NAFLD/NASH: The Hidden Complication of Type 2 Diabetes

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Disclosures

- I have no actual or potential conflict of interest in relation to this program/presentation.
- I will mention off-label medication use.
- I do serve as a principal investigator for current investigational studies with
  - Eli Lilly
  - Novo Nordisk

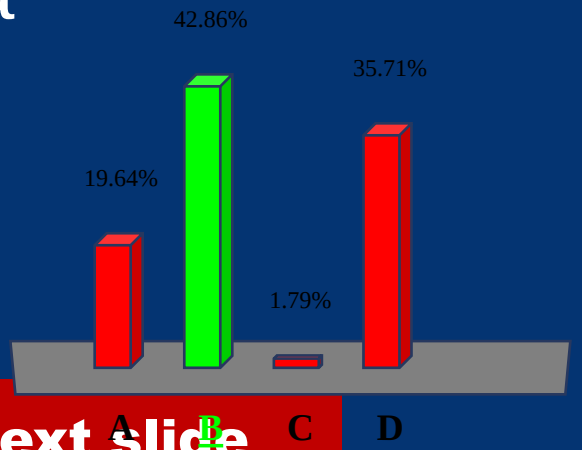
55 year old Indian Female presents for follow up

- 8 year history of T2DM, hypertension, dyslipidemia comes for follow up
- Medications: Metformin 500 mg BID, Atorvastatin 20 mg QD, Losartan/HCTZ 50/12.5 mg QD
- Examination: remarkable for BMI 28 kg/m^2, with central adiposity. Remainder was normal
- Laboratory: A1c – 7.9%, TC- 185 mg/dl, TG – 242 mg/dl, HDL – 33 mg/dl, LDL-C – 74 mg/dl ALT – 45 IU/L, AST – 48 IU/L, platelet count 227K

Question: Management of in Patient with Type 2 Diabetes

What is her greatest risk for mortality?

A. Cirrhosis
B. Cardiovascular disease
C. Hepatocellular carcinoma
D. A & C



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Question: Management of Patient with Type 2 Diabetes

What is her greatest risk for mortality?

A. Cirrhosis
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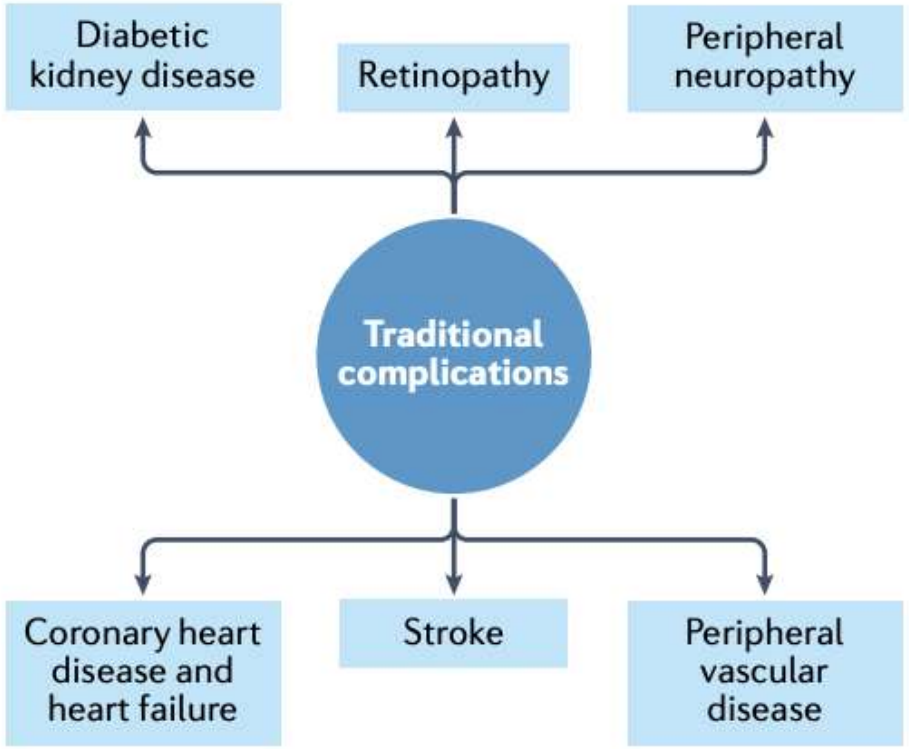
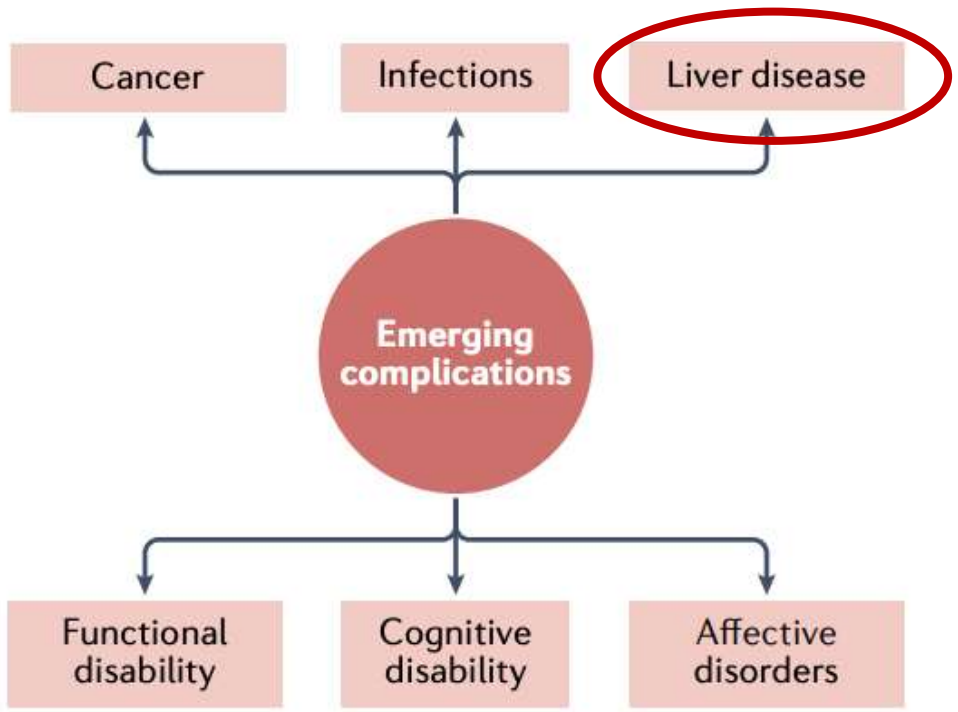
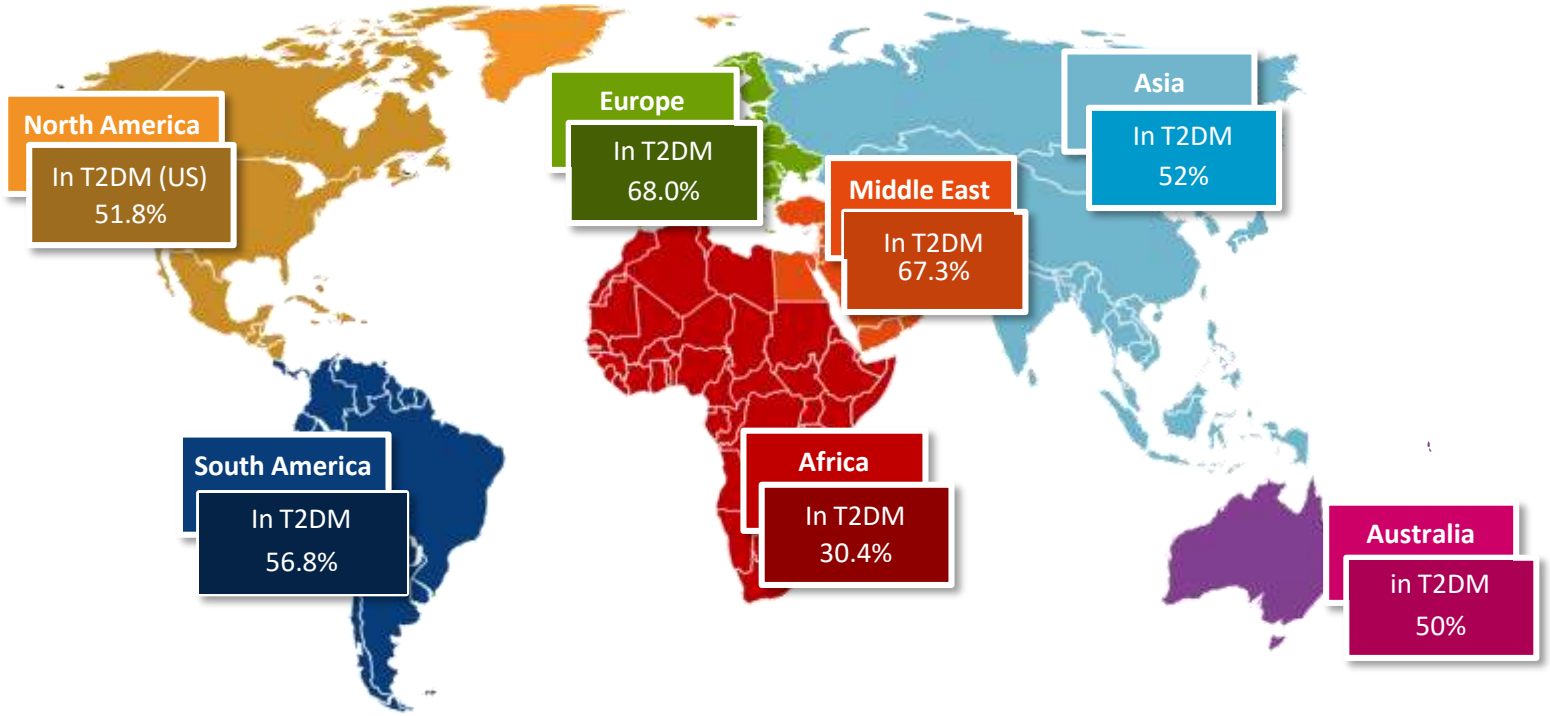
Traditional and Emerging Complications of Diabetes





Tomic D et al. Nat Rev Endocrinol 2022;18:525-539

Prevalence of NAFLD in Type 2 Diabetes by Region



Worldwide prevalence of NAFLD is 25%

Worldwide prevalence of NAFLD among people with T2DM is 55.5%

Fewer than 1/10 are identified

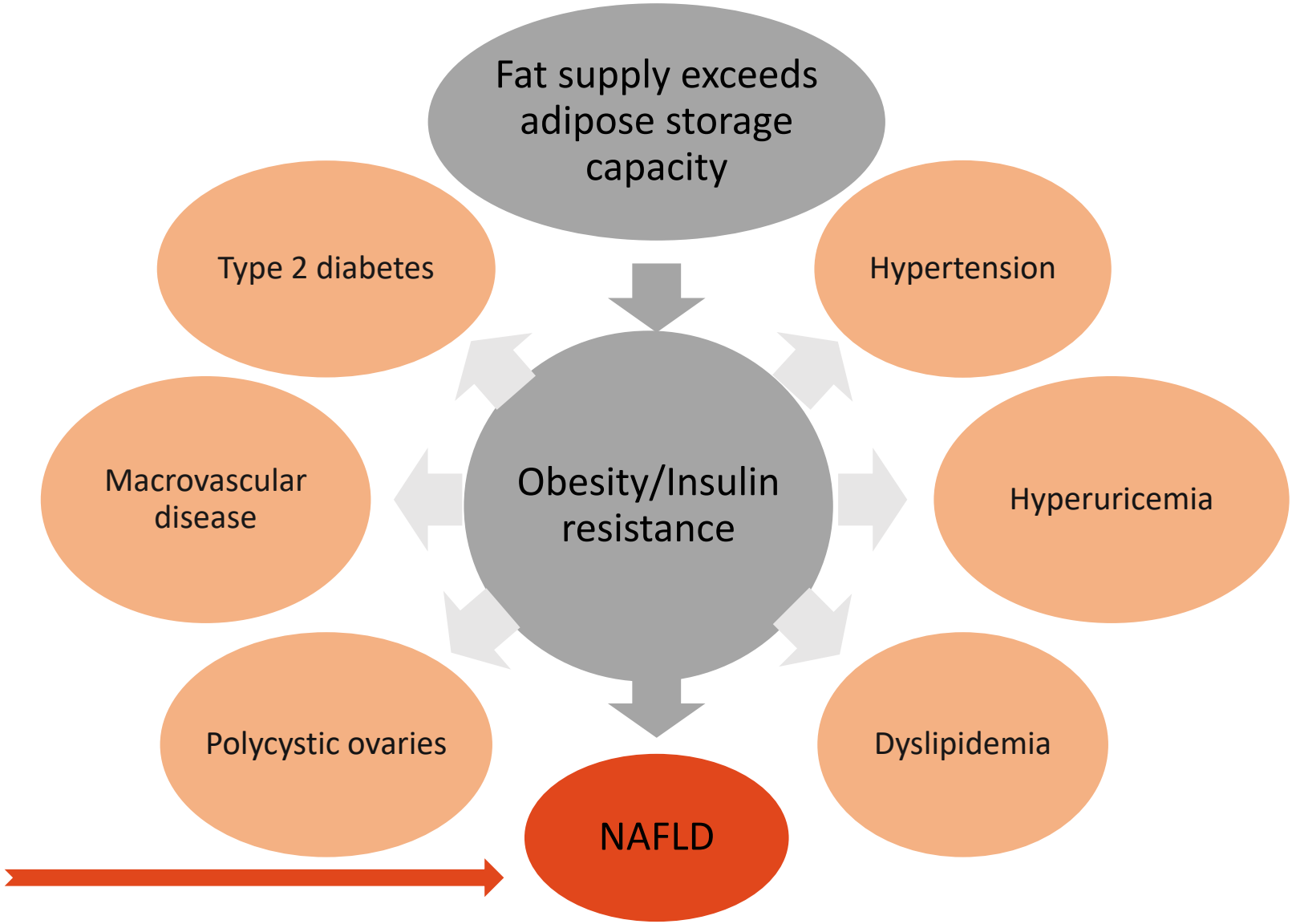
Prevalence of NASH in general population is between 1.5–6.5%

Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)

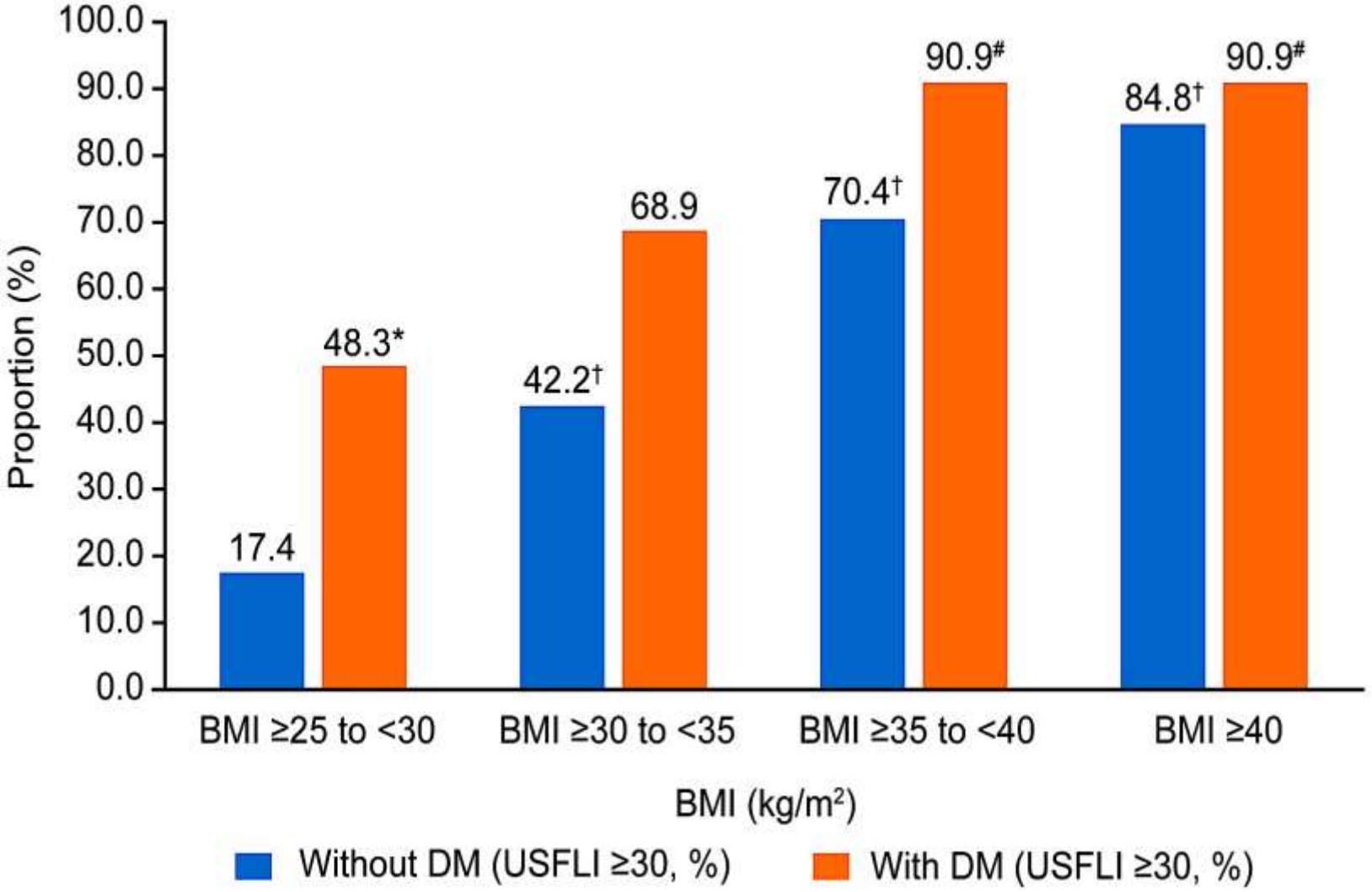
NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; Peds, pediatric patients; T2DM, Type 2 diabetes mellitus

Younossi ZM. J Hepatol 2019;70:531–44; Younossi ZM, et al. Clin Liver Dis 2018;11:92–4; Younossi ZM, et al. J Hepatol 2019;71:793–801;

NAFLD: Obesity and Insulin Resistance as Pathogenic Drivers



Risk for Hepatic fibrosis in NAFLD: Interplay between Obesity and Type DM

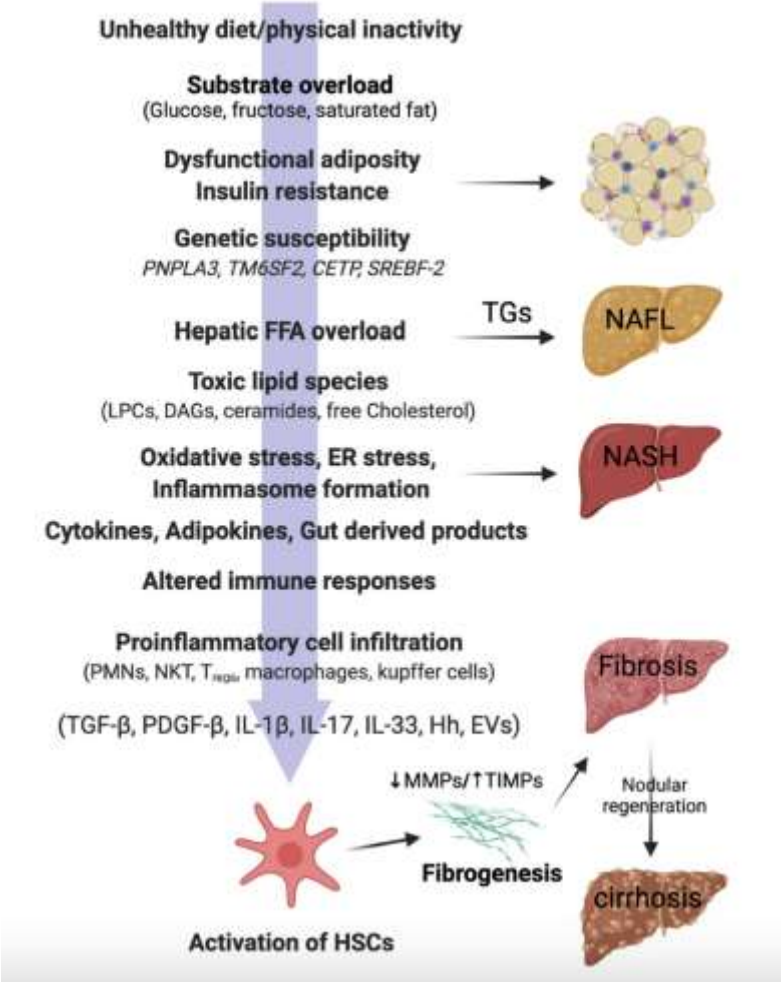


Barb D et al. Obesity, 29:1950-1960,2021

LEAN NAFLD

- Defined by BMI < 25 kg/m^2 (<23 kg/m^2 – Asians)
- Comprises at least 10 – 20% of population with NAFLD
- Pathophysiology is similar to those with BMI > 25 kg/m^2
- Risks of liver disease, CV disease and cancer similar to obese phenotype
- Response to weight loss similar to those with BMI > 25 kg/m^2

Pathophysiology of NAFLD – Similar between Lean and Obese Phenotypes

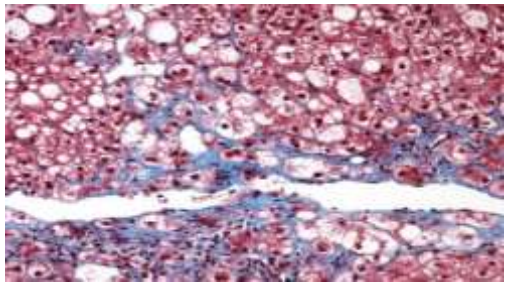


Other contributors

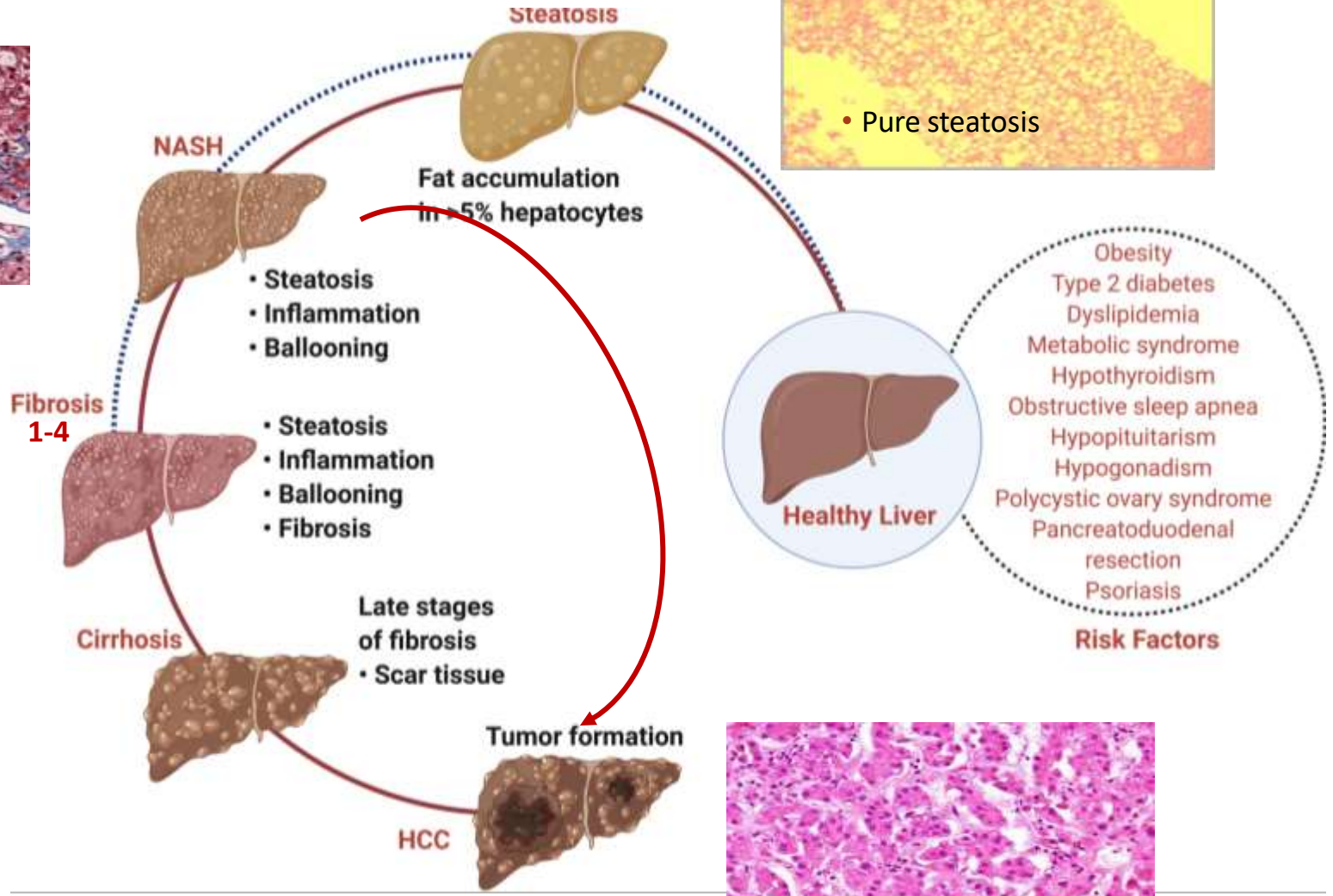
- Distribution of adipose tissue
- Sarcopenia
- Genetic predisposition
- Gut mitochondrial dysbiosis

Kuchay M et al. Biomedicines 2021, 9, 1346. https://doi.org/10.3390/biomedicines9101346

Natural History of NAFLD



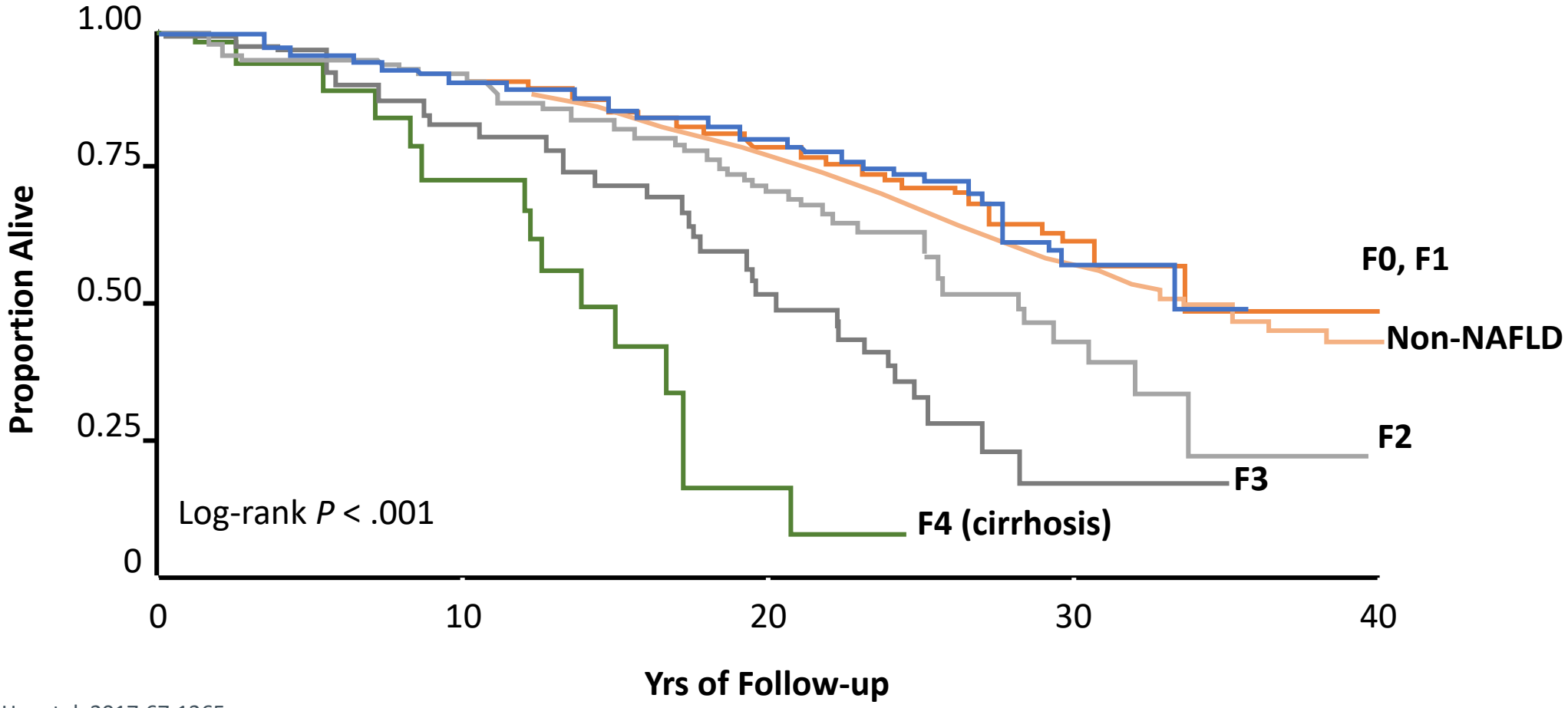
In 29 mo, 22% with F3 NASH progressed to Cirrhosis



Negi C et al. Metabolism published online 2022

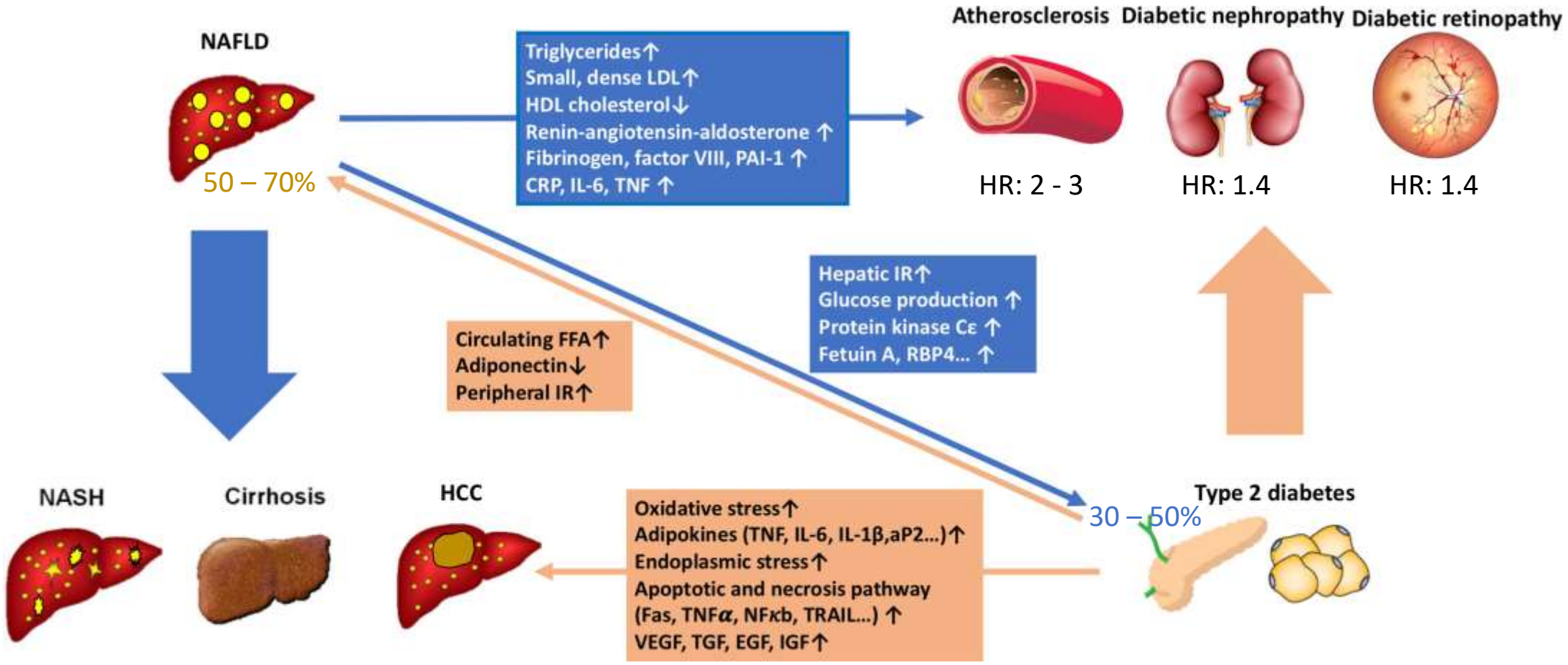
Liver Fibrosis Is a Risk for Adverse Outcomes

- Retrospective survival analysis of 646 NAFLD patients and matched controls



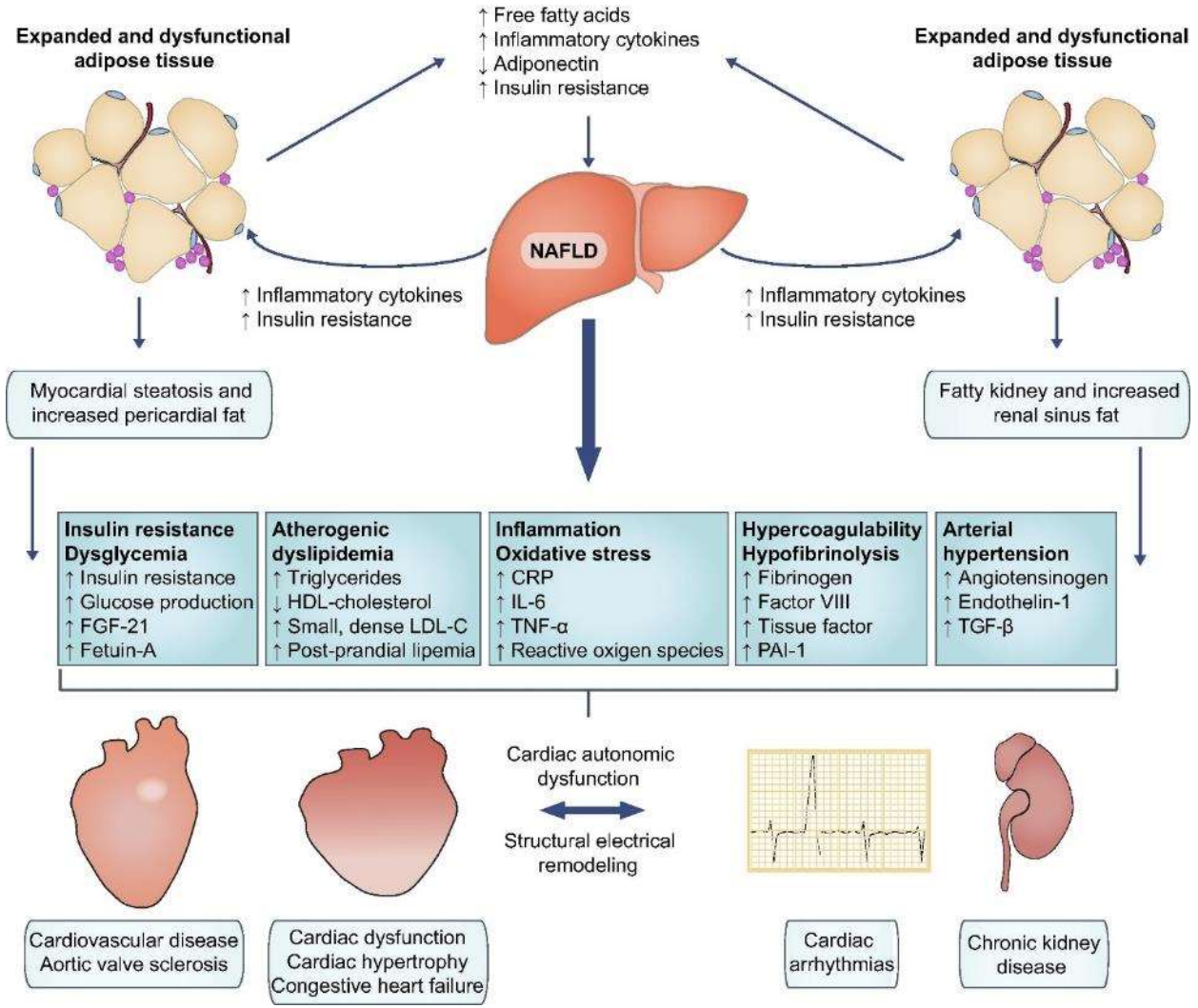
Hagström. J Hepatol. 2017;67:1265.

Bidirectional Relationship between DM and NAFLD



Xia M et al. Frontiers in Pharmacology: https://doi.org/10.3389/fphar.2019.00877, Mantovani A Diabetes Care 2018, Ebert T. Presented at 58th Annual EASD, 2022

Putative connection between Adisopathy, NAFLD, CVD and CKD

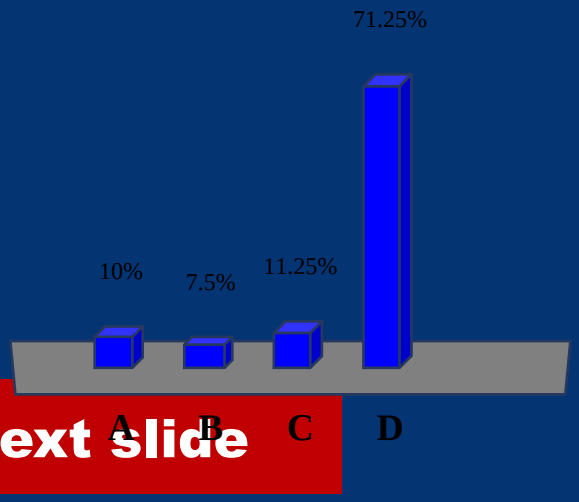


Byrne CD, Targher G. J Hepatol 2015;62:S47–64

Question: Getting back to our patient

How would you assess her risk for NASH with fibrosis

A. Ultrasound of the liver
B. Liver biopsy
C. FIB-4 Index
D. A & C



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Question: Management of Patient with Type 2 Diabetes

Which of the following is indicated?

A. Ultrasound of the liver
B. Liver biopsy
C. FIB-4 Index
D. No reason to screen

Indeed, her FIB-4 Index – 1.73 – intermediate risk

NAFLD Presentation

Symptoms

- Usually asymptomatic; majority discovered by chance
- Fatigue frequently present
- Right upper quadrant discomfort

Often an “incidental finding”

- Incidental abnormal LFTs (ALT/AST >30)*
- Incidental “bright liver” on imaging
- Incidental hepatomegaly

Strong Clinical Predictors of NASH and Fibrosis

- Age > 50 yrs
- T2D
- First-degree relative with NAFLD cirrhosis
- Alcohol Intake

Other Risk Factors

- Sedentary lifestyle/high fructose intake
- Overweight/obese
- Metabolic syndrome (3 or more features)
- Ethnicity (Hispanic/Asian)
- Dyslipidemia
- Polycystic ovary syndrome

De Alwis. Dig Dis. 2016;34:19.

*Per AACE 2022 NALFD Guidelines

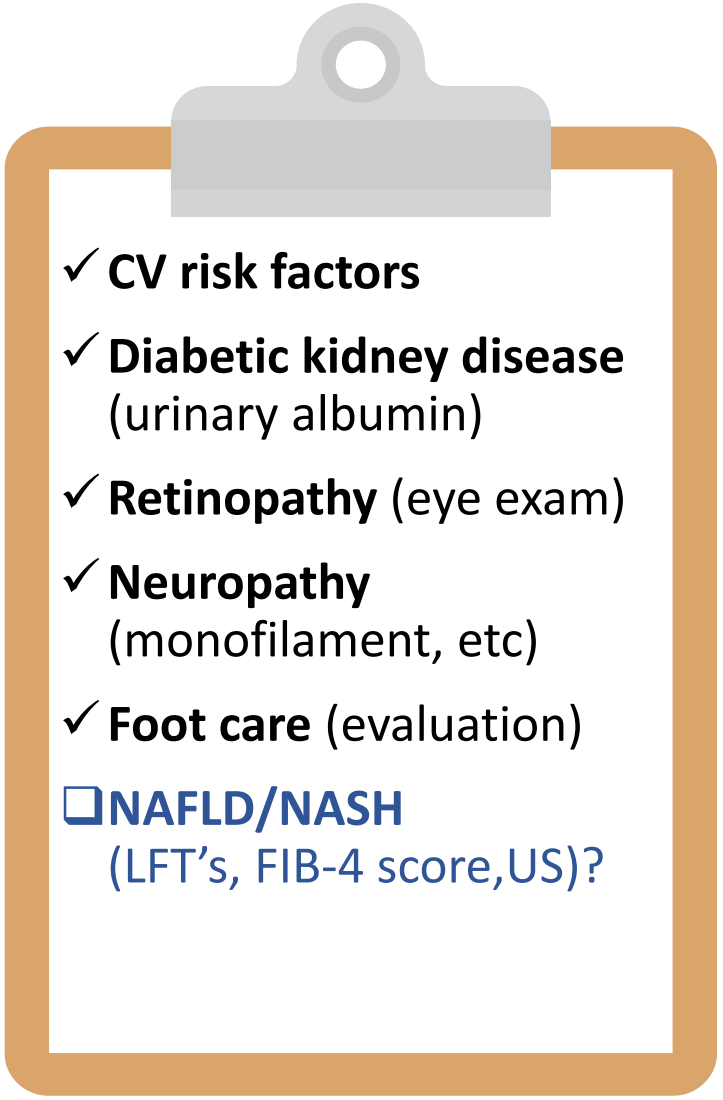
Guideline Recommendations: Who Should We Screen?

AASLD[1]	EASL-EASD-EASO[2]	ADA[3]
In T2D, **suspect NAFLD and NASH** and determine patient's risk of advanced fibrosis	NASH and advanced fibrosis **screening recommended** in persons at high risk (age > 50 yrs, T2D, metabolic syndrome)	NASH and fibrosis **screening recommended** in persons with T2D or prediabetes and elevated ALT or fatty liver
Increasing number of metabolic diseases = **increasing risk of progressive liver disease**		

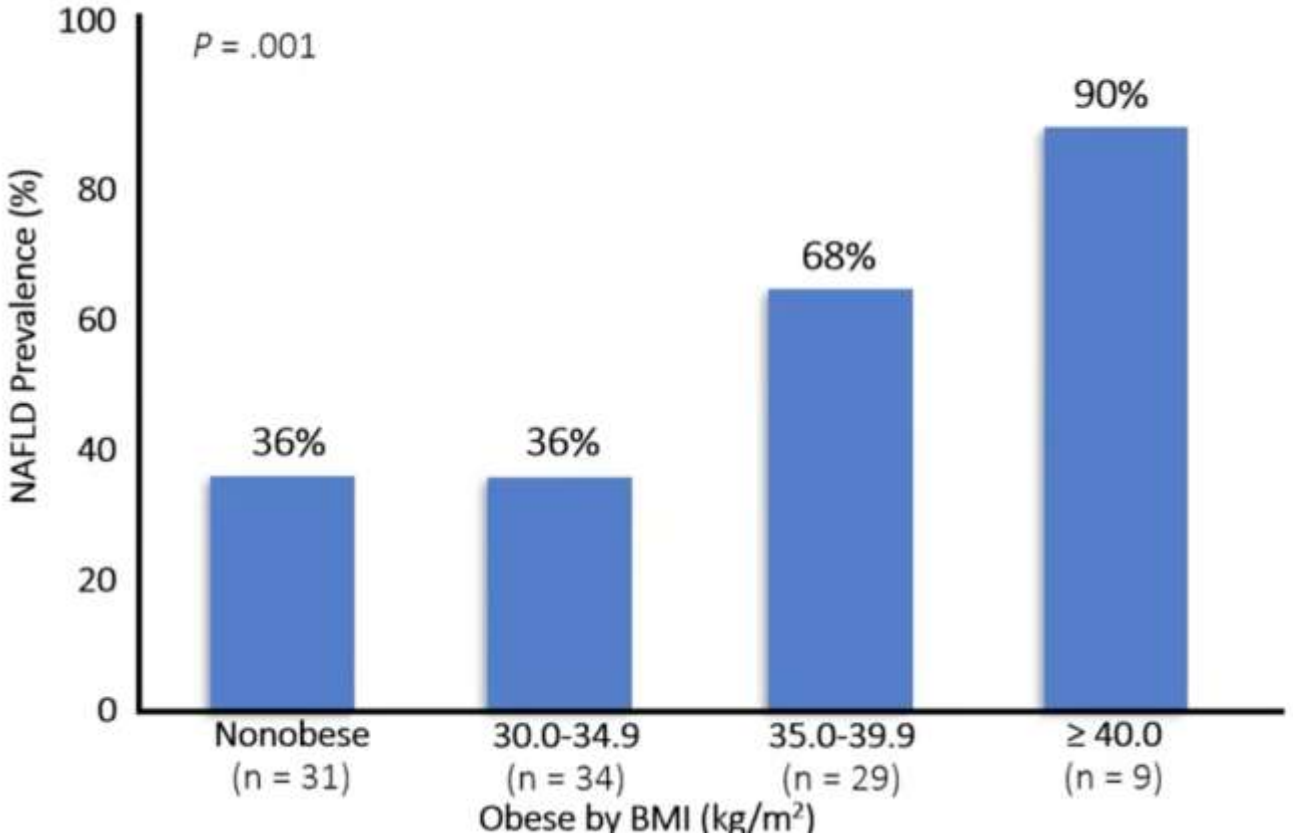
AASLD, EASL, and ADA guidelines call out **patients with T2D** as warranting workup

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. ADA. Diabetes Care. 2019;42:S34.

Should Screening for NASH be Part of Standard Screening for Everyone With T2D?



Prevalence of NAFLD and NASH in Patients with T2DM and normal AST/ALT



Patients with T2DM and normal AST or ALT evaluated for liver triglyceride content by H-MRS, insulin sensitivity, and adipose tissue insulin resistance (N = 103)

Prevalence of NAFLD in overall cohort: 50%

Among these patients, prevalence of NASH: 56%

40% of those with NAFLD will have normal ultrasound

Portillo-Sanchez. JCEM 2015; 100:231, Stahl World J Gastro 2015; 21: 11077

Noninvasive Tests Exclude or Determine Advanced Hepatic Fibrosis

- FIB-4 recognized by AASLD as useful in identifying patients with a higher likelihood of F3 or F3-F4[1]

Cutoff Scores for Measurement of Advanced Hepatic Fibrosis[2,3]

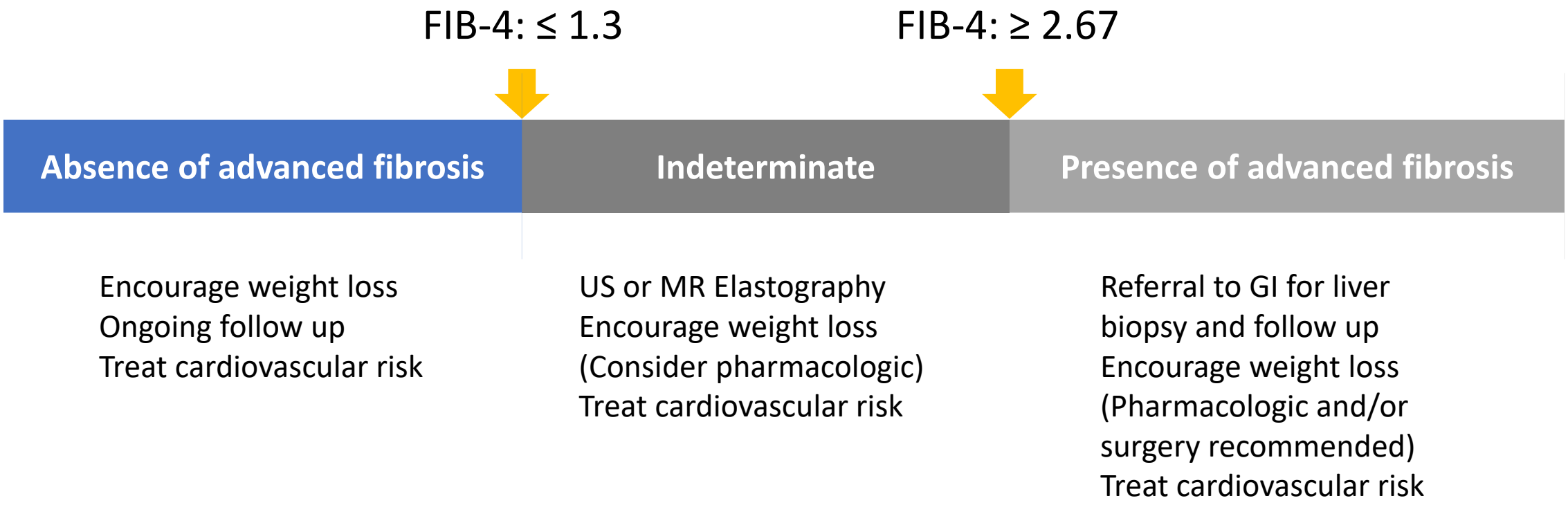
1. Vallet-Pichard. Hepatology. 2007;46:32. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Shah. Clin Gastroenterol Hepatol. 2009;7:1104.

FIB-4 Score:
Online Calculator Easily Interpret Noninvasive Tests

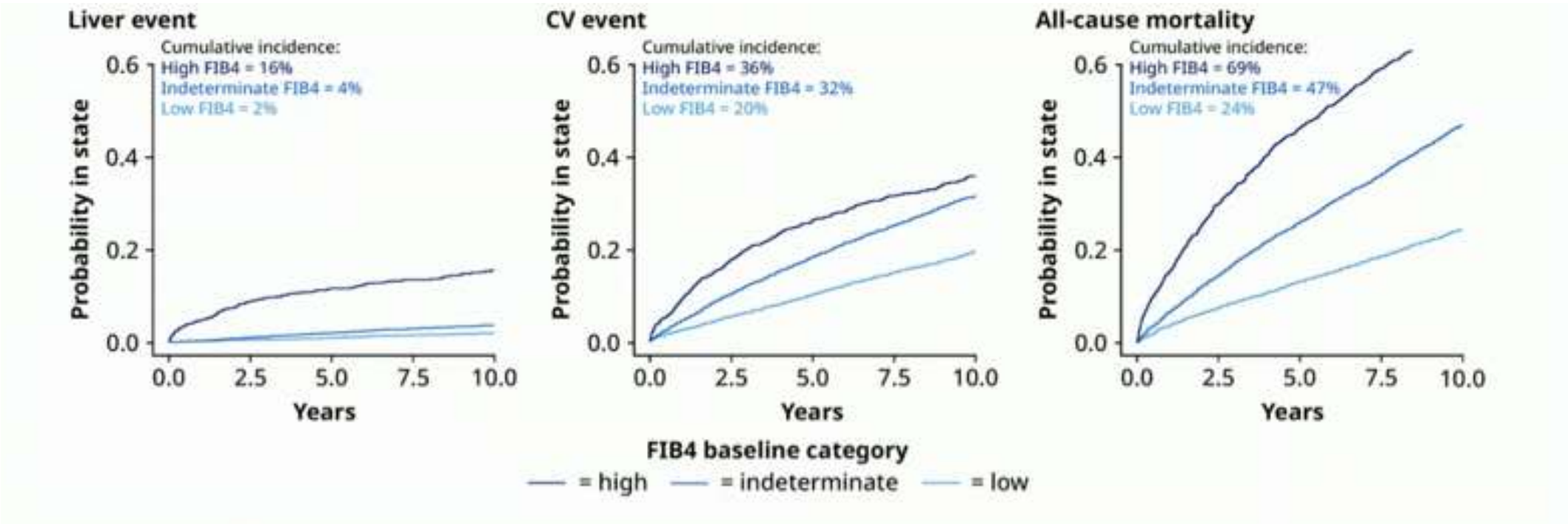
- **Based on age, platelet count, AST, ALT**
- Good negative predictive value for **ruling out** fibrosis

Available at: https://www.mdcalc.com.

How to use the Results of the FIB-4 Index



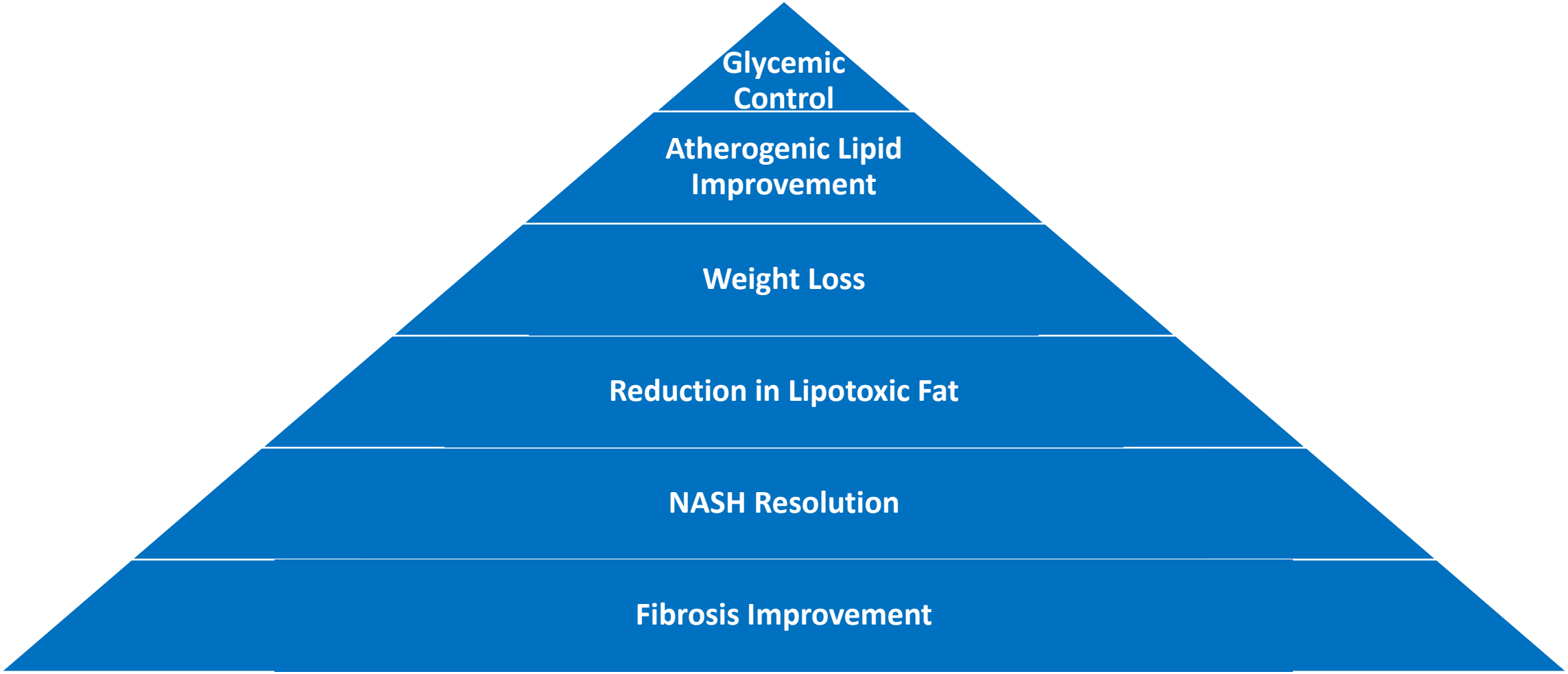
Liver, CV Events and All-cause Mortality in UK Population by FIB-4 Cutoffs (Adults without known liver disease (N=49,000)



Jara, M. Presesnted at the 58th Annual Meeting of the EASD, September 2022

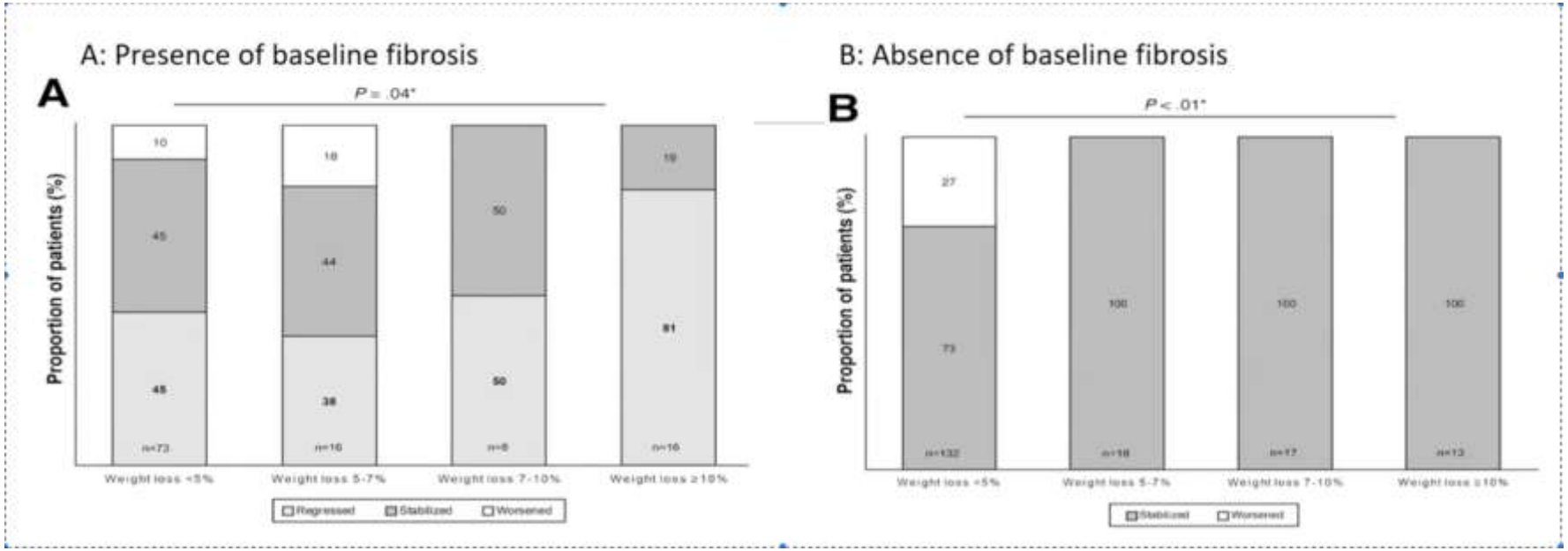
What do we know about treatment for NAFLD?

Potential Goals for Treatment of NASH



Management of NAFLD/NASH with Weight Loss

- N=293
- 52 week intervention of -750 kcal calorie restriction diet, 200 min walking/wk, 6 wk behavioral modification sessions.



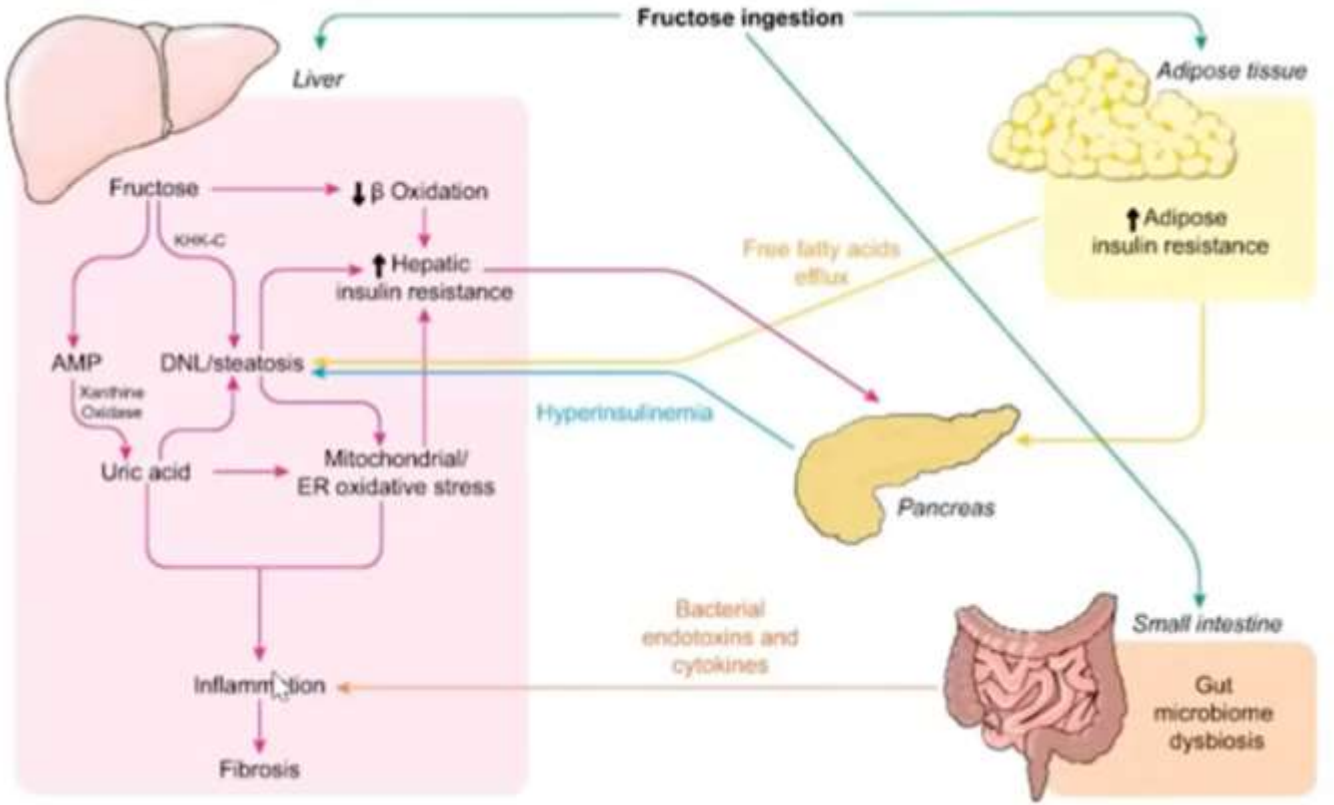
- Improvement in fibrosis was proportional to amount of weight loss

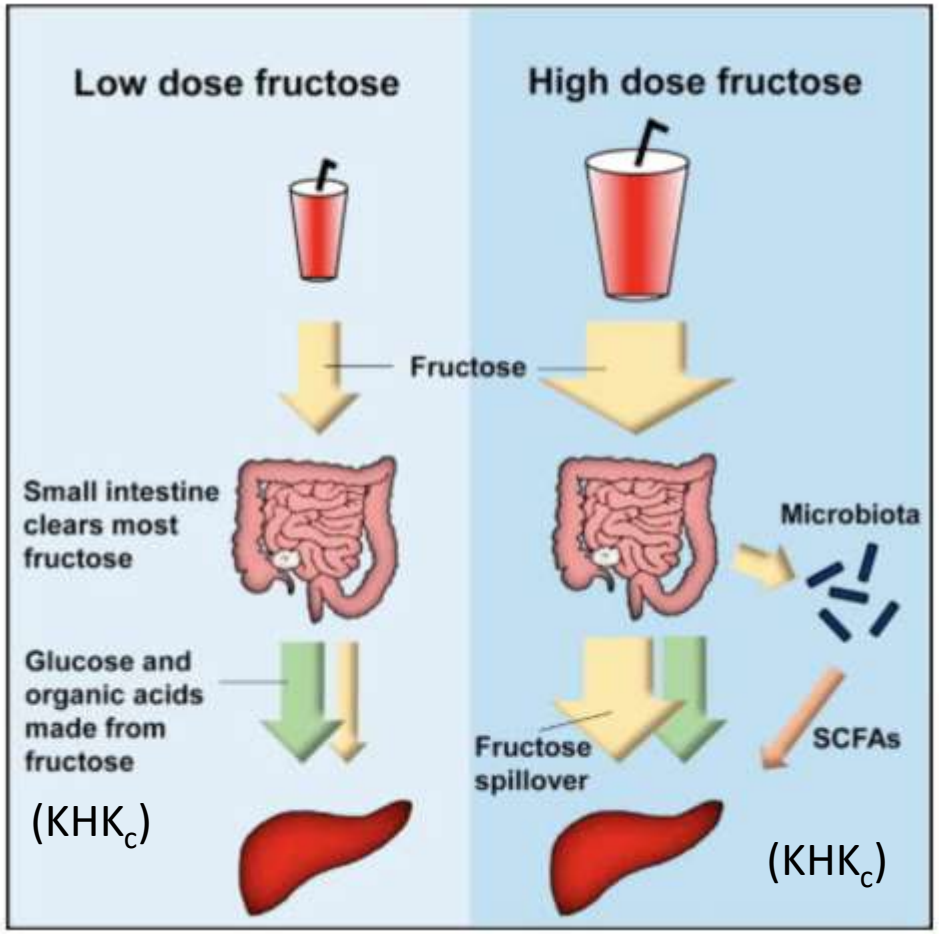
Vilar-Gomez *et al.* Gastroenterology. 2015

Which Diets Are Advisable in NAFLD?

- Low dietary sugar?
- Nonnutritive sweeteners?
- Low-caloric, low-fat, or low-carbohydrate diet?
- Popular diets (eg, very low–carbohydrate ketogenic diets)?

Fructose Induced Mechanism for Development and Progression of NAFLD

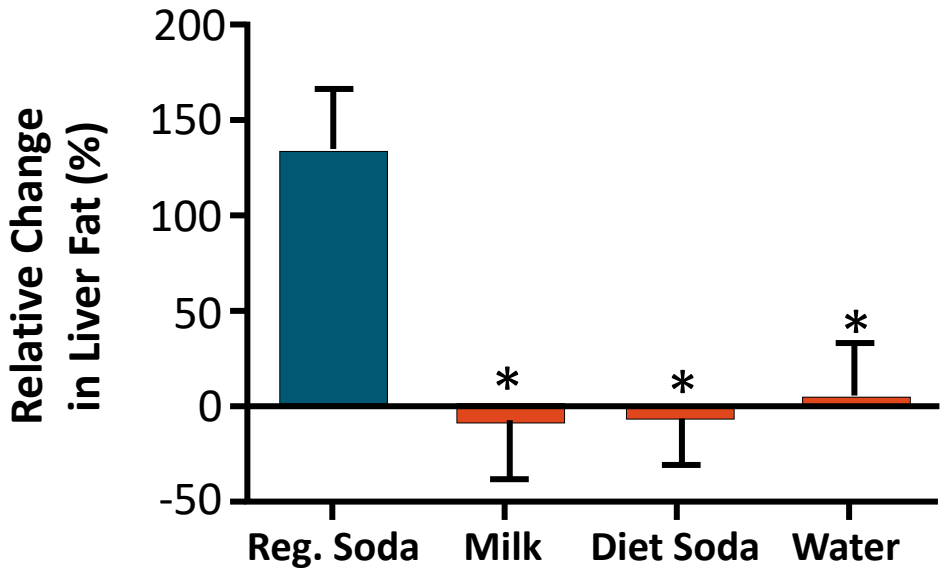




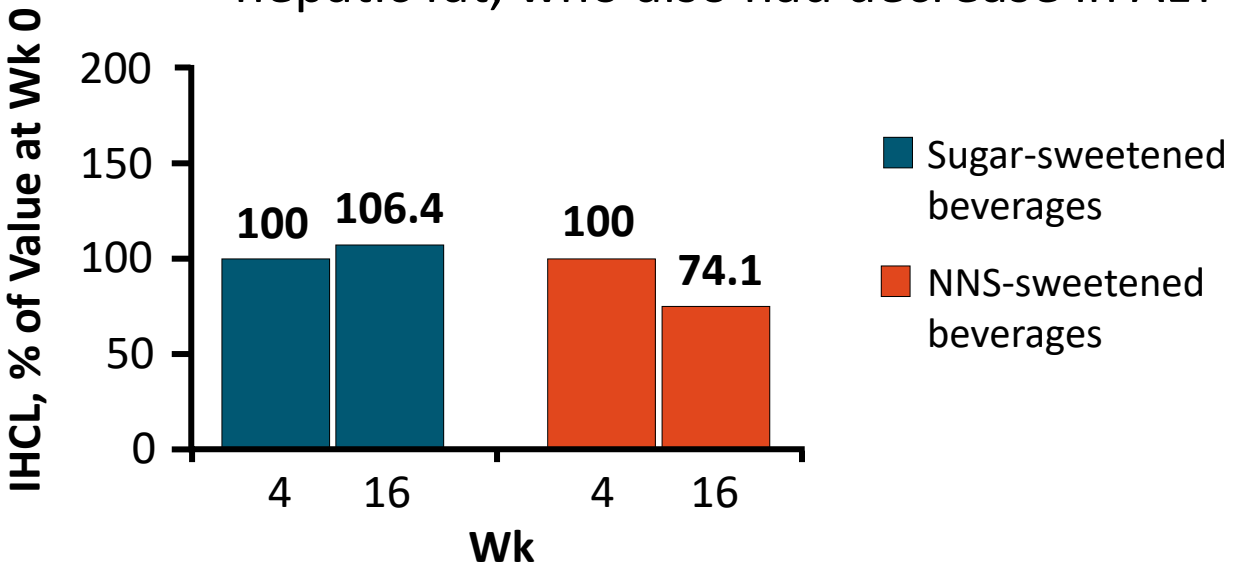
Jensen T et al. J of Hepatology 2018; 5:1063-1075

Sugar-Sweetened Beverages vs Nonnutritive Sweetener Beverages: Liver Fat Studies

- **6-mo study[1]:**
  N = 60 overweight or obese participants given different drinks
  - Regular soda increased liver fat; diet soda with NNS did not



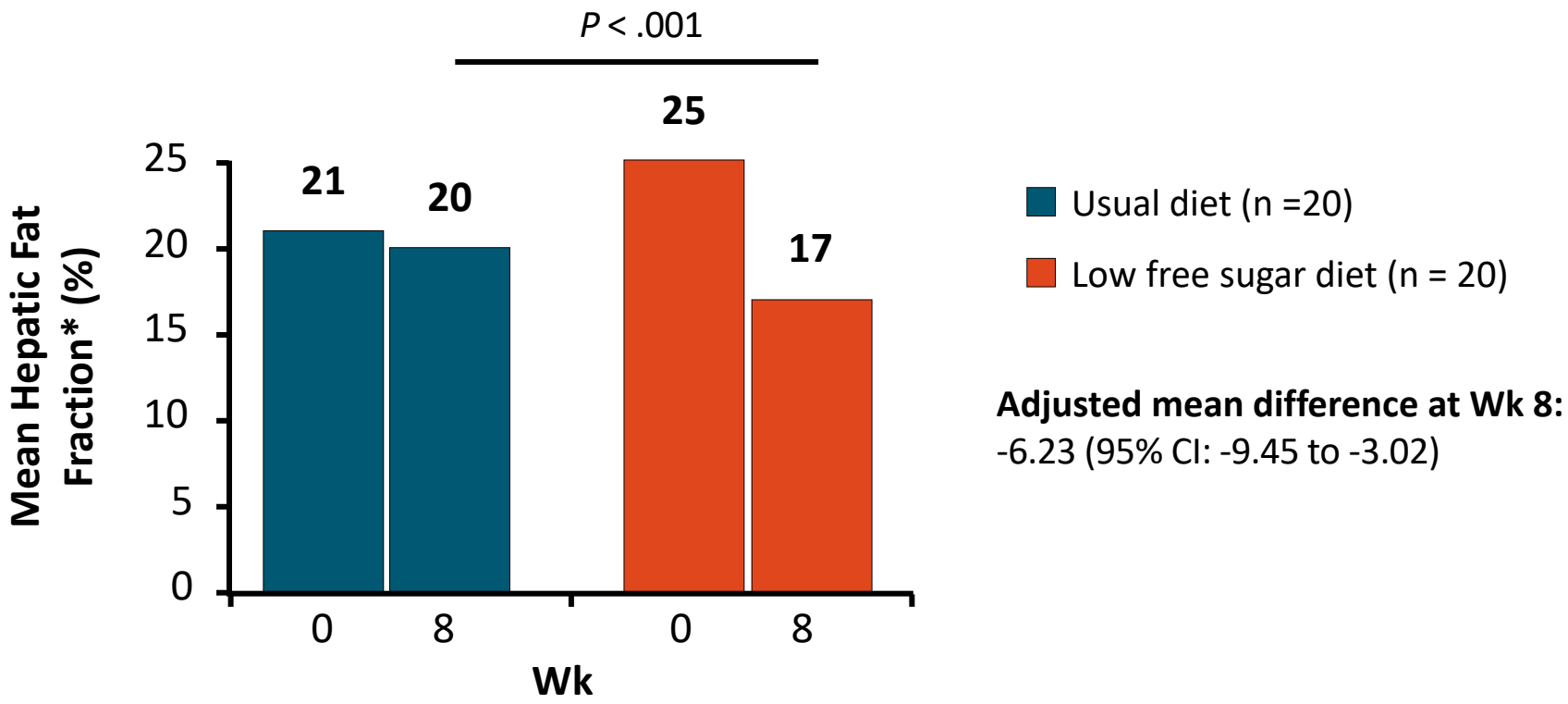
- **12-wk study[2]:**
  N = 31 overweight participants (27 completed) replacing sugar with NNS
  - Biggest effect in those with higher hepatic fat, who also had decrease in ALT



1. Maersk. Am J Clin Nutr. 2012;95:283. 2. Campos. Obesity (Silver Spring). 2015;23:2335.

Low Free Sugar Diet

- Open-label, randomized trial of **low free sugar diet**(< 3% of daily calories) vs **usual diet** in adolescent boys with histologically diagnosed NAFLD



*Measured by MRI-PDFF.

Schwimmer. JAMA. 2019;321:256.

Very Low Carbohydrate Ketogenic Diet vs Low Calorie Diet: 2 months

Assessment of VAT and Liver Fat

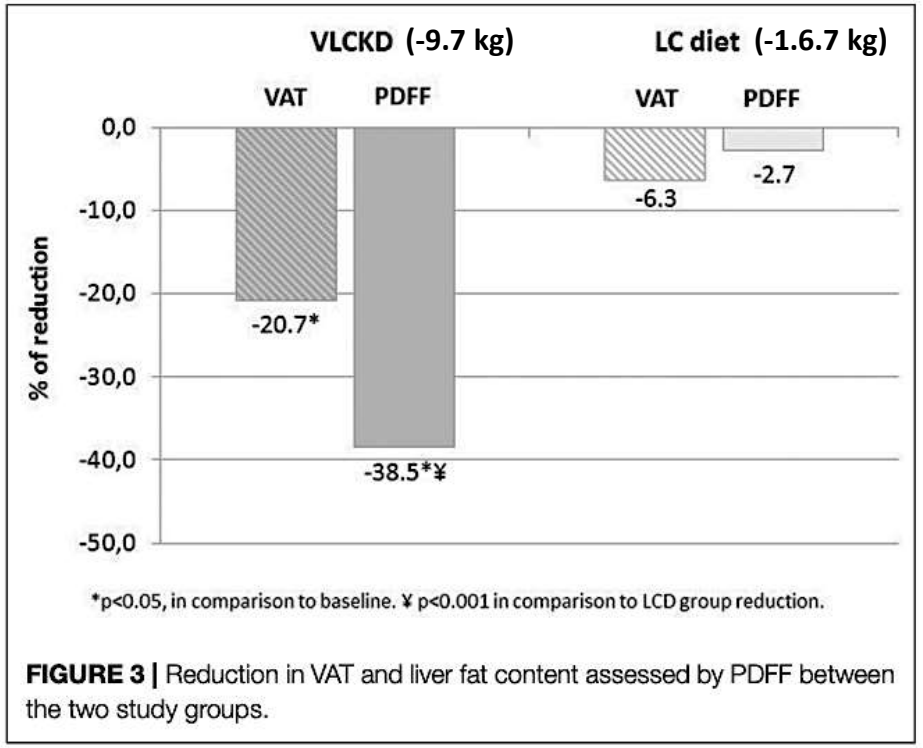
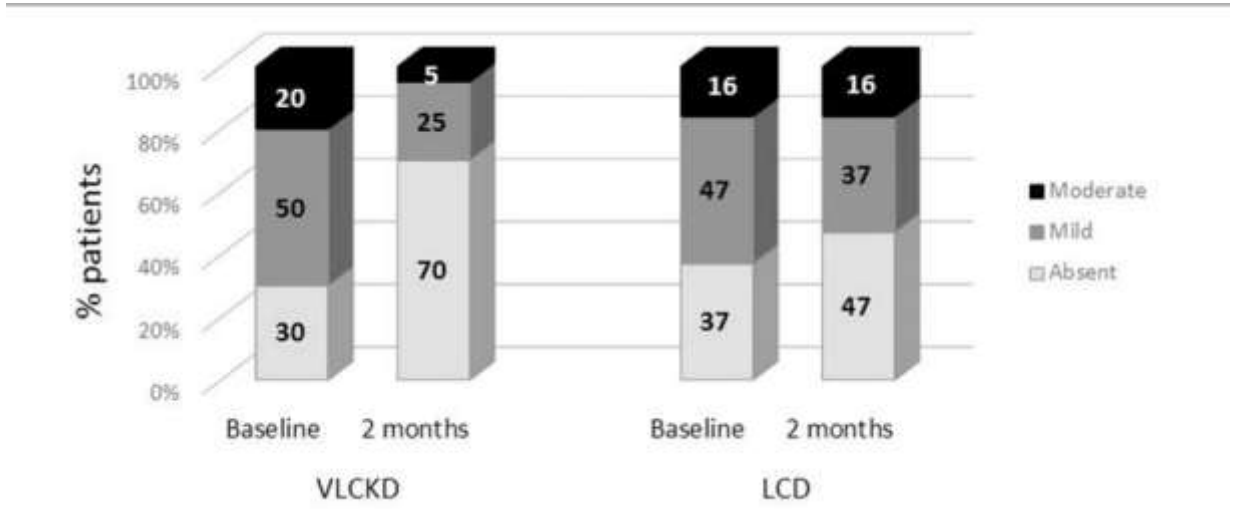


FIGURE 3 | Reduction in VAT and liver fat content assessed by PDFF between the two study groups.

Comparison of Liver Steatosis

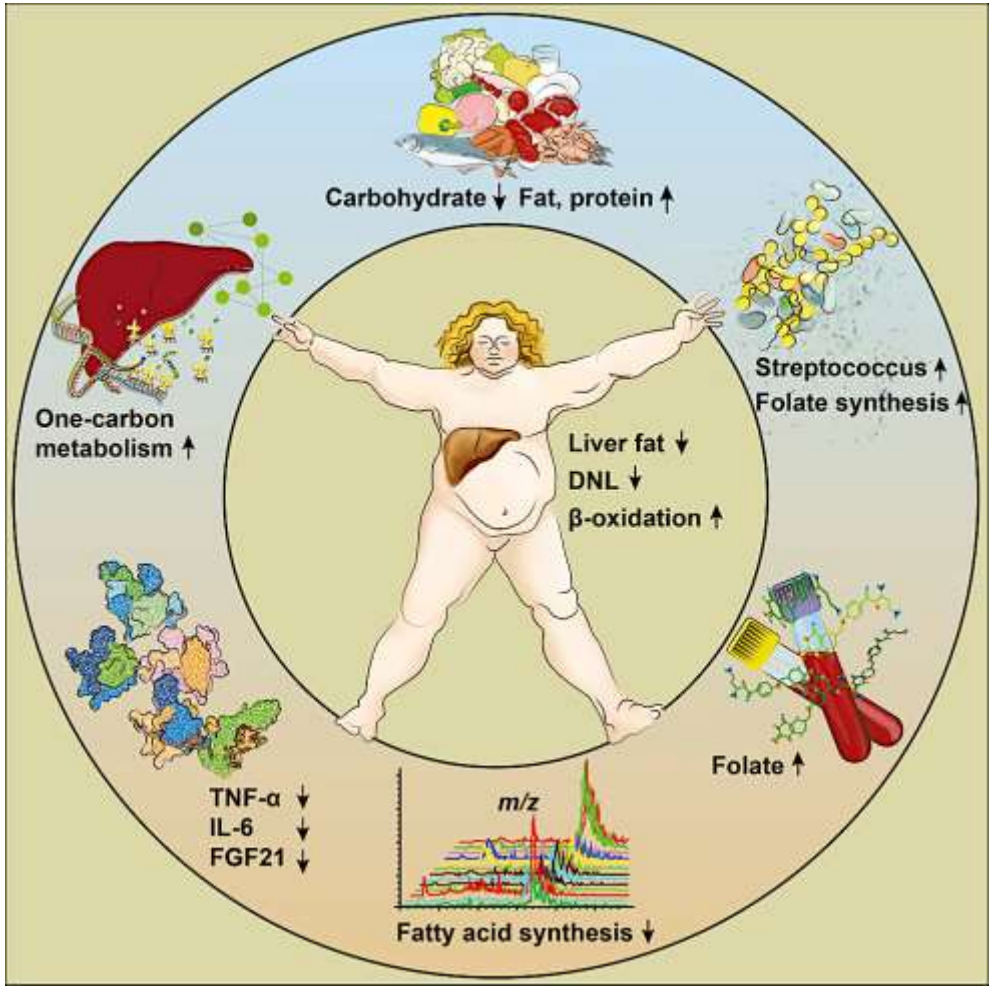


Cunha G Front. Endocrinol. 11:607. doi: 10.3389/fendo.2020.00607

Carbohydrate Restriction has Rapid Benefits in Hepatic Steatosis

14 day study of low carbohydrate diet on liver fat content (by MRS)

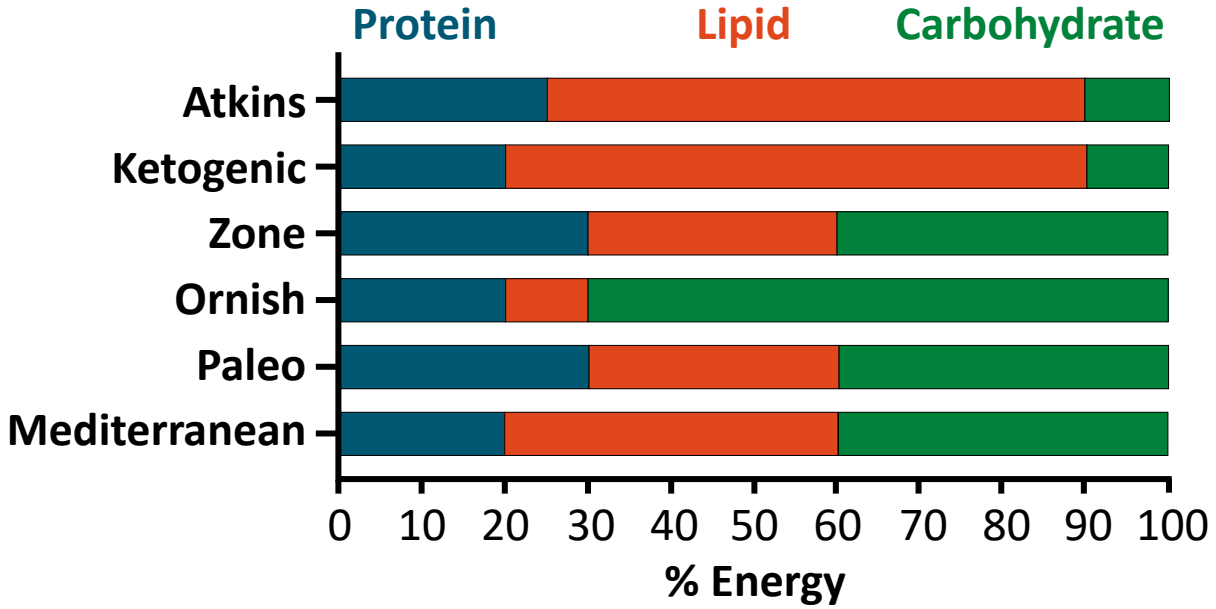
- 10 obese subjects with high liver fat
- Diet: <30 gm CHO, isocaloric to minimize impact of weight loss
- Weight loss: 1.8%
- Mean reduction of liver fat: 43.8%
- Returned to baseline 1 – 3 mos



Mardinoglu, A et al. 2018, Cell Metabolism 27, 559–571

Popular Diet Strategies

- Popular diets employ different strategies:
  - **Macronutrient** manipulation
    - High protein or low carb
  - **Timing** manipulation
    - Intermittent fasting
  - **Food/food group** restrictions
    - Gluten free, paleo



- Factors for successful weight loss
  - Adherence
  - Negative energy balance
  - High-quality foods

Freire. Nutrition. 2019;69:110549.

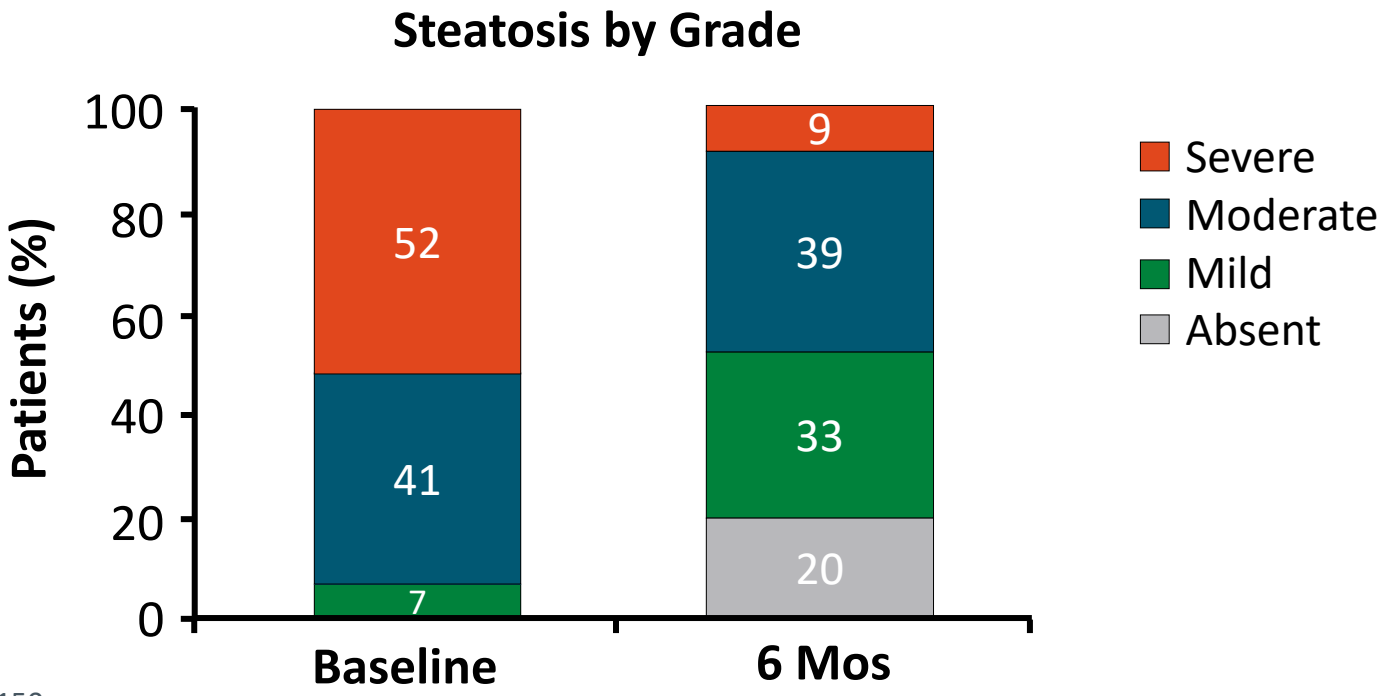
Mediterranean Diet in NAFLD: Observational Study

Design

- 6-mo observational study of **Mediterranean diet** intervention with monthly nutrition counseling in patients with NAFLD (N = 46)

Results

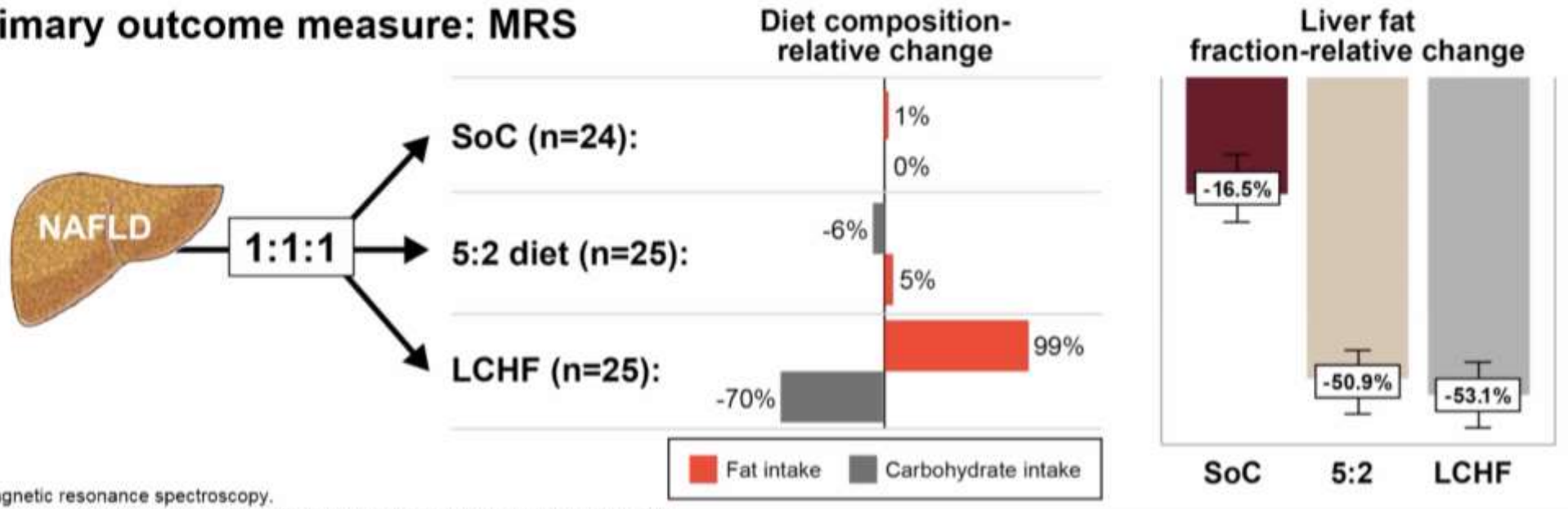
- Frequency of grade ≥ 2 steatosis decreased in > 80%, with resolution in 20%



Gelli. World J Gastroenterol. 2017;23:3150.

The Impact of Diet on NAFLD: Low Carbohydrate vs Intermittent Fasting

- **Open-label RCT in 74 subjects with NAFLD**
- **Study groups**
  - Standard of care (SoC)
  - Intermittent caloric restriction 5:2
  - Low-carbohydrate high fat (LCHF)
- **Primary outcome measure: MRS**



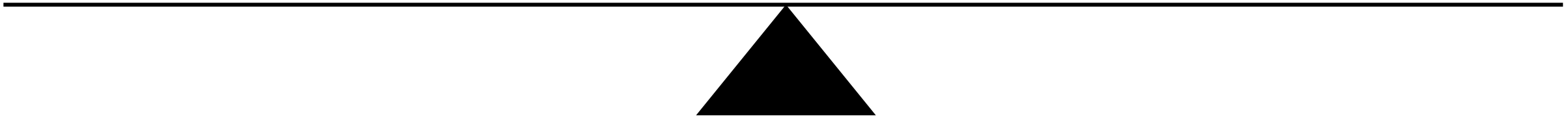
MRS: magnetic resonance spectroscopy.

Holmer M, et al. *JHEP Rep*. 2021;3:100256. Reproduced for educational purposes only.

Popular Diets in NAFLD

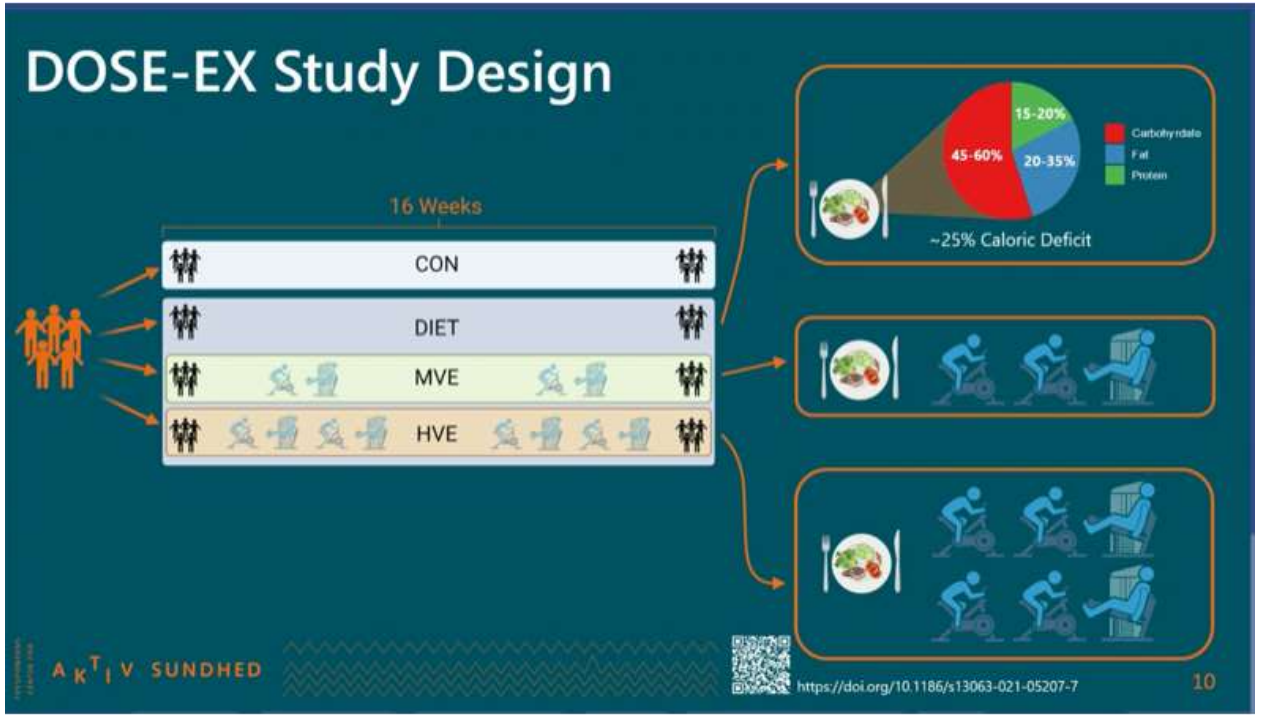
Mediterranean diet good choice for a balanced diet with strong evidence for benefit

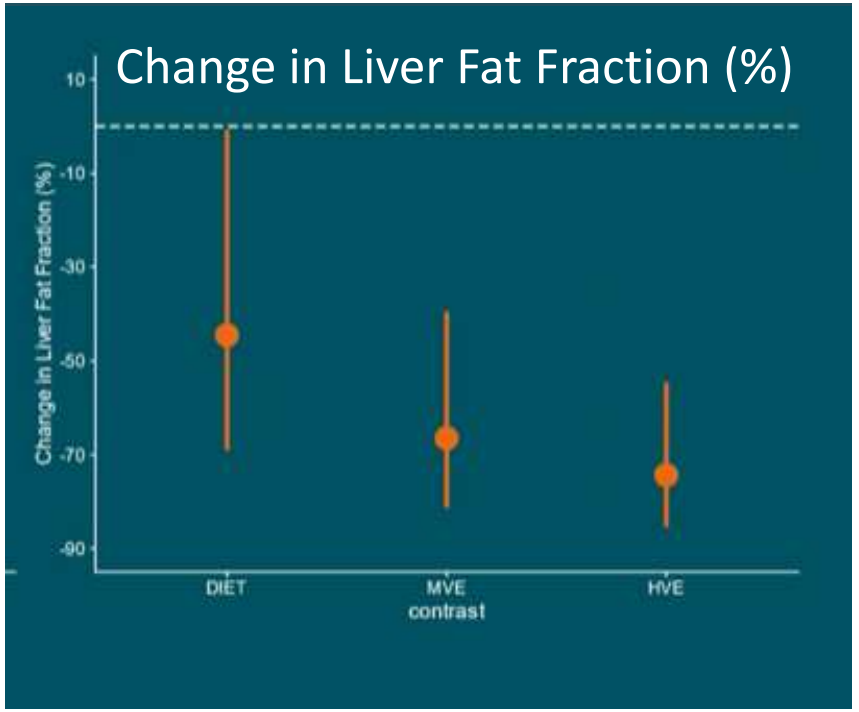
More restrictive diets can work in the short term, but adherence is difficult and long-term data are lacking



None has evidence of consistent superiority
Keys are restricting simple sugars, weight loss and patient preference and adherence

Effect of Addition of Exercise to Diet on Hepatic Steatosis





Durrer C. Presented at the 58th Annual Meeting of EASD, September 2022

Lifestyle Modification in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

Energy restriction

- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- 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 carbohydrate
- Low-carbohydrate ketogenic diets or high protein

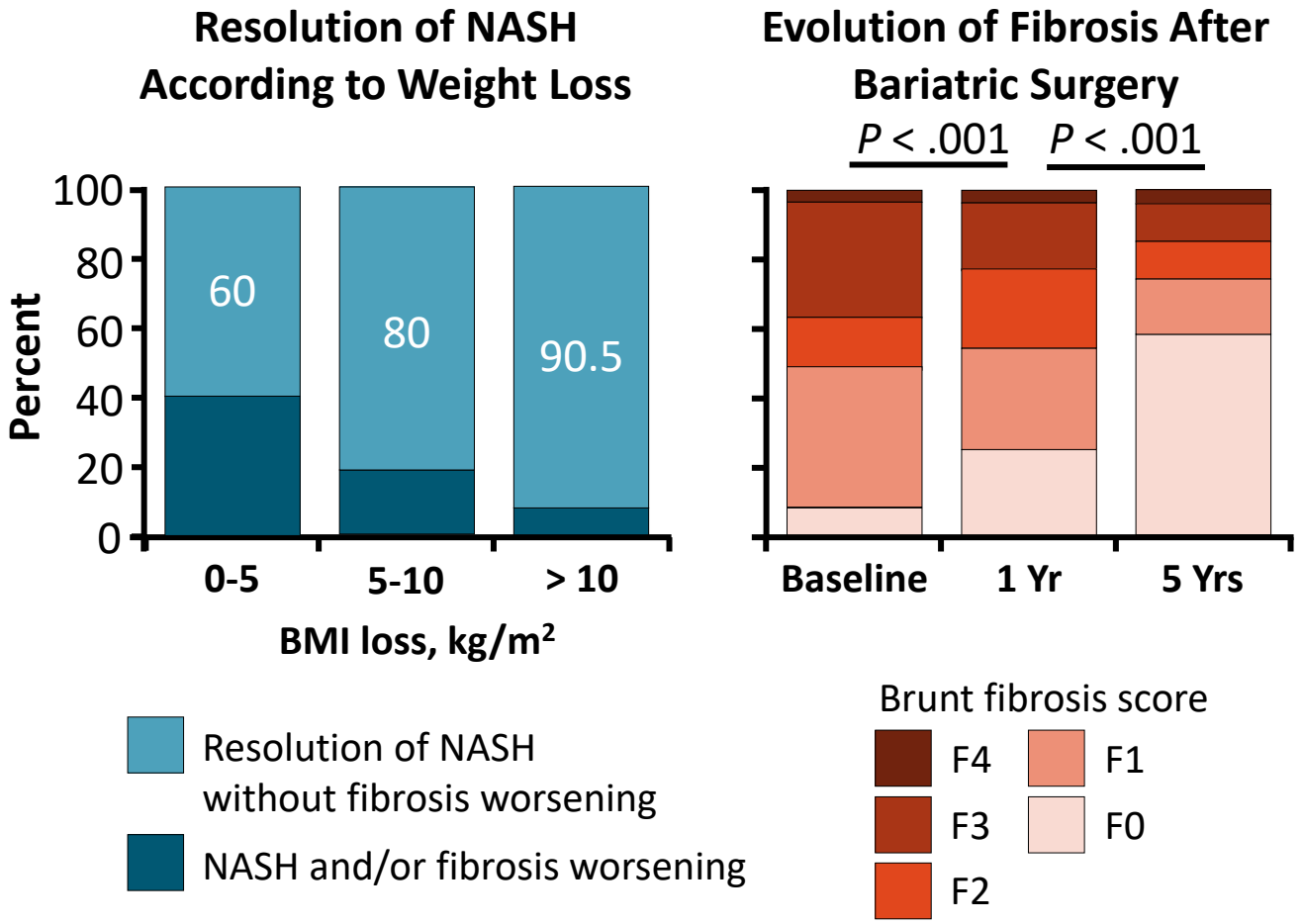
Physical activity

- 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

Impact of Bariatric Surgery on NASH

- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yrs post surgery, 64 of 94 patients (84%) had NASH resolution with no worsening of fibrosis
  - NASH improvement correlated with weight loss



Lassailly. Gastroenterology. 2020;159:1290.

Sustained Weight Loss Through Lifestyle Modification

Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr[1]
≥10%[1]	**Fibrosis regression**	<10%
≥7%[1]	NASH resolution	18%
≥5%[1-3]	Ballooning/inflammation improvement	30%
≥3%[1-4]	Steatosis improvement	Not reported

1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.
3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

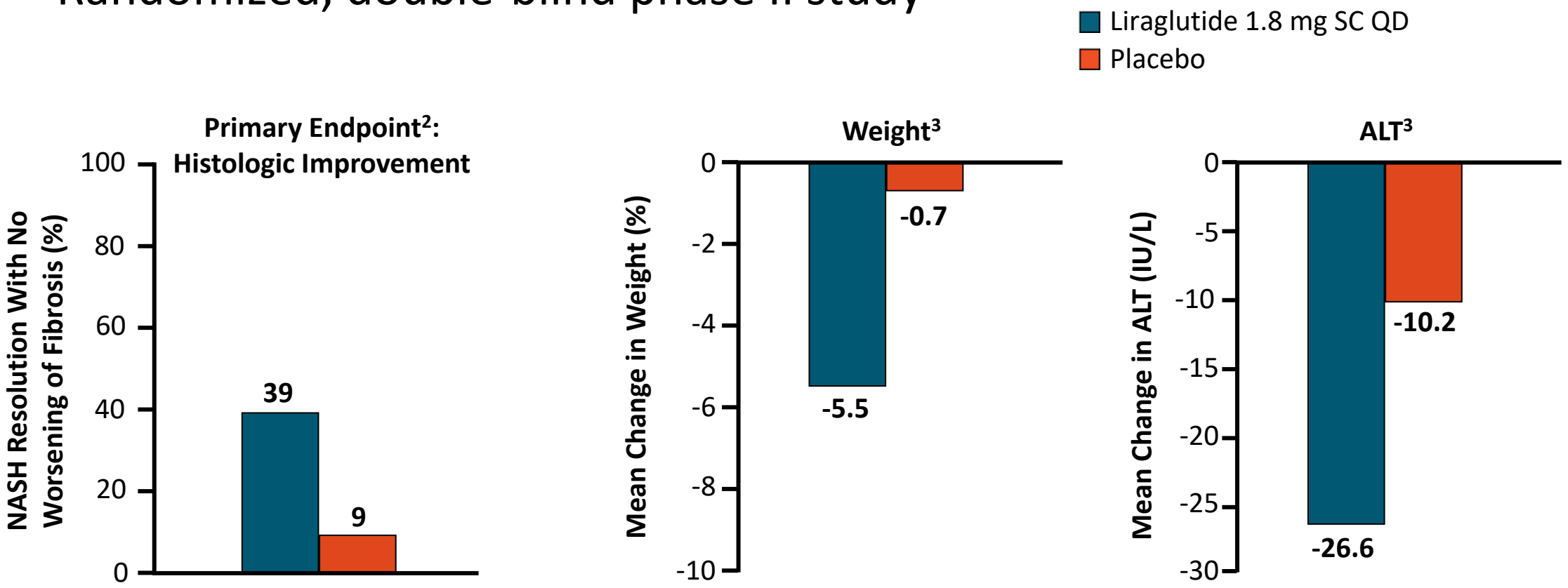
Slide credit: clinicaloptions.com

Weight Loss Medications Approved in the US

Name	Average Weight Loss	% of Subjects losing ≥ 10%	Side Effects
Olristat	3 – 5%	NA	GI upset, diarrhea, malabsorption of fat soluble vitamins
Phentermine/Topiramate ER	10%	53%	Dry mouth, anxiety, dysgeusia, paresthesias
Naltrexone/Bupropion SR	6%	25%	Nausea, dizziness, headache, transient increase SBP
Liraglutide 3 mg	10 – 12%	39%	Nausea, vomiting, gallbladder disease, diarrhea
Semaglutide 2.4 mg	15%	75%	Nausea, vomiting, gallbladder disease, diarrhea

LEAN: 48-Wk Results of Liraglutide in Overweight Patients With NASH

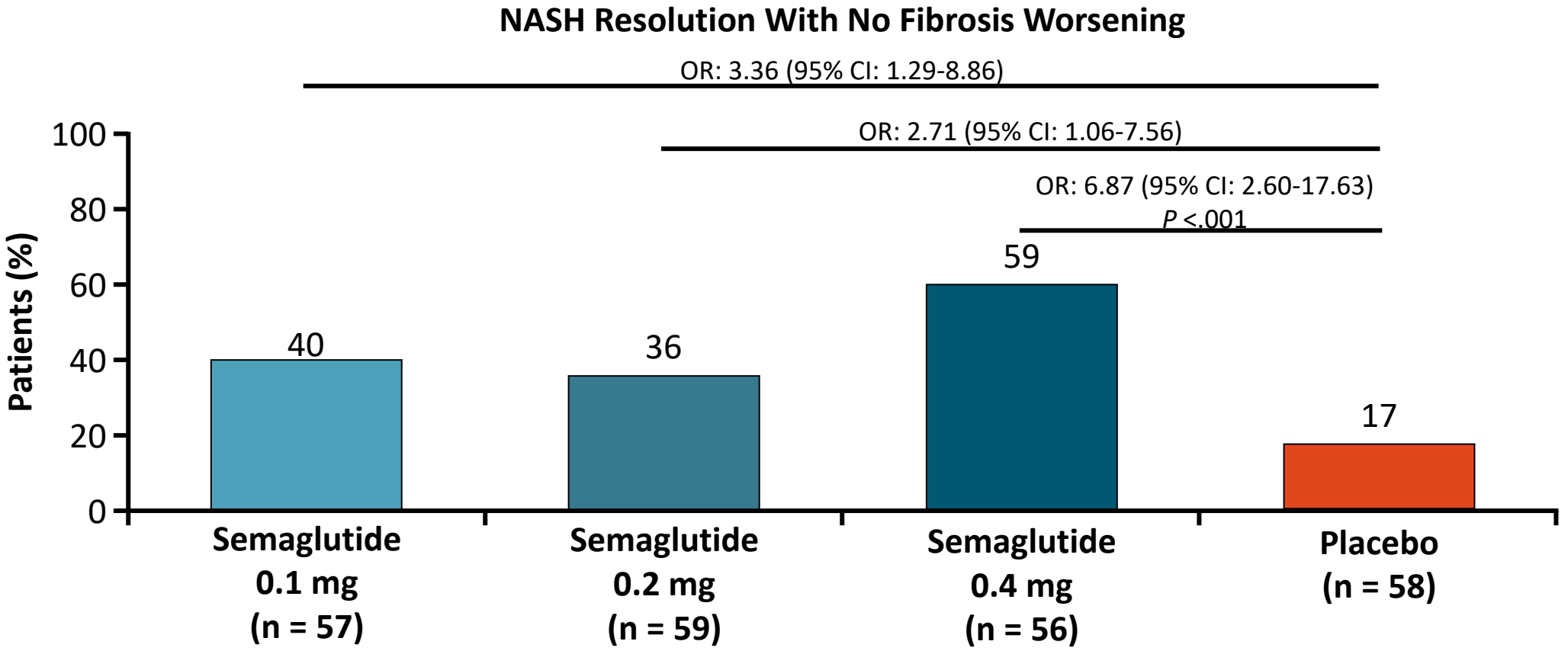
- Randomized, double-blind phase II study[1]



1. Armstrong. BMJ Open. 2013;3:e003995. 2.Armstrong. Lancet. 2016;387:679. 3. Armstrong. EASL 2015. Abstr G01.

Semaglutide in NASH: Primary Endpoint at 72 Wk

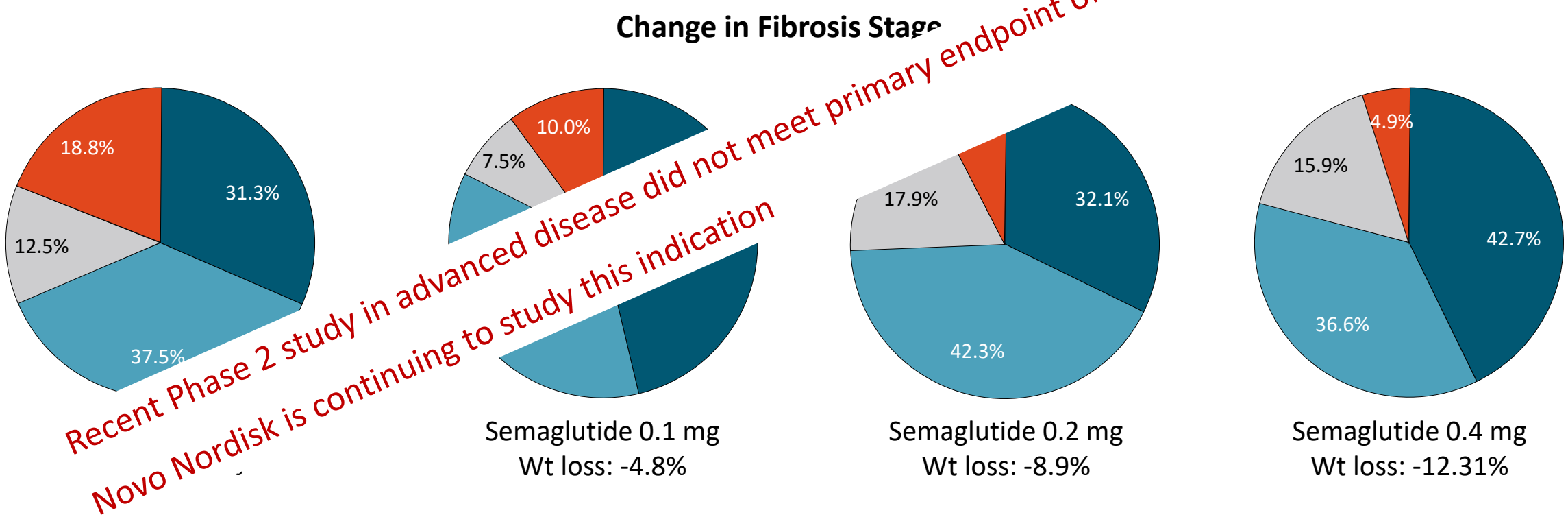
- Randomized, double-blind, multicenter phase II trial in adults with BMI >25 kg/m^2 and biopsy-proven NASH



Newsome. NEJM. 2021;384:1113.

Prevention of Fibrosis Progression

- Secondary endpoint of phase II study of semaglutide in



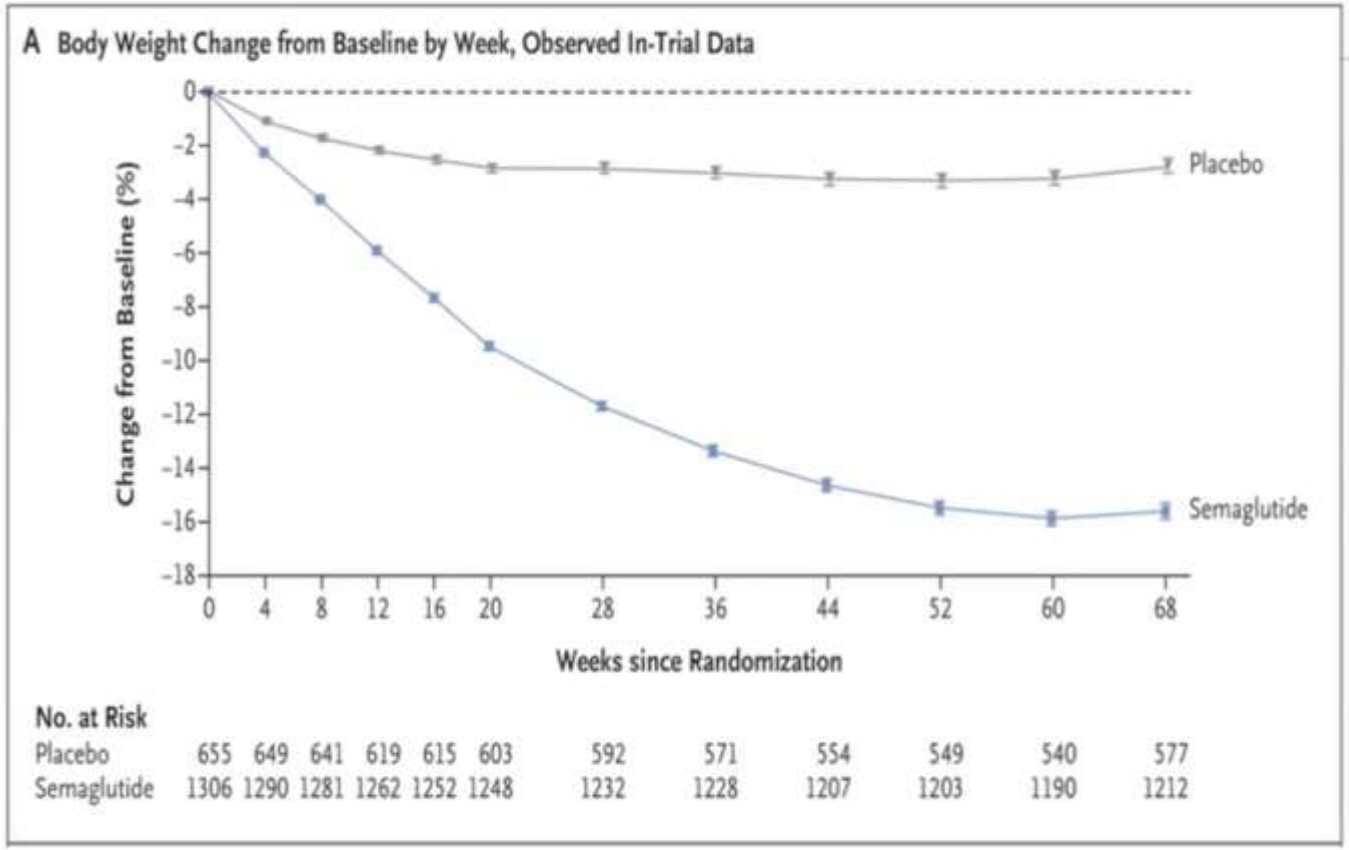
Recent Phase 2 study in advanced disease did not meet primary endpoint of decrease fibrosis

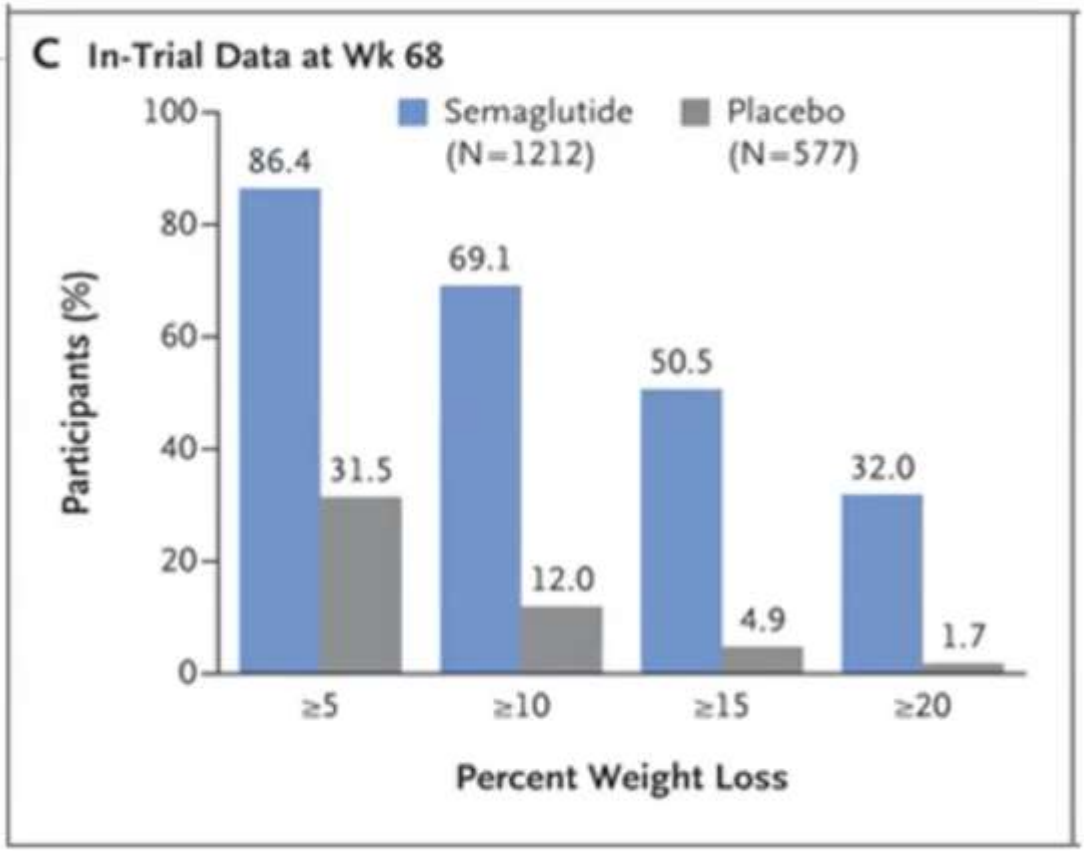
Novo Nordisk is continuing to study this indication

Semaglutide 2.4 mg associated with mean weight loss of 14.9% in patients without diabetes

Newsome P NEJM. 2021;384:1113, Wilding J. NEJM. 2021;18:989

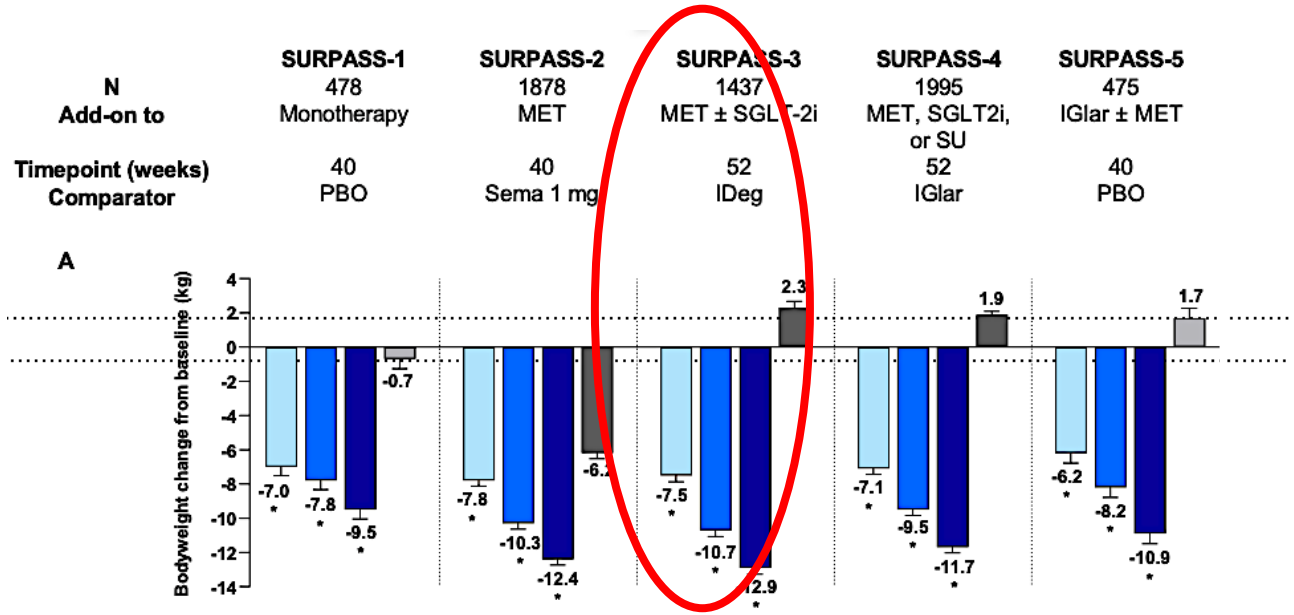
STEP 1 Trial: Semaglutide 2.4 mg in Patients Without Diabetes

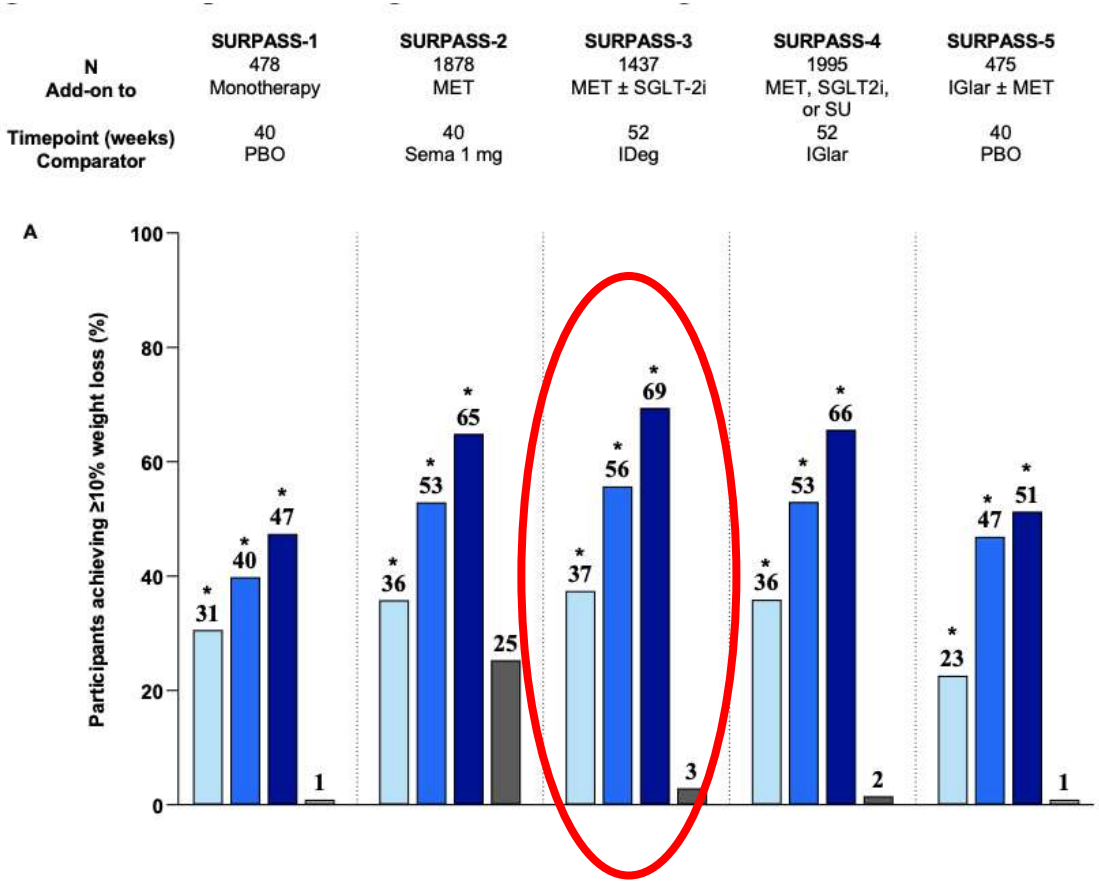




Wilding JP et al N Engl J Med 2021

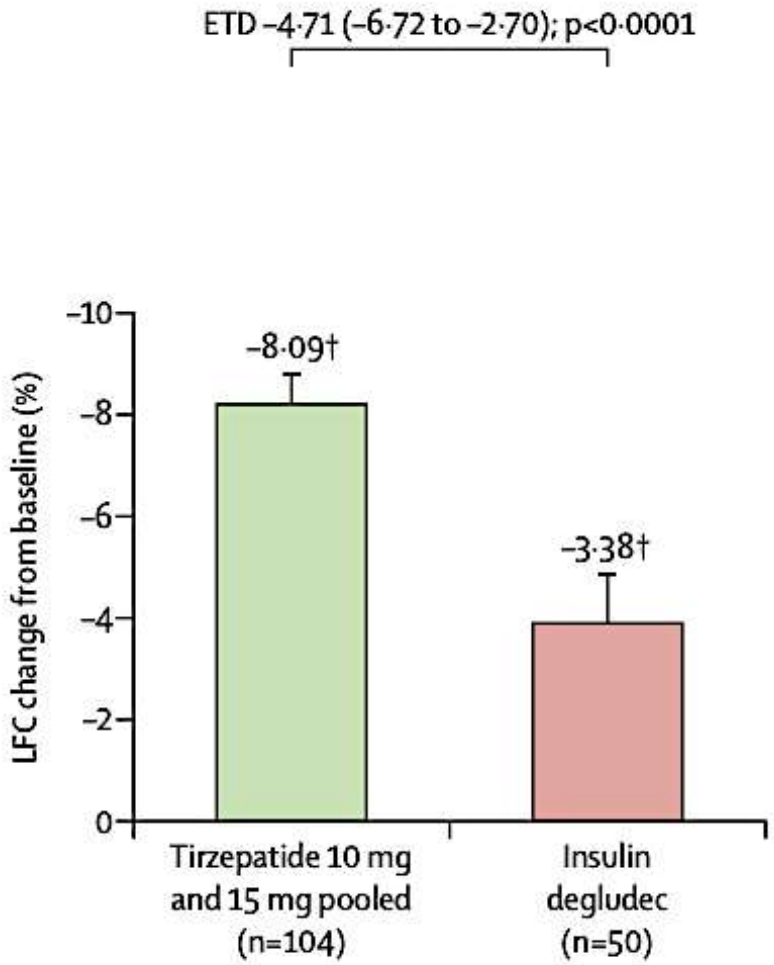
Tirzepatide (GLP-1/GIP Co-agonist): Change in Body Weight in the SURPASS Studies

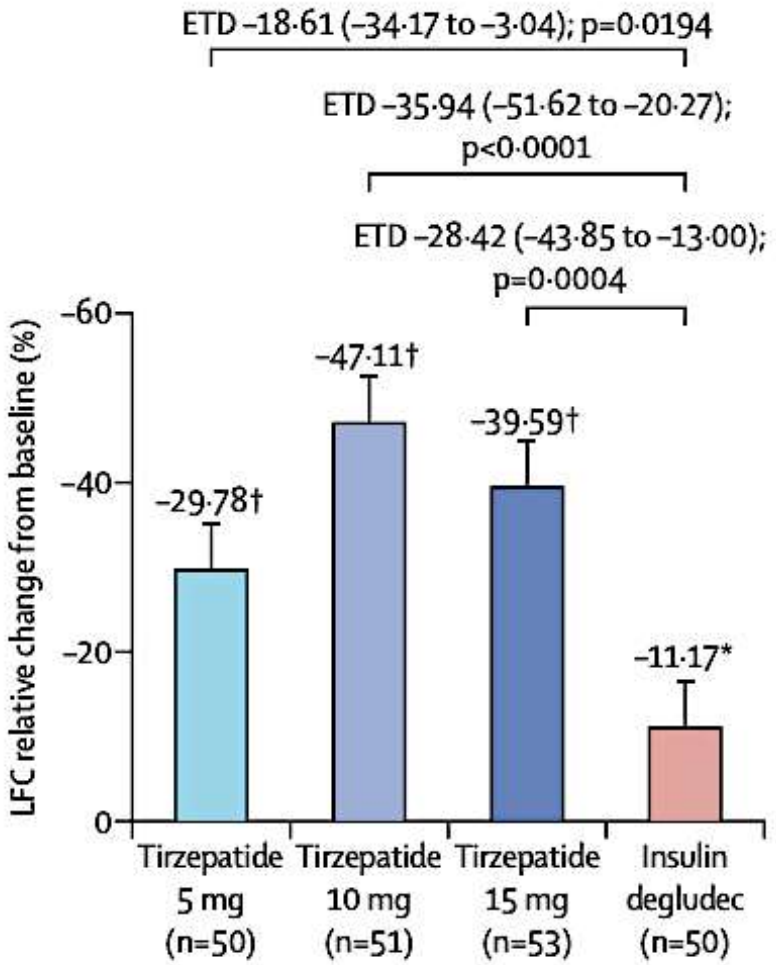




Rosenstock J et al. Lancet 2021;398:143-155; Frias J et al. New Engl J Med 2021;385:503-551; Ludvik B et al. Lancet 2021;398:583-598; DelPrato S et al. Lancet 2021;398:1811-1824; Dahl D et al JAMA 2022;327:534-545.

Change in Liver Fat Content (MRI): Tirzepatide (Dual GLP-1/GIP RA) vs Insulin Degludec (52 weeks)



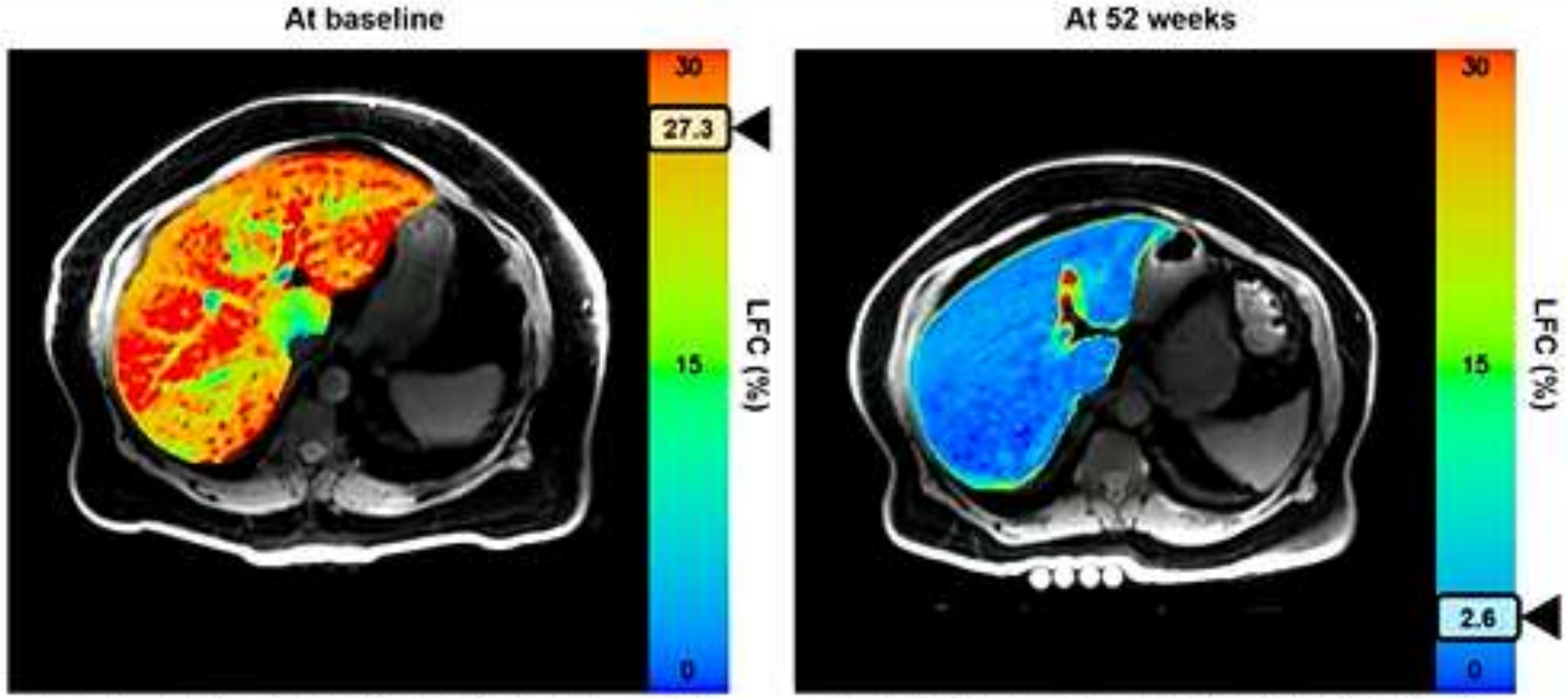


Reduction in LFC correlated with:
-reduction in weight
-reduction in VAT
-reduction in A1c

Castaldelli A et al. Lancet Diab & Endocrinol Published online April 22, 2022

SURPASS 3 MRI Substudy – MRI scan at baseline and at 52 weeks

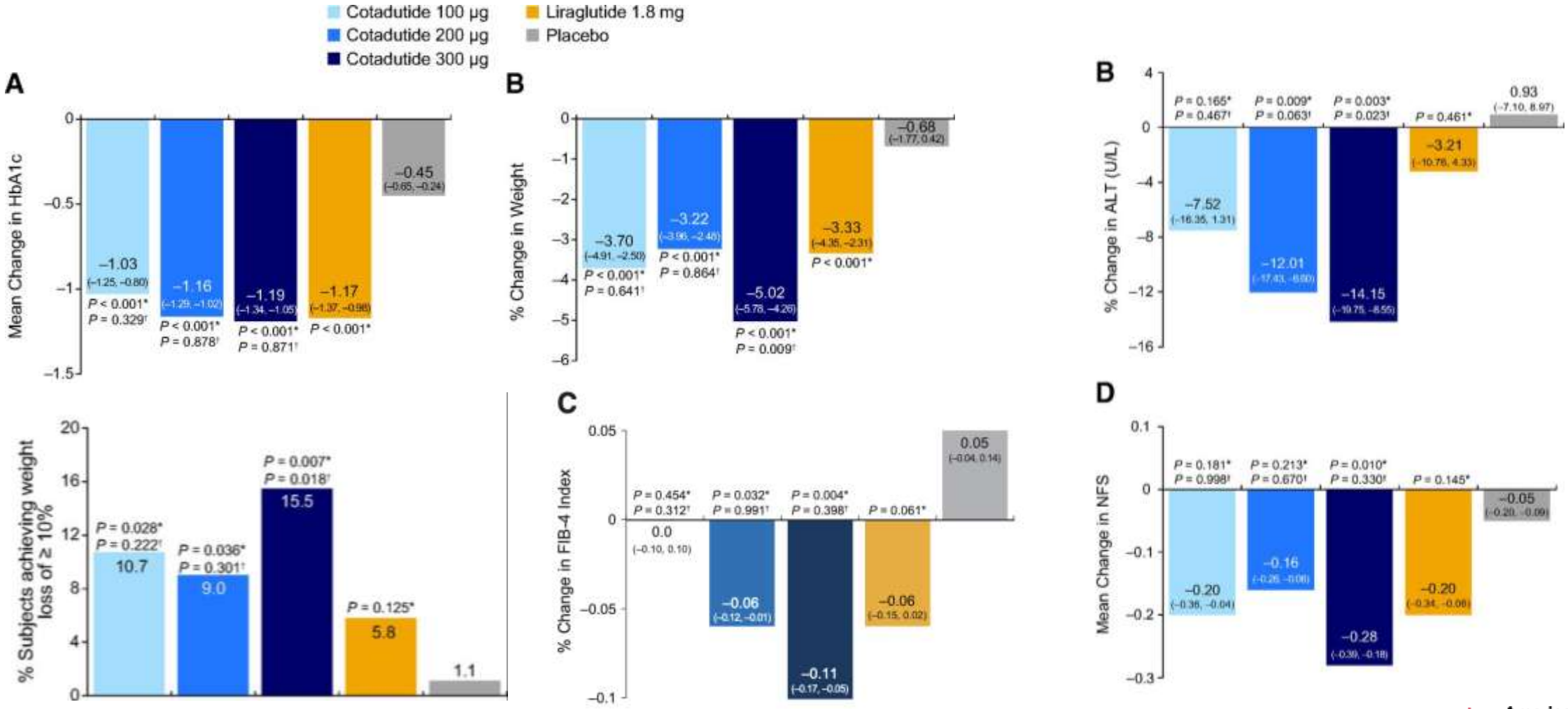
Male, 59 Years, on Metformin + SGLT-2i Randomised to Tirzepatide 5 mg



BMI: 44.8 kg/m²; body weight: 134.2 kg; WC: 139.7 cm
HbA_{1c}: 78.1 mmol/mol (9.3%)
FSG: 10.3 mmol/L (186 mg/dL)

BMI: 36.2 kg/m²; body weight: 108.4 kg; WC: 124.4 cm
HbA_{1c}: 43.2 mmol/mol (6.1%)
FSG: 5.9 mmol/L (107 mg/dL)

Effects of Cotadutide (GLP-1/Glucagon Co-Agonist) on Metabolic and Hepatic Parameters in Overweight or Obesity and Type 2 Diabetes: 54-Week



Diabetes Care. 2021;44(6):1433-1442. doi:10.2337/dc20-2151

American Diabetes Association.

SGLT2 Inhibitors in T2D and NAFLD: Umbrella Review of Systematic Reviews

Studies

- 7 systematic reviews of SGLT2 inhibitors (including between 67 and 498 patients)
  - 4 evaluated effects on **liver enzymes**
  - 4 reported changes in **liver fat**
  - 2 reported changes in **fibrosis biomarkers**

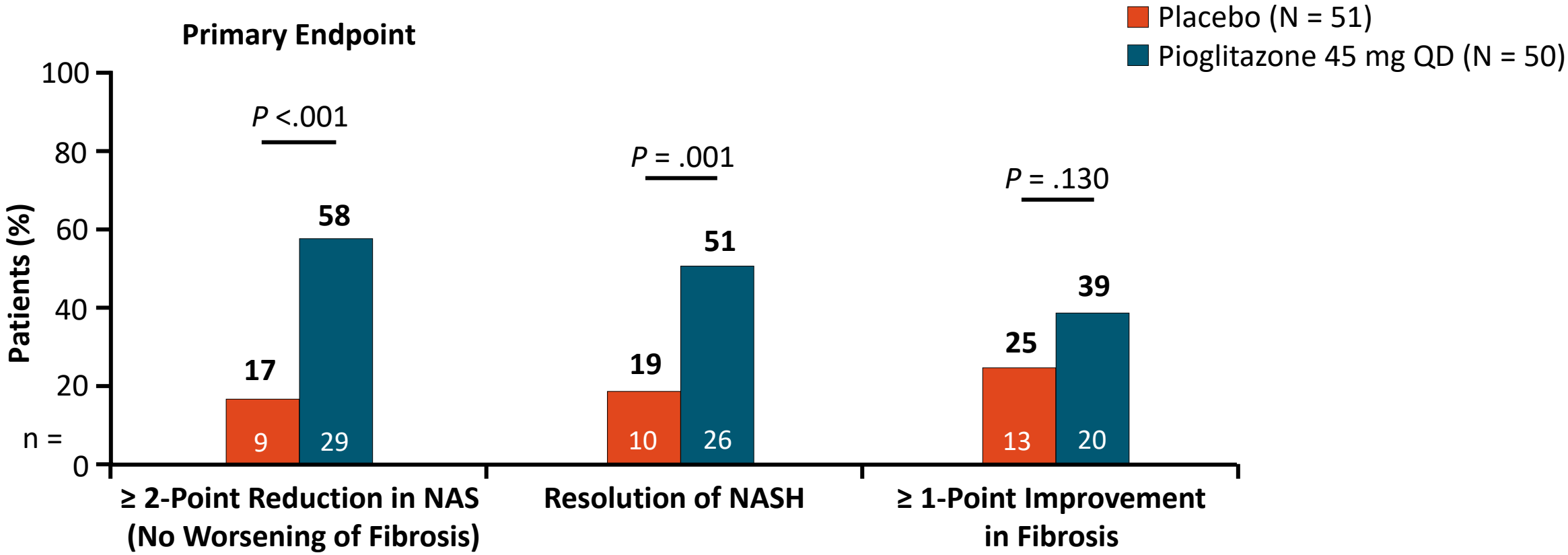
Results

- ✗ None rated as high quality, only 1 as moderate quality
- ✓ 5 systematic reviews indicated that SGLT2 inhibitors could **decrease liver fat and liver enzymes**
- ✓ 1 small, single-arm histologic study showed **improvement in steatosis**
- ✗ No evidence of **liver fibrosis** improvement

Shao. BMJ Open Diab Res Care. 2020;8:e001956.

Pioglitazone in NASH With Prediabetes/T2D: 18-Mo Outcomes

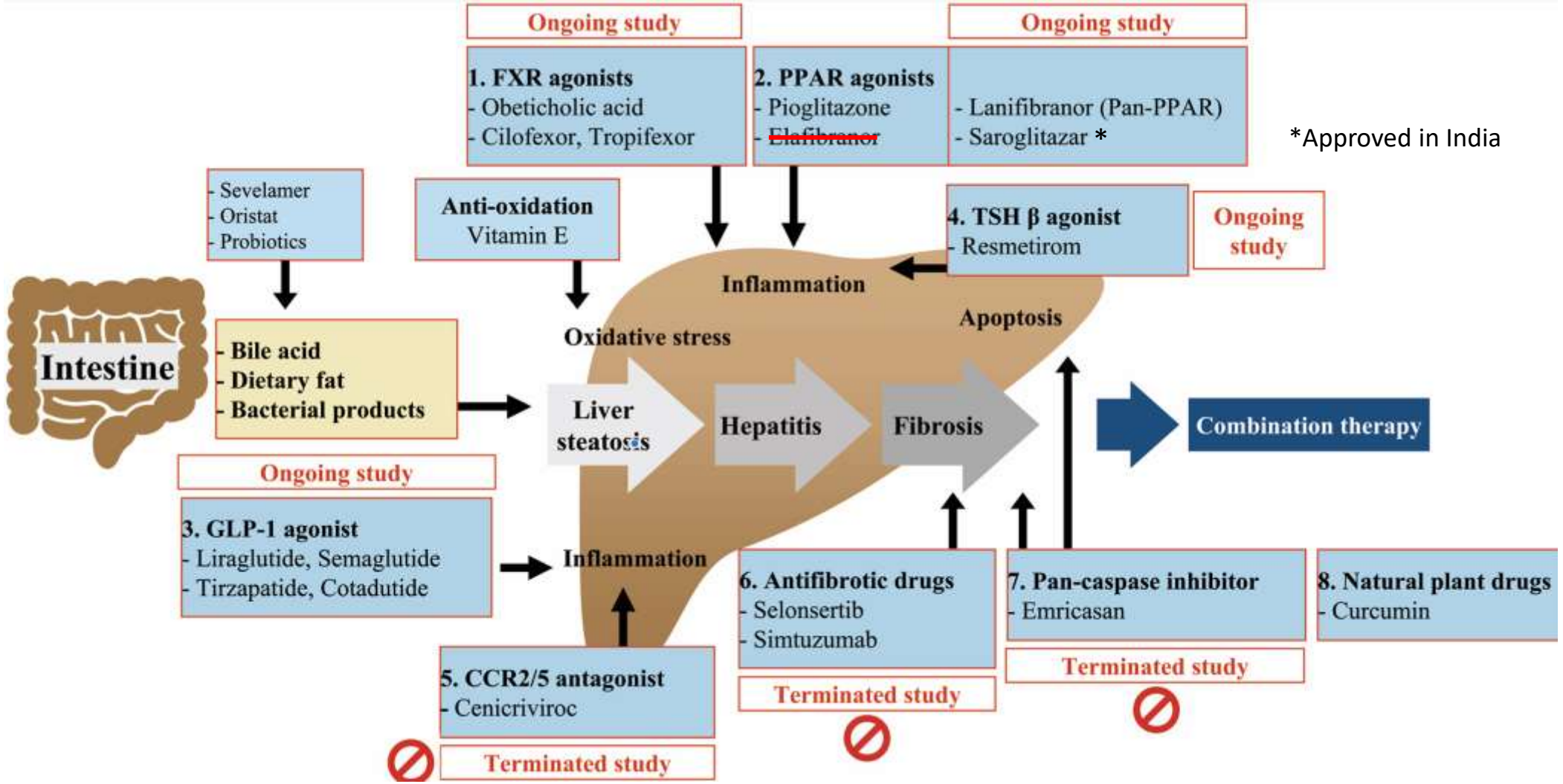
- Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or T2D (N = 101)[1]



Cusi. Ann Intern Med. 2016;165:305.

Pharmacologic targets of NASH: Current Status

At least 318 Current studies ongoing



Prasoppokakorn T et al, J*ournal of Clinical and Translational Hepatology* 2021;9:939-946

Obeticholic Acid in NASH: Interim Results of the Phase 3 REGENERATE study

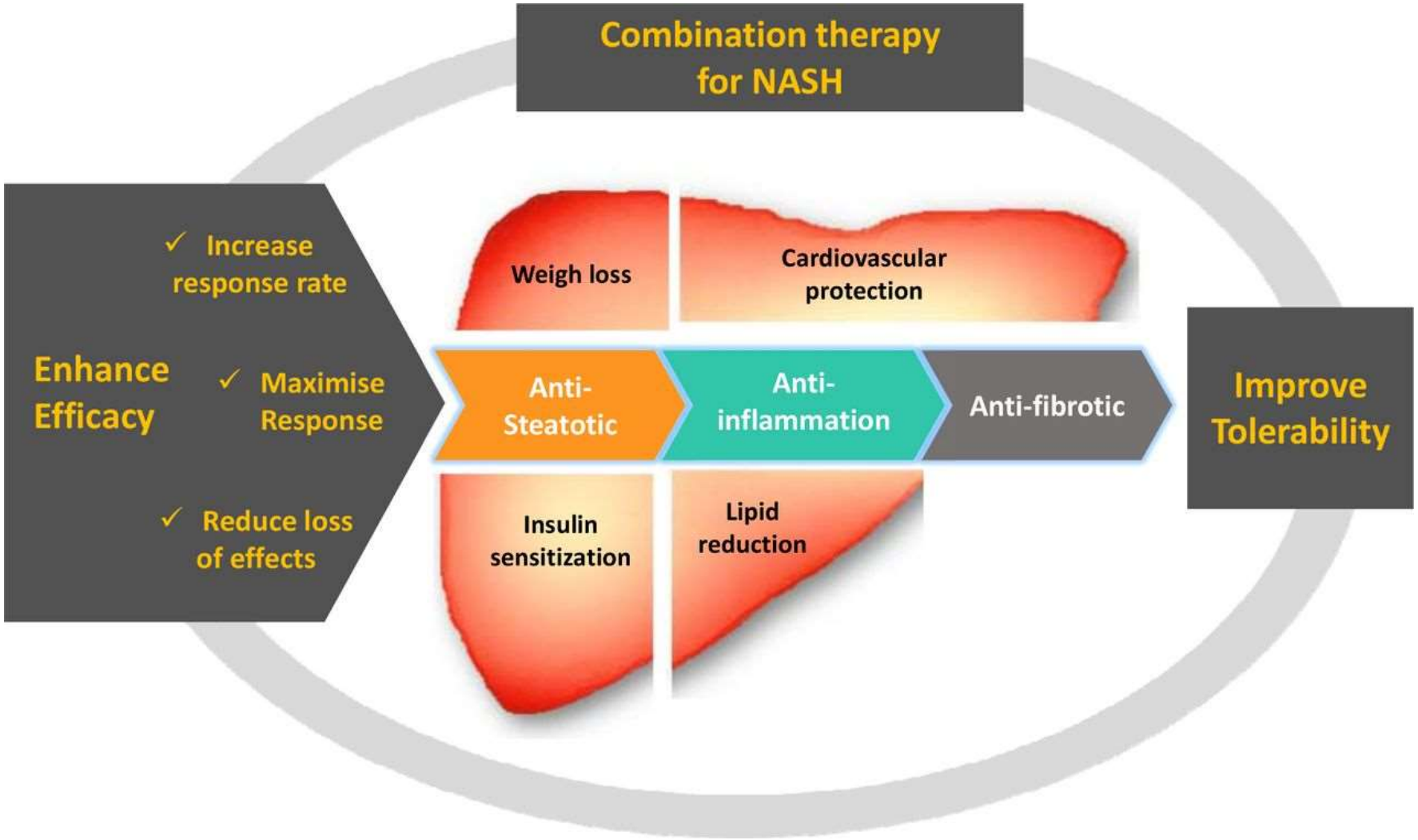
Primary Endpoints	Placebo N=311	OCA – 10 mg N=312	OCA – 25 mg N=308
≥ 1 stage improvement in fibrosis with no worsening of NASH	9.6%	14.1% p=NS	22.4% p<0.0001
Resolution of NASH without worsening of liver fibrosis	3.5%	6.1% p=NS	6.1% p=NS

High frequency of pruritis (55% at 25 mg)

Increased LDL-cholesterol

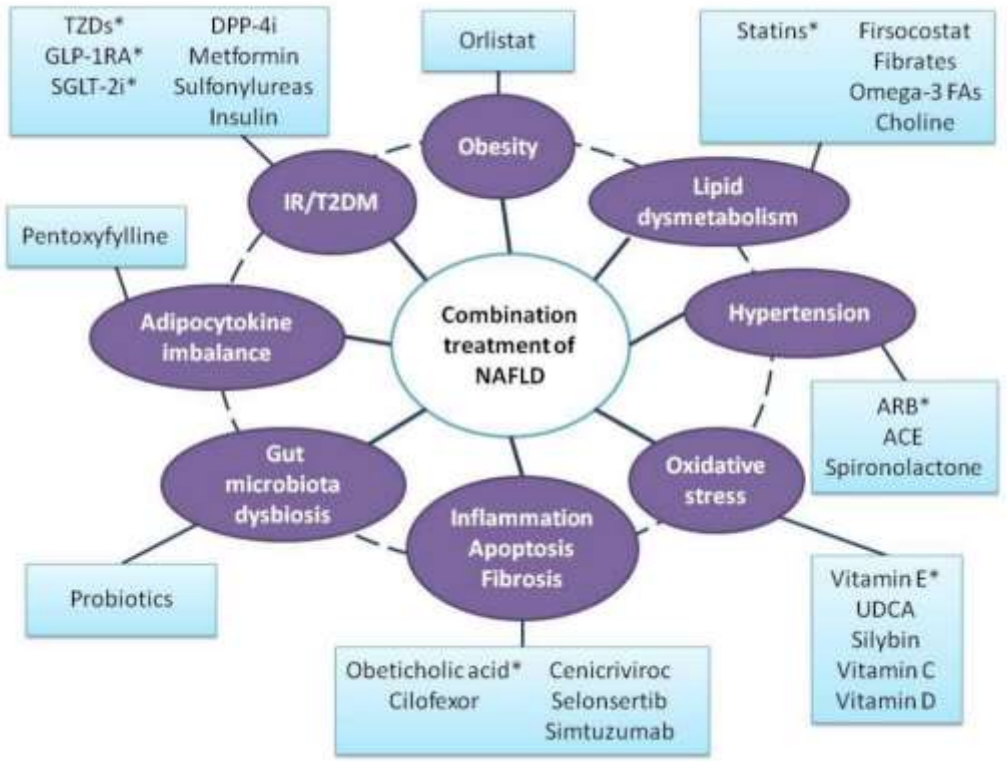
Intercept Press Release July 7, 2022

Rationale for combination therapy to treat non-alcoholic steatohepatitis (NASH).



Jean-François Dufour et al. Gut 2020;69:1877-1884

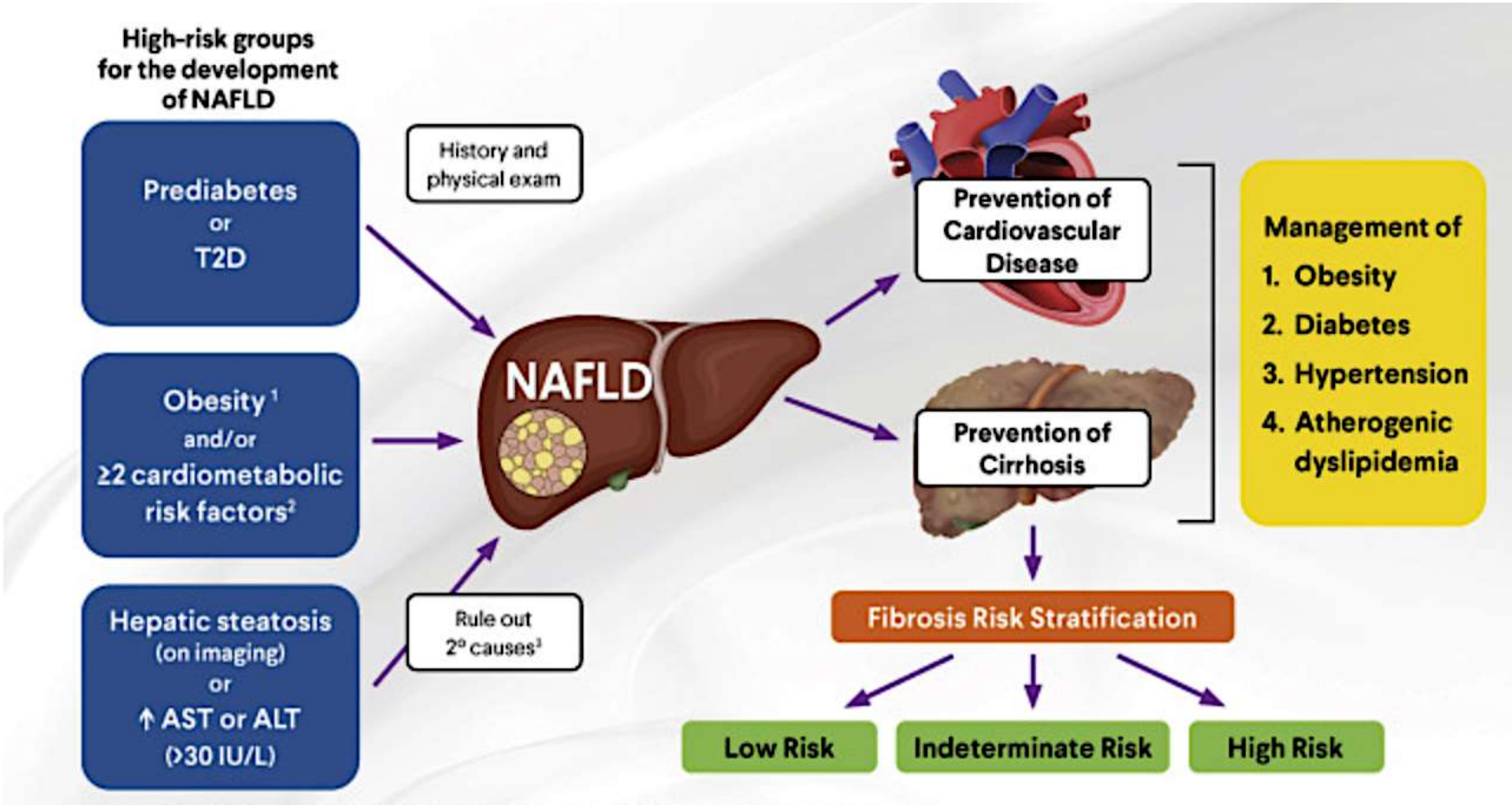
Combination Therapies May Be Needed for NASH



- FXR agonist + SGLT-2i
- Semaglutide + Empagliflozin
- Semaglutide + Cilofexor
- Semaglutide + Cilofexor + fircostat
- Obeticholic acid + Atorvastatin
- Cilofexor + Fircostat
- Fircostat + fenofibrate

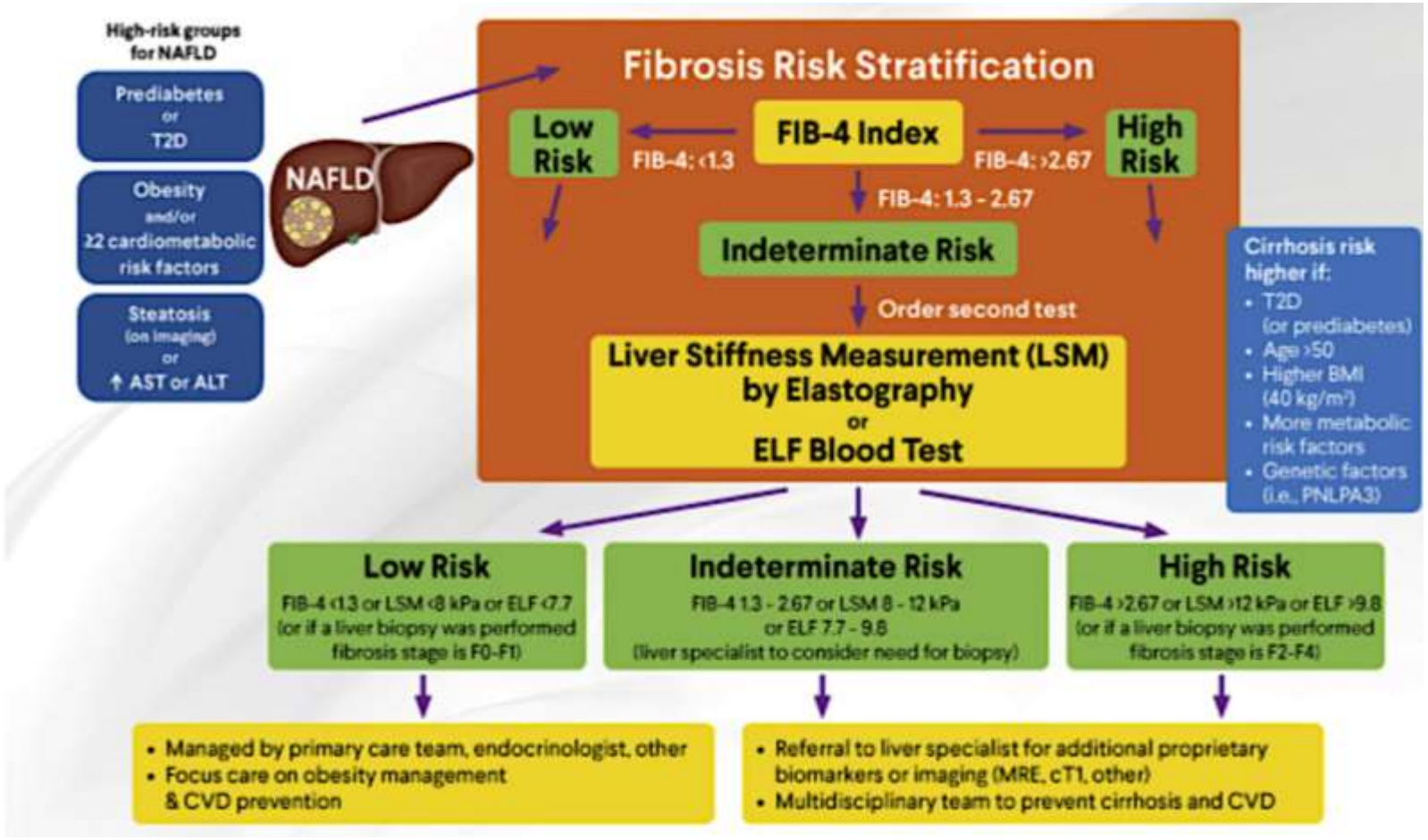
Makri, E et al J. Pers. Med. 2022, 12, 1166. https:// doi.org/10.3390/jpm12071166

Management of Patient with NAFLD



AACE Guidelines NAFLD, Endocrine Practice 2022

Prevention of Cirrhosis in NAFLD



AACE Guidelines NAFLD, Endocrine Practice 2022

Weight Loss is Universal Recommendation for NAFLD

	Low Risk	Intermediate Risk	High risk
Lifestyle intervention	Yes	Yes	Yes
Weight loss recommended	Yes May benefit from structured weight loss program, anti-obesity medication, bariatric surgery	Yes Greater need for structured weight loss program, anti-obesity medication, bariatric surgery	Yes Strong need for structured weight loss program, anti-obesity medication, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes	Yes
CVD risk reduction	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medicatios with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medicatios with efficacy in NASH (pioglitazone, GLP-1 RA)

Kanwal et al, Gastroenterology 2021

Summary

- NAFLD is **highly prevalent** with variable rates of progression to NASH and advanced hepatic fibrosis
- It is crucial to identify those with **NASH advanced hepatic fibrosis** because it can quickly progress to cirrhosis and HCC, liver transplant, and death
- This is rarely done, so most patients with NAFLD/NASH are undiagnosed.
- Importantly, these patients are at **very high risk for CVD** and aggressive control of CVRF is warranted
- Patients with **T2D** warrant evaluation, with FIB-4 score and ? US
  - Other risk factors include ALT or AST > 30, obesity, metabolic syndrome, age, first-degree relative with NASH cirrhosis
- Imaging should be done to measure stiffness in those with intermediate risk scores

Summary

- Diet and exercise recommended for all
  - As little as **3%** weight loss can improve steatosis, **7% to 10%** can resolve NASH and reverse fibrosis
  - Avoidance of alcohol
  - Consider bariatric surgery
- No FDA-approved NASH treatments, but guidelines recommend:
  - **Vitamin E** (if no T2D)
  - **Pioglitazone** (if T2D/preDM)
- For Diabetes, treatment of weight as co-primary outcome in obese patients
  - **GLP-1 RAs** have emerging evidence for NASH resolution
  - **SGLT2 inhibitors** have emerging evidence for reducing liver fat, enzymes
- Multiple agents are being studied
- Likely will need therapies targeted at stage of progression, perhaps in combination


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
спасибо
obrigado
dziękuję
bedankt
merci
go raibh maith agat
sukriya
kop khun krap
terima kasih
grazie
arigatō
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tapadh leat
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Questions?