BMJ Open Diabetes Research & Care

Cardiovascular and renal outcomes among patients with type 2 diabetes using SGLT2 inhibitors added to metformin: a population-based cohort study from the UK

Antonio Gonzalez Perez ,[1,2,3] David Vizcaya,[4] Maria E Sáez,[1,2] Marcus Lind,[5,6,7] Luis A Garcia Rodriguez[1]

To cite: Gonzalez Perez A, Vizcaya D, Sáez ME, *et al*. Cardiovascular and renal outcomes among patients with type 2 diabetes using SGLT2 inhibitors added to metformin: a population-based cohort study from the UK. *BMJ Open Diab Res Care* 2023;**11**:e003072. doi:10.1136/bmjdrc-2022-003072

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2022-003072).

Received 1 August 2022
Accepted 26 December 2022

For numbered affiliations see end of article.

Correspondence to
Dr Antonio Gonzalez Perez; agonzalez@ceife.es

ABSTRACT

Introduction Large numbers of patients with type 2 diabetes receive treatment with a sodium-glucose co-transporter-2 inhibitor (SGLT2i). We investigated whether the cardiorenal preventative effects found in clinical trials are also seen in clinical practice where patient characteristics and adherence to treatment differ.

Research design and methods Using UK primary care electronic health records, we followed two cohorts of patients with type 2 diabetes prescribed metformin: SGLT2is (N=12 978) and a matched comparator of patients not using an SGLT2i at the start of follow-up (N=44 286). Independent follow-ups were performed to identify the study outcomes: cardiovascular (CV) composite (comprising non-fatal myocardial infarction (MI)/ischemic stroke (IS) requiring hospitalization and CV death), severe renal disease, and all-cause mortality. Cox regression was used to estimate adjusted HRs.

Results Mean follow-up was 2.3 years (SGLT2i cohort) and 2.1 years (comparison cohort). Mean age was 59.6 years (SD ±10.2, SGLT2i cohort) and 60.4 years (SD ±10.0, comparison cohort). SGLT2i new users were associated with a reduced risk of the CV composite (HR 0.75, 95% CI: 0.61 to 0.93), severe renal disease (HR 0.55, 95% CI: 0.46 to 0.67), and all-cause mortality (HR 0.56, 95% CI: 0.49 to 0.63), with risk reductions similar irrespective of baseline chronic kidney disease. Reduced risks were seen for IS (HR 0.51, 95% CI: 0.36 to 0.74) but not MI (HR 0.98, 95% CI: 0.74 to 1.28). Results were consistent in sensitivity analyses.

Conclusions In this population-based study, SGLT2is were associated with significant CV, renal and survival benefits among individuals with type 2 diabetes on metformin; the CV benefit was driven by a reduced risk of ischemic stroke.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In randomized controlled trials (RCTs), sodium-glucose co-transporter-2 inhibitors (SGLT2is) have shown good efficacy in reducing the risk of adverse cardiovascular (CV) and renal events in patients with type 2 diabetes.

⇒ These benefits of SGLT2is have also been seen in observational studies, but have shown uncertainty around the evidence for benefits on myocardial infarction (MI).

⇒ RCTs and observational studies differ in the characteristics of patients studied and in their adherence to treatment.

WHAT THIS STUDY ADDS

⇒ In this matched retrospective cohort study among patients with type 2 diabetes using metformin, those who started an SGLT2i had significantly reduced risks of all-cause mortality (44% risk reduction), severe renal disease (50% risk reduction), a CV composite outcome (non-fatal MI/ischemic stroke requiring hospitalization/CV death; 25% risk reduction) and ischemic stroke (49% risk reduction) compared with those who did not start an SGLT2i. The risk of non-fatal MI was not significantly different between groups.

⇒ While clinical trials have shown a beneficial effect of SGLT2is in reducing risk of heart failure and CV events, our findings, based on observational data, help to understand that ischemic stroke (and not MI) is the likely driver of the reduction in CV events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results confirm that the benefits of SGLT2i in patients with type 2 diabetes observed in clinical trials are applicable to populations at low CV risk in real-world settings, thereby supporting an increasing role of SGLT2i in diabetes care.

INTRODUCTION

Sodium-glucose co-transporter-2 inhibitors (SGLT2is) are a relatively new class of glucose-lowering medication that are increasingly being used to treat patients with type 2 diabetes. Although initially introduced as second-line treatment after metformin,[1] these drugs have also shown efficacy in treating patients with renal and cardiovascular (CV) conditions. Large CV randomized controlled trials (RCTs) have shown that SGLT2is reduce the risk of hospitalization due to heart failure or CV death in patients with type 2 diabetes

by 23%.[2] Accordingly, SGLT2is are now recommended in the European Society of Cardiology guidelines as a first-line treatment option for patients with type 2 diabetes who are either drug naïve or on metformin, and with atherosclerotic CV disease or at high CV risk.[3] Furthermore, in April 2021, the US Food and Drug Administration approved the use of SGLT2is to treat chronic kidney disease (CKD) in patients with or without type 2 diabetes.[4]

Some studies have explored the extent to which the effects of SGLT2is found in RCTs are seen in clinical practice.[5–10] These have also generally found clear evidence that SGLT2is are associated with a reduced risk of mortality and adverse CV/renal outcomes when compared with other glucose-lowering drugs, although evidence relating to myocardial infarction (MI) is less certain.[5 9] Specifically, a recent large study failed to observe any reduction in MI risk associated with SGLT2i use.[10] We aimed to provide further evidence on this topic by investigating whether the benefits of SGLT2is on adverse CV and renal outcomes, and mortality, in patients with type 2 diabetes, that are seen in clinical trials, can be reproduced in an observational study from the UK among patients taking metformin.

RESEARCH DESIGN AND METHODS

Study design and data source

We undertook a population-based comparative cohort study using data from the IQVIA Medical Research Data-UK (IMRD-UK) primary care database, formerly known as The Health Improvement Network. The database contains the anonymized electronic health records (EHRs) of approximately 6% of the UK population[11] and the data held are representative of the UK in terms of age, sex and geographic distribution.[12] Clinical and prescribing information is entered by primary care practitioners (PCPs) as part of routine patient care. Medical events (including diagnoses, hospital referrals, etc) are recorded using Read codes,[13] with a free-text field that enables manual data entry for the addition of further details. Demographics, lifestyle factors and results of laboratory tests, including those for renal function (eg, serum creatinine (SCr) values), are also recorded. Data from secondary care are entered into the patient's primary care record retrospectively, and all prescriptions are automatically recorded upon issue.

Source population and cohort identification

Identification of the SGLT2i and comparison cohorts is shown in online supplemental figure 1. The source population included all individuals aged 20–89 years with a diagnosis of type 2 diabetes in the IMRD-UK and on treatment with metformin during the study inclusion period (January 1, 2013–December 31, 2018). Individuals in the source population were also required to have been registered with their PCP for at least 2 years and with no previous recorded prescription for an SGLT2i. From this source population, we identified patients with a first SGLT2i prescription issued during the study period (N=19 300); the date of issue was the start date. For each member of the SGLT2i cohort, we used risk-set sampling to randomly select up to four individuals who had not been issued an SGLT2i prescription on the start date, matched on age, sex, frequency of PCP visits in the previous year, and previous use of other types of glucose-lowering medication, if any (sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP4is), glucagon-like peptide 1 receptor (GLP-1) agonists, or insulin)—this cohort was the 'comparison cohort' (online supplemental figure 2). Sampling was sequential without replacement, therefore the risk-set for a member of the SGLT2i cohort could include individuals who were non-users of SGLT2i at that time but who could receive a first prescription for an SGLT2i at a later stage. When an individual was sampled (either as an SGLT2i initiator or as a matched non-initiator), they left the source population and were no longer eligible for sampling in future matched sets. There were 12 978 individuals in the SGLT2i cohort and 44 286 individuals in the comparison cohort. The start date for each member of the comparison cohort was the same as the state date for its matched SGLT2i initiator.

Follow-up and study outcomes

Individuals in the two study cohorts were followed from the start date until the earliest of: the study outcome, death, age 90 years, or the end of the follow-up period (December 31, 2019). Separate follow-ups were performed for each outcome of interest, excluding individuals with a record of that outcome before the start date. We evaluated three study outcomes: a composite CV outcome, severe renal disease, and all cause-mortality. The composite CV outcome included non-fatal MI, non-fatal ischemic stroke (IS) requiring hospitalization, and CV death. Severe renal disease was defined as an estimated glomerular filtration rate (eGFR) value <30 mL/min/1.73 m^2 (based on either eGFR values entered directly or eGFR values calculated from recorded SCr values using the CKD-EPI formula), or a Read code for end-stage renal disease (ESRD), renal replacement or dialysis.

Other patient variables

Information on other patient variables was determined relative to the start date. We obtained data on patient demographics (age and sex), lifestyle variables, comorbidities, co-medications and healthcare use. For lifestyle variables (body mass index, smoking, and alcohol intake), the most recent available record before the start date was obtained; individuals with no data in their EHR were allocated to a category 'missing' for that variable. Comorbidities were identified anytime before the start date, and included CV disease and risk factors, cerebrovascular, respiratory, gastrointestinal, and neurological disease, diabetes-related complications (nephropathy and neuropathy), and major bleeding. We determined baseline renal function using the most recently recorded

eGFR value in the year before the start date. We also determined baseline glycated hemoglobin (HbA1c), and albumin-to-creatinine ratio, based on the most recent value recorded in the year before the start date, as well as frailty using the electronic frailty index based on an algorithm developed and validated in the IMRD-UK database.[14] Co-medication use was determined from prescriptions issued before the start date, and included non-SGLT2i glucose-lowering medications (insulin, metformin, sulfonylureas, thiazolidinediones, meglitinides, GLP-1 agonists, and DPP4is), and other relevant medications. Polypharmacy was defined as the number of different medications issued in the previous year. We also determined healthcare use based on the number of primary care visits, referrals, and hospitalization in the year before the start date.

Statistical analysis

Baseline characteristics of the study cohorts were described using frequency counts and percentages for categorical variables and means with SD for continuous variables. Incidence rates of the study outcomes were calculated by dividing the number of observed cases by the respective total person-time, with 95% CIs estimated assuming a Poisson distribution. We fitted separate Cox proportional hazards regression models to estimate the HR for the outcome associated with SGLT2i use (vs comparator), adjusted for all covariates as potential confounders, including CV and other comorbidities, co-medications, healthcare use, and lifestyle factors (see online supplemental table 1). We used three different strategies of analysis. First, we performed an intention-to-treat (ITT) analysis where we assumed that exposure status (SGLT2i or comparator) remained the same throughout follow-up—this approach was considered as the main analysis. Second, we performed an on-treatment (OT) analysis where we censored individuals if and when their initial exposure changed (ie, discontinued SGLT2i for individuals in the SGLT2i cohort or initiated SGLT2i for individuals in the comparison cohort). Third, we carried out an as-treated (AT) analysis where person-time was classified according to actual SGLT2i exposure during follow-up irrespective of the study cohort (that was based on initial exposure at the start date). Exposure to SGLT2i in the AT analysis was categorised in relation to the time window after the end of the last SGLT2i consecutive prescription: *current use* (<30 days), *recent use* (between 30 and 90 days), *past use* (91–365 days), and *non-use* (>365 days, or no previous prescription). We performed sensitivity analyses where we restricted analyses to individuals with eGFR values recorded in the year before the start of follow-up, and stratified results by CKD status at the start date, and by whether the start date was before or after the publication of the EMPAREG-OUTCOME Study in 2015.[15] As differential mortality could influence the results, we performed further sensitivity analyses using Fine and Gray models to calculate adjusted subdistribution HRs (SHRs) where death was considered a competing risk for the CV/renal outcomes.[16] Finally, we also performed an alternative analysis using inverse probability of treatment weighting using propensity scores to adjust for potential confounders.[17] Analyses were undertaken using Stata V.12.1 (Statacorp).

RESULTS

Table 1 shows the characteristics of the two study cohorts at the start of follow-up. The proportions of the different drug use in the SGLT2i cohort were: dapagliflozin (61.1%), empagliflozin (24.1%) and canagliflozin (14.8%). Mean age and sex distribution were similar in the SGLT2i cohort (59.6 years (SD ±10.2), 39.1% female) and comparison cohort (60.4 years (SD ±10.0), 39.1% female), as was the prevalence of CV diseases, diabetes-related complications, and frailty. However, notable differences were seen in the prevalence of CKD (9.0% in the SGLT2i cohort and 15.9% in the comparison cohort), previous use of GLP-1 agonists (15.4% among initiators of SGLT2i compared with 10.6% among non-initiators), and the proportion of patients with HbA1c over 8% at baseline (78.9% in the SGLT2i cohort and 34.9% in the comparison cohort). For each study outcome, the mean follow-up was 2.3 years for the SGLT2i cohort and 2.1 years for the comparison cohort.

Composite CV outcome

Results for the composite CV outcome of non-fatal MI/IS or CV death are shown in table 2. The incidence rate of the composite CV outcome was 46.6 cases per 10 000 person-years (95% CI: 38.9 to 55.5) in the SGLT2i cohort, and 58.4 cases per 10 000 person-years (95% CI: 53.3 to 63.8) in the comparison cohort. Crude incidence rates were similar between the SGLT2i and comparison cohorts for non-fatal MI (30.5 vs 30.0 cases per 10 000 person-years), and notably different for non-fatal IS (14.3 vs 25.1 cases per 10 000 person-years). In the ITT analysis, after adjusting for confounders, the SGLT2i cohort had a 25% reduced risk of the composite CV outcome (HR 0.75, 95% CI: 0.61 to 0.93). A similar effect size was obtained with the Fine and Gray model (ITT analysis, SHR 0.77, 95% CI: 0.62 to 0.95) and in the AT analysis (HR 0.76, 95% CI: 0.61 to 0.95 for *current use*), while in the OT analysis, a greater reduced risk was seen (HR 0.54, 95% CI: 0.40 to 0.74). Compared with the comparison cohort, the SGLT2i cohort had a 49% reduced risk of IS (HR 0.51, 95% CI: 0.36 to 0.74) and no difference in the risk of MI (HR 0.98, 95% CI: 0.74 to 1.28). Similar results were observed in the sensitivity analyses (online supplemental tables 2 and 3), except for the CKD stratified analyses. Thus, the CV benefits seen with use of SGLT2is were limited to individuals free of CKD at the start of follow-up: HRs for the CV composite were 0.70 (95% CI: 0.55 to 0.89) for no CKD, and 1.08 (95%

Table 1 Selected characteristics of the SGLT2i initiator and non-SGLT2i initiator (comparison) cohorts at the start of follow-up

Variable	SGLT2i N=12 978 n (%)	Non-SGLT2i (comparison) N=44 286 n (%)
Age (years)		
18–39	380 (2.9)	975 (2.2)
40–59	6179 (47.6)	20 117 (45.4)
60–79	6233 (48)	22 477 (50.8)
≥80	186 (1.4)	717 (1.6)
Mean (SD)	59.6 (10.2)	60.4 (10.0)
Sex		
Male	7900 (60.9)	27 557 (62.2)
Female	5078 (39.1)	16 729 (37.8)
BMI (kg/m^2)		
<20	26 (0.2)	215 (0.5)
20–24	541 (4.2)	3856 (8.7)
25–29	2862 (22.1)	12 771 (28.8)
≥30	9456 (72.9)	26 978 (60.9)
Missing	93 (0.7)	466 (1.1)
Smoking		
Non-smoker	4929 (38)	17 059 (38.5)
Current smoker	1830 (14.1)	7232 (16.3)
Ex-smoker	6215 (47.9)	19 976 (45.1)
Missing	4 (0)	19 (0)
Alcohol use (units/week)		
None	3264 (25.2)	11 403 (25.7)
1–9	6246 (48.1)	20 485 (46.3)
10–20	1645 (12.7)	5792 (13.1)
21–41	469 (3.6)	1792 (4)
>41	236 (1.8)	992 (2.2)
Missing	1118 (8.6)	3822 (8.6)
Comorbidities		
Myocardial infarction	804 (6.2)	3098 (7)
IHD	1899 (14.6)	6976 (15.8)
CeVD	744 (5.7)	2974 (6.7)
Heart failure	323 (2.5)	1576 (3.6)
Hyperlipidemia	4120 (31.7)	14 148 (31.9)
Hypertension	7881 (60.7)	27 142 (61.3)
Obesity	4414 (34)	12 732 (28.7)
CKD	1170 (9.0)	7059 (15.9)
Diabetic retinopathy	4028 (31)	14 090 (31.8)
Diabetic neuropathy	272 (2.1)	986 (2.2)
DKD	291 (2.2)	1062 (2.4)
Frailty		
Fit	3999 (30.8)	13 971 (31.5)
Mild frailty	6230 (48)	19 714 (44.5)
Moderate frailty	2266 (17.5)	8258 (18.6)
Severe frailty	483 (3.7)	2343 (5.3)
HbA1c		
>8% (>64 mmol/mol)	10 240 (78.9)	15 462 (34.9)
7–8% (53–64 mmol/mol)	2186 (16.8)	12 743 (28.8)
<7% (<53 mmol/mol)	410 (3.2)	13 382 (30.2)
Missing	142 (1.1)	2699 (6.1)
ACR (mg/g)		
Normal (≤30)	5856 (45.1)	18 593 (42)
Microalbuminuria (>30–<300)	1715 (13.2)	4932 (11.1)
Macroalbuminuria (≥300)	211 (1.6)	842 (1.9)
Missing	5196 (40)	19 919 (45)
PCP visits*		
0–12	2807 (21.6)	11 068 (25)
13–24	6607 (50.9)	21 499 (48.5)
25–34	2242 (17.3)	7198 (16.3)
≥35	1322 (10.2)	4521 (10.2)
eGFR (mL/min/1.73 m^2)		
<15	0 (0)	3 (0)
15–29	1 (0)	148 (0.3)
30–44	75 (0.6)	1262 (2.8)
45–59	550 (4.2)	3648 (8.2)
60–89	5711 (44)	17 701 (40)
≥90	6339 (48.8)	18 216 (41.1)
Missing	302 (2.3)	3308 (7.5)

*In the year before the start date (start of follow-up).
ACR, albumin-to-creatinine ratio; BMI, body mass index; CeVD, cerebrovascular disease; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; IHD, ischemic heart disease; PCP, primary care practitioner; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

CI: 0.67 to 1.73) for with CKD (online supplemental table 4).

Severe renal disease

Results for severe renal disease are shown in table 3. The incidence rate of severe renal disease was 47.2 cases per 10 000 person-years (95% CI: 39.8 to 55.7) in the SGLT2i cohort, and 122.1 cases per 10 000 person-years (95% CI:115.0 to 129.5) in the comparison cohort. In the ITT analysis, we observed a 45% reduced risk of severe

Table 2 Fully adjusted HRs (95% CI) for MI, IS and the CV composite outcomes associated with SGLT2i initiation versus non-SGLT2i initiation in patients with type 2 diabetes on metformin

SGLT2i exposure	Individuals	Person-years	Cases	IR per 10 000 person-years	Adjusted HR (95% CI)*	P value*
CV composite						
ITT						
Non-initiator	39 744	82 416	481	58.4	1.0 (ref)	
SGLT2i initiator	11 811	27 242	127	46.6	0.75 (0.61 to 0.93)	0.01
OT						
Non-initiator	39 744	74 382	439	59.0	1.0 (ref)	
SGLT2i initiator	11 811	15 316	48	31.3	0.54 (0.40 to 0.74)	<0.01
AT						
Non-use	42 166	78 149	455	58.2	1.0 (ref)	
Current use of SGLT2i	16 860	26 897	115	42.8	0.76 (0.61 to 0.95)	0.02
Recent use of SGLT2i	8843	1424	14	98.3	1.62 (0.95 to 2.78)	0.08
Past use of SGLT2i	5429	3188	24	75.3	1.19 (0.78 to 1.81)	0.41
Myocardial infarction						
ITT						
Non-initiator	39 744	82 416	247	30.0	1.0 (ref)	
SGLT2i initiator	11 811	27 242	83	30.5	0.98 (0.74 to 1.28)	0.86
OT						
Non-initiator	39 744	74 382	226	30.4	1.0 (ref)	
SGLT2i initiator	11 811	15 316	31	20.2	0.67 (0.45 to 0.99)	0.05
AT	42 166	78 149	235	30.1	1.0 (ref)	
Non-use						
Current use of SGLT2i	16 860	26 897	75	27.9	0.94 (0.71 to 1.25)	0.67
Recent use of SGLT2i	8843	1424	9	63.2	1.92 (0.97 to 3.77)	0.06
Past use of SGLT2i	5429	3188	11	34.5	1.05 (0.57 to 1.94)	0.88
Ischemic stroke						
ITT						
Non-initiator	39 744	82 416	207	25.1	1.0 (ref)	
SGLT2i initiator	11 811	27 242	39	14.3	0.51 (0.36 to 0.74)	<0.01
OT						
Non-initiator	39 744	74 382	187	25.1	1.0 (ref)	
SGLT2i initiator	11 811	15 316	14	9.1	0.37 (0.21 to 0.65)	<0.01
AT						
Non-use	42 166	78 149	194	24.8	1.0 (ref)	
Current use of SGLT2i	16 860	26 897	37	13.8	0.57 (0.39 to 0.83)	<0.01
Recent use of SGLT2i	8843	1424	4	28.1	1.11 (0.41 to 3.01)	0.84
Past use of SGLT2i	5429	3188	11	34.5	1.24 (0.66 to 2.31)	0.50

Note that while ITT and OT categories are mutually exclusive, individuals might contribute to multiple AT categories during follow-up. Therefore, the sum of individuals contributing to each AT category exceeds the total number of individuals in the initial study cohorts.
*Adjusted estimates obtained using a Cox proportional hazards regression model including all variables in online supplemental table 1.
AT, as-treated; CV, cardiovascular; IR, incidence rate; IS, ischemic stroke; ITT, intention-to-treat; MI, myocardial infarction; OT, on-treatment; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

renal disease in the SGLT2i cohort, after adjusting for confounders (HR 0.55, 95% CI: 0.46 to 0.67). The estimate from the Fine and Gray model was virtually identical (ITT analysis, SHR 0.57, 95% CI: 0.47 to 0.69). Risk estimates were lower in both the OT analysis (HR 0.34, 95% CI: 0.25 to 0.47) and the AT analysis (*current use*, HR 0.31,

Table 3 Fully adjusted HRs (95% CI) for severe renal disease associated with SGLT2i initiation versus non-SGLT2i initiation in patients with type 2 diabetes on metformin

SGLT2i exposure	N	Person-years	Severe renal disease cases	IR per 10 000 person-years	Adjusted HR (95% CI)*	P value*
ITT						
Non-initiator	43 852	90 437	1104	122.1	1.0 (ref)	
SGLT2i initiator	12 957	30 062	142	47.2	0.55 (0.46 to 0.67)	<0.01
OT						
Non-initiator	43 852	81 643	1076	131.8	1.0 (ref)	
SGLT2i initiator	12 957	16 933	43	25.4	0.34 (0.25 to 0.47)	<0.01
AT						
Non-use	46 522	85 758	1131	131.9	1.0 (ref)	
Current use of SGLT2i	18 469	29 681	72	24.3	0.31 (0.24 to 0.40)	<0.01
Recent use of SGLT2i	9706	1565	10	63.9	0.70 (0.38 to 1.32)	0.27
Past use of SGLT2i	5963	3495	33	94.4	0.82 (0.58 to 1.17)	0.28

Note that while ITT and OT categories are mutually exclusive, individuals might contribute to multiple AT categories during follow-up. Therefore, the sum of individuals contributing to each AT category exceeds the total number of individuals in the initial study cohorts.
*Adjusted estimates obtained using a Cox proportional hazards regression model including all variables in online supplemental table 1.
AT, as-treated; IR, incidence rate; ITT, intention-to-treat; OT, on-treatment; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

95% CI: 0.24 to 0.40). Incidence rates of severe renal disease varied by baseline CKD status, being 28.8 and 40.4 per 10 000 person-years in the SGLT2i and comparison cohorts free of CKD, compared with 232.3 and 594.6 per 10 000 person-years in the SGLT2i and comparison cohorts with CKD. HRs, however, were similar irrespective of baseline CKD status (online supplemental table 4). Similar results were observed in all other sensitivity analyses (online supplemental tables 2 and 3).

All-cause mortality

Results for all-cause mortality are shown in table 4. The mortality rate was 10.1 per 1000 person-years (95% CI: 9.0 to 11.3) in the SGLT2i cohort, and 19.4 per 1000 person-years (95% CI: 18.5 to 20.3) in the comparison cohort. After adjustment for confounders, we observed a 44% reduced mortality among the SGLT2i cohort (HR 0.56, 95% CI: 0.49 to 0.63). The reduced risk of death among the SGLT2i cohort was also seen in the OT analysis (HR

Table 4 Fully adjusted HRs (95% CI) for all-cause mortality associated with SGLT2i initiation versus non-SGLT2i initiation in patients with type 2 diabetes on metformin

SGLT2i exposure	Individuals	Person-years	Deaths	IR per 1000 person-years	Adjusted HR (95% CI)*	P value*
ITT						
Non-initiator	44 286	92 756	1796	19.36	1.0 (ref)	
SGLT2i initiator	12 978	30 286	307	10.14	0.56 (0.49 to 0.63)	<0.01
OT						
Non-initiator	44 286	83 900	1732	20.64	1.0 (ref)	
SGLT2i initiator	12 978	16 969	102	6.01	0.34 (0.27 to 0.42)	<0.01
AT						
Non-use	47 008	88 154	1810	20.53	1.0 (ref)	
Current use of SGLT2i	18 513	29 758	176	5.91	0.35 (0.30 to 0.41)	<0.01
Recent use of SGLT2i	9772	1579	30	19	1.08 (0.75 to 1.55)	0.69
Past use of SGLT2i	6028	3550	87	24.5	1.21 (0.97 to 1.51)	0.09

Note that while ITT and OT categories are mutually exclusive, individuals might contribute to multiple AT categories during follow-up. Thus, the sum of individuals contributing to each AT category exceeds the total number of individuals in the initial study cohorts.
*Adjusted estimates obtained using a Cox proportional hazards regression model including all variables in online supplemental table 1.
AT, as-treated; IR, incidence rate; ITT, intention-to-treat; OT, on-treatment; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

0.34, 95% CI: 0.27 to 0.42) and the AT analysis (*current use*, HR 0.35, 95% CI: 0.30 to 0.41). Mortality rates in the SGLT2i and comparison cohorts were 9.2 and 15.1 per 1000 person-years, respectively, among individuals free of CKD, compared with 21.1 and 41.3 per 1000 person-years, respectively, in individuals with CKD; however, HRs were similar in the stratified analysis by baseline CKD status (online supplemental table 2). Similar results were observed in all other sensitivity analyses (online supplemental tables 3 and 4).

DISCUSSION

In this population-based study of patients with type 2 diabetes using metformin, use of SGLT2is was associated with a 25% reduced risk of the composite CV outcome when compared with non-SGLT2i use, which was driven by a reduced risk of IS. Use of SGLT2is was also associated with a clear 44% reduction in the risk of all-cause mortality, and an almost 50% reduction in the risk of severe renal disease. Because CKD was less frequent among initiators of SGLT2i, confounding could explain the observed decreased renal risk. However, we were able to observe identical effects irrespective of baseline CKD status, a noteworthy finding considering the large differences in background risk between these groups.

Overall, our findings are consistent with the CV and renal benefits of SGLT2is seen both in RCTs that apply strict eligibility criteria, and previous observational studies. Of note, by design, we explored CV benefits among individuals without previous CV disease, just as the renal benefits were explored among individuals free of severe renal disease at baseline. Therefore, it is important to highlight that our study was able to observe notable risk reductions among relatively young patients (ie, mean age of 60 years) at low CV risk. A recent meta-analysis based on six placebo-controlled RCTs found that SGLT2is were associated with a 10% reduction in the risk of major adverse CV events, and a 38% reduced risk of adverse kidney outcomes.[18] A meta-analysis of cohort studies found SGLT2is to be associated with an 11% reduced risk of non-fatal IS versus DPP4is, a non-significant 7% reduction in the risk of MI, and 26% reduced risk of all-cause mortality.[19] In that study, the magnitude of the risk reductions was increased to 21% for stroke and 37% for all-cause mortality when pooling OT estimates rather than those from their ITT analysis, in line with the lower HRs seen in our OT analyses. A recent large international cohort study using data from claims, medical records and national registries reported a 51% reduced risk of renal events among individuals initiating SGLT2is versus other glucose-lowering drugs.[5] In another previous cohort study that compared SGLT2is with DPP4is using UK primary EHRs, Idris *et al*[10] found the former to be associated with reduced risks of around 30% for all-cause mortality, 25% for CKD hospitalization in patients with no history of CV/renal disease, and 51% for CKD hospitalization in those with, or at high risk of, CV disease; no reduction in risk seen for MI. In the USA, Xie *et al*[9] reported a 19% reduced risk of all-cause mortality among users of metformin taking SGLT2is versus sulfonylureas as add-on therapy. Interestingly, our study did not show any CV benefits of SGLT2i among individuals with CKD at baseline. Further research is needed to confirm this observation.

More than 460 million persons worldwide are currently living with diabetes, with type 2 accounting for around 90% of cases, and prevalence projected to increase.[20] Furthermore, many individuals have prediabetes or undetected hyperglycemia at the level of diabetes. Renal complications are strongly associated with an increased risk of stroke, MI, heart failure and mortality in persons with type 2 diabetes,[21–24] and a key goal for diabetes care is to reduce organ injury and obtain a life expectancy similar to persons without diabetes.[25] It is therefore crucial to consider various treatment options based on the current evidence base, in addition to treatment costs.[26] Among large RCTs of novel glucose-lowering agents on CV/renal outcomes, different treatments have shown divergent effects.[27–31] Although no trial has performed a head-to-head comparison, several trials of DPP4is have failed to show any preventive renal effects.[27] For GLP-1 analogs, a renal preventive effect of around 15%–20% has been shown, mainly due to effects on macroalbuminuria, but with no or little effect on renal function/ESRD.[28 29] In contrast, SGLT2is have shown renal preventive effects, both in trials and real-world studies, and our present study suggests this effect is independent from baseline CKD status. As SGLT2is have also demonstrated a cardiorenal preventive effect in persons without diabetes, and in those with renal function <45 mL/min/1.73 m^2 where the glucose-lowering effect is reduced, these beneficial effects must act via other mechanisms.[32] One likely mechanism is through lowering of the intraglomerular pressure, which is essential for preventing further renal progression.[32] Moreover, renal complications are associated with increased activation of the renin–angiotensin–aldosterone system, altered metabolism and increased inflammation—all detrimental for CV complications.[33 34]

Although SGLT2is show a preventive effect on renal complications, it is important to note that renal function still progresses significantly in treated patients receiving this drug treatment.[5] Furthermore, a small number of patients do not tolerate SGLT2is particularly well. Owing to the increased risk of ESRD, CV disease and mortality in patients with impaired renal function, there is therefore a need for other complementary or alternative renal preventive treatments in type 2 diabetes care. Recently, finerenone, a drug that reduces mineralocorticoid receptor activation, has shown preventive effects on CKD progression and CV

disease in patients with type 2 diabetes and established CKD, and represents one such additional treatment option.[35 36]

Strengths of our study include the use of a large sample size from a data source representative of the UK general population; hence, our results have good generalizability. Also, as chronic disease, such as diabetes, is largely managed in primary care, where all prescriptions are automatically recorded upon issue, medication use is likely to be well captured. We used different strategies of analysis—ITT, AT, and OT—as often used in clinical trials, as well as Fine and Gray models to account for the competing risk of death, and these showed our findings to be robust. Furthermore, we were able to use multivariable methods to adjust for potential confounding stemming from observed baseline imbalances. Some of them, such as previously mentioned differences in GLP-1 agonist use, could have favored SGLT2i initiators had we not used these methods. One study limitation is the reliance on recorded eGFR values to classify individuals by baseline CKD status and to identify severe renal events during follow-up. Although exposure to different glucose-lowering drugs could influence the frequency of renal function investigations, potentially biasing our results, virtually identical risk estimates were seen in the sensitivity analysis restricted to individuals whose renal function at baseline could be ascertained. One limitation is that renal function deterioration during follow-up could potentially affect SGLT2i use—either initiation or discontinuation of the drug for this very reason—and this would influence the results of the OT and AT analyses, where longitudinal change in drug use was considered. Also, it is not uncommon for people to discontinue life-extending medications in the last stages of life, and as we cannot exclude this as an explanation for the further reduced risk of mortality seen with current use of SGLT2is (as shown in the OT and AT analysis), caution is therefore needed when interpreting the time-dependent exposure mortality estimates. Also, causes of death are not systematically recorded in IMRD-UK, and accordingly, we could only identify a small number of CV deaths, which was insufficient for analysis as a separate endpoint. As noted earlier, the average follow-up was approximately 2 years, so evidence from this study regarding longer periods of use is scarce. We explored several endpoints using multiple strategies of analysis. While this might inflate type I error, consistency with previous evidence from trials and observational studies makes it unlikely that our results are explained by multiple testing. Finally, as we focused on endpoints within our CV composite outcome, we did not evaluate heart failure as explored in clinical trials.

In conclusion, our results indicate that among individuals with type 2 diabetes on metformin, use of SGLT2 is associated with significant CV, renal and survival benefits under normal conditions of use, confirming findings from RCTs on this topic. However, it is important to be aware of the level of unmet need that still exists in this patient population, as shown in the high incidence of CV and renal outcomes in this present study, especially among those with concurrent CKD.

Author affiliations
[1]Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain
[2]Andalusian Bioinformatics Research Centre (CAEBi), Seville, Spain
[3]Pharmacoepidemiology Research Group, Institute for Health Research (IRYCIS), Madrid, Spain
[4]Bayer Pharmaceuticals, Sant Joan Despi, Spain
[5]Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[6]Department of Medicine, NU Hospital Organization, Uddevalla, Sweden
[7]Department of Internal Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

Acknowledgements We thank Susan Bromley of EpiMed Communications (Abingdon, UK), for medical writing assistance funded by Bayer in accordance with Good Publication Practice.

Contributors Study concept—DV, AGP and LAGR. Study design—AGP, MES, LAGR and DV. Data extraction and analysis—AGP. Interpretation of the data—all authors. Review of manuscript drafts—all authors. Final approval of the manuscript for publication—all authors. Guarantor-LAGR

Funding This study was funded by Bayer (grant number N/A).

Disclaimer The sponsor has no role in the study design, the collection, analysis and interpretation of data, writing the report or the decision to submit the report for publication, apart from in the form of salary paid to DV.

Competing interests AGP, MES and LAGR work for CEIFE, which has received research funding from Bayer. LAGR also declares honoraria for attendance at advisory board meetings for Bayer. DV is an employee of Bayer. ML has received research grants from Eli Lilly and Novo Nordisk and been a paid consultant or received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Novo Nordisk.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Independent Scientific Research Committee for IMRD-UK (reference number: SRC-19THIN059). Data collection for IMRD-UK was approved by the South East Multicentre Research Ethics Committee in 2003 and individual studies using IMRD-UK data do not require separate ethical approval if only anonymized data are used. This study used anonymized routinely collected primary care electronic health records; therefore, informed consent was not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD
Antonio Gonzalez Perez http://orcid.org/0000-0001-9771-5982

REFERENCES

1 Davies MJ, D'Alessio DA, Fradkin J, *et al*. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetologia* 2018;61:2461–98.
2 Zelniker TA, Wiviott SD, Raz I, *et al*. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;393:31–9.
3 Cosentino F, Grant PJ, Aboyans V, *et al*. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;41:255–323.
4 AstraZeneca. Farxiga approved in the US for the treatment of chronic kidney disease in patients at risk of progression with and without type-2 diabetes. Available: https://www.astrazeneca.com/media-centre/press-releases/2021/farxiga-approved-in-the-us-for-ckd.html [Accessed 04 Jun 2021].
5 Heerspink HJL, Karasik A, Thuresson M, *et al*. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol* 2020;8:27–35.
6 Birkeland KI, Jørgensen ME, Carstensen B, *et al*. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. *Lancet Diabetes Endocrinol* 2017;5:709–17.
7 Kim Y-G, Han SJ, Kim DJ, *et al*. Association between sodium glucose co-transporter 2 inhibitors and a reduced risk of heart failure in patients with type 2 diabetes mellitus: a real-world nationwide population-based cohort study. *Cardiovasc Diabetol* 2018;17:91.
8 Kosiborod M, Lam CSP, Kohsaka S, *et al*. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. *J Am Coll Cardiol* 2018;71:2628–39.
9 Xie Y, Bowe B, Gibson AK, *et al*. Comparative effectiveness of sodium-glucose cotransporter 2 inhibitors vs sulfonylureas in patients with type 2 diabetes. *JAMA Intern Med* 2021;181:1043–53.
10 Idris I, Zhang R, Mamza JB, *et al*. Lower risk of hospitalization for heart failure, kidney disease and death with sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in type 2 diabetes regardless of prior cardiovascular or kidney disease: a retrospective cohort study in UK primary care. *Diabetes Obes Metab* 2021;23:2207–14.
11 IQVIA. The health improvement network (THIN). Available: https://www.iqvia.com/locations/uk-and-ireland/thin
12 Blak BT, Thompson M, Dattani H, *et al*. Generalisability of the health improvement network (thin) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011;19:251–5.
13 NHS Digital. Read codes. Available: https://digital.nhs.uk/services/terminology-and-classifications/read-codes
14 Clegg A, Bates C, Young J, *et al*. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2016;45:353–60.
15 Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28.
16 Fine JP, Gray RJ. A proportional hazards model for the Subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
17 Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168:656–64.
18 McGuire DK, Shih WJ, Cosentino F, *et al*. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021;6:148–58.
19 Mascolo A, Scavone C, Scisciola L, *et al*. SGLT-2 inhibitors reduce the risk of cerebrovascular/cardiovascular outcomes and mortality: a systematic review and meta-analysis of retrospective cohort studies. *Pharmacol Res* 2021;172:105836.
20 International Diabetes Federation. *IDF diabetes atlas*. Ninth edition, 2019.
21 González-Pérez A, Saez M, Vizcaya D, *et al*. Incidence and risk factors for mortality and end-stage renal disease in people with type 2 diabetes and diabetic kidney disease: a population-based cohort study in the UK. *BMJ Open Diabetes Res Care* 2021;9:e002146.
22 Tancredi M, Rosengren A, Svensson A-M, *et al*. Excess mortality among persons with type 2 diabetes. *N Engl J Med* 2015;373:1720–32.
23 Tancredi M, Rosengren A, Olsson M, *et al*. The relationship between three eGFR formulas and hospitalization for heart failure in 54 486 individuals with type 2 diabetes. *Diabetes Metab Res Rev* 2016;32:730–5.
24 Hedén Ståhl C, Lind M, Svensson A-M, *et al*. Long-Term excess risk of stroke in people with type 2 diabetes in Sweden according to blood pressure level: a population-based case-control study. *Diabet Med* 2017;34:522–30.
25 American Diabetes Association. Introduction: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care* 2021;44:S1.
26 Buse JB, Wexler DJ, Tsapas A, *et al*. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care* 2020;43:487–93.
27 Cornel JH, Bakris GL, Stevens SR, *et al*. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. *Diabetes Care* 2016;39:2304–10.
28 Mann JFE, Ørsted DD, Brown-Frandsen K, *et al*. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;377:839–48.
29 Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019;394:131–8.
30 Wanner C, Inzucchi SE, Lachin JM, *et al*. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–34.
31 Mosenzon O, Wiviott SD, Cahn A, *et al*. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol* 2019;7:606–17.
32 Fioretto P, Zambon A, Rossato M, *et al*. SGLT2 inhibitors and the diabetic kidney. *Diabetes Care* 2016;39 Suppl 2:S165–71.
33 Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, *et al*. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;382:339–52.
34 Go AS, Chertow GM, Fan D, *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–305.
35 Bakris GL, Agarwal R, Anker SD, *et al*. Effect of Finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;383:2219–29.
36 Pitt B, Filippatos G, Agarwal R, *et al*. Cardiovascular events with Finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;385:2252–63.