GLP-1–BASED THERAPIES

2026 Clinical Update

Diabetes • Obesity • Cardiovascular • Kidney • Liver • Sleep

Clinician-focused review of current U.S. indications, outcomes evidence, safety, and practical prescribing

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Disclosures

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Learning objectives

Review the 2026 GLP-1 / dual GIP–GLP-1 therapeutic landscape.

Match agents to diabetes, obesity, ASCVD, CKD, HFpEF, OSA, and MASH priorities.

Translate outcomes-trial evidence into practical prescribing decisions.

Recognize contraindications, adverse effects, peri-procedural issues, and common pitfalls.

Identify what is established now versus what remains investigational.

GLP-1–BASED THERAPIES

U.S. FDA approval milestones | 2005–2026

INJECTION • ORAL • DUAL AGONIST

2005

BYETTA
exenatide
BID injection

2010

VICTOZA
liraglutide
Daily injection

2012

BYDUREON
exenatide ER
Weekly injection

2014

TRULICITY
dulaglutide
Weekly injection

2014

SAXENDA
liraglutide 3 mg
Daily • weight

2016

ADLYXIN
lixisenatide
Daily injection

2017

OZEMPIC
semaglutide
Weekly injection

2019

RYBELSUS
semaglutide
Daily oral

2021

WEGOVY
semaglutide
Weekly • weight

2022

MOUNJARO
tirzepatide
Weekly • GIP/GLP-1

2023

ZEPBOUND
tirzepatide
Weekly • weight

2025

WEGOVY PILL
semaglutide
Daily oral • weight

2026

FOUNDAYO
orforglipron
Daily oral • weight

Selected U.S. FDA approvals; not all products remain marketed. Tirzepatide is a dual GIP/GLP-1 receptor agonist.

Sources: FDA GLP-1RA approval table (2023); FDA approval releases for Wegovy tablet (2025) and Foundayo (2026).

fda.gov/media/172331/download • novonordisk-us.com/media/press-releases/wegovy-pill-fda-approval-obesity.html • fda.gov/news-events/press-announcements






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GLP-1 MEDICATIONS

Myths, Misconceptions & Medical Facts

Evidence-based clinical education | November 2026

1 “They are only cosmetic weight-loss drugs”

MYTH

GLP-1 medicines exist just to make people thinner.

FACT

Selected agents treat type 2 diabetes, chronic obesity, and specific cardiovascular, kidney or other conditions. Indications vary by product.

CLINICAL TAKEAWAY Match agent and indication to clinical need.

ADA Standards of Care 2026, Sections 8–9

3 “They cause only muscle loss”

MYTH

Weight lost on treatment is mostly muscle.

FACT

Weight loss typically includes substantial fat loss and some lean mass loss. The proportions vary by person, treatment and measurement.

CLINICAL TAKEAWAY Prioritize protein, resistance exercise and functional assessment.

10 “Benefits are limited to A1C and weight”

MYTH

There are no heart or kidney benefits.

FACT

Some GLP-1 agents have demonstrated cardiovascular and kidney outcome benefits in specific patient populations; evidence is not identical across agents.

CLINICAL TAKEAWAY Choose treatments with proven outcomes for the patient’s comorbidities.

5 “They are proven to cause thyroid cancer in humans”

MYTH

Rodent findings establish human thyroid cancer causation.

FACT

Rodent C-cell tumors prompted boxed warnings for some agents. Human relevance remains unknown. Specific labels contraindicate MTC history or MEN2.

CLINICAL TAKEAWAY Ask about personal/family MTC and MEN2 history.

FDA Wegovy prescribing information, 2026

The 2026 therapeutic landscape

The class has evolved from glucose lowering to multi-organ risk modification.

GLP-1 receptor agonists

Semaglutide • dulaglutide • liraglutide

Glucose + weight + CV / kidney benefits in selected populations

Dual GIP / GLP-1

Tirzepatide

Very high glycemic and weight efficacy; HFpEF/OSA/CV evidence now clinically important

Oral evolution

Oral semaglutide now has obesity/CV use; orforglipron adds a once-daily oral GLP-1 option for obesity

2026 regulatory milestones

- Wegovy HD 7.2 mg approved for adult weight management
- Wegovy tablets: weight + CV-risk indications
- Wegovy injection: accelerated MASH indication
- Mounjaro: CV-risk reduction in high-risk T2D

Clinical message

Think beyond A1C. Agent selection should account for ASCVD, HF, CKD, obesity, MASH, hypoglycemia risk, tolerability, cost/access, and patient preference.

Sources: ADA Standards of Care 2026; FDA/DailyMed Wegovy and Mounjaro labeling; FDA 2026 approvals.

Mechanisms: why incretin therapy has broad effects

GLP-1 receptor agonism

↑ glucose-dependent insulin secretion

↓ glucagon when glucose is elevated

↓ gastric emptying

↑ satiety / ↓ food intake

Clinical result:

A1C reduction + weight loss + low intrinsic hypoglycemia risk

GIP + GLP-1 agonism

Tirzepatide combines GIP and GLP-1 activity.

GIP contributes to insulinotropic and metabolic effects and may augment weight loss and glycemic efficacy.

Clinical result:

Very high weight and A1C efficacy

Organ-level outcomes

CV: fewer MACE in selected populations

Kidney: slower CKD progression with semaglutide

HFpEF: fewer worsening-HF events with tirzepatide

OSA: lower AHI with tirzepatide

MASH: histologic improvement with semaglutide

ADA 2026: GLP-1–based therapy is outcome-directed

Key changes are less about “which drug lowers A1C?” and more about “which drug addresses the patient’s risk profile?”

Clinical setting	2026 ADA direction
ASCVD / high ASCVD risk	Use GLP-1 RA and/or SGLT2 inhibitor with demonstrated CV benefit, independent of A1C.
CKD	Use SGLT2 inhibitor or GLP-1 RA with demonstrated benefit; GLP-1 preferred for glycemia in advanced CKD.
Obesity + symptomatic HFpEF	Use tirzepatide or a GLP-1 RA with demonstrated HF benefit.
T2D + MASLD/MASH + overweight/obesity	Consider GLP-1 RA with MASH benefit or dual GIP/GLP-1 with potential MASH benefit.
Without severe hyperglycemia	GLP-1–based therapy is preferred to insulin for initial/add-on glucose lowering.

Source: American Diabetes Association, Standards of Care in Diabetes—2026, Section 9.

Key agents and what differentiates them

U.S. indications evolve rapidly—always verify the current label.

Agent	Class	Major 2026 clinical roles	Practical distinction
Semaglutide	GLP-1 RA	T2D; obesity; CV risk reduction; MASH; oral + injectable formulations	Broadest indication portfolio
Tirzepatide	Dual GIP/GLP-1	T2D; obesity; OSA; HFpEF/obesity evidence; CV risk reduction in high-risk T2D	Very high weight/A1C efficacy
Dulaglutide	GLP-1 RA	T2D + established CV benefit	Weekly; extensive CV outcomes evidence
Liraglutide	GLP-1 RA	T2D; obesity; CV benefit	Daily injection; established outcomes data
Orforglipron	Oral GLP-1 RA	Adult obesity / overweight + comorbidity	Once-daily oral; no fasting requirement

Sources: current U.S. product labeling; FDA 2026 novel drug approvals.

Expected glycemic and weight effects: think in ranges, not promises

Semaglutide
A1C: typically ~1–2% or more depending on baseline and regimen

Weight: substantial; obesity-dose trials often produce double-digit % loss

Best fit: broad cardiometabolic benefit + familiar weekly GLP-1 RA

Tirzepatide
A1C: often ~2%+ in T2D trials

Weight: among the highest medication-associated losses currently available

Best fit: T2D + obesity when maximum metabolic efficacy is desired

Oral options
Oral semaglutide: obesity/CV use now available

Orforglipron: daily oral GLP-1 for obesity; no empty-stomach requirement

Best fit: needle-averse patients when coverage/label fits

Cardiovascular disease: a major 2026 expansion

Semaglutide
SELECT established CV event reduction in adults with obesity/overweight and established CVD. Current Wegovy labeling includes MACE risk reduction.

Oral semaglutide
Rybelsus labeling now includes MACE risk reduction in adults with T2D at high CV risk.

Tirzepatide / Mounjaro
SURPASS-CVOT: tirzepatide was noninferior to dulaglutide for CV death, MI, or stroke in T2D with ASCVD; U.S. labeling expanded in 2026 to CV risk reduction.

Clinical implication
If ASCVD/high CV risk is present, GLP-1–based therapy can be selected for risk reduction—not merely because A1C is above goal.

Sources: SELECT; PIONEER 6 / Rybelsus FDA approval; SURPASS-CVOT NEJM 2025; current U.S. labeling.

Chronic kidney disease: from albuminuria to hard outcomes

FLOW: semaglutide
In T2D + CKD, semaglutide reduced the risk of major kidney outcomes and CV death compared with placebo.

2026 ADA: GLP-1 RA with demonstrated benefit is an important option for T2D + CKD, including advanced CKD.

Tirzepatide
Post-hoc analyses show slower eGFR decline and less albuminuria, but dedicated kidney outcome evidence is less mature than semaglutide's FLOW evidence.

Clinical strategy
Use SGLT2 inhibitor when indicated for kidney/HF benefit.

Add or prioritize GLP-1–based therapy for glycemia, weight, CV risk and CKD benefit according to the patient's phenotype and tolerability.

Sources: ADA Standards 2026; FLOW trial; NEJM 2024. Note: SGLT2 inhibitors remain foundational for many CKD/HF phenotypes.

Obesity + HFpEF: GLP-1–based therapy enters the HF treatment conversation

SUMMIT: tirzepatide

731 patients with HFpEF and obesity.

CV death or worsening HF: 9.9% vs 15.3% with placebo

HR 0.62 (95% CI 0.41–0.95)

KCCQ clinical summary score improved more with tirzepatide.

Most discontinuations were GI-related.

2026 practice point

For T2D + obesity + symptomatic HFpEF, ADA 2026 recommends a dual GIP/GLP-1 RA with demonstrated benefit or a GLP-1 RA with demonstrated HF benefit.

Do not treat this as a replacement for guideline-directed HF therapy; it is an additional metabolic/HF tool.

Source: SUMMIT, NEJM 2025; ADA Standards of Care 2026.

Obstructive sleep apnea: the first FDA-approved drug treatment for OSA

Tirzepatide / Zepbound

FDA-approved for moderate-to-severe OSA in adults with obesity, alongside reduced-calorie diet and increased physical activity.

SURMOUNT-OSA: AHI fell substantially more than placebo; improvements included body weight, hypoxic burden, BP and patient-reported outcomes.

Clinical integration

OSA therapy remains multidisciplinary.

Tirzepatide can be particularly relevant when obesity is a major driver and pharmacologic weight treatment is otherwise indicated.

Continue/optimize PAP when indicated; medication is not a universal replacement.

Sources: FDA Zepbound OSA approval (12/20/2024); SURMOUNT-OSA, NEJM 2024.

MASH: semaglutide becomes a liver-directed therapy

Current U.S. indication

Wegovy injection is approved for noncirrhotic MASH with moderate-to-advanced fibrosis (F2–F3) in adults.

Approval is accelerated and based on histologic improvement; confirmatory clinical-outcome evidence remains important.

What the trial showed

At week 72 in the phase 3 study:

- MASH resolution without worsening fibrosis: 63% vs 34%
- Fibrosis improvement without worsening MASH: 37% vs 22%

Tirzepatide also showed promising phase 2 MASH results, but that does not equal an FDA indication.

Source: FDA MASH approval; ESSENCE interim analysis. Tirzepatide SYNERGY-NASH is investigational for MASH as of this deck.

Oral GLP-1 therapy: a major 2026 practical change

Wegovy tablets (semaglutide)

Current U.S. labeling includes adult weight reduction and CV-risk reduction.

25 mg once daily maintenance after titration.

Take in the morning on an empty stomach with up to 4 oz water; wait ≥30 minutes before food, beverages, or other oral medications.

Foundayo (orforglipron)

FDA-approved April 2026 for adult obesity or overweight with ≥1 weight-related comorbidity.

Once daily oral GLP-1 RA.

Distinct practical advantage: does not require fasting/empty-stomach administration.

As of this deck, the FDA indication is weight management—not T2D.

Sources: current Wegovy labeling (revised 6/2026); FDA Foundayo approval 4/1/2026.

Practical prescribing: start low, go slow, stay flexible

Principle	Practical approach
Start low	Use the labeled starting dose; do not “rush” escalation for faster weight loss.
Titrate to response + tolerability	Hold or extend an escalation step when GI symptoms are limiting.
Treat the patient, not the dose	A lower tolerated maintenance dose can be clinically successful.
Reassess other glucose-lowering drugs	Insulin and sulfonylureas may need reduction to avoid hypoglycemia.
Track more than A1C	Weight, BP, renal function when clinically indicated, GI symptoms, retinopathy risk, nutrition, and patient-reported benefit.
Avoid duplicate incretin therapy	Do not combine GLP-1-containing products with one another unless specifically supported by labeling.

Safety: what matters most in routine practice

GI effects
Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal discomfort.

Mitigate: smaller meals, slower titration, hydration.

Gallbladder / pancreas
Evaluate persistent severe abdominal pain. Suspected pancreatitis → discontinue and evaluate. Watch for biliary disease.

Retinopathy
Rapid glucose improvement can worsen diabetic retinopathy in susceptible patients. Monitor those with established retinopathy/high risk.

Kidney / volume
Vomiting/diarrhea can cause volume depletion and AKI. Consider renal monitoring in patients with kidney disease or severe GI symptoms.

Gastroparesis / aspiration
Avoid in severe gastroparesis. Delayed gastric emptying raises peri-procedural aspiration considerations; follow current anesthesia/procedural guidance.

Thyroid warning
Boxed warning is based on rodent C-cell tumors. Contraindicated with personal/family MTC or MEN2.

2026 labeling also reflects removal of suicidal-ideation warnings from affected GLP-1 products after FDA review found no increased risk.

Contraindications and “pause points”

Before prescribing

☐ Personal/family history of medullary thyroid carcinoma or MEN2

☐ Prior serious hypersensitivity

☐ Pregnancy / reproductive planning

☐ Severe gastroparesis or major GI disease

☐ Active/suspected pancreatitis

☐ Significant gallbladder symptoms

☐ High hypoglycemia risk from insulin/SU without a plan to adjust

☐ Established diabetic retinopathy needing close follow-up

Before procedures

Ask about GLP-1/GIP therapy at every pre-op/procedural encounter.

Because gastric emptying is delayed, aspiration risk has become a key peri-procedural issue.

Management of withholding vs continuation should follow the most current anesthesia/procedural guidance and patient-specific risk assessment rather than a one-size-fits-all rule.

Compounded GLP-1 products: the 2026 regulatory landscape

FDA position

FDA has emphasized that compounded products are not FDA-approved and are not reviewed for safety, effectiveness, or quality before marketing.

In 2026 FDA announced actions concerning mass-marketed non-FDA-approved compounded GLP-1 products and proposed removing semaglutide, tirzepatide and liraglutide from the 503B bulk substances list.

Clinical message

When an FDA-approved product is available and appropriate, discuss its known formulation, dose, labeling, quality controls, and pharmacovigilance.

Do not treat retatrutide or cagrilintide as approved/compounded substitutes: they remain investigational and are not FDA-approved for any indication.

Sources: FDA statements on unapproved GLP-1 drugs and 503B bulks, 2026.

What is next? 2026 pipeline to watch

Retatrutide
Triple agonist: GIP + GLP-1 + glucagon.

Very large weight-loss signals in phase 2/3 development.

CV and kidney outcomes are being studied.

NOT FDA-approved as of October 2026.

Next-generation oral agents
Oral GLP-1 programs are moving beyond traditional semaglutide formulations.

Potential advantages: convenience, manufacturing, patient acceptance.

Key questions: durability, GI tolerability, cost, adherence, and hard outcomes.

Combination / muscle preservation
The field is moving toward combinations designed to improve fat loss while preserving lean mass, and toward broader cardiometabolic indications.

Treat pipeline claims as investigational until regulatory approval and outcome evidence are available.

FDA 2026: retatrutide is not an approved component of FDA-approved drugs and cannot lawfully be used as a compounded substitute.

A practical 2026 treatment-selection algorithm

1. **Does the patient have T2D?**
   Yes → GLP-1–based therapy is preferred to insulin when severe hyperglycemia/crisis is absent.

2. **ASCVD / high CV risk?**
   Favor an agent with demonstrated CV benefit.

3. **CKD?**
   Consider GLP-1 RA with demonstrated kidney/CV benefit; pair with SGLT2 inhibitor when indicated.

4. **Obesity / major weight goal?**
   Semaglutide or tirzepatide are high-efficacy options; consider oral options when appropriate.

5. **HFpEF + obesity?**
   Tirzepatide or GLP-1 RA with demonstrated HF benefit can be particularly attractive.

6. **OSA + obesity?**
   Tirzepatide has an FDA indication for moderate-to-severe OSA in adults with obesity.

7. **MASH F2–F3?**
   Semaglutide (Wegovy) is FDA-approved; continue multidisciplinary liver care.

Case application

Patient

58-year-old with T2D, A1C 8.6%, BMI 36, prior MI, eGFR 48, albuminuria, OSA, and HFpEF.

Current: metformin + basal insulin + SGLT2 inhibitor.

Goals: reduce CV/renal risk, weight, A1C, and HF/OSA burden while minimizing hypoglycemia.

2026 reasoning

1. GLP-1–based therapy has outcome rationale independent of A1C.
2. Semaglutide: strong CV/kidney evidence and weight efficacy.
3. Tirzepatide: very high weight/A1C efficacy + HFpEF and OSA evidence/indications.
4. Reassess basal insulin dose as glucose improves.
5. Continue SGLT2 inhibitor when appropriate for CKD/HF benefit.
6. Monitor GI tolerance, volume status, retinopathy, nutrition, and procedural plans.

2026 TAKE-HOME POINTS

GLP-1–based therapy is now a cardiometabolic platform, not simply an A1C-lowering class.

Match the molecule to the phenotype: ASCVD, CKD, obesity, HFpEF, OSA, and MASH matter.

Tirzepatide offers exceptional weight/A1C efficacy and now has major CV/HFpEF/OSA relevance.

Semaglutide has the broadest current U.S. outcome/indication portfolio, including MASH and oral options.

Slow titration and proactive GI management improve persistence.

Always distinguish FDA-approved indications from promising pipeline science.

Selected references

American Diabetes Association. Standards of Care in Diabetes—2026. Diabetes Care. 2026;49(Suppl 1).

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FDA. FDA Approves First Medication for Obstructive Sleep Apnea — Zepbound. 12/20/2024.

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Selected sources; full prescribing information and primary publications should be consulted for detailed dosing and safety.