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Combination of Empagliflozin and Metformin Therapy: A Consideration of its Place in Type 2 Diabetes Therapy

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Abstract

Type 2 diabetes mellitus (T2DM) is characterized by multiple metabolic abnormalities and current approaches to treatment involve a stepwise approach, frequently involving the use of combination therapy. The addition of the sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin, to metformin therapy has been shown to be effective and well tolerated in patients with T2DM and is 1 of the several recommended treatment options. The publication of the EMPA-REG OUTCOME study, which showed that empagliflozin is associated with cardiovascular (CV) and renal benefits, has resulted in changes in treatment guidelines for T2DM. Because many patients with T2DM will require treatment with more than 1 glucose-lowering agent, consideration of the role of empagliflozin in combination therapy is relevant. The clinical data reviewed show that the combination of empagliflozin/metformin offers the potential to improve glycemic control in T2DM and reduces body weight and blood pressure, vs each agent individually, with a manageable risk profile. This combination could be suitable for patients with T2DM who are inadequately controlled by metformin, in particular, for patients who would benefit from modest reductions in blood pressure and body weight or who have risk factors for CV disease or declining renal function. Empagliflozin/metformin is also available as a single-pill combination, which has the potential to provide a simplified treatment regimen and could lead to improved clinical outcomes compared with coadministration of individual tablets.

Keywords: Type 2 diabetes mellitus, empagliflozin, metformin, combination therapy, single-pill combination

Introduction

Type 2 diabetes mellitus (T2DM) is a major and growing cause of morbidity and mortality worldwide.[1] Despite continued advances in the treatments available for T2DM, glycemic control is frequently suboptimal.[2,3] Because T2DM is characterized by multiple metabolic abnormalities, current treatment algorithms involving a stepwise approach to the use of combination therapy involving agents with complementary modes of action are frequently necessary.[4,5] Although

metformin remains the preferred initial monotherapy for T2DM, unless it is contraindicated or not tolerated, the latest treatment algorithm from the American Diabetes Association (ADA) recommends initial combination therapy when glycated hemoglobin (HbA_{1c}) levels are ≥9.0%.[5] This approach may allow patients to achieve HbA_{1c} targets more rapidly than with sequential drug therapy. Similarly, the treatment algorithm issued by the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) states that dual combination therapy is usually required and should be initiated when HbA_{1c} levels are ≥7.5%, using agents with complementary modes of action.[4]

Metformin is generally prescribed as first-line pharmacologic therapy in T2DM and both the ADA and AACE algorithms list sodium-glucose cotransporter-2 (SGLT2) inhibitors as a suggested option for dual combination therapy.[4,5] SGLT2 inhibitors have a unique mechanism of action which does not depend on the presence of insulin or the degree of insulin resistance and are suitable for coadministration with all classes of glucose-lowering agents.[6] Empagliflozin is an SGLT2 inhibitor that, in common with other agents in this class, reduces elevated blood glucose levels by inhibiting SGLT2, the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate, thereby increasing urinary glucose excretion.[6–8] In contrast, although the mechanism of action of metformin is not fully understood, its antihyperglycemic effects are thought to arise from the suppression of hepatic gluconeogenesis.[9] Given the complementary mechanisms of action of empagliflozin and metformin,[10] combination therapy with these 2 drugs has the potential to offer improved glucose control compared with that achieved with the individual agents. An oral, fixed-dose, single-pill combination of empagliflozin and metformin is also available for patients with T2DM, in a range of dose combinations to facilitate individualization of therapy.[11] This approach to therapy can reduce the pill burden for patients, leading to a simplified dosing regimen, which may assist adherence to therapy,[12] and has also been associated with improved patient satisfaction with therapy and reduced medical costs compared with “loose-dose” combinations in patients with T2DM.[13] This improvement in adherence to therapy may ultimately lead to enhanced glycemic control in T2DM.[12,14] Furthermore, growing evidence in support of initial combination therapy for patients with T2DM irrespective of the HbA_{1c} levels given in current treatment guidelines,[15] or the use of early intensification of therapy,[16,17] suggests an increasing role for fixed-dose combinations in the management of T2DM.

In 2016, the Food and Drug Administration (FDA) added a new indication for empagliflozin, to reduce the risk of major adverse cardiovascular (CV) events in patients with T2DM and CV disease (CVD)[18] following the publication of EMPA-REG OUTCOME (EMPAgliflozin Removal of Excess Glucose: Cardiovascular OUTCOME Event Trial in Type 2 Diabetes Mellitus Patients) (NCT01131676).[19] EMPA-REG OUTCOME was a randomized, double-blind trial that assessed the effect of empagliflozin (10 mg or 25 mg daily) vs placebo, added to standard care, on CV outcomes in 7020 patients with T2DM and existing CVD over a median follow-up of 3.1 years. Most (74%) patients in the empagliflozin group were also receiving background metformin. Treatment with empagliflozin was associated with a 14% relative risk reduction (RRR) in the composite outcome of CV death, nonfatal myocardial infarction, or nonfatal stroke; 38% RRR in CV death; and 32% RRR in death by any cause.[19] The relative risk of hospitalization for heart failure was also reduced by 35%.[19] The underlying mechanisms for the CV benefits of empagliflozin are not fully understood, but changes in arterial stiffness, alterations in cardiac oxygen demand, cardiorenal effects, reductions in albuminuria and uric acid, and the established effects of SGLT2 inhibitors (eg, lowering glucose,

weight and blood pressure [BP]) have been postulated.[19] The EMPA-REG OUTCOME trial also demonstrated microvascular benefits of empagliflozin in terms of slowing the progression of kidney disease (defined as incident or worsening nephropathy) vs placebo, when added to standard care.[20] An exploratory analysis of data from the EMPA-REG OUTCOME trial indicated that empagliflozin added to standard care is associated with both short- and long-term renal benefits, in terms of significant reductions in urinary albumin-to-creatinine ratio, in patients with T2DM and established CVD.[21] These findings are reflected in current guidance for diabetes management issued by the ADA[22] and the AACE/ACE,[4] which refer to possible benefits of empagliflozin on cardiac and renal outcomes.

In response to the findings of EMPA-REG OUTCOME,[19] the role of empagliflozin in the treatment of T2DM is likely to be evaluated in a range of treatment combinations and considered for use in earlier stages of T2DM. Because metformin[23–26] has also been associated with improvements in CV outcomes, combination therapy with empagliflozin might also confer CV benefits in patients with T2DM. In view of the potential benefits of dual therapy with empagliflozin and metformin in patients with T2DM, in addition to the frequent need for dual therapy,[4,5] this review will focus on the efficacy and safety of empagliflozin/metformin combination therapy.

Data sources and selection

A literature search using the PubMed database was conducted to identify articles on combined treatment of T2DM with empagliflozin and metformin. The search “empagliflozin AND metformin” yielded 127 English-language articles (January 9, 2018). The titles and/or abstracts were individually reviewed for relevance. Titles were excluded if they were review articles, meta-analyses, or pooled analyses (73 articles). Articles were also excluded if their primary focus was not on empagliflozin therapy in patients receiving metformin or reported preclinical research (35 articles). In total, 19 articles were selected for inclusion in the review.

Efficacy of the empagliflozin/metformin combination

The administration of empagliflozin plus metformin as initial combination therapy in patients with T2DM has been evaluated in a dedicated clinical trial,[27] in addition to several studies of empagliflozin administration as add-on to metformin, either alone[28–34] or in addition to other agents.[35–40] These trials are summarized below (Table 1). Because the use of single-pill (ie, fixed-dose) combination formulations may improve patient adherence to treatment by simplifying complex treatment regimens,[12,13] a fixed dose, single-pill combination of empagliflozin/metformin has been developed and is available in several dose combinations (5 mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, and 12.5 mg/1000 mg).[8] The FDA approval of the single-pill combination of empagliflozin and metformin was based on pharmacokinetic analyses in healthy subjects that compared the single-pill combination with coadministration of individual tablets of empagliflozin and metformin.[11] Evidence of the efficacy of the single-pill combination is available from studies in which the 2 agents were coadministered.

Table 1.

Summary of studies in patients with type 2 diabetes mellitus included in this review.

Study and citation	Clinical trial registration number	Phase	ackground therapy	Treatment groups (N[a])	Study length	Primary end point (exploratory end point for extension study)	Adjusted mean change in HbA_{1c} from baseline, %
Dedicated empagliflozin + metformin initial combination							
Initial combination Hadjadj et al[27]	**NCT01719003**	**3**	**None**	**Empagliflozin 12.5 mg + metformin 1000 mg twice daily (n = 169)**	**24 wk**	**Change in HbA_{1c} from baseline at week 24**	−2.08
				Empagliflozin 12.5 mg + metformin 500 twice daily (n = 165)			−1.93
				Empagliflozin 5 mg + metformin 1000 twice daily (n = 167)			**−2.07**
				Empagliflozin 5 mg + metformin 500 mg twice daily (n = 161)			−1.98
				Empagliflozin 25 mg once daily (n = 164)			−1.36
				Empagliflozin 10 mg once daily (n = 169)			−1.35
				Metformin 1000 mg twice daily (n = 164)			−1.75
				Metformin 500 mg twice daily (n = 168)			−1.18
				Open-label empagliflozin 12.5 mg twice daily + metformin 1000 mg twice daily (n = 53)			(Not reported)
Empagliflozin added to stable metformin							
Twice daily vs once daily	**NCT01649297**	**2b**	**Metformin**	**Empagliflozin 5 mg twice daily (n = 219)**	**16 wk**	**Change in HbA_{1c} fr**	−0.66

Study and citation	Clinical trial registration number	Phase	ackground therapy	Treatment groups (N[a])	Study length	Primary end point (exploratory end point for extension study)	Adjusted mean change in HbA_{1c} from baseline, %
Ross et al[28]						**om baseline at week 16**	
				Empagliflozin 10 mg once daily (n = 220)			−0.64
				Empagliflozin 12.5 mg twice daily (n = 219)			−0.83
				Empagliflozin 25 mg once daily (n = 218)			−0.72
				Placebo (n = 107)			−0.22
Dose ranging (study 1) Rosenstock et al[33]	**NCT00749190**	**2**	**Metformin**	**Empagliflozin 1 mg once daily (n = 71)**	**12 wk**	**Change in HbA_{1c} fr om baseline at week 12**	−0.09
				Empagliflozin 5 mg once daily (n = 71)			−0.23
				Empagliflozin 10 mg once daily (n = 71)			−0.56
				Empagliflozin 25 mg once daily (n = 70)			−0.55
				Empagliflozin 50 mg once daily (n = 70)			−0.49
				Placebo (n = 71)			+0.15
				Open-label sitagliptin 100 mg once daily (n = 71)			−0.45
Treatment-naïve (study 2)	**NCT00789035**	**2b**	**None**	**Empagliflozin 5 mg once daily (n = 81)**	**12 wk**	**Change in HbA_{1c} fr**	−0.4

Study and citation	Clinical trial registration number	Phase	ackground therapy	Treatment groups (N[a])	Study length	Primary end point (exploratory end point for extension study)	Adjusted mean change in HbA_{1c} from baseline, %
Ferrannini et al[32]						om baseline at week 12	
				Empagliflozin 10 mg once daily (n = 81)			−0.5
				Empagliflozin 25 mg once daily (n = 82)			−0.6
				Placebo (n = 82)			+0.1
				Open-label metformin (n = 80)			−0.7
Ferrannini et al[31] (open-label extension of study 1 and study 2)	NCT00881530		None or metformin	Open-label extension[b]			
				Patients receiving empagliflozin 10 mg (n = 272; 166 as add-on to metformin)	78 wk	(Included change from baseline of preceding study to week 78 of extension study in HbA_{1c})	−0.34
				Patients receiving empagliflozin 25 mg (n = 275; 166 as add-on to metformin)			−0.63
				Patients receiving metformin comparator (n = 56)			−0.56
				Patients receiving sitagliptin comparator (n = 56)			−0.40

Study and citation	Clinical trial registration number	Phase	ackground therapy	Treatment groups (N[a])	Study length	Primary end point (exploratory end point for extension study)	Adjusted mean change in HbA_{1c} from baseline, %
EMPA-REG MET Häring et al[30]	**NCT01159600**	**3**	**Metformin**	**Empagliflozin 10 mg once daily (n = 217)**	**24 wk**	**Change in HbA_{1c} from baseline at week 24**	−0.70
				Empagliflozin 25 mg once daily (n = 213)			−0.77
				Placebo (n = 207)			−0.13
Merker et al[34] (double-blind extension, EMPA-REG EXTEND MET)	NCT01289990		Metformin	Double-blind extension	≥52-wk double-blind extension	(Included change from baseline to week 76 in HbA_{1c})	
				Empagliflozin 10 mg once daily (n = 173)			−0.7
				Empagliflozin 25 mg once daily (n = 152)			−0.8
				Placebo (n = 138)			−0.1
EMPA-REG H2H-SU Ridderstråle et al[29]	NCT01167881	3	Metformin	Empagliflozin 25 mg once daily (n = 765)	104 wk	Change in HbA_{1c} from baseline at weeks 52 and 104	−0.73/−0.66
				Glimepiride 1-4 mg once daily (n = 780)			−0.66/−0.55 (At weeks 52/104)

Empagliflozin added to treatment backgrounds that could include metformin

Study and citation	Clinical trial registration number	Phase	ackground therapy	Treatment groups (N[a])	Study length	Primary end point (exploratory end point for extension study)	Adjusted mean change in HbA_{1c} from baseline, %
EMPA-REG METSU Häring et al[35]	NCT01159600	3	Metformin and sulfonylurea	Empagliflozin 10 mg once daily (n = 225)	24 wk	Change in HbA_{1c} from baseline at week 24	−0.82
				Empagliflozin 25 mg once daily (n = 216)			−0.77
				Placebo (n = 225)			−0.17
Häring et al[40] (double-blind extension, EMPA-REG EXTEND METSU)	NCT01289990		Metformin and sulfonylurea	Double-blind extension	≥52-wk double-blind extension	(Included change from baseline to week 76 in HbA_{1c})	
				Empagliflozin 10 mg once daily (n = 163)			−0.7
				Empagliflozin 25 mg once daily (n = 165)			−0.7
				Placebo (n = 145)			0.0
Empagliflozin and linagliptin add-on to metformin DeFronzo et al[36]	NCT01422876	3	Metformin	Empagliflozin 25 mg/linagliptin 5 mg (n = 134)	52 wk	Change in HbA_{1c} from baseline at week 24	−1.19
				Empagliflozin 10 mg/linagliptin 5 mg (n = 135)			−1.08
				Empagliflozin 25 mg (n = 140)			−0.62
				Empagliflozin 10 mg			−0.66

Study and citation	Clinical trial registration number	Phase	ackground therapy	Treatment groups (N[a])	Study length	Primary end point (exploratory end point for extension study)	Adjusted mean change in HbA_{1c} from baseline, %
				(n = 137)			
				Linagliptin 5 mg (n = 128)			−0.70
Linagliptin as add-on to empagliflozin and metformin Tinahones et al[39]	NCT01778049	3	Empagliflozin 10 mg and metformin	Linagliptin 5 mg + placebo (n = 126)	24 wk	Change in HbA_{1c} from baseline at week 24	−0.54
				Placebo (n = 128)			−0.20
			Empagliflozin 25 mg and metformin	Linagliptin 5 mg + placebo (n = 112)			−0.58
				Placebo (n = 112)			−0.09
Empagliflozin as add-on to linagliptin and metformin Søfteland et al[41]	NCT01734785	3	Linagliptin 5 mg and metformin	Empagliflozin 10 mg (n = 112)	24 wk	Change in HbA_{1c} from baseline at week 24	−0.66
				Empagliflozin 25 mg (n = 110)			−0.56
				Placebo (n = 110)			0.14
EMPA-REG PIO Kovacs et al[38]	NCT01289990	3	Pioglitazone ± metformin	Empagliflozin 10 mg once daily (n = 165)	24 wk	Change in HbA_{1c} from baseline at week 24	−0.59
				Empagliflozin 25 mg once daily (n = 168)			−0.72
				Placebo (n = 165)			−0.11
Kovacs et al[37] (double-	NCT01210001		Pioglitazone ± metfor	Double-blind extension	≥52-wk	(Included change	

Study and citation	Clinical trial registration number	Phase	ackground therapy	Treatment groups (N[a])	Study length	Primary end point (exploratory end point for extension study)	Adjusted mean change in HbA_{1c} from baseline, %
blind extension, EMPA-REG EXTEND PIO)			min		double-blind extension	from week 76 in baseline to HbA_{1c})	
					Empagliflozin 10 mg once daily (n = 106)		−0.61
					Empagliflozin 25 mg once daily (n = 106)		−0.70
					Placebo (n = 93)		−0.01
EMPA-REG BASAL Rosenstock et al[42]	NCT01011868	2b	Basal insulin ± metformin ± sulfonylurea	Empagliflozin 10 mg (n = 169)	78 wk	Change in HbA_{1c} from baseline at week 18	−0.6
				Empagliflozin 25 mg (n = 155)			−0.7
				Placebo (n = 170)			0.0
EMPA-REG MDI Rosenstock	NCT01306214	3	MDI insulin ± metformin	Empagliflozin 10 mg (n = 188)	52 wk	Change in HbA_{1c} from	−0.94

Study and citation	Clinical trial registration number	Phase	ackground therapy	Treatment groups (N[a])	Study length	Primary end point (exploratory end point for extension study)	Adjusted mean change in HbA_{1c} from baseline, %
et al[43]						baseline at week 18	
				Empagliflozin 25 mg (n = 189)			−1.02
				Placebo (n = 188)			−0.50

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Abbreviations: HbA_{1c}, glycated hemoglobin; MDI, multiple daily injections.

[a] Randomized and received treatment (these values might differ from the total randomized).

[b] Patients receiving empagliflozin 1, 5, or 50 mg or placebo were re-randomized to receive empagliflozin 10 or 25 mg—included patients are those who received treatment in both the initial and extension trials.

Dedicated Empagliflozin/Metformin Combination Therapy Study

In a phase 3 study, the efficacy and safety of initial combination therapy were evaluated vs the monotherapies in drug-naïve patients with HbA_{1c} >7.5% to ≤12.0%.[27] At week 24, adjusted mean reductions in HbA_{1c} from baseline were significantly greater for patients receiving empagliflozin/metformin twice daily than those receiving either empagliflozin once daily ($P < .001$) or metformin twice daily ($P < .01$). Significantly greater proportions of patients treated with combination therapy reached HbA_{1c} <7.0% at week 24 compared with patients who received either agent alone ($P < .05$ for all comparisons). The reduction in adjusted mean body weight from baseline to week 24 in the empagliflozin/metformin groups was greater than that achieved with either agent alone ($P < .001$ for all combination groups vs both metformin dose groups). In addition, empagliflozin/metformin significantly reduced both systolic BP (SBP) and diastolic BP (DBP) compared with metformin alone (adjusted mean differences in changes from baseline for the combination vs metformin alone: −2.8 to −4.0 mm Hg for SBP and −1.9 to −2.3 mm Hg for DBP; all comparisons $P < .05$), but not compared with empagliflozin alone. Overall, combination therapy was well tolerated, and the improvements in glycemic control vs monotherapies were achieved without significant increases in the risk of hypoglycemia.

Studies where Empagliflozin was Added to Stable Metformin

Several studies have evaluated the addition of empagliflozin to stable metformin therapy. In a phase 2b study, the efficacy and safety of empagliflozin were evaluated in patients with T2DM and HbA_{1c} ≥7.0 to ≤10.0% who were receiving metformin.[28] Patients receiving stable-dose metformin were randomized to receive add-on treatment with once-daily vs twice-daily empagliflozin. For the primary end point of change in HbA_{1c} from baseline at week 16, add-on treatment to metformin with empagliflozin twice daily was shown to be noninferior to once-daily empagliflozin. The adjusted mean difference in change in HbA_{1c} from baseline was −0.11% for empagliflozin 12.5 mg twice daily vs 25 mg once daily and −0.02% for empagliflozin 5 mg twice daily vs 10 mg once daily ($P < .001$ for noninferiority for both comparisons). The proportions of patients with HbA_{1c} ≥7.0% at baseline who achieved <7.0% at week 16 were similar for twice-daily and once-daily empagliflozin (49.0% and 47.6% for empagliflozin 12.5 mg twice daily and 25 mg once daily, respectively; $P < .001$ for each vs placebo; and 36.1% and 34.7% for 5 mg twice daily and 10 mg once daily, respectively; $P = .014$ and $P = .022$ for each vs placebo; and 25.0% for placebo). Changes in body weight from baseline at week 16 were significantly greater in all empagliflozin treatment groups (−3.20 to −2.71 kg) compared with placebo (−0.97 kg; $P < .001$ for superiority for all comparisons). Patients in all empagliflozin groups had significantly greater reductions in SBP (−4.2 to −2.5 mm Hg) compared with placebo (1.6 mm Hg; $P \leq .002$ for superiority for all comparisons). Reductions in DBP were also significantly greater for empagliflozin 12.5 mg twice daily, 25 mg once daily, and 5 mg twice daily (−2.6 to −1.6 mm Hg) than placebo (0.4 mm Hg; $P \leq .009$ for all comparisons), but the difference between empagliflozin 10 mg once daily (−0.8 mm Hg) and placebo was not statistically significant.

Similar findings were reported in a phase 2 dose-ranging study, which randomized 495 patients with T2DM and HbA_{1c} >7.0% to ≤10.0% on metformin to receive add-on empagliflozin (1, 5, 10, 25, or 50 mg once daily), placebo, or open-label sitagliptin (100 mg once daily) for 12 weeks (study 1).[33] All empagliflozin doses, with the exception of 1 mg, resulted in statistically significant reductions in mean HbA_{1c} from baseline at week 12 compared with placebo (empagliflozin doses 5 to 50 mg once daily, range −0.23% to −0.56% vs placebo +0.15%; $P \leq .001$ for all comparisons). The empagliflozin 10, 25, and 50 mg dose groups showed a similar mean HbA_{1c} reduction to sitagliptin (−0.49% to −0.56% vs −0.45%, respectively; $P \leq .0001$). Similarly, the proportions of patients with HbA_{1c} ≤7.0% at week 12 were significantly higher in the empagliflozin 10, 25, and 50 mg dose groups (35.7% to 38.0%; $P \leq .01$) and the sitagliptin group (33.8%; $P \leq .01$) than in the placebo group (15.5%). A trend toward a dose-dependent reduction in SBP and DBP for empagliflozin was observed, with the greatest decrease in the 25-mg group (−8.5 mm Hg SBP and −4.2 mm Hg DBP vs −2.2 mm Hg SBP and 1.0 mm Hg DBP for placebo). A 78-week open-label extension of this dose-ranging trial (study 1), plus another 12-week trial of empagliflozin monotherapy (5, 10, or 25 mg once daily) vs open-label metformin in treatment-naïve patients (no background metformin) (study 2),[32] provided further evidence for the efficacy of empagliflozin/metformin combination therapy.[31] In the open-label extension trial,[31] patients from study 1 and study 2 who had been randomized to receive empagliflozin 10 mg or 25 mg continued on the same dose, whereas patients who had been randomized to receive empagliflozin 1, 5, or 50 mg or placebo were re-randomized to either empagliflozin 10 or 25 mg for a further 78 weeks. A total of 332 patients received empagliflozin (10 or 25 mg) as add-on to metformin. Patients from the respective comparator arms (study 1, sitagliptin as add-on to metformin and study 2, metformin) continued open-label treatment for an additional 78 weeks. This extension study demonstrated that long-term treatment with empagliflozin 10 or 25 mg plus metformin was associated with sustained reductions in HbA_{1c}, body weight, and BP.

The efficacy and tolerability of empagliflozin as add-on to metformin in patients with T2DM was assessed in a 24-week phase 3 trial (NCT01131676), EMPA-REG MET (EMPAgliflozin Removal of Excess Glucose METformin).[30] Patients with HbA_{1c} levels of ≥7.0% to ≤10.0% while receiving metformin were randomized to once-daily empagliflozin (10 or 25 mg) or placebo. Both empagliflozin groups had significantly greater reductions in HbA_{1c} levels from baseline at week 24 compared with placebo (adjusted mean: −0.70% and −0.77% for empagliflozin 10 and 25 mg, respectively, vs −0.13% for placebo; $P < .001$ vs placebo for both). Similarly, more patients in the empagliflozin groups achieved HbA_{1c} <7.0% at week 24 compared with placebo (37.7% and 38.7% for 10 and 25 mg doses, respectively, vs 12.5% for placebo; $P < .001$ vs placebo for both). Adjusted mean changes in body weight were also significantly greater in the empagliflozin groups (−2.08 and −2.46 kg for 10 and 25 mg doses, respectively, vs −0.45 kg for placebo; $P < .001$ vs placebo for both). In addition, changes in SBP from baseline to week 24 were significantly greater for patients receiving empagliflozin 10 mg (−4.5 mm Hg) and 25 mg (−5.2 mm Hg) compared with placebo (−0.4 mm Hg; $P < .001$ vs placebo for both). The change in DBP from baseline to week 24 was also significantly greater than placebo (no change) for empagliflozin 10 mg (−2.0 mm Hg; $P = .006$) and 25 mg (−1.6 mm Hg; $P = .026$). Patients from this trial continued into the ≥52-week extension, which demonstrated that both empagliflozin doses added to metformin led to sustained and clinically meaningful reductions in HbA_{1c}, body weight, and SBP vs placebo.[34]

The efficacy and safety of empagliflozin as add-on to metformin in patients with T2DM have also been compared with glimepiride added to metformin in the phase 3 EMPA-REG H2H-SU (Head-to-Head Sulfonylurea) trial (NCT01167881).[29] Patients with HbA_{1c} concentrations of 7.0% to 10.0% despite receiving metformin were randomized to once-daily empagliflozin 25 mg or glimepiride 1 mg to 4 mg as add-on to metformin for 104 weeks. The primary efficacy end point was the change in HbA_{1c} from baseline to weeks 52 and 104. Empagliflozin was noninferior to glimepiride at both time points (adjusted mean change from baseline in HbA_{1c} at week 52, −0.66% for glimepiride and −0.73% for empagliflozin, $P < .0001$ for noninferiority; at week 104, −0.55% and −0.66%, respectively, $P < .0001$ for noninferiority and $P = .0153$ for superiority). The proportion of patients who achieved HbA_{1c} <7.0% was the same for glimepiride and empagliflozin at week 52 (39% in both groups) and similar at week 104 (31% and 34%, respectively; $P = .14$). In contrast, there were significant reductions in body weight for patients receiving empagliflozin, compared with an increase for patients receiving glimepiride at weeks 52 (−3.2 vs +1.6 kg, respectively; $P < .0001$) and 104 (−3.1 vs +1.3 kg, respectively; $P < .0001$). Reductions in SBP and DBP were also significantly greater for empagliflozin-treated vs glimepiride-treated patients (adjusted mean SBP changes, −3.6 and +2.2 mm Hg, respectively, at week 52, and −3.1 and +2.5 mm Hg, respectively, at week 104). Corresponding adjusted mean changes for DBP were −1.9 and +0.9 mm Hg, respectively, at week 52, and −1.8 and +0.9 mm Hg, respectively, at week 104; $P < .0001$ for all comparisons.

Studies where Empagliflozin was Added to Metformin Plus Other Agents

Sulfonylurea

The efficacy and tolerability of empagliflozin as add-on to metformin plus a sulfonylurea in patients with T2DM was investigated in the phase 3 EMPA-REG METSU trial (EMPAgliflozin Removal of

Excess Glucose METformin plus SUlfonylurea) (NCT01159600).[35] The patients with T2DM with HbA_{1c} ≥7.0% to ≤10.0% on metformin and a sulfonylurea were randomized to receive additional once-daily empagliflozin 10 mg (n = 225), 25 mg (n = 216), or placebo (n = 225). The adjusted mean changes in HbA_{1c} from baseline to week 24 were significantly greater for empagliflozin 10 mg (−0.82%) and 25 mg (−0.77%) compared with placebo (−0.17%; $P < .001$ for both comparisons). A greater proportion of patients achieved HbA_{1c} <7.0% at week 24 who were treated with empagliflozin 10 mg (26.3%) and 25 mg (32.2%) compared with placebo (9.3%; $P < .001$ for both doses). Adjusted mean changes in body weight were greater for patients treated with empagliflozin 10 mg (−2.16 kg) and 25 mg (−2.39 kg) compared with placebo (−0.39 kg; $P < .001$ for both doses). Reductions in SBP were greater in patients treated with empagliflozin 10 mg (−4.1 mm Hg) and 25 mg (−3.5 mm Hg) compared with placebo (−1.4 mm Hg; $P = .005$ and $P = .032$ vs placebo, respectively). Changes in DBP from baseline to week 24 were not significantly different for empagliflozin and placebo-treated patients. A total of 472 patients continued into the ≥52-week extension of this trial (NCT01289990) which demonstrated that the clinically meaningful reductions in HbA_{1c}, body weight, and SBP were sustained through week 76.[40]

Linagliptin

The efficacy and safety of combinations of empagliflozin and linagliptin as add-on to metformin treatment in patients with T2DM with HbA_{1c} >7 to ≤10.5% were assessed in a phase 3 trial (NCT01422876).[36] Patients were randomized and treated with empagliflozin 25 mg/linagliptin 5 mg (n = 134), empagliflozin 10 mg/linagliptin 5 mg (n = 135), empagliflozin 25 mg (n = 140), empagliflozin 10 mg (n = 137), or linagliptin 5 mg (n = 128) for 52 weeks. Adjusted mean reductions in HbA_{1c} from baseline to week 24 were greater for both empagliflozin 25 mg/linagliptin 5 mg (−1.19%) and empagliflozin 10 mg/linagliptin 5 mg (−1.08%) compared with monotherapy with empagliflozin (−0.62% [25 mg] and −0.66% [10 mg]) or linagliptin (−0.70%) as add-on to metformin ($P < .001$ for all comparisons). The HbA_{1c} reductions were sustained through week 52. A greater proportion of patients had HbA_{1c} <7.0% at week 52 who received empagliflozin 25 mg/linagliptin 5 mg (48.0%) and empagliflozin 10 mg/linagliptin 5 mg (51.6%) compared with empagliflozin monotherapy (25 mg [32.6%] and 10 mg [32.0%]) or linagliptin (28.6%) as add-on to metformin ($P \leq .02$ for all comparisons). Adjusted mean reductions in body weight from baseline to week 52 were greater for empagliflozin 25 mg/linagliptin 5 mg (−3.1 kg) and empagliflozin 10 mg/linagliptin 5 mg (−2.7 kg) compared with linagliptin monotherapy (−0.3 kg; $P < .001$ for both comparisons), but not compared with empagliflozin monotherapy (−2.8 kg [25 mg] and −2.9 kg [10 mg]). Similarly, adjusted mean changes in SBP from baseline to week 52 were greater for empagliflozin 25 mg/linagliptin 5 mg (−3.6 mm Hg) and empagliflozin 10 mg/linagliptin 5 mg (−2.8 mm Hg) compared with linagliptin monotherapy (+0.3 mm Hg; $P < .05$ for both comparisons), but similar to empagliflozin monotherapy (−2.8 mm Hg [25 mg] and −3.5 mm Hg [10 mg]). Diastolic BP was also reduced from baseline to week 52, but the difference between empagliflozin 25 mg/linagliptin 5 mg (−2.2 mm Hg) and empagliflozin 10 mg/linagliptin 5 mg (−2.2 mm Hg) compared with linagliptin monotherapy (−0.6 mm Hg) was only of borderline significance ($P = .05$) and was similar to empagliflozin monotherapy (−1.9 mm Hg [25 mg] and 1.8 mm Hg [10 mg]).

Two further studies assessed the efficacy and safety of linagliptin vs placebo as add-on to empagliflozin and metformin (NCT01778049).[39] Patients with HbA_{1c} ≥8.0% to ≤10.5% on stable-dose metformin were randomized and received open-label empagliflozin 10 mg (study 1, n = 352) or 25 mg (study 2, n = 354) as add-on therapy for 16 weeks. Patients with HbA_{1c} ≥7.0% and ≤10.5% were then randomized to add-on double-blind, double-dummy linagliptin 5 mg or placebo for 24 weeks (study 1, n = 254; study 2, n = 224). At week 24, adjusted mean reductions in HbA_{1c} from baseline were greater for patients who received empagliflozin 10 mg/metformin and linagliptin (−0.53%) compared with placebo (−0.21%; $P = .001$) and empagliflozin 25 mg/metformin and linagliptin (−0.58%) compared with placebo (−0.10%; $P < .001$). A greater proportion of patients had HbA_{1c} <7.0% at week 24 who received empagliflozin 10 mg/metformin and linagliptin (25.9%) compared with placebo (10.9%; $P < .001$) and empagliflozin 25 mg/metformin and linagliptin (36.0%) compared with placebo (15.0%; $P < .001$). Changes in body weight, SBP, and DBP were similar for patients receiving empagliflozin 10 mg/metformin and empagliflozin 25 mg/metformin and linagliptin compared with placebo.

Pioglitazone

The efficacy and safety of empaglflozin as add-on to pioglitazone ± metformin were assessed in the phase 3 EMPA-REG PIO trial (NCT01210001 [EMPAgliflozin Removal of Excess Glucose PIOglitazone]).[38] Patients with HbA_{1c} ≥7.0% to ≤10.0% on pioglitazone ± metformin were randomized and treated with empagliflozin 10 mg once daily (n = 165), empagliflozin 25 mg once daily (n = 168), or placebo (n = 165) for 24 weeks. Adjusted mean changes in HbA_{1c} from baseline to week 24 were greater for empagliflozin 10 mg (−0.6%) and 25 mg (−0.7%) compared with placebo (−0.1%; $P < .001$ for both comparisons). A greater proportion of patients had HbA_{1c} <7.0% at week 24 who received empagliflozin 10 mg (23.8%) and 25 mg (30.0%) compared with placebo (7.7%; $P < .001$ for both comparisons). Patients who received empagliflozin 10 and 25 mg had reductions in body weight from baseline to week 24 (−1.62 and −1.47 kg, respectively), whereas patients who received placebo had an increase (+0.34 kg; $P < .001$ for both comparisons). Reductions in SBP from baseline to week 24 were seen in patients who received empagliflozin 10 and 25 mg (−3.1 and −4.0 mm Hg, respectively), whereas patients who received placebo had a slight increase (+0.7 mm Hg; $P < .01$ for both comparisons). Similarly, patients who received empagliflozin 10 and 25 mg had reductions in DBP from baseline to week 24 (−1.5 and −2.2 mm Hg, respectively), whereas patients who received placebo had a slight increase (+0.3 mm Hg; $P \leq .01$ for both comparisons). Of the patients treated in the original study, 305 continued into the ≥52-week extension (NCT01289990), which demonstrated sustained reduction in HbA_{1c}, body weight, and BP compared with placebo through week 76.[37]

These studies provide further evidence that the addition of empagliflozin to metformin therapy provides clinically meaningful reductions in HbA_{1c}, SBP, and weight vs placebo.

Safety

Empagliflozin is generally well tolerated but is associated with an increased incidence of genital mycotic infection and, to a lesser degree, urinary tract infection (UTI).[44] There have been postmarketing reports of serious UTIs in patients receiving SGLT2 inhibitors, including rare but potentially fatal urosepsis and pyelonephritis.[45] In the studies reviewed, UTIs occurred in 1.9% to 14.3% of patients who received empagliflozin (10 or 25 mg) and metformin.[27–31,33,34] Overall, data from empagliflozin clinical trials have shown that the frequency of events consistent with UTI is similar for empagliflozin and placebo (approximately 15% for each) and these events were mild or moderate in intensity for approximately 97% of patients, leading to treatment discontinuation in a small proportion of patients (0.6% for both empagliflozin 10 mg and 25 mg vs 0.3% for placebo).[46] Adverse events consistent with genital infections were generally less frequent than UTIs in patients who received empagliflozin (10 or 25 mg) and metformin, and the frequency ranged from 0.0% to 12.0%.[27–31,33–40,41,43] Overall, data from empagliflozin clinical trials showed that the frequency of events consistent with genital infection was higher with empagliflozin than placebo (6.0% for both the 10 and 25 mg doses vs 1.6% for placebo).[46] Genital mycotic infections were more common in female patients, but treatment discontinuation due to genital infection was infrequent (0.6% for empagliflozin 10 mg and 0.5% for 25 mg vs ≤0.1% for placebo).[46]

Although metformin is generally well tolerated, without an associated risk of weight gain and a low risk of hypoglycemia, the most common adverse events relate to gastrointestinal (GI) intolerance.[47] Gradual dose escalation can minimize the GI effects of metformin,[8] and extended-release metformin has been shown to improve GI tolerability.[48] To facilitate individualization of therapy, the empagliflozin/metformin single pill is available in both an immediate-release form,[8] for twice-daily dosing, and extended-release form for once-daily dosing.[49]

The incidence of hypoglycemic adverse events was low (≤4.0%) for patients receiving empagliflozin/metformin in the studies reviewed.[27-31,33,34] However, the number of hypoglycemic adverse events was higher in patients receiving concomitant sulfonylurea (11.5% to 23.7%)[35,40] and multiple daily injections of insulin (51.1% to 57.7%)[43] with empagliflozin/metformin. In contrast, the inclusion of linagliptin[36,39,41] or pioglitazone[37,38] in addition to empagliflozin/metformin did not increase the risk of hypoglycemia (0.0% to 3.6%).

The prescribing information for metformin and the empagliflozin/metformin single-pill combination have boxed warnings for metformin-associated lactic acidosis.[8] However, this condition is rare.[50] The US labeling for metformin-containing products has been updated to indicate that such products may be used by patients with T2DM and mild impairment in kidney function, as well as some patients with moderate impairment. Specifically, the empagliflozin/metformin single-pill combination is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2 due to the metformin component.

Diabetic ketoacidosis (DKA) is a rare adverse event associated with SGLT2 inhibitor therapy.[51] It is possibly associated with patients with type 1 diabetes mellitus who are incorrectly diagnosed with T2DM and can occur in the absence of typical precipitating factors. In a recent review of the literature, the incidence of DKA associated with SGLT2 inhibitor therapy was shown to be less than 1/1000 in randomized controlled trials and 1.6/1000 person-years in cohort studies.[51] Although these

DKA episodes can be fatal, such cases represented 1.5% to 1.6% of all reported cases.[51,52] Further research is needed to better understand the risks and triggers for this adverse event.[51,52]

Empagliflozin/Metformin Combination Therapy in Clinical Practice

The efficacy and safety of the empagliflozin/metformin combination are well understood based on studies of these agents, both as individual components and in combination, that have shown this combination to be effective and well tolerated. The clinical data reviewed here show that the empagliflozin/metformin combination therapy has the potential to improve glycemic control and reduce body weight and BP compared with each agent individually and with a manageable risk profile. Furthermore, because of the potential benefits of empagliflozin on renal outcomes, the empagliflozin/metformin combination might also be suitable for patients at risk from declining kidney function, provided their eGFR is adequate to permit use of metformin. Because the risk of metformin-associated lactic acidosis increases with the severity of renal impairment, eGFR should be determined before starting treatment and monitored at least once a year (more frequently in patients with eGFR, <60 mL/min/1.73 m^2).[8] In addition, physicians should consider factors that might increase the risk of acute kidney injury, including hypovolemia, chronic renal insufficiency, chronic heart failure, and concomitant medications (eg, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs). Empagliflozin/metformin combination therapy might need to be temporarily discontinued if there is a risk of developing hypovolemia (eg, due to acute illness, fasting, GI illness, or excessive heat exposure), and patients should be monitored for signs of acute kidney injury.[8]

The findings of the EMPA-REG OUTCOME trial indicate that initial empagliflozin/metformin combination therapy could be a suitable choice for initial therapy in patients with T2DM and established CVD. It is possible that the CV benefits demonstrated in the EMPA-REG OUTCOME trial will encourage the earlier use of combinations involving metformin and empagliflozin in patients with established CVD. The ADA Standards of Care notes that empagliflozin can be added to therapy for patients who have long-standing, suboptimally controlled T2DM and established atherosclerotic CVD.[22] The individual components of the combination pill have positive outcome data on the reduction in CV death, and empagliflozin is indicated to reduce the risk of death in adults with T2DM and established CVD.

Conclusions

In conclusion, the single-pill combination of empagliflozin/metformin may present a useful treatment option for patients with T2DM who are inadequately controlled with metformin and need to progress to dual therapy. This option may be particularly suitable for patients who would benefit from the additional benefits of modest BP and weight reduction, as well as individuals with risk factors for CVD or declining renal function. The single-pill combination could also simplify therapy and potentially improve clinical outcomes compared with coadministration of individual tablets. Additional research is needed to further identify the advantages of early combination therapy in T2DM and to provide guidance on the selection of specific combination therapies to meet the individual needs of patients with T2DM.

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