

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

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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)	-	-	-	-

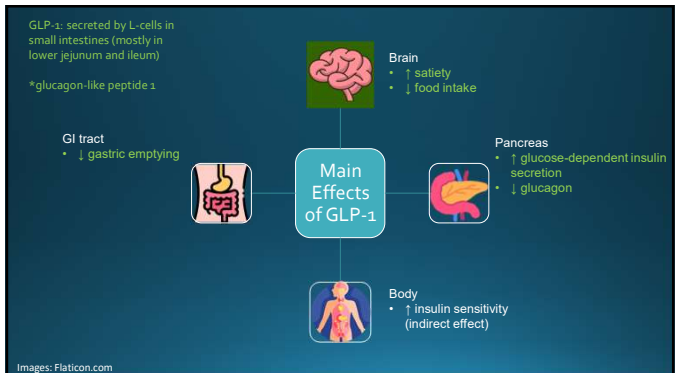
Learning Objectives

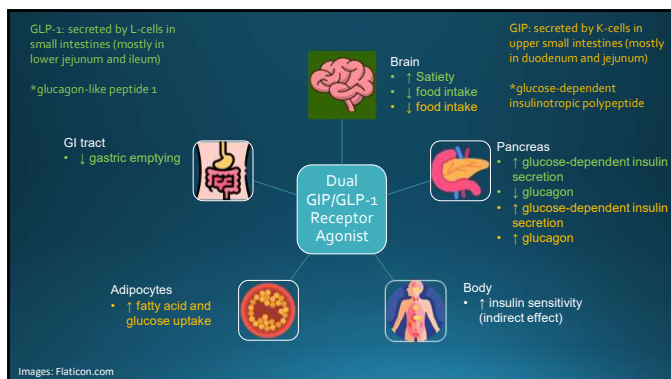
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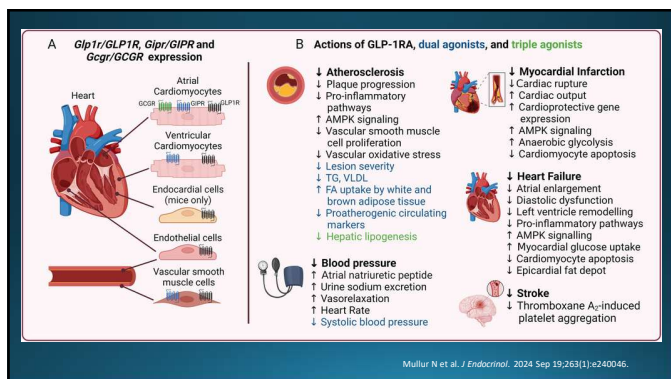
GLP-1-based Medications and Cardiovascular Outcomes



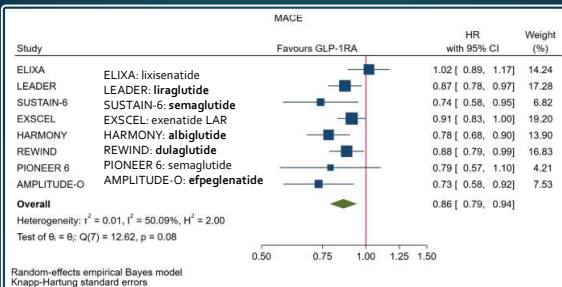
AUDIENCE POLL #3

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



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



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.

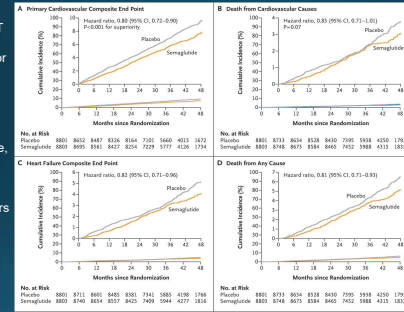
Time-to-First-Event Analysis for Primary and Confirmatory Secondary Efficacy End Points.

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.

NEW ENGLAND JOURNAL OF MEDICINE

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

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of $\leq 5.7\%$ among patients with baseline glycated hemoglobin level of $\geq 5.7\%$ — 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	-1.01±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 -35.96)
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 (-2.22 to -1.12)
Triglyceride level — %	-18.34	-3.20	-15.64 (-16.68 to -14.58)

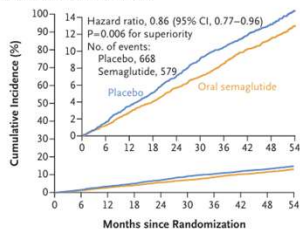
AM Lincoff et al. *N Engl J Med* 2023; 389:2221-2232.

Oral Semaglutide – SOUL RCT

- Population:** 9650 patients 50 years and older 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.

A 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

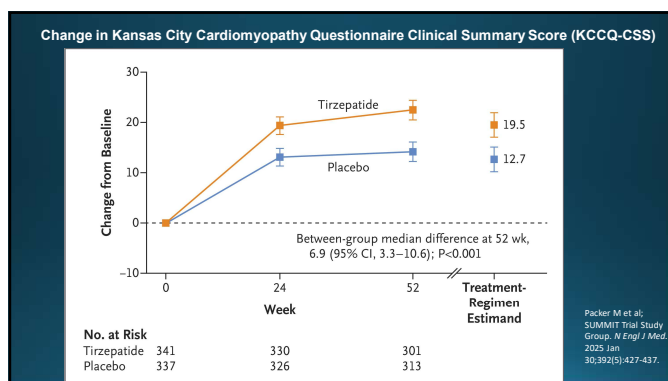
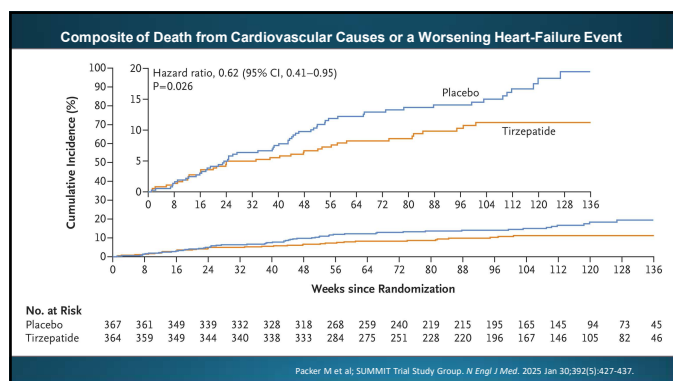
- Oral semaglutide ↓ MACE compared to placebo
- Effect of PO semaglutide on MACE appeared to be larger among participants with A1c > 8%
- Trial population may not be representative of the global population with T2DM (~30% women, ~3% Black)

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 $\geq 50\%$
 - 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.



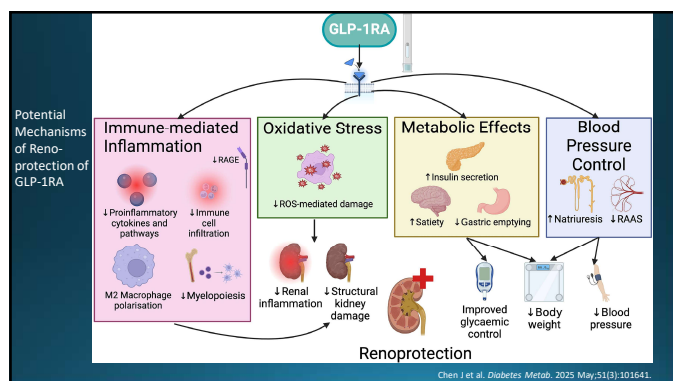
GLP-1-based Medications and Nephroprotection

image: FlatIcon.com

AUDIENCE POLL #4

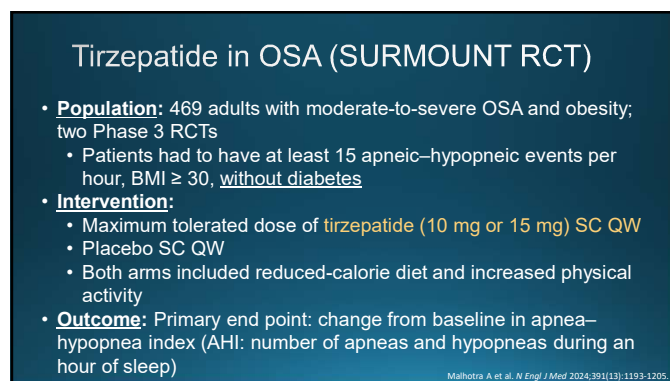
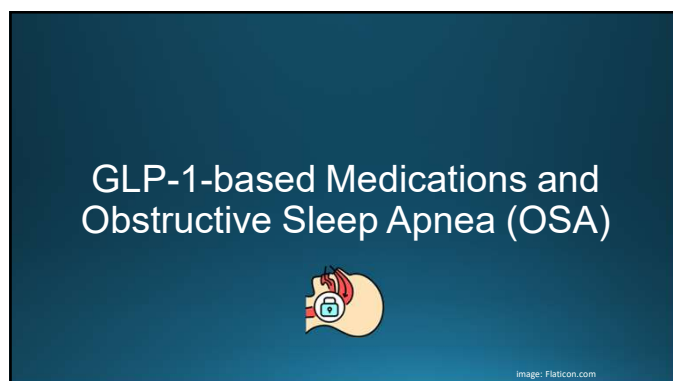
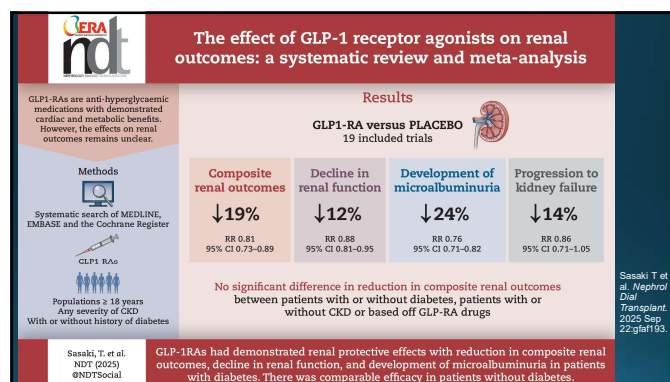
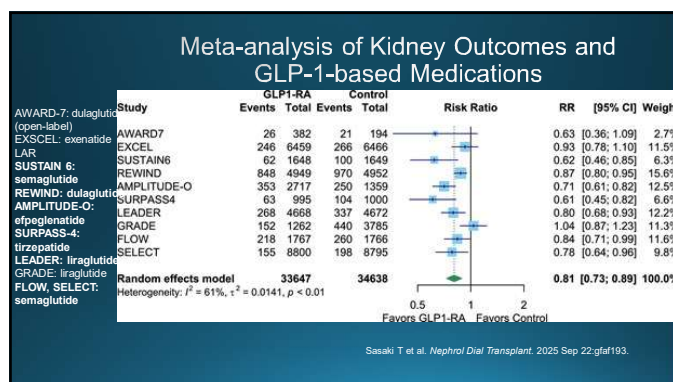
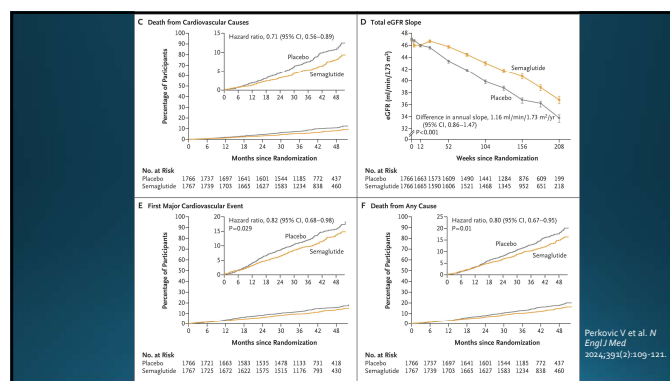
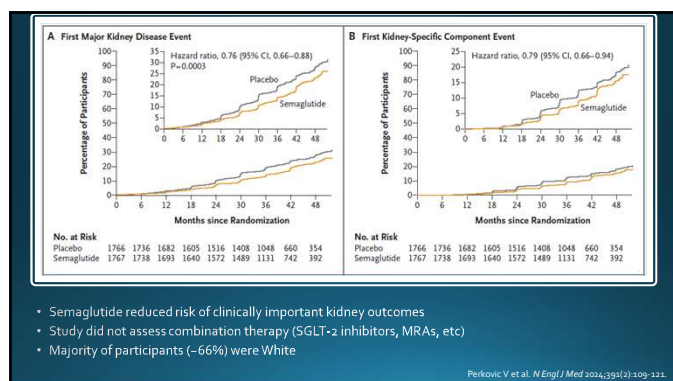
In the FLOW RCT, which supported semaglutide's recent FDA label expansion for kidney risk reduction, the primary composite endpoint (kidney failure, $\geq 50\%$ sustained eGFR reduction, or kidney/CV death) was reduced by ____ compared to placebo:

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



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.



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

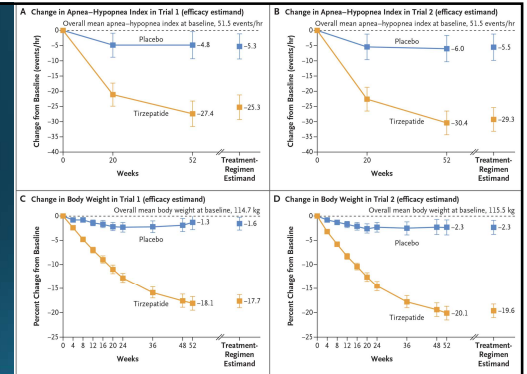
Trial 2

- 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.

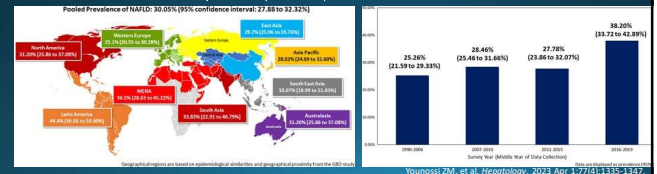
GLP-1-based Medications and Metabolic Dysfunction-Associated Steatohepatitis (MASH)



Image: FlatIcon.com

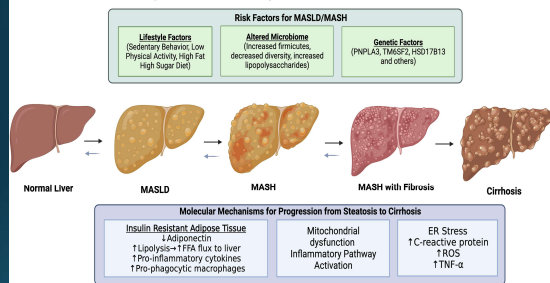
MASLD and MASH

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



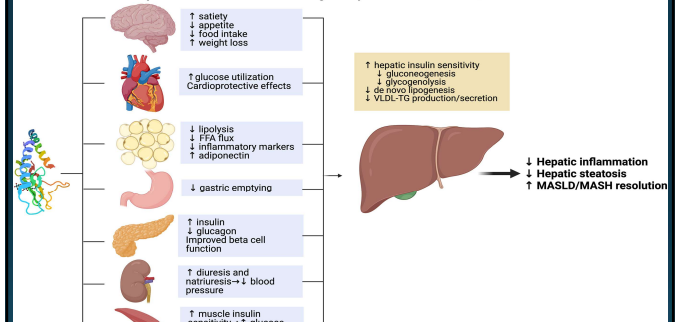
Younossi ZM, et al. *Hepatology*. 2023 Apr 1;77(4):1335-1347.

Pathogenesis of Metabolic Dysfunction-Associated Liver Disease



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

Pleiotropic Effects of GLP1-RA Leading to Improvement of MASLD/MASH

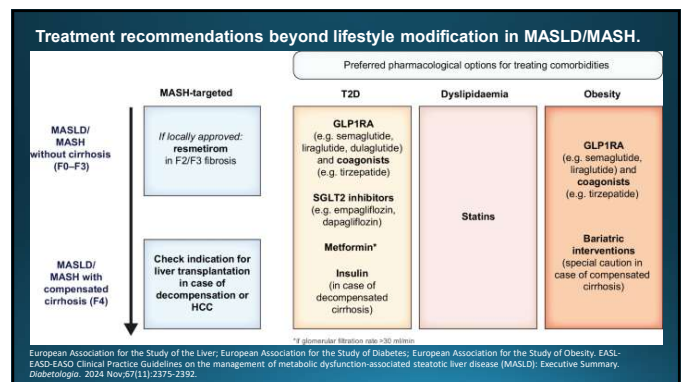
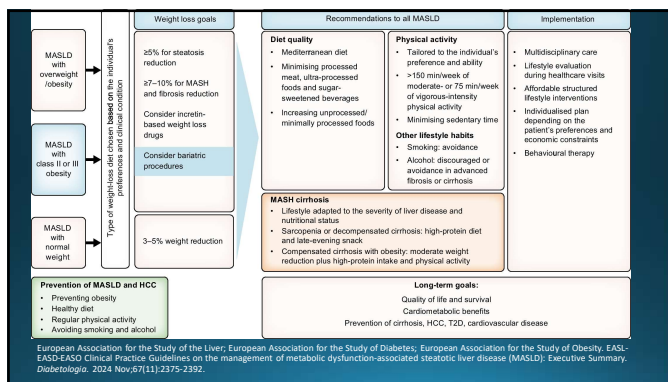
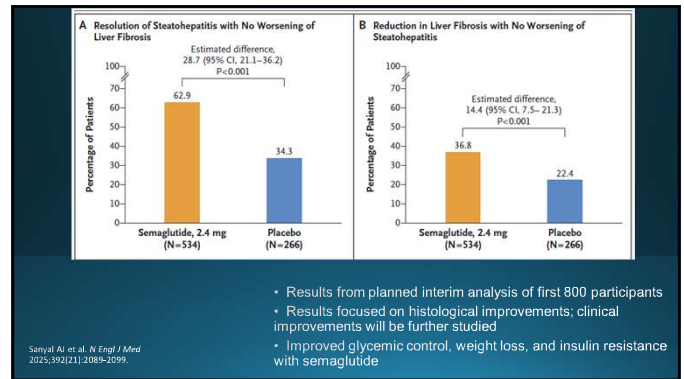


Abushamat LA et al. *Clin Gastroenterol Hepatol*. 2024 Aug;22(8):1565-1574.

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(11):2089–2099.



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: