Glucagon-Like Peptide-1 Receptor Agonists in Diabetes and Obesity

Real-World Effectiveness, Cardiometabolic Value, and Implications for Health Benefit Design

Chelko

Health Plan Advisors + Fiduciaries

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have reshaped the management of type 2 diabetes mellitus and obesity. While randomized clinical trials demonstrate substantial weight loss, improved glycemic control, and modest reductions in major adverse cardiovascular events, real-world experience diverges meaningfully from trial efficacy. Discontinuation, limited lifestyle support, and high cost materially affect outcomes.

This white paper synthesizes clinical trial evidence, real-world data, and economic considerations to define the appropriate role of GLP-1 RAs within modern cardiometabolic care and health benefit design.

Introduction

GLP-1 receptor agonists represent one of the most consequential pharmacologic developments in metabolic disease management in decades. Initially approved for glycemic control in type 2 diabetes, their pleiotropic effects on appetite regulation, weight loss, insulin resistance, and cardiovascular risk have driven rapid adoption across diabetes and obesity care. Concurrently, their high and recurring cost has generated significant scrutiny among employers, payers, and policymakers.

Clinical enthusiasm has largely been shaped by outcomes observed in tightly controlled clinical trials. However, routine clinical practice differs substantially from trial environments, with fewer behavioral supports, greater heterogeneity in patients, and far lower persistence. Understanding these differences is essential for evaluating both the clinical and economic value of GLP-1 therapy.

GLP-1 Receptor Agonists in Type 2 Diabetes

Metformin remains the foundation of type 2 diabetes treatment due to its durability, safety profile, weight neutrality, and minimal cost. In patients who maintain hemoglobin A1C within individualized targets on metformin, the incremental glucose-lowering impact of adding a GLP-1 receptor agonist is typically modest.

Accordingly, contemporary guidelines emphasize risk-based indications for GLP-1 initiation rather than glycemia alone. The primary value of GLP-1 therapy in diabetes lies beyond glucose lowering, driven instead by weight reduction and broader cardiometabolic risk modification, particularly among patients with obesity or established cardiovascular disease.

Weight Loss: Trial Efficacy Versus Real-World Effectiveness

Clinical trials such as STEP and SURMOUNT report levels of weight loss rarely achieved with pharmacotherapy alone. These outcomes reflect deliberate integration of reduced-calorie diets, physical activity expectations, and structured behavioral counseling—components that materially contribute to observed weight loss and persistence.

In contrast, real-world GLP-1 use typically occurs without comparable lifestyle scaffolding. Nutrition counseling, structured exercise programming, and longitudinal coaching are inconsistently provided. As a result, real-world effectiveness is substantially lower, and discontinuation rates are high.

Table 1. GLP-1 Receptor Agonist Use in Clinical Trials Versus Real-World Practice

Dimension	Clinical Trials	Real-World Practice
Dietary intervention	Required, structured calorie reduction	Variable or absent
Physical activity	Prescribed and reinforced	Inconsistent or unmonitored
Behavioral coaching	Frequent, scheduled and monitored	Rare or episodic
Follow-up frequency	High, protocol-driven	Low to moderate
Medication persistence	High	Low

The absence of structured lifestyle support explains much of the gap between trial efficacy and real-world outcomes, including reduced persistence and rapid weight regain following discontinuation.

Structured Lifestyle Interventions and Body Composition

Lifestyle support is a central determinant of GLP-1 effectiveness. Trial protocols integrate frequent counseling, behavioral reinforcement, and dose-escalation monitoring. In routine practice, GLP-1s are often deployed as medication-only interventions.

Emerging evidence indicates that a meaningful proportion of GLP-1–associated weight loss may consist of lean mass, particularly in the absence of resistance training and adequate protein intake. These findings raise concerns regarding sarcopenic obesity and functional decline with long-term use.

Cardiovascular Outcomes and Comparative Value

Large cardiovascular outcome trials demonstrate that GLP-1 receptor agonists reduce major adverse cardiovascular events. However, these benefits are incremental and occur in addition to—not instead of—established cardiovascular therapies such as statins, blood-pressure control, and renin-angiotensin system inhibitors.

Table 2. Conceptual Comparison of Cardiovascular Risk-Reduction Strategies

Therapy category	Primary clinical role	Relative value profile
Statins / BP therapy / ACE-I	Foundational ASCVD risk reduction	High value; cost-saving
SGLT2 inhibitors	HF and CKD risk reduction	Moderate value in selected populations
GLP-1 receptor agonists	Adjunctive cardiometabolic modification	Low–moderate value; context-dependent

From a value perspective, GLP-1 receptor agonists function best as adjunctive cardiometabolic modifiers rather than primary cardiovascular drugs.

Economic Considerations and Benefit Design Implications

The high annual cost of GLP-1 therapy magnifies the clinical consequences of poor persistence. When used without targeted eligibility criteria and lifestyle integration, GLP-1 coverage is structurally inefficient and unlikely to achieve the outcomes observed in trials.

Value is maximized when GLP-1 therapy addresses overlapping risks—diabetes control, obesity, and cardiovascular disease—within carefully selected populations.

Conclusion

GLP-1 receptor agonists represent a genuine advance in cardiometabolic care, but their effectiveness and value are highly context-dependent. Trial efficacy does not reliably translate into real-world benefit absent structured behavioral support and disciplined deployment.

For employers and payers, the relevant question is no longer whether GLP-1s work, but whether they are used in ways that justify their cost and deliver durable benefit.

References

A. Clinical Trials & Guidelines

- ADA *Standards of Care in Diabetes* (2025–2026)
- STEP trials (semaglutide)
- SURMOUNT trials (tirzepatide)
- LEADER, SUSTAIN-6, REWIND CVOTs

B. Real-World Evidence

- Rodriguez et al., *JAMA Network Open* – GLP-1 discontinuation
- Truveta / claims-based persistence analyses
- Cleveland Clinic real-world obesity outcomes
- Omada Health observational data

C. Lifestyle & Body Composition

- Lundgren et al., *Lancet Healthy Longevity*
- Heymsfield et al., *Obesity Reviews*
- Lean-mass and resistance-training analyses

D. Cardiovascular & Economic Context

- Kalayci et al., *EHJ CV Pharmacotherapy* (meta-analysis)
- ACC clinical guidance
- The Lancet health-economic commentary
- Employer/payer cost analyses (e.g., Aon)

Welcome to Value-Based Drug Management

Early on, Chelko learned that rebate-driven prescription drug deals were costing employers dearly. We were also at the forefront of identifying troubling specialty drug use and cost trends.

These discoveries led us to develop deep subject matter expertise with respect to the management of drug benefits programs and specialty drug spend within the medical benefit (usually 40% of drug spend).

As a result, we developed a very distinctive prescription drug benefits management practice that delivers tremendous results for our clients.

With pharmacists on our team, we go well beyond the traditional financial analysis (i.e., ensuring very competitive discounts, fees, and rebates). Our team's hands-on approach includes clinical reviews and recommendations at both the plan and claimant levels (i.e., Prior Authorization Management, Site of Care, Cell & Gene Therapy Management, etc.).

While others mistakenly chase discounts and rebates, we focus on removing waste and excessive profiteering from plans and helping members more affordably get the medications they need.

Our approach not only results in much lower costs to the plan, but also improves member experience and outcomes. The results have been impressive — individually and in the aggregate, and we believe our references would say the same.

We have helped clients save hundreds of thousands, and even millions, of dollars on specialty drugs for specific claimants, and have helped them reduce overall specialty drug spend by 30%.

More Than Advisors

Chelko has always conducted analysis and provided recommendations free of any conflicts of interest. This includes our unique policy of never accepting overrides or contingent rewards from vendors—unheard of among our competitors.

And now, with a brighter spotlight on fiduciary responsibilities related to health and welfare benefit plans, we've decided to take our commitment a step further.

Chelko is willing to serve as a fiduciary alongside our clients—the first health and welfare benefits consulting firm in the country to do so.

We've always acted as fiduciaries—helping our clients steward their plans and manage them as if they were our own. Now we're making it official.

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The Chelko Consulting Group offers proven health benefits expertise for plan sponsors to confidently make decisions that reduce cost and improve member experience within their medical, prescription drug, dental, vision, and wellness plans. And we've been doing it for 25 years.