Review Article

# THE EMERGING ROLE OF ADJUNCTIVE NONINSULIN ANTIHYPERGLYCEMIC THERAPY IN THE MANAGEMENT OF TYPE 1 DIABETES

*Bruce W. Bode, MD, FACE[1]; Satish K. Garg, MD[2]*

## ABSTRACT

***Objective:*** Review available data on adjunctive therapies for type 1 diabetes (T1D), with a special focus on newer antihyperglycemic agents.

***Methods:*** Published data on hypoglycemia, obesity, mortality, and goal attainment in T1D were reviewed to determine unmet therapeutic needs. PubMed databases and abstracts from recent diabetes meetings were searched using the term "type 1 diabetes" and the available and investigational sodium-glucose cotransporter (SGLT) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 inhibitors, and metformin.

***Results:*** The majority of patients with T1D do not meet glycated hemoglobin (A1C) goals established by major diabetes organizations. Hypoglycemia risks and a rising incidence of obesity and metabolic syndrome featured in the T1D population limit optimal use of intensive insulin therapy. Noninsulin antihyperglycemic agents may enable T1D patients to achieve target A1C levels using lower insulin doses, which may reduce the risk of hypoglycemia. In pilot studies, the SGLT2 inhibitor dapagliflozin and the GLP-1 receptor agonist liraglutide reduced blood glucose, weight, and insulin dose in patients with T1D. Phase 2 studies with the SGLT2 inhibitor empagliflozin and the dual SGLT1 and SGLT2 inhibitor sotagliflozin, which acts in the gut and the kidney, have demonstrated reductions in A1C, weight, and glucose variability without an increased incidence of hypoglycemia.

***Conclusion:*** Newer antihyperglycemic agents, particularly GLP-1 agonists, SGLT2 inhibitors, and dual SGLT1 and SGLT2 inhibitors, show promise as adjunctive treatment for T1D that may help patients achieve better glucose control without weight gain or increased hypoglycemia. **(Endocr Pract. 2016;22:220-230)**

**Abbreviations:**
**A1C** = glycated hemoglobin; **BMI** = body mass index; **CI** = confidence interval; **DKA** = diabetic ketoacidosis; **DPP-4** = dipeptidyl peptidase 4; **GLP-1** = glucagon-like peptide 1; **PYY** = polypeptide tyrosine tyrosine; **SGLT** = sodium-glucose cotransporter; **SGLT1** = sodium-glucose cotransporter 1; **SGLT2** = sodium-glucose cotransporter 2; **T1D** = type 1 diabetes; **T2D** = type 2 diabetes; **TDD** = total daily dosage

## INTRODUCTION

Type 1 diabetes (T1D) affects approximately 22 million adults and 0.4 million children worldwide (1), with U.S. estimates ranging between 1 and 3 million (2,3). Models based on a rising incidence of T1D have projected that the number of individuals <20 years of age with T1D may triple by 2050 (4). Insulin is necessary for the survival of these patients; however, while intensive insulin therapy reduces long-term micro- and macrovascular diabetes complications (5,6), it is usually associated with increased risk of hypoglycemia and weight gain. On average, patients with T1D experience >40 hypoglycemia events per year (7,8). In addition, overweight and obesity, which are partly associated with intensive insulin therapy, have risen in the T1D population, with rates that approach those found in the general population (9,10). Dyslipidemia, hypertension, and abdominal obesity also increasingly occur in

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From [1]Atlanta Diabetes Associates, Emory University School of Medicine, Atlanta, Georgia, and the [2]Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Aurora, Colorado.
Address correspondence to Dr. Satish K. Garg, Barbara Davis Center for Diabetes, University of Colorado Denver, 1775 Aurora Court, Room M20-1323, Aurora, CO 80045.
E-mail: satish.garg@ucdenver.edu.
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***See accompanying article, p. 277.***



 

T1D patients, putting them at higher risk of cardiovascular disorders (11).

These factors likely contribute to low rates of glycated hemoglobin (A1C) goal attainment. Table 1 shows recent data from the T1D Exchange, a clinic registry including >26,000 patients with T1D ranging in age from <1 to 93 years. Fewer than one-third of adults had an A1C value <7.0%, the level recommended for most adults with T1D, and mean values were considerably higher than that level, especially among young adults (10,12). Among patients 13 to 18 years of age participating in the SEARCH for Diabetes in Youth study, 45% met the A1C target of <7.5% currently recommended by the American Diabetes Association for adolescents (12,13), while only 17% of the same age group participating in the T1D Exchange met this goal (10). The American Association of Clinical Endocrinologists (AACE) recommends a target of <6.5% for youth and adults with T1D, if it can be achieved without undue hypoglycemia (14). However, only 5% of adolescent and 10% of adult participants in the T1D Exchange meet the AACE goal (15). Glycemic variability is also common among T1D patients and may aggravate the development of diabetic complications through oxidative stress (16,17). Uncontrolled T1D has devastating consequences for patients and their families. The rising incidence of this disease, along with high rates of suboptimal glycemic control, highlights the need for new strategies to manage glucose in these patients.

## LIMITATIONS OF THERAPIES APPROVED FOR T1D

### Insulin

#### *Hypoglycemia*

Hypoglycemia is the main limiting factor of intensive insulin therapy, with rates of severe hypoglycemia ranging between 115 and 320 events per 100 patient-years in T1D (7,8). Although modern insulin analogs have reduced the risk of hypoglycemia, it remains an ever-present danger (18), with consequences that range from acute, relatively mild adverse effects such as headache and tremor to serious risks, including cardiovascular events, coma, and death (19-21). A meta-analysis of controlled clinical trials in type 2 diabetes (T2D) has shown that severe hypoglycemia doubles the risk of cardiovascular events (20), and in an observational study of T1D and T2D patients, mortality over a 5-year period was 3.4 times higher among those reporting severe hypoglycemia at baseline (22). Sudden death may occur when severe hypoglycemia reduces baroreceptor sensitivity and increases sympathoadrenal system activity, which can trigger a fatal ventricular dysrhythmia (23). Multiple episodes of hypoglycemia can lead to autonomic dysfunction and hypoglycemia unawareness, initiating a cycle of recurrent hypoglycemia (24).

#### *Weight Gain*

Intensive insulin therapy also contributes to weight gain and the cardiometabolic consequences of obesity: hypertension, dyslipidemia, and increased atherosclerosis and cardiovascular risk (11,25-28). Among 16,061 participants in the T1D Exchange, 46% were either overweight (28%) or obese (18%) (10). Obesity rates in adults approached those in the general U.S. population; 31% of individuals between 26 and 49 years and 29% of patients ≥50 years of age had a body mass index (BMI) ≥30 kg/m$^2$, compared with 35% of adults ≥20 years of age in the general U.S. population (10,29). Among children and adolescents in the T1D Exchange, obesity prevalence ranged between 12 and 18%, with the highest rate found in patients 2 to 5 years old. This contrasts with the general population, in which 8% of those 2 to 5 years old are obese, rising to 21% of those 12 to 19 years old. Overweight youth accounted for 23% of the T1D Exchange population, compared with only 15% in the general population (10,29). An analysis of data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study documented the rise in overweight and obesity since the 1980s, when the use of multiple daily insulin injections and pump therapy began to increase (9). Over the same period, more sedentary lifestyles and availability of calorie-dense foods have been associated with rising obesity in the general population (30), so a reasonable conjecture is that these same conditions may have contributed to higher obesity rates in T1D. Hypoglycemia also plays a role in weight gain in T1D through defensive eating and possibly through a biological mechanism involving reduced motor activity and thermogenesis, which was demonstrated in an animal model (31).

**Table 1**
**Mean A1C Levels and Percentage Meeting Target A1C Among Adult T1D Exchange Participants (10)**

| | Age (years) | | |
|---|---|---|---|
| | **18-25 (n = 2,867)** | **26-49 (n = 2,606)** | **≥50 (n = 2,125)** |
| Mean A1C (%) | 8.7 ± 1.9 | 7.7 ± 1.3 | 7.6 ± 1.1 |
| Percentage of patients with A1C <7% (%) | 14 | 30 | 29 |

Abbreviations: A1C = glycated hemoglobin; T1D = type 1 diabetes.

Excessive weight gain in T1D is a concern because of its association with the metabolic syndrome and increased risk of cardiovascular disease, the primary cause of death among adult patients with T1D (6,32). In the Diabetes Control and Complications Trial (DCCT), hypertension and dyslipidemia were higher among overweight and obese patients in the intensive insulin therapy group compared with overweight and obese patients receiving standard insulin therapy (33). Intensive insulin therapy improved lipid levels in patients whose weight remained normal, but patients in the fourth quartile of weight gain, with a mean BMI of 31 kg/m$^2$, exhibited significantly higher levels of triglycerides, total cholesterol, low-density-lipoprotein cholesterol, and apolipoprotein B compared with the other quartiles. Over 6 years of DCCT follow-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, increases in central obesity, insulin resistance, lipids, and blood pressure (all elements of the metabolic syndrome) were sustained, and atherosclerosis was more extensive, among patients whose BMI increased by ≥4.39 kg/m$^2$, regardless of treatment group during the controlled trial (34).

***Diabetic Ketoacidosis***

Fear of the consequences of hypoglycemia and weight gain may promote suboptimal dosing of insulin, which in the T1D population can lead to diabetic ketoacidosis (DKA), a common, frequently fatal complication. DKA is usually caused by insulin deficiency at the tissue level, resulting in lipolysis and protein breakdown, which leads to ketonemia and metabolic acidosis (35). In situations of insulin deficiency, elevated glucagon accelerates ketonemia and hyperglycemia, although glucagon is not essential for the development of DKA (36). Among 2,561 patients participating in a recent T1D Exchange survey, 3% overall and 8% of those with an A1C ≥9% experienced an episode of DKA within the past 3 months (10). In an observational study using data from the Swedish National Diabetes Register and Swedish Register for Cause-Specific Mortality, DKA led to 14% of deaths among T1D patients, a figure that rose to 31% among patients under 30 years of age (32). As discussed later in this review, near-euglycemic DKA has also been reported in patients taking sodium-glucose cotransporter 2 (SGLT2) inhibitors (37).

## ESTABLISHED ADJUNCTIVE THERAPIES FOR T1D

Adjunctive therapy is not often employed to treat T1D. In the recent study of T1D Exchange participants, only 2% of adults reported taking pramlintide, the only agent approved by the U.S. Food and Drug Administration (FDA) for this purpose (10). Nevertheless, pramlintide effectively improves blood glucose. In a placebo-controlled study of pramlintide added to optimally titrated insulin, pramlintide significantly reduced postprandial glucose excursions by 175 ± 40 mg/hour/dL (incremental area under the curve $[AUC]_{0\text{-}3h}$; $P<.0005$ versus placebo) after 29 weeks (38). A1C decreased by 0.5% in both the pramlintide and placebo groups, but at a cost of a 1.2-kg weight gain in the placebo group, while the pramlintide group lost 1.3 kg ($P<.0001$). Pramlintide also led to a 28% decrease in mealtime insulin dose and a 12% decrease overall. However, nearly two-thirds of the pramlintide group reported nausea (63% versus 36% of placebo patients; $P<.01$), and more hypoglycemia occurred in the pramlintide group (0.57 ± 0.09 events/patient-year versus 0.30 ± 0.06 events/patient-year; $P<.05$). In a 1-year, placebo-controlled study, pramlintide significantly reduced A1C, weight, and insulin doses relative to placebo and did not increase the rate of severe hypoglycemia. However, substantially more gastrointestinal adverse events occurred among patients receiving pramlintide (39). Along with thrice daily injections, the increased risk of hypoglycemia and gastrointestinal events may account for the limited uptake of pramlintide as an adjunctive T1D therapy (14,40).

No other noninsulin antihyperglycemic agent is approved for the treatment of T1D, although metformin was used by 6% of T1D Exchange participants, making it the most commonly used adjunctive T1D treatment in that population (10). Studies of metformin have shown significant reductions in weight, insulin dose, and A1C (41-43), although in a meta-analysis, A1C reductions were not statistically significant (43). A definitive answer on the efficacy and safety of metformin in T1D may come from the REducing with MetfOrmin Vascular Adverse Lesions in type 1 diabetes (REMOVAL) study, which should be complete in 2016 (44). Meanwhile, other older agents, such as colesevelam, α-glucosidase inhibitors, and thiazolidinediones, have shown little or no promise in terms of glycemic control for patients with T1D (45,46).

## NEWER ANTIHYPERGLYCEMIC THERAPIES FOR ADJUNCTIVE TREATMENT OF T1D

The SGLT inhibitors and the glucagon-like peptide 1 (GLP-1) receptor agonists may provide an effective approach to reducing some of the risks associated with intensive insulin therapy for T1D. Table 2 summarizes recent studies of these classes, as well as studies of dipeptidyl peptidase 4 (DPP-4) inhibitors, which increase native GLP-1 levels by inhibiting enzymatic degradation.

### SGLT1 and SGLT2 Inhibitors

Several SGLT2 inhibitors have been approved for the treatment of T2D in recent years, and a dual SGLT1 and SGLT2 inhibitor is in phase 3 trials. Studies of these agents in T1D have shown promise in terms of reducing A1C, weight, and insulin dose. Some studies have also shown a reduced incidence of hypoglycemia.

**Table 2**
**Summary of Results From Studies of Sodium Glucose Cotransporter Inhibitors and Incretin Agents**

| Agent/study design | No. patients | Study duration | Key efficacy findings | Key safety findings |
|---|---|---|---|---|
| Dapagliflozin/ randomized, double-blind, placebo-controlled, dose ranging study (53) | 70 | 2 weeks | 24-h daily average blood glucose:<br>Dapagliflozin: –41.3 mg/dL (95% CI –66.9 to –15.7 mg/dL)<br>Placebo: –20.4 mg/dL (95% CI –60.5 to 24.7 mg/dL)<br><br>MAGE:<br>Dapagliflozin: –63.1 mg/dL (95% CI –111.5 to –14.8 mg/dL)<br>Placebo: –8.1 mg/dL (95% CI –89.7 to 73.51 mg/dL)<br><br>Mean percent change in TDD:<br>Dapagliflozin: –16.2% (95% CI –29.4% to –0.5%)<br>Placebo: 1.7% (95% CI –22.8% to 33.9%) | Total number of hypoglycemia events decreased with dapagliflozin vs. placebo (23 vs. 39 events, respectively)<br><br>One major hypoglycemia event occurred with dapagliflozin 10 mg; was attributed to patient noncompliance with insulin dosing instructions; treatment was discontinued<br><br>No DKA |
| Empagliflozin/ single-arm, open label study (54,55) | 40 | 8 weeks | Mean change in A1C: –0.4% ± 0.5% from baseline of 8.0% ($P$<.0001)<br><br>Mean change in capillary glucose: –36 ± 82 mg/dL ($P$ = .008)<br><br>Mean change in TDD: –8.9 ± 10.8 units ($P$<.0001)<br>Weight: –2.7 ± 2.7 kg ($P$<.0001)<br><br>Renal hyperfiltration: –33 mL/min/1.73 $m^2$ from baseline among patients with baseline GFR ≥ 135 mL/min/1.73 $m^2$ ($P$<.01) | Symptomatic hypoglycemia: –0.08 ± 0.13 events per patient per day ($P$ = .0004)<br><br>2 cases severe hypoglycemia requiring assistance<br>2 DKA cases |
| Empagliflozin/ randomized, double-blind, placebo-controlled study (56,57) | 75 | 28 days | Mean change in A1C:<br>Empagliflozin 25 mg:<br>–0.67% from baseline of 8.15%<br>Placebo: –0.18% from baseline of 8.18%<br>Treatment difference:<br>–0.49% (95% CI –0.75% to –0.22%; $P$<.001)<br><br>FPG and mean daily glucose not significantly different from placebo<br><br>Glucose exposure (mean change from baseline in AUC):<br>Empagliflozin 25 mg: –19.0 ± 5.1 mg/dL per hour ($P$<.05 vs. placebo)<br>Placebo: –3.1 ± 5.1 mg/dL per hour<br><br>Glucose variability (interquartile range; mean change from baseline):<br>Empagliflozin 25 mg: –20.7 ± 3.7 mg/dL ($P$<.001 vs. placebo)<br>Placebo: 6.5 ± 3.7 mg/dL<br><br>Time in glucose range 70-180 mg/dL (mean change from baseline):<br>Empagliflozin 25 mg: 2.9 ± 0.5 h/day ($P$<.001 vs. placebo)<br>Placebo: 0.2 ± 0.5 h/day<br><br>Weight (mean change from baseline):<br>Empagliflozin 25 mg: –1.7 ± 0.3 kg<br>Placebo: 0.2 ± 0.3 kg<br>Treatment difference: –1.9 kg (95% CI –2.7 to –1.0 kg; $P$<.001)<br><br>Insulin dose:<br>Empagliflozin 25 mg: –0.09 U/kg<br>Placebo: –0.01 U/kg<br>Treatment difference: –0.08 (95% CI –0.15 to –0.01; $P$ = .023) | Similar rates of hypoglycemia in empagliflozin- and placebo-treated patients<br><br>1 episode of severe hypoglycemia in placebo group<br><br>UTI reported by 1 patient receiving empagliflozin 25 mg<br><br>No DKA |

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**Table 2 (*Continued*)**
**Summary of Results From Studies of Sodium Glucose Cotransporter Inhibitors and Incretin Agents**

| Agent/study design | No. patients | Study duration | Key efficacy findings | Key safety findings |
|---|---|---|---|---|
| Sotagliflozin/ randomized, double-blind, placebo-controlled (70) | 33 | 4 weeks | Mean change in A1C:<br>Sotagliflozin: –0.55% from baseline of 7.94% (*P* = .002 vs. placebo)<br>Placebo: –0.06% from baseline of 7.98%<br><br>3-h postmeal plasma glucose AUC:<br>Sotagliflozin: 595 mg · h/dL (*P* = .005 vs. placebo)<br>Placebo: 761 mg · h/dL<br><br>CGM-measured mean daily glucose (mean change from baseline):<br>Sotagliflozin: –14.0% (*P* = .01 vs. placebo)<br>Placebo: 5.9%<br><br>MAGE (mean change from baseline):<br>Sotagliflozin: –20.0% (*P* = .041 vs. placebo)<br>Placebo: 7.5%<br><br>Time spent in glucose ranges:<br>70-180 mg/dL:<br>Sotagliflozin: 11.6% (*P* = .003 vs. placebo)<br>Placebo: –0.2%<br>>180 mg/dL:<br>Sotagliflozin: –10.1% (*P* = .002 vs. placebo)<br>Placebo: 2.5%<br><br>Bolus insulin dose:<br>Sotagliflozin: –32% (*P* = .007 vs. placebo)<br>Placebo: –6.4%<br><br>TDD:<br>Sotagliflozin: –15% (*P* = .03 vs. placebo)<br>Placebo: –0.7%<br><br>Weight:<br>Sotagliflozin: –1.7 kg (*P* = .005 vs. placebo)<br>Placebo: 0.5 kg | Fewer cases of hypoglycemia in sotagliflozin vs. placebo groups<br><br>Increased rate nausea in sotagliflozin vs. placebo group<br><br>No gastrointestinal AE led to treatment discontinuation<br><br>2 cases of DKA in sotagliflozin group |
| Liraglutide/ retrospective observational study (77) | 27 obese patients | 180 ± 14 day observation period | Mean glucose concentrations: –21 mg/dL (*P* = .002 vs. baseline)<br>A1C: –0.43% (*P* = .001 vs. baseline)<br>Body weight: –4.64 kg (*P*<.0001 vs. baseline)<br>TDD: –13 units (*P* = .008 vs. baseline)<br>Bolus insulin dose: –11 units (*P* = .011 vs. baseline) | No change in rate of hypoglycemia |
| Liraglutide/ prospective randomized, double-blind, placebo-controlled study (76) | 72 | 12 weeks | Mean change in average blood glucose:<br>Lira 1.2 mg: –10.0 ± 2 mg/dL (*P*<.0001 vs. placebo)<br>Lira 1.8 mg: –10.0 ± 1 mg/dL (*P*<.0001 vs. placebo)<br>Mean change in A1C:<br>Lira 1.2 mg: –0.78% (*P* = .001 vs. placebo)<br>Lira 1.8 mg: –0.42% (*P* = .39 vs. placebo)<br>Body weight:<br>Lira 1.2 mg: –5.0 kg (*P*<.001 vs. placebo)<br>Lira 1.8 mg: –5.0 kg (*P*<.0001 vs. placebo)<br>TDD:<br>Lira 1.2 mg: –12.4 ± 3.9 units (*P*<.05 vs. placebo)<br>Lira 1.8 mg: 10.0 ± 2.3 units (*P*<.05 vs. placebo) | Safety data not reported in meeting abstract |

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**Table 2 (*Continued*)**
**Summary of Results From Studies of Sodium Glucose Cotransporter Inhibitors and Incretin Agents**

| Agent/study design | No. patients | Study duration | Key efficacy findings | Key safety findings |
|---|---|---|---|---|
| Liraglutide/ prospective randomized, double-blind, placebo-controlled crossover hypoglycemic clamp study (78) | 45 | 4 weeks per treatment period | 4-week treatment periods:<br>No differences between liraglutide and placebo in SMBG, postprandial glucose, A1C, fasting C-peptide, or FPG<br><br>Glucagon during hypoglycemic clamp at nadir glucose (45 mg/dL):<br>Liraglutide 1.2 mg vs. placebo crossover:<br>Liraglutide 1.2 mg: 28.8 pg/mL ($P$ = .126 vs. placebo)<br>Placebo: 37.2 pg/mL<br><br>Liraglutide 1.8 mg vs. placebo crossover:<br>Liraglutide 1.8 mg: 28.4 pg/mL ($P$ = .092 vs. placebo)<br>Placebo: 37.5 pg/mL<br><br>No differences in incremental changes in response to hypoglycemia in glucagon or other counterregulatory hormones<br><br>No significant differences in other counterregulatory hormones (epinephrine, norepinephrine, cortisol, and growth hormone), hypoglycemic symptoms score, subjective hypoglycemic awareness, or cognitive function | No differences in number of hypoglycemic episodes between liraglutide and placebo treatment periods<br><br>No severe hypoglycemia occurred during study<br><br>86% of patients taking liraglutide 1.2 mg and 93% of patients taking liraglutide 1.8 mg experienced gastrointestinal AEs |
| Sitagliptin/ single arm, open-label study (71) | 25 | 46 weeks | No change in A1C or FPG<br>Weight: –1.9 ± 2.6 kg<br>BMI : –0.7 kg/m$^2$ ($P$<.001)<br>Insulin dose: –0.13 units/kg/day ($P$<.001) | Incidence of AEs not reported |
| Sitagliptin/ randomized, double-blind, crossover trial (73) | 20 | 8 weeks | A1C: –0.27% ± 0.11% ($P$ = .025 vs. placebo after controlling for crossover period, treatment, and insulin dose)<br>Mean blood glucose: –10.8 mg/dL ($P$ = .012 vs. placebo)<br>Time in euglycemic range: 0.4 ± 0.2 h ($P$ = .046)<br>Total daily insulin dose: –0.051 ± 0.18 U/kg ($P$ = .01 vs. placebo)<br>Total daily basal insulin dose: –0.005 ± 0.01 U/kg ($P$ = 0.55 vs. placebo)<br>Total daily bolus insulin dose –0.045 ± 0.02 ($P$ = 0.02 vs. placebo)<br>No difference in weight | No increase in hypoglycemia and no occurrence of serious AEs |
| Sitagliptin/ randomized, double-blind, placebo-controlled trial (72) | 141 | 16 weeks | No change in A1C, glucagon, insulin dose, or weight | No difference in rates of hypoglycemia |

Abbreviations: A1C = glycated hemoglobin; AE = adverse event; AUC = area under the curve; BMI = body mass index; CGM = continuous glucose monitoring; DKA = diabetic ketoacidosis; FPG = fasting plasma glucose; GFR = glomerular filtration rate; MAGE = mean amplitude of glucose excursions; SMBG = self-monitoring of blood glucose; TDD = total daily dosage of insulin; UTI = urinary tract infection.

### *SGLT2 Inhibitors*

The SGLT2 protein is expressed in the proximal convoluted tubule of the kidney, the major pathway of filtered glucose re-absorption, which helps maintain an adequate glucose supply during fasting periods to meet the energy needs of the brain and other vital organs, as reviewed extensively elsewhere (47,48). Inhibition of SGLT2 increases glucose excretion in the kidney, thereby improving glycemic control in persons with diabetes. Because this mechanism does not depend on pancreatic insulin secretion, the class has potential as adjunctive therapy for T1D (49,50).

Support for this hypothesis comes from studies of SGLT2 inhibitors in patients with T2D who take insulin. In these patients, SGLT2 inhibitors result in significant decreases in A1C and weight without a significant increase in hypoglycemia (51,52).

Currently, the class is infrequently used for off-label adjunctive therapy in T1D; <1% of patients in the T1D Exchange report taking them (10). Nevertheless, while small in scale, studies of SGLT2 inhibition in T1D have offered promising results (Table 2). In a 2-week proof-of-concept study involving 70 patients, dapagliflozin 10 mg induced increases in urinary glucose excretion that were associated with a reduction in 24-hour glucose of 43.1 mg/dL (95% confidence interval [CI], –66.9 to –15.7 mg/dL) and in the mean amplitude of glucose excursions of 63.1 mg/dL (95% CI, –111.5 to –14.8 mg/dL), while smaller decreases in these parameters occurred with placebo (Table 2) (53). The total daily dosage (TDD) of insulin decreased in the dapagliflozin group by 16% (95% CI, –111.5 to –14.8 mg/dL) compared with a small increase in the placebo group of 1.7% (95% CI, –22.8 to 33.9%). This study lacked sufficient power, and the CIs for dapagliflozin and

placebo overlapped for all the efficacy parameters. A phase 3 study of dapagliflozin is ongoing (44).

As described in Table 2, a single-arm, 8-week study with empagliflozin showed statistically significant reductions in fasting plasma glucose and A1C, hypoglycemia, insulin dose, and weight (54). In another study of the same cohort, empagliflozin significantly reduced the glomerular filtration rate (GFR) among patients with hyperfiltration at baseline (GFR ≥135 mL/min/1.73 $m^2$) during euglycemic and hyperglycemic clamp conditions, while filtration rates in patients with normal renal function at baseline remained unchanged (55). These findings are important, as SGLT2 inhibition might preserve renal function. The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) study is currently underway in T2D patients at risk for nephropathy to determine whether renal function can be maintained in this high-risk group of patients (44).

In the Empagliflozin as Adjunctive to inSulin thErapy in Type 1 Diabetes (EASE-1) study, a randomized, double-blind, placebo-controlled phase 2 trial involving 75 patients (Table 2), empagliflozin 25 mg significantly reduced A1C, measures of glycemic variability, and weight, with lower insulin doses, over 28 days (56,57). From a mean baseline of 8.2%, empagliflozin reduced A1C by 0.49% relative to placebo ($P$<.001) and weight by 1.9 kg relative to placebo ($P$<.001) (56). Glucose exposure, measured by the hourly mean AUC over 24 hours, decreased by 19.0 ± 5.1 and 3.1 ± 5.1 mg/dL per hour in the empagliflozin and placebo groups, respectively ($P$<.05), and glucose variability fell by 20.7 ± 3.7 mg/dL with empagliflozin while increasing 6.5 ± 3.7 mg/dL with placebo ($P$<.001) (57). All of these changes accompanied significant reductions in insulin dose among empagliflozin-treated patients (Table 2). Symptomatic hypoglycemia was similar between treatment groups; a single episode of severe hypoglycemia occurred in the placebo group (56). Additional evidence will come from the EASE-2 study, an ongoing 52-week phase 3 trial of the efficacy and safety of empagliflozin in T1D.

As of this writing, no studies of canagliflozin in T1D have yet been published, but a phase 3 study is underway (44).

### *SGLT2 Inhibitors and Euglycemic DKA*

A case series published in June 2015 described 13 episodes of "euglycemic DKA" occurring in 9 patients taking an SGLT2 inhibitor (37). In the 7 patients who had T1D, blood glucose at presentation ranged from 96 to 233 mg/dL and averaged 179 mg/dL—levels much lower than typically seen in DKA. All of the cases reported to date have involved canagliflozin, and most occurred within the first few weeks of initiating this agent. The exact pathogenesis for DKA associated with SGLT2 inhibitors is not known and is currently under investigation (58). The proposed mechanism of near-euglycemic DKA is that it results from dehydration associated with glycosuria, which leads to starvation ketosis aggravated by increased glucagon and lactate levels (37,59). The FDA is evaluating post-marketing reports of SGLT2 inhibitor–associated DKA and has emphasized that SGLT2 inhibitors are not currently approved for use in patients with T1D (58).

### *Dual SGTL1 and SGLT2 Inhibition*

SGLT1 is responsible for approximately 10% of glucose re-absorption in the kidney, but in the gut, it is the primary transporter through which glucose and galactose are absorbed in the intestine (48). Inhibition of SGLT1 reduces glucose absorption in the proximal intestine, which in turn increases distal glucose delivery, reducing postprandial glucose excursions and promoting the release of GLP-1 and polypeptide tyrosine tyrosine (PYY) from intestinal L cells (60). These changes may lead to weight loss by increasing satiety (61,62). In addition, higher GLP-1 levels reduce glucagon levels and possibly ketogenesis (63).

Phlorizin, a nonselective SGLT1 and SGLT2 inhibitor used in early studies to elucidate the role of SGLT in diabetes, was associated with significant gastrointestinal effects similar to those experienced by individuals with genetic mutations that disable SGLT1 (48). As a result, SGLT2 inhibitors were designed to be highly selective for SGLT2 compared to SGLT1, with progressively higher selectivity ranging from 260-fold for canagliflozin to 2,700-fold for empagliflozin (Table 3) (64). Meanwhile, animal and genetics studies demonstrated that partial inhibition of SGLT1 was compatible with normal gastrointestinal function (65,66). On the basis of these findings, sotagliflozin (LX4211), a novel dual SGLT1 and SGLT2 inhibitor, was developed with 20-fold selectivity for SGLT2 over SGLT1. As shown in Table 3, the potency of sotagliflozin on SGLT1 is greater than that of the more selective SGLT2 inhibitors, with a half-maximal inhibitory concentration ($IC_{50}$, the concentration of a drug required for 50% inhibition in vitro) of 36 nmol/L, while its potency on SGLT2 ($IC_{50}$ of 1.8 nmol/L) falls within the range of the SGLT2 inhibitors (64,67). In preclinical studies, sotagliflozin significantly decreased postprandial glucose and increased urinary glucose excretion as well as secretion of GLP-1 and PYY (68,69). It is being studied in phase 3 clinical trials as a treatment for both T1D and T2D.

In a 29-day, double-blind phase 2 study described in Table 2, 33 subjects with T1D were randomly assigned to once daily treatment of sotagliflozin 400 mg or placebo (70). Sotagliflozin significantly reduced postprandial glucose ($P$ = .005 versus placebo) and led to a 32% reduction in bolus insulin dose ($P$ = .007 versus placebo), an effect that may be due to the effects of SGLT1 inhibition on gastrointestinal glucose absorption. Basal insulin doses did not change significantly during the study, but the TDD of insulin decreased significantly by 15% ($P$ = .03 versus

**Table 3**
**Potency ($IC_{50}$), Selectivity, and Highest Dose of SGLT Inhibitors (62,65)**

| Compound | SGLT1 $IC_{50}$ (nmol/L) | SGLT2 $IC_{50}$ (nmol/L) | SGLT2/SGLT1 selectivity | Highest dose in phase 2 or 3 clinical trials (mg) |
|---|---|---|---|---|
| Canagliflozin | 710 | 2.7 | 260 | 300 |
| Dapagliflozin | 1,400 | 1.2 | 1,200 | 10 |
| Empagliflozin | 8,300 | 3.1 | 2,700 | 25 |
| Sotagliflozin | 36 | 1.8 | 20 | 400 |

Abbreviations: $IC_{50}$ = half-maximal inhibitory concentration; SGLT1 = sodium-glucose cotransporter 1; SGLT2 = sodium-glucose cotransporter 2.

placebo). Mean daily glucose measured with continuous glucose monitoring decreased significantly by 14% from baseline compared with a 5.9% increase in the placebo group ($P = .01$), and the amount of time spent in the euglycemic range (70 to 180 mg/dL) increased significantly by 11.6% ($P = .003$ versus placebo), while time spent with blood glucose >180 mg/dL decreased significantly ($P = .002$ versus placebo). PYY levels also significantly increased ($P = .02$) (70).

Fewer episodes of symptomatic hypoglycemia occurred in the sotagliflozin-treated patients compared with the placebo group, while sotagliflozin treatment was associated with a higher rate of gastrointestinal adverse events, primarily nausea (4 sotagliflozin patients versus 1 placebo patient). Nausea was of limited duration and did not lead to drug discontinuation. Two patients treated with insulin pumps in the sotagliflozin group experienced DKA during the trial due to infusion set issues, which the investigators assessed as insulin pump related and not related to the study drug (70). It is possible that dual SGLT1 and SGLT2 inhibitors might lower the risk of DKA by increasing GLP-1 and thereby reducing glucagon levels, but clinical studies will be needed to verify this hypothesis.

### Incretin Agents

Approximately 2% of adult patients in the T1D Exchange report using a GLP-1 receptor agonist, and <1% report using a DPP-4 inhibitor as adjunctive therapy (10). Studies of the incretin classes in T1D have been reviewed in detail elsewhere, so are discussed only briefly here (45,46). As shown in Table 2, the efficacy of DPP-4 inhibitors appears to be limited in T1D, with short-term glucose improvements that appear to wane in longer studies (71-73).

Small studies with GLP-1 receptor agonists have shown some benefits (74-78). In a 12-week, phase 2, randomized, placebo-controlled trial involving 72 patients (Table 2), liraglutide 1.2 mg significantly reduced A1C by 0.78% ($P<.001$ versus placebo), although the decrease observed with the 1.8 mg dose was not statistically significant. Weight decreased significantly by 5 kg with both doses ($P<.001$ versus placebo), and the TDD was reduced by 12.4 and 10.0 units with liraglutide 1.2 and 1.8 mg, respectively ($P<.05$ versus placebo) (76). A recent placebo-controlled crossover trial showed that liraglutide did not affect counterregulatory responses in 45 patients with T1D who underwent a hypoglycemic clamp procedure after 4 weeks of adjunctive therapy with liraglutide or placebo (Table 2) (78). Over the 4-week treatment periods, hypoglycemic events occurred at similar rates with placebo and liraglutide, and no severe events occurred during the study. During the hypoglycemic clamp, liraglutide-treated patients had lower basal glucagon concentrations than placebo-treated patients, but there was no difference in incremental glucagon response to hypoglycemia. The concentrations of other counterregulatory hormones such as epinephrine, norepinephrine, cortisol, and growth hormone also increased in response to hypoglycemia, with no differences observed between liraglutide and placebo treatment in terms of hypoglycemia symptom score, hypoglycemia awareness, or cognitive function. Recently announced (but unpublished as of this writing) results from phase 3 trials with liraglutide have not borne out the promise of these smaller studies, and the manufacturer has discontinued investigations of liraglutide as a treatment for T1D (79). Other ongoing trials will examine the effects of albiglutide, lixisenatide, and once-weekly exenatide (44).

## CONCLUSION

Patients with T1D require insulin for survival and benefit from intensive insulin therapy in terms of diabetic complications and mortality (5,6). However, weight gain and hypoglycemia pose serious risks that may contribute to low rates of A1C goal attainment in the T1D population. Pramlintide is the only noninsulin agent approved for adjunctive treatment of T1D, yet it is used by few patients, possibly because of high rates of gastrointestinal side effects and increased risk of hypoglycemia. Several recently introduced antihyperglycemic classes hold promise as additional adjunctive therapy options that may help patients overcome barriers to optimal control. In small-scale studies involving patients with T1D, the GLP-1 receptor

agonist liraglutide and the SGLT2 inhibitors dapagliflozin and empagliflozin have demonstrated improvements in glycemic control with lower insulin doses and no increase in hypoglycemia. These agents have also decreased glycemic variability and time spent in hyperglycemia as well as produced weight loss in overweight patients. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor under investigation for treatment of T1D and T2D, reduces overall glycemia and weight through its action in the kidney, similar to SGLT2 inhibitors. In addition, this agent also leads to smaller meal-related glycemic excursions, lower glycemic variability, and reduced prandial insulin dosages by decreasing glucose absorption from the intestine.

The GLP-1 receptor agonists, SGLT2 inhibitors, and dual SGLT1 and SGLT2 inhibitors each have mechanisms of action that complement insulin and may permit it to be used more effectively in T1D, improving overall glycemic control with less risk of weight gain. However, a complete understanding of the efficacy and safety of these agents in T1D awaits completion of phase 3 clinical trials.

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## DISCLOSURE

Dr. Bruce W. Bode owns stock in Aseko and serves as a consultant for Halozyme, Janssen Pharmaceuticals, Medtronic, Novo Nordisk, Sanofi, and Valeritas and is on the speaker's bureaus for Astra Zeneca, GlaxoSmithKline, Janssen Pharmaceuticals, Eli Lilly and Company, Medtronic, Merck and Company, Novo Nordisk, Sanofi, and Valeritas; his employer (Atlanta Diabetes Associates) has received grant and research support from Abbott, Andromeda, Biodel, DexCom, GlaxoSmithKline, Halozyme, Janssen Pharmaceuticals, Eli Lilly/Boehringer Ingelheim, MannKind, Medtronic, the National Institutes of Health, Novo Nordisk, Pfizer, Sanofi, and Valeritas.

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