Incretin Based Therapy in MASLD

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Agenda

- Definition
- Natural course
- Clinical outcomes
- Diagnostic approach
- Overview of clinical studies

  liraglutide

  Semaglutide

  Tirzepatide

  Survodutide

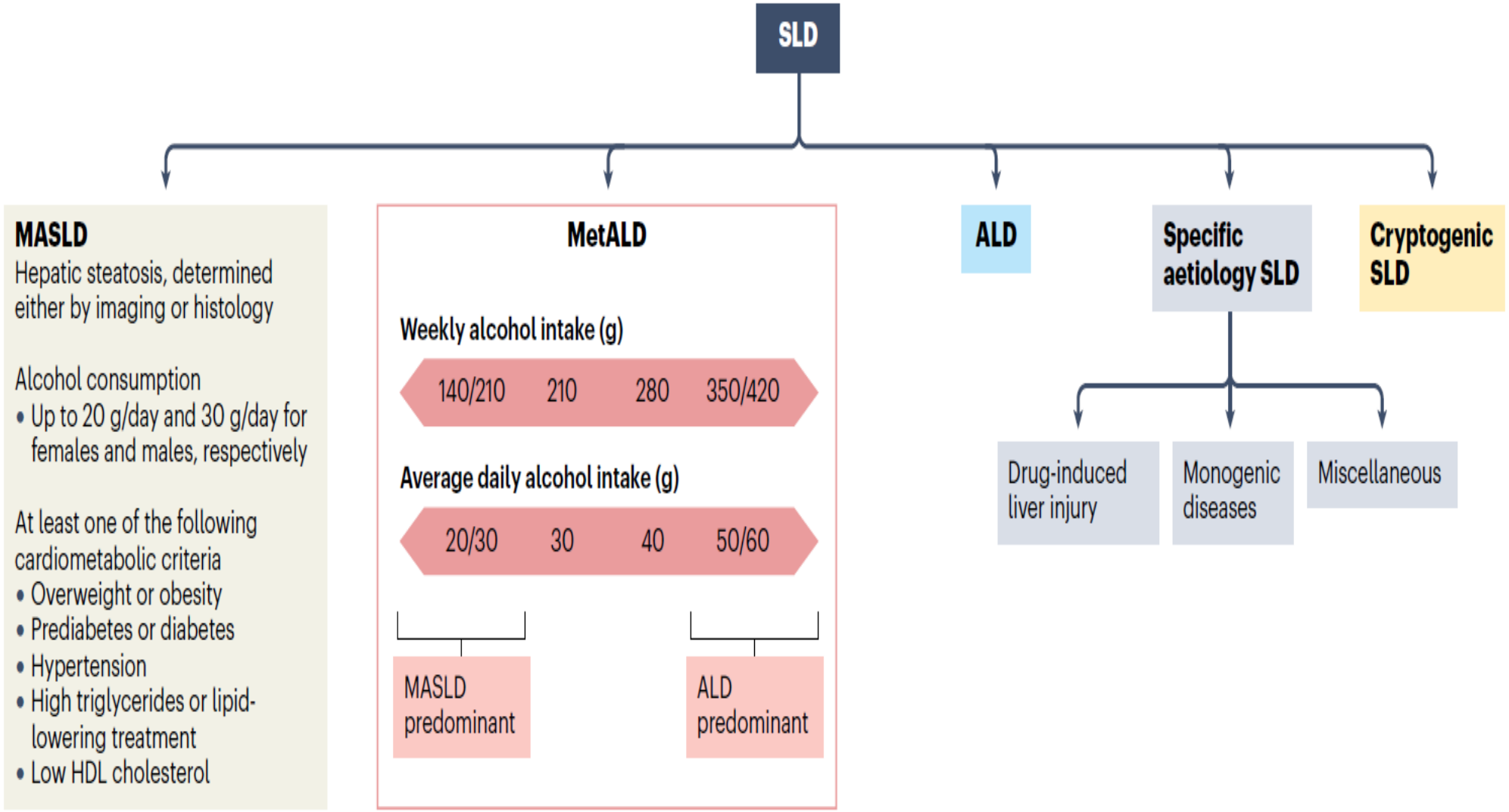
  Retatrutide
- Mechanistic roles of GLP-1 RAs in MASLD pathogenesis
- What do guidelines tell us?
- Take home message

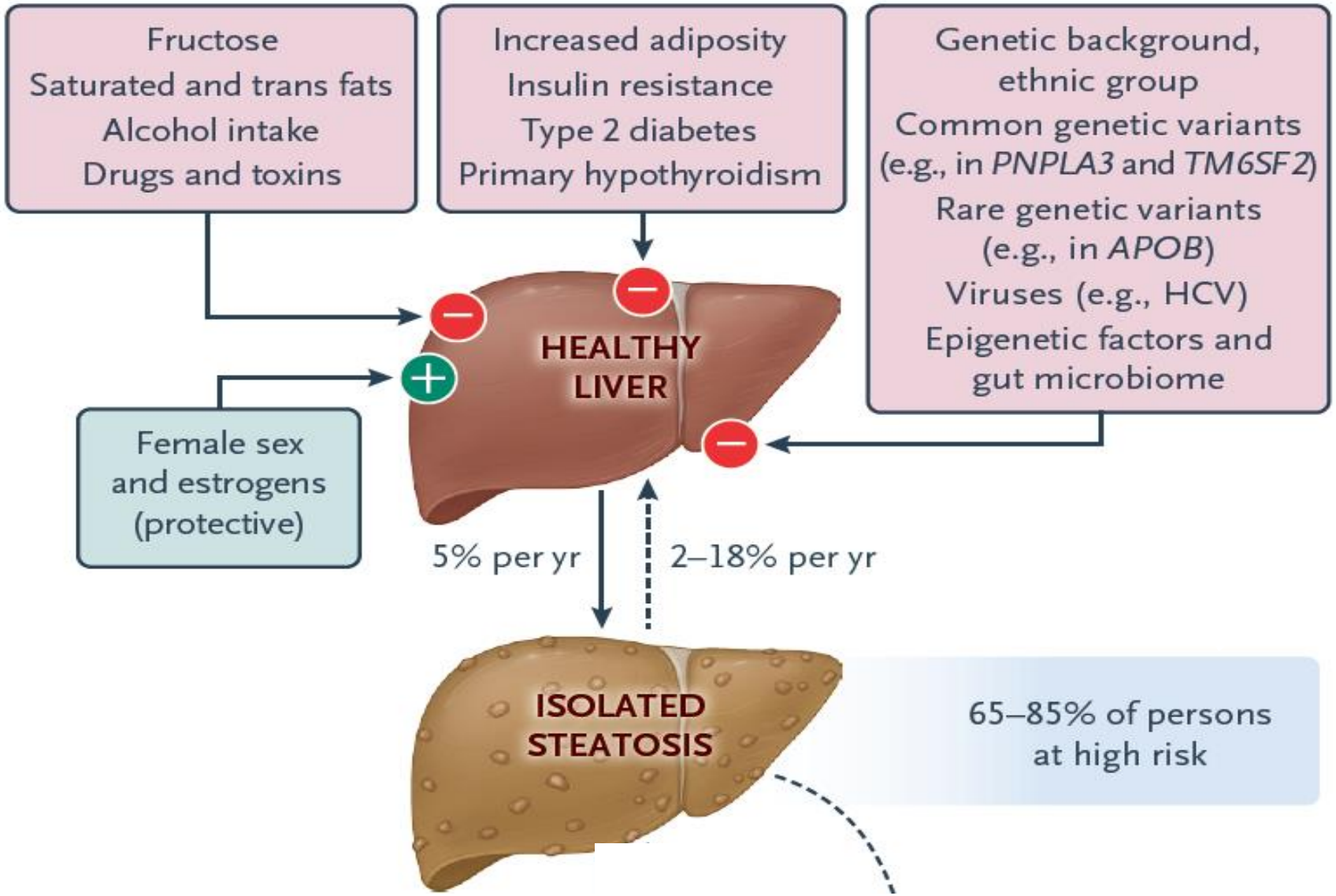
Defining criteria of steatotic liver diseases

Features	Type of liver disease				
	NAFLD	MAFLD	MASLD	MetALD	ALD
Hepatic steatosis	Required	Required	Required	Required	Required
Cardiometabolic criteria	Not required	Either type 2 diabetes mellitus or overweight/obesity or two of the following: High waist circumference Hypertension or antihypertensive treatment Elevated triglyceride levels or lipid-lowering treatment Low HDL-cholesterol levels or lipid-lowering treatment Prediabetes Homeostasis model assessment of insulin resistance score ≥2.5 Plasma high-sensitivity C-reactive protein level >2 mg/l	At least one of the following: Overweight/obesity or high waist circumference Prediabetes or diabetes Hypertension or antihypertensive treatment Elevated triglyceride levels or lipid-lowering treatment Low HDL-cholesterol levels or lipid-lowering treatment	At least one of the following: Overweight/obesity or high waist circumference Prediabetes or diabetes Hypertension or antihypertensive treatment Elevated triglyceride levels or lipid-lowering treatment Low HDL-cholesterol levels or lipid-lowering treatment	Not required
Alcohol consumption	<20 g/day for women and <30 g/day for men	No thresholds	<20 g/day for women and <30 g/day for men	20–50 g/day for women and 30–60 g/day for men	>50 g/day for women and >60 g/day for men
Viral hepatitis and other causes of liver disease	Excluded	Allows for concomitant liver diseases, such as viral hepatitis	Allows for concomitant liver diseases, such as viral hepatitis	Allows for concomitant liver diseases, such as viral hepatitis	Allows for concomitant liver diseases, such as viral hepatitis

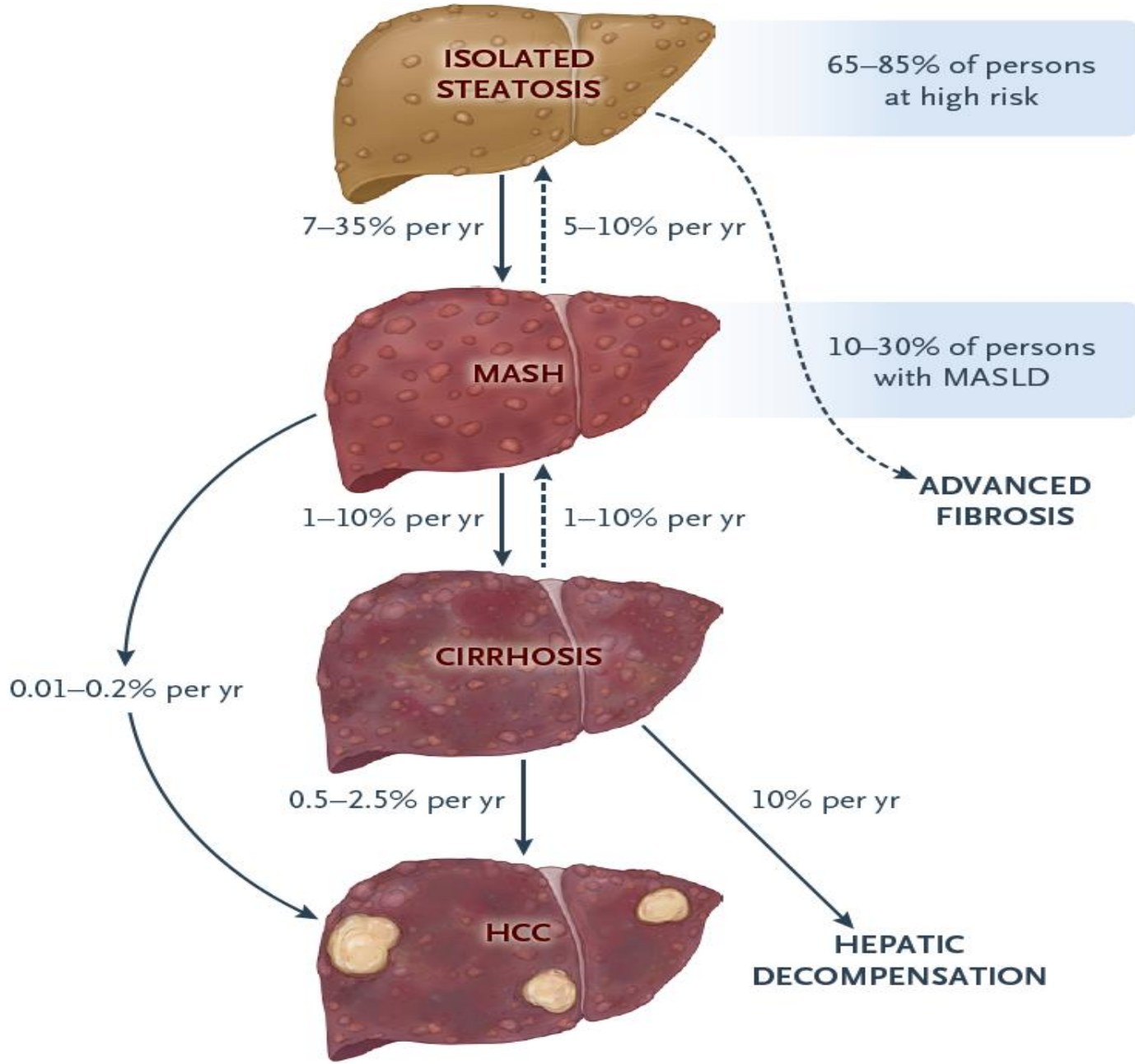
Huang, D.Q., Wong, V.W.S., Rinella, M.E. et al. Metabolic dysfunction-associated steatotic liver disease in adults. Nat Rev Dis Primers 11, 14 (2025)

The updated definition for SLD



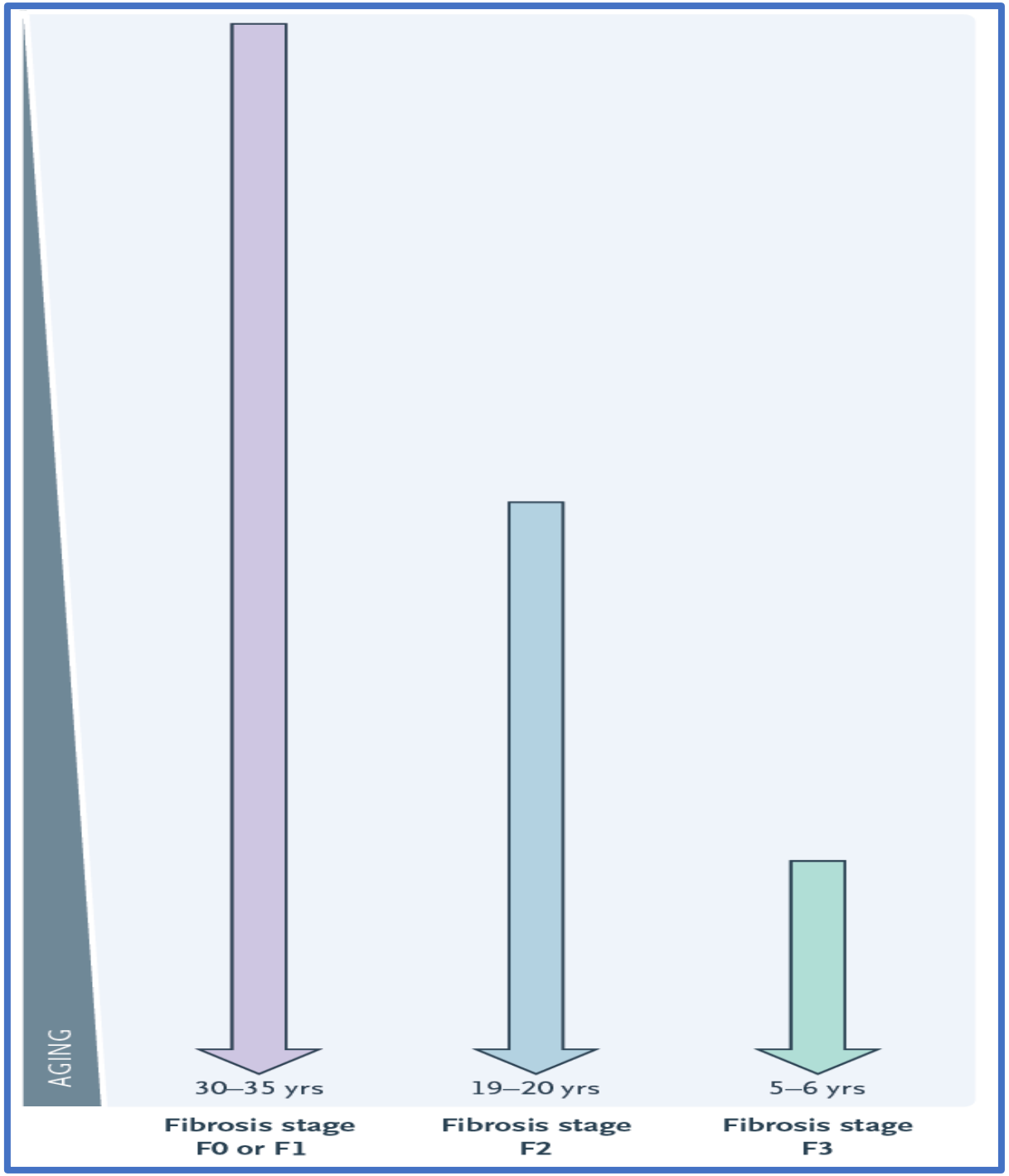


N Engl J Med 2025;393:683-98.



N Engl J Med 2025;393:683-98.

Time to Cirrhosis or Hepatic Decompensation



Epidemiology of Steatotic liver Disease

- ✓ The overall prevalence of steatotic liver disease is currently >30%.
- ✓ The prevalence of the potentially progressive form of steatosis or steatohepatitis is 12% - 14%.

Among persons with T2D:

- ✓ 70% have steatosis.
- ✓ 30% to 40% of persons with diabetes have steatohepatitis.
- ✓ 15% have clinically significant liver fibrosis (stages ≥F2).

Journal of Hepatology 2019 vol. 71 j 793–801
N Engl J Med 2025;393:683-98

Table 2. Nonalcoholic Fatty Liver Disease Activity Score[a]

Histologic feature	Category	Score
Steatosis, %	<5	0
	5-33	1
	34-66	2
	>66	3
Hepatocyte ballooning degeneration	None	0
	Few balloon cells	1
	Many balloon cells or prominent ballooning	2
Lobular inflammation	None	0
	<2 foci per 200 × field	1
	2-4 foci per 200 × field	2
	>4 foci per 200 × field	3
Sum of steatosis, ballooning, and lobular inflammation scores		NAS score (0-8)

Fibrosis (F) grade	
None	0
Perisinusoidal or periportal	1
Mild, zone 3, perisinusoidal	1A
Moderate, zone 3, perisinusoidal	1B
Portal/periportal	1C
Perisinusoidal and portal/periportal	2
Bridging fibrosis	3
Cirrhosis	4

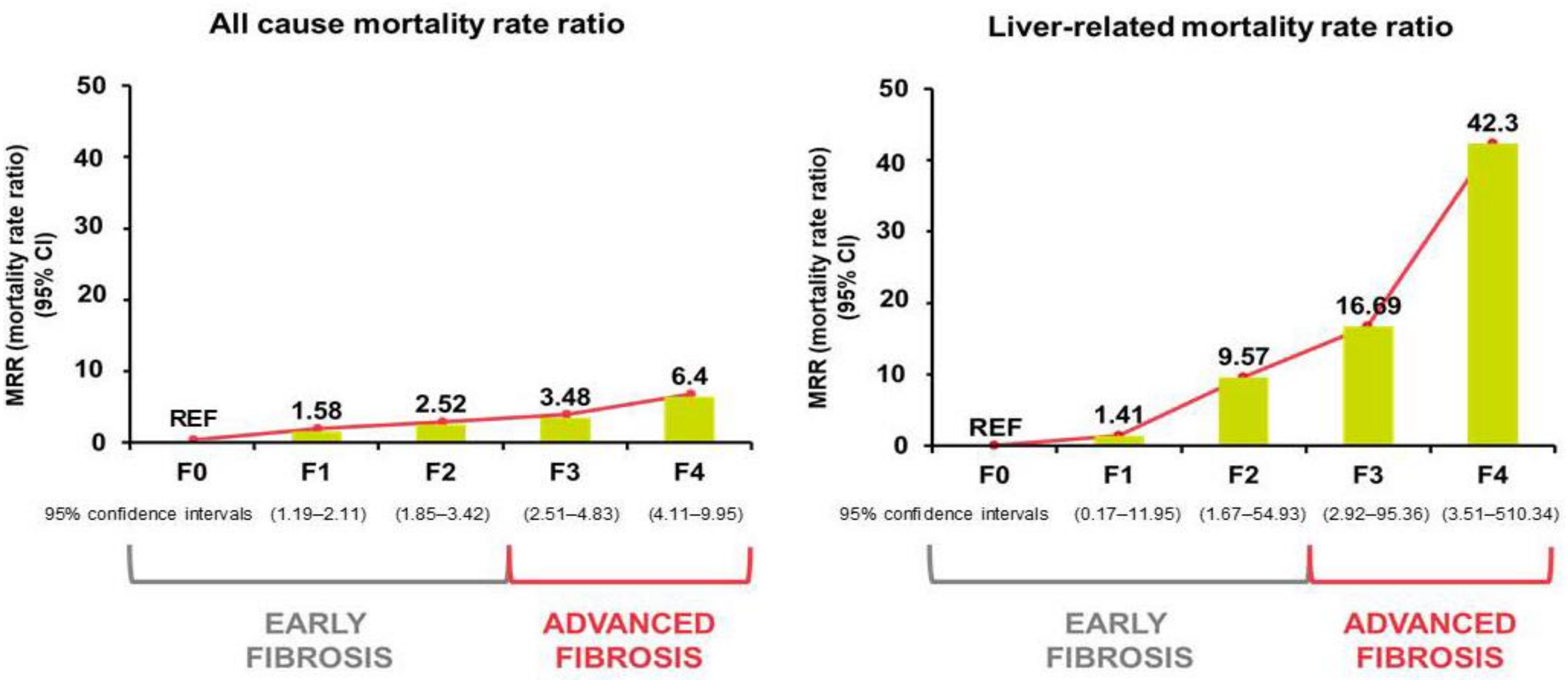
Important Outcomes in Patients With MASLD

Approximate increase in the risk of new-onset adverse clinical outcomes
Type 2 diabetes (if no type 2 diabetes at baseline) — 2.2×
Fatal or nonfatal cardiovascular disease — 1.5×
Heart failure — 1.5×
Atrial fibrillation — 1.2×
CKD (stage ≥3) — 1.5×
Extrahepatic cancers — 1.5×
Cirrhosis or HCC — 2–10×

N Engl J Med 2025;393:683-98.

The risk of liver-related mortality increases exponentially with increasing fibrosis stage

Impact of fibrosis stage on liver-related mortality in a meta-analysis of five multinational cohorts (17,452 PYF)



N Engl J Med 2025;393:683-98.

Dulai PS, et al. Hepatology 2017.

Sex-Specific Impact of Metabolic Dysfunction-Associated Fatty Liver Disease on Incident Cardiovascular Diseases and Mortality

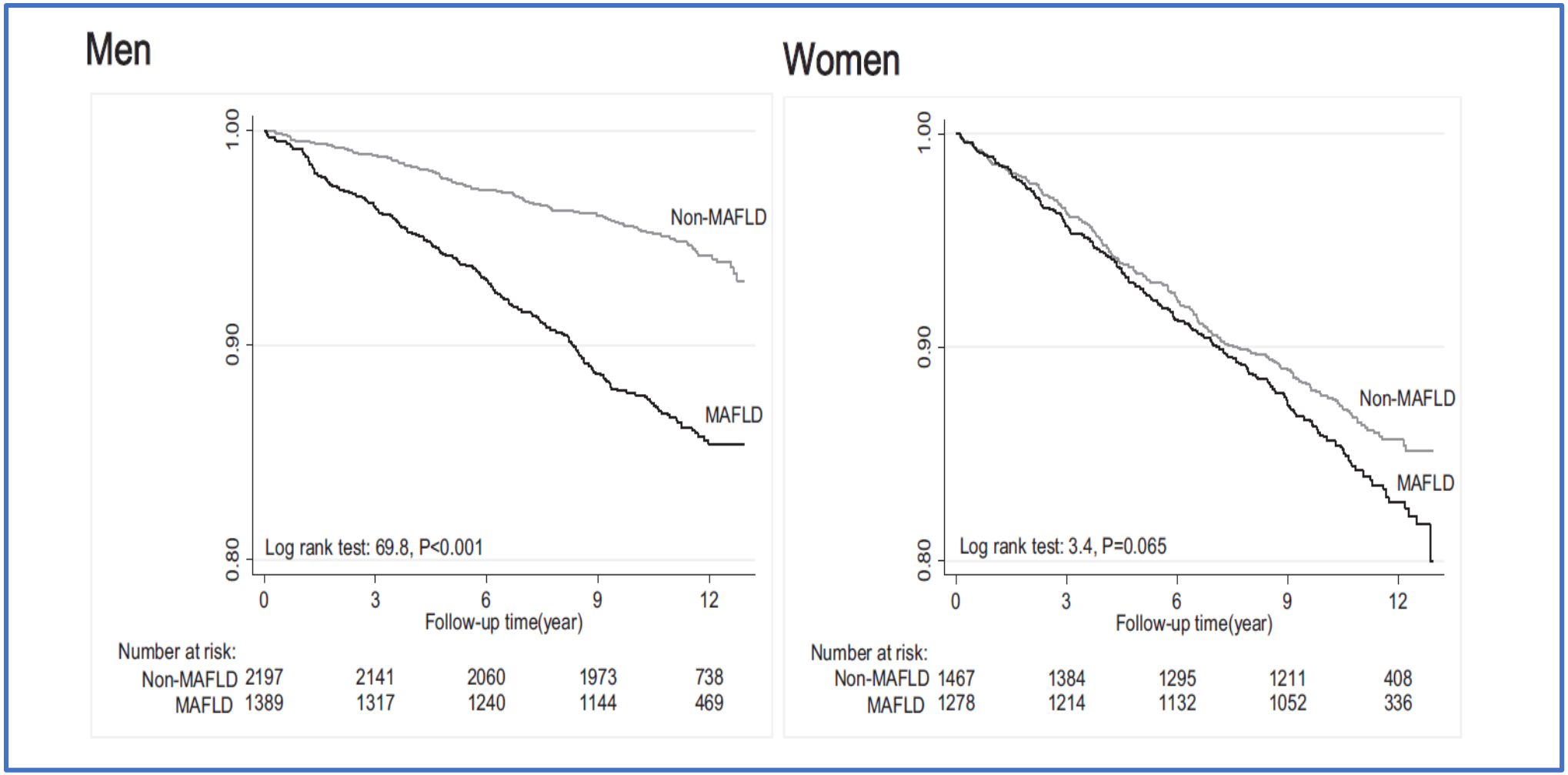
Mahsa Abbaszadeh[1] | Farhad Hosseinpanah[2] | Maryam Tohidi[3] | Sahar Karimpour Reyhan[1] | Maryam Mahdavi[2] | Majid Valizadeh[2]

- Aim: To investigate the prevalence and impact of MAFLD) on cardiovascular disease (CVD) and mortality in men and women over a 12-yearfollow-up period

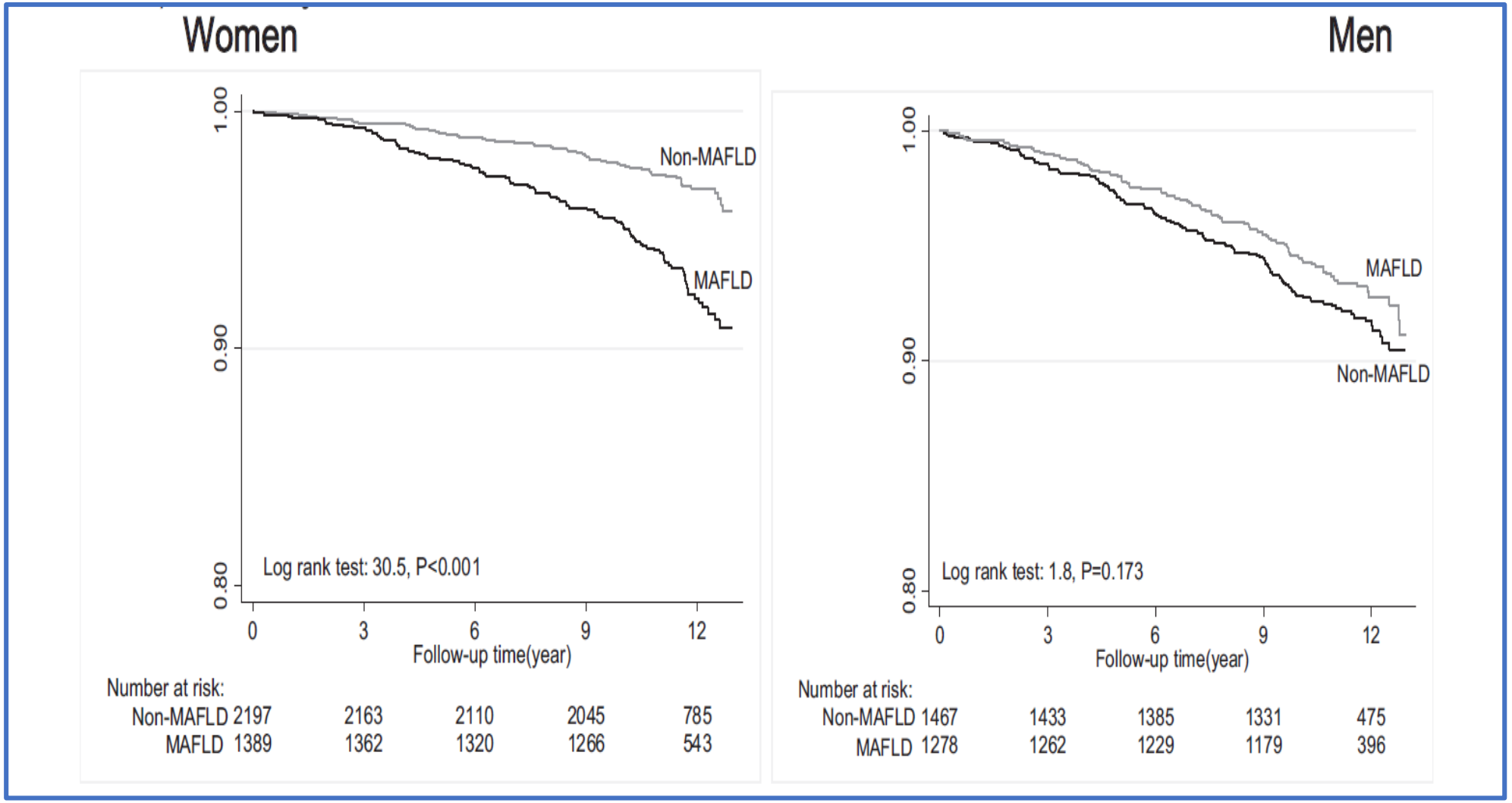
- 7101 individuals aged ≥ 30 were enrolled

Endocrinol Diabetes Metab.2025 May;8(3):e70035.

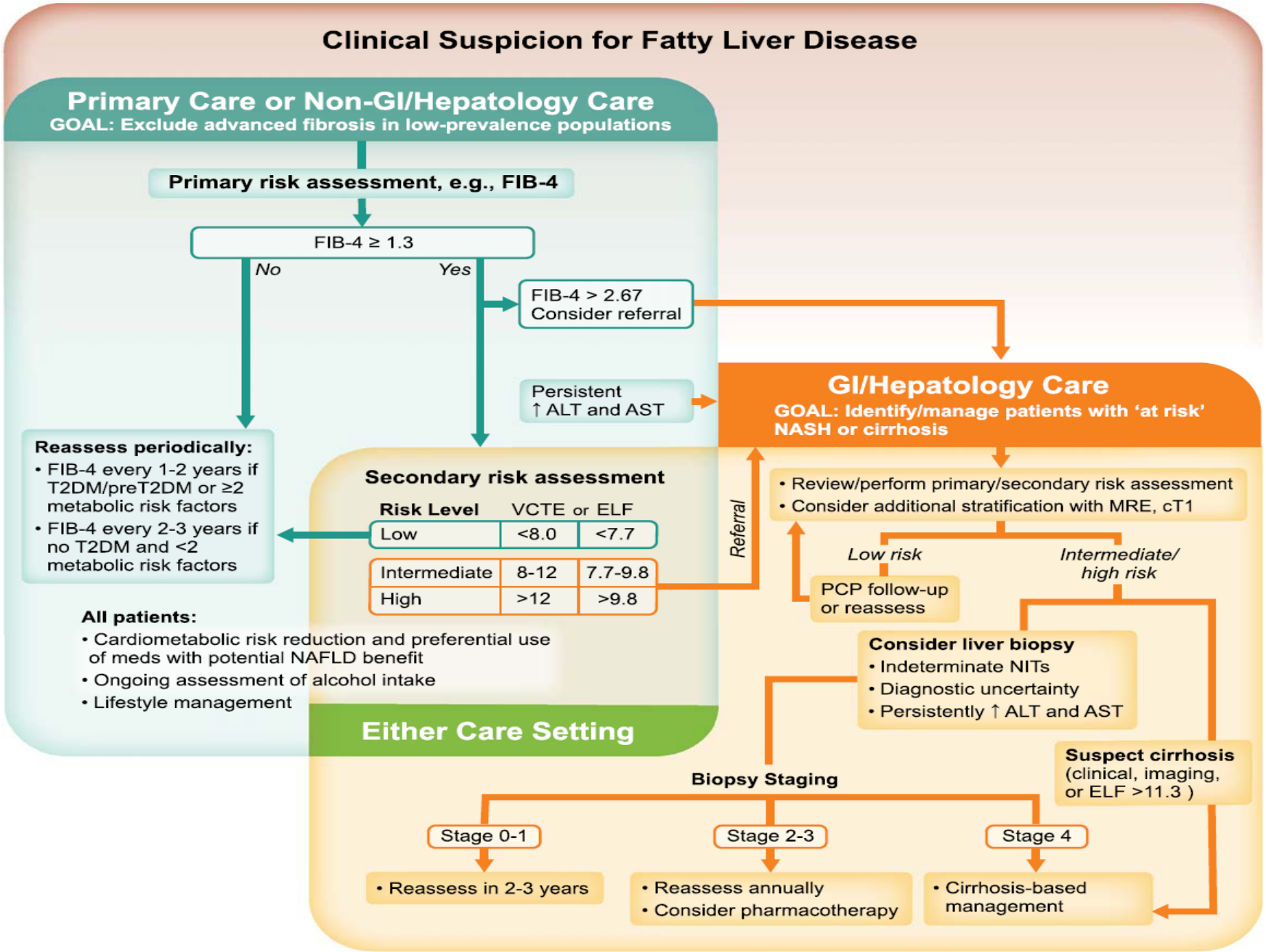
Kaplan–Meier curves for the risk of cardiovascular disease in MAFLD



Kaplan–Meier curves for the risk of mortality in MAFLD



	CVD		Mortality	
	Non-MAFLD	MAFLD	Non-MAFLD	MAFLD
Female ($n = 3586$)				
Number of person-years	23880.9	14430.7	24441.8	15358.7
Number of incidences	119	185	66	98
Incidence rate per 10,000 person-years (95% CI)	49.8 (41.6–59.6)	128.2 (111.0–148.1)	27.0 (21.2–34.4)	63.8 (52.3–77.7)
Hazard ratio (95% CI)				
Unadjusted model	1 (reference)	2.57 (2.05–3.24)[a]	1 (reference)	2.35 (1.72–3.20) *
Model 1#	1 (reference)	1.67 (1.32–2.11)[a]	1 (reference)	1.42 (1.04–1.94) *
Model 2	1 (reference)	1.62 (1.28–2.05)[a]	1 (reference)	1.33 (0.97–1.84)
Model 3	1 (reference)	1.61 (1.27–2.40)[a]	1 (reference)	1.32 (0.96–1.82)
Model 4	1 (reference)	1.48 (1.16–1.88)[a]	1 (reference)	1.38 (1.00–1.91)
Male ($n = 2745$)				
Number of person-years	14,927.8	1,3050.7	15889.3	14026.8
Number of incidences	194	204	117	85
Incidence rate per 10,000 person-years (95% CI)	129.9 (112.9–149.6)	156.3 (136.3–179.3)	73.6 (61.4–88.3)	60.6 (49.0–74.9)
Hazard ratio (95% CI)				
Unadjusted model	1 (reference)	1.20 (0.99–1.46)	1 (reference)	0.82 (0.62–1.09)
Model 1#	1 (reference)	1.42 (1.16–1.73)[a]	1 (reference)	1.17 (0.89–1.56)
Model 2	1 (reference)	1.48 (1.21–1.82)[a]	1 (reference)	1.17 (0.87–1.58)
Model 3	1 (reference)	1.48 (1.20–1.81)[a]	1 (reference)	1.17 (0.87–1.58)
Model 4	1 (reference)	1.36 (1.10–1.67)[a]	1 (reference)	1.17 (0.86–1.59)



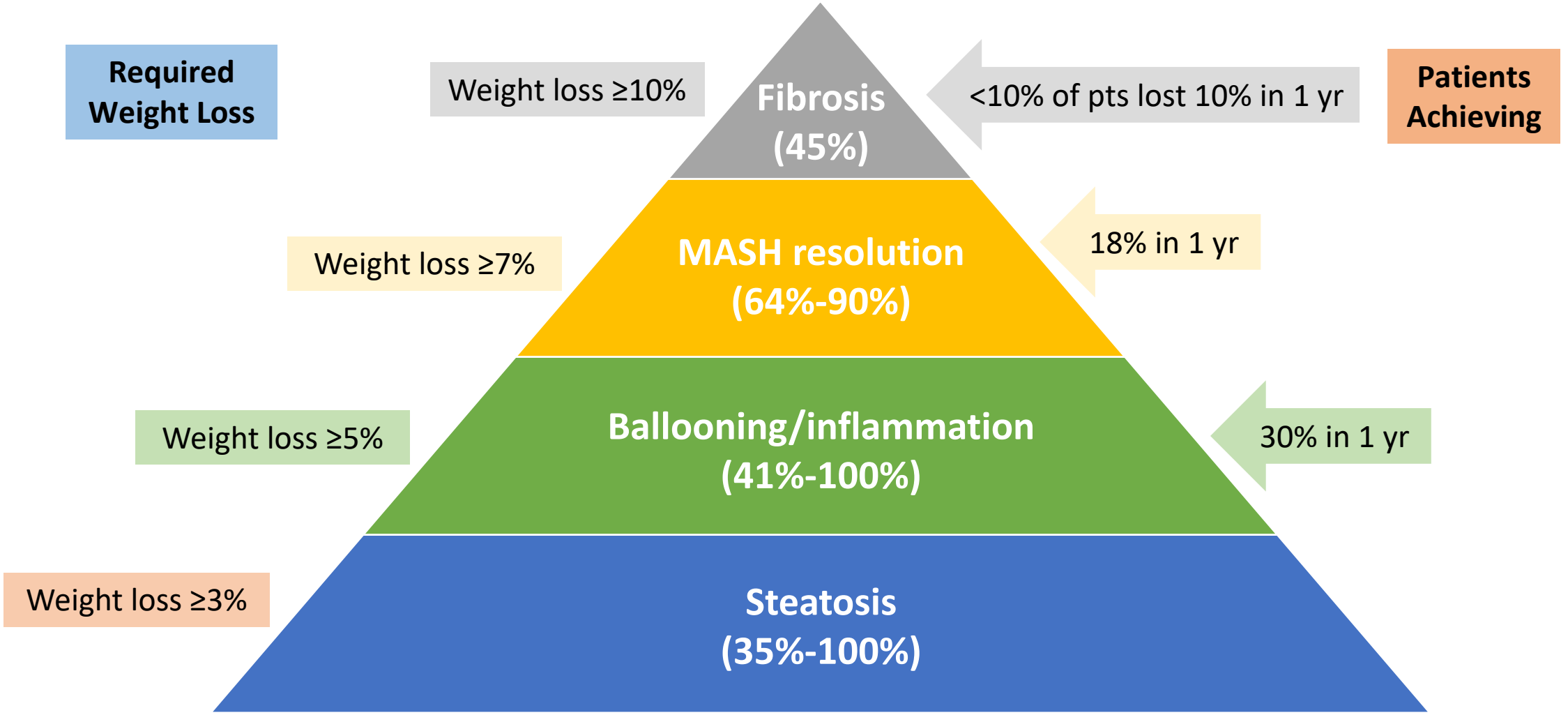
Journal of Hepatology, December 2023. vol. 79 j 1542–1556

Treatments

- Behavioral modifications
- Dietary modifications
- Physical activity
- Medications
- Bariatric surgery

Weight Loss Works—But It Can Be Difficult

7% to 10% decrease in body weight is necessary to achieve steatohepatitis remission and fibrosis regression



Hannah. Clin Liver Dis. 2016:20;339

New Drugs for the Treatment of NASH: What Are the Endpoints for Approval?

Conditional FDA Approval Endpoints

- 1 stage improvement in fibrosis without worsening of NASH
- Resolution of NASH without worsening of fibrosis

Full Approval

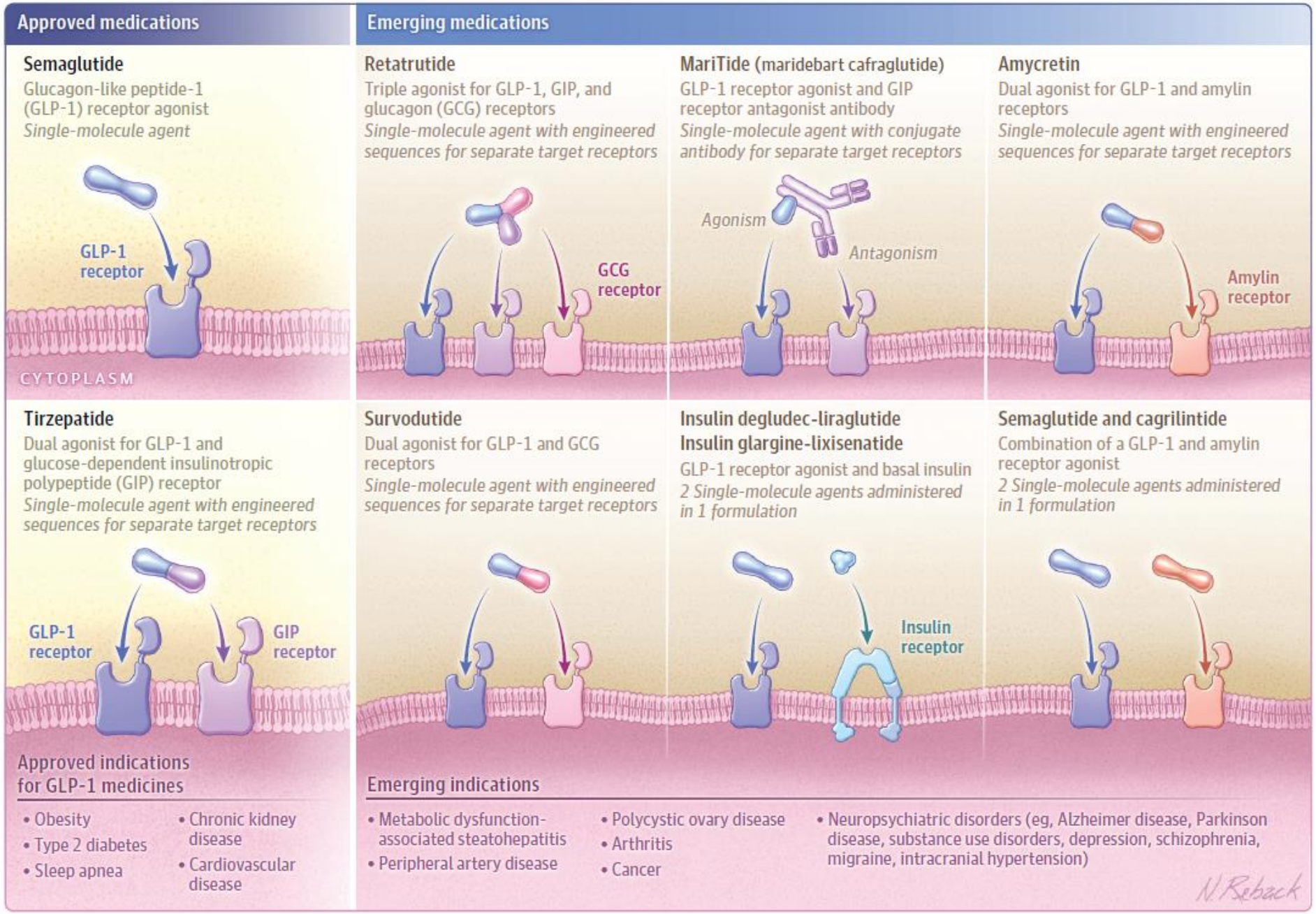
- Progression to cirrhosis
  - Number of individuals who progressed to cirrhosis in the treatment-arm vs placebo
- Clinical endpoints
  - Hepatic decompensation (clinical ascites, SBP, HE, variceal bleeding or HRS [HCC])
- MELD ≥15

Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

- First proof-of-concept study of a GLP-1 RA in NASH
- 52 patients with NASH (most with obesity and some with T2D) were randomized to daily liraglutide 1.8 mg vs placebo for 48 weeks

	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide *vs* placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019

Lancet 2016; 387: 679–90



JAMA. 2025;334(14):1231–1234. doi:10.1001/jama.2025.14392

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

- A 72-week, double-blind **phase 2** trial involving patients with biopsy confirmed NASH and liver fibrosis of stage F1, F2, or F3

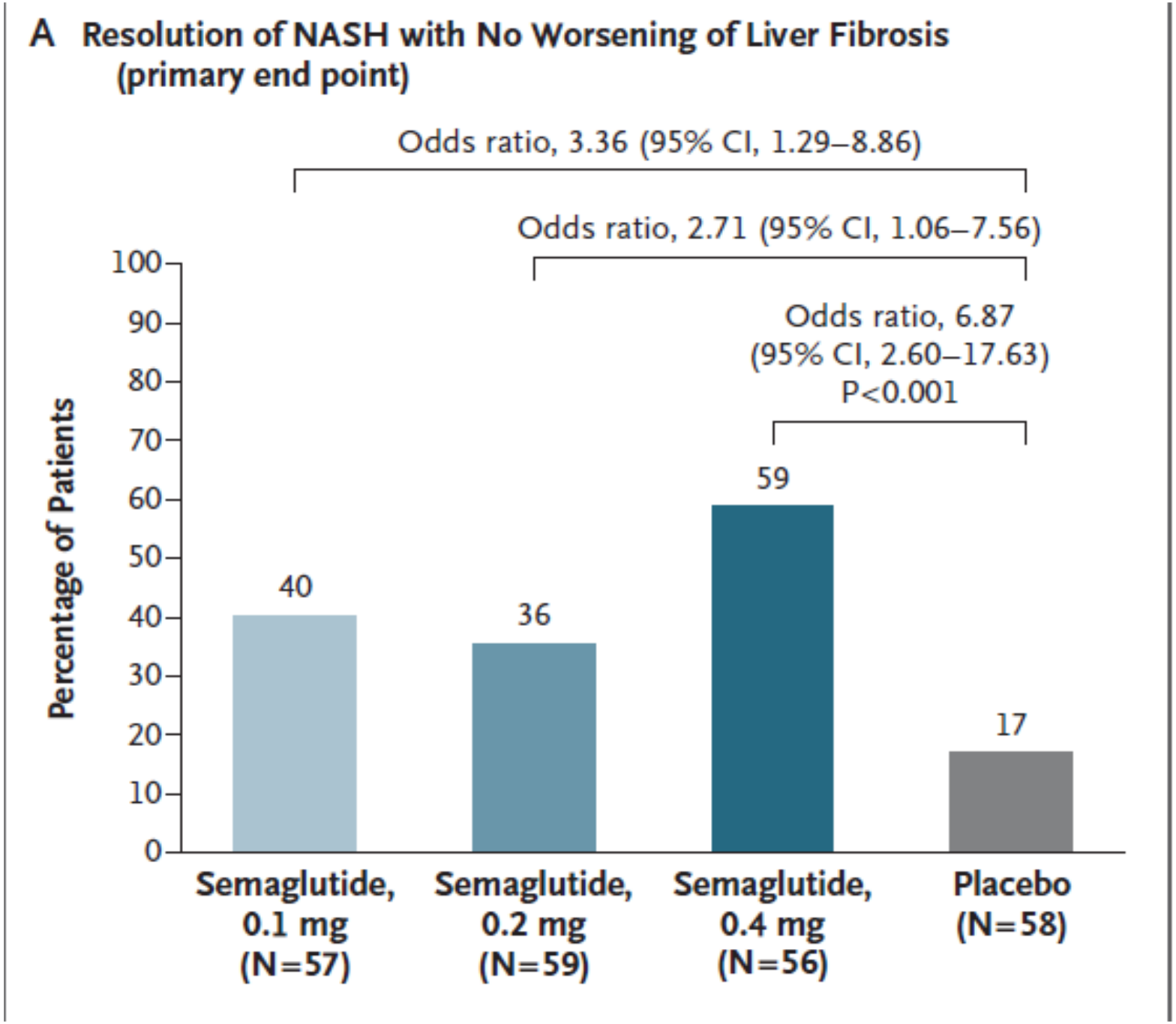
- Patients were randomly assigned to receive once-daily subcutaneous semaglutide at a dose of 0.1, 0.2, or 0.4 mg or corresponding placebo.

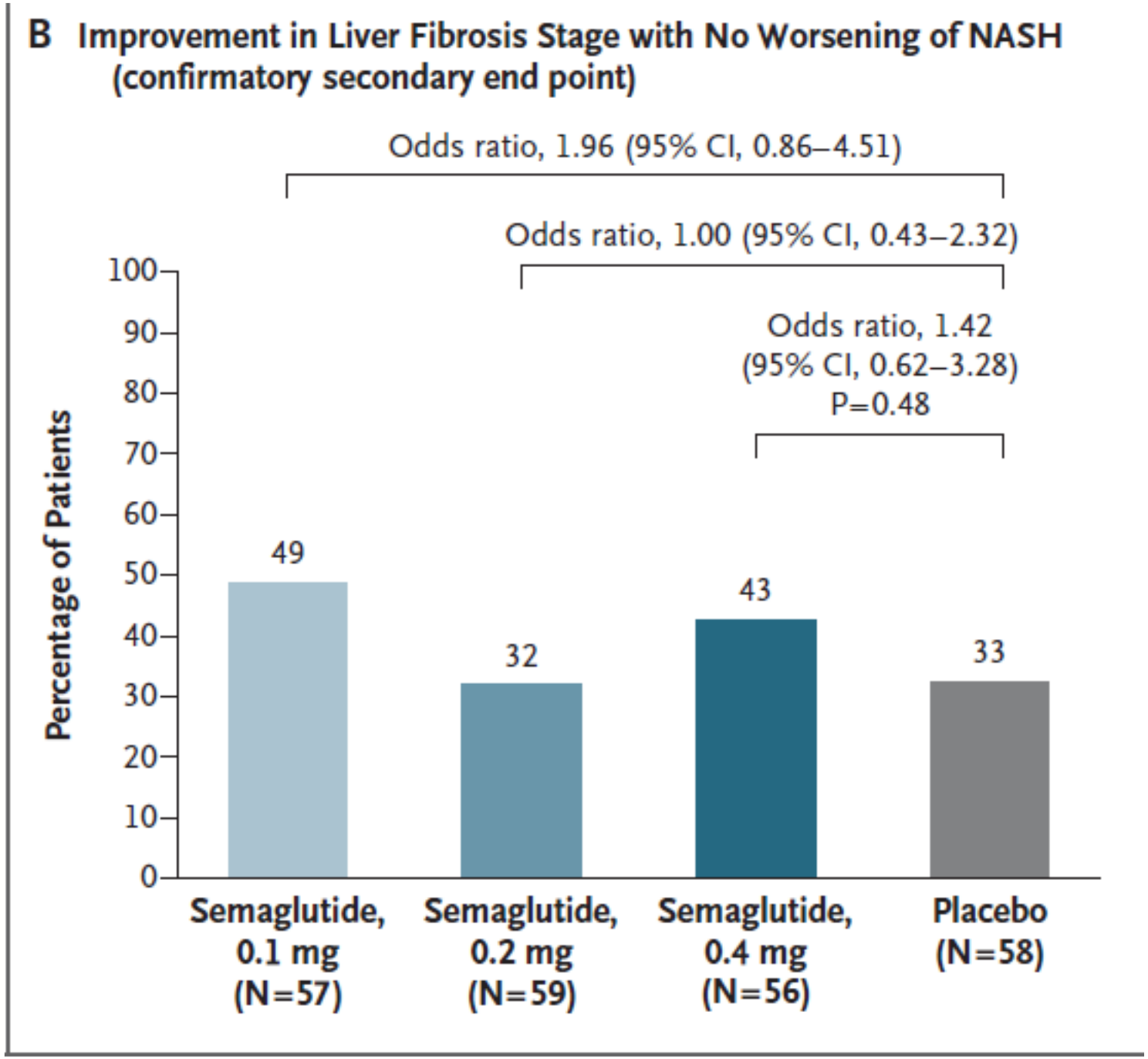
- The primary end point was resolution of NASH with no worsening of fibrosis.

- The confirmatory secondary end point was an improvement of at least one fibrosis stage with no worsening of NASH

N Engl J Med. 2021 Mar 25;384(12):1113-1124

Characteristic	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Age — yr	55.2±10.9	58.1±9.9	54.3±10.2	52.4±10.8
Female sex — no. (%)	51 (64)	52 (67)	47 (57)	44 (55)
Body weight — kg	98.4±21.1	97.1±22.0	96.6±20.1	101.3±23.3
Body-mass index	36.1±6.4	35.6±6.1	35.2±6.6	36.1±6.6
Type 2 diabetes — no. (%)	49 (61)	51 (65)	49 (60)	50 (62)
Glycated hemoglobin level among patients with type 2 diabetes — %†	7.4±1.3	7.2±1.0	7.2±1.2	7.3±1.2
Liver-enzyme levels — U/liter				
Alanine aminotransferase	55±90	53±78	54±84	55±92
Aspartate aminotransferase	44±82	43±73	44±78	42±83
Liver fibrosis stage — no. (%)‡				
F1	23 (29)	19 (24)	26 (32)	22 (28)
F2	18 (22)	18 (23)	14 (17)	22 (28)
F3	39 (49)	41 (53)	42 (51)	36 (45)
Total activity score for nonalcoholic fatty liver disease§	4.9±0.8	4.9±0.9	4.8±0.9	4.9±0.9
Noninvasive measures of liver steatosis and fibrosis				
Liver steatosis, as assessed by FibroScan — dB/m¶	332.0±46.2	347.4±55.0	335.7±55.8	348.6±35.2
Liver stiffness, as assessed by FibroScan — kPa¶	10.4±78.5	12.3±74.0	11.5±87.1	8.7±90.0
Enhanced liver fibrosis test score‖	9.8±1.0	9.8±0.9	9.9±1.0	9.6±0.9


A Resolution of NASH with No Worsening of Liver Fibrosis (primary end point)
Odds ratio, 3.36 (95% CI, 1.29–8.86)
Odds ratio, 2.71 (95% CI, 1.06–7.56)
Odds ratio, 6.87 (95% CI, 2.60–17.63) P<0.001
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
40
36
59
17
Semaglutide, 0.1 mg (N=57)
Semaglutide, 0.2 mg (N=59)
Semaglutide, 0.4 mg (N=56)
Placebo (N=58)


B Improvement in Liver Fibrosis Stage with No Worsening of NASH
(confirmatory secondary end point)
Odds ratio, 1.96 (95% CI, 0.86–4.51)
Odds ratio, 1.00 (95% CI, 0.43–2.32)
Odds ratio, 1.42
(95% CI, 0.62–3.28)
P=0.48
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
49
32
43
33
Semaglutide, 0.1 mg (N=57)
Semaglutide, 0.2 mg (N=59)
Semaglutide, 0.4 mg (N=56)
Placebo (N=58)

Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

Arun J. Sanyal, M.D.,[1] Philip N. Newsome, M.B., Ch.B., Ph.D.,[2,3] Iris Kliers, M.D.,[4] Laura Harms Østergaard, M.Sc.,[4] Michelle T. Long, M.D.,[4] Mette Skalshøi Kjær, M.D., Ph.D.,[4] Anna M.G. Cali, M.D.,[4] Elisabetta Bugianesi, M.D., Ph.D.,[5] Mary E. Rinella, M.D.,[6] Michael Roden, M.D.,[7-9] and Vlad Ratziu, M.D., Ph.D.,[10] for the ESSENCE Study Group*

- Ongoing **phase 3**, multicenter, randomized, double-blind, placebo-controlled trial

- 1197 patients with biopsy-defined MASH and fibrosis stage 2 or 3 in a 2:1 ratio were randomized to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 240 weeks

- This is the results of a planned interim analysis conducted at week 72 involving the first 800 patients are reported here (part 1).

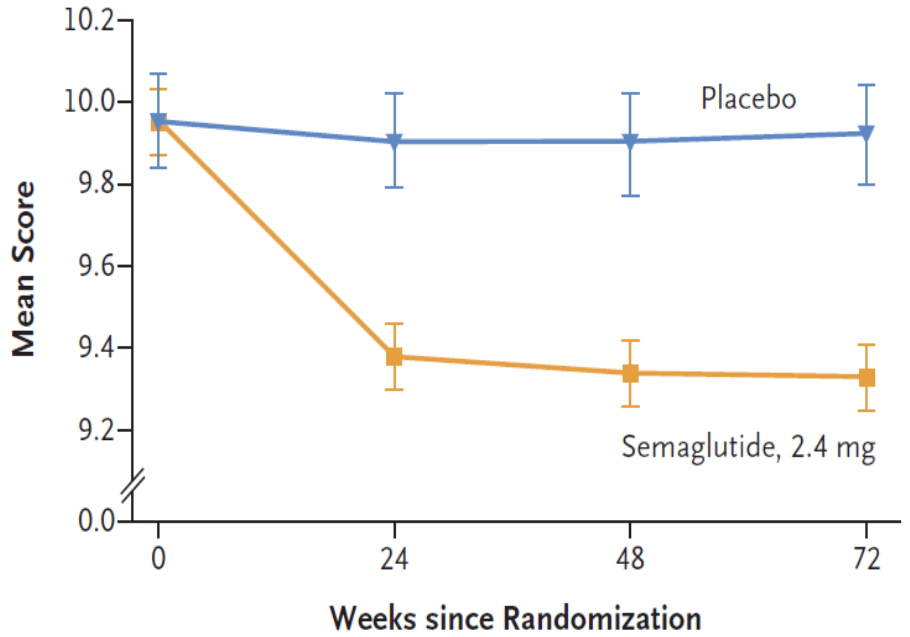
- The primary end points were the resolution of steatohepatitis without worsening of liver fibrosis and reduction in liver fibrosis without worsening of steatohepatitis

N Engl J Med 2025;392:2089-99

Table 1. Characteristics of the Patients at Baseline.*

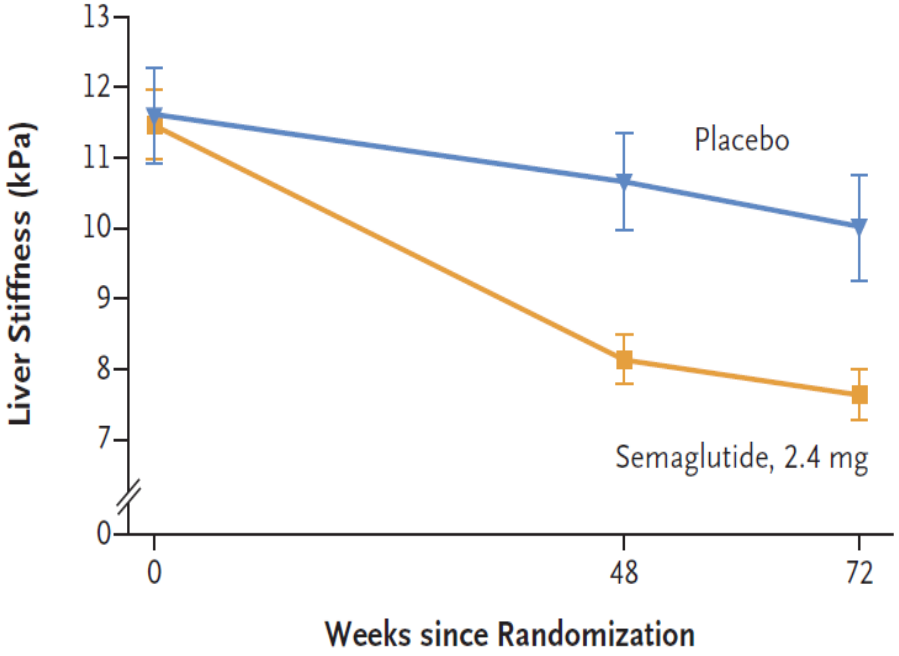
Characteristic	Semaglutide, 2.4 mg (N=534)	Placebo (N=266)
Age — yr	56.3±11.4	55.4±12.0
Female sex — no. (%)	313 (58.6)	144 (54.1)
Race or ethnic group — no. (%)†		
Asian	142 (26.6)	74 (27.8)
White	361 (67.6)	179 (67.3)
Black	3 (0.6)	2 (0.8)
Other	21 (3.9)	10 (3.8)
Missing data	7 (1.3)	1 (0.4)
Hispanic or Latino ethnic group†	95 (17.8)	51 (19.2)
Body weight — kg	95.4±24.5	97.6±24.6
Waist circumference — cm	111.8±15.6	113.1±16.0
Body-mass index	34.3±7.2	35.0±7.1
Percentage of lean patients — no. (%)‡	14 (2.6)	8 (3.0)
Type 2 diabetes — no. (%)	296 (55.4)	151 (56.8)
Laboratory measures		
Alanine aminotransferase — U/liter§	67.8±42.3	67.9±44.7
Aspartate aminotransferase — U/liter¶	53.2±28.6	52.8±33.1
Fibrosis stage — no. (%)		
2	169 (31.6)	81 (30.5)
3	365 (68.4)	185 (69.5)
Median score on Fibrosis-4 Index (IQR)‖	1.58 (1.12–2.24)	1.50 (1.08–2.28)
Enhanced liver fibrosis score**	9.95±0.94	9.95±0.98
Controlled attenuation measure — dB/m†††‡‡	329±45	330±49
Liver stiffness — kPa‡‡§§	12.8±6.6	12.9±7.6
Propeptide of type III collagen — ng/ml	52.9±24.9	52.9±28.1

A Enhanced Liver Fibrosis Score

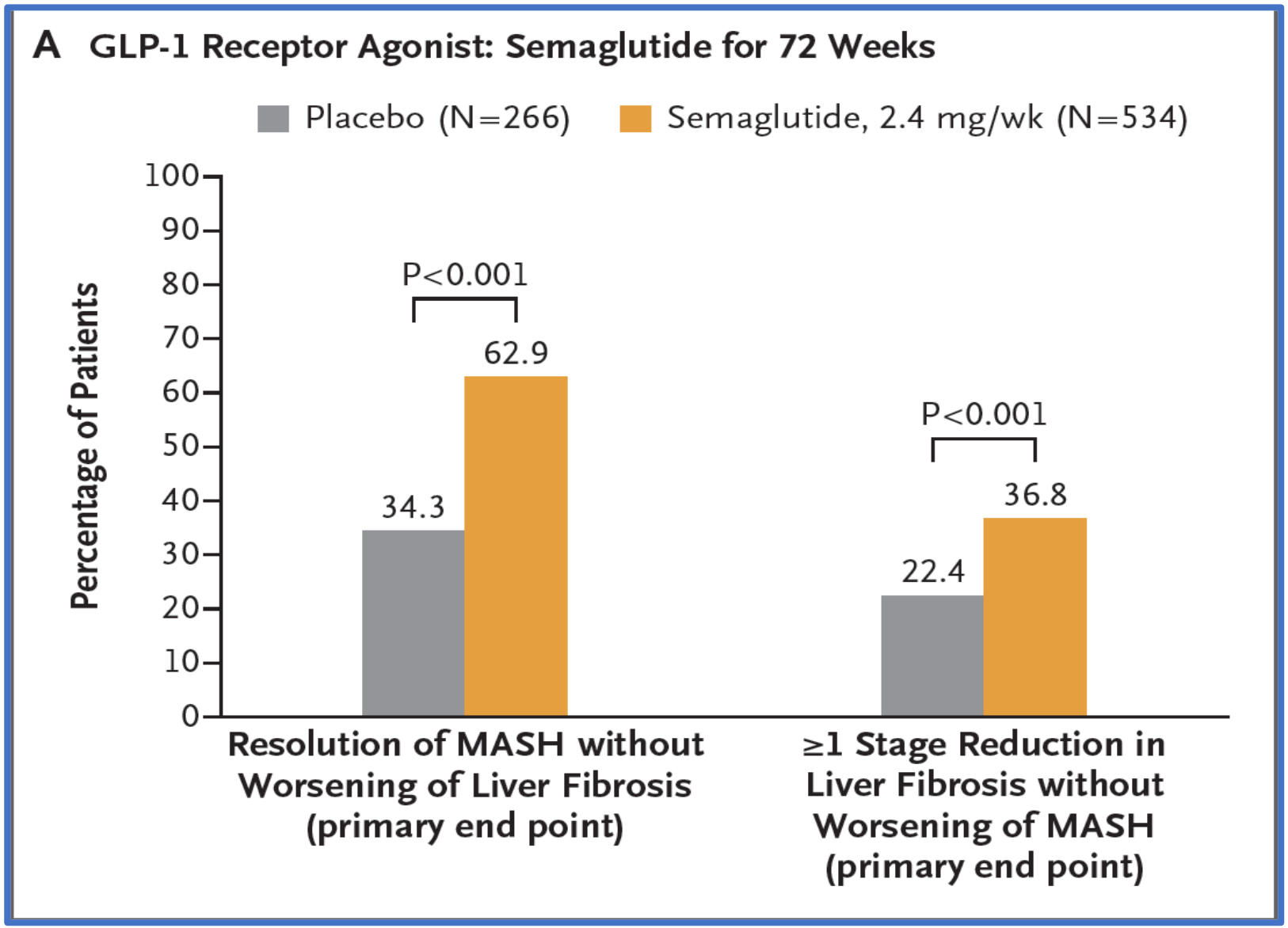


No. of Patients				
Placebo	266	252	246	237
Semaglutide, 2.4 mg	534	511	504	492

B Liver Stiffness Measured by Vibration-Controlled Transient Elastography



No. of Patients			
Placebo	216	204	193
Semaglutide, 2.4 mg	417	399	381


A GLP-1 Receptor Agonist: Semaglutide for 72 Weeks
Placebo (N=266)
Semaglutide, 2.4 mg/wk (N=534)
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
P<0.001
62.9
34.3
P<0.001
36.8
22.4
Resolution of MASH without Worsening of Liver Fibrosis (primary end point)
≥1 Stage Reduction in Liver Fibrosis without Worsening of MASH (primary end point)

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

- Question: Does tirzepatide, a once weekly GIP and GLP-1 agonist, decrease fibrosis in and resolve metabolic-dysfunction associated steatohepatitis (MASH)?

- Design: **Phase 2** multicenter, dose-finding, double-blind, placebo-controlled, randomized controlled trial (RCT)

- Participants randomized 1:1:1:1 to 1 of 4 study arms: 1) tirzepatide 5 mg once weekly; 2) tirzepatide 10 mg once weekly; 3) tirzepatide 15 mg once weekly; or 4) placebo once weekly, all administered subcutaneously for 52 weeks

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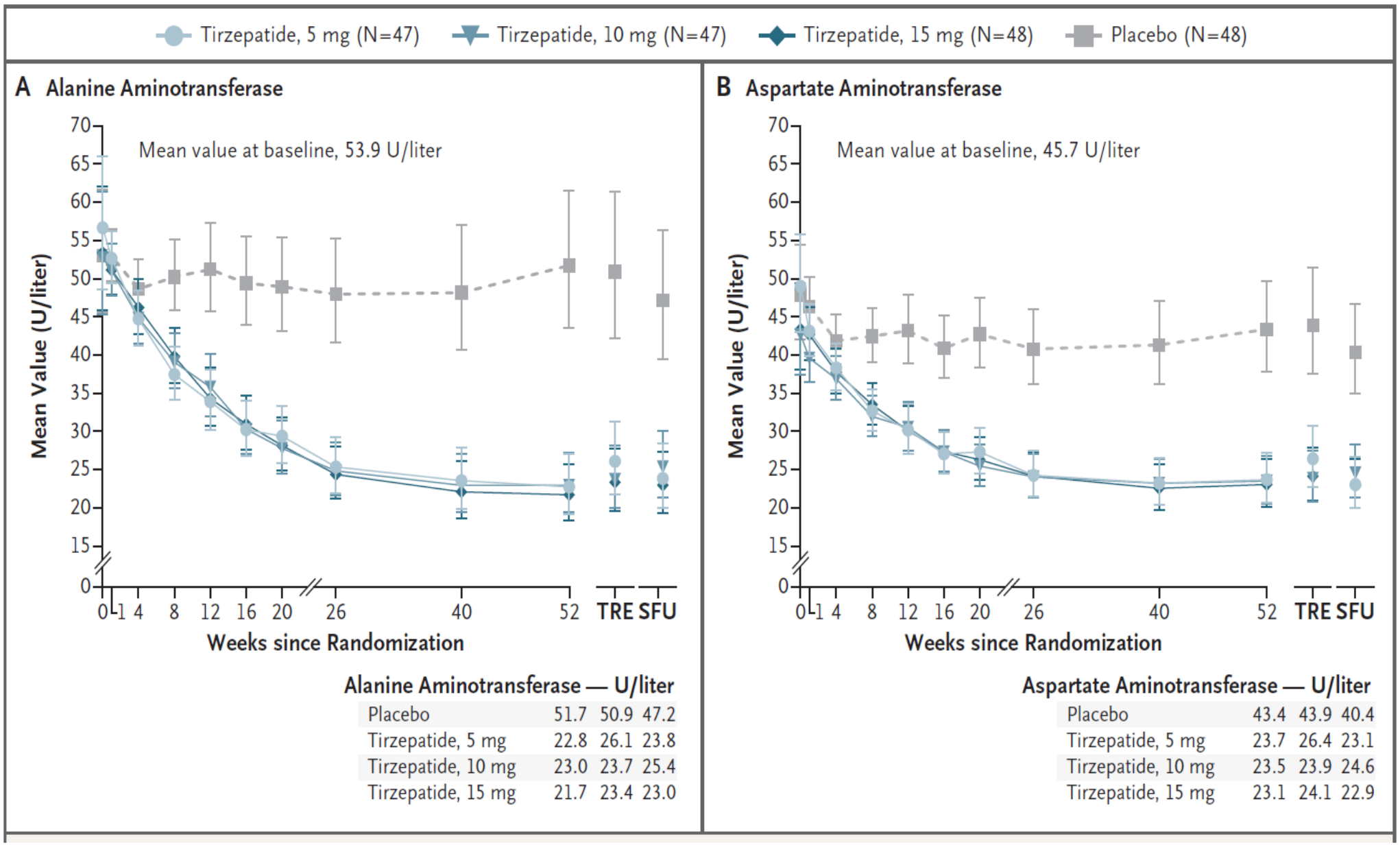
N Engl J Med 2024;391:299-310

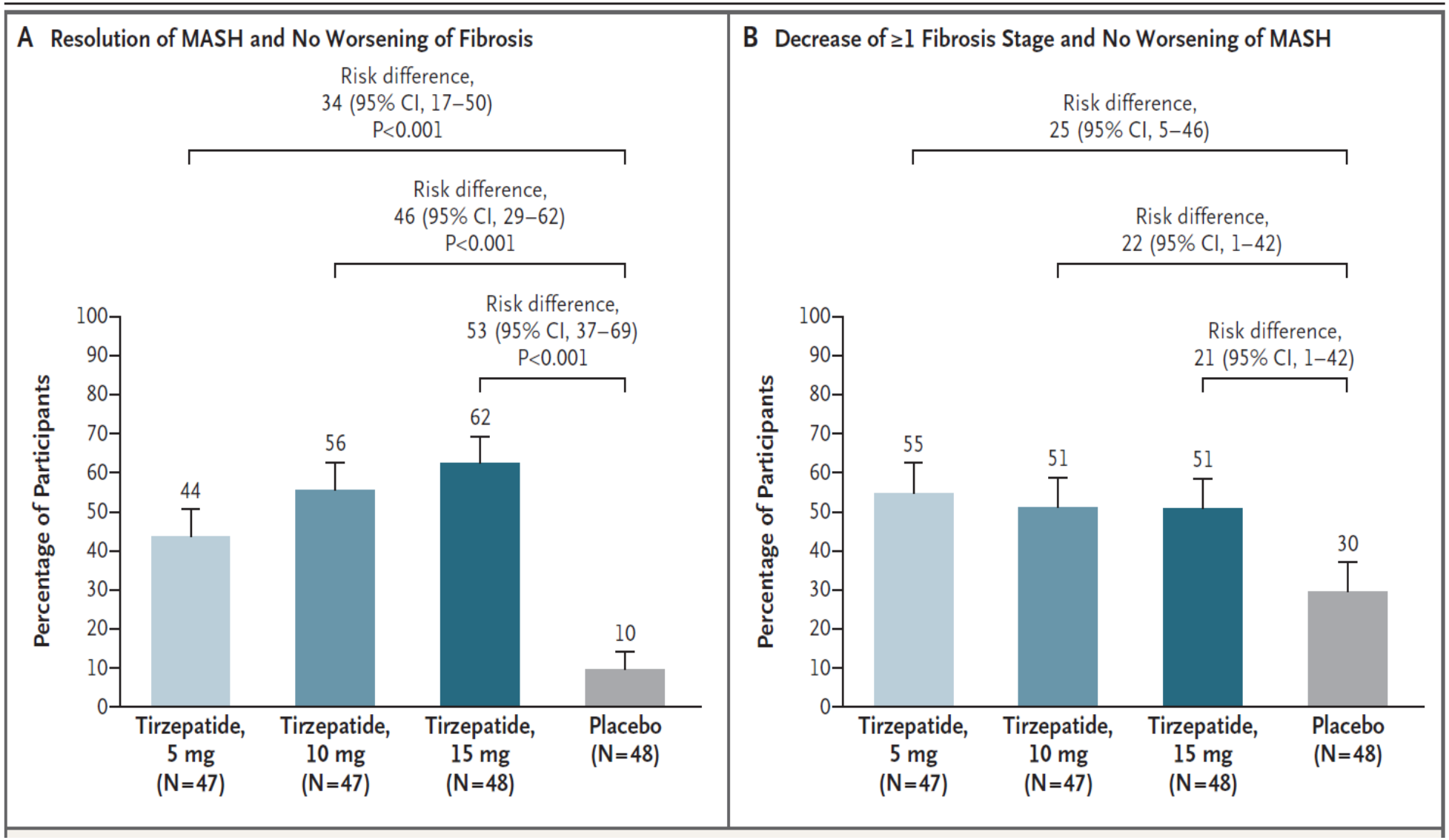
Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

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)	55.5±28.2	47.0±23.8	47.5±20.7	52.3±21.3	50.6±23.7
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



Alanine Aminotransferase — U/liter			
Placebo	51.7	50.9	47.2
Tirzepatide, 5 mg	22.8	26.1	23.8
Tirzepatide, 10 mg	23.0	23.7	25.4
Tirzepatide, 15 mg	21.7	23.4	23.0

Aspartate Aminotransferase — U/liter			
Placebo	43.4	43.9	40.4
Tirzepatide, 5 mg	23.7	26.4	23.1
Tirzepatide, 10 mg	23.5	23.9	24.6
Tirzepatide, 15 mg	23.1	24.1	22.9


A Resolution of MASH and No Worsening of Fibrosis
Risk difference, 34 (95% CI, 17–50) P<0.001
Risk difference, 46 (95% CI, 29–62) P<0.001
Risk difference, 53 (95% CI, 37–69) P<0.001
Percentage of Participants
100
90
80
70
60
50
40
30
20
10
0
44
56
62
10
Tirzepatide, 5 mg (N=47)
Tirzepatide, 10 mg (N=47)
Tirzepatide, 15 mg (N=48)
Placebo (N=48)
B Decrease of ≥1 Fibrosis Stage and No Worsening of MASH
Risk difference, 25 (95% CI, 5–46)
Risk difference, 22 (95% CI, 1–42)
Risk difference, 21 (95% CI, 1–42)
Percentage of Participants
55
51
51
30
Tirzepatide, 5 mg (N=47)
Tirzepatide, 10 mg (N=47)
Tirzepatide, 15 mg (N=48)
Placebo (N=48)

Clinical Gastroenterology and Hepatology 2024;22:1847–1857

HEPATOLOGY

Safety and Efficacy of Novel Incretin Co-agonist Cotadutide in Biopsy-proven Noncirrhotic MASH With Fibrosis

Sudha S. Shankar,[1,2] Samuel J. Daniels,[1,*] Darren Robertson,[1,*] Janeli Sarv,[3] José Sánchez,[3] Debra Carter,[4] Lutz Jermutus,[5] Benjamin Challis,[6] and Arun J. Sanyal[7]

ORIGINAL ARTICLE

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Arun J. Sanyal, M.D., Pierre Bedossa, M.D., Ph.D., Mandy Fraessdorf, Ph.D., Guy W. Neff, M.D., Eric Lawitz, M.D., Elisabetta Bugianesi, M.D., Quentin M. Anstee, Ph.D., F.R.C.P., Samina Ajaz Hussain, M.D., Philip N. Newsome, M.B., Ch.B., Ph.D., Vlad Ratziu, M.D., Azadeh Hosseini-Tabatabaei, Pharm.D., Ph.D., Jörn M. Schattenberg, M.D., Mazen Noureddin, M.D., M.H.Sc., Naim Alkhouri, M.D., and Ramy Younes, M.D., Ph.D., for the 1404-0043 Trial Investigators*

ORIGINAL ARTICLE

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

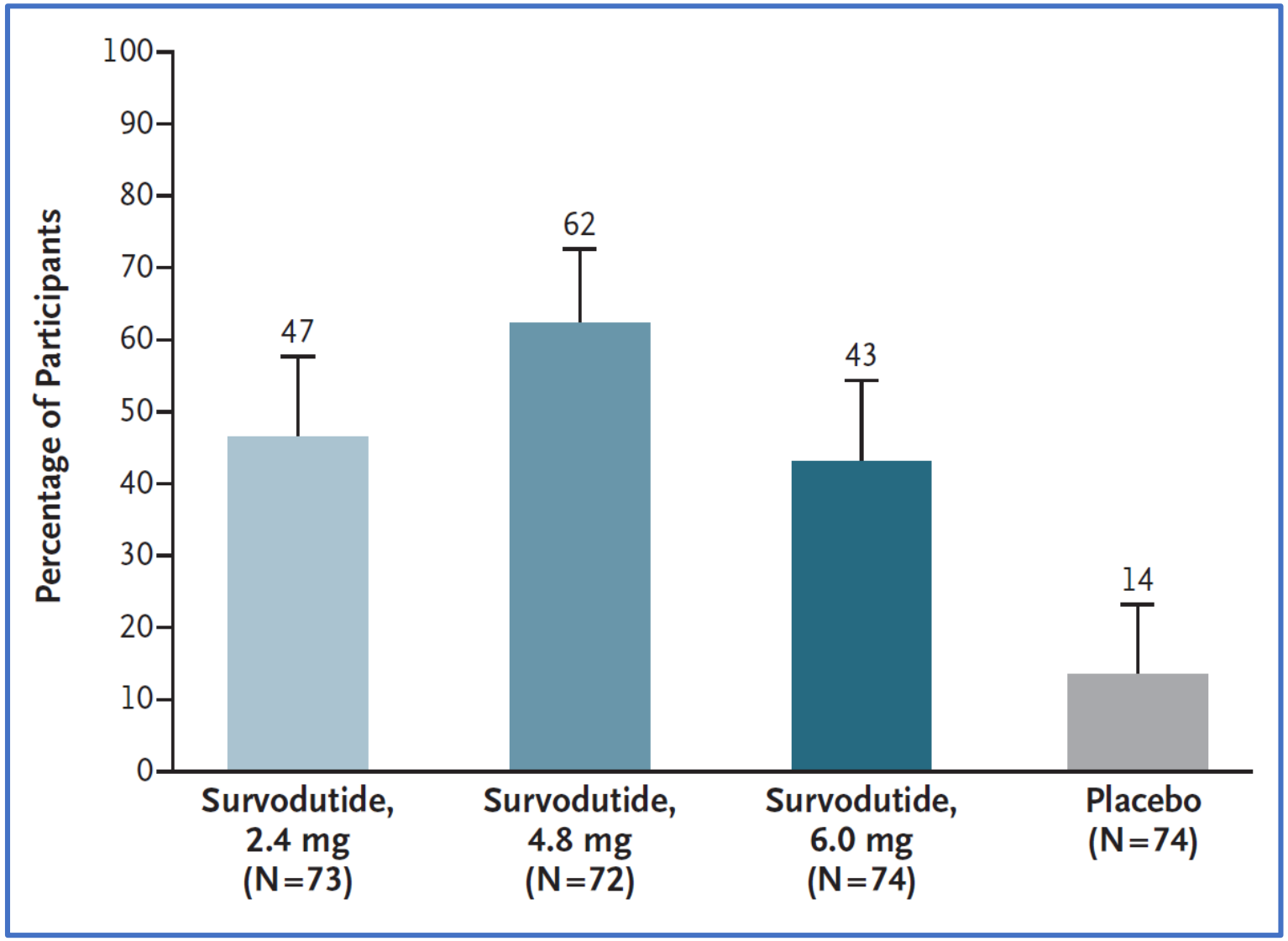
- In this 48-week, phase 2 trial, we randomly assigned adults with biopsy-confirmed MASH and fibrosis stage F1 through F3 in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of survodutide at a dose of 2.4, 4.8, or 6.0 mg or placebo.

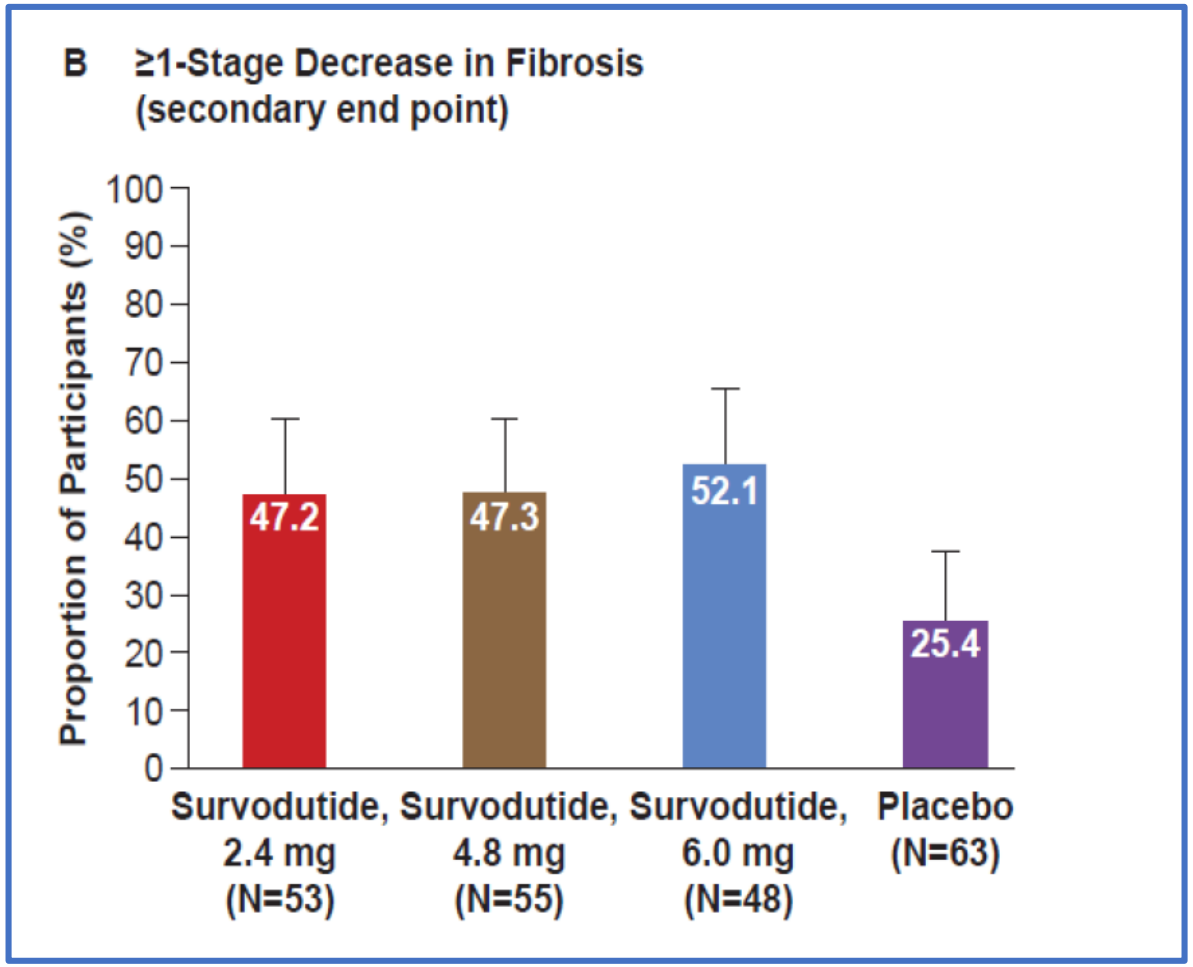
- The trial had two phases: a 24-week rapid-dose-escalation phase, followed by a 24-week maintenance phase.

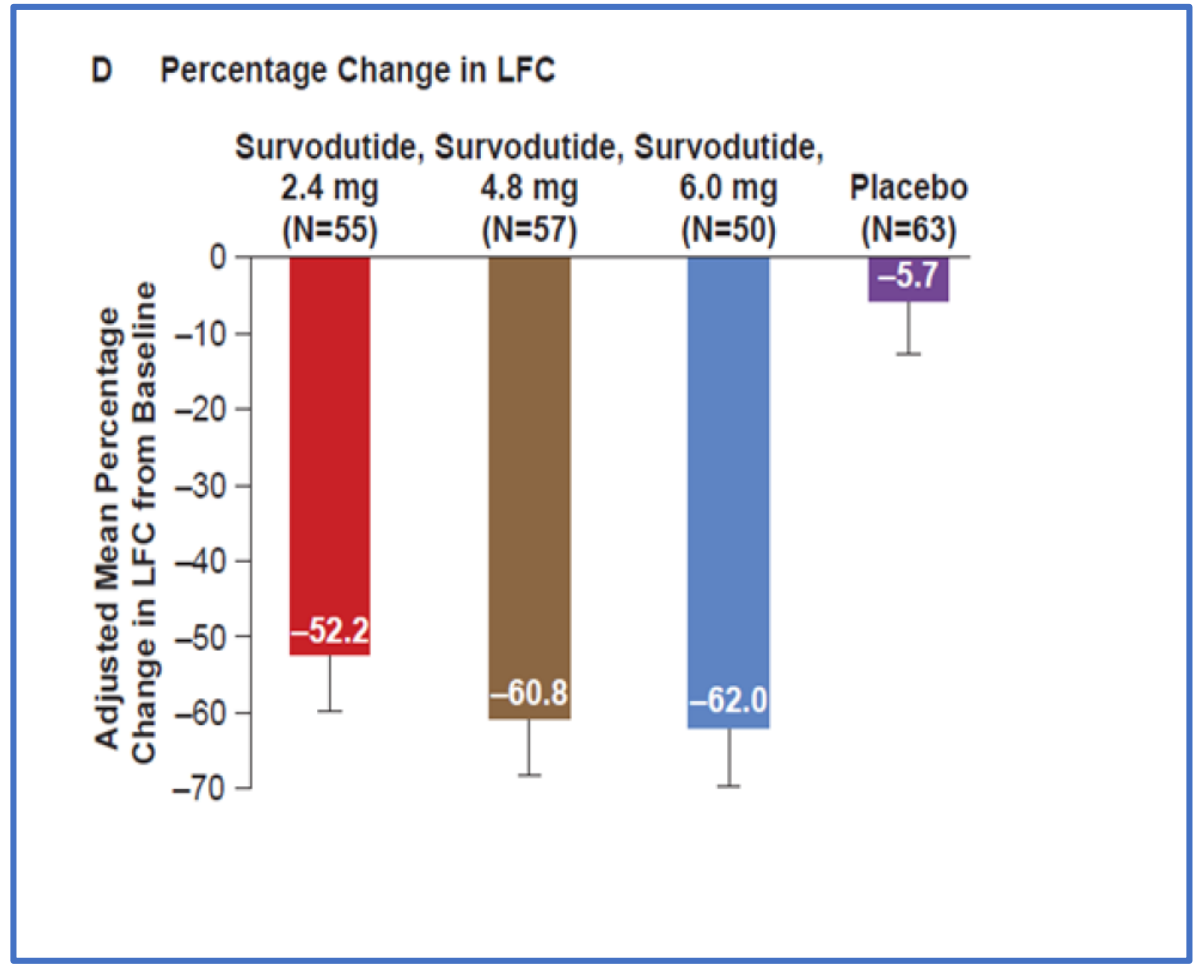
- The primary end point was histologic improvement (reduction) in MASH with no worsening of fibrosis

N Engl J Med 2024;391:311-9

Primary End Point after 48 Weeks of Planned Treatment




B ≥1-Stage Decrease in Fibrosis
(secondary end point)
Proportion of Participants (%)
100
90
80
70
60
50
40
30
20
10
0
47.2
47.3
52.1
25.4
Survodutide, 2.4 mg (N=53)
Survodutide, 4.8 mg (N=55)
Survodutide, 6.0 mg (N=48)
Placebo (N=63)


D Percentage Change in LFC
Survodutide, 2.4 mg (N=55)
Survodutide, 4.8 mg (N=57)
Survodutide, 6.0 mg (N=50)
Placebo (N=63)
Adjusted Mean Percentage Change in LFC from Baseline
0
−10
−20
−30
−40
−50
−60
−70
−52.2
−60.8
−62.0
−5.7

nature medicine

Article

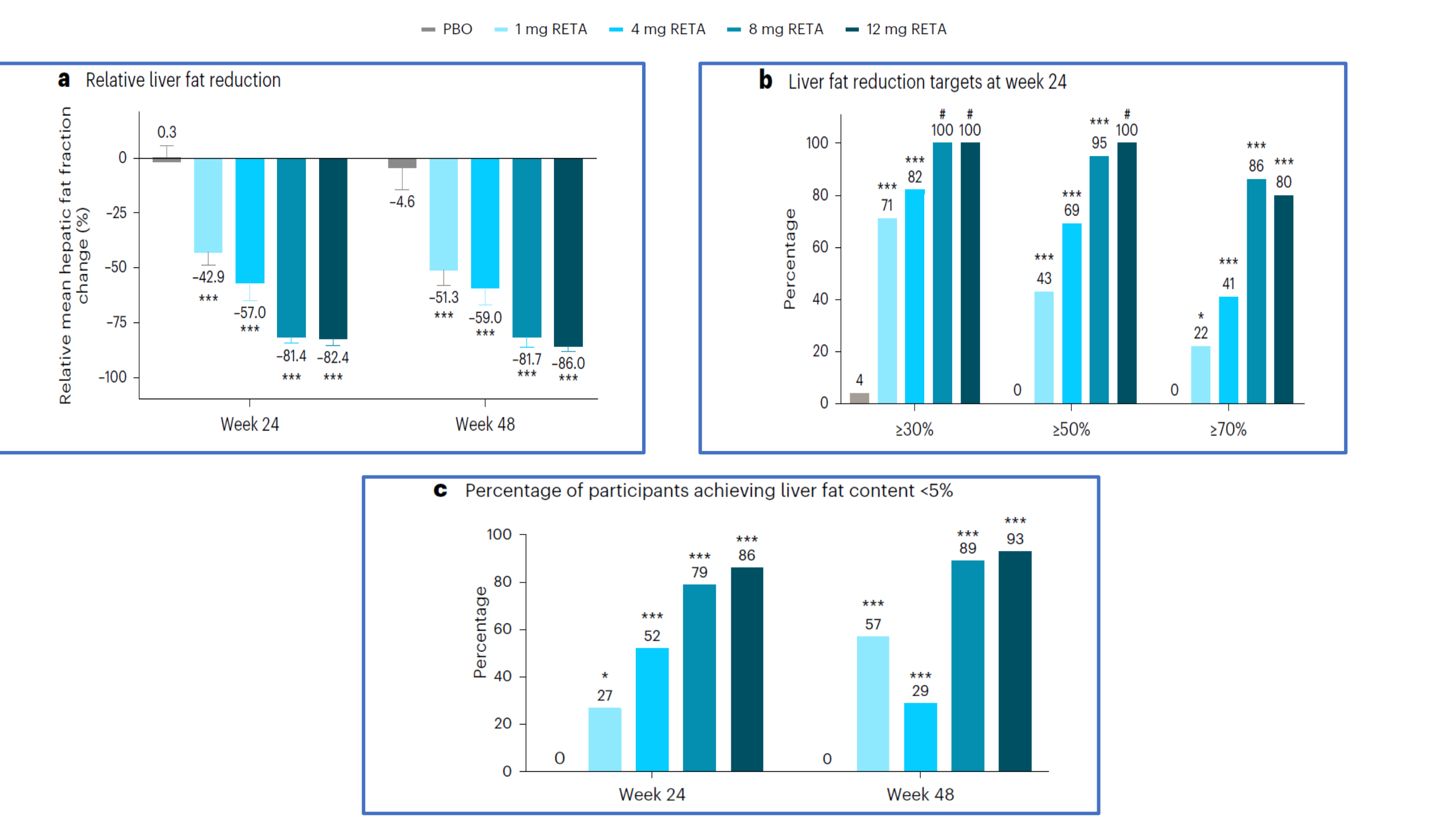
https://doi.org/10.1038/s41591-024-03018-2

Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial

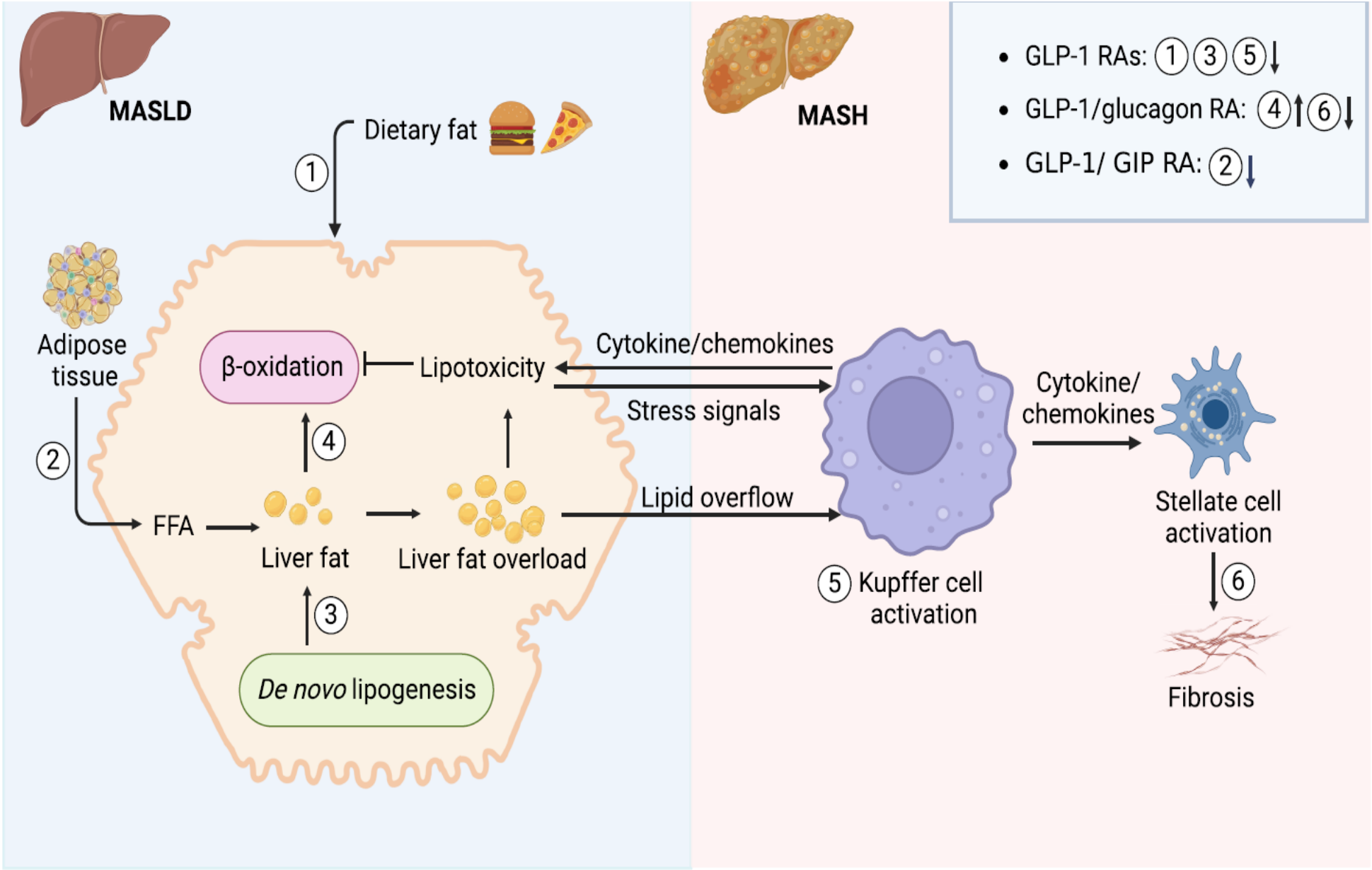
- Randomized, double-blind, placebo-controlled trial

- Participants (n = 98) were randomly assigned to 48 weeks of once-weekly subcutaneous retatrutide (1, 4, 8 or 12 mg dose) or placebo

- The primary objective of this substudy was to assess mean relative change from baseline in liver fat (LF) at 24 weeks

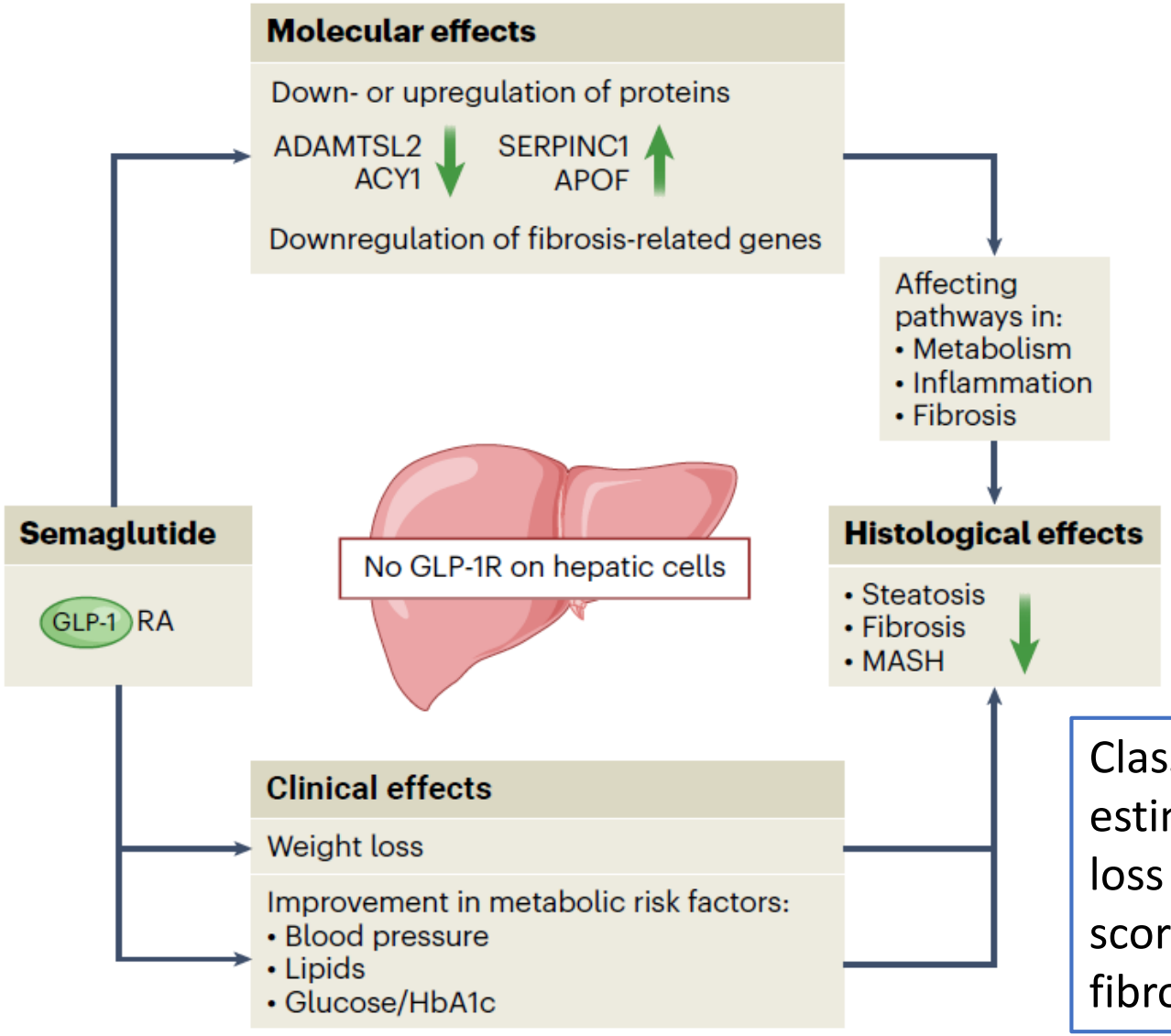

PBO
1 mg RETA
4 mg RETA
8 mg RETA
12 mg RETA
a Relative liver fat reduction
Relative mean hepatic fat fraction change (%)
0
-25
-50
-75
-100
0.3
-42.9
***
-57.0
***
-81.4
***
-82.4
***
-4.6
-51.3
***
-59.0
***
-81.7
***
-86.0
***
Week 24
Week 48
b Liver fat reduction targets at week 24
Percentage
100
80
60
40
20
0
4
***
71
***
82
#
100
#
100
0
***
43
***
69
***
95
#
100
0
*
22
***
41
***
86
***
80
≥30%
≥50%
≥70%
c Percentage of participants achieving liver fat content <5%
Percentage
100
80
60
40
20
0
0
*
27
***
52
***
79
***
86
0
***
57
***
29
***
89
***
93
Week 24
Week 48

Mechanistic roles of GLP-1 RAs in MASLD and MASH pathogenesis



The Journal of Clinical Endocrinology & Metabolism, 2025, 110, 2964–2979

Academic debate on the weight-dependent and weight-independent benefits of GLP-1RTAs in patients with MASH is ongoing



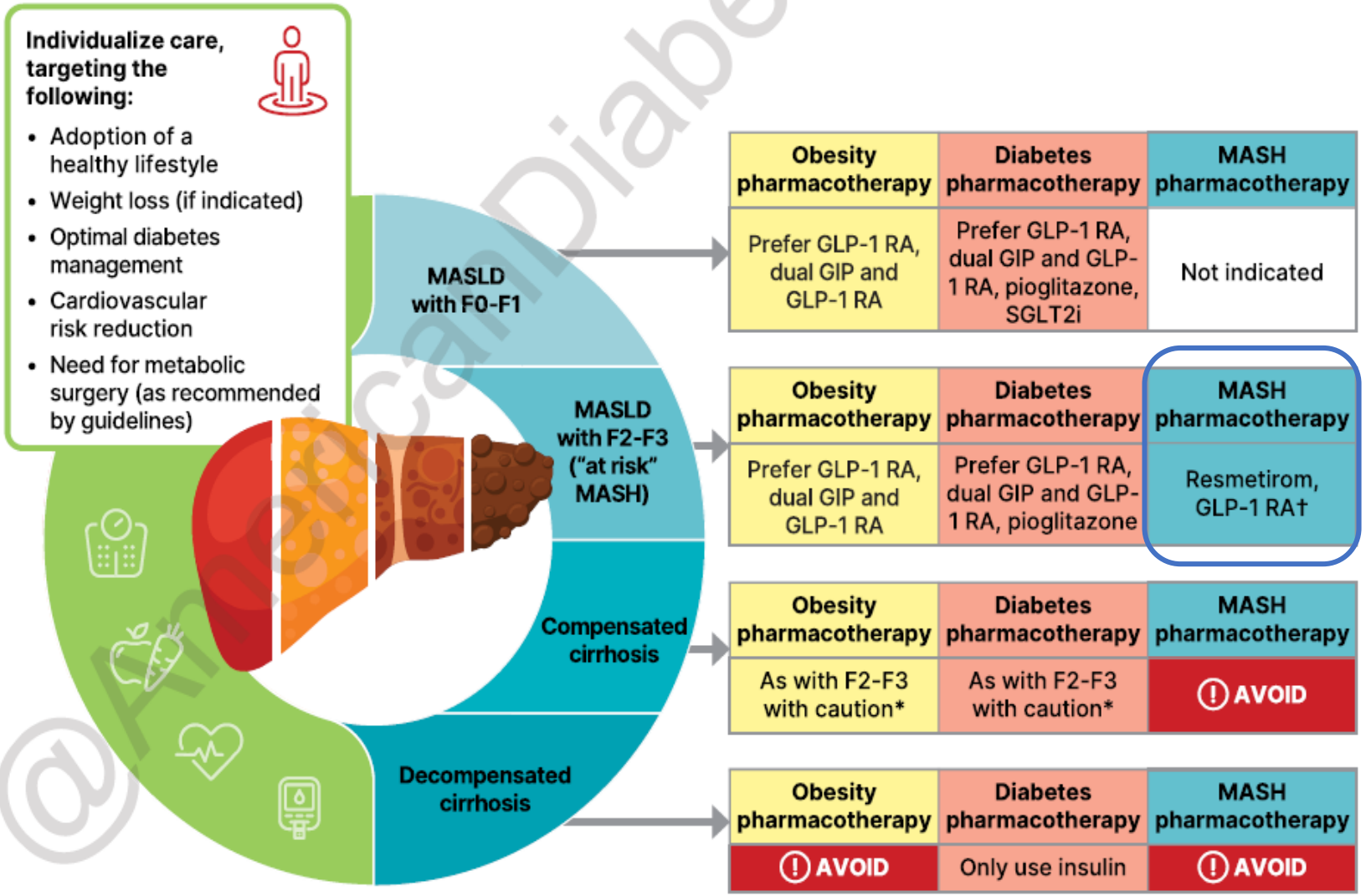
Classical mediation analysis and natural effect model, estimated that effect sizes attributed directly to weight loss were 82% for improvement in histological steatosis score, 69.3% for MASH resolution, but **only 25.1%** for fibrosis regression

Nature Medicine volume 31, pages2865–2866 (2025)

Nat Med 31, 3128–3140 (2025)

ADA 2026

Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm



Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, SGLT2i	Not indicated

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone	Resmetirom, GLP-1 RA†

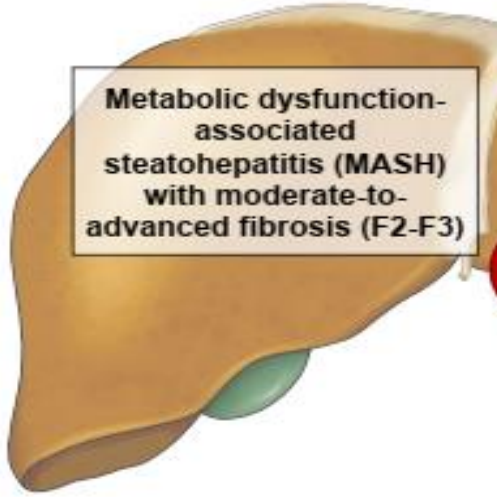
Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
As with F2-F3 with caution*	As with F2-F3 with caution*	ⓘ AVOID

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
ⓘ AVOID	Only use insulin	ⓘ AVOID

Semaglutide Therapy for MASLD

November 2025 Updates to AASLD Practice Guidance

Use of NITs for determining eligibility for semaglutide (Wegovy®) for the treatment of MASH with moderate-to-advanced fibrosis (F2-F3)



Metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced fibrosis (F2-F3)

Recommended

Imaging-based NIT	VCTE: LSM 8 - 15 kPa[a] MRE: LSM 3.1 - 4.4 kPa[a]
Blood-based NIT	ELF 9.2 - 10.5
Liver histology	MASH with F2-F3[b]

May be used

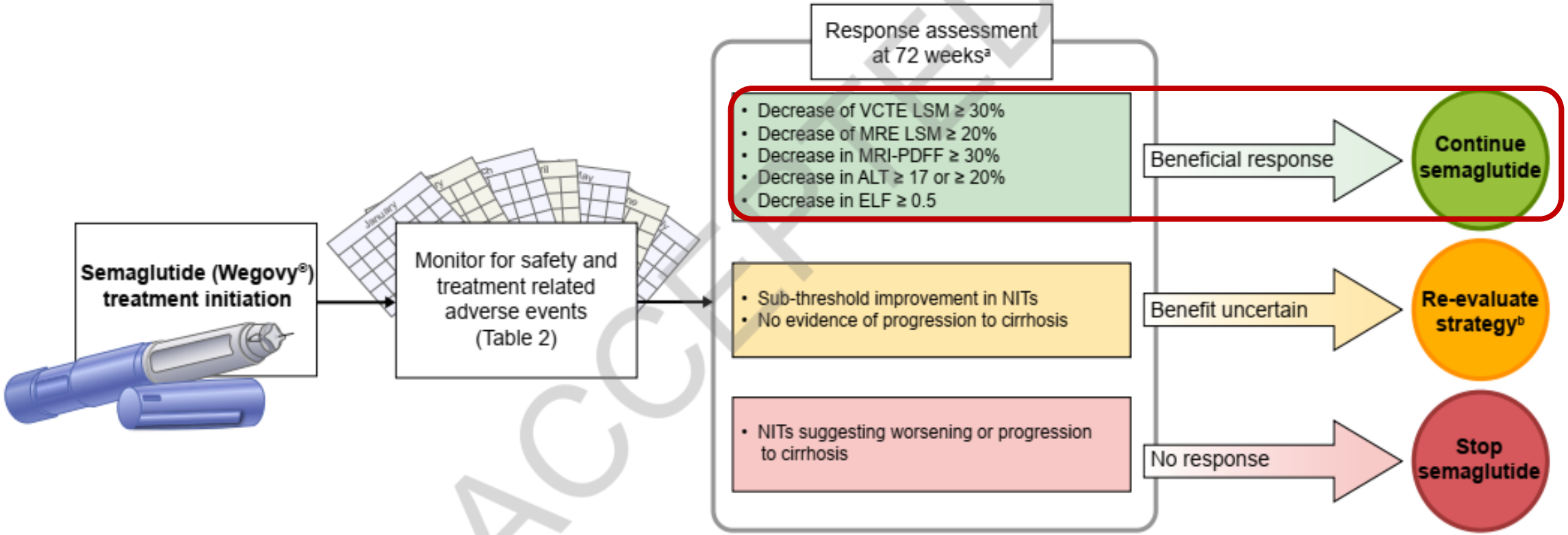
- LSM values outside the recommended ranges[c]
  - VCTE: LSM 15-20 kPa
  - MRE: LSM 4.4-5 kPa
  - ELF: 10.5-11.3
- Other NIT data consistent with F2-F3

Not recommended

- Cirrhosis, including LSM via VCTE >20 kPa, MRE >5 kPa, or ELF score >11.3
- Concomitant active liver disease
- Pregnancy, personal or family history of medullary thyroid carcinoma (MTC), or patients with multiple endocrine neoplasia syndrome type 2 (MEN2)

Hepatology.2025 Nov 7. doi: 10.1097/HEP.0000000000001608. Online ahead of print.

Assessment of safety and response to semaglutide (Wegovy®) for the treatment of MASH with moderate-to-advanced fibrosis (F2-F3)



Hepatology.2025 Nov 7. doi: 10.1097/HEP.0000000000001608. Online ahead of print.

Take home message

- GLP-1 receptor agonists and dual/triple incretin agonists represent a paradigm shift in MASLD/ NASH therapy
- By targeting the root metabolic causes of steatosis and inflammation, they have achieved histological improvements (NASH resolution and even fibrosis regression)
- The Phase 3 ESSENCE trial definitively showed semaglutide's efficacy in MASH , making it one of the first agents to meet both FDA recommended histologic endpoints in NASH
- After the positive SYNERGY-NASH results in 2024 , Tirzepatide has entered the spotlight as a potential NASH drug. Phase 3 outcome trials in NASH are being organized
- Cotadutide , Survodutide (Dual GLP-1/GCGR) and especially Retatrutide (Triple) in phase 2 trial produced remarkable reductions in liver fat, generating excitement that dual and triple therapy could address both NASH and fibrosis at rates approaching bariatric surgery