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ORIGINAL RESEARCH

Clinical Implications of Estimated Glomerular Filtration Rate Dip Following Sodium-Glucose Cotransporter-2 Inhibitor Initiation on Cardiovascular and Kidney Outcomes

Yan Xie , MPH; Benjamin Bowe , MPH; Andrew K. Gibson , MPH; Janet B. McGill, MD; Geetha Maddukuri, MD; Ziyad Al-Aly , MD

BACKGROUND: The frequency of the initial short-term decline in estimated glomerular filtration rate (eGFR), eGFR dip, following initiation of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and its clinical implications in real-world practice are not clear.

METHODS AND RESULTS: We built a cohort of 36 638 new users of SGLT2i and 209 025 new users of other antihyperglycemics. Inverse probability weighting was used to estimate the excess rate of eGFR dip, risk of the composite cardiovascular outcome of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or all-cause mortality, and risk of the composite kidney outcome of eGFR decline >50%, end-stage kidney disease, or all-cause mortality. In the first 6 months of therapy, compared with other antihyperglycemics, excess rates of eGFR dip >10% and eGFR dip >30% were 9.86 (95% CI: 8.83–11.00) and 1.15 (0.70–1.62) per 100 SGLT2i users, respectively. In mediation analyses that accounted for eGFR dipping, SGLT2i use was associated with reduced risk of cardiovascular and kidney outcomes (hazard ratio, 0.92 [0.84–0.99] and 0.78 [0.71–0.87], respectively); the magnitude of the association reduced by eGFR dipping was small for both outcomes. SGLT2i was associated with reduced risk of both outcomes in those with higher than average probability of eGFR dip >10% or 30%. Compared with discontinuation, continued use of SGLT2i at 6 months was associated with reduced risk of cardiovascular and kidney outcomes in those with no eGFR dip or eGFR dip ≤10%, in those with eGFR dip >10%, and in those with eGFR dip >30%.

CONCLUSIONS: The salutary association of SGLT2i with cardiovascular and kidney outcomes was maintained regardless of eGFR dipping; concerns about eGFR dipping should not preclude use, and occurrence of eGFR dip after SGLT2i initiation may not warrant discontinuation.

Key Words: cardiovascular outcomes ■ diabetes mellitus ■ estimated glomerular filtration rate ■ kidney ■ kidney function ■ kidney outcomes ■ sodium-glucose cotransporter-2 inhibitors

Several randomized clinical trials provided evidence that sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce the risk of major cardiovascular and kidney outcomes in people with type 2 diabetes mellitus.^{1–7} Evidence from recent trials suggests that the salutary properties of SGLT2i may even extend to

people without diabetes mellitus.^{8–10} However, in several randomized trials, SGLT2i use was associated with an initial estimated glomerular filtration rate (eGFR) decline, eGFR dip, within a few weeks and up to 6 months following initiation of therapy.¹¹ The eGFR dip is generally followed by recovery and stabilization during the

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CLINICAL PERSPECTIVE

What Is New?

- In the first 6 months of treatment, estimated glomerular filtration rate (eGFR) dipping was more common among sodium-glucose cotransporter-2 inhibitor (SGLT2i) users than other antihyperglycemics; however, most eGFR dips were <30%.
- eGFR dipping did not abrogate the beneficial association between SGLT2i and cardiovascular and kidney outcomes.
- Continued use of SGLT2i (versus discontinuation) was associated with reduced risk of cardiovascular and kidney outcomes regardless of degree of eGFR dipping.

What Are the Clinical Implications?

- Real-world effectiveness of SGLT2i on cardiovascular and kidney outcomes was maintained regardless of eGFR dipping.
- Concern about dipping should not preclude initiation of SGLT2i, and occurrence of an eGFR dip following SGLT2i initiation should not, on its own, motivate SGLT2i discontinuation.
- As a means of achieving longer-term reduction in risk of cardiovascular and kidney outcomes, practitioners may consider continuation of treatment with SGLT2i regardless of eGFR dipping.

Nonstandard Abbreviations and Acronyms

CDW	Corporate Data Warehouse
CREDESCENCE	Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
SGLT2i	sodium-glucose cotransporter-2 inhibitor(s)
VA	US Department of Veterans Affairs

subsequent months; in the long-term, SGLT2i use was associated with relative eGFR preservation compared with placebo.¹¹

However, the frequency and extent of eGFR dip in SGLT2i users relative to other antihyperglycemics, whether eGFR dipping erodes SGLT2i effectiveness on cardiovascular and kidney outcomes, and whether eGFR dip is associated with increased risk of discontinuation of SGLT2i in real-world practice are not known. Furthermore, whether continued SGLT2i use (versus discontinuation) following an intervening SGLT2i dip is associated with reduced risk of cardiovascular and kidney outcomes is unknown. Addressing this knowledge gap will illuminate our understanding of the clinical ramifications of the eGFR dip in SGLT2i users.

Herein, we leveraged the breadth and depth of the US Department of Veterans Affairs (VA) electronic healthcare databases to build a cohort of 36 638 incident users of SGLT2i, and 209 025 incident users of other antihyperglycemics, and aimed to characterize the rates of eGFR dipping in each antihyperglycemic group, identify characteristics associated with eGFR dipping in SGLT2i users, examine whether and to what extent the effectiveness of SGLT2i on cardiovascular and kidney outcomes was abrogated by an intervening eGFR dip, and finally evaluate the risk of major cardiovascular outcomes and kidney outcomes associated with SGLT2i continuation versus discontinuation according to eGFR dipping category.

METHODS

Because of the sensitive nature of the data used in this study, the data sets could only be accessed after obtaining approval from the VA.

Cohort Design

Participants who received antihyperglycemic medication from the VA Health Care System between October 1, 2015, and July 31, 2019, were selected (n=1 293 984). Participants were separated first into an SGLT2i group, which included patients who received an SGLT2i prescription between October 1, 2016, and July 31, 2019 (n=59 133). The other antihyperglycemic group was then selected from participants who did not receive SGLT2i prescription between October 1, 2016, and July 31, 2019. The other antihyperglycemic group included patients who either added on or switched from their existing non-SGLT2i antihyperglycemic medication to a non-SGLT2i antihyperglycemic prescription between October 1, 2016, and July 31, 2019 (n=423 193), where the first date of meeting this criterion was considered time of treatment initiation. In each group, participants without a history of SGLT2i exposure within the 1 year before treatment initiation were selected (SGLT2i

group, n=55 466; and other antihyperglycemic group, n=420 625). We further excluded participants with history of type 1 diabetes mellitus, those with end-stage kidney disease, or those who were enrolled in the healthcare system for <1 year at treatment initiation (SGLT2i group, n=51 816; and other antihyperglycemic group, n=387 467). Within participants who remained in the cohort, 46 122 in the SGLT2i group and 312 794 in the other antihyperglycemic group had measurements of glycated hemoglobin (HbA1c), low-density lipoproteins, blood pressure, height, weight, and had eGFR measurement ≥ 30 mL/min per 1.73 m² within the 1 year before treatment initiation. To evaluate the change in eGFR within the first 6 months (180 days) after treatment initiation, we removed participants who had no eGFR measurement or who experienced the composite cardiovascular or kidney outcome in this time period (SGLT2i group, n=36 638; and other antihyperglycemic group, n=209 025). Participants were followed until the occurrence of an outcome or administrative end of follow-up (January 31, 2020). Informed consent was waived for this study. The cohort flowchart is presented in Figure S1, and study timeline is presented in Figure S2.

Data Sources

Data from the VA Corporate Data Warehouse (CDW) were used in this study.^{12–26} CDW Outpatient and Inpatient Encounters domains included *International Classification of Diseases, Tenth Revision (ICD-10)*, diagnosis codes, *ICD-10* procedure codes, and Current Procedural Terminology codes.²⁷ Medication prescriptions were obtained from the CDW Outpatient Pharmacy domain. Laboratory measurements from the CDW Laboratory Results domain were also collected and used.²⁸ The CDW Vital Signs domain provided vital measurements, and the CDW Patient domain and VA Vital Status provided demographic information.²⁹

Exposure and Outcomes

Prescriptions of SGLT2i or other antihyperglycemic medications were identified from outpatient pharmacy records. The distribution of antihyperglycemic medications at treatment initiation is presented in Table S1.^{15,30}

Differences in rates of eGFR dip >10% and >30% between the SGLT2i and other antihyperglycemic groups were examined. eGFR dip was evaluated on the basis of the difference between baseline eGFR, defined as the average eGFR within 1 year before treatment initiation, and the lowest eGFR value measured within 6 months after the treatment initiation. The difference was transformed into percentage change compared with baseline eGFR. The CKD Epidemiology Collaboration creatinine equation was used to compute eGFR based on serum creatinine, age, race, and sex.³¹

SGLT2i discontinuation was defined as a >90-day gap between the last supply date of a prescription and the next prescription, where the date of the last supply was within 6 months after treatment initiation. The associations between discontinuation of SGLT2i and the cardiovascular and kidney outcomes were examined. The composite cardiovascular outcome was defined as non-fatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or all-cause mortality. The composite kidney outcome was defined as eGFR decline >50% from treatment initiation, end-stage kidney disease, or all-cause mortality. Time of end-stage kidney disease was identified by first occurrence of eGFR <15 mL/min per 1.73 m², long-term dialysis, or kidney transplant.

Covariates

Baseline Covariates

Covariate selection was informed by prior knowledge.^{15,17,18,20,22,24,32} Covariates that may influence antihyperglycemic prescription included age, race (White, Black, and other, where other race included non-White and non-Black participants), sex, HbA1c, eGFR, systolic blood pressure, diastolic blood pressure, low-density lipoproteins, body mass index (computed from height and weight), smoking status (never, former, or current), type of hospital system where the antihyperglycemic was prescribed (outpatient clinic or healthcare system), and the calendar year of enrollment. eGFR was the average eGFR within 1 year before treatment initiation. Clinical comorbidities, such as congestive heart failure, cardiovascular diseases, cancer, alcoholism, hypoglycemia, diabetic ketoacidosis, acute kidney injury, bladder and urinary tract infections, venous thromboembolism, pancreatitis, bone fracture, and albuminuria, were also included.³³ Acute kidney injury was defined as an increased serum creatinine of 0.3 mg/dL or 50% within 30 days, and albuminuria status was categorized into no albuminuria (≤ 30 mg/g), microalbuminuria (>30– ≤ 300 mg/g), and macroalbuminuria (>300 mg/g). History use of glucagon-like peptide 1 agonists, dipeptidyl peptidase-4 inhibitors, sulfonylureas, thiazolidinediones, metformin, insulin, α -glucosidase inhibitors, meglitinides, amylin analogues, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β -blockers, loop diuretics, nonloop diuretics, and calcium channel blockers was also used as covariates.³³ Covariates were ascertained within the 1 year before the treatment initiation.

Characteristics Within 6 Months After Treatment Initiation

To examine characteristics that may be associated with SGLT2i discontinuation, we additionally evaluated the occurrence of adverse events, including hypoglycemia,

diabetic ketoacidosis, amputation, bladder and urinary tract infections, venous thromboembolism, pancreatitis, bone fracture, hospitalizations that were not related to adverse events, and HbA1c change (categorized as increase or lack of increase in HbA1c) within the 6 months after treatment initiation.

Statistical Analysis

Characteristics of the cohort and by treatment group and eGFR dip categories are presented as mean and SD, or number and percentage, as appropriate. A schematic of the analytic approach is presented in Figure S3.

Rates of eGFR Dip and Predictors of the Dip

Differences in rate of eGFR dips, including dip >10% and dip >30%, between the SGLT2i group and other antihyperglycemic group were examined by weighted generalized estimating equations for logistic regression. To balance potential confounders between treatments, inverse probability of treatment weighting method was applied.³⁴ Probability of receiving the assigned treatment at treatment initiation was estimated from logistic regression based on covariates ascertained at treatment initiation. The inverse probability of treatment weighting was then constructed as the inverse probability stabilized by the prevalence of treatments at time of treatment initiation. The inverse probability of treatment weighting was then truncated at the 0.1 and 99.9 percentiles to further stabilize the weighting.³⁵ Absolute rate per 100 patients in each group and the excess rates associated with SGLT2i were estimated on the basis of the predicted probability. We additionally evaluated the excess rates in subgroups based on race, eGFR category, and albuminuria category, and in those with congestive heart failure and those using angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, loop diuretics, and nonloop diuretics. We also investigated the characteristics that may be associated with eGFR dip >10% and dip >30% in SGLT2i users using logistic regressions.

eGFR Dip and the Effectiveness of SGLT2i on Cardiovascular and Kidney Outcomes

We evaluated the mediation effect of eGFR dip on the associations between SGLT2i and composite cardiovascular and kidney outcomes through inverse odds ratio (OR) weighting for causal mediation analysis.³⁶ In mediation analyses, we estimated the direct effect independent of eGFR dip >10% and, in separate analyses, eGFR dip >30%. The total effect of SGLT2i, accounted for eGFR dipping as a mediator was estimated from a Cox model weighted by inverse probability of treatment weighting. Direct effect of SGLT2i was estimated from

a similarly weighted Cox model where the model was additionally weighted for the inverse OR of having the mediator in the SGLT2i group. The magnitude of effect abrogated by the mediator was then computed from the difference between hazard ratios (HRs) for the direct effect independent of eGFR dip and the HRs for the total effect. Event rate differences between direct and total effect were estimated on the basis of survival probability, where the difference represented the difference in the rate of the outcome between the SGLT2i and other antihyperglycemic groups that was mediated by differences in the rate of eGFR dipping.

To assess whether the salutary association of SGLT2i on composite cardiovascular and kidney outcomes was abrogated in SGLT2i users with a high probability of experiencing an eGFR dip associated with SGLT2i, we estimated the association between SGLT2i and risk of the composite cardiovascular outcome and the composite kidney outcome in SGLT2i users with a higher or lower than average predicted probability of having an eGFR dip >10%, and separately eGFR dip >30%, associated with SGLT2i (ie, the excess probability of having an eGFR dip associated with SGLT2i compared with other antihyperglycemics after consideration of baseline characteristics). We first estimated the predicted baseline probability of eGFR dip associated with covariates at treatment initiation within the other antihyperglycemic group using logistic regression. Using results from this model, we then computed the baseline probability of dip in the SGLT2i group. Then, the probability of eGFR dip associated with SGLT2i ($P_{\text{SGLT2i dip}}$), conditional on the baseline probability of dipping, was estimated within the SGLT2i group. The SGLT2i users were then separated into high and low risk of experiencing an eGFR dip associated with SGLT2i, based on $P_{\text{SGLT2i dip}}$ being above or below the mean predicted probability. The association between SGLT2i and the risk of outcomes in users with predicted probability of SGLT2i-related eGFR dip higher or lower than the average probability was examined after adjusting for covariates at treatment initiation.

Association Between SGLT2i Discontinuation and Risk of Outcomes

We then examined the association between SGLT2i discontinuation with characteristics occurring between treatment initiation and 6 months after treatment initiation, which included eGFR dip, adverse events, hospitalization, and HbA1c change. Logistic regression was used and adjusted for probability of discontinuation. The probability was estimated from a logistic regression where discontinuation was predicted by the set of baseline covariates.

Associations between SGLT2i discontinuation and composite cardiovascular or kidney outcomes were

examined from Cox survival models weighted by the inverse probability of discontinuation weight, where the weight was constructed on the basis of the probability of discontinuation and updated by additionally including factors that occur between treatment initiation and 6 months after treatment initiation. The effects were estimated in all cohorts, and within those with no eGFR dip or dip $\leq 10\%$, eGFR dip $>10\%$, and eGFR dip $>30\%$, separately. The composite cardiovascular and kidney event rates in 1 year by discontinuation and continuation of SGLT2i and their differences were calculated on the basis of the estimated survival probabilities.

Evaluation of Potential Biases

Balance of covariates between the SGLT2i and other antihyperglycemic group, and between SGLT2i continuation and discontinuation, was examined through propensity score distribution and standardized difference of covariates. To test the robustness of our analyses, we tested a negative outcome control as a means to detect the presence of spurious associations.³⁷ Traffic-related injury was used as the negative outcome control as there is neither biologic plausibility nor a priori evidence suggesting the presence of a relationship with either SGLT2i use or SGLT2i discontinuation.

Other Statistical Considerations

The 95% CIs for rate difference were generated on the basis of 1000 times bootstrapping. A 95% CI for ratio measure that does not cross 1 or for rate that does not cross 0 was considered statistically significant. All analyses were done using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC). The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System, Saint Louis, MO.

RESULTS

There were 36 638 individuals in the SGLT2i group and 209 025 individuals in the other antihyperglycemic group, corresponding to 447 399 person-years. Among incident SGLT2i users, there were 20 458 (55.84%) with no eGFR dip, 16 180 (44.16%) with eGFR dip $>10\%$, and 2326 (6.35%) with eGFR dip $>30\%$ within the first 6 months of SGLT2i initiation. Baseline demographic and health characteristics in these groups are provided in Table 1.

Rates of eGFR Dip in the First 6 Months Among SGLT2i Users and Users of Other Antihyperglycemics

Unadjusted rates of eGFR dip $>10\%$ within the first 6 months were 44.16 (95% CI: 43.66–44.67) and 30.37

(30.17–30.56) per 100 people in the SGLT2i and other antihyperglycemic group, respectively (Table S2). In adjusted analyses, compared with other antihyperglycemics, excess rate of eGFR dip $>10\%$ was 9.86 (8.83–11.0) per 100 users of SGLT2i (Figure S4). Results showed consistently higher rates of eGFR dip $>10\%$ in the SGLT2i group than other antihyperglycemics in prespecified subgroups (Table S3).

Unadjusted rates of eGFR dip $>30\%$ within the first 6 months were 6.35 (95% CI: 6.10–6.60) and 4.12 (4.03–4.20) in the SGLT2i and other antihyperglycemic groups, respectively. In adjusted analyses, the excess rate of eGFR dip $>30\%$ attributable to SGLT2i was small (1.15 [0.70–1.62] per 100 users of SGLT2i) (Figure 1), and it was nonsignificant in several prespecified subgroups (Table S3).

Characteristics Associated With eGFR Dip Among SGLT2i Users

Black race, lower eGFR category, congestive heart failure, history of acute kidney injury, microalbuminuria, macroalbuminuria, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, loop diuretic use, and nonloop diuretic use were associated with higher risk of eGFR dip $>10\%$ and eGFR dip $>30\%$ (Table 2).

eGFR Dip and the Effectiveness of SGLT2i on Cardiovascular and Kidney Outcomes

To estimate whether and to what extent the protective association between SGLT2i and cardiovascular and kidney outcomes may be abrogated by an intervening eGFR dip (conditioned on the probability of eGFR dip), we first developed mediation analyses where eGFR dip was considered a mediator. In analyses for the composite cardiovascular outcome, the total effect size that accounted for eGFR dipping as a mediator was 0.92 (95% CI: 0.84–0.99); estimates of the association independent of eGFR dip $>10\%$ and eGFR dip $>30\%$ yielded an HR of 0.88 (0.81–0.92) and 0.90 (0.82–0.98), respectively, suggesting that the magnitude of risk reduction abrogated by eGFR dipping was 3.78% (2.22%–5.44%) and 1.18% (0.62%–2.22%) for eGFR dip $>10\%$ and eGFR dip $>30\%$, respectively (Figure 2 and Table S4).

In analyses, for the composite kidney outcome, the total effect size that accounted for eGFR dipping as a mediator was 0.78 (95% CI: 0.71–0.87); estimates of the association independent of eGFR dip $>10\%$ and eGFR dip $>30\%$ yielded an HR of 0.73 (0.65–0.82) and 0.76 (0.68–1.86), suggesting that the magnitude of risk reduction abrogated by eGFR dipping was 4.76% (3.17%–6.85%) and 1.66% (0.87%–3.01%) for eGFR dip $>10\%$ and eGFR dip $>30\%$, respectively (Figure 2 and Table S4).

Table 1. Baseline Characteristics by Treatment Group and by eGFR Dip in SGLT2i Group

Baseline Characteristics	Other Antihyperglycemics (n=209 025)	SGLT2i			
		All SGLT2i (n=36 638)	No eGFR Dip or Dip ≤10% (n=20 458; 55.84%)	eGFR Dip >10% (n=16 180; 44.16%)	eGFR Dip >30% (n=2326; 6.35%)
Age, mean (SD), y	65.73 (10.55)	65.30 (9.11)	64.71 (9.36)	66.06 (8.71)	66.26 (8.12)
Race, n (%)					
White	145 909 (69.80)	27 169 (74.16)	15 479 (75.66)	11 690 (72.25)	1623 (69.78)
Black	39 357 (18.83)	5297 (14.46)	2685 (13.12)	2612 (16.14)	413 (17.76)
Other*	23 759 (11.37)	4172 (11.39)	2294 (11.21)	1878 (11.61)	290 (12.47)
Sex, n (%)					
Men	197 727 (94.59)	35 016 (95.57)	19 529 (95.46)	15 487 (95.72)	2217 (95.31)
Women	11 298 (5.41)	1622 (4.43)	929 (4.54)	693 (4.28)	109 (4.69)
eGFR, mean (SD), mL/min per 1.73 m ²	76.05 (20.45)	78.84 (17.51)	80.77 (17.79)	75.72 (16.73)	73.38 (16.62)
eGFR category, n (%)					
eGFR ≥90 mL/min per 1.73 m ²	57 407 (27.46)	10 120 (27.62)	7006 (34.25)	3114 (19.25)	342 (14.70)
90 mL/min per 1.73 m ² >eGFR≥60 mL/min per 1.73 m ²	97 261 (46.53)	19 882 (54.27)	10 455 (51.10)	9427 (58.26)	1261 (54.21)
60 mL/min per 1.73 m ² > eGFR≥45 mL/min per 1.73 m ²	36 044 (17.24)	5881 (16.05)	2697 (13.18)	3184 (19.68)	627 (26.96)
45 mL/min per 1.73 m ² >eGFR ≥30 mL/min per 1.73 m ²	18 313 (8.76)	755 (2.06)	300 (1.47)	455 (2.81)	96 (4.13)
HbA1c, mean (SD), %	8.75 (1.93)	8.71 (1.37)	8.71 (1.39)	8.70 (1.34)	8.76 (1.40)
Body mass index, mean (SD), kg/m ²	32.87 (6.53)	34.25 (6.41)	34.17 (6.41)	34.35 (6.39)	34.69 (6.58)
Low-density lipoprotein, mean (SD), mg/dL	89.97 (36.93)	80.95 (33.77)	82.10 (34.00)	79.50 (33.43)	79.05 (35.05)
Systolic blood pressure, mean (SD), mm Hg	132.92 (17.06)	132.35 (16.04)	131.97 (15.67)	132.82 (16.49)	133.71 (17.31)
Diastolic blood pressure, mean (SD), mm Hg	76.32 (10.43)	75.03 (9.81)	75.32 (9.73)	74.65 (9.89)	74.15 (9.89)
Congestive heart failure, n (%)	12 896 (6.17)	3416 (9.32)	1496 (7.31)	1920 (11.87)	417 (17.93)
Alcoholism, n (%)	12 148 (5.81)	1479 (4.04)	817 (3.99)	662 (4.09)	111 (4.77)
Bone fracture, n (%)	2656 (1.27)	423 (1.115)	208 (1.02)	215 (1.33)	51 (2.19)
Cancer, n (%)	42 861 (20.51)	7599 (20.74)	3986 (19.48)	3613 (22.33)	573 (24.63)
Cardiovascular disease, n (%)	51 284 (24.53)	14 635 (39.94)	7671 (37.50)	6964 (43.04)	1117 (48.02)
Diabetic ketoacidosis, n (%)	840 (0.40)	70 (0.19)	39 (0.19)	31 (0.19)	5 (0.21)
Hypoglycemia, n (%)	3855 (1.84)	1224 (3.34)	586 (2.86)	638 (3.94)	124 (5.33)
Pancreatitis, n (%)	2474 (1.18)	446 (1.22)	210 (1.03)	236 (1.46)	45 (1.93)
Bladder and urinary tract infections, n (%)	7328 (3.51)	746 (2.04)	377 (1.84)	369 (2.28)	76 (3.27)
Venous thromboembolism, n (%)	1359 (0.65)	214 (0.58)	113 (0.55)	101 (0.62)	14 (0.60)
Acute kidney injury, n (%)	18 821 (9.00)	3101 (8.46)	1388 (6.78)	1713 (10.59)	406 (17.45)
Albuminuria, n (%)					
None (≤30 mg/g)	88 410 (42.30)	14 414 (39.34)	8871 (43.36)	5543 (34.26)	595 (25.58)
Microalbuminuria (>30–≤300 mg/g)	102 139 (48.86)	18 608 (50.79)	10 053 (49.14)	8555 (52.87)	1306 (56.15)
Macroalbuminuria (>300 mg/g)	18 476 (8.84)	3616 (9.87)	1534 (7.50)	2082 (12.87)	425 (18.27)
Metformin, n (%)	109 958 (52.61)	29 760 (81.23)	16 616 (81.22)	13 144 (81.24)	1876 (80.65)
Insulin, n (%)	56 150 (26.86)	20 705 (56.51)	10 892 (53.24)	9813 (60.65)	1543 (66.34)
Sulfonylureas, n (%)	61 094 (29.23)	17 734 (48.40)	9999 (48.88)	7735 (47.81)	1048 (45.06)
DPP4, n (%)	9683 (4.63)	9362 (25.56)	5298 (25.90)	4064 (25.12)	509 (21.88)
GLP1, n (%)	2921 (1.40)	4798 (13.10)	2616 (12.79)	2182 (13.49)	333 (14.32)
Thiazolidinediones, n (%)	3918 (1.87)	3081 (8.41)	1666 (8.14)	1415 (8.75)	211 (9.07)
Total No. of diabetes mellitus medications used, mean (SD)	1.18 (0.81)	2.35 (0.93)	2.32 (0.94)	2.39 (0.92)	2.39 (0.92)
ACEI/ARB, n (%)	118 277 (56.59)	25 686 (70.11)	13 906 (67.97)	11 780 (72.80)	1801 (77.43)

(Continued)

Table 1. Continued

Baseline Characteristics	Other Antihyperglycemics (n=209 025)	SGLT2i			
		All SGLT2i (n=36 638)	No eGFR Dip or Dip ≤10% (n=20 458; 55.84%)	eGFR Dip >10% (n=16 180; 44.16%)	eGFR Dip >30% (n=2326; 6.35%)
Calcium channel blockers, n (%)	56 994 (27.27)	11 133 (30.39)	5716 (27.94)	5417 (33.48)	877 (37.70)
β-Blockers, n (%)	79 898 (38.22)	18 992 (51.84)	9859 (48.19)	9133 (56.45)	1478 (63.54)
Diuretics, n (%)					
Loop diuretics	25 216 (12.06)	5970 (16.29)	2690 (13.15)	3280 (20.27)	662 (28.46)
Nonloop diuretics	51 521 (24.65)	9771 (26.67)	5030 (24.59)	4741 (29.30)	759 (32.63)
Statins, n (%)	144 393 (69.08)	31 222 (85.22)	17 179 (83.97)	14 043 (86.79)	2066 (88.82)
Type of hospital system, n (%)					
Outpatient clinic	126 384 (60.46)	19 387 (52.92)	10 959 (53.57)	8428 (52.09)	1174 (50.47)
Healthcare system	82 641 (39.54)	17 251 (47.08)	9499 (46.43)	7752 (47.91)	1152 (49.53)
Year of treatment initial, n (%)					
2016	18 247 (8.73)	746 (2.04)	412 (2.01)	334 (2.06)	35 (1.50)
2017	76 758 (36.72)	6747 (18.42)	3868 (18.91)	2879 (17.79)	388 (16.68)
2018	72 696 (34.78)	13 478 (36.79)	7608 (37.19)	5870 (36.28)	812 (34.91)
2019	41 324 (19.77)	15 667 (42.76)	8570 (41.89)	7097 (43.86)	1091 (46.90)
Smoking status, n (%)					
Never	95 093 (45.49)	17 062 (46.57)	9555 (46.71)	7507 (46.40)	1093 (46.99)
Former	65 260 (31.22)	12 092 (33.00)	6685 (32.68)	5407 (33.42)	753 (32.37)
Current	48 672 (23.29)	7484 (20.43)	4218 (20.62)	3266 (20.19)	480 (20.64)

Data are presented as mean (SD) or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DPP4, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide-1 agonist; HbA1c, glycated hemoglobin; and SGLT2i, sodium-glucose co-transporter-2 inhibitor.

*Other race includes non-White and non-Black participants.

To determine whether the association between SGLT2i and cardiovascular and kidney outcomes remained significant in people with higher than average probability of experiencing an eGFR dip following SGLT2i initiation, we tested the association in groups based on the predicted probability of eGFR dipping associated with SGLT2i exposure (categorized as above and below average; where average probability for eGFR dip >10% and eGFR dip >30% was 11.64% and 1.92%, respectively). The results suggest that the association between SGLT2i and cardiovascular and kidney outcomes remained significant even in those with higher than average probability of eGFR dip >10% and eGFR dip >30% (Figure 3 and Table S5). The association was also significant in those with below average probability of eGFR dipping (Figure 3 and Table S5).

eGFR Dip and Characteristics Associated With SGLT2i Discontinuation at 6 Months

Rates of SGLT2i discontinuation at 6 months were 21.83% in the overall SGLT2i group, and 22.10%, 20.12%, and 29.58% in those with no eGFR dip, 10%<eGFR dip≤30%, and eGFR dip >30%, respectively.

In analyses that balanced demographic and health characteristics at baseline, we considered a battery of putative characteristics that may be associated with SGLT2i discontinuation and occurred following SGLT2i initiation and before 6 months. eGFR dip >30%, but not eGFR dip of 10% to 30%, was associated with increased risk of SGLT2i discontinuation (Table S6). The analyses also identified adverse events, including amputation, pancreatitis, bladder and urinary tract infections, hospitalization, and HbA1c increase, as characteristics associated with increased odds of SGLT2i discontinuation (Table S6).

Risk of Cardiovascular and Kidney Outcomes Associated With SGLT2i Continuation or Discontinuation at 6 Months by eGFR Dipping Category

We examined the risk of a composite cardiovascular outcome (of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or all-cause mortality) associated with continued use of SGLT2i versus discontinuation at 6 months in each eGFR dipping category. The results suggested that compared with discontinuation, continued use of SGLT2i

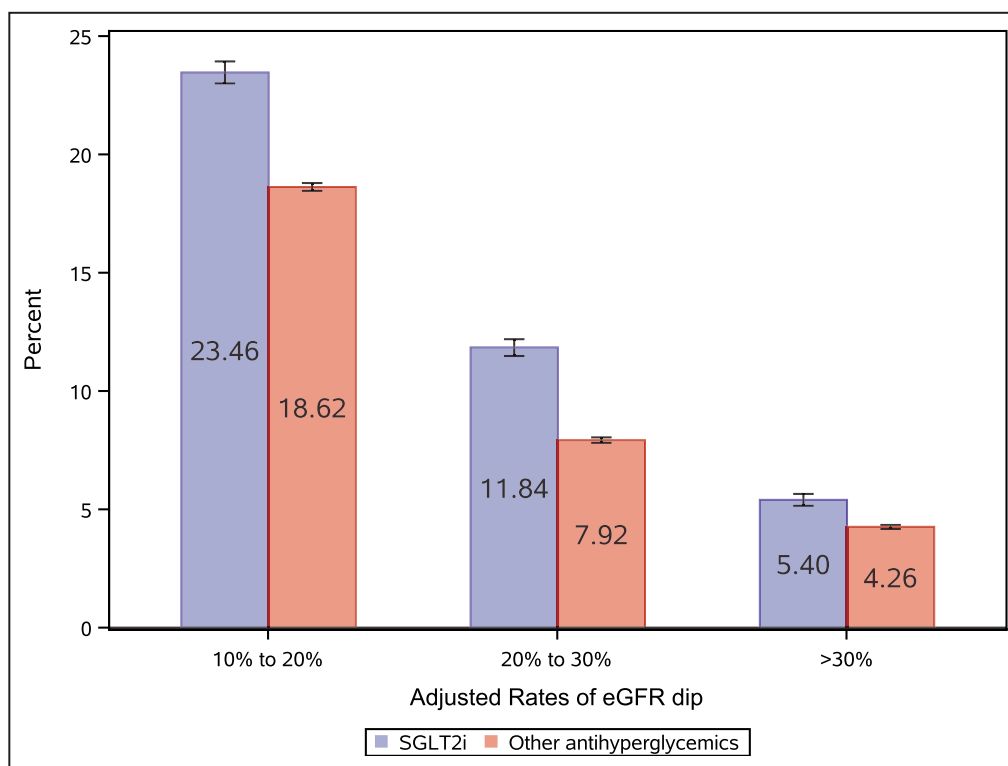


Figure 1. Adjusted rates of estimated glomerular filtration rate (eGFR) dip in the first 6 months among users of sodium-glucose cotransporter-2 inhibitor (SGLT2i) and other antihyperglycemics. Adjusted rates of eGFR dip >10% to 20%, >20% to 30%, and >30% in the SGLT2i group (blue) and the other antihyperglycemic group (red); model was adjusted for covariates at treatment initiation. Error bars represent 95% CIs.

was associated with reduced risk of cardiovascular outcomes in nondippers, in those with eGFR dip >10%, and in those with eGFR dip >30% (Figure 4 and Table S7).

We then examined the risk of a composite kidney outcome (of eGFR decline >50%, end-stage kidney disease, or all-cause mortality) associated with continued use of SGLT2i versus discontinuation in each eGFR dipping category. The results suggested that compared with discontinuation, continued use of SGLT2i was associated with reduced risk of composite kidney outcome in nondippers, in those with eGFR dip >10%, and in those with eGFR dip >30% (Figure 4 and Table S7).

Evaluation of Potential Biases

Propensity score distribution and standardized difference of covariates across treatment groups and across discontinuation status are presented in Figures S5 through S7. Plots suggested good overlap of the propensity score across groups, and all covariates are well balanced after weighting. A negative outcome control was applied following the same analytic algorithm to examine if the associations observed were attributable to possible spurious biases. Traffic-related

injury, which should not causally exhibit an association with SGLT2i use or SGLT2i continuation, was used as negative outcome control. There was no significant association between SGLT2i and traffic-related injury (OR: 0.96 [95% CI: 0.83–1.10]) or between SGLT2i continuation and traffic-related injury (HR: 0.93 [95% CI: 0.63–1.36]).

DISCUSSION

In this cohort study of 36 638 incident users of SGLT2i and 209 025 incident users of other antihyperglycemics, our results suggest that eGFR dip was more frequent following initiation of SGLT2i than other antihyperglycemics; however, most eGFR dips were <30%. Mediation analyses suggested that eGFR dip following initiation of SGLT2i does not substantially abrogate the effectiveness of SGLT2i on cardiovascular and kidney outcomes. Analyses based on the predicted probability of eGFR dipping suggested that even in those with higher than average probability of eGFR dipping, SGLT2i use was still associated with reduced risk of cardiovascular and kidney outcomes. Although eGFR dip <30% was not associated with SGLT2i discontinuation, eGFR dip >30% (a relatively infrequent event) was associated

Table 2. Characteristics Associated With eGFR Dip Among SGLT2i Users

Characteristics	Adjusted Odds Ratio (95% CI)	
	eGFR Dip >10%	eGFR Dip >30%
Age	1.00 (0.99–1.00)	0.99 (0.98–0.99)
Race (reference=White)		
Black	1.40 (1.31–1.49)	1.29 (1.15–1.46)
Other*	1.02 (0.95–1.09)	1.01 (0.88–1.15)
Women	1.09 (0.98–1.21)	1.20 (0.97–1.48)
eGFR category (reference=eGFR \geq 90 mL/min per 1.73 m ²)		
90 mL/min per 1.73 m ² >eGFR \geq 60 mL/min per 1.73 m ²	2.02 (1.91–2.14)	1.90 (1.66–2.16)
60 mL/min per 1.73 m ² >eGFR \geq 45 mL/min per 1.73 m ²	2.44 (2.26–2.63)	2.89 (2.48–3.38)
45 mL/min per 1.73 m ² >eGFR \geq 30 mL/min per 1.73 m ²	2.90 (2.46–3.41)	3.01 (2.31–3.92)
Albuminuria (reference=no albuminuria)		
Microalbuminuria (>30– \leq 300 mg/g)	1.22 (1.16–1.27)	1.46 (1.32–1.61)
Macroalbuminuria (>300 mg/g)	1.63 (1.50–1.76)	1.90 (1.65–2.18)
HbA1c	1.00 (0.99–1.02)	1.03 (1.00–1.06)
Low-density lipoprotein	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Systolic blood pressure	1.00 (1.00–1.00)	1.00 (1.00–1.01)
Diastolic blood pressure	1.00 (0.99–1.00)	0.99 (0.99–1.00)
Congestive heart failure	1.19 (1.09–1.29)	1.30 (1.13–1.49)
Cardiovascular disease	1.04 (0.99–1.09)	1.06 (0.97–1.17)
Acute kidney injury	1.12 (1.03–1.21)	1.45 (1.28–1.65)
ACEI/ARB	1.10 (1.04–1.15)	1.22 (1.10–1.35)
Diuretics (reference=no diuretic use)		
Loop diuretics	1.38 (1.29–1.48)	1.70 (1.50–1.93)
Nonloop diuretics	1.29 (1.23–1.36)	1.59 (1.44–1.77)
Statins	0.98 (0.92–1.04)	0.99 (0.86–1.14)

Models additionally adjusted for sex, body mass index, smoking status, type of hospital system, cancer, alcoholism, hypoglycemia, diabetic ketoacidosis, bladder and urinary tract infections, venous thromboembolism, pancreatitis, bone fracture, and history use of glucagon-like peptide-1 agonist, dipeptidyl peptidase-4 inhibitor, sulfonylureas, thiazolidinediones, metformin, insulin, α -glucosidase inhibitors, meglitinides, amylin analogues, β -blockers, and calcium channel blockers. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; and SGLT2i, sodium-glucose co-transporter-2 inhibitor.

*Other race includes non-White and non-Black participants.

with SGLT2i discontinuation. Compared with those who discontinue SGLT2i in the first 6 months of therapy, and after accounting for characteristics that were associated with discontinuation, SGLT2i continuation was associated with reduced risk of cardiovascular and kidney outcomes regardless of eGFR dipping.

Our findings suggest that eGFR dipping is not uncommon following SGLT2i initiation in real-world setting (rate of eGFR dip >10% was 9.86 [95% CI: 8.83–11.0] per 100 users of SGLT2i); however, most eGFR dips were <30% as rate of eGFR dip >30% was relatively infrequent (1.15 [0.70–1.62] per 100 users of SGLT2i). In the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), 28.3% of empagliflozin users experienced an eGFR dip >10% and 1.4% experienced an eGFR dip of >30%.³⁸ In the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial, rates of eGFR dip >10% and >30%

were 21% and 4%, respectively.⁴ The relatively higher rates of eGFR dipping in these randomized trials compared with the real-world data provided in this report are likely a reflection of the higher underlying risk of eGFR dip among trial participants.

Our mediation analyses, which considered the contribution of an intervening eGFR dip following initiation of SGLT2i, suggested that dipping does not abrogate the salutary association between SGLT2i and cardiovascular and kidney outcomes. Furthermore, our analyses suggest that even in those with higher than average probability of eGFR dipping, the association between SGLT2i and cardiovascular and kidney outcomes remained protective. Last, the results suggested that even after accounting for characteristics associated with discontinuation at 6 months, continuation of SGLT2i use was associated with reduced risk of the composite cardiovascular and kidney outcomes. Taken together, the constellation of findings suggests that, although eGFR dipping may be more common in SGLT2i users (than

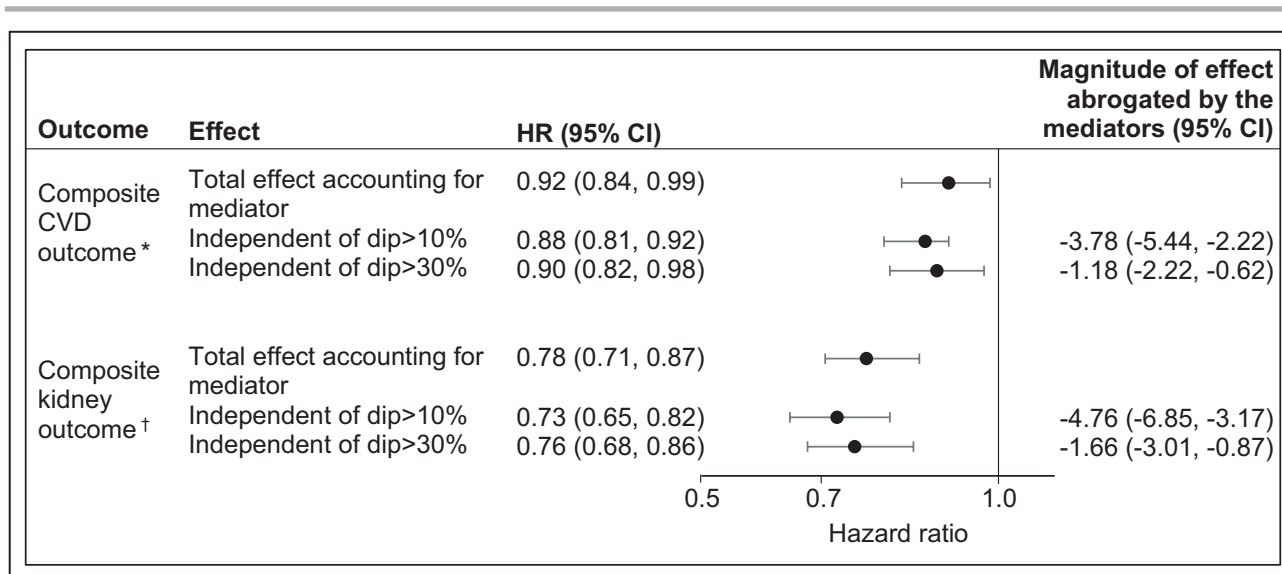


Figure 2. Risk of composite cardiovascular and kidney outcomes associated with sodium-glucose cotransporter-2 inhibitor (SGLT2i) (vs other antihyperglycemics) based on mediation analyses.

Mediation analyses based on inverse odds ratio weighting and adjusted for covariates measured at treatment initiation. The total effect accounted for estimated glomerular filtration rate (eGFR) dipping as the mediator. The estimates independent of eGFR dip represent the effect that was not mediated by eGFR dip. The magnitude of effect abrogated by the mediator was estimated from the difference between hazard ratios (HRs) independent of eGFR dip and the HRs for the total effect and presented as a percentage. CVD indicates cardiovascular disease. *Composite CVD outcome of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or all-cause mortality. †Composite kidney outcome of eGFR decline >50%, end-stage kidney disease, or all-cause mortality.

other antihyperglycemics), concern about dipping should not preclude initiation of SGLT2i. Another key message from our analyses is that regardless of eGFR dip in the

first 6 months following initiation of SGLT2i, continued use of SGLT2i may be more beneficial to long-term kidney and cardiovascular outcomes than discontinuation;

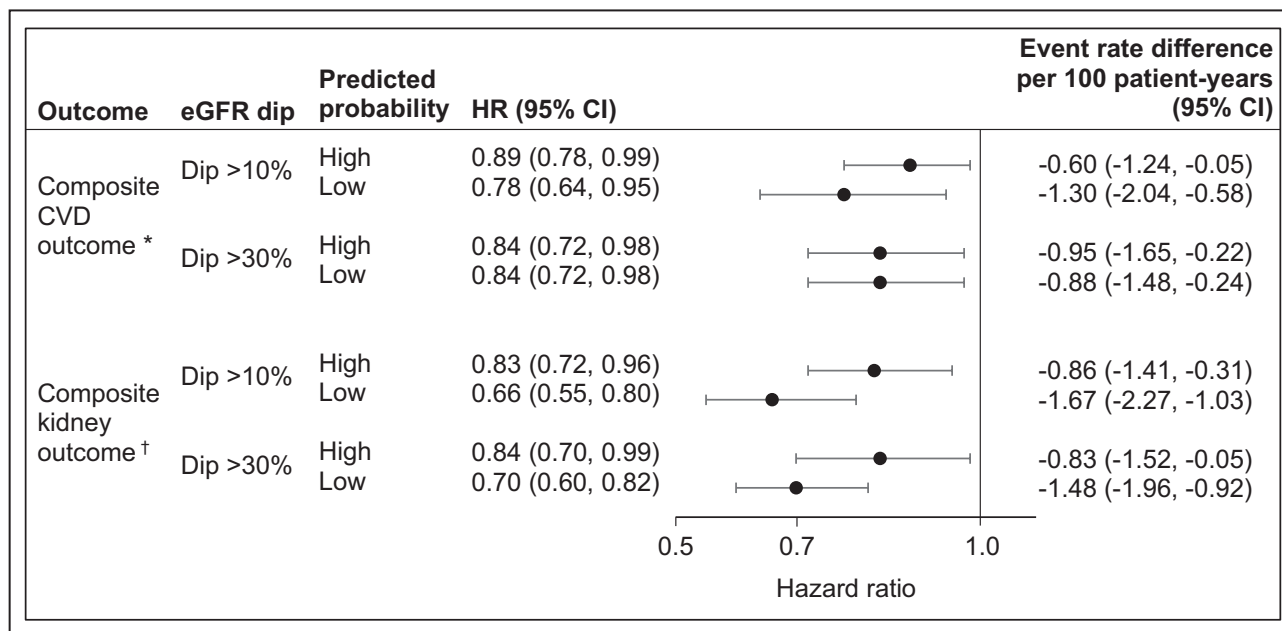


Figure 3. Risk of composite cardiovascular and kidney outcomes associated with sodium-glucose cotransporter-2 inhibitor (SGLT2i) (vs other antihyperglycemics) in groups based on predicted probability of SGLT2i-related estimated glomerular filtration rate (eGFR) dip.

High and low probability of eGFR dip, categorized as above and below average predicted probability of eGFR dip associated with SGLT2i. Average predicted probability was 11.64% and 1.92% for eGFR dip >10% and eGFR dip >30%, respectively. Model was adjusted for covariates measured at treatment initiation. CVD indicates cardiovascular disease; and HR, hazard ratio.

*Composite CVD outcome of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or all-cause mortality. †Composite kidney outcome of eGFR decline >50%, end-stage kidney disease, or all-cause mortality.

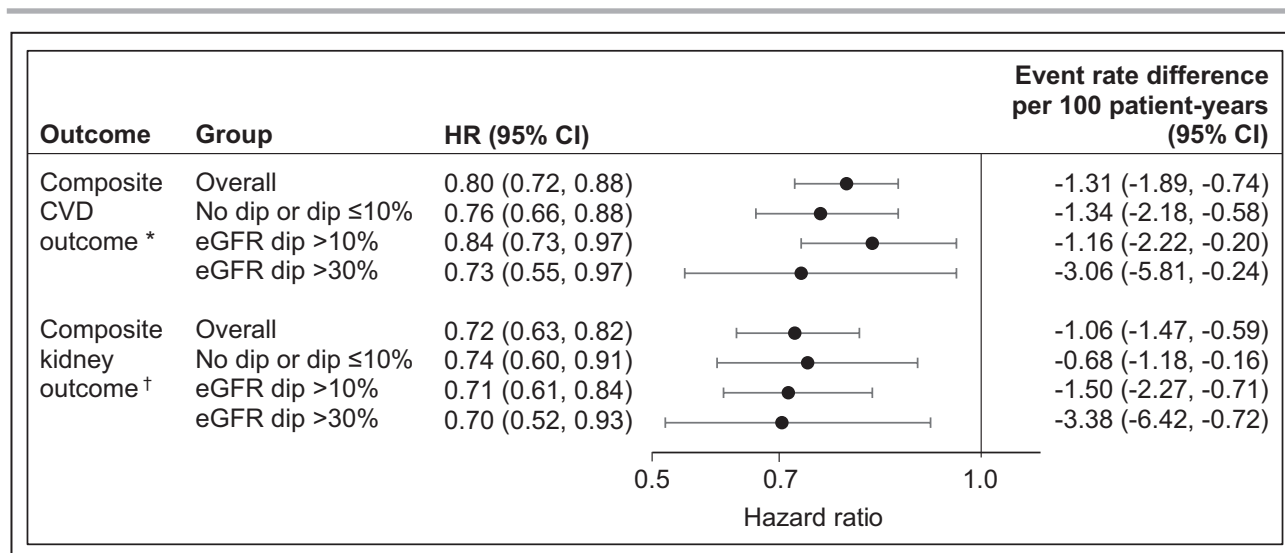


Figure 4. Risk of composite cardiovascular and kidney outcomes associated with sodium-glucose cotransporter-2 inhibitor (SGLT2i) continuation vs discontinuation by estimated glomerular filtration rate (eGFR) dipping category.

Model adjusted for both covariates measured at treatment initiation and characteristics evaluated within 6 months after treatment initiation. CVD indicates cardiovascular disease; and HR, hazard ratio.

*Composite CVD outcome of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or all-cause mortality.

†Composite kidney outcome of eGFR decline >50%, end-stage kidney disease, or all-cause mortality.

practitioners may consider continuation of treatment with SGLT2i as a means of achieving longer-term reduction in risk of cardiovascular and kidney outcomes.

Our analyses of factors associated with eGFR discontinuation suggest that the occurrence of adverse events, hospitalization, or increase in HbA1c (a marker of worsening glycemic control) was associated with discontinuation of SGLT2i. Furthermore, eGFR dip >30% was also associated with increased risk of discontinuation. These results may be useful in guiding efforts to examine whether some of these patient groups may benefit from resumption of treatment with SGLT2i.³⁹

The mechanism underpinning the eGFR dip in SGLT2i is not entirely clear.^{11,40,41} It has been suggested that this initial dip is reminiscent of the mild decline in eGFR observed in some patients following initiation of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, which is generally attributed to postglomerular (efferent) vasodilatation and reduced hyperfiltration.^{11,42} Several other hypotheses are being tested, including potential contribution of enhanced proximal tubular natriuresis leading to activation of tubuloglomerular feedback and resultant preglomerular (afferent) vasoconstriction.^{11,40,41,43} The constellation of evidence from randomized controlled trials and real-world studies suggests that the initial eGFR dip is likely a functional (and reversible) dip that does not reflect kidney injury and is then followed by eGFR stabilization, and ultimately reduced risk of adverse cardiovascular and kidney outcomes.^{11,17,18,41} The results of our analyses are congruent with this

understanding and support the assessment that eGFR dip does not substantially erode the effectiveness of SGLT2i on cardiovascular and kidney outcomes, and that even in those with eGFR dip >30%, continued therapy with SGLT2i was more beneficial for longer-term cardiovascular and kidney outcomes than discontinued therapy.

This study has several limitations. We used observational real-world data from the VA to build our cohort, which was mostly composed of older, White, and male participants, which may limit the generalizability of study findings. Although our analytic approach evaluated SGLT2i versus other active non-SGLT2i antihyperglycemics, considered known confounders, and applied inverse probability weighting to generate balance in characteristics between the 2 treatment groups, we cannot completely rule out the possibility of residual confounding. Although we used validated definitions to define covariates, exposures, and outcomes based on diagnostic codes, procedure codes, laboratory data, and pharmacy data, we cannot completely rule out misclassification. Because empagliflozin represents >97% of SGLT2i use at the VA, we restricted our analyses to empagliflozin, and we did not examine within SGLT2i class differences. We defined discontinuation based on pharmacy records; hence, the exact discontinuation date may not be accurate. Although we estimated the probability of discontinuation by leveraging a priori knowledge through inclusion of a comprehensive set of covariates, the direct clinical reason (or indication) of medication discontinuation may not have been accounted for in our analyses. The

estimation of absolute rate difference was based on the baseline risk in our cohort, which may vary in other populations with different baseline risks.

The study has several strengths. We used large-scale real-world data from the VA, which operates the largest integrated healthcare system in the United States; VA data are captured during routine clinical care, which might more closely recapitulate real-world experiences.^{17,18,44} The selection of antihyperglycemics or discontinuation in VA was less likely driven by financial considerations. We developed our research aims, study design, and execution to specifically address the knowledge gap of real-world clinical implications of eGFR dip and the effect of discontinuation versus continuation on clinical outcomes, which may not be addressed in randomized controlled trials.⁴⁵ In addition to reporting relative risk, we reported absolute risk differences that may be meaningful in informing clinical decision making.⁴⁵ We used a new user design (new SGLT2i users) with active comparator (new other antihyperglycemic users) and applied advanced statistical methods, including inverse probability of treatment weighting, and additionally accounted for events in the first 6 months of therapy that may be associated with discontinuation to evaluate the risk of outcomes in users who continue versus discontinue SGLT2i. We additionally evaluated both risk of major cardiovascular and kidney outcomes to address questions relevant to the clinical community. Finally, the successful testing of negative controls, generally used to detect spurious associations, lessens concern that the observed associations of interest may be attributable to biases.

In sum, our results suggest that eGFR dipping is not uncommon following initiation of SGLT2i; however, most eGFR dips were <30%. The salutary association between SGLT2i and cardiovascular and kidney outcomes was not abrogated by eGFR dipping. Continuation of SGLT2i (versus discontinuation) was associated with reduced risk of cardiovascular and kidney outcomes in those with no eGFR dip, and in those with eGFR dip >10% and eGFR dip >30%.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S7

Figures S1–S7

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SUPPLEMENTAL MATERIAL

Table S1. Distribution of antihyperglycemics at treatment initiation.

Medication class	Medication names	Distribution at treatment initiation
SGLT2i	Empagliflozin	36638 (14.91%)
Biguanide	Metformin	58873 (23.96%)
Insulin	Insulin	33563 (13.66%)
Sulfonylureas	Glyburide, Glipizide, Glimepiride	56568 (23.03%)
DPP4	Alogliptin, Sitagliptin, Saxagliptin, Linagliptin	31744 (12.92%)
GLP1	Liraglutide, Exenatide, Semaglutide, Dulaglutide, Lixisenatide,	15646 (6.37%)
Thiazolidinediones	Pioglitazone, Rosiglitazone	10428 (4.24%)
Alpha-glucosidase inhibitors	Miglitol, Acarbose	1902 (0.77%)
Meglitinides	Nateglinide, Repaglinide	283 (0.12%)
Amylin analogues	Pramlintide	18 (0.01%)

SGLT2i=sodium-glucose co-transporter-2 inhibitor. DPP4=dipeptidyl peptidase-4 inhibitor. GLP1=glucagon-like peptide-1 receptor agonist.

Table S2. Unadjusted rate of eGFR dip>10% and dip> 30% in SGLT2i and the other antihyperglycemics group.

	Unadjusted rate of eGFR dip>10% per 100 patients (95% Confidence interval)		Unadjusted rate of eGFR dip>30% per 100 patients (95% Confidence interval)	
	SGLT2i	Other antihyperglycemics	SGLT2i	Other antihyperglycemics
Overall cohort	44.16 (43.66, 44.67)	30.37 (30.17, 30.56)	6.35 (6.10, 6.60)	4.12 (4.03, 4.20)
Race-White	43.03 (42.44, 43.62)	29.7 (29.47, 29.94)	5.97 (5.70, 6.26)	3.94 (3.84, 4.04)
Race-Black	49.31 (47.97, 50.66)	31.42 (30.96, 31.88)	7.80 (7.11, 8.55)	4.15 (3.96, 4.36)
Race-Other	45.02 (43.51, 46.53)	32.69 (32.10, 33.29)	6.95 (6.22, 7.76)	5.16 (4.88, 5.44)
eGFR≥90 mL/min/1.73 m²	30.77 (29.88, 31.68)	22.72 (22.38, 23.06)	3.38 (3.04, 3.75)	2.39 (2.27, 2.52)
90>eGFR≥60 mL/min/1.73 m²	47.42 (46.72, 48.11)	31.09 (30.8, 31.38)	6.34 (6.01, 6.69)	3.58 (3.46, 3.70)
60>eGFR≥45 mL/min/1.73 m²	54.14 (52.86, 55.41)	34.67 (34.18, 35.17)	10.66 (9.9, 11.48)	5.65 (5.42, 5.89)
45>eGFR≥30 mL/min/1.73 m²	60.26 (56.73, 63.70)	42.00 (41.29, 42.72)	12.72 (10.53, 15.3)	9.38 (8.96, 9.81)
No albuminuria (≤30 mg/g)	38.46 (37.67, 39.26)	26.20 (25.91, 26.49)	4.13 (3.82, 4.47)	2.59 (2.49, 2.70)
Microalbuminuria (>30- ≤300 mg/g)	45.98 (45.26, 46.69)	31.57 (31.28, 31.85)	7.02 (6.66, 7.39)	4.54 (4.42, 4.67)
Macroalbuminuria (>300 mg/g)	57.58 (55.96, 59.18)	43.65 (42.94, 44.37)	11.76 (10.75, 12.85)	9.08 (8.68, 9.50)
Congestive heart failure *	56.21 (54.54, 57.86)	43.33 (42.48, 44.19)	12.21 (11.15, 13.35)	9.69 (9.19, 10.21)
Acute Kidney Injury *	55.24 (53.48, 56.98)	44.84 (44.13, 45.55)	13.09 (11.95, 14.33)	11.50 (11.05, 11.96)
ACE/ARB *	45.86 (45.25, 46.47)	31.89 (31.63, 32.16)	7.01 (6.71, 7.33)	4.74 (4.62, 4.86)
Loop diuretics *	54.94 (53.68, 56.20)	40.93 (40.32, 41.54)	11.09 (10.32, 11.91)	8.51 (8.17, 8.86)
Non-loop diuretics *	48.52 (47.53, 49.51)	31.90 (31.50, 32.31)	7.77 (7.25, 8.32)	4.29 (4.12, 4.47)

SGLT2i=sodium-glucose co-transporter-2 inhibitor. eGFR=estimated glomerular filtration rate. HbA1c=glycated hemoglobin. ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers.

* Within patients with history of the disease or used the medication

Table S3. Adjusted rates of eGFR dip>10% in SGLT2i and the other antihyperglycemics group

	Adjusted odds ratio (95% confidence interval)	Adjusted rate per 100 patients (95% confidence interval)		Excess rate per 100 patients associated with SGLT2i (95% confidence interval)
		SGLT2i	Other antihyperglycemics	
Overall cohort	1.54 (1.47, 1.61)	40.65 (40.11, 41.19)	30.79 (30.59, 30.98)	9.86 (8.83, 11.00)
Race-White	1.48 (1.41, 1.57)	39.10 (38.49, 39.72)	30.19 (29.96, 30.43)	8.91 (7.77, 10.01)
Race-Black	1.93 (1.72, 2.18)	47.22 (45.7, 48.74)	31.62 (31.17, 32.08)	15.60 (12.81, 18.65)
Race-Other	1.45 (1.26, 1.66)	41.65 (40.05, 43.27)	33.05 (32.46, 33.65)	8.40 (5.38, 11.88)
eGFR≥90 mL/min/1.73 m²	1.28 (1.16, 1.41)	27.30 (26.36, 28.26)	22.71 (22.37, 23.05)	4.59 (2.75, 6.51)
90>eGFR≥60 mL/min/1.73 m²	1.62 (1.53, 1.72)	43.00 (42.26, 43.74)	31.76 (31.47, 32.05)	11.28 (9.78, 12.64)
60>eGFR≥45 mL/min/1.73 m²	1.63 (1.47, 1.81)	47.14 (45.79, 48.50)	35.3 (34.81, 35.80)	11.84 (9.06, 14.75)
45>eGFR≥30 mL/min/1.73 m²	1.49 (1.13, 1.95)	52.03 (48.26, 55.79)	42.21 (41.5, 42.93)	9.78 (3.35, 16.55)
No albuminuria (≤30 mg/g)	1.43 (1.33, 1.54)	33.96 (33.14, 34.80)	26.43 (26.14, 26.72)	7.53 (5.99, 9.20)
Microalbuminuria (>30- ≤300 mg/g)	1.63 (1.53, 1.74)	43.49 (42.73, 44.26)	32.05 (31.76, 32.33)	11.44 (9.94, 12.91)
Macroalbuminuria (>300 mg/g)	1.48 (1.29, 1.7)	53.60 (51.85, 55.34)	43.83 (43.11, 44.54)	9.77 (6.40, 13.09)
Congestive heart failure *	1.41 (1.22, 1.62)	52.02 (50.27, 53.77)	43.55 (42.7, 44.4)	8.47 (5.18, 1.76)
Acute Kidney Injury *	1.30 (1.11, 1.54)	51.81 (49.9, 53.72)	45.20 (44.49, 45.9)	6.61 (2.96, 11.04)
ACE/ARB *	1.57 (1.50, 1.66)	42.95 (42.31, 43.6)	32.35 (32.09, 32.62)	10.60 (9.27, 11.90)
Loop diuretics *	1.45 (1.30, 1.61)	50.53 (49.20, 51.86)	41.38 (40.78, 41.99)	9.15 (6.52, 12.01)
Non-loop diuretics *	1.66 (1.53, 1.81)	44.40 (43.35, 45.46)	32.44 (32.04, 32.84)	11.96 (9.76, 13.87)

SGLT2i=sodium-glucose co-transporter-2 inhibitor. eGFR=estimated glomerular filtration rate. HbA1c=glycated hemoglobin. ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers. Model adjusted for covariates measured at treatment initiation.
 * Within patients with history of the disease or used the medication

Adjusted rates of eGFR dip>30% in SGLT2i and the other antihyperglycemics group

	Adjusted odds ratio (95% confidence interval)	Adjusted rate per 100 patients (95% confidence interval)		Excess rate per 100 patients associated with SGLT2i (95% confidence interval)
		SGLT2i	Other antihyperglycemics	
Overall cohort	1.28 (1.17, 1.41)	5.40 (5.16, 5.66)	4.26 (4.17, 4.34)	1.15 (0.70, 1.62)

Race-White	1.22 (1.09, 1.37)	4.93 (4.66, 5.21)	4.07 (3.97, 4.17)	0.86 (0.39, 1.36)
Race-Black	1.95 (1.55, 2.47)	8.10 (7.31, 8.97)	4.32 (4.12, 4.52)	3.80 (2.03, 5.63)
Race-Other	0.97 (0.77, 1.21)	5.17 (4.49, 5.95)	5.34 (5.07, 5.64)	-0.17 (-1.20, 1.02)
eGFR≥90 mL/min/1.73 m²	1.18 (0.92, 1.51)	2.91 (2.57, 3.29)	2.48 (2.36, 2.61)	0.43 (-0.24, 1.16)
90>eGFR≥60 mL/min/1.73 m²	1.36 (1.20, 1.53)	5.03 (4.71, 5.36)	3.76 (3.64, 3.88)	1.27 (0.72, 1.81)
60>eGFR≥45 mL/min/1.73 m²	1.39 (1.18, 1.64)	7.97 (7.26, 8.73)	5.85 (5.62, 6.1)	2.11 (0.97, 3.37)
45>eGFR≥30 mL/min/1.73 m²	1.3 (0.84, 2.01)	11.94 (9.7, 14.61)	9.46 (9.04, 9.89)	2.48 (-1.67, 6.98)
No albuminuria (≤30 mg/g)	1.19 (0.99, 1.43)	3.15 (2.85, 3.47)	2.65 (2.55, 2.76)	0.49 (-0.02, 1.10)
Microalbuminuria (>30- ≤300 mg/g)	1.35 (1.19, 1.53)	6.24 (5.88, 6.62)	4.71 (4.58, 4.84)	1.53 (0.84, 2.28)
Macroalbuminuria (>300 mg/g)	1.13 (0.92, 1.39)	10.18 (9.17, 11.29)	9.1 (8.7, 9.53)	1.08 (-0.67, 2.99)
Congestive heart failure *	1.30 (1.04, 1.63)	12.29 (11.19, 13.49)	9.71 (9.21, 10.23)	2.58 (0.23, 5.00)
Acute Kidney Injury *	1.00 (0.77, 1.29)	11.68 (10.51, 12.96)	11.72 (11.27, 12.18)	-0.04 (-2.36, 3.09)
ACE/ARB *	1.29 (1.16, 1.43)	6.22 (5.92, 6.54)	4.90 (4.78, 5.03)	1.32 (0.69, 1.97)
Loop diuretics *	1.18 (0.99, 1.40)	10.19 (9.41, 11.02)	8.79 (8.44, 9.14)	1.40 (-0.09, 3.24)
Non-loop diuretics *	1.46 (1.25, 1.71)	6.31 (5.81, 6.84)	4.41 (4.24, 4.59)	1.90 (1.13, 2.77)

SGLT2i=sodium-glucose co-transporter-2 inhibitor. eGFR=estimated glomerular filtration rate. HbA1c=glycated hemoglobin. ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin-receptor blockers. Model adjusted for covariates measured at treatment initiation.

* Within patients with history of the disease or used the medication

Table S4. Risk of composite cardiovascular and kidney outcomes associated with SGLT2i (vs. other antihyperglycemics) based on mediation analyses.

	Mediator	Hazard ratio of total effect accounted for mediator (95% confidence interval)	Hazard ratio independent of the mediator (95% confidence interval)	Magnitude of effect abrogated by the mediator (95% confidence interval)
Composite cardiovascular outcome *	eGFR Dip>10%	0.92 (0.84, 0.99)	0.88 (0.81, 0.92)	-3.78 (-5.44, -2.22)
	eGFR Dip>30%		0.90 (0.82, 0.98)	-1.18 (-2.22, -0.62)
Composite Kidney outcome †	eGFR Dip>10%	0.78 (0.71, 0.87)	0.73 (0.65, 0.82)	-4.76 (-6.85, -3.17)
	eGFR Dip>30%		0.76 (0.68, 0.86)	-1.66 (-3.01, -0.87)

Mediation analyses based on inverse odds ratio-weighting for causal mediation analysis and adjusted for covariates measured at treatment initiation.

The total effect accounted for eGFR dipping as the mediator. The hazard ratio independent of mediator represent the effect which was not mediated by eGFR dip. The magnitude of effect abrogated by the mediator was estimated from the difference between hazard ratios independent of eGFR dip and the hazard ratios for the total effect.

* Composite cardiovascular outcome was defined as non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure or all-cause mortality

† Composite kidney outcome was defined as eGFR decline>50%, ESKD or all-cause mortality

Table S5. Risk of composite cardiovascular and kidney outcomes associated with SGLT2i by predicted probability of SGLT2i related eGFR dip.

Outcomes	Group based on probability of eGFR dip	Adjusted hazard ratio (95% confidence interval)	Event rate difference per 100 patient-years (95% confidence interval)
Composite cardiovascular outcome *	High probability of dip>10%	0.92 (0.85, 0.99)	-0.60 (-1.24, -0.05)
	Low probability of dip>10%	0.84 (0.77, 0.93)	-1.30 (-2.04, -0.58)
	High probability of dip>30%	0.89 (0.82, 0.97)	-0.95 (-1.65, -0.22)
	Low probability of dip>30%	0.89 (0.82, 0.97)	-0.88 (-1.48, -0.24)
Composite kidney outcome †	High probability of dip>10%	0.72 (0.65, 0.79)	-0.86 (-1.41, -0.31)
	Low probability of dip>10%	0.62 (0.55, 0.69)	-1.67 (-2.27, -1.03)
	High probability of dip>30%	0.70 (0.62, 0.78)	-0.83 (-1.52, -0.05)
	Low probability of dip>30%	0.66 (0.60, 0.73)	-1.48 (-1.96, -0.92)

High and low probability of eGFR dip categorized based on probability of eGFR dipping associated with SGLT2i above or below the average, which are 11.64% for dip>10% and 1.92% for dip>30%. Model adjusted for covariates measured at treatment initiation.

* Composite cardiovascular outcome was defined as non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure or all-cause mortality

† Composite kidney outcome was defined as eGFR decline>50%, ESKD or all-cause mortality

Table S6. Characteristics associated with discontinuation among SGLT2i users.

	Prevalence (%)	Discontinuation rate per 100 patients * (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
eGFR dip category			
No dip or dip≤10% (reference)	20454 (55.84)	22.10 (21.53, 22.67)	1.00
10%< dip≤ 30%	13850 (37.81)	20.12 (19.46, 20.79)	0.83 (0.78, 0.87)
Dip> 30%	2326 (6.35)	29.58 (27.72, 31.43)	1.23 (1.11, 1.36)
Adverse events			
Bone fracture	263 (0.72)	25.10 (19.86, 30.33)	1.07 (0.80, 1.39)
Amputation	40 (0.11)	45.00 (29.58, 60.42)	2.85 (1.44, 5.66)
Diabetic ketoacidosis	38 (0.10)	31.58 (16.80, 46.36)	1.49 (0.73, 3.02)
Hypoglycemia	820 (2.24)	26.46 (23.44, 29.48)	1.07 (0.91, 1.26)
Pancreatitis	295 (0.81)	27.46 (22.37, 32.55)	1.24 (0.94, 1.62)
Bladder & urinary tract infections	521 (1.42)	45.11 (40.83, 49.38)	2.58 (2.15, 3.10)
Venous thromboembolism	141 (0.38)	24.82 (17.69, 31.95)	1.08 (0.73, 1.62)
Hospitalization not related to adverse events	2326 (6.35)	29.58 (27.72, 31.43)	1.50 (1.33, 1.69)
Increased HbA1c	8413 (22.97)	30.81 (29.82, 31.80)	1.90 (1.80, 2.02)

Characteristics were evaluated within 6 months after treatment initiation. Model adjusted for covariates measured at treatment initiation.

* Discontinuation rate per 100 patients within those with the characteristics

Table S7. Risk of composite cardiovascular and kidney outcomes associated with SGLT2i continuation vs. discontinuation by eGFR dipping category.

Outcomes	Group	Adjusted hazard ratio (95% confidence interval)	Adjusted event rate per 100 patient-years in those who continue SGLT2i (95% confidence interval)	Adjusted event rate per 100 patient-years in those who discontinue SGLT2i (95% confidence interval)	Event rate difference per 100 patient-years (95% confidence interval)
Composite cardiovascular outcome *	Overall	0.80 (0.72, 0.88)	5.28 (5.01, 5.59)	6.58 (6.05, 7.16)	-1.31 (-1.89, -0.74)
	No dip or dip≤10%	0.76 (0.66, 0.88)	4.41 (4.05, 4.76)	5.76 (5.09, 6.53)	-1.34 (-2.18, -0.58)
	Dip> 10%	0.84 (0.73, 0.97)	6.43 (5.92, 6.97)	7.61 (6.74, 8.54)	-1.16 (-2.22, -0.20)
	Dip> 30%	0.73 (0.55, 0.97)	8.50 (7.00, 10.06)	11.63 (9.17, 14.45)	-3.06 (-5.81, -0.24)
Composite kidney outcome †	Overall	0.72 (0.63, 0.82)	2.76 (2.52, 2.98)	3.81 (3.37, 4.20)	-1.06 (-1.47, -0.59)
	No dip or dip≤10%	0.74 (0.60, 0.91)	1.92 (1.67, 2.15)	2.62 (2.09, 3.10)	-0.68 (-1.18, -0.16)
	Dip> 10%	0.71 (0.61, 0.84)	3.85 (3.45, 4.29)	5.32 (4.59, 6.09)	-1.50 (-2.27, -0.71)
	Dip> 30%	0.70 (0.52, 0.93)	8.22 (6.82, 9.88)	11.66 (9.14, 14.34)	-3.38 (-6.42, -0.72)

Model adjusted for both covariates measured at treatment initiation and characteristics evaluated within 6 months after treatment initiation.

* Composite cardiovascular outcome was defined as non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure or all-cause mortality

† Composite kidney outcome was defined as eGFR decline>50%, ESKD or all-cause mortality

Figure S1. Cohort construction flow.

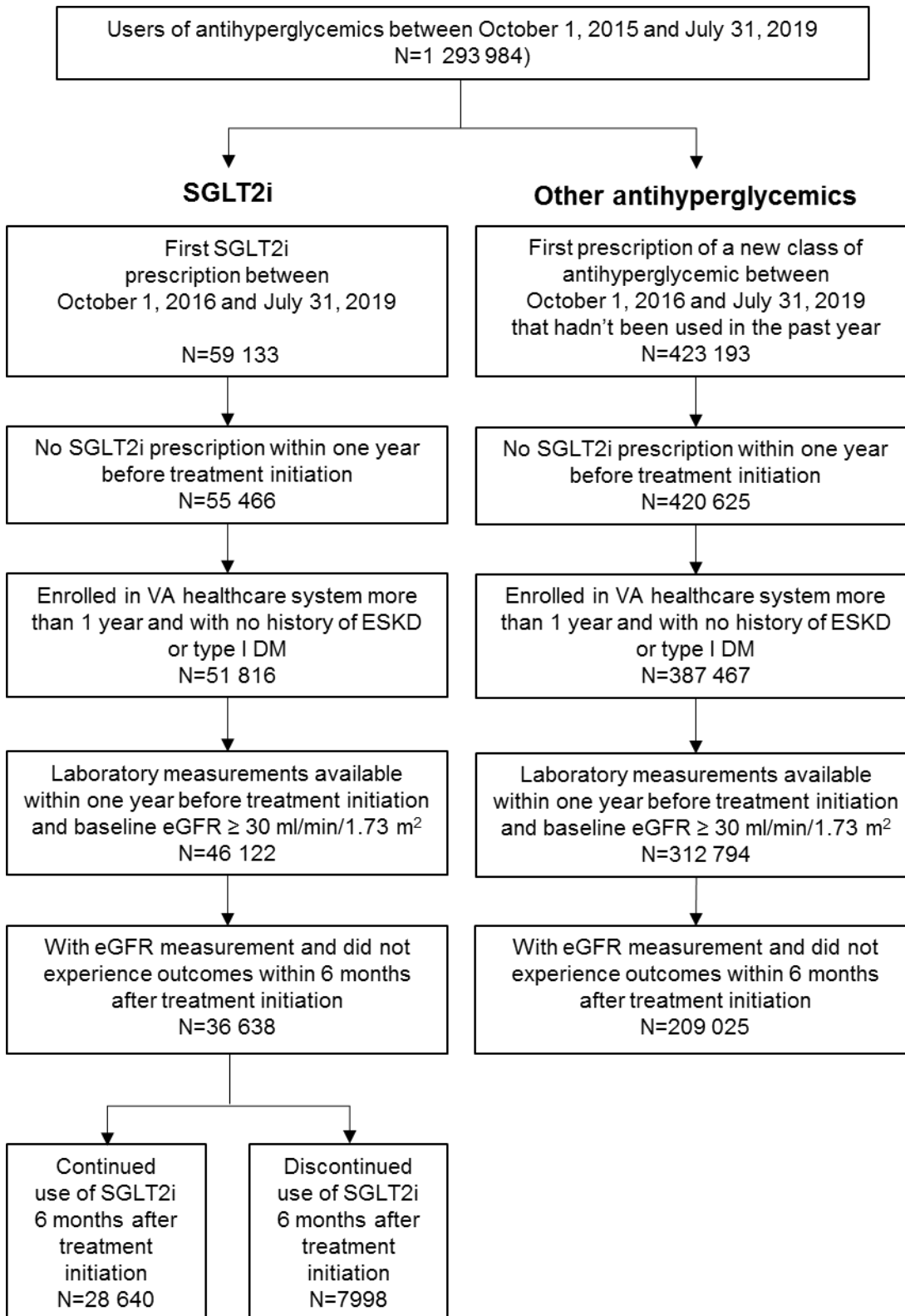


Figure S2. Study timeline.

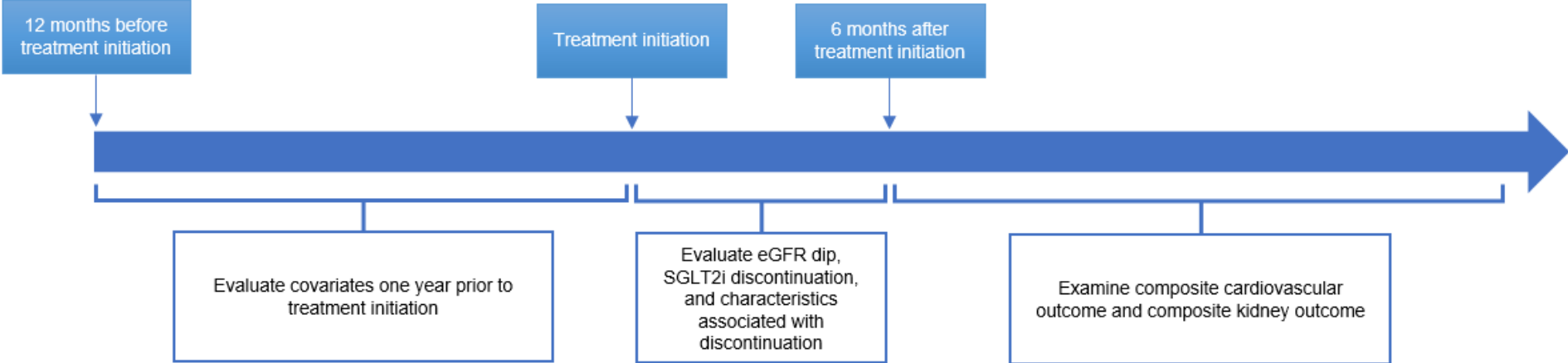


Figure S3. Analytic approach flowchart.

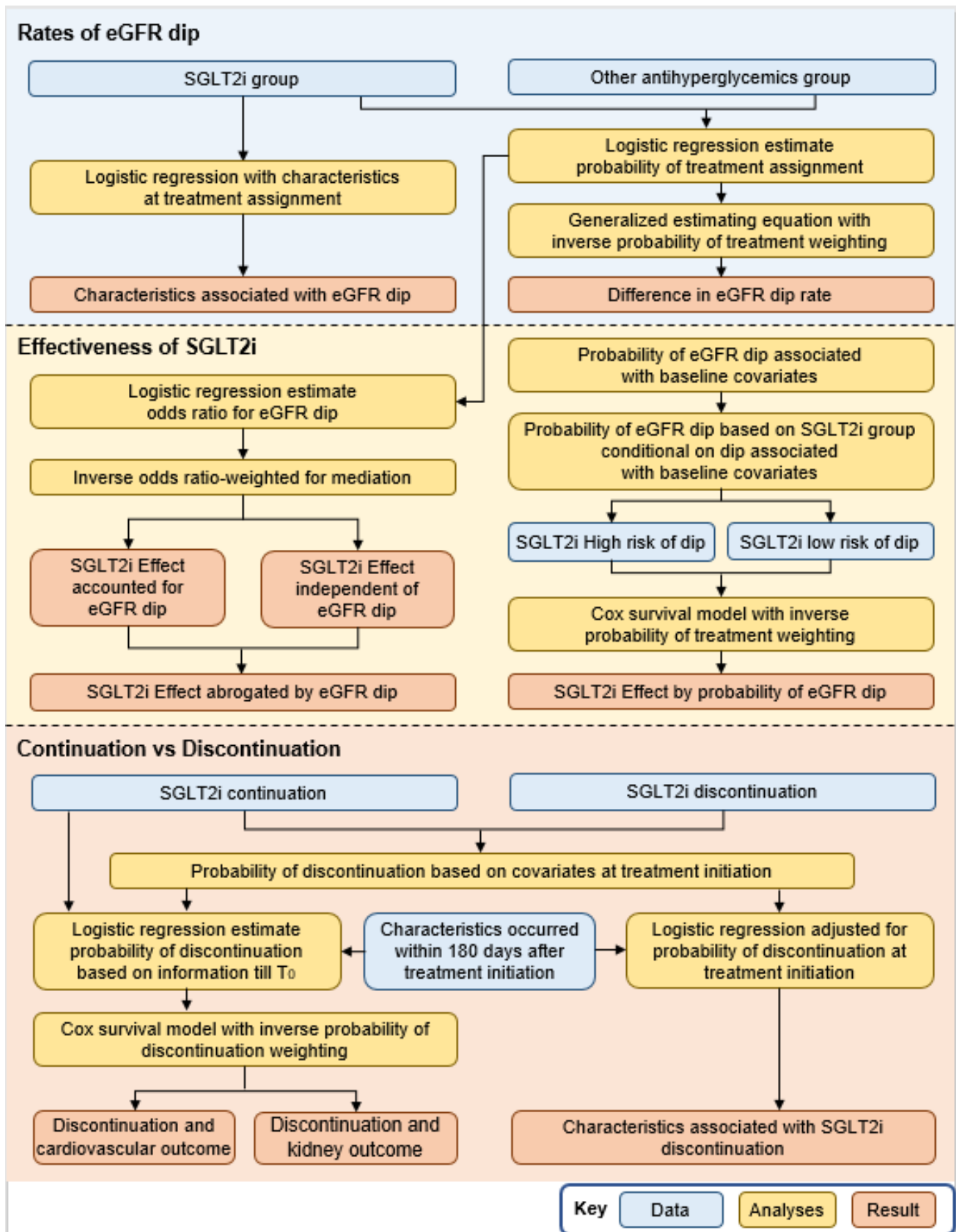
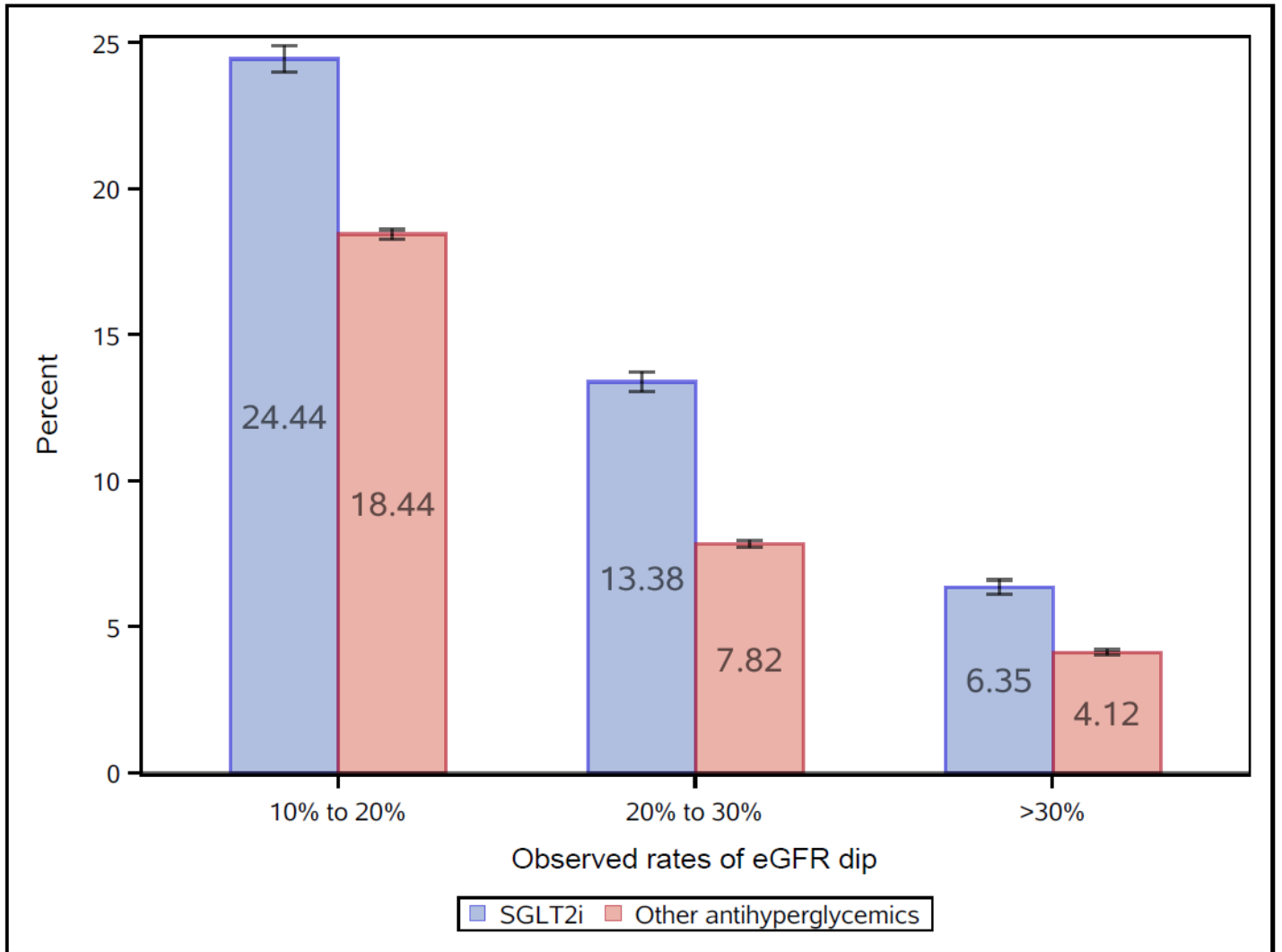


Figure S4. Rates of eGFR dip in the first 6 months among users of SGLT2i and other antihyperglycemics.



Observed rates of eGFR dip >10 to 20%, >20 to 30% and >30% in the SGLT2i group (blue) and the other antihyperglycemics group (red).

Figure S5a. Propensity score distribution in the SGLT2i and other antihyperglycemics groups before weighting

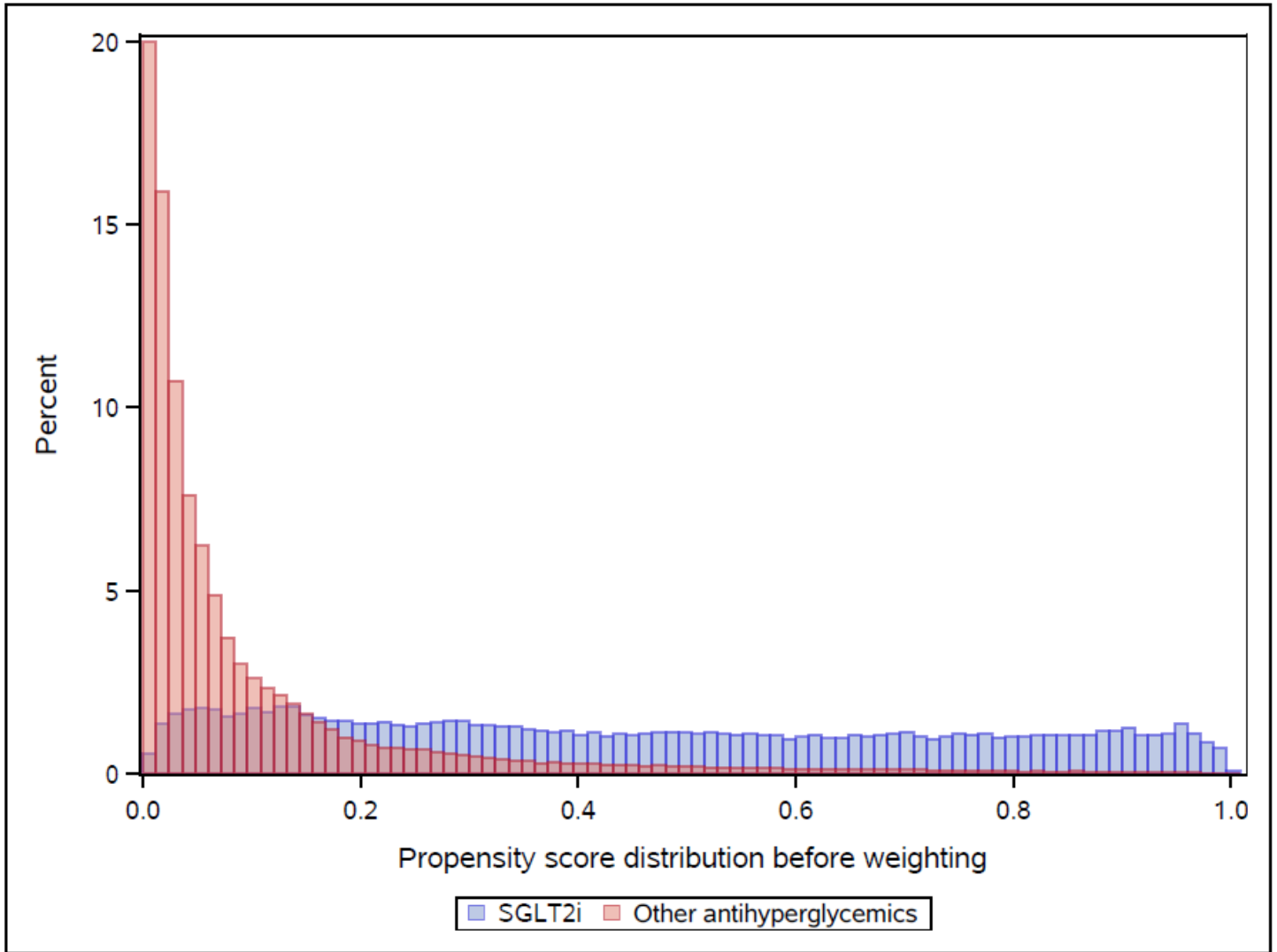


Figure S5b. Propensity score distribution in the SGLT2i and other antihyperglycemics groups after weighting.

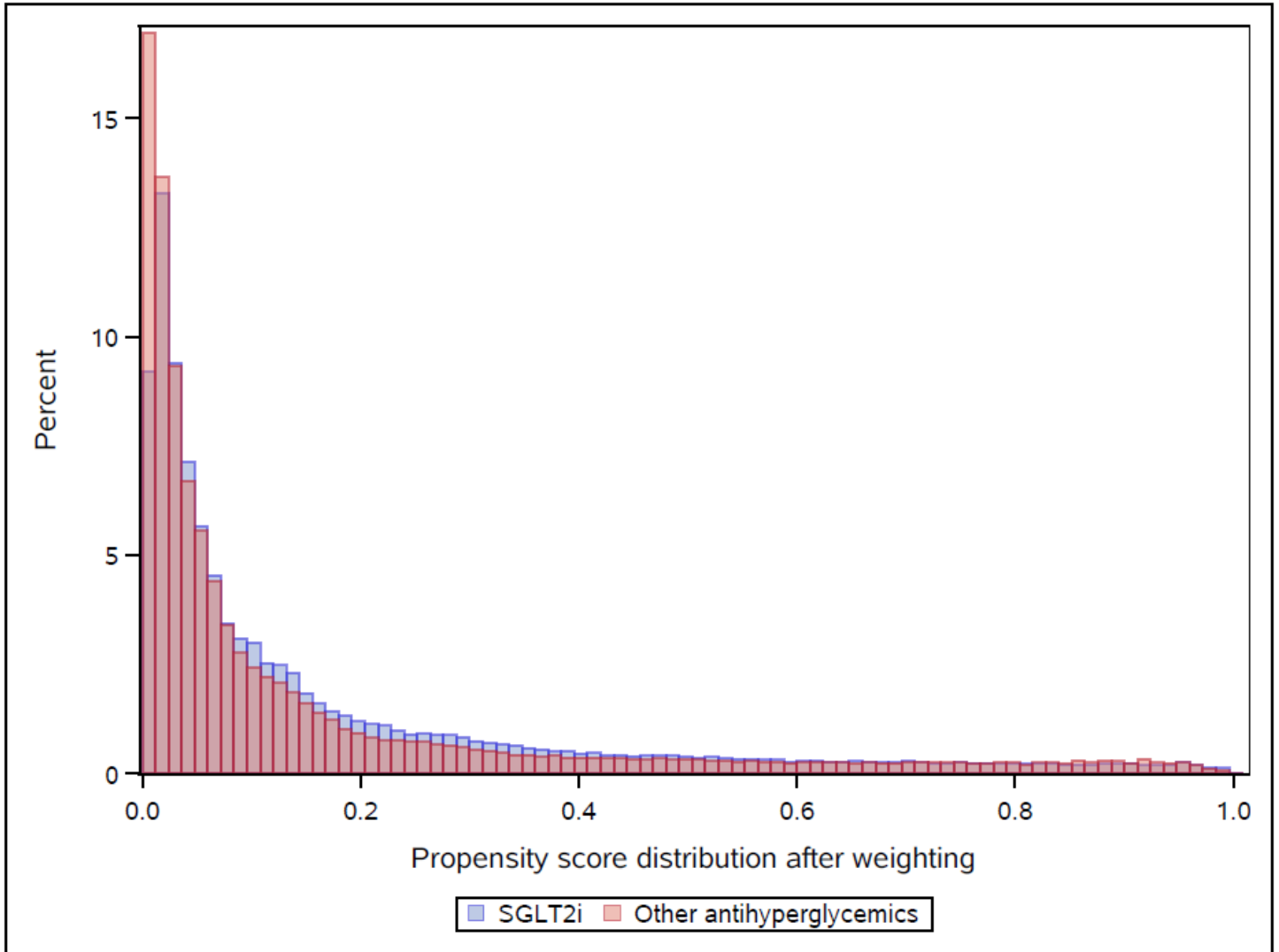


Figure S6a. Propensity score distribution before weighting for those who continued and those who discontinued SGLT2i treatment in the first 6 months.

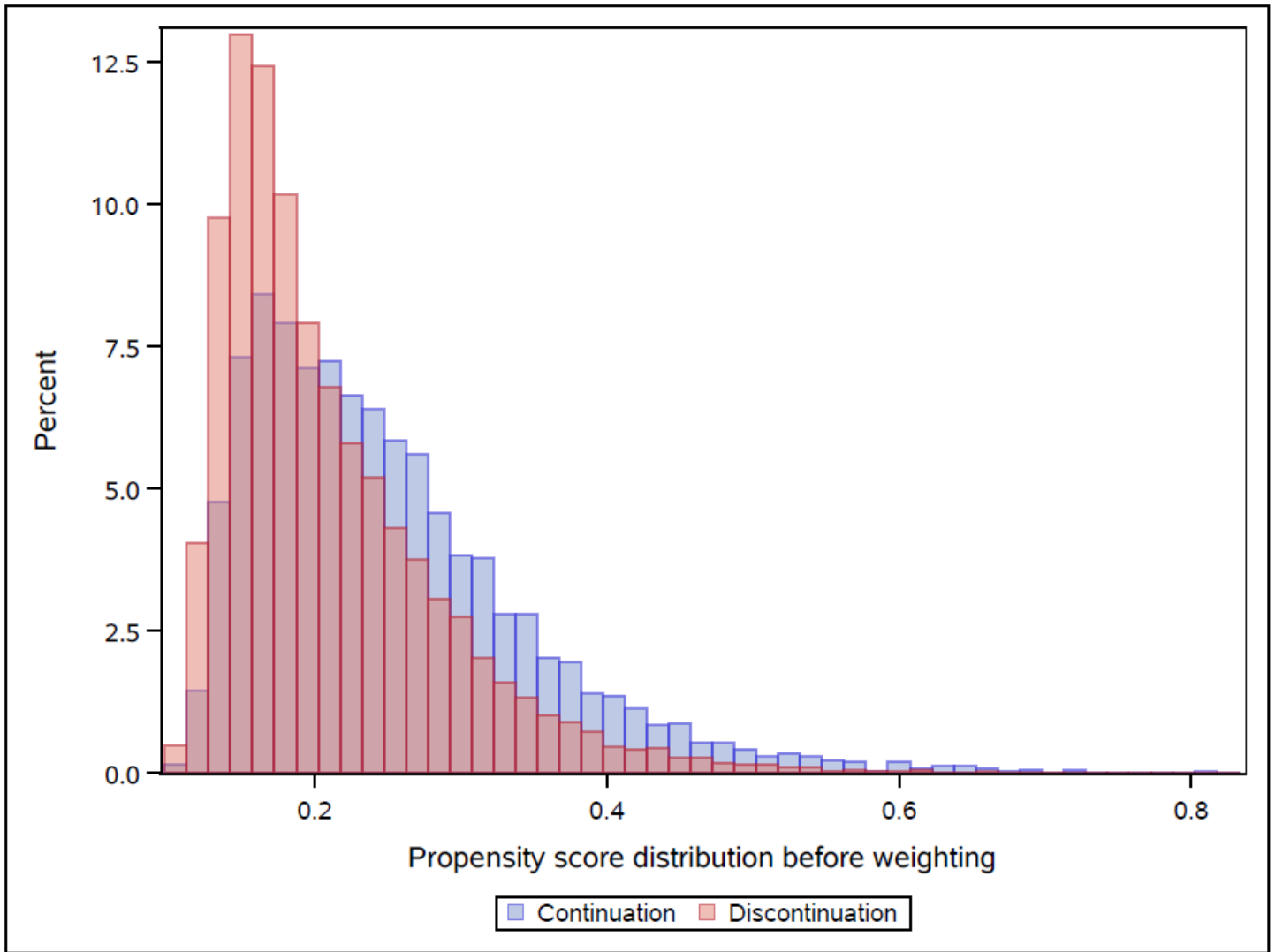


Figure S6b. Propensity score distribution after weighting for those who continued and those who discontinued SGLT2i treatment in the first 6 months.

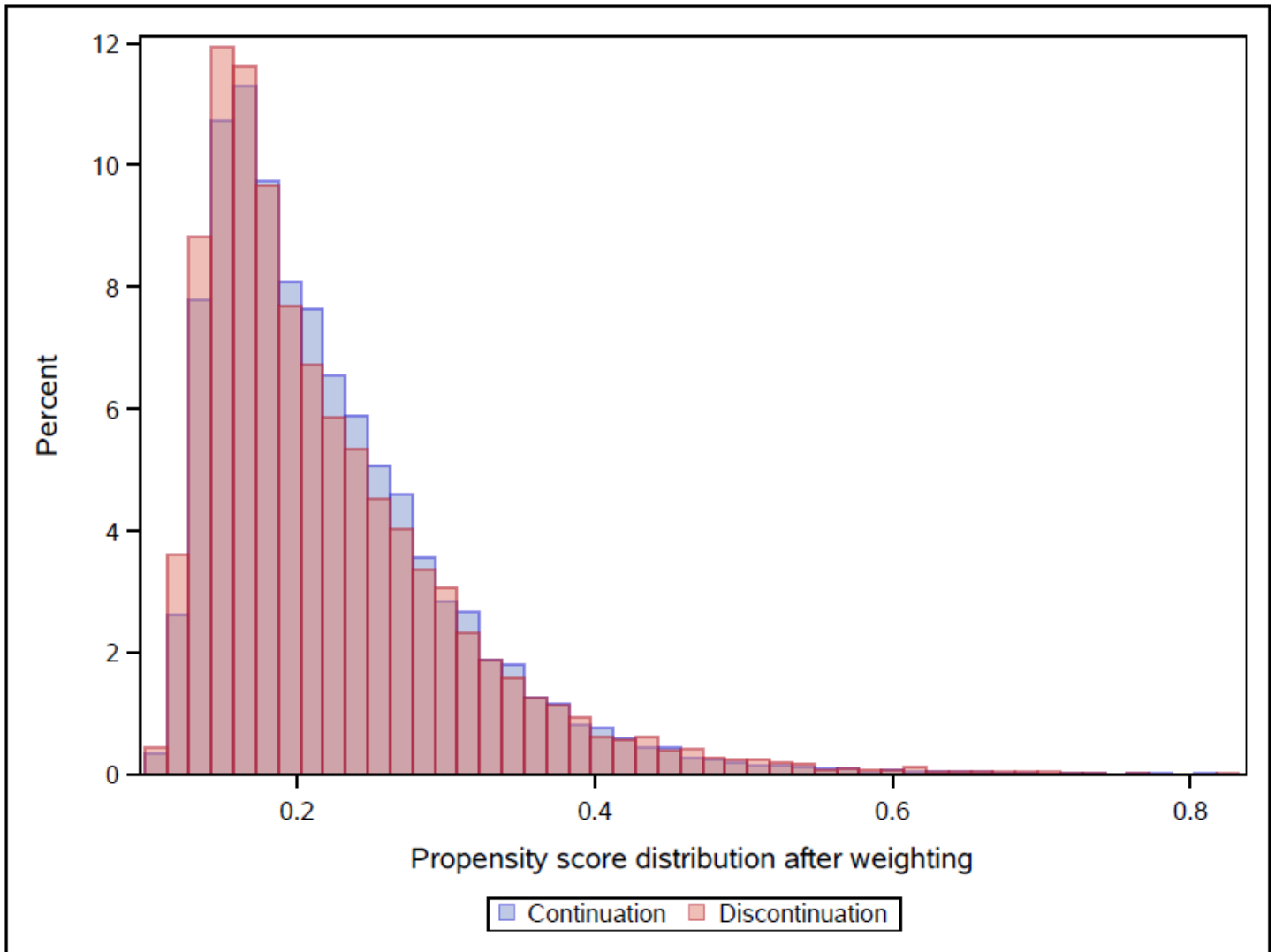
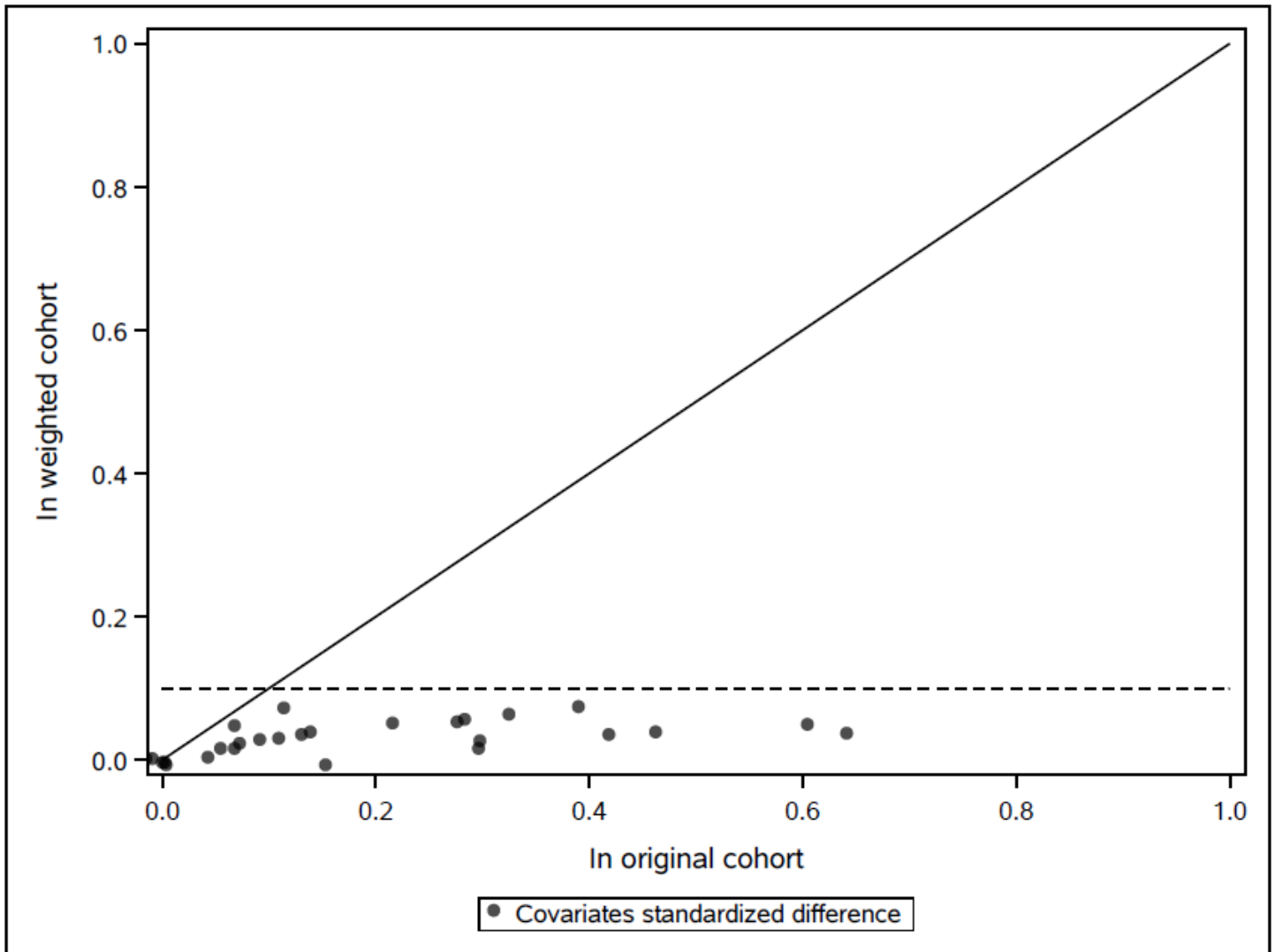
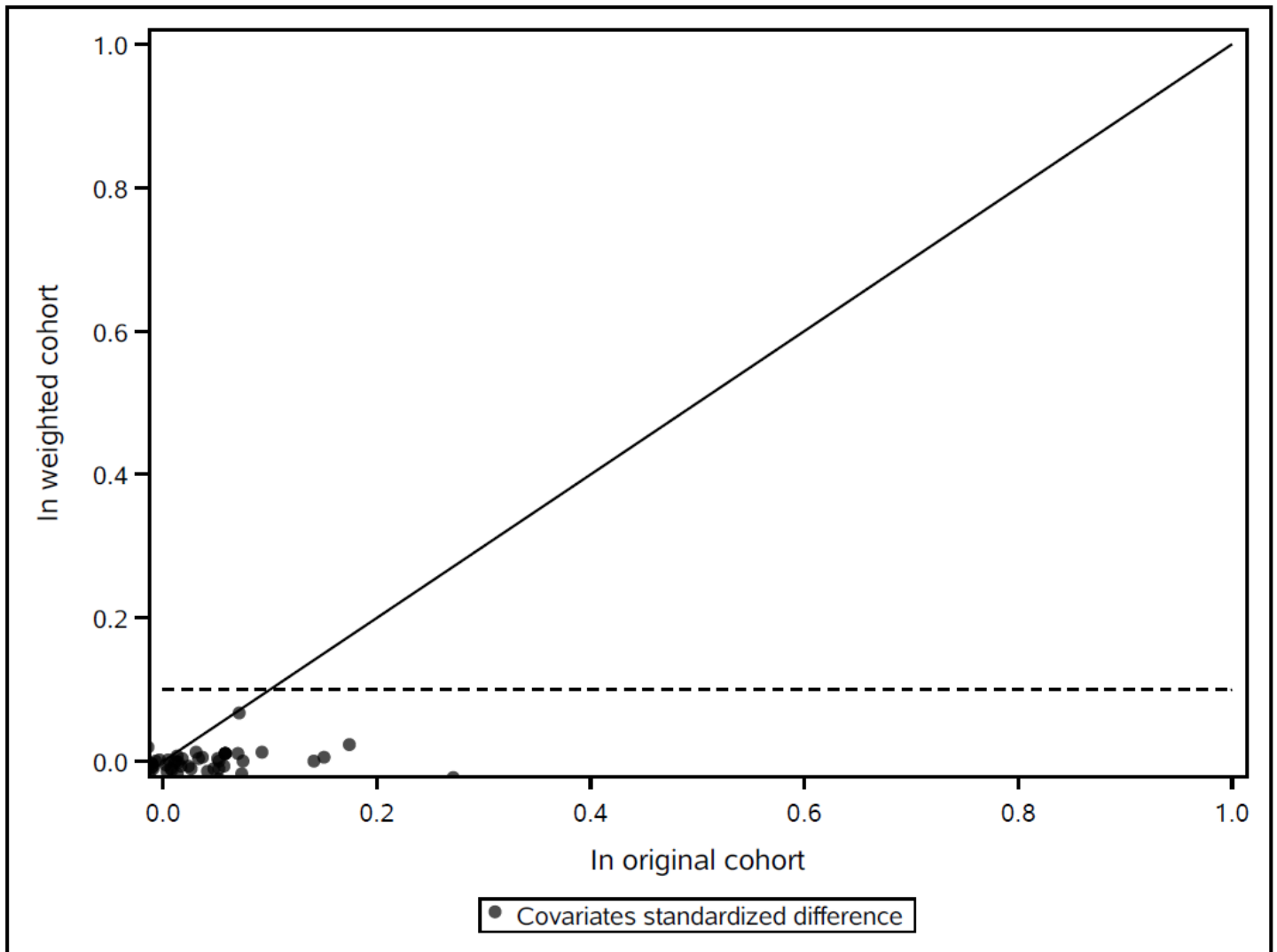


Figure S7a. Standardized difference of covariates between the treatment groups (SGLT2i and other antihyperglycemics) in the original cohort and the weighted cohort.



Standardized difference below 0.1 (below the dashed line) indicated the covariate is well balanced in the weighted cohort.

Figure S7b. Standardized difference of covariates between those who continued and those who discontinued SGLT2i treatment in the first 6 months in the original cohort and the weighted cohort.



Standardized difference below 0.1 (below the dashed line) indicated the covariate is well balanced in the weighted cohort.