

**Liraglutide effects in insulin-treated patients in LEADER**

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**Background and aims:** Combining glucagon-like peptide 1 (GLP-1) analogues and insulin has complementary benefits, but long-term data are sparse. In the LEADER cardiovascular (CV) outcomes trial, rates of major CV events and hypoglycaemia were lower when liraglutide vs placebo was added to standard of care. A substantial number of patients in this trial were treated with insulin, providing detailed information on the combination insulin + GLP-1 for a median follow-up of 3.8 years.

**Materials and methods:** This post hoc subgroup analysis assessed metabolic parameters (HbA<sub>1c</sub>, weight, systolic BP and LDL cholesterol), severe hypoglycaemia and CV outcomes by baseline insulin use: no insulin vs basal-only vs other. The LEADER trial included 9340 patients; at baseline, 5171 (55%) patients were not on insulin treatment, 3159 (34%) were on basal-only insulin and 1010 (11%) were treated with other insulin regimens (9.7% premix). Insulin use at baseline was balanced overall between randomised treatment groups, but fewer patients randomised to liraglutide (29%) vs placebo (43%) initiated in-trial insulin.

**Results:** In the basal-only subgroup, liraglutide reduced HbA<sub>1c</sub> vs placebo (estimated treatment difference [ETD] -0.48%, 95% CI -0.57; -0.38), with a significant reduction in severe hypoglycaemia rate (estimated rate ratio 0.42, 95% CI 0.26; 0.68). Liraglutide also reduced weight (ETD -2.5 kg, 95% CI -3.0; -2.1) and there were trends for reductions in systolic BP (ETD -1.1 mmHg, 95% CI -2.4; 0.1) and LDL cholesterol (ETD -1.3 mg/dL, 95% CI -3.6; 1.0). The CV risk reduction observed with liraglutide in the full trial population was similar in the basal-only subgroup (estimated HR 0.84, 95% CI 0.70; 1.00). Results were similar in the no-insulin subgroup. There was heterogeneity in the results for the smaller, other insulin subgroup with reductions in HbA<sub>1c</sub> and weight, but no significant differences in other endpoints.

**Conclusion:** In basal insulin-treated patients with T2D and high CV risk, treatment with liraglutide improved glycaemic control, reduced body weight and halved the severe hypoglycaemia risk, with a similar CV risk reduction to patients not on insulin.

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