in the saxagliptin + dapagliflozin + metformin group achieved a target HbA_{1c} < 7% (41% vs 18% vs 22%).

No deaths were reported in any of the groups. The incidence of serious adverse events (AEs) was similar in all 3 groups (1% vs 3% vs 1%). The incidence of AEs leading to treatment discontinuation was also similar (0.6% vs 0% vs 0%). With respect to AEs of special interest, the incidence of urinary tract infections was also similar in all 3 groups (0.6% vs 5% vs 4%), and the incidence of hypoglycemia was low (1% in all groups). Genital infections were not recorded in the saxagliptin + dapagliflozin + metformin group (0% vs 0.6% vs 6%).

In his concluding remarks, Dr Rosenstock stated that when compared with monotherapy, the addition of saxagliptin and dapagliflozin to metformin in poorly controlled TD2M patients led to greater reductions in HbA_{1c} and allowed more patients to achieve a target HbA_{1c} < 7%. Dual add-on therapy was also well tolerated and did not increase the risk of hypoglycemia in patients.

Combining Empagliflozin and Linagliptin With Metformin Reduces HbA_{1c} in Patients With T2DM

Written by Nicola Parry

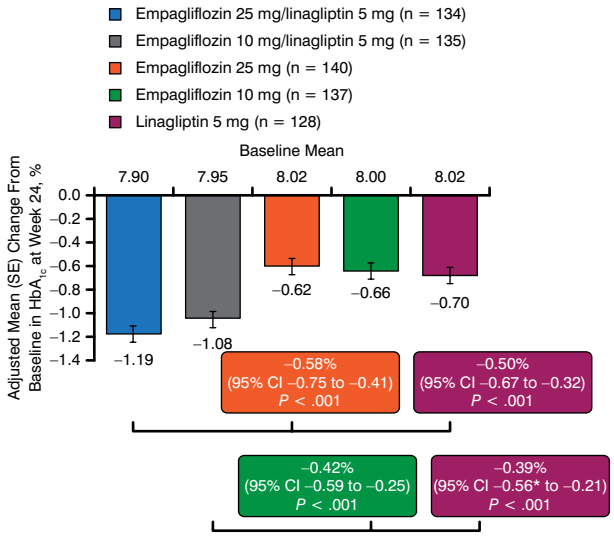
Combined empagliflozin and linagliptin as add-on therapy to metformin provided enhanced glucose-reducing efficacy when compared with either drug as monotherapy in individuals with type 2 diabetes mellitus (T2DM), stated Ralph A. DeFronzo, MD, University of Texas, San Antonio, Texas, USA, while presenting results from a phase 3 double-blind, parallel-group study.

According to Dr DeFronzo, sodium-glucose cotransporter 2 inhibitors, such as empagliflozin, are a new class of drugs for the management of T2DM. Linagliptin is a dipeptidyl peptidase 4 inhibitor and is considered to provide additional benefit in T2DM treatment when combined with empagliflozin, due to its ability to inhibit glucagon and enhance insulin secretion.

This study aimed to investigate the efficacy and safety of empagliflozin and linagliptin, individually and in combination as add-on therapy to metformin in adults with T2DM.

Patients in this study were all > 18 years of age, with a body mass index of ≤ 45 kg/m^2 and HbA_{1c} levels between 7% and 10.5%. All subjects had to have received a stable background therapy of metformin for ≥ 12 weeks before randomization. Patients were excluded who had an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 during screening or placebo run-in.

Figure 1. Change in Mean HbA_{1c} From Baseline at 24 Weeks



SE, standard error.

Source: DeFronzo R et al. *Diabetes*. 2014 (abstr 130-LB).

*On May 1, 2015, −0.26 was changed to −0.56.

Dr DeFronzo and colleagues randomized 677 patients to empagliflozin–25 mg + linagliptin–5 mg (n = 137), empagliflozin–10 mg + linagliptin–5 mg (n = 136), empagliflozin–25 mg (n = 135), empagliflozin–10 mg (n = 134), and linagliptin–5 mg (n = 135). The primary end point was the change from baseline in HbA_{1c} at week 24. The study continued to week 52.

At 24 weeks, patients treated with both fixed-dose combinations of empagliflozin + linagliptin showed significant HbA_{1c} reductions as compared with the monotherapies, with a higher percentage of the combinations achieving HbA_{1c} < 7% (P < .001; Figure 1). Adjusted mean HbA_{1c} changes from baseline for those receiving the combination therapies were –1.19% for empagliflozin –25 mg + linagliptin–5 mg and –1.08% for empagliflozin –10 mg + linagliptin–5 mg. For those receiving one of the monotherapies, the changes observed were –0.62% for empaglifozin–25 mg, –0.66% for empagliflozin –10 mg, and –0.70% for linagliptin–5 mg [DeFronzo R et al. *Diabetes*. 2014 (abstr 130-LB)].

This effect continued to 52 weeks, at which point significantly higher percentages of patients treated with both fixed-dose combinations continued to show reductions in HbA_{1c} < 7% as compared with the monotherapies (P < .001). Adjusted mean HbA_{1c} changes from baseline for the combinations at 52 weeks were –1.21% for empagliflozin –25 mg + linagliptin–5 mg and –1.05% for empagliflozin

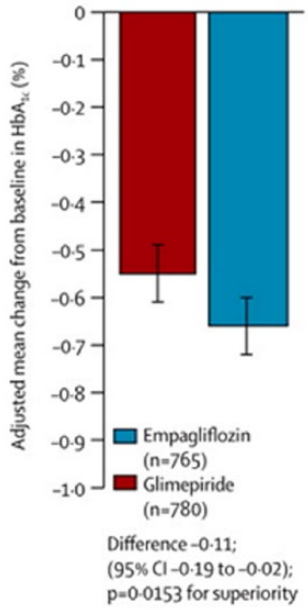
–10 mg + linagliptin–5 mg. The individual monotherapies showed changes of –0.64% for empagliflozin –25 mg, –0.69% for empagliflozin–10 mg, and –0.48% for linagliptin–5 mg. While the combinations demonstrated efficacy beyond that of the individual monotherapies, Dr DeFronzo noted that the effects were "not completely additive."

Empagliflozin monotherapy and the fixed-dose combinations reduced systolic blood pressure from baseline by a range of 2.8 to 3.6 mm Hg. Combination therapy with empagliflozin–25 mg + linagliptin–5 mg and empagliflozin –10 mg + linagliptin–5 mg significantly reduced systolic blood pressure when compared with linagliptin –5 mg monotherapy ($P = .005$ and $P = .02$, respectively).

Combined empagliflozin and linagliptin was well tolerated, and the safety profile was similar to that demonstrated by the individual components. The incidence of hypoglycemia was similar in all 5 groups (between 2% and 5%), as was the incidence of adverse events leading to treatment discontinuation (between 2% and 9%), urinary tract infection (between 14% and 20%), and genital infection (between 3% and 12%).

In his concluding remarks, Dr DeFronzo said that these results show that combination therapies are more effective in reducing HbA_{1c} versus monotherapy with the same drugs.

Figure 1. Change in Mean HbA_{1c} From Baseline at 104 Weeks



Reprinted from *The Lancet Diabetes & Endocrinology*, 2, Ridderstrale M 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, 691-700, Copyright 2014, with permission from Elsevier.

Empagliflozin Superior to Glimepiride as Second-line Treatment in T2DM

Written by Nicola Parry

Empagliflozin is superior to glimepiride as an add-on treatment option for patients with type 2 diabetes mellitus (T2DM) who have not achieved good glycemic control on metformin, according to results from the Efficacy and Safety of Empagliflozin (BI 10773) With Metformin in Patients With Type 2 Diabetes trial [Ridderstråle M et al. *Lancet Diabetes Endocrinol*. 2014], announced lead investigator Martin Ridderstråle, MD, Steno Diabetes Center, Gentofte, Denmark.

Metformin represents traditional first-line therapy for patients with T2DM, but there is no consensus regarding optimal second-line treatment. According to Prof Ridderstråle, empagliflozin is a selective sodium-glucose cotransporter 2 inhibitor, a new class of drugs for the management of T2DM, while glimepiride is a sulfonylurea.

This phase 3 double-blind study aimed to compare the efficacy and safety of empagliflozin and glimepiride as second-line therapy in patients with T2DM who are not adequately controlled on metformin. The study included patients >18 years with a body mass index ≤45 kg/m^2 and with HbA_{1c} levels between 7% and 10% who were on a stable background therapy of metformin for ≥12 weeks before randomization. The investigators excluded subjects with an estimated glomerular filtration rate <60 mL/min/1.73 m^2 during screening or placebo run-in.

The researchers randomized participants (n = 1549) in a 1:1 ratio to oral empagliflozin (25 mg, QD) or oral glimepiride (1 to 4 mg, QD) as add-on to metformin for 104 weeks. The primary end point was the change from baseline in HbA_{1c} levels at weeks 52 and 104 and included noninferiority and superiority criteria.

From baseline to 104 weeks, patients treated with empagliflozin had significantly greater reductions in mean HbA_{1c} levels when compared with patients treated with glimepiride. Empagliflozin was noninferior to glimepiride at baseline and 104 weeks. The adjusted mean difference in change from baseline in HbA_{1c} with empagliflozin versus glimepiride was –0.11% (95% CI, –0.19 to –0.02; $P = .015$ for superiority; see Figure 1). The investigators also observed significant reductions with empagliflozin in body weight (–3.1 vs 1.3 kg; $P < .001$), systolic blood pressure (–3.1 vs 2.5 mm Hg; $P < .001$), and diastolic blood pressure (–1.8 vs 0.9 mm Hg; $P < .001$). The incidence of death was similar in the 2 groups (0.7% vs 0.6%).