A population-based cohort defined risk of hyperkalemia after initiating SGLT-2 inhibitors, GLP1 receptor agonists or DPP-4 inhibitors to patients with chronic kidney disease and type 2 diabetes

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Hyperkalemia is a common adverse event in patients with chronic kidney disease (CKD) and type 2 diabetes and limits the use of guideline-recommended therapies such as renin-angiotensin system inhibitors. Here, we evaluated the comparative effects of sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i) on the risk of hyperkalemia. We conducted a population-based active-comparator, new-user cohort study using claims data from Medicare and two large United States commercial insurance databases (April 2013-April 2022). People with CKD stages 3-4 and type 2 diabetes who newly initiated SGLT-2i vs. DPP-4i (141671 patients), GLP-1RA vs. DPP-4i (159545 patients) and SGLT-2i vs. GLP-1RA (93033 patients) were included. The primary outcome was hyperkalemia diagnosed in inpatient or outpatient settings. Secondary outcomes included hyperkalemia diagnosed in inpatient or emergency department setting, and serum potassium levels of 5.5 mmol/L or more. Pooled hazard ratios and rate differences were estimated after propensity score matching to adjust for over 140 potential confounders. Initiation of SGLT-2i was associated with a lower risk of hyperkalemia compared with DPP-4i (hazard ratio 0.74; 95% confidence interval 0.68-0.80) and contrasted to GLP-1RA (0.92; 0.86-0.99). Compared with DPP-4i, GLP-1RA were also associated with a lower risk of hyperkalemia (0.80; 0.75-0.86). Corresponding absolute rate differences/1000 person-years were -24.8 (95% confidence interval -31.8 to -17.7), -5.0 (-10.9 to 0.8), and -17.7 (-23.4 to -12.1), respectively. Similar findings were observed for the secondary outcomes, among subgroups, and across single agents within the SGLT-2i and GLP-1RA classes. Thus, SGLT-2i and GLP-1RA are associated with a lower risk of hyperkalemia than DPP-4i in patients with CKD and type 2 diabetes, further supporting the use of these drugs in this population.

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Lay Summary

Hyperkalemia means that the potassium level in the blood is too high. It commonly occurs in people who have type 2 diabetes and kidney disease. Hyperkalemia often leads physicians to stop medications that protect the kidney, such as angiotensin-converting enzyme inhibitors, because these medications also increase potassium levels in the blood. It is therefore important to find treatments that can prevent hyperkalemia. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and dipeptidyl peptidase-4 inhibitors (DPP-4i) are commonly used medications to lower blood glucose in patients with type 2 diabetes. We were interested in investigating whether these medications could prevent hyperkalemia. In this study, we found that people with type 2 diabetes and kidney disease who used SGLT-2i and GLP-1RAs had a lower risk of developing hyperkalemia than people who started DPP-4i. Our study, therefore, supports the use of these medications in people with type 2 diabetes and kidney disease.

Hyperkalemia is a common problem among people with chronic kidney disease (CKD) and type 2 diabetes (T2D).[1] Lower kidney function and T2D are independent risk factors for developing hyperkalemia.[2,3] Furthermore, various common medication classes that are

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used to improve clinical outcomes in these patients, such as renin-angiotensin system inhibitors (RASi)[4] and mineralocorticoid receptor antagonists (MRAs), increase the risk of hyperkalemia.[5–9] In addition to the risk of life-threatening arrhythmias, the occurrence of hyperkalemia negatively affects clinical outcomes in patients with CKD and T2D because of the necessity of discontinuing or reducing the dose of guideline-recommended medications, such as RASi.[10,11]

In recent years, sodium-glucose cotransporter-2 inhibitors (SGLT-2i), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and dipeptidyl peptidase-4 inhibitors (DPP-4i) have become common drugs for treating T2D[12,13] in clinical practice, with the former 2 drug classes showing cardiovascular and kidney benefits.[14–16] Moreover, SGLT-2i have been shown to reduce the risk of hyperkalemia compared with placebo in randomized trials.[17,18] However, several key knowledge gaps remain: first, it is unknown whether the beneficial effects of SGLT-2i for reducing hyperkalemia that were observed in highly controlled trial conditions are similarly observed in real-world settings. Second, head-to-head comparisons between SGLT-2i, GLP-1RAs, and DPP-4i are currently lacking. Last, there are small-scale randomized trials that suggest GLP-1RAs influence tubular handling of electrolytes and increase potassium excretion,[19,20] although it is unknown whether this increase in potassium excretion also leads to a reduced risk of hyperkalemia in clinical settings.

The aim of this study was, therefore, to investigate the comparative effectiveness of SGLT-2i, GLP-1RAs, and DPP-4i in lowering the risk of hyperkalemia among patients with CKD and T2D in a real-world setting.

METHODS

Data source

We used data from 3 large US administrative claims databases: Optum's deidentified Clinformatics Data Mart Database (CDM), IBM MarketScan, and Medicare fee-for-service Parts A, B, and D. CDM and IBM MarketScan include a national commercially insured US population. Medicare is a federal health insurance program providing health care coverage for US residents aged ≥65 years or <65 years with disabilities. All databases contain deidentified longitudinal information, including patient demographics, health care use, inpatient and outpatient medical diagnoses and procedures, outpatient laboratory results (≈45% of patients in CDM and 5%–10% of patients in IBM MarketScan), and prescription dispensing records. The study was approved by the Mass General Brigham Institutional Review Board with waiver of informed consent, and signed data license agreements were in place for all data sources.

Study design and study population

We constructed 3 active-comparator, new-user cohorts[21–23] of patients who newly initiated SGLT-2i versus DPP-4i (cohort 1), GLP-1RA versus DPP-4i (cohort 2), and SGLT-2i versus GLP-1RA (cohort 3) between April 2013 and the end of available data (April 2022 in CDM, December 2020 in IBM MarketScan, and December 2019 in Medicare) (Supplementary Figure S1). New initiation was defined as a filled prescription for 1 of the 2 drug classes in each pairwise comparison, with no dispensing of either drug in the previous 365 days. Eligible patients were required to be aged ≥18 years (aged ≥65 years for Medicare), have at least 12 months of continuous insurance enrollment before drug initiation, and have diagnoses for CKD and T2D. We defined CKD as at least 1 inpatient or 2 outpatient diagnosis codes for CKD stage 3 to 4[24] (Supplementary Table S1). This definition was based on a previously validated algorithm, which showed sufficient accuracy to identify a CKD population (positive predictive value, >80%).[25] Exclusion criteria were a history of type 1 diabetes, secondary or gestational diabetes, CKD stage 5/end-stage kidney disease, nursing home admission, organ transplant, pancreatitis, cirrhosis, acute hepatitis, or multiple endocrine neoplasia type 2 (Supplementary Table S1). Furthermore, we excluded individuals who had a hyperkalemia diagnosis or used potassium binders in the 90 days preceding cohort entry to decrease the possibility that early outcomes during follow-up would be related to a previous hyperkalemia diagnosis (i.e., reverse causation bias) or that the drugs under comparison were started differentially based on history of hyperkalemia (i.e., confounding).

Treatment strategies and follow-up

Our treatment strategies of interest were initiation of SGLT-2i, GLP-1RA, or DPP-4i. Follow-up began on the day after cohort entry and continued in an "as-treated" approach until treatment discontinuation or switch to a drug in the comparator class, outcome occurrence, death, end of continuous health plan enrollment, or end of available data, whichever occurred first. Discontinuation was defined as no prescription refill for the index exposure within the 30 days after the most recent prescription had ended, based on days' supply. We chose an as-treated follow-up approach as our primary analysis to address the high rate of treatment discontinuation in routine care[26] and reduce exposure misclassification.[22]

Study outcomes

The primary outcome was a diagnosis code for hyperkalemia in the inpatient or outpatient setting (definitions provided in Supplementary Table S2). Secondary outcomes included a hyperkalemia diagnosis in the inpatient or emergency department setting, and a composite of serum potassium level ≥5.5 mmol/L in the outpatient setting or hyperkalemia diagnosis in the inpatient setting. The latter outcome was only assessed in CDM among the individuals who had at least 1 serum potassium level measured in the 365 days before cohort entry, as IBM MarketScan and Medicare contain few or no laboratory measurements.

We also performed an internal validation study in CDM to test the specificity and sensitivity of the claims-based hyperkalemia definitions. We included all adult individuals who had a serum potassium measurement (LOINC [Logical Observation Identifier Names and Codes] 6298-4, 77142-8, 12812-4, 12813-2, and 42569-4) and assessed whether there was a hyperkalemia diagnosis in the 90-day window after the serum potassium measurement. Among 12.3 million individuals, we found a specificity of 99.5% and a sensitivity of 22.3% for the primary outcome definition when serum potassium level ≥5.5 mmol/L was used to define hyperkalemia, and specificity of 99.3% and sensitivity of 37.1% when serum potassium level ≥6.0 mmol/L was used to define hyperkalemia. Because specificity is high and misclassification is likely nondifferential, even when sensitivity is low, the relative risk estimates will be unbiased.[27] However, when sensitivity is low, absolute rate differences will be biased toward the null. Hence, the observed associations on the absolute scale for the primary outcome will represent an underestimate of the true absolute rate difference.

Covariates

Patient baseline characteristics were measured during the 365 days before cohort entry date. On the basis of subject matter knowledge and previous studies evaluating outcomes of medication use in people with CKD and T2D,[28] we chose covariates that were associated with the outcome or were confounders or confounder proxies. Ascertainment of comorbid conditions was based on *International Classification of Diseases, Ninth Revision*, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, diagnosis and procedure codes, and ascertainment of drug use was based on generic drug names, in the 365 days before and including the cohort entry date. Covariates of interest included the following: (i) demographics, including age, sex, and race (race was only available in CDM and Medicare); (ii) comorbid conditions; (iii) diabetes-specific complications; (iv) use of cardiovascular and diabetes drugs; (v) use of other comedications; (vi) measures of health care use, including number of hospitalizations, emergency department visits, cardiologist and nephrologist visits, and number of laboratory tests; (vii) healthy behavior markers, including vaccinations and screening; and (viii) calendar year. To address potential confounding by frailty, we also used a claims-based frailty index.[29] Race was self-reported in the claims data sources. There were no missing data for the other covariates, as the absence of a diagnosis or procedure code was interpreted as the absence of a particular condition.

Statistical analysis

To adjust for baseline confounders, we used 1:1 propensity score matching using the nearest neighbor method and a caliper of 0.01 of the propensity score.[30] We estimated the probability of receiving SGLT-2i versus DPP-4i (cohort 1), GLP-1RA versus DPP-4i (cohort 2), and SGLT-2i versus GLP-1RA (cohort 3) as a function of >140 preexposure covariates using multivariable logistic regression. We included all covariates from Supplementary Table S3 in the propensity score model, except for laboratory results, which were only available in a subset of patients (≈22% of the overall population). Covariate balance before and after matching was assessed using standardized mean differences.[31,32] We also assessed balance in laboratory results to assess potential residual confounding by unmeasured factors, because these were not included in the propensity score. For each outcome, we calculated numbers of events, incidence rates, incidence rate differences, and hazard ratios (HRs) in the propensity score–matched cohorts. The HRs and incidence rate differences with their 95% confidence intervals (CIs) were estimated in each data source and then pooled using a fixed-effects meta-analysis. HRs were estimated using Cox regression, and incidence rate differences were determined using generalized linear regression with identity link function and normal error distribution.[33] We constructed survival plots with the Aalen-Johansen estimator, which does not overestimate risks in the presence of the competing risk of death.[34] Analyses were performed using R, version 3.6.2, and the Aetion Evidence Platform, version 4.53.[35]

Subgroup analyses and effectiveness of individual agents

We performed subgroup analyses in the following prespecified subgroups: age (<75 vs. ≥75 years), sex, race (White vs. Black), baseline cardiovascular disease, heart failure, and use of RASi, MRA, and loop diuretics (definitions for cardiovascular disease and heart failure are provided in Supplemental Table S3). Subgroup analyses according to race were only performed in the Medicare group. 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. For subgroup analyses, propensity score estimation and matching were reperformed for each subgroup. In secondary analyses, to investigate potential differences between agents within the SGLT-2i and GLP-1RA classes, we assessed the associations between empagliflozin, canagliflozin, dapagliflozin, liraglutide, dulaglutide, exenatide, and semaglutide versus DPP-4i.

Sensitivity analyses

We performed the following sensitivity analyses: first, we defined treatment discontinuation as no prescription refill within 60 days (instead of 30 days); second, to investigate the influence of informative censoring, we applied an intention-to-treat follow-up approach, where follow-up was continued for a maximum of 180 and 365 days regardless of treatment discontinuation or switch; third, we excluded all patients who had a history of hyperkalemia or potassium binder use in the prior 365 days, and used a broad outcome defined as hyperkalemia diagnosis in the inpatient or outpatient setting or initiation of potassium binders during follow-up.

RESULTS

Baseline characteristics of study populations

Flowcharts for study inclusion are shown in Supplementary Figure S2. After 1:1 propensity score matching, the SGLT-2i versus DPP-4i cohort included 21,196 propensity score–matched pairs, the GLP-1RA versus DPP-4i cohort included 33,402 pairs, and the SGLT-2i versus GLP-1RA cohort included 27,997 propensity score–matched pairs. After matching, baseline characteristics in the 3 cohorts were well balanced, with standardized mean difference <0.10 (Table 1 and Supplementary Tables S4–S6). In the SGLT-2i versus DPP-4i cohort, mean age was 72 years, 56% were men, 90% had CKD stage 3, 59% had cardiovascular disease, and 26% had heart failure. Among those with available laboratory measurements (22% of the overall population), mean estimated glomerular filtration rate was 43 ml/min per 1.73 m^2 and mean serum potassium level was 4.5 mmol/L. Furthermore, 81% used angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, 10% used MRA, 35% used loop diuretics, and 36% used insulin during the baseline period. Baseline characteristics were similar across the 3 cohorts, although insulin use was higher for the GLP-1RA versus DPP-4i cohort (46% vs. 34%–36%). In the SGLT-2i versus DPP-4i cohort, the most commonly used SGLT-2i were empagliflozin (52.5%), followed by canagliflozin (32.9%) and dapagliflozin (14.4%). In the GLP-1RA versus DPP-4i cohort, the most commonly used GLP-1RAs were liraglutide (38.5%), dulaglutide (36.0%), exenatide (13.1%), and semaglutide (10.3%) (Supplementary Table S7).

Hyperkalemia risk associated with SGLT-2i, GLP-1RA, and DPP-4i

After propensity score matching, the mean follow-up for the primary outcome was 7.8 months in the SGLT-2i versus DPP-4i cohort, 8.0 months in the GLP-1RA versus DPP-4i cohort, and 7.6 months in the SGLT-2i versus GLP-1RA cohort (Supplementary Table S8). Initiation of SGLT-2i was

Table 1 | Selected baseline characteristics of patients with chronic kidney disease and type 2 diabetes initiating SGLT-2i versus DPP-4i, GLP-1RA versus DPP-4i, and SGLT-2i versus GLP1-1RA after 1:1 propensity score matching

	SGLT-2i vs. DPP-4i		GLP-1RA vs. DPP-4i		SGLT-2i vs. GLP-1RA	
Characteristic	SGLT-2i	DPP-4i	GLP-1RA	DPP-4i	SGLT-2i	GLP-1RA
Total	21,196	21,196	33,402	33,402	27,997	27,997
Demographics						
Age, mean (SD), yr	72.2 (7.4)	72.2 (7.4)	71.8 (7.1)	71.7 (7.1)	72.3 (7.4)	72.3 (7.4)
Male sex, n (%)	11,918 (56.2)	11,832 (55.8)	16,607 (49.7)	16,634 (49.8)	15,466 (55.2)	15,496 (55.3)
Race/ethnicity, n (%)[a]						
White	13,804 (65.1)	13,810 (65.2)	22,228 (66.5)	22,305 (66.8)	17,917 (64.0)	17,915 (64.0)
Black	2179 (10.3)	2152 (10.2)	3672 (11.0)	3630 (10.9)	2846 (10.2)	2822 (10.1)
Other	3030 (14.3)	3051 (14.4)	4036 (12.1)	4001 (12.0)	4157 (14.8)	4183 (14.9)
Burden of comorbidities, mean (SD)						
Combined comorbidity score	4.1 (2.5)	4.1 (2.4)	4.1 (2.4)	4.1 (2.4)	4.0 (2.4)	4.0 (2.4)
Frailty score	0.21 (0.06)	0.21 (0.06)	0.21 (0.06)	0.21 (0.06)	0.20 (0.06)	0.21 (0.06)
Comorbidities, n (%)						
CKD stage 3	19,064 (89.9)	19,031 (89.8)	28,113 (84.2)	28,060 (84.0)	25,011 (89.3)	24,946 (89.1)
CKD stage 4	2132 (10.1)	2165 (10.2)	5289 (15.8)	5342 (16.0)	2986 (10.7)	3051 (10.9)
Hyperkalemia	1138 (5.4)	1130 (5.3)	1989 (6.0)	1965 (5.9)	1571 (5.6)	1614 (5.8)
Hypokalemia	1054 (5.0)	1081 (5.1)	1803 (5.4)	1750 (5.2)	1329 (4.7)	1367 (4.9)
Acute kidney injury	3536 (16.7)	3554 (16.8)	6247 (18.7)	6187 (18.5)	4528 (16.2)	4535 (16.2)
Hypertension	20,413 (96.3)	20,397 (96.2)	32,229 (96.5)	32,224 (96.5)	26,949 (96.3)	26,959 (96.3)
Hyperlipidemia	18,845 (88.9)	18,835 (88.9)	29,606 (88.6)	29,538 (88.4)	24,931 (89.0)	24,924 (89.0)
Cardiovascular disease[b]	12,588 (59.4)	12,497 (59.0)	19,184 (57.4)	19,310 (57.8)	16,346 (58.4)	16,216 (57.9)
Acute myocardial infarction	1008 (4.8)	997 (4.7)	1306 (3.9)	1280 (3.8)	1187 (4.2)	1187 (4.2)
Heart failure	5543 (26.2)	5589 (26.4)	8516 (25.5)	8421 (25.2)	6971 (24.9)	6931 (24.8)
Atrial fibrillation	3960 (18.7)	3936 (18.6)	5891 (17.6)	5855 (17.5)	5006 (17.9)	4993 (17.8)
Ischemic stroke	3098 (14.6)	3070 (14.5)	4817 (14.4)	4856 (14.5)	4005 (14.3)	4004 (14.3)
Peripheral arterial disease	3918 (18.5)	3890 (18.4)	6188 (18.5)	6194 (18.5)	5159 (18.4)	5188 (18.5)
Diabetes-related conditions, n (%)						
Diabetic nephropathy	14,493 (68.4)	14,495 (68.4)	22,821 (68.3)	22,823 (68.3)	18,975 (67.8)	18,940 (67.7)
Diabetic retinopathy	3836 (18.1)	3773 (17.8)	6496 (19.4)	6559 (19.6)	5044 (18.0)	5033 (18.0)
Diabetic neuropathy	7631 (36.0)	7654 (36.1)	12,694 (38.0)	12,647 (37.9)	9995 (35.7)	9973 (35.6)
Hypoglycemia	3857 (18.2)	3871 (18.3)	6005 (18.0)	6022 (18.0)	4941 (17.6)	4988 (17.8)
No. of distinct medications, mean (SD)	15.4 (6.4)	15.5 (6.5)	15.7 (6.3)	15.8 (6.5)	15.6 (6.5)	15.7 (6.4)
Diabetes medications on day of entry to cohort, n (%)						
No. of diabetes drugs, mean (SD)	2.20 (0.85)	2.21 (0.83)	2.15 (0.84)	2.16 (0.84)	2.44 (0.95)	2.45 (0.96)
Metformin	12,365 (58.3)	12,438 (58.7)	16,144 (48.3)	16,281 (48.7)	16,013 (57.2)	16,053 (57.3)
Sulfonylureas	9640 (45.5)	9760 (46.0)	14,924 (44.7)	15,180 (45.4)	13,944 (49.8)	14,003 (50.0)
DPP-4i	N/A	N/A	N/A	N/A	10,902 (38.9)	10,930 (39.0)
SGLT-2i	N/A	N/A	2619 (7.8)	2600 (7.8)	N/A	N/A
GLP-1RA	3452 (16.3)	3416 (16.1)	N/A	N/A	N/A	N/A
Insulin	7643 (36.1)	7770 (36.7)	15,258 (45.7)	15,149 (45.4)	9588 (34.2)	9568 (34.2)
Other medication use, n (%)						
ACEi or ARB	17,203 (81.2)	17,201 (81.2)	26,588 (79.6)	26,572 (79.6)	22,813 (81.5)	22,864 (81.7)
ARNI	326 (1.5)	337 (1.6)	288 (0.9)	298 (0.9)	365 (1.3)	364 (1.3)
Mineralocorticoid receptor antagonists	2080 (9.8)	2079 (9.8)	3215 (9.6)	3178 (9.5)	2605 (9.3)	2621 (9.4)
β-Blockers	12,828 (60.5)	12,874 (60.7)	20,382 (61.0)	20,386 (61.0)	16,912 (60.4)	16,868 (60.2)
Calcium channel blockers	9330 (44.0)	9245 (43.6)	15,064 (45.1)	15,051 (45.1)	12,612 (45.0)	12,649 (45.2)
Loop diuretics	7314 (34.5)	7285 (34.4)	12,929 (38.7)	12,865 (38.5)	9496 (33.9)	9545 (34.1)
Statins	17,815 (84.0)	17,738 (83.7)	27,679 (82.9)	27,649 (82.8)	23,666 (84.5)	23,537 (84.1)
Antiplatelet agents	3940 (18.6)	3988 (18.8)	5799 (17.4)	5863 (17.6)	5167 (18.5)	5160 (18.4)
Anticoagulants	3368 (15.9)	3294 (15.5)	5119 (15.3)	5117 (15.3)	4270 (15.3)	4272 (15.3)
Potassium binders	94 (0.4)	89 (0.4)	216 (0.6)	221 (0.7)	162 (0.6)	173 (0.6)
Potassium supplements	3133 (14.8)	3207 (15.1)	5129 (15.4)	5133 (15.4)	4040 (14.4)	3992 (14.3)
Health care utilization markers						
No. of hospitalizations, mean (SD)	0.3 (0.78)	0.3 (0.79)	0.3 (0.8)	0.3 (0.8)	0.3 (0.8)	0.3 (0.8)
No. of emergency department visits, mean (SD)	0.8 (1.95)	0.9 (1.82)	0.9 (2.1)	0.9 (1.9)	0.8 (1.9)	0.8 (2.0)
No. of internist visits, mean (SD)	22.5 (27.85)	22.7 (27.69)	21.3 (25.9)	21.3 (25.9)	22.3 (27.4)	22.4 (27.0)
No. of cardiologist visits, mean (SD)	5.7 (10.8)	5.6 (10.9)	5.1 (9.7)	5.1 (9.7)	5.4 (10.1)	5.4 (10.2)
No. of endocrinologist visits, mean (SD)	1.9 (7.17)	1.8 (6.81)	2.1 (7.2)	2.0 (7.0)	1.7 (6.5)	1.8 (6.7)
No. of nephrologist visits, mean (SD)	1.9 (5.56)	1.8 (5.24)	2.3 (5.9)	2.3 (5.8)	1.9 (5.6)	1.9 (5.6)
Potassium test order, n (%)	928 (4.4)	944 (4.5)	1554 (4.7)	1572 (4.7)	1152 (4.1)	1210 (4.3)

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Table 1 | (Continued) **Selected baseline characteristics of patients with chronic kidney disease and type 2 diabetes initiating SGLT-2i versus DPP-4i, GLP-1RA versus DPP-4i, and SGLT-2i versus GLP1-1RA after 1:1 propensity score matching**

	SGLT-2i vs. DPP-4i		GLP-1RA vs. DPP-4i		SGLT-2i vs. GLP-1RA	
Characteristic	SGLT-2i	DPP-4i	GLP-1RA	DPP-4i	SGLT-2i	GLP-1RA
Laboratory measurements, mean (SD)						
eGFR, ml/min per 1.73 m^2[c]	45 (16)	42 (15)	42 (15)	42 (15)	45 (16)	42 (15)
Serum potassium, mmol/L[c]	4.5 (0.4)	4.5 (0.5)	4.5 (0.4)	4.5 (0.5)	4.5 (0.4)	4.5 (0.4)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; N/A, not applicable; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.
[a]Pooled across Clinformatics Data Mart Database and Medicare database only, and therefore does not add up to 100%.
[b]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.
[c]After propensity score matching, eGFR was available for 21.5% of participants in the SGLT-2i versus DPP-4i cohort, 17.6% for the GLP-1RA versus DPP-4i cohort, and 20.0% for the SGLT-2i versus GLP-RA cohort. Serum potassium level was available in 21.3%, 17.4%, and 19.8%, respectively.

associated with a lower risk of hyperkalemia compared with DPP-4i, with an adjusted HR of 0.74 (95% CI, 0.68–0.80) and incidence rate difference of –24.8 (95% CI, –31.8 to –17.7) per 1000 person-years (Table 2). Furthermore, GLP-1RAs were associated with a lower risk of hyperkalemia compared with DPP-4i, with an adjusted HR of 0.80 (95% CI, 0.75–0.86) and incidence rate difference of –17.7 (95% CI, –23.4 to –12.1) per 1000 person-years. The adjusted HR for SGLT-2i versus GLP-1RA was 0.92 (95% CI, 0.86–0.99), with an incidence rate difference of –5.0 (95% CI, –10.9 to 0.8). The lower risk of hyperkalemia for SGLT-2i and GLP-1RA compared with DPP-4i was observed within the first 6 months of follow-up (Figure 1). When comparing SGLT-2i versus GLP-1RA, the cumulative incidence curves for hyperkalemia overlapped for the first 9 months of follow-up and started to diverge thereafter. Absolute risks and absolute risk differences at 6-month intervals are reported in Supplementary Table S9. At 2 years of follow-up, the absolute risk was 4.3% (95% CI, 2.8%–5.7%) lower for SGLT-2i versus DPP-4i and 2.3% (95% CI, 1.2%–3.5%) lower for GLP-1RA versus DPP-4i.

When the outcome definition was changed to hyperkalemia diagnosis in the inpatient or emergency department setting, the results were consistent for SGLT-2i versus DPP-4i and GLP-1RA versus DPP-4i comparisons, with HRs of 0.76 (95% CI, 0.58–0.99) and 0.66 (95% CI, 0.54–0.80), respectively. Furthermore, the HR for SGLT-2i versus GLP-1RA was 1.06 (95% CI, 0.82–1.38) (Supplementary Table S10). Similar

Table 2 | Comparative effectiveness of SGLT-2i versus DPP-4i, GLP-1RA versus DPP-4i, and SGLT-2i versus GLP-1RA on risk of hyperkalemia diagnosis in inpatient or outpatient setting before and after 1:1 propensity score matching

	Before 1:1 propensity score matching		After 1:1 propensity score matching	
SGLT-2i vs. DPP-4i	SGLT-2i	DPP-4i	SGLT-2i	DPP-4i
Sample size, n	25,257	116,414	21,196	21,196
Total events, n	1160	9682	960	1441
Follow-up, PY	15,085	92,642	12,758	14,408
Incidence rate/1000 PY (95% CI)	76.9 (72.5 to 81.5)	104.5 (102.4 to 106.6)	75.3 (70.6 to 80.2)	100.0 (94.9 to 105.3)
Rate difference/1000 PY (95% CI)	**–27.6 (–32.5 to –22.7)**	Ref	**–24.8 (–31.8 to –17.7)**	Ref
Hazard ratio (95% CI)	**0.69 (0.65 to 0.74)**	Ref	**0.74 (0.68 to 0.80)**	Ref
	Before 1:1 propensity score matching		**After 1:1 propensity score matching**	
GLP-1RA vs. DPP-4i	**GLP-1RA**	**DPP-4i**	**GLP-1RA**	**DPP-4i**
Sample size, n	44,208	115,337	33,402	33,402
Total events, n	2257	9507	1723	2401
Follow-up, PY	27,195	91,990	20,763	23,839
Incidence rate/1000 PY (95% CI)	83.0 (79.6 to 86.5)	103.3 (101.3 to 105.5)	83.0 (79.1 to 87.0)	100.7 (96.7 to 104.8)
Rate difference/1000 PY (95% CI)	**–20.5 (–24.4 to –16.4)**	Ref	**–17.7 (–23.4 to –12.1)**	Ref
Hazard ratio (95% CI)	**0.76 (0.73 to 0.80)**	Ref	**0.80 (0.75 to 0.86)**	Ref
	Before 1:1 propensity score matching		**After 1:1 propensity score matching**	
SGLT-2i vs. GLP-1RA	**SGLT-2i**	**GLP-1RA**	**SGLT-2i**	**GLP-1RA**
Sample size, n	31,708	61,325	27,997	27,997
Total events, n	1480	3401	1300	1462
Follow-up, PY	19,310	39,918	17,059	17,994
Incidence rate/1000 PY (95% CI)	76.6 (72.8 to 80.7)	85.2 (82.4 to 88.1)	76.2 (72.1 to 80.5)	81.3 (77.1 to 85.5)
Rate difference/1000 PY (95% CI)	**–8.6 (–13.4 to –3.7)**	Ref	**–5.0 (–10.9 to 0.8)**	Ref
Hazard ratio (95% CI)	**0.88 (0.83 to 0.94)**	Ref	**0.92 (0.86 to 0.99)**	Ref

CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; PY, person-years; Ref, reference; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.
Data in bold are the rate difference/1000 person-years (95% CI) and HR (95% CI).

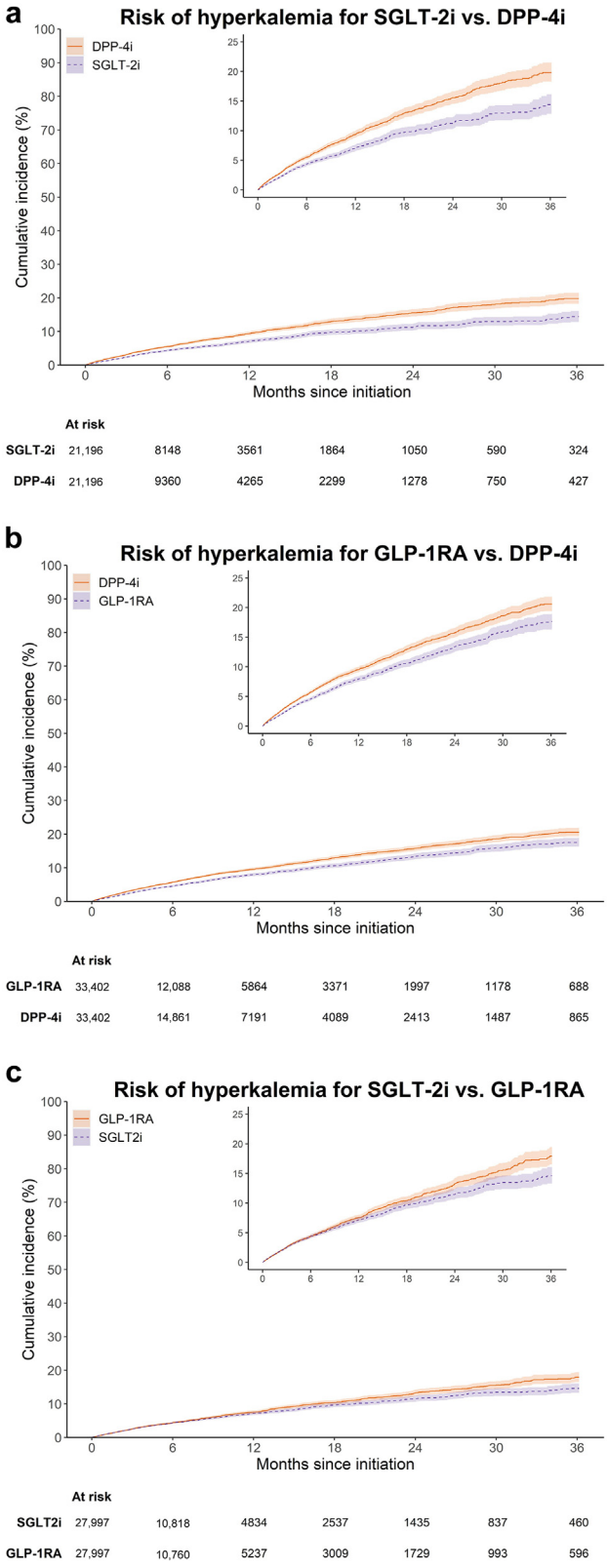


Figure 1 | Cumulative incidence curves for (a) sodium-glucose cotransporter-2 inhibitors (SGLT-2i) versus dipeptidyl peptidase-4 inhibitors (DPP-4i), (b) glucagon-like peptide-1 receptor agonists (GLP-1RAs) versus DPP-4i, and (c) SGLT-2i versus GLP-1RAs on risk of hyperkalemia diagnosis in inpatient or outpatient setting after 1:1 propensity score matching.

findings were observed when using a laboratory-based outcome definition (serum potassium level, ≥5.5 mmol/L) in the subset of patients who had serum potassium measurements available in the CDM data set, although CIs were wide (Supplementary Table S11): HRs were 0.88 (95% CI, 0.69–1.13) for SGLT-2i versus DPP-4i, 0.86 (95% CI, 0.69–1.06) for GLP-1RA versus DPP-4i, and 1.14 (95% CI, 0.91–1.43) for SGLT-2i versus GLP-1RA.

Subgroup analyses, effectiveness of individual agents, and sensitivity analyses

Findings were consistent across all subgroups for all 3 cohorts (Figure 2), including in patients with history of heart failure and cardiovascular disease, as well as patients on medications that influence potassium levels (i.e., RASi, MRAs, and loop diuretics). The lower risk of hyperkalemia was consistent among individual agents within the SGLT-2i class (HRs between 0.72 and 0.77) and GLP-1RA classes (HRs between 0.75 and 0.86) (Supplementary Table S12). Findings were also consistent among all sensitivity analyses (Supplementary Table S13).

DISCUSSION

In this large, nationwide, US cohort study of persons with CKD and T2D, we found that both SGLT-2i and GLP-1RAs were associated with a lower risk of hyperkalemia compared with DPP-4i. Furthermore, we observed consistent findings across subgroups of demographics, comorbid conditions, and medications known to influence potassium levels, and in multiple sensitivity analyses, as well as across individual agents within the SGLT-2i and GLP-1RA classes.

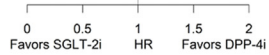
Our findings have important clinical implications. Hyperkalemia occurs frequently among patients with CKD and T2D, particularly those with low kidney function.[1] These patients are also at the highest risk for adverse cardiovascular and renal events. Our findings suggest that both SGLT-2i and GLP-1RAs are associated with a lower risk of hyperkalemia. Initiating these medications may therefore enable patients to use other guideline-recommended therapies that are associated with an increased risk of hyperkalemia, such as inhibitors of the renin-angiotensin-aldosterone system (angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, MRA, and angiotensin receptor/neprilysin inhibitor). Indeed, hyperkalemia often leads to dose reduction or discontinuation of these therapies, which has been associated with worse clinical outcomes.[10,11]

Our study has several novel findings. A previous meta-analysis of 6 randomized trials found that SGLT-2i lowered the risk of hyperkalemia compared with placebo in people with T2D.[17] Our results extend the protective effects of SGLT-2i on hyperkalemia observed in controlled trial settings to the broad group of patients with CKD and T2D seen in routine clinical practice. There are several differences between the trials and our observational study worth highlighting. First, our study population was on average 10 years older, included a larger proportion of women, and included a larger proportion of patients with heart failure. Second,

a

SGLT-2i vs. DPP-4i

	No. (%) of patients	SGLT-2i No. events	DPP-4i No. events	SGLT-2i IR/1000 PY	DPP-4i IR/1000 PY	Rate difference (95% CI)	HR (95% CI)
Overall	21,196 (100.0%)	960	1141	75.2	100.0	-24.8 (-31.8 to -17.7)	0.74 (0.68 to 0.80)
Age ≥75 yr	7884 (37.5%)	356	520	81.3	99.4	-18.2 (-30.2 to -6.2)	0.77 (0.70 to 0.85)
Age <75 yr	13,143 (62.5%)	606	888	72.9	96.3	-23.4 (-32.0 to -14.8)	0.66 (0.59 to 0.74)
Male	11,779 (55.9%)	574	824	78.6	102.3	-23.7 (-33.2 to -14.2)	0.76 (0.69 to 0.84)
Female	9277 (44.1%)	378	604	70.2	96.4	-26.2 (-36.7 to -15.8)	0.71 (0.62 to 0.80)
White[a]	9842 (90.6%)	411	636	74.2	98.2	-24.0 (-34.4 to -13.5)	0.74 (0.65 to 0.84)
Black[a]	1017 (9.4%)	32	58	63.2	85.0	-21.8 (-52.8 to 9.2)	0.70 (0.46 to 1.09)
Heart failure	5390 (25.7%)	319	420	108.9	126.1	-17.2 (-34.2 to -0.2)	0.84 (0.72 to 0.97)
No heart failure	15,621 (74.3%)	635	948	65.5	84.9	-19.5 (-26.9 to -12.0)	0.75 (0.68 to 0.83)
CVD	12,477 (59.3%)	639	932	88.8	114.3	-25.5 (-35.6 to -15.5)	0.76 (0.68 to 0.84)
No CVD	8571 (40.7%)	319	504	58.6	79.4	-20.9 (-30.3 to -11.4)	0.72 (0.63 to 0.83)
ACEi/ARB/ARNI	14,210 (67.5%)	659	977	74.5	97.2	-22.7 (-31.0 to -14.3)	0.75 (0.68 to 0.83)
No ACEi/ARB/ARNI	6843 (32.5%)	287	434	75.0	101.0	-26.1 (-38.9 to -13.2)	0.73 (0.63 to 0.85)
MRA	1253 (6.0%)	99	123	137.7	155.3	-17.6 (-56.2 to 21.0)	0.88 (0.67 to 1.14)
No MRA	19,571 (94.0%)	850	1264	71.2	93.1	-21.9 (-28.9 to -14.8)	0.75 (0.69 to 0.82)
Loop diuretic	4969 (23.7%)	297	432	104.4	132.6	-28.2 (-45.4 to -11.0)	0.76 (0.66 to 0.89)
No loop diuretic	16,013 (76.3%)	663	960	67.7	86.8	-19.1 (-26.6 to -11.6)	0.77 (0.70 to 0.85)
RAASi (ACE/ARB/ARNI/MRA)	14,728 (70.0%)	701	1012	77.0	98.3	-21.3 (-29.7 to -13.0)	0.77 (0.70 to 0.84)
No RAASi	6315 (30.0%)	264	400	74.3	99.8	-25.5 (-38.7 to -12.2)	0.74 (0.63 to 0.86)



b

GLP-1RA vs. DPP-4i

	No. (%) of patients	GLP-1RA No. events	DPP-4i No. events	GLP-1RA IR/1000 PY	DPP-4i IR/1000 PY	Rate difference (95% CI)	HR (95% CI)
Overall	33,402 (100.0%)	1723	2401	83.0	100.7	-17.7 (-23.4 to -12.1)	0.80 (0.75 to 0.86)
Age ≥75 yr	16,060 (48.3%)	815	1137	82.2	98.3	-16.1 (-24.2 to -8.1)	0.81 (0.73 to 0.90)
Age <75 yr	17,181 (51.7%)	775	1058	71.7	86.6	-14.9 (-22.2 to -7.7)	0.82 (0.75 to 0.89)
Male	16,334 (49.2%)	949	1243	94.6	107.4	-12.8 (-21.3 to -4.4)	0.86 (0.79 to 0.94)
Female	16,866 (50.8%)	771	1112	72.8	91.7	-18.9 (-26.4 to -11.5)	0.78 (0.71 to 0.85)
White[a]	16,979 (88.9%)	845	1232	84.1	104.2	-20.1 (-28.3 to -12.0)	0.79 (0.72 to 0.86)
Black[a]	2127 (11.1%)	89	152	76.3	98.2	-21.9 (-44.2 to 0.3)	0.73 (0.56 to 0.95)
Heart failure	6052 (24.7%)	355	486	105.3	127.9	-22.6 (-38.4 to -6.8)	0.80 (0.70 to 0.92)
No heart failure	18,455 (75.3%)	828	1182	70.4	89.2	-18.8 (-25.8 to -11.8)	0.78 (0.71 to 0.85)
CVD	7439 (47.1%)	469	586	97.0	111.4	-14.5 (-27.1 to -1.9)	0.87 (0.77 to 0.97)
No CVD	8340 (52.9%)	376	517	65.3	81.6	-16.2 (-25.9 to -6.6)	0.79 (0.69 to 0.90)
ACEi/ARB/ARNI	21,445 (64.6%)	1136	1626	82.5	103.7	-21.2 (-28.2 to -14.2)	0.78 (0.73 to 0.84)
No ACEi/ARB/ARNI	11,766 (35.4%)	561	826	81.7	107.2	-25.5 (-35.4 to -15.5)	0.75 (0.68 to 0.84)
MRA	2052 (6.2%)	145	223	110.4	152.9	-42.6 (-69.5 to -15.7)	0.71 (0.57 to 0.88)
No MRA	31,174 (93.8%)	1535	2130	79.5	96.2	-16.8 (-22.5 to -11.1)	0.81 (0.76 to 0.87)
Loop diuretic	9156 (27.5%)	551	825	96.2	130.6	-34.4 (-46.4 to -22.4)	0.73 (0.65 to 0.81)
No loop diuretic	24,085 (72.5%)	1164	1553	77.7	90.6	-12.9 (-19.2 to -6.5)	0.84 (0.78 to 0.91)
RAASi (ACE/ARB/ARNI/MRA)	22,367 (67.3%)	1194	1642	83.5	98.9	-15.4 (-22.1 to -8.7)	0.82 (0.76 to 0.89)
No RAASi	10,864 (32.7%)	514	744	80.4	105.2	-24.8 (-35.1 to -14.5)	0.76 (0.68 to 0.85)

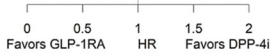


Figure 2 | Comparative effectiveness of (a) sodium-glucose cotransporter-2 inhibitors (SGLT-2i) versus dipeptidyl peptidase-4 inhibitors (DPP-4i), (b) glucagon-like peptide-1 receptor agonists (GLP-1RAs) versus DPP-4i, and (Continued)

c

SGLT-2i vs. GLP-1RA

	No. (%) of patients	SGLT-2i No. events	GLP-1RA No. events	SGLT-2i IR/1000 PY	GLP-1RA IR/1000 PY	Rate difference (95% CI)	HR (95% CI)
Overall	27,977 (100.0%)	1300	1462	76.2	81.2	-5.0 (-10.9 to 0.8)	0.92 (0.86 to 0.99)
Age ≥75 yr	10,595 (38.0%)	518	535	84.1	80.3	3.8 (-6.2 to 13.7)	1.03 (0.91 to 1.16)
Age <75 yr	17,262 (62.0%)	696	811	64.3	70.9	-6.6 (-13.4 to 0.23)	0.89 (0.81 to 0.98)
Male	15,345 (55.4%)	775	866	81.3	87.4	-6.1 (-14.3 to 2.1)	0.92 (0.84 to 1.02)
Female	12,336 (44.6%)	531	605	73.1	76.5	-3.3 (-12.0 to 5.4)	0.93 (0.82 to 1.04)
White[a]	13,089 (90.3%)	568	616	75.4	76.5	-1.1 (-9.7 to 7.6)	0.97 (0.87 to 1.09)
Black[a]	1405 (9.7%)	54	62	75.4	80.7	-5.3 (-33.7 to 23.1)	0.92 (0.64 to 1.32)
Heart failure	6897 (24.8%)	417	423	109.2	105.7	3.5 (-11.1 to 18.0)	1.02 (0.89 to 1.17)
No heart failure	20,889 (75.2%)	885	1006	67.7	71.3	-3.7 (-9.9 to 2.6)	0.93 (0.85 to 1.02)
CVD	16,292 (58.8%)	873	915	92.3	91.8	0.6 (-8.0 to 9.1)	0.99 (0.90 to 1.09)
No CVD	11,434 (41.2%)	442	534	59.8	67.8	-8.0 (-16.0 to 0.0)	0.87 (0.77 to 0.99)
ACEi/ARB/ARNI	18,926 (68.0%)	951	1051	79.8	83.0	-3.2 (-10.4 to 3.9)	0.94 (0.86 to 1.02)
No ACEi/ARB/ARNI	8891 (32.0%)	349	442	69.3	81.2	-11.9 (-22.4 to -1.4)	0.84 (0.73 to 0.97)
MRA	1600 (5.8%)	124	112	132.1	107.9	24.2 (-6.5 to 54.8)	1.19 (0.92 to 1.55)
No MRA	26,226 (94.2%)	1169	1322	73.1	78.0	-4.9 (-10.8 to 1.1)	0.92 (0.85 to 1.00)
Loop diuretic	6626 (23.8%)	390	412	100.6	99.6	1.0 (-12.9 to 14.9)	1.00 (0.87 to 1.15)
No loop diuretic	21,157 (76.2%)	914	1043	70.1	75.9	-5.8 (-12.2 to 0.7)	0.91 (0.83 to 0.99)
RAASi (ACE/ARB/ARNI/MRA)	19,601 (70.3%)	983	1086	80.2	83.8	-3.7 (-10.7 to 3.4)	0.94 (0.86 to 1.02)
No RAASi	8265 (29.7%)	327	401	70.0	79.7	-9.7 (-20.6 to 1.2)	0.86 (0.75 to 0.99)

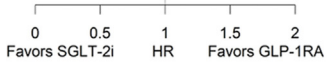


Figure 2| (Continued) **(c) SGLT-2i versus GLP-1RAs on risk of hyperkalemia diagnosis in inpatient or outpatient setting among subgroups after 1:1 propensity score matching.** *Only data from Centers for Medicare & Medicaid Services. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IR, incidence rate; MRA, mineralocorticoid receptor antagonist; PY, person-years; RAASi, renin-angiotensin-aldosterone system inhibitor.

because of monitoring protocols, trials have a much higher adherence to drug therapy compared with routine clinical practice; in our population-based study, 61% of participants in routine care discontinued treatment during follow-up. Third, there are differences in the incidence rate of hyperkalemia between the previous meta-analysis of trials and our observational study, likely explained by population differences: among the 6 included trials, the incidence rate for hyperkalemia varied between 1.6 (DECLARE-TIMI [Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction] trial) and 56.9 (DAPA-CKD [Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease] trial) hyperkalemia events per 1000 person-years.[17] In contrast, the incidence rate for the primary outcome in our study was higher, between 75.3 and 100.0 hyperkalemia events per 1000 person-years. The difference in incidence rates is likely an underestimate, as the trial relied on serial serum potassium measurements, and our study used claims diagnoses; the findings from our internal validation study suggest that the true incidence rate in our study may be ≈3-fold higher. Fourth, our study provides a head-to-head comparison of SGLT-2i, GLP-1RA, and DPP-4i, rather than placebo. Although SGLT-2i initiators had a lower risk of hyperkalemia compared with DPP-4i, we found only small differences between SGLT-2i and GLP-1RA, and any differences between the latter 2 agents are likely to be small.

The protective association observed for GLP-1RA on the risk of hyperkalemia in a clinical setting has, to our knowledge, not been reported previously. There may be several plausible mechanisms for this finding, although additional research should elucidate the precise mechanisms for our observations. GLP-1RAs regulate water and electrolyte balance in the postprandial state through rapid feed-forward effects on the kidney, and influence tubular handling of electrolytes, including sodium.[20] The increased

proximal sodium excretion due to GLP-1RAs may augment potassium secretion by the principal cells in the cortical collecting duct by increasing the electronegative charge.[36] Furthermore, a small randomized trial in 35 overweight participants with T2D showed that after 8 weeks of treatment, the GLP-1RA lixisenatide increased the fractional and absolute excretion of potassium itself,[19] although another study by the same group did not find differences in fractional potassium excretion for liraglutide compared with sitagliptin.[37] We observed that the protective effect of GLP-1RA occurred rapidly (within the first 6 months). In addition to these direct effects on electrolytes, GLP-1RAs may also slow progression of kidney disease and albuminuria,[38–40] which may decrease the risk of hyperkalemia in the long-term.

Our study also had sufficient sample size to investigate single agents within the SGLT-2i and GLP-1RA class and enable us to assess whether the reduced risk of hyperkalemia was a class effect or only observed for specific agents. The consistency of HRs (between 0.72 and 0.77 for single SGLT-2i agents and between 0.75 and 0.86 for single GLP-1RA agents) suggests that the protective associations of SGLT-2i and GLP-1RA on hyperkalemia represent a class effect.

Our study has several strengths, including its large sample size and the use of an active-comparator new user design, which reduces confounding by indication and mitigates time-related biases, such as immortal and prevalent user bias. Furthermore, our analysis adjusted for a rich set of >140 confounders, and we confirmed our results in multiple sensitivity analyses. Our study also has limitations. First, we cannot rule out confounding in our observational study, and we lacked information on dietary habits (e.g., intake of high potassium-containing foods). However, we adjusted for a wide variety of confounders and confounder proxies, including many comorbid conditions, medications, diabetes-specific complications, measures of health care use, and healthy behavior markers, which reflect overall health status.[22] Furthermore, in the subset of patients with available data, we did not observe large imbalances in laboratory measurements that were not included in the propensity score model, including estimated glomerular filtration rate and serum potassium level. Confounding is also expected to be less severe for "unintended effects" or "unexpected outcomes,"[23] such as hyperkalemia, as physicians do not specifically prescribe SGLT-2i or GLP-1RA with the aim to reduce the risk of hyperkalemia.[41] Second, our primary outcome was defined on the basis of claims-based diagnosis codes, rather than serum potassium measurements. In an internal validation study, we found high specificity (>99%) for serum potassium level ≥5.5 or 6.0 mmol/L; thus, relative risks in our study should not be affected. Because sensitivity was low (≈37%), the absolute risk and rate differences represent an underestimate of the true benefit, and SGLT-2i/GLP-1RA will likely have even larger absolute benefits than that observed in our study compared with DPP-4i. Third, our study had relatively short follow-up, because of a high proportion of patients who discontinued the treatment. However, this represents the reality of routine clinical practice in which many patients have lower adherence to medication compared with trials. Furthermore, the lower risk for hyperkalemia observed for SGLT-2i and GLP-1RA occurred within the first few months of follow-up. As in any study based on health insurance claims, exposure misclassification is possible, especially if patients refill, but do not take, their medications; however, in our primary analysis, we censored patients if they did not refill medications within a month following the end of the medication supply; moreover, we do not expect any potential exposure misclassification to differ across the treatment groups.

In conclusion, in this cohort study of US individuals with CKD and T2D, SGLT-2i and GLP-1RAs were associated with a lower risk of hyperkalemia, compared with DPP-4i. Initiation of these drugs may enable the use of other guideline-recommended medications that improve clinical outcomes but increase serum potassium level, such as RASi.

DISCLOSURE

EP is investigator of an investigator-initiated grant to the Brigham and Women's Hospital from Boehringer Ingelheim, not directly related to the topic of the submitted work. DJW reports serving on Data Monitoring Committees for Novo Nordisk, not related to the topic of this work. All the other authors declared no competing interests.

DATA STATEMENT

A data use agreement is required for each of these data sources. Our data use agreements do not permit us 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/licenses.

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AUTHOR CONTRIBUTIONS

ELF and JMP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: ELF, EP, and JMP. Acquisition and analysis of interpretation of data: all authors. Drafting of the manuscript: ELF. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: ELF, JM, and AC.

Administrative, technical, or material support: all authors. Supervision: EP and JMP.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. Definitions of inclusion and exclusion criteria.

Supplementary Table S2. Outcome definitions.

Supplementary Table S3. Definition of subgroup variables cardiovascular disease and heart failure.

Supplementary Table S4. Full list of baseline characteristics in patients with chronic kidney disease (CKD) and type 2 diabetes, stratified by sodium-glucose cotransporter-2 inhibitor (SGLT-2i) versus dipeptidyl peptidase-4 inhibitor (DPP-4i) initiation in the pooled cohort, before and after 1:1 propensity score matching.

Supplementary Table S5. Full list of baseline characteristics in patients with chronic kidney disease (CKD) and type 2 diabetes, stratified by glucagon-like peptide-1 receptor agonist (GLP-1RA) versus dipeptidyl peptidase-4 inhibitor (DPP-4i) initiation in the pooled cohort, before and after 1:1 propensity score matching.

Supplementary Table S6. Full list of baseline characteristics in patients with chronic kidney disease (CKD) and type 2 diabetes, stratified by sodium-glucose cotransporter-2 inhibitor (SGLT-2i) versus glucagon-like peptide-1 receptor agonist (GLP-1RA) initiation in the pooled cohort, before and after 1:1 propensity score matching.

Supplementary Table S7. Individual sodium-glucose cotransporter-2 inhibitor (SGLT-2i), glucagon-like peptide-1 receptor agonist (GLP-1RA), and dipeptidyl peptidase-4 inhibitor (DPP-4i) agents included in the analysis after 1:1 propensity score matching.

Supplementary Table S8. Follow-up and censoring reasons after 1:1 propensity score matching for (**A**) sodium-glucose cotransporter-2 inhibitor (SGLT-2i) versus dipeptidyl peptidase-4 inhibitor (DPP-4i), (**B**) glucagon-like peptide-1 receptor agonist (GLP-1RA) versus DPP-4i, and (**C**) SGLT-2i versus GLP-1RA.

Supplementary Table S9. Absolute risks and risk differences for the primary outcome at 6-month intervals for sodium-glucose cotransporter-2 inhibitor (SGLT-2i) versus dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like peptide-1 receptor agonist (GLP-1RA) versus DPP-4i, and SGLT-2i versus GLP-1RA.

Supplementary Table S10. Comparative effectiveness of (**A**) sodium-glucose cotransporter-2 inhibitor (SGLT-2i) versus dipeptidyl peptidase-4 inhibitor (DPP-4i), (**B**) glucagon-like peptide-1 receptor agonist (GLP-1RA) versus DPP-4i, and (**C**) SGLT-2i versus GLP-1RA on risk of hyperkalemia diagnosis in inpatient or emergency department setting (secondary outcome) before and after 1:1 propensity score matching.

Supplementary Table S11. Comparative effectiveness of (**A**) sodium-glucose cotransporter-2 inhibitor (SGLT-2i) versus dipeptidyl peptidase-4 inhibitor (DPP-4i), (**B**) glucagon-like peptide-1 receptor agonist (GLP-1RA) versus DPP-4i, and (**C**) SGLT-2i versus GLP-1RA on risk of serum potassium level ≥5.5 mmol/L before and after 1:1 propensity score matching.

Supplementary Table S12. Comparative effectiveness of individual sodium-glucose cotransporter-2 inhibitor (SGLT-2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) agents compared with dipeptidyl peptidase-4 inhibitor (DPP-4i) on risk of hyperkalemia diagnosis in the inpatient or outpatient setting, after 1:1 propensity score matching.

Supplementary Table S13. Sensitivity analyses: incidence rate differences and hazard ratios for (**A**) sodium-glucose cotransporter-2 inhibitor (SGLT-2i) versus dipeptidyl peptidase-4 inhibitor (DPP-4i), (**B**) glucagon-like peptide-1 receptor agonist (GLP-1RA) versus DPP-4i, and (**C**) SGLT-2i versus GLP-1RA after 1:1 propensity score matching.

Supplementary Figure S1. Overview of study design.

Supplementary Figure S2. Patient flowchart.

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