REVIEW

Options for empagliflozin in combination therapy in type 2 diabetes mellitus

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Objective: To update clinicians with an overview of empagliflozin for the treatment of type 2 diabetes mellitus (T2DM), with focus on use in combination regimens.

Methods: Keyword searches were conducted in the Medline database to identify literature reporting clinical trials of at least 12 weeks' duration using empagliflozin treatment in patients with T2DM.

Results: When given as monotherapy or in combination therapy (as add-on or single-pill therapy) with metformin, pioglitazone, sulfonylurea, linagliptin, and insulin, empagliflozin produced clinically meaningful reductions in glycated hemoglobin levels, plasma glucose concentrations, bodyweight, and blood pressure. These changes were sustained during long-term treatment. In a dedicated cardiovascular event trial, empagliflozin on top of standard of care demonstrated a significant reduction in the risk of cardiovascular mortality and all-cause mortality. Across the clinical trials, empagliflozin combination therapies were well tolerated, and empagliflozin used alone was not associated with increased risk of hypoglycemia versus placebo. Indeed, the combination of empagliflozin and metformin had a significantly reduced rate of hypoglycemia compared with the combination of metformin and a sulfonylurea. On the other hand, empagliflozin treatment did have increased risk of genital infections compared with placebo. In clinical trials to date, diabetic ketoacidosis was not seen more frequently with empagliflozin than with placebo, but physicians should be alert to the possibility of this rare event.

Conclusion: Empagliflozin has the potential to make an important contribution to the treatment of patients with T2DM. In some patients, empagliflozin may be used as monotherapy, but it is most likely to be used in combination with other therapies. Given the reduced risk of mortality seen when empagliflozin was added to standard care in patients at high cardiovascular risk, as well as the lack of alternative options for patients at lower cardiovascular risk, empagliflozin may be added to ongoing regimens for a significant proportion of patients.

Keywords: combination therapy, DPP-4 inhibitors, empagliflozin, metformin, SGLT2 inhibitors, type 2 diabetes

Introduction

Selective sodium glucose co-transporter-2 (SGLT2) inhibitors target the kidney to reduce glucose reabsorption and promote urinary glucose excretion (ie, glucosuria), thereby lowering hyperglycemia in patients with type 2 diabetes mellitus (T2DM).[1,2] In fact, patients starting SGLT2 inhibitor therapy may need to be advised that they will test positive for urinary glucose, since many still perceive this as a sign of poor control. Urinary glucose excretion caused by SGLT2 inhibitor therapy also promotes modest reductions in blood pressure (BP) and bodyweight,[3] potential additional advantages for many patients with T2DM who are frequently overweight and hypertensive.

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A number of SGLT2 inhibitors are in clinical development, and three are currently approved in the United States (US): canagliflozin,[4] dapagliflozin,[5] and empagliflozin.[6] All three are administered as oral, once-daily regimens. Empagliflozin is the most recently available, but has subsequently become the first drug in the class to demonstrate cardiovascular safety.[7] Even more excitingly, it was the first antihyperglycemic drug ever to show cardiovascular risk reduction in a dedicated cardiovascular outcome study – although metformin and pioglitazone have previously been associated with reductions in cardiovascular risk as secondary end points – no drug has previously demonstrated reduced risk of clinical cardiovascular events in a prospective outcomes trial.[8,9]

The empagliflozin cardiovascular outcome study, known as EMPA-REG OUTCOME, was conducted in more than 7,000 T2DM patients at high cardiovascular risk.[7] Patients were already receiving the standard of care for lipids and BP as well as for blood glucose, with approximately 74% on metformin, and more than 50% on insulin. Since empagliflozin is available in two doses, patients were randomized to either of the empagliflozin doses (10 or 25 mg) or placebo, and the results with both empagliflozin doses were pooled. During the study, all cardiovascular outcome events and all deaths were prospectively adjudicated and the primary outcome was time to occurrence of major adverse cardiovascular events (MACE: death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The study was stopped after a median observation period of 3.1 years, when 772 primary events were recorded. Patients assigned empagliflozin had a 14% reduction in risk of a primary outcome event versus patients assigned placebo (hazard ratio, 0.86; 95% confidence interval [CI], 0.74–0.99; $P < 0.001$ for noninferiority and $P = 0.04$ for superiority). This was mainly driven by a 38% reduction in the risk of death from cardiovascular causes, while risks for nonfatal myocardial infarction or nonfatal stroke were not significantly different between the empagliflozin and placebo groups. The study investigators also noted that the reduction in risk of death occurred early in the trial and was continued throughout follow-up. There was no significant difference between the groups in the risk of hospitalization for angina, but the empagliflozin group had significantly lower risks of death from any cause and hospitalization for heart failure versus the placebo group.

While these results are exciting for empagliflozin and the landscape of T2DM treatment in general, it is worth remembering that the patients in this study are not representative of all T2DM patients. Notably, they were specifically recruited due to their high cardiovascular risk, and most had been diagnosed with T2DM for at least 5 years, probably reflecting the relatively high proportion on insulin. However, the addition of empagliflozin to ongoing stable regimens does reflect widespread use of empagliflozin in clinical practice.

As with all new drugs for T2DM, a number of Phase II and III clinical trials have been conducted for empagliflozin to test the drug in different groups of patients with T2DM, as well as in combination regimens with the other most common drug classes. A meta-analysis of empagliflozin studies was published in 2014,[10] but since then a number of studies have been reported in the literature, and a further meta-analysis is reportedly planned.[11] This narrative review provides a broad overview of empagliflozin, with an updated review of clinical trial data. The focus of the review is on empagliflozin in combination regimens, because empagliflozin – like dapagliflozin and canagliflozin – is expected to be most commonly used in combination with other glucose-lowering drugs. When discussing combination regimens for T2DM, single-pill and fixed-dose options inevitably come to mind, and single-pill tablets combining empagliflozin with other glucose-lowering agents have been developed.[12–14] However, in this review, studies reporting separate drugs used in combination as well as single-pill combinations are considered to allow physicians to first select an appropriate regimen, and then determine whether a single-pill combination is suitable (if one is available). After reviewing the empagliflozin studies, the key differentiators to consider when choosing an SGLT2 inhibitor are considered.

Review methods

For this narrative review, a Medline search was conducted in June 2015 for the keyword "empagliflozin" in any field. No restrictions were placed on language or on the start date for record entries. Abstracts were reviewed, and records reporting randomized, double-blind clinical trials of empagliflozin lasting 12 weeks or longer and conducted in patients with T2DM were selected. Of the 105 results retrieved that contained the key word "empagliflozin", 16 publications fulfilled the stated review criteria:[15–30] empagliflozin monotherapy studies (n=3); studies of empagliflozin as add-on therapy to stable regimens of other antidiabetes drugs (n=9); single-pill combination studies (n=2); and various regimens that included a mixture of monotherapy and combination therapy (n=2).

Empagliflozin monotherapy

Key efficacy and safety data from studies of empagliflozin monotherapy are presented in Tables 1 and 2.[15–17] In summary,

Table 1 Empagliflozin monotherapy studies: key efficacy data

Study	Study details	Regimen details	N	Treatment and dose (mg/d)	Efficacy parameters (change from baseline)[a]				
					HbA$_{1c}$ (%)	FPG (mg/dL)	FPG (mmol/L)	Body weight (kg)	SBP (mmHg)
Roden et al[15]	Phase III, 24 wk	Monotherapy	228	Pbo	0.08	11.7	0.65	−0.33	−0.3
			224	EMPA 10	−0.66	−19.5	−1.08	−2.26	−2.9
			224	EMPA 25	−0.78	−24.5	−1.36	−2.48	−3.7
			223	SITA 100	−0.66	−6.8	−0.38	0.18	0.5
			87	EMPA 25 (HbA$_{1c}$ >10.0%)	−3.70	−87.6	−4.86	−2.43	−4.0
Ferrannini et al[16]	Phase II, 12 wk	Monotherapy	82	Pbo	0.1	0.72	0.04	−0.75	Not reported
			81	EMPA 5	−0.4	−23.24	−1.29	−1.81	Not reported
			81	EMPA 10	−0.5	−29.00	−1.61	−2.33	Not reported
			82	EMPA 25	−0.6	−30.99	−1.72	−2.03	Not reported
			80	MET (O/L)	−0.7	−29.91	−1.66	−1.32	Not reported
Kadowaki et al[17]	Phase II, 12 wk	Monotherapy	109	Pbo	0.30	4.06	0.23	−0.9	−1.38
			110	EMPA 5	−0.42	−22.65	−1.26	−2.5	−2.85
			109	EMPA 10	−0.40	−25.28	−1.40	−2.6	−5.57
			109	EMPA 25	−0.65	−33.70	−1.87	−2.9	−4.60
			110	EMPA 50	−0.61	−32.54	−1.81	−3.1	−5.21

Notes: [a]Where publications reported FPG in mg/dL, these were converted to mmol/L using a factor of 0.0555, and vice versa. To convert HbA$_{1c}$ from % to mmol/mol, use the calculator from the NGSP (National Glycohemoglobin Standardization Program) available from http://www.ngsp.org/convert1.asp. MET dosing: 1000 mg/d for 4 weeks, thereafter increased to 1000 mg twice daily, or up to maximum tolerated dose, if needed.
Abbreviations: EMPA, empagliflozin; FPG, fasting plasma glucose; HbA$_{1c}$, glycated hemoglobin; MET, metformin; O/L, open label; Pbo, placebo; SBP, systolic blood pressure.

data from two 12-week empagliflozin dose-ranging studies and a 24-week Phase III study of the two approved empagliflozin doses (10 and 25 mg) demonstrated that empagliflozin monotherapy was associated with improvements in the concentration of glycated hemoglobin (HbA$_{1c}$), with mean reductions of up to –0.78% (Table 1).[15–17] These improvements were accompanied by reductions in fasting plasma glucose (FPG) as well as by modest reductions in bodyweight and systolic BP. The incidence of hypoglycemia and of urinary tract infection (UTI) was similar to that observed with placebo, but there was an increased risk of genital infection (Table 2). For example, in the 24-week Phase III study, none of the patients in the placebo group reported genital infections during the trial compared with 3% of the empagliflozin 10 mg group and 4% of the empagliflozin 25 mg group.[15]

Empagliflozin combination therapy with other oral glucose-lowering agents

As SGLT2 inhibitors have a novel and noninsulin-dependent mechanism of action, empagliflozin could potentially be used in combination with any class of glucose-lowering agents. To date, clinical trials evaluating empagliflozin in combination with metformin, pioglitazone, sulfonylurea, linagliptin, and insulin have been published: Tables 3 and 4 show key efficacy and safety data from these studies.[18–30]

Empagliflozin–metformin combination therapy

As metformin is the recommended first-line glucose-lowering agent in patients with T2DM,[31] it is an obvious choice for empagliflozin combination therapy. In a Phase II dose-ranging study, empagliflozin as add-on to metformin gave significant reductions in HbA$_{1c}$ versus placebo for all doses tested except the 1 mg dose.[18] In a Phase III placebo-controlled trial, after 24 weeks, treatment with empagliflozin (10 and 25 mg) plus metformin provided significant reductions in HbA$_{1c}$, bodyweight, and BP – both systolic and diastolic – versus placebo plus metformin (Table 3).[19] Very few patients had confirmed hypoglycemic adverse events (AEs; defined as plasma glucose ≤70 mg/dL and/or requiring assistance), but these were more common in the empagliflozin groups (0.5%, 1.8%, and 1.4% of placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively); none of the patients required assistance.[19] Events consistent with UTI occurred in a similar proportion of patients receiving placebo or empagliflozin, and events consistent with genital infection were more common in the empagliflozin groups (Table 4).[19]

In a 2-year, head-to-head study of empagliflozin (25 mg) versus glimepiride (1–4 mg once daily; mean dose 2.7 mg/d) in patients on stable metformin, patients treated with empagliflozin had greater improvements in glucose control.[20] At 52 weeks, mean reductions in HbA$_{1c}$ were –0.73% for the

Table 2 Empagliflozin monotherapy studies: key safety data

Study	Study details	Regimen details	N	Treatment and dose (mg/d)	Safety parameters (number and percentage of patients with a special interest adverse event)			
					Hypoglycemia, n (%)	Urinary tract infection, n (%) [males and females, n (%) if stated]	Genital infection, n (%) [males and females, n (%) if stated]	Volume depletion, n (%)
Roden et al[15]	Phase III, 24 wk	Monotherapy	228	Pbo	1 (<1)	12 (5) [M3/124 (2), F9/105 (9)]	0 [M0/124, F0/105]	Not reported
			224	EMPA 10	1 (<1)	15 (7) [M3/142 (2), F12/82 (15)]	7 (3) [M4/142 (3), F3/82 (4)]	Not reported
			224	EMPA 25	1 (<1)	12 (5) [M2/144 (1), F10/79 (13)]	9 (4) [M2/144 (1), F7/79 (9)]	Not reported
			223	SITA 100	1 (<1)	11 (5) [M4/141 (3), F7/82 (9)]	2 (1) [M1/141 (1), F1/82 (1)]	Not reported
			87	EMPA 25 (HbA$_{1c}$ >10.0%)	0	3 (3) [M2/64 (3), F1/23 (4)]	1 (1) [M1/64 (2), F0/23]	Not reported
Ferrannini et al[16]	Phase II, 12 wk	Monotherapy	82	Pbo	1 (1.2)	1 (1.2)	0	Not reported
			81	EMPA 5	0	2 (2.5)	0	Not reported
			81	EMPA 10	0	1 (1.2)	3 (3.7)	Not reported
			82	EMPA 25	0	1 (1.2)	2 (2.4)	Not reported
			80	MET (O/L)	1 (1.2)	2 (2.5)	0	Not reported
Kadowaki et al[17]	Phase II, 12 wk	Monotherapy	109	Pbo	0	1 (0.9) [M1/80 (1.3), F0/29]	0 [M0/80, F0/29]	1 (0.9)
			110	EMPA 5	0	0 [M0/84, F0/26]	1 (0.9) [M1/84 (1.2), F0/26]	0
			109	EMPA 10	0	1 (0.9) [M1/77 (1.3), F0/32]	1 (0.9) [M1/77 (1.3), F0/32]	1 (0.9)
			109	EMPA 25	1 (0.9)	1 (0.9) [M0/84, F1/25 (4.0)]	0 [M0/84, F0/25]	1 (0.9)
			110	EMPA 50	1 (0.9)	1 (0.9) [M0/85, F1/25 (4.0)]	1 (0.9) [M1/85 (1.2), F0/25]	0

Note: Number of male and female patients in the safety set was not available for all studies; in those cases only percentages are shown. MET dosing: 1000 mg/d for 4 weeks, thereafter increased to 1000 mg twice daily, or up to maximum tolerated dose, if needed.
Abbreviations: EMPA, empagliflozin; F, female; HbA$_{1c}$, glycated hemoglobin; M, male; MET, metformin; O/L, open label; Pbo, placebo.

empagliflozin 25 mg group and –0.66% for the glimepiride (1–4 mg group; at 104 weeks), mean reductions were –0.66% and –0.55% for the respective groups. Significant reductions in bodyweight were observed with empagliflozin versus an increase with glimepiride (Table 3).[20] Confirmed hypoglycemic AEs were more frequent in patients treated with glimepiride versus empagliflozin.[20] The proportion of patients with events consistent with UTI was similar in both groups; however, events consistent with genital infection occurred in a higher proportion of the empagliflozin group (Table 4).[20]

Lastly, a comparison of empagliflozin twice-daily (12.5 and 5 mg) and once-daily (25 and 10 mg) regimens, all versus

placebo, in patients on stable metformin revealed similar therapeutic effects and tolerability of both regimens, confirming the potential for empagliflozin to be given as single-pill combination with metformin immediate-release (Table 3).[29]

Empagliflozin–DPP-4 inhibitor combination therapy

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a commonly used second-line option for T2DM, having the advantages of well-established tolerability with no increased risk of hypoglycemia and being bodyweight-neutral.[31] Empagliflozin has been studied as a single-pill combination with linagliptin

Table 3 Empagliflozin combination therapy studies: key efficacy data

Study	Study details	Regimen details	N	Treatment and dose (mg/d)	Efficacy parameters (change from baseline)[a]				
					HbA$_{1c}$ (%)	FPG (mg/dL)	FPG (mmol/L)	Body weight (kg)	SBP (mmHg)
Add-on to stable therapy									
Rosenstock et al[18]	Phase II, 12 wk	Add-on to stable metformin: MET ≥1,500 mg/d or MTD	71	Pbo	0.15	5	0.28	-1.2	-2.23
			71	EMPA 1	-0.09	-2	-0.11	-1.6	-2.17
			71	EMPA 5	-0.23	-16	-0.89	-2.3	-3.03
			71	EMPA 10	-0.56	-22	-1.22	-2.7	-4.39
			70	EMPA 25	-0.55	-27	-1.50	-2.6	-8.51
			70	EMPA 50	-0.49	-28	-1.55	-2.9	-3.16
			71	O/L SITA	-0.45	-13	-0.72	-0.8	-1.79
Häring et al[19]	Phase III, 24 wk	Add-on to stable metformin: MET ≥1,500 mg/d or MTD	207	Pbo	-0.13	6.38	0.35	-0.45	-0.4
			217	EMPA 10	-0.70	-20.04	-1.11	-2.08	-4.5
			213	EMPA 25	-0.77	-22.28	-1.24	-2.46	-5.2
			69	O/L EMPA 25 (HbA$_{1c}$ >10.0%)	-3.23	-54.41	-3.02	-1.91	-2.4
Ridderstråle et al[20]	Phase III, 104 wk	Add-on to stable metformin: MET ≥1,500 mg/d or MTD	780	GLIM 1–4 (52 wk)	-0.66	-8.65	-0.48	1.6	2.2
				GLIM 1–4 (104 wk)	-0.55	-3.06	-0.17	1.3	2.5
			765	EMPA 25 (52 wk)	-0.73	-19.46	-1.08	-3.2	-3.6
				EMPA 25 (104 wk)	-0.66	-15.31	-0.85	-3.1	-3.1
Ross et al[29]	Phase II, 16 wk	Add-on to stable metformin: MET ≥1,500 mg/d	107	Pbo	-0.22	0	0	-0.97	1.6
			219	EMPA 12.5 mg twice daily	-0.83	-27.0	-1.5	-3.20	-4.1
			218	EMPA 25 mg once daily	-0.72	-23.4	-1.3	-2.89	-3.8
			219	EMPA 5 mg twice daily	-0.66	-21.6	-1.2	-2.93	-4.2
			220	EMPA 10 mg once daily	-0.64	-18.0	-1.0	-2.71	-2.5
Kovacs et al[21]	Phase III, 24 wk	Add-on to stable pioglitazone ± metformin: PIO ≥30 mg/d, MET ≥1,500 mg/d or MTD	165	Pbo	-0.11	6.47	0.36	0.34	0.7
			165	EMPA 10	-0.59	-17.0	-0.94	-1.62	-3.1
			168	EMPA 25	-0.72	-22.0	-1.22	-1.47	-4.0

(Continued)

Table 3 (*Continued*)

Study	Study details	Regimen details	N	Treatment and dose (mg/d)	Efficacy parameters (change from baseline)[a]				
					HbA$_{1c}$ (%)	FPG (mg/dL)	FPG (mmol/L)	Body weight (kg)	SBP (mmHg)
Häring et al[22]	Phase III, 24 wk	Add-on to stable metformin plus sulfonylurea: MET ≥1,500 mg/d or MTD, SU ≥half max labeled dose or MTD	225	Pbo	−0.17	5.58	0.31	−0.39	−1.4
			225	EMPA 10	−0.82	−23.24	−1.29	−2.16	−4.1
			216	EMPA 25	−0.77	−23.24	−1.29	−2.39	−3.5
			101	O/L EMPA 25 (HbA$_{1c}$ >10.0%)	−2.89	−54.41	−3.02	−1.76	−4.3
Rosenstock et al[23]	Phase III, 52 wk	Add-on to MDI of insulin ± metformin: INS titrated for treat-to-target (wk 19–40)			(Wk 18)	(Wk 18)	(Wk 18)	(Wk 52)	(Wk 52)
			188	Pbo	−0.50	−3.42	0.19	0.44	−2.9
			186	EMPA 10	−0.94	−17.66	−0.98	−1.95	−3.4
			189	EMPA 25	−1.02	−24.50	−1.36	−2.04	−3.8
Rosenstock et al[30]	Phase II, 78 wk	Add-on to basal insulin ± metformin ± sulfonylurea Insulin unchanged in wk 1–18			(Wk 18)	(Wk 18)	(Wk 18)	(Wk 18)	(Wk 18)
			170	Pbo	0	10.4	0.6	0	−0.3
			169	EMPA 10	−0.6	−17.9	−1.0	−1.7	−3.7
			155	EMPA 25	−0.7	−19.1	−1.1	−0.9	−3.3
Ferrannini et al[24]	78 wk	Extension of two Phase II studies[16,18] Monotherapy	106	EMPA 10	−0.34	−30	−1.66	−2.2	0.1
			109	EMPA 25	−0.47	−28	−1.55	−2.6	−1.7
			56	MET ≤1,000 mg twice daily or MTD	−0.56	−26	−1.44	−1.3	2.0
		Add-on to metformin	166	EMPA 10	−0.34	−21	−1.17	−3.1	−3.3
			166	EMPA 25	−0.63	−32	−1.78	−4.0	−3.0
			56	SITA 100	−0.40	−16	−0.89	−0.4	1.8
Single-pill combination therapy									
Lewin et al[25]	Phase III, 52 wk	Treatment-naïve			(Wk 24)	(Wk 24)	(Wk 24)	(Wk 24)	(Wk 52)
			134	EMPA 25/LINA 5	−1.08	−29.55	−1.64	−2.0	−2.5
			135	EMPA 10/LINA 5	−1.24	−28.21	−1.57	−2.7	−2.1
			133	EMPA 25	−0.95	−24.24	−1.34	−2.1	−2.1
			132	EMPA 10	−0.83	−22.39	−1.24	−2.3	−2.2
			133	LINA 5	−0.67	−5.92	−0.33	−0.8	−0.4
DeFronzo et al[26]	Phase III, 52 wk	Add-on to stable metformin: MET ≥1,500 mg/d or MTD			(Wk 24)	(Wk 24)	(Wk 24)	(Wk 24)	(Wk 52)
			134	EMPA 25/LINA 5	−1.19	−35.3	−1.96	−3.0	−3.6
			135	EMPA 10/LINA 5	−1.08	−32.2	−1.79	−2.6	−2.8
			140	EMPA 25	−0.62	−18.8	−1.04	−3.2	−2.8
			137	EMPA 10	−0.66	−20.8	−1.15	−2.5	−3.5
			128	LINA 5	−0.70	−13.1	−0.73	−0.7	0.3

Special populations	Phase	Population	N				(Wk 24)	(24-hour SBP via ABPM)
Tikkanen et al[27]	Phase III, 12 wk, adults with T2DM and hypertension	Treatment-naïve or on stable anti-diabetes treatment (oral or other)	271	Pbo	0.03 (Wk 24)	0.40 (Wk 24)	7.21 (Wk 24)	-0.18 (Wk 24)	0.48 (Wk 24)
			276	EMPA 10	-0.59	-0.92	-16.58	-1.68	-2.95
			276	EMPA 25	-0.62	-1.28	-23.06	-2.16	-3.68
Barnett et al[28]	Phase III, 52 wk, adults with T2DM and CKD	Add-on to stable anti-diabetes treatment (oral or other) Stage 2 CKD	95	Pbo	0.06	0.31	5.59	-0.33	0.7
			98	EMPA 10	-0.46	-0.77	-13.87	-1.76	-2.9
			97	EMPA 25	-0.63	-1.00	-18.02	-2.33	-4.5
		Stage 3 CKD	187	Pbo	0.05	0.6	10.81	-0.08	0.4
			187	EMPA 25	-0.37	-0.5	-9.00	-0.98	-3.9
		Stage 4 CKD	37	Pbo	-0.18	0.6	10.81	-0.1	1.2
			37	EMPA 25	0.04	-0.2	3.60	-1.4	-7.4

Notes: [a]Where publications reported FPG in mg/dL, these were converted to mmol/L using a factor of 0.0555, and vice versa. To convert HbA$_{1c}$ from percent to mmol/mol, use the calculator from the NGSP (National Glycohemoglobin Standardization Program) available from http://www.ngsp.org/convert1.asp. MET dosing: 1000 mg/d for 4 weeks, thereafter increased to 1000 mg twice daily, or up to maximum tolerated dose, if needed.
Abbreviations: ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease; EMPA, empagliflozin; FPG, fasting plasma glucose; GLIM, glimepiride; HbA$_{1c}$, glycated hemoglobin; INS, insulin; LINA, linagliptin; MDI, multiple daily injections; MET, metformin; MTD, maximum tolerated dose; O/L, open label; Pbo, placebo; PIO, pioglitazone; SBP, systolic blood pressure; SITA, sitagliptin; SU, sulfonylurea; T2DM, type 2 diabetes mellitus.

in treatment-naïve patients[25] and as an add-on to stable metformin;[26] both studies compared the single-pill combination with the individual components.

In the treatment-naïve patients, HbA$_{1c}$ reductions after 24 weeks were significantly greater for the empagliflozin 25 mg/linagliptin 5 mg single-pill formulation than linagliptin 5 mg ($P<0.001$) but not compared with empagliflozin 25 mg ($P=0.179$), and were significantly greater for the empagliflozin 10 mg/linagliptin 5 mg single-pill formulation compared with the individual components ($P<0.001$ for both).[25] The proportion of patients with a baseline HbA$_{1c}$ ≥7% who had reached HbA$_{1c}$ <7% at week 24 was greater for empagliflozin/linagliptin groups (55.4%, 62.3%, 41.5%, 38.8%, and 32.3% for empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg, respectively).[25] The proportion of patients reporting AEs was similar across treatment groups, and there were no confirmed hypoglycemic events requiring assistance.[25]

Similar results were reported in the add-on to stable metformin study; however, reductions in HbA$_{1c}$ at week 24 were significantly greater for both the empagliflozin/linagliptin doses compared with the individual components ($P<0.001$ for each).[26] In both of these studies, HbA$_{1c}$ reductions with empagliflozin/linagliptin were sustained at week 52.[25,26] Furthermore, both studies demonstrated that reductions in bodyweight from baseline to week 52 were significantly greater with empagliflozin/linagliptin compared with linagliptin, but not significantly different compared with the respective empagliflozin components.[25,26]

Empagliflozin–pioglitazone combination therapy

Pioglitazone is one of the options recommended by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guidelines for second-line therapy,[32] or as an alternative first-line therapy when metformin is not tolerated. It has the advantages of improving insulin resistance, low hypoglycemia risk, and generic options/costs; but is commonly associated with peripheral edema and weight gain, as well as less frequently with congestive heart failure and bone fractures,[33] and a possible increased risk of bladder cancer.[33,34] Since safety concerns were raised, use of pioglitazone has fallen to about half the previous levels, although this is still several million prescriptions per year in the US alone.[35]

In a 24-week study of empagliflozin as an add-on to pioglitazone (approximately 75% of patients also received

Table 4 Empagliflozin combination therapy studies: key safety data

Study	Study details	Regimen details	N	Treatment and dose (mg/d)	Safety parameters (Number and percentage of patients with a special interest adverse event)			
					Hypoglycemia, n (%)	Urinary tract infection, n (%) [males and females, n (%) if stated]	Genital infection, n (%) [males and females, n (%) if stated]	Volume depletion, n (%)
Add-on to stable therapy								
Rosenstock et al[18]	Phase II, 12 wk	Add-on to stable metformin: MET ≥1,500 mg/d or MTD	71	Pbo	0	2 (2.8)	0	Not reported
			71	EMPA 1	0	2 (2.8)	1 (1.4)	Not reported
			71	EMPA 5	3 (4.2)	2 (2.8)	4 (5.6)	Not reported
			71	EMPA 10	0	3 (4.2)	7 (9.9)	Not reported
			70	EMPA 25	0	4 (5.7)	0	Not reported
			70	EMPA 50	1 (1.4)	3 (4.3)	2 (2.9)	Not reported
			71	O/L SITA	2 (2.8)	3 (4.2)	2 (2.8)	Not reported
Häring et al[19]	Phase III, 24 wk	Add-on to stable metformin: MET ≥1,500 mg/d or MTD	207	Pbo	1 (0.5)	10 (4.9) [M3/116 (2.6), F7/91 (7.7)]	0 [M0/116, F0/91]	Not reported
			217	EMPA 10	4 (1.8)	11 (5.1) [M0/125, F11/92 (12.0)]	8 (3.7) [M1/125 (0.8), F7/92 (7.6)]	Not reported
			213	EMPA 25	3 (1.4)	12 (5.6) [M1/120 (0.8), F11/93 (11.8)]	10 (4.7) [M1/120 (0.8), F9/93 (9.7)]	Not reported
			69	O/L EMPA 25 (HbA$_{1c}$ >10.0%)	2 (2.9)	5 (7.2) [M1/41 (2.4), F4/28 (14.3)]	1 (1.4) [M0/41, F1/28 (3.6)]	Not reported
Ridderstråle et al[20]	Phase III, 104 wk	Add-on to stable metformin: MET ≥1,500 mg/d or MTD	780	GLIM 1–4 (52 wk)	Not reported	Not reported	Not reported	Not reported
				GLIM 1–4 (104 wk)	195 (25)	102 (13) [M21/421 (5), F81/359, (23)]	17 (2) [M5/421 (1), F12/359 (3)]	8 (1)
			765	EMPA 25 (52 wk)	Not reported	Not reported	Not reported	Not reported
				EMPA 25 (104 wk)	32 (4)	105 (14) [M31/432, (7), F74/333 (22)]	90 (12) [M41/432, (9), F49/333 (15)]	11 (1)
Ross et al[29]	Phase II, 16 wk	Add-on to stable metformin: MET ≥1,500 mg/d	107	Pbo	1 (0.9)	4 (3.7) [M1 (1.8), F3 (5.8)]	3 (2.8) [M1 (1.8), F2 (3.8)]	0
			219	EMPA 12.5 mg twice daily	0	13 (5.9) [M6 (4.8), F7 (7.5)]	9 (4.1) [M3 (2.4), F6 (6.5)]	1 (0.5)
			218	EMPA 25 mg once daily	1 (0.5)	12 (5.5) [M3 (2.5), F9 (9.0)]	9 (4.1) [M1 (0.8), F8 (8.0)]	0
			219	EMPA 5 mg twice daily	1 (0.5)	17 (7.8) [M4 (3.3), F13 (13.5)]	8 (3.7) [M3 (2.4), F5 (5.2)]	0
			220	EMPA 10 mg once daily	1 (0.5)	21 (9.5) [M5 (4.5), F16 (14.7)]	7 (3.2) [M2 (1.8), F5 (4.6)]	2 (0.9)

Study	Phase, duration	Population	N	Treatment				
Kovacs et al[21]	Phase III, 24 wk	Add-on to stable pioglitazone ± metformin: PIO ≥30 mg/d, MET ≥1,500 mg/d or MTD	165	Pbo	3 (1.8)	27 (16.4) [M6/73 (8.2), F21/92 (22.8)]	4 (2.4) [M1/73 (1.4), F3/92 (3.3)]	Not reported
			165	EMPA 10	2 (1.2)	28 (17.0) [M3/83 (3.6), F25/82 (30.5)]	14 (8.5) [M6/83 (7.2), F8/82 (9.8)]	Not reported
			168	EMPA 25	4 (2.4)	20 (11.9) [M2/85 (2.4), F18/83 (21.7)]	6 (3.6) [M1/85 (1.2), F5/83 (6.0)]	Not reported
Häring et al[22]	Phase III, 24 wk	Add-on to stable metformin plus sulfonylurea: MET ≥1,500 mg/d or MTD, SU ≥half max labeled dose or MTD	225	Pbo	19 (8.4)	18 (8.0) [M3/112 (2.7), F15/113 (13.3)]	2 (0.9) [M1/112 (0.9), F1/113 (0.9)]	Not reported
			225	EMPA 10	36 (16.1)	23 (10.3) [M3/113 (2.7), F20/112 (18.0)]	6 (2.7) [M1/113 (0.9), F5/112 (4.5)]	Not reported
			216	EMPA 25	25 (11.5)	18 (8.3) [M0/114, F18/102 (17.5)]	5 (2.3) [M1/114 (0.9), F4/102 (3.9)]	Not reported
			101	O/L EMPA 25 (HbA$_{1c}$ >10.0)	7 (6.9)	3 (3.0) [M0/54, F3/47 (6.4)]	2 (2.0) [M1/54 (1.9), F1/47 (2.1)]	Not reported
Rosenstock et al[23]	Phase III, 52 wk	Add-on to MDI of insulin ± metformin: INS titrated for treat-to-target (wk 19–40)	188	Pbo	109 (58.0)	29 (15.4) [M0/75, F29/113 (25.7)]	3 (1.6) [M1/75 (1.3), F2/113 (1.8)]	Not reported
			186	EMPA 10	95 (51.1)	29 (15.6) [M5/97 (5.2), F24/89 (27.0)]	8 (4.3) [M1/97 (1.0), F7/89 (7.9)]	Not reported
			189	EMPA 25	109 (57.7)	29 (15.3) [M3/84 (3.6), F26/105 (24.8)]	18 (9.5) [M7/84 (8.3), F11/105 (10.5)]	Not reported
Rosenstock et al[30]	Phase II, 78 wk	Add-on to basal insulin ± metformin ± sulfonylurea. Insulin unchanged in wk 1–18	170	(Wk 78) Pbo	60 (35%)	(Wk 78) 15 (9%) [M3/90 (3), F12/80 (15)]	(Wk 78) 3 (2%) [M0, F3/80 (4)]	Not reported
			169	EMPA 10	61 (36%)	25 (15%) [M5/93 (5), F20/76 (26)]	13 (8%) [M7/93 (8), F6/76 (8)]	Not reported
			155	EMPA 25	56 (36%)	18 (12%) [M7/93 (8), F11/62 (18)]	8 (5%) [M4/93 (4), F4/62 (7)]	Not reported
Ferrannini et al[24]	78 wk	Extension of two Phase II studies[16,18] Monotherapy	106	EMPA 10	1 (0.9)	4 (3.8) [M0/49, F4/57 (7.0)]	5 (4.7) [M2/49 (4.1), F3/57 (5.3)]	Not reported
			109	EMPA 25	2 (1.8)	7 (6.4) [M4/57 (7.0), F3/52 (5.8)]	6 (5.5) [M3/57 (5.3), F3/52 (5.8)]	Not reported
			56	MET ≤1,000 mg twice daily or MTD	2 (3.6)	2 (3.6) [M0/28, F2/28 (7.1)]	1 (1.8) [M0/28, F1/28 (3.6)]	Not reported
		Add-on to metformin	166	EMPA 10	3 (1.8)	15 (9.0) [M2/83 (2.4), F13/83 (15.7)]	5 (3.0) [M2/83 (2.4), F3/83 (3.6)]	Not reported
			166	EMPA 25	4 (2.4)	21 (12.7) [M3/88 (3.4), F18/78 (23.1)]	6 (3.6) [M3/88 (3.4), F3/78 (3.8)]	Not reported
			56	SITA 100	2 (3.6)	7 (12.5) [M3/29 (10.3), F4/27 (14.8)]	0 [M0/29, F0/27]	Not reported

(Continued)

Table 4 (*Continued*)

Study	Study details	Regimen details	N	Treatment and dose (mg/d)	Safety parameters (Number and percentage of patients with a special interest adverse event)			
					Hypoglycemia, n (%)	Urinary tract infection, n (%) [males and females, n (%) if stated]	Genital infection, n (%) [males and females, n (%) if stated]	Volume depletion, n (%)
Single-pill combination therapy								
Lewin et al[25]	Phase III, 52 wk	Treatment-naïve	136	EMPA 25/LINA 5	0	17 (12.5) [M4 (5.6), F13 (20.3)]	8 (5.9) [M5 (6.9), F3 (4.7)]	1 (0.7)
			136	EMPA 10/LINA 5	0	21 (15.4) [M5 (6.8), F16 (25.8)]	4 (2.9) [M1 (1.4), F3 (4.8)]	3 (2.2)
			135	EMPA 25	1 (0.7)	14 (10.4) [M3 (3.8), F11 (19.3)]	6 (4.4) [M1 (1.3), F5 (8.8)]	0
			135	EMPA 10	4 (3.0)	22 (16.3) [M6 (9.2), F16 (22.9)]	7 (5.2) [M2 (3.1), F5 (7.1)]	0
			135	LINA 5	1 (0.7)	14 (10.4) [M2 (2.7), F12 (20.0)]	4 (3.0) [M1 (1.3), F3 (5.0)]	0
DeFronzo et al[26]	Phase III, 52 wk	Add-on to stable metformin: MET ≥1,500 mg/d or MTD	134	EMPA 25/LINA 5	5 (3.6)	14 (10.2) [M2/72 (2.7), F12/62 (18.8)]	3 (2.2) [M2/72 (2.7), F1/62 (1.6)]	1 (0.7)
			135	EMPA 10/LINA 5	3 (2.2)	13 (9.6) [M2/83 (2.4), F11/52 (21.2)]	8 (5.9) [M2/83 (2.4), F6/52 (11.5)]	2 (1.5)
			140	EMPA 25	5 (3.5)	19 (13.5) [M2/65 (3.0), F17/75 (22.7)]	12 (8.5) [M3/65 (4.5), F9/75 (12.0)]	2 (1.4)
			137	EMPA 10	2 (1.4)	16 (11.4) [M3/78 (3.7), F13/59 (22.0)]	11 (7.9) [M5/78 (6.2), F6/59 (10.2)]	1 (0.7)
			128	LINA 5	3 (2.3)	20 (15.2) [M3/64 (4.5), F17/64 (26.2)]	3 (2.3) [M2/64 (3.0), F1/64 (1.5)]	4 (3.0)
Special populations								
Tikkanen et al[27]	Phase III, 12 wk, adults with T2DM and hypertension	Treatment-naïve or on stable anti-diabetes treatment (oral or other)	272	Pbo	13 (4.8)	10 (3.7) [M1 (0.6), F9 (8.7)]	1 (0.4) [M1 (0.6), F0]	1 (0.4)
			276	EMPA 10	18 (6.5)	11 (4.0) [M1 (0.6), F10 (9.5)]	14 (5.1) [M8 (4.7), F6 (5.7)]	1 (0.4)
			276	EMPA 25	17 (6.2)	13 (4.7) [M4 (2.6), F9 (7.4)]	15 (5.4) [M6 (3.9), F9 (7.4)]	0

Barnett et al[28]	Phase III, 52 wk, adults with T2DM and CKD	Add-on to stable anti-diabetes treatment (oral or other)	Stage 2 CKD	95	Pbo	23 (24.2)	15 (15.8) [M5/56 (8.9), F10/39 (25.6)]	6 (6.3) [M2/56 (3.6), F4/39 (10.3)]	1 (1.1)
				98	EMPA 10	26 (26.5)	14 (14.3) [M5/60 (8.3), F9/38 (23.7)]	7 (7.1) [M6/60 (10.0), F1/38 (2.6)]	1 (1.0)
				97	EMPA 25	22 (22.7)	9 (9.3) [M2/61 (3.3), F7/36 (19.4)]	5 (5.2) [M0/61, F5/36 (13.9)]	0
			Stage 3 CKD	187	Pbo	53 (28.3)	29 (15.5) [M4/106 (3.8), F25/81 (30.9)]	2 (1.1) [M1/106 (0.9), F1/81 (1.2)]	5 (2.7)
				187	EMPA 25	52 (27.8)	31 (16.6) [M6/107 (5.6), F25/80 (31.3)]	5 (2.7) [M2/107 (1.9), F3/80 (3.8)]	7 (3.7)
			Stage 4 CKD	37	Pbo	12 (32.4)	3 (8.1) [M0/19, F3/18 (16.7)]	0 [M0/19, F0/18]	2 (5.4)
				37	EMPA 25	14 (37.8)	7 (18.9) [M2/21 (9.5), F5/16 (31.3)]	1 (2.7) [M0/21, F1/16 (6.3)]	2 (5.4)

Note: Number of male and female patients in the safety set was not available for all studies; in those cases only percentages are shown. MET dosing: 1000 mg/d for 4 weeks, thereafter increased to 1000 mg twice daily, or up to maximum tolerated dose, if needed.

Abbreviations: CKD, chronic kidney disease; EMPA, empagliflozin; F, female; GLIM, glimepiride; HbA_{1c}, glycated hemoglobin; INS, insulin; LINA, linagliptin; M, male; MDI, multiple daily injections; MET, metformin; MTD, maximum tolerated dose; O/L, open label; Pbo, placebo; PIO, pioglitazone; SITA, sitagliptin; SU, sulfonylurea; T2DM, type 2 diabetes mellitus.

metformin), empagliflozin led to significant reductions in HbA_{1c} versus placebo, with reductions of –0.59% and –0.72% in the empagliflozin 10 and 25 mg groups versus –0.11% in the placebo group (Table 3).[21] Similarly significant reductions were observed in FPG, bodyweight, systolic BP, and diastolic BP for empagliflozin versus placebo groups.[21] The frequency of hypoglycemia events was low, and none required assistance.[21] The authors reported that the proportion of patients with AEs consistent with UTI was unexpectedly high in all treatment groups (12%–17%) and hypothesized it may have resulted from ascertainment bias at the study centers.[21] There was no increased frequency of AEs typically associated with pioglitazone, such as edema, heart failure, and bone fracture.[21]

Empagliflozin–sulfonylurea combination therapy

The efficacy of sulfonylureas in glucose-lowering is well known, as are their unwanted effects (weight gain, hypoglycemia risk). Although no longer in favor with many clinicians, sulfonylureas are still widely prescribed due to the associated extensive experience in terms of patient-years and their low cost.

Empagliflozin as add-on to sulfonylureas plus metformin in a 24-week study significantly improved glucose control, bodyweight, and systolic BP versus placebo (Table 3).[22] Mean reductions in HbA_{1c} were of a similar order to those seen when empagliflozin was added to metformin (–0.82% with empagliflozin 10 mg, –0.77% with empagliflozin 25 mg, and –0.17 with placebo). Hypoglycemia events were more common with empagliflozin than placebo (Table 4), although none of these events required assistance.[22] As sulfonylureas raise insulin levels irrespective of glucose concentration, which increases the risk of hypoglycemia, it may be expected that empagliflozin-sulfonylurea combination therapy would increase the risk of hypoglycemic events, which is reflected in empagliflozin labeling information.[6]

Empagliflozin combination therapy with injected agents

Many patients with advanced T2DM require treatment with insulin to maintain glycemic control, progressing from basal insulin to prandial dosing, and then to multiple daily injections.[31] Combining insulin with oral glucose-lowering agents can help to reduce daily insulin requirements,[31] which may reduce weight gain and the hypoglycemia risk associated with insulin therapy.

In a 78-week study, empagliflozin 10 or 25 mg in combination with basal insulin gave significant reductions in HbA_{1c} and FPG, and significant improvements in bodyweight and systolic BP (Table 3).[30] During the first 18 weeks, when the insulin dose was kept constant, HbA_{1c} levels were unchanged in the placebo group (mean change, 0%) compared with reductions of –0.6% and –0.7% in the empagliflozin 10 and 25 mg groups, respectively. After week 18, the insulin dose was adjusted at the investigator's discretion for any confirmed FPG >110 mg/dL; patients could also be on background metformin and/or a sulfonylurea, which remained unchanged. At week 78, although titration was not systematically required, mean insulin dose (a key secondary end point) was significantly reduced in both empagliflozin groups versus an increase with placebo (adjusted mean ± standard error [SE] changes from baseline: 5.5±1.6, −1.2±1.5, and −0.5±1.6 IU with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively; P=0.002 and P=0.009 for empagliflozin 10 and 25 mg, respectively, versus placebo). Rates of hypoglycemia were similar across all treatment groups (Table 4). Genital infections occurred more frequently in the empagliflozin groups, being reported in 2% of the placebo group (with no infections reported in males), 8% of the empagliflozin 10 mg group, and 5% of the empagliflozin 25 mg group (Table 4).

In a 52-week study of T2DM patients inadequately controlled on multiple daily injections of insulin (with or without metformin), empagliflozin 10 and 25 mg improved glucose control and reduced bodyweight versus placebo (Table 3).[23] Insulin dose was to remain stable during weeks 1–18, and, at week 18, mean reductions in HbA_{1c} were –0.94% with empagliflozin 10 mg, –1.02% with empagliflozin 25 mg, and –0.50% with placebo. Subsequently, insulin doses were to be adjusted to glucose targets in weeks 19–40 (preprandial glucose <5.5 mmol/L [<100 mg/dL]; postprandial glucose <7.8 mmol/L [<140 mg/dL]), and then stable in weeks 41–52. After 52 weeks, the secondary end point of mean insulin dose was reduced in both empagliflozin groups versus placebo (adjusted mean difference in insulin dose from baseline to week 52 versus placebo: –8.8 IU/d [95% CI, –14.8 to –2.8] for empagliflozin 10 mg, P=0.004; and –11.2 IU/d [95% CI, –17.2 to –5.2] for empagliflozin 25 mg, P<0.001).[23] The proportion of patients with confirmed hypoglycemia was similar across all treatment groups (Table 4). Severe hypoglycemia (requiring assistance) occurred in three patients each in the placebo and empagliflozin 10 mg groups, and also in one patient in the empagliflozin 25 mg group.[23] Urinary tract infections were reported in similar proportions of patients (Table 4), while genital infections were more common in both empagliflozin groups than in the placebo group (Table 4).

Besides insulin, glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are also commonly used injected glucose-lowering agents in T2DM. A combination of an SGLT2 inhibitor and a GLP-1 RA would be ideal in many respects, particularly regarding the potential combined weight loss. To date, no clinical trial results of SGLT2 inhibitors in combination with a GLP-1 RA have been published, although one such trial is known to be underway, assessing the combination of canagliflozin and liraglutide (ClinicalTrials.gov identifier: NCT02324842). Preliminary reports indicate that clinicians are trying the SGLT2 inhibitor/GLP-1 RA combination in clinical practice, and suggest additional weight loss is typically observed, although the study sizes have been fairly small.[36,37]

Achieving target HbA_{1c} <7.0%

According to current ADA guidelines, lowering HbA_{1c} to <7.0% is associated with reductions in microvascular complications of diabetes, and also macrovascular disease (if implemented promptly in newly-diagnosed patients); therefore, HbA_{1c} <7.0% is considered a reasonable target in many nonpregnant adults.[38] Consequently, studies often measure the percentage of patients with baseline HbA_{1c} ≥7.0% who have HbA_{1c} reduced to <7.0% at the end of treatment, even though comparison between studies is questionable, as a patient's baseline HbA_{1c} is a correlate of the likelihood of achieving the target HbA_{1c}.[39,40]

Table 5 summarizes these data for 24-week clinical trials evaluating empagliflozin versus placebo. More patients with baseline HbA_{1c} ≥7.0% (mean baseline HbA_{1c} approximately 7.9%) achieved HbA_{1c} <7.0% at week 24 with empagliflozin monotherapy (10 or 25 mg) than with placebo (35% and 44% versus 12%, respectively), while 28% of patients receiving sitagliptin 100 mg similarly achieved HbA_{1c} <7.0%.[15] A smaller proportion of patients with very poor glycemic control (mean baseline HbA_{1c} 11.5%) achieved HbA_{1c} <7.0% at week 24 with empagliflozin 25 mg (28%; open-label study). A similar trend was observed in studies of empagliflozin in combination with metformin, pioglitazone, and a sulfonylurea.[19,21,22,28] In the 104-week study of empagliflozin versus glimepiride, both as add-on to metformin, the proportion of patients achieving HbA_{1c} <7.0% at week 104 was similar between groups (empagliflozin 34%; glimepiride 31%).[20] However, the authors commented that significantly fewer patients received rescue therapy on empagliflozin (14.8%) than on glimepiride (23.7%; odds ratio, 0.530 [95% CI, 0.404, 0.696]; P<0.0001).[20]

Table 5 Patients with T2DM and $HbA_{1c} \geq 7.0\%$ at baseline who reached $HbA_{1c} < 7.0\%$ at end of treatment period: data from 24-week placebo-controlled empagliflozin trials

Study	Study duration (wk)	EMPA regimen and background therapy	N	Treatment and dose (mg/d)	Mean baseline HbA_{1c} (%)	Patients with $HbA_{1c} < 7.0\%$, n (%)[a]
Roden et al[15]	24	Monotherapy in treatment naïve patients	228	Pbo	7.91	25/208 (12)
			224	EMPA 10	7.87	72/204 (35)
			224	EMPA 25	7.86	88/202 (44)
			223	SITA 100	7.85	75/200 (38)
			87	O/L EMPA 25 ($HbA_{1c} > 10.0\%$)	11.50	24/87 (28)
Häring et al[19]	24	Add-on to stable metformin ($\geq$1,500 mg/d or MTD or MDLL)	207	Pbo	7.90	23 (12.5)
			217	EMPA 10	7.94	75 (37.7)
			213	EMPA 25	7.86	74 (38.7)
			69	O/L EMPA 25 ($HbA_{1c} > 10.0\%$)	11.07	6 (8.7)
Kovacs et al[21]	24	Add-on to stable pioglitazone ($\geq$30 mg/d) ± metformin ($\geq$1,500 mg/d or MTD)	165	Pbo	8.2	12 (7.7)
			165	EMPA 10	8.1	36 (23.8)
			168	EMPA 25	8.1	48 (30.0)
Häring et al[22]	24	Add-on to stable metformin ($\geq$1,500 mg/d or MTD) plus sulfonylurea ($\geq$half-max labeled dose or MTD)	225	Pbo	8.15	20 (9.3)
			225	EMPA 10	8.07	55 (26.3)
			216	EMPA 25	8.10	65 (32.2)
			101	O/L EMPA 25 ($HbA_{1c} > 10.0\%$)	11.18	9 (8.9)

Note: [a]Patients with $HbA_{1c} \geq 7.0\%$ at baseline who reached $HbA_{1c} < 7.0\%$ at end of treatment period.
Abbreviations: EMPA, empagliflozin; HbA_{1c}, glycated hemoglobin; MDLL, maximum dose per local label; MTD, maximum tolerated dose; O/L, open label; Pbo, placebo; SITA, sitagliptin; T2DM, type 2 diabetes mellitus.

Discussion: a patient-centered approach – how could it work in practice?

Overweight and obese patients

The impact of medications on bodyweight is a key consideration in T2DM.[41] While the impact of weight loss on the risk of cardiovascular events has not been definitively proven, its importance is well established for other factors, such as mobility or quality of life.[42] In empagliflozin clinical studies, modest reductions in bodyweight of approximately 2–5 kg (5–10 pounds) were reported. Furthermore, imaging studies confirmed that 90% of the weight loss observed with empagliflozin was due to decreased fat mass, with reduction in abdominal visceral adipose tissue and abdominal subcutaneous adipose tissue.[20] This is comparable to the weight loss observed with metformin or GLP-1 RAs of approximately 3 kg (6 pounds).[43,44] As already mentioned, DPP-4 inhibitors are weight-neutral, while sulfonylureas, insulin, and thiazolidinediones are associated with weight gain.

As effective therapies for weight loss are limited, clinicians recognize the value of additional weight loss from glucose-lowering agents. For example, although off-label, metformin has been used for weight loss,[45] and the GLP-1 RA, liraglutide, was approved for use in chronic

weight management.[46,47] For obese patients motivated to lose weight, the combination of metformin, GLP-1 RA, and SGLT2 inhibitor is worth considering. In addition, as mentioned, adding empagliflozin in patients with T2DM who require insulin may help to offset insulin-associated weight gain.

Patients with renal impairment

Renal impairment is common in patients with T2DM.[48] Patients with advanced renal impairment are a difficult-to-treat population due to the presence of associated comorbidities, reduced drug elimination, and an increased risk of hypoglycemia.[49]

Empagliflozin is contraindicated in patients with severe or end-stage renal disease (and would not be expected to have efficacy in these groups), but has been studied in patients with chronic kidney disease (CKD).[28] In a 52-week study of patients with T2DM and stage 2, 3, or 4 CKD (defined as estimated glomerular filtration rate [eGFR] $\geq$60 to <90, $\geq$30 to <60, or $\geq$15 to <30mL/min/1.73 m² for stage 2, 3, and 4, respectively), empagliflozin treatment resulted in significant reductions in HbA_{1c} versus placebo, accompanied by improvements in weight and BP.[28] Empagliflozin was well tolerated; however, each CKD group had small decreases

in eGFR, which returned to baseline levels after the end of treatment (during a 3-week follow-up period).[28]

Hypoglycemia

Where glucose lowering is needed without risking hypoglycemia, SGLT2 inhibitors have greater glucose-reducing effects than DPP-4 inhibitors when considering a second-line add-on to metformin.[50] They can also be used in combination with DPP-4 inhibitors, if a three-drug combination is required.[26] Similarly, a combination of metformin, pioglitazone, and an SGLT2 inhibitor would not be expected to increase the risk of hypoglycemia.[21] For patients receiving insulin secretagogues (eg, sulfonylureas) or insulin, a dose reduction should be considered when adding empagliflozin to reduce hypoglycemia risk.[6] In my experience, this is especially important for patients whose HbA_{1c} levels are closer to target.

Hypertension

The majority of patients with T2DM have hypertension,[51] and the ADA recommends a BP goal of <140/90 mmHg for patients with diabetes, noting that lower targets may be appropriate in some patients.[52] Lifestyle advice, including dietary changes and increased activity, is recommended for all patients with BP >120/80 mmHg, with pharmacotherapy for those with BP >140/90 mmHg. Typically, multiple drug therapy will be required, and should include an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker.[52] An SGLT2 inhibitor would not be chosen specifically to reduce BP or to replace an antihypertensive drug, but the magnitude of antihypertensive effects with empagliflozin might enable patients to achieve BP goals or to reduce their dose of diuretic.

Empagliflozin was studied in patients with T2DM and hypertension (mean seated systolic BP 130–159 mmHg and diastolic BP 80–99 mmHg).[27] After 12 weeks, empagliflozin 10 and 25 mg significantly reduced mean 24-hour systolic BP, measured via ambulatory BP monitoring (ABPM), versus placebo (adjusted mean difference versus placebo in change from baseline in mean 24-hour systolic BP [ABPM] was –3.44 mmHg [95% CI, –4.78 to –2.09] with 10 mg empagliflozin and –4.16 mmHg [95% CI, –5.50 to –2.83] with 25 mg empagliflozin; $P<0.001$ for both).[27] One patient on placebo and one patient on empagliflozin 10 mg reported events consistent with volume depletion.[27] The authors also commented that the risk of hypotension in normotensive patients treated with empagliflozin was low.[27] This is supported by a meta-analysis of SGLT2 inhibitor clinical trials, in which no significant increase in orthostatic hypotension was detected.[53] However, the potential for volume depletion

events should be considered in patients at risk (eg, elderly, receiving diuretics, low systolic BP) before starting therapy with any SGLT2 inhibitor.[4–6]

A further clinical trial is ongoing to study the effect of empagliflozin in African-American patients with T2DM and hypertension (ClinicalTrials.gov identifier: NCT02182830), as this is a patient group at a high risk of macrovascular and microvascular complications in T2DM.[54]

Oral regimens and adherence

An oral, once-daily treatment is preferable for most patients,[55,56] consistent with the recommended dosing schedule for currently available SGLT2 inhibitors. Where an SGLT2 inhibitor is used in combination with another oral glucose-lowering agent, a single-pill combination might be considered to reduce pill burden. For empagliflozin, a single-pill combination with the DPP-4 inhibitor linagliptin is approved by the US Food and Drug Administration (FDA)[12] and under regulatory review by the European Medicines Agency (EMA), while a single-pill combination with metformin is approved by both the EMA and FDA.[13,14] In practice, unless a patient expresses anxiety about increasing the number of pills, an appropriate regimen can be chosen first, and a single-pill combination considered thereafter (if one is available), rather than single-pill combinations driving the treatment choice.

Treatment safety

As glucose-lowering drugs will be taken for many years, long-term safety is a primary concern. The long-term cardiovascular safety of empagliflozin was investigated in the EMPA-REG OUTCOME study – as discussed in the Introduction. This was designed first as a safety trial with the option to test for superiority provided all safety end points were met.[7] The study showed that empagliflozin did not increase the risk of major cardiovascular events, and in fact reduced the risk. Given the large number of patients in the study (7,020 were randomized and treated, and 97% completed the study), a large amount of information on AEs was also collected for other safety analyses. Notably, the empagliflozin and placebo groups had similar rates of bone fractures, providing reassurance regarding this potential AE with empagliflozin, while it was recently added as a warning or precaution to the US label of canagliflozin.[57] In addition, the empagliflozin and placebo groups had similar rates of diabetic ketoacidosis,[7] a recently identified potential safety issue with SGLT2 inhibitor therapy, following a number of reports in clinical practice.[58,59] Diabetic ketoacidosis is usually accompanied by high blood glucose levels, although

blood glucose levels were only moderately increased (ie, euglycemic ketoacidosis) in some of these safety case reports, and one case of euglycemic ketoacidosis in a patient on empagliflozin has been reported in the literature.[60] The pathophysiological cause of this AE is not yet fully elucidated, but possible mechanisms have been suggested.[61] While the results seen in EMPA-REG OUTCOME appear to show no increased risk, physicians and patients should pay close attention to possible symptoms.[58]

Many physicians have been wary of using SGLT2 inhibitors because of the risk of UTI or genital infections. Based on my observations in clinical practice, genital infections are unlikely to be a problem in circumcised men. In women, higher genital infection rates have been reported in clinical trials (Tables 2 and 4), and physicians should be aware that some women seen in routine clinical practice will have recurrent infections and will need to discontinue SGLT2 inhibitor therapy. However, other physicians are happy to use SGLT2 inhibitors, given their overall efficacy and safety profile – including the benefit of weight loss. The relationship between SGLT2 inhibitors and risk of UTI is less clear than for genital infections:[62] some studies with empagliflozin showed no increased risk, while others reported increased UTI frequency with empagliflozin versus placebo/comparator. The very large EMPA-REG OUTCOME trial showed no difference between placebo and empagliflozin in urinary tract infection rates.[7] However, a pooled analysis of five empagliflozin studies noted an increase in UTI with empagliflozin, and also that UTI was more likely in patients with a history of chronic or recurrent UTI.[6]

Renal safety and changes in lipid profiles also need consideration. For lipids, monitoring LDL-C and treating with standard of care is recommended, but the underlying cause of changes observed during SGLT2 inhibitor therapy is unexplained. Nevertheless, the long-term cardiovascular safety demonstrated by empagliflozin is encouraging, and the increase in HDL-C seen alongside LDL-C changes has kept the LDL-to-HDL ratio unchanged. Observed eGFR changes with empagliflozin are also currently unexplained, but appear reversible on stopping treatment, and it has been speculated that preglomerular vasoconstriction of hyperfiltering glomeruli may be involved.[28] Regarding safety in patients with renal impairment, when empagliflozin was studied in patients with stage 2 and 3 CKD over 52 weeks, it was well tolerated, although an increased risk of AEs such as volume depletion events and UTI in stage 4 CKD was acknowledged.[28]

Choosing an SGLT2 inhibitor

Although this review has focused on empagliflozin, canagliflozin and dapagliflozin are also available in the US and in other parts of the world. Therefore, the question arises of what the potential differences between empagliflozin and other gliflozins are. Currently, there are no head-to-head comparisons of SGLT2 inhibitors: the only direct comparisons are based on pharmacodynamic data in healthy individuals,[63] or data from preclinical studies.[64] Although all three SGLT2 inhibitors became available relatively recently, all have extensive clinical development programs, giving a large number of patient-years of experience. However, empagliflozin is the only drug in the class with demonstrated cardiovascular benefit – although cardiovascular outcome trials are underway for dapagliflozin and canagliflozin, these are not expected to complete for several years.[65] Furthermore, the EMPA-REG OUTCOME investigators have been careful to point out that their study recruited a selected group of patients with higher than average cardiovascular risk.[7] Therefore, how far the results can be generalized to patients at lower risk is not clear, but it must be borne in mind that no other glucose-lowering agent has been tested and demonstrated benefit in this group. While such studies might be anticipated, the results would likely not be available for many years; in the meantime, empagliflozin would appear to be the preferred agent when starting an SGLT2 inhibitor is being considered.

The further key difference between the three agents is in the level of renal impairment allowed by US prescribing information (Table 6).[4–6] While some experts argue that lack of an effect with dapagliflozin in patients with CKD likely results from underpowered studies,[66] in practice, the precautions advised by the FDA for patients with moderate renal impairment will make a difference as to which agent

Table 6 Dosage and administration of SGLT2 inhibitors according to renal function (eGFR)

Canagliflozin[4]	Assess renal function before initiating canagliflozin therapy
	Canagliflozin is limited to 100 mg once daily in patients who have an eGFR of 45 to <60 mL/min/1.73 m²
	Do not initiate canagliflozin if eGFR is <45 mL/min/1.73 m²
	Discontinue canagliflozin if eGFR falls persistently below 45 mL/min/1.73 m²
Dapagliflozin[5]	Assess renal function before initiating dapagliflozin therapy
	Do not initiate if eGFR <60 mL/min/1.73 m²
	Discontinue dapagliflozin if eGFR falls persistently below 60 mL/min/1.73 m²
Empagliflozin[6]	Assess renal function before initiating empagliflozin therapy
	Do not initiate empagliflozin if eGFR is <45 mL/min/1.73 m²
	Discontinue empagliflozin if eGFR falls persistently below 45 mL/min/1.73 m²

Abbreviation: eGFR, estimated glomerular filtration rate.

is chosen. If FDA prescribing information is followed, dapagliflozin would need to be discontinued at higher eGFR levels (ie, eGFR persistently <60 mL/min/1.73 m²),[5] while canagliflozin would require dose reduction at higher eGFR levels than empagliflozin (canagliflozin is limited to 100 mg once daily with eGFR of 45 to <60 mL/min/1.73 m²).[4]

Conclusion

The empagliflozin clinical trials program was designed to test empagliflozin in various combination regimens, and in a range of T2DM patient subpopulations: the resulting data have shown that empagliflozin is worth considering as an addition to the treatment regimen of many patients with T2DM, provided they have sufficient renal function. Empagliflozin has the potential to make an important contribution to the treatment of T2DM in combination therapies in patients with poor glucose control, with the added advantages of body weight loss and BP reduction.

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Disclosure

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