

# Clinical and Safety Outcomes With GLP-1 Receptor Agonists and SGLT2 Inhibitors in Type 1 Diabetes: A Real-World Study

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## Abstract

**Context:** Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) are used off-label in the management of type 1 diabetes mellitus (T1DM) in real-world practice as adjuvant therapies to insulin. There are few real-world data regarding efficacy and safety of this practice.

**Objective:** This work aimed to determine the efficacy and safety of GLP-1RAs and sodium-glucose SGLT2is in the management of T1DM in real-world practice.

**Methods:** A retrospective chart review was performed of all instances of GLP-1RA and/or SGLT2i use greater than 90 days in adult patients with T1DM at a single academic center. We report the clinical and safety outcomes over the duration of use.

**Results:** We identified 104 patients with T1DM who ever used a GLP-1RA (76 patients) or SGLT2i (39 patients) for more than 90 days. After 1 year of therapy, GLP-1RA users had statistically significant reductions in weight (90.5 kg to 85.4 kg;  $P < .001$ ), glycated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) (7.7% to 7.3%;  $P = .007$ ), and total daily dose of insulin (61.8 units to 41.9 units;  $P < .001$ ). SGLT2i users had statistically significant reductions in HbA<sub>1c</sub> (7.9% to 7.3%;  $P < .001$ ) and basal insulin (31.3 units to 25.6 units;  $P = .003$ ). GLP-1RA users compared to SGLT2i users had greater reduction in weight ( $P = .027$ ) while HbA<sub>1c</sub> reduction was comparable between the groups. Over a mean total duration of use of 29.5 months/patient for both groups, more SGLT2i users experienced diabetic ketoacidosis (DKA) (12.8% vs 3.9%). Therapy was discontinued because of adverse events 26.9% of the time for GLP-1RA users vs 27.7% for SGLT2i users.

**Conclusion:** GLP-1RA and SGLT2i use in T1DM is associated with clinically relevant benefits. DKA remains a clinical concern with SGLT2i use, requiring careful patient selection and monitoring, with the risk to benefit ratio of treatment evaluated at an individual level.

**Key Words:** GLP-1RA, SGLT2i, T1DM, real-world outcomes, safety

**Abbreviations:** ASCVD, atherosclerotic cardiovascular disease; CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; ICD, *International Classification of Diseases*; LDL, low-density lipoprotein; RCT, randomized clinical trial; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TDD insulin, total daily dose of insulin; uACR, urine microalbumin to creatinine ratio.

Type 1 diabetes mellitus (T1DM) accounts for 5% to 10% of all cases of diabetes, with a worldwide incidence of around 15 cases per 100 000 individuals per year (1). Despite the considerable advancements made since the discovery of insulin by Sir Frederick G. Banting in 1921 (2), patients with T1DM still face difficulties managing the disease and continue to have high rates of diabetes-associated complications. Only 21% of adults in the United States (3) and 24.3% worldwide (4) reach the American Diabetes Association–recommended glycated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) goal of less than 7% (1). Obesity has become more prevalent in patients with T1DM—increasing from 3.4% in 1986 to 22.7% in 2007 (5). The lifetime risk of developing diabetic kidney disease in this population remains close to 50% (6), and cardiovascular disease (CVD) risk is 4 to 10 times that of patients without

diabetes (7). New pharmacological classes like glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) have been demonstrated, in patients with type 2 diabetes mellitus (T2DM), not only to improve glycemic control without increasing the risk of hypoglycemia, but also promote weight loss, decrease the risk of cardiovascular events, and, in the case of SGLT2is, reduce the rate of progression of chronic kidney disease and hospitalizations for heart failure (8–10).

Such benefits would be highly desirable in those with T1DM but initial enthusiasm has been hampered by safety concerns. Several randomized controlled trials were conducted with GLP-1 RAs (11–15) as well as SGLT2is (16–21) in patients with T1DM. These have shown modest improvements in HbA<sub>1c</sub>, weight reduction, and reduced insulin

requirement, but also a potential for increased risk of severe hypoglycemia and ketosis. Of note though, all the studies were of short duration and focused primarily on glycemic control rather than long-term outcomes. The long-term risk-benefit ratio for these agents in T1DM is still not known.

Despite none of these agents being approved in the United States for treatment of T1DM, their off-label use is not uncommon, especially in adults. As of 2016, it was estimated that in the United States, approximately 13% of those with T1DM above the age of 26 years were using an adjuvant therapy in addition to insulin, with approximately 3% using an SGLT2i and 2.5% a GLP-1 RA (22). Considering the wealth of positive outcome data reported with these classes of medications in patients with and without T2DM, the prevalence of their use in T1DM has likely increased even further since 2016. Understanding the safety and efficacy of these agents when used in the real-world setting provides important information that can help inform people with T1DM and their providers regarding the role of these adjuvant therapies in their treatment regimen.

We aimed to determine the efficacy and long-term safety of GLP-1RAs and SGLT2is when used as adjuvant therapy by people with T1DM in a real-world setting.

## Materials and Methods

### Study Design and Population

We performed a retrospective cohort study of all instances of GLP-1 RA and SGLT2i use as adjuvant therapy by people with T1DM at a single, large academic institution (UT Southwestern Medical Center, Dallas, Texas, USA). The project received ethical approval by the institutional review board of the University of Texas Southwestern Medical Center; patient consent was not required.

A 2-step process was carried out for data extraction. First, the electronic medical record was queried to identify all people with T1DM based on charting of *International Classification of Diseases, ninth revision (ICD-9)* and *10th revision (ICD-10)* codes (ICD-9 250.x1, 250.x3; ICD-10 E10.xx) who were ever prescribed either a GLP-1RA or an SGLT2i. The second step involved a manual review of each identified record for diagnosis validation and additional data extraction. During this step the diagnosis of T1DM was confirmed based on all available information, including clinical notes, medical history, confirmation of chronic insulin use, supporting laboratory studies (ie, C-peptide and T1DM-related autoantibodies [glutamic acid decarboxylase 65, islet cell antibodies, and insulinoma-associated antigen-2 antibodies]). Actual treatment start and, if applicable, stop dates for GLP-1RA and/or SGLT2i treatment were manually extracted using prescription records and actual use was confirmed by review of the clinical documentation. An instance of use was defined as a period of GLP-1RA or SGLT2i use of at least 90 days with less than a 90-day break in use. If the patient stopped using the medication for more than 90 days, then restarted, this was counted as a subsequent instance of use.

The final population included people with T1DM, aged 18 years or older at the time of the first eligible instance of use. We excluded those who did not receive their ongoing care at the institution if clinical and laboratory data of interest were not available, those for whom the diagnosis of T1DM was in doubt based on available information, and those for whom a start and stop date could not be determined.

The baseline period for each eligible instance included 90 days prior and 14 days after each index date (first day of each instance of use). The following data were recorded for each baseline period: age, sex, race, ethnicity, duration of diabetes, presence of comorbidities (diabetic retinopathy, neuropathy, diabetic kidney disease, atherosclerotic cardiovascular disease [ASCVD]), height, weight, insulin dose (total daily dose [TDD], daily basal dose, and total daily bolus dose), type of insulin regimen, and laboratory data (total cholesterol, low-density lipoprotein [LDL], triglycerides, estimated glomerular filtration rate [eGFR], urine microalbumin to creatinine ratio [uACR] and HbA<sub>1c</sub>). For certain variables, the baseline period was extended, to take into account how often certain data are collected in clinical practice to maximize the amount of baseline data collected, but for all variables the baseline period ended 14 days after index date. For HbA<sub>1c</sub>, the baseline period started at 5 months before the index date. For total cholesterol, LDL, triglycerides, and eGFR, the baseline period started at 1 year before index date, and for uACR, 2 years prior. If multiple values within the baseline period were available, the value closest to the index date was used. Additionally, all events of diabetic ketoacidosis (DKA) and pancreatitis for a period of 3 years before the first index date were recorded.

The duration of each eligible instance was calculated using index date(s) and stop date(s). All ongoing instances were censored October 31, 2021. A reason for initiation of each instance and, if applicable, reason for ending each instance was extracted from the clinical notes, as were the specific agent(s) used during each instance. All hospitalizations and emergency room visits (irrespective of the reason for presentation), episodes of pancreatitis, DKA, severe hypoglycemia, and treatment-related adverse events occurring during each eligible instance were extracted by manual chart review, as was insulin dosing data (total daily dose, basal, and total daily bolus). Laboratory data of interest (total cholesterol, LDL, triglycerides, serum creatinine, uACR, and HbA<sub>1c</sub>) and all recorded weights were automatically extracted from the electronic medical record.

Study data were collected and managed using REDCap electronic data capture tools hosted at University of Texas Southwestern Medical Center (23, 24).

For concomitant users of medications from both classes (3 patients), follow-up data for the drug initiated first were censored at the index date the second drug.

### Data Analysis

All recurring data elements of interest were collected, then grouped into 3-month intervals. If multiple values within each interval were available, the median value was calculated over each 3-month interval. The mixed model for repeated measures was used to analyze the change over time (baseline to 12 months) in HbA<sub>1c</sub>, weight, TDD insulin, basal insulin, bolus insulin, total cholesterol, LDL, triglycerides, eGFR, and uACR with either GLP-1RA or SGLT2i use, as well as to compare the changes in these variables between groups. Additionally, subgroup analyses by baseline HbA<sub>1c</sub> and weight (divided by respective group median of HbA<sub>1c</sub> 7.8% and weight 87.8 kg, respectively) were carried out. Nonnormally distributed variables were log-transformed for analysis. Data are presented as estimated means (95% CI) unless otherwise noted. A *P* value less than .05 (2-tailed) was considered statistically significant with no adjustment for multiple testing. All analyses were performed using SAS 9.4 (SAS

Institute). All other variables (ie, reasons for starting and stopping therapy, adverse events) were reported descriptively using group proportions.

## Results

### Baseline Characteristics

A total of 104 patients with T1DM who ever used GLP-1RA/SGLT2i for at least 90 days up until October 31, 2021, were identified. There were 65 patients who used GLP-1RA exclusively, 28 who used SGLT2i exclusively, and 11 patients who used both agents either concurrently or sequentially (Fig. 1). Most patients in both groups were non-Hispanic White (93.1% GLP-1RA users and 87.5% SGLT2i users) with a predominance of female patients among GLP-1RA users compared to SGLT2i users (72.3% vs 43.7%). Both groups had a comparable proportion of patients on continuous subcutaneous insulin infusion (CSII) at baseline (72.9% of GLP-1RA users vs 71.9% SGLT2i users) (Table 1). Prevalence of neuropathy and any type of retinopathy was similar across both groups, but a higher proportion of SGLT2i users had any albuminuria (31.3% vs 5.6% SGLT2i vs GLP-1RA users, respectively) or heart failure (6.3% vs 0%). A higher proportion of GLP-1RA users vs SGLT2i users (13.9 vs 9.4%) experienced DKA before initiating therapy (see Table 1).

Data were available for 108 instances of GLP-1RA use across 76 patients representing a total of 184.25 patient-years of GLP-1RA exposure (Table 2). For SGLT2i users, there were 47 instances across 39 SGLT2i users with a total of 90.8 patient-years of exposure. The mean number of instances of use per patient was 1.4 and 1.2 with mean duration of an instance of 20.5 (SD 21.8) months and 24.2 (SD 19.2) months for GLP-1RA users and SGLT2i users, respectively. GLP-1RA users were more likely to have repeated instances of use with 35.5% of GLP-1RA vs 20.5% of SGLT2i users having more than 1 instance of use. Liraglutide was the most frequently used GLP-1RA (57.4% of instances), while empagliflozin was the most frequently used SGLT2i (66.7% of instances).

Documented reasons for initiating adjuvant therapy were weight loss (69.4% of GLP-1RA instances vs 37.8% SGLT2i instances), improved glycemic control (50.9% vs 73.3%), improved glucose variability (13.0% vs 24.4%), and reduced insulin requirements (7.4 vs 26.7%) (see Table 2). ASCVD risk-reduction and nephroprotection were documented reasons for starting SGLT2i therapy in 11.1% and 13.3% instances, respectively; these reasons were never documented for initiating GLP-1RAs (see Table 2). Documented reasons for discontinuing adjuvant therapy were side effects (26.9% GLP-1RA instances vs 27.7% SGLT2i instances), insurance denial/cost (11.1% vs 13.4%), pregnancy/planning pregnancy (7.4% vs 0%), DKA (1.9% vs 6.7%), and no perceived benefit from therapy (10.2% vs 2.2%). Gastrointestinal side effects (defined as any mention of nausea/vomiting/significant appetite suppression, significant diarrhea/constipation, abdominal pain, gastrointestinal acid reflux) were the documented reason for discontinuation in 19.4% of GLP-1RA instances vs 0% of SGLT2i instances.

### Efficacy Outcomes

#### Glycated hemoglobin A<sub>1c</sub>

Mean baseline HbA<sub>1c</sub> for SGLT2i users was 7.9% (7.5, 8.4) vs 7.7% (7.4, 8.0) for GLP-1RA users (Table 3). After 12 months

of use, both groups had statistically significant reductions in HbA<sub>1c</sub> to a mean HbA<sub>1c</sub> of 7.3% (6.9-7.7) for SGLT2i users ( $P < .001$ ) and 7.3% (7.0-7.7) ( $P = .007$ ) for GLP-1RA users. The difference in the change in HbA<sub>1c</sub> at 12 months compared to baseline between the 2 groups was not statistically significant ( $P = .248$ ). Similar results were observed in the subgroup analyses with nonsignificant interaction across subgroups of baseline HbA<sub>1c</sub> or weight (Fig. 2A).

#### Weight

Baseline weight for GLP-1RA and SGLT2i users were 90.4 kg (85.3-95.8) and 89.2 kg (82.1-96.9), respectively. After 12 months of use, GLP-1RA users had a statistically significantly lower mean body weight (85.4 kg [80.3-90.8 kg];  $P < .001$ ) and while SGLT2i users also had a numerically lower body weight, this change was not statistically significant (87.5 kg [80.1-95.5 kg];  $P = .168$ ) (see Table 3). The difference in the change in weight between the 2 groups after 12 months was statistically significant, favoring GLP-1RA for weight loss ( $P = .027$ ). For all subgroups (high vs low HbA<sub>1c</sub>; high vs low weight at baseline), there was a statistically significant difference in the change in weight at 12 months between GLP-1RA vs SGLT2i users, with all changes favoring GLP-1RA use (Fig. 2B).

#### Insulin requirements

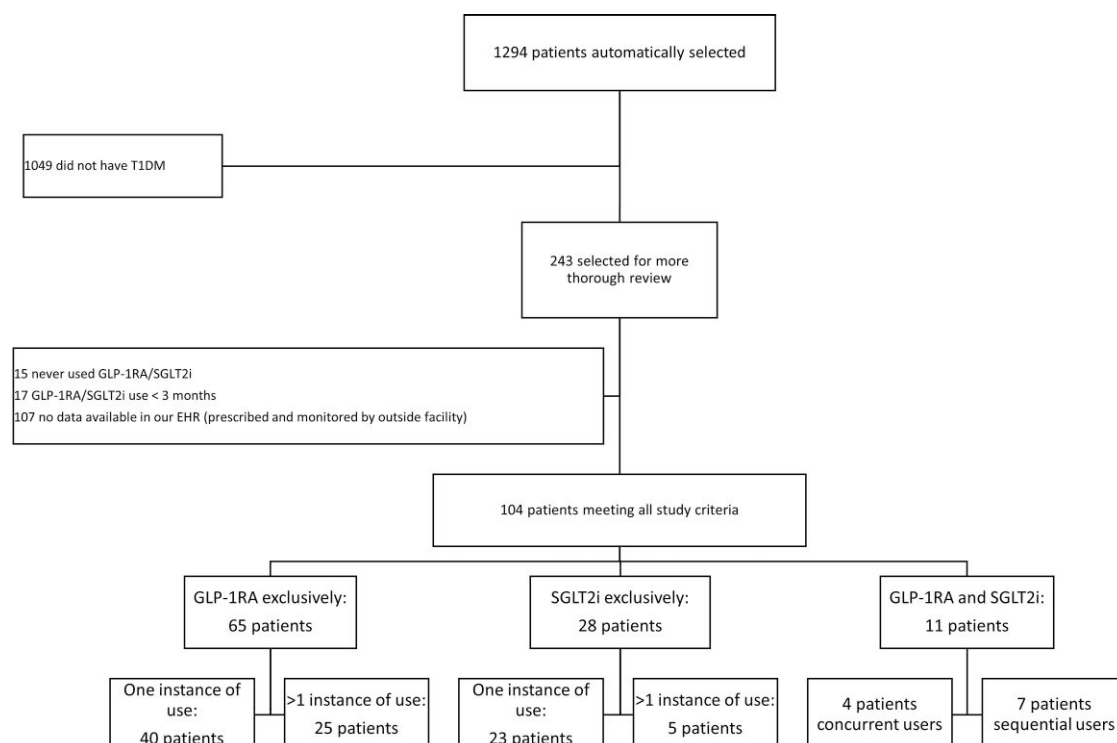
After 12 months, GLP-1RA users had statistically significant reductions in TDD insulin (baseline 61.8 units [53.3-71.7] vs 12 months 49.9 [42.4-58.8] units;  $P < .001$ ), basal insulin (30.7 units [27.1-34.7] vs 26.0 units [22.6-29.8];  $P < .001$ ) and bolus insulin (37.9 units [30.6-45.1] vs 27.9 units [19.5-36.1];  $P = .004$ ) (see Table 3). SGLT2i users, however, had a significant change only in basal insulin (baseline 31.3 units [26.2-37.5] vs 12 months 25.6 units [21.0-31.3];  $P = .003$ ). Changes in TDD and bolus insulin were not statistically significant ( $P = .798$  and  $.719$ , respectively) for SGLT2i users. The difference between groups in the change in TDD, basal insulin, and bolus insulin after 12 months of treatment were not statistically significant. For patients with an HbA<sub>1c</sub> greater than 7.8% or those with weight less than 87.9 kg at baseline, there was a statistically significant difference in the change of TDD insulin between groups ( $P = .013$  and  $.025$ , respectively) after 12 months of medication use, favoring GLP-1RA use in these subgroups (Fig. 2C). For patients with a weight of less than 87.9 kg at baseline, there was also a statistically significant difference in the change in bolus insulin between groups ( $P = .007$ ), favoring GLP-1RA use (Fig. 2D).

#### Renal outcomes

For both GLP-1RA and SGLT2i users, after 12 months of medication use there was no statistically significant change in eGFR or uACR compared to baseline, nor were there significant changes between groups in these renal outcomes (see Table 3).

#### Lipid outcomes

GLP-1RA users had a statistically significant reduction in total cholesterol (baseline 183.0 mg/dL [173.5-192.5 mg/dL] vs 12 months 156.6 mg/dL [135.1-178.0 mg/dL];  $P = .015$ ) and LDL (baseline 103.9 mg/dL [95.7-112.0 mg/dL] vs 12 months 77.0 mg/dL [58.2-95.8 mg/dL];  $P = .005$ ) after 12 months of use, though there was no significant change in triglyceride



**Figure 1.** Patient population and distribution.

values (see Table 3). Changes in total cholesterol, LDL, and triglycerides from baseline to 12 months were not significant for SGLT2i users. We found no statistically significant differences between groups in the changes of any lipid parameters.

### Safety Outcomes

While on therapy, there were 5 SGLT2i users (12.8% of SGLT2i users) who had 6 unique episodes of DKA—a rate of 6.6 episodes/100 patient-years (Table 4). At baseline, the rate of DKA for those who would go on to use SGLT2i was 2.6 episodes/100 patient-years (see Table 1). Three GLP-1RA users (3.9% of GLP-1RA users) had 3 unique episodes of DKA while on therapy (1.6 episodes/100 patient-years [see Table 4]) compared to 6.6 events/100 patient-years before starting GLP-1RA (see Table 1).

Of the 8 patients who experienced DKA, 7 were insulin pump users. Of the 9 episodes of DKA, 3 of the 9 were related to pump occlusion/failure, a further 3 of 9 occurred shortly after transitioning to an insulin pump, 2 of 9 episodes were due to infection, and the cause for DKA was unknown in 1 episode.

Only one episode of severe hypoglycemia was documented in each group while on adjuvant therapy (0.5/100 patient-years of GLP-1RA and 1.1/100 patient-years of SGLT2i use) (see Table 4).

There were no documented episodes of pancreatitis while on adjuvant treatment in either group (see Table 4).

GLP-1RA users had 13.6 hospitalizations/100 patient-years vs 15.4 hospitalizations/100 patient-years for SGLT2i (see Table 4). GLP-1RA users had 13.6 emergency room visits/100 patient-years while SGLT2i users had 3.3 emergency room visits/100 patient-years.

### Discussion

We evaluated the efficacy and safety of GLP-1RA and SGLT2i as adjuvant therapies in addition to insulin in the management of T1DM in the real-world clinical setting. The documented reasons for initiating these agents were weight loss, improved glycemic control, reduced insulin dose, and reduced glucose variability; GLP-1RAs were most commonly initiated for weight loss and improved glycemic control, while SGLT2is were more commonly initiated for improved glycemic control, reduced insulin dose, and reduced glucose variability. After 12 months of therapy, those treated with GLP-1RAs had clinically significant reductions in HbA<sub>1c</sub>, weight, TDD insulin, basal insulin, bolus insulin, total cholesterol, and LDL, while those treated with SGLT2i had significant reductions in HbA<sub>1c</sub> and basal insulin. HbA<sub>1c</sub> improvement was similar between the groups treated with GLP-1RA vs SGLT2i, but weight reduction was greater with GLP-1RA vs SGLT2i, a finding independent of baseline weight or HbA<sub>1c</sub>. Compared to SGLT2i, GLP-1RA produced significant reductions in TDD insulin in users with a baseline HbA<sub>1c</sub> greater than 7.8% and weight less than 87.9 kg, and similar results were seen for bolus insulin in patients with weight less than 87.9 kg. Despite having a lower rate of DKA before therapy start compared to GLP-1RA users, SGLT2i users had more documented episodes of DKA while on therapy and most of these episodes were related to insulin pump use. The incidence of severe hypoglycemia was low in both groups and there were no episodes of pancreatitis in either group while on treatment. The most common reason for discontinuing either therapy was side effects.

Our report encompasses the largest number of patients with T1DM treated with GLP-1RA adjuvant therapy in the real-world clinical setting reported to date (N = 76) and had the



**Table 1. Patient baseline characteristics at time of first adjuvant therapy prescription**

	GLP-1RA (N = 72)	SGLT-2i (N = 32)
Age (mean [SD]), y	41.0 (12.0)	46.8 (14.4)
Sex (% [n])		
Male	27.7 (22)	56.3 (18)
Female	72.3 (52)	43.7 (14)
Race (% [n])		
White	93.1 (67)	87.5 (28)
Black or African American	5.6 (4)	9.4 (3)
Asian	1.4 (1)	3.1 (1)
American Indian/Alaska Native	0 (0)	0 (0)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)
Ethnicity (% [n])		
Non-Hispanic/Latino	87.5 (63)	96.9 (31)
Hispanic/Latino	9.7 (7)	0 (0)
Duration of diabetes (mean [SD]), y	20.9 (11.3)	22.0 (15.3)
Method of insulin delivery (% [n])		
CSII	72.2 (52)	71.9 (23)
MDIs	27.8 (20)	28.1 (9)
Neuropathy (% [n])	13.9 (10)	15.6 (5)
Retinopathy (% [n])		
None	75.0 (54)	65.6 (21)
Proliferative	8.3 (6)	18.8 (6)
Nonproliferative	11.1 (8)	12.5 (4)
Unknown type	5.6 (4)	3.1 (1)
ASCVD (% [n]) <sup>a</sup>	8.3 (6)	12.5 (4)
Heart failure (% [n]) <sup>b</sup>	0 (0)	6.3 (2)
Albuminuria (% [n])		
Microalbuminuria	4.2 (3)	21.9 (7)
Macroalbuminuria	1.4 (1)	9.4 (3)
History of acute pancreatitis (% [n]) <sup>c</sup>	4.2 (3)	0 (0)
Event rate of acute pancreatitis (per 100 patient-y) <sup>d</sup>	1.3	0
History of diabetic ketoacidosis (% [n]) <sup>d</sup>	13.9 (10)	9.4 (3)
Event rate of diabetic ketoacidosis (per 100 patient-y) <sup>d</sup>	6.6	2.6

For patients who used both medications (either one class after the next, or concurrently), baseline characteristics reported at time of first adjuvant therapy use. Percentages may not add up to 100% if missing data. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CSII, continuous subcutaneous insulin infusion; GLP-1RA, glucagon-like peptide-1 receptor agonist; MDIs, multiple daily injections; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

<sup>a</sup>Includes prior stroke, myocardial infarction, peripheral arterial disease, or documented coronary artery disease.

<sup>b</sup>Heart failure included patients both with reduced and preserved ejection fraction.

<sup>c</sup>Any time before starting adjuvant therapy.

<sup>d</sup>Based on events occurring 3 years before starting adjuvant therapy

longest on-treatment safety assessment period (median 29.5 months/patient). The largest prior report, by Kuhadiya et al (25), involved only 27 patients followed for 180 days. Another report by Harrison et al (26) involved 11 patients followed for 10 to 20 weeks. Our findings regarding the clinical outcomes with GLP-1RA use in T1DM in the real-world are similar to those seen in the major randomized clinical trials

**Table 2. Patterns of adjuvant therapy use in our cohort of patients with type 1 diabetes**

	GLP-1RA (N = 108)	SGLT2i (N = 47)
No. of instances <sup>a</sup> of use	N = 108	N = 47
Instances per patient	1.4	1.2
Instance duration, mo	20.5 (21.8)	24.2 (19.2)
Duration of first instance, mo	20.0 (21.6)	25.8 (19.3)
Total exposure time, mo	29.5 (26.8)	29.5 (22.0)
Instances per patient		
1	64.5 (49)	79.5 (31)
2	30.3 (23)	20.5 (8)
3	3.9 (3)	0 (0)
4	1.3 (1)	0 (0)
Ongoing therapy (as of Oct. 31, 2021) <sup>b</sup>	40.8 (31)	59.0 (23)
GLP-1RA product <sup>c</sup>		
Liraglutide	57.4 (62)	—
Semaglutide	43.5 (47)	—
Dulaglutide	23.1 (25)	—
Exenatide	7.4 (8)	—
Albiglutide	0.9 (1)	—
SGLT2i product <sup>c</sup>		
Empagliflozin	—	66.7 (30)
Dapagliflozin	—	28.9 (13)
Canagliflozin	—	17.8 (8)
Documented reasons for starting agent <sup>d</sup>		
Weight loss	69.4 (75)	37.8 (17)
Improved glycemic control	50.9 (55)	73.3 (33)
Improve glucose variability	13.0 (14)	24.4 (11)
Reduce insulin requirement	7.4 (8)	26.7 (12)
ASCVD risk reduction	0 (0)	11.1 (5)
Nephroprotection	0 (0)	13.3 (6)
Heart failure	0 (0)	4.4 (2)
Documented reasons for discontinuing agent <sup>d</sup>		
Any side effect	26.9 (29)	27.7 (13)
GI side effects	19.4 (21)	0 (0)
Insurance denial/Cost	11.1 (12)	13.4 (6)
No benefit	10.2 (11)	2.2 (1)
Pregnancy/Planning pregnancy	7.4 (8)	0 (0)
Difficulty with injections	1.9 (2)	N/A
Genitourinary infection	0 (0)	6.7 (3)
DKA	1.9 (2)	6.7 (3)
Ketonemia/ketonuria (without DKA)	0 (0)	4.4 (2)
Hypoglycemia	1.9 (2)	0 (0)
Polyuria	0 (0)	4.4 (2)
Pancreatitis	0 (0)	0 (0)

Data are mean (SD) or % (N).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DKA, diabetic ketoacidosis; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; N/A, not available; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

<sup>a</sup>An instance is defined as a period of GLP-1RA or SGLT2i use of at least 90 days with less than a 90-day break in use. If the patient stopped using the medication for more than 90 days, then restarted, this was counted as a second instance of use.

<sup>b</sup>Reported as percentage of total number of GLP-1RA users (76) and SGLT2i users (39).

<sup>c</sup>Adds up to more than 100% as changes in product within an instance were possible.

<sup>d</sup>Adds up to more than 100% as multiple reasons could be documented.

**Table 3. Change in outcomes over 12 months of GLP-1RA/SGLT2i use**

	GLP-1RA	SGLT2i	Between-group <i>P</i> <sup>d</sup>
HbA <sub>1c</sub> , %			
Baseline	7.7 (7.4-8.0)	7.9 (7.5- 8.4)	
12 mo	7.3 (7.0-7.7)	7.3 (6.9-7.7)	
<i>P</i> (within-group change over 12 mo)	.007	< .001	.248
Weight, kg			
Baseline	90.4 (85.3-95.8)	89.2 (82.1-96.9)	
12 mo	85.4 (80.3-90.8)	87.5 (80.1-95.5)	
<i>P</i> (within-group change over 12 mo)	< .001	.168	.027
TDD insulin, units			
Baseline	61.8 (53.3-71.7)	58.0 (47.5-71.5)	
12 mo	49.9 (42.4-58.8)	57.0 (44.3-72.3)	
<i>P</i> (within-group change over 12 mo)	< .001	0.798	.073
Basal insulin, units			
Baseline	30.7 (27.1-34.7)	31.3 (26.2-37.5)	
12 mo	26.0 (22.6-29.8)	25.6 (21.0-31.3)	
<i>P</i> (within-group change over 12 mo)	< .001	.003	.689
Bolus insulin, units			
Baseline	37.9 (30.6-45.1)	32.9 (22.5-43.4)	
12 mo	27.9 (19.5-36.1)	35.0 (22.1-47.8)	
<i>P</i> (within-group change over 12 mo)	.004	.719	.068
eGFR, mL/min/1.73 m <sup>2</sup>			
Baseline	85.2 (78.5-91.2)	82.3 (73.6-91.0)	
12 mo	83.5 (74.4-92.3)	81.1 (71.0-91.2)	
<i>P</i> (within-group change over 12 mo)	.653	.762	.915
Microalbumin:creatinine ratio, mg/g			
Baseline	10.4 (6.4-17.1)	25.1 (13.3-47.2)	
12 mo	10.4 (3.6-30.4)	22.9 (6.4-82.0)	
<i>P</i> (within-group change over 12 mo)	.999	.878	.907
Total cholesterol, mg/dL			
Baseline	183.0 (173.5-192.5)	170.1 (157.2-183.0)	
12 mo	156.6 (135.1-178.0)	168.8 (148.0-189.5)	
<i>P</i> (within-group change over 12 mo)	.015	.893	.086
LDL, mg/dL			
Baseline	103.9 (95.7-112.0)	92.4 (81.4-103.3)	
12 mo	77.0 (58.2-95.8)	88.6 (70.5-106.7)	
<i>P</i> (within-group change over 12 mo)	.005	.661	.074
Triglycerides, mg/dL			
Baseline	93.4 (81.8-106.7)	91.4 (76.5-109.2)	
12 mo	89 (52.1-95.8)	92.1 (68.7-123.5)	
<i>P</i> (within-group change over 12 mo)	.678	.958	.915

Data presented are estimated (least square) means (95% CI). A *P* value of less than .05 (2-tailed) was selected to indicate statistical significance. HbA<sub>1c</sub>, weight, TDD insulin, basal insulin, triglycerides, and microalbumin:creatinine ratio were exponentiated back from the least square means of log data.

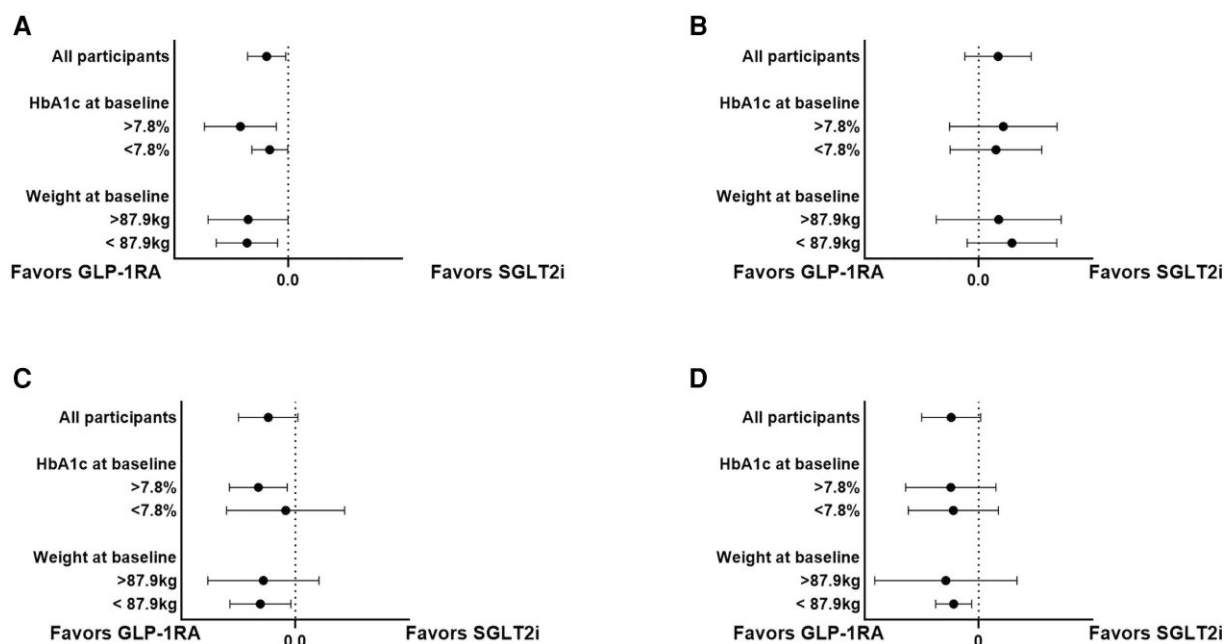
Abbreviations: eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; LDL, low-density lipoprotein; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TDD insulin, total daily dose of insulin.

<sup>d</sup>Between-group *P* value represents *P* for the difference in change in variable from baseline to 12 months between GLP-1RA and SGLT2i users.

(RCTs), as well as the other real-world studies (Table 5). The 2 largest RCTs involving the use of GLP-1RA (liraglutide) as an adjunct to insulin therapy in T1DM were the phase 3 studies, ADJUNCT-1 (14) and ADJUNCT-2 (13). In both trials, there were significant reductions in weight, HbA<sub>1c</sub>, and TDD insulin compared to placebo after 52 weeks in ADJUNCT-1, and 24 weeks in ADJUNCT-2, in which insulin doses were capped

at randomization (see Table 5). Our data confirm the findings from RCTs that treatment with GLP-1RA as adjuvant therapy in T1DM in the real-world setting is associated with improved glycemic control, weight loss, and lowers insulin requirements, without substantial safety concerns.

Our real-world clinical outcomes with SGLT2i use were not fully concordant with those seen in the RCTs (see Table 5). In



**Figure 2.** Forest plot of subgroup analysis of differences in changes in weight, glycated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), total daily dose of insulin (TDD) insulin, and bolus insulin from baseline to 12 months between glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) users. A, weight outcomes; B, HbA<sub>1c</sub> outcomes; C, TDD insulin outcomes; D, bolus insulin outcomes. Data are estimated difference in change in variable between GLP-1RA and SGLT2i users from baseline to 12 months using least square means data. Error bars represent 95% CI. Data for weight, HbA<sub>1c</sub>, and TDD represent log data.

**Table 4. Adverse events experienced during GLP-1RA or SGLT2i use**

Event	GLP-1RA (N = 76)		SGLT2i (N = 39)	
	% (n) <sup>a</sup>	Rate <sup>b</sup>	% (n)	Rate <sup>b</sup>
DKA	3.9 (3)	1.6	12.8 (5)	6.6
Severe hypoglycemia	1.3 (1)	0.5	2.6 (1)	0
Pancreatitis	0 (0)	0	0 (0)	1.1
Hospitalizations <sup>c</sup>	21.1 (16)	13.6	28.2 (11)	15.4
Emergency room visits <sup>c</sup>	19.7 (15)	13.6	7.7 (3)	3.3

Abbreviations: DKA, diabetic ketoacidosis; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

<sup>a</sup>Number of patients with at least one event.

<sup>b</sup>Rate reported as events/100 patient-years.

<sup>c</sup>For any reason, not just diabetes related.

the phase 3 RCTs with dapagliflozin (17, 18), empagliflozin (19), and sotagliflozin (20, 21, 29), there were significant reductions, compared to placebo, in weight, HbA<sub>1c</sub>, and TDD insulin. In our cohort we noted significant reductions only in HbA<sub>1c</sub> and basal insulin. While this could be due to our smaller sample size, other larger real-world studies also had conflicting results. Palanca et al (28) reviewed 199 patients with T1DM treated with SGLT2i over 52 weeks and found significant reductions in HbA<sub>1c</sub>, weight, and insulin requirements, as seen in the previously mentioned RCTs. However, Seufert and colleagues (27) reviewed 233 patients treated with SGLT2i over 52 weeks and only found significant reductions in HbA<sub>1c</sub> but not weight or TDD insulin, just as we did. Whether the benefits of SGLT2i use in T1DM noted in RCTs fully translate to real-world practice needs to be further investigated.

In our cohort total cholesterol and LDL decreased significantly after 1 year of GLP-1RA use, as seen in clinical trials involving patients with T2DM (33, 34). Renal function (both eGFR and uACR) remained stable after 1 year of either SGLT2i or GLP-1RA use.

Adverse events remain an area of concern. While other clinical trials and real-world data assessed events over 1 year of medication use, we collected safety events over a mean duration of use of 29.5 months/patient both for GLP-1RA and SGLT2i users—the longest such real-world report to date. In our cohort, SGLT2i users experienced DKA approximately 4 times more than GLP-1RA users. Interestingly, a greater proportion of GLP-1RA users had DKA before initiating therapy compared to SGLT2i users—this may indicate that providers preferentially chose a GLP-1RA for patients at risk for DKA given that SGLT2is have an established DKA risk. Overall, the risk for DKA with GLP-1RA was small (1.6 events/100 patient years) though higher than that observed in ADJUNCT-1 (approximately 0.9 events/100 patient years). We found that a higher percentage of SGLT2i users experienced DKA (12.8%) in our cohort compared to that seen in RCTs (2.2%–4.3%) (32), as well as other real-world trials (0%–3.5%) (27, 28) of shorter duration. The DKA event rate in those using an SGLT2i was also higher in our study compared to that reported in RCTs (6.6 events/100 patient years vs 4.76–5.94 events/100 patient years) (17, 19); however, this rate was in-line with that reported in other larger real-world studies (4.5–7.3 events/100 patient-years) (35). It is not surprising that in the real world DKA would occur more frequently than in a clinical trial, where patient selection is more stringent and there is frequent and intense monitoring and structured patient education. However, in the real-world cohort described by Palanca et al (28), the number of patients who experienced DKA was low at 3.5%, which might have

**Table 5. Summary of outcomes from major real-world and randomized control trials involving GLP-1RA or SGLT2i use published in the literature**

Trial	No.	Study duration, wk	Treatment	TDD insulin (% change)	HbA <sub>1c</sub> (%-point change)	Body wt change (kg)	DKA (% with events)	Severe hypoglycemia (% with events)
SGLT2i studies								
Real-world evidence								
Edwards et al, 2022	39	52	Various agents	−0.017	−0.6	−1.7	12.8 <sup>a</sup>	2.6 <sup>a</sup>
Seufert et al (27)	233	52	Various agents	1.5	−0.63	NR <sup>b</sup>	0	NR
Palanca et al (28)	199	52	Various agents	−8.5	−0.5	−2.9	3.5	NR
Randomized controlled trials								
DEPICT 1 (17)	833	52	Dapagliflozin 5 mg	−8.8	−0.27	−2.31	4	10.5
			Dapagliflozin 10 mg	−13.2	−0.31	−3.65	3.4	8.4
			Placebo	−1.8	−0.06	−0.25	1.9	11.5
DEPICT-2 (18)	815	24	Dapagliflozin 5 mg	−8.8	−0.37	−3.21	2.6	8.9
			Dapagliflozin 10 mg	−9	−0.42	−3.74	2.2	9.6
			Placebo	2	0.01	0	0	8.5
EASE 2 (19)	730	52	Empagliflozin 10 mg	−12.9	−0.84	−3	4.3	4.1
			Empagliflozin 25 mg	−13.5	−0.9	−3.4	3.3	2.7
			Placebo	−1.4	−0.45	0.2	1.2	3.1
EASE 3 (19)	975	26	Empagliflozin 2.5 mg	−8.5	−0.58	−1.6	0.8	1.2
			Empagliflozin 10 mg	−11.3	−0.75	−2.8	4.3	4.1
			Empagliflozin 25 mg	−14.1	−0.82	−3.2	3.3	2.7
			Placebo	−1.4	−0.3	0.2	1.2	2.5
inTANDEM1 (21)	793	52	Sotagliflozin 200 mg	−3.87	−0.26	−1.94	3.4	6.5
			Sotagliflozin 400 mg	−8.5	−0.32	−3.12	4.2	6.5
			Placebo	4.2	−0.01	1.2	0.4	9.7
inTANDEM2 (20)	782	52	Sotagliflozin 200 mg	−3.5	−0.18	−1.88	2.3	5
			Sotagliflozin 400 mg	−7.9	−0.28	−2.63	3.4	2.3
			Placebo	4.2	−0.04	0.3	0	5
inTANDEM3 (29)	1402	24	Sotagliflozin 400 mg	−6.8	−0.79	−2.21	3	3
			Placebo	2.9	−0.33	0.77	0.6	2.4
GLP-1 RA studies								
Real-world evidence								
Edwards et al, 2022	76	52	Various agents	−19	−0.4	−5	3.9 <sup>a</sup>	1.3 <sup>a</sup>
Harrison et al (26)	11	10	Various agents	−19.2	−0.4	−3	NR	0
Kuhadiya et al (25)	27	25	Liraglutide	−17.8	−0.43	−4.6	NR	0
Randomized controlled trials								
ADJUNCT-1 (14)	1398	52	Liraglutide 1.8 mg	−5	−0.54	−4	0.87	8.1
			Liraglutide 1.2 mg	−2	−0.49	−2.7	0.29	6.3
			Liraglutide 0.6 mg	4	−0.43	−1.3	1.1	9.1
			Placebo	4	−0.34	0.9	0	10.6

(continued)



Table 5. Continued

Trial	No.	Study duration, wk	Treatment	TDD insulin (% change)	HbA <sub>1c</sub> (%-point change)	Body wt change (kg)	DKA (% with events)	Severe hypoglycemia (% with events)
ADJUNCT-2 (13)	835	26	Liraglutide 1.8 mg	−13	−0.33	−5.1	0	2.4
			Liraglutide 1.2 mg	−10	−0.21	−4	0.48	6.2
			Liraglutide 0.6 mg	−8	−0.22	−2.5	0	7.1
			Placebo	−3	0.02	−0.2	0	4.9
MAG1C (30)	108	26	Exenatide 10 mcg	−11.6	−0.3	−4.3	0	5.8
			Placebo	3.3	−0.2	0.1	0	3.8
Lira-1 (11)	100	24	Liraglutide 1.8 mg	7	−0.5	−5.9	0	0
			Placebo	22.1	−0.3	0.2	0	2
Lira-pump trial (31)	44	26	Liraglutide 1.8 mg	−10.2	−0.5	−6.8	0	0
			Placebo	5.2	0.2	−0.4	4.5	0

Some data regarding SGLT2i adapted from Evans et al (32).

Abbreviations: DKA, diabetic ketoacidosis; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA<sub>1c</sub>, glycated hemoglobin A<sub>1c</sub>; NR, not reported; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TDD insulin, total daily dose of insulin.

<sup>a</sup>Safety events were collected over the entire duration of therapy (average 29.5 months).

<sup>b</sup>Only body mass index—reported change was not statistically significant.

been achieved by their strict selection criteria (SGLT2i were never initiated within a year of a DKA) and detailed education employed regarding the risks, prevention, and monitoring for DKA. As such, perhaps DKA mitigation is achievable if consistently employed in real-life practice.

There were very few documented events of severe hypoglycemia in our cohort, much fewer than reported in clinical trials both of SGLT2i and GLP-1RA, but similar to the hypoglycemic rate reported in other real-world studies. A likely explanation for this difference in the rate of severe hypoglycemia between real-world studies and RCTs is the fact that these events are not elicited from patients and/or documented appropriately in real life. Given the increased risk of severe hypoglycemia with the use of adjuvant therapies in T1DM, it is critical that severe hypoglycemia be carefully screened for before the initiation of adjuvant therapy and any occurrence of hypoglycemia elicited at each follow-up visit to ensure ongoing safety.

This is the first study comparing outcomes across GLP-1RA and SGLT2i in T1DM, and we observed interesting trends in patient selection, clinical outcomes, and safety findings. Patients started on an SGLT2i were more frequently male and had albuminuria or prior CVD (especially heart failure)—likely due to the proven cardiorenal protection benefits of this class. Indeed, nephroprotection was the documented reason for initiation in 13.6% of instances in which an SGLT2i was started vs 0% of GLP-1RA instances, and ASCVD risk reduction was the documented reason for 11.1% of instances vs 0% of instances of GLP-1RA use, despite GLP-1RA also having proven ASCVD event reduction. GLP-1RAs were more frequently started for weight loss than SGLT2i, which is expected given their known weight loss benefits in patients with T2DM. We showed that GLP-1RA had statistically significant weight loss compared to baseline and GLP-1RA was

favorable for weight loss over SGLT2i, making this agent a promising adjuvant therapy in situations for which obesity or need for weight loss are treatment goals.

SGLT2is were more frequently initiated to improve glycemic control and reduce insulin requirements; however, SGLT2i users had a significant reduction only in bolus insulin requirement. With SGLT2is having an insulin-independent mechanism of action through lowering of the renal glucose threshold and subsequent glucosuria leading to a reduction in blood glucose (9), significant reductions in both basal and bolus insulin requirements in T1DM may have been expected. It is possible that in our patient population, in which HbA<sub>1c</sub> in SGLT2i users ranged from 7.5% to 8.4% at baseline, postprandial hyperglycemia may not have been as significant an issue and thus the efficacy of this mechanism of glucose control less relevant. In contrast, GLP-1RA had clinically significant reductions in daily total, basal, and bolus insulin requirements in spite of its major mechanism of action being glucose-dependent insulin release from the pancreas, which is not relevant in T1DM. This suggests that the benefits in HbA<sub>1c</sub> improvement and reduced insulin doses (particularly bolus insulin) with GLP-1RA use may be due to weight loss (with resultant improved insulin sensitivity) and appetite suppression/delayed gastric emptying. This shows that even in T1DM, weight management and dietary modification may play an important role in glycemic control. GLP-1RAs have also been shown to directly suppress hepatic glucose production (36), which may also explain the noted glycemic benefits.

GLP-1RA users experienced on average a 0.4%-point reduction in HbA<sub>1c</sub>, which might not be viewed by some as clinically relevant. However, benefits of any therapy need to be viewed holistically at a patient level and in the context of all potential benefits (and associated risks). The reduction in HbA<sub>1c</sub> occurred in the context of the added benefit of weight

loss and reduced insulin requirement. While not assessed in this study, use of GLP-1RA has been associated with improved quality of life (13, 14) as well as ASCVD benefits in those at high risk of complications (10). Therefore, when viewed holistically at the person level, all of these small changes can add up to substantial overall clinical benefits, especially considering that improving glycemic control in patients with long-standing T1DM can be challenging.

Several limitations are noteworthy. First, while this is the largest real-world study of GLP-1RA use in T1DM, our overall sample is still limited, especially in the SGLT2i group. We did not match the groups, nor did we employ any control groups; however, the goal of the study was to capture the real-world use of these agents and compare their pattern of use, clinical outcomes, and safety as experienced by real-world patients. We did not analyze outcomes by type of GLP-1RA agent used (once-weekly vs daily GLP-1RA), by dose of GLP-1RA or SGLT2i used, or by background diabetes treatment (continuous subcutaneous insulin infusion [CSII] or multiple daily injections). Given the limited sample size, this study does not have the power to detect any clinically meaningful differences in such smaller groups. However, such subanalyses may have provided clinically relevant information and should be areas for research in future studies. These adjuvant agents were sometimes initiated to improve glucose variability; however, information regarding glucose variability was not collected as data from the continuous glucose monitors (if used) were seldom available in the medical record. Minorities were underrepresented in our cohort, which limits the generalizability of the findings, but also highlights the importance of considering social determinants of health when prescribing such therapies. Given the retrospective design, findings are limited to the accuracy of information documented in the medical record, and confounders could be present. Few of our patients had measurements of C-peptide and therefore stratification on this parameter was not possible. Prior studies suggested there might be greater reductions in HbA<sub>1c</sub> and lower rates of symptomatic hypoglycemia when GLP-1RAs are initiated in patients with T1DM with detectable C-peptide (14). As such, it would be relevant to determine if C-peptide levels could be used in clinical practice to predict responders to adjuvant therapies.

## Conclusions

GLP-1RAs may be a useful addition to insulin as an adjuvant therapy for management of T1DM in clinical practice as it can bring about significant reductions in weight, HbA<sub>1c</sub>, and daily insulin requirements. While SGLT2is demonstrated efficacy in improving HbA<sub>1c</sub> and reducing basal insulin dose, reductions in weight and TDD insulin demonstrated in clinical trials were not observed in this real-world cohort. DKA remains a clinical concern when SGLT2is are initiated in patients with T1DM in the real world, and careful patient selection and education are needed to mitigate this risk. Potential adverse events such as severe hypoglycemia with both agents, as well as urinary tract infection/mycotic infections with SGLT2is should also be closely monitored while patients are on these therapies. Most important, to adequately determine the risk-benefit of these agents in those with T1DM, it is paramount that the knowledge regarding the demonstrated long-term cardiorenal outcomes in those with T2DM be translated to patients with T1DM, who also are at significant risk of such complications.

## Disclosures

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## Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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