflecting an increased prevalence of chronic kidney disease in people with hypertension,¹⁰ as well as a doubling of the risk of progression to end stage renal disease among people with hypertension.⁴⁸ As the cost of managing people with chronic kidney disease varies based on practice patterns, we also assessed the impact of using alternative cost estimates on results.

To address limitations in classic univariate sensitivity analysis, we performed Monte Carlo simulation, which allows for the simultaneous sensitivity analysis of all variables over their plausible range.^{49,50} It does so by replacing estimates of probabilities, utilities, and costs with specific probability distributions, which are based on the reported means and variances for each variable. Statistical distributions were created around all of the variables for which there was substantial uncertainty of measurement, including use of a β distribution for proportions (that is, the risk of end stage renal disease and

mortality), use of a normal distribution for normally distributed variables (that is, certain costs, relative risks, and utility measures), and log normal distribution for skewed variables (that is, certain costs).

RESULTS

Baseline analyses

Compared with no screening, population based screening for chronic kidney disease was associated with an incremental cost of \$C463 and a gain of 0.0044 QALYs per patient overall, representing a cost per QALY gained of \$C104 900 (table 6). In a cohort of 100 000 people, screening would be expected to reduce the number of people developing end stage renal disease over their lifetime from 675 to 657 (fig 1). In subgroups of people aged <65 and ≥ 65 , the cost per QALY gained associated with screening was \$C 200 100 and \$C93 700, respectively (table 6).

Table 6 | Cost effectiveness of population based screening for chronic kidney disease and for targeted screening of high risk groups based on age, diabetes, and hypertension

Outcome	Incremental cost (\$C)	Incremental QALYs	Cost (\$C) per QALY
Overall	463	0.0044	104 900
Age <65	148	0.0007	200 100
Age ≥65	997	0.0106	93 700
With diabetes	578	0.0256	22 600
Without diabetes	440	0.0008	572 000
Without diabetes and hypertension	350	0.0003	1 411 100
Without diabetes with hypertension	470	0.0014	334 000

In subgroups of people with and without diabetes, the cost per QALY gained was \$22 600 and \$572 000, respectively. In a cohort of 100 000 people with diabetes, screening would be expected to reduce the number of people developing end stage renal disease over their lifetime from 1796 to 1741 (fig 1). In people without diabetes with and without hypertension, the cost per QALY gained was \$C334 000 and \$C1 411 100, respectively (table 6).

Sensitivity analyses

Tables 7, 8, and 9 show the results of sensitivity analyses conducted for the model overall, while tables 10 and 11 show the results of sensitivity analyses on the effectiveness of angiotensin blockade in patients with and without diabetes, respectively. Sensitivity analyses showed that screening restricted to people with diabetes was generally associated with a cost per QALY gained of <\$25 000, which was robust to changes in all plausible variables (tables 7-10). Screening in people without diabetes, however, was associated with a cost per QALY of around \$50 000 only under scenarios

where identification of chronic kidney disease would result in use of treatments that could improve survival by at least 15%, and when the risk of progression to end stage renal disease in the absence of treatment was substantially higher than in the base case (table 11).

Probabilistic sensitivity analysis

Figures 2 and 3 show scatterplots of the incremental cost effectiveness of population based screening compared with no screening overall, highlighting uncertainty in the analysis, which is largely attributed to uncertainty regarding the impact of angiotensin blockade on mortality in people without diabetes and with chronic kidney disease. Given the current evidence of benefit for angiotensin blockade on both mortality and end stage renal disease in people with diabetes and chronic kidney disease, screening of people with diabetes led to better clinical outcomes in all simulations. Our analysis indicates a 37% probability that targeted screening for chronic kidney disease among people with diabetes is associated with a cost per QALY gained of <\$20 000 and a 99% probability that the cost per QALY gained is <\$50 000.

DISCUSSION

Population based screening for chronic kidney disease is unlikely to be cost effective in unselected people or in those without diabetes. Although the prevalence of chronic kidney disease might be high enough to make screening worthy of consideration, particularly among older people,¹⁰ most people who would be found to have chronic kidney disease under a population based screening strategy would not have diabetes and would be likely to have non-proteinuric chronic kidney disease, relatively slow loss of kidney function, and low potential to benefit from angiotensin blockade.³⁹ Therefore, the overall benefit of detecting and treating asymptomatic chronic kidney disease among people without diabetes is low. On the other hand, in people with diabetes, rates of progression to end stage renal disease are much higher, and there is strong evidence that angiotensin blockade reduces such progression^{33 36 42} and improves survival.⁵¹ Given this, our study found that screening for chronic kidney disease in people with diabetes is associated with a cost per QALY in a range that is generally considered acceptable.⁵²⁻⁵⁴

Strengths and limitations

We modelled progression of chronic kidney disease and mortality stratified by age, diabetes, and presence or absence of proteinuria using a large cohort of patients with chronic kidney disease followed over five years and estimated the benefit of screening from high quality meta-analyses of angiotensin blockade. Given that previous analyses examining the cost effectiveness of screening have used urine based screening methods,^{12 13} and as this might miss a considerable proportion of people with chronic kidney disease,¹⁰ we used estimated glomerular filtration rate to screen for

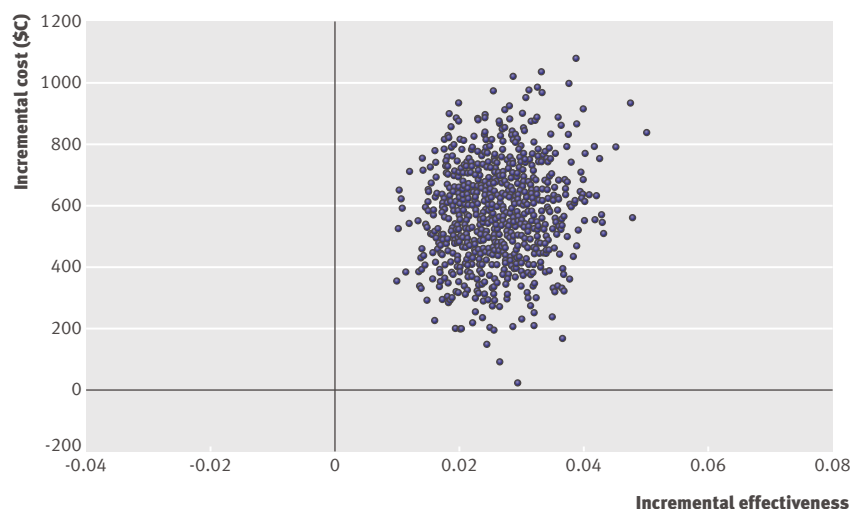


Fig 3 | Incremental cost effectiveness scatterplot of population based screening for chronic kidney disease compared with no screening in people with diabetes

Table 7 | Sensitivity analysis of cost per QALY of screening for chronic kidney disease with varied rates of screening, use of angiotensin blockade, and adherence

Outcome	Incremental cost (\$C)	Incremental QALYs	Cost (\$C) per QALY
Baseline			
Overall	463	0.0044	104 900
People with diabetes	578	0.0256	22 600
People without diabetes	440	0.0008	572 000
Screening adherence rate increased to 100% (baseline 50%)			
Overall	926	0.0088	104 900
People with diabetes	1153	0.0511	22 600
People without diabetes	880	0.0015	572 000
Adherence with angiotensin blockade increased to 100% (baseline 75%)			
Overall	458	0.0059	77 800
People with diabetes	599	0.0341	16 400
People without diabetes	434	0.0010	423 100
20% of patients already receiving angiotensin blockade (baseline 0%)			
Overall	487	0.0035	141 100
People with diabetes	621	0.020	31 100
People without diabetes	464	0.0006	761 100

the presence of chronic kidney disease. One limitation of our analysis is that we did not compare our results to a strategy of screening with urinalysis or a combined strategy of glomerular filtration rate and urinalysis, though all patients detected as having chronic kidney disease were assumed to undergo urinalysis. Proteinuria is a powerful predictor of an increased risk of end stage renal disease and death in people with chronic kidney disease.⁵⁵ While screening with estimated glomerular filtration rate might identify more people than screening with urinalysis, most people identified are at lower risk of adverse outcomes and do not seem to gain additional benefit from angiotensin blockade.³⁹

Our analysis was limited by the validity and availability of randomised trials (and meta-analyses) reporting the effectiveness of managing patients with chronic kidney disease. In general though, our analyses were guided by estimates of effectiveness from high quality meta-analyses. Screening in people without diabetes was unattractive given that angiotensin blockade does not seem to reduce mortality in people with non-diabetic renal disease.^{38,39} When we assumed that angiotensin blockade reduced mortality by 16% among people without diabetes (consistent with results of a large trial in which most participants did not have chronic kidney disease³⁷), the cost per QALY for screening people without diabetes became more attractive (\$40 800), though it is unclear whether this is a reasonable assumption. It could also be argued that people who are identified as having chronic kidney disease would be more likely to receive statins, which have been proved to improve survival in people with mild to moderate chronic kidney disease.⁵⁶⁻⁵⁹ In our analysis, however, we assumed that people at risk of cardiovascular events would already be receiving statins or aspirin (even without screening for chronic kidney disease). We therefore modelled only the

impact of adding angiotensin blockade. In scenarios where we modelled the impact of treating identified patients with statins as well (resulting in a reduction in mortality of 16%⁵⁸ at an additional cost of \$620 a year), then the cost per QALY for screening in people without diabetes was \$53 700.

We assumed that the incidence of end stage renal disease and death, which was determined in a cohort of people with known chronic kidney disease, would be similar to a cohort of previously unidentified patients with chronic kidney disease who were detected through screening. Although this assumption might overestimate, or underestimate, the true risks, our results were robust to plausible changes in these variables. We also assumed that people with chronic kidney disease identified by screening would not be receiving angiotensin blockade, which seems reasonable given that they had not previously had their glomerular filtration rate measured. Of note, the results did not vary significantly when up to 20% of patients screened were already receiving angiotensin blockade. Finally, our results are most relevant to the Canadian setting. Given that our prevalence estimates are based

Table 8 | Sensitivity analysis of cost per QALY for screening for chronic kidney disease (CKD) with varied incidence of disease and rates of progression to end stage renal disease (ESRD) in untreated patients

Outcome	Incremental cost (\$C)	Incremental QALYs	Cost (\$C) per QALY
Baseline			
Overall	463	0.0044	104 900
People with diabetes	578	0.0256	22 600
People without diabetes	440	0.0008	572 000
Incidence of CKD increased by 50% (baseline see table 4)			
Overall	682	0.0066	103 000
People with diabetes	853	0.0384	22 200
People without diabetes	646	0.0012	547 400
Incidence of CKD decreased by 50% (baseline see table 4)			
Overall	244	0.0022	110 300
People with diabetes	300	0.0128	23 500
People without diabetes	232	0.0004	603 300
Reduce risk of progression to ESRD by 50% (baseline see table 2)			
Overall	521	0.0041	126 400
People with diabetes	682	0.0259	26 300
People without diabetes	495	0.0004	1 172 900
Reduce risk of progression to ESRD by 25% (baseline see table 2)			
Overall	490	0.0043	114 500
People with diabetes	623	0.0257	24 183
People without diabetes	465	0.0006	771 100
Increase risk of progression to ESRD by 50% (baseline see table 2)			
Overall	420	0.0046	90 400
People with diabetes	513	0.0252	20 351
People without diabetes	398	0.0011	376 500
Increase risk of progression to ESRD by 100% (baseline see table 2)			
Overall	387	0.0048	80 200
People with diabetes	474	0.0249	19 100
People without diabetes	367	0.0013	282 200

Table 9 | Sensitivity analysis of cost per QALY for screening for chronic kidney disease (CKD), exploring impact of variations in costs and quality of life

Outcome	Incremental cost (\$C)	Incremental QALYs	Cost (\$C) per QALY
Baseline			
Overall	463	0.0044	104 900
People with diabetes	578	0.0256	22 600
People without diabetes	440	0.0008	572 000
Costs for screening, CKD management, dialysis, and transplantation increased 50%			
Overall	695	0.0044	157 000
People with diabetes	865	0.0256	33 800
People without diabetes	660	0.0008	857 900
Costs for screening, CKD management, dialysis, and transplantation decreased 50%			
Overall	232	0.0044	52 400
People with diabetes	295	0.0256	11 500
People without diabetes	220	0.0008	286 000
Assuming newly diagnosed patients will have no additional cost for antihypertensive medications			
Overall	177	0.0044	40 100
People with diabetes	175	0.0256	6900
People without diabetes	169	0.0008	219 800
Physician costs for screening (both GP visits) reduced to 0 (baseline \$C35.26)*			
Overall	445	0.0044	100 800
People with diabetes	558	0.0256	21 800
People without diabetes	422	0.0008	548 500
Only 20% of people with stage 3 disease referred to specialist (remaining 80% managed by GP)			
Overall	416	0.0044	94 247
People with diabetes	514	0.0256	20 116
People without diabetes	395	0.0008	513 478
Annual cost of medication, physicians fees, and laboratory costs associated with managing patients with diagnosis increased by 50%			
Overall	745	0.0044	168 700
People with diabetes	975	0.0256	38 100
People without diabetes	706	0.0008	918 300
Annual cost of dialysis increased by 50% (baseline \$C64 218)			
Overall	420	0.0044	95 100
People with diabetes	501	0.0256	19 600
People without diabetes	399	0.0008	519 000
Annual cost of dialysis decreased by 50% (baseline \$C64 218)			
Overall	444	0.0044	100 500
People with diabetes	531	0.0256	20 800
People without diabetes	422	0.0008	548 600
High estimate utility value (0.90) associated with living with CKD (baseline 0.85)			
Overall	463	0.0048	97 100
Diabetes	577	0.0273	21 200
Non-diabetes	440	0.0009	488 700
Low estimate utility value (0.75) associated with living with CKD (baseline 0.85)			
Overall	463	0.0037	124 700
Diabetes	577	0.0222	26 000
Non-diabetes	440	0.00051	867 400
Discount rates decreased to 0%⁷¹ (baseline 5%)			
Overall	622	0.0087	71 800
People with diabetes	796	0.0536	14 800
People without diabetes	588	0.0011	520 200
Discount rates decreased to 3%⁷¹ (baseline 5%)			
Overall	515	0.0057	91 084
People with diabetes	645	0.0335	19 250
People without diabetes	489	0.0009	540 733

ESRD=end stage renal disease.

*Assumes that CKD screening would be done during annual visit and costs of screening would include only cost of laboratory tests.

on a large North American cohort study,¹⁰ our estimates of efficacy based on randomised trials conducted throughout the world, and that Canada has publicly funded healthcare and relative costs that are likely similar to Europe, we think that our results are likely to be valid in other countries.

Comparison with other studies

Previous studies have examined only the cost effectiveness of screening with urinalysis or urine based quantitative proteinuria.^{12 13 60} Like our study, these studies found that targeted screening of high risk groups (but not population based screening) might be cost effective.^{12 13} An analysis by Boulware et al suggested that screening for chronic kidney disease with measurement of proteinuria in patients with hypertension was associated with a cost per QALY of less than US \$ 20 000.¹² These analyses, however, assumed that angiotensin blockade would improve survival in people without diabetes,¹² an assumption not supported by available data in patients with chronic kidney disease.^{38 39} A study examining the cost effectiveness of population based screening for urinary albumin excretion, with treatment of those noted to have albumin excretion >15 mg/day with fosinopril to prevent cardiovascular events, based on the PREVENT study cohort, reported a cost per life year gained of €16 700.⁶⁰

Population based screening for chronic kidney disease has been advocated by some,^{4 15 16} and the National Kidney Foundation/Kidney Dialysis Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease have recommended screening for people at high risk of kidney disease, including those with diabetes and hypertension and aged over 60.¹¹⁴ Given that considerable resources would be required to set up a population based screening programme, our results are important. Our analyses suggest that screening for chronic kidney disease with estimated glomerular filtration rate is not cost effective in older people or in those without diabetes with hypertension but for people with diabetes is associated with a cost per QALY gained in the range of other funded interventions. We could not determine whether screening with urinalysis might be more cost effective overall or in certain subgroups compared with estimated glomerular filtration rate.

Conclusions

Our results suggest that population based screening for chronic kidney disease with assessment of estimated glomerular filtration rate is not cost effective overall or in subgroups of people without diabetes but with hypertension or in elderly people. Targeted chronic kidney disease screening with estimated glomerular filtration rate in people with diabetes is associated with a cost per QALY that is similar to other publicly funded interventions.

Table 10 | Sensitivity analysis of effectiveness of angiotensin blockade for management of CKD in people with diabetes

Outcome	Incremental cost (\$C)	Incremental QALYs	Cost (\$C) per QALY
Baseline	578	0.0256	22 600
Scenario analyses on relative risk (RR) of mortality associated with angiotensin blockade			
RR mortality with and without proteinuria improved to 0.75 (baseline 0.79 for patients with proteinuria and 0.84 without proteinuria)	633	0.0378	16 700
Best case scenario: RR mortality with angiotensin blockade improved to 0.75 (as above) and 1.5-fold increased risk of progression to ESRD for untreated patients	579	0.0371	15 600
Worst case scenario: RR mortality with and without proteinuria increased to 0.95 (baseline as above)	464	0.0079	58 700
Scenario analyses on relative risk of ESRD associated with angiotensin blockade			
RR of developing ESRD in patients with CKD and diabetes with and without proteinuria from angiotensin blockade improved to 0.5 and 0.72, respectively (baseline 0.64 for patients with proteinuria and 1.0 without proteinuria)	301	0.0274	11 000
RR of developing ESRD in patients with CKD and diabetes with and without proteinuria from angiotensin blockade increase to 0.9 and 1.0, respectively (baseline as above)	839	0.0204	35 000

CKD=chronic kidney disease; ESRD=end stage renal disease.

Table 11 | Sensitivity analysis of effectiveness of angiotensin blockade for management of CKD in people without diabetes

Outcome	Incremental cost (\$C)	Incremental QALYs	Cost (\$C) per QALY
Baseline	440	0.0008	572 000
Scenario analyses on relative risk (RR) of mortality associated with angiotensin blockade			
RR mortality in people with and without proteinuria improved to 0.84 ³⁷ (baseline 1.0)	480	0.0118	40 800
RR mortality in people with and without proteinuria increased to 2.17 (table 4) (baseline 1.0)	250	-0.052	Dominated
Addition of statin to all patients found to have CKD: assumes all people without diabetes found to have CKD also receive statin and that this improves survival by 16%, ⁵⁸ incorporated additional costs of statin	633	0.0118	53 700
Scenario analyses on relative risk of ESRD associated with angiotensin blockade			
RR of developing ESRD associated with angiotensin blockade improves to 0.52 and 1.0 for patients with and without proteinuria, respectively (baseline 0.59 for patients with proteinuria and 1.01 without proteinuria)	417	0.0009	448 900
RR of developing ESRD associated with angiotensin blockade is less attractive at 0.9 and 1.2 for patients with and without proteinuria, respectively (baseline as above)	549	-0.0002	Dominated

CKD=chronic kidney disease; ESRD=end stage renal disease.

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Ethical approval: This study was approved by the Calgary Health Region ethics board.

Data sharing: No additional data available.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Chronic kidney disease is common, and in many patients is asymptomatic and remains undiagnosed

Previous analyses have examined the cost effectiveness of screening with urinalysis rather than estimated glomerular filtration rate, the standard method for diagnosing chronic kidney disease

WHAT THIS STUDY ADDS

Population based screening for chronic kidney disease with estimated glomerular filtration rate assessment is not cost effective overall

Targeted screening of people with diabetes is associated with an acceptable cost per QALY in publicly funded healthcare systems.

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