Short commentary on empagliflozin and its potential clinical impact

Deborah Hinnen

Abstract: Sodium glucose cotransporter type 2 (SGLT2) inhibitors are a new class of drug developed to treat type 2 diabetes mellitus (T2DM). They target the kidney by reducing renal glucose reabsorption and promoting urinary glucose excretion, which reduces hyperglycemia in individuals with T2DM. The SGLT2 inhibitor empagliflozin has gained approval in the EU and in the USA for the treatment of adults with T2DM (there is no current indication in type 1 diabetes). Empagliflozin has shown a good efficacy and safety profile from clinical trials when given as monotherapy, and as an add-on therapy to other glucose-lowering agents. This short commentary reviews the key efficacy and safety data from empagliflozin phase III trials and examines the potential role this agent may have in the management of T2DM.

Keywords: empagliflozin, sodium glucose cotransporter type 2 inhibitors, type 2 diabetes mellitus

Introduction

Recognition of the kidney's role in glucose homeostasis has provided a new target in the treatment of type 2 diabetes mellitus (T2DM). Sodium glucose cotransporter type 2 (SGLT2) inhibitors reduce renal glucose reabsorption and promote urinary glucose excretion (UGE), thus reducing elevated blood glucose concentrations in individuals with T2DM. The SGLT2 inhibitors dapagliflozin and canagliflozin are approved for marketing in the European Union (EU) and in the USA and, as mentioned above, a third agent, empagliflozin, the focus of this review, has marketing approval in the EU and in the USA.

Mechanism of action of SGLT2 inhibitors

Renal glucose reabsorption

At a normal plasma glucose concentration, the kidneys of a healthy individual filter approximately 180 g glucose per day. Almost all of this is reabsorbed and returned to the bloodstream, and virtually no glucose (i.e. <0.1%) enters the urine. If the plasma glucose concentration is elevated beyond the maximum capacity at which the kidney can reabsorb glucose, the excess glucose is excreted into the urine. With normal renal function, approximately 90% of the filtered glucose load in the

kidney is reabsorbed via active transport mediated by the membrane-bound protein SGLT2 [Wright *et al.* 2011]. This occurs past the glomerulus, in the first section of the proximal renal tubule at the brush-border of the cells. The remaining 10% of the filtered glucose is reabsorbed further along the proximal tubule via the action of SGLT type 1 (SGLT1). Reabsorbed glucose is passively released from the proximal tubular cells at the basolateral membrane, facilitated by the protein glucose transporter type 2, and returned to the bloodstream. It is important to note that the action of SGLT2 and SGLT1 is independent of insulin.

Inhibition of SGLT2

The rationale for SGLT2 inhibition as a potential glucose-lowering therapy in T2DM is that it significantly reduces renal glucose reabsorption and causes glucose to be excreted into the urine (i.e. glucosuria); consequently, glucose is removed from the body and the level of hyperglycemia is decreased (Figure 1) [Abdul-Ghani and DeFronzo, 2008]. Individuals suffering from familial renal glucosuria, a rare genetic disorder caused by mutations of the SGLT2 gene, experience varying degrees of UGE in the order of less than 10 g/day to more than 200 g/day [Santer and Calado, 2010]. Despite this, affected individuals are usually otherwise asymptomatic [Santer

Ther Adv Endocrinol Metab

2015, Vol. 6(2) 68–81

DOI: 10.1177/

2042018815578599

© The Author(s), 2015.

Reprints and permissions:

[http://www.sagepub.co.uk/](http://www.sagepub.co.uk/journalsPermissions.nav)

[journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Correspondence to:
**Deborah Hinnen, APN,
BC-ADM, CDE, FAAN**
Memorial Hospital
Diabetes Center
University of Colorado
Health 175 S. Union
Boulevard, Suite 305
Colorado Springs, CO
80910 USA
[deborah.hinnen@](mailto:deborah.hinnen@uchealth.org)
[uchealth.org](mailto:deborah.hinnen@uchealth.org)

Figure 1. Normal renal glucose transport (a) and the effect of sodium glucose cotransporter type 2 (SGLT2) inhibition (b). SGLT1, sodium glucose cotransporter type 1.

and Calado, 2010], which implies that pharmacologic inhibition of SGLT2 may not be harmful. Initial research on SGLT2 inhibition was carried out using phlorizin, a naturally occurring and nonselective SGLT2 inhibitor [Ehrenkranz *et al.* 2005]. However, the poor oral bioavailability and gastrointestinal side effects associated with phlorizin required the use of modified phlorizin derivatives, and led to the development of the currently marketed SGLT2 inhibitors.

Review of empagliflozin clinical trials data

Empagliflozin is a potent inhibitor of SGLT2 and has a selectivity for SGLT2 *versus* SGLT1 greater than 2500 fold [Grempler *et al.* 2012].

Empagliflozin is being investigated in adults with T2DM in a phase III clinical trial program that has enrolled more than 14,500 patients, and consists of more than 10 multinational clinical trials [Boehringer Ingelheim GmbH, 2013]. A summary of efficacy data from recently published empagliflozin registration (phase III) trials is presented in Table 1, with details of further empagliflozin phase III trials given in Table 2.

Effect on glycemic control

Empagliflozin, given either as monotherapy or as an add-on therapy to other glucose-lowering agents, has been shown to provide statistically

Table 1. Empagliflozin phase III clinical trial publications (published to September 2014).

Study, regimen and duration	N	Treatment and dose (mg/day)*, \$	HbA _{1c} (%)		Change from baseline ^{‡§}			
			Baseline, mean (SD)	Change from baseline	Fasting plasma glucose, mg/dl (mmol/liter)	Body weight (kg)	Systolic blood pressure (mmHg)	
EMPA-REG MONO [Roden <i>et al.</i> 2013] Monotherapy; 24 weeks	899							
	228	Placebo	7.91 [0.78]	0.08	11.7 [0.65]	-0.33	-0.3	
	224	10	7.87 [0.88]	-0.66	-19.5 [-1.08]	-2.26	-2.9	
	224	25	7.86 [0.85]	-0.78	-24.5 [-1.36]	-2.48	-3.7	
	223	SITA 100	7.85 [0.79]	-0.66	-6.85 [-0.38]	0.18	0.5	
	87	25 (HbA _{1c} >10.0)	11.50 [1.39]	-3.70	-84.3 [-4.86]	-2.43	-4.0	
EMPA-REG MET [Häring <i>et al.</i> 2014] Add-on to MET; 24 weeks	637							
	207	Placebo	7.90 [0.88]	-0.13	6.38 [0.35]	-0.45	-0.4	
	217	10	7.94 [0.79]	-0.70	-20.04 [-1.11]	-2.08	-4.5	
	213	25	7.86 [0.87]	-0.77	-22.28 [-1.24]	-2.46	-5.2	
	69	25 (HbA _{1c} >10.0)	11.07 [1.29]	-3.23	-10.27 [-0.57]	-1.91	-2.4	
	666							
EMPA-REG METSU [Häring <i>et al.</i> 2013] Add-on to MET + SU; 24 weeks	225	Placebo	8.15 [0.83]	-0.17	5.52 [0.31]	-0.39	-1.4	
	225	10	8.07 [0.81]	-0.82	-23.30 [-1.29]	-2.16	-4.1	
	216	25	8.10 [0.83]	-0.77	-23.27 [-1.29]	-2.39	-3.5	
	101	25 (HbA _{1c} >10.0)	11.18 [1.25]	-2.89	-54.41 [-3.02]	-1.76	-4.3	
	498							
	165	Placebo	8.20 [0.92]	-0.11	6.47 [0.36]	0.34	0.7	
EMPA-REG PIO [Kovacs <i>et al.</i> 2013] Add-on to PIO ± MET; 24 weeks	165	10	8.10 [0.89]	-0.59	-17.0 [-0.94]	-1.62	-3.1	
	168	25	8.10 [0.82]	-0.72	-22.0 [-1.22]	-1.47	-4.0	

(Continued)

Table 1. (Continued)

Study, regimen and duration	N	Treatment and dose (mg/day)*, \$	HbA _{1c} (%)		Change from baseline†,§		
			Baseline, mean (SD)	Change from baseline	Fasting plasma glucose, mg/dl (mmol/liter)	Body weight (kg)	Systolic blood pressure (mmHg)
EMPA-REG RENAL [Barnett <i>et al.</i> 2014] Patients with renal impairment; 52 weeks (efficacy reported at 24 weeks)	95	Placebo	8.09 [0.80]	0.06	5.59 [0.31]	-0.33	0.7
	98	10	8.02 [0.84]	-0.46	-13.87 [-0.77]	-1.76	-2.9
	97	25	7.96 [0.73]	-0.63	-18.02 [-1.00]	-2.33	-4.5
	187	Placebo	8.09 [0.80]	0.05	10.81 [0.6]	-0.08	0.40
	187	25	8.02 [0.84]	-0.37	-9.00 [-0.5]	-0.98	-3.88
	37	Placebo	8.16 [0.99]	-0.18	10.81 [0.6]	-0.1	1.2
EMPA-REG BP [Tikkanen <i>et al.</i> 2015] Patients with hypertension; 12 weeks	37	25	8.06 [1.05]	0.04	3.60 [-0.2]	-1.4	-7.4
	271	Placebo	7.90 [0.72]	0.03	7.21 [0.40]	-0.18	-0.67
	276	10	7.87 [0.77]	-0.59	-16.58 [-0.92]	-1.68	-4.60
	276	25	7.92 [0.72]	-0.62	-23.06 [-1.28]	-2.16	-5.47
	188	Placebo	8.33 [0.05]	-0.50	3.42 [0.19]	0.34	-1.20
	186	10	8.39 [0.05]	-0.94	-17.66 [-0.98]	-0.97	-3.60
EMPA-REG MDI [Rosenstock <i>et al.</i> 2014] Patients with obesity; add-on to MDI INS ± MET; 52 weeks (efficacy reported at 18 weeks)	189	25	8.29 [0.05]	-1.02	-24.50 [-1.36]	-1.54	-2.90
	780	GLIM 1-4	7.92 [0.86]	-0.55	-3.06 [-0.17]	1.30	2.50
	765	25	7.92 [0.81]	-0.66	-15.32 [-0.85]	-3.10	-3.10

*Empagliflozin given once daily.

\$High HbA_{1c} groups are open-label unless otherwise stated.

†Data are presented as reported in each publication.

§Data for high glycemic subgroup are presented for monotherapy study only.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; GLIM, glimepiride; HbA_{1c}, glycated hemoglobin; INS, insulin; MDI, multiple daily injections; MET, metformin; PIO, pioglitazone; SD, standard deviation; SITA, sitagliptin; SU, sulfonylurea.

Table 2. Additional empagliflozin phase III clinical trials (as listed in ClinicalTrials.gov June 2014).

NCT trial identifier	Title	Recruitment	URL
NCT01289990	Safety and Efficacy of Empagliflozin (BI 10773) and Sitagliptin Versus Placebo Over 76 Weeks in Patients With Type 2 Diabetes	Completed	http://ClinicalTrials.gov/show/NCT01289990
NCT01422876	Efficacy and Safety of Empagliflozin (BI 10773)/Linagliptin (BI 1356) Fixed Dose Combination in Treatment naïve and Metformin Treated Type 2 Diabetes Patients	Completed	http://ClinicalTrials.gov/show/NCT01422876
NCT01368081	Empagliflozin (BI 10773) Comprehensive Add-on Study in Japanese Subjects with Type 2 Diabetes Mellitus	Completed	http://ClinicalTrials.gov/show/NCT01368081
NCT01947855	Post Prandial Glucose (PPG) Study of Empagliflozin in Japanese Patients With Type 2 Diabetes Mellitus	Completed	http://ClinicalTrials.gov/show/NCT01947855
NCT01778049	Linagliptin as Add on Therapy to Empagliflozin 10 mg or 25 mg with Background Metformin in Patients with Type 2 Diabetes	Recruiting	http://ClinicalTrials.gov/show/NCT01778049
NCT01719003	Safety and Efficacy Study of Empagliflozin and Metformin for 24 Weeks in Treatment Naïve Patients with Type 2 Diabetes	Recruiting	http://ClinicalTrials.gov/show/NCT01719003
NCT01734785	Safety and Efficacy of the Combination of Empagliflozin and Linagliptin Compared to Linagliptin Alone Over 24 Weeks in Patients with Type 2 Diabetes	Recruiting	http://ClinicalTrials.gov/show/NCT01734785
NCT01131676 EMPA-REG OUTCOME™ [Zinman <i>et al.</i> 2014]	BI 10773 Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients	Active, not recruiting	http://ClinicalTrials.gov/show/NCT01131676
NCT01984606	Efficacy and Safety of Empagliflozin Versus Sitagliptin in Patients with Type 2 Diabetes	Not yet recruiting	http://ClinicalTrials.gov/show/NCT01984606
NCT01257334	Patients with Type 2 Diabetes Mellitus with Insufficient Glycaemic Control Despite Treatment with Metformin Alone or Metformin in Combination with a Sulfonylurea	Enrolling by invitation	http://ClinicalTrials.gov/show/NCT01257334
NCT, National Clinical Trials.			

significant and clinically relevant improvements in glycemic control in patients with T2DM *versus* placebo [Häring *et al.* 2013, 2014; Kovacs *et al.* 2013; Roden *et al.* 2013; Barnett *et al.* 2014; Tikkanen *et al.* 2015], as measured by the change in the level of glycated hemoglobin (HbA_{1c}) (Table 1). For example, empagliflozin monotherapy (given once daily for 24 weeks) produced a placebo-adjusted mean change from baseline in HbA_{1c} of -0.7% [95% confidence interval (CI) $-0.9, -0.6$] and -0.9% (95% CI $-1.0, -0.7$) for the 10 mg and 25 mg doses, respectively ($p < 0.0001$ for each) [Roden *et al.* 2013]. Furthermore, 35–44% of patients receiving empagliflozin achieved HbA_{1c} levels below 7.0% *versus* 12% of those in the placebo group [Roden *et al.*

2013]. Similar changes from baseline in HbA_{1c} levels at week 24 were reported when empagliflozin was given in combination with metformin [adjusted mean difference from placebo + metformin (95% CI) -0.6 ($-0.7, -0.4$) and -0.6 ($-0.8, -0.5$) for 10 mg and 25 mg, respectively; $p < 0.001$ for each] [Häring *et al.* 2014], metformin plus sulfonylurea [adjusted mean difference from placebo + metformin + sulfonylurea (95% CI) -0.6 ($-0.8, -0.5$) and -0.6 ($-0.7, -0.5$) for 10 mg and 25 mg, respectively; $p < 0.001$ for each] [Häring *et al.* 2013], and pioglitazone with/without metformin [adjusted mean difference from placebo + pioglitazone (95% CI) -0.5 ($-0.7, -0.3$) and -0.6 ($-0.8, -0.4$) for 10 mg and 25 mg, respectively; $p < 0.001$ for each] [Kohan

et al. 2014]. Although a smaller reduction in HbA_{1c} was observed for empagliflozin (only 25 mg dose used) as an add-on to metformin compared with glimepiride (mean dose 2.7 mg/day) plus metformin [week 52, adjusted mean difference from glimepiride (97.5% CI) -0.07 (-0.15, 0.01); $p < 0.0001$ noninferiority], the difference in the observed effect size confirmed empagliflozin was noninferior to glimepiride [Ridderstråle *et al.* 2014]. Comparable efficacy data were reported from analyses of randomized, controlled trials of canagliflozin [Babu, 2013; Nigro *et al.* 2013; US Food and Drug Administration, 2014b], and dapagliflozin [Chao, 2012; US Food and Drug Administration, 2014a; Zhang *et al.* 2014].

Effect on body weight and blood pressure

In addition to reducing HbA_{1c}, empagliflozin therapy also produced modest reductions in body weight and blood pressure [Häring *et al.* 2013, 2014; Kovacs *et al.* 2013; Roden *et al.* 2013; Barnett *et al.* 2014; Tikkanen *et al.* 2015]. For example, empagliflozin given as monotherapy (10 mg and 25 mg given once daily for 24 weeks) reduced body weight by 1.93–2.15 kg (4.25–4.74 lb) *versus* placebo, and by 2.45–2.67 kg (5.40–5.89 lb) *versus* sitagliptin comparator, while systolic blood pressure decreased by 2.6–3.4 mmHg and 3.4–4.2 mmHg *versus* placebo and sitagliptin comparator, respectively [Roden *et al.* 2013]. Comparable efficacy data were reported from analyses of randomized, controlled trials of canagliflozin [Babu, 2013; Nigro *et al.* 2013] and dapagliflozin [Chao, 2012; Zhang *et al.* 2014]. Data from longer-term trials of dapagliflozin and canagliflozin revealed the body weight reduction observed with SGLT2 inhibitor therapy was due to reduced body fat mass caused caloric loss following UGE rather than simply due to fluid loss [Cefalu *et al.* 2013; Bolinder *et al.* 2014]. An ongoing 4-year trial of empagliflozin treatment in T2DM (EMPA-REG H2H-SU) is investigating various parameters, including changes from baseline in body fat mass [Ridderstråle *et al.* 2013].

Effect on β -cell function and insulin sensitivity

Empagliflozin therapy also improved pancreatic β -cell function and insulin sensitivity in patients with T2DM, when 25 mg was given as a single dose or given once daily for 4 weeks [Ferrannini *et al.* 2014]. Increased insulin sensitivity was also reported in patients with T2DM treated with dapagliflozin (10 mg given once daily for 2 weeks)

[Merovci *et al.* 2014]. In each of these studies endogenous glucose production increased and fasting plasma glucose decreased, which may be at least partially explained by the concentration change in the insulin-to-glucagon ratio that has been observed with SGLT2 inhibitor therapy [Ferrannini *et al.* 2014; Merovci *et al.* 2014]. Canagliflozin also improved β -cell function in patients with T2DM, per model-based measures [Polidori *et al.* 2014].

Safety: urinary tract and genital infections

In phase II–III clinical trials, SGLT2 inhibitors have been shown to be generally well tolerated, with a low incidence of hypoglycemia [Jabbour, 2014; Scheen, 2014]. Empagliflozin was well tolerated when given as monotherapy and in all combination therapies used to date, and few serious adverse events were reported. A pooled analysis of data from four phase III trials of empagliflozin reported an increase in genital infection (3.6–4.2%) *versus* placebo (0.7%), but no significant increase in the incidence of urinary tract infection (7.5–9.3% for empagliflozin groups *versus* 8.2% for placebo) [Kim *et al.* 2013]. A similar trend was reported in pooled analyses of phase III trials data for canagliflozin [Nicolle *et al.* 2014; Nyirjesy *et al.* 2014] and dapagliflozin [Johnsson *et al.* 2013a, 2013b]. For all three SGLT2 inhibitors, these events were predominantly mild in severity and responded to standard treatment [Johnsson *et al.* 2013a, 2013b; Kim *et al.* 2013; Nicolle *et al.* 2014; Nyirjesy *et al.* 2014]. Furthermore, while these events could be attributed to higher urinary glucose concentrations, the exact role of glucosuria as a contributory factor in genitourinary infection and urinary tract infection remains unresolved [Geerlings *et al.* 2014].

Safety: hypoglycemia

Hypoglycemia is an important concern to patients with T2DM [Barendse *et al.* 2012], and severe episodes may carry significant health risks [Seaquist *et al.* 2013]. SGLT2 inhibitor therapy would not be expected to lead to an increased risk of hypoglycemia due to the insulin-independent mode of action of these agents (i.e. they do not affect endogenous glucose production in response to hypoglycemia [McCrimmon *et al.* 2002], and do not stimulate insulin release when glucose levels decline [Rossetti *et al.* 1987; Han *et al.* 2008]) and, based on the available published evidence, this was found to be the case [Rosenwasser *et al.*

2013; Vasilakou *et al.* 2013]. Further data indicate that SGLT2 inhibition results in a compensatory increase in endogenous glucose production, with an accompanying elevation in glucagon levels [Ferrannini *et al.* 2014; Merovci *et al.* 2014], which would also prevent hypoglycemia. However, the choice of concomitant glucose-lowering agent used when an SGLT2 inhibitor is given as add-on combination therapy does appear to affect the frequency of hypoglycemia [Rosenwasser *et al.* 2013; Vasilakou *et al.* 2013]. In clinical trials, empagliflozin did not increase the risk of hypoglycemia when used as monotherapy [Roden *et al.* 2013] or as add-on to metformin [Häring *et al.* 2014] or pioglitazone [Kovacs *et al.* 2013]. In addition, as add-on to basal insulin, empagliflozin did not increase the risk of hypoglycemia more than would be anticipated with basal insulin [Rosenstock *et al.* 2013]. However, similar to observations reported for dapagliflozin and canagliflozin, hypoglycemia was more frequent when empagliflozin was added to a regimen including a sulfonylurea [Häring *et al.* 2013]; thus, the prescribing information for these agents recommends considering a lower dose of insulin secretagogue (e.g. sulfonylurea) or insulin to reduce the risk of hypoglycemia [European Medicines Agency, 2014a, 2014b, 2014d; US Food and Drug Administration, 2014a, 2014b, 2014c].

Safety: volume depletion

Due to the mode of action of empagliflozin, osmotic diuresis accompanying therapeutic glucosuria may result in a modest reduction in blood pressure. Therefore, caution should be exercised when treating patients at risk of volume depletion, including those with renal impairment, older patients, and patients receiving antihypertensive therapy with a history of hypotension. Volume status should be assessed and, if necessary, corrected prior to treatment, and monitoring for hypotension should continue [European Medicines Agency, 2014d; US Food and Drug Administration, 2014c].

Safety: cardiovascular parameters

Data on cardiovascular safety must be provided for all new antidiabetes therapies. No significant adverse cardiovascular outcomes were reported in the trials of empagliflozin published to date [Gangadharan Komala and Mather, 2014]; however, the Empagliflozin Cardiovascular Outcome

Event Trial (EMPA-REG OUTCOME™) is underway and is examining patients with T2DM and high cardiovascular risk [Zinman *et al.* 2014]. Cardiovascular outcomes trials for canagliflozin [Neal *et al.* 2013] and dapagliflozin (DECLARE-TIMI 58) [ClinicalTrials.gov identifier: NCT01730534] are also in progress [Inzucchi *et al.* 2015]. Dose-related increases in low-density lipoprotein cholesterol (LDL-C) observed with canagliflozin have caused some concern [Rodríguez-Gutiérrez and Gonzalez-Saldivar, 2014], given that LDL-C is an independent predictor of cardiovascular risk. Consequently, monitoring of LDL-C is recommended after initiating canagliflozin treatment [US Food and Drug Administration, 2014b]. For dapagliflozin, overall small mean changes in LDL-C, increases in high-density lipoprotein cholesterol (HDL-C), and decreases in triglycerides were reported [Ptaszynska *et al.* 2013]. For empagliflozin, a pooled analysis reported small increases in HDL-C and LDL-C and small decreases in triglycerides [Hach *et al.* 2013]. The labelling information of these three SGLT2 inhibitors warns that dose-dependent increases in LDL-C can occur, and recommends monitoring LDL-C levels [US Food and Drug Administration, 2014a, 2014b, 2014c].

Safety: malignancy risk

The risk of bladder cancer with SGLT2 inhibitors has been of interest since an imbalance in bladder cancer was observed in a pooled analysis of dapagliflozin clinical trials [US Food and Drug Administration, 2014a]. While the number of cases was too low to determine if this was due to an effect of dapagliflozin [10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patients (0.03%) treated with placebo/comparator], current US prescribing information advises 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 [US Food and Drug Administration, 2014a]. The European regulators note that, while there was a slight increased relative risk of tumors in some organ systems (including bladder), there was a decreased risk in other systems, resulting in no overall increased risk with dapagliflozin, and that a causal relationship between dapagliflozin and risk of bladder cancer is unlikely [European Medicines Agency, 2014a]. Nevertheless, they too have adopted a cautious approach, and advised against using dapagliflozin in patients

concomitantly treated with pioglitazone (since epidemiologic data suggest a small increased risk of bladder cancer in patients with diabetes treated with pioglitazone). For empagliflozin and canagliflozin, analyses have not identified an increased risk [US Food and Drug Administration, 2013; European Medicines Agency, 2014c, 2014d], which seems to further support that there is no class risk and the cases seen with dapagliflozin were due to chance; however, it will be important to collect further data to confirm this.

Safety: bone fractures and changes in bone mineral density

Bone fractures were more common in patients receiving dapagliflozin (7.7%) than those receiving placebo (0%) in a long-term study carried out in patients with T2DM and moderate renal impairment [Kohan *et al.* 2014]; however, there was no evidence that dapagliflozin induced bone demineralization or increased fracture rates in individuals with normal renal function or mild renal impairment [European Medicines Agency, 2012]. The US regulatory authority concluded that clinical trials of canagliflozin demonstrated a modest dose-dependent increase in bone resorption, which could contribute to bone fragility [US Food and Drug Administration, 2013]. For empagliflozin, the overall number of patients with bone fractures was low and bone fracture was no more common with empagliflozin than with placebo [European Medicines Agency, 2014e]. Furthermore, no loss in bone mineral density was observed after up to 2 years of empagliflozin treatment [European Medicines Agency, 2014e].

Safety: serum electrolytes

Increased serum potassium (hyperkalemia) can occur during canagliflozin therapy, and is listed as a warning/precaution in the canagliflozin labelling information [US Food and Drug Administration, 2014b]. This is more likely to occur in patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin–angiotensin–aldosterone system. As digoxin toxicity also causes hyperkalemia, digoxin levels should be monitored in patients receiving concomitant canagliflozin [US Food and Drug Administration, 2014b]. No significant changes in mean serum potassium occurred

in trials using empagliflozin [Barnett *et al.* 2014], or dapagliflozin [Kohan *et al.* 2014].

Dose-related increases in serum magnesium were also observed with canagliflozin therapy [US Food and Drug Administration, 2014b]. In a pool of four placebo-controlled trials, the mean change in serum magnesium was +8.1% and +9.3% with canagliflozin 100 mg and 300 mg, respectively *versus* −0.6% with placebo [US Food and Drug Administration, 2014b]. In a phase III trial of canagliflozin in patients with T2DM and stage 3 chronic kidney disease (CKD) [estimated glomerular filtration rate (eGFR) ≥ 30 and < 50 ml/min/1.73 m²], serum magnesium increased by 9.1% and 14.6% for canagliflozin 100 mg and 30 mg, respectively *versus* no change (0%) for placebo [Yale *et al.* 2013]. For dapagliflozin, mean serum magnesium values remained within the normal range in patients with T2DM and moderate renal impairment (eGFR ≥ 30 to < 60 ml/min/1.73 m²) [European Medicines Agency, 2012]. Data from a trial using empagliflozin reported a small increase in mean magnesium (+0.1 mmol/liter from baseline) with empagliflozin 25 mg *versus* no change with empagliflozin 10 mg or placebo in patients with stage 2 or 3 CKD (eGFR ≥ 60 to < 90 ml/min/1.73 m² or ≥ 30 to < 60 ml/min/1.73 m², respectively) [Barnett *et al.* 2014].

Potential clinical impact of empagliflozin

How will this agent be used?

Empagliflozin could be used as monotherapy or in combination with other agents. Metformin is recommended as the first-line drug for patients starting glucose-lowering therapy, but empagliflozin monotherapy might be suitable for patients who are unable to tolerate metformin, or for those in whom metformin is contraindicated. The convenience of oral, once-daily dosing with empagliflozin may have a potentially positive impact on overall compliance and treatment adherence. The novel mode of action of SGLT2 inhibitors suggests that these agents can be given in combination with any of the existing glucose-lowering agents, including insulin, as they do not share a common mechanistic pathway. As shown in the clinical trials data, empagliflozin has been used safely and effectively to improve glycemic control when given in combination with metformin, sulfonylureas, thiazolidinediones, and insulin. In addition, empagliflozin fixed-dose combination (i.e. single pill) products are in development. For

example, a single-pill product containing empagliflozin plus linagliptin has undergone phase III clinical trials and a marketing application has been submitted (Table 2), and single-pill empagliflozin plus metformin formulations are also in clinical development. The results of a 52-week phase III trial [ClinicalTrials.gov identifier: NCT01422876] to investigate the efficacy and safety of fixed-dose combinations of empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/linagliptin 5 mg in patients with T2DM were published recently. In treatment-naïve patients ($n = 677$), reductions from baseline in HbA_{1c} with the empagliflozin 25 mg/linagliptin 5 mg combination were significantly greater *versus* linagliptin 5 mg but not *versus* empagliflozin 25 mg. The empagliflozin 10 mg/linagliptin 5 mg combination, however, produced significantly greater reductions from baseline in HbA_{1c} *versus* both individual components [Lewin *et al.* 2015]. In patients whose condition is inadequately controlled on metformin ($n = 686$), combinations of empagliflozin/linagliptin significantly reduced HbA_{1c} compared with empagliflozin or linagliptin alone as an add-on to metformin. The proportion of adverse events was similar across all groups [DeFronzo *et al.* 2015]. Based on the data from these two studies, US approval has been granted for a fixed-dose combination of empagliflozin and linagliptin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both empagliflozin and linagliptin is appropriate [US Food and Drug Administration, 2015].

SGLT2 inhibitors also have the potential to be used as an insulin-sparing agent in patients with T2DM already receiving insulin, providing an alternative to increasing the insulin dose or frequency. This was observed in a 78-week study using empagliflozin as an add-on to basal insulin, when insulin dose fell by approximately 6 IU from baseline compared with placebo [Rosenstock *et al.* 2013]. This study also reported improved glycemic control and reduced body weight, without an increased risk of hypoglycemia [Rosenstock *et al.* 2013].

Which patients with T2DM are candidates for empagliflozin?

As the mode of action of SGLT2 inhibitors, including empagliflozin, is independent of pancreatic β -cell function or the degree of insulin resistance, these agents have the potential to be used at any stage of T2DM. Thus, SGLT2 inhibitors such

as empagliflozin may have the potential to show efficacy as the disease process of T2DM advances and β -cell function declines. This is in contrast to other types of antidiabetes agents that are dependent upon β -cell function and show a decline in glucose-lowering potential over time (e.g. sulfonylureas) [DeFronzo *et al.* 2013].

Furthermore, SGLT2 inhibitors have demonstrated particular efficacy in improving glycemic control in patients with high HbA_{1c} [$\geq 10\%$ (86 mmol/mol)] at baseline, as shown in phase III trials of monotherapy with dapagliflozin [Ferrannini *et al.* 2010], canagliflozin [Stenlöf *et al.* 2013], and empagliflozin [Roden *et al.* 2013], in which HbA_{1c} reductions of 2.1–3.7% were reported.

SGLT2 inhibitors, including empagliflozin, are also potentially of value to patients with T2DM in whom reductions in weight and blood pressure are required; thus, reducing these cardiovascular risk factors. Moreover, as described above, SGLT2 inhibitor therapy has the added benefit of not increasing the risk of hypoglycemia, unless these agents are used in combination with insulin or an insulin secretagogue. SGLT2 inhibitors also have a prospective use in type 1 diabetes mellitus, and preliminary data with empagliflozin were published recently [Cherney *et al.* 2014; Lamos *et al.* 2014; Perkins *et al.* 2014].

Are there any special populations who should avoid using empagliflozin?

In patients with renal impairment, a reduction in efficacy of SGLT2 inhibitors is anticipated, based on the need for adequate renal function for their mode of action. A phase III trial using empagliflozin showed significant reductions in HbA_{1c} in patients with T2DM with mild or moderate CKD (stage 2, eGFR ≥ 60 to < 90 ml/min per 1.73 m²; stage 3, eGFR ≥ 30 to < 60 ml/min per 1.73 m²), accompanied by weight loss and reductions in blood pressure (Table 1) [Barnett *et al.* 2014]. Similar efficacy results were reported in a phase III trial of canagliflozin in patients with T2DM with stage 3 CKD (eGFR ≥ 30 and < 50 ml/min/1.73 m²) [Yale *et al.* 2013]. However, a study of dapagliflozin in patients with T2DM with moderate renal impairment (stage 3, eGFR ≥ 30 to < 60 ml/min per 1.73 m²) showed no significant improvement in HbA_{1c} *versus* placebo, although reductions in weight and blood pressure were observed [Kohan *et al.* 2014]. Consequently, the labeling documents for dapagliflozin, canagliflozin, and empagliflozin

give warnings and precautions for their use in patients with moderate to severe renal impairment [European Medicines Agency, 2014d; US Food and Drug Administration, 2014a, 2014b].

Regarding the use of SGLT2 inhibitors in patients with T2DM with hepatic impairment, pharmacokinetic parameters for empagliflozin were elevated in patients with hepatic impairment, but were less than twofold the values in patients with normal hepatic function, and no dose adjustment was deemed necessary [Macha *et al.* 2014]. In patients with severe hepatic impairment, therapeutic experience with empagliflozin is limited, and the drug is not currently recommended for those with severe hepatic impairment [European Medicines Agency, 2014d]. Nonetheless, it may be prudent to monitor liver function in patients receiving SGLT2 inhibitors.

The treatment of older patients with T2DM is generally challenging because of the increased prevalence of comorbid conditions, and an increased susceptibility to treatment-related hypoglycemia. For SGLT2 inhibitor therapy in older patients, volume status should be assessed and monitored, and any hypovolemia should be corrected before initiating therapy [US Food and Drug Administration, 2014a]. As stated in the dapagliflozin prescribing information, older patients with impaired renal function may be more susceptible to increased serum creatinine and decreased estimated glomerular filtration rate during dapagliflozin therapy [US Food and Drug Administration, 2014a]. For canagliflozin, a recent pooled analysis of data from older patients showed early transient decreases in eGFR during the first 3–6 weeks of canagliflozin treatment, which then stabilized or lessened at the 26-week endpoint [Sinclair *et al.* 2014]. For empagliflozin [European Medicines Agency, 2014d], as for dapagliflozin [European Medicines Agency, 2014a], no dose adjustment is recommended based on age. While no analyses in older patients have yet been reported in the literature, the European labeling notes an increased risk for volume depletion in patients aged 75 years and older, and thus, caution should be exercised in such individuals; empagliflozin is not recommended in patients aged 85 years and older due to limited therapeutic experience [European Medicines Agency, 2014d].

A complete list of warnings and precautions for SGLT2 inhibitor therapy is given in the respective prescribing information for dapagliflozin,

canagliflozin, and empagliflozin [European Medicines Agency, 2014d; US Food and Drug Administration, 2014a, 2014b].

Summary

Via the inhibition of SGLT2, empagliflozin reduces renal glucose reabsorption, promotes UGE, and lowers hyperglycemia in patients with T2DM. In clinical trials of empagliflozin used as monotherapy and as add-on combination therapy with other antidiabetes agents, empagliflozin decreased HbA_{1c} and was associated with reductions in body weight and systolic blood pressure. Apart from the adverse effects anticipated from the presence of increased urinary glucose, as is observed with all SGLT2 inhibitors (i.e. genital infection, and to a lesser degree, urinary infection), empagliflozin is well tolerated and has a favorable safety profile that is comparable to that of placebo. In conclusion, empagliflozin has the potential to make an important contribution to the treatment of T2DM.

Acknowledgments

The author meets criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The author received no direct compensation related to the development of the manuscript. Writing support was provided by Debra Brocksmith, MB ChB, PhD, and Charlie Bellinger, BSc, of Envision Scientific Solutions, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Conflict of interest statement

The author receives speaker fees from Janssen, Boehringer Ingelheim/Lilly, AstraZeneca/Bristol-Myers Squibb, Sanofi, and Roche. She also serves on advisory boards for Boehringer Ingelheim/Lilly and Sanofi.

Funding

Writing support was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc.

References

Abdul-Ghani, M. and DeFronzo, R. (2008) Inhibition of renal glucose reabsorption: a novel strategy for

- achieving glucose control in type 2 diabetes mellitus. *Endocr Pract* 14: 782–790.
- Babu, A. (2013) Canagliflozin for the treatment of type 2 diabetes. *Drugs Today (Barc)* 49: 363–376.
- Barendse, S., Singh, H., Frier, B. and Speight, J. (2012) The impact of hypoglycaemia on quality of life and related patient-reported outcomes in type 2 diabetes: a narrative review. *Diab Med* 29: 293–302.
- Barnett, A., Mithal, A., Manassie, J., Jones, R., Rattunde, H., Woerle, H. *et al.* (2014) Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2: 369–384.
- Boehringer Ingelheim GmbH (2013) Pooled analysis data showed improvements in glycaemic parameters, body weight and blood pressure with investigational agent empagliflozin in adults with type 2 diabetes. Available at: http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2013/24_september_2013empagliflozin.html (accessed 10 March 2014).
- Bolinder, J., Ljunggren, Ö., Johansson, L., Wilding, J., Langkilde, A., Sjöström, C. *et al.* (2014) Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab* 16: 159–169.
- Cefalu, W., Leiter, L., Yoon, K., Arias, P., Niskanen, L., Xie, J. *et al.* (2013) Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 382: 941–950.
- Chao, E. (2012) Dapagliflozin: an evidence-based review of its potential in the treatment of type-2 diabetes. *Core Evid* 7: 21–28.
- Cherney, D., Perkins, B., Soleymanlou, N., Maione, M., Lai, V., Lee, A. *et al.* (2014) Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 129: 587–597.
- DeFronzo, R., Eldor, R. and Abdul-Ghani, M. (2013) Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. *Diabetes Care* 36(Suppl. 2): S127–S138.
- DeFronzo, R., Lewin, A., Patel, S., Liu, D., Kaste, R., Woerle, H. *et al.* (2015) Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care* 38: 384–393.
- Ehrenkranz, J., Lewis, N., Kahn, C. and Roth, J. (2005) Phlorizin: a review. *Diabetes Metab Res Rev* 21: 31–38.
- European Medicines Agency (2012) Forxiga (dapagliflozin). EMA Assessment Report. Procedure no. EMEA/H/C/002322. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002322/WC500136024.pdf (accessed 10 March 2014).
- European Medicines Agency (2014a) Forxiga (dapagliflozin). Summary of product characteristics (October 2014). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002322/WC500136026.pdf (accessed 10 March 2015).
- European Medicines Agency (2014b) Invokana (canagliflozin). Summary of product characteristics (September 2014). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002649/WC500156456.pdf (accessed 10 March 2015).
- European Medicines Agency (2014c) Jardiance (empagliflozin). CHMP Assessment Report (March 2014). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002677/WC500168594.pdf (accessed 10 March 2015).
- European Medicines Agency (2014d) Jardiance (empagliflozin). Summary of product characteristics (June 2014). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002677/human_med_001764.jsp&mid=WC0b01ac058001d124 (accessed 10 March 2015).
- European Medicines Agency (2014e) Summary of the risk management plan (RMP) for Jardiance (empagliflozin) (April 2014). Available at: http://www.fimea.fi/download/27456_Jardiance_RMP_summary-EN.pdf (accessed 10 March 2015).
- Ferrannini, E., Muscelli, E., Frascerra, S., Baldi, S., Mari, A., Heise, T. *et al.* (2014) Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 124: 499–508.
- Ferrannini, E., Ramos, S., Salsali, A., Tang, W. and List, J.F. (2010) Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care* 33: 2217–2224.
- Gangadharan Komala, M. and Mather, A. (2014) Empagliflozin for the treatment of type 2 diabetes. *Expert Rev Clin Pharmacol* 7: 271–279.
- Geerlings, S., Fonseca, V., Castro-Diaz, D., List, J. and Parikh, S. (2014) Genital and urinary tract

infections in diabetes: Impact of pharmacologically-induced glucosuria. *Diabetes Res Clin Pract* 103: 373–381.

Grempler, R., Thomas, L., Eckhardt, M., Himmelsbach, F., Sauer, A., Sharp, D. *et al.* (2012) Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab* 14: 83–90.

Hach, T., Gerich, J., Salsali, A., Kim, G., Hantel, S., Woerle, H. *et al.* (2013) Empagliflozin improves glycemic parameters and cardiovascular risk factors in patients with type 2 diabetes (T2DM): pooled data from four pivotal phase III trials. Abstract 69-LB. *Diabetes* 62(Suppl. 1A): LB19.

Han, S., Hagan, D., Taylor, J., Xin, L., Meng, W., Biller, S. *et al.* (2008) Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. *Diabetes* 57: 1723–1729.

Häring, H., Merker, L., Seewaldt-Becker, E., Weimer, M., Meinicke, T., Broedl, U. *et al.* (2014) Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 37: 1650–1659.

Häring, H., Merker, L., Seewaldt-Becker, E., Weimer, M., Meinicke, T., Woerle, H. *et al.* (2013) Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 36: 3396–3404.

Inzucchi, S., Zinman, B., Wanner, C., Ferrari, R., Fitchett, D., Hantel, S. *et al.* (2015) SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res* 12: 90–100.

Jabbour, S. (2014) SGLT2 inhibitors to control glycemia in type 2 diabetes mellitus: a new approach to an old problem. *Postgrad Med* 126: 111–117.

Johnsson, K., Ptaszynska, A., Schmitz, B., Sugg, J., Parikh, S. and List, J. (2013a) Urinary tract infections in patients with diabetes treated with dapagliflozin. *J Diabetes Complications* 27: 473–478.

Johnsson, K., Ptaszynska, A., Schmitz, B., Sugg, J., Parikh, S. and List, J. (2013b) Vulvovaginitis and balanitis in patients with diabetes treated with dapagliflozin. *J Diabetes Complications* 27: 479–484.

Kim, G., Gerich, J., Salsali, A., Hach, T., Hantel, S., Woerle, H. *et al.* (2013) Empagliflozin (EMPA) increases genital infections but not urinary tract infections (UTIs) in pooled data from four pivotal phase III trials. Abstract 74-LB. *Diabetes* 62(Suppl. 1): LB21.

Kohan, D., Fioretto, P., Tang, W. and List, J. (2014) Long-term study of patients with type 2 diabetes and

moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int* 85: 962–971.

Kovacs, C., Seshiah, V., Swallow, R., Jones, R., Rattunde, H., Woerle, H. *et al.* (2013) Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab* 16: 147–158.

Lamos, E., Younk, L. and Davis, S. (2014) Empagliflozin, a sodium glucose co-transporter 2 inhibitor, in the treatment of type 1 diabetes. *Expert Opin Investig Drugs* 23: 875–882.

Lewin, A., DeFronzo, R., Patel, S., Liu, D., Kaste, R., Woerle, H. *et al.* (2015) Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. *Diabetes Care* 38: 394–402.

Macha, S., Rose, P., Mattheus, M., Cinca, R., Pinnetti, S., Broedl, U. *et al.* (2014) Pharmacokinetics, safety and tolerability of empagliflozin, a sodium glucose cotransporter 2 inhibitor, in patients with hepatic impairment. *Diabetes Obes Metab* 16: 118–123.

McCrimmon, R., Evans, M., Jacob, R., Fan, X., Zhu, Y., Shulman, G. *et al.* (2002) AICAR and phlorizin reverse the hypoglycemia-specific defect in glucagon secretion in the diabetic BB rat. *Am J Physiol Endocrinol Metab* 283: E1076–E1083.

Merovci, A., Solis-Herrera, C., Daniele, G., Eldor, R., Fiorentino, T., Tripathy, D. *et al.* (2014) Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest* 124: 509–514.

Neal, B., Perkovic, V., de Zeeuw, D., Mahaffey, K., Fulcher, G., Stein, P. *et al.* (2013) Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS) – a randomized placebo-controlled trial. *Am Heart J* 166: 217–223 e211.

Nicolle, L., Capuano, G., Fung, A. and Usiskin, K. (2014) Urinary tract infection in randomized phase III studies of canagliflozin, a sodium glucose co-transporter 2 inhibitor. *Postgrad Med* 126: 7–17.

Nigro, S., Riche, D., Pheng, M. and Baker, W. (2013) Canagliflozin, a novel SGLT2 inhibitor for treatment of type 2 diabetes. *Ann Pharmacother* 47: 1301–1311.

Nyirjesy, P., Sobel, J., Fung, A., Mayer, C., Capuano, G., Ways, K. *et al.* (2014) Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *Curr Med Res Opin* 30: 1109–1119.

- Perkins, B., Cherney, D., Partridge, H., Soleymanlou, N., Tschirhart, H., Zinman, B. *et al.* (2014) Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. *Diabetes Care* 37: 1480–1483.
- Polidori, D., Mari, A. and Ferrannini, E. (2014) Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves model-based indices of beta cell function in patients with type 2 diabetes. *Diabetologia* 57: 891–901.
- Ptaszynska, A., Hardy, E., Johnsson, E., Parikh, S. and List, J. (2013) Effects of dapagliflozin on cardiovascular risk factors. *Postgrad Med* 125: 181–189.
- Ridderstråle, M., Andersen, K., Zeller, C., Kim, G., Woerle, H. and Broedl, U. (2014) Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol* 2: 691–700.
- Ridderstråle, M., Svaerd, R., Zeller, C., Kim, G., Woerle, H. and Broedl, U. (2013) Rationale, design and baseline characteristics of a 4-year (208-week) phase III trial of empagliflozin, an SGLT2 inhibitor, versus glimepiride as add-on to metformin in patients with type 2 diabetes mellitus with insufficient glycemic control. *Cardiovasc Diabetol* 12: 129.
- Roden, M., Weng, J., Eilbracht, J., Delafont, B., Kim, G., Woerle, H. *et al.* (2013) Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 1: 208–219.
- Rodríguez-Gutiérrez, R. and Gonzalez-Saldivar, G. (2014) Canagliflozin. *Cleve Clin J Med* 81: 87–88.
- Rosenstock, J., Jelaska, A., Frappin, G., Salsali, A., Kim, G., Woerle, H. *et al.* (2014) Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care* 37: 1815–1823.
- Rosenstock, J., Jelaska, A., Kim, G., Broedl, U. and Woerle, H. (2013) Empagliflozin as add-on to basal insulin for 78 weeks improves glycemic control with weight loss in insulin-treated (T2DM). Abstract 1102-P. *Diabetes* 62(Suppl. 1): A285.
- Rosenwasser, R., Sultan, S., Sutton, D., Choksi, R. and Epstein, B. (2013) SGLT-2 inhibitors and their potential in the treatment of diabetes. *Diabetes Metab Syndr Obes* 6: 453–467.
- Rossetti, L., Smith, D., Shulman, G., Papachristou, D. and DeFronzo, R. (1987) Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. *J Clin Invest* 79: 1510–1515.
- Santer, R. and Calado, J. (2010) Familial renal glucosuria and SGLT2: from a mendelian trait to a therapeutic target. *Clin J Am Soc Nephrol* 5: 133–141.
- Scheen, A. (2014) Evaluating SGLT2 inhibitors for type 2 diabetes: pharmacokinetic and toxicological considerations. *Expert Opin Drug Metab Toxicol* 10: 647–663.
- Sequist, E., Anderson, J., Childs, B., Cryer, P., Dagogo-Jack, S., Fish, L. *et al.* (2013) Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 36: 1384–1395.
- Sinclair, A., Bode, B., Harris, S., Vijapurkar, U., Mayer, C., Fung, A. *et al.* (2014) Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *BMC Endocr Disord* 14: 37.
- Stenlöf, K., Cefalu, W., Kim, K., Alba, M., Usiskin, K., Tong, C. *et al.* (2013) Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab* 15: 372–382.
- Tikkanen, I., Narko, K., Zeller, C., Green, A., Salsali, A., Broedl, U. *et al.* (2015) Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care* 38: 420–428.
- US Food and Drug Administration (2013) Invokana (canagliflozin) tablets. NDA 204042. *FDA Briefing Document* (10 January 2013). Rockville, MD: US Food and Drug Administration.
- US Food and Drug Administration (2014a) Farxiga (dapagliflozin) label (January 2014). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf. (accessed 1 August 2014)
- US Food and Drug Administration (2014b) Invokana (canagliflozin) label (May 2014). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204042s002lbl.pdf (accessed 10 March 2015).
- US Food and Drug Administration (2014c) Jardiance® (empagliflozin) label (August 2014). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204629s000lbl.pdf (accessed 10 March 2015).
- US Food and Drug Administration (2015) Glyxambi® (empagliflozin and linagliptin) label (January 2015). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206073s000lbl.pdf (accessed 10 March 2015).
- Vasilakou, D., Karagiannis, T., Athanasiadou, E., Mainou, M., Liakos, A., Bekiari, E. *et al.* (2013)

Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 159: 262–274.

Wright, E., Loo, D. and Hirayama, B. (2011) Biology of human sodium glucose transporters. *Physiol Rev* 91: 733–794.

Yale, J., Bakris, G., Cariou, B., Yue, D., David-Neto, E., Xi, L. *et al.* (2013) Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 15: 463–473.

Zhang, M., Zhang, L., Wu, B., Song, H., An, Z. and Li, S. (2014) Dapagliflozin treatment for type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab Res Rev* 30: 204–221.

Zinman, B., Inzucchi, S., Lachin, J., Wanner, C., Ferrari, R., Fitchett, D. *et al.* (2014) Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™). *Cardiovasc Diabetol* 13: 102.

Visit SAGE journals online
<http://tae.sagepub.com>

SAGE journals