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REVIEW

Ertugliflozin in the treatment of type 2 diabetes mellitus

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Abstract

More than 422 million people worldwide have diabetes, with 90–95% having type 2 diabetes (T2D). Glycemic control of T2D has demonstrated reductions in microvascular complications but recent data have demonstrated improvements in macrovascular outcomes with sodium–glucose cotransporter 2 (SGLT2) inhibitors. Ertugliflozin is the most recent SGLT2 inhibitor approved in the USA and Europe for the treatment of T2D. This narrative review aims to present and discuss the efficacy, safety, cardiovascular (CV), and renal outcomes related to the use of ertugliflozin in T2D. Ertugliflozin has been evaluated in eight clinical trials (*n*=5248) with a focus on glycemic control. These trials have demonstrated improvement in glycosylated hemoglobin (0.6–1%), fasting plasma glucose (30–50 mg/dL), 2-hour postprandial glucose (60–70 mg/dL), decreased body weight (2–3 kg), and lowering of blood pressure (3–5 mmHg) in patients with T2D when ertugliflozin is used as monotherapy or in addition to metformin, sitagliptin, insulin, and/or sulfonylureas. The findings from the VERTIS-CV trial (*n*=8246) were recently published and demonstrated that ertugliflozin use in patients with T2D and atherosclerotic CV disease is safe but did not demonstrate superiority in the lowering of major CV events compared to placebo. Other SGLT2 inhibitors, such as empagliflozin and canagliflozin, have demonstrated this benefit. The VERTIS-CV trial demonstrated that the use of ertugliflozin led to a decrease in the number of hospitalizations for heart failure and this lends further support that this benefit is a class effect of SGLT2 inhibitors.

Keywords: adverse effects, blood pressure, body weight, ertugliflozin, diabetes mellitus, drug interactions, metabolic effects, sodium–glucose cotransporter 2 inhibitors.

Citation

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Introduction

More than 422 million people worldwide have diabetes, with 90–95% having type 2 diabetes (T2D).[1] While glycemic control has improved in this population, many patients with T2D do not achieve their glycemic goals.[2] There are a multitude of oral and injectable agents for use as monotherapy or in combination for patients with T2D; drug selection is driven by a number of factors, including the ability to lower glycosylated hemoglobin (A1C), side effects, cost, risk of hypoglycemia, patient preference, and cardiovascular disease (CVD) risk reduction.[3] Emphasis should be placed on shared decision-making and individualization of drug therapy and efforts should be made toward the timely and purposeful intensification of therapy.[2,3]

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are the newest therapeutic class of oral agents for the treatment of T2D. This therapeutic class currently includes four agents approved in the USA and Europe: canagliflozin, dapagliflozin, empagliflozin, and now ertugliflozin, the newest SGLT2 inhibitor. Ertugliflozin (Steglatro™) was approved by the US Food and Drug Administration (FDA) on December 22, 2017, and by the European Medicines Agency (EMA) on January 25, 2018.[4,5] Fixed-dose combinations of ertugliflozin and metformin (Segluromet™) and ertugliflozin and sitagliptin (Steglujan™) have also been approved by both agencies.[4,5]

This narrative review aims to present and discuss the efficacy, safety, cardiovascular (CV), and renal outcomes related to the use of ertugliflozin in T2D. We conducted an English-language MEDLINE search from 1995 through June 2020 using the terms 'PF-04971729,' 'ertugliflozin,' 'sodium–glucose cotransporter 2 inhibitor,' and 'SGLT2 inhibitor' alone and in various combinations. All adult human studies comparing primary outcomes of safety and efficacy of ertugliflozin for T2D were eligible for inclusion. A manual search for references from these trials and review articles was performed to identify additional relevant articles.

Pharmacology

Mechanism of action

The kidneys filter approximately 162 g of glucose per 24 hours in order to maintain a normal fasting plasma glucose (FPG) of approximately 100 mg/dL.[6] The kidneys also play a key role in reclaiming filtered glucose utilizing glucose transporters, SGLT2 and SGLT1. Glucose transporters are mostly responsible for passive glucose uptake whereas SGLTs participate in active glucose transport across membranes.[6] SGLT2 is responsible for up to 90% of glucose reabsorption.[7] The expression and activity of SGLT2 are increased in patients with T2D, leading to increased filtering and absorption of glucose and a resulting state of hyperglycemia.[8] The physiologic mechanism of SGLT2 coupled with its overexpression in patients with T2D makes it a drug treatment target for improved glycemia in patients with T2D. Additionally, SGLT2 inhibitors have a number of other mechanisms that are not associated with glycemia improvements. The increased natriuresis, reductions in plasma volume, improved vascular resistance, reduced blood pressure, and changes in tissue sodium handling are the likely mechanisms for benefits seen in the heart failure (HF) and chronic kidney disease (CKD) populations.[9] Additionally, the increased shift in ketone body metabolism, decreased serum uric acid levels, reduced adipose tissue-mediated inflammation, decreased oxidative stress, and suppression of damage mediated by advanced glycation end products are likely associated with the CV benefits seen with SGLT2 inhibitors as a class.[9]

Ertugliflozin highly selectively inhibits SGLT2, as other SGLT2 inhibitors do, in order to reduce the renal reabsorption of filtered glucose and decrease the renal threshold for glucose, which in turn increase urinary glucose excretion (UGE).[10,11] The use of SGLT2 inhibitors results in the reabsorption of glucose into the bloodstream and promotes glucosuria. Like other SGLT2 inhibitors, ertugliflozin works independently of insulin secretion and sensitivity. Ertugliflozin acts synergistically in combination with other oral agents – specifically metformin, sitagliptin, and sulfonylureas – as well as in combination with insulin. While ertugliflozin on its own confers little risk of hypoglycemia, it may increase the risk when used in combination with agents that have a known risk of hypoglycemia (e.g. insulin, sulfonylureas).[10,12] The general guidance when considering the administration of an SGLT2 inhibitor is that if a patient is taking either insulin or a sulfonylurea and is at a higher risk for hypoglycemia (e.g. elderly, impaired renal function), then a reduction of either the insulin or sulfonylurea dose prior to starting an SGLT2 inhibitor is recommended.

Pharmacokinetics

Ertugliflozin has been studied in both healthy human subjects and in patients with T2D, with its pharmacokinetic (PK) profile being similar in these populations. Ertugliflozin is nearly 100% orally bioavailable and reaches its peak concentration within 1 hour (fasted state) or 2 hours (if taken with a high-fat, high-calorie meal). The area under the curve is not altered with concurrent administration with food compared to the fasted state. The half-life ($t_{1/2}$) of ertugliflozin in patients with T2D is 16.6 hours, making it appropriate for once-daily dosing. Ertugliflozin reaches steady-state concentrations after 4–6 days of once-daily dosing.[10,12] One study conducted in patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <60 mL/min/1.73 m^2) who received ertugliflozin 5 mg daily or 15 mg daily failed to reach its primary endpoint of change in A1C. At the end of 26 weeks, no difference in the change in A1C between the ertugliflozin 5 mg and placebo groups was observed.[10,13] Based on the reduced efficacy in this moderate renal impairment population, ertugliflozin is not recommended for use in patients with T2D and an eGFR of <60 mL/min/1.73 m^2.[10,13] The response to SGLT2 inhibitors as assessed by urinary glucose excretion declines with increasing severity of renal impairment as assessed by a decrease in eGFR. Ertugliflozin has been studied in patients with mild or moderate hepatic impairment (Child–Pugh class A and B) with no clinically meaningful changes in ertugliflozin PK; it has not been studied in patients with more severe hepatic impairment (Child–Pugh class C).[10,14] No dose adjustment of ertugliflozin is needed in patients with mild or moderate hepatic impairment based on phase I studies in this population.[14] Ertugliflozin is metabolized by uridine diphosphate glucuronosyltransferase (UGT)1A9-mediated and UGT2B7-mediated O-glucuronidation to two pharmacologically inactive glucuronides. Cytochrome P450-mediated metabolism is minimal.[10,14,15]

Pharmacodynamics

Glucosuria is the predominant pharmacodynamic (PD) parameter affected by ertugliflozin. Urinary glucose excretion with ertugliflozin has been characterized in both healthy subjects and patients with T2D. Ertugliflozin exhibits dose-dependent UGE in patients with T2D. A study by Amin et al.[16] evaluated the blood pressure-lowering and other effects of ertugliflozin in patients with T2D and hypertension. Patients received ertugliflozin 1, 5, or 25 mg, hydrochlorothiazide 12.5 mg, or placebo. Patients who received ertugliflozin had a least-square mean 24-hour UGE of 46.33 g (1 mg), 64.54 g (5 mg), and 74.49 g (25 mg), respectively, demonstrating increased UGE with increasing doses of ertugliflozin, which aligns with the A1C reduction increasing in a dose-dependent fashion.[16] Secondary endpoints in this study included change in body weight, FPG, and systolic/diastolic blood pressure. Significant reductions in body weight were seen with all four doses of ertugliflozin compared to placebo (1 mg to 1.9 kg, 5 mg to 2.5 kg, 10 mg to 2.9 kg, 25 mg to 2.66 kg).[16] FPG was reduced by –1.17 to 1.90 mmol/L compared to placebo in all ertugliflozin dose groups ($p<0.0001$).[16] Systolic blood pressure (SBP) reductions were seen with the 5, 10, and 25 mg doses of ertugliflozin (–3.48 mmHg, $p=0.056$; –2.88 mmHg, $p=0.096$; –3.37 mmHg, $p=0.064$; respectively) but these were not statistically significant.[16]

Similar to other SGLT2 inhibitors, the 24-hour UGE in patients with T2D and normal renal function is the greatest and declines in the setting of reduced eGFR. In a PK and PD study by Sahasrabudhe et al.,[17] healthy subjects and patients with T2D with normal renal function (eGFR ≥90 mL/min/1.73 m^2) and patients with T2D and mild (eGFR 60–89 mL/min/1.73 m^2), moderate (eGFR 30–59 mL/min/1.73 m^2), and severe (eGFR <30 mL/min/1.73 m^2) renal impairment were given a single 15 mg dose of ertugliflozin and their 24-hour UGE was measured. Patients with T2D and normal renal function demonstrated the greatest UGE with a mean UGE of 75.12 ± 24.36 g, followed by healthy subjects with normal renal function (mean UGE 48.16 ± 14.04 g) and patients with T2D and mild renal impairment (mean UGE 48.67 ± 37.72 g), patients with T2D and moderate renal impairment (mean UGE 32.64 ± 21.32 g), and finally patients with T2D and severe renal impairment (mean UGE 11.29 ± 5.81 g).[17]

An additional PD parameter that has been evaluated in subjects treated with ertugliflozin is the QTc interval. A phase I, three-period crossover study of ertugliflozin was conducted in healthy subjects to evaluate the effect of supratherapeutic ertugliflozin dosing (100 mg) compared with placebo and with moxifloxacin 400 mg on the QTc interval. In the 42 healthy subjects evaluated, ertugliflozin demonstrated no clinically relevant QTc prolongation, even at doses that were nearly seven times the maximum therapeutic dose.[18]

Clinical trials

Seven clinical trials have evaluated ertugliflozin as monotherapy, additive therapy to metformin, additive therapy to metformin and sitagliptin, and compared to glimepiride. Additionally, two clinical trials have evaluated special populations with one trial in patients with CKD and one in patients with established atherosclerotic CVD (ASCVD). A complete list of published ertugliflozin clinical trials can found in Table 1.[13,19–28]

Monotherapy

A phase III, double-blind, placebo-controlled study randomized 461 patients with T2D inadequately controlled with diet and exercise alone (A1C ≥7.0% and ≤10.0%) to ertugliflozin 5 or 15 mg per day or placebo for 26 weeks.[19] The primary efficacy endpoint was the change in A1C from baseline to week 26. Ertugliflozin treatment led to a significant reduction in A1C (−0.79% with 5 mg, −0.96% with 15 mg) compared with placebo (+0.2%; $p<0.001$). In a similar manner, ertugliflozin reduced FPG levels, 2-hour postprandial glucose (PPG) levels, and body weight significantly more than placebo (all $p<0.001$). No statistical difference in SBP lowering was seen when comparing ertugliflozin 15 mg *versus* placebo (–3.93 *versus* –2.22 mmHg, respectively) at 26 weeks.[19] No differences in symptomatic hypoglycemia, urinary tract infections (UTIs), or hypovolemia were seen between ertugliflozin and placebo.

A significantly greater incidence of genital mycotic infections (GMIs) occurred in ertugliflozin-treated patients compared to placebo.[19]

An extension of the previously discussed trial continued for an additional 26 weeks in 384 patients and had an active control arm of metformin titrated to a target dose of 1000 mg twice daily.[20] Patients continued in the 26-week extension on ertugliflozin 5 or 15 mg treatment arms and patients who received placebo during the initial 26 weeks received an active control medication of metformin. Ertugliflozin treatment continued to demonstrate sustained reductions in A1C (−0.9% with 5 mg, −1.0% with 15 mg) from baseline to 52 weeks. In addition, 25.6% and 28.5% of patients receiving 5 and 15 mg doses, respectively, achieved an A1C <7%. The study investigators did not perform a statistical comparison of ertugliflozin to the placebo/metformin group at week 52 for glycemic efficacy as metformin was added in after the initial 26-week phase of the study. Consistent with the initial phase of this trial, patients treated with ertugliflozin demonstrated a higher incidence of GMIs both in men and women in the 15 mg dosing group and in women in the 5 mg dosing group. Of note, there was a decrease in both body weight and SBP in patients treated with ertugliflozin. Similar to the initial 26-week phase, there was no difference in symptomatic hypoglycemia, UTIs, or hypovolemia in patients treated with ertugliflozin compared to active treatment with placebo/metformin.

Compared to sitagliptin

A phase III, double-blind, placebo-controlled study randomized 291 patients with T2D inadequately controlled with diet and exercise alone (A1C ≥8.0% and <10.5%) to ertugliflozin 5 mg plus sitagliptin 100 mg, or ertugliflozin 15 mg plus sitagliptin 100 mg, or placebo for 26 weeks.[21] The primary efficacy endpoint was the change in A1C from baseline to week 26. Both ertugliflozin/sitagliptin treatments led to a significant reduction in A1C (−1.6% with 5/100 mg, −1.7% with 15/100 mg) compared with placebo (−0.4%; $p<0.001$). In a similar manner, ertugliflozin/sitagliptin reduced FPG levels, 2-hour PPG levels, body weight, and SBP significantly more than placebo (all $p<0.001$). Overall, rates of adverse events were low and there was no difference in adverse events between the treatment and placebo arms. This trial demonstrated that the addition of ertugliflozin to sitagliptin was effective and safe in a population of patients with uncontrolled T2D.

Addition to metformin

A double-blind trial randomized 621 patients with T2D who had inadequate glycemic control (A1C >7.0% and <10.0%) despite receiving metformin ≥1500 mg per day for at least 8 weeks prior to randomization to receive ertugliflozin 5 or 15 mg per day or placebo for 26 weeks.[22] Ertugliflozin administration resulted in greater reductions in A1C (−0.7% with 5 mg and −0.9% with 15 mg) compared with placebo

Table 1. Ertugliflozin clinical trials in type 2 diabetes: glycemic control.[13,19–28]

Trial	N	Patient population	Follow-up mean (wk)	Primary outcome (doses in mg strength)	Other glycemic outcomes (doses in mg strength)
VERTIS MONO[19] (NCT01958671)	461	T2D uncontrolled with diet and exercise alone	52 (26 P run in followed by 26 A control)	A1C change: –0.79% (E5) *versus* 0.2% (P); $p<0.001$; –0.96% (E15) *versus* 0.2% (P); $p<0.001$	FPG*: –34.56 (E5) *versus* (P); $p<0.001$; –43.92 (E15) *versus* (P); $p<0.001$ 2hPPG*: -68.94 (E5) *versus* (P); $p<0.001$; –67.32 (E15) *versus* (P); $p<0.001$
VERTIS MONO Extension[20] (NCT01958671)	384	T2D uncontrolled with diet and exercise alone	52 (26 P run in followed by 26 A control)	A1C change: –0.9% (E5); –1.0% (E15) no comparison to P as allowed to initiate metformin in this group	FPG*: –28.8 (E5); –32.4 (E15) A1C <7%: 25.6% (E5) *versus* 28.5% (E15)
VERTIS SITA[21] (NCT02226003)	291	T2D uncontrolled with diet and exercise alone	26	A1C change: –1.6% (E5/S100) *versus* –0.4% (P); $p<0.001$; –1.7% (E15/S100) *versus* –0.4% (P); $p<0.001$	FPG*: –9.3 (P) *versus* –48.2 (E5/S100) *versus* –55.4 (E15/S100); $p<0.001$ A1C <7%: 8.3% (P) *versus* 35.7% (E5/S100) *versus* 31.3% (E15/S100); $p<0.001$
VERTIS MET[22] (NCT26378978)	621	T2D uncontrolled with metformin	26	A1C change: –0.7% (E5) *versus* 0% (P); $p<0.001$; –0.9% (E15) *versus* 0% (P); $p<0.001$	FPG*: –34.56 (E5) *versus* (P); $p<0.001$; –43.92 (E15) *versus* (P); $p<0.001$ A1C <7%: 35% (E5) *versus* 16% (P); 40% (E15) *versus* 16% (P)
VERTIS FACTORIAL[23] (NCT02099110)	1233	T2D uncontrolled with metformin	26	A1C change: –1.0% (E5) *versus* –1.1% (E15) *versus* –1.1% (S100) *versus* –1.5% (E5/S100) *versus* –1.4% (E15/S100)	FPG*: –35.7 (E5) *versus* –36.9 (E15) – 25.6 (S100) *versus* –44.0 (E5/S100) *versus* – 48.7 (E15/S100) A1C <7%: 26.4% (E5) *versus* 31.9% (E15) *versus* 32.8% (S100) *versus* 52.3% (E5/S100) *versus* 49.2% (E15/S100)
VERTIS SITA2[24] (NCT02036515)	464	T2D uncontrolled with metformin and sitagliptin	26	A1C change: –0.8% (E5) *versus* –0.2% (P); $p<0.001$; –0.9% (E15) *versus* –0.2% (P); $p<0.001$	FPG*: –1.8 (P) *versus* –27.0 (E5) *versus* –32.4 (E15); $p<0.001$ A1C <7%: 17.0% (P) *versus* 32.1% (E5) *versus* 39.9% (E15); $p<0.001$
VERTIS SU[25] (NCT01999218)	1326	T2D uncontrolled with metformin	52	A1C change: –0.6% (E5) *versus* –0.7% (G); $p<0.001$; –0.6% (E15) *versus* –0.8% (G); $p<0.001$	FPG*: –18.0 (E5) *versus* –16.2 (G); NS; –23.4 (E15) *versus* –16.2 (G); $p<0.001$ A1C <7%: 34.4% (E5) *versus* 43.5% (G); $p=0.01$; 38.0% (E15) *versus* 43.5% (G); NS

(Continued)

Table 1. ***(Continued)***

Trial	N	Patient population	Follow-up mean (wk)	Primary outcome (doses in mg strength)	Other glycemic outcomes (doses in mg strength)
VERTIS RENAL[13] (NCT01986855)	468	T2D uncontrolled with stage 3 CKD with insulin and/or sulfonylureas	52	A1C change: –0.3% (E5) *versus* –0.3% (P); p=0.81; –0.4% (E15) *versus* –0.3% (P); p=0.16	Stage 3A CKD cohort A1C Change: –0.3% (E5) *versus* –0.3% (P); p=0.83; –0.4% (E15) *versus* –0.3% (P); p=0.50
VERTIS CV[26–28] (NCT01986881)	8246	T2D uncontrolled with ASCVD	182	MACE (CV death, MI, stroke): 11.9% (E) *versus* 11.9% (P); p<0.001 for non-inferiority	CV death: 1.8% (E) *versus* 1.9% (P); p=0.39 (ITT); non-fatal MI: 1.7% (E) *versus* 1.6% (P); p=0.66; non-fatal stroke: 0.8% (E) *versus* 0.8% p=0.006 (ITT)

A, active; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; E, ertugliflozin; FPG, fasting plasma glucose; G, glimepiride; HHF, hospitalization for heart failure; ITT, intention to treat; MACE, major cardiovascular event; mg, milligram; MI, myocardial infarction; NS, non-significant; P, placebo; S, sitagliptin; T2D, type 2 diabetes; 2hPPG, 2-hour postprandial glucose; wk, weeks; *mg/dL.

(–0.0%; all p<0.001). FPG (–1.5 mmol/L with 5 mg, –2.2 mmol/dL with 15 mg, –0.1 mmol/L with placebo; all p<0.001), A1C <7% (35.3% with 5 mg, 40.0% with 15 mg, 15.8% with placebo; all p<0.001), body weight (–3.0 kg with 5 mg, –2.9 kg with 15 mg, –1.3 kg with placebo; all p<0.001), SBP (–4.4 mmHg with 5 mg [p=0.002], –5.2 mmHg with 15 mg [p<0.001], –0.7 with placebo), and diastolic blood pressure (–1.6 mmHg with 5 mg [p=0.013], –2.2 mmHg with 15 mg [p=0.001], –0.1 mmol/L with placebo) were also reduced significantly more with ertugliflozin at both doses compared with placebo.[22] Adverse effects were generally similar between groups but GMIs occurred more frequently with ertugliflozin than placebo (women: placebo, 0.9%; ertugliflozin 5 mg, 5.5%; ertugliflozin 15 mg, 6.3%; p=0.032; men: placebo, 0%; ertugliflozin 5 mg, 3.1%; ertugliflozin 15 mg, 3.2%; no p value reported). Overall, ertugliflozin added to metformin improved glycemic control compared to placebo with an increase in the incidence of GMIs.[22]

A 52-week study randomized 1233 patients with uncontrolled T2D (A1C ≥7.5% and <11%) currently receiving at least metformin 1500 mg per day to ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, ertugliflozin 5 mg plus sitagliptin 100 mg, or ertugliflozin 15 mg plus sitagliptin 100 mg daily.[23] The primary efficacy endpoint was A1C reduction at 26 weeks. At 26 weeks, the A1C reductions were greater with dual therapy with ertugliflozin 5 mg plus sitagliptin 100 mg and ertugliflozin 15 mg plus sitagliptin 100 mg than with the individual medications of ertugliflozin 5 or 15mg, or sitagliptin 100 mg (–1.5%, –1.5%, –1.0%, –1.1%, and –1.1%, respectively; all p<0.001). Combination therapy with ertugliflozin and sitagliptin demonstrated an approximately 20% greater achievement of A1C <7% than any individual medication (50% *versus* 30%). Greater lowering of FPG occurred with the combination therapy of ertugliflozin plus sitagliptin. In addition, there was a decrease in body weight and SBP seen in the combination therapy group that was sustained out to 52 weeks. There was no statistical difference in the risk of symptomatic hypoglycemia (6.1% with ertugliflozin 15 mg plus sitagliptin 100 mg *versus* 2.8% with sitagliptin 100 mg), UTIs (4.9% with ertugliflozin 15 mg plus sitagliptin 100 mg *versus* 5.3% with sitagliptin 100 mg), or hypovolemia (0.8% with ertugliflozin 15 mg plus sitagliptin 100 mg *versus* 0.4% with sitagliptin 100 mg) between the treatment arms; non-significant findings did not have reported p values.[23] A higher rate of GMIs was seen in patients treated with ertugliflozin than in those treated with sitagliptin (women: 9.3% with ertugliflozin 15 mg plus sitagliptin 100 mg *versus* 2.2% with sitagliptin 100 mg; p<0.05; men: 4.0% with ertugliflozin 15 mg plus sitagliptin 100 mg *versus* 2.2% with sitagliptin 100 mg; p<0.05).[23] These findings demonstrated that the co-administration of ertugliflozin and sitagliptin is a safer and more effective means to improve glycemic control than either medication individually.

Addition to metformin plus sitagliptin

A double-blind trial randomized 464 patients with T2D who had inadequate glycemic control (A1C ≥7.0% and <10.5%) despite receiving metformin ≥1500 mg per day plus sitagliptin 100 mg per day prior to enrollment to ertugliflozin 5 or 15 mg per day or placebo for 26 weeks.[24] The primary efficacy endpoint was change in A1C from baseline at 26 weeks. Ertugliflozin administration resulted in greater reductions in A1C (–0.8% with 5 mg and –0.9% with 15 mg) compared with

placebo (−0.2%; all $p<0.001$). Significant improvements were seen with A1C <7% goal attainment with ertugliflozin 5 and 15 mg *versus* placebo (32.1%, 39.9%, and 17%, respectively; all $p<0.001$). FPG (ertugliflozin 5 mg, −1.5 mmol/L; ertugliflozin 15 mg, −1.8 mmol/L; placebo, −0.1 mmol/L; $p<0.001$ for comparison to placebo), body weight (ertugliflozin 5 mg, −3.4 kg; ertugliflozin 15 mg, −3.0 kg; placebo, −1.3 kg; $p<0.001$ for comparison to placebo), and SBP (ertugliflozin 5 mg, −3.8 mmHg; ertugliflozin 15 mg, −4.8 mmHg; placebo, −0.9 mmHg; $p<0.001$ for comparison to placebo) were also reduced significantly more with ertugliflozin at both doses compared with placebo and maintained out to 52 weeks.[24] As with previous trials, there was a higher rate of GMIs in the ertugliflozin group and the rate was more pronounced in women compared to men. No statistical difference in symptomatic hypoglycemia, UTIs, and hypovolemia was seen between ertugliflozin and placebo. Overall, the addition of ertugliflozin to metformin plus sitagliptin demonstrated improved glycemic control with a higher rate of GMIs, consistent with previous trials.

Compared to glimepiride added to metformin

A 52-week study randomized 1326 patients with uncontrolled T2D (A1C ≥7.0% and <9.0%) currently receiving as least metformin 1500 mg per day to ertugliflozin 5 mg, ertugliflozin 15 mg, or glimepiride titrated from 1 mg daily up to 6 or 8 mg daily (to either maximum dose according to the local country label or maximum tolerated dose).[25] The primary efficacy endpoint was to assess if ertugliflozin 15 mg was non-inferior to glimepiride relative to A1C reduction at 52 weeks. At 52 weeks, the A1C reductions were similar between ertugliflozin 5 mg, 15 mg, and glimepiride (−0.6%, −0.6%, and −0.7%, respectively). Ertugliflozin 15 mg daily demonstrated non-inferiority to glimepiride relative to A1C reductions at 52 weeks. In addition, ertugliflozin demonstrated statistically significant reductions in body weight (ertugliflozin 5 mg, −3.0 kg; ertugliflozin 15 mg, −3.4 kg; glimepiride, 0.9 kg; $p<0.001$ *versus* glimepiride) and SBP (ertugliflozin 5 mg, −2.2 mmHg; ertugliflozin 15 mg, −3.8 mmHg; glimepiride, 1.0 mmHg; $p<0.001$ *versus* glimepiride).[25] Of note, ertugliflozin demonstrated a lower rate of symptomatic hypoglycemia and a higher rate of GMIs compared to glimepiride with no other adverse events being different between the study arms. These findings demonstrate that ertugliflozin was non-inferior to glimepiride when added to metformin to improve glycemic control measured by change in A1C.

Special populations

Renal disease

The VERTIS RENAL (Ertugliflozin in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus) was a 52-week study that randomized 468 patients with stage 3 CKD (eGFR ≥30 and <60 mL/min/1.73 m^2) with uncontrolled T2D (A1C >7.0% and <10.5%) currently receiving insulin and/or sulfonylureas to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo daily.[13] The primary efficacy endpoint was the change in A1C between ertugliflozin and placebo at 26 weeks. Secondary efficacy endpoints were specifically evaluated in the stage 3A CKD cohort at week 26 and included change in A1C from baseline, body weight, SBP, and FPG. At 26 weeks, the A1C reductions were similar between ertugliflozin 5 mg, 15 mg, and placebo (−0.3%, −0.4%, and −0.4%, respectively). Reductions in body weight, FPG, and SBP were greater than in placebo in the stage 3A CKD cohort at week 26. Secondary safety analyses were performed assessing post-treatment eGFR at 52 weeks compared to baseline. Further, the urinary albumin to creatinine ratio was assessed at week 26. More patients in the ertugliflozin groups had a reduction in eGFR at weeks 26 and 52 (week 26: 5 mg and ertugliflozin 15 mg groups 10.3% and 8.7%, respectively; week 52: 13.5% and 14.0%, respectively) than in the placebo group (week 26: 2.6%; week 52: 7.3%). At weeks 26 and 52, the overall incidence of adverse effects was similar across groups.

Cardiovascular disease

The role of using SGLT2 inhibitors in patients with T2D and CVD has been established by large clinical trials of empagliflozin and canagliflozin.[29,30] The VERTIS-CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease) enrolled and followed patients with T2D and ASCVD.[26–28] This trial randomized 8246 patients 40 years of age or older with uncontrolled T2D (A1C >7.0% and <10.5%) and evidence or history of atherosclerosis to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo daily. The primary efficacy endpoint was the composite outcome of major CV events, which included CV death, non-fatal myocardial infarction, and stroke, with a mean duration of follow-up of 3.5 years. The primary efficacy outcome occurred in 11.9% of patients in the ertugliflozin treatment arm *versus* 11.9% of those in the placebo treatment arm (HR 0.97, 95% CI 0.85–1.11; $p<0.001$ for non-inferiority). No difference in primary efficacy endpoint was noted between doses of ertugliflozin. The secondary endpoint of CV death or hospitalization for HF (HHF) demonstrated a non-significant difference between ertugliflozin and placebo (HR 0.88, 95% CI 0.75–1.03; $p=0.11$ for superiority). HHF did demonstrate a significantly lower rate for ertugliflozin than placebo (HR 0.70, 95% CI 0.54–0.90; $p=0.006$ for superiority). The secondary renal endpoint of renal death, dialysis/transplant, or doubling of serum creatinine demonstrated a non-significant difference between ertugliflozin and placebo (HR 0.81, 95% CI 0.63–1.04; $p=0.08$ for superiority). The HHF and renal endpoints are in alignment with previous large CV outcomes trials of SGLT2 inhibitors. Similar reductions in A1C, body weight, and SBP were noted in this trial as compared to previous ertugliflozin trials. One key point to highlight is that the VERTIS-CV trial did not demonstrate superiority of ertugliflozin over placebo for CV or renal outcomes. The trend toward lower HF risk among ertugliflozin was not statistically significant but does highlight

that the HF benefit with SGLT2 inhibitors is likely a class effect. It is important to evaluate differences between the EMPA-REG trial, which showed CV event lowering with empagliflozin, *versus* VERTIS-CV, which did not. Both trials enrolled patients of a similar age and with established ASCVD (75% of patients with coronary artery disease in both trials) who had baseline A1Cs in the 8% range and were considered obese based on body mass index. There was a larger percent of patients who identified as Asian in EMPA-REG (21%) compared to VERTIS-CV (6%), which could contribute to different findings. Additionally, the VERTIS-CV trial included more patients with known HF (24% *versus* 10% in EMPA-REG). Only minor differences in the proportions of patients with impaired renal function were seen across the two trials (VERTIS-CV included 22% of patients with an eGFR <60 mL/min/1.73 m^2 while EMPA-REG included 26% of patients with an eGFR <60 mL/min/1.73 m^2). Without a future study to evaluate the CV event lowering of ertugliflozin, its neutral impact demonstrated in the VERTIS-CV trial will be viewed as inferior to the positive CV event lowering demonstrated with empagliflozin and canagliflozin.

FDA-approved indication

As previously stated, ertugliflozin (Steglatro™) was approved by the FDA in 2017, and by the EMA in early 2018, as an adjunct to diet and exercise to improve glycemic control in adults with T2D. The FDA recommended a starting dose of 5 mg once daily that can be increased to 15 mg once daily if the medication is tolerated and there is a need for additional glycemic control.[10] Ertugliflozin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2 and initiation of ertugliflozin is not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2.

ADA and AACE/ACE recommendations

The American Diabetes Association (ADA) recommends the use of SGLT2 inhibitors with the presence of comorbid ASCVD, HF, or CKD. If ASCVD predominates, the ADA recommends the use of an SGLT2 inhibitor with positive CV outcome data, which includes empagliflozin or canagliflozin.[3] If HF predominates, the ADA recommends the use of an SGLT2 inhibitor with positive HF outcome data, which includes canagliflozin, dapagliflozin, and empagliflozin.[3] If CKD predominates, they recommend for the use of an SGLT2 inhibitor with positive renal outcomes; canagliflozin, dapagliflozin, and empagliflozin have all demonstrated benefit in reducing CKD progression in major CV outcome trials.[3] The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines for the management of T2D, updated in 2020, recommend the use of SGLT2 inhibitors. These guidelines specifically recommend the use of SGLT2 inhibitors with proven efficacy to lower CV events in patients with established ASCVD, high CV risk, HF with reduced ejection fraction, or stage 3 CKD.[31] These recommendations specifically list canagliflozin, dapagliflozin, and empagliflozin as SGLT2 inhibitors with proven efficacy to lower CV and renal events. In the absence of high CV risk or these established co-morbidities, they do not recommend one SGLT2 inhibitor over another. The conclusion of both guidelines is that SGLT2 inhibitors with positive CV and renal outcomes should be used when those co-morbidities are present over other SGLT2 inhibitors (i.e. ertugliflozin) with neutral results.

Adverse effects

The safety of ertugliflozin has been evaluated in T2D monotherapy and combination therapy phase III trials over the past few years. In the largest ertugliflozin trial, which compared ertugliflozin (5 or 15 mg) with glimepiride (initial dose of 1 mg but could be titrated up to 8 mg per day), the most common adverse effects were GMIs in women (glimepiride initial dose 1 mg, 1.4%; ertugliflozin 5 mg, 7.7%; ertugliflozin 15 mg, 10%); GMIs in men (glimepiride initial dose 1 mg, 0.0%; ertugliflozin 5 mg, 2.1%; ertugliflozin 15 mg, 4.4%); symptomatic hypoglycemia (glimepiride initial dose 1 mg, 19.2%; ertugliflozin 5 mg, 3.1%; ertugliflozin 15 mg, 5.2%); UTI (glimepiride initial dose 1 mg, 6.9%; ertugliflozin 5 mg, 6.7%; ertugliflozin 15 mg, 6.4%); hypovolemia (glimepiride initial dose 1 mg, 0.7%; ertugliflozin 5 mg, 1.3%; ertugliflozin 15 mg, 0.7%).[25] As demonstrated in clinical trials, the most common adverse effect is GMIs in both women and men. This is an adverse effect that should be discussed with patients prior to treatment and monitored while receiving treatment with ertugliflozin. In most clinical trials, there was no difference in the incidence of symptomatic hypoglycemia, UTIs, and hypovolemia when compared to placebo or active treatment. When SGLT2 inhibitors are combined with sulfonylureas or insulin, consideration needs to be given to reducing the dose of the sulfonylurea or insulin in order to reduce the risk of symptomatic hypoglycemia. SGLT2 inhibitors combined with other glycemic-lowering agents have not demonstrated an increased risk of symptomatic hypoglycemia. Hypovolemia occurs infrequently and can be managed by adjusting diuretic and antihypertensive treatments in patients at risk. The risk of amputation was observed in one trial with canagliflozin but this has not been seen with any other SGLT2 inhibitors other than through reports with observational data. Acute kidney injury was seen with some early observation studies, but more recent data support the role of SGLT2 inhibitors as conferring renal protection. Euglycemic diabetes ketoacidosis (DKA) occurs rarely with SGLT2 inhibitors in patients with T2D. One study has reported the incident rate of DKA to vary between 0.16 and 0.76 events per 1000 patient years.[32] Counter to this is the frequency of DKA in patients with type 1 diabetes and SGLT2 inhibitor exposure shown to be as high as 10% in one canagliflozin study.[33] Weight loss and lowering of BP are known effects that have been seen in clinical trials with ertugliflozin and other SGLT2 inhibitors. Depending on the patient, these may be added benefits but should be closely monitored in patients who are normal weight and/or have low or normal BP prior to initiation of therapy.

Drug interactions

A PK analysis evaluated whether there were any drug interactions between ertugliflozin and common antihyperglycemic agents. This analysis evaluated the potential for drug interactions with metformin, glimepiride, and sitagliptin.[34] Based on the results of the analyses, there was no indication of any concern or need for dose adjustment when co-administering ertugliflozin with any of the earlier listed medications. Prescribing information highlights that there may be an increased risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue.[10] It is suggested that a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with ertugliflozin. Future studies are needed to evaluate whether drug interactions exist among other antihyperglycemic agents not previously evaluated.

Implications for practice

There are currently four FDA-approved and EMA-approved SGLT2 inhibitors, with ertugliflozin being the most recent to be approved in the USA (in late 2017) and by the EMA (in early 2018). There is extensive experience from clinical trials demonstrating ertugliflozin's impact on glycemic control in T2D with improvements in A1C, FPG, and 2-hour PPG, both in monotherapy and combination therapy with metformin, sitagliptin, and glimepiride. Clinical trials support the role of both the 5 mg and 15 mg doses of ertugliflozin, with a recommendation to start with the 5 mg dose as the initial dose. The use of SGLT2 inhibitors in patients with T2D and CVD is established from large clinical trials of empagliflozin and canagliflozin, both of which now have FDA indications for patients with established CVD and T2D to further reduce their risk of future CVD.[29–30] Renal function should be assessed prior to initiation of an SGLT2 inhibitor.

The initiation of canagliflozin and ertugliflozin is not recommended if the eGFR is <30 mL/min/1.73 m^2 while initiation of dapagliflozin and empagliflozin is not recommended if the eGFR is <45 mL/min/1.73 m^2. Dapagliflozin has demonstrated no difference in the primary CVD composite outcome in a large CVD trial but secondary analysis of the same trial data showed a reduction in CV death and HF.[35] Subsequently, dapagliflozin demonstrated lower CV deaths and HHF in the HF population with or without T2D in the DAPA-HF trial.[36] Based on these findings, it is perceived that there may be an SGLT2 inhibitor class effect on CV risk. The VERTIS-CV study demonstrated that, in patients with established ASCVD, ertugliflozin was non-inferior to placebo for reducing major CV events. Consistent with other SGLT2 inhibitors (e.g. dapagliflozin), ertugliflozin demonstrated a trend toward a lower risk of HHF compared to placebo, which was one of the key secondary endpoints assessed in the 3.5-year trial. The results of VERTIS-CV could impact the overall use of ertugliflozin in the management of patients with and without known CVD, but both the ADA and AACE/ACE recommendations give preference to SGLT2 inhibitors with demonstrated benefit (canagliflozin, dapagliflozin, and empagliflozin) in established ASCVD, HF, and CKD.

Conclusion

Ertugliflozin is the most recently FDA-approved SGLT2 inhibitor for improving glycemic control in patients with T2D. Clinical trials have demonstrated improvement in A1C, FPG, and PPG as well as decreased body weight and lowering of SBP in patients with T2D when ertugliflozin is used as monotherapy or in addition to metformin and/or sitagliptin. The most common adverse event documented with ertugliflozin is a GMI, which is a known adverse event with all SGLT2 inhibitors. In patients with ASCVD, ertugliflozin has been demonstrated to be safe but has not been demonstrated to be superior in lowering major CV events like other SGLT2 inhibitors (empagliflozin and canagliflozin). Further, it appears that the benefit of reducing HHF is a class effect of SGLT2 inhibitors as this benefit was seen in the VERTIS-CV study.

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