NKOTB: New and Emerging Roles for GLP-1-based Medications

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Learning Objectives

At the conclusion of this presentation, pharmacists should be able to:

- List recent FDA-approved indications for GLP-1-based medications.
- Recognize proposed mechanisms by which GLP-1-based medications may impact conditions beyond type 2 diabetes and adiposity-based chronic disease.
- Describe key findings from major clinical trials evaluating new therapeutic potential of GLP-1-based medications.

Disclosures

- Devra Dang has no actual or potential conflict of interest with the content of this presentation.

- Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, precautions, and warnings.

GLP-1-based Medications with FDA-Approval for **T2DM** in Adults

- Exenatide – 4/2005 (Byetta), 1/2012 (Bydureon), 11/2024 (generic)
- Liraglutide – 1/2010 (Victoza), 12/2024 (first generic)
- Albiglutide – 4/2014 (Tanzeum, discontinued 2017)
- Dulaglutide – 9/2014 (Trulicity)
- Lixisenatide – 7/2016 (Adlyxin, discontinued 2023)
- Semaglutide – 12/2017 (Ozempic), 9/2019 (Rybelsus)
- Tirzepatide – 5/2022 (Mounjaro)

- Insulin glargine-lixisenatide – 11/2016 (Soliqua 100/33)
- Insulin detemir-liraglutide – 11/2016 (Xultophy 100/3.6)

GLP-1-based Medications with FDA-Approval for **Overweight & Obesity** in Adults

- Liraglutide – 12/2014 (Saxenda), generic 8-2025
- Semaglutide – 6/2021 (Wegovy)
- Tirzepatide – 11/2023 (Zepbound)

Are there other FDA-approved indications?

"Step by Step" (Learning Objectives)

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AUDIENCE POLL #1

Which of the following GLP-1-based medication has an FDA indication for reducing risk sustained eGFR decline, end-stage kidney disease and CV death in adults with type 2 diabetes mellitus and CKD?

- A. dulaglutide
- B. liraglutide
- C. semaglutide
- D. tirzepatide

AUDIENCE POLL #2

Which of the following GLP-1-based medication has an FDA indication for management of obstructive sleep apnea (OSA)?

- A. dulaglutide
- B. liraglutide
- C. semaglutide
- D. tirzepatide

GLP-1-Based Medications – FDA Approved Indications

Indication → / Medication ↓	T2DM	Weight Management	Obstructive Sleep Apnea (OSA)	CV Risk Reduction	Kidney Risk Reduction	Metabolic dysfunction–Associated Steatohepatitis (MASH)	Approved in Pediatric Population
Dulaglutide (Trulicity)	✓	-	-	✓	-	-	✓ 10 years and older (T2DM)
Exenatide (Bydureon, Byetta)	✓	-	-	-	-	-	✓ 10 years and older (T2DM; Bydureon only)
Lixisenatide (Adlyxin)	✓	-	-	-	-	-	-

GLP-1-Based Medications – FDA Approved Indications

Indication → / Medication ↓	T2DM	Weight Management	Obstructive Sleep Apnea (OSA)	CV Risk Reduction	Kidney Risk Reduction	Metabolic dysfunction–Associated Steatohepatitis (MASH)	Approved in Pediatric Population
Liraglutide (Saxenda, Victoza)	✓ (Victoza)	✓ (Saxenda)	-	✓ (Victoza)	-	-	✓ Victoza: 10 yrs & older (T2DM) Saxenda: 12 yrs & older (obesity)
Semaglutide (Ozempic, Rybelsus, Wegovy)	✓ (Ozempic, Rybelsus)	✓ (Wegovy)	-	✓ (Ozempic, Rybelsus, Wegovy)	✓ (Ozempic)	✓ (Wegovy)	✓ Wegovy: 12 yrs & older (obesity)
Tirzepatide (Mounjaro, Zepbound)	✓ (Mounjaro)	✓ (Zepbound)	✓ (Zepbound)	-	-	-	-

Learning Objectives

At the conclusion of this presentation, pharmacists should be able to:

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- **Recognize proposed mechanisms by which GLP-1-based medications may impact conditions beyond type 2 diabetes and adiposity-based chronic disease.**
- Describe key findings from major clinical trials evaluating new therapeutic potential of GLP-1-based medications.

GLP-1: secreted by L-cells in small intestines (mostly in lower jejunum and ileum)

*glucagon-like peptide 1

Brain
- ↑ satiety
- ↓ food intake

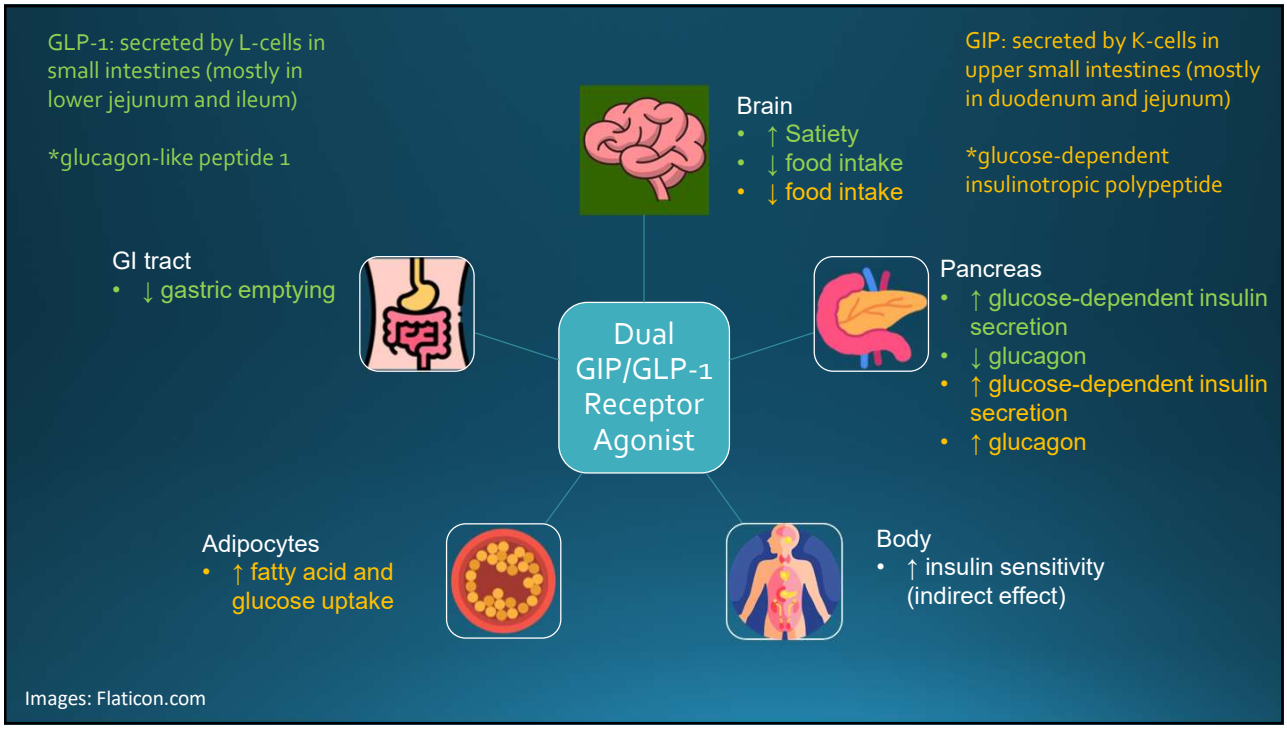
GI tract
- ↓ gastric emptying

Main Effects of GLP-1

Pancreas
- ↑ glucose-dependent insulin secretion
- ↓ glucagon

Body
- ↑ insulin sensitivity (indirect effect)

Images: Flaticon.com



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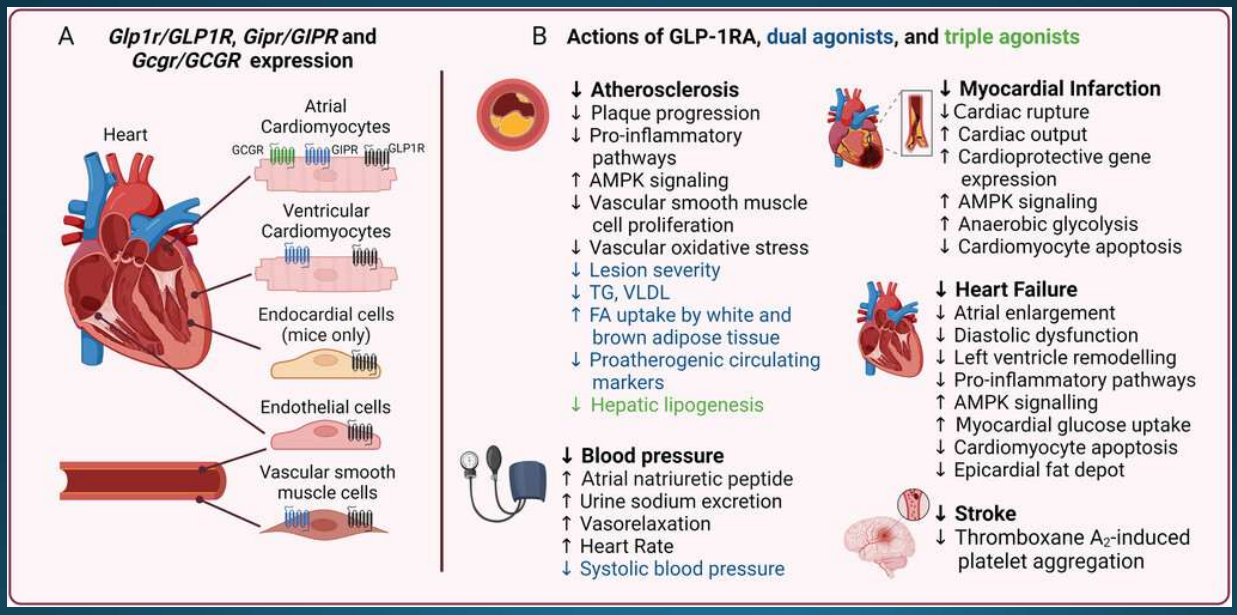
Describe key findings from major clinical trials evaluating new therapeutic potential of GLP-1-based medications.

GLP-1-based Medications and Cardiovascular Outcomes

AUDIENCE POLL #3

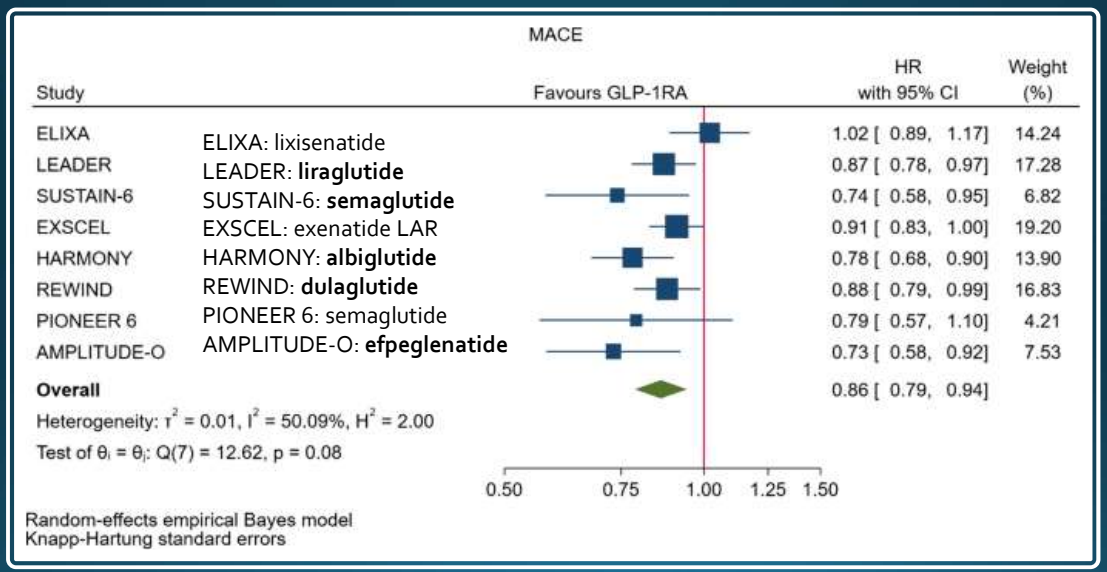
Which of the following mechanisms contribute to the cardiovascular risk reduction observed with GLP-1-based medications?

- A. Direct blockade of angiotensin II receptors and weight loss
- B. Improved endothelial function, decreased blood pressure, and weight loss
- C. Sodium-glucose cotransporter inhibition
- D. Increasing sympathetic nervous system activity



Mullur N et al. *J Endocrinol*. 2024 Sep 19;263(1):e240046.

Meta-Analysis of GLP-1 RA and Major Adverse Cardiovascular Events (MACE)



Giugliano D et al. *Cardiovasc Diabetol*. 2021 Sep 15;20(1):189.

Semaglutide 2.4 mg Cardiovascular Outcomes (SELECT RCT)

- **Population**: 17,604 adults 45 years or older with pre-existing CVD, BMI ≥27, and **without hx of diabetes**
- **Intervention**:
  - Semaglutide 2.4 mg SC QW
  - Placebo SC QW
- **Outcome**: Primary endpoint – composite of:
  - First occurrence of death from CV causes
  - Nonfatal MI
  - Nonfatal stroke

Lincoff AM et al. *N Engl J Med* 2023;389(24):2221-2232.

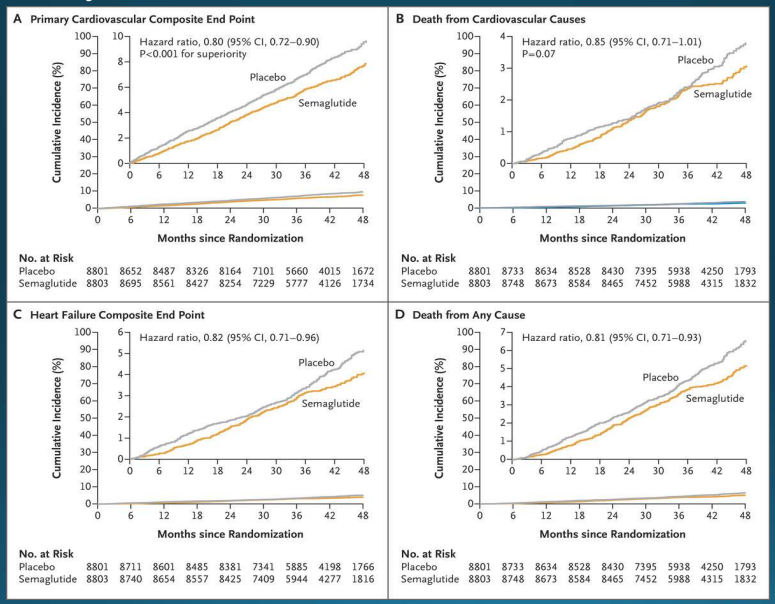
Semaglutide 2.4 mg SELECT RCT

45 years of age or older with preexisting CVD (but without DM) and BMI ≥ 27

8803 semaglutide, 8801 placebo
~ 3 years

Mean age: ~62 yrs
Male: 72%
White: 84%
67% with preDM
68% with h/o MI

Time-to-First-Event Analysis for Primary and Confirmatory Secondary Efficacy End Points.



Change in weight from baseline
semaglutide: -9.39%
placebo: -0.88%

Treatment difference: -8.5%

↓ CV composite endpoint, heart failure composite endpoint, and death from any causes

AM Lincoff et al. *N Engl J Med* 2023; 389:2221-2232.

The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide 2.4 mg arm:

↓ SBP, DBP

Improved lipids

Higher % of participants with improved A1c (back in normal range)

↓ CRP

Higher rates of GI ADEs

Table 3. Supportive Binary and Continuous Secondary End Points.*

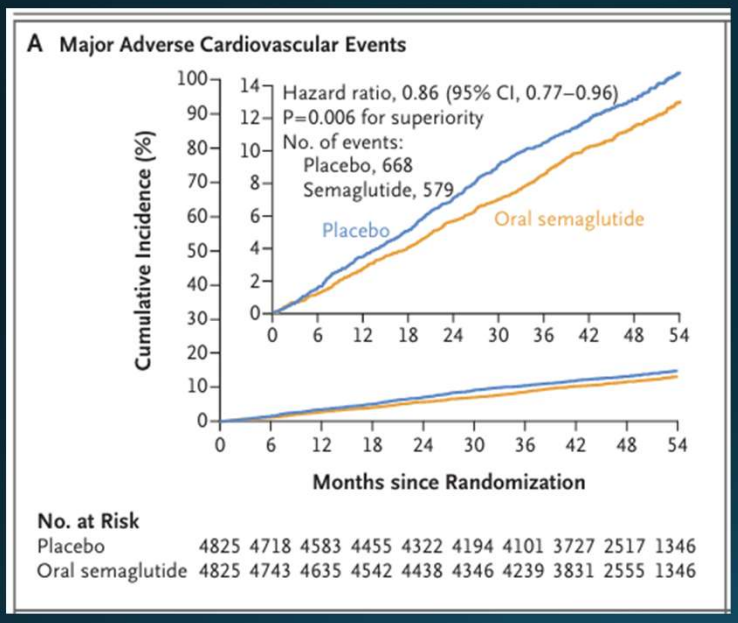
End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

AM Lincoff et al. *N Engl J Med* 2023; 389:2221-2232.

Oral Semaglutide – SOUL RCT

- **Population**: 9650 patients 50 years and oldeo with T2DM, A1c 6.5-10%, and known ASCVD, CKD, or both
- **Intervention**:
  - Semaglutide 14 mg PO daily, in addition to standard care
  - Placebo PO daily in addition to standard care
- **Outcome**: Primary endpoint – MACE, a composite of death from CV causes, nonfatal MI, and nonfatal stroke
  - Secondary outcomes – major kidney disease events

McGuire DK et al. *N Engl J Med* 2025;392(20):2001-2012.



- Oral semaglutide ↓ MACE compared to placebo
- Effect of PO semaglutide on MACE appeared to be larger among participants with A1c > 8%
- Trial population may not be representative of the global population with T2DM (~30% women, ~3% Black)

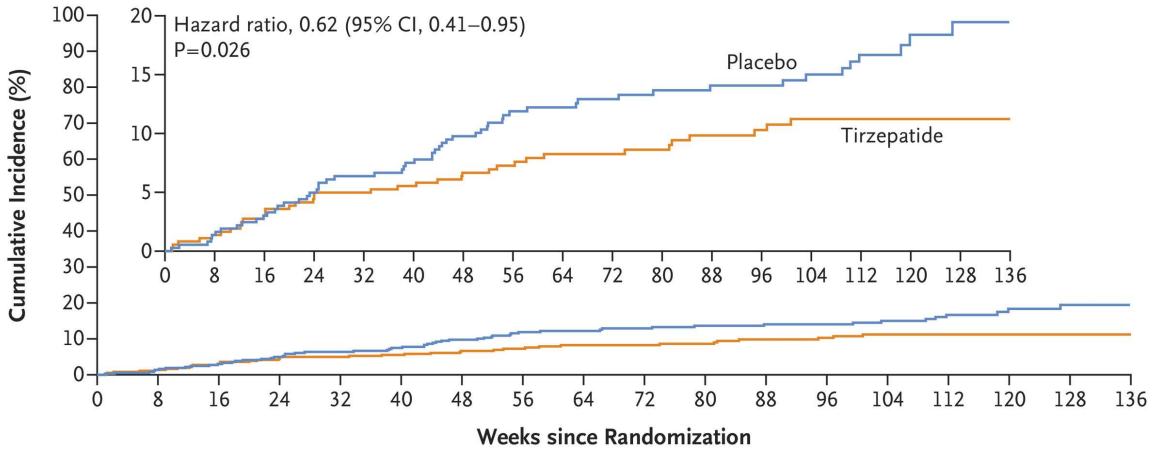
McGuire DK et al. *N Engl J Med* 2025;392(20):2001-2012.

Tirzepatide in HFpEF and Obesity (SUMMIT RCT)

- **Population**: 731 patients, 40 years and older,
  - with HF (NYHA class II-IV) with EF ≥ 50%
  - and BMI ≥ 30
- **Intervention**:
  - Tirzepatide SC titrated to 15 mg once weekly, in addition to standard care
  - Placebo SC once weekly in addition to standard care
- **Outcome**: Primary endpoints
  - Death from cardiovascular causes or a worsening heart-failure event,
  - Change at 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS)

Packer M et al; SUMMIT Trial Study Group. *N Engl J Med*. 2025 Jan 30;392(5):427-437.

Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event

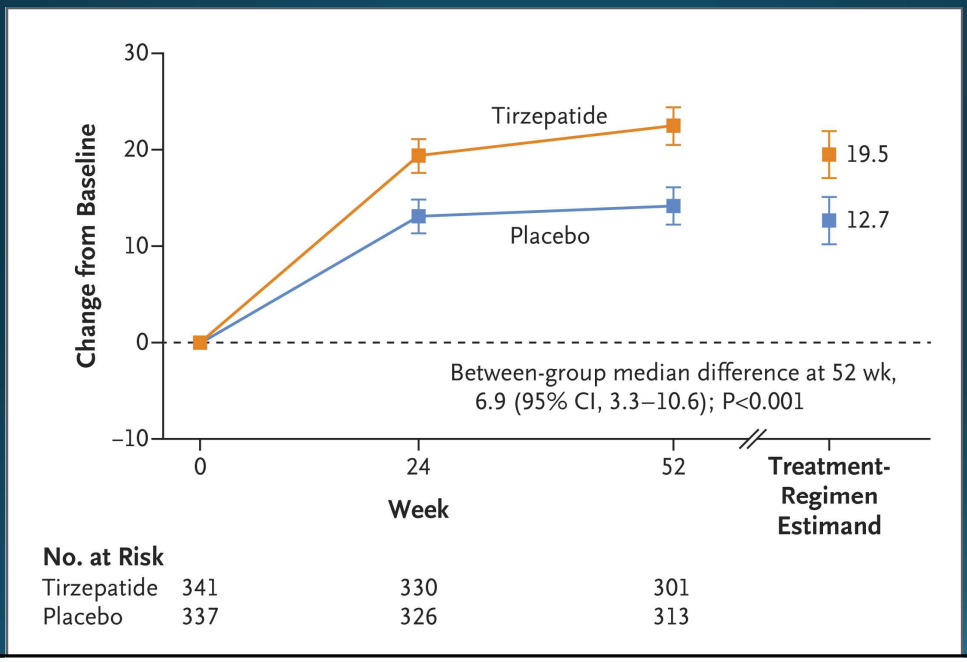


No. at Risk

Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

Packer M et al; SUMMIT Trial Study Group. *N Engl J Med*. 2025 Jan 30;392(5):427-437.

Change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS)



No. at Risk

Tirzepatide	341	330	301
Placebo	337	326	313

Packer M et al; SUMMIT Trial Study Group. *N Engl J Med*. 2025 Jan 30;392(5):427-437.

GLP-1-based Medications and Nephroprotection

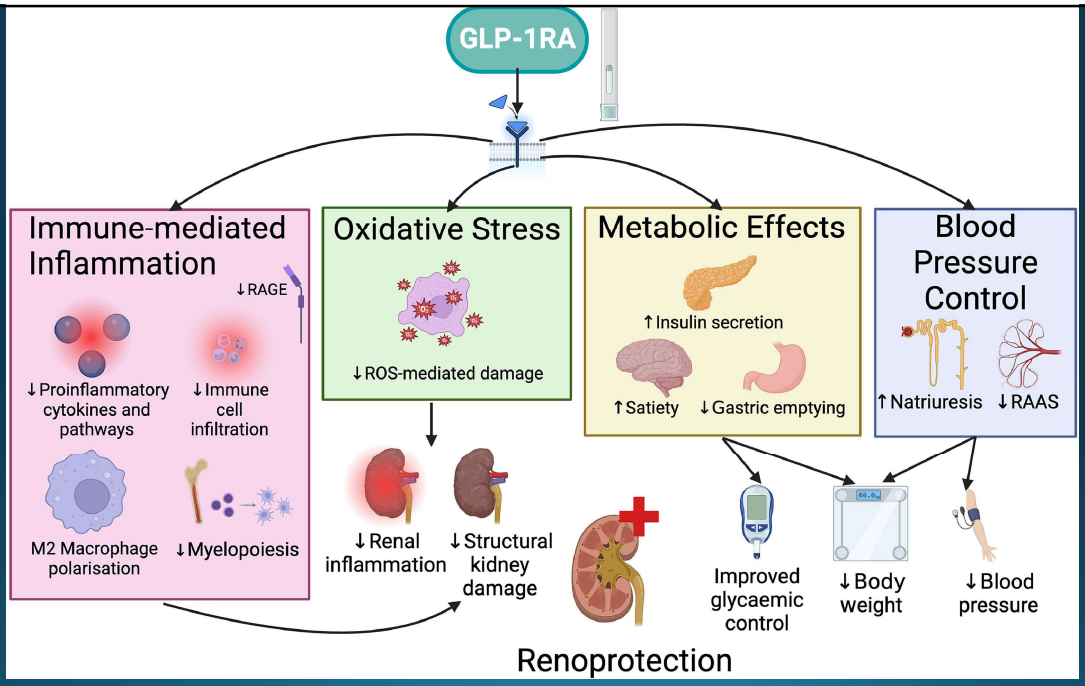
image: Flaticon.com

AUDIENCE POLL #4

In the FLOW RCT, which supported semaglutide's recent FDA label expansion for kidney risk reduction, the primary composite endpoint (kidney failure, ≥50% sustained eGFR reduction, or kidney/CV death) was reduced by ____ compared to placebo:

- A. ~10%
- B. ~25%
- C. ~50%
- D. ~60%

Potential Mechanisms of Reno-protection of GLP-1RA

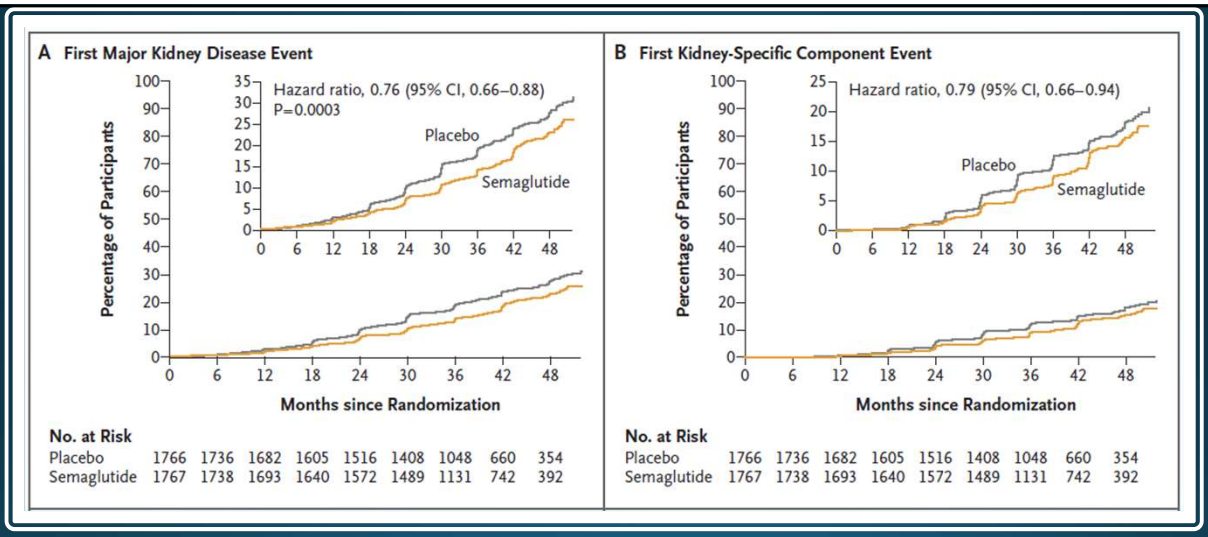


Chen J et al. *Diabetes Metab*. 2025 May;51(3):101641.

Semaglutide in T2DM and CKD (FLOW RCT)

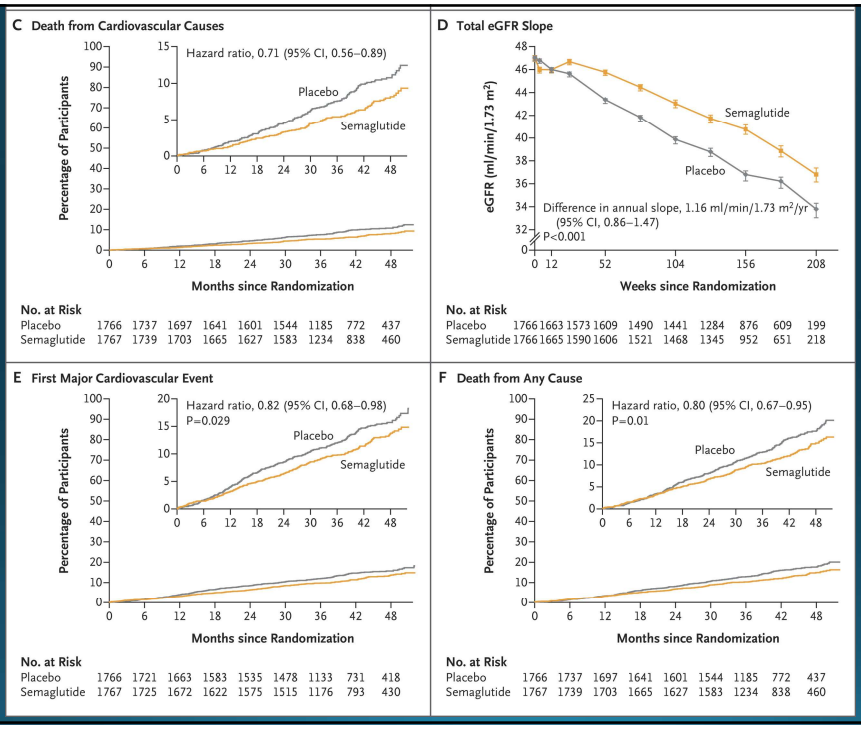
- **Population**: 3533 participants with T2DM & CKD (eGFR 50-75 mL/min/1.73 m2 and UACR >100 and <5000) receiving ACEI or ARB; mean age = 67, 70% men
- **Intervention**:
  - Semaglutide 1 mg SC QW
  - Placebo SC QW
- **Outcome**: Primary endpoints – major kidney disease events, a composite of:
  - Onset of kidney failure (initiation of dialysis, kidney transplantation, eGFR < 15 mL/min/1.73 m2)
  - 50% reduction or more in eGFR from baseline
  - Death from kidney or CV-related causes

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



- Semaglutide reduced risk of clinically important kidney outcomes
- Study did not assess combination therapy (SGLT-2 inhibitors, MRAs, etc)
- Majority of participants (~66%) were White

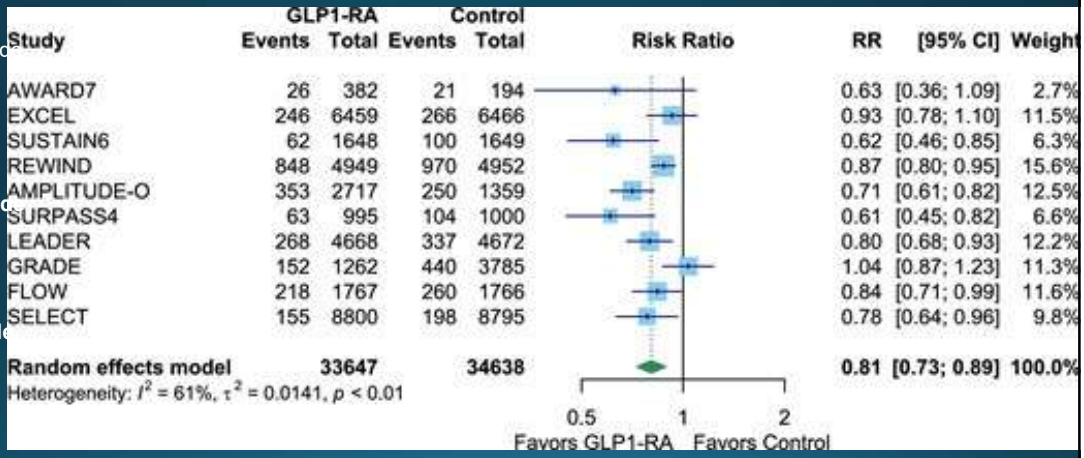
Perkovic V et al. *N Engl J Med* 2024;391(2):109-121.



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

Meta-analysis of Kidney Outcomes and GLP-1-based Medications

AWARD-7: dulaglutid
(open-label)
EXSCEL: exenatide
LAR
SUSTAIN 6:
semaglutide
REWIND: dulaglutid
AMPLITUDE-O:
efpeglenatide
SURPASS-4:
tirzepatide
LEADER: liraglutid
GRADE: liraglutide
FLOW, SELECT:
semaglutide



Sasaki T et al. *Nephrol Dial Transplant.* 2025 Sep 22:gfaf193.

The effect of GLP-1 receptor agonists on renal outcomes: a systematic review and meta-analysis

GLP1-RAs are anti-hyperglycaemic medications with demonstrated cardiac and metabolic benefits. However, the effects on renal outcomes remains unclear.

Methods

Systematic search of MEDLINE, EMBASE and the Cochrane Register

GLP1-RAs

Populations ≥ 18 years
Any severity of CKD
With or without history of diabetes

Results

GLP1-RA versus PLACEBO
19 included trials

Composite renal outcomes	Decline in renal function	Development of microalbuminuria	Progression to kidney failure
↓19%	↓12%	↓24%	↓14%
RR 0.81 95% CI 0.73–0.89	RR 0.88 95% CI 0.81–0.95	RR 0.76 95% CI 0.71–0.82	RR 0.86 95% CI 0.71–1.05

No significant difference in reduction in composite renal outcomes between patients with or without diabetes, patients with or without CKD or based off GLP-RA drugs

Sasaki, T. *et al.*
NDT (2025)
@NDTSocial

GLP-1RAs had demonstrated renal protective effects with reduction in composite renal outcomes, decline in renal function, and development of microalbuminuria in patients with diabetes. There was comparable efficacy in patients without diabetes.

Sasaki T et al. *Nephrol Dial Transplant.* 2025 Sep 22:gfaf193.

GLP-1-based Medications and Obstructive Sleep Apnea (OSA)

image: Flaticon.com

Tirzepatide in OSA (SURMOUNT RCT)

- **Population:** 469 adults with moderate-to-severe OSA and obesity; two Phase 3 RCTs
  - Patients had to have at least 15 apneic–hypopneic events per hour, BMI ≥ 30, without diabetes
- **Intervention:**
  - Maximum tolerated dose of tirzepatide (10 mg or 15 mg) SC QW
  - Placebo SC QW
  - Both arms included reduced-calorie diet and increased physical activity
- **Outcome:** Primary end point: change from baseline in apnea–hypopnea index (AHI: number of apneas and hypopneas during an hour of sleep)

Malhotra A et al. *N Engl J Med* 2024;391(13):1193-1205.

Tirzepatide in OSA (SURMOUNT RCT)

Trial 1

- Participants **NOT receiving PAP** therapy
- 234 adults
- Mean age: 48 years old
- 67% men
- Mean AHI: ~50 events per hour
- Mean BMI: 39
- Without DM

Trial 2

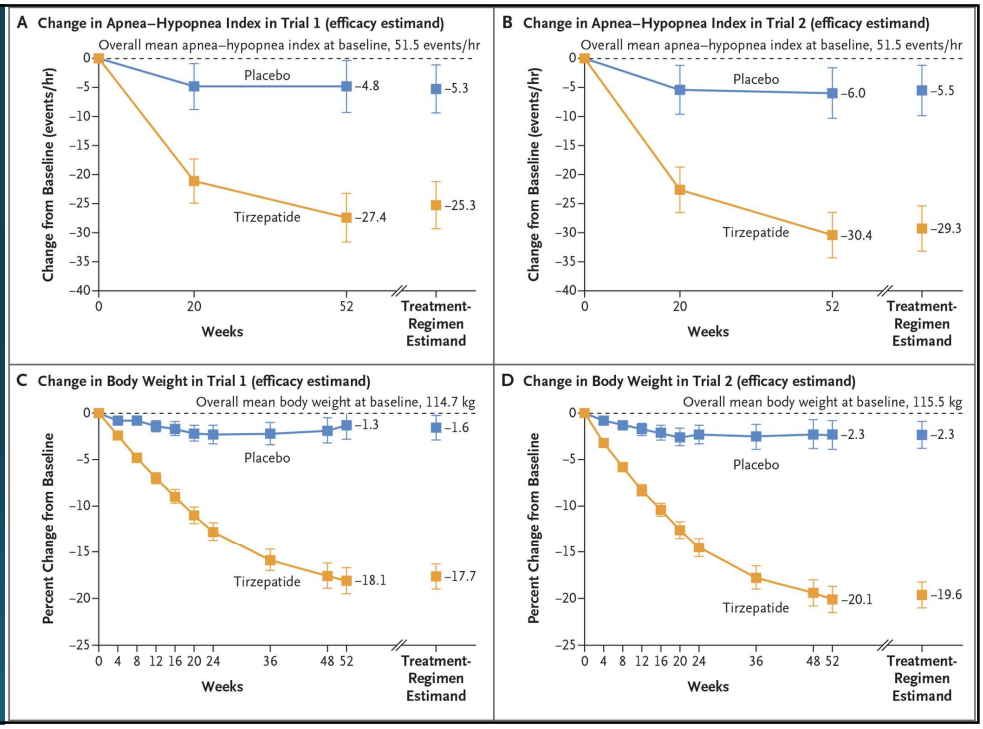
- Participants **receiving PAP** therapy
- 235 adults
- Mean age: 52 years old
- 72% men
- Mean AHI: ~50 events per hour
- Mean BMI: 39
- Without DM

PAP = positive airway pressure

Malhotra A et al. *N Engl J Med* 2024;391(13):1193-1205.

- ~50% reduction in AHI
- All key secondary endpoints also favored tirzepatide
- Common ADEs were gastrointestinal in nature
- Authors intend to further study clinical outcomes

Malhotra A et al. *N Engl J Med* 2024;391(13):1193-1205.

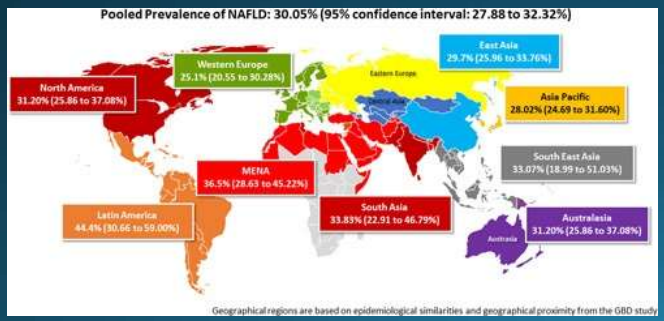


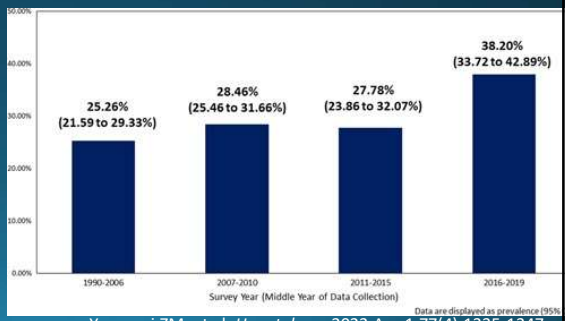
GLP-1-based Medications and Metabolic Dysfunction-Associated Steatohepatitis (MASH)

image: Flaticon.com

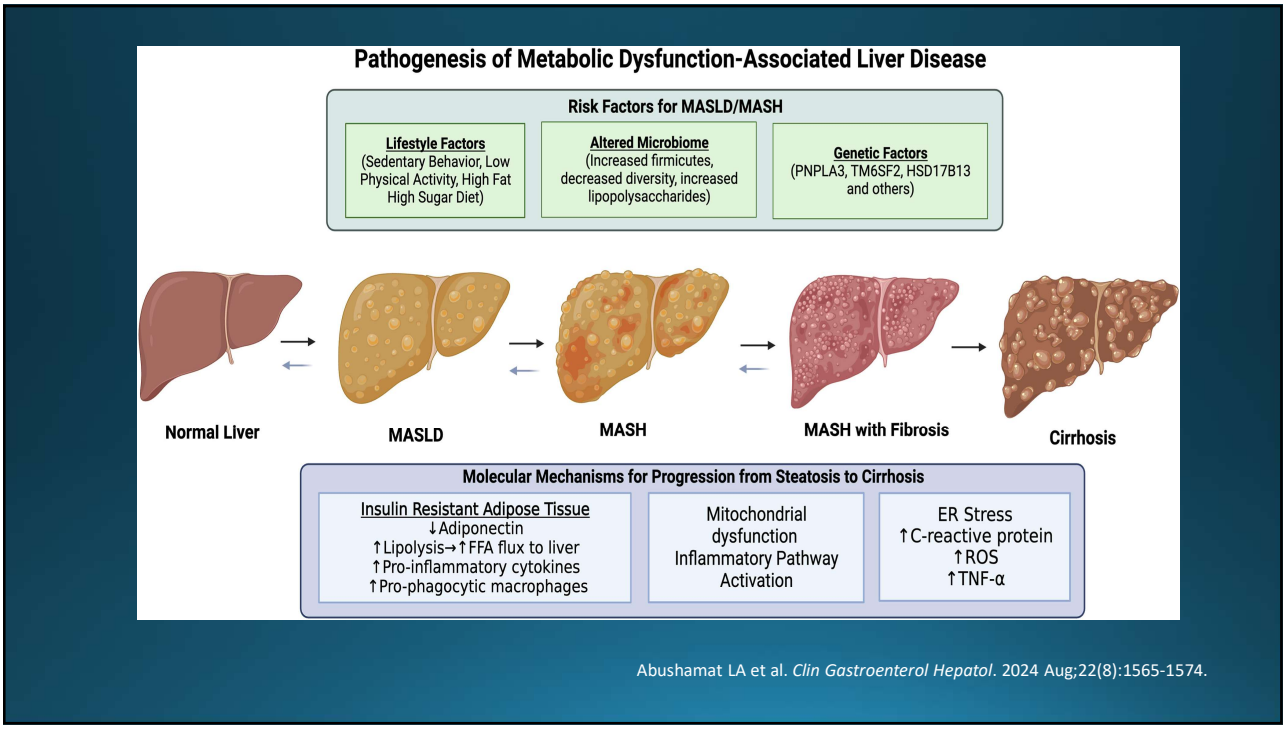
MASLD and MASH

- Metabolic-dysfunction associated steatotic liver disease (MASLD)
- Metabolic-dysfunction steatohepatitis (MASH)
- Previously: non-alcoholic liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

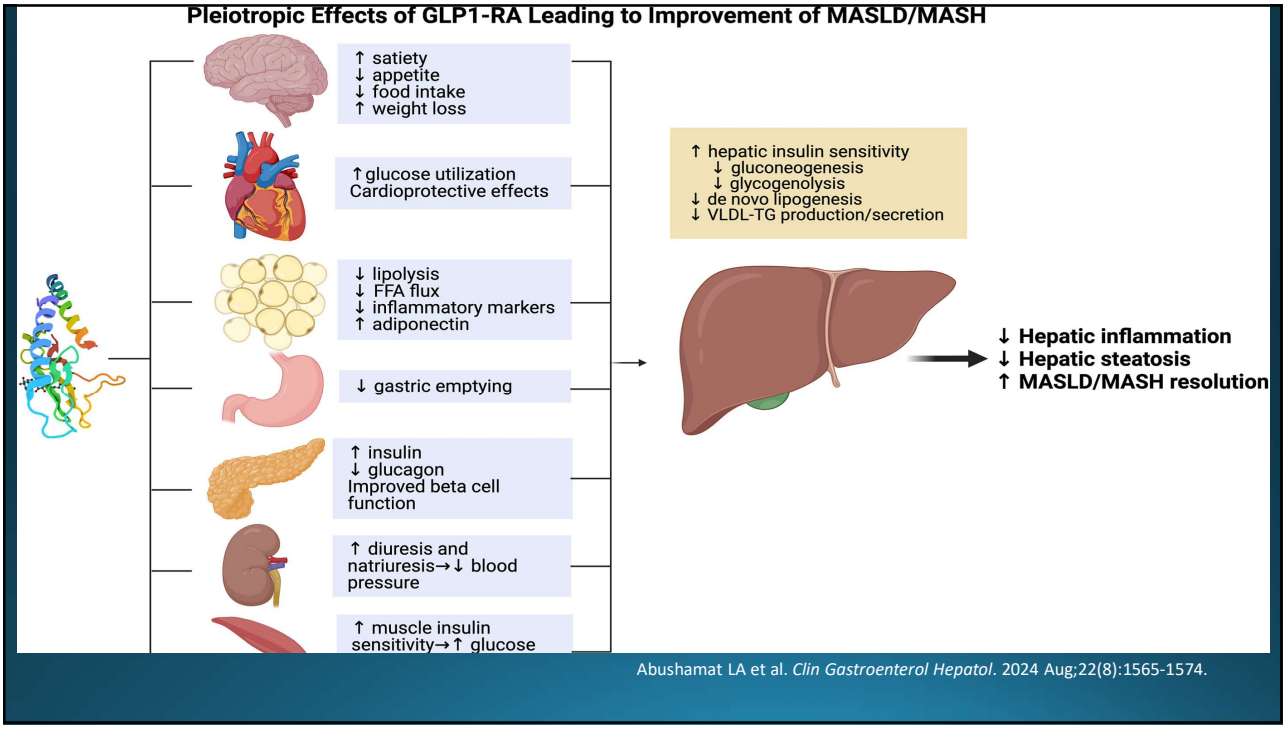




Younossi ZM, et al. *Hepatology*. 2023 Apr 1;77(4):1335-1347.



Abushamat LA et al. *Clin Gastroenterol Hepatol*. 2024 Aug;22(8):1565-1574.

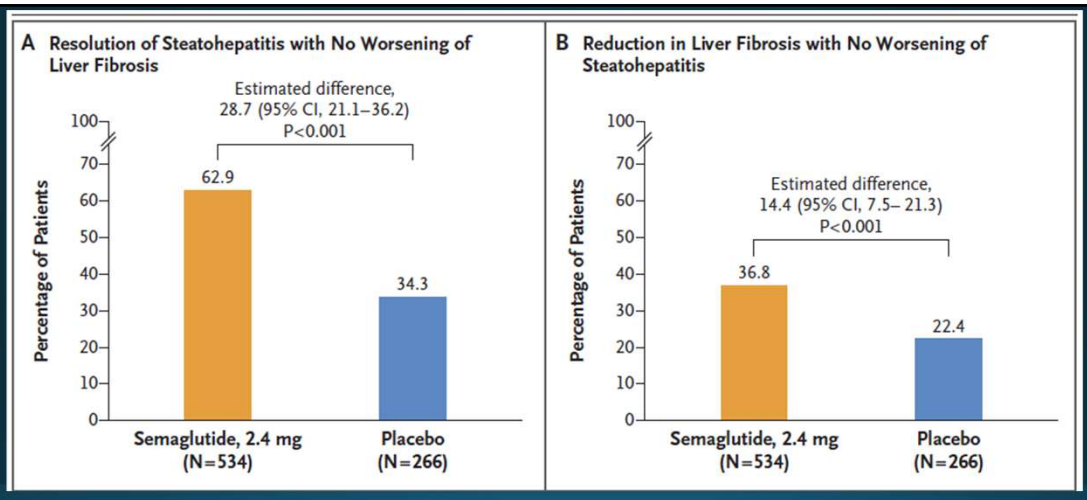


Abushamat LA et al. *Clin Gastroenterol Hepatol*. 2024 Aug;22(8):1565-1574.

Semaglutide in MASH (ESSENCE RCT)

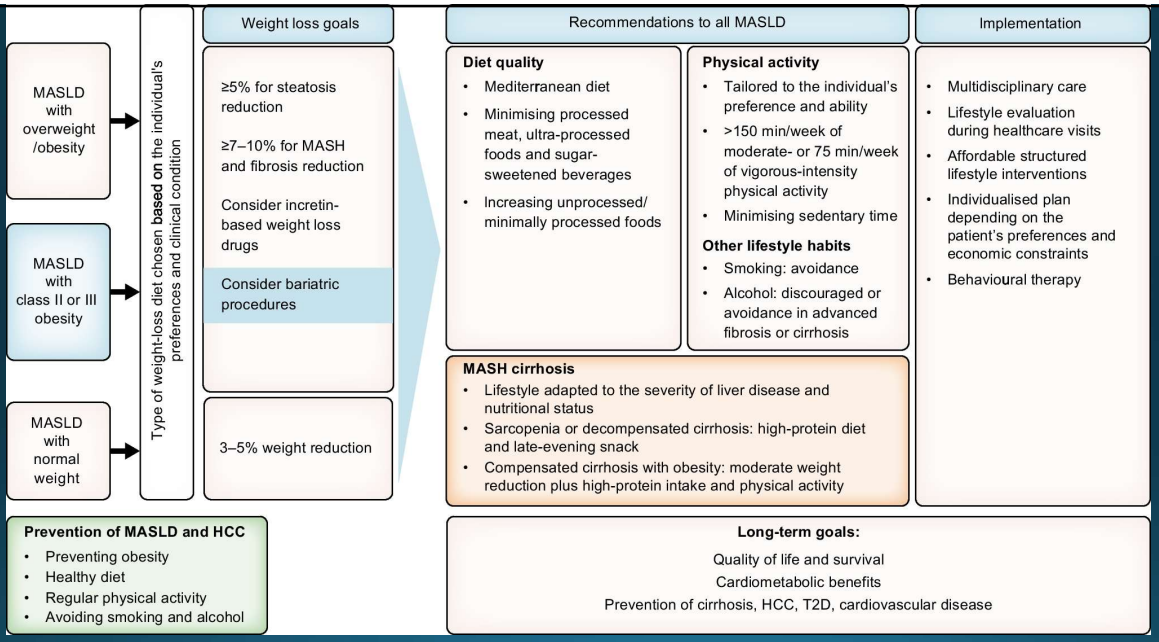
- **Population:** 1197 adults with biopsy-defined Metabolic dysfunction–associated steatohepatitis (MASH) and fibrosis stage 2 or 3
  - Excluded participants with other chronic liver diseases, high alcohol use, or recent GLP-1RA therapy
- **Intervention:**
  - Semaglutide 2.4 mg SC QW
  - Placebo SC QW x240 weeks
  - Planned interim analysis at 72 weeks
- **Outcome:** Primary endpoints – resolution of steatohepatitis with no worsening of liver fibrosis, reduction in liver fibrosis with no worsening of steatohepatitis

Sanyal AJ et al. *N Engl J Med* 2025;392(21):2089-2099.



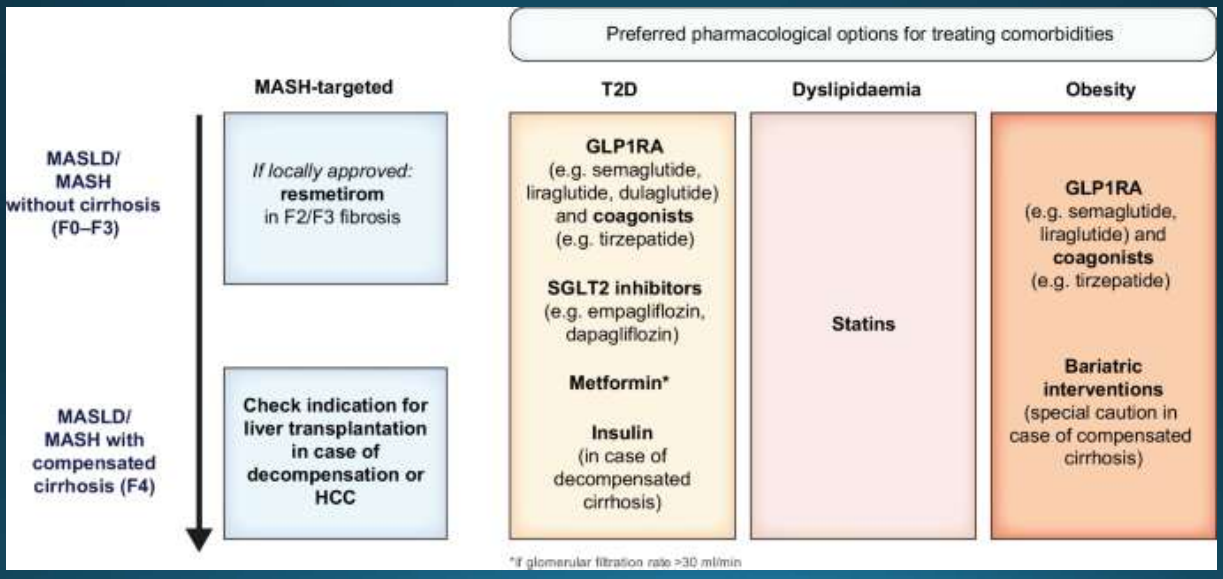
- Results from planned interim analysis of first 800 participants
- Results focused on histological improvements; clinical improvements will be further studied
- Improved glycemic control, weight loss, and insulin resistance with semaglutide

Sanyal AJ et al. *N Engl J Med* 2025;392(21):2089-2099.



European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary. *Diabetologia*. 2024 Nov;67(11):2375-2392.

Treatment recommendations beyond lifestyle modification in MASLD/MASH.



European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary. *Diabetologia*. 2024 Nov;67(11):2375-2392.

Putting it All Together

- Patient selection – match to population in RCTs as closely as possible
  - Patients with or without DM
  - Patients with or without adiposity-based chronic disease
  - Patients with or without ASCVD or at high risk for CVD
  - Patients with CKD
  - Patients with HFpEF
  - Patients with MASLD or MASH
- Alternative, established agents can be just as, or more, effective
- Combination therapy?
  - Especially with SGLT2 inhibitors
  - Background therapy of established therapy (renin-angiotensin system inhibitors, statins, etc.)
  - Therapeutic lifestyle changes
- Balance efficacy with warnings, ADRs, DDIs, etc.
- Guidelines

Session Code for CE Credit: