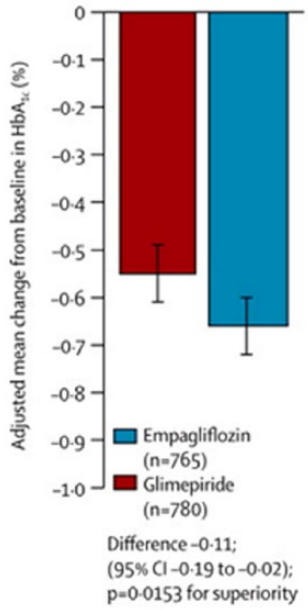
–10 mg + linagliptin–5 mg. The individual monotherapies showed changes of –0.64% for empagliflozin –25 mg, –0.69% for empagliflozin–10 mg, and –0.48% for linagliptin–5 mg. While the combinations demonstrated efficacy beyond that of the individual monotherapies, Dr DeFronzo noted that the effects were "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%).

Empagliflozin was also associated with significantly fewer hypoglycemic adverse events (AEs) than glimepiride (24% vs 3%; $P<.001$). In the empagliflozin group, serious AEs were reported in 16% of patients, compared with 11% in the glimepiride group. The incidence of AEs leading to treatment discontinuation was similar in both groups (5% vs 4%). Urinary tract infection was recorded in 13.7% and 13.1% of patients receiving empagliflozin and glimepiride, respectively, and genital infection in 11.8% and 2.2% of patients, respectively.

Prof Ridderstråle concluded that, compared with glimepiride, empagliflozin as add-on therapy to metformin produced a small but significantly superior difference in the reduction of HbA_{1c} and provided sustained reductions in body weight and blood pressure. Patients treated with empagliflozin had fewer AEs, particularly hypoglycemia.

LIRA-ADD2BASAL: Liraglutide Added to Basal Insulin Analogs Improves Glycemic Control

Written by Kate Mann

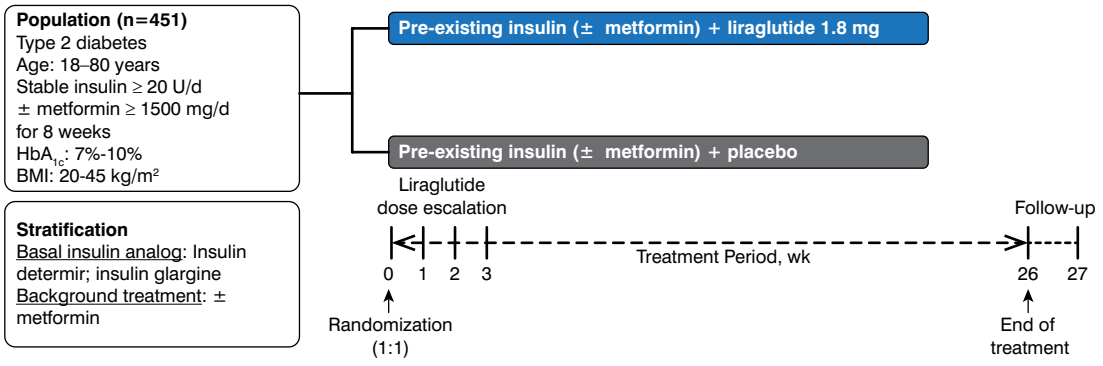
Jorma Lahtela, MD, PhD, Tampere University Hospital, Tampere, Finland, presented the results of the randomized, placebo-controlled Effect of Liraglutide Versus Placebo When Added to Basal Insulin Analogues With or Without Metformin in Subjects With Type 2 Diabetes trial [LIRA-ADD2BASAL; NCT01617434; Lahtela J et al. EASD 2014 (Oral Presentation 37)], comparing the efficacy and safety of liraglutide versus placebo when added to basal insulin analogs (insulin detemir or insulin glargine) in patients with type 2 diabetes mellitus (T2DM). Liraglutide 1.8 mg added to basal insulin analogs significantly improved glycemic control and reduced weight and blood pressure compared with placebo. Typical gastrointestinal symptoms and nonsevere hypoglycemia were reported more frequently with liraglutide than with placebo.

The 2012 American Diabetes Association/European Association for the Study of Diabetes position statement for the management of hyperglycemia recommends, as 1 of the 3-drug combinations, the addition of glucagon-like peptide–1 (GLP-1) receptor agonists to basal insulin analogs (or conversely, insulin to GLP-1 receptor agonists) after initial therapy with metformin [Inzucchi SE et al. *Diabetes Care.* 2012]. The goal of this trial was to establish the superior efficacy and acceptable safety of liraglutide, compared with placebo, when added to preexisting basal insulin analog with or without metformin in patients with inadequately controlled T2DM.

Patients were randomized 1:1 to receive once daily liraglutide 1.8 mg or placebo added to preexisting treatment for 26 weeks in this multicenter, multinational, double-blind, parallel-group design study (Figure 1). Patients with T2DM, aged 18 to 80 years, with body mass indexes (BMIs) of 20 to 45 kg/m^2 and HbA_{1c} level of 7% to 10%, and on stable insulin analog dose ≥ 20 U/d with or without stable metformin ≥ 1500 mg/d were eligible for participation. Insulin adjustments above the pretrial dose were not allowed.

A total of 450 patients were randomized in the trial, with a mean duration of diabetes of 12.1 years, a mean BMI of 32 kg/m^2, and a geometric mean pretrial insulin dose of 40.5 U. The mean baseline HbA_{1c} level was similar between groups (8.2% liraglutide, 8.3% placebo).

Figure 1. Study Design of LIRA-ADD2BASAL



BMI, body mass index.

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