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REVIEW ARTICLE

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# Sodium-glucose co-transporter inhibitors as adjunctive treatment to insulin in type 1 diabetes: A review of randomized controlled trials

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## Abstract

Many patients with type 1 diabetes (T1D) struggle to achieve glycaemic control and experience significant fluctuations in glucose concentrations, despite insulin treatment. Sodium-glucose co-transporter (SGLT)-2 inhibitors and dual SGLT-1/2 inhibitors increase glucose elimination via the kidneys and reduce hyperglycaemia via insulin-independent mechanisms. This review examines available efficacy and safety data for these agents under investigation as adjunctive therapy for T1D. Across randomized trials of up to 52 weeks, SGLT-2 inhibitors or SGLT-1/2 inhibitors as an adjunct to insulin demonstrated significant reductions in glycated haemoglobin, glucose exposure, and measures of glycaemic variability, as well as increased time in the target glycaemic range, compared with placebo. Non-glycaemic benefits included reductions in body weight and insulin doses, as well as improvements in some cardiovascular risk factors and treatment satisfaction. SGLT-2 inhibitors and SGLT-1/2 inhibitors were associated with similar rates of hypoglycaemia but a higher incidence of genitourinary infections, compared with placebo. Diabetic ketoacidosis occurred more often with SGLT-2 inhibitors and SGLT-1/2 inhibitors vs placebo, although the incidence was generally low. Risk mitigation strategies in light of clinical trial data are also discussed. Positive data from randomized controlled trials of the SGLT-2 inhibitor dapagliflozin have led to the approval of dapagliflozin as an adjunct to insulin in adults with T1D having body mass index ≥27 kg/m$^2$ in whom insulin does not provide adequate glycaemic control in Europe and to approval as an adjunct to insulin for adults with T1D in Japan.

**KEYWORDS**
canagliflozin, dapagliflozin, empagliflozin, SGLT-2 inhibitor, type 1 diabetes

## 1 | INTRODUCTION

Individuals with type 1 diabetes (T1D) comprise approximately 5% to 10% of the overall population with diabetes, while those with type 2 diabetes (T2D) comprise the majority. Accordingly, most research efforts aimed at developing new glucose-lowering treatments have focused on T2D, leading to the approval of multiple classes of glucose-lowering agents. In contrast, insulin analogues and the amylin analogue pramlintide, which is infrequently used, remain essentially the only treatment options available for T1D in the United States.

Insulin therapy is designed to mimic endogenous insulin secretion patterns and has been the mainstay for patients with T1D. However, a basal-bolus regimen cannot perfectly mimic endogenous insulin secretion, and while exogenous insulin is essential for preventing

excessively high blood glucose concentrations, insulin-treated patients often oscillate between hyperglycaemia and hypoglycaemia. Intensive treatment with insulin titrated to provide tight control of glycated haemoglobin (A1C) was shown to lower the risk of long-term microvascular and macrovascular complications in the Diabetes Control and Complications Trial; yet, overtreatment with insulin poses an increased risk of hypoglycaemia.[1-3]

Data from the T1D Exchange Clinic Registry, which initially enrolled almost 26 000 patients with T1D from 67 diabetes-oriented clinics in the United States,[4] showed that only ~30% of patients aged ≥26 years achieved A1C <7.0%, with a lower rate (14%) for patients aged 18 to 25 years.[5] Furthermore, many patients with T1D experience significant glycaemic variability, including postprandial glucose excursions and hypoglycaemic episodes, as well as problems achieving "time in range" (TIR), defined as the percentage of time with glucose within the target range (usually >70 to ≤180 mg/dL).[6,7] While insulin therapy is essential, many patients with T1D experience increased insulin resistance as their weight increases, requiring high doses of insulin that are often associated with adverse side effects, including hypoglycaemia, dyslipidaemia, and weight gain, which in turn increases the risk of hypertension. Therefore, clinicians have sought additional therapies that may benefit insulin-resistant patients with T1D. However, the use of adjunctive glucose-lowering therapies remains low. Among the 16 061 patients in the 2015 update to the T1D Exchange Clinic Registry, 3% of patients were taking metformin and <1% each were taking pramlintide, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose co-transporter (SGLT)-2 inhibitors, or others (including thiazolidinediones and sulphonylureas).[5]

Pramlintide, a soluble, injectable analogue of the β-cell hormone amylin, is approved for use with mealtime insulin in patients with T1D or T2D[8] and has been shown to reduce postprandial hyperglycaemia and weight gain.[9-12] Factors limiting its use include a high incidence of nausea, increased risk of insulin-induced postprandial hypoglycaemia, and the need for additional injections, as it cannot be mixed with insulin in the current formulation.

Off-label use of metformin as adjunctive treatment to insulin has been investigated for T1D. A meta-analysis of eight randomized controlled trials (RCTs) found that while metformin was associated with reductions in daily insulin dose, body weight, and cholesterol compared with placebo, no significant differences were found for A1C, fasting plasma glucose, or triglycerides.[13]

Newer classes of glucose-lowering therapies for T2D have also been investigated for T1D. A meta-analysis of five RCTs concluded that the addition of DPP-4 inhibitors to insulin therapy showed no clear glycaemic benefit for patients with T1D vs insulin monotherapy.[14] An RCT investigating the addition of the GLP-1RA liraglutide or placebo to insulin therapy in patients with T1D observed greater reductions in A1C, blood glucose concentrations, blood pressure (BP), and body weight with liraglutide.[15] These results suggest potential benefits of GLP-1RA treatment as adjunctive therapy, although GLP-1RAs are not currently approved for, nor in the process of seeking approval for, a T1D indication.[16,17]

SGLT-2-selective inhibitors, which reduce hyperglycaemia by increasing the elimination of glucose via the kidneys, were developed to treat patients with T2D. Accumulated evidence suggests that increased glucose elimination is predominantly explained by a marked reduction in the reabsorption of renal glucose.[18] SGLT-2 is expressed in the S1 segment of the renal proximal tubule and accounts for 80% to 90% of filtered glucose reabsorption by the kidney, while SGLT-1 is localized to the S2/S3 segment and accounts for the remaining 10% to 20%, although the relative contribution of SGLT-1 to glucose reabsorption appears increased under circumstances of SGLT-2 inhibition.[19,20] SGLT-1 mediates the bulk of glucose transport in the intestine, and inhibition of SGLT-1 reduces intestinal glucose reabsorption, thereby attenuating postprandial hyperglycaemia.[18]

Four SGLT-2 inhibitors are approved for the treatment of T2D in the United States—dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin.[21-24] In patients with T2D, SGLT-2 inhibitors have been shown to reduce A1C and fasting and postprandial glucose concentrations.[25-27] Non-glycaemic benefits include weight loss and improvement in some cardiovascular risk factors.

Because SGLT-2 inhibitors reduce hyperglycaemia through an insulin-independent, glucose-dependent mechanism, and may therefore complement insulin therapy or provide additional benefits in insulin-resistant patients, the use of SGLT-2 inhibitors as adjunctive treatment to insulin for T1D has become an area of increasing interest to investigators. Likewise, the dual SGLT-1/2 inhibitor sotagliflozin is under investigation.

We sought to consolidate the available evidence on the effects of treatment with SGLT-2 inhibitors and dual SGLT-1/2 inhibitors among patients with T1D. As such, this review summarizes the efficacy and safety data reported in prospective, double-blind RCTs of these agents as adjunctive treatment to insulin therapy in adults with T1D. A literature search of the PubMed database was conducted on 5 July 2018 for English-language articles using the following search terms within titles and abstracts: SGLT-2 inhibitor OR sodium-glucose co-transporter-2 inhibitor OR dapagliflozin OR empagliflozin OR canagliflozin OR ertugliflozin OR sotagliflozin AND T1D. Additional articles were identified from the bibliographies of resultant articles. Selected studies included double-blind RCTs in adults with T1D. To date, several large clinical trials have investigated adjunctive treatment with dapagliflozin, canagliflozin, empagliflozin, and sotagliflozin among adults with T1D, while clinical data regarding the effects of ertugliflozin in T1D are not currently available.

## 2 | EFFECTS OF SGLT-2 INHIBITORS AND SGLT-1/2 INHIBITORS AMONG PATIENTS WITH T1D

### 2.1 | Dapagliflozin

An early 2-week exploratory RCT investigated the feasibility of adding dapagliflozin to insulin among patients with T1D (n = 70).[28] Dapagliflozin 10 mg increased urinary glucose excretion by 88 g/24 h, whereas placebo was associated with a reduction in urinary glucose

**TABLE 1** Effects of SGLT-2 inhibitors and SGLT-1/2 inhibitors as an adjunct to insulin on A1C and body weight in RCTs[a]

| Study/NCT identifier | Study design (duration) | Treatment (n) BL A1C; BL body weight | Treatment difference for change from BL in A1C (95% CI [*P*-value]) | Treatment difference for change from BL in body weight (95% CI [*P*-value]) |
|---|---|---|---|---|
| Dapagliflozin | | | | |
| Dandona et al[31] (DEPICT-1)/ NCT02268214 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study (24 weeks) | Dapagliflozin 5 mg (n = 259): A1C, 8.53%; weight, 80.8 kg<br>Dapagliflozin 10 mg (n = 259): A1C, 8.52%; weight, 82.0 kg<br>Placebo (n = 260): A1C, 8.53%; weight, 84.3 kg | Dapagliflozin 5 mg: −0.42% (−0.56 to −0.28 [*P* < .0001])<br>Dapagliflozin 10 mg: −0.45% (−0.58 to −0.31 [*P* < .0001]) | Dapagliflozin 5 mg: −2.96% (−3.63 to −2.28 [*P* < .0001])<br>Dapagliflozin 10 mg: −3.72% (−4.38 to −3.05 [*P* < .0001]) |
| Dandona et al[32] (DEPICT-1)/ NCT02268214 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 extension study (52 weeks) | Dapagliflozin 5 mg (n = 259): A1C, 8.53%; weight, 81.0 kg<br>Dapagliflozin 10 mg (n = 259): A1C, 8.52%; weight, 82.1 kg<br>Placebo (n = 260): A1C, 8.53%; weight, 84.4 kg | Dapagliflozin 5 mg: −0.33% (−0.49 to −0.17)<br>Dapagliflozin 10 mg: −0.36% (−0.53 to −0.20) | Dapagliflozin 5 mg: −2.95% (−3.83 to −2.06)<br>Dapagliflozin 10 mg: −4.54% (−5.40 to −3.66) |
| Mathieu et al[33] (DEPICT-2)/ NCT02460978 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study (24 weeks) | Dapagliflozin 5 mg (n = 271): A1C, 8.45%; weight, 78.7 kg<br>Dapagliflozin 10 mg (n = 270): A1C, 8.43%; weight, 80.1 kg<br>Placebo (n = 272): A1C, 8.43%; weight, 78.9 kg | Dapagliflozin 5 mg: −0.37% (−0.49 to −0.26 [*P* < .0001])<br>Dapagliflozin 10 mg: −0.42% (−0.53 to −0.30 [*P* < .0001]) | Dapagliflozin 5 mg: −3.21% (−3.96 to −2.45 [*P* < .0001])<br>Dapagliflozin 10 mg: −3.74% (−4.49 to −2.99 [*P* < .0001]) |
| Empagliflozin | | | | |
| Pieber et al[34] (EASE-1)/ NCT01969747 | Double-blind, randomized, parallel-group, placebo-controlled, dual-centre phase 2 study (4 weeks) | Empagliflozin 2.5 mg (n = 19): A1C, 8.35%; weight, 75.9 kg<br>Empagliflozin 10 mg (n = 19): A1C, 8.28%; weight, 87.1 kg<br>Empagliflozin 25 mg (n = 18): A1C, 8.15%; weight, 76.9 kg<br>Placebo (n = 19): A1C, 8.18%; weight, 79.8 kg | Empagliflozin 2.5 mg: −0.35% (−0.62 to −0.09 [*P* = .010])<br>Empagliflozin 10 mg: −0.36% (−0.62 to 0.10 [*P* = .008])<br>Empagliflozin 25 mg: −0.49% (−0.75 to −0.22 [*P* < .001]) | Empagliflozin 2.5 mg: −1.5 kg (−2.4 to −0.7 [*P* < .001])<br>Empagliflozin 10 mg: −1.8 kg (−2.7 to −0.9 [*P* < .001])<br>Empagliflozin 25 mg: −1.9 kg (−2.7 to −1.0 [*P* < .001]) |
| Rosenstock et al[35] (EASE-2)/ NCT02414958 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study (52 weeks) | Empagliflozin 10 mg (n = 243): A1C, 8.10%; weight, 86.2 kg<br>Empagliflozin 25 mg (n = 241): A1C, 8.06%; weight, 85.6 kg<br>Placebo (n = 239): A1C, 8.13%; weight, 83.4 kg | 26 weeks<br>Empagliflozin 10 mg: −0.54% (*P* < .0001)<br>Empagliflozin 25 mg: −0.53% (*P* < .0001) | 26 weeks<br>Empagliflozin 10 mg: −2.7 kg (−3.3 to −2.1 [*P* < .0001])<br>Empagliflozin 25 mg: −3.3 kg (−3.8 to −2.7 [*P* < .0001]) |
| | | | 52 weeks<br>Empagliflozin 10 mg: −0.39% (*P* < .0001)<br>Empagliflozin 25 mg: −0.45% (*P* < .0001) | 52 weeks<br>Empagliflozin 10 mg: −3.2 kg (−3.9 to −2.5 [*P* < .0001])<br>Empagliflozin 25 mg: −3.6 kg (−4.3 to −2.8 [*P* < .0001]) |
| Rosenstock et al[35] (EASE-3)/ NCT02580591 | Double-blind, randomized, parallel-group, placebo-controlled, | Empagliflozin 2.5 mg (n = 237): A1C, 8.14%; weight, 81.6 kg | Empagliflozin 2.5 mg: −0.28% (*P* < .0001)<br>Empagliflozin 10 mg: −0.45% (*P* < .0001) | Empagliflozin 2.5 mg: −1.8 kg (−2.3 to −1.2 [*P* < .0001]) |

**TABLE 1** (Continued)

| Study/NCT identifier | Study design (duration) | Treatment (n) BL A1C; BL body weight | Treatment difference for change from BL in A1C (95% CI [*P*-value]) | Treatment difference for change from BL in body weight (95% CI [*P*-value]) |
|---|---|---|---|---|
| | multicentre, phase 3 study (26 weeks) | Empagliflozin 10 mg (n = 244): A1C, 8.19%; weight, 83.7 kg<br>Empagliflozin 25 mg (n = 242): A1C, 8.19%; weight, 83.3 kg<br>Placebo (n = 238): A1C, 8.19%; weight, 80.7 kg | Empagliflozin 25 mg: −0.52% (*P* < .0001) | Empagliflozin 10 mg: −3.0 kg (−3.6 to −2.5 [*P* < .0001])<br>Empagliflozin 25 mg: −3.4 kg (−4.0 to −2.9 [*P* < .0001]) |
| Canagliflozin | | | | |
| Henry et al[36]/ NCT02139943 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 2 study (18 weeks) | Canagliflozin 100 mg (n = 117): A1C, 7.9%; weight, 84.1 kg<br>Canagliflozin 300 mg (n = 117): A1C, 8.0%; weight, 82.9 kg<br>Placebo (n = 117): A1C, 7.9%; weight, 83.0 kg | Canagliflozin 100 mg: −0.29% (−0.43 to −0.14)<br>Canagliflozin 300 mg: −0.25% (−0.40 to −0.11) | Canagliflozin 100 mg: −2.8 kg (−3.5 to −2.1); −3.4% (−4.2 to −2.5)<br>Canagliflozin 300 mg: −4.4 kg (−5.2 to −3.7); −5.3% (−6.2 to −4.5) |
| Sotagliflozin | | | | |
| Buse et al[37] (inTandem1)/ NCT02384941 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (52 weeks) | Sotagliflozin 200 mg (n = 263): A1C, 7.61%; weight, 87.0 kg<br>Sotagliflozin 400 mg (n = 262): A1C, 7.56%; weight, 86.5 kg<br>Placebo (n = 268): A1C, 7.54%; weight, 87.3 kg | 24 weeks<br>Sotagliflozin 200 mg: −0.36% (−0.45 to −0.27 [*P* < .001])<br>Sotagliflozin 400 mg: −0.41% (−0.50 to −0.32 [*P* < .001]) | 24 weeks<br>Sotagliflozin 200 mg: −2.35 kg (−2.85 to −1.85 [*P* < .001]); −2.79% (−3.36 to −2.22 [*P* < .001])<br>Sotagliflozin 400 mg: −3.45 kg (−3.95 to −2.94 [*P* < .001]); −4.02% (−4.59 to −3.45 [*P* < .001]) |
| | | | 52 weeks<br>Sotagliflozin 200 mg: −0.25% (−0.37 to −0.14 [*P* < .001])<br>Sotagliflozin 400 mg: −0.31% (−0.43 to −0.20 [*P* < .001]) | 52 weeks<br>Sotagliflozin 200 mg: −3.14 kg (−3.81 to −2.46 [*P* < .001]); −3.63% (−4.39 to −2.87 [*P* < .001])<br>Sotagliflozin 400 mg: −4.32 kg (−5.00 to −3.64 [*P* < .001]); −4.96% (−5.72 to −4.19 [*P* < .001]) |
| Danne et al[38] (inTandem2)/ NCT02421510 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (52 weeks) | Sotagliflozin 200 mg (n = 261): A1C, 7.74%; weight, 81.9 kg<br>Sotagliflozin 400 mg (n = 263): A1C, 7.71%; weight, 82.0 kg<br>Placebo (n = 258): A1C, 7.79%; weight, 81.1 kg | 24 weeks<br>Sotagliflozin 200 mg: −0.37% (−0.48 to −0.25 [*P* < .001])<br>Sotagliflozin 400 mg: −0.35% (−0.47 to −0.24 [*P* < .001]) | 24 weeks<br>Sotagliflozin 200 mg: −1.98 kg (−2.53 to −1.44 [*P* < .001]); −2.48% (−3.14 to −1.82 [*P* < .001])<br>Sotagliflozin 400 mg: −2.58 kg (−3.12 to −2.04 [*P* < .001]); −3.08% (−3.74 to −2.42 [*P* < .001]) |
| | | | 52 weeks<br>Sotagliflozin 200 mg: −0.21% (−0.35 to −0.07 [*P* = .003]) | 52 weeks<br>Sotagliflozin 200 mg: −2.18 kg (−2.88 to −1.48 [*P* < .001]); |

**TABLE 1** (Continued)

| Study/NCT identifier | Study design (duration) | Treatment (n) BL A1C; BL body weight | Treatment difference for change from BL in A1C (95% CI [*P*-value]) | Treatment difference for change from BL in body weight (95% CI [*P*-value]) |
|---|---|---|---|---|
| | | | Sotagliflozin 400 mg: −0.32% (−0.46 to −0.18 [*P* < .001]) | −2.78% (−3.63 to −1.93 [*P* < .001]) Sotagliflozin 400 mg: −2.92 kg (−3.62 to −2.22 [*P* < .001]); −3.50% (−4.35 to −2.65); [*P* < .001]) |
| Garg et al[39] (inTandem3)/ NCT02531035 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (24 weeks) | Sotagliflozin 400 mg (n = 699): A1C, 8.26%; weight, 82.4 kg Placebo (n = 703): A1C, 8.21%; weight, 81.6 kg | Sotagliflozin 400 mg: −0.46% (−0.54 to −0.38 [*P* < .001]) | Sotagliflozin 400 mg: −2.98 kg (−3.31 to −2.66 [*P* < .001]) |

Abbreviations: A1C, glycated haemoglobin; BL, baseline; CI, confidence interval; DEPICT, Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes; EASE, Empagliflozin as Adjunctive to Insulin Therapy; RCTs, randomized controlled trials; SGLT, sodium-glucose co-transporter.

[a]Phase 2 and 3 RCTs of ≥4 weeks that included >50 patients.

excretion (−21.5 g/24 h). By day 7, dapagliflozin 10 mg resulted in reductions from baseline in mean daily glucose (−41.3 vs −20.4 mg/dL with placebo), mean amplitude of glycaemic excursion (−63.1 vs −8.1 mg/dL), and mean percent change in total daily insulin dose (−16.2% vs +1.7%). Insulin doses were not reduced upon initiation of dapagliflozin; however, the dose was adjusted as needed to avoid hypoglycaemia. Hypoglycaemia was commonly reported with all treatments, with one major event of hypoglycaemia in the dapagliflozin 10-mg group. No diabetic ketoacidosis (DKA) occurred.

A subsequent post hoc analysis of this pilot study investigated the correlation between reduction in insulin dose and both glycaemic efficacy and fasting β-hydroxybutyrate, a marker of DKA.[29] The analysis identified trends for the correlation between change in total daily insulin dose and 24-hour glucose at day 7 ($r$ = –0.264; $P$ = .056), as well as change in total daily insulin dose and β-hydroxybutyrate at day 7 ($r$ = –0.187; $P$ = .133) and day 14 ($r$ = –0.274; $P$ = .047), with higher β-hydroxybutyrate concentrations when the insulin dose was reduced by >20%. The results suggest that insulin dose reductions should not exceed 20% to ensure optimal glycaemic efficacy of combination therapy and to reduce any potential increased risk of DKA.

The addition of dapagliflozin 10 mg to treatment with insulin plus a GLP-1RA, liraglutide, was assessed among patients with T1D (n = 30) in a 12-week randomized, placebo-controlled study.[30] During the trial, insulin doses were titrated to a target glucose range of 70 to 160 mg/dL. Dapagliflozin significantly reduced A1C from baseline (–0.66%), whereas there was no significant change with placebo ($P$ < .01 vs placebo). Dapagliflozin was also associated with a reduction in weight from baseline (−1.9 vs +0.7 kg with placebo [$P$ < .05]). No significant changes from baseline were observed in either treatment group for systolic BP (SBP), diastolic BP (DBP), or total insulin dose. The treatment groups had similar rates of hypoglycaemia. However, two patients treated with dapagliflozin developed DKA.

DEPICT-1 (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) was the first large, multicentre, double-blind, phase 3 RCT to investigate the efficacy and safety of dapagliflozin (5 or 10 mg) as adjunctive treatment to adjustable insulin therapy in patients with T1D (n = 833).[31] Upon initiation of dapagliflozin, it was recommended that basal and bolus insulin doses be reduced symmetrically to achieve a reduction in total daily insulin dose ≤20%, followed by titration back towards the baseline dose. After 24 weeks, both doses of dapagliflozin significantly reduced A1C and body weight from baseline compared with placebo (Table 1). Greater proportions of patients treated with dapagliflozin 5 or 10 mg achieved a ≥0.5% reduction in A1C with no severe hypoglycaemic events (50% and 51%, respectively, vs 25% with placebo [both $P$ < .001]). Dapagliflozin also significantly reduced glucose exposure and glycaemic variability and increased TIR (Supporting Information, Table S1). In addition, dapagliflozin was associated with significant reductions in total daily insulin dose vs placebo (Table 2). Reductions in total insulin dose were accounted for by proportional reductions from baseline in basal and bolus insulin doses.

Results from the extension period of DEPICT-1 demonstrated sustained improvements in glycaemic control and body weight.[32] After 52 weeks, both doses of dapagliflozin significantly reduced A1C from baseline vs placebo (Table 1). Body weight reductions from baseline were maintained with dapagliflozin 5 mg, with additional weight reduction observed with dapagliflozin 10 mg (Table 1). Among patients with hypertension at baseline, SBP exhibited a trend towards greater reduction relative to placebo with dapagliflozin 5 mg (−1.12 mm Hg) and 10 mg (−5.38 mm Hg). Total insulin dose remained reduced at 52 weeks. Over the entire study, genital infection adverse events (AEs) occurred more frequently with dapagliflozin compared with placebo and was more common in women than men (Table 3). Rates of hypoglycaemia were similar

**TABLE 2** Effects of SGLT-2 inhibitors and SGLT-1/2 inhibitors as an adjunct to insulin on insulin doses in RCTs[a]

| Study/NCT identifier | Study design; n (duration) | Treatment difference for change from BL in total daily insulin dose (95% CI [*P*-value]) | Treatment difference for change from BL in basal insulin dose (95% CI [*P*-value]) | Treatment difference for change from BL in bolus insulin dose (95% CI [*P*-value]) |
|---|---|---|---|---|
| Dapagliflozin | | | | |
| Dandona et al[31] (DEPICT-1)/ NCT02268214 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study; n = 778 (24 weeks) | Dapagliflozin 5 mg: −8.80% (−12.56 to −4.88 [*P* < .0001])<br>Dapagliflozin 10 mg: −13.17% (−16.75 to −9.43 [*P* < .0001]) | Mean change ± SE[b]<br>Dapagliflozin 5 mg: −11.6% ± 1.3%<br>Dapagliflozin 10 mg: −13.7% ± 1.3%<br>Placebo: −0.6% ± 1.5% | Mean change ± SE[b]<br>Dapagliflozin 5 mg: −14.3% ± 2.1%<br>Dapagliflozin 10 mg: −18.0% ± 2.1%<br>Placebo: −4.6% ± 2.4% |
| Mathieu et al[33] (DEPICT-2)/ NCT02460978 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study; n = 813 (24 weeks) | Dapagliflozin 5 mg: −10.78% (−13.73 to −7.72 [*P* < .0001])<br>Dapagliflozin 10 mg: −11.08% (−14.04 to −8.02 [*P* < .0001]) | Mean change ± SE[b]<br>Dapagliflozin 5 mg: −11.19% ± 1.5%<br>Dapagliflozin 10 mg: −16.71% ± 1.4%<br>Placebo: +1.46% ± 1.7% | Mean change ± SE[b]<br>Dapagliflozin 5 mg: −11.60% ± 2.0%<br>Dapagliflozin 10 mg: −8.30% ± 2.1%<br>Placebo: −2.59% ± 2.2% |
| Empagliflozin | | | | |
| Pieber et al[34] (EASE-1)/ NCT01969747 | Double-blind, randomized, parallel-group, placebo-controlled, dual-centre phase 2 study; n = 75 (4 weeks) | Empagliflozin 2.5 mg: −0.07 U/kg (−0.14 to 0.00 [*P* = .044])<br>Empagliflozin 10 mg: −0.09 U/kg (−0.16 to −0.02 [*P* = .013])<br>Empagliflozin 25 mg: −0.08 U/kg (−0.15 to −0.01 [*P* = .023]) | Values NR | Values NR |
| Rosenstock et al[35] (EASE-2)/ NCT02414958 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study; n = 730 (52 weeks) | 26 weeks<br>Empagliflozin 10 mg: −0.09 U/kg (−0.11 to −0.07 [*P* < .0001]); −13.3%<br>Empagliflozin 25 mg: −0.09 U/kg (−0.11 to −0.07 [*P* < .0001]); −12.7% | 26 weeks<br>Empagliflozin 10 mg: −0.05 U/kg (−0.06 to −0.03 [*P* < .0001])<br>Empagliflozin 25 mg: −0.05 U/kg (−0.06 to −0.04 [*P* < .0001]) | 26 weeks<br>Empagliflozin 10 mg: −0.05 U/kg (−0.07 to −0.03 [*P* < .0001])<br>Empagliflozin 25 mg: −0.04 U/kg (−0.06 to −0.03 [*P* < .0001]) |
| | | 52 weeks<br>Empagliflozin 10 mg: −0.09 U/kg (−0.11 to −0.06 [*P* < .0001]); −12.0%<br>Empagliflozin 25 mg: −0.09 U/kg (−0.12 to −0.07 [*P* < .0001]); −12.9% | 52 weeks<br>Empagliflozin 10 mg: −0.05 U/kg (−0.06 to −0.03 [*P* < .0001])<br>Empagliflozin 25 mg: −0.06 U/kg (−0.07 to −0.04 [*P* < .0001]) | 52 weeks<br>Empagliflozin 10 mg: −0.04 U/kg (−0.06 to −0.01 [*P* = .0010])<br>Empagliflozin 25 mg: −0.04 U/kg (−0.06 to −0.01 [*P* = .0010]) |
| Rosenstock et al[35] (EASE-3)/ NCT02580591 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study; n = 975 (26 weeks) | Empagliflozin 2.5 mg: −0.05 U/kg (−0.07 to −0.03 [*P* < .0001]); −6.4%<br>Empagliflozin 10 mg: −0.07 U/kg (−0.09 to −0.05 [*P* < .0001]); −9.5%<br>Empagliflozin 25 mg: −0.09 U/kg (−0.11 to −0.07 [*P* < .0001]); −12.6% | Empagliflozin 2.5 mg: −0.02 U/kg (−0.04 to −0.01 [*P* = .0003])<br>Empagliflozin 10 mg: −0.04 U/kg (−0.05 to −0.02 [*P* < .0001])<br>Empagliflozin 25 mg: −0.05 U/kg (−0.07 to −0.04 [*P* < .0001]) | Empagliflozin 2.5 mg: −0.03 U/kg (−0.04 to −0.01 [*P* = .0027])<br>Empagliflozin 10 mg: −0.03 U/kg (−0.05 to −0.02 [*P* < .0001])<br>Empagliflozin 25 mg: −0.04 U/kg (−0.06 to −0.03 [*P* < .0001]) |
| Canagliflozin | | | | |
| Henry et al[36]/ NCT02139943 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 2 study; n = 351 (18 weeks) | Canagliflozin 100 mg: −4.1 U/d (−7.9 to −0.3); −8.9%<br>Canagliflozin 300 mg: −7.6 U/d (−11.3 to −3.8); −12.9% | Canagliflozin 100 mg: −4.3 U/d (−6.2 to −2.4); −19.0%<br>Canagliflozin 300 mg: −5.3 U/d (−7.2 to −3.4); −22.4% | Canagliflozin 100 mg: −0.3 U/d (−3.3 to +2.7); +6.1%<br>Canagliflozin 300 mg: −3.2 U/d (−6.2 to −0.2); −12.1% |

**TABLE 2** (Continued)

| Study/NCT identifier | Study design; n (duration) | Treatment difference for change from BL in total daily insulin dose (95% CI [*P*-value]) | Treatment difference for change from BL in basal insulin dose (95% CI [*P*-value]) | Treatment difference for change from BL in bolus insulin dose (95% CI [*P*-value]) |
|---|---|---|---|---|
| Sotagliflozin | | | | |
| Buse et al[37] (inTandem1)/ NCT02384941 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study; n = 793 (52 weeks) | 24 weeks<br>Sotagliflozin 200 mg: −2.98 U (−5.20 to −0.76 [*P* = .009]); −6.16% (−9.01 to −3.32 [*P* < .001])<br>Sotagliflozin 400 mg: −6.36 U (−8.58 to −4.14 [*P* < .001]); −9.70% (−12.54 to −6.85 [*P* < .001]) | 24 weeks<br>Sotagliflozin 200 mg: −1.74 U (−2.83 to −0.64 [*P* = .002]); −5.51% (−8.71 to −2.30 [*P* < .001])<br>Sotagliflozin 400 mg: −2.98 U (−4.08 to −1.89 [*P* < .001]); −9.12% (−12.32 to −5.91 [*P* < .001]) | 24 weeks<br>Sotagliflozin 200 mg: −1.50 U (−3.30 to +0.30 [*P* = .10]); −5.70% (−12.82 to +1.42 [*P* = .12])<br>Sotagliflozin 400 mg: −3.30 U (−5.09 to −1.50 [*P* < .001]); −12.67% (−19.79 to −5.55 [*P* < .001]) |
| | | 52 weeks<br>Sotagliflozin 200 mg: −4.59 U (−7.21 to −1.97 [*P* < .001]); −8.02% (−11.28 to −4.75 [*P* < .001])<br>Sotagliflozin 400 mg: −8.74 U (−11.37 to −6.12 [*P* < .001]); −12.64% (−15.93 to −9.36 [*P* < .001]) | 52 weeks<br>Sotagliflozin 200 mg: −2.80 U (−4.14 to −1.47 [*P* < .001]); −7.69% (−11.52 to −3.86 [*P* < .001])<br>Sotagliflozin 400 mg: −4.35 U (−5.70 to −3.01 [*P* < .001]); −11.87% (−15.71 to −8.02 [*P* < .001]) | 52 weeks<br>Sotagliflozin 200 mg: −2.06 U (−4.05 to −0.08 [*P* = .041]); −5.53% (−14.54 to +3.48 [*P* = .23])<br>Sotagliflozin 400 mg: −4.55 U (−6.54 to −2.57 [*P* < .001]); −15.63% (−24.67 to −6.59 [*P* < .001]) |
| Danne et al[38] (inTandem2)/ NCT02421510 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study; n = 782 (52 weeks) | 24 weeks<br>Sotagliflozin 200 mg: −4.80 U (−6.85 to −2.76 [*P* < .001]); −8.23% (−11.68 to −4.79 [*P* < .001])<br>Sotagliflozin 400 mg: −4.96 U (−7.00 to −2.92 [*P* < .001]); −9.47% (−12.90 to −6.04 [*P* < .001]) | 24 weeks<br>Sotagliflozin 200 mg: −1.59 U (−2.63 to −0.54 [*P* = .003]); −5.82% (−10.04 to −1.59 [*P* = .007])<br>Sotagliflozin 400 mg: −1.38 U (−2.42 to −0.34 [*P* = .009]); −4.67% (−8.88 to −0.47 [*P* = .030]) | 24 weeks<br>Sotagliflozin 200 mg: −3.20 U (−4.86 to −1.53 [*P* < .001]); −12.94% (−20.50 to −5.38 [*P* < .001])<br>Sotagliflozin 400 mg: −3.59 U (−5.25 to −1.93 [*P* < .001]); −16.37% (−23.90 to −8.83 [*P* < .001]) |
| | | 52 weeks<br>Sotagliflozin 200 mg: −2.81 U (−5.06 to −0.57 [*P* = .014]); −6.26% (−10.18 to −2.33 [*P* = .002])<br>Sotagliflozin 400 mg: −3.37 U (−5.61 to −1.13 [*P* = .003]); −8.17% (−12.09 to −4.25 [*P* < .001]) | 52 weeks<br>Sotagliflozin 200 mg: −1.70 U (−2.89 to −0.52 [*P* = .005]); −6.73% (−11.47 to −1.99 [*P* = .005])<br>Sotagliflozin 400 mg: −2.20 U (−3.38 to −1.02 [*P* < .001]); −6.68% (−11.41 to −1.96 [*P* = .006]) | 52 weeks<br>Sotagliflozin 200 mg: −1.08 U (−2.90 to +0.74 [*P* = .24]); −7.70% (−16.35 to +0.95 [*P* = .08])<br>Sotagliflozin 400 mg: −1.09 U (−2.91 to +0.73 [*P* = .24]); −12.15% (−20.79 to −3.51 [*P* = .006]) |
| Garg et al[39] (inTandem3)/ NCT02531035 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study; n = 1402 (24 weeks) | Sotagliflozin 400 mg: −5.25 U/d (−6.67 to −3.83 [*P* < .001]); −9.71% (−12.30 to −7.12 [*P* < .001]) | Sotagliflozin 400 mg: −2.60 U/d (−3.39 to −1.81 [*P* < .001]); −9.88% (−13.75 to −6.00 [*P* < .001]) | Sotagliflozin 400 mg: −2.84 U/d (−4.05 to −1.64 [*P* < .001]); −12.32% (−18.17 to −6.48 [*P* < .001]) |

Abbreviations: BL, baseline; CI, confidence interval; DEPICT, Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes; EASE, Empagliflozin as Adjunctive to Insulin Therapy; NR, not reported; RCTs, randomized controlled trials; SGLT, sodium-glucose co-transporter.

[a]Phase 2 and 3 RCTs of ≥4 weeks that included >50 patients.

[b]Treatment differences and confidence intervals not reported.

**TABLE 3** Rates of hypoglycaemia, genital infections, and urinary tract infections with SGLT-2 inhibitors and SGLT-1/2 inhibitors as an adjunct to insulin in RCTs[a]

| Study/NCT identifier | Study design (duration) | Hypoglycaemia by treatment, n/N (%) | Severe hypoglycaemia by treatment, n/N (%) | Genital infections by treatment, n/N (%)[b] | Urinary tract infections by treatment (%) |
|---|---|---|---|---|---|
| Dapagliflozin | | | | | |
| Dandona et al,[31] Dandona et al[32] (DEPICT-1)/ NCT02268214 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study (52 weeks [24 weeks + 28 week extension]) | 24 weeks<br>Dapagliflozin 5 mg: 220/277 (79.4%)<br>Dapagliflozin 10 mg: 235/296 (79.4%)<br>Placebo: 207/260 (79.6%) | 24 weeks<br>Dapagliflozin 5 mg: 21/277 (7.6%)<br>Dapagliflozin 10 mg: 19/296 (6.4%)<br>Placebo: 19/260 (7.3%) | 24 weeks<br>Women:<br>Dapagliflozin 5 mg: 25/158 (15.8%)<br>Dapagliflozin 10 mg: 23/144 (16.0%)<br>Placebo: 7/128 (5.5%)<br>Men:<br>Dapagliflozin 5 mg: 9/119 (7.6%)<br>Dapagliflozin 10 mg: 10/152 (6.6%)<br>Placebo: 0/132 (0.0%) | 24 weeks<br>Dapagliflozin 5 mg: 19/277 (6.9%)<br>Dapagliflozin 10 mg: 11/296 (3.7%)<br>Placebo: 13/260 (5.0%) |
| | | 52 weeks<br>Dapagliflozin 5 mg: 227/277 (81.9%)<br>Dapagliflozin 10 mg: 241/296 (81.4%)<br>Placebo: 212/260 (81.5%) | 52 weeks<br>Dapagliflozin 5 mg: 29/277 (10.5%)<br>Dapagliflozin 10 mg: 25/296 (8.4%)<br>Placebo: 30/260 (11.5%) | 52 weeks[c]<br>Women:<br>Dapagliflozin 5 mg: 21.5%<br>Dapagliflozin 10 mg: 18.8%<br>Placebo: 6.3%<br>Men:<br>Dapagliflozin 5 mg: 7.6%<br>Dapagliflozin 10 mg: 8.6%<br>Placebo: 0.0% | 52 weeks<br>Dapagliflozin 5 mg: 32/277 (11.6%)<br>Dapagliflozin 10 mg: 16/296 (5.4%)<br>Placebo: 21/260 (8.1%) |
| Mathieu et al[33] (DEPICT-2)/ NCT02460978 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study (24 weeks) | Dapagliflozin 5 mg: 223/271 (82.3%)<br>Dapagliflozin 10 mg: 231/270 (85.6%)<br>Placebo: 234/272 (86.0%) | Dapagliflozin 5 mg: 17/271 (6.3%)<br>Dapagliflozin 10 mg: 23/270 (8.5%)<br>Placebo: 21/272 (7.7%) | Women[c]<br>Dapagliflozin 5 mg: 15.7%<br>Dapagliflozin 10 mg: 12.8%<br>Placebo: 3.3%<br>Men[c]<br>Dapagliflozin 5 mg: 2.5%<br>Dapagliflozin 10 mg: 1.7%<br>Placebo: 0.0% | Dapagliflozin 5 mg: 18/271 (6.6%)<br>Dapagliflozin 10 mg: 10/270 (3.7%)<br>Placebo: 12/272 (4.4%) |
| Empagliflozin | | | | | |
| Pieber et al[34] (EASE-1)/ NCT01969747 | Double-blind, randomized, parallel-group, placebo-controlled, dual-centre phase 2 study (4 weeks) | Empagliflozin 2.5 mg: 16/19 (84.2%)<br>Empagliflozin 10 mg: 13/19 (68.4%)<br>Empagliflozin 25 mg: 17/18 (94.4%)<br>Placebo: 17/19 (89.5%) | Empagliflozin 2.5 mg: 0/19 (0.0%)<br>Empagliflozin 10 mg: 0/19 (0.0%)<br>Empagliflozin 25 mg: 0/18 (0.0%)<br>Placebo: 1/19 (5.3%) | Empagliflozin 2.5 mg: 0/19 (0.0%)<br>Empagliflozin 10 mg: 0/19 (0.0%)<br>Empagliflozin 25 mg: 0/18 (0.0%)<br>Placebo: 0/19 (0.0%) | Empagliflozin 2.5 mg: 0/19 (0.0%)<br>Empagliflozin 10 mg: 0/19 (0.0%)<br>Empagliflozin 25 mg: 1/18 (5.6%)<br>Placebo: 0/19 (0.0%) |
| Rosenstock et al[35] (EASE-2)/ NCT02414958 (EASE-3)/ NCT02580591 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 studies (EASE-2: 52 weeks; EASE-3: 26 weeks) | Overall incidence NR | EASE-2 and EASE-3 pooled<br>Empagliflozin 10 mg: 20/491 (4.1%)<br>Empagliflozin 25 mg: 13/489 (2.7%)<br>Placebo: 15/484 (3.1%) | EASE-2 and EASE-3 pooled<br>Empagliflozin 10 mg: 63/491 (12.8%)<br>Empagliflozin 25 mg: 70/489 (14.3%)<br>Placebo: 21/484 (4.3%) | EASE-2 and EASE-3 pooled<br>Empagliflozin 10 mg: 47/491 (9.6%)<br>Empagliflozin 25 mg: 41/489 (8.4%)<br>Placebo: 41/484 (8.5%) |
| | | | EASE-3<br>Empagliflozin 2.5 mg: 3/241 (1.2%)<br>Placebo: 6/241 (2.5%) | EASE-3<br>Empagliflozin 2.5 mg: 13/241 (5.4%)<br>Placebo: 6/241 (2.5%) | EASE-3<br>Empagliflozin 2.5 mg: 13/241 (5.4%)<br>Placebo: 11/241 (4.6%) |

**TABLE 3** (Continued)

| Study/NCT identifier | Study design (duration) | Hypoglycaemia by treatment, n/N (%) | Severe hypoglycaemia by treatment, n/N (%) | Genital infections by treatment, n/N (%)[b] | Urinary tract infections by treatment (%) |
|---|---|---|---|---|---|
| Canagliflozin | | | | | |
| Henry et al[36]/ NCT02139943 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 2 study (18 weeks) | Canagliflozin 100 mg: 115/117 (98.3%)<br>Canagliflozin 300 mg: 116/117 (99.1%)<br>Placebo: 113/117 (96.6%) | Canagliflozin 100 mg: 3/117 (2.6%)<br>Canagliflozin 300 mg: 8/117 (6.8%)<br>Placebo: 2/117 (1.7%) | Women:<br>Canagliflozin 100 mg: 2/117 (4.2%)<br>Canagliflozin 300 mg: 11/117 (21.2%)<br>Placebo: 3/117 (5.6%)<br>Men:<br>Canagliflozin 100 mg: 0/117 (0.0%)<br>Canagliflozin 300 mg: 0/117 (0.0%)<br>Placebo: 0/117 (0.0%) | Canagliflozin 100 mg: 5/117 (4.3%)<br>Canagliflozin 300 mg: 6/117 (5.1%)<br>Placebo: 2/117 (1.7%) |
| Sotagliflozin | | | | | |
| Buse et al[37] (inTandem1)/ NCT02384941 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (52 weeks) | Sotagliflozin 200 mg: 260/263 (98.9%)<br>Sotagliflozin 400 mg: 258/262 (98.5%)<br>Placebo: 266/268 (99.3%) | Sotagliflozin 200 mg: 17/263 (6.5%)<br>Sotagliflozin 400 mg: 17/262 (6.5%)<br>Placebo: 26/268 (9.7%) | Sotagliflozin 200 mg: 24/263 (9.1%)<br>Sotagliflozin 400 mg: 34/262 (13.0%)<br>Placebo: 9/268 (3.4%) | Sotagliflozin 200 mg: 26/263 (9.9%)<br>Sotagliflozin 400 mg: 11/262 (4.2%)<br>Placebo: 19/268 (7.1%) |
| Danne et al[38] (inTandem2)/ NCT02421510 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (52 weeks) | Sotagliflozin 200 mg: 255/261 (97.7%)<br>Sotagliflozin 400 mg: 260/263 (98.9%)<br>Placebo: 252/258 (97.7%) | Sotagliflozin 200 mg: 13/261 (5.0%)<br>Sotagliflozin 400 mg: 6/263 (2.3%)<br>Placebo: 13/258 (5.0%) | Sotagliflozin 200 mg: 24/261 (9.2%)<br>Sotagliflozin 400 mg: 29/263 (11.0%)<br>Placebo: 6/258 (2.3%) | Sotagliflozin 200 mg: 11/261 (4.2%)<br>Sotagliflozin 400 mg: 18/263 (6.8%)<br>Placebo: 13/258 (5.0%) |
| Garg et al[39] (inTandem3)/ NCT02531035 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (24 weeks) | Sotagliflozin 400 mg: 673/699 (96.3%)<br>Placebo: 670/703 (95.3%) | Sotagliflozin 400 mg: 21/699 (3.0%)<br>Placebo: 17/703 (2.4%) | Sotagliflozin 400 mg: 45/699 (6.4%)<br>Placebo: 15/703 (2.1%) | Sotagliflozin 400 mg: 25/699 (3.6%)<br>Placebo: 27/703 (3.8%) |

Abbreviations: DEPICT, Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes; EASE, Empagliflozin as Adjunctive to Insulin Therapy; RCTs, randomized controlled trials; SGLT, sodium-glucose co-transporter.

[a]Phase 2 and 3 RCTs of ≥4 weeks that included >50 patients.

[b]Incidence by sex available for some studies.

[c]n/N, not reported.

with dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo (Table 3). Rates of adjudicated DKA were higher with dapagliflozin 5 mg and 10 mg vs placebo (Table 4).

Significant reductions in A1C, body weight, and total daily insulin dose were also observed with dapagliflozin compared to placebo after 24 weeks in DEPICT-2 (n = 813; Tables 1 and 2).[33] In DEPICT-2, it was recommended to reduce the total daily insulin dose by ≤20% upon initiation of dapagliflozin, followed by titration back towards the baseline dose. Greater proportions of patients treated with dapagliflozin 5 or 10 mg had an A1C reduction of ≥0.5% with no severe hypoglycaemic events (39.5% and 41.6%, respectively, vs 20.1% with placebo). The addition of dapagliflozin also improved glycaemic variability and increased TIR vs placebo (Table S1). The safety profile of dapagliflozin in DEPICT-2 was similar to that seen in DEPICT-1 (Tables 3 and 4).

## 2.2 | Empagliflozin

Various doses of empagliflozin (2.5, 10, or 25 mg) were assessed as adjunctive therapy to insulin among 75 patients with T1D in a 4-week phase 2 RCT (EASE-1).[34] The insulin regimen was kept stable for the first week of treatment and was adjusted to achieve optimal glycaemic control according to the investigator's judgment thereafter. Daily urinary glucose excretion increased significantly from baseline with all doses of empagliflozin vs placebo after 1 week, with increases sustained at week 4 (treatment differences, +78.8 to +114.7 g/24 h [$P < .001$ for all]). After 4 weeks, all empagliflozin doses resulted in significantly greater reductions from baseline vs placebo in A1C and body weight (Table 1). The total daily insulin dose significantly decreased with all empagliflozin doses (Table 2), driven by a reduction in the mean bolus insulin dose. No significant differences between

treatment groups were observed for changes in SBP or DBP. EASE-1 also demonstrated improvements in glucose exposure and glycaemic variability with empagliflozin (Table S1).[41] AEs, including hypoglycaemia, were similar across groups, except one patient in the empagliflozin 25-mg group developed a urinary tract infection (Table 3).[34] No DKA was reported (Table 4).

The effects of empagliflozin in T1D were further investigated in two RCTs of similar design (EASE-2 [52 weeks] and EASE-3 [26 weeks]; n = 1707).[35] Insulin therapy was optimized at the investigator's discretion for 6 weeks before randomization, at which time total insulin dose was reduced by 10% among patients with A1C <8.0%. Insulin dosing adjustments continued thereafter as needed. In EASE-2 and EASE-3, empagliflozin 2.5 mg (EASE-3 only), empagliflozin 10 mg, and empagliflozin 25 mg resulted in significant reductions from baseline in A1C and body weight at week 26, which were sustained at week 52 in EASE-2 (Table 1). Empagliflozin was associated with increased TIR and decreased glycaemic variability in both studies (Table S1). Furthermore, empagliflozin significantly reduced total daily insulin usage in EASE-2 and EASE-3, with equivalent reductions in basal/bolus components (Table 2). Significant reductions in BP with empagliflozin were also observed. In EASE-2, week-52 placebo-adjusted reductions in SBP/DBP were −3.4/−1.7 and −4.7/−1.5 mm Hg with empagliflozin 10 and 25 mg, respectively, while in EASE-3 26-week reductions of −2.1/−0.3, −3.9/−1.7, and −3.7/−1.4 mm Hg were observed with empagliflozin 2.5, 10, and 25 mg, respectively.

A pooled analysis of safety data from EASE-2 and EASE-3 showed similar rates of adjudicated severe hypoglycaemia with empagliflozin 10 mg, empagliflozin 25 mg, and placebo, with comparable rates seen in EASE-3 for empagliflozin 2.5 mg and placebo (Table 3).[35] Empagliflozin was associated with more frequent genital infections in the pooled analysis and in EASE-3 (Table 3). Empagliflozin 10 and 25 mg increased the risk of DKA vs placebo, while DKA rates were similar between empagliflozin 2.5 mg and placebo (Table 4). One patient treated with empagliflozin 25 mg had a fatal DKA event related to delayed diagnosis and treatment.

## 2.3 | Canagliflozin

An 18-week phase 2 RCT evaluated the effects of canagliflozin vs placebo as an adjunct to insulin therapy among 351 patients with T1D.[36] To mitigate the risk of hypoglycaemia, patients with A1C ≤8.0% and >8.0% were recommended to reduce their basal insulin dose by 20% and 10%, respectively. During treatment, patients were instructed to adjust insulin dosing according to titration algorithms. At week 18, more patients achieved the primary end point (composite goal of A1C reduction ≥0.4% with no increase in body weight) with canagliflozin 100 or 300 mg vs placebo (36.9% and 41.4% vs 14.5%, respectively [$P < .001$]). Consistent with this result, canagliflozin 100 and 300 mg resulted in greater placebo-subtracted reductions in A1C and body weight (Table 1). The addition of canagliflozin led to reductions in total daily insulin dose and basal/bolus doses (Table 2). Rates of overall hypoglycaemia were similar with canagliflozin or placebo, with a low incidence of severe hypoglycaemia (Table 3). However, canagliflozin was associated with an increased incidence of genital mycotic infections in women and urinary tract infections overall (Table 3). Patients receiving canagliflozin 100 and 300 mg also had higher rates of osmotic diuresis-related AEs (7.7% and 9.4% vs 2.6% with placebo) and volume depletion-related AEs (3.4% and 0.9% vs 0.0%). Treatment with canagliflozin 100 and 300 mg was associated with an increased risk of ketone-related AEs (5.1% and 9.4%, respectively, vs 0.0% with placebo), including DKA (Table 4).

In a post hoc analysis of this study, patients' satisfaction with their treatment before and after treatment was assessed using the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) and change (DTSQc) versions.[42] At 18 weeks, patients treated with canagliflozin 100 or 300 mg experienced larger changes in DTSQc scores vs placebo (+12.1 and +12.8, respectively, vs +7.3 with placebo) and greater proportions of patients treated with canagliflozin showed any improvement in treatment satisfaction (93.6% and 98.2%, respectively, vs 80.6% with placebo). A subset of patients (n = 89) also underwent continuous glucose monitoring (CGM) to determine the effects of canagliflozin on glycaemic variability, with significant improvements observed for canagliflozin (Table S1).

## 2.4 | Sotagliflozin

To date, three large phase 3 RCTs in the inTandem clinical programme have evaluated the efficacy and safety of sotagliflozin combined with insulin therapy for the treatment of patients with T1D. The international inTandem3 trial (n = 1402) assessed the effects of sotagliflozin 400 mg added to insulin.[39] Upon initiation of sotagliflozin, patients received a 30% lower dose of mealtime insulin at their first meal, after which investigators adjusted insulin doses according to titration algorithms. In the North American inTandem1 trial (n = 793), patients had their insulin therapy optimized according to fasting and postprandial glucose targets for 6 weeks before randomization to sotagliflozin 200 or 400 mg, with insulin dosing adjustments continuing throughout the trial.[37] The inTandem2 trial (n = 782) was a study of similar design to inTandem1, but undertaken at multiple sites in Europe.[38]

In the inTandem3 trial, a larger proportion of patients receiving sotagliflozin 400 mg vs placebo achieved the composite goal of A1C <7.0% with no episodes of severe hypoglycaemia or DKA after 24 weeks (28.6% vs 15.2%, respectively [$P < .001$]).[39] Sotagliflozin-treated patients had greater reductions from baseline in A1C and body weight (Table 1), as well as reductions in SBP (treatment difference vs placebo, −3.8 mm Hg; $P < .001$) and DBP (−1.3 mm Hg; $P < .001$). Reductions in total daily insulin dose, basal insulin dose, and bolus insulin dose with sotagliflozin were also observed (Table 2). Rates of overall hypoglycaemia were similar for patients treated with sotagliflozin or placebo, as were rates of adjudicated severe hypoglycaemia (Table 3). However, sotagliflozin was associated with a higher rate of adjudicated DKA (Table 4), as well as genital mycotic infections (Table 3). Sotagliflozin was also associated with an increased incidence of diarrhoea (4.1% vs 2.3% with placebo) and volume depletion (1.9% vs 0.3%).

**TABLE 4** Rates of DKA with SGLT-2 inhibitors and SGLT-1/2 inhibitors as an adjunct to insulin in RCTs[a]

| Study/NCT identifier | Study design (duration) | DKA risk mitigation strategies employed | Definition of DKA | DKA occurrence by treatment, n/N (%) |
|---|---|---|---|---|
| Dapagliflozin | | | | |
| Dandona et al,[31] Dandona et al[32] (DEPICT-1)/ NCT02268214 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study (52 weeks [24 weeks +28 week extension]) | Patients were advised on how to identify symptoms of DKA, and provided with blood ketone meters and instructions for use<br>Investigators were educated on management of ketonaemia to help halt progression to DKA | Potential DKA was identified based on symptoms, diagnoses, or home ketone values and review of AEs<br>Definite DKA determined by independent blinded adjudication committee based on laboratory criteria of acidosis (venous pH <7.3 and/or serum bicarbonate ≤18 mEq/L) and symptoms/signs according to the ADA consensus statement on diagnosis of DKA[40] | *24 weeks*<br>Dapagliflozin 5 mg: 4/277 (1.4%)<br>Dapagliflozin 10 mg: 5/296 (1.7%)<br>Placebo: 3/260 (1.2%)<br>*52 weeks*<br>Dapagliflozin 5 mg: 11/277 (4.0%)<br>Dapagliflozin 10 mg: 10/296 (3.4%)<br>Placebo: 5/260 (1.9%) |
| Mathieu et al[33] (DEPICT-2)/ NCT02460978 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 study (24 weeks) | Patients were advised on how to identify and manage symptoms of DKA, and provided with blood ketone meters and instructions for use | Potential DKA was identified based on symptoms, diagnoses, or home ketone values and review of AEs<br>Definite DKA confirmed by independent blinded adjudication committee based on acidosis (blood pH <7.3 and/or serum bicarbonate ≤18 mEq/L) and symptoms/signs according to the ADA consensus statement on diagnosis of DKA[40] | Dapagliflozin 5 mg: 7/271 (2.6%)<br>Dapagliflozin 10 mg: 6/270 (2.2%)<br>Placebo: 0/272 (0.0%) |
| Empagliflozin | | | | |
| Pieber et al[34] (EASE-1)/ NCT01969747 | Double-blind, randomized, parallel-group, placebo-controlled, dual-centre phase 2 study (4 weeks) | Patients were asked to record their blood ketone concentrations | Not defined in the publication | Empagliflozin 2.5 mg: 0/19 (0.0%)<br>Empagliflozin 10 mg: 0/19 (0.0%)<br>Empagliflozin 25 mg: 0/18 (0.0%)<br>Placebo: 0/19 (0.0%) |
| Rosenstock et al[35] (EASE-2)/ NCT02414958 (EASE-3)/ NCT02580591 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre, phase 3 studies (EASE-2: 52 weeks; EASE-3: 26 weeks) | Patients were provided with blood BHB meters; patients were educated on signs and symptoms of DKA, ketone monitoring, and to seek medical care in case of increased BHB (>1.5 mmol/L)<br>Investigators received recommendations on prevention and diagnosis of DKA | Potential DKA was identified based on symptoms, blood BHB values, and review of ketoacidosis-related AEs<br>Definite DKA determined by an independent blinded adjudication committee based on confirmed ketosis (BHB >1.5 mmol/L or urine ketones) plus confirmed acidosis (blood pH ≤7.3; bicarbonate <15 mEq/L) | *EASE-2 and EASE-3 pooled*<br>Empagliflozin 10 mg: 21/491 (4.3%)<br>Empagliflozin 25 mg: 16/489 (3.3%)<br>Placebo: 6/484 (1.2%)<br>*EASE-3*<br>Empagliflozin 2.5 mg: 2/241 (0.8%)<br>Placebo: 3/241 (1.2%) |
| Canagliflozin | | | | |
| Henry et al[36]/ NCT02139943 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 2 study (18 weeks) | Not reported in the publication | DKA AE (classified using a pre-specified list of preferred terms) requiring hospitalization | Canagliflozin 100 mg: 5/117 (4.3%)<br>Canagliflozin 300 mg: 7/117 (6.0%)<br>Placebo: 0/117 (0.0%) |

**TABLE 4** (Continued)

| Study/NCT identifier | Study design (duration) | DKA risk mitigation strategies employed | Definition of DKA | DKA occurrence by treatment, n/N (%) |
|---|---|---|---|---|
| Sotagliflozin | | | | |
| Buse et al[37] (inTandem1)/ NCT02384941 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (52 weeks) | Patients were provided with urine ketone strips, blood BHB meters and strips, and information on identifying and treating ketosis<br>Investigators received recommendations on diagnosis and management of ketosis and DKA | Potential DKA identified by symptoms, blood ketone values, and searching ketosis-related AE terms<br>DKA was diagnosed based on anion-gap metabolic acidosis related to excessive ketone production without a satisfactory alternative cause[40]<br>Definite DKA confirmed by an independent blinded adjudication committee | Sotagliflozin 200 mg: 9/263 (3.4%)<br>Sotagliflozin 400 mg: 11/262 (4.2%)<br>Placebo: 1/268 (0.4%) |
| Danne et al[38] (inTandem2)/ NCT02421510 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (52 weeks) | Patients were provided with urine ketone strips, blood BHB meters and strips, and information on identifying and treating ketosis<br>Investigators received recommendations on diagnosis and management of ketosis and DKA | Potential DKA identified by symptoms, blood ketone values, and searching ketosis-related AE terms<br>DKA was diagnosed based on anion-gap metabolic acidosis related to excessive ketone production without a satisfactory alternative cause[40]<br>Definite DKA confirmed by an independent blinded adjudication committee | Sotagliflozin 200 mg: 6/261 (2.3%)<br>Sotagliflozin 400 mg: 9/263 (3.4%)<br>Placebo: 0/258 (0.0%) |
| Garg et al[39] (inTandem3)/ NCT02531035 | Double-blind, randomized, parallel-group, placebo-controlled, multicentre phase 3 study (24 weeks) | Patients were provided with urine ketone strips, blood BHB meters and strips, and information on identifying and treating ketosis<br>Investigators received recommendations on diagnosis and management of ketosis and DKA | Potential DKA identified by symptoms, blood ketone values, and searching ketosis-related AE terms<br>DKA was diagnosed based on anion-gap metabolic acidosis related to excessive ketone production without a satisfactory alternative cause[40]<br>Definite DKA confirmed by an independent blinded adjudication committee | Sotagliflozin 400 mg: 21/699 (3.0%)<br>Placebo: 4/703 (0.6%) |

Abbreviations: ADA, American Diabetes Association; AE, adverse event; BHB, beta-hydroxybutyrate; DEPICT, Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes; DKA, diabetic ketoacidosis; EASE, Empagliflozin as Adjunctive to Insulin Therapy; RCTs, randomized controlled trials; SGLT, sodium-glucose co-transporter.

[a]Phase 2 and 3 RCTs of ≥4 weeks that included >50 patients.

In the inTandem1 trial, the addition of sotagliflozin following insulin optimization resulted in significant reductions from baseline in A1C at week 24, which were sustained at week 52 (Table 1).[37] In a substudy (n = 136), sotagliflozin 400 mg significantly decreased measures of glycaemic variability (Table S1). Both doses of sotagliflozin significantly reduced total daily insulin usage at 24 and 52 weeks, with reductions observed for basal and bolus insulin doses (Table 2). Body weight decreased with sotagliflozin 200 mg (Table 1), and significant reductions in BP were also observed. Placebo-adjusted reductions in SBP at week 52 were −2.8 mm Hg ($P = .005$) and −4.4 mm Hg ($P < .001$) with sotagliflozin 200 and 400 mg, respectively. Corresponding changes in DBP were −1.4 mm Hg ($P = .020$) and −2.3 mm Hg ($P < .001$), respectively. At 24 weeks, sotagliflozin was associated with a greater increase in treatment satisfaction assessed by the DTSQs scale (placebo-adjusted difference, +2.5 points with either dose [both $P < .001$]) and a greater reduction in the Diabetes Distress Screening Scale score (sotagliflozin 200 mg, −0.7; sotagliflozin 400 mg, −0.8 [both $P < .001$]). The incidence of overall hypoglycaemia was similar across groups, as was adjudicated severe hypoglycaemia (Table 3). However, sotagliflozin 200 and 400 mg were associated with increased frequencies of diarrhoea (8.4% and 10.3% vs 6.7% with placebo) and genital mycotic infections (Table 3).

Adjudicated DKA was also more common with sotagliflozin vs placebo (Table 4).

In the inTandem2 trial, sotagliflozin 200 and 400 mg resulted in significant reductions from baseline in A1C (Table 1).[38] A 24-week CGM substudy of inTandem2 (n = 142) showed reductions in glycaemic variability with sotagliflozin (Table S1). Sotagliflozin reduced total daily insulin usage, with more prominent reductions in bolus insulin compared with basal insulin (Table 2). Body weight decreased with both doses of sotagliflozin (Table 1). Reductions in SBP were observed at 52 weeks for sotagliflozin 200 mg (−3.0 mm Hg [$P$ = .002]) and 400 mg (−2.8 mm Hg [$P$ = .003]). At 24 weeks, patients treated with sotagliflozin had greater increases in treatment satisfaction relative to placebo, as assessed by the DTSQs scale (sotagliflozin 200 mg, +2.0; sotagliflozin 400 mg, +1.7 [both $P$ < .001]), and greater reductions relative to placebo in the Diabetes Distress Screening Scale score (200 mg, −0.3 [$P$ = .025]; 400 mg, −0.4 [$P$ = .003]). Hypoglycaemia occurred frequently across all treatment groups, although rates of adjudicated severe hypoglycaemia were low (Table 3). Sotagliflozin 200 and 400 mg were associated with higher rates of diarrhoea (4.6% and 7.2%, respectively, vs 3.5% with placebo) and genital mycotic infections (Table 3). Adjudicated DKA also occurred more frequently with sotagliflozin vs placebo (Table 4).

## 3 | DKA RISK

As summarized thus far, although the incidence of DKA was low overall, SGLT-2 inhibitors and SGLT-1/2 inhibitors were associated with an increased risk of DKA when added to insulin in patients with T1D (Table 4). Furthermore, reports of DKA among patients with T1D treated with SGLT-2 inhibitors have been noted in case studies.[43-47] The prescribing information for each SGLT-2 inhibitor approved for T2D also contains a warning regarding the risk of DKA.[21-24] Thus, clinicians and investigators are interested in learning more regarding the potential risk of DKA with this drug class and strategies for mitigating risk.

DKA risk was assessed in a post hoc analysis of an 18-week study of canagliflozin added to insulin in patients with T1D.[48] Patients treated with canagliflozin 100 or 300 mg had an increased incidence of any ketone-related AE (5.1% and 9.4%, respectively, vs 0.0% with placebo). Demographic and disease characteristics at baseline were similar among patients with and without a ketone-related AE, as was weight reduction at week 18. Serious AEs of DKA occurred in 4.3% and 6.0% of patients treated with canagliflozin 100 and 300 mg, respectively. Serious DKA events were concomitant with circumstances known to precipitate DKA, such as infection, reduction in insulin dose due to pump failure or poor adherence, and reduced carbohydrate intake. However, data on changes in insulin dose at the time of serious DKA events were unavailable.

In EASE-2 and EASE-3, DKA was associated with precipitating factors, including concomitant illness/infection or reduced insulin intake.[35] A subgroup analysis identified female sex and insulin pump use as important baseline risk factors for DKA.

Blau et al examined cases of acidosis reported with canagliflozin, dapagliflozin, or empagliflozin from the date of drug approval through 15 May 2015, in a search of the US Food and Drug Administration Adverse Event Reporting System.[49] The search yielded 259 reports of acidosis (192 reports of ketoacidosis) for SGLT-2 inhibitors, although these records included patients with T2D as well as T1D. Quantifiable metabolic information supporting a diagnosis of ketoacidosis was available for 51 of these reports, 20 cases of which occurred in patients with T1D.

Thus, accumulated evidence supports an association between the use of SGLT-2 inhibitors or SGLT-1/2 inhibitors as adjunctive therapy to insulin with DKA in patients with T1D. However, implementation of risk reduction strategies upon initiating these agents may help reduce the incidence of DKA. To this end, patient and provider education should include guidance on insulin titration, the possibility of euglycaemic DKA, and precipitating factors for DKA. A reasonable insulin titration strategy, based on the DEPICT-1 trial, would be to reduce insulin doses by no more than 20% with initiation of SGLT-2 inhibitors and SGLT-1/2 inhibitors, followed by titration back towards the initial insulin dose. Furthermore, insulin dose reduction may be individualized and differ depending on the patient's degree of glycaemic control. For example, in the canagliflozin study reported by Henry et al, insulin dose reductions of 20% and 10% were recommended for patients with A1C ≤8.0% and >8.0%, respectively.[36] Patients should also be educated on the possibility of euglycaemic DKA, and physicians should recommend that patients test their ketones. Patients should be made aware of precipitating factors for DKA, including acute illness and infections, heavy alcohol intake, strenuous exercise, decreased carbohydrate intake, and insufficient insulin dosing (eg, missed doses or pump failure). Patients should be instructed to check ketones and potentially withhold SGLT-2 inhibitors or SGLT-1/2 inhibitors if they feel ill or if one of the above risk factors is present. If ketones are elevated, patients should increase fluid and carbohydrate intake, as well as insulin doses. The patient should seek immediate medical care if ketone levels do not normalize or if the patient experiences symptoms of DKA, including vomiting and the inability to take in fluids.

In addition to the above suggestions for mitigating DKA risk, we recommend that guidelines for uniform DKA risk mitigation be developed to assist providers prescribing this drug class to these patients. Importantly, an international consensus committee recently provided recommendations for mitigating DKA risk, including appropriate patient selection, insulin dose adjustments, initiation and dosing of SGLT-2 inhibitors and SGLT-1/2 inhibitors, and ketone monitoring, as well as discontinuation of these agents in the case of DKA and treatment of DKA.[50]

## 4 | CLINICAL IMPLICATIONS

Positive results from clinical trials of SGLT-2 inhibitors and an SGLT-1/2 inhibitor for patients with T1D have led to new recommendations issued by regulatory agencies in Europe and the United States. The

European Medicines Agency Committee for Medicinal Products for Human Use (CMPH) recommended approving sotagliflozin and extending the indication of dapagliflozin, each as an adjunct to insulin, in adults with T1D having body mass index (BMI) ≥27 kg/m$^2$ in whom insulin does not provide adequate glycaemic control despite optimization of therapy.[51,52] In March 2019, the European Commission approved dapagliflozin for use in patients with T1D as indicated above,[53] while the decision on sotagliflozin is pending. Likewise, the Japanese Ministry of Health, Labour, and Welfare approved dapagliflozin as an adjunct to insulin for adults with T1D.[54] Another SGLT-2 inhibitor used for the treatment of T2D in Japan, ipragliflozin, was approved for a T1D indication in late 2018.[55] In early 2019, the US Food and Drug Administration's (FDA) Endocrinologic and Metabolic Drugs Advisory Committee delivered a tie vote on the use of sotagliflozin as an adjunct to insulin in patients with T1D, in whom optimal control of blood glucose levels is not achieved with insulin alone.[56,57] A key point of consideration involved discussion of the benefits of sotagliflozin weighed against the risk of DKA, including appropriate selection of patients and whether the risk of DKA can be mitigated in the real world. However, the US FDA ultimately declined to approve sotagliflozin as an adjunct to insulin in patients with T1D.[58]

Given the apparent increased risk of DKA with SGLT-2 inhibitor and SGLT-1/2 inhibitor use in T1D, it will be imperative to carefully select the patients in whom these medications will be prescribed. There is little direct evidence to help define the ideal patient population, but the risk factors that drive DKA in patients taking these medications are likely similar to those in the general T1D population. Thus, fundamental guidelines for patient selection can be suggested. If approved, SGLT inhibitors should be considered in patients with T1D who have demonstrated both adherence to their prescribed insulin regimen, and the ability to understand and utilize relevant education relating to DKA risk and risk mitigation strategies. These medications should be avoided in patients who have had recent or recurrent DKA, who have difficulty adhering to the prescribed insulin regimen, or who have difficulty processing or synthesizing relevant diabetes-related information.

Due to the associated weight loss, SGLT-2 inhibitors and SGLT-1/2 inhibitors may particularly benefit those who are overweight or obese. The majority of patients in the studies reviewed herein had a BMI in the overweight or obese ranges, representative of the general adult T1D population.[59,60] It is unclear whether higher BMI is associated with a decreased risk of DKA in patients taking these medications, and data addressing this question would be welcome. Further research is also needed to better characterize other DKA risk factors during SGLT-2 inhibitor and SGLT-1/2 inhibitor use, and to evaluate the efficacy of specific risk mitigation strategies, including insulin dose titration and ketone testing.

## 5 | CONCLUSIONS

While insulin regimens remain the mainstay of treatment for T1D, emerging clinical data demonstrate beneficial effects of adjunctive treatment with SGLT-2 inhibitors and SGLT-1/2 inhibitors for patients with T1D. Across RCTs, the addition of these agents to insulin showed glycaemic improvements for patients with T1D, including reductions in A1C, glucose exposure, and measures of glycaemic variability, and increased TIR. Furthermore, SGLT-2 inhibitors and SGLT-1/2 inhibitors showed non-glycaemic benefits, including reductions in body weight and total daily insulin dose, and improvements in some cardiovascular risk factors. Although data were limited to a few studies, patient-reported satisfaction with treatment also improved with adjunctive treatment.

Safety data showed no increased risk of hypoglycaemia with the addition of SGLT-2 inhibitors or SGLT-1/2 inhibitors to insulin treatment. However, the benefits of adding these agents for patients with T1D must be weighed against the increased risk of DKA. Careful monitoring of ketones and implementing moderate reductions in insulin dose (≤20%) when initiating SGLT-2 and SGLT-1/2 inhibitors may help reduce the risk of DKA. Physicians should inform patients of the potential risk of DKA and provide education on risk mitigation.

Thus, evidence from RCTs of up to 1 year demonstrated that SGLT-2 inhibitors and SGLT-1/2 inhibitors as adjunctive therapy to insulin provided additional glycaemic and non-glycaemic benefits for patients with T1D. Longer-term randomized trials and extension studies are needed to determine the long-term outcomes with adjunctive treatment with these agents for patients with T1D.

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## CONFLICT OF INTEREST

S.V.E. has served on medical advisory boards for BrightSight, InPen (Companion Medical), Lexicon Pharmaceuticals, and Novo Nordisk; on medical advisory boards and speaker's bureaus for AstraZeneca, Lilly USA, MannKind, Merck, and Sanofi-Aventis; and is a board member of Senseonics and the Team Type 1 Foundation. S.B. declares no competing interests.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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