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

- No actual or potential conflict of interest with the content of this presentation.
- This activity may contain discussion of unlabeled/unapproved use of drugs.
- Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, precautions, and warnings.
- The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy.

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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?

AUDIENCE POLL

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

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 and Rybelsus)	✓ (Wegovy)	-	✓ (Ozempic, Rybelsus, Wegovy)	✓ (Ozempic)	✓ (Wegovy)	✓ Wegovy: 12 yrs & older (obesity)
Tirzepatide (Mounjaro, Zepbound)	✓ (Mounjaro)	✓ (Zepbound)	✓ (Zepbound)	-	-	-	-

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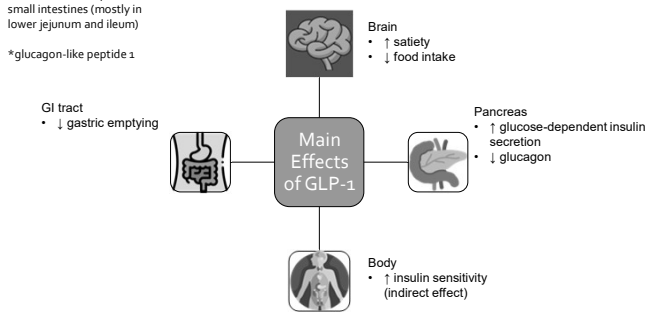
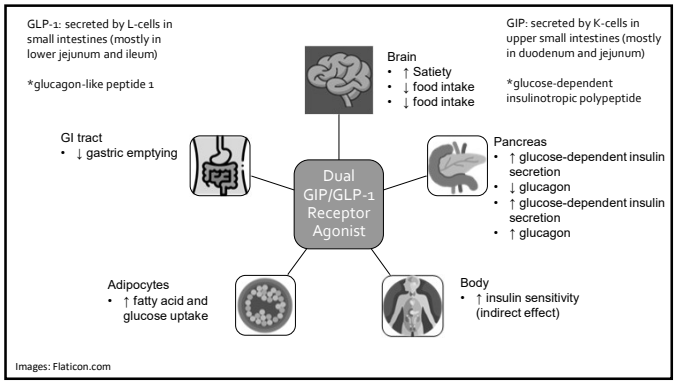
GLP-1: secreted by L-cells in small intestines (mostly in lower jejunum and ileum)

*glucagon-like peptide 1



Images: Flaticon.com



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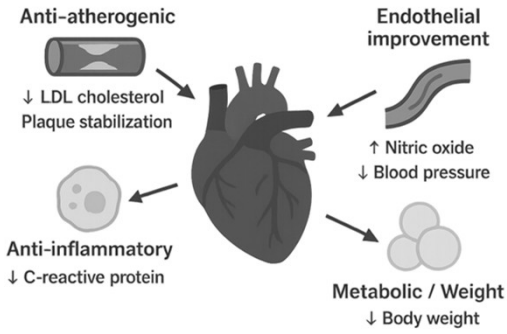
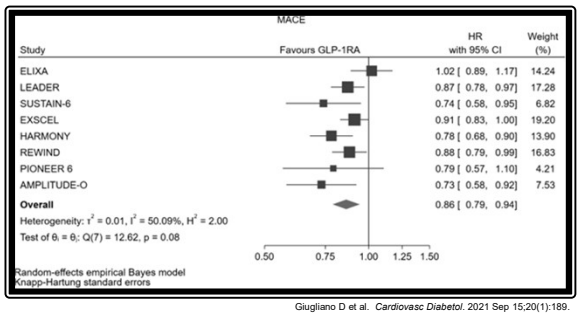
GLP-1-based Medications and Cardiovascular Protection



Yang HM. *J. Clin. Med.* 2025, *14*(19), 6758



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 **NO 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

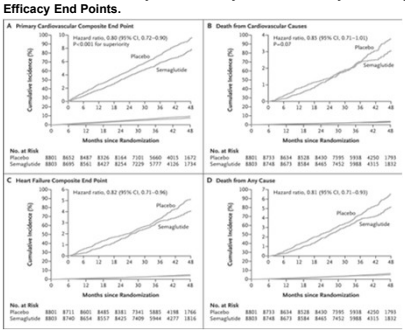
Lincoff AM et al. *N Engl J Med* 2023;389(24):2221-2232.

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

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%

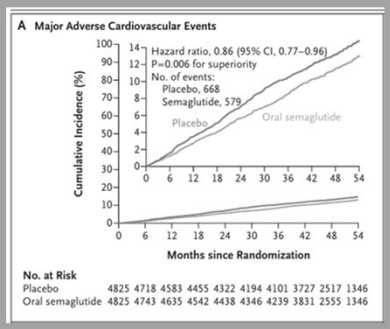
↓ CV composite endpoint, heart failure composite endpoint, and death from any causes

AM Lincoff et al. N Engl J Med 2023. DOI: 10.1056/NEJMoa2307563

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 associated with a significantly lower risk of MACE than 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.

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

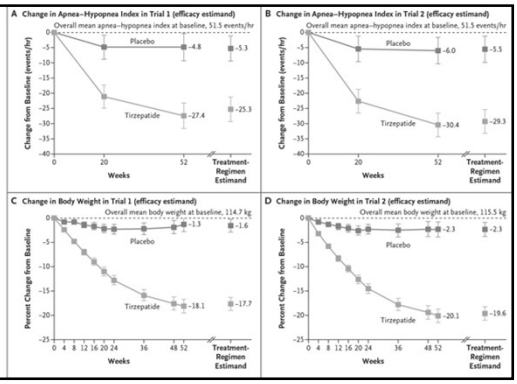
Trial 2

- 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 Chronic Kidney Disease (CKD)

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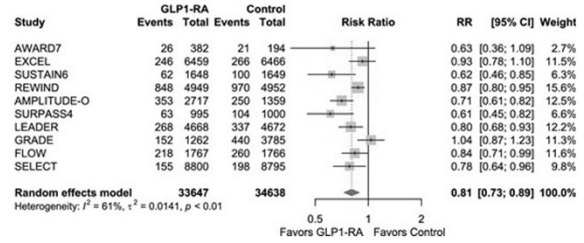
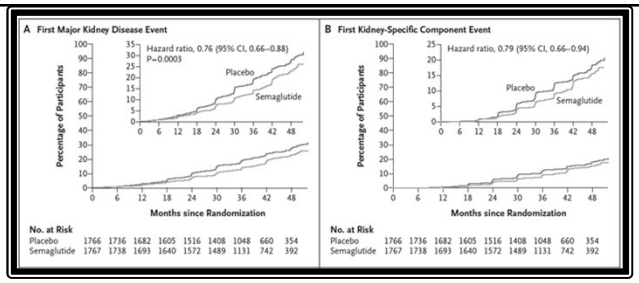


Sasaki T et al. *Nephrol Dial Transplant*. 2025 Sep 22:gfaf193.

Semaglutide in CKD (FLOW RCT)

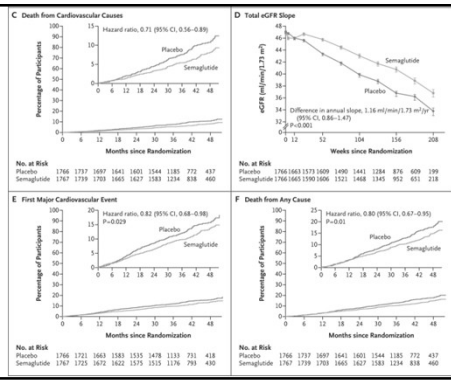
- **Population**: 3533 participants with T2DM & CKD (eGFR 50-75 mL/min/1.73 m2 and UACR >100 and <5000) receiving ACEI or ARB; mean age = 67, 70% men
- **Intervention**:
  - Semaglutide 1 mg SC QW
  - Placebo SC QW
- **Outcome**: Primary endpoints – major kidney disease events, a composite of:
  - Onset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

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

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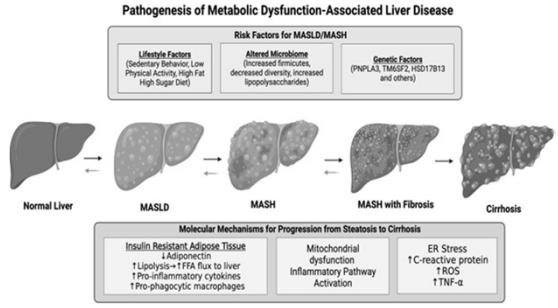
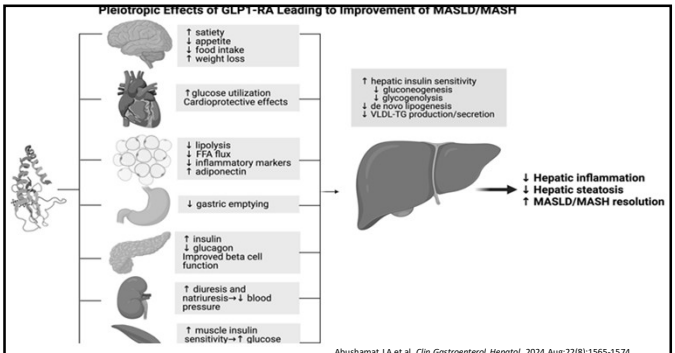


Abushamat LA et al. *Clin Gastroenterol Hepatol*. 2024 Aug;22(8):1565-1574.

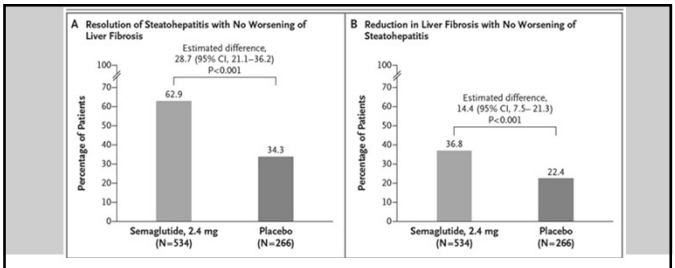


Abushamat LA et al. *Clin Gastroenterol Hepatol*. 2024 Aug;22(8):1565-1574.

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.

Putting it All Together

- Patient selection
- Early initiation of medication in the course of T2DM
- Balance efficacy with warnings, ADRs, DDIs, etc.

- Guidelines recommendations

Guidelines Recommendations

- American Diabetes Association (ADA)'s Standards of Medical Care for Diabetes
- KDIGO–ADA Consensus Guideline for Diabetes Management in Chronic Kidney Disease
- American College of Cardiology

Session Code for CE Credit: