CMEO Snack

Welcome to the Glow-Up* Era of MASH Management

*Modern term meaning “dramatic, positive change"

Supported by an educational grant from Novo Nordisk Inc.

CMEO Snack 4

GLP1s Got That Rizz*: The Future of MASH and Metabolic Syndrome Care

*Modern term (short for charisma) meaning “cool confidence and style"

Monica Tincopa, MD, MSc

Assistant Professor, Department of Medicine
Division of Gastroenterology & Hepatology
UCSD Health
San Diego, California

Monica Tincopa, MD, MSc

Assistant Professor, Department of Medicine
Division of Gastroenterology & Hepatology
UCSD Health
San Diego, California

Naim Alkhouri, MD

Chief Medical Officer
Summit Clinical Research
Director of Research
Clinical Research Institute of Ohio (CRIOH)
Director of the Steatotic Liver Program
North Shore Gastroenterology
Cleveland, Ohio

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LEARNING OBJECTIVE

Evaluate the potential role of GLP-1 RAs in the future treatment of MASH and other components of the metabolic syndrome

Comorbidities in MASH and MASH Prevalence in Biopsied Patients with MASLD (by Global Region)

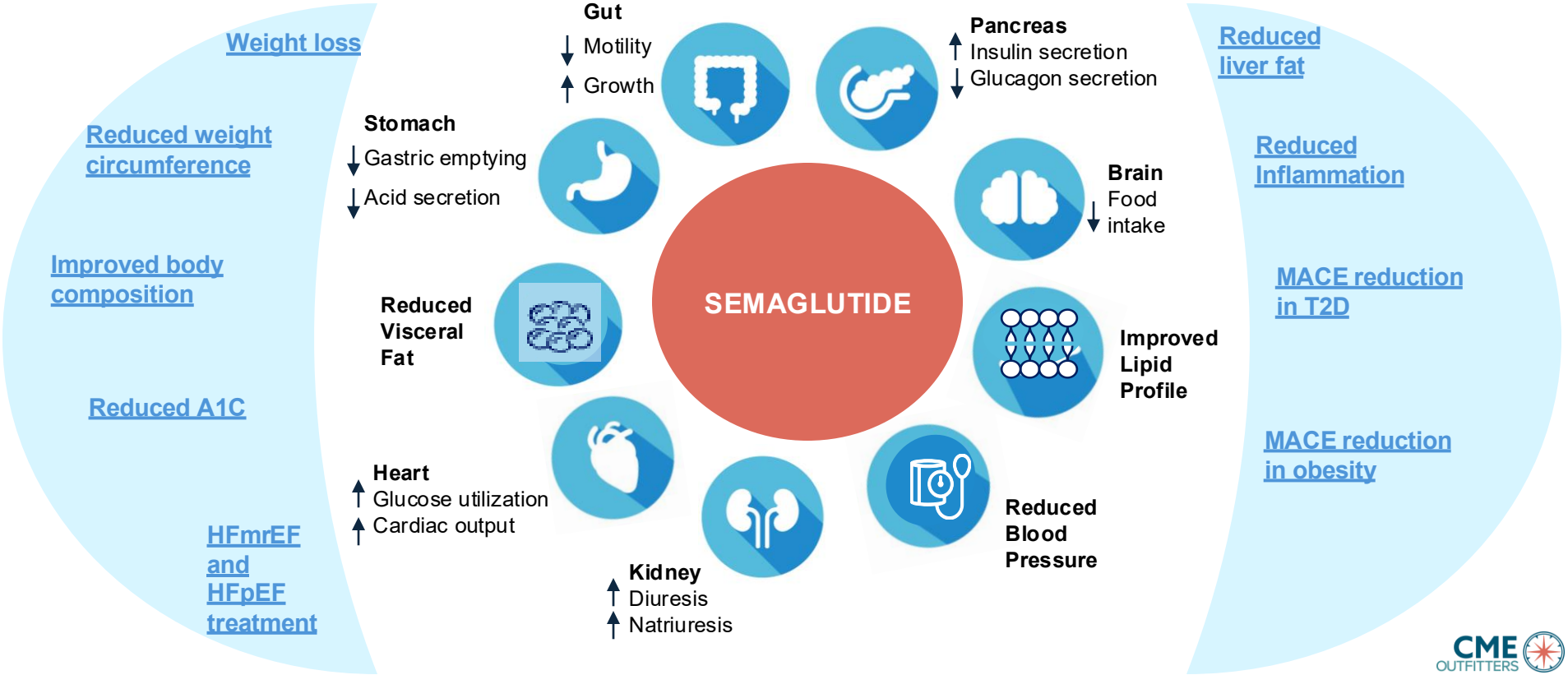
Comorbidity	Continent and Referral Status	N	Prevalence, %		95% CI, %	I^2 (%)
Obesity	Europe, referral	1	89.19		(74.51–95.88)	NA
	North America, random or voluntary	1	80.00		(64.83–89.67)	NA
	Oceania, referral	1	95.24		(82.86–98.81)	NA
	South America, referral	1	45.45		(26.47–65.86)	NA
	Overall	4	81.83	82%	(55.16–94.28)	84.80
Diabetes	Europe, referral	1	2.78		(0.17–32.21)	NA
	North America, random or voluntary	1	25.00		(14.01–40.54)	NA
	North America, referral	5	54.09		(37.26–70.04)	96.10
	Oceania, referral	1	35.71		(22.81–51.08)	NA
	South America, referral	1	36.36		(19.34–57.67)	NA
	Overall	9	43.63	44%	(30.28–57.98)	93.29
Hyperlipidemia	North America, referral	1	83.07		(79.92–85.81)	NA
	Oceania, referral	1	61.90		(46.57–75.18)	NA
	South America, referral	1	63.64		(42.33–80.66)	NA
	Overall	3	72.13	72%	(54.59–84.78)	86.63
Hypertriglyceridemia	North America, referral	1	83.33		(36.87–97.72)	NA
	Overall	1	83.33	83%	(36.87–97.72)	NA
Metabolic syndrome	North America, referral	2	70.65		(54.64–82.79)	89.54
	Overall	2	70.65	71%	(54.64–82.79)	89.54
Hypertension	North America, random or voluntary	1	77.50		(62.12–87.86)	NA
	North America, referral	3	65.56		(51.53–77.32)	89.64
	Overall	4	67.97	68%	(56.31–77.74)	85.26

CME OUTFITTERS

CI = confidence interval; MASH = metabolic dysfunction-associated steatohepatitis; MASLD = metabolic dysfunction-associated steatotic liver disease; NA = not applicable.

Younossi ZM, et al. *Hepatology.* 2016;64(1):73-84.

Semaglutide: Cardiometabolic Benefits



HF = heart failure; MACE = major adverse cardiovascular event; T2D = type 2 diabetes.
Adapted from Natale F, et al. *J Cardiovasc Dev Dis.* 2024;11(5):145.

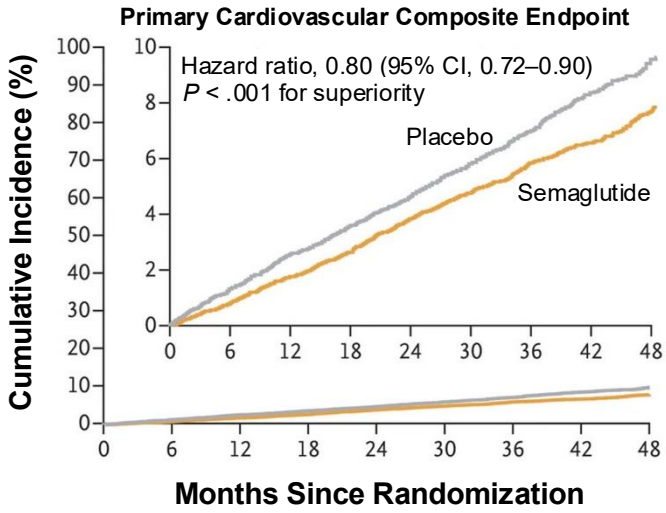
Audience Response

In the SELECT trial, semaglutide 2.4 mg once weekly was studied in adults with overweight or obesity and established cardiovascular disease (without diabetes). Which of the following extra-hepatic benefits was NOT observed with semaglutide?

A. Reduction in risk of all-cause death
B. Reduction in risk of developing kidney disease
C. Reduction in risk of hospitalization for hemorrhagic stroke
D. Reduction in risk of developing diabetes
E. I don’t know

Semaglutide: Insights from the SELECT Trial

Semaglutide and CVD Outcomes Obesity No Diabetes



20% RRR

BMI >27
Prior CVD

The SELECT trial indicated further benefits with semaglutide 2.4 mg versus placebo

19% RRR	Risk of all-cause death
22% RRR	Risk of developing kidney disease
73% RRR	Risk of developing diabetes
21% RRR	Risk of hospitalization/urgent HF visit

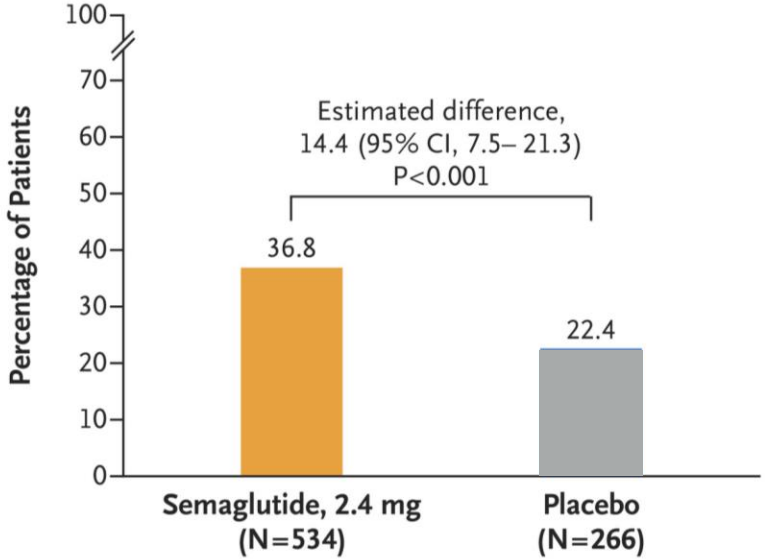
Semaglutide 2.4 mg significantly reduces the risk of MACE versus placebo; both added to standard of care for CV risk factor management over a mean follow-up period of ~40 months.

BMI = body mass index; RRR = relative risk reduction.

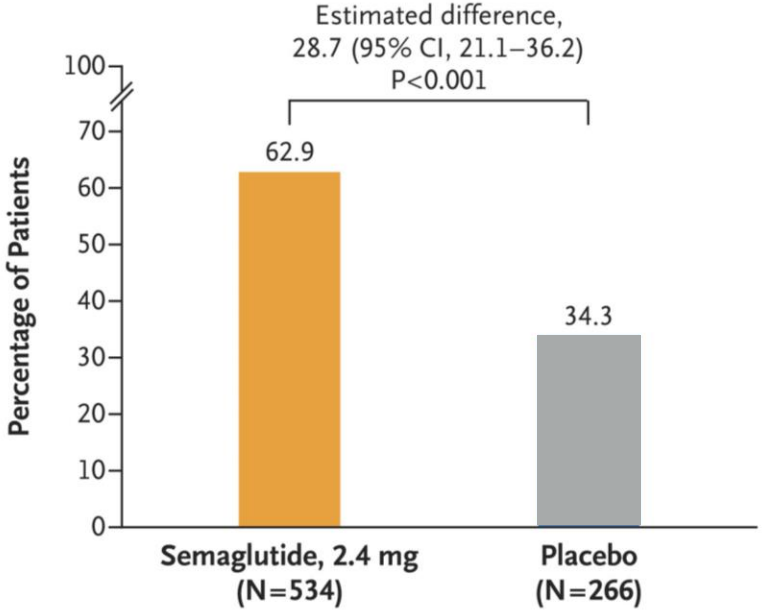
Lincoff AM, et al. *N Engl J Med*. 2023;389(24):2221-2232. Kahn SE, et al. *Diabetes Care*. 2024;47(8):1350-1359. Phizackerley D. *BMJ*. 2024;384:q53.
Plutzky J, et al. Presented at ECO 2025; Malaga, Spain; May 11-14, 2025.

Semaglutide: Insights from the ESSENCE Trial

Reduction in Liver Fibrosis with No Worsening of Steatohepatitis

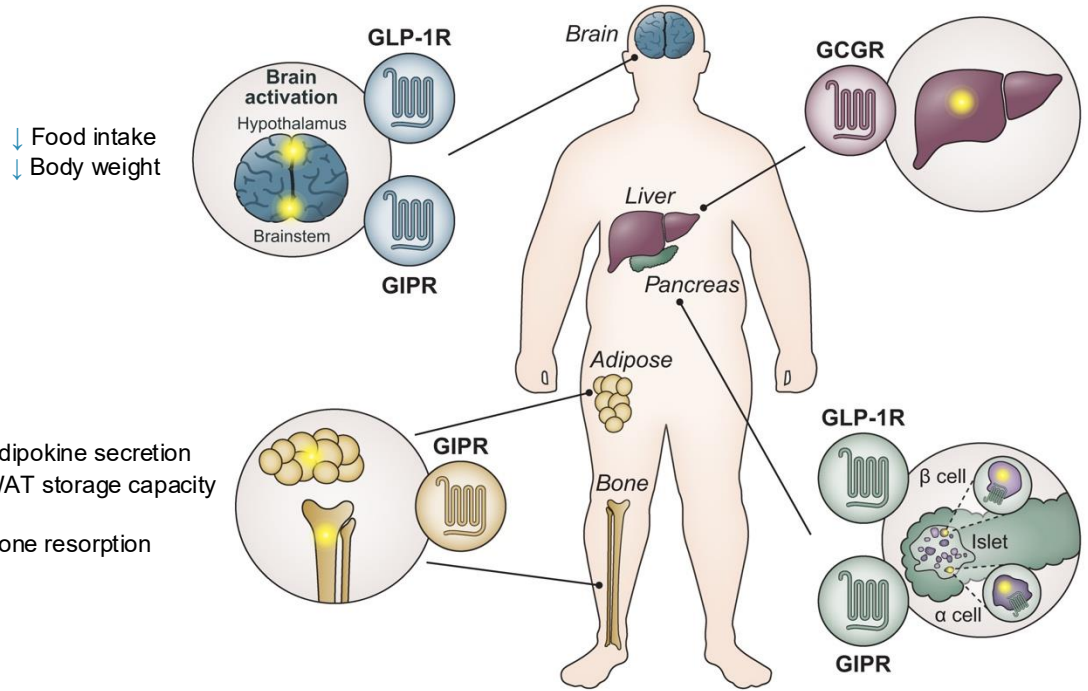


Resolution of Steatohepatitis with No Worsening of Liver Fibrosis



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

GLP-1 RAs and Dual/Triple Agonists: Major Modes and Sites of Action



PKA/PLC phosphorylation
- ↑ Mitochondrial turnover
- ↑ Mitochondrial function
- ↓ Oxidative stress

PKA phosphorylation
- ↓ Glycogen synthesis
- ↑ Gluconeogenesis
- ↓ Lipogenesis
- ↓ Steatosis
- ↓ Inflammation
- ↓ Stellate cell activation
- ↓ Fibrosis

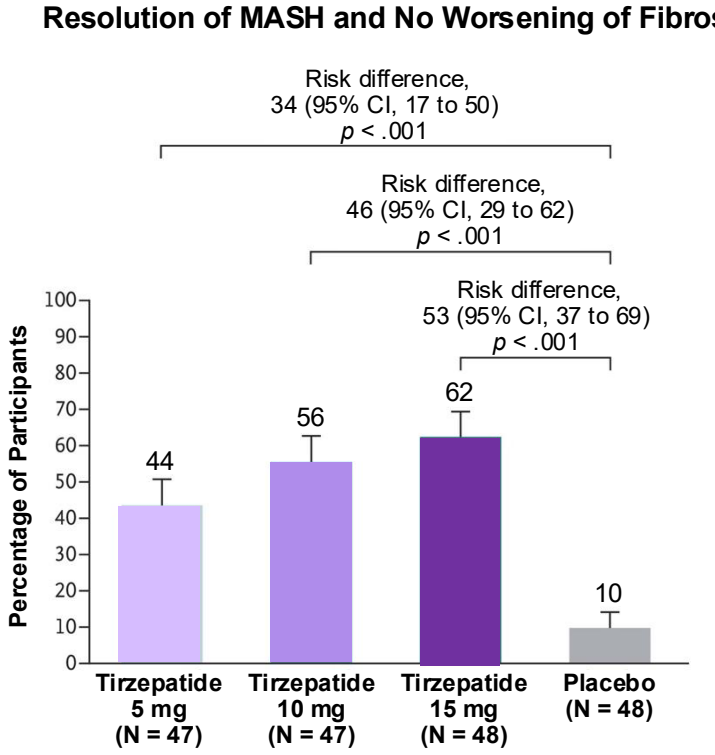
↑ Insulin secretion (high glucose)

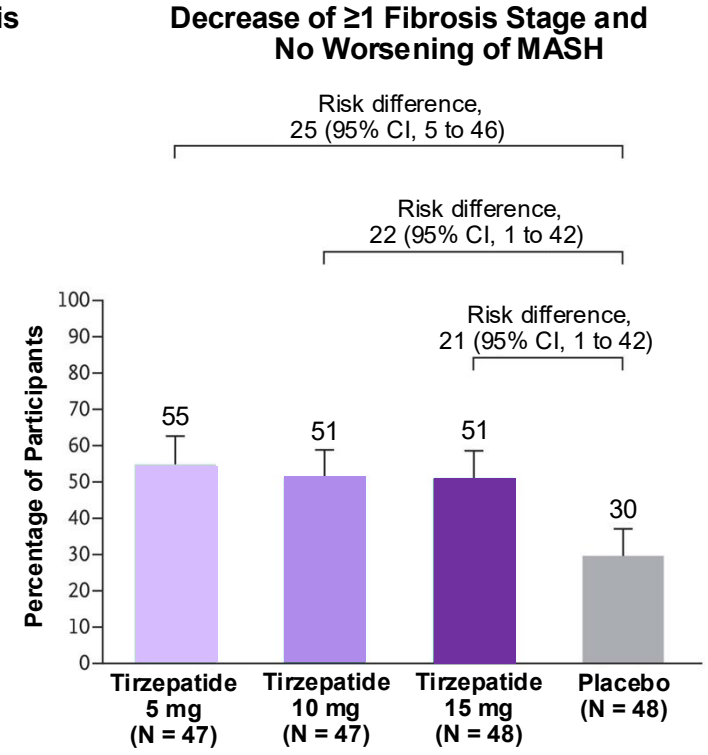
↑ GCG secretion (low glucose)
↑ Insulin secretion (high glucose)

Incretin/Trial Phase
GLP-1RA Semaglutide Phase III (ESSENCE)
GLP-1RA/GIP Tirzepatide Phase IIb (SYNERGY-NASH) Tirzepatide and retatrutide Phase III (SYNERGY-OUTCOMES)
GCGR/GLP-1RA Survodutide Phase IIb (1404-0043) Survodutide Phase III (LIVERAGE)
GLP-1 and glucagon receptors dual agonist Efinopegdutide NCT0682112

Newsome PN, Ambery P. *J Hepatol*. 2023;79(6):1557-1565. Loomba R, et al. *N Engl J Med*. 2024;391:299-310. Sanyal AJ, et al. *N Engl J Med*. 2024;391(4):311-319.

Tirzepatide for MASH with Liver Fibrosis

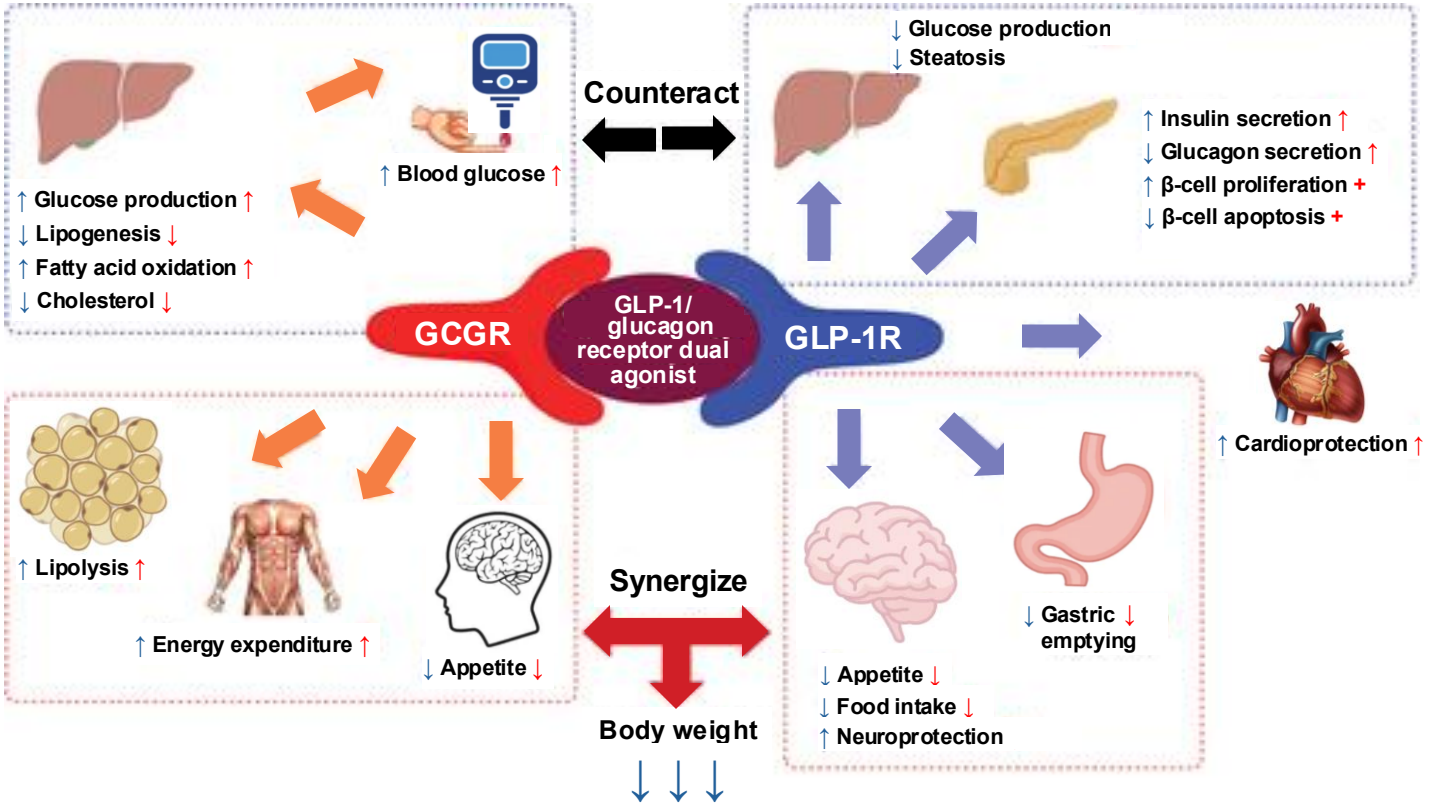




In patients with MASH and moderate or severe fibrosis, tirzepatide for 52 weeks was more effective than placebo in resolving MASH without worsening of fibrosis.

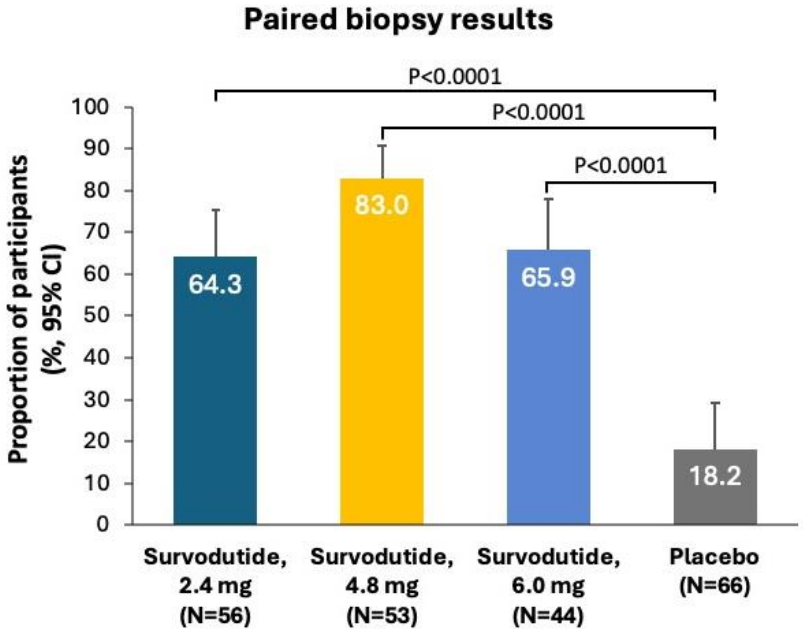
Adapted from Loomba R, et al. *N Engl J Med.* 2024;391:299-310.

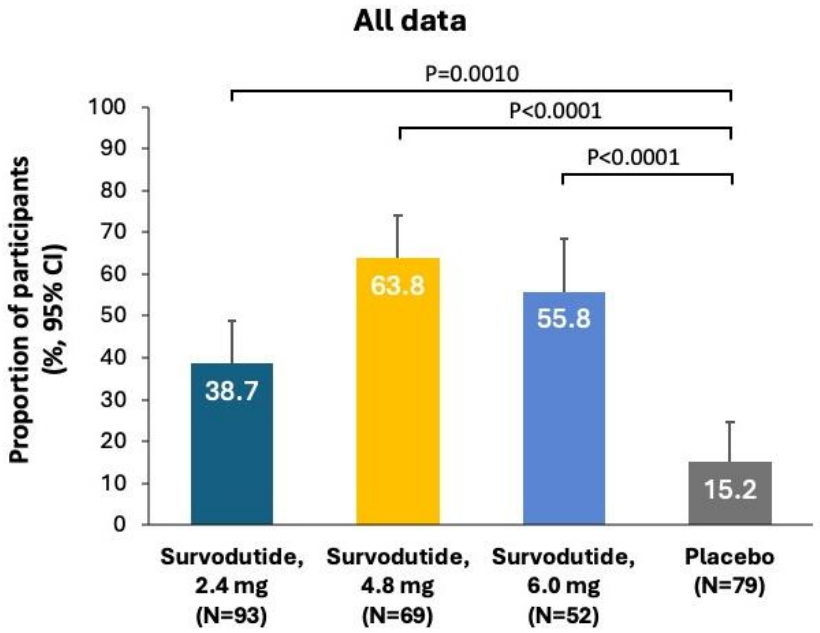
GLP-1R/GCGR Dual Agonism Affects the Liver Through Multiple Direct and Indirect Mechanisms



Lu W, et al. *Expert Opin Ther Pat*. 2023;33(9):597-612.

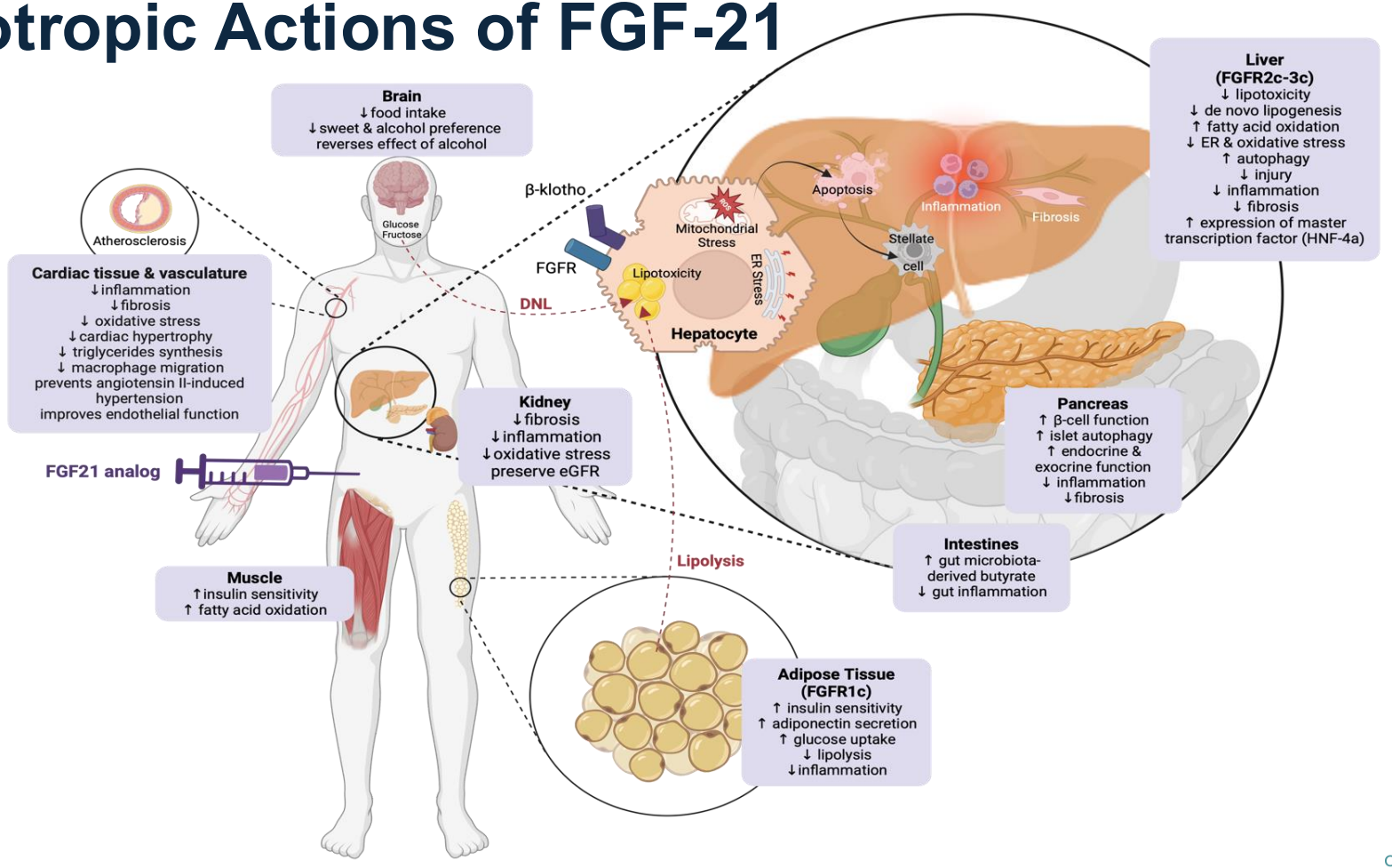
Improvement in MASH: Survodutide at Week 48 (F1–F3)





Sanyal AJ, et al. *N Engl J Med*. 2024;391:311-319. Sanyal AJ, et al. *J Hepatol*. 2024;80(S1):S4-S5.

Pleiotropic Actions of FGF-21

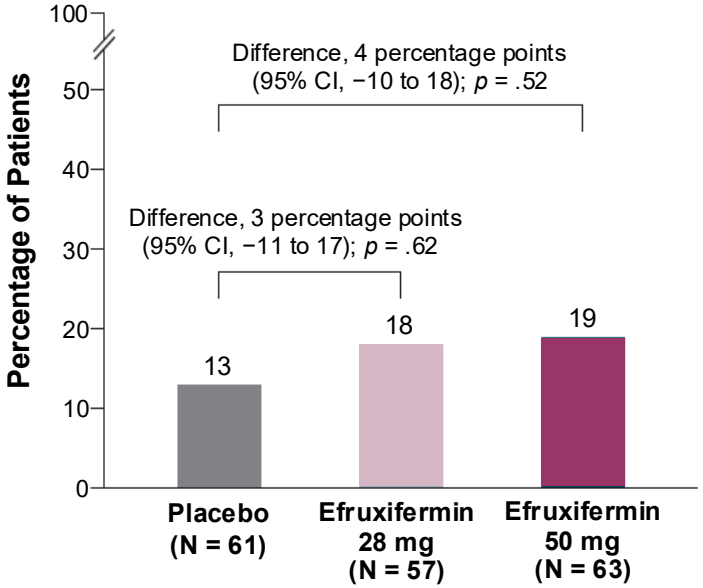


FGF-21 = fibroblast growth factor 21.

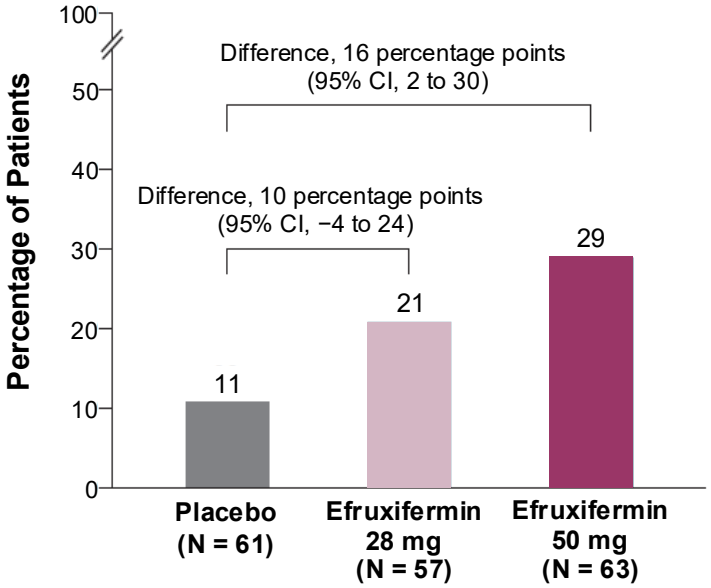
Harrison SA, et al. *J Hepatol*. 2024;81(3):562-576.

EFX

Reduction in Fibrosis of ≥1 Stage Without MASH Worsening at Week 36



Reduction in Fibrosis of ≥1 Stage Without MASH Worsening at Week 96



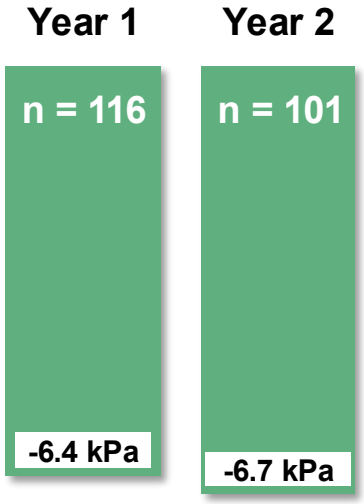
Shown is the percentage of patients with a reduction in fibrosis without a worsening of MASH at week 36, primary outcome (figure on left), and at week 96, a secondary outcome (figure on right). MASH worsening was defined as an increase from baseline in any of the subscores of the nonalcoholic fatty liver disease (NAFLD) activity score (NAS): ballooning, inflammation, and steatosis. Data are provided as the mean for the trial group and least-squares-mean difference for the comparison between efruxifermin and placebo with a 95% CI. Confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive effects of efruxifermin.

EFX = efruxifermin.

Noureddin M, et al. *N Engl J Med*. 2025;392:2413-2424.

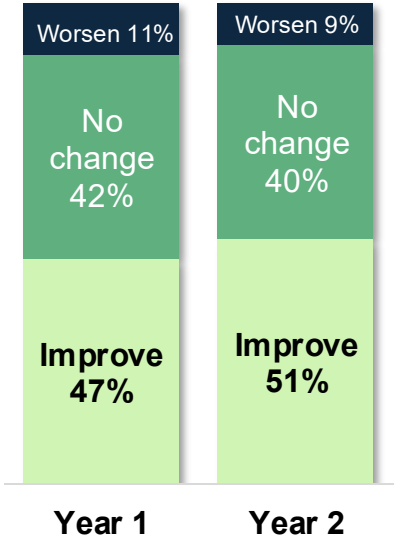
Sustained Reductions in Liver Stiffness (LSM) After 2-Year Treatment with Resmetirom

Mean Change from Baseline in VCTE

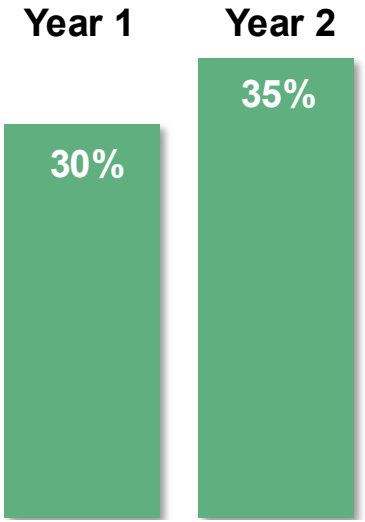


Statistically significant compared to baseline*

Percentage with 25% Change from Baseline in VCTE



Percentage with Conversion from F4 to consistent with F3*



After 2 years on resmetirom, >50% of patients achieved sustained ≥25% reduction in LSM by VCTE

*Patients with confirmed F4 at baseline (liver biopsy F4 and/or platelets <140/MRE ≥5 with VCTE ≥15) showed a transition from F4 to potential F3 at year 2 (VCTE<15 and ≥25% decrease from baseline)

*Year 1: -6.4 (-9.2, -3.7) kPa; Year 2: -6.7 (-9.4 ,-4.1) kPa (95% CIs). Panel 3 analyzed patients with both 1- and 2-year data.
VCTE = vibration controlled transient elastography.
Alkhouri N, et al. *J Hepatol*. 2025;82:S9-S10.

Faculty Discussion

Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

Within the next 3 months:

- *Apply evidence-based insights from pivotal MASH trials to identify appropriate patient profiles for emerging therapies*
- *Differentiate at least three major classes of emerging agents for MASH—including thyroid hormone receptor β agonists, FGF-21 analogs, and dual incretin or glucagon co-agonists—by their mechanism of action and key clinical trial evidence*
- *Integrate ongoing updates on FGF-21 analog development into clinical education and decision-making frameworks by tracking at least two leading candidates and their Phase III outcomes*

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.

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Other programs in this series include:

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