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REVIEW ARTICLE

Empagliflozin for Type 2 Diabetes Mellitus: An Overview of Phase 3 Clinical Trials

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Abstract: ***Introduction*:** Sodium glucose cotransporter 2 (SGLT2) inhibitors have a unique mechanism of action leading to excretion of glucose in the urine and subsequent lowering of plasma glucose. This mechanism is independent of β-cell function; thus, these agents are effective treatment for type 2 diabetes mellitus (T2DM) at theoretically any disease stage. This class should not confer an additional risk of hypoglycemia (unless combined with insulin or an insulin secretagogue) and has the potential to be combined with other classes of glucose-lowering agents. Empagliflozin is one of three currently approved SGLT2 inhibitors in the United States, and has shown a favorable benefit-risk ratio in phase 3 clinical trials as monotherapy and as add-on to other glucose-lowering therapy in broad patient populations. In addition to its glucose-lowering effects, empagliflozin has been shown to reduce body weight and blood pressure without a compensatory increase in heart rate. Moreover, on top of standard of care, empagliflozin is the first glucose-lowering agent to demonstrate cardiovascular risk reduction in patients at high risk of cardiovascular disease in a prospective outcomes trial: a 14% reduction in risk of the 3-point composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Like other SGLT2 inhibitors, empagliflozin is associated with a higher rate of genital mycotic infections than placebo and has the potential for volume depletion–associated events.

***Conclusion*:** This review summarizes the empagliflozin phase 3 clinical trials program and its potential significance in the treatment of patients with T2DM. Evidence from these clinical trials show reductions in glycated hemoglobin (–0.59 to –0.82%) with a low risk of hypoglycemia except when used with insulin or insulin secretagogues, and moderate reductions in body weight (–2.1 to –2.5 kg) and systolic blood pressure (–2.9 to –5.2 mm Hg), thus supporting the use of empagliflozin as monotherapy or in addition to other glucose-lowering agents. In addition, evidence from the recent EMPA-REG OUTCOME study, which demonstrated relative risk reductions in major adverse cardiac events (14%), cardiovascular mortality (38%) and all-cause mortality (32%), as well as hospitalization for heart failure (36%), supports use of empagliflozin in patients with T2DM and increased cardiovascular risk.

Keywords: Empagliflozin, phase 3, sodium glucose cotransporter 2, SGLT2 inhibitor, type 2 diabetes mellitus.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease with a complex pathophysiology [1]. Increasing insulin resistance, progressive deterioration of β-cell function, dysfunctional adipocytes, gastrointestinal incretin defects, increased glucose reabsorption from the kidneys, hyperglucagonemia, and neurotransmitter dysfunction may contribute to development of diabetes [1]. Glucose control is a central focus in the management of T2DM [2], and reducing hyperglycemia has been shown to decrease microvascular complications of diabetes [3, 4]. The kidney plays an important role in glucose homeostasis, partly via the reabsorption of glucose from the glomerular filtrate [5]. Active glucose reabsorption in the kidney is mediated by two sodium glucose cotransporter (SGLT) proteins, SGLT1 and SGLT2 [6]. The vast majority of glucose reabsorption (~90%) is mediated by SGLT2 and occurs in the first part of the proximal convoluted tubule at the cell brush border; the remainder (~10%) is reabsorbed more distally in the proximal convoluted tubule via the action of SGLT1 [5]. The reabsorbed glucose then diffuses from the basolateral membrane of the proximal tubular cells and into the bloodstream via passive glucose transporter proteins [6]. SGLT2 is predominantly expressed in the kidney, whereas SGLT1 is also expressed in the small intestine and has a key role in glucose and galactose absorption [6].

Inhibition of SGLT2-mediated glucose transport in the kidney lowers the threshold at which urinary glucose excre-

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tion (UGE) occurs, which leads to loss of glucose in the urine and a reduction in hyperglycemia [7]. SGLT2 inhibition has been reported to reduce the renal threshold to approximately 3.3 mmol/L (60 mg/dL) in healthy individuals and to approximately 3.9–5.0 mmol/L (70–90 mg/dL) in individuals with T2DM [8]. This is the rationale for the use of SGLT2 inhibitors for glucose-lowering therapy in T2DM. Furthermore, as SGLT2 inhibitors have a unique mechanism of action that does not depend on a functioning pancreatic β-cell, they have several potential advantages over other classes of glucose-lowering agents in the treatment of T2DM [5, 7]. They should theoretically be effective in patients with any degree of β-cell function (*i.e.*, in early vs advanced disease), should not confer an additional risk of hypoglycemia (unless combined with insulin or an insulin secretagogue), and have the potential to provide additional glucose lowering when combined with other classes of antihyperglycemic agents. In addition, the associated UGE results in loss of calories (possibly producing, weight reduction) and the osmotic diuretic effect may reduce blood pressure [9].

Several SGLT2 inhibitors are approved for clinical use in the treatment of T2DM in adults. Canagliflozin, dapagliflozin, and empagliflozin have approval in the United States and European Union [10]. Ipragliflozin, tofogliflozin, and luseogliflozin have approval in Japan only [11-13]. Two further compounds are in development: ertugliflozin is an SGLT2 inhibitor in phase 3 trials, including a cardiovascular safety study, whereas sotagliflozin is a dual inhibitor of SGLT1 and SGLT2 currently being studied in type 1 diabetes mellitus (T1DM) [14, 15]. This review focuses on empagliflozin, the data from its phase 3 clinical trials program, its pharmacokinetic and pharmacodynamic properties, and its significance in the treatment of patients with T2DM.

2. SUMMARY OF EMPAGLIFLOZIN PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetic and pharmacodynamic profile of empagliflozin has been recently reviewed [16] and a summary of those data is presented here. Empagliflozin (Fig. **1**) is an orally active, potent, and selective SGLT2 inhibitor, with the highest selectivity for SGLT2 over SGLT1 compared with other SGLT2 inhibitors tested (>2500-fold for empagliflozin compared with >1875-fold for tofogliflozin, >1200-fold for dapagliflozin, >550-fold for ipragliflozin, and >250-fold for canagliflozin) [17]. Empagliflozin has an IC_{50} of 3.1 nM for the human SGLT2 receptor and its binding is competitive with glucose [17]. Following a single oral radiolabeled dose ([^{14}C]-empagliflozin 50 mg), empagliflozin was rapidly absorbed and excreted primarily unchanged in urine and feces, and metabolism occurred primarily via glucuronide conjugation [18]. Rapid absorption of empagliflozin was also observed following single and multiple oral doses (0.5–800 mg), and peak plasma concentrations were reached after approximately 1.0–3.0 h [19-21]. The mean terminal half-life ranged from 5.6–13.1 h in single rising-dose studies [19] and from 10.3–18.8 h in multiple-dose studies [20, 21]. Following multiple oral doses, increases in exposure were dose proportional [20, 21].

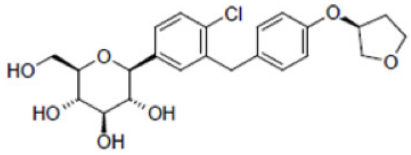

Fig. (1). Chemical structure of empagliflozin.

No clinically relevant alterations in pharmacokinetics were observed in patients with mild-to-severe hepatic impairment [22] or in those with mild-to-severe renal impairment and renal failure/end-stage renal disease [23]. When empagliflozin was coadministered with other commonly prescribed medications, including other oral glucose-lowering agents, warfarin, antihypertensive agents (diuretics, calcium antagonists, and angiotensin-converting enzyme [ACE] inhibitors), simvastatin, and an oral contraceptive, the resultant data did not reveal any relevant drug-drug interactions [16].

In terms of pharmacodynamic parameters, rates of UGE were higher with empagliflozin versus placebo (cumulative amount over 24 h, empagliflozin, 46 g to 90 g vs 5.8 g with placebo) [20] and increased with dose (74 g and 90 g with empagliflozin 10 mg and 25 mg; virtually no change with placebo) [21], but no relevant impact on urine volume was observed [20, 21]. Increased UGE resulted in proportional reductions in fasting plasma glucose (FPG) and mean daily glucose (MDG) concentrations [20, 21]. No relevant differences in mean UGE were reported in patients with hepatic impairment versus those with normal hepatic function [22]. Patients with increasing degrees of renal impairment showed decreasing cumulative UGE [23].

3. EMPAGLIFLOZIN PHASE 3 CLINICAL TRIALS

The clinical trials program that supported the regulatory approval for empagliflozin comprised several multinational clinical trials that enrolled more than 13,000 adults with T2DM. Empagliflozin was assessed as monotherapy, as add-on to other oral glucose-lowering therapy, as add-on to insulin (basal and multiple daily injections) (Table **1**), and as a single-pill combination with a dipeptidyl peptidase 4 (DPP-4) inhibitor (linagliptin) in phase 3 trials (Table **2**) [24-30]. Empagliflozin has also been assessed in special subpopulations with T2DM, including patients with chronic kidney disease (CKD) [25, 31], hypertension [32, 33], high risk of cardiovascular disease [34], or obesity [35], as well as in elderly patients [36] and Japanese patients [37] (Table **3**). This paper summarizes the results of completed phase 3 trials of empagliflozin.

3.1. Summary of Efficacy Data

3.1.1. Glycemic Efficacy

Empagliflozin has demonstrated improvements in glycemic control as monotherapy and as add-on therapy to other glucose-lowering agents, including insulin (Fig. **2**). These studies ranged from 24–104 weeks, with a primary endpoint of change from baseline in glycated hemoglobin (HbA1c). All 24-week studies had extension trials going out to 76 weeks. The results from individual phase 3 studies are discussed herein.

Table 1. Summary of completed phase 3 clinical trials of empagliflozin in patients with T2DM.

Study	Treatment	Patients* (n)	Background Glucose-lowering Therapy	Treatment Duration (weeks)	Baseline HbA1c (%)
Roden *et al.* [29] NCT01177813 EMPA-REG MONO	Empa 10 mg Empa 25 mg Sita 100 mg Placebo	224 224 223 228	No background therapy	24	7.88
Häring *et al.* [24] NCT01159600 EMPA-REG MET	Empa 10 mg Empa 25 mg Placebo	217 213 207	Add-on to met	24	7.9
Häring *et al.* [25] NCT01159600 EMPA-REG MET SU	Empa 10 mg Empa 25 mg Placebo	225 216 225	Add-on to met+SU	24	8.1
Kovacs *et al.* [26] NCT01210001 EMPA-REG PIO	Empa 10 mg Empa 25 mg Placebo	165 168 165	Add-on to pio or pio+met	24	8.1
Rosenstock *et al.* [30] NCT01011868 EMPA-REG BASAL	Empa 10 mg Empa 25 mg Placebo	169 155 170	Add-on to basal insulin	78‡	8.2
Ridderstråle *et al.* [28] NCT01167881 EMPA-REG H2H-SU	Empa 25 mg Glim 1–4 mg	765 780	Add-on to met	104	7.9
Phase 3 extension trials: patients continued previous treatment as randomized in 24-week trials					
Roden *et al.* [38] NCT01289990 EMPA-REG EXTEND MONO (extension of NCT01177813)	Empa 10 mg Empa 25 mg Placebo Sita 100 mg	224 224 228 223	No background therapy	76†	7.88
Merker *et al.* [40] NCT01289990 EMPA-REG EXTEND MET (extension of NCT01159600)	Empa 10 mg Empa 25 mg Placebo	217 213 207	Add-on to met	76†	7.9
Häring *et al.* [74] NCT01289990 EMPA-REG EXTEND MET SU (extension of NCT01159600)	Empa 10 mg Empa 25 mg Placebo	225 216 225	Add-on to met+SU	76†	8.1–8.2
Kovacs *et al.* [26] NCT01289990 EMPA-REG EXTEND PIO (extension of NCT01210001)	Empa 10 mg Empa 25 mg Placebo	165 168 165	Add-on to pio or pio+met	76†	8.1

* Full analysis set; for extension studies, the full analysis set included patients who received at least one study drug dose and had a baseline HbA1c measurement in the initial study.
† 76-week treatment duration includes 52-week double-blind extension period and 24-week initial study.
‡ The insulin dose was held stable for the first 18 weeks and then titrated based on the investigator's discretion.
Empa, empagliflozin; glim, glimepiride; HbA1c, glycated hemoglobin; met, metformin; MONO, monotherapy; pio, pioglitazone; sita, sitagliptin; SU, sulfonylurea; T2DM, type 2 diabetes mellitus.
Note: EMPA-REG BASAL had no extension study.

Table 2. Summary of completed phase 3 clinical trials of empagliflozin containing single-pill combinations in patients with T2DM.

Study	Treatment	Patients* (n)	Background Therapy	Treatment Duration (weeks)	Baseline HbA1c (%)
Lewin *et al.* [42] NCT01422876	Empa 25 mg + lina 5 mg Empa 10 mg + lina 5 mg Empa 10 mg Empa 25 mg Lina 5 mg	134 135 132 133 133	No background therapy	52	8.0–8.1
DeFronzo *et al.* [43] NCT01422876	Empa 25 mg + lina 5 mg Empa 10 mg + lina 5 mg Empa 10 mg Empa 25 mg Lina 5 mg	134 135 137 140 128	Add-on to met	52	7.9–8.1

* Full analysis set.
Empa, empagliflozin; HbA1c, glycated hemoglobin; lina, linagliptin; met, metformin; T2DM, type 2 diabetes mellitus.

Table 3. Summary of completed phase 3 clinical trials of empagliflozin in special populations with T2DM.

Study	Study Population	Treatment	Patients* (n)	Background Glucose-lowering Therapy	Treatment Duration	Baseline HbA1c (%)	Primary Outcome Measure
Rosenstock *et al.* [35] NCT01306214 EMPA-REG MDI	Patients with BMI ≥30 and ≤45 kg/m^2	Empa 10 mg Empa 25 mg Placebo	186 189 188	Add-on to MDI insulin ± met	52 weeks	8.3	Change in HbA1c from baseline to week 18
Tikkanen *et al.* [32] NCT01370005 EMPA-REG BP	Patients with hypertension†	Empa 10 mg Empa 25 mg Placebo	276 276 271	No background therapy OR pretreated with any OAD or GLP-1 analog or insulin for ≥12 weeks	12 weeks	7.9	Change in HbA1c and mean 24-h SBP from baseline to week 12
Barnett *et al.* [31] NCT01164501 EMPA-REG RENAL	Patients with BMI ≥45 kg/m^2 and renal impairment‡	Stage 2 CKD Empa 10 mg Empa 25 mg Placebo Stage 3 CKD Empa 25 mg Placebo Stage 4 CKD Empa 25 mg Placebo	 98 97 95 187 187 37 37	Any glucose-lowering drug (excluding SGLT2 inhibitor)	52 weeks	8.0–8.1	Change in HbA1c from baseline to week 24
Araki *et al.* [37] NCT01368081	Japanese patients with T2DM	Add-on to SU Empa 10 mg Empa 25 mg Add-on to biguanide Empa 10 mg Empa 25 mg	 136 137 68 65	Add-on to any one OAD	52 weeks	7.5–8.1	Safety (AE reporting, changes from baseline in vital signs, and clinical laboratory parameters)

(Table 3) Contd….

Study	Study Population	Treatment	Patients* (n)	Background Glucose-lowering Therapy	Treatment Duration	Baseline HbA1c (%)	Primary Outcome Measure
		Add-on to TZD					
		Empa 10 mg	137				
		Empa 25 mg	136				
		Add-on to AGI					
		Empa 10 mg	69				
		Empa 25 mg	70				
		Add-on to DPP-4 inhibitor					
		Empa 10 mg	68				
		Empa 25 mg	71				
		Add-on to glinide					
		Empa 10 mg	70				
		Empa 25 mg	70				
Zinman *et al.* [34] NCT01131676 EMPA-REG OUTCOME	Patients with T2DM and high risk of CV events	Empa 10 mg Empa 25 mg Placebo	2345¶ 2342¶ 2333¶	Standard of care	3.1 years (median observation time)	8.1	Composite of death from CV causes, nonfatal MI (excluding silent MI), or nonfatal stroke

* Full analysis set.
† Mean seated office SBP 130–159 mm Hg and DBP 80–99 mm Hg.
‡ eGFR >15 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2.
¶ Randomized patients.
AE, adverse event; AGI, alpha-glucosidase inhibitor; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; empa, empagliflozin; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; MDI, multiple daily injection; met, metformin; MI, myocardial infarction; OAD, oral glucose-lowering drug; SBP, systolic blood pressure; SGLT2, sodium glucose cotransporter 2; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

3.1.1.1. Monotherapy

In a 24-week, placebo-controlled, phase 3 study of empagliflozin with sitagliptin (100 mg once daily) as an active control (EMPA-REG MONO), reductions from baseline in HbA1c were greater with both doses of empagliflozin compared with placebo ($p<0.0001$), but not greater compared with sitagliptin ($p=0.970$ [empagliflozin 10 mg] and $p=0.106$ [empagliflozin 25 mg]; Fig. **2A**) [29]. In patients with HbA1c ≥8.5% at baseline, empagliflozin 10 mg and 25 mg were both associated with significantly greater reductions in HbA1c at week 24 than with sitagliptin. Adjusted mean changes (95% CI) from baseline in HbA1c were –1.44% (–1.64 to –1.23) with empagliflozin 10 mg and –1.43% (–1.65 to –1.21) with empagliflozin 25 mg, compared with –1.04% (–1.25 to –0.83) with sitagliptin ($p=0.0077$ and $p=0.0119$, respectively). At week 24, adjusted mean changes from baseline in FPG were greater with empagliflozin 10 mg and empagliflozin 25 mg than with placebo or sitagliptin ($p<0.0001$ for both doses; Fig. **2B**). These improvements in glycemic control were sustained over a 52-week extension study (EMPA-REG EXTEND MONO), with placebo-adjusted mean (95% CI) changes from baseline to week 76 (*i.e.*, the 24-week study plus the 52-week extension) of −0.78% (−0.94% to −0.63%; $p<0.001$) for the empagliflozin 10-mg group, −0.89% (−1.04% to −0.73%; $p<0.001$) for the empagliflozin 25-mg group, and −0.66% (−0.82% to −0.51%; $p<0.001$) for the sitagliptin 100-mg group [38]. Both empagliflozin groups, as well as the sitagliptin group, had significant reductions in FPG versus the placebo group (all $p<0.001$); furthermore, both empagliflozin doses provided significantly larger reductions when compared with sitagliptin (both $p<0.001$) [38].

3.1.1.2. Add-on to Oral Glucose-Lowering Drugs

3.1.1.2.1. Add-on to Metformin

While metformin monotherapy is effective initially in achieving glycemic goals, most patients will require additional therapies as the disease progresses [39]. This study evaluated the addition of empagliflozin in patients who were inadequately controlled with metformin (EMPA-REG MET),

many of whom had long-standing T2DM (>60% of patients >1 to 10 years) [24]. In this 24-week study, reductions from baseline in HbA1c were greater with both doses of empagliflozin compared with placebo (p<0.001; Fig. **2A**) [24]. Additionally, placebo-adjusted differences in MDG (95% CI) were –0.42 mmol/L (–0.72 to –0.13; p=0.006) and –0.69 mmol/L (–0.99 to –0.39; p<0.001) with empagliflozin 10 mg and 25 mg, respectively. Adjusted mean changes from baseline in FPG (Fig. **2B**) and 2-h postprandial plasma glucose (PPG) were greater with empagliflozin 10 mg and empagliflozin 25 mg than they were with placebo (both doses p<0.001 vs placebo for FPG and PPG).

A 52-week extension study (EMPA-REG EXTEND MET) also showed sustained reductions in HbA1c, with placebo-adjusted mean change from baseline to week 76 of –0.6% (95% CI –0.8 to –0.5; p<0.001) and –0.7% (95% CI –0.9 to –0.6; p<0.001) with empagliflozin 10 mg and 25 mg, respectively [40]. Adjusted mean reductions in FPG at 76 weeks were significantly greater with both doses of empagliflozin compared with placebo (both p<0.001).

In a 104-week study comparing empagliflozin 25 mg to the sulfonylurea glimepiride, as add-on to metformin (EMPA-REG H2H-SU) [28], empagliflozin treatment resulted in a greater mean reduction in HbA1c compared with glimepiride (difference vs glimepiride, –0.11; 95% CI –0.19 to –0.02; p<0.0001 for noninferiority and p=0.0153 for superiority). At 104 weeks, adjusted mean changes from baseline in FPG were greater with empagliflozin than with glimepiride (p<0.0001 vs glimepiride). In substudies investigating 2-h PPG and MDG at 104 weeks, empagliflozin treatment resulted in significantly greater reductions in 2-h PPG (p=0.0289 vs glimepiride) and MDG (p=0.0936 vs glimepiride) [28]. A 208-week extension study has recently completed, but data have not been published yet.

3.1.1.2.2. Add-on to Metformin Plus Sulfonylurea

Progression to triple therapy in patients with T2DM may be a necessity [2, 41]. As β-cell function deteriorates, utilization of agents that depend on insulin-dependent pathways, such as metformin and sulfonylureas, becomes more challenging. Addition of a third agent, such as the SGLT2 inhibitor empagliflozin, whose mechanism of action is independent of insulin, may provide patients with improved glycemic control at any stage of disease. In this 24-week phase 3 study comparing empagliflozin 10 mg and 25 mg with placebo as add-on to metformin plus sulfonylurea (EMPA-REG MET SU) [25], reductions from baseline in HbA1c were greater with both doses of empagliflozin compared with placebo (p<0.001; Fig. **2A**). At 24 weeks, MDG, FPG (Fig. **1B**), and 2-h PPG were significantly lower with both doses of empagliflozin compared with placebo (p<0.001 vs placebo for MDG and FPG; p=0.003 vs placebo for 2-h PPG).

In the open-label arm (empagliflozin 25 mg, baseline HbA1c >10%) of this study, the mean (SE) change from baseline in HbA1c at week 24 was –2.89% (0.16), with 8.9% of patients achieving target HbA1c of 7.0% at 24 weeks. The mean (SE) changes from baseline in MDG and FPG were –3.39 mmol/L (0.58) and –3.02 mmol/L (0.37), respectively.

3.1.1.2.3. Add-on to Pioglitazone with or without Metformin

Thiazolidinediones (TZD) are an alternative first-line therapy when metformin is contraindicated or poorly tolerated and also a second-line, add-on therapy in the American Diabetes Association (ADA) recommendations; this class of therapy is given a lower priority in the American Association of Clinical Endocrinologists (AACE) treatment algorithm because of its adverse event profile [2, 41].

In a 24-week study comparing empagliflozin to placebo as add-on to pioglitazone with or without metformin (EMPA-REG PIO) [27], reductions from baseline in HbA1c were greater with both doses of empagliflozin compared with placebo (p<0.001; Fig. **2A**). Both doses of empagliflozin resulted in a significant reduction in FPG compared with placebo (p<0.001 for both doses; Fig. **2B**). In a 52-week extension of this study, these trends were maintained: placebo-adjusted mean changes from baseline in HbA1c were –0.59% (95% CI –0.79% to –0.40%; p<0.001) with empagliflozin 10 mg and –0.69% (95% CI –0.88% to –0.50%; p<0.001) with empagliflozin 25 mg [26]. Both doses of empagliflozin resulted in significant reductions in FPG compared with placebo (both p<0.001).

3.1.1.3 Add-on to Basal Insulin

Guidelines call for initiation of insulin therapy in patients who cannot achieve glycemic goals with oral glucose-lowering agents [2, 41]. There is a need for oral agents that can be added to insulin therapy to achieve glycemic targets without weight gain or risk of hypoglycemia. A 78-week study randomized patients with inadequate glycemic control (HbA1c >7.0%–10.0%) despite treatment with stable basal insulin glargine or detemir (≥20 IU/day) or neutral protamine Hagedorn (NPH) insulin (≥14 IU/day) (EMPA-REG BASAL), with or without concomitant metformin and/or sulfonylurea, to receive add-on therapy with once-daily empagliflozin 10 mg, 25 mg, or placebo [30]. The insulin dose was held stable for the first 18 weeks and then titrated at the investigator's discretion.

The decrease in HbA1c levels from baseline to week 18 (primary endpoint) was significantly greater with both doses of empagliflozin than with placebo (both p<0.001; Fig. **2A**). For both doses of empagliflozin, placebo-adjusted mean reductions in FPG from baseline were significantly greater compared with placebo (both p<0.001; Fig. **2B**).

3.1.1.3.1. Changes in Body Weight

Compared with placebo, empagliflozin 10 mg and 25 mg, given as monotherapy, add-on to metformin, or as add-on to metformin plus sulfonylurea, consistently resulted in significant reductions in body weight from baseline, at 24 weeks (except EMPA-REG BASAL at 18 weeks; and EMPA-REG H2H-SU at 52 weeks) ranging from 2.1–2.5 kg (p<0.001; Fig. **2C**) [24, 25, 28, 29, 40]. When added to pioglitazone (with or without metformin) or insulin, agents known to cause weight gain, reductions in body weight from baseline were smaller than in the above-mentioned trials, ranging from 0.9–1.7 kg [26, 30].

In a 104-week study comparing empagliflozin 25 mg to glimepiride as add-on to metformin [28], empagliflozin

treatment significantly reduced body weight compared with an increase observed with glimepiride (difference vs glimepiride, –4.5 kg [95% CI –4.8 to –4.1; p<0.0001]). In the body composition substudy [28], dual-energy x-ray absorptiometry scans showed that 90% of the weight loss with empagliflozin was due to reductions in total fat mass (difference vs glimepiride, –2.2% [95% CI –3.5 to –1.0; p=0.0004]). Similarly, magnetic resonance imaging showed that empagliflozin treatment significantly reduced both abdominal visceral adipose tissue (VAT) (p=0.0039 vs glimepiride) and subcutaneous adipose tissue (SAT) (p<0.0001 vs glimepiride) at 104 weeks. However, there was no significant change in the VAT/SAT ratio at 104 weeks for empagliflozin compared with glimepiride.

3.1.1.3.2. Changes in Blood Pressure

Compared with placebo, empagliflozin 10 mg and 25 mg, given as monotherapy or given as add-on to metformin, metformin plus sulfonylurea, pioglitazone, or basal insulin, consistently resulted in significant reductions in systolic blood pressure (SBP) from baseline at 24 weeks (except EMPA-REG BASAL at 18 weeks; and EMPA-REG H2H-SU at 52 weeks, ranging from –2.9 to –5.2 mm Hg (p≤0.032; Fig. **2D**) [24-30]. Additionally, treatment differences in SBP (95% CI) for empagliflozin 10 mg and empagliflozin 25 mg compared with sitagliptin were –3.4 mm Hg (–5.7 to –1.2; p=0.0031) and –4.2 mm Hg (–6.5 to –2.0; p=0.0003), respectively [29]. In a 104-week study comparing empagliflozin 25 mg to glimepiride as add-on to metformin, empagliflozin treatment significantly reduced SBP compared with an increase observed with glimepiride (difference vs glimepiride, –5.6 mm Hg [95% CI –6.8 to –4.4; p<0.0001]) [28].

Similar findings were observed for diastolic blood pressure (DBP). Compared with placebo, empagliflozin 10 mg and 25 mg given as add-on therapy to metformin, pioglitazone, or basal insulin consistently resulted in significant reductions in DBP from baseline in the EMPA-REG MET, EMPA-REG PIO, EMPA-REG BASAL, and EMPA-REG H2H-SU trials (p<0.01; Fig. **2E**) [24-30]. Empagliflozin 10 mg and 25 mg given as add-on to metformin and sulfonylurea did not significantly reduce DBP vs placebo (p=0.557 and p=0.534 for 10 mg and 25 mg, respectively) [25]. Additionally, treatment differences in DBP (95% CI) for empagliflozin 10 mg and 25 mg compared with sitagliptin were –1.7 mm Hg (–0.3 to –0.4; p=0.0130) and –2.6 mm Hg (–3.9 to –1.3; p=0.0001), respectively [29]. In a 104-week study comparing empagliflozin 25 mg to glimepiride as add-on to metformin, empagliflozin treatment significantly reduced DBP compared with an increase observed with glimepiride (difference *vs*. glimepiride, –2.7 mm Hg [95% CI –3.4 to –1.9; p<0.0001]) [28].

3.1.1.4. Single-Pill Combinations Containing Empagliflozin

Empagliflozin has also been evaluated as a single-pill combination therapy with the DPP-4 inhibitor, linagliptin, in phase 3 studies in treatment-naïve patients [42] and as add-on to metformin [43]. The complementary mechanisms of action of the two classes address different aspects of the underlying T2DM pathophysiology, which is a key consideration for combination therapy [44]. Additionally, both agents are associated with a low risk of hypoglycemia unless used in combination with insulin or insulin secretagogues, and weight neutrality (DPP-4 inhibitors) or weight loss (SGLT2 inhibitors).

In a study of treatment-naïve patients, reductions in HbA1c at 24 weeks were significantly greater for the single-pill combination of empagliflozin 10 mg/linagliptin 5 mg compared with the individual components (p<0.001 for both; Fig. **3**) [42]. At week 52, reductions in HbA1c with empagliflozin 10 mg/linagliptin 5 mg were significantly greater compared with the individual components (both p<0.001). Empagliflozin 25 mg/linagliptin 5 mg also resulted in a significant reduction in HbA1c at both week 24 and week 52 compared with linagliptin 5 mg (p<0.001), but not compared with empagliflozin 25 mg (p=0.176 at week 24; p=0.176 at week 52). Both combinations significantly reduced FPG from baseline compared with linagliptin 5 mg (p<0.001) at week 24 and week 52 (p<0.001). However, the reductions in FPG with both combinations did not reach statistical significance when compared with the empagliflozin 10-mg or empagliflozin 25-mg groups at either week 24 or week 52.

In the add-on to metformin study, mean (SE) reductions from baseline in HbA1c at week 24 were significantly greater with both combinations than with monotherapy with linagliptin or empagliflozin (p<0.001 vs both; Fig. **2**) [43]. The reductions in HbA1c were sustained with both dose combinations at week 52 and were significantly greater compared with the individual components (p<0.001 vs all individual components). Both combinations significantly reduced FPG from baseline compared with linagliptin 5 mg, empagliflozin 10 mg, and empagliflozin 25 mg (p<0.01 for all comparisons) at week 24. This trend was maintained at week 52. However, the reduction in FPG at week 52 with empagliflozin 10 mg/linagliptin 5 mg did not reach significance when compared with empagliflozin 10 mg (p=0.069).

Two phase 3 trials using the single-pill combination of empagliflozin and linagliptin (NCT01734785 and NCT01778049) completed in March 2015. Results are expected to publish in 2016.

3.1.1.4.1. Changes in Body Weight

Treatment with empagliflozin/linagliptin single-pill combinations (25 mg/5 mg and 10 mg/5 mg doses) resulted in reductions in body weight at week 24 and week 52 [42, 43]. These reductions were statistically significant compared with linagliptin 5 mg at both week 24 and week 52 in the study of treatment-naïve patients (p<0.001 at week 24; p=0.002 for empagliflozin 25 mg/linagliptin 5 mg vs linagliptin 5 mg and p=0.017 for empagliflozin 10 mg/linagliptin 5 mg vs linagliptin 5 mg at week 52) and in the add-on to metformin study (p<0.001 for both time points). However, reductions in body weight with combination treatment were not significantly different compared with reductions achieved in either empagliflozin 10 mg or empagliflozin 25 mg treatment groups in both treatment-naïve and metformin-treated patient groups.

3.1.1.4.2. Changes in Blood Pressure

In treatment-naïve patients, changes from baseline in SBP and DBP at week 52 were not significantly different

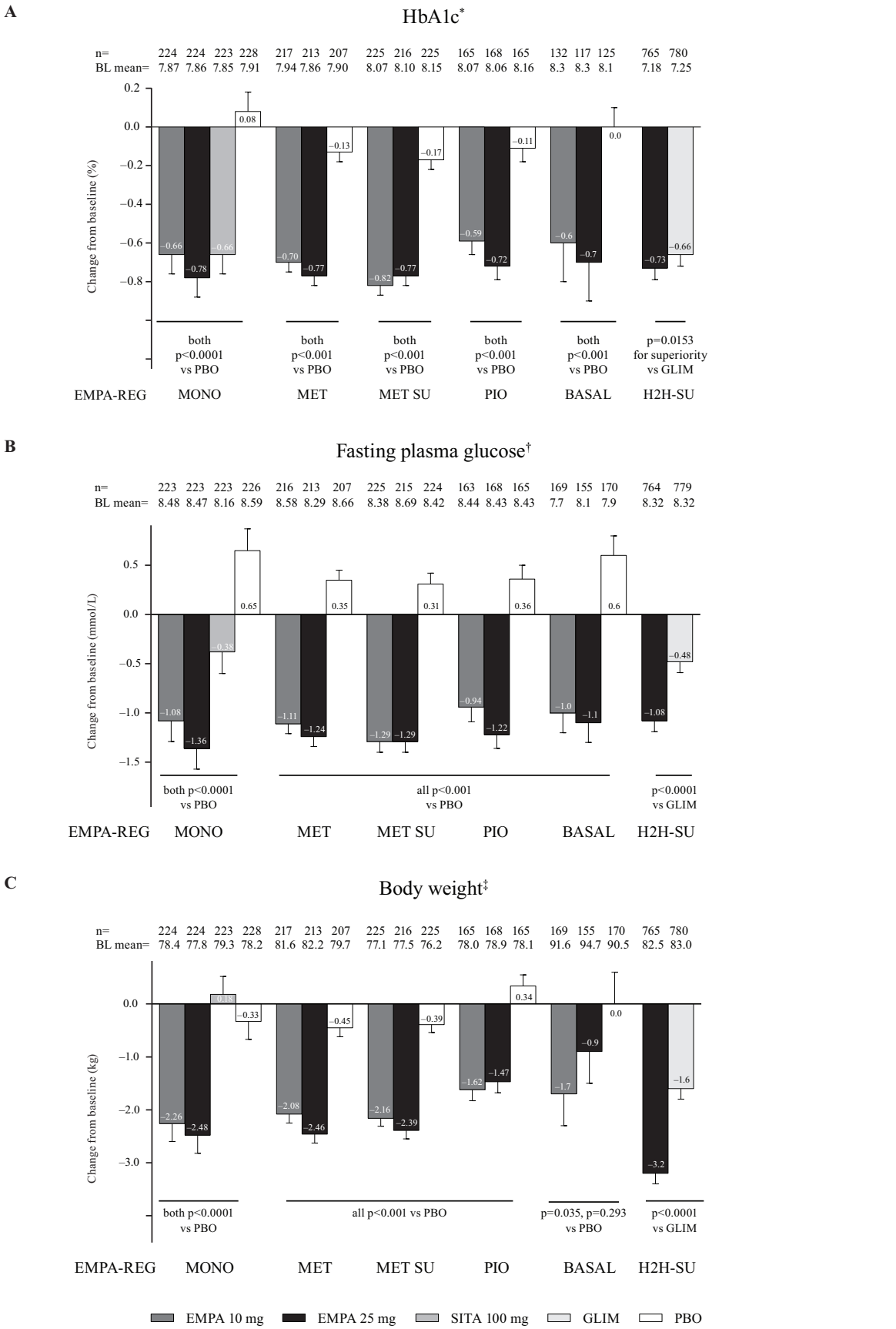
A
HbA1c*
n= 224 224 223 228 217 213 207 225 216 225 165 168 165 132 117 125 765 780
BL mean= 7.87 7.86 7.85 7.91 7.94 7.86 7.90 8.07 8.10 8.15 8.07 8.06 8.16 8.3 8.3 8.1 7.18 7.25
Change from baseline (%)
0.2
0.0
−0.2
−0.4
−0.6
−0.8
0.08
−0.13
−0.17
−0.11
0.0
−0.66
−0.78
−0.66
−0.70
−0.77
−0.82
−0.77
−0.59
−0.72
−0.6
−0.7
−0.73
−0.66
both p<0.0001 vs PBO
both p<0.001 vs PBO
both p<0.001 vs PBO
both p<0.001 vs PBO
both p<0.001 vs PBO
p=0.0153 for superiority vs GLIM
EMPA-REG MONO MET MET SU PIO BASAL H2H-SU
B
Fasting plasma glucose†
n= 223 223 223 226 216 213 207 225 215 224 163 168 165 169 155 170 764 779
BL mean= 8.48 8.47 8.16 8.59 8.58 8.29 8.66 8.38 8.69 8.42 8.44 8.43 8.43 7.7 8.1 7.9 8.32 8.32
Change from baseline (mmol/L)
0.5
0.0
−0.5
−1.0
−1.5
0.65
0.35
0.31
0.36
0.6
−0.38
−1.08
−1.36
−1.11
−1.24
−1.29
−1.29
−0.94
−1.22
−1.0
−1.1
−1.08
−0.48
both p<0.0001 vs PBO
all p<0.001 vs PBO
p<0.0001 vs GLIM
EMPA-REG MONO MET MET SU PIO BASAL H2H-SU
C
Body weight‡
n= 224 224 223 228 217 213 207 225 216 225 165 168 165 169 155 170 765 780
BL mean= 78.4 77.8 79.3 78.2 81.6 82.2 79.7 77.1 77.5 76.2 78.0 78.9 78.1 91.6 94.7 90.5 82.5 83.0
Change from baseline (kg)
0.0
−1.0
−2.0
−3.0
0.13
−0.33
−0.45
−0.39
0.34
0.0
−0.9
−1.6
−2.26
−2.48
−2.08
−2.46
−2.16
−2.39
−1.62
−1.47
−1.7
−3.2
both p<0.0001 vs PBO
all p<0.001 vs PBO
p=0.035, p=0.293 vs PBO
p<0.0001 vs GLIM
EMPA-REG MONO MET MET SU PIO BASAL H2H-SU
EMPA 10 mg
EMPA 25 mg
SITA 100 mg
GLIM
PBO

Fig. (2). Contd…

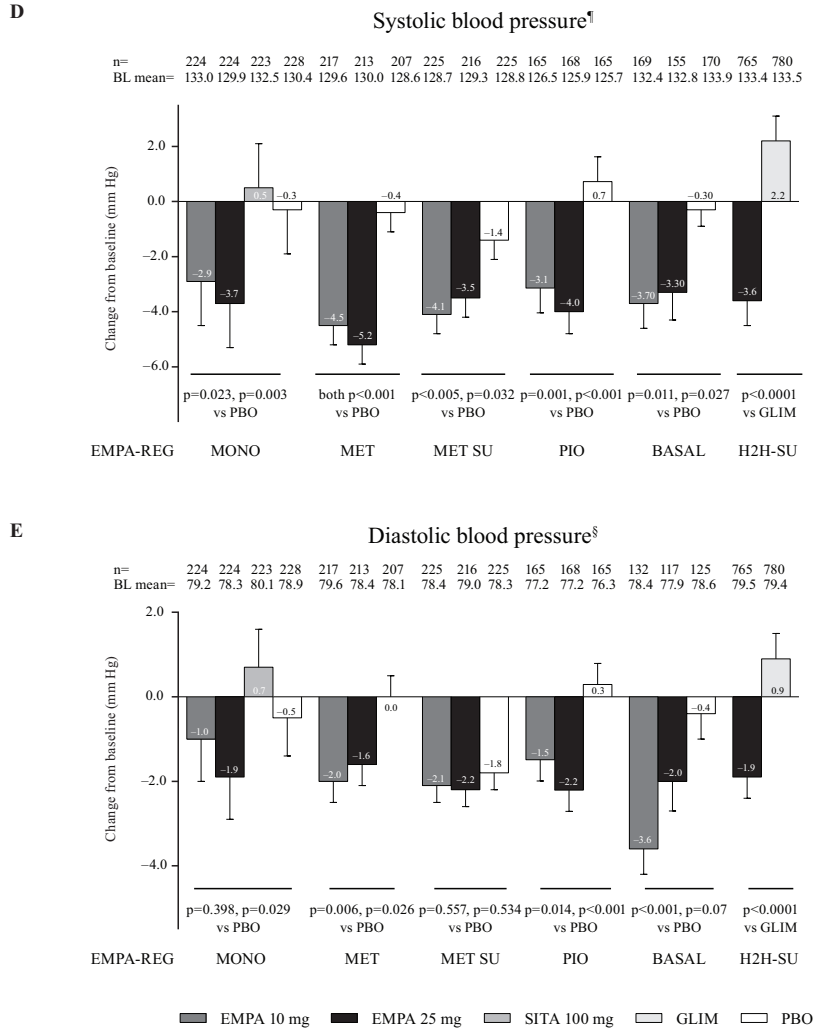

Fig. (2A-E). Results from six phase 3 clinical studies showing changes from BL in HbA1c, fasting plasma glucose, body weight, and systolic and diastolic blood pressure at 24 weeks (except EMPA-REG BASAL at 18 weeks; and EMPA-REG H2H-SU at 52 weeks). For all studies, values are adjusted mean change from baseline to week 18 (EMPA-REG BASAL), week 52 (EMPA-REG H2H-SU), or week 24 (all other studies), in the FAS, based on ANCOVA using last observation carried forward. For EMPA-REG H2H-SU and EMPA-REG MONO, error bars are 95% CIs; for all other studies, error bars are SE.

* For EMPA-REG BASAL, FAS week 18 completers; for EMPA-REG MONO, neither EMPA dose was statistically significantly different vs SITA.

† For EMPA-REG MONO, both EMPA doses were also significant (p<0.001) *vs.* SITA.

‡ For EMPA-REG MONO, both EMPA doses were also significant (p<0.0001) *vs.* SITA.

¶ For EMPA-REG MONO, both EMPA doses were also significant (p=0.0031 and p=0.0003) *vs.* SITA.

§ For EMPA-REG MONO, EMPA 10 mg *vs.* SITA (p=0.0130); EMPA 25 mg *vs.* SITA (p=0.0001).

ANCOVA, analysis of covariance; BL, baseline; EMPA, empagliflozin; FAS, full analysis set; GLIM, glimepiride; HbA1c, glycated hemoglobin; MET, metformin; MONO, monotherapy; PBO, placebo; PIO, pioglitazone; SITA, sitagliptin; SU, sulfonylurea.

between empagliflozin/linagliptin and the individual components [42]. In patients inadequately controlled on metformin therapy, reduction in SBP at week 52 with both doses was significantly greater compared with linagliptin 5 mg (10 mg/5 mg, p=0.022; 25 mg/5 mg, p=0.005), but not with the respective empagliflozin doses (p=0.609 and p=0.578, respectively) [43]. Also in this patient group, reductions in DBP at week 52 with both combination doses were marginally significant when compared with linagliptin 5 mg (both p=0.05), but did not approach statistical significance when compared with empagliflozin.

3.1.2. Efficacy in Specific Populations

3.1.2.1. Patients with Renal Impairment

In a phase 3 study comparing empagliflozin with placebo as add-on to metformin plus sulfonylurea, changes from baseline in HbA1c were analyzed in renal function subgroups [25]. Both doses of empagliflozin significantly reduced HbA1c from baseline at 24 weeks versus placebo in subgroups of patients with normal renal function (estimated glomerular filtration rate [eGFR] ≥90 mL/min/1.73 m^2; p<0.001 for both doses *vs.* placebo), mild renal impairment

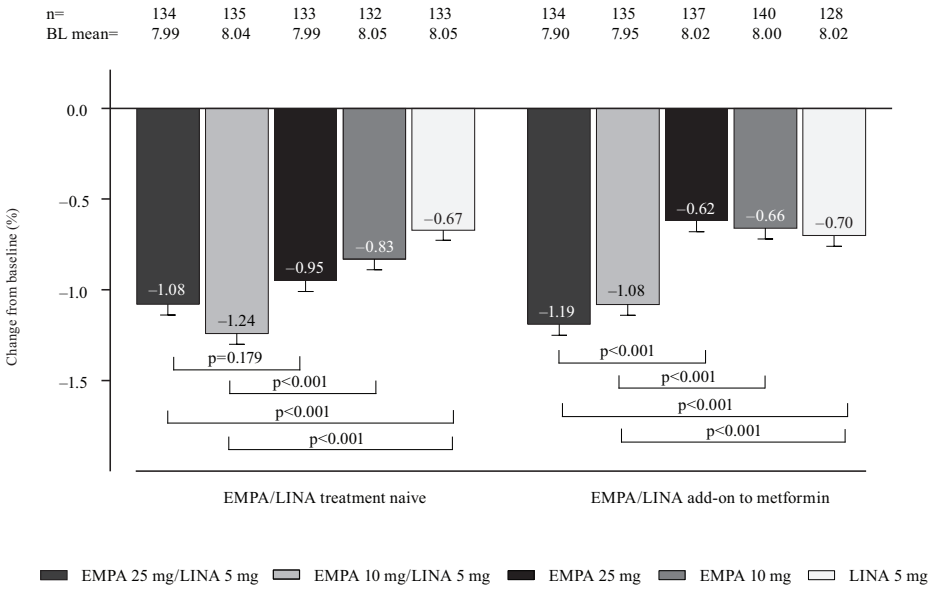

Fig. (3). Empagliflozin/linagliptin clinical studies [42, 43]. BL, baseline; EMPA, empagliflozin; LINA, linagliptin. American Diabetes Association [Initial Combination of Empagliflozin and Linagliptin in Subjects with Type 2 Diabetes] American Diabetes Association, 2015. American Diabetes Association [Combination of Empagliflozin and Linagliptin as Second-Line Therapy in Subjects With Type 2 Diabetes Inadequately Controlled on Metformin] American Diabetes Association, 2015. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

(eGFR ≥60 to <90 mL/min/1.73 m^2; p<0.001 for both doses vs placebo), and moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2; p=0.009 for empagliflozin 10 mg and p=0.006 for empagliflozin 25 mg, both vs placebo).

In a phase 3 study to assess the efficacy and safety of empagliflozin in patients with T2DM and CKD, empagliflozin 25 mg significantly reduced HbA1c at week 24 (primary endpoint) in patients with stage 2 and 3 CKD compared with placebo (p<0.0001), with reductions sustained until week 52 (p<0.0001 vs placebo for both time points) [31]. In patients with stage 2 CKD (eGFR ≥60 to <90 mL/min/1.73 m^2), empagliflozin 25 mg significantly reduced HbA1c versus placebo at both week 24 and week 52 (treatment difference, –0.68% and –0.65%, respectively; p<0.0001 for both). Reductions were also observed in SBP and body weight at both time points (p≤0.0024 for both parameters vs placebo). In patients with stage 3 CKD (eGFR ≥30 to <60 mL/min/1.73 m^2) reductions of HbA1c were observed with empagliflozin 25 mg versus placebo at week 24 and week 52 (treatment difference, –0.42% and –0.44%, respectively; p<0.001 for both). Furthermore, significant reductions in SBP and body weight were observed in the stage 3 CKD population at week 24 and week 52 (p≤0.0023 for both parameters vs placebo). In contrast, in patients with stage 4 CKD (eGFR ≥15 to <30 mL/min/1.73 m^2), empagliflozin 25 mg did not reduce HbA1c versus placebo at week 24 or week 52, whereas changes in SBP and body weight were observed.

This study also addressed concerns of possible deterioration in renal function due to treatment with SGLT2 inhibitors [31]. Empagliflozin treatment for 52 weeks resulted in small decreases in eGFR, which returned to baseline levels by the end of the 3-week follow-up. Urine albumin to creatinine ratios improved with empagliflozin compared with placebo at week 52.

3.1.2.2. Patients with Hypertension

Empagliflozin has been assessed in patients with T2DM and hypertension (mean seated office SBP, 130–159 mm Hg and DBP 80–99 mm Hg) [32]. Reductions in HbA1c in this patient population were consistent with those reported for empagliflozin monotherapy. Treatment with empagliflozin 10 mg and empagliflozin 25 mg resulted in placebo-adjusted reductions from baseline in mean (95% CI) 24-h SBP (25 mg, –3.44 mm Hg [–4.78 to –2.09]; 10 mg, –4.16 mm Hg [–5.50 to –2.83]) and mean (95% CI) 24-h DBP (–1.36 mm Hg [–2.15 to –0.56] and –1.72 mm Hg [–2.51 to –0.93], respectively) (p<0.001 for all) [32].

In cohorts of patients with T2DM and hypertension (cohort 1, 12-week treatment) or T2DM (cohort 2, 24-week treatment), empagliflozin reduced pulse pressure and SBP in both cohorts compared with placebo, particularly in subgroups of patients with advanced age (≥75 years) and high baseline SBP (>140 mm Hg) [33]. Empagliflozin treatment also reduced arterial stiffness and vascular resistance in both cohorts [33].

3.1.2.3. Elderly Patients

In the pivotal empagliflozin phase 3 trials, a total of 2721 (32%) patients treated with empagliflozin were ≥65 years of age and 491 (6%) were ≥75 years of age [36]. No formal analyses of data from these elderly patients have been published to date.

The US labeling information states that empagliflozin is expected to have reduced efficacy in elderly patients with renal impairment [36]. It also states that the risk of volume depletion–related adverse reactions increased in patients who were ≥75 years of age to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively

[36]. In addition, the risk of urinary tract infections (UTIs) increased in patients who were ≥75 years of age to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively [36].

3.1.2.4. Obese Patients

In a 52-week phase 3 study of empagliflozin as add-on to multiple daily injections of insulin in obese individuals (body mass index ≥30 and ≤45 kg/m^2), empagliflozin was shown to improve glycemic control, reduce insulin dosage requirements, and decrease body weight compared with placebo [35]. Empagliflozin treatment significantly reduced HbA1c from baseline to week 18, the primary endpoint (placebo-adjusted mean [± SE] change –0.44 ± 0.08 [95% CI –0.59 to –0.29] and –0.52 ± 0.07 [95% CI –0.67 to –0.37] for empagliflozin 10 mg and 25 mg, respectively; both p<0.001). Significant reductions in HbA1c from baseline were also seen at week 52 with both empagliflozin 10 mg and 25 mg (both p<0.001 vs placebo).

Insulin titration was permitted between week 19 and week 52 to achieve glycemic targets. At week 52, insulin dose (IU/day) was significantly reduced, with placebo-adjusted mean (± SE) changes from baseline of –8.8 ± 3.1 (95% CI –14.8 to –2.8; p=0.004) with empagliflozin 10 mg and –11.2 ± 3.1 (95% CI –17.2 to –5.2; p<0.001) with empagliflozin 25 mg. Of note, both doses of empagliflozin produced significant reductions in body weight from baseline compared with placebo at week 18 (both p<0.001) and week 52 (both p<0.001) in this difficult-to-treat population of obese patients with uncontrolled hyperglycemia despite treatment with high-dose multiple daily injections of insulin.

3.1.2.5. Japanese Patients

In a 52-week study of empagliflozin 10 mg and 25 mg as add-on to monotherapy with one oral glucose-lowering agent (sulfonylurea, biguanide, TZD, alpha-glucosidase inhibitor, DPP-4 inhibitor, or glinide), adjusted mean (± SE) changes from baseline in HbA1c and FPG ranged from –0.77% (0.06) to –1.00% (0.06) and 16.4 (1.8) to 33.1 (2.2) mg/dL, respectively [37]. Add-on therapy with empagliflozin also resulted in reductions in SBP, DBP, and body weight at the end of the 52-week treatment period.

3.1.2.6. Patients with Active Coronary Disease

The recently completed EMPA-REG OUTCOME® study is the first to demonstrate protection from cardiovascular outcomes with a glucose-lowering agent, the SGLT2 inhibitor empagliflozin, on top of standard care [34]. The primary outcome of this study was time to occurrence of major adverse cardiovascular events (MACE) as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the key secondary composite outcome was the primary outcome plus hospitalization for unstable angina. The primary outcome occurred in 10.5% of patients in the empagliflozin group and in 12.1% of patients on placebo (HR 0.86; 95% CI 0.74 to 0.99; p<0.001 for noninferiority and p=0.04 for superiority), resulting in a 14% reduction in risk of the 3-point MACE. The HRs for the comparison between empagliflozin 10 mg and placebo (HR 0.85; 95% CI 0.71 to 1.01; p=0.07) and empagliflozin 25 mg and placebo (HR 0.86; 95% CI 0.73 to 1.02; p=0.09) were identical to those in the pooled analysis of the empagliflozin 10-mg and 25-mg doses, but were not significant owing to the smaller number of outcome events in the individual dosage groups. Additionally, empagliflozin resulted in a 38% reduction of cardiovascular death and improved survival by reducing all-cause mortality by 32%. The mechanisms that could mediate these effects include changes in arterial stiffness, cardiac function, cardiac oxygen demand, as well as cardiorenal effects, and established effects on hyperglycemia, weight, visceral adiposity, and blood pressure [34]. Secondary analyses also showed that hospitalization for heart failure or cardiovascular death occurred in a significantly lower percentage of patients treated with empagliflozin (5.7%) than with placebo (8.5%; HR 0.66; 95% CI 0.55 to 0.79; p<0.001), with the risk reduction consistent in patients with versus without heart failure at baseline [45].

3.2. Summary of Safety and Tolerability Data

3.2.1. Hypoglycemia

SGLT2 inhibitors are not expected to increase the risk of hypoglycemia, as they have no direct effect on insulin release and do not impair endogenous glucose production in response to hypoglycemia [46-48]. Data from phase 3 trials have confirmed that empagliflozin is associated with low risk of hypoglycemia when given as monotherapy [29] or as add-on therapy with most other glucose-lowering agents (Tables **4** and **5**) [24, 27].

Empagliflozin added to metformin therapy was shown to have a lower risk of hypoglycemia compared with glimepiride added to metformin (frequency of confirmed hypoglycemic events: 2% and 24% for empagliflozin and glimepiride, respectively) [28]. However, the risk of hypoglycemia was increased when empagliflozin was used in combination with either insulin or sulfonylurea [25, 30, 35]. This increased risk of hypoglycemia was no more than what would be anticipated with these agents, which carry an inherent risk of hypoglycemia [2]. The US labeling information recommends lowering the dose of insulin or insulin secretagogue when used in combination with empagliflozin [36].

3.2.2. Volume Depletion

Empagliflozin, by virtue of its mechanism of action, may be associated with osmotic diuresis resulting in intravascular volume contraction (Tables **4** and **5**). This mechanism may result in symptomatic hypotension, particularly in vulnerable patient groups such as elderly, those with renal impairment, and individuals on diuretics [36]. Small changes in hematocrit levels, not associated with events consistent with volume depletion, have been noted in phase 3 trials [25, 27, 29, 31]. The US labeling information for empagliflozin recommends assessment of volume status prior to initiating therapy with empagliflozin in patients at risk of volume depletion and continued monitoring during the course of treatment [36].

3.2.3. Genital Mycotic Infections

In phase 3 trials, empagliflozin monotherapy was associated with a higher frequency of genital mycotic infections compared with placebo, potentially due to glucosuria creating

Table 4. Summary of AEs of special interest in key empagliflozin phase 3 studies.

Study	Treatment*	Hypoglycemia† (%)	Urinary Tract Infection, % (male [M], female [F])	Genital Infection, % (male [M], female [F])	Events Consistent With Volume Depletion, n (%)
Roden *et al.* [29] NCT01177813 EMPA-REG MONO	Empa 10 mg	<1	7.0 (M2.0, F15.0)	3.0 (M3.0, F4.0)	NA
	Empa 25 mg	<1	5.0 (M1.0, F13.0)	4.0 (M1.0, F9.0)	
	Sita 100 mg	<1	5.0 (M3.0, F9.0)	1.0 (M1.0, F1.0)	
	Placebo	<1	5.0 (M2.0, F9.0)	0	
Häring *et al.* [24] NCT01159600 EMPA-REG MET	Empa 10 mg	1.8	5.1 (M0.0, F12.0)	3.7 (M0.8, F7.6)	NA
	Empa 25 mg	1.4	5.6 (M0.8, F11.8)	4.7 (M0.8, F9.7)	
	Placebo	0.5	4.9 (M2.6, F7.7)	0	
Häring *et al.* [25] NCT01159600 EMPA-REG MET SU	Empa 10 mg	16.1	10.3 (M2.7, F18.0)	2.7 (M0.9, F4.5)	NA
	Empa 25 mg	11.5	8.3 (M0.0, F17.5)	2.3 (M0.9, F3.9)	
	Placebo	8.4	8.0 (M2.7, F13.3)	0.9 (M0.9, F0.9)	
Kovacs *et al.* [26] NCT01210001 EMPA-REG PIO	Empa 10 mg	1.2	17.0 (M3.6, F30.5)	8.5 (M7.2, F9.8)	NA
	Empa 25 mg	2.4	11.9 (M2.4, F21.7)	3.6 (M1.2, F6.0)	
	Placebo	1.8	16.4 (M8.2, F22.8)	2.4 (M1.4, F3.3)	
Rosenstock *et al.* [30] NCT01011868 EMPA-REG BASAL	Empa 25 mg	4.0	14.0 (M7.0, F22.0)	12.0 (M9.0, F15.0)	11 (1.0)
	Glim 1–4 mg	25.0	13.0 (M5.0, F23.0)	2.0 (M1.0, F3.0)	8 (1.0)
Ridderstråle *et al.* [28] NCT01167881 EMPA-REG H2H-SU	Empa 10 mg	36.0	15.0 (M5.0, F26.0)	8.0 (M8.0, F8.0)	NA
	Empa 25 mg	36.0	12.0 (M8.0, F18.0)	5.0 (M4.0, F6.0)	
	Placebo	35.0	9.0 (M3.0, F15.0)	2.0 (M0.0, F4.0)	

* All treatment once daily.
† Events consistent with hypoglycemia, plasma glucose ≤3.9 mmol/L (≤70 mg/dL) and/or requiring assistance.
AE, adverse event; empa, empagliflozin; glim, glimepiride; met, metformin; MONO, monotherapy; NA, not applicable; pio, pioglitazone; sita, sitagliptin; SU, sulfonylurea.

Table 5. Summary of AEs of special interest in empagliflozin phase 3 studies in special populations.

Study	Treatment*	Hypoglycemia† (%)	Urinary Tract Infection, % (male [M], female [F])	Genital Infection, % (male [M], female [F])	Events Consistent With Volume Depletion, n (%)
Rosenstock *et al.* [35] NCT01306214 EMPA-REG MDI	Empa 10 mg	95 (51.1)	15.6 (M5.2, F27.0)	4.3 (M1.0, F7.9)	NA
	Empa 25 mg	109 (57.7)	15.3 (M3.6, F24.8)	9.5 (M8.3, F10.5)	
	Placebo	109 (58.0)	15.4 (M0.0, F25.7)	1.6 (M1.3, F1.8)	
Tikkanen *et al.* [32] NCT01370005 EMPA-REG BP	Empa 10 mg	18 (6.5)	4.0 (M 0.6, F 9.5)	5.1 (M4.7, F5.7)	1 (0.4)
	Empa 25 mg	17 (6.2)	4.7 (M2.6, F7.4)	5.4 (M3.9, F7.4)	0
	Placebo	13 (4.8)	3.7 (M0.6, F8.7)	0.4 (M0.0, F0.4)	1 (0.4)
Barnett *et al.* [31] NCT01164501 EMPA-REG RENAL	Stage 2 CKD				
	Empa 10 mg	26 (26.5)	14.3 (M8.3, F23.7)	7.1 (M10.0, F2.6)	1 (1.0)
	Empa 25 mg	22 (22.7)	9.3 (M3.3, F19.4)	5.2 (M0.0, F13.9)	0
	Placebo	23 (24.2)	15.8 (M8.9, F25.6)	6.3 (M3.6, F10.3)	1 (1.1)
	Stage 3 CKD				
	Empa 25 mg	52 (27.8)	16.6 (M5.6, F31.3)	2.7 (M1.9, F3.8)	7 (3.7)
	Placebo	53 (28.3)	15.5 (M3.8, F30.9)	1.1 (M0.9, F1.2)	5 (2.7)

(Table 5) Contd….

Study	Treatment*	Hypoglycemia† (%)	Urinary Tract Infection, % (male [M], female [F])	Genital Infection, % (male [M], female [F])	Events Consistent With Volume Depletion, n (%)
	Stage 4 CKD				
	Empa 25 mg	14 (37.8)	18.9 (M9.5, F31.3)	2.7 (M0.0, F6.3)	2 (5.4)
	Placebo	12 (32.4)	8.1 (M0, F16.7)	0.0 (M0.0, F0.0)	2 (5.4)
Araki *et al.* [37] NCT01368081	SU background				
	Empa 10 mg	6 (4.4)	4.4 (M2.0, F10.8)	1.5 (M2.0, F0.0)	4 (2.9)
	Empa 25 mg	9 (6.6)	4.4 (M1.0, F12.2)	0.0 (M0.0, F0.0)	2 (1.5)
	Biguanide background				
	Empa 10 mg	0	5.9 (M5.3, F6.7)	5.9 (M2.6, F10.0)	3 (4.4)
	Empa 25 mg	1 (1.5)	4.6 (M2.3, F9.1)	3.1 (M2.3, F4.5)	0 (0.0)
	TZD background				
	Empa 10 mg	2 (1.5)	4.4 (M1.8, 17.4)	1.5 (M0.0, F8.7)	1 (0.7)
	Empa 25 mg	1 (0.7)	4.4 (M1.0, 14.7)	0.7 (M0.0, F2.9)	3 (2.2)
	AGI background				
	Empa 10 mg	0	4.3 (M0.0, F16.7)	2.9 (M0.0, F11.1)	2 (2.9)
	Empa 25 mg	0	4.3 (M0.0, F16.7)	5.7 (M0.0, F22.2)	2 (2.9)
	DPP-4 inhibitor background				
	Empa 10 mg	0	7.4 (M0.0, F18.5)	1.5 (M2.4, F0.0)	1 (1.5)
	Empa 25 mg	1 (1.4)	1.4 (M2.1, F0.0)	1.4 (M0.0, F4.3)	0 (0.0)
	Glinide background				
	Empa 10 mg	0	4.3 (M0.0, F13.0)	0.0 (M0.0, F0.0)	0 (0.0)
	Empa 25 mg	2 (2.9)	2.9 (M1.8, F7.7)	0.0 (M0.0, F0.0)	0 (0.0)
Zinman *et al.* [34] NCT01131676 EMPA-REG OUTCOME	Empa 10 mg	656 (28.0)	18.2 (M10.9, F35.5)	6.5 (M5.4, F9.2)	115 (4.9)
	Empa 25 mg	647 (27.6)	17.8 (M10.1, F37.3)	6.3 (M4.6, F10.8)	124 (5.3)
	Placebo	650 (27.9)	18.1 (M9.4, F40.6)	1.8 (M1.5, F2.6)	115 (4.9)

* All treatment once daily.
† Events consistent with hypoglycemia, plasma glucose ≤3.9 mmol/L (≤70 mg/dL) and/or requiring assistance.
AE, adverse event; AGI, alpha-glucosidase inhibitor; BP, blood pressure; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; empa, empagliflozin; MDI, multiple daily injection; SU, sulfonylurea; TZD, thiazolidinediones.

a favorable environment for microorganisms, and such events occurred more frequently in female patients (Table **4**) [49]. A similar trend in increased frequency of genital infections was observed in studies of empagliflozin as add-on to other glucose-lowering agents (Tables **4** and **5**) [49, 50]. However, the majority of these events were mild, with very few discontinuations due to these events [36].

3.2.4. Urinary Tract Infections

Some empagliflozin studies have shown an increase in the incidence of UTIs in patients receiving empagliflozin compared with placebo (Tables **4** and **5**). A pooled analysis of four phase 3 trials did not show any evidence of increased risk of UTIs for empagliflozin compared with placebo [50]. However, the US labeling information notes that in a pool of five placebo-controlled clinical trials, the incidence of UTIs (*e.g.*, UTIs, asymptomatic bacteriuria, cystitis) was increased in patients treated with empagliflozin compared with placebo (7.6%, 9.3%, and 7.6% with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively) [36]. Furthermore, the US label states that patients with a history of chronic or recurrent UTIs were more likely to experience a UTI. In this pooled analysis, UTIs occurred more frequently in female patients treated with empagliflozin than in male patients. The incidence of UTIs in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively [36]. In addition, the risk of UTIs increased in patients who were ≥75 years of age to 10.5%, 15.7%, and 15.1% in patients receiving placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively [36]. The rate of treatment discontinuation due to

UTIs was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. There have been post-marketing reports of serious UTIs, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin; thus, patients should be evaluated for signs and symptoms of UTIs and treated promptly, if indicated [36].

3.2.5. Laboratory Values

Key laboratory measurements from phase 3 trials of empagliflozin are listed in Tables **6** and **7**. Low-density lipoprotein cholesterol (LDL-C) is an independent predictor of cardiovascular risk. Small increases in high-density lipoprotein cholesterol (HDL-C), LDL-C, and triglycerides with empagliflozin have been reported in a pooled analysis of four placebo-controlled trials of empagliflozin, with no change in the LDL-C/HDL-C ratio [51].

Increased uric acid levels are associated with an increased risk of ischemic heart disease and stroke [52]. In a pooled analysis of 17 placebo-controlled trials plus 6 extension studies, empagliflozin was reported to reduce blood uric acid levels compared with placebo, with reductions of –0.6 mg/dL for both doses of empagliflozin compared with placebo (0.1 mg/dL) [53].

Increases in serum potassium and serum magnesium levels are of particular concern in patients with renal impairment. In phase 3 studies of empagliflozin in patients with renal impairment, no significant changes in mean serum potassium levels from baseline were noted with empagliflozin treatment compared with placebo [31]. In this patient population, treatment with empagliflozin 25 mg resulted in small increases in serum magnesium levels from baseline (0.24 mg/dL) [31]. Albuminuria is a known marker for indicating glomerular damage [52]. Empagliflozin was shown to reduce albuminuria in patients with T2DM and renal impairment, with more patients with stage 3 CKD on empagliflozin 25 mg converting from macroalbuminuria or microalbuminuria at baseline to microalbuminuria or no albuminuria, respectively [31].

3.2.6. Bone Safety

SGLT2 inhibitors increase the concentration of phosphate in serum, likely through increased tubular reabsorption, a mechanism that can adversely affect bone [54]. Recent clinical data have shown that bone fractures occurred more frequently with canagliflozin than with placebo and occurred as early as 12 weeks after starting the drug [55]. Additionally, canagliflozin caused greater loss of bone mineral density at the hip than placebo in elderly individuals [56]. Thus, a warning has been added to the canagliflozin label [57].

A pooled analysis of >11,000 patients in the empagliflozin clinical trials program (including phase 1 and 2) reported no increase in bone fractures with empagliflozin compared with placebo [58]. There was no observed loss of bone mineral density with empagliflozin after up to 2 years of treatment [59].

3.2.7. Neoplasia

The overall number of patients receiving empagliflozin who developed cancer of the kidney or bladder was low and comparable to placebo [59]. Two cases of bladder cancer and one case of breast cancer were reported with empagliflozin treatment compared with zero cases of bladder cancer and two cases of breast cancer for comparators [60]. The causality of these cancers to empagliflozin is unlikely and could be due to numerical imbalances. Of note, no imbalances in cancer were observed in the EMPA-REG OUTCOME trial [34].

3.2.8. Diabetic Ketoacidosis

Reports of diabetic ketoacidosis (DKA) in patients treated with SGLT2 inhibitors have appeared for the three agents available in the United States (dapagliflozin, canagliflozin, and empagliflozin) [61-64], as well as others only available in Japan [65]. Some of these cases involved patients with T1DM, although SGLT2 inhibitors are not indicated for use in T1DM. Several cases of DKA reported following treatment with SGLT2 inhibitors were unusual because the blood glucose levels were only slightly or moderately increased (*i.e.*, euglycemic ketoacidosis), which is not typical in DKA [64]. Furthermore, factors such as major illness, reduced food and fluid intake, and reduced insulin dose were identified as potential triggers for the ketoacidosis in some cases [66]. No imbalance in the incidence of DKA has been observed with empagliflozin compared with placebo in the phase 2 and 3 empagliflozin clinical trial program thus far [61]. Investigations into this potential safety signal are being carried out by the US Food and Drug Administration and by the European Medicines Agency in the European Union [66, 67].

4. ONGOING EMPAGLIFLOZIN PHASE 3 TRIALS

A 24-week study of empagliflozin and metformin combination therapy (both given twice daily) has investigated the efficacy and safety of four dose combinations of empagliflozin and metformin versus their respective monotherapies in treatment-naïve patients with T2DM (NCT01719003). A 24-week study of empagliflozin in hypertensive black/African American patients with T2DM, designed to assess its efficacy and safety in this ethnic/racial population (NCT02182830), is currently recruiting.

CONCLUSION

Based on clinical trial results of empagliflozin monotherapy and as add on to other glucose-lowering agents, improvements in glycemic control, as well as moderate reductions in body weight and systolic blood pressure can be expected when patients start empagliflozin therapy. Empagliflozin is well tolerated, with a low risk of hypoglycemia unless administered with insulin or insulin secretagogues. Genital mycotic infections were observed more frequently in patients receiving empagliflozin than placebo, although most were mild to moderate in nature. Moreover, on top of standard of care, empagliflozin demonstrated cardiovascular benefits, a 14% reduction in risk of the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, which can benefit patients with T2DM and at high risk of cardiovascular disease.

Table 6. Summary of laboratory values in key empagliflozin phase 3 studies.

Study	Treatment*	HDL-C (mmol/L), Change From Baseline†	LDL-C (mmol/L), Change From Baseline†	TG (mmol/L), Change From Baseline†	Hematocrit (%), Change From Baseline†	eGFR (mL/min/1.73 m^2 [MDRD] equation), Change From Baseline†	Uric Acid (µmol/L) Change From Baseline†
Roden *et al.* [29] NCT01177813 EMPA-REG MONO	Empa 10 mg	0.11 (0.01)	0.06 (0.04)	–0.30 (0.10)	2.1 (3.3)	0.7 (12.8)	–58.0 (80.0)
	Empa 25 mg	0.13 (0.01)	0.11 (0.04)	–0.18 (0.10)	2.1 (3.1)	1.3 (10.8)	–62.0 (83.0)
	Sita 100 mg	0.02 (0.01)	0.03 (0.04)	0.06 (0.10)	–0.8 (2.9)	–1.8 (12.6)	17 (77)
	Placebo	0.04 (0.01)	0.04 (0.04)	–0.07 (0.10)	–0.5 (3.1)	–0.02 (10.1)	–14 (91)
Häring *et al.* [24] NCT01159600 EMPA-REG MET	Empa 10 mg	0.08 (0.01)	0.15 (0.04)	0.00 (0.08)	2.4 (3.4)	0.1 (13.5)	−45.0 (91.0)
	Empa 25 mg	0.06 (0.01)	0.15 (0.04)	–0.04 (0.08)	2.7 (3.4)	−1.7 (10.5)	−56.0 (86.0)
	Placebo	0.00 (0.01)	0.03 (0.04)	0.11 (0.08)	−0.8 (3.0)	1.0 (11.2)	3.0 (80.0)
Häring *et al.* [25] NCT01159600 EMPA-REG MET SU	Empa 10 mg	0.05 (0.01)	0.04 (0.04)	0.03 (0.09)	2.5 (3.4)	−1.3 (10.6)	−28.0 (87.0)
	Empa 25 mg	0.05 (0.01)	0.10 (0.04)	0.17 (0.09)	2.7 (3.4)	−2.5 (13.4)	−26.0 (81.0)
	Placebo	–0.02 (0.01)	0.02 (0.04)	0.08 (0.09)	−0.8 (3.1)	−1.9 (10.1)	11.0 (81.0)
Kovacs *et al.* [26] NCT01210001 EMPA-REG PIO	Empa 10 mg	0.04 (0.02)	0.09 (0.05)	–0.18 (0.06)	2.1 (4.4)	−2.1 (14.4)	−37.0 (83.0)
	Empa 25 mg	0.02 (0.02)	0.04 (0.05)	0.00 (0.06)	2.6 (3.4)	−3.4 (15.6)	−29.0 (81.0)
	Placebo	–0.01 (0.02)	0.00 (0.05)	–0.01 (0.06)	−0.6 (3.6)	–0.5 (12.5)	13.0 (69.0)
Rosenstock *et al.* [30] NCT01011868 EMPA-REG BASAL	Empa 10 mg	0.07 (0.02)	–0.05 (0.04)	0.02 (0.08)	1.8 (3.2)	–4.8 (12.1)	–5.0 (69.0)
	Empa 25 mg	0.05 (0.02)	0.05 (0.05)	0.14 (0.09)	2.5 (3.0)	–5.7 (13.4)	–23.0 (68.0)
	Placebo	0.03 (0.01)	–0.03 (0.04)	0.03 (0.08)	–0.6 (3.1)	–6.3 (13.0)	1.0 (68.0)
Ridderstråle *et al.* [28] NCT01167881 EMPA-REG H2H-SU	Empa 25 mg	0.08 (0.01)	0.19 (0.02)	0.05 (0.04)	4.3 (4.4)	1.7 (13.3)	−52.0 (82.0)
	Glim 1–4 mg	–0.01 (0.01)	0.04 (0.02)	0.12 (0.04)	0.6 (4.1)	–1.8 (12.9)	16 (90.0)

Change from baseline data are adjusted mean (SE) or mean (SD).

* All treatment once daily.

† Change from baseline at last value on treatment for hematocrit (and eGFR in study NCT01011868); change from baseline at week 24 for eGFR (week 104 in study NCT01167881); change from baseline at week 78 for LDL-C, HDL-C, and TG in study NCT01011868; hematocrit and uric acid values normalized to standard.

eGFR, estimated glomerular filtration rate; empa, empagliflozin; glim, glimepiride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDI, multiple daily injection; MDRD, Modification of Diet in Renal Disease; met, metformin; MONO, monotherapy; pio, pioglitazone; sita, sitagliptin; SU, sulfonylurea; TG, triglycerides.

Table 7. Summary of laboratory values in empagliflozin phase 3 studies in special populations.

Study	Treatment*	HDL-C (mmol/L), Change From Baseline†	LDL-C (mmol/L), Change From Baseline†	TG (mmol/L), Change From Baseline†	Hematocrit (%), Change From Baseline†	eGFR (mL/min/1.73 m^2 [MDRD] equation), Change From Baseline†	Uric acid (µmol/L) Change From Baseline†
Rosenstock *et al.* [35] NCT01306214 EMPA-REG MDI	Empa 10 mg	0.01 (0.01)	–0.06 (0.05)	0.20 (0.10)	4.8 (4.1)	–1.6 (11.5)	−23.0 (95.0)
	Empa 25 mg	0.01 (0.01)	0.06 (0.05)	–0.03 (0.10)	4.4 (4.1)	–1.6 (11.3)	−42.0 (92.0)
	Placebo	–0.02 (0.01)	0.12 (0.05)	0.01 (0.10)	0.7 (4.1)	–2.0 (11.4)	12.0 (81.0)
Tikkanen *et al.* [32] NCT01370005 EMPA-REG BP	Empa 10 mg	0.03 (0.01)	0.08 (0.03)	–0.03 (0.06)	0.03 (0.02)	–0.20 (8.99)	–41.21 (58.47)
	Empa 25 mg	0.03 (0.01)	0.17 (0.03)	0.03 (0.06)	0.02 (0.02)	–2.60 (9.98)	–38.46 (58.51)
	Placebo	0.01 (0.01)	0.01 (0.03)	0.11 (0.06)	0.00 (0.02)	–0.27 (9.18)	–8.17 (43.68)

(Table 7) Contd…

Study	Treatment*	HDL-C (mmol/L), Change From Baseline†	LDL-C (mmol/L), Change From Baseline†	TG (mmol/L), Change From Baseline†	Hematocrit (%), Change From Baseline†	eGFR (mL/min/1.73 m^2 [MDRD] equation), Change From Baseline†	Uric acid (µmol/L) Change From Baseline†
Barnett *et al.* [31] NCT01164501 EMPA-REG RENAL	Stage 2 CKD						
	Empa 10 mg	0.00 (0.02)	0.10 (0.07)	–0.03 (0.10)	2.1 (4.0)	–2.04 (9.9)	–31.0 (90.0)
	Empa 25 mg	0.02 (0.02)	0.09 (0.07)	0.04 (0.10)	2.5 (3.5)	–2.47 (11.7)	–30.0 (111.0)
	Placebo	–0.05 (0.02)	0.08 (0.07)	0.29 (0.10)	–1.8 (3.0)	–0.71 (9.7)	–4.0 (80.0)
	Stage 3 CKD						
	Empa 25 mg	0 (0.02)	0.12 (0.05)	0.15 (0.06)	3.7 (4.0)	–2.8 (8.2)	–5.0 (123.0)
	Placebo	–0.05 (0.02)	0.10 (0.05)	0.08 (0.06)	–0.6 (3.4)	–0.3 (7.4)	–6.0 (114.0)
	Stage 4 CKD						
	Empa 25 mg	–0.07 (0.04)	0.14 (0.15)	–0.72 (0.79)	–0.2 (7.0)	–1.4 (6.0)	51.0 (144.0)
	Placebo	–0.05 (0.04)	0.10 (0.12)	–0.03 (0.15)	–1.6 (6.9)	–1.1 (5.8)	9.0 (124.0)
Araki *et al.* [37] NCT01368081	SU background						
	Empa 10 mg	6.6 (0.8)	4.9 (1.8)	–15.8 (5.9)	4.9 (3.1)	2.7 (10.7)	–0.5 (1.1)
	Empa 25 mg	5.9 (0.8)	4.3 (1.8)	–11.9 (5.9)	5.1 (3.6)	2.5 (9.8)	–0.3 (1.3)
	Biguanide background						
	Empa 10 mg	4.8 (0.9)	8.0 (2.7)	–11.3 (7.0)	4.6 (3.2)	5.1 (10.5)	–1.0 (1.4)
	Empa 25 mg	6.1 (1.0)	4.8 (2.8)	–9.2 (7.2)	3.6 (3.6)	4.2 (13.6)	–0.8 (1.2)
	TZD background						
	Empa 10 mg	5.4 (1.0)	4.0 (2.0)	–7.3 (5.7)	3.9 (3.7)	4.0 (10.6)	–0.4 (1.3)
	Empa 25 mg	8.2 (1.0)	1.6 (2.0)	–6.2 (5.7)	4.1 (4.2)	6.0 (11.3)	–0.4 (1.1)
	AGI background						
	Empa 10 mg	7.9 (1.3)	4.4 (2.9)	–22.9 (8.0)	4.5 (3.3)	3.5 (10.4)	–0.7 (1.2)
	Empa 25 mg	8.2 (1.3)	8.1 (2.8)	–3.9 (7.9)	5.5 (4.2)	3.7 (12.6)	–0.5 (1.3)
	DPP-4 inhibitor background						
	Empa 10 mg	5.7 (0.9)	2.8 (2.2)	–9.3 (8.5)	4.0 (3.2)	0.3 (10.2)	–0.7 (1.0)
	Empa 25 mg	5.2 (0.9)	8.1 (2.2)	–2.5 (8.3)	4.1 (3.4)	1.2 (8.7)	–0.4 (1.1)
	Glinide background						
	Empa 10 mg	7.1 (1.2)	5.9 (2.6)	–17.9 (5.8)	4.5 (3.5)	1.9 (11.1)	–0.2 (1.1)
	Empa 25 mg	5.6 (1.2)	7.8 (2.6)	–7.2 (5.8)	4.6 (3.8)	4.2 (12.8)	–0.5 (1.2)
Zinman *et al.* [34] NCT01131676 EMPA-REG OUTCOME	Empa 10 mg	—	—	—	4.8 (5.5)	–2.3 (12.1)	—
	Empa 25 mg				5.0 (5.3)	–2.9 (11.8)	
	Placebo				0.9 (4.7)	–2.0 (11.5)	

Change from baseline data are adjusted mean (SE) or mean (SD).

* All treatment once daily.

† Change from baseline at last value on treatment; HDL-C, LDL-C, and TG change from baseline at week 12 in study NCT01370005 and change from baseline at week 52 in study NCT01368081; change from baseline at week 52 for eGFR, HDL-C, LDL-C, and TG in study NCT01164501; change from baseline to last measurement ≤3 days after last intake of study medication in study NCT01131676; hematocrit and uric acid values normalized to standard; data for HDL-C, LDL-C, and TG were presented as mg/dL in study NCT01368081; data for uric acid, HDL-C, LDL-C, and TG were presented as changes over time in study NCT01131676.

AGI, alpha-glucosidase inhibitor; BP, blood pressure; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; empa, empagliflozin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDI, multiple daily injection; MDRD, Modification of Diet in Renal Disease; SU, sulfonylurea; TG, triglycerides; TZD, thiazolidinediones.

The ADA/European Association for the Study of Diabetes (EASD) updated position statement recommends that SGLT2 inhibitors be used at any stage of T2DM owing to their insulin-independent mechanism of action [2]. They are positioned as a "reasonable second-line or third-line" option as add-on to other glucose-lowering therapy. The AACE/American College of Endocrinology (ACE) and ADA Standards of Medical Care in Diabetes guidelines recommend SGLT2 inhibitors as an initial therapeutic option when metformin is contraindicated [68, 69]. SGLT2 inhibitors are also recommended as a component of dual and triple therapy.

The single-pill combination of empagliflozin and linagliptin (a DPP-4 inhibitor) has been approved for use as an adjunct to diet and exercise in adults with T2DM in the United States [70]. The ADA/EASD guidelines recommend initial combination therapy in patients with high baseline HbA1c (≥9%), and the AACE/ACE guidelines also recommend combination therapy with two or more glucose-lowering therapies in patients with HbA1c ≥7.5% and >9%, respectively. In these cases, initial treatment with a single-pill combination of empagliflozin and linagliptin may be an option.

FUTURE DIRECTIONS AND USES FOR EMPAGLIFLOZIN AND SGLT2 INHIBITORS

Although currently not approved for use in patients with T1DM, empagliflozin and other SGLT2 inhibitors have the potential for use in the treatment of T1DM. A phase 2 study (NCT01969747) investigating the pharmacodynamics, efficacy, and safety of empagliflozin as adjunct to insulin in patients with T1DM has yielded promising results [71]. In this study, empagliflozin treatment improved HbA1c, increased UGE, and decreased body weight from baseline. Further studies are warranted to explore the utility and establish the safety of empagliflozin in the treatment of T1DM, especially in light of DKA cases reported in clinical trials in T1DM [72, 73].

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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