Management of patients with NASH: is it the main problem?

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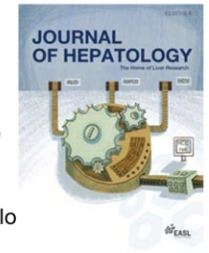
New nomenclature

SPECIAL ARTICLE

A multi-society Delphi consensus statement on new fatty liver disease nomenclature

Rinella, Mary E.[1]; Lazarus, Jeffrey V.[2,3]; Ratziu, Vlad[4]; Francque, Sven M.[5,6]; Sanyal, Arun J.[7]; Kanwal, Fasiha[8,9]; Romero, Diana[2]; Abdelmalek, Manal F.[10]; Anstee, Quentin M.[11,12]; Arab, Juan Pablo[13,14,15]; Arrese, Marco[15,16]; Bataller, Ramon[17]; Beuers, Ulrich[18]; Boursier, Jerome[19]; Bugianesi, Elisabetta[20]; Byrne, Christopher[21,22]; Castro Narro, Graciela E.[16,23,24]; Chowdhury, Abhijit[25]; Cortez-Pinto, Helena[26]; Cryer, Donna[27]; Cusi, Kenneth[28]; El-Kassas, Mohamed[29]; Klein, Samuel[30]; Eskridge, Wayne[31]; Fan, Jiangao[32]; Gawrieh, Samer[33]; Guy, Cynthia D.[34]; Harrison, Stephen A.[35]; Kim, Seung Up[36]; Koot, Bart[37]; Korenjak, Marko[38]; Kowdley, Kris[39]; Lacaille, Florence[40]; Loomba, Rohit[41]; Mitchell-Thain, Robert[42]; Morgan, Timothy R.[43,44]; Powell, Elisabeth[45,46,47]; Roden, Michael[48,49,50]; Romero-Gómez, Manuel[51]; Silva, Marcelo[52]; Singh, Shivaram Prasad[53]; Sookoian, Silvia C.[15,54,55]; Spearman, C. Wendy[56]; Tiniakos, Dina[11,57]; Valenti, Luca[58,59]; Vos, Miriam B.[60]; Wong, Vincent Wai-Sun[61]; Xanthakos, Stavra[62]; Yilmaz, Yusuf[63]; Younossi, Zobair[64]; Hobbs, Ansley[2]; Villota-Rivas, Marcela[65]; Newsome, Philip N[66,67]; on behalf of the NAFLD Nomenclature consensus group

Journal Pre-proof



A multi-society Delphi consensus statement on new fatty liver disease nomenclature

Mary E. Rinella, Jeffrey V. Lazarus, Vlad Ratziu, Sven M. Francque, Arun J. Sanyal, Fasiha Kanwal, Diana Romero, Manal F. Abdelmalek, Quentin M. Anstee, Juan Pablo Arab, Marco Arrese, Ramon Bataller, Ulrich Beuers, Jerome Boursier, Elisabetta Bugianesi, Christopher D. Byrne, Graciela E. Castro Narro, Abhijit Chowdhury, Helena Cortez-Pinto, Donna Cryer, Kenneth Cusi, Mohamed El-Kassas, Samuel Klein, Wayne Eskridge, Jiangao Fan, Samer Gawrieh, Cynthia D. Guy, Stephen A. Harrison, Seung Up Kim, Bart Koot, Marko Korenjak, Kris Kowdley, Florence Lacaille, Rohit Loomba, Robert Mitchell-Thain, Timothy R. Morgan, Elisabeth Powell, Michael Roden, Manuel Romero-Gómez, Marcelo Silva, Shivaram Prasad Singh, Silvia C. Sookoian, C. Wendy Spearman, Dina Tiniakos, Luca Valenti, Miriam B. Vos, Vincent Wai-Sun Wong, Stavra Xanthakos, Yusuf Yilmaz, Zobair Younossi, Ansley Hobbs, Marcela Villota-Rivas, Philip N. Newsome, senior, on behalf of the NAFLD Nomenclature consensus group

ELSEVIER

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In Press, Journal Pre-proof What's this?

A multi-society Delphi consensus statement on new fatty liver disease nomenclature

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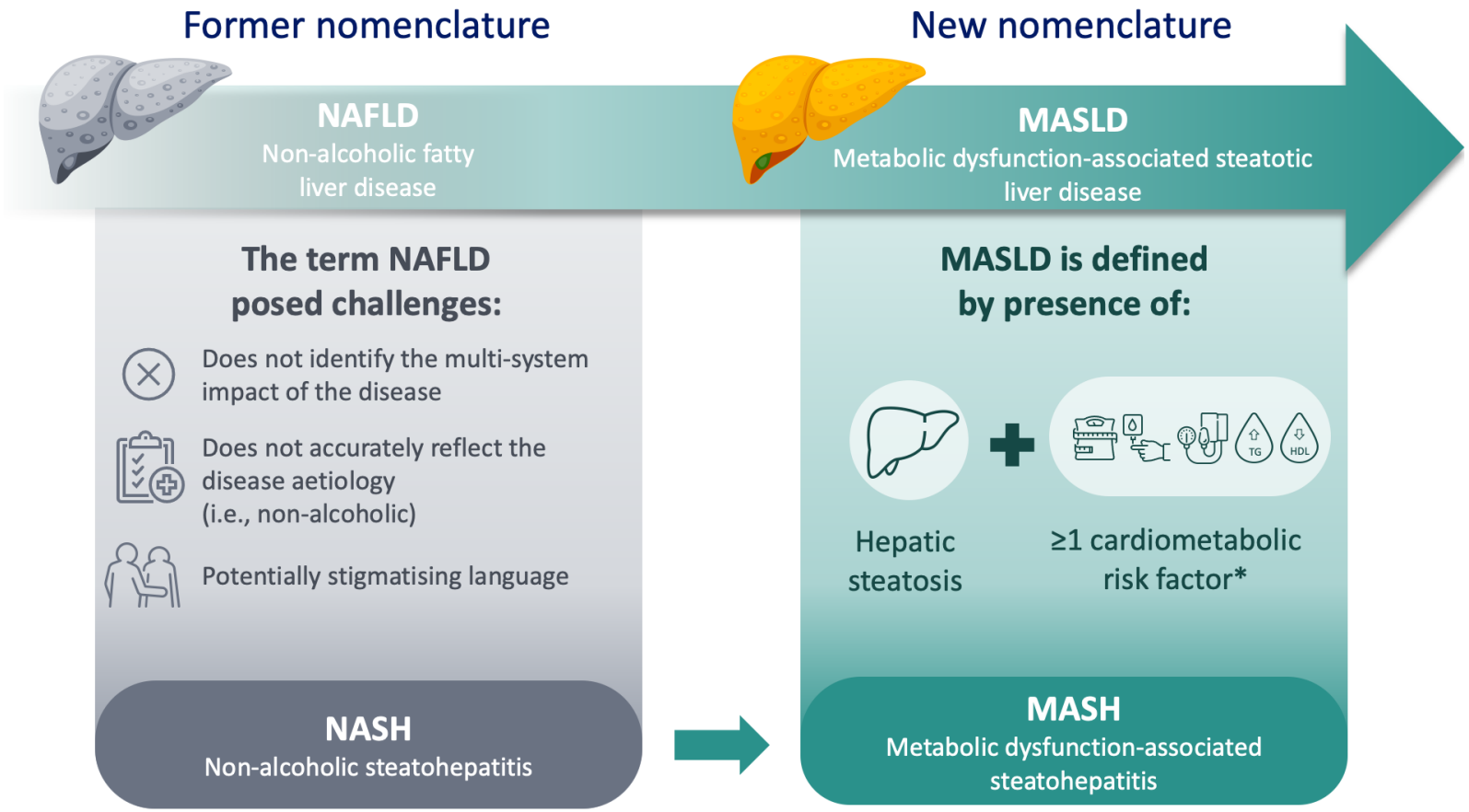
MASLD: epatopatia dismetabolica



Rinella ME et al; NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023 & Hepatology 2023

*Cardiometabolic criteria

Adult Criteria

At least 1 out of 5:

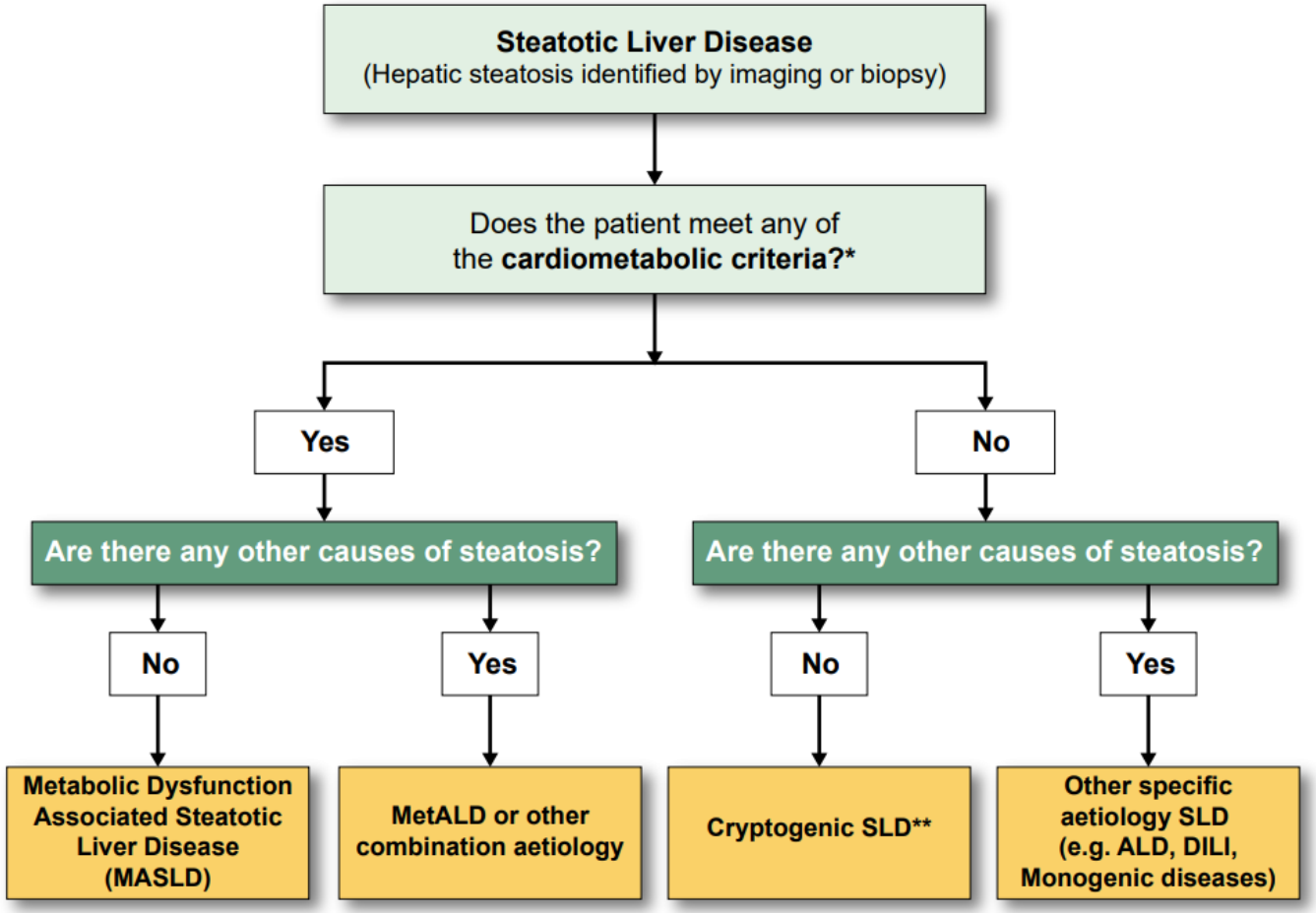
- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

Pediatric Criteria

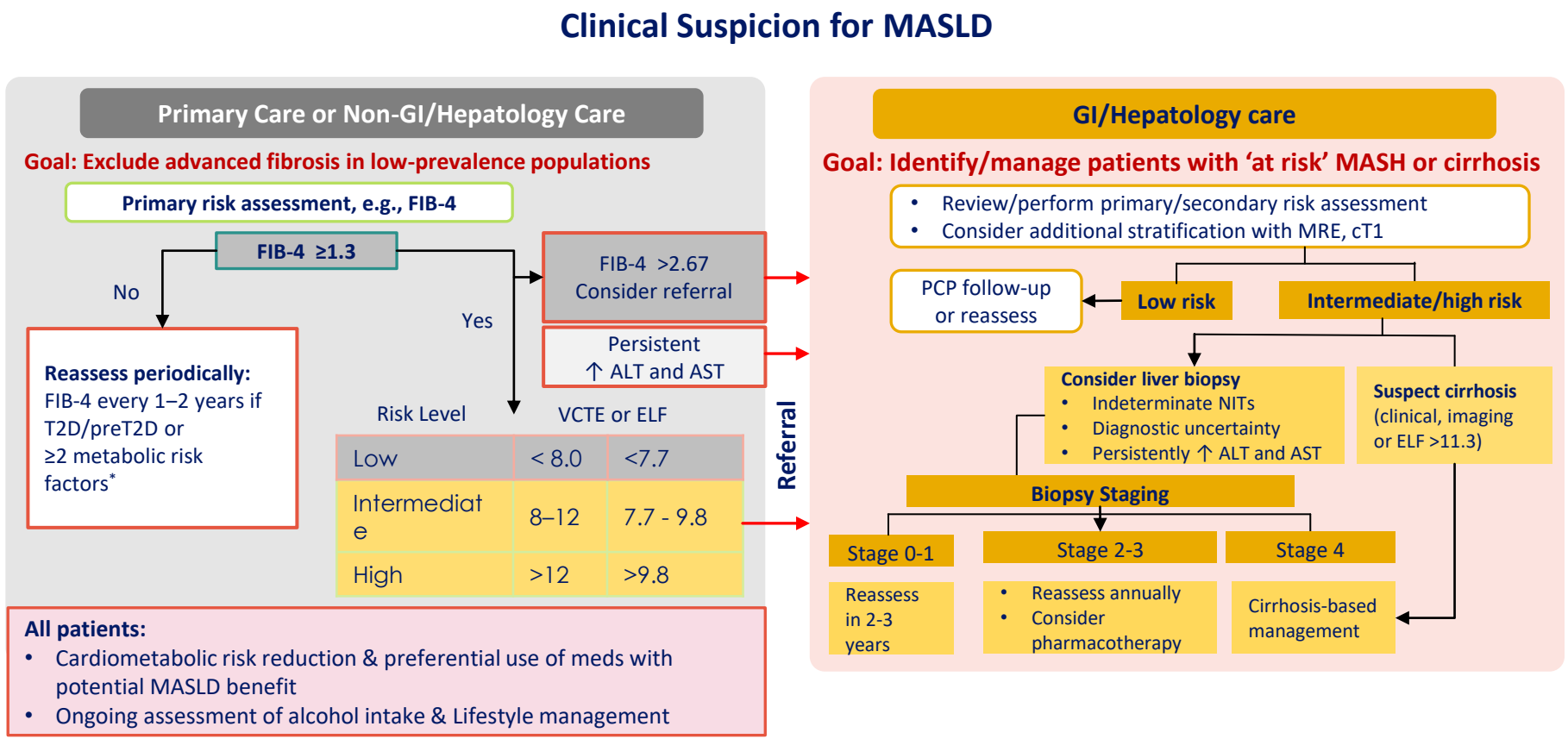
At least 1 out of 5:

- ☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

Decision Support Tool

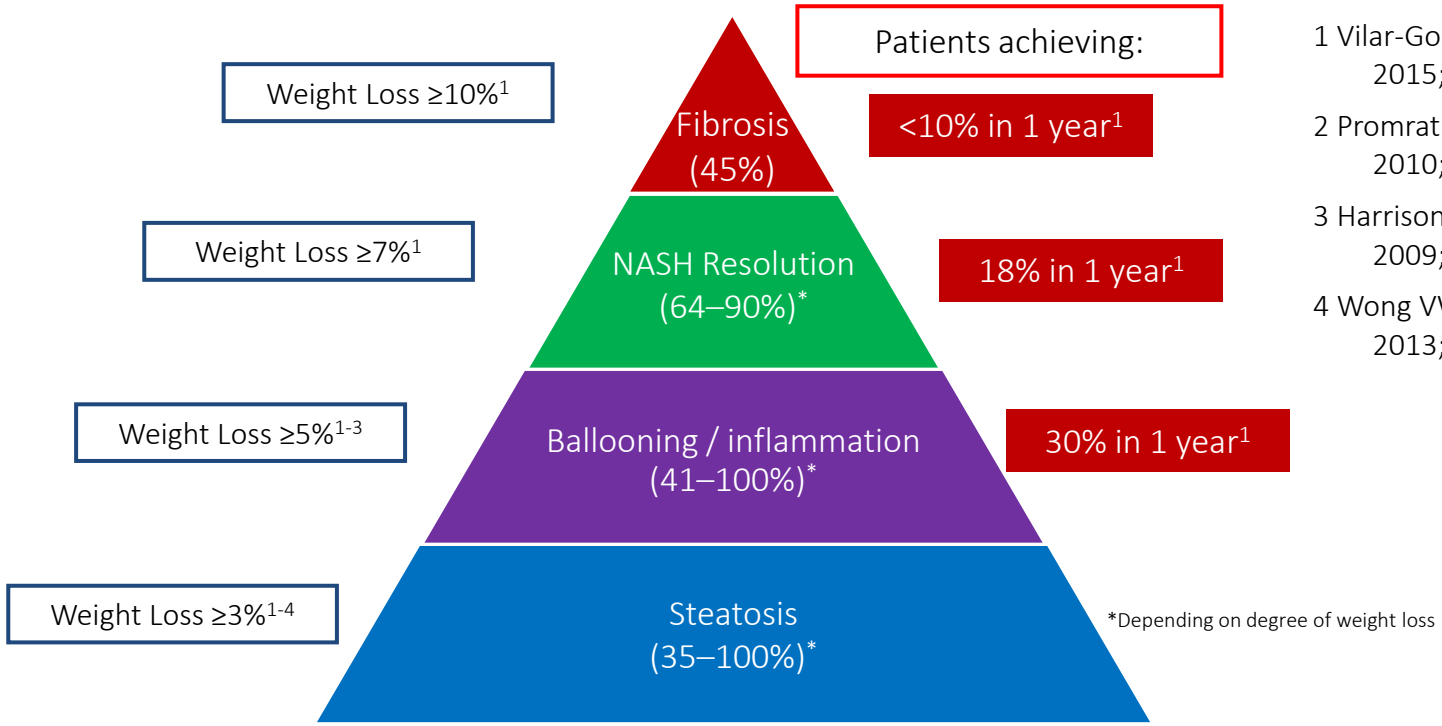


AASLD clinical practice algorithm 2023



AASLD, American Association for the Study of Liver Disease; Rinella ME et al. Hepatology 2023

Treatment: diet and lifestyle changes



1 Vilar-Gomez E, et al. Gastroenterology. 2015;149:367-78.

2 Promrat K, et al. Hepatology. 2010;51:121-9

3 Harrison SA, et al. Hepatology. 2009;49:80-6.

4 Wong VW, et al. J Hepatol. 2013;59:536-42

Slide courtesy of S. Harrison

Components of a lifestyle approach to MASLD

Energy restriction
- Calorie restriction (500/day)
- Long-term maintenance approach

Fructose intake
- Avoid fructose-containing food and drink

Coffee consumption
- No liver-related limitations

Comprehensive lifestyle approach

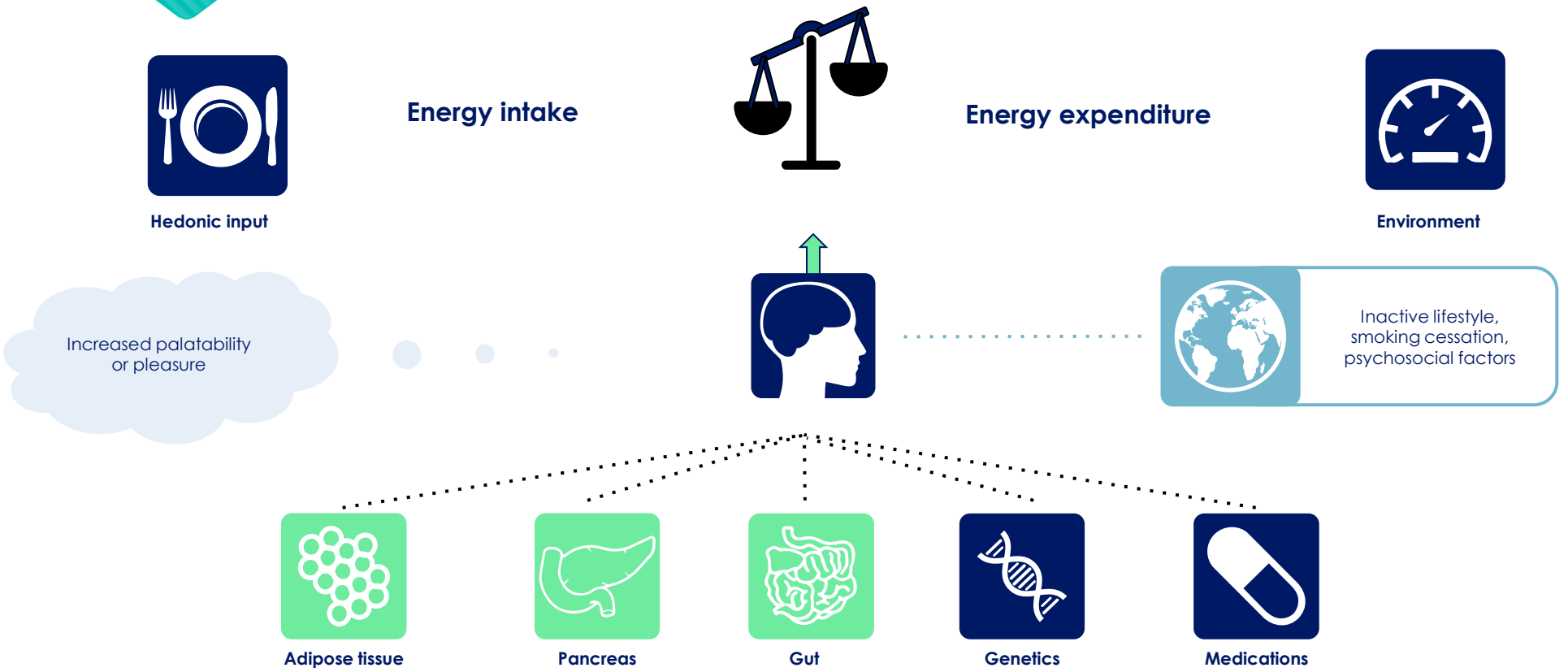
Daily alcohol intake
- Strictly below 30 g men and 20 g women

Macronutrient composition
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Obesity is a complex and multifactorial disease



1. Badman, Flier. *Science* 2005;307:1909–14; 2. US Department of Health and Human Services, 1998. NIH Publication No. 98-4083

Gut microbiome influences insuline-resistance

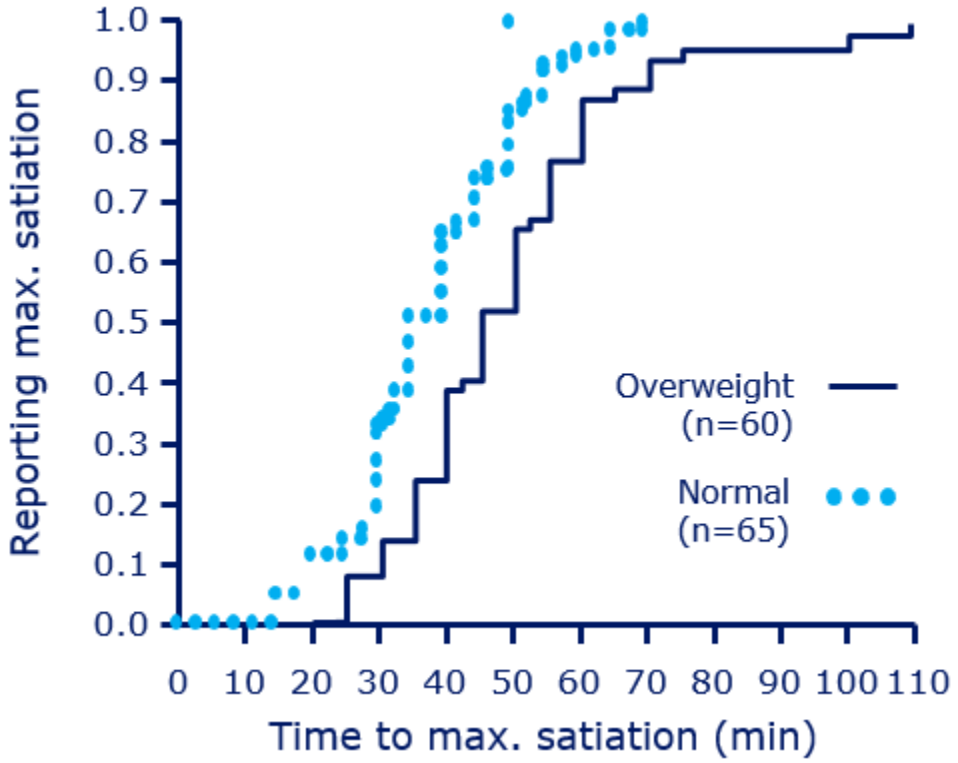
Obese gut microbiota

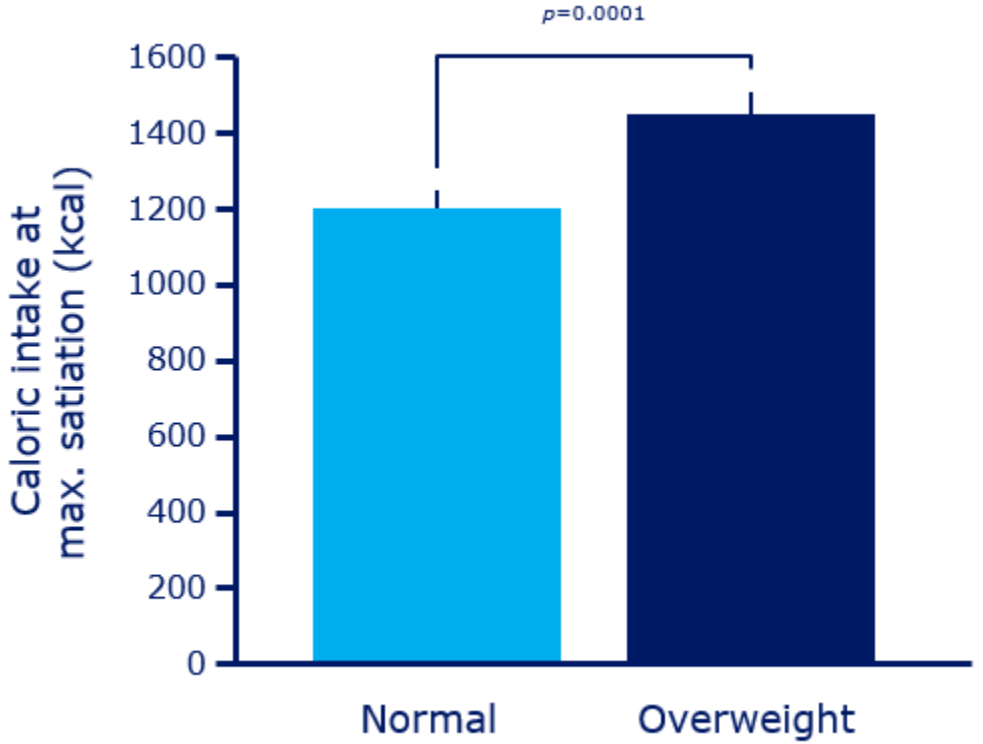
Obese gut microbiota		Lean gut microbiota
Decreased satiety	**Brain**	Increased satiety
Increased (LPS) inflammation	**Adipose tissue**	Decreased (LPS) inflammation
Increased SCFA (lipogenesis)	**Liver**	Decreased SCFA (lipogenesis)
Decreased PYY, GLP-1	**Epithelium**	Increased PYY, GLP-1
Decreased fatty acid oxidation, FIAF, AMPK	**Muscle**	Increased fatty acid oxidation, FIAF, AMPK
Decreased butyrate production	**Large intestine**	Increased butyrate production

Lean gut microbiota

AMPK, adenosine monophosphate-activated protein kinase; FIAF, fasting-induced adipocyte factor; GLP-1, glucagon-like peptide-1; LPS, lipopolysaccharide;PYY, peptide YY; SCFA, short-chain fatty acid

Time to satiation is delayed in overweight subjects

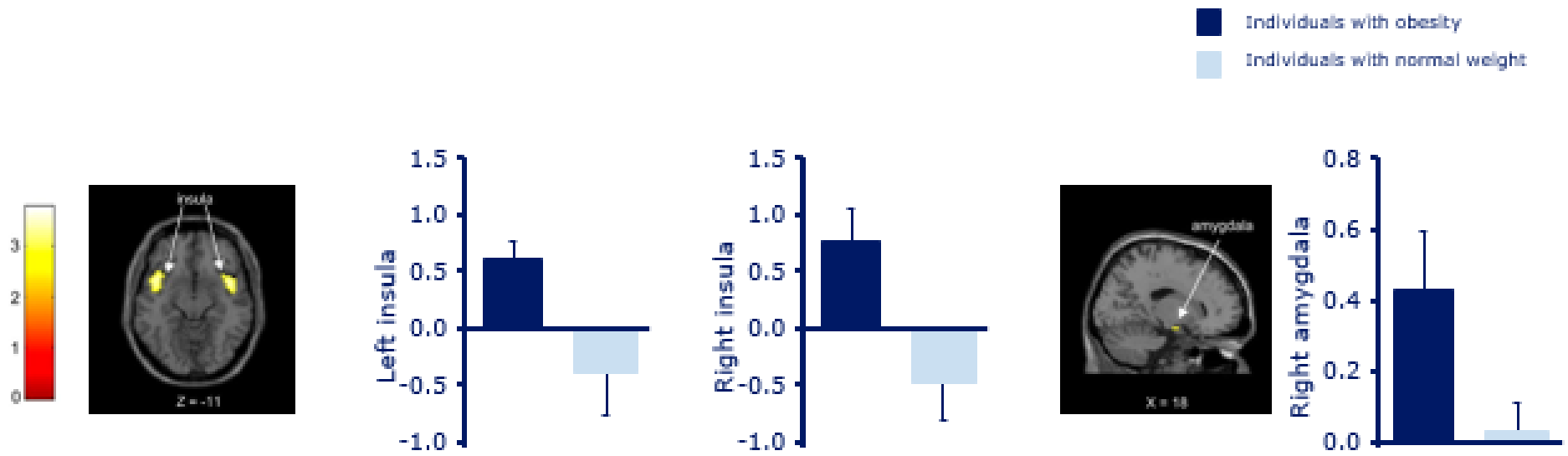




Delgado-Aros *et al. Gastroenterology.* 2004;126:432–40

Appetite centre activation is increased in obesity

Individuals with obesity showed increased brain responses to food pictures in appetite- and reward-related brain regions (insula and amygdala) versus controls



Z is the MNI space Z coordinate of the axial slice and X is the Montreal Neurological Institute space X coordinate of the sagittal slice. The color scale reflects the T value of the functional activity. Results are presented at a threshold of $p<0.05$, family-wise error corrected on the basis of cluster extent. In the graphs on the right, the BOLD signal intensity (effect size) for each group is plotted (arbitrary units), mean and SEM

van Bloemendaal *et al. Diabetes.* 2014;63:4186-96

CMAJ 2020 August 4;192:E875-91. doi: 10.1503/cmaj.191707

First approval

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

Authors: Stephen A. Harrison, M.D., Pierre Bedossa, M.D., Ph.D., Cynthia D. Guy, M.D., Jörn M. Schattenberg, M.D., Rohit Loomba, M.D., M.H.Sc., Rebecca Taub, M.D., Dominic Labriola, Ph.D., +22, for the MAESTRO-NASH Investigators* Author Info & Affiliations

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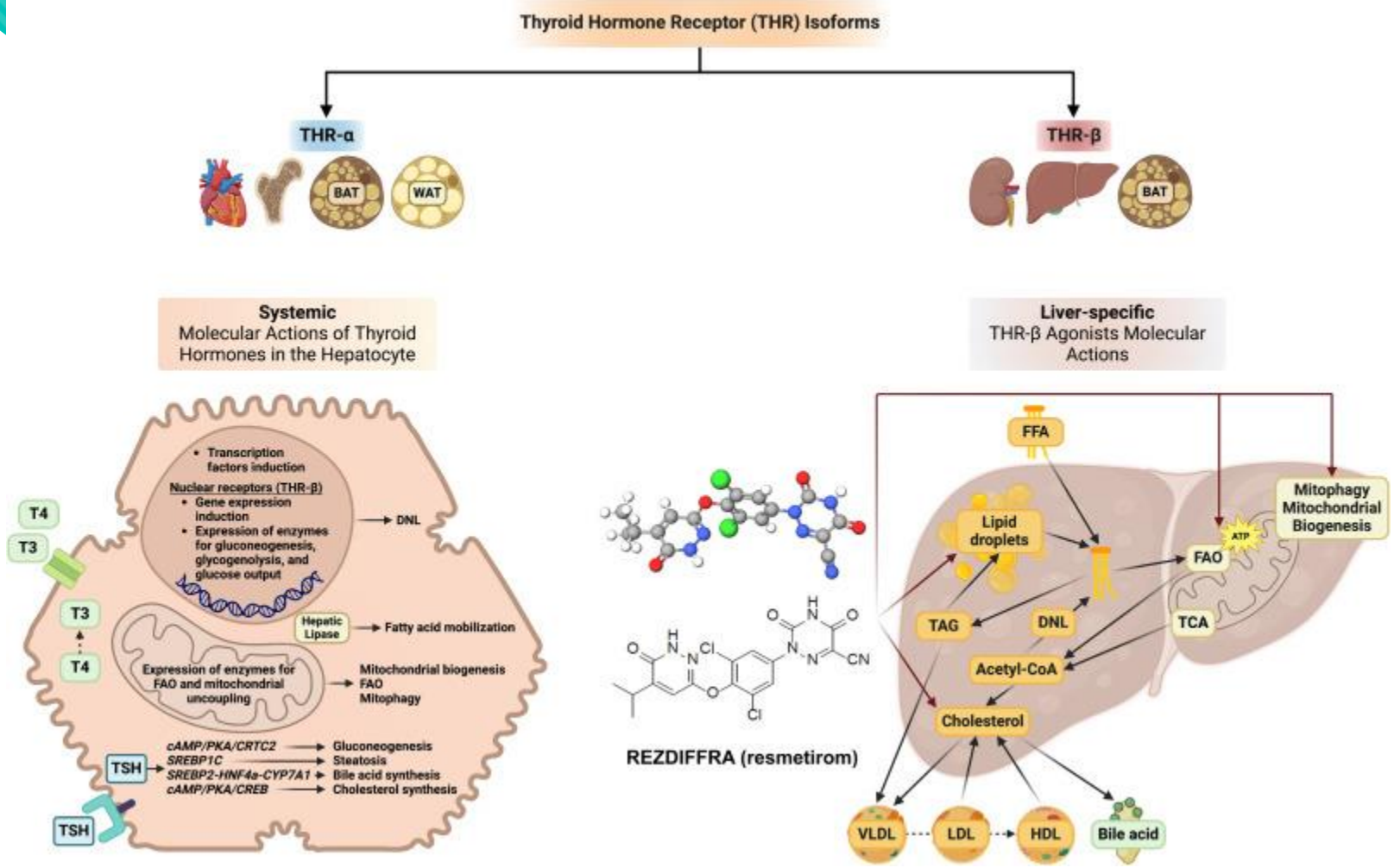
Mechanism of action

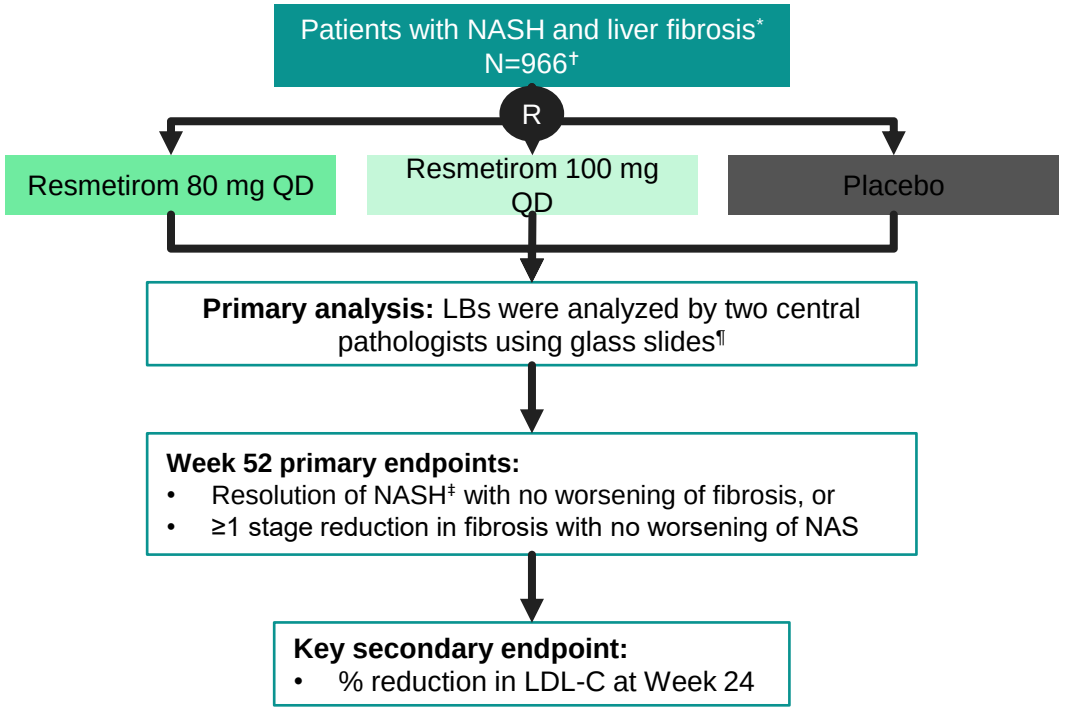


Primary results from MAESTRO-NASH: a pivotal phase 3 52-week serial liver biopsy study in 966 patients with NASH and fibrosis

MAESTRO-NASH (NCT03900429) is an ongoing 54-month, phase 3, registrational double-blind, placebo-controlled clinical trial

AIM: To analyze the Week 52 primary endpoints of the MAESTRO-NASH trial

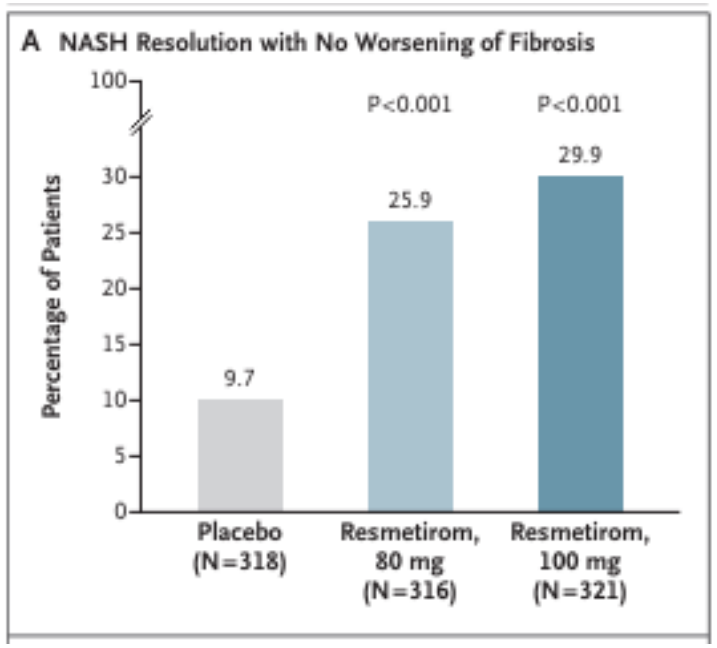
- The primary analysis results were combined using a statistical algorithm to generate a single treatment effect
- The mITT population excluded 11 patients with LBs after Week 60 due to COVID site issues

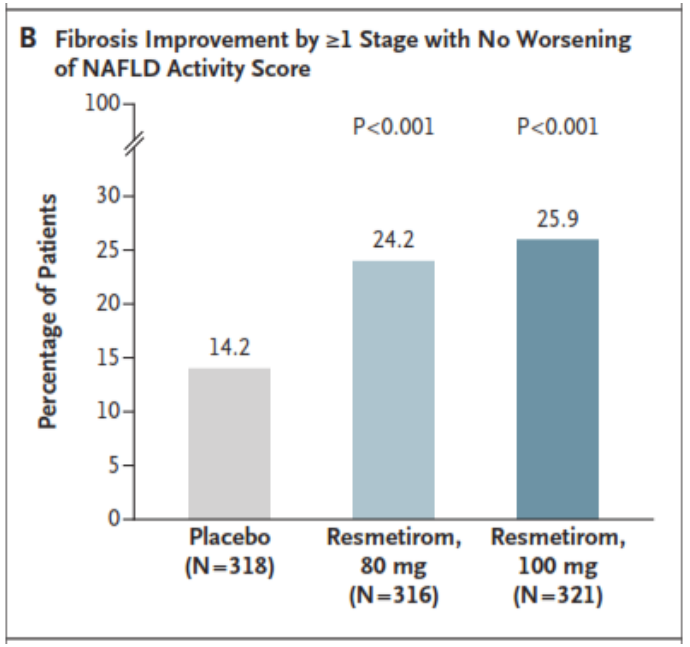


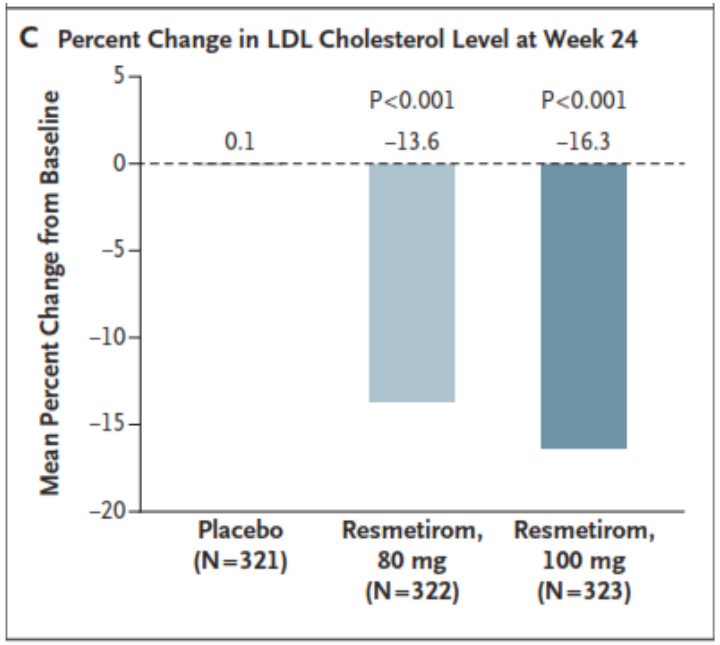
*Eligibility criteria: presence of >3 metabolic risk factors, FibroScan VCTE ≥8.5 kPa, baseline MRI-PDFF ≥8% and biopsy-proven NASH with fibrosis stage 1B, 2, or 3 and NAS ≥4 with at least 1 in each NAS component; †Enrolled at ~200 centers; ‡Ballooning 0, inflammation 0,1 with ≥2-pt reduction in NAS; ¶If readers disagreed on the response for either primary endpoint, a supportive consensus read using digitized images was conducted.

Harrison S, et al. EASL 2023; GS-001

Primary results from MAESTRO-NASH: 52-week serial liver biopsy study in 966 patients







Harrison et al, NEJM 2024

Safety and tolerability of resmetirom

Primary endpoint: incidence of treatment-emergent adverse events (TEAEs)

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)
≥1 TEAEs	148 (86.5)	279 (86.1)	289 (88.4)	260 (81.8)
Grade 1 (mild)	51 (29.8)	99 (30.6)	99 (30.3)	90 (28.3)
Grade 2 (moderate)	85 (49.7)	151 (46.6)	165 (50.5)	141 (44.3)
≥Grade 3 (severe)	12 (7.0)	29 (9.0)	25 (7.6)	29 (9.1)
≥1 drug-related TEAEs	63 (36.8)	119 (36.7)	114 (34.9)	77 (24.2)
≥1 serious TEAEs	7 (4.1)	24 (7.4)	19 (5.8)	20 (6.3)
≥1 drug-related serious TEAEs	0	0	0	1 (0.3)
TEAEs leading to study discontinuation	2 (1.2)	10 (3.1)	8 (2.4)	4 (1.3)
GI-related TEAEs leading to study discontinuation	0	6 (1.9)	5 (1.5)	2 (0.6)
Liver enzymes ≥3× ULN (ALT or AST)	1 (0.5)	1 (0.3)	2 (0.6)	6 (1.9)

Resmetirom was well tolerated

TEAEs in excess of placebo included diarrhea and nausea at the initiation of treatment

Harrison et al, Nat Med 2023

Thank for your attention!