AAVBC

American Academy of Value Based Care

Landscape and Utilization of GLP-1 Receptor Agonists in Value-Based Care

2026

Landscape and Utilization of GLP-1 RAs in VBC Quick Reference Guide

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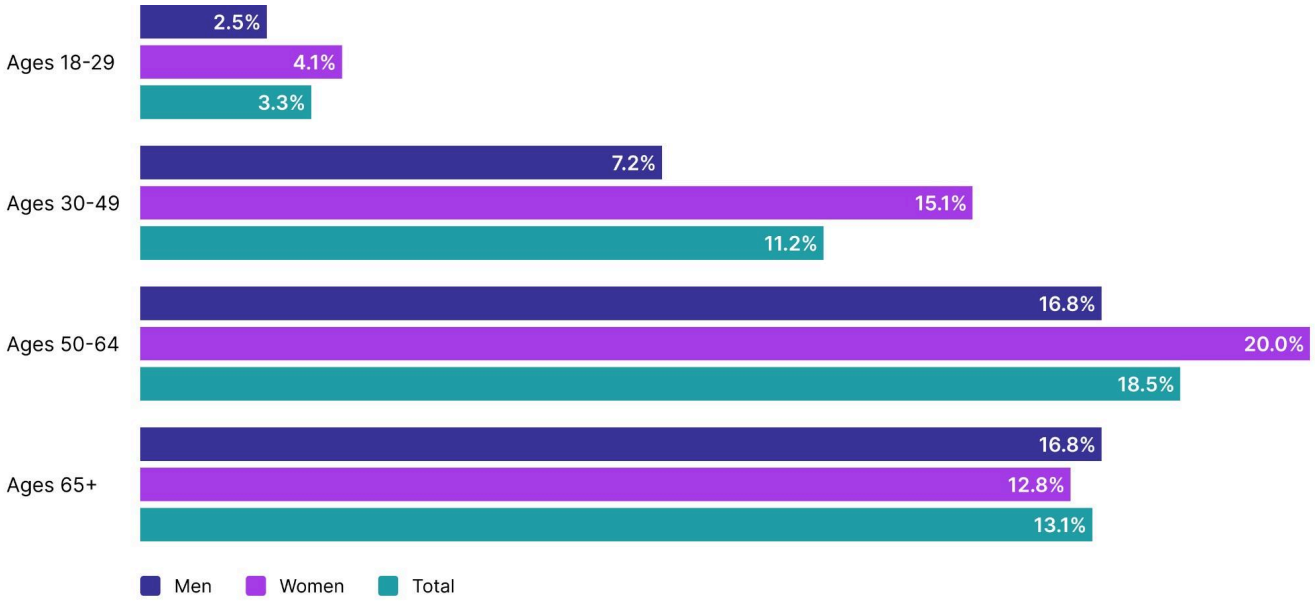
Introduction

Utilization management in value-based care (VBC) is not about restricting access; it is about aligning clinical deployment with sustainability, evidence, and patient-centered outcomes. When utilization of a therapy accelerates rapidly, it signals the need for structured review to ensure appropriate and durable use.

Percentage of U.S. Adults Reporting GLP-1 Agonist Use, by Age and Sex



SOURCE: Authors' analysis of RAND American Life Panel survey data, April–May 2025.
NOTE: n = 8,793.

Figure 1. GLP-1 use is highest among adults aged 50-64 (18.5% overall), with consistently higher reported use among women across age groups. These data illustrate demographic concentration of exposure, relevant for population-level monitoring and sustainability planning in value-based care models.

A 2025 analysis of U.S. outpatient prescription spending found that annual spending on GLP-1 receptor agonists (GLP-1 RA) increased from **$13.66 billion** in 2018 to **$71.66 billion** in 2023 (inflation-adjusted), with a **62% increase** between 2022 and 2023 alone.[1] During this period, semaglutide- and tirzepatide-based products accounted for approximately 70% of total GLP-1 RA spending, reflecting a marked concentration in higher-cost agents.[1]

Independent claims-based analyses have similarly documented a dramatic rise in GLP-1 utilization for obesity and overweight. FAIR Health reported a 587% increase in GLP-1 prescribing for obesity between 2019 and 2024.[2] A RAND analysis further estimated that nearly 12% of U.S. adults have used GLP-1 medications for weight loss, with highest use among women aged 50-64.[3]

This degree of spending velocity and population exposure has material implications for Medicare Advantage (MA) plans, accountable care organizations (ACOs), and Advanced Primary Care (APC) models operating under shared financial accountability.

Medicare Utilization and Spending Trends

Utilization growth has also been pronounced within Medicare, where policy constraints create a unique tension between demand and coverage.

Medicare currently covers GLP-1 therapies for type 2 diabetes, cardiovascular disease, and sleep apnea, but **coverage for weight loss remains prohibited under federal law** — even as clinical evidence supporting their use for obesity has continued to strengthen. Despite this statutory constraint, utilization and spending have grown substantially, driven by expanding FDA-approved indications for conditions Medicare does cover.[4] Furthermore, to address this gap, CMS has announced the **BALANCE (Better Approaches to Lifestyle and Nutrition for Comprehensive health) model**, which will begin in **2026 for Medicaid and 2027 for Medicare**, allowing voluntary participation by manufacturers, states, and Part D plans to test expanded access to obesity pharmacotherapy alongside lifestyle interventions.[4]

At the same time, the **Medicare Drug Price Negotiation Program** will introduce negotiated pricing for certain GLP-1 therapies, including **semaglutide beginning in 2027 and dulaglutide in 2028**, which could partially offset future spending growth as utilization expands.

Beneficiary Utilization (Part D Enrollees)

Agent	2019	2024	Change
Ozempic (semaglutide)	<150,000	~2 million	>13× increase
Mounjaro (tirzepatide)	54,000 *(2022 baseline)*	~1 million	~18× increase over 2 years
Older agents (Byetta, Victoza, Trulicity)	Higher share	Declining	Shift toward newer agents

This pattern reflects growing use of newer GLP-1s while use of older products has declined.The introduction of new oral formulations, which may be easier for some patients to take, could result in additional shifts in utilization among GLP-1s.

Spending (Medicare Part D)

Measure	Figure
Gross Part D GLP-1 spend, 2024	**$27.5 billion** (5× increase from 2019)
Estimated net spend after rebates (~50%)	**~$14 billion (est. 10% of total Part D spending)**

Measure	Figure
Semaglutide products' share of 2024 gross spend	>50% (Ozempic 47%, Rybelsus 7%, Wegovy 1%)
Mounjaro share of 2024 gross spend	~23%
Obesity	Yes (specific agents)

Claims Volume (Medicare Part D)

Metric	2019	2024	Change
Total GLP-1 Part D claims	4.8 million	21.8 million	4× increase
Mounjaro (tirzepatide)	54,000 *(2022 baseline)*	~1 million	~18× increase over 2 years
Older agents (Byetta, Victoza, Trulicity)	Higher share	Declining	Shift toward newer agents

Claims doubled between 2022 and 2024 alone.

Medicare Part D Gross Spending on GLP-1s Increased 5-Fold between 2019 and 2024[4]

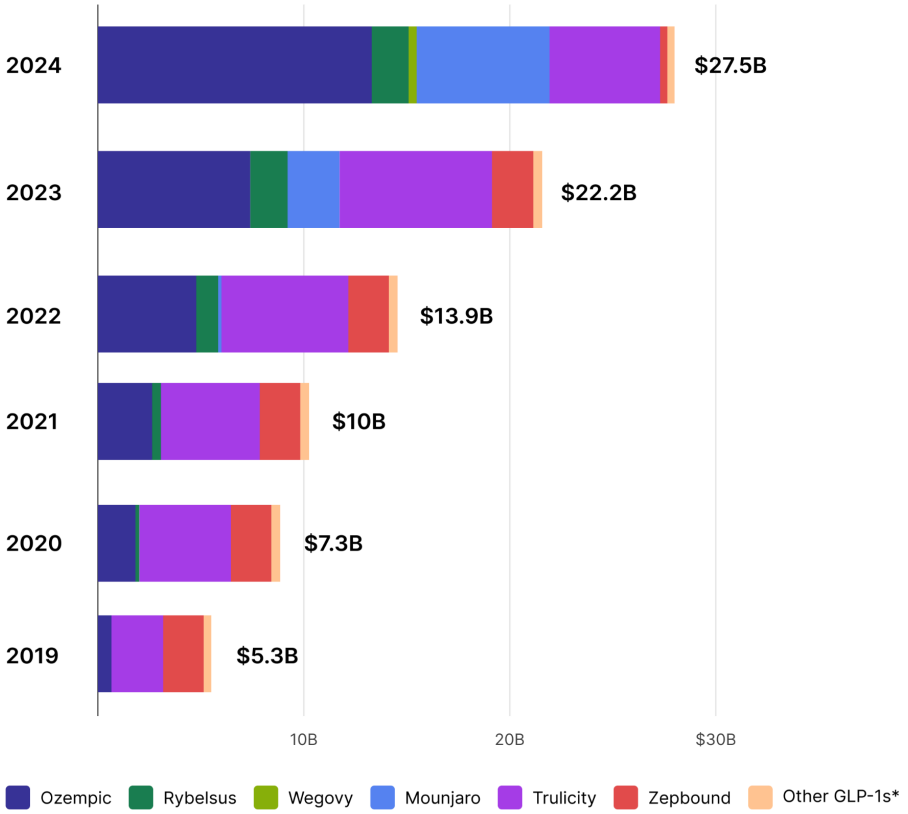


Figure 2. Medicare Part D spending on GLP-1 receptor agonists increased from **$5.3 billion in 2019** to **$27.5 billion in 2024**, representing more than a five-fold rise in gross drug spending. Earlier in the period, spending was concentrated in long-established agents such as **dulaglutide (Trulicity: $2.27B in 2019)** and **liraglutide (Victoza: $1.89B in 2019)**. By 2024, utilization had shifted substantially toward newer therapies, with **semaglutide (Ozempic) accounting for $12.97B**, **tirzepatide (Mounjaro) $6.34B**, **dulaglutide (Trulicity) $5.45B**, and **oral semaglutide (Rybelsus) $1.89B** in gross Part D spending. Smaller but emerging contributions include **semaglutide (Wegovy) $0.30B**, while **earlier GLP-1 therapies and other agents together accounted for approximately $0.56B**. Because manufacturer rebates in Part D are commonly estimated at **~50%**, net spending is likely substantially lower than the gross totals shown.

For value-based care organizations, these trends highlight the growing fiscal and clinical significance of incretin therapies within the Medicare population and underscore the importance of structured deployment strategies that balance access, evidence-based indications, and long-term sustainability.

Structural Shift in Chronic Disease Management

GLP-1 receptor agonists now occupy a central role in treatment algorithms for type 2 diabetes and obesity. The 2025 American Diabetes Association (ADA) Standards of Care recommend GLP-1 RAs for individuals with type 2 diabetes and established atherosclerotic cardiovascular disease, chronic kidney disease, or high cardiometabolic risk, independent of baseline HbA1c in certain contexts.[5]

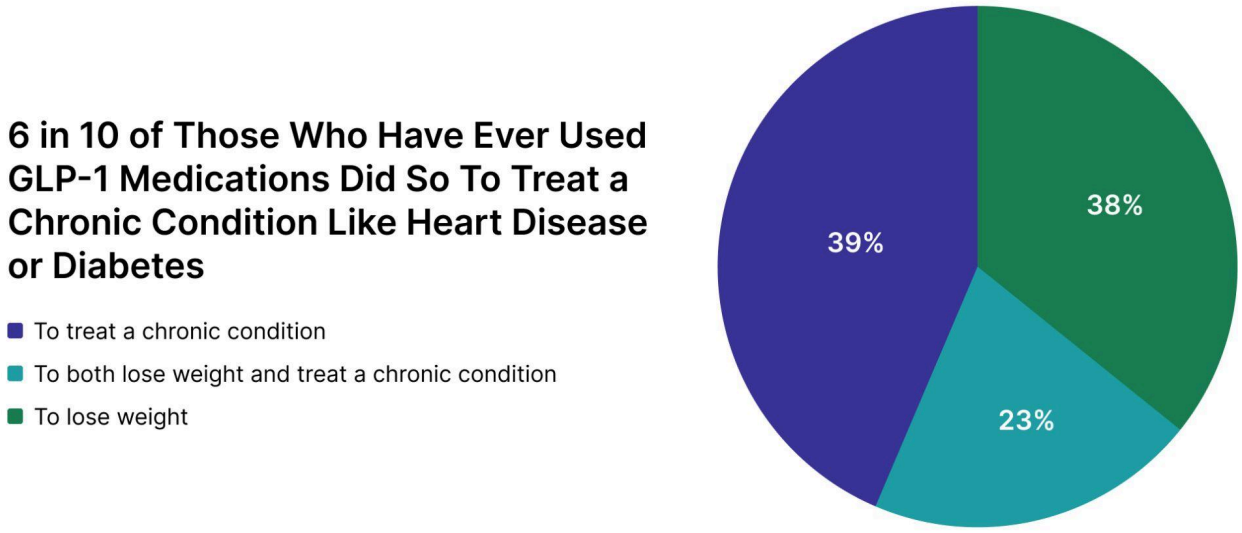


Figure 3. Indications for GLP-1 Medication Use Among Prior Users (U.S.). Among individuals who have ever used a GLP-1 medication, 39% report use primarily to treat a chronic condition, 38% primarily for weight loss, and 23% for both indications. These findings highlight the dual clinical and weight-management roles GLP-1 therapies now occupy in practice.[5]

Cardiovascular outcome trials (CVOTs) have demonstrated reductions in major adverse cardiovascular events (MACE) with several GLP-1 agents, including liraglutide (LEADER), semaglutide (SUSTAIN-6), and dulaglutide (REWIND).[7-9] Oral semaglutide has also demonstrated cardiovascular benefit in high-risk populations.[10]

Kidney outcome data further strengthen the evidence base. In the FLOW trial, semaglutide reduced the composite endpoint of kidney failure, sustained ≥50% decline in eGFR, or renal death in patients with type 2 diabetes and chronic kidney disease.[11] KDIGO 2024 guidelines recognize GLP-1 RAs as appropriate adjunctive therapy in patients with diabetes and CKD when additional glycemic or cardiovascular risk reduction is needed.[12]

In obesity without diabetes, semaglutide and tirzepatide have demonstrated substantial weight reduction in randomized trials.[13,14] However, weight regain after discontinuation remains common, emphasizing the importance of durability and long-term care integration.[15]

The Central Tension: Cost Versus Value

The clinical efficacy of GLP-1 RAs is well established in glycemic control, weight reduction, and cardiovascular risk modification.[5-10] However, high acquisition costs create financial pressure in risk-bearing systems.

The Congressional Research Service has noted variability in Medicare coverage for GLP-1 drugs, particularly for obesity indications, with statutory limitations affecting reimbursement pathways.[16] Medicaid coverage similarly varies across states.[17]

For VBC entities, the timing mismatch is central: pharmacy costs are immediate, whereas reductions in cardiovascular events, hospitalizations, or kidney failure accrue over years. ICER's 2025 evidence report concluded that long-term value depends heavily on sustained adherence and complication reduction rather than short-term weight loss alone.[18]

Real-world persistence data reinforce this concern. In commercially insured adults without diabetes, one study found substantial discontinuation rates within the first year of therapy.[19] If adherence and persistence decline, projected downstream savings may not fully materialize.

Sustainability in Value-Based Care

VBC models must reconcile three realities:

1. GLP-1 therapies provide clinically meaningful benefits in selected populations
2. Spending growth has been rapid and concentrated in high-cost agents
3. Population-level adoption is expanding beyond narrowly defined cardiometabolic cohorts

Sustainability requires:

- Alignment with evidence-based indications (ADA, KDIGO)[5,12]
- Clear documentation of clinical complexity
- Longitudinal monitoring and reassessment
- Equity-conscious coverage strategies
- Transparency in measuring real-world outcomes

The objective is not utilization suppression. It is stewardship, ensuring that GLP-1 therapy is deployed where benefit is most likely and sustained.

Mechanisms of Action and the Basis for Broad Clinical Effects

Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone secreted from intestinal L-cells in response to nutrient ingestion. Native GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon release, slows gastric emptying, and promotes satiety.[20,21] Synthetic GLP-1 receptor agonists (GLP-1 RAs) are structurally modified to resist rapid enzymatic degradation by dipeptidyl peptidase-4 (DPP-4), extending biologic activity from minutes to hours or days depending on formulation.[20]

GLP-1 receptors are expressed across multiple organ systems, including pancreatic β-cells, the central nervous system, cardiovascular tissue, kidney, and gastrointestinal tract.[19] This broad receptor distribution helps explain why clinical effects extend beyond glycemic control.

Why the Effects Appear Broad

The apparent "breadth" of GLP-1 therapy does not reflect a single pharmacologic pathway. Rather, it reflects:[18]

1. Multisystem receptor expression
2. Central regulation of appetite and caloric intake
3. Downstream reduction in adiposity and insulin resistance
4. Secondary improvements in blood pressure, lipids, and inflammation

Because adiposity and insulin resistance are upstream drivers of multiple chronic diseases, therapies that meaningfully reduce these processes may produce multisystem benefits.

For value-based care environments, mechanistic clarity supports appropriate deployment. It reinforces that:

- Cardiovascular and kidney benefits are evidence-based for specific agents and populations[5-10]
- Weight-mediated improvements require sustained therapy and monitoring
- Discontinuation may attenuate long-term benefit[13,15]
- Broad physiologic effects do not imply universal indication

Mechanism informs stewardship. Evidence determines indication.

FDA-Approved Indications and Emerging Clinical Signals

The rapid expansion of GLP-1 receptor agonist (GLP-1 RA) use has blurred distinctions between regulatory approval, outcome trial evidence, and emerging investigational signals. For value-based care

environments, clarity regarding labeled indications is essential for appropriate deployment and documentation integrity.

FDA-Approved Indications (Established Labeling)

Type 2 Diabetes Mellitus

Multiple GLP-1 RAs are FDA-approved for glycemic control in adults with type 2 diabetes (T2DM), including liraglutide, semaglutide (injectable and oral), dulaglutide, exenatide, lixisenatide, and tirzepatide (dual GIP/GLP-1 receptor agonist).[5]

AADA 2026 Standards of Care: While SGLT2 inhibitors remain the first-line therapy for heart failure in patients with diabetes, the ADA now recognizes GLP-1 RAs as complementary agents that provide additional cardiometabolic benefits, particularly for those with a high obesity burden.[5]

- **AADA HFpEF Update:** GLP-1 RAs and dual GIP/GLP-1 RAs are now specifically recommended for patients with T2DM, obesity, and symptomatic heart failure **with preserved ejection fraction (HFpEF)**[5]

Cardiovascular Risk Reduction (Label-Specific)

Several GLP-1 receptor agonists have FDA-approved labeling for reduction of major adverse cardiovascular events (MACE) in adults with T2DM and established cardiovascular disease, based on cardiovascular outcome trials (CVOTs):[7-9]

- **Liraglutide (LEADER)**[7]
- **Injectable semaglutide (SUSTAIN-6)**[8]
- **Dulaglutide (REWIND)**[9]
- **Oral semaglutide (SOUL trial–based approval)**[10]

These approvals are **agent-specific and should not be interpreted as a uniform class effect.** Cardiovascular labeling varies by product and population studied.

Chronic Kidney Disease (Agent Specific Context (T2DM + CKD))

In **January 2025**, the FDA approved semaglutide (Ozempic) to reduce the risk of kidney failure, sustained eGFR decline, and cardiovascular death in adults with T2DM and CKD.[11,12]

- **The FLOW Trial**: Demonstrated a **24% relative risk reduction** in major kidney events, moving GLP-1 RAs from "adjunctive" to "primary" renal labeling[11]

GLP-1 RAs are not primary renal hemodynamic agents in the way SGLT2 inhibitors are. However, outcome data support their adjunctive role in appropriate T2DM + CKD populations.[12]

Kidney benefit is currently **agent-specific**, not a generalized class indication.

Obesity and Chronic Weight Management

Semaglutide 2.4 mg (Wegovy®) and tirzepatide (Zepbound®) are FDA-approved for chronic weight management in adults with:

- BMI ≥30 kg/m², or
- BMI ≥27 kg/m² with at least one weight-related comorbidity

These approvals are based on randomized trials demonstrating substantial and sustained weight reduction.[13, 14]

However, discontinuation studies demonstrate frequent weight regain following cessation, reinforcing that pharmacologic obesity management may require long-term continuation to sustain benefit.[15]

Obesity treatment labeling is separate from diabetes-focused products.

Metabolic Dysfunction-Associated Steatohepatitis (MASH)

Phase 3 data demonstrated higher rates of MASH resolution with semaglutide compared with placebo.[22]

Regulatory actions have followed for specific agents; however:

- Long-term fibrosis progression data remain under evaluation
- Durability of histologic response requires ongoing study

This remains a rapidly evolving regulatory domain.

Emerging or Investigational Signals (Not Universal Labeling)

Neuroprotection and Cognitive Outcomes

GLP-1 receptors are expressed in the central nervous system, prompting investigation into neurodegenerative conditions.[20]

However:

- Robust clinical outcome data remain limited
- No GLP-1 RA currently carries FDA approval for neurocognitive indications

Neuroprotective benefit should not be assumed outside investigational settings.

Cardiovascular Prevention in Obesity Without Diabetes

The SELECT trial demonstrated cardiovascular event reduction with semaglutide in adults with obesity and established cardiovascular disease without diabetes.[23]

This finding expands the clinical conversation but applies specifically to:

- The studied population
- The studied dosing regimen
- The defined cardiovascular risk cohort

Generalization beyond trial criteria is not supported

Expanded Renal Indications

Comparative and observational analyses suggest differential effects between GLP-1 RAs and SGLT2 inhibitors in kidney and heart failure outcomes.[5, 12]

However:

- SGLT2 inhibitors remain foundational for heart failure and renal hemodynamic protection[5]
- GLP-1 RAs should generally be considered complementary rather than substitutive in CKD and HF populations[12]

No GLP-1 RA currently carries a primary heart failure indication.

FDA-Approved Indications Summary

Clinical Domain	FDA-Labeled Indication	Outcome Trial Evidence	Evidence Strength	Operational Note
Type 2 Diabetes	Yes	HbA1c reduction; CVOTs[5,7-9]	High	Risk-based use per ADA
ASCVD Risk Reduction	Agent-specific	Reduction in MACE; LEADER[7], SUSTAIN-6[8], REWIND[9]	High	Not uniform class effect
CKD (T2DM + CKD)	Primary	Reduced kidney events; FLOW[11]	High (agent-specific)	Complement SGLT2
Obesity	Yes (specific agents)	Sustained weight reduction; STEP[13], SURMOUNT[14]	High	Chronic therapy often required[13]
MASH	Accelerated regulatory action	Histologic resolution; Phase 3 data[22]	Moderate–High	Long-term outcomes pending
Neuroprotection	No	Mechanistic rationale[20]	Investigational	Not standard care

Agent-Specific Summary

Agent	FDA-Approved Indications	Cardiovascular/Kidney Outcome Evidence	Key VBC Considerations
Liraglutide	• T2DM (glycemic control)	LEADER demonstrated reduced MACE in T2DM with ASCVD[7]	CV-labeled agent; weight reduction modest vs newer agents

Agent	FDA-Approved Indications	Cardiovascular/Kidney Outcome Evidence	Key VBC Considerations
	• ASCVD risk reduction in T2DM • Obesity (separate weight-loss formulation)		
Semaglutide (injectable)	• T2DM • ASCVD risk reduction in T2DM • Obesity (2.4 mg formulation)	SUSTAIN-6 (CV benefit)[8] FLOW (CKD benefit in T2DM+CKD)[11]	Broadest multi-domain evidence base; high pharmacy concentration
Semaglutide (oral)	• T2DM • ASCVD risk reduction (high-risk T2DM)	CV benefit demonstrated in high-risk T2DM[10]	Oral option; adherence variability may affect durability
Dulaglutide	• T2DM • ASCVD risk reduction in T2DM	REWIND demonstrated reduced MACE[9]	Weekly administration; CV-labeled
Exenatide	• T2DM	CV safety demonstrated (non-inferior)	Older agent; limited differentiation in VBC models
Lixisenatide	• T2DM	CV safety (non-inferior)	No superiority in CV outcomes
Tirzepatide*	• T2DM • Obesity	CV outcomes evolving; weight reduction; SURMOUNT[14]	Dual GIP/GLP-1 agonist; high weight efficacy; cost concentration

* Tirzepatide is a dual GIP/GLP-1 receptor agonist but is included due to similar clinical deployment patterns

Emerging/Expanding Signals (Not Universal FDA Indication)

Clinical Domain	Current Status	Evidence Reference
MASH (Metabolic Dysfunction–Associated Steatohepatitis)	Regulatory action following Phase 3 data (agent-specific)	Semaglutide Phase 3[22]
CV prevention in obesity without diabetes	Demonstrated in SELECT population; indication expansion context-specific	SELECT[23]
Neurocognitive/neuroprotective use	Investigational; not standard indication	Mechanistic review[20]
Primary renal protection outside T2DM	Not established; adjunctive role in T2DM+CKD	FLOW[11]; KDIGO[12]

Brand Differentiation and Treatment Positioning

GLP-1–based therapies are not clinically or contractually interchangeable. Molecule, indication labeling, cardiovascular outcomes data, dosing cadence, and rebate alignment collectively determine appropriate positioning within value-based care strategy.

FDA-Approved GLP-1 RAs (U.S.) — Brand-Level Clarity

As formulary management, claims data, and prior authorization are typically brand-specific, clarity at the product level is essential.

Active Ingredient	Brand Names (U.S.)	Dosing Frequency	Pharmacologic Class
Semaglutide	Ozempic (T2DM) Wegovy (Obesity) Rybelsus(T2DM)	Weekly (Injection) Daily (Oral)	**GLP-1 RA**
Tirzepatide (Dual & Triple Agonists)	Mounjaro (T2DM) Zepbound (Obesity)	Weekly (Injection)	**Dual GLP-1/GIP RA**
Liraglutide	Victoza (T2DM) Saxenda (Obesity)	Daily (Injection)	**GLP-1 RA**
Dulaglutide	Trulicity (T2DM)	Weekly (Injection)	**GLP-1 RA**
Orforglipron (Small Molecule, Non-peptide)	Pending U.S. Brand (Expected 2026)	Daily (Oral)	**Non-peptide, Small Molecule GLP-1 RA**

Semaglutide Products (U.S.)

Brand Name	Initial FDA Approval	Dosage Forms (U.S.)	Current Approved Uses
Ozempic[8, 11] (Injection)	Dec 5, 2017	2 mg/3 mL pen (0.25 mg, 0.5 mg) 4 mg/3mL pen (1 mg) 8 mg/3 mL pen (2 mg)	• Type 2 diabetes mellitus (T2DM) • Reduction of major adverse CV events (MACE) in T2DM with established CVD • Reduction of risk of worsening kidney disease in T2DM
Rybelsus (Oral Tablets)[10]	Sept 20, 2019	3 mg, 7 mg, 14 mg	• T2DM • Reduction of MACE in T2DM with established CVD
Wegovy (Injection)[13, 21-23]	June 4, 2021	0.25 mg/0.5 mL 0.5 mg/0.5 mL 1 mg/0.5 mL 1.7 mg/0.75 mL 2.4 mg/0.75 mL	• Chronic weight management (obesity/overweight with comorbidity) • Reduction of MACE in obesity/overweight with established CVD • Noncirrhotic metabolic dysfunction–associated steatohepatitis (MASH)*
Ozempic Tablets (formerly Rybelsus R2 formulation)[10]	Jan 30, 2026	1.5 mg, 4 mg, 9 mg	• T2DM • Reduction of MACE in T2DM with established CVD

Brand Name	Initial FDA Approval	Dosage Forms (U.S.)	Current Approved Uses
Wegovy Tablets[22-24]	Dec 22, 2025	1.5 mg, 4 mg, 9 mg, 25 mg tablets	• Chronic weight management • Reduction of MACE in obesity/overweight with established CVD

*MASH approval pending confirmation of full regulatory status depending on labeling updates

Clinical note for operations: Although the active molecule is semaglutide, **dose, labeling, and coverage pathways differ** substantially by brand and formulation, particularly between weight-management (Wegovy injection/pill) and diabetes-focused products (Ozempic, Rybelsus). When reviewing utilization data, **confirm the brand-level NDC rather than assuming all semaglutide prescriptions reflect equivalent clinical intent.** Indication labeling determines coverage eligibility, Star Ratings relevance, and rebate structure.

The "Wegovy Pill" (25 mg) is a distinct c**linical entity from Rybelsus**. While both are oral semaglutide, the Wegovy pill is approved at a **25 mg** dose specifically for obesity (based on the OASIS 4 trial).[24] It is the first oral GLP-1 approved for weight loss.

Tirzepatide Products

Brand Name	Initial FDA Approval	Dosage Forms (U.S.)	Current Approved Uses
Mounjaro (Injection)[26]	May 13, 2022	Single-dose prefilled pen 2.5 mg 5 mg 7.5 mg 10 mg 12.5 mg 15 mg	• **Type 2 diabetes mellitus (T2DM)** (adjunct to diet/exercise)
Zepbound (Injection)[27]	Nov 8, 2023	Single-dose prefilled pen 2.5 mg 5 mg 7.5 mg 10 mg 12.5 mg 15 mg	• **Chronic weight management** (obesity, or overweight + ≥1 comorbidity) **Moderate–severe OSA in adults with obesity**

Liraglutide Products

Brand Name	Initial FDA Approval	Dosage Forms (U.S.)	Current Approved Uses
Victoza (Injection)[7]	Jan 25, 2010	Multi-dose prefilled pen 6mg/mL solution	• Type 2 diabetes mellitus (T2DM) • Reduction of major adverse CV events (MACE) in adults with T2DM and established CVD • T2DM in pediatric patients (≥10 years)
Saxenda (Injection)	Dec 23, 2014	Multi-dose prefilled pen 6mg/mL solution	• Chronic weight management (obesity) • Overweight with ≥1 weight-related comorbidity • Pediatric obesity (≥12 years)

Generic Availability Note: Both **liraglutide injections for diabetes and weight management** now have FDA-approved generic versions in the US. A generic referencing **Victoza** (daily liraglutide injection) received approval and launch beginning in late 2024–2025, and a generic version of **Saxenda** (liraglutide for obesity) was approved and launched in 2025. These generic forms provide medically equivalent alternatives that may improve access and reduce costs, though product availability can vary across pharmacies and plans.

Dulaglutide

Brand Name	Initial FDA Approval	Dosage Forms (U.S.)	Current Approved Uses
Trulicity (Injection)	**Sep 18, 2014**	Single-dose prefilled pen 0.75 mg 1.5 mg 3 mg 4.5 mg	• Type 2 diabetes mellitus (T2DM) • Reduction of major adverse cardiovascular events (MACE) in adults with T2DM and established CVD

Orforglipron (Small Molecule, Non-peptide)

Brand Name	FDA Status	Dosage Forms (U.S.)	Anticipated Indications Under Regulatory Review
Pending U.S. Brand[30]	Regulatory review anticipated (2026)	Oral tablet (once daily)	• Type 2 diabetes mellitus (T2DM) • Chronic weight management (obesity/overweight)

Utilization Implications

1. Brand-Level Management Is Mandatory

GLP-1–based therapies are managed at the brand and NDC level, not at the molecule level. Although active ingredients may be identical (e.g., semaglutide), indication labeling, coverage criteria, and rebate contracts differ substantially across diabetes and obesity brands.

Operational directive: Always evaluate utilization, prior authorization, and spend at the brand-specific level.

Even when the **active ingredient is identical**, coverage rules differ materially by brand:

- Diabetes-labeled products (e.g., Ozempic, Mounjaro, Victoza, Trulicity) typically process under **T2DM criteria and CV risk documentation**
- Obesity-labeled products (e.g., Wegovy, Zepbound, Saxenda) often require:
  - BMI documentation
  - Comorbidity criteria
  - Structured weight-loss history
- Medicare Part D coverage differs significantly for obesity-only products[16]

Operational takeaway: Always analyze utilization at the **brand-level NDC**, not the molecule level.

2. Molecule ≠ Brand ≠ Coverage Pathway

Products labeled for:

- **Type 2 diabetes (T2DM)** → processed through glycemic management criteria and CV risk documentation
- **Chronic weight management** → typically require BMI documentation, comorbidity criteria, and benefit verification
- **Expanded cardiometabolic indications (ASCVD, CKD, OSA)** → broaden eligible populations and alter value modeling

Not all brands within the same molecule carry identical cardiovascular or renal labeling.

3. Cardiovascular Outcomes Data Alters Value Proposition

GLP-1 receptor agonists with FDA-approved MACE reduction labeling represent a meaningful opportunity to reduce serious cardiovascular events in the people most likely to benefit.

High-value phenotype:

- T2DM + established ASCVD
- Obesity + established ASCVD

For these individuals, the clinical rationale rests on hard outcome data like reductions in nonfatal MI, stroke, and cardiovascular death. When therapy is initiated appropriately, supported by structured follow-up and lifestyle co-management, and sustained over time, reductions in avoidable hospitalizations, emergency visits, and cardiovascular procedures follow as a natural consequence of better care.

4. Dosing Frequency Influences Persistence and Spend

Form factor is a utilization lever, not just a patient preference issue.[19]

- **Weekly injectables** generally demonstrate stronger adherence and persistence patterns
- **Daily injectables** may carry higher discontinuation risk but can offer lower acquisition cost (especially with generics)
- **Oral formulations** may increase uptake and reduce injection barriers, potentially expanding total utilization

5. Dual Agonist Escalation Strategy

Tirzepatide's dual GIP/GLP-1 mechanism delivers meaningfully greater glycemic control and weight reduction than GLP-1 monotherapy — a clinical difference that matters most for patients carrying the greatest metabolic burden.

The people most likely to benefit:

- Individuals with advanced obesity (BMI ≥40) where greater weight reduction translates to meaningful functional and cardiometabolic gains
- People with severe cardiometabolic burden where incremental efficacy has downstream clinical consequences
- Patients who have not achieved adequate response on GLP-1 monotherapy despite appropriate dosing and adherence

Not typically optimal as universal first-line therapy in cost-sensitive MA panels.

6. Generic Availability Expands Access – With Important Clinical Tradeoffs

Generic liraglutide creates a legitimate lower-cost entry point into GLP-1 therapy — a meaningful development for patients facing significant access barriers. But applied as a rigid step requirement, it introduces real clinical risk.

Daily dosing is a meaningful adherence burden compared to once-weekly alternatives. For patients with established ASCVD or progressive CKD, delaying access to the agent with the strongest outcome data is not a neutral decision.

A sound framework balances both realities:

- Use generic liraglutide where cost is the primary barrier and daily dosing is feasible
- Build clear, evidence-based exceptions for patients where clinical urgency justifies direct access to a preferred agent
- Keep formulary decisions visible to care teams so clinicians can advocate for the patients in front of them

7. Population Expansion Risk

Label expansions (CV risk reduction in obesity, OSA indication, potential MASH approval) significantly increase eligible populations.

Without tightly defined prior authorization criteria, eligible lives may expand faster than actuarial projections

AAVBC Treatment Positioning

Clinical Scenario	Preferred Positioning Consideration	Utilization Rationale
T2DM + Established ASCVD	GLP-1 RA with cardiovascular outcomes labeling	Highest cost-offset potential via MACE reduction; strong alignment with risk-adjusted MA populations
T2DM + CKD	GLP-1 RA with renal outcomes data	Supports downstream ESRD cost mitigation and risk-adjusted documentation

Clinical Scenario	Preferred Positioning Consideration	Utilization Rationale
Obesity + Established ASCVD (without diabetes)	Weight-labeled semaglutide	CV risk reduction now extends beyond diabetes populations
Advanced Obesity (BMI ≥40 or severe metabolic burden)	Consider dual GLP-1/GIP agonist	Greater weight and A1C reduction may justify higher acquisition cost in high-risk phenotypes
High BMI + Prediabetes	Weight-labeled GLP-1 with structured follow-up	Potential prevention strategy; requires strict eligibility management
Cost-Sensitive Medicare Advantage Panel	Weekly injectable with strongest rebate alignment or generic liraglutide step	Balance persistence benefits with actuarial control
Needle Aversion/ Injection Refusal	Oral semaglutide or future oral GLP-1	Improves uptake; may expand total utilization — monitor carefully
Step Therapy Required	Generic liraglutide before escalation	Introduces cost floor prior to higher-cost weekly agents

2025 ADA Risk-Based Treatment Positioning and Implications for Prior Authorization

The 2025 American Diabetes Association (ADA) Standards of Care emphasize individualized, risk-based selection of glucose-lowering therapy rather than rigid stepwise sequencing.[5]

Metformin remains an appropriate initial therapy for many individuals with type 2 diabetes. However, in patients with established atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or elevated cardiometabolic risk, GLP-1 receptor agonists with demonstrated cardiovascular benefit may be initiated independent of baseline HbA1c or prior metformin exposure.[5]

GLP-1 receptor agonists are therefore positioned not solely as glycemic agents, but as therapies with organ-protective implications in appropriately selected populations.[5,7-9,11]

In value-based care environments, this shift has important operational implications for prior authorization, formulary logic, and documentation standards.

Evolving Beyond Universal "Metformin-First" Requirements

Historically, many utilization policies required documented metformin use (often ≥3 months) before approval of a GLP-1 receptor agonist.

Under risk-based ADA guidance, however, delaying initiation in individuals with established ASCVD or CKD may not align with contemporary standards of care. For **high-risk patients, therapy selection is increasingly driven by organ-protection considerations rather than HbA1c escalation alone.**

In VBC-aligned systems, utilization criteria are gradually incorporating comorbidity-based triggers rather than uniform step-therapy requirements.

The clinical logic is prevention of major adverse cardiovascular or renal events — not acceleration of glycemic failure.[5,7-9,11]

Comorbidity-Driven Authorization Frameworks

Traditional authorization logic frequently centered on HbA1c thresholds (eg, >7.0% or >8.0%).
Risk-based positioning reframes eligibility around documented comorbidities such as:

- ASCVD
- Stage 3+ CKD
- High cardiometabolic risk

In such contexts, GLP-1 therapy may be appropriate even when glycemic parameters are near target, because the therapeutic objective extends beyond glucose reduction.[5]

For clinicians, this underscores the importance of:

- Comprehensive patient evaluation and accompanying MEAT documentation with ICD-10
- Clear problem list maintenance
- Explicit notation of ASCVD and CKD staging

Documentation must reflect true clinical complexity, not merely laboratory values.

Summary: Prior Authorization in Transition

Feature	Traditional Fee-for-Service Model	Risk-Aligned VBC Model
Primary Trigger	HbA1c above threshold	Documented ASCVD/CKD/cardiometabolic risk
Step Therapy	Mandatory metformin failure	Risk-based flexibility in high-risk patients
Review Process	Manual, time-delayed	Increasing automation in integrated systems
Primary Metric	Pharmacy spend control	Reduction in long-term complication risk

This evolution reflects alignment with ADA 2025 guidance rather than simple formulary expansion.[5]

The objective in VBC settings is not medication proliferation. It is deployment of organ-protective therapy in populations where outcome data demonstrate benefit.

Cost vs Value Analysis

The central question in value-based care is not whether GLP-1 therapies are effective. Randomized trials demonstrate meaningful reductions in cardiovascular events, improved glycemic control, weight reduction,

and, in selected agents, renal protection.[5,7-9,11] The question is whether real-world deployment translates into durable, population-level reductions in total cost of care.

Upfront Cost Exposure

GLP-1 receptor agonists are high-acquisition-cost medications. When prescribed at scale, even moderate increases in eligible populations can generate substantial near-term pharmacy expenditure.[1, 4]

Cost exposure is influenced by:

- Drug acquisition price
- Duration of therapy
- Population penetration rate
- Persistence and adherence

Unlike acute interventions, GLP-1 therapy for obesity or cardiometabolic risk reduction is typically long-term. Discontinuation often leads to weight regain and potential attenuation of benefit.[15]

Thus, financial exposure accumulates over time.

Estimated Medication Costs (U.S.)

Agent (Brand)	FDA-Approved Indications	Current WAC (Monthly)	Self-Pay / Direct Options	Medicare Part D Coverage Status	Approx. Patient OOP (Medicare)
Semaglutide injection (Ozempic)	T2DM; ASCVD risk reduction; CKD risk reduction	~$969–$1,027	$199–$499/mo via NovoCare Pharmacy; $199 intro offer	Covered for T2DM, ASCVD, CKD indications; NOT for weight loss	~$50–$68/mo (covered plans); varies by formulary tier
Semaglutide injection (Wegovy)	Chronic weight management; CVD risk reduction (obesity/ overweight + established CVD); MASH (F2–F3)	~$1,349	$499/mo via NovoCare Pharmacy; $199 intro offer	Covered for CVD risk reduction indication only; NOT for weight loss alone	~$50/mo under BALANCE pilot (mid-2026); otherwise varies
Semaglutide oral tablet (Wegovy tablet)	Chronic weight management; CVD risk reduction	~$1,349	$199 intro offer via NovoCare	Limited; same coverage rules as injectable Wegovy	~$50/mo under BALANCE pilot (mid-2026)
Semaglutide oral tablet (Rybelsus)	T2DM (glycemic control)	~$997	NovoCare direct pricing available	Covered for T2DM; NOT for weight loss	~$51–$60/mo (covered plans)
Tirzepatide injection (Mounjaro)	T2DM	~$1,060–$1,069	$299–$449/mo via LillyDirect	Covered for T2DM (>90% of Part D plans); NOT for weight loss	~$50/mo under BALANCE pilot (mid-2026); ~$60–$68/mo

Agent (Brand)	FDA-Approved Indications	Current WAC (Monthly)	Self-Pay / Direct Options	Medicare Part D Coverage Status	Approx. Patient OOP (Medicare)
					current covered plans
Tirzepatide injection (Zepbound)	Chronic weight management; OSA (obesity)	~$1,060	$299–$449/mo via LillyDirect	Covered for OSA indication; NOT for weight loss alone	~$50/mo under BALANCE pilot (mid-2026); otherwise varies
Dulaglutide injection (Trulicity)	T2DM; ASCVD risk reduction	~$987	Limited direct options	Covered for T2DM and ASCVD indications	~$51–$60/mo (covered plans)
Liraglutide injection — brand (Victoza)	T2DM; ASCVD risk reduction	~$1,050–$1,300	Limited direct options	Covered for T2DM and ASCVD indications	Varies by plan
Liraglutide injection — generic	T2DM	Significantly lower than brand; varies by pharmacy	Available at most retail pharmacies	Covered for T2DM	Lower OOP than brand; varies by plan

On WAC vs. net price: WAC is the manufacturer's list price before rebates, discounts, or patient assistance programs. Most insured patients do not pay WAC. Net prices paid by plans are not publicly disclosed and vary significantly.

On IRA negotiated prices (effective January 2027): Ozempic, Wegovy, and Rybelsus have been selected for Medicare price negotiation. The negotiated price will be $274/month — this is what Medicare pays the manufacturer, not the patient copay.

On the BALANCE/GENEROUS pilot (mid-2026): Under this voluntary federal pilot, Medicare and Medicaid will cover Ozempic, Wegovy, Mounjaro, and Zepbound at a government price of $245/month, with an estimated patient copay of ~$50/month. Eligibility criteria and plan opt-in requirements apply.

On Novo Nordisk WAC reduction (January 2027): Novo Nordisk has announced a WAC reduction to $675/month for all semaglutide products effective January 1, 2027 — a 50% reduction for Wegovy and 35% for Ozempic/Rybelsus.

Generic liraglutide: Generic availability introduces a lower-cost entry point but pricing varies significantly by pharmacy and dispensing channel. Confirm current pricing at point of prescribing.

Direct Access and Self-Pay Options for GLP-1 Therapy (As of Q1 2026)

For patients who lack insurance coverage or choose to pay outside of their plan, manufacturer-direct and federal platforms have meaningfully expanded access to FDA-approved GLP-1 therapies at substantially reduced prices. These channels are particularly relevant for people whose plans exclude obesity indications, or who face high deductibles that make insurance-routed fills more expensive than self-pay alternatives.

Care teams should be familiar with these options so they can counsel patients accurately — and so that patients are not driven toward unapproved compounded products by lack of information about legitimate lower-cost pathways.

Platform/ Program	Medications Available	How It Works	Current Self-Pay Price (Q1 2026)	Key Limitations
NovoCare Pharmacy (Novo Nordisk)	Wegovy (injection and pill), Ozempic, Rybelsus	Prescriber sends Rx directly; home delivery or pickup at 9,000+ CVS locations	Intro offer: $199/mo for first 2 months (0.25–0.5 mg doses); standard: $349/mo for most doses; $499/mo for Ozempic 2 mg; Wegovy pill: $149/mo for 1.5mg and 4mg doses (through April 15, 2026)	Government beneficiaries (Medicare/Medicaid) excluded; introductory pricing expires March 31, 2026; does not count toward insurance deductible or OOP maximum
LillyDirect (Eli Lilly)	Zepbound; Mounjaro and Trulicity (announced , rollout ongoing)	Online platform; vial format for Zepbound reduces dispensing cost; requires refill within 45 days for Self Pay Journey pricing	Zepbound: $299/mo (2.5 mg starter), $399/mo (5 mg), $449/mo (7.5–15 mg maintenance); Mounjaro/Trulicity: 50–60% off list price (announced)	Medicare/Medicaid excluded; 45-day refill window required for ongoing pricing; does not apply to insurance-routed prescriptions
TrumpRx.gov (Federal portal)	Ozempic, Wegovy (injection and pill), Mounjaro, Zepbound	Portal launched February 5, 2026; directs patients to manufacturer platforms or participating pharmacies; does not dispense directly	Injectable semaglutide: ~$349/mo; Wegovy pill: ~$149/mo; Zepbound: ~$299–$346/mo	Cash-pay only; does not count toward insurance deductible or OOP maximum; no integrated clinical support — prescriber and monitoring remain separate; Medicare/Medicaid coverage through this channel still being finalized
GoodRx/ Telehealth partners	Ozempic, Wegovy (through partner platforms)	Telehealth subscription + fulfillment via Novo Nordisk partnership; pricing aligned with NovoCare standard rates	Starting at $199 (introductory, through March 2026); $349/mo thereafter for most doses	Telehealth fee applies separately; clinical oversight varies by platform; not a substitute for ongoing primary care management
Amazon Pharmacy	Varies by formulary and discount availability	Integrated discount tools + Prime delivery; cash-pay rates available	Competitive with retail cash-pay; verify current pricing at point of prescribing	Pricing varies; no manufacturer direct pricing guarantee; clinical support not integrated

Dosing & Comparison Framework

Oral Semaglutide (PIONEER Program): What Higher Doses Add

Approved oral semaglutide doses (T2DM): 3 mg → 7 mg → 14 mg daily (titration). PIONEER 1 demonstrated a clear dose–response for HbA1c lowering (largest with 14 mg).

Investigational higher doses: 25 mg and 50 mg daily studied in PIONEER PLUS, showing additional HbA1c and weight reduction vs 14 mg.

PIONEER Trial Comparison Table

Trial	Oral Semaglutide Dose	Comparator	Population/ Setting	Key Glycemic Finding
PIONEER 1[31]	3 mg/7 mg /14 mg	Placebo	Monotherapy	Placebo-adjusted HbA1c change at 26 wks showed dose-response; greatest reduction with 14 mg
PIONEER 2[32]	14 mg	Empagliflozin 25 mg	On metformin	HbA1c reduction favored oral semaglutide at 26 wks (≈-1.3% vs -0.9%, treatment policy)
PIONEER 3[33]	3 mg/7 mg/14 mg	Sitagliptin 100 mg	On metformin ± SU	Greater HbA1c reduction with oral semaglutide (dose-responsive) vs sitagliptin
PIONEER 4[34]	14 mg	Liraglutide 1.8 mg (inj) + placebo arm	On metformin ± SGLT2i	HbA1c change at 26 wks **similar to liraglutide (noninferior)** with greater weight loss vs liraglutide in trial reporting
PIONEER PLUS[35]	**25 mg/50 mg** (investigational)	Oralsemaglutide 14 mg	T2DM needing intensification	Higher doses showed additional HbA1c and weight reduction vs 14 mg at 52 wks, but dosing remains investigational for T2DM (value must be weighed against tolerability and durability)

What Do Get by Going Higher

Decision Point	What Higher Dose May Add	What It Costs Clinically (Stewardship Lens)
7 mg → 14 mg	Meaningful incremental HbA1c lowering and additional weight reduction in dose–response data	Higher likelihood of GI intolerance during escalation; persistence depends on titration support. Base of risk assessment and goals of care
14 mg → 25/50 mg (investigational)	Further HbA1c and weight reductions vs 14 mg in intensification populations	Not FDA-approved dosing (T2DM) at present; requires careful benefit–tolerability assessment and clear documentation of rationale if ever used via future labeling pathways

Clinical Value: Event Reduction and Organ Protection

Cardiovascular outcome trials demonstrate reduced major adverse cardiovascular events in high-risk populations for several GLP-1 agents.[7-9] The FLOW trial further demonstrated reduction in composite kidney endpoints with semaglutide in patients with T2DM and CKD.[11]

These event reductions represent potential offsets to high-cost complications, including:

- Myocardial infarction
- Stroke
- Cardiovascular death
- Progression to kidney failure

However, these benefits were demonstrated under **controlled trial conditions with structured follow-up and high adherence.**[7-9,11]

Real-World Persistence: The Durability Question

In a real-world analysis of commercially insured adults without diabetes, 1-year persistence with GLP-1 therapy was approximately 32%, and adherence (PDC ≥80%) was 27%.[19]

Lower persistence reduces the likelihood that long-term cardiometabolic benefits observed in trials will be fully realized at the population level.

For value-based care organizations, adherence is not a secondary metric; it is central to whether projected value materializes.

ICER Assessment of Long-Term Value

The Institute for Clinical and Economic Review (ICER) evaluated semaglutide and tirzepatide for chronic weight management and concluded that long-term value depends heavily on sustained treatment and complication reduction rather than short-term weight loss alone.[18]

ICER emphasized:

- Sensitivity to adherence assumptions
- Uncertainty in long-term event reduction durability
- High budget impact at scale

Value, therefore, is conditional — not automatic.

Value is most likely realized when:

- Therapy is targeted to high-risk individuals (ASCVD, CKD)
- Adherence is supported through integrated care
- Therapy duration aligns with sustained benefit
- Cardiovascular and renal endpoints are the primary objective

Value is least likely when:

- Therapy is initiated in low-risk populations
- Discontinuation rates are high
- Prescribing is disconnected from longitudinal care
- Monitoring and documentation are inconsistent

Time Horizon Matters

Pharmacy costs are immediate. Cardiovascular and renal event reduction accrues over years.

- In fee-for-service systems, this temporal mismatch discourages prevention-oriented prescribing
- VBC systems with shared risk, longer time horizons allow prevention to align with financial accountability

However, **mobility of insured populations and contract turnover introduce additional uncertainty into long-term return projections.**

Clinical Stewardship Principles

1. Target therapy to populations with demonstrated outcome benefit.
2. Support adherence and longitudinal engagement.
3. Avoid extrapolating trial benefits to unsupported populations.
4. Reassess therapy when clinical response is inadequate.
5. Monitor real-world outcome data within the organization.

Cost containment is not the goal; **sustainable prevention is.**

Budget Impact Example (Illustrative Only)

If 1,000 high-risk patients are treated with a GLP-1 therapy at $12,000 annually:

Annual pharmacy exposure ≈$12 million

If therapy prevents:

- 15 major cardiovascular events (estimated event cost $40,000–$60,000 each)
- 5 dialysis initiations (>$90,000 annually)

The potential offset may meaningfully narrow the net cost — but only if persistence is high and targeting is appropriate.

These projections are highly sensitive to:

- Adherence
- Duration of therapy
- Risk selection
- Drug price net of rebates

Safety Considerations and Monitoring Framework

GLP-1 receptor agonists are generally well tolerated and have demonstrated favorable safety profiles in large randomized trials.[7-10,13] However, their expanding use across broader populations requires structured monitoring and clear patient counseling.

Safety considerations in value-based care are not barriers to access — they are safeguards that preserve trust, durability, and clinical integrity.

Absolute Contraindications (FDA-Labeled)[26-29,36]

Contraindication	Clinical Rationale
Personal or family history of medullary thyroid carcinoma (MTC)	Boxed warning based on rodent C-cell tumor findings
Multiple Endocrine Neoplasia syndrome type 2 (MEN2)	Increased theoretical C-cell risk
Known serious hypersensitivity to product	Risk of anaphylaxis or severe allergic reaction
Pregnancy (weight-loss indications)	Obesity drugs contraindicated during pregnancy

Safety Considerations[26-29,36]

Safety Topic	What Clinicians Should Know	Clinical Context
Gastrointestinal Intolerance	Nausea, vomiting, diarrhea, constipation, and early satiety are common and dose-related, especially during titration	Most frequent cause of discontinuation. Slow dose escalation and anticipatory counseling improve persistence and long-term benefit
Gastroparesis (Severe GI Motility Disorders)	Use is **not recommended in patients with severe gastroparesis** or significant pre-existing gastric motility disorders	GLP-1 RAs delay gastric emptying. In patients with symptomatic gastroparesis, therapy may worsen bloating, nausea, or vomiting and impair nutrition
Hypoglycemia (Combination Therapy)	Low intrinsic hypoglycemia risk when used alone. Risk increases when combined with insulin or sulfonylureas	Background insulin/SU dose reduction is often required to prevent avoidable hypoglycemia
Pancreatitis	**Not recommended,** avoid if history of, or high risk of pancreatitis. Large CV outcome trials have not demonstrated a consistent increased risk.Not an absolute contraindication, but caution is advised in patients with prior pancreatitis	Persistent, severe abdominal pain warrants evaluation. Routine amylase/lipase monitoring in asymptomatic patients is not recommended
Gallbladder Disease	Increased risk of cholelithiasis or cholecystitis, particularly during rapid weight loss	Rapid adipose mobilization increases biliary cholesterol saturation. Evaluate new right upper quadrant pain during significant weight reduction
Thyroid C-Cell Tumor (Boxed Warning)	**Black box warning.Contraindicated** in patients with personal or family history of medullary thyroid carcinoma (MTC) or MEN2	Based on rodent data. Human trials have not demonstrated a confirmed signal. Careful family history screening is essential prior to initiation

Safety Topic	What Clinicians Should Know	Clinical Context
Renal Considerations	Not intrinsically nephrotoxic. AKI risk arises primarily from dehydration due to severe GI losses	Monitor renal function in high-risk patients, especially during significant vomiting or diarrhea. Encourage hydration. Consult nephrologist
Heart Rate Increase	Small mean increases in resting heart rate observed in trials	Usually clinically insignificant, but use **caution in patients with symptomatic tachyarrhythmias or unstable cardiovascular status**
Lean Mass Loss	Weight loss may include lean mass reduction if protein intake and resistance activity are inadequate	Particularly relevant in older adults. Weight reduction should preserve functional capacity
Weight Regain After Discontinuation	Weight regain is common after stopping therapy	Obesity treatment is chronic. Initiation should include discussion of long-term maintenance strategy

Serious adverse events remain uncommon in large randomized trials.[7-10]

The most significant real-world safety issue is not catastrophic toxicity but premature discontinuation due to unmanaged intolerance, which undermines both clinical and economic durability. Emerging expert consensus also emphasizes nutritional and lifestyle supportive care, including attention to body composition, physical activity, and nutritional adequacy during GLP-1–based therapy.[19,37]

Monitoring and Follow-Up Framework

Renal Function and Volume Status Monitoring

GLP-1 receptor agonists are **not intrinsically nephrotoxic**.

Renal safety concerns are primarily related to **volume depletion from gastrointestinal intolerance**, not direct kidney injury.

Renal and Volume Monitoring Overview

Monitoring Domain	What to Assess	When to Assess	Clinical Rationale
Baseline Renal Function	Serum creatinine, eGFR	Prior to initiation	Renal status may influence agent selection and dosing considerations (particularly for exenatide formulations)
Ongoing Renal Monitoring (High-Risk Patients)	Creatinine, eGFR	During dose escalation or if significant vomiting/diarrhea occurs	AKI risk is primarily dehydration-related rather than drug-mediated nephrotoxicity
Volume Contraction Indicators	BUN/Cr ratio (>20:1 suggests pre-renal state), orthostatic hypotension, tachycardia	If persistent GI symptoms occur	Early identification of volume depletion prevents pre-renal AKI

Monitoring Domain	What to Assess	When to Assess	Clinical Rationale
CKD Stage-Specific Monitoring	eGFR trend, volume status	At baseline and cautious use in Stage 3+ CKD	Advanced CKD increases vulnerability to volume shifts and electrolyte disturbances

Clinical principle: GLP-1 receptor agonists are not nephrotoxic; dehydration is the primary renal safety concern

CKD Stage–Guided Clinical Considerations

- **Monitoring of hydration status and renal function is recommended**[5,12]
- **Mild Impairment:** Generally no adjustment needed
- **Moderate Impairment:** Avoid **Exenatide weekly**. Use **Exenatide twice-daily** with extreme caution during dose escalation
- **Severe Renal Dysfunction:** GLP-1 agonists are generally **not recommended**

Stage	Severity	eGFR/CrCl Range	GLP-1 Clinical Action
Stage 1	Normal	≥90	No adjustment needed
Stage 2	Mild	60 – 89	No adjustment needed for most
Stage 3	Moderate	30 – 59	Avoid Exenatide ER; monitor others closely
Stage 4	Severe	15 – 29	Contraindicated for most GLP-1s
Stage 5	Failure	<15 (or Dialysis)	Contraindicated

Abbreviations: GFR, Glomerular Filtration Rate (the volume of fluid filtered from the kidney glomerular capillaries into the Bowman's capsule per unit time); CrCl, Creatinine Clearance (an estimate of GFR based on the rate at which the kidneys clear creatinine from the blood)

Exenatide (especially ER formulation): Avoid in moderate-to-severe renal impairment due to reduced clearance.[5]

Semaglutide, liraglutide, dulaglutide: Not primarily renally cleared; no dose adjustment required in mild–moderate CKD per labeling, though monitoring remains appropriate.[5,11,12]

Additional Renal Risk Modifiers

Population	Consideration
Older Adults (≥70 years)	Increased susceptibility to dehydration during titration; use gradual dose escalation. Risk-benefit evaluation is necessary before increasing doses, especially for twice-daily formulations
Concurrent Diuretic Therapy	Higher risk of volume contraction; reinforce hydration counseling
SGLT2 Co-Administration	Monitor volume status during early combination therapy initiation

Monitoring should focus on:

- Titration tolerance
- Hydration status
- CKD staging
- Medication reconciliation

Not routine renal surveillance in stable, asymptomatic patients.[5, 12]

Hepatic Impairment Considerations

Monitoring Domain	Clinical Action	Rationale
Mild–Moderate Hepatic Impairment (Child-Pugh A/B)	No routine dose adjustment required	GLP-1 RAs are not primarily hepatically metabolized
Severe Hepatic Impairment (Child-Pugh C)	Individualized assessment	Limited data in severe hepatic dysfunction

GLP-1 receptor agonists generally **do not require dose adjustment in mild–moderate hepatic impairment**, as they are not primarily hepatically metabolized.[5,36]

Ocular Monitoring (Diabetic Retinopathy & Vision Changes)

While GLP-1 receptor agonists (RAs) are transformative for metabolic health, emerging data and clinical observations necessitate a heightened focus on **ocular vigilance**. **Ocular monitoring is recommended in patients with pre-existing diabetic retinopathy**, particularly during periods of rapid glycemic improvement.[5,8]

Early Worsening of Diabetic Retinopathy

Rapid reductions in HbA1c are a known trigger for **transient worsening of diabetic retinopathy**, a phenomenon observed across multiple diabetes therapies.

This effect was observed in the **SUSTAIN-6 cardiovascular outcomes trial**, where semaglutide was associated with increased diabetic retinopathy complications in patients with pre-existing disease and large HbA1c reductions.[8]

Risk factors include:

- High baseline HbA1c
- Pre-existing proliferative diabetic retinopathy
- Rapid glycemic improvement

Complications may include:

- Vitreous hemorrhage
- Retinal neovascularization

- Need for laser therapy or intravitreal treatment[8]

NAION: The "Eye Stroke" Risk

The most concerning correlation is with **Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)**.[38]

- **Mechanism:** Ischemia of the optic nerve head, potentially linked to drug-induced changes in microvascular perfusion
- **Clinical Significance:** Recent observational studies have suggested a higher incidence of NAION in patients prescribed semaglutide
- **Patient Counseling:** Patients must be instructed to report any **sudden, painless, unilateral vision loss** immediately, as this often results in permanent visual field deficits

Paradoxical Retinopathy Progression

Rapid intensification of glycemic control is a known trigger for the "early worsening" of diabetic retinopathy.

- **The "Glucose Gap":** A swift, significant drop in HbA1c can lead to transient ischemia in the retinal capillaries
- **Risk Factors:** Patients with high baseline HbA1c and pre-existing proliferative or severe non-proliferative diabetic retinopathy (NPDR) are at the highest risk
- **Complications:** This can escalate to **vitreous hemorrhage** or neovascularization if not monitored

Visual Changes During Glycemic Adjustment

Patients may experience temporary visual disturbances during rapid changes in blood glucose.

Mechanism:

- Osmotic shifts affecting the lens refractive index
- Changes in aqueous humor glucose concentration

These changes are typically transient and resolve as glycemic control stabilizes.[5]

Monitoring Ocular Symptoms

Action Item	Clinical Rationale
Baseline Fundoscopy	Essential for all patients with T2DM prior to GLP-1 initiation to stage existing retinopathy
Gradual Titration	Mitigates the "shock" to the retinal microvasculature by avoiding an overly aggressive drop in HbA1c
Specialist Referral	Proactive co-management with Ophthalmology for any patient with pre-existing moderate-to-severe NPDR
Warning Signs Education	Ensure patients can distinguish between "minor blurriness" and "neuropathic vision loss" (NAION)

Glycemic Monitoring & Drug Interactions

Monitoring Domain	Clinical Action	Rationale
HbA1c	Every 3–6 months	Assess glycemic response[5]
Insulin/SU Dose Adjustment	Reduce insulin or sulfonylurea at initiation if appropriate	Prevent avoidable hypoglycemia[5]
Warfarin (INR)	Monitor INR when initiating or adjusting GLP-1 therapy	GLP-1 RAs can delay gastric emptying, but semaglutide labeling notes no clinically relevant effect on warfarin exposure in studied interaction data.[36]
Weight Trajectory	Monitor at each visit	Evaluate therapeutic response, tolerability and durability[5,13,19]

Pancreatitis & Thyroid Surveillance

Monitoring Domain	Clinical Action	Rationale
Severe Persistent Abdominal Pain	Evaluate for pancreatitis	Rare signal; prompt evaluation warranted[7-9,36]
Routine Amylase/Lipase Testing	Not recommended in asymptomatic patients	No evidence supporting routine surveillance
Calcitonin Screening	Not routinely recommended	FDA does not recommend routine calcitonin monitoring for MTC; screen history for MEN2/MTC[36]

Perioperative Management – Gastric Emptying and Aspiration Risk

Scenario	Recommended Action	Scenario
Elective Surgery	Consider temporary discontinuation prior to procedure; timing individualized based on hospital protocols and anesthesia guidance	**Elective Surgery** Common 1-2 weeks before surgery
Active GI Symptoms on Procedure Day	Consider postponement or full-stomach precautions	**Active GI Symptoms on Procedure Day**
Prolonged Discontinuation in T2DM	Arrange glycemic bridging strategy if needed	**Prolonged Discontinuation in T2DM**

Clinical principle: Perioperative management should be coordinated with anesthesia; blanket discontinuation policies may not apply uniformly.[36,39]

Example Perioperative plan

Condition	Action Plan
Pre-Procedure	Temporarily discontinue the GLP-1 agonist regardless of indication (T2DM or obesity). Discontinue 2 weeks prior to surgical intervention
Diabetes Bridge	If stopping the GLP-1 for an extended period, consult an endocrinologist to

Condition	Action Plan
	manage potential hyperglycemia
Symptomatic on Procedure Day	If nausea, vomiting, or bloating is present, consider postponing the procedure
Non-Adherence	If the patient did not stop the medication, evaluate gastric volume via ultrasound or proceed with "full stomach" (Rapid Sequence Induction) precautions
Abbreviations: T2DM, Type 2 Diabetes Mellitus; GLP-1 RA, GLP-1 Receptor Agonist	

Example Monitoring Timeline

Time Point	What to Monitor	Why It Matters	Practical Notes
Pre-Initiation (Baseline)	• HbA1c • Weight & BMI • eGFR/serum creatinine • Medication reconciliation (insulin/SU) • ASCVD/CKD documentation • Retinopathy status (if T2DM)	Establish clinical baseline; identify hypoglycemia risk; stage kidney disease; assess retinopathy risk prior to rapid glycemic change	Document comorbidities clearly (ASCVD, CKD stage) for risk-based therapy positioning
Weeks 2–4 (Early Titration)	• GI tolerance • Volume status (if significant GI symptoms) • Insulin/SU dose adjustment	Most discontinuation occurs during titration; dehydration risk highest during persistent vomiting	Slow titration improves persistence and durability
Weeks 8–12	• Weight trajectory • HbA1c (if glycemic indication) • Symptom review	Assess early therapeutic response and tolerability	Avoid premature discontinuation if benefits emerging
3–6 Months	• HbA1c • Weight • Blood pressure • Lipid profile (if ASCVD risk)	Confirm metabolic response; assess cardiometabolic improvement	CV benefit in trials assumes sustained therapy
6–12 Months	• Reassess benefit vs tolerance • Renal function (CKD patients) • Nutritional adequacy (protein intake)	Evaluate durability; detect lean mass risk; confirm kidney stability[9]	Weight loss without strength preservation warrants intervention
Annually (or per diabetes guidelines)	• Dilated eye exam (if T2DM) • CKD staging • Global ASCVD risk reassessment	Monitor for retinopathy progression and CKD trajectory	Rapid HbA1c drops may transiently worsen retinopathy

Key Monitoring Principles in VBC Settings

1. Most clinically meaningful monitoring occurs during the first 12 weeks (tolerability and dose stabilization).
2. Long-term value depends on persistence and metabolic durability, not early weight change alone.
3. Retinopathy risk is related to rapid glucose shifts, not direct retinal toxicity, never overlook changes in vision
4. Renal monitoring focuses on volume status, not intrinsic nephrotoxicity.
5. Documentation of ASCVD and CKD stage is essential for risk-aligned therapy selection.

When to Stop or De-Escalate Therapy

Clinical Scenario	Recommended Action	Rationale
Intolerable GI symptoms despite slow titration	Hold dose escalation; consider dose reduction or discontinuation	Persistence is essential for benefit; unmanaged intolerance drives premature discontinuation
Recurrent dehydration or AKI related to GI losses	Temporarily discontinue; reassess volume status and renal function before restarting	Renal risk is volume-mediated, not intrinsic nephrotoxicity
Confirmed pancreatitis	Discontinue permanently	Avoid re-exposure in confirmed cases; evaluate alternative therapy
Personal or family history of MTC or MEN2 identified after initiation	Discontinue	Contraindicated per labeling
No meaningful clinical response after adequate trial (≥3–6 months at therapeutic dose)	Reassess indication, adherence, and lifestyle integration; consider discontinuation	Long-term value depends on demonstrated benefit
Excessive lean mass loss or functional decline (frailty risk)	Reassess nutritional intake; consider dose reduction or discontinuation	Weight reduction should not compromise functional status
Persistent hypoglycemia despite insulin/SU adjustment	Reduce background agents; if unresolved, consider GLP-1 dose adjustment	Hypoglycemia risk is combination-mediated
Patient preference after informed discussion	Shared decision-making; plan transition strategy	Therapy for obesity and cardiometabolic risk is typically chronic; discontinuation commonly leads to weight regain
Elective surgery requiring interruption	1-2 week temporary hold per anesthesia guidance; restart when clinically stable	the FDA notes these drugs delay gastric emptying, which can lead to residual food in the stomach even after standard fasting periods

After Discontinuation: Structured Transition & Metabolic Continuity

Discontinuing GLP-1 therapy should be a **clinical transition**, not therapeutic withdrawal.

Stopping therapy should be based on:

- Safety concerns
- Lack of meaningful clinical benefit
- Functional decline
- Shared, patient-centered decision-making

It should **not** be driven solely by short-term weight fluctuation.

In value-based care environments, reassessment ensures therapy remains aligned with:

- Cardiometabolic risk reduction

- Functional status preservation
- Sustainable long-term benefit

Preserving Lean Mass & Functional Capacity

Weight reduction without structured support may result in lean mass loss, particularly in older adults or individuals with low baseline muscle mass.[15]

Following discontinuation, clinicians should:

- Reinforce adequate protein intake (typically 1.0–1.5g/kg/day unless contraindicated)
- Encourage progressive resistance training (2–3 sessions/week)
- Monitor for signs of frailty or strength decline
- Avoid overly aggressive caloric restriction

The objective is not simply weight maintenance — it is preservation of metabolic and functional health.

Integration with Non-Pharmacologic Care

A structured non-pharmacologic plan should be activated or intensified at discontinuation.

Domain	Clinical Focus	Rationale
Medical Nutrition Therapy	Structured, calorie-appropriate, whole-food dietary pattern; adequate protein intake (generally 1.0–1.5 g/kg/day unless contraindicated); fiber ≥25–30 g/day	Supports glycemic stability, satiety regulation, and lean mass preservation during weight maintenance phase[5]
Resistance Training	Progressive strength training 2–3 times per week	Preserves muscle mass, improves insulin sensitivity, supports functional capacity[5,37]
Aerobic Conditioning	150–300 minutes/week moderate-intensity activity	Improves cardiovascular risk profile independent of weight change[5]
Behavioral Support	Sleep optimization, stress regulation, structured meal planning	Enhances durability of metabolic improvements and reduces relapse risk[5]
Supplementation (Selective Use)	Consider creatine monohydrate (typically 3–5 g daily) in appropriate adults engaged in resistance training; ensure adequate hydration; assess renal status in CKD	Creatine may support lean mass retention and strength during caloric deficit. Particularly relevant in older adults at risk of sarcopenia. Avoid in advanced CKD without specialist guidance[5,37]
Follow-Up Monitoring	Weight, HbA1c (if T2DM), blood pressure, functional status	Detect early metabolic regression or functional decline

AAVBC Tips:

GLP-1 receptor agonists are important tools for metabolic disorders and serve a longitudinal role in the broader metabolic care and strategy.

Whether continuing or stopping therapy, the goal remains constant:

- Reduce cardiovascular events
- Slow kidney disease progression
- Preserve strength and function
- Sustain metabolic health

Stewardship includes knowing **when to continue — and when to transition thoughtfully.**

Navigating High Demand and Off-Label GLP-1 Requests

Clinical Integrity Framework for Primary Care

GLP-1 receptor agonists now occupy a prominent place in public discourse. Media coverage, social amplification, and peer influence have increased patient-initiated requests, including requests that fall outside FDA-approved or evidence-supported indications.

In value-based care environments, the objective is not denial. It is stewardship: aligning therapy with demonstrated benefit, clinical risk, and long-term sustainability.

Common Clinical Scenarios

Scenario	Clinical Reality	Stewardship Approach
BMI <27 without comorbidity requesting weight loss therapy	Outside FDA indication for obesity[11]	Provide lifestyle-based care; discuss evidence boundaries
Normal glycemic control (A1c 5.7–6.0%) without ASCVD/CKD requesting GLP-1	No evidence for organ-protective benefit in this population[4]	Reframe goals toward lifestyle and risk prevention
Cosmetic or rapid weight-loss request (event-driven)	Obesity treatment is chronic; discontinuation commonly leads to regain[13]	Emphasize durability and chronic-disease framing
Plateau after modest weight loss requesting dose escalation beyond labeling	Limited evidence beyond approved dosing	Reassess adherence, nutrition, and physical activity
Supply-constrained environment	Access variability impacts high-risk patients	Prioritize evidence-based, high-risk populations

Evidence Boundary Clarification

Clinicians benefit from clear internal differentiation:

FDA-Approved Indications

- Type 2 diabetes

- Chronic weight management (BMI ≥30 or ≥27 with comorbidity)
- Cardiovascular risk reduction in specific T2DM populations

Evidence-Supported but Label-Limited Contexts

- CKD adjunctive benefit in T2DM
- ASCVD risk modification

Emerging Signals (Not established and non-FDA approved standard of Care)

- MASLD/MASH improvements (trial data evolving)
- Neuroprotective hypotheses
- Broader cardiometabolic prevention in low-risk populations

This clarity protects both patients and clinicians.

Structured Clinical Response Framework

Step	Clinical Focus	Key Questions/Actions	Why It Matters (VBC Context)
1. Clarify the Clinical Goal	Identify therapeutic objective	• Is the goal weight reduction? • Glycemic improvement? • Cardiovascular risk reduction? • Functional improvement? • Align the goal with evidence-supported indications	Ensures therapy is matched to demonstrated benefit rather than social or cosmetic drivers
2. Assess Medical Necessity	Evaluate cardiometabolic risk burden	Determine whether evidence supports organ-protective benefit • BMI category • ASCVD diagnosis • CKD stage • A1c trajectory • BP and lipid profile	Risk-based therapy selection aligns with ADA guidance[4] and supports durable outcome improvement
3. Determine Evidence Alignment	Categorize indication	• FDA-approved? • Evidence-supported but label-limited? • Emerging signal only? • Outside evidence scope?	Protects clinical integrity and avoids therapy drift beyond data.
4. Provide Transparent Education	Communicate clearly and respectfully	Example framing: "GLP-1 therapies have strong evidence in people with diabetes, cardiovascular disease, or obesity meeting certain criteria. In your case, the evidence for long-term benefit is limited. My responsibility is to recommend treatments where benefit clearly outweighs risk."	Maintains therapeutic alliance while reinforcing evidence boundaries.
5. Consider Reasonable Off-Label Use (If Applicable)	Evaluate appropriateness	Off-label use may be reasonable when: • Severe obesity with high cardiometabolic risk • Rapid metabolic progression toward T2DM • Clear shared decision-making • Structured monitoring plan in place	Off-label does not mean inappropriate. Clinical reasoning and documentation are essential

Step	Clinical Focus	Key Questions/Actions	Why It Matters (VBC Context)
6. Document Clinical Rationale	Maintain integrity of record	Document: • Risk profile • Indication category • Expected benefit • Monitoring plan • Discussion of uncertainty (if applicable)	Documentation should reflect clinical judgment — not coverage optimization

The objective is not restriction. It is alignment with demonstrated benefit and long-term health outcomes.

Sustainability and Equity in GLP-1 Utilization

Stewardship in a High-Impact Therapeutic Era

GLP-1 receptor agonists represent one of the most clinically significant therapeutic advances in cardiometabolic medicine in the past decade. Trials have demonstrated reductions in major adverse cardiovascular events, meaningful weight reduction, and kidney outcome benefits in selected populations.[7-11,13,14]

At the same time, utilization growth has been rapid, concentrated in high-cost agents, and increasingly driven by public demand. This creates a structural tension in value-based care environments:[1-4,16,17]

- Pharmacy costs are realized immediately
- Cardiovascular and renal savings accrue over years
- Clinical benefit depends on sustained adherence and appropriate selection

Sustainability is not about limiting access. It is about ensuring durable benefit where evidence demonstrates meaningful impact.

GLP-1 Stewardship Principles in Value-Based Care

1. Target therapy to **ASCVD/CKD/high cardiometabolic risk** populations.
2. Support **persistence through titration and GI intolerance management**.
3. Pair pharmacotherapy with **nutrition and resistance training**.
4. Monitor **long-term outcomes, not just short-term weight loss**.

Financial Sustainability in Risk-Bearing Systems

In Medicare Advantage (MA), ACO, and advanced primary care models:

- Medication costs affect total cost of care in-year
- Shared savings and downside risk arrangements magnify exposure
- Benefit realization requires longitudinal persistence
- Short-term, episodic use without sustained cardiometabolic benefit undermines projected value[18]

Therefore, sustainability depends on:

- Risk-based patient selection
- Adherence support during titration
- Avoidance of cosmetic or short-term deployment
- Integration with nutrition, physical activity, and behavioral support

The therapy is powerful. Its value depends on disciplined use.

Sustainability & Equity Framework in GLP-1 Deployment

Domain	Current Landscape	Risk if Unstructured	Equity-Aligned Clinical Approach
Utilization Patterns	GLP-1 use is concentrated in specific age and gender groups, with highest reported exposure among women aged 50–64[3]	Therapy expansion driven by demand rather than disease burden may misalign access with clinical risk	Anchor access decisions to documented cardiometabolic risk rather than demographic trends
Disease Burden Distribution	Cardiometabolic disease disproportionately affects individuals with lower socioeconomic status, rural populations, racial and ethnic minority groups, and those with limited longitudinal care access	High-risk populations may experience delayed or reduced access if supply and prescribing capacity are consumed by lower-risk use	Prioritize individuals with established ASCVD, CKD, or severe obesity consistent with outcome data[7-11, 13, 14]
Supply & Access Pressure	Rapid prescription growth and concentration in high-cost agents[1-4]	Supply strain may disadvantage patients with advanced disease	Implement transparent, comorbidity-based access criteria to protect highest-risk patients
Cosmetic or Event-Driven Demand	Social amplification increases short-term or appearance-driven requests	Diversion from chronic disease management; reduced availability for organ-protective indications	Reinforce chronic disease framing; align therapy with long-term health objectives
Coverage Instability	Insurance transitions and formulary variability affect continuity	Abrupt discontinuation increases weight regain and undermines benefit[15]	Plan long-term strategy before initiation; anticipate coverage transitions
Risk Assessment Bias	Under-documentation of ASCVD/CKD in underserved populations	High-risk patients may appear “low risk” in claims-based systems	Maintain accurate documentation of comorbidities and CKD staging

Sustainable GLP-1 deployment requires:

Domain	Sustainable Approach
Patient Selection	Risk-based, evidence-aligned criteria
Monitoring	Structured titration and follow-up
Documentation	Accurate representation of clinical complexity

Domain	Sustainable Approach
Access Policy	Transparent, comorbidity-based frameworks
Equity Lens	Prioritize highest-risk populations
Durability	Long-term treatment planning

AAVBC Recommendation and Key Takeaways

GLP-1 receptor agonists represent one of the most clinically impactful and financially consequential therapeutic classes in contemporary cardiometabolic care. In value-based care environments, their deployment must be deliberate, evidence-aligned, and outcome-accountable.

AAVBC recommends that VBC organizations adopt a structured GLP-1 governance framework grounded in the following principles:

Key Takeaways

1. GLP-1 RAs Are Organ-Protective Therapies in Defined Populations

They are not simply weight-loss agents. Large cardiovascular outcome trials demonstrate reductions in major adverse cardiovascular events in selected patients with T2DM and ASCVD. Kidney outcome data further support benefit in T2DM with CKD. Their value lies in long-term cardiometabolic risk reduction.

2. Risk-Based Selection Is Becoming Standard

The 2025 ADA Standards emphasize individualized, risk-based therapy selection.[5] GLP-1 RAs may be initiated independent of HbA1c in patients with established ASCVD or CKD.

Therapy choice should be guided by:

- Documented comorbidity
- Cardiometabolic risk burden
- Functional status — not step-therapy hierarchy alone

3. Rapid Utilization Growth Requires Stewardship:

Spending increased from $13.66B in 2018 to $71.66B in 2023.[1] GLP-1 use has expanded substantially across demographic groups. Growth alone does not equal value. Sustainability depends on appropriate patient selection and durable adherence.

4. Safety Is Manageable — Persistence Is the Real Challenge

Most adverse effects are gastrointestinal and dose-related. Serious safety signals remain uncommon in large trials. The primary real-world risk is early discontinuation due to unmanaged intolerance, which undermines long-term benefit.

5. Obesity Treatment Is Chronic

Weight regain after discontinuation is common.

Initiation should include:

- Discussion of long-term expectations
- Nutrition and resistance activity counseling
- Durability planning

Short-term use rarely preserves benefit.

6. Monitoring Should Be Structured and Practical

High-impact monitoring includes:

- Early titration follow-up
- Insulin/SU adjustment
- Renal function during GI intolerance
- Retinopathy vigilance in high-risk T2DM

Routine surveillance for rare complications in asymptomatic patients is not supported by trial evidence.

7. Off-Label and High-Demand Requests Require Clinical Clarity

Stewardship is not denial.

Clinicians should:

- Clarify therapeutic goals
- Align with evidence boundaries
- Document clinical reasoning
- Engage in transparent shared decision-making

GLP-1 RAs are not cosmetic accelerators. They are evidence-supported therapies in defined populations.

8. Equity and Sustainability Are Aligned

Unstructured expansion risks:

- Diverting therapy from highest-risk individuals

- Widening access disparities
- Undermining long-term value

Prioritizing patients with documented ASCVD, CKD, or severe obesity supports both clinical outcomes and equity.

9. Value in VBC Is Measured in Outcomes, Not Utilization

In value-based environments:

- Pharmacy costs are immediate
- Cardiovascular and renal savings accrue over years
- Benefit depends on persistence and appropriate selection

Deployment should focus on:

- Preventing events
- Slowing disease progression
- Preserving function
- Sustaining access over time

Appendix

GLP1-RA Mechanisms of Action: Continued

Pancreatic Effects: Glucose-Dependent Insulin Regulation

Activation of the GLP-1 receptor increases cyclic AMP within pancreatic β-cells, enhancing insulin secretion in a glucose-dependent manner while suppressing glucagon during hyperglycemia.[20] Because insulin secretion diminishes as glucose levels normalize, GLP-1 RAs carry a relatively low intrinsic hypoglycemia risk when not combined with insulin or sulfonylureas.[5]

This glucose-dependent mechanism underpins improvements in HbA1c observed across randomized trials and supports the ADA's recommendation of GLP-1 RAs for individuals with type 2 diabetes and established cardiometabolic risk.[5]

Central Nervous System Effects: Appetite and Satiety Signaling

GLP-1 receptors within the hypothalamus and brainstem modulate appetite, satiety, and food reward pathways.[20] Central receptor activation reduces caloric intake and increases early satiety. In obesity trials, semaglutide and tirzepatide produced substantial mean weight reductions, largely attributable to decreased energy intake rather than increased energy expenditure.[13,14]

This neuroendocrine signaling pathway explains why GLP-1 therapies have transitioned from glucose-lowering agents to foundational pharmacologic tools in obesity management.

Gastrointestinal Effects: Postprandial Modulation

GLP-1 slows gastric emptying, reducing postprandial glucose excursions.[20] This contributes to improved glycemic variability but also explains common adverse effects such as nausea and early satiety. Tachyphylaxis to gastric-emptying effects may occur over time, whereas central appetite suppression appears more sustained.[20]

Understanding this distinction is important when counseling patients regarding tolerability and expected adaptation.

Cardiovascular Effects: Mechanisms Beyond Glucose Lowering

Cardiovascular outcome trials have demonstrated reductions in major adverse cardiovascular events (MACE) with several GLP-1 RAs.[6,9] The magnitude of cardiovascular risk reduction exceeds what would be predicted from HbA1c lowering alone, suggesting additional biologic mechanisms.

Proposed contributors include:

- Modest reductions in systolic blood pressure
- Improvements in lipid profiles
- Reduction in visceral adiposity
- Anti-inflammatory signaling
- Endothelial function enhancement[20]

While the precise hierarchy of these mechanisms remains under investigation, outcome data confirm cardiovascular benefit in high-risk populations for specific agents.[6,9]

Renal Effects: Hemodynamic and Metabolic Interplay

Kidney benefits observed in trials is thought to reflect a combination of improved glycemic control, weight reduction, and blood pressure lowering.[20] In the FLOW trial, semaglutide reduced the risk of kidney failure, sustained ≥50% eGFR decline, or renal death in individuals with type 2 diabetes and chronic kidney disease.[11] KDIGO 2024 guidelines recognize GLP-1 RAs as appropriate adjunctive therapy when additional cardiovascular or glycemic risk reduction is required.[12]

Although SGLT2 inhibitors remain foundational for heart failure and kidney hemodynamic protection, GLP-1 RAs appear to provide complementary benefit in selected populations.[11,12]

Hepatic and Metabolic Effects

Weight reduction, improved insulin sensitivity, and reduced hepatic fat accumulation contribute to emerging data in metabolic dysfunction-associated steatohepatitis (MASH). Recent phase 3 data

demonstrated higher rates of MASH resolution with semaglutide compared with placebo.[20] These findings align with the broader metabolic effects mediated through weight loss and improved insulin resistance.

Landmark GLP-1 & Dual Incretin Trial Programs

Glycemic Efficacy (HbA1c Reduction)

Major Glycemic Outcome Programs

Trial Program	Agent & Dose	Comparator	Population	Approximate HbA1c Reduction
SURPASS (1–6)	Tirzepatide (5–15 mg)	Semaglutide 1 mg; Insulin; Placebo	T2DM (varied stages)	−2.0% to −2.6%
SUSTAIN (1–11)	Semaglutide 0.5–1.0mg (inj)	Sitagliptin; Liraglutide; Dulaglutide; Insulin	T2DM	−1.5% to −1.8%
SUSTAIN FORTE	Semaglutide 2.0 mg	Semaglutide 1.0 mg	T2DM (dose intensification)	−2.2%
PIONEER (1–8)	Oral semaglutide 3–14 mg	Placebo; Sitagliptin; Empagliflozin; Liraglutide	T2DM	Up to −1.4% (14 mg)
PIONEER PLUS	Oral semaglutide 25–50 mg	Oral semaglutide 14 mg	T2DM (intensification)	−1.8% to −2.0%
AWARD-11	Dulaglutide 3.0–4.5 mg	Dulaglutide 1.5 mg	T2DM	−1.7% to −1.9%
LEADER	Liraglutide 1.8 mg	Placebo	T2DM + high CV risk	−1.1%
FLOW (Renal Trial)	Semaglutide 1.0 mg	Placebo	T2DM + CKD	−0.8% to −1.0%

Cardiovascular Outcome Trials (MACE)

Major Cardiovascular Outcomes Trials (CVOTs)

Trial	Agent	Population	Primary MACE Outcome	Result
LEADER (2016)	Liraglutide	T2DM + ASCVD	3-point MACE	13% RRR
SUSTAIN-6 (2016)	Semaglutide (inj)	T2DM + high CV risk	3-point MACE	26% RRR
REWIND (2019)	Dulaglutide	Broad T2DM (incl. primary prevention)	3-point MACE	12% RRR
EXSCEL (2017)	Exenatide QW	Broad T2DM	3-point MACE	Neutral
ELIXA (2015)	Lixisenatide	Post-ACS T2DM	3-point MACE	Neutral

Trial	Agent	Population	Primary MACE Outcome	Result
HARMONY (2018)	Albiglutide	T2DM + CVD	3-point MACE	22% RRR
AMPLITUDE-O (2021)	Efpeglenatide	T2DM + CV/renal risk	MACE	27% RRR
SOUL (2025)	Oral Semaglutide 14mg	T2DM + established CVD	MACE	14% RRR
SELECT (2023)	Semaglutide 2.4mg	Obesity + CVD (no diabetes)	MACE	20% RRR

Cardiovascular benefit is agent-specific and trial-population specific. Not all GLP-1 RAs demonstrated superiority.

Renal Outcome Trials

Kidney Outcomes

Trial	Agent	Population	Primary Renal Finding
FLOW (2024)	Semaglutide 1.0 mg	T2DM + CKD	24% reduction in kidney failure, ≥50% eGFR decline, or renal death
LEADER	Liraglutide	High-risk T2DM	22% reduction in new/worsening nephropathy
SUSTAIN-6	Semaglutide	High-risk T2DM	36% reduction in new/worsening nephropathy
AWARD-7	Dulaglutide	T2DM + Stage 3–4 CKD	Slower eGFR decline vs insulin
AMPLITUDE-O	Efpeglenatide	T2DM + CV/renal risk	32% reduction in renal composite

SGLT2 inhibitors remain foundational renal hemodynamic therapy. GLP-1 RAs provide complementary risk reduction in appropriate populations.

Weight Management Trials

Obesity & Chronic Weight Management

Trial	Agent	Population	Duration	Mean Weight Reduction
STEP 1	Semaglutide 2.4 mg	Obesity	68 wks	−14.9%
STEP 5	Semaglutide 2.4 mg	Obesity	104 wks	−15.2%
STEP 8	Semaglutide vs Liraglutide	Obesity	68 wks	−15.8% (semaglutide)
SURMOUNT-1	Tirzepatide 5–15 mg	Obesity	72 wks	−15% to −20.9%
SURMOUNT-4	Tirzepatide (withdrawal study)	Obesity	88 wks	Demonstrated regain after discontinuation
OASIS-1	Oral Semaglutide 50 mg	Obesity	68 wks	−15.1%
SELECT	Semaglutide 2.4 mg	Obesity + CVD	~4 yrs	−9.4%

Durability of weight reduction depends on continued therapy and integration with lifestyle intervention.

Hepatology (MASH/MASLD)

Liver-Focused Programs

Agent	Mechanism	Trial Phase	Key Finding
Semaglutide	GLP-1	Phase 3	62.9% MASH resolution without fibrosis worsening
Tirzepatide	GLP-1/GIP	Phase 2b	62% MASH resolution; fibrosis improvement
Retatrutide	GLP-1/GIP/GCGR	Phase 2	Significant liver fat reduction

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