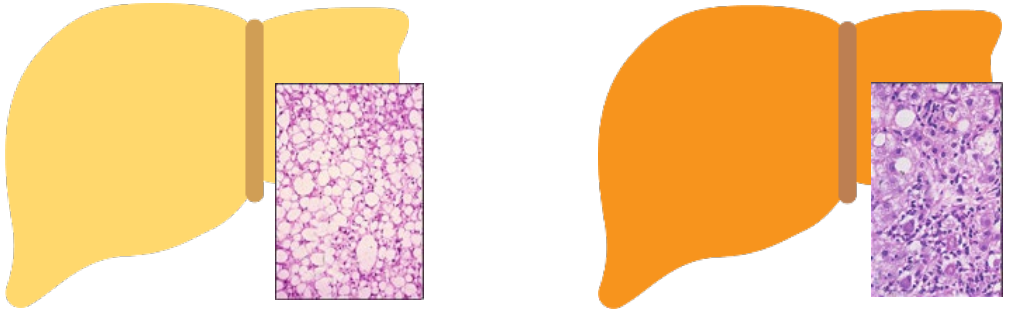
MASLD/MASH management - What lies ahead?



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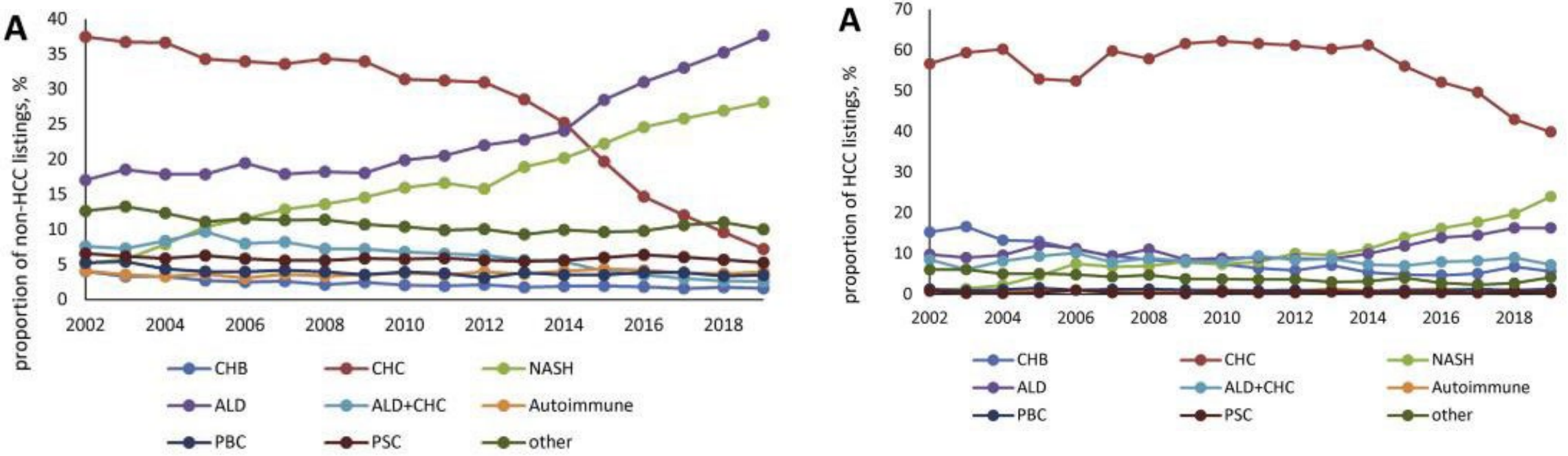
GHASSA
GASTROENTEROLOGY & HEPATOLOGY ASSOCIATION OF SUB SAHARAN AFRICA

MASLD and Liver Transplantation

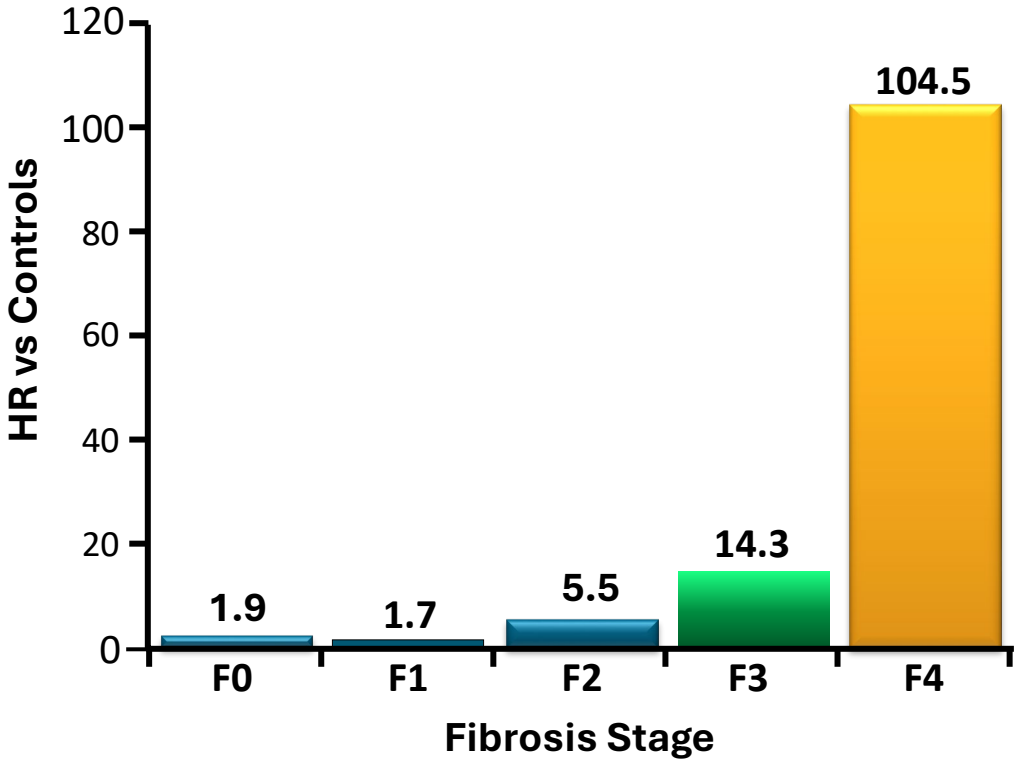


- Now a leading indication for liver transplantation in the USA
  - Equals alcohol associated liver disease
  - **#1** indication for transplant in women > 65 years

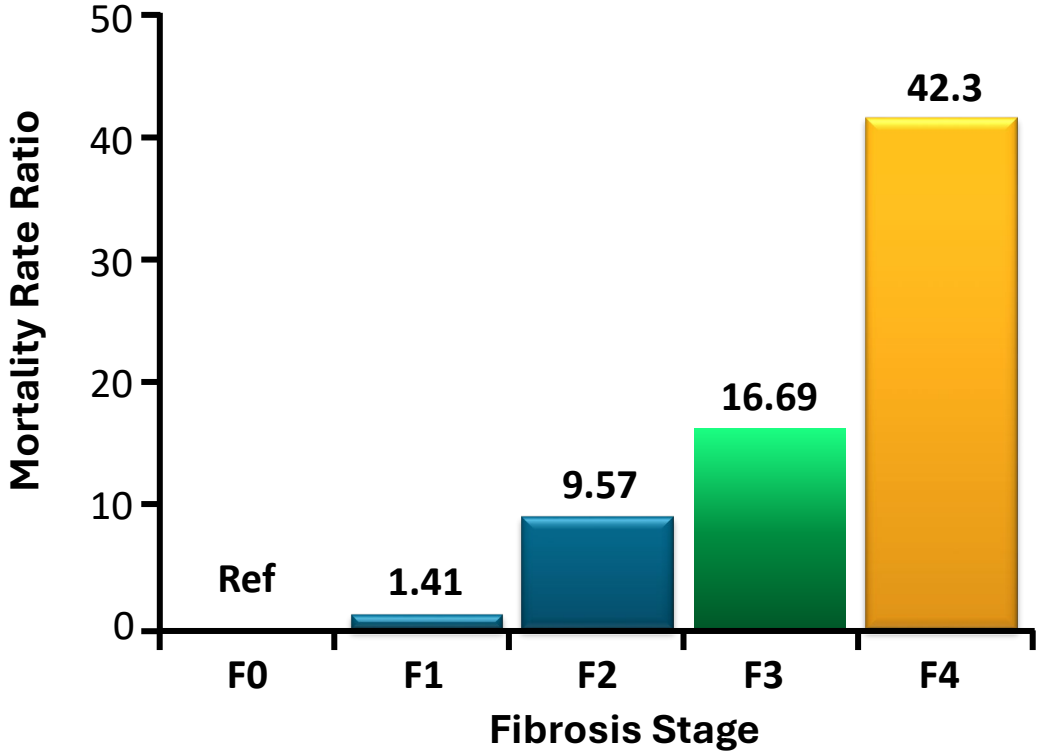
Younossi et al. Clin Gastroenterol Hepatol 2018

MASLD outcomes and the centrality of liver fibrosis

Risk of Severe Liver Disease[1]



Liver-Related Mortality[2]

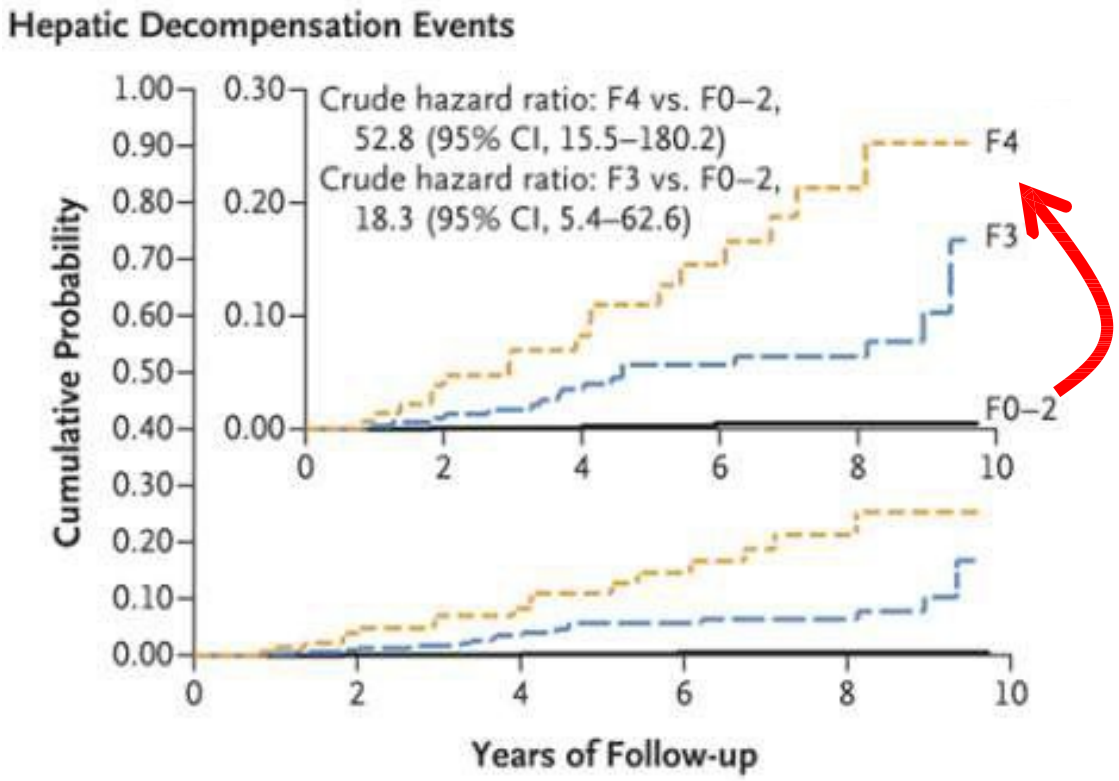


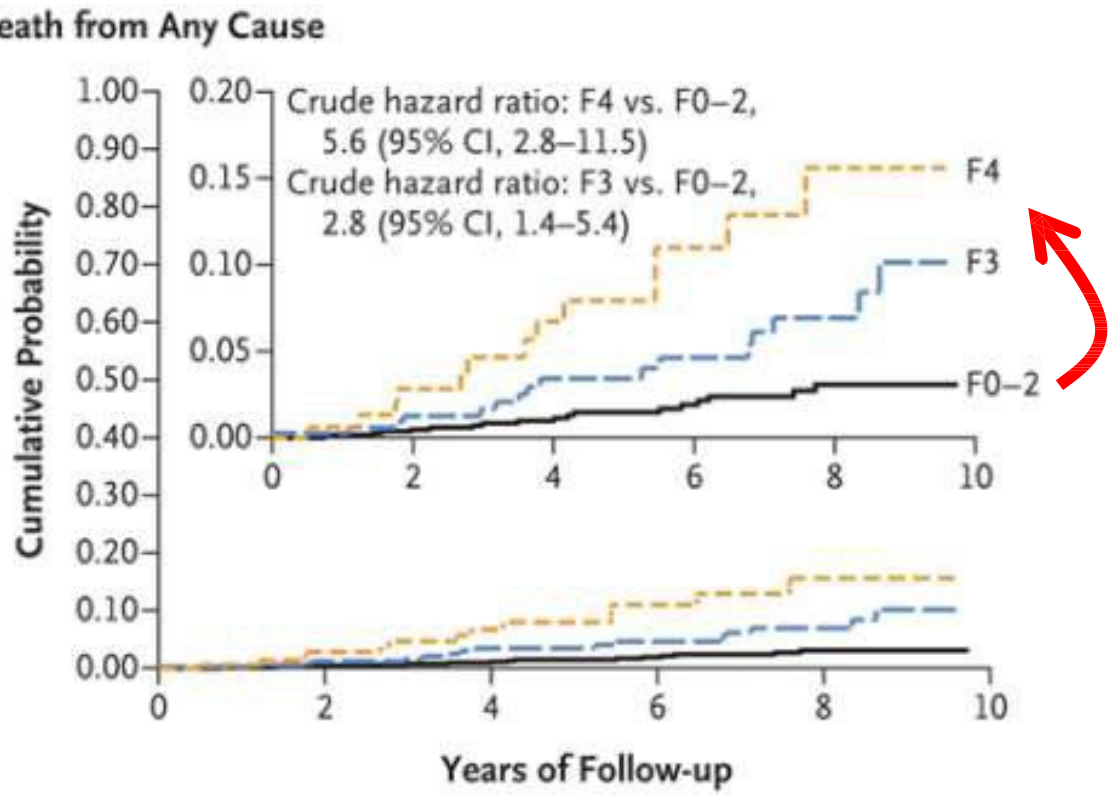
1. Hagström. J Hepatol. 2017;67:1265. 2. Dulai. Hepatology. 2017;65:1557.

Advanced (F3-4) liver fibrosis

Increases eventual risk for liver-related events + death from any cause

NASH CRN Prospective Study (1773 patients)

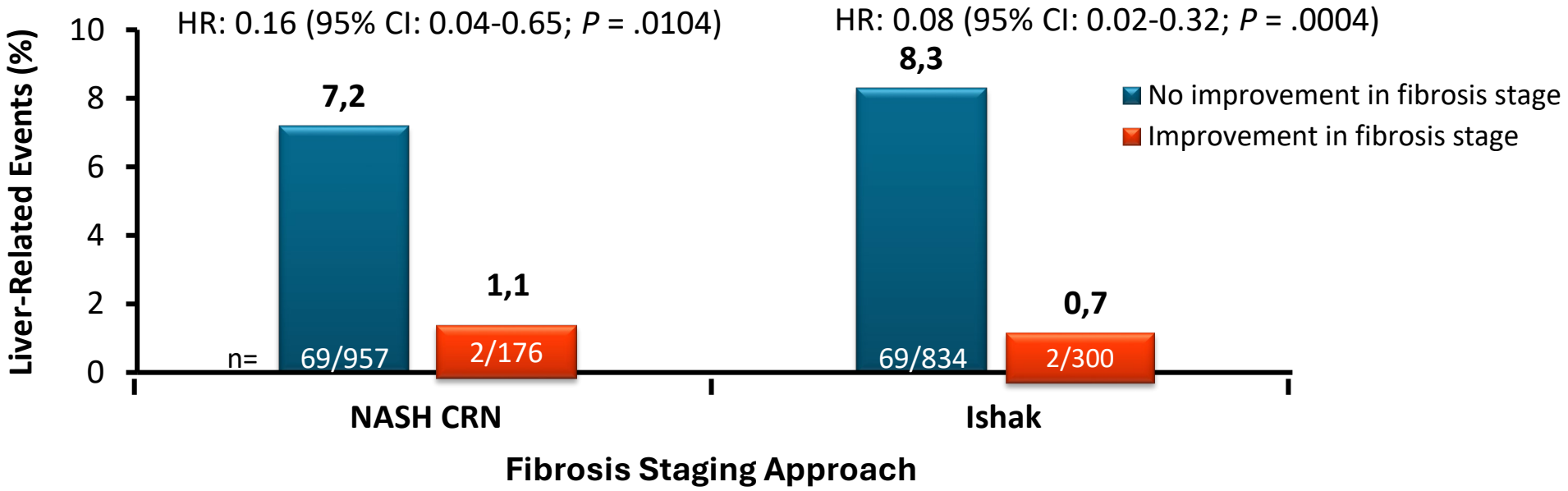




Sanyal et al. N Engl J Med 2021

Regression of MASH fibrosis/cirrhosis improves outcomes

- Pooled analysis of 1135 patients with MASH cirrhosis from STELLAR-4 (selonsertib, ASK i) and simtuzumab studies
  - Improvement in MASH fibrosis stage associated with lower risk of liver-related events

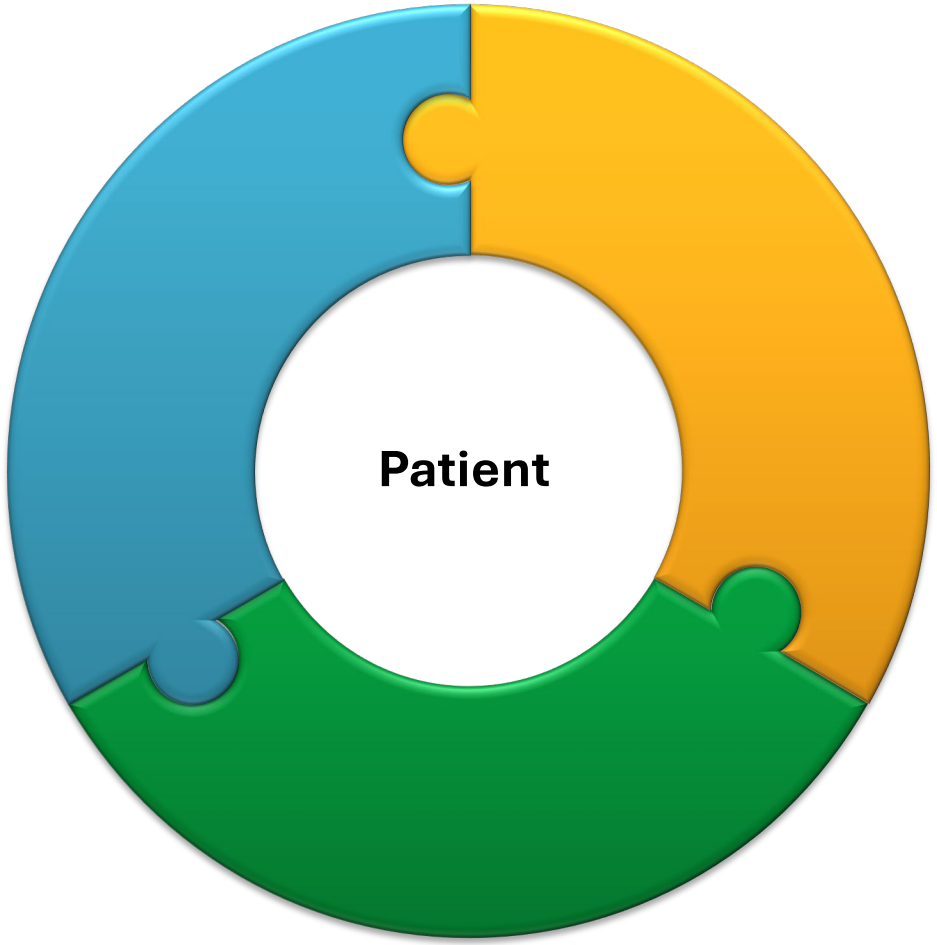


Sanyal. Hepatology. 2021;75:1235.

Early intervention is key – aim to target fibrosis

Metabolic syndrome comorbidities

Obesity: GLP-1 RA
Diabetes: Pioglitazone; GLP-1 RA; SGLT2
Dyslipidemia
Hypertension
Sleep apnea



Sedentary lifestyle/ Overweight

Weight loss
Exercise
Diet

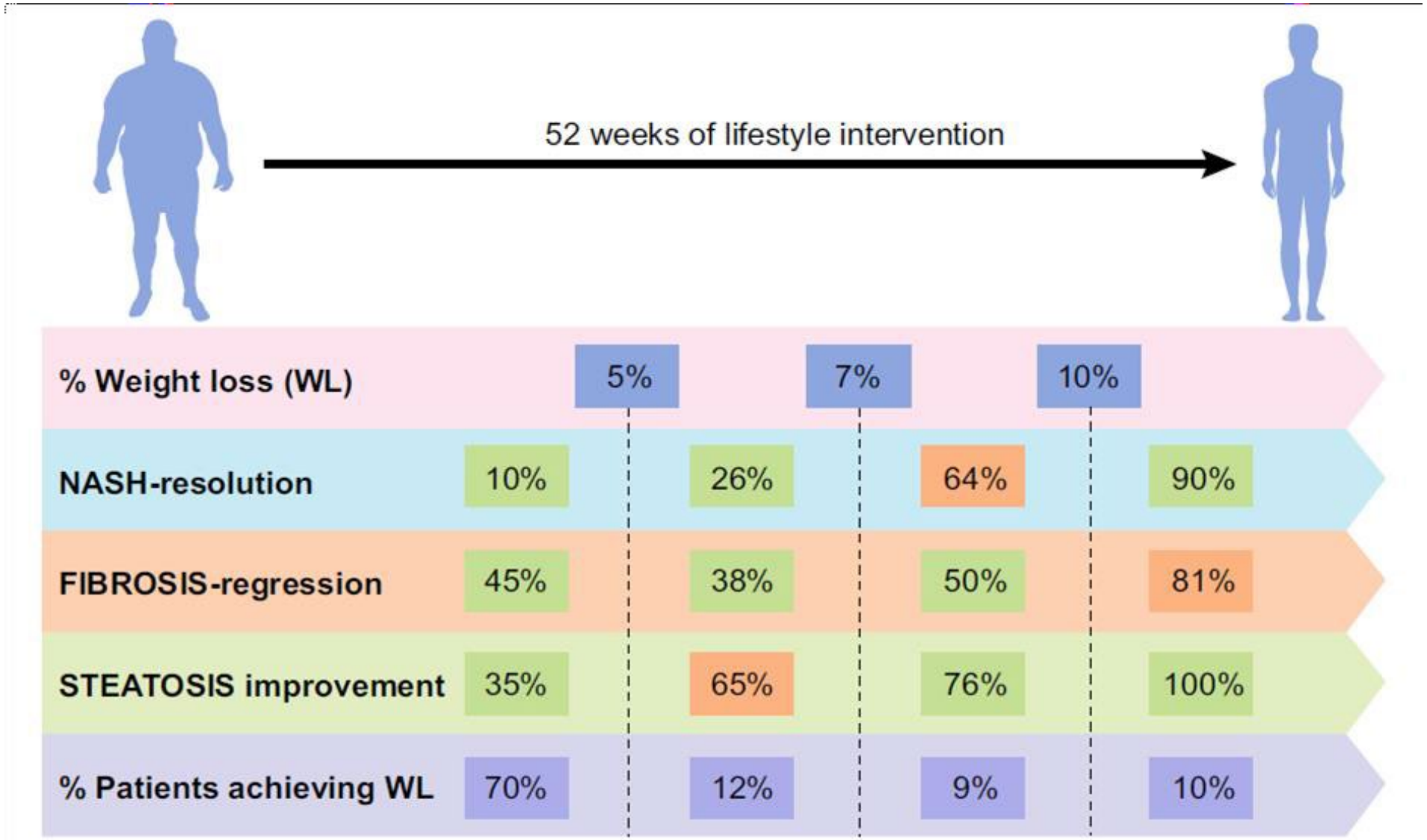
>8200 daily steps
→ Protection from incident diseases
- Obesity
- Sleep apnea
- GORD
- Major depression
- Diabetes
- Hypertension

Modifiers

Alcohol, smoking, fructose, coffee

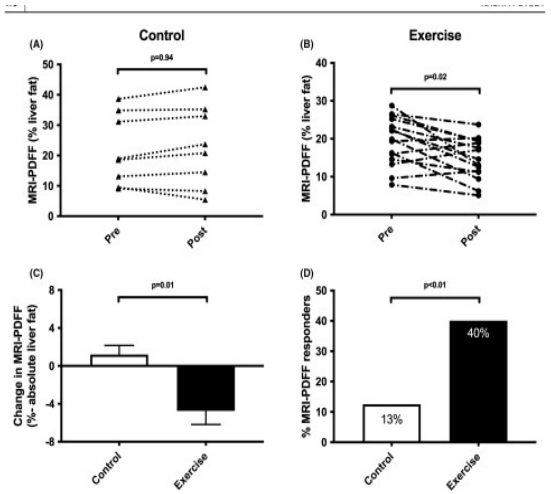
Cusi. Endo Pract. 2022;28:528. Master. Nat Med. 2022;28:2301.

Weight loss in MASLD

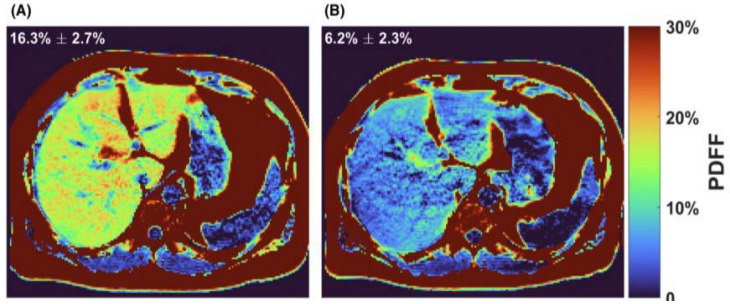


Romero-Gomez *J Hepatol* 2017

Physical activity in MASLD



- **Exercise reduces liver fat by 20-30% -** even sans weight loss
- **Kind of exercise: Aerobic vs. Resistance**
  Average effective routine**: 3x/week x 12 week**
  - Both improved liver fat
  - Resistance training alone – less of an overall quantum of liver fat reduction
- **Intensity**
  - Patients with **vigorous** but not **moderate** physical activity **↓ NASH** (OR 0.65)

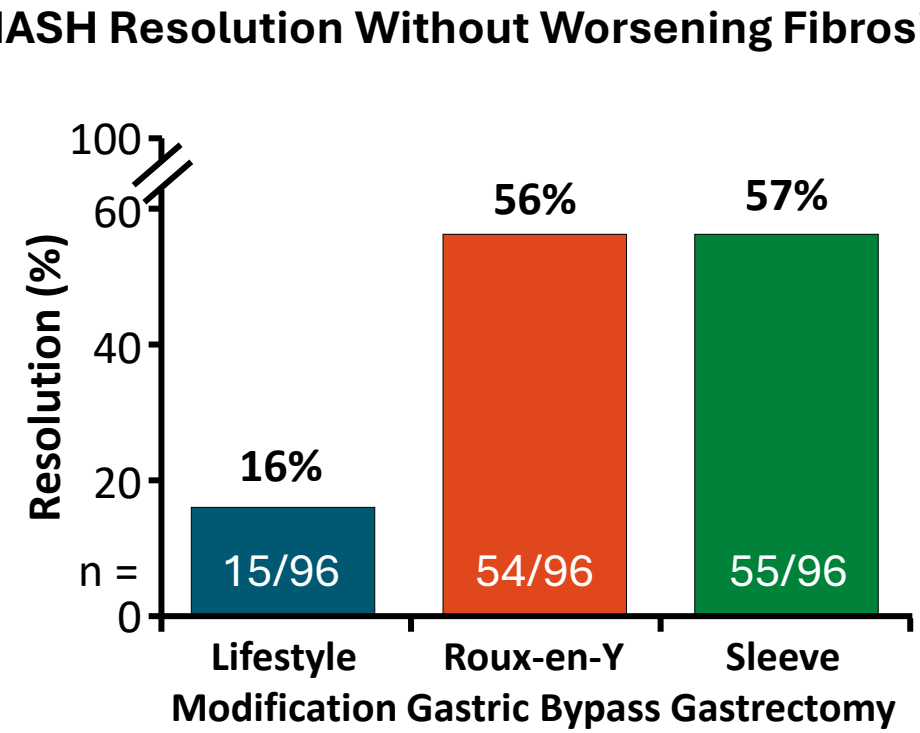


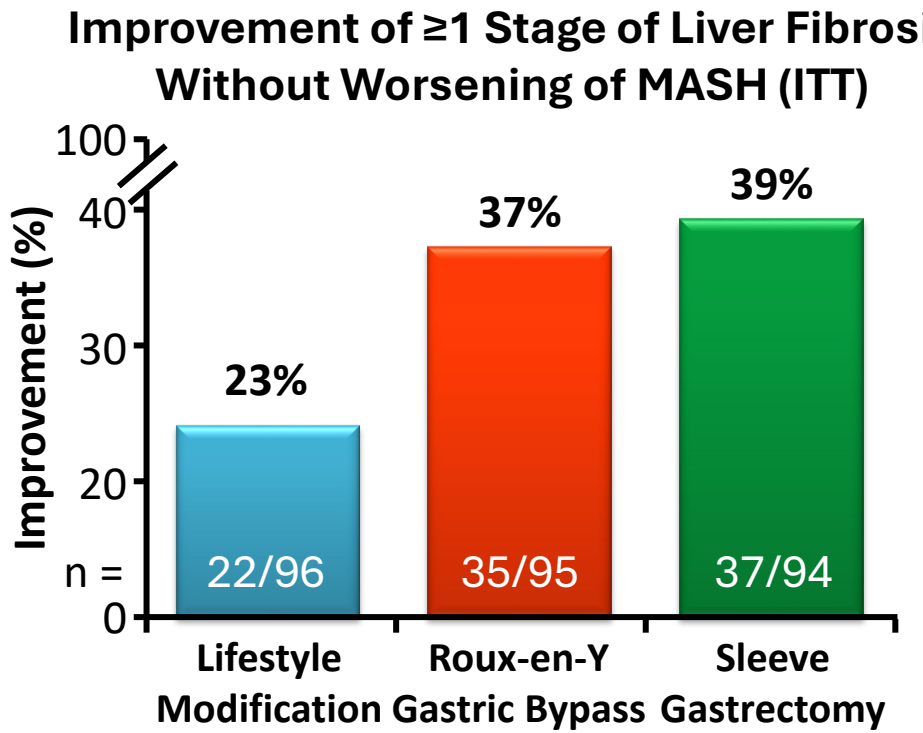
- **Frequency**
  - Moderate intensity ≥5x/week greatest benefit
  - Dose response: Moderate-vigorous ≥ 250 min/week
  - Doubling time in vigorous activity ↓ risk of advanced fibrosis (OR 0.53)

Kistler et al. *AJG* 2011; St George et al. *Hepatology* 2009; Hashida et al. *J Hepa*tol 2017 ; Schweitzer et al. *Hepatology* 2017; Stine Hepatology 2022; Stine Clin Liv Disease 2022

Bariatric Surgery and MASLD

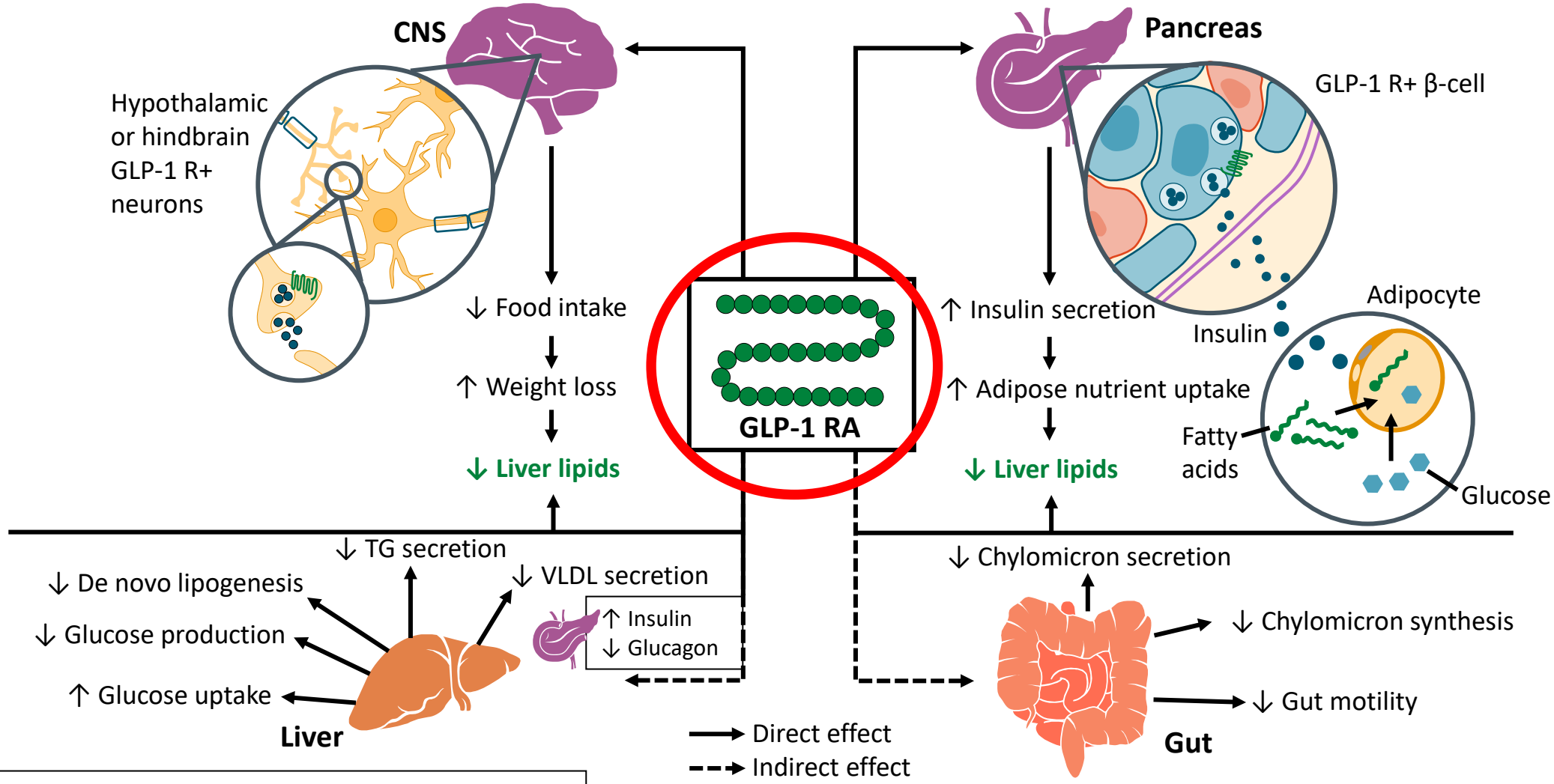
- Improvement in liver histology reported in several studies





Harrison. Hepatology. 2009;49:80. Promrat. Hepatology. 2010;51:121. Chalasani. Gastroenterology. 2012;142:1592. Lassailly. Gastroenterology. 2020;159:1290. Verrastro. Lancet. 2023;401:1786. Boon-Bee Goh. World J Gastroenterol. 2018;24:3112.

Glucagon-like peptide-1 (*GLP*-1) *agonists*



GIP –glucose-dependent insulinotropic polypeptide

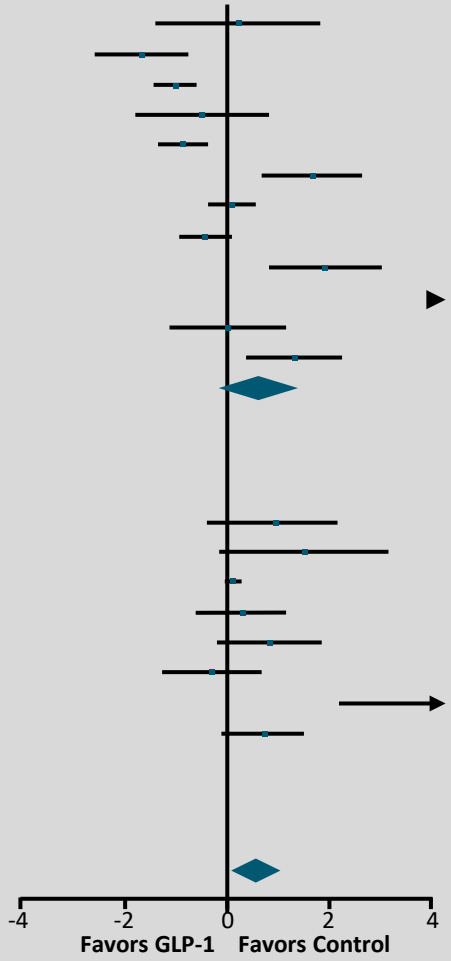
GR - Glucagon Receptor

Yabut. Endocr Rev. 2022

GLP-1 RA's effects on Adiponectin

Mean Difference and 95% CIs for effect of GLP-1 RAs on Adiponectin

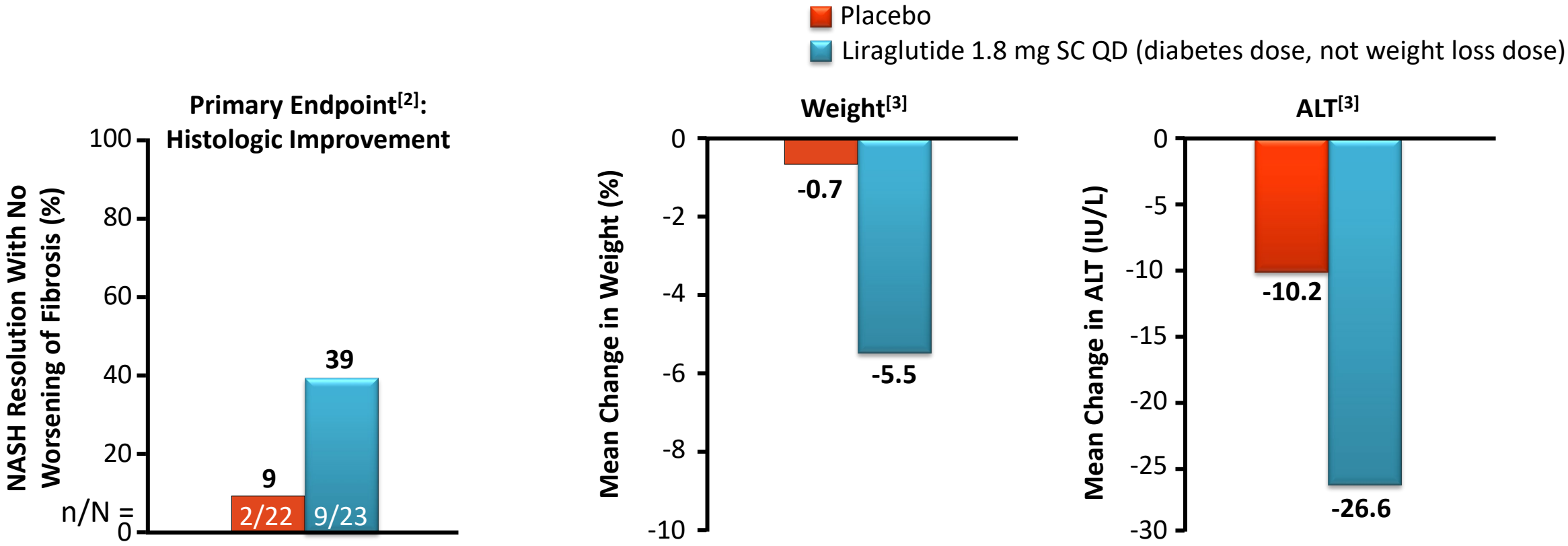
	GLP-1			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean (µg/mL)	SD (µg/mL)	Total	Mean (µg/mL)	SD (µg/mL)	Total	Weight, %	IV, Random, 95% CI (µg/mL)	IV, Random, 95% CI (µg/mL)
1.1.1 Exenatide									
Bi 2014	5.5	1.8	11	5.3	2.91	22	3.8	0.20 (-1.42 to 1.82)	
Bunck 2010	-1.8	0.82	30	-0.14	2.35	29	5.3	-1.66 (-2.56 to -0.76)	
Derosa 2012	-0.2	0.6	86	0.8	0.65	85	6.3	-1.00 (-1.37 to -0.63)	
Dutour 2016	0.1	1.1	22	0.6	2.88	22	4.5	-0.50 (-1.79 to 0.79)	
Elkind-Hirsch 2008	0.65	0.94	28	1.5	0.8	28	6.2	-0.85 (-1.31 to -0.39)	
Fan 2013	2.01	2.92	49	0.35	2.31	68	5.2	1.66 (0.68 to 2.64)	
Gurkan 2014	0.1	0.59	17	0	0.7	17	6.2	0.10 (-0.34 to 0.54)	
Liang 2013	1	0.5	34	1.42	1.99	67	6.1	-0.42 (-0.93 to 0.09)	
Quan 2017	2.1	4.21	100	0.2	3.65	100	4.9	1.90 (0.81 to 2.99)	
Sathyanarayana 2011	15.3	2.38	11	7.3	1.22	10	3.8	8.00 (6.40 to 9.60)	
Savvidou 2016	2	2.55	55	2	3.22	48	4.8	0.00 (-1.13 to 1.13)	
Shi 2017	1.57	1.41	15	0.26	1.25	16	5.3	1.31 (0.37 to 2.25)	
Subtotal (95% CI)			**458**			**512**	**62.4**	**0.60 (-0.23 to 1.42)**	
Heterogeneity: $Tau^2 = 1.88$; $Chi^2 = 177.48$; df = 11 ($P < .00001$); $I^2 = 94\%$									
Test for overall effect: Z = 1.42 ($P = .16$)									
1.1.2 Liraglutide									
Ahmadi 2018	1.5	4.15	63	0.6	2.9	58	4.5	0.90 (-0.37 to 2.17)	
Armstrong 2016	1.25	1.19	7	-0.257	1.88	7	3.7	1.51 (-0.14 to 3.16)	
Frøssing 2018	0.5	0.3	48	0.4	0.3	24	6.5	0.10 (-0.05 to 0.25)	
Ghanim 2020	0.14	1.93	37	-0.16	1.68	27	5.4	0.30 (-0.59 to 1.19)	
Li 2015	0.77	1.75	33	-0.03	1.34	11	5.1	0.80 (-0.19 to 1.79)	
Takeshita 2015	0.2	2.4	54	0.5	2.61	58	5.3	-0.30 (-1.23 to 0.63)	
Yan 2019	6.9	8.5	48	1.02	9.83	51	1.4	5.88 (2.27 to 9.49)	
Yang 2013	0.97	0.94	10	0.24	0.86	10	5.6	0.73 (-0.06 to 1.52)	
Subtotal (95% CI)			**300**			**246**	**37.6**	**0.55 (0.04 to 1.06)**	
Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 18.78$; df = 7 ($P = .009$); $I^2 = 63\%$									
Test for overall effect: Z = 2.10 ($P = .04$)									
Total (95% CI)			**758**			**758**	**100.0**	**0.59 (0.10 to 1.08)**	
Heterogeneity: $Tau^2 = 0.95$; $Chi^2 = 207.35$; df = 19 ($P = .00001$); $I^2 = 92\%$									
Test for overall effect: Z = 2.36 ($P = .02$)									
Test for subgroup differences: $Chi^2 = 0.01$; df = 1 ($P = .92$); $I^2 = 0\%$									



Simental-Mendía. Br J Clin Pharmacol. 2021;87:4140

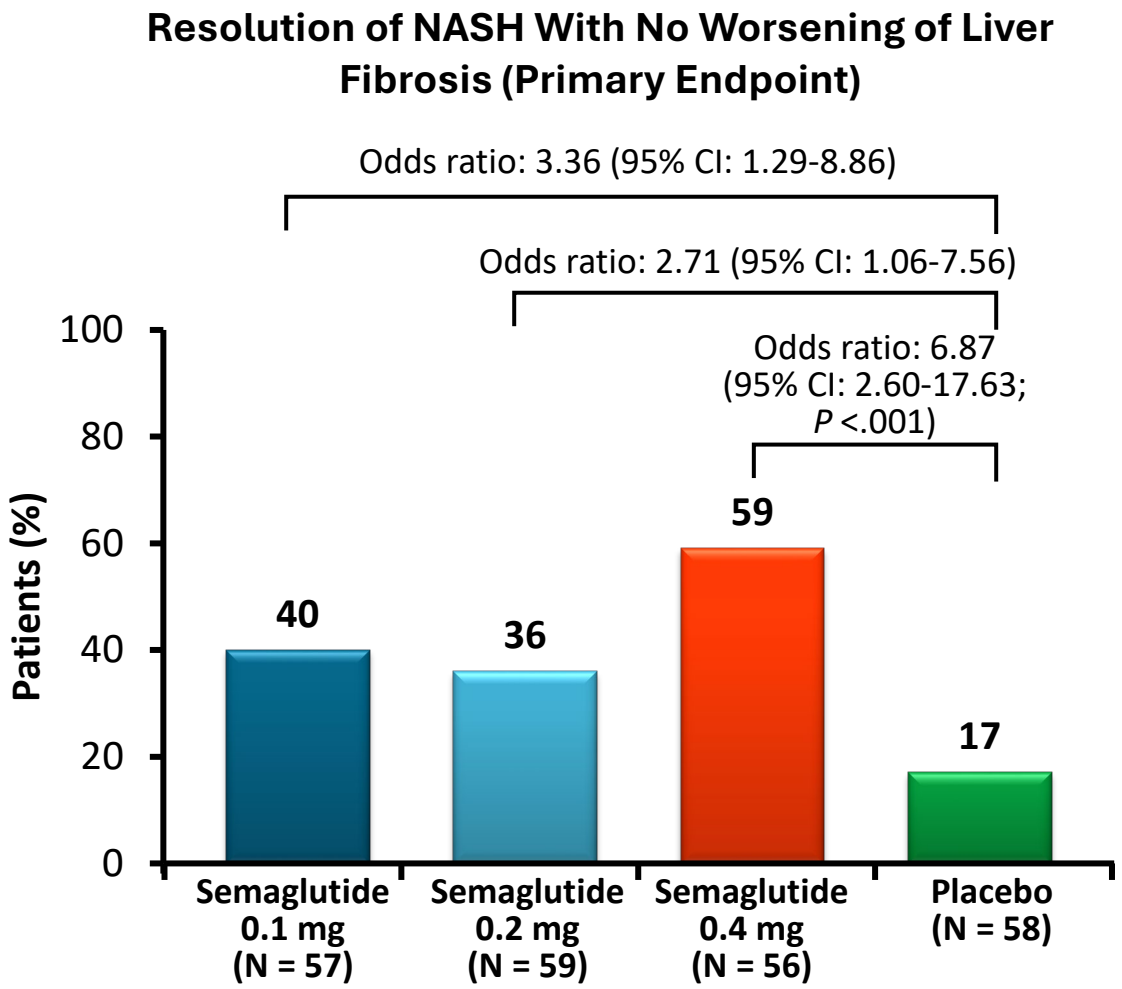
LEAN study: 48-week Liraglutide vs Placebo in overweight NASH

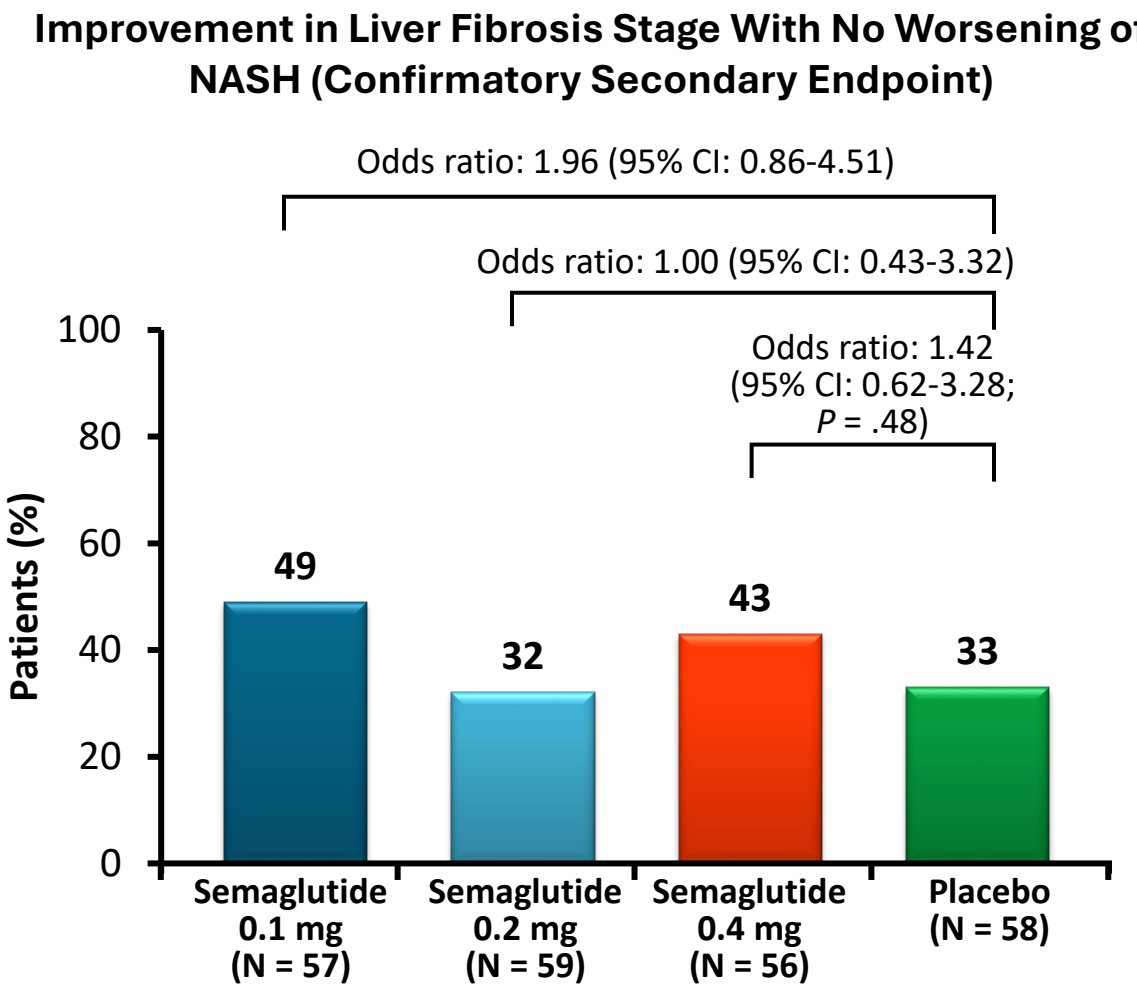
- Liraglutide GLP-1 agonist - Randomized, double-blind phase II study[1]



Armstrong. Lancet. 2016;387:679.

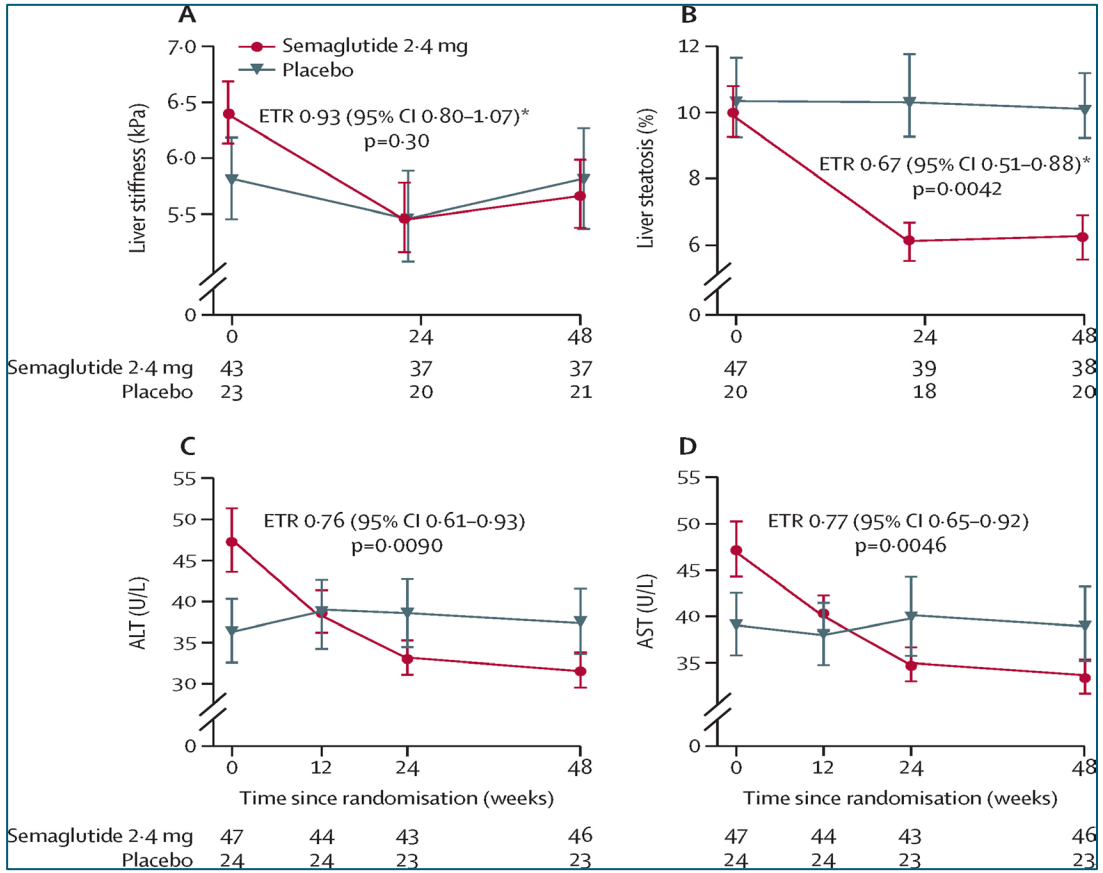
Semaglutide (Ozempic®, Wegovy®)

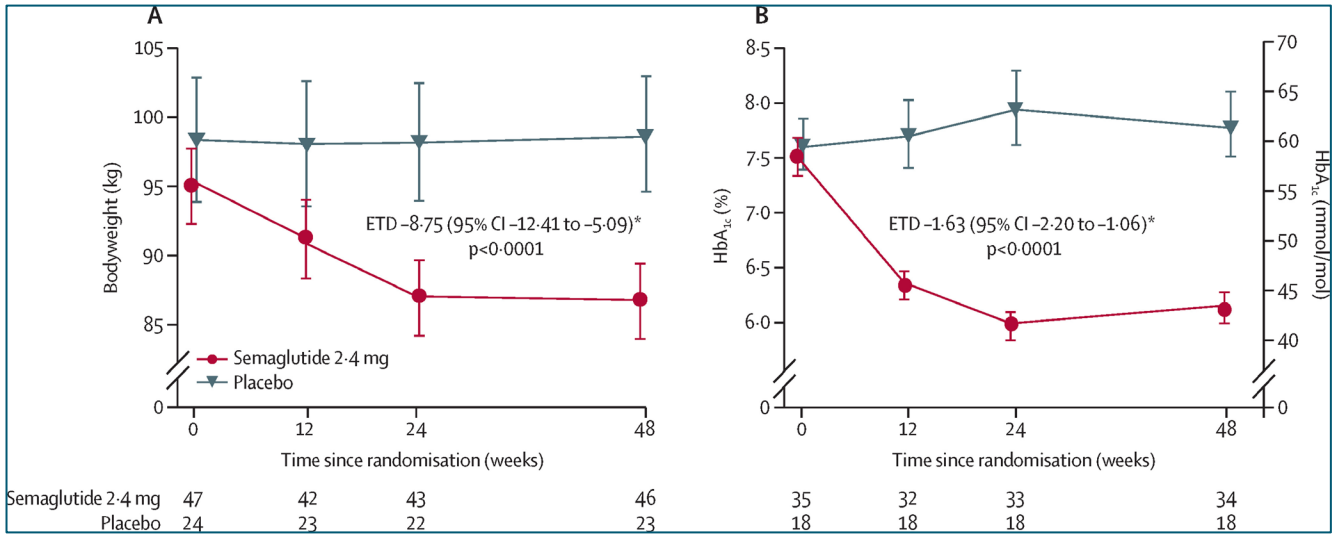




Newsome. NEJM. 2021:384:1113.

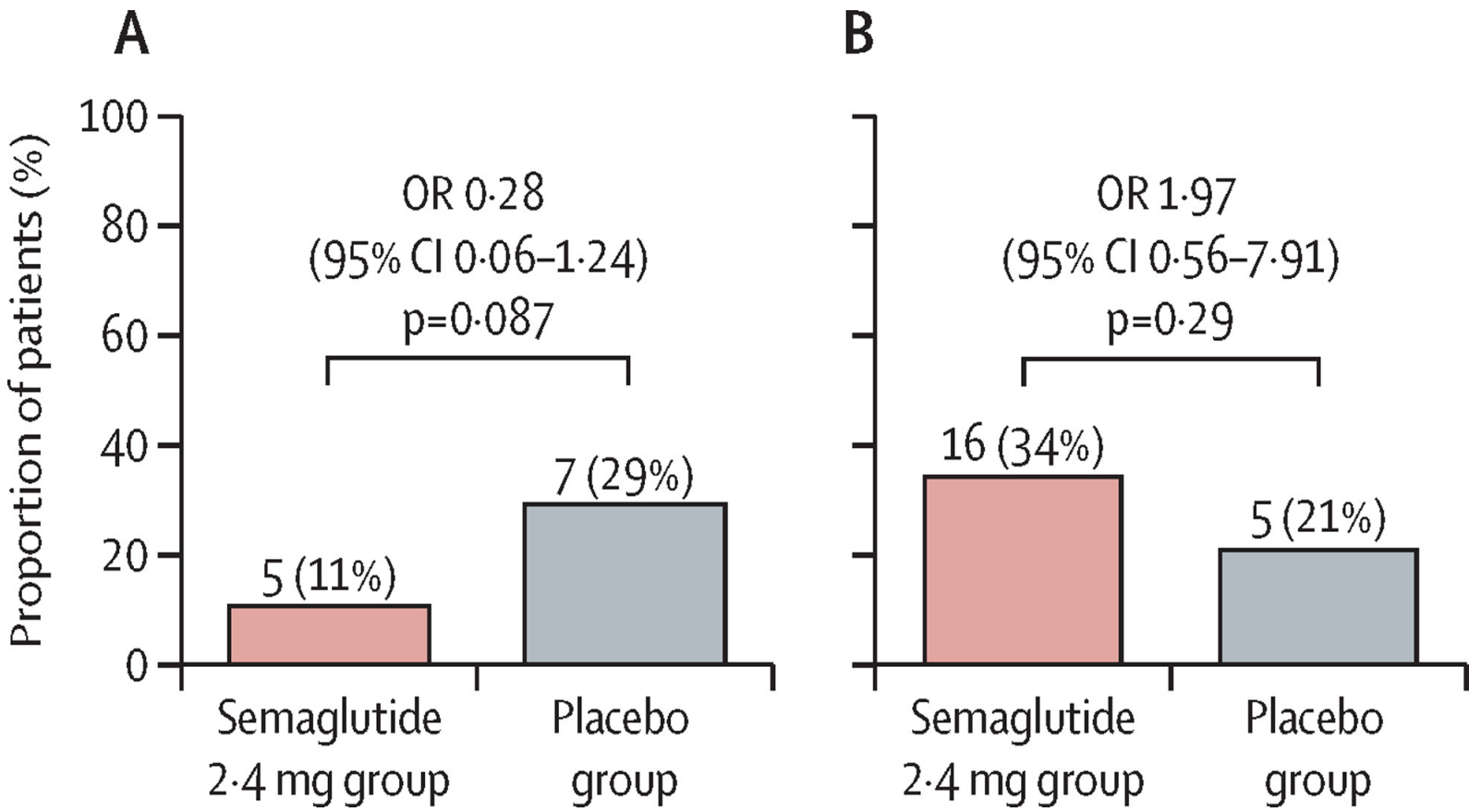
Semaglutide 2·4 mg once weekly in patients with NASH related cirrhosis: a randomized, placebo-controlled phase 2 trial





The Lancet Gastroenterology & Hepatology Volume 8 Issue 6 Pages 511-522 (June 2023)

Improvement in liver fibrosis and no worsening of NASH (A) and resolution of NASH (B) at 48 weeks

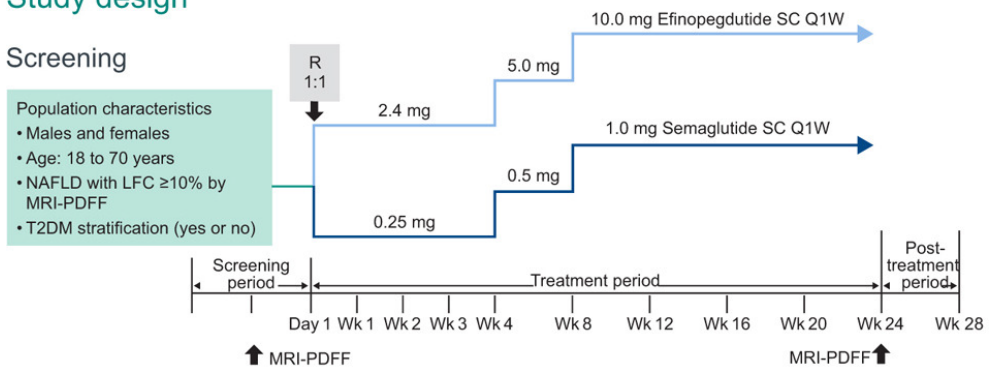


The Lancet Gastroenterology & Hepatology Volume 8 Issue 6 Pages 511-522 (June 2023)

Efinopegtutide

A phase 2a active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with NAFLD

Study design



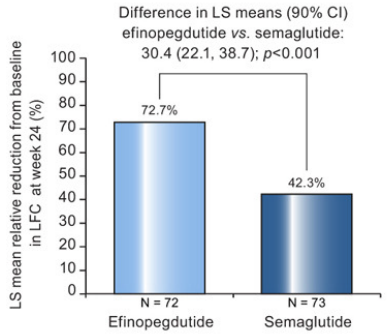
Safety results

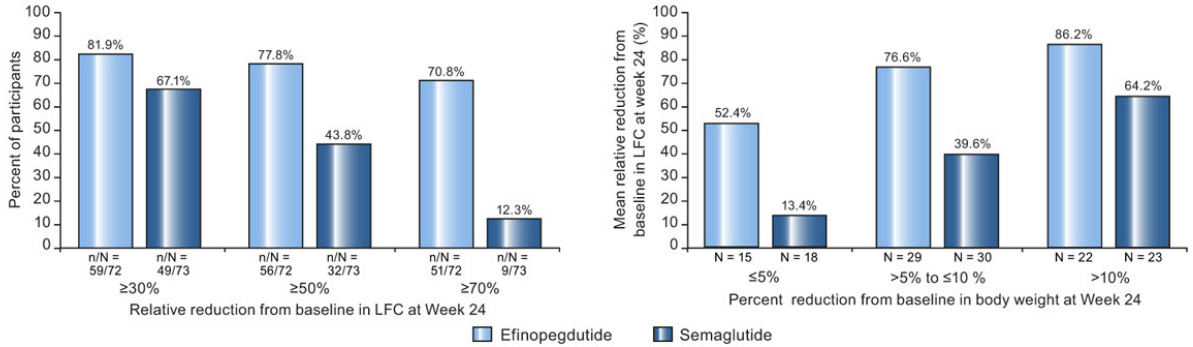
	Efinopegdutide n = 72	Semaglutide n = 73
Participants with an AE, %	88.9%	72.6%
Deaths	0	0
Serious drug-related AEs	0	

Efficacy results

Primary efficacy endpoint

Relative reduction from baseline in LFC at week 24





J Hepatology 79 (4) Oct 2023

Survodutide

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Survodutide, 2.4 mg (N=73)	Survodutide, 4.8 mg (N=72)	Survodutide, 6.0 mg (N=74)	Placebo (N=74)	Total (N=293)
Age — yr	49.6±13.7	50.2±12.9	50.4±13.1	53.0±11.5	50.8±12.8
Female sex — no. (%)	36 (49)	34 (47)	41 (55)	44 (59)	155 (53)
Body weight — kg	101.44±18.20	99.95±26.12	103.87±23.70	98.09±20.78	100.84±22.37
Waist circumference — cm	113.10±11.37	112.09±14.87	116.99±14.62	113.02±14.23	113.81±13.91
Body-mass index†	35.30±5.05	35.00±6.97	37.42±6.84	35.49±6.44	35.81±6.41
Type 2 diabetes					
Participants with condition — no. (%)	28 (38)	26 (36)	30 (41)	30 (39)	114 (39)
Glycated hemoglobin — %	6.90±1.12	6.90±1.06	6.92±0.91	7.08±0.87	6.96±0.96
Systolic blood pressure — mm Hg	128.8±14.8	132.4±14.1	127.0±14.8	129.4±12.5	129.4±14.1
Diastolic blood pressure — mm Hg	80.4±8.2	81.8±9.4	79.4±8.1	81.2±8.4	80.7±8.5
Liver-enzyme levels — U/liter					
Alanine aminotransferase	59.4±50.3	59.6±40.0	54.9±39.9	57.3±36.6	57.8±41.8
Aspartate aminotransferase	47.4±37.5	44.8±27.5	45.6±39.0	51.3±40.9	47.3±36.5
Total NAFLD activity score‡	5.2±1.0	5.3±1.0	5.1±1.0	5.2±1.1	5.2±1.0
Subscore for steatosis — no. (%)‡					
0	0	0	0	0	0
1	6 (8)	0	1 (1)	3 (4)	10 (3)
2	38 (52)	38 (53)	49 (66)	43 (58)	168 (57)
3	29 (40)	34 (47)	24 (32)	28 (38)	115 (39)
Liver fibrosis stage — no. (%)					
F1A	0	3 (4)	3 (4)	2 (3)	8 (3)
F1B	17 (23)	7 (10)	14 (19)	9 (12)	47 (16)
F1C	3 (4)	3 (4)	6 (8)	3 (4)	15 (5)
F2	30 (41)	36 (50)	24 (32)	30 (41)	120 (41)
F3	23 (32)	23 (32)	27 (36)	30 (41)	103 (35)
MRI-PDFF — %	19.75±7.56	21.09±8.26	17.85±6.34	19.62±7.59	19.57±7.51

* Plus–minus values are means ±SD. Subcutaneous doses were administered once weekly. Percentages may not total 100 because of rounding. MRI-PDFF denotes magnetic resonance imaging proton density fat fraction.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The nonalcoholic fatty liver disease (NAFLD) activity score (ranging from 0 to 8) represents the sum of subscores for steatosis (scale of 0 to 3), lobular inflammation (scale of 0 to 3), and hepatocellular ballooning (scale of 0 to 2), with higher scores indicating more severe disease.

The NEW ENGLAND JOURNAL of MEDICINE

Phase 2 Trial of Survodutide in MASH and Fibrosis

A PLAIN LANGUAGE SUMMARY

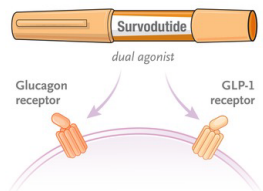
Based on the NEJM publication: A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis by A.J. Sanyal et al. (published June 7, 2024)

In this trial, researchers evaluated the efficacy and safety of multiple subcutaneous doses of survodutide, a dual agonist of the glucagon receptor and glucagon-like peptide-1 (GLP-1) receptor, in participants with metabolic dysfunction–associated steatohepatitis (MASH) and liver fibrosis.

MASH, previously called NASH (nonalcoholic steatohepatitis), is associated with increased morbidity and mortality. The prevalence of MASH is predicted to increase worldwide.

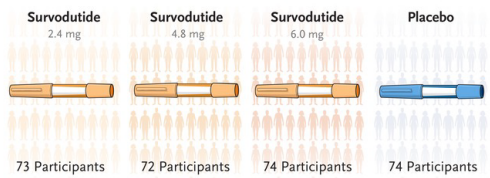
WHY WAS THE TRIAL DONE?

Compounds in development for treating MASH include GLP-1 receptor agonists. However, dual agonism of the glucagon and GLP-1 receptors may be more effective than GLP-1 receptor agonism alone, because the extrahepatic benefits of GLP-1 receptor agonism are combined with the direct hepatic effects of glucagon receptor agonism.



HOW WAS THE TRIAL CONDUCTED?

293 adults with biopsy-confirmed MASH and fibrosis stage F1 through F3 were randomly assigned to receive once-weekly subcutaneous survodutide, at a target dose of 2.4, 4.8, or 6.0 mg, or placebo. A 24-week rapid-dose-escalation phase was followed by a 24-week maintenance phase. The primary end point was histologic improvement (reduction) in MASH with no worsening of fibrosis at week 48.



24-week rapid-dose-escalation phase followed by a 24-week maintenance phase

PARTICIPANTS

WHO
- 293 adults
- 18–80 years of age
- Women: 53%; Men: 47%

CLINICAL STATUS
- Biopsy-confirmed MASH
- Fibrosis stage F1 through F3

TRIAL DESIGN

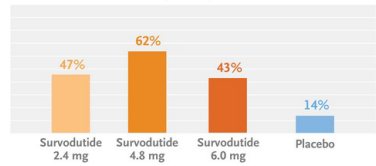
- PHASE 2
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- DOSE-FINDING
- LOCATION: 155 SITES IN 25 COUNTRIES

RESULTS

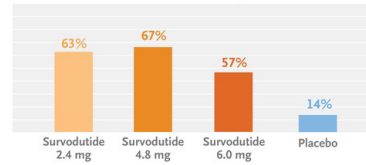
Survodutide was associated with significant improvement in MASH with no worsening of fibrosis at 48 weeks as compared with placebo.

A decrease in liver fat content by at least 30% — a secondary end point — was more common with survodutide than with placebo.

Histologic Improvement in MASH
(P<0.001)

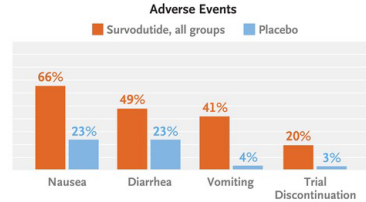


Decrease in Liver Fat Content by at Least 30%



The most common adverse events were nausea, diarrhea, and vomiting, all of which occurred more frequently with survodutide than with placebo. Trial discontinuation due to adverse events also occurred more often with survodutide than with placebo.

Adverse Events



LIMITATIONS AND REMAINING QUESTIONS

- Most participants were White, which may restrict the generalizability of the findings.
- The benefit of survodutide with respect to fibrosis will need to be examined in future studies.

CONCLUSIONS

In a phase 2 trial involving participants with MASH and liver fibrosis, survodutide was superior to placebo with respect to improvement in MASH without worsening of fibrosis over 48 weeks.

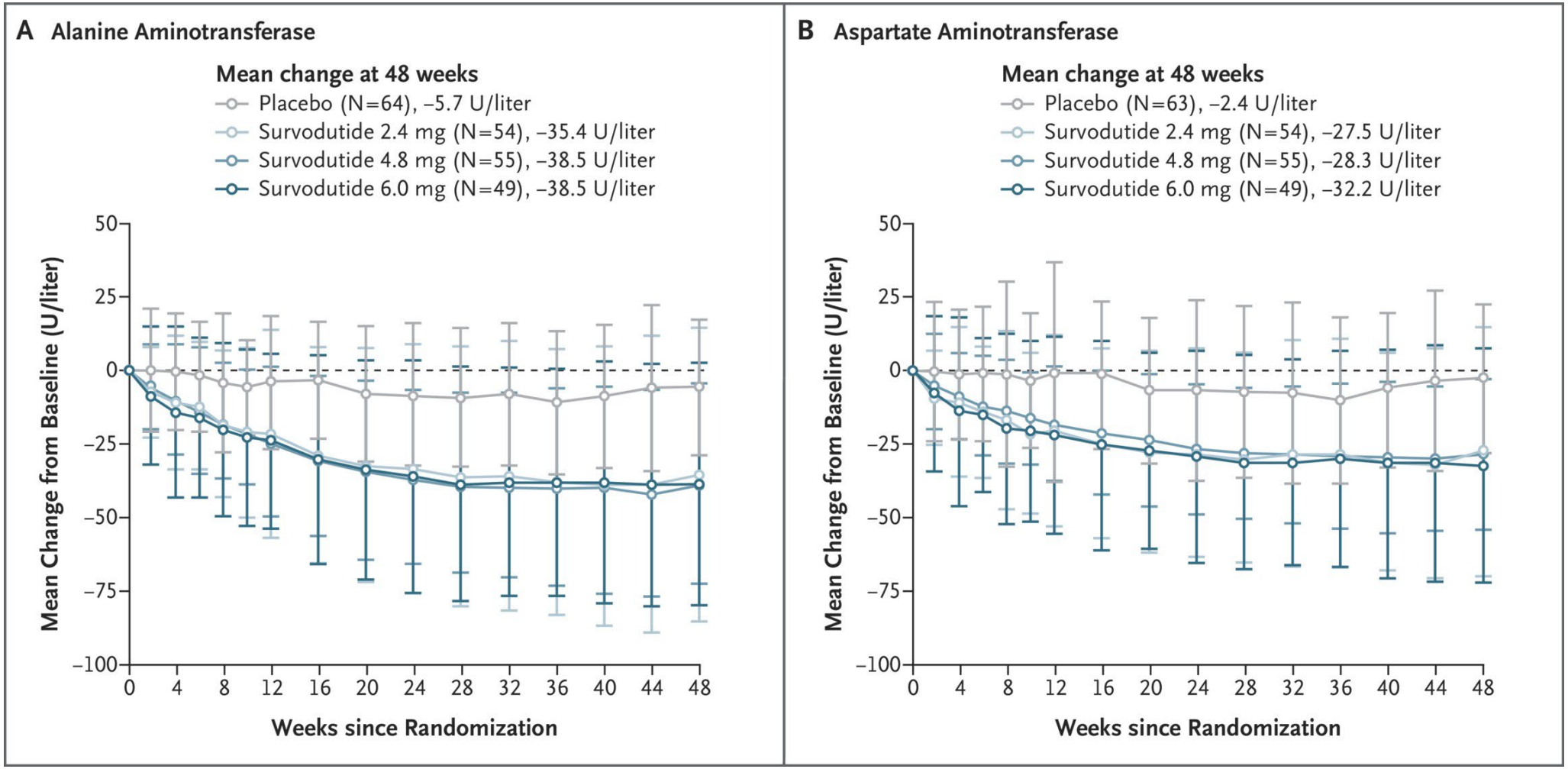
LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04771273; EudraCT number, 2020-002723-11
Trial funding: Boehringer Ingelheim
Full citation: Sanyal AJ, Bedossa P, Fraessdorf M, et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. N Engl J Med 2024;391:311-9. DOI: 10.1056/NEJMoa2401755

Sanyal AJ et al. N Engl J Med 2024;391:311-319

Change in Liver-Enzyme Levels over Time



Tirzapetide

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Tirzepatide, 5 mg (N=47)	Tirzepatide, 10 mg (N=47)	Tirzepatide, 15 mg (N=48)	Placebo (N=48)	Total (N=190)
Age — yr	55.0±11.6	54.3±12.1	54.9±10.0	53.5±11.6	54.4±11.3
Female sex — no. (%)	27 (57)	26 (55)	29 (60)	27 (56)	109 (57)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	1 (2)	1 (2)	1 (2)	0	3 (2)
Asian	5 (11)	6 (13)	6 (12)	5 (10)	22 (12)
Black	0	1 (2)	0	0	1 (<1)
White	41 (87)	39 (83)	41 (85)	43 (90)	164 (86)
Hispanic or Latino ethnic group — no. (%)†	19 (40)	15 (32)	17 (35)	18 (38)	69 (36)
Body weight — kg	100.7±22.2	102.6±23.8	100.0±18.1	96.0±21.6	99.8±21.5
Body-mass index‡	36.1±6.0	36.6±6.3	35.9±5.7	36.0±6.7	36.1±6.1
Type 2 diabetes — no. (%)	26 (55)	27 (57)	29 (60)	29 (60)	111 (58)
Liver fibrosis stage — no. (%)§					
F2	17 (36)	25 (53)	22 (46)	17 (35)	81 (43)
F3	30 (64)	22 (47)	26 (54)	31 (65)	109 (57)
NAFLD activity score¶	5.4±1.0	5.3±0.9	5.0±0.9	5.3±1.0	5.3±0.9
Alanine aminotransferase (U/liter)	67.9±39.9	61.2±35.9	58.7±25.4	59.7±30.3	61.8±33.2
Aspartate aminotransferase (U/liter)	39.5±20.2	37.0±19.8	34.9±16.7	36.2±21.5	36.6±19.7
Glycated hemoglobin — %	6.6±1.3	6.4±1.1	6.4±0.9	6.8±1.2	6.5±1.1
Liver fat content — %‖	19.0±6.9	17.6±7.5	18.8±8.3	18.2±6.8	18.4±7.3
Extracellular hepatic water content — msec**	920.5±120.5	894.1±88.5	923.3±88.1	917.7±92.0	913.0±97.5
Liver stiffness — kPa††	12.6±5.9	11.1±4.3	11.4±5.7	12.0±5.1	11.8±5.3
Fibrosis-4 index score‡‡	1.8±1.1	1.5±0.7	1.5±0.6	1.6±0.7	1.6±0.8
NIS4 test score§§	0.8±0.2	0.7±0.2	0.8±0.2	0.8±0.2	0.8±0.2
Enhanced Liver Fibrosis test score¶¶	9.9±1.0	9.8±0.8	9.7±0.6	9.9±0.8	9.8±0.8
Pro-C3 — μg/liter‖‖	145.3±103.2	127.9±76.8	115.6±49.7	127.4±57.9	128.9±74.6

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participants. Participants could be recorded as both White and Hispanic or Latino.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The fibrosis stages according to the nonalcoholic steatohepatitis (NASH) Clinical Research Network are as follows: F0 indicates no fibrosis, F1 mild (perisinusoidal or periportal) fibrosis, F2 moderate (perisinusoidal and portal or periportal) fibrosis, F3 severe (bridging) fibrosis, and F4 cirrhosis.[18]
¶ The nonalcoholic fatty liver disease (NAFLD) activity score is the unweighted sum of scores for steatosis (on a scale of 0 to 3), lobular inflammation (on a scale of 0 to 3), and hepatocellular ballooning (on a scale of 0 to 2) and ranges from 0 to 8 on the basis of the NASH Clinical Research Network scoring system.[18] Higher scores indicate more severe disease.
‖ Liver fat content was assessed by means of the magnetic resonance imaging proton density fat fraction (MRI-PDFF); values of 5% or higher are consistent with hepatic steatosis.[2]
** Extracellular hepatic water content, which is a measure of hepatic fibroinflammation, was assessed by means of iron-corrected T1-weighted MRI. Values of 875 msec or higher have a high specificity for metabolic dysfunction–associated steatohepatitis (MASH) with an NAFLD activity score of 4 or higher and a fibrosis stage of F2 or higher.[19]
†† Liver stiffness was assessed by means of vibration-controlled transient elastography (FibroScan). Higher values indicate more severe fibrosis. Advanced fibrosis is considered to be unlikely if the value is below 8 kPa and to be likely if the value is 12 kPa or higher.[2]
‡‡ The score on the Fibrosis-4 index is derived from platelet count, alanine aminotransferase and aspartate aminotransferase levels, and age. Advanced fibrosis is considered to be unlikely if the score is below 1.3 and to be likely if the score is 2.67 or higher.[2]
§§ The NIS4 test consists of a panel of four serum biomarkers, including microRNA-34a, α-2 macroglobulin, YKL-40, and glycated hemoglobin. The presence of MASH with an NAFLD activity score of 4 or higher and a fibrosis stage of F2 or higher is considered to be unlikely if the value is below 0.36 and to be likely if the value is 0.63 or higher.[21]
¶¶ The Enhanced Liver Fibrosis test consists of a panel of three serum biomarkers associated with matrix turnover: hyaluronic acid, tissue inhibitor of metalloproteinase 1, and procollagen type III N-terminal peptide. Advanced fibrosis is considered to be unlikely if the value is below 7.7 and to be likely if the value is 9.8 or higher. A score of 9.8 or higher indicates an increased risk of progression to cirrhosis and liver-related clinical events.[2]
‖‖ N-terminal type III collagen propeptide (Pro-C3) is a serum biomarker that detects the formation of type III collagen. On the basis of the first-generation assay, a level of higher than 13.45 μg per liter was indicative of advanced fibrosis.[22] The results shown here were measured with the use of the second generation assay; to compare these results with published data that were measured with the first-generation assay, multiply by 0.152.

The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide for MASH with Liver Fibrosis

A PLAIN LANGUAGE SUMMARY

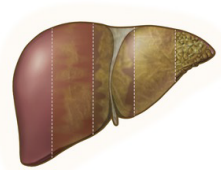
Based on the NEJM publication: Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis by R. Loomba et al. (published June 8, 2024)

In this trial, researchers assessed the efficacy and safety of once-weekly tirzepatide in persons with metabolic dysfunction–associated steatohepatitis (MASH) and moderate or severe fibrosis.

MASH, formerly known as NASH (nonalcoholic steatohepatitis), is a progressive liver disease characterized by excess fat in the liver, hepatic inflammation, and hepatocyte injury, with or without fibrosis.

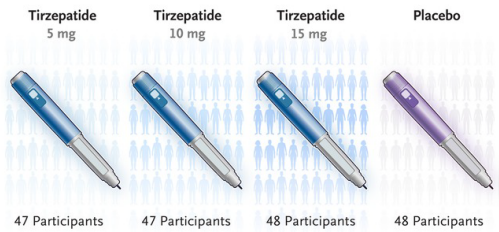
WHY WAS THE TRIAL DONE?

MASH is associated with liver-related complications and death. Tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist, has been shown to reduce liver fat and improve biomarkers of MASH and fibrosis in persons with type 2 diabetes. The efficacy and safety of tirzepatide in persons with MASH and moderate or severe fibrosis are unclear.

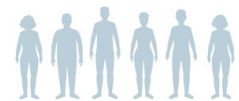


HOW WAS THE TRIAL CONDUCTED?

190 adults with a body-mass index (BMI) between 27 and 50, histologically confirmed MASH, and moderate or severe fibrosis received once-weekly subcutaneous tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at week 52.



PARTICIPANTS



WHO
- 190 participants
- 18 to 80 years of age
- Women: 57%; Men: 43%

CLINICAL STATUS
- Biopsy-confirmed MASH
- Stage 2 or 3 fibrosis
- BMI, 27 to 50
- With or without type 2 diabetes mellitus

TRIAL DESIGN

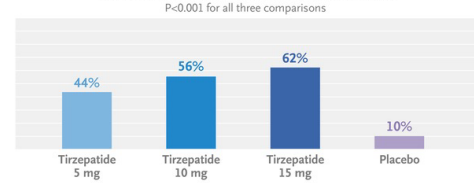
- PHASE 2
- MULTICENTER
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 10 COUNTRIES

RESULTS

The percentage of participants who had resolution of MASH without worsening of fibrosis was significantly higher in all three tirzepatide groups than in the placebo group.

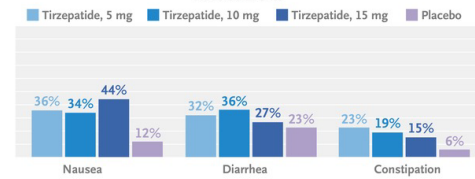
Resolution of MASH and No Worsening of Fibrosis

P<0.001 for all three comparisons



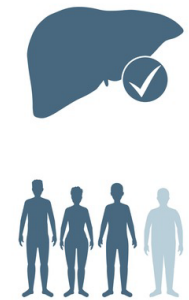
Gastrointestinal events were the most common adverse events with tirzepatide and were mostly mild or moderate in severity.

Adverse Events



FIBROSIS STAGE

The percentage of participants who had an improvement (decrease) of at least one fibrosis stage without worsening of MASH (a key secondary end point) also favored the tirzepatide groups.



LIMITATIONS AND REMAINING QUESTIONS

- The small sample size did not provide adequate statistical power to evaluate the effect of tirzepatide on fibrosis.
- The trial was too short to assess the effect of tirzepatide on major adverse liver outcomes.
- Persons with MASH that had progressed to cirrhosis were not included in the trial.

CONCLUSIONS

In participants with MASH and moderate or severe fibrosis, once-weekly tirzepatide at a dose of 5 mg, 10 mg, or 15 mg was more effective than placebo for resolution of MASH without worsening of fibrosis.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04166773
Trial funding: Eli Lilly
Full citation: Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391:299-310. DOI: 10.1056/NEJMoa2401943

Loomba R et al. N Engl J Med2024;391:299-310

Thyroid hormone regulation of hepatic glucose metabolism

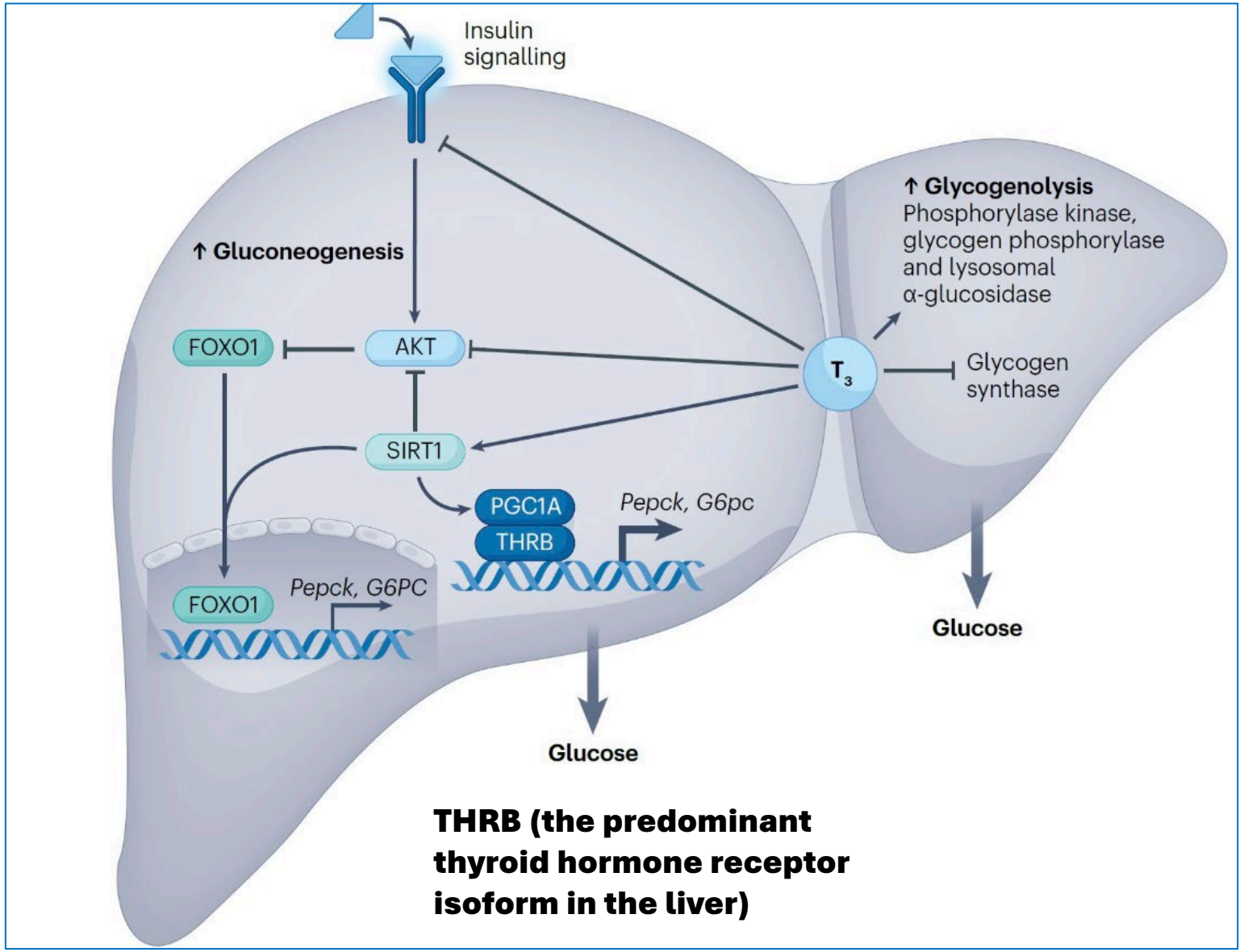
Hypothyroidism causes MASH

Deiodinase 1 mRNA and protein expression and activity are downregulated as MASH progresses to produce ‘intrahepatic’ hypothyroidism.

Increased lipogenesis and decreased fatty acid β-oxidation cause steatosis and lipotoxicity that lead to inflammation and fibrosis in MASH.

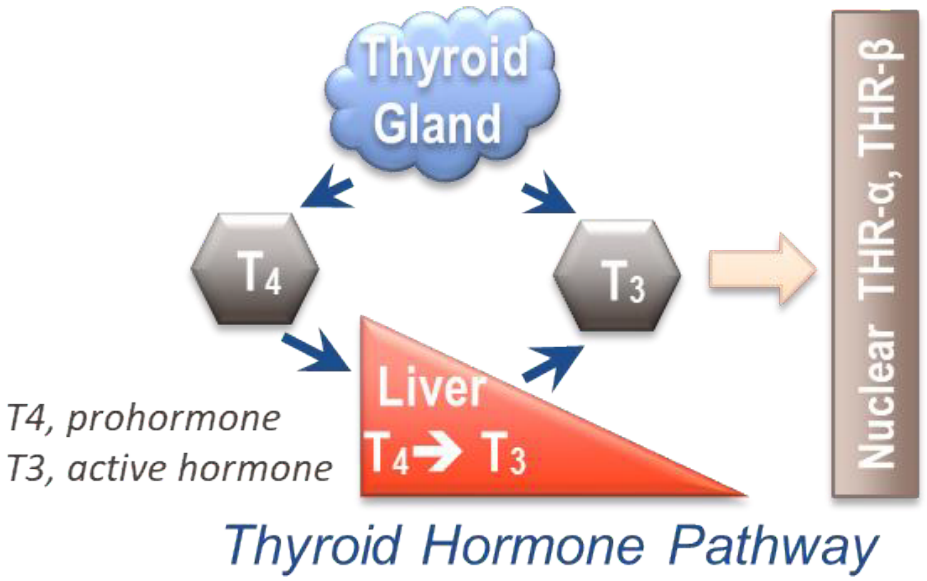
Thyroid hormones increase β-oxidation of fatty acids and mitochondrial turnover to reverse inflammation and fibrosis.

Thyroid hormones or thyromimetics are effective therapeutic agents for MASH



Nature Reviews Gastroenterology & Hepatology (2024)

Liver thyroid hormone receptor-beta



In humans, thyroid hormone receptor-β (THR-β) agonism:

- Lowers LDL-cholesterol
- Lowers triglycerides
- Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

Sinha and Yen. Cell Biosci 2016;6:46

RESEARCH SUMMARY

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

CLINICAL PROBLEM

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease characterized by ≥5% hepatic steatosis with hepatocellular damage and inflammation. There are currently no approved pharmacologic treatments for NASH. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH.

CLINICAL TRIAL

Design: An ongoing, phase 3, multinational, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

Intervention: 966 patients with NASH and fibrosis of stage F1B, F2, or F3 were assigned in a 1:1:1 ratio to receive once-daily resmetirom (80 mg or 100 mg) or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by ≥1 stage with no worsening of the NAFLD activity score.

RESULTS

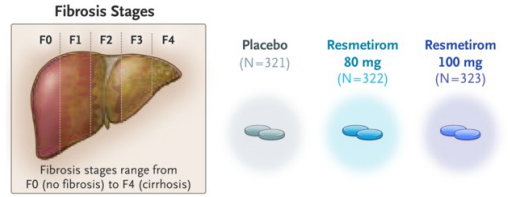
Efficacy: Among evaluable patients, both doses of resmetirom were superior to placebo with respect to the two primary end points.

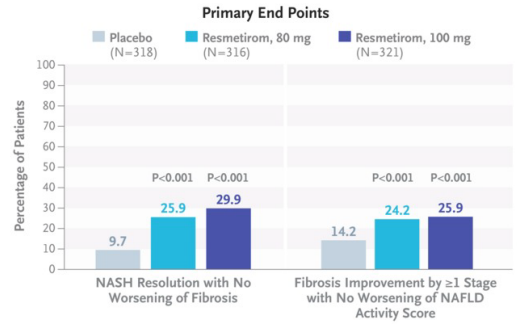
Safety: More than 90% of the patients in each group had adverse events, most of which were mild or moderate in severity. Diarrhea and nausea occurred more often with resmetirom than with placebo. The incidence of serious adverse events was similar among the groups.

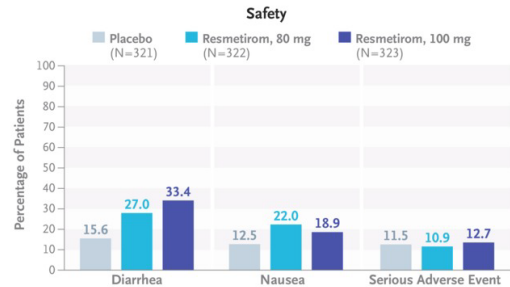
LIMITATIONS AND REMAINING QUESTIONS

- The trial lacked clinical-outcomes data to correlate with the histologic data. The trial is planned to continue to 54 months to evaluate liver-related outcomes, including progression to cirrhosis.
- Almost 90% of the participants were White, which limits the generalizability of the findings to other racial or ethnic groups.

Links: Full Article | NEJM Quick Take | Editorial

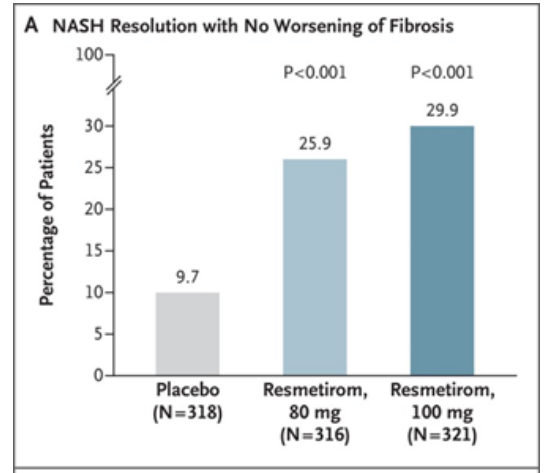


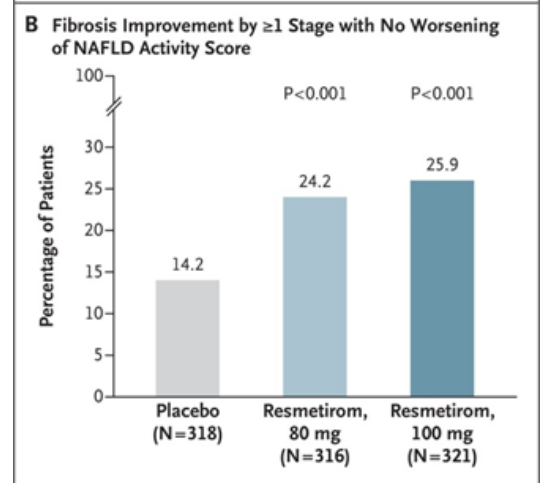


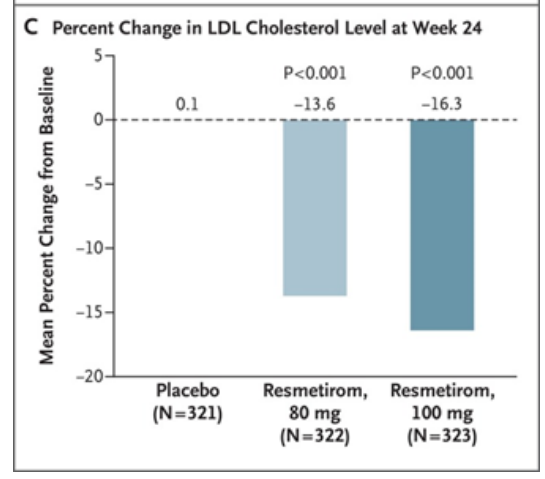


CONCLUSIONS

In patients with NASH and liver fibrosis, once-daily treatment with resmetirom was superior to placebo with respect to NASH resolution and fibrosis improvement by ≥1 stage at 52 weeks of follow-up.

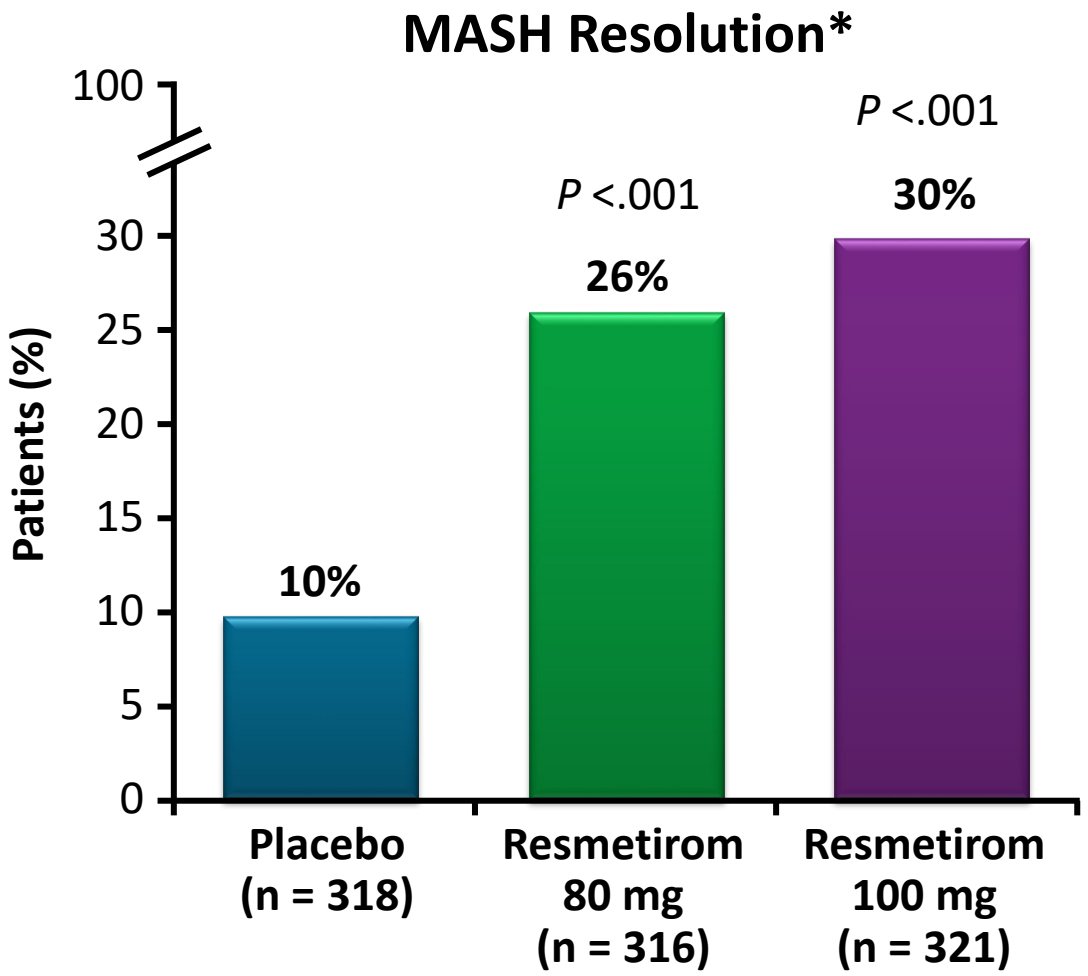


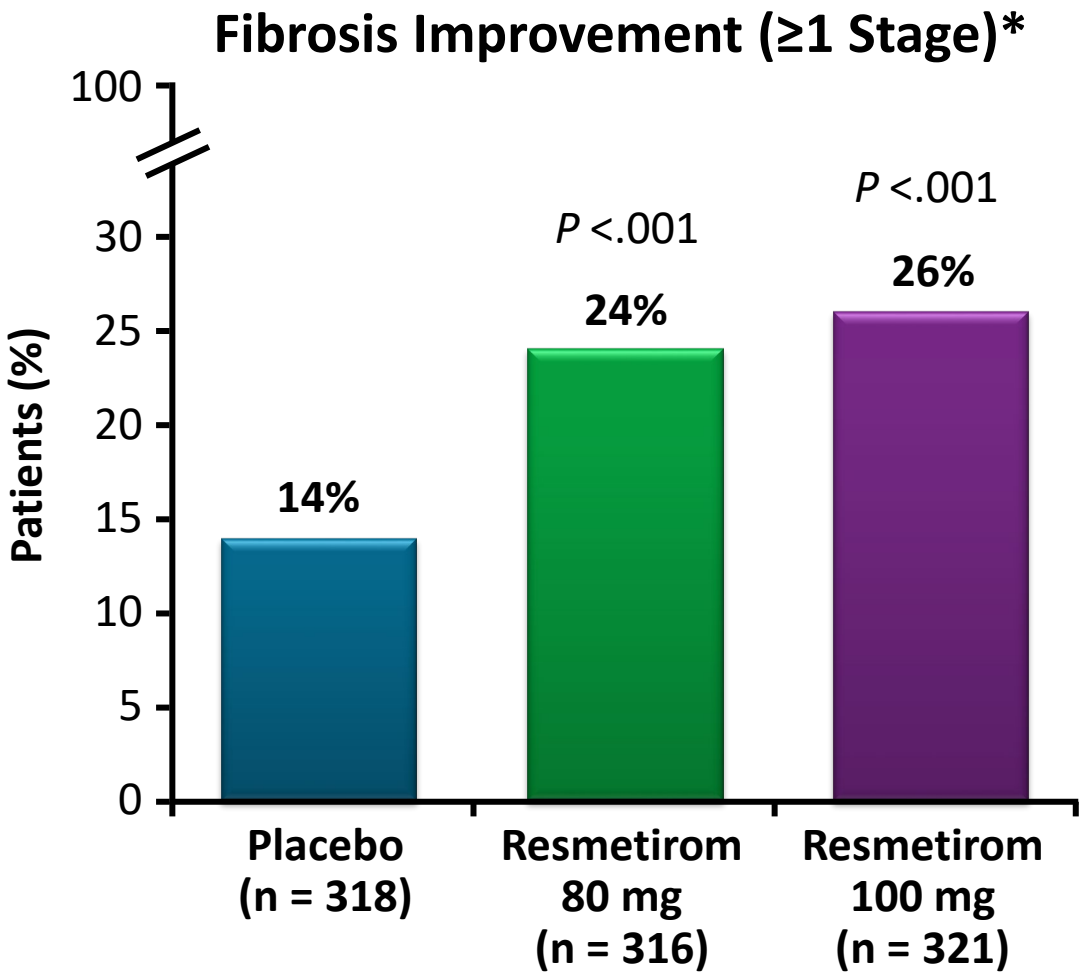




THR-β agonist: Resmetirom

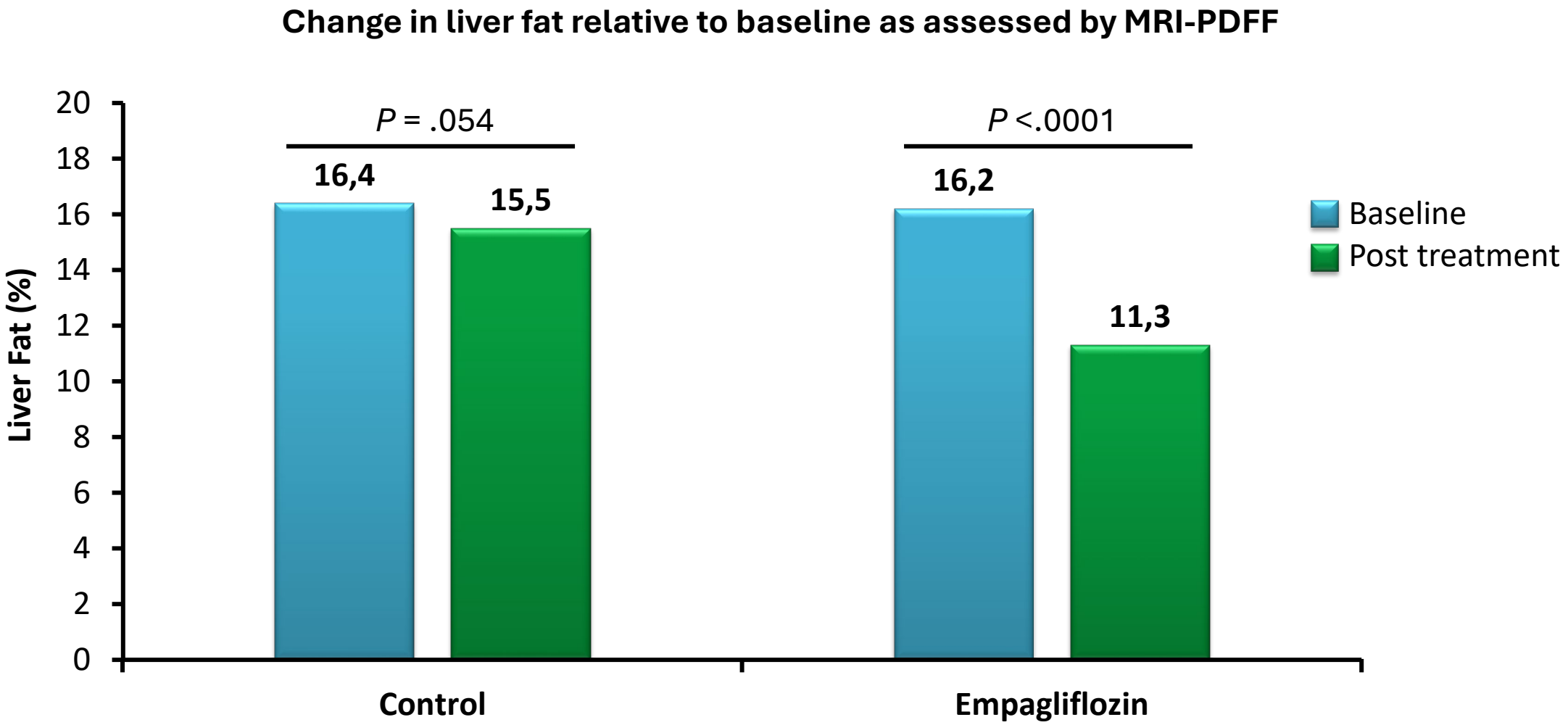
FDA approved March 2024 under accelerated approval for MASH with F2 or F3 fibrosis





*Liver biopsy (ITT) at week 52. Harrison. NEJM. 2024;390:497.

SGLT2 Inhibitors - Empagliflozin



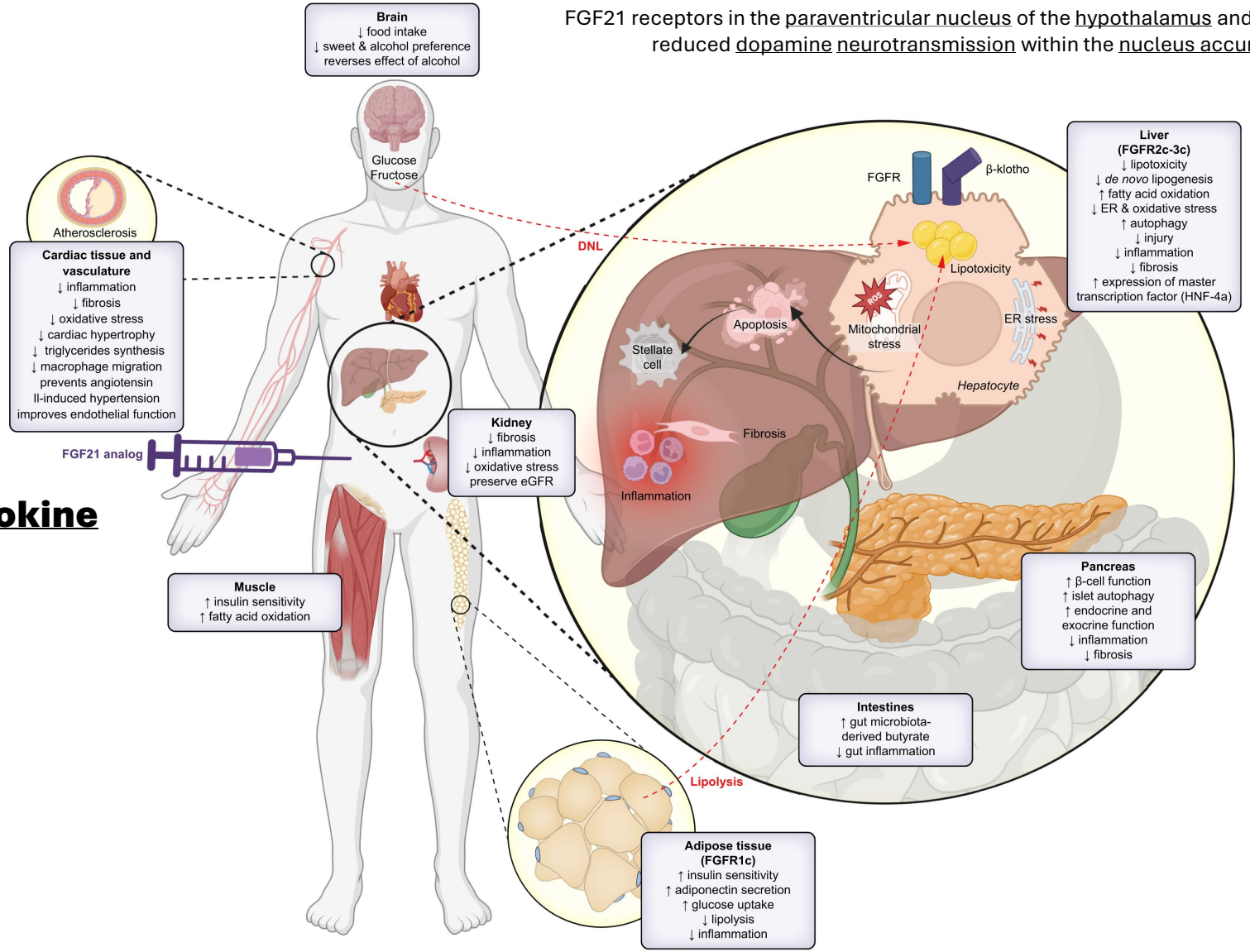
Sodium-Dependent Glucose Cotransporters 1, 2

Kuchay. Diabetes Care. 2018;41:1801.

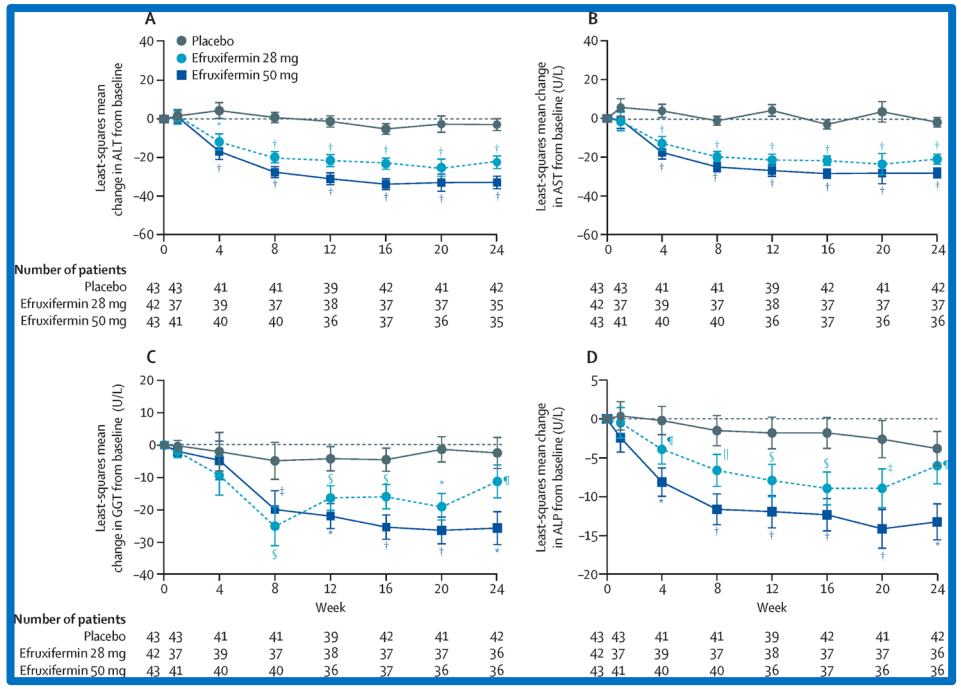
FGF21 analogues e.g. Efruxifermin, pegozafermin

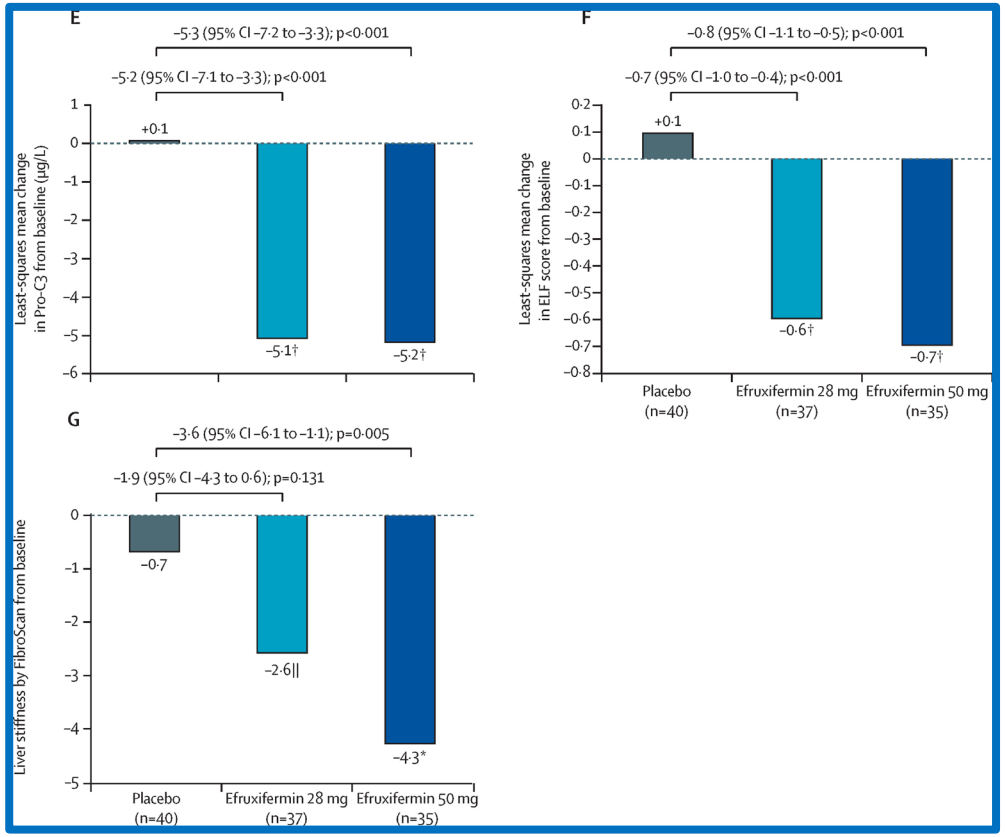
FGF21 receptors in the paraventricular nucleus of the hypothalamus and correlates with reduced dopamine neurotransmission within the nucleus accumbens

FGF21 is a hepatokine



Safety and efficacy of once-weekly Efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial





"Efruxifermin improved liver fibrosis and resolved NASH over 24 weeks in patients with F2 or F3 fibrosis, with acceptable tolerability, supporting further assessment in phase 3 trials"

Harrison, Stephen A et al. The Lancet Gastroenterology & Hepatology, Volume 8, Issue 12, 1080 - 1093

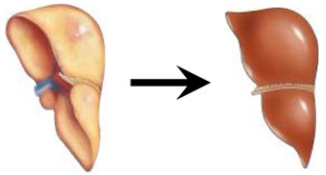
Safety and Efficacy of Efruxifermin in Combination with a GLP-1 Receptor Agonist in patients with NASH/MASH and Type 2 Diabetes in a randomized phase 2b Study

12 weeks of Efruxifermin added to stable F1-F3 patients on GLP-RA (semaglutide, 48.4%; dulaglutide, 45.2%; liraglutide, 6.5%)

Administration of once-weekly efruxifermin, for 12 weeks, to patients with type 2 diabetes and MASH with fibrosis (F1–F3) receiving a stable GLP1-RA:

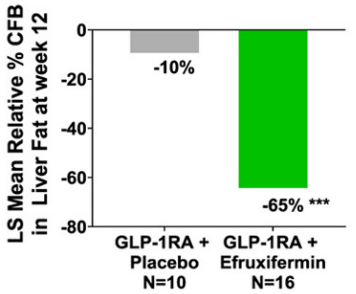
50 mg efruxifermin (n=21)

vs placebo (n=10)

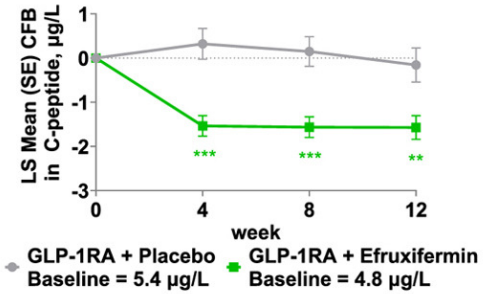


Improved liver and metabolic health:

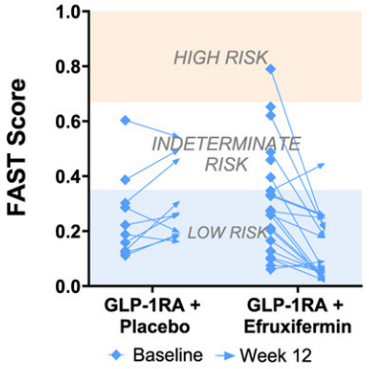
Decreased liver fat



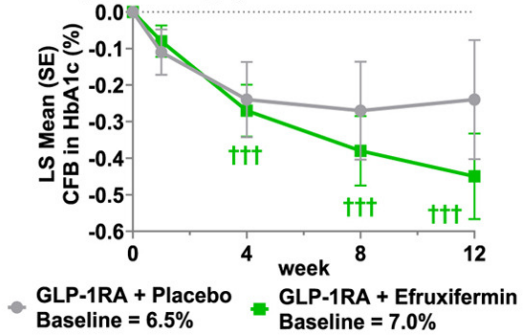
Improved insulin sensitivity



Reduced risk of MASH progression



Improved glycemic control



Clinical Gastroenterology and Hepatology

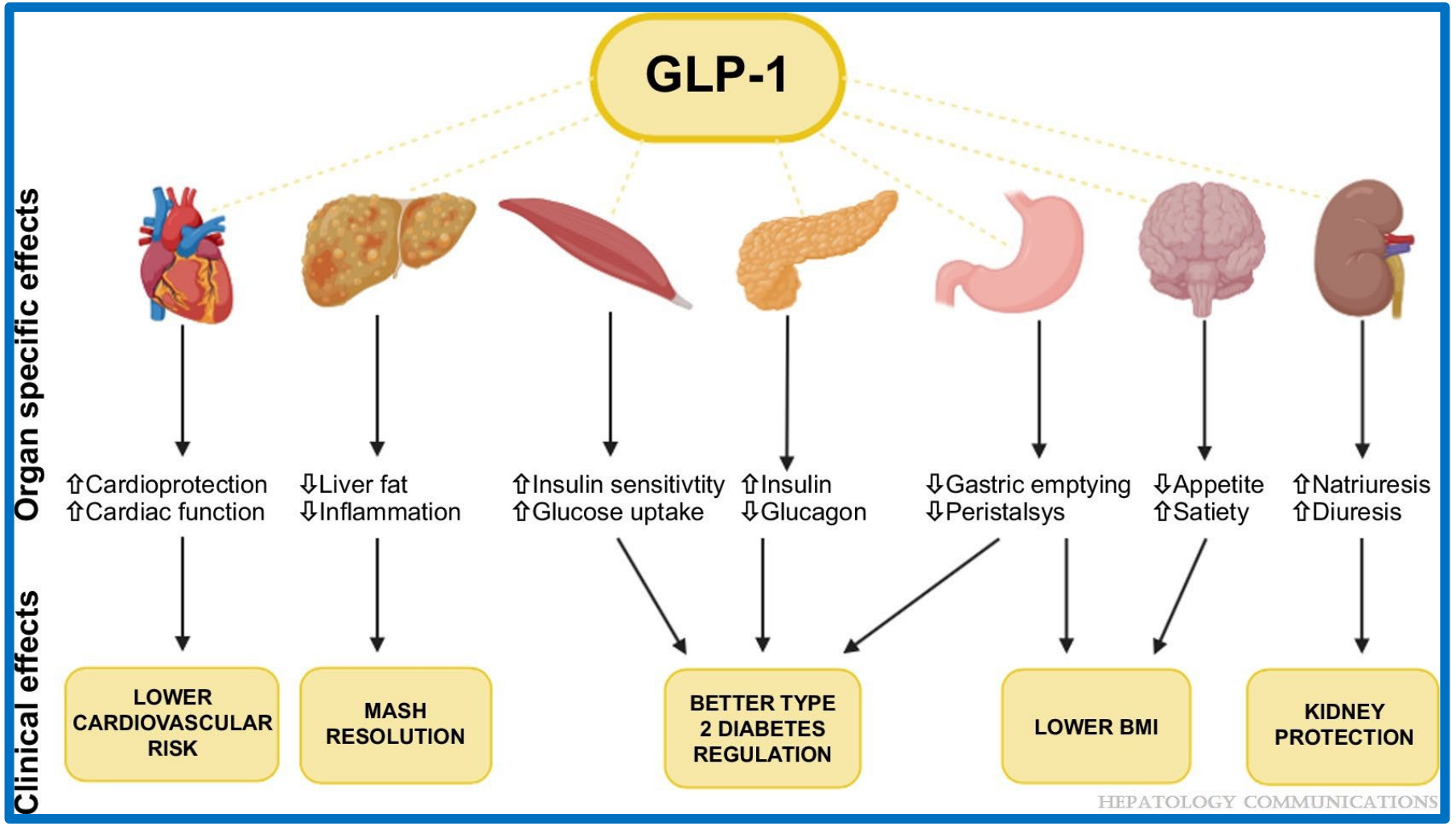
Harrison, Stephen A. et al. Clinical Gastroenterology and Hepatology, 2024

My thoughts – in conclusion

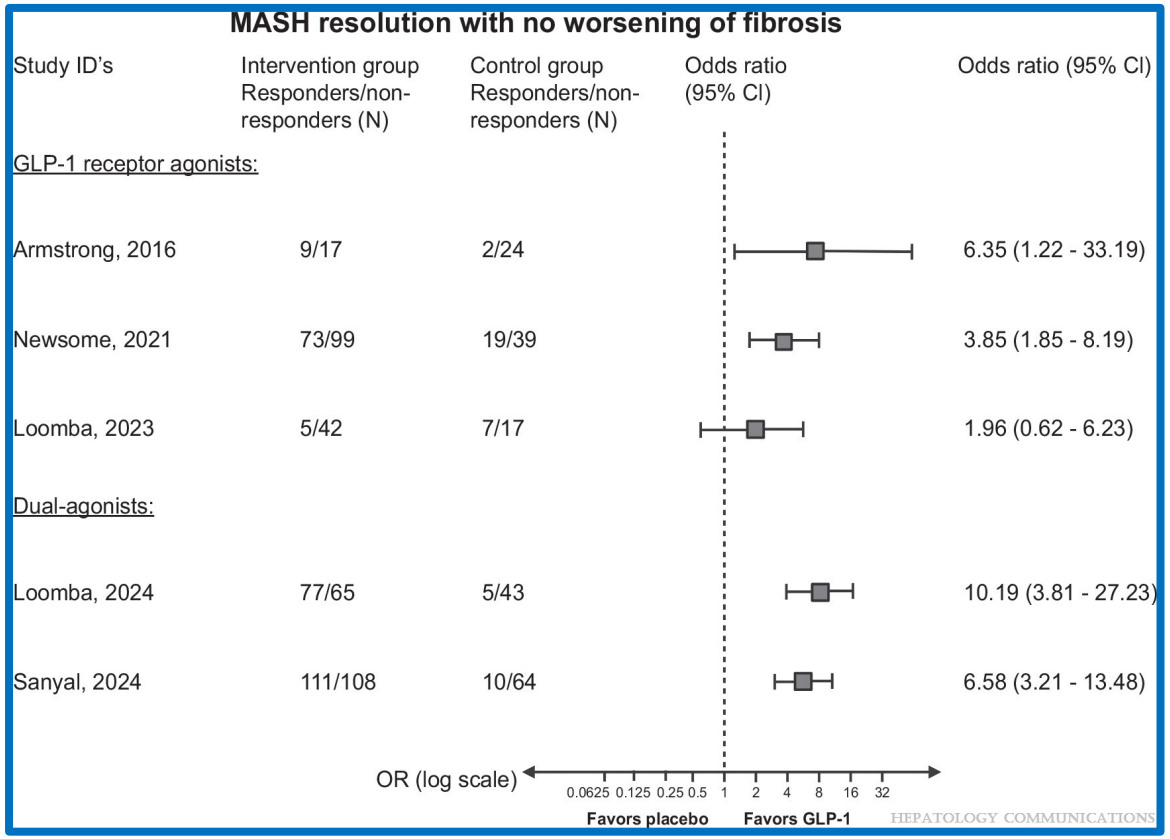
- Very promising data and therapeutic prospects
- TRHB and FGF21 agonists – improve fibrosis! (and MASH)
- GLP RA's – improve MASH, mostly flat on liver fibrosis

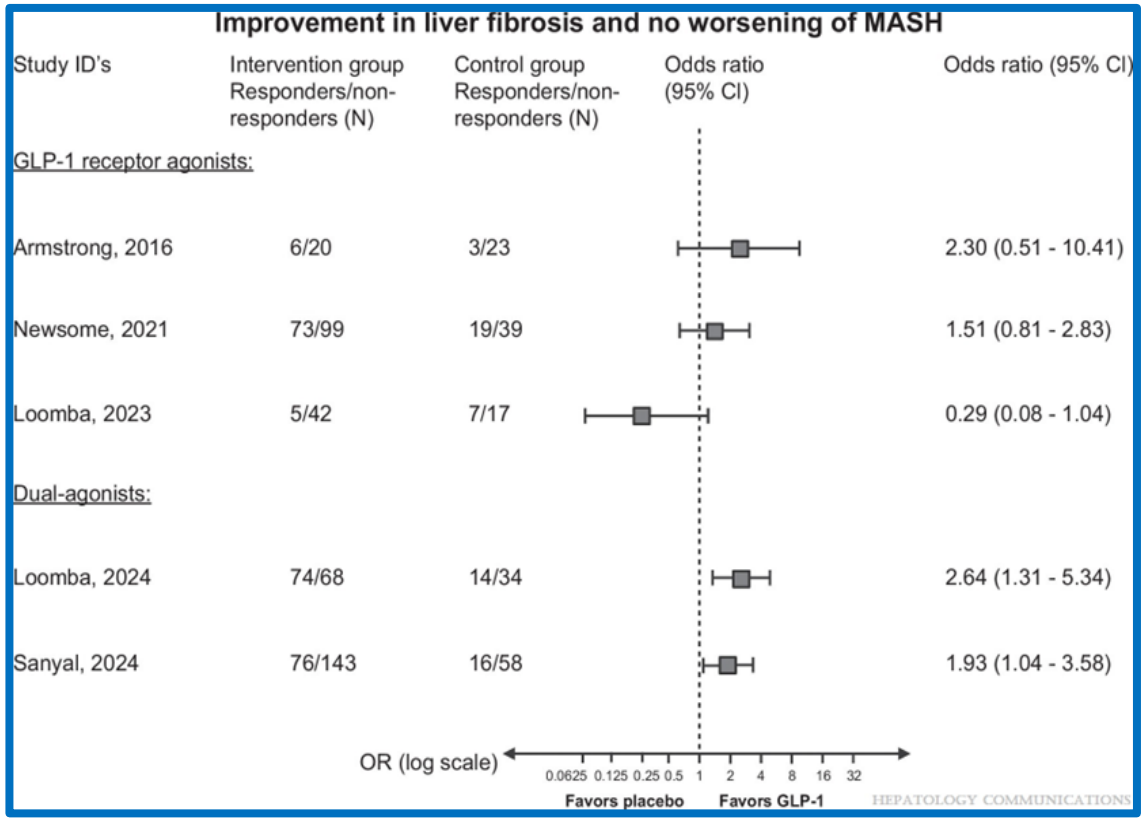
BUT

Protean effects of GLP-RA

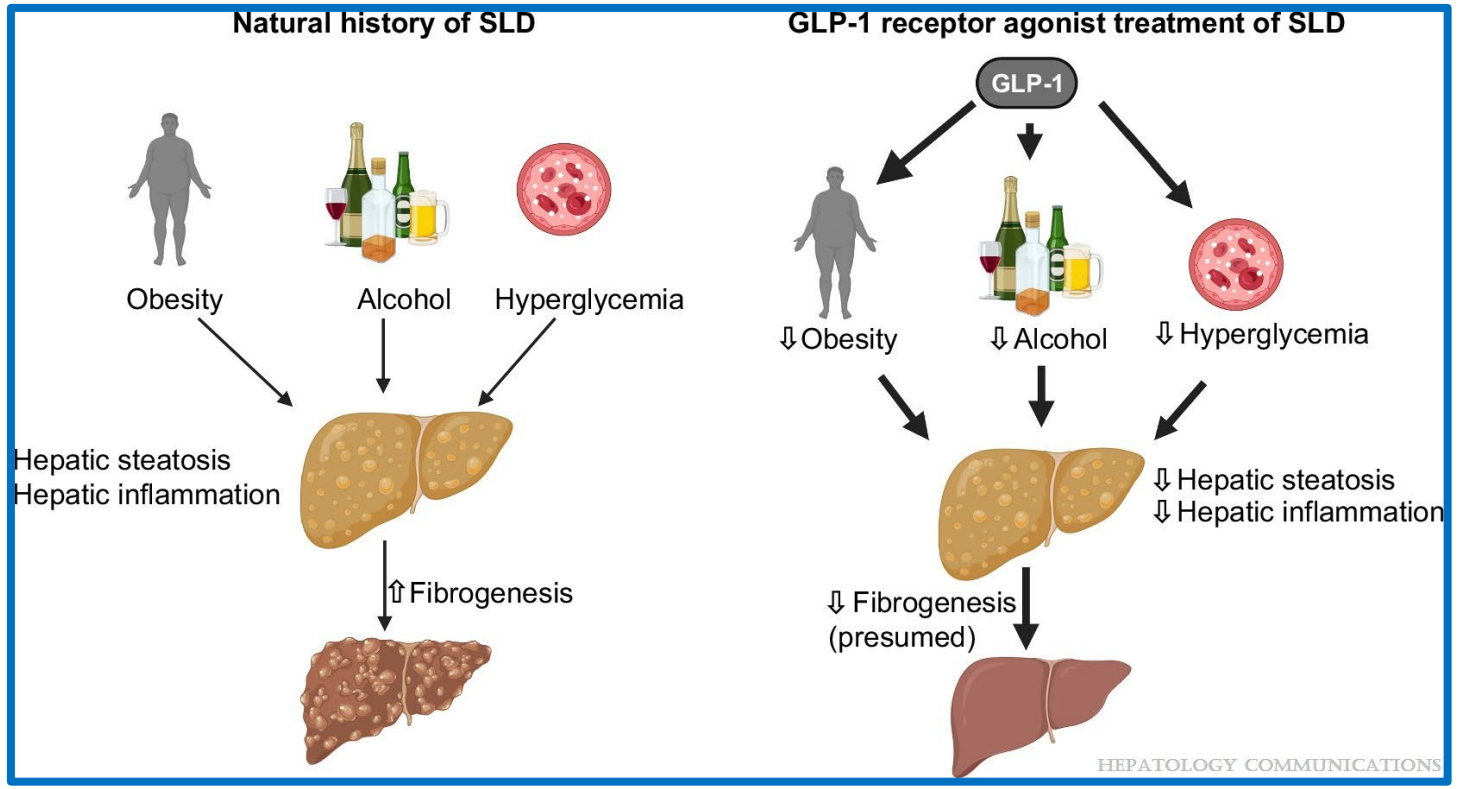


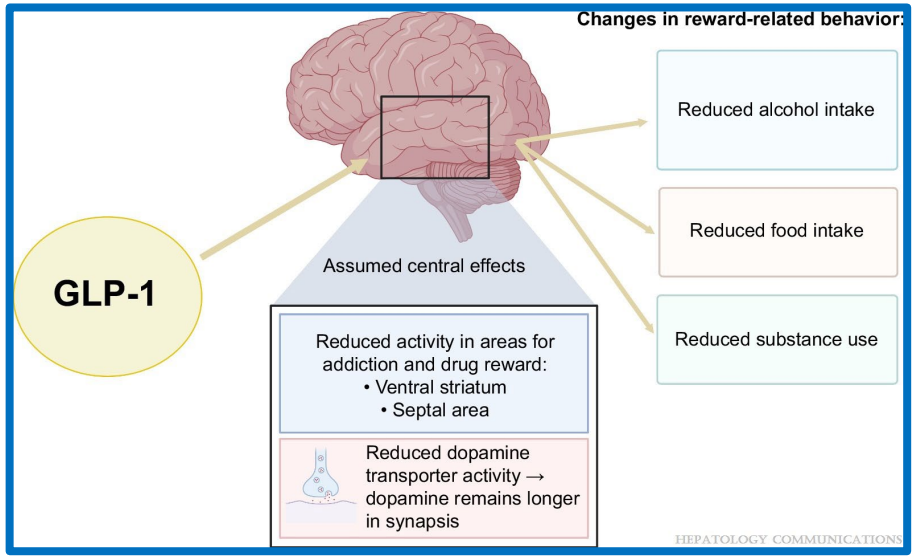
GLA RAs – the issue to date





Protean (liver) effects of GLP-RA





For the now and immediate future

- The mirror will trump the liver (fibrosis)
- GLP RA’s will dominate !