Obesità: inquadramento clinico e innovazioni terapeutiche

21 Ottobre 2023

Cona, Ferrara

Semaglutide e steatoepatite non alcolica

FABIO NASCIMBENI

UOC Medicina Interna ad Indirizzo Metabolico - AOU di Modena

DISCLOSURE INFORMATION

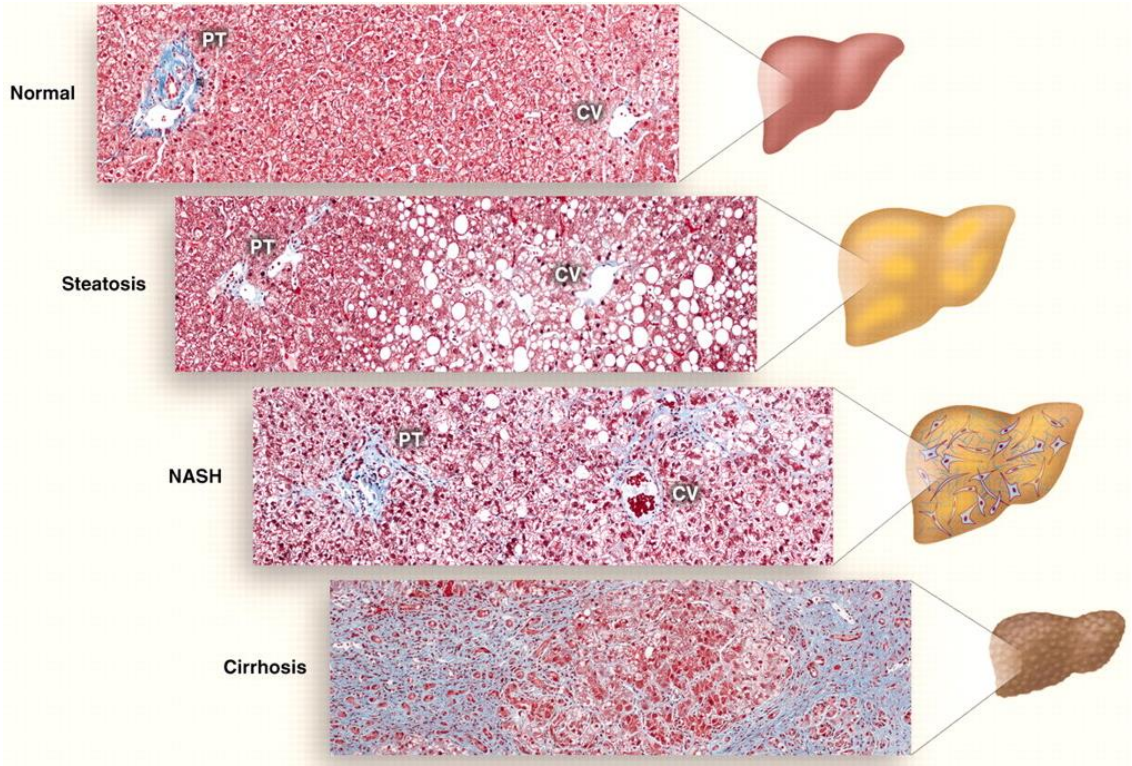
Il Sottoscritto Fabio Nascimbeni

dichiara che

negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Principal Investigator o Sub-Investigator in trial clinici sponsorizzati con Amgen, Amryt, Bio89, Boehringer, Daiichi-Sankyo, GSK, Intercept, Inventiva, Lilly, Novartis, Sanofi.

The spectrum of NAFLD



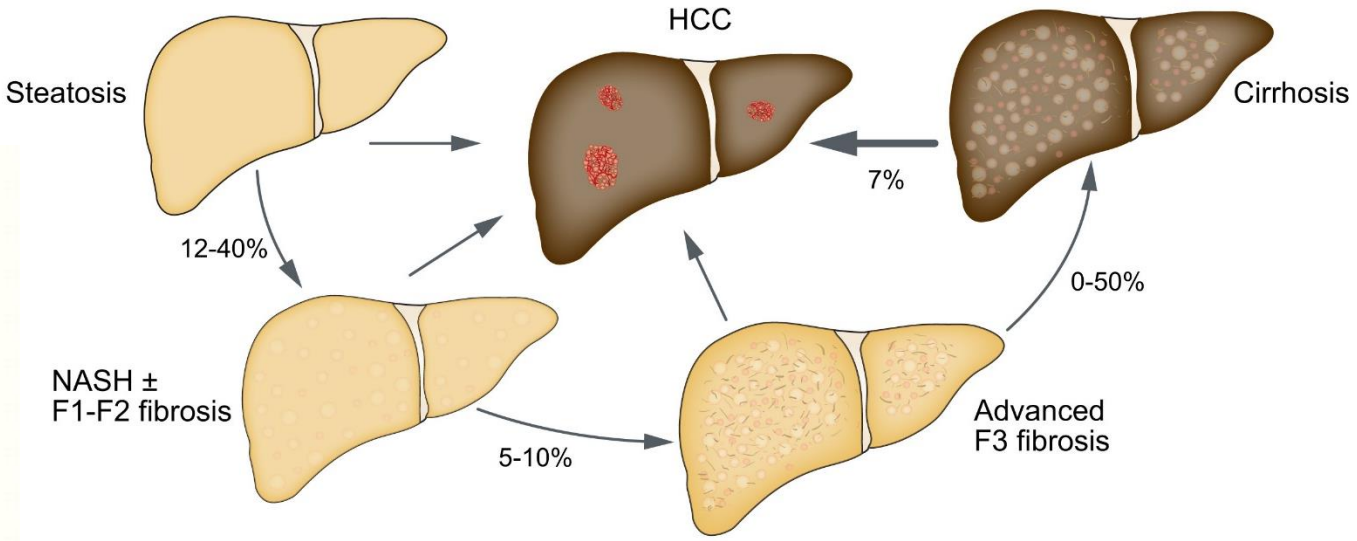
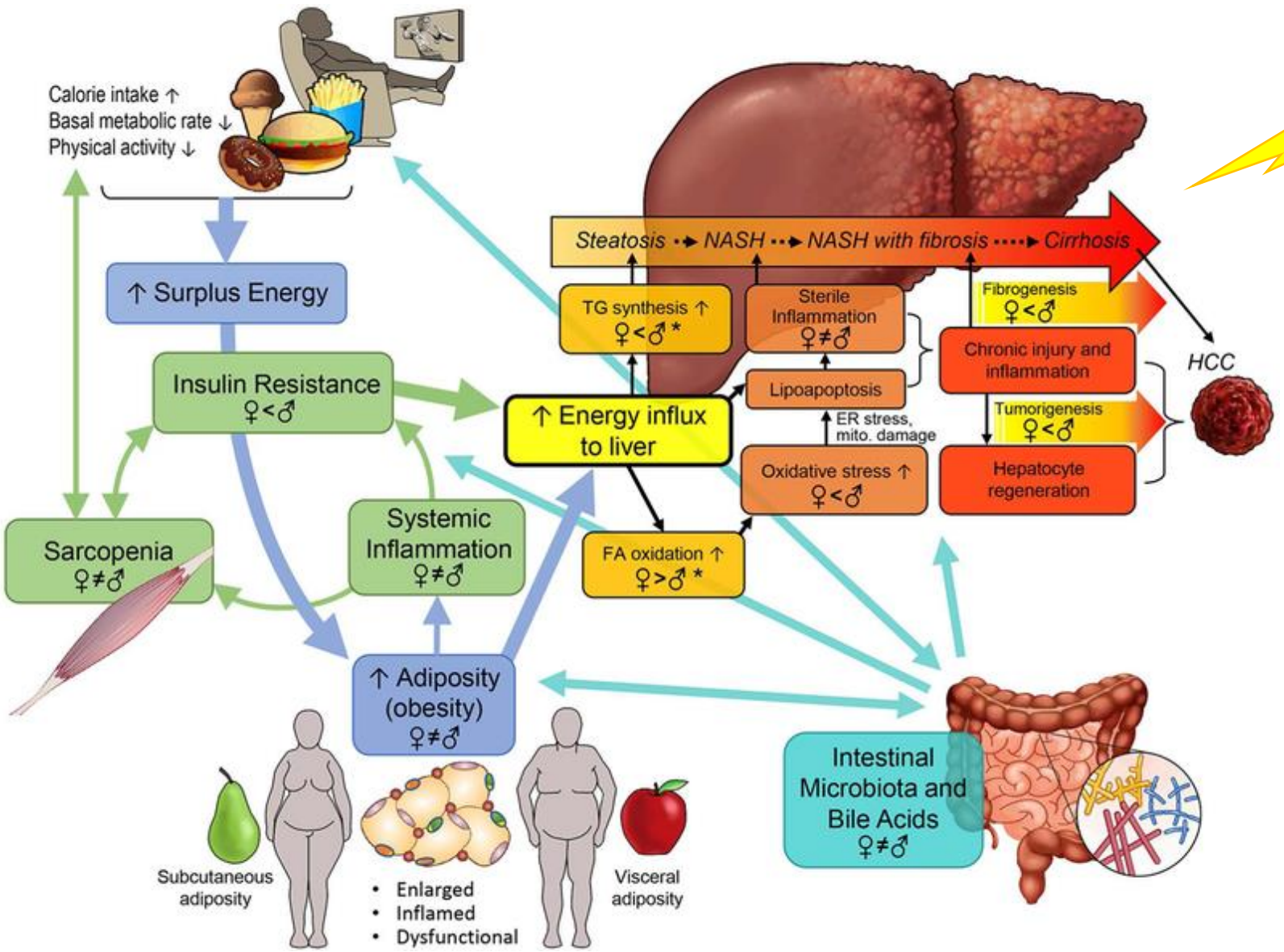


Table 1. Prevalence of Selected Comorbidities in Patients With Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Comorbidity	NAFLD, %	NASH, %
Obesity	51.3	81.8
Type 2 diabetes mellitus	22.5	43.6
Dyslipidemia	69.2	72.1
Hypertriglyceridemia	40.7	83.3
Hypertension	39.3	68.0
Metabolic Syndrome	42.5	70.7

Cohen, Science. 2011;332:1519-23
Younossi, Hepatology. 2016;64:73-84
Francque, JHEP Reports 2021; 3: 100322

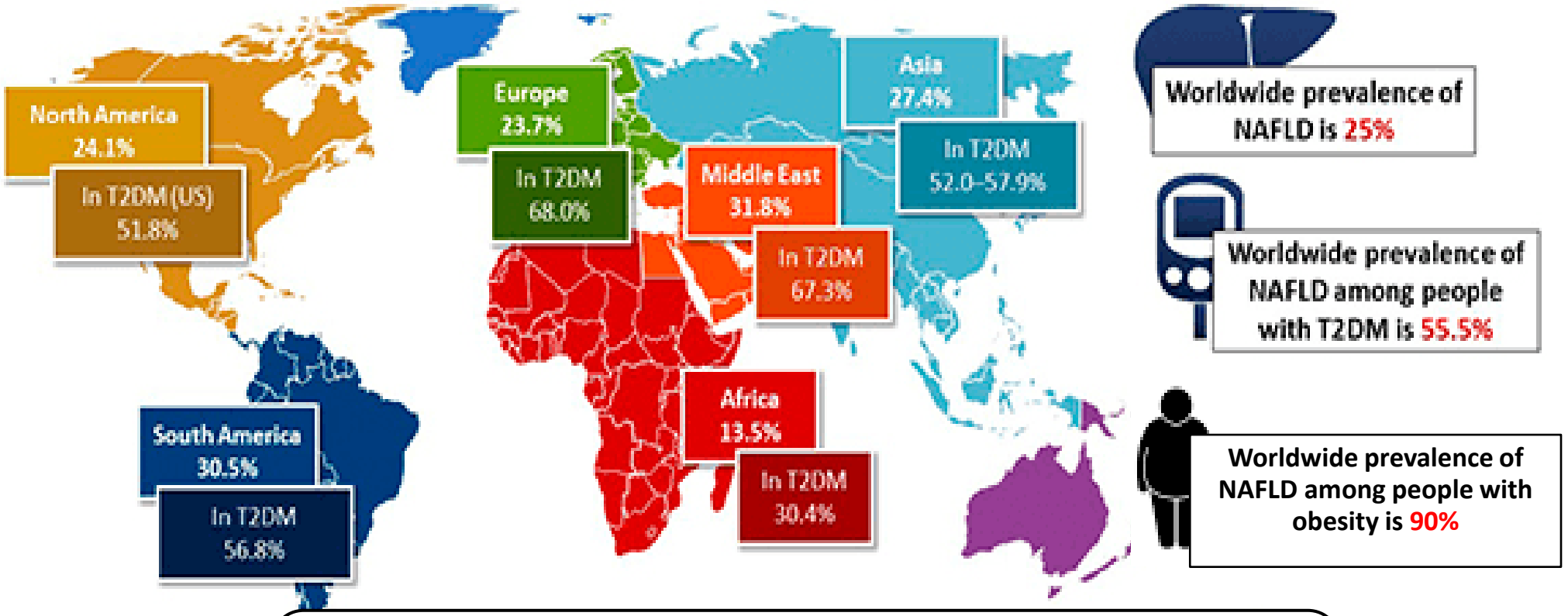
Pathogenesis of NAFLD



Genetic and epigenetic factors (PNPLA3, TM6SF2, MBOAT7, APOB, …)

Lonardo, Nascimbeni et al. Hepatology. 2019 Oct; 70(4): 1457–1469.

Global epidemiology of NAFLD and NASH

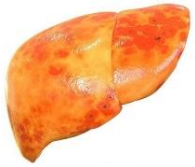


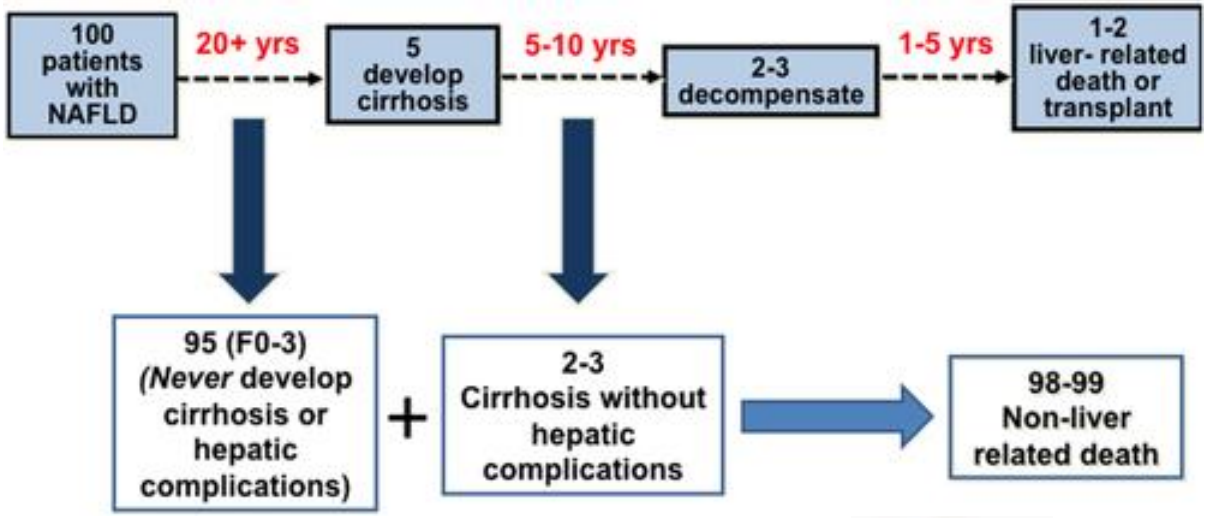
Prevalence of NASH in general population is between 1.5-6.5%
Prevalence of NASH among T2DM is 24.7-50%
Prevalence of NASH among obesity is 14-47%

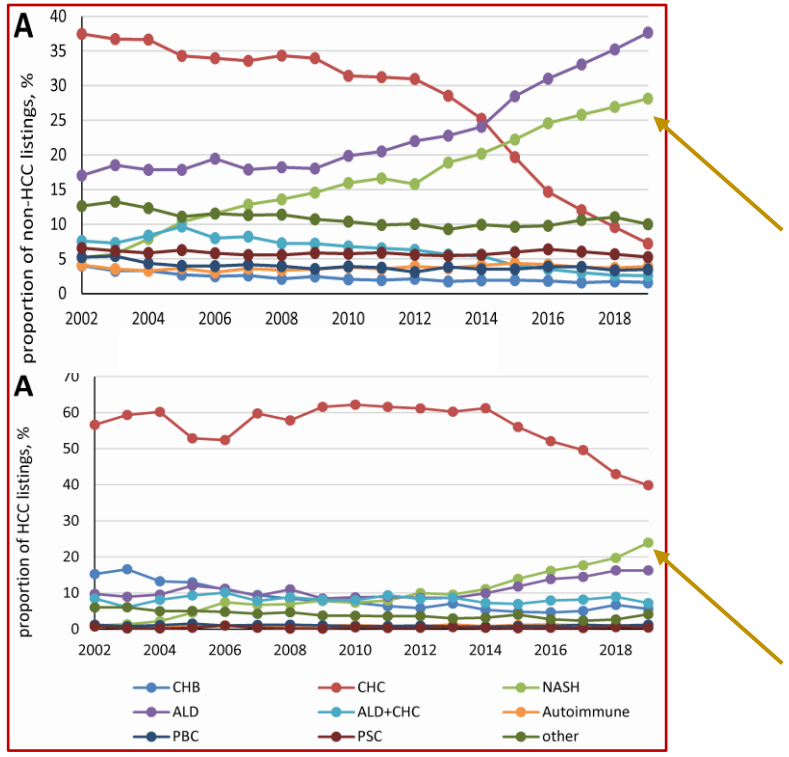
Younossi, Hepatology. 2016;64:73-84
Younossi, J Hepatol. 2019;70:531-544

Natural history of NAFLD

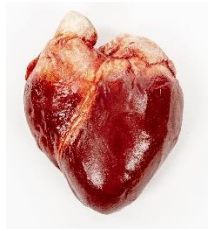
Liver-related events:







Extra-hepatic events:

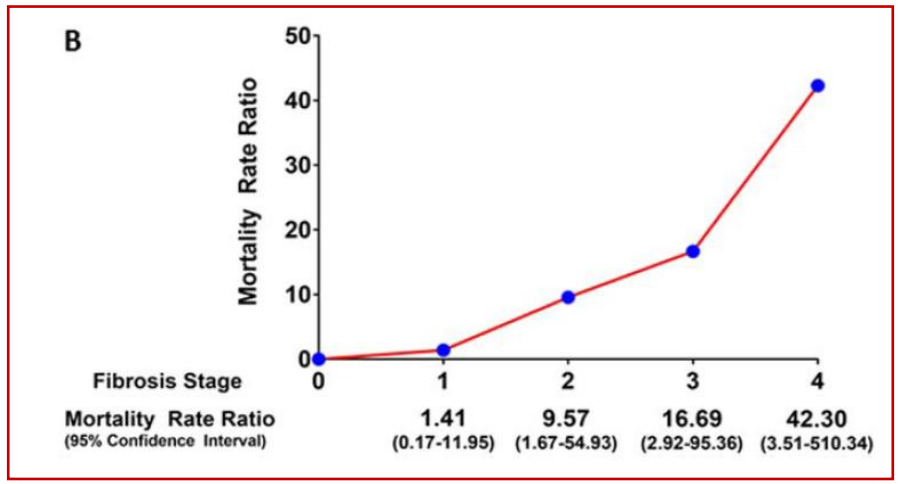


Outcome	Number
Death or OLT	(n = 193)
Cardiovascular disease	74 (38.3%)
Nonliver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)
HCC	2 (1%)
Liver transplantation	1 (0.5%)
Infections	15 (7.8)
Other	35 (18.1%)
Pulmonary	5
Autoimmune disease	4
Renal failure	4
Accidents/trauma	10
Pancreatitis	2
Nonvariceal GI bleeding	4
Surgery complications	2
Others	4
Unknown	15 (7.8)

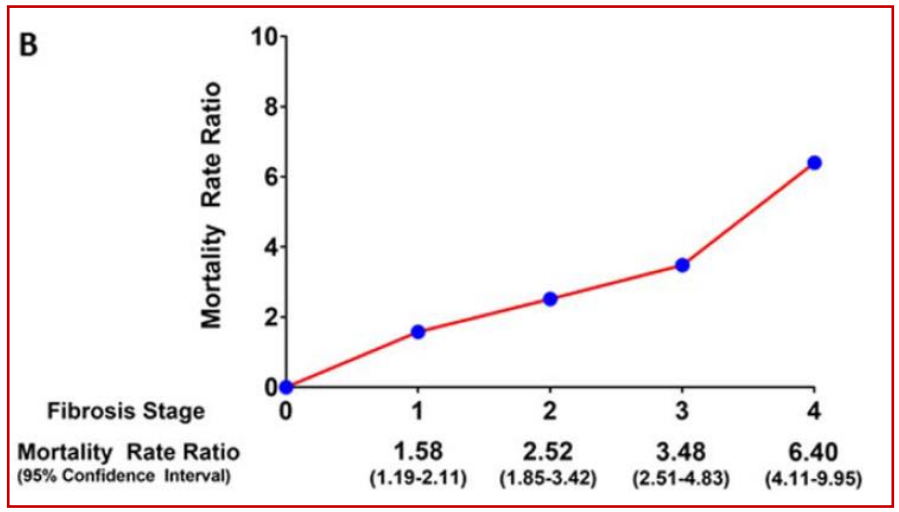
Angulo, Gastroenterology. 2015;149:389-97
Rinella, Hepatology. 2016;64:19-22
Younossi. Clin Gastro Hepatol. 2020

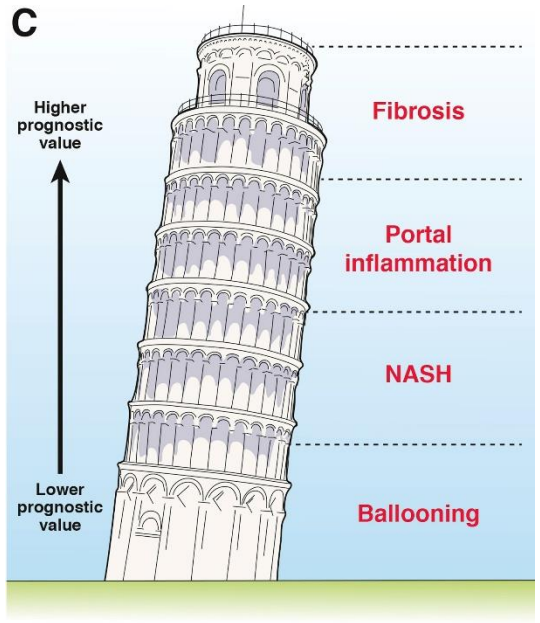
NAFLD severity drives morbidity and mortality

Liver-related Mortality

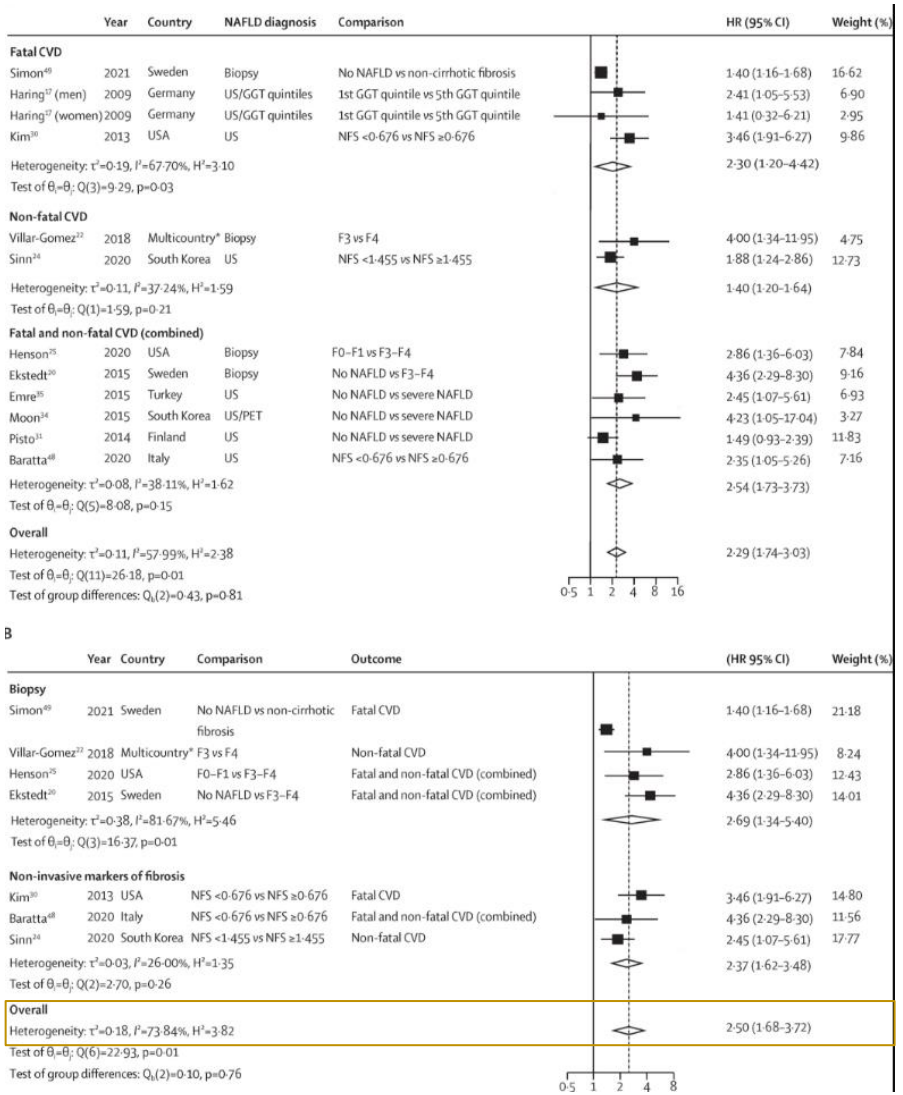


All Cause Mortality



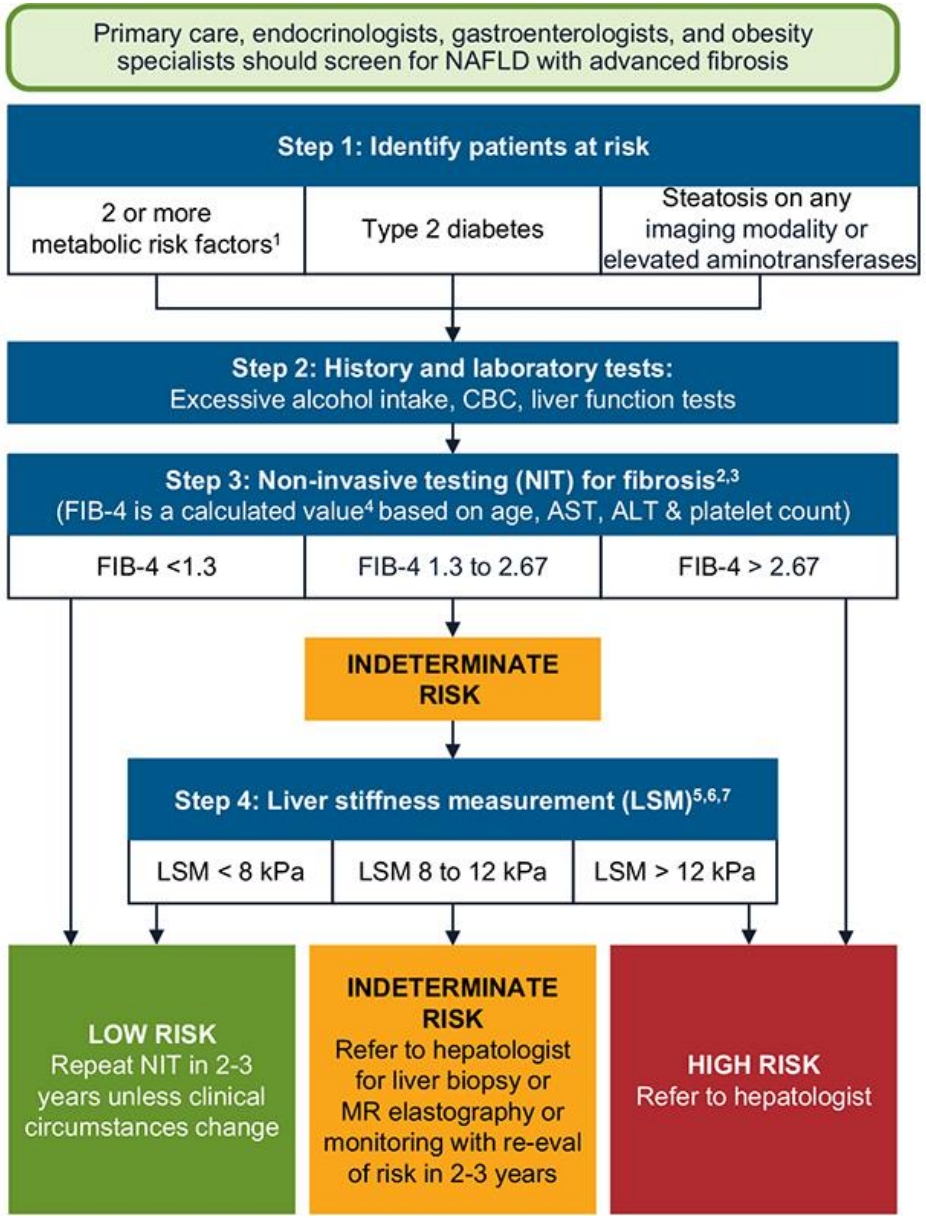


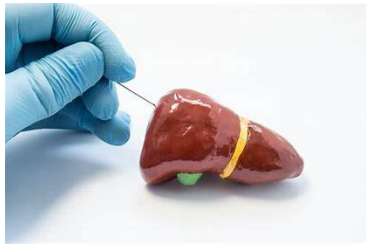
Incident fatal and non-fatal CV events



Dulai, Hepatology. 2017;65:1557-65
Targher, The Lancet Gastroenterology and Hepatology 2021

NAFLD risk stratification – Screening for NASH with advanced fibrosis





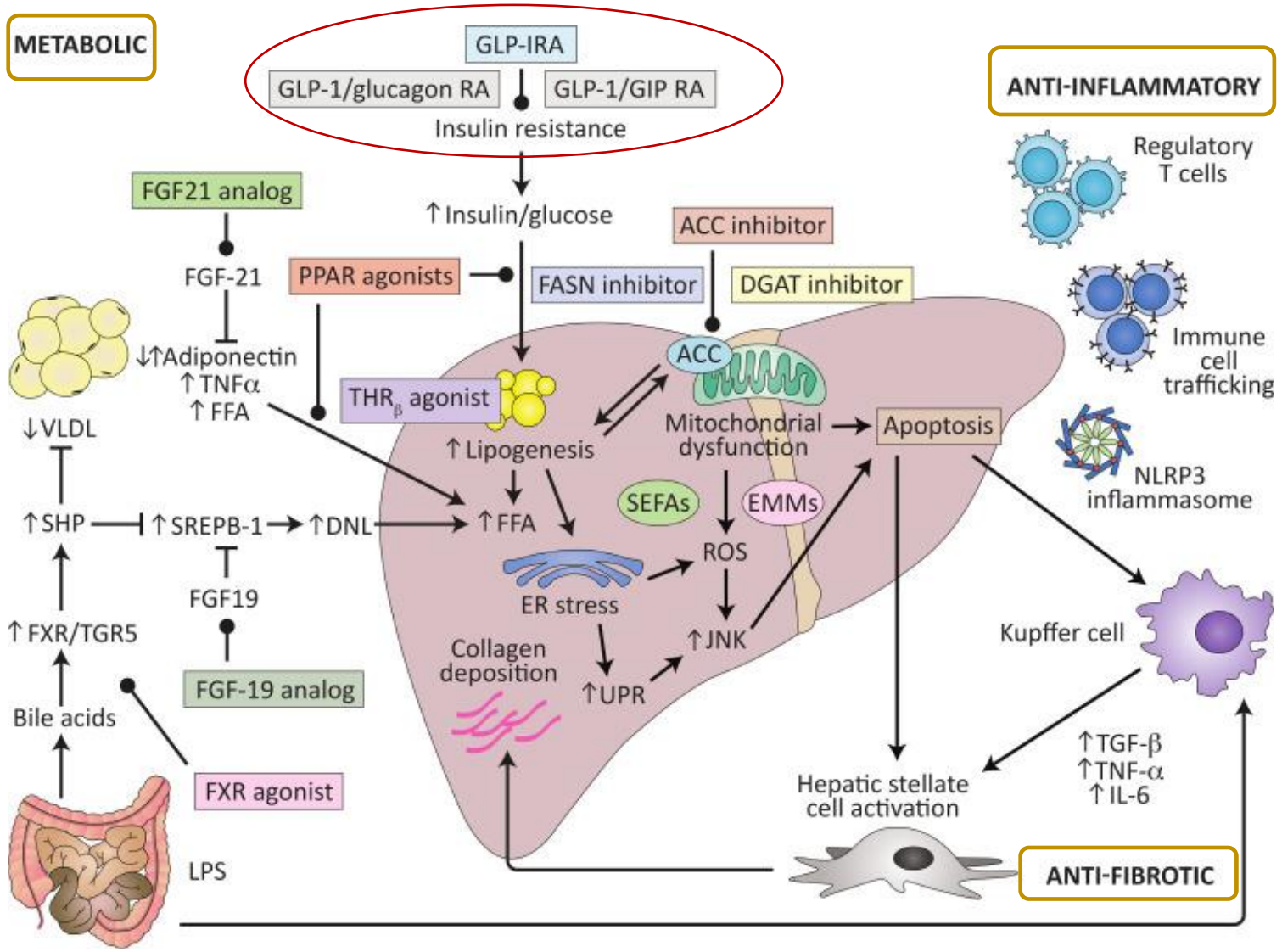
Castera, Gastroenterology 2019;156:1264-81
Kanwal, Gastroenterology 2021; 161: 1657–1669

NAFLD/NASH management

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Kanwal, Gastroenterology 2021; 161: 1657–1669

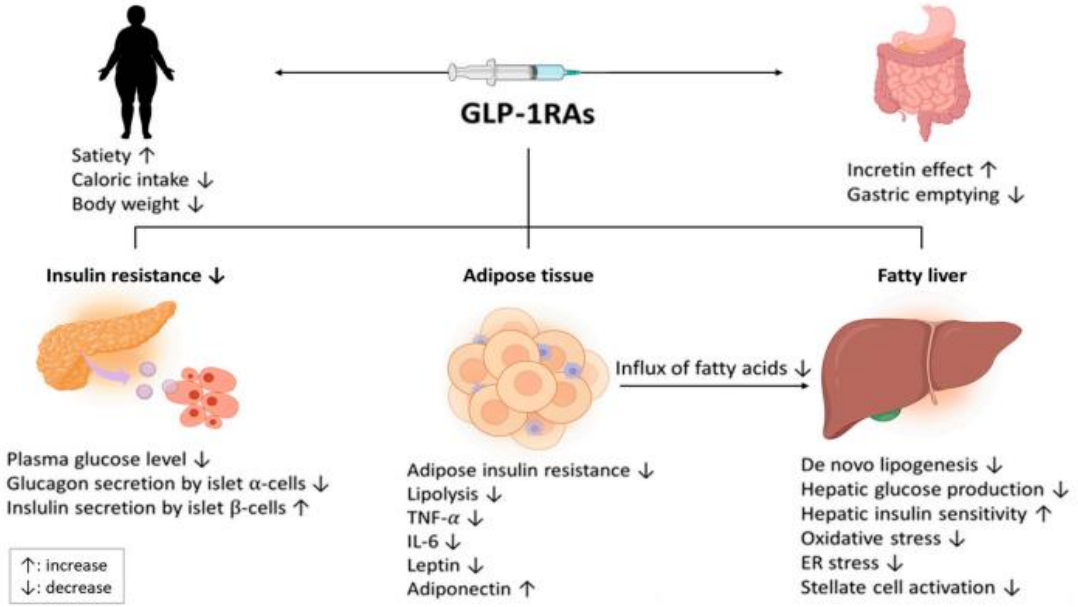
NAFLD/NASH and pharmacological targets

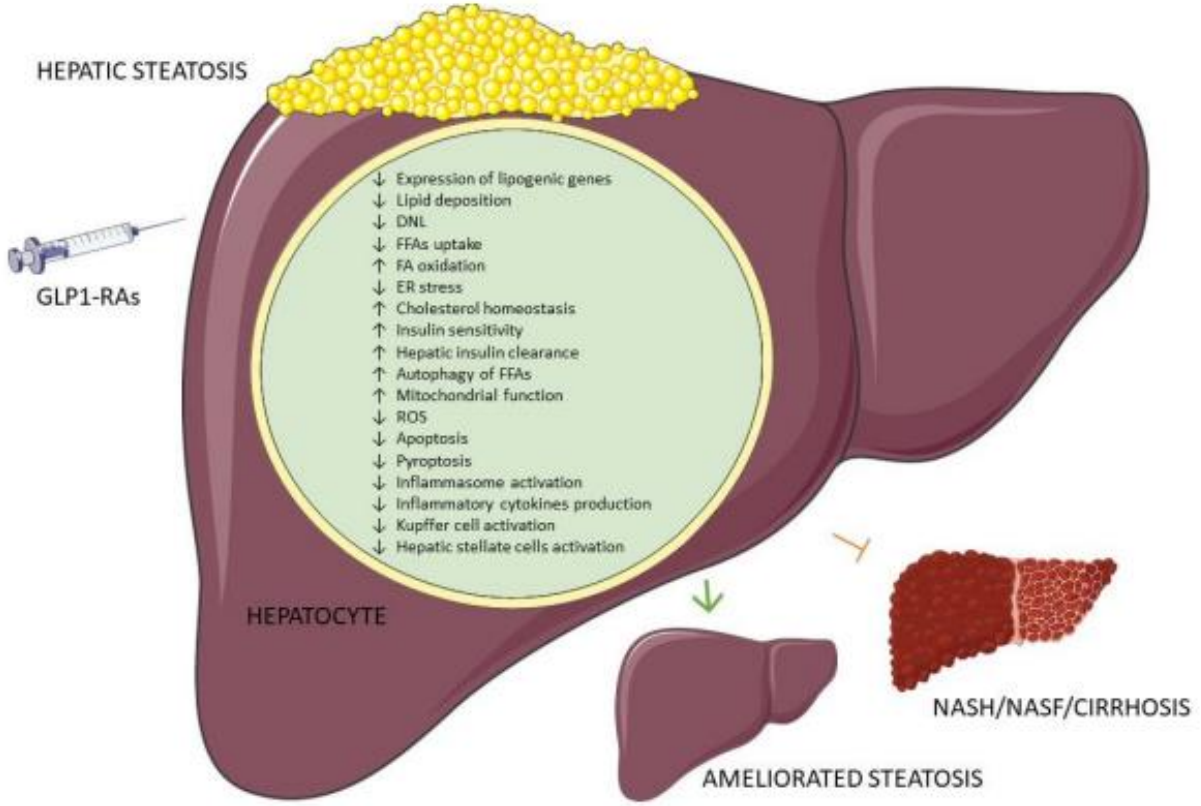


ACC: acetyl-CoA carboxylase; DGAT: diacylglycerol acyltransferases; EMM: endogenous metabolic modulator; FASN: fatty acid synthase; FGF: fibroblast growth factor; FXR: farnesoid X receptor; GIP: glucose-dependent insulinotropic polypeptide; GLP: glucagon like peptide; PPAR: peroxisome proliferator-activated receptors; SEFA: structurally engineered fatty acid; THR: thyroid hormone receptor

Konerman, J Hepatol. 2017;68:362-75
Dufour, Gut. 2022 Oct; 71(10): 2123–2134

Therapeutic mechanisms of GLP1RAs on NASH





Lee et al, Int. J. Mol. Sci. 2023;24:9324
Petrovic et al, Curr. Issues Mol. Biol. 2023;45:4544–4556

The milestone for GLP1RAs on NASH: the LEAN TRIAL

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

THE LANCET

Methods This multicentre, double-blinded, randomised, placebo-controlled phase 2 trial was conducted in four UK medical centres to assess subcutaneous injections of liraglutide (1·8 mg daily) compared with placebo for patients who are overweight and show clinical evidence of non-alcoholic steatohepatitis. Patients were randomly assigned (1:1) using a computer-generated, centrally administered procedure, stratified by trial centre and diabetes status. The trial was designed using A'Hern's single-group method, which required eight (38%) of 21 successes in the liraglutide group for the effect of liraglutide to be considered clinically significant. Patients, investigators, clinical trial site staff, and pathologists were masked to treatment assignment throughout the study. The primary outcome measure was resolution of definite non-alcoholic steatohepatitis with no worsening in fibrosis from baseline to end of treatment (48 weeks), as assessed centrally by two independent pathologists. Analysis was done by intention-to-treat analysis, which included all patients who underwent end-of-treatment biopsy. The trial was registered with ClinicalTrials.gov, number NCT01237119.

Findings Between Aug 1, 2010, and May 31, 2013, 26 patients were randomly assigned to receive liraglutide and 26 to placebo. Nine (39%) of 23 patients who received liraglutide and underwent end-of-treatment liver biopsy had resolution of definite non-alcoholic steatohepatitis compared with two (9%) of 22 such patients in the placebo group (relative risk 4·3 [95% CI 1·0–17·7]; p=0·019). Two (9%) of 23 patients in the liraglutide group versus eight (36%) of 22 patients in the placebo group had progression of fibrosis (0·2 [0·1–1·0]; p=0·04). Most adverse events were grade 1 (mild) to grade 2 (moderate) in severity, transient, and similar in the two treatment groups for all organ classes and symptoms, with the exception of gastrointestinal disorders in 21 (81%) of 23 patients in the liraglutide group and 17 (65%) of 22 patients in the placebo group, which included diarrhoea (ten [38%] patients in the liraglutide group *vs* five [19%] in the placebo group), constipation (seven [27%] *vs* none), and loss of appetite (eight [31%] *vs* two [8%]).

	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
Changes from baseline in histopathological parameters				
Total NAFLD activity score				
Change in score	−1·3 (1·6)	−0·8 (1·2)	−0·5 (−1·3 to 0·3)	0·24
Patients with improvement	17 (74%)	14 (64%)	1·2 (0·8 to 1·7)	0·46
Hepatocyte ballooning score				
Mean change	−0·5 (0·7)	−0·2 (0·6)	−0·3 (−0·7 to 0·1)	0·15
Patients with improvement	14 (61%)	7 (32%)	1·9 (1·0 to 3·8)	0·05
Steatosis				
Change in score	−0·7 (0·8)	−0·4 (0·8)	−0·2 (−0·6 to 0·2)	0·32
Patients with improvement	19 (83%)	10 (45%)	1·8 (1·1 to 3·0)	0·009
Lobular inflammation				
Change in score	−0·2 (0·6)	−0·2 (0·5)	−0·01 (−0·3 to 0·3)	0·97
Patients with improvement	11 (48%)	12 (55%)	0·9 (0·5 to 1·6)	0·65
Kleiner fibrosis stage				
Change in score	−0·2 (0·8)	0·2 (1·0)	−0·4 (−0·8 to 0·1)	0·11
Patients with improvement	6 (26%)	3 (14%)	1·9 (0·5 to 6·7)	0·46†
Patients with worsening	2 (9%)	8 (36%)	0·2 (0·1 to 1·0)	0·04†

Data are n (%) or mean (SD). The mean of the two independent pathologists' scores for overall non-alcoholic fatty liver disease (NAFLD) activity score, steatosis, ballooning, inflammation, and fibrosis were used to compare the two treatment groups. The pathologists' agreement for overall NAFLD activity score using a weighted kappa was 0·854.
*p values and mean changes from baseline were calculated by linear regression analysis using the baseline characteristic score and treatment as model covariates (equivalent to ANCOVA); for categorical comparisons, p values were determined by χ^2 analysis. †p value was determined by Fisher's exact test.

Table 2: **Changes in liver histology after 48 weeks of treatment**

Armstrong et al. Lancet. 2016;387:679-690

Post-hoc analysis of semaglutide trials on liver enzymes and markers of inflammation

Weight management trial (NCT02453711):
957 subjects from a phase 2, randomised, double-blind, multinational, placebo- and active-controlled dose-finding trial of semaglutide in combination with both dietary and exercise counselling. Semaglutide was given once daily for 52 weeks at subcutaneous doses of 0.05, 0.1, 0.2, 0.3 or 0.4 mg to individuals with obesity of non-endocrine origin (body mass index ≥30 kg/m2) without diabetes.

Cardiovascular outcomes trial (SUSTAIN-6; NCT01720446):
3297 subjects from a phase 3, randomised, double-blind, multinational, placebo-controlled trial of semaglutide given for the treatment of type 2 diabetes. Semaglutide was given once weekly at subcutaneous doses of 0.5 or 1.0 mg/week for 104 weeks to individuals at least 50 years of age with type 2 diabetes and a haemoglobin A1c level ≥7%, at high risk for, or with a prior history of, cardiovascular events and/or who had chronic kidney disease

Newsome et al. Aliment Pharmacol Ther. 2019;50:193–203

Post-hoc analysis of semaglutide trials on ALT levels

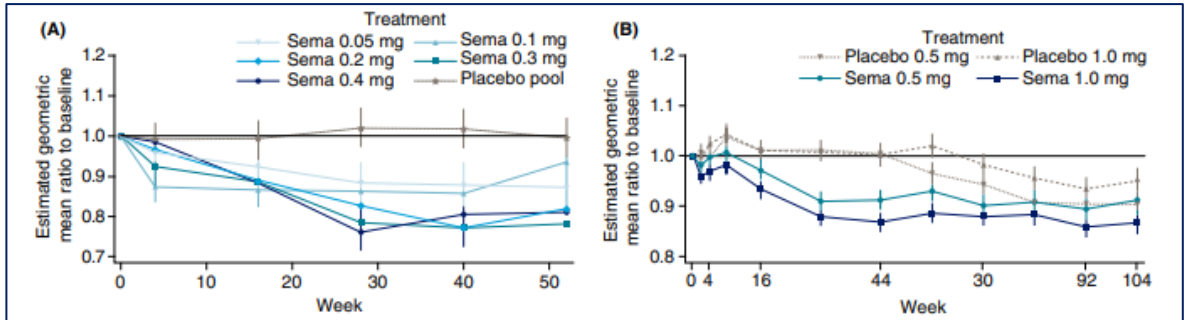
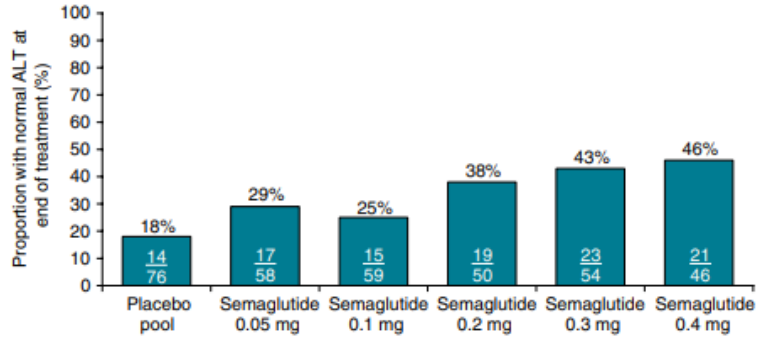


FIGURE 2 Estimated (mixed model for repeated measurements) mean ALT changes from baseline by treatment group and study visit for individuals with high baseline ALT in (A) weight management trial NCT02453711 and (B) cardiovascular outcomes trial SUSTAIN-6. ALT, alanine aminotransferase

FIGURE 4 Normalisation of ALT at week 52 among subjects with elevated baseline ALT in weight management trial NCT02453711. ALT, alanine aminotransferase



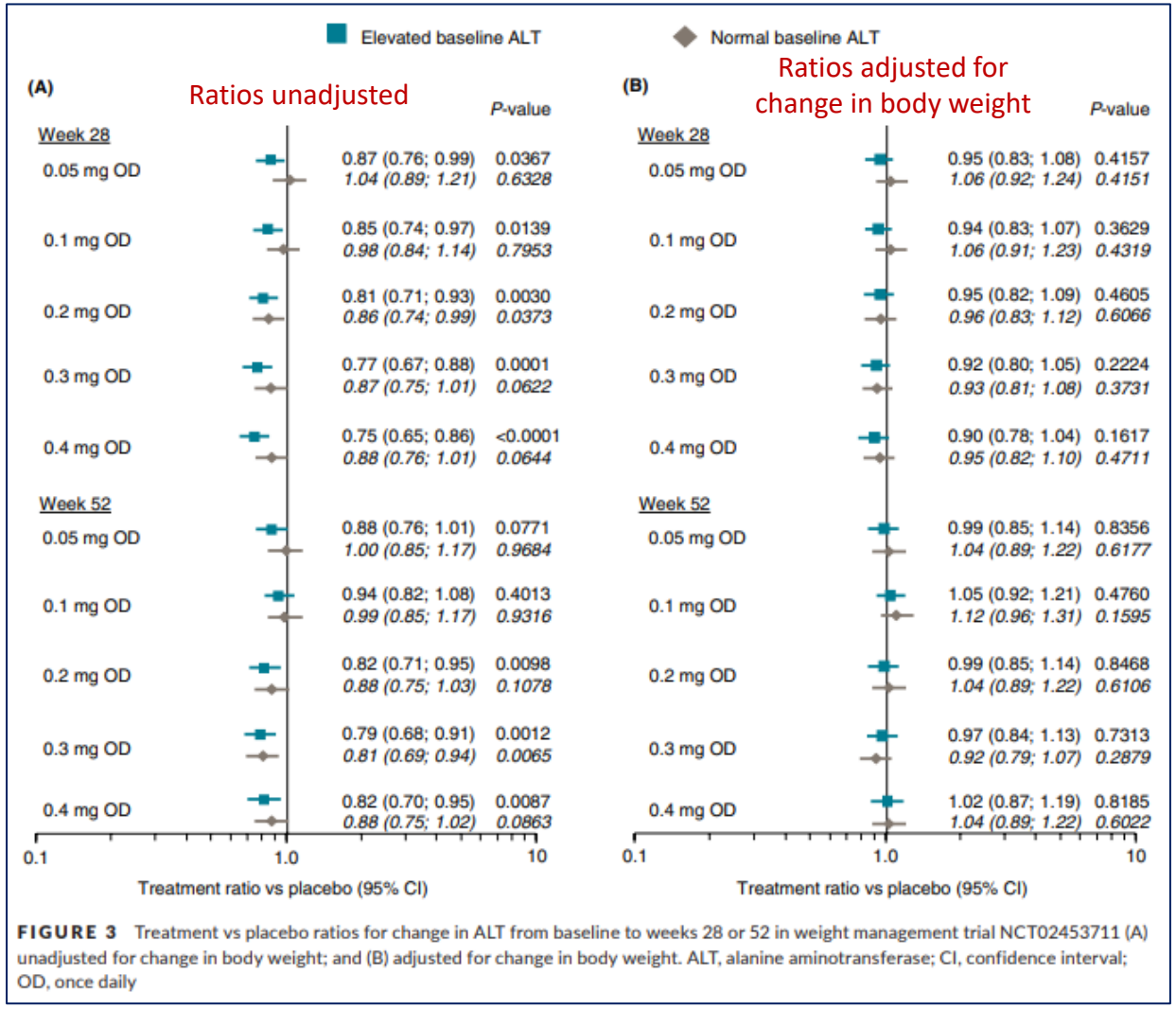


FIGURE 3 Treatment vs placebo ratios for change in ALT from baseline to weeks 28 or 52 in weight management trial NCT02453711 (A) unadjusted for change in body weight; and (B) adjusted for change in body weight. ALT, alanine aminotransferase; CI, confidence interval; OD, once daily

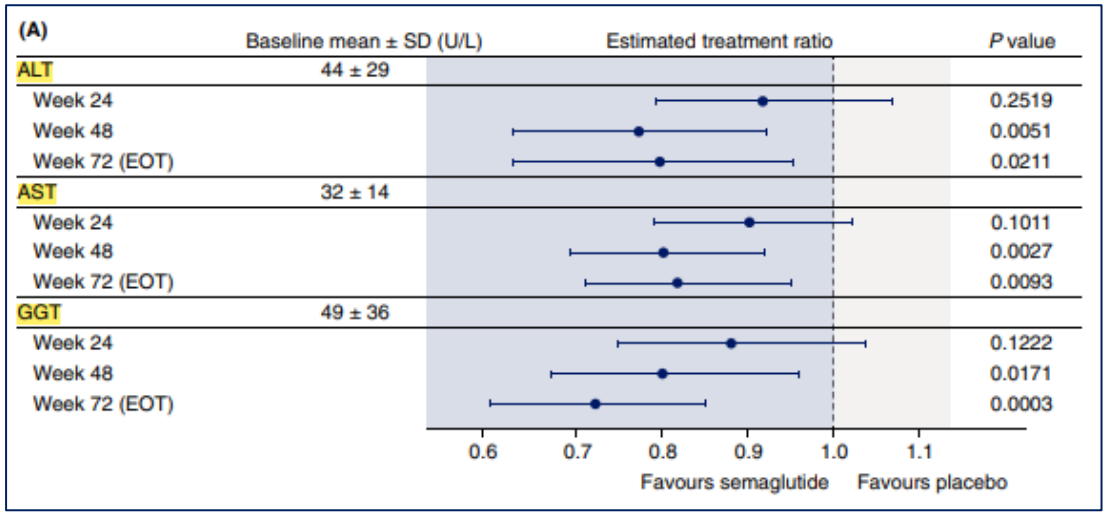
Newsome et al. Aliment Pharmacol Ther. 2019;50:193–203

Semaglutide and NASH: magnetic resonance imaging clinical trial

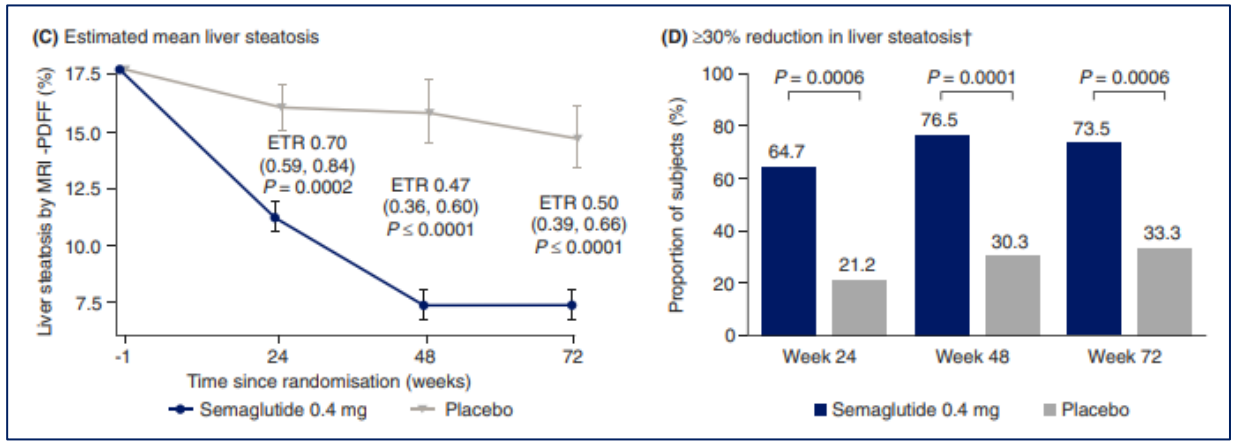
72-week randomised, double-blind, 1:1 placebo-controlled trial with once-daily subcutaneous semaglutide 0.4 mg (n = 34) or placebo (n = 33).

67 subjects with liver stiffness 2.50-4.63 kPa by magnetic resonance elastography (MRE) and liver steatosis ≥10% by MRI proton density fat fraction (MRI-PDFF).

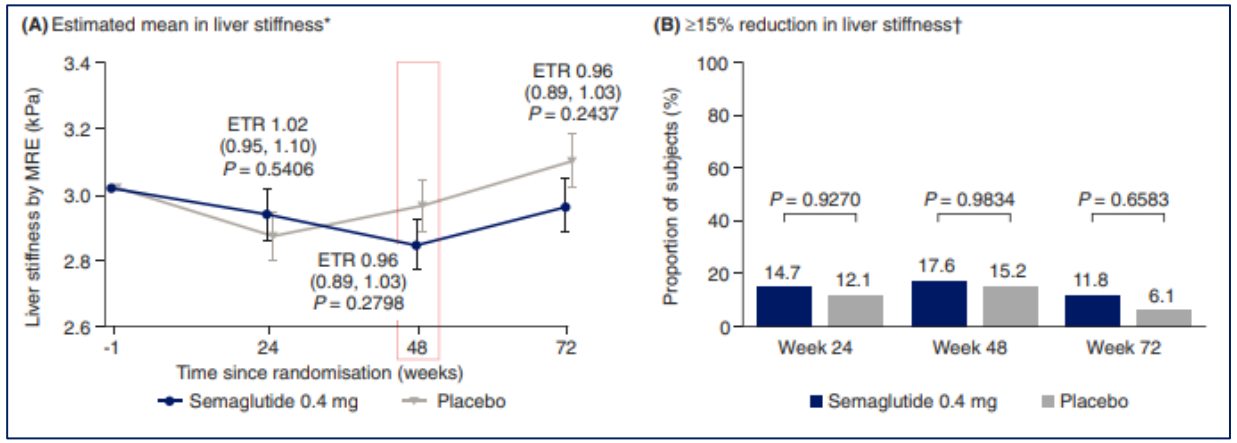
The primary endpoint was change from baseline to week 48 in liver stiffness assessed by MRE.



Steatosis



Fibrosis



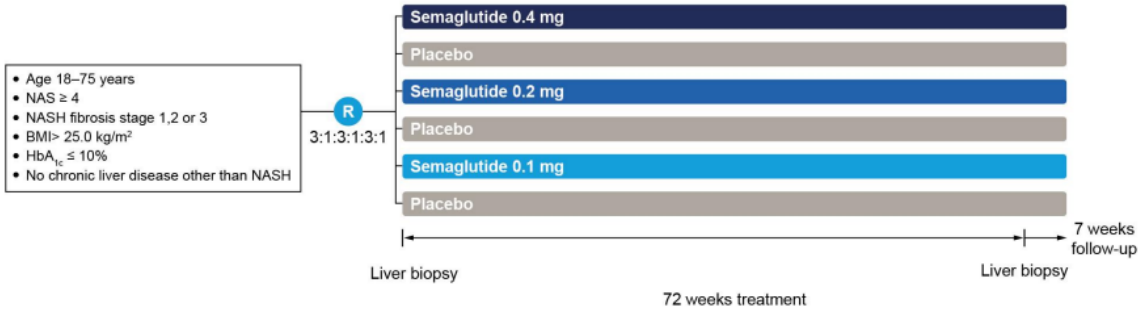
Flint et al. Aliment Pharmacol Ther. 2021;54:1150–1161

Semaglutide and NASH: phase 2 liver biopsy clinical trial

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

The NEW ENGLAND JOURNAL of MEDICINE

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*



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

320 patients were randomly assigned, in a 3:3:3:1:1:1 ratio, 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. (only for F2-F3 patients)

Table 1. Demographic and Baseline Clinical Characteristics.*

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

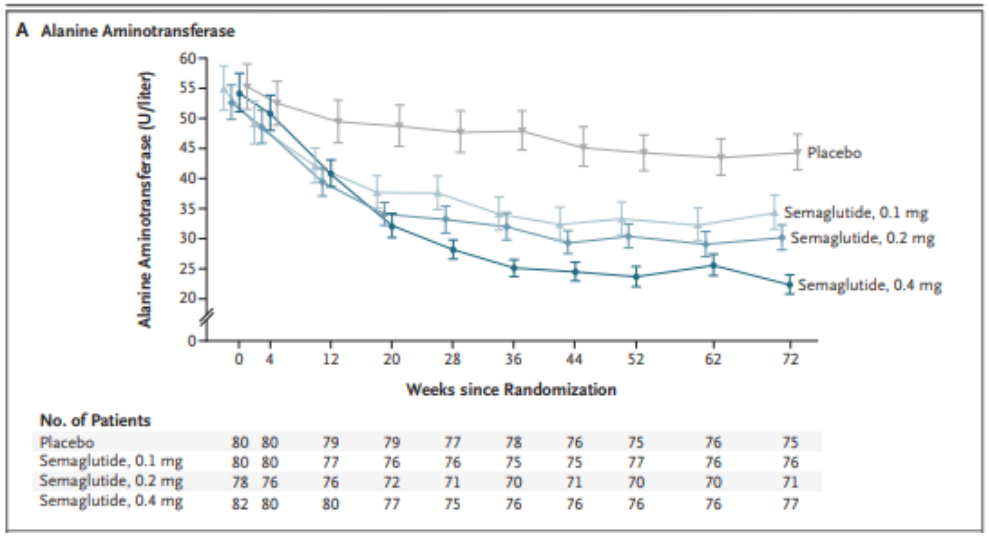
Newsome et al. N Engl J Med 2021;384:1113-24

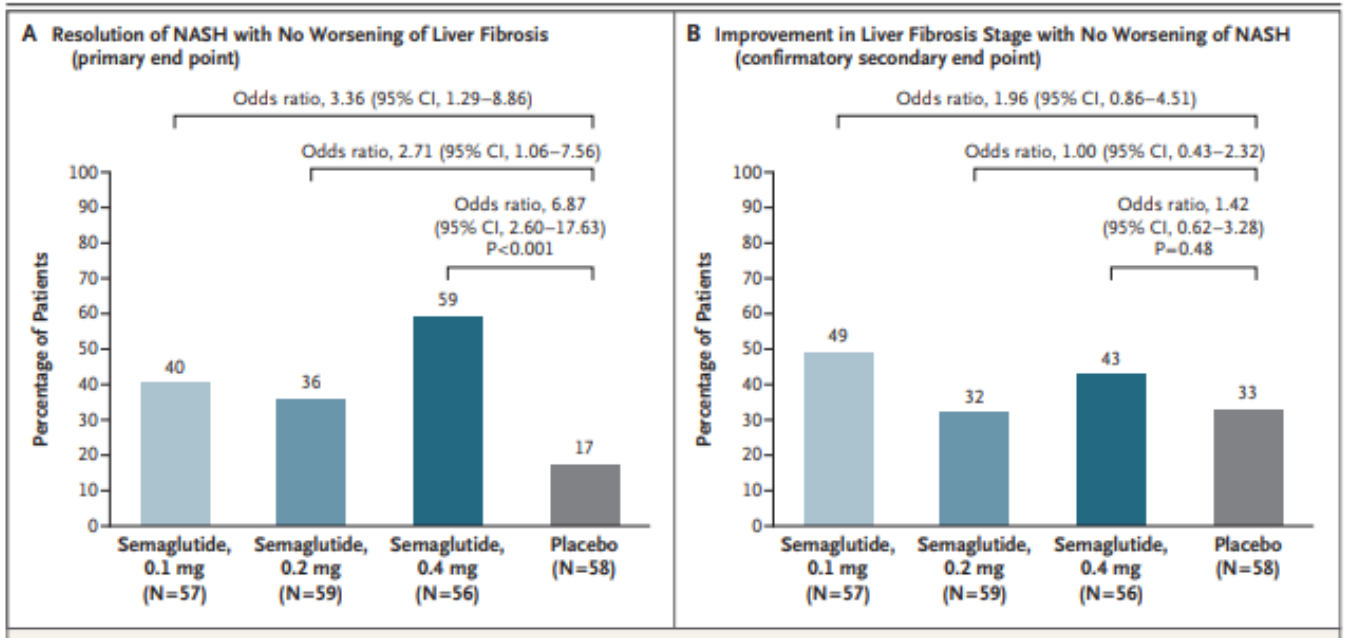
Semaglutide and NASH: phase 2 liver biopsy clinical trial - Efficacy

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

The NEW ENGLAND JOURNAL of MEDICINE

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*



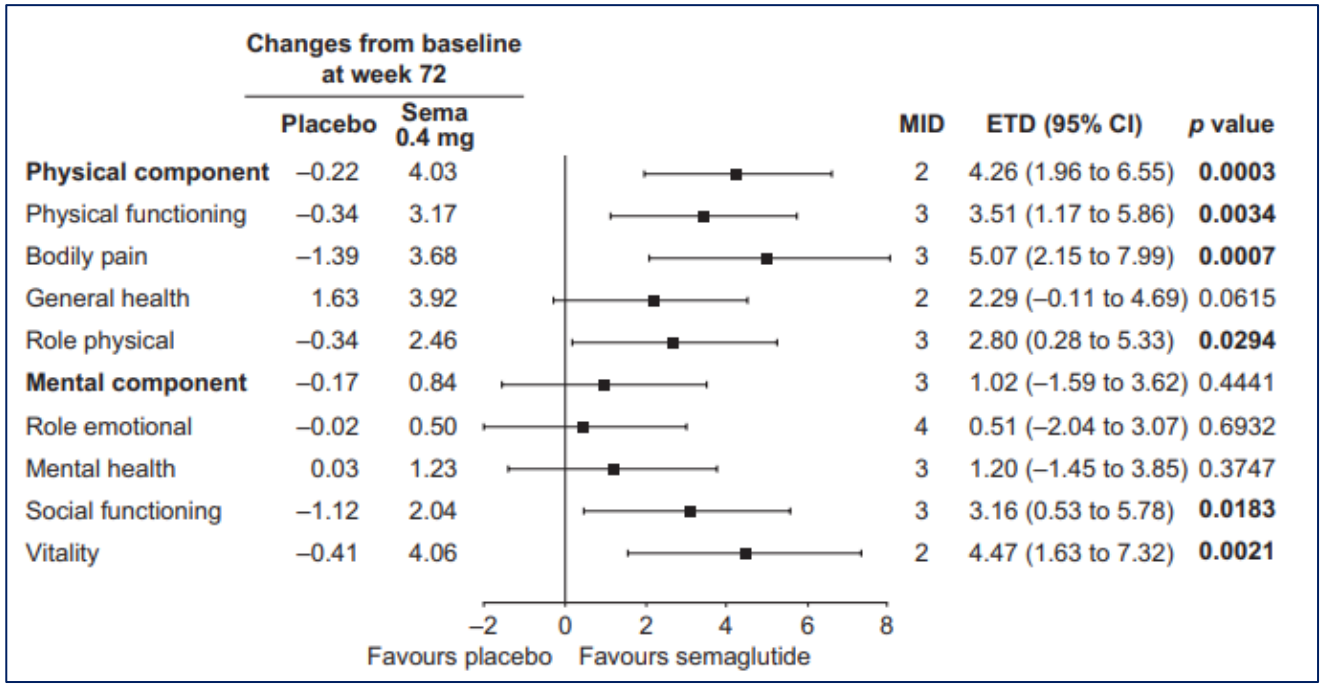


Newsome et al. N Engl J Med 2021;384:1113-24

Semaglutide and NASH: phase 2 liver biopsy clinical trial – Safety and QoL

Table 3. Selected Adverse Events.*

Event	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=81)	Placebo Group (N=80)
	number of patients (percent)			
Any adverse event	72 (90)	76 (97)	76 (94)	67 (84)
Adverse events from gastrointestinal disorders system organ class	51 (64)	60 (77)	55 (68)	36 (45)
Adverse events from any system organ class, according to preferred term†				
Nausea	24 (30)	29 (37)	34 (42)	9 (11)
Constipation	13 (16)	17 (22)	18 (22)	10 (12)
Decreased appetite	16 (20)	18 (23)	18 (22)	4 (5)
Diarrhea	23 (29)	22 (28)	16 (20)	11 (14)
Vomiting	14 (18)	17 (22)	12 (15)	2 (2)
Back pain	7 (9)	5 (6)	10 (12)	7 (9)
Headache	7 (9)	10 (13)	10 (12)	8 (10)
Nasopharyngitis	11 (14)	15 (19)	10 (12)	12 (15)
Arthralgia	0	4 (5)	9 (11)	7 (9)
Fatigue	7 (9)	8 (10)	7 (9)	7 (9)
Abdominal pain	9 (11)	8 (10)	6 (7)	3 (4)
Abdominal distension	1 (1)	8 (10)	4 (5)	4 (5)
Dyspepsia	4 (5)	9 (12)	4 (5)	5 (6)
Adverse events that resulted in premature discontinuation of treatment				
All adverse events	3 (4)	10 (13)	4 (5)	4 (5)
Gastrointestinal disorders	1 (1)	6 (8)	2 (2)	0
Serious adverse events				
Any serious adverse event	12 (15)	15 (19)	12 (15)	8 (10)
Gastrointestinal disorders	2 (2)	2 (3)	4 (5)	0
Musculoskeletal and connective-tissue disorders	0	1 (1)	3 (4)	1 (1)
Infections and infestations	2 (2)	2 (3)	2 (2)	1 (1)
Neoplasms, including benign, malignant, and unspecified	0	4 (5)	1 (1)	0
Nervous-system disorders	0	3 (4)	1 (1)	0
Metabolism and nutrition disorders	2 (2)	1 (1)	0	1 (1)
Neoplasms‡	10 (12)	11 (14)	14 (17)	6 (8)
Malignant neoplasms	1 (1)	2 (3)	0	0
Polyp in large intestine§	1 (1)	4 (5)	3 (4)	0
Renal cyst§	3 (4)	1 (1)	0	1 (1)
Fatal events	0	1 (1)¶	0	0



Newsome et al. N Engl J Med 2021;384:1113-24
Romero-Gomez et al. Aliment Pharmacol Ther. 2023;58:395–403.

Semaglutide and NASH-CIRRHOSIS: phase 2 liver biopsy clinical trial

Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial

THE LANCET

48-week double-blind, placebo-controlled phase 2 trial.

71 patients with compensated biopsy-confirmed NASH-related cirrhosis and body-mass index (BMI) of 27 kg/m² or more were randomly assigned (2:1) to receive either once-weekly subcutaneous semaglutide 2·4 mg or placebo.

The primary endpoint was the proportion of patients with an improvement in liver fibrosis of one stage or more without worsening of NASH after 48 weeks.

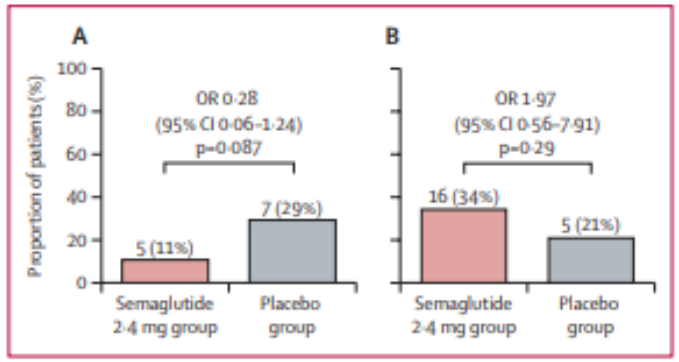


Figure 2: **Improvement in liver fibrosis and no worsening of NASH (A) and resolution of NASH (B) at 48 weeks**
p-values are two-sided and taken from a Cochran–Mantel–Haenszel test stratified by baseline diabetes status. Patients with missing outcomes were imputed as non-responders. NASH=non-alcoholic steatohepatitis. OR=odds ratio.

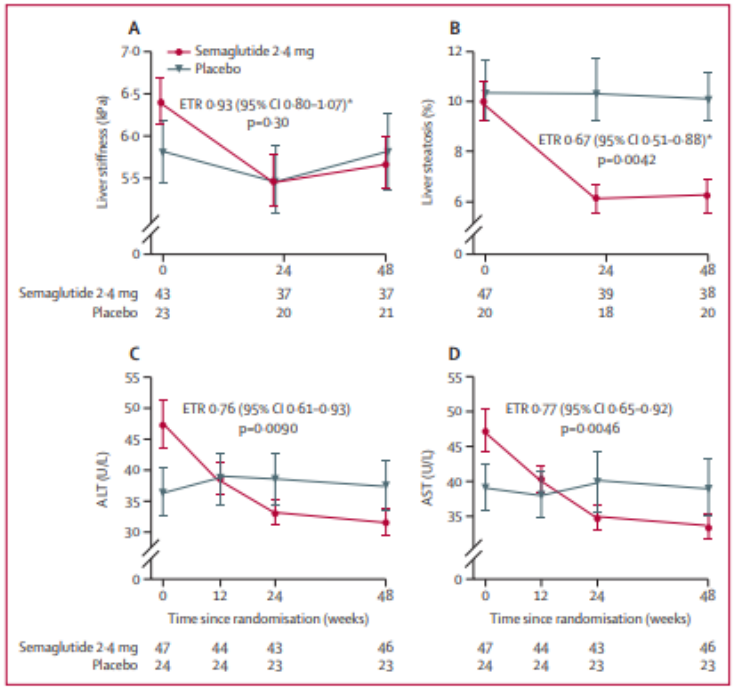


Figure 3: **Change in imaging parameters and liver enzymes from baseline to week 48**

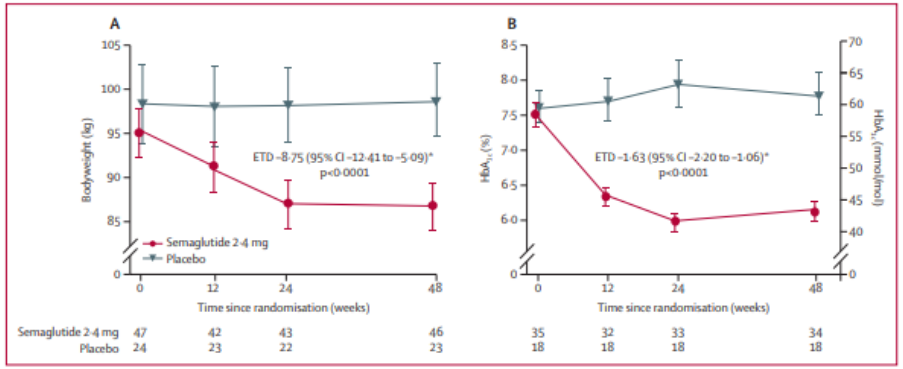


Figure 4: **Change in (A) bodyweight and (B) HbA_{1c} (in patients with type 2 diabetes) from baseline to week 48**
Number of observations per treatment group and visit is presented in the lower part of each plot. Error bars show the SE of the mean for observed values. ANCOVA=analysis of covariance. ETD=estimated treatment difference. *ETDs with 95% CI and two-sided p-values were calculated using the same ANCOVA analysis. Missing data were imputed from the observed data in the placebo group using the same ANCOVA model but without treatment as factor.

In this phase 2 study of patients with NASH-related compensated cirrhosis, semaglutide 2·4 mg once weekly did not significantly improve fibrosis or achievement of NASH resolution compared with placebo. However, in patients with cirrhosis, semaglutide did lead to improvements in cardiometabolic risk parameters (weight loss, glycaemic control, and lipids), did not lead to new safety concerns, and was well tolerated based on the established profile of the GLP-1RA class. Despite the lack of histological changes with semaglutide, improvements were seen in non-invasive markers of disease activity. We also noted a clinically significant reduction in liver fat by MRI-PDFF.

Loomba et al. Lancet Gastroenterol Hepatol 2023; 8: 511–22

Semaglutide and NASH: ongoing phase 3 liver biopsy clinical trial

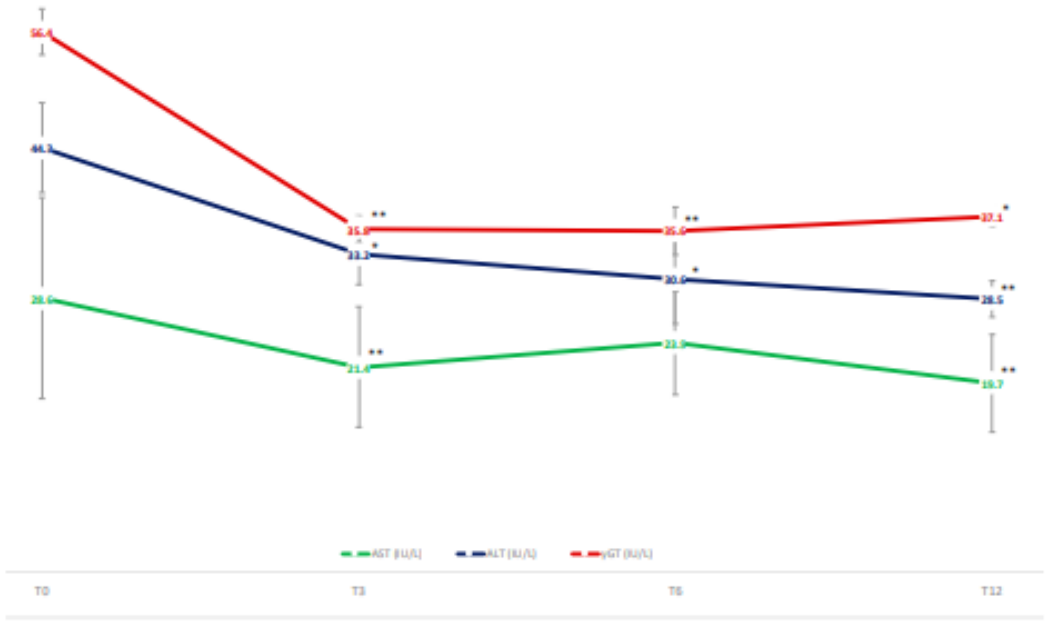
Research Study on Whether Semaglutide Works in People With Non-alcoholic Steatohepatitis (NASH) (ESSENCE) - ClinicalTrials.gov ID NCT04822181

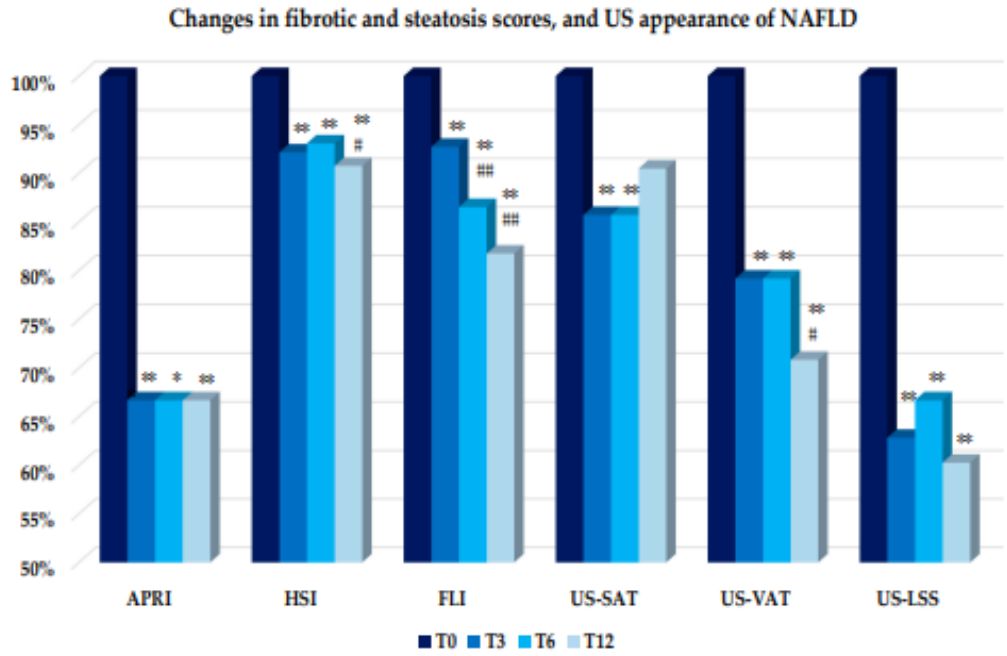
- 1200 pts
- NASH with NAS ≥4 and F2-3
- Semaglutide 2.4 mg/week vs. placebo
- 72 weeks: Resolution of steatohepatitis and no worsening of liver fibrosis; Improvement in liver fibrosis and no worsening of steatohepatitis
- 240 weeks: Time to first liver-related clinical event

Semaglutide and NAFLD in real-life

Once-Weekly Subcutaneous Semaglutide Improves Fatty Liver Disease in Patients with Type 2 Diabetes: A 52-Week Prospective Real-Life Study

Sara Volpe [1], Giuseppe Lisco [1], Margherita Fanelli [1], Davide Racaniello [1], Valentina Colaianni [1], Domenico Triggiani [1], Rossella Donghia [2], Lucilla Crudele [1], Roberta Rinaldi [2], Carlo Sabbà [1], Vincenzo Triggiani [1], Giovanni De Pergola [2] and Giuseppina Piazzolla [1,*]





Volpe et al. Nutrients 2022, 14, 4673

A glimpse into the future: COMBINATION THERAPY

Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: A randomised, open-label phase II trial

JOURNAL OF HEPATOLOGY

Phase II, open-label, proof-of-concept trial.

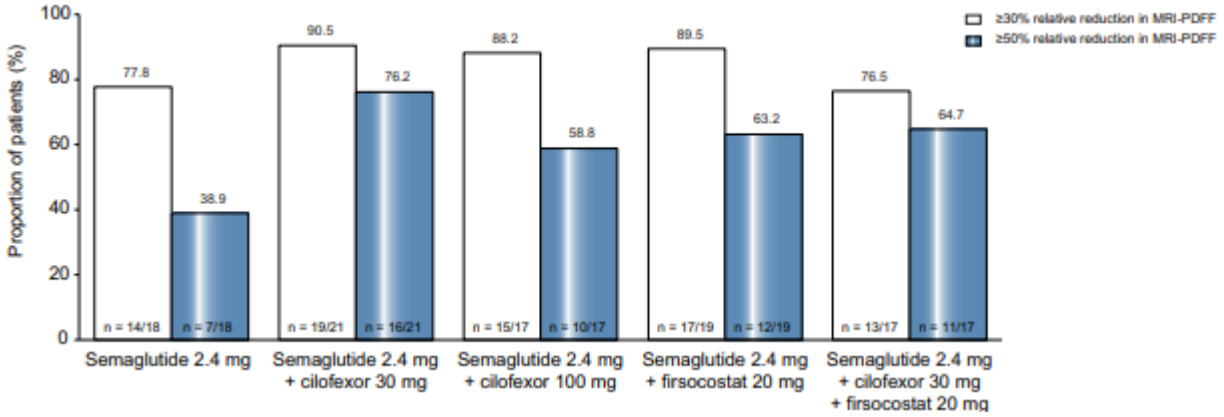
108 patients with NASH (F2–F3 on biopsy, or MRI-proton density fat fraction [MRI-PDFF] >10% and liver stiffness by transient elastography >7 kPa) were **randomised (1:1:1:1:1) to 24 weeks' treatment with semaglutide 2.4 mg once weekly as monotherapy or combination therapy with cilofexor 30 mg (SEMA + CILO 30), or cilofexor 100 mg (SEMA + CILO 100), or firsocostat 20 mg (SEMA + FIR) or cilofexor 30 mg plus firsocostat 20 mg (SEMA + CILO + FIR).**

The primary endpoint was safety. All efficacy endpoints were exploratory

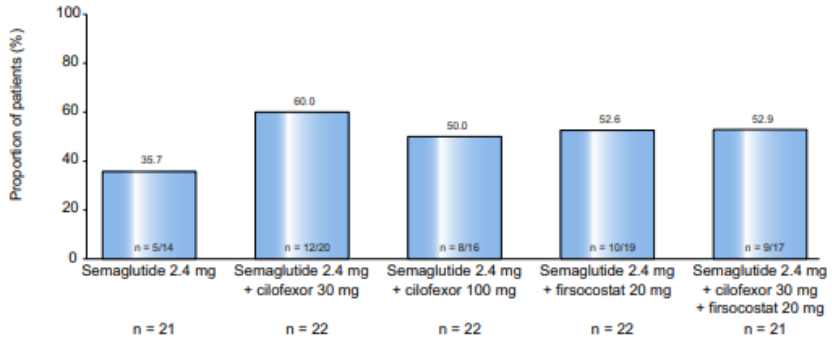
CILOFEXOR: non-steroidal agonist of farnesoid X receptor (FXR) that inhibits lipogenesis, gluconeogenesis and bile acid synthesis

FIRSOCOSTAT: acetyl-coenzyme A carboxylase (ACC) inhibitor that reduces hepatic de novo lipogenesis

MRI steatosis



Liver stiffness improvement (>25% relative reduction)



Alkhouri et al. Journal of Hepatology 2022;77:607–618

A glimpse into the future: DUAL/TRIPLE INCRETINS AGONISTS

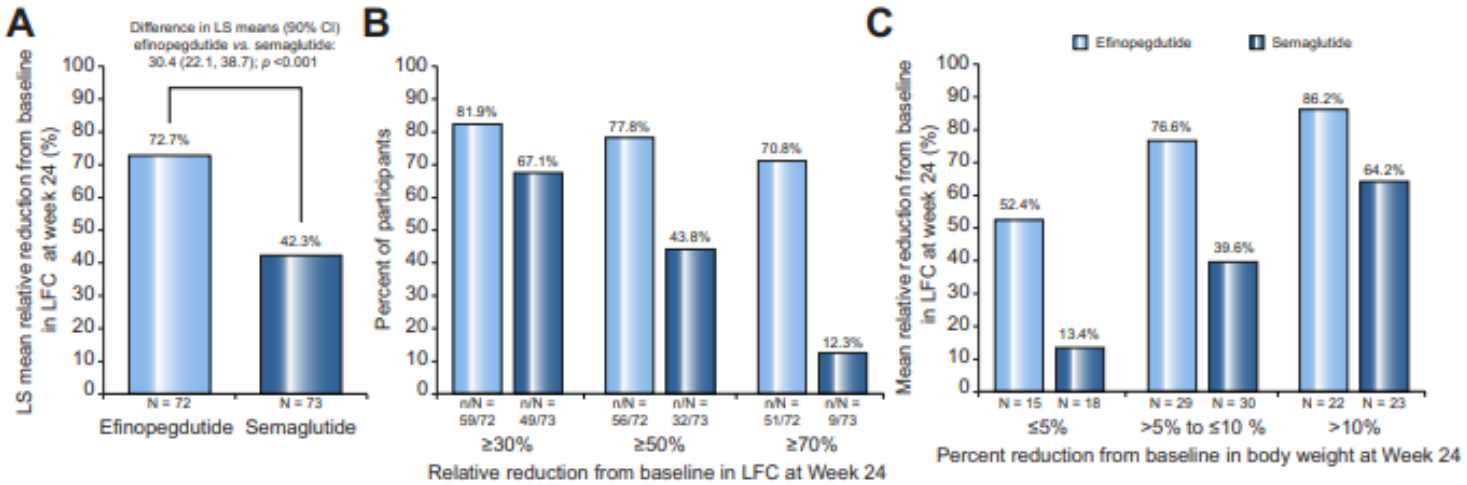
A phase IIa active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease

JOURNAL OF HEPATOLOGY

Phase IIa, randomized, active-comparator-controlled, parallel-group, open-label study.

145 participants with an MRI-PDFF liver fat content (LFC) of >10% at screening were randomized **1:1 to efinopegdutide 10 mg or semaglutide 1 mg, both administered subcutaneously once weekly for 24 weeks**.

The primary efficacy endpoint was **relative reduction from baseline in LFC (%)** after 24 weeks of treatment.



<u>EFINOPEGDUTIDE:</u> glucagon-like peptide-1 (GLP-1)/glucagon receptor co-agonist

Romero-Gomez et al. Journal of Hepatology, October 2023;79:888–897

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GRAZIE PER L'ATTENZIONE