# MASLD/MASH Management:
## Endocrinology Perspective

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AACE Strategic Roundtable on Multidisciplinary Approaches for the Management of MASLD and MASH

May 8th 2026

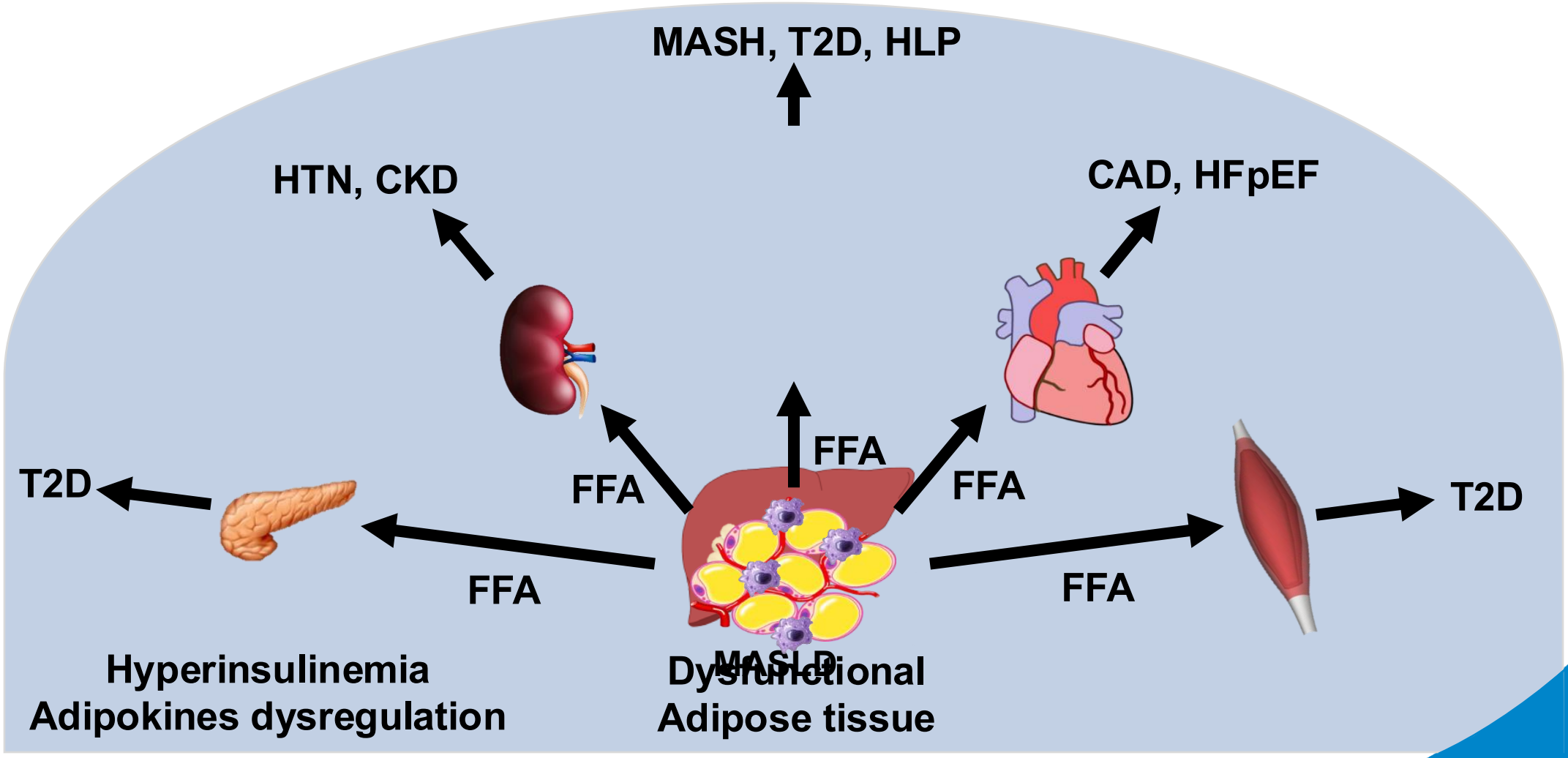
# Disclosures

- Advisor, Consultant, Speaker, or Research (through institution): NovoNordisk, Boehringer-Ingelheim, Madrigal

# Outline

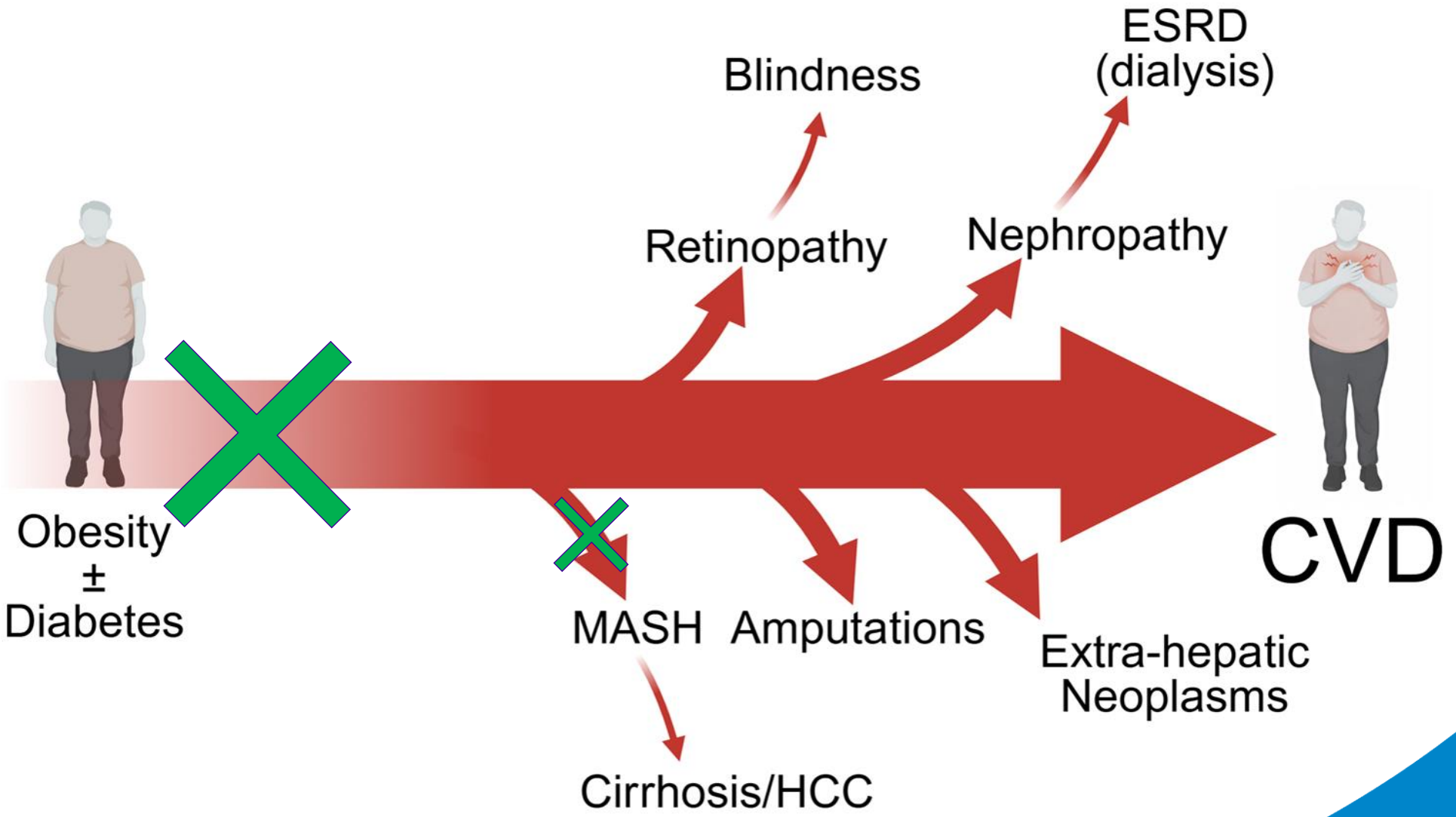
- MASH as a systemic condition that requires systemic therapy.
- GLP-1RA in MASH: Weight-dependent or weight independent?
- Considerations for the successful use of GLP-1RA in MASH.
- Pharmacological options beyond GLP-1RAs and resmetirom.

# MASLD is a systemic disease



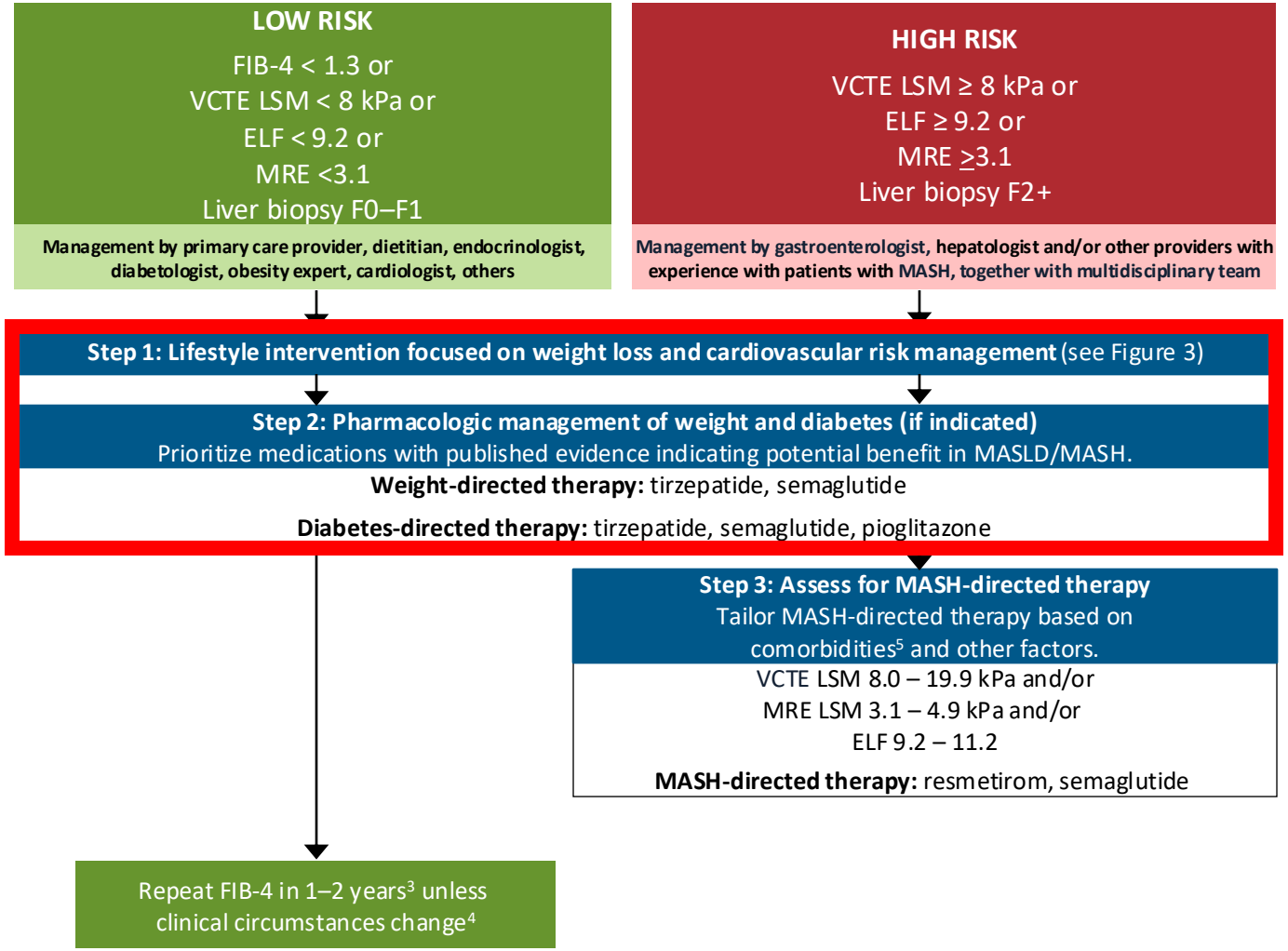

Bril F. Lipotoxicity figure. Zenodo. 2025. doi:10.5281/zenodo.16294108.

# MASLD is tightly related to insulin resistance

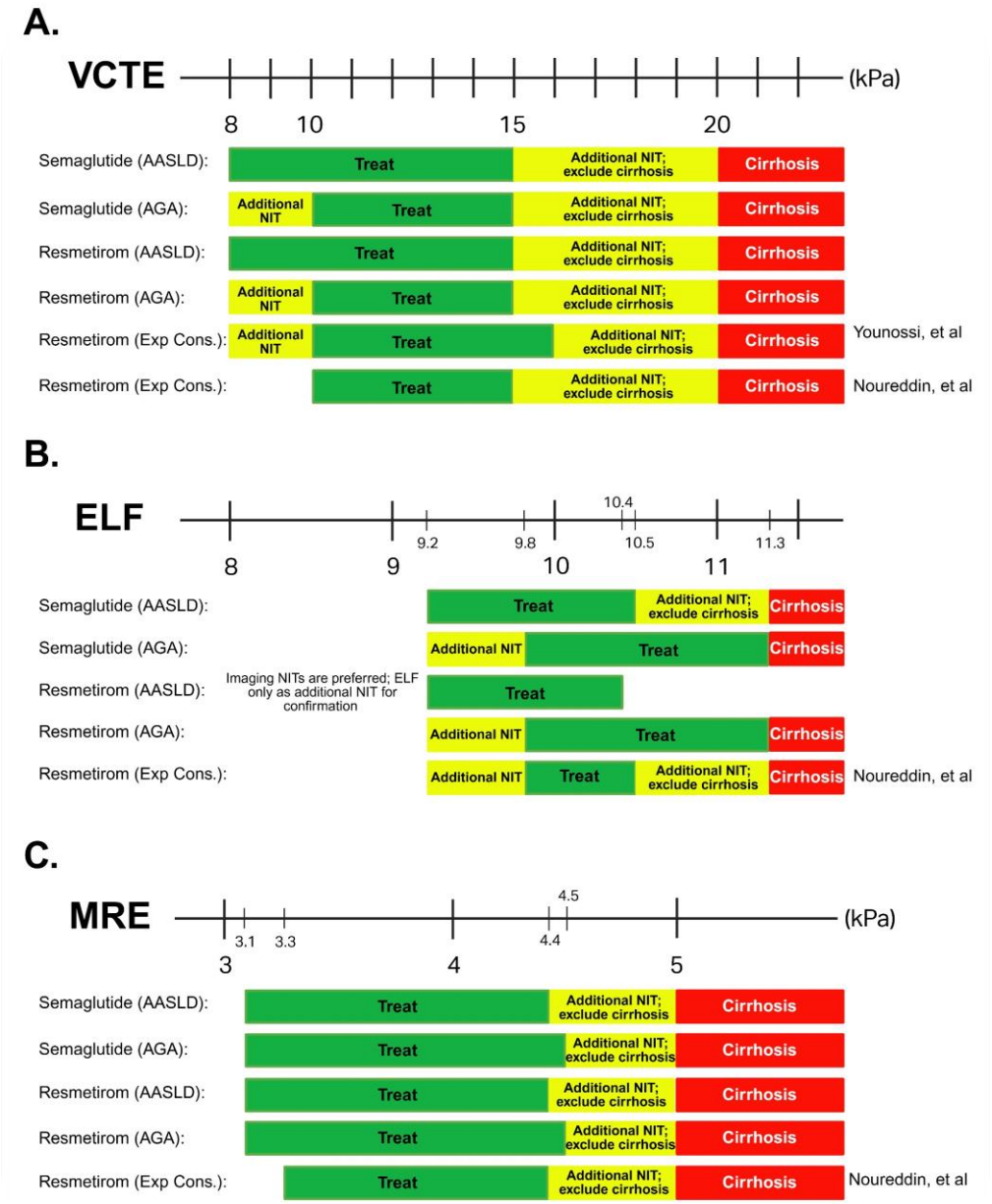



Bril, F. (2026). Fates of Obesity and T2D.
Zenodo. https://doi.org/10.5281/zenodo.18190420

# That principle aligns with updated Clinical Care Pathways



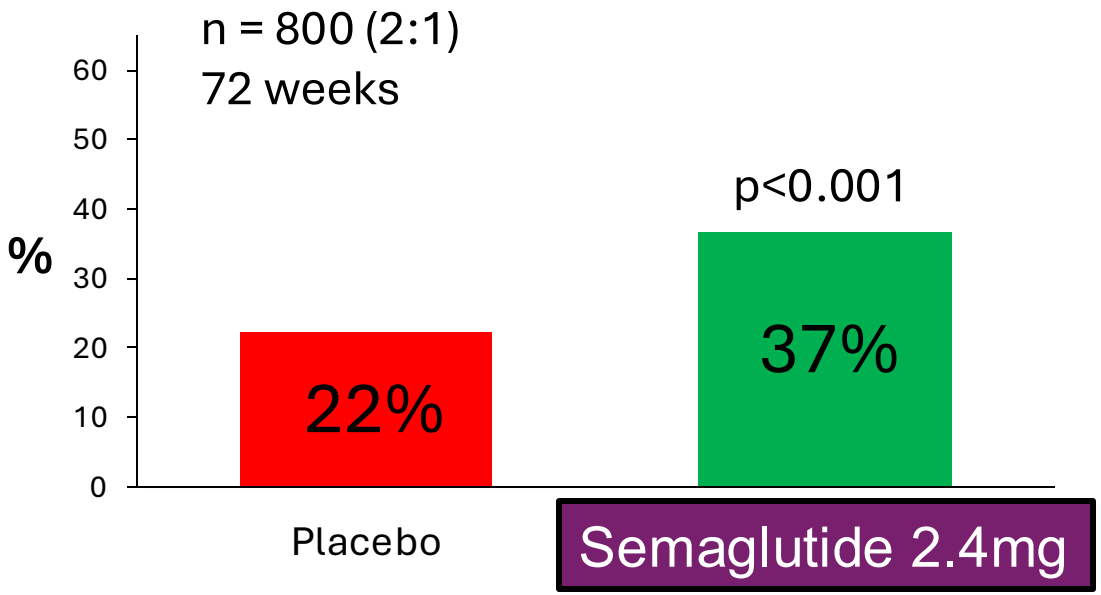

Kanwal F, Bril F, Wong VW, et al. Gastroenterology 2026:S0016-5085(26)00198-8.




Bril F. Diabetes Obes Metab. 2026;28(Suppl 2):63-80.

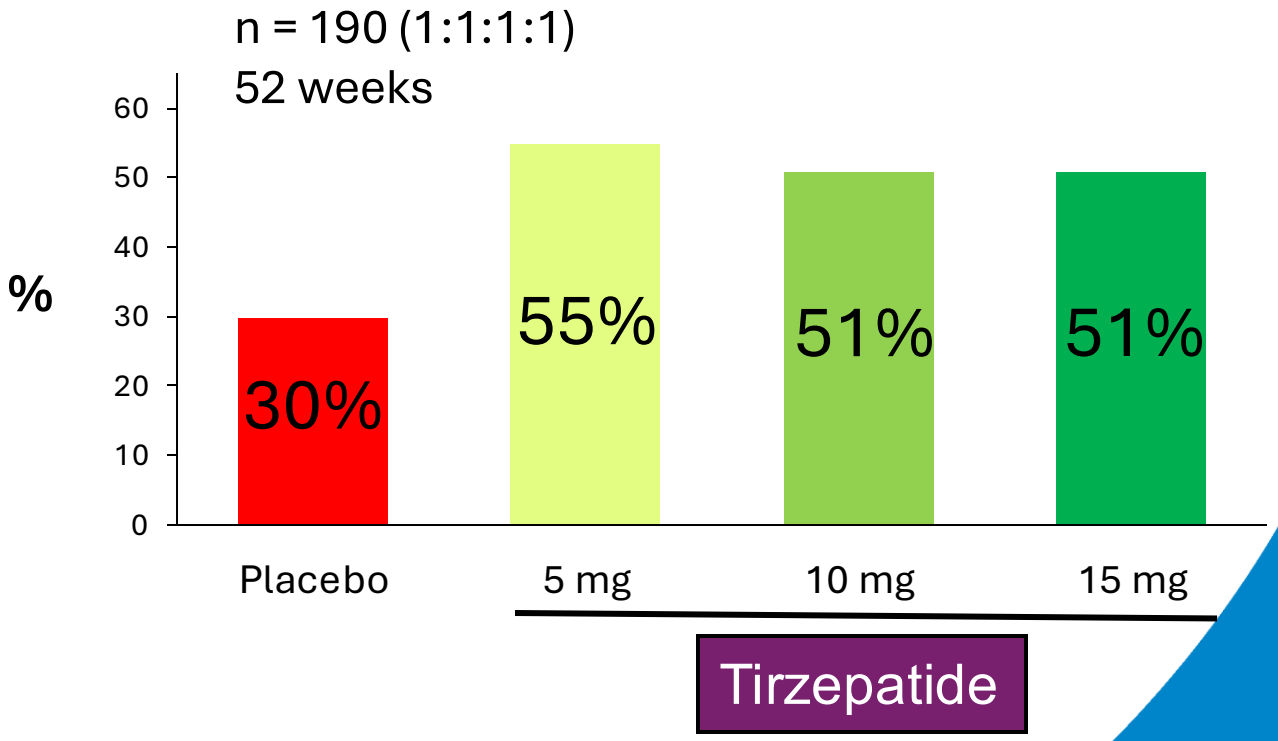
# GLP-1RAs in MASH

## ESSENCE (Phase 3)




-8.5%

## SYNERGY-NASH (Phase 2)



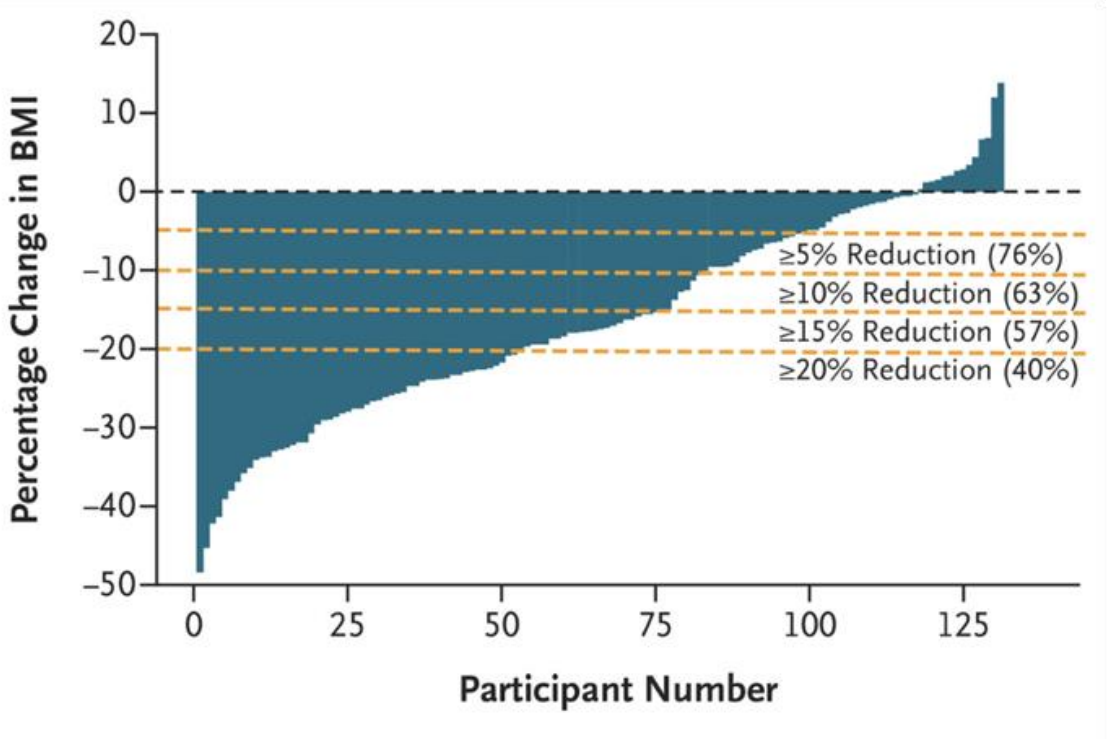

-9.9% -12.5% -14.8%

Sanyal et al. NEJM 2025;392:2089-2099; Loomba et al. NEJM 2024;391:299-310.

# GLP-1RAs in MASH: Dose

## STEP TEENS

N Engl J Med 2022;387:2245-2257.




## SURMOUNT-1 trial

N Engl J Med 2022;387:205-216.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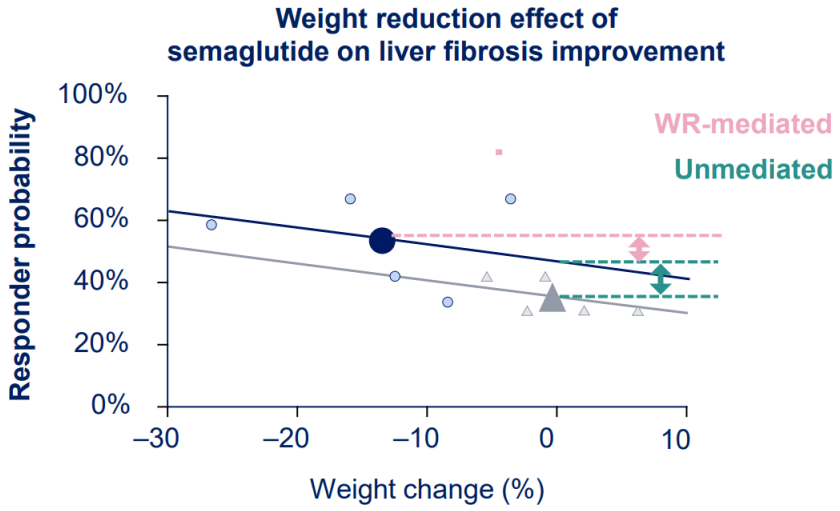
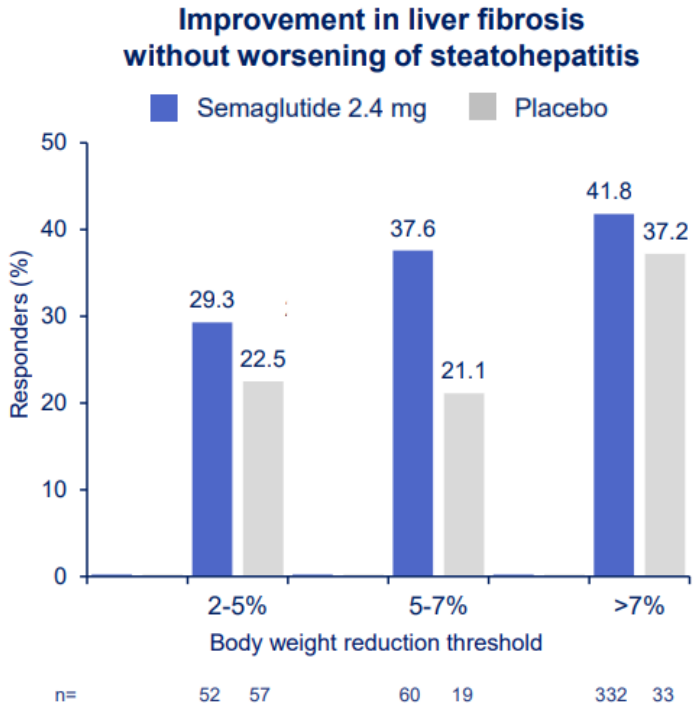
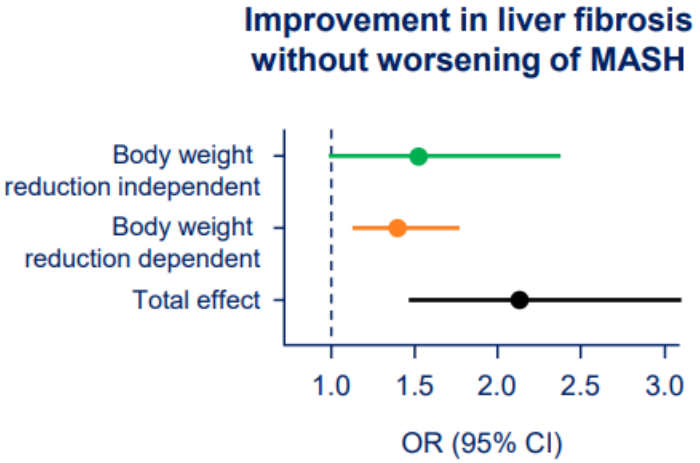
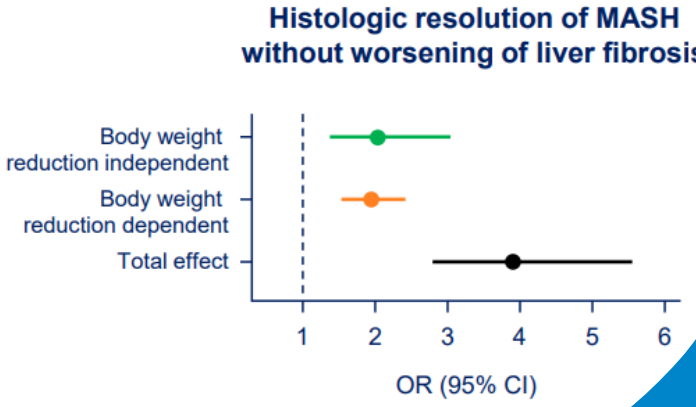
# GLP-1RAs in MASH: Weight Dependent?




Jara et al. Nat Med 2025;31:3128-3140; Newsome et al. AASLD 2025.

# GLP-1RAs in MASH: Weight Dependent?

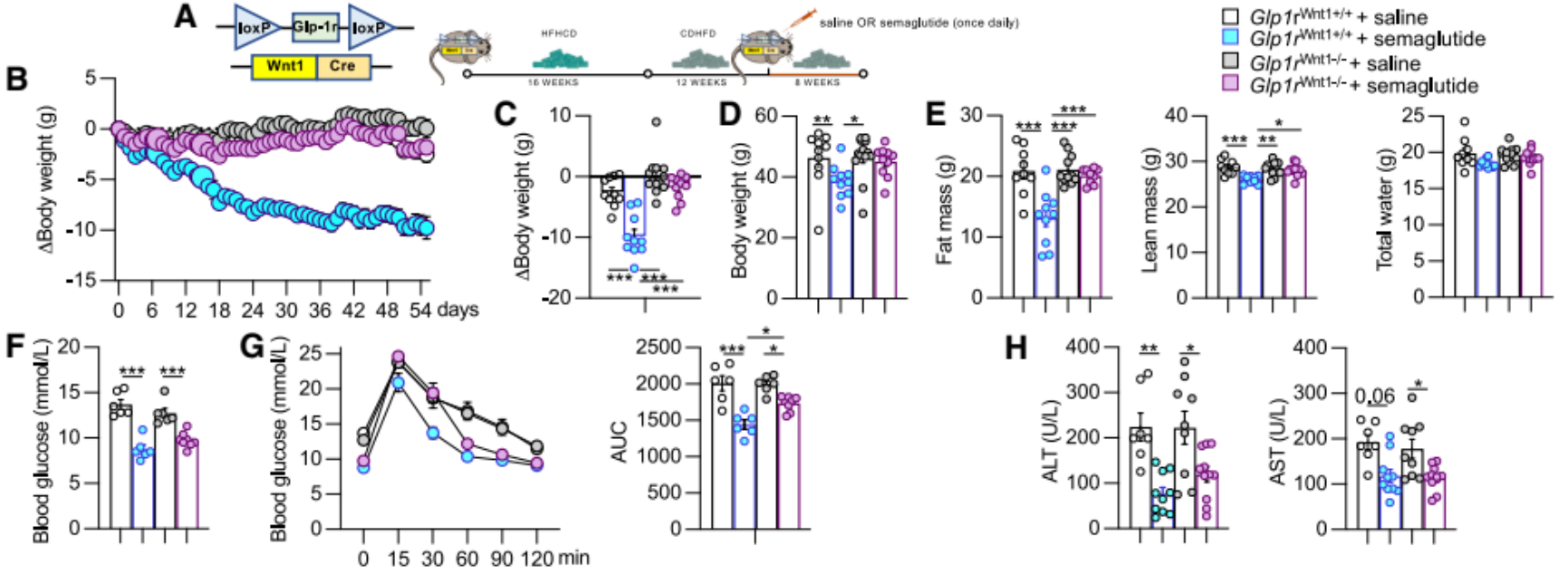
If the relationship was simple…

# GLP-1RAs in MASH: Weight Dependent?

Article

Cell Metabolism

**The weight-loss-independent hepatoprotective benefits of semaglutide are orchestrated by intrahepatic sinusoidal endothelial GLP-1 receptors**




Gonzalez-Rellan MJ, et al. Cell Metab. 2026:S1550-4131(26)00105-1.

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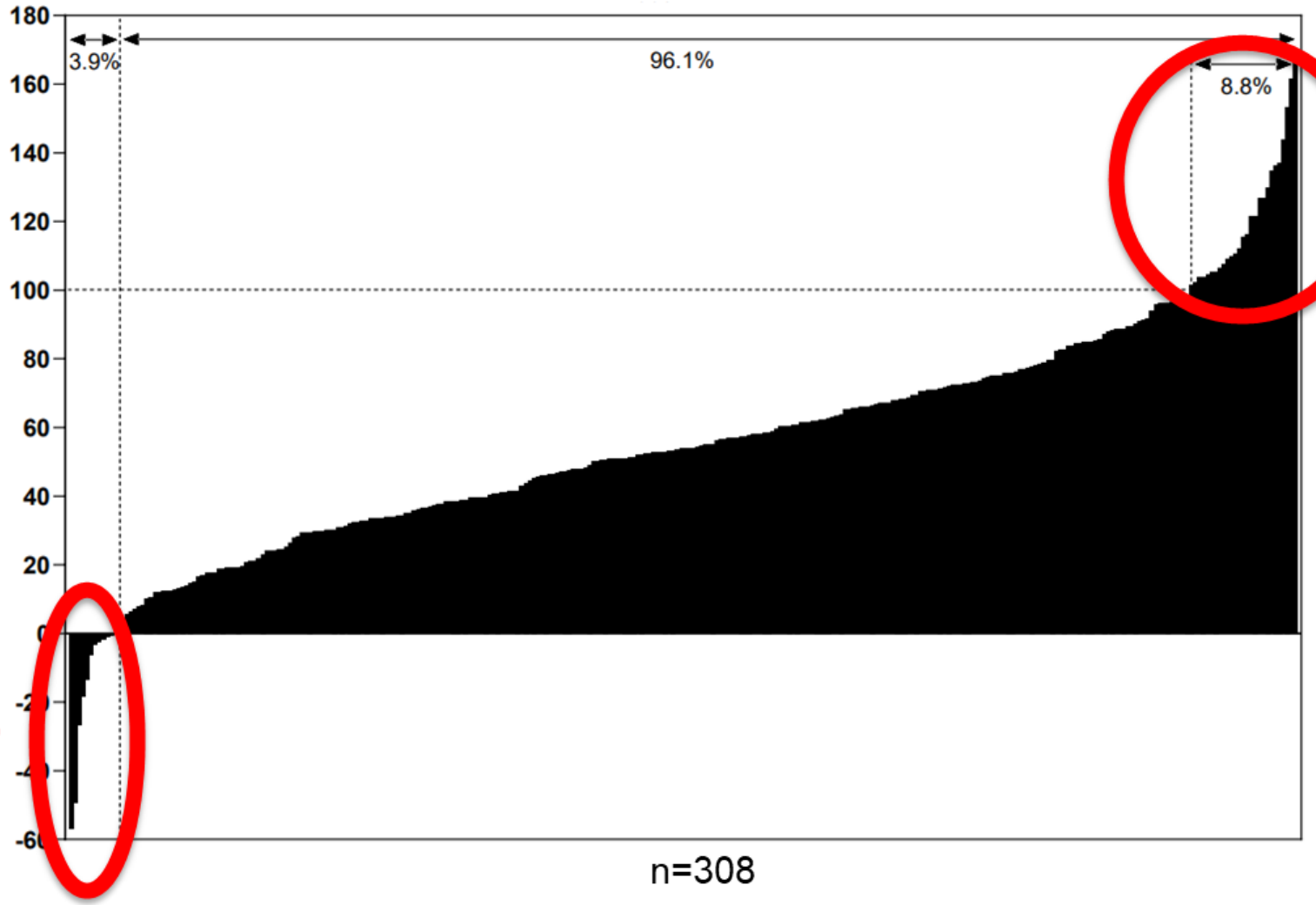
# GLP-1RAs in MASH: Duration

## SURMOUNT-4 trial post-hoc analysis

JAMA. 2024;331:38-48.




% Weight regain from weeks 36 to 88 (1 year) in those achieving ≥10% weight reduction

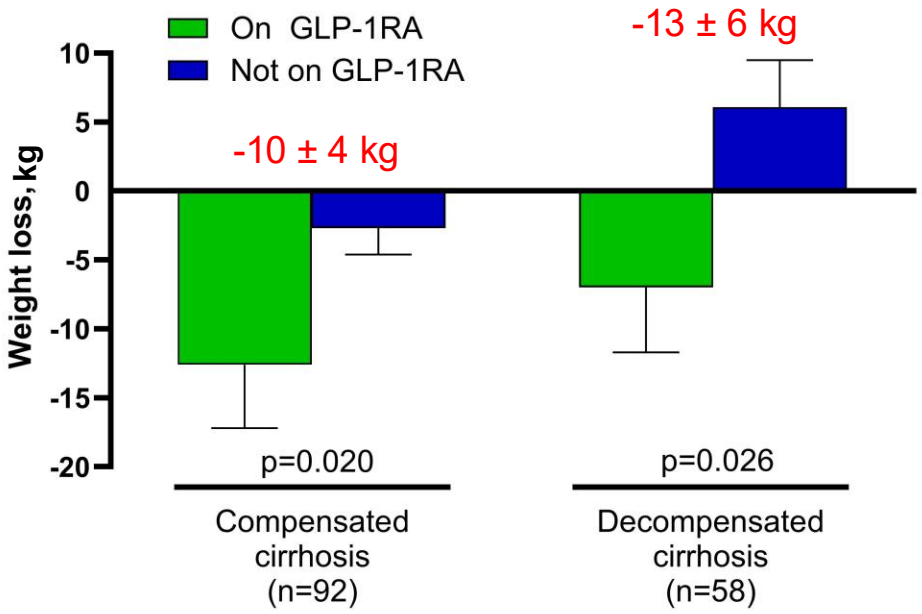
Further weight loss (3.9%)

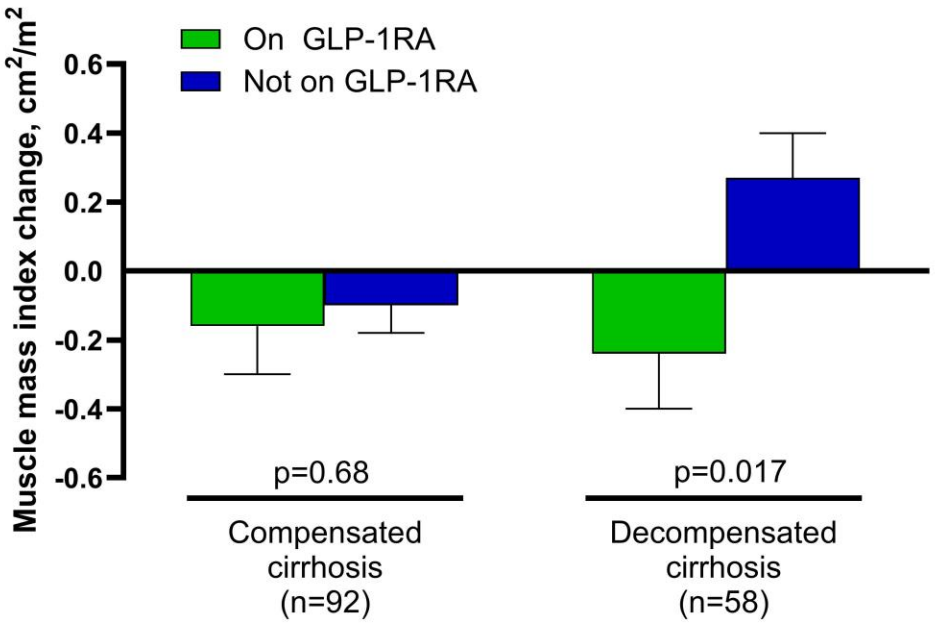
Rebound (8.8%)

# GLP-1RAs in MASH: Side effects

- GI symptoms. Not as bad tolerated as reported. Discontinuation rates are given by costs/insurance.
- Pancreatitis? No association vs. small risk.
- Neuroendocrine tumors?
- Thyroid cancer. In rodents GLP-1RA are associated with medullary thyroid cancer (very rare).
- Bone turnover/Sarcopenia
- Retinopathy 2/2 A1c reduction. Nonarteritic anterior ischemic optic neuropathy (Cai CX, et al. JAMA Ophthalmol. 2025).

# GLP-1RA and Risk of Sarcopenia




Compensated cirrhosis – No GLP-1RA: β=0.0167, p=0.091
Compensated cirrhosis – GLP-1RA: β=0.0240, p=0.072
Decompensated cirrhosis – No GLP-1RA: β=0.0190, p=0.124
**Decompensated cirrhosis – GLP-1RA: β=0.0553, p<0.001**

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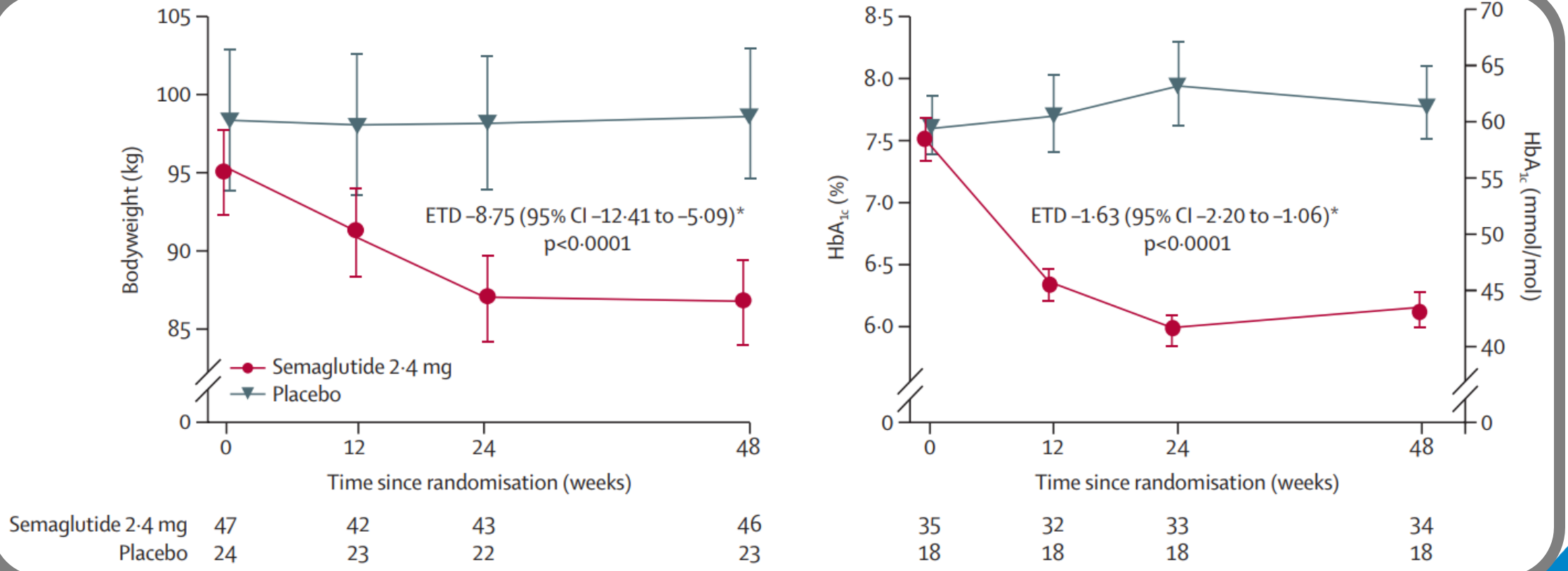
Edwards D, et al. Presented at DDW 2026.

# Effect of Semaglutide in Compensated Cirrhosis



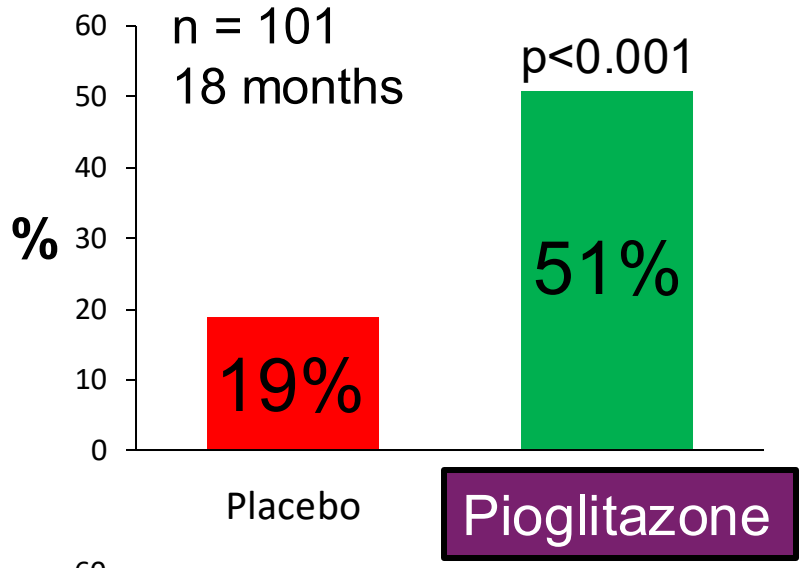

| | | | | |
|---|---|---|---|---|
| Semaglutide 2·4 mg | 47 | 42 | 43 | 46 |
| Placebo | 24 | 23 | 22 | 23 |

| | | | | |
|---|---|---|---|---|
| Semaglutide 2·4 mg | 35 | 32 | 33 | 34 |
| Placebo | 18 | 18 | 18 | 18 |

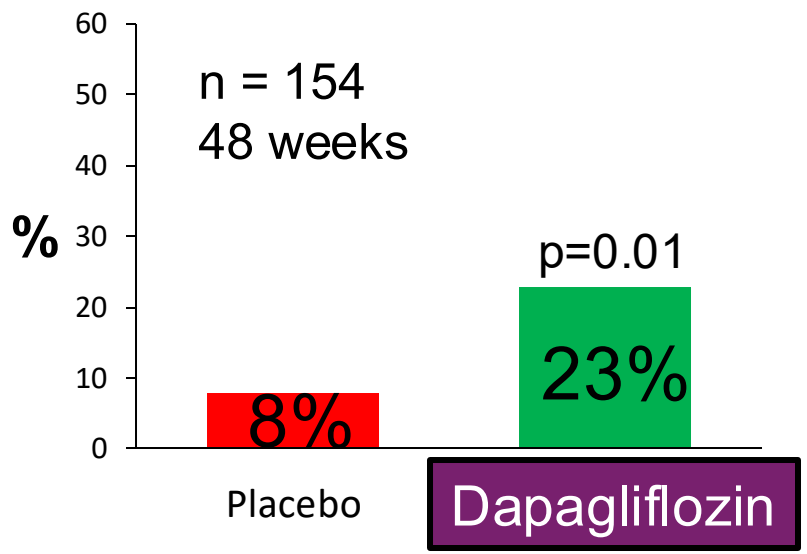
No histological improvement in MASH or liver fibrosis.

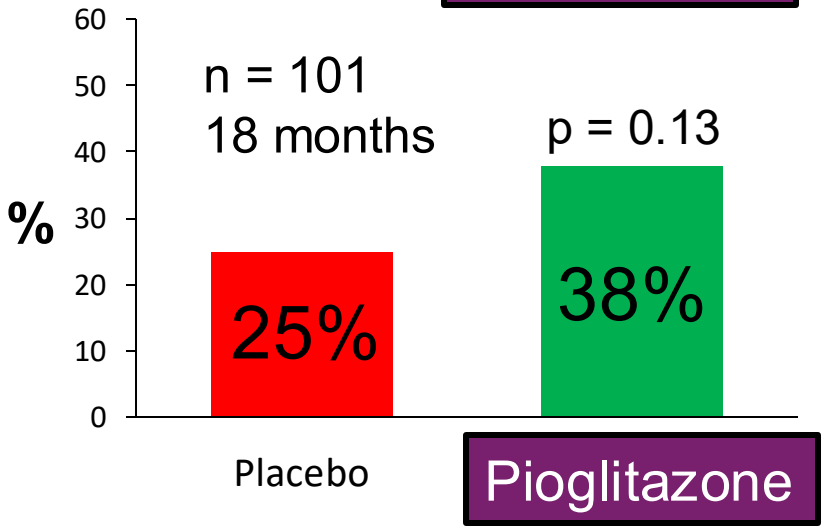
Loomba R, et al. Lancet Gastroenterol Hepatol. 2023;8(6):511-522.

# Glucose-lowering agents in MASH

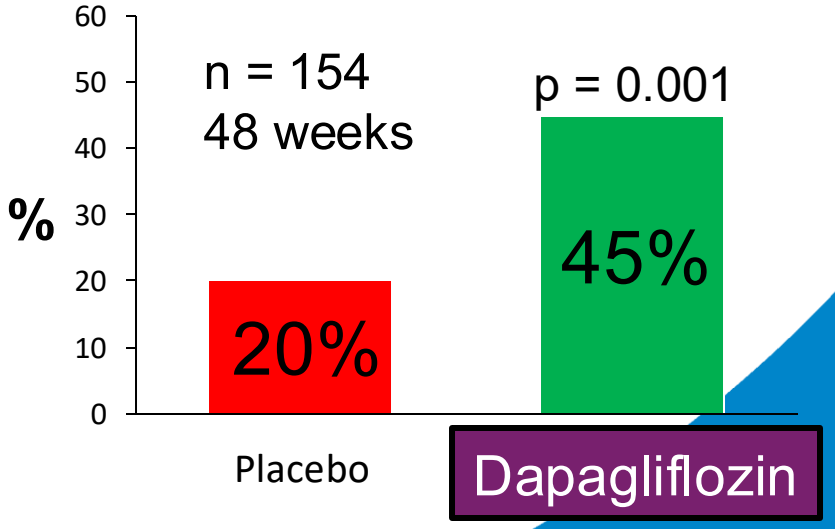



Resolution of MASH




Improvement in fibrosis

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Cusi et al. Ann Intern Med 2016; Lin et al. BMJ 2025.

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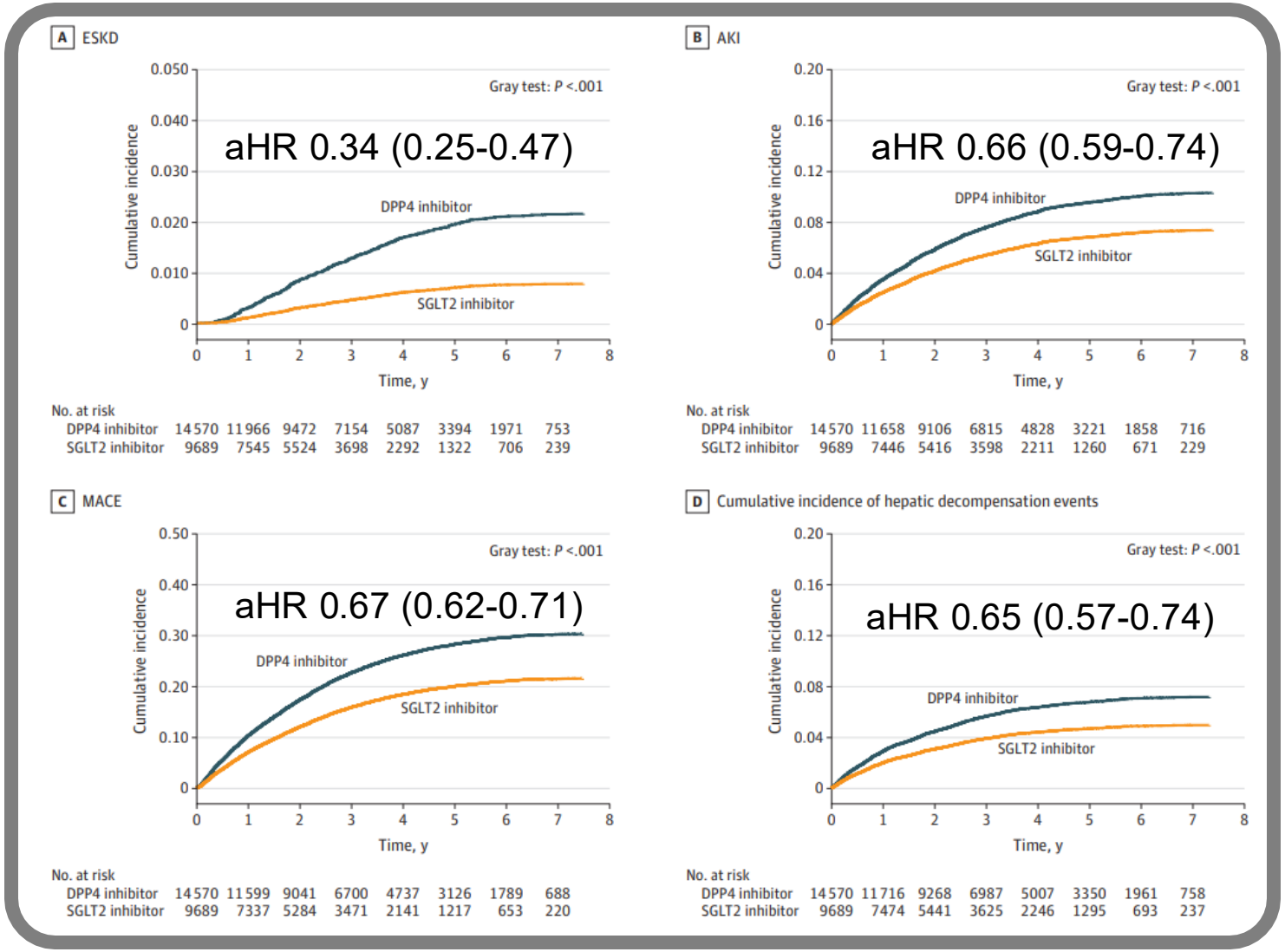
# Effect of SGLT-2i in Compensated Cirrhosis




Retrospective cohort study from NHIRD, Taiwan, 2016-2023

Chung MC, et al. JAMA Netw Open. 2026;9(2):e2560429

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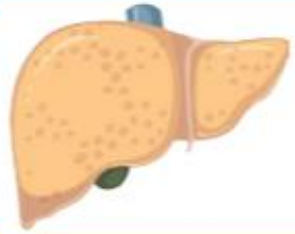
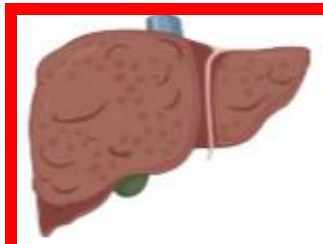
## Individualize care, targeting the following:

- Adoption of a healthy lifestyle
- Weight loss (if indicated)
- Optimal diabetes management
- Cardiovascular risk reduction
- Need for metabolic surgery

**MASLD**

| |  | Obesity pharmacotherapy | Diabetes pharmacotherapy | MASH pharmacotherapy |
|---|---|---|---|---|
| **MASLD with F0-F1** | | Prefer GLP-1RA, dual GIP and GLP-1 RA | Prefer GLP-1RA, dual GIP and GLP-1 RA, pioglitazone, SGLT2i | Not indicated |
| **MASLD with F2-F3 ("at risk" MASH)** |  | Prefer GLP-1RA, dual GIP and GLP-1 RA | Prefer GLP-1RA, dual GIP and GLP-1 RA, pioglitazone ± SGLT-2 inh | Resmetirom, GLP-1RA[a] |
| **Compensated cirrhosis** |  | As with F2/F3 with caution* | As with F2/F3 with caution* | AVOID |
| **Decompensated cirrhosis** |  | AVOID | Only use insulin | AVOID |

Cusi K, et al. Diabetes Care. 2025;48(7):1057-1082.

# *'Metabolic cocktail'*

**Semaglutide / Tirzepatide**

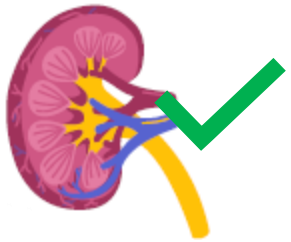
**Pioglitazone**

**SGLT-2 inhibitors**

Prevents fluid retention and weight gain with pio

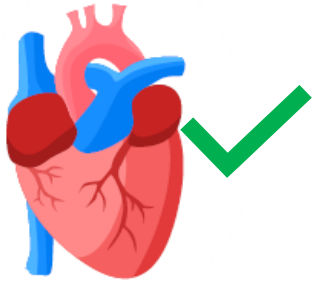
Prevents weight gain with pio

**Metformin**



**ACE inh**

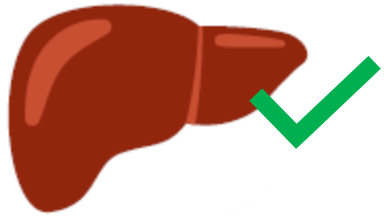
**Finerenone**



**Statins**

**ACE inh**

**B-b**



**Resmetirom**

# Conclusions

- Early identification of MASH is essential to introduce effective pharmacological therapy
- PCPs have a central role in managing these patients
- This includes CV risk management and introducing medications with known metabolic benefits.