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GLP-1RA vs DPP-4i Use and Rates of Hyperkalemia and RAS Blockade Discontinuation in Type 2 Diabetes

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IMPORTANCE Hyperkalemia is a common complication in people with type 2 diabetes (T2D) that may limit the use of guideline-recommended renin-angiotensin system inhibitors (RASis). Emerging evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1RAs) increase urinary potassium excretion, which may translate into reduced hyperkalemia risk.

OBJECTIVE To compare rates of hyperkalemia and RASi persistence among new users of GLP-1RAs vs dipeptidyl peptidase-4 inhibitors (DPP-4is).

DESIGN, SETTING, AND PARTICIPANTS This cohort study included all adults with T2D in the region of Stockholm, Sweden, who initiated GLP-1RA or DPP-4i treatment between January 1, 2008, and December 31, 2021. Analyses were conducted between October 1, 2023, and April 29, 2024.

EXPOSURES GLP-1RAs or DPP-4is.

MAIN OUTCOMES AND MEASURES The primary study outcome was time to any hyperkalemia (potassium level >5.0 mEq/L) and moderate to severe (potassium level >5.5 mEq/L) hyperkalemia. Time to discontinuation of RASi use among individuals using RASis at baseline was assessed. Inverse probability of treatment weights served to balance more than 70 identified confounders. Marginal structure models were used to estimate per-protocol hazard ratios (HRs).

RESULTS A total of 33 280 individuals (13 633 using GLP-1RAs and 19 647 using DPP-4is; mean [SD] age, 63.7 [12.6] years; 19 853 [59.7%] male) were included. The median (IQR) time receiving treatment was 3.9 (1.0-10.9) months. Compared with DPP-4i use, GLP-1RA use was associated with a lower rate of any hyperkalemia (HR, 0.61; 95% CI, 0.50-0.76) and moderate to severe (HR, 0.52; 95% CI, 0.28-0.84) hyperkalemia. Of 21 751 participants who were using RASis, 1381 discontinued this therapy. The use of GLP-1RAs vs DPP-4is was associated with a lower rate of RASi discontinuation (HR, 0.89; 95% CI, 0.82-0.97). Results were consistent in intention-to-treat analyses and across strata of age, sex, cardiovascular comorbidity, and baseline kidney function.

CONCLUSIONS In this study of patients with T2D managed in routine clinical care, the use of GLP-1RAs was associated with lower rates of hyperkalemia and sustained RASi use compared with DPP-4i use. These findings suggest that GLP-1RA treatment may enable wider use of guideline-recommended medications and contribute to clinical outcomes in this population.

Supplemental content

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Hyperkalemia is a common electrolyte abnormality in patients with type 2 diabetes (T2D), particularly in those with chronic kidney disease and heart failure,[1-5] that is associated with adverse health outcomes.[6] Hyperkalemia and/or fear of hyperkalemia limits the optimal use of guideline-recommended renin-angiotensin system inhibitors (RASis).[7] Novel diabetes medication classes may exert pleiotropic effects, including kaliuresis. These effects have been described recently for sodium-glucose cotransporter-2 inhibitors (SGLT-2is),[8-11] but less is known about the potential effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on potassium homeostasis. In animal models, administration of GLP-1RAs increased urinary potassium excretion and normalized serum potassium levels.[12] In humans, small-scale clinical trials show that GLP-1RAs influence the tubular handling of electrolytes and increase potassium excretion.[13-15] Whether these observations have clinical implications remains unclear. A recent study using US claims data[9] observed that users of GLP-1RAs experienced a 20% lower rate of hyperkalemia diagnoses compared with users of dipeptidyl peptidase-4 inhibitors (DPP-4is). The potential limitations of this study include the reliance on diagnostic codes for hyperkalemia outcomes, which have poor sensitivity,[16,17] and the absence of information on important modifiers, such as estimated glomerular filtration rate (eGFR). Furthermore, it is unknown whether the use of GLP-1RAs could improve the persistence of RASi therapy. In this study, we used routinely collected health records and laboratory data from the region of Stockholm, Sweden, to compare the rates of hyperkalemia among patients with T2D who used GLP-1RA or DPP4-i treatment. We also explored whether the use of GLP-1RAs or DPP4-is was associated with the enabled use of RASi therapy.

Key Points

Question Is the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) vs dipeptidyl peptidase-4 inhibitors (DPP-4is) associated with different rates of hyperkalemia or prolonged renin-angiotensin system (RAS) inhibitor use in people with type 2 diabetes (T2D)?

Findings In this cohort study of 33 280 patients with T2D, the use of GLP-1RAs was associated with a lower rate of hyperkalemia and prolonged RAS inhibitor use compared with the use of DPP-4is.

Meaning These findings confirm that the use of GLP-1RAs in routine care is associated with a lower risk of hyperkalemia in people with T2D and that GLP-1RA use may enable the use of guideline-recommended RAS inhibitors, thus contributing to their overall cardioprotective and renoprotective effect.

Methods

Data Source

We used data from the Stockholm Creatinine Measurements (SCREAM) project, a health care utilization cohort of all residents in Stockholm, Sweden, between January 1, 2006, and December 31, 2021.[18] The region of Stockholm had a population of 2.3 million citizens in 2021 and provides universal health care with a single unified health system. Administrative databases with complete information on demographic data, health care use, diagnoses, therapeutic and surgical procedures, and vital status were enriched with performed laboratory tests and prescriptions dispensed at pharmacies. Registries were linked and deidentified by the Swedish National Board of Welfare and are considered to have no or minimal loss to follow-up. The regional ethical review boards and the Swedish National Board of Welfare approved the study and deemed it not to require informed consent because it used deidentified data.

Following the target trial emulation framework,[19,20] we specified the protocol of a hypothetical trial that would evaluate the comparative effectiveness of GLP-1RA vs DPP-4i use on hyperkalemia risk (see study design details in eTable 1 in Supplement 1). The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Cohort Design

We included all adult (aged >18 years) Stockholm residents with T2D who were new users of GLP-1RAs or DPP-4is. New users were people who filled their first GLP-1RA or DPP-4i dispensation between January 1, 2008, and December 31, 2021, with no previous recorded dispensation of either drug in the previous year. The date of the first GLP-1RA or DPP-4i dispensation was defined as the index date, at which point baseline covariates were defined and follow-up started.

People who had missing data on age, sex, or eGFR at index date or had a history of kidney failure (long-term dialysis, kidney transplantation, or eGFR of <15 mL/min/1.73 m^2), pancreatitis, cirrhosis, or acute hepatitis were excluded. Furthermore, we excluded patients who had a recorded potassium level greater than 5.5 mEq/L (to convert to millimoles per liter, multiply by 1) or who were dispensed a potassium binder in the 6 months before index date. This approach was taken to decrease the possibility of reverse causation bias (ie, that early outcomes during follow-up would be related to a previous hyperkalemia diagnosis) (eTable 2 and eFigure 1 in Supplement 1).

Treatment Strategies

We compared 2 treatment strategies: initiation of any GLP-1RA (ie, exenatide, liraglutide, lixisenatide, dulaglutide, or semaglutide) and continuation of treatment during follow-up vs initiation of any DPP-4i (ie, sitagliptin, vildagliptin, linagliptin, or saxagliptin) and continuation of treatment during follow-up. Discontinuation of GLP-1RA or DPP-4i treatment was defined as no further dispensation recorded within 30 days after the estimated supply of the most recent dispensation. Because many patients discontinue their initial treatment in clinical practice (eTable 3 in Supplement 1), which would force the observational analogue of the intention-to-treat effect to null, we estimated the observational analogue of the per-protocol effect as our main analysis.

Table 1. Key Baseline Characteristics for Individuals Included in the Primary Cohort

Characteristic	No. (%)			
	Overall (N = 33 280)	DPP-4i (n = 19 647)	GLP-1RA (n = 13 633)	SAMD[a]
Age, mean (SD), y	63.7 (12.6)	66.0 (12.4)	60.37 (12.0)	0.463
Sex				
Male	19 853 (59.7)	11 958 (60.9)	7895 (57.9)	0.060
Female	13 427 (40.3)	7689 (39.1)	5738 (42.1)	
Potassium, mean (SD), mEq/L	4.18 (0.36)	4.19 (0.36)	4.16 (0.35)	0.067
Duration of diabetes, median (IQR), y	6.46 (2.60-10.90)	6.55 (2.74-10.67)	6.32 (2.42-11.26)	0.021
HbA_{1c}, mean (SD), %	8.0 (1.5)	7.9 (1.4)	8.2 (1.7)	0.155
eGFR, median (IQR), mL/min/1.73 m^2	89.1 (70.6-100.5)	86.5 (66.5-98.5)	92.9 (76.4-103.0)	0.320
UACR, median (IQR), mg/g	11.9 (5.3-30.9)	12.9 (5.3-30.9)	10.8 (5.1-30.1)	0.014
Medical history				
Heart failure and cardiomyopathy	1854 (5.6)	1171 (6.0)	683 (5.0)	0.042
Atrial fibrillation	2699 (8.1)	1752 (8.9)	947 (6.9)	0.073
Diabetic nephropathy	1178 (3.5)	653 (3.3)	525 (3.9)	0.028
Diabetic retinopathy or cataract	3096 (9.3)	1634 (8.3)	1462 (10.7)	0.082
Diabetic neuropathy	1076 (3.2)	594 (3.0)	482 (3.5)	0.029
Diabetic peripheral vascular complication, gangrene, or ulcer	486 (1.5)	271 (1.4)	215 (1.6)	0.016
COPD	2877 (8.6)	1443 (7.3)	1434 (10.5)	0.111
Other lung disease	2092 (6.3)	1012 (5.2)	1080 (7.9)	0.112
Psychiatric disorder	4001 (12.0)	1949 (9.9)	2052 (15.1)	0.156
Medication use in the previous 6 mo				
RASi	21 751 (65.3)	12 611 (64.2)	9140 (67.0)	0.058
RASi use pattern[b]				
New users	1285 (3.9)	769 (3.9)	516 (3.8)	0.063
Prevalent users (good adherence)	17 012 (51.1)	9813 (49.9)	7199 (52.8)	
Prevalent users (poor adherence)	3454 (10.4)	2029 (10.3)	1425 (10.5)	
Nonusers	11 529 (34.6)	7036 (35.8)	4493 (33.0)	
Calcium channel blocker	10 968 (33.0)	6318 (32.2)	4650 (34.1)	0.041
Loop diuretic	4103 (12.3)	2553 (13.0)	1550 (11.4)	0.050
MRA	1717 (5.2)	950 (4.8)	767 (5.6)	0.036
Thiazide	8410 (25.3)	4880 (24.8)	3530 (25.9)	0.024
β-Blocker	12 810 (38.5)	7839 (39.9)	4971 (36.5)	0.071
Platelet inhibitor	9181 (27.6)	5959 (30.3)	3222 (23.6)	0.151
Anticoagulant	3381 (10.2)	2086 (10.6)	1295 (9.5)	0.037
Lipid-lowering drug	20 215 (60.7)	11 874 (60.4)	8341 (61.2)	0.015
Antidepressant	4982 (15.0)	2588 (13.2)	2394 (17.6)	0.122
Diabetes drugs in the previous 6 mo				
Metformin	26 376 (79.3)	15 503 (78.9)	10 873 (79.8)	0.021
Sulfonylurea	7363 (22.1)	5012 (25.5)	2351 (17.2)	0.203
SGLT2 inhibitor	2457 (7.4)	925 (4.7)	1532 (11.2)	0.243
Insulin	6941 (20.9)	2711 (13.8)	4230 (31.0)	0.422
Other antidiabetics	1438 (4.3)	991 (5.0)	447 (3.3)	0.088
Health service utilization in the previous year				
Hospital admissions for diabetes	4458 (13.4)	2788 (14.2)	1670 (12.2)	0.057
Outpatient visits for diabetes	9416 (28.3)	4907 (25.0)	4509 (33.1)	0.179

Abbreviations: COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin A_{1c}; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; SAMD, standardized absolute mean difference; SGLT2, sodium-glucose cotransporter-2; UACR, urine albumin-creatinine ratio.

SI conversion factors: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01; potassium to millimoles per liter, multiply by 1.

[a] An SAMD greater than 0.1 indicates a meaningful imbalance between groups.

[b] Ongoing RASi use was ascertained by the overlap between the date of GLP-1RA or DPP-4i treatment start and the estimated pill supply of the last recorded RASi dispensation. New RASi users (if RASi treatment was initiated at the same time or within a year from the initiation of GLP-1RA or DPP-4i use), prevalent users with good adherence (there was a history of RASi dispensations for at least 1 year before the index date and the proportion of days covered in the year was ≥75%), and prevalent users with poor adherence (proportion of days covered <75%).

Table 2. Number and Rate of First Hyperkalemia Events in New Users of GLP-1RAs vs DPP-4is in Per-Protocol Analyses[a]

Outcome and exposure	No. of participants	No. of events	Follow-up, median (IQR), mo	Events per 1000 person-years (95% CI)[b]	Estimate, % (95% CI)		HR (95% CI)	
					12-mo Absolute risk	12-mo Risk difference	Crude	Weighted[c]
Any hyperkalemia								
DPP-4i	19 647	592	3.9 (1.0 to 11.8)	39.0 (36.0 to 42.2)	4.6 (4.2 to 5.1)	0 [Reference]	1.0 [Reference]	1.0 [Reference]
GLP-1RA	13 633	160	3.0 (1.0 to 7.9)	21.0 (18.0 to 24.4)	2.9 (2.3 to 3.5)	−1.7 (−2.4 to −1.1)	0.51 (0.43 to 0.61)	0.62 (0.50 to 0.76)
Moderate to severe hyperkalemia								
DPP-4i	19 647	150	4.9 (1.0 to 12.8)	9.6 (8.2 to 11.2)	2.5 (2.1 to 3.1)	0 [Reference]	1.0 [Reference]	1.0 [Reference]
GLP-1RA	13 633	29	3.0 (1.0 to 8.9)	3.8 (2.5 to 5.2)	1.1 (0.9 to 1.3)	−0.5 (−0.9 to −0.2)	0.37 (0.25 to 0.56)	0.52 (0.28 to 0.84)

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio.

[a] Any hyperkalemia is defined as a plasma or serum potassium level greater than 5.00 mEq/L and moderate to severe hyperkalemia as a plasma or serum potassium level greater than 5.50 mEq/L (to convert to millimoles per liter, multiply by 1).

[b] Number of events, person-years, and incidence rates were calculated in the unweighted population.

[c] Weights were calculated based on age, sex, calendar year, duration of diabetes at index date, time-varying laboratory measurements (eg, potassium level, estimated glomerular filtration rate, glycated hemoglobin A_{1c}, and urinary albumin-creatinine ratio), comorbidities (eg, acute coronary syndrome and heart failure), diabetes drugs use, other medication use (eg, renin-angiotensin system inhibitors and mineralocorticoid receptor antagonists), and health care resource utilization.

Outcomes

The primary outcome was hyperkalemia, defined by the presence of an elevated potassium level exceeding the commonly used threshold of 5.0 mEq/L. For completeness, we also evaluated the secondary outcomes of moderate to severe hyperkalemia (potassium level >5.5 mEq/L). We computed both the time to the first-recorded event (ie, first occurrence) and the incidence rate over time (ie, recurrence). For the latter and given that 1 patient can develop multiple hyperkalemia episodes during follow-up, hyperkalemia events within 7 days were grouped and considered the same event (see definitions in eTable 4 in Supplement 1).

Follow-Up

Patients were followed up from index date to the occurrence of the study outcomes, death, emigration from the region, or end of follow-up (December 31, 2021). Because the per-protocol outcome was our main estimand of interest, patients were additionally censored when they deviated from their initially assigned treatment (ie, when they stopped treatment or switched to the comparator drug).

Covariates

Two sets of covariates were considered in our analysis for confounding adjustment: baseline and time-varying characteristics. Baseline characteristics included demographics (eg, age and sex), laboratory measurements (eg, potassium level, eGFR, glycated hemoglobin A_{1c} [HbA_{1c}], and urinary albumin-creatinine ratio [UACR]), comorbidities (eg, acute coronary syndrome and heart failure), diabetes drugs use, use of other medications (eg, RASi and mineralocorticoid receptor antagonists [MRAs]), health care resource use, and calendar year. Time-varying covariates were updated at each month during the follow-up and included laboratory measurements, comorbidities, medications use, and health care resource use (see definitions in eTable 5 in Supplement 1).

Statistical Analysis

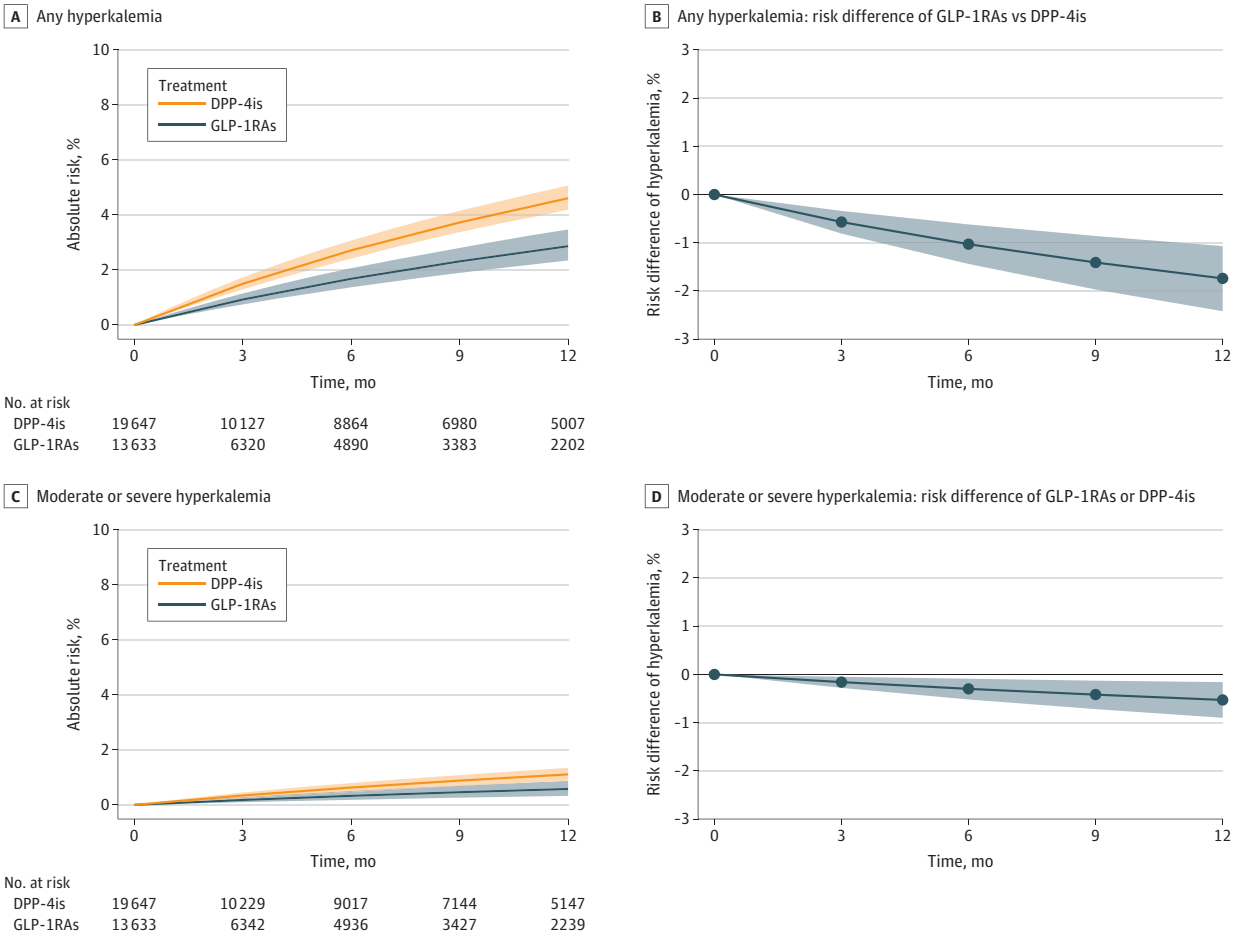
Analyses were conducted between October 1, 2023, and April 29, 2024. Baseline characteristics were summarized and presented as means (SDs) or medians (IQRs) for continuous variables, depending on the distribution, and as numbers (percentages) for categorical variables. The balance of baseline characteristics between the 2 groups was assessed by standardized absolute mean differences (SAMDs), using an SAMD of greater than 0.1 as the threshold for meaningful imbalance. We calculated crude incidence rates per 1000 person-years for study outcomes following Poisson distributions.[21] The details of our approaches for data analysis through the marginal structural model and control for confounding through inverse probability of treatment weighting and inverse probability of censoring weighting can be found in the eMethods in Supplement 1.

Covariates such as plasma or serum potassium, HbA_{1c}, and UACR were missing in 1.9%, 1.2%, and 10.8% of study participants, respectively. We used multiple imputation by chained equations to impute 5 complete datasets for each outcome separately using classification and regression trees. The imputation model included the treatment variable, all covariates, the event indicator for the outcome, and the Nelson-Aalen estimate of the baseline and each month's cumulative hazard. The effect estimates were calculated separately in each imputed dataset and then pooled using the Rubin rule.[22] All statistical analyses were performed using R software, version 4.2.1 (R Foundation for Statistical Computing).

Secondary Analysis: Persistence to RAS Inhibitor Therapy

We analyzed persistence to RASi therapy in the subpopulation of patients using RASis at the time of GLP-1RA or DPP-4i initiation. Current RASi users were defined as those with an overlap between the date of GLP-1RA or DPP-4i treatment start and the estimated pill supply of the last recorded RASi

Figure. Weighted Cumulative Incidence Curves for Hyperkalemia of Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RAs) vs Dipeptidyl Peptidase-4 Inhibitors (DPP-4is) in Per-Protocol Analyses



Weights were calculated based on age, sex, calendar year, duration of diabetes at index date, time-varying laboratory measurements (eg, potassium level, estimated glomerular filtration rate, glycated hemoglobin, and urinary albumin-creatinine ratio), comorbidities (eg, acute coronary syndrome and heart failure), diabetes drugs use, other medication use (eg, renin-angiotensin system inhibitors and mineralocorticoid receptor antagonists), and health care resource utilization. Any hyperkalemia is defined as a plasma or serum potassium level greater than 5.00 mEq/L and moderate to severe hyperkalemia as a plasma or serum potassium level greater than 5.50 mEq/L (to convert to millimoles per liter, multiply by 1). Shaded bands represent 95% CIs.

dispensation. Discontinuation of RASi use was defined as the absence of a RASi dispensation during 90 days after the estimated pill supply of the most recent fill had ended. In addition to the covariates described earlier, we additionally adjusted models for the pattern of RASi use as follows: new RASi users (if treatment was initiated at the same time or within a year from GLP-1RA or DPP-4i initiation), prevalent users with good adherence (if there was a history of RASi dispensations for at least 1 year before index date and the proportion of days covered in the year was ≥75%), and prevalent users with poor adherence (proportion of days covered <75%).

Subgroup and Sensitivity Analyses

Subgroup analyses tested the potential effect modification by conditions that predispose patients to hyperkalemia[2] (old age [≥70 vs <70 years], male sex, low eGFR [≥60 vs <60 mL/min/1.73 m^2], and history of cardiovascular disease) as well as medications that affect hyperkalemia risks[8,23,24] (SGLT2 inhibitors, insulin, MRAs, and pattern of RASi use). For each subgroup analysis, inverse probabilities of treatment weighting and inverse probabilities of censoring weighting were reestimated.[25] Multiplicative interaction was tested by including interaction terms between treatment strategies and the variable of interest to the weighted marginal structural model.

To test the robustness of our results, we estimated the 12-month intention-to-treat effect, assuming that all patients consumed the medication as assigned during this period. To evaluate the potential influence of residual confounding, we explored the effects of treatments on alternative outcomes: major adverse cardiovascular events, which we considered a positive control outcome based on pivotal clinical trials,[26,27] and diverticular disease, which we considered a negative control outcome that should not be affected by either treatment. To investigate the possibility of differential outcome ascertainment, we calculated and compared the rates of potassium testing during follow-up in each treatment group. Finally, 2 addi-

Table 3. Number and Rate of Repeated Hyperkalemia Events in New Users of GLP-1RAs vs DPP-4is in Per-Protocol Analyses[a]

Outcome and exposure	No. of participants	No. of events	Follow-up, median (IQR), mo	Events per 1000 person-years (95% CI)[b]	Mean (95% CI), %		IRR (95% CI)	
					12-mo Cumulative count	12-mo Cumulative count difference	Crude	Weighted[c]
Any hyperkalemia								
DPP-4i	19 647	990	4.9 (1.0 to 12.8)	63.0 (59.2 to 67.0)	7.3 (6.3-8.3)	0 [Reference]	1.0 [Reference]	1.0 [Reference]
GLP-1RA	13 633	223	3.0 (1.0 to 8.9)	28.8 (25.3 to 32.7)	3.1 (2.2 to 4.0)	−4.3 (−5.7 to −2.9)	0.45 (0.39 to 0.52)	0.48 (0.42 to 0.56)
Moderate to severe hyperkalemia								
DPP-4i	19 647	197	4.9 (1.0 to 12.8)	12.6 (10.9 to 14.4)	1.5 (1.1 to 1.9)	0 [Reference]	1.0 [Reference]	1.0 [Reference]
GLP-1RA	13 633	31	3.0 (1.0 to 8.9)	4.0 (2.8 to 5.5)	0.5 (0.2 to 0.9)	−1.0 (−1.5 to −0.5)	0.33 (0.21 to 0.46)	0.39 (0.28 to 0.55)

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; IRR, incidence rate ratio.

[a] Any hyperkalemia is defined as a plasma or serum potassium level greater than 5.00 mEq/L and moderate to severe hyperkalemia as a plasma or serum potassium level greater than 5.50 mEq/L (to convert to millimoles per liter, multiply by 1).

[b] Number of events, person-years, and incidence rates were calculated in the unweighted population.

[c] Weights were calculated based on age, sex, calendar year, duration of diabetes at index date, time-varying laboratory measurements (eg, potassium level, estimated glomerular filtration rate, glycated hemoglobin, and urinary albumin-creatinine ratio), comorbidities (eg, acute coronary syndrome and heart failure), diabetes drugs use, other medication use (eg, renin-angiotensin system inhibitors and mineralocorticoid receptor antagonists), and health care resource utilization.

tional sensitivity analyses were included. We modeled our main analyses for the outcomes of severe hyperkalemia (potassium level >6.0 mEq/L) and clinically recognized hyperkalemia events (composite of receiving a clinical diagnosis of hyperkalemia in the primary position of a hospitalization or emergency department visit or the initiation of potassium binders) (eTable 4 in Supplement 1). We evaluated different definitions of RASi discontinuation, prolonging the grace periods to 120 and 180 days.

Results

Patient Characteristics

After applying the inclusion and exclusion criteria, we included 33 280 adults with T2D (mean [SD] age, 63.7 [12.6] years; 19 853 [59.7%] male and 13 427 [40.3%] female). Of these participants, 19 647 were new DPP-4i users (82.5% sitagliptin, 13.8% linagliptin, 2.3% saxagliptin, and 0.8% vildagliptin) and 13 633 patients were new GLP-1RA users (57.4% liraglutide, 33.5% semaglutide, 5.1% dulaglutide, 2.7% exenatide, and 1.0% lixisenatide) (eFigure 2 in Supplement 1). Key baseline characteristics are summarized in **Table 1**, and all baseline characteristics used as covariates in our analysis are presented in eTable 7 in Supplement 1.

Users of GLP-1RAs were younger than DPP-4i users (mean [SD] age, 60.4 [12.0] vs 66.0 [12.4] years) and had higher HbA_{1c} levels (mean [SD], 8.2% [1.7%] vs 7.9% [1.4%] [to convert to proportion of total hemoglobin, multiply by 0.01]), higher eGFR (median [IQR], 92.9 [76.4-103.0] vs 86.5 [66.5-98.5] mL/min/1.73 m^2), and lower UACR (median [IQR], 10.8 [5.1-30.1] vs 12.9 [5.3-30.9] mg/g). Users of GLP-1RAs had a higher prevalence of chronic obstructive pulmonary disease (10.5% vs 7.3%) and psychiatric disorders (15.1% vs 9.9%). Users of GLP-1RAs more often used antidepressants (17.2% vs 13.5%) and less often used platelet inhibitors (22.6% vs 30.3%) than did DPP-4i users. Users of GLP-1RAs received more SGLT2 inhibitors (11.2% vs 4.7%) and insulin (31.0% vs 13.8%) and less sulfonylurea (17.2% vs 25.5%) and β-blockers (36.5% vs 39.9%). Users of GLP-1RAs had a higher frequency of outpatient visits to the diabetologist (33.1% vs 25.0%) in the year prior than did DPP-4i users. All baseline covariates were balanced after weighting with an SAMD less than 0.1 (eFigure 4 in Supplement 1).

GLP-1RA vs DPP-4i Use and Rates of Hyperkalemia

During a median (IQR) follow-up of 3.9 (1.0-10.9) months, 752 individuals experienced at least 1 hyperkalemia event. The incidence rates for hyperkalemia were 21.0 (95% CI, 18.0-24.4) per 1000 person-years for GLP-1RA initiators and 39.0 (95% CI, 36.0-42.2) for DPP-4i initiators. The weighted hazard ratio (HR) for hyperkalemia was 0.62 (95% CI, 0.50-0.76) (**Table 2**). Weighted cumulative incidence curves (**Figure**, A and B) depict an early separation of absolute risks favoring GLP-1RAs that was maintained throughout. The 12-month absolute risks of hyperkalemia were 2.9% (95% CI, 2.3%-3.5%) in the GLP-1RA group and 4.6% (95% CI, 4.2%-5.1%) in the DPP-4i group, resulting in a weighted risk difference of −1.8% (95% CI, −2.4% to −1.1%). The rate of moderate to severe hyperkalemia (HR, 0.52; 95% CI, 0.28-0.84) also favored GLP-1RAs over DPP-4is (Table 2 and Figure, C and D).

Some patients experienced multiple hyperkalemia events, and during a median (IQR) follow-up of 3.9 (1.0-11.0) months, we detected 1213 repeated hyperkalemia episodes (at least 7 days apart) in 33 280 patients. The adjusted incidence rate ratio of GLP-1RAs vs DPP-4is was 0.48 (95% CI, 0.42-0.56) (**Table 3**). The incidence rate ratio of moderate to severe hyperkalemia of 0.39 (95% CI, 0.28-0.55) also favored GLP-1RAs over DPP-4is (Table 3; eFigure 3 in Supplement 1).

Table 4. Number and Rate of RASi Discontinuation Events in New Users of GLP-1RAs vs DPP-4is in Per-Protocol Analyses[a]

Exposure	No. of participants	No. of events	Follow-up, median (IQR), mo	Events per 1000 person-years (95% CI)[b]	Estimate, % (95% CI)		HR (95% CI)	
					12-mo Absolute risk	12-mo Risk difference	Crude	Weighted[c]
DPP-4i	12 611	1648	3.9 (1.0 to 11.8)	170.2 (162.2 to 178.6)	19.1 (18.0 to 20.3)	0 [Reference]	1.0 [Reference]	1.0 [Reference]
GLP-1RA	9140	733	3.0 (1.0 to 7.9)	146.2 (136.0 to 157.0)	17.2 (15.8 to 18.7)	−2.0 (−3.7 to −0.1)	0.79 (0.73 to 0.87)	0.89 (0.82 to 0.97)

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; RASi, renin-angiotensin system inhibitor.

[a] RASi discontinuation is the absence of a dispensation during at least 90 days after the estimated pill supply of the most recent pharmacy fill had ended.

[b] Number of events, person-years, and incidence rates were calculated in the unweighted population.

[c] Weights were calculated based on age, sex, calendar year, duration of diabetes at index date, time-varying laboratory measurements (eg, potassium level, estimated glomerular filtration rate, glycated hemoglobin, and urinary albumin-creatinine ratio), comorbidities (eg, acute coronary syndrome and heart failure), diabetes drugs use, other medication use (eg, renin-angiotensin system inhibitors and mineralocorticoid receptor antagonists), and health care resource utilization.

GLP-1RA vs DPP-4i Use and Persistence of RASi Therapy

A total of 21 751 participants (65.4%) were using RASis at the time of GLP-1RA or DPP-4i initiation (eTable 8 in Supplement 1). In this subpopulation, GLP-1RA users were younger than DPP-4i users (mean [SD] age, 62.9 [10.5] vs 67.9 [11.2] years) and had a higher HbA_{1c} level (mean [SD], 8.1% [1.6%] vs 7.9% [1.4%]) and eGFR (median [IQR], 89.4 [71.7-99.7] vs 82.0 [61.3-95.2] mL/min/1.73 m^2) (eTable 8 in Supplement 1). All baseline covariates were balanced after weighting (eFigure 5 in Supplement 1).

During a median (IQR) follow-up of 3.9 (1.0-10.9) months, 2351 participants stopped RASi therapy. The incidence rates for RASi discontinuation were 146.2 (95% CI, 136.0-157.0) per 1000 person-years for GLP-1RA users and 170.2 (95% CI, 162.2-178.6) for DPP-4i users, corresponding to a weighted HR of 0.89 (95% CI, 0.82-0.97) (**Table 4**). The 12-month absolute risks of RASi discontinuation were 19.1% (95% CI, 18.0%-20.3%) in the DPP-4i group and 17.2% (95% CI, 15.8%-18.7%) in the GLP-1RA group, resulting in a weighted risk difference of −2.0% (95% CI, −3.7% to −0.1%) favoring use of GLP-1RAs (Table 4).

Subgroup and Sensitivity Analyses

Subgroup analyses showed consistency of our main results across the strata of age, sex, eGFR, atherosclerotic cardiovascular disease, and SGLT2 inhibitors, insulin, or RASi adherence (eTable 9 in the Supplement). There was a suggestion for heterogeneity of effect by the presence of heart failure and MRA use.

Results of intention-to-treat analyses with 12-month follow-up aligned with our main analyses but was of a smaller magnitude (eTable 10 and eFigures 4-6 in Supplement 1). In alignment with clinical trials, the rate of major adverse cardiovascular events was lower for GLP-1RA vs DPP-4i users (per-protocol HR, 0.56; 95% CI, 0.39-0.75) (eTable 11 in Supplement 1). No difference was observed in the rates of diverticular disease between treatments (per-protocol HR, 1.04; 95% CI, 0.76-1.41) (eTable 11 in Supplement 1). No major differences were observed in the frequency of potassium testing across treatment groups (eTable 12 in Supplement 1). Users of GLP-1RAs vs DPP-4is had a lower rate of the less frequent event of severe hyperkalemia and less often received a clinical diagnosis or prescription of potassium binders (eTable 13 in Supplement 1). Defining RASi discontinuation with longer grace periods also provided results consistent with our main analysis (eTable 14 in Supplement 1).

Discussion

In this large cohort study of more than 33 000 adults with T2D managed in routine care, we found that GLP-1RA use was associated with a lower rate of hyperkalemia and prolonged RASi use compared with DPP-4i use. These findings were consistent across subgroups and various sensitivity analyses. Collectively, this study provides credible observational evidence supporting mechanistic evidence on the pleiotropic effects of GLP-1RAs on potassium homeostasis.

Our study expands on the results of a preceding US study[9] with some strengths and novel findings. A strength is the reliance on plasma potassium values to detect hyperkalemia, as many of these events are not coded with clinical diagnoses.[16,17] This approach may explain why the absolute and relative proportion of events in the US study[9] are of lower magnitude compared with ours. Access to routine potassium tests also allowed us to explore the severity of hyperkalemia and recurrent events over time, which are novel additions to the literature. The US study focused on T2D with stages 3 to 4 chronic kidney disease, and our study expands this finding to the full spectrum of eGFR with absence of effect modification by baseline kidney function. Stopping or switching treatments was common, resulting in a median treatment duration of 4 months for GLP-1RAs. This low persistence is not exclusive to Stockholm because it aligns with other real-world studies,[28,29] serving as a reminder that in routine clinical practice, patients often have lower medication adherence than in trials. Thus, another strength of our study is the emulation of per-protocol effects, demonstrating larger hyperkalemia reduction rates when follow-up was restricted to periods of drug use. Finally, our ascertainment of drug use is based on pharmacy fills, which is a more accurate surrogate of drug intake than a physician's prescription. However, we cannot ensure that medications were taken as instructed.

Another novel finding is that compared with DPP-4i users, GLP-1RA users had lower rates of RASi discontinuation. Although the observational nature of our study does not allow us to determine whether the lower hyperkalemia rates causally explain this finding, many studies show that hyperkalemia often leads to dose reduction or discontinuation of RASi use in clinical practice[23] and that this clinical decision is associated with worse clinical outcomes.[30] Although the lower hyperkalemia rates may be a consequence of the effects of GLP-1RAs on delaying the progression of kidney diseases and albuminuria,[31-35] which may benefit potassium levels in the long term, this may not fully explain why RASi treatments are less likely to be discontinued.

Emerging mechanistic evidence suggests that our findings are plausible. By inhibiting or downregulating the Na^+/H^+ exchanger isoform 3 in the proximal tubule, GLP1-RAs increase the flow of tubular fluid and the sodium load delivered to the distal nephron, which in turn induces an increase in urinary potassium excretion by the collecting duct.[13,36] A small randomized clinical trial in 35 participants with overweight and T2D showed that after 8 weeks of treatment, the GLP-1RA lixisenatide increased the fractional and absolute urinary potassium excretion,[14] although a subsequent study by the same group did not find differences in fractional potassium excretion for liraglutide compared with sitagliptin.[15] In a pooled analysis of the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) (n = 944) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) (n = 12 800) trials,[37] the incidence of hyperkalemia events leading to permanent discontinuation of finerenone or placebo was not modified by the ongoing use of GLP-1RAs (1.8% vs 0.9% with GLP-1RAs and 1.7% vs 0.6% without GLP-1RAs, respectively). The latter observation needs to be evaluated in the context of post hoc and subgroup analyses and the reporting protocols for serious adverse events.

Strengths and Limitations

Additional strengths of our study include the use of a target trial emulation, which reduces confounding by indication and mitigates time-related biases, and the setting of a universal tax-funded health system, which minimizes selection bias from disparate access to health care. Limitations of our study include the lack of information on confounders, such as dietary potassium or the use of potassium-containing supplements,[38] and the fact that our definition of duration of diabetes is a proxy given that we lack medical records before 1997. We explored, however, the potential of confounding in our estimates by comparing the rates of potassium testing between both groups and by the use of positive and negative control outcomes and believe our results are robust. This study was not powered to explore interaction or synergism between SGLT2 inhibitors and GLP-1RAs in full. An additional limitation is the lack of information on race and ethnicity. Thus, our findings may be limited in terms of generalizability to other world regions with larger ethnic variations.

Conclusions

This cohort study of patients with T2D undergoing routine care found that GLP-1RAs were associated with lower rates of hyperkalemia and sustained RASi use compared with DPP-4is. Treatment with GLP-1RAs may enable wider use of the guideline-recommended cardioprotective and renoprotective medications and contribute to improving clinical outcomes in this population.

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Correction: This article was corrected on January 27, 2025, to fix the key for panels A and C in the Figure, in which the colors had been swapped; in both panels, the yellow line represents DPP-4is, and the blue line represents GLP-1RAs. Additionally, in the last sentence of the "GLP-1RA vs DPP-4i Use and Persistence of RASi Therapy" subsection, the 12-month absolute risk data for the GLP-1RA group were incorrectly attributed to the DPP-4i group, and vice versa, which has now been corrected; a rounding error in some of the numbers was also corrected.

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