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# Weight changes following antidiabetic mediation use: Real-world evidence from health system data

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## Abstract

**Objective:** Newer antidiabetic medications such as sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1RA) result in weight loss in clinical trials. However, the real-world effectiveness remains unclear. The magnitude of weight change associated with antidiabetic medication using real-world data was examined.

**Methods:** Patients with diabetes who initiated SGLT2i ($n = 906$), GLP1RA ($n = 782$), dipeptidyl peptidase-4 inhibitors (DPP4i, $n = 1881$), or sulfonylureas ($n = 3255$) in Geisinger Health System were identified. Outcomes were percent weight change per year and time to 5% weight loss. Propensity scores were used to account for differences across groups.

**Results:** The mean ± SD age of patients was 57.5 ± 14.1 years, 3381 (49.5%) were female, and 6450 (94.5%) had body mass index ≥25 kg/m$^2$. Compared with sulfonylureas, newer antidiabetic medications were associated with significant weight loss (−3.2% [95% confidence interval: −3.8%, −2.6%] per year for SGLT2i; −2.9% [−3.6%, −2.3%] per year for GLP1RA; and −1.7% [−2.1%, −1.3%] per year for DPP4i). SGLT2i and GLP1RA were also associated with significant weight loss compared with DPP4i. Among patients with overweight or obesity, SGLT2i and GLP1RA users were more likely to achieve 5% weight loss compared with sulfonylureas and DPP4i.

**Conclusions:** In real-world practice, SGLT2i and GLP1RA were associated with significant weight loss compared with sulfonylureas and DPP4i. These results may further motivate uptake of SGLT2i and GLP1RA, especially among patients who were overweight or had obesity.

KEYWORDS

diabetes, GLP1RA, obesity, SGLT2i, weight control

## 1 | INTRODUCTION

The increasing prevalence of obesity contributes substantially to the ongoing epidemic of type 2 diabetes (T2DM), and 87% of patients with T2DM are overweight or have obesity.[1] Obesity increases the risk of cardiovascular disease (CVD)[2] and death among patients with diabetes,[3-5] whereas weight loss improves glycemic control and CVD risk factors, and reduces the need for glucose-lowering medications.[6,7] Clinical guidelines recommend that patients with T2DM and obesity lose 5%–10% of their body weight (typically 5–10 kg) as an initial strategy.[8,9]

Older antidiabetic medications such as sulfonylureas are associated with weight gain, whereas the newer drug classes, including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP1RA), may have weight loss effects. In randomized controlled trials (RCTs), patients with diabetes randomized to SGLT2i or GLP1RA at diabetes doses lost approximately 2–3 kg compared to placebo.[10-13] The potential weight loss effects together with the cardiorenal benefits of SGLT2i and GLP1RA make such treatments appealing for patients with T2DM and overweight or obesity. However, real-world evidence is limited about the magnitude of weight change associated with antidiabetic medications, especially for SGLT2i.[14,15] In addition, whether there is a clinically significant difference in weight change between these medications is unclear as most RCTs lack head-to-head comparisons.

Using data from a large health system, the association between commonly used antidiabetic medications and weight change was assessed. The hypothesis was that compared with sulfonylureas and DPP4i, SGLT2i and GLP1RA were associated with clinically significant weight loss.

## 2 | METHODS

### 2.1 | Data source and study population

Electronic health record (EHR) data from the Geisinger, a health care system that serves approximately 45 counties in central and northeastern Pennsylvania were used. The EHR provides information on patient sociodemographic, inpatient and outpatient encounters, outpatient prescriptions and laboratory results. Patients with T2DM who initiated SGLT2i, GLP1RA, DPP4i, or sulfonylureas between 2015 and 2018, had at least 1 year of prior engagement with Geisinger system, had at least 1 weight measurement within 1 year prior to medication initiation (T0), and had at least 1 weight measurement within 1 year after T0 were included (Figure 1). Patients with end-stage kidney disease (ESKD), bariatric surgery, anorexia nervosa, or pregnancy within 1 year prior to T0 were excluded. Diabetes was defined as (1) the presence of International Classification of Disease 9 or 10 Clinical Modification (ICD-9 or 10-CM) codes for diabetes (250, E10, E11, or E13) in the inpatient setting or problem list or at

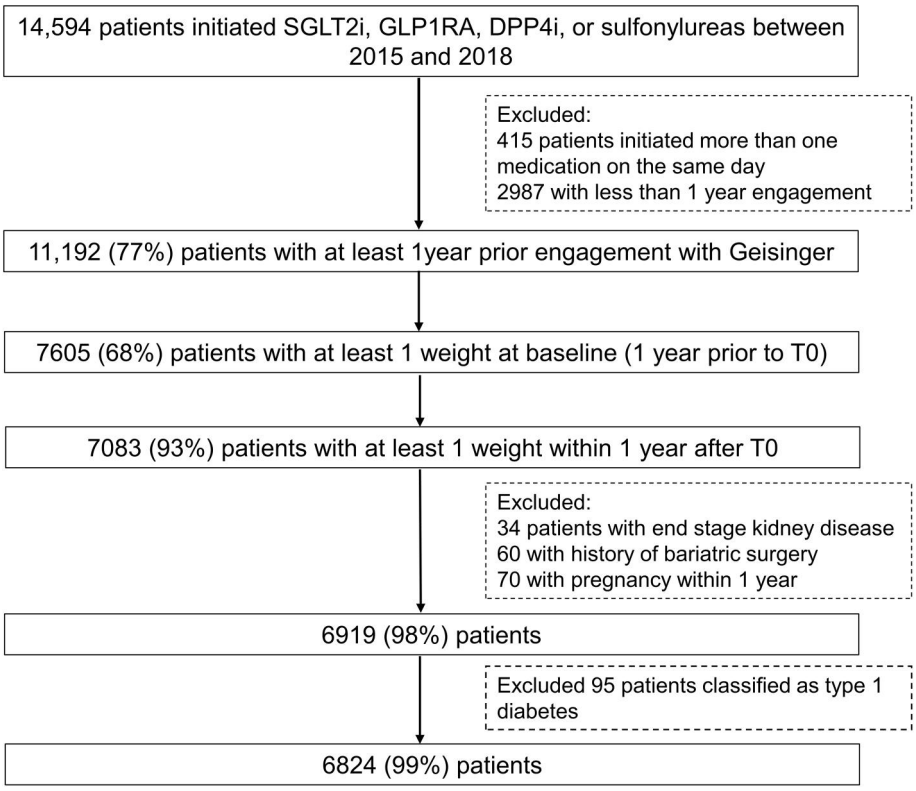


FIGURE 1 Derivation of Study Population. DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; IPTW, inverse-probability of treatment weighting; SGLT2i, sodium-glucose co-transporter 2 inhibitors

**TABLE 1** Specific medication and dosage for SGLT2i and GLP1RA

| | Most commonly used dosage (%) |
|---|---|
| SGLT2i ($n$ = 906) | |
| Empagliflozin ($n$ = 624) | 10 mg (77.9%) |
| | 25 mg (13.5%) |
| | 12.5 mg (8.6%) |
| Canagliflozin ($n$ = 227) | 100 mg (75.7%) |
| | 300 mg (17.2%) |
| | 50 mg (3.1%) |
| | 150 mg (4.0%) |
| Dapagliflozin ($n$ = 55) | 5 mg (49.1%) |
| | 10 mg (50.9%) |
| GLP1RA ($n$ = 782) | |
| Liraglutide ($n$ = 602) | 1.8 mg (97.3%) |
| | 3.6 mg (2.7%) |
| Dulaglutide ($n$ = 68) | 0.75 mg (88.2%) |
| | 1.5 mg (11.8%) |
| Exenatide ($n$ = 51) | 2 mg (96.1%) |
| | 5 mg (3.9%) |
| Semaglutide ($n$ = 34) | 0.5 mg (97.1%) |
| | 1 mg (2.9%) |
| Albiglutide ($n$ = 25) | 30 mg (92.0%) |
| | 50 mg (8.0%) |
| DPP4i (1881) | |
| Sitagliptin ($n$ = 1656) | 100 mg (57.8%) |
| | 50 mg (33.6%) |
| | 25 mg (8.6%) |
| Linagliptin ($n$ = 203) | 5 mg (98.0%) |
| | 2.5 mg (2.0%) |
| Saxagliptin ($n$ = 20) | 5 mg (65.0%) |
| | 2.5 mg (35.0%) |
| Alogliptin ($n$ = 2) | 12.5 mg (100%) |
| Sulfonylureas ($n$ = 3255) | |
| Glipizide ($n$ = 1734) | 5 mg (64.3%) |
| | 2.5 mg (20.2%) |
| | 10 mg (15.5%) |
| Glimepiride ($n$ = 1195) | 2 mg (42.8%) |
| | 1 mg (41.3%) |
| | 4 mg (15.5%) |
| | 0.5 mg (0.4%) |
| Glyburide ($n$ = 321) | 2.5 mg (55.4%) |
| | 5 mg (35.8%) |
| | 1.25 mg (6.9%) |
| | 3 mg (1.9%) |
| Chlorpropamide ($n$ = 5) | 100 mg (100%) |

Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

least 2 codes in other encounters within 2 years, (2) prescription of anti-diabetic medication (excluding conditions such as polycystic ovarian syndrome and gestational diabetes), or (3) hemoglobin A1c (HbA1c) ≥ 7% and at least 2 fasting glucoses >7 mmol/L within 1 year.[16] T2DM was defined using the validated algorithm in Geisinger based on ICD codes, prescription of glucagon, oral hypoglycemic agents, C-peptide and diabetes antibody test, and urine acetone test strips.[17] A total of 6919 patients with diabetes were identified and 6824 patients classified as T2DM were included for the analyses. This study was approved by the Geisinger Medical Center Institutional Review Board and the Johns Hopkins University Institutional Review Board.

## 2.2 | Exposure

Prescriptions of SGLT2i, GLP1RA, DPP4i, and sulfonylureas were identified from outpatient prescription records (see specific medication and dosage in Table 1). A new user, active comparator study design was used. Patients who initiated any of the four new classes of medication between 2015 and 2018 were identified and categorized per an intention-to-treat approach by their first prescription class. Prescription records within 1 year prior to T0 were examined to confirm no prescription record of the above four medications. Patients who initiated more than one class of study medication on the same day were excluded ($n$ = 415). In primary analyses, sulfonylureas were considered as the reference group because they were most commonly prescribed. Pair-wise comparisons among the medication groups were further performed. Proportion of days covered within 1 year was calculated to measure medication adherence. All patients were included regardless of whether the patient received metformin or not at baseline.

## 2.3 | Outcomes

Baseline weight was defined as the nearest weight prior to T0 (but within 1 year time window). For weight measurements after T0, monthly average weight was extracted for analysis. The primary outcome was percent weight change per year within 1 year after T0 among all patients.[18] The secondary outcome was time to first achieving 5% weight loss among patients with overweight/obesity at T0. For the secondary outcome, patients were followed from T0 until

achieving 5% weight loss, death, last encounter with Geisinger, or 30 January 2019, whichever came first.

## 2.4 | Covariates

Patient characteristics including sociodemographic, baseline body mass index (BMI), comorbidities, duration of diabetes diagnosis, lab measurements, and concurrent use of medication were included. Sociodemographic information included age, sex, race, medication initiation year, insurance (yes/no), smoking (current, former, never), and drinking (yes/no). Comorbidities included stroke, coronary heart disease (CHD), heart failure (HF), depression, anxiety disorders, thyroid diseases, osteoarthritis, and cancer diagnosis. These comorbidities were defined by (1) the presence of ICD codes prior to T0 in the inpatient setting or problem list or (2) at least two codes in other encounters within 2 years (See specific codes in Table 2). Hypertension was defined by the presence of ICD codes (401–405, I10-I16), prescription of anti-hypertensive medication (excluding patients with codes 346, G43, 427, I47, 413, I20, 592, N20, 333.1, G25.0, G25.1, 456.0, 456.1, 572.3, K76.6 or I85), or earliest date of at least 2 systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg within 2 years.[16] Charlson comorbidity index (CCI) was calculated to summarize the overall comorbidity burden.[19] Duration of diabetes diagnosis was defined as the interval between the earliest date a patient met diabetes diagnosis criteria in Geisinger and T0. The most recent outpatient serum creatinine, HbA1c, and serum albumin within 1 year prior to T0 were used for analysis. The Chronic Kidney Disease (CKD) Epidemiology Collaboration equation was used to estimate GFR based on serum creatinine level.[20] Concurrent use of medications that may affect body weight were examined, including metformin, insulin, anticonvulsants, antidepressants, antihistamines, antipsychotics, beta-blockers, corticosteroids and oral contraceptives, diuretics, and weight loss medications.[21] Baseline BMI was defined as the nearest BMI within 1 year prior to T0. Time between baseline BMI measurement date and T0 was also included in analyses. We further checked HbA1c level, use of insulin and metformin at 1 year after medication initiation to assess the glycemic control and therapy other than the study medications during follow-up, but these covariates were not included in statistical analysis.

## 2.5 | Statistical analysis

Approximately 38% of patients were missing at least one covariate: with 31% missing serum albumin, 18% missing HbA1c, 1.6% missing

**TABLE 2** Diagnosis codes of comorbidities and procedures

| Conditions | ICD-9-CM codes | ICD-10-CM codes |
|---|---|---|
| Type 2 diabetes[a] | 250.x0, 250.x2 | E11, E13 |
| Type 1 diabetes[a] | 250.x1, 250.x3 | E10 |
| Stroke | 430–438 | I60-I69 or V12.54 |
| Coronary heart disease | 410, 411.8, 414 | I21-I25 |
| Heart failure | 428 | I50 |
| Depression | 293.84, 300.00, 300.01, 300.02, 300.09, 300.10, 300.21, 300.22, 300.23, 300.29, 300.3, 300.5, 300.89, 309.81, 313.0,313,1, 313.21, 313.22, 313.3, 313.82, 313.83 | F40-F48, F06.4, F93.8 |
| Anxiety disorder | 296.20–296.26, 296.30–296.36, 296.90, 296.99, 300.4, 309.1–309.4, 309.8, 309.9, 311, 780.7, V111, V628.4 | F32.0-F32.5, F32.9, F33.0-F33.3, F33.41, F33.42, F33.9, F34.1, F34.8, F39, F43.21- F43.25, F43.8, F43.20, F94.8, Z65.8, R45.851, R53.1, R53.82, R 53.83,R53.2, G93.3, G93.9 |
| Thyroid disorder | 240–246, | E00-E07, E89.0 |
| Osteoarthritis | 715.1, 715.00 | M15-M19 |
| Cancer within 2 years before initiation | 140–172, 174–208, 238.6, | C00-C26, C30-C34, C37-C41, C43,C45-C58, C60 -C85, C88, C90-C97 |
| Stroke | 430–438 | I60-I69 or V12.54 |
| Eating disorder | 307 | F50 |
| Procedure | **CPT-4 codes** | |
| Bariatric surgery | 435–439 | |
| Pregnancy | 590–598 | |

*Note*: The bolded "CPT-4 codes" emphasizes that the codes for the following 2 rows (Batriatric surgery; Pregnancy) are different from codes in previous rows (CPT-4 codes vs. ICD-9/10-CM codes).

Abbreviation: ICD, International Classification of Disease.

[a]T2DM was defined using the validated algorithm in Geisinger based on ICD codes, prescription of glucagon, oral hypoglycemic agents, C-peptide and diabetes antibody test, and urine acetone test strips.[17]

drinking, and 0.1% missing smoking information. Multiple imputation by chained equation was used to impute 40 datasets.[22] Patient characteristics, exposure, and outcomes were included in the imputation model.

In each imputed dataset, the generalized propensity score of receiving each of the 4 treatments was estimated using multinomial logistic regression.[23] Aforementioned patient characteristics were included in the model. Inverse probability of treatment weighting (IPTW) based on the propensity scores was applied to create a pseudo-population where treatment assignment is independent of measured covariates. Estimated weights were truncated at 99% to prevent outliers from strongly affecting the analyses. To describe baseline characteristics of the study population, one imputed dataset was randomly selected and numbers (percentage), mean ± standard deviation (SD), or median (interquartile interval, IQI) were reported, as appropriate. Using sulfonylureas group as a reference, pair-wise standardized mean differences (SMD) in patient characteristics before and after IPTW were used to test balance in covariates. The SMD <10% was considered good balance.[24]

Linear mixed effects model with random intercepts and slopes were used to compare percent weight change among the treatment groups. Log-transformed weight was used as the outcome variable in the model. The model included treatment group, linear time, and interaction between treatment group and time. The weighted model further included covariates that remained imbalanced after IPTW, and interaction terms of these covariates with time. Rubin's rules were used to combine IPTW estimators from linear mixed model in each imputed dataset.[25] To better illustrate weight change over time, predicted weight change at 3, 6, 9, and 12 months after T0 was plotted based on the best linear unbiased predictor from one linear mixed effects model. The model was not extended beyond 1 year because of limited number of weight available beyond 1 year.

For the outcome of time to achieving 5% weight loss, the log rank test was used to compare unweighted Kaplan–Meier curves among the treatment groups. Hazard ratios (HRs) were estimated from Cox proportional hazard regression with and without IPTW. The proportional hazards assumption was tested by checking Schoenfeld's partial residuals. Pooled IPTW HRs from each imputed dataset was estimated in the same way as in the primary outcome.

Stratified analyses were performed by age (<60 vs. ≥60 years), sex, CVD (CHD, HF, or stroke), baseline estimated glomerular filtration rate (eGFR) level (<60 vs. ≥60 ml/min/1.73 $m^2$), and concurrent use of insulin and metformin. Additional stratified analysis by baseline BMI was performed only with an outcome of time to 5% weight loss. A two-sided $p$ value < 0.05 was considered statistically significant. Statistical analyses were performed with SAS 9.4 (SAS Institute) and R (www.R-project.org/).[26]

## 3 | RESULTS

### 3.1 | Study population

A total of 6824 patients with T2DM from Geisinger met the inclusion criteria with sulfonylureas being the most commonly used: 906 (13.3%) SGLT2i users, 782 (11.5%) GLP1RA users, 1881 (27.5%) DPP4i users, and 3255 (47.7%) sulfonylureas users. Sociodemographic and clinical features of each treatment group were summarized in Table 3. The median (IQI) proportion of days covered within 1 year were 87.2% (31.4%,100%) for SGLT2i users, 85.3% (36.0%,100%) for GLP1RA users, 100% (63.4%, 100%) for DPP4i users, and 100% (50.1%, 100%) for sulfonylureas users.

After IPTW, good balance was achieved for most covariates. However, patients in the GLP1RA group were younger (SMD = 0.14), had slightly higher baseline BMI (SMD = 0.11), and higher CCI compared with patients in the sulfonylureas group (Table 4).

At 1 year after medication initiation, after IPTW, the mean HbA1c was similar across the groups (7.3% ± 1.2 in the SGLT2i, 7.2% ± 1.5 in the GLP1RA, 7.4% ± 1.4 in the DPP4i, and 7.3% ± 1.4 in the sulfonylureas group, all pair-wise SMDs <0.1). The concurrent use of metformin was also similar across the groups (all pair-wise SMDs <0.1), while use of insulin was higher in the SGLT2i and GLP1RA groups than the use in the sulfonylureas group (16.3% in the SGLT2i, 14.8% in the GLP1RA, 12.3% in the DPP4i, and 10.8% in the sulfonylureas group, SGLT2i-sulfonylureas and GLP1RA-sulfonylureas SMDs >0.1, other pair-wise SMDs <0.1).

### 3.2 | Rate of weight change within 1 year

The median (IQI) number of weight measurements within 1 year were 5.[3,9] In linear mixed effects models, the newer antidiabetic medications were all associated with more weight loss compared with sulfonylureas, with greater effects in SGLT2i (−3.2% [95% confidence interval (CI): −3.8%, −2.6%] per year) and GLP1RA (−2.9% [95% CI: −3.6%, −2.3%] per year, Table 5). After IPTW, the associations attenuated slightly but remained significant. SGTL2i and GLP1RA were also associated with statistically significant weight loss compared with DPP4i (−1.3% [95% CI: −2.0%, −0.7%] per year for SGLT2i; −1.2% [95% CI: −1.9%, −0.5%] per year for GLP1RA). Effect sizes were similar between SGLT2i and GLP1RA (−0.1%, 95% CI: −1.6%, 1.2%; Figure 2).

### 3.3 | Achieving 5% weight loss

There were 6450 patients (94.5%) with overweight or obesity. During median (IQI) follow-up of 12.0 (4.8–24.6) months, 39.6% of patients in the sulfonylureas group, 45.7% in the SGLT2i group,

**TABLE 3** Patient characteristics before applying IPTW

| | SGLT2i | GLP1RA | DPP4i | Sulfonylureas |
|---|---|---|---|---|
| Number of patients | 906 | 782 | 1881 | 3255 |
| Age at medication initiation, years, mean ± SD | 56.6 ± 11.4 | 51.7 ± 13.2 | 59.9 ± 13.9 | 58.7 ± 14.3 |
| Female, *n* (%) | 422 (46.6) | 451 (57.7) | 920 (48.9) | 1538 (47.3) |
| White race, *n* (%) | 849 (93.7) | 709 (90.7) | 1736 (92.3) | 3023 (92.9) |
| Medication year, *n* (%) | | | | |
| 2015 | 125 (13.8) | 134 (17.1) | 554 (29.5) | 1096 (33.7) |
| 2016 | 124 (13.7) | 162 (20.7) | 543 (28.9) | 1091 (33.5) |
| 2017 | 302 (33.3) | 235 (30.1) | 480 (25.5) | 644 (19.8) |
| 2018 | 355 (39.2) | 251 (32.1) | 304 (16.2) | 424 (13.0) |
| Days between baseline weight and $T_0$, median (IQI) | 0 (0, 18) | 0 (0, 12) | 0 (0, 12) | 0 (0, 7) |
| No insurance, *n* (%) | 11 (1.2) | 7 (0.9) | 23 (1.2) | 64 (2.0) |
| Baseline BMI, kg/m$^2$, mean ± SD | 36.7 ± 8.0 | 39.9 ± 8.7 | 35.5 ± 8.4 | 35.5 ± 8.1 |
| BMI category, *n* (%) | | | | |
| <24.9 | 31 (3.4) | 12 (1.5) | 124 (6.6) | 183 (5.6) |
| 25.0- 29.9 | 150 (16.6) | 71 (9.1) | 367 (19.5) | 616 (18.9) |
| 30.0-34.9 | 237 (26.2) | 149 (19.1) | 528 (28.1) | 939 (28.8) |
| ≥35.0 | 488 (53.9) | 550 (70.3) | 862 (45.8) | 1517 (46.6) |
| Comorbidities, *n* (%) | | | | |
| Hypertension | 847 (93.5) | 708 (90.5) | 1747 (92.9) | 2935 (90.2) |
| Stroke | 76 (8.4) | 45 (5.8) | 166 (8.8) | 224 (6.9) |
| CHD | 188 (20.8) | 150 (19.2) | 427 (22.7) | 665 (20.4) |
| HF | 51 (5.6) | 67 (8.6) | 154 (8.2) | 270 (8.3) |
| Depression | 455 (50.2) | 428 (54.7) | 864 (45.9) | 1376 (42.3) |
| Anxiety | 348 (38.4) | 354 (45.3) | 625 (33.2) | 1037 (31.9) |
| Thyroid disorder | 188 (20.8) | 249 (31.8) | 468 (24.9) | 707 (21.7) |
| OA | 236 (26.0) | 210 (26.9) | 510 (27.1) | 806 (24.8) |
| Cancer within 1 year | 30 (3.3) | 18 (2.3) | 69 (3.7) | 146 (4.5) |
| Charlson comorbidity index, mean ± SD | 4.5 ± 2.4 | 4.2 ± 2.7 | 5.0 ± 2.8 | 4.7 ± 2.8 |
| Duration of diabetes diagnosis, year, median (IQI) | 3.3 (1.1, 6.6) | 3.1 (0.6, 6.4) | 2.5 (0.6, 5.9) | 2.3 (0.3, 5.5) |
| Smoking, *n* (%) | | | | |
| Never | 394 (43.5) | 311 (39.8) | 801 (42.7) | 1395 (42.9) |
| Past | 361 (39.9) | 321 (41.0) | 759 (40.4) | 1281 (39.4) |
| Current | 150 (16.6) | 150 (19.2) | 317 (16.9) | 575 (17.7) |
| Drinking, *n* (%) | 404 (45.1) | 359 (46.4) | 793 (42.9) | 1240 (38.8) |
| eGFR, ml/min/1.73 m$^2$, mean ± SD | 99.3 ± 16.8 | 92.8 ± 22.5 | 87.4 ± 23.1 | 89.3 ± 23.1 |
| eGFR category, *n* (%) | | | | |
| G1 | 579 (63.9) | 487 (62.3) | 1035 (55.0) | 1895 (58.2) |
| G2 | 293 (32.3) | 220 (28.1) | 559 (29.7) | 911 (28.0) |
| G3 | 33 (3.6) | 66 (8.5) | 260 (13.8) | 415 (12.8) |
| G4/5 | 1 (0.1) | 9 (1.2) | 27 (1.4) | 34 (1.0) |
| Serum albumin, g/dl, mean ± SD | 4.3 ± 0.3 | 4.3 ± 0.3 | 4.2 ± 0.3 | 4.2 ± 0.4 |

TABLE 3 (Continued)

| | SGLT2i | GLP1RA | DPP4i | Sulfonylureas |
|---|---|---|---|---|
| HbA1c, %, mean ± SD | 8.6 ± 1.7 | 8.1 ± 1.9 | 8.2 ± 1.6 | 8.4 ± 1.7 |
| Concurrent medications, n (%) | | | | |
| Metformin | 614 (67.8) | 472 (60.4) | 1347 (71.6) | 2246 (69.0) |
| Insulin | 188 (20.8) | 240 (30.7) | 228 (12.1) | 202 (6.2) |
| Anticonvulsant | 113 (12.5) | 133 (17.0) | 244 (13.0) | 351 (10.8) |
| Antidepressants | 134 (14.8) | 160 (20.5) | 320 (17.0) | 488 (15.0) |
| Antihistamines | 72 (7.9) | 80 (10.2) | 159 (8.5) | 273 (8.4) |
| Antipsychotics | 16 (1.8) | 17 (2.2) | 43 (2.3) | 75 (2.3) |
| Beta-blockers | 252 (27.8) | 201 (25.7) | 653 (34.7) | 1067 (32.8) |
| Steroids/oral contraceptives | 120 (13.2) | 140 (17.9) | 308 (16.4) | 609 (18.7) |
| Diuretics | 275 (30.4) | 274 (35.0) | 680 (36.2) | 1105 (33.9) |
| Weight loss medication | 12 (1.3) | 36 (4.6) | 11 (0.6) | 10 (0.3) |

Abbreviations: BMI, body mass index; CHD, coronary heart disease; DPP4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide 1 receptor agonists; HF, heart failure; IQI, inter-quartile interval; IPTW, inverse-probability of treatment weighting; OA, osteoarthritis; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

45.7% in the GLP1RA group, and 48.2% in the DPP4i group ever achieved 5% weight loss. Compared with sulfonylureas, the newer antidiabetic medications were associated with higher likelihood of achieving 5% weight loss (Figure 3A). The associations remained significant after IPTW (HR 1.5, 95% CI: 1.3–1.7 for SGLT2i; HR 1.6, 95% CI: 1.3–1.8 for GLP1RA; HR 1.3, 95% CI: 1.2–1.4 for DPP4i, Figure 3B and Table 6). SGLT2i and GLP1RA were also associated with higher likelihood of achieving 5% weight loss compared with DPP4i (HR 1.1, 95% CI: 1.01–1.3 for SGLT2i; HR 1.2, 95% CI: 1.01–1.4 for GLP1RA). No significant difference between SGLT2i and GLP1RA was observed (HR: 0.96, 95% CI: 0.8–1.3).

### 3.4 | Stratified analyses

There was no significant effect modification of the associations between treatment group and percent weight change by age, sex, CKD (eGFR < 60 ml/min/1.73 $m^2$), CVD, use of metformin, or use of insulin (Figure 4A–C) nor was there effect modification by age, sex, CKD, CVD, or baseline BMI for the outcome of achieving 5% weight loss. However, among patients using metformin, the associations between treatment group and 5% weight loss were stronger compared with the associations in patients not using metformin ($p$ for overall interaction by metformin use = 0.003; Figure 4D–F). The associations between treatment and 5% weight loss were stronger among non-insulin users ($p$ for overall interaction by insulin use = 0.004). In this study population, insulin users at baseline gained significantly more weight compared with insulin non-users at baseline (predicted weight change associated with insulin use at 12 months, 5.5% [95% CI: 4.9%, 6.2%]).

## 4 | DISCUSSION

In this real-world comparison of antidiabetic medications, SGLT2i and GLP1RA were associated with significant weight loss compared with DPP4i and sulfonylureas. With established cardiorenal protective effects of SGLT2i and GLP1RA, these findings further encourage the use of SGLT2i and GLP1RA, especially among patients with overweight or obesity.

Both SGLT2i and GLP1RA has consistently demonstrated weight-loss effect across multiple RCTs.[27,28] Major cardiovascular RCTs suggest that both medications have weight loss effect.[10-13] However, real-world data on weight change is limited.[14,15] Participants in RCTs may be better motivated to lose weight and are closely monitored thus the weight loss effects in RCTs may have limited generalizability to real-world settings. In addition, most RCTs did not have head-to-head comparisons between commonly used medications. This study confirmed the real-world weight loss benefits of SGLT2i and GLP1RA compared with sulfonylureas and DPP4i. Weight loss and maintenance are challenging for patients with T2DM. In the Look AHEAD trial, about 32% of patients were not able to achieve at least 5% weight loss after 1 year and 50% of patients who achieved 5% weight loss gained some or even all of their initial weight loss by 8 years.[29] Given the challenge of weight control among patients with diabetes, data in this study suggest that SGLT2i and GLP1RA may be better choices than sulfonylureas and DPP4i, for patients with overweight or obesity. Interestingly, SGLT2i and GLP1RA have similar weight loss effect in the present study. The modest weight loss effect of GLP1RA may be attributable to lower real-world dosage in this study compared with clinical trials.[30] These results suggest that in addition to GLP1RA, SGLT2i could potentially be an effective weight control agent for patients with diabetes.

**TABLE 4** Patient characteristics by treatment group after inverse probability of treatment weighting

| | SGLT2i | GLP1RA | DPP4i | Sulfonylureas |
|---|---|---|---|---|
| Number of patients | 906 | 782 | 1881 | 3255 |
| Age at medication initiation, years, mean ± SD | 57.4 ± 11.6 | 55.6 ± 12.6 | 57.8 ± 14.1 | 57.9 ± 14.2 |
| Female, % | 48.5 | 51.7 | 49.1 | 48.4 |
| White race, % | 93.2 | 92.6 | 92.6 | 92.7 |
| Medication year, % | | | | |
| 2015 | 25.1 | 25.6 | 27.8 | 28.3 |
| 2016 | 27.4 | 27.7 | 27.8 | 28.4 |
| 2017 | 27.1 | 25.1 | 24.7 | 24.6 |
| 2018 | 20.4 | 21.6 | 19.7 | 18.8 |
| Days between baseline weight and $T_0$, median (IQI) | 0 (0,9) | 0 (0,9) | 0 (0, 12) | 0 (0,8) |
| No insurance, % | 1.3 | 1.2 | 1.7 | 1.6 |
| Baseline BMI, kg/m$^2$, mean (SD) | 36.5 ± 7.9 | 37.6 ± 7.9 | 36.3 ± 8.9 | 36.1 ± 8.4 |
| BMI category, % | | | | |
| <24.9 | 3.6 | 1.4 | 6.1 | 5 |
| 25.0- 29.9 | 17.1 | 15.2 | 17.9 | 17.4 |
| 30.0-34.9 | 24.9 | 20.5 | 26.4 | 27.6 |
| ≥35.0 | 54.4 | 62.9 | 49.7 | 49.9 |
| Comorbidities, % | | | | |
| Hypertension | 91.7 | 91.8 | 91.2 | 91.3 |
| Stroke | 6.1 | 6.8 | 7.3 | 7.1 |
| CHD | 18.8 | 19.5 | 20.9 | 20.7 |
| HF | 7.5 | 6.7 | 8.3 | 7.8 |
| Depression | 45.3 | 47.3 | 45.7 | 45.7 |
| Anxiety | 36.9 | 36.1 | 34.7 | 34.8 |
| Thyroid disorder | 21.7 | 23.3 | 23.7 | 23.1 |
| OA | 24.4 | 25.1 | 25.4 | 25.9 |
| Cancer within 1 year | 3.1 | 3 | 3.9 | 4 |
| Charlson comorbidity index, mean ± SD | 4.5 ± 2.4 | 4.4 ± 2.7 | 4.7 ± 2.8 | 4.7 ± 2.7 |
| Duration of diabetes diagnosis, year, median (IQI) | 2.5 (0.8, 5.5) | 2.5 (0.4, 5.6) | 2.4 (0.5, 5.8) | 2.5 (0.4, 5.7) |
| Smoking, % | | | | |
| Never | 40.0 | 41.1 | 42.7 | 42.4 |
| Former | 43.2 | 41.5 | 39.8 | 40.3 |
| Current | 16.8 | 17.5 | 17.4 | 17.3 |
| Drinking, % | 41.9 | 41.5 | 41.8 | 42.1 |
| eGFR, ml/min/1.73 m$^2$, mean ± SD | 91.7 ± 18.9 | 93.0 ± 20.9 | 89.8 ± 22.4 | 89.9 ± 22.6 |
| eGFR category, % | | | | |
| G1 | 62.5 | 65.5 | 59 | 59 |
| G2 | 27.3 | 25.1 | 28.7 | 28.8 |
| G3 | 9.7 | 8.6 | 11.2 | 11.2 |
| G4/5 | 0.5 | 0.8 | 1 | 1 |
| Serum albumin, g/dl, mean ± SD | 4.2 ± 0.3 | 4.2 ± 0.3 | 4.2 ± 0.4 | 4.2 ± 0.3 |

TABLE 4 (Continued)

| | SGLT2i | GLP1RA | DPP4i | Sulfonylureas |
|---|---|---|---|---|
| HbA1c, %, mean ± SD | 8.3 ± 1.6 | 8.5 ± 2.0 | 8.4 ± 1.7 | 8.4 ± 1.7 |
| Concurrent medications, % | | | | |
| Metformin | 68.9 | 72.1 | 68.9 | 69.0 |
| Insulin | 14.4 | 14.1 | 12.7 | 12.3 |
| Anticonvulsant | 11.7 | 13.1 | 12.4 | 12 |
| Antidepressants | 15.3 | 17.9 | 15.8 | 16.3 |
| Antihistamines | 9.2 | 8.2 | 8.3 | 8.9 |
| Antipsychotics | 2.5 | 3.7 | 2.2 | 2.2 |
| Beta-blockers | 30.1 | 30.5 | 31.5 | 31.8 |
| Steroids/oral contraceptives | 17.4 | 17.6 | 17.1 | 17.7 |
| Diuretics | 32.2 | 34.1 | 34.3 | 33.7 |
| Weight loss medication[a] | 1.4 | 1 | 1.2 | 0.7 |

*Note*: Continuous variables were presented as weighted mean ± standard deviation or median (interquartile range). Categorical variables were presented as weighted proportion.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; DPP4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide 1 receptor agonists; HF, heart failure; IQI, inter-quartile interval; OA, osteoarthritis; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

[a]Weight loss medications included naltrexone-bupropion, orlistat, phentermine, phentermine-topiramate, lorcaserin, phentermine, benzphetamine, diethylpropion, and phendimetrazine.

TABLE 5 Associations between treatment group and % weight change within 1 year (% per year) among all patients with diabetes

| | Before IPTW | After IPTW |
|---|---|---|
| Sulfonylureas (n = 3285) | 0 (Ref) | 0 (Ref) |
| SGLT2i (*n* = 925) | −3.2% (−3.8, −2.6) | −3.0% (−3.6, −2.1) |
| GLP1RA (*n* = 810) | −2.9% (−3.6, −2.3) | −2.9% (−3.5, −2.2) |
| DPP4i (*n* = 1899) | −1.7% (−2.1, −1.3) | −1.7% (−2.2, −1.3) |

Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; IPTW, inverse-probability of treatment weighting; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

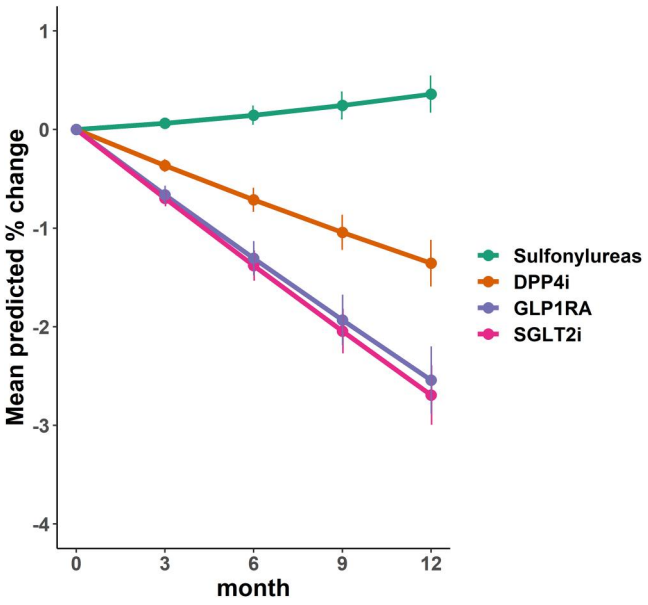


FIGURE 2 Mean change in weight after index prescription estimated by best linear unbiased prediction (BLUP) after applying inverse probability of treatment weighting and adjustment. DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; SGLT2i, sodium-glucose co-transporter 2 inhibitors

SGLT2i directly cause body weight loss mainly via glucose excretion and calorie loss in the kidneys, and result in the elimination of about 60–100 g of glucose per day in the urine.[31] However, the compensatory increases in food intake and changes in energy expenditure may attenuate the energy imbalance and limit the effect size of weight loss.[32,33] Combination therapy of SGLT2i with a drug that reduces food intake is appealing to mitigate the counteracting physiologic mechanisms. Metformin results in weight loss mainly by reducing appetite and food intake[32] while GLP1RA reduces the appetite and feelings of hunger, slowing the release of food from the stomach, and increasing feelings of fullness after eating.[34] Combining SGLT2i and metformin or SGLT2i and GLP1RA may achieve greater reduction in weight.[32] Evidence demonstrates that combination therapy of SGLT2i and GLP1RA has additive weight loss effect compared with SGLT2i alone.[34] In the present study, SGLT2i achieved greater weight loss in patients using metformin and demonstrated a potential synergetic effect in weight loss. Additional studies

are needed to better understand the impact of combined use of weight loss-promoting medications in this population.

This study has several strengths. First, the study sample contained patients with T2DM from a large health care system, which provided real-world evidence of the comparative effectiveness of SGLT2i, GLP1RA, DPP4i, and sulfonylureas regarding the weight change. This is one of the first population-based studies to quantify weight change following different classes of diabetes medication using real-world data. Second, rigorous study design was applied including multiple imputation and generalized propensity score weighting to minimize selection bias and confounding by indication.

This study also has limitations. First, the majority of the study population were white and insured, which may limit generalizability of the findings. Second, despite the use of propensity score weighting to minimize confounding, there might still exist residual or unmeasured confounding. Specifically, information about diet, physical activity, or detailed data about socioeconomic status was not available. Third, the follow-up duration was relatively short, which limits the capacity to detect long-term effects. Fourth, an intention-to-treat approach was applied in the study, which likely underestimated the association between antidiabetic medications and weight change. However, the overall medication adherence was good. HbA1c levels and the use of metformin at 1 year were comparable across groups and use of insulin was greater in the SGLT2i and GLP1RA groups. This supported that the weight loss effects observed in the SGLT2i and GLP1RA groups were not driven by unintentional weight loss from poor glycemic control, greater use of metformin, or lower use of insulin during follow-up. Finally, this study was done without regard to medication dosage.

In summary, this real-world study confirmed the weight loss benefit of SGLT2i and GLP1RA compared with sulfonylureas and DPP4i. Given the cardiorenal benefits of SGLT2i and GLP1RA, findings in this study strongly support the use of SGLT2i and GLP1RA among patients with T2DM.

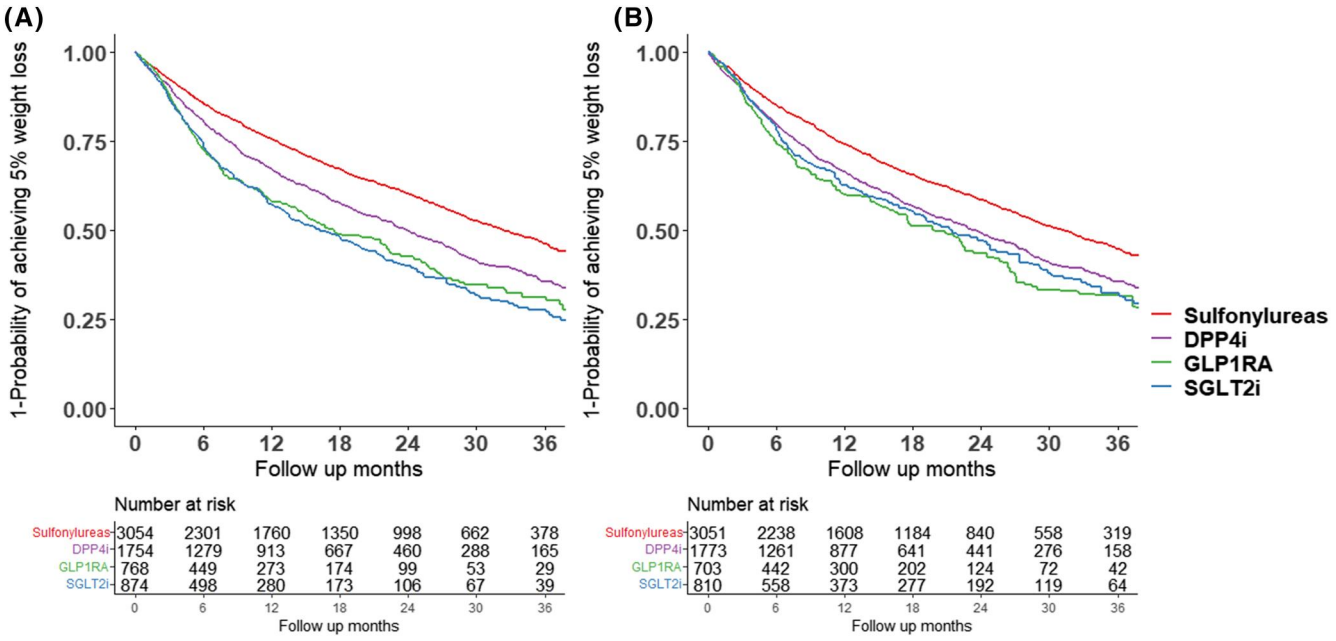


**FIGURE 3** Unadjusted Kaplan–Meier curve (A) and adjusted Kaplan–Meier curve (B) of achieving 5% weight loss anytime during the follow-up by treatment group among patients with overweight or obesity. DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; SGLT2i, sodium-glucose co-transporter 2 inhibitors

| | Weight loss ≥5%, n (%) | Unadjusted HR (95% CI) | IPTW HR (95% CI) |
|---|---|---|---|
| Sulfonylureas (n = 3054) | 1209 (39.6) | 1.0 (Ref) | 1.0 (Ref) |
| SGLT2i (*n* = 874) | 399 (45.7) | 1.8 (1.6, 2.0) | 1.5 (1.3, 1.7) |
| GLP1RA (*n* = 768) | 345 (44.9) | 1.7 (1.5, 1.9) | 1.6 (1.3, 1.8) |
| DPP4i (*n* = 1754) | 846 (48.2) | 1.34 (1.2, 1.5) | 1.3 (1.2, 1.4) |

Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; IPTW, inverse-probability of treatment weighting; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

**TABLE 6** Associations between treatment group and achieving 5% weight loss any time during the follow-up among patients with diabetes and overweight or obesity

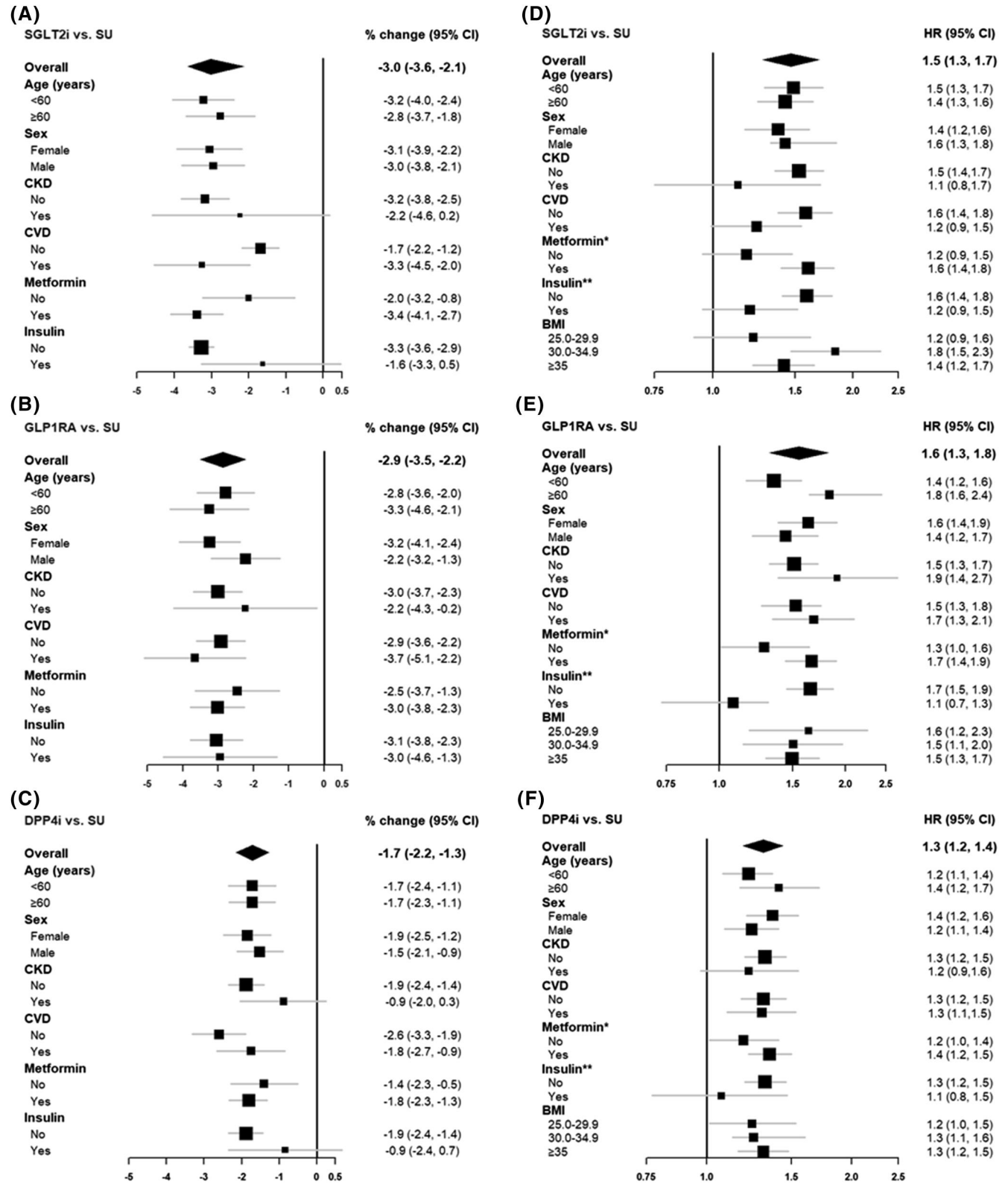


**FIGURE 4** Stratified analyses (IPTW) on percent weight change and achieving 5% weight loss by age, sex, CKD, CVD, metformin use, insulin use, and BMI categories#. Adjusted % weight change in (A) SGLT2i versus sulfonylureas, (B) GLP1RA versus sulfonylureas, and (C) DPP4i versus sulfonylureas. Adjusted Hazard ratio (HR) for ≥5% weight loss in (D) SGLT2i versus sulfonylureas, (E) GLP1RA versus sulfonylureas, and (F) DPP4i versus sulfonylureas. *overall *p* for interaction between treatment group and metformin use = 0.003. **overall *p* for interaction between treatment group and insulin use = 0.004. All other *p* for interaction >0.05. #Stratified analyses by BMI categories were only performed for achieving 5% weight loss. BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonists; SGLT2i, sodium-glucose co-transporter 2 inhibitors; SU, sulfonylureas

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## CONFLICT OF INTEREST

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