# Implementation of chronic kidney disease guidelines for sodium-glucose co-transporter-2 inhibitor use in primary care in the UK: a cross-sectional study

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## Summary

**Background** The cardiovascular and kidney benefits of sodium-glucose co-transporter-2 (SGLT2) inhibitors in people with chronic kidney disease (CKD) are well established. The implementation of updated SGLT2 inhibitor guidelines and prescribing in the real-world CKD population remains largely unknown.

**Methods** A cross-sectional study of adults with CKD registered with UK primary care practices in the Oxford-Royal College of General Practitioners Research and Surveillance Centre network on the 31st December 2022 was undertaken. Pseudonymised data from electronic health records held securely within the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID) were extracted. An update to a previously described ontological approach was used to identify the study population, using a combination of Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) indicating a diagnosis of CKD and laboratory confirmed CKD based on Kidney Disease: Improving Global Outcomes (KDIGO) diagnostic criteria. We examined the extent to which SGLT2 inhibitor guidelines apply to and are then implemented in adults with CKD. A logistic regression model was used to identify factors associated with SGLT2 inhibitor prescribing, reported as odds ratios (ORs) with 95% confidence intervals (CI). The four guidelines under investigation were the United Kingdom Kidney Association (UKKA) Clinical Practice Guideline SGLT2 Inhibition in Adults with Kidney Disease (October 2021), American Diabetes Association (ADA) and KDIGO Consensus Report on Diabetes Management in CKD (October 2022), National Institute for Health and Care Excellence (NICE) Guideline Type 2 Diabetes in Adults: Management (June 2022), and NICE Technology Appraisal Dapagliflozin for Treating CKD (March 2022).

**Findings** Of 6,670,829 adults, we identified 516,491 (7.7%) with CKD, including 32.8% (n = 169,443) who had co-existing type 2 diabetes (T2D). 26.8% (n = 138,183) of the overall CKD population had a guideline directed indication for SGLT2 inhibitor treatment. A higher proportion of people with CKD and co-existing T2D were indicated for treatment, compared to those without T2D (62.8% [n = 106,468] vs. 9.1% [n = 31,715]). SGLT2 inhibitors were prescribed to 17.0% (n = 23,466) of those with an indication for treatment, and prescriptions were predominantly in those with co-existing T2D; 22.0% (n = 23,464) in those with T2D, and <0.1% (n = 2) in those without T2D. In adjusted multivariable analysis of people with CKD and T2D, females (OR 0.69, 95% CI 0.67–0.72, p <0.0001), individuals of Black ethnicity (OR 0.84, 95% CI 0.77–0.91, p <0.0001) and those of lower socio-economic status (OR 0.72, 95% CI 0.68–0.76, p <0.0001) were less likely to be prescribed an SGLT2 inhibitor. Those with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 $m^2$ had a lower likelihood of receiving an SGLT2 inhibitor, compared to those with an eGFR ≥60 mL/min/1.73 $m^2$ (eGFR 45–60 mL/min/1.73 $m^2$ OR 0.65, 95% CI 0.62–0.68, p <0.0001, eGFR 30–45 mL/min/1.73 $m^2$ OR 0.73, 95% CI 0.69–0.78, p <0.0001, eGFR 15–30 mL/min/1.73 $m^2$ OR 0.52, 95% CI 0.46–0.60, p <0.0001, eGFR <15 mL/min/1.73 $m^2$ OR 0.03, 95% CI 0.00–0.23, p = 0.0037, respectively). Those with albuminuria (urine albumin-to-creatinine ratio 3–30 mg/mmol) were less likely to be prescribed an SGLT2 inhibitor, compared to those without albuminuria (OR 0.78, 95% CI 0.75–0.82, p <0.0001).

**Interpretation** SGLT2 inhibitor guidelines in CKD have not yet been successfully implemented into clinical practice, most notably in those without co-existing T2D. Individuals at higher risk of adverse outcomes are paradoxically less likely to receive SGLT2 inhibitor treatment. The timeframe between the publication of guidelines and data extraction

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may have been too short to observe changes in clinical practice. Enhanced efforts to embed SGLT2 inhibitors equitably into routine care for people with CKD are urgently needed, particularly in those at highest risk of adverse outcomes and in the absence of T2D.

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Keywords: Sodium-glucose transporter 2 inhibitors; Electronic health records; Guideline adherence; Primary health care; Chronic kidney disease

### Research in context

#### Evidence before this study

We searched PubMed for studies published until the 1st September 2023, using the following search terms found in the title, abstract or Medical Subject Headings (MeSH): sodium-glucose transporter 2 inhibitors; renal insufficiency, chronic; guideline adherence; and prescribing. Additionally, we searched the references and citations of identified papers. The cardiovascular and kidney benefits of sodium-glucose co-transporter-2 (SGLT2) inhibitors in people with chronic kidney disease (CKD) are well established. The implementation of SGLT2 inhibitor guidelines and prescribing in the real-world CKD population remains largely unknown.

#### Added value of this study

In this study, we present a detailed analysis of the implementation of four SGLT2 inhibitor guidelines in a large and nationally representative primary care population with CKD. We found that these guidelines, which incorporate the findings from the latest clinical trials, applied to only 26.8% of people with CKD, including 62.8% with co-existing type 2 diabetes (T2D) and 9.1% without T2D. Of those indicated for treatment, SGLT2 inhibitors were prescribed to 22.0% with co-existing CKD and T2D, and <0.1% with CKD without T2D. In multivariable analysis of people with CKD and T2D, we observed disparities in the use of SGLT2 inhibitors and that individuals at higher risk of adverse outcomes were paradoxically less likely to receive treatment.

#### Implications of all the available evidence

People living with CKD do not yet have adequate access to SGLT2 inhibitor therapy. Enhanced efforts are needed to embed SGLT2 inhibitors equitably into routine care for people with CKD, particularly in those at highest risk of adverse outcomes and in the absence of T2D.

## Introduction

The protective cardiovascular and kidney effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors in individuals with and without diabetes have been well established in randomised controlled trials.[1–3] These findings represent a major therapeutic advance in the treatment of chronic kidney disease (CKD), providing a unique opportunity to simultaneously manage cardiovascular risk and kidney disease progression. This has prompted updates to SGLT2 inhibitor drug licences and the publication of clinical guidelines relating to their use in CKD.

The most comprehensive of these is the United Kingdom Kidney Association (UKKA) Clinical Practice Guideline, initially published in October 2021[4] and updated in April 2023.[5] This makes clear recommendations for the use of SGLT2 inhibitors in different groups with CKD, including people with and without type 2 diabetes (T2D), with and without albuminuria, and those with established heart failure or ischaemic heart disease. Additionally, guidance specific to the use of SGLT2 inhibitors in people with co-existing CKD and T2D has been published by various organisations, including the National Institute for Health and Care Excellence (NICE), Kidney Disease: Improving Global Outcomes (KDIGO), and American Diabetes Association (ADA).[6–8]

The extension of drug licences and publication of updated clinical guidelines relating to the use of SGLT2 inhibitors in CKD are important milestones. However, the successful implementation of these guidelines into routine clinical practice is key to ensuring that the cardio-renal protection offered by these drugs is translated into improvements in cardiovascular and kidney health for people with CKD in real-world clinical practice. There are limited data on the number of people with CKD in routine clinical practice who meet the latest guideline directed indications for treatment with SGLT2 inhibitors. Moreover, the prescribing patterns of SGLT2 inhibitors in response to these updated guidelines in the real-world CKD population remains largely unknown. Understanding treatment opportunity gaps, highlighting potential barriers and disparities are essential in guiding the successful implementation of SGLT2 inhibitor guidelines.

The aim of this study was to examine the extent to which the latest SGLT2 inhibitor guidelines apply to and

are then implemented in adults with CKD in real-world clinical practice.

The main objectives were to:

1) estimate the proportion of the CKD population that met guideline directed indications for SGLT2 inhibitor treatment, and examine reasons why individuals were not indicated for treatment,
2) estimate the proportion of the CKD population indicated for treatment who were prescribed an SGLT2 inhibitor, and
3) describe the characteristics of the CKD population with an indication for treatment, and explore factors associated with SGLT2 inhibitor prescribing.

## Methods

### Study design and data source

We conducted a cross-sectional study of adults with CKD using data from the Primary Care Sentinel Cohort (PCSC) of the Oxford-Royal College of General Practitioners Research (RCGP) and Surveillance Centre (RSC) database. We extracted pseudonymised data from electronic health records held securely within the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID), a Trusted Research Environment. The PCSC is a primary care network of 738 volunteer practices and 6,670,829 adults at the time of data extraction, which is broadly representative of the English population.[9]

The study was conducted in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement guidance.[10] Ethical approval for the study was granted by the St George's Research Ethics Committee, Joint Research and Enterprise Services, St George's University of London in January 2022 (reference number 2022.0003). Informed consent for this specific study was not required. The study used pseudonymised patient level data in accordance with the ethical approval. Data from individuals who opted out of data sharing were not used.

### Study population

We identified adults (≥18 years) with CKD registered with primary care practices in the PCSC of the Oxford-RCGP RSC network on the 31st December 2022. An update to a previously described ontological approach was used to identify the study population, using a combination of Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) indicating a diagnosis of CKD, an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 $m^2$ (based on a minimum of 2 serum creatinine measurements taken at least 90 days apart), and proteinuria defined as urine albumin-to-creatinine ratio (ACR) >3 mg/mmol or urine protein-to-creatinine ratio (PCR) >15 mg/mmol (based on a minimum of 2 measurements taken at least 90 days apart).[11] eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation.[12]

We identified individuals that had a guideline directed indication for SGLT2 inhibitor treatment according to four published guidelines, representing the most recent and specific guidance on the use of SGLT2 inhibitors in CKD. The guidelines under investigation were the UKKA Clinical Practice Guideline SGLT2 Inhibition in Adults with Kidney Disease (UKKA Clinical Practice Guideline), ADA and KDIGO Consensus Report on Diabetes Management in CKD (ADA-KDIGO Consensus Report), NICE Guideline Type 2 Diabetes in Adults: Management (NICE Guideline), and NICE Technology Appraisal Dapagliflozin for Treating CKD (NICE Technology Appraisal).[5–8]

Individuals were classified as meeting guideline directed indications for SGLT2 inhibitor treatment if they fulfilled at least one of the published criteria. The guideline recommendations and how we defined them in our primary care CKD population are summarised in Table 1. The flow diagram of participant inclusion is illustrated in Fig. 1.

### Data analysis

We extracted demographic and clinical characteristics of the CKD population including clinical measures, co-morbidities, and prescribed medications. Data were captured at the time of extraction using the most recently available information prior to the 31st December 2022. Additionally, for individuals prescribed an SGLT2 inhibitor, we identified the date a drug in the SGLT2 inhibitor class was first prescribed and captured information at the time point closest to the first prescription. Where there was no record of a co-morbidity or prescription, it was assumed the co-morbidity was not present, or the individual was not receiving the treatment.

Ethnicity was grouped into five categories, White, Asian, Black, Mixed, and Other, based on the Office for National Statistics definitions.[13] Socio-economic status was determined by the Index of Multiple Deprivation (IMD) score, which was converted into quintiles ranging from 1 (most deprived) to 5 (least deprived).[14] The IMD score combines information from seven domains to product an overall measure of relative deprivation for small areas of England. The domains of deprivation include income deprivation, employment deprivation, education, skills and training deprivation, health deprivation and disability, crime, barriers to housing and services, and living environment deprivation.[14] IMD score was calculated based on the postcode of the individual's registered home address.

Continuous variables were cleaned, and outlying values excluded and assigned as missing based on expert opinion within the research team and previously published ranges.[15] Blood pressure outliers were defined

| UKKA Clinical Practice Guideline SGLT2 Inhibition in Adults with Kidney Disease | | Nearest match from routinely collected primary care data |
|---|---|---|
| **≥18 years of age + T2D + CKD (irrespective of primary kidney disease) + one of the following 4 groups:** | | ≥18 years of age. Ontological approach combining SNOMED CT concepts relevant to T2D and CKD, including diagnostic codes, blood test results, urine test results and prescriptions. |
| **UKKA 1** | eGFR 20–45 mL/min/1.73 $m^2$ | eGFR 20–45 mL/min/1.73 $m^2$ using CKD-EPI |
| **UKKA 2** | eGFR >45 mL/min/1.73 $m^2$ + urine ACR ≥25 mg/mmol | eGFR >45 mL/min/1.73 $m^2$ using CKD-EPI<br>Urine ACR ≥25 mg/mmol |
| **UKKA 3** | Established coronary disease or stable symptomatic heart failure | Ontological approach combining SNOMED CT concepts relevant to ischaemic heart disease and heart failure. |
| **UKKA 4** | eGFR >45–60 mL/min/1.73 $m^2$ + urine ACR <25 mg/mmol | eGFR >45–60 mL/min/1.73 $m^2$ using CKD-EPI<br>Urine ACR <25 mg/mmol |
| **≥18 years of age + without T2D + CKD (irrespective of primary kidney disease) + one of the following 3 groups:** | | ≥18 years of age. Ontological approach combining SNOMED CT concepts relevant to CKD, including diagnostic codes, blood test results, urine test results and prescriptions. |
| **UKKA 5** | Stable symptomatic heart failure | Ontological approach combining SNOMED CT concepts relevant to heart failure. |
| **UKKA 6** | eGFR ≥20 mL/min/1.73 $m^2$ + urine ACR ≥25 mg/mmol | eGFR ≥20 mL/min/1.73 $m^2$ using CKD-EPI<br>Urine ACR ≥25 mg/mmol |
| **UKKA 7** | eGFR 20–45 mL/min/1.73 $m^2$ + urine ACR <25 mg/mmol | eGFR 20–45 mL/min/1.73 $m^2$ using CKD-EPI<br>Urine ACR <25 mg/mmol |
| **Single agent RAS inhibitor** at maximum tolerated dose to be given in combination with SGLT2 inhibitor if indicated and tolerated | | Current prescription for RAS inhibitor |
| **Excluding patients with T1D, kidney transplant or polycystic kidney disease** | | Ontological approach combining SNOMED CT concepts relevant to T1D, namely diagnostic codes, blood tests results and prescriptions. Ontological approach combining SNOMED CT concepts relevant to kidney transplant and polycystic kidney disease. |
| **ADA-KDIGO Consensus Report on Diabetes Management in CKD** | | **Nearest match from routinely collected primary care data** |
| **≥18 years of age + T2D + CKD + the following group:** | | ≥18 years of age. Ontological approach combining SNOMED CT concepts relevant to T2D and CKD, including diagnostic codes, blood test results, urine test results and prescriptions. |
| **ADA-KDIGO 1** | eGFR ≥20 mL/min/1.73 $m^2$ | eGFR ≥20 mL/min/1.73 $m^2$ using CKD-EPI |
| **Single agent RAS inhibitor** at maximum tolerated dose to be given in combination with SGLT2 inhibitor if indicated and tolerated | | Current prescription for RAS inhibitor |
| **Excluding patients with kidney transplant** | | Ontological approach combining SNOMED CT concepts relevant to kidney transplant. |
| **NICE Guideline T2D in Adults: Management** | | **Nearest match from routinely collected primary care data** |
| **≥18 years of age + T2D + CKD + one of the following 2 groups:** | | ≥18 years of age. Ontological approach combining SNOMED CT concepts relevant to T2D and CKD, including diagnostic codes, blood test results, urine test results and prescriptions. |
| **NICE 1** | eGFR ≥25 mL/min/1.73 $m^2$ + urine ACR >30 mg/mmol | eGFR ≥25 mL/min/1.73 $m^2$ using CKD-EPI<br>Urine ACR >30 mg/mmol |
| **NICE 2** | eGFR ≥25 mL/min/1.73 $m^2$ + urine ACR 3–30 mg/mmol | eGFR ≥25 mL/min/1.73 $m^2$ using CKD-EPI<br>Urine ACR 3–30 mg/mmol |
| **RAS inhibitor** titrated to highest licenced and tolerated dose | | Current prescription for RAS inhibitor |
| **NICE Technology Appraisal Dapagliflozin for Treating CKD** | | **Nearest match from routinely collected primary care data** |
| **≥18 years of age + CKD + one of the following 2 groups:** | | ≥18 years of age. Ontological approach combining SNOMED CT concepts relevant to CKD, including diagnostic codes, blood test results, urine test results and prescriptions. |
| **NICE 3** | eGFR 25–75 mL/min/1.73 $m^2$ + T2D | eGFR 25–75 mL/min/1.73 $m^2$ using CKD-EPI<br>Ontological approach combining SNOMED CT concepts relevant to T2D, namely diagnostic codes, blood tests results and prescriptions. |
| **NICE 4** | eGFR 25–75 mL/min/1.73 $m^2$ + urine ACR ≥22.6 mg/mmol | eGFR 25–75 mL/min/1.73 $m^2$ using CKD-EPI<br>Urine ACR ≥22.6 mg/mmol |
| **Excluding patients with T1D or kidney transplant** | | Ontological approach combining SNOMED CT concepts relevant to T1D, namely diagnostic codes, blood tests results and prescriptions.<br>Ontological approach combining SNOMED CT concepts relevant to kidney transplant. |
| **RAS inhibitor** titrated to highest licenced and tolerated dose | | Current prescription for RAS inhibitor |

For each guideline directed indication we identified the nearest match from routine primary care data, using a combination of demographics, diagnostic tests, prescriptions, and variables curated from SNOMED CT using an ontological approach. SNOMED CT—Systematized Nomenclature of Medicine Clinical Terms, RAS inhibitor—renin-angiotensin system inhibitor, CKD—chronic kidney disease, T1D—type 1 diabetes, T2D—type 2 diabetes, CKD-EPI—Chronic Kidney Disease Epidemiology Collaboration, SGLT2 inhibitor—sodium-glucose co-transporter-2 inhibitor, eGFR—estimated glomerular filtration rate, urine ACR—urine albumin-to-creatinine ratio, urine PCR—urine protein-to-creatinine ratio, NICE—National Institute for Health and Care Excellence, ADA—American Diabetes Association, UKKA—United Kingdom Kidney Association, KDIGO—Kidney Disease: Improving Global Outcomes. In UKKA Clinical Practice Guideline urine ACR 25 mg/mmol is considered equivalent to urine PCR 35 mg/mmol.

*Table 1:* **Guideline directed indications for SGLT2 inhibitors in CKD and how we defined them in our primary care population.**

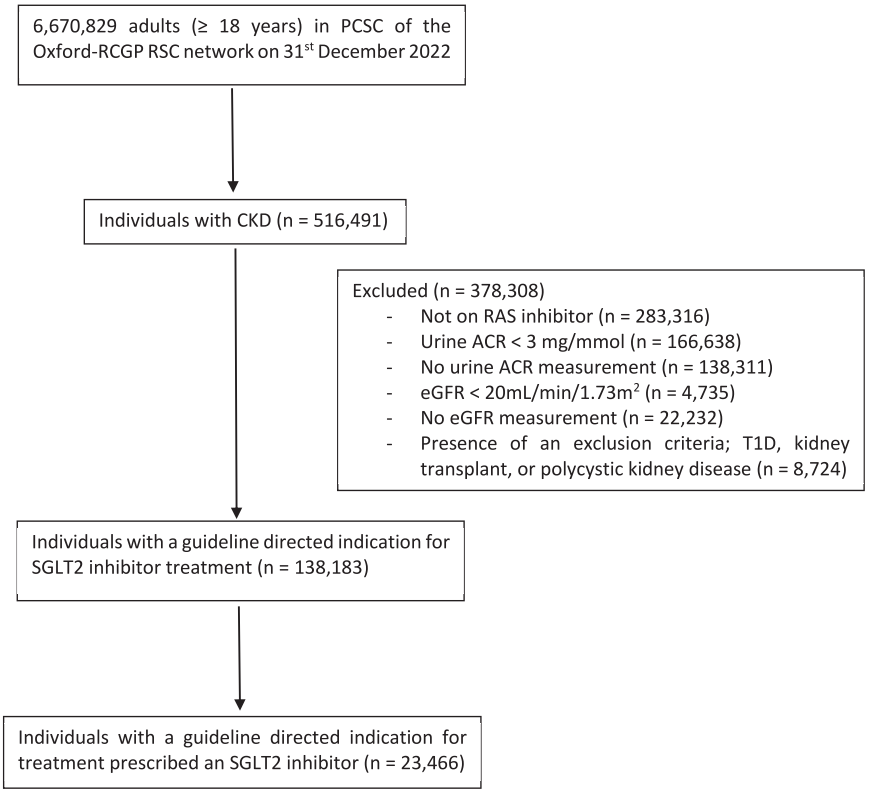


***Fig. 1:*** Participant flow diagram. There may be multiple reasons why an individual did not meet guideline directed indications for SGLT2 inhibitor treatment. The exclusion reasons relating to urine ACR (urine ACR <3 mg/mmol and no urine ACR measurement) do not apply to all guideline recommendations. PCSC—Primary Care Sentinel Cohort, Oxford-RCGP RSC—Oxford-Royal College of General Practitioners Research and Surveillance Centre, CKD—chronic kidney disease, T1D—type 1 diabetes, SGLT2 inhibitor—sodium-glucose co-transporter 2 inhibitor, eGFR—estimated glomerular filtration rate, urine ACR—urine albumin-to-creatinine ratio, RAS inhibitor—renin-angiotensin system inhibitor.

as a systolic blood pressure of <70 mmHg or >260 mmHg, and a diastolic blood pressure of <40 mmHg or >150 mmHg. Body mass index (BMI) values were excluded if they were recorded as <10 kg/m$^2$ or >100 kg/m$^2$. Glycated haemoglobin (HbA1c) outliers were defined as <20 mmol/mol and >200 mmol/mol, and creatinine outliers were defined as <20 μmol/L or >3000 μmol/L.

## Statistical analysis

Descriptive statistics were used to report the primary and secondary outcome measures and describe the characteristics of the CKD population. Mean (standard deviation [SD]) or median (interquartile range [IQR]) were used to describe continuous variables and frequencies and percentages were used to describe categorical variables.

### *Primary outcome measure*

The primary outcome was the proportion of the CKD population that met guideline directed indications for SGLT2 inhibitor treatment, according to four guidelines. This included the UKKA Clinical Practice Guideline, ADA-KDIGO Consensus Report, NICE Guideline, and NICE Technology Appraisal.[5–8] We estimated the proportion that met at least one indication for SGLT2 inhibitor treatment and this proportion separately for each guideline, by dividing the number of individuals in the CKD population that fulfilled guideline recommendations for treatment by the total CKD population. If an individual was missing data for clinical measures relating to the recommendations (e.g., eGFR or urine ACR) we assumed that they did not meet the guideline recommendations for treatment. We also reported the reasons why individuals were not indicated for treatment, separately for each guideline.

### *Secondary outcome measure*

The secondary outcome was the proportion of the CKD population indicated for treatment, according to guideline directed indications, who were prescribed an SGLT2 inhibitor. This was estimated for those that met at least one indication for SGLT2 inhibitor treatment

and separately for each guideline, by diving the number of individuals in the CKD population prescribed an SGLT2 inhibitor by the CKD population that fulfilled guideline recommendations for treatment.

*Tertiary outcome measure*

The tertiary outcome was a description of the characteristics of the CKD population that met at least one guideline directed indication for SGLT2 inhibitor treatment, and factors associated with SGLT2 inhibitor prescribing. We compared the characteristics of those prescribed an SGLT2 inhibitor to those who were not. We used a logistic regression model to investigate factors associated with SGLT2 inhibitor prescribing. Exposure variables under consideration were age (years), sex (male, female), ethnicity (White, Asian, Black Mixed, Other), socio-economic status (IMD quintile 1–5), eGFR category (≥60 mL/min/1.73 $m^2$, 45–59 mL/min/1.73 $m^2$, 30–44 mL/min/1.73 $m^2$, 15–29 mL/min/1.73 $m^2$, <15 mL/min/1.73 $m^2$), urine ACR category (<3 mg/mmol, 3–30 mg/mmol, >30 mg/mmol), history of cardiovascular disease (absent, present), and history of heart failure (absent or present). We constructed directed acyclic graphs to identify confounders (Supplementary Figure S1). This information was used to develop three separate models to investigate the association between the exposure variables and SGLT2 inhibitor prescribing (outcome variable): crude, unadjusted model, multivariable model 1, and multivariable model 2. The crude, unadjusted model was used to allow the reader to better understand the confounding aspects of the associations. Multivariable model 1 was used to investigate the association between socio-demographic characteristics, including age, sex, ethnicity, and socio-economic status and SGLT2 inhibitor prescribing. Multivariable model 2 was used to investigate the association between eGFR, urine ACR, cardiovascular disease and heart failure and SGLT2 inhibitor prescribing.

Multivariable model 1 was adjusted for the following confounders; age (years), sex (male, female), ethnicity (White, Asian, Black Mixed, Other), socio-economic status (IMD quintile 1–5), BMI category (<18.5 kg/$m^2$, ≥18.5–<25 kg/$m^2$, ≥25–<30 kg/$m^2$, ≥30–<35 kg/$m^2$, ≥35–<40 kg/$m^2$, ≥40 kg/$m^2$), HbA1c category (<53 mmol/mol, ≥53–<64 mmol/mol, ≥64–<75 mmol/mol, ≥75–<85 mmol/mol, ≥85 mmol/mol), eGFR category (≥60 mL/min/1.73 $m^2$, 45–59 mL/min/1.73 $m^2$, 30–44 mL/min/1.73 $m^2$, 15–29 mL/min/1.73 $m^2$, <15 mL/min/1.73 $m^2$), urine ACR category (<3 mg/mmol, 3–30 mg/mmol, >30 mg/mmol), history of cardiovascular disease (absent or present), history of heart failure (absent, present), and history of hypertension (absent, present). Multivariable model 2 was adjusted for the confounders in multivariable model 1 in addition to the duration of T2D (years) and current prescription for a diuretic (absent, present). Odds ratios (ORs) with 95% confidence intervals (CI) and p-values were reported for each variable. All data analyses were undertaken in R version 4.3.0 (2023-04-21).

### Missing data

We reported missing data when describing the characteristics of the CKD population. For the logistic regression model clinical measures (including BMI, eGFR, urine ACR and HbA1c) were assigned as missing if they were recorded more than two years prior to either the 31st December 2022, or the date of first SGLT2 inhibitor prescription for those prescribed an SGLT2 inhibitor.

We addressed missing data in the logistic regression model. We assumed that missing data for ethnicity and socio-economic status were unlikely to be missing at random. Individuals with missing ethnicity data were assigned to the 'White' ethnicity category. Where the postcode of an individual's registered home address was missing, we used the postcode of the practice they were registered at to infer the individual's socio-economic status.

We assumed that missing data for clinical measures (including BMI, eGFR, urine ACR and HbA1c) were missing at random, and that any systematic differences in the characteristics between individuals with and without missing values could be explained by differences in the observed data.[16] Multivariate imputation by chained equations was used to impute missing values based on the observed values for a given individual and regressed on other variables in the imputation model.[17] We replaced missing values with predictions from the regression model that reflected the relationships observed in the data. We made multiple predictions (n = 5) for each missing value, creating multiple 'complete' datasets and the result were combined using Rubin's rules.

### Sub-group analyses

We reported all outcome measures according to T2D status, separately applying the guidelines to the CKD population with T2D (CKD-T2D cohort) and the CKD population without T2D (CKD without T2D cohort). Individual recommendations in each of the four guidelines were examined separately, to gain a better understanding of how they apply to the CKD population and SGLT2 inhibitor prescribing.

### Sensitivity analyses

We performed two sensitivity analyses of the logistic regression model, exploring factors associated with SGLT2 inhibitor prescribing using 1) complete cases, and 2) missing indicator method, to examine the impact of using multiple imputation to address missing data in the primary analysis.

### Patient and public involvement

No patients or members of the public were involved in the design or conduct of the study or interpretation of

the results. However, we plan to work in partnership with patients and the public to disseminate the findings.

### Role of the funding source

There was no funding source for this study. The authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication. PS had final responsibility for the decision to submit for publication.

## Results

### Implementation of SGLT2 inhibitor guidelines

*Primary outcome*

Of 6,670,829 adults we identified 516,491 (7.7%) with CKD, including 32.8% (n = 169,443) who had co-existing T2D. In the overall CKD cohort, 85.6% (n = 442,069) had a diagnostic code for CKD, including 1.4% (n = 7168) who had a code for dialysis or kidney transplantation. Additionally, 39.3% (n = 203,212) had an eGFR <60 mL/min/1.73 $m^2$ (based on 2 serum creatinine readings taken a minimum of 90 days apart) and 20.3% (n = 104,930) had proteinuria (defined as a urine ACR ≥3 mg/mmol or urine PCR ≥15 mg/mmol based on 2 readings taken a minimum of 90 days apart).

In the overall CKD cohort, 26.8% (n = 138,183) met at least one guideline directed indication for SGLT2 inhibitor treatment. A higher proportion of people with CKD and co-existing T2D were indicated for treatment, compared to those without T2D (62.8% [n = 106,468] vs. 9.1% [n = 31,715]) (Fig. 2).

The extent to which the guidelines applied to the CKD population, reported separately for each guideline, are shown in Supplementary Figure S2. The ADA-KDIGO Consensus Report applied to the largest proportion of people with CKD and T2D (62.4% [n = 105,707]), and the NICE Guideline applied to the lowest proportion (33.2% [n = 56,205). In those without T2D, the UKKA Clinical Practice Guideline was applicable to the highest proportion of people (9.1% [n = 31,571]).

*Secondary outcome*

In the overall CKD cohort, SGLT2 inhibitors were prescribed to 17.0% (n = 23,466) of those who met at least one guideline directed indication for treatment. SGLT2 inhibitors were predominantly prescribed in people with co-existing T2D; 22.0% (n = 23,464) of the CKD-T2D cohort and <0.1% (n = 2) of the CKD without T2D cohort indicated for treatment were prescribed an SGLT2 inhibitor (Fig. 3).

SGLT2 inhibitor prescribing according to each separate guideline is shown in Supplementary Figure S3. In the CKD-T2D population, the highest prescribing rates were observed in those meeting the NICE Guideline (24.7% [n = 13,908]), and the lowest in those who met the NICE Technology Appraisal (18.7% [n = 12,290]). The 2 individuals with CKD without T2D indicated for an SGLT2 inhibitor that were prescribed one both met the UKKA Clinical Practice Guideline, recommending treatment in those with CKD and heart failure in the absence of T2D.

Supplementary Figures S4 and S5 consider the individual indications for SGLT2 inhibitor treatment in each of the four guidelines separately.

### Exploring reasons why individuals did not meet guideline directed indications for treatment

There were multiple reasons why individuals did not meet guideline directed indications for SGLT2 inhibitor treatment (Fig. 4). Of those who were not indicated for

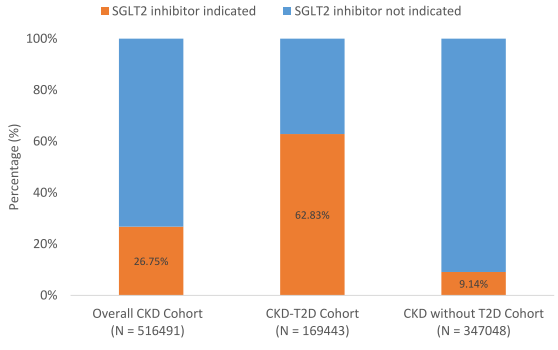


***Fig. 2:*** Proportion of CKD population that met at least one guideline directed indication for SGLT2 inhibitor treatment. The red represents the CKD population that met at least one guideline directed indication for SGLT2 inhibitor treatment. The blue represents the CKD population that did not meet a guideline directed indication for SGLT2 inhibitor treatment. N refers to the total number of people in the cohort. CKD—chronic kidney disease, T2D—type 2 diabetes, SGLT2 inhibitor—sodium-glucose co-transporter 2 inhibitor.

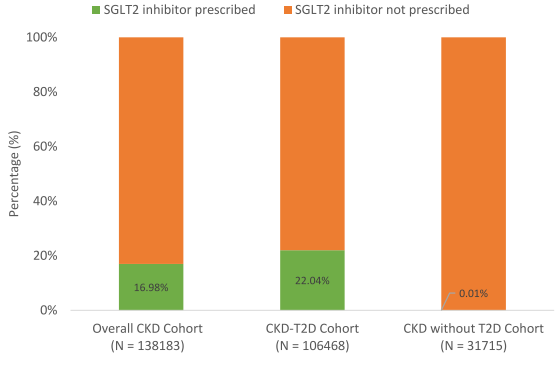


***Fig. 3:*** Proportion of CKD population indicated for treatment prescribed an SGLT2 inhibitor. The green represents the CKD population with an indication for SGLT2 inhibitor treatment that was prescribed an SGLT2 inhibitor. The red represents the CKD population with an indication for SGLT2 inhibitor treatment that was not prescribed an SGLT2 inhibitor. N refers to the total number of people in the cohort. CKD—chronic kidney disease, T2D—type 2 diabetes, SGLT2 inhibitor—sodium-glucose co-transporter 2 inhibitor.

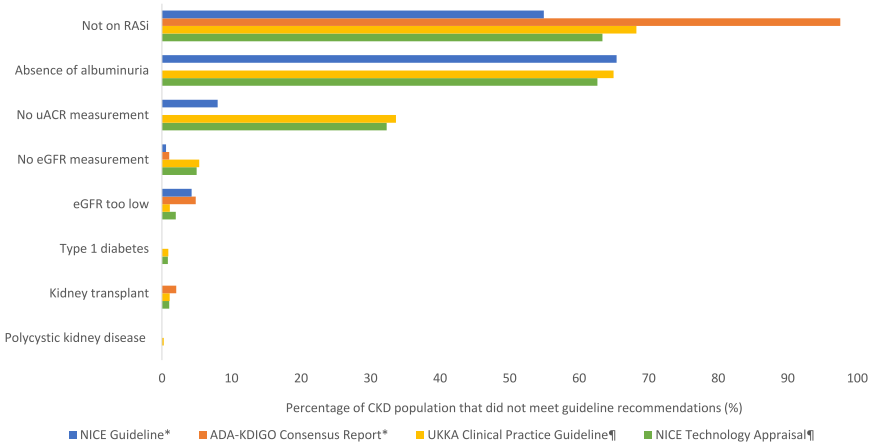


*Fig. 4:* Exploration of why patients did not meet guideline directed indications for SGLT2 inhibitor treatment. The blue represents the NICE Guideline, the red represents the ADA-KDIGO Consensus Report, the yellow represents the UKKA Clinical Practice Guideline, and the green represents the NICE Technology Appraisal. Percentages do not add up to 100% as there may be multiple reasons why patients did not meet guideline directed indications for SGLT2 inhibitor treatment. eGFR too low defined as eGFR <20 mL/min/1.73 $m^2$ or 25 mL/min/1.73 $m^2$ depending on the guideline. *Applies to CKD-T2D cohort. ¶Applies to overall CKD cohort. CKD—chronic kidney disease, T2D—type 2 diabetes, SGLT2 inhibitor—sodium-glucose co-transporter 2 inhibitor, NICE—National Institute for Health and Care Excellence, ADA—American Diabetes Association, KDIGO—Kidney Disease: Improving Global Outcomes, UKKA—United Kingdom Kidney Association, RAS inhibitor—renin-angiotensin system inhibitor, eGFR—estimated glomerular filtration rate, uACR—urine albumin-to-creatinine ratio.

treatment, over half were not prescribed a renin-angiotensin system (RAS) inhibitor (UKKA Clinical Practice Guideline—68.2% [n = 283,316], ADA-KDIGO Consensus Report—97.6% [n = 62,183], NICE Guideline—54.9% [n = 62,183], NICE Technology Appraisal—63.3% [n = 283,316]). Albuminuria thresholds were incorporated into the recommendations of three of the four guidelines we investigated. Almost two thirds did not meet indications for treatment due to either the absence of albuminuria, or albuminuria at a level below the guideline threshold (UKKA Clinical Practice Guideline—65.0% [n = 269,720], NICE Guideline—65.4% [n = 74,034], NICE Technology Appraisal—62.6% [n = 280,132]), and up to a further third due to a lack of albuminuria assessment (UKKA Clinical Practice Guideline—33.7% [n = 139,740], NICE Guideline—8.0% [n = 9061], NICE Technology Appraisal—32.3% [n = 144,538]). Less than 5.0% were not indicated for treatment due to eGFR being too low (defined as eGFR <25 mL/min/1.73 $m^2$ or <20 mL/min/1.73 $m^2$, depending on the guideline), and a small proportion (<2.0%) due to type 1 diabetes, polycystic kidney disease and kidney transplantation.

### Factors associated with SGLT2 inhibitor prescribing

We explored factors associated with SGLT2 inhibitor prescribing in individuals meeting at least one guideline directed indication for SGLT2 inhibitor treatment. This analysis was restricted to those with CKD and co-existing T2D, as there were only 2 individuals without T2D prescribed an SGLT2 inhibitor. Baseline demographic and clinical differences between those prescribed an SGLT2 inhibitor and those who were not are summarised in Table 2.

In adjusted multivariable analysis in people with CKD and T2D (Table 3), female sex (OR 0.69, 95% CI 0.67–0.72, p <0.0001), Black ethnicity (OR 0.84, 95% CI 0.77–0.91, p <0.0001) and increasing age (OR 0.95, 95% CI 0.95–0.95, p <0.0001) were associated with a lower likelihood of SGLT2 inhibitor prescription. Lower socio-economic status was associated with lower odds of SGLT2 inhibitor prescribing, with an OR of 0.72 (95% CI 0.68–0.76, p <0.0001), 0.78 (95% CI 0.74–0.82, p <0.0001), 0.85 (95% CI 0.81–0.90, p <0.0001), and 0.94 (95% CI 0.89–0.99, p = 0.026) for IMD quintile 1 (most deprived), IMD quintile 2, IMD quintile 3, and IMD quintile 4, respectively when compared to IMD quintile 5 (least deprived).

Having an eGFR <60 mL/min/1.73 $m^2$ was associated with lower likelihood of SGLT2 inhibitor prescribing compared to those with an eGFR ≥60 mL/min/1.73 $m^2$ (eGFR 45–60 mL/min/1.73 $m^2$ OR 0.65, 95% CI 0.62–0.68, p <0.0001, eGFR 30–45 mL/min/1.73 $m^2$ OR 0.73, 95% CI 0.69–0.78, p <0.0001, eGFR 15–30 mL/min/1.73 $m^2$ OR 0.52, 95% CI 0.46–0.60, p <0.0001, eGFR <15 mL/min/1.73 $m^2$ OR 0.03, 95% CI 0.00–0.23, p = 0.0037, respectively). The presence of albuminuria (urine ACR 3–30 mg/mmol) was also associated with a lower likelihood of SGLT2 inhibitor use, compared to those without albuminuria (OR 0.78, 95% CI 0.75–0.82, p <0.0001). Heart failure and cardiovascular disease were associated with a higher likelihood of SGLT2

| Characteristic | CKD Cohort (N = 138,183) | | CKD-T2D Cohort (N = 106,468) | |
|---|---|---|---|---|
| | SGLT2 inhibitor prescribed (N = 23,466) | SGLT2 inhibitor not prescribed (N = 114,717) | SGLT2 inhibitor prescribed (N = 23,464) | SGLT2 inhibitor not prescribed (N = 83,004) |
| **Age—years** | 68.2 ± 11.7 | 75.4 ± 12.0 | 68.2 ± 11.7 | 74.3 ± 11.5 |
| **Female sex—n (%)** | 7748 (33.0) | 54,443 (47.5) | 7748 (33.0) | 38,168 (46.0) |
| **Ethnicity—n (%)** | | | | |
| White | 18,365 (78.3) | 96,119 (83.8) | 18,365 (78.3) | 67,720 (81.6) |
| Asian | 2982 (12.7) | 8224 (7.2) | 2982 (12.7) | 7404 (8.9) |
| Black | 921 (3.9) | 4004 (3.5) | 920 (3.9) | 3386 (4.1) |
| Mixed | 242 (1.0) | 851 (0.7) | 242 (1.0) | 704 (0.8) |
| Other | 243 (1.0) | 800 (0.7) | 243 (1.0) | 659 (0.8) |
| Missing | 713 (3.0) | 4719 (4.1) | 712 (3.0) | 3131 (3.8) |
| **IMD quintile—n (%)** | | | | |
| 1 (most deprived) | 5021 (21.4) | 20,568 (17.9) | 5021 (21.4) | 16,160 (19.5) |
| 2 | 4542 (19.4) | 21,267 (18.5) | 4542 (19.4) | 15,976 (19.2) |
| 3 | 4425 (18.9) | 22,438 (19.6) | 4423 (18.9) | 16,071 (19.4) |
| 4 | 4477 (19.1) | 23,291 (20.3) | 4477 (19.1) | 16,246 (19.6) |
| 5 (least deprived) | 4038 (17.2) | 22,176 (19.3) | 4038 (17.2) | 15,058 (18.1) |
| Missing | 963 (4.1) | 4977 (4.3) | 963 (4.1) | 3493 (4.2) |
| **Body mass index** | | | | |
| Body mass index—kg/$m^2$ | 31.2 ± 6.5 | 30.1 ± 6.4 | 31.2 ± 6.5 | 30.7 ± 6.5 |
| Missing | 83 (0.4) | 512 (0.4) | 83 (0.4) | 207 (0.2) |
| **Blood pressure—mmHg** | | | | |
| Systolic | 131.3 ± 17.8 | 135.3 ± 17.1 | 131.3 ± 17.8 | 135.9 ± 16.7 |
| Missing | 10,268 (43.8) | 47,319 (41.2) | 10,266 (43.8) | 34,510 (41.6) |
| Diastolic | 75.1 ± 11.1 | 74.7 ± 10.9 | 75.1 ± 11.1 | 74.9 ± 10.7 |
| Missing | 10,327 (44.0) | 47,443 (41.4) | 10,325 (44.0) | 34,597 (41.7) |
| **HbA1c** | | | | |
| HbA1c—mmol/mol | – | – | 61.4 ± 18.2 | 55.9 ± 15.8 |
| Missing | – | – | 231 (1.0) | 281 (0.3) |
| **Duration T2D—years** | – | – | 12.4 ± 8.5 | 13.3 ± 8.2 |
| **eGFR** | | | | |
| Mean (SD)—mL/min/1.73 $m^2$ | 73.7 ± 24.8 | 63.3 ± 22.3 | 73.7 ± 24.8 | 67.2 ± 22.2 |
| Distribution—n (%) | | | | |
| ≥60 mL/min/1.73 $m^2$ | 15,294 (65.2) | 56,659 (49.4) | 15,294 (65.2) | 47,345 (57.0) |
| ≥45 to <60 mL/min/1.73 $m^2$ | 4950 (21.1) | 30,897 (26.9) | 4949 (21.1) | 22,748 (27.4) |
| ≥30 to <45 mL/min/1.73 $m^2$ | 2586 (11.0) | 22,807 (19.9) | 2585 (11.0) | 10,545 (12.7) |
| ≥15 to <30 mL/min/1.73 $m^2$ | 609 (2.6) | 3970 (3.5) | 609 (2.6) | 2111 (2.5) |
| <15 mL/min/1.73 $m^2$ | 5 (0.0) | 311 (0.3) | 5 (0.0) | 228 (0.3) |
| Missing | 22 (0.1) | 73 (0.1) | 22 (0.1) | 27 (0.0) |
| **Urine ACR** | | | | |
| Median (IQR)—mg/mmol | 4.6 (1.7–14.4) | 3.0 (1.1–10.1) | 4.6 (1.7–14.4) | 3.3 (1.2–10.0) |
| Distribution—n (%) | | | | |
| <3 mg/mmol | 7934 (33.8) | 52,485 (45.8) | 7934 (33.8) | 37,339 (45.0) |
| ≥3 to ≤30 mg/mmol | 10,747 (45.8) | 41,863 (36.5) | 10,747 (45.8) | 34,645 (41.7) |
| >30 mg/mmol | 3311 (14.1) | 12,688 (11.1) | 3311 (14.1) | 8517 (10.3) |
| Missing | 1474 (6.3) | 7681 (6.7) | 1472 (6.3) | 2503 (3.0) |
| **CMMS—median (IQR)** | 1.0 (0.5–1.5) | 1.0 (0.5–1.5) | 1.0 (0.5–1.5) | 1.0 (0.5–1.5) |
| **Co-morbidities—n (%)** | | | | |
| Cardiovascular disease | 11,717 (49.9) | 57,001 (49.7) | 11,715 (49.9) | 35,234 (42.4) |
| Heart failure | 7172 (30.6) | 29,223 (25.5) | 7170 (30.6) | 12,192 (14.7) |
| Hypertension | 19,577 (83.4) | 102,071 (89.0) | 19,575 (83.4) | 74,950 (90.3) |
| Type 2 diabetes | 23,464 (100) | 83,004 (72.4) | – | – |

(Table 2 continues on next page)

| Characteristic | CKD Cohort (N = 138,183) | | CKD-T2D Cohort (N = 106,468) | |
|---|---|---|---|---|
| | SGLT2 inhibitor prescribed (N = 23,466) | SGLT2 inhibitor not prescribed (N = 114,717) | SGLT2 inhibitor prescribed (N = 23,464) | SGLT2 inhibitor not prescribed (N = 83,004) |
| (Continued from previous page) | | | | |
| **Medications—n (%)** | | | | |
| Diuretic | 9933 (42.3) | 43,995 (38.4) | 9931 (42.3) | 28,580 (34.4) |

IMD—index of multiple deprivation, CKD—chronic kidney disease, T2D—type 2 diabetes, eGFR—estimated glomerular filtration rate, urine ACR—urine albumin-to-creatinine ratio, HbA1c—glycated haemoglobin, CMMS—Cambridge Multi-Morbidity Score, SGLT2 inhibitor—sodium-glucose co-transporter-2 inhibitor, IQR—interquartile range, SD—standard deviation. Plus-minus values are means ± standard deviations. Percentages may not total 100% due to rounding. Clinical measures (including body mass index, eGFR, urine ACR and HbA1c) were assigned as missing if they were recorded more than two years prior to either 31st December 2022, or the date of first SGLT2 inhibitor prescription for those prescribed an SGLT2 inhibitor. Cardiovascular disease defined as ischaemic heart disease, stroke, and peripheral arterial disease.

*Table 2:* **Baseline characteristics of CKD cohort indicated for SGLT2 inhibitor treatment stratified by T2D Status and prescription of SGLT2 inhibitor.**

inhibitor use (OR 3.59, 95% CI 3.42–3.77, p <0.0001, OR 1.08, 95% CI 1.04–1.12, p <0.0001, respectively).

These findings were broadly consistent in the sensitivity analyses using complete cases and missing indicator method (Supplementary Tables S1 and S2, respectively).

## Discussion

In this study, we present a detailed analysis of the implementation of four SGLT2 inhibitor guidelines in a large and nationally representative primary care population with CKD. We found that these guidelines, which incorporate the findings from the latest clinical trials, applied to only 26.8% of people with CKD, including 62.8% with co-existing T2D and 9.1% without T2D. This is likely to be an under-estimate of the population with CKD who may benefit from treatment. The key barriers limiting the extent to which SGLT2 inhibitor guidelines apply to real-world clinical practice were the under-utilisation of RAS inhibitor therapy and inadequate assessment of albuminuria. These gaps in the implementation of guidelines are in keeping with previous data. Estimates from large observational studies show that despite long established evidence and substantial clinical experience, RAS inhibitors remain under-used in CKD.[18,19] Sub-optimal albuminuria testing in the CKD population, particularly in people without diabetes, continues to be a problem, with estimates ranging from as low as 10–50%.[19,20]

Our findings highlight that SGLT2 inhibitor guidelines in CKD have not yet been successfully implemented into routine clinical practice in England, particularly in those without T2D. Of those indicated for treatment, SGLT2 inhibitors were prescribed to 22.0% with co-existing CKD and T2D, and <0.1% with CKD without T2D. These observations are consistent with studies performed in other settings, notably in the United States, which has a significantly different healthcare structure. A cross-sectional study of 72,240 adults with CKD stages 3–5 in the Mass General Brigham CKD registry in March 2021 estimated that SGLT2 inhibitors were prescribed in 6.0% of people with diabetes and 0.3% without diabetes.[21] Similar findings were observed in a cross-sectional analysis of SGLT2 inhibitor prescriptions in people with T2D in the Veterans Health Administration (VHA) over a 2-year period until 31st December 2020.[22] SGLT2 inhibitors were prescribed to 11.0% of those with T2D and 10.0% of those with T2D and co-existing CKD. Importantly, in contrast to the present study these studies were published prior to the dissemination of the latest SGLT2 inhibitor guidelines, and the VHA study did not examine those with non-diabetic CKD.

We observed that individuals at higher risk of adverse outcomes were paradoxically less likely to receive SGLT2 inhibitor treatment. An eGFR <60 mL/min/1.73 $m^2$ and the presence of albuminuria (urine ACR 3–30 mg/mmol) were both associated with a lower likelihood of SGLT2 inhibitor use, compared to individuals with normal eGFR and without albuminuria. Similar results were reported in people with T2D and CKD in the VHA study.[22] They found that albuminuria (urine ACR >300 mg/g) was associated with a lower likelihood of receiving an SGLT2 inhibitor, compared to individuals without albuminuria (OR 0.91, 95% CI 0.89–0.93). Moreover, SGLT2 inhibitors were less likely to be used in those at higher risk of end-stage kidney disease (ESKD) (>5% ESKD risk vs. <1% ESKD risk OR 0.63, 95% CI 0.59–0.67). Taken together these findings suggest that SGLT2 inhibitor guidelines in CKD, incorporating the latest trial evidence, have thus far had limited impact on clinical practice. This is particularly relevant as the cardio-renal protection of SGLT2 inhibitors extends to those with an eGFR <30 mL/min/1.73 $m^2$, and those with lower eGFR and albuminuria are most likely to benefit.[1–3] Conversely, we found that a history of heart failure and cardiovascular disease were associated with a greater likelihood of SGLT2 inhibitor use, which may reflect the more established use in these clinical scenarios.

We identified disparities in the use of SGLT2 inhibitors in people with CKD and T2D, which may worsen existing inequalities in kidney and cardiovascular health outcomes of people with CKD.[23] The observed lower

| Variable | n prescribed SGLT2i/N indicated | Percentage indicated prescribed SGLT2i, % | Unadjusted Odds Ratio (95% CI) | p-value | Multivariable Model 1[a] Odds Ratio (95% CI) | p-value | Multivariable Model 2[b] Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | 23,464/106,468 | 22.04 | 0.94 (0.94–0.95) | <0.0001 | 0.95 (0.95–0.95) | <0.0001 | – | – |
| **Sex** | | | | | | | | |
| Male | 15,716/60,552 | 25.95 | 1.0 (Reference) | | | | – | – |
| Female | 7748/45,916 | 16.87 | 0.58 (0.56–0.60) | <0.0001 | 0.69 (0.67–0.72) | <0.0001 | – | – |
| **Ethnicity** | | | | | | | | |
| White | 19,077/89,928 | 21.21 | 1.0 (Reference) | | 1.0 (Reference) | | – | – |
| Asian | 2982/10,386 | 28.71 | 1.50 (1.43–1.57) | <0.0001 | 1.06 (1.00–1.12) | 0.033 | – | – |
| Black | 920/4306 | 21.37 | 1.01 (0.94–1.09) | 0.81 | 0.84 (0.77–0.91) | <0.0001 | – | – |
| Mixed | 242/946 | 25.58 | 1.28 (1.10–1.48) | 0.0011 | 0.97 (0.82–1.14) | 0.69 | – | – |
| Other | 243/902 | 26.94 | 1.37 (1.18–1.59) | <0.0001 | 1.10 (0.93–1.31) | 0.26 | – | – |
| **IMD quintile** | | | | | | | | |
| 5 (least deprived) | 4113/19,402 | 21.20 | 1.0 (Reference) | | | | | |
| 4 | 4662/21,563 | 21.62 | 1.03 (0.98–1.08) | 0.30 | 0.94 (0.89–0.99) | 0.026 | – | – |
| 3 | 4577/21,254 | 21.53 | 1.02 (0.97–1.07) | 0.41 | 0.85 (0.81–0.90) | <0.0001 | – | – |
| 2 | 4902/22,167 | 22.11 | 1.06 (1.01–1.11) | 0.024 | 0.78 (0.74–0.82) | <0.0001 | – | – |
| 1 (most deprived) | 5210/22,082 | 23.59 | 1.15 (1.10–1.20) | <0.0001 | 0.72 (0.68–0.76) | <0.0001 | – | – |
| **eGFR mL/min/1.73 m$^2$** | | | | | | | | |
| ≥60 | 17,575/64,886 | 27.09 | 1.0 (Reference) | | – | – | 1.0 (Reference) | |
| ≥45 to <60 | 3657/26,431 | 13.84 | 0.43 (0.42–0.45) | <0.0001 | – | – | 0.65 (0.62–0.68) | <0.0001 |
| ≥30 to <45 | 1905/12,470 | 15.28 | 0.49 (0.46–0.51) | <0.0001 | – | – | 0.73 (0.69–0.78) | <0.0001 |
| ≥15 to <30 | 325/2447 | 13.28 | 0.41 (0.37–0.47) | <0.0001 | – | – | 0.52 (0.46–0.60) | <0.0001 |
| <15 | 2/234 | 0.85 | 0.06 (0.01–0.39) | 0.0086 | – | – | 0.03 (0.00–0.23) | 0.004 |
| **Urine ACR mg/mmol** | | | | | | | | |
| <3 | 9646/47,071 | 20.49 | 1.0 (Reference) | | – | – | 1.0 (Reference) | |
| ≥3 to ≤30 | 10,263/46,797 | 21.93 | 1.09 (1.06–1.13) | <0.0001 | – | – | 0.78 (0.75–0.82) | <0.0001 |
| >30 | 3555/12,600 | 28.21 | 1.53 (1.44–1.61) | <0.0001 | – | – | 1.08 (1.01–1.15) | 0.020 |
| **Co-morbidities** | | | | | | | | |
| CVD | | | | | | | | |
| Absent | 15,562/70,634 | 22.03 | 1.0 (Reference) | | – | – | 1.0 (Reference) | |
| Present | 7902/35,834 | 22.05 | 1.00 (0.97–1.03) | 0.94 | – | – | 1.08 (1.04–1.12) | 0.0001 |
| Heart failure | | | | | | | | |
| Absent | 17,012/87,824 | 19.37 | 1.0 (Reference) | | – | – | 1.0 (Reference) | |
| Present | 6452/18,644 | 34.61 | 2.20 (2.13–2.28) | <0.0001 | – | – | 3.59 (3.42–3.77) | <0.001 |

CVD—cardiovascular disease, IMD—index of multiple deprivation, eGFR—estimated glomerular filtration rate, urine ACR—urine albumin-to-creatinine ratio, HbA1c—glycated haemoglobin, BMI—body mass index, CI—confidence interval, SGLT2i—sodium-glucose co-transporter 2 inhibitor, CKD—chronic kidney disease, T2D—type 2 diabetes. CVD defined as ischaemic heart disease, stroke, and peripheral arterial disease. [a]Multivariable model 1 includes the following covariates: age (years), sex (male, female), ethnicity (White, Asian, Black Mixed, Other), IMD quintile (IMD quintile 1–5), BMI category (<18.5 kg/m$^2$, ≥18.5–<25 kg/m$^2$, ≥25–<30 kg/m$^2$, ≥30–<35 kg/m$^2$, ≥35–<40 kg/m$^2$, ≥40 kg/m$^2$), HbA1c category (<53 mmol/mol, ≥53–<64 mmol/mol, ≥64–<75 mmol/mol, ≥75–<85 mmol/mol, ≥85 mmol/mol), eGFR category (≥60 mL/min/1.73 m$^2$, 45–59 mL/min/1.73 m$^2$, 30–44 mL/min/1.73 m$^2$, 15–29 mL/min/1.73 m$^2$, <15 mL/min/1.73 m$^2$), urine ACR category (<3 mg/mmol, 3–30 mg/mmol, >30 mg/mmol), cardiovascular disease (absent, present), heart failure (absent, present), and hypertension (absent, present). [b]Multivariable model 2 includes the covariates in model 1 in addition to duration of type 2 diabetes (years) and diuretic prescription (absent, present). N = 106,468.

***Table 3:*** **Multivariable logistic regression model exploring factors associated with SGLT2 inhibitor prescribing in CKD-T2D cohort meeting guideline directed indications for SGLT2 inhibitor treatment.**

likelihood of SGLT2 inhibitor use in females, individuals of Black ethnicity, older people, and those of lower socio-economic status is consistent with published data from the United States. A cross-sectional analysis of 1 million adults with T2D from the VHA found non-White ethnic groups had a significantly lower likelihood of SGLT2 inhibitor prescription compared with patients of White ethnicity, after adjusting for patient and system level factors.[24] Similarly, a retrospective cohort study of SGLT2 inhibitor use in nearly 1 million people with T2D in the United States showed Black ethnicity, female sex, and lower socio-economic status were associated with a lower likelihood of SGLT2 inhibitor use.[25] These disparities were reproduced in a study of Medicare insured adults with T2D and CKD. Increasing age was associated with a lower likelihood of SGLT2 inhibitor use, and patients of Black ethnicity were significantly less likely to be prescribed an SGLT2 inhibitor compared to patients of White ethnicity, which persisted at all levels of socio-economic status.[26]

Identifying suitable individuals and initiating treatment is key to ensuring that the benefits of SGLT2 inhibitors translate to meaningful population level improvements in cardiovascular and kidney health outcomes for people living with CKD in real-world clinical practice.

Our findings highlight that people with CKD in England do not yet have adequate access to SGLT2 inhibitor therapy. We call for enhanced efforts to improve the utilisation of SGLT2 inhibitors in people with CKD, particularly in those at highest risk of adverse outcomes and without co-existing T2D. These efforts should focus on optimising RAS inhibitor use, improving the assessment of albuminuria, and developing strategies to facilitate the use of SGLT2 inhibitors in primary care. Central to this is the education of patients and healthcare professionals, and the implementation of pathways to support SGLT2 prescribing in primary care, with a particular focus on CKD without T2D. Interventions targeted towards equitable use of SGLT2 inhibitors are needed to prevent a worsening of the existing disparities in cardiovascular and kidney outcomes in diverse people living with CKD.[23] Organisations such as the London Kidney Network are already working closely with stakeholders and policymakers to address these factors.[27] These efforts should be supported and expanded nationally. Financial incentives in primary care should also be considered, including the incorporation of albuminuria assessment, as well as RAS inhibitor and SGLT2 inhibitor prescribing into pay-for-performance indicators for CKD.

This study has several limitations. Selection bias is a potential issue as practices participate in the Oxford-RCGP RSC network on a voluntary basis, and as a result, are slightly larger than average, unevenly distributed across regions, and marginally less deprived than the national population.[9] Despite these small differences the dataset is large and broadly representative of the English national population.[9] The timeframe between the publication of guidelines and data extraction for the study was relatively short (between 2 and 14 months). It may therefore have been too soon to observe changes in clinical practice.

Missing data and misclassification bias, arising from absent or incorrect coding are limitations of using routinely collected primary care data.[28] However, data quality and completeness in the Oxford-RCGP RSC network is enhanced by practice engagement through a dedicated team of practice liaison officers and an ontological approach to developing code sets.[9,11,29–31] Ontologies describe key concepts within a domain and their relationships, recognising that clinical concepts can be represented differently within a terminology, and ensuring the process of code set development is explicit and robust.[30] Moreover, the Quality and Outcomes Framework (QOF), a pay-for-performance incentive scheme introduced in England in 2004, has improved the coding of chronic diseases in primary care.[32]

We addressed missing data using multiple imputation techniques and performed sensitivity analyses with complete cases and using the missing indicator method, the findings of which were broadly consistent with the primary analysis. We adjusted for potential confounders in our models, but there may be unmeasured variables leading to residual confounding.

We were unable to establish if the reason an individual was not prescribed an SGLT2 inhibitor was due to a contraindication or intolerance from side effects, which may have led to an under-estimation of the proportion of patients indicated for SGLT2 inhibitor treatment. We were unable to determine if people were on the maximum tolerated dose of RAS inhibitor, or if the reason it was not prescribed was due to a contraindication. We assumed that individuals with a prescription were on the maximum tolerated dose, but this may have over-estimated the number of individuals meeting guideline recommendations for SGLT2 inhibitor treatment. The absence of RAS inhibitor prescription due to a contraindication is likely to represent a small proportion of people and is therefore unlikely to have a substantial impact on our findings.

This study, in a large and nationally representative primary care population with CKD, highlights that SGLT2 inhibitor guidelines have not yet been successfully adopted into clinical practice, most notably in people without co-existing T2D. The under-utilisation of RAS inhibitor therapy and inadequate assessment of albuminuria are key barriers limiting the extent to which these guidelines apply to patients in real-world clinical practice. Individuals at higher risk of adverse outcomes are paradoxically less likely to receive SGLT2 inhibitor treatment, and disparities in the utilisation of these drugs may worsen existing inequalities in kidney and cardiovascular health of people living with CKD. Enhanced efforts to embed SGLT2 inhibitors equitably into routine care for people with CKD are urgently needed, particularly in those at highest risk of adverse outcomes and in the absence of T2D.

#### Contributors

PS, RS, NC, MF and SdeL conceptualised the study. AF designed the study with input from all authors. FX performed the data extraction. AF performed the analysis with contributions from WH, WE, MJ, and JM. All authors, led by AF, were involved in data interpretation. AF led the drafting of the manuscript with contributions from all authors. All authors reviewed and approved the final draft of the manuscript. AF and WH directly accessed and verified the underlying data. PS had final responsibility for the decision to submit for publication and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

#### Data sharing statement

Access to pseudonymised patient level data will be considered upon reasonable request to the corresponding author. Researchers wishing to access such data will need to submit a data request form alongside a valid ethical approval and study protocol to the scientific committee at

the University of Oxford. Once approved, the researcher will need to complete the mandatory information governance training after which they will have access to the data. Once the analysed, only aggregated tables of results can be exported after appropriate statistical disclosure checks. Patient level data cannot be taken outside of the secure servers at the University of Oxford.

### Declaration of interests

AF, WE, MJ, JM, XF and NC declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

WH has had part of his academic salary funded from grant awards with Eli Lilly and Co., Novo Nordisk Ltd, AstraZeneca UK Ltd and Merck Sharp & Dohme Ltd. WH has no other relationships or activities that could appear to have influenced the submitted work. MF was awarded a grant from Merck Sharp & Dohme Ltd through the Nuffield Department of Primary Care Health Sciences, University of Oxford for an investigator led diabetes project unrelated to this study. MF has received personal speaker fees from Sanofi. MF has no other relationships or activities that could appear to have influenced the submitted work. DB was awarded grants through St George's University of London for NIHR portfolio studies in nephrology and cardiology, unrelated to this study, from AstraZeneca Externally Sponsored Scientific Research, Kidney Research UK, South-West London ICS Innovation Fund, and the Canadian Institute of Healthcare Research. DB has received consulting fees from Bayer, and payment for presentations from Bayer and Vifor Pharma. DB has received payment for sitting on an Advisory Board for the ORCHID and ADOPTION randomised controlled trials. DB has no other relationships or activities that could appear to have influenced the submitted work. RS is an unpaid trustee of the Blood Pressure Association. RS has no other relationships or activities that could appear to have influenced the submitted work. SdeL has received grants through the Nuffield Department of Primary Care Health Sciences, University of Oxford for investigator led studies in diabetes and cardio-metabolic disease, unrelated to this study, from GSK, Eli Lilly and Co., Novo Nordisk Ltd, Sanofi, and Merck Sharp & Dohme Ltd. SdeL has no other relationships or activities that could appear to have influenced the submitted work. PS received honoraria for presentations from AstraZeneca Ltd and Bayer Ltd. She received financial support from Bayer Ltd to attend the American Society of Nephrology Conference 2022 and Pharmacosmos to attend the European Renal Association Annual Scientific Meeting 2023. PS sits on the Executive Committee and is a trustee of the British & Irish Hypertension Society and Blood Pressure UK, which are all unpaid positions. PS has no other relationships or activities that could appear to have influenced the submitted work.

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102426.

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