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ORIGINAL RESEARCH

Switching to Versus Addition of Incretin-Based Drugs Among Patients With Type 2 Diabetes Taking Sodium-Glucose Cotransporter-2 Inhibitors

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BACKGROUND: Evidence is limited in comparing treatment modification by substitution or add-on of glucose-lowering medications in patients with type 2 diabetes. This observational study aims to compare switching versus add-on of incretin-based drugs among patients with type 2 diabetes on background sodium-glucose cotransporter-2 inhibitors (SGLT2i).

METHODS AND RESULTS: This population-based, retrospective cohort study was conducted using the IQVIA Medical Research Data, including adults with type 2 diabetes on background SGLT2i from 2005 to 2020. New users of incretin-based drugs were allocated into the "Switch" group if they had discontinued SGLT2i treatment, or the "Add-on" group if their background SGLT2i was continued. Baseline characteristics of patients were balanced between groups. Study outcomes were all-cause mortality, cardiovascular diseases, kidney diseases, hypoglycemia, and ketoacidosis. Patients were observed from the index date of initiating incretin-based drugs until the earliest of an outcome event, death, or data cut-off date. Changes in anthropometric and metabolic parameters were also compared between groups from baseline to 12-month follow-up. A total of 2888 patients were included, classified into "Switch" (n=1461) or "Add-on" group (n=1427). Median follow-up was 18 months with 5183 person-years. Overall, no significant differences in the risks of study outcomes were observed between groups; however, patients in the "Add-on" group achieved significantly greater reductions in glycated hemoglobin, weight, percentage weight loss, and systolic blood pressure than their "Switch" counterparts.

CONCLUSIONS: Initiating incretin-based drugs as add-on among patients with type 2 diabetes on background SGLT2i was associated with risks of clinical end points comparable to switching treatments, in addition to better glycemic and weight control observed with the combination approach.

Key Words: add-on therapy ■ dipeptidyl peptidase-4 inhibitor ■ glucagon-like peptide-1 receptor agonist ■ sodium-glucose cotransporter-2 inhibitor ■ switching therapy ■ type 2 diabetes

Considering the progressive nature of type 2 diabetes (T2D), patients often require multiple antidiabetic agents over their course of disease for optimal glycemic control, where the stepwise approach of initiating new glucose-lowering medications following the failure of existing therapy in meeting individualized glycated hemoglobin (HbA1c) targets remains the preferred regimen by various international guidelines.[1–4] When treatment intensification is needed sequential to first-line metformin monotherapy,

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CLINICAL PERSPECTIVE

What Is New?

- In this retrospective cohort study of patients with type 2 diabetes who were on background sodium-glucose cotransporter-2 inhibitors (SGLT2i), new users of incretin-based drugs were allocated into the "Switch" group if they had discontinued SGLT2i treatment, or the "Add-on" group if their background sodium-glucose cotransporter-2 inhibitors was continued.
- Over a median follow-up of 18 months, no significant differences in the risks of all-cause mortality, cardiovascular diseases, kidney diseases, hypoglycemia, and ketoacidosis were observed between groups.
- Patients in the "Add-on" group achieved significantly greater reductions in glycated hemoglobin, weight, percentage weight loss, and systolic blood pressure than their "Switch" counterparts.

What Are the Clinical Implications?

- While no significant differences in the risks of various clinical end points were identified between switching and add-on approaches in the current study, they should be interpreted with caution given the relatively short follow-up period and hence the small number of events that occurred.
- Meanwhile, several metabolic benefits of the combination ("Add-on") approach were significantly greater than that of switching, including better glycemic control, reduction in weight and blood pressure over 12-month follow-up.
- Further studies with longer observation periods and randomized controlled trials are needed to clarify the risks and benefits of the 2 treatment modalities.

Nonstandard Abbreviations and Acronyms

CCI	Charlson Comorbidity Index
DPP4i	dipeptidyl peptidase-4 inhibitors
ESKD	end-stage kidney disease
GLP1RA	glucagon-like peptide-1 receptor agonists
IMRD	IQVIA Medical Research Data
IPTW	inverse probability of treatment weights
SBP	systolic blood pressure
SGLT2i	sodium-glucose cotransporter-2 inhibitors
T2D	type 2 diabetes

introduction of antidiabetic drugs with complementary mechanisms of action is recommended to help address the ominous octet of T2D pathophysiology.[5–8] Among the different drug classes, sodium-glucose cotransporter-2 inhibitors (SGLT2i) offer substantial metabolic benefits beyond glycemic control, reducing the risks of cardiovascular diseases (CVD), progression of diabetic nephropathy, and mortality, in addition to promoting weight loss, lowering blood pressure (BP), and incurring a low risk of hypoglycemia.[1,8–11] With increasing availability and its repositioning as a second-line glucose-lowering medication,[1,2,4,10,11] it can be anticipated that an increasing number of patients will be put on a combination regimen of metformin and SGLT2i, and it would be intriguing to explore the preferred option for subsequent treatment intensification.

Incretin-based therapy consisting of dipeptidyl peptidase-4 inhibitors (DPP4i) and glucagon-like peptide-1 receptor agonists (GLP1RA) are alternative antidiabetic agents with demonstrated efficacy and general tolerability.[1,8] While specific GLP1RA have exerted beneficial effects in terms of cardiovascular outcomes, especially lowering the risks of major adverse cardiovascular events and mortality, alongside considerable weight loss and BP reduction,[2,9–12] DPP4i are less potent in the stimulation of incretin effect. Hence they are mostly associated with cardiovascular neutrality and clinical benefits of a smaller magnitude than GLP1RA.[1,8,13,14] Because both drug classes act by promoting insulin secretion while suppressing that of glucagon in a glucose-dependent manner, they may compensate for the increased glucagon level and endogenous glucose production induced by SGLT2i to facilitate better glycemic control, and offer distinct mechanisms of action in targeting the metabolic defects of T2D that are complementary to those of metformin and SGLT2i, respectively, all without posing an additional risk of hypoglycemia.[14–18] Accordingly, incretin-based drugs appear to be an attractive option over sulfonylureas or thiazolidinediones as treatment intensification, with respect to cardiorenal outcomes, clinical parameters, and risk of hypoglycemia.[1,14]

Aside from the selection of antidiabetic agents based on patient preferences, cardiorenal status, and drug safety profile, the choice of drug initiation approach may also influence therapeutic efficacy via factors such as medication burden and patient adherence, correction of T2D pathophysiology, time to achieving individualized targets, clinical inertia, and overall cost-effectiveness that takes diabetic complications into account.[1,6,8] A retrospective cohort study utilizing electronic medical records from the UK Clinical Practice Research Datalink (CPRD) found that among patients with T2D with inadequate glycemic control, adding a new glucose-lowering medication

was associated with clinically significant reduction in HbA1c, which was not evident among those switching to another therapy or continuing with the original treatment.[19] Recently, several clinical trials and meta-analyses have demonstrated that the combination of SGLT2i with incretin-based drugs may produce sub-additive or additive effects in glycemic control and improvements in metabolic parameters than either drug class with placebo[20–26]; yet, there is very limited evidence on the comparison of cardiorenal end points and mortality for combination therapy versus each treatment alone.[27,28]

With reference to clinical guidelines recommending the substitution and/or addition of new anti-diabetic agents upon limited response to existing glucose-lowering therapy, as well as the research gap in evaluating any additional cardiorenal benefits of combining SGLT2i with incretin-based drugs over individual treatments and across different patient subgroups,[9,10,12,14,18,29,30] this observational study aims to compare the all-cause mortality, cardiorenal outcomes, adverse effects, and changes in clinical parameters associated with incretin-based drugs as switching versus add-on therapy among patients with T2D on background SGLT2i in a real-life setting. Because glucose-lowering medications with duplicating mechanisms of action are generally not recommended in combination regimens,[6] this study will consider the initiation of DPP4i or GLP1RA as substitution versus add-on to SGLT2i separately, and compare their safety and efficacy under respective treatment condition.

METHODS

Data Source and Study Design

This population-based, retrospective cohort study was conducted using the IMRD, a database comprising anonymized electronic primary health care records for 15 million patients from >750 general practices across the United Kingdom. IMRD incorporates data supplied by The Health Improvement Network, a propriety database of Cegedim SA. It contains coded patient-level longitudinal information on demographics, symptoms, clinical diagnoses recorded using Read Codes, medication prescriptions, consultations, and anthropometric, clinical, and laboratory measures. The data set is representative of the UK population by age, sex, medical conditions, and death rates adjusted for demographics, and has similar distribution of major chronic diseases, including diabetes, CVD, and mental illnesses, compared with the UK national statistics.[31,32] Validity of the diagnoses of ischemic cerebrovascular events and chronic kidney disease (CKD) with Read Codes in The Health Improvement Network database has been confirmed,[33,34] in addition to the accuracy of diabetes, hypertension, and CVD.[35] Studies have utilized this database to explore the associations between glucose-lowering medications and mortality, macrovascular, and microvascular diseases in patients with T2D.[36–38] We implemented a new user design based on IMRD data. New users of incretin-based drugs were first-time-ever users of GLP1RA or DPP4i drugs.

Study Population

General practices were included in the study from the latest of the following dates: 12 months after reporting acceptable mortality rates (a measure of data-recording quality), 12 months after beginning the use of electronic medical records, and study start date (January 1, 2005). This was to maximize data and recording quality.[39]

People aged ≥18 years who had registered with an eligible general practice for a minimum of 12 months, with a record of T2D (using Read codes in Table S1 or Chapter 6.1 of the British National Formulary), and received 2 or more consecutive prescriptions for SGLT2i drug, were eligible for inclusion. Prescriptions of SGLT2i, GLP1RA, and DPP4i were identified using drug codes (Table S1). Eligible patients were categorized into the "Switch" group if they had initiated prescriptions for index incretin-based drugs, either GLP1RA or DPP4i drug, but discontinued that of SGLT2i, defined by either the absence of ongoing refills or a gap of 60 days; or "Add-on" group if they had received prescriptions for incretin-based drugs while not discontinuing that of background SGLT2i. Patients in the "Add-on" group with overlapping duration of 2 drug classes of <60 days were excluded. The date of initiating incretin-based drugs was considered the index date (baseline).

Follow-Up Period

Participants were followed up from the index date until the earliest of the following occurrences: outcome diagnosis, death, participant left the practice, practice ceased to contribute to the database, or the end of study (June 30, 2020).

Baseline Covariates

Baseline covariates of patients included age, sex, smoking status, drinking status, duration of T2D, duration of SGLT2i prescription, anthropometric and clinical measurements, laboratory readings, drug prescription within 1 year, and comorbidity status at baseline. Baseline body mass index, fasting glucose, HbA1c, average systolic blood pressure (SBP) and diastolic blood pressure within 1 year before baseline, total cholesterol to high-density lipoprotein-cholesterol ratio, low-density lipoprotein-cholesterol, and triglycerides were

taken from the closest reading before the index date. The estimated glomerular filtration rate (eGFR) was estimated by serum creatinine, age, and sex based on the Modification of Diet in Renal Disease Study formula. Use of insulin, oral antidiabetic drugs (metformin, sulfonylureas, and thiazolidinediones), antihypertensive drugs (in particularly angiotensin-converting enzyme inhibitors/angiotensin receptor blockers), lipid-lowering agents, antiplatelets, and anticoagulants at baseline were identified using the prescription records within 1-year window before the index date. Past medical records of bariatric surgery were also extracted. Presence of any CVD, heart failure (HF), atrial fibrillation, hypertension, CKD, end-stage kidney disease (ESKD), diabetic retinopathy, peripheral neuropathy, mental or psychiatric disorder, and cancer were documented at baseline, as well as the comorbidity status determined by Charlson Comorbidity Index. The occurrence of hypoglycemia and ketoacidosis within 1 year before the index date was also recorded.

Outcome Measures

Study outcomes were all-cause mortality, CVD (composite of coronary heart disease, acute myocardial infarction, other ischemic heart disease, HF, stroke, transient ischemic attack, and peripheral vascular disease), HF (an outcome of interest with SGLT2i use), CKD, ESKD, hypoglycemia, and ketoacidosis by treatment groups. Outcome events and comorbidities were identified by Read Codes (Table S1). The diagnosis of CKD was identified by relevant Read Codes,[33] 2 consecutive measurements of eGFR <60 mL/min per 1.73 m^2, or 2 consecutive measurements of urine albumin-creatinine ratio ≥30 mg/g[40]; and ESKD by recorded eGFR of <15 mL/min per 1.73 m^2. Secondary outcomes were changes in anthropometric (SBP, diastolic blood pressure, body mass index, percentage total weight loss) and metabolic (HbA1c, low-density lipoprotein-cholesterol, total cholesterol/high-density lipoprotein-cholesterol, triglycerides, eGFR) parameters from baseline to 12-month follow-up (the assessment closest to 12-month follow-up over the period of 6–18 months).

Statistical Analysis

To account for incomplete baseline data, multiple imputation by chained equations was performed. Each missing baseline datum was imputed 5 times by random chained equation using other known baseline covariates. Five complete imputed data sets were analyzed individually to generate model estimates, which were then pooled into to a single estimate using Rubin's rules.

For confounding adjustment, inverse probability of treatment weights (IPTW) using the propensity score was applied to balance covariates across 2 treatment groups. Logistic regression models were fitted by using the indicator variables of treatment group as the dependent variable and baseline covariates as independent variables. The predicted probability of receiving treatment based on the patient's baseline covariates in the model is called propensity score. Patients with similar propensity scores were classified as having similar characteristics. We applied IPTW based on the propensity scores. Propensity score weights <1st percentile or >99th percentile in each group were trimmed. In the context of IPTW, multiple imputation followed by pooling treatment effect estimates across imputed data sets is the preferred approach.[41] Balance of baseline covariates between groups were assessed using the standardized mean difference, with a value of <0.1 indicating balance.

Number of outcome events, person-years, and incidence rate with 95% PoissonCI for each treatment group were calculated. Cox proportional hazards regression model was used to examine the association between treatment groups and incidence of events, and estimate hazard ratios (HR) of treatment effects and their 95% CI. Proportional hazard assumption was tested by Schoenfeld residuals with *P* values adjusted by Bonferroni method.

Secondary outcomes were compared between baseline and 12-month follow-up by paired *t* test within the same treatment group. Effects of switching from SGLT2i (dapagliflozin or empagliflozin) to either GLP1RA (exenatide or liraglutide) or DPP4i (sitagliptin, linagliptin, or alogliptin) were assessed, whereas the effects of initiating GLP1RA or DPP4i in addition to SGLT2i were investigated within the Add-on group.

Subgroup analyses were conducted based on incretin-based drug class (GLP1RA or DPP4i); stratification of baseline HbA1c (≤9% versus >9%); any prescription records of insulin, metformin, or sulfonylureas within 1 year before baseline; and types of SGTL2i (dapagliflozin or empagliflozin), GLP1RA (exenatide or liraglutide), and DPP4i (sitagliptin, linagliptin, or alogliptin) used (which were administered by >20% of patients). In sensitivity analyses, different scenarios were tested to assess the robustness of treatment effects, including (1) "as-treated" analysis to censor the follow-up period at the discontinuation of incretin-based drugs, subsequent switch from GLP1RA to DPP4i, or switch from DPP4i to GLP1RA; (2) competing risk analysis accounting for competing risk of death; (3) multiple imputation of missing baseline covariates without IPTW; and (4) complete-case with IPTW.

All statistical analyses were performed using Stata version 16.0 (StataCorp LP, College Station, Texas). All significance tests were 2-tailed and *P* values of <0.05 were taken to indicate statistical significance.

Ethical Approval

Use of the IMRD database has been approved by the NHS Health Research Authority (NHS Research Ethics Committee reference: 18/LO/0441); in accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (reference number: 20SRC070). This study used de-identified data provided by patients as part of their routine primary care, and no informed consent was required for this study.

RESULTS

Among 31 171 adults with T2D receiving 2 or more consecutive prescription records of SGLT2i, a total of 2888 patients had initiated incretin-based drugs and received 2 or more consecutive prescription records of GLP1RA or DPP4i on or after January 1, 2005, of whom 1461 were switched from SGLT2i to incretin-based drugs (Switch group: GLP1RA n=412; DPP4i n=1049), while 1427 were prescribed with a combination of SGLT2i and incretin-based drugs (Add-on group: GLP1RA n=409; DPP4i n=1018) (Figure 1). Background SGLT2i therapy had been initiated for a mean of 1.4 (SD 1.1) years at baseline (Table 1). The 3 types of SGLT2i used were dapagliflozin (60.2%), empagliflozin (27.7%), and canagliflozin (12.1%). Over half (52.6%) of the patients used exenatide for GLP1RA initiation, followed by liraglutide (32.3%), dulaglutide (10.7%), and lixisenatide (4.4%). For patients initiating DPP4i, 39.2% used sitagliptin, 25.0% used linagliptin, 24.6% used alogliptin, 10.8% used saxagliptin, and 0.3% used vildagliptin. Baseline characteristics of patients in the 2 treatment groups after multiple imputation and weighting are listed in Table 1. Overall, the mean age of this cohort was 57.9 (SD 11.2) years, with baseline HbA1c of 9.0% (1.5%), duration of T2D for 8.7 (6.4) years, and Charlson Comorbidity Index of 4.1 (1.9). Demographic and clinical characteristics of patients were balanced between groups. Data completion rates of baseline covariates are detailed in Table S2.

The median follow-up period of patients in Switch and Add-on groups were 19.2 (interquartile range, 9.1–34.6) and 17.0 (8.0–28.5) months, respectively (Table 2). After weighting, incidence rate of all-cause mortality during follow-up was 11.82 and 12.57 per 1000 person-years among Switch and Add-on users, respectively. Overall, there were no significant difference in risks of all-cause mortality (HR, 0.908 [95% CI, 0.541–1.523]; P=0.713), CVD (HR, 0.746 [95% CI, [0.464–1.198]; P=0.225), HF (HR, 1.238 [95% CI, 0.501–3.058]; P=0.644), CKD (HR, 1.128 [95% CI, 0.761–1.670]; P=0.549); ESKD (HR, 1.942 [95% CI, 0.205–18.433]; P=0.563), hypoglycemia (HR, 1.180 [95% CI, 0.595–2.342]; P=0.636), and ketoacidosis (HR, 0.854 [95% CI, 0.113–6.480]; P=0.879) between treatment groups (Table 3). Similar risks of outcome events were observed between the 2 groups across subgroup and sensitivity analyses (Tables S3 and S4, respectively). Test for proportional hazard assumption by Schoenfeld residuals showed there is no evidence that the proportional hazard assumption has been violated.

Changes in anthropometric and laboratory parameters from baseline to 12-month follow-up were also compared within each treatment group (Figure 2) and by differences between the 2 groups (Figure S1). A significantly greater reduction in mean HbA1c (–0.7% versus –0.5%, P<0.001) was observed in the Add-on group compared with the Switch group, which were also evident among DPP4i users. When stratified by glycemic control at baseline, considerably larger decreases in HbA1c were noted at 12-month follow-up among patients with baseline level of >9% than those with ≤9%. In addition, patients in the Add-on group managed to achieve greater mean reduction in weight (–2.4 versus –0.7 kg, P<0.001) and percentage total weight loss (2.2% versus 0.5%, P<0.001) than those in the Switch group, regardless of the incretin-based drug class. A significantly larger decrease in body mass index (–0.8 versus –0.2 kg/m^2, P<0.001) was evident among Add-on versus Switch users, particularly with DPP4i. While within-group changes in SBP were statistically insignificant, a trend towards BP lowering among patients in the Add-on group resulted in a significant difference from those in the Switch group (–1.1 versus 0.5 mm Hg, P=0.047). Notably, a larger decrease in total cholesterol/high-density lipoprotein-cholesterol ratio was only significant among DPP4i users of Add-on versus Switch treatment groups. Overall, there were no significant differences in 12-month changes of DBP, low-density lipoprotein-cholesterol, triglycerides, and eGFR between the Switch and Add-on groups.

DISCUSSION

In this cohort of patients with T2D with inadequate glycemic control despite being on a background glucose-lowering therapy of SGLT2i and other antidiabetic agents, no significant differences in the risks of all-cause mortality, cardiorenal outcomes, and other clinical end points were identified between the initiation of incretin-based drugs as substitution or addition to the existing drug regimen. Nevertheless, treatment modification with the stepwise combination approach (add-on) resulted in significant improvements of several metabolic parameters over 12-month follow-up compared with replacing SGLT2i with another new drug class (switch).

To our knowledge, the study design of this "new user" retrospective cohort analysis is unique in terms

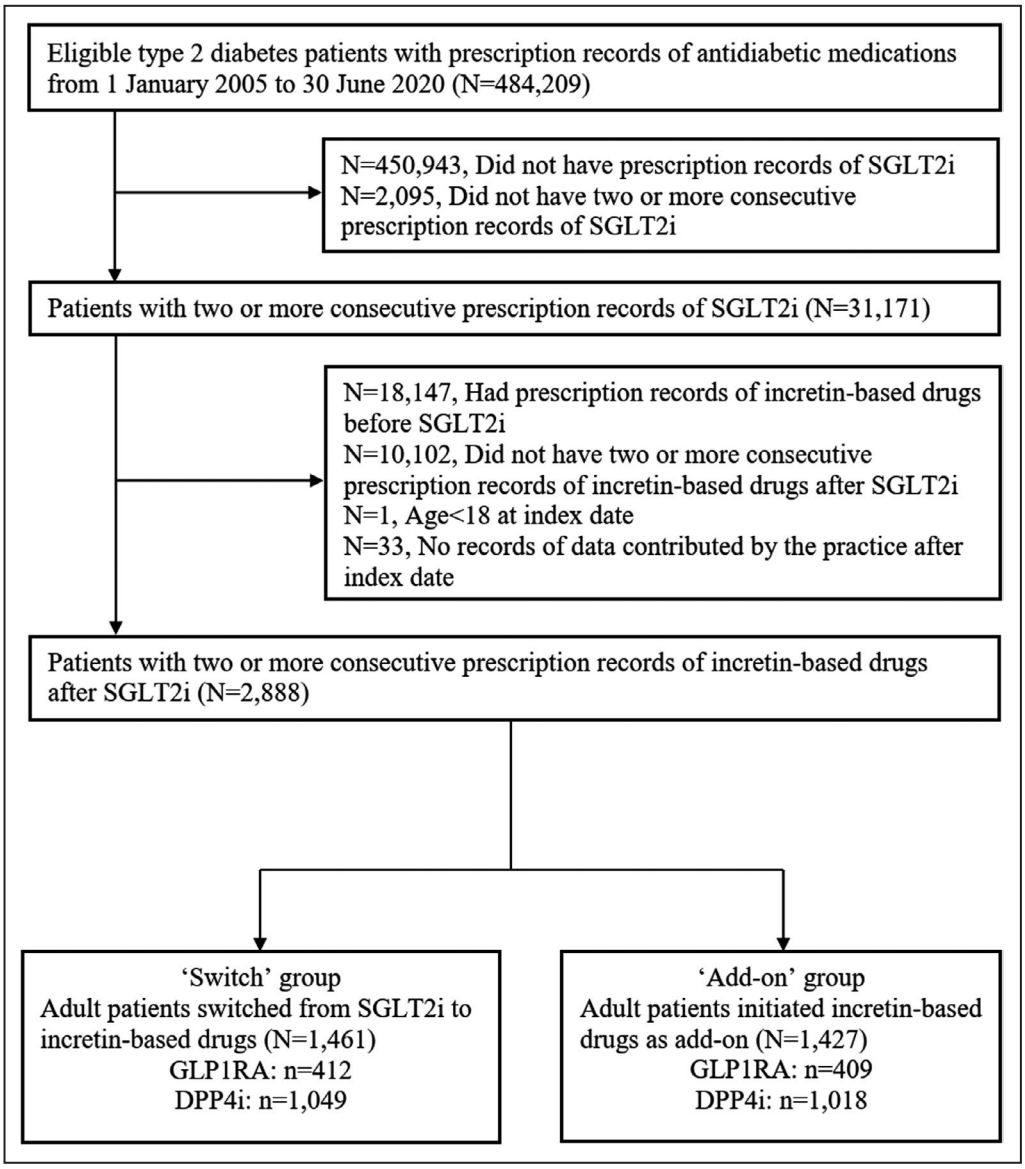

Figure 1. Flowchart of identifying eligible patients with type 2 diabetes who had initiated incretin-based drugs as substitution ("Switch") or add-on ("Add-on") to background SGLT2i therapy.
DPP4i indicates dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide-1 receptor agonists; and SGLT2i, sodium-glucose cotransporter-2 inhibitors.

of comparing multiple clinical end points and metabolic changes with respect to the adjustment of treatment modalities and the selection of newer antidiabetic agents (namely, SGLT2i and incretin-based drugs). The current literature is limited and inconclusive on any additional benefits of combining SGLT2i with incretin-based drugs in reducing the macrovascular and microvascular complications of diabetes. While a post hoc analysis of DECLARE-TIMI 58 concluded that the addition of dapagliflozin to baseline use of GLP1RA could lower the risks of hospitalization for heart failure and a composite of cardiovascular mortality and hospitalization for heart failure versus placebo, another post hoc analysis of EXSCEL could only observe significant risk reduction in all-cause and cardiovascular death with the combination of exenatide plus SGLT2i versus either placebo or exenatide alone, alongside a trend towards reducing the risk of major adverse cardiovascular events.[27,42] Regarding specific renal outcomes (composite of eGFR reduction, ESKD, or renal death; and new-onset albuminuria), the former study also demonstrated a trend towards benefit for the addition of dapagliflozin versus placebo to baseline DPP4i or GLP1RA therapy.[42] Similarly, using sulfonylureas as an active comparator, an observational cohort study of propensity score-matched patients with T2D found that adding SGLT2i to background GLP1RA therapy could lower the risks of composite cardiovascular outcomes and hospitalization for heart failure.[28]

Table 1. Baseline Characteristics of Patients With Type 2 Diabetes Who Initiated Incretin-Based Drugs as Substitution ("Switch") or Add-on to SGLT2i Before and After Propensity Score Weighting

Baseline characteristics	Before weighting				After weighting
	Total (N=2888)	Switch (N=1461)	Add-on (N=1427)	SMD	SMD
Socio-demographics					
Sex (%)				0.15	0.01
Female	46.3%	50.0%	42.5%		
Male	53.7%	50.0%	57.5%		
Age (mean±SD), y	57.9 (11.2)	58.8 (11.6)	57.0 (10.8)	0.16	0.03
Clinical characteristics (mean±SD)					
SBP, mm Hg	131.6 (13.9)	132.1 (13.8)	131.1 (14.1)	0.07	0.00
DBP, mm Hg	77.9 (9.0)	77.8 (8.8)	78.0 (9.3)	0.02	0.00
BMI, kg/m^2	34.7 (7.0)	34.8 (7.0)	34.5 (7.0)	0.03	0.01
<25	4.9%	5.3%	4.5%	0.07	0.08
25 to <30	22.4%	21.2%	23.7%		
30 to <35	28.8%	28.5%	29.0%		
≥35	43.9%	45.0%	42.8%		
Weight, kg	99.1 (21.9)	98.7 (22.0)	99.5 (21.7)	0.03	0.01
TC, mmol/L	4.5 (1.2)	4.5 (1.1)	4.5 (1.2)	0.01	0.02
LDL-C, mmol/L	2.7 (1.2)	2.7 (1.2)	2.8 (1.1)	0.04	0.02
TC/HDL-C ratio	4.2 (1.5)	4.2 (1.5)	4.2 (1.5)	0.01	0.00
Triglyceride, mmol/L	2.7 (2.0)	2.6 (1.9)	2.7 (2.1)	0.04	0.03
Fasting glucose, mmol/L	11.1 (4.8)	11.1 (4.9)	11.1 (4.8)	0.00	0.01
HbA1c, %	9.0 (1.5)	9.0 (1.6)	9.0 (1.4)	0.02	0.00
≤7	3.3%	3.8%	2.7%	0.07	0.05
>7 to 9	54.4%	53.5%	55.4%		
>9	42.3%	42.7%	41.9%		
Creatinine (serum), μmol/L	74.7 (20.4)	75.5 (23.8)	73.8 (16.3)	0.08	0.06
eGFR, mL/min per 1.73 m^2	114.1 (29.6)	112.3 (30.4)	116.0 (28.7)	0.12	0.01
Urine ACR, mg/g	58.2 (257.5)	64.4 (303.9)	51.5 (195.7)	0.05	0.00
Lifestyle factors (%)					
Smoking status				0.03	0.06
Nonsmoker	47.8%	47.6%	47.9%		
Current smoker	16.6%	16.2%	17.1%		
Ex-smoker	35.6%	36.1%	35.0%		
Drinking status				0.04	0.02
Nondrinker	26.2%	26.9%	25.5%		
Current drinker	67.6%	66.7%	68.4%		
Ex-drinker	6.2%	6.3%	6.1%		
Comorbidity status (%)					
Cardiovascular diseases	19.0%	20.5%	17.4%	0.08	0.02
Heart failure	2.5%	2.9%	2.1%	0.05	0.02
Atrial fibrillation	4.7%	5.9%	3.6%	0.11	0.01
Hypertension	59.0%	60.3%	57.7%	0.05	0.01
Chronic kidney disease	19.6%	21.8%	17.4%	0.11	0.02
End-stage kidney disease	0.1%	0.1%	0.1%	0.02	0.01
Diabetic retinopathy	20.7%	19.7%	21.7%	0.05	0.00
Peripheral neuropathy	10.2%	11.6%	8.8%	0.09	0.01
Mental or psychiatric disorder	19.2%	19.6%	18.9%	0.02	0.02

(*Continued*)

Table 1. (Continued)

Baseline characteristics	Before weighting				After weighting
	Total (N=2888)	Switch (N=1461)	Add-on (N=1427)	SMD	SMD
Cancer	5.5%	6.0%	4.9%	0.05	0.00
Hypoglycemia within 1 y	1.0%	1.2%	0.8%	0.05	0.00
Ketoacidosis within 1 y	0.1%	0.1%	0.1%	0.02	0.01
Charlson comorbidity index*	4.1 (1.9)	4.3 (2.0)	3.9 (1.8)	0.20	0.03
Charlson comorbidity index*, (%)				0.18	0.10
1–2	19.3%	18.5%	20.0%		
3	24.4%	20.9%	27.9%		
4 or above	56.4%	60.5%	52.1%		
Duration of type 2 diabetes, y	8.7 (6.4)	8.8 (6.6)	8.6 (6.1)	0.03	0.00
Treatment use within 1 y (%)					
Insulin	57.3%	61.3%	53.1%	0.17	0.02
Basal insulin	11.3%	13.3%	9.1%	0.13	0.10
Oral antidiabetic drugs					
Metformin	91.9%	92.1%	91.6%	0.02	0.00
SU	45.9%	50.8%	40.9%	0.20	0.01
TZD	8.3%	9.7%	6.9%	0.10	0.01
Antihypertensive drugs	75.8%	76.5%	75.1%	0.03	0.00
ACEI/ARB	64.7%	65.0%	64.4%	0.01	0.00
Lipid-lowering drugs	84.0%	82.8%	85.4%	0.07	0.01
Antiplatelet drugs	28.9%	29.6%	28.2%	0.03	0.00
Anticoagulant	7.9%	9.8%	5.9%	0.15	0.03
Bariatric surgery	0.5%	0.4%	0.5%	0.01	0.02
Duration of SGLT2i, y	1.4 (1.1)	1.3 (1.1)	1.5 (1.2)	0.14	0.02
Drug type (%)					
SGLT2i				0.12	0.03
Canagliflozin	12.1%	14.0%	10.2%		
Dapagliflozin (Propanediol)	60.2%	58.8%	61.6%		
Empagliflozin	27.7%	27.2%	28.2%		
GLP1RA				0.28	0.04
Exenatide	52.6%	48.8%	56.5%		
Dulaglutide	10.7%	14.8%	6.6%		
Liraglutide	32.3%	32.5%	32.0%		
Lixisenatide	4.4%	3.9%	4.9%		
DPP4i				0.10	0.03
Sitagliptin	39.2%	39.5%	39.0%		
Vildagliptin	0.3%	0.6%	0.1%		
Saxagliptin	10.8%	11.0%	10.5%		
Linagliptin	25.0%	25.4%	24.7%		
Alogliptin	24.6%	23.6%	25.7%		

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SGLT2i, sodium glucose cotransporter-2 inhibitors; SMD, standardized mean difference; SU, sulfonylureas; TZD, thiazolidinedione; and Urine ACR, urine albumin-to-creatinine ratio.

*The calculation of Charlson Comorbidity Index does not include acquired immune deficiency syndrome (AIDS).

Contrary to the few existing studies that explored the cardiorenal outcomes and mortality of SGLT2i and incretin-based drug combination relative to placebo, either treatment alone, or an active comparator, this study focused on evaluating these effects on new users of GLP1RA or DPP4i who had received SGLT2i

Table 2. Number and Incidence Rate of All-Cause Mortality, Cardiovascular Diseases, Heart Failure, Chronic Kidney Disease, End-Stage Kidney Disease, Hypoglycemia, and Ketoacidosis Events

	Before weighting							After weighting	
	Cumulative incidence		Crude incidence rate (Cases / 1000 person-y)			Median follow-up periods (Months)	Mean follow-up periods (Months)	Incidence rate (Cases/1000 person-y)	
Events	Cases with event	Rate	Estimate	95% CI*	Person-y			Estimate	95% CI*
Total (N=2888)									
All-cause mortality	64	2.22%	12.35	(9.51, 15.77)	5183	18	22	12.20	(10.15, 14.48)
Cardiovascular diseases	75	3.21%	18.43	(14.49, 23.10)	4070	17	21	19.53	(16.58, 22.74)
Heart failure	21	0.75%	4.17	(2.58, 6.37)	5041	18	21	4.11	(2.92, 5.51)
Chronic kidney disease	112	4.83%	28.13	(23.16, 33.85)	3981	17	21	27.39	(23.89, 31.23)
End-stage kidney disease	4	0.14%	0.77	(0.21, 1.98)	5170	18	22	0.76	(0.30, 1.44)
Hypoglycemia	38	1.33%	7.47	(5.28, 10.25)	5089	18	21	7.81	(6.17, 9.68)
Ketoacidosis	4	0.14%	0.77	(0.21, 1.98)	5173	18	22	0.75	(0.30, 1.44)
Switch (N=1461)									
All-cause mortality	36	2.46%	12.90	(9.04, 17.87)	2790	19	23	11.82	(9.02, 15.08)
Cardiovascular diseases	37	3.19%	17.06	(12.02, 23.52)	2168	19	22	17.04	(13.28, 21.45)
Heart failure	13	0.92%	4.82	(2.57, 8.24)	2699	19	23	4.55	(2.85, 6.74)
Chronic kidney disease	64	5.60%	31.04	(23.90, 39.63)	2062	17	22	28.95	(23.93, 34.70)
End-stage kidney disease	3	0.21%	1.08	(0.22, 3.15)	2779	19	23	0.98	(0.31, 2.22)
Hypoglycemia	23	1.59%	8.43	(5.35, 12.65)	2727	19	23	8.41	(6.03, 11.22)
Ketoacidosis	2	0.14%	0.72	(0.09, 2.59)	2786	19	23	0.73	(0.16, 1.81)
Add-on (N=1427)									
All-cause mortality	28	1.96%	11.70	(7.77, 16.91)	2393	17	20	12.57	(9.64, 15.92)
Cardiovascular diseases	38	3.23%	19.98	(14.14, 27.42)	1902	16	19	22.10	(17.70, 27.09)
Heart failure	8	0.57%	3.42	(1.47, 6.73)	2342	17	20	3.67	(2.17, 5.71)
Chronic kidney disease	48	4.07%	25.01	(18.44, 33.16)	1919	16	20	25.85	(21.14, 31.26)
End-stage kidney disease	1	0.07%	0.42	(0.01, 2.33)	2391	17	20	0.53	(0.08, 1.54)
Hypoglycemia	15	1.06%	6.35	(3.55, 10.47)	2362	17	20	7.20	(5.01, 9.85)
Ketoacidosis	2	0.14%	0.84	(0.10, 3.03)	2387	17	20	0.77	(0.16, 1.83)

DPP4i indicates dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonists; and SGLT2i, sodium glucose cotransporter-2 inhibitors.
*95% CI of incidence rates were constructed by Poisson distribution.

Table 3. HR of All-cause Mortality, Cardiovascular Diseases, Heart Failure, Chronic Kidney Disease, End-Stage Kidney Disease, Hypoglycemia, and Ketoacidosis Events

Events	Switch vs Add-on		
	HR	95% CI	*P* value
All-cause mortality	0.908	(0.541–1.523)	0.713
Cardiovascular disease	0.746	(0.464–1.198)	0.225
Heart failure	1.238	(0.501–3.058)	0.644
Chronic kidney disease	1.128	(0.761–1.670)	0.549
End-stage kidney disease	1.942	(0.205–18.433)	0.563
Hypoglycemia	1.180	(0.595–2.342)	0.636
Ketoacidosis	0.854	(0.113–6.480)	0.879

HR indicates hazard ratio.

therapy for a mean of 1.4 years, and attempted to answer the intriguing question of whether switching to another new drug class or adding it to the existing drug regimen would influence patient outcomes in real-world clinical practice. This research question is of clinical relevance because patient adherence could be affected by factors including pill burden, treatment complexity, and medication cost; whereas a combination of antidiabetic agents with distinct mechanisms of action could potentially offer additional benefits to glycemic and metabolic control by targeting different pathophysiological defects of T2D,[6,7,14] which remains to be proven and justified. While no significant differences in the risks of developing various clinical end points between switching and add-on could be identified in the current study, they should be interpreted with caution given the relatively short follow-up period and hence the small number of events that occurred.

In theory, the combination of SGLT2i with incretin-based drugs could exert complementary actions on cardiorenal protection and ameliorating adverse effects, with SGLT2i mainly lowering the risks of HF and diabetic nephropathy via hemodynamic benefits, GLP1RA acting to reduce major adverse cardiovascular events with anti-atherogenic and anti-inflammatory properties, and DPP4i attenuating the elevated risk of genital infections associated with SGLT2i use through modulating the immune system.[7,14,18,43,44] Furthermore, SGLT2i may compensate for the possible negative actions of GLP1RA and potential risk of specific DPP4i in HF progression, while incretin-based drugs may alleviate the development of ketoacidosis associated with SGLT2i use by counteracting its increased glucagon secretion and subsequent ketogenesis.[14,29,45,46] Nevertheless, it has also been proposed that the production of ketone bodies induced by SGLT2i may partly be responsible for its decrease in cardiac and renal workload, and hence the observed clinical benefits; therefore, any complementary effects of SGLT2i and incretin-based drug combination may depend on the degree of glucagon suppression, duration of pharmacological treatment, and any changes in drug efficacy over time.[45]

Regarding the choice of treatment modality, our results were consistent with that of the retrospective cohort study utilizing the UK CPRD, demonstrating that the add-on approach could achieve HbA1c reduction substantially larger than that of switching therapy, when patients were showing limited response to the original drug regimen[19]; however, changes in other anthropometric and metabolic parameters have not been compared between the 2 treatment approaches. This study suggested that, in addition to better glycemic control, the stepwise combination (add-on) therapy could produce reduction in weight and SBP significantly larger than that of substituting SGLT2i with incretin-based drugs over 12-month follow-up, which were generally in line with several clinical trials observing greater improvements with the addition of GLP1RA or DPP4i to SGLT2i versus placebo add-on or either drug class alone.[23,25,47–50] While these studies would be classified as the comparison between "adding a new drug class" and "continuing the original therapy," our study provided further evidence to support the use of "combination therapy" (add-on) over "replacing SGLT2i with incretin-based drugs" (switching) in terms of metabolic changes.

With reference to the pharmacological profile of these 3 drug classes, it can be postulated that GLP1RA would exert compensatory effects on the increased glucagon level and endogenous glucose production of SGLT2i to further reduce the HbA1c level, promote additive weight loss via the suppression of appetite to counteract the reported increase in food intake associated with SGLT2i use, and produce a synergistic effect on BP lowering with vasodilation and mild natriuresis that are distinct from SGLT2i-induced natriuresis and reduction of intravascular volume.[7,14,29,43] Notably, reduction in HbA1c has also been consistently shown to be sub-additive with the combination of SGLT2i and incretin-based drugs versus either treatment alone, which could be attributed to the interference of drugs combined and the failure of GLP1RA or DPP4i in adequately blocking the elevated endogenous glucose production of SGLT2i, especially at higher HbA1c levels.[7,14,17,18,20,51] Yet, our results reinforced the proposition that add-on or combination therapy would facilitate better glycemic control, even when compared with switching from a drug class with "limited response" to another with different mechanisms of action.

Concerning the initiation of DPP4i to existing SGLT2i therapy, our study revealed that the add-on approach could result in significantly larger reduction in HbA1c,

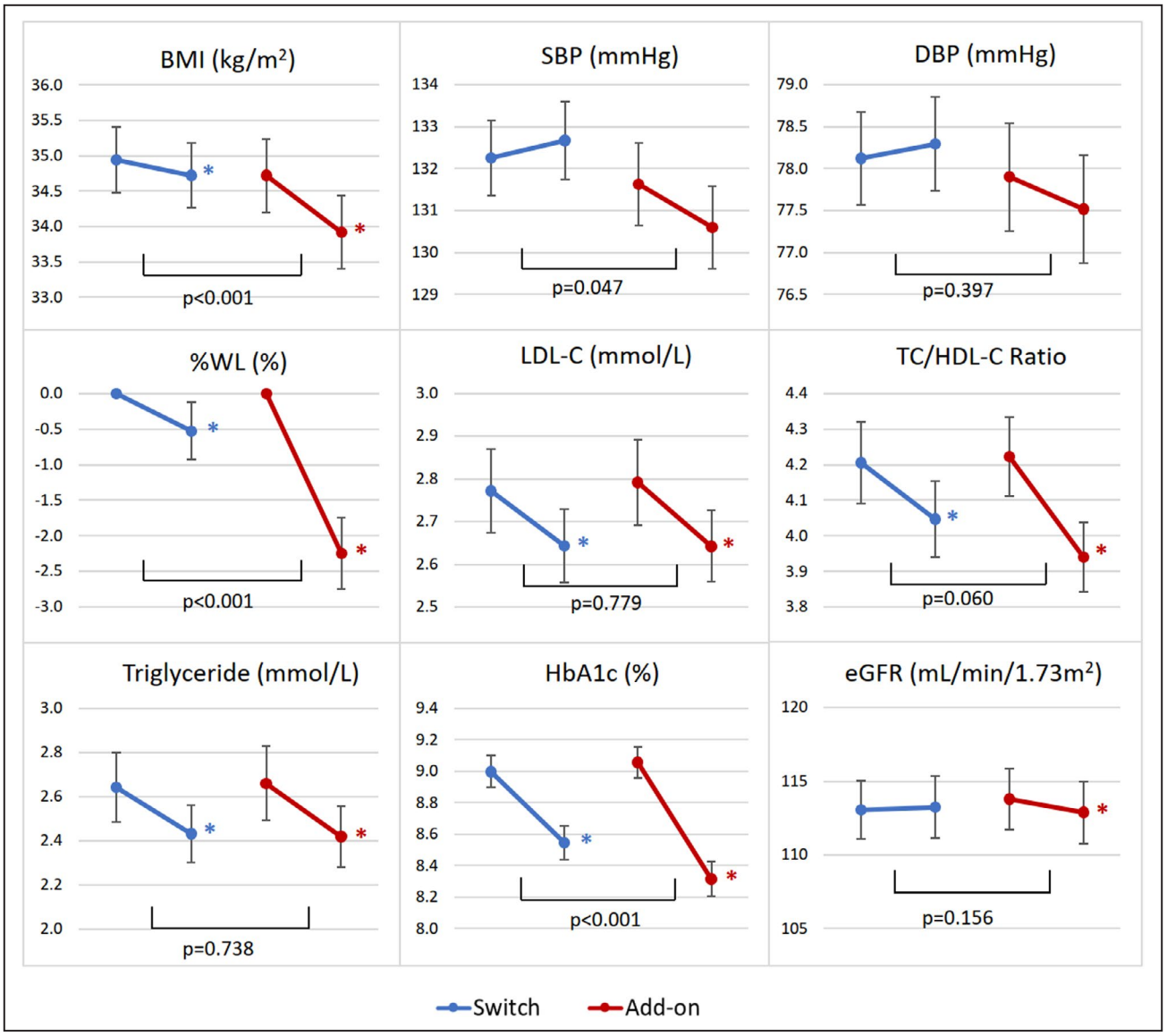

Figure 2. Mean and 95% CI of 12-month changes in anthropometric and laboratory parameters of patients with type 2 diabetes who had initiated incretin-based drugs as substitution ("Switch") or add-on ("Add-on") to background SGLT2i therapy.

%WL indicates percentage weight loss; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitors; and TC, total cholesterol. *Significant difference (P<0.05) in mean of change from baseline to 12-month follow-up.

weight, and total cholesterol/high-density lipoprotein-cholesterol ratio than that of substitution or switching. While some studies argued that beyond glycemic control, the addition of DPP4i to SGLT2i might not confer any additional benefits on weight loss, lowering BP, or improving the lipid profile compared with SGLT2i alone,[14,18,20,22] our study suggested that the combination therapy would be preferred to discontinuing SGLT2i and replacing it with DPP4i. Consistent with the fact that DPP4i is weight neutral and generally less potent than GLP1RA (including the suppression of endogenous glucose production), initiation of the latter could produce more clinically relevant reduction in HbA1c, weight, and BP.[10,13,14,18,49] Nonetheless, DPP4i may still offer renal benefits in terms of decreasing albuminuria,[42] and can be an alternative to patients preferring an oral route of administration.

Utilizing the IMRD representative of the United Kingdom population, this study attempted to evaluate the clinical and metabolic outcomes of patients with T2D initiating incretin-based drugs as substitution for (switching) or in combination with (add-on) background

SGLT2i therapy in the real-world setting. Various baseline characteristics of patients had been taken into account, which were further adjusted with multiple imputations and propensity score weighting to balance the confounding factors between groups. Despite such unique study design in addressing the clinical question of whether switching or add-on would be the preferred treatment approach, and the focus on newer antidiabetic agents with demonstrated cardiorenal safety or benefits, several limitations of this study should be acknowledged. First, given that SGLT2i is a relatively new drug class approved for T2D management, the follow-up period of new users of incretin-based drugs who had been on previous SGLT2i therapy would be fairly short, and hence the small number of events occurred over a median of 18 months. This could limit the interpretation of our results, because differences in cardiovascular or renal events might not be evident within this short observation period. Accordingly, our study might be underpowered to draw definite conclusions about cardiorenal outcomes, in addition to our limited sample size. Second, this patient cohort had relatively poor glycemic (mean HbA1c 9.0%) and metabolic control at baseline; thus the current findings might not be generalizable to other patient populations with different clinical characteristics. Furthermore, this patient cohort had a mean duration of diabetes of 8.7 years and were prescribed various glucose-lowering medications within 1 year at baseline; hence the results would not be applicable to patients with T2D at an earlier stage of the disease. Third, over half of the GLP1RA users in this cohort were prescribed exenatide, which is not associated with cardio- or renoprotective effects, while none were given semaglutide, which is associated with reduction in major adverse cardiovascular events, stroke, composite renal outcome, and mortality.[9] Such drug type distribution might have influenced our results. Fourth, biological mechanisms of the greater metabolic benefits observed with the add-on approach versus switching therapy remain to be elucidated. Some unmeasured confounding factors might have also played a role in the significant differences, such as more intensive therapy and lifestyle management of the metabolic risk factors in patients managed by physicians pursuing the add-on approach. Lastly, cost-effectiveness of different treatment modalities and quality of life indices of patients were not evaluated in the current study, which would also be relevant in the decision-making process.

CONCLUSIONS

In this patient cohort with T2D with inadequate glycemic control on background SGLT2i therapy, no significant differences in the risks of developing various clinical end points could be identified in the initiation of incretin-based drugs as substitution (switching) or add-on to the existing drug regimen. Meanwhile, several metabolic benefits of the combination approach were significantly greater than that of switching, including the reduction of HbA1c, weight, and SBP over 12-month follow-up. Further studies with longer observation periods and randomized controlled trials are needed to clarify the risks and benefits of the 2 treatment modalities.

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Data Availability Statement

The IQVIA Medical Research Data (IMRD) were obtained from IQVIA. For further information on access to the database, please contact IQVIA (contact details can be found at https://www.iqvia.com/locations/united-kingdom/information-for-members-of-the-public/medical-research-data).

Supplemental Material

Data S1
Tables S1–S4
Figure S1

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SUPPLEMENTAL MATERIAL

Data S1. STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-11
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	Fig1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-13
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig1
		(b) Give reasons for non-participation at each stage	Fig1
		(c) Consider use of a flow diagram	Fig1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-14

			(b) Indicate number of participants with missing data for each variable of interest	Supp Table2
			(c) Summarise follow-up time (eg, average and total amount)	14, Table2
Outcome data		15*	Report numbers of outcome events or summary measures over time	14-15
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-15
			(*b*) Report category boundaries when continuous variables were categorized	NA
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14, Supp Tables 3-4
Discussion				
Key results	18		Summarise key results with reference to study objectives	15
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20		Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-20
Generalisability	21		Discuss the generalisability (external validity) of the study results	16-20
Other information				
Funding	22		Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting.

The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/).

Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Table S1. Read codes of comorbidities and event outcomes.

Cardiovascular diseases	
G3...00	Ischaemic heart disease
G3...11	Arteriosclerotic heart disease
G3...12	Atherosclerotic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome

G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease
G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort
G33z400	Ischaemic chest pain
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis

G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease
G340100	Double coronary vessel disease
G341.00	Aneurysm of heart
G341.11	Cardiac aneurysm
G341000	Ventricular cardiac aneurysm
G341100	Other cardiac wall aneurysm
G341111	Mural cardiac aneurysm
G341200	Aneurysm of coronary vessels
G341300	Acquired atrioventricular fistula of heart
G341z00	Aneurysm of heart NOS
G342.00	Atherosclerotic cardiovascular disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency
G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G34z000	Asymptomatic coronary heart disease
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G37..00	Cardiac syndrome X
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G39..00	Coronary microvascular disease

G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
Gyu3.00	[X]Ischaemic heart diseases
Gyu3000	[X]Other forms of angina pectoris
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3500	[X]Subsequent myocardial infarction of other sites
Gyu3600	[X]Subsequent myocardial infarction of unspecified site
1O1..00	Heart failure confirmed
2JZ..00	On optimal heart failure therapy
662f.00	New York Heart Association classification - class I
662g.00	New York Heart Association classification - class II
662h.00	New York Heart Association classification - class III
662i.00	New York Heart Association classification - class IV
8B29.00	Cardiac failure therapy
G58..00	Heart failure
G58..11	Cardiac failure
G580.00	Congestive heart failure
G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure
G580.14	Biventricular failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G580400	Congestive heart failure due to valvular disease
G581.00	Left ventricular failure
G581.11	Asthma - cardiac
G581.13	Impaired left ventricular function
G581000	Acute left ventricular failure
G582.00	Acute heart failure
G583.00	Heart failure with normal ejection fraction
G583.11	HFNEF - heart failure with normal ejection fraction
G583.12	Heart failure with preserved ejection fraction
G584.00	Right ventricular failure
G58z.00	Heart failure NOS
G58z.12	Weak heart
G5y4z00	Post cardiac operation heart failure NOS
661M500	Heart failure self-management plan agreed
661N500	Heart failure self-management plan review

662p.00	Heart failure 6 month review
662T.00	Congestive heart failure monitoring
662W.00	Heart failure annual review
679W100	Education about deteriorating heart failure
8H2S.00	Admit heart failure emergency
8HBE.00	Heart failure follow-up
8HTL000	Referral to rapid access heart failure clinic
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G581.12	Pulmonary oedema - acute
G58z.11	Weak heart
SP11111	Heart failure as a complication of care
SP11200	Cardiorespiratory failure as a complication of care
G554000	Congestive cardiomyopathy
G6...00	Cerebrovascular disease
G60..00	Subarachnoid haemorrhage
G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage

G620.00	Extradural haemorrhage - nontraumatic
G621.00	Subdural haemorrhage - nontraumatic
G622.00	Subdural haematoma - nontraumatic
G623.00	Subdural haemorrhage NOS
G62z.00	Intracranial haemorrhage NOS
G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G633.00	Multiple and bilateral precerebral arterial occlusion
G634.00	Carotid artery stenosis
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery

G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G655.00	Transient global amnesia
G656.00	Vertebrobasilar insufficiency
G657.00	Carotid territory transient ischaemic attack
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute
G67..00	Other cerebrovascular disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS
G672.00	Hypertensive encephalopathy
G672.11	Hypertensive crisis
G673.00	Cerebral aneurysm, nonruptured
G673000	Dissection of cerebral arteries, nonruptured
G673100	Carotico-cavernous sinus fistula
G673200	Carotid artery dissection
G673300	Vertebral artery dissection
G674.00	Cerebral arteritis
G674000	Cerebral amyloid angiopathy

G675.00	Moyamoya disease
G676.00	Nonpyogenic venous sinus thrombosis
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G678.00	Cereb autosom dominant arteriop subcort infarcts leukoenceph
G679.00	Small vessel cerebrovascular disease
G67A.00	Cerebral vein thrombosis
G67B.00	Reversible cerebral vasoconstriction syndrome
G67B.11	Call-Fleming syndrome
G67y.00	Other cerebrovascular disease OS
G67z.00	Other cerebrovascular disease NOS
G68..00	Late effects of cerebrovascular disease
G680.00	Sequelae of subarachnoid haemorrhage
G681.00	Sequelae of intracerebral haemorrhage
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6y..00	Other specified cerebrovascular disease
G6z..00	Cerebrovascular disease NOS
Gyu6.00	[X]Cerebrovascular diseases
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6700	[X]Other specified cerebrovascular diseases
Gyu6C00	[X]Sequelae of stroke;not specfd as h'morrhage or infarction
Gyu6D00	[X]Sequelae/other unspecified cerebrovascular diseases
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
G73z000	Intermittent claudication
G73z011	Claudication

G73..12	Ischaemia of legs
G73zz00	Peripheral vascular disease NOS
G73z.00	Peripheral vascular disease NOS
G73yz00	Other specified peripheral vascular disease NOS
G73..11	Peripheral ischaemic vascular disease
G73..00	Other peripheral vascular disease
G73..13	Peripheral ischaemia
2G63.00	Ischaemic toe
G702.00	Extremity artery atheroma
G742z00	Peripheral arterial embolism and thrombosis nos
G702z00	Extremity artery atheroma NOS
G76A.00	Arterial insufficiency
G73y100	Peripheral angiopathic disease EC NOS
R055011	[d]peripheral circulatory failure
G73y.00	Other specified peripheral vascular disease
14NB.00	H/O: peripheral vascular disease procedure
Gyu7400	[X]Other specified peripheral vascular diseases
7A56600	Percutaneous transluminal placement peripheral stent artery
G733.00	Ischaemic foot
G73z012	Vascular claudication
G734.00	Peripheral arterial disease
16I..00	Claudication distance

Chronic kidney disease

14D..11	Kidney disease
1Z10.00	Chronic kidney disease stage 1
1Z12.00	Chronic kidney disease stage 3
1Z13.00	Chronic kidney disease stage 4
1Z14.00	Chronic kidney disease stage 5
1Z1G.00	Chronic kidney disease stage 3B without proteinuria
K13z.00	Kidney and ureter disease NOS
S76..00	Injury to kidney
S760000	Kidney injury without open wound into cavity, unspecified
S760z00	Kidney injury without mention of open wound into cavity NOS

Hypoglycaemia

66A6.00	Last hypo. attack
66A7.00	Frequency of hypo. attacks
66A7000	Frequency of hospital treated hypoglycaemia
66A7100	Frequency of GP or paramedic treated hypoglycaemia
66Ad.00	Hypoglycaemic attack requiring 3rd party assistance
66Ad000	Hypo atck - atndn ambulan crew
66AJ200	Loss of hypoglycaemic warning

66AJ300	Recurrent severe hypos
66AJ400	Hypoglycaemic warning absent
671F100	Hypoglycaemic management discussed
679L100	Hypoglycaemia education
C110.00	Hypoglycaemic coma
C110.11	Insulin coma
C110z00	Hypoglycaemic coma NOS
C112.00	Hypoglycaemia unspecified
C112000	Reactive hypoglycaemia NOS
C112100	Spontaneous hypoglycaemia NOS
C112z00	Hypoglycaemia unspecified NOS
C116.00	Other hypoglycaemia
C116000	Post-prandial hypoglycaemia
C11y100	Drug-induced hypoglycaemia without coma
Cyu3000	[X]Other hypoglycaemia
J693000	Post gastrointestinal tract surgery hypoglycaemia
671F100	Hypoglycaemic management discussed
679L100	Hypoglycaemia education
ZV65318	[V]Dietary counselling in hypoglycaemia
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11	Type I diabetes mellitus with hypoglycaemic coma
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE11	Type I diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma

Ketoacidosis

46Tf.00	Urine ketoacid level
C101.00	Diabetes mellitus with ketoacidosis
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C101y00	Other specified diabetes mellitus with ketoacidosis
C101z00	Diabetes mellitus NOS with ketoacidosis
C103.00	Diabetes mellitus with ketoacidotic coma
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C103z00	Diabetes mellitus NOS with ketoacidotic coma
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis

C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C362600	Metabolic ketoacidaemia
C362700	Ketoacidaemia NEC

Table S2. Data completion rates of type 2 diabetes (T2D) patients who had initiated incretin-based drugs as substitution ('Switch') or add-on ('Add-on') to background sodium-glucose cotransporter-2 inhibitors (SGLT2i) therapy before multiple imputation

Baseline characteristics	Total (N = 2,888)	Switch (N = 1,461)	Add-on (N = 1,427)
Socio-Demographic (%, n)			
Sex	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Age	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Clinical Characteristics (%, n)			
SBP	99.8% (2,882)	99.7% (1,457)	99.9% (1,425)
DBP	99.8% (2,882)	99.7% (1,457)	99.9% (1,425)
LDL-C	90.5% (2,614)	90.4% (1,321)	90.6% (1,293)
TC/HDL-C Ratio	97.4% (2,814)	97.3% (1,422)	97.5% (1,392)
Triglyceride	94.3% (2,724)	95.0% (1,388)	93.6% (1,336)
BMI	98.8% (2,854)	99.0% (1,446)	98.7% (1,408)
Weight	98.8% (2,854)	99.0% (1,446)	98.7% (1,408)
Fasting Glucose	84.7% (2,446)	86.8% (1,268)	82.6% (1,178)
HbA1c	99.7% (2,880)	99.7% (1,456)	99.8% (1,424)
Creatinine (Serum)	99.3% (2,869)	99.1% (1,448)	99.6% (1,421)
eGFR	99.3% (2,869)	99.1% (1,448)	99.6% (1,421)
Urine ACR	77.7% (2,243)	79.5% (1,162)	75.8% (1,081)
Smoking status	99.8% (2,883)	99.9% (1,459)	99.8% (1,424)
Drinking status	96.5% (2,786)	97.1% (1,419)	95.8% (1,367)
Charlson's Index[†]	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Duration of type 2 diabetes	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Treatment use within 1 year (%)			
Insulin	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Basal insulin	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Oral anti-diabetic drugs			
Metformin	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
SU	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
TZD	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Anti-hypertensive drugs	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
ACEI/ARB	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Lipid-lowering drugs	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Antiplatelet drugs	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Anticoagulant	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Bariatric surgery	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)
Duration of SGLT2i	100.0% (2,888)	100.0% (1,461)	100.0% (1,427)

SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein-cholesterol; BMI = body mass index; HbA1c = glycated hemoglobin; eGFR = estimated glomerular filtration rate; urine ACR = urine albumin to creatinine ratio; SU = sulfonylureas; TZD = thiazolidinediones; ACEI = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blockers; SGLT2i = sodium-glucose cotransporter-2 inhibitors

Table S3. Subgroup analysis of all-cause mortality, cardiovascular disease, heart failure, and chronic kidney disease.

Subgroup	All-cause mortality			Cardiovascular diseases			Heart failure			Chronic kidney disease		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Overall	0.908	(0.541, 1.523)	0.713	0.746	(0.464, 1.198)	0.225	1.238	(0.501, 3.058)	0.644	1.128	(0.761, 1.670)	0.549
GLP-1RA	0.576	(0.211, 1.567)	0.280	0.470	(0.194, 1.143)	0.096	0.446	(0.080, 2.483)	0.357	1.212	(0.576, 2.548)	0.613
DPP4i	1.084	(0.590, 1.991)	0.795	0.898	(0.514, 1.569)	0.705	1.942	(0.602, 6.270)	0.267	1.094	(0.691, 1.734)	0.701
Dapagliflozin	0.884	(0.482, 1.622)	0.691	0.828	(0.471, 1.456)	0.512	1.210	(0.420, 3.482)	0.724	1.477	(0.886, 2.462)	0.134
Empagliflozin	0.751	(0.259, 2.176)	0.597	0.621	(0.222, 1.742)	0.365	1.885	(0.174, 20.363)	0.602	1.015	(0.499, 2.065)	0.967
Exenatide	0.551	(0.100, 3.020)	0.492	NA	NA	NA	NA	NA	NA	0.855	(0.242, 3.012)	0.807
Liraglutide	0.723	(0.166, 3.152)	0.666	0.675	(0.147, 3.112)	0.615	NA	NA	NA	1.233	(0.363, 4.190)	0.737
Sitagliptin	0.831	(0.305, 2.270)	0.718	0.623	(0.275, 1.412)	0.257	0.526	(0.091, 3.025)	0.471	1.133	(0.591, 2.172)	0.707
Linagliptin	1.521	(0.594, 3.896)	0.382	0.997	(0.311, 3.194)	0.995	4.626	(0.588, 36.377)	0.145	0.997	(0.419, 2.375)	0.995
Alogliptin	1.709	(0.422, 6.913)	0.452	1.406	(0.408, 4.844)	0.589	NA	NA	NA	1.393	(0.353, 5.498)	0.636
Baseline HbA1c≤9	0.568	(0.278, 1.162)	0.121	0.802	(0.406, 1.583)	0.525	1.421	(0.404, 5.000)	0.584	1.118	(0.645, 1.940)	0.691
Baseline HbA1c>9	1.461	(0.652, 3.272)	0.357	0.777	(0.399, 1.514)	0.459	1.124	(0.312, 4.054)	0.858	1.163	(0.656, 2.063)	0.605
Insulin[#]	1.187	(0.650, 2.169)	0.577	0.688	(0.397, 1.192)	0.182	1.720	(0.540, 5.471)	0.358	1.161	(0.729, 1.849)	0.530
Metformin[#]	0.791	(0.449, 1.393)	0.417	0.727	(0.441, 1.200)	0.213	1.120	(0.448, 2.796)	0.809	1.086	(0.721, 1.636)	0.693
SU[#]	0.877	(0.406, 1.895)	0.738	0.680	(0.376, 1.232)	0.203	1.943	(0.523, 7.224)	0.321	1.197	(0.683, 2.099)	0.530

GLP1RA = glucagon-like peptide-1 receptor agonists; DPP4i = dipeptidyl peptidase-4 inhibitors; HbA1c = glycated hemoglobin; SU = sulfonylureas; HR = hazard ratio; CI = confidence interval; NA = not applicable

Notes:

* Significant at 0.05 level by Cox proportional hazard regression

Drug use within 1 year prior to baseline

† There was no cardiovascular disease event in the ‘Switch’ group among exenatide users.

Table S4. Hazard ratio of all-cause mortality, cardiovascular diseases, heart failure, chronic kidney disease, end-stage kidney disease, hypoglycemia, and ketoacidosis events in sensitivity analysis.

Events	Multiple imputation			Complete case with IPTW and trimmed propensity score		
	HR	95% CI	P-value	HR	95% CI	P-value
All-cause mortality	1.041	(0.635, 1.706)	0.874	1.021	(0.518, 2.013)	0.952
Cardiovascular diseases	0.820	(0.521, 1.291)	0.391	0.904	(0.519, 1.574)	0.722
Heart failure	1.394	(0.580, 3.353)	0.458	1.683	(0.528, 5.364)	0.379
Chronic kidney disease	1.260	(0.864, 1.836)	0.230	0.937	(0.580, 1.514)	0.791
End-stage kidney disease	2.652	(0.284, 24.755)	0.392	2.080	(0.219, 19.766)	0.523
Hypoglycemia	1.342	(0.691, 2.607)	0.385	0.808	(0.347, 1.883)	0.622
Ketoacidosis	0.733	(0.101, 5.326)	0.759	0.215	(0.021, 2.170)	0.193

Events	As-treated analysis			Competing risk		
	HR	95% CI	P-value	SHR	95% CI	P-value
All-cause mortality	0.351	(0.066, 1.873)	0.220			
Cardiovascular diseases	0.832	(0.508, 1.363)	0.465	0.751	(0.467, 1.205)	0.235
Heart failure	1.173	(0.460, 2.992)	0.738	1.248	(0.506, 3.077)	0.630
Chronic kidney disease	1.152	(0.761, 1.743)	0.504	1.131	(0.764, 1.675)	0.537
End-stage kidney disease	NA	NA	NA	1.949	(0.205, 18.506)	0.561
Hypoglycemia	1.284	(0.615, 2.683)	0.505	1.182	(0.596, 2.345)	0.632
Ketoacidosis	0.917	(0.125, 6.737)	0.932	0.867	(0.114, 6.583)	0.890

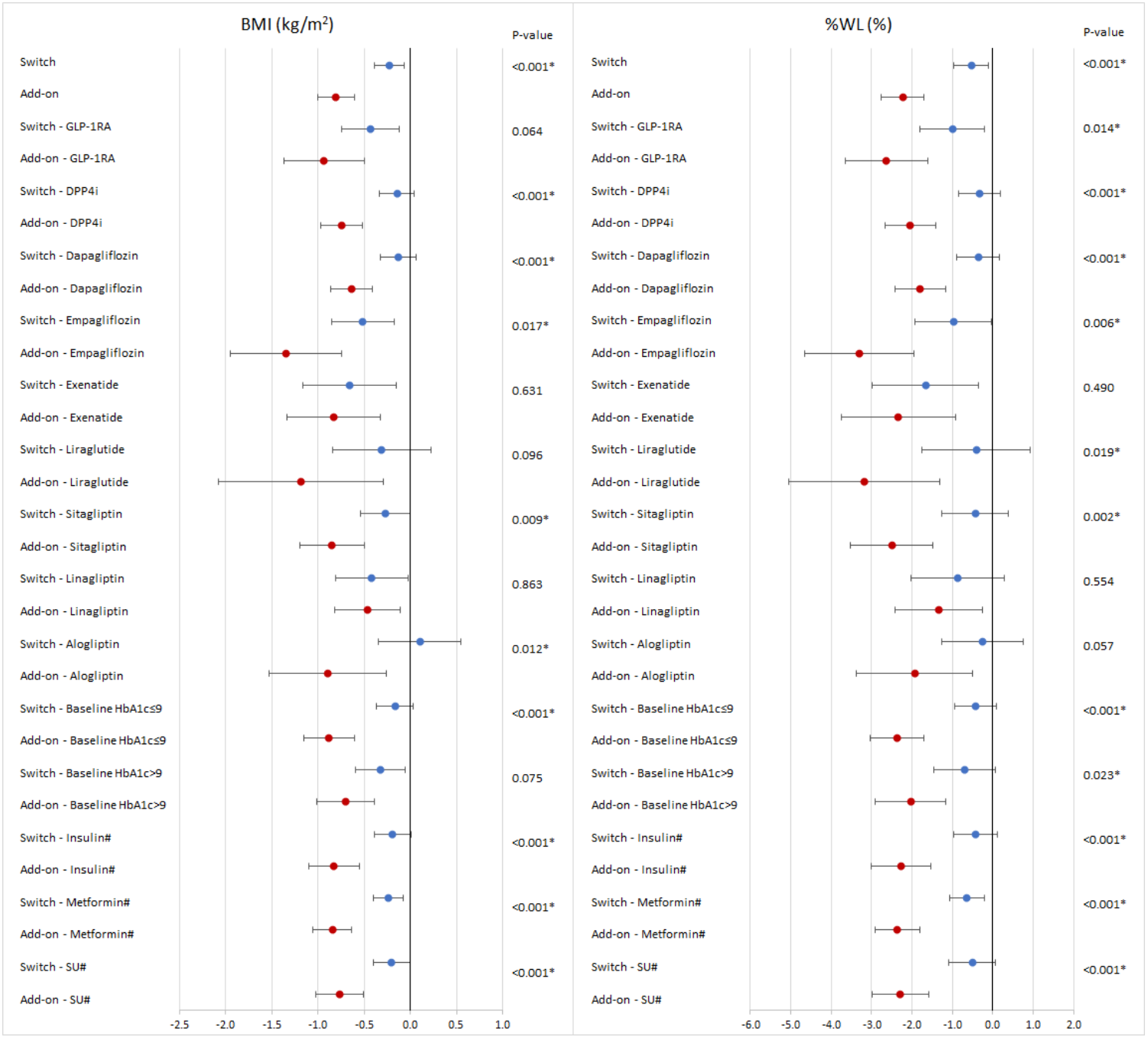
IPTW = inverse probability of treatment weights; HR = hazard ratio; SHR = sub-hazard ratio; CI = confidence interval; NA = not applicable

Notes:

* Significant at 0.05 level by Cox proportional hazard regression

† There was no end-stage kidney disease event observed between baseline and the last date of drug prescription in the ‘Add-on’ group in as-treated analysis.

Figure S1. Mean and 95% confidence interval of 12-month changes in anthropometric and laboratory parameters of type 2 diabetes (T2D) patients who had initiated incretin-based drugs as substitution ('Switch') or add-on ('Add-on') to background sodium-glucose cotransporter-2 inhibitors (SGLT2i) therapy by patient subgroups

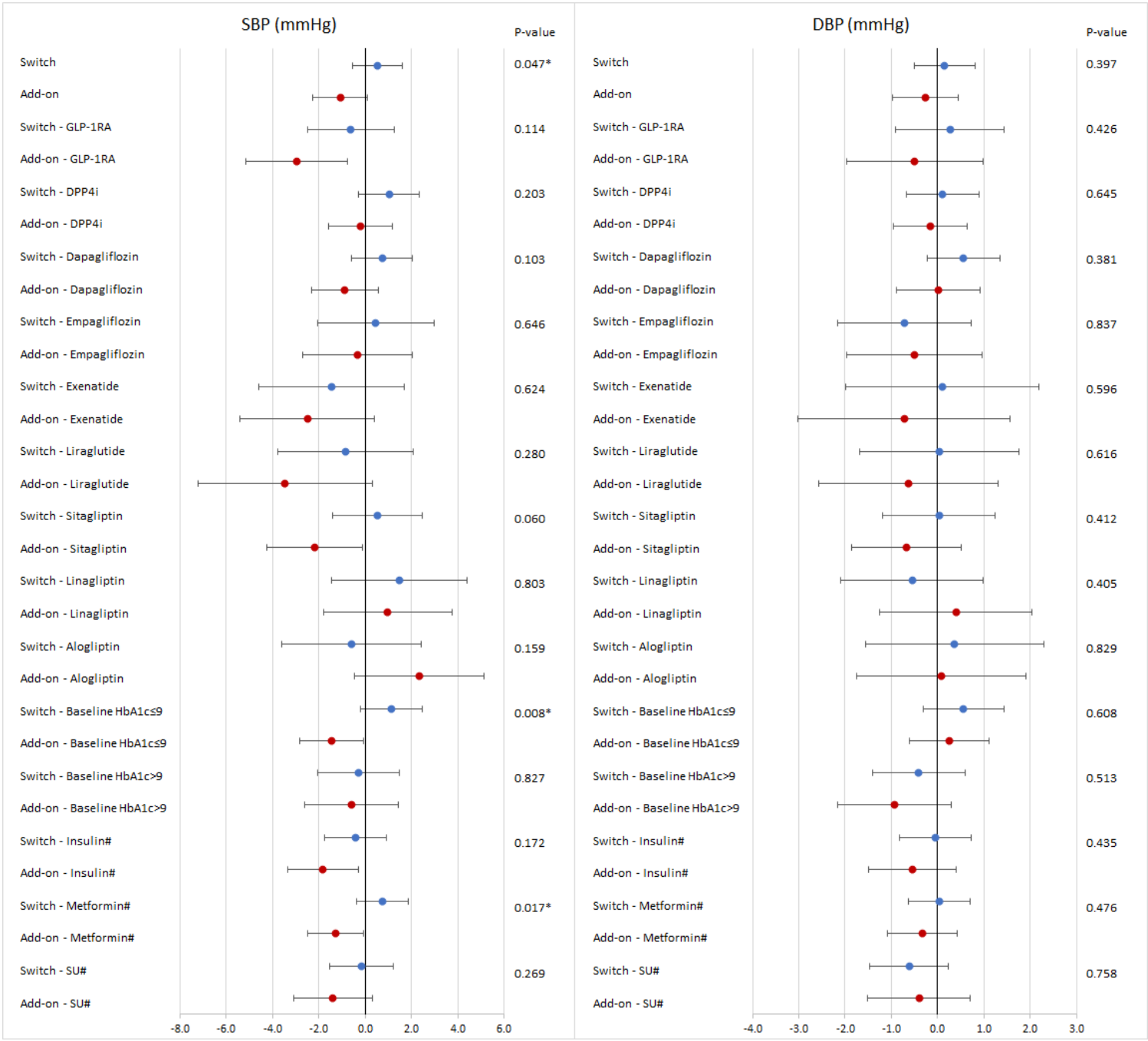


SGLT2i = sodium-glucose cotransporter-2 inhibitors; GLP1RA = glucagon-like peptide-1 receptor agonists; DPP4i = dipeptidyl peptidase-4 inhibitors; BMI = body mass index; %WL = percentage weight loss

Note:

Drug use within 1 year prior to baseline

* Significant difference ($p<0.05$) in mean of change from baseline to 12-month follow-up between groups by univariate linear regression

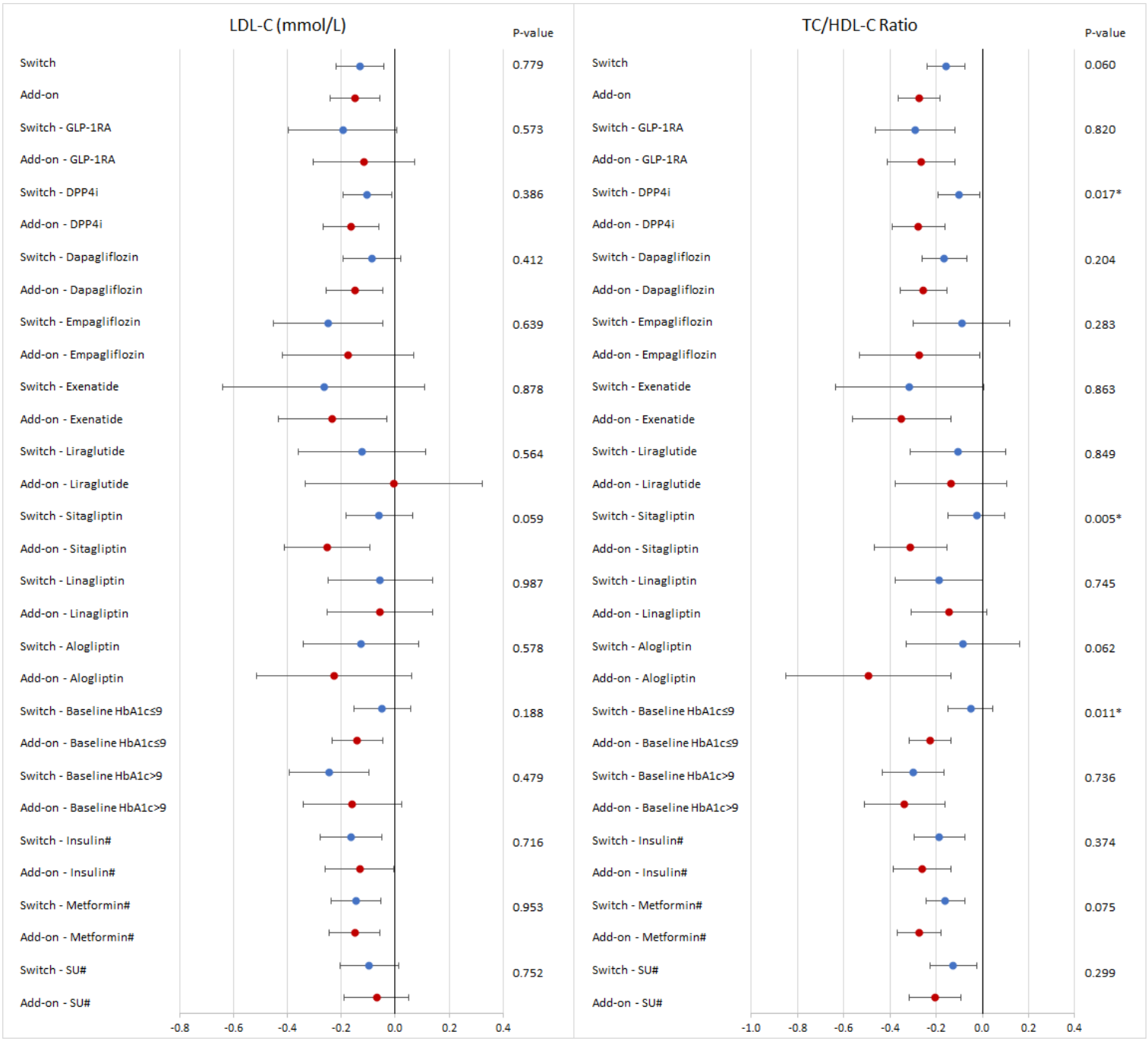


SGLT2i = sodium-glucose cotransporter-2 inhibitors; GLP1RA = glucagon-like peptide-1 receptor agonists; DPP4i = dipeptidyl peptidase-4 inhibitors; SBP = systolic blood pressure; DBP = diastolic blood pressure

Note:

Drug use within 1 year prior to baseline

* Significant difference ($p<0.05$) in mean of change from baseline to 12-month follow-up between groups by univariate linear regression

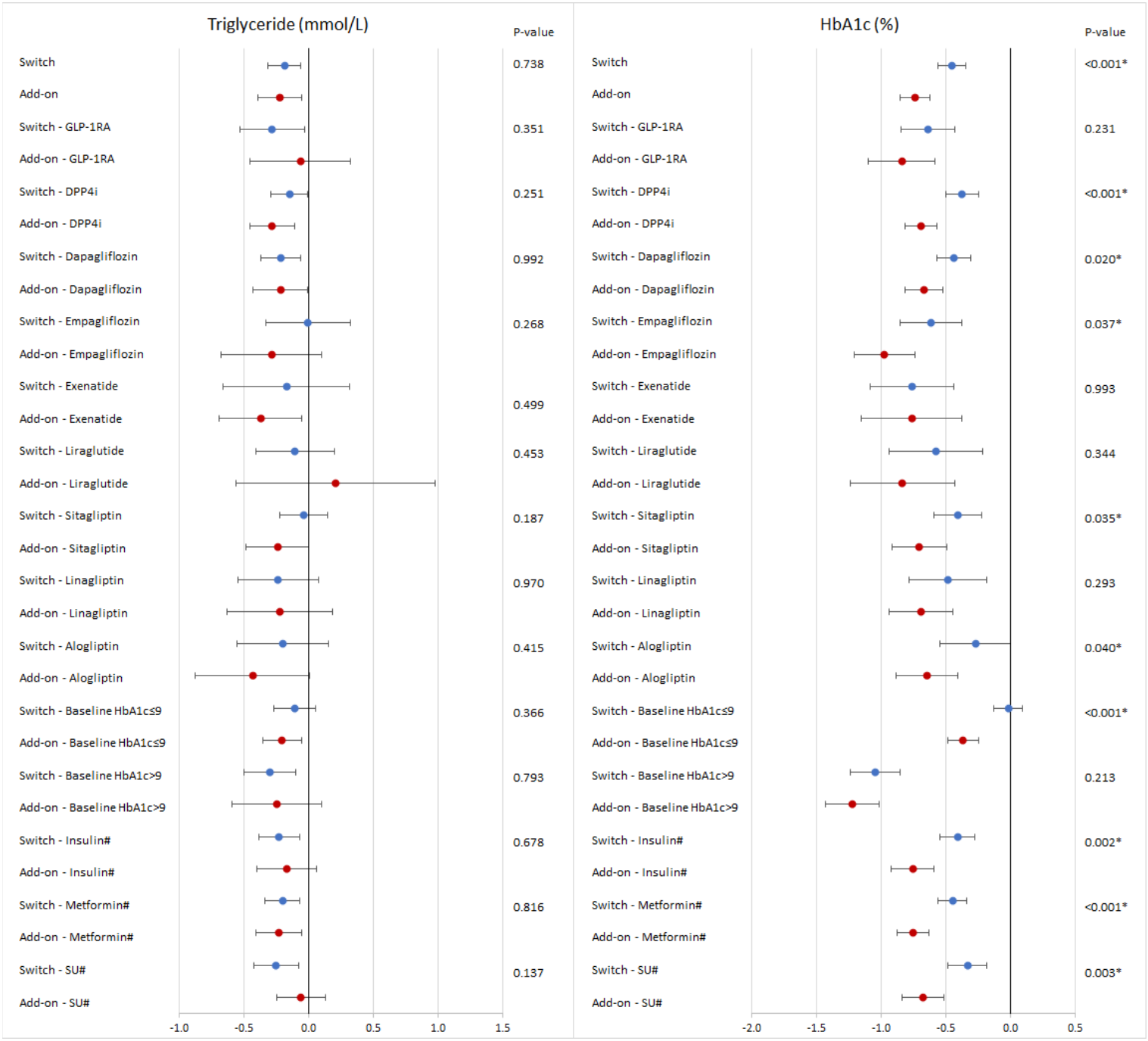


SGLT2i = sodium-glucose cotransporter-2 inhibitors; GLP1RA = glucagon-like peptide-1 receptor agonists; DPP4i = dipeptidyl peptidase-4 inhibitors; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein-cholesterol

Note:

Drug use within 1 year prior to baseline

* Significant difference ($p<0.05$) in mean of change from baseline to 12-month follow-up between groups by univariate linear regression

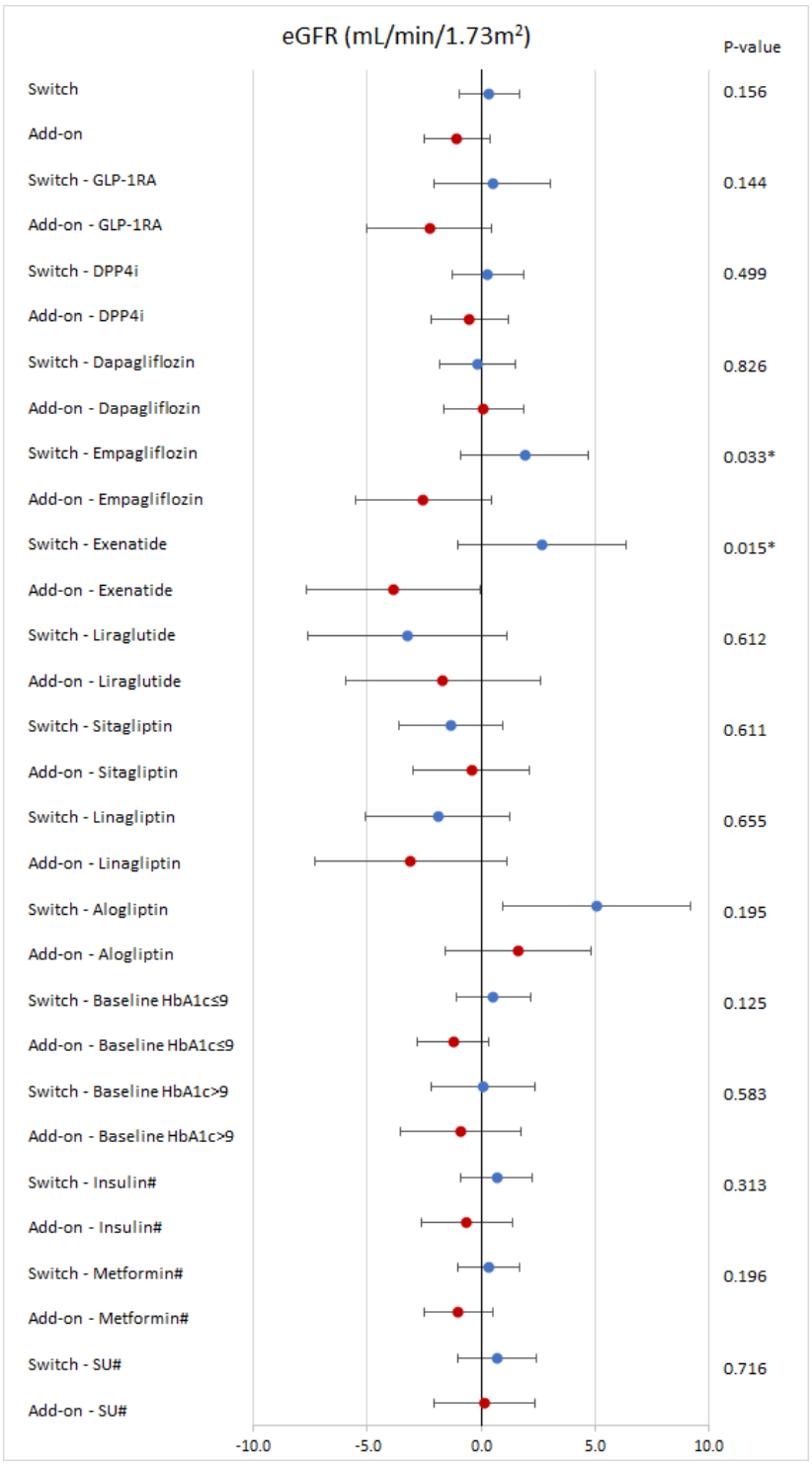


SGLT2i = sodium-glucose cotransporter-2 inhibitors; GLP1RA = glucagon-like peptide-1 receptor agonists; DPP4i = dipeptidyl peptidase-4 inhibitors; HbA1c = glycated hemoglobin

Note:

Drug use within 1 year prior to baseline

* Significant difference ($p<0.05$) in mean of change from baseline to 12-month follow-up between groups by univariate linear regression



SGLT2i = sodium-glucose cotransporter-2 inhibitors; GLP1RA = glucagon-like peptide-1 receptor agonists; DPP4i = dipeptidyl peptidase-4 inhibitors; eGFR = estimated glomerular filtration rate

Note:

Drug use within 1 year prior to baseline

* Significant difference ($p<0.05$) in mean of change from baseline to 12-month follow-up between groups by univariate linear regression