SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors and risk of hyperkalemia among people with type 2 diabetes in clinical practice: population based cohort study

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ABSTRACT

OBJECTIVES

To evaluate the comparative effectiveness of sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors in preventing hyperkalemia in people with type 2 diabetes in routine clinical practice.

DESIGN

Population based cohort study with active-comparator, new user design.

SETTING

Claims data from Medicare and two large commercial insurance databases in the United States from April 2013 to April 2022.

PARTICIPANTS

1:1 propensity score matched adults with type 2 diabetes newly starting SGLT-2 inhibitors versus DPP-4 inhibitors (n=778 908), GLP-1 receptor agonists versus DPP-4 inhibitors (n=729 820), and SGLT-2 inhibitors versus GLP-1 receptor agonists (n=873 460).

MAIN OUTCOME MEASURES

Hyperkalemia diagnosis in the inpatient or outpatient setting. Secondary outcomes were hyperkalemia defined as serum potassium levels ≥5.5 mmol/L and hyperkalemia diagnosis in the inpatient or emergency department setting.

RESULTS

Starting SGLT-2 inhibitor treatment was associated with a lower rate of hyperkalemia than DPP-4 inhibitor treatment (hazard ratio 0.75, 95% confidence interval (CI) 0.73 to 0.78) and a slight reduction in rate compared with GLP-1 receptor agonists (0.92, 0.89 to 0.95). Use of GLP-1 receptor agonists was associated with a lower rate of hyperkalemia than DPP-4 inhibitors (0.79, 0.77 to 0.82). The three year absolute risk was 2.4% (95% CI 2.1% to 2.7%) lower for SGLT-2 inhibitors than DPP-4 inhibitors (4.6% *v* 7.0%), 1.8% (1.4% to 2.1%) lower for GLP-1 receptor agonists than DPP-4 inhibitors (5.7% *v* 7.5%), and 1.2% (0.9% to 1.5%) lower for SGLT-2 inhibitors than GLP-1 receptor agonists (4.7% *v* 6.0%). Findings were consistent for the secondary outcomes and among subgroups defined by age, sex, race, medical conditions, other drug use, and hemoglobin A1c levels on the relative scale. Benefits for SGLT-2 inhibitors and GLP-1 receptor agonists on the absolute scale were largest for those with heart failure, chronic kidney disease, or those using mineralocorticoid receptor antagonists. Compared with DPP-4 inhibitors, the lower rate of hyperkalemia was consistently observed across individual agents in the SGLT-2 inhibitor (canagliflozin, dapagliflozin, empagliflozin) and GLP-1 receptor agonist (dulaglutide, exenatide, liraglutide, semaglutide) classes.

CONCLUSIONS

In people with type 2 diabetes, SGLT-2 inhibitors and GLP-1 receptor agonists were associated with a lower risk of hyperkalemia than DPP-4 inhibitors in the overall population and across relevant subgroups. The consistency of associations among individual agents in the SGLT-2 inhibitor and GLP-1 receptor agonist classes suggests a class effect. These ancillary benefits of SGLT-2 inhibitors and GLP-1 receptor agonists further support their use in people with type 2 diabetes, especially in those at risk of hyperkalemia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hyperkalemia is associated with increased mortality and limits the use of guideline recommended drugs such as renin-angiotensin system inhibitors among people with type 2 diabetes

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors are increasingly being used in the treatment of type 2 diabetes

The comparative effectiveness of these drugs in preventing hyperkalemia in routine clinical practice is unclear

WHAT THIS STUDY ADDS

In this population based cohort study of people with type 2 diabetes in the United States, starting SGLT-2 inhibitors or GLP-1 receptor agonists was associated with a lower risk of hyperkalemia compared with DPP-4 inhibitors

Benefits were consistent among demographic and clinical subgroups, and among single agents within the SGLT-2 inhibitor and GLP-1 receptor agonist classes

In addition to improving cardiovascular and kidney outcomes, the potential benefit of preventing hyperkalemia further solidifies the use of SGLT-2 inhibitors and GLP-1 receptor agonists in people with type 2 diabetes

Introduction

People with type 2 diabetes are prone to developing hyperkalemia, especially those with comorbid conditions such as heart failure and chronic kidney disease.[1-3] However, several drugs that improve clinical outcomes in people with type 2 diabetes and related comorbidities increase serum potassium levels, such as inhibitors of the renin-angiotensin-aldosterone system.[4-9] Hyperkalemia is associated with a risk of life threatening cardiac arrhythmias and increased mortality,[10] and the occurrence of hyperkalemia frequently leads to dose reduction or discontinuation of cardiorenal protective drugs. Stopping these drugs is associated with increased risk of adverse cardiovascular outcomes.[11-14] Therefore, strategies that reduce the risk of hyperkalemia in this population are urgently needed.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have become cornerstone drug classes in the treatment of type 2 diabetes[15 16] owing to their cardiovascular and kidney benefits.[17-20] Post hoc analyses of randomized trials have recently shown that SGLT-2 inhibitors also lower the risk of hyperkalemia compared with placebo, an outcome that was not defined as primary or secondary in those trials.[21-23] However, we do not know whether these benefits are also observed outside the highly controlled setting of randomized trials, and whether all agents within the SGLT-2 inhibitor class similarly reduce the risk of hyperkalemia. Furthermore, large scale epidemiological studies are needed that investigate the effects of GLP-1 receptor agonists on the risk of hyperkalemia in people with type 2 diabetes, with only a few small clinical studies suggesting plausible mechanisms for increased potassium excretion.[24 25] GLP-1 receptor agonists might lead to increased potassium secretion owing to enhancement in sodium delivery to the cortical collecting duct and altered tubular electronegativity.[25 26] Additionally, long term kidney preservation by SGLT-2 inhibitors or GLP-1 receptor agonists might contribute to reduced hyperkalemia risks. Notably, a recent study found that GLP-1 receptor agonist use was associated with lower hyperkalemia risk in patients with chronic kidney disease, but whether these benefits extend to the broader population with type 2 diabetes is unknown.[27] The aim of this study was to investigate the comparative effectiveness of SGLT-2 inhibitors, GLP-1 receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors in lowering the risk of hyperkalemia among adults with type 2 diabetes.

Methods

Data sources

We used data from Medicare fee-for-service (parts A, B, and D) and two commercial insurance databases: Optum's deidentified Clinformatics Data Mart Database (CDM) and MarketScan. All three databases contain deidentified longitudinal information on patient demographics, healthcare use, inpatient and outpatient medical diagnoses and procedures, prescription dispensing records, and outpatient laboratory test results (available for approximately 45% of the population in CDM and 5-10% of patients in MarketScan). This study was approved by the Mass General Brigham institutional review board and granted waiver of informed consent because only deidentified claims data were used. Data use agreements were in place.

Study design and study population

We identified three study cohorts of patients who started SGLT-2 inhibitors versus DPP-4 inhibitors (cohort 1), GLP-1 receptor agonists versus DPP-4 inhibitors (cohort 2), and SGLT-2 inhibitors versus GLP-1 receptor agonists (cohort 3) from April 2013 to the end of available data (December 2019 in Medicare, December 2020 in MarketScan, and April 2022 in CDM). Cohort entry was the date of a newly filled prescription of SGLT-2 inhibitors, GLP-1 receptor agonists, or DPP-4 inhibitors. We chose DPP-4 inhibitors as comparator because they were commonly used as second or third line diabetes drugs during our study period, similar to SGLT-2 inhibitors or GLP-1 receptor agonists. In contrast, patients using metformin or insulin probably have less or more advanced diabetes, which would increase the risk of unmeasured confounding by diabetes severity and baseline risk of hyperkalemia. We restricted the study cohorts to patients with a diagnosis of type 2 diabetes and without use of any of the two drug classes being compared for the past 365 days, aged ≥18 years (≥65 years for Medicare), and with at least 12 months of continuous insurance enrollment before cohort entry. We excluded patients who had a history of type 1 diabetes, secondary or gestational diabetes, chronic kidney disease stage 5 or end stage kidney disease, nursing home admission, or a history of organ transplantation, pancreatitis, cirrhosis, acute hepatitis, or multiple endocrine neoplasia type 2 within 365 days before cohort entry. To decrease the risk of reverse causation bias (ie, that early outcomes would be related to a previous hyperkalemia diagnosis before starting the drug and therefore not related to the treatments under study), we further excluded people who had a hyperkalemia diagnosis in the inpatient or outpatient setting or potassium binder use in the 90 days before cohort entry. Supplemental table 1 provides definitions for inclusion and exclusion criteria and supplemental figure 1 gives an overview of the longitudinal design.

Outcomes and follow-up

The primary outcome was the occurrence of a diagnosis code for hyperkalemia in the inpatient or outpatient setting (supplemental table 2 gives definitions). Secondary outcomes were the occurrence of serum potassium ≥5.5 mmol/L during follow-up in the outpatient setting, and hyperkalemia diagnosis in the inpatient or emergency department setting. The laboratory based hyperkalemia outcome definition (serum potassium ≥5.5 mmol/L) was only assessed in CDM because Medicare and MarketScan contain no or too few laboratory test results. For this analysis, we restricted the study population to people who had at least two serum potassium measurements in the 365 days before cohort entry.

To test the specificity and sensitivity of the claims based hyperkalemia definitions, an internal validation study was performed in CDM. Briefly, we included all 12.3 million adults with serum potassium measurements (logical observation identifiers names and codes (LOINC) 6298-4, 77142-8, 12812-4, 12813-2, 42569-4). Then, we assessed whether there was a hyperkalemia diagnosis in the three months after the serum potassium test. For the primary outcome definition (ie, hyperkalemia diagnosis in inpatient or outpatient setting), specificity was 99.5% and sensitivity was 22.3% when we used serum potassium ≥5.5 mmol/L to define hyperkalemia; specificity

was 99.3% and sensitivity was 37.1% when serum potassium ≥6.0 mmol/L was used as the gold standard. Relative risk estimates will be unbiased when specificity is high and non-differential, even if sensitivity is low.[28] However, absolute rate differences will be biased towards the null when sensitivity is low.

We started follow-up on the day after cohort entry and continued until outcome occurrence or until any of the following occurred: treatment discontinuation or starting a drug in the comparator class, death, end of continuous health plan enrollment, or end of available data. We did not censor participants when they started other diabetes drugs (eg, sulfonylureas) during follow-up. We defined discontinuation as no prescription refill for the index exposure in the 30 days after the end of the days' supply for the most recent prescription.

Confounders

We measured potential confounders during the 365 days before and including cohort entry date. We identified covariates that were confounders, confounder proxies or predictors for the outcome based on subject matter knowledge and previous studies that evaluated outcomes associated with drug use in people with type 2 diabetes.[29] These included age, sex, race (race was only available in CDM and Medicare), and geographical region; comorbidities, such as heart failure and chronic kidney disease; diabetes specific complications, such as diabetic nephropathy, neuropathy, and retinopathy; use of drugs used to treat diabetes and cardiovascular disease, for example, insulin and renin-angiotensin system inhibitors; use of other drugs; measures of healthcare use, such as number of emergency department visits, hospital admissions, endocrinologist and internist visits, and laboratory tests; healthy behavior markers, such as screening and vaccinations; and calendar year. We also adjusted for a claims based frailty index[30] to address potential confounding by frailty and for a claims based combined comorbidity score.[31] Comorbidities and drug use were assessed in the 365 days before and including the cohort entry date and based on international classification of diseases (version 9 and 10) diagnosis and procedure codes, and generic drug names, respectively. In the subset of patients who had creatinine measurements available, we calculated estimated glomerular filtration rate using the race-free 2021 CKD-EPI (chronic kidney disease epidemiology collaboration) equation.[32]

Statistical analysis

To adjust for confounding, we used 1:1 propensity score matching with the nearest neighbor method and a caliper of 0.01 of the propensity score.[33] We used multivariable logistic regression models to estimate the propensity scores. These models were fitted separately for each of the data sources (ie, CDM, MarketScan, and Medicare) and for each drug comparison (SGLT-2 inhibitors *v* DPP-4 inhibitors, GLP-1 receptor agonists *v* DPP-4 inhibitors, and SGLT-2 inhibitors *v* GLP-1 receptor agonists), for a total of nine propensity score models. All covariates listed in supplemental table 3 were included in the propensity score models, except for the laboratory test results, which were only available for a subset of patients. Because race was only available in CDM and Medicare, it was only used in the six propensity scores developed in the CDM and Medicare cohorts. Continuous covariates (eg, age) were entered as main terms and quadratic terms. We assessed covariate balance before and after propensity score matching with standardized mean differences, with a standardized mean difference <0.10 indicating sufficient balance.[34 35] Because laboratory test results were not included in the propensity score, we considered their balance after propensity score matching to reflect residual unmeasured confounding. Hazard ratios were estimated with Cox regression models, and incidence rate differences were estimated with generalized linear regression models using an identity link function and normal error distribution.[36] Effect estimates and their standard errors were estimated separately in each of the three data sources, and then pooled with fixed effects meta-analysis. Cumulative incidence curves were estimated with the Aalen-Johansen estimator in the propensity score matched cohort, which accounts for the competing risk of death.[37] Absolute risks and risk differences at six month intervals were obtained from the cumulative incidences. There were no missing data for covariates other than the laboratory measurements. Analyses were performed using R version 3.6.2 and the Aetion Evidence Platform version 4.53.[38]

Subgroup and sensitivity analyses

To investigate potential treatment effect modification, we performed a number of subgroup analyses in the following prespecified strata: age (<65 years *v* ≥65 years), sex, race (white *v* black, based on Medicare data only, where the race variable has been validated against self-reported race[39]), heart failure, cardiovascular disease, chronic kidney disease, use of renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonists, loop diuretics and insulin on the cohort entry date, and by baseline hemoglobin A1c level (<7.5% *v* 7.5-9.0% *v* ≥9.0%). We re-estimated propensity scores and reperformed matching for each subgroup stratum.[40]

To examine the robustness of our findings, we performed the following sensitivity analyses: treatment discontinuation was defined as no prescription refill for the index drug within 60 days rather than 30 days; to investigate the potential influence of informative censoring, we followed patients for a maximum of 180 and 365 days, regardless of treatment discontinuation or starting a drug in the comparator class; finally, we excluded patients with a history of hyperkalemia or potassium binder use in the previous 365 days.

Individual agents in SGLT-2 inhibitor and GLP-1 receptor agonist classes

We investigated potential differences in the risk of hyperkalemia for individual agents in the SGLT-

2 inhibitor or GLP-1 receptor agonist classes by constructing separate cohorts for empagliflozin, canagliflozin, dapagliflozin, liraglutide, dulaglutide, exenatide, and semaglutide versus DPP-4 inhibitors, re-estimated the propensity scores and reperformed the matching, and calculated effect estimates for the primary outcome. The SGLT-2 inhibitor cohorts were restricted to the dates when both drugs under comparison were on the market (April 2013 for canagliflozin *v* DPP-4 inhibitors, January 2014 for dapagliflozin *v* DPP-4 inhibitors, and August 2014 for empagliflozin *v* DPP-4 inhibitors).

Patient and public involvement

There were no funds or time allocated for patient and public involvement, so we were unable to involve patients. Nevertheless, this study was inspired by conversations with patients in clinical practice. We also asked a member of the public to provide feedback on the article before resubmission. To be compliant with our data use agreements, we are not allowed to reidentify and contact patients who were included in the study dataset to share the results of this research.

Results

Baseline characteristics of study populations

Figure 1 reports patient inclusion flowcharts. After 1:1 propensity score matching, there were 389 454 propensity score matched pairs in the SGLT-2 inhibitor versus DPP-4 inhibitor cohort, 364 910 pairs in the GLP-1 receptor agonist versus DPP-4 inhibitor cohort, and 436 730 matched pairs in the SGLT-2 inhibitor versus GLP-1 receptor agonist cohort. After matching, all baseline characteristics in the three cohorts were well balanced, with standardized mean differences <0.10. Laboratory test results, including potassium, were also balanced, despite not being included in propensity score models (table 1, supplemental tables 3-5).

In the SGLT-2 inhibitor versus DPP-4 inhibitor cohort, the mean age was 63 years, 54% were male, and 30% had a history of cardiovascular disease. Commonly used drugs included metformin (81%), angiotensin converting enzyme inhibitors

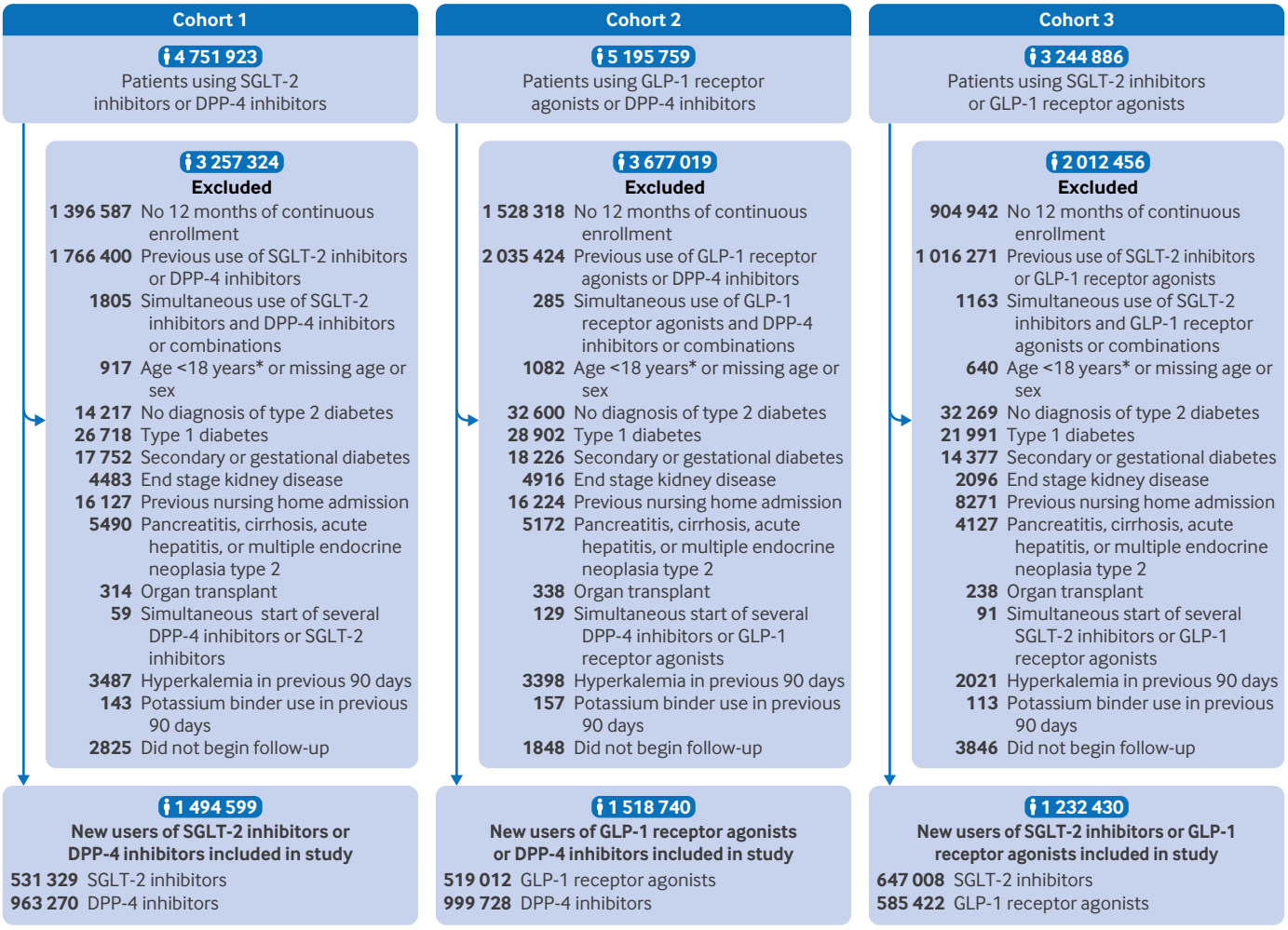

Fig 1 | Patient flowchart. *<65 years for Medicare. DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2

Table 1 | Selected baseline characteristics of people with type 2 diabetes starting SGLT-2 inhibitors versus DPP-4 inhibitors, GLP-1 receptor agonists versus DPP-4 inhibitors, and SGLT-2 inhibitors versus GLP-1 receptor agonists after 1:1 propensity score matching

	SGLT-2 inhibitors *v* DPP-4 inhibitors		GLP-1 receptor agonists *v* DPP-4 inhibitors		SGLT-2 inhibitors *v* GLP-1 receptor agonists	
Characteristics	**SGLT-2 inhibitors**	**DPP-4 inhibitors**	**GLP-1 receptor agonists**	**DPP-4 inhibitors**	**SGLT-2 inhibitors**	**GLP-1 receptor agonists**
Total No of participants	389 454	389 454	364 910	364 910	436 730	436 730
Age, mean (SD)	62.7 (9.5)	62.6 (9.5)	62.3 (9.5)	62.2 (9.5)	62.0 (9.6)	62.1 (9.6)
Men	209 774 (53.9)	209 725 (53.9)	175 506 (48.1)	175 496 (48.1)	218 999 (50.1)	219 612 (50.3)
Race or ethnicity*						
White	174 543 (70.6)	174 447 (70.6)	169 932 (72.2)	170 330 (72.3)	202 025 (71.7)	201 210 (71.4)
Black	26 576 (10.8)	26 595 (10.8)	27 134 (11.5)	26 972 (11.5)	31 322 (11.1)	31 444 (11.2)
Hispanic	10 047 (4.1)	10 077 (4.1)	6022 (2.6)	5734 (2.4)	7985 (2.8)	8445 (3.0)
Asian	24 361 (9.9)	24 491 (9.9)	21 824 (9.3)	21 886 (9.3)	27 183 (9.7)	27 333 (9.7)
Other	11 830 (4.8)	11 747 (4.8)	10 588 (4.5)	10 578 (4.5)	13 169 (4.7)	13 252 (4.7)
Burden of comorbidities						
Combined comorbidity score, mean (SD)	1.1 (2.0)	1.1 (1.9)	1.3 (2.0)	1.3 (2.0)	1.2 (2.0)	1.2 (1.9)
Frailty score, mean (SD)	0.16 (0.05)	0.16 (0.05)	0.16 (0.05)	0.16 (0.05)	0.16 (0.05)	0.16 (0.05)
Comorbidities						
Hypertension	304 807 (78.3)	304 512 (78.2)	288 327 (79.0)	288 447 (79.0)	345 667 (79.1)	346 112 (79.3)
Hyperlipidemia	304 587 (78.2)	304 319 (78.1)	283 838 (77.8)	283 746 (77.8)	342 881 (78.5)	343 544 (78.7)
Cardiovascular disease†	117 292 (30.1)	118 619 (30.5)	110 719 (30.3)	111 001 (30.4)	131 703 (30.2)	131 728 (30.2)
Acute myocardial infarction	7046 (1.8)	6919 (1.8)	5773 (1.6)	5787 (1.6)	7064 (1.6)	7163 (1.6)
Heart failure	30 258 (7.8)	29 856 (7.7)	30 446 (8.3)	30 430 (8.3)	34 535 (7.9)	34 862 (8.0)
Atrial fibrillation	28 818 (7.4)	28 444 (7.3)	26 880 (7.4)	26 898 (7.4)	31 381 (7.2)	31 448 (7.2)
Ischemic stroke	27 158 (7.0)	26 909 (6.9)	25 207 (6.9)	25 176 (6.9)	29 450 (6.7)	29 512 (6.8)
Peripheral arterial disease	30 878 (7.9)	30 640 (7.9)	30 505 (8.4)	30 299 (8.3)	35 457 (8.1)	35 803 (8.2)
Acute kidney injury	10 108 (2.6)	9964 (2.6)	12 602 (3.5)	12 640 (3.5)	12 198 (2.8)	12 370 (2.8)
Chronic kidney disease stage 3-4	26 571 (6.8)	26 061 (6.7)	39 986 (11.0)	40 063 (11.0)	35 547 (8.1)	36 485 (8.4)
Hyperkalemia‡	4048 (1.0)	3997 (1.0)	4637 (1.3)	4622 (1.3)	5099 (1.2)	5209 (1.2)
Hypokalemia	8566 (2.2)	8595 (2.2)	8975 (2.5)	9015 (2.5)	9614 (2.2)	9614 (2.2)
Diabetes related conditions						
Diabetic nephropathy	44 852 (11.5)	44 602 (11.5)	51 426 (14.1)	51 345 (14.1)	57 905 (13.3)	58 320 (13.4)
Diabetic retinopathy	34 775 (8.9)	34 610 (8.9)	35 787 (9.8)	35 378 (9.7)	42 897 (9.8)	43 186 (9.9)
Diabetic neuropathy	73 165 (18.8)	72 803 (18.7)	77 527 (21.2)	77 020 (21.1)	91 832 (21.0)	92 506 (21.2)
Hypoglycemia	37 841 (9.7)	37 954 (9.7)	38 539 (10.6)	38 397 (10.5)	46 861 (10.7)	47 085 (10.8)
No of distinct drugs, mean (SD)	12.11 (5.90)	12.09 (5.98)	12.90 (6.00)	12.90 (6.27)	12.92 (6.15)	12.94 (5.95)
Diabetes drugs on day of cohort entry						
No of diabetes drugs, mean (SD)	2.20 (0.83)	2.20 (0.78)	2.24 (0.90)	2.24 (0.84)	2.37 (0.94)	2.37 (0.96)
Metformin	315 259 (80.9)	316 007 (81.1)	278 632 (76.4)	279 537 (76.6)	342 059 (78.3)	341 792 (78.3)
Sulfonylureas	148 938 (38.2)	149 790 (38.5)	136 649 (37.4)	137 785 (37.8)	173 718 (39.8)	173 516 (39.7)
DPP-4 inhibitors	—	—	—	—	126 648 (29.0)	127 553 (29.2)
SGLT-2 inhibitors	—	—	51 830 (14.2)	51 994 (14.2)	—	—
GLP-1 receptor agonists	38 561 (9.9)	35 525 (9.1)	—	—	—	—
Insulin	77 967 (20.0)	76 981 (19.8)	96 000 (26.3)	94 123 (25.8)	114 963 (26.3)	115 746 (26.5)
Other drug use						
ACEi or ARB	281 918 (72.4)	281 578 (72.3)	263 230 (72.1)	262 922 (72.1)	319 598 (73.2)	319 716 (73.2)
ARNI	1485 (0.4)	1409 (0.4)	1098 (0.3)	1113 (0.3)	1592 (0.4)	1678 (0.4)
Mineralocorticoid receptor antagonists	14 276 (3.7)	14 108 (3.6)	14 902 (4.1)	14 821 (4.1)	17 491 (4.0)	17 622 (4.0)
β blockers	137 684 (35.4)	136 690 (35.1)	130 890 (35.9)	130 648 (35.8)	155 722 (35.7)	156 071 (35.7)
Calcium channel blockers	106 730 (27.4)	106 158 (27.3)	100 578 (27.6)	100 012 (27.4)	120 189 (27.5)	120 647 (27.6)
Loop diuretics	46 067 (11.8)	45 439 (11.7)	51 757 (14.2)	51 596 (14.1)	56 323 (12.9)	56 592 (13.0)
Statins	277 161 (71.2)	276 857 (71.1)	257 353 (70.5)	257 159 (70.5)	314 054 (71.9)	314 785 (72.1)
Antiplatelet agents	39 170 (10.1)	38 620 (9.9)	35 038 (9.6)	34 732 (9.5)	42 626 (9.8)	42 905 (9.8)
Anticoagulants	26 476 (6.8)	26 452 (6.8)	25 522 (7.0)	25 527 (7.0)	29 630 (6.8)	29 736 (6.8)
Potassium binders‡	248 (0.1)	230 (0.1)	364 (0.1)	357 (0.1)	358 (0.1)	353 (0.1)
Potassium supplements	28 010 (7.2)	27 929 (7.2)	29 695 (8.1)	29 744 (8.2)	33 029 (7.6)	33 069 (7.6)
Healthcare use markers						
No of hospital admissions, mean (SD)	0.12 (0.45)	0.12 (0.43)	0.13 (0.48)	0.13 (0.46)	0.12 (0.44)	0.12 (0.45)
No of emergency department visits, mean (SD)	0.40 (1.25)	0.40 (1.15)	0.46 (1.41)	0.46 (1.27)	0.41 (1.23)	0.41 (1.27)
No of internist visits, mean (SD)	14.56 (18.90)	14.56 (19.34)	14.94 (19.41)	14.99 (19.59)	14.94 (19.18)	14.96 (19.47)
No of cardiologist visits, mean (SD)	2.38 (6.39)	2.35 (6.19)	2.34 (6.27)	2.33 (6.14)	2.31 (6.03)	2.32 (6.29)
No of endocrinologist visits, mean (SD)	1.14 (4.99)	1.11 (4.99)	1.35 (5.48)	1.32 (5.39)	1.45 (5.51)	1.46 (5.69)
No of nephrologist visits, mean (SD)	0.18 (2.23)	0.18 (1.65)	0.28 (2.13)	0.28 (2.13)	0.21 (2.30)	0.22 (1.90)
Potassium test order	9266 (2.4)	9238 (2.4)	9808 (2.7)	9841 (2.7)	10 873 (2.5)	10 923 (2.5)
Laboratory measurements, mean (SD)						
eGFR, mL/min/1.73 m^2	80 (23)	79 (23)	79 (24)	79 (24)	80 (23)	79 (24)
Serum potassium, mmol/L	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)

Data are numbers (%) unless stated otherwise.
ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARNI=angiotensin-receptor neprilysin inhibitor; CKD=chronic kidney disease; DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; HbA_{1c}=hemoglobin A1c; SD=standard deviation; SGLT-2=sodium-glucose cotransporter-2.
*Only available in Optum's deidentified Clinformatics Data Mart (CDM) and Medicare databases. Percentages are relative to sample size of CDM and Medicare databases so total adds up to 100%.
†Cardiovascular disease was defined as a composite of myocardial infarction, stable angina, acute coronary syndrome, coronary atherosclerosis, history of coronary procedure, heart failure, ischemic stroke and peripheral vascular disease.
‡People diagnosed with hyperkalemia or those who used potassium binders in 90 days before cohort entry were excluded. Number represents patients with hyperkalemia diagnosis or use of potassium binders more than 90 days before cohort entry.

or angiotensin II receptor blockers (72%), statins (71%), and β blockers (35%). Mean estimated glomerular filtration rate was 79 mL/min/1.73 m^2 and mean serum potassium level was 4.4 mmol/L among the subset with available laboratory test results. Baseline characteristics were comparable in the GLP-1 receptor agonist versus DPP-4 inhibitor cohort, and the SGLT-2 inhibitor versus GLP-1 receptor agonist cohort. In the SGLT-2 inhibitor versus DPP-4 inhibitor cohort, 40.7% started empagliflozin, 38.7% started canagliflozin, and 20.3% started dapagliflozin (supplemental table 6). The most commonly used GLP-1 receptor agonists were liraglutide (37.2%), dulaglutide (31.8%), exenatide (15.7%), and semaglutide (13.0%).

Risk of hyperkalemia after starting SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors

Mean on-treatment follow-up ranged between 8.1 and 8.8 months, reflecting the large rate of discontinuation in routine clinical practice (supplemental table 7). Use of SGLT-2 inhibitors versus DPP-4 inhibitors was associated with a lower rate of hyperkalemia in the propensity score matched cohort, with an adjusted hazard ratio of 0.75 (95% confidence interval (CI) 0.73 to 0.78). Incidence rates were 25.3 versus 18.5 events per 1000 person years, corresponding to an incidence rate difference of −6.88 (95% CI −7.65 to −6.11) events per 1000 person years (table 2). Similarly, use of GLP-1 receptor agonists versus DPP-4 inhibitors was associated with a lower rate of hyperkalemia, with an adjusted hazard ratio of 0.79 (0.77 to 0.82). Incidence rates were 28.5 versus 22.1 events per 1000 person years, corresponding to an incidence rate difference of −6.36 (−7.24 to −5.48) per 1000 person years. The adjusted hazard ratio for SGLT-2 inhibitors versus GLP-1 receptor agonists was 0.92 (0.89 to 0.95). Incidence rates were 22.1 versus 19.8 events per 1000 person years, corresponding to an incidence rate difference of −2.31 (−3.05 to −1.57). Figure 2 shows cumulative incidence curves for all three cohorts and supplemental table 8 reports corresponding absolute risks and risk differences at six month intervals. The lower risk of hyperkalemia for SGLT-2 inhibitors and GLP-1 receptor agonists versus DPP-4 inhibitors appeared within six months of follow-up. At three years of follow-up, the absolute risk was 2.4% (95% CI 2.1% to 2.7%) lower for SGLT-2 inhibitors than DPP-4 inhibitors (4.6% *v* 7.0%), and 1.8% (1.4% to 2.1%) lower for GLP-1 receptor agonists than DPP-4 inhibitors (5.7% *v* 7.5%).

When using serum potassium ≥5.5 mmol/L as the outcome definition, hazard ratios were 0.86 (0.78 to 0.95) for SGLT-2 inhibitors versus DPP-4 inhibitors, 0.82 (0.73 to 0.91) for GLP-1 receptor agonists versus DPP-4 inhibitors, and 1.01 (0.91 to 1.12) for SGLT-2 inhibitors versus GLP-1 receptor agonists (supplemental table 9). Furthermore, when using hyperkalemia diagnosis in the inpatient or emergency department setting, adjusted hazard ratios were 0.77 (0.69 to 0.85), 0.65 (0.59 to 0.72), and 0.96 (0.86 to 1.06), respectively (supplemental table 10).

Subgroup and sensitivity analyses

SGLT-2 inhibitors and GLP-1 receptor agonists showed protective associations for hyperkalemia across all subgroups compared with DPP-4 inhibitors (fig 3, fig 4). Benefits for SGLT-2 inhibitors and GLP-1 receptor agonists on the absolute scale were largest for those with heart failure, chronic kidney disease, or those using mineralocorticoid receptor antagonists. Findings for the SGLT-2 inhibitor versus GLP-1 receptor agonist cohort were consistent, with absence of large differences in hyperkalemia rate between the two drug classes across subgroups (fig 5). Findings were also consistent across sensitivity analyses (supplemental table 11).

Effectiveness of individual agents in SGLT-2 inhibitor and GLP-1 receptor agonist classes compared with DPP-4 inhibitors

Compared with DPP-4 inhibitors, the lower rate of hyperkalemia was consistent for single agents within the SGLT-2 inhibitor class: hazard ratios were 0.76 (0.72 to 0.80) for canagliflozin, 0.85 (0.79 to 0.91) for dapagliflozin, and 0.75 (0.71 to 0.78) for empagliflozin (table 3). Hazard ratios were consistent among individual GLP-1 receptor agonist agents compared with DPP-4 inhibitors, with hazard ratios of 0.80 (0.76 to 0.84) for dulaglutide, 0.78 (0.73 to 0.84) for

Table 2 | Comparative effectiveness of SGLT-2 inhibitors versus DPP-4 inhibitors, GLP-1 receptor agonists versus DPP-4 inhibitors, and SGLT-2 inhibitors versus GLP-1 receptor agonists in reducing risk of hyperkalemia in inpatient or outpatient setting after 1:1 propensity score matching

Participants, events, follow-up, rates, and hazard ratios	SGLT-2 inhibitors *v* DPP-4 inhibitors		GLP-1 receptor agonists *v* DPP-4 inhibitors		SGLT-2 inhibitors *v* GLP-1 receptor agonists	
	SGLT-2 inhibitors	DPP-4 inhibitors	GLP-1 receptor agonists	DPP-4 inhibitors	SGLT-2 inhibitors	GLP-1 receptor agonists
No of participants	389 454	389 454	364 910	364 910	436 730	436 730
Total events	5351	7093	5296	7549	6169	6169
Follow-up, person years	290 105	280 045	239 221	264 892	308.736	279 265
Incidence rate per 1000 person years (95% CI)	18.45 (17.95 to 18.95)	25.33 (24.74 to 25.92)	22.14 (21.55 to 22.74)	28.50 (27.86 to 29.15)	19.78 (19.29 to 28.77)	22.09 (21.54 to 22.65)
Rate difference per 1000 person years (95% CI)	−6.88 (−7.65 to −6.11)	Reference	−6.36 (−7.24 to −5.48)	Reference	−2.31 (−3.05 to −1.57)	Reference
Hazard ratio (95% CI)	0.75 (0.73 to 0.78)	Reference	0.79 (0.77 to 0.82)	Reference	0.92 (0.89 to 0.95)	Reference

CI=confidence interval; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2.

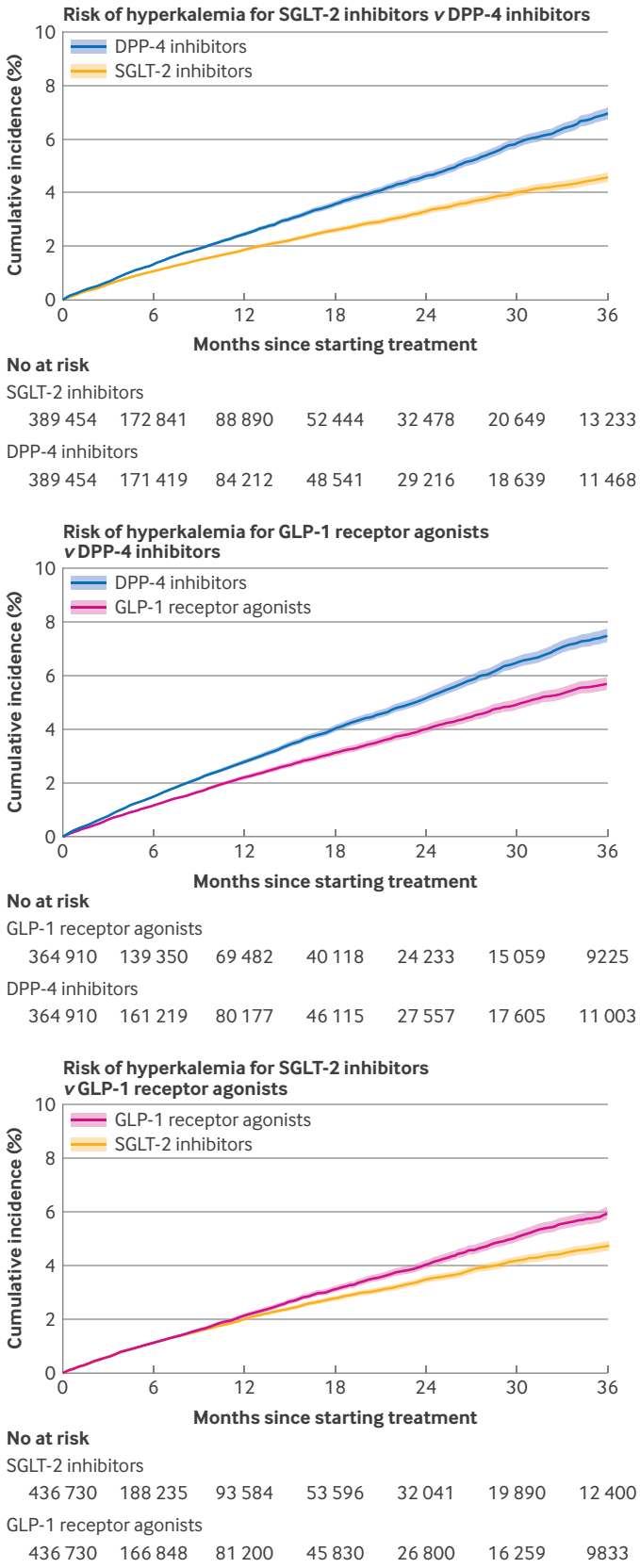

Fig 2 | Cumulative incidence curves for SGLT-2 inhibitors versus DPP-4 inhibitors (upper panel), GLP-1 receptor agonists versus DPP-4 inhibitors (middle panel), and SGLT-2 inhibitors versus GLP-1 receptor agonists (lower panel) for primary outcome of risk of hyperkalemia diagnosis in inpatient or outpatient setting after 1:1 propensity score matching. DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2

exenatide, 0.79 (0.75 to 0.83) for liraglutide, and 0.74 (0.68 to 0.80) for semaglutide (table 4).

Discussion

Statement of principal findings

In this cohort study using three nationwide administrative claims databases in the United States, we found a lower rate of hyperkalemia in people with type 2 diabetes who started SGLT-2 inhibitors or GLP-1 receptor agonists compared with DPP-4 inhibitors. These observations were consistent in subgroups and several sensitivity analyses, and across comparisons of single agents within the SGLT-2 inhibitor and GLP-1 receptor agonist classes.

Novelty and comparison with previous studies

Our study provides several new findings and builds upon current evidence. An individual participant meta-analysis using data from six randomized clinical trials and comprising 49 875 patients found that SGLT-2 inhibitors reduced the risk of hyperkalemia compared with placebo.[21] Our study provides additional evidence by extending these results to a broader group of >750 000 people with type 2 diabetes in routine clinical practice. Additionally, our study provides evidence of the association between GLP-1 receptor agonists and hyperkalemia, which has been lacking in large scale epidemiological studies or trial analyses. The relative rate reduction observed for GLP-1 receptor agonists versus DPP-4 inhibitors (21% reduction) was similar to the reduction observed for SGLT-2 inhibitors versus DPP-4 inhibitors (25% relative reduction in hazard). In head-to-head comparisons of SGLT-2 inhibitors versus GLP-1 receptor agonists, we only observed small differences (hazard ratio 0.92 in the primary analysis), and in several secondary and sensitivity analyses we observed no association. We interpret these findings to indicate that no large differences exist in the rate of hyperkalemia between SGLT-2 inhibitors and GLP-1 receptor agonists, although the subgroup with chronic kidney disease showed a larger effect size on the relative scale. However, these subgroup findings should be considered hypothesis generating and interpreted with caution because many subgroup analyses were performed. Finally, our large study population allowed us to investigate associations with a precision sufficient to exclude the presence of clinically meaningful treatment effect heterogeneity by relevant patient subgroups. We were also able to exclude the presence of large differences in the reduction of hyperkalemia risk across individual SGLT-2 inhibitor and GLP-1 receptor agonist agents compared with DPP-4 inhibitors.

Possible explanations and clinical implications

There are several potential mechanisms by which SGLT-2 inhibitors and GLP-1 receptor agonists might lower the risk of hyperkalemia. SGLT-2 inhibitors and GLP-1 receptor agonists could increase the delivery of sodium and water to the cortical collecting duct of the kidney. Increased absorption of sodium by the

	No of patients (%)	No of events		IR/1000 PY		Rate difference (95% CI)	Hazard ratio (95% CI)
		SGLT-2 inhibitors	DPP-4 inhibitors	SGLT-2 inhibitors	DPP-4 inhibitors		
Overall	389 454 (100)	5351	7093	18.45	25.33	-6.88 (-7.65 to -6.11)	0.75 (0.73 to 0.78)
Age ≥65 years	199 707 (51.4)	3782	5340	27.26	36.29	-9.03 (-10.33 to -7.73)	0.75 (0.72 to 0.78)
Age <65 years	188 609 (48.6)	1592	1751	10.57	13.32	-2.75 (-3.57 to -1.94)	0.80 (0.75 to 0.86)
Male	205 620 (52.9)	3123	4042	19.09	26.58	-7.49 (-8.55 to -6.43)	0.75 (0.71 to 0.78)
Female	182 980 (47.1)	2240	2989	17.82	23.39	-5.57 (-6.69 to -4.45)	0.78 (0.74 to 0.83)
White*	106 959 (91.4)	1983	2815	26.10	34.46	-8.36 (-10.08 to -6.65)	0.75 (0.71 to 0.80)
Black*	10 009 (92.6)	118	218	20.87	32.08	-11.20 (-16.89 to -5.52)	0.64 (0.51 to 0.81)
Heart failure	28 900 (7.4)	968	1349	52.72	71.01	-18.29 (-23.33 to -13.25)	0.74 (0.68 to 0.80)
No heart failure	359 668 (92.6)	4385	5755	16.19	22.10	-5.92 (-6.66 to -5.17)	0.76 (0.73 to 0.79)
CVD	115 765 (29.8)	2565	3585	31.72	43.51	-11.79 (-13.67 to -9.91)	0.74 (0.70 to 0.78)
No CVD	272 290 (70.2)	2761	3396	13.24	17.23	-3.99 (-4.75 to -3.23)	0.79 (0.75 to 0.83)
CKD	40 778 (10.5)	1446	2241	56.98	79.73	-22.75 (-27.17 to -18.33)	0.70 (0.66 to 0.75)
No CKD	348 362 (89.5)	3916	4900	14.81	19.49	-4.67 (-5.39 to -3.96)	0.78 (0.75 to 0.82)
ACEi/ARB/ARNI	237 170 (60.9)	3759	4922	20.39	27.30	-6.92 (-7.92 to -5.91)	0.77 (0.73 to 0.80)
No ACEi/ARB/ARNI	152 219 (39.1)	1623	2213	15.40	22.05	-6.65 (-7.84 to -5.47)	0.72 (0.68 to 0.77)
MRA	9867 (2.5)	376	561	54.32	80.79	-26.47 (-35.12 to -17.82)	0.68 (0.60 to 0.78)
No MRA	379 229 (97.5)	4999	6579	17.67	24.08	-6.41 (-7.17 to -5.65)	0.76 (0.73 to 0.79)
Loop diuretic	29 710 (7.6)	969	1367	46.51	63.52	-17.01 (-21.47 to -12.55)	0.74 (0.68 to 0.80)
No loop diuretic	359 276 (92.4)	4405	5743	16.38	22.27	-5.89 (-6.64 to -5.14)	0.76 (0.73 to 0.79)
Insulin	56 986 (14.6)	1221	1625	28.35	41.53	-13.18 (-15.75 to -10.61)	0.71 (0.66 to 0.76)
No insulin	332 630 (85.4)	4177	5540	16.95	22.89	-5.94 (-6.73 to -5.15)	0.77 (0.74 to 0.79)
HbA_{1c} <7.5%†	12 834 (28.1)	227	338	24.19	36.36	-12.17 (-17.16 to -7.18)	0.67 (0.56 to 0.79)
HbA_{1c} 7.5-9.0%†	17 139 (37.5)	308	404	24.57	32.36	-7.79 (-11.97 to -3.61)	0.76 (0.66 to 0.89)
HbA_{1c} ≥9.0%†	15 730 (34.4)	241	289	22.49	28.83	-6.34 (-10.71 to -1.97)	0.79 (0.66 to 0.93)

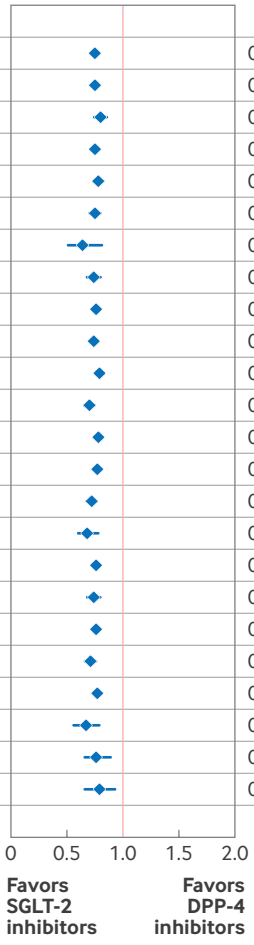

Fig 3 | Comparative effectiveness of SGLT-2 inhibitors versus DPP-4 inhibitors for primary outcome of risk of hyperkalemia diagnosis in inpatient or outpatient setting among subgroups after 1:1 propensity score matching. Number of propensity score matched patients in subgroups do not exactly add up to overall number of propensity score matched patients in main analysis because propensity score matching was performed within each subgroup; therefore, it is possible that more patients are matched within subgroups. ACE=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARNI=angiotensin receptor/neprilysin inhibitor; CI=confidence interval; CVD=cardiovascular disease; CKD=chronic kidney disease; DPP-4=dipeptidyl peptidase-4; IR=incidence rate; MRA=mineralocorticoid receptor antagonist; PY=person years; SGLT-2=sodium-glucose cotransporter-2. *Only data from Medicare; †only data from Optum's deidentified Clinformatics Data Mart Database

principal cells might increase the electronegative charge, leading to increased potassium secretion.[25 26 41 42] A small randomized trial of 35 participants with type 2 diabetes showed increased fractional and absolute excretion of potassium after eight weeks of treatment with the GLP-1 receptor agonist lixisenatide.[24] Furthermore, both drug classes have been shown to slow progression of kidney function decline and albuminuria, and the preserved kidney function might contribute to the prevention of hyperkalemia in the long term.[43-48]

Our findings have important clinical implications. Hyperkalemia is a common electrolyte disorder among patients with type 2 diabetes, especially in those with concurrent heart failure or decreased kidney function, and who use guideline recommended treatments that increase potassium levels, such as angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or mineralocorticoid receptor antagonists.[10] The occurrence of hyperkalemia frequently leads to dose reduction or discontinuation of these drugs, and this discontinuation is associated with adverse cardiovascular and kidney outcomes.[11-13] Although newer potassium binders such as patiromer and sodium zirconium cyclosilicate might allow the use of renin-angiotensin system inhibitors,[49-51] they add to the pill burden, and their benefits on hard clinical outcomes are unknown. Identifying additional strategies that prevent hyperkalemia is therefore a key priority. Our findings suggest that SGLT-2 inhibitors and GLP-1 receptor agonists are associated with lower risk of hyperkalemia. This ancillary benefit further

	No of patients (%)	No of events		IR/1000 PY		Rate difference (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
		GLP-1 receptor agonists	DPP-4 inhibitors	GLP-1 receptor agonists	DPP-4 inhibitors			
Overall	364 910 (100)	5296	7549	22.14	28.50	-6.36 (-7.24 to -5.48)		0.79 (0.77 to 0.82)
Age ≥65 years	188 835 (51.9)	4016	5864	33.94	41.91	-7.96 (-9.46 to -6.46)		0.80 (0.77 to 0.84)
Age <65 years	175 331 (48.1)	1308	1717	10.84	13.81	-2.98 (-3.86 to -2.10)		0.78 (0.73 to 0.84)
Male	173 414 (47.7)	2873	3951	24.45	30.73	-6.28 (-7.59 to -4.96)		0.81 (0.77 to 0.85)
Female	190 266 (52.3)	2499	3567	20.68	26.40	-5.72 (-6.90 to -4.53)		0.80 (0.76 to 0.84)
White*	104 881 (90.8)	2246	3405	33.91	42.67	-8.76 (-10.76 to -6.75)		0.78 (0.74 to 0.83)
Black*	10 634 (9.2)	189	288	31.50	38.81	-7.31 (-13.65 to -0.96)		0.79 (0.66 to 0.95)
Heart failure	30 690 (8.4)	1097	1601	61.31	76.80	-15.49 (-20.72 to -10.27)		0.79 (0.73 to 0.85)
No heart failure	333 786 (91.6)	4278	5895	19.37	24.20	-4.83 (-5.68 to -3.98)		0.81 (0.78 to 0.85)
CVD	111 574 (30.6)	2693	4024	39.08	49.78	-10.71 (-12.84 to -8.58)		0.78 (0.74 to 0.82)
No CVD	252 997 (69.4)	2613	3568	15.34	19.35	-4.01 (-4.88 to -3.15)		0.81 (0.77 to 0.85)
CKD	52 864 (14.5)	2178	3135	66.12	83.83	-17.70 (-21.74 to -13.66)		0.78 (0.74 to 0.82)
No CKD	311 590 (85.5)	3175	4345	15.40	19.19	-3.79 (-4.57 to -3.01)		0.82 (0.79 to 0.86)
ACEi/ARB/ARNI	220 539 (60.6)	3633	5159	24.11	30.54	-6.43 (-7.57 to -5.28)		0.80 (0.77 to 0.84)
No ACEi/ARB/ARNI	143 593 (39.4)	1677	2386	19.09	25.05	-5.97 (-7.33 to -4.61)		0.78 (0.73 to 0.83)
MRA	10 681 (2.9)	435	621	62.88	79.84	-16.96 (-25.58 to -8.34)		0.78 (0.69 to 0.89)
No MRA	353 953 (97.1)	4860	6954	20.95	27.14	-6.18 (-7.05 to -5.32)		0.79 (0.76 to 0.82)
Loop diuretic	34 563 (9.5)	1154	1825	50.93	70.35	-19.42 (-23.79 to -15.06)		0.72 (0.67 to 0.77)
No loop diuretic	330 086 (90.5)	4130	5778	19.10	24.30	-5.20 (-6.06 to -4.35)		0.80 (0.78 to 0.83)
Insulin	71 215 (19.4)	1728	2400	35.94	47.75	-11.81 (-14.36 to -9.25)		0.76 (0.72 to 0.81)
No insulin	296 291 (80.6)	3637	5179	19.00	23.77	-4.77 (-5.66 to -3.88)		0.82 (0.79 to 0.85)
HbA_{1c} <7.5%†	11 498 (28.1)	171	268	23.24	32.51	-9.28 (-14.50 to -4.05)		0.71 (0.58 to 0.86)
HbA_{1c} 7.5-9.0%†	14 448 (35.3)	234	328	23.96	31.38	-7.42 (-12.00 to -2.84)		0.77 (0.65 to 0.91)
HbA_{1c} ≥9.0%†	14 950 (36.6)	234	294	25.91	30.83	-4.92 (-9.76 to -0.07)		0.84 (0.71 to 1.00)

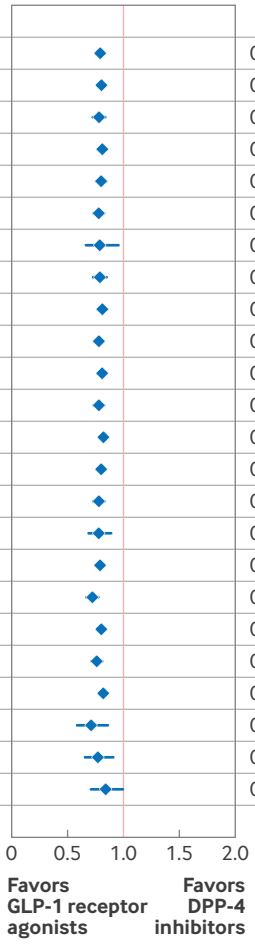

Fig 4 | Comparative effectiveness of GLP-1 receptor agonists versus DPP-4 inhibitors for primary outcome of risk of hyperkalemia diagnosis in inpatient or outpatient setting among subgroups after 1:1 propensity score matching. Number of propensity score matched patients in subgroups do not exactly add up to overall number of propensity score matched patients in main analysis because propensity score matching was performed within each subgroup; therefore, it is possible that more patients are matched within subgroups. ACE=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARNI=angiotensin receptor/neprilysin inhibitor; CI=confidence interval; CVD=cardiovascular disease; CKD=chronic kidney disease; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; IR=incidence rate; MRA=mineralocorticoid receptor antagonist; PY=person years. *Only data from Medicare; †only data from Optum's deidentified Clinformatics Data Mart Database

supports the use of SGLT-2 inhibitors and GLP-1 receptor agonists in people with type 2 diabetes.

Unanswered questions and future research

In our analyses, we focused on hyperkalemia as an outcome. A recent post hoc analysis of the CREDENCE (canagliflozin and renal events in diabetes with established nephropathy clinical evaluation) and DAPA-CKD (dapagliflozin and prevention of adverse outcomes in chronic kidney disease) trials found that SGLT-2 inhibitor use was associated with a lower rate of discontinuation of renin-angiotensin-aldosterone system inhibitors compared with placebo during follow-up in patients with albuminuric chronic kidney disease. Future studies should investigate whether these effects are also observed for GLP-1 receptor agonists, and whether this is mediated by a lower risk of hyperkalemia. Similarly, studies could investigate whether SGLT-2 inhibitors or GLP-1 receptor agonists have an effect on the use of loop diuretics.

Strengths and weaknesses of the study

The strengths of our study include its large sample size, more than 15-fold larger than the individual participant meta-analysis of randomized trials previously discussed,[21] which allowed investigation of important subgroups and individual agents, and rich adjustment for >140 potential confounders. Furthermore, we applied rigorous methods, including the use of an active comparator and new user cohort design, which reduces confounding and mitigates time related and selection bias caused by prevalent users.[52 53]

	No of patients (%)	No of events		IR/1000 PY		Rate difference (95% CI)	Hazard ratio (95% CI)
		SGLT-2 inhibitors	GLP-1 receptor agonists	SGLT-2 inhibitors	GLP-1 receptor agonists		
Overall	436 730 (100)	6107	6169	19.78	22.09	-2.31 (-3.05 to -1.57)	0.92 (0.89 to 0.95)
Age ≥65 years	217 226 (49.9)	4353	4523	29.18	32.66	-3.48 (-4.77 to -2.19)	0.90 (0.86 to 0.94)
Age <65 years	217 872 (50.1)	1761	1633	11.08	11.68	-0.61 (-1.37 to 0.16)	0.96 (0.90 to 1.03)
Male	220 289 (50.5)	3465	3482	20.91	24.19	-3.28 (-4.34 to -2.22)	0.89 (0.85 to 0.93)
Female	215 797 (49.5)	2671	2689	18.66	19.90	-1.24 (-2.28 to -0.21)	0.95 (0.90 to 1.00)
White*	116 322 (91.6)	2283	2407	27.56	31.63	-4.07 (-5.77 to -2.38)	0.88 (0.83 to 0.93)
Black*	10 692 (8.4)	147	176	23.75	28.28	-4.53 (-10.20 to 1.14)	0.84 (0.67 to 1.04)
Heart failure	34 879 (8)	1138	1155	52.48	57.43	-4.94 (-9.44 to -0.44)	0.92 (0.85 to 1.00)
No heart failure	400 858 (92)	4961	4934	17.35	19.08	-1.73 (-2.45 to -1.01)	0.92 (0.88 to 0.96)
CVD	133 988 (30.7)	3028	3162	33.49	38.50	-5.01 (-6.80 to -3.21)	0.88 (0.84 to 0.93)
No CVD	301 758 (69.3)	3034	3089	13.94	15.70	-1.76 (-2.50 to -1.01)	0.90 (0.86 to 0.95)
CKD	53 301 (12.2)	1906	2206	57.33	65.65	-8.32 (-12.08 to -4.56)	0.87 (0.82 to 0.92)
No CKD	383 034 (87.8)	4244	3909	15.42	15.96	-0.53 (-1.22 to 0.15)	0.98 (0.94 to 1.02)
ACEi/ARB/ARNI	270 319 (62)	4423	4278	22.10	23.74	-1.64 (-2.60 to -0.67)	0.95 (0.91 to 0.99)
No ACEi/ARB/ARNI	165 699 (38)	1716	1863	15.78	18.91	-3.13 (-4.27 to -1.99)	0.85 (0.80 to 0.91)
MRA	12 785 (2.9)	486	472	57.10	58.82	-1.72 (-9.06 to 5.62)	0.98 (0.86 to 1.12)
No MRA	423 563 (97.1)	5657	5696	18.86	21.00	-2.14 (-2.87 to -1.41)	0.91 (0.88 to 0.95)
Loop diuretic	37 316 (8.6)	1163	1189	45.85	49.92	-4.06 (-7.93 to -0.19)	0.93 (0.86 to 1.01)
No loop diuretic	398 606 (91.4)	4896	4954	17.30	19.45	-2.14 (-2.87 to -1.42)	0.91 (0.87 to 0.94)
Insulin	88 730 (20.3)	1705	1751	27.60	30.95	-3.34 (-5.30 to -1.39)	0.91 (0.85 to 0.97)
No insulin	347 894 (79.7)	4468	4386	18.04	19.80	-1.76 (-2.55 to -0.97)	0.93 (0.89 to 0.97)
HbA_{1c} <7.5%†	14 433 (26.6)	245	210	25.32	23.53	1.79 (-2.70 to 6.28)	1.08 (0.90 to 1.30)
HbA_{1c} 7.5-9.0%†	19 140 (35.2)	324	315	25.03	25.40	-0.37 (-4.28 to 3.54)	0.98 (0.84 to 1.15)
HbA_{1c} ≥9.0%†	20 738 (38.2)	309	284	23.76	24.19	-0.43 (-4.30 to 3.43)	0.99 (0.84 to 1.17)

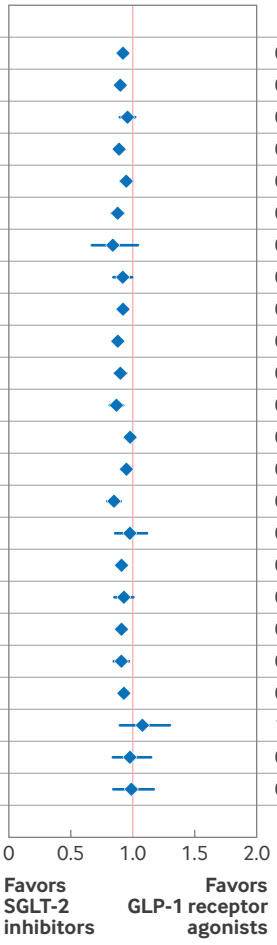

Fig 5 | Comparative effectiveness of SGLT-2 inhibitors versus GLP-1 receptor agonists for primary outcome of risk of hyperkalemia diagnosis in inpatient or outpatient setting among subgroups after 1:1 propensity score matching. Number of propensity score matched patients in subgroups do not exactly add up to overall number of propensity score matched patients in main analysis because propensity score matching was performed within each subgroup; therefore, it is possible that more patients are matched within subgroups. ACE=angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARNI=angiotensin receptor/neprilysin inhibitor; CI=confidence interval; CVD=cardiovascular disease; CKD=chronic kidney disease; GLP-1=glucagon-like peptide-1; IR=incidence rate; MRA=mineralocorticoid receptor antagonist; PY=person years; SGLT-2=sodium-glucose cotransporter-2. *Only data from Medicare; †only data from Optum's deidentified Clinformatics Data Mart Database

Our study has several limitations. We cannot rule out the presence of unmeasured confounding. However, our analysis accounted for a wide set of confounders,[53] and balance was achieved even among the laboratory test results that were not included in the adjustment. Furthermore, confounding by indication is less likely

Table 3 | Comparative effectiveness of individual SGLT-2 inhibitor agents versus DPP-4 inhibitors in reducing risk of hyperkalemia in inpatient or outpatient setting after 1:1 propensity score matching

Participants, events, follow-up, rates, and hazard ratios	Canagliflozin *v* DPP-4 inhibitors		Dapagliflozin *v* DPP-4 inhibitors		Empagliflozin *v* DPP-4 inhibitors	
	Canagliflozin	DPP-4 inhibitors	Dapagliflozin	DPP-4 inhibitors	Empagliflozin	DPP-4 inhibitors
No of participants	172 464	172 464	124 349	124 349	210 866	210 866
Total events	2348	3379	1402	1734	2854	3702
Follow-up, person years	134 040	142 681	84 154	85 008	143 456	136 671
Incidence rate per 1000 person years (95% CI)	17.52 (16.82 to 18.24)	23.68 (22.89 to 24.49)	16.66 (15.80 to 17.56)	20.40 (19.45 to 21.38)	19.89 (19.17 to 20.64)	27.09 (26.22 to 27.97)
Rate difference per 1000 person years (95% CI)	−6.17 (−7.23 to −5.10)	Reference	−3.74 (−5.04 to −2.44)	Reference	−7.19 (−8.33 to −6.05)	Reference
Hazard ratio (95% CI)	0.76 (0.72 to 0.80)	Reference	0.85 (0.79 to 0.91)	Reference	0.75 (0.71 to 0.78)	Reference

SGLT-2 inhibitor cohorts were restricted to dates when both drugs under comparison were on the market (ie, April 2013 for canagliflozin *v* DPP-4 inhibitors, January 2014 for dapagliflozin *v* DPP-4 inhibitors, and August 2014 for empagliflozin *v* DPP-4 inhibitors). CI=confidence interval; DPP-4=dipeptidyl peptidase-4; SGLT-2=sodium-glucose cotransporter 2.

Table 4 | Comparative effectiveness of individual GLP-1 receptor agonist agents versus DPP-4 inhibitors in reducing risk of hyperkalemia in inpatient or outpatient setting after 1:1 propensity score matching

Participants, events, follow-up, rates, and hazard ratios	Dulaglutide *v* DPP-4 inhibitors		Exenatide *v* DPP-4 inhibitors		Liraglutide *v* DPP-4 inhibitors		Semaglutide *v* DPP-4 inhibitors	
	Dulaglutide	DPP-4 inhibitors	Exenatide	DPP-4 inhibitors	Liraglutide	DPP-4 inhibitors	Semaglutide	DPP-4 inhibitors
No of participants	183 669	183 669	87 825	87 825	180 747	180 747	88 687	88 687
Total events	2988	3,585	1019	1834	2598	4146	842	1311
Follow-up, person years	134 568	124 691	49 312	69 226	112 743	142 599	42 147	47 594
Incidence rate per 1000 person years (95% CI)	22.20 (21.42 to 23.02)	28.75 (27.82 to 29.71)	20.66 (19.41 to 21.97)	26.49 (25.29 to 27.73)	23.04 (22.17 to 23.95)	29.07 (28.20 to 29.97)	19.98 (18.65 to 21.37)	27.55 (26.07 to 29.08)
Rate difference per 1000 person years (95% CI)	−6.55 (−7.78 to −5.31)	Reference	−5.83 (−7.58 to −4.07)	Reference	−6.03 (−7.28 to −4.78)	Reference	−7.57 (−9.58 to −5.56)	Reference
Hazard ratio (95% CI)	0.80 (0.76 to 0.84)	Reference	0.78 (0.73 to 0.84)	Reference	0.79 (0.75 to 0.83)	Reference	0.74 (0.68 to 0.80)	Reference

CI=confidence interval; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.

because hyperkalemia is an unintended effect of glucose lowering drugs and currently not an indication that would drive a choice of one of the three investigated drug classes.[54 55] We also used a claims based definition for our primary outcome, with excellent specificity (>99%), but low sensitivity (22.3%). Therefore, although relative risk estimates are not expected to be biased under the assumption of non-differential measurement error, differences on the absolute scale are probably an underestimate of the true benefit of SGLT-2 inhibitors and GLP-1 receptor agonists. We believe non-differential measurement error might be a plausible assumption in our study because hyperkalemia has not been a safety concern for either of these drug classes. Furthermore, we adjusted for a wide number of measures of healthcare use (eg, number of outpatient visits and number of laboratory tests) to ensure patients were comparable at baseline with respect to healthcare surveillance and would have a similar opportunity for potassium monitoring during follow-up.

Mean follow-up in our study was relatively short (around eight to nine months) owing to high rates of treatment discontinuation. Nevertheless, this represents the reality of routine clinical practice in which many patients discontinue their treatment during follow-up. Therefore, our results reflect the outcomes that could be expected in patients from clinical practice after starting these drugs. We believe this timeframe should be sufficient to show the effects of GLP-1 receptor agonists and SGLT-2 inhibitors because mechanistic studies have found rapid effects of GLP-1 receptor agonists on potassium handling,[24 25] and post hoc analyses of randomized trials of SGLT-2 inhibitors have shown separation of survival curves within one year for hyperkalemia.[22 23] Finally, our findings are representative of the insured population in the United States, but might not be generalizable to uninsured patients.

Conclusion

In this analysis of three nationwide US databases, use of SGLT-2 inhibitors and GLP-1 receptor agonists was associated with a lower rate of hyperkalemia compared with DPP-4 inhibitors. This study further supports the use of these agents in a broad range of people with type 2 diabetes.

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Data sharing: A data use agreement is required for each of these data sources. These data use agreements do not permit the authors

to share patient level source data or data derivatives with individuals and institutions not covered under the data use agreements. The databases used in this study are accessible to other researchers by contacting the data providers and acquiring data use agreements or licenses.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Web appendix: Supplemental material