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

Devra Dang, PharmD, CDCES, FNAP
Clinical Professor
UConn School of Pharmacy

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)	-	-	-	-

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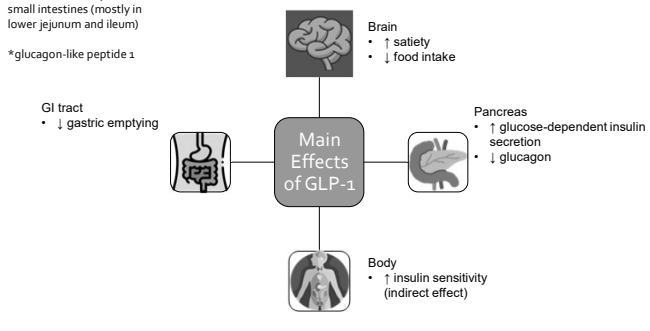
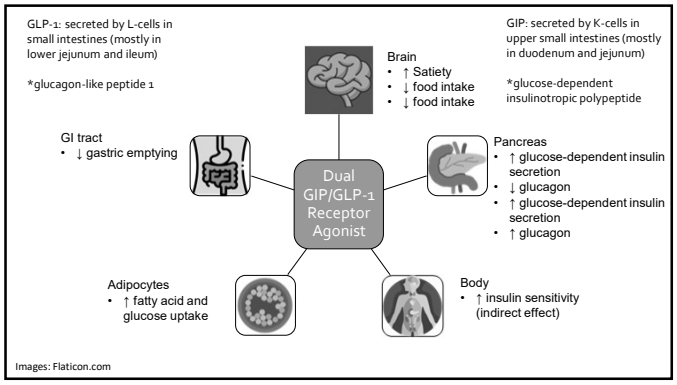
GLP-1: secreted by L-cells in small intestines (mostly in lower jejunum and ileum)

*glucagon-like peptide 1



Images: Flaticon.com



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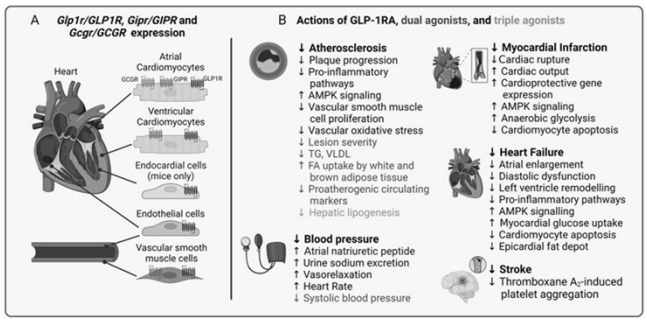
Describe key findings from major clinical trials evaluating new therapeutic potential of GLP-1-based medications.

GLP-1-based Medications and Cardiovascular Outcomes

AUDIENCE POLL #3

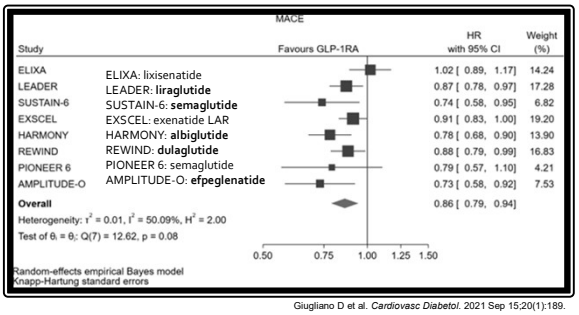
Which of the following mechanisms contribute to the cardiovascular risk reduction observed with GLP-1-based medications?

- 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.

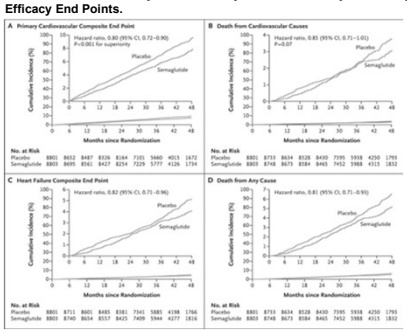
Time-to-First-Event Analysis for Primary and Confirmatory Secondary Efficacy End Points.

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



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.

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.**[a]

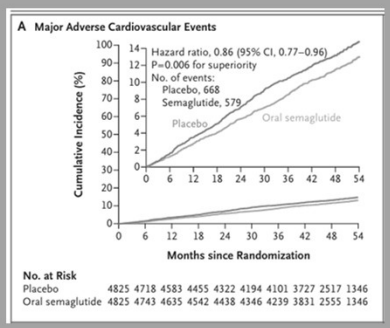
End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)[†]
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)[‡]			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (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.



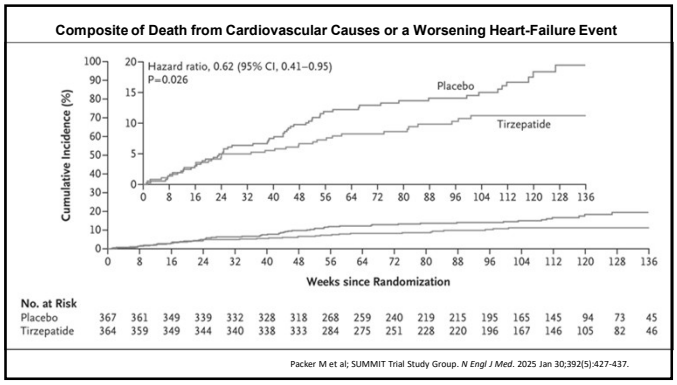
- Oral semaglutide ↓ MACE compared to placebo
- Effect of PO semaglutide on MACE appeared to be larger among participants with A1c > 8%
- Trial population may not be representative of the global population with T2DM (~30% women, ~3% Black)

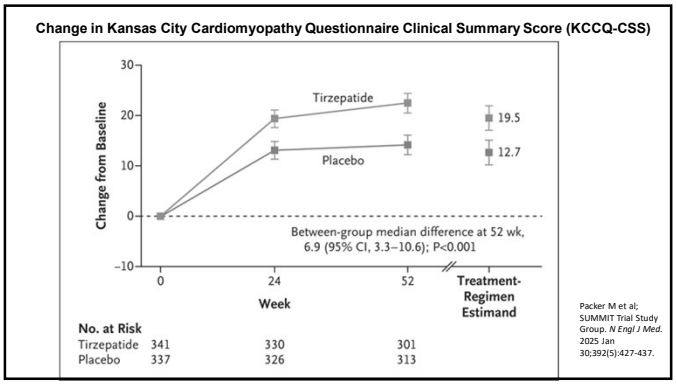
McGuire DK et al. *N Engl J Med* 2025;392(20):2001-2012.

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.





GLP-1-based Medications and Nephroprotection

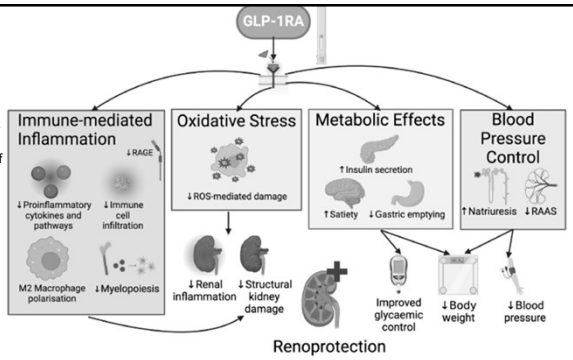
image: Flaticon.com

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

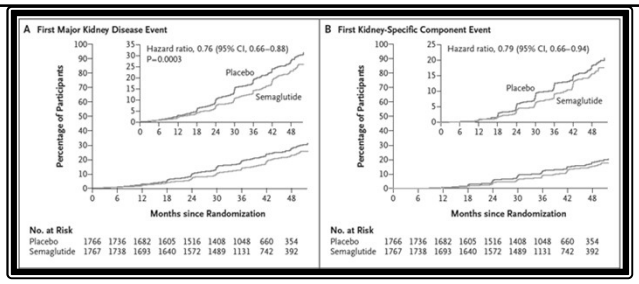


Chen J et al. *Diabetes Metab*. 2025 May;51(3):101641.

Semaglutide in T2DM and CKD (FLOW RCT)

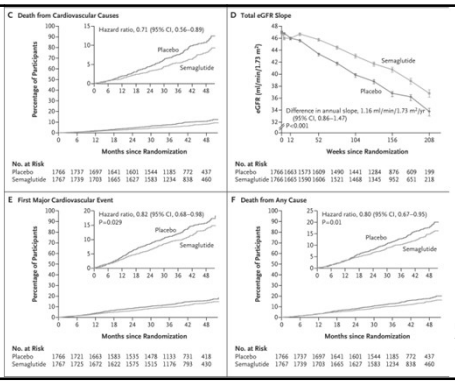
- **Population:** 3533 participants with T2DM & CKD (eGFR 50-75 mL/min/1.73 m2 and UACR >100 and <5000) receiving ACEI or ARB; mean age = 67, 70% men
- **Intervention:**
  - Semaglutide 1 mg SC QW
  - Placebo SC QW
- **Outcome:** Primary endpoints – major kidney disease events, a composite of:
  - Onset 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.



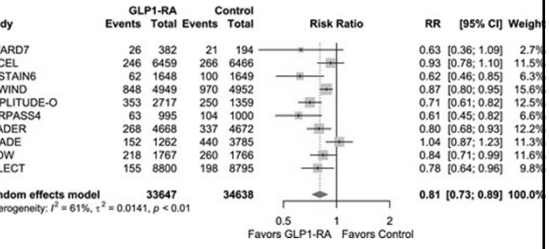
- Semaglutide reduced risk of clinically important kidney outcomes
- Study did not assess combination therapy (SGLT-2 inhibitors, MRAs, etc)
- Majority of participants (~66%) were White

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



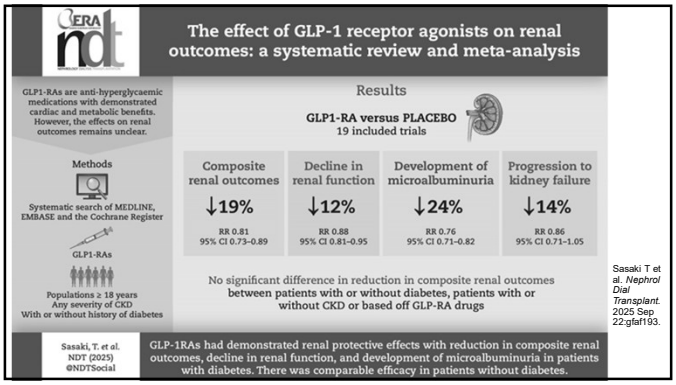
Perkovic V et al. *N Engl J Med* 2024;391(2):109-121.

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



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

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



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

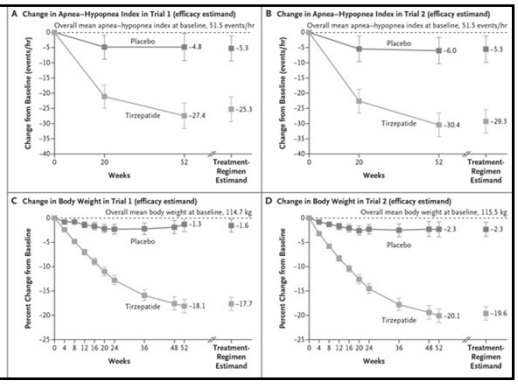
Trial 2

- 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



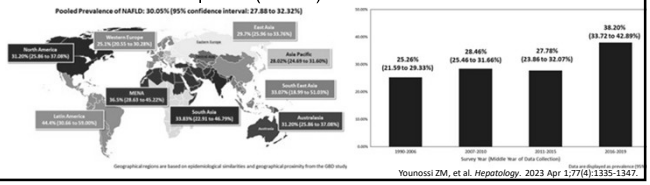
Malhotra A et al. *N Engl J Med* 2024;391(13):1193-1205.

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

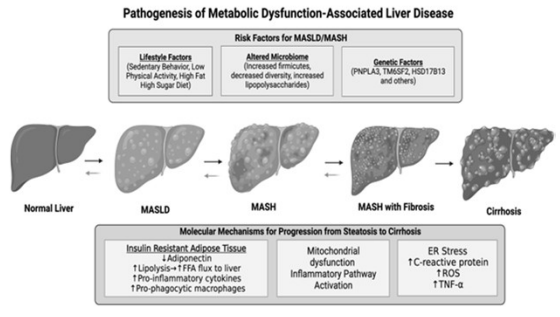
image: Flaticon.com

MASLD and MASH

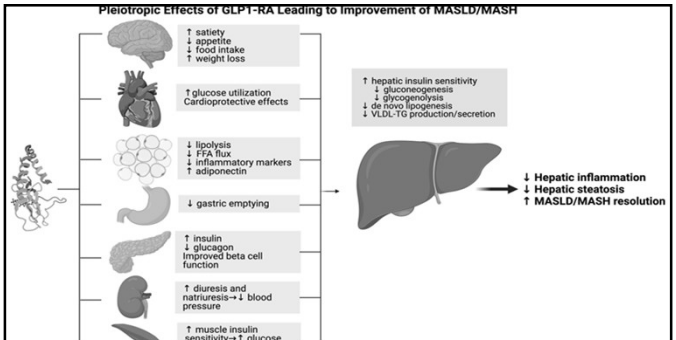
- Metabolic-dysfunction associated steatotic liver disease (MASLD)
- Metabolic-dysfunction steatohepatitis (MASH)
- Previously: non-alcoholic liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)



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.

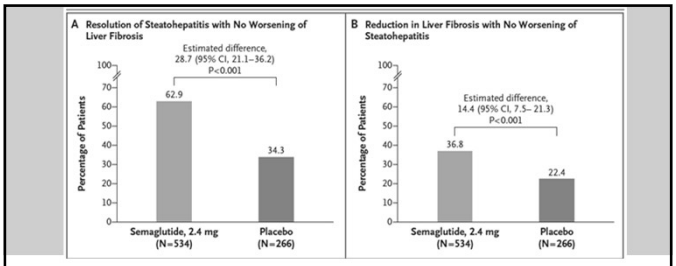


Abushamat LA et al. *Clin Gastroenterol Hepatol*. 2024 Aug;22(8):1565-1574.

Semaglutide in MASH (ESSENCE RCT)

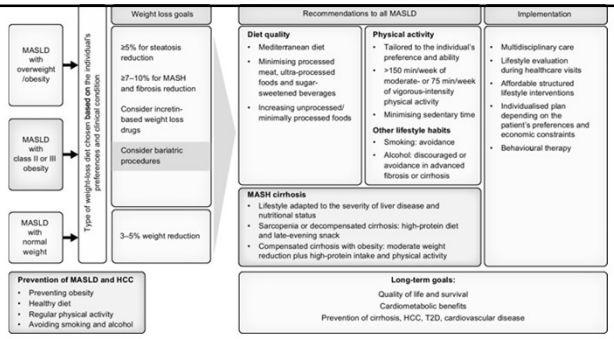
- **Population:** 1197 adults with biopsy-defined Metabolic dysfunction–associated steatohepatitis (MASH) and fibrosis stage 2 or 3
  - Excluded participants with other chronic liver diseases, high alcohol use, or recent GLP-1RA therapy
- **Intervention:**
  - Semaglutide 2.4 mg SC QW
  - Placebo SC 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.



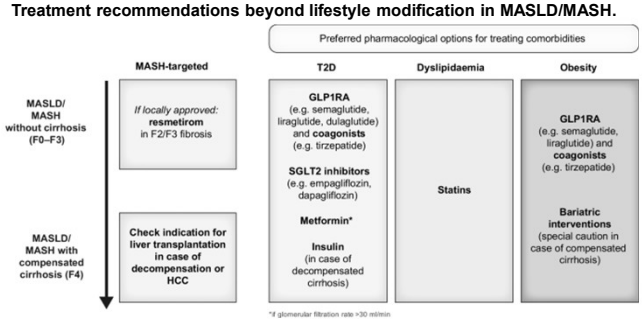
- Results from planned interim analysis of first 800 participants
- Results focused on histological improvements; clinical improvements will be further studied
- Improved glycemic control, weight loss, and insulin resistance with semaglutide

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: