

Oral GLP-1: Is it time to rethink insulin glargine for T2D?

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Injectable insulin glargine has long been the fallback once oral and injectable diabetes drugs stop controlling blood sugar. ACHIEVE-4, the largest and longest cardiovascular outcomes trial run on the oral GLP-1 pill orforglipron, published in The Lancet, tested whether a once-daily pill could take that role instead, in patients already at high cardiovascular risk.¹

KEY TAKEAWAYS

- The Pivot: Orforglipron is the first oral, non-peptide GLP-1 drug shown non-inferior to insulin glargine on cardiovascular safety, while beating it on glycaemic control, weight loss and hypoglycaemia.
- The Data: MACE-4 occurred in 4.2% of orforglipron patients versus 5.0% on insulin glargine; HbA1c improved 0.50 points more and weight loss 8.9 points more with orforglipron, while severe hypoglycaemia was two-thirds lower (6.8% vs 19.2%).
- The Action: Consider orforglipron as an oral alternative to insulin glargine in patients with type 2 diabetes and cardiovascular risk who have not exhausted oral and injectable options, while setting expectations for gastrointestinal side effects that affected almost two-thirds of patients.

Orforglipron is an oral, non-peptide GLP-1 receptor agonist already approved for obesity in the United States and the United Kingdom. Peptide GLP-1 drugs have established cardiovascular benefit in trials, but no non-peptide oral version had been tested for cardiovascular safety at this scale before ACHIEVE-4.¹

The trial randomised 2,749 adults with type 2 diabetes and established cardiovascular or chronic kidney disease, 1,371 to daily oral orforglipron at the maximum tolerated dose and 1,378 to daily injectable insulin glargine, titrated as usual. Nearly 86% of participants had established cardiovascular disease and 37.5% had chronic kidney disease; mean baseline HbA1c was 8.2% and mean BMI was 33.1.

The Numbers

Over a median follow-up of two years, the primary composite of cardiovascular death, non-fatal heart attack, non-fatal stroke or hospitalisation for unstable angina occurred in 4.2% of orforglipron patients against 5.0% with insulin glargine, a hazard ratio 16% lower for orforglipron that did not reach statistical significance on its own, but cleanly met the trial's non-inferiority threshold.¹

On the drugs' actual job, the gap opened wide. HbA1c improved by an estimated 0.50 percentage points more with orforglipron, and by week 52, 65.7% of orforglipron patients reached an HbA1c below 7.0%, against 46.0% with insulin

glargine; 53.8% reached 6.5% or below, against 26.8%.

Weight loss showed a similar spread: orforglipron produced an estimated 8.9 percentage points more weight reduction. At week 52, 63.1% of orforglipron patients lost at least 5% of body weight, against 13.4% on insulin glargine; 35.6% lost at least 10%, against 4.4%.

Two safety measures favoured the pill outright. Clinically significant or severe hypoglycaemia hit 6.8% of orforglipron patients against 19.2% on insulin glargine, and 19 deaths (1.4%) occurred in the orforglipron group against 43 (3.2%) with insulin glargine, with all but one death in either group judged unrelated to treatment.

Gastrointestinal adverse events told the opposite story: 62.1% of orforglipron patients reported one, against 14.2% on insulin glargine, and GI complaints were the leading reason patients stopped taking orforglipron.

While the overall safety profile of orforglipron appears favorable compared to insulin glargine, particularly regarding hypoglycaemia and all-cause mortality, the significantly higher incidence of gastrointestinal adverse events (GI AEs) warrants careful consideration. These events, predominantly nausea, vomiting, and diarrhoea, are common with GLP-1 receptor agonists and are often dose-dependent. The high discontinuation rate due to GI AEs in the orforglipron arm (not explicitly stated but implied as the leading reason for cessation) highlights a critical practical challenge for patient adherence and long-term treatment success. Clinicians will need to manage patient expectations regarding these side effects and implement strategies for gradual dose escalation and symptomatic relief to improve tolerability. The ACHIEVE-4 trial's findings suggest a trade-off: superior glycaemic control and weight loss with orforglipron, coupled with a reduced risk of hypoglycaemia and potentially mortality, but at the cost of a higher burden of GI side effects.

The non-inferiority finding for cardiovascular outcomes, while not reaching statistical significance for superiority, is a crucial validation for orforglipron. This trial, ACHIEVE-4, is the first large-scale cardiovascular outcomes trial (CVOT) for a non-peptide oral GLP-1 receptor agonist, enrolling 2,749 adults with type 2 diabetes and established cardiovascular or chronic kidney disease. The primary composite endpoint of cardiovascular death, non-fatal heart attack, non-fatal stroke, or hospitalisation for unstable angina occurred in 4.2% of orforglipron patients versus 5.0% with insulin glargine, yielding a hazard ratio of 0.84 (95% CI 0.65-1.08). This result comfortably met the pre-specified non-inferiority margin of 1.3, establishing that orforglipron is not worse than insulin glargine for major adverse cardiovascular events (MACE). While the trial was not powered to demonstrate superiority for MACE, the observed trend towards a lower event rate with orforglipron is consistent with the established cardiovascular benefits of peptide GLP-1 receptor agonists. This finding provides clinicians with confidence in prescribing orforglipron to high-risk patients without concerns of increased cardiovascular risk, a significant advantage over some older diabetes medications.

Clinical Implications and Future Directions

The ACHIEVE-4 trial presents a compelling case for rethinking the role of insulin glargine as a first-line injectable for many patients with type 2 diabetes, particularly those with established cardiovascular or chronic kidney disease.

Orforglipron, an oral non-peptide GLP-1 receptor agonist, demonstrated superior glycaemic control, significant weight loss, and a dramatically lower risk of clinically significant or severe hypoglycaemia compared to titrated insulin glargine over a median follow-up of two years. Specifically, orforglipron led to an estimated 0.50 percentage point greater reduction in HbA1c and an estimated 8.9 percentage point greater weight reduction. The stark difference in hypoglycaemia rates (6.8% vs. 19.2%) is particularly impactful, addressing a major barrier to insulin adherence and a significant safety concern for patients and clinicians alike. These benefits, coupled with the oral route of administration, offer a substantial improvement in patient convenience and potentially adherence, which are critical factors in long-term diabetes management.

However, the clinical integration of orforglipron will require careful consideration of its side effect profile. The high incidence of gastrointestinal adverse events (62.1% vs. 14.2% for insulin glargine) and the fact that these were the leading reason for discontinuation highlight a practical challenge. While often transient and manageable with careful titration, these side effects can significantly impact patient quality of life and adherence. Clinicians will need to engage in thorough patient education regarding potential GI symptoms, strategies for managing them (e.g., smaller meals, slower titration), and the overall benefits of the medication. The trial design, comparing orforglipron to insulin glargine, provides a direct head-to-head comparison that is highly relevant to clinical practice, as insulin glargine remains a widely used basal insulin. The observed reduction in all-cause mortality (1.4% vs. 3.2%) with orforglipron, although not a primary endpoint and with most deaths deemed unrelated to treatment, warrants further investigation and adds to the overall favorable safety signal.

While ACHIEVE-4 provides robust evidence for orforglipron's efficacy and cardiovascular non-inferiority, certain limitations should be acknowledged. The trial was not blinded for treatment, which could introduce bias, particularly in the reporting of subjective side effects like GI complaints. Furthermore, the trial's

CLINICAL IMPLICATIONS

The headline finding here is not the cardiovascular non-inferiority, expected and now confirmed, it is that a pill beat an injection on every efficacy measure that matters day to day, in patients sick enough to need insulin in the first place. A hazard ratio 16% lower for MACE-4, even without statistical significance on its own, is not a result that argues against orforglipron on cardiovascular grounds; it is a result that clears the bar this trial was designed to test.

The hypoglycaemia numbers deserve equal billing with the headline weight and HbA1c figures. A two-thirds reduction in clinically significant hypoglycaemia, from 19.2% to 6.8%, is the kind of result that changes a patient's daily experience of managing diabetes, not just their lab values, and it is easy to lose under the more dramatic weight-loss percentages.

None of that erases the tolerability cost. Gastrointestinal adverse events in 62% of patients, against 14% with

insulin glargine, is a substantial burden, and it was the leading driver of discontinuation in the orforglipron arm. A clinician recommending this switch needs to set that expectation plainly, not let the weight and glucose numbers do the talking alone.

Eli Lilly funded the trial and will use it to position orforglipron as a genuine insulin alternative, not just an add-on therapy, for patients with cardiovascular risk who have not yet escalated to injectable insulin. The case is real. Whether an individual patient should take it comes down to the same tolerability conversation that governs every GLP-1 prescription, just with a pill instead of a needle on one side of the ledger now.

Orforglipron is also approved for obesity outside diabetes, and ACHIEVE-4 says nothing directly about that population's cardiovascular risk, since every participant here had established cardiovascular or kidney disease and type 2 diabetes already. A cardiologist or endocrinologist reading this trial for reassurance about orforglipron in a lower-risk patient is reading past what it actually tested.

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