

Update in Incretin-Based Therapies

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Disclosure

Consultant: Aqua; AstraZeneca; Bayer; BDI, Inc.;
Boehringer Ingelheim; Fractyl; Lilly; Novo Nordisk;
Roche; Sparrow; Vertex; vTV Therapeutics; Zealand
Research Grant: Boehringer Ingelheim; COUR;
GentiBio; Merck; MetSera
Stock Options: BDI, Inc.

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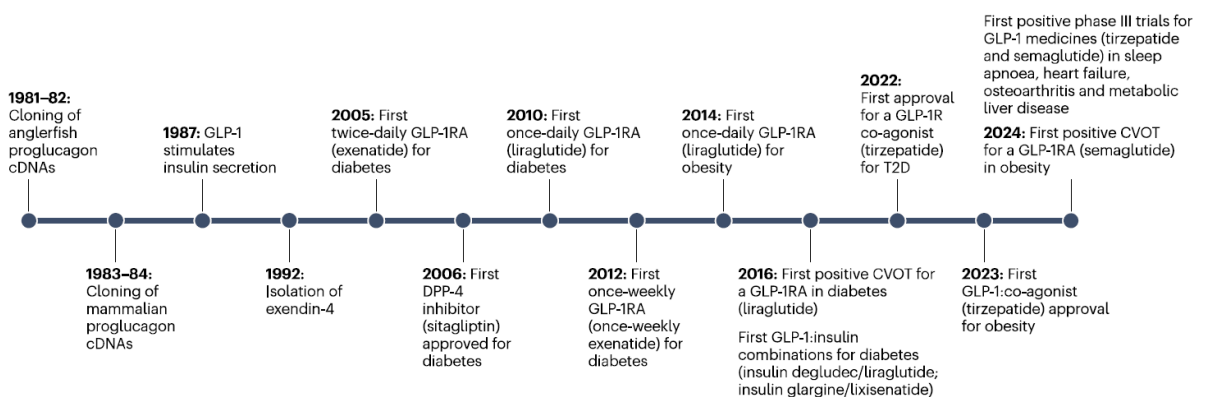
What's New? – The Highlights



- Updates in cardio-kidney-metabolic risk reduction
- Safety and other considerations
- Beyond type 2 diabetes
- Newer agents in development

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GLP1-Based Therapeutics Timeline



Drucker D. Nat Rev Drug Discov. 2025 Apr 25.
doi: 10.1038/s41573-025-01183-8

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GLP1-Based Therapy: Actions and Evidence



GLP-1 actions

↓ Albuminuria	↓ Gut motility
↓ Atherosclerosis	↓ Inflammation
↓ Body weight	↑ Islet hormone secretion
↑ Blood flow	↑ Natriuresis
↓ Blood pressure	↓ Oxidative stress
↑ Cell survival	↑ Plaque stability
↓ Cell death	↓ Platelet aggregation
↓ Fibrosis	↓ Postprandial lipaemia
↓ Glucose	↓ Thrombosis

Established indications

Obesity
Type 2 diabetes
Obstructive sleep apnoea
Cardiovascular disease
• Myocardial infarction
• Heart failure
• Stroke
Metabolic liver disease
Diabetic kidney disease
Osteoarthritis

Investigational indications

CNS disorders
• Neurodegenerative disorders
• Substance use disorders
• Neuropsychiatric disease
• Monogenic obesity
Type 1 diabetes
Allergic airways disease
Peripheral artery disease
Chronic kidney disease
Hypertension
Psoriatic arthritis
Alcohol-related liver disease

Drucker D. Nat Rev Drug Discov. 2025 Apr
25. doi: 10.1038/s41573-025-01183-8

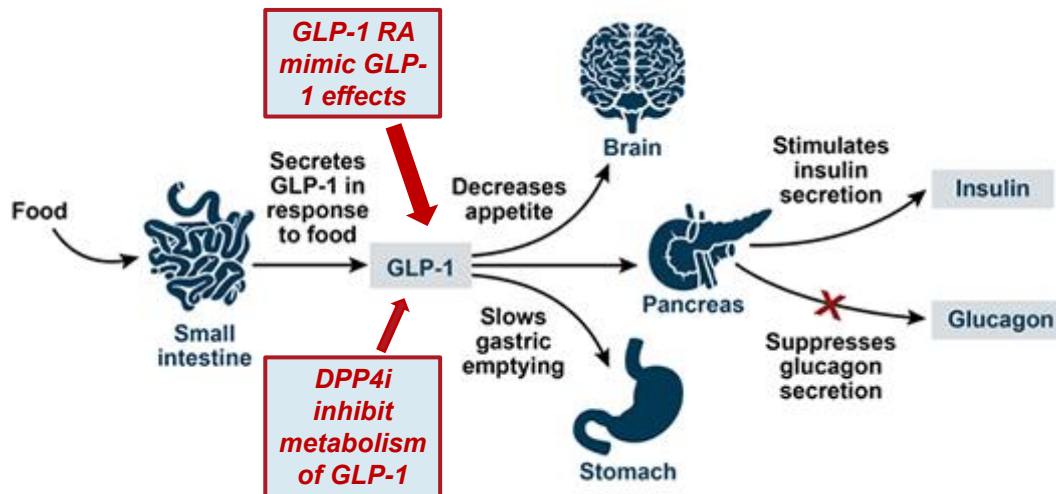
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Role of Incretin-Based Therapy in CKM Disease



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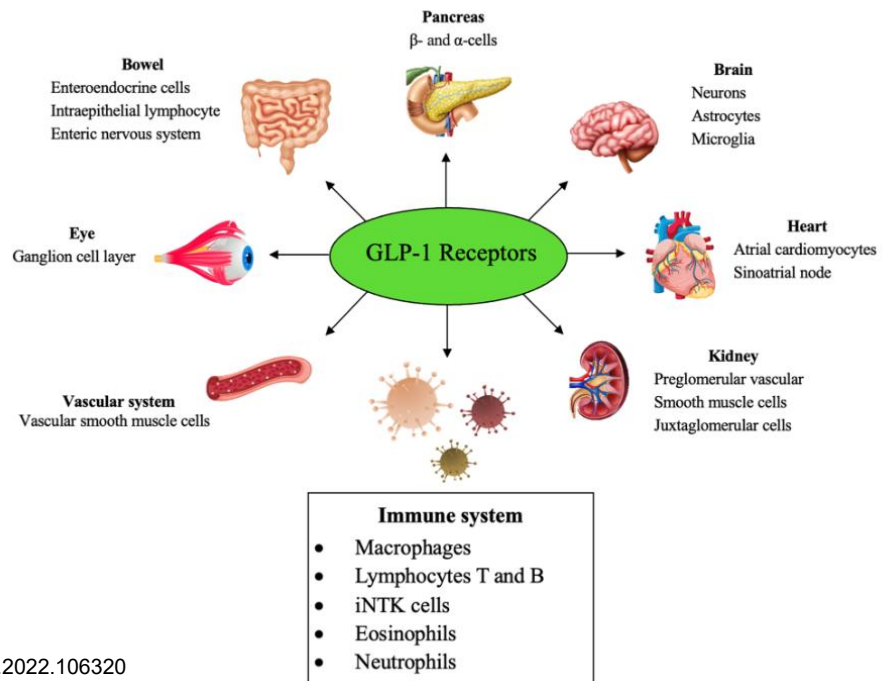
Effects of Incretin-Based Therapy



Meier JJ et al. Nat Rev Endocrinol. 2012

7

Tissue Expression of GLP-1 Receptors

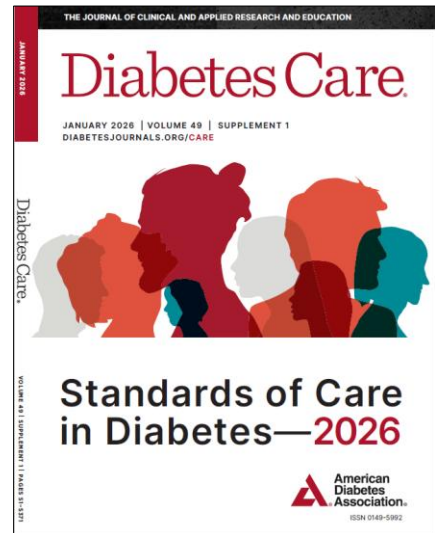


<https://doi.org/10.1016/j.phrs.2022.106320>

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Standards of Care in Diabetes—2026

Intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care.



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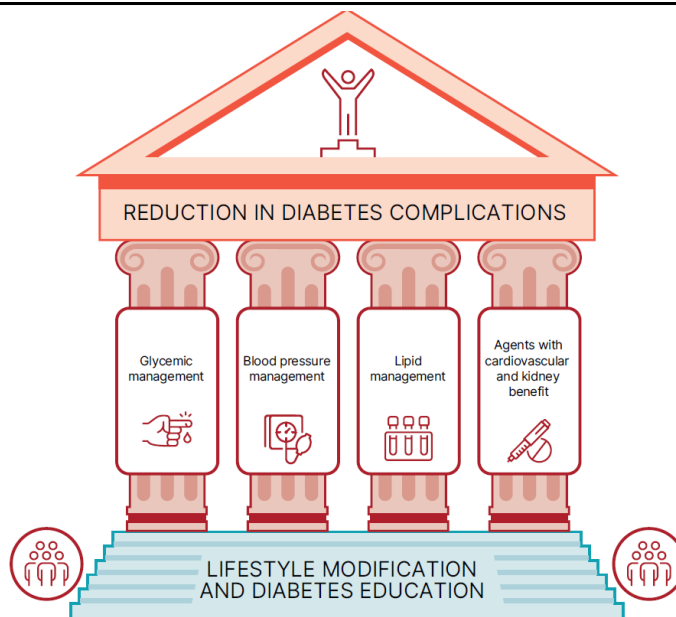


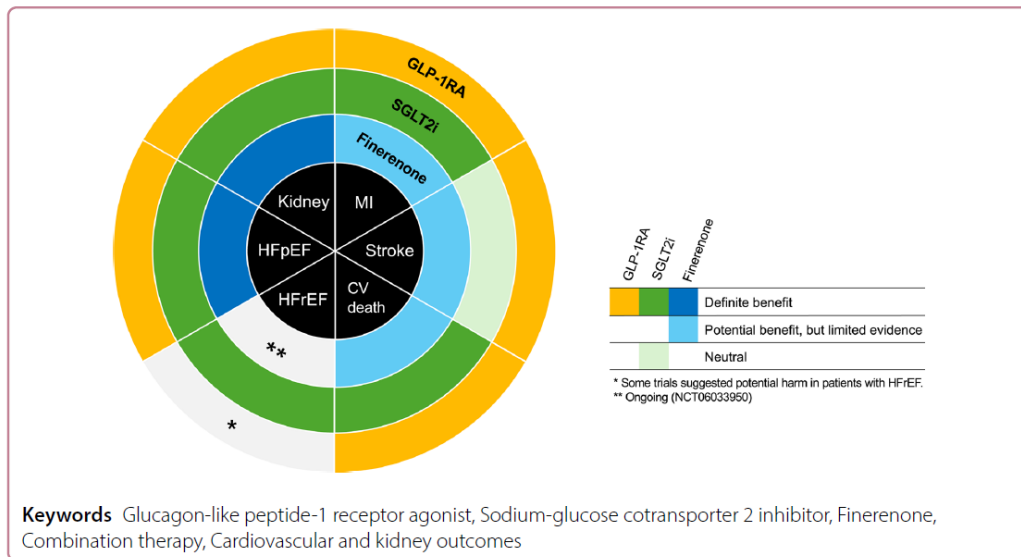
Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications.



Figure 10.1 Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes - 2026 Diabetes Care* 2026;49(Suppl. 1):S216-S245

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GLP-1RAs, SGLT2is, and CV and Kidney Outcomes



Sawami et al. Cardiovascular Diabetology (2024) 23:410

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Use of glucose-lowering medications in the management of type 2 diabetes

(For recommendations for specific conditions, including non-glucose-lowering medications, refer to pertinent sections)

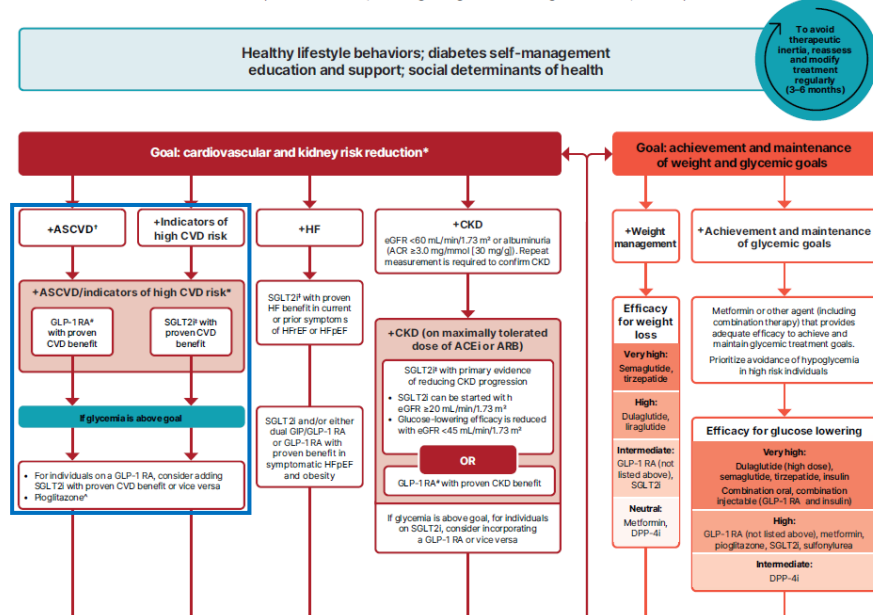


Figure 9.4 Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes - 2026. Diabetes Care 2026;49(Suppl. 1):S183-215



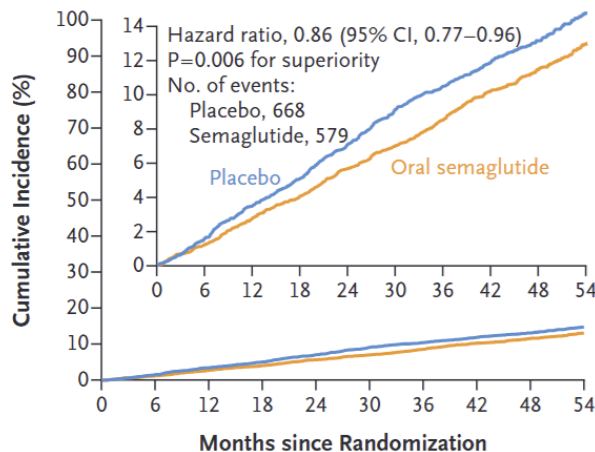
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Oral Semaglutide: SOUL CV Outcomes Trial



In people with T2D, ASCVD, CKD or both, the use of **oral** semaglutide was associated with a significantly lower risk of MACE than placebo

Major Adverse Cardiovascular Events



No. at Risk

Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346
Oral semaglutide	4825	4743	4635	4542	4438	4346	4239	3831	2555	1346

N Engl J Med 2025;392:2001-12.DOI: 10.1056/NEJMoa2501006

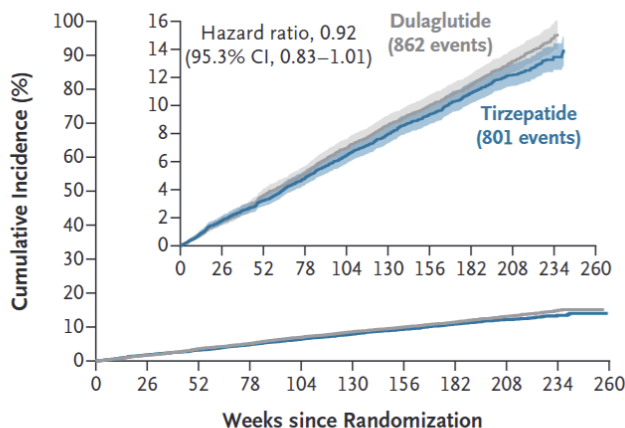
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SURPASS CVOT: Tirzepatide Compared to Dulaglutide



In people with T2D and ASCVD, tirzepatide was noninferior to dulaglutide (a drug with proven CV outcomes benefit) with respect to MACE outcomes

Composite of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke



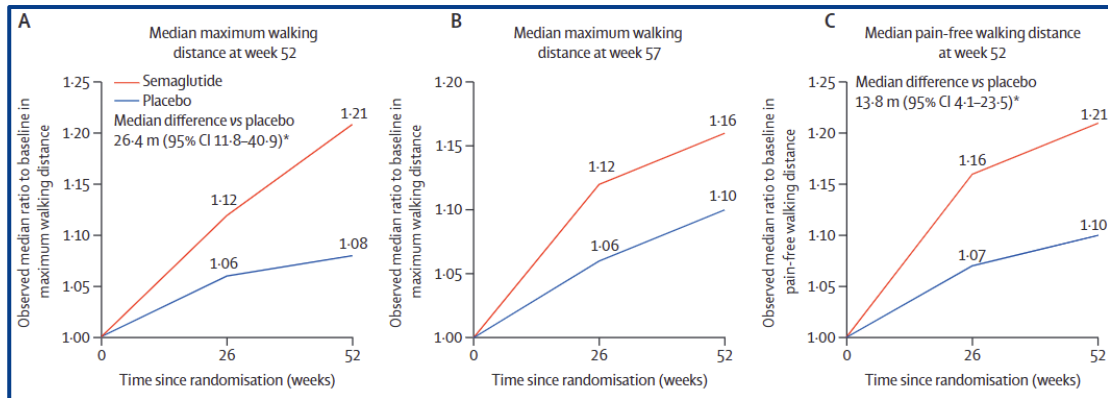
No. at Risk

Dulaglutide	6579	6421	6267	6125	5954	5822	5618	5249	3226	777	0
Tirzepatide	6586	6433	6309	6167	6029	5907	5703	5307	3305	803	0

N Engl J Med 2025;393:2409-20.DOI: 10.1056/NEJMoa2505928

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Semaglutide in T2D with Symptomatic PAD

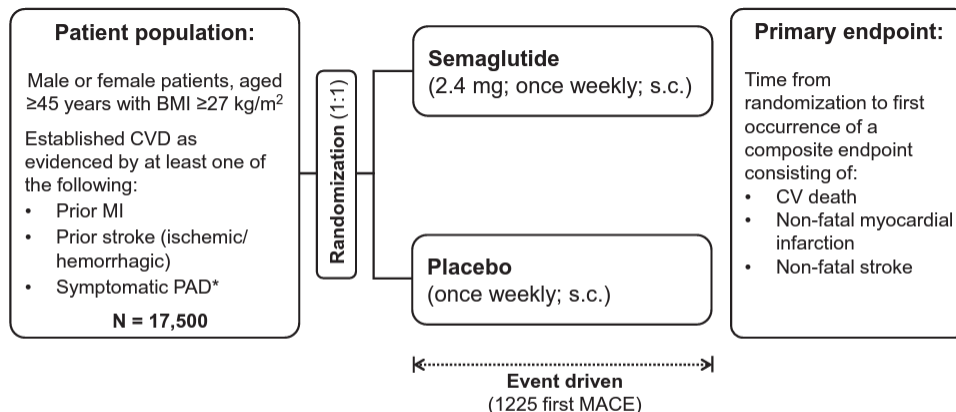


Compared to placebo, semaglutide 1.0 mg weekly increased walking distance in patients with symptomatic PAD and T2D

Lancet 2025; 405: 1580–93. [https://doi.org/10.1016/S0140-6736\(25\)00509-4](https://doi.org/10.1016/S0140-6736(25)00509-4)

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SELECT CV Outcomes Trial: Patients Without DM

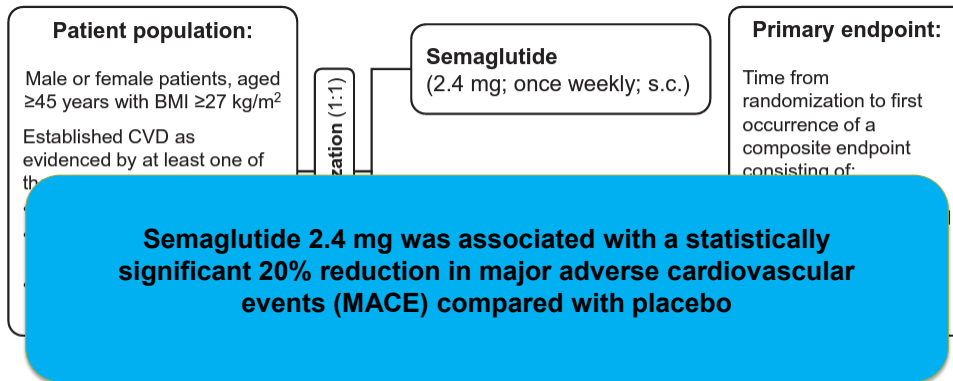


SELECT: trial design, population, and primary end point. The figure provides a snapshot of key components of SELECT trial design.*Symptomatic PAD defined as intermittent claudication with ankle-brachial index <0.85 (at rest) **OR** peripheral arterial revascularization procedure **OR** amputation due to atherosclerotic disease.

AmHeartJ2020;229:61-9

16

SELECT CV Outcomes Trial: Patients Without DM



(1225 first MACE)

SELECT: trial design, population, and primary end point. The figure provides a snapshot of key components of SELECT trial design. *Symptomatic PAD defined as intermittent claudication with ankle-brachial index < 0.85 (at rest) **OR** peripheral arterial revascularization procedure **OR** amputation due to atherosclerotic disease.

AmHeartJ2020;229:61-9

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64-year-old Woman Presents for Routine Follow Up. She Has No Complaints.

- **PMH:**
 - T2D x 12 yrs
 - HTN
 - Dyslipidemia
 - Obesity (BMI 31 kg/m²)
- **SH:**
 - Married
 - No tobacco, alcohol
 - Walks 30 minutes 3 days/week
 - Sleeps 5-6 hours/night
 - Works as an accountant

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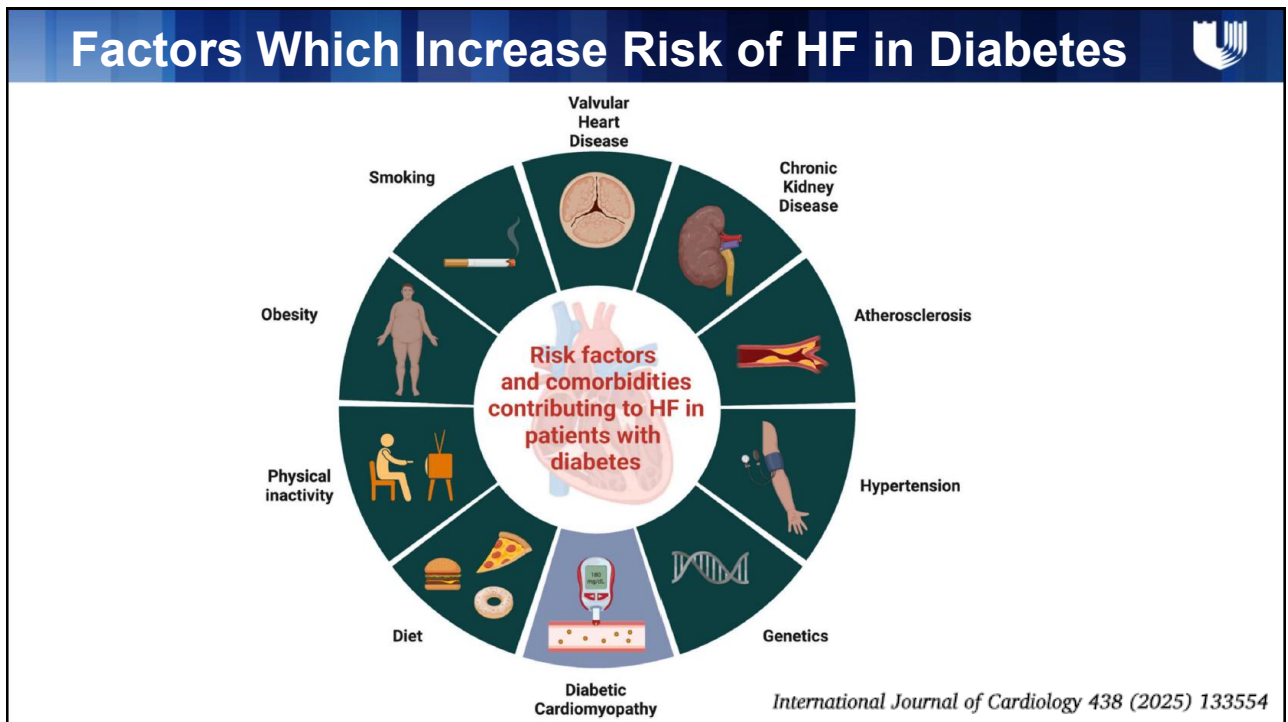
64-year-old Woman Presents for Routine Follow Up. She Has No Complaints.

- **Medications:**
 - Metformin 1000 mg BID
 - Semaglutide 1 mg weekly
 - Losartan 100 mg daily
 - Atorvastatin 40 mg daily
- **Vitals:**
 - BP 128/82 mmHg, HR 78, RR 18
 - Heart, lung exam unremarkable
 - Trace bilateral LE edema
- **Labs:**
 - HbA1c 7.0%
 - eGFR: 74 mL/min/1.73 m²
 - Rest of CMP WNL
 - UACr: 38 mg/g
 - CBC WNL
 - Total cholesterol: 188
 - HDL: 42
 - LDL-C: 90
 - TG: 146

ARS Question #1

What Else Should Be Performed at This Time?

- A. No additional testing
- B. Coronary CT scan
- C. N-terminal pro-BNP
- D. Echocardiogram

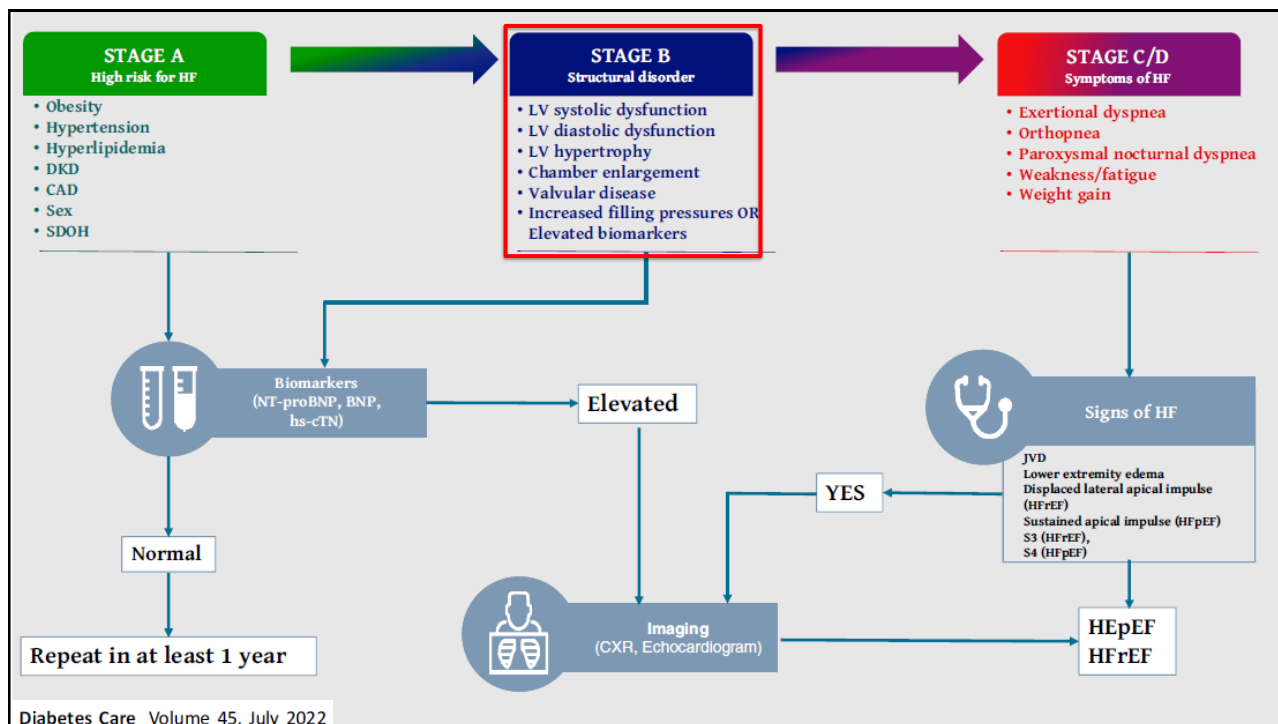


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Cardiovascular Disease – Screening

- In asymptomatic individuals, routine screening for coronary artery disease is not recommended
- Adults with diabetes are at increased risk for the development of asymptomatic cardiac structural or functional abnormalities (stage B heart failure) or symptomatic (stage C) heart failure. Consider screening adults with diabetes by measuring a natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) to facilitate prevention of stage C heart failure.
- In asymptomatic individuals with diabetes and abnormal natriuretic peptide levels, echocardiography is recommended to identify stage B heart failure.

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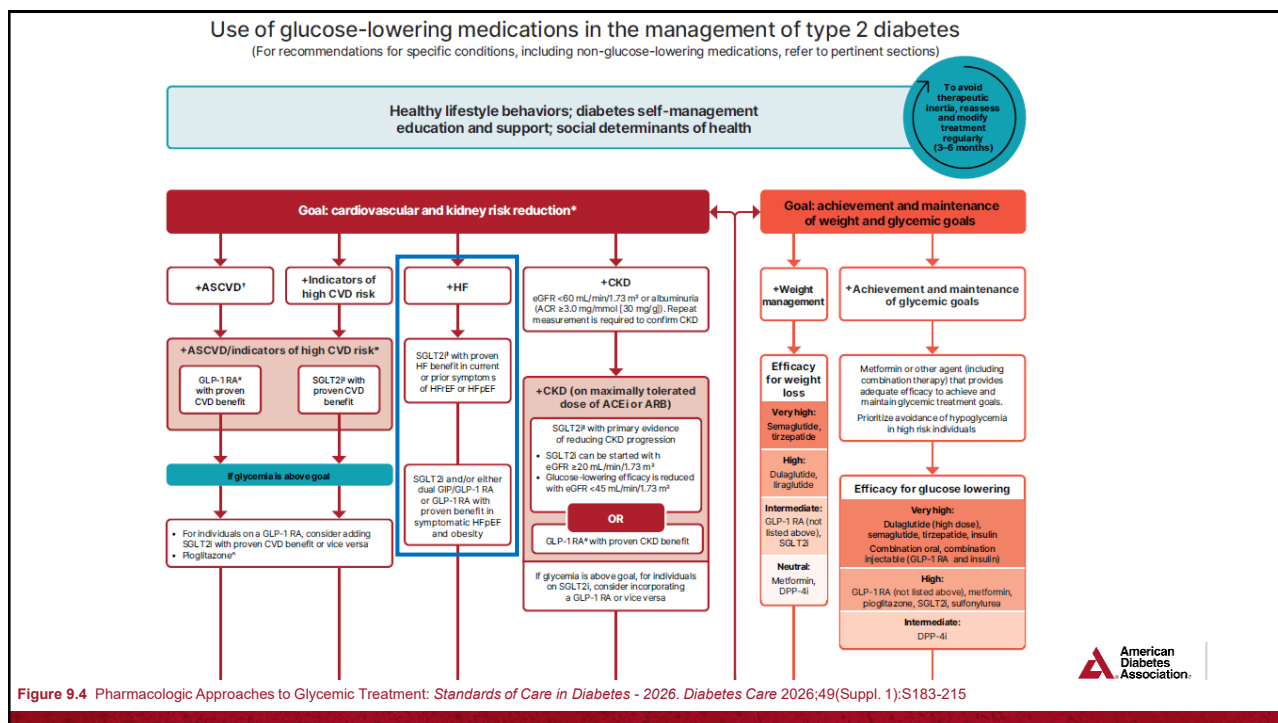


Figure 9.4 Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes - 2026. Diabetes Care 2026;49(Suppl. 1):S183-215

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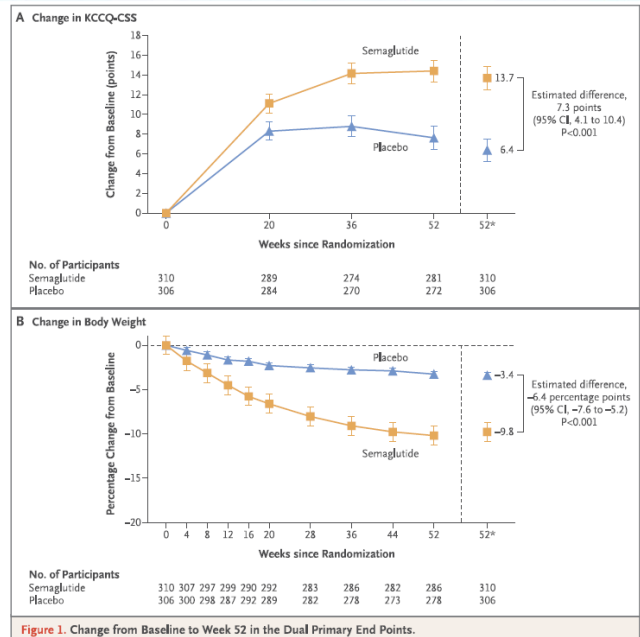
STEP-HFpEF Diabetes Trial



Effects of GLP-1RA Therapy on Symptoms and Physical Function in HFpEF + T2D

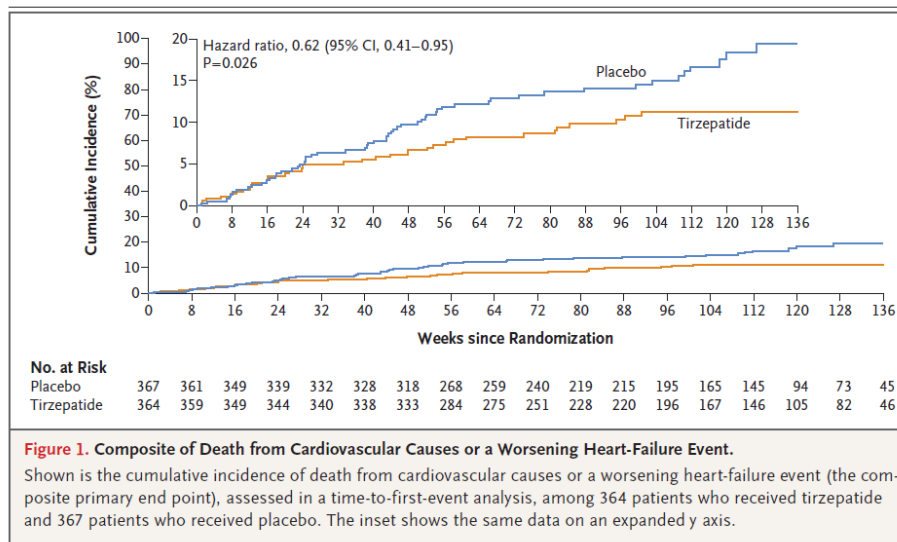
- Semaglutide treatment of HFpEF patients
 - + obesity, +HF symptoms, +T2D
- Results**
 - Semaglutide increased KCCQ-CSS by 13.7 points (ETD 7.3 pts vs. PBO)
 - Semaglutide decreased body weight by 9.8% (ETD -6.4% vs. PBO)
 - No increase in SAEs vs. PBO

N Engl J Med. 2024 Apr 18;390(15):1394-1407. doi: 10.1056/NEJMoa2313917. Epub 2024 Apr 6. PMID: 38587233



25

Tirzepatide in HFpEF and Obesity



*About 48% of participants had T2D

N Engl J Med 2025;392:427-437 DOI: 10.1056/NEJMoa2410027

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Use of glucose-lowering medications in the management of type 2 diabetes

(For recommendations for specific conditions, including non-glucose-lowering medications, refer to pertinent sections)

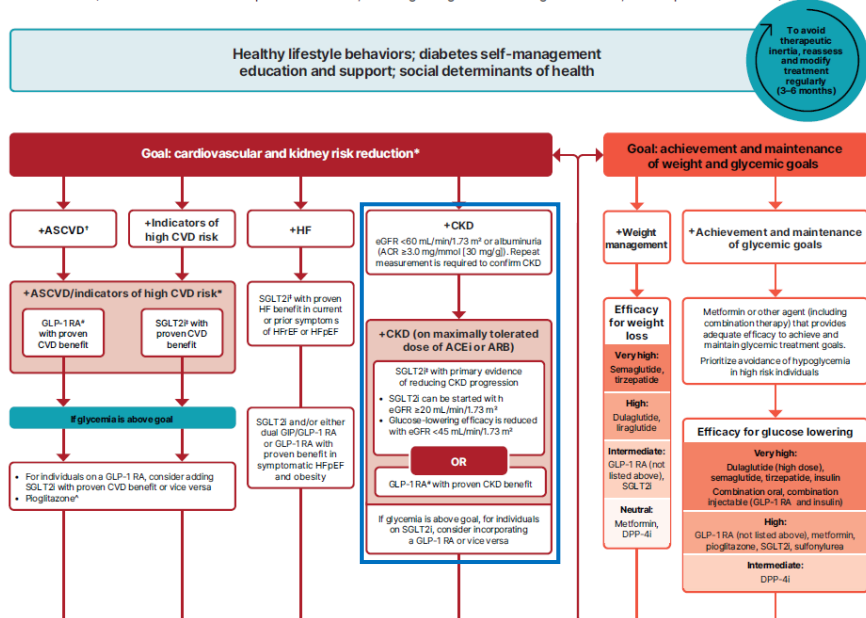


Figure 9.4 Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes - 2026. Diabetes Care 2026;49(Suppl. 1):S183-215

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FLOW Study of Semaglutide in T2D with CKD

Methods

Participants:



- Adults with T2D
- eGFR ≥50 to <75 mL/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 mL/min/1.73 m² and UACR >100 to <5000 mg/g

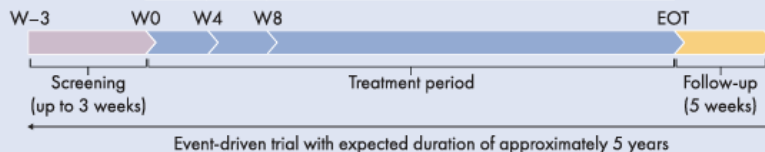
Composite primary endpoint:



- Time to first occurrence of:
- Kidney failure (persistent eGFR <15 mL/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes

Randomisation 1:1

N=3534



Baseline characteristics



68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) mL/min/1.73 m²; median UACR of 568 (range: 2–11 852) mg/g



Advanced type 2 diabetes:

Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%



15.5% receiving SGLT-2is

CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Nephrol Dial Transplant. 2023 Aug 31;38(9):2041-2051. doi: 10.1093/ndt/gfad009. PMID: 36651820; PMCID: PMC10469096.

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FLOW Study of Semaglutide in T2D with CKD



Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Primary outcome: major kidney disease events — no. (%)†	331 (18.7)	410 (23.2)	0.76 (0.66 to 0.88)	—	0.0003
Components of primary outcome — no. (%)					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3)	213 (12.1)	0.73 (0.59 to 0.89)	—	—
Persistent eGFR <15 ml/min/1.73 m ²	92 (5.2)	110 (6.2)	0.80 (0.61 to 1.06)	—	—
Initiation of kidney-replacement therapy	87 (4.9)	100 (5.7)	0.84 (0.63 to 1.12)	—	—
Death from kidney-related causes	5 (0.3)	5 (0.3)	0.97 (0.27 to 3.49)	—	—
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Composite of kidney-specific components of the primary outcome	218 (12.3)	260 (14.7)	0.79 (0.66 to 0.94)	—	—
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m ²	-2.19	-3.36	—	1.16 (0.86 to 1.47)	<0.001
Major cardiovascular events — no. (%)	212 (12.0)	254 (14.4)	0.82 (0.68 to 0.98)	—	0.029
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Nonfatal myocardial infarction	52 (2.9)	64 (3.6)	0.80 (0.55 to 1.15)	—	—
Nonfatal stroke	63 (3.6)	51 (2.9)	1.22 (0.84 to 1.77)	—	—
Death from any cause — no. (%)	227 (12.8)	279 (15.8)	0.80 (0.67 to 0.95)	—	0.01

median participant follow-up was 3.4 years

N Engl J Med. 2024 May 24. doi: 10.1056/NEJMoa2403347. Online ahead of print. PMID: 38785209

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ARS Question #2

Which of the Following Patients Should Be Screened Now for CKD, Including Measurement of Both eGFR and UACR?

- A. Anyone with newly diagnosed Type 1 or Type 2 diabetes
- B. An individual with newly diagnosed Type 2 diabetes
- C. An individual with newly diagnosed Type 1 diabetes
- D. An individual diagnosed with Type 1 diabetes two years ago



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Screening and Diagnosis: KDIGO



Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?



Spot urine ACR



and
eGFR

What to do with a positive result?



Repeat and confirm:

- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD



Initiate evidence-based treatments

What defines CKD diagnosis?



Persistent urine ACR ≥ 30 mg/g
and/or



Persistent eGFR < 60 mL/min/1.73 m²
and/or



Other evidence of kidney damage

de Boer IH et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Oct 3;doi220027. doi: 10.2337/dc22-0027. Epub ahead of print. PMID: 36189689.

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				Albuminuria categories Description and range		
				A1	A2	A3
CKD is classified based on:				Normal to mildly increased	Moderately increased	Severely increased
- GFR (G) - Albuminuria (A)				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥ 300 mg/g ≥ 30 mg/mmol
GFR categories (mL/min/1.73 m ²) Description and range	G1	Normal or high	≥ 90	Screen 1	Treat 1	Treat and refer 2
	G2	Mildly decreased	60-89	Screen 1	Treat 1	Treat and refer 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15-29	Treat and refer 3	Treat and refer 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

■ Low risk (if no other markers of kidney disease, no CKD)
■ Moderately increased risk

■ High risk
■ Very high risk

Figure 11.1—Risk of CKD progression, cardiovascular disease risk, and mortality; frequency of visits; and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, and hyperparathyroidism). These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as should the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Adapted from de Boer et al. (1).

Figure 11.1
Chronic Kidney Disease and Risk Management:
Standards of Care in Diabetes – 2026 Diabetes Care 2026;49(Suppl. 1):S246-S260

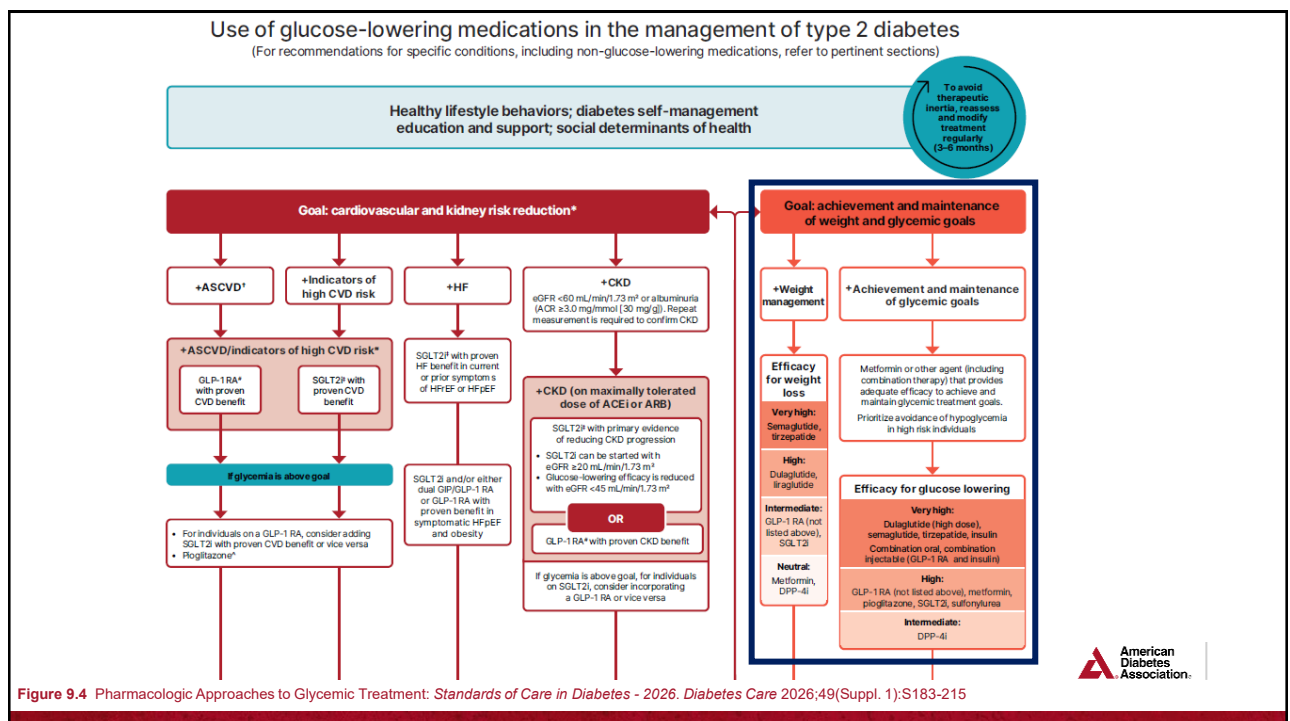


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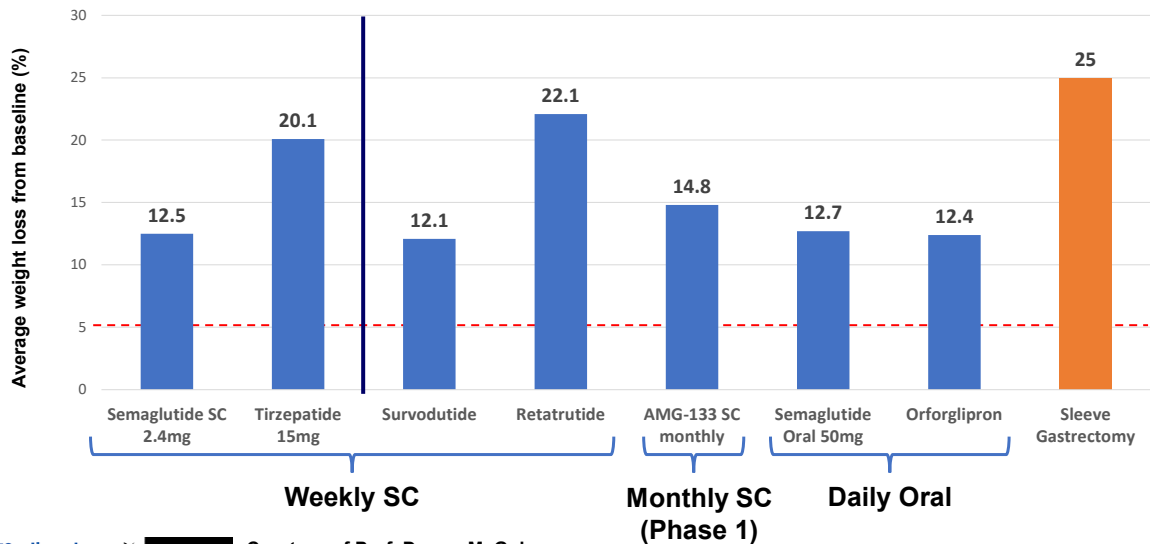
Metabolic Management: Increased Emphasis on Weight

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Average Weight Loss Achieved with Obesity Pharmacotherapies and Sleeve Gastrectomy

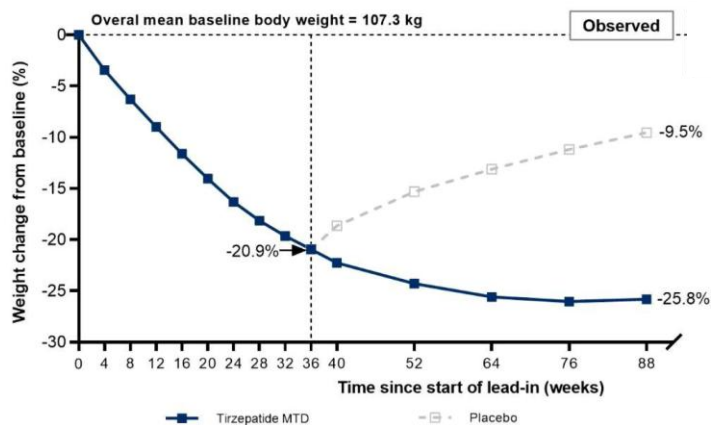


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Durability of Weight Loss: SURMOUNT-4 Topline Results: Randomized Withdrawal of Tirzepatide

Weight Percent Change Over 88 Weeks

N=783
BMI >30kg/m²; or
>27kg/m² + ≥comorbidity
Without Diabetes



Holst JJ et al. 59th EASD Scientific Sessions 2023; NCT04660643

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Are There Solutions to the Weight Regain Issue?



Further study needed:

- Which people are less likely to regain?
- Intermittent vs. down-titration of dosing
- Change to a different class of AOM for weight maintenance
- Intensive lifestyle modification
- Metabolic surgery/procedures
 - Duodenal mucosal resurfacing (REMAIN-1* study)
- *Accept that these are chronic therapies for most*

*[ClinicalTrials.gov ID NCT06484114](https://clinicaltrials.gov/ct2/show/study/NCT06484114)

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Incretin-Based Drug Safety



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GLP-1 RAs: GI Adverse Effects



- Usually not severe or persistent over the long term
- Dose dependent (at initiation and up-titration)
- Titrate per manufacturer's recommendations (or slower!)
- Patient counselling key to success

Smaller meals

Low-fat diet

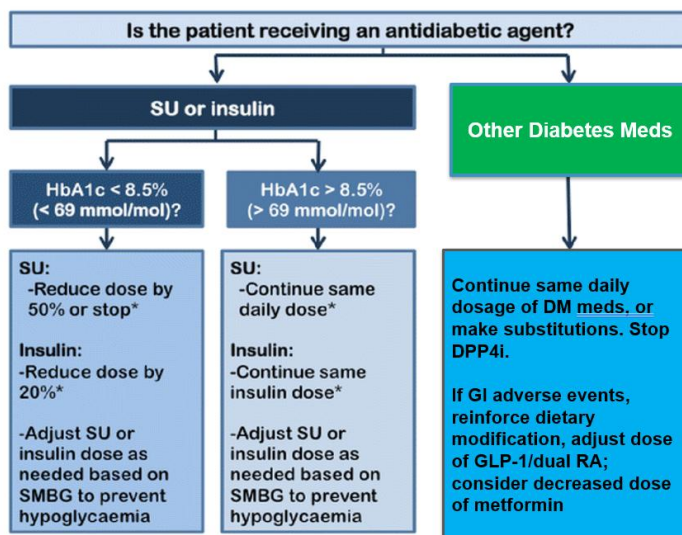
Potential GI side effects

Injection technique

Cefalu. Diabetes Care. 2014;37:2647.
Gorgojo-Martínez. J Clin Med. 2023;12:145.

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Adding GLP-1/Dual RA to Other Diabetes Medications



Do not use DPP4i, GLP-1RA, dual incretin agents together

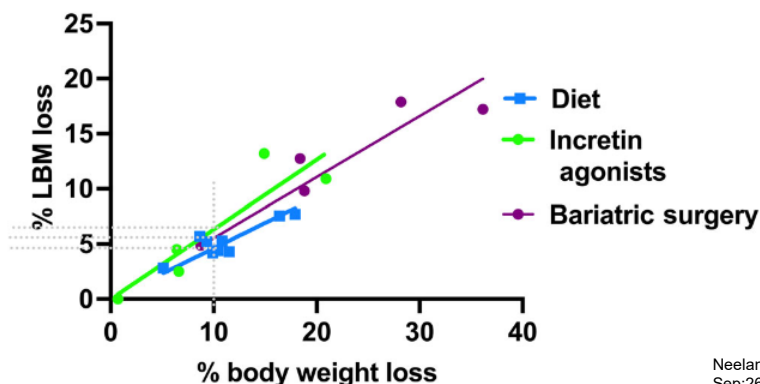
Gomez-Peralta F et al. Diabetes Ther 2017

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Body Composition

Large % lean body mass (LBM) loss reported with potent agents

- LBM includes muscle, organs, bone and body fluids
- Effects on skeletal muscle loss not consistently assessed
- May not differ significantly from that seen with metabolic surgery



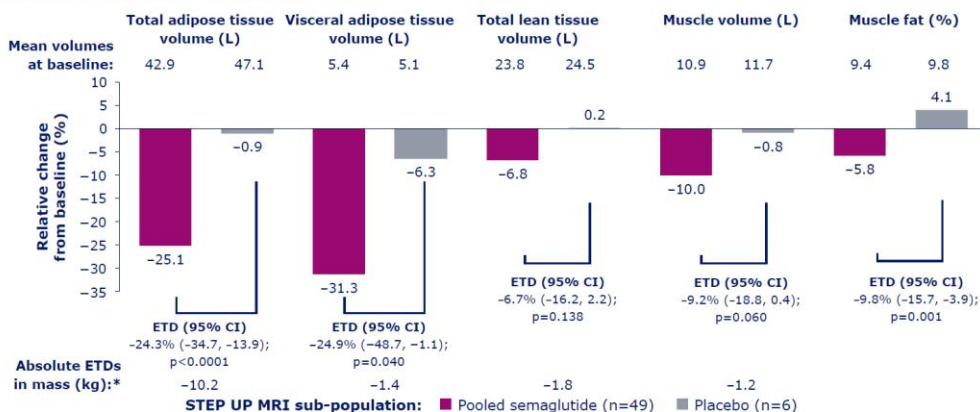
Neeland et al. Diabetes Obes Metab. 2024 Sep;26 Suppl 4:16-27. doi: 10.1111/dom

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STEP-UP Trial of Semaglutide 7.2 mg Dose

Prespecified Analysis of MRI Sub-Study Results

Relative change in different tissue volumes (%) from baseline to week 72



Data are estimated for the in-trial period using the treatment policy estimand (effect regardless of trial product discontinuation, dose reduction, or initiation of any other obesity therapies or surgery).

*ETDs in adipose and lean tissue volumes were converted to ETDs in mass by multiplying the former by the corresponding tissue densities of 0.92 (adipose tissue) or 1.1 (lean tissue).¹

CI, confidence interval; ETD, estimated treatment difference; MRI, magnetic resonance imaging.

1. Behnke AR et al. AMA Arch Intern Med 1953;91:585-601.

Hjeltnesæth J et al. Presented at the European Association for the Study of Diabetes (EASD) 61st Annual Meeting, 15-19 September 2025; Vienna, Austria.

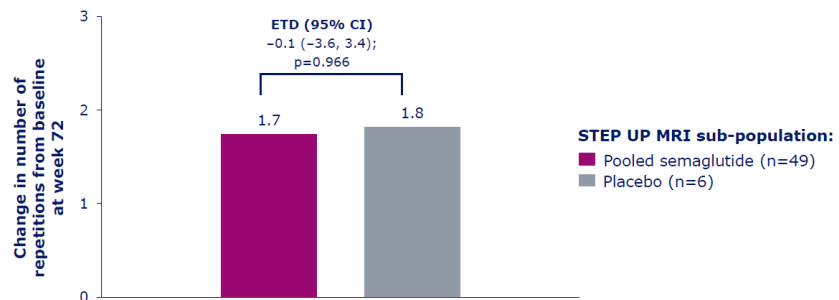
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STEP-UP Trial of Semaglutide 7.2 mg Dose



Change in number of sit-to-stand repetitions from baseline to week 72

Number of sit-to-stand repetitions	Pooled semaglutide (n=49)	Placebo (n=6)
Baseline	13 (4)	13 (2)
Week 72	15 (4)	15 (1)



In the table, observed data are mean (standard deviation). In the figure, data are estimated for the in-trial period using the treatment policy estimand (effect regardless of trial product discontinuation, dose reduction, or initiation of any other obesity therapies or surgery).
CI, confidence interval; ETD, estimated treatment difference; MRI, magnetic resonance imaging; STEP, Semaglutide Treatment Effect in People with obesity.

Hjeltnesæth J et al. Presented at the European Association for the Study of Diabetes (EASD) 61st Annual Meeting, 15–19 September 2025; Vienna, Austria.

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Obesity Pharmacotherapy Lifestyle: An Example



Risk Area	Recommended Nutritional Strategies
Severe Caloric Restriction	- Encourage a minimum intake of ~1200 kcal/day for females and 1500 kcal/day for males; - Recommend energy-dense, nutrient-rich foods; - Monitor for signs of fatigue, dizziness, or reduced function.
Lean Body Mass Loss	- Priorities protein intake of 1–1.4 g/kg/day, spaced across meals/snacks; - Encourage resistance exercise; - Consider oral nutrition supplements (ONS) if intake is inadequate.
Micronutrient Deficiency	- Emphasize high-bioavailability foods (e.g., red meat, dairy, fortified cereals, leafy greens); - Recommend multivitamins and targeted supplements based on intake or lab results.
Dehydration and Electrolyte Loss	- Promote daily fluid intake of 1.5–2 L; - Adjust intake for climate, activity, and comorbidities; - Suggest oral rehydration solutions for persistent GI symptoms Monitor for hypotension, especially in those on antihypertensives or diuretics.
Ketosis Risk	Ensure carbohydrate intake meets at least 130 g/day Avoid combining pharmacotherapy with ketogenic or very low-carbohydrate diets unless medically supervised.

Al-Najim et al. Nutrients 2025, 17, 1934. <https://doi.org/10.3390/nu17111934>

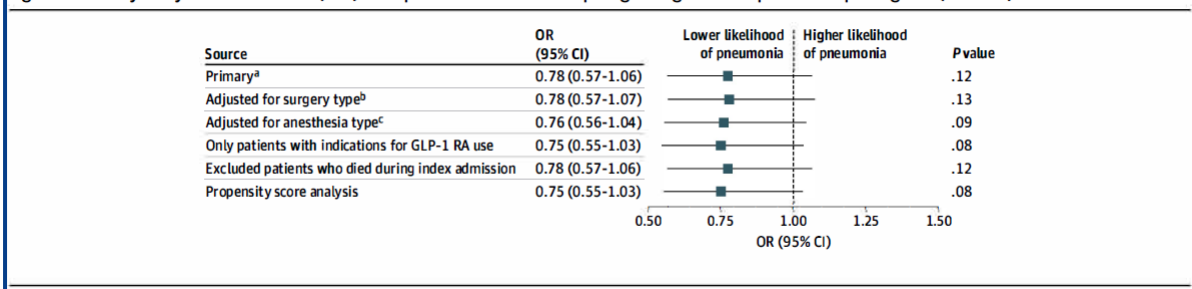
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Peri-Operative Safety



- Retrospective cohort study of 366 476 patients
- GLP-1 RA users (vs non-users) had no differences in odds of postoperative aspiration PNA (OR, 0.78; 95% CI, 0.57-1.06; P = .12) or acute respiratory failure (OR, 0.98; 95% CI, 0.89-1.06; P = .57) after adjusting for sex, age, geographic region, comorbidities, and surgical acuity.**
- The results remained consistent in sensitivity analyses:

Figure. Sensitivity Analyses of Odds Ratios (ORs) for Aspiration Pneumonia Comparing Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) Users and Nonusers



JAMA Network Open. 2025;8(3):e250081. doi:10.1001/jamanetworkopen.2025.0081

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Incretin Therapy: Beyond Type 2 Diabetes

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SURMOUNT-OSA

Study Design:

- Two randomized, blinded, PBO controlled studies (one in patients on, and one in patients off CPAP)
- Adults with mod to severe OSA with AHI at least 15/hr, BMI at least 30. NO DIABETES (but 65% had prediabetes)
- Assigned to tirzepatide or PBO with uptitration to 10-15 max tolerated dose of 10 or 15 mg weekly
- Primary outcome: change in AHI over 52 weeks, with multiple other outcomes related to AHI and other sleep indices, PROs, markers of inflammation

CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; AHI = apnea/hypopnea index
PBO = placebo; PRO = patient-reported outcomes

N Engl J Med 2024;391:1193-1205



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SURMOUNT-OSA

Results:

- In general, the cohort had severe OSA
- Higher study completion rates in patients assigned to tirzepatide; most got to 10-15 mg
- Tirzepatide Rx resulted in significant improvement in AHI in both sub-trials
- Improvements in AHI by percentage were around 55-60%
- 40-50% of those on tirzepatide were essentially cured of OSA (AHI <5/hr)
- 65-75% improvement in hypoxic burden

CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; AHI = apnea/hypopnea index
PBO = placebo; PRO = patient-reported outcomes

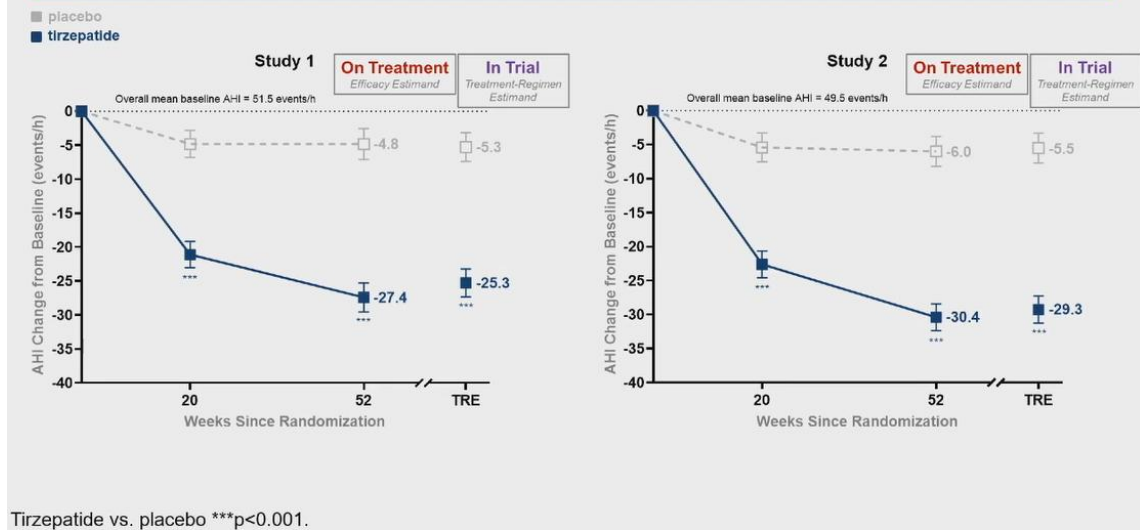
N Engl J Med 2024;391:1193-1205



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Change From Baseline in AHI Over 52 Weeks

Absolute Change



N Engl J Med 2024;391:1193-1205



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Metabolic-Associated Steatotic Liver Disease (MASLD) and Metabolic-Associated Steatohepatitis (MASH)

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MASLD and MASH- Screening

- Screen adults with T2D or prediabetes, particularly those with obesity or other cardiometabolic risk factors or established CVD, for risk of MASH-related cirrhosis using a calculated FIB-4 index, even if they have normal liver enzymes.
- Adults with T2D or prediabetes with a FIB-4 ≥ 1.3 should have additional risk stratification by liver stiffness measurement with transient elastography, or enhanced liver fibrosis (ELF) test.
- Refer adults with T2D or prediabetes at higher risk for significant liver fibrosis (i.e., as indicated by FIB-4, liver stiffness measurement, or ELF) to a liver specialist for further evaluation and management.

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Care in Diabetes - 2026. *Diabetes Care* 2026;49(Suppl. 1):S61-S88



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Diagnostic algorithm for the prevention of cirrhosis in people with metabolic dysfunction-associated steatotic liver disease (MASLD)

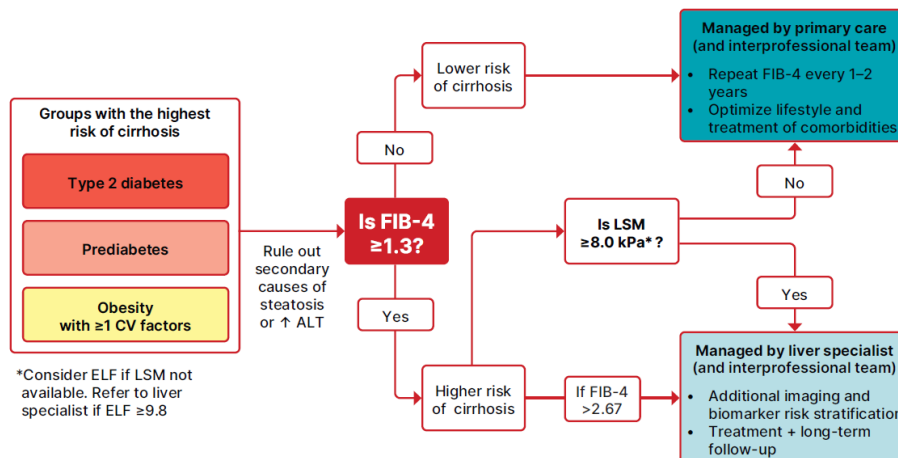
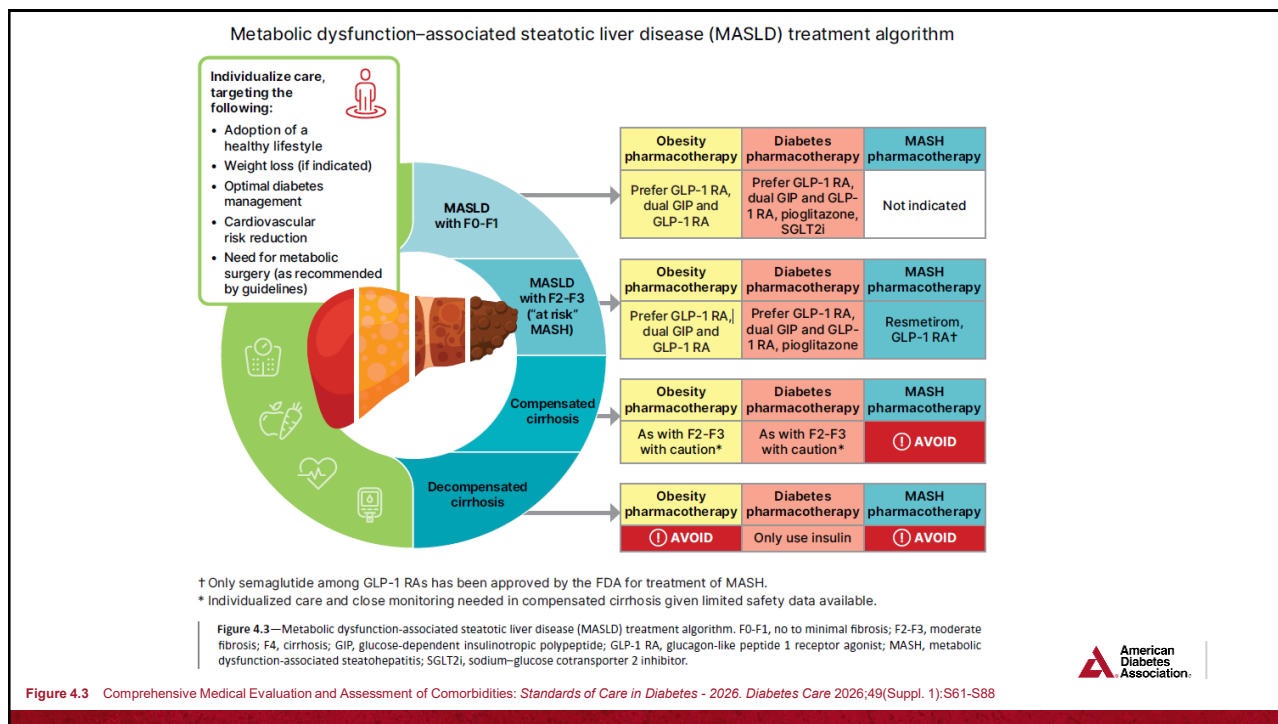


Figure 4.2—Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD). CV, cardiovascular; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement, as measured by vibration-controlled transient elastography. *In the absence of LSM, consider ELF a diagnostic alternative. If ELF ≥ 9.8 , an individual is at high risk of metabolic dysfunction-associated steatohepatitis with advanced liver fibrosis ($\geq F3$ – $F4$) and should be referred to a liver specialist.

Figure 4.2
Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Care in Diabetes - 2026. *Diabetes Care* 2026;49(Suppl. 1):S61-S88



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On the Horizon

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New Combinations of GLP1-Related Therapies



Developmental goals:

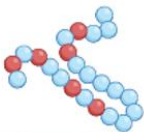
- Increased potency
- Improved tolerability
- Less frequent dosing
- Easier to manufacture, transport, store and administer
- Greater impact on non-metabolic outcomes
- ?lower cost

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New Combinations of GLP1-Related Therapies

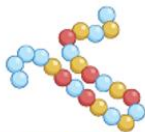


Survodutide



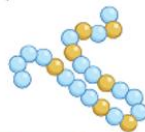
GCGR-GLP-1RA
 ↓Steatohepatitis
 ↑Weight loss

Retatrutide



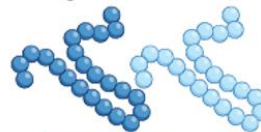
GCGR-GIPR-GLP-1RA
 ↓Steatohepatitis
 ↓Inflammation
 ↑Weight loss

Tirzepatide



GIPR-GLP-1RA
 ↑Insulin sensitivity
 ↓Inflammation
 ↑Weight loss

Cagri-Sema



AMLN-GLP-1RA
 ? Tolerability
 ? Lean mass
 ↑Weight loss

Orforglipron

Small molecule
 Easier to manufacture
 No pen, refrigeration

GLP-1RA
 Oral administration
 ↓Cost
 ↑Supply

AT-7687



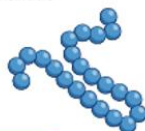
GIPRAnt
 ↑Insulin sensitivity
 ↑Weight loss

Maritide



GIPRAnt-GLP-1RA
 ↑Insulin sensitivity
 ↓Inflammation
 ↑Weight loss
 Less frequent administration

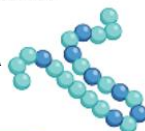
Pramlintide



AMLNRA
 ↑Tolerability
 ? Lean mass
 ↑Weight loss

Petrelintide

Dual amylin+
 Calcitonin RA



DACRA
 ↑Tolerability
 ? Lean mass
 ↑Weight loss

Dapiglutide



GLP2R-GLP-1RA
 ↓Inflammation
 ↑Weight loss

Drucker D. Nat Rev Drug Discov. 2025 Apr 25;doi: 10.1038/s41573-025-0070-1

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Recent Developments



FDA Approval of First Small Molecule, Nonpeptide GLP-1RA

FDA Approves First New Molecular Entity Under National Priority Voucher Program

Action marks the fastest approval of an NME since 2002

For Immediate Release: April 01, 2026

The U.S. Food and Drug Administration today approved Foundayo (orforglipron), marking the fifth approval under the Commissioner's National Priority Voucher (CNPV) pilot program. Issued 50 days after filing — and 294 days before the application's PDUFA date of January 20, 2027 — this decision represents a historic milestone as the first new molecular entity (NME) approved under the program. It is also the fastest approval of an NME since 2002.

Foundayo is approved for use in combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.

<https://www.fda.gov/news-events/press-announcements/fda-approves-first-new-molecular-entity-under-national-priority-voucher-program>

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In Conclusion



- Incretin-based therapies offer tremendous clinical potential
- Novel GLP-1 receptor agonists, combinations and methods of administration are in development
- Addressing therapeutic challenges (durability of effects, body composition, comparators and costs) will further enhance use
- Patient education and counselling will be key to success

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