

Optimizing T2D Outcomes with GLP-1-Centered Treatment



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Learning Objectives

Participants in this presentation should be able to...

Incorporate cardio-kidney-metabolic risk reduction principles into T2D management by identifying patients who may benefit from GLP-1 RA-based therapy beyond glycemic control.

Differentiate current and emerging GLP-1 RA-based therapies by mechanism of action, route of administration, dosing/titration considerations, glycemic and extra-glycemic effects, and safety/tolerability profile to inform personalized treatment selection.

Implement practical strategies to initiate, titrate, and sustain GLP-1 RA-based treatment in primary care, including proactive adverse effect management, patient counseling, shared decision-making, and navigation of access barriers.

I. The Evolving Goals of T2D Management in Primary Care



T2D, CVD/HF, and CKD^{1,2}

- Among the most disruptive public health issues of the century
- Strong interconnection between diseases affecting the three systems (metabolic, cardiovascular, renal)
- Coexistence of all three referred to as “**cardio-renal-metabolic**” syndrome

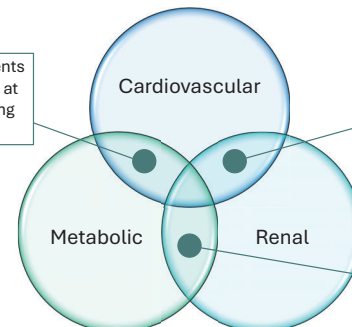


T2D, type 2 diabetes; CVD, cardiovascular disease; CKD, chronic kidney disease; HF, heart failure

1. Ndumele CE, et al. *Circulation*. 2023;148(20):1606-1635. 2. Marassi M and Fadini GP. *Cardiovasc Diabetol*. 2023;22:195.

Coexistence of Cardio-Renal-Metabolic Systems

At least 50% of patients with T2D have or are at high risk of developing CV disease¹



T2D and hypertension are the leading causes of >75% of ESKD cases in the US³

CKD affects up to 40% of patients with T2D²

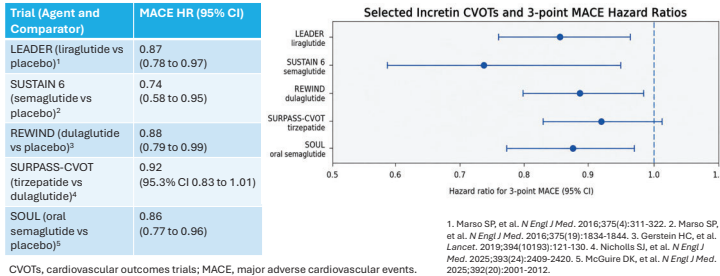
ESKD, end-stage kidney disease

1. Wong K, et al. *J Diabetes Complications*. 2012;26:169-174. 2. Feng X, et al. *Kidney Med*. 2022;4(1):100385. 3. Burrows NR, et al. *MMWR Morb Mortal Wkly Rep*. 2022;71(11):412-415.

Why Glycemic Control Alone is Not Enough in T2D

MACE benefit with GLP-1-based therapies

- Liraglutide, semaglutide (injectable and oral), and dulaglutide have shown significant reductions in MACE versus placebo; tirzepatide was noninferior to liraglutide.



T2D and CKD Outcomes with Semaglutide: FLOW Trial

- Patients: 3533 adults with T2D and CKD randomized 1:1 to semaglutide 1.0 mg once weekly or placebo
- Trial stopped early at median follow-up of 3.4 years
- Results (all statistically significant in favor of semaglutide):

Outcome	Semaglutide vs Placebo
Primary outcome: major kidney disease events, a composite of the onset of kidney failure, at least a 50% reduction in the eGFR from baseline, or death from kidney or cardiovascular causes	HR 0.76; 95% CI, 0.66 to 0.88; P = .0003
Kidney-specific components of the primary outcome	HR 0.79; 95% CI, 0.66 to 0.94
Death from CV causes	HR 0.71; 95% CI, 0.56 to 0.89
Risk of MACE	HR 0.82; 95% CI, 0.68 to 0.98; P = .029
Risk of death from any cause	HR 0.80; 95% CI, 0.67 to 0.95; P = .01

Conclusion: semaglutide reduced the risk of clinically important kidney outcomes and death from CV causes in patients with T2D and CKD. It demonstrated statistically significant reductions in MACE.

CV, cardiovascular; eGFR, estimated glomerular filtration rate

Perkovic V, et al. *N Engl J Med*. 2024;391(2):109-121.

Beyond HbA1c: Current Standards of Care in T2D¹

Glycemic control alone is not sufficient as the therapeutic target.

- ADA Standards of Care:¹
 - GLP-1 RA with demonstrated CV benefit and/or SGLT2 inhibitor recommended for T2D with ASCVD, HF, or CKD
 - Independent of HbA1c and independent of metformin use
 - GLP-1 RA-based therapy preferred injectable prior to insulin in T2D, unless inappropriate or contraindicated
- Clinical features that may prompt consideration of GLP-1 RA-based treatment include overweight/obesity, ASCVD risk, and CKD.

ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; HbA1c, glycated hemoglobin

1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl. 1):S183-S215.

Beyond HbA1c: Current Standards of Care in T2D¹

Glycemic control alone is not sufficient as the therapeutic target.

- Treatment selection should also address weight goals, hypoglycemia risk, medication burden, adverse effects, access, and patient preference.
- A regimen that meets an HbA1c target but relies heavily on hypoglycemia-prone or weight-promoting agents may still miss CKM risk-reduction opportunities.
 - Patients with ASCVD, CKD, or obesity who are treated only with metformin, sulfonylureas, or insulin should be reassessed for agents that address risk beyond glucose lowering.

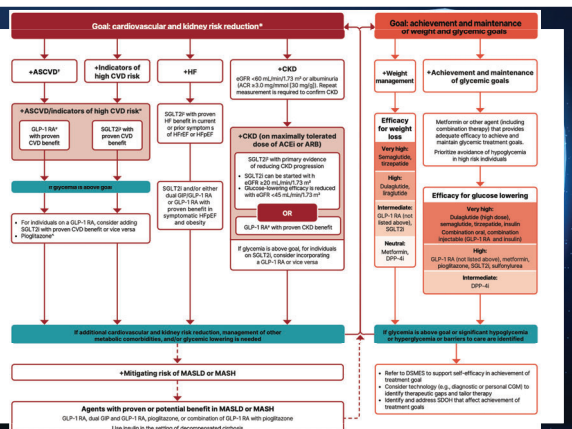
ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; HbA1c, glycated hemoglobin

1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl. 1):S183-S215.

ADA 2026 Pharmacologic Therapy Algorithm

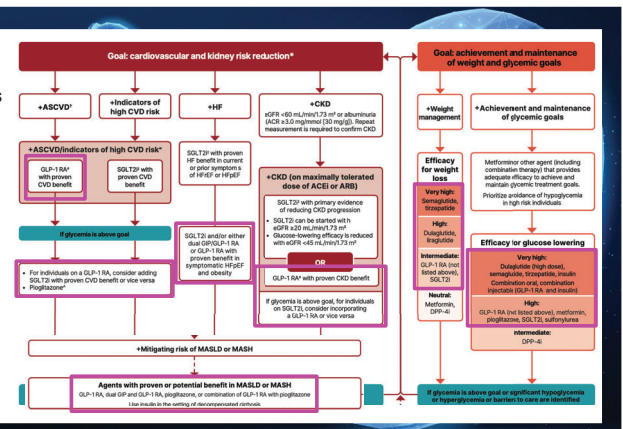
CGM, continuous glucose monitoring; DPP-4i, dipeptidyl peptidase 4 inhibitor; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MASLD, metabolic dysfunction-associated steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; SGLT2i, sodium-glucose cotransporter 2 inhibitor

American Diabetes Association Professional Practice Committee. *Diabetes Care*. 2026;49(Suppl. 1):S183-S215. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2026.

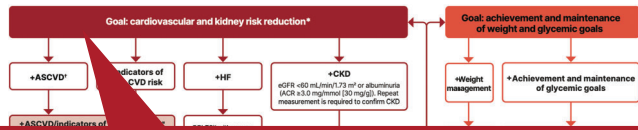


GLP-1 RA Therapies in the Standards of Care of Care

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Use of Glucose-Lowering Medications in the Management of T2D



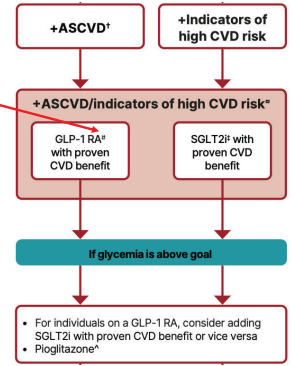
Goal: cardiovascular and kidney risk reduction*

*In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of attainment of glycemic goal.

American Diabetes Association Professional Practice Committee. Diabetes Care. 2026;49(Suppl_1):S183-S215. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2026.

High-risk or established ASCVD

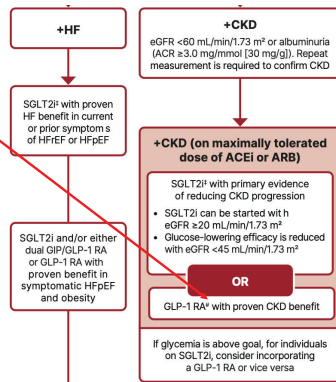
*For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, myocardial infarction, stroke, and kidney endpoints in individuals with T2D with established or high risk of CVD.



American Diabetes Association Professional Practice Committee. Diabetes Care. 2026;49(Suppl_1):S183-S215. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2026.

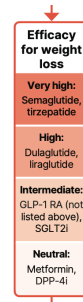
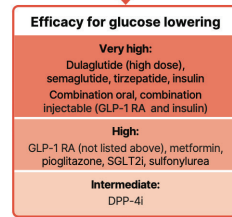
HF or CKD

*One kidney outcome trial (FLOW) demonstrated benefit in reducing persistent eGFR reduction and CV death for semaglutide in CKD and T2D.



American Diabetes Association Professional Practice Committee. Diabetes Care. 2026;49(Suppl_1):S183-S215. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2026.

Weight loss/glucose-lowering efficacy

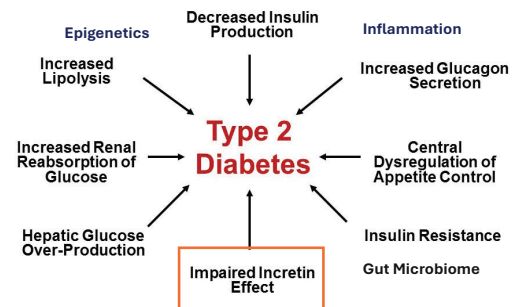


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II. GLP-1 RA-Based Therapies: Mechanisms, Evidence, and Differentiation

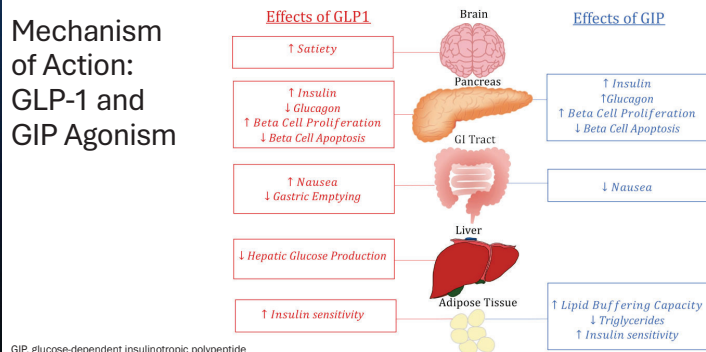


Pathophysiologic Defects in T2D^{1,2}



1. DeFronzo RA. Diabetes. 2009;58(4):773-795. 2. Miller E, et al. Cleve Clin J Med. 2019;86(7):494-504.

Mechanism of Action: GLP-1 and GIP Agonism



GIP, glucose-dependent insulinotropic polypeptide

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Characteristics of GLP-1 RAs Approved for T2D^{1,2}

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide*	Dulaglutide Exenatide extended-release Liraglutide Semaglutide
Half-life	2-4 h exenatide shortest	13 h – several days (5-7-day range)
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycemia	Strong reduction	Modest reduction
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Slowed/substantial	Initial/then diminished
Blood pressure	Modest reduction	Modest reduction
Heart rate	No effect or small increase (0-2 bpm)	Moderate increase (2-5 bpm)
Body weight reduction	1-5 kg	2-5 kg
Induction of nausea	20-50%, attenuates slowly (weeks to many months)	20-40%, attenuates quickly (4-8 weeks)

*Discontinued in the United States

1. Nauck MA, et al. *Mol Metab*. 2021;46:101102. 2. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl. 1):S183-S215.

Injectable GLP-1 RA Dosing and Administration for T2D

	Short-acting	Long-acting			
	Exenatide	Liraglutide	Exenatide Extended-Release	Dulaglutide	Semaglutide
Dose	5 mcg twice daily for 1 month; increase to 10 mcg twice daily	0.6 mg once daily x 1 week; increase to 1.2 mg daily; can increase to 1.8 mg daily, each after at least 1 week	2 mg once weekly	0.75 mg once weekly; increase to 1.5 mg; can increase to 3 mg and 4.5 mg if needed, each after 4 weeks	0.25 mg once weekly; increase to 0.5 mg; increase to 1 mg once weekly; increase to 2 mg once weekly if needed, each after 4 weeks
Administration frequency	Twice daily (within 60 minutes before meals)	Once daily	Once weekly	Once weekly	Once weekly
Delivery	Multi-use pen (2 strengths)	Multi-use pen	Single-use pen	Single-use pen (4 strengths)	Multi-use pen (3 pen options)
Renal dosing	CrCl <30 mL/min, not recommended; CrCl 30-50 mL/min, use caution	None	eGFR <45 mL/min, not recommended	None	None

Byetta [Package Insert]. September 2025. Accessed June 8, 2026. Victoza [Package Insert]. October 2025. Accessed June 8, 2026. Bydureon Bcise [Package Insert]. May 2025. Accessed June 8, 2026. Trulicity [Package Insert]. March 2026. Accessed June 8, 2026. Ozempic [Package Insert]. Updated October 2025. Accessed June 8, 2026.

Oral Semaglutide: Dosing & Administration

Administration Instructions:

- Take at least 30 minutes before the first food, beverage, or other oral medication of the day
- Take with no more than 4 ounces of plain water only
- Swallow tablets whole: do not crush or chew
- Store in packaging until use

Dosing (3 mg to 14 mg formulation)	Dosing (1.5 mg to 9 mg formulation)
Start with 3 mg once daily for 30 days	Start with 1.5 mg once daily for 30 days
Increase to 7 mg once daily for 30 days	Increase to 4 mg once daily for 30 days
Dose may be increased to 14 mg once daily if needed	Dose may be increased to 9 mg once daily if needed

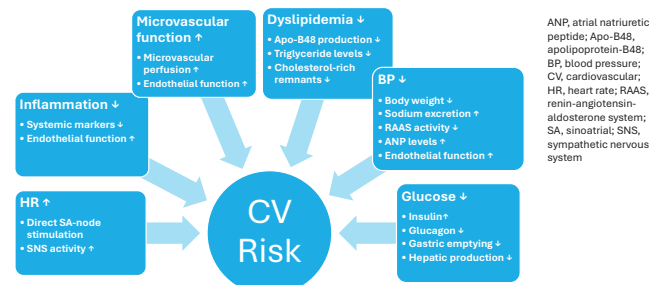
Ozempic, Rybelus [Package Insert]. January 2026. Accessed June 8, 2026.

Tirzepatide Indication and Dosing

- Indication:**
 - Adjunct to diet and exercise to improve glycemic control in T2D
- Availability:**
 - Pre-filled single dose pens or single-dose vial in the following strengths: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg
 - Also available as a multi-dose vial or single-patient-use Kwipen
- Dosing:**
 - Initial dose: 2.5 mg subcutaneously once weekly
 - Increase to 5 mg once weekly after 4 weeks of the 2.5 mg dose
 - Dose can be increased in 2.5 mg increments every 4 weeks up to a maximum recommended dose of 15 mg once weekly.

Mounjaro [Package Insert]. Updated January 2026. Accessed June 8, 2026.

CV Effects of GLP-1 RA-Based Therapies^{1,2}



1. Heuvelman V, et al. *Cardiovasc Res*. 2020;116(5):916-930. 2. Hammoud R, et al. *Nat Rev Endocrinol*. 2023;19(4):201-216.

GLP-1 RA–Based Therapy Benefits in Patients with HF

- Among patients with HF, impact primarily through indirect cardiometabolic mechanisms with emerging evidence for direct myocardial and vascular effects¹⁻³
 - Decrease visceral fat/weight loss
 - Decrease arterial pressure
 - Decrease myocardial inflammation
 - Decrease systemic glucose levels

1. Deis T, et al. *Circ Heart Fail*. 2024;17(11):e011813. 2. Shchendrygina A, et al. *Card Fail Rev*. 2024;10:e10. 3. Packer et al for the SUMMIT Trial Study Group. *N Engl J Med*. 2025;392:427-437.

Semaglutide and Tirzepatide in Patients with HFpEF

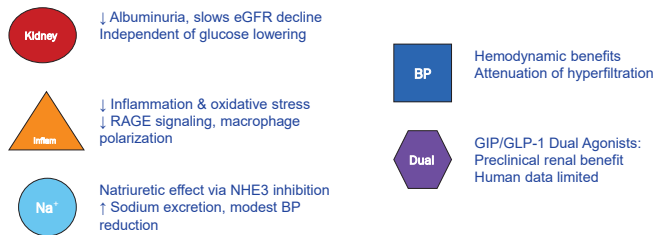
- Study used 5 cohort studies with US claims data (2018–2024).¹
- Patients had HFpEF, obesity, and type 2 diabetes.
- Primary outcome: hospitalization for heart failure or all-cause mortality
- Semaglutide and tirzepatide reduced risk >40% vs sitagliptin.
- Tirzepatide showed no meaningful benefit over semaglutide.
- No substantial safety concerns observed

Comparison	Hazard Ratio (HR)	95% CI	Risk Reduction
Semaglutide vs Sitagliptin	0.58	0.51–0.65	>40%
Tirzepatide vs Sitagliptin	0.42	0.31–0.57	>40%
Tirzepatide vs Semaglutide	0.86	0.70–1.06	No meaningful difference

HFpEF, heart failure with preserved ejection fraction

1. Krüger N, et al. *JAMA*. 2025;334(14):1255-1266.

Renal Mechanisms of GLP-1 RA–Based Therapy



NHE3, sodium/proton exchanger (isoform 3); RAGE, receptor for advanced glycation end products

1. De Boer, et al. *Kidney Int*. 2022;102(5):974-989. Weiker et al. *JAMA Internal Medicine*. 2023;183(7):705-714.

GLP-1 RA–Based Therapy in MASLD/MASH

Evidence from RCTs & Guidelines¹⁻³

- GLP-1 RAs (semaglutide 2.4 mg): Phase 3 ESSENCE trial**
 - 62.9% MASH resolution, 36.8% reduction in liver fibrosis, and 10.5% weight reduction in patients with MASH and stage 2 or 3 fibrosis
 - Semaglutide 2.4 mg FDA approved for MASH with stage 2 or 3 fibrosis
- Dual agonist (tirzepatide 5-15 mg): Phase 2 SYNERGY-NASH trial**
 - Up to 62% MASH resolution and up to 55% improvement of ≥1 fibrosis stage in patients with MASH and stage 2 or 3 fibrosis
- Meta-analyses:** Consistent reductions in hepatic steatosis, liver enzymes, and steatohepatitis without worsening fibrosis

Mechanisms of Benefit

- ↓ Hepatic steatosis
- ↑ Insulin sensitivity & improved cardiometabolic risk factors
- Synergistic incretin effects (dual agonists)

Safety

- Generally well tolerated
- GI side effects most common

Clinical Guidance⁴

- First-line pharmacologic therapy** for MASLD/MASH in patients with type 2 diabetes or obesity
- Strongest evidence-based pharmacologic option available

GI, gastrointestinal

1. Targher, et al. *N Engl J Med*. 2025;393(7):683-698. 2. Cusi K, et al. *Diabetes Care*. 2025;48(7):1057-1082. 3. Sanyal AJ, et al. *N Engl J Med*. 2025;392(21):2089-2099. 4. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl. 1):S183-S215.

GLP-1 RAs: Patient Counseling Considerations

- Cardiovascular outcomes/data differ among agents within the GLP-1 RA class.
- Nausea and other GI symptoms are the most frequent adverse effects.
 - Usually subsides within a few weeks
 - Only 5-10% discontinue treatment due to nausea/vomiting.
- Pancreatitis
 - All patients with diabetes have an increased risk of acute pancreatitis.
 - A causal relationship has not been established.
 - Educate patients on symptoms
- Gallbladder disease
- Monitor for retinopathy progression
- Contraindicated if personal or family history of medullary thyroid cancer or MEN2

MEN2, multiple endocrine neoplasia type 2

1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl. 1):S183-S215.

Pancreatitis With Incretin-Based Therapies: Additional Considerations¹

US FDA and EMA assessments

- Assertions of causal association are not consistent with current data.^a
- Data from CVOTs indicate no increased risk of pancreatitis.
- Product information and labeling reflect current understanding of risk.

Label information

- Ask about pancreatitis history and risk factors (eg, gallstones, alcoholism, elevated triglyceride levels, kidney problems).
- Educate patients about and monitor for pancreatitis signs and symptoms—discontinue promptly if they occur.
- Report cases of pancreatitis to www.fda.gov/medwatch.

^aPreclinical data, clinical trial data, epidemiological data

US FDA, United States Food and Drug Administration; EMA, European Medicines Agency

1. Egan AG, et al. *N Engl J Med*. 2014;370:794-797.

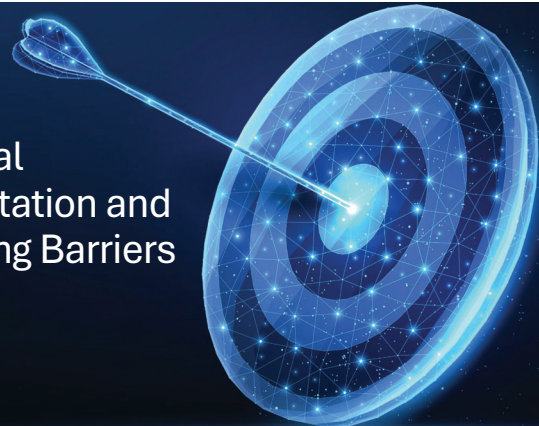
Eye Risks With GLP-1 RA–Based Therapies

Observational data link GLP-1 RAs to rare eye conditions:¹⁻³

- Diabetic retinopathy (DR, ~7% increased risk); though GLP-1 RAs reduced risk of DR complications
- Neovascular age-related macular degeneration (nAMD): abnormal blood vessel growth under retina
- Nonarteritic ischemic anterior optic neuropathy (NAION): impaired blood flow to optic nerve
- Risks are very rare and based on observational data:
 - ~1 in 1,000 older diabetic patients may develop nAMD over 3 years.
 - ~1 additional NAION case per 10,000 patients over 4 years
- Risk may increase with longer use; unclear if specific drugs, doses, or routes matter.
- Diabetes itself is a risk factor for these conditions.
- Recommend baseline and annual eye exams, counsel patients to report vision changes immediately
- Reassure: benefits of GLP-1s outweigh rare ocular risks for most patients

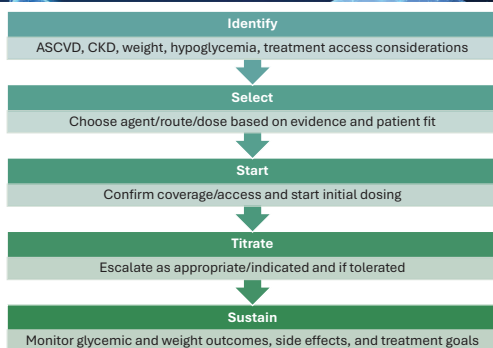
1. Ramsey DJ, et al. *JAMA Netw Open*. 2025;8(8):e2526321. 2. Shor R, et al. *JAMA Ophthalmol*. 2025;143(7):587-594. 3. Hsu AY, et al. *JAMA Ophthalmol*. 2025;143(5):400-407.

III. Practical Implementation and Overcoming Barriers



Translating Evidence Into Clinical Action

Example GLP-1 RA–based therapy implementation workflow for primary care^{1,2}



1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl_1):S183-S215. 2. Gorgojo-Martinez JIG, et al. *J Clin Med*. 2022;12(1):145.

Incorporating Patient Preferences and Treatment Goals

- Shared decision-making considerations should include:^{1,2}
 - Route
 - Dosing frequency
 - GI effects
 - Weight goals
 - Cost
 - Prior medication experience
 - How quickly the patient is ready to titrate
- Patient preferences show heterogeneity (REVISE study)³.
 - Some patients prefer oral daily therapy, whereas others prefer weekly injections to reduce daily treatment burden.

1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl_1):S183-S215. 2. Gorgojo-Martinez JIG, et al. *J Clin Med*. 2022;12(1):145. 3. Boyle K, et al. *Diabetes Obes Metab*. 2021;23(2):508-519.

Patient Counseling: What to Say Before the First Dose

- Counseling should **normalize early appetite changes** and **mild GI symptoms**^{1,2}.
 - Severe abdominal pain, persistent vomiting, dehydration, or gallbladder symptoms require contacting the clinic or getting emergency care if serious.
- Patients should receive a **clear, specific plan** for missed doses, injection technique or oral administration instructions, refill timing, and when not to escalate.

1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl_1):S183-S215. 2. Gorgojo-Martinez JIG, et al. *J Clin Med*. 2022;12(1):145.

Managing Nausea and Appetite Changes

- Nausea commonly occurs early in therapy or after dose escalation^{1,2}.
 - Often mitigated by slower eating, smaller portions, lower-fat meals, avoiding escalation during symptoms, and temporary dose reduction when needed.
- Appetite reduction is expected and should be communicated to the patient^{1,2}.
 - Monitor for inadequate protein intake, frailty risk, dehydration, or medication malnutrition concerns in older adults.

GLP-1 RA Nausea Management²

Nausea Severity	Clinical Approach
Mild, tolerable	Continue dose; reinforce smaller meals and slow eating
Moderate or persistent	Consider slower escalation/longer time at current dose
Recurrent after escalation	Step back to prior tolerated dose or pause escalation
Severe or red flags	Hold therapy and evaluate for dehydration, pancreatitis, gallbladder disease, or other causes

1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl_1):S183-S215. 2. Gorgojo-Martinez JIG, et al. *J Clin Med*. 2022;12(1):145.

Managing Vomiting, Diarrhea, Constipation, and Dehydration

- Vomiting or diarrhea requires assessment of oral intake, volume status, renal function risk, and concomitant medications that can worsen dehydration.^{1,2}
- Constipation management should start with hydration, fiber as tolerated, physical activity, and proactive counseling before symptoms lead to discontinuation.

Triaging GLP-1 RA Adverse Effects^{1,2}

Presentation	Continue/Counsel	Hold/Evaluate	Urgent Assessment
Nausea only	Small meals, lower-fat foods	Persistent symptoms despite dose delay	Severe abdominal pain
Vomiting	If brief and hydration maintained	Persistent vomiting or reduced intake	Dehydration, syncope, acute kidney injury concern
Diarrhea	Hydration, monitor	Persistent diarrhea with weakness	Severe dehydration or blood/fever
Constipation	Hydration/fiber/movement	No bowel movement with pain/distension	Obstruction symptoms

1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl_1):S183-S215. 2. Gorgojo-Martinez JJG, et al. *J Clin Med*. 2022;12(1):145.

Considerations for Switching GLP-1 RAs

- Switching GLP-1 RA-based therapies:¹⁻³
 - May be reasonable for inadequate efficacy, intolerable GI effects, route preference, formulary changes, supply issues, or need for a different dosing schedule
 - The starting dose after switching should reflect the patient's current tolerability, prior dose, time since last dose, and reason for switching.
 - Not simply the target dose of the new agent

1. Almindoz JP, et al. *Clin Diabetes*. 2020;38(4):390-402. 2. Jain AB, et al. *Int J Clin Pract*. 2021;75(2):e13731. 3. Gorgojo-Martinez JJG, et al. *J Clin Med*. 2022;12(1):145.

Combining GLP-1 RA-Based Therapies with Other T2D Treatments¹

- Combining GLP-1 RA-based therapy with **SGLT2 inhibitors** can address complementary CKM goals when glycemia, weight, ASCVD, CKD, or HF risks overlap.
- Adding GLP-1 RA-based therapy to **basal insulin** can improve glycemia with less hypoglycemia and weight gain than prandial insulin intensification in many patients.
- GLP-1 RA therapy should **not be combined with DPP-4 inhibitors** because overlapping incretin mechanisms add little clinical value.

1. American Diabetes Association Professional Practice Committee for Diabetes. *Diabetes Care*. 2026;49(Suppl_1):S183-S215.

Patient Case Scenario #1

A 63-year-old woman with T2D has an HbA1c of 8.6% on metformin and basal insulin, BMI 35 kg/m², hypertension, eGFR 52 mL/min/1.73 m², and a goal of weight loss with fewer hypoglycemia concerns.



- **Key therapy decision:** evaluate GLP-1 RA-based therapy to improve glycemia and weight while reassessing basal insulin dose and kidney/CV risk management

Patient Case Scenario #2

A 58-year-old woman with T2D has an HbA1c of 8.1% on metformin and an SGLT2 inhibitor, established ASCVD, and persistent postprandial hyperglycemia.



- **Key therapy decision:** add a GLP-1 RA with demonstrated CV benefit and match route/titration to her goals and tolerability concerns

Patient Case Scenario #3

A 52-year-old man with long-standing T2D has HbA1c of 9.0% on metformin, sulfonylurea, and basal insulin; he reports nausea with prior GLP-1 therapy, limited health literacy, and cost concerns.



- **Key therapy decision:** determine whether a slower GLP-1 RA titration, different agent/route, sulfonylurea reduction, and access support can simplify therapy while avoiding recurrent intolerance

IV. What's Next: Innovations and Emerging GLP-1 RA–Based Options



Single-Target New Innovations and Emerging GLP-1 RA–Based Therapies

Emerging oral approaches for T2D include:

- Higher-dose oral semaglutide
- Small-molecule oral GLP-1 RAs

Higher-dose semaglutide injection is being evaluated in T2D, with STEP UP T2D providing evidence in adults with obesity and T2D.

New/Emerging Oral Agents and Higher-Dose Injectable

Agent	Route	Key Data/ Status
Oral semaglutide 25/50 mg ¹	Oral	PIONEER PLUS: HbA1c –1.8% (25 mg) and –2.0% (50 mg) at 52 weeks
Orforglipron ²	Oral	ACHIEVE-1: HbA1c –1.24% to –1.48% at 40 weeks
Danuglipron	Oral	Development discontinued due to liver toxicity concerns
Semaglutide 7.2 mg ³	Subcutaneous Injection	STEP UP T2D: placebo-adjusted HbA1c treatment difference –1.5% at 72 weeks

1. Aroda VR, et al. *Lancet*. 2023;402(10403):693-704. 2. Rosenstock J, et al. *N Engl J Med*. 2025;393(11):1065-1076. 3. Lingvay I, et al. *Lancet Diabetes Endocrinol*. 2025;13(11):935-948.

Emerging GLP-1 RA – Elecglipton in T2D

Targets GLP-1 Receptors

Data from a phase 2b trial

Trial	Patients	Elecglipton once daily, oral	Placebo	Statistical Significance
SOLSTICE ¹	N=406 Adults with T2D inadequately controlled on metformin or SGLT2 inhibitor monotherapy	Dose range: 5 mg, 15 mg, 25 mg, 50 mg, 75 mg HbA1c reduction: –0.91% to –1.88%	HbA1c reduction: –0.15%	HbA1c improvements were statistically significant versus placebo for elecglipton

1. Aroda VR, et al. *Lancet*. 2026 Jun 8:S0140-6736(26)00802-0.

Potential Advantages of New/Emerging Single-Target Therapies

- Oral dosing may better match patients' preferences and result in improved adherence/persistence^{1,2}.
- Higher doses may provide additional glycemic and weight loss efficacy needed by some patients.
- Weekly injectable GLP-1 therapy may be preferred by those who desire less frequent dosing².

1. Lv L, et al. *Prim Care Diabetes*. 2024;18(6):511-517. 2. Boye K, et al. *Diabetes Obes Metab*. 2021;23(2):508-519.

Innovations in Dual/Multi-Agonists and Combination Products

Rationale for targeting multiple metabolic pathways simultaneously

- GLP-1, amylin, glucagon, GIP targeting
- Multi-hormone-based weight loss arises through distinct and overlapping neural pathways = synergy with combined therapy².
- Historically, the most robust results come from combinations, while avoiding some off-target safety issues seen with earlier small-molecule approaches⁵.

Hormone	Description
GLP-1	A satiety hormone acting on receptors in appetite centers; slows gastric emptying, increases insulin secretion and decreases glucagon secretion in a glucose-dependent manner ^{1,2}
Amylin	Influences energy intake and homeostatic/hedonic appetite regulation ²
Glucagon	Effects on hepatic glucose production and hepatic lipid metabolism, decreases hepatic storage of fat ³
GIP	Improves glycemic control and reduces adiposity ⁴

1. Dehestani B, *J Obes Metab Syndr*. 2021;30(4):320-325. 2. Davies MJ, et al. *N Engl J Med*. 2025;393(7):648-659. 3. Winther JB, et al. *Diabetes Obes Metab*. 2024;26(9):3501-3512. 4. Samms RJ, et al. *Diabetes*. 2025;74(8):1326-1333. 5. Hay DL, et al. *Pharmacol Rev*. 2015;67(3):564-600.

New/Emerging Dual/Multi-Agonists and Combination Products in T2D

Includes fixed-dose combinations and single molecules targeting GLP-1 with amylin, GIP, and/or glucagon pathways

Agent	Target
Cagrilintide/semaglutide	Amylin + GLP-1
Retatrutide	GLP-1 + GIP + glucagon
Mazdutide	GLP-1 + glucagon
Zenagamtide (amycretin)	GLP-1 + amylin

1. Dehestani B, *J Obes Metab Syndr*. 2021;30(4):320-325. 2. Davies MJ, et al. *N Engl J Med*. 2025;393(7):648-659. 3. Winther JB, et al. *Diabetes Obes Metab*. 2024;26(9):3501-3512. 4. Samms RJ, et al. *Diabetes*. 2025;74(8):1326-1333. 5. Hay DL, et al. *Pharmacol Rev*. 2015;67(3):564-600.

Cagrilintide/Semaglutide in T2D

Combines an amylin receptor agonist with a GLP-1 RA to target appetite and glycemic pathways through complementary mechanisms¹

• Data from three phase 3 trials, REDEFINE 2, REIMAGINE 2, and REIMAGINE 3

Trial	Patients	Cagrilintide 2.4 mg/ Semaglutide 2.4 mg	Comparator	Statistical Significance
REDEFINE 2 ¹	N=1,206 BMI ≥27 kg/m ² , HbA1c 7%–10%, T2D	HbA1c: –1.8% Body weight: –13.7%	Placebo HbA1c: –0.4% Body weight: –3.4%	HbA1c reduction: –1.4%, <i>P</i> <.001 Body weight reduction: –10.4%, <i>P</i> <.001
REIMAGINE 2 ²	N=2,713 T2D inadequately controlled with metformin ± SGLT2	HbA1c: –1.91% Body weight: –14.2%	Semaglutide 2.4 mg HbA1c: –1.75% Body weight: –1.5%	HbA1c (<i>P</i> =.0035) and body weight (<i>P</i> <.0001) and significant with cagrilintide 2.4 mg/semaglutide 2.4 mg vs cagrilintide 2.4 mg
REIMAGINE 3 ³	N=274 Adults with T2D treated with once-daily basal insulin ± metformin	HbA1c: –2.33% Body weight: –12.0%	Placebo HbA1c: –0.66% Body weight: +1.1%	Statistically significant vs placebo for HbA1c and body weight (<i>P</i> <.0001)

1. Davies MJ, et al. *N Engl J Med*. 2025;393(7):648–659. 2. Buse JB, et al. *Lancet Diabetes Endocrinol*. 2026 Jun 7:S2213–8587(26)00125–7. 3. Rosenstock J, et al. *Lancet*. 2026 Jun 7:S0140–6736(26)00222–6.

Retatrutide in T2D

Targets GLP-1, GIP, and glucagon receptors, with the goal of combining glycemic, appetite/weight, and hepatic metabolic effects

• Data from one phase 3 trial, TRANSCEND-T2D-1

Trial	Patients	Retatrutide 4 mg	Retatrutide 9 mg	Retatrutide 12 mg	Placebo	Statistical Significance
TRANSCEND -T2D-1 ¹	N=537 Adults with T2D inadequately controlled with diet/exercise alone	HbA1c: –1.69% Body weight: –11.5%	HbA1c: –1.86% Body weight: –13.9%	HbA1c: –1.94% Body weight: –15.3%	HbA1c: –0.81% Body weight: –2.6%	HbA1c reduction: all <i>P</i> <.0001

1. Bajaj HS, et al. *Lancet*. 2026 Jun 6:S0140–6736(26)00967–0.

Mazdutide in T2D

Targets GLP-1 and glucagon receptors

• Data from three phase 3 trials, DREAMS-1, DREAMS-2, and DREAMS-3

Trial	Patients	Mazdutide 4 mg	Mazdutide 6 mg	Comparator	Statistical Significance
DREAMS-1 ¹	N=320 Chinese adults with T2D inadequately controlled with diet/exercise	HbA1c: –1.57% Body weight: –5.61%	HbA1c: –2.15% Body weight: –7.81%	Placebo HbA1c: –0.14% Body weight: –1.26%	HbA1c reduction: both <i>P</i> <.0001 Body weight reduction: both <i>P</i> <.001
DREAMS-2 ²	N=731 Chinese adults with T2D inadequately controlled with metformin ± other oral agents	HbA1c: –1.69% Body weight: –9.24%	HbA1c: –1.73% Body weight: –7.13%	Dulaglutide 1.5 mg HbA1c: –1.36% Body weight: –2.86%	HbA1c reduction: both superior, <i>P</i> =.0032(4 mg) and <i>P</i> =.0003(6 mg) Body weight reduction: both superior, <i>P</i> <.0001
DREAMS-3 ³	N=349 Chinese adults with early-stage T2D and obesity	—	HbA1c: –2.03% Body weight: –10.29%	Semaglutide 1 mg HbA1c: –1.84% Body weight: –6.00%	HbA1c reduction: superior, <i>P</i> <.05 Body weight reduction: superior, <i>P</i> <.05

1. Zhu D, et al. *Nature*. 2026;652(8108):174–180. 2. Guo L, et al. *Nature*. 2026;652(8108):181–188. 3. PR Newswire. October 26, 2025. Accessed June 8, 2026. <https://www.prnewswire.com/news-releases/innovos-mazdutide-shows-superiority-in-glycemic-control-with-weight-loss-over-semaglutide-in-a-head-to-head-phase-3-clinical-trial-dreams-3-302594633.html>

Zenagamtide (Amycretin) in T2D

Targets GLP-1 and amylin

• Data from a phase 2 trial

Trial	Patients	Zenagamtide once weekly, subcutaneous	Zenagamtide once daily, oral	Placebo	Statistical Significance
Phase 2 trial ¹	N=448 Adults with T2D inadequately controlled on metformin ± SGLT2 inhibitor	Six dose groups: 0.4, 1.5, 5, 10, 20, and 40 mg once weekly HbA1c reduction: up to –1.8% Body weight reduction: up to –14.6%	Three dose groups: 6, 25, and 50 mg once daily HbA1c reduction up to –1.5% Body weight reduction up to –10.1%	HbA1c reduction: –0.2% (subcutaneous) and –0.4% (oral) Body-weight change: –2.6% (subcutaneous) and –2.5% (oral)	HbA1c improvements were statistically significant versus placebo for subcutaneous and oral zenagamtide

1. GlobelNewswire. November 25, 2025. Accessed June 8, 2026. <https://www.globelnewswire.com/news-release/2025/11/25/3194155/0/en/novo-nordisk-phase-2-trial-with-amycretin-reports-significant-weight-loss-and-hba1c-reduction-in-type-2-diabetes.html>

Special Resource Toolkit

Visit the website via the QR code or the URL below for more information on this topic, to download the deck, or to review the presentation.



URL: <https://www.pcmg-us.org/toolkit/glp1>

Summary and Key Takeaways

GLP-1 RA–based therapy now supports broader cardio-kidney-metabolic risk management in T2D

- T2D treatment decisions should be guided by **ASCVD, CKD, HF, obesity/weight goals, hypoglycemia risk, treatment burden, and patient preferences**, not HbA1c alone.
- Evidence from CV and kidney outcomes trials supports use of selected GLP-1 RA–based therapies to address **long-term organ protection** in appropriate patients with T2D.
- Practical implementation requires proactive counseling on **GI adverse effects, gradual titration, nutrition strategies, dehydration risk, medication adjustment, and expectations for persistence**.
- **Emerging GLP-1 RA–based options**, including higher-dose oral semaglutide, oral orforglipron, higher-dose injectable semaglutide, cagrilintide/semaglutide, retatrutide, mazdutide, and amylin/GLP-1–based approaches, may expand future treatment choices.