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. 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).

Several studies have examined the effectiveness of screening for chronic kidney disease with estimated glomerular filtration rate or urinalysis. 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, whereas population based screening would detect one for every 16-21 people screened. Existing cost effectiveness studies have examined screening only with urinalysis. 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.

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, others have suggested a population based approach. 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. While most programmes entailed...
**Baseline characteristics of patient cohort from Alberta Kidney Disease Network.**

| Characteristics                | 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 265                      | 90 090 (31)        | 15 139 (50)                     | 75 697 (29)                       |
| Women                         | 168 555 (58)       | 14 533 (48)                     | 153 598 (59)                      |
| CKD (estimated GFR in ml/min/1.73 m²): |                     |                                 |                                   |
| 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 (30)               | 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)                           |

**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 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.

**Overview of analysis**

- The prevalence of undiagnosed chronic kidney disease in different subgroups of patients stratified by age (65 or 265) and diabetes was determined from a North American population based survey.
- The natural course of chronic kidney disease was then determined within the Alberta Kidney Disease Network, 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).

**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. In the survey, conducted by the National Center for Health Statistics in the United States, data (including estimated
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 | 0.0215 | 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 | 0.0423 |
| 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 45-50† | 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.†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,24 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 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 disease, enabling appropriate assessment and management. While detection of previously undiagnosed 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 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)33 |
| Age ≥65 | 0.212 (0.202 to 0.223)33 |
| 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)42 |

*From Alberta Kidney Disease Network cohort.
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 $48 (table 5). In patients found to have chronic kidney disease, the cost of screening was about $83, 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 $64,218, assuming that nearly 81% of people were treated in haemodialysis centres. The cost of transplantation was estimated at $84,531 for year one and $35,545 for subsequent years.

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. We estimated utilities for relevant health states (dialysis and transplantation) based on contemporary Canadian studies.

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 people with diabetes and proteinuria being estimated from microHOPE study, which excluded patients with overt nephropathy.

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 |
|-----------|----------------------------------------|--------------------------------------|
| Proportion of general population aged ≥65 | 0.629<sup>31</sup> | — |
| Proportion of general population with diabetes: | | |
| Age <65 | 0.044<sup>61</sup> | — |
| Age ≥65 | 0.183<sup>61</sup> | — |
| Incidence of CKD in general population: | | |
| Age <65 | 0.035<sup>15</sup> | 0.075<sup>10</sup> |
| Age ≥65 | 0.186<sup>10</sup> | 0.277<sup>10</sup> |
| Proportion of patients identified as having CKD in whom kidney biopsy is undertaken | — | 0.20<sup>72</sup> |
| Adherent with screening | 0.50 (0.25 to 0.75)<sup>10</sup> | — |
| Utility (range 0-1): | | |
| People with CKD | 0.85 (0.55 to 0.9)<sup>53</sup> | — |
| Age <65 on dialysis | 0.639 (0.45 to 0.7)<sup>64</sup> | — |
| Age ≥65 on dialysis | 0.572 (0.55 to 0.8) | — |
| Patients with functioning transplant | 0.816 (0.65 to 0.9)<sup>64</sup> | — |
| Relative risks associated with angiotensin blockade in patients with CKD: | | |
| ESRD in people with proteinuria | — | 0.59 (0.37 to 0.94)<sup>39</sup> | 0.64 (0.4 to 1.03)<sup>35</sup> |
| ESRD in people without proteinuria | — | 1.01 (0.44 to 2.32)<sup>39</sup> | 1.00 (0.67 to 2.30)<sup>37</sup> |
| Death in people with proteinuria | — | 1.00 (0.55 to 2.93)<sup>38</sup> | 0.79 (0.63 to 0.99)<sup>35</sup> |
| Death in people without proteinuria | — | 1.00 (0.36 to 2.17)<sup>18</sup> | 0.84 (0.75 to 0.95)<sup>17</sup> |
| Annual discount rate: | | |
| Costs | 0.05 (0 to 0.06)<sup>17</sup> | — |
| Utilities | 0.05 (0 to 0.06)<sup>19</sup> | — |

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

*While Jafar et al<sup>39</sup> and Giatras et al<sup>38</sup> 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<sup>66</sup> 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 different in relative risk of mortality associated with use of ACE inhibitors.

†While Strippoli et al<sup>35</sup> 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 microHOPE study,<sup>37</sup> while relative risk of ESRD and mortality for patients with diabetes without proteinuria was estimated from microHOPE study,<sup>37</sup> which excluded patients with overt nephropathy.
people without diabetes but with known hypertension, reflecting an increased prevalence of chronic kidney disease in people with hypertension, as well as a doubling of the risk of progression to end stage renal disease among people with hypertension. 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. 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 beta 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 $C104900 (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 $C200100 and $C93700, respectively (table 6).

| Table 5 | Average cost of care associated with managing patients with newly diagnosed chronic kidney disease (CKD) Figures are $C, 2009 |
|---|---|
| Costs with source | Cost estimate by CKD stage* (GFR) |
| | Stage 3 | Stage 4 | Stage 5 |
| | (30-60 ml/min) | (15-30 ml/min) | (<15 ml/min) |
| Cost of screening (Alberta Schedule of Medical Benefits): | | | |
| People found to have CKD | 83 | | |
| People without CKD | 48 | | |
| Specialist visits for people found to have CKD (Alberta Schedule of Medical Benefits): | | | |
| Year 1 | 226 | 226 | 302 |
| Years 2 and on | 189 | 189 | 302 |
| Testing for people with CKD: | | | |
| Urine studies**‡‡: | | | |
| Year 1 | 130 | 130 | 130 |
| Years 2 and on | 109 | 109 | 109 |
| Haematology and serology§§: | | | |
| Year 1 | 129 | 180 | 326 |
| Years 2 and on | 108 | 158 | 304 |
| Radiological studies (year 1)$§§: | | | |
| Renal ultrasonography** | 325 | | |
| Biopsy/pathology (year 1); | | | |
| Renal biopsy (when indicated)¶¶ | 538 | | |
| Medications for people with known CKD (all years): | | | |
| ACE inhibitor67** | 378 | 378 | 378 |
| Additional anti-hypertensives67†† | 857 | 857 | 857 |
| Mean cost of erythropoietin stimulating agent (ESA) for people with known CKD receiving ESA68‡‡ | 2668/patient |
| Multidisciplinary CKD clinics6970§§ | 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.1232
**Assumes that 75%69 of people are treated with ACE inhibitor (generic ramipril $0.63/day), and 25% with angiotensin blockers (lisinopril $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, 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
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 $334,000 and $1,411,100, 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 with and without hypertension, the cost per QALY gained was $334,000 and $1,411,100, respectively (table 6).

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

| 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           |

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).
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%)

| Outcome | Incremental cost ($C) | Incremental QALYs | Cost ($C) per QALY |
|---------|-----------------------|-------------------|-------------------|
| 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. 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.

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. 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 disease), 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. 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% at an additional cost of $620 a year), then the cost per QALY for screening in people without diabetes was $33 700.

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            | 37 500            |
| 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 ($) | Incremental QALYs | Cost ($) 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                  | 0.0005           | 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.

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 PREVEND 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,41 51 6 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 60.14 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.
publicly funded healthcare systems. Targeted screening of people with diabetes is associated with an acceptable cost per QALY in rate assessment is not cost effective overall.

**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.

**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 (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%,1,4 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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**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**

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**Data sharing:** No additional data available.

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