ENFERMEDAD HEPÁTICA METABÓLICA

Moderadores *Ramiro Alcántara y José Miguel Rosales*

Nuevas opciones terapéuticas en MASLD: ¿inflamación, fibrosis, o ambas?

AEEH
Asociación Española
para el Estudio del Hígado

Prof. Dr. Manuel Romero-Gómez
UGC Aparato Digestivo, Hospital Universitario Virgen del Rocío, Sevilla.
Ciberehd, ISCIII, Madrid.
SeLiver Group. Instituto de Biomedicina de Sevilla (HUVR/CSIC/US), Sevilla
Departamento de Medicina, Facultad de Medicina, Universidad de Sevilla, Sevilla.
Presidente AEEH 2023-2025

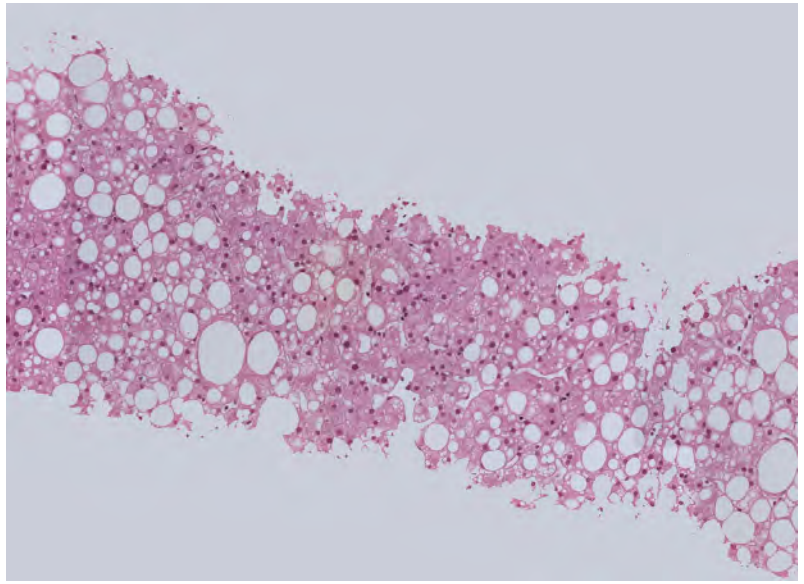
Conflictos de interés

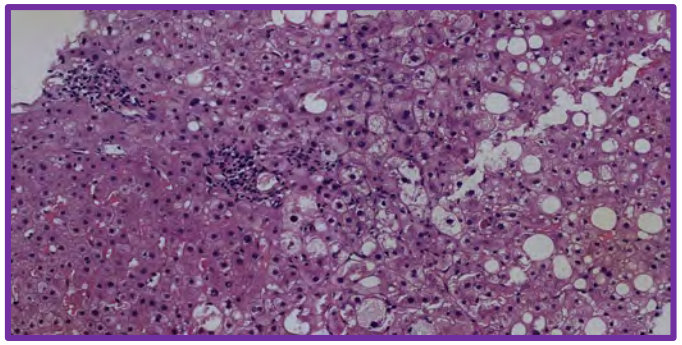
Consulting for: Alpha-sigma, Boehringer-Ingelheim, Julius Clinical, MSD, Prosciento, Rubió, Siemens, Thera, UCB-Pharma.

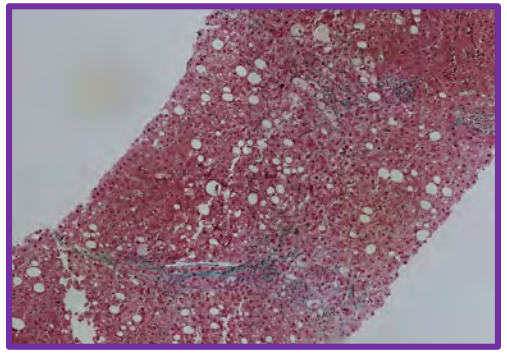
Research Grants: Gilead, NovoNordisk, Siemens, Theratechnologies, Echosens.

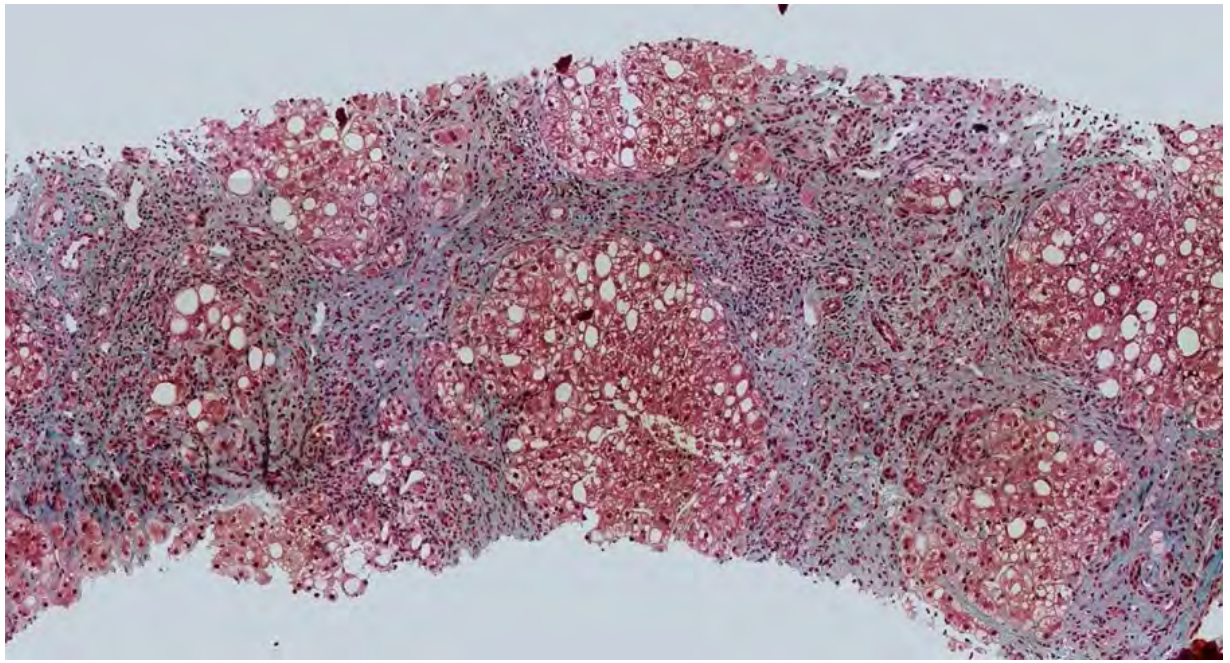
European funding programs: FP7 (FLIP), IMI2 (LITMUS), Grip-ON-MASH (IHI-3), UNMASK (EP_PerMed), MetaboMASH (CaixaResearch)

Inflammation vs. Fibrosis or both
This is the question

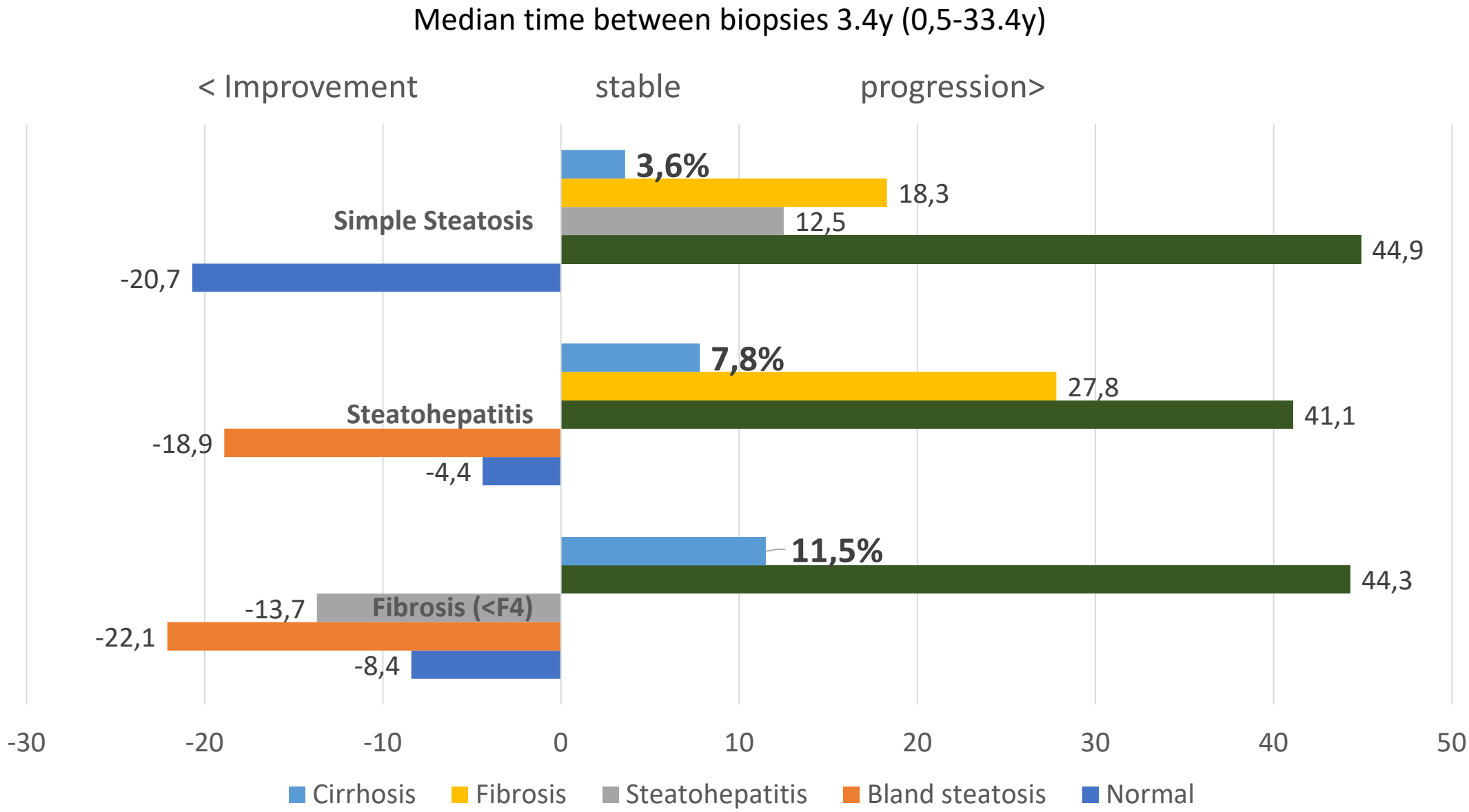








MASLD a dynamic disease even in patients with simple steatosis



Simon et al. J Hepatol 2023 ; doi.org/10.1016/j.jhep.2023.08.008.

MASLD histology transitions and long-term risk of cirrhosis-related outcomes and mortality

N=718 adults non-cirrhotic MASLD and paired liver biopsies 3.4y and followed-up for 11.7-12.5y

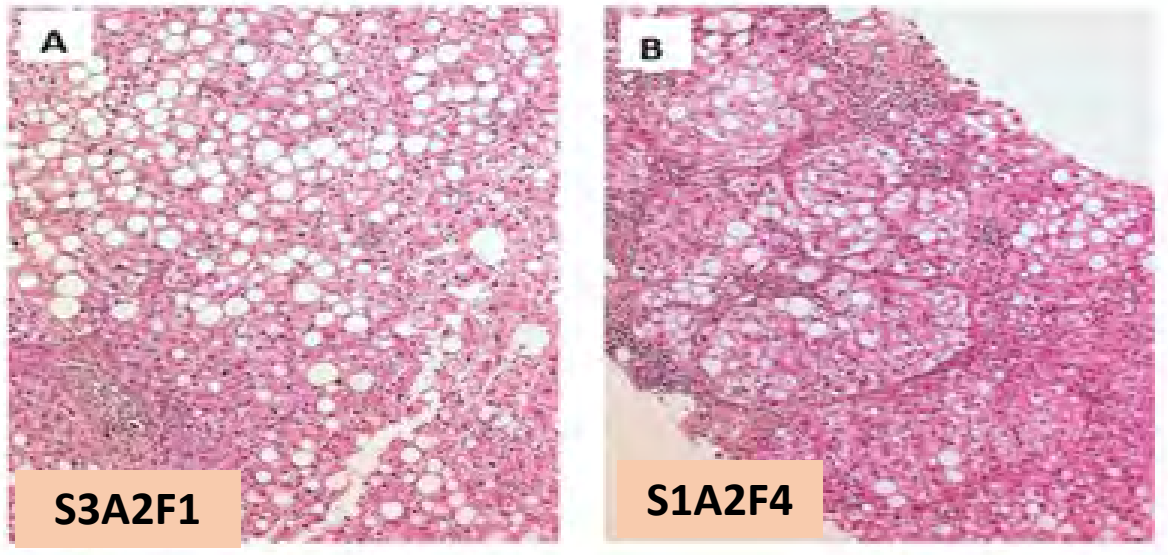
· Any progression: 30.4% **· Incident fibrosis 24.0%** **· Incident cirrhosis 5.6%**

	Hospitalization rate for ESLD	
Stable/Regression	11.4/1000PY	
Any progression	23.8/1000PY	aHR=1.65, 95%CI=1.17-2.32
Progression to cirrhosis	80.1/1000PY	aHR=3.25, 95%CI=1.60-6.57
from simple steatosis to incident fibrosis	18.9/1000PY	aHR=2.88, 95%CI=1.70-4.87
From steatosis to non-fibrotic MASH	12/1000PY	aHR=1.30, 95%CI=0.60-2.82

Simon et al. J Hepatol 2023 (In Press); doi.org/10.1016/j.jhep.2023.08.008.

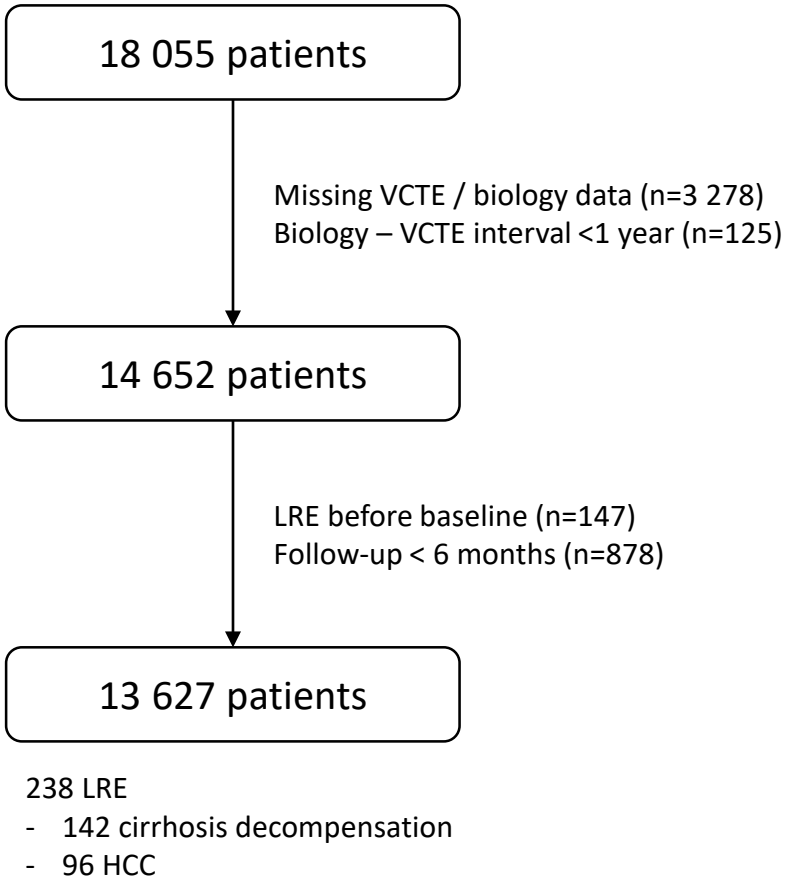
Histological diagnostic criteria

Steatosis (0, 1, 2 , 3)	Ballooning (0, 1, 2)	Lobular Inflammation (0, 1, 2)	Diagnosis
0	0, 1, 2	0, 1, 2	No MASLD
1, 2, 3	0	0	MASLD
	0	1	MASLD
	0	2	MASLD
	1	0	MASLD
	1	1	MASH
	1	2	MASH
	2	0	MASLD
	2	1	MASH
	2	2	MASH



Bedossa P et al. Hepatology 2012;56:1751

To develop a model that uses the dynamics of serial measurements of NITs to provide a personalized prediction of liver-related events in MASLD



	n=13 627
Male sex (%)	8201 (60.2%)
Age (years)	53.2 [41.7 ; 61.8]
BMI (kg/m²)	27.0 [24.5 ; 30.1]
Albumin (g/l)	45.0 [43.0 ; 47.0]
Bilirubin (µmol/)	12.0 [8.55 ; 16.0]
AST (IU/l)	31.0 [23.0 ; 47.0]
ALT (IU/l)	38.0 [24.0 ; 64.0]
Platelet (G/l)	240 [200 ; 284]
Fasting glucose (mmol/l)	5.70 [5.17 ; 6.72]
VCTE (kPa)	5.90 [4.60 ; 8.20]
FIB-4	1.10 [0.72 ; 1.67]
Follow-up duration (years)	4.0 [2.1 ; 5.9]

Boursier J et al. EASL 2025

Joint latent class modelling

Longitudinal VCTE, adjusted on sex and FIB4

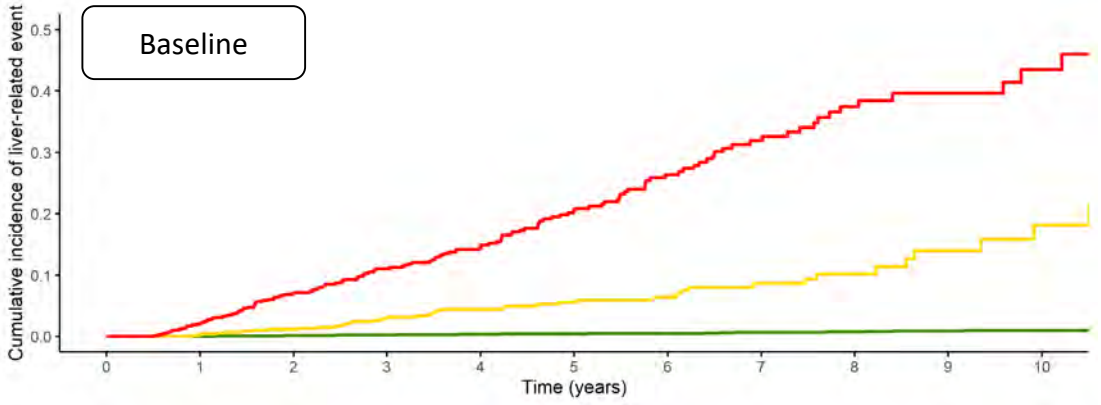
Survival Age, platelets

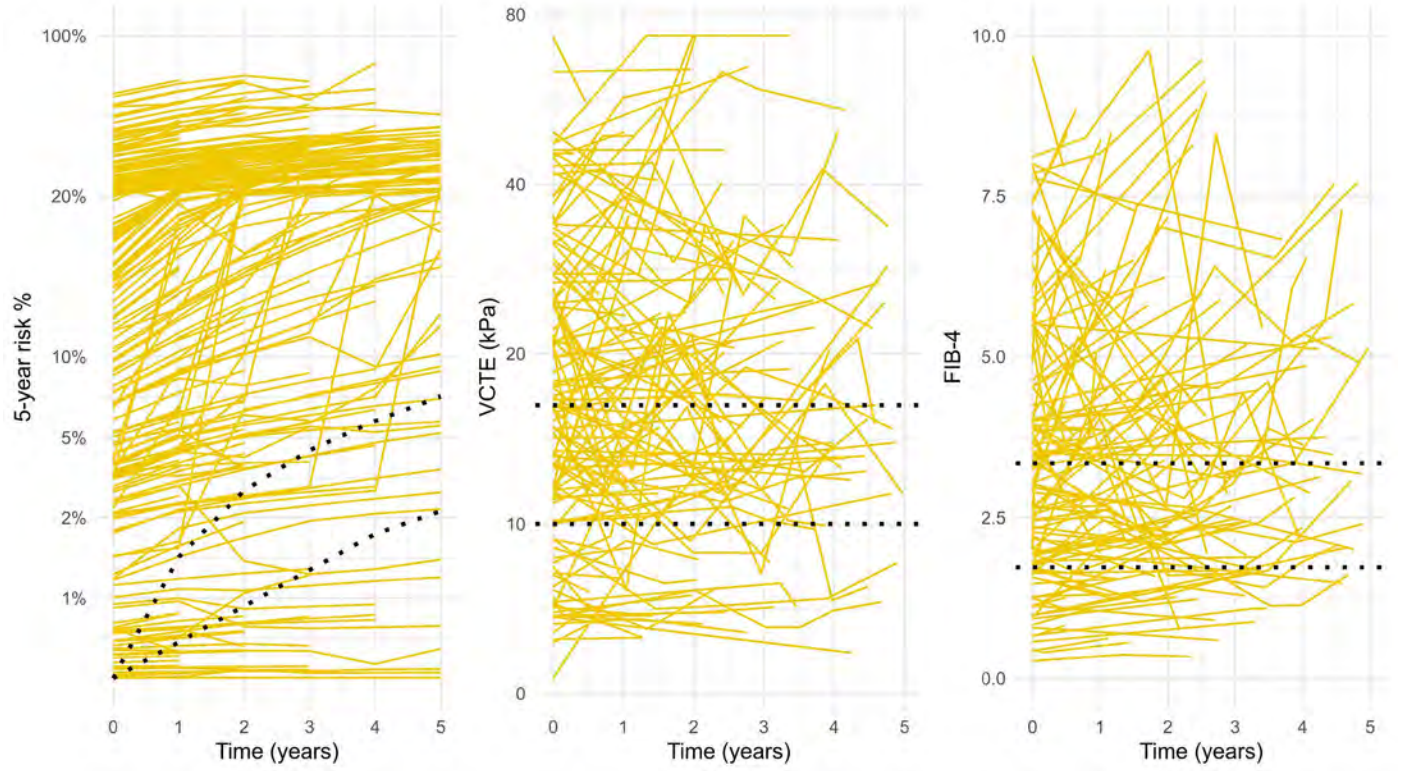
238 patients who experienced LRE

JLCM **Age, sex, platelets, FIB4, VCTE**

Calculated thresholds:

- 85% sensitivity: 0.45% per year
- 95% specificity: 1.51% per year





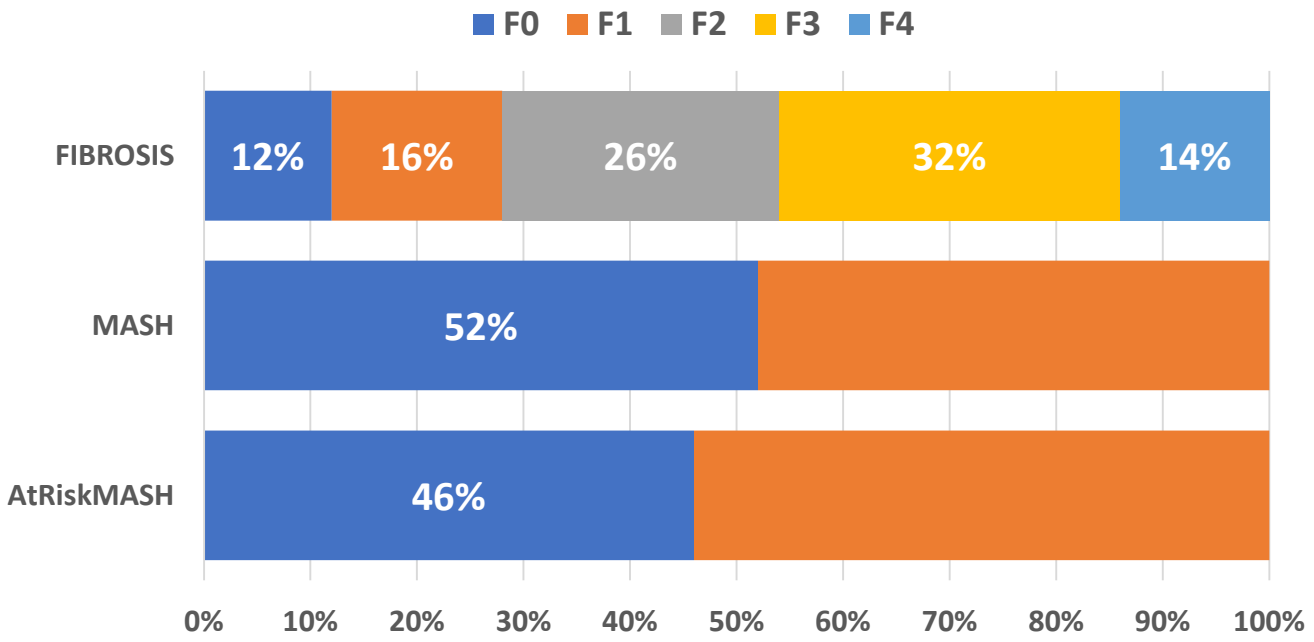
Boursier J et al. EASL 2025

Prospective evaluation of MASLD biomarkers for the diagnosis of steatohepatitis and fibrosis in the LITMUS Imaging Study

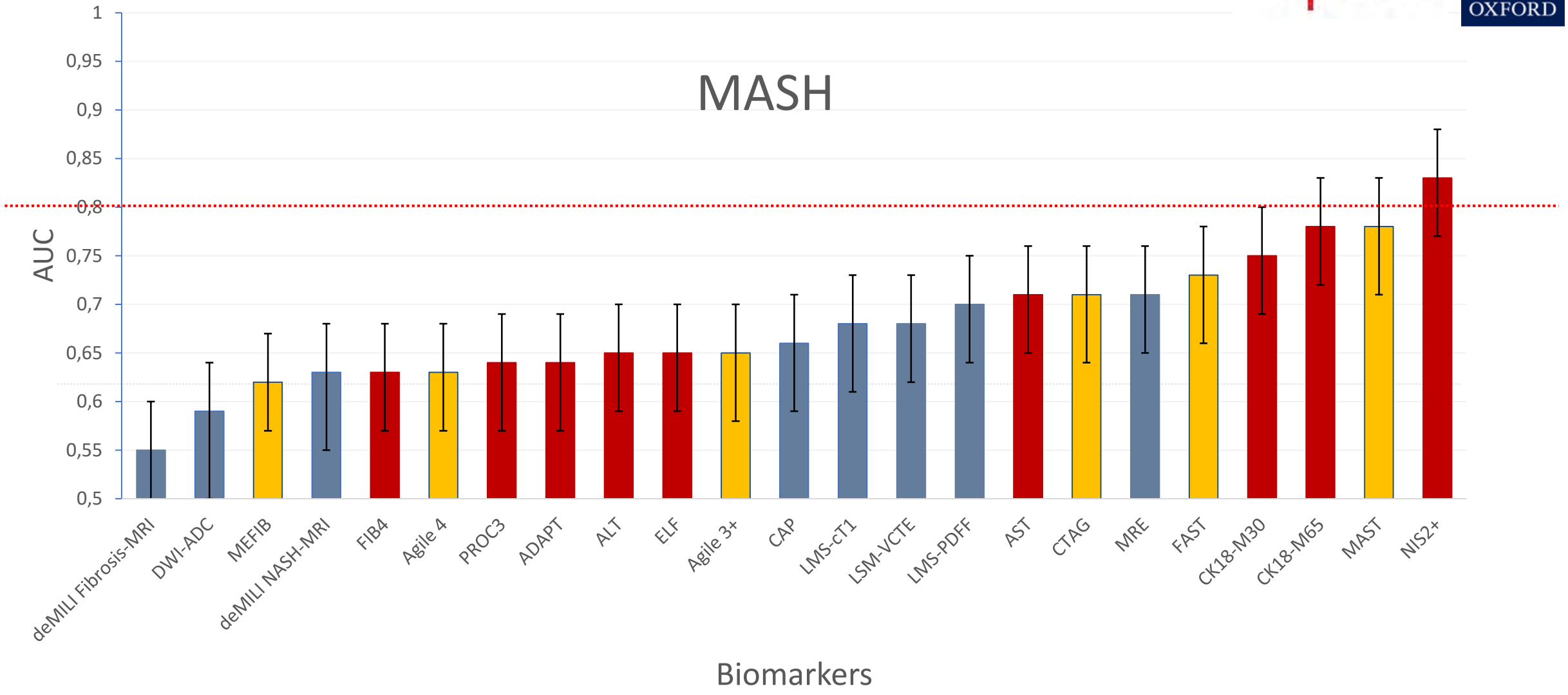
Paired imaging and centrally read histology available in **357 cases**

Mean interval between biopsy and imaging assessments: **7 weeks** (SD 5.1)

	Total (N=357)
Age (Years), mean (SD)	55.4 (13.2)
Gender (Male); N (%)	196 (55)
Ethnicity White; N (%)	335 (94)
BMI; kg/m²; Mean (SD)	33.8 (5.6)
Type2 Diabetes; N (%)	177 (50)
Hypertension; N (%)	200 (56)



Pavlides M et al. EASL 2025



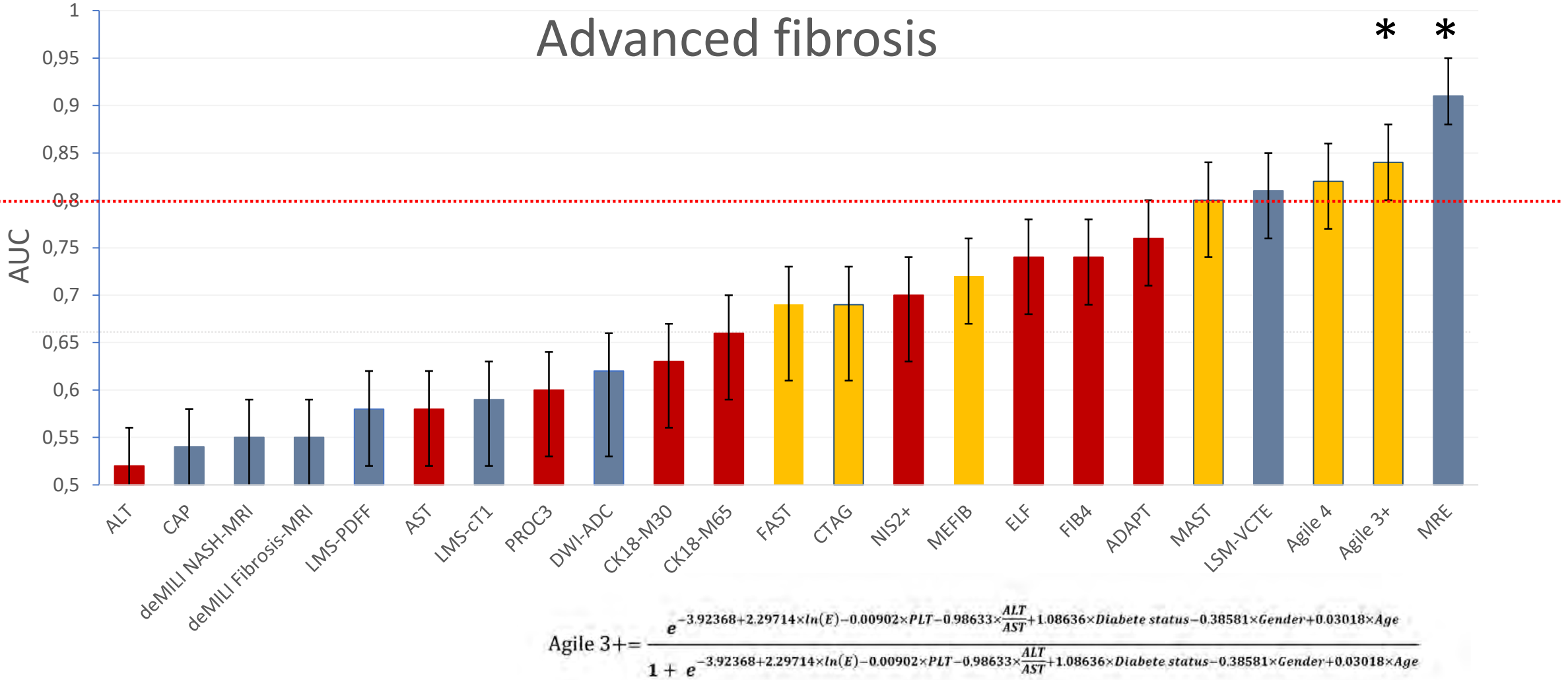
Blood-based biomarkers

Imaging modalities

Combinations of blood-based and imaging modalities

Pavlides M et al. EASL 2025

Advanced fibrosis



$$\text{Agile 3+} = \frac{e^{-3.92368+2.29714\times ln(E)-0.00902\times PLT-0.98633\times\frac{ALT}{AST}+1.08636\times Diabete\ status-0.38581\times Gender+0.03018\times Age}}{1+e^{-3.92368+2.29714\times ln(E)-0.00902\times PLT-0.98633\times\frac{ALT}{AST}+1.08636\times Diabete\ status-0.38581\times Gender+0.03018\times Age}}$$

Blood-based biomarkers

Imaging modalities

Combinations of blood-based and imaging modalities

Pavlides M et al. EASL 2025

Gastroenterology 2015;149:367–378

CLINICAL—LIVER

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis

Eduardo Vilar-Gomez,[1,2] Yadina Martinez-Perez,[1] Luis Calzadilla-Bertot,[1] Ana Torres-Gonzalez,[1] Bienvenido Gra-Oramas,[3] Licet Gonzalez-Fabian,[3] Scott L. Friedman,[4] Moises Diago,[5] and Manuel Romero-Gomez[2]

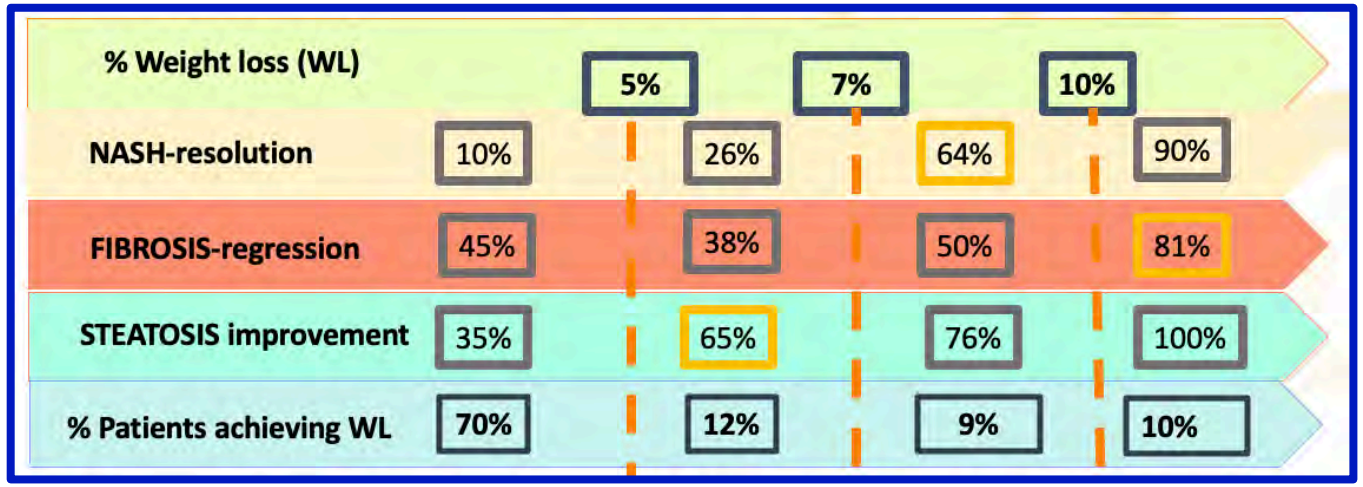
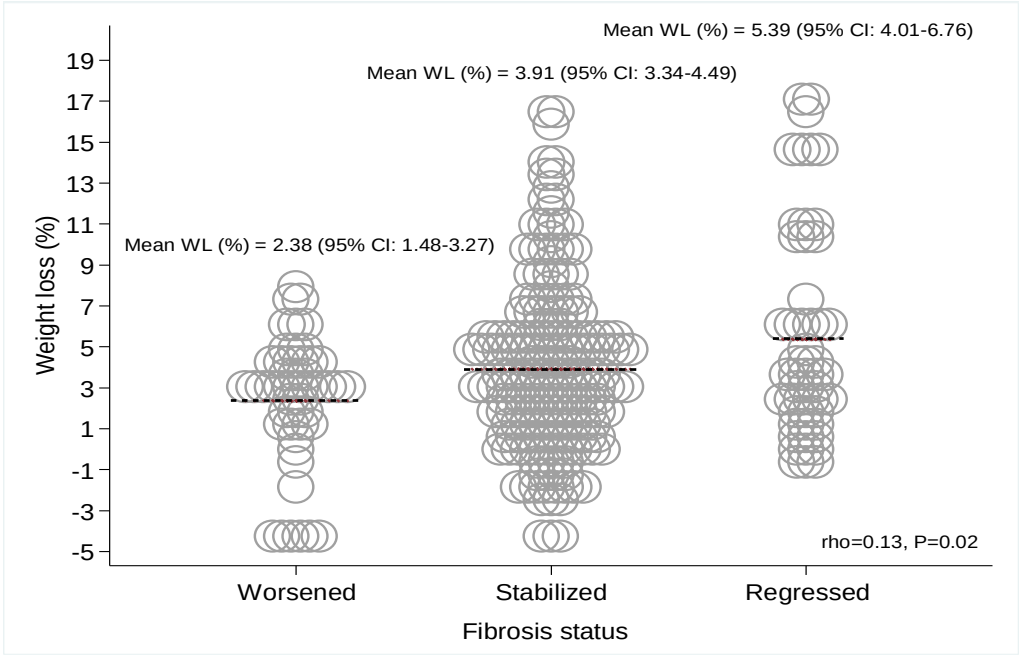


Table 2. Improvement of Histologic Outcomes Across Different Categories of Weight Loss at the End of Treatment

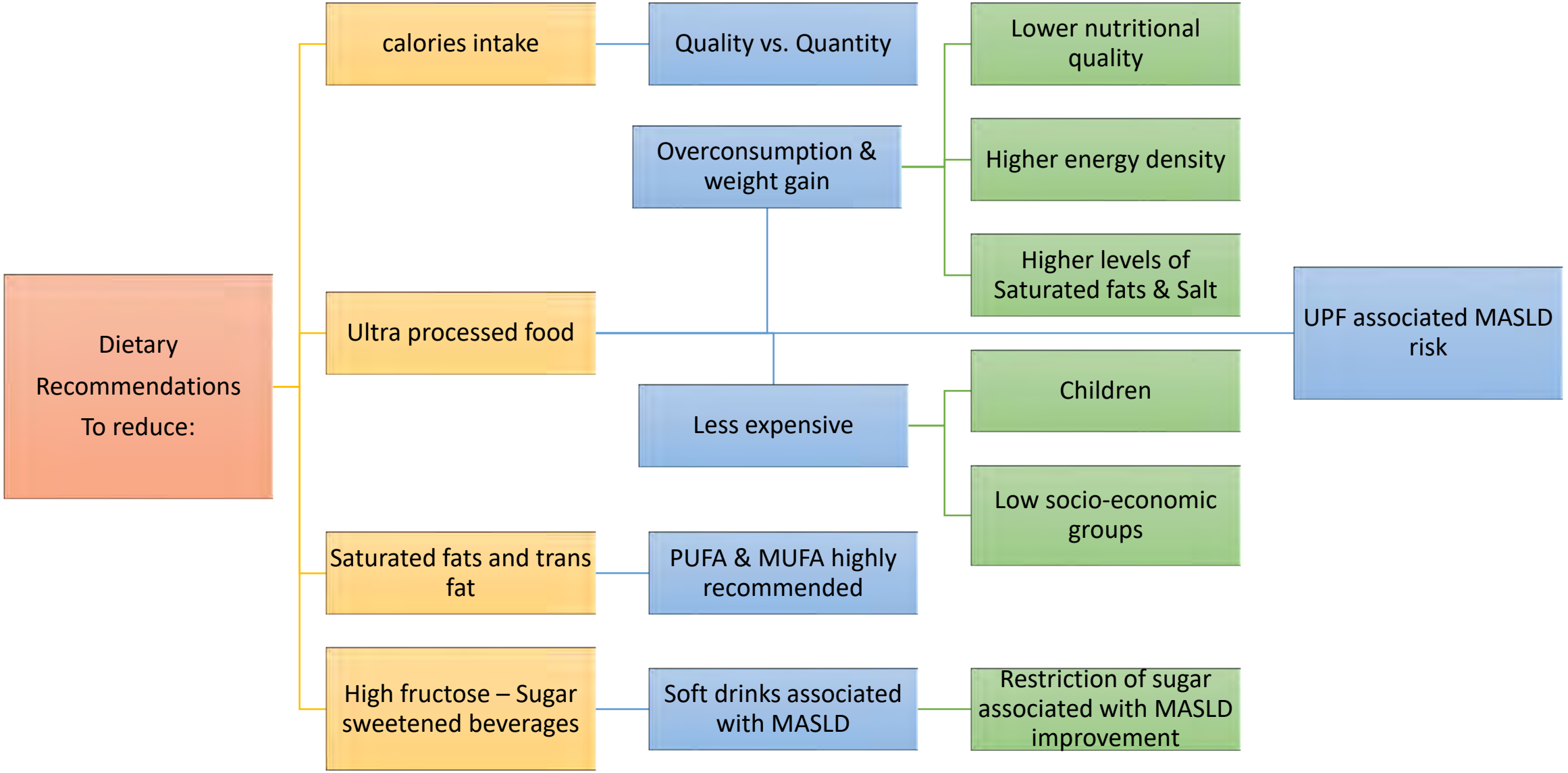
Variables	Overall (n = 293)	WL <5 (n = 205)	WL = 5–6.99 (n = 34)	WL = 7–9.99 (n = 25)	WL ≥10 (n = 29)	*P* value
Weight loss, %	3.8 ± 2.7	1.78 ± 0.16	5.86 ± 0.09	8.16 ± 0.22	13.04 ± 6.6	—
Resolution of steatohepatitis[a]	72 (25)	21 (10)	9 (26)	16 (64)	26 (90)	<.01

Hypocaloric low-fat diet promotes steatosis and NASH resolution and regression of fibrosis



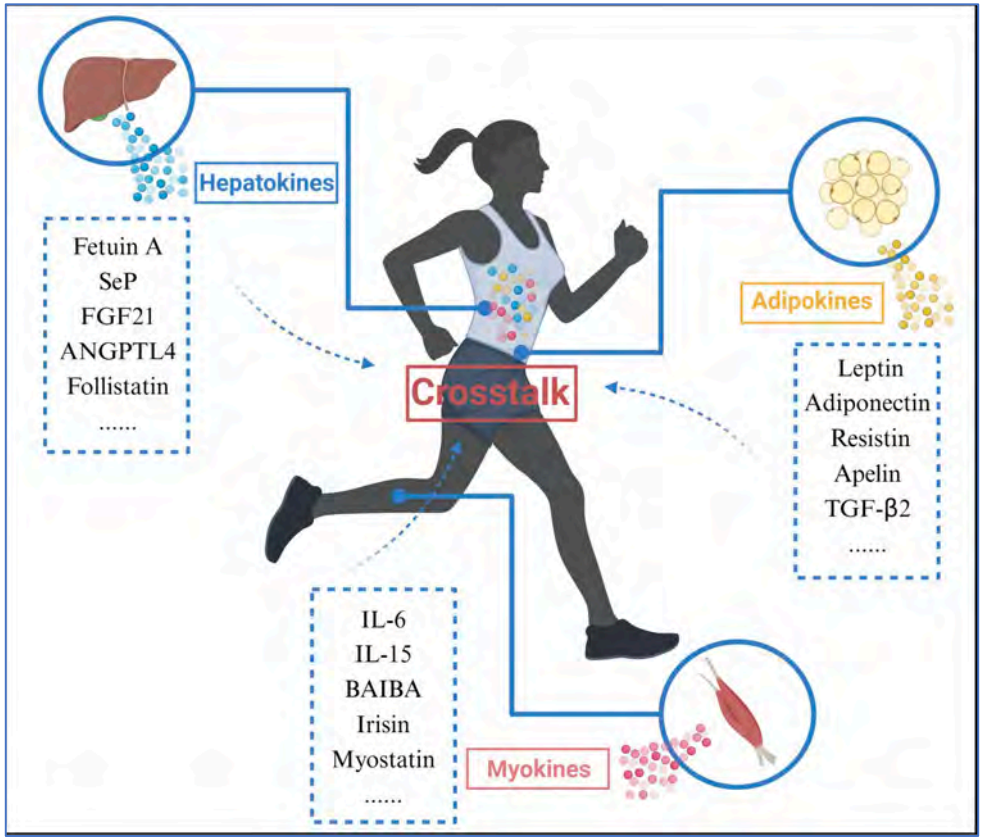
Vilar-Gomez et al. Gastro 2015; Romero-Gómez M et al. J Hepatol 2017

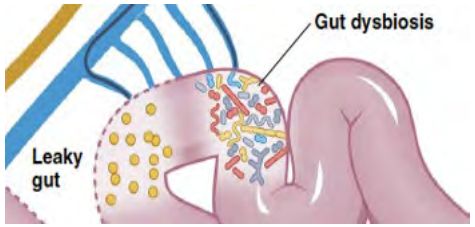
Modification of dietary habits

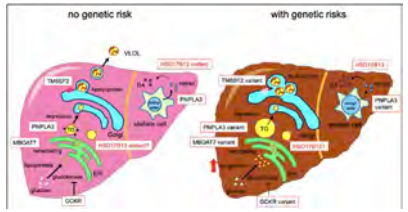


Romero-Gómez et al. BMJ 2023; 383:e075179
Zhao et al. JAMA 2023;330:537-46; Zhang et al. Am J Clin Nutr 2021;113:1265-74; Schwimmer et al. JAMA 2019; 321:256-65;
Zhang et al. Int J Epidemiol 2022;51:237-49; Hall et al. Cell Metab 2019;30:226-236; Golovaty et al. J Nutr 2020;150:91-98

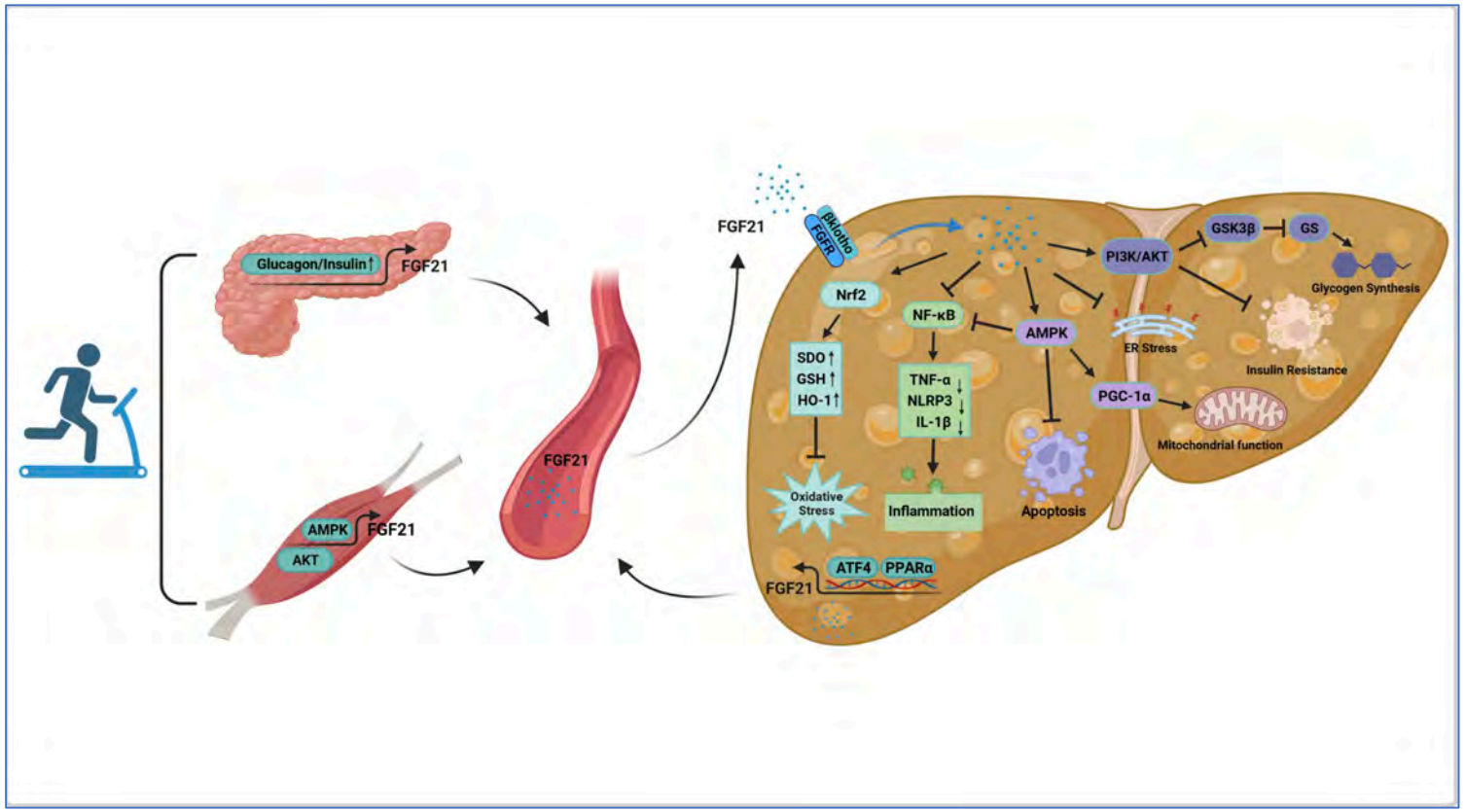
Impact of physical activity on MASLD







Regular exercise is known to have many positive effects on health, such as **reducing the risk of cardiovascular disease**, **reducing serum triglyceride levels**, **increasing aerobic capacity and fat mobilization**, **improving insulin sensitivity**, **strengthening muscle strength and endurance**, and **improving the quality of life**, and it is **the healthiest, most economical and most effective strategy to prevent and treat NAFLD without causing liver damage in humans**.



Wang Z, et al. FGF21: A Sharp Weapon in the Process of Exercise to Improve NAFLD. Front Biosci (Landmark Ed) 2023;28:351.

N=96 biopsy-proven MASLD

Nutritional and physical activity intervention in MASLD: RCT EHmetD+IA

Nutritional intervention with Mediterranean Diet, recall every 4 weeks and 2L olive oil every other 4 week

Control group

General EASL recommendations of moderate-intensity exercise 150-300'/week divided in 3-5 sessions

Structured Physical Activity(PA)

GYM +

3 days at gym: 30' moderate-intensity walking + 30' weight exercise + 1 day/week moderate-intensity walking at home

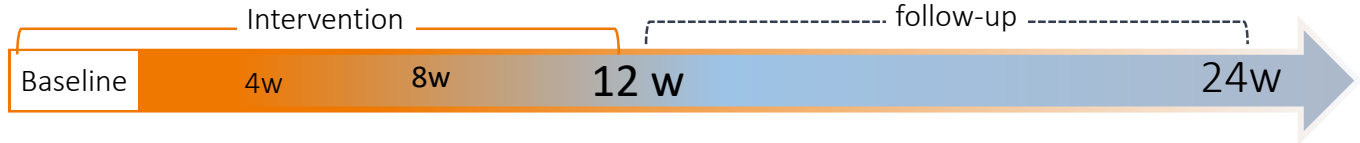
1 day/week at gym: 30' moderate-intensity walking + 30' **weight exercise** + 3 days at home: **30'** moderate-intensity **exercise** guided by virtual platform

Nutritional adherence: **Predimed**

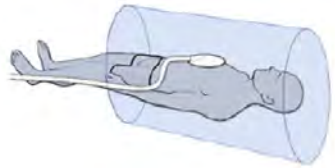
Physical activity: **IPAQ** **Smartwatch**

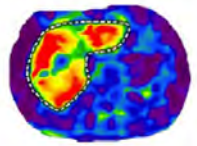
Body composition: **BIA**

QoL

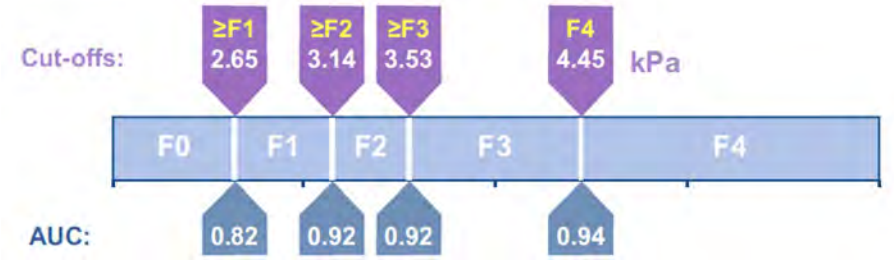


MRI-PDFF > 30%





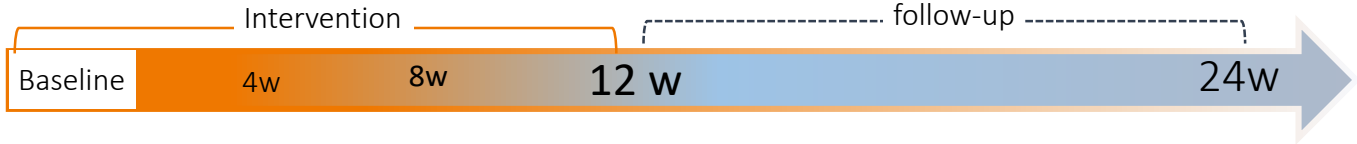
MRE

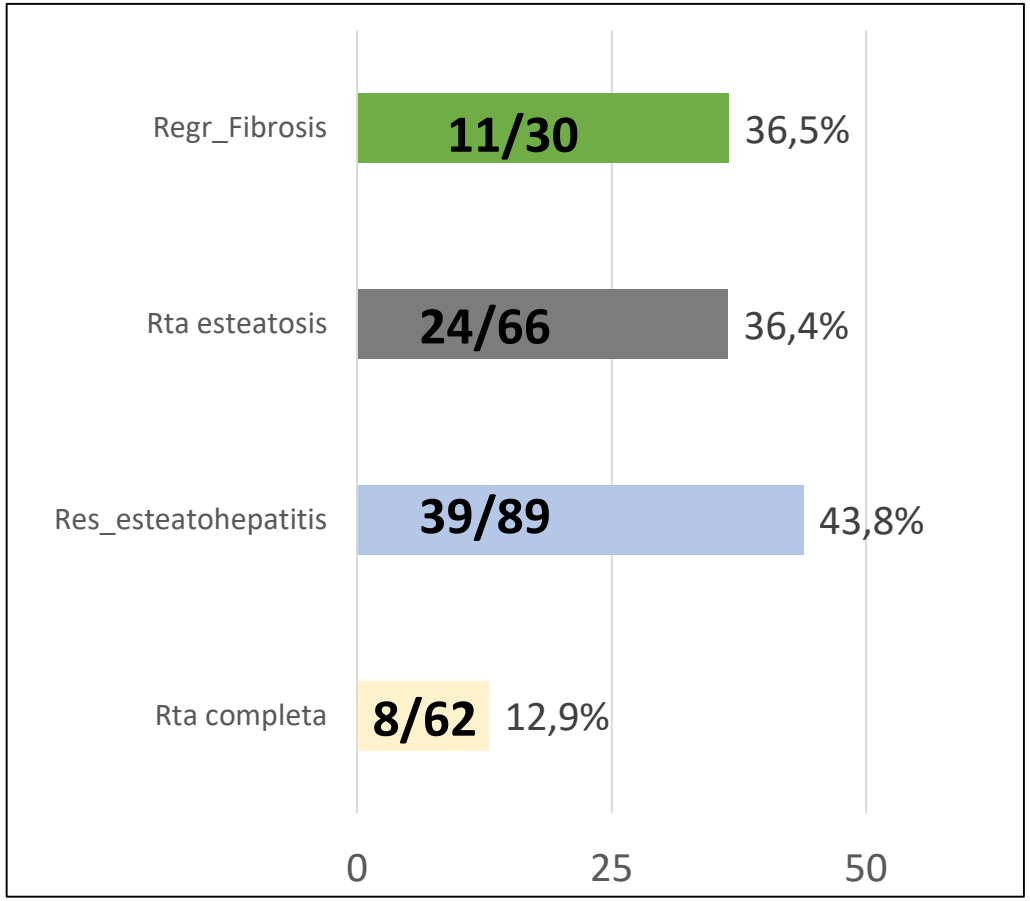


Liang et al. J Hepatol 2023;
Lara-Romero et al. EASL 2024

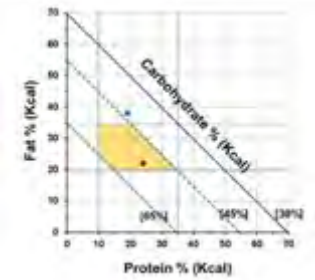
Características basales

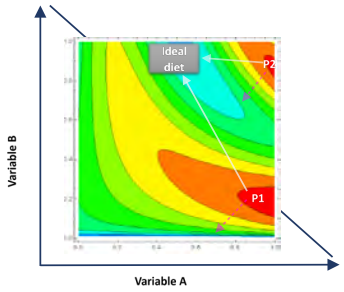
N=96	N (%)			N (%)
Mujeres	51 (53.1%)	Esteatosis	G1	51 (55,4%)
> 60 años	54 (56.3%)		G2	29 (31,5%)
HTA	63 (65.6%)		G3	12 (13,0%)
DLP	43 (44,8%)	Esteatohepatitis	No	3 (3,4%)
DM2	46 (47,9%)		A1-A2	58 (65,2%)
Obesidad	67 (69,8%)		A3-A4	29 (32,6%)
AST > 45U/L	19 (19%)	Fibrosis	F0	23 (24,7%)
ALT/FA < 0,5	50 (52,1%)		F1	26 (28%)
			F2	12 (12,9%)
			F3	26 (28%)
			F4	6 (6,5%)





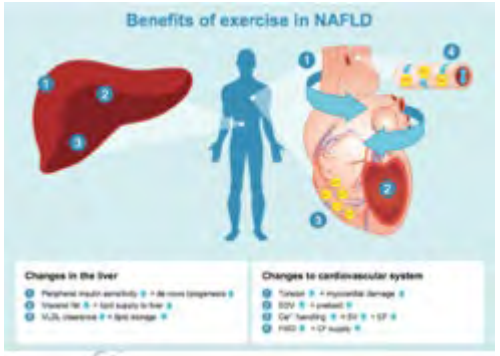
Dietary recommendation
Hypocaloric Mediterranean Diet
Nutritional Geometry





MASLD

LIFE-STYLE INTERVENTION



Aerobic /resistant exercise
150 min/week

RESPONDERS

RESPONDERS improvement of at least 1 stage of fibrosis by MRE

36.5% (11/30)

% Weight loss
ALT normalization

Improvement of Obesity, T2DM, dyslipidemia & AHT

NON-RESPONDERS

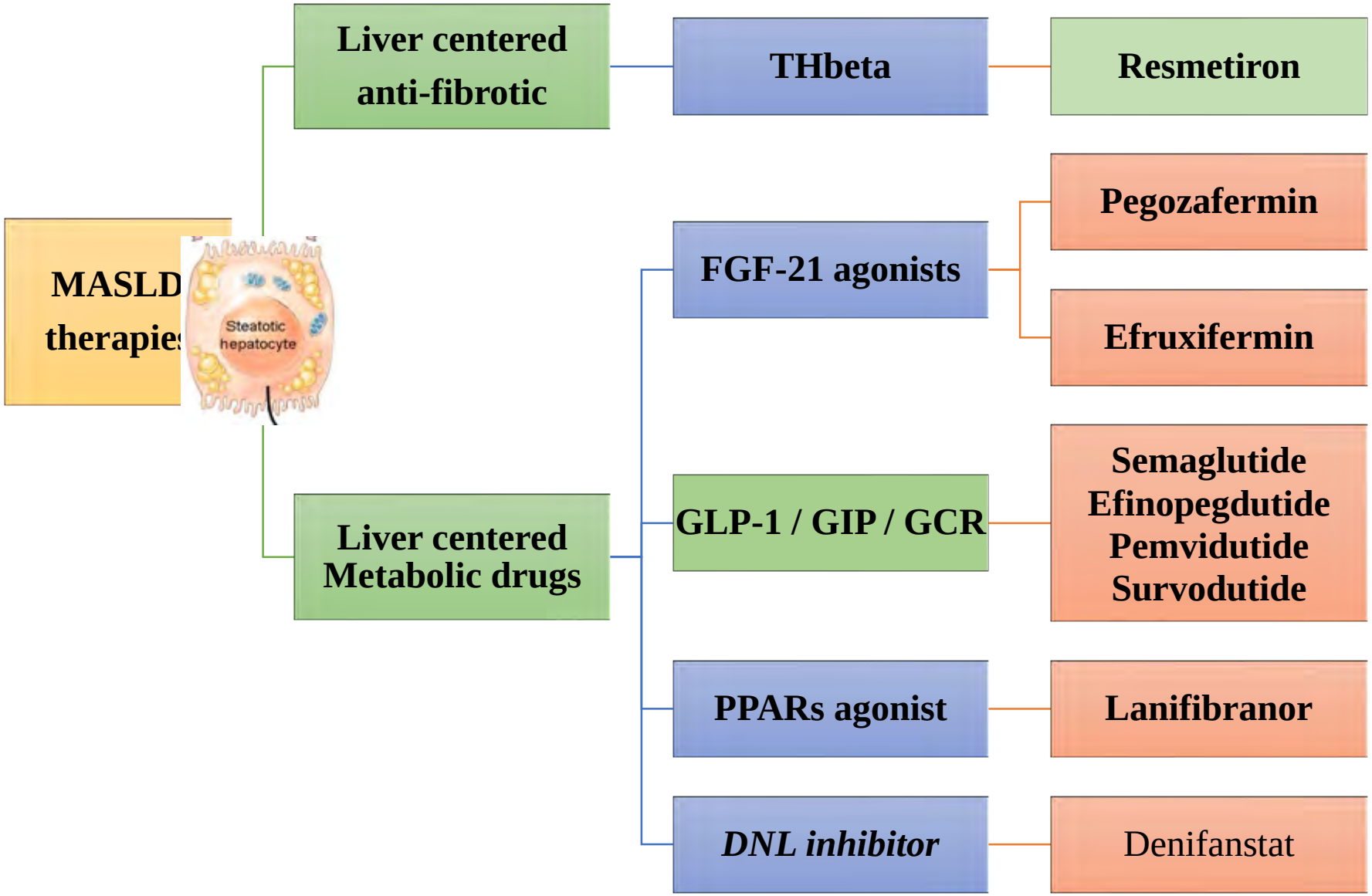
Drug therapy

Resmetiron
Semaglutide

Lanifibranor
Survodutide
Efinopegdutide
Pegozafermin
Efruxifermin

Romero Gómez M, Aller R, Martín-Bermudo F. Semin Liver Dis 2022

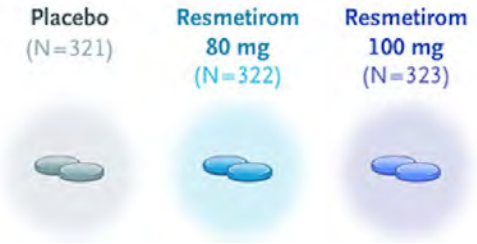
Pharmacological therapy for MAFLD

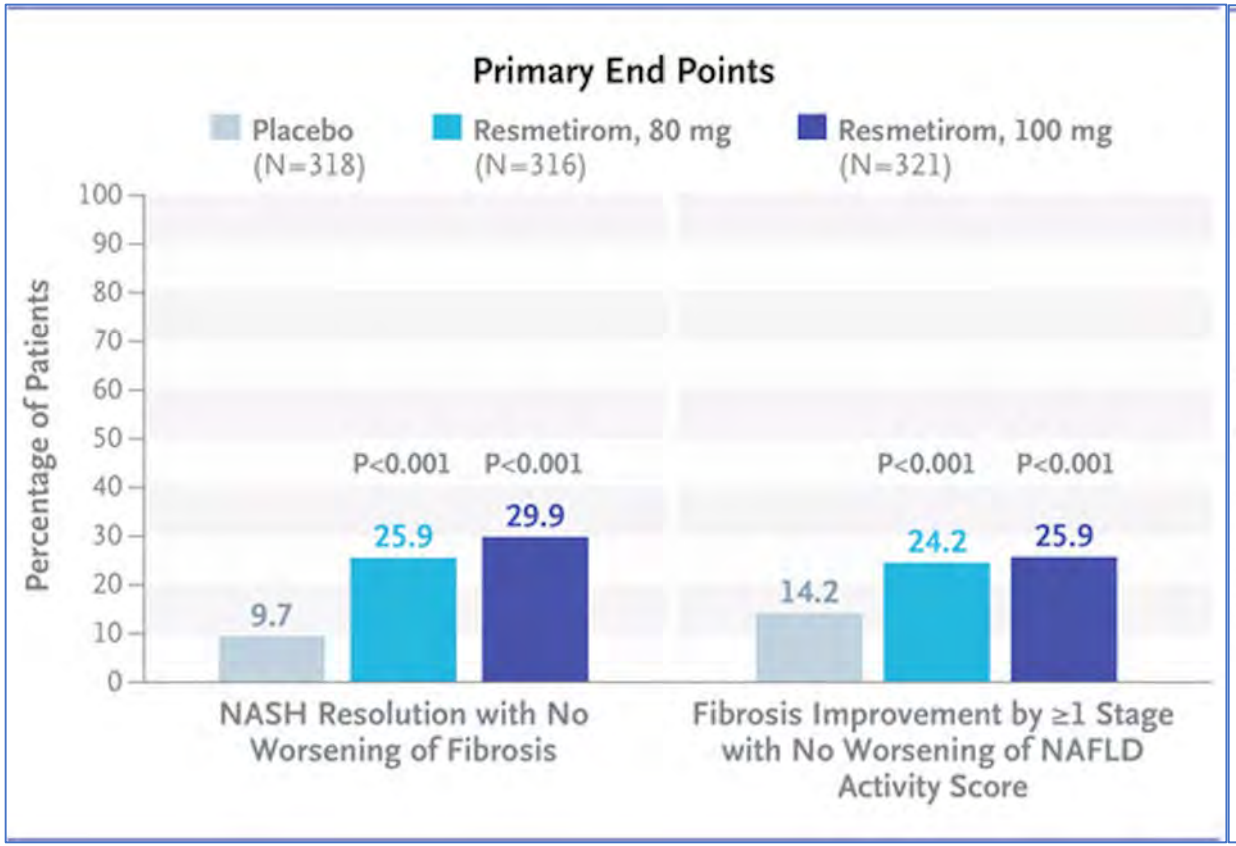


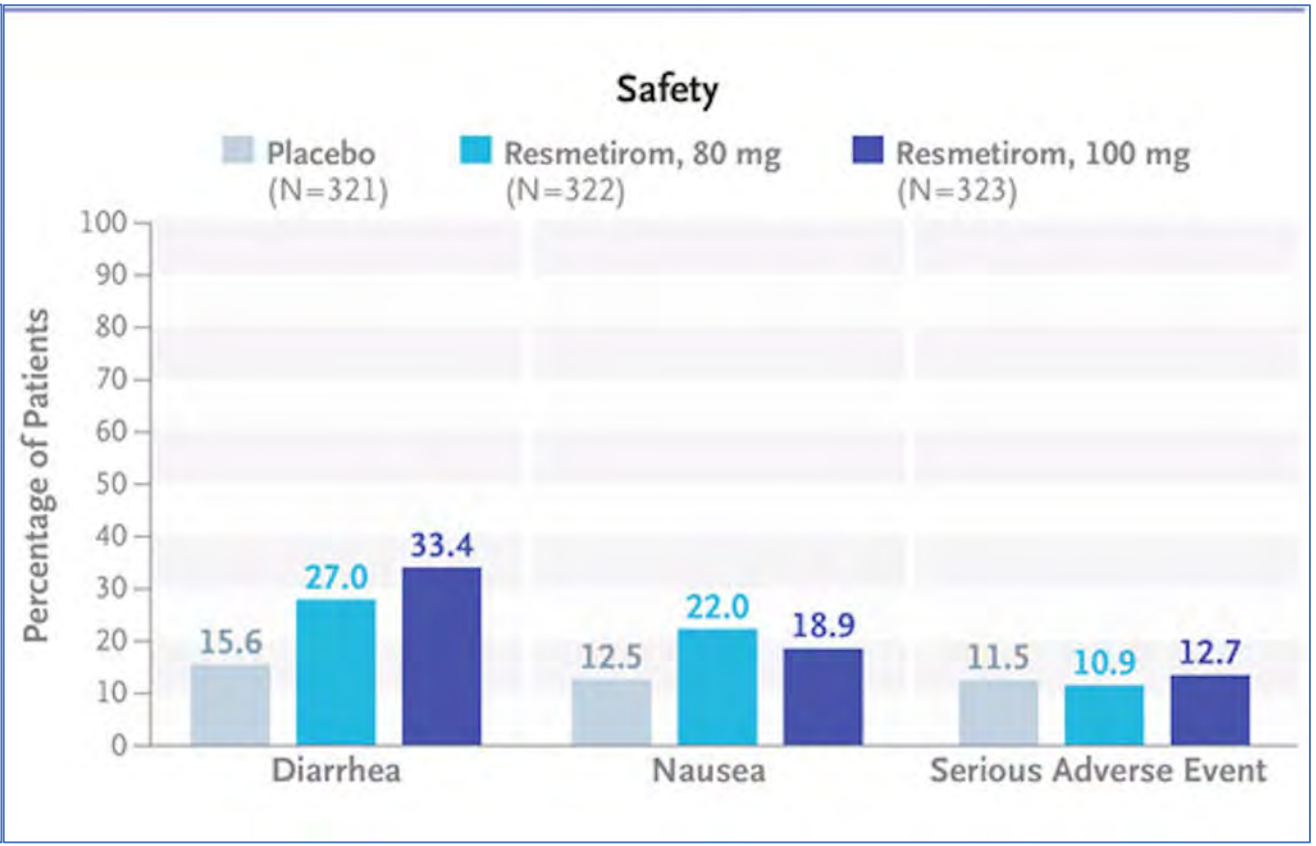
A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

N=966

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

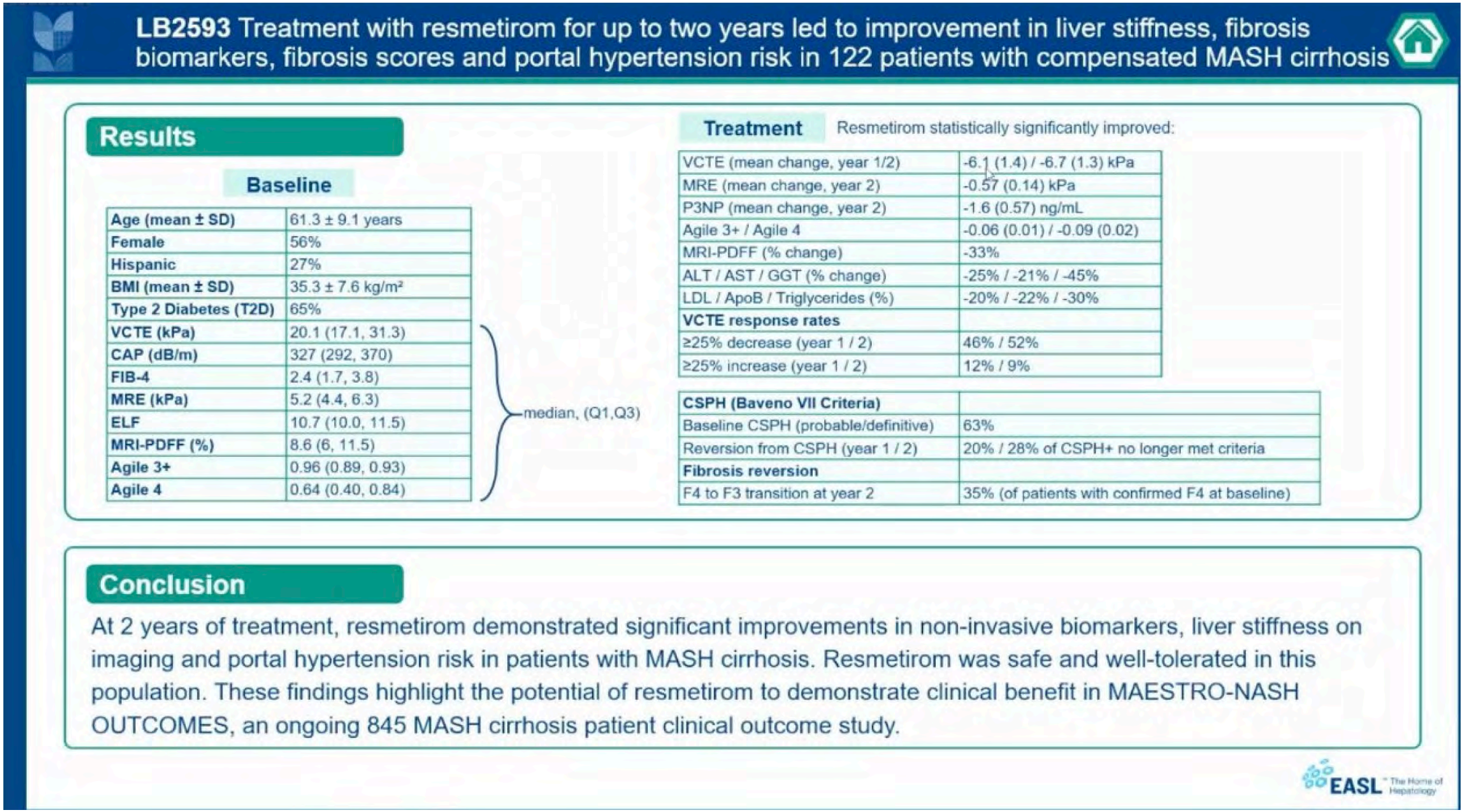






Harrison S et al. NEJM 2024

Resmetirom 2y in patients living with cirrhosis



LB2593 Treatment with resmetirom for up to two years led to improvement in liver stiffness, fibrosis biomarkers, fibrosis scores and portal hypertension risk in 122 patients with compensated MASH cirrhosis

Results

Baseline

Age (mean ± SD)	61.3 ± 9.1 years
Female	56%
Hispanic	27%
BMI (mean ± SD)	35.3 ± 7.6 kg/m²
Type 2 Diabetes (T2D)	65%
VCTE (kPa)	20.1 (17.1, 31.3)
CAP (dB/m)	327 (292, 370)
FIB-4	2.4 (1.7, 3.8)
MRE (kPa)	5.2 (4.4, 6.3)
ELF	10.7 (10.0, 11.5)
MRI-PDFF (%)	8.6 (6, 11.5)
Agile 3+	0.96 (0.89, 0.93)
Agile 4	0.64 (0.40, 0.84)

median, (Q1,Q3)

Treatment

Resmetirom statistically significantly improved:

VCTE (mean change, year 1/2)	-6.1 (1.4) / -6.7 (1.3) kPa
MRE (mean change, year 2)	-0.57 (0.14) kPa
P3NP (mean change, year 2)	-1.6 (0.57) ng/mL
Agile 3+ / Agile 4	-0.06 (0.01) / -0.09 (0.02)
MRI-PDFF (% change)	-33%
ALT / AST / GGT (% change)	-25% / -21% / -45%
LDL / ApoB / Triglycerides (%)	-20% / -22% / -30%
VCTE response rates	
≥25% decrease (year 1 / 2)	46% / 52%
≥25% increase (year 1 / 2)	12% / 9%

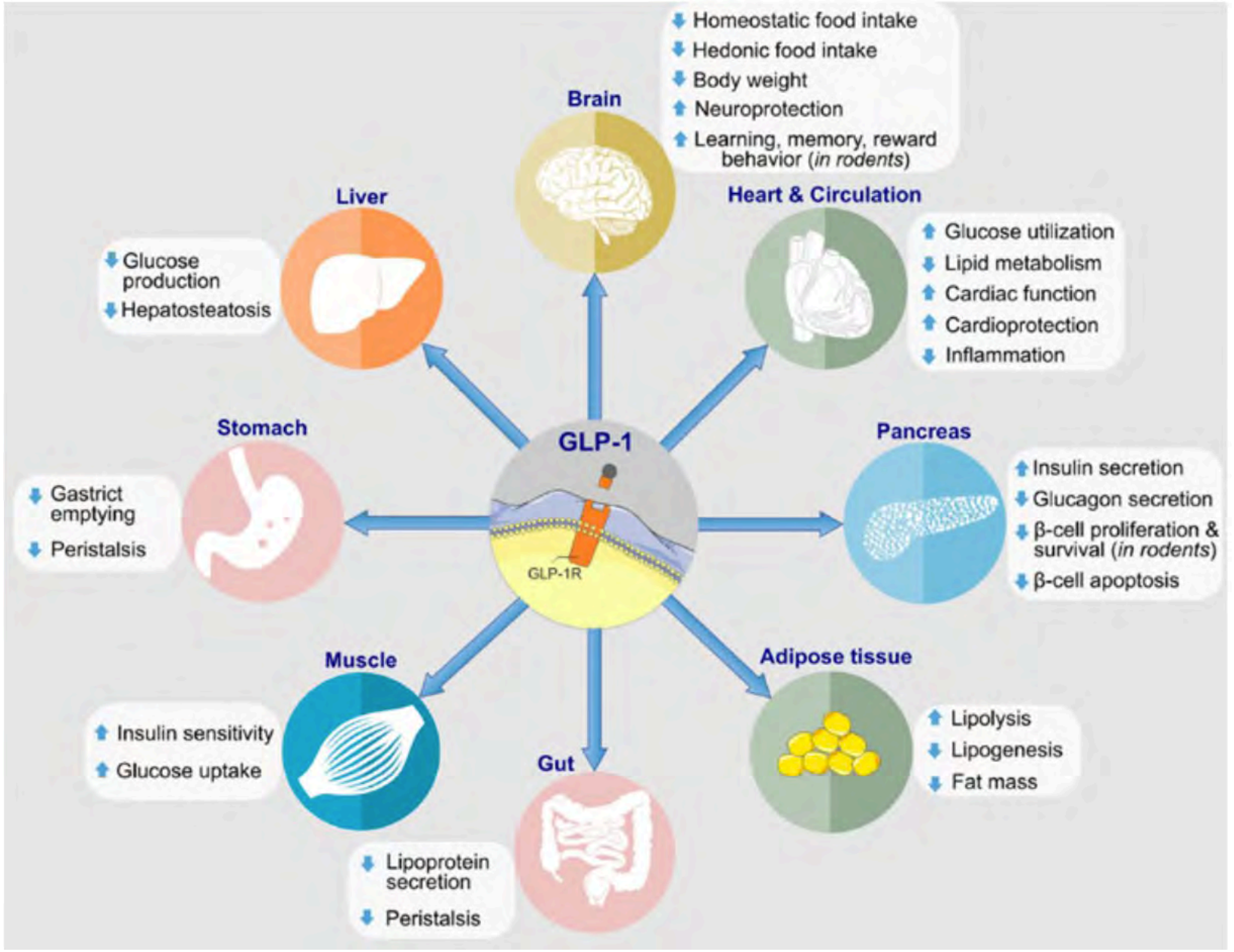
CSPH (Baveno VII Criteria)	
Baseline CSPH (probable/definitive)	63%
Reversion from CSPH (year 1 / 2)	20% / 28% of CSPH+ no longer met criteria
Fibrosis reversion	
F4 to F3 transition at year 2	35% (of patients with confirmed F4 at baseline)

Conclusion

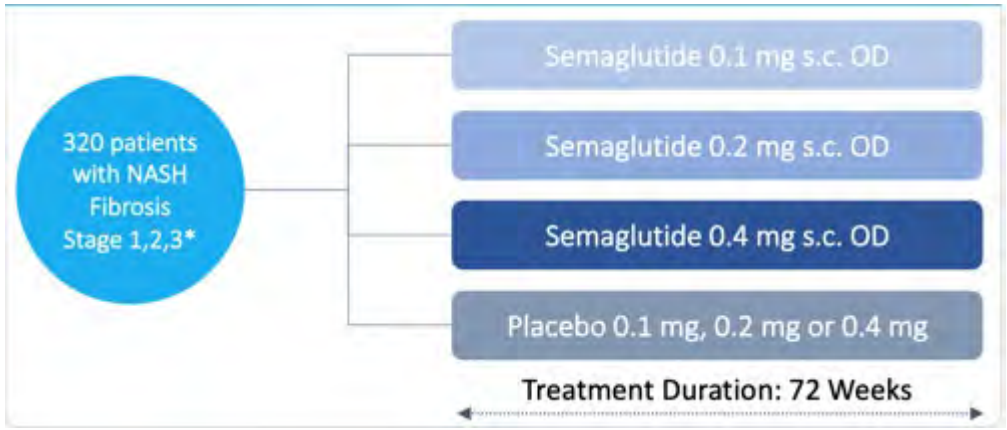
At 2 years of treatment, resmetirom demonstrated significant improvements in non-invasive biomarkers, liver stiffness on imaging and portal hypertension risk in patients with MASH cirrhosis. Resmetirom was safe and well-tolerated in this population. These findings highlight the potential of resmetirom to demonstrate clinical benefit in MAESTRO-NASH OUTCOMES, an ongoing 845 MASH cirrhosis patient clinical outcome study.

EASL The Home of Hepatology

GLP-1 receptor agonists in MASLD: mechanism of action



Semaglutide in MASLD: Phase 2



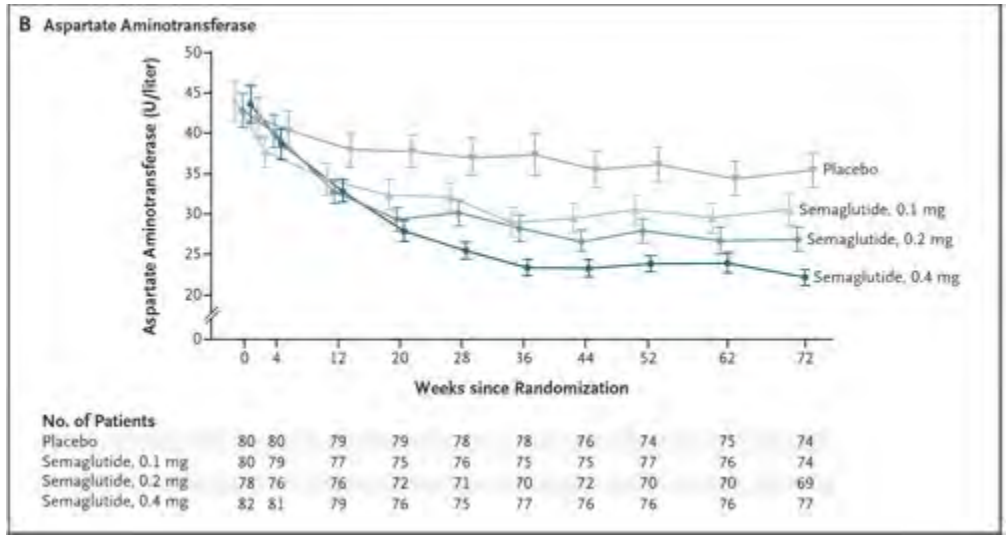
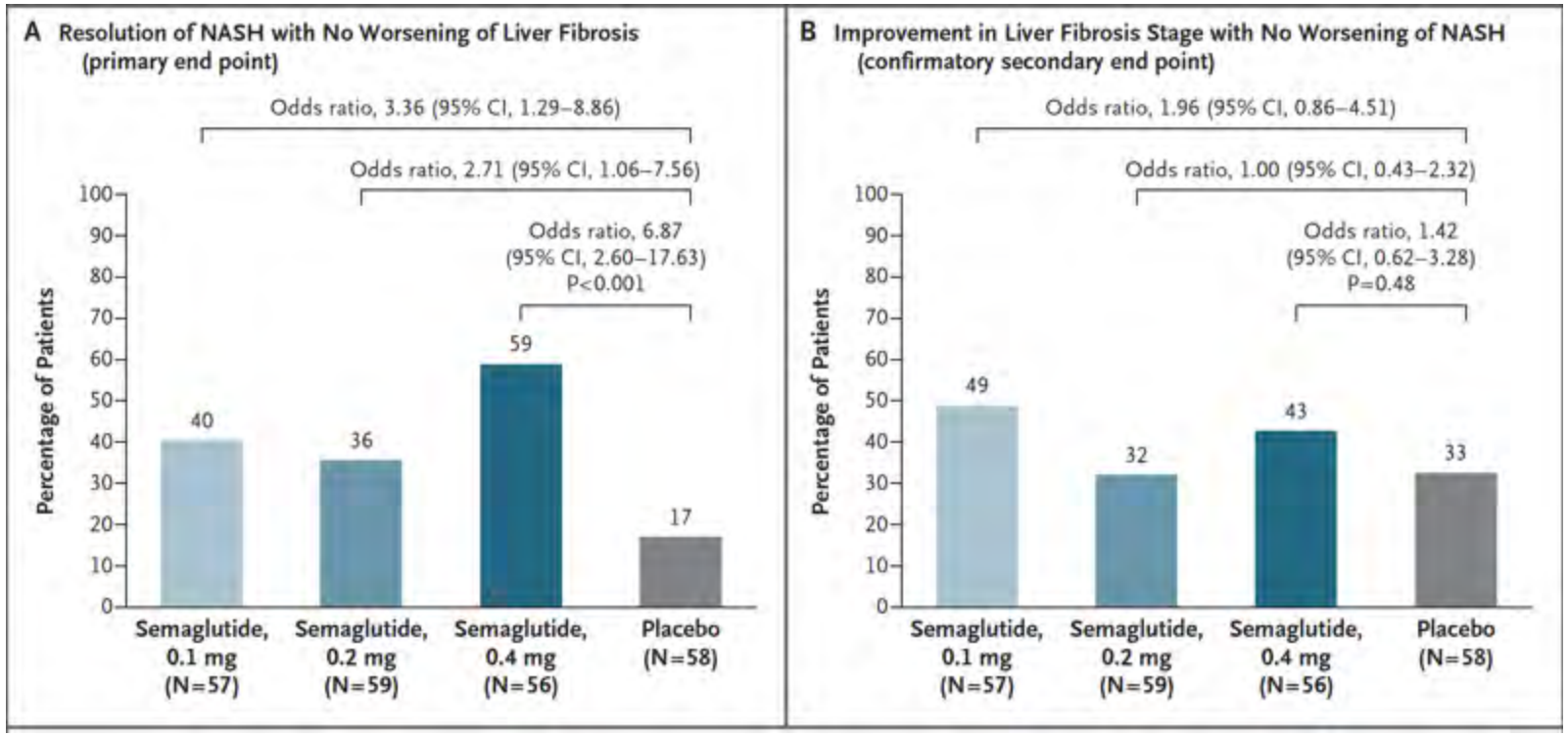


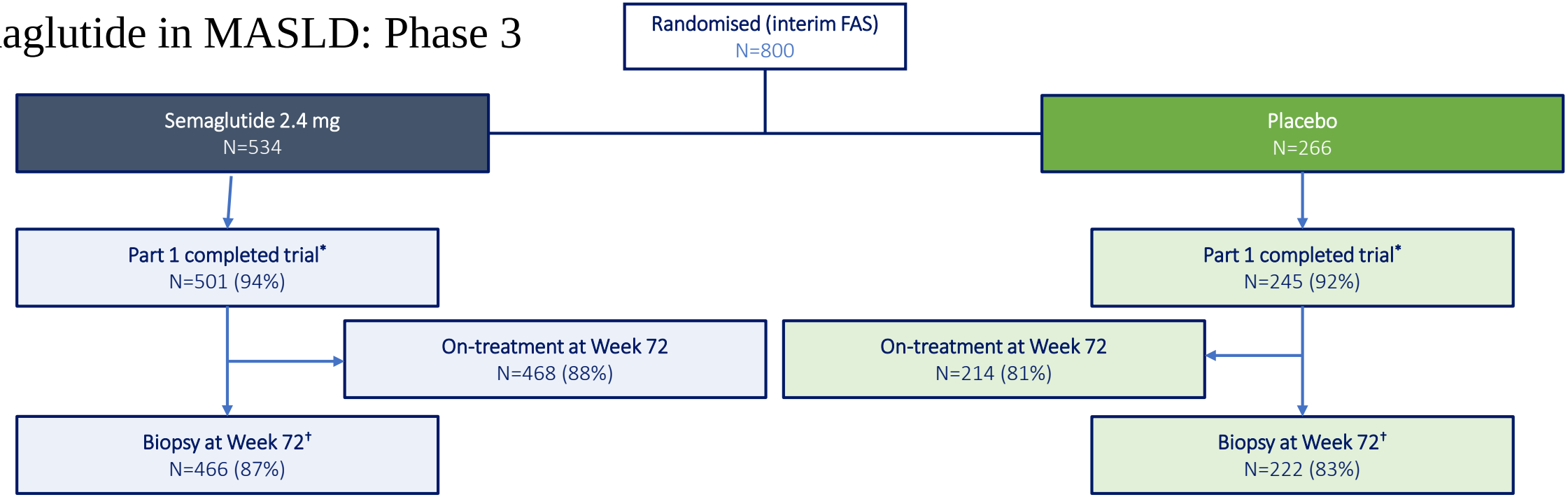
Table 2. Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*

End Point	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)
Ratio of value at wk 72 to value at baseline				
Alanine aminotransferase	0.63	0.58	0.42	0.81
Aspartate aminotransferase	0.70	0.65	0.52	0.84
Caspase-cleaved cytokeratin-18 fragment M30†	0.55	0.50	0.47	0.78
Caspase-cleaved cytokeratin-18 fragment M65†	0.53	0.52	0.42	0.71
Total cholesterol	0.97	1.00	0.93	0.94
Triglycerides	0.88	0.90	0.73	0.97
Liver stiffness, as assessed by FibroScan‡	0.76	0.71	0.72	1.02
Change from baseline to wk 72				
Enhanced liver fibrosis test score	−0.34	−0.39	−0.56	0.01
Body weight — %	−4.84	−8.91	−12.51	−0.61
Glycated hemoglobin level among patients with type 2 diabetes — percentage points§	−0.63	−1.07	−1.15	−0.01



Newsome P et al. NEJM 2020

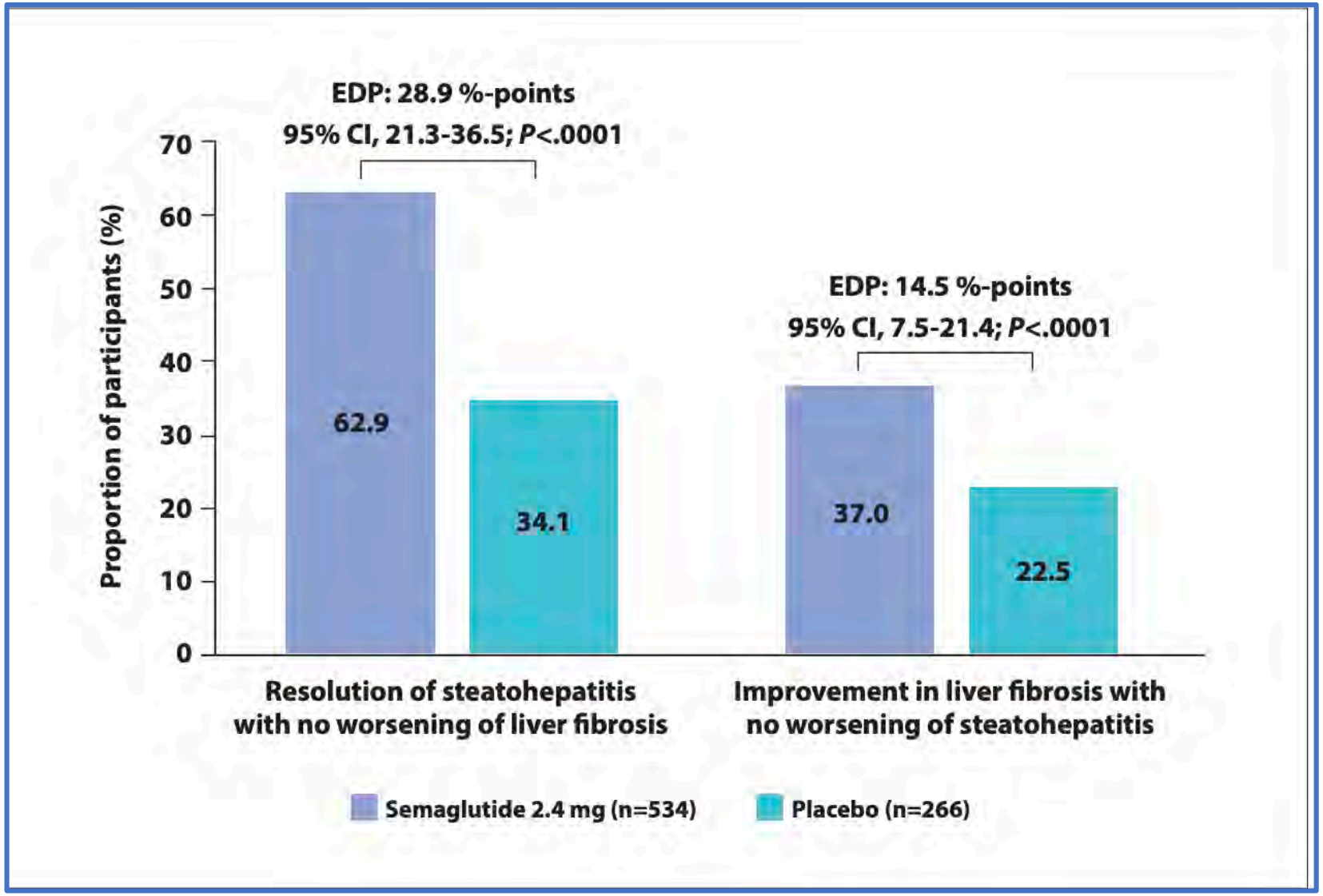
Semaglutide in MASLD: Phase 3



Characteristics	Semaglutide 2.4 mg (N=534)	Placebo (N=266)	Characteristics	Semaglutide 2.4 mg (N=534)	Placebo (N=266)
Age, years	56.3 ± 11.4	55.4 ± 12.0	Alanine aminotransferase, U/L	67.8 ± 42.3	67.9 ± 44.7
Sex, female, n (%)	313 (58.6)	144 (54.1)	Fibrosis stage 3, n (%)	365 (68.4)	185 (69.5)
Type 2 diabetes, n (%)	296 (55.4)	151 (56.8)	Liver stiffness by VCTE, kPa	12.8 ± 6.6	12.9 ± 7.6
HbA_{1c}, %	6.6 ± 1.1	6.4 ± 1.0	ELF™ score	10.0 ± 0.9	10.0 ± 1.0
HbA_{1c}, %, with T2diabetes	7.2 ± 1.1	6.9 ± 1.0	PRO-C3, ng/ml	52.9 ± 24.9	52.9 ± 28.1
Body mass index, kg/m^2	34.3 ± 7.2	35.0 ± 7.1			

*A trial completer for Part 1 is defined as a participant that either attended the Week 72 visit or died before the visit. †Participants with a pathologist consensus result for all 4 liver histology parameters for the Week 72 biopsy.
FAS, full analysis set; MASH, metabolic dysfunction-associated steatohepatitis. Newsome PN et al. Oral Presentation at American Association for the Study of the Liver The Liver Meeting; Late Breaker 5018; November 19 2024; San Diego, USA.

Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis



Sanyal et al. NEJM 2025;

GLP-1/GCR

Efinopegdutide

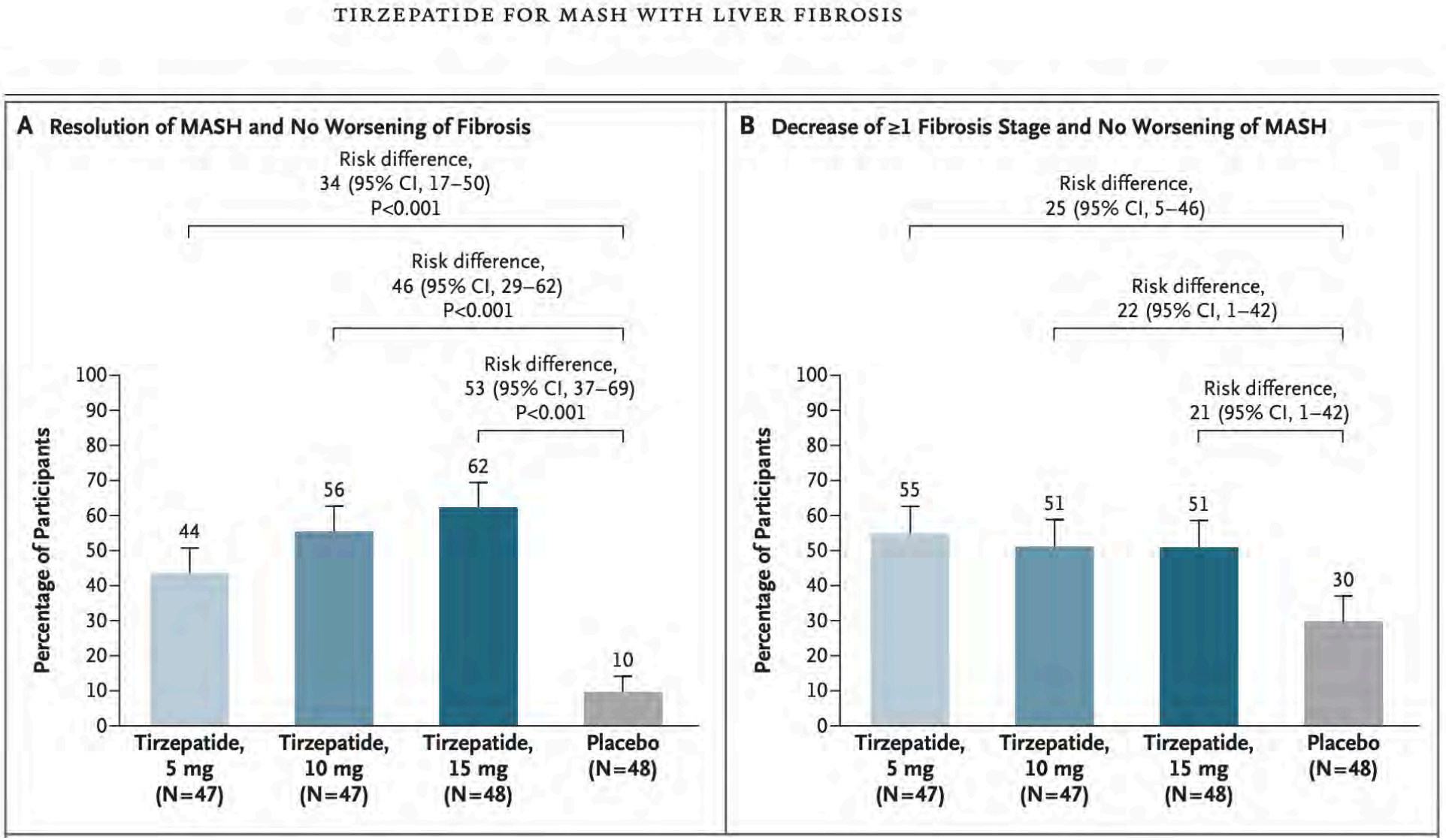
Survodutide

Pemvidutide

GLP-1/GIP

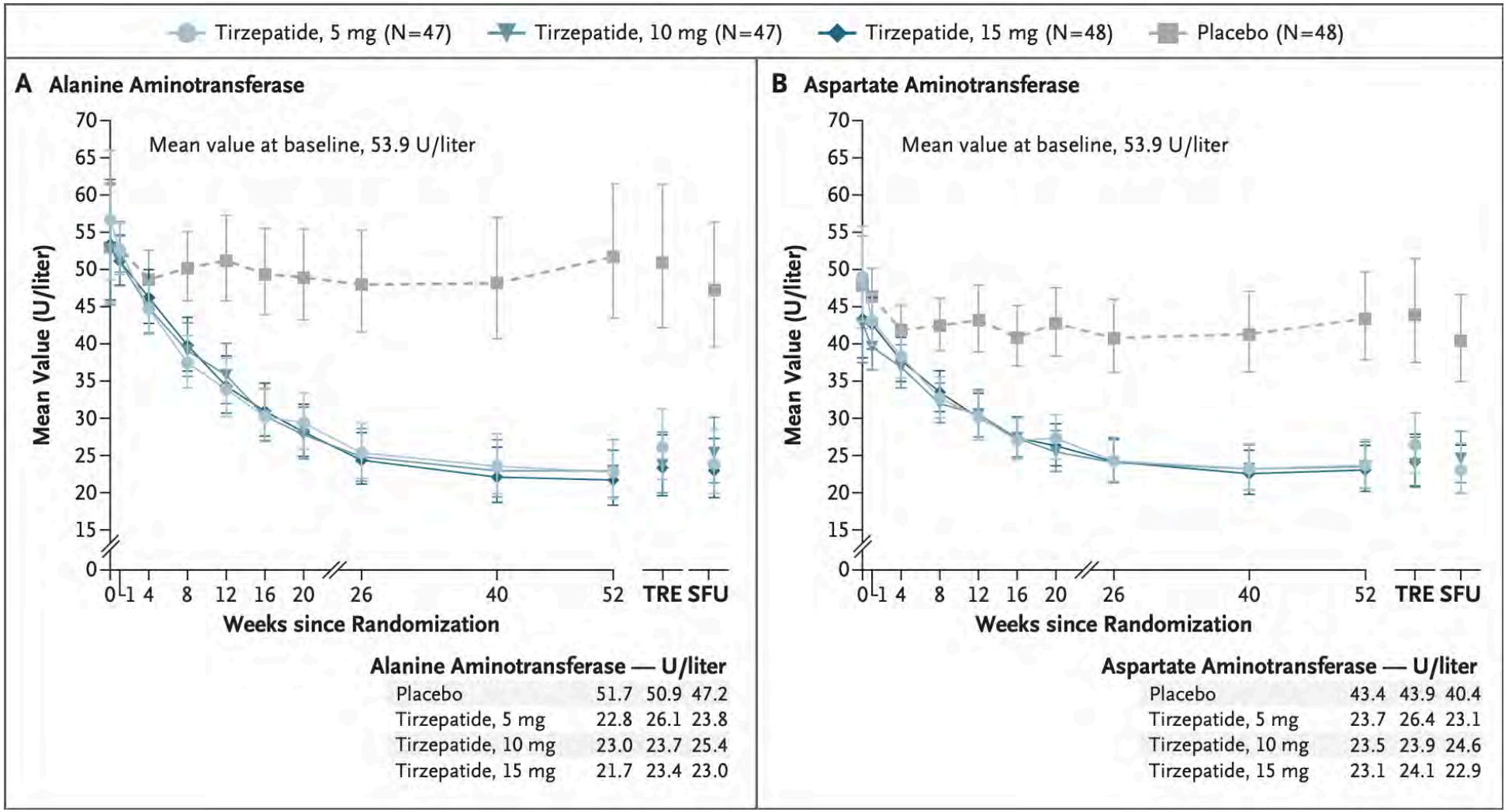
Tirzepatide

Tirzepatide in MASLD: Removing fat in the liver



Loomba et al. NEJM 2024;391:291

Tirzepatide in MASLD: Removing fat in the liver

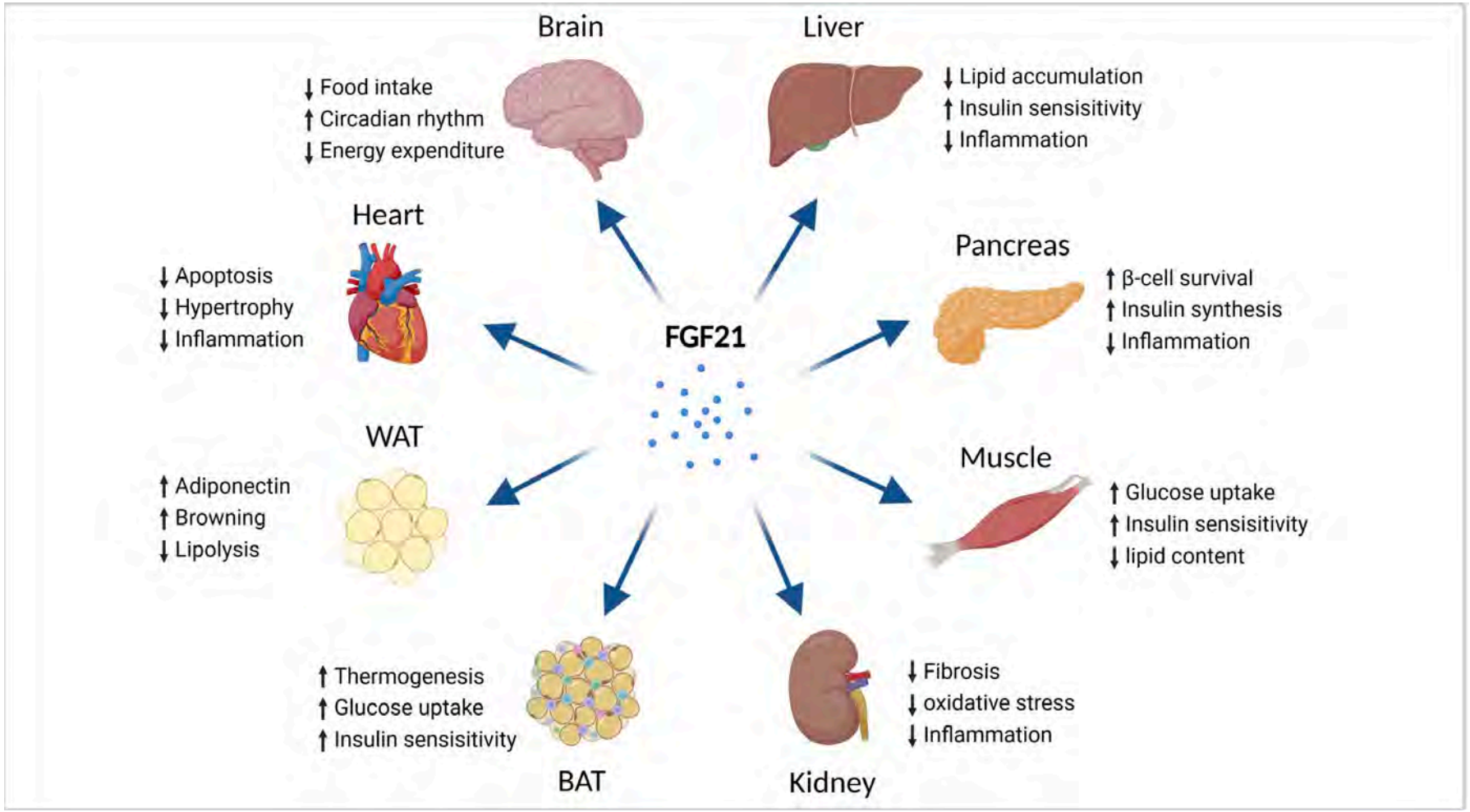


Alanine Aminotransferase — U/liter			
Placebo	51.7	50.9	47.2
Tirzepatide, 5 mg	22.8	26.1	23.8
Tirzepatide, 10 mg	23.0	23.7	25.4
Tirzepatide, 15 mg	21.7	23.4	23.0

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

Loomba et al. NEJM 2024;391:291

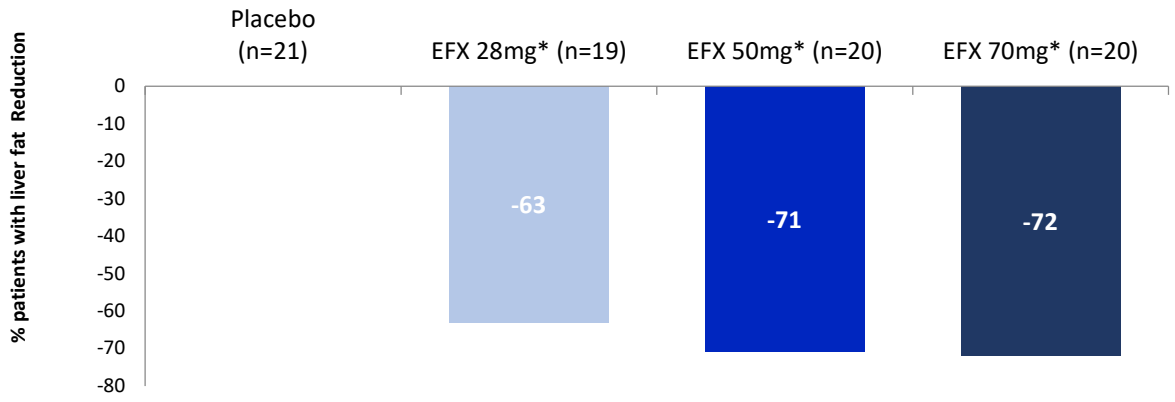
FGF21 a hepatokines linking physical activity and MASLD



Wang Z, et al. FGF21: A Sharp Weapon in the Process of Exercise to Improve NAFLD. Front Biosci (Landmark Ed) 2023;28:351.

Efruxifermin: FGF21 analog

N=80
4 arms



Measure (Mean)	Placebo (n=21)	EFX (Once Weekly Dose) p<0.001		
		28mg (n=19)	50mg (n=20)	70mg (n=20)
Absolute Reduction in Liver Fat (%)	-0.3	-12.3	-13.4	-14.1
Reduction in ALT (U/L)	-6	-24	-30	-32

N=52
4 arms

	NASH resolution	Fibrosis regression 1 stage	Fibrosis regression 2 stages
Placebo (n=2)	1/2 (50%)	0/2 (0%)	0%
EFX 28 mg (n=13)	6/3 (46%)	6/13 (46%)	4/13 (31%)
EFX 50 mg (n=13)	7/13 (54%)	8/13 (62%)	5/13 (38%)
EFX 70 mg (n=14)	6/14 (43%)	6/14 (43%)	1/14 (14%)

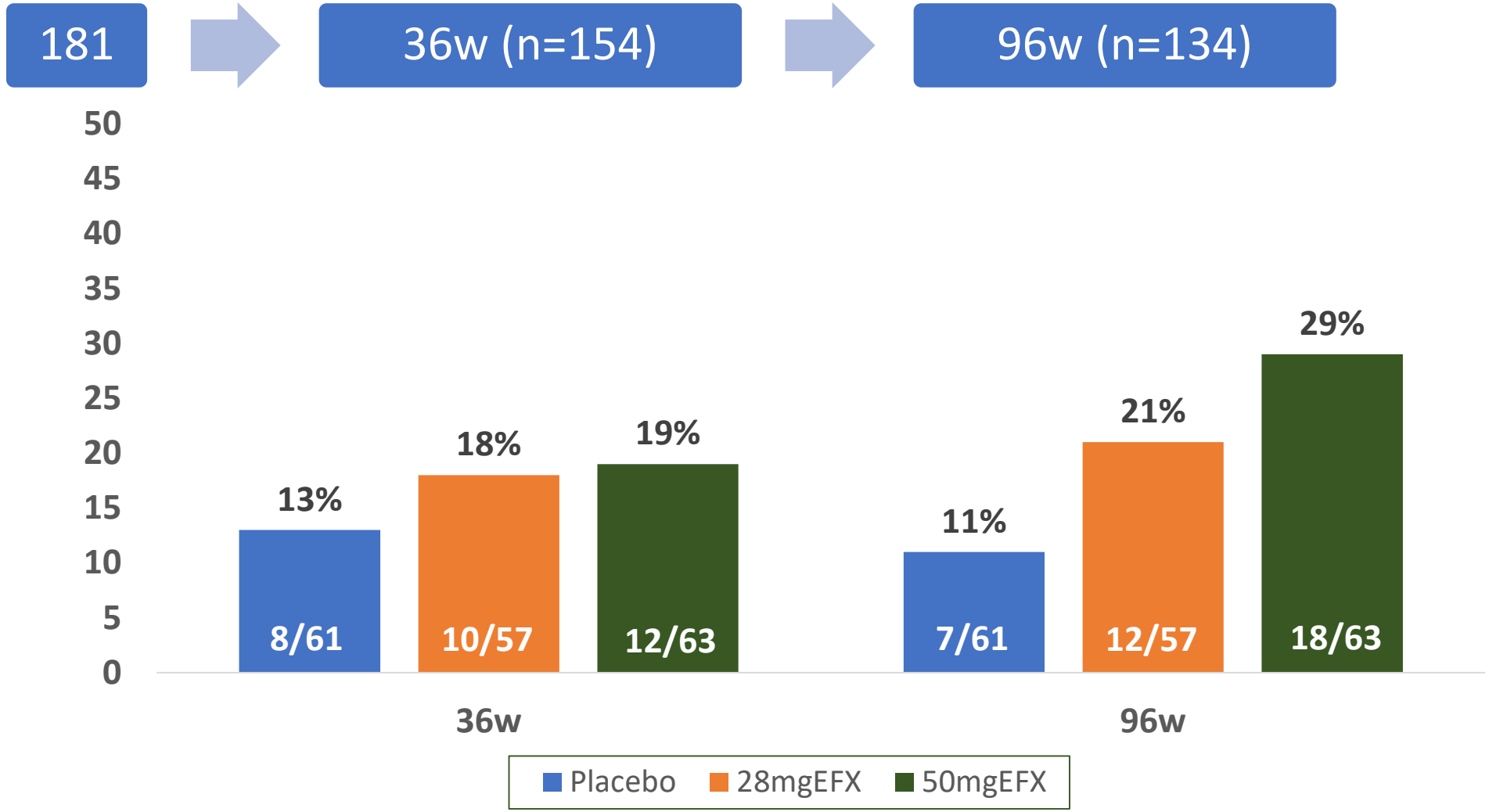
Efruxifermin

Akero. Akero Announces Strongly Positive Histological Data Across All Efruxifermin Dose Groups in 16-Week Phase 2a BALANCED Study in NASH Patients. 2020 Jun 30. Press Release. https://ir.akerotx.com/news-releases/news-release-details/akero-announces-strongly-positive-histological-data-across-all/

Harrison et al. Nature Medicine 2021;27:1262-1271

Efruxifermin in patients living with cirrhosis

N=181 patients with MASH who had biopsy-confirmed compensated cirrhosis



Noureddin M et al. NEJM 2025 (In Press)

Mensajes para llevar

- ✓ La EHmet es una enfermedad dinámica que progresa y regresa en todo su espectro de enfermedad.
- ✓ Se puede conseguir a regresión de la fibrosis avanzada mediante dieta y ejercicio, resmetirom, semaglutida y efruxifermin.
- ✓ Se han desarrollado biomarcadores fiables de fibrosis hepática en EHmet (Agile 3+ y MRE) que permiten su monitorización y predicen la aparición de eventos clínicos.
- ✓ La resolución de la esteatohepatitis sin regresión de la fibrosis es una respuesta incompleta.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