Integral BioStrategy

INSIGHT

GLP-1's Forgotten Patients

GLP-1s won the average patient. The opening is everyone they leave behind.

Ivan A. Valdez, PhD

June 2026 · integralbiostrategy.com

The incretin drugs are one of modern medicine's genuine breakthroughs. Semaglutide takes the average patient to 15–17% body weight; tirzepatide to roughly 22.5% — and the benefit runs well past the scale. In landmark trials, semaglutide cut major cardiovascular events by about 20% in people with obesity and no diabetes,[1] and lowered kidney-disease events and deaths in type 2 diabetes.[2] For a field that spent decades with little to offer, this is a different era, and the enthusiasm is earned.

And precisely because they work so well for the average patient, they bring the next opportunity into sharp relief. Optimize hard for an average — scored on weight and glucose — and you begin to see who the average hides. Three groups stand out, and together they are large, growing, and largely unaddressed.

1 · The lean and the progressor.

Not everyone with type 2 diabetes is there because of excess fat. For a meaningful share, the disease is driven by failing β-cell function, not adiposity — glucose is the downstream readout of a problem upstream of weight. And this is no Western edge case: in Asian Indians, **24–39% of young-onset type 2 diabetes occurs at normal BMI — versus ~9% in white Europeans** — a lean, β-cell-driven phenotype common across South and East Asia,[3] where diabetes is rising fastest. This is not a niche left over from the obesity story; it is a large and growing population that drugs built for the obese average were never designed to fix.

2 · The older and the frail.

Weight is not one thing. A substantial share of the weight lost on incretin therapy is lean mass, not fat — by some body-composition estimates as much as ~40% (typically 20–30%).[4] We have optimized the *magnitude* of weight loss and barely measured its *composition*. For older patients, for the frail, for anyone whose function depends on muscle, "how much" is the wrong question; "what kind" is the right one — and most programs still aren't built to answer it.

3 · The patient who stops.

These drugs suppress the disease; they don't resolve it — and the benefit lasts only as long as the dose. In the **STEP 1** trial extension, people who had lost 17.3% on semaglutide regained two-thirds of it within a year of stopping, and their cardiometabolic gains drifted back toward baseline; the investigators concluded that ongoing treatment is required to maintain the effect.[5] Yet most don't stay on: 53.6% discontinue within a year — 64.8% among those without diabetes. A therapy that works only while taken, taken by a minority a year on, defines a maintenance problem the field has mostly waved at.

Underneath all three is the harder point. These drugs *suppress* weight and glucose; they have not been shown to *modify* the underlying disease. We have known since **UKPDS** that on every glucose-lowering therapy, control and β-cell function deteriorate progressively[6] — getting the number down was never the same as halting the disease. Which raises the question the field has not answered: if controlling glucose doesn't stop the disease, what does? That is the conversation worth leading — and the one this work means to open.

> **If controlling glucose doesn't stop the disease — *what does?***

None of this is an argument against incretins; it is the opposite. They worked well enough to reveal what they don't fix, and that remainder is where the next decade of metabolic medicine sits: muscle-preserving combinations,[7] durable maintenance, and disease-modifying approaches for the patient whose disease was never primarily about fat. The need is large, growing, and today largely untapped.

For anyone developing or investing in a metabolic asset, the question is no longer "how much weight does it take off?" Every program implicitly chooses who it leaves behind. The ones that win next will have chosen deliberately — and will know exactly who that is, and what their asset is meant to change.

Wondering who *your* asset leaves behind? **Request a confidential read** of where it sits.

The trials behind this piece

Trial	Published	What it showed
UKPDS[6]	1995	Type 2 diabetes is progressive — glycaemic control and β-cell function decline on every therapy.
ADOPT[6]	2006	Glucose-lowering monotherapy loses durability within a few years.
STEP 1 (extension)[5]	2022	A year after stopping semaglutide, about two-thirds of the lost weight returned.
SELECT[1]	2023	Semaglutide cut major cardiovascular events ~20% in adults with obesity and no diabetes.
FLOW[2]	2024	Semaglutide cut kidney-disease events ~24% and lowered death in type 2 diabetes with chronic kidney disease.
Body composition (meta-analysis)[4]	2024	GLP-1 weight loss includes lean (muscle) mass, not only fat — the *composition*, not just the amount.

∫ **The integrated read —** three decades tell one story. The disease is progressive (**UKPDS**, **ADOPT**); today's drugs suppress it better than anything before — weight, heart, and kidney (**STEP 1**, **SELECT**, **FLOW**) — yet the benefit holds only while the drug is taken, and the underlying decline continues. The frontier these trials point to is not better suppression; it is what finally *modifies* the disease — and for whom.

References

[1] SELECT — Lincoff et al., *N Engl J Med* 2023 (doi:10.1056/NEJMoa2307563): semaglutide reduced cardiovascular death, MI, or stroke (HR 0.80) in overweight/obesity without diabetes.

[2] FLOW — Perkovic et al., *N Engl J Med* 2024 (doi:10.1056/NEJMoa2403347): semaglutide reduced major kidney-disease events (HR 0.76) and all-cause death in type 2 diabetes with chronic kidney disease.

[3] Siddiqui et al., *Diabetologia* 2022 (doi:10.1007/s00125-022-05671-z); non-obese type 2 diabetes across Asia reviewed in Chuang & Tan, *J Biomed Sci* 2017 (doi:10.1186/s12929-016-0307-7).

[4] GLP-1 weight loss includes significant lean (muscle) mass alongside fat — meta-analysis of 19 randomized trials, Jiao et al., *Diabetes Obes Metab* 2024 (doi:10.1111/dom.16012). The lean fraction is sizeable (≈45% of weight lost with semaglutide, ≈25% with tirzepatide) and its clinical significance is not yet established — Ryan, *Rev Endocr Metab Disord* 2025 (doi:10.1007/s11154-025-09967-4).

[5] Wilding et al., *Diabetes Obes Metab* 2022 — **STEP 1** trial extension (doi:10.1111/dom.14725).

[6] **UKPDS** 16, *Diabetes* 1995 (PMID 7589820) — glycaemic deterioration with progressive loss of β-cell function on all therapies; monotherapy durability also fails over time, **ADOPT**, Kahn et al., *N Engl J Med* 2006 (doi:10.1056/NEJMoa066224).

[7] Muscle-preserving approaches in development — myostatin/activin-pathway inhibition (bimagrumab) and GLP-1 combinations with glucagon or amylin; reviewed in Ryan, *Rev Endocr Metab Disord* 2025 (doi:10.1007/s11154-025-09967-4).