La protezione metabolica delle gliflozine e il futuro della cura delle patologie epatiche

Ilaria Dicembrini

Diabetologia e Malattie Metaboliche, AOU Careggi
Endocrinologia, Università di Firenze

Conflitti di interesse

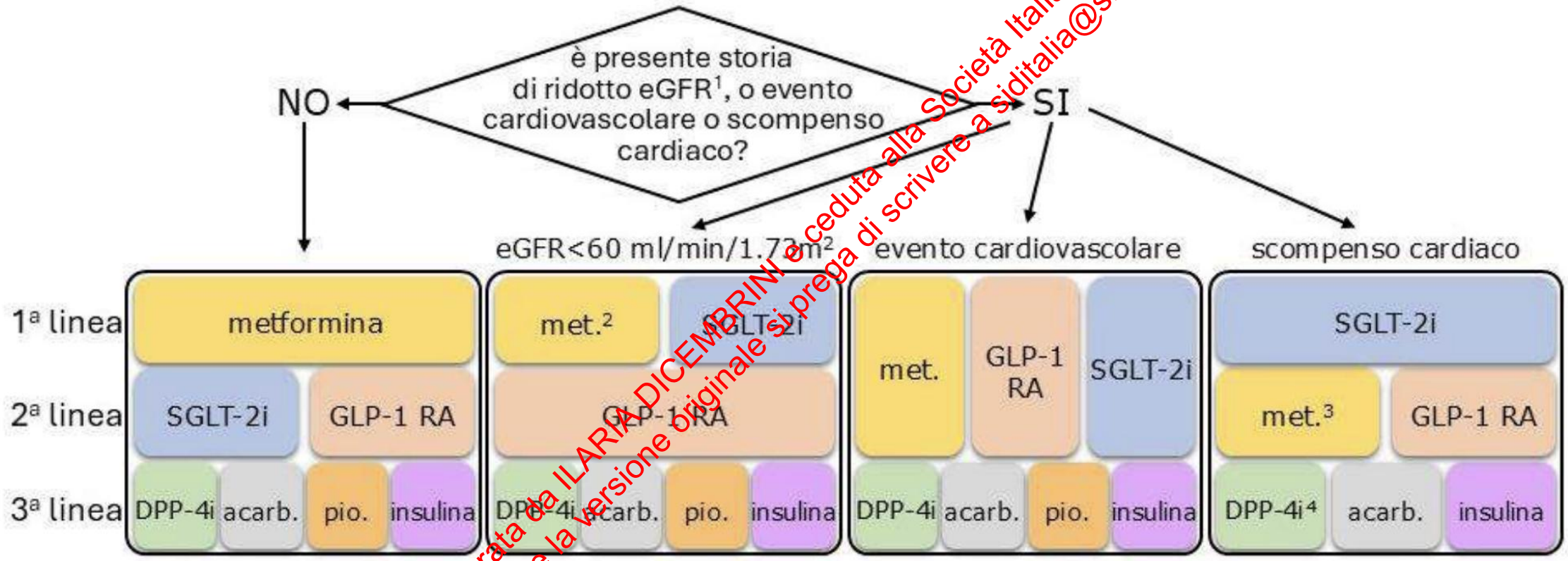
Negli ultimi due anni, I. Dicembrini ha ricevuto compensi per relazioni e/o consulenze da **Astra Zeneca, *Boehringer Ingelheim, Dexcom, Eli Lilly,* Medtronic, *Novo Nordisk, Sanofi.***

La struttura di appartenenza ha ricevuto:

- Finanziamenti per ricerca indipendente non condizionata da ***Abbott***
- Compensi per studi clinici sponsorizzati da ***Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Genentech, Molteni, Novo Nordisk***

Italian Guidelines for the treatment of T2 Diabetes, 2025

Drug therapy



NB: l'indicazione ai farmaci di terza linea (DPP-4i, acarbosio, pioglitazone, insulina) deve essere considerata solo dopo l'utilizzo in combinazione di metformina, SGLT-2i e GLP-1 RA, qualora tollerati e non controindicati. L'indicazione per DPP-4i è valida solo se GLP-1 RA non indicati o non tollerati. 1. si intende eGFR secondo CKD-EPI < 60 ml/min/1.73m²; 2. se la metformina non è controindicata per eGFR<30 ml/min/1.73m²; 3. se la metformina non è controindicata per ridotta funzione cardiaca; 4. eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.

UNIVERSITÀ DEGLI STUDI FIRENZE

nature reviews gastroenterology & hepatology

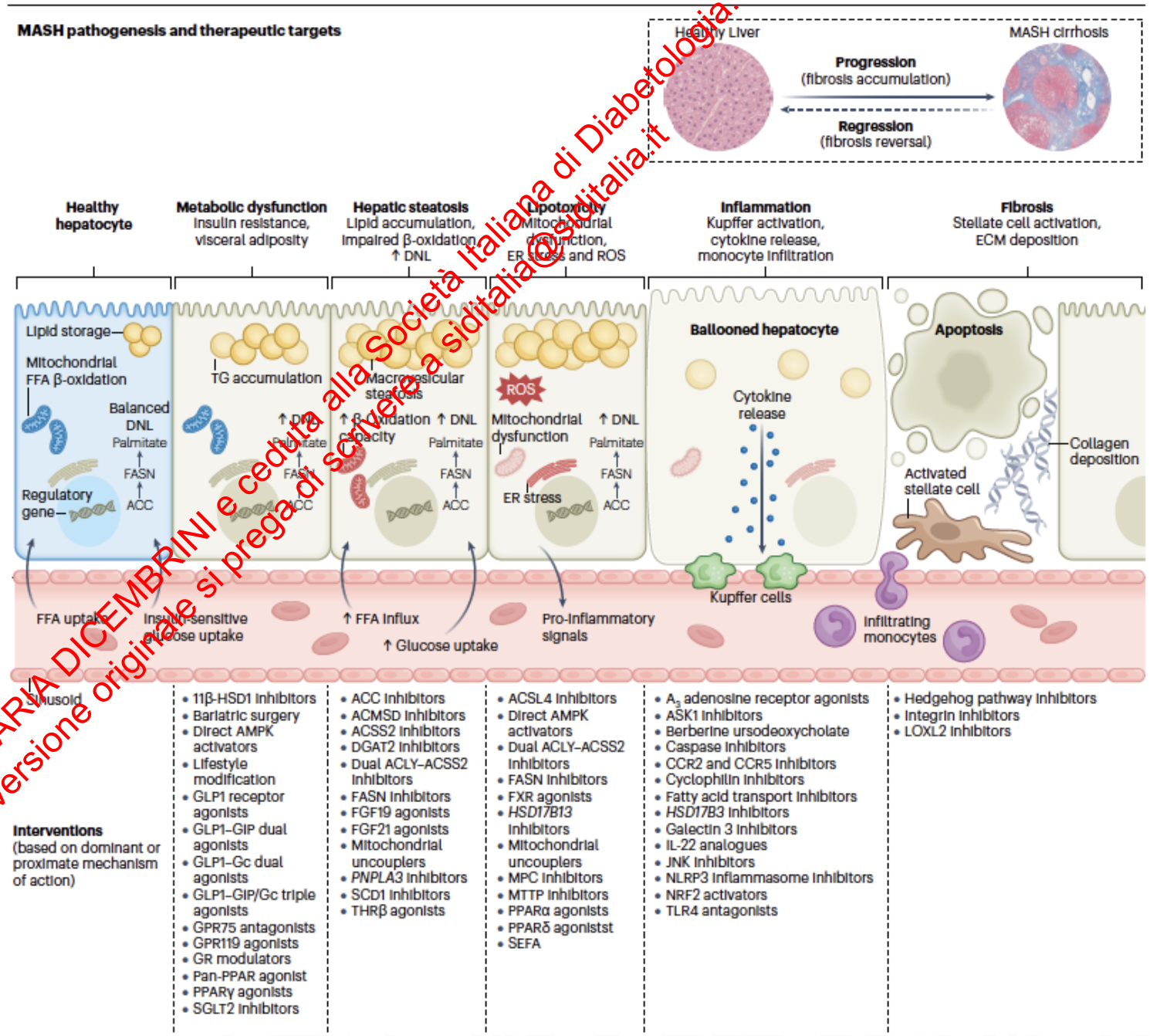
https://doi.org/10.1038/s41575-026-01187-8

Review article

Check for updates

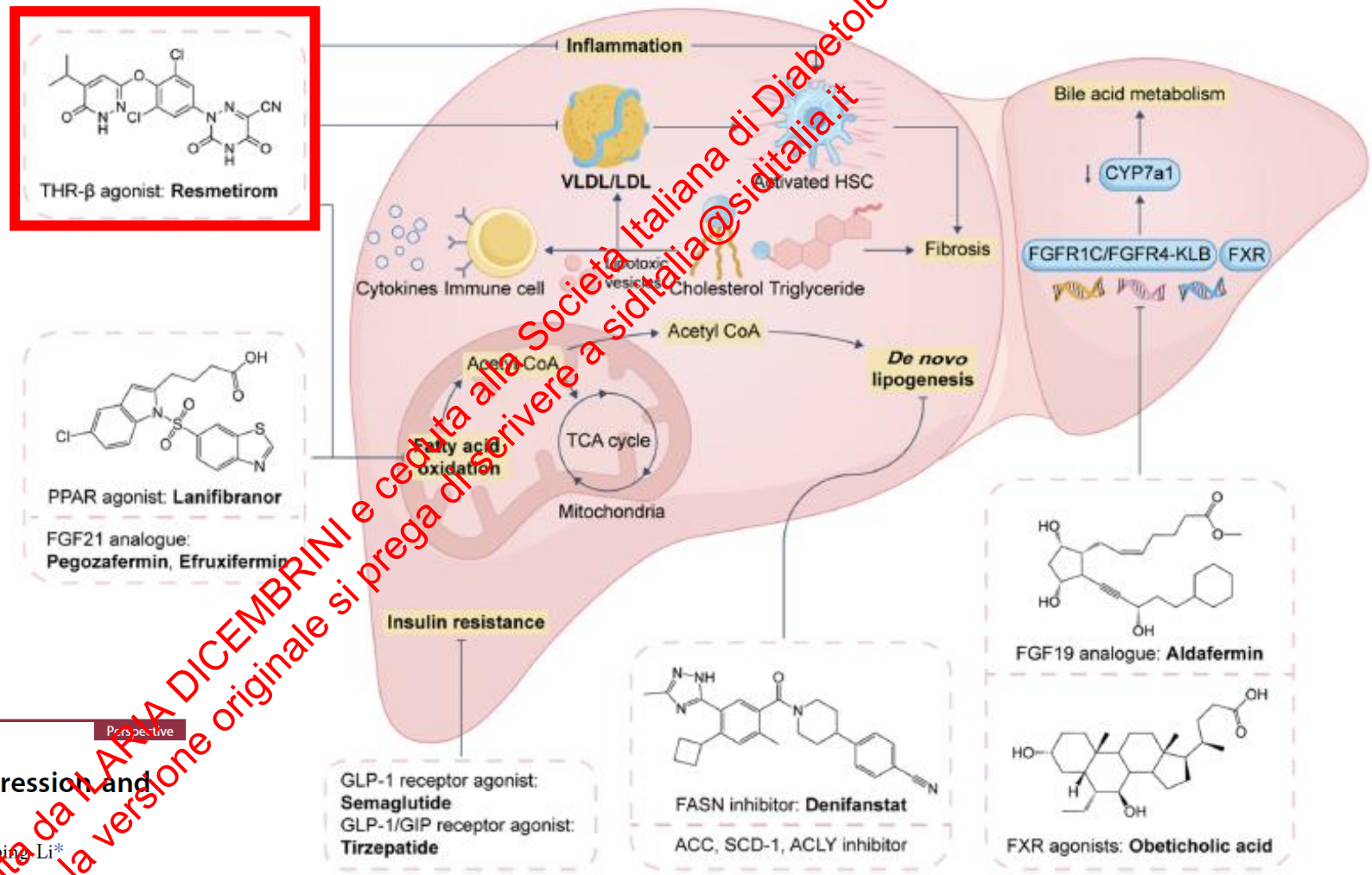
Therapeutic targets for metabolic dysfunction-associated steatohepatitis: a personalized approach to disease management

Mary E. Rinella[1] & Silvia Sookoian[2,3]



Rinella ME, et al. Nat Rev Gatroenterol Hepatol, 2026

UNIVERSITÀ DEGLI STUDI FIRENZE



Journal of Medicinal Chemistry

pubs.acs.org/jmc Perspective

Targeting THR-β for MASLD Treatment: Current Progression and Emerging Prospects

Jingwei Li,[⊥] Ruixian Chen,[⊥] Jinhang Zhang,[⊥] Jinhan He, Yuxi Wang,* and Yanping Li*

Cite This: *J. Med. Chem.* 2026, 69, 823−844 Read Online

Li J et al. J Med Chem 69:823-44, 2026

nature medicine

Article

https://doi.org/10.1038/s41591-023-02603-1

Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial

Received: 6 March 2023

Accepted: 20 September 2023

Stephen A. Harrison[1], Rebecca Taub[2], Guy W. Neff[3], K. Jean Lucas[4], Dominic Labriola[2], Sam E. Moussa[5], Naim Alkhouri[6] & Mustafa R. Bashir[7]

MAESTRO-NAFLD-1 RCT

Treatment: Resmetirom
Comparator: placebo
Patients: 1,145 NAFLD/NASH with F1-F3 (Fibroscan)
Primary endpoint: Safety (AE)
Follow-up: 52 wk

Data are *n* (%)	Resmetirom 100 mg OL (*n*=171)	Resmetirom 100 mg DB (*n*=324)	Resmetirom 80 mg DB (*n*=327)	Placebo DB (*n*=318)
TEAEs occurring in ≥5%				
Diarrhea	51 (29.8)	101 (31.2)	77 (23.5)	44 (13.8)
Onset ≤12 weeks	43 (25.1)	81 (25.0)	61 (18.7)	28 (8.8)
Duration, days, median (Q1, Q3)	26 (5, 64)	15 (3, 69)	20 (4, 59)	22 (3, 97)
Onset >12 weeks	8 (4.7)	20 (6.2)	16 (4.9)	16 (5.0)
Nausea	24 (14.0)	59 (18.2)	39 (11.9)	25 (7.9)
Onset ≤12 weeks	12 (7.0)	47 (14.5)	27 (8.3)	15 (4.7)
Onset >12 weeks	12 (7.0)	12 (3.7)	12 (3.7)	10 (3.1)
Abdominal pain	9 (5.3)	23 (7.1)	14 (4.3)	14 (4.4)

Harrison SA et al. Nat Med 29:2919-2928, 2023

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

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

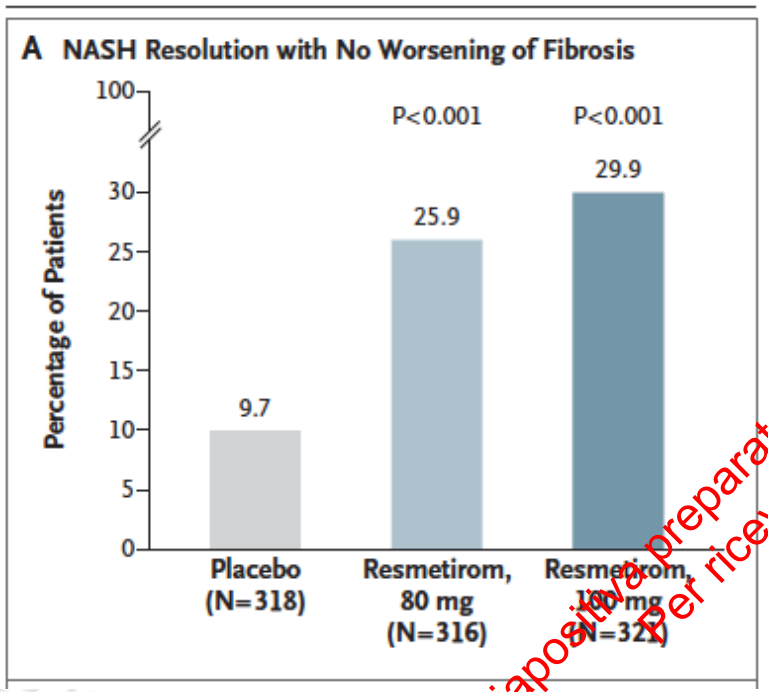
S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

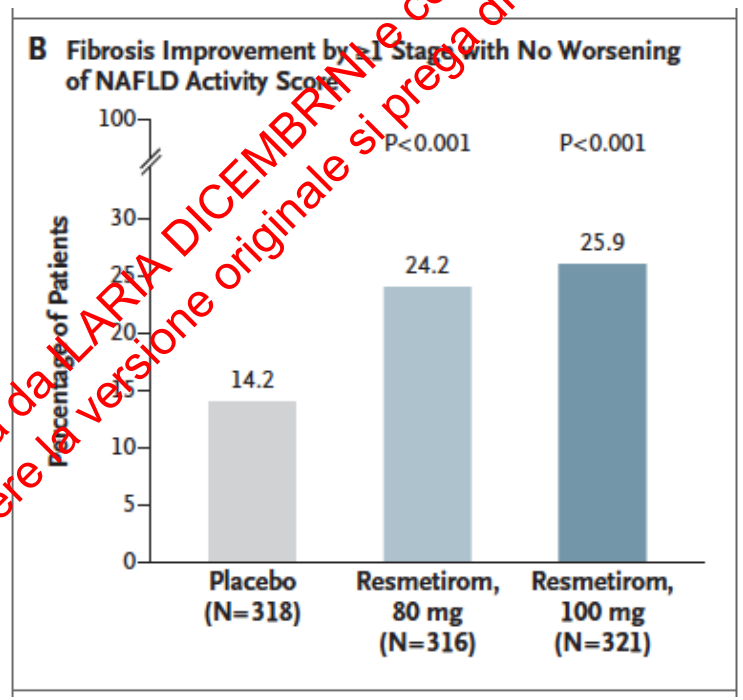
MAESTRO-NASH RCT

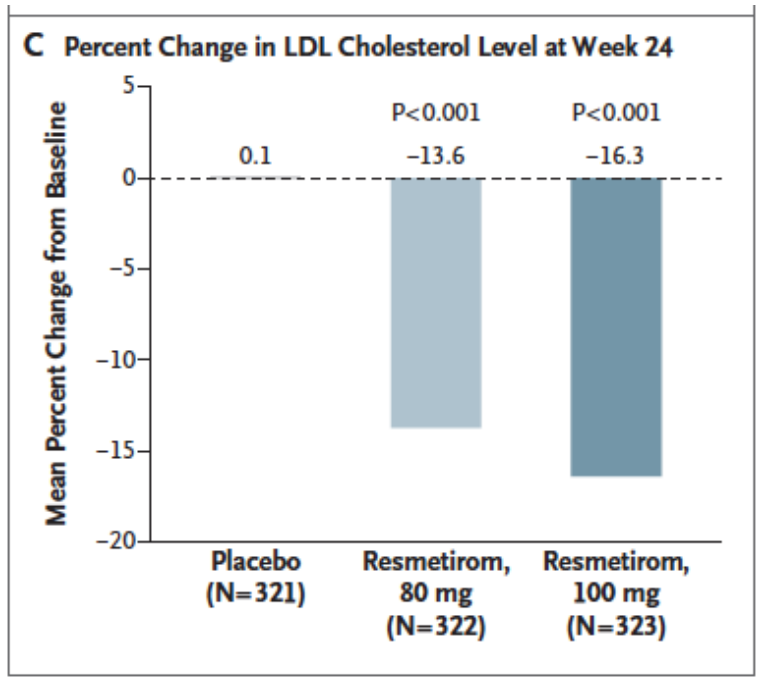
Treatment: Resmetirom
Comparator: placebo
Patients: 966 NASH with F1B-F3 (biopsy)
Co-primary endpoints:

1. Improvement of NASH with no worsening of fibrosis
2. Improvement of fibrosis with no worsening of NASH

Follow-up: 52 wk







Harrison SA et al. N Engl J Med 390:497-509, 2024

UNIVERSITÀ DEGLI STUDI FIRENZE

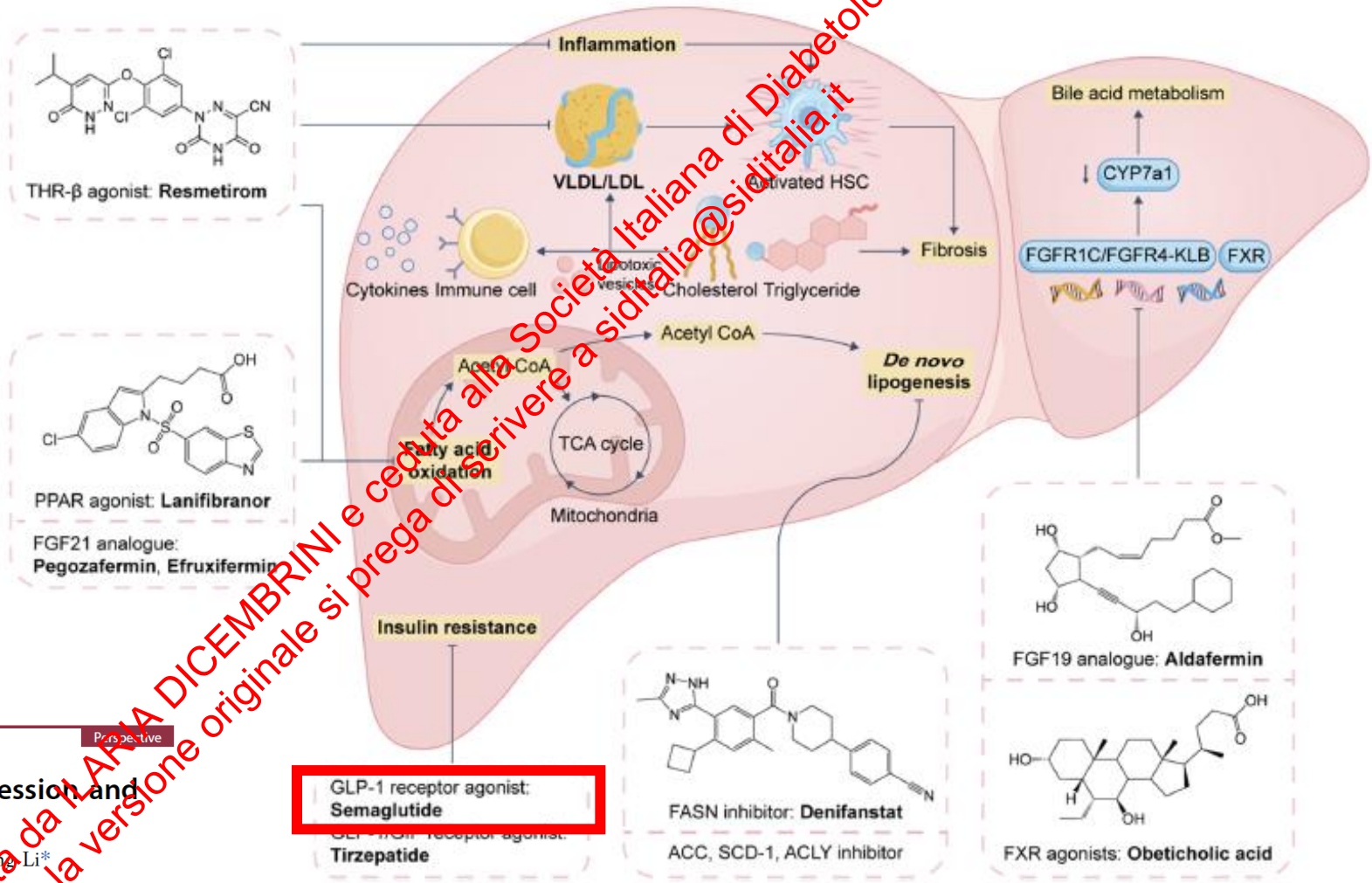
Journal of Medicinal Chemistry

pubs.acs.org/jmc Perspective

Targeting THR-β for MASLD Treatment: Current Progression and Emerging Prospects

Jingwei Li,[⊥] Ruixian Chen,[⊥] Jinhang Zhang,[⊥] Jinhan He, Yuxi Wang,* and Yanping Li*

Cite This: *J. Med. Chem.* 2026, 69, 823−844 Read Online



Li J et al. J Med Chem 69:823-44, 2026

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

ESSENCE trial

Treatment: semaglutide 2.4 mg OAW
Comparator: placebo
Principal outcome: cyrrhosis-free survival (composite of cyrrhosis and all-cause mortality)
Patients: 1,197 patients with MASH and fibrosis stage 2-3 (biopsy)
Follow-up: 240 wk

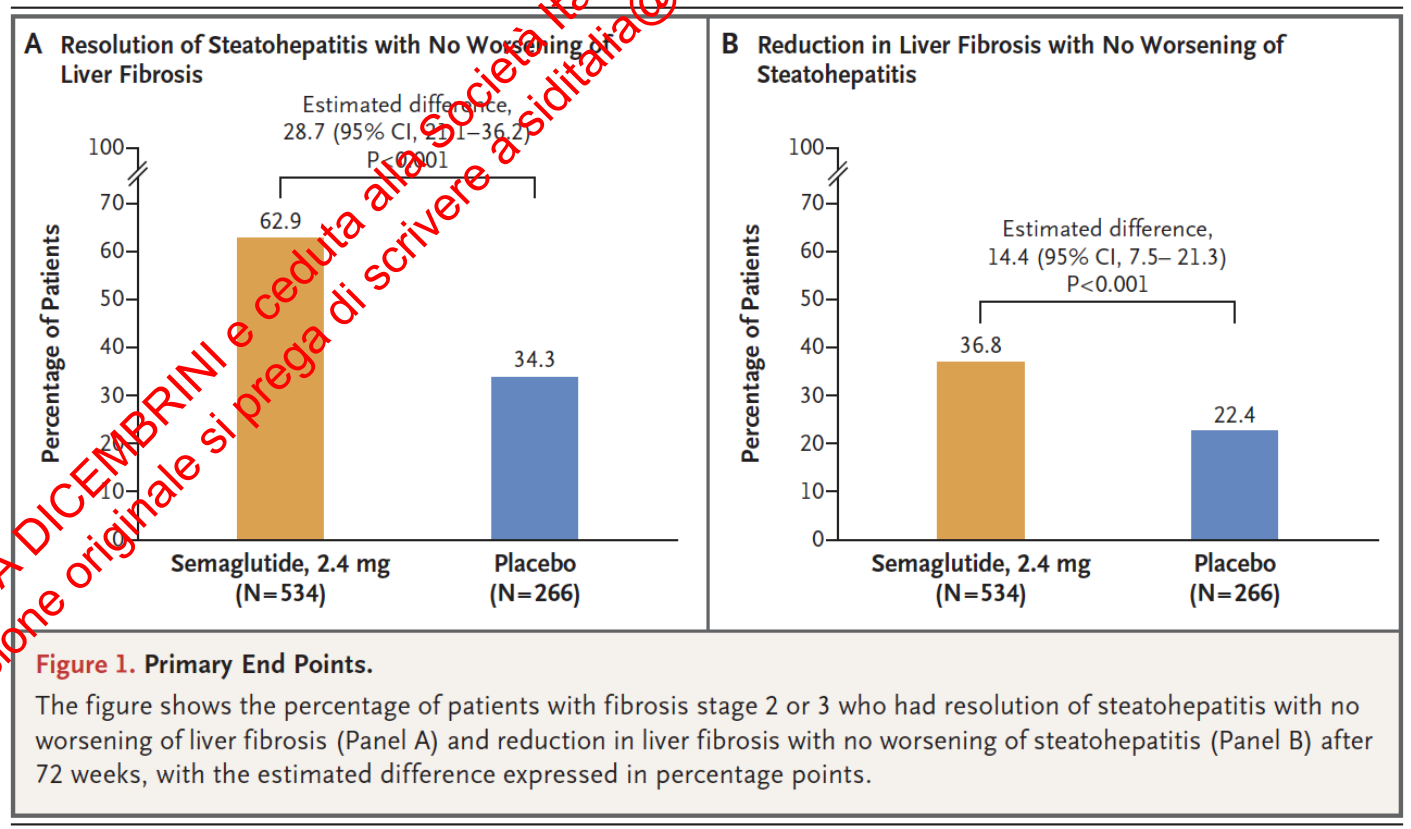


Figure 1. Primary End Points.
The figure shows the percentage of patients with fibrosis stage 2 or 3 who had resolution of steatohepatitis with no worsening of liver fibrosis (Panel A) and reduction in liver fibrosis with no worsening of steatohepatitis (Panel B) after 72 weeks, with the estimated difference expressed in percentage points.

Interim analysis at 72 wk

-11% weight

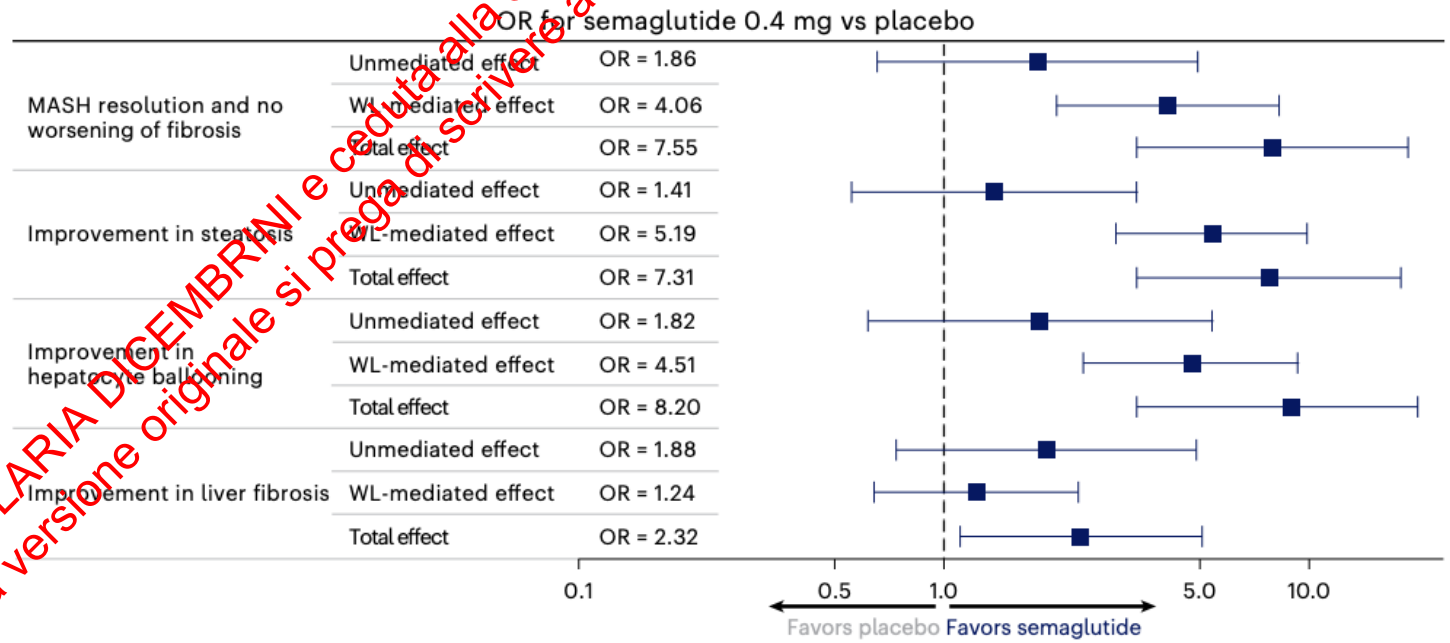
Sanyal AJ et al. *N Engl J Med* 2025

Article

Modulation of metabolic, inflammatory and fibrotic pathways by semaglutide in metabolic dysfunction-associated steatohepatitis

Mediation analysis using natural effects model of an RCT

Treatment: semaglutide 0.4 mg OAW
Comparator: placebo
Principal outcome: Histological resolution of steatohepatitis and no fibrosis worsening
Patients: 320 patients with MASH and fibrosis stage 1-3 (biopsy), BMI>25 kg/m²
Follow-up: 72 wk



Jara M et al. Nat Med. 2025 Sep;31(9):3128-3140.

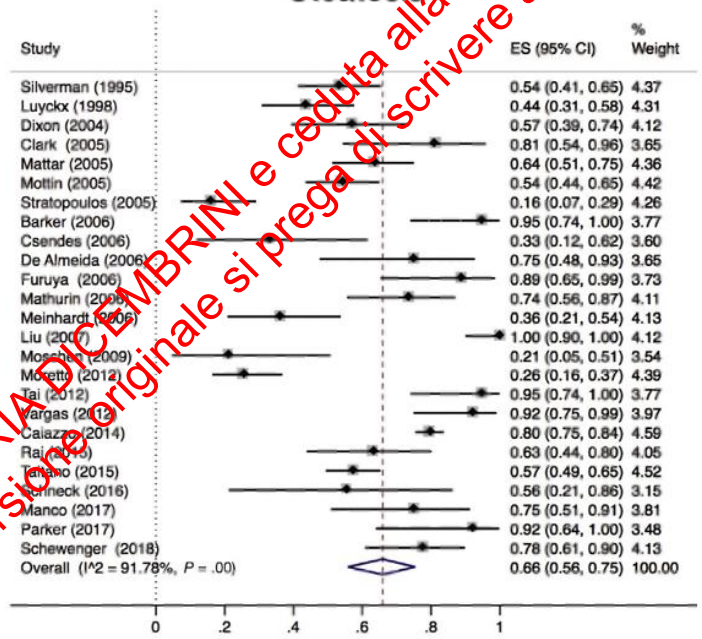
SYSTEMATIC REVIEWS AND META-ANALYSES

Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-analysis

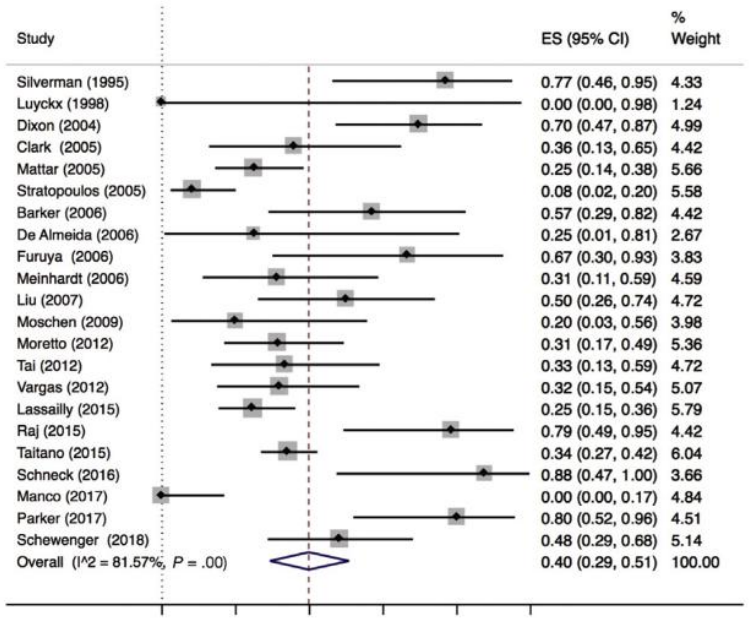
Systematic Meta-analysis
32 cohort studies

Treatment: bariatric surgery
Principal outcome: Histological NAFLD and NASH
Patients: 3,093 patients
Follow-up: 52 weeks

-66%



-40%



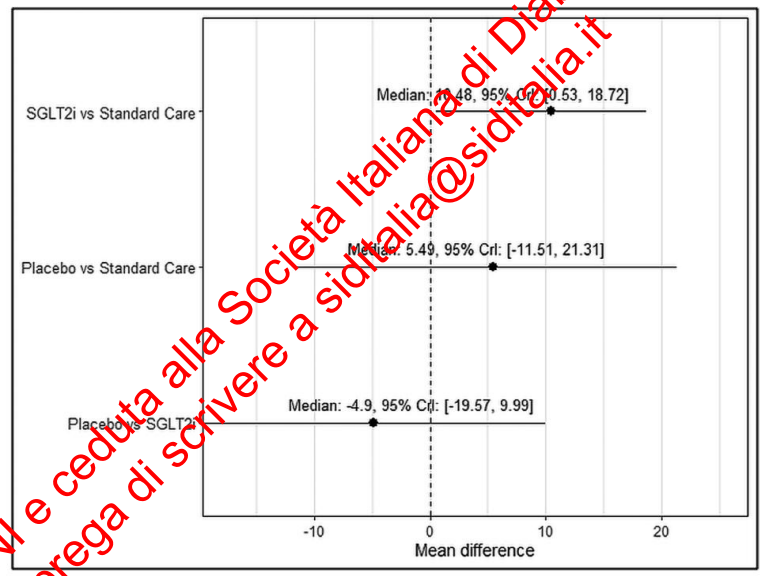
Lee Y et al. Clin Gastroenterol Hepatol. 2019;17(6):1040-1060

REVIEW ARTICLE OPEN ACCESS

Comparative Efficacy of SGLT2 Inhibitors in MASLD: Bayesian Network Meta-Analysis of CAP–LSM Outcomes and Time Effects

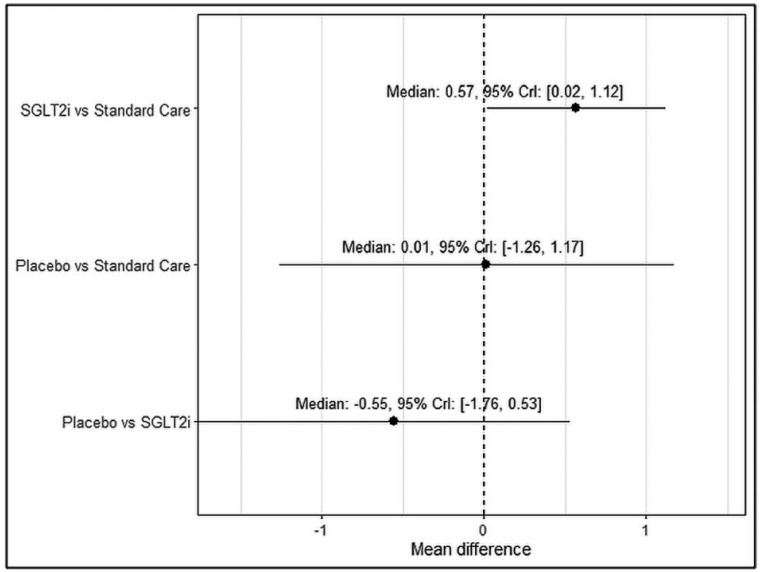
Network Metanalysis of RCT (n=14)

Treatment: SGLT-2i
Comparator: standard care
Principal outcome: controlled attenuation parameter (CAP) and liver stiffness measurement (LSM)
Patients: 855 MASLD patients
Follow-up: 6 months



CAP

LSM



Gomez DP et al. JGH Open. 2026;10(3):e70364.

Diabetes, Obesity and Metabolism

WILEY

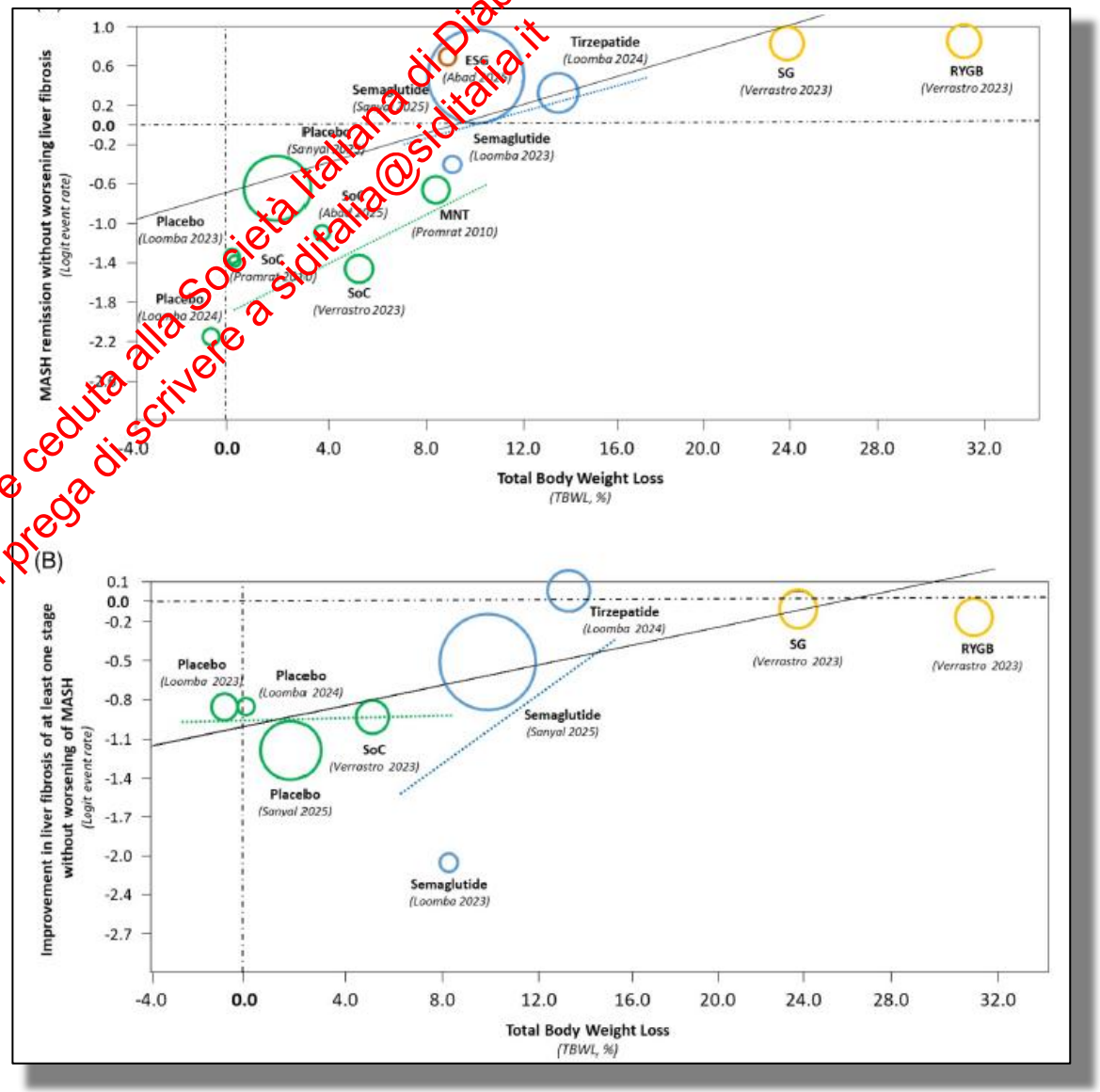
ORIGINAL ARTICLE OPEN ACCESS

Weight Loss as a Determinant of Histological Improvement in Metabolic Dysfunction-Associated Steatotic Liver Disease in People With Obesity. A Systematic Review and Network Meta-Analysis of Randomised Clinical Trials

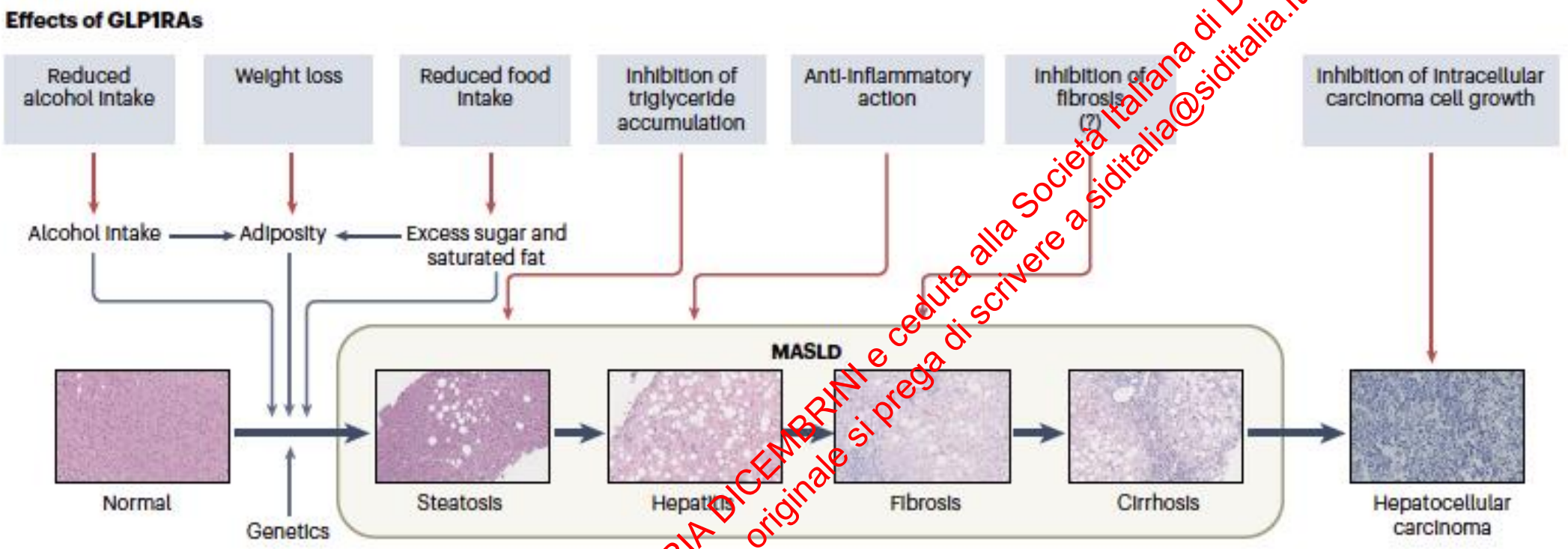
Matteo Monami[1] | Amanda Belluzzi[2] | Silvio Buscemi[3] | Luca Busetto[4] | Ricardo Cohen[5] | Maurizio De Luca[2] | Andrea Galli[1] | Edoardo Mannucci[1] | Tarissa Z. Petry[5] | Benedetta Ragghianti[1] | Paolo Sbraccia[6] | Dror Dicker[7]

Network Meta-analysis of RCTs

Treatment: any treatment for obesity
Comparator: placebo, any for obesity
Principal outcome: resolution of MASH
Patients: Obese with MASH



Monami M et al. Diabetes Obes Metab 28:4253-60; 2026




nature reviews clinical oncology

https://doi.org/10.1038/s41571-026-01135-0

Review article

Check for updates

Glucagon-like peptide 1 receptor agonists and cancer risk: the good, the bad and the unknown

Edoardo Mannucci & Ilaria Dicembrini

Mannucci E, Dicembrini I. Nature Rev Clin Oncol, 2026

UNIVERSITÀ DEGLI STUDI FIRENZE

nature reviews clinical oncology

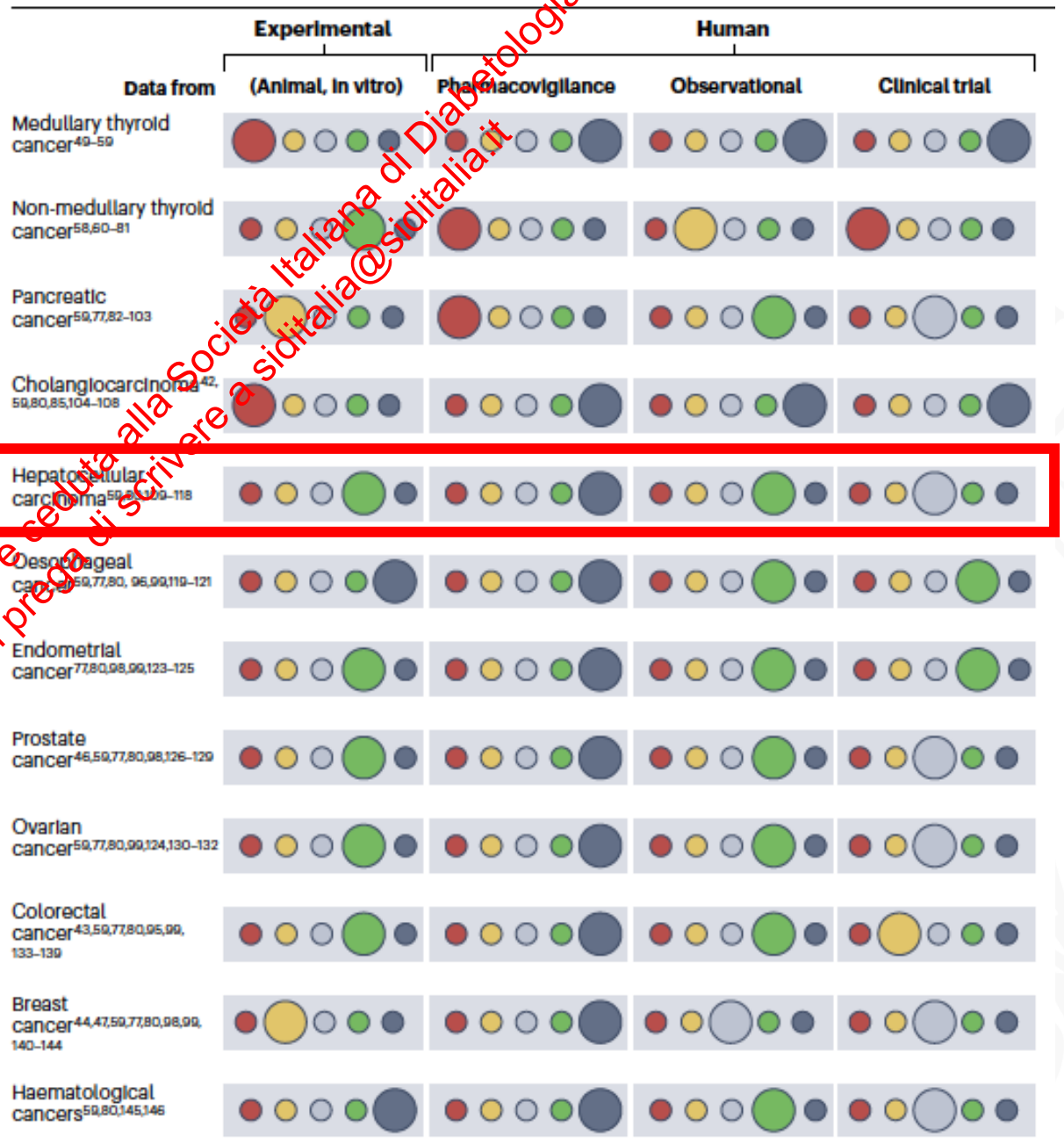
https://doi.org/10.1038/s41571-026-01135-0

Review article

Check for updates

Glucagon-like peptide 1 receptor agonists and cancer risk: the good, the bad and the unknown

Edoardo Mannucci & Ilaria Dicembrini



Mannucci E, Dicembrini I. Nature Rev Clin Oncol , 2026

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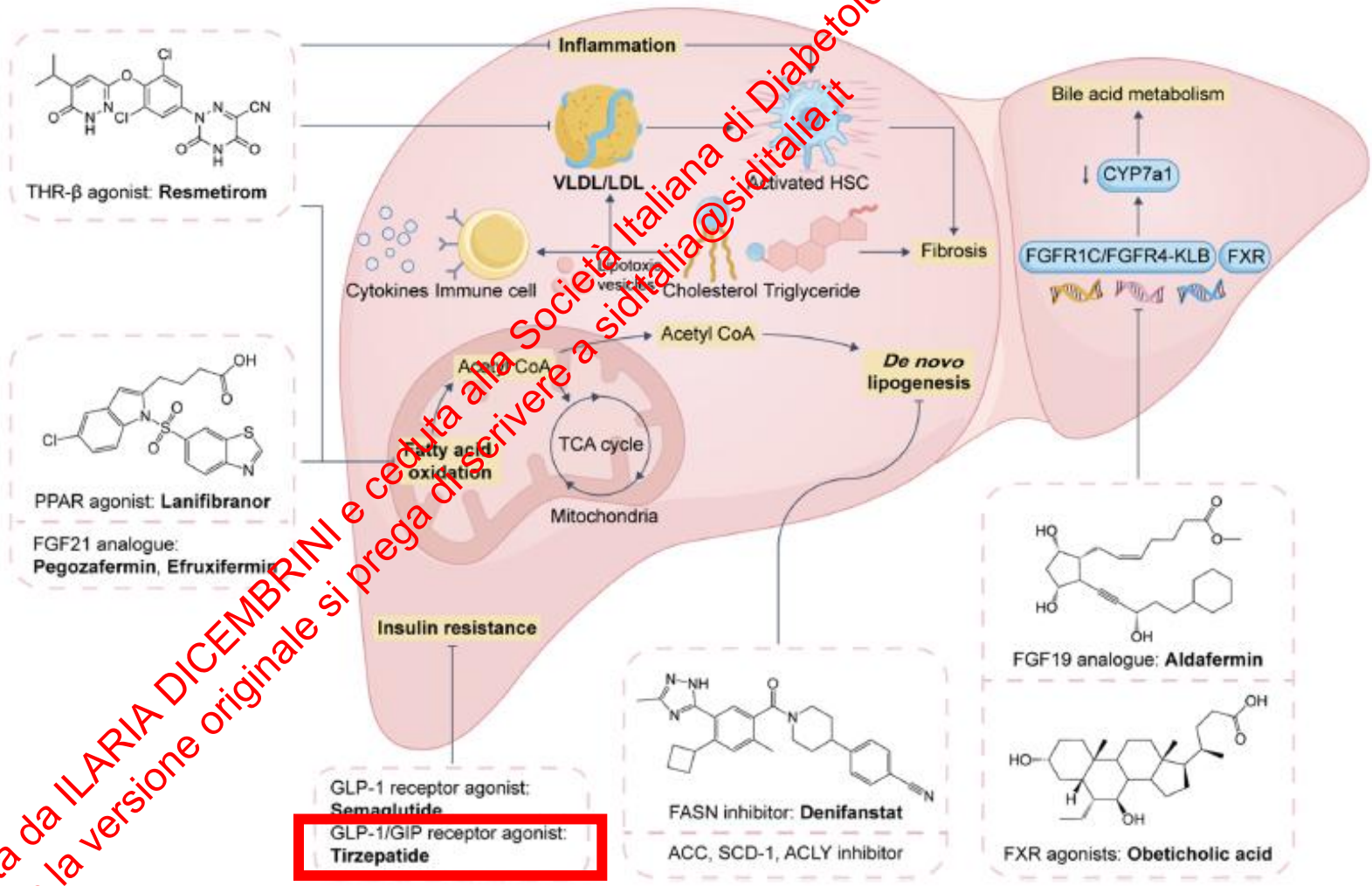
Journal of Medicinal Chemistry
pubs.acs.org/jmc Perspective

Targeting THR-β for MASLD Treatment: Current Progression and Emerging Prospects

Jingwei Li,[⊥] Ruixian Chen,[⊥] Jinhang Zhang,[⊥] Jinhan He, Yuxi Wang,* and Yanping Li*

Cite This: J. Med. Chem. 2026, 69, 823−844 Read Online



Li J et al. *J Med Chem* 69:823-44, 2026

The NEW ENGLAND JOURNAL of MEDICINE

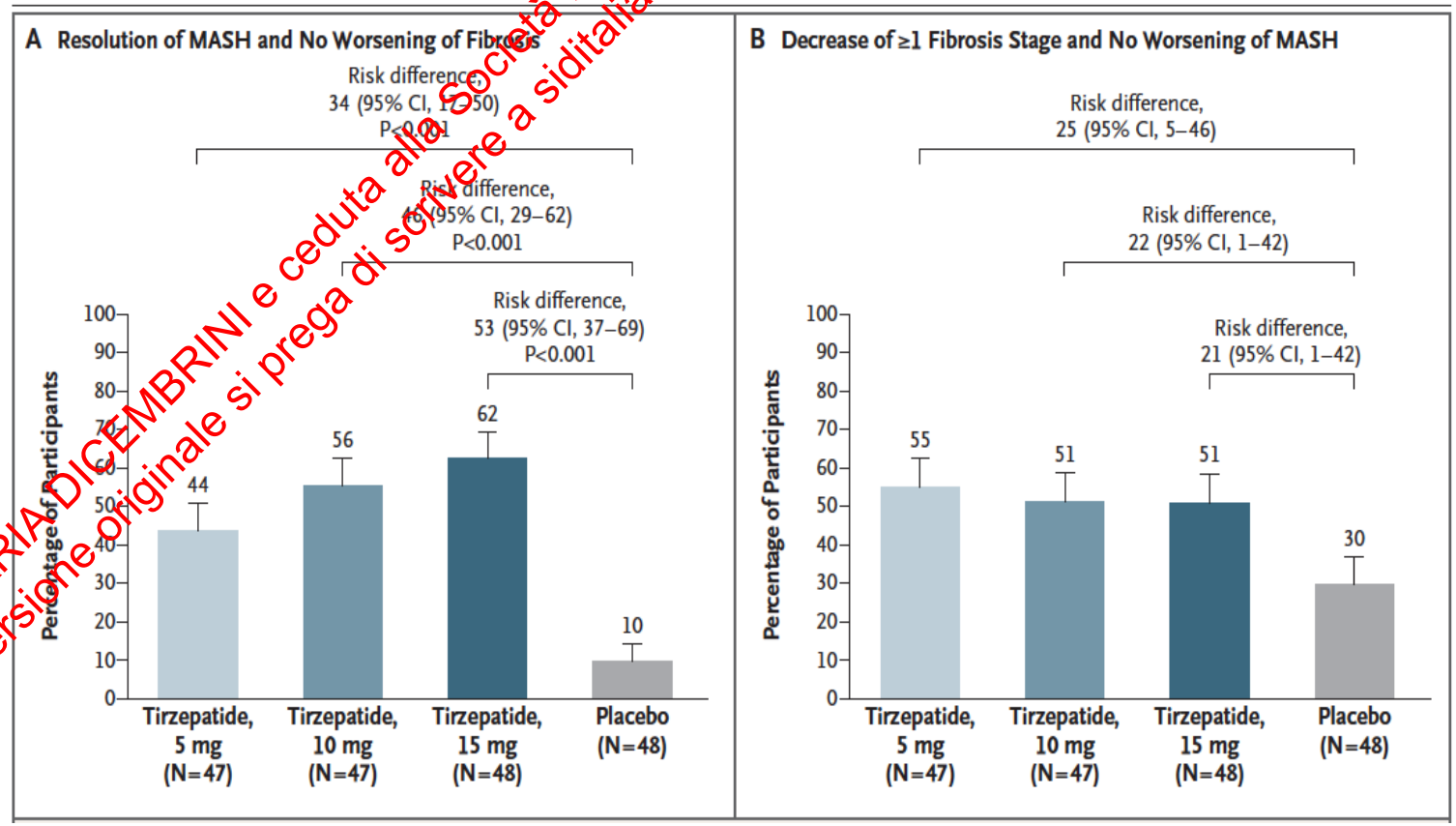
ESTABLISHED IN 1812 JULY 25, 2024 VOL. 391 NO. 4

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*

Phase 2 trial on MASH

Treatment: Tirzepatide 5-15 mg
Comparator: placebo
Principal outcome: Improvement of fibrosis with no worsening of MASH
Patients: 157 patients with MASH and moderate/severe fibrosis
Follow-up: 52 weeks



-10/-15% weight

Loomba R et al. *N Engl J Med* 391:299-310; 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

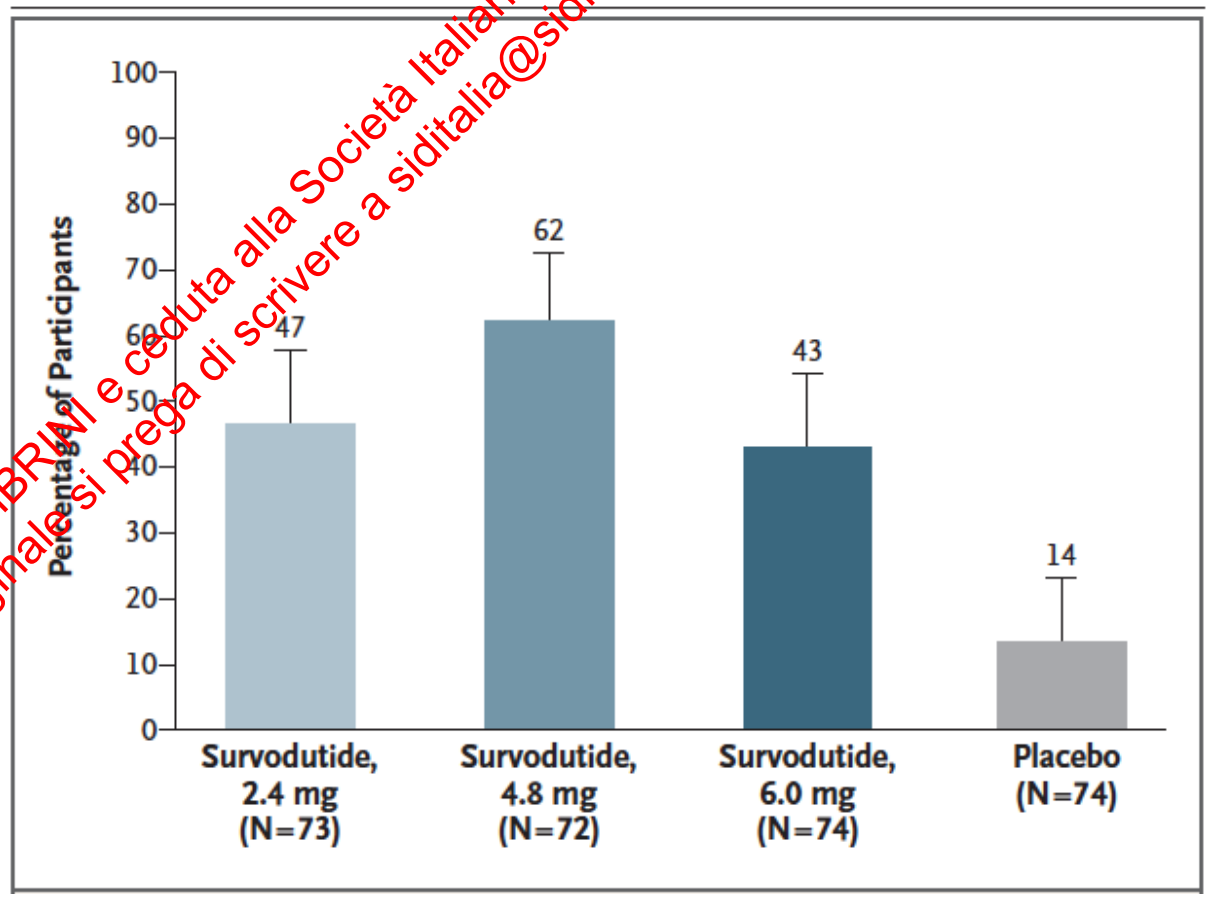
A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

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*

Phase 2 RCT on MASH

Treatment: Survodutide
Comparator: placebo
Patients: 247 with NASH, F1-F3 (biopsy)
Primary endpoint: Improvement MASH with no worsening of fibrosis
Follow-up: 24 wk

-19% weight with 4.8 mg



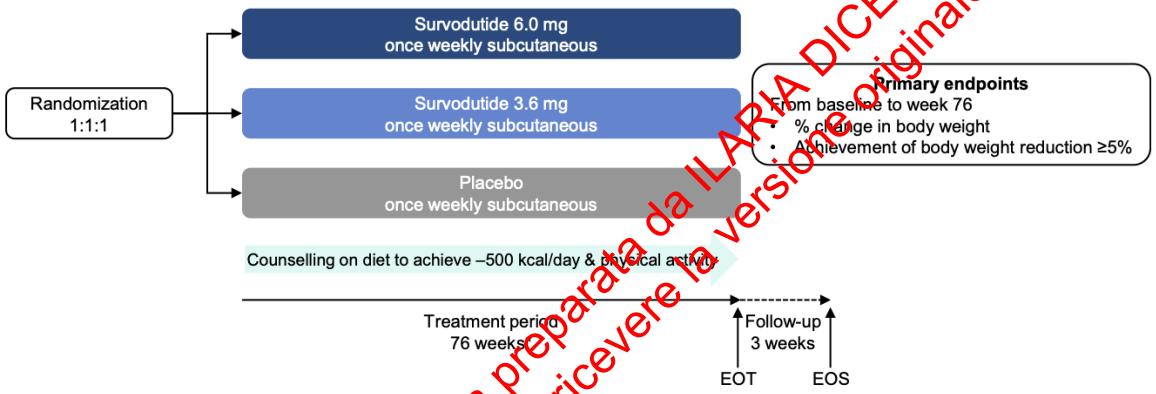
Sanyal AJ et al. *N Engl J Med* 391:311-9, 2024

ORIGINAL ARTICLE

WILEY

Baseline characteristics in the SYNCHRONIZE™-2 randomized phase 3 trial of survodutide, a glucagon receptor/GLP-1 receptor dual agonist, for obesity in people with type 2 diabetes

Sean Wharton MD[1,2] | Carel W. le Roux MBChB[3,4] | Biykem Bozkurt MD[5] | Elke Platz MD[6] | Gabriele Bleckert PhD[7] | Samina Ajaz Hussain MD[8] | Martina Brueckmann MD[8,9] | Elena Startseva MD[8] | Isabel M. Kloer MD[8] | Lee M. Kaplan MD[10]



Wharton S, et al Diabetes Obes Metab. 2026;28(2):1490-1498.

BRIEF REPORT

Survodutide for the Treatment of Obesity

Baseline Characteristics of the SYNCHRONIZE Cardiovascular Outcomes Trial

Elke Platz, MD, MS,[a] Lee M. Kaplan, MD, PhD,[b] Carel W. le Roux, MD, PhD,[c] Sean Wharton, MD,[d] Svenja Burger, PhD,[e] Samina Ajaz Hussain, MD,[f] Martina Brueckmann, MD,[f,g] Elena Startseva, MD, MBA,[f] Constanze Fey, PhD,[f] Mikhail N. Kosiborod, MD,[h] Biykem Bozkurt, MD, PhD[i]

Representative, high-risk population

	Age	Women	BMI	eGFR <60 ml/min/1.73 m²	HbA1c ≥6.5%
Overall cohort (n=5,508)	61 years	40%	37 kg/m²	21%	30%

	Age	Women	BMI	NYHA II/III	NT-proBNP	KCCQ-CSS
Heart failure sub-cohort (n=596)	64 years	35%	39 kg/m²	81%/16%	426 pg/ml	67

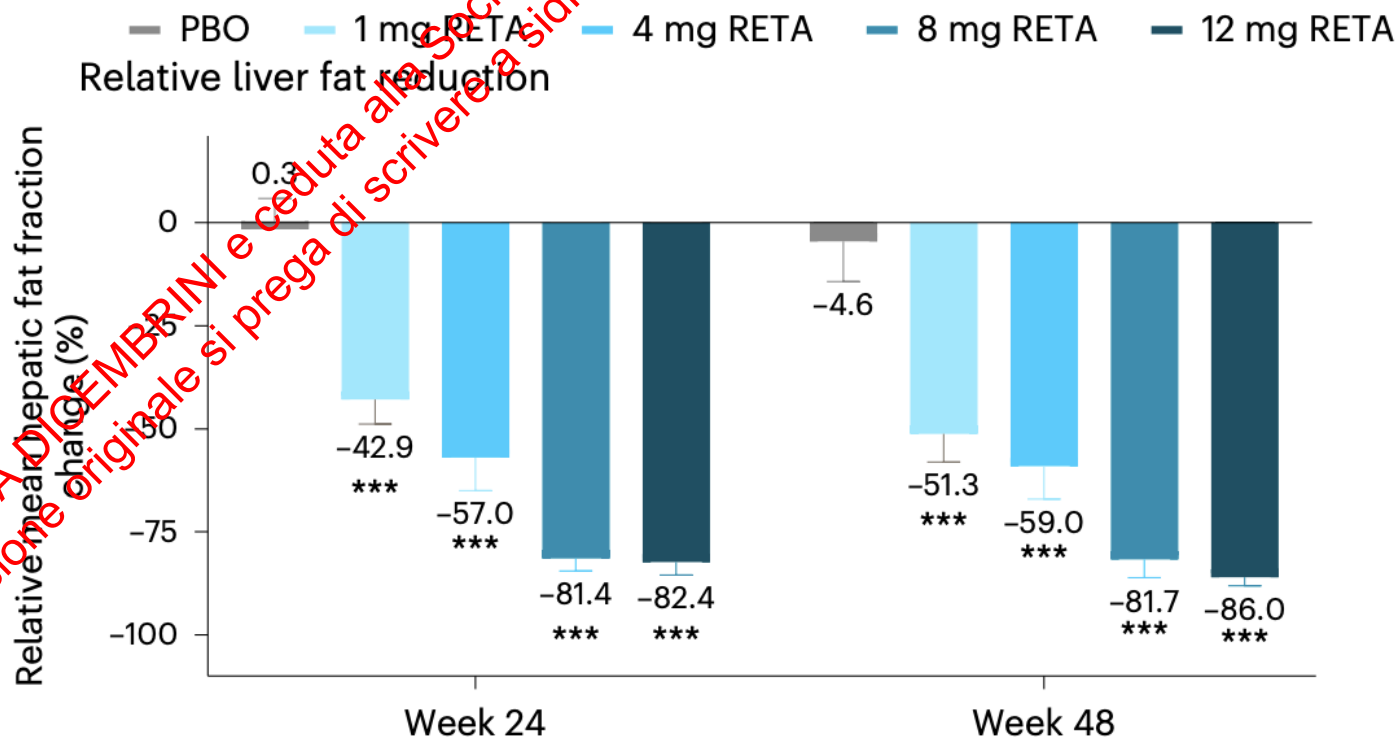
Platz E, et al. JACC Heart Fail. 2026 May;14(5):102780.

Article

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

Phase 2a RCT on MASH

Treatment: Retatrutide (1, 4, 8 or 12 mg/week)
Comparator: placebo
Patients: 247 with NASH, F1-F3 (biopsy)
Primary endpoint: liver fat (LF by magnetic resonance imaging proton density fat fraction (MRI–PDFF) at 24 week
Follow-up: 48 wk



-9/-26% weight

Sanyal AJ et al. Nat Med. 2024;30(7):2037-2048.

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Journal of Medicinal Chemistry
pubs.acs.org/jmc Perspective

Targeting THR-β for MASLD Treatment: Current Progression and Emerging Prospects

Jingwei Li,[⊥] Ruixian Chen,[⊥] Jinhang Zhang,[⊥] Jinhan He, Yuxi Wang,* and Yanping Li*

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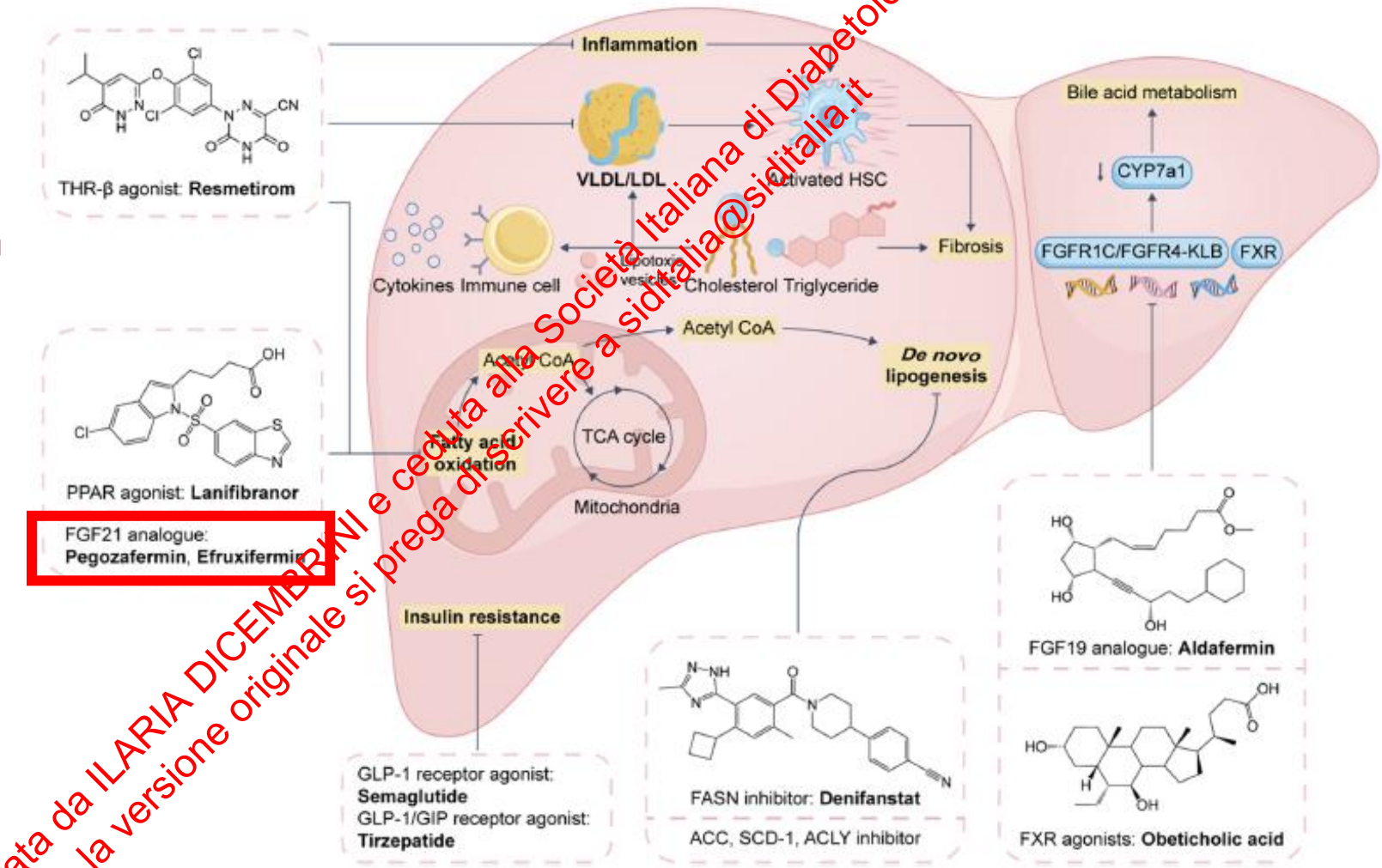


Li J et al. *J Med Chem* 69:823-44, 2026

Articles

Safety and efficacy of once-weekly efruxifermin versus placebo in metabolic dysfunction-associated steatohepatitis (HARMONY): 96-week results from a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial

Mazen Noureddin, Juan P Frias, Guy W Neff, K Jean Lucas, Cynthia Behling, Pierre Bedossa, Julie Dubourg, Doreen Chan, Mark Burch, Erica Fong, Brittany de Temple, Matt Minerva, Kim Barrett, Reshma Shringarpure, Erik J Tillman, Timothy Rolph, Andrew Cheng, Kitty Yale

HARMONY (phase 2b) RCT

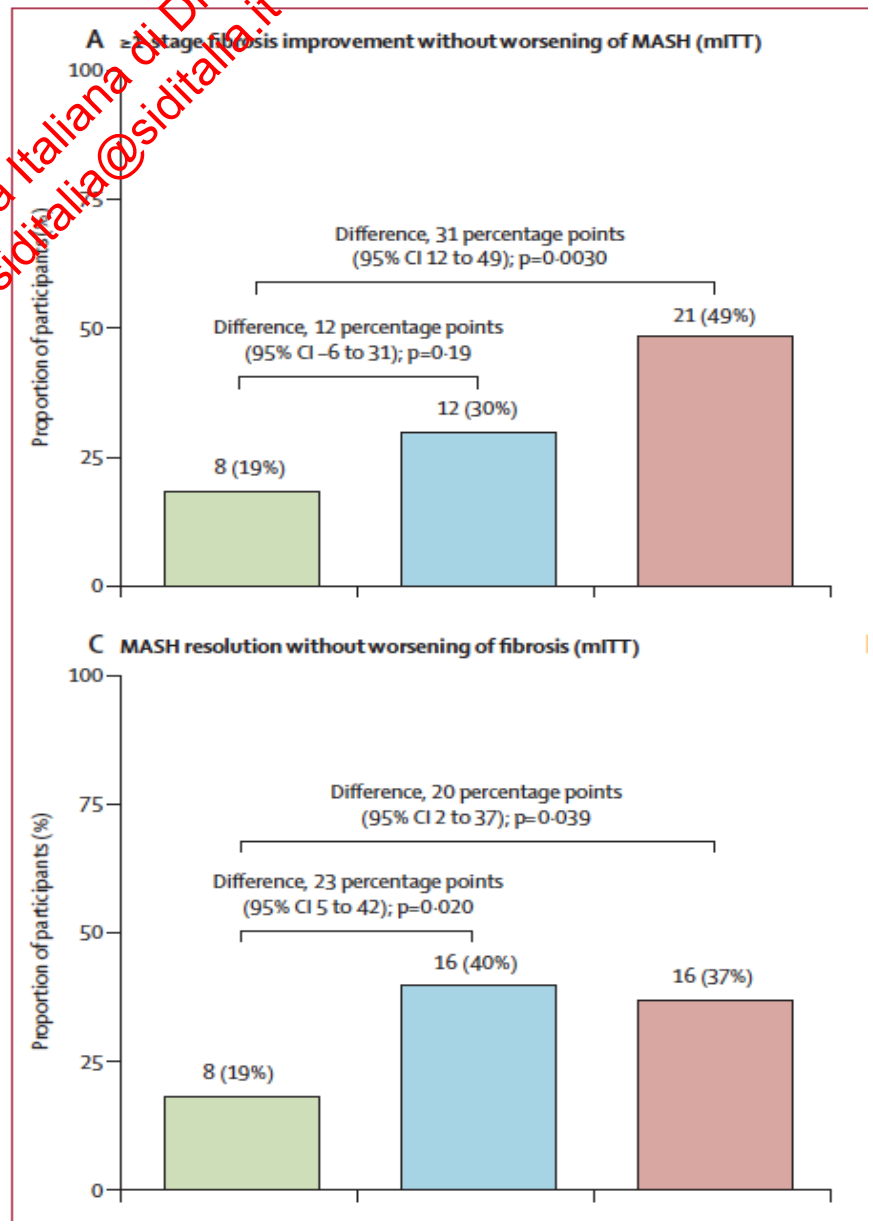
Treatment: Efruxifermin 28 or 50 mg

Comparator: placebo

Patients: 126 with MASH, F2-F3 (biopsy)

Primary endpoint: Improvement fibrosis with no worsening of MASH

Follow-up: 96 wk



Noureddin M et al. Lancet 406:719-30, 2025

UNIVERSITÀ DEGLI STUDI FIRENZE

Journal of Medicinal Chemistry
pubs.acs.org/jmc Perspective

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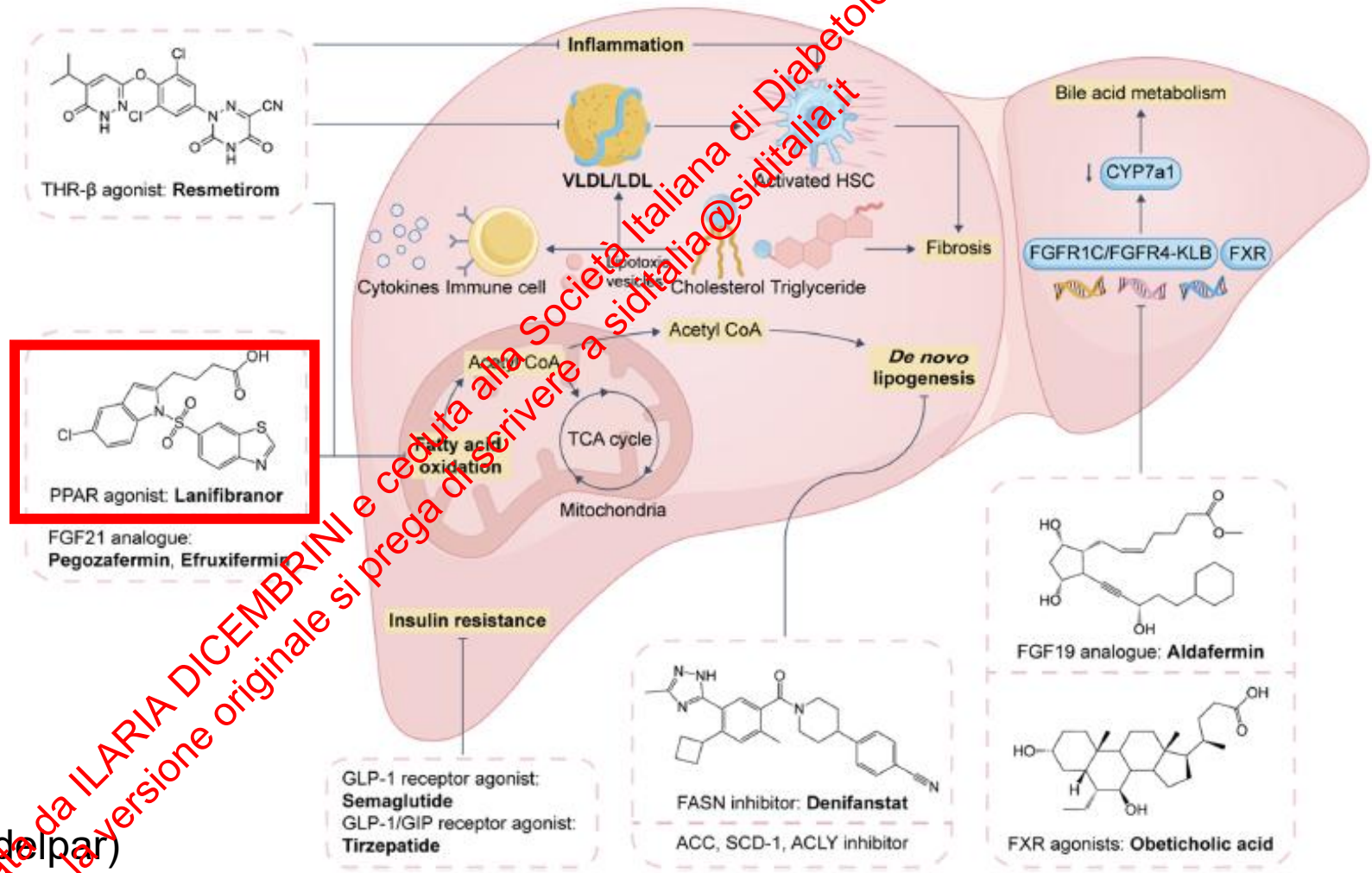
Jingwei Li,[⊥] Ruixian Chen,[⊥] Jinhang Zhang,[⊥] Jinhan He, Yuxi Wang,* and Yanping Li*

Cite This: *J. Med. Chem.* 2026, 69, 823−844 Read Online



γ (pioglitazone), ⍺ (fibrati), δ (seladelpar)

Li J et al. *J Med Chem* 69:823-44, 2026

Annals of Internal Medicine ORIGINAL RESEARCH

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized Trial

Kenneth Cusi, MD; Beverly Orsak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fermin Tio, MD; Jean Hardies, PhD; Celia Darland, RD; Nicolas Musi, MD; Amy Webb, MD; and Paola Portillo-Sanchez, MD

RCT
Treatment: Pioglitazone
Comparator: placebo
Patients: 101 IGT/T2DM with NASH (biopsy)
Primary endpoints: Improv. NASH with no wors. fibrosis
Follow-up: 18 mo (+ 18 mo open-label pioglitazone)

Table 2. Effect of 18 mo of Pioglitazone Treatment on Primary and Secondary Liver Histologic Outcomes*

Outcome	Placebo (n = 51)	Pioglitazone (n = 50)	Treatment Difference (95% CI)	P Value
Primary outcome				
≥2-point reduction in NAS (in 2 categories) without worsening of fibrosis, *n (%)*	9 (17)	29 (58)	41 (23 to 59)	<0.001
Secondary outcomes				
Resolution of NASH, *n (%)*†	10 (19)	26 (51)	32 (13 to 51)	<0.001
Steatosis				
≥1-point improvement, *n (%)*	13 (26)	35 (71)	44 (25 to 63)	<0.001
Mean change in score (SD)	−0.2 (0.8)	−1.1 (1.0)	−0.9 (−1.3 to −0.5)	<0.001
Inflammation				
≥1-point improvement, *n (%)*	11 (22)	25 (49)	27 (8 to 46)	0.004
Mean change in score (SD)	−0.1 (0.8)	−0.6 (0.9)	−0.6 (−0.9 to −0.2)	<0.001
Ballooning				
≥1-point improvement, *n (%)*	12 (24)	25 (51)	27 (7 to 47)	0.004
Mean change in score (SD)	−0.2 (0.7)	−0.6 (0.6)	−0.4 (−0.7 to −0.2)	0.001
Fibrosis				
≥1-point improvement, *n (%)*	13 (25)	20 (39)	14 (−6 to 34)	0.130
Mean change in score (SD)	0 (1.2)	−0.5 (1.0)	−0.5 (−0.9 to 0)	0.039

Cusi K et al. Ann Intern Med 165:305-15, 2016

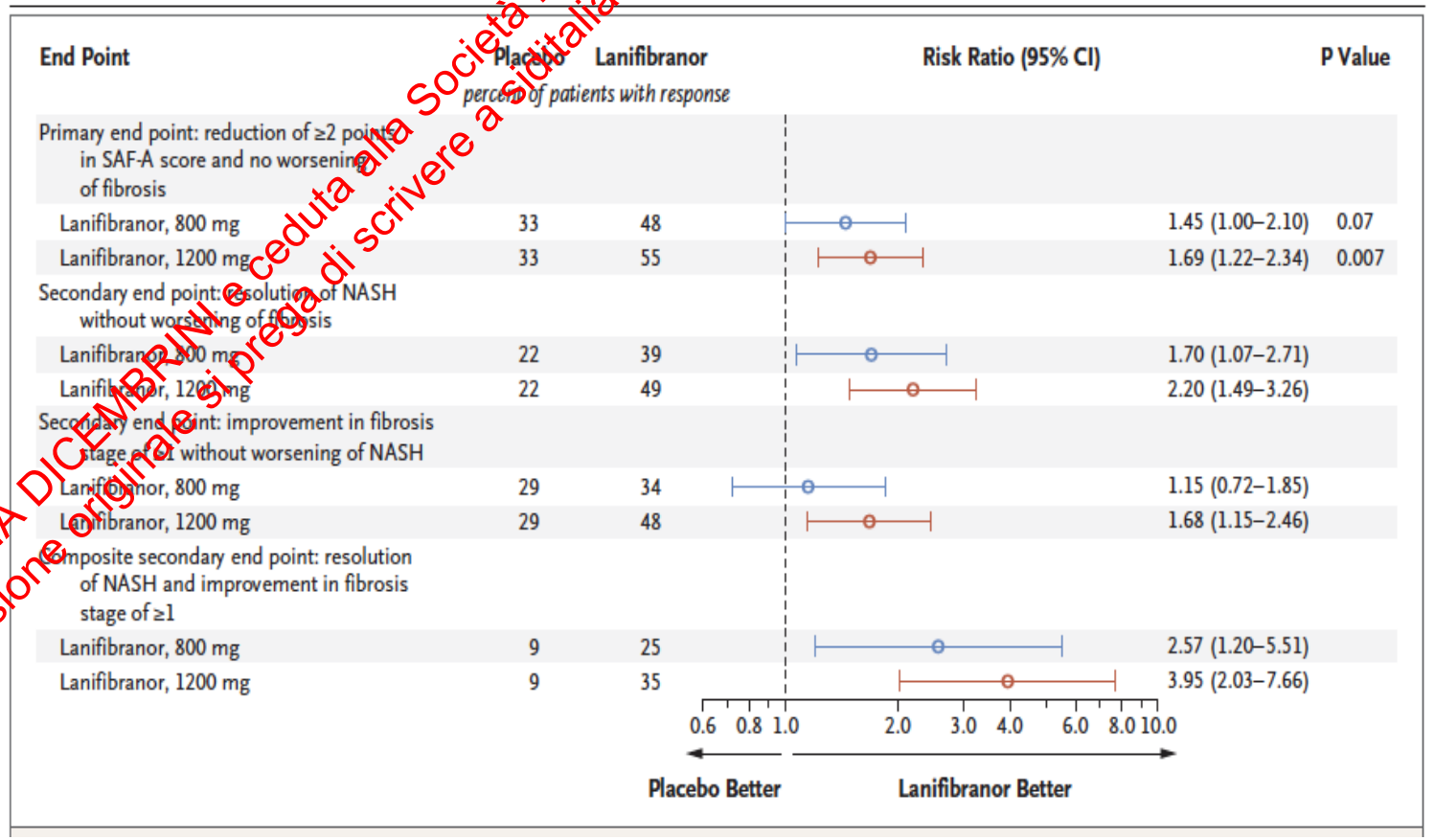
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2021 VOL. 385 NO. 17

A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

S.M. Francque, P. Bedossa, V. Ratziu, Q.M. Anstee, E. Bugianesi, A.J. Sanyal, R. Loomba, S.A. Harrison, R. Balabanska, L. Mateva, N. Lanthier, N. Alkhouri, C. Moreno, J.M. Schattenberg, D. Stefanova-Petrova, L. Vonghia, R. Rouzier, M. Guillaume, A. Hodge, M. Romero-Gómez, P. Huot-Marchand, M. Baudin, M.-P. Richard, J.-L. Abitbol, P. Broqua, J.-L. Junien, and M.F. Abdelmalek, for the NATIVE Study Group*

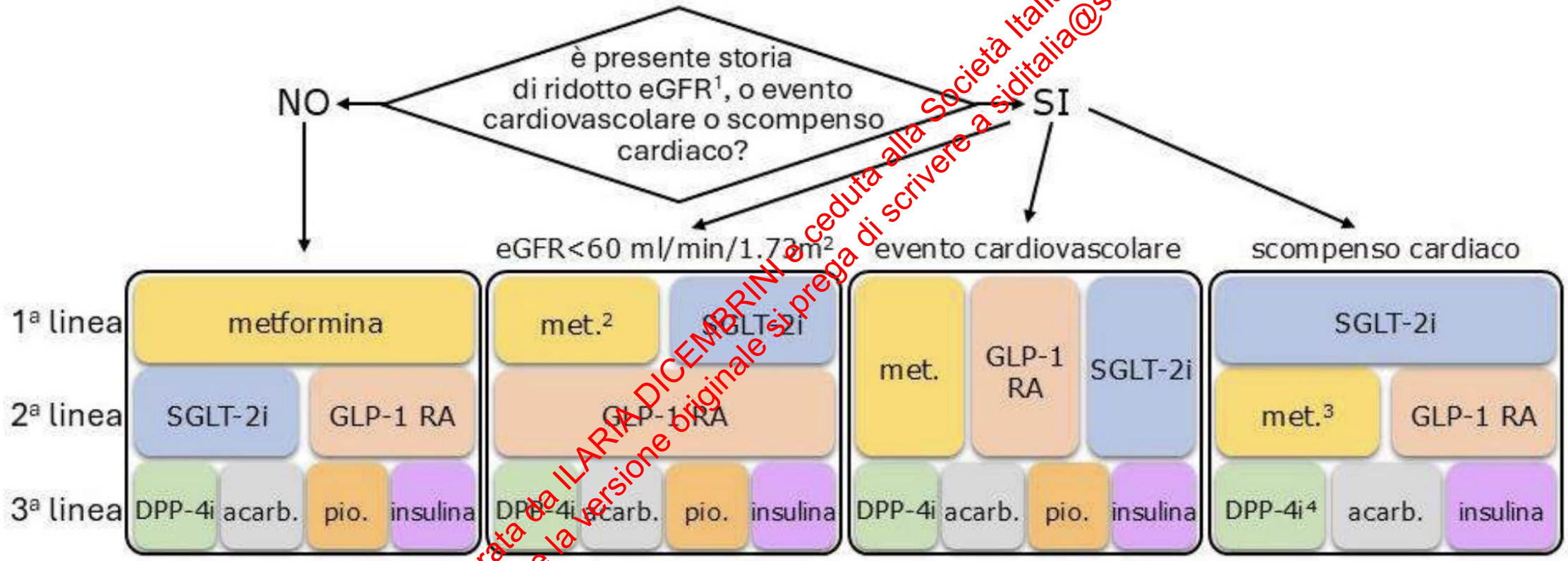
NATIVE (phase 2b) RCT
Treatment: Lanfibranor
Comparator: placebo
Patients: 247 with NASH, F1-F3 (biopsy)
Primary endpoint: Improv. NASH
Follow-up: 24 wk



Francque SM et al. *N Engl J Med* 385:1547-58, 2021

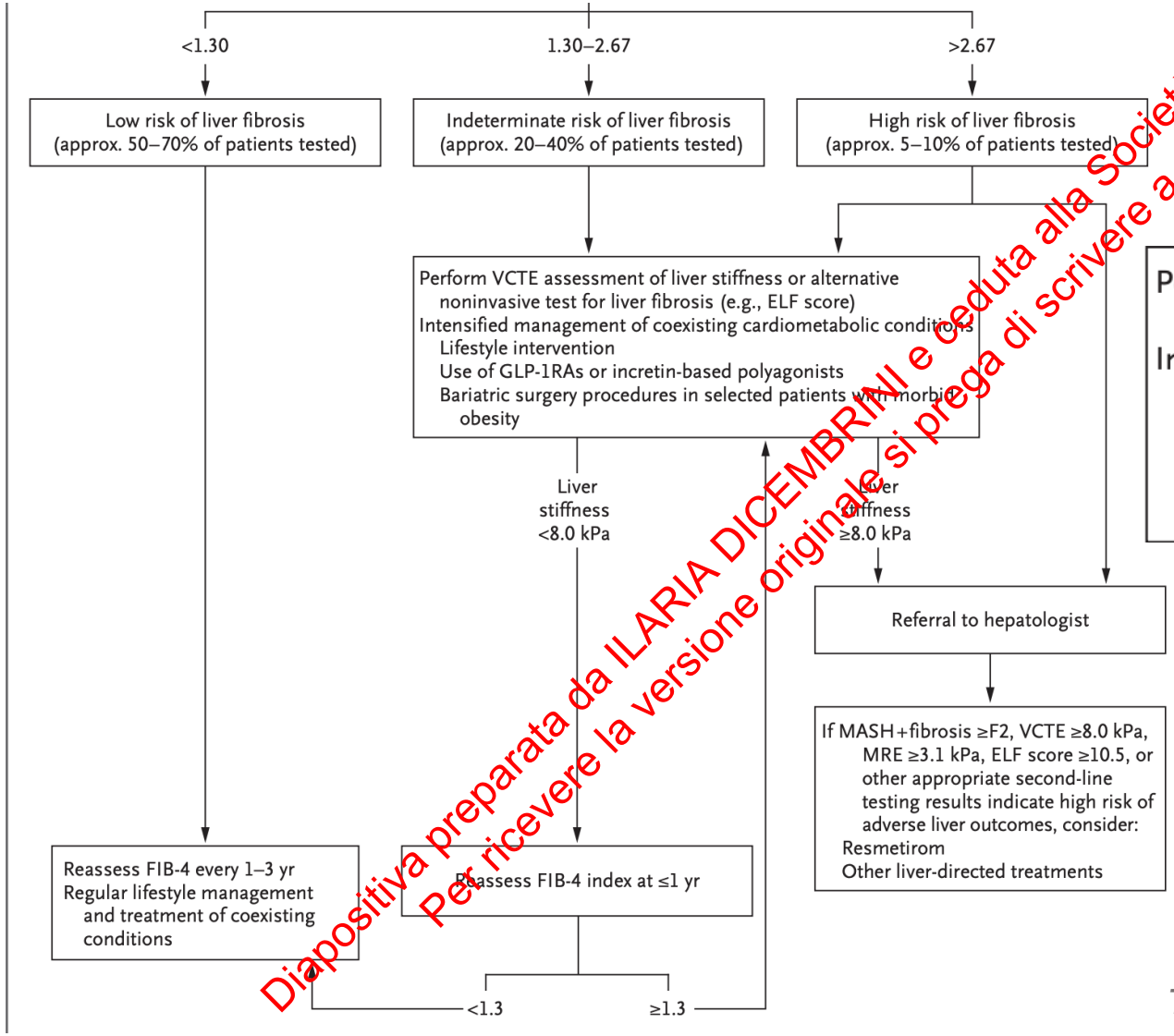
Italian Guidelines for the treatment of T2 Diabetes, 2025

Drug therapy



NB: l'indicazione ai farmaci di terza linea (DPP-4i, acarbosio, pioglitazone, insulina) deve essere considerata solo dopo l'utilizzo in combinazione di metformina, SGLT-2i e GLP-1 RA, qualora tollerati e non controindicati. L'indicazione per DPP-4i è valida solo se GLP-1 RA non indicati o non tollerati. 1. si intende eGFR secondo CKD-EPI < 60 ml/min/1.73m²; 2. se la metformina non è controindicata per eGFR<30 ml/min/1.73m²; 3. se la metformina non è controindicata per ridotta funzione cardiaca; 4. eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.

Algoritmo diagnostico per la stratificazione mediante FIB-4 e VCTE



Perform VCTE assessment of liver stiffness or alternative noninvasive test for liver fibrosis (e.g., ELF score)
Intensified management of coexisting cardiometabolic conditions
Lifestyle intervention
Use of GLP-1RAs or incretin-based polyagonists
Bariatric surgery procedures in selected patients with morbid obesity

Targher G, et al. N Engl J Med. 2025;393(7):683-698.