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

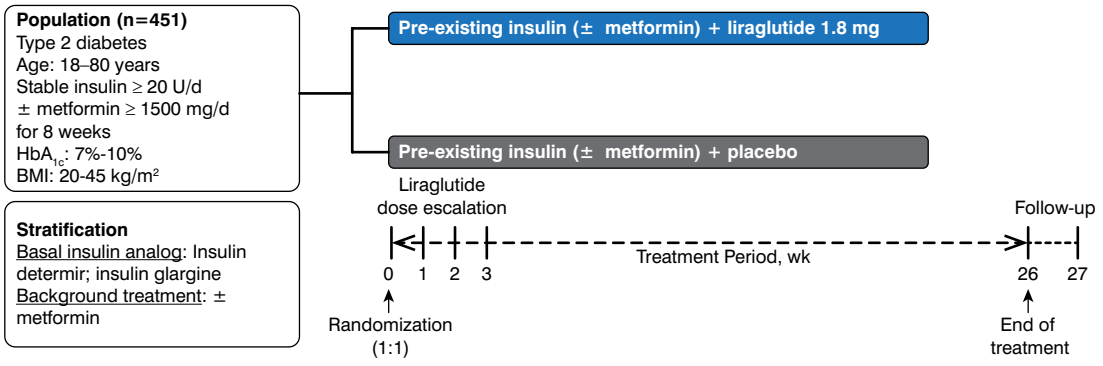
Jorma Lahtela, MD, PhD, Tampere University Hospital, Tampere, Finland, presented the results of the randomized, placebo-controlled Effect of Liraglutide Versus Placebo When Added to Basal Insulin Analogues With or Without Metformin in Subjects With Type 2 Diabetes trial [LIRA-ADD2BASAL; NCT01617434; 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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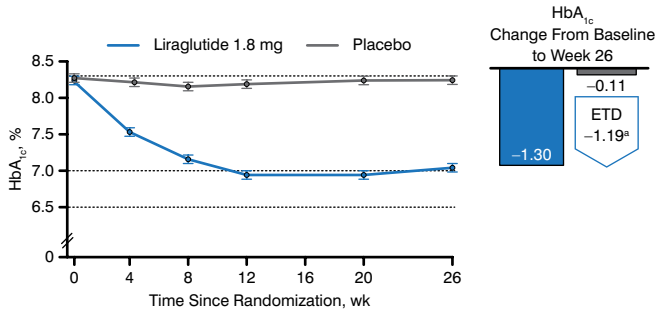
Figure 2. Change in HbA_{1c} in Patients Taking Liraglutide Versus Placebo Added to Basal Insulin Analogs



Estimated means ± standard errors, from mixed model for repeated measurements.
ETD, estimated treatment difference.
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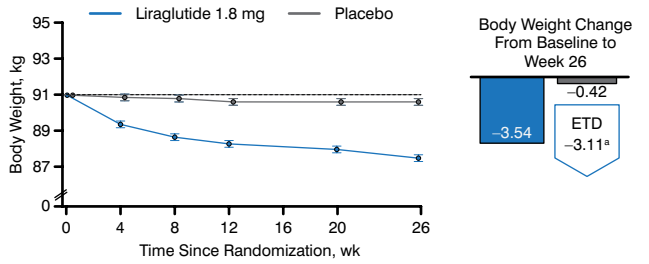
[a]95% CI, –1.39 to –0.99 (P<.0001).

Figure 3. Change in Weight in Patients Taking Liraglutide Versus Placebo Added to Basal Insulin Analogs



Estimated mean change from baseline to week 26, from mixed model for repeated measurements.
ETD, estimated treatment difference.
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[a]95% CI, –3.85 to –2.37 (P<.0001).

Three hundred sixty-five patients completed the trial. The primary end point was the change in HbA_{1c} from baseline to week 26. Patients taking liraglutide had a greater decrease in HbA_{1c} from baseline than those taking placebo (–1.3 and –0.11, respectively; Figure 2), and more liraglutide recipients reached HbA_{1c} < 7.0% (59.2% vs 14.0%) and HbA_{1c} ≤ 6.5% (42.9% vs 3.6%) (P<.0001 for both) despite using a lower mean estimated daily dose of basal insulin analog compared with placebo (35.8 vs 40.0 U).

Patients taking liraglutide also achieved greater decreases from baseline in fasting plasma glucose (FPG; –26 and –3 mg/dL, respectively), incremental postprandial self-measured plasma glucose (–17 and –7 mg/dL, respectively), body weight (Figure 3), systolic blood pressure (SBP) (–6 and –1 mm Hg, respectively), and lipids.

Nausea and vomiting occurred more frequently with liraglutide than placebo (22% vs 3% and 9% vs 1%, respectively). Minor hypoglycemia (plasma glucose < 56 mg/dL) occurred in 18% and 12% of liraglutide and placebo recipients, respectively. No severe hypoglycemic events (requiring assistance of another person) were reported during this trial.

In summary, the addition of liraglutide to insulin detemir or insulin glargine with or without metformin significantly improved glycemic control, which was attributed to the effect of liraglutide on both FPG and postprandial glucose levels. Additionally, liraglutide induced greater weight loss and reductions in SBP and selected lipids compared with placebo. Adverse effects were similar to those seen in other trials of liraglutide.

Dulaglutide Noninferior to Liraglutide for Glycemic Control in Patients With T2DM

Written by Maria Vinall

Results from the Assessment of Weekly Administration of LY2189265 in Diabetes-6 [AWARD-6; NCT01624259] trial, presented by Santiago Tofé Provedano, MD, Clinica Juaneda, Endocrinologia, Palma de Mallorca, Spain, show that once-weekly dulaglutide provides glycemic control that is noninferior to once-daily liraglutide with a similar safety and tolerability profile [Dungan KM et al. *Lancet*. 2014].

AWARD-6 was a phase 3 randomized, open-label, parallel-arm, 26-week study comparing the efficacy and safety of once-weekly dulaglutide 1.5 mg (n = 299), a long-acting glucagon-like peptide-1 receptor agonist, with once-daily liraglutide 1.8 mg (n = 300). Liraglutide was initiated at a dose of 0.6 mg/d and was titrated to 1.2 mg/d in week 2 and 1.8 mg/d in week 3. The study comprised type 2 diabetes (T2D) patients with an HbA_{1c} ≥ 7% and ≤ 10% who were on a stable dose of metformin (≥ 1500 mg) for ≥ 3 months.

Participants (~ 50% women and mostly white [86%]) had a mean age of 57 years and a mean HbA_{1c} of 8.1%. Most were obese (mean body mass index [BMI] 34 kg/m^2). The mean duration of diabetes was 7 years; mean daily metformin dose was more than 2000 mg. The primary study endpoint was the noninferiority of the change in HbA_{1c} from baseline to 26 weeks using a noninferiority margin of 0.4%. Superiority at week 26 (controlled for Type 1 error) was a key secondary endpoint and was to be tested if the noninferiority endpoint was met.

Dulaglutide was noninferior to liraglutide at 26 weeks (mean difference in HbA_{1c} –0.06%; 95% CI, –0.19