Glucose Control and Cardiovascular Outcomes in Clinical Trials of Sodium Glucose Co-transporter 2 Inhibitor Treatments in Type 2 Diabetes

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Abstract

Currently available medications for the treatment of type 2 diabetes have limitations, and many patients do not achieve glycemic control. Recently, a new approach has emerged using sodium glucose co-transporter 2 (SGLT2) inhibitors that decrease glucose reabsorption in the kidneys, increasing urinary glucose excretion. These agents offer the potential to improve glycemic control independently of insulin pathways while avoiding hypoglycemia. Two drugs of this class, canagliflozin and dapagliflozin, have been approved by the US Food and Drug Administration (FDA); another, empagliflozin, has been filed for regulatory approval and several others are in advanced development. These drugs have been shown to effectively reduce blood glucose, fasting plasma glucose, and glycated hemoglobin (HbA_{1C}) levels in phase III clinical trials when used as monotherapy and as add-on therapy to other diabetes medications, including insulin. Another advantage of the SGLT2 inhibitors over existing treatments is the improvement in cardiovascular risk factors, particularly in terms of reductions in blood pressure and body weight. SGLT2 inhibitors have been generally well tolerated. While more long-term safety data are required to elucidate the benefit–risk profile of SGLT2 inhibitors, the rationale for their use in type 2 diabetes therapy is strong.

Keywords

Type 2 diabetes, sodium glucose co-transporter-2 inhibitors, canagliflozin dapagliflozin, empagliflozin

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Diabetes imposes a substantial burden on societies worldwide: approximately 25 million individuals in the US have diabetes, of which more than 95 % is type 2.[1] Furthermore, its incidence is increasing, a further 79 million adults in the US have pre-diabetes and one in three US adults could have diabetes by 2050.[1] In addition, the age of diagnosis of type 2 diabetes is decreasing.[2] Lifestyle interventions remain essential to the management of type 2 diabetes; however, most patients will not reach their therapeutic goals with these interventions alone and will require pharmacologic therapies.[3] Diabetes is associated with substantially increased cardiovascular (CV) risk; diabetic patients requiring glucose-lowering therapy aged 30 years or over have a CV risk comparable to nondiabetics with a prior myocardial infarction.[4] Therefore antidiabetic therapies should not only reduce glycated hemoglobin (HbA_{1c}), but also CV mortality.

Currently, there are several classes of pharmacologic agents approved for the treatment of diabetes in the US, involving numerous mechanisms of action including the stimulation of insulin production in the pancreas; decreasing sugar release from the liver; or decreasing or delaying sugar uptake from the gut. However, despite the widespread availability of these therapies, only half of patients with type 2 diabetes attain the American Diabetes Association (ADA) recommended target of HbA_{1c} of 7.0 %, blood pressure (BP) targets of <130/80 mmHg, and low-density lipoprotein-cholesterol (LDL-C) targets of <100 mg/dl.[5] Furthermore, the incidence of CV mortality in patients with type 2 diabetes has not substantially decreased in the last decade.[6] The CV safety of antidiabetic medications has become an area of concern since treatment with the thiazolidinedione medication rosiglitazone was associated with an increased risk for CV events.[7] As a result, the US Food and Drug Administration (FDA) now requires evidence that new treatments for diabetes do not increase CV risk.[8]

Uncertainty remains regarding the CV safety of existing therapies. Dipeptidylpeptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs have not been associated with increased CV risks,[9,10] and the latter may be cardioprotective.[10,11] Saxagliptin has been associated

Table 1: Key Completed Phase III Clinical Studies in the Investigation of Dapagliflozin in the Treatment of Type 2 Diabetes

Study Ref	Study Design	Number of Patients and Treatments	Key Endpoints/Findings
Bailey et al. 2010[38]	24-week multicenter, double-blind, parallel-group, placebo-controlled trial	Adult patients (n=546) receiving daily metformin (≥1,500 mg/day) and inadequate glycemic control—3 doses of dapagliflozin (2.5 mg, 5 mg, or 10 mg), or placebo OD oral	Mean HbA_{1c} was decreased by -0.67 % (p=0.0002) in the 2.5 mg group, -0.70 % (p<0.0001) in the 5 mg group, and -0.84 % (p<0.0001) in the 10 mg group versus -0.30 % placebo
Ferrannini et al. 2010[39]	24-week parallel-group, double-blind, placebo-controlled trial	Patients (n=485) with newly diagnosed type 2 diabetes (HbA_{1c} 7.0–10 %, n=485) given placebo or 2.5, 5, or 10 mg dapagliflozin OD. Patients with HbA_{1c} 10.1–12 % given morning dose of 5 or 10 mg/day dapagliflozin	Mean HbA_{1c} was decreased by -0.77 % with 5 mg and by -0.89 % with 10 mg, versus -0.23 % placebo (p <0.001)
Nauck et al. 2011[40]	52-week, double-blind, active-controlled noninferiority trial	Patients with type 2 diabetes inadequately controlled with metformin (n=814, baseline mean HbA_{1c}, 7.7 %) metformin monotherapy, to add-on dapagliflozin (n = 406) or glipizide (n = 408) up-titrated over 18 weeks	Mean HbA_{1c} reduction with dapagliflozin was statistically noninferior to glipizide at 52 weeks (-0.52 % versus 0.52 %), dapagliflozin reduced weight and produced less hypoglycemia than glipizide
Strojek et al. 2011[41]	24-week, double-blind, placebo-controlled, parallel-group, multicenter trial	Patients (n=597) with uncontrolled type 2 diabetes (HbA_{1c} 7–10 %) receiving sulfonylurea monotherapy. Patients given placebo or dapagliflozin (2.5, 5, or 10 mg/day) and open-label glimepiride 4 mg/day	Mean HbA_{1c} reduction (-0.63 % and -0.82 %) were seen with 5 mg and 10 mg when added to glimepiride compared to placebo (-0.13 %) (all p<0.0001), dapagliflozin reduced weight and was well tolerated but genital infections were reported more often with dapagliflozin
Wilding et al. 2012 [42]	24-week, placebo-controlled, multicenter trial followed by a 24-week extension period	Patients (n=808) with inadequately controlled type 2 diabetes received placebo or 2.5, 5, or 10 mg of dapagliflozin OD for 48 weeks	Mean HbA_{1c} reduction of -0.40 %, -0.49 %, and -0.57 % in the 2.5, 5, and 10 mg groups compared with 0.39 % placebo. Daily insulin dose decreased by 0.63 to 1.95 U with dapagliflozin and increased by 5.65 U with placebo, dapagliflozin reduced weight without increasing major hypoglycemic episodes

HbA_{1c} = glycated hemoglobin; OD = once daily.

with an increased risk for hospitalizations for heart failure.[12] Studies investigating the CV risks associated with insulin, sulfonylureas (SU), and metformin have yielded mixed results.[13,14]

Since over 85 % of people with diabetes are overweight or obese,[15] and excess weight is a major contributor to the development of insulin resistance and impaired glucose tolerance,[16] as well as being a major CV risk,[17] the impact of antidiabetic therapies on weight is also important. Most oral antidiabetic agents (OADs) have been associated either with weight gain (thiazolidinediones,[18] SU,[19] meglitinides[20]) or are weight-neutral (metformin,[21] alpha-glucosidase inhibitors,[22] DPP-4 inhibitors,[23] bile acid sequestrants[24]). Treatment with insulin and insulin analogs is also associated with weight gain, which may be substantial.[25] GLP-1 analogs have been associated with moderate weight loss,[10] but their use is limited by the need for administration by injection and gastrointestinal side effects.[26]

The increasing prevalence of type 2 diabetes, in combination with limitations of current therapies, has driven the search for alternative glucose-lowering agents. This review will consider the safety and efficacy of a new class of oral drug, sodium glucose co-transporter 2 (SGLT2) inhibitors and the key clinical trial evidence supporting their use in diabetes treatment.

Introduction to Sodium Glucose Co-transporter 2 Inhibitors

A new therapeutic approach to type 2 diabetes has emerged using SGLT2 inhibitors, whose mechanism of action is independent of insulin and involves glucose reabsorption in the kidneys. The kidneys play an important role in glycemic control, filtering, and reabsorbing glucose back into the circulatory system.[27] Renal glucose transport involves two types of membrane-associated carrier proteins: facilitated glucose transporters (GLUTs), which function as passive transporters, and sodium glucose co-transporters (SGLTs), which are secondary active co-transporters.[27,28] Among the latter, SGLT2s, found in the early proximal tubule, are responsible for approximately 90 % of glucose reabsorption.[27,29] In type 2 diabetes, SGLT2 is upregulated, resulting in reduced glucosuria and hyperglycemia, suggesting that an adaptive response to conserve glucose becomes maladaptive in diabetes.[28]

The concept of inhibiting glucose reabsorption arose from the discovery of inherited and acquired diseases in which SGLT2 mutations cause alterations in renal glucose handling, resulting in glucosuria.[30] Selective SGLT2 inhibitors decrease glucose reabsorption in the kidneys, increasing urinary glucose excretion. Such agents may offer several advantages as antidiabetic agents: the unique potential to cause negative energy balance and the correction of the effect of hyperglycemia on insulin secretion and action.[31,32] The use of SGLT2 inhibitors will, however, require a change in the perception of glucosuria. This has historically been considered to indicate poor glucose control but during SGLT2 inhibitor treatment it indicates effective removal of excess glucose from the blood to the urine.[33]

Phlorizin, discovered in 1835, was the first SGLT inhibitor, but is not suitable for clinical use owing to its poor bioavailability and gastrointestinal side effects, a result of its action on SGLT1, found mainly in the small intestine.[27] Following the clinical failure of other SGLT inhibitors, numerous selective SGLT2 inhibitors are currently in clinical development. Canagliflozin (Invokana®, Johnson & Johnson) received approval from the FDA in March 2013,[34] dapagliflozin (Farxiga®, Bristol-Myers Squibb) received FDA approval in January 2014, and empagliflozin (Boehringer Ingelheim)[35] has also been submitted for FDA approval. Several other agents are in late-stage clinical

Table 2: Key Completed Phase III Clinical Studies in the Investigation of Canagliflozin in the Treatment of Type 2 Diabetes

Study Ref	Study Design	Number of Patients and Treatments	Key Endpoints/Findings
Stenlof et al. 2013[49]	26-week, double-blind, placebo-controlled	Patients (n=584) with type 2 diabetes inadequately controlled with diet and exercise received canagliflozin 100 or 300 mg or placebo OD	Mean changes from baseline in HbA_{1c} with canagliflozin 100 and 300 mg -0.77 %, -1.03 %, respectively, compared with placebo -0.14 %; p<0.001 for both. Canagliflozin reduced body weight and was well tolerated
Bode et al. 2013[45]	26-week double-blind, placebo-controlled,	Patients (n=716) on background therapy received canagliflozin 100 mg or 300 mg or placebo (1:1:1) daily	Mean changes from baseline in HbA_{1c} with canagliflozin 100 and 300 mg -0.60 %, -0.73 %, respectively, compared with placebo -0.03 %; p<0.001 for both. Canagliflozin improved glycemic control, reduced body weight and systolic BP, and was generally well tolerated
Schernthaner et al. 2013[48]	52-week, double-blind, active-controlled trial	Patients (n=755) using stable metformin plus sulfonylurea received canagliflozin 300 mg or sitagliptin 100 mg daily	Canagliflozin 300 mg demonstrated noninferiority and showed superiority to sitagliptin 100 mg in reducing HbA_{1c} (-1.03 % and -0.66 %). Canagliflozin provided better improvement in glycemic control and body weight reduction than sitagliptin, but with increased genital infections in patients using metformin plus sulfonylurea
Cefalu et al. 2013[46]	52 week, double-blind, active-controlled, noninferiority trial	Patients (n=1,450) receiving metformin received canagliflozin 100 mg or 300 mg, or glimepiride (up-titrated to 6 mg or 8 mg per day) orally OD	Canagliflozin 100 mg was noninferior to glimepiride, and canagliflozin 300 mg was superior to glimepiride in reducing HbA_{1c} (-0.12 %). Canagliflozin reduced HbA_{1c} more than glimepiride, and was well tolerated
Lavalle-González et al. 2013[47]	52-week double-blind, 4-arm, parallel-group	Patients with inadequate glycemic control (HbA_{1c} ≥7.0 % and ≤10.5 %) on metformin received canagliflozin 100 mg or 300 mg, sitagliptin 100 mg, or placebo for 26 weeks, followed by a 26 week, active-controlled period (placebo group switched to sitagliptin)	At week 26, canagliflozin 100 mg and 300 mg reduced HbA_{1c} versus placebo (-0.79 %, -0.94 %, -0.17 %, respectively; p<0.001). At week 52, canagliflozin 100 mg and 300 mg demonstrated noninferiority, and canagliflozin 300 mg demonstrated superiority, to sitagliptin in lowering HbA_{1c} (-0.73 %, -0.88 %,-0.73 %, respectively); differences (95 % CI) versus sitagliptin were 0 % and -0.15 %, respectively

CI = confidence interval; HbA_{1c} = glycated hemoglobin; OD = once daily.

development. These agents have excellent oral bioavailability allowing once-daily administration, renal clearance, and a limited potential for drug–drug interactions,[36] offering the potential for combined therapies with different classes of antidiabetic medicines to achieve tighter glycemic control.

Clinical Trials Investigating the Use of Sodium Glucose Co-transporter 2 Inhibitors in Type 2 Diabetes

Completed trials of SGLT2 inhibitors have evaluated their effects on a range of different measures of glucose control including the change in HbA_{1c}, fasting and postprandial glucose, and the proportion of patients achieving HbA_{1c} targets. To date, all SGLT2 inhibitors in clinical development have demonstrated benefits in these parameters, as well as demonstrating safety and tolerability.

Dapagliflozin

Clinical trial data describing the efficacy of dapagliflozin are summarized in *Table 1*. Reductions in fasting glucose varied with dose, ranging from around 0.8 mmol/l with 2.5 mg dapagliflozin to between 1.2 and 4.7 mmol/l with 10 mg dapagliflozin. Mean decreases in HbA_{1c} were 0.6 % with a dose of 2.5 mg, and between 0.8 % and 2.7 % with a 10 mg dose.[37] Completed and ongoing phase III clinical trials included or will include a total of over 35,000 patients with type 2 diabetes and have demonstrated that dapagliflozin treatment results in reductions in HbA_{1c} as monotherapy, dual therapy, and triple therapy with OADs, as well as with combination therapy with insulin with or without OADs.[38–42] In January 2012 the FDA declined approval of dapagliflozin, requesting additional clinical data to enable a better assessment of the benefit–risk profile following safety concerns of an enhanced risk for bladder cancer.[43] However, approval was granted in January 2014.

Canagliflozin

Clinical trials demonstrating the efficacy and safety of canagliflozin are given in *Table 2*. Completed and ongoing phase III clinical trials included a total of over 10,000 patients and have demonstrated that canagliflozin provides better glycemic control than sitagliptin and glimepiride.[44–49] In a pooled analysis of four clinical trials involving a total of over 500 patients, canagliflozin use was associated with significant mean reductions in HbA_{1c} (absolute reductions of 0.45–0.92 %) and fasting plasma glucose (decreases ranged from 16.2 % to 42.4 %).[44]

Empagliflozin

Key clinical trials investigating the efficacy and safety of empagliflozin are summarized in *Table 3*. Completed and ongoing phase III clinical trials have included or will include a total of more than 14,000 patients with type 2 diabetes. Empagliflozin has demonstrated good efficacy, safety, and tolerability profiles when used alone or as an add-on treatment to metformin and glimepiride.[50–54] A pooled analysis of data from four phase III trials involving 2,477 patients treated with empagliflozin 10 mg, 25 mg, or placebo, showed significant reductions from baseline in HbA_{1c} of 0.70 % and 0.76 %, respectively, compared with a change of -0.08 % for placebo at week 24.[55]

Clinical trial data for other SGLT2 inhibitors currently in development are given in *Table 4*.[56] These include phase III trials (tofogliflozin,[57] ertugliflozin,[58] ipragliflozin,[59,60] and luseogliflozin[61]) and phase I/II trials (remogliflozin etanobate,[62] sotagliflozin,[63] and ISIS 388686[64]).

Effects on Cardiovascular Risk Factors of Sodium Glucose Co-transporter 2 Inhibitors

Several large clinical trials assessing the CV safety of SGLT2 inhibitors are ongoing (see *Table 5*). The most comprehensive data currently available

Table 3: Key Completed Phase III Clinical Studies in the Investigation of Empagliflozin in the Treatment of Type 2 Diabetes

Study Ref	Study Design	Number of Patients and Treatments	Key Endpoints/Findings
Häring H et al. 2013[51]	24-week, double-blind, placebo-controlled trial	Patients (n=666) treated with OD empagliflozin 10 mg, 25 mg (or placebo); add-on treatment to metformin + sulfonylurea	Mean changes from baseline in HbA_{1c} -0.17 % for placebo versus -0.82 % and -0.77 % for empagliflozin 10 and 25 mg, respectively (both p<0.001). Empagliflozin significantly reduced weight, and systolic (but not diastolic) blood pressure versus placebo. Empagliflozin 10 and 25 mg for 24 weeks improved glycemic control, weight, and systolic blood pressure and were well tolerated
Ridderstråle et al. 2013[53] (EMPA-REG H2H-SU trial)	Ongoing 4-year double-blind parallel-group study (with 2-week placebo run-in)	Patients (n=1,545) received empagliflozin 25 mg OD or glimepiride 1–4 mg OD for 2 years + metformin IR (+2-year double-blind extension)	Largest study comparing efficacy and safety of an SGLT2 inhibitor with an SU in patients with type 2 diabetes inadequately controlled on metformin. It will investigate long-term glycemic control and effects on beta-cell function, cardiovascular risk factors, and markers of renal function/damage
Roden et al. 2013[54]	24-week, multicenter, placebo-controlled, trial	Patients (n=899) placebo, empagliflozin 10 mg, 25 mg, or sitagliptin; patients not previously receiving drug treatment	Mean changes from baseline in HbA_{1c} -0.74 % for empagliflozin 10 mg, -0.85 % for 25 mg, and -0.73 % for sitagliptin (p<0.0001)
Kovacs et al. 2014 (EMPA-REG PIO trial)[52]	24-week, placebo-controlled trial	Patients (n=498) treated with OD empagliflozin 10 mg, 25 mg, or placebo as add-on to pioglitazone ± metformin	Mean changes from baseline in HbA_{1c} were -0.6 % and -0.7 %, for empagliflozin 10 mg and 25 mg, respectively, versus -0.1 % with placebo (both p<0.001). Reductions in FPG and weight also noted
Barnett et al. 201450	52-week double-blind, parallel-group, multicenter placebo-controlled trial	Patients with stage 2 (n=290), stage 3 (n=374), and stage 4 (n=74) CKD received empagliflozin 10 mg or 25 mg or placebo OD for 52 weeks	In patients with stage 2 CKD, adjusted mean treatment differences versus placebo in changes from baseline in HbA1c at week 24 were -0.52 % for empagliflozin 10 mg and -0.68 % for empagliflozin 25 mg (both p<0.0001). In patients with stage 3 CKD, adjusted mean treatment difference versus placebo in change from baseline in HbA1c at week 24 was -0.42 % for empagliflozin 25 mg (p<0.0001)

CKD = chronic kidney disease; FPG = fasting plasma glucose; HbA_{1c} = glycated hemoglobin; IR = immediate release; OD = once daily; SU = sulfonylurea.

are from a meta-analysis of data from 14 phase II/III studies involving 6,228 patients that assessed the CV safety of all doses of dapagliflozin (2.5 to >10 mg). The primary end point was a composite of time to first event of CV death, myocardial infarction (MI), stroke, or hospitalization for unstable angina. The estimated hazard ratio (HR) was 0.674 (95 % CI 0.421–1.078), suggesting that dapagliflozin was not associated with an increased risk for CV events and may confer a reduced CV risk.[65] The reductions in HbA_{1c} achieved in clinical trials of SGLT2 inhibitors are clinically meaningful in terms of CV risk: a 0.8 % reduction in HbA_{1c} could reduce CV risk by about 8 %.[66] Furthermore, SGLT2 inhibitors have demonstrated benefits in terms of other CV risk factors.

Blood Pressure

The importance of tight BP control in patients with type 2 diabetes is well established. In the UK Prospective Diabetes Study (UKPDS), patients assigned to the tight BP control arm had a clinically meaningful reduction in the risk for deaths related to diabetes and its related complications.[67] Since SGLT2 reabsorbs glucose and sodium in the renal proximal tubule, it was postulated that SGLT2 inhibitors would have diuretic properties, thereby reducing BP. In phase III studies, dapagliflozin has been associated with reductions of systolic BP at week 24 of -3.6, -5.1, and -5.0 mmHg as monotherapy,[39] add-on to metformin,[38] and add-on to SU,[41] respectively. In a recent clinical study, 75 subjects were randomized to placebo, dapagliflozin, or hydrochlorothiazide (HCTZ), a diuretic used in the treatment of hypertension. Treatment with placebo or HCTZ resulted in changes from baseline in 24-hour ambulatory mean systolic BP of -0.9, -3.3, and -6.6 mmHg, respectively, at week 12, adjusted for baseline systolic BP. Plasma volume appeared to decrease with dapagliflozin but did not change with placebo or HCTZ treatment, suggesting that dapagliflozin has a diuretic-like capacity to lower BP.[68]

Canagliflozin has been associated with similar reductions in systolic BP (at week 24, -3.7 mmHg -5.4 mmHg from placebo with 100 mg and 300 mg doses, respectively, p≤0.001).[44]

Empagliflozin has also been found to have beneficial effects on BP. In a recent pooled analysis of data from four phase III trials, at week 24, patients given empagliflozin 10 mg and 25 mg showed reductions in systolic BP of 3.9 mmHg and 4.3 mmHg, and diastolic BP of 1.8 mmHg and 2.0 mmHg, respectively, compared with reductions of 0.5 mmHg in systolic BP and 0.6 mmHg in diastolic BP in patients treated with placebo (see *Figure 1*).[55] Empagliflozin treatment resulted in generally greater reductions in BP when baseline BP was higher.

Table 4: Further Sodium Glucose Co-transporter 2 Inhibitors in Development

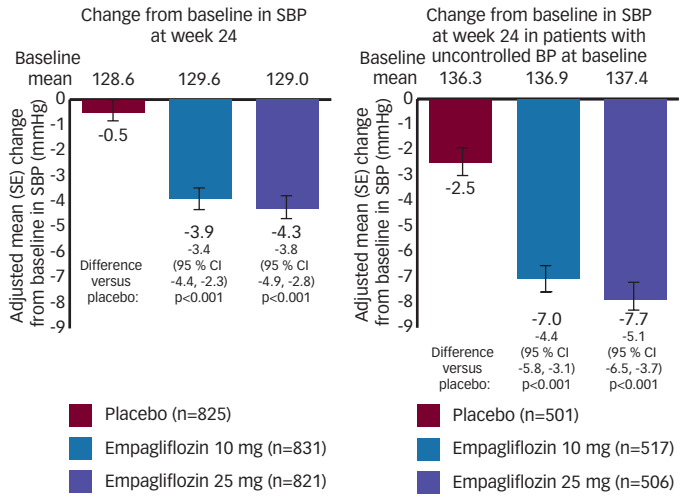
Drug	Development Stage
Ipragliflozin (ASP1941)	3 phase III trials completed (NCT01672762, NCT01514838, NCT01505426)
Ertugliflozin (PF-04971729)	5 phase III trials recruiting (NCT02033889, NCT01986855, NCT01986881, NCT01958671, NCT01999218), 1 phase III planned (NCT02036515)
Luseogliflozin	Phase III (no clinical trials found in EU or US databases)
Remogliflozin	Phase II (no clinical trials found in EU or US databases)
Tofogliflozin	Phase III (no clinical trials found in EU or US databases)
ISIS 388686	Phase I (no clinical trials found in EU or US databases)
Sotagliflozin	Phase II (no clinical trials found in EU or US databases)

Table 5: Key Ongoing Clinical Trials of Sodium Glucose Co-transporter-2 Inhibitors Assessing Cardiovascular Safety

Trial	Number of Patients/Treatments	Primary and Other Endpoints	Expected Completion Date
Empagliflozin			
EMPA-REG OUTCOME™ - Cardiovascular Outcome Event Trial in patients with type 2 diabetes NCT01131676	Empagliflozin (10 mg and 25 mg OD) versus usual care in patients with increased CV risk; n=7,000	Time to the first occurrence of any of listed CV events	First half 2015
Canagliflozin			
CANVAS - CANagliflozin cardioVascular Assessment Study NCT01032629	Canagliflozin or placebo; n=4,330	Major adverse CV events, including CV death, nonfatal MI	June 2018
Evaluation of the effects of Canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy (CREDENCE) NCT02065791	Canagliflozin or placebo; n=3,627	Time to the first occurrence of end-stage kidney disease, doubling of serum creatinine, renal, or CV death	January 2019
Dapagliflozin			
Multicenter trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events (DECLARE-TIMI58) NCT01730534.	Dapagliflozin versus placebo up to 6 years; n=22,200	Time to CV death, MI, or ischemic stroke, time to first hospitalization for congestive heart failure, time to all-cause mortality, body weight change from baseline	April 2019

CV = cardiovascular; MI = myocardial infarction; OD = once daily.

Figure 1: Effects of Empagliflozin on Systolic Blood Pressure in Patients with Type 2 Diabetes—Pooled Data from 4 Phase III Trials



CI = confidence interval; SBP = systolic blood pressure; SE = standard error.
Source: Hach et al. 2013.[55]

Lipid Parameters

SGLT2 inhibitors are associated with small mean changes in lipid parameters: increases in high-density lipoprotein-cholesterol (HDL-C) have been reported but also increases in LDL-C.[69] In a pooled analysis of data from 3,731 patients in 12 phase IIb/phase III trials of dapagliflozin, changes from baseline in HDL-C were +6.5 % and +5.5 % for dapagliflozin 5 and 10 mg, respectively, versus +3.8 % placebo, and in LDL-C +0.6 % and +2.7 % dapagliflozin 5 and 10 mg, respectively, versus -0.4 % placebo.[70] Pooled data from four phase III trials investigating empagliflozin found small changes from baseline in LDL-C of +3.1 mg/dl and +3.9 mg/dl for empagliflozin 10 mg and 25 mg, respectively, compared with +0.8 mg/dl for placebo. Changes from baseline in HDL-C were +2.7 mg/dl for both doses versus 0.0 mg/dl for placebo. Changes from baseline in triglyceride levels of -9.7 mg/dl and -1.8 mg/dl, respectively, compared with +2.7 mg/dl for placebo.[55] The significance of the increased LDL-C with SGLT2 inhibitors requires further investigation.

In some clinical trials of SGLT2 inhibitors, plasma lipid analysis has been conducted using nuclear magnetic resonance (NMR) spectroscopy. This method was used on plasma samples from the CANagliflozin Treatment and Trial Analysis – DPP-4 Inhibitor Comparator Trial (CANTATA-D, DIA3006) trial.[47] The trial compared canagliflozin 100 mg and 300 mg treatment with placebo over a 26-week randomized period in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy. Increased cholesterol levels are a concern with these treatments and NMR analysis of plasma at baseline and week 26 showed slightly greater increases in LDL particle concentrations in patients treated with either canagliflozin doses compared with placebo. This pattern of increased LDL particle concentrations with canagliflozin was similar for both large and small LDL particles but there was little difference between the two cangliflozin doses in LDL particle concentrations. In the CANagliflozin Treatment and Trial Analysis - Monotherapy (CANTATA-M) trial, NMR spectroscopy showed small increases in Apo B levels during 26 weeks of treatment of type 2 diabetes patients insufficiently controlled with diet and exercise.[71] In placebo-treated patients Apo B levels were shown to decrease by 0.2 % but in 100 mg and 300 mg cangliflozin-treated patients these levels rose by 1.3 % and 3.2 %, respectively.

Body Weight

Other benefits of SGLT2 inhibitors include clinically meaningful body weight reduction, which give a strong rationale for their use in overweight and obese patients, as well as in addition to therapies that are associated with weight gain. The glycosuria induced by dapagliflozin monotherapy is associated with a net calorie loss of approximately 200–300 kilocalories per day.[72] In phase III studies, dapagliflozin has been associated with adjusted mean change from baseline in body weight at 24 weeks of -3.2 kg as monotherapy,[39] -2.9 kg as add-on to metformin,[38] -2.26 kg as add-on to SU,[41] and -1.61 kg as add-on to insulin.[42] Pooled analysis of four clinical trials showed that the use of

canagliflozin was associated with weight loss ranging from 0.7 to 3.5 kg at 24 weeks.[44] In a pooled analysis of four phase III trials, empagliflozin was associated with weight losses of 2.05 kg and 2.25 kg, respectively, from baseline at 24 weeks, compared with a reduction of 0.24 kg for placebo (see *Figure 2*).[55] Since a proportion of the weight reduction observed with SGLT2s is related to reduction in visceral fat mass, this could potentially be important for CV risk reduction.

Safety of Sodium Glucose Co-transporter 2 Inhibitors

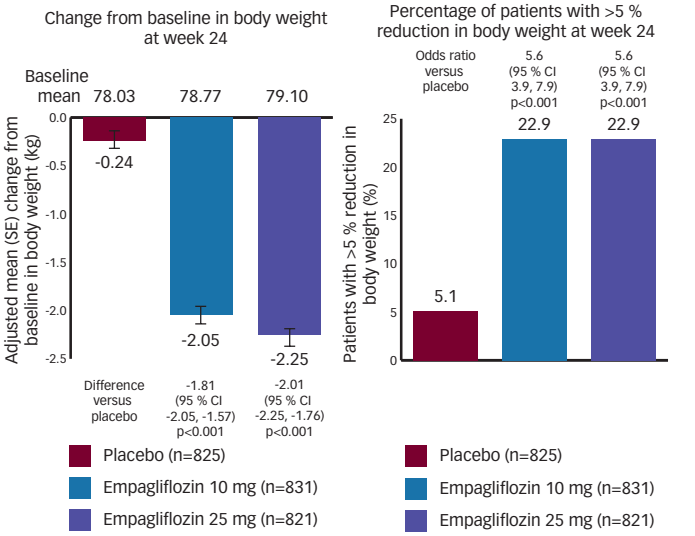
Hypoglycemia is a rare adverse event (AE) during SGLT2 inhibitor therapy.[73] In an analysis from the CANagliflozin cardioVascular Assessment Study (CANVAS) study, hypoglycemic AEs were higher with canagliflozin compared with placebo only in patients taking concomitant insulin, SU, or meglitinide.[74] In the pooled analysis of empagliflozin trials, hypoglycemic AEs were reported by 2.9 % of patients on placebo, 5.2 % of patients on empagliflozin 10 mg, and 4.0 % of patients on empagliflozin 25 mg; none required assistance. Most of these occurred in patients taking metformin plus SU (8.4 %, 16.1 %, and 11.5 % on placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively). Among all patients on monotherapy, metformin only or pioglitazone, the incidence of confirmed hypoglycemic AEs was much lower (0.8 %, 1.2 %, and 1.3 % of patients on placebo, empagliflozin 10 mg, or empagliflozin 25 mg, respectively).[55]

The key AE associated with inhibition of SGLT2 is mycotic genital infection due to elevated glucose levels in the urine. Infections affect predominantly women and mostly comprise mycotic vulvo-vaginitis; in men, mycotic balanitis is the most common infection. Clinical trial data also indicate a low risk for urinary tract infections (UTI). The rates of genito-urinary AEs rise with the duration of follow-up; between 4 and 8 % have been reported in patients treated with dapagliflozin compared with placebo.[37] In a pooled analysis of more than 5,000 patients participating in trials of canagliflozin, symptomatic UTIs were observed in approximately 4 % of patients treated with canagliflozin and approximately 3 % of those treated with placebo. The rates of serious UTIs or UTIs leading to therapy discontinuation were not significantly different in the two groups.[75] In a pooled analysis from 2,477 patients participating in phase III empagliflozin trials, the rates of UTI were not statistically different (8.2 %, 9.3 %, and 7.5 %) in the placebo, lower-dose, and higher-dose groups, respectively.[76] Clinical trial data indicate that infections are typically mild in nature, may be circumvented with rigorous hygiene, respond well to treatment, and are unlikely to lead to discontinuation of the drug.

Dapagliflozin has been associated with a mean increase in daily urine output of 107–375 ml/day secondary to a mild osmotic diuresis.[77] Study populations received counseling about symptoms of dehydration and the importance of adequate fluid consumption, and this has proven effective. One patient in a phase II study with dapagliflozin developed dehydration and renal impairment, which resolved with oral rehydration and withholding angiotensin-converting enzyme (ACE) inhibitor and diuretic treatment.[78] While further research is required to ascertain the long-term safety of these effects in patients taking SGLT2 inhibitors, patients with autosomal recessive renal glucosuria resulting from a mutation in the SGLT2 have not reported clinical complications resulting from chronic elevated urinary glucose, and the condition is considered benign.[30]

A relatively high proportion of patients with diabetes may be treated with ACE inhibitors and diuretic therapy, and are likely to have an increased

Figure 2: Effects of Empagliflozin on Body Weight in Patients with Type 2 Diabetes—Pooled Data from 4 Phase III Trials



CI = confidence interval; SE = standard error. Source: Hach et al. 2013.[55]

prevalence of comorbidities, such as renal impairment, CV disease, and autonomic neuropathy. Further evidence from phase III studies is therefore required to evaluate the long-term safety and efficacy of SGLT2 inhibition in these patient populations. However, recently presented data on the renal safety of SGLT2 inhibitors have been reassuring. An analysis of pooled phase III trial data of patients with CKD taking canagliflozin (n=1,085),[79] as well as 52-week phase III studies of patients with CKD taking canagliflozin[80] and patients with renal impairment[81] and stage 2 and 3 CKD taking empagliflozin[50] showed no significant association between SGLT2 inhibitor use and impairment of renal function. SGLT2 inhibitors reduced HbA_{1c} and were well tolerated in these patients.

Reductions in serum uric acid levels have been consistent across trials and have been suggested to arise from inhibition of sodium-coupled uric acid reabsorption in the renal proximal tubule.[39,82] Uric acid may be a potential CV risk factor, although its association with CV disease has not yet been fully elucidated.[83,84] It is not yet known whether reductions in serum uric acid will translate into long-term beneficial effects on kidney function or CV risk.

Future Developments in Sodium Glucose Co-transporter 2 Inhibitor Treatments

A projection for 20 years based on a population simulation model (Archimedes) that includes National Health and Nutrition Examination Survey (NHANES) study data showed that patients receiving dapagliflozin were likely to experience reductions in the incidence of MI, stroke, CV death, and all-cause death of 13.8 %, 9.1 %, 9.6 %, and 5.0 %, respectively. In addition, there would be relative reductions in the incidence of end-stage renal disease, foot amputation, and diabetic retinopathy of 18.7 %, 13.0 %, and 9.8 %, respectively, compared with the current standard of care.[85]

Additional and larger phase III clinical trials to fully define the potential role of canagliflozin and other SGLT2 inhibitors in the management of diabetes, including studies involving the elderly, children, and patients

with renal or hepatic dysfunction, are planned or currently ongoing. The diuretic effect observed with SGLT2 inhibitors may make them the preferred class of drugs to be used in conjunction with thiazolidinediones, which have been shown to cause fluid retention, especially in the presence of heart failure. However, since most antidiabetic agents have been associated with increased risk for all-cause mortality in patients with heart failure and diabetes,[86] future trials should add heart failure as part of the primary endpoint.

SGLT2 inhibitors also offer potential in the treatment of type 1 diabetes. In a phase IIa trial in type I diabetes, patients taking dapagliflozin had improved glycemic control and required less insulin than those on placebo.[87] In a pilot proof-of-concept trial in type 1 diabetes, empagliflozin as adjunct to insulin therapy improved glycemic control while reducing insulin requirement, weight, and episodes of hypoglycemia.[88] Individuals with type 1 diabetes are at high risk for the development of hypertension, for which hyperglycemia-mediated neurohormonal activation is an important contributing factor. Mechanistic trials in type 1 diabetes indicate that empagliflozin causes an improvement in arterial stiffness and reduction in renal hyperfiltration.[89,90]

Summary and Concluding Remarks

SGLT2 inhibitors are novel oral antidiabetic agents that offer the potential to improve glycemic control independently of insulin secretion while avoiding hypoglycemia, offering a modest reduction in BP and promoting weight loss. Their efficacy is not affected by the extent of insulin resistance or beta-cell dysfunction and therefore they can be used at any stage in the natural history of type 2 diabetes. However, while the rationale for beneficial effects of SGLT2 inhibitors is strong, further evidence of CV safety will be necessary to ensure their widespread use in clinical practice. Evidence that will define the CV risks of this new drug class is expected within the next 1–5 years. As clinical experience with the SGLT2 inhibitors increases, following the launch of more drugs in this class, their safety profile will become clearer and will inform future treatment decisions.

Given the ever-expanding incidence of diabetes in populations worldwide and suboptimal glycemic control achieved with currently available agents, the need for novel agents, with new modes of action remains an urgent clinical and public health priority. SGLT2 inhibitors are a useful addition to the treatment armamentarium. ■

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