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To cite this article: Georgios Chatzopoulos & Konstantinos Tziomalos (2020) An up-to-date evaluation of sotagliflozin for the treatment of type 1 diabetes, Expert Opinion on Pharmacotherapy, 21:15, 1799-1803, DOI: [10.1080/14656566.2020.1793961](https://doi.org/10.1080/14656566.2020.1793961)

To link to this article: <https://doi.org/10.1080/14656566.2020.1793961>



Published online: 27 Oct 2020.



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DRUG EVALUATION



## An up-to-date evaluation of sotagliflozin for the treatment of type 1 diabetes

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### ABSTRACT

**Introduction:** The majority of patients with type 1 diabetes mellitus (T1DM) do not achieve glycemic targets. In addition, treatment with insulin is associated with increased risk for hypoglycemia and weight gain. Accordingly, there is an unmet need for new safe and effective glucose-lowering agents in this population. Sotagliflozin, a dual inhibitor of sodium-glucose co-transporters 1 and 2, has been recently approved for use in patients with T1DM.

**Areas covered:** The authors review the major trials that have evaluated the safety and efficacy of sotagliflozin and provide their expert opinion.

**Expert opinion:** Even though sotagliflozin reduces HbA<sub>1c</sub> levels and does not appear to increase the risk for hypoglycemia in most patients, the substantially increased risk for diabetic ketoacidosis limits the use of this agent to a carefully selected subgroup of patients with T1DM. Based on the existing evidence, sotagliflozin should be considered only in patients who have failed to achieve adequate glycemic control despite optimal insulin therapy, are at low risk for diabetic ketoacidosis, have been adequately trained to recognize this complication and are able to be in close contact with their physician.

### ARTICLE HISTORY

Received 15 April 2020  
Accepted 6 July 2020

### KEYWORDS

Diabetic ketoacidosis; hypoglycemia; sodium-glucose co-transporter; sotagliflozin; type 1 diabetes

## 1. Introduction

Type 1 diabetes mellitus (T1DM) currently affects more than 29 million patients worldwide and its prevalence is increasing [1,2]. Insulin represents the mainstay of pharmacological management of T1DM but despite the advances of insulin formulations, the majority of patients with T1DM have suboptimal glycemic control [3,4]. In addition, treatment with insulin is associated with increased risk for hypoglycemia and weight gain, which are both associated with increased cardiovascular risk [5,6]. Accordingly, there is an unmet need for effective and safe treatments in this population.

Recent data suggest that sotagliflozin, a dual inhibitor of sodium-glucose co-transporters (SGLT) 1 and 2, might have a role in the management of T1DM [7–9]. In the present paper, we provide an overview of the safety and efficacy of sotagliflozin in this population.

## 2. Overview of the market

Metformin, sitagliptin and liraglutide have been evaluated in patients with T1DM but their glucose-lowering efficacy is minimal in this population [10–13]. Pramlintide was the first non-insulin agent that was approved for use in patients with T1DM in the US [14]. However, it is associated with increased risk for hypoglycemia and gastrointestinal adverse events and is therefore infrequently used in the US and has not been approved for use in Europe [15]. Recently, dapagliflozin, a SGLT2 inhibitor, has been approved by the European Medicines Agency for use in adult patients with T1DM who have a body mass index  $\geq 27$  kg/m<sup>2</sup> and have inadequate

glycemic control despite optimal insulin therapy [16]. Even though this agent improves glycemic control without increasing the risk of hypoglycemia and also induces weight loss, it is associated with increased risk for diabetic ketoacidosis [17–19]. The sponsors of dapagliflozin and empagliflozin have submitted New Drug Applications in the United States, but the Food and Drug Administration (FDA) has decided not to approve any of these drugs for use in patients with T1DM. Moreover, the FDA-approved Prescribing Information for dapagliflozin lists as a limitation of use that the drug is ‘not for treatment of T1DM or diabetic ketoacidosis’.

## 3. Introduction to sotagliflozin

Sotagliflozin (2S, 3 R, 4 R, 5S, 6 R)-2-[4-chloro-3-[(4-ethoxyphenyl)-methyl]-phenyl]-6-methylsulfanyloxane-3, 4, 5-triol is an oral dual inhibitor of sodium-glucose co-transporters (SGLT) 1 and 2 [20]. These transporters are expressed in the proximal intestine and in the proximal tubule of the kidneys, respectively [20]. SGLT1 are also expressed in the salivary glands, liver, lung, skeletal muscle, heart, pancreatic alpha cells and brain but their role in these tissues is unclear [20]. Their inhibition results in blunting and delaying absorption of glucose from the gastrointestinal tract and in reduced renal reabsorption of glucose, respectively [20] (Box 1).

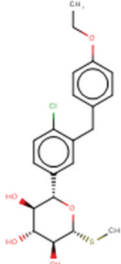
## 4. Chemistry, pharmacodynamics and pharmacokinetics of sotagliflozin

Sotagliflozin is 20 times more selective for SGLT2 than for SGLT1, with a half-maximal inhibitory concentration for

**Article highlights**

- Sotagliflozin reduces HbA<sub>1c</sub> levels and does not appear to increase the risk for hypoglycemia in most patients
- Sotagliflozin is associated with substantially increased risk for ketoacidosis
- Sotagliflozin should be considered only in patients who have failed to achieve adequate glycemic control despite optimal insulin therapy, are at low risk for diabetic ketoacidosis, have been adequately trained to recognize this complication and are able to be in close contact with their physician

**Box 1. Drug summary box**

Drug name	Sotagliflozin
Phase	Registered
Indication	Type 1 Diabetes
Pharmacology description	Sodium/glucose cotransporter inhibitor
Route of administration	Oral
Chemical structure	

Pivotal trial(s)

[23][24]

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these transporters of 0.0018 and 0.036  $\mu$ M, respectively [21]. The median  $T_{max}$  ranges between 1.25 and 3 hours after administration of a single dose and between 2.5 and 4 hours after administration of multiple doses [22]. At least 71% of sotagliflozin is absorbed and plasma exposure increases by 1.5–2.5 times when sotagliflozin is taken with a high-caloric meal [22]. Almost 98% of both sotagliflozin and its main metabolite, 3-O-glycuronide, are bound to plasma proteins and this binding is unaffected by impairments in renal or hepatic function [1]. The apparent volume of distribution after administration of a single 400 mg dose is 9,392 l [22]. The primary route of metabolism of sotagliflozin is glycuronidation by the uridine 5'-diphosphoglucuronosyltransferases UGT1A9 [22]. The main route of elimination is renal and exposure to sotagliflozin is up to 1.7 and up to 2.7 times greater in patient with mild and moderate renal impairment, respectively (i.e. with creatinine clearance 60–90 and 30–60 ml/min, respectively) [22]. In contrast, mild impairment of hepatic function (Child-Pugh A) does not affect the plasma exposure of sotagliflozin; however, patients with moderate and severe hepatic impairment (Child-Pugh B and C, respectively) have 3 and 6 times greater plasma exposure, respectively [22]. Age, body

weight, sex and race have no clinically meaningful effects on the pharmacokinetics of sotagliflozin [22].

**5. Clinical efficacy of sotagliflozin**

Several randomized, placebo-controlled, phase III studies evaluated the efficacy of sotagliflozin in patients with T1DM (Table 1). In the inTandem3 trial (n = 1,402), more patients treated with sotagliflozin 400 mg/day group achieved HbA<sub>1c</sub> levels < 7.0% at 24 weeks than patients treated with placebo (29.6 vs. 15.8%, respectively) [23]. Sotagliflozin reduced HbA<sub>1c</sub> levels by 0.46% compared with placebo and also reduced the mean daily total insulin dose by 5.3 units. In addition, treatment with sotagliflozin reduced systolic blood pressure (SBP) by 3.5 mmHg in patients with baseline SBP  $\geq$  130 mmHg and also reduced body weight by 2.98 kg compared with placebo [23]. Sotagliflozin did not affect glomerular filtration rate (GFR) or urinary albumin excretion [23].

The inTandem1 (n = 793) and inTandem2 trials (n = 782) compared the safety and efficacy of treatment with sotagliflozin 200 or 400 mg/day versus placebo for 52 weeks [24,25]. Reductions in HbA<sub>1c</sub> levels appeared to wane at 52 weeks; indeed, HbA<sub>1c</sub> was reduced by 0.41% at week 24 and by 0.31% at week 52 in the inTandem1 trial and by 0.35% at week 24 and by 0.32% at week 52 in the inTandem2 trial [24,25]. On the other hand, masked continuous glucose monitoring revealed that sotagliflozin 400 mg/day increased the glucose time in range (i.e. between 70–180 mg/dl) by 11.7% compared with placebo [26]. Moreover, sotagliflozin 400 mg/day significantly reduced postprandial glucose levels (by 50 mg/dl), possibly due to the reduction in gastrointestinal absorption of glucose due to SGLT1 inhibition [26,27]. Reductions in body weight

**Table 1.** Randomized, placebo-controlled studies that evaluated the efficacy and safety of sotagliflozin in patients with type 1 diabetes mellitus.

Trial	n	Duration	Efficacy	Safety
inTandem3 [23]	1,402	24 weeks	<ul style="list-style-type: none"> <li>↓ HbA<sub>1c</sub> by 0.46%</li> <li>↓ SBP by 3.5 mmHg</li> <li>↓ weight by 2.98 kg</li> </ul>	<ul style="list-style-type: none"> <li>↔ Severe hypoglycemia</li> <li>DKA: 3.0% vs. 0.6% with placebo</li> <li>Diarrhea: 4.1% vs. 2.3% with placebo</li> <li>Genital infections: 6.4% vs. 2.1% with placebo</li> </ul>
inTandem1 [24]	793	52 weeks	<ul style="list-style-type: none"> <li>↓ HbA<sub>1c</sub> by 0.31%</li> <li>↓ SBP by 4.2 mmHg</li> <li>↓ weight by 4.3 kg</li> </ul>	<ul style="list-style-type: none"> <li>↔ Hypoglycemia</li> <li>DKA: 4.2% vs. 0.4% with placebo</li> <li>Diarrhea: 10.3% vs. 6.7% with placebo</li> <li>Genital infections: 13.0% vs. 3.4% with placebo</li> </ul>
inTandem2 [25]	782	52 weeks	<ul style="list-style-type: none"> <li>↓ HbA<sub>1c</sub> by 0.32%</li> <li>↓ SBP by 2.8 mmHg</li> <li>↓ weight by 2.9 kg</li> </ul>	<ul style="list-style-type: none"> <li>↓ Hypoglycemia</li> <li>DKA: 3.4% vs. 0% with placebo</li> <li>Diarrhea: 7.2% vs. 3.5% with placebo</li> <li>Genital infections: 11.0% vs. 2.3% with placebo</li> </ul>

SBP: systolic blood pressure; ↔: no change; DKA: diabetic ketoacidosis.

(2.9–4.3 kg) and SBP (2.8–4.2 mmHg) were again observed during treatment with sotagliflozin [24,25]. Moreover, satisfaction with treatment was higher in the sotagliflozin group than in the placebo group whereas diabetes-related distress was less severe in the former [24,25]. A pooled analysis of the inTandem-1 and -2 trials showed no effect of sotagliflozin 400 mg/day on GFR or on albuminuria [28]. However, it is possible that the duration of these trials was too short to reveal a change in renal function.

## 6. Safety and tolerability of sotagliflozin

In the inTandem3 trial, rates of severe hypoglycemia (defined as a hypoglycemic event that required assistance from another person or resulted in loss of consciousness or a seizure, regardless of the patient's glucose level) were similar in the sotagliflozin and the placebo groups among patients using subcutaneous insulin injections but were 2 times higher in the former among patients using insulin pump [23]. In contrast, rates of documented hypoglycemia with blood glucose levels < 55 mg/dl were lower in the sotagliflozin group [23]. Rates of hypoglycemia were lower in the sotagliflozin 400 mg/day group than in the placebo group in the inTandem2 trial and were similar in the 2 groups in the inTandem1 trial [24,25]. Moreover, continuous glucose monitoring did not show any increase in the risk of hypoglycemia in the sotagliflozin group in these 2 trials [26]. On the other hand, based on phase 2 data with canagliflozin, it seems likely that SGLT2 inhibitors are associated with an increased risk of hypoglycemia when combined with insulin in patients with T1DM [29]. However, in subsequent studies with other SGLT2 inhibitors, the clinical trial staff developed considerable skill in decreasing insulin doses to mitigate the SGLT2 inhibitor-induced risk of severe hypoglycemia [23–25]. It is far from clear that the same skill will be routinely available in 'real world' situations to prevent the potential risk of SGLT2 inhibitor-induced hypoglycemia in insulin-treated T1DM patients.

SGLT2 inhibitors increase the risk of diabetic ketoacidosis possibly due to noninsulin-dependent glucose clearance, increase in circulating glucagon levels and volume depletion [30]. It has been suggested that dual inhibition of SGLT1 and 2 might reduce the risk of diabetic ketoacidosis because of the lower risk for dehydration and reduction in glucagon levels [31]. However, in the inTandem3 trial, rates of diabetic ketoacidosis were 5 times higher in patients treated with sotagliflozin (3.0% vs. 0.6% in the placebo group) in both insulin pump users and non-users [23]. Notably, patients using insulin pump had considerably higher rates of diabetic ketoacidosis than patients receiving multiple insulin injections, particularly in the sotagliflozin group (4.4% vs. 2.1% in the sotagliflozin group, respectively; 0.7% vs. 0.5% in the placebo group, respectively) [23]. Based on the existing evidence, it is unclear whether insulin pump increases the risk for diabetic ketoacidosis compared with multiple insulin injections [32]. In the inTandem1 trial, rates of diabetic ketoacidosis were more than 10 times higher in the sotagliflozin group (4.2% vs. 0.4% in the placebo group) whereas in the inTandem2 trial none of the patients in the placebo group experienced diabetic ketoacidosis

compared with 3.4% in the sotagliflozin arm [23,24]. Increased risk of diabetic ketoacidosis was observed in clinical trials with all approved SGLT2 inhibitors (i.e. dapagliflozin, empagliflozin and canagliflozin) [17–19,29,33]. It should be emphasized that patients included in these trials were followed-up regularly, were educated in the identification of recognizing the symptoms of diabetic ketoacidosis and were provided with test strips for measuring ketones and BHB levels [23–25]. Moreover, patients at high risk for diabetic ketoacidosis, including those with an episode of diabetic ketoacidosis during the last month prior to screening or with 2 or more episodes during the last 6 months prior to screening and patients with beta-hydroxy butyrate levels > 0.6 mmol/l at screening were excluded from these trials [23–25]. Therefore, it is possible that in a real-life setting, where these preventive measures are not feasible and more diverse population will receive this treatment, the incidence of diabetic ketoacidosis will be higher in patients treated with sotagliflozin. Indeed, in an observational study, the rate of diabetic ketoacidosis was 1.8 times more frequent during treatment with sotagliflozin (4.5–7.3/100 person-years) than the rate observed in clinical trials [34]. Moreover, this risk was particularly increased in female patients aged 25–44 years (19.7/100 person-years) [34]. In addition, diabetic ketoacidosis can occur even with low or normal glucose levels [35]. Notably, patients with T1DM consider the risk of diabetic ketoacidosis more important than HbA<sub>1c</sub> reduction, the risk of hypoglycemia and the use of oral versus injectable treatment [36]. It is recommended that SGLT inhibitors should be discontinued before scheduled surgical procedures, and patients and clinicians should remain in close consultation regarding other forms of behavioral and physiological stress [35].

The inhibition of glucose absorption by the gastrointestinal tract and by the kidneys by sotagliflozin is expected to increase the incidence of osmotic diarrhea and glucosuria-induced genital mycotic infections, respectively. Indeed, in the inTandem3 trial, diarrhea was almost 2 times more frequent in the former (4.1% vs. 2.3% in the placebo group) and genital infections were 3 times more frequent in the sotagliflozin group (6.4% vs. 2.1% in the placebo group) [23]. Similarly, in the inTandem1 and inTandem2 trials, diarrhea and genital mycotic infections occurred 1.5–2 and 4–5 times more frequently, respectively, in patients treated with sotagliflozin [24,25]. These adverse events resulted in treatment discontinuation in 0.9–1.6% of patients treated with sotagliflozin [23–25].

In the inTandem3 trial, the incidence of urinary tract infection and bone fracture did not differ between the 2 groups and no cases of amputation were reported during the trial [23]. In the inTandem1 and inTandem2 trials, cases of bone fracture were numerically higher in the sotagliflozin arm but were infrequent [24,25]. Notably, patients with T1DM have a higher risk for fractures than the general population [37]. Moreover, canagliflozin has been associated with increased risk for fractures and amputation in patients with type 2 diabetes mellitus (T2DM) whereas other SGLT2 inhibitors, namely empagliflozin and dapagliflozin, have not [38–41]. It is unclear whether these different results are due to differences between SGLT2 inhibitors or differences between patients with T2DM and T1DM. It is also possible that the

duration of the inTandem trials (24–52 weeks) was too short to reveal an increased incidence of fractures and amputations.

## 7. Regulatory affairs

Sotagliflozin has been approved by the European Medicinal Agency as an adjunct to insulin in patients with T1DM with a body mass index  $\geq 27$  kg/m<sup>2</sup> who have failed to achieve adequate glycemic control despite optimal insulin therapy [42]. In contrast, the sponsor of sotagliflozin has submitted New Drug Applications in the United States but the FDA has decided not to approve this drug for use in patients with T1DM.

## 8. Expert opinion

Sotagliflozin reduces HbA<sub>1c</sub> levels. Given that the majority of patients with T1DM have suboptimal glycemic control, the addition of sotagliflozin is expected to be useful in achieving glycemic targets. Moreover, sotagliflozin appears to reduce fluctuations in glucose levels and to alleviate postprandial hyperglycemia, which appear to be associated with increased risk for micro- and macrovascular complications in this population. On the other hand, the glucose-lowering efficacy of sotagliflozin appears to wane after 24 weeks of treatment and it is unclear whether it is sustainable during long-term administration. Indeed, there are no data regarding the effects of sotagliflozin on HbA<sub>1c</sub> levels beyond 52 weeks of treatment. Moreover, the design of the inTandem trials might have favored sotagliflozin, since HbA<sub>1c</sub> levels were masked and this might have resulted in suboptimal insulin titration in the placebo group.

Another potential advantage of adding sotagliflozin is that this agent does not appear to increase the risk for hypoglycemia. In contrast, the alternative option for improving glycemic control, i.e. titration of insulin dose, is associated with increased risk for hypoglycemia. However, in the inTandem2 trial, patients using insulin pump were more likely to experience hypoglycemia during treatment with sotagliflozin than with placebo. Therefore, adding sotagliflozin might be less appropriate for this group of patients.

The major drawback for the use of sotagliflozin is the increase in the risk of diabetic ketoacidosis. All inTandem trials consistently showed a 5–10 times higher risk for this potentially fatal complication in patients assigned to receive sotagliflozin. Patients using insulin pump were at substantially higher risk. Notably, patients at high risk for diabetic ketoacidosis were excluded from these trials and several measures to mitigate the risk of diabetic ketoacidosis were enforced that might not be feasible in everyday, typical clinical practice. Furthermore, diabetic ketoacidosis can develop during treatment with SGLT inhibitors even in the absence of elevated glucose levels and this might obscure timely recognition and treatment. Moreover, several symptoms of diabetic ketoacidosis including weight loss, abdominal pain, frequent urination, increased thirst, are also potential adverse events related to the use of sotagliflozin and this might also delay the diagnosis of diabetic ketoacidosis.

Finally, up to 10.3% of patients treated with sotagliflozin experience diarrhea and up to 13.0% experience genital mycotic infections. Even though relatively few patients discontinued treatment due to these adverse events in the inTandem trials, it is possible that discontinuation rates or reduced adherence to treatment will be more frequent during the long-term use of sotagliflozin in everyday clinical practice.

Overall, even though sotagliflozin reduces HbA<sub>1c</sub> levels and does not appear to increase the risk for hypoglycemia in most patients, the substantially increased risk for diabetic ketoacidosis limits the use of this agent to a carefully selected subgroup of patients with T1DM. Based on the existing evidence, sotagliflozin should be considered only in patients who have failed to achieve adequate glycemic control despite optimal insulin therapy, are at low risk for diabetic ketoacidosis, have been adequately trained to recognize this complication and are able to be in close contact with their physician.

## Funding

This manuscript has not been funded.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

## References

Papers of special note have been highlighted as either of interest (\*) or of considerable interest (\*\*\*) to readers.

1. World Health Organization. Global report on diabetes. [cited 2020 Apr 8]. Available from [https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257\\_eng.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf?sequence=1)
2. Imperatore G, Boyle JP, Thompson TJ, et al.; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care*. 2012;35:2515–2520.
3. Miller KM, Foster NC, Beck RW, et al.; T1D Exchange Clinic Network. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. *Diabetes Care*. 2015;38:971–978.
4. McKnight JA, Wild SH, Lamb MJ, et al. Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med*. 2015;32:1036–1050.
5. Lu CL, Shen HN, Hu SC, et al. A population-based study of all-cause mortality and cardiovascular disease in association with prior history of hypoglycemia among patients with Type 1 diabetes. *Diabetes Care*. 2016;39:1571–1578.
6. Purnell JQ, Braffett BH, Zinman B, et al.; DCCT/EDIC Research Group. Impact of excessive weight gain on cardiovascular outcomes in Type 1 diabetes: results from the Diabetes Control and Complications Trial/

- Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. *Diabetes Care*. 2017;40:1756–1762.
7. Taylor SI, Blau JE, Rother KI, et al. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. *Lancet Diabetes Endocrinol*. 2019;7:949–958.
  8. Langford BE, Evans M, Haskins-Coulter T, et al. Systematic literature review and network meta-analysis of sodium-glucose co-transporter inhibitors vs metformin as add-on to insulin in type 1 diabetes. *Diabetes Obes Metab*. 2020;22:39–50.
  9. Patel K, Carbone A. Sodium-glucose cotransporters as potential therapeutic targets in patients with Type 1 diabetes mellitus: an update on phase 3 clinical trial data. *Ann Pharmacother*. 2019;53:1227–1237.
  10. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5:597–609.
  11. Garg SK, Moser EG, Bode BW, et al. Effect of sitagliptin on post-prandial glucagon and GLP-1 levels in patients with type 1 diabetes: investigator-initiated, double-blind, randomized, placebo-controlled trial. *Endocr Pract*. 2013;19:19–28.
  12. Mathieu C, Zinman B, Hemmingsson JU, et al.; ADJUNCT ONE Investigators. Efficacy and safety of liraglutide added to insulin treatment in Type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. *Diabetes Care*. 2016;39:1702–1710.
  13. Dejgaard TF, Frandsen CS, Hansen TS, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:221–232.
  14. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S98–S110.
  15. Lyons SK, Hermann JM, Miller KM, et al. Use of adjuvant pharmacotherapy in Type 1 diabetes: international comparison of 49,996 Individuals in the prospective diabetes follow-up and T1D exchange registries. *Diabetes Care*. 2017;40:e139–e140.
  16. Forxiga: summary of product characteristics. [cited 2020 Apr 1]. Available from: [https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf)
  17. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled Type 1 diabetes: the DEPICT-1 52-week study. *Diabetes Care*. 2018;41:2552–2559.
  18. Mathieu C, Dandona P, Gillard P, et al.; DEPICT-2 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled Type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. *Diabetes Care*. 2018;41:1938–1946.
  19. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;5:864–876.
  20. McCrimmon RJ, Henry RR. SGLT inhibitor adjunct therapy in type 1 diabetes. *Diabetologia*. 2018;61:2126–2133.
  21. Zambrowicz B, Freiman J, Brown PM, et al. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. *Clin Pharmacol Ther*. 2012;9:158–169.
  22. Zynquista: summary of product characteristics. [cited 2020 Apr 1]. Available from: [https://www.ema.europa.eu/en/documents/product-information/zynquista-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/zynquista-epar-product-information_en.pdf)
  23. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with Type 1 diabetes. *N Engl J Med*. 2017;377:2337–2348.
  - **The first randomized, placebo-controlled, phase III trial that evaluated the safety and efficacy of sotagliflozin in patients with type 1 diabetes.**
  24. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with Type 1 diabetes: the North American inTandem1 study. *Diabetes Care*. 2018;41:1970–1980.
  - **A randomized, placebo-controlled, phase III trial that evaluated the safety and efficacy of treatment with sotagliflozin for 52 weeks in patients with type 1 diabetes.**
  25. Danne T, Cariou B, Banks P, et al. HbA(1c) and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with Type 1 diabetes: the European inTandem2 study. *Diabetes Care*. 2018;41:1981–1990.
  - **A randomized, placebo-controlled, phase III trial that evaluated the safety and efficacy of treatment with sotagliflozin for 52 weeks in patients with type 1 diabetes.**
  26. Danne T, Cariou B, Buse JB, et al. Improved time in range and glycemic variability with sotagliflozin in combination with insulin in adults with Type 1 diabetes: a pooled analysis of 24-week continuous glucose monitoring data from the Intandem program. *Diabetes Care*. 2019;42:919–930.
  27. Powell DR, Zambrowicz B, Morrow L, et al. Sotagliflozin decreases postprandial glucose and insulin concentrations by delaying intestinal glucose absorption. *J Clin Endocrinol Metab*. 2020;105(4):dgz258.
  28. van Raalte DH, Bjornstad P, Persson F, et al. The impact of sotagliflozin on renal function, albuminuria, blood pressure, and hematocrit in adults with Type 1 diabetes. *Diabetes Care*. 2019;42:1921–1929.
  29. Henry RR, Thakkar P, Tong C, et al. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with Type 1 diabetes. *Diabetes Care*. 2015;38:2258–2265.
  30. Peters AL, Buschur EO, Buse JB, et al. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care*. 2015;38:1687–1693.
  31. Sands AT, Zambrowicz BP, Rosenstock J, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in Type 1 diabetes. *Diabetes Care*. 2015;38:1181–1188.
  32. Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157:336–347.
  33. Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in Type 1 diabetes: the EASE trials. *Diabetes Care*. 2018;41:2560–2569.
  34. Hampf C, Swain RS, Horgan C, et al. Use of sodium-glucose cotransporter 2 inhibitors in patients with Type 1 diabetes and rates of diabetic ketoacidosis. *Diabetes Care*. 2020;43:90–97.
  35. Handelsman Y, Henry RR, Bloomgarden ZT, et al. American association of clinical endocrinologists and american college of endocrinology position statement on the association of SglT-2 inhibitors and diabetic ketoacidosis. *Endocr Pract*. 2016;22:753–762.
  36. Perkins BA, Rosenstock J, Skyler JS, et al. Exploring patient preferences for adjunct-to-insulin therapy in Type 1 diabetes. *Diabetes Care*. 2019;42:1716–1723.
  37. Weber DR, Haynes K, Leonard MB, et al. Type 1 diabetes is associated with an increased risk of fracture across the life span: a population-based cohort study using The Health Improvement Network (THIN). *Diabetes Care*. 2015;38:1913–1920.
  38. Neal B, Perkovic V, Mahaffey KW, et al. CANVAS program collaborative group. canagliflozin and cardiovascular and renal events in Type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
  39. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
  40. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in Type 2 diabetes. *N Engl J Med*. 2019;380:347–357.
  41. Erythropoulou-Kaltsidou A, Polychronopoulos G, Tziomalos K. Sodium-glucose co-transporter 2 inhibitors and fracture risk. *Diabetes Ther*. 2020;11:7–14.
  42. European Medicines Agency: Zynquista Assessment Report. [cited 2020 Apr 1]. Available from: [https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-zynquista\\_en.pdf](https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-zynquista_en.pdf)