EXPERT OPINION

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Empagliflozin, a sodium glucose co-transporter 2 inhibitor, in the treatment of type 1 diabetes

Elizabeth M Lamos, Lisa M Younk & Stephen N Davis[†]
[†]*University of Maryland School of Medicine, Department of Medicine, Baltimore, USA*

Introduction: Available anti-hyperglycemic therapy in type 1 diabetes (T1DM) is currently restricted to insulin, pramlintide, and pancreas or islet cell transplantation. The imperfect replication of normal insulin secretion and glucose control has been a driver for development of other anti-hyperglycemic agents for this population. Empagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, is currently under investigation as an add-on therapy to insulin in T1DM.

Areas covered: Within the drug evaluation, the authors describe the mechanism of action of SGLT2 inhibitors and preliminary results from studies investigating treatment in rodent models and in individuals with T1DM.

Expert opinion: Studies on adjunct therapeutic effects of empagliflozin in individuals with T1DM are limited, but initial reports show favorable effects on reducing HbA1c, body weight, total daily insulin dose and hypoglycemic events. Intriguingly, this drug may confer a degree of renal protection by reducing glomerular hyperfiltration that can arise in the diabetic state. Currently, the primary concern seems to be the presence of ketone levels indicating an under-insulinized state. Long-term effects can only be inferred from studies in type 2 diabetes mellitus at this time. Empagliflozin represents a novel non-insulin-mediated therapy that warrants further investigation.

Keywords: empagliflozin, glycemic control, sodium glucose co-transporter 2 inhibitor, type 1 diabetes mellitus

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1. Introduction

Diabetes mellitus is conservatively the seventh leading cause of mortality worldwide [1]. Type 1 diabetes (T1DM) is characterized by a complete (or near complete) deficiency of insulin and comprises < 5% of the cases of diabetes mellitus. Therapy for T1DM focuses on insulin replacement therapy, usually as a combination of longer- and shorter-acting insulin (basal–bolus) or continuous subcutaneous insulin infusion (insulin pump).

The Diabetes Control and Complications Trial and its extension trial, Epidemiology of Diabetes Interventions and Complications, demonstrated that a period of intensive control (HbA1c ~ 7%) with insulin therapy reduced the risk of eye disease (76%), kidney disease (50%), peripheral neuropathy (60%) and non-fatal heart attack, stroke or death from cardiovascular disease (57%). The most significant downfall of intensive treatment was an increased risk for hypoglycemia, including episodes that required third-party assistance (two- to threefold increase compared to standard therapy) [2,3]. Despite the proven benefits of tighter metabolic control in T1DM on reducing tissue complications of the disease, this risk and the associated fear of hypoglycemia, as well as weight gain, are significant limitations to treatment [4], and we have not been able to translate an HbA1c target of 7% into

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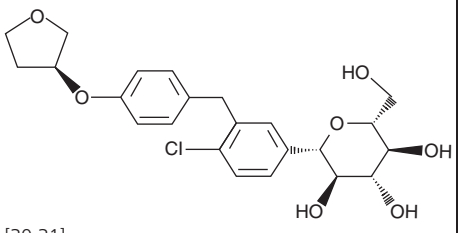
Box 1. Drug summary.

Drug name	Empagliflozin
Phase	2
Indication	Adjunct to insulin therapy in type 1 diabetes mellitus
Pharmacology description	Sodium glucose co-transporter 2 inhibitor
Route of administration	Oral
Chemical structure*	
Pivotal trial(s)	[30,31]

*Recreated from PubChem Compound, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=11949646 [Accessed 17 January 2014].

clinical practice. In fact, the mean HbA1c level of the T1DM population in the United States is still just below 8% [5].

Thus, attaining tight metabolic control without hypoglycemia in T1DM remains a therapeutic challenge. Adjunctive approved options in addition to insulin include pramlintide (amylin analog) and ultimately pancreas or islet cell transplantation. The lack of alternative therapies in T1DM is limited in a disease that has high morbidity and mortality and effects a young population. Targeting reabsorption of glucose via the kidney by inhibition of sodium glucose co-transporters (SGLTs) presents an interesting insulin-independent mechanism by which exposure to hyperglycemia is reduced. The role of SGLT2 inhibitors in T1DM treatment, specifically focusing on empagliflozin (one of two SGLT2 inhibitors being investigated in this population), will be discussed (Box 1).

2. Introduction to empagliflozin

2.1 Background physiology

Plasma glucose is filtered by the glomerulus and reabsorbed in the proximal convoluted tubule (PCT) within the kidney (**Figure 1**). Glucose transport across the epithelial membrane of the PCT is coupled with sodium transport via SGLTs. Initially, the sodium gradient between the luminal and intracellular spaces drives secondary active transport of glucose into the epithelial cell. Glucose transporter 2 (GLUT2) then passively reabsorbs glucose into the blood [6,7]. The nephron reabsorbs all of the filtered plasma glucose, up to about 180 g/24 h at a transport maximum of 375 mg/min [6,8]. This occurs when the plasma glucose concentration (or renal threshold) is generally ~ 180 mg/dl (10 – 11 mmol/l), with variations among nephrons due to heterogeneity of glucose reabsorption among renal tubules [9]. Under normal conditions, there is no glucose in the urine. Once the absorptive capacity of the PCT is exceeded and the filtered glucose load rises to a level of ~ 250 mg/min and SGLTs are saturated, glycosuria occurs [8,10].

SGLT2, the main carrier protein, is located within the S1 segment of the early PCT and accounts for nearly 90% of the renal reabsorbed glucose. SGLT2 has a low affinity for glucose and a high capacity for glucose transport [11]. SGLT1 mediates a smaller percentage (< 10%) of glucose reabsorption within the late PCT with a lower capacity for glucose transport. By inhibiting SGLT2, renal glucose absorption decreases, urinary glucose excretion (UGE) increases and this ultimately leads to lower plasma glucose levels [12-14].

In the setting of diabetes, glycosuria is not detected until the plasma glucose is > ~ 180 mg/dl (the non-diabetic plasma glucose threshold, see above). This altered response is thought to be the result of an increased renal threshold observed in diabetes. In T1DM and type 2 diabetes mellitus (T2DM), the glucose transport maximum is increased and may be the result of increased SGLT and GLUT expression [15-18]. Thus, increased SGLTs transporters appear to paradoxically preserve the elevated plasma glucose rather than excreting the excess filtered glucose into the urine [9].

The role of SGLTs in the pathogenesis of diabetic nephropathy has been investigated in a number of rodent models (reviewed by Vallon *et al*.) [19]. Individuals with diabetes can develop renal hemodynamic changes that have been linked to the development of diabetic nephropathy. Proximal tubular growth and subsequent increase in glomerular filtration rate (GFR) have been linked to the renal expression of SGLTs and changes in sodium reabsorption in diabetic rodent models. The consequences of SGLT2 inhibition under hyperglycemic conditions on diabetic nephropathy have yet to be defined.

2.2 Pharmacokinetics and pharmacodynamics

Currently, two SGLT2 selective inhibitors have been approved for clinical use in T2DM: dapagliflozin (US and EU) and canagliflozin (US only). Empagliflozin, a third SGLT2 inhibitor, is currently seeking approval in the EU and US for T2DM treatment. Dapagliflozin and empagliflozin are currently the only SGLT2 inhibitors being studied for therapy in T1DM, with empagliflozin actively seeking approval for clinical use in this population. Empagliflozin is an orally administered highly selective SGLT2 inhibitor that can be taken without regard to food intake. Exposure to empagliflozin, as assessed by $AUC_{0-\infty}$ and C_{max}, increases in a dose proportional manner when studied in healthy individuals [20]. UGE was 67 g/24 h in healthy individuals treated with empagliflozin 50 mg/day for 5 days [21]. In single-dose studies of empagliflozin (2.5, 10, 25, 100 mg over 8 days) in individuals with T2DM, 24 h UGE ranged from 46 to 90 g, compared to ~ 6 g in placebo-treated controls [22]. After 4 weeks of empagliflozin treatment (10, 25 or 100 mg) in individuals with T2DM on no more

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Article highlights.

- Therapies for lowering glucose and/or reducing glycemic variability are limited primarily to insulin in patients with type 1 diabetes (T1DM).
- Few studies have explored the use of sodium glucose co-transporter 2 (SGLT2) inhibitors in T1DM.
- Preliminary results indicate empagliflozin, an SGLT2 inhibitor, is associated with improved HbA1c and body weight and reductions in total daily insulin dose and hypoglycemic events.
- An additional therapeutic benefit of empagliflozin may be renal protection through reduced glomerular hyperfiltration.
- Potential effects of empagliflozin treatment include genitourinary infections and positive ketone levels.
- SGLT2 inhibitors offer a potential non-insulin-mediated therapeutic mechanism for improving glycemic control in T1DM but require further examination in this population.

This box summarizes key points contained in the article.

than two oral anti-hyperglycemic agents, UGE increased by 74 – 90 g compared to no change in the placebo group (baseline UGE 4 – 8 g) [23]. After administration of empagliflozin 50 mg to individuals with reduced eGFR, renal impairment resulted in progressively decreased renal clearance of empagliflozin and UGE_{24h}. However, it was well tolerated with any degree of renal dysfunction and no dose adjustment was recommended [24]. Empagliflozin has demonstrated reduced fasting and postprandial glucose levels in healthy subjects and individuals with T2DM [20,23,25].

Studies of SGLT2 inhibition in animal models of T1DM are few. Dapagliflozin, administered as a single oral dose in streptozotocin (STZ)-treated rats, induced a 55% reduction in blood glucose [26]. Sergliflozin, an unapproved SGLT2 inhibitor, improved postprandial hyperglycemia in STZ-treated rats. The degree of the glucose-lowering effect of sergliflozin was positively correlated with the severity of the hyperglycemia [27].

In another study, STZ-treated diabetic Sprague-Dawley rats (resembling human T1DM) were administered empagliflozin, with or without subcutaneously injected insulin glargine 1.5 IU, or insulin glargine 6 IU monotherapy [28]. Acutely, empagliflozin in combination with insulin glargine 1.5 IU demonstrated a similar glucose lowering effect as insulin glargine 6 IU. In a second study arm, rats were treated for 28 days with: i) empagliflozin alone; ii) empagliflozin plus insulin glargine; and iii) one insulin-releasing implant (human insulin; 2 IU/24 h), or iv) two insulin-releasing implants (4 IU/24 h). End of study glucose exposure (AUC over 12 h on day 28) was statistically lower with empagliflozin in combination with insulin glargine compared to a control group (no intervention; $p < 0.001$) and reduced blood glucose more than in rats with one insulin-releasing implant ($p < 0.001$). However, glucose monitoring did suggest that the effect of empagliflozin waned by the end of the 12-h study period. HbA1c measured on day 28 was similarly and significantly reduced in the group treated with combination therapy and the group that received two implants compared to baseline ($p < 0.001$). Body weight increased significantly in the combination treatment group compared to control ($p < 0.001$) but was lower than in animals with the two implants ($p < 0.05$). Monotherapy with empagliflozin did not increase plasma ketones compared to controls. The authors did not report any hypoglycemic events.

2.3 Preliminary clinical efficacy

A few studies have investigated the use of SGLT2 inhibitors to reduce hyperglycemia in individuals with T1DM (**Table 1**). Henry *et al*. reported in a 2013 American Diabetes Association presentation that, in a small (n = 70) 2-week Phase IIa study, individuals with T1DM (mean HbA1c 8.5%) administered dapagliflozin (1, 2.5, 5, or 10 mg) in addition to their regular insulin regimen had improved glycemic control and required less insulin compared to those on placebo [29]. Seven-point glucose measurements trended downward in all treatment groups. There was a dose-dependent increase in mean 24 h UGE from baseline. Fasting plasma glucose (FPG) significantly declined from baseline compared to placebo (placebo: -8.1%; 1 mg: -26%; 5 mg: -42%; 10 mg: -36%). Hypoglycemic events were similar in all groups. Asymptomatic but positive urine ketones were reported in all treatment groups. Few subjects receiving dapagliflozin had genitourinary effects.

Effects of empagliflozin in individuals with T1DM were also reported recently [30,31]. The study investigated the use of empagliflozin in moderately controlled T1DM (mean HbA1c 8%) with normal albuminuria [30]. Outcomes were compared to a 2-week run-in period. After 8 weeks of treatment with empagliflozin 25 mg/day, HbA1c decreased by 0.4% ($p < 0.0001$), symptomatic hypoglycemia declined ($p = 0.0004$) and mean total daily insulin dose declined by 16% ($p < 0.0001$). Mean UGE significantly increased from 19 to 134 g/24 h at 8 weeks of treatment ($p < 0.0001$). FPG declined by 22% (-36 mg/dl or -2 mmol/l, $p = 0.008$). Weight significantly decreased by 2.7 kg, ($p < 0.0001$) with a decrease in waist circumference by 3.8 cm ($p < 0.0001$). Adverse events included hypoglycemia, which declined from 0.12 to 0.04 events/day, polyuria (79%) and polydipsia (74%). There were two reported episodes of ketoacidosis. One was associated with gastroenteritis and the other to insulin pump failure.

The same study then reported the effect of 8 weeks of empagliflozin 25 mg/day on renal hemodynamics in individuals with T1DM [31]. Renal hemodynamic changes associated with diabetes have been described previously [19]. The adaptive response to conserve glucose is preserved in individuals with diabetes, whereby glucose reabsorptive capacity is paradoxically increased despite excess blood glucose levels. Renal hemodynamic changes in diabetes include glomerular hyperfiltration and kidney growth [32]. Given the mechanism

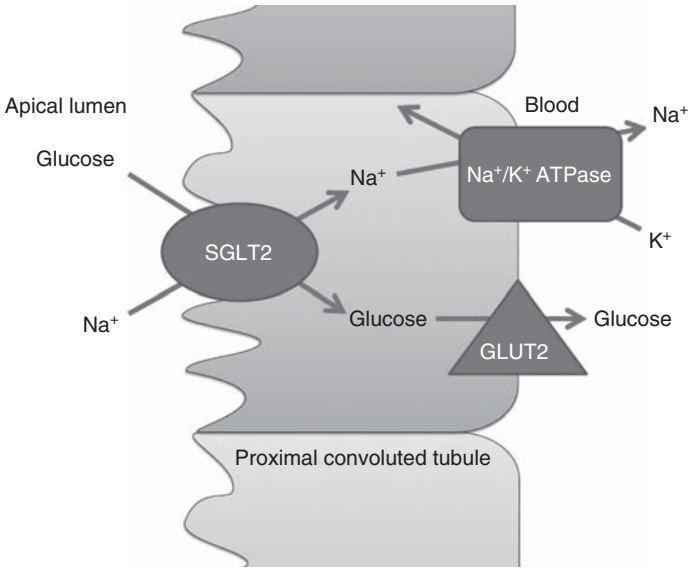

Figure 1. Mechanism of SGLT2 within the proximal convoluted tubule.
GLUT2: Glucose transporter 2; K^+: Potassium; Na^+: Sodium; SGLT2: Sodium glucose co-transporter.

Table 1. Clinical studies of SGLT2 inhibitors in individuals with T1DM.

Study	Therapy	Duration	N	Hba1c (%)	FPG	Daily insulin	UGE (g/d)	Weight (kg)	Adverse events	Limitations
Perkins *et al*. [30]	Empagliflozin 25 mg daily	2 week run-in; 8 week single-arm open label	40	↓ 0.4*	↓ (2 mmol/l)*	↓ (~ 9 U/day)*	↑ 19	↓ 2.6*	Mainly pollakuria, thirst Few with hypoglycemia, ketoacidosis, or nausea/vomiting	Single-arm study design; small N
Henry *et al*. [29]	Dapagliflozin 1,2.5, 5, or 10 mg daily versus placebo	2 week RDBPC	70	NR	↓ (20 – 42%)‡	↓ (11 – 19%)‡	NR	NR	Hypoglycemia, ketoacidosis, gastroparesis§	Designed for proof-of-concept; small N
Clinical Trial NCT01392560 (ATIRMA Trial)	Empagliflozin 25 mg daily	8-week open-label	Completed, some results reported [30,31]							
Clinical Trial NCT01969747 (EASE-2)	Empagliflozin 2.5, 10, or 25 mg versus placebo	14 day run-in; 28 day RDBPC	Recruiting							

*Statistically significant $p < 0.01$.
‡Unknown significance.
§Abstract with limited information.
FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; NR: Not reported; RDBPC: Randomized, double-blind, placebo-controlled; SGLT2: Sodium glucose co-transporter; T1DM: Type 1 diabetes mellitus; U: Units; UGE: Urinary glucose excretion; ↓: Decline; ↑: Increase.

by which SGLT2 inhibitors affect glycosuria, this study sought to investigate if SGLT2 inhibition with empagliflozin would impact renal hyperfiltration in subjects with T1DM. Individuals were stratified based on GFR (> 135 ml/min/1.73 m^2 or T1DM-H, n = 27 or 90 – 134 ml/min/1.73 m^2 or TIDM-N, n = 13). Individuals underwent a euglycemic (4 – 6 mmol/l) and hyperglycemic clamp (9 – 11 mmol/l) at baseline and after treatment with empagliflozin. Basal and prandial insulin was reduced by 30% with empagliflozin administration. In both groups, UGE increased significantly (18 – 107 g/24 h for T1DM-N and 19 – 147 g/24 h for T1DM-H, within group $p < 0.01$ and between group, $p < 0.05$) over the study duration.

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During euglycemia, declines in hyperfiltration (172 ± 23 to 139 ± 25 ml/min/1.73 m^2, $p < 0.01$), plasma nitric oxide ($p < 0.01$), effective renal plasma flow ($p < 0.01$), renal blood flow ($p < 0.01$) and systolic blood pressure ($p < 0.05$) were observed in individuals with T1DM-H administered empagliflozin. Renal vascular resistance ($p < 0.01$), circulating aldosterone ($p = 0.02$) and angiotensin II ($p = 0.04$) increased. These findings were similar when tested under hyperglycemic clamp conditions. In subjects with T1DM-N, renal hemodynamic function, blood pressure and nitric oxide remained unchanged during both euglycemic and hyperglycemic conditions. Plasma aldosterone increased in T1DM-N under both conditions. These results suggest that SGLT2 inhibition with empagliflozin may attenuate renal hyperfiltration in T1DM. The authors concluded that this is likely the consequence of pre-glomerular vasoconstriction and increased distal tubule sodium exposure due to inhibition of proximal tubular SGLT.

Additionally, the study then investigated whether improved glycemic control with empagliflozin over an 8-week period would affect systemic hemodynamic effects [33]. During euglycemia, systolic blood pressure significantly declined 2 mmHg ($p = 0.02$). Diastolic blood pressure and pulse did not significantly change. There was no significant change in blood pressure or pulse during hyperglycemia. Carotid radial pulse wave velocity and radial augmentation index declined significantly under euglycemic and hyperglycemic conditions. Carotid femoral pulse wave velocity declined significantly during hyperglycemia. Carotid and aortic augmentation indices significantly declines compared to baseline during both conditions ($p < 0.0001$). Effects on heart rate variability and sympathetic nervous system markers (plasma adrenaline and noradrenaline) were not significant under both conditions. The authors concluded that the reduction in hyperglycemia secondary to treatment with empagliflozin reduced arterial stiffness and may play a part in the small reduction in blood pressure associated with SGLT2 inhibition.

3. Conclusion

There are limited treatment options for individuals with T1DM. Practitioners have relied on insulin therapy (outside of pancreas transplant) because this targets the pathophysiology of the disease. However, because insulin analogs and insulin administration (i.e., basal-bolus therapy or insulin pump) have failed to continuously and effectively mirror the elegant accuracy and precision of the human pancreas, many individuals with T1DM suffer significant glucose variability, hyperglycemia at the expense of reduced hypoglycemia, and weight gain. There is a renewed interest in re-evaluating other non-insulin-mediated anti-hyperglycemic adjunct therapeutic options in T1DM (i.e., acarbose, DPP-4 inhibitors or GLP-1 agonists) and SGLT2 inhibition potentially offers a novel 'smoothing' effect, whereby total daily insulin dosing can be reduced, weight gain and hypoglycemia are abated, and overall glycemia is improved. SGLT2 inhibition in the treatment of T2DM has not been universal or formalized but with continued experience and familiarity will likely become a second- or third-line agent when therapy is individualized for cost, patient preference and comorbidities. The role of empagliflozin and other SGLT2 inhibitors as adjunct therapy in treatment of T1DM remains unclear but promising.

4. Expert opinion

SGLT2 inhibitors, such as empagliflozin, have both basal and postprandial anti-hyperglycemic effects. Because induced increases in urinary glucose occur in a non-insulin-mediated manner, individuals with T1DM can potentially benefit from addition of this medication to achieve target glycemic control. No direct study comparing UGE in individuals with T1DM to healthy or T2DM who are treated with empagliflozin has been completed. However, UGE is increased from baseline in T1DM compared to placebo and healthy [21,30] and UGE is at least comparable to that demonstrated in T2DM depending on the dose of empagliflozin administered [22,23]. The preliminary studies with empagliflozin and dapagliflozin in T1DM individuals suggest that total insulin use can be decreased with use of these treatments [29,31]. The reduction in FPG and declining seven-point glucose measurements suggest that both basal and prandial insulin should be reduced in individuals with T1DM with adjunct SGLT2 inhibition. To guide reduction, the Cherney *et al.* study reduced both basal and prandial insulin by 30% with administration of empagliflozin 25 mg/day, but this likely needs to be individualized based on baseline glycemic control. Insulin dose reduction may help limit the potential adverse effects of insulin on hypoglycemia and weight gain.

The available studies suggest that SGLT2 inhibitors can be safely co-administered with background insulin therapy and that the risk of hypoglycemia is not increased. This again is likely related to the non-insulin-mediated action of SGLT2 inhibitors. The lack of increased hypoglycemic events may also be impacted by the reduced total daily insulin dosing observed. No comment on glucose variability was discussed, but based on the mechanism of action of SGLT2 inhibitors, they may offer a 'smoothing' effect.

Individuals with T1DM will produce ketones when fatty acids are broken down as alternate fuel, a situation that can arise during the fasting or insulin-deficient state or during 'sick-days'. Ketosis is dangerous and is a major contributor to morbidity and mortality in individuals with T1DM that can lead to hospitalization, intensive care management, increased health care utilization and even death. All T1DM studies reported ketone production, albeit individual studies did not demonstrate an increase in ketone production in those groups administered SGLT2 inhibition compared to controls. Based on the mechanism of action of SGLT2, namely inhibition of glucose reabsorption, it is unlikely that SGLT2 inhibitors themselves are 'ketogenic.' The presence of ketones ultimately demonstrates an insulinopenic state, whereby cellular glucose

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uptake is reduced. It is unclear if this is the result of the reduced total daily insulin dosing, which may be adequate to lower blood glucose but insufficient to drive complete glucose uptake in cells. Alternatively, perhaps the positive ketones are a consequence of the waning effect of SGLT2 inhibition detected toward the end of the 12-h study period in the aforementioned rodent study [28]. Under this circumstance, there could be a period of hyperglycemic insulinopenia ultimately leading to ketone production. This situation may be negated by changes in the dosing strategy of both SGLT2 inhibition and/or insulin and necessitate further characterization as elevated ketone production can be life-threatening in this population.

It is unknown if SGLT2 inhibition would be effective or harmful in situations of acute illness, during which individuals with T1DM can be intravascularly volume deplete. The study by Cherney *et al*. does suggest that in individuals with T1DM and hyperfiltration, the blood pressure lowering effect observed with empagliflozin administration was the consequence of effective circulating volume contraction via a diuretic effect [31]. Ketone production in all subjects was low (5%). The compounding effect of illness and dehydration on ketone production is unknown.

Additionally, there are limited data on the long-term safety of empagliflozin or other SGLT2 inhibitors in individuals with T1DM or even in rodent models. A short Phase IIa dapagliflozin study did not demonstrate an increase in all adverse events, but a few patients had genitourinary effects that have been previously characterized and associated with SGLT2 inhibitors. Nasopharyngitis (26%) and genitourinary infections (14%) were most commonly documented in T1DM individuals who took empagliflozin, with 5% of subjects reporting ketoacidosis [31]. There was no placebo group for comparison. It is unknown whether the increases in genitourinary infections could be significant in individuals with T1DM who are sensitive to ketone production in the setting of illness.

The role of SGLT2 inhibition in individuals with T1DM and renal insufficiency is unclear and currently requires extrapolation of data from studies of SGLT2 inhibition in individuals with T2DM. Empagliflozin studied in individuals with T2DM was safe and well tolerated [22]. However, dapagliflozin is not recommended in moderate to severe renal disease; canagliflozin has been associated with a reduction in GFR in moderate renal impairment and has a recommendation of dose reduction in the population. The question remains as to whether or not diabetic renal disease in T2DM can be compared to renal disease in the individual with T1DM. The small trial of empagliflozin studied under euglycemic and hyperglycemic clamp conditions suggests that there is unlikely to be a detrimental effect on renal hemodynamics and is encouraging that there could be a favorable role in individuals with T1DM and renal hyperfiltration. One clinical study has been completed (NCT01392560) evaluating the effect of empagliflozin treatment on glomerular filtration in subjects with T1DM but results have not been reported [34].

There are no data on the long-term safety of empagliflozin in individuals with T1DM with hepatic or cardiovascular disease. Studies in individuals with T2DM indicate that dosing of empagliflozin is safe with hepatic impairment [35]. The one large cardiovascular outcome-based study of canagliflozin treatment in T2DM (CANVAS – CANagliflozin cardioVascular Assessment Study) is ongoing, with primary and secondary end points focused toward cardiovascular risk and major adverse cardiac events [36]. Cherney *et al*. demonstrated reduced systolic blood pressure and arterial stiffness in T1DM with empagliflozin treatment [31,33]. Data from T2DM studies of empagliflozin demonstrated small improvements in blood pressure and HDL-C levels [37,38]. Total cholesterol, LDL-C, triglycerides and heart rate were unchanged. LDL-C was mildly increased in one study [38]. These cardiovascular parameters have not been studied in individuals with T1DM.

Data are limited in the direct study of empagliflozin or other SGLT2 inhibitors in subjects with T1DM. At this time, insight regarding the use of SGLT2 inhibitors in this population can only be gained by extrapolation from studies in rodent models of T1DM, a few small studies in humans and an understanding of the non-insulin-mediated action of SGLT2 inhibitors. One study, currently underway, that may help to further characterize empagliflozin in patients with T1DM is a placebo-controlled, double-blind design comparing three doses of empagliflozin (2.5, 10 and 25 mg) over 25 days in patients with T1DM as adjunct to insulin therapy (NCT01969747) [39].

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Declaration of interest

SN Davis is a consultant for Sanofi Aventis and Boehringer Ingelheim. The authors have no other 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 apart from those disclosed.

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Affiliation

Elizabeth M Lamos[1] MD, Lisa M Younk[2] BS & Stephen N Davis[†2,3] MBBS FRCP FACP
[†]Author for correspondence
[1]Assistant Professor of Medicine, Endocrinology, Diabetes and Nutrition,
University of Maryland School of Medicine,
660 West Redwood Street, Howard Hall 469,
Baltimore, MD 21201, USA
[2]Clinical Research Specialist,
University of Maryland School of Medicine,
Department of Medicine, 3-013 Bressler Research Building, 655 W. Baltimore St., Baltimore,
MD 21201, USA
[3]Theodore E. Woodward Professor and Chair of Medicine, Physician-in-Chief,
University of Maryland School of Medicine,
22 South Greene St. N3W42, Baltimore,
MD 21201, USA
Tel: +1 410 328 2488;
Fax: +1 410 328 8688;
E-mail: sdavis@medicine.umaryland.edu

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