Estimating the population-level impacts of improved uptake of SGLT2 inhibitors in patients with chronic kidney disease: a cross-sectional observational study using routinely collected Australian primary care data

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Summary

Background Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce the risk of kidney failure and death in patients with chronic kidney disease (CKD) but are underused. We evaluated the number of patients with CKD in Australia that would be eligible for treatment and estimated the number of cardiorenal and kidney failure events that could be averted with improved uptake of SGLT2 inhibitors.

Methods This cross-sectional observational study leveraged nationally representative primary care data from 392 Australian general practices (MedicineInsight) between 1 January 2020 and 31 December 2021. We identified patients that would have met inclusion criteria of key SGLT2 inhibitor trials and applied these data to age and sex-stratified estimates of CKD prevalence for the Australian population (using national census data), estimating the number of preventable events using trial event rates. Key outcomes included cardiorenal events (CKD progression, kidney failure, or death due to cardiovascular or kidney disease) and kidney failure.

Findings In MedicineInsight, 44.2% of adults with CKD would have met CKD eligibility criteria for an SGLT2 inhibitor; baseline use was 4.1%. Applying these data to the Australian population, 230,246 patients with CKD would have been eligible for treatment with an SGLT2 inhibitor. Optimal implementation of SGLT2 inhibitors (75% uptake) could reduce cardiorenal and kidney failure events annually in Australia by 3644 (95% CI 3526–3764) and 1312 (95% CI 1242–1385), respectively.

Interpretation Improved uptake of SGLT2 inhibitors for patients with CKD in Australia has the potential to prevent large numbers of patients experiencing CKD progression or dying due to cardiovascular or kidney disease. Identifying strategies to increase the uptake of SGLT2 inhibitors is critical to realising the population-level benefits of this drug class.

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Research in context

Evidence before this study

Large-scale, placebo-controlled, randomised trials of sodium glucose cotransporter-2 (SGLT2) inhibitors have demonstrated that this drug class substantially reduces the risk of kidney failure and cardiovascular events in people with chronic kidney disease (CKD), regardless of diabetes status. As a result, almost all major clinical practice guidelines recommend that SGLT2 inhibitors are routinely offered to patients with CKD. The inclusion of SGLT2 inhibitors on the World Health Organization's List of Essential Medicines further underscores their efficacy, cost-effectiveness, and safety.

Despite this, uptake of SGLT2 inhibitors remains low across many healthcare settings. In the United Kingdom and North America, approximately 10% of people with diabetes and CKD receive an SGLT2 inhibitor, with even fewer patients with non-diabetic kidney disease being treated. The slow uptake of SGLT2 inhibitors may reflect multiple factors such as knowledge gaps amongst prescribers, therapeutic inertia, concerns about potential adverse effects, and cost. Nevertheless, the limited use of SGLT2 inhibitors in primary care highlights a major opportunity to improve population health. There is currently no reliable data on the uptake of SGLT2 inhibitors in people with CKD in Australia or the Western Pacific.

Added value of this study

In this cross-sectional observational study using nationally representative primary care data from 392 general practices in Australia during 2020–2021, we found that use of SGLT2 inhibitors in people with CKD was low. Overall, 44.2% of people with CKD were eligible for treatment with an SGLT2 inhibitor, based on major kidney outcome trials, but only 4.1% were receiving one. In people with diabetes and CKD, 14.4% of people were receiving an SGLT2 inhibitor. Applying conservative estimates of CKD prevalence from this cohort to national census data, we estimated that 230,246 people with CKD would have been eligible for treatment with an SGLT2 inhibitor. Based on trial event rates, 75% uptake of SGLT2 inhibitors in eligible people with CKD could reduce cardiorenal and kidney failure events annually in Australia by 3644 (95% CI 3526–3764) and 1312 (95% CI 1242–1385), respectively.

Implications of all the available evidence

Improved uptake of SGLT2 inhibitors could substantially reduce the burden of kidney failure and cardiovascular disease in patients with CKD in Australia. Identifying and understanding barriers to improved uptake, as well as developing and evaluating strategies for implementation, are needed to realise the population benefits of SGLT2 inhibitors for people with CKD in Australia.

Introduction

Sodium glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of chronic kidney disease (CKD) progression by approximately 40%, regardless of diabetes or primary kidney diagnosis.[1] Consequently, this drug class is now considered foundational therapy for CKD alongside renin-angiotensin system (RAS) blockade in major clinical practice guidelines.[1–4]

Despite clear evidence from multiple large, randomised trials that SGLT2 inhibitors reduce the risk of kidney failure or death in people with CKD, the uptake of these agents in routine practice remains low. In the United Kingdom and United States, only about 10% of patients with diabetes and CKD are prescribed an SGLT2 inhibitor; paradoxically, those at higher risk of kidney failure are less likely to receive one.[5] An almost identical phenomenon is observed for adjacent disease states, such as type 2 diabetes with atherosclerotic cardiovascular disease and heart failure (regardless of diabetes), whereby uptake of SGLT2 inhibitors has been limited and those at highest risk are less likely to receive one.[6] The explanation for the underuse of SGLT2 inhibitors in routine practice is complex and not fully understood but highlights a major opportunity to improve population health if the uptake of SGLT2 inhibitors is improved.

Understanding the potential population-level benefits of SGLT2 inhibitors in patients with CKD might encourage policymakers, health systems and clinicians to improve access and increase the use of SGLT2 inhibitors. Therefore, using routinely collected primary care data in Australia, we sought to evaluate the number of patients with CKD who would be eligible for treatment with an SGLT2 inhibitor, based on inclusion and exclusion criteria of SGLT2 inhibitor kidney outcome trials, and estimate the annual number of cardiorenal events and patients progressing to kidney failure that could be averted at the population-level with improved uptake of SGLT2 inhibitors in patients with CKD.

Methods

This study abides by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational studies.[7]

Data sources

We used routinely collected data from MedicineInsight, a nationally-representative primary care data source. MedicineInsight includes de-identified patient information, clinical data and comorbidities, prescription medications and laboratory test results (including estimated glomerular filtration rate [eGFR] and urine albumin:creatinine ratio [UACR]) on patients visiting primary care practices participating in MedicineInsight from all states and territories in Australia. Demographic characteristics of patients attending MedicineInsight participating general practices are largely representative of the broader Australian population in terms of age, gender and socioeconomic status.[8,9] Detailed information about MedicineInsight has been previously published.[10] This study was approved by the MedicineInsight Data Governance Committee (2020-004) and Research Ethics Review Committee of the Sydney Local Health District, NSW, Australia (X21-0428, 2020/ETH00963).

Population

Among a cohort of all adults (age ≥18 years) with ≥1 clinical encounter and ≥1 eGFR measurement (with or without a UACR measurement) at 392 general practices between 1 January 2020 and 31 December 2021 (n = 1,217,398), we identified patients with eGFR <60 mL/min/1.73 m^2 and/or UACR >3.4 mg/mmol. These patients were categorised into three groups based on the eGFR and UACR eligibility criteria of three SGLT2 inhibitor kidney outcome trials: CREDENCE, DAPA-CKD and EMPA-KIDNEY.[11–13]

For each SGLT2 inhibitor trial-based group, the index date was defined as the date of the qualifying eGFR or UACR value in MedicineInsight during the study period. We applied key exclusion criteria from each trial that could be defined using data from MedicineInsight (Supplementary Table S1), except for maximum tolerated or labelled dose of RAS blockade to better reflect real world practice. Identification of the study cohorts is displayed in Supplementary Figure S1.

We used age- and sex-stratified estimates of CKD prevalence derived from MedicineInsight[14] mapped to corresponding population census data in 2021 from the Australian Bureau of Statistics[15] to estimate the number of prevalent patients with CKD in Australia based on conservative, moderate and high-estimate models (Supplementary Table S2). The conservative model (CKD defined as two consecutive eGFR measurements <60 mL/min/1.73 m^2, ≥90 days apart, and/or two consecutive UACR >3.4 mg/mmol, ≥90 days apart) was used in the main analysis with moderate and high estimate models (defined in Supplementary Table S2) used as sensitivity analyses.

Outcomes

The primary outcome in this study was a composite cardiorenal outcome that included CKD progression (sustained 40–57% decline in eGFR), kidney failure or death due to cardiovascular disease or kidney failure, based on the primary outcomes of the three SGLT2 inhibitor outcome trials.

Secondary outcomes included a kidney composite outcome that was defined as the primary outcome excluding cardiovascular death, and kidney failure alone. Kidney failure was defined as maintenance dialysis, kidney transplantation or a sustained low eGFR (<15 mL/min/1.73 m^2 in CREDENCE and DAPA-CKD and <10 mL/min/1.73 m^2 in EMPA-KIDNEY). Because CKD progression was defined using different eGFR decline thresholds across each of the trials, we also conducted a sensitivity analysis using a standardised kidney composite outcome of 40% decline in eGFR, kidney failure or death due to kidney failure.[14] Ketoacidosis was also evaluated as the main recognised serious adverse effect of SGLT2 inhibitor use.[1]

Statistical analysis

We computed incidence rates, expressed as the number of events per 1000 patient-years, in SGLT2 inhibitor and placebo groups for key outcomes in each trial, based on published reports. Applying relative treatment effects from each trial to the placebo event rate for key outcomes, we estimated absolute risk reductions (ARR) and numbers-needed-to-treat (NNT) to prevent one adverse outcome over 1 and 3 years. The NNT and 95% CI were calculated based on the inverse of the absolute risk reduction.[15] Next, we estimated the annual number of potentially preventable events in Australia (or potential ketoacidosis events caused) with implementation of each of the three SGLT2 inhibitors. We did so by applying the proportion of patients eligible for treatment with each of the three SGLT2 inhibitors to age and sex stratified estimates of the number of Australians with CKD using national census data, as previously described. We then applied trial event rates to national estimates of the number of patients with CKD eligible for treatment, with differences in event rates calculated from the SGLT2 inhibitor and placebo arms in each trial and 95% CIs obtained by estimating the variance in the incidence rate difference.[16] The overall number of patients eligible for treatment and maximum number of potentially preventable events was based on EMPA-KIDNEY, which had the broadest inclusion criteria of the three trials. We defined optimal implementation as 75% uptake of SGLT2 inhibitors among eligible patients and explored the effect of varying levels of treatment uptake on the number of potentially preventable events. Finally, we estimated the number of potentially preventable events with optimal implementation of SGLT2 inhibitors across major subsets of patients: diabetes (yes/no), eGFR (<45 and ≥45 mL/min/1.73 m^2) and UACR (≤33.9 and >33.9 mg/mmol).

All analyses were done using Stata version 17 (StataCorp LLC, College Station, TX).

Role of the funding source
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Results

In MedicineInsight, 147,110 (12.1%) adults had an eGFR <60 mL/min/1.73 m^2 and/or UACR >3.4 mg/mmol between 1 January 2020 and 31 December 2021. After applying key trial-specific inclusion and exclusion criteria (Supplementary Tables S1 and S3), 11,046 (7.5%) of 147,110 patients were eligible for CREDENCE, 25,455 (17.3%) for DAPA-CKD, and 65,049 (44.2%) for EMPA-KIDNEY.

Baseline characteristics of patients eligible for an SGLT2 inhibitor in MedicineInsight and randomised trials are displayed in Table 1. Compared to randomised trials, patients in MedicineInsight were typically older, more likely to be female, have higher eGFR, and less likely to have diabetes (apart from CREDENCE which exclusively enrolled patients with diabetes) and cardiovascular disease (except EMPA-KIDNEY). Median UACR was similar for EMPA-KIDNEY eligible patients, but lower for patients eligible for CREDENCE and DAPA-CKD. The use of RAS blockade was considerably lower in MedicineInsight (approximately 65%) compared to the randomised trials in which almost all patients were receiving RAS blockade, as mandated for study entry. Use of SGLT2 inhibitors in MedicineInsight ranged from 4.1% in EMPA-KIDNEY eligible patients to 14.4% in CREDENCE eligible patients.

Based on Australian population census data, 39,098, 90,100 and 230,246 patients would have been eligible for CREDENCE, DAPA-CKD and EMPA-KIDNEY, respectively, based on a conservative model of CKD prevalence (Supplementary Table S4). EMPA-KIDNEY had the broadest inclusion criteria of all three SGLT2 inhibitor trials, encompassing the eGFR and UACR criteria for the other trials, therefore representing patients eligible for treatment with any SGLT2 inhibitor (Fig. 1; Supplementary Table S5).

For the primary cardiorenal outcome, absolute risk reductions at 3 years ranged from 4.7 to 6.0% with corresponding NNTs of 14–21 (Fig. 2). Absolute risk reductions for kidney failure alone at 3 years were 2.2–3.7% with NNTs of 27–45. In sensitivity analyses, ARR and NNTs for the standardised kidney outcome were similar to the main kidney composite outcome (Supplementary Table S6).

Based on EMPA-KIDNEY trial eligibility criteria, optimal implementation of SGLT2 inhibitors in eligible patients with CKD was projected to result in 3644 fewer cardiorenal events (95% CI 3526–3764), 3454 fewer kidney-composite events (95% CI 3339–3571) and 1312 fewer (95% CI 1242–1385) patients progressing to kidney failure annually based on a conservative estimate of CKD prevalence (Fig. 3 and Supplementary Figure S2 and Table S7). Absolute benefits for these outcomes substantially outweighed the risk of ketoacidosis (Fig. 3). Fig. 4 displays the number of potentially preventable events in Australia with varying levels of SGLT2 inhibitor uptake; even modest increases in SGLT2 inhibitor use (i.e., 25% uptake) may have resulted in 437 fewer patients (95% CI 397–480) in Australia reaching kidney failure annually.

Implementation of SGLT2 inhibitors was projected to reduce cardiorenal events in patients regardless of diabetes or eGFR (Fig. 5). Because patients with UACR ≤33.9 mg/mmol were either excluded (CREDENCE) or represented in relatively small numbers in randomised trials, cardiorenal events prevented were predominantly observed for patients with UACR >33.9 mg/mmol. Event rates, and treatment effects across subgroups in each trial are displayed in Supplementary Table S8. Estimated cardiorenal events potentially prevented using three models of CKD prevalence are displayed in Supplementary Table S9.

Discussion

In this observational study using a nationally representative primary care data source, we observed that nearly 45% of patients with CKD may be eligible for treatment with any SGLT2 inhibitor, based on key trial inclusion and exclusion criteria. Our estimates suggest that increased uptake of SGLT2 inhibitors in CKD could translate to significant population-level benefits including preventing large numbers of people experiencing CKD progression, kidney failure or death due to cardiovascular disease or kidney failure annually. These benefits outweighed the relatively small absolute increased risk of ketoacidosis.

Our findings build upon a growing body of literature that highlight the potential population health impacts of optimal implementation of this important drug class in people across the cardiorenal-metabolic spectrum. SGLT2 inhibitors have been shown to reduce the risk of heart failure hospitalisation and death from any cause in patients with heart failure, irrespective of ejection fraction or diabetes, and now form a central component of guideline-directed therapy for heart failure.[17] Estimates from the United States indicate that almost 5 million patients with heart failure would be eligible for treatment with an SGLT2 inhibitor which, if optimally implemented, could prevent or postpone approximately 630,000 episodes of worsening heart failure or cardiovascular death over three years.[18] An analysis of a Canadian provincial outpatient nephrology service found that implementing SGLT2 inhibitors in the 17.5% of

	CREDENCE eligible patients		DAPA-CKD eligible patients		EMPA-KIDNEY eligible patients	
	MedicineInsight	CREDENCE	MedicineInsight	DAPA-CKD	MedicineInsight	EMPA-KIDNEY
	N = 11,046	N = 4401	N = 25,455	N = 4304	N = 65,049	N = 6609
Age, years; (SD)	71.4 (11.0)	63.0 (9.2)	72.0 (11.9)	61.8 (12.1)	74.4 (13.1)	63.8 (13.9)
Female sex, n (%)	3992 (36.1)	1494 (33.9)	10,672 (41.9)	1425 (33.1)	31,955 (49.1)	2192 (33.2)
Smoker; n (%)	1106 (10.0)	639 (14.5)	2093 (8.2)	584 (13.6)	4728 (7.3)	N/A[a]
Prior disease; n (%)						
Type 2 diabetes	11,046 (100)	4401 (100)	12,514 (49.2)	2906 (67.5)	22,952 (35.3)	3039 (46.0)
Cardiovascular disease	3160 (28.6)	2220 (50.4)	6656 (26.2)	1610 (37.4)	17,263 (26.5)	1765 (26.7)
Heart failure	853 (7.7)	652 (14.8)	2298 (9.0)	468 (10.9)	7845 (12.1)	658 (10)
Systolic BP (mmHg)	135.7 (16.0)	140 (15.6)	138.1 (19.2)	137.1 (17.4)	135.3 (17.2)	136.5 (18.3)
Diastolic BP (mmHg)	75.3 (10.5)	78.3 (9.4)	77.4 (12.6)	77.5 (10.5)	75.4 (12.0)	78.1 (11.8)
BMI (kg/m^2)	32.0 (8.0)	31.3 (6.2)	31.2 (7.7)	29.5 (6.2)	30.8 (8.4)	29.7 (6.8)
HbA1c (%)	7.5 (1.5)	8.3 (1.3)	7.0 (1.6)	7.1 (1.7)	6.9 (1.6)	6.3 (NA)
eGFR (mL/min/1.73 nm^2)						
Mean eGFR (SD)	68.0 (16.8)	56.2 (18.2)	56.0 (13.9)	43.1 (12.4)	51.3 (19.5)	37.5 (14.8)
≥60	7627 (69.0)	1769 (40.2)	12,298 (48.3)	454 (10.5)	20,985 (32.3)	1424 (21.5)
45 to <60	2020 (18.3)	1266 (28.8)	7107 (27.9)	1328 (30.9)	6688 (10.3)	
30 to <45	1399 (12.7)	1191 (27.1)	4898 (19.2)	1898 (44.1)	31,492 (48.4)	2905 (44.0)
<30	0 (0.0)	174 (4.0)	1152 (4.5)	624 (14.5)	5884 (9.1)	2280 (34.5)
UACR[b] (mg/mmol)						
Median (IQI)	72.9 (46.9–138.9)	104.8 (52.3–207.1)	58.0 (33.9–124.9)	107.3 (N/A)	52.9 (32.0–117.9)	46.6 (10.6–134.5)
<3.4 (A1)	0 (0.0)	31 (0.7)	0 (0.0)	1 (0.0)	12,062 (18.5)[a]	1332 (20.2)
3.4–33.9 (A2)	0 (0.0)	496 (11.4)	4949 (19.4)	444 (10.3)	6426 (9.9)[a]	1862 (28.2)
>33.9 (A3)	11,046 (100)	3874 (88.0)	20,506 (80.6)	3859 (89.7)	23,138 (35.6)[a]	3415 (51.7)
KDIGO risk category; n (%)						
Moderate	0 (0)	0 (0)	2791 (11.0)	49 (1.1)	4872 (7.5)	1672 (25.3)
High	7627 (69.1)	1809 (41.1)	10,844 (42.6)	570 (13.2)	17,366 (26.7)	
Very high	3419 (31.0)	2592 (58.9)	11,820 (46.4)	3685 (85.6)	13,106 (20.2)	4937 (74.7)
Medication use; n (%)						
ACEi or ARB	7503 (67.9)	4395 (99.9)	16,039 (63.0)	4224 (98.1)	36,929 (56.8)	5613 (84.9)
Diuretic	1580 (14.3)	2057 (46.7)	3938 (15.5)	1882 (43.7)	12,088 (18.6)	2776 (42.0)
Statin	6930 (62.7)	3036 (69.0)	12,966 (50.9)	2794 (64.9)	29,484 (45.3)	4376 (66.2)
SGLT2 inhibitor	1586 (14.4)	N/A	1603 (6.3)	N/A	2672 (4.1)	N/A

SD: standard deviation; IQI: interquartile interval; BP: blood pressure; BMI: body mass index; HbA1c: glycated haemoglobin; eGFR: estimated glomerular filtration rate; UACR: urine albumin:creatinine ratio; KDIGO: Kidney Disease Improving Global Outcomes; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; SGLT2: sodium glucose cotransporter 2. [a]Data not available in EMPA-KIDNEY. [b]Among EMPA-KIDNEY eligible individuals in whom UACR data were available.

Table 1: **Baseline characteristics of patients with CKD eligible for treatment with an SGLT2 inhibitor in MedicineInsight (2020–2021) and SGLT2 inhibitor kidney outcome trials.**

patients who would have met trial inclusion criteria would result in savings of CA$2.31 million over 2.6 years for that province alone.[19] Similarly large numbers of patients with diabetes have been shown to be eligible for treatment with an SGLT2 inhibitor with considerable population-level benefits anticipated with optimal implementation.[20,21]

Use of SGLT2 inhibitors has been shown to be cost-effective in economic evaluations across different settings and cardiometabolic diseases,[22] as reflected in the inclusion of SGLT2 inhibitors in the World Health Organisation List of Essential Medicines.[23] Indeed compared to population wide approaches for preventing kidney failure due to diabetes such as lifestyle modification and sugar sweetened beverage taxes, Australian modelling has demonstrated that widespread implementation of SGLT2 inhibitors would be the most effective strategy for reducing the incidence of kidney failure due to diabetes.[24] Our results extend previous work to patients with CKD in primary care, regardless of diabetes, comparing eligibility for different agents within the medication class based on trial inclusion and exclusion criteria.

While the use of SGLT2 inhibitors is increasing modestly over time across some jurisdictions, most patients with CKD who would benefit from treatment are not receiving them in routine clinical practice, despite strong recommendations from major clinical practice guidelines advocating for their use. In fact, data from the United Kingdom and North America indicate that

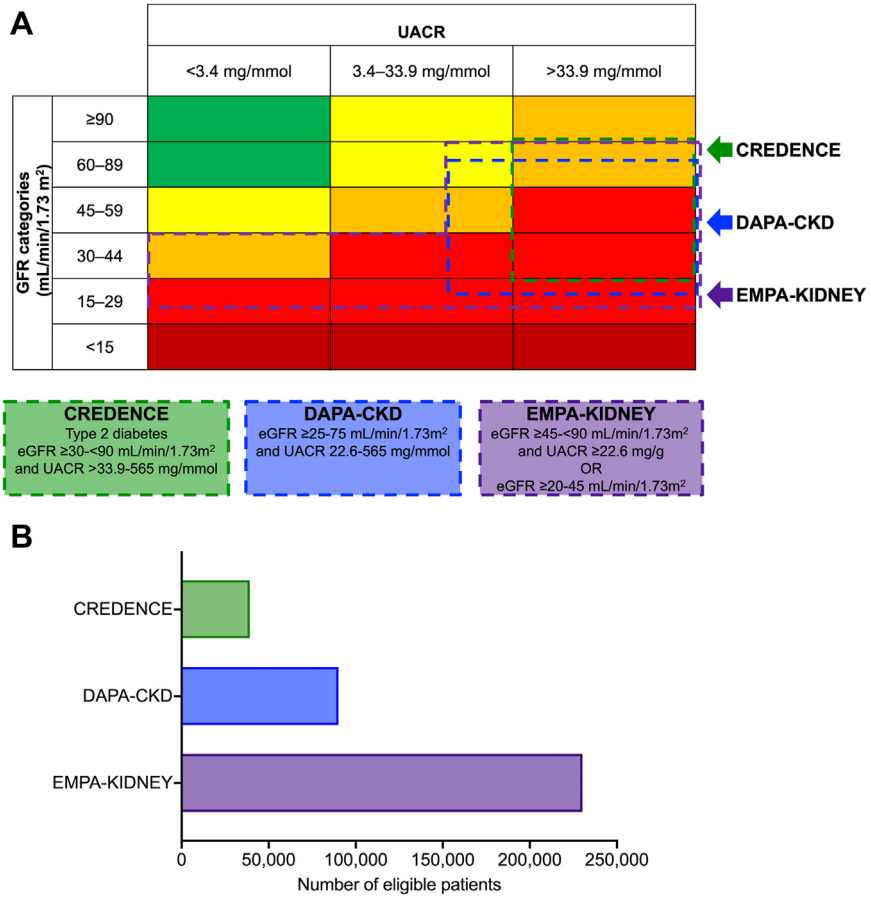

Fig. 1: (A) eGFR and UACR inclusion criteria in SGLT2 inhibitor kidney outcome trials and (B) number of Australian primary care patients with CKD estimated to be eligible for treatment with an SGLT2 inhibitor (based on a conservative CKD prevalence model). eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio.

patients with CKD are less likely to receive an SGLT2 inhibitor than those with normal kidney function, despite the fact patients with CKD are at much higher risk of cardiovascular events and CKD progression and thus stand to gain more in absolute terms.[5] This 'risk-treatment paradox' is evident across the cardio-renal-metabolic spectrum, with people who have established atherosclerotic cardiovascular disease also less likely to receive an SGLT2 inhibitor, despite greater absolute treatment benefits.[6] The reason for the underuse of SGLT2 inhibitors is complex and likely related to factors such as access and cost, perceived safety concerns, and therapeutic inertia to varying degrees. However, RAS blockade remains underused in people with CKD even two decades after landmark trials that established these medications as standard of care for patients with albuminuric CKD,[25] suggesting that financial cost alone is not the only driver of underuse.

Taken together, the data highlight the urgency of efforts to maximise the implementation of SGLT2 inhibitors into routine clinical practice to reduce cardiorenal risk. Identifying patients at risk of CKD progression and increasing the uptake of proven therapies are priority areas of research. Even in patients with diabetes or hypertension, screening for albuminuria is underperformed with approximately two thirds of patients with albuminuria undetected.[26] The COORDINATE-Diabetes cluster randomized trial showed that a coordinated, multifaceted intervention of assessment, education and feedback to clinicians improved the prescription of evidence-based therapies (SGLT2 inhibitors, GLP-1 receptor agonists and statins) in people with diabetes and atherosclerotic cardiovascular disease.[27] In patients with heart failure, the STRONG-HF trial demonstrated that intensive post-discharge follow-up can optimise the prescription and dosing of guideline-directed heart failure therapy and reduce hospital readmission or all-cause death.[28] COORDINATE-Diabetes and STRONG-HF highlight the need to evaluate implementation strategies to

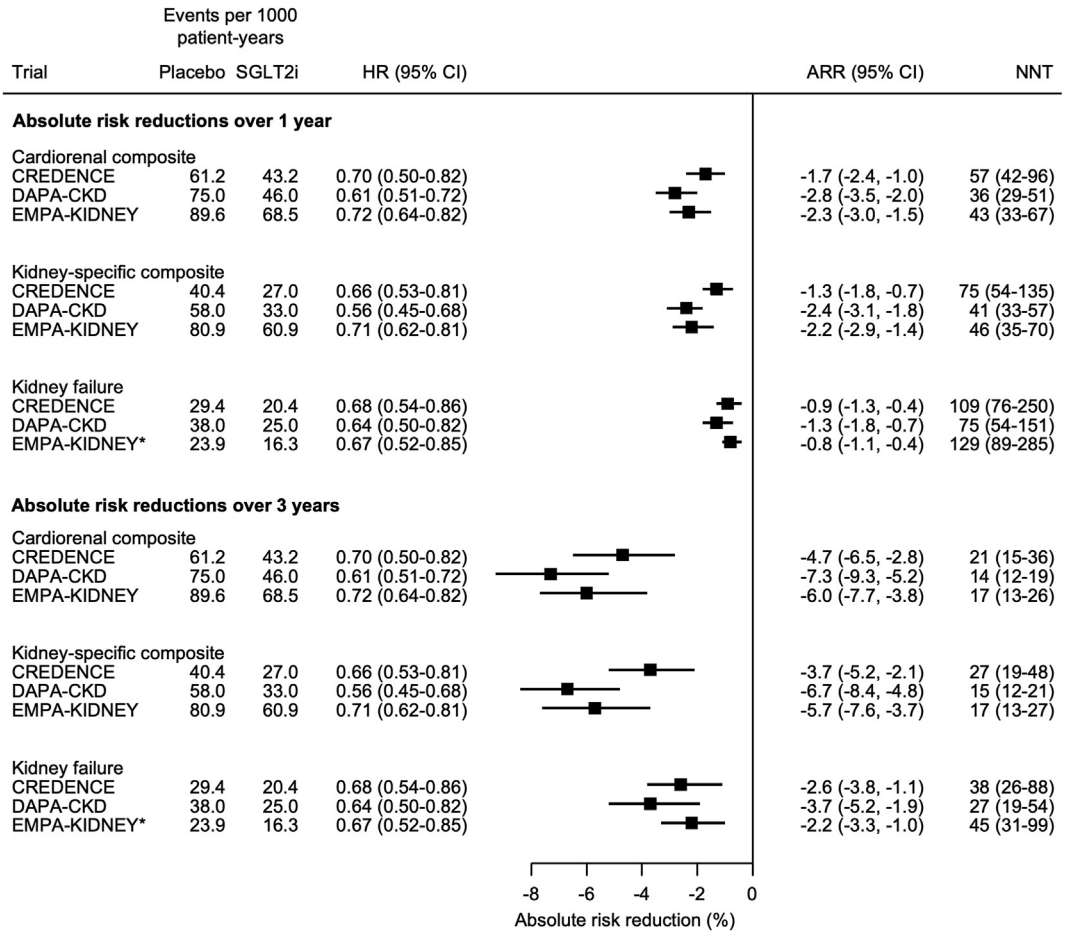

Fig. 2: Treatment effects, absolute risk reductions and numbers-needed-to-treat at 1 and 3 years in SGLT2 inhibitor kidney outcome trials. *Event rates estimated based on number of events over a median follow-up of 2 years. SGLT2i: sodium glucose cotransporter 2 inhibitor; HR: hazard ratio; CI: confidence interval; ARR: absolute risk reduction; NNT: number needed to treat.

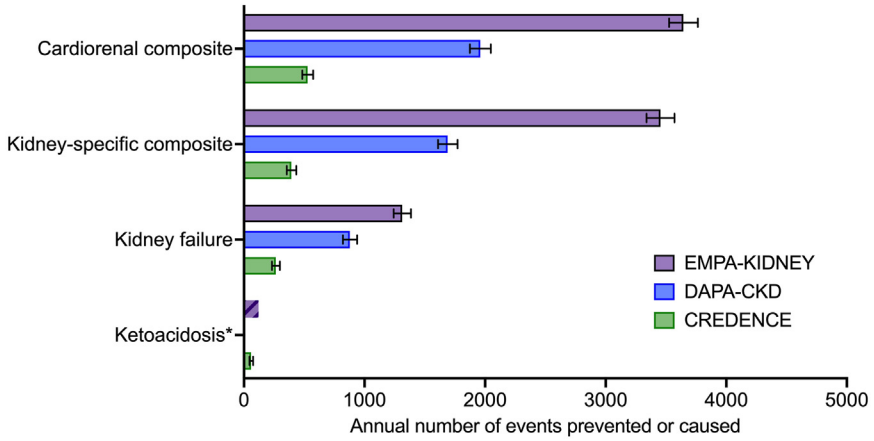

Fig. 3: Estimated annual number of cardiorenal events expected to be prevented or ketoacidosis events caused in Australia with optimal implementation (75% uptake) of SGLT2 inhibitors in patients with CKD. *No ketoacidosis events were observed in SGLT2 inhibitor-treated participants in DAPA-CKD. Hazard ratio for ketoacidosis not calculated in EMPA-KIDNEY because there were fewer than 10 events.

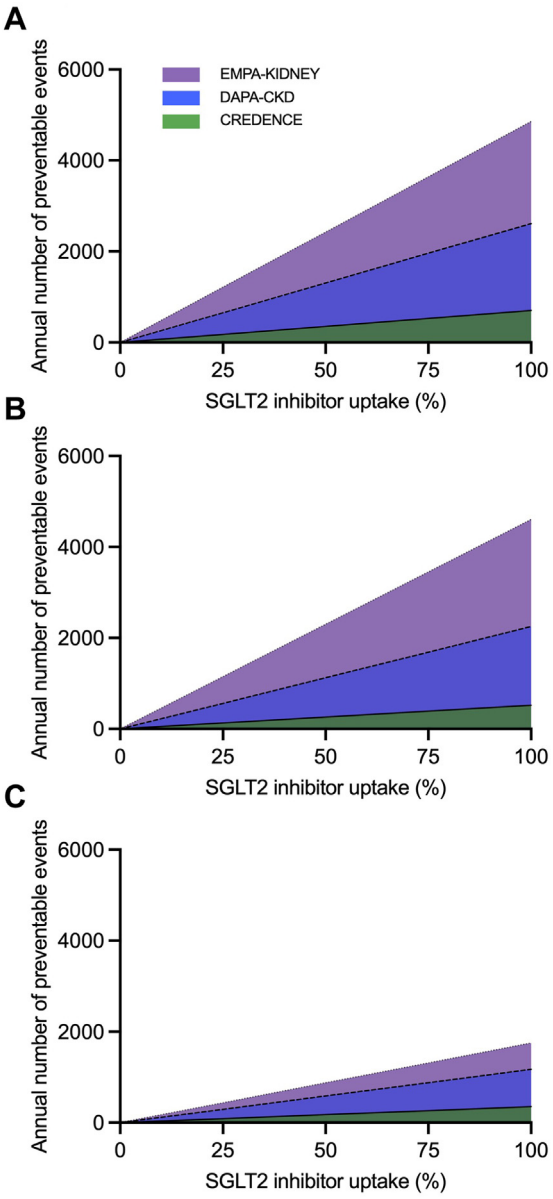

Fig. 4: Estimated annual number of (A) cardiorenal, (B) kidney-specific composite and (C) kidney failure events expected to be prevented in Australia with different levels of SGLT2 inhibitor uptake in patients with CKD.

increase the uptake of proven therapies, including SGLT2 inhibitors, for patients with CKD to ensure that those who might benefit most from treatment are able to receive it.

This study has several strengths. The study encompassed a contemporaneous, well characterized, nationally representative, primary care cohort in Australia reflecting the timeframe in which key SGLT2 inhibitor trials and major guideline updates were published. We estimated the impacts of improved uptake of SGLT2 inhibitors in a range of scenarios based on different CKD prevalence estimates and varying levels of treatment uptake.

Important limitations should be recognised when interpreting these findings. First, as we did not have access to longer-term clinical outcomes (e.g., hospital admissions), we extrapolated event rates from SGLT2 inhibitor trials to the cohort, as has been done in analogous work in diabetes and in heart failure.[18,20,29] However, these event rates may not be applicable to routine practice due to differences in baseline risk. Indeed, we observed important differences in patient characteristics (including eGFR and UACR) and use of RAS blockade between these groups. Treatment adherence in routine practice is typically lower than clinical trials and may wane over time. These factors may reduce the estimated population-level impacts of improved SGLT2 inhibitor uptake. On the other hand, we used a conservative estimate of CKD prevalence and focused only on SGLT2 kidney outcome trials. It is likely that many more patients with CKD would be eligible for an SGLT2 inhibitor for the treatment of type 2 diabetes or heart failure (regardless of diabetes), since a large number of these patients will have concomitant CKD. It is possible that SGLT2 inhibitor use has increased since 2020–2021, although absolute increases are likely to be small. Finally, while MedicineInsight is largely representative of the broader Australia population in terms of demographic characteristics and CKD prevalence,[30] there are inherent data limitations that may have impacted the estimation of the patient population eligible to receive SGLT2 inhibitor treatment. For example, we were unable to apply some exclusion criteria (e.g., polycystic kidney disease) as we did not have data on CKD aetiology. However, the impact of this is likely minimal given these conditions occur uncommonly at a population level.

In conclusion, large numbers of patients with CKD in Australia are eligible for treatment with SGLT2 inhibitors. Improved uptake of SGLT2 inhibitors for patients with CKD has the potential to prevent large numbers of patients experiencing CKD progression or dying due to cardiovascular or kidney disease. Identifying strategies to increase the uptake of SGLT2 inhibitors is critical to realising the population-level benefits of this drug class.

Contributors

BLN, MJ, JW, SK, SVB, MG and PER contributed to the concept and rationale for the study and interpretation of the results. KN and MJ were responsible for acquisition of the data extract from MedicineInsight. BLN, MJ, JW and PER developed the study protocol and oversaw the implementation of the study analytical plan. BLN, MJ and PER drafted the initial manuscript. All authors contributed to the design of the study, interpretation of the data and critical revision of the manuscript.

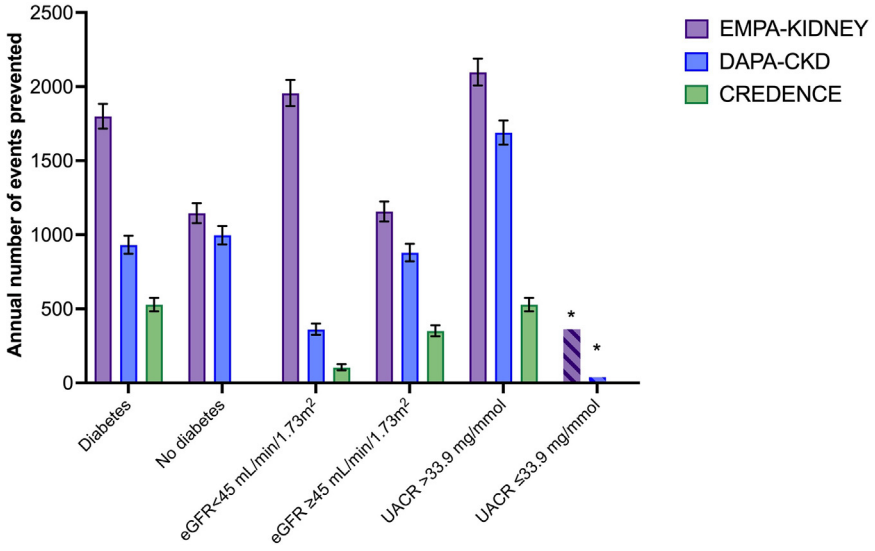

Fig. 5: Estimated annual number of cardiorenal events expected to be prevented in Australia with optimal implementation (75% uptake) of SGLT2 inhibitors in patients with CKD according to diabetes status, eGFR and UACR. Note: All patients in CREDENCE had diabetes and UACR >33.9 mg/g; UACR ≤33.9 mg/g subgroup includes patients with no UACR measured. eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio.*In the EMPA-KIDNEY trial, effect modification by baseline UACR for the primary outcome was observed (P-trend 0.02) such that the benefits of SGLT2 inhibition in EMPA-KIDNEY were greater in patients with UACR >33.9 mg/mmol. CREDENCE and DAPA-CKD did not recruit participants with UACR <33.9 and <22.6 mg/mmol, respectively.

Data sharing statement

The current study is based on data from MedicineInsight, a national general practice data source developed by NPS MedicineWise and managed by the Australian Commission on Safety and Quality in Health Care. The 2021 Australian population census data is publicly available via the Australian Bureau of Statistics website (www.abs.gov.au). All relevant data are within the manuscript and its Supplementary Appendix.

Declaration of interests

The Renal Division of The George Institute for Global Health has received sponsorship funding provided by Boehringer Ingelheim and Eli Lilly Alliance, and is supported by the University of New South Wales Scientia Program. The design, analysis, interpretation or writing of this manuscript was performed independent of all funding bodies. All study authors assumed final responsibility for all aspects of the study, including the decision to submit the manuscript for publication.

BLN has received fees for travel support, advisory boards, scientific presentations and steering committee roles from AstraZeneca, Bayer, Boehringer and Ingelheim, Cambridge Healthcare Research, Janssen, and Medscape with all honoraria paid to The George Institute for Global Health. He serves as Secretariat of the SGLT2 Meta-Analysis Cardio-Renal Trialists Consortium and is a member of the Caring for Australians and New Zealanders with Kidney Impairment (CARI) living guidelines on SGLT2 inhibitors.

MJ is responsible for research projects that have received unrestricted research funding from Boehringer Ingelheim and Eli Lilly Alliance.

SK has received consultancy fees from Chinook and Dimerix Pharmaceuticals. This study was supported by an unrestricted research grant from Boehringer Ingelheim.

SVB has served on advisory board of Bayer, AstraZeneca, GSK and Vifor Pharma; received speakers fees from Bayer, AstraZeneca, Pfizer and Vifor Pharma, and non-financial research support from Bayer with all fees paid to his institution.

MJJ is supported by an NHMRC Investigator Grant; is responsible for research projects that have received funding from Amgen, Baxter, CSL, Dimerix, Eli Lilly, Gambro, and MSD; has received fees for Advisory, Steering Committee and/or Scientific Presentations from Akebia, Amgen, Astra Zeneca, Baxter, Bayer, Boehringer Ingelheim, Cesas Linx, Chinook, CSL, Janssen, Medscape, MSD, Occuryx, Roche and Vifor; with any consultancy, honoraria or travel support paid to her institution.

VP has received fees for advisory boards, steering committee roles, or scientific presentations from AbbVie, Astellas, AstraZeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, Tricida, and Vitae.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100988.

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