Sodium-Glucose Transporter Inhibition in Pediatric Type 1 Diabetes Mellitus

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Abstract

Adjunctive therapies to insulin in the treatment of type 1 diabetes mellitus (T1D) have gained popularity in efforts to achieve glycemic targets, and sodium-glucose transporter inhibitors (SGLT inhibitors) are an appealing option due to associated weight loss, low risk of hypoglycemia, and significant improvements in cardiorenal outcomes seen in persons with type 2 diabetes mellitus (T2D). The increased risk of diabetic ketoacidosis (DKA), including euglycemic DKA, has led many to be wary of their use in T1D, especially given limited data regarding cardiorenal protection in this population and limited pediatric data overall. The phase 3 trials of these agents in T1D have yielded lower HbA1c, decreased total daily insulin dose, and small but significant weight loss with no increase in hypoglycemia. These trials also reported increased risks of genital mycotic infection and DKA. SGLT inhibitors have been approved as adjunctive therapy to insulin in adults with T1D in Europe and Japan, but the United States Food and Drug Administration has rejected similar applications. While several approaches to mitigate the risk of DKA have been developed, no randomized trials using such tools have been conducted. More research is needed to minimize risk of DKA and to better evaluate the cardiorenal impact of these agents in persons with T1D.

Keywords

sodium-glucose transporter 2 inhibitors; type 1 diabetes mellitus; glycemic control; diabetic ketoacidosis; cardiorenal benefits

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Introduction

While insulin therapy is the cornerstone of treatment for type 1 diabetes mellitus (T1D), adjunctive therapies have gained popularity over the last decade in efforts to reach target glycemic control. Among the available medications, sodium-glucose transporter (SGLT) inhibitors are an appealing option due to their favorable side effect profile and compelling data regarding non-glycemic benefits of therapy, though there are significant concerns regarding risk for diabetic ketoacidosis (DKA). Here, we will review the data regarding the use of SGLT inhibitors in T1D and in the pediatric population along with identification of future directions for investigation.

Physiology of SGLT inhibition

The SGLT receptors are sodium-glucose cotransporters located in the GI tract (SGLT1) and kidney (SGLT1 and SGLT2). Most SGLT-active drugs are SGLT2 inhibitors, and work in the proximal tubule of the kidney to block the reuptake of glucose, which is filtered into the urine, leading to its excretion[1]. Prolonged hyperglycemia leads to hyperfiltration due to suppressed tubuloglomerular feedback from decreased sodium delivery to the distal tubule. Treatment with SGLT2 inhibitors increases the distal sodium delivery, which leads to increased sodium reabsorption at the macula densa, restored tubuloglomerular feedback, and vasoconstriction in the kidney. This mechanism explains the initial drop in glomerular filtration rate (GFR) that is seen when these medications are initiated, as well as the decrease in albumin excretion due to decreased glomerular pressure[2]. Increased distal sodium delivery causes increased naturiesis, which may be responsible for decreasing oxygen consumption in the kidney. This is associated with improved long-term kidney outcomes[3].

The amount of glucose lowering achieved by SGLT2 inhibition depends on the amount of glucose filtered, which in turn is impacted by the degree of hyperglycemia and the GFR in the kidney[3]. The glucose-lowering effect of these agents is minimal in patients with chronic kidney disease (CKD) stage 3 or higher, due to GFR impairment[2]. The mechanism of the profound cardiac and kidney effects, however, may be unrelated to the glycemic impact and may be related to the effects of inhibition of sodium reabsorption[2].

The mechanism of the kidney hemodynamic effects of SGLT inhibition may differ between persons with T1D and type 2 diabetes mellitus (T2D). In younger people with T1D, SGLT2 inhibition leads to afferent arteriolar vasoconstriction and a decrease in GFR related to increased distal tubule sodium delivery, as outlined above, while older people with T2D may have prostaglandin-mediated efferent arteriolar vasodilation, which improves vascular resistance in the kidney.[2,3]

Sotagliflozin is a unique SGLT inhibitor, which inhibits both SGLT1 and SGLT2, decreasing glucose absorption in the GI tract through the SGLT1 mechanism in addition to the effects of SGLT2 inhibition in the kidney (of note, the impact on the SGLT1 receptors in the kidney is minimal)[4]. This can help to mitigate the postprandial blood glucose peak, and the dual mechanism of this drug was specifically designed for people with T1D. As SGLT1

inhibition leads to increased glucose excretion through the GI tract, this class of medications can cause diarrhea as well as the side effects of SGLT2 inhibition discussed below.

Rationale and prevalence of SGLT inhibitor use in T1D

T1D is characterized by absolute insulin deficiency and must be treated with insulin. As the adverse secondary effects of insulin, such as hypoglycemia and weight gain, are dose-dependent, clinicians and people with T1D have begun to seek adjunctive therapies to reduce insulin requirements while also aiming to achieve glycemic targets.

The appeal of SGLT inhibition in T1D is clear. As the mechanism of action is independent of insulin, it should be just as effective in persons with T1D as in persons with T2D. Common secondary effects include modest weight loss and modest lowering of systolic blood pressure with minimal increase in risk of hypoglycemia[2]. Patients with T1D taking SGLT inhibitors have been able to reduce total daily insulin usage by 10–15%[2]. Additionally, recent trials of patients with T2D have revealed significant reductions in major adverse cardiac event (MACE) endpoints[5–7] and reduced progression of diabetic nephropathy and chronic kidney disease[6–9]. These are also common complications in people with T1D. In a 2016 evaluation of the Type 1 Diabetes Exchange Network data, 17% of older adults with T1D had microalbuminuria and 6% had had a myocardial infarction[10]. Intensive glycemic control alone does not seem to reduce progression to end-stage kidney disease in patients with diabetes who have stage 3 CKD[11]. Thus, there is an unmet need for agents that can modify the risk of progression of these conditions, which could have a significant impact on health outcomes in this population.

The CREDENCE trial showed that canagliflozin was associated with a significant decrease in the composite renal outcome of end-stage kidney disease, doubling of serum creatinine, or kidney-related or cardiovascular death in patients with T2D, with a need to treat 22 patients over 2.5 years in order to prevent one of these events (NNT, number needed to treat)[12]. It was the first trial to include patients with GFR of 30–45 ml/min/1.73m2, and the findings supported continuing patients with GFR <30 ml/min/1.73m2 on canagliflozin until the initiation of kidney replacement therapy or the development of complications. This suggests that, though the glycemic effects of SGLT inhibitors may be limited to patients with preserved GFR, the cardiorenal effects may be mediated by an alternate mechanism that continues to have an impact even as GFR falls[2,12]. As noted above, the mechanism of SGLT2 inhibition on hemodynamics in the kidney differs between older adults with T2D and younger adults with T1D[3]. While many have postulated that the clinical benefits seen in the population with T2D will be transferrable to people with T1D, this remains unstudied and uncertain, especially in pediatrics. The data that does exist on the impact of SGLT inhibitors on kidney outcomes in people with T1D is limited to surrogate outcomes.[13]

Prevalence of adjunctive therapy use

Metformin has been used for decades to impact insulin sensitivity in patients with insulin resistance, some of whom also have insulin deficiency. The newer antihyperglycemic agents have also begun to be used off-label in this population. An analysis of the Type 1 Diabetes Exchange (T1DX) and Prospective Diabetes Follow-up (DPV) registries revealed that 5.4%

of the T1D population in the United States and 1.3% in Germany/Austria, respectively, were using non-insulin antihyperglycemic agents in addition to insulin[14]. Metformin was used most frequently of all agents in both registries, the interpretation of which is complicated given that metformin is also a first line therapy for polycystic ovarian syndrome. SGLT inhibitors were used by 0.63% of the T1DX population and 0.13% of the DPV population[14]. As this analysis was done prior to the publication of most of the kidney and cardiovascular SGLT inhibitor outcomes studies, it is possible that this prevalence is now even higher.

Concerns about SGLT inhibitor use in T1D

While the most common secondary effects of SGLT inhibitors (e.g., related to BP, weight) are largely favorable, there are adverse effects that include increases in genital infections[5–7] and DKA[7,9,15], reported in patients with both T1D and T2D. The increased occurrence of euglycemic DKA (euDKA) without significant hyperglycemia is especially concerning given that normal or modestly elevated glucose levels (i.e., 200 to 300 mg/dL) often lead to a delay in diagnosis and could portend worse outcomes.

DKA is characterized by relative or absolute insulin deficiency, which leads to an increase in counter-regulatory hormones causing hepatic gluconeogenesis, unchecked lipolysis, and free fatty acid-induced insulin resistance.[16] While typically the absence of insulin leads to hyperglycemia, certain conditions such as pregnancy[17] and reduced carbohydrate intake[18] can lead to a lower-than-expected elevation of glucose. The pathophysiology of euDKA in SGLT inhibition relates to the primary mechanism of action of this class of agents. As excess glucose is excreted by the kidney, there is a method in place to lower blood glucose even in settings of absolute insulin deficiency. A recent six-hour insulin pump suspension trial revealed that beta hydroxybutyrate, free fatty acid, and glucagon levels were similar in patients who had taken canagliflozin with those who had not, while the glucose was significantly lower in those taking canagliflozin.[19] These findings suggest that SGLT inhibitors do not directly cause DKA but lead to a delay in the detection of insulin deficiency given the absent or only modest rise in glucose levels. If an individual does not become hyperglycemic, they may not be aware of impending DKA, which could allow progression to DKA in situations where it could otherwise be avoided.

With knowledge of both the potential benefits that could be derived from SGLT inhibitor use in patients with T1D and the significant risk of DKA, the Advanced Technologies and Treatment for Diabetes Congress convened an international panel of experts to determine an International Consensus on Risk Management of DKA in Patients with T1D Treated with SGLT inhibitors[20]. Their recommendations to mitigate the risk of DKA included screening for baseline ketone levels (with blood measurements preferred over urine) prior to starting therapy, decreasing insulin doses by no more than 10–20% at a time, starting with lowest possible dose of SGLT inhibitor, measuring ketones routinely with SGLT inhibitor use even in the absence of symptoms, and educating patients regarding when to stop SGLT inhibitor use along with immediate home management of euglycemic ketosis.[20] Several groups have developed acronyms to educate patients on steps to take if they do develop ketosis. **STICH** stands for STop SGLT inhibitor, inject Insulin, eat 30 grams of Carbohydrates, and Hydrate.[21]**STOP** DKA stands for Stop SGLT inhibitor if symptomatic

with nausea, lethargy, or loss of appetite, Test blood glucose and ketones every 2–4 hours, take Oral fluids and carbohydrates, following the Protocol for amount of carbohydrates to eat and insulin to take.[22] With these steps, along with careful selection of patients who do not have other factors leading to high risk for DKA, such as disordered eating behaviors or low carbohydrate diets, the consensus panel felt that SGLT inhibitors could be safely used in some patient with T1D.

Randomized Trials of SGLT inhibitors in T1D

Given the compelling evidence for benefit in T2D, these agents have been studied in T1D as well. Phase 3 trials of efficacy as an adjunctive therapy to insulin in patients with T1D have been conducted for dapagliflozin, empagliflozin, sotagliflozin, and ipragliflozin[23–25] (Table 1), and canagliflozin was studied in a phase 2 trial[26].

Canagliflozin—One of the first trials to evaluate SGLT inhibitors in T1D was a phase 2 trial in which 351 adults with T1D treated with insulin were randomized to adjunctive therapy with canagliflozin 100 mg, 300 mg, or placebo. Over 18 weeks, mean HbA1c was 0.29% lower in the 100 mg arm and 0.25% lower in the 300 mg arm compared with the placebo group. Significantly more patients in the 100 mg and 300 mg intervention arms achieved the composite endpoint of an HbA1c decrease of 0.4% and no increase in body weight than in the placebo group (36.9%, 41.4%, and 14.5%, respectively). While the rates of hypoglycemia were similar across the three groups, there were dose-dependent increases in ketosis events, DKA, and female genital mycotic infections with the SGLT inhibitor. No data on kidney-related markers were reported.[26] A phase 3 trial of canagliflozin has not been performed.

Dapagliflozin—Dapagliflozin was evaluated in a series of phase 3 studies known as the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT) trials[27–30]. There were two iterations, DEPICT-1 and DEPICT-2, which randomized 833 and 813 participants, respectively, to dapagliflozin 5 mg, 10 mg, or placebo. Both trials followed patients for 24 weeks with more intensive monitoring, followed by a 28-week extension for a total of 52 weeks. HbA1c decreased significantly from baseline compared with placebo in the intervention arms of DEPICT-1 (0.42% and 0.45% for the 5 and 10 mg doses, respectively), but this improvement had lessened by 52 weeks (0.33% and 0.36%, respectively). This may be related to less intensive follow-up during this period and could better reflect real-world outcomes. CGM data were collected at 24 weeks, and there were significant increases in glucose time in range 70–180 mg/dL along with lower mean glucose and tighter mean amplitude of glucose excursion (MAGE). Participants experienced small but statistically significant dose-dependent weight loss, which was maintained or extended at 52 weeks. Total daily insulin dose (TDD) decreased in both groups, in a dose-dependent manner. There was no difference in rates of severe hypoglycemia, but there were four-to-five-fold increases in genital infections and two-to-three-fold increases in DKA[27,28]. These findings were all replicated in the DEPICT-2 trial, which had similar methods[29,30]. Follow up analyses revealed that the 10mg dose was associated with a significant decrease in urine albumin to creatinine ratio of –31.1%; there was no significant change seen in GFR.[13]

Empagliflozin—Empagliflozin was evaluated in people with T1D in the Empagliflozin as Adjunctive to inSulin thErapy (EASE) trials[31]. The 52-week EASE-2 and 26-week EASE-3 studies were phase 3 randomized placebo-controlled trials of empagliflozin 2.5 mg (EASE-3 only), 10 mg, and 25 mg as adjunctive therapy to insulin in adults with T1D. They found significant decreases in HbA1c, body weight, and total daily insulin dose with no increased hypoglycemia. Kidney markers were not evaluated in these trials. The HbA1c improvement at 52 weeks in EASE-2 was somewhat less than was seen at 26 weeks but remained statistically significant; this may reflect more real-world conditions as the study follow up was less intensive in the second half of the follow up. Increases in genital infections and DKA were seen in the intervention arms. The 2.5 mg dose, which was evaluated only in EASE-3, is below the full glucosuric threshold. It is unsurprising, then, that it had more modest (though still statistically significant) improvements in HbA1c and weight loss along with reductions in daily insulin dose. Importantly, it was associated with lower risk of genital infection and DKA; the rate of DKA was actually lower in the 2.5 mg intervention arm than in the placebo arm.[31] This dose may represent a more appealing balance of risk and benefit for patient with T1D.

Ipragliflozin—Ipragliflozin is an SGLT2 inhibitor available in Japan, and a phase 3 randomized trial was conducted to evaluate its efficacy in adults with T1D [25,32]. In total, 175 participants were randomized 2:1 to receive ipragliflozin 50 mg (n=115) or placebo (n=60) and followed for 24 weeks. HbA1c decreased significantly in the treatment group compared with placebo group by an adjusted mean difference of 0.36%, as did body weight and total daily insulin dose. There was no increase in severe hypoglycemia with ipragliflozin but there were increases in genital infections and episodes of ketone-associated events although there were no episodes of DKA reported[25]. A 28-week study extension included 54 participants in the placebo group crossing over to ipragliflozin 50 mg and 112 in the intervention group continuing to receive active drug. Of the 166 participants entering the extension study, 68 had the dose of ipragliflozin increased to 100 mg at 32 weeks if glycemic control was inadequate and there were no safety concerns. Overall, HbA1c levels improved beginning 4 weeks after active drug was initiated, both in the treatment group during the initial trial and in the placebo group that crossed during the extension period. This improvement was maintained through the end of the 52 week study with an overall HbA1c improvement of 0.33% from baseline. There were similar decreases in total daily dose and body weight in the crossover group as was seen in the initial RCT. Occurrence of severe hypoglycemia was low, and no DKA events were reported although genital infections and ketosis events occurred. There were differences in adverse events in those taking 100 mg of ipragliflozin[32].

Sotagliflozin—Sotagliflozin is a combined SGLT1/SGLT2 inhibitor that was designed for use in people with T1D. The inTandem studies were phase 3 randomized placebo controlled trials conducted to evaluate sotagliflozin in T1D and were conducted in the United States (inTandem1), Europe (inTandem2), and worldwide (inTandem3)[4,33,34]. In all arms of the study, there were significant decreases in HbA1c at 24 weeks, which were sustained (although to a lesser degree) at 52 weeks. In the 24-week global inTandem3 study of 1402 participants randomized 1:1 to sotagliflozin 400 mg or placebo, significantly more achieved the primary endpoint of HbA1c <7% in the treatment versus the placebo

study arms, 28.6% vs.15.2%, respectively. In the North American and European trials, participants were randomized 1:1:1 to sotogliflozin 200 mg, 400 mg, or placebo. Other outcomes, including safety outcomes, were assessed at 24 and 52 weeks. Significant weight loss and reductions in blood pressure and total daily insulin dose were observed variably in the different studies and with the different doses of sotogliflozin. Notably, there were lower rates of severe hypoglycemia in inTandem1 and inTandem2 with higher doses of sotagliflozin while similar rates of hypoglycemia in inTandem3. Rates of DKA and genital infections were higher in the active treatments groups compared with placebo, with rates increasing in a dose-dependent manner. Follow up analysis revealed a significant decrease in GFR at 4 weeks (−2.8 ml/min/1.73m2, p<0.001), which returned to baseline by 52 weeks (−0.5 ml/min/1.73m2, p=0.52). An initial decrease in urine albumin to creatinine ratio in the subset of patients with microalbuminuria (−31.4% p=0.0032) at 4 weeks was not sustained at 52 weeks (−18.3%, p=0.18).[13,35]

Pediatric Populations

Few studies have evaluated the use of SGLT inhibitors in children. There have been case reports of its use, along with GLP1 agonists and metformin, in children with Prader-Willi Syndrome[36]. Further, there are no SGLT inhibitors approved for use in pediatric patients with T2D although phase 3 regulatory studies are ongoing. Indeed, metformin, the GLP1 analog liraglutide, and insulin remain the only approved therapies in children[37,38]. The pharmacokinetics and pharmacodynamics of canagliflozin and empagliflozin have been evaluated in two separate studies in adolescents with findings that are comparable with those seen in adults with T2D, which is not surprising given that most children with T2D have body weights in the adult range[39,40]. One proof-of-concept randomized trial has been conducted with a single dose of dapagliflozin 10 mg compared with placebo, administered to 33 children with T1D; insulin needs were monitored during a hyperglycemic clamp (160–220 mg/dL) over 24 hours. Urinary glucose excretion increased by 610% with a concomitant 13.6% decrease in insulin requirements[41], which aligns with what has been seen in adults. To date, no phase 3 studies have been published of clinical use of SGLT inhibitors in pediatric patients with T1D or T2D. Studies of pediatric T2D are notoriously difficult to conduct for a variety of reasons, including small numbers of eligible patients and logistical barriers to participation in clinical trials[37], deriving a need for renewed efforts with more practical study designs, for example, utilizing a single control group for comparison with two different anti-hyperglycemic agents, such as an SGLT2 inhibitor and a DPP4 inhibitor.

Regulatory Approval of SGLT inhibitors in People with T1D

Internationally, several SGLT inhibitors have been approved as adjunctive therapy for T1D. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has approved dapagliflozin for adults with T1D[42] and has preemptively approved sotagliflozin[43], though it is not yet available commercially in that market. The European Commission also approved in 2019 both dapagliflozin[44] and sotagliflozin[45] for adults with T1D who have body mass index (BMI) 27 kg/m2. Ipragliflozin has had regulatory approval for adults with T1D in Japan since 2018[46]. [43] In contrast, the United States Food and Drug Administration has not approved any SGLT inhibitor for people with T1D. Sotagliflozin, dapagliflozin, and empagliflozin were all evaluated by the FDA in the last few years. Dapagliflozin and

empagliflozin have already been approved for use in adults with T2D, and thus were being evaluated for new indications in adults with T1D based on the DEPICT and EASE trials, while sotagliflozin had submitted an initial application for approval in adults with T1D based on the inTandem trials. Notably, the FDA submission for empagliflozin as adjunct to insulin was only for the 2.5 mg dosage. However, all applications were rejected[47–49], with the FDA citing the increased risk of DKA as the primary concern. One recent international study on patient preferences reported that adults with T1D favored a low dose SGLT inhibitor with lower risk of DKA, albeit with reduced efficacy[50]. Nonetheless, at this time, use of SGLT inhibitors in the United States remains off-label.

Future directions in research

Now that SGLT inhibitors have received approval in adults with T1D in a number of countries and are frequently being used off-label in others, the next stage of research needs to include methods to mitigate risks of DKA and genital infection. The International Consensus Guidelines are a start in formalizing the use of these agents in the T1D population[20], but much more research is needed to improve their safety in routine clinical use. Studies to determine the optimal method and frequency of ketone measurement are needed to catch ketosis in the early stages in order to reduce progression to DKA. Additional, creative study designs are currently being employed in phase 3 studies of these agents in youth with T2D to meet to needs of this growing population so they can benefit from an expanded repertoire of approved medications.

The striking improvements in cardiovascular and kidney outcomes with SGLT inhibitor use have only been studied in patients with T2DM. It remains important to important assess if these cardiorenal benefits also accrue to those with T1D, which would help shift the benefit-risk ratio, especially given the risk of DKA conferred by SGLT inhibitor therapy in T1D[51]. The need for long-term outcomes studies with large patient samples would require substantial numbers of clinical sites, extended follow-up periods, and tremendous expense, all of which challenge the feasibility of such trials given the smaller population of people with T1D. Subjects with a wide variety of underlying complications, such as microalbuminuria, CKD, and heart disease, would need to be included, which would complicate such trials further as this is an even more limited population. There are several RCTs in progress to assess the impact of SGLT inhibitors in people with T1D. The ATTEMPT study is comparing dapagliflozin to placebo with a primary outcome of measured GFR in adolescents with T1D.[52] The Astronaut study, which was recently completed, is studying renal oxygenation outcome changes in response to dapagliflozin in adults with T1D and albuminuria.[53] Practicality suggests that the best T1D-specific data may come from nonrandomized observational studies of patients taking SGLT inhibitors as adjunctive therapy to insulin[54].

Conclusions

Providing therapeutic options beyond insulin for people with T1D is an important endeavor, and SGLT inhibitors have been promising, given their overall favorable side effect profile with minimal hypoglycemia and improved weight loss. There have been multiple studies

with a variety of SGLT inhibitors demonstrating improved glycemic control, weight loss, lower blood pressure, and decreased insulin doses in persons with T1D, but at the cost of increased genital infections and ketosis-associated adverse events. The regulatory bodies in different countries have interpreted the benefit-risk balance differently, with SGLT inhibitors approved for adults with T1D in Europe and Japan but rejected in the United States. Regardless of regulatory approval, these agents are being prescribed for people with T1D worldwide, and more research is needed to determine the best practices for reducing risk of DKA.

Acknowledgements:

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Clinical Summary

-   SGLT inhibitor use in persons with T1D offer potential opportunities for improved glycemic control, weight loss, and lower blood pressure with a low risk of hypoglycemia while increasing risk of genital infections and DKA.

-   Increased occurrence of DKA appears related to lack of recognition of developing ketosis, often in the setting of euglycemia or only mildly elevated glucose levels; protocols to mitigate this risk have been developed.

-   The impact of SGLT inhibition in pediatric patients with T1D requires investigation and the cardiorenal effects of SGLT inhibition in T1D have not yet been studied in randomized controlled trials.

Table 1:

Phase 3 Randomized Trials of SGLT Inhibitors in T1DM

Trial/Agent/NCT	Number of participants	Duration of trial (weeks)	HbA1c change*	Weight change*	TDD change*	Severe hypoglycemia	DKA	Genital mycotic infections
DEPICT-1 24 weeks Dapagliflozin NCT02268214 [27]	N=833; n=277 5 mg, n=296 10 mg, n=260 placebo	24	5 mg: −0.42% (p<0.0001) 10 mg: −0.45% (p<0.0001)	5 mg: −2.96% (p<0.0001) 10 mg: −3.72% (p<0.0001)	5 mg: −8.8% (p<0.0001) 10 mg: −13.2% (p<0.0001)	5 mg: 8% 10 mg: 6% Placebo: 7%	5 mg: 1% 10 mg: 2% Placebo: 1%	5 mg: 12% 10 mg: 11% Placebo: 3%
DEPICT-1 52-week extension Dapagliflozin NCT02268214 [28]	N=708; n=235 5 mg, n=255 10 mg, n=218 placebo	52	5 mg: −0.33% (95% CI −0.49,−0.17) 10 mg: −0.36% (95% CI −0.53,−0.20)	5 mg: −2.95% (95% CI −3.83,−2.06) 10 mg: −4.54% (95% CI −5.40,−3.66)	Decrease at 24 weeks maintained	5 mg: 10.5% 10 mg: 8.4% Placebo: 11.5%	5 mg: 4.0% 10 mg: 3.4% Placebo: 1.9%	5 mg: 15.5% 10 mg: 13.5% Placebo: 3.1%
DEPICT-2 Dapagliflozin NCT02460978 [29]	N=813; n=271 5 mg, n=270 10 mg, n=272 placebo	24	5 mg: −0.37% (p<0.0001) 10 mg: −0.42% (p<0.0001)	5 mg: −3.21% (p<0.0001) 10 mg: −3.71% (p<0.0001)	5 mg: −10.78% (p<0.0001) 10 mg: −11.08% (p<0.0001)	5 mg: 6.3% 10 mg: 8.5% Placebo: 7.7%	5 mg: 2.6% 10 mg: 2.2% Placebo: 0%	5 mg: 10.0% 10 mg: 7.8% Placebo: 1.8%
DEPICT-2 52-week extension Dapagliflozin NCT02460978 [30]	n=717; n=231 5 mg, n=226 10 mg, n=216 placebo	52	5 mg: −0.20% (95% CI −0.34,−0.06) 10 mg: −0.25% (95% CI −0.38,−0.11)	5 mg: −4.42% (95% CI −5.19,−3.64) 10 mg: −4.86% (95% CI −5.63,−4.08)	Decrease at 24 weeks maintained	5 mg: 8.9% 10 mg: 9.6% Placebo: 8.5%	5 mg: 4.1% 10 mg: 3.7% Placebo: 0.4%	5 mg: 11.1% 10 mg: 10.4% Placebo: 3.7%
EASE-2 Empagliflozin NCT02414958 [31]	N=723; n=243 10 mg, n=241 25 mg, n=239 placebo	26	10 mg: −0.54% (p<0.0001) 25 mg: −0.53% (p<0.0001)	10 mg: −2.7kg (p<0.0001) 25 mg: −3.3kg (p<0.0001)	10 mg: −13.3% (p<0.0001) 25 mg: −12.7% (p<0.0001)	See Pooled Data	See Pooled Data	See Pooled Data
EASE-2 52-week extension Empagliflozin NCT02414958 [31]	N=617; n=204 10 mg, n=220 25 mg, n=193 placebo	52	10 mg: −0.39% (p<0.0001) 25 mg: −0.45% (p<0.0001)	10 mg: −3.2kg (p<0.0001) 25 mg: −3.6kg (p<0.0001)	10 mg: −12.0% (p<0.0001) 25 mg: −12.9% (p<0.0001)	See Pooled Data	See Pooled Data	See Pooled Data
EASE-3 Empagliflozin NCT02580591 [31]	N=961; n=237 2.5 mg, n=244 10 mg, n=242 25 mg, n=238 placebo	26	2.5 mg: −0.28% (p<0.0001) 10 mg: −0.45% (p<0.0001) 25 mg: −0.52% (p<0.0001)	2.5 mg: −1.8kg (p<0.0001) 10 mg: −3.0kg (p<0.0001) 25 mg: −3.4kg (p<0.0001)	2.5 mg: −6.4% (p<0.0001) 10 mg: −9.5% (p<0.0001) 25 mg: −12.6% (p<0.0001)	2.5 mg: 1.2% Placebo: 2.5% See Pooled Data for 10 mg and 25 mg	2.5 mg: 0.8% Placebo: 1.2% See Pooled Data for 10 mg and 25 mg	2.5 mg: 5.4% Placebo: 2.5% See Pooled Data for 10 mg and 25 mg
EASE-2 and EASE3 Pooled Empagliflozin NCT02414958, NCT02580591 [31]	N=1464; n=491 10 mg, n=489 25 mg, n=484 placebo	26	Not reported	Not reported	Not reported	10 mg: 4.1% 25 mg: 2.7% Placebo: 3.1%	10 mg: 4.3% 25 mg: 3.3% Placebo: 1.2%	10mg: 12.8% 25 mg: 14.3% Placebo: 4.3%
Kaku et al Ipragliflozin NCT02897219 [25,30]	N=174; n=115 50 mg, n=59 placebo	24**	50 mg: −0.36% (p=0.001)	50 mg: −2.87kg (p<0.001)	50 mg: −15.26% (p<0.001)	50 mg: 1.7% Placebo: 0.0%	50 mg: 0.0% Placebo: 0.0%	50 mg: 5.2% Placebo: 0.0%

Trial/Agent/NCT	Number of participants	Duration of trial (weeks)	HbA1c change*	Weight change*	TDD change*	Severe hypoglycemia	DKA	Genital mycotic infections
InTandem-1 Sotagliflozin NCT02384941 [33]	N=793; n=263 200 mg, n=262 400 mg, N=268 placebo	24	200 mg: −0.36% (p<0.001) 400 mg: −0.41% (p<0.001)	200 mg: −2.3kg (p<0.001) 400 mg: −3.4kg (p<0.001)	200 mg: −6.16% (p<0.001) 400 mg: −9.70% (p<0.001)	See 52-week data	See 52-week data	See 52-week data
InTandem-1 52week extension Sotagliflozin NCT02384941 [33]	N=793; n=263 200 mg, n=262 400 mg, n=268 placebo	52	200 mg: −0.25% (p<0.001) 400 mg: −0.31% (p<0.001)	200 mg: −3.1kg (p<0.001) 400 mg: −4.3kg (p<0.001)	200 mg: −8.02% (p<0.001) 400 mg: −12.64% (p<0.001)	200 mg: 6.5% 400 mg: 6.5% Placebo: 9.7%	200 mg: 3.4% 400 mg: 4.2% Placebo: 0.4%	200 mg: 9.1% 400 mg: 13.0% Placebo: 3.4%
InTandem-2 Sotagliflozin NCT02421510 [34]	N=782; n=261 200 mg, n=263 400 mg, n=258 placebo	24	200 mg: −0.37% (p<0.001) 400 mg: −0.35% (p<0.001)	200 mg: −2.0kg (p<0.001) 400 mg: −2.6kg (p<0.001)	200 mg: −8.23% (p<0.001) 400 mg: −9.47% (p<0.001)	See 52-week data	See 52-week data	See 52-week data
InTandem-2 52week extension Sotagliflozin NCT02421510 [34]	N=782; n=261 200 mg, n=263 400 mg, n=258 placebo	52	200 mg: −0.21% (p<0.001) 400 mg: −0.32% (p<0.001)	200 mg: −2.2kg (p<0.001) 400 mg: −2.9kg (p<0.001)	200mg: −6.26% (p=0.002) 400mg −8.17% (p<0.001)	200 mg: 5.0% 400 mg: 2.3% Placebo: 5.0%	200 mg: 2.3% 400 mg: 3.4% Placebo: 0%	200 mg: 9.2% 400 mg: 11.0% Placebo: 2.3%
InTandem-3 Sotagliflozin [4]	N=1402; n=699 400 mg, n=703 placebo	24	400 mg: −0.46% (p<0.001)	400 mg: −3.0kg (p<0.001)	400 mg: −9.7% (p<0.001)	400 mg: 3.0% Placebo: 2.4%	400 mg: 3.0% Placebo: 0.6%	400 mg: 6.4% Placebo: 2.1%

*
compared with placebo

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Note 28 week open-label extension study with placebo cross-over to active treatment plus dose escalation of both groups at 32 weeks, not included in table; described above[30]