Stemming the Tide on MASLD/MASH:

It Starts on the Frontlines in Endocrinology and Primary Care Clinics

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Disclosures of Conflicts of Interest

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  Advisor/Consultant: Boston Pharma, Fibronostics, GSK, Intercept, Madrigal, Merck, Novo Nordisk, Pfizer, The Kinetix Group
  Contracted Researcher: HistoIndex, Pfizer, Siemens, The Kinetix Group
- **Nicholas Pennings, DO**
  Advisor/Consultant: Abbott, Novo Nordisk
  Other: Medifast
- **Fernando Bril, MD**
  Advisor/Consultant: Boehringer Ingelheim, Novo Nordisk

Learning Objectives

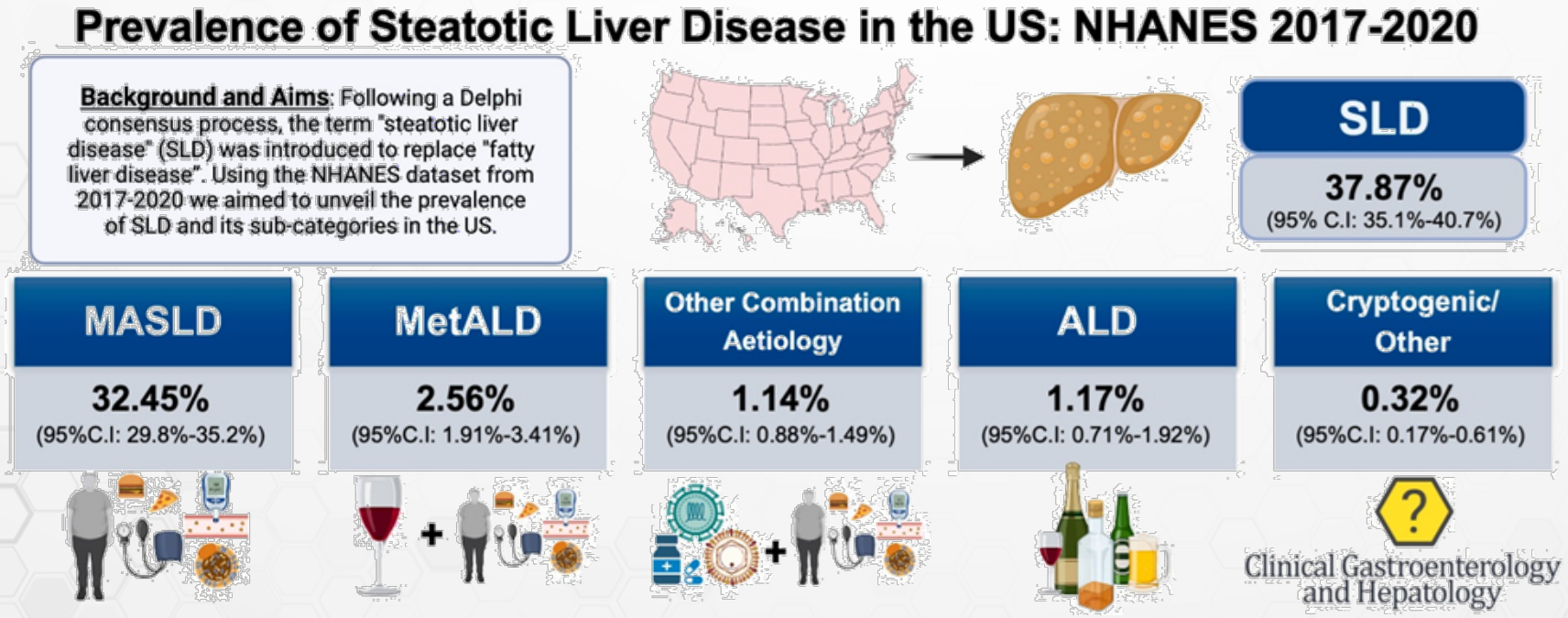
- Perform a health assessment to identify metabolic dysfunction-associated liver disease (MASLD) in a patient with documented metabolic risk factors for MASLD/metabolic dysfunction-associated steatohepatitis (MASH)
- Use noninvasive tests (NITs) and biomarkers available in endocrinology and primary care practice settings to stratify risk of advanced hepatic fibrosis
- Recommend evidence-based, guideline-concordant treatment for a patient with MASLD based on results of NITs and/or biomarkers
- Interpret results of data from phase 3 clinical trials on emerging glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for lowering cardiometabolic risk and treating MASH
- Interpret results of NITs to determine when a patient with MASLD/MASH should be referred for specialty care

Why Are We Here?

Nicholas Pennings, DO

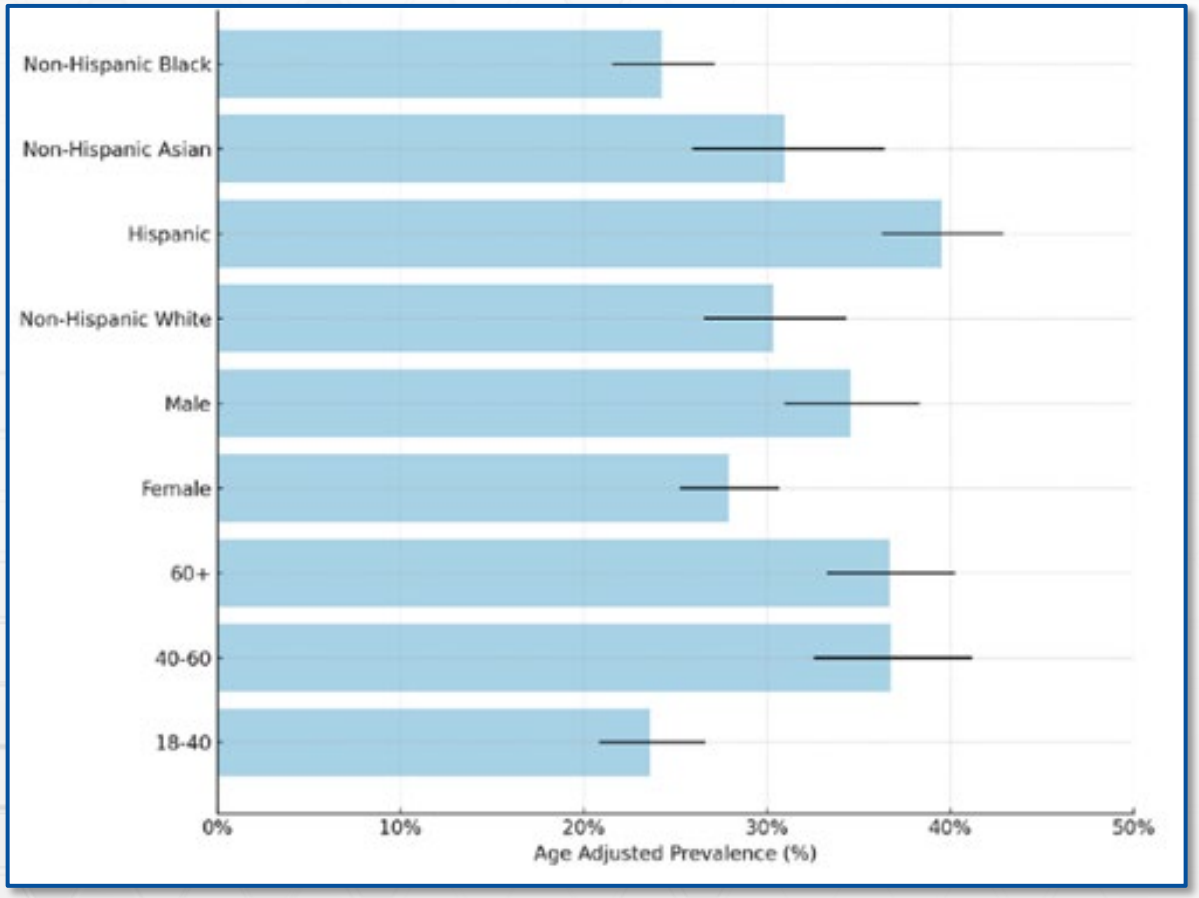
The MASLD/MASH Epidemic

- Just because you don't see it doesn't mean it's not there
- MASLD/MASH is common



ALD, alcohol-related liver disease; MetALD, metabolic dysfunction and alcohol-related steatotic liver disease; SLD, steatotic liver disease
Kalligeros M, et al. *Clin Gastroenterol Hepatol*. 2024;22(6):1330-1332.e4.

Who Is at Greatest Risk?



- Hispanic male over 40 is at greatest risk
- Occurs in all ages, genders, and races

Kalligeros M, et al. *Clin Gastroenterol Hepatol*. 2024;22(6):1330-1332.e4.

Why Is It Important?

- Life expectancy for patients with MASLD is 2.8 years SHORTER
- CVD risk was 2.6x higher in patients with MASLD
- Most common cause of mortality in patients with MASLD is CVD
- At highest risk are those diagnosed in midlife (40-60 years)
- Vague symptoms – if any, fatigue/RUQ pain

CVD, cardiovascular disease

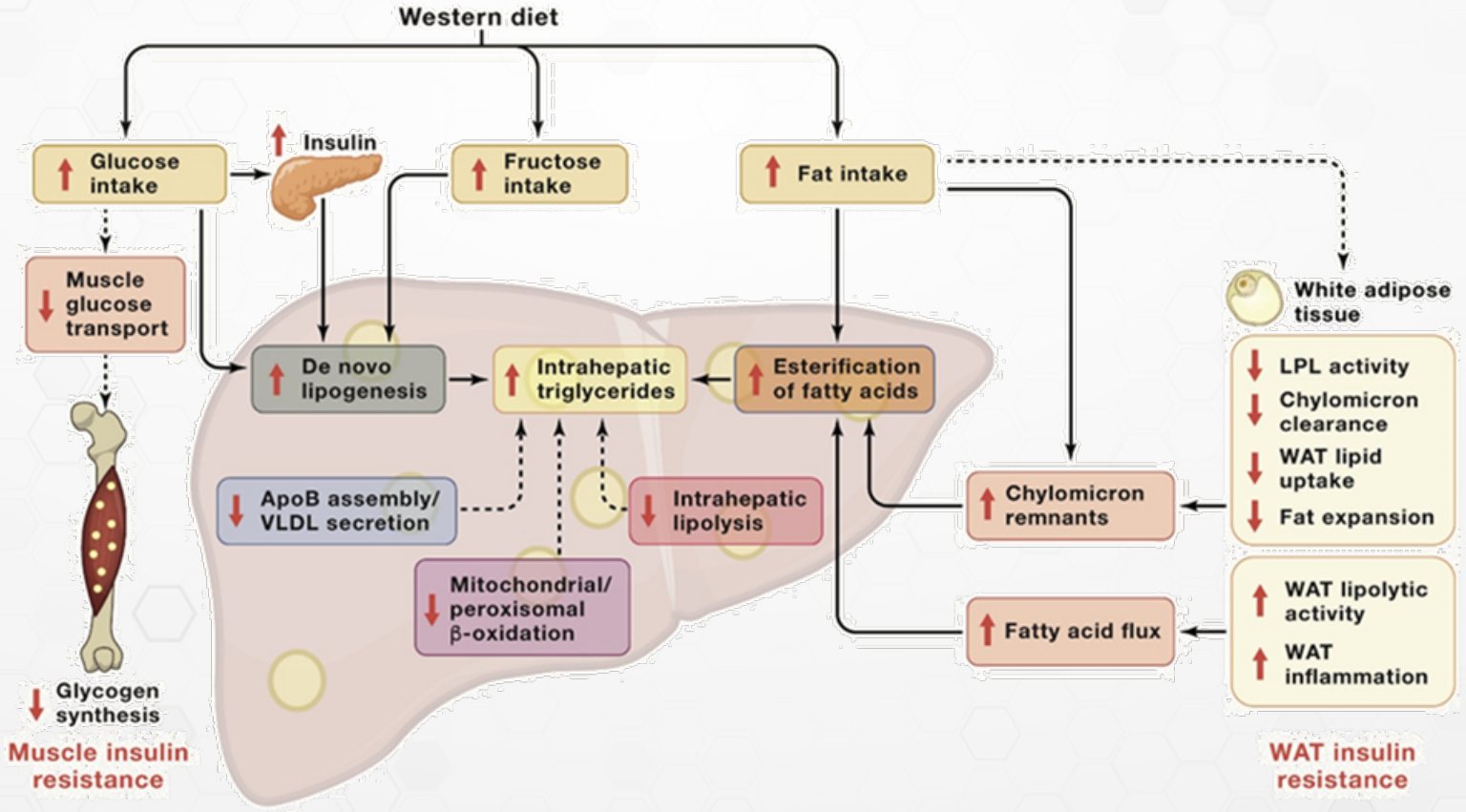
Shang Y, et al. *Hepatology*. 2022;76(5):1495-1505. Younossi ZM, et al. *Clin Mol Hepatol*. 2025;31(Suppl):S32-S50. Geier A, et al. *Clin Gastroenterol Hepatol*. 2021;19(5):1020-1029.e7. Povsic M, et al. *Adv Ther*. 2019;36(7):1574-1594.

Jen Is a 53-Year-Old White Woman Living in San Antonio, Texas

Medical History	Obesity since childhood, T2D, hyperlipidemia **"I've always been a big girl. I weighed 200 lb in 5th grade."** Celiac disease, rheumatoid arthritis, COVID Brain tumor Gastric sleeve surgery in 2011
Family History	Obesity and T2D in all family members; 2 sisters with MASH-related death, 1 sister alive with MASH-related cirrhosis
Patient Journey: 1995–2025	1995: elevated liver enzymes noted 2021: entered clinical trial (FXR agonist) at PINNACLE Clinical Research, first VCTE = 9.9 kPa 2024: VCTE = 3.0, liver fat = 40% (MRI-PDFF) Main symptom 1995-2021: fatigue which became severe and impacted daily functioning and QoL **"I experienced weight stigma from every single provider except the rheumatologist and doctors at PINNACLE, including recent visit with a PA, where I was told over and over again, your problem is your weight."**
Current	170 lb, BMI 24.4, kPa 3.0, F0, HbA1c = 4.5%, normotensive, normal lipid panel **"This is the first time in my life I'm not overweight."**

HbA1c, hemoglobin A1c; T2D, type 2 diabetes; VTCE, vibration-controlled transient elastography.

Pathophysiology of Obesity & MASLD/MASH



Loomba R, et al. *Cell*. 2021;184(10):2537-2564.

Bias Towards PWO Adds to Complexity

- Obesity Bias
  - Obesity oversimplified
    - Calories in/calories out
  - Patients labeled
    - Lazy
    - Unmotivated
    - Noncompliant
    - Weak-willed
  - Physiology ignored
    - Physiologic appetite response
    - Metabolic adaption
    - Obesogenic environment
- Obesity Stigma
  - Social judgment
    - Lack of self-discipline
    - Personal responsibility
  - Health professionals
    - Negative attitudes towards PWO
    - Patients are at fault
  - Healthcare environment
    - Negative staff comments
    - Office – magazines in WR, unaccommodating chairs, scales in hallways, undersized gowns and BP cuffs

PWO, people with obesity.

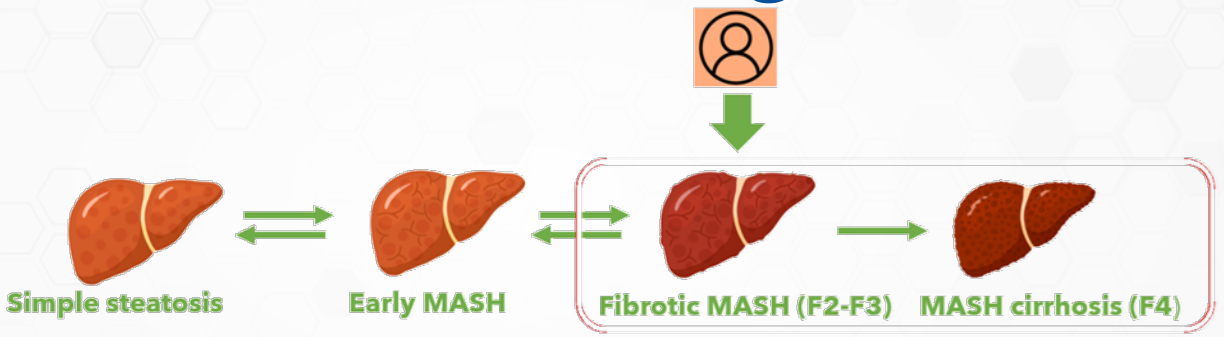
Rubino F, et al. *Nat Med*. 2020;26(4):485-497.
Sumithran P, et al. *N Engl J Med*. 2011;365(17):1597-604.

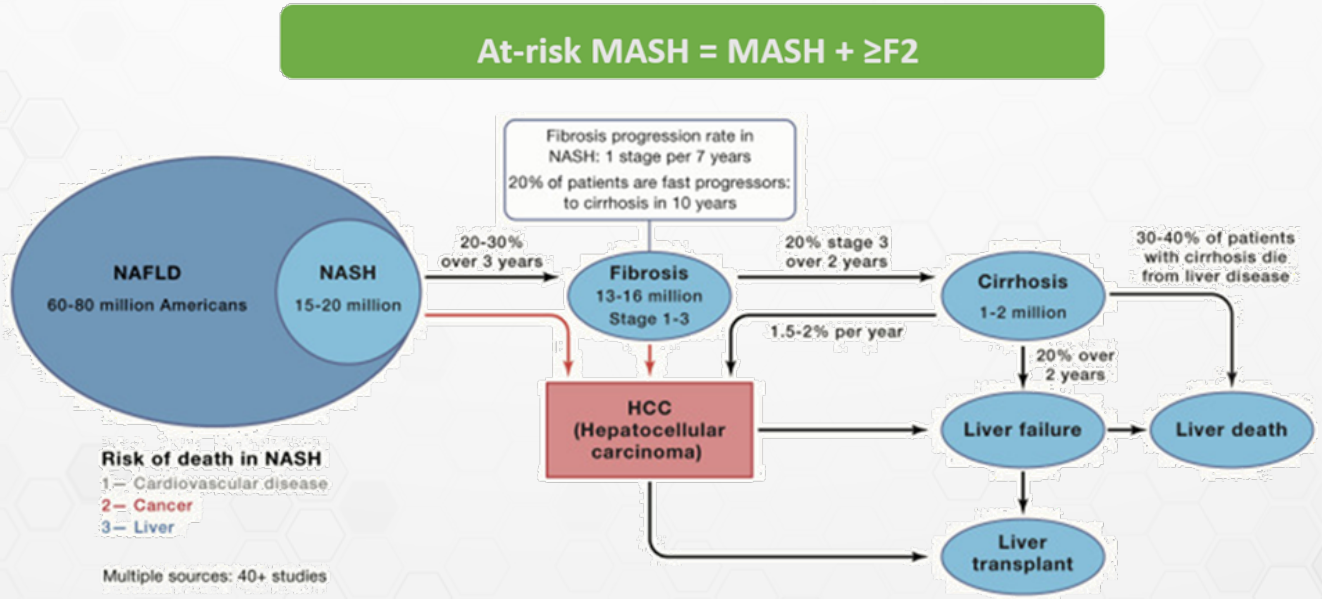
Obesity Care Is Not Prioritized

- Treatment challenges
  - Lack of training
    - > Limited obesity education for medical students and residents[1]
  - Lack of time
    - > Complex patients with multiple medical problems with limited allocation of time to address patient needs in primary care setting; yet, treating obesity improves most chronic medical conditions seen in primary care[2]
  - Lack of concern
    - > Both patient and provider[3]

1. Butsch WS, et al. *BMC Med Educ*. 2020;20(1):23. 2. Pennings N, et al. *Obes Pillars*. 2025;14:100172. 3. Kaplan LM, et al. *Obesity (Silver Spring)*. 2018;26(1):61-69.

MASLD/MASH Is a Progressive Disease



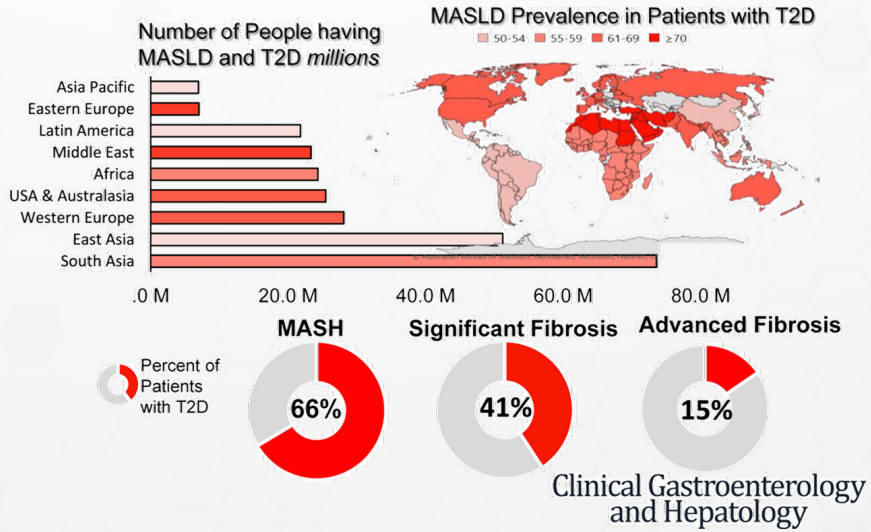


Rinella ME, et al. Hepatology. 2023;77(5):1797-1835. Loomba R, et al. Cell. 2021;184(10):2537-2564.

Why Endocrinologists and PCPs Need to Treat MASLD/MASH

- Most T2D is treated by PCPs and endocrinologists
- MASLD/MASH is common with T2D
- T2D and MASLD have a common origin – both are related to insulin resistance and associated metabolic dysfunction

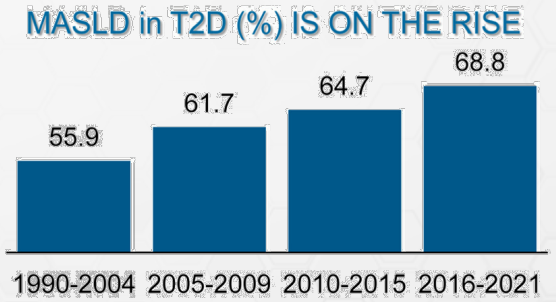
THE GLOBAL EPIDEMIOLOGY OF NON-ALCOHOLIC FATTY LIVER DISEASE AND NON-ALCOHOLIC TEATOHEPATITIS AMONG PATIENTS WITH TYPE 2 DIABETES



Globally

436 Million Adults with T2D

65% of T2D with MASLD

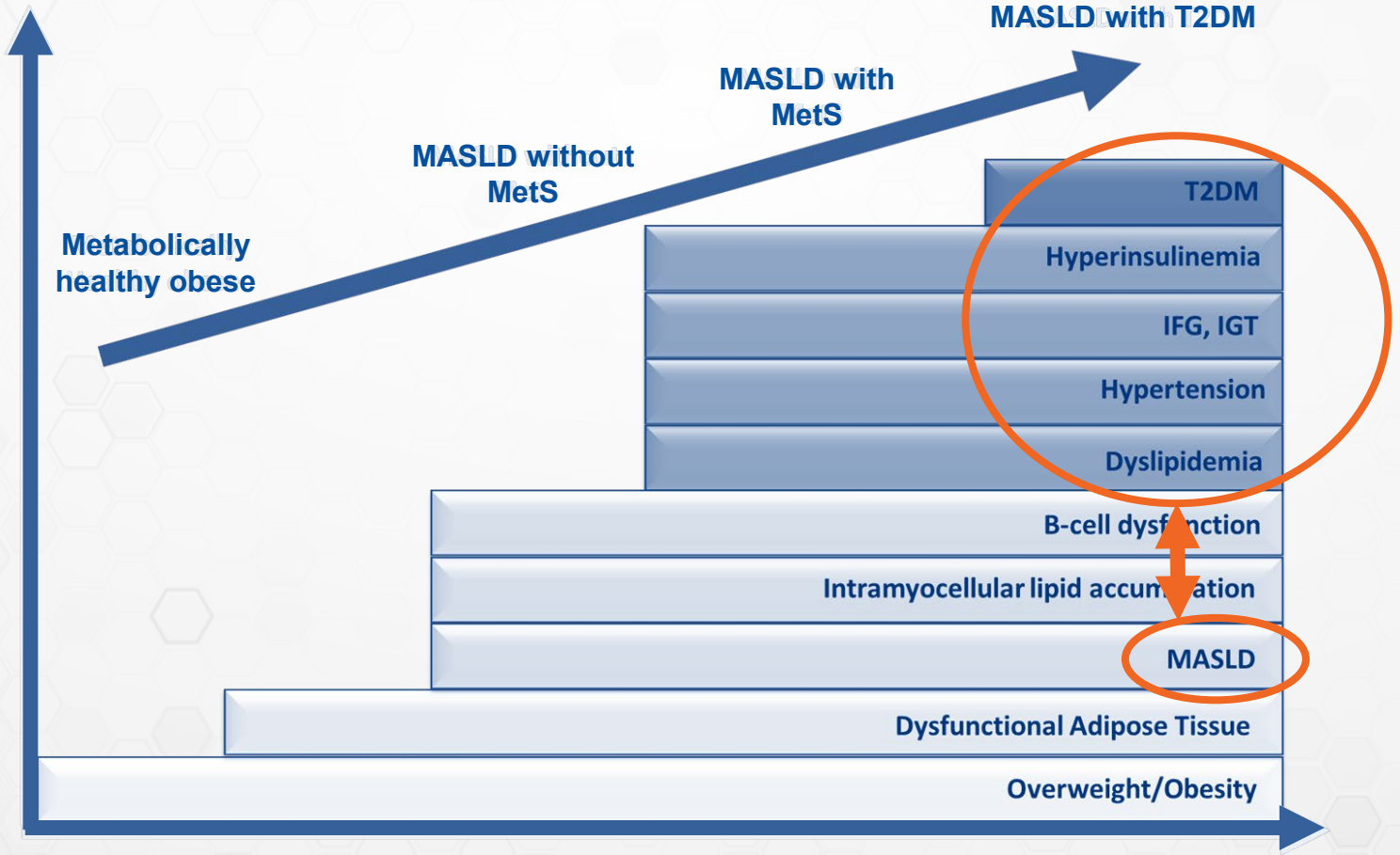


Younossi ZM, et al. *Clin Gastroenterol Hepatol.* 2024;22(10):1999-2010.e8.

What Can PCPs and Endocrinologists Do About It?

Fernando Bril, MD

MASLD: A Systemic Process and a Barometer of Metabolic Health



IFG, impaired fasting glucose; IGT, impaired glucose tolerance. T2DM, type 2 diabetes mellitus.
Bril F, et al. Clin Liver Dis. 2023;27(2):187-210.

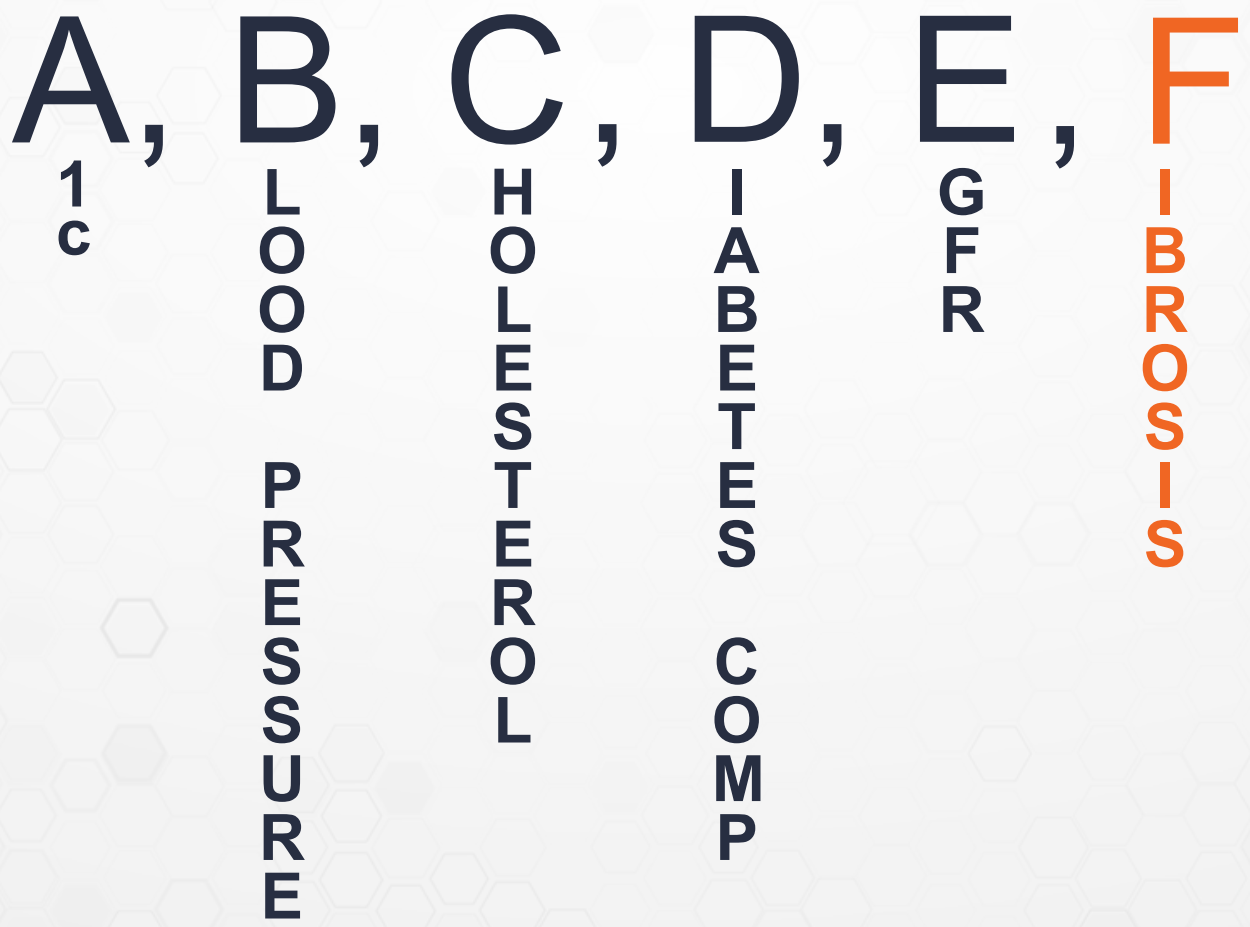
Populations at Risk of More Progressive Disease

AACE	AASLD	ADA
PreD or T2DM	T2DM	PreD or T2DM
Obese	"Medically complicated obesity"	Obesity with ≥1 CV factor
≥2 cardiometabolic RF		
Steatosis by imaging	All patients with hepatic steatosis or clinically suspected MASLD	
Elevated liver enzymes	More than mild OH use	
	First degree relative with MASH-cirrhosis	

AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; ADA, American Diabetes Association.

Cusi K, et al. *Endocr Pract.* 2022;28(5):528-562.
Rinella ME, et al. *Hepatology*. 2023;77(5):1797-1835.
ADA Professional Practice Committee. Diabetes Care. 2025;48(Supplement_1):S59-S85.

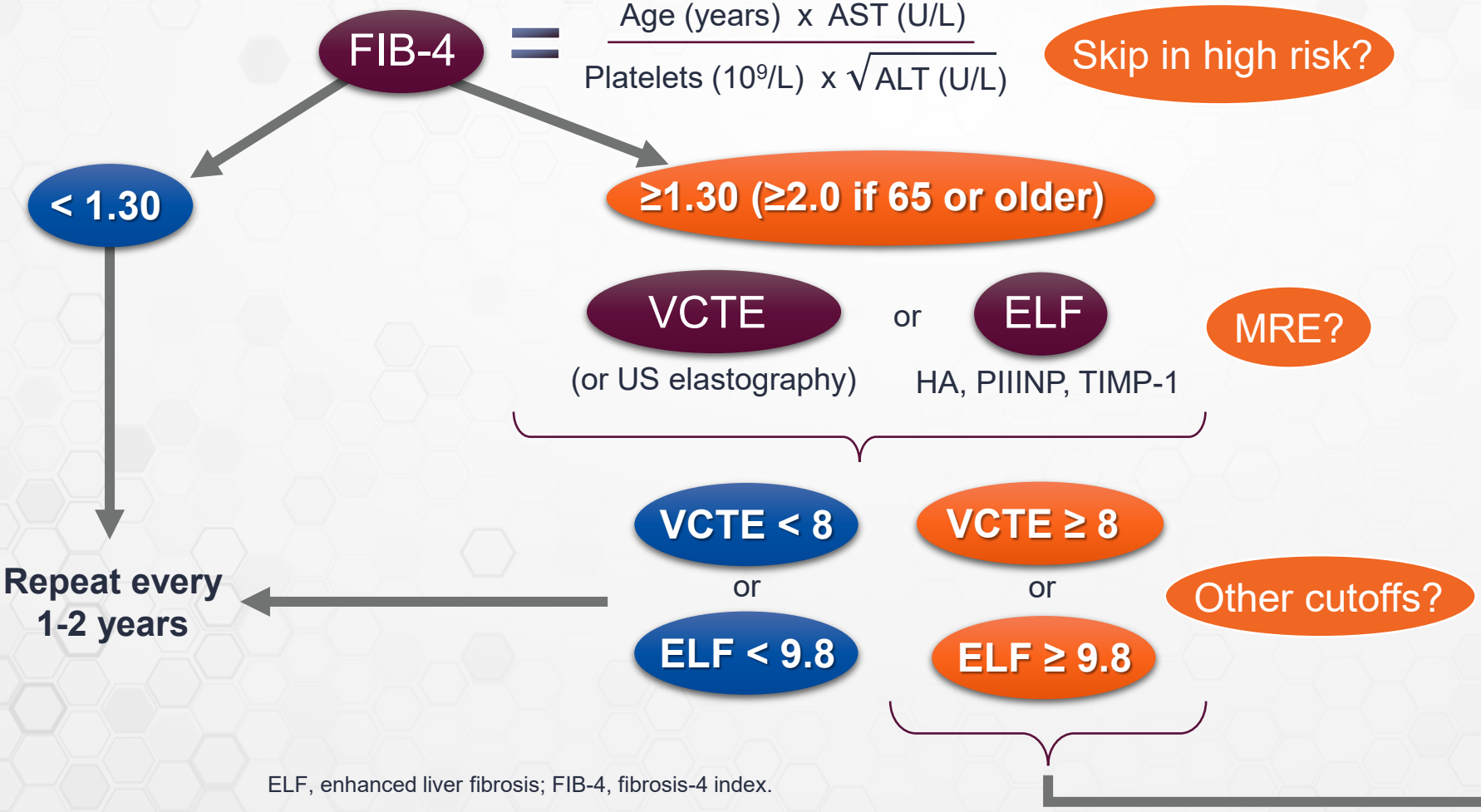
Comprehensive Evaluation of Patients With Cardiometabolic Risk Factors



Screening and Referral Algorithm

Primary Care or Endocrinology Clinics

"Exclude advanced fibrosis"



Hepatology clinics

- Rule out other causes
- Additional stratification with other NITs (MRE)
- Consider biopsy
- Treatment

ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index.

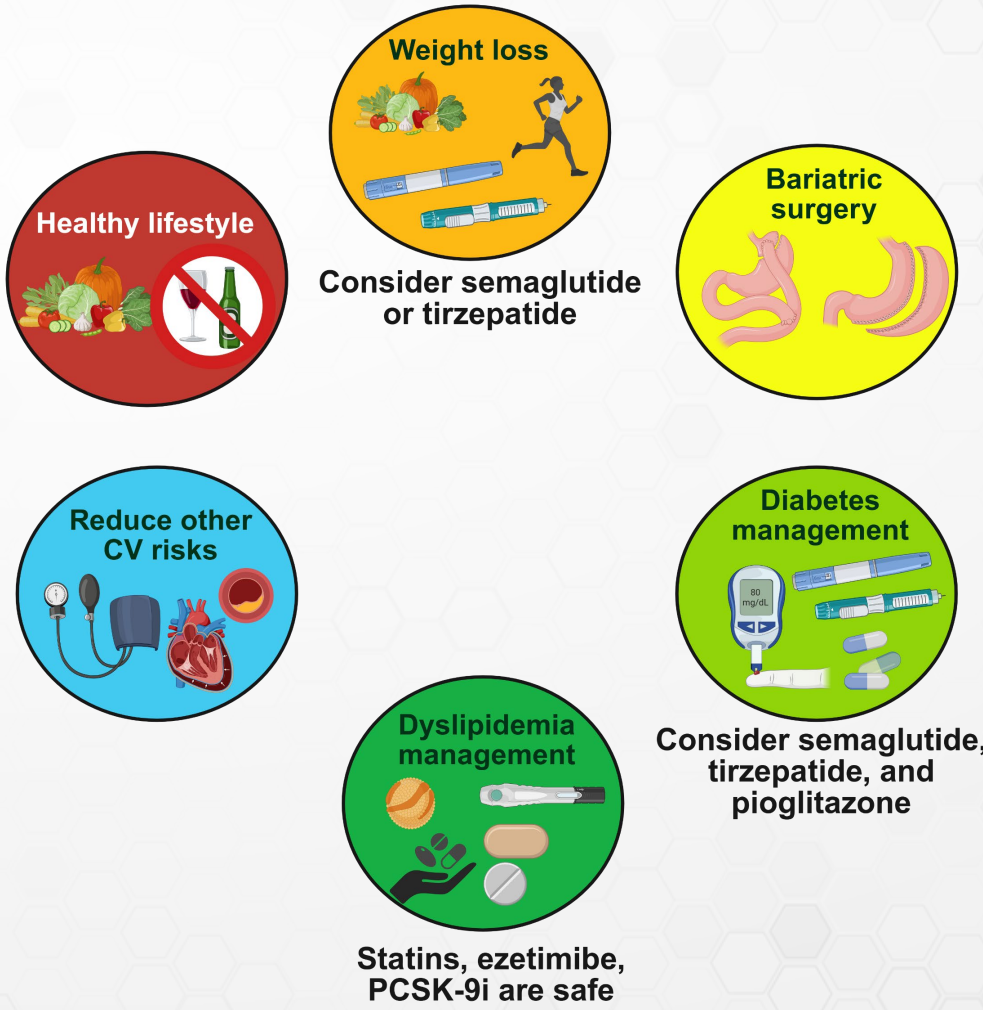
Is There Any Role for ALT and AST?

Current cutoffs are too high: 30 U/L for men, 19 U/L for women (ALT); 20 U/L for AST?

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Comprehensive Management of Patients With MASLD and Cardiometabolic Risk Factors

Individualize care focusing on:



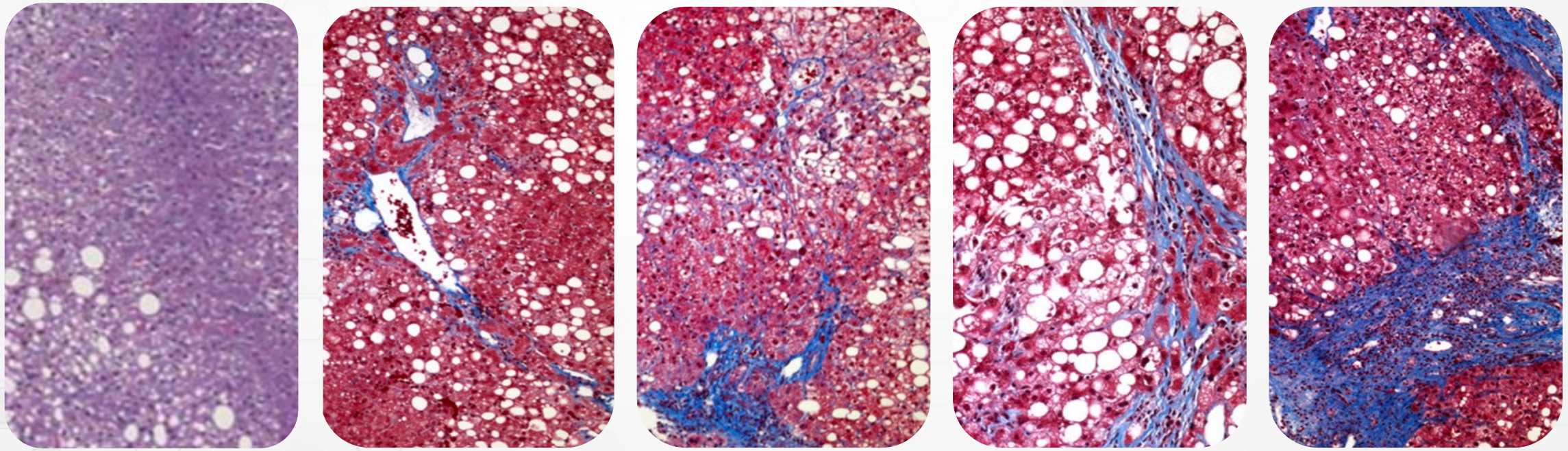
Bril F. Zenodo; 2025. doi:10.5281/zenodo.15490680

How Do We Manage Patients With Significant Fibrosis?

Meena Bansal, MD

How to Manage MASLD/MASH

F0 F1 F2 F3 F4



GLP-1 RA / Weight-Loss Strategies

Liver-Directed Therapy

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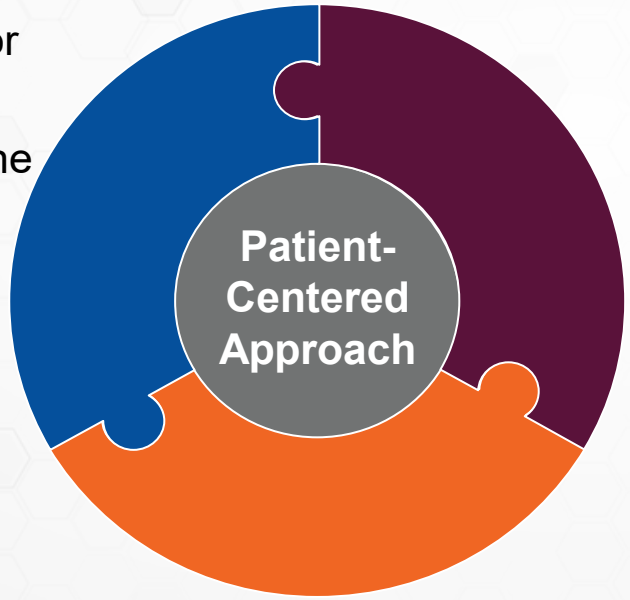
Lifestyle Recommendations for Treating MASH

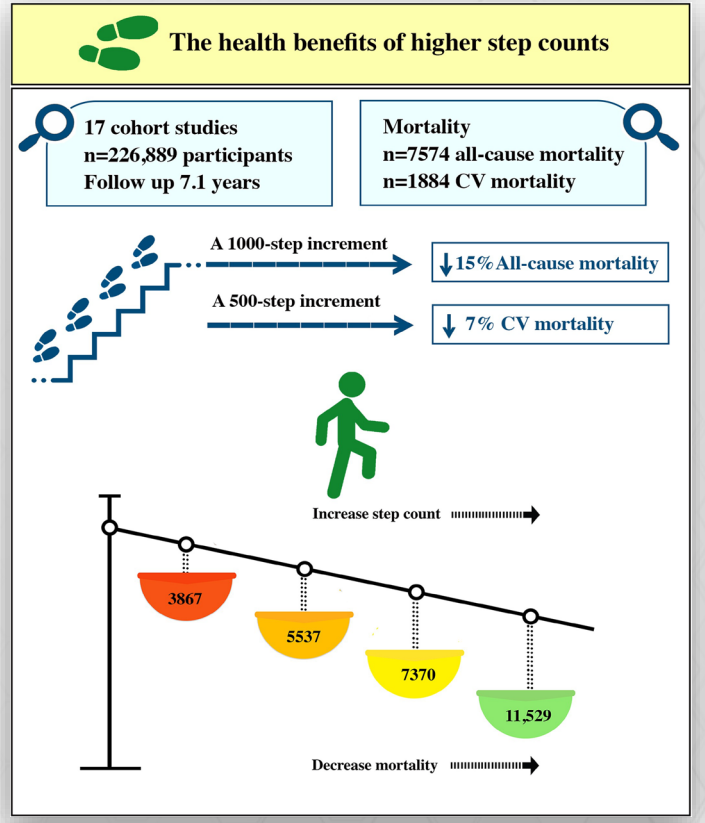
Treat Each Comorbidity

- Obesity: GLP-1 RA or GLP-1 RA/GIP
- Diabetes: Pioglitazone and/or GLP-1 RA
- Dyslipidemia-statin
- Hypertension
- Sleep apnea



Tackle Overweight/Obese Status

- Weight loss
- Exercise
- Diet



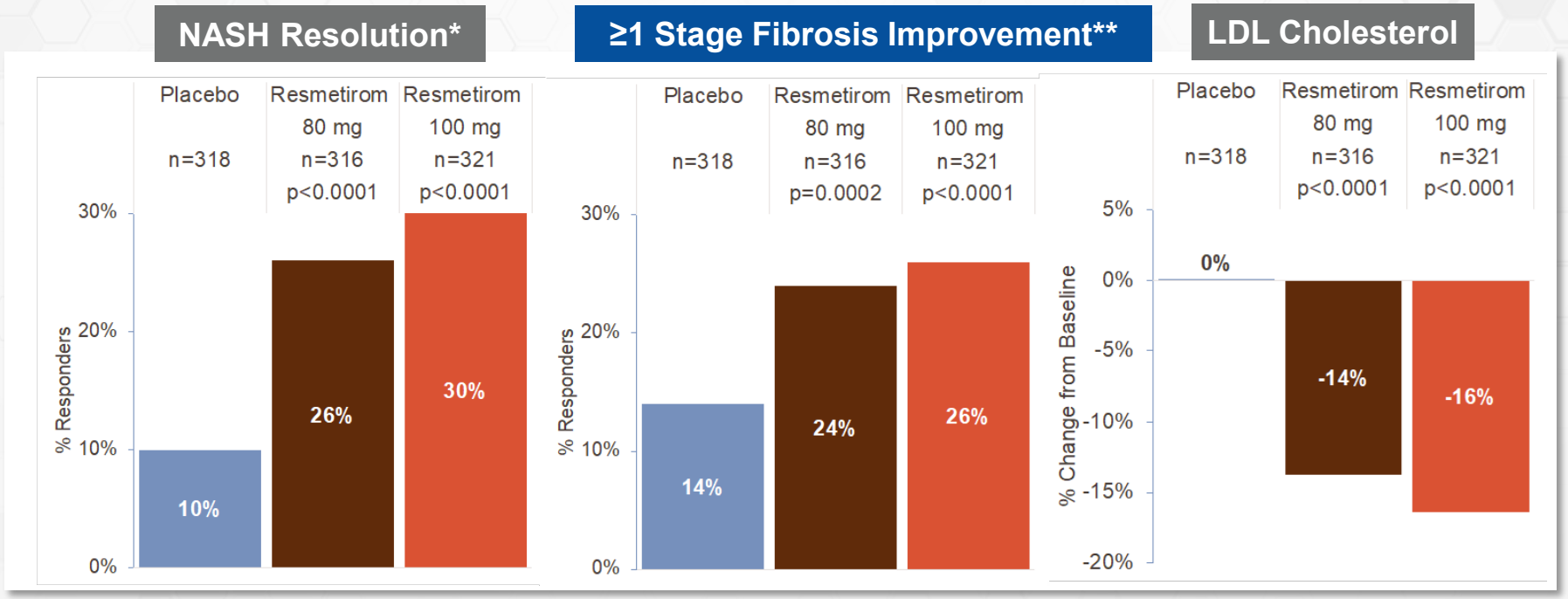
Cofactors: Dietary Modifiers

- Alcohol, smoking, fructose, coffee, Mediterranean diet

GIP RA, glucose-dependent insulinotropic peptide receptor agonists.

Cusi K, et al. *Endocr Pract*. 2022;28(5):528-562.
Banach M, et al. *Eur J Prev Cardiol*. 2023;30(18):1975-1985.

Phase 3 Trial: Dual Primary Endpoints (Week 52): Primary Analysis (Resmetirom)



Both primary liver biopsy endpoints and the key secondary endpoint of LDL cholesterol lowering were met

Patients will continue to be followed for at least 5 years for clinical outcomes
FDA provided accelerated approval March 14, 2024

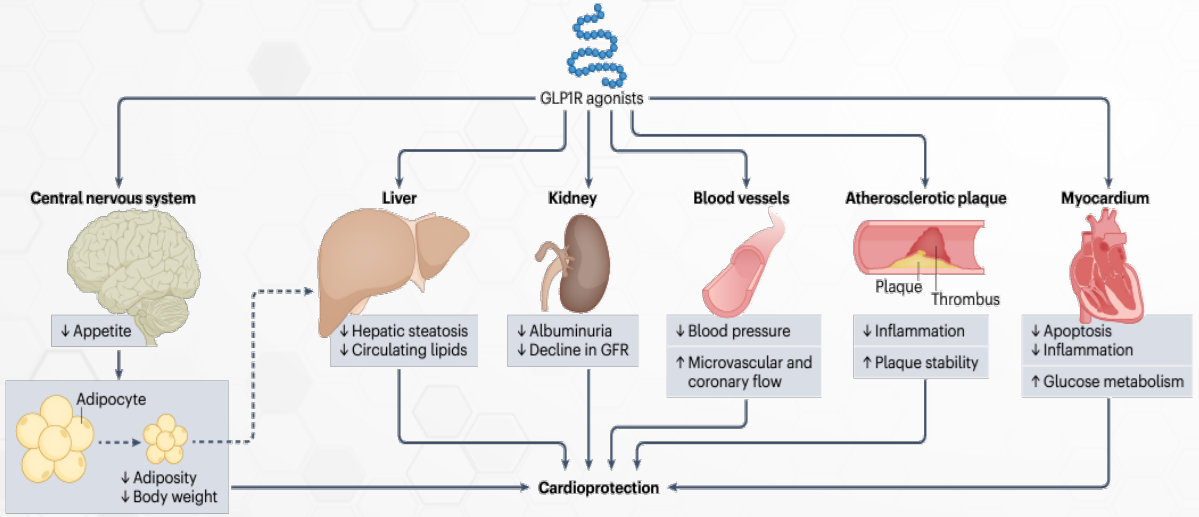
LDL, low-density lipoprotein; NASH, nonalcoholic steatohepatitis.
* NASH Resolution with no worsening of fibrosis.
** ≥1 stage fibrosis improvement with no worsening of NASH.
Harrison SA, et al. *N Engl J Med*. 2024;390(6):497-509.

Change From Baseline in Liver Enzymes* & SHBG

- Significant reduction of liver enzymes relative to placebo, both percentage change and absolute reduction
- Associated with the neutral biomarker SHBG that increases in proportion to resmetirom, reflecting target engagement (exposure)

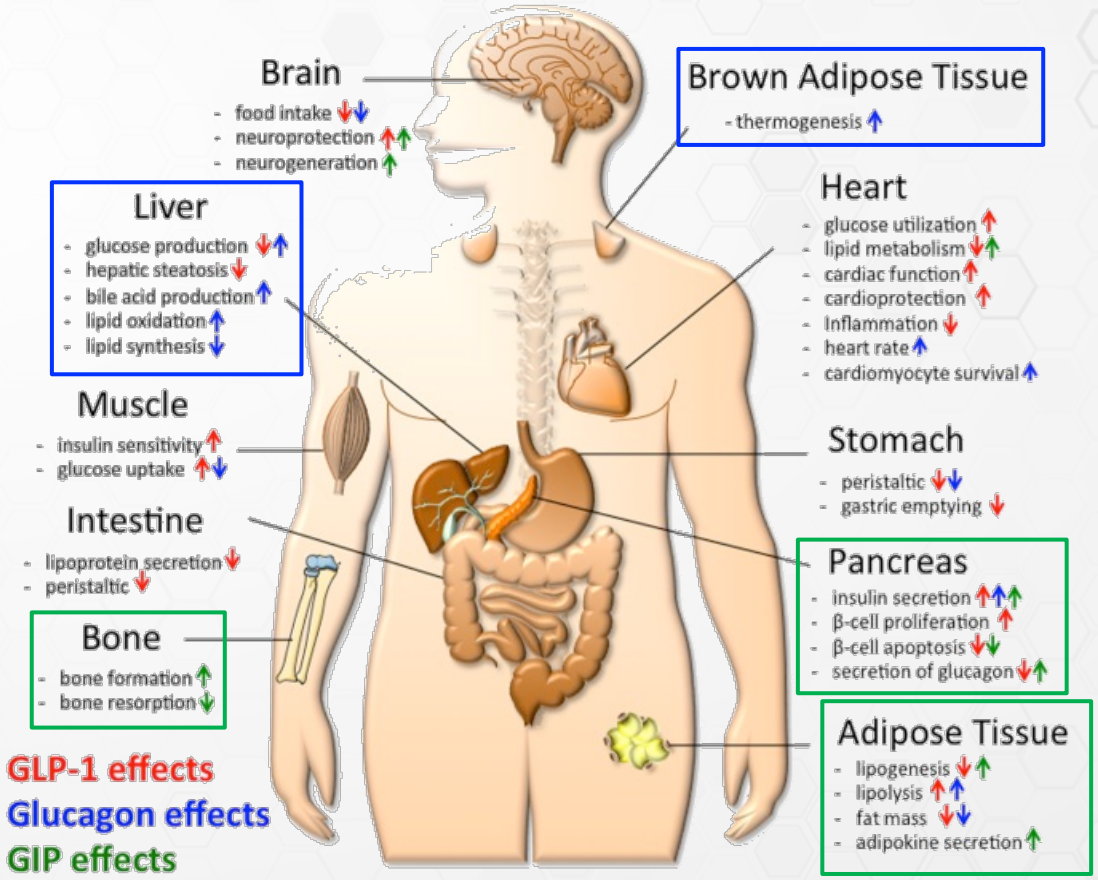
GGT, gamma-glutamyl transferase; SHBG, sex hormone binding globulin.
* Evaluated in patients with baseline ALT ≥30 IU.
Harrison SA, et al. *N Engl J Med.* 2024;390(6):497-509

Pleotrophic Effects of Incretins



No GLP-1 receptors in liver

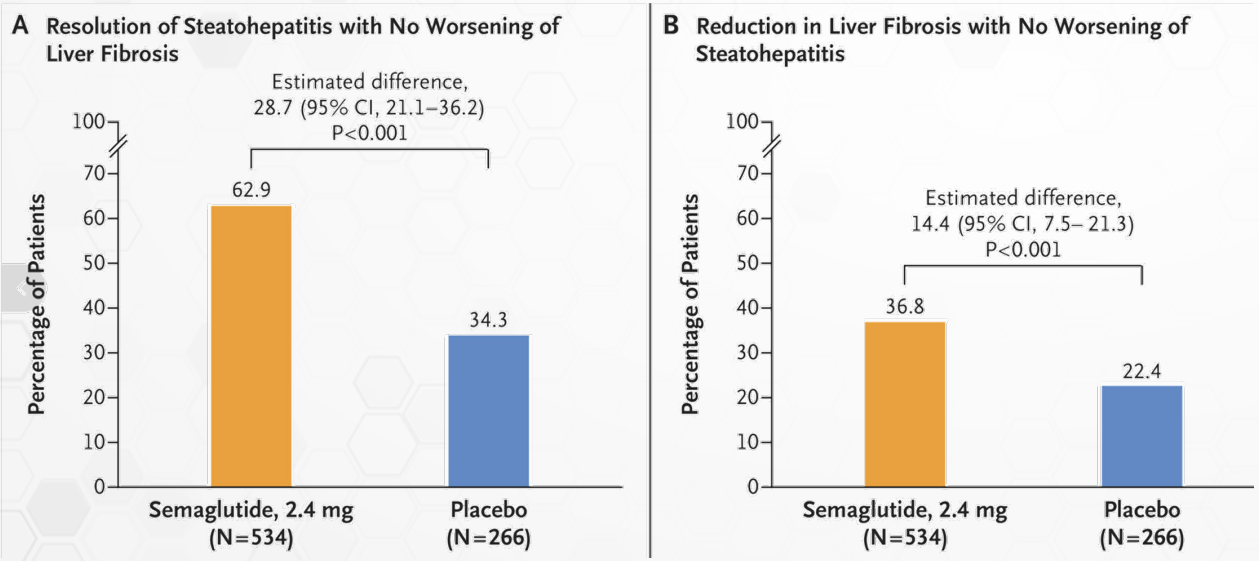
? Infiltrating T cell or macrophage subsets



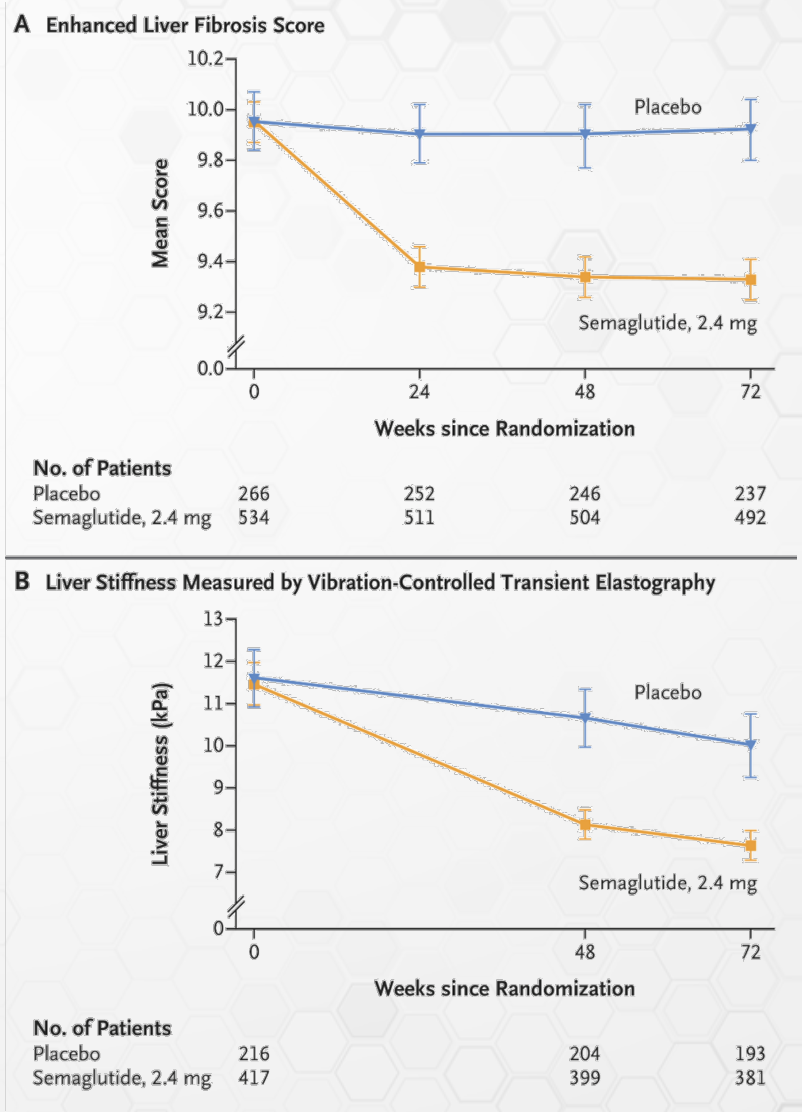
Ussher JR, Drucker DJ. *Nat Rev Cardiol*. 2023;20(7):463-474.
Brandt SJ, et al. *J Endocrinol*. 2018;238(2):R109-R119.

Semaglutide: GLP-1 RA Promotes MASH Resolution and Fibrosis Regression

Phase 3 ESSENCE trial

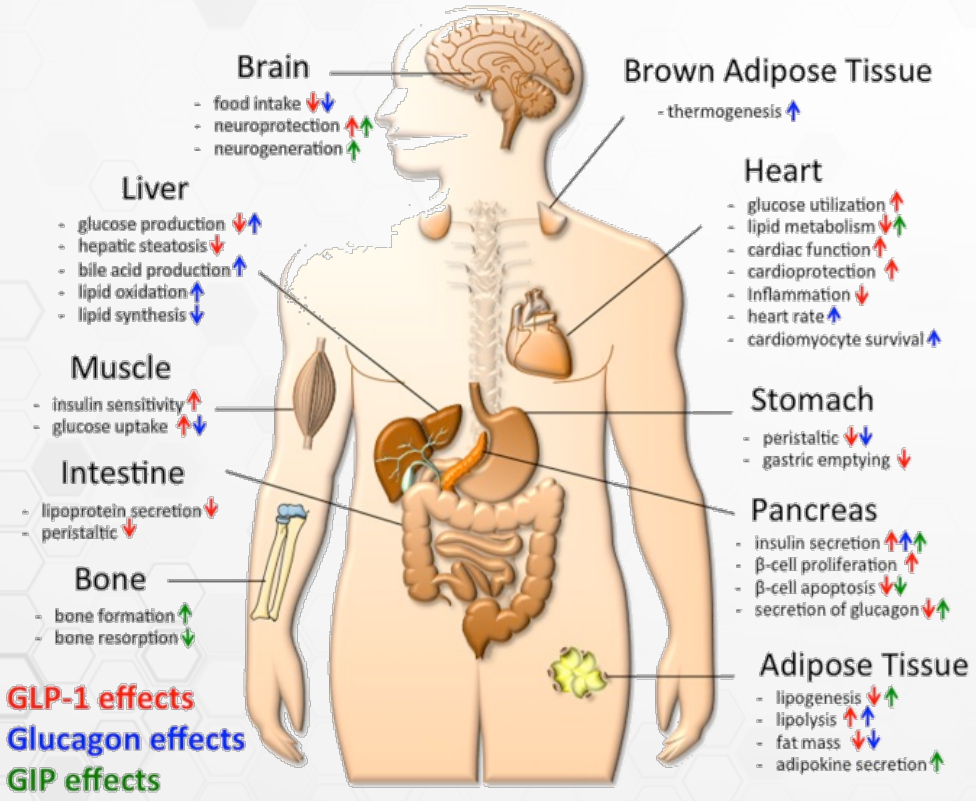


56% Type 2 DM
73% Obesity



Sanyal AJ, et al. *N Engl J Med*. Published online April 30, 2025. doi:10.1056/NEJMoa2413258

Twincretin as a Potential Therapeutic for Management of MASLD: Dual GIP and GLP-1 RA Tirzepatide

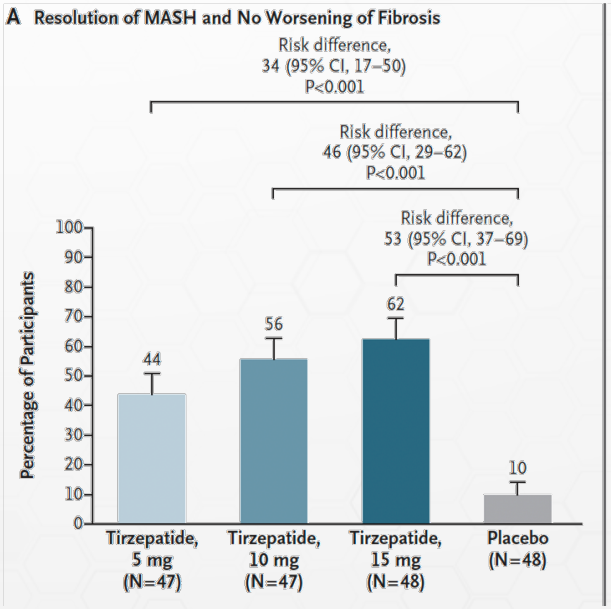


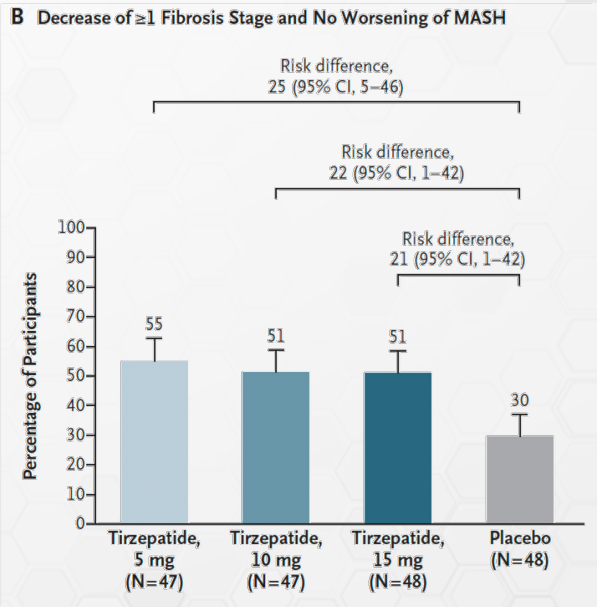
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

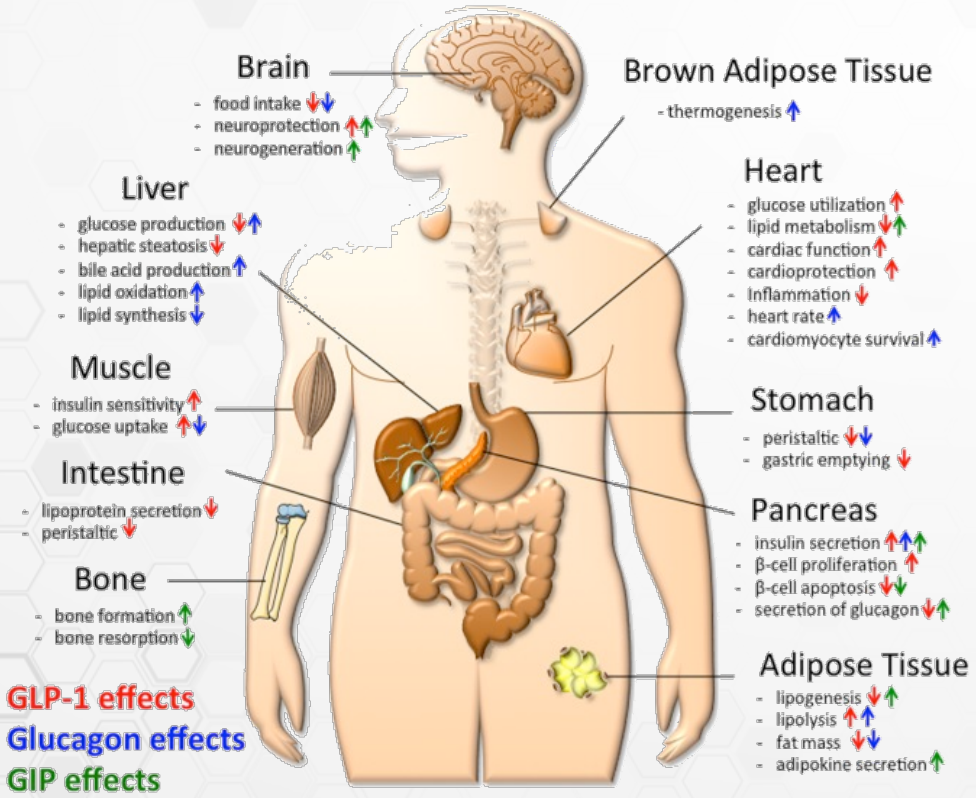
R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*





Brandt SJ, et al. *J Endocrinol.* 2018;238(2):R109-R119.

Twincretin as a Potential Therapeutic for Management of MASLD: GLP-1 RA/Glucagon RA Survodutide



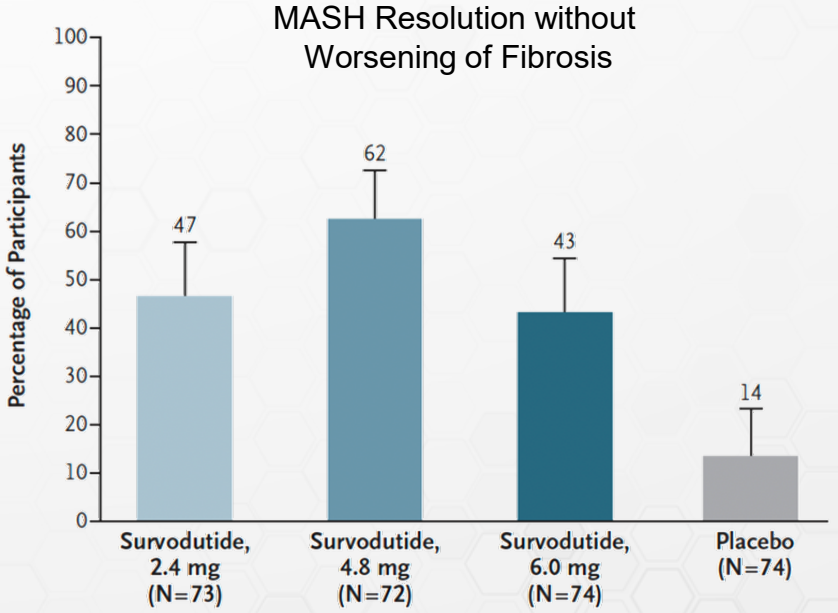
Brandt SJ, et al. *J Endocrinol*. 2018;238(2):R109-R119.

ORIGINAL ARTICLE

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Authors: 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* -8 Author Info & Affiliations

Published June 7, 2024 | DOI: 10.1056/NEJMoa2401755



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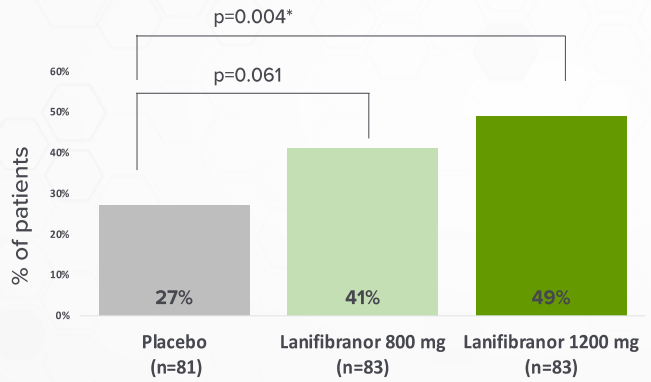
Emerging Incretin Targets and Agents

Drug	Target	Efficacy
Survodutide[1]	GLP-1 + GCG	Histologic improvement in MASH without worsening of fibrosis ($P < 0.001$)
Tirzepatide[2]	GLP-1 + GIP	Resolution of MASH without worsening of fibrosis ($P < 0.001$)
Retatrutide[3]	GLP-1 + GIP + glucagon	Reduction in hepatic fat fraction ($P < 0.001$)
Cotadutide[4]	GLP-1 + glucagon	Reduction in absolute and relative hepatic fat fraction (NCS)
Efinopegdutide[5]	GLP-1 + glucagon	Relative reduction in liver fat content vs semaglutide ($P < 0.001$)

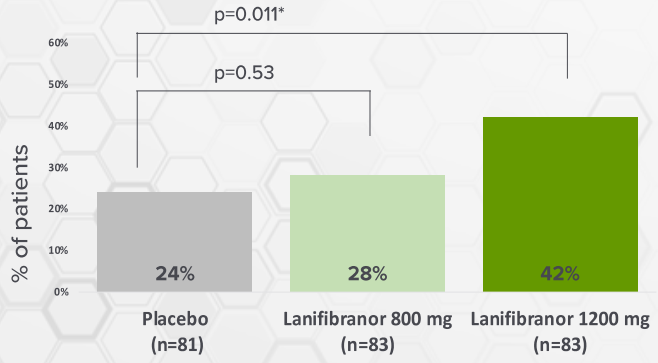
1. Sanyal AJ, et al; 1404-0043 Trial Investigators. *N Engl J Med*. 2024;391(4):311-319.
2. Loomba R, et al; SYNERGY-NASH Investigators. *N Engl J Med*. 2024;391(4):299-310.
3. Sanyal AJ, et al. *Nat Med*. 2024;30(7):2037-2048.
4. Shankar SS, et al. *Clin Gastroenterol Hepatol*. 2024;22(9):1847-1857.e11.
5. Romero-Gómez M, et al. *J Hepatol*. 2023;79(4):888-897.

Lanifibranor: Phase 2b NATIVE Trial (24-Week Treatment)

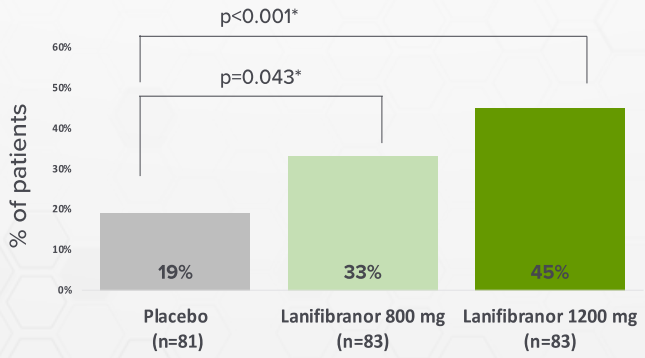
Primary Endpoint: Reduction of ≥2 Points of SAF Activity Score and No Worsening of Fibrosis



Secondary Endpoint: Improvement of ≥1 Stage of Fibrosis and No Worsening of NASH



Secondary Endpoint: Resolution of NASH and No Worsening of Fibrosis



- **Reduction in ALT, AST, GGT**
- **Improved glycemic indices**
- **Good cardiometabolic profile (increased HDL, decreased triglycerides)**
- **Decrease in markers of active fibrogenesis (Pro-C3, TIMP-1/MMP-2)**
- **Weight gain an issue but plateau effect reassuring**
  - 2.7 kg in 1200-mg group
  - 2.4 kg in 800-mg group
  - Shift from visceral to subcutaneous fat
  - Combo with GLP-1 and SGLT2 promising offset and further improvement in MACE

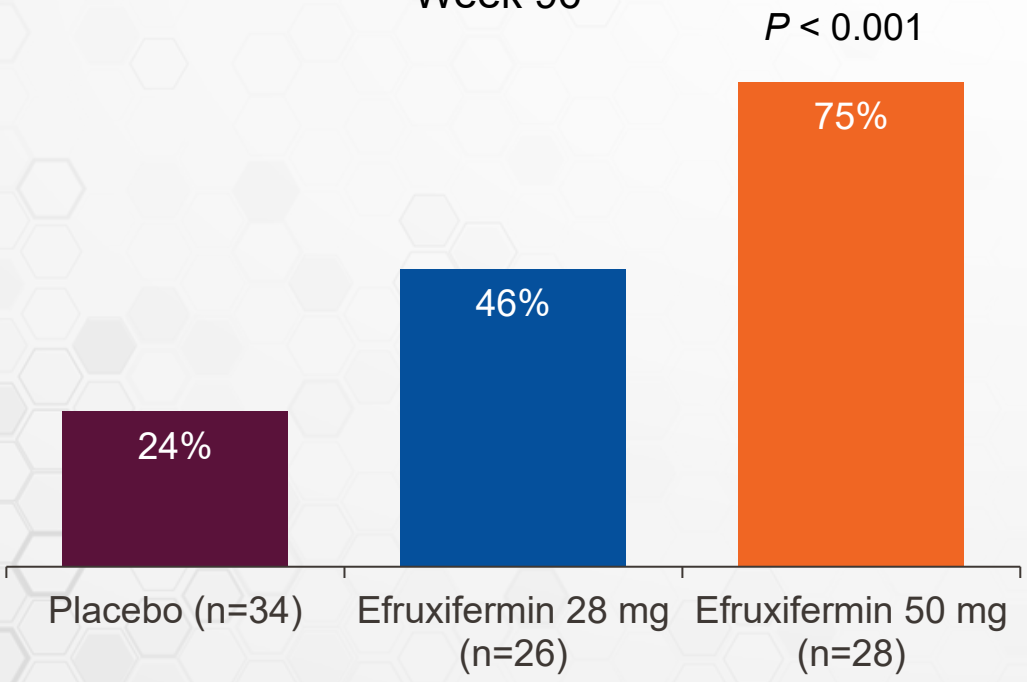
Ideal candidate: DM, non-obese, no history of CHF

Francque SM, et al. *N Engl J Med*. 2021;385(17):1547-1558.

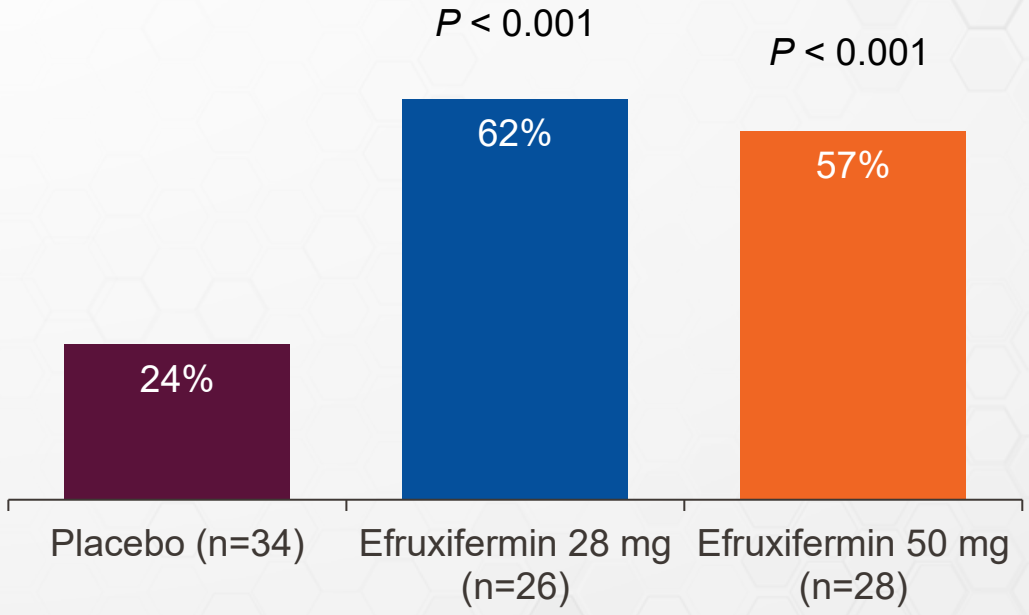
Efruxifermin: Phase 2b HARMONY Trial

Efruxifermin is a long-acting FGF21 analog

Primary Endpoint: Fibrosis Improvement
Efruxifermin 50-mg Dose Achieved Statistical Significance
Week 96



Key Secondary Endpoint: NASH Resolution
Both Efruxifermin Doses Achieved Statistical Significance
Week 96

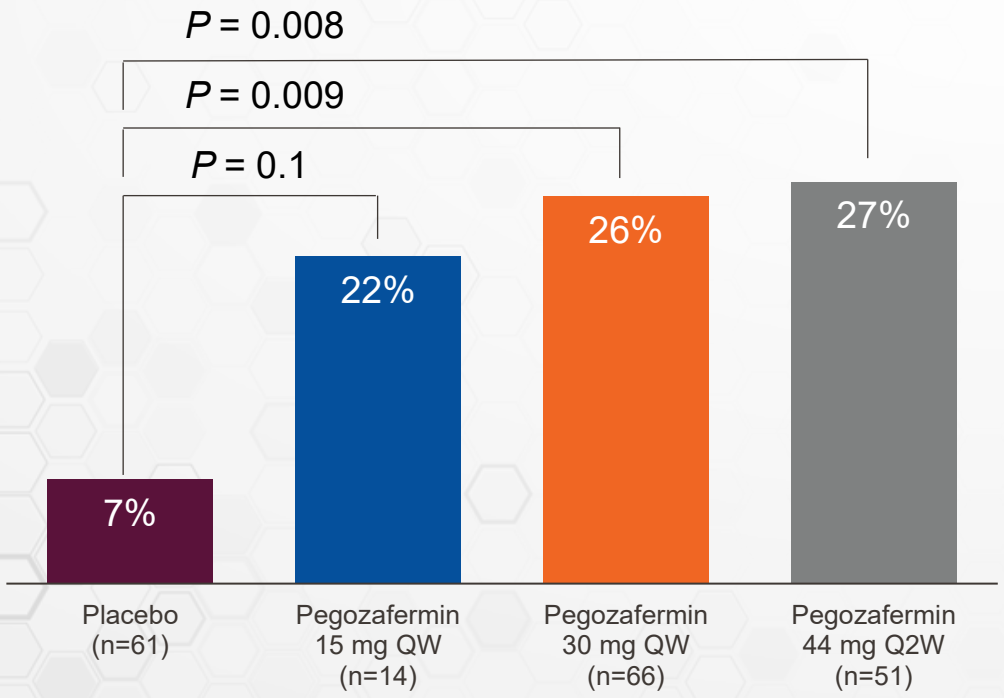


Phase 2b HARMONY study. Biospace.com. March 4, 2024.
https://www.biospace.com/article/releases/akero-therapeutics-reports-statistically-significant-histological-improvements-at-week-96-in-phase-2b-harmony-study/
Harrison SA, et al. Lancet Gastroenterol Hepatol. 2023:8(12):1080-1093.

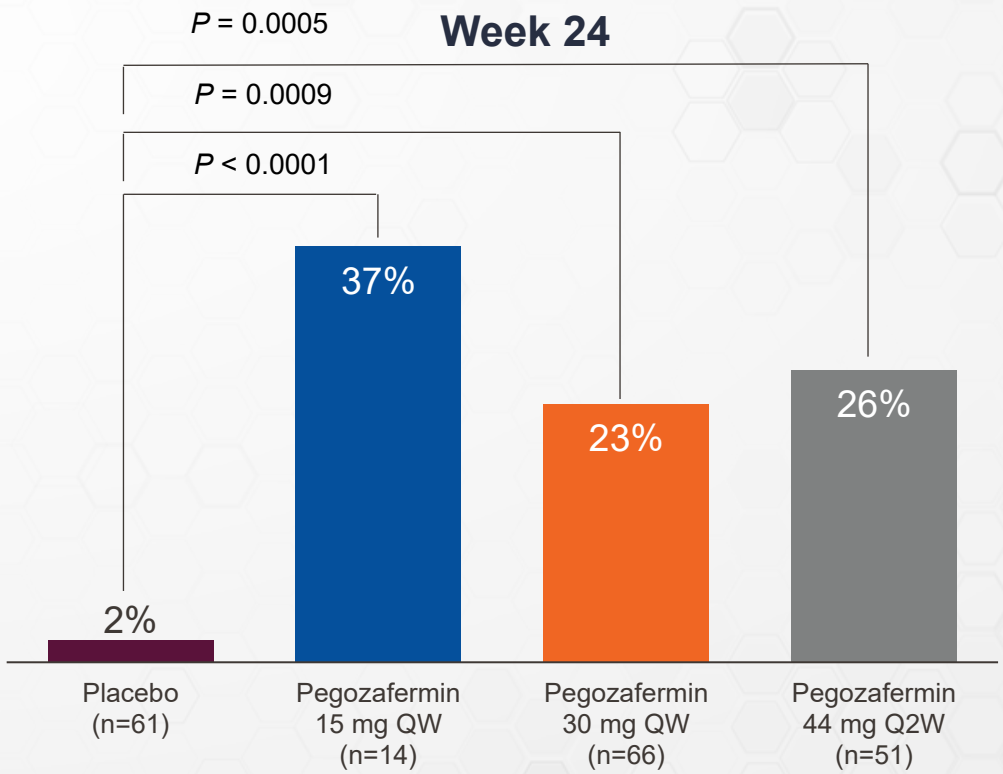
Pegozafermin: Phase 2b ENLIVEN Trial

Pegozafermin is a long-acting Fc FGF21 fusion protein

≥1-Point Fibrosis Improvement Week 24



NASH Resolution Week 24



QW, every week; Q2W, every 2 weeks.

Loomba R, et al. N Engl J Med. 2023;389(11):998-1008.

Take-Home Points

- First FDA-approved therapy for MASH: resmetirom
- Phase 3 ESSENCE data promising
- Weight loss improves MASH and fibrosis –
  no matter how you achieve it!!
- Rich pipeline of emerging therapies
- Personalize approach and attention to comorbidities
  - Diet and exercise remain foundational
    - > Exercise can improve MASH independent of weight loss
  - Multiple benefits to comorbidities: MASH, CVD, CKD, AUD, OSA

Concluding Remarks / Q & A

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