MASLD: una nuova frontiera terapeutica per i GLP-1 RA?

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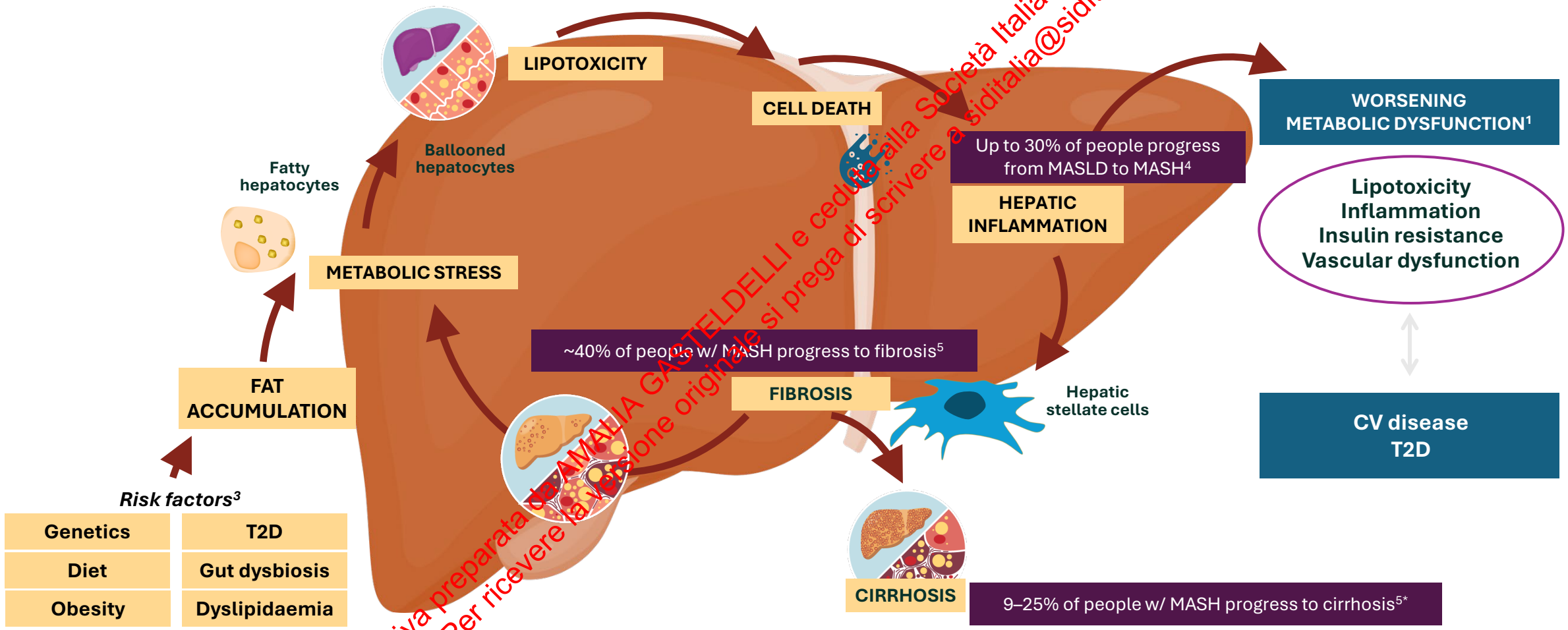
Disclosure of Conflicts of Interest

Consultant: Boehringer Ingelheim, Eli Lilly and Company, Metadeq Diagnostics;

Advisory boards: Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk, Metadeq Diagnostics, Pfizer, Regeneron Pharmaceuticals;

Lecture fees or other payments: Eli Lilly and Company, Merck Sharp & Dohme, Madrigal, Novo Nordisk and Pfizer.

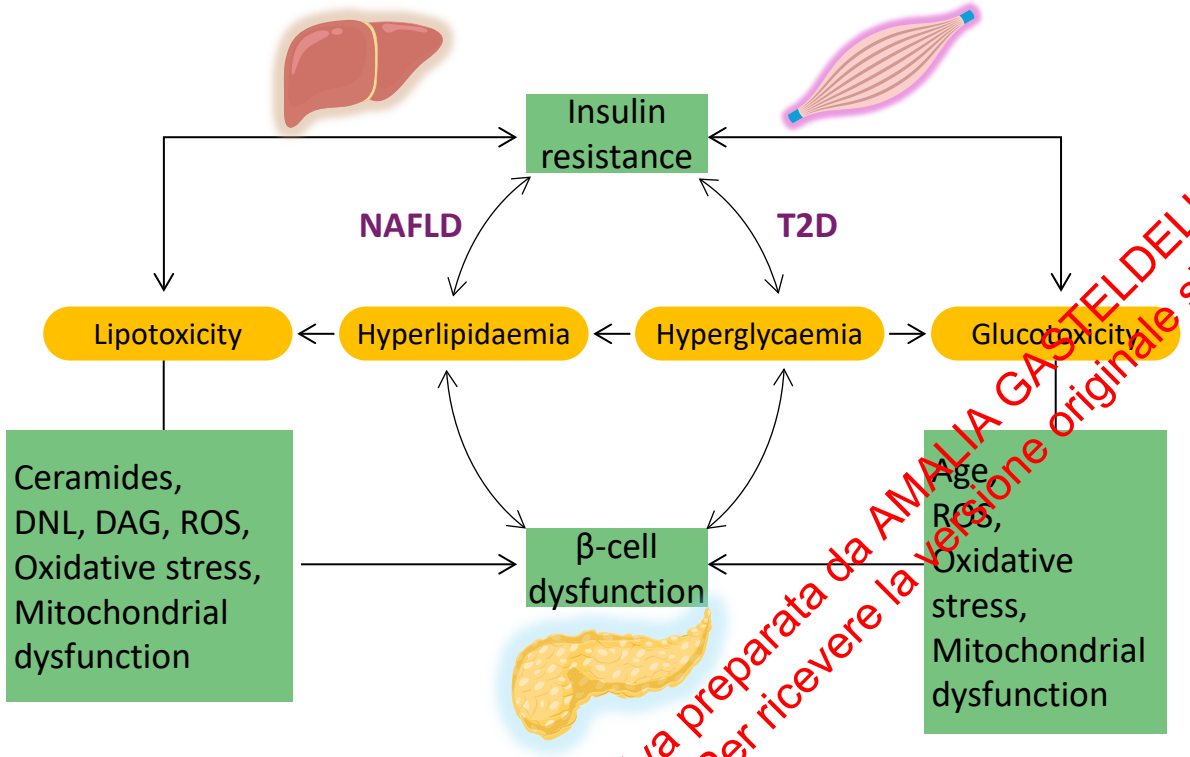
In MASLD/MASH, liver fat accumulation drives inflammation and fibrosis while further worsening metabolic dysfunction



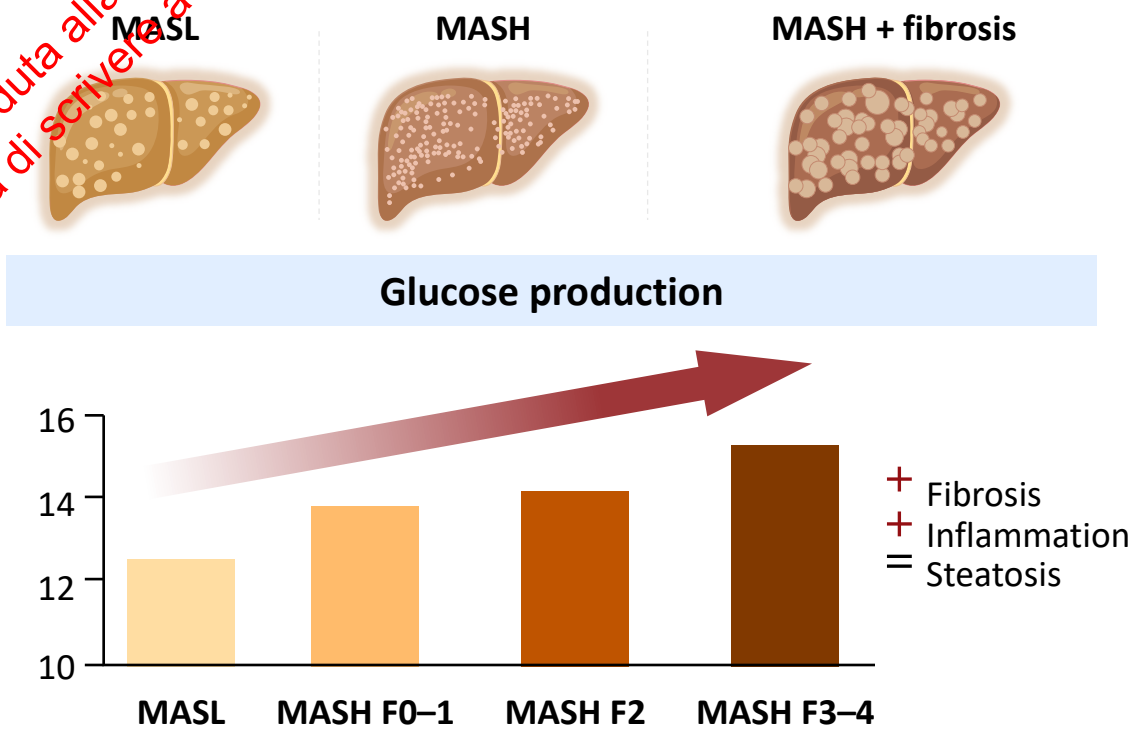
1. Ndumele CE, et al. Circulation 2023;148:1636–1664;
2. Wegermann K, et al. Clin Liver Dis (Hoboken) 2018;11:87–91;
3. Gancheva S, et al. Diabetes Res Clin Pract 2024;217:111846;
4. EASL–EASD–EASO. J Hepatol 2024;81:492–542;
5. Povsic M, et al. Adv Ther 2019;36:1574–1594

Lipotoxicity and glucotoxicity are key mediators of MASLD/MASH pathogenesis

In MASLD lipotoxicity and insulin resistance are the pathophysiological mechanisms responsible of development and progression of MASLD[1]

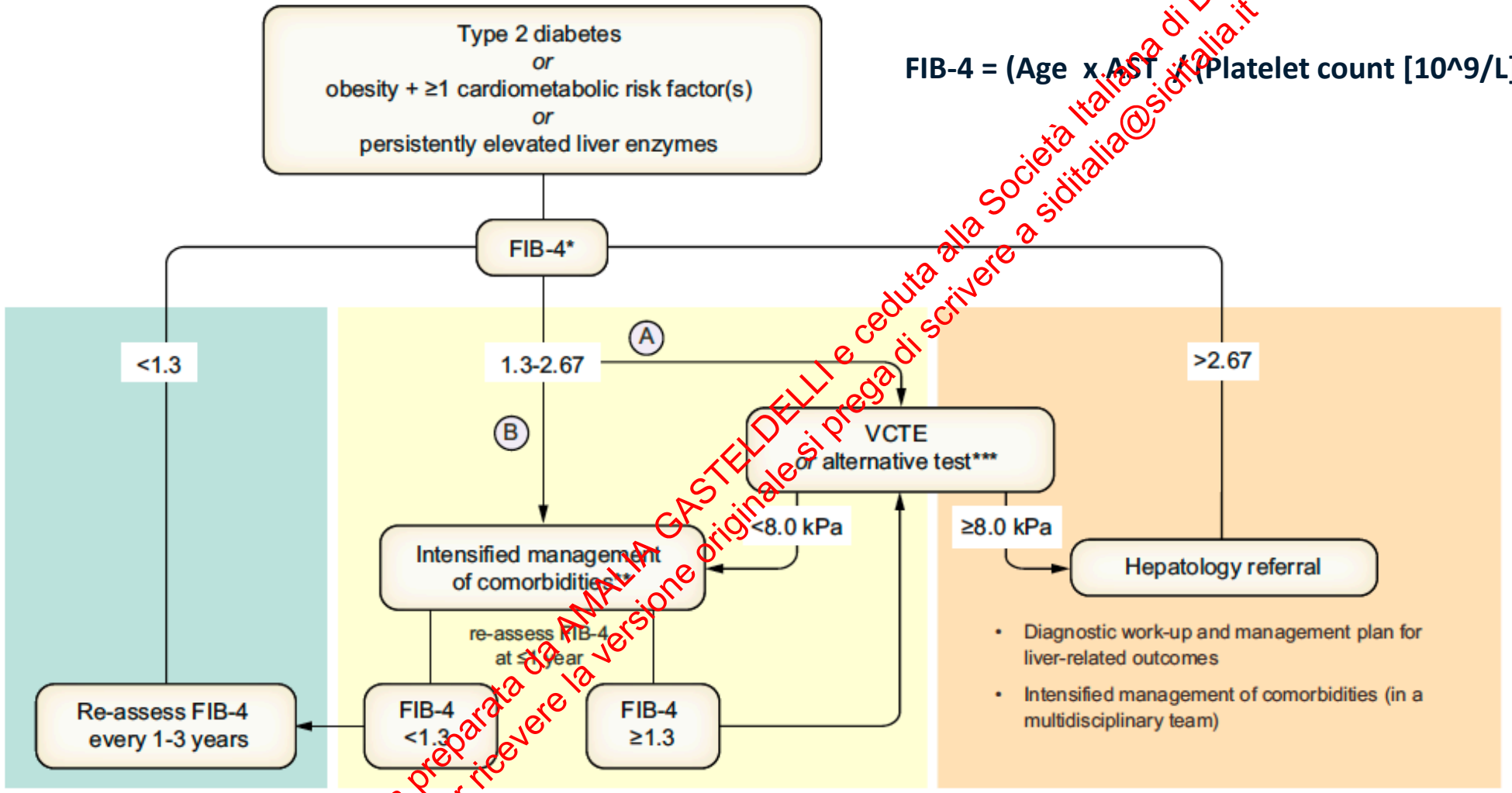


Individuals with MASH and ≥F2 fibrosis showed higher glucose production than those with MASL[2]



1. Gastaldelli A & Cusi K. JHEP Rep 2019;1:312–328; 2. Sabatini S, et al. Cell Rep Med 2024;5:101820.

Proposed use of NITs in primary care/diabetology clinic to exclude advanced fibrosis

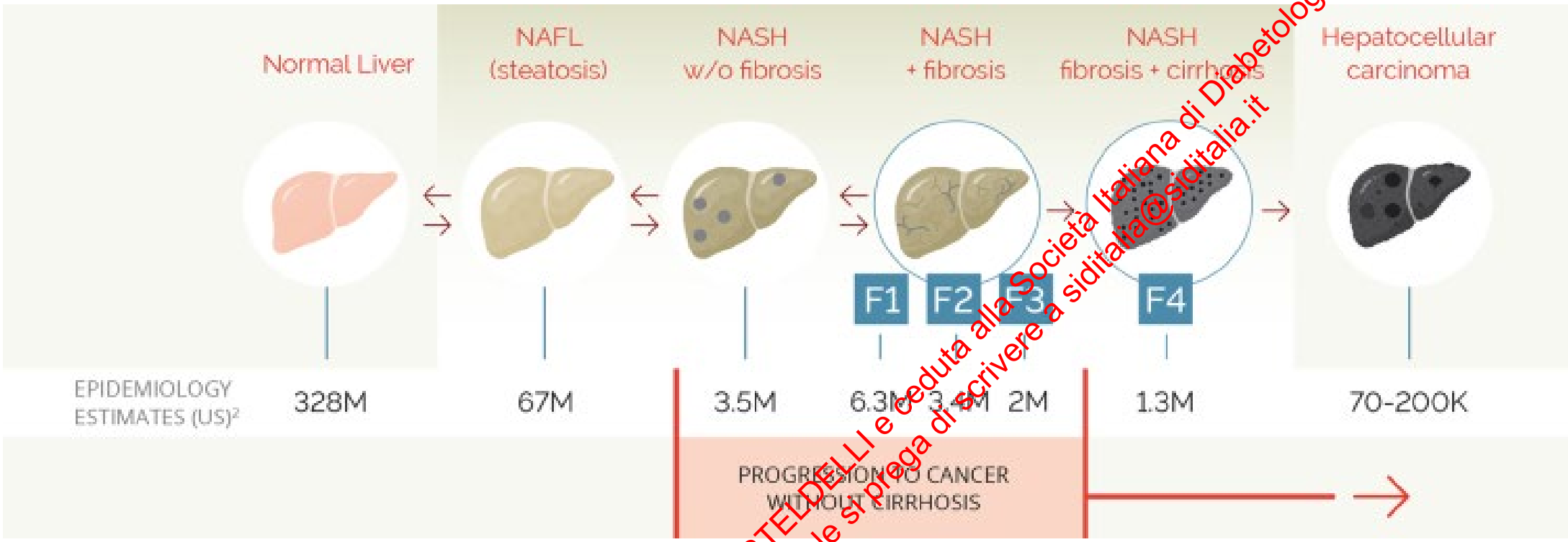


FIB-4 = (Age x AST) / (Platelet count [10^9/L] x √ALT)

* FIB-4 thresholds valid for age ≤65 years; for age >65 years: lower FIB-4 cut-off is 2.0)
** *e.g.* lifestyle intervention, treatment of comorbidities (*e.g.* GLP1RA), bariatric procedures
*** *e.g.* MRE, SWE, ELF, with adapted thresholds
Ⓐ and Ⓑ are options, depending on medical history, clinical context and local resources

EASL, EASD, EASO. J Hepatol., Diabetologia, Obesity Facts 2024.

Filozof, .. Sanyal, Hepatol Commun. 2017

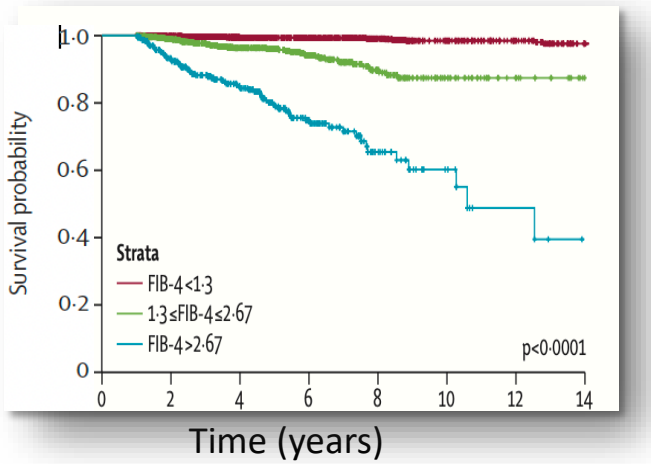


In MASH programs, there is **one common study objective** (i.e., improvement in liver clinical outcomes)
but **different primary endpoints** (i.e., reduction in NAS, resolution of MASH by histology, improvement in fibrosis, and reduction in progression to cirrhosis).

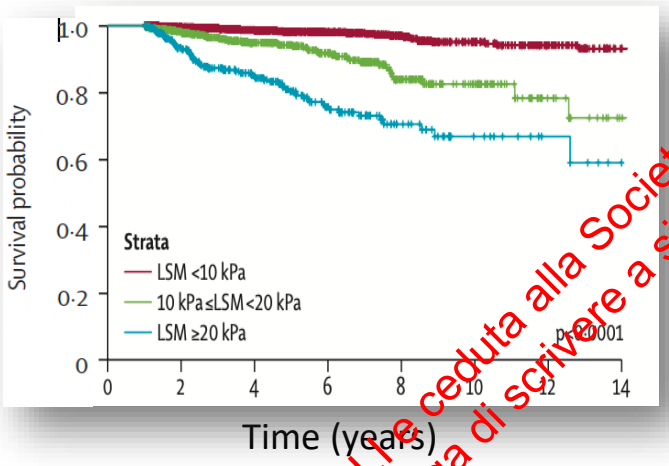
Why focusing on liver fibrosis?

Changes in NITs predict clinical outcomes

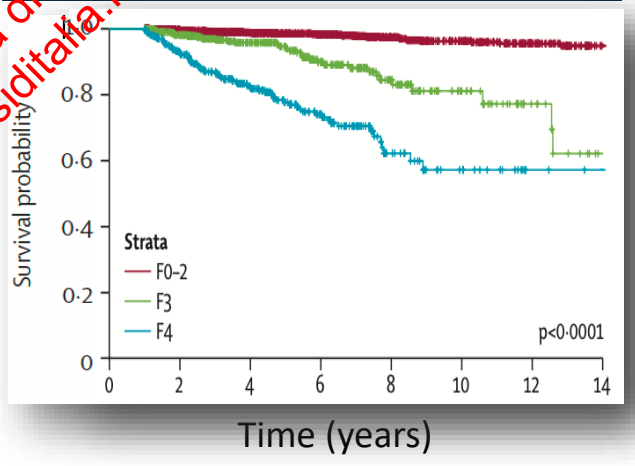
Baseline FIB-4



Baseline LSM



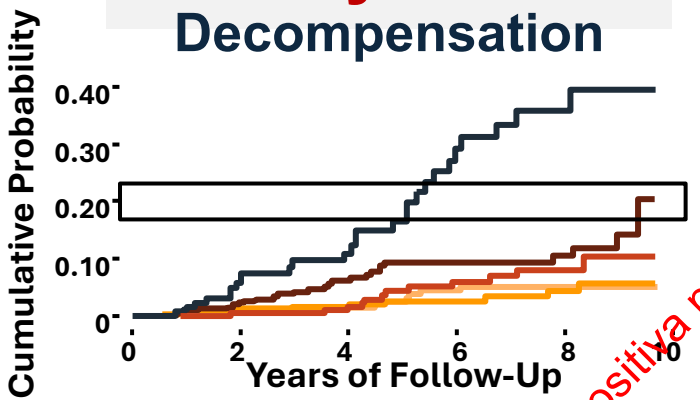
Liver biopsy



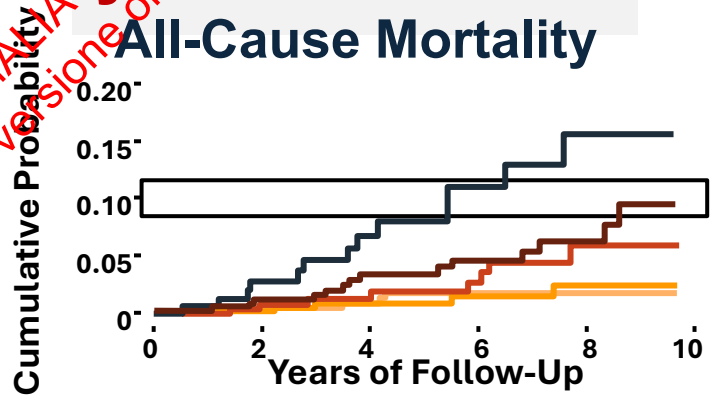
FIB-4 and LSM predict aggregated survival probabilities in MASLD similar to liver biopsy, *Mozes FE et al. Lancet GH 2023; 8: 704-13*

Mortality in MASH is closely tied to fibrosis stage

Decompensation



All-Cause Mortality



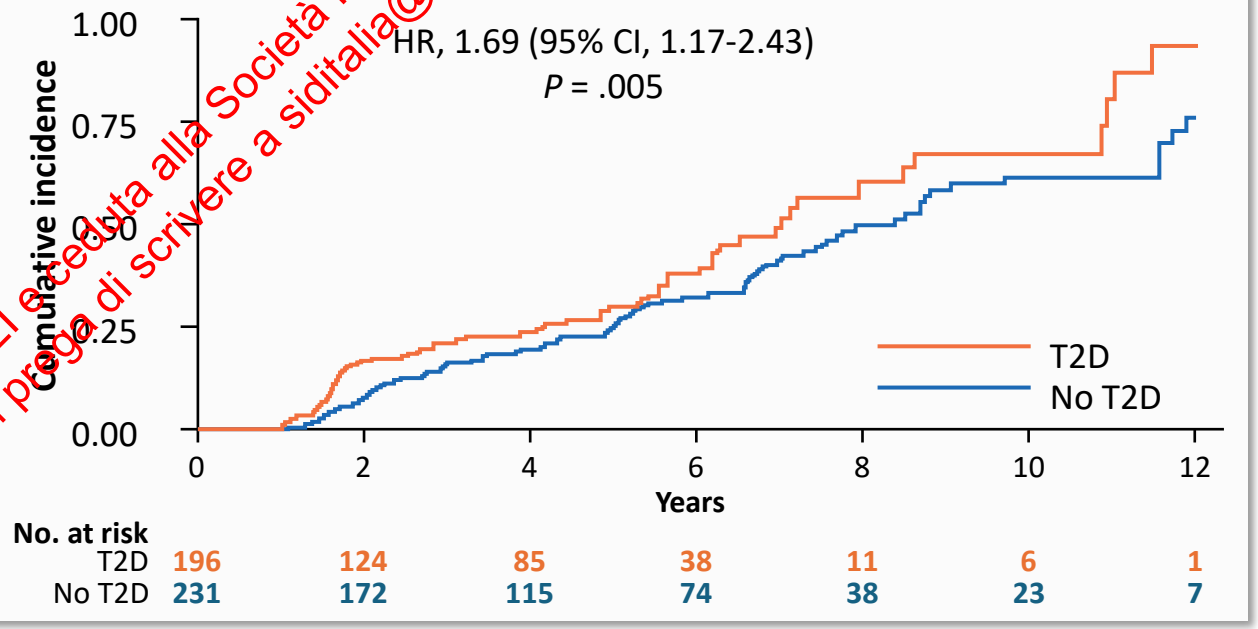
No Fibrosis Fibrosis Stage 1 Fibrosis Stage 2 Fibrosis Stage 3 Fibrosis Stage 4

Adapted from Sanyal AJ, et al. *N Engl J Med*. 2021;385(17):1559–1569.

Type 2 Diabetes Increased the Risk of MASLD and Fibrosis Progression

T2D increased the risk of MASLD and advanced fibrosis in MASLD[1,a]

T2D was an independent predictor of ≥1 stage increase in fibrosis in MASLD[2,b]



A history of T2D was an independent risk factor for cirrhosis or HCC in patients with MASLD/MASH

HR (95% CI), 2.30 (1.90-2.78)[3,c]

- [a]Data from a large multinational cohort that included 25,607 patients with MASLD, 6034 of whom were considered to have T2D. Multivariate analyses adjusted for age, gender, elevated ALT, lifestyle factors, and (advanced fibrosis only) BMI, hyperglyceridaemia, and hypercholesterolaemia. [b]Data from a multicenter study of 447 adult patients with MASLD with paired liver biopsies more than 1 year apart. HR calculated using Cox proportional hazards model adjusted for age, gender, BMI, Hispanic ethnicity, and baseline fibrosis stage. [c]Data from a matched cohort study which included 4 electronic databases of 136,703 patients with a diagnosis of NAFLD or NASH prior to 1 January 2016.
- ALT, alanine transaminase; BMI, body mass index; HR, hazard ratio; MASLD, metabolic dysfunction–associated steatotic liver disease; OR, odds ratio; T2D, type 2 diabetes.
- 1. Nabi O et al. *Liver Int*. 2022;42(3)595-606. 2. Huang DQ et al. *Gastroenterology*. 2023;165(2):463-472.e5. 3. Alexander M et al. *BMC Med*. 2019;17(1):95.

From Gastaldelli&Newsome JCEM 2025, EASL-EASD-EASO CPG J Hepatol 2024

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

Matthew James Armstrong, Piers Gaunt, Guruprasad P Aithal, Darren Barton, Diana Hull, Richard Parker, Jonathan M Hazlehurst, Kathy Guo, LEAN trial team*, George Abouda, Mark A Aldersley, Deborah Stocken, Stephen C Gough, Jeremy W Tomlinson, Rachel M Brown, Stefan G Hübscher, Philip N Newsome

LEAN-study: the first with GLP-1RA in MASH

Liraglutide ***met the primary endpoint of histological resolution of MASH with no worsening in fibrosis****. In addition to improvements in histological steatosis and hepatocyte ballooning, fewer patients receiving liraglutide had progression of fibrosis than in the placebo group.*

Liraglutide improved several key components of the metabolic syndrome, including weight and glycaemic control.

	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

Single and dual GLP-1 RA are effective on resolution of MASH with no worsening of fibrosis (phase 2 studies)

MASLD/MASH+T2D

GLP1-RA
(e.g. semaglutide, liraglutide, dulaglutide)

GLP1 coagonists
(e.g. tirzepatide)

Pioglitazone

GLP-1RA

Semaglutide 2.4mg daily for 72w

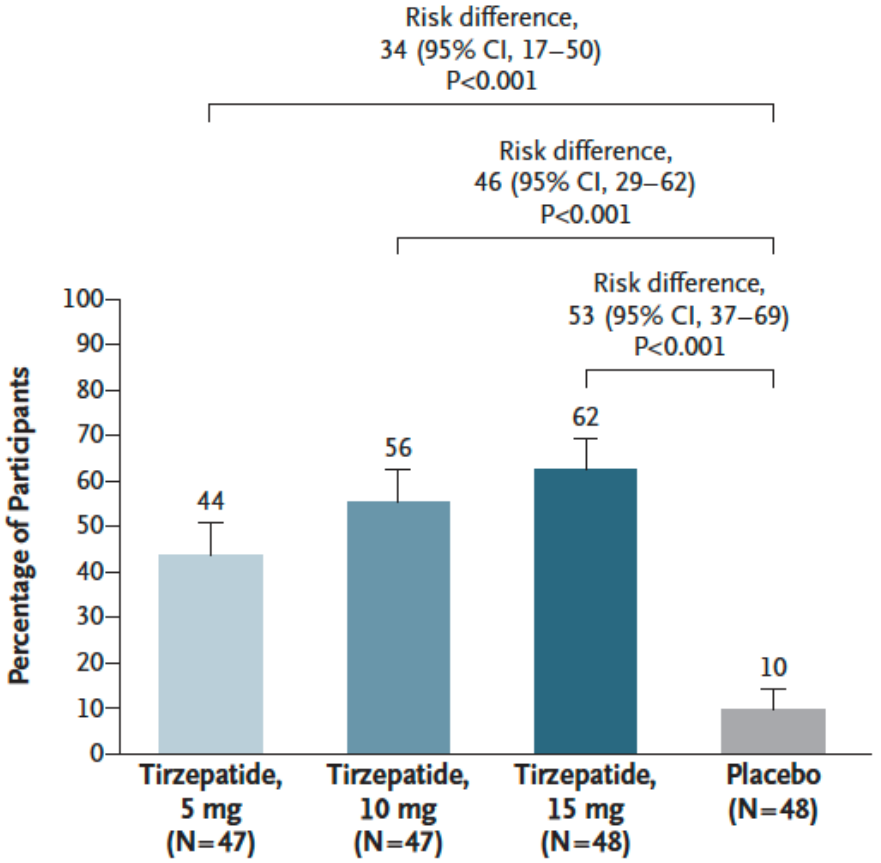
Newsome P et al, AASLD 2024

ΔWeight -10.5% -2.0%

GLP-1/GIP

Tirzepatide 5-15mg weekly for 52w

Loomba et al, NEJM 2024

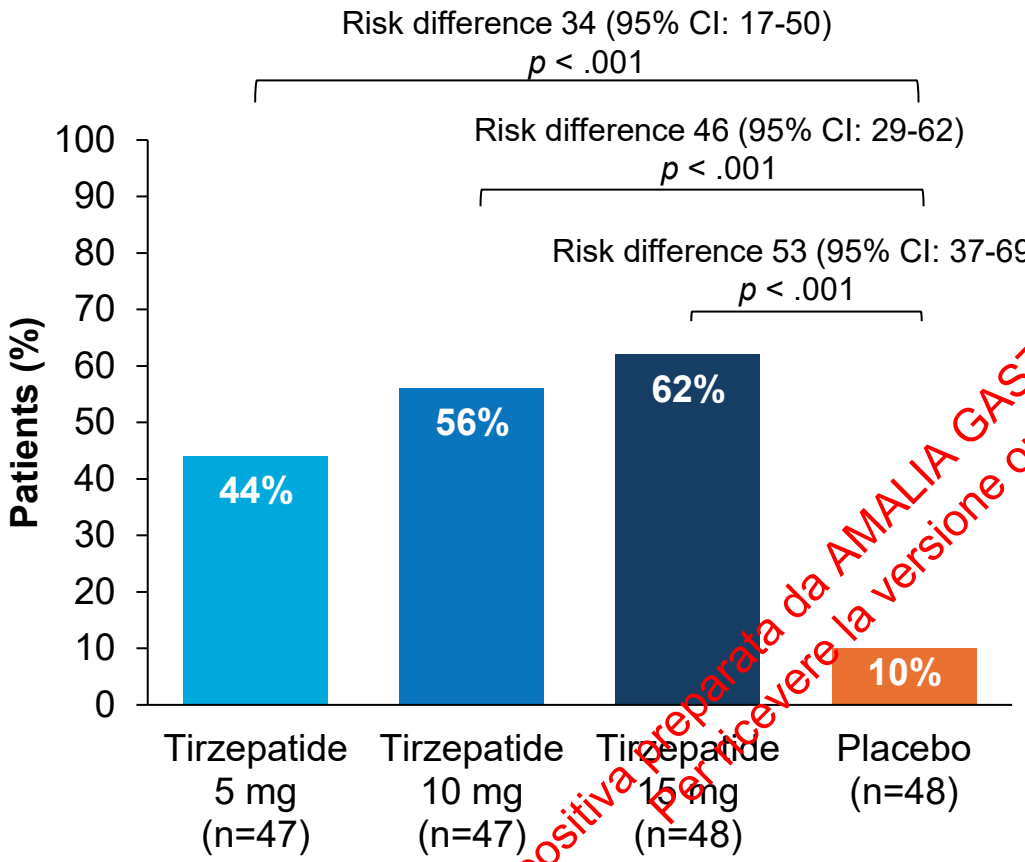


-10.7% -13.3% -15.6% -0.8%

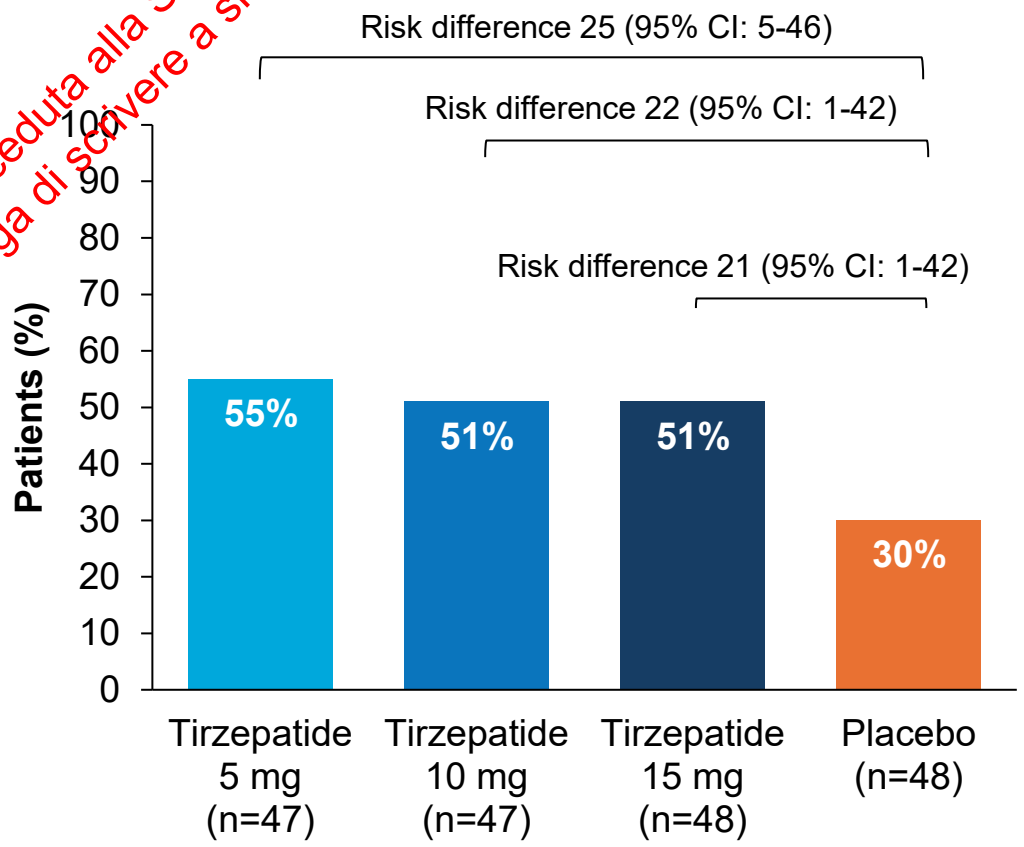
Dual GIP and GLP-1RA Tirzepatide: Phase 2b Trial

Subcutaneous Doses Were Administered Once Weekly for 52 Weeks

Primary endpoint: resolution of MASH with no worsening of liver fibrosis



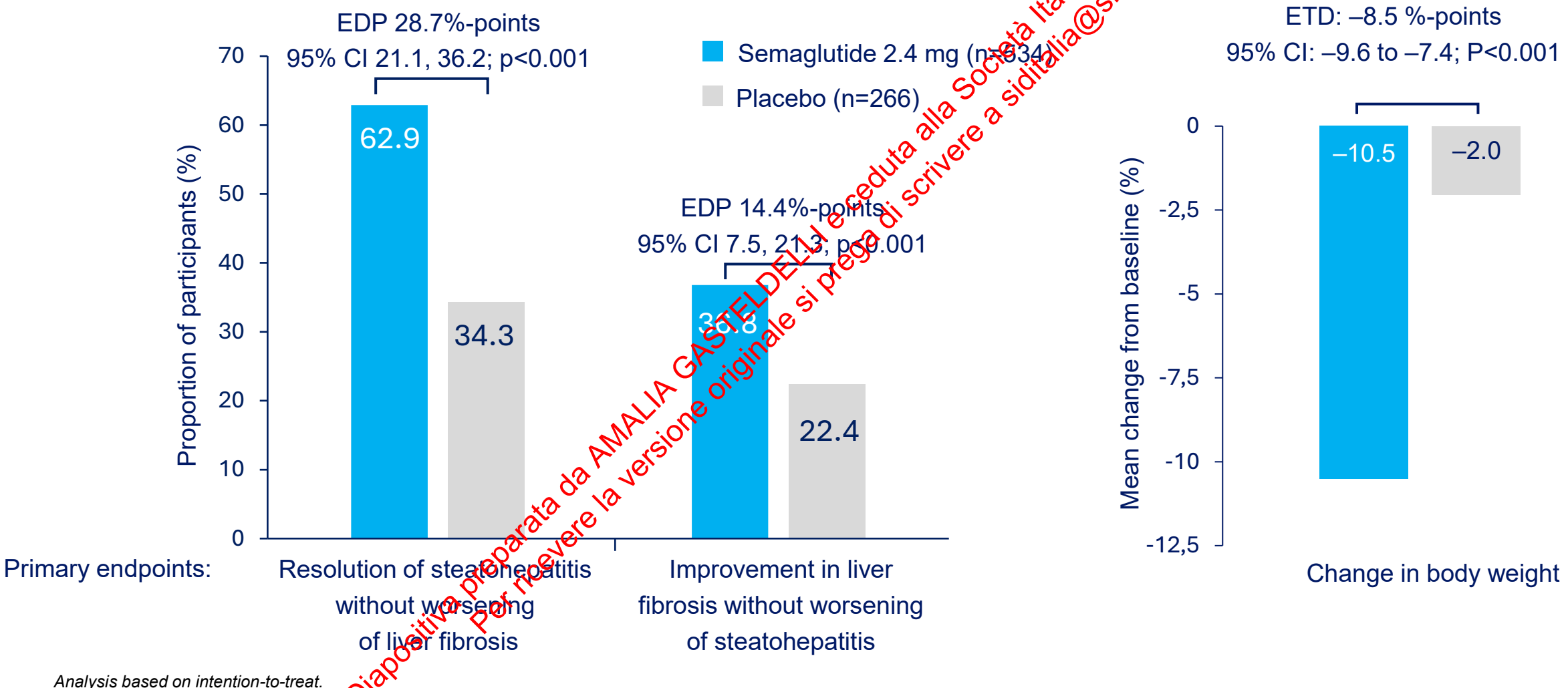
Secondary endpoint: improvement in liver fibrosis with no worsening of MASH



All data pertain to participants without end-of-treatment biopsies who were considered as nonresponders.

Loomba R, et al. *N Engl J Med*. 2024;391:299-310. Reproduced for educational purposes only.

Semaglutide 2.4 mg delivered significant improvements in liver histology and substantial body weight reduction



Analysis based on intention-to-treat.
CI, confidence interval; EDP, estimated difference in responder proportions; ETD, estimated treatment difference; SF-36, Short Form-36.
Sanyal AJ, Newsome PN et al. N Engl J Med 2025;392:2089–2099.

Clinical trials in MASH: is remission due to weight loss?

Weight loss

Diet and lifestyle intervention 1 year

Bariatric surgery 1 year

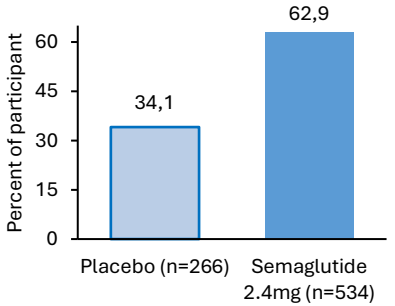
Reduction of MASH with no worsening of fibrosis

Semaglutide 0.4mg daily for 72w

Tirzepatide 5-15mg weekly for 52w

Survodutide 2.4-6.0mg weekly for 48w

Semaglutide 2,4mg weekly for 72w



Pioglitazone, 45 mg/d for 18 months

Lanifibranor 800-1200mg daily for 52w

Resmetirom 80-100mg daily for 52w

F Carli et al JHep Reports 2024

Clinical trials in MASH: effect on fibrosis

Diet and lifestyle intervention 1 year

Bariatric surgery 1 year

FIBROSIS

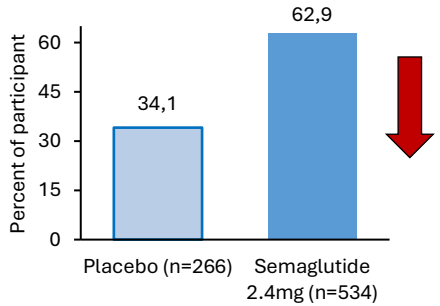
GLP-1RA

Semaglutide 0.4mg daily for 72w

Tirzepatide 5-15mg weekly for 52w

Survodutide 2.4-6.0mg weekly for 48w

Semaglutide 2,4mg weekly for 72w



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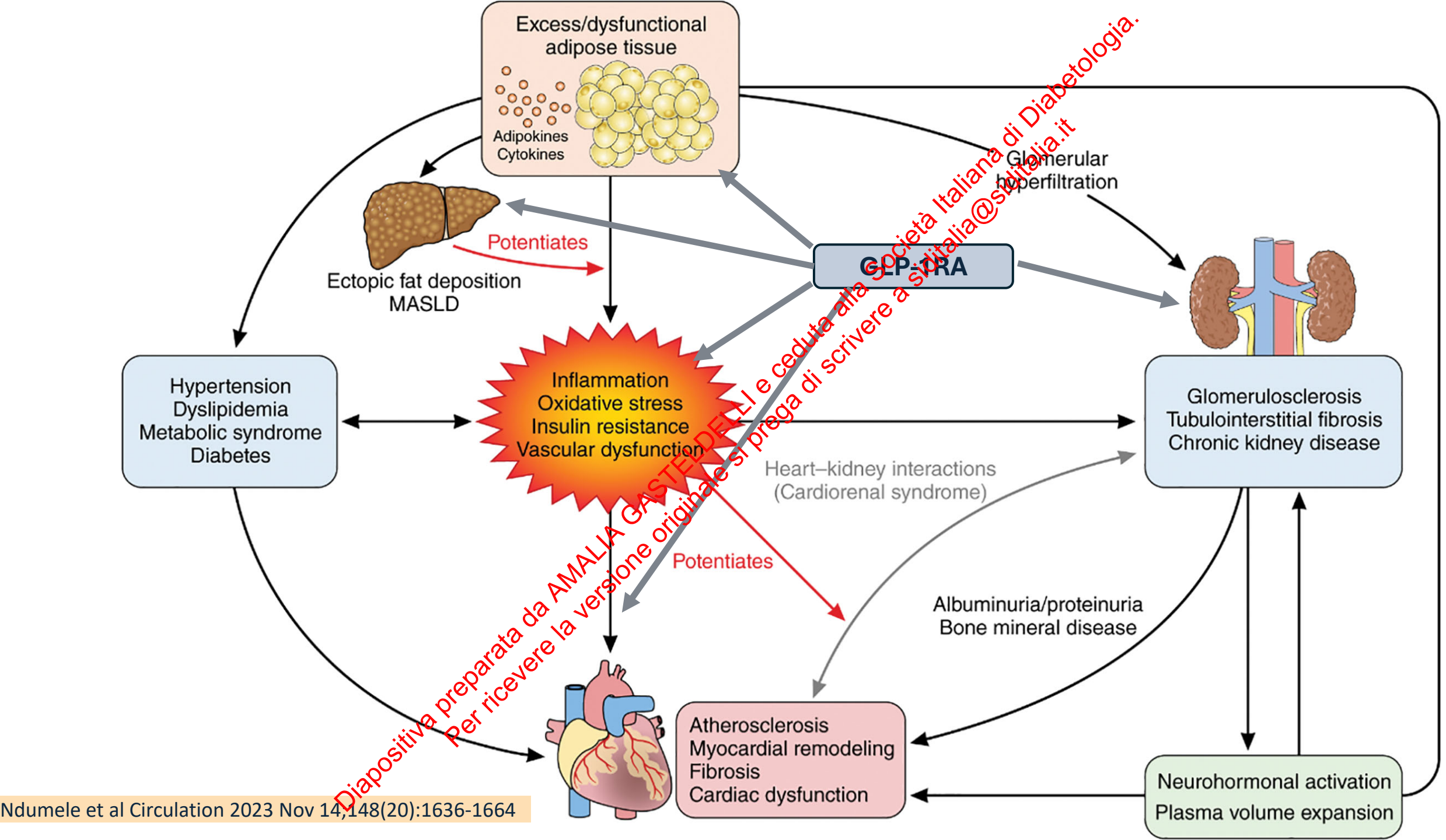
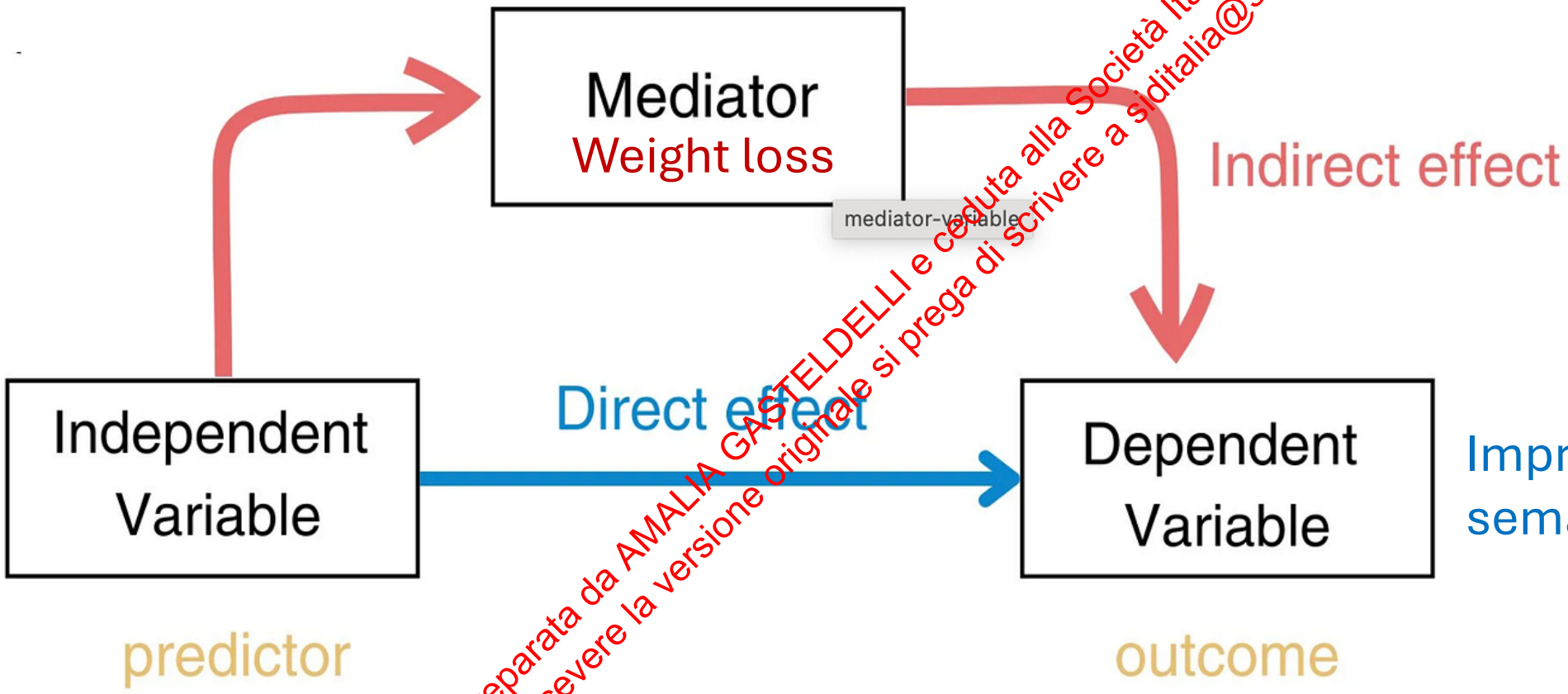
F Carli et al JHep Reports 2024



Ndumele et al Circulation 2023 Nov 14;148(20):1636-1664

To what extent is the efficacy of semaglutide on MASH liver parameters mediated through weight loss?

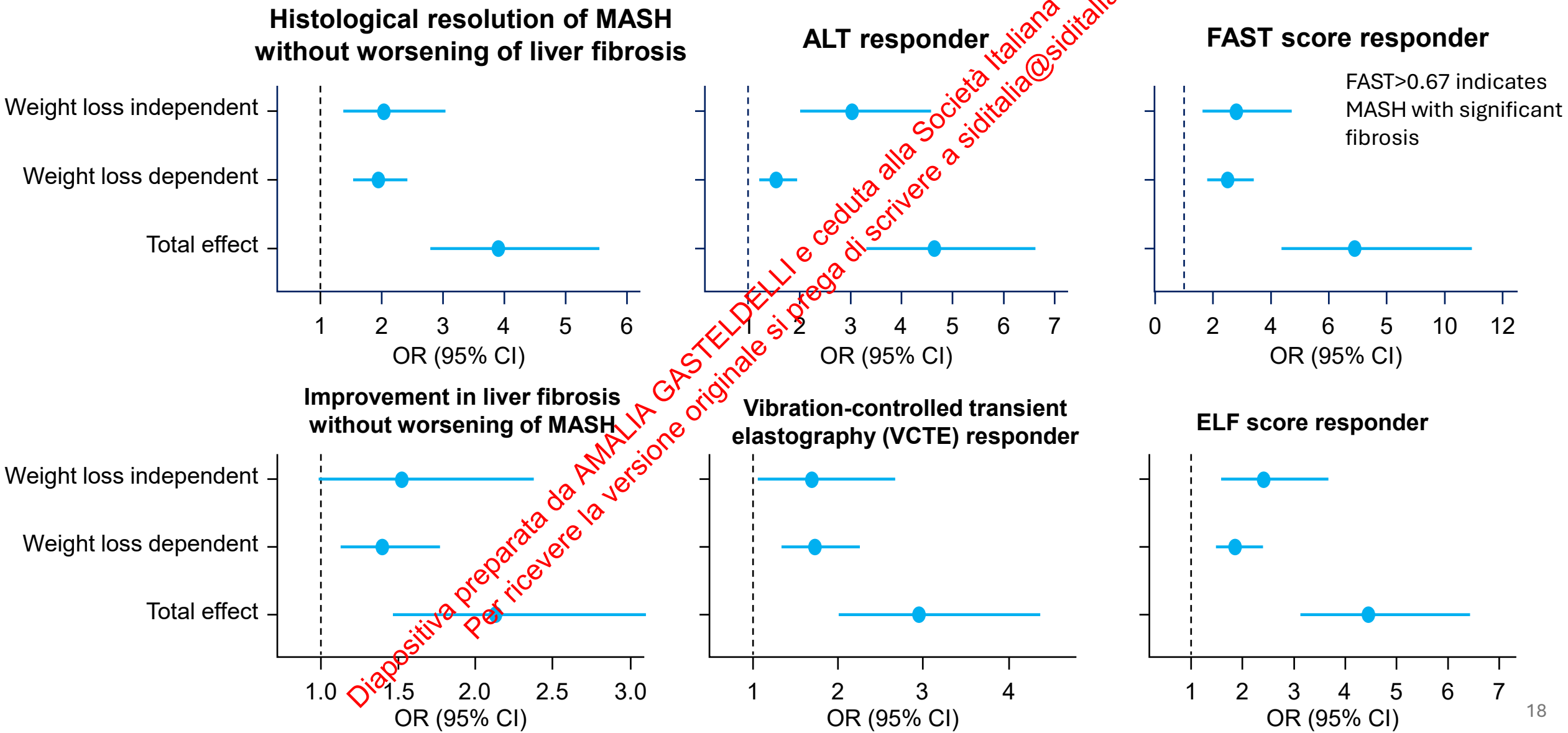


Improvement after semaglutide

Mediation analysis is a statistical tool used to identify direct vs indirect associations

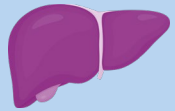
The effect of semaglutide on MASH-related histological and NIT responder endpoints is only partially mediated by weight loss

Schattenberg et al presentation at UEG 2025



In people living with obesity, visceral fat accumulation contributes to liver fat deposition and metabolic dysfunction

Liver fat

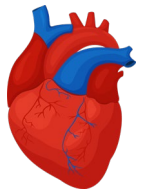


- ↑ Insulin resistance
- ↑ HGP
- ↑ VLDL production
- ↓ Insulin clearance
- MASLD → cirrhosis
- *De novo* lipogenesis

Visceral fat

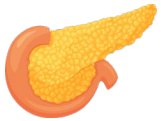
- ↑ Insulin resistance
- ↑ Portal FFA → MASLD
- ↑ Lipolysis
- ↑ Cytokine release
- ↑ Microphages
- ↓ Adiponectin

Cardiac fat



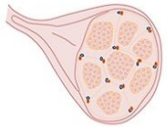
- ↑ Cardiac insulin resistance
- ↓ Energy metabolism
- ↓ Mitochondrial function
- Diastolic dysfunction

Pancreatic fat



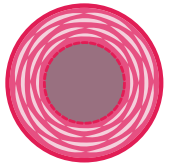
- ↑ Insulin resistance
- Impaired insulin secretion
- ↑ β-cell apoptosis
- ↑ T2D

Intramyocellular fat



- ↑ Insulin resistance
- ↑ Mitochondrial function
- ↓ VO_2 max

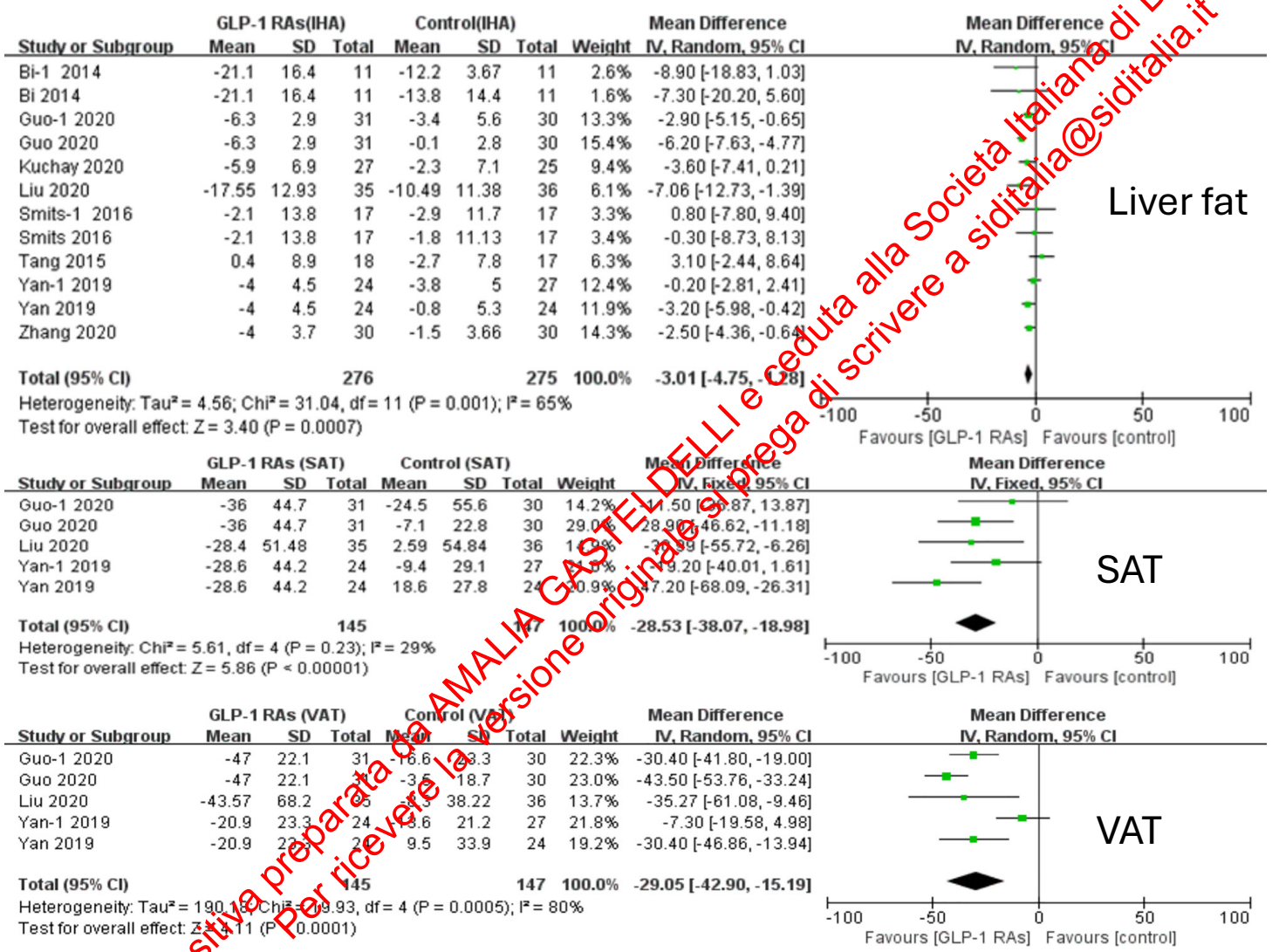
Perivascular fat



- ↓ Carotid elasticity
- Endothelial dysfunction
- Atherosclerosis
- Plaque formation

- Bray GA & Bouchard C. Handbook of Obesity - Volume 1: Epidemiology, Etiology, and Pathophysiology, 3rd ed., 2014. CRC Press, Boca Raton, USA.

Meta analyses: GLP-1RA reduces also SAT and VAT



Study or Subgroup	GLP-1 RAs(IHA) Mean	SD	Total	Control(IHA) Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bi-1 2014	-21.1	16.4	11	-12.2	3.67	11	2.6%	-8.90 [-18.83, 1.03]
Bi 2014	-21.1	16.4	11	-13.8	14.4	11	1.6%	-7.30 [-20.20, 5.60]
Guo-1 2020	-6.3	2.9	31	-3.4	5.6	30	13.3%	-2.90 [-5.15, -0.65]
Guo 2020	-6.3	2.9	31	-0.1	2.8	30	15.4%	-6.20 [-7.63, -4.77]
Kuchay 2020	-5.9	6.9	27	-2.3	7.1	25	9.4%	-3.60 [-7.41, 0.21]
Liu 2020	-17.55	12.93	35	-10.49	11.38	36	6.1%	-7.06 [-12.73, -1.39]
Smits-1 2016	-2.1	13.8	17	-2.9	11.7	17	3.3%	0.80 [-7.80, 9.40]
Smits 2016	-2.1	13.8	17	-1.8	11.13	17	3.4%	-0.30 [-8.73, 8.13]
Tang 2015	0.4	8.9	18	-2.7	7.8	17	6.3%	3.10 [-2.44, 8.64]
Yan-1 2019	-4	4.5	24	-3.8	5	27	12.4%	-0.20 [-2.81, 2.41]
Yan 2019	-4	4.5	24	-0.8	5.3	24	11.9%	-3.20 [-5.98, -0.42]
Zhang 2020	-4	3.7	30	-1.5	3.66	30	14.3%	-2.50 [-4.36, -0.64]
Total (95% CI)			**276**			**275**	**100.0%**	**-3.01 [-4.75, -1.28]**

Heterogeneity: Tau² = 4.56; Chi² = 31.04, df = 11 (P = 0.001); I² = 65%
Test for overall effect: Z = 3.40 (P = 0.0007)

Liver fat

Study or Subgroup	GLP-1 RAs (SAT) Mean	SD	Total	Control (SAT) Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Guo-1 2020	-36	44.7	31	-24.5	55.6	30	14.2%	-11.50 [-36.87, 13.87]
Guo 2020	-36	44.7	31	-7.1	22.8	30	29.0%	-28.90 [-46.62, -11.18]
Liu 2020	-28.4	51.48	35	2.59	54.84	36	14.0%	-30.99 [-55.72, -6.26]
Yan-1 2019	-28.6	44.2	24	-9.4	29.1	27	21.5%	-19.20 [-40.01, 1.61]
Yan 2019	-28.6	44.2	24	18.6	27.8	24	20.9%	-47.20 [-68.09, -26.31]
Total (95% CI)			**145**			**147**	**100.0%**	**-28.53 [-38.07, -18.98]**

Heterogeneity: Chi² = 5.61, df = 4 (P = 0.23); I² = 29%
Test for overall effect: Z = 5.86 (P < 0.00001)

SAT

Study or Subgroup	GLP-1 RAs (VAT) Mean	SD	Total	Control (VAT) Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Guo-1 2020	-47	22.1	31	-16.6	23.3	30	22.3%	-30.40 [-41.80, -19.00]
Guo 2020	-47	22.1	31	-3.5	18.7	30	23.0%	-43.50 [-53.76, -33.24]
Liu 2020	-43.57	68.2	35	-8.3	38.22	36	13.7%	-35.27 [-61.08, -9.46]
Yan-1 2019	-20.9	23.3	24	-13.6	21.2	27	21.8%	-7.30 [-19.58, 4.98]
Yan 2019	-20.9	23.3	24	9.5	33.9	24	19.2%	-30.40 [-46.86, -13.94]
Total (95% CI)			**145**			**147**	**100.0%**	**-29.05 [-42.90, -15.19]**

Heterogeneity: Tau² = 190.19; Chi² = 19.93, df = 4 (P = 0.0005); I² = 80%
Test for overall effect: Z = 4.11 (P < 0.0001)

VAT

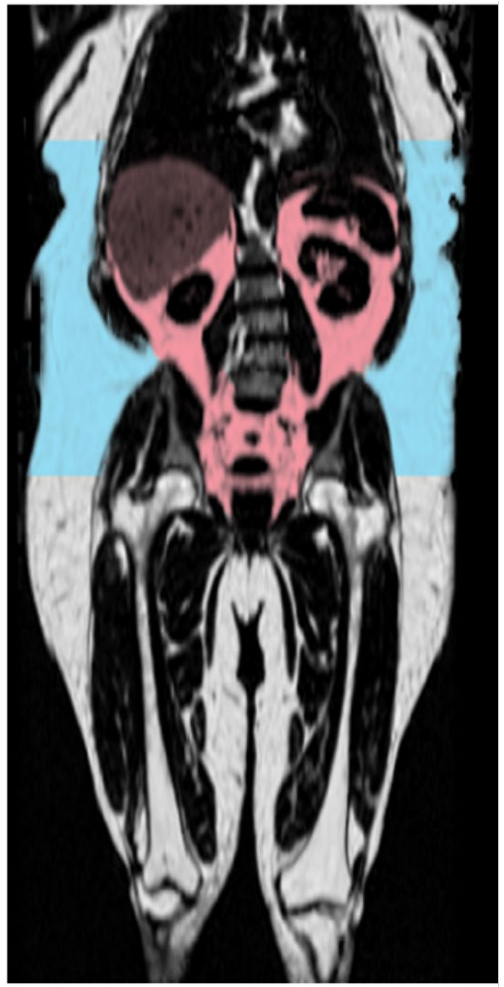
Favours [GLP-1 RAs] Favours [control]

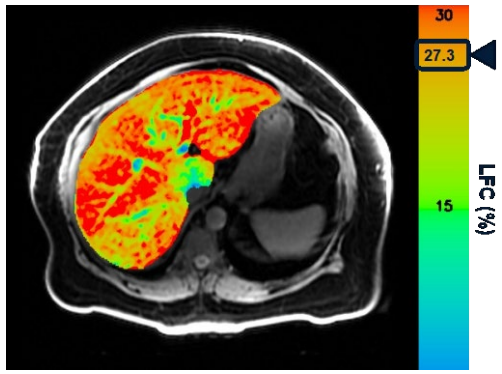
Zhu Y et al Front Endocrinol 2021

Gastaldelli et al Lancet Diabetes Endocrinol 2022, EASD 2022

MRI Scan: Male, 59 Years, on Metformin + SGLT-2i Randomised to Tirzepatide 5 mg

At Baseline





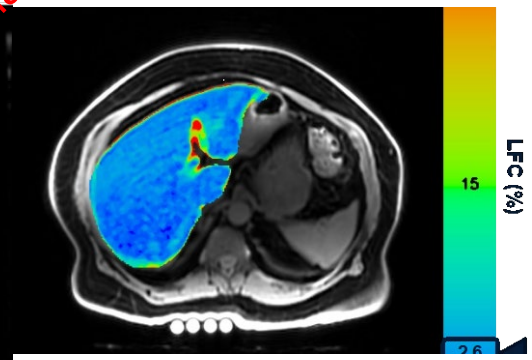
VAT: 8.3 L
ASAT: 19.9 L
Total abdominal fat: 28.2 L
Liver fat content: 27.3%

BMI: 44.8 kg/m^2
Body weight: 134.2 kg
Waist circumference: 139.7 cm

HbA_{1c}: 78.1 mmol/mol (9.3%)
FSG: 10.3 mmol/L (186 mg/dL)

Triglycerides: 3.93 mmol/L
HDL-C: 0.88 mmol/L
Free fatty acids: 0.79 mmol/L
Adiponectin: 2.3 mg/L
Leptin: 68.1 µg/L

At Week 52



VAT: 5.2 L; CFB: -3.1 L (-37%)
ASAT: 14.9 L; CFB: -5.0 L (-25%)
Total abdominal fat: 20.2 L
Liver fat content: 2.6%

BMI: 36.2 kg/m^2
Body weight: 108.4 kg
Waist circumference: 124.4 cm

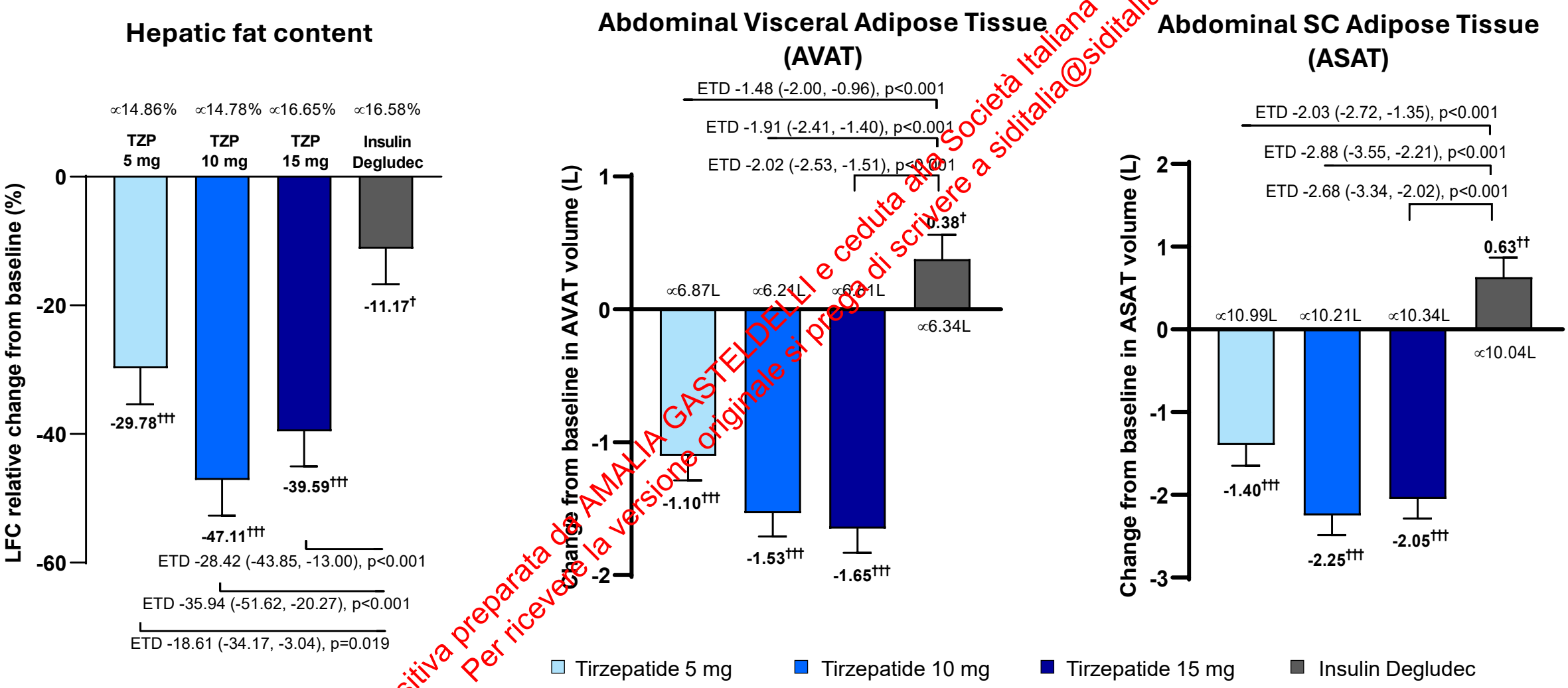
HbA_{1c}: 43.2 mmol/mol (6.1%)
FSG: 5.9 mmol/L (107 mg/dL)

Triglycerides: 1.86 mmol/L
HDL-C: 1.22 mmol/L
Free fatty acids: 0.28 mmol/L
Adiponectin: 4.1 mg/L
Leptin: 31.6 µg/L

Gastaldelli et al Lancet Diabetes Endocrinol 2022, EASD 2022

Effect of Tirzepatide on Hepatic and Abdominal fat

Comparison Between Individual Doses of Tirzepatide and Insulin Degludec at Week 52



Data are LSM (SE); ANCOVA analysis. mITT (MRI analysis set). Estimated treatment differences (ETD) are LSM (95% confidence interval) vs. insulin degludec. † p<0.05; †† p<0.01; ††† p<0.001 vs. baseline within treatment group. ∝ represents the mean value at baseline for the respective group.

Abbreviations: ANCOVA = analysis of covariance; LSM = least-squares mean; mITT = modified Intent-to-Treat; MRI = magnetic resonance imaging; SC = subcutaneous; SE = standard error.

Conclusions

In MASLD it is important to improve both glucose and lipid metabolism and to improve IR, in particular in adipose tissue and liver.

Weight loss is the most effective way to resolve MASLD, although not all drugs work through weight loss

Resolution of fibrosis is difficult and only few drugs and bariatric surgery were able to succeed in it

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MASLD Study Group

EGIR European Group for the study of Insulin Resistance

Study Groups

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