Empagliflozin/linagliptin single-tablet combination: first-in-class treatment option

V. Woo

SUMMARY

Background: The availability of a dual sodium glucose co-transporter 2/dipeptidyl peptidase-4 inhibitor combination in a single-tablet combination (STC) represents a new therapeutic option for patients with type 2 diabetes. Empagliflozin/linagliptin STC has been recently approved by the US Food and Drug Administration for the treatment of type 2 diabetes mellitus (T2DM). Aim: The aim of this study was to describe the latest clinical evidence on the efficacy and safety profiles of empagliflozin/linagliptin STCs in comparison with the individual components. Results: Empagliflozin/linagliptin STC given as initial therapy or on metformin background lowered mean glycated haemoglobin (HbA1c) by approximately 1.1% (mean baseline HbA1c, 8.0%). Furthermore, the STC reduced mean body weight by 2.0–3.0 kg from baseline. With the STC treatment, no confirmed incidents of hypoglycaemia were reported in drug-naive patients; in patients taking metformin hypoglycaemia occurred at low rates which were comparable with monotherapy. Use of STCs in the treatment of T2DM can simplify drug dosing regimen, reduce pill burden and increase treatment adherence. Empagliflozin/linagliptin STC is a combination that offers potential additional benefits such as body weight loss and moderate reductions in blood pressure, without increasing risk of hypoglycaemia. Conclusion: Empagliflozin/linagliptin STC appears to be a rational choice for a wide range of patients in need of multiple agents for controlling hyperglycaemia. The STC should be particularly useful in patients in whom hypoglycaemia, weight gain and treatment adherence are of concern.

Introduction

The standard pharmacotherapy for management of type 2 diabetes mellitus (T2DM) involves initiation with monotherapy (usually metformin) unless there are contraindications or intolerance, followed by sequential addition of other single agents, when target glycaemic control is not achieved or maintained for 3 months (1,2). Combination therapy as first line is a treatment option when glycated haemoglobin (HbA1c) at entry is well above target. The joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends initial combination therapy in patients with baseline HbA1c ≥ 9% and who are less likely to achieve treatment goals on monotherapy (1,2). The American Association of Clinical Endocrinologists and American College of Endocrinology’s (AACE/ACE) comprehensive diabetes management algorithm recommends initial dual therapy when HbA1c is ≥ 7.5%, and combination therapy with insulin (symptomatic hyperglycaemia) or without insulin (asymptomatic hyperglycaemia) when HbA1c is ≥ 9% (3). Initial combination therapy potentially offers advantages such as rapid reduction in HbA1c, avoidance of extended periods of hyperglycaemic state and harmful effects of glucotoxicity, and avoidance of maximal doses of monotherapy which may augment adverse effects associated with that monotherapy (4,5). The strategy also allows for implementation of a multi-pronged approach for control of hyperglycaemia by...
use of drugs with complementary mechanisms of action. Combination therapy is aimed at aggressive attainment and maintenance of glycaemic targets. However, aggressive treatment to achieve glycaemic control may not always be suitable depending on the patient and disease characteristics, and therefore, glycaemic targets must be individualised according to the needs of each patient. When the need for combination therapy has been established, drugs with complementary mechanisms of action should be employed for optimum glycaemic control (3).

A common caveat is that combining two or more antihyperglycaemic agents (AHAs) can increase the risk of hypoglycaemia and/or weight gain, particularly if thiazolidinediones, sulfonylureas and/or insulin are used (6,7). The two relatively recent classes of AHAs – dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium glucose co-transporter 2 (SGLT2) inhibitors – as monotherapies are associated with low incidence of hypoglycaemia and weight neutrality (DPP-4 inhibitors) or weight loss (SGLT2 inhibitors), and thus can be useful options in a combination. DPP-4 inhibitors are rapidly replacing sulfonylureas as a second-line treatment (8). Both DPP-4 inhibitors and SGLT2 inhibitors are given orally allowing for administration as loose-pill or single-tablet combination (STC). Benefits of STCs over loose-pill combinations in the treatment of T2DM may include improved patient adherence, patient satisfaction and lower overall healthcare costs (9).

Empagliflozin/linagliptin is the first-in-class dual inhibitor combination therapy (SGLT2/DPP-4), recently approved by the US Food and Drug Administration (FDA) (10). The STC is available in two dosage strengths: empagliflozin 10 mg/linagliptin 5 mg and empagliflozin 25 mg/linagliptin 5 mg. According to public information, a new drug application for approval in the USA has been filed for the dapagliflozin/saxagliptin STC (11).

Results of three randomised controlled trials (RCTs) investigating the efficacy and safety of SGLT2/DPP-4 inhibitor combinations have been reported (12–14). This review summarises these results and compares the profiles of the SGLT2/DPP-4 inhibitor combinations. Characteristics of linagliptin and empagliflozin as individual drugs are also discussed.

**Methods**

A non-systematic search was conducted on PubMed using the following terms alone or in combination: linagliptin, empagliflozin, dapagliflozin, saxagliptin, combination and type 2 diabetes. Relevant references were identified after screening the titles. Abstract databases for the ADA and EASD spanning the years 2012–2014 were searched using the keywords: linagliptin, empagliflozin, dapagliflozin and saxagliptin. Relevant ongoing studies were identified from www.clinicaltrials.gov using the keywords: linagliptin, empagliflozin, dapagliflozin and saxagliptin. Other sources included drug manufacturers’ websites, Google Scholar and references known to the author.

**Mechanisms of action**

The antihyperglycaemic effects of DPP-4 inhibitors mainly stem from increasing the half-life of glucagon-like peptide-1 (GLP-1) – the incretin that is otherwise rapidly degraded by DPP-4 (15). DPP-4 is a proteolytic enzyme with several biochemical substrates (16), including GLP-1 and glucose-dependent insulinotropic peptide, which play critical roles in blood glucose regulation. GLP-1 acts primarily by stimulating pancreatic β cells for insulin secretion after meal intake, suppressing glucagon production, delaying gastric emptying and inducing satiety (17). SGLT2 inhibitors promote elimination of excess glucose via urine. SGLT2 is a membrane protein expressed primarily in the S1 segments of the renal proximal tubule. SGLT2 reabsorbs about 90% of the glucose filtered by the kidney (18). In patients with T2DM, the glucose reabsorption capacity of the kidney is increased. This is likely because of over-expression of SGLT2 and GLUT2, a facilitative glucose transporter (19,20). SGLT2 inhibition counteracts the excess glucose reabsorption in kidney by blocking the physiological activity of the protein. The excess glucose is then excreted via urine (21).

Metabolic studies in patients with T2DM have shown that SGLT2 inhibition is associated with an increase in endogenous glucose production (EGP), likely as a response to glucosuria (22,23). In the study with empagliflozin, a single dose of empagliflozin 25 mg in the fasted state led to glucosuria of approximately 8 g/3 h and an increase in EGP of 25% (averaging to 7 g over those 3 h). After meal EGP was also increased relative to baseline [median area under the curve (AUC), 40 g (interquartile range, IQR 14) vs. 34 g (IQR, 11); p < 0.01], although oral glucose appearance was not altered. Increased EGP was, at least partly, because of increased plasma glucagon concentration and decreased insulin concentration, which lowered the plasma insulin/glucagon ratio [from 9 (IQR, 5) to 7 (IQR, 4) mol/mol, p < 0.0001 vs. baseline] (22).

Merovci et al. compared dapagliflozin 10 mg/day with placebo over 2 weeks. On day 2, the mean dapagliflozin minus placebo difference in EGP/4 h (0.76 ± 0.10 mg/kg/min or 16.6 g; p < 0.05)
amounted to glycosuria over those 4 h of approximately 15 g (23). The plasma glucagon/insulin ratio with dapagliflozin on day 14 (mean ± SE, 27 ± 7) was higher than that with placebo (mean ± SE, 8 ± 2). Based on these findings, the investigators postulated that: `combination therapy with SGLT2 inhibitor plus DPP-4 inhibitor or GLP-1 analog would exert an additive or even synergistic effect to lower plasma glucose concentration and HbA1c in individuals with T2DM'.

Given the glucagon-suppressing (24–26) and insulin-stimulating effects that have been demonstrated with DPP-4 inhibition, a DPP-4 inhibitor co-administered with an SGLT2 inhibitor could counterbalance – to some extent – the decreased plasma insulin/glucagon ratio, and enhance the glucose-lowering effects of SGLT2 inhibitor treatment.

**Linagliptin**

The recommended oral dose of linagliptin is 5 mg once daily (27). Linagliptin is mainly excreted non-renally (28). The efficacy and exposure of linagliptin is not significantly affected by renal impairment (29), and therefore, it can be used without dose adjustment in patients with renal impairment. In addition, although linagliptin is mainly eliminated by a hepatobiliary route, no dose adjustment is recommended in patients with hepatic impairment (27).

In a large clinical trial programme, linagliptin, with or without other antidiabetes drugs, has shown mean reductions in HbA1c ranging from −0.5% to −2.8% (30–38). In patients with T2DM who are unable to reach the target HbA1c with metformin alone, 24-week treatment with linagliptin as an add-on therapy to metformin significantly lowered mean HbA1c by 0.6% relative to placebo (37). Initial dual therapy with linagliptin plus metformin significantly lowered HbA1c after 24 weeks compared with metformin alone (adjusted mean ± SE change from baseline, −1.6 ± 0.1% with linagliptin 2.5 mg plus metformin 1000 mg twice daily vs. −1.1 ± 0.1% with metformin 1000 mg twice daily; treatment difference, −0.5 ± 0.1%, p < 0.0001) (33). In a 24-week study comparing initial linagliptin plus metformin treatment with linagliptin monotherapy in newly diagnosed patients with pronounced hyperglycaemia (baseline HbA1c range, ≥ 8.5% to ≤ 12.0%), the adjusted mean ± SE changes in HbA1c were −2.8 ± 0.1% with linagliptin/metformin combination and −2.0 ± 0.1% with linagliptin alone (treatment difference, −0.8%, p < 0.0001) (36).

In individual trials and pooled analyses, compared with placebo, linagliptin did not increase the risk of hypoglycaemia (except when a sulfonylurea or insulin was used as background therapy), weight gain, pancreatic cancer, acute pancreatitis or cardiovascular adverse events (AEs). Higher incidence rates of hypoglycaemia with linagliptin relative to placebo have been observed when sulfonylurea was used as background therapy (34,35,39). A recent comprehensive safety analysis of linagliptin pooled data from 22 randomised, placebo-controlled trials (n = 7400). In this analysis, pancreatitis occurred at very low and comparable rates in the linagliptin and placebo groups (both < 0.1%) (39). In the same safety analysis, linagliptin did not increase the incidence of cardiac disorders (including conditions such as coronary artery disease, arrhythmias, heart failure and valve disorders); event rates were low and similar to that of placebo (3.2% and 3.3% of patients in the linagliptin and placebo groups, respectively) (39). Ongoing dedicated cardiovascular and renal outcomes trials with linagliptin in patients with a history of cardiovascular disease or its risk factors, or renal impairment, include CAROLINA® (NCT01243424), CARMELINA® (NCT01897532) and MARLINA-T2D™ (NCT01792518).

The US prescribing information for linagliptin includes a section on postmarketing reports of acute pancreatitis, including fatal pancreatitis in individuals taking linagliptin, and recommends discontinuation if pancreatitis is suspected (27). A recent joint investigation by the FDA and the European Medicines Agency (EMA) concluded that a determination of causality between incretin-based therapies and pancreatitis or pancreatic cancer is not supported by the available data, and that the product labelling for these drugs is appropriate (40). However, safety signals for pancreatitis will continue to be monitored (40).

**Empagliflozin**

Empagliflozin is available as 10 and 25 mg tablets. The recommended dose is 10 mg once daily, which can be increased to 25 mg once daily (41). Because of its renal mechanism of action, renal function status affects the use of empagliflozin. Empagliflozin is contraindicated in patients with severe renal impairment, end-stage renal disease or who are on dialysis. The US prescribing information recommends assessment of renal function prior to initiation of treatment, and that treatment with empagliflozin should not be initiated (or should be discontinued if already being used) if the estimated glomerular filtration rate (eGFR) is less than 45 ml/min/1.73 m² (41).

In phase 3 clinical trials, empagliflozin, with or without other AHAs, has shown glycaemic efficacy
Empagliflozin/linagliptin: first-class single-tablet combination

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HbA1c ranging from −0.5% to −0.9%) without increased risk of hypoglycaemia (42–45). As 24-week treatment added on to metformin and a sulfonylurea, empagliflozin significantly lowered HbA1c relative to placebo [placebo-adjusted difference (95% confidence interval; CI), −0.6% (−0.8 to −0.5) with empagliflozin 10 mg and −0.6% (−0.7 to −0.5) with empagliflozin 25 mg; both p < 0.001] (42). In a head-to-head RCT comparing empagliflozin 25 mg/day (n = 796) with glimepiride 1–4 mg/day (n = 780) added to metformin, empagliflozin was non-inferior to glimepiride in lowering HbA1c at 52 and 104 weeks (44). At 104 weeks, the glimepiride adjusted mean difference in HbA1c change with empagliflozin was −0.1% (−0.2 to −0.02); p < 0.0001. Overall AEs occurred at similar rates between groups, while the rates of serious adverse events (SAEs) were slightly higher with empagliflozin (16%) than with glimepiride (11%), with 4% of patients in the empagliflozin group and 25% of patients in the glimepiride group having experienced hypoglycaemia (44).

In clinical trials, treatment with empagliflozin, as with other SGLT2 inhibitors, has been shown to reduce body weight (placebo/active comparator-corrected mean reductions, −1.76 to −4.5 kg) (42–45). This observation is likely because of caloric loss following glycosuria. In a meta-analysis of RCTs (10 trials, n = 6203), empagliflozin 25 mg showed a significant reduction in body weight [weighted mean difference; WMD (95% CI), −1.84 kg (−2.30 to −1.38)] and no increased risk of hypoglycaemia [odds ratio; OR (95% CI), 1.10 (0.87–1.39)] vs. placebo (46).

In a 12-week study in patients with T2DM and hypertension [n = 825; mean seated systolic blood pressure (SBP) 130–159 mmHg and diastolic blood pressure (DBP) 80–99 mmHg], empagliflozin elicited significant changes in blood pressure relative to placebo [difference vs. placebo in mean 24-h SBP (95% CI), −3.44 mmHg (−4.78 to −2.09) with 10 mg and −4.16 mmHg (−5.50 to −2.83) with 25 mg; DBP (95% CI), −1.36 mmHg (−2.15 to −0.56) with 10 mg and −1.72 mmHg (−2.51 to −0.93) with 25 mg]. The investigators suggested that empagliflozin maintained the variations in blood pressure according to the circadian clock, as the reductions in daytime SBP and DBP were greater than those at night. Adjusted mean differences vs. placebo in HbA1c were −0.6% (95% CI, −0.7 to −0.5) with empagliflozin 10 mg and −0.7% (95% CI, −0.8 to −0.6) with empagliflozin 25 mg (both p < 0.001) (47). Similarly, in the meta-analysis, empagliflozin 25 mg showed positive effects on SBP [WMD (95% CI), −4.19 mmHg (−5.17 to −3.20)] vs. placebo (46). Empagliflozin has also been shown to reduce plasma uric acid levels. In a pooled analysis of four pivotal phase 3 trials, empagliflozin 10 mg and 25 mg significantly reduced uric acid compared with placebo at week 24 [placebo-corrected mean (SE) changes, −28.95 (1.82) μmol/l and −29.55 (1.83) μmol/l, respectively; both p < 0.001] (48).

The US prescribing information for empagliflozin indicates that female genital mycotic infections and urinary tract infections (UTIs) are the most common AEs associated with the drug (41). In the meta-analysis, the incidence of UTIs did not increase with empagliflozin 10 or 25 mg relative to placebo [ORs (95% CI), 1.20 (0.92–1.57) and 1.03 (0.81 to 1.32)] (46). However, genital infections were observed in a greater proportion of patients treated with empagliflozin than in those receiving placebo [ORs (95% CI), 4.39 (2.10–9.19) with 10 mg and 3.31 (1.55–7.09) with 25 mg] (46).

Empagliflozin causes osmotic diuresis, which can lead to adverse effects associated with volume depletion (dehydration, hypotension, hypovolaemia, orthostatic hypotension and syncope). Assessment and correction of volume depletion is recommended before initiating empagliflozin treatment (41). Lipid changes with empagliflozin have not been consistently observed. While a clinical impact is not yet clear, patients on empagliflozin should be monitored for lipid changes. A large cardiovascular outcomes trial (n = 7034) in patients with T2DM and a heightened risk of cardiovascular disease is investigating the long-term cardiovascular safety profile and the potential cardiovascular protective effects of empagliflozin (49).

SGLT2/DPP-4 inhibitor STCs

Efficacy

A pharmacokinetics study of empagliflozin and linagliptin dosed together revealed that there were no drug-drug pharmacokinetic interactions (50). The overall drug exposure (AUC) and peak drug concentration (C_{max}) for both drugs remained unaffected after co-administration, indicating that they can be used in combination without dose adjustment. Data from clinical studies with empagliflozin/linagliptin and dapagliflozin/saxagliptin combinations are emerging. Results of three phase 3 RCTs, which compared the combinations with corresponding monotherapies, have been reported to date (12–14). Baseline characteristics of these study populations are shown in Table 1. While all three studies were comparable with respect to study size, mean baseline age, body mass index and gender distribution, the mean HbA1c at baseline in the dapagliflozin/saxagliptin...
Empagliflozin/linagliptin and dapagliflozin/saxagliptin combinations have also been evaluated in patients taking metformin as background therapy. Both empagliflozin/linagliptin STCs – E25/L5 and E10/L5 taken once daily resulted in significant mean differences in HbA1c and FPG compared with the respective mono-treatments after 24 weeks (Table 3) (12). Higher proportions of patients achieved HbA1c < 7% with E25/L5 (61.8%) and E10/L5 STCs (57.8%) than with their respective mono-treatments (32.6%, 28.0% and 36.1% with E25, E10 and L5, respectively). Mean differences in body weight with the empagliflozin/linagliptin STCs were significant vs. linagliptin mono-treatment but not vs. the two empagliflozin mono-treatments. Glycaemic efficacy of the empagliflozin/linagliptin STCs was maintained over 52 weeks. Adjusted mean differences in SBP and DBP at 52 weeks were significant between the STCs and linagliptin alone [−3.8 mmHg (−6.5, −1.2) and −1.6 mmHg (−3.2, 0) with E25/L5; −3.1 mmHg (−5.7, −0.4) and −1.6 mmHg (−3.2, 0) with E10/L5], but not between the STCs and the empagliflozin mono-treatments.

In patients on metformin, 24-week treatment with the dapagliflozin 10 mg/saxagliptin 5 mg (D10/S5) combination significantly reduced HbA1c compared with the respective mono-treatments (Table 3) (14). Adjusted mean (SE) change in HbA1c was −1.47% (0.08) [mean (SD) baseline, 8.93% (1.19)]. Mean ± SE changes in FPG were −38 ± 2.8, −14 ± 2.9 and −32 ± 2.8 mg/dl with the D10/S5 combination, saxagliptin mono-treatment and dapagliflozin mono-treatment, respectively. Higher proportions of patients achieved HbA1c < 7% with D10/S5 (41%) than with the mono-treatments (18% and 22% with S5 and D10, respectively). Body weight reductions with the combination and dapagliflozin mono-treatment were comparable; saxagliptin mono-treatment did not change the mean body weight (Table 3). In this study, change in blood pressure was part of the safety assessment. At 24 weeks,
Empagliflozin/linagliptin: first-in-class single-tablet combination

Overall mean reductions in SBP were observed with D10/S5 combination (−1.9 mmHg) and D10 mono-treatment (−3.5 mmHg). Slight reductions in DBP were seen across all treatment groups (−1.0, −0.4 and −1.4 mmHg with D10/S5, S5 and D10, respectively).

**Safety**

In the empagliflozin/linagliptin STC study in drug-naïve patients, rates of overall AEs and drug-related AEs were similar across all groups (Table 4) (13). No patients in the STC groups experienced confirmed hypoglycaemic events, and rates of such events were low in the mono-treatment groups. Events consistent with UTIs were observed in similar proportions of patients across all groups, and occurred more frequently in women; none led to treatment discontinuation. Events consistent with genital infections occurred at similar rates in all groups, but two patients who had genital infections discontinued treatment (one in the E25/L5 group and one in the E10 group). At the follow-up visit – 4 weeks after the last dose – modest changes in eGFR ranging from 1.5 ± 11.5 to 4.0 ± 11.7 ml/min/1.73 m² were reported. Both the STCs and empagliflozin mono-treatments decreased uric acid (−56.5 to −71.4 μmol/l), whereas linagliptin mono-treatment slightly increased uric acid levels from baseline (3.0 μmol/l). No incidence of worsening of heart failure or hospitalisation because of heart failure was reported.

In the empagliflozin/linagliptin study in patients taking metformin, frequencies of overall AEs, SAEs, drug-related AEs and AEs leading to discontinuation were comparable across all groups (Table 4) (12). Confirmed hypoglycaemia occurred at low rates across all groups, with none of individuals who had a hypoglycaemic event needing assistance. Events consistent with UTIs occurred at comparable rates across all groups; one patient in the E10 group experienced severe urosepsis needing hospitalisation and discontinued treatment. Proportions of patients experiencing events consistent with genital infection were comparable between groups. Two patients in the E25/L5 group with genital infections discontinued treatment. Mean (SD) changes in eGFR at follow-up ranged from −0.5 (13.0) to 4.8 (13.7) ml/min/1.73 m². No incidence of worsening of heart failure or hospitalisation because of heart failure was reported. Both STCs and empagliflozin mono-treatments reduced mean uric acid levels relative to the

| Table 2 Primary and key secondary end-points at 24 weeks with empagliflozin/linagliptin STCs in drug-naïve patients (13) |
|---------------------------------------------------------------|
| E25/L5 STC | E10/L5 STC |
| N | 134 | 135 |
| HbA1c (%) Baseline | 7.99 (0.95)* | 8.04 (0.96)* |
| Change from baseline | −1.08 (0.06)† | −1.24 (0.06)‡ |
| Difference vs. mono-treatment (95% CI) | −0.14 (−0.33, 0.06) vs. E25 | −0.41 (−0.61, −0.22)§ vs. L5 |
| Patients with HbA1c < 7% (%) | 55.4 | 62.3 |
| Difference vs. mono-treatment (95% CI) | 1.89 (1.1, 3.3)*** vs. E25 | 2.96 (1.7, 5.2)¶ vs. E10 |
| FPG (mg/dl) Baseline | 156.1 (35.8)* | 157.2 (35.4)* |
| Change from baseline | −29.6 (2.7) | −28.2 (2.7) |
| Difference vs. mono-treatment (95% CI) | −5.3 (−12.7, 2.1) vs. E25 | −5.8 (−13.3, 1.6) vs. E10 |
| Body weight (kg) Baseline | 87.9 (18.2)* | 87.3 (18.4)* |
| Change from baseline | −2.0 (0.4) | −2.7 (0.4) |
| Difference vs. mono-treatment (95% CI) | 0.1 (−0.9, 1.1) vs. E25 | −0.5 (−1.5, 0.5) vs. E10 |

STC, single-tablet combination; E25, empagliflozin 25 mg; E10, empagliflozin 10 mg; L5, linagliptin 5 mg. *Data are mean (SD) in the full analysis set (patients who received ≥1 dose of the study drug and had baseline and ≥1 HbA1c measurement after treatment). †Data are adjusted mean (SE) analysed using analysis of covariance (ANCOVA) model on the full analysis set using last observation carried forward (LOCF) method for imputation of missing values. §Values are odds ratios for combination vs. the respective mono-treatments. ‡p < 0.001. ***p < 0.05.

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Table 3  Primary and key secondary end-points at 24 weeks with empagliflozin/linagliptin and dapagliflozin/saxagliptin combinations in patients on metformin background therapy (12,14)

| Drug-naive patients | E25/L5 STC | E10/L5 STC | D10/SS LPC |
|---------------------|------------|------------|------------|
| N                   | 134        | 135        | 176        |
| HbA1c (%)           |            |            |            |
| Baseline            | 7.90 (0.79)* | 7.95 (0.80)* | 8.93 ± 1.19* |
| Change from baseline| −1.19 (0.06)† | −1.08 (0.06)† | −1.47 (0.08)† |
| Difference vs. mono-treatment (95% CI) | −0.58 (−0.75, −0.41)† vs. E25 | −0.42 (−0.59, −0.25)† vs. E10 | −0.27 (−0.48, −0.05)† vs. D10 |
| Body weight (kg)    |            |            |            |
| Baseline            | 76/123     | 74/128     | 74/177     |
| Change from baseline| −16.4 (−23.4, −9.5)† vs. E25 | −16.1 (−23.5, −8.0)† vs. E10 | −20.2 (−29.0, −11.3)† vs. D10 |
| Difference vs. mono-treatment (95% CI) | −22.2 (−29.3, −15.1)† vs. L5 | −19.1 (−26.2, −12.0)† vs. L5 | −24.0 (−31.6, −15.9)‡ vs. S5 |
| FPG (mg/dl)         |            |            |            |
| Baseline            | 3.50 (1.92, 6.36)† vs. L5 | 2.80 (1.56, 5.00)† vs. L5 | 23 (14.7, 31.5) vs. S5 |
| Change from baseline| −2.3 (−3.2, −1.4)† vs. L5 | −1.9 (−2.8, −1.1)† vs. L5 | −2.1 (−2.7, −1.4) vs. S5 |

Data are %. E25, empagliflozin 25 mg; E10, empagliflozin 10 mg; L5, linagliptin 5 mg; D10, dapagliflozin 10 mg; S5, saxagliptin 5 mg; STC, single-tablet combination; LPC, loose-pill combination. *Values are mean (SD). †Values are mean (SE) analysed using analysis of covariance (ANCOVA) model on the full analysis set using last observation carried forward (LOCF) method for imputation of missing values. ‡p < 0.001. ‡‡p < 0.0001. ‡¶p = 0.0166. **Values are odds ratios for combination vs. the respective mono-treatments. ††p < 0.01. †‡p < 0.002.

Table 4  Safety profiles of empagliflozin/linagliptin STCs at 52 weeks in drug-naive patients and in patients on metformin background therapy (12,13)

| Drug-naive patients | E25/L5 STC | E10/L5 STC | E25 | E10 | L5 |
|---------------------|------------|------------|-----|-----|----|
| N                   | 136        | 136        | 135 | 135 | 135 |
| Overall AEs         | 103 (75.7) | 99 (72.8)  | 93  | 69.9 | 110 |
| Serious AEs         | 6 (4.4)    | 7 (5.1)    | 9   | 6.7 | 10.4 |
| Drug-related AEs    | 23 (16.9)  | 14 (10.3)  | 22  | 16.3 | 16.1 |
| AEs leading to discontinuation | 9 (6.6) | 8 (5.9) | 5 (3.7) | 7 (5.20) | 2 (1.5) |
| Hypoglycaemia       | 0          | 0          | 1   | 0.7 | 4 (3.0) |
| AEs consistent with urinary tract infections | 17 (12.5) | 21 (15.4) | 14 (10.4) | 22 (16.3) | 14 (10.4) |
| AEs consistent with genital infections | 8 (5.9) | 4 (2.9) | 6 (4.4) | 7 (5.2) | 4 (3.0) |
| AEs consistent with volume depletion | 1 (0.7) | 3 (2.2) | 0   | 0   | 0   |

Table 4  Safety profiles of empagliflozin/linagliptin STCs at 52 weeks in drug-naive patients and in patients on metformin background therapy (12,13)

| Patients on metformin | E25/L5 STC | E10/L5 STC | E25 | E10 | L5 |
|-----------------------|------------|------------|-----|-----|----|
| N                     | 134        | 135        | 134 | 140 | 128 |
| Overall AEs           | 98 (71.5)  | 94 (69.1)  | 103 | 73.0 | 96 (68.6) |
| Serious AEs           | 6 (4.4)    | 9 (6.6)    | 10  | 7.1 | 6 (4.3) |
| Drug-related AEs      | 18 (13.1)  | 23 (16.9)  | 26  | 18.4 | 26 (18.6) |
| AEs leading to discontinuation | 3 (2.2) | 2 (1.5) | 4 (2.8) | 9 (6.4) | 4 (3.0) |
| Hypoglycaemia         | 5 (3.6)    | 3 (2.2)    | 5   | 3.5 | 2 (1.4) |
| AEs consistent with urinary tract infections | 14 (10.2) | 13 (9.6) | 19 (13.5) | 16 (11.4) | 20 (15.2) |
| AEs consistent with genital infections | 3 (2.2) | 8 (5.9) | 12 | 8.5 | 11 (7.9) |
| AEs consistent with volume depletion | 1 (0.7) | 2 (1.5) | 2 (1.4) | 1 (0.7) | 4 (3.0) |

E25, empagliflozin 25 mg; E10, empagliflozin 10 mg; L5, linagliptin 5 mg; D10, dapagliflozin 10 mg; S5, saxagliptin 5 mg; STC, single-tablet combination. *Treated set, patients who received ≥ 1 doses of the treatment.
Empagliflozin/linagliptin: first-in-class single-tablet combination

Empagliflozin 25 mg; E10, empagliflozin 10 mg; L5, linagliptin 5 mg.

Triglycerides (mmol/l)

|         | Drug-naive patients | Patients on metformin |
|---------|---------------------|-----------------------|
|         | E25/L5 STC          | E10/L5 STC            |
|         | N=136               | 134                   |
| N=136   | 136                 | 135                   |
| N=136   | 136                 | 134                   |
| N=136   | 136                 | 135                   |
| Total cholesterol (mmol/l) |                |                       |
| Baseline | 5.0 ± 0.1           | 4.6 ± 0.1             |
|         | 5.1 ± 0.1           | 4.6 ± 0.1             |
| Change from baseline | 0.1 ± 0.1           | 0.2 ± 0.1             |
|         | 0.0 ± 0.1           | 0.1 ± 0.1             |
| Difference vs. mono-treatment (p-value) | −0.1 ± 0.1 vs. E25 (0.443) | 0.0 ± 0.1 vs. L5 (0.036) |
|         | −0.1 ± 0.1 vs. E10 (0.164) | 0.1 ± 0.1 vs. L5 (0.135) |
|         | 0.2 ± 0.1 vs. L5 (0.036) | 0.1 ± 0.1 vs. L5 (0.164) |
|         | 0.1 ± 0.1 vs. L5 (0.135) | 0.1 ± 0.1 vs. L5 (0.596) |
| HDL cholesterol (mmol/l) |                |                       |
| Baseline | 1.2 ± 0.0           | 1.2 ± 0.0             |
|         | 1.1 ± 0.0           | 1.2 ± 0.0             |
| Change from baseline | 0.1 ± 0.0           | 0.1 ± 0.0             |
|         | 0.1 ± 0.0           | 0.1 ± 0.0             |
| Difference vs. mono-treatment | 0.0 ± 0.0 vs. E25 (0.126) | 0.0 ± 0.0 vs. E10 (0.007) |
|         | 0.1 ± 0.0 vs. L5 (0.004) | 0.1 ± 0.0 vs. L5 (<0.001) |
|         | 0.1 ± 0.0 vs. L5 (0.003) | 0.0 ± 0.0 vs. L5 (0.052) |
| LDL cholesterol (mmol/l) |                |                       |
| Baseline | 2.9 ± 0.1           | 2.6 ± 0.1             |
|         | 3.0 ± 0.1           | 2.5 ± 0.1             |
| Change from baseline | 0.0 ± 0.1           | 0.1 ± 0.1             |
|         | −1.0 ± 0.1          | 0.0 ± 0.1             |
| Difference vs. mono-treatment (p-value) | 0.0 ± 0.1 vs. E25 (0.759) | 0.0 ± 0.1 vs. E10 (0.355) |
|         | −0.1 ± 0.1 vs. L5 (0.155) | 0.0 ± 0.1 vs. L5 (0.639) |
|         | 0.1 ± 0.1 vs. L5 (0.391) | 0.0 ± 0.1 vs. L5 (0.712) |
| Triglycerides (mmol/l) |                |                       |
| Baseline | 2.0 ± 0.1           | 1.7 ± 0.1             |
|         | 2.1 ± 0.1           | 1.8 ± 0.1             |
| Change from baseline | −0.1 ± 0.1          | −0.1 ± 0.1            |
|         | 0.0 ± 0.1           | 0.0 ± 0.1             |
| Difference vs. mono-treatment (p-value) | 0.0 ± 0.1 vs. E25 (0.905) | 0.0 ± 0.1 vs. E10 (0.227) |
|         | 0.1 ± 0.1 vs. L5 (0.534) | 0.1 ± 0.1 vs. L5 (0.292) |
|         | −0.1 ± 0.1 vs. L5 (0.271) | 0.0 ± 0.1 vs. L5 (0.897) |

Data are mean ± SE analysed using analysis of covariance (ANCOVA) model with treatment, region and eGFR at baseline as fixed effects and baseline HbA1c and baseline end-point value as linear covariates. *Treated set. HDL, high-density lipoprotein; LDL, low-density lipoprotein; STC, single-tablet combination; E25, empagliflozin 25 mg; E10, empagliflozin 10 mg; L5, linagliptin 5 mg.

With the dapagliflozin/saxagliptin combination (D10/S5), overall AEs occurred in 49% (87/179) of patients, and the proportion was comparable with the respective mono-treatments. Hypoglycaemia rates were low (1%) across all treatment groups. UTIs occurred in one patient, whereas none suffered from genital infections. In the D10/S5 combination group, one patient discontinued study participation because of a decreased eGFR.

Ongoing clinical trials with SGLT2/DPP-4 inhibitor combinations

For patients in whom a dual therapy with either metformin and linagliptin or metformin and empagliflozin does not achieve the glycaemic treatment goal, a third AHA is necessary. Clinical trials designed to investigate addition of a third agent in such populations are currently underway. NCT01778049 is a Phase 3 RCT being conducted in patients with insufficient glycaemic control on metformin monotherapy, who were treated with empagliflozin 10 or 25 mg plus metformin for 16 weeks. Patients not reaching glycaemic goals were then randomised to linagliptin or placebo. This study is comparing the efficacy and safety of linagliptin 5 mg, administered as an STC with empagliflozin 25 or 10 mg, against placebo over 24 weeks in this patient population. Another study, NCT01734785, is a Phase 3 RCT being conducted in patients with insufficient glycaemic control on metformin monotherapy, who were treated with linagliptin 5 mg plus metformin for 16 weeks. Patients not reaching glycaemic goals were then randomised to empagliflozin 10 mg,
Empagliflozin 25 mg or placebo. This study is comparing the efficacy and safety of empagliflozin 10 and 25 mg, administered as an STC with linagliptin 5 mg, against placebo over 24 weeks in this patient population. Similarly, phase 3 RCTs investigating dapagliflozin 10 mg as an add-on treatment to saxagliptin 5 mg plus metformin (NCT01646320) and saxagliptin 5 mg as an add-on treatment to dapagliflozin 10 mg plus metformin (NCT01619059) are currently in progress.

Discussion

Most patients with T2DM will reach a point at which they need a combination of AHAs to achieve and maintain glycaemic targets. Metformin retains its place as first-line therapy for the treatment of T2DM, but for second- and third-line treatments, medication choices are variable depending on individual patient characteristics. Risk of hypoglycaemia and weight gain are two main side effects of AHAs, which can be compounded by poly-pharmaceutical approaches. Dual inhibitor combination therapy (SGLT2/DPP-4) with empagliflozin and linagliptin offers the potential for weight loss and moderate reductions in blood pressure, as well as reduced blood glucose without increased risk of hypoglycaemia. When metformin alone does not reach or maintain glycaemic targets, physicians might consider linagliptin plus metformin or empagliflozin plus metformin fixed-dose combinations before progressing to triple therapy with metformin plus empagliflozin/linagliptin STC. However, depending on the severity of hyperglycaemia, simultaneous addition of both drugs to metformin background might be appropriate. Phase 3 studies with SGLT2/DPP-4 dual inhibitor combination therapy in patients taking metformin have demonstrated HbA1c reductions from baseline without an excessive risk of hypoglycaemia. When metformin is not a suitable option, insulin and GLP-1 receptor agonists may also be considered. However, patient aversion to injectable therapies must be overcome. In cases of severe hyperglycaemia, dual inhibitor combination therapy added to insulin may help patients to achieve control without the increased risk of hypoglycaemia or weight gain that accompanies escalating the dose of insulin. Although there is no direct clinical evidence supporting use of empagliflozin/linagliptin combination along with insulin, the current data on efficacy and safety of the individual drugs plus insulin make this an intriguing treatment regimen (38,51). In a RCT (≥ 52 weeks duration), 24-week treatment with linagliptin 5 mg/day added on to basal insulin caused a greater reduction in HbA1c than placebo [mean (SD), −0.58% (0.08) and 0.07% (0.08), respectively] [treatment difference (95% CI), −0.65% (−0.74, −0.55); p < 0.0001] (38). The efficacy was maintained for up to 76 weeks. At week 52, daily insulin dose was increased to a greater extent in the placebo group than in the linagliptin group [mean (SD) changes, 4.2 (0.8) IU and 2.6 (0.8) IU, respectively; p < 0.003]. Notably, the addition of linagliptin did not cause an increase in body weight (mean change −0.3 kg and −0.04 kg with placebo at 52 weeks). The rates of investigator-defined hypoglycaemia were 31.4% with linagliptin and 32.9% with placebo, although a higher proportion of patients in the placebo group (50.4%) than in the linagliptin group (38.2%) received rescue therapy. Empagliflozin treatment in obese patients with insufficient glycaemic control despite multiple daily injections of insulin lowered HbA1c relative to placebo (at week 18, placebo-corrected mean ± SE reductions were −0.44 ± 0.08 with 10 mg and −0.52 ± 0.07 with 25 mg [both p < 0.001]) (51). Empagliflozin 25 and 10 mg both reduced mean insulin dose and body weight over 52 weeks (placebo-corrected changes, −9 to −11 IU/day and −2.4 to −2.5 kg), without increasing the risk of hypoglycaemia.

Several other available oral fixed-dose combinations contain immediate-release metformin as one of the components and are usually taken twice daily, while the dual inhibitor combination therapy (SGLT2/DPP-4) is taken once daily. Thus, this combination offers an advantage of reduced pill burden.

Conclusion

Dual inhibitor combination therapy (SGLT2/DPP-4) with empagliflozin/linagliptin STCs has been investigated in drug-naive patients and in patients on metformin background therapy. After 24 weeks of treatment the mean reduction in HbA1c with the STCs ranged from −1.08% to −1.24%. The dapagliflozin and saxagliptin combination has also been studied in patients on metformin background therapy. Numerically, the mean change from baseline in HbA1c with the dapagliflozin and saxagliptin combination was slightly higher (−1.47%) than values obtained with both empagliflozin/linagliptin STCs, the difference might partly be because of a higher baseline HbA1c in the dapagliflozin and saxagliptin combination study population. In drug-naive patients, empagliflozin/linagliptin STCs significantly improved glycaemic control (HbA1c and FPG) compared with all respective monotherapies except empagliflozin 25 mg, whereas with metformin co-therapy, the STCs significantly improved glycaemic control relative to all respective monotherapies. Empagliflozin/linagliptin STCs achieved
statistically significant mean differences in body weight reduction compared with linagliptin but not empagliflozin mono-treatments in both the studies. In drug-naive patients, SBP and DBP changes did not alter significantly between the treatment groups, but in patients taking metformin, SBP and DBP were significantly lower with the STCs than with linagliptin mono-treatment. Empagliflozin/linagliptin STCs were well-tolerated with low rates of hypoglycaemia. Incidences of hypoglycaemia, events consistent with UTIs and genital infection with the STCs, occurred at similar frequencies compared with respective mono-treatments. In patients with T2DM in need of a dual or triple therapy, dual inhibitor combination therapy appears to be an important option as an initial therapy, or additional therapy when metformin alone is not sufficient or suitable.

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References
1 Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35: 1364–79.
2 Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38: 140–9.
3 Garber AJ, Abrahamsson MJ, Barzilay JJ et al. AACE/ACE: comprehensive diabetes management algorithm 2015. Endocr Pract 2015; 21: 438–47.
4 Zinman B. Initial combination therapy for type 2 diabetes mellitus: is it ready for prime time? Am J Med 2011; 124: S19–34.
5 Bell DS. Combine and conquer: advantages and disadvantages of fixed-dose combination therapy. Diabetes Obs Metab 2013; 15: 291–300.
6 Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obs Metab 2014; 14: 410–7.
7 Turnbull FM, Abraira C, Anderson RJ et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetesologia 2009; 52: 2288–98.
8 Davidson JA. The placement of DPP-4 inhibitors in clinical practice recommendations for the treatment of type 2 diabetes. Endocr Pract 2013; 19: 1050–61.
9 Hutchins V, Zhang B, Fleurence RL et al. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. Curr Med Res Opin 2011; 27: 1157–68.
10 Boehringer Ingelheim. Glyxambi (empagliflozin/linagliptin) prescribing information. https://www.glyxambi.com/ (accessed February 11, 2015).
11 AstraZeneca. February 2015 press release. http://www.astrazeneca.com/Media/Press-releases/Article/20140205-AZN-fourth-quarter-and-full-year-results-2014 (accessed February 11, 2015).
12 DeFronzo RA, Lewin A, Patel S et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care 2015; 38: 384–93.
13 Lewin A, DeFronzo RA, Patel S et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care 2015; 38: 394–402.
14 Rosenstock J, Hansen L, Zee P et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 2015; 38: 376–83.
15 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368: 1696–705.
16 De Meester I, Durinx C, Bal G et al. Natural subtypes of dipeptidyl peptidase IV. Adv Exp Med Biol 2000; 477: 67–87.
17 Drucker DJ. The biology of incretin hormones. Cell Metab 2006; 3: 153–65.
18 Marsenick O. Glucose control by the kidney: an emerging target in diabetes. Am J Kidney Dis 2009; 53: 875–83.
19 DeFronzo RA, Hompesch M, Kasischyanul S et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care 2013; 36: 3169–76.
20 Rahmoune H, Thompson PW, Ward JM et al. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 2005; 54: 3427–34.
21 DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab 2012; 14: 5–14.
22 Ferrannini E, Muscelli E, Frascerra S et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014; 124: 499–508.
23 Merović A, Solis-Herrera C, Daniele G et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014; 124: 509–14.
24 Ahren B, Landin-Olsson M, Jansson PA et al. Inhibition of dipeptidyl peptidase-4 reduces glycaemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab 2004; 89: 2078–84.
25 Balas B, Baig MR, Watson C et al. The dipeptidyl peptidase IV inhibitor vildagliptin suppresses endogenous glucose production and enhances insulin function after single-dose administration in type 2 diabetic patients. J Clin Endocrinol Metab 2007; 92: 1249–55.
26 Muscelli E, Casaloro A, Gastaldelli A et al. Mechanisms for the antihyperglycemic effect of sitagliptin in patients with type 2 diabetes. J Clin Endocrinol Metab 2012; 97: 2818–26.
27 Boehringer Ingelheim. Tradjenta (linagliptin) prescribing information. http://bidocs.boehringer-ingelheim.com/BIFWebAccess/ViewServlet.ser?docBase=remenrntkfoldPath=/Prescribing+Information/Pils/Tradjenta/Tradjenta.pdf (accessed 13 March, 2015).
28 Blech S, Ludwig-Schwellinger E, Grafe-Mody EU et al. The metabolism and disposition of the oral dipeptidyl peptidase-4 inhibitor, linagliptin, in humans. Drug Metab Dispos 2010; 38: 667–78.
29 Grafe-Mody U, Friedrich C, Port A et al. Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin(*). Diabetes Obes Metab 2011; 13: 939–46.
30 Bajaj M, Gilman R, Patel S et al. Linagliptin improved glycemic control without weight gain or hypoglycemia in patients with type 2 diabetes inadequately controlled by a combination of metformin and pioglitazone: a 24-week randomized, double-blind study. Diabet Med 2014; 31: 1505–14.
31 Del Prato S, Barnett AH, Huisman H et al. Effect of linagliptin monotherapy on glycemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab 2011; 13: 258–67.
32 Gomis R, Espadero RM, Jones R et al. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 2011; 13: 653–61.
Effects of adding linagliptin to basal insulin regimens in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2012; 34: 1909–19 e15.

Lewin AJ, Arvay L, Liu D et al. Efficacy and tolerability of linagliptin added to a sulfonylurea regimen in patients with inadequately controlled type 2 diabetes mellitus: an 18-week, multicenter, randomized, double-blind, placebo-controlled trial. *Clin Ther* 2012; 34: 1909–19 e15.

Owens DR, Swallow R, Dugi KA, Woorle HJ. Efficacy and safety of linagliptin as add-on therapy to metformin plus sulfonlurea: a 24-week randomized study. *Diabet Med* 2011; 28: 1352–61.

Ross SA, Caballero AE, Del Prato S et al. Initial combination of linagliptin and metformin compared with linagliptin monotherapy in patients with newly diagnosed type 2 diabetes and marked hyperglycaemia: a randomized, double-blind, active-controlled, parallel group, multinational clinical trial. *Diabet Obes Metab* 2015; 17: 136–44.

Taskinen MR, Rosenstock J, Tamminen I et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabet Obes Metab* 2011; 13: 65–74.

Yki-Jarvinen H, Rosenstock J, Duran-Garcia S et al. Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a ≥ 52-week randomized, double-blind study. *Diabetes Care* 2013; 36: 3875–81.

Lehrke M, Marx N, Patel S et al. Safety and tolerability of linagliptin in patients with type 2 diabetes: a comprehensive pooled analysis of 22 placebo-controlled studies. *Clin Ther* 2014; 36: 1130–46.

Egan AG, Blind E, Dunder K et al. Pancreatic safety of incretin-based drugs – FDA and EMA assessment. *N Engl J Med* 2014; 370: 794–7.

Boehringer Ingelheim. Jardiance (empagliflozin) prescribing information. https://www.jardiance.com (accessed 13 March, 2015).

Haring HU, Merker L, Seewaldt-Becker E et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2013; 36: 3396–404.

Kovacs CS, Seshiah V, Swallow R et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab* 2014; 16: 147–58.

Riddlerstrale M, Andersen KR, Zeller C et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol* 2014; 2: 691–700.

Roden M, Weng J, Eilbracht J et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2013; 1: 208–19.

Lialkos A, Karagiannis T, Athanasiadou E et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2014; 16: 984–93.

Tikkanen I, Narko K, Zeller C et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care* 2015; 38: 420–8.

Hach T, Gerich J, Salsali A et al. Empagliflozin improves glycemic parameters and cardiovascular risk factors in patients with type 2 diabetes (T2DM): pooled data from four pivotal phase III trials. *Diabetes 2013; 62: LB69.

Zinman B, Inzucchi SE, Lachin JM et al. Rationale, design, and baseline characteristics of a randomised, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetol* 2014; 13: 102.

Friedrich C, Metzmann K, Rose P et al. A randomised, open-label, crossover study to evaluate the pharmacokinetics of empagliflozin and linagliptin after coadministration in healthy male volunteers. *Clin Ther* 2013; 35: A33–42.

Rosenstock J, Jelaska A, Frappin G et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycaemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care* 2014; 37: 1815–23.

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