The potential role of sodium glucose co-transporter 2 inhibitors in the early treatment of type 2 diabetes mellitus

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SUMMARY

Background: Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class of pharmacologic agents developed for the treatment of type 2 diabetes mellitus (T2DM). Their unique mechanism of action is independent of pancreatic beta-cell function or the degree of insulin resistance, giving these agents the potential for use in combination with any of the existing classes of glucose-lowering agents, including insulin. This makes SGLT2 inhibitors an option for patients with long-standing T2DM, but they also have a promising role for early intervention in T2DM, and that role is explored in this review. **Methods:** A literature search was performed to identify relevant English language articles relating to SGLT2 inhibitors, particularly dapagliflozin, canagliflozin and empagliflozin. **Results:** Clinical trials of dapagliflozin, canagliflozin and empagliflozin, given as monotherapy or in combination with other glucose-lowering agents, reported clinically significant improvements in glycaemic control, body weight and systolic blood pressure. SGLT2 inhibitors were well tolerated and had a generally favourable safety profile. Few serious adverse events have been reported to date. The frequency of hypoglycaemic events was low, similar to that of placebo, and the choice of co-administered glucose-lowering agent was the major determinant of hypoglycaemic risk. Increased genital and urinary tract infections were consistently reported with SGLT2 inhibitors. **Conclusions:** SGLT2 inhibitors, with their unique insulin-independent mode of action, could have a significant impact on the early management of T2DM, by addressing some of the specific risk factors associated with this disease. SGLT2 inhibitors induce beneficial changes in a number of cardiovascular risk factors, such as lowering blood pressure and body weight, in addition to improved glycaemic control, although information on clinical cardiovascular outcomes is currently limited.

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Introduction

Diabetes mellitus is a significant health burden in the United States, occurring in 9.3% of the population (approximately 29.1 million individuals) (1). Type 2 diabetes mellitus (T2DM) is more common than type 1, and accounts for 90–95% of all cases of diabetes mellitus (2). T2DM is a complex cardio-metabolic disorder characterised by insulin resistance, pancreatic beta-cell failure and hyperglycaemia (3). People with T2DM are at increased risk of developing macrovascular complications (coronary artery disease, peripheral artery disease and stroke), as well as microvascular complications (diabetic retinopathy, nephropathy and neuropathy). Early and effective intervention in T2DM to obtain good glycaemic con-

trol is vital to reduce the risks of long-term diabetic complications (4). The benefits of early and intensive glycaemic control in reducing microvascular complications in T2DM are well established (5–8), and these benefits are maintained over the long-term (9). Results from randomised controlled trials (RCTs) have not shown the same consistency regarding reductions in macrovascular complications (9,10); however, several meta-analyses of RCTs reported tight glycaemic control had a positive effect on cardiovascular outcomes (11–13).

Lifestyle modification, particularly regarding weight control in overweight/obese individuals, is a crucial component of T2DM therapy, but most patients eventually require glucose-lowering pharmacotherapy to control hyperglycaemia. Although initial drug mono-

therapy is recommended, usually with metformin (14), given the progressive nature of T2DM, combination therapy is eventually required for most patients to achieve adequate glycaemic control. A number of classes of glucose-lowering agents are available, but some of them are associated with side effects (e.g. weight gain, hypoglycaemia) that need to be considered when the choice of pharmacotherapy is made. Thus, there is a continual need for novel T2DM pharmacotherapies with improved efficacy and safety/tolerability.

Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class of pharmacologic agents for T2DM treatment; they reduce hyperglycaemia by targeting the kidney to promote urinary glucose excretion. SGLT2 inhibitors have a unique mechanism of action that is independent of pancreatic beta-cell function or the degree of insulin resistance, conferring these agents the potential to be used at any stage of the disease, and in combination with any of the existing classes of glucose-lowering agents, including insulin. In turn, this would allow them to be used at any stage of disease course, and may have created the perception that they are particularly appropriate for patients with long-standing T2DM. The aim of this review is to examine the evidence supporting the role of SGLT2 inhibitors as an early intervention in patients recently diagnosed with T2DM.

Methods

To identify relevant English language articles relating to SGLT2 inhibitors, a MEDLINE search was performed using 'SGLT2' as a search term, as well as the individual drug names for SGLT2 inhibitors with marketing approvals in the US; namely, dapagliflozin, canagliflozin and empagliflozin. Characteristics of clinical trials to be included in the review were not pre-defined, although detailed review of efficacy and safety was restricted to phase 3 studies. Key parameters reviewed were the changes in glycated haemoglobin (HbA1c) levels, fasting plasma glucose (FPG) levels, body weight and blood pressure (BP). Abstracts were obtained from the websites of major diabetes and endocrinology congresses, and were included if the corresponding manuscript had not been published. Additional data were obtained from the websites of the European Medicines Agency, US Food and Drug Administration, and the website of the pharmaceutical companies sponsoring the development of individual SGLT2 inhibitors.

Early intervention in T2DM

Given the complex nature of T2DM, there is agreement that drug treatment should be tailored to each patient, according to their individual glycaemic target (i.e. HbA1c) and other factors, such as duration and stage of disease, life expectancy, risk of hypoglycaemia and risk of cardiovascular disease (CVD) (15). The recommended glycaemic target for many non-pregnant adults with T2DM is < 7.0% (14). This can be individualised so that a more stringent target (e.g. < 6.5%) is applied to a newly diagnosed person with no complications (e.g. without CVD) (14). Some clinicians believe the target HbA1c should be reduced further to ≤ 6.0% in newly diagnosed T2DM patients with no CVD (16). Conversely, a less stringent target (e.g. < 8.0%) could be applied to T2DM patients with advanced CVD, reduced life expectancy and multiple comorbidities. Whatever the precise goal, it is also well established that early and effective intervention in T2DM provides a greater opportunity to reduce the risks of long-term diabetes complications (15).

As described in a recent review by DeFronzo and colleagues, an individual has already lost approximately 80% of their beta-cell function by the time a diagnosis of T2DM is made; thus, drug therapy must be started promptly to compensate for the progressive beta-cell failure that is already well established in such individuals (16). They suggest treatment should be based on the reversal of known pathogenic abnormalities (beta-cell failure and insulin resistance) and not simply on HbA1c reductions (16). To accomplish this, they proposed early combination therapy with thiazolidinediones (TZDs) and glucagon-like peptide 1 receptor (GLP-1R) agonists added to metformin, as these agents improve and preserve beta-cell function, and TZDs are also potent insulin sensitizers while GLP-1R agonists promote weight loss (17–22). However, these drugs have limitations; for example, TZDs are associated with weight gain, fluid retention and bone fractures (21,23), whereas GLP-1R agonists are given via subcutaneous injection, and are associated with gastrointestinal side effects (24). Dipeptidyl peptidase-4 (DPP-4) inhibitors provide an alternative incretin-based option to GLP-1R agonists, but are weight-neutral rather than associated with weight loss (25). Thus, there remains a need for additional treatment options in the early stages of T2DM.

SGLT2 inhibitors: background and mechanism of action

In addition to the core pathologic defects of beta-cell failure and insulin resistance, a number of other factors contribute to disease progression in T2DM. Together, these have been termed the 'ominous octet', as shown in Figure 1. The dysregulation of
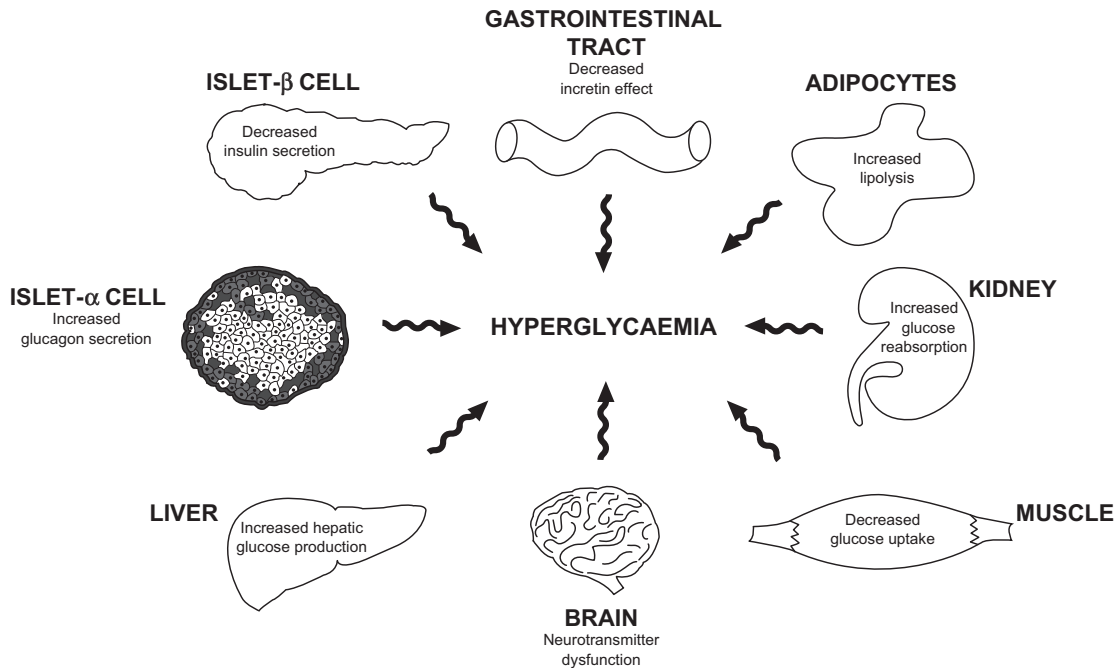
Figure 1 The ominous octet. In addition to the insulin resistance in the muscle and liver, and impaired insulin secretion in the β-cell, the fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cell (hyperglucagonaemia), kidney (increased glucose reabsorption) and brain (insulin resistance) all play important roles in the development of glucose intolerance in type 2 diabetic individuals (3). Reproduced with permission from DeFronzo R et al. *Diabetes*, 2009; 58:773–795. Copyright ©2009 American Diabetes Association. All rights reserved

kidney-mediated maintenance of glucose homoeostasis is one component of the ominous octet (3). Renal glucose resorption capacity is increased in individuals with diabetes (26–28), and the kidneys continue to reabsorb glucose even when plasma glucose concentrations are high, with levels that usually exceed the transport maximum of glucose of healthy individuals. This leads to the continuous movement of glucose from the kidneys into the circulation, even in the presence of hyperglycaemia, thus perpetuating hyperglycaemia and increasing the risk for diabetes-associated complications. In addition, renal gluconeogenesis is elevated in patients with T2DM, resulting in increased glucose release in these individuals. Renal gluconeogenesis is negatively regulated by insulin and renal glucose production increases with increasing insulin resistance, with 40% of the increased endogenous glucose release in patients with T2DM attributable to increased renal gluconeogenesis (29).

SGLT2 is a low-affinity, high-capacity glucose transporter located in the early part of the proximal tubule, involved in the reabsorption of the vast majority (~90%) of glucose in the kidney (30). As the actions of SGLT2 promote glucose conservation and the maintenance of plasma glucose concentrations, inhibition of SGLT2 may have the opposite effect; namely, to reduce hyperglycaemia by stimulating urinary glucose excretion (31). Observations in individuals with SGLT2 gene alterations suggest that functional depletion of SGLT2 may not have long-term deleterious effects, at least in the individuals followed up to date. The resulting disorder, known as familial renal glucosuria, causes urinary glucose excretion, with the amount of glucose excreting ranging from < 10 g/day to > 200 g/day (32,33). Affected individuals are usually otherwise asymptomatic (33), and the condition is not known to be associated with T2DM or other pathological sequelae.

As the action of SGLT2 is independent of insulin, its inhibition should not be influenced by pancreatic beta-cell mass or function, or by the degree of insulin resistance present. Therefore, SGLT2 inhibitors have the potential to be used at any stage of T2DM. They may even have the potential to show efficacy as the disease progresses, unlike some other types of antidiabetes agents that show a decline in glucose-lowering potential caused by their dependence on beta-cell function (e.g. sulfonylureas or glinides). Additionally, the non–insulin-dependent mechanism of action of SGLT2 inhibitors gives them the potential to be used in combination with any of the existing classes of glucose-lowering agents, including insulin. Other metabolic characteristics of SGLT2 inhibitors

may also be anticipated. For example, SGLT2 inhibitors should not increase the risk of hypoglycaemia, as inhibition of SGLT2 does not affect endogenous glucose production (34), does not stimulate insulin release when glucose levels decline and does not cause urinary glucose excretion when plasma glucose levels fall below threshold values (35–37). SGLT2 inhibitors should also promote some weight loss (36), resulting from the reduction in available calories caused by urinary glucose excretion. This ability to induce weight loss, along with the ability to act as a diuretic, would also suggest a potential BP-lowering effect for SGLT2 inhibitors (38).

Clinical experience with SGLT2 inhibitors

Dosing, pharmacology and current indications

Dapagliflozin, canagliflozin and empagliflozin are approved for use in the US and European Union (Table 1) (39–44). In addition, various fixed-dose combination products involving an SGLT2 inhibitor plus a second oral glucose-lowering agent (including metformin, metformin extended-release and DPP-4 inhibitors) are in clinical development. A fixed-dose combination product containing dapagliflozin plus metformin (in 5/850 mg and 5/1000 mg tablets) was recently granted marketing authorisation in the EU (45), and an extended-release version of this combination has been recently approved for use in the US (in 5/500 mg, 10/500 mg, 5/1000 mg and 10/1000 mg tablets) (46). A fixed-dose combination of canagliflozin plus metformin has also been granted marketing authorisation, both in the EU (in 50/850 mg, 150/850 mg, 50/1000 mg and 150/1000 mg) and the US (in 50/500 mg, 150/500 mg, 50/1000 mg and 150/1000 mg) (47,48).

As new agents, SGLT2 inhibitors are beginning to be incorporated in treatment guidelines. The 2013 American Association of Clinical Endocrinologists algorithm included SGLT2 inhibitors as a therapeutic alternative in patients with T2DM in whom metformin is not tolerated or otherwise contraindicated (49). The algorithm also stated that SGLT2 inhibitors could be used as add-on therapy to two or three other agents, including insulin, in patients who would benefit from weight loss (49). In 2015, the American Diabetes Association and European Association for the Study of Diabetes issued an update to their joint position statement, including SGLT2

Table 1 SGLT2 inhibitors approved for use in the US

Drug	Approved dosages	Selectivity for SGLT2 vs. SGLT1	Indications*	Dose adjustment in renal impairment[†]
Canagliflozin (43)	100 mg, 300 mg	> 250-fold	Adjunct to diet and exercise to improve glycaemic control in adults with T2DM	No dose adjustment needed in pts with eGFR $\geq$ 60 ml/min/1.73 m^2 Limited to 100 mg in pts with eGFR 45 to < 60 ml/min/1.73 m^2 Should not be initiated in pts with eGFR < 45 ml/min/1.73 m^2 Contraindicated in severe renal impairment (eGFR $\leq$ 30 ml/min/1.73 m^2), end-stage renal disease, or dialysis
Dapagliflozin (41)	5 mg, 10 mg	> 1200-fold	Adjunct to diet and exercise to improve glycaemic control in adults with T2DM	No dose adjustment needed in pts with eGFR $\geq$ 60 ml/min/1.73 m^2 Should not be initiated in pts with eGFR < 60 ml/min/1.73 m^2 Contraindicated in severe renal impairment, end-stage renal disease, or dialysis
Empagliflozin (40)	10 mg, 25 mg	> 2500-fold	Adjunct to diet and exercise to improve glycaemic control in adults with T2DM	No dose adjustment is needed in pts with eGFR $\geq$ 45 ml/min/1.73 m^2 Should not be initiated in pts with eGFR < 45 ml/min/1.73 m^2 Contraindicated in severe renal impairment, end-stage renal disease, or dialysis

*Indications shown are for US prescribing information. In the EU, all three drugs shown are indicated as monotherapy when diet and exercise alone do not provide adequate glycaemic control in pts for whom the use of metformin is considered inappropriate because of intolerance or contraindications (39,42,44). [†]Use in specific populations and contraindications are based on US prescribing information at the time of writing; EU advice may differ. Metabolism of dapagliflozin, canagliflozin and empagliflozin occurs in the liver and kidneys, and elimination of the drugs occurs predominantly via faeces but also in the urine (40,111,112). T2DM, type 2 diabetes mellitus; pts, patients; eGFR, estimated glomerular filtration rate.

inhibitors among the options for second-line therapy after metformin, and as alternative first-line options in patients with contraindications to metformin, or as add-on to insulin to improve glycaemic control and reduce the requirement for insulin (50).

Efficacy

A summary of efficacy data from the main phase 3 clinical trials of dapagliflozin, canagliflozin and empagliflozin are presented in Table 2 (51–69).

Glycaemic control

In patients with T2DM, treatment with the SGLT2 inhibitors dapagliflozin, canagliflozin and empagliflozin, given as monotherapy and/or in combination with other antidiabetes agents, produced clinically and statistically significant improvements in HbA1c vs. placebo. In some cases, improvements were also significantly greater than with active comparators; for example, comparison of efficacy data for an SGLT2 inhibitor (canagliflozin) vs. a DPP-4 inhibitor (sitagliptin) is presented in Figure 2 (62). Data on HbA1c and FPG from individual clinical trials are presented in Table 2.

In addition to mean changes in blood glucose levels, attainment of the widely used HbA1c target of < 7.0% was measured, as this outcome provides a guide to the likelihood of achieving goals in practice. All three SGLT2 inhibitors significantly increased the odds of achieving goal, although differences between trials in the placebo group attainment rate was notable, presumably reflecting baseline characteristics of patients in individual trials. In treatment-naïve patients in whom hyperglycaemia was insufficiently controlled with diet and exercise alone, 24 weeks of monotherapy with dapagliflozin 10 mg led to 51% of patients achieving HbA1c < 7.0%, vs. 32% of those in the placebo group (51). Treatment with dapagliflozin added on to stable metformin led to significantly greater proportions of subjects in the dapagliflozin 5-mg and 10-mg groups achieving HbA1c < 7.0% after 24 weeks vs. placebo (37.5% and 40.6%, respectively, vs. 25.9% with placebo) (52). Canagliflozin monotherapy given for 26 weeks resulted in 44.5% and 62.4% of subjects receiving 100 mg and 300 mg, respectively, achieving HbA1c < 7.0%, vs. 20.6% of those on placebo (59). When canagliflozin was used with metformin, HbA1c < 7.0% occurred in 54% and 60% of subjects receiving 100 mg and 300 mg, respectively, vs. 56% of those receiving the active comparator glimepiride (60). Empagliflozin monotherapy given for 24 weeks led to HbA1c < 7.0% in 35.3% and 43.6% of subjects receiving empagliflozin 10 mg and 25 mg, respectively, vs. 37.5% for the active comparator group (sitagliptin 100 mg), and

12.0% in the placebo group (66). When empagliflozin was given in combination with metformin, HbA1c < 7.0% occurred in 37.7% and 38.7% of empagliflozin 10-mg and 25-mg groups, respectively, vs. 12.5% of the placebo group (67).

As the mechanism of action of SGLT2 inhibitors relies on the glomerular filtration rate, reduced efficacy is predicted in patients with impaired renal function. Dapagliflozin did not improve HbA1c in patients with T2DM and moderate renal impairment (eGFR $\geq$ 30 to < 60 ml/min/1.73 m^2) after 52 weeks (70), whereas canagliflozin 100 mg and 300 mg significantly lowered HbA1c compared with placebo in patients with T2DM and eGFR $\geq$ 30 to < 50 ml/min/1.73 m^2 after 26 weeks, with placebo-corrected changes of −0.30% and −0.40%, respectively (71). In patients with T2DM and moderate renal impairment (eGFR $\geq$ 30 to < 60 ml/min/1.73 m^2), empagliflozin 25 mg significantly lowered HbA1c vs. placebo with a placebo-corrected mean treatment difference of −0.42% at week 24 (72).

Blood pressure

A recent meta-analysis of 27 RCTs, predominantly involving dapagliflozin ($n = 12$) and canagliflozin ($n = 9$), reported that SGLT2 inhibitor use was associated with a statistically significant reduction in systolic blood pressure (SBP) from baseline (−4.0 mmHg; 95% confidence interval [CI], −4.4, −3.5; Cochrane p = 0.986; $I^2 = 0\%$) (73). This reduction was similar when placebo-controlled RCTs and active-controlled RCTs were pooled separately (73). A meta-analysis of 10 dapagliflozin RCTs reported that decreases in SBP (seated) were greater in the dapagliflozin group compared with the placebo group [weighted mean difference (WMD): −3.57 mmHg; 95% CI, −4.38, −2.77; p < 0.00001; $I^2 = 0\%$] (74). For canagliflozin, a pooled analysis of six phase 3 RCTs recorded placebo-corrected reductions in SBP of −3.3 mmHg and −4.5 mmHg with 100 mg and 300 mg, respectively (75). For empagliflozin, a pooled analysis of four phase 3 RCTs investigating empagliflozin as monotherapy or add-on therapy (with metformin, metformin plus sulfonylurea or pioglitazone $\pm$ metformin) reported reductions in SBP for empagliflozin groups vs. placebo (placebo-corrected change from baseline −3.4 mmHg and −3.8 mmHg for empagliflozin 10 mg and 25 mg, respectively) (76). Furthermore, a study using ambulatory BP monitoring for patients with T2DM and hypertension found that empagliflozin 10 mg and 25 mg significantly reduced mean 24-h SBP vs. placebo (−2.95 and −3.68 mmHg vs. +0.48 mmHg, respectively; p < 0.001 vs. placebo for each dose) (77).

Table 2 Efficacy data summary from the main phase 3 clinical trials of dapagliflozin, canagliflozin and empagliflozin*
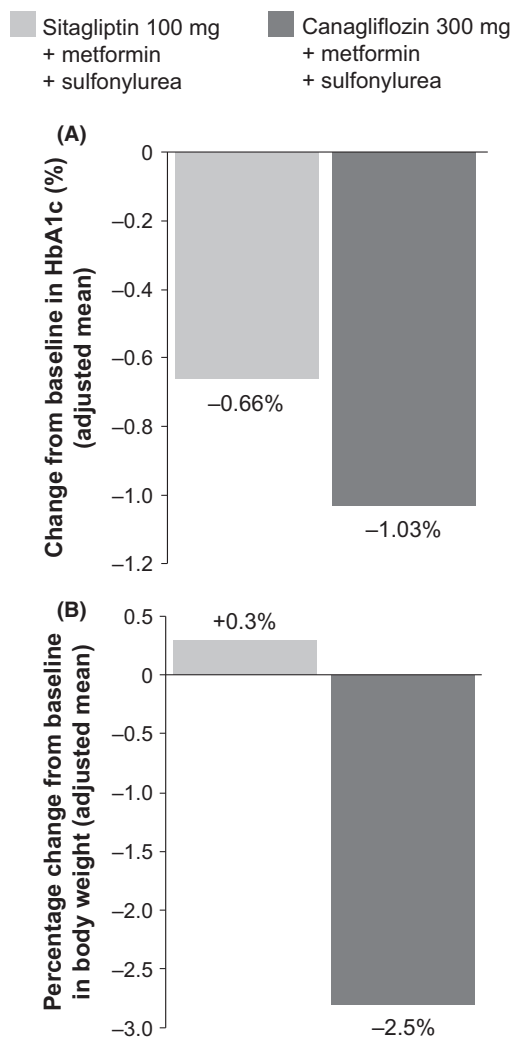
Study details (N§)	Treatment, dose (mg/day)	Change from baseline†,‡			
		HbA1c (%)	FPG (mg/dl)	Body weight (kg)	SBP (mmHg)
Dapagliflozin					
Monotherapy, 24 weeks (N = 485) (51)	Pbo	−0.23	−4.1	−2.2	−0.9
	Dapa 5/10	−0.77 to −0.89	−24.1 to −29.6	−2.8 to −3.6	−2.3 to −5.2
Monotherapy (A1c ≥10.1), 24 weeks (N = 73) (51)	Dapa 5/10	−2.88/−2.66	−77.1/−84.3	−2.1/−1.9	−5.7/−2.5
Add-on to MET, 24 weeks (N = 546) (52)	Pbo	−0.30	−5.95	−0.9	−0.2
	Dapa 5/10	−0.70/−0.84	−21.44/−23.42	−3.0/−2.9	−4.3/−5.1
Initial combination with MET XR, 24 weeks (N = 1244) (53)	Pbo + MET XR	−1.35 to −1.44	−33.51 to −34.78	−1.29 to −1.36	−1.2 to −1.8
	Dapa 5/10 + MET XR	−1.98 to −2.05	−60.36 to −61.09	−2.66 to −3.33	−2.9 to −3.30
Add-on to SU (GLIM), 24 weeks (N = 597) (54)	Pbo	−0.13	−1.98	−0.72	−1.2
	Dapa 5/10	−0.63 to −0.82	−21.26 to −28.47	−1.56 to −2.26	−4.0 to −5.0
Add-on to DPP4i (SITA) ± MET, 24 weeks (N = 432) (55)	Pbo + SITA	0.1	4.6	−0.1	−4.2
	Dapa 10 + SITA	−0.5	−22.0	−1.9	−6.6
	Pbo + SITA + MET	−0.0	3.0	−0.5	−5.5
	Dapa 10 + SITA + MET	−0.4	−26.2	−2.4	−5.3
Add-on to MET, 52 weeks (N = 814) (56)	Dapa 2.5–10	−0.52	−22.34	−3.22	−4.3
	GLIP 5–20	−0.52	−18.74	1.44	0.8
Add-on to TZD, 48 weeks (N = 420) (57)	Pbo	−0.54	−13.1	2.99	2.0
	Dapa 5/10	−0.95 to −1.21	−22.8 to −33.1	0.69 to 1.35	−1.0 to −2.2
Add-on to INS (≥ 30 units/day) ± OAD, 48 weeks (N = 800) (58)	Pbo	−0.47	N/r	0.82	−1.49
	Dapa 5/10	−0.96 to −1.01	N/r	−1.00 to −1.61	−4.09 to −4.33
Canagliflozin					
Monotherapy, 26 weeks (N = 584) (59)	Pbo	0.14	9.00	−0.5	0.4
	Cana 100/300	−0.77 to −1.03	−27.03 to −34.23	−2.5 to −3.4	−3.3 to −5.0
Monotherapy (A1c>10.0 ≤ 12.0) (N = 94) (59)	Cana 100/300	−2.1 to −2.6	−81.1 to −86.5	−3.0 to −3.8	−4.5 to −5.0
Add-on to MET, 52 weeks (N = 1450) (60)	GLIM 1–8	−0.81	−18.0	0.7	0.2
	Cana 100/300	−0.82 to −0.93	−25.2 to −27.0	−3.7 to −4.0	−3.3 to −4.6
Add-on to MET, 52 weeks (N = 1284) (61)	SITA 100	−0.73	−17.7	−1.3%	−0.7
(26 weeks Pbo + comparator; 26 weeks comparator)	Cana 100/300	−0.73 to −0.88	−26.2 to −35.2	−3.8 to −4.2%	−3.5 to −4.7
Add-on to MET + SU, 52 weeks (N = 755) (62)	SITA 100	−0.66	−2.2	0.1	0.9
	Dapa 300	−1.03	−28.7	−2.3	−5.1
Add-on to MET + SU, 26 weeks (N = 469) (63)	Pbo	−0.13	3.60	−0.8	−2.7
	Cana 100/300	−0.85 to −1.06	−18.02 to −30.63	−1.9 to −2.5	−4.3 to −4.9

Table 2 Continued

Study details (N§)	Treatment, dose (mg/day)	Change from baseline[†,‡]			
		HbA1c (%)	FPG (mg/dl)	Body weight (kg)	SBP (mmHg)
Add-on to MET + TZD (PIO), 26 weeks (+26-week extension) (N = 342) (64)	Pbo	−0.26	2.5	−0.2	−1.2
	Cana 100/300	−0.89 to −1.03	−26.8 to −33.2	−2.6 to −3.8	−4.7 to −5.3
Add-on to INS (≥ 30 units/day) ± OADs Substudy efficacy duration 18 weeks (N = 1708) (65)	Cana 100/300¶	−0.65 to −0.73¶	−22.52 to −29.01¶	−1.9 to −2.4%¶	−2.6 to −4.4¶
Empagliflozin					
Monotherapy, 24 weeks (N = 899) (66)	Pbo	0.08	11.7	−0.33	−0.3
	SITA 100	−0.66	−6.85	0.18	0.5
	Empa 10/25	−0.66 to −0.78	−19.5 to −24.5	−2.26 to −2.48	−2.9 to −3.7
Monotherapy (A1c > 10.0), 24 weeks (N = 87) (66)	Empa 25	−3.70	−84.3	−2.43	−4.0
Add-on to MET, 24 weeks (N = 637) (67)	Pbo	−0.13	6.38	−0.45	−0.4
	Empa 10/25	−0.70 to −0.77	−20.04 to −22.28	−2.08 to −2.46	−4.5 to −5.2
Add-on to MET + SU, 24 weeks (N = 666) (68)	Pbo	−0.17	5.52	−0.39	−1.4
	Empa 10/25	−0.77 to −0.82	−23.27 to −23.30	−2.16 to −2.39	−3.5 to −4.1
Add-on to TZD (PIO) ± MET, 24 weeks (N = 498) (69)	Pbo	−0.11	6.47	0.34	0.7
	Empa 10/25	−0.59 to 0.72	−17.0 to −22.0	−1.47 to −1.62	−3.1 to −4.0
Add-on to MET, 104 weeks (N = 1549) (79)	GLIM 1–4	−0.55	−3.06	1.3	2.5
	Empa 25	−0.66	−15.32	−3.1	−3.1

*All included studies were conducted in adults (≥ 18 years old). [†]Data for high glycaemic subgroups are presented for monotherapy studies only. [‡]Data are presented as reported in each publication; the range of changes shown is for approved doses of the drug only. [¶]Number of patients randomized. [§]Number of patients randomized. [¶]Adjusted mean difference from placebo. HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; SBP, systolic blood pressure; Pbo, placebo; Dapa, dapagliflozin; A1c, glycated haemoglobin; MET, metformin; GLIP, glipizide; XR, extended-release formulation; SU, sulfonylurea; GLIM, glimepiride; DPP4i, dipeptidyl peptidase-4 inhibitor; SITA, sitagliptin; TZD, thiazolidinedione; INS, insulin; OAD, oral antidiabetes drug; N/r, not reported (in original publication); Cana, canagliflozin; PIO, pioglitazone; Empa, empagliflozin.

Sitagliptin 100 mg
+ metformin
+ sulfonylurea

Canagliflozin 300 mg
+ metformin
+ sulfonylurea

(A)

Change from baseline in HbA1c (%) (adjusted mean)

−0.66%

−1.03%

(B)

Percentage change from baseline in body weight (adjusted mean)

+0.3%

−2.5%

Figure 2 Efficacy data for an SGLT2 inhibitor vs. a DPP-4 inhibitor. Panel A shows a greater reduction in HbA1c from baseline to week 52 in patients receiving canagliflozin ($N = 377$) vs. sitagliptin ($N = 378$), when both agents were given in combination with metformin and a sulfonylurea. Mean baseline HbA1c was 8.12% and 8.13% in the canagliflozin and sitagliptin groups, respectively. As shown in panel B, there was a decrease in body weight from baseline to week 52 in the canagliflozin group, compared with an increase in body weight for the sitagliptin group. DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin (62)

Body weight

In the aforementioned meta-analysis, when the data from 16 RCTs were pooled together, compared with control, SGLT2 inhibitor use was associated with statistically significant reduction in body weight from baseline (WMD: −1.9 kg; 95% CI, −2.5, −1.2), which was greater in the active-controlled RCTs than the placebo-controlled RCTs (73). The body weight reduction observed in a 2-year trial of dapagliflozin added to metformin (−4.5 kg for dapagliflozin plus

metformin vs. −2.1 kg for placebo plus metformin) was principally caused by a reduction in body fat mass, as shown by dual energy X-ray absorptiometry, which demonstrated the weight loss is because of caloric loss caused by urinary glucose excretion and not simply because of fluid loss (78). This was confirmed in a 1-year trial of canagliflozin vs. glimepiride (both administered with metformin), where approximately two-thirds of the reduction in body weight was from body fat mass (−3.7 to −4.0 kg for canagliflozin groups vs. +0.7 kg for glimepiride) (60), as well as a 2-year study of empagliflozin vs. glimepiride (again both administered as add-on to metformin), in which nearly 90% of weight loss with empagliflozin was because of a reduction in fat mass (79).

Pancreatic beta-cell function

T2DM patients receiving SGLT2 inhibitor therapy showed improvements in pancreatic beta-cell function as measured by Homeostasis Model Assessment 2 (HOMA-2%B). For dapagliflozin given as monotherapy or as add-on to metformin, the placebo-corrected mean improvement in HOMA-2%B across dapagliflozin groups (2.5 mg, 5 mg and 10 mg doses) ranged from 13.2% to 17.3% for monotherapy and from 8.3% to 13.4% as add-on to metformin (80). In an additional study, dapagliflozin given as add-on to sitagliptin (± metformin), showed 24.9% increase in beta-cell function, per HOMA-2%B analysis, vs. a 5.2% increase for the placebo group (55). There are some further early clinical data suggesting improvements in insulin resistance with dapagliflozin (81). For canagliflozin given as monotherapy or as add-on to metformin plus sulfonylurea, the mean improvement in HOMA-2%B for canagliflozin 300 mg was 22.8% for monotherapy (placebo-corrected, week 26) (59), and 12.6% as add-on to metformin plus sulfonylurea (active control-corrected, week 52) (62). In this latter canagliflozin study, other indices of beta-cell function were evaluated (including proinsulin/insulin ratio, and the proinsulin/C-peptide ratio) (62). The data reflected improvements in beta-cell function, which was deemed to be due either to the reversal of glucotoxicity, or the 'unloading' of the beta-cell as systemic glucose levels decrease (82). A recent study examining the metabolic response to empagliflozin in T2DM patients, using a model to reconstruct insulin secretion and its control by glucose (83), found that beta-cell glucose sensitivity was enhanced and insulin sensitivity improved following empagliflozin therapy (84). Increased insulin sensitivity following SGLT2 inhibitor therapy in T2DM was also reported in a recently published study using dapagliflozin (85).

Interestingly, despite reducing FPG, SGLT2 inhibition with dapagliflozin or empagliflozin increased endogenous glucose production, and this may be at least partially explained by a concentration change in the insulin-to-glucagon ratio that was observed with SGLT2 inhibitor therapy (84,85).

Safety

A summary of safety data from the main phase 3 clinical trials of dapagliflozin, canagliflozin and empagliflozin are presented in Table 3 (51–69). Events of interest from these trials included hypoglycaemia, urinary tract infection (UTI), and genital mycotic infection. Dapagliflozin, canagliflozin and empagliflozin were generally well tolerated when given as monotherapy and in all combination therapies used to date, and trials have reported few serious adverse events.

Hypoglycaemia

Monotherapy with dapagliflozin, canagliflozin or empagliflozin was not associated with an increased risk of hypoglycaemia (51,59,66). Clinical trials show the frequency of hypoglycaemia with SGLT2 inhibitor combination therapy appears to be dependent upon the choice of glucose-lowering therapy that is co-administered: an increased frequency of hypoglycaemic events is reported when used in combination with insulin or sulfonylureas (see Table 3). These data correlate with behaviour predicted of SGLT2 inhibitors; namely, as SGLT2 inhibitors act independently of insulin to reduce blood glucose levels, no increased risk of hypoglycaemia is anticipated when used in combination with drugs that do not affect insulin levels (e.g. metformin or TZDs). Conversely, when given with insulin or insulin secretagogues such as sulfonylureas, the reduced blood glucose levels would be expected to increase the risk of hypoglycaemic risk (unless the dosage of insulin/sulfonylurea was reduced). This is stated in the prescribing information, in which consideration of a lower dose of insulin or an insulin secretagogue is advised to reduce the risk of hypoglycaemia (39–41,43).

Genital mycotic infection

Monotherapy with dapagliflozin, canagliflozin or empagliflozin was associated with an increased incidence in symptoms suggestive of genital mycotic infection (51,59,66). These events were more common in women than in men, where subgroup analyses by gender were available (51,59,66). A similar trend was observed with add-on combination therapy involving dapagliflozin, canagliflozin and empagliflozin, and was consistent across studies (Table 3). This was confirmed by analyses of pooled data from phase 3 trials of these three SGLT2 inhibitors (86–88). Furthermore, the majority of these events were mild in severity and responded to standard therapies, and very few patients discontinued treatment because of these events (86–88).

Urinary tract infection

The association of SGLT2 inhibitors with UTIs is less straightforward (89). Treatment with canagliflozin (100 and 300 mg) and dapagliflozin (5 and 10 mg) has been shown to be accompanied by a slightly increased incidence of UTIs compared with placebo (90,91). The infections were generally mild to moderate or similar in severity to infections in the control groups, clinically manageable and did not lead to study discontinuations; furthermore, there was no meaningful increase in upper UTIs (91). For empagliflozin (10 and 25 mg), systematic review and meta-analysis of available data have not shown evidence of increased risk of UTIs compared with placebo (88,92). The empagliflozin prescribing information notes an increased risk of UTIs in elderly patients (aged ≥ 75 years) to 15.7% and 15.1% with 10 mg and 25 mg, respectively, vs. 10.5% with placebo (40), as well as increased risk in patients with worsening renal impairment, similar to what has been observed with canagliflozin, although details of these empagliflozin analyses have yet to be published (40,71).

Bone safety

Bone fractures were more common in patients with T2DM and moderate renal impairment who were receiving dapagliflozin than those receiving placebo (7.7% vs. 0% for dapagliflozin groups and placebo, respectively) (70); however, there was no evidence that dapagliflozin induced bone demineralisation or increased fracture rates in individuals with either normal renal function or mild renal impairment (42). Additional data revealed no meaningful changes, compared with placebo, in markers of bone turnover or bone mineral density from baseline over 102 weeks for dapagliflozin added to metformin (78). A regulatory authority assessment of bone safety with canagliflozin treatment (~10,000 patients with T2DM from phase 3 trials) reported apparent canagliflozin-associated increases in overall fractures (2.5% and 2.3% for 100 mg and 300 mg, respectively) vs. control groups (1.7%) (93). The regulators noted that, while small, these differences approached statistical significance, and concluded that canagliflozin demonstrated a modest dose-dependent increase in bone resorption, which may contribute to bone fragility (93). For empagliflozin, a pooled analysis of more than 11,000 patients with T2DM (from phase

Table 3 Safety data summary from the main phase 3 clinical trials of dapagliflozin, canagliflozin and empagliflozin*

Reference	Study details	Treatment and dose (mg/day)	Patients with a special interest adverse event[†]		
			Hypoglycaemia (%)	Urinary tract infection (%)	Genital infection (%)[‡]
Dapagliflozin					
Monotherapy (51)	Phase 3, 24 weeks	Pbo	2.7	4.0	1.3
		Dapa 5/10	0 to 2.9	5.7 to 12.5	2.6 to 12.9
Monotherapy (A1c ≥ 10.1) (51)	Phase 3, 24 weeks	Dapa 5/10	2.9/0	8.8/15.4	5.9/17.9
Add-on to MET (52)	Phase 3, 24 weeks	Pbo	3	8	5
		Dapa 5/10	4/4	7/8	13/9
Initial combination with MET XR (53)	Phase 3, 24 weeks	Pbo + MET XR	0–2.9	7.5	2.0–2.4
		Dapa 5 + MET XR	2.6	7.7	6.7
		Dapa 10 + MET XR	3.3	7.6	8.5
Add-on to SU (GLIM) (54)	Phase 3, 24 weeks	Pbo	4.8	0.7	0.7
		Dapa 5	6.9	6.9	6.2
		Dapa 10	7.9	5.3	6.6
Add-on to DPP4i (SITA) (55)	Phase 3, 24 weeks[§]	Pbo	1.8	4.0	0.4
		Dapa 10	2.7	4.9	8.4
Add-on to MET (56)	Phase 3, 52 weeks	GLIP 5–20	39.7	6.4	2.7
		Dapa 2.5–10	3.4	10.8	12.3
Add-on to TZD (PIO) (57)	Phase 3, 48 weeks	Pbo	0.7	7.9	2.9
		Dapa 5/10	2.1/0	8.5/5.0	9.2/8.6
Add-on to INS (≥ 30 units/day) ± OADs (58)	Phase 3, 48 weeks	Pbo	51.8	5.1	2.5
		Dapa 5	55.7	10.8	9.9
		Dapa 10	53.6	10.2	10.7
Canagliflozin					
Monotherapy (59)	Phase 3, 26 weeks	Pbo	2.6	4.2	2.1 (M0%, F3.8%)
		Cana 100	3.6	7.2	6.2 (M2.5%, F8.8%)
		Cana 300	3.0	5.1	6.6 (M5.6%, F7.4%)
Monotherapy (A1c >10.0 ≤ 12.0) (59)	Phase 3, 26 weeks	Cana 100	N/r	6.4	12.7 (M4.3%; F20.8%)
		Cana 300	N/r	4.5	4.5 (M5.3%; F4.0%)
Add-on to MET (60)	Phase 3, 52 weeks	GLIM 1–8	34	5	1.7 (M1%, F2%)
		Cana 100	6	6	8.9 (M7%, F11%)
		Cana 300	5	6	11.1 (M8%, F14%)
Add-on to MET (61)	Phase 3, 52 weeks[¶]	SITA 100	4.1	6.3	1.9 (M1.2%, F2.6%)
		Cana 100	6.8	7.9	8.4 (M5.2%, F11.3%)
		Cana 300	6.8	4.9	6.5 (M2.4%, F9.9%)
Add-on to MET + SU (62)	Phase 3, 52 weeks	SITA 100	40.7	5.6	2.1 (M0.5%, F4.3%)
		Cana 300	43.2	4.0	11.9 (M9.2%, F15.3%)
Add-on to MET + SU (63)	Phase 3, 52 weeks**;[††]	Pbo	17.9	7.7	3.2 (M1.3%; F5.0%)
		Cana 100	33.8	8.3	13.3 (M7.9%; F18.5%)
		Cana 300	36.5	8.3	11.5 (M5.7%; F18.8%)

Table 3 Continued

Reference	Study details	Treatment and dose (mg/day)	Patients with a special interest adverse event†		
			Hypoglycaemia (%)	Urinary tract infection (%)	Genital infection (%)‡
Add-on to MET + TZD (PIO) (64)	Phase 3, 52 weeks††,‡‡	Pbo / SITA	4.4	7.8	2.6 (M0%; F7.7%)
		Cana 100	6.1	5.3	8.0 (M3.9%; F16.7%)
		Cana 300	6.1	7.9	12.3 (M4.8%; F21.6%)
Add-on to INS ≥ 30 units/day ± OADs (65)	Phase 3, 18 weeks efficacy substudy	Pbo	37	2.1	(M0.5%, F2.2%)
		Cana 100	49	2.3	(M4.0%, F11.8%)
		Cana 300	48	3.4	(M8.3%, F9.9%)
Empagliflozin					
Monotherapy (66)	Phase 3, 24 weeks	Pbo	<1	5 (M2%, F9%)	0
		SITA 100	<1	5 (M3%, F9%)	1 (M1%, F1%)
		Empa 10	<1	7 (M2%, F15%)	3 (M3%, F4%)
		Empa 25	<1	5 (M1%, F13%)	4 (M1%, F9%)
Monotherapy (A1c > 10.0) (66)		Empa 25	0	3 (M3%; F4%)	1 (M2%; F0%)
Add-on to MET (67)	Phase 3, 24 weeks	Pbo	0.5	4.9 (M2.6%, F7.7%)	0
		Empa 10	1.8	5.1 (M0%, F12.0%)	3.7 (M0.8%, F7.6%)
		Empa 25	1.4	5.6 (M0.8%, F11.8%)	4.7 (M0.8%, F9.7%)
Add-on to MET + SU (68)	Phase 3, 24 weeks	Pbo	8.4	8.0 (M2.7%, F13.3%)	0.9 (M0.9%, F0.9%)
		Empa 10	16.1	10.3 (M2.7%, F18.0%)	2.7 (M0.9%, F4.5%)
		Empa 25	11.5	8.3 (M0%, F17.5%)	2.3 (M0.9%, F3.9%)
Add-on to TZD (PIO) ± MET (69)	Phase 3, 24 weeks	Pbo	1.8	16.4 (M8.2%, F22.8%)	2.4 (M1.4%, F3.3%)
		Empa 10	1.2	17.0 (M3.6%, F30.5%)	8.5 (M7.2%, F9.8%)
		Empa 25	2.4	11.9 (M2.4%, F21.7%)	3.6 (M1.2%, F6.0%)
Add-on MET	Phase 3, 104 weeks	GLIM 1-4	25	13 (M5%, F23%)	2 (M1%, F3%)
		Empa 25	4	14 (M7%, F22%)	12 (M9%, F15%)

*All included studies were conducted in adults (≥ 18 years). †Data are presented as reported in each publication, the changes (range where applicable) is for approved doses of the drug only. ‡Genital mycotic infection specified in canagliflozin studies. §Safety data provided for entire cohort only. ¶26 weeks Pbo + SITA; 26 weeks SITA only. **26 weeks + 26 weeks extension. ††Safety data reported at week 52. ‡‡ 26 weeks + 26 weeks extension, Pbo group switched to SITA during extension. Pbo, placebo; M, male; F, female; Dapa, dapagliflozin; A1c, glycated haemoglobin; MET, metformin; XR, extended-release formulation; SU, sulfonylurea; GLIM, glimepiride; DPP4j, dipeptidyl peptidase-4 inhibitor; SITA, sitagliptin; GLIP, glipizide; TZD, thiazolidinedione; PIO, pioglitazone; INS, insulin; OAD, oral antidiabetes drug; Cana, canagliflozin; Empa, empagliflozin.

1, 2 and 3 trials) reported no increase in bone fractures with empagliflozin vs. placebo (1.6% and 1.1% for empagliflozin 10 mg and 25 mg, respectively, and 1.6% for placebo) (94). However, longer term studies of SGLT2 inhibitors are required to determine fracture rates or changes in bone mineral density, and bone safety is being followed in postmarketing studies mandated by the regulatory agencies for empagliflozin, dapagliflozin and canagliflozin (42,95,96).

Volume depletion

Osmotic diuresis associated with use of SGLT2 inhibitors may result in intravascular volume contractions, and to adverse events associated with volume depletion such as hypotension (orthostatic, ambulatory and systolic), dehydration, postural dizziness and syncope. In a pooled analysis of five placebo-controlled trials, adverse events related to volume depletion were reported in 0.5% and 0.3% of patients on empagliflozin 10 mg and 25 mg, respectively, compared with 0.3% with placebo (40). Across 12 dapagliflozin studies, 0.6% of patients on dapagliflozin 5 mg and 0.8% on 10 mg had volume depletion events vs. 0.4% with placebo (41). In a pooled analysis of eight trials comparing canagliflozin with placebo or an active comparator, adverse events related to volume depletion were reported in 2.3% and 3.4% of patients on canagliflozin 100 mg and 300 mg, respectively, vs. 1.5% with comparators (43). Elderly patients, patients with impaired renal function, with low SBP or on diuretics are at particular risk of symptomatic hypotension on initiating SGLT2 inhibitors and it is recommended that the volume status of these patients is assessed and corrected prior to treatment initiation and monitored afterwards (40,41,43).

Neoplasia

An imbalance in cases of bladder cancer was observed in clinical trials of dapagliflozin (newly diagnosed bladder cancer where study drug exposure was ≥ 1 year at the time of diagnosis: four cases in patients on dapagliflozin vs. no cases in patients on placebo/comparator) (41). Consequently, the prescribing information advises that dapagliflozin should not be used in patients with active bladder cancer, and should be used with caution in patients with a prior history of bladder cancer (41). The overall incidence of bladder cancer was low in safety analyses across the clinical programs for canagliflozin (canagliflozin, five cases; comparators, four cases) and empagliflozin (empagliflozin, two cases; comparators, no cases), and prescribing information does not currently advise against use in patients with a prior history of bladder cancer (39,40,43).

Lipid levels

Low-density lipoprotein cholesterol (LDL-C) is an independent predictor of cardiovascular risk (97). Dose-related increases in LDL-C have been reported with canagliflozin (98). In data pooled from four 26-week RCTs, the mean percentage increase from baseline in LDL-C for 100 mg and 300 mg canagliflozin relative to placebo were 4.5% and 8.0%, respectively (43). Statistically significant increases in high-density lipoprotein cholesterol (HDL-C) from baseline were observed with canagliflozin in four of eight placebo-controlled phase 3 trials, but decreases in triglyceride levels with canagliflozin were small and were generally not statistically significant (93). A review of dapagliflozin RCTs reported that overall small mean changes in HDL-C (+2.1% to +9.3%), triglycerides (−0.9 to −10.6%) and LDL-C (−0.5 to +9.5%) levels were observed in patients receiving dapagliflozin, but the effect on lipid levels was clinically insignificant in the individual studies (99). For empagliflozin, a pooled analysis of four RCTs reported small increases in HDL-C and LDL-C and small decreases in triglycerides with empagliflozin compared with placebo after 24 weeks (HDL-C: +0.07 mmol/l [2.70 mg/dl] for both empagliflozin 10 mg and 25 mg doses, vs. 0.00 mmol/l for placebo; p < 0.001 vs. placebo for both doses; LDL-C: +0.08 mmol/l [+3.10 mg/dl] and +0.10 mmol/l [+3.87 mg/dl] for empagliflozin 10 mg and 25 mg, respectively, vs. +0.02 mmol/l [+0.77 mg/dl] for placebo; p < 0.01 vs. placebo for 25 mg dose; triglycerides: −0.11 mmol/l [−9.73 mg/dl] and −0.02 mmol/l [−1.77 mg/dl] for empagliflozin 10 mg and 25 mg, respectively, vs. +0.03 mmol/l [+2.65 mg/dl] for placebo; p < 0.05 vs. placebo for 10-mg dose) (76). Monitoring of LDL-C and treatment by standard care is recommended after initiating treatment with SGLT2 inhibitors (40,41,43).

Cardiovascular safety

Although SGLT2 inhibitors appear to have a beneficial effect on cardiovascular risk factors such as HbA1c, body weight and BP (100), there is a lack of data on clinical outcomes such as stroke, myocardial infarction (MI) and cardiovascular death. A recent report based on simulation modelling described significant reductions in the risk of MI, stroke, cardiovascular death and all-cause death that could be expected with SGLT2 inhibitor treatment vs. standard care (101).

Raised uric acid levels are associated with ischaemic heart disease and stroke (102,103). Reductions in mean blood uric acid levels (from normal baseline levels) to week 24 of up to −55.32 μmol/l (−0.93 mg/dl) were observed in an analysis of four

dapagliflozin RCTs (99). Decreases in serum urate were observed after 26 weeks for canagliflozin in add-on combination therapy compared with placebo (−8.8% and −9.4% for canagliflozin 100 mg and 300 mg, respectively, vs. +0.7% for placebo) (63), and after 52 weeks compared with active comparator (−9.9% and −10.3% for canagliflozin 100 mg and 300 mg, respectively, vs. +8.0% for glimepiride (60); and −6.5% for canagliflozin 300 mg vs. +6.2% for sitagliptin) (62). Empagliflozin reduced blood uric acid vs. placebo at week 24 in a pooled analysis of four RCTs [−28.95 µmol/l (−0.49 mg/dl) and −29.55 µmol/l (−0.50 mg/dl) for empagliflozin 10 mg and 25 mg, respectively, vs. +1.03 µmol/l (+0.02 mg/dl) for placebo; $p < 0.001$ vs. placebo for both dose groups] (76).

Large cardiovascular trials are underway for dapagliflozin, canagliflozin and empagliflozin. The Dapagliflozin Effect on Cardiovascular Events (DECLARE; ClinicalTrials.gov identifier: NCT01730534) began recruitment in 2013, with the intention of recruiting 27,000 patients with T2DM and a high risk of cardiovascular events. The first recruitment phase of the Canagliflozin Cardiovascular Assessment Study (CANVAS; ClinicalTrials.gov identifier: NCT01-032629) (104) was completed in 2012 with the interim analysis showing no significant increase in risk of cardiovascular events (105), and the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME™, ClinicalTrials.gov identifier: NCT01131676) (96) has also completed recruitment. A cardiovascular trial for the SGLT2 inhibitor ertugliflozin has also recently started recruitment (Cardiovascular Outcomes Following Treatment with Ertugliflozin in Participants with Type 2 Diabetes Mellitus and Established Vascular Disease; ClinicalTrials.gov identifier: NCT01986881).

Discussion

Clinical trials of dapagliflozin, canagliflozin and empagliflozin have investigated their efficacy, safety and tolerability as monotherapy and as add-on combination therapy with other anti-diabetes agents, including metformin, sulfonylureas, TZDs, DPP-4 inhibitors and insulin. These SGLT2 inhibitors produced clinically significant reductions in HbA1c, FPG, body weight and SBP. In terms of safety, dapagliflozin, canagliflozin and empagliflozin were well tolerated and had a generally favourable safety profile, similar to that of placebo. To date, few serious adverse events have been reported from clinical trials. The frequency of hypoglycaemic events was low, similar to that of placebo, and lower than comparators known to have increased risk of hypoglycaemia, with

the choice of co-administered glucose-lowering agent being the major determinant of hypoglycaemic risk (79). Genital infections and UTIs have been consistently reported with SGLT2 inhibitors, and reported episodes were mostly mild and non-recurrent.

As described by the Global Partnership for Effective Diabetes Management, overall risk factor management in the early treatment of T2DM is vital (4,15). This encompasses good glycaemic control as the basis of such management to prevent the onset or delay the progression of diabetes complications (4), and the reduction of cardiovascular risk factors to improve patient outcomes (4). Clinical trial data demonstrate that SGLT2 inhibitors induce beneficial changes in a number of cardiovascular risk factors, such as lowering BP and body weight, in addition to decreasing HbA1c. However, currently available information on clinical outcomes such as stroke, MI and cardiovascular death is limited, and we must await the completion of the various ongoing cardiovascular trials. In addition, the potential renal effect of SGLT2 inhibitors beyond lowering blood glucose, identified from preliminary clinical data, may influence the natural course of renal function decline in individuals with diabetes mellitus.

There is preliminary evidence to suggest that SGLT2 inhibitors may have a protective effect on the kidney beyond blood glucose lowering (106). Like agents that block the renin–angiotensin system, SGLT2 inhibitors also reduce single-nephron glomerular filtration rate in the chronically altered kidney function states, although by different mechanisms, and SGLT2 inhibitors also cause modest reductions in plasma uric acid, as well as SBP (described above) (106). Evidence for this renoprotective effect is supported by a pilot study in type 1 diabetes (T1DM) subjects with renal hyperfiltration who were given short-term treatment with empagliflozin (107). Empagliflozin led to a significant reduction in hyperfiltration during clamped euglycaemic and hyperglycaemic conditions, probably by affecting tubular-glomerular feedback mechanisms; in contrast, renal hemodynamic parameters were unchanged in T1DM subjects with normal renal function (107). Empagliflozin was also associated with a decline in arterial stiffness in young patients with T1DM (108), and empagliflozin improved glycaemic control when given as an adjunctive to insulin in a recent proof-of-concept study (109). Preliminary results describing the use of dapagliflozin in T1DM have also been presented (110).

The novel mechanism of action of SGLT2 inhibitors makes them suitable for use in combination with any glucose-lowering agent, including insulin. The complementary effects of SGLT2 inhibition with

other antihyperglycaemic agents may provide additional benefits to T2DM patients, such as glucose lowering plus weight loss, without increasing the risk of hypoglycaemia. Obviously, the ideal combination therapy using SGLT2 inhibitors would need to be tailored to an individual's risk factors. The fixed-dose combination products emerging onto the market, or soon to do so, may provide further options in this area. Moreover, as SGLT2 inhibitors are not dependent on the production of insulin, they could be used at any stage of T2DM, from newly diagnosed patients to those with long-standing disease. Even in T2DM patients already receiving insulin, SGLT2 inhibitors may provide an alternative to increasing the dose or frequency of insulin.

In conclusion, the available evidence suggests that SGLT2 inhibitors could have a significant impact on the early management of patients with recent-onset T2DM, either as monotherapy or in combination with other classes of glucose-lowering agents, by addressing many of the overall risk factors associated with this disease. The anticipated ability of SGLT2 inhibitors to alleviate known cardiovascular risk factors such as BP and body weight also supports their use early in the management of T2DM. The prevention of vascular complications is crucial in the early treatment of T2DM, and ongoing outcome studies within the SGLT2 inhibitors class will explore whether their mechanism of action has such potential beyond lowering glucose.

Acknowledgements

Author contributions

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