MASH EPIDEMIOLOGY AND MANAGEMENT

GastroHealth Symposium

February 21, 2026.

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OBJECTIVES

- A new naming convention
- Epidemiology and disease burden
- Pathogenesis
- Patient identification
- Assessing disease severity
- Where do we go from here?

SLD, MASLD, AND MASH

- After the 2023 EASL Meeting in Vienna, a multi-national group of liver disease societies announced new nomenclature that is both "Affirmative And Non-Stigmatizing."

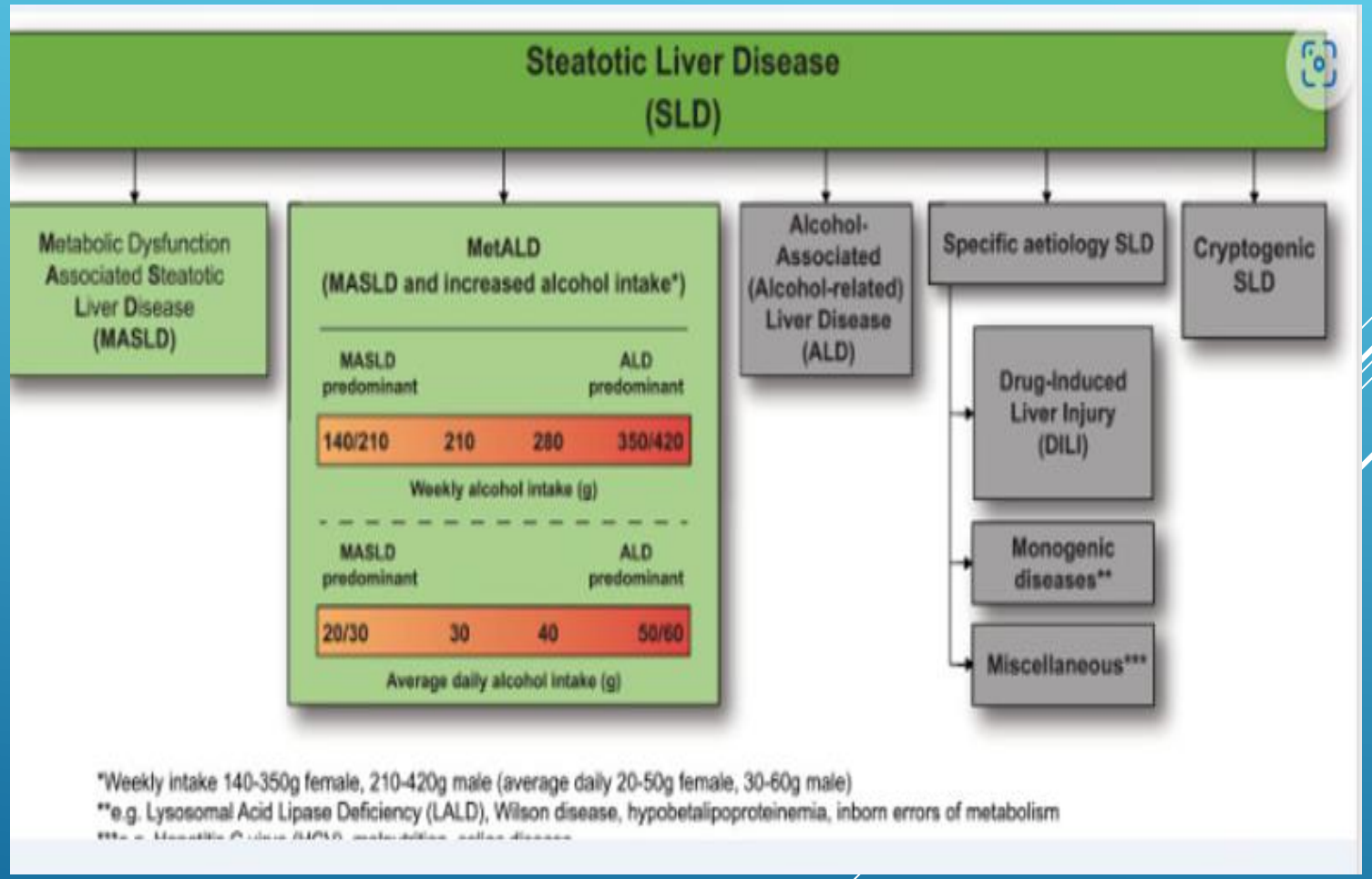
- The umbrella term is now **Steatotic Liver Disease (SLD**) to encompass the various etiologies of steatosis.

- Nonalcoholic fatty liver disease (NAFLD) will now be **Metabolic-dysfunction Associated Steatotic Liver Disease (MASLD).** MASLD encompasses patients who have hepatic steatosis and have at least one of five cardiometabolic risk factors(abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol).

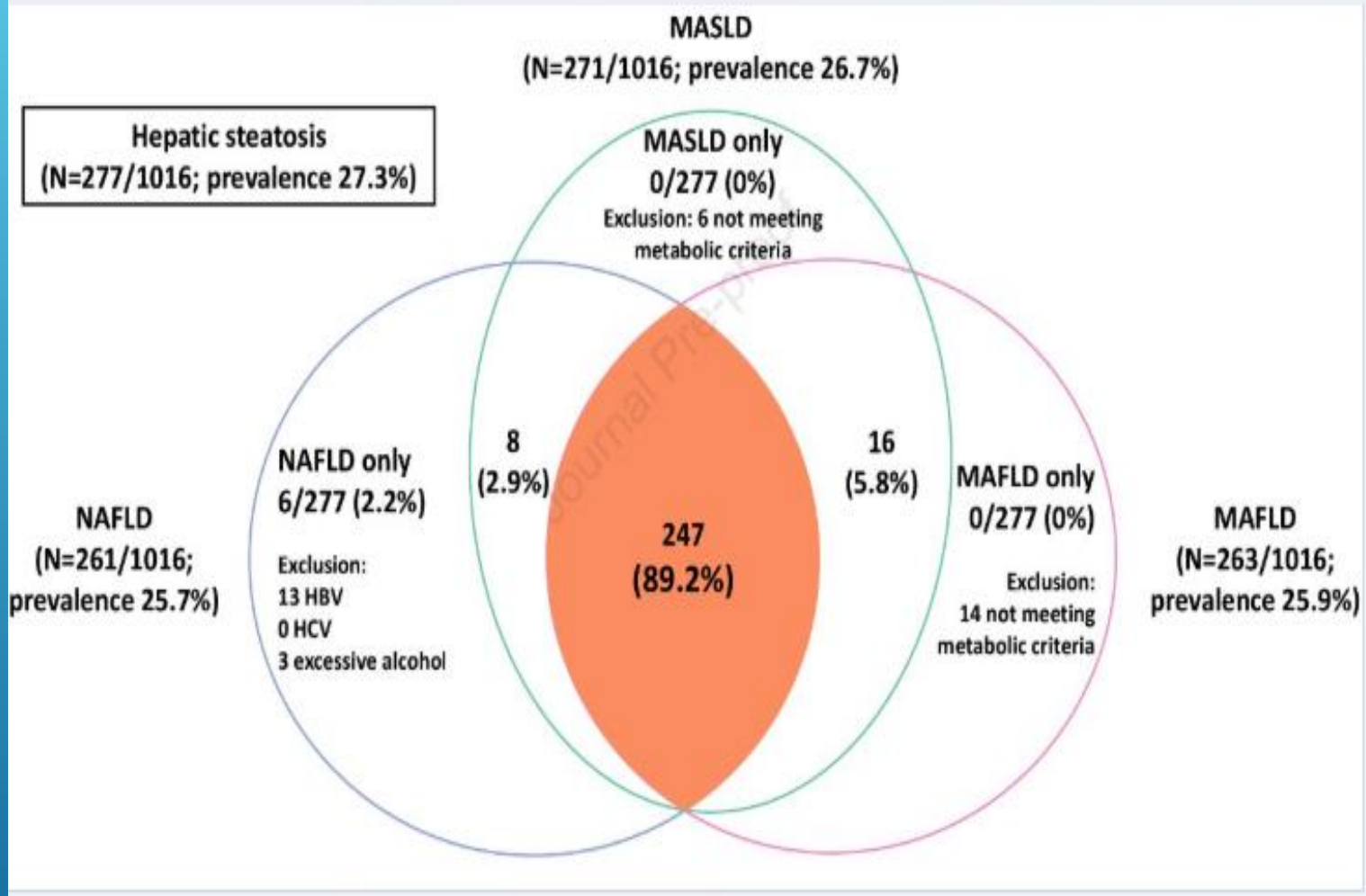
- **Metabolic dysfunction-Associated Steatohepatitis (MASH)** is the replacement term for nonalcoholic steatohepatitis (NASH).

SLD, MASLD, AND MASH

- more than a “non” disease
  ”alcoholic” is stigmatizing
  ”fatty” is stigmatizing
- current definition is one of exclusion and doesn’t recognize that multiple liver diagnosis may exist on a background of steatosis
- Need hepatic steatosis and at least 1 of 5 cardiometabolic criteria



Rinella et al Annals of Hepatology/J Hep/Hep 2023
AASLD MASLD Slide deck 2023

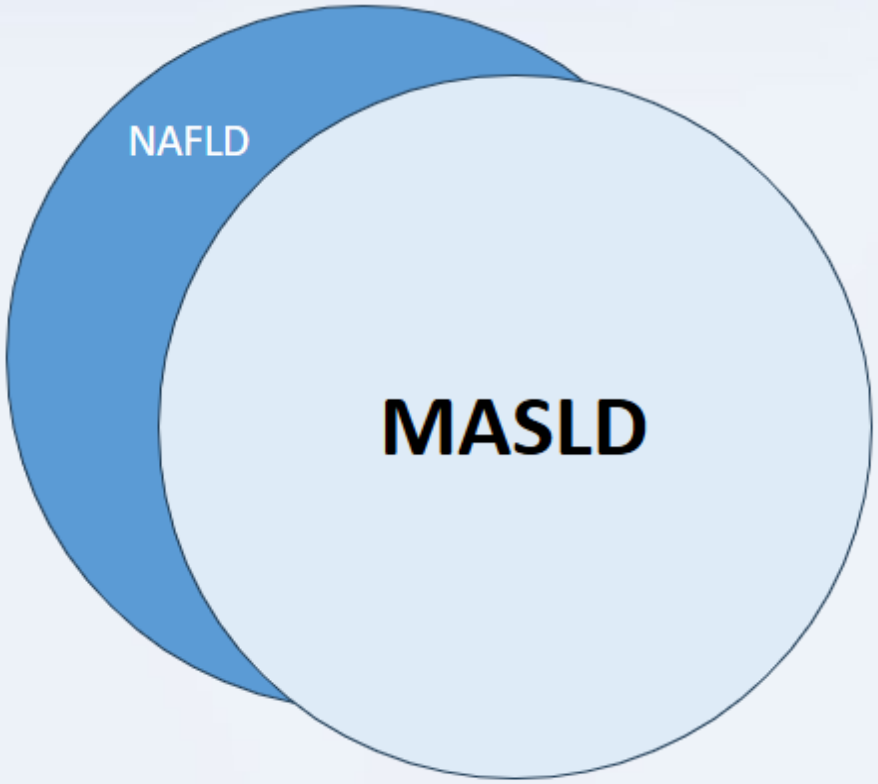


	% not fulfilling MASLD	% not fulfilling MAFLD
Community sample (HK) NAFLD	2.3%	5.4%
Incident NAFLD	10%	24%
Biopsy proven NAFLD	0.2%	2.2%

- **MASLD closer overlap with NAFLD than MAFLD in 3 Asian cohorts**

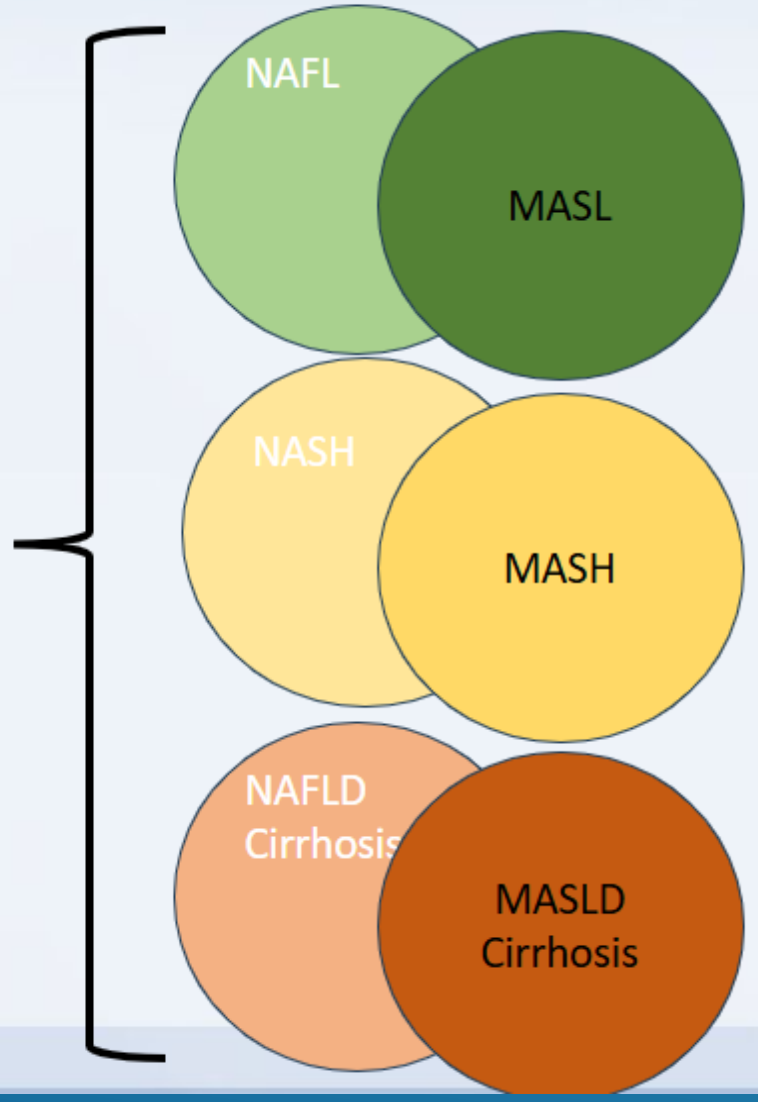
MASLD-NAFLD overlap = 92.1%

Does MASLD = NAFLD in the U.S.?



99% overlap between NAFLD and MASLD

TARGET-NASH data – 5746 patients



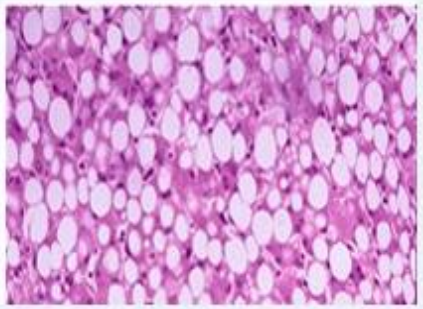
96.3% overlap. 57 patients that did not meet criteria due to lack of cardiometabolic risk factors

99.7% overlap. Six patients that did not meet criteria due to lack of cardiometabolic risk factors

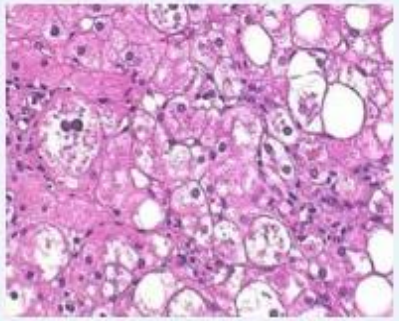
99.8% overlap. Four patients that did not meet criteria due to lack of cardiometabolic risk factors

Barritt et al Amer Jour Gastro 2024

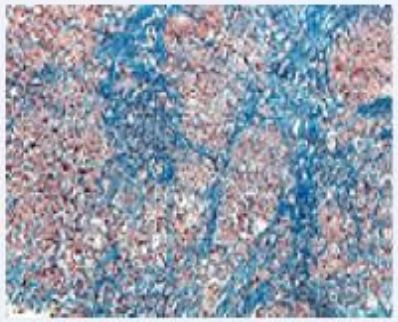
MASLD is a spectrum of disease



Steatosis



Metabolic dysfunction-Associated Steatohepatitis (MASH)

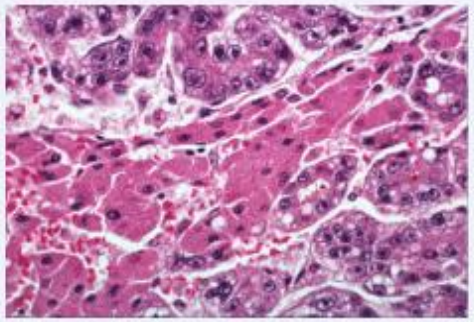


MASLD Cirrhosis

Cryptogenic Cirrhosis?

?

Hepatocellular Carcinoma

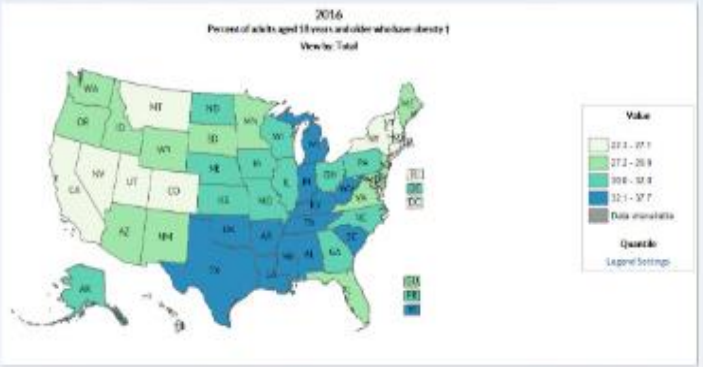


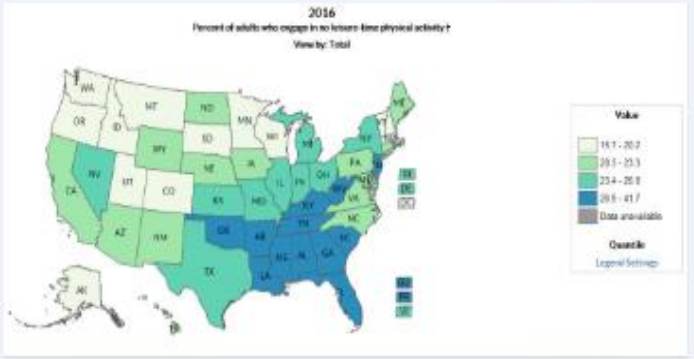
Liver Transplant

MASLD is common

- Prevalence depends on population studied and method used to make diagnosis
  - 1 in 3 American adults has simple steatosis (NAFL)
  - Ultrasound data estimates prevalence ~50% in Texas
  - NHANES III estimates range from 8-24%
  - Prevalence in bariatric surgery patients may be as high as 90%, up to 55% may have MASH and 12% with bridging fibrosis
  - Global prevalence 24%

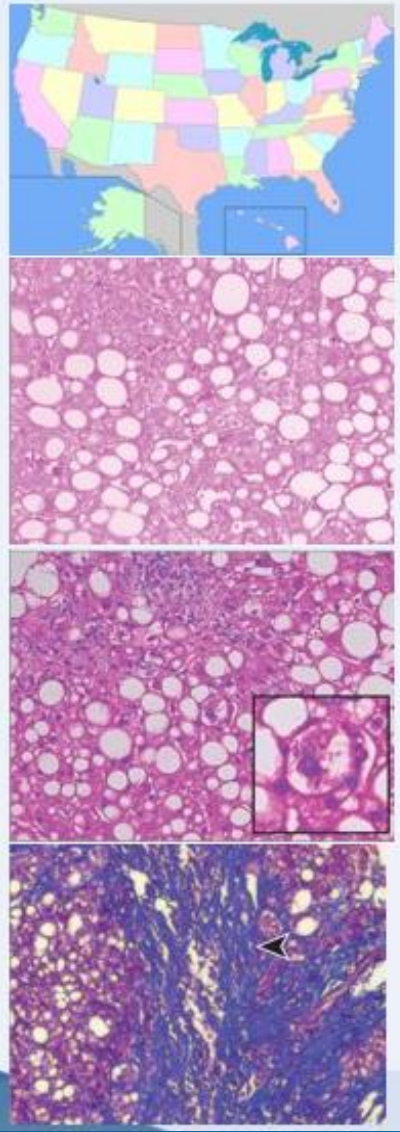
- Incidence of new MASLD rising in step with increasing rates of obesity, diabetes and physical inactivity





Williams, Gastro 2011, Clark et al AJG 2007, Younossi et al Hepatology 2016, www.cdc.gov accessed 2017

Just how common?



United States population
= **325,000,000**

Prevalence of simple steatosis = 30% = **97,500,000**

Patients with steatosis who progress to MASH = 20% =**19,500,000**

Patients with MASH who may progress to cirrhosis over 20 years = 20% =**3,900,000**

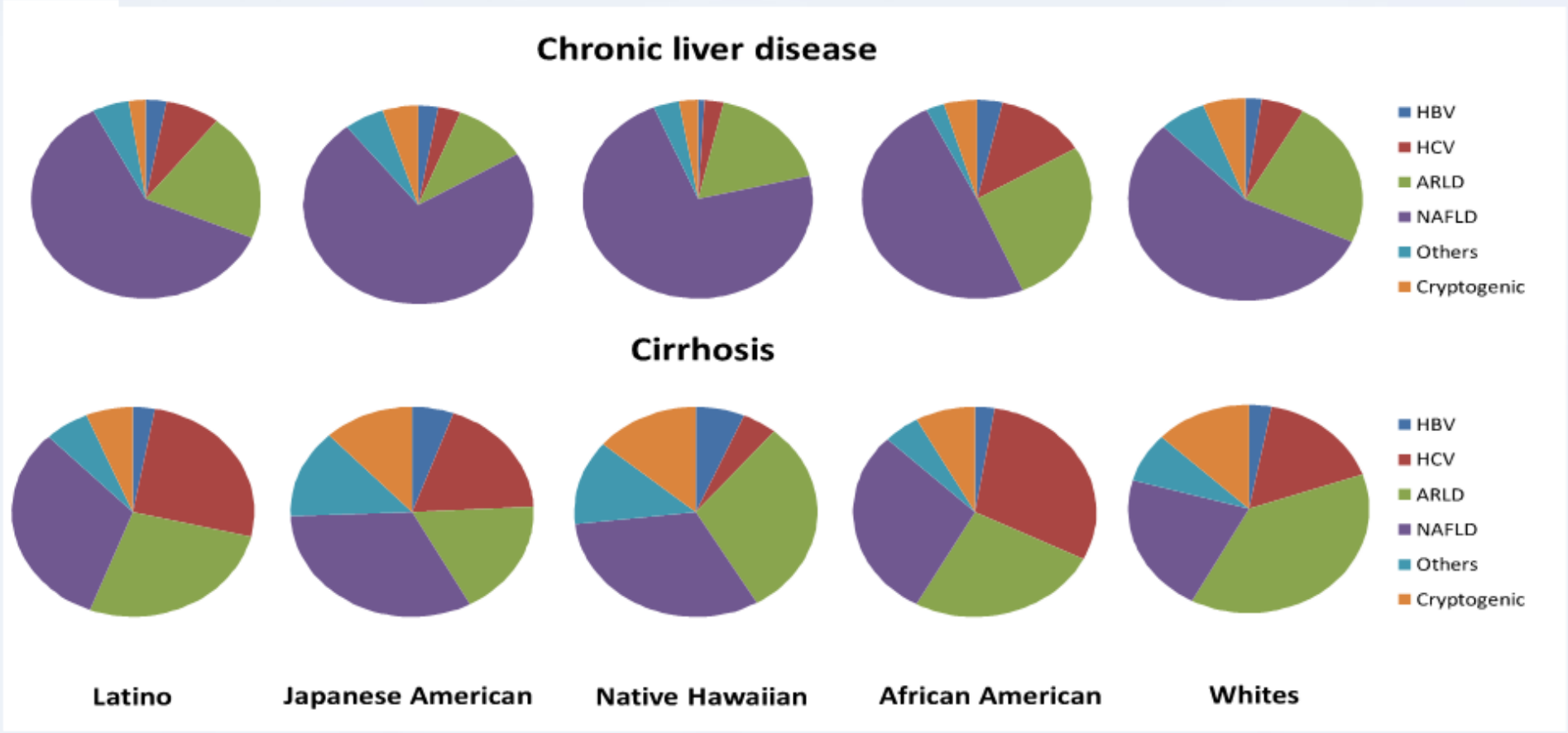
<u>Perspective:</u>

Patients with HCV ~ 3.5 million
Patients with Ulcerative Colitis ~ 800,000
Patients with Crohn's Disease ~ 700,000

If only 1% of patients with MASH cirrhosis are listed for OLT, this would be more than double the current size of the national waitlist

Rinella M. JAMA .2015, www.hepchope.com, www.cdc.gov

MASLD is the most common cause of chronic liver disease and cirrhosis in the US

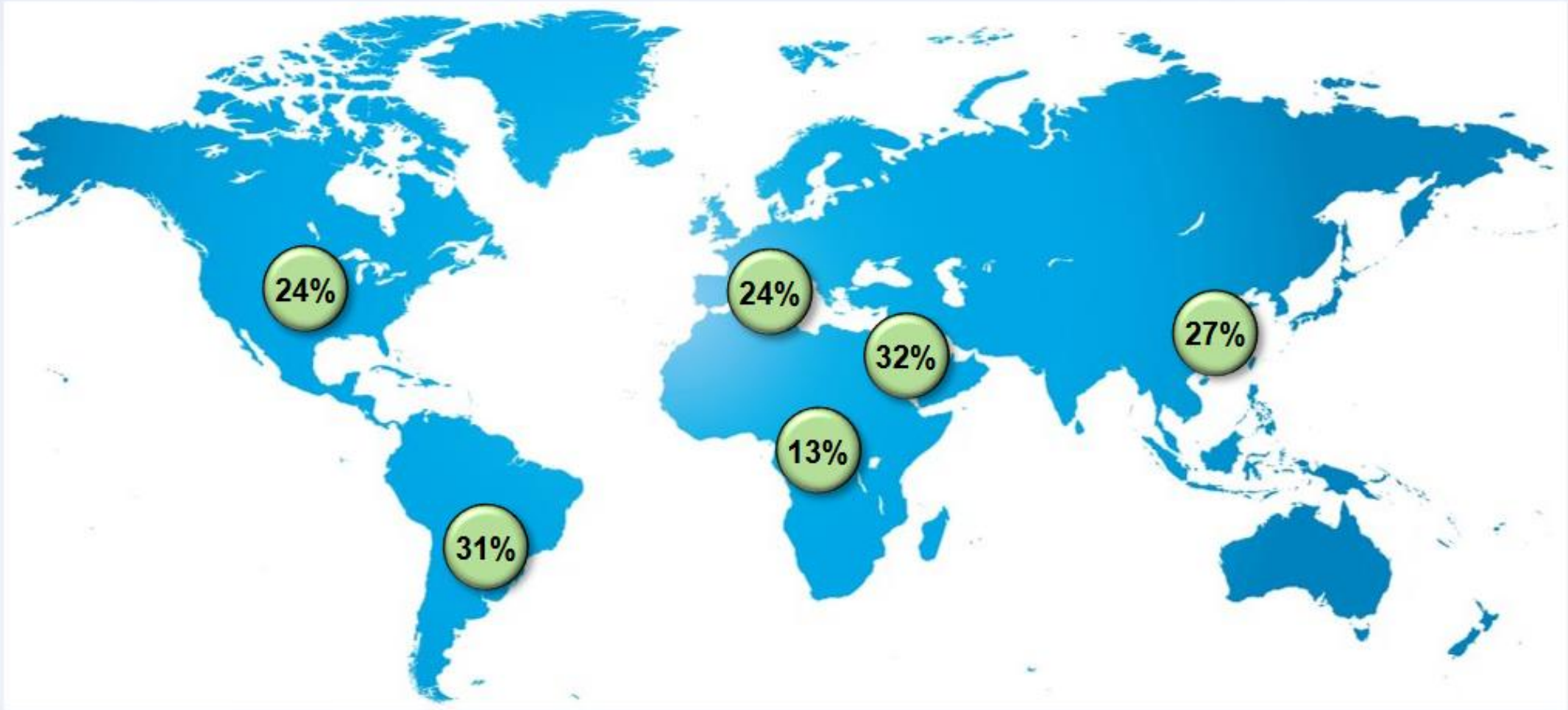


** via ICD-9 coding data

Setiawan VW, et al Hepatology 2016

MASLD is NOT a Western disease

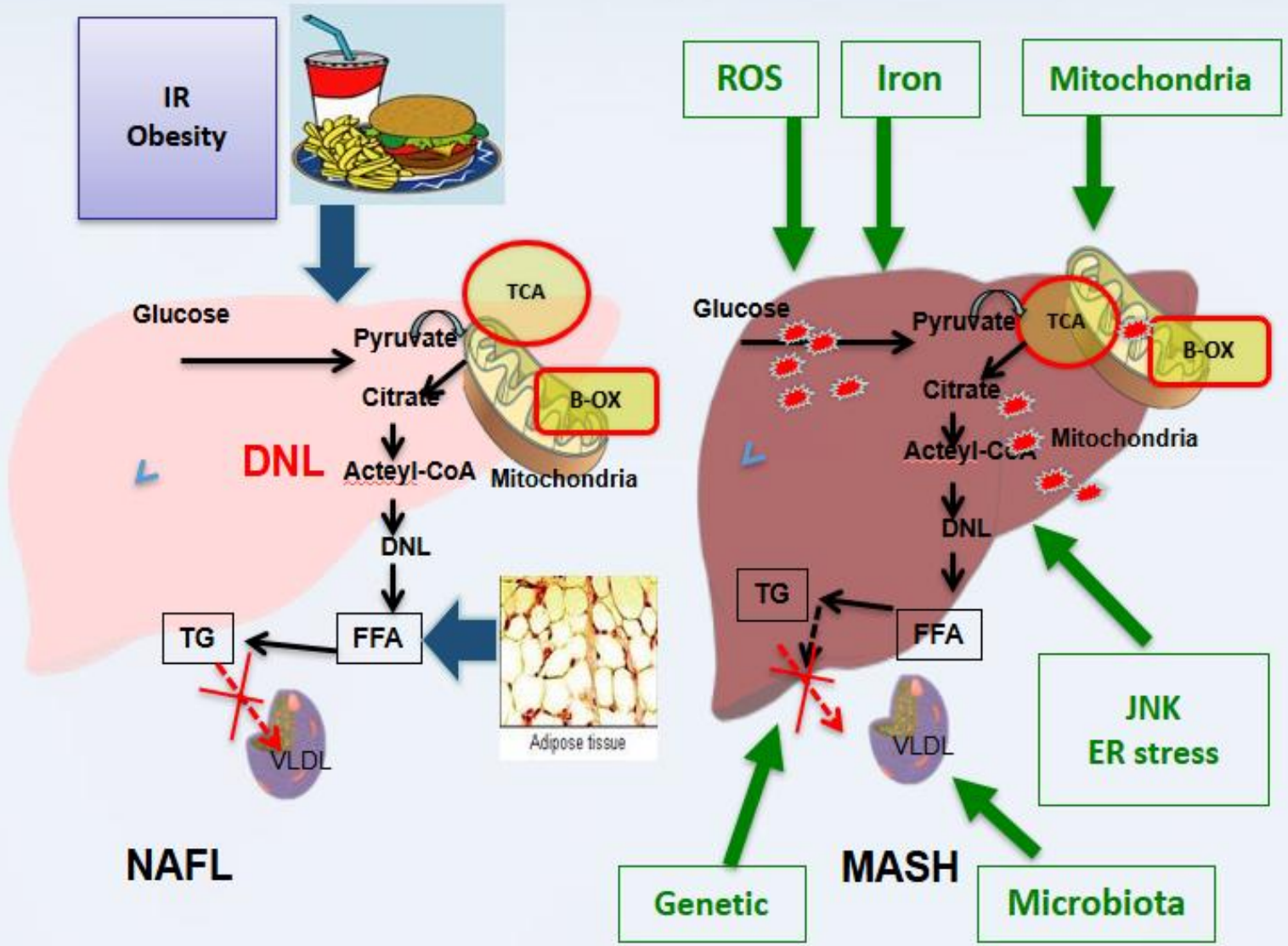
Estimated Global Prevalence of MASLD = 25%



Meta-analysis: MASLD diagnosed by imaging (US, CT, MRI/SPECT; n=45 studies).

Younossi ZM, et al. *Hepatology.* 2016.

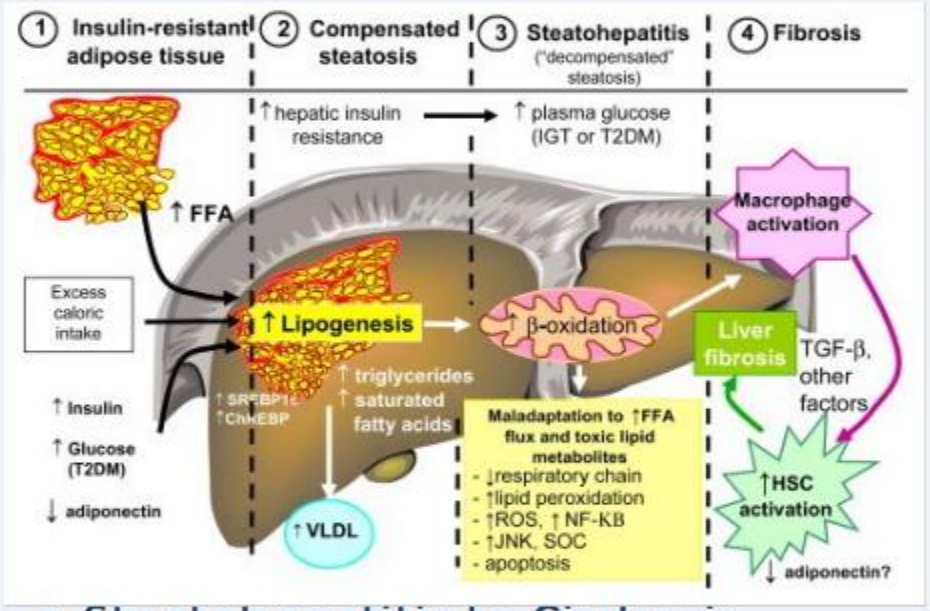
MASLD: Pathogenesis



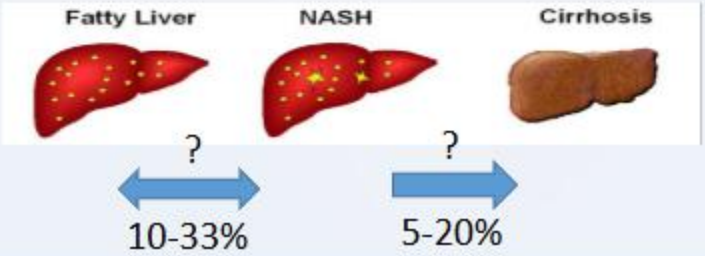
Noureddin, Mato J & Lu SC. Exp Bio Med. 2015

MASLD is a progressive disease

- Steatosis to Steatohepatitis



- Steatohepatitis to Cirrhosis



Who will progress?

- Risk Factors
  - Central obesity
  - Hypertension
  - Dyslipidemia
  - Type 2 Diabetes
  - Advancing age
  - Genetic modifiers (PNPLA3, TM6SF2)
- **ALT is not a reliable indicator of disease severity**

In 2023, the AASLD updated its 2018 Guidance on NASH to address:

- *Comorbid Conditions Associated with MASLD*
- *Initial Evaluation of Patients with MASLD*
- *Associated Endocrine Disorders*
- *MASLD in Lean Individuals*
- *Biomarkers and NITS for Diagnosis and Assessment of MASLD*
- *Lifestyle Interventions*
- *Bariatric Surgery*
- *The Use of Available Medications*
- *Surrogate Markers for Histological Treatment Response*

MASLD DIAGNOSIS REQUIRES EXCLUSION OF COMPETING AND CO-EXISTING ETIOLOGIES

- **Viral hepatitis, autoimmune liver disease, hemochromatosis, Wilson's disease,alpha-1-antitrypsin, drug induced liver injury**

- **Serum ferritin is commonly mildly elevated in MASLD**
  - If ferritin and transferrin saturation are elevated, exclude genetic hemochromatosis
  - Consider liver biopsy in setting of high ferritin and iron saturation
  - Ferritin >1.5xULN may be associated with more advanced fibrosis in MASH

- **Autoantibodies can have positive low titers in MASLD (ANA>1:160, ASMA>1:40)**
  - May require liver biopsy to assess for autoimmune disease if

  >5x ULN enzymes, high globulins, high total protein to albumin ratio

Risk Factors Associated With MASLD

Common Comorbidities With Established Association

- Obesity
- Type 2 diabetes
- Dyslipidemia
- Metabolic syndrome*
- Polycystic ovary syndrome

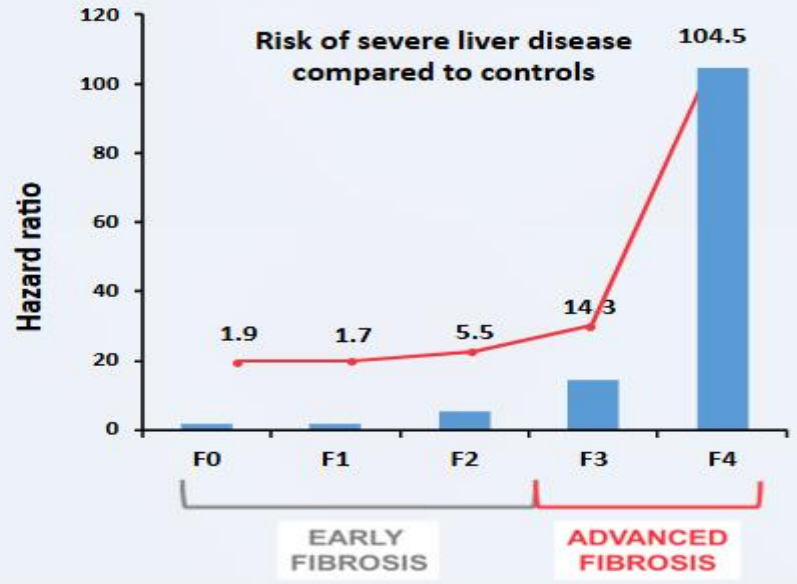
Other Conditions Associated With MASLD

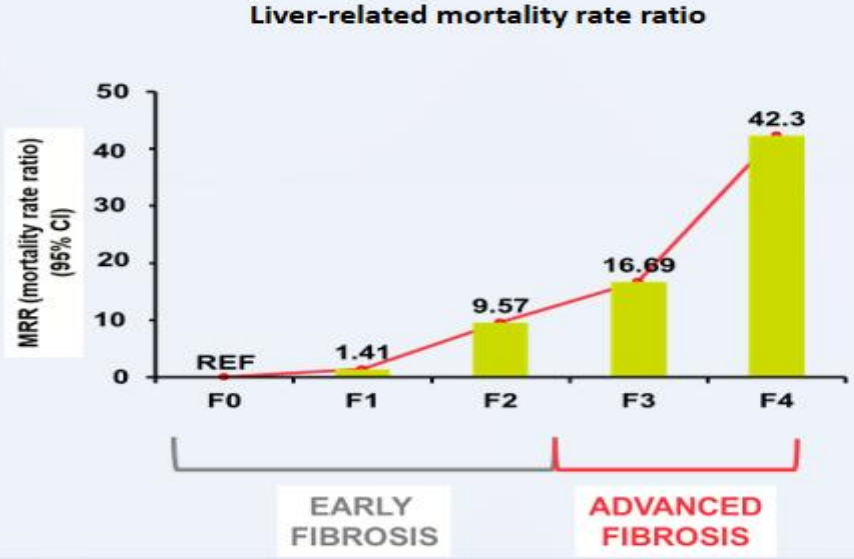
- Hypothyroidism
- Obstructive sleep apnea
- Hypopituitarism
- Hypogonadism
- Pancreatoduodenal resection
- Psoriasis

Chalasani N, et al. Hepatology. 2018.

Why is assessing fibrosis important?

Increasing fibrosis increases the risk of liver-related morbidity and mortality





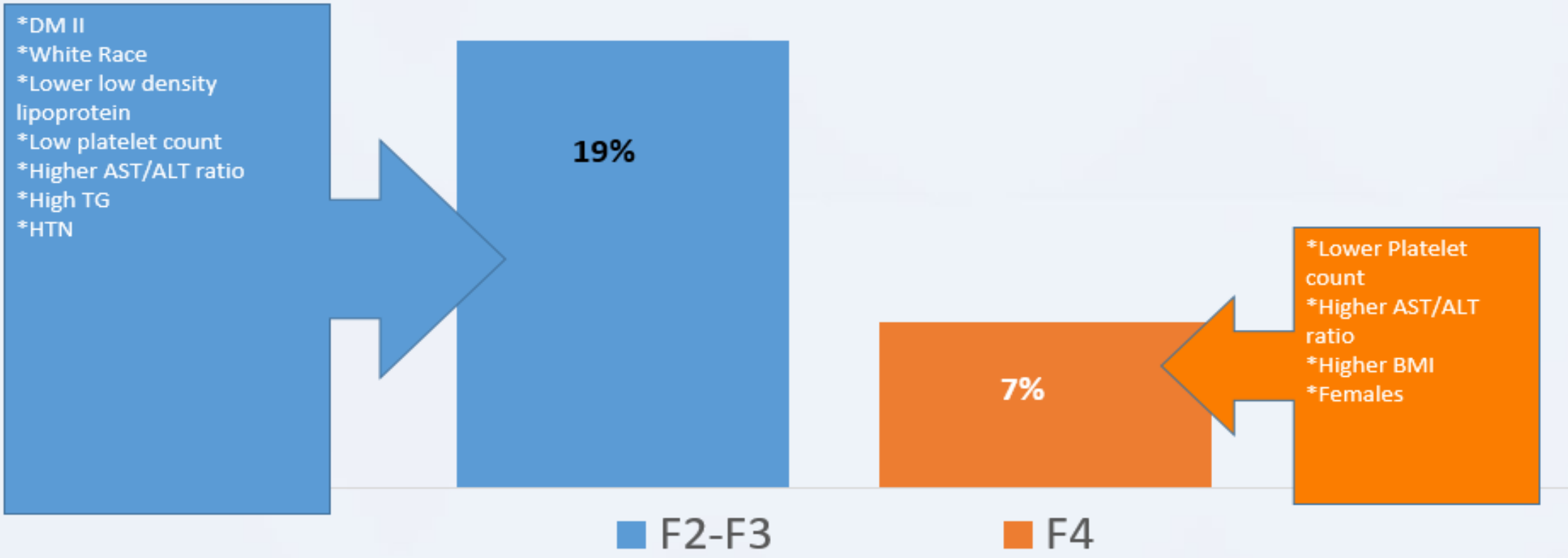
Hagström H et al. J Hepatol 2017; Dulai PS et al. Hepatology 2017

- ***Advanced fibrosis exponentially increases the risk of liver-related morbidity and mortality. Both of these graphs illustrate that the risk of liver-related morbidity (Hagström et al, 2017) and mortality (Dulai et al, 2017) increase as fibrosis stage increases and patients with advanced fibrosis are at the greatest risk.***

Hagström H et al. *J Hepatol* 2017;67:1265 –1273.
Dulai PS et al. *Hepatology* 2017;65(5):1557–1565.

Liver Enzymes do Not Predict Severity of Disease!

Prevalence of F2-F3 and F4 biopsy-proven MASLD and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <40 U/L



Gawrieh et al AJG;2019

Some of the Noninvasive Diagnosis of Fibrosis in MASLD

Serologic Markers

- **Simple (Free!)**
  - FIB-4
  - NFS
- **Complex**
  - Fibrospect
  - ELF
  - Pro-C3

Imaging

- **Elastography**
  - VCTE
  - MRE
  - Multiparametric
  - ARFI

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

AASLD

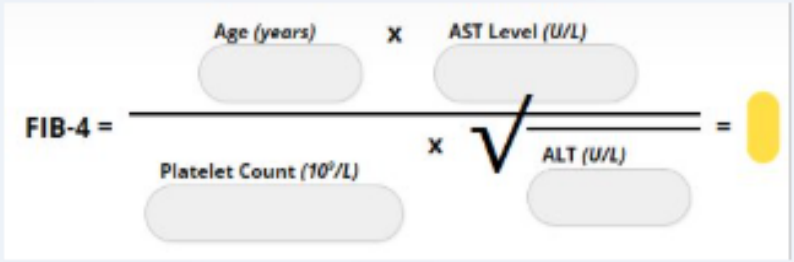
Pro-C3

Non-invasive assessment of disease

- Several clinical prediction scores for assessing severity of disease
  - MASLD fibrosis score (NFS)

    = 1.675+ (0.037*age) + (0.094*BMI) + (1.13 if DM) + (0.99* AST/ALT)- (0.013*plt) – (0.66*alb)

  - FIB-4

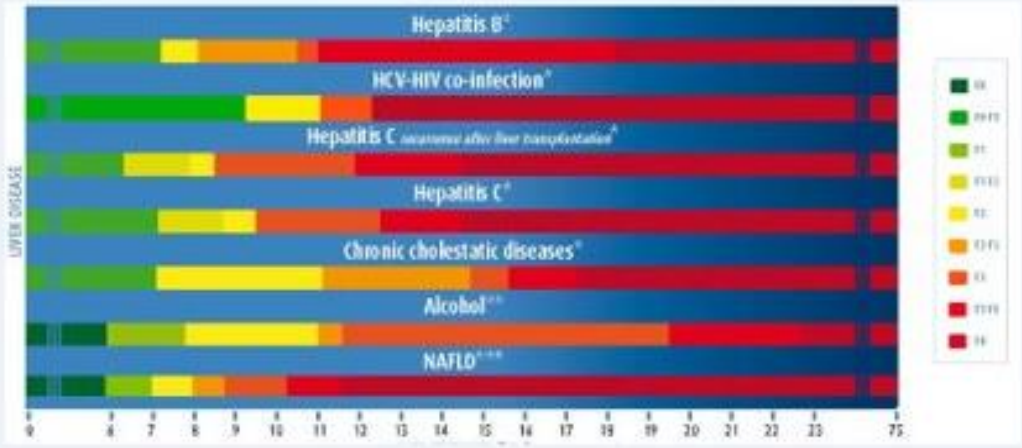


- Both are reasonable to use.
  - Comparable AUROC scores for advanced fibrosis
    - NFS 0.81, FIB-4 0.82
  - Inexpensive
  - On hand held devices
  - Many others with similar accuracy

Sterling et al, Hepatol 2006, Angulo et al, Hepatol 2007, Angulo et al, Hepatol 2010, Kim et al, Radiology 2013

Non-invasive imaging

- Vibration Controlled Transient Elastography (VCTE)
  - Liver stiffness measured in kilopascals and correlated with fibrosis stage, F0-F4
  - Must know disease etiology to interpret score
  - AUROC for F3 or higher disease 0.93 in MASLD

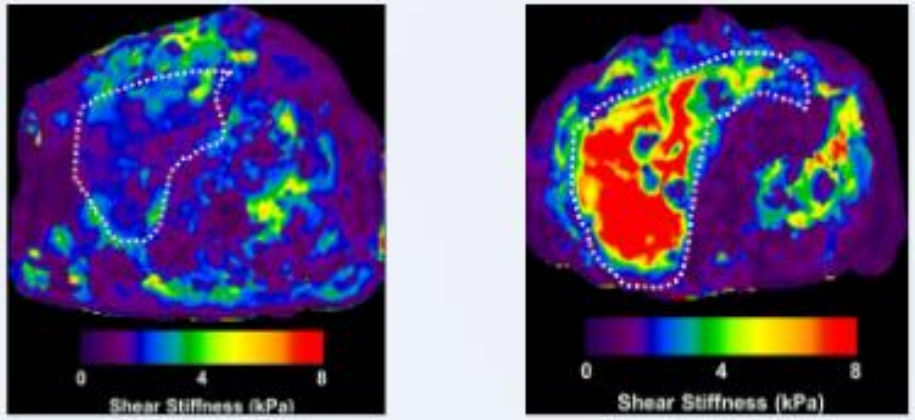


- Controlled Attenuation Parameter (CAP)
  - Steatosis measured in dB/m and correlated with steatosis grade, S0-S3
  - AUROC score for S1 and greater 0.86

Wong, Hepatol 2010; Karlas, J Hepatol 2017

Magnetic resonance imaging technology

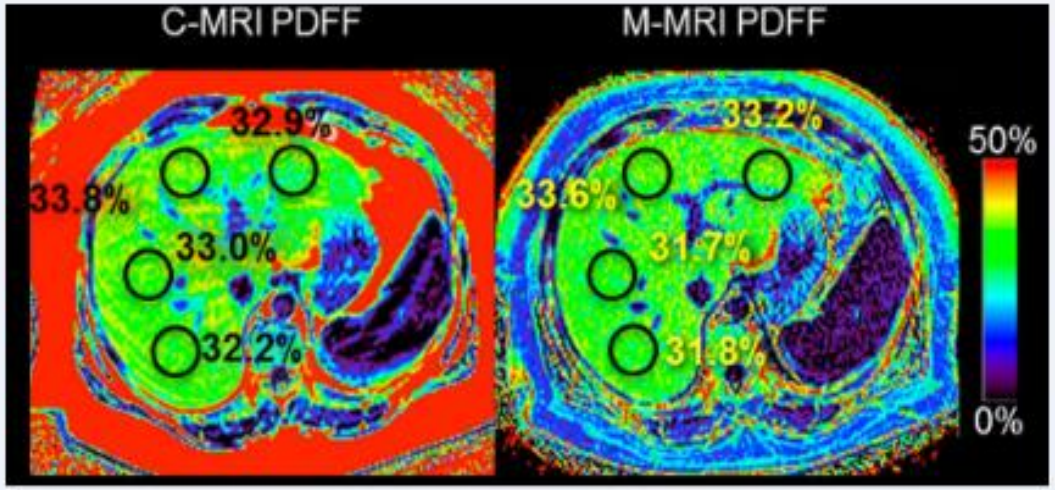
- MR-Elastography (MRE) for Fibrosis
  - 2D and 3D MRE have AUROC >0.92
  - Multiple single center trials show MRE>VCTE



No fibrosis

Advanced fibrosis

- MR-Proton density fat fraction for steatosis (MR-PDFF)
  - MR-PDFF>CAP for fat quantification



Kim, Radiology 2013, Caussy, Hepatology 2018, Hsu, Clin Gastroenterol Hepatol 2018

Liver biopsy – a flawed gold standard?

- Liver biopsy is the referent standard for assessing MASH

- Reviewed how MASH biopsies were reported and assessed agreement with a centralized pathologist
- 21-40% of reports missing key descriptors of MASH

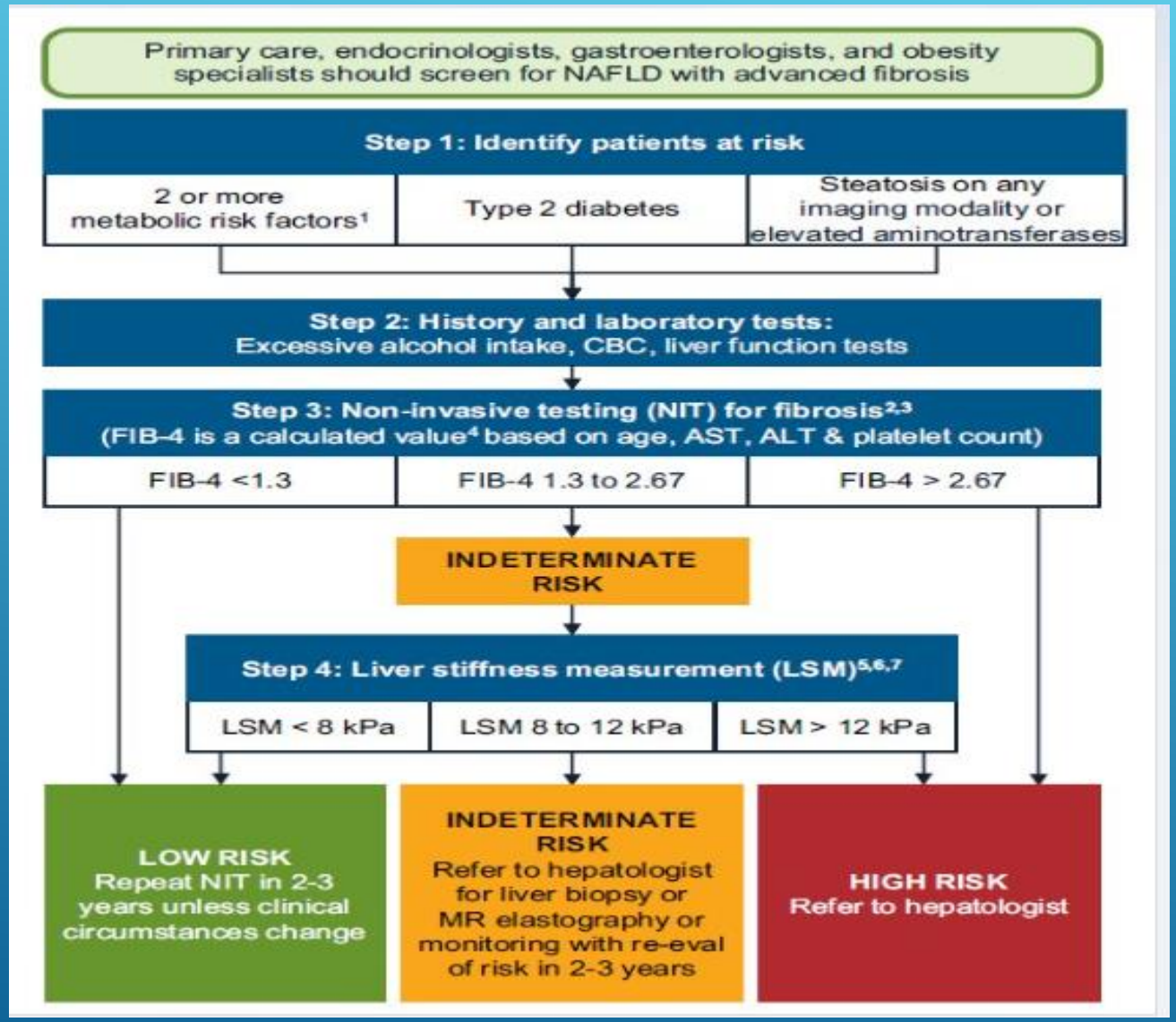
MASH clinically defined as:

- Elevated ALT + hepatic steatosis on biopsy or imaging,
- ≥1 of the following: BMI ≥ 30kg/m2, type 2 diabetes mellitus, dyslipidemia.

- 75-91% concordance between the expert central pathologist diagnosis and TARGET-MASH clinical definition for MASH

Histological Characteristic	Number of Pathology Reports Compared	Weighted Kappa Statistic (95% CI)	Concordance Interpretation
Steatosis	57	0.364 (0.2029, 0.5242)	**Fair**
Lobular Inflammation	29	-0.081 (-0.1847, 0.0220)	**Poor**
Portal Inflammation	31	0.210 (-0.0376, 0.4580)	**Fair**
Hepatocyte Ballooning	26	0.117 (-0.0708, 0.3038)	**Slight**
Fibrosis Stage	69	0.575 (0.4603, 0.6894)	**Moderate**
Scoring System			
NAFLD Activity Score	38	0.237 (0.0591, 0.4150)	**Fair**
Brunt Grade (Inflammation)	26	0.384 (0.1591, 0.6082)	**Fair**
Brunt Stage (Fibrosis)	69	0.590 (0.4775, 0.7019)	**Moderate**

CLINICAL PATHWAY MASLD



Gastroenterology 2021;161:1657–1669

TREATMENT

- Lifestyle interventions
- Currently available pharmacotherapy
- Surgical intervention
- Products in development

WHAT DOESN'T WORK

- Focusing only on the liver
- Providers may have a hard time convincing some patients that an (a)symptomatic disease is worth their attention
- Liver cirrhosis and decompensation events are abstract and seem decades away for people who have not had a personal/family experience with ESLD
- BUT…. Liver disease is important!

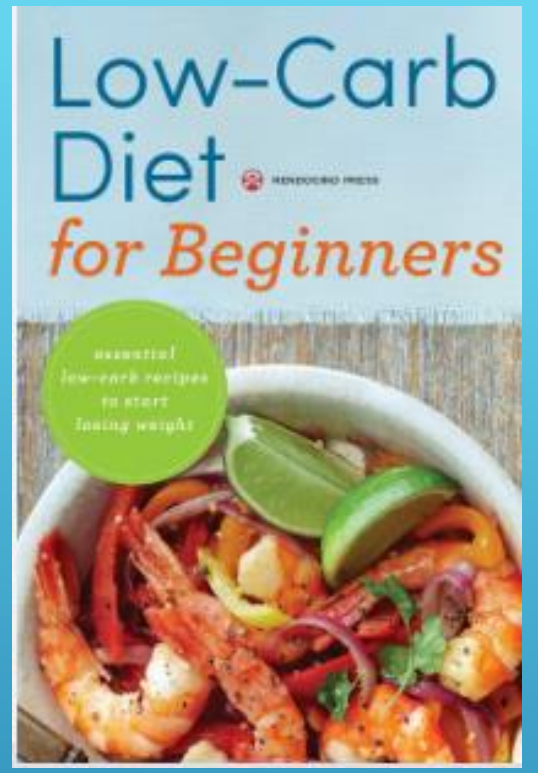
What works:

- An appeal to the gut
- There is so much (mis)information about diet available, many patients are over whelmed
- Many patients have well meaning but maladaptive dietary strategies
- Counsel about liquid calories, alcohol avoidance, and portion control
- **Consider referring any patient who will listen to a nutritionist!**

Abbas et al Am J Gastroenterol 2022

Nutritional Resources		
US department of agriculture (USDA)	www.nutrition.gov	USDA sponsored website with nutrition and recipe resources from credible sources
American Liver Foundation	www.liverfoundation.org	Multiple patient resources for a variety of liver disease
NIH Nutrition	www.niddk.nih.gov/health-information/diet-nutrition	General nutrition information with weight loss and nutrition myth busting
Supplemental Nutrition Assistance Program (SNAP)	www.fns.usda.gov/snap/supplemental-nutrition-assistance-program	USDA resource to provide nutrition benefits to supplement the food budget of needy families so they can purchase healthy food
MyPlate	www.myplate.gov	USDA resource with dietary guidelines and information about food planning during the pandemic
Academy of Nutrition and Dietetics	www.eatright.org	Health eating advice and links to find nutritionists in a patient's home zip code

- Basics to consider
- Mediterranean diet
- Reduced carbohydrate diet
- Coffee (black)



COFFEE!

- >2.25 billion cups of coffee consumed worldwide daily
- Coffee has been credited in improving many liver diseases
- HCC, ETOH, HCV
- MASLD
- Reduces intrahepatic fat
- How much is enough?
- Those who drink 2+ cups daily have ½ rate of chronic liver disease compared to those who drink <1cup daily
- 38% lower risk of HCC (any vs. none)

CV risk?

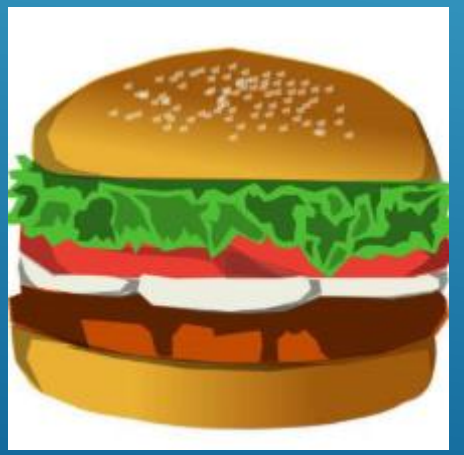
- meta-analysis of prospective studies overall, no significant association between coffee consumption and the risk of CV disease was observed

Park, Am J Cardiol 2022, Ruhl, Gastro 2005, Ray, Nat Rev Gast Hepatol, 2013. Sinha, Hepatology, 2013. Barritt, AGA Perspectives, 2013

AVOID!!

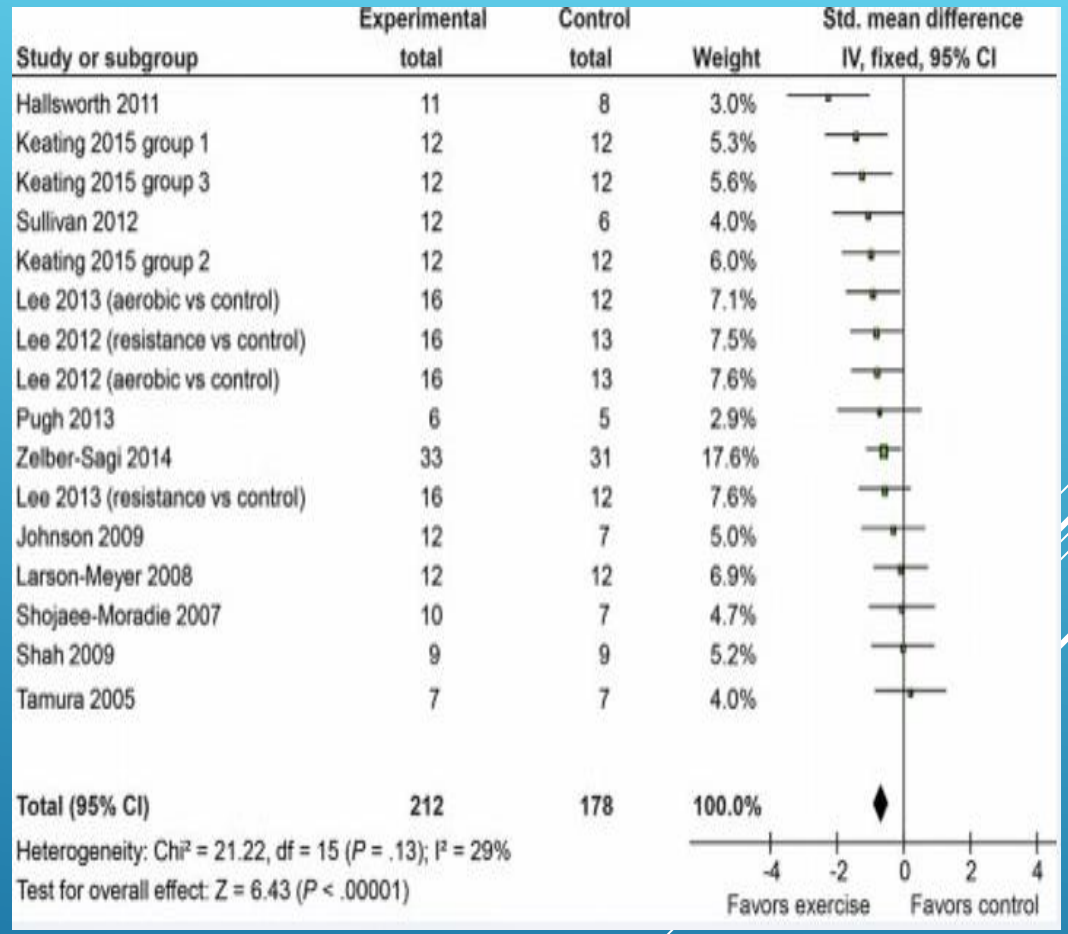
- - Lots of fatty protein

- "Fast Food"
- Heavily processed foods
- Sweetened soft drinks and juices
- Alcohol
- Bakery products



EXERCISE!

Exercise resources		
NIH National Institute on Aging	www.nia.nih.gov/health/exercise-physical-activity	Variety of resources including staying motivated to exercise, exercising with chronic conditions, and physical activity tracking tools
National Council on Aging	www.ncoa.org	Exercise programs that promote senior fitness
Silver Sneakers	https://tools.silversneakers.com	Access to live online exercise classes, on-demand videos, and thousands of fitness locations and classes
Academy of Nutrition and Dietetics	www.eatright.org	Workout ideas, nutrition advice, and tips for family exercise
MOVE! Options of Care for Veterans	www.move.va.gov	resources for veterans to implement lifestyle changes and provide motivation for exercise



Orci et al. Clin Gastro Hepatol 2016

AEROBIC VS RESISTANCE

2017 Systematic Review

- Median effective protocols:
- Aerobic: 4.8 METs, 40 min/session,3x/wk for 12 wks
- Resistance: 3.5 METs, 45min/session, 3x/wk for 12 wks
- **Both reduce hepatic steatosis**
- Consider resistance training inpatients with poor cardio respiratory fitness/ unable to do aerobic exercise

Hashida R, et al. J Hepatol 2017; 66(1): 142-152.

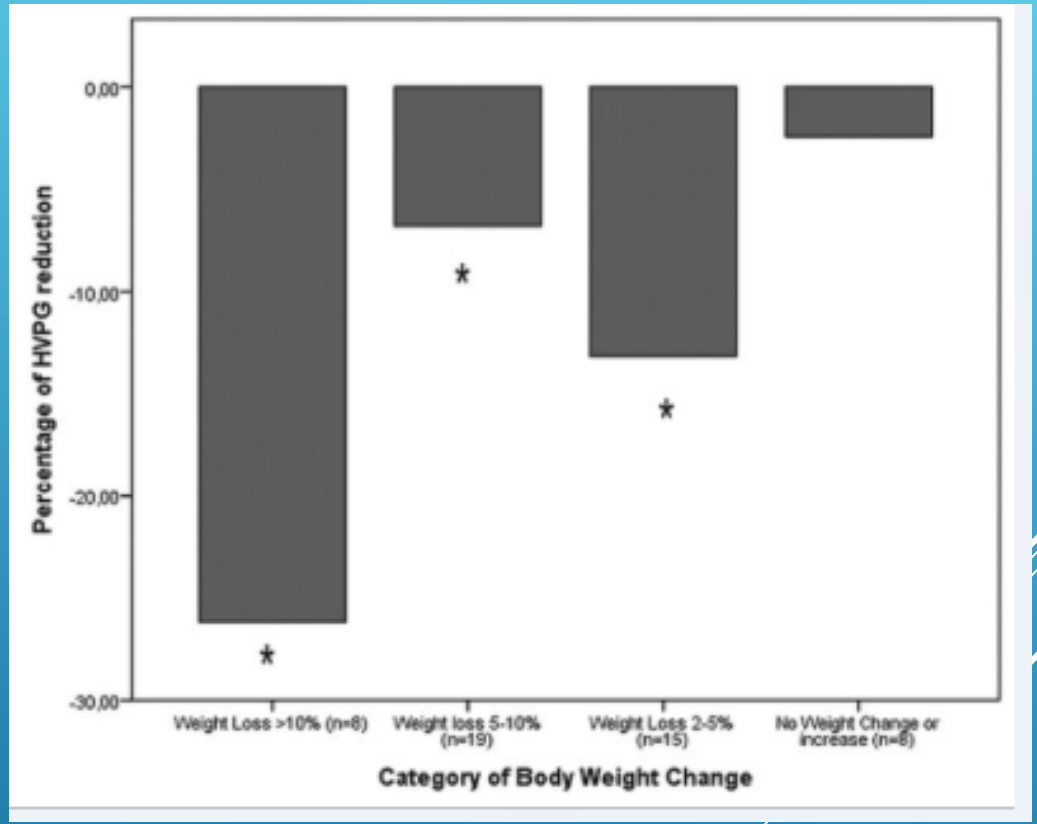
Table 6. Comparisons of patients' characteristics and changes in hepatic steatosis between aerobic and resistance exercise.

	Aerobic exercise	Resistance exercise	*p* value
Number of protocols (number of articles)	13 (9)	4 (4)	
Number of enrolled subjects	314	68	
Age (years old)	44.2 (15.2-61)	52.0 (45.9-55.5)	0.1064
Sex (Male; %)	63.45	100	0.6018
BMI	31 (27-36)	32 (29-25)	0.4190
Body weight (kg)	85 (69-107)	94 (72-98)	0.4953
Dietary counseling (Yes)	46.2% (6/13)	25.0% (1/4)	0.4522
Changes in BMI	-1 (-4 to 1)	-0.5 (-1 to 0)	0.4106
Changes in ALT level	-12 (-56 to 4)	-15 (-19 to 0)	0.5325
Changes in Intrahepatic lipids (%)	-2 (-3 to 0)	-7.5 (-13 to -2)	0.3150

Note. Data are expressed as median (range) or number. BMI, body mass index, ALT, alanine aminotransferase.

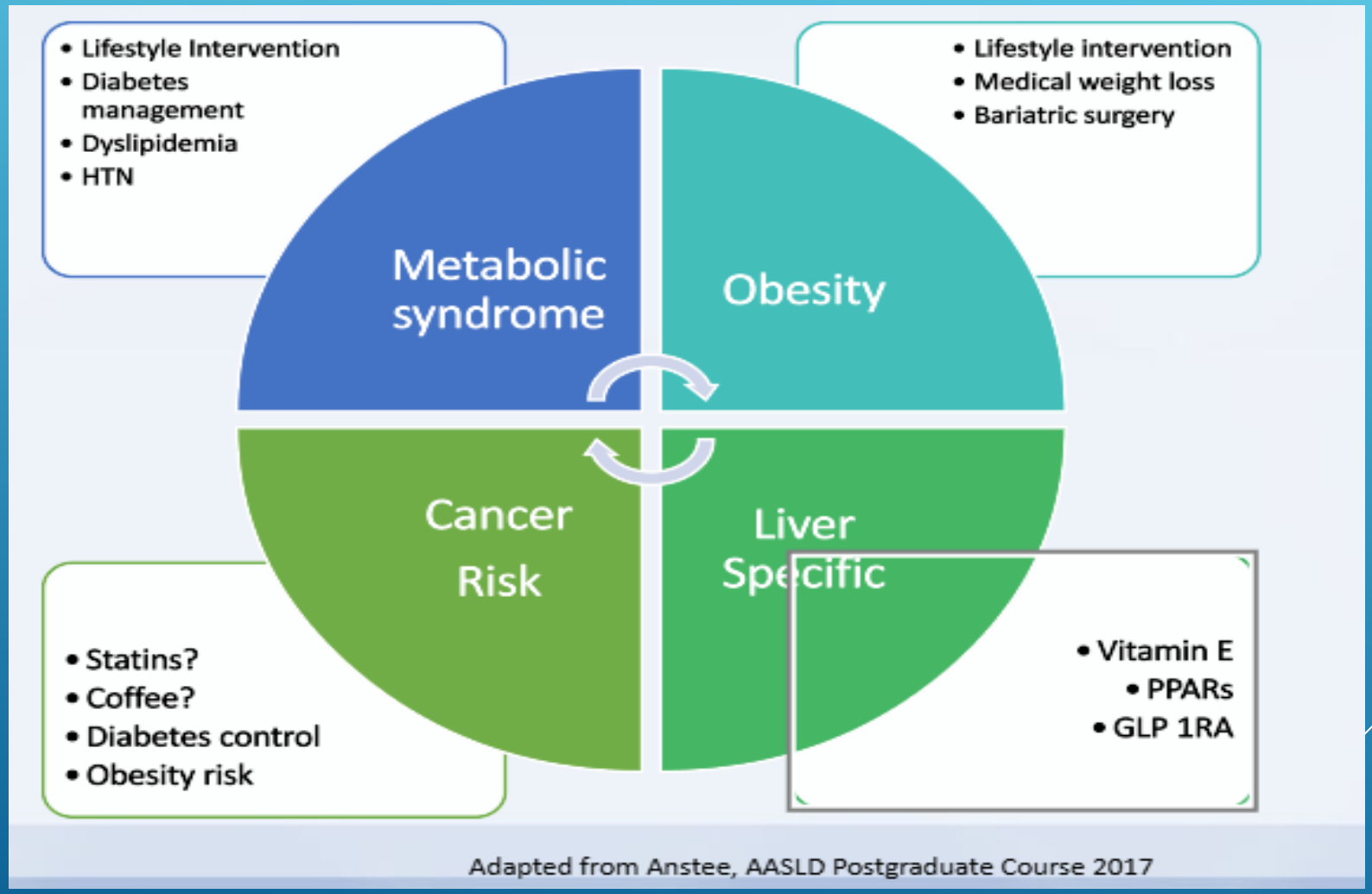
IT'S NEVER TOO LATE

- Weight loss might safely reduce portal pressure in obese cirrhotic patients with portal hypertension
- Spanish multicenter study of 60 obese patients with cirrhosis and HPVG >6mmHg who underwent a 16 week lifestyle intervention aimed at reducing body weight through diet and exercise
  - Lifestyle intervention decreased body weight by −5.0±4.0 Kg;($p<0.0001$ vs. baseline)
  - associated with a significant decrease in waist circumference and percentage of body fat



Berzigotti et al, Hepatology 2017

MEDICAL MANAGEMENT

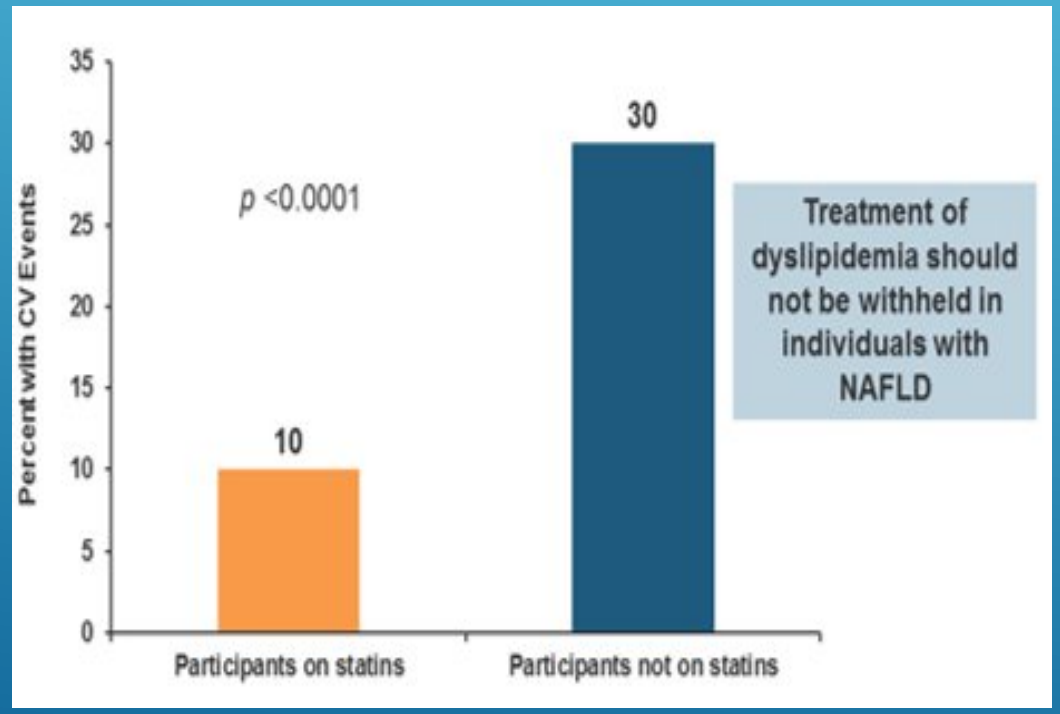


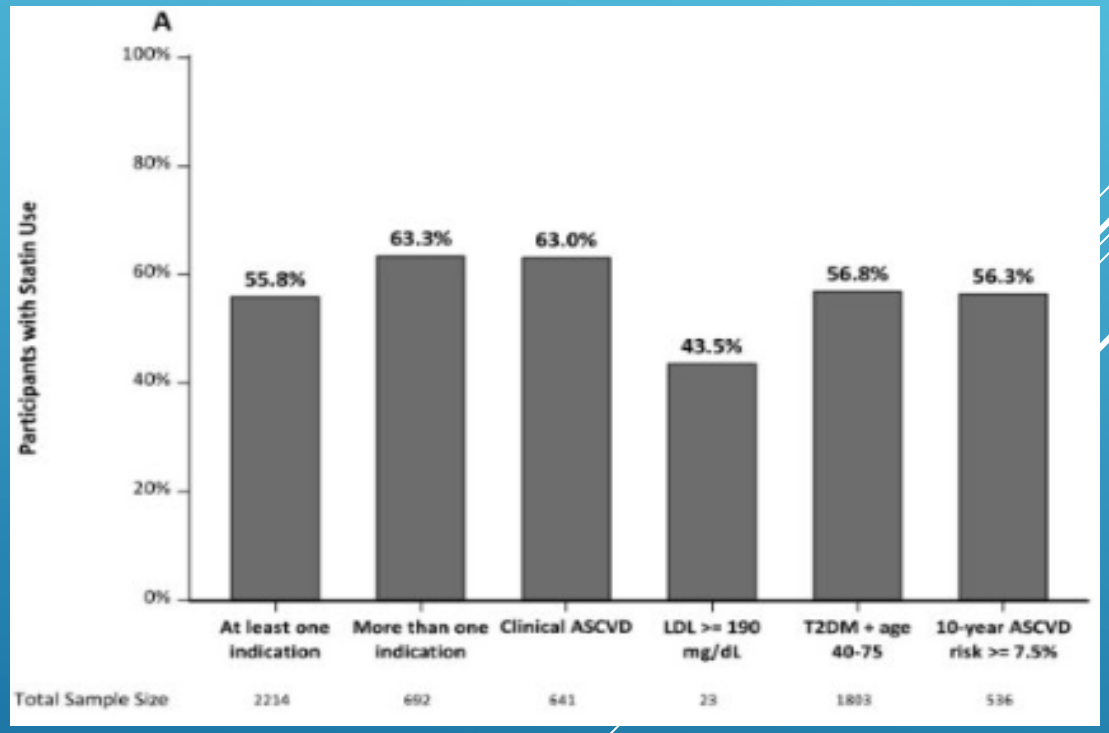
CURRENT THERAPY

	Studies	Key Studies - histology	Steatosis	MASH	Fibrosis	Comments / Caveats
Vitamin E (800 IU/daily)	5, most small, variable doses 2 meta-analyses	-Adult, **non-DM**: PIVENS (Sanyal, NEJM 2010) -Kids: TONIC (Lavine, JAMA 2011)	↓	↓	—	• ? Increased all-cause mortality • Not for pts with T2DM • Prostate cancer risk • Long term safety
Metformin	many	*Meta-analysis, 9 studies	—	—	—	• Improved ALT, AST, BMI
Pioglitazone (PPARγ agonist) (30-45mg daily)	#Meta – 8 RCT	-PIVENS: 30mg daily **-Pre-DM and T2DM** n=101, 45mg daily (Cusi, Ann Int Med 2016)	↓	↓	— ↓	• Benefits not sustained after d/c • Weight gain, edema, bone loss, ?bladder ca
Liraglutide (GLP-1 agonist)	T2DM, imaging MASLD; LEAN-J	-^LEAN (vs. placebo) 52 pts, 48wks	↓	↓ (Not NAS)	—	• Decrease BMI, glucose • GI side effects

A Sanyal AJ, et. Al. Gastro 2014; 147; 377-384-e1. Scorletti E, et al. Hepatol 2014; 60:1211-21.
*Li Y, et al. Biomed Rep 2013;1(1): 57-64. Chalasani N, et al. Hepatology 2018: 67(1):328-57.
Musso G., et al. JAMA Int Med 2017; 177(5): 633-40.^Armstrong M, et al. Lancet 2016; 387: 679-90.

STATINS REDUCE CV EVENTS IN MASLD PATIENTS





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

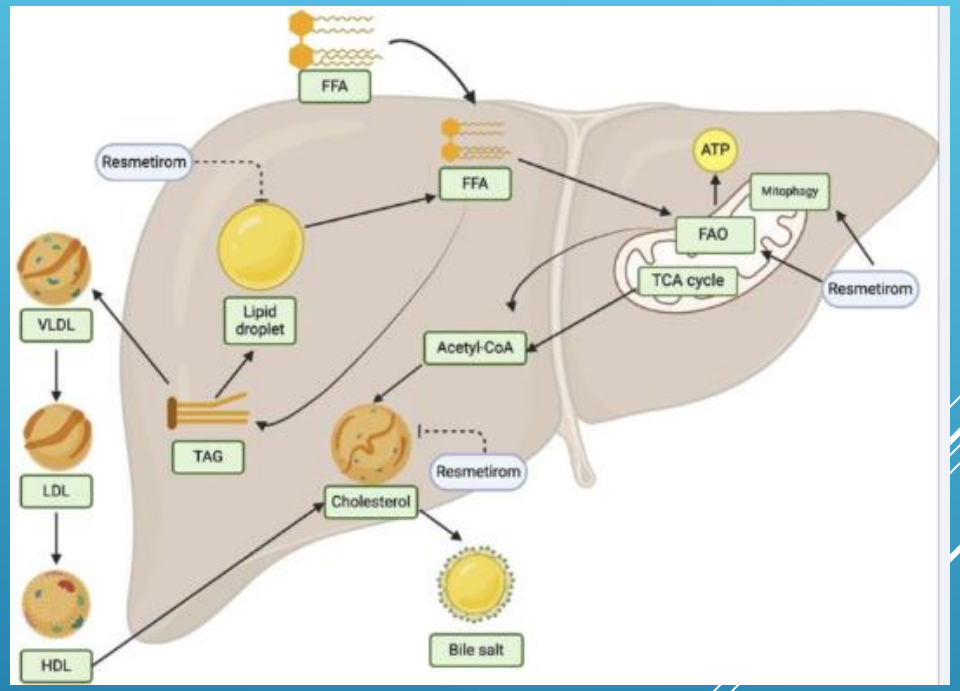
S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin,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

Interim analysis of an ongoing, phase 3,multinational, double blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

Harrison et al NEJM 2024

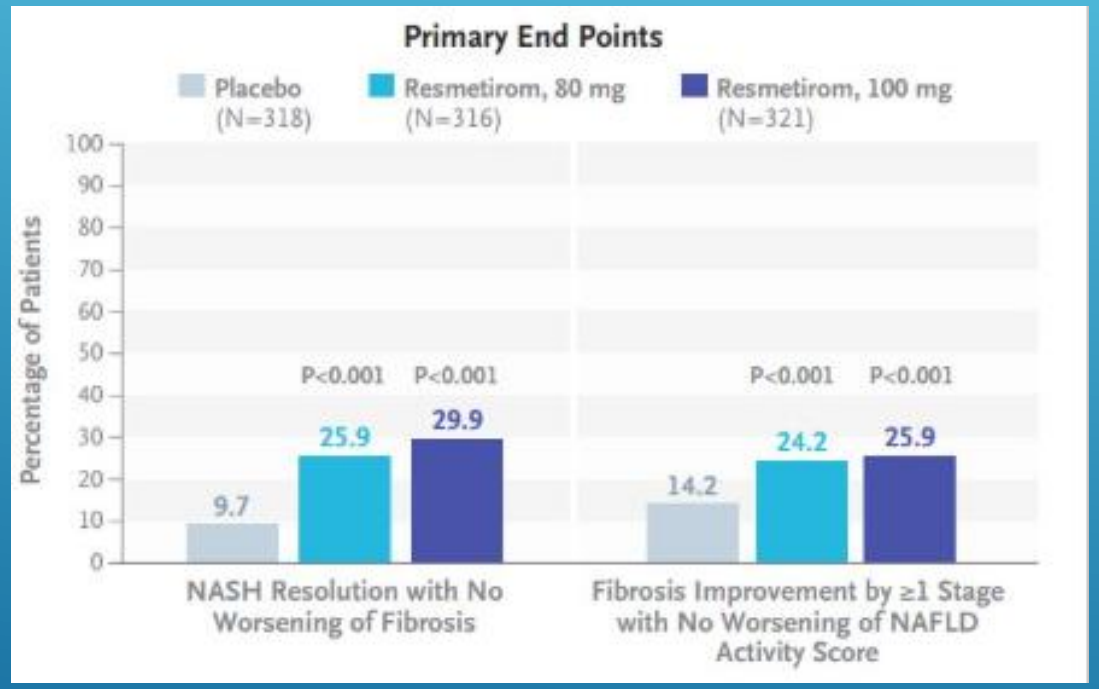
THYROID HORMONE B AGONISTS - MOA

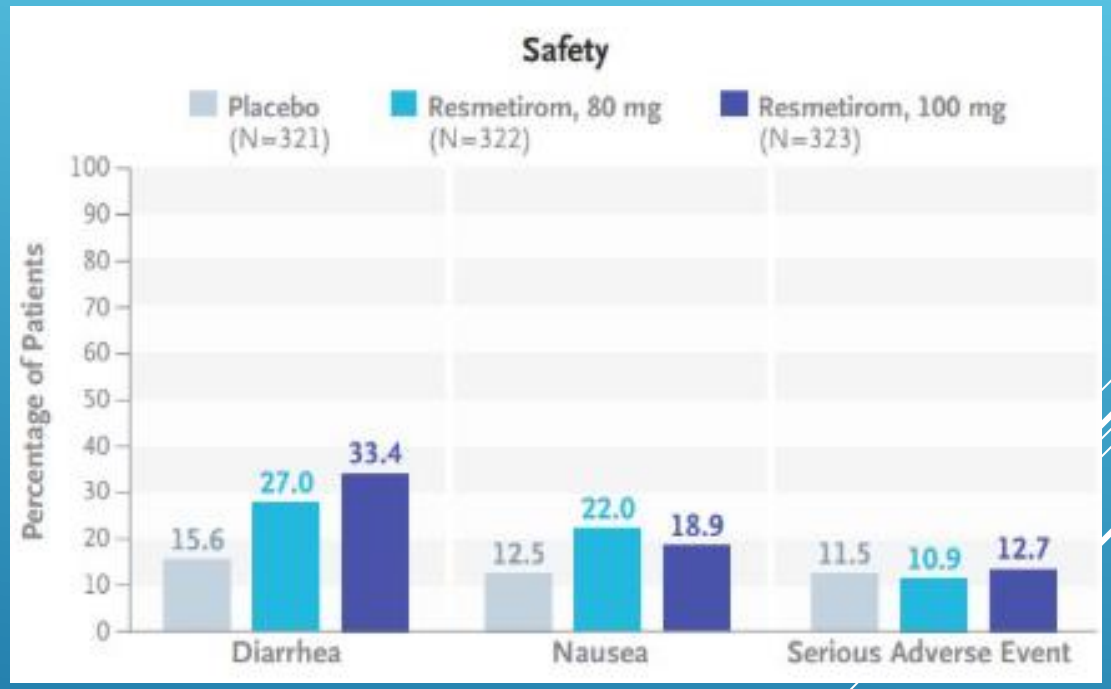
- THB responsible for regulation of multiple metabolic pathways
- Conversion of lipids to FAA
- Fatty acid oxidation
- Cholesterol excretion via bile acids
- Reduced level of activity in MASH
- THR-B is specific to the liver, THR-a receptor acts on thyroid and bone

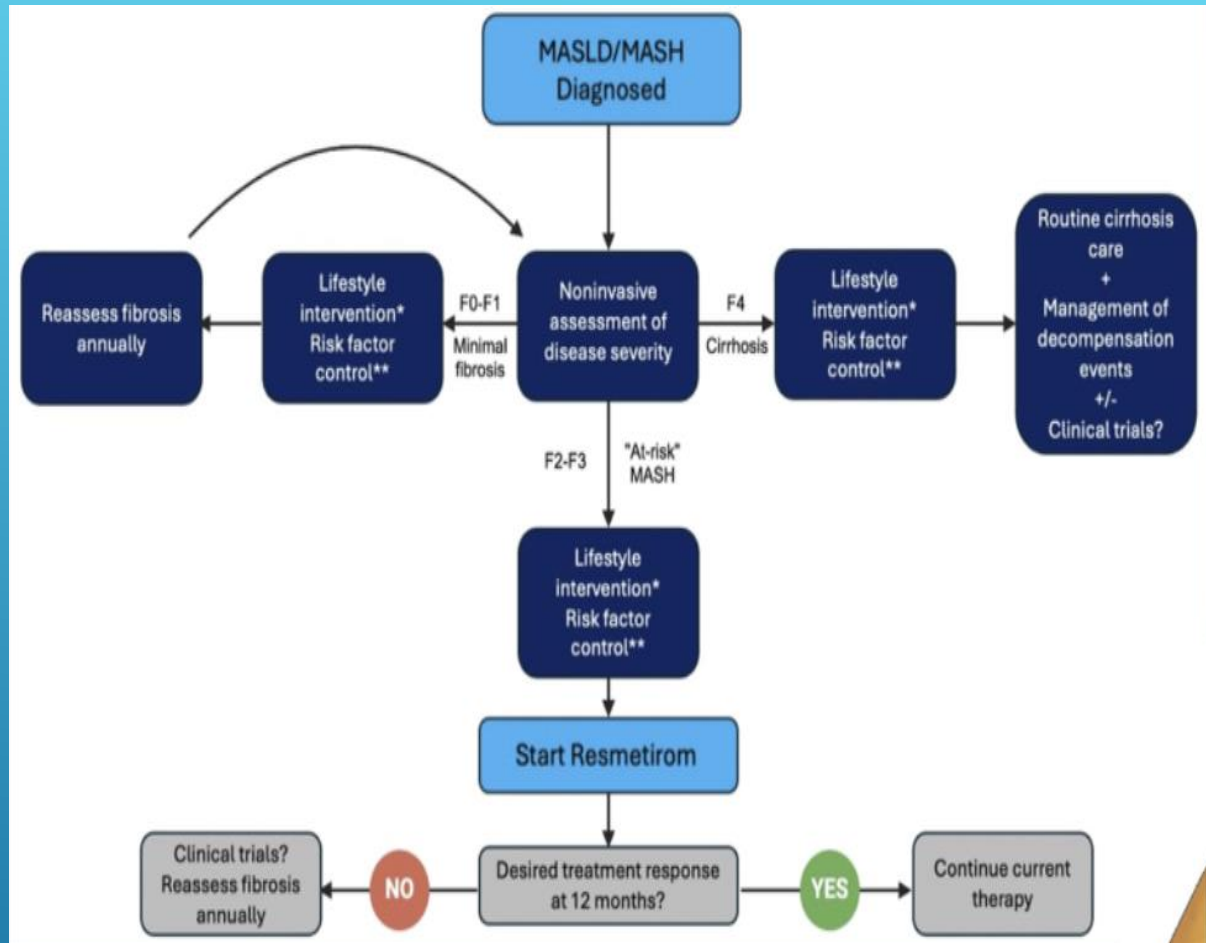


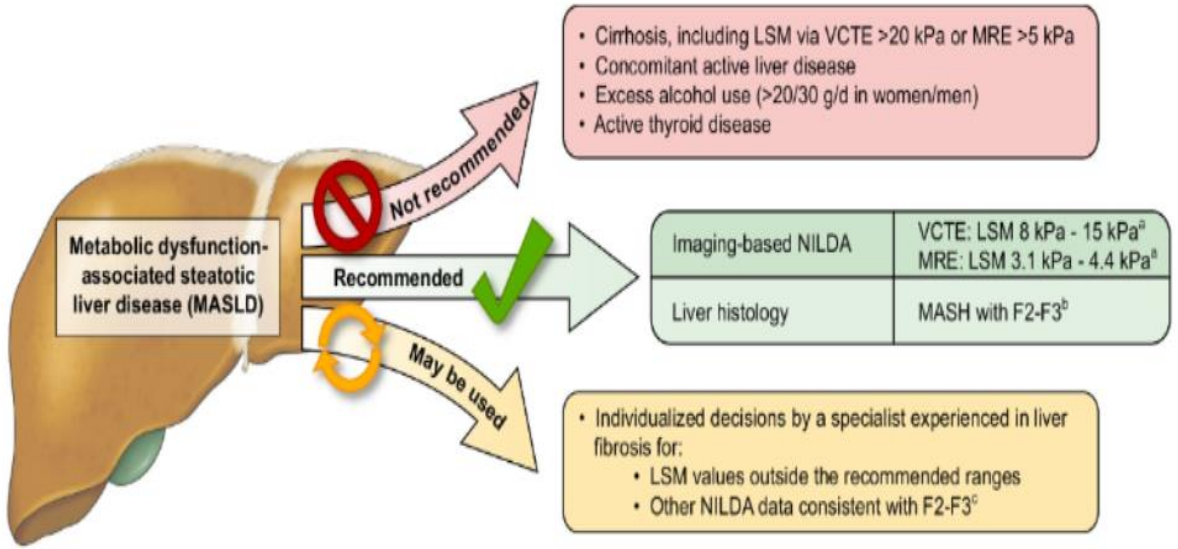
Barritt and Stine AJG 2024

RESULTS/SAFETY



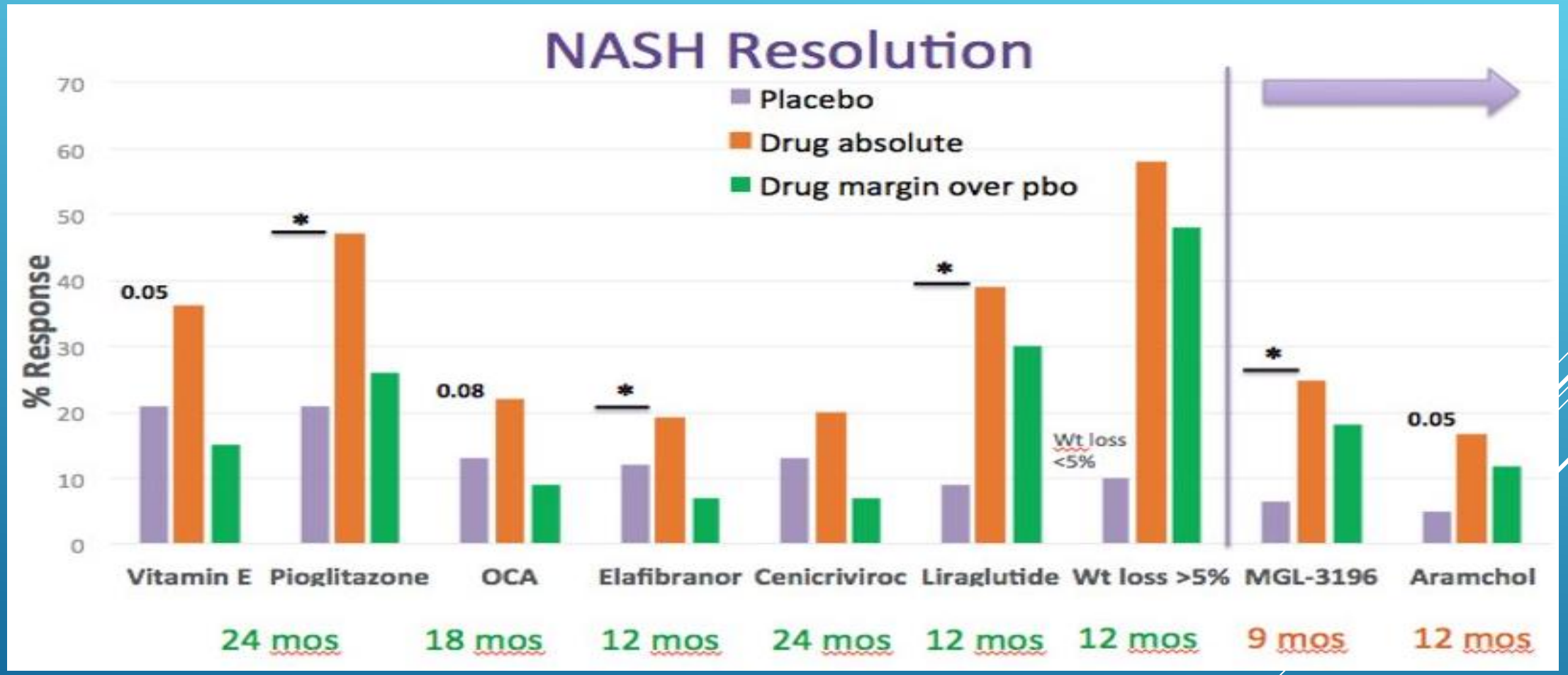






Barritt and Stine AJG 2024; Chen et al Hepatology 2024

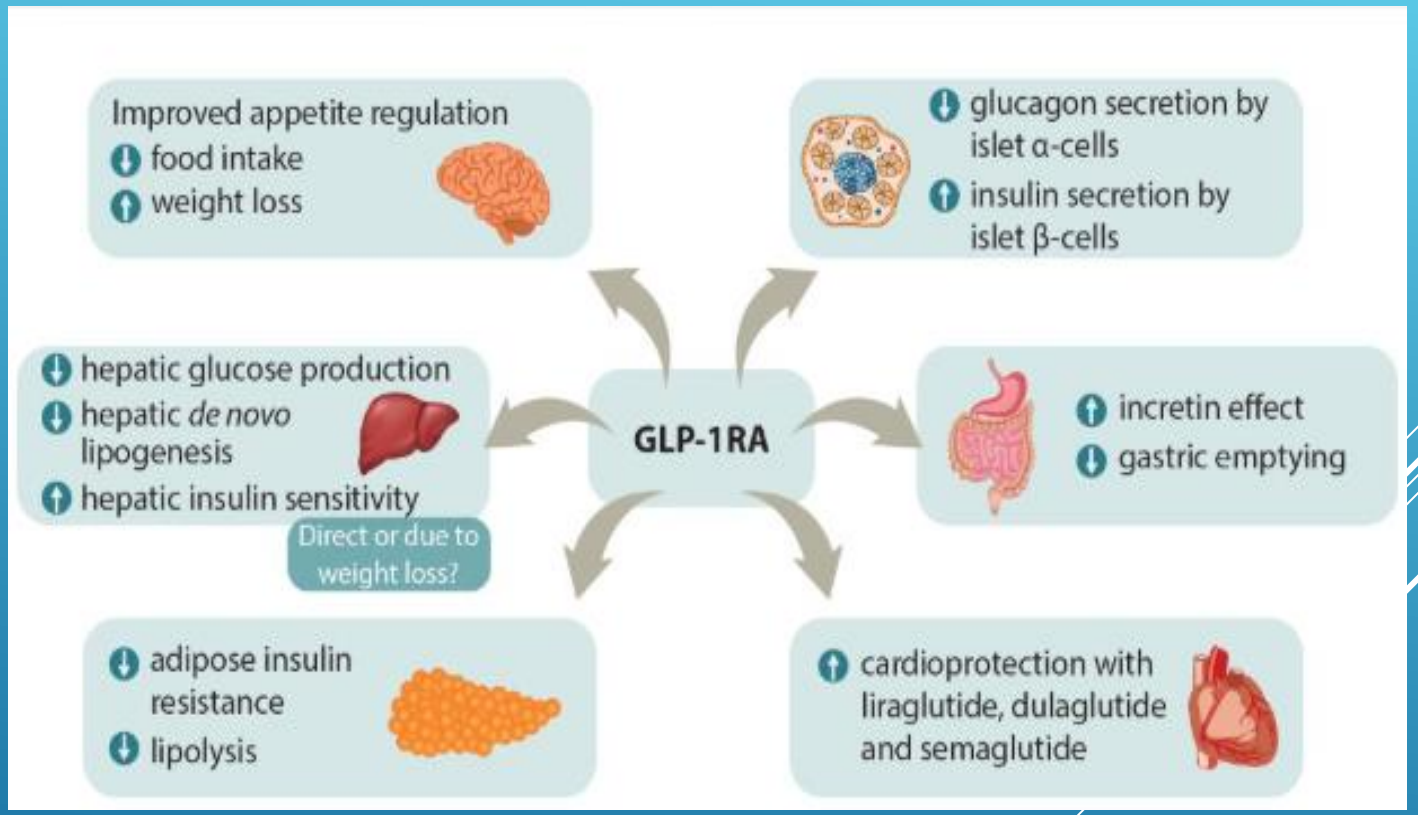
WHY FOCUS ON WEIGHT LOSS?



Adapted from Rinella, MASLD Debrief AASLD 2018

MEDICAL WEIGHT LOSS

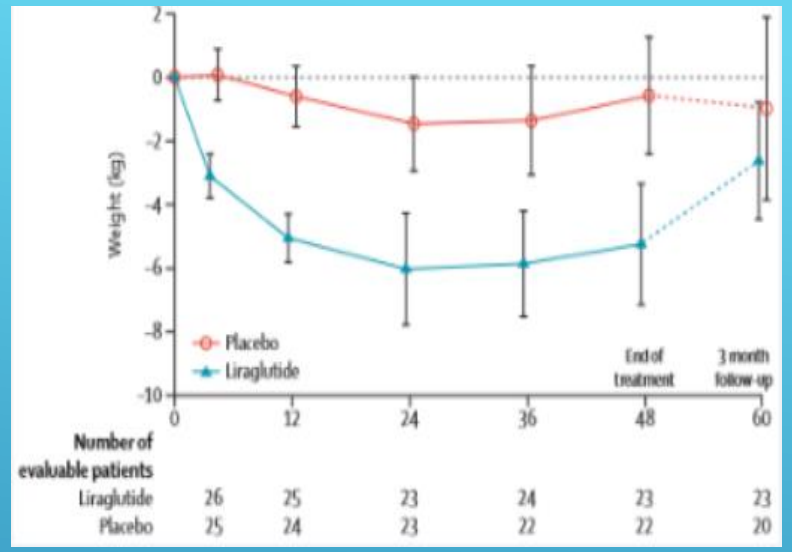
- The association of MASH with metabolic disorders, particularly obesity and type 2 diabetes, provides rationale for investigating the use of GLP-1RAs inpatients with MASH



Barritt and Noureddin APT 2021

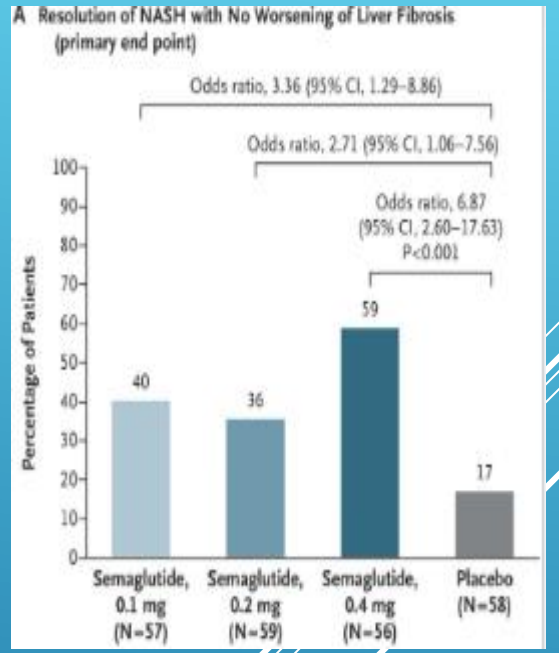
Liraglutide in MASH

- Resolution of MASH in 9/23 (39%) liraglutide vs.2/22 (9%) placebo p=0.019
- Secondary outcomes showed improvements in weight and ALT



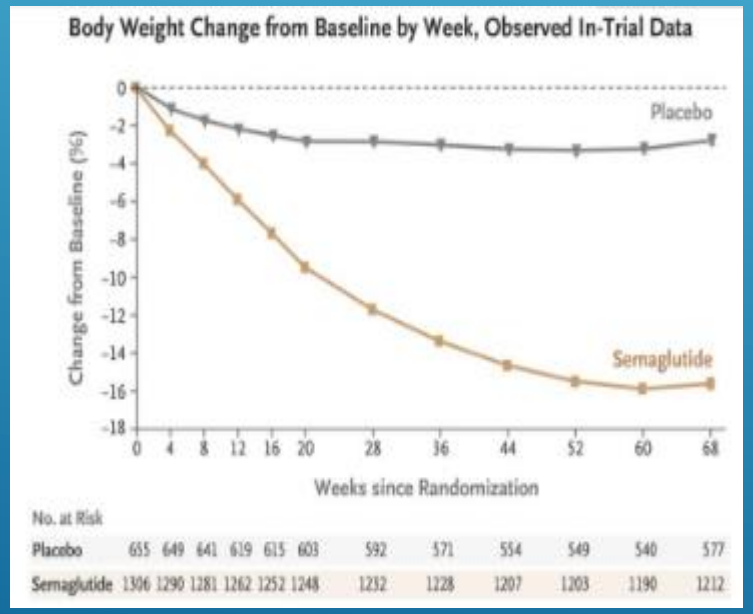
Semaglutide in MASH- phase 2

- MASH resolution semaglutide 0.4mg (59%) vs placebo (17%)
- Fibrosis improvement not different than placebo
- 13% weight loss vs 1% placebo



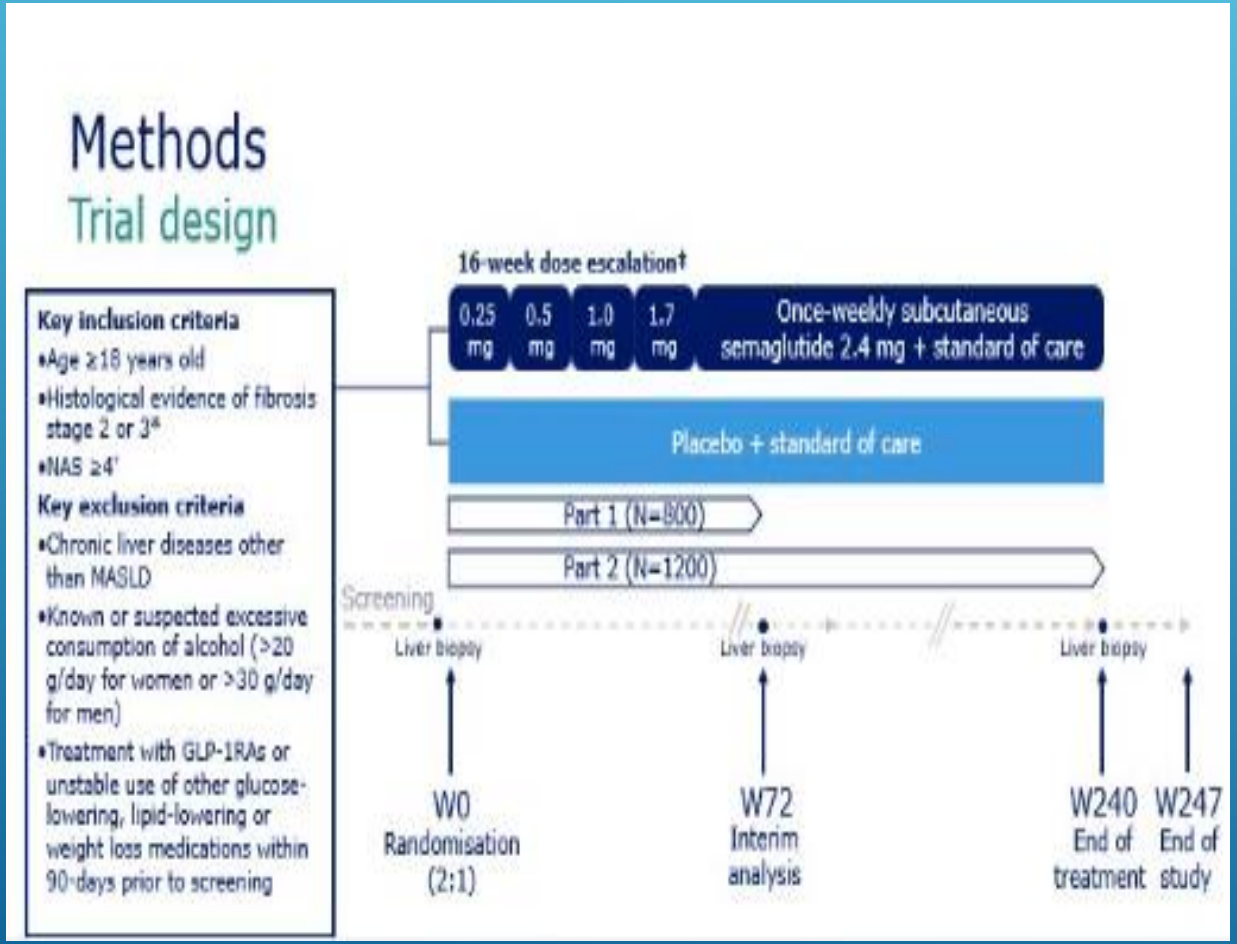
Semaglutide in obesity

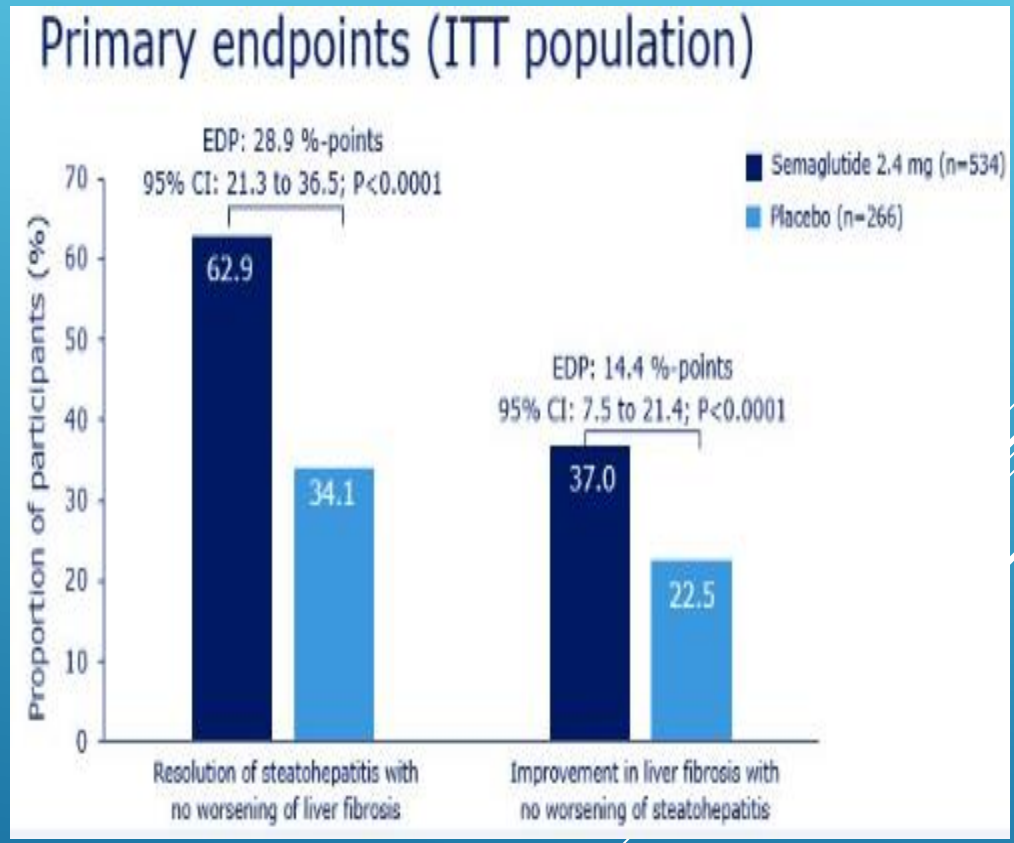
- 15% weight loss after 68 weeks vs 2% in placebo
- 86% achieved 5% loss, 69% achieved 10% loss, 50% achieved 15% or more weight loss



Armstrong et al Lancet 2016; Newsome et al NEJM 2021; Wilding et al NEJM 2021; Barritt et al APT 2022

PHASE 3 SEMAGLUTIDE – ESSENCE TRIAL



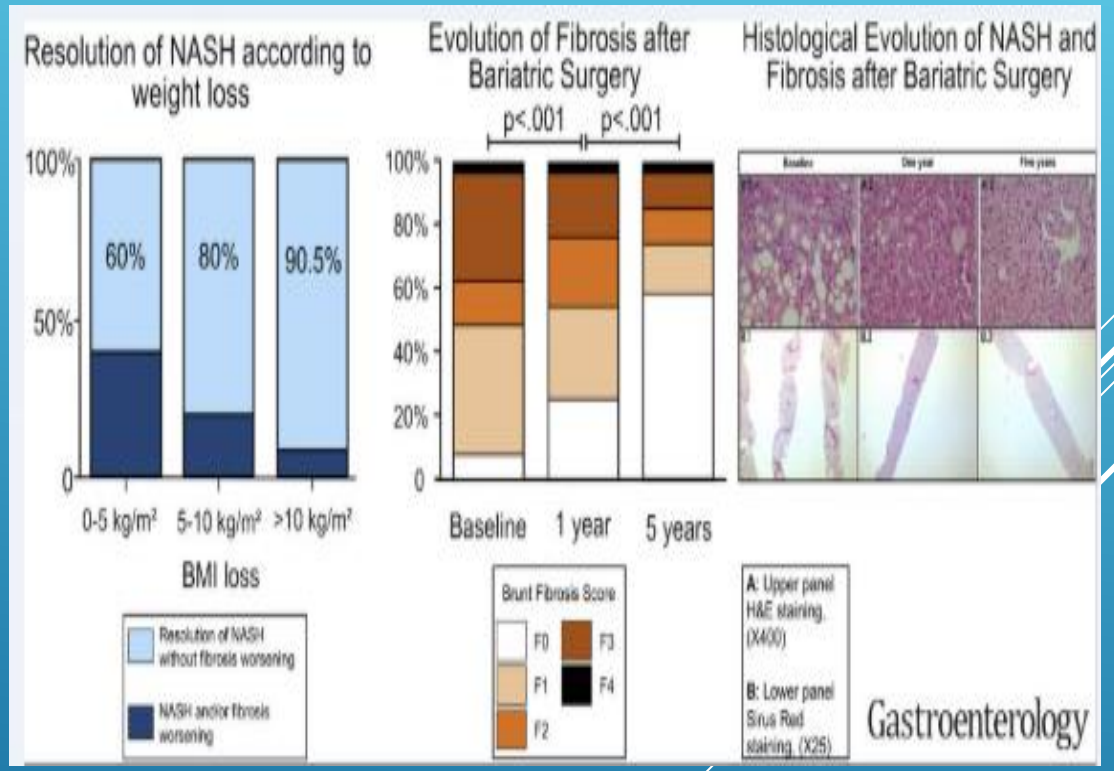


Newsome et al, AASLD *late breaker* 2024

SURGICAL WEIGHT LOSS

Bariatric Surgery?

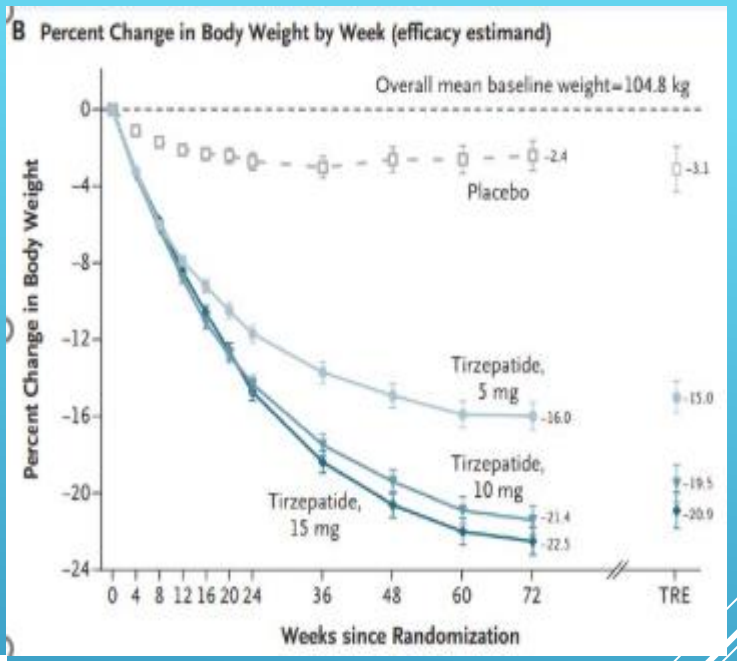
- Multiple studies have shown that weight loss following bariatric surgery leads to biochemical and histological improvement of MASH
- Improvements occur in those with correction of insulin resistance and metabolic syndrome



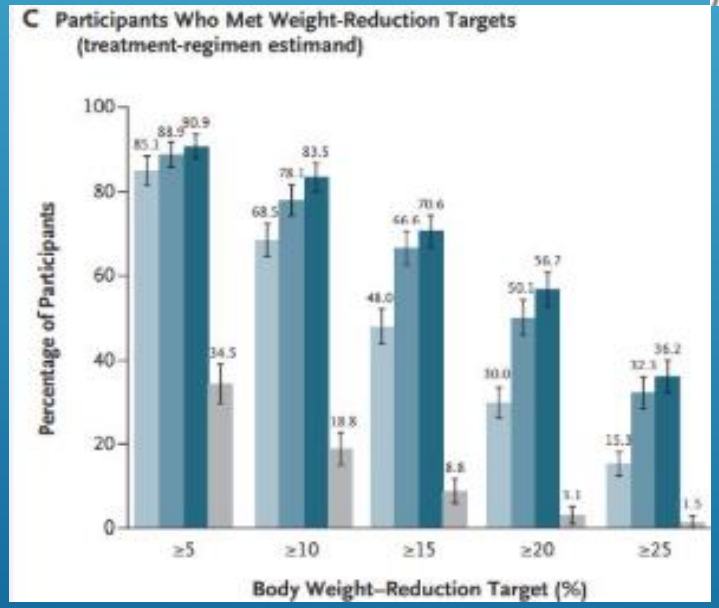
ESTABLISHED IN 1812 JULY 21, 2022 VOL. 387 NO. 3

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*



- Glucose dependent insulinotropic polypeptide and glucagon-like peptide1 receptor agonist
- Phase 3 DBRCT of >2500patients
- Significant weight loss across all treatment arms



GLP1RA + GLUCAGON RECEPTOR AGONIST

- Role of glucagon receptor(GCGR) in MASLD
  - Glucagon receptors mainly expressed in liver, kidney, and pancreas with lesser amounts in adipose and GI tract
  - Direct glucagon agonism in theliver leads to increased energy expenditure, lipolysis, and mobilization of hepatic fat

- Dual agonism of GCGR and GLP-1receptor may be more effective thanGLP-1 receptor monoagonism for treating MASH
  -Extrahepatic benefits of GLP-1 receptor agonism (glucose control, reduced appetite, and weight loss) are combined with direct hepatic effects of GCGR

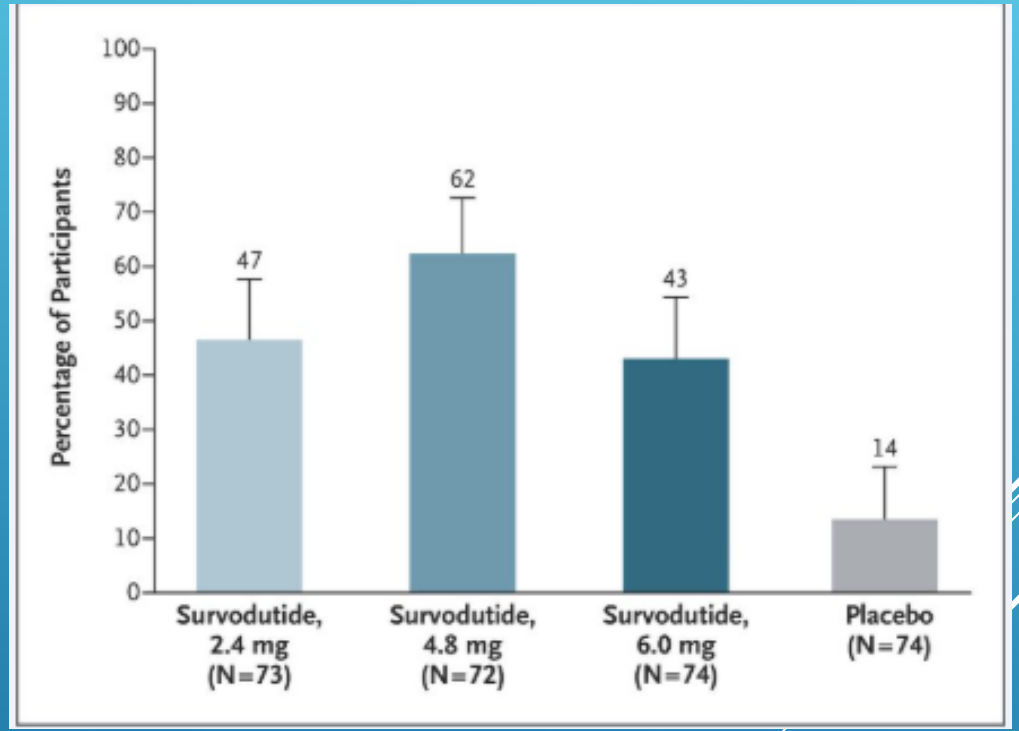
- Combination with GLP-1 outside of the liver can also mitigate some adverse effect
  -Balancing blood glucose and insulin levels
- Ratio is key to mitigate some side effects

SURVODUTIDE FOR MASH

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*



- Planned treatment analysis:
- 47-62% improved MASH without worsening of fibrosis

LANIFABRANOR

- Phase 2b RCT of 247 subjects with MASH without cirrhosis
- 2 doses of Lanifibrabor vs placebo
- Used Steatosis, Activity, Fibrosis(SAF-A) score (0-4)
- 1* outcome decrease by 2 or more points

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

Francque SM et al. DOI: 10.1056/NEJMoa2036205

Decrease of ≥2 Points in SAF-A Score and No Worsening of Fibrosis

	Lanifibranor	Placebo	Risk Ratio (95%CI)	P Value
Lanifibranor, 800 mg	48%	33%	1.45 (1.00–2.10)	P=0.07
Lanifibranor, 1200 mg	55%	33%	1.69 (1.22–2.34)	P=0.007

MORE WORK TO DO

If/when there are successful FDA approved interventions for MASH, questions and challenges will remain

- Are these lifetime drugs?
- Are medications interventions to pause disease while patients fix lifestyle problems?
- Are there adverse liver events?
- What is the CV risk/benefit?
- What is the cancer risk/reduction?
- Clinical trial ***efficacy*** vs. ***real world effectiveness***