Management of Nonalcoholic Fatty Liver Disease

Phunchai Charatcharoenwitthaya, MD.

Gastroenterology Division, Medicine Department

Faculty of Medicine Siriraj Hospital, Mahidol University

Case

- 69-year-old woman with obesity
- Underlying disease: T2DM, HTN, and dyslipidemia.
- Taking metformin (1000 mg twice daily), losartan and atorvastatin.
- Personal history: no alcohol use or blood transfusion.
- Blood testing: mild elevation of AST and ALT ~1.5-2.0 x ULN
- Ultrasound of the liver shows fatty liver
- Physical examination: central adiposity with BMI of 35.0 kg/m^2.

Case: An obese woman with T2DM

Laboratory test results:

- Fasting glucose = 127 mg/dL (70-99 mg/dL)
- Hemoglobin A1c = 7.5% (4.0%-5.6%)
- AST = 39 U/L (7-40 U/L)
- ALT = 52 U/L (7-40 U/L)
- Albumin = 3.5 g/dL (3.4-5.4 g/dL)
- Platelet count = 132 x 10^3/µL (150-450 x 10^3/µL)
- Triglycerides = 290 mg/dl (<150 mg/dL)

Clinical Questions:

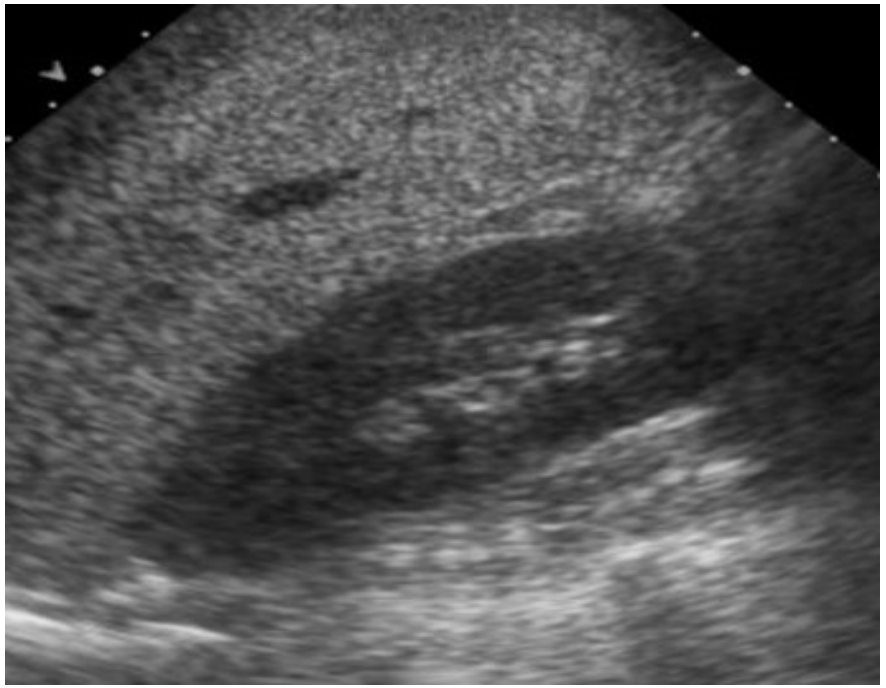
1. **Does this patient have NAFLD?**
2. Could this patient have significant liver fibrosis?
3. What is optimal management ?

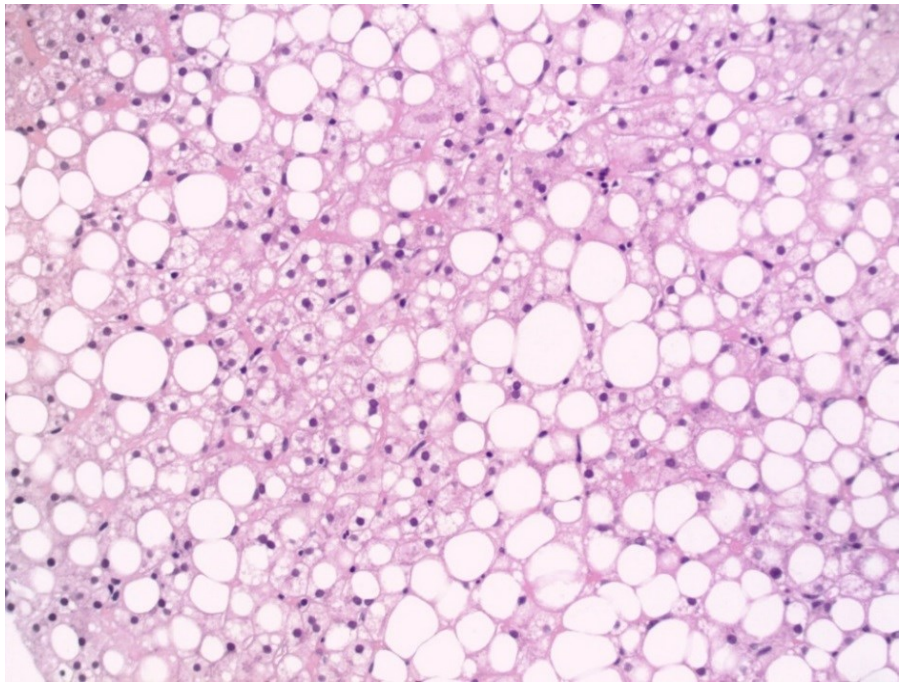
Nonalcoholic Fatty Liver Disease (NAFLD)

Diagnostic criteria

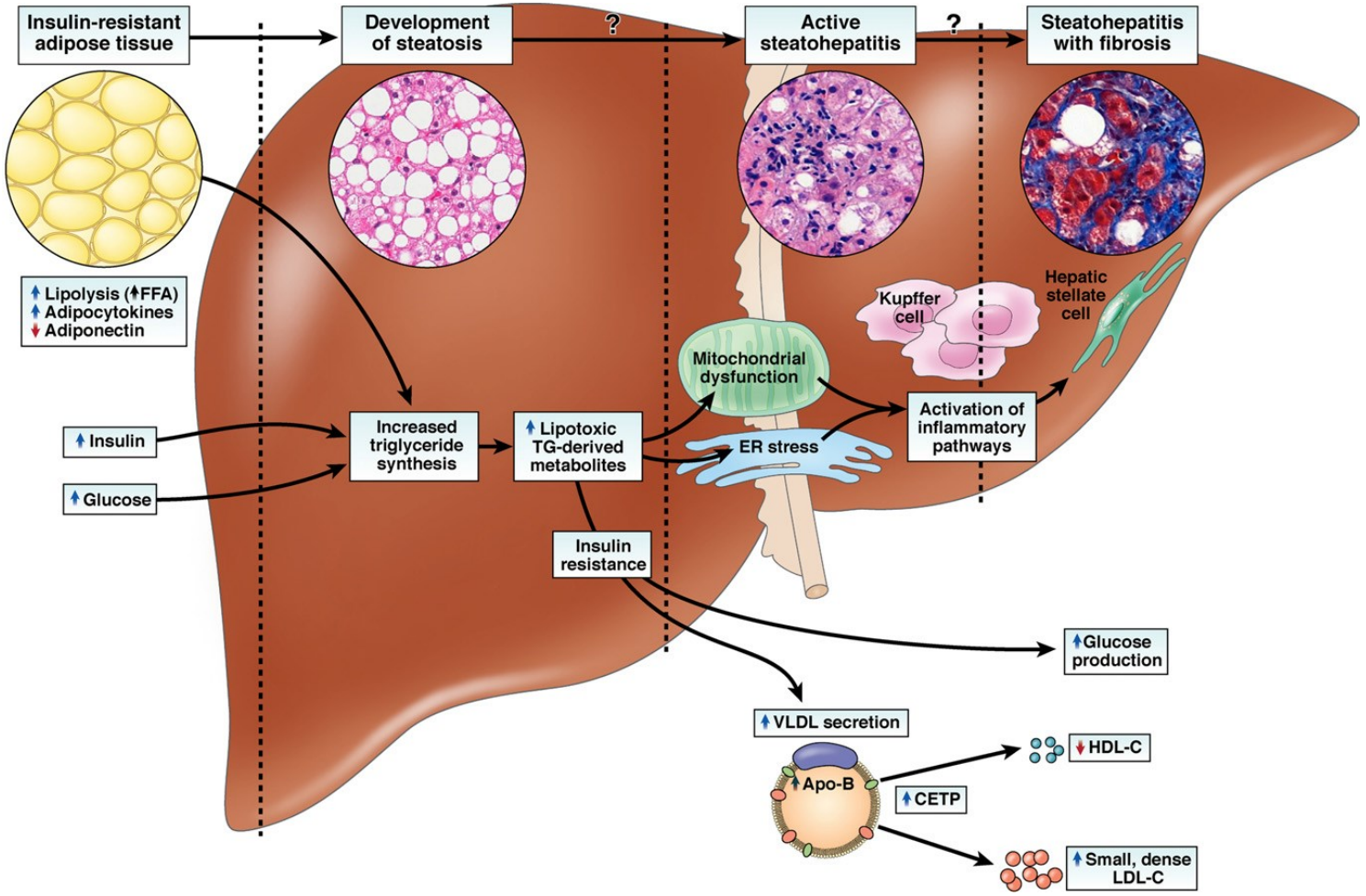
- Steatosis in ≥ 5% hepatocytes
- Minimal alcohol use
- No other etiology for liver disease
- No secondary causes of NAFLD
  - Medications
  - HIV
  - Lipodystrophy

Moderate drinking defined as less than 2 drink/day for male and 1 drink/day for female



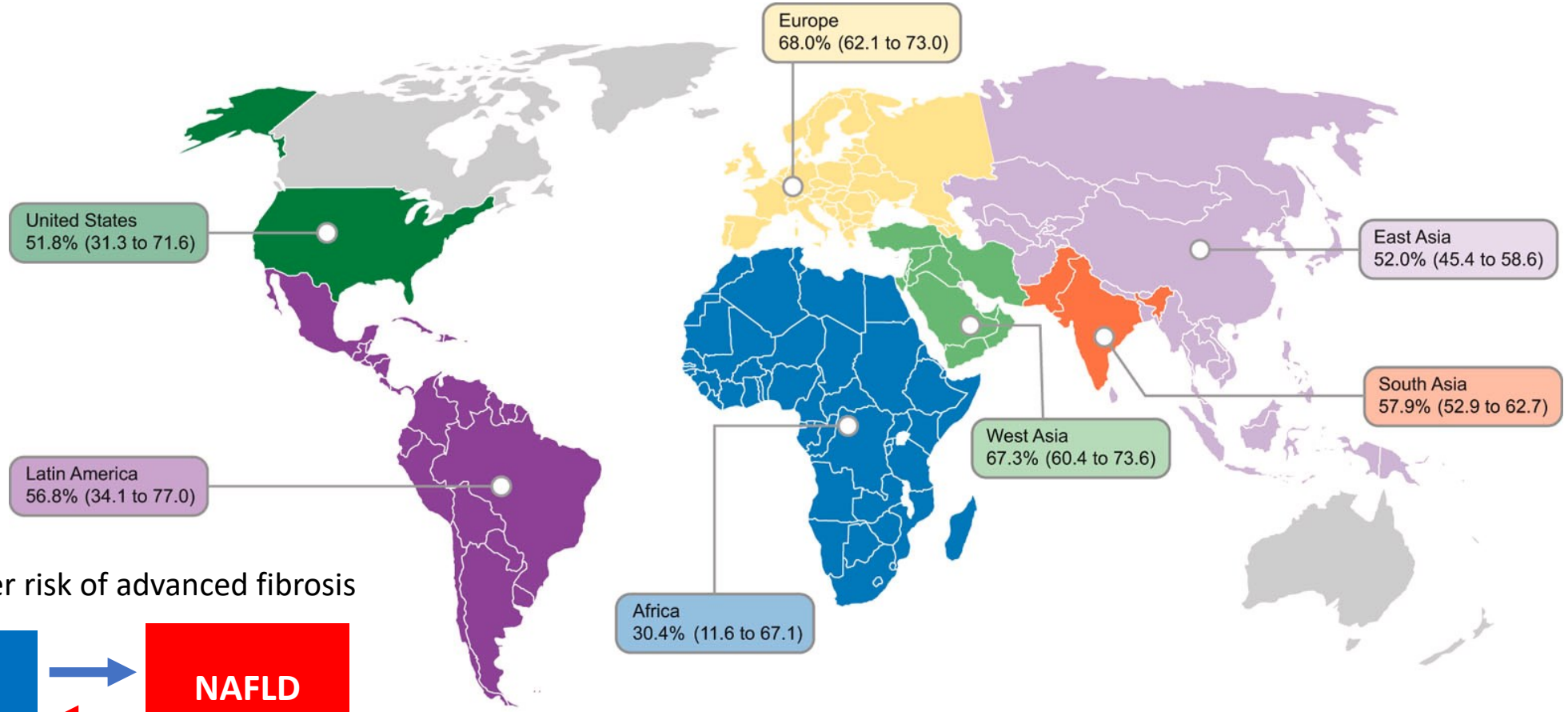


The Pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD)

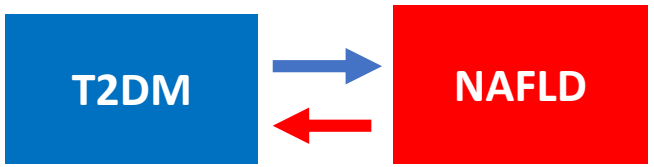


Cusi K. Gastroenterology 2012

Global Prevalence of NAFLD among T2DM: 55.5%



T2DM: Higher risk of advanced fibrosis

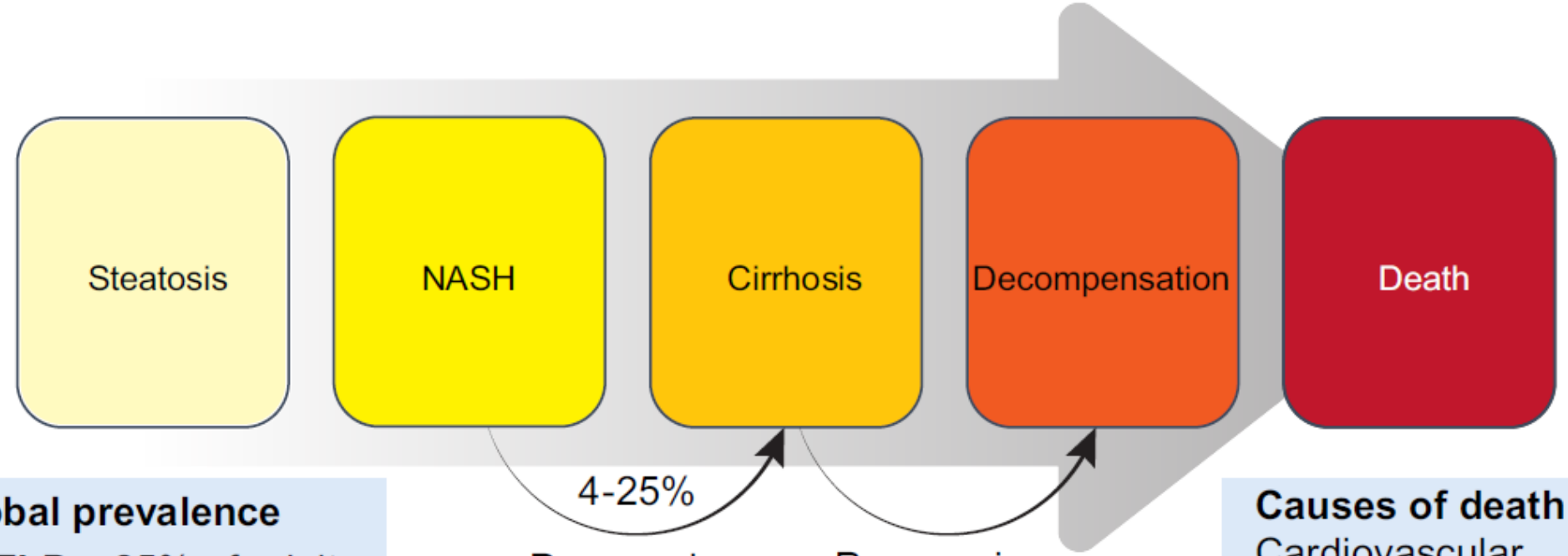


NAFLD: increase the risk of CVD (promotes dyslipidemia, hyperinsulinemia, inflammation)

Prevalence of NASH: 37.3%
Prevalence of fibrosis: 17%

Younossi et al, J Hepatology 2019

The Spectrum of NAFLD



Global prevalence

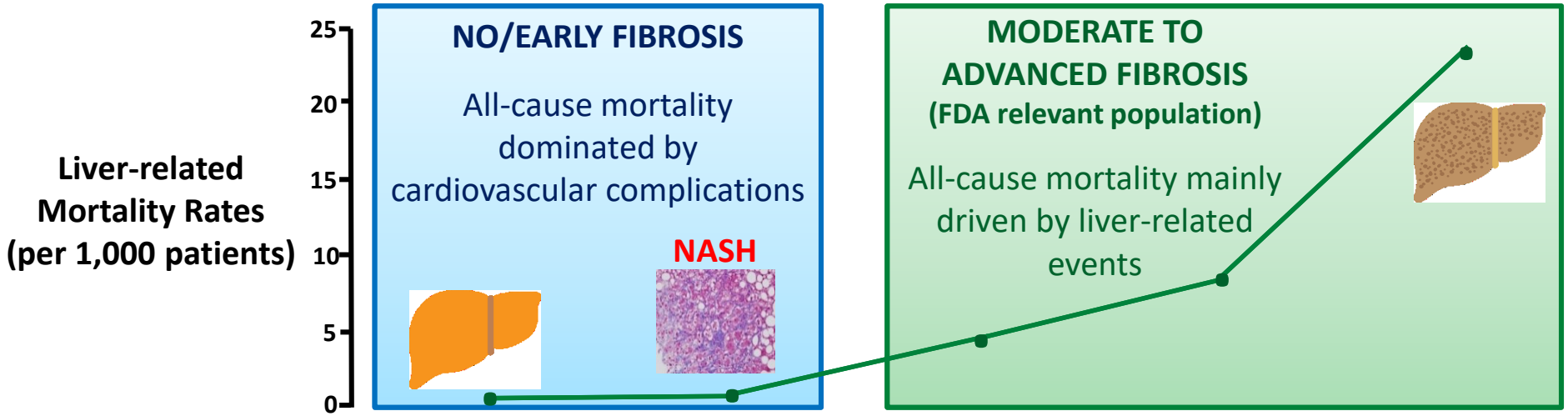
NAFLD: 25% of adults
Diabetes: 425 million
Obesity: 671 million
Overweight: 1.3 billion

Causes of death

Cardiovascular
Malignancy
Liver (1-2%)
HCC progression:
1% per year

Asrani et al. J Hepatol. 2019

Prognostic Significance of Liver Histology in NAFLD



Fibrosis stage	F0	F1	F2	F3	F4
Prevalence	NAFLD ~25%		NASH 1.5% to 6.45%		
Main Cause of Death	Cardiovascular Disease		Liver Disease		
Time to progression	One fibrosis stage every 7 years				

Angulo P, et al. Gastroenterology. 2015; Dulai PS, et al. Hepatology. 2017

Case: An obese woman with T2DM

Clinical or Laboratory Scores

Simple

- Fibrosis-4 (FIB-4)[1,2]
- NAFLD fibrosis score[1,2]
- AST/platelet ratio index[1]

Proprietary

- Enhanced Liver Fibrosis Test[1] (not available in US)
- NIS4
- ADAPT/Pro-C3[3] (not available in US)
- *FibroSure*[1]
- Hepascore

Imaging

Elastography

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]

Clinical Questions:

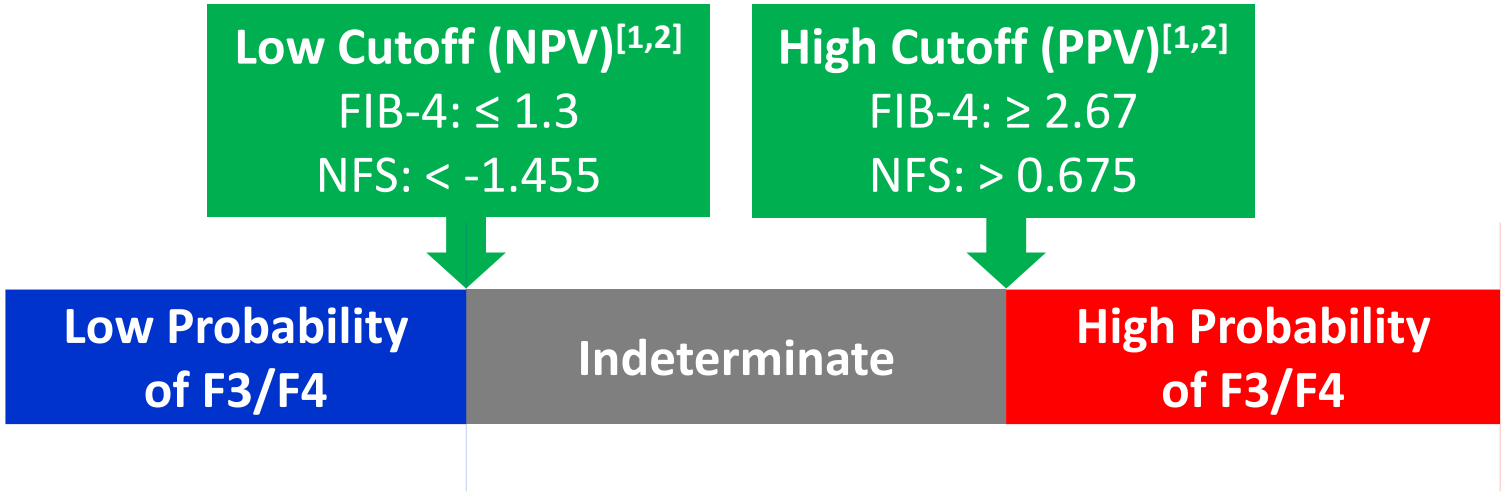
1. Does this patient have NAFLD?
2. **Could this patient have significant liver fibrosis?**
3. What is optimal management ?

1. EASL. J Hepatol. 2015; 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012.
3. Daniels. Hepatology. 2019. 4. Sigrist. Theranostics 2017.

Diagnosis: Nonproprietary Panels

FIB-4
- Age
- ALT
- AST
- Platelets

NAFLD Fibrosis Score (NFS)
- BMI
- Albumin
- IFG/DM?

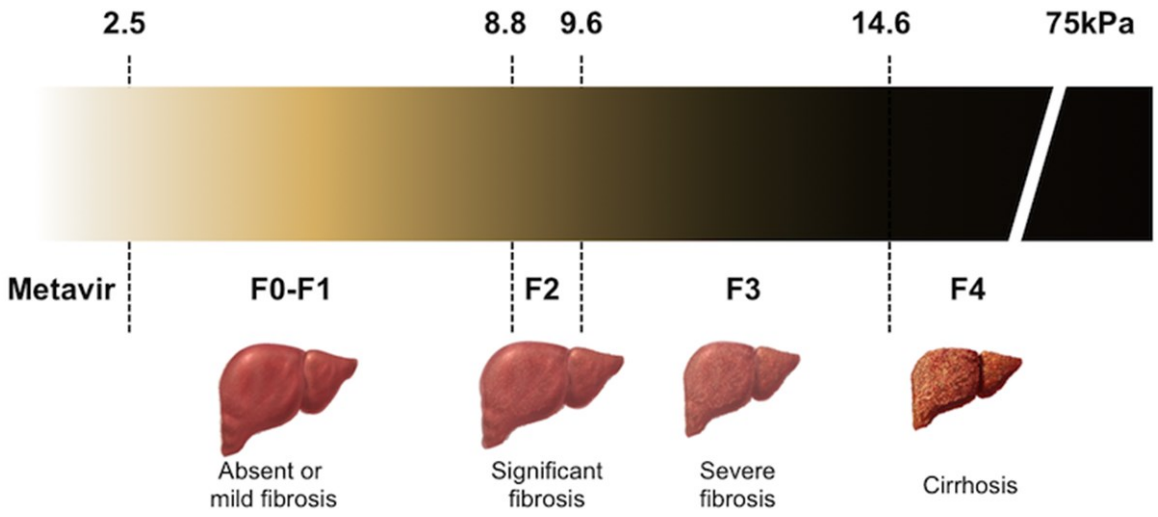


$$\text{FIB-4} = \frac{\text{Age (yrs)} \times \text{AST (U/L)}}{\text{Plts } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

NFS = -1.675 + 0.037 x age [yrs] + 0.094 x BMI (kg/m^2) + 1.13 x IFG/DM (yes = 1, no = 0)
+ 0.99 x AST/ALT – 0.013 x plts (10^9/L) – 0.66 x albumin (g/dL)

1. Alkhouri. Gastroenterol Hepatol (N Y). 2012. 2. Shah. Clin Gastroenterol Hepatol. 2009.

Hepatic Elastography for Staging Fibrosis



- Most reliable in **ruling out advanced hepatic fibrosis (NPV > PPV)**[2]
  - Fibrosis unlikely with a low value (< 6 kPa)
- Higher values increase the likelihood of more severe fibrosis, predicts the risk of decompensation and complications[3]
- **Overestimation of fibrosis can occur** in cases of hepatitis, cholestasis, liver congestion, obesity, and if mass lesions are present in the liver[1,3]

1. Vuppalanchi. Hepatology. 2018;67:134. 2. Hashemi. Caspian J Intern Med. 2016;7:242.
3. Kemp. Australian Family Physician. 2013;42:468.

Patients with Suspected NAFLD

1st line: GP/Internist/Endocrinologist

Rule-out other causes of liver disease

(Alcohol, HBV,HCV)

Rule-out advanced fibrosis

FIB-4 or NAFLD fibrosis score

FIB-4 < 1.3 (age<65 y) <2.0 (age >65 y)

NFS < -1.455

Low risk

FIB-4 >1.3 (age<65 y) >2.0 (age >65 y)

NFS < -1.455

Intermediate to high risk

Attempt lifestyle modification and exercise

No further assessment repeat evaluation at 1 year?

2nd line: GI/Hepatologist

Rule-in advanced fibrosis

Transient Elastography

Failure (XL probe)

3.0-6.7%

Consider MRE, 2D SWE or ARFI according to local availability

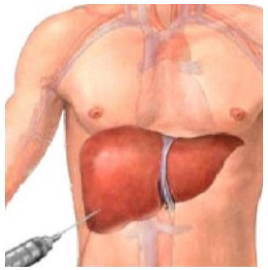
LSM < 8 kPa

Low risk

LSM ≥ 8 kPa

Intermediate to high risk

Consider Liver Biopsy



Attempt lifestyle modification and exercise

Consider repeat evaluation (1year)

Eligible for therapeutic trial?

Castera L, et al. Gastroenterology 2019.
Chan WK, et al. Clinical Gastroenterol Hepatol. 2019.

Case: An obese woman with T2DM

Fibrosis-4 (FIB-4) Calculator

Share

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

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

Age (years): 69 × AST Level (U/L): 39

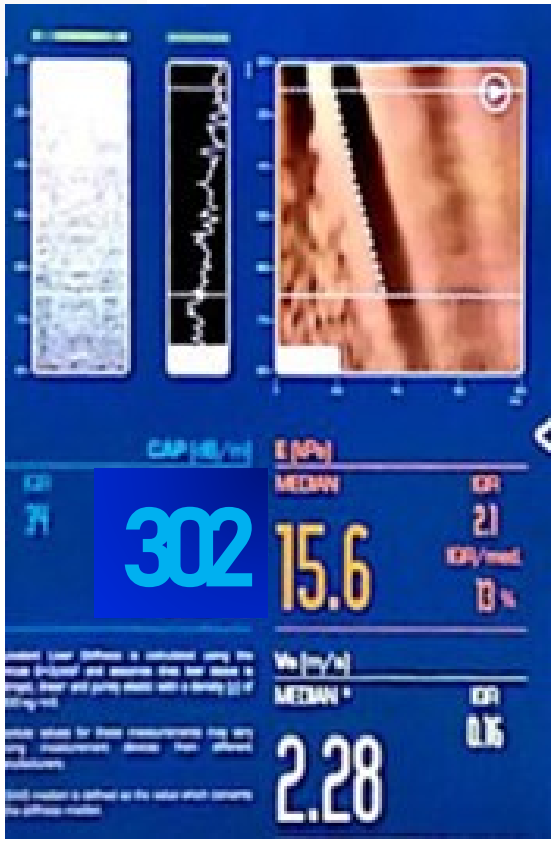
Platelet Count (10^9/L): 132 × √ ALT (U/L): 52

= 2.83

NAFLD Fibrosis Score

Result

Impaired Fasting Glucose/Diabetes:	Yes
Age :	69
AST :	39
ALT :	52
Platelet Count :	132
BMI :	35
Albumin :	3.5



Clinical Questions:

1. Does this patient have NAFLD?
2. **Could this patient have significant liver fibrosis?**
3. What is optimal management ?

Case: An obese woman with T2DM

Role for general physician (in addition to promoting lifestyle interventions):

- ✓Not only to optimize glycemic control
- ✓Identify patients at risk for disease progression
- ✓Optimal management for NAFLD
- ✓Cardiovascular risk management

Clinical Questions:

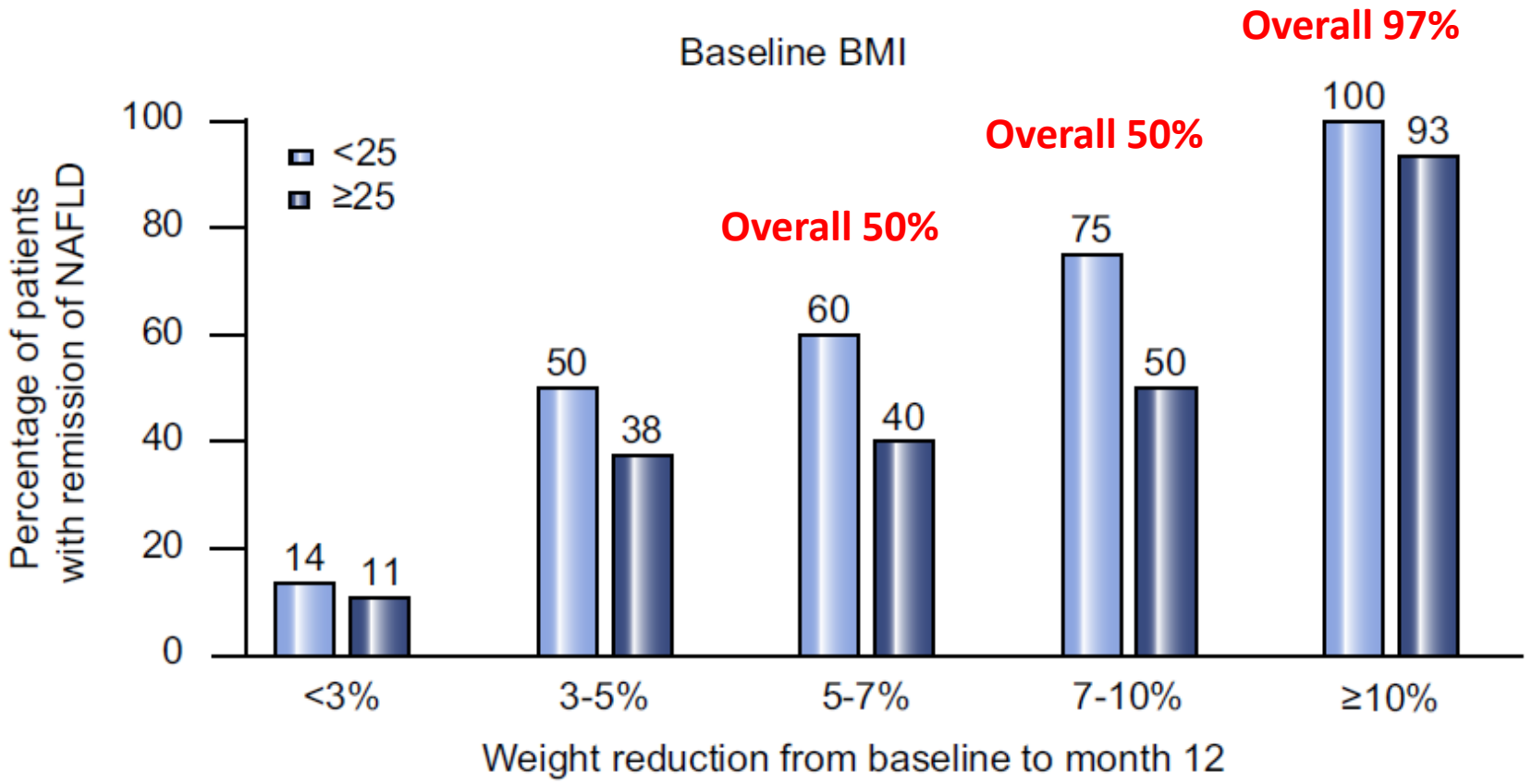
1. Does this patient have NAFLD?
2. Could this patient have significant liver fibrosis?
3. **What is NAFLD management?**

Lifestyle Intervention is the Most Effective Non-pharmacologic Therapy for Patients with NAFLD

Author	N	Lifestyle intervention (*vs. control*)	Duration, weeks	Mean weight loss	Hepatic triglyceride	Liver histology	Cardiovascular risk
Promrat[7]	31 NASH	Low-fat (25%) diet + 200 min/week moderate-intensity PA + CBT	48	-8.7 kg	n.a.	Improved steatosis, NAS	No difference in glucose or HOMA-IR
Eckard[8]	41 NAFLD	Low-fat (20%) diet + moderate exercise *vs.* low-carbohydrate (50%) diet + moderate exercise *vs.* moderate PA/exercise	26	-0.2 lbs *vs.* -3.0 lbs *vs.* 0.1 lbs	n.a.	Improved NAS *vs.* Improved NAS *vs.* No improvement	n.a.
Ueno[9]	25 NAFLD	Low (30%) fat diet + 210 min/week vigorous PA	12	n.a.	n.a.	Improved steatosis	Improved cholesterol and triglyceride
Wong[6]	145 NAFLD	Low-fat, low GI diet + 210 mins/week moderate PA	52	-5.6 kg	-6.7% (MRS)	n.a.	Improved LDL-cholesterol
Gepner[3]	278 Obese or dyslipidaemia (53% NAFLD)	Low-fat diet *vs.* low-carbohydrate/ med. diet ± 180 min/week moderate PA	78	-3.2%*	-5.8% *vs.* -7.3%	n.a.	Improved HbA1c
Sun[5]	1,024 NAFLD	Low-fat (30%), low-sugar diet + 27 MET/hr/week PA/exercise	52	-7 kg	No difference (CT)	n.a.	Improved HOMA-IR and cholesterol
St George[4]	152 elevated ALT and HOMA-IR	Low saturated fat, caloric restricted diet + 150 min/week moderate PA + 3 *vs.* 6 counselling sessions	12	-1.9 kg *vs.* -2.8 kg	n.a.	n.a.	Improved cholesterol and triglyceride

*No difference between groups. ALT, alanine aminotransferase; GI, glycaemic index; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model of assessment - insulin resistance; MET, metabolic equivalent of tasks; NAFLD, non-alcoholic fatty liver disease; n.a., not assessed; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; PA, physical activity.

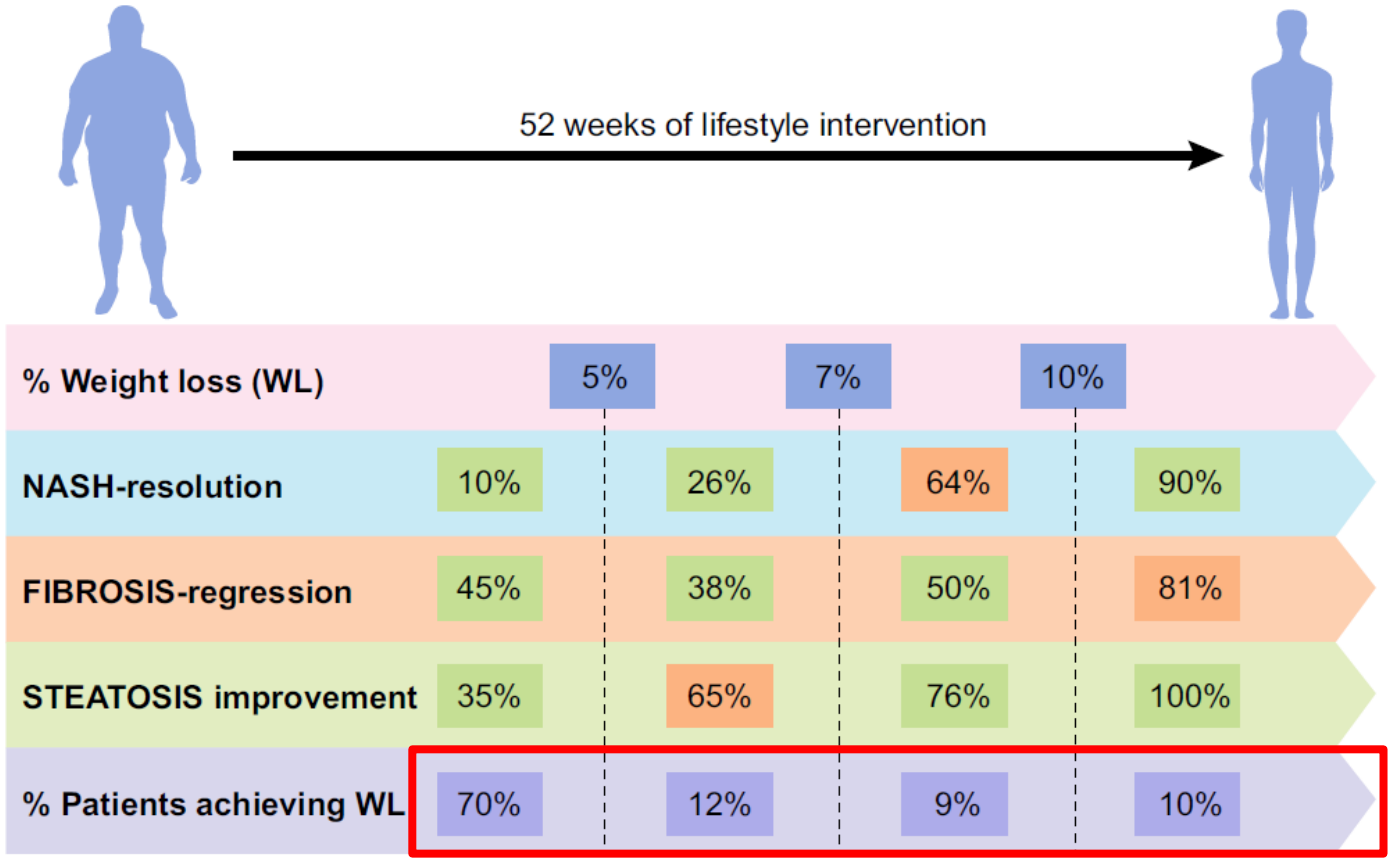
A 12-month RCT involving an American Dietetic Association Low Fat, Low-glycemic Index Diet with 90–150 min/week of Moderate-intensity Exercise



Wong et al. J Hepatol 2018

The Impact of Lifestyle-induced Weight Loss on Liver Histology

A single-arm clinical trial of 261 patients with biopsy-proven NASH who underwent repeat liver biopsies after 12 months of low-fat hypocaloric diet (750 kcal less than daily requirement) in association with 200 min/week of low intensity exercise (walking).



Romero-Gomez et al. J Hepatol 2017; Vilar-Gomez et al. Gastroenterology 2015

Extra-hepatic Benefits of Lifestyle Intervention in NAFLD

Improvement in metabolic control (fasting glucose and insulin sensitivity)

- 8-weeks resistance exercise decreased FG form 6.0 to 5.5 mmol/l
- HOMA-IR decreased from 5.9 to 4.6 (indicating and increase in insulin sensitivity)

Change in body composition

- 12-week HIIT reduced body fat by 1.8 kg despite patients remaining weight neutral
- 12-weeks combination exercise reduced visceral fat by 12%

Reduction in circulating triglycerides and improvements in whole-body fat oxidation

- 12-weeks combination exercise reduced triglycerides by 23%
- 8-weeks resistance exercise decreased RQ during exercise

Improvements in cardiac function

- 12-weeks HIIT improved diastolic function and reduced cardiac torsion in NAFLD

Hallsworth & Adams. JHEP Reports 2019

Hypocaloric Diet is an Important Component of Non-pharmacologic Therapy for Patients with NAFLD

Author	N	Lifestyle intervention *(vs. control)*	Duration, weeks	Mean weight loss	Hepatic triglyceride	Liver histology	Cardiovascular risk
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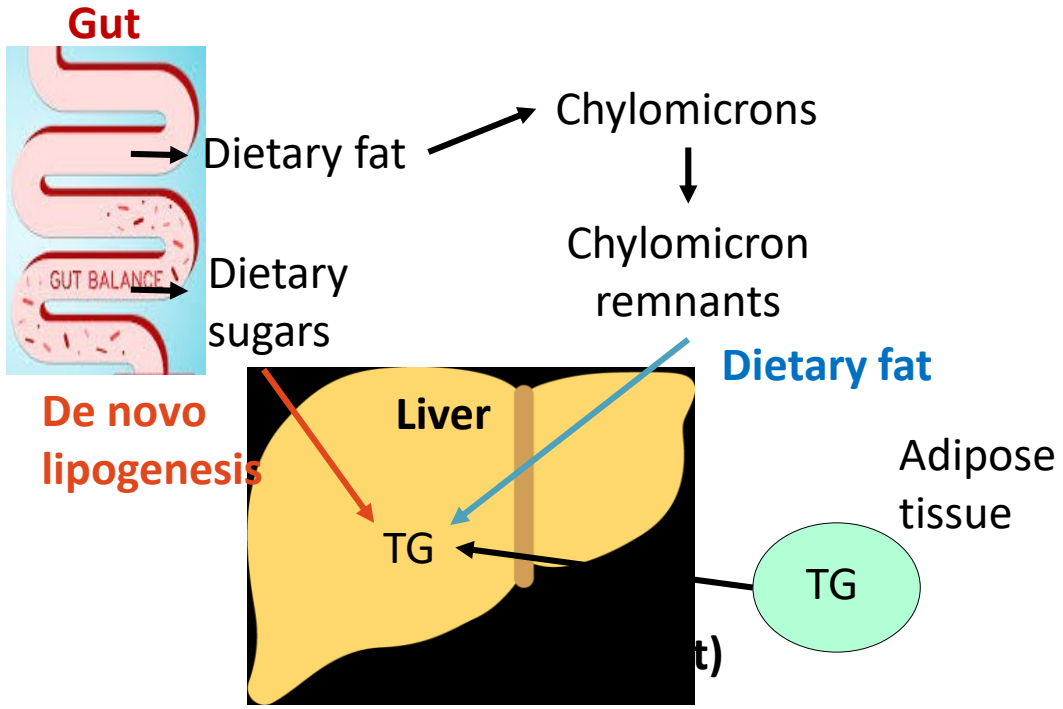
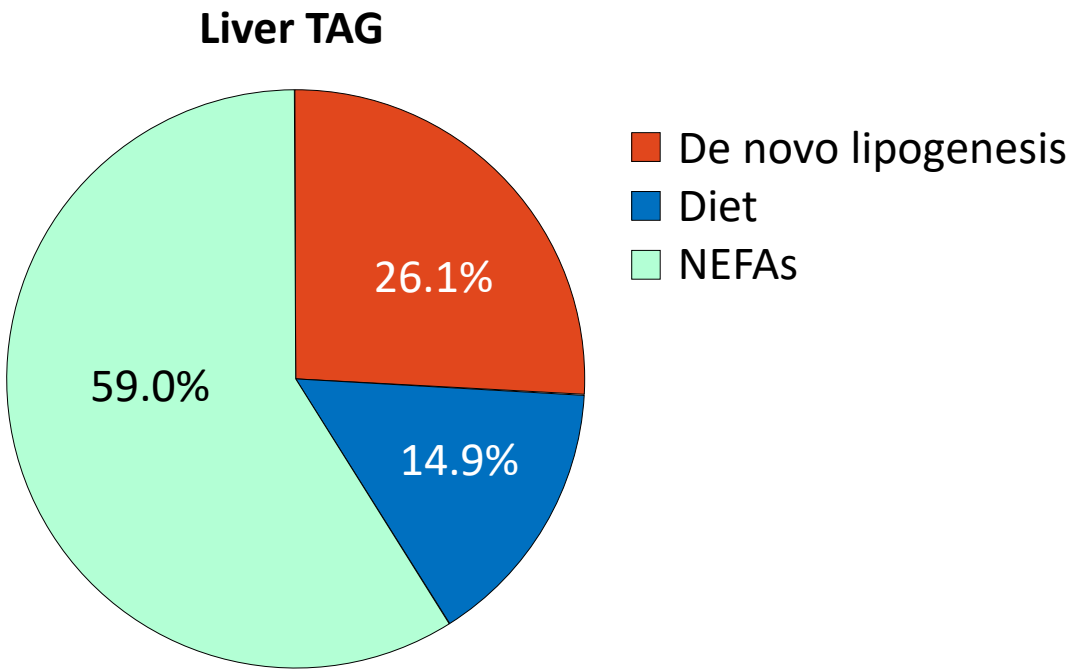
Sources of Hepatic Triglycerides: Dietary Fat, Dietary Sugar, or Stored Fat?

- Study using multiple stable isotope fatty acid labeling in patients with NAFLD scheduled to undergo liver biopsy (N = 9)
  - Allows quantitation of 3 fatty acid delivery pathways

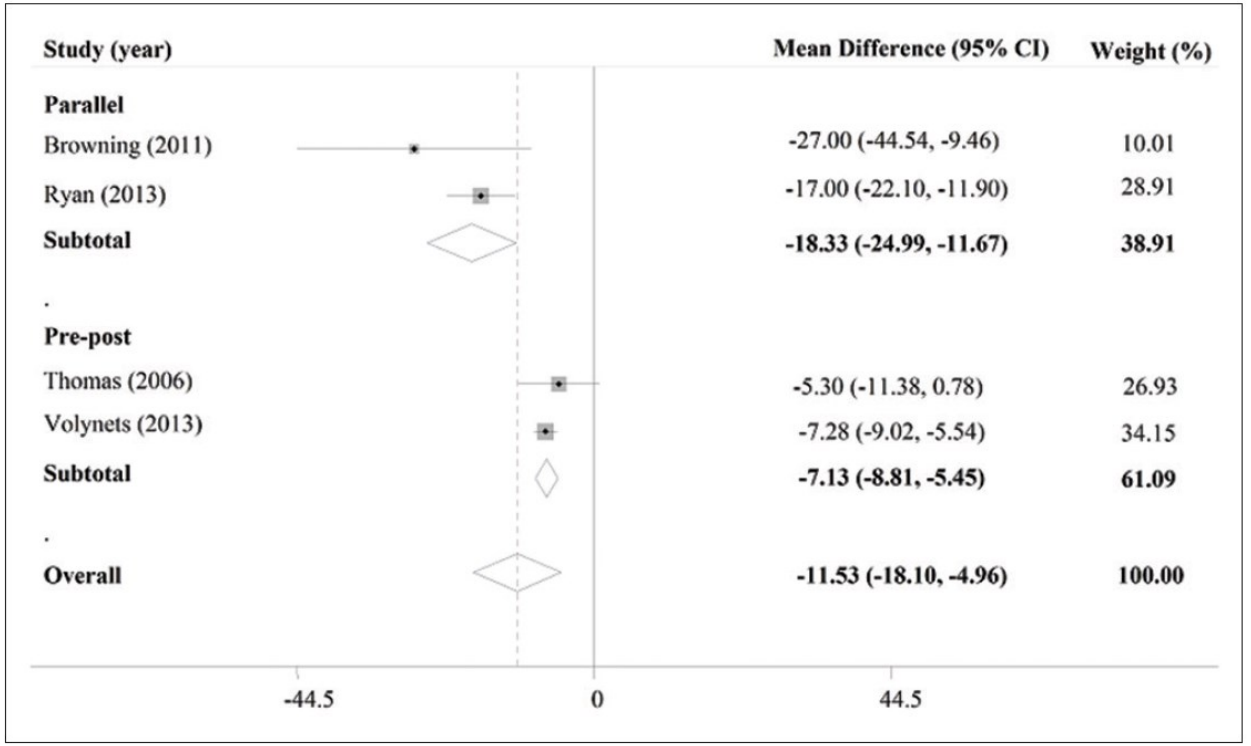




Donnelly. J Clin Invest. 2005

Meta-analysis of Low-Carbohydrate Diets in NAFLD

- Meta-analysis of 10 international clinical trials of **low-carbohydrate (< 50%) diets** in patients **with NAFLD**
  - 10 evaluated ALT (n = 238)
  - 9 evaluated AST (n = 216)
  - 5 evaluated GGT (n = 91)
  - 4 evaluated intrahepatic lipid content (n = 50)



Low-carbohydrate diets associated with **significant reduction in intrahepatic lipid content**, but did not affect the concentration of liver enzymes

Haghighatdoost et al. J Res Med Sci. 2016

Head-to-Head Comparisons of Low-Carb vs Low-Fat Diets

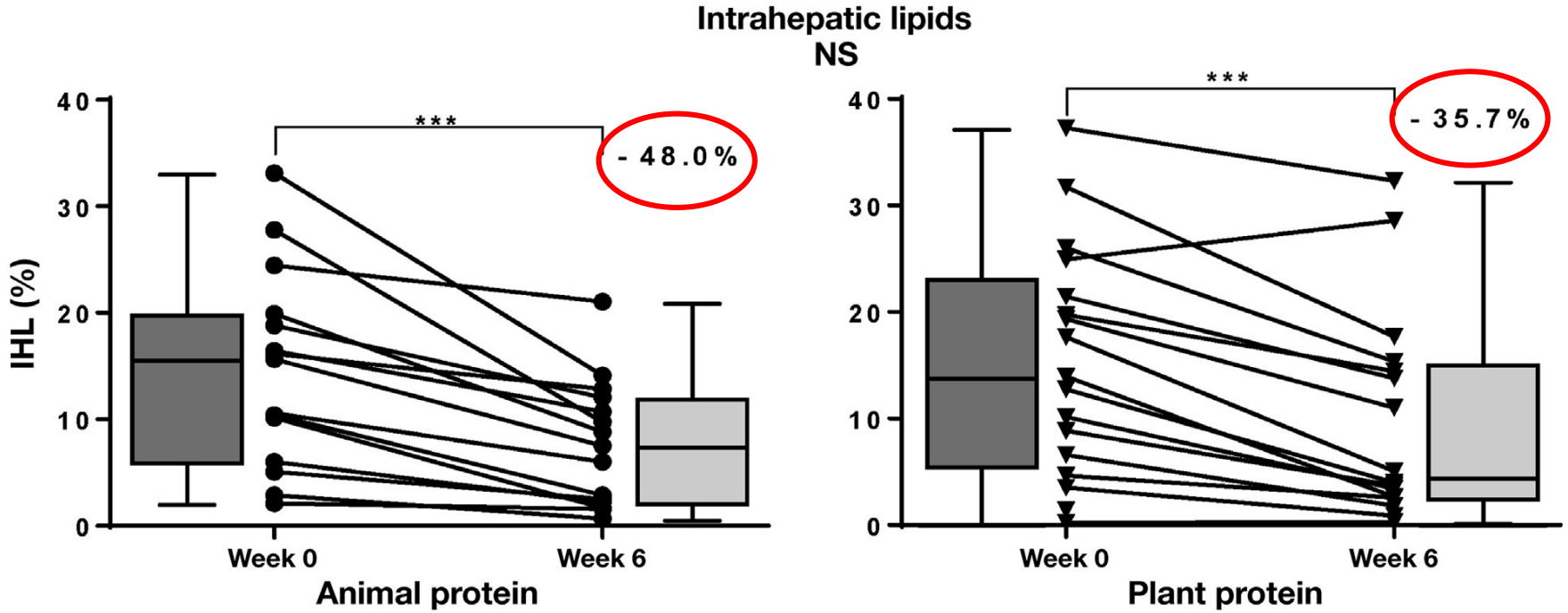
Study Population	N	Mos	Comparison	Results	Difference Between Diets?
Obese with insulin resistance[1]	52	4	60% carb + 25% fat vs 40% carb + 45% fat	▪ Significant reductions in weight, SSPG, circulating insulin, serum ALT ▪ ALT reductions greater with 40% carb diet	Yes
Overweight and obese, otherwise healthy[2]	170	6	Reduced carb vs reduced fat	▪ Similar reductions in weight, body fat, visceral fat, ALT, intrahepatic lipids	No
Obese with or without NAFLD[3]	162	3	Low fat vs low carb	▪ Reductions in weight, BP, cholesterol ▪ In patients with NAFLD, similar reductions in glucose, triglycerides, transaminases	No

1. Ryan. Diabetes Care. 2007; 2. Haufe. Hepatology. 2011; 3. de Luis. Nutr Hosp. 2010

NAFLD – Isocaloric Protein-Rich Diet Reduces Steatosis

Intrahepatic lipid content (^{1}H-MRS) before and after

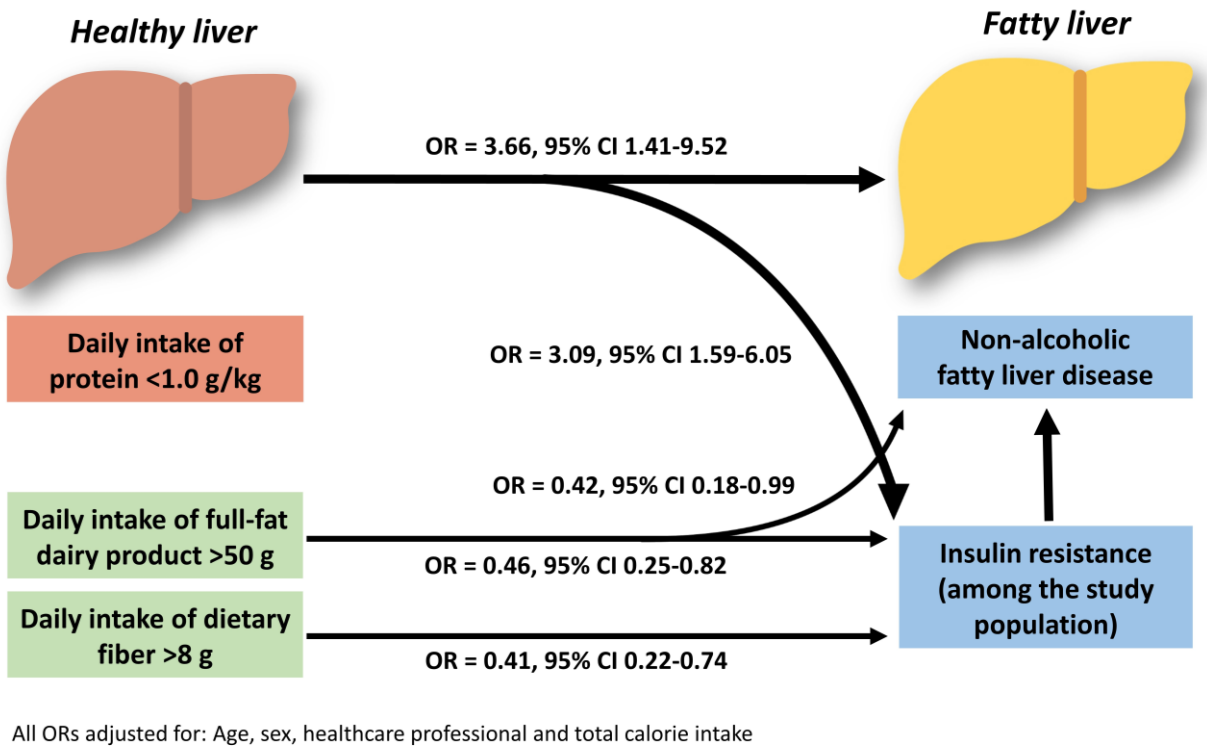
6 weeks isocaloric protein-rich diet (30% calories) in T2DM patients



Both Animal and Plant protein-rich diets showed beneficial effect associated with the improvement of insulin sensitivity.

Markova et al. Gastroenterology 2017

Dietary Composition and Its Association with Newly Diagnosed NAFLD and Insulin Resistance

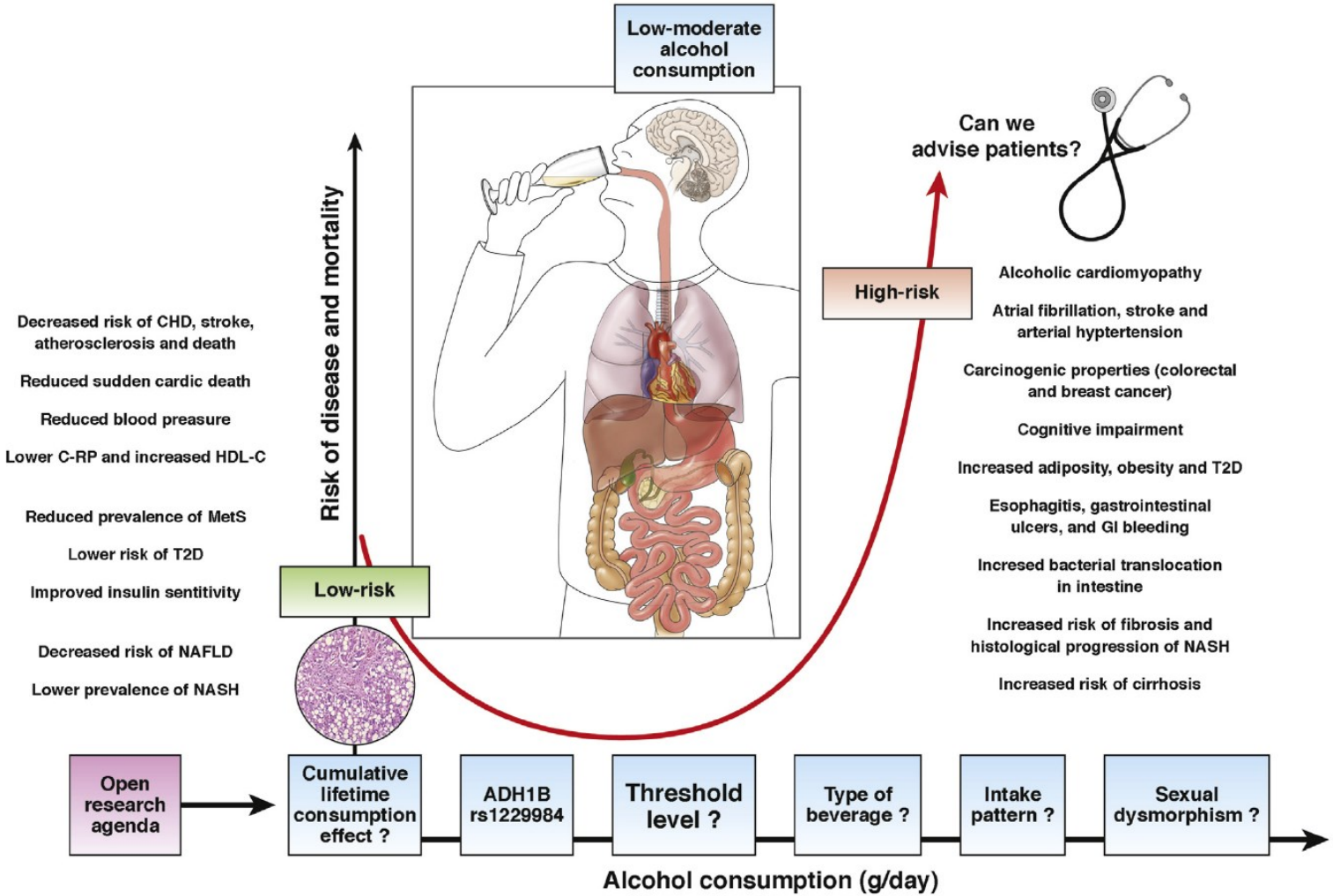


All ORs adjusted for: Age, sex, healthcare professional and total calorie intake

- We enrolled 252 adults: 41 medical personnel with NAFLD & 211 persons without NAFLD took photographs of their meals and documented their food intake in a food diary for 7 consecutive days.
- Total energy intake and the proportion of carbohydrate, fat, and protein consumption did not differ between participants with NAFLD and those without NAFLD.
- A high intake of full-fat dairy products and dietary fiber has been associated with a potential protective effect against NAFLD and insulin resistance.

Charatcharoenwitthaya et al. Nutrients. 2021

The Current Epidemiologic Evidence of Modest Alcohol Consumption on Liver Disease



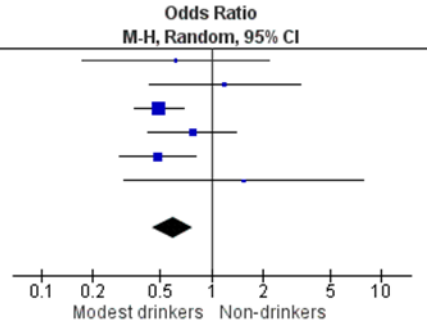
Sookoian & Pirola Gastroenterology 2016

Modest Alcohol Consumption in NAFLD

Steatohepatitis

Study or Subgroup	Modest drinkers Events	Modest drinkers Total	Non-drinkers Events	Non-drinkers Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Dixon 2001	4	17	16	48	4.6%	0.62 [0.17, 2.19]	2001
Cotrim 2009	66	75	49	57	6.9%	1.20 [0.43, 3.33]	2009
Dunn 2012	176	331	176	252	43.4%	0.49 [0.35, 0.69]	2012
Yamada 2018	31	77	47	101	18.3%	0.77 [0.42, 1.41]	2018
Ajmera 2018	96	168	86	117	24.0%	0.48 [0.29, 0.80]	2018
Tan 2020	14	16	45	55	2.8%	1.56 [0.30, 7.96]	2020
Total (95% CI)		**684**		**630**	**100.0%**	**0.59 [0.45, 0.78]**	
Total events	387		419				

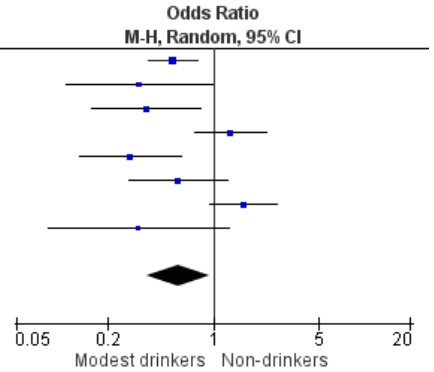
Heterogeneity: Tau² = 0.01; Chi² = 5.65, df = 5 (P = 0.34); I² = 12%
Test for overall effect: Z = 3.75 (P = 0.0002)



Advanced fibrosis

Study or Subgroup	Modest drinkers Events	Modest drinkers Total	Non-drinkers Events	Non-drinkers Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Dunn 2012	69	331	83	252	16.5%	0.54 [0.37, 0.78]	2012
Kwon 2014	8	52	9	25	9.2%	0.32 [0.11, 0.98]	2014
Hagstrom 2017	11	60	23	60	11.8%	0.36 [0.16, 0.83]	2017
Kimura 2018	27	93	50	208	14.8%	1.29 [0.75, 2.24]	2018
Mitchell 2018	12	91	26	74	12.4%	0.28 [0.13, 0.61]	2018
Yamada 2018	13	77	26	101	12.7%	0.59 [0.28, 1.23]	2018
Ajmera 2018	66	168	34	117	15.2%	1.58 [0.95, 2.62]	2018
Tan 2020	3	16	23	55	7.4%	0.32 [0.08, 1.26]	2020
Total (95% CI)		**888**		**892**	**100.0%**	**0.59 [0.36, 0.95]**	
Total events	209		274				

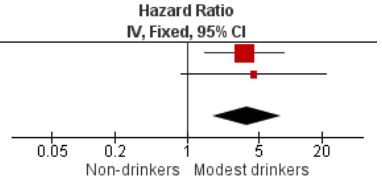
Heterogeneity: Tau² = 0.33; Chi² = 27.80, df = 7 (P = 0.0002); I² = 75%
Test for overall effect: Z = 2.16 (P = 0.03)



Development of HCC

Study or Subgroup	log[Hazard Ratio]	SE	Non-drinkers Total	Modest drinkers Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Ascha 2010	1.2809	0.4467	120	68	77.3%	3.60 [1.50, 8.64]	2010
Kimura 2018	1.4884	0.8246	93	208	22.7%	4.43 [0.88, 22.30]	2018
Total (95% CI)			**213**	**276**	**100.0%**	**3.77 [1.75, 8.15]**	

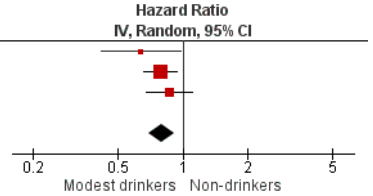
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 3.38 (P = 0.0007)



Mortality for light alcohol consumption

Study or Subgroup	log[Hazard Ratio]	SE	Modest drinkers Total	Non-drinkers Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Hajifathalian 2019 (1)	-0.4463	0.2149	874	3318	10.6%	0.64 [0.42, 0.98]	2019
Aberg 2020 (2)	-0.2357	0.0917	4429	993	58.3%	0.79 [0.66, 0.95]	2020
Aberg 2020 (3)	-0.1393	0.1257	1443	0	31.0%	0.87 [0.68, 1.11]	2020
Total (95% CI)			**6746**	**4311**	**100.0%**	**0.80 [0.69, 0.91]**	

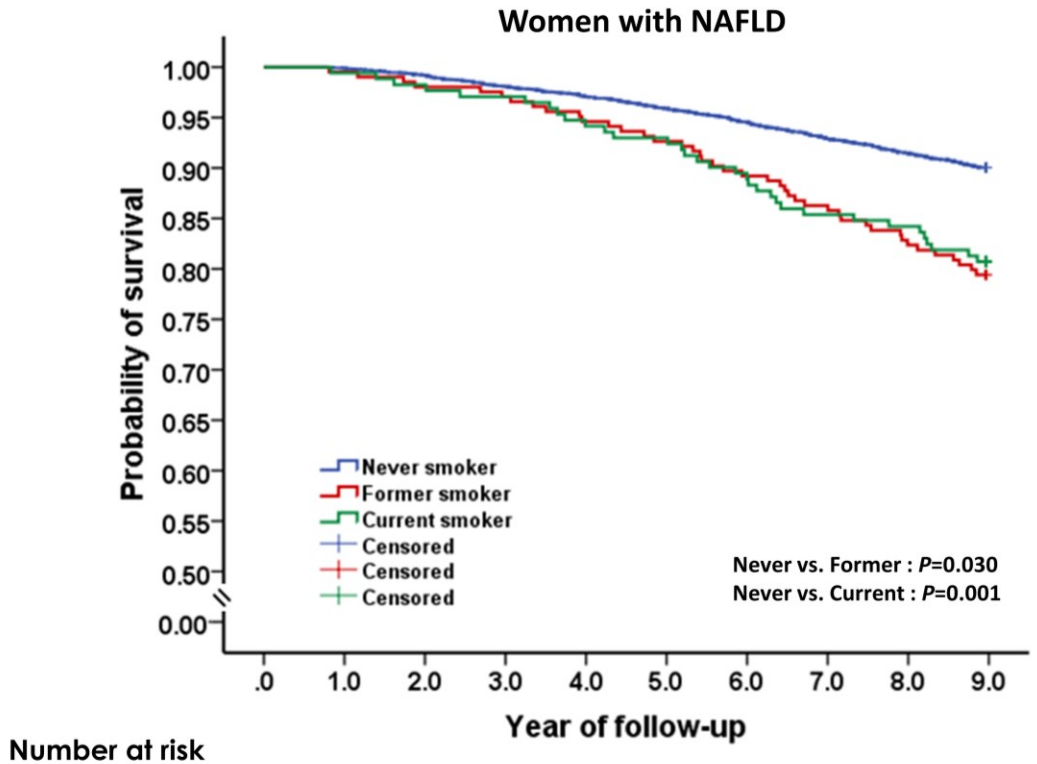
Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 3.26 (P = 0.001)



Footnotes
(1) Alcohol drinkers 0.5-1.4 drinks/day vs. Non-drinkers
(2) Alcohol drinkers 0-9 g/day vs. Non-drinkers
(3) Alcohol drinkers 10-19 g/day vs. Non-drinkers

Wongtrakul W, Niltwat S, Charatcharoenwitthaya P. Front Med. 2021

The Synergistic Effect of Modest Alcohol Intake and Cigarette Smoking on Overall Mortality in Patients with NAFLD



Number at risk

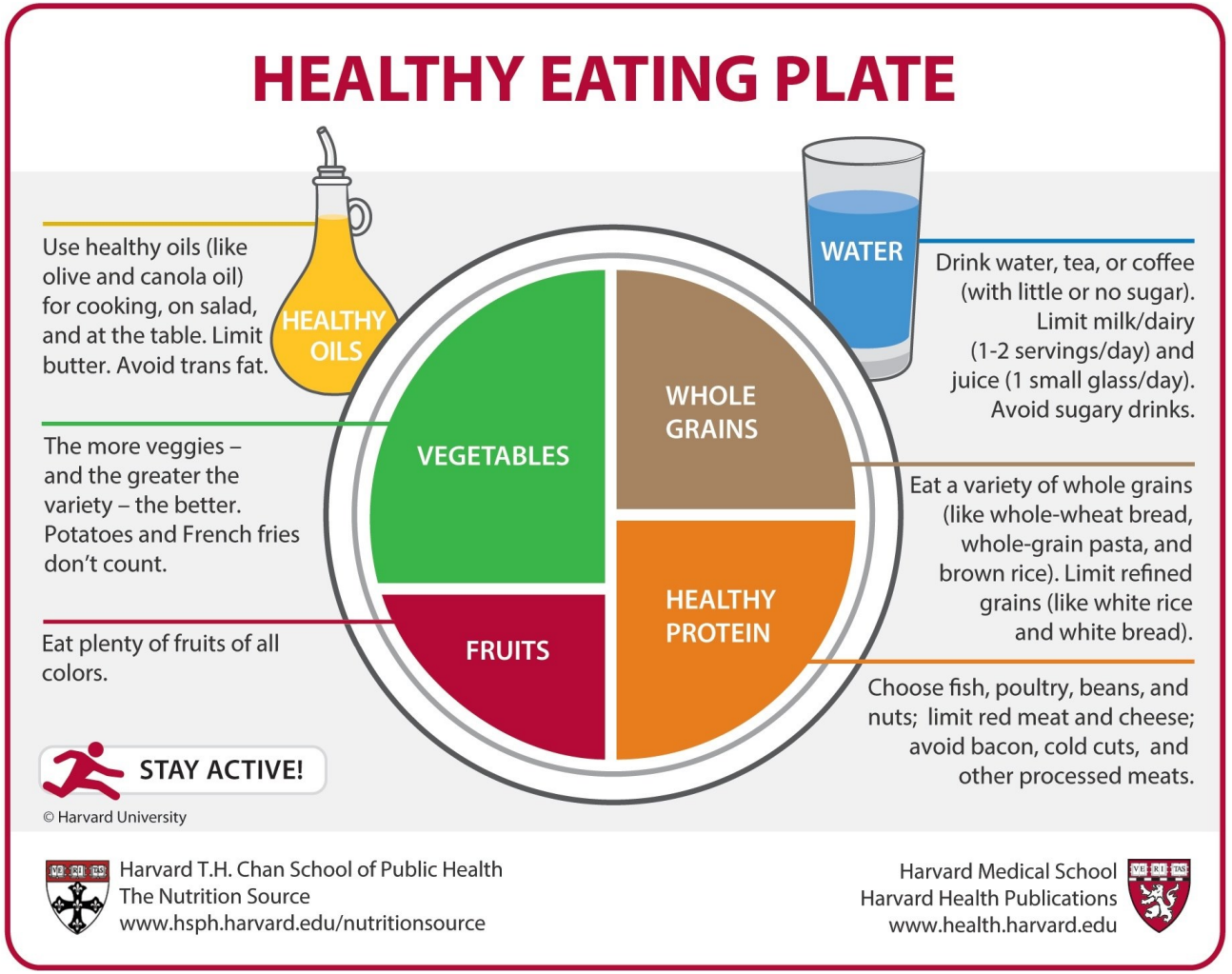
Never smoker	4839	4834	4799	4746	4697	4640	4575	4496	4426	4357
Former smoker	204	203	200	198	193	189	182	176	168	162
Current smoker	171	170	168	166	161	159	152	146	144	138

- **A population-based cohort study**
  - 7,529 Thai people with NAFLD
  - A mean follow-up of 8.5±1.4 years
- **Women who had both current smoking and drink alcohol 10-20 grams per day had significantly increased risk of death**
  - Adjusted Hazard ratio: 13.8, 95% CI: 1.66–145 after adjusting for age, BMI, exercise, comorbidities, lipid profiles, and handgrip strength

Charatcharoenwitthaya et al. Front Med (Lausanne). 2020

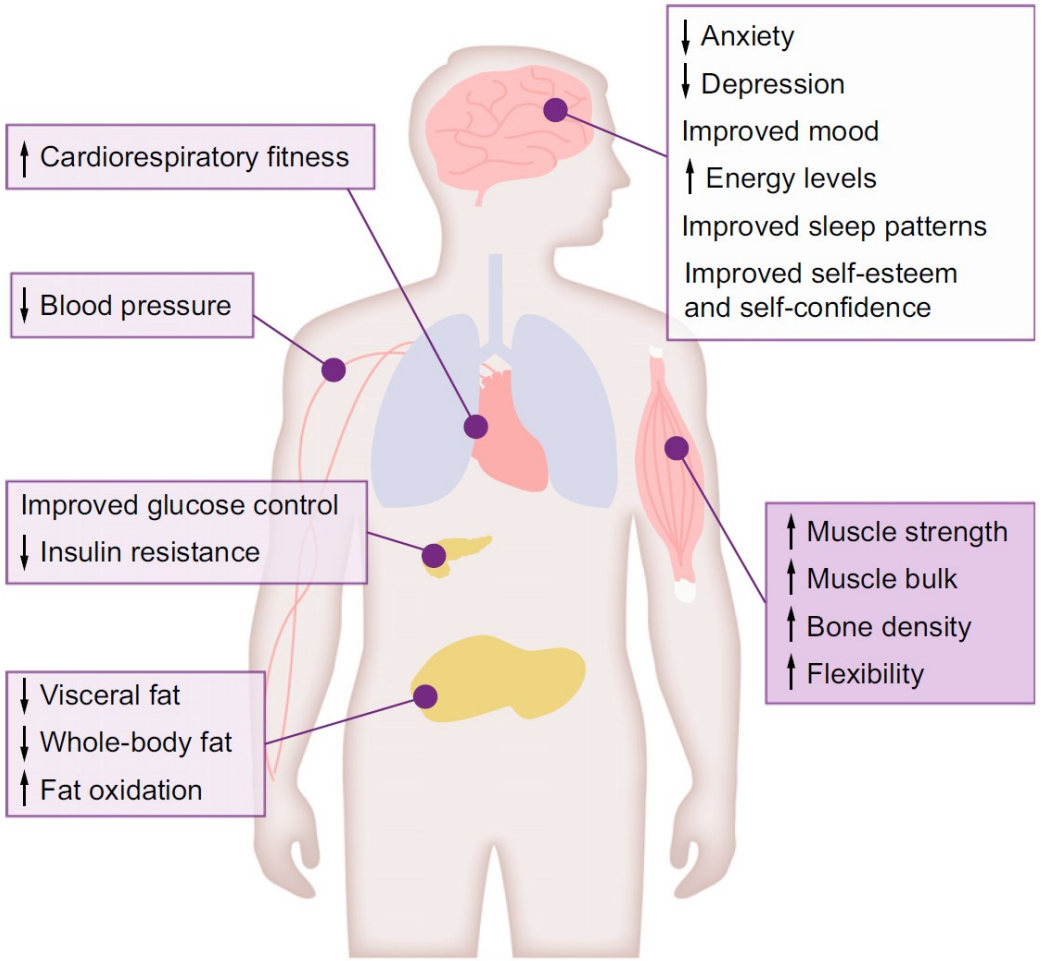
Dietary Modification: Recommendation

- "Healthy eating" (instead of "dieting")
- Eliminate sugar-sweetened beverages (get history from every patient—it's shocking)
- Use healthy oils (olive, canola)
- More vegetable and the greater variety
- Portion control
- Avoid fast food
  - Calorie dense (1300 cal and more fat than a stick of butter in some commonly marketed burgers)
- Avoid eating at night



https://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/

Benefits of Physical Activity and Exercise for NAFLD



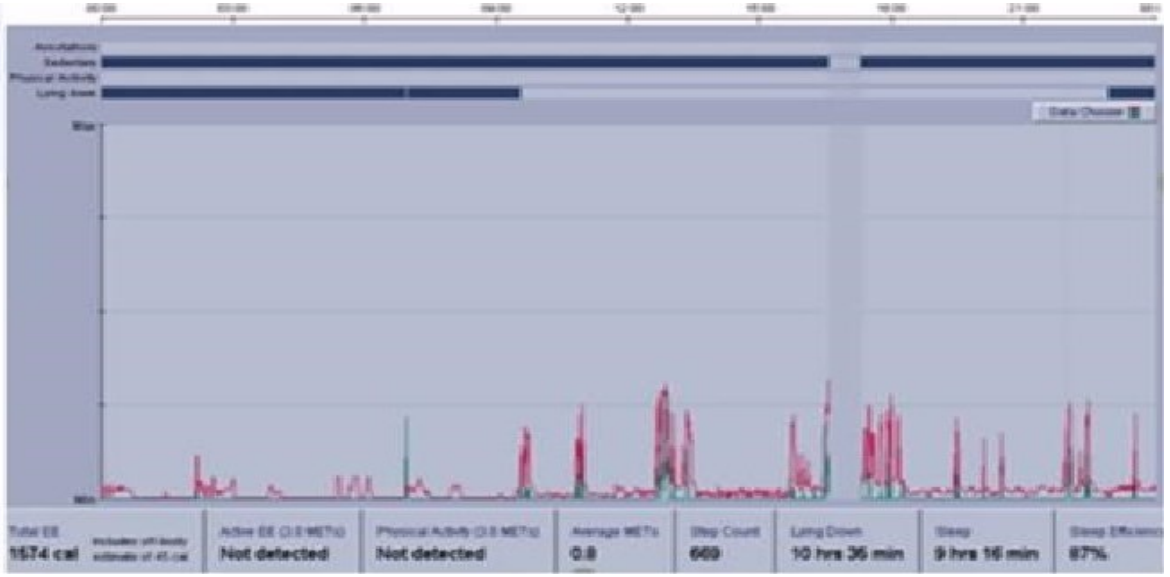
Hallsworth K & Adams LA. JHEP Reports 2019

Physical Activity and Sedentary Behavior in NAFLD

People with NAFLD took less steps/day than those without fatty liver (8281 vs. 9987steps/day)
People with NAFLD spend more time pursuing sedentary behaviors than healthy controls (>5 hours extra sedentary time/week)

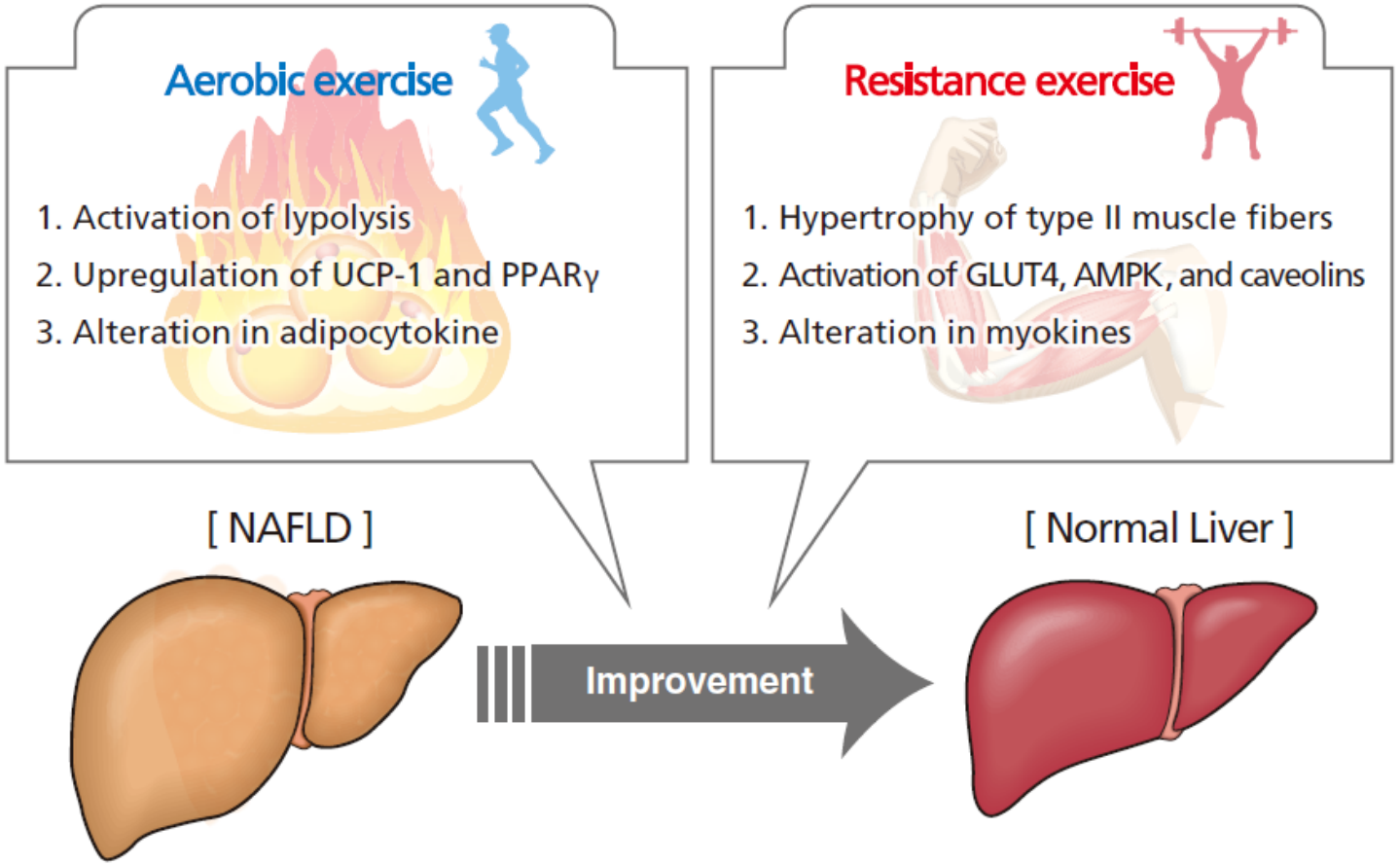
63yr old female without NAFLD

63yr old female with NAFLD



Hallsworth K, et al. Frontline Gastroenterology 2015

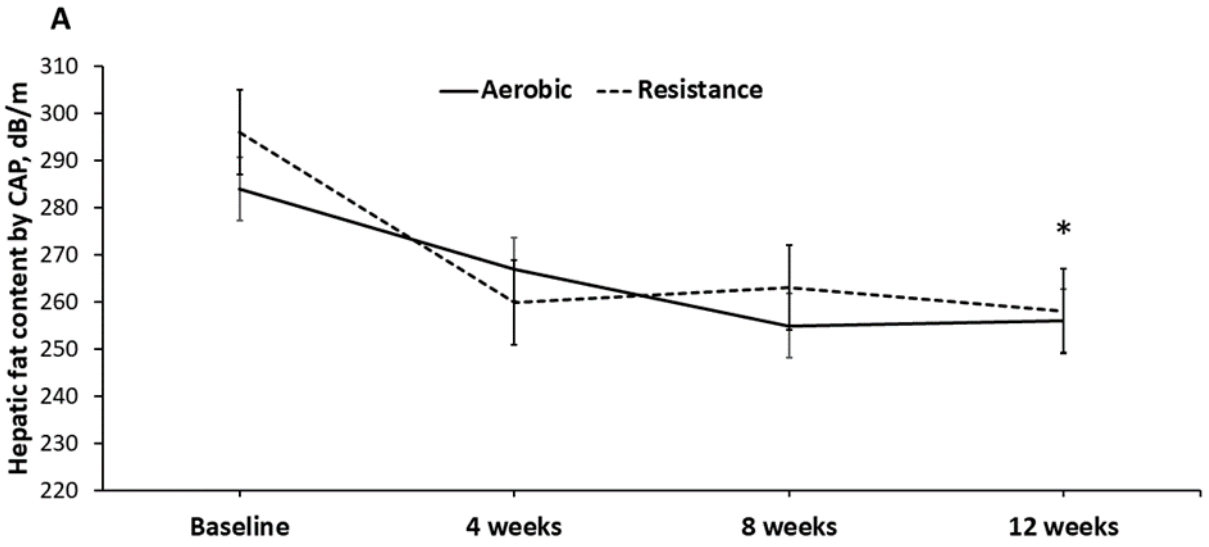
Different Mechanisms for the Improvement of NAFLD between Aerobic and Resistance Exercises

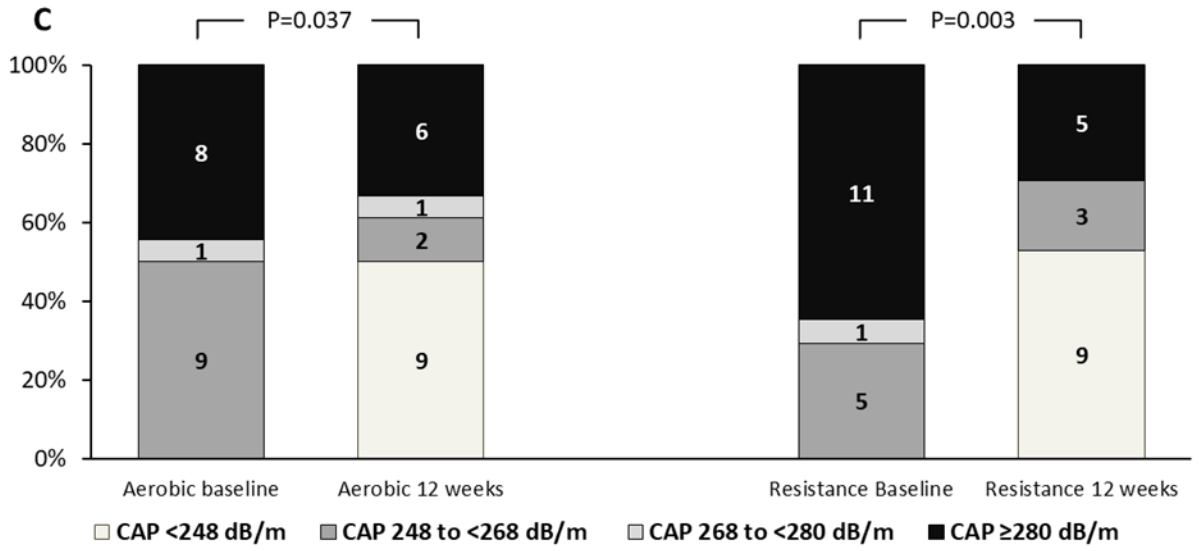


Hashida R, et al. J Hepatol 2017

Moderate-Intensity Aerobic vs Resistance Exercise and Dietary Modification in Patients With NAFLD: RCT

With a 12-week supervised training program of moderate-intensity exercise, 18 NAFLD subjects exercised for an average of 3.35 ± 0.30 sessions a week in the aerobic group, and 17 NAFLD subjects exercised an average of 3.39 ± 0.28 sessions a week in the resistance group.





Charatcharoenwitthaya et al. Clin Transl Gastroenterol. 2021

Recommendations for Exercise Prescription for NAFLD

- **Aerobic (e.g. jogging, cycling):**
  - **150-300 min/week of moderate-to-vigorous intensity** (50%-70% VO_2peak) **≥3 days/week**
- **Resistance (strength training):**
  - **2-3 sets of 8-12 repetitions** (70-85% 1RM) **2-3 days/week**
- For weight maintenance: ↑ volume of exercise
- For improvement in cardiorespiratory fitness and glycemic control: ↑ intensity of exercise
- "**Exercise prescription should be individualized to promote adoption and long-term adherence to the exercise regimen**, which may be facilitated by behavioral and cognitive strategies."

Keating SE, et al. Expert Rev Gastroenterol Hepatol 2015

Case: An obese woman with T2DM

What specific treatment has been shown to result in a significant proportion of patients achieving resolution of NASH when compared with placebo?

A. Vitamin E

B. Pioglitazone

C. Liraglutide

D. Semaglutide

Clinical Questions:

1. Does this patient have NAFLD?
2. Could this patient have significant liver fibrosis?
3. **What is specific NAFLD treatment?**

Pharmacotherapy in NAFLD Reserved for Patients With NASH and Fibrosis

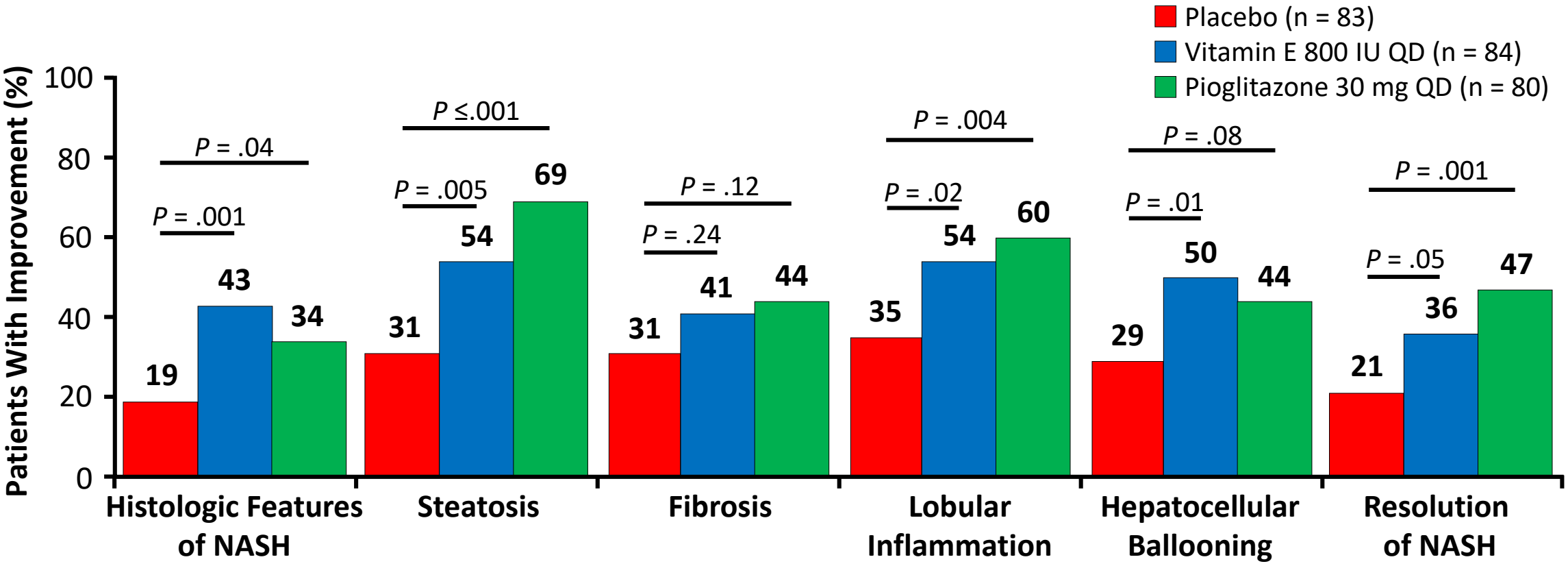
AASLD[1]	EASL-EASD-EASO[2]	APASL[3]
▪ Pharmacologic treatments should generally be limited to those with ***biopsy-proven NASH and fibrosis***	▪ Pharmacotherapy should be reserved for *patients* ***with NASH, esp. significant fibrosis***. ▪ Patients at high risk of progression (diabetes, MetS, persistently increased ALT,) could also be candidates	▪ Patients ***without steatohepatitis or fibrosis*** should receive counseling for a healthy diet and physical activity and ***no pharmacotherapy*** for their liver disease

	AASLD 2018	EASL-EASD-EASO 2016	APASL 2020
Vitamin E	**Recommended** in nondiabetic patients with biopsy-proven NASH (800 IU/day)	**Recommended** (800 IU/day)	Insufficient evidence, no firm recommendation
Pioglitazone	**Recommended** in patients with and without T2D and biopsy-proven NASH	**Recommended** in patients with T2D and biopsy-proven NASH	

1. Chalasani. Hepatology. 2018; 2. EASL, EASD, EASO. J Hepatol. 2016; 3. Eslam. Hepatol Intern. 2020.

PIVENS: Pioglitazone and Vitamin E in NASH at 96 Wk

- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



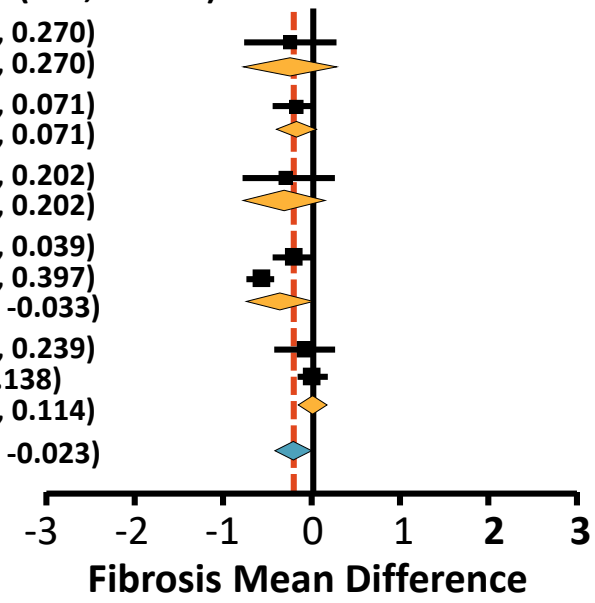
Sanyal et al. N Engl J Med. 2010.

Meta-analysis: Vitamin E Reduces NAS and Fibrosis in NAFLD

- Meta-analysis of N = 1317 patients with NAFLD in 15 RCTs
  - Study limitations: variations in definition of NAFLD; moderately small sample sizes

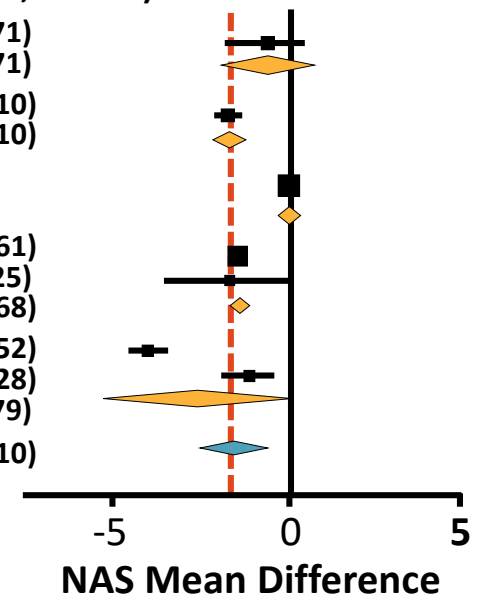
Fibrosis

Studies	Vitamin E vs Placebo (MD, 95% CI)
Harrison 2003	-0.250 (-0.770, 0.270)
--Subgroup 6 mo	-0.250 (-0.770, 0.270)
Zohrer 2017	-0.170 (-0.411, 0.071)
-Subgroup 12 mo	-0.170 (-0.411, 0.071)
Brill 2019	-0.300 (-0.802, 0.202)
--Subgroup 18 mo	-0.300 (-0.802, 0.202)
Sanyal 2010	-0.200 (-0.439, 0.039)
Dufour 2006	-0.570 (-0.743, 0.397)
--Subgroup 24 mo	-0.395 (-0.757, -0.033)
Lavine 2011	-0.100 (-0.439, 0.239)
Nobili 2008	0 (-0.138, 0.138)
--Subgroup 24 mo	-0.014 (-0.142, 0.114)
Overall (I^2 = 77.09%; P = 0)	-0.224 (-0.426, -0.023)



NAS

Studies	Vitamin E vs Placebo (MD, 95% CI)
Aller 2015	-0.600 (-1.771, 0.571)
--Subgroup first 3 mo	-0.600 (-1.771, 0.571)
Zohrer 2017	-1.700 (-2.090, -1.310)
--Subgroup 12 mo	-1.700 (-2.090, -1.310)
Brill 2019	0 (-0.190, 0.190)
--Subgroup 18 mo	0 (-0.190, 0.190)
Sanyal 2010	-1.400 (-1.639, -1.161)
Dufour 2006	-1.700 (-3.525, 0.125)
--Subgroup 24 mo	-1.405 (-1.642, -1.168)
Nobili 2008	-4.000 (-4.548, -3.452)
Lavine 2011	-1.100 (-1.872, -0.328)
--Subgroup 24 mo	-2.563 (-5.405, 0.279)
Overall (I^2 = 97.53%; P = 0)	-1.503 (-2.495, -0.510)



- Most promising patient for vitamin E treatment: an obese patient aged 15-50 yr, baseline AST >50 IU/L, daily intake of 400-800 IU vitamin E, liability to lose 5-10 kg

Abdel-Maboud. Therap Adv Gastroenterology. 2020.

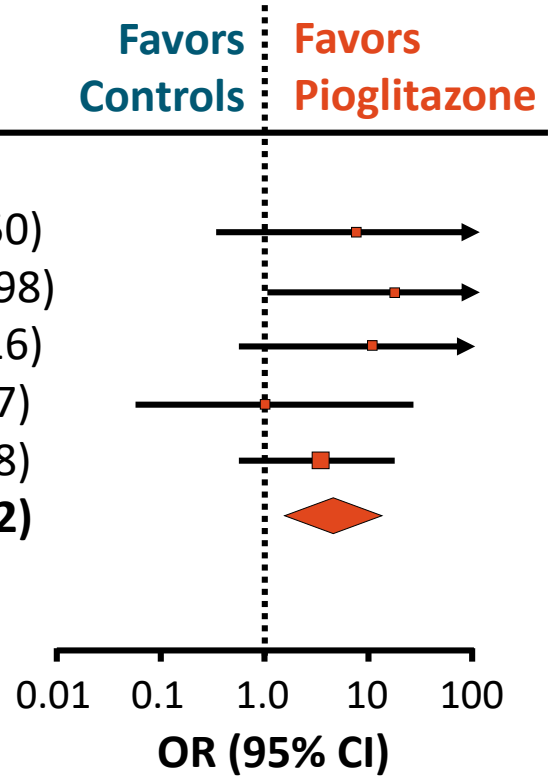
Pioglitazone in NASH Without Diabetes

- Subset of n = 5 pioglitazone studies in systemic review and metanalysis of randomized trials examining outcomes in NASH patients with advanced fibrosis at baseline (N = 298 patients)
- In biopsy-proven NASH, pioglitazone associated with **improvement in advanced fibrosis**

Source	Pioglitazone No. of Events	Pioglitazone No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)
Pioglitazone					
Aithal 2008	3	31	0	30	7.49 (0.37-151.50)
Belfort 2006	7	26	0	21	16.54 (0.89-308.98)
Cusi 2016	4	50	0	51	9.97 (0.52-190.16)
Sanyal 2004	1	10	1	10	1.00 (0.05-18.57)
Sanyal 2010	6	80	2	83	3.28 (0.64-16.78)
Total (95% CI)	**21**	**197**	**3**	**195**	**4.53 (1.52-13.52)**

Heterogeneity: $T^2 = 0$; $x^{2/2} = 2.39$; $P = .66$; $I^2 = 0\%$

Overall effect: z = 2.71; $P = .007$



Musso. JAMA Intern Med. 2017;177:633.

How to Use Pioglitazone in NASH?

Start pioglitazone at 30 mg/day

Monitor every 3 months for potential AEs:

- Weight gain: 2.5-5.2%
- Edema: 5-8% (more if combined with insulin)
- Bone loss: should be monitored (obtain DXA)
- Bladder cancer? Likely very small (18 out of 23 studies negative)

Poor candidates:

- BMI ≥40 kg/m^2, high dose-insulin or amlodipine use, osteoporosis

Do not use in CHF

- Rates of CHF in a meta-analysis of 19 trials, 2.3% vs. 1.8% in control group (p=0.002).

Case: An obese woman with T2DM

What second-line therapy after metformin (for management of hyperglycemia) has been shown to result in a significant proportion of patients achieving resolution of NASH when compared with placebo?

A. Pioglitazone

B. Liraglutide

C. Semaglutide

D. Empagliflozin

Clinical Questions:

1. Does this patient have NAFLD?
2. Could this patient have NASH with fibrosis?
3. **What is CV risk management ?**

Pharmacotherapy in NAFLD and NASH (Off Label)

Compound	Mechanism of Action	Weight Loss	Trial in NAFLD/NASH	Outcome
Liraglutide[2]	GLP-1 RA	Approved for treatment of obesity	Phase IIb LEAN	Resolution of histologic NASH without fibrosis worsening
Semaglutide[3]	GLP-1 RA	+++	Phase II	Resolution of histologic NASH without fibrosis worsening
Canagliflozin[5]	SGLT2	++	Multiple studies	Improvement in liver triglycerides by ^{1}H-MRS; improvement in steatosis biomarkers
Empagliflozin[6,7]	SGLT2	+	Multiple studies	Improvement of liver fat by MRI-PDFF; improvement in CAP and liver stiffness

1. Chalasani. Hepatology. 2018; 2. Armstrong. Lancet. 2016; 3. Newsome. NEJM. 2021.
4. Shao. Diabetes/Metabolism Research Reviews. 2014; 5. Cusi. Diabetes Obes Metab. 2019.
6. Kuchay. Diabetes Care. 2018; 7. Taheri. Advanc Ther. 2020.

Metabolic Effects of GLP1RA Leading to An Improvement in Hepatic Parameters

Weight loss

Glucose control
Improvement of glucotoxicity
Improvement of insulin resistance

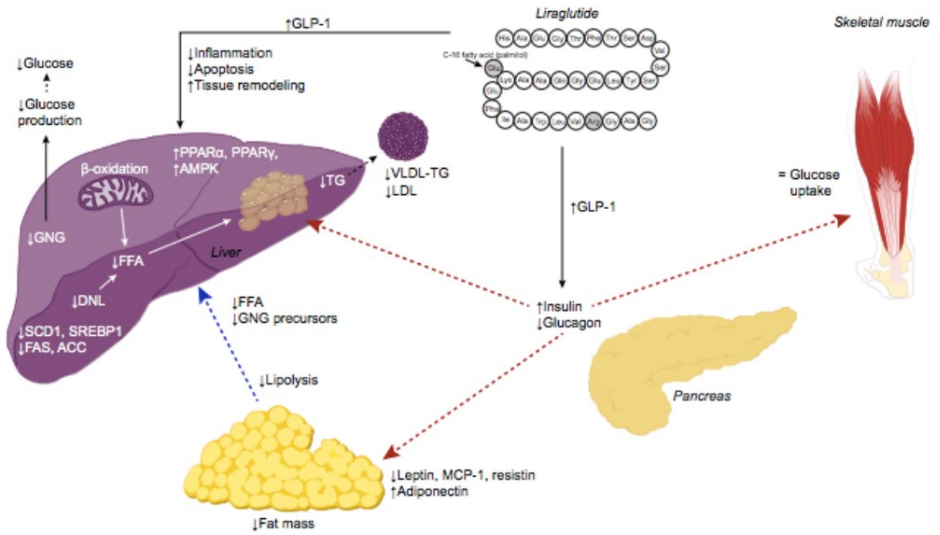
Inhibition/modulation of
de novo lipogenesis

Decrease inflammatory markers and
oxidative stress

N=14 subgroup

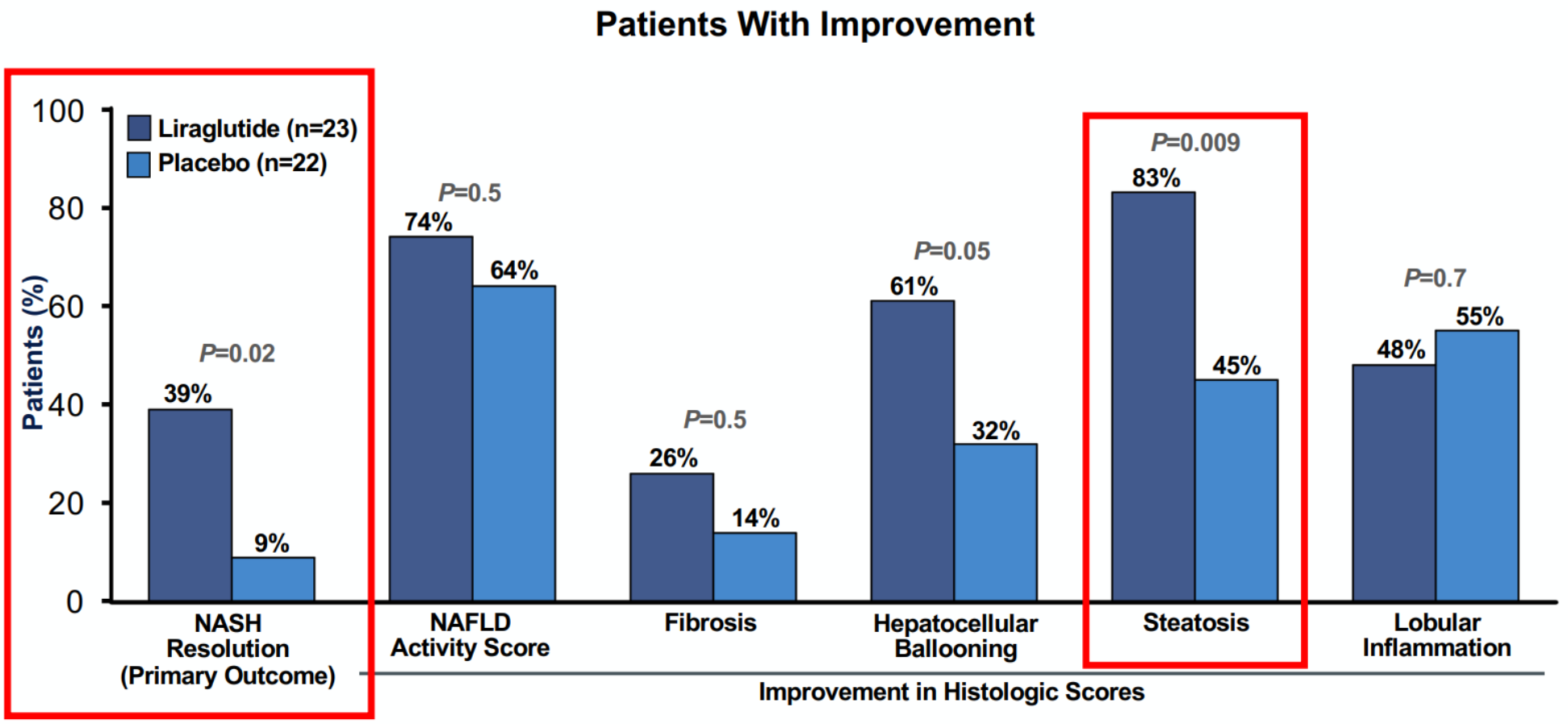
↓ Body weight 4-6% (Lira); 13% (Sema)
↓ IHTG ~ 37-44%

↓FFA flux to the liver
↓ DNL
↓ lipolysis - independent of weight loss ?



Gastaldelli & Marchesini. J Hepatol 2016

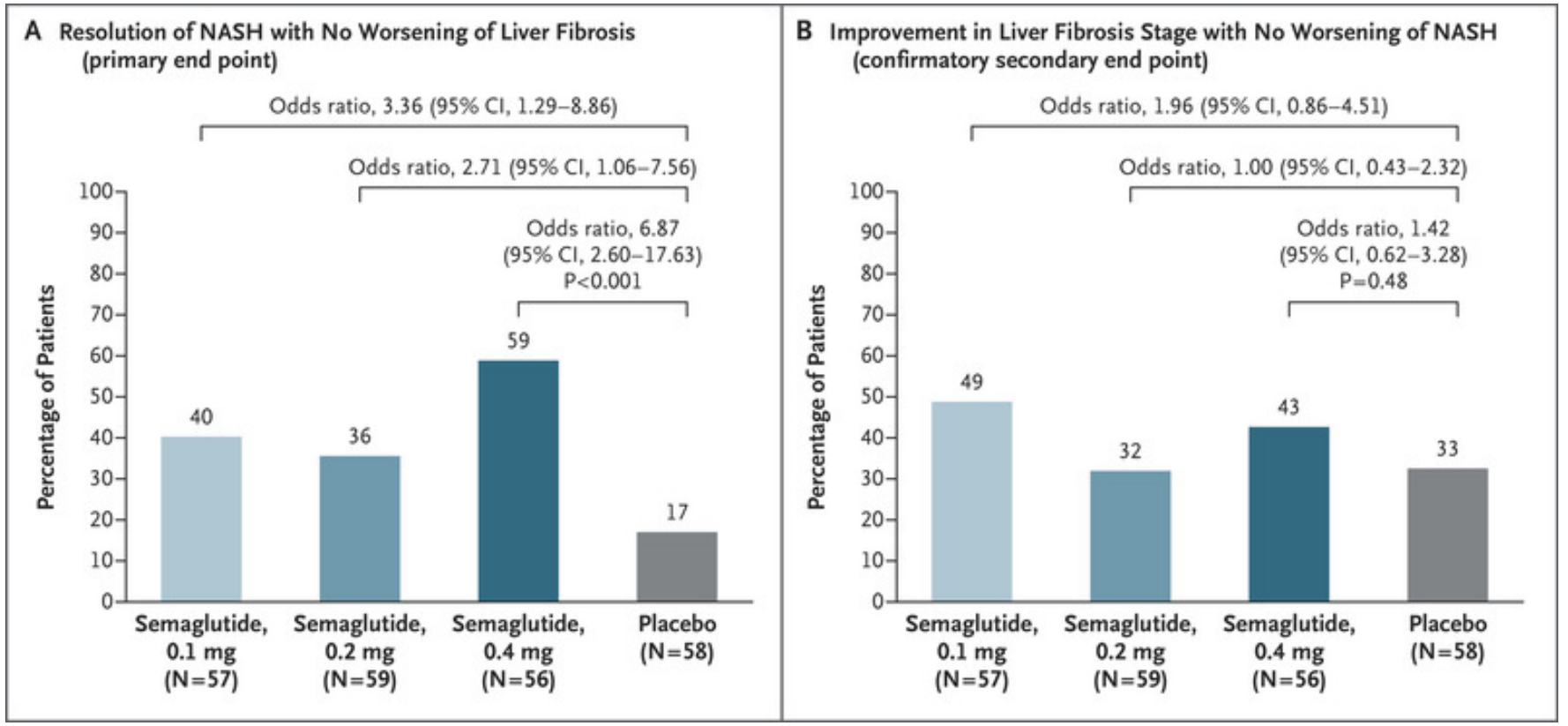
LEAN Study (Liraglutide Efficacy and Action in NASH): Changes in Liver Histologic Features at Week 48



Armstrong MJ, et al. Lancet. 2016;387:679-690

Semaglutide in NASH Study: Changes in Liver Histologic Features at Week 72

- Population: 320 patients (62% T2DM) randomized to daily semaglutide 0.1, 0.2, and 0.4 mg.
- Primary outcome: NASH resolution without worsening of fibrosis after 72 weeks (yes/no)
- Results: Semaglutide 0.1, 0.2, and 0.4 mg (40.4%, 35.6%, and 58.9%) vs placebo (17.2%; all p<0.05)



Newsome PN et al. N Engl J Med 2020

Metabolic Effects of SGLT2 inhibition Leading to Improvement in Hepatic Parameters

SGLT2 inhibitor

Glucagon effect

(Insulin/Glucagon ratio)

- Caloric loss (↑Glucosuria)
  - 80g/day=320cal/day)

↓ Body weight
↓ Both visceral and SQ fat
↓ IHTG ~ 10-22%

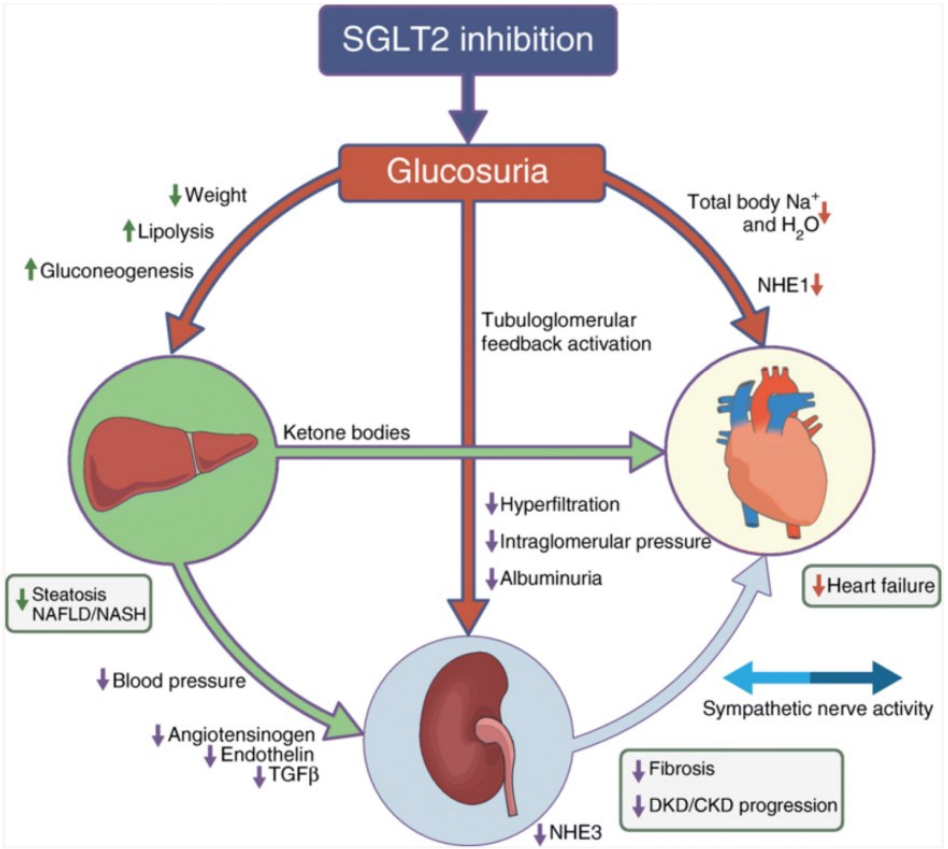
- Improve CV and renal outcomes

Weight loss 2.1-3.4%

Glucose control
Improvement of glucotoxicity
Improvement of insulin resistance

Inhibition/modulation of de novo lipogenesis

Decrease inflammatory markers and oxidative stress



1). Gerich JE. Diabet Med. 2010; 2).Bakris GL, et al. Kidney Int. 2009; 3). Ferrannini E, et al. Nat Rev Endocrinol. 2012; 4). Wanner, C. & Marx, N. Diabetologia 2018; 5). Jung CH, et al. J Obes Metab Syndr 2019.

Effect of SGLT2 Inhibitors on Intrahepatic Triglycerides in Patients with T2DM and NAFLD

Author, year	Agent	*n*	Duration (weeks)	Comparator	Main study results		
					Body weight*	ALT	Liver fat*
Prospective open-label studies							
Ito et al., 2017 (42)	Ipragliflozin	66	24	Pioglitazone	↓ 3.7%	↓	↓¶
Ohta et al., 2017 (43)	Ipragliflozin	20	24	Standard care	↓ 2.5%	↓	↓ 39%
Shibuya et al., 2018 (44)	Luseogliflozin	32	24	Standard care	↓ 3.2%	Unchanged	↓¶
Kuchay et al., 2018 (45)	Empagliflozin	50	20	Standard care	↓ 1.1%	↓	↓ 26%
Shimizu et al., 2019 (46)	Dapagliflozin	57	24	Standard care	↓ 3.1%	↓	↓†
Inoue et al., 2019 (47)	Canagliflozin	20	52	Standard care	↓ 3.4%	↓	↓ 31%
Randomized controlled trials							
Bolinder et al., 2012 (48)	Dapagliflozin	67	24	Placebo	↓ 2.2%	—	Unchanged
Eriksson et al., 2018 (49)	Dapagliflozin	84	12	Placebo	↓ 2.2%	↓	↓ 10%§
Cusi et al., 2019 (50)	Canagliflozin	56	24	Placebo	↓ 3.4%	Unchanged	↓ 18%§
Latva-Rasku et al., 2019 (51)	Dapagliflozin	32	8	Placebo	↓ 2.1%	Unchanged	↓ 13%
Kahl et al., 2019 (52)	Empagliflozin	84	24	Placebo	↓ 2.4%	Unchanged	↓ 22%

Arrows indicate statistically significant changes vs. comparator. *Comparison-corrected (open-label) or placebo-corrected relative treatment difference in weight and liver fat measured with MRI-based imaging techniques. ¶Liver fat measured as liver-to-spleen attenuation ratio on computed tomography. In Ito et al. (42) the decrease in liver fat was similar to pioglitazone (comparator). †Significant improvement in liver fat by controlled attenuation parameter (CAP; Fibroscan). §Not significant compared with placebo.

Cusi K., Diabetes Care. 2020;43:275-279.

Combination of Pioglitazone and SGLT2i

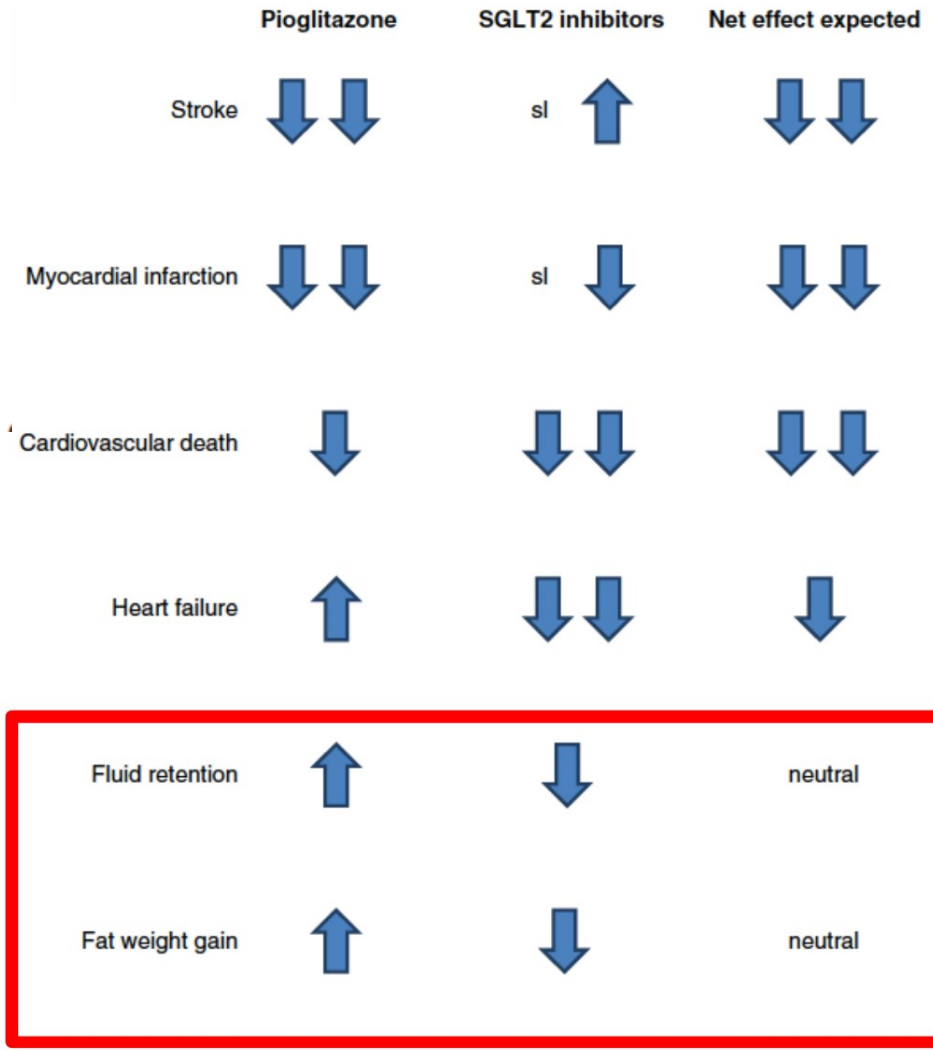
perspective

Diabetes, Obesity and Metabolism 18: 454–462, 2016.

Revitalization of pioglitazone: the optimum agent to be combined with a sodium-glucose co-transporter-2 inhibitor

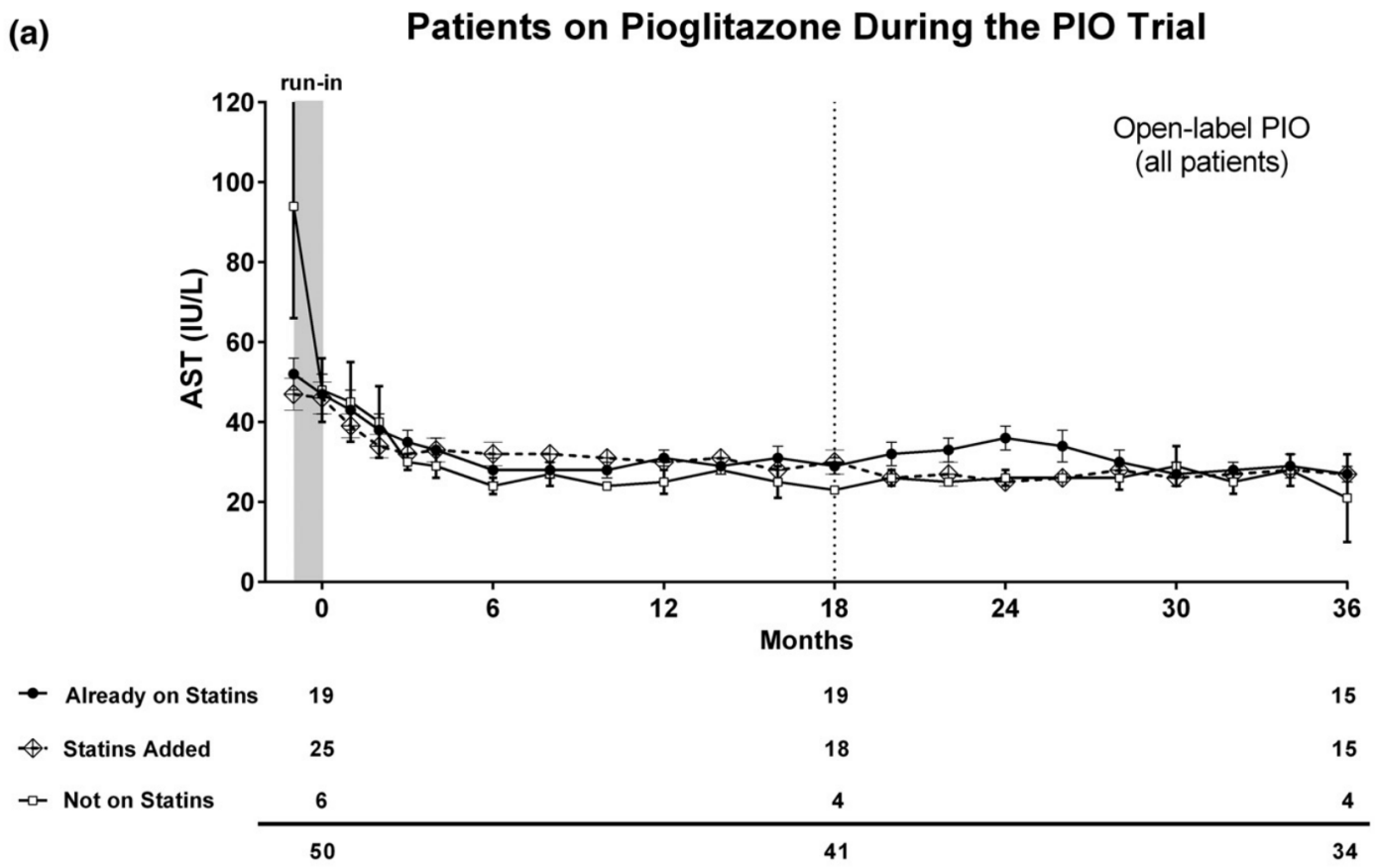
R. A. DeFronzo[1], R. Chilton[2], L. Norton[1], G. Clarke[3], R. E. J. Ryder[4] & M. Abdul-Ghani[1]

[1] *Diabetes Division, University of Texas Health Science Center and Texas Diabetes Institute, San Antonio, TX, USA*
[2] *Cardiology Division, University of Texas Health Science Center and Texas Diabetes Institute, San Antonio, TX, USA*
[3] *Diabetes Division and Department of Radiology, University of Texas Health Science Center and Texas Diabetes Institute, San Antonio, TX, USA*
[4] *Diabetes and Endocrine Unit, City Hospital, Birmingham, UK*



Dapagliflozin + Pioglitazone
Diabetes Care 35:1473–1478, 2012
Empagliflozin + Pioglitazone
Kovacs et al, clin Ther. 2015;37:1773-1788

Liver Safety of Statins in Prediabetes or T2DM and Nonalcoholic Steatohepatitis



Adding or continuing statin therapy in NASH is safe.

Bril F, et al. J Clin Endocrinol Metab 2017

Statin Use is Associated with Reduced Cancer-related Mortality in Patients with NAFLD: A National Prospective Cohort Study

11,328 patients identified as having NAFLD from a total of 23,505 NHANES participants during 1999-2014

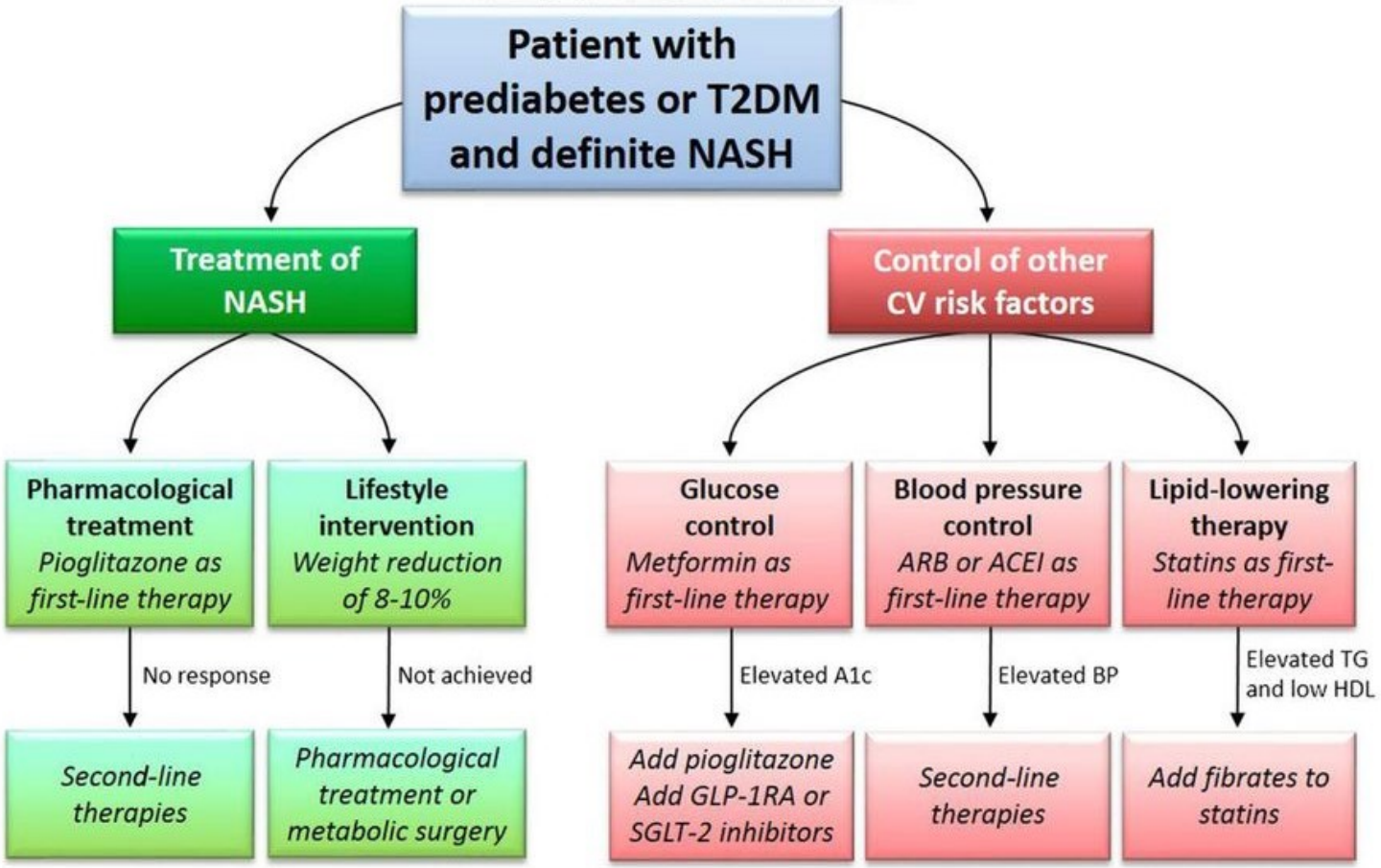
	Cancer mortality		All-cause mortality	
	HR* (95% CI)	P-value	HR (95% CI)	P-value
Statin use	0.56 (0.43-0.75)	<0.001	0.64 (0.56-0.72)	<0.001
Lipophilic statin use	0.61 (0.45-0.81)	0.001	0.66 (0.58-0.75)	<0.001
Hydrophilic statin use	0.30 (0.13-0.68)	0.004	0.53 (0.40-0.70)	<0.001

*Cox regression models and compared to statin non-users. All analyses are adjusted for gender, age, smoking history, body mass index, presence of diabetes and hypertension, and existing diagnosis of coronary artery disease, congestive heart failure, cerebrovascular accidents, or cancer at enrollment

Any statin use, regardless of lipophilic or hydrophilic type, is connected to a significant decrease in cancer-related and overall mortality in patients with NAFLD.

Hajifathalian K, et al. AASLD 2020

Management of Patients with T2DM and NASH



Fernando Bril & Kenneth Cusi. Dia Care 2017

Conclusion

1. **Patients with T2DM are at risk for progression from NAFLD to NASH with fibrosis**

   - NAFLD is common in patients with obesity and T2DM (up to 70% have NAFLD; 30% may have NASH and 15% F2-4)

   - Screening is needed high risk populations with obesity + T2DM

2. **Pharmacological Management of Patient with NAFLD**

   - Focused on cardiometabolic impact = ↓CVD

   - Although there are no FDA-approved drugs, use combination of therapies that improve NAFLD and also target CVD: PIO, GLP1RA, SGLT2i?.