The Epidemic of Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)

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Disclosure

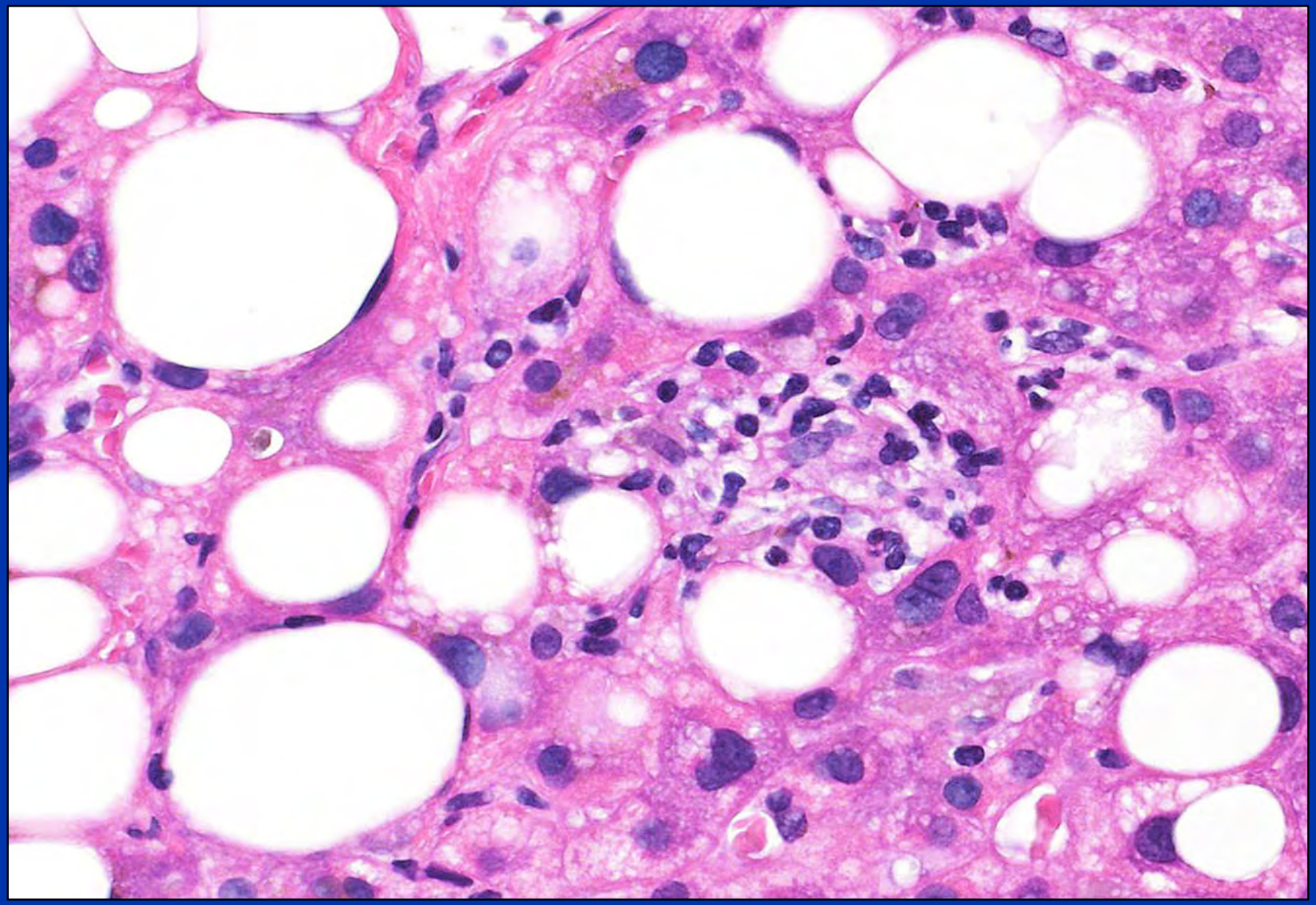
Consulting: Many pharmaceutical companies

Clinical Trials: AbbVie, Amgen, Astra Zeneca, Bristol Myers Squibb, Cerenis, Eli Lilly, Esperion, The Medicines Company, Novartis, Novo Nordisk, Silence Therapeutics and Pfizer.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.

If you treat diabetes and/or obesity,
It is important to understand fatty liver disease:
It’s common and it can be deadly!

Pathology: Initial Appearance of NAFLD



History of NAFLD and NASH

- A causal relationship between hepatic fat accumulation and the development of fibrosis has been observed in 1839 followed by the microscopic finding that ‘fatty degeneration’ develops close to inflammatory deposits and scarring.

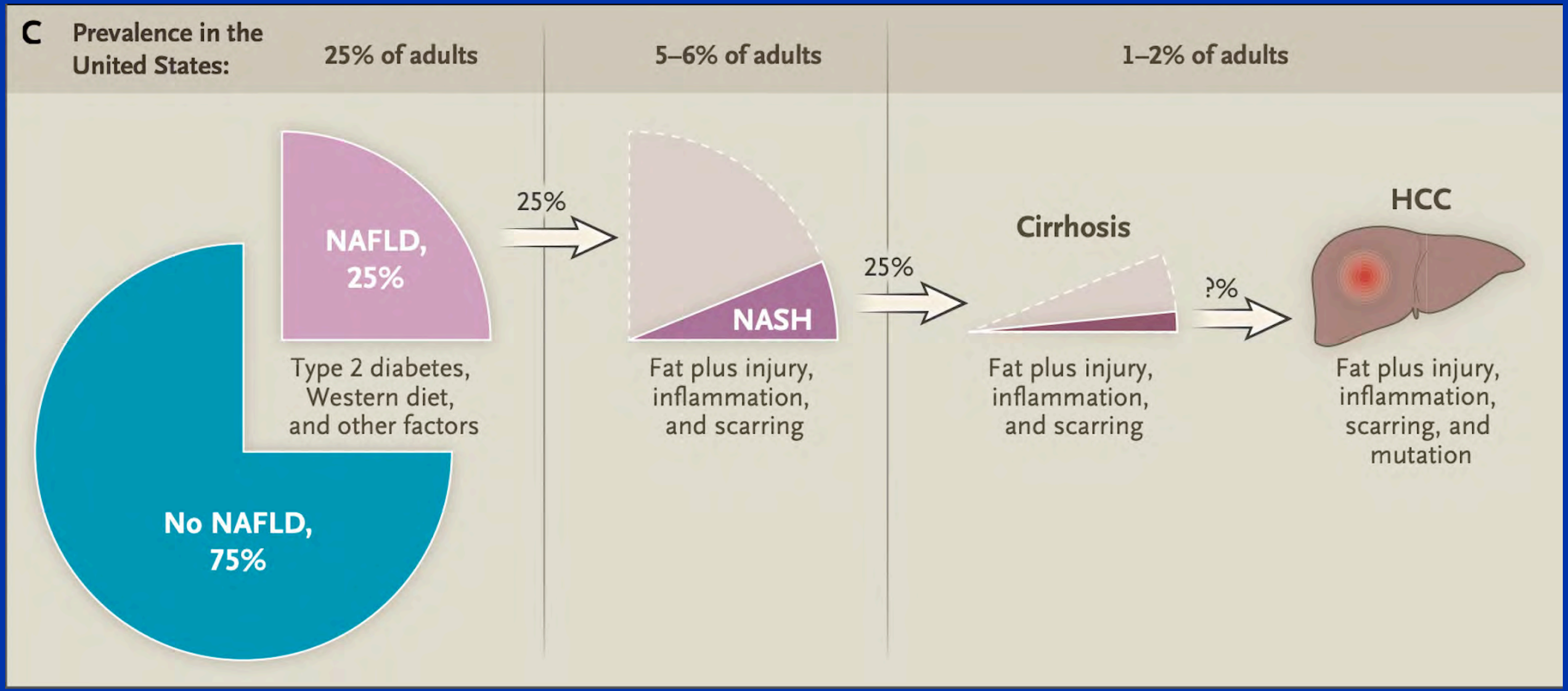
- The term ‘fatty liver hepatitis’ first appeared in 1962 in the German literature while the term ‘non-alcoholic steatohepatitis’ (NASH) was coined in 1980, defined by the histopathological hallmarks of steatosis, lobular inflammation, liver cell damage with ballooning and, eventually, appearance of Mallory-Denk bodies.*

Gut 2021;70:1570–1579.

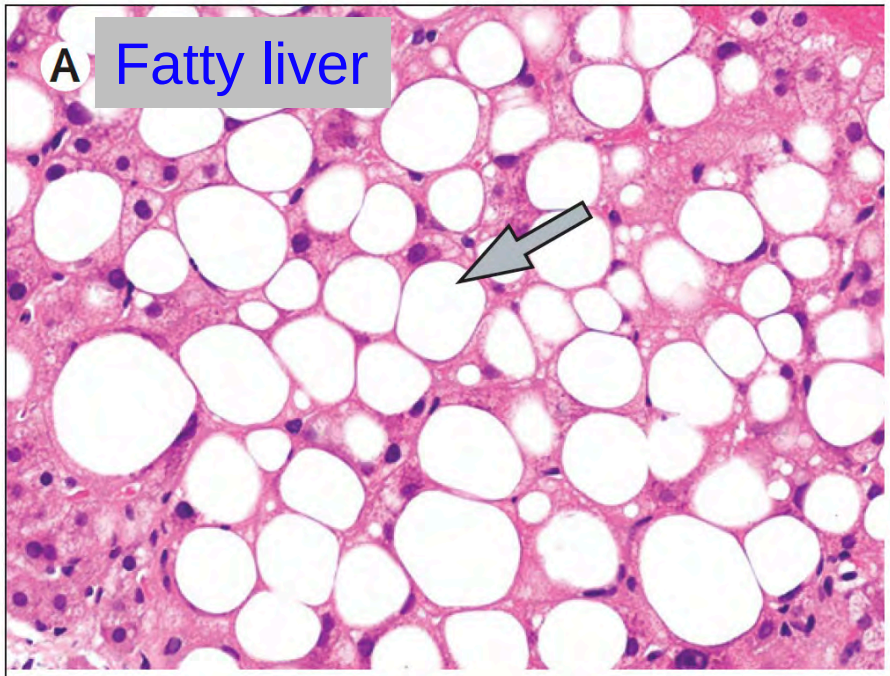
*Dtsch Med Wochenschr 1962;87:1049–55.

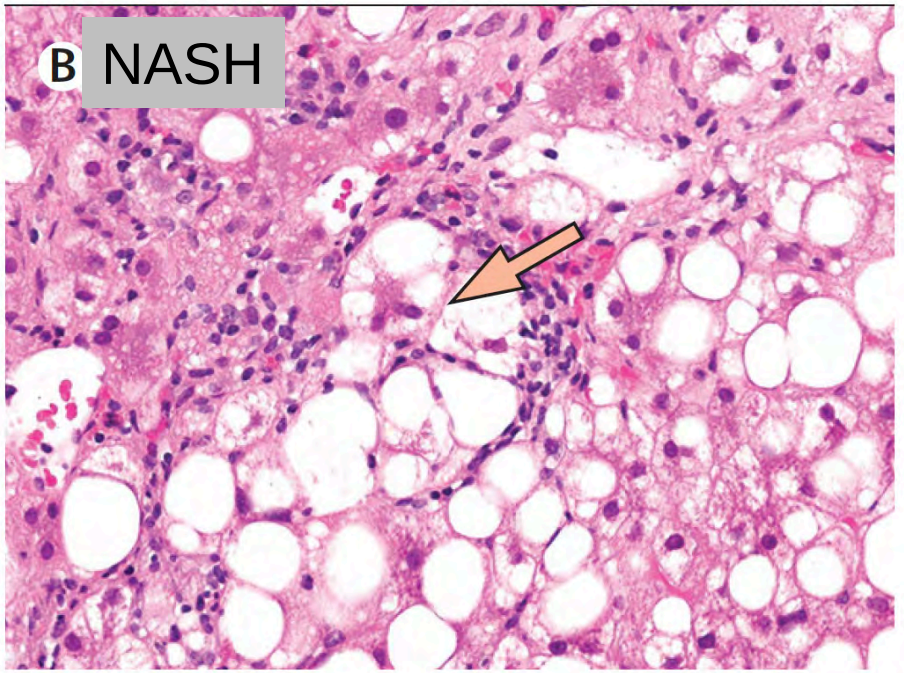
Prevalence and Disease Progression

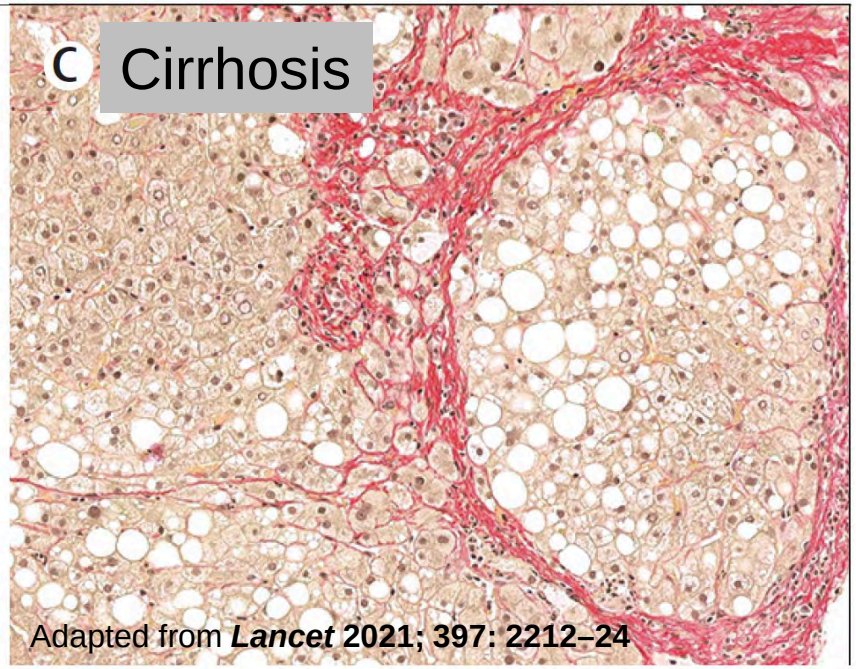
Three stages of Non-alcoholic Fatty Liver Disease (NAFLD)

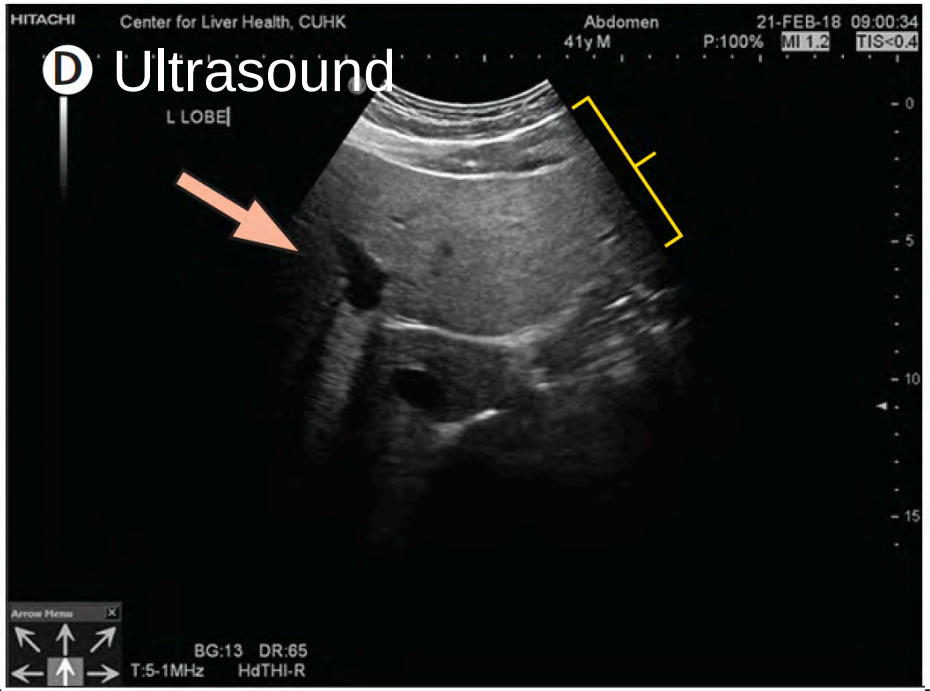


N Engl J Med 2017;377:2063-72.


A Fatty liver


B NASH


C Cirrhosis
Adapted from *Lancet* 2021; 397: 2212–24


HITACHI
Center for Liver Health, CUHK
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41y M
21-FEB-18 09:00:34
P:100%
MI 1.2
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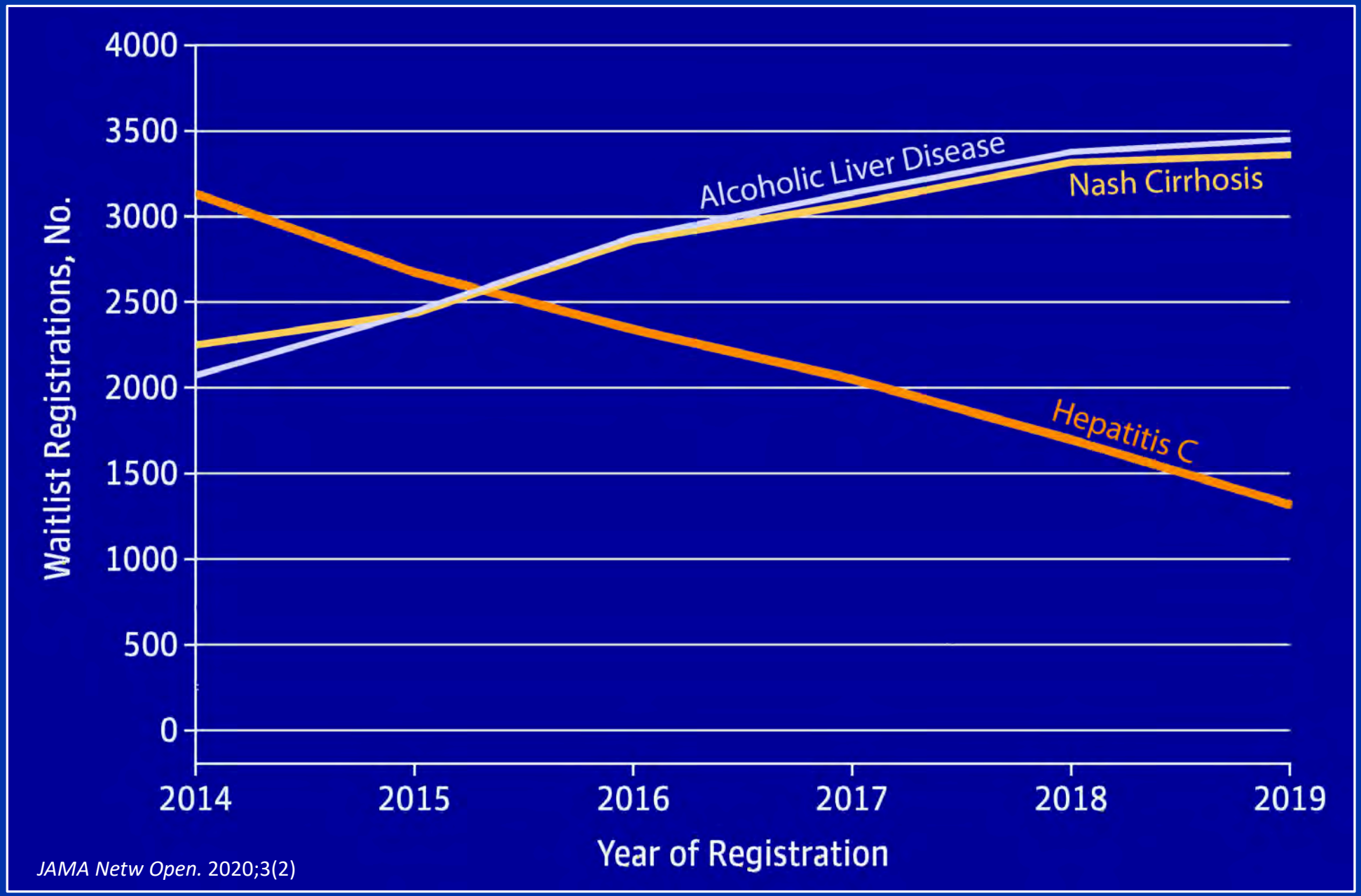
D Ultrasound
L LOBE
BG:13 DR:65
T:5-1MHz HdTHI-R

Recent Trends in Liver Transplantation Waitlist



JAMA Netw Open. 2020;3(2)

Future Projections

What will the future bring in regard to NAFLD? As the global epidemic of obesity fuels metabolic conditions, the clinical and economic burden of NAFLD will become enormous. Models based on published estimates predict a growth of up to 30% in total NAFLD cases between 2016 and 2030. NASH prevalence will increase by 15%–56%, while advanced liver disease and liver- related mortality will more than double as a result of ageing Western populations.

Hepatology 2016;64:1577–86.

J Hepatol 2018;69:896–904.

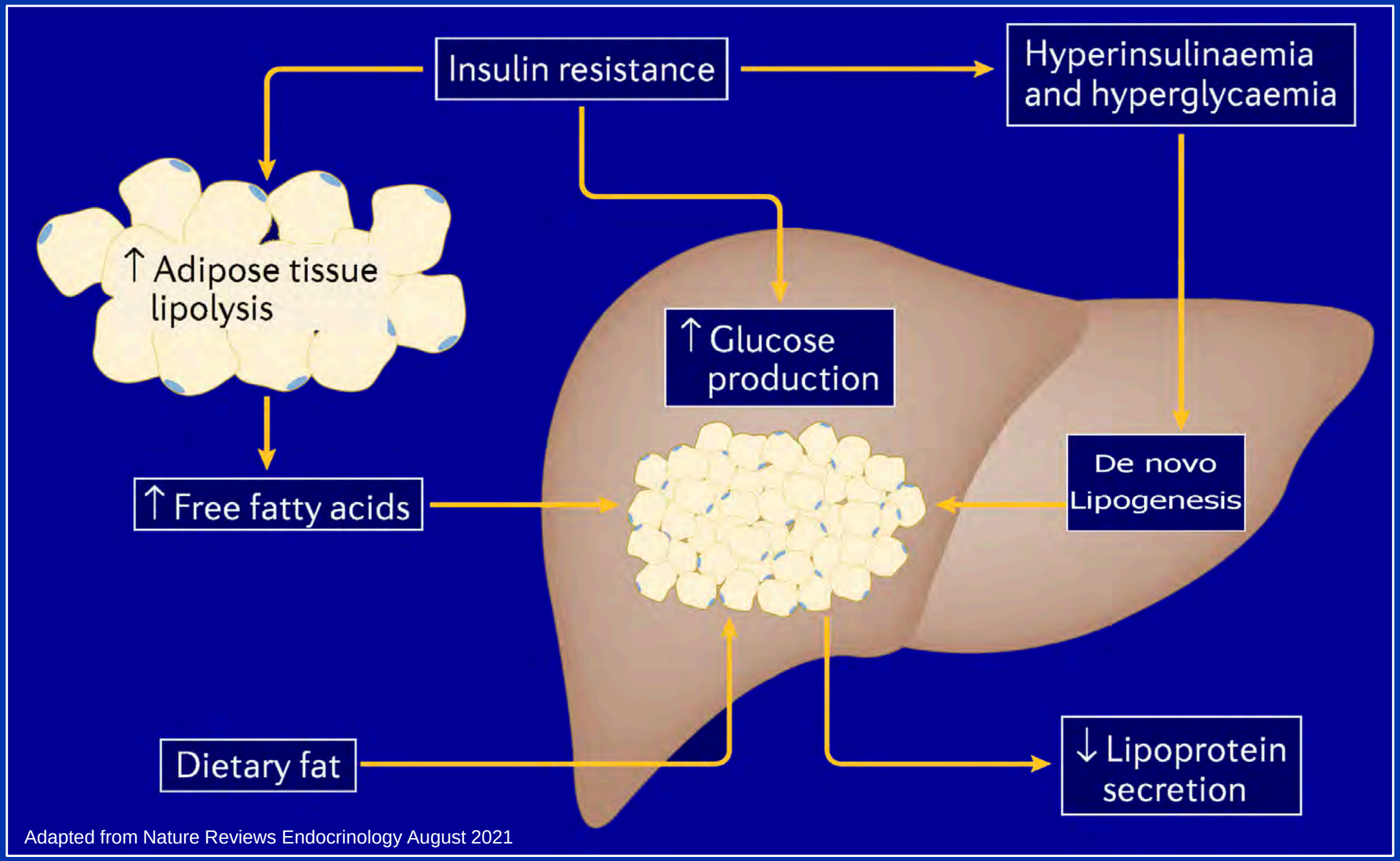
Co-Morbid Conditions Associated With NAFLD and NASH

Characteristic	General US Population	Patients with NAFLD	Patients with NASH
Obesity	40%	51%	82%
Hypertriglyceridemia	25%	41%	83%
Dyslipidemia	18%	70%	72%
Metabolic Syndrome	34%	43%	71%
Hypertension	29%	40%	68%
Type 2 Diabetes	14%	23%	44%

Hepatology 64, 73–84 (2016).

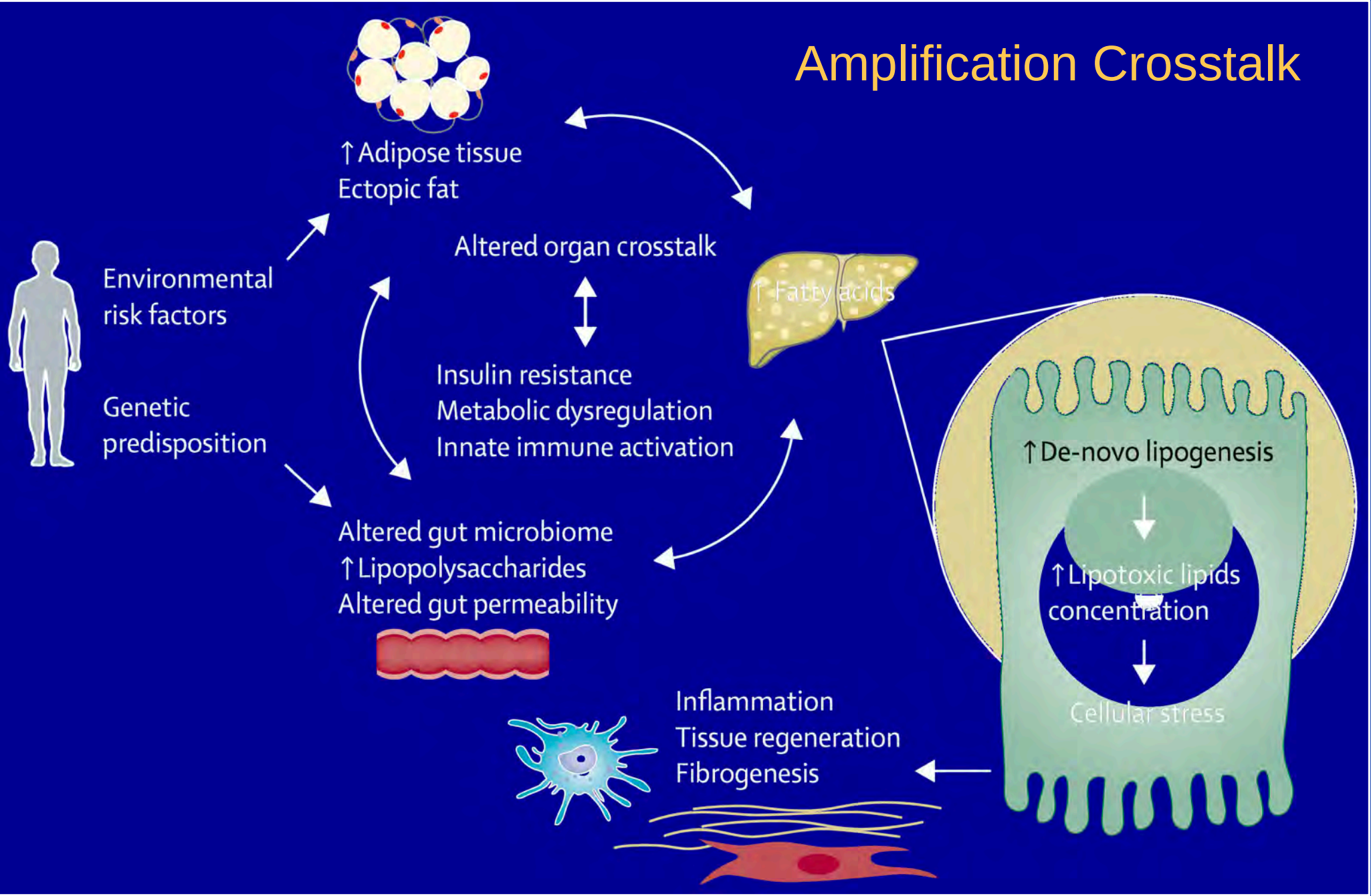
Pathophysiology

Key Factors in Hepatic Lipid Accumulation



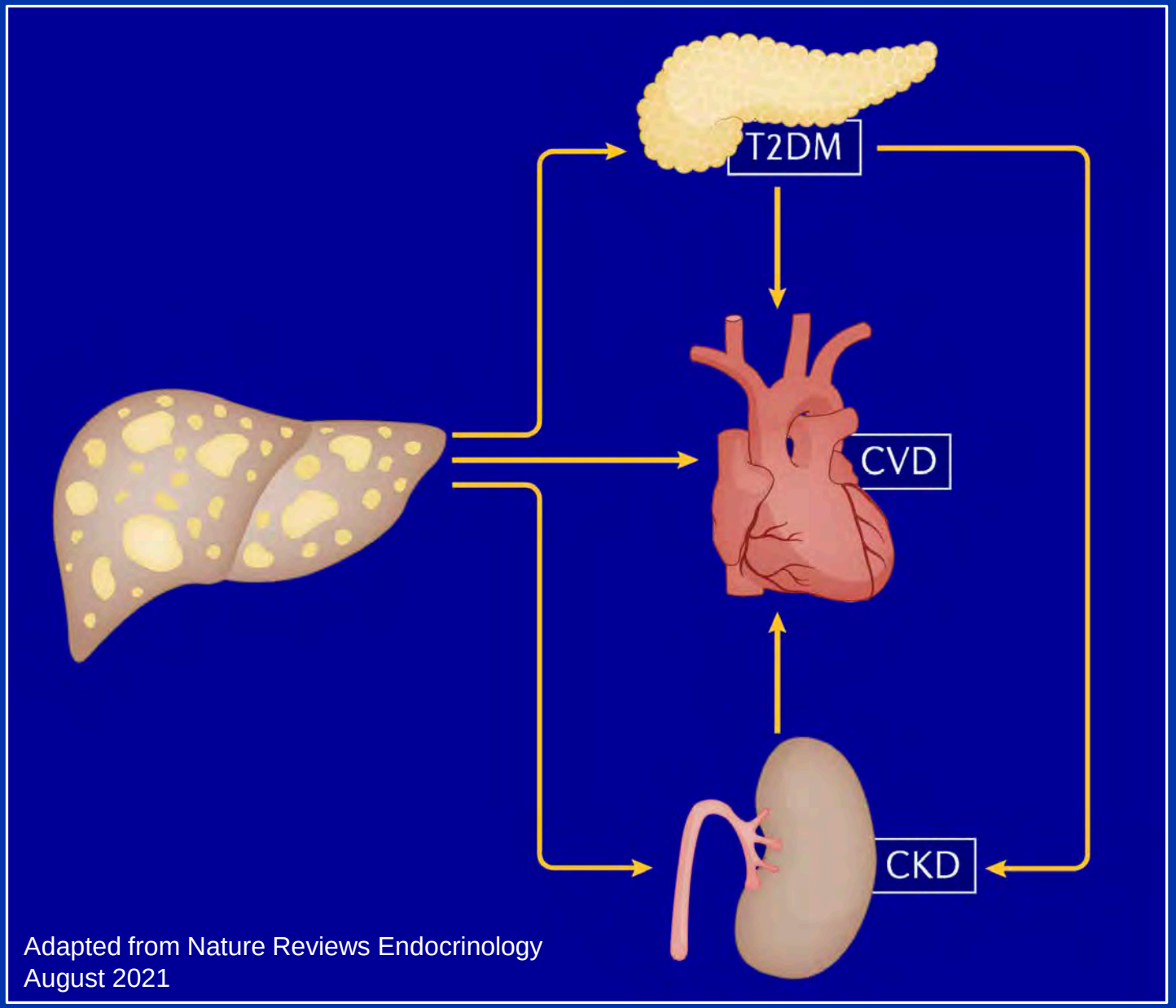
Adapted from Nature Reviews Endocrinology August 2021

Amplification Crosstalk



Consequences of NAFLD

Downstream Effects of NAFLD



Adapted from Nature Reviews Endocrinology
August 2021

Accelerated Cardiovascular Disease

- Meta-analysis of 16 observational studies with 34,043 adults (36.3% with NAFLD)
- Approximately 2,600 adverse CVD outcomes (>70% CVD deaths) over a median period of 6.9 years
- Patients with NAFLD had a higher risk of fatal and/or non-fatal CVD, odds ratio 1.64, 95% CI 1.26–2.13.
- Patients with *severe* NAFLD more likely to develop fatal and non-fatal CVD events (OR 2.58; 1.78–3.75).

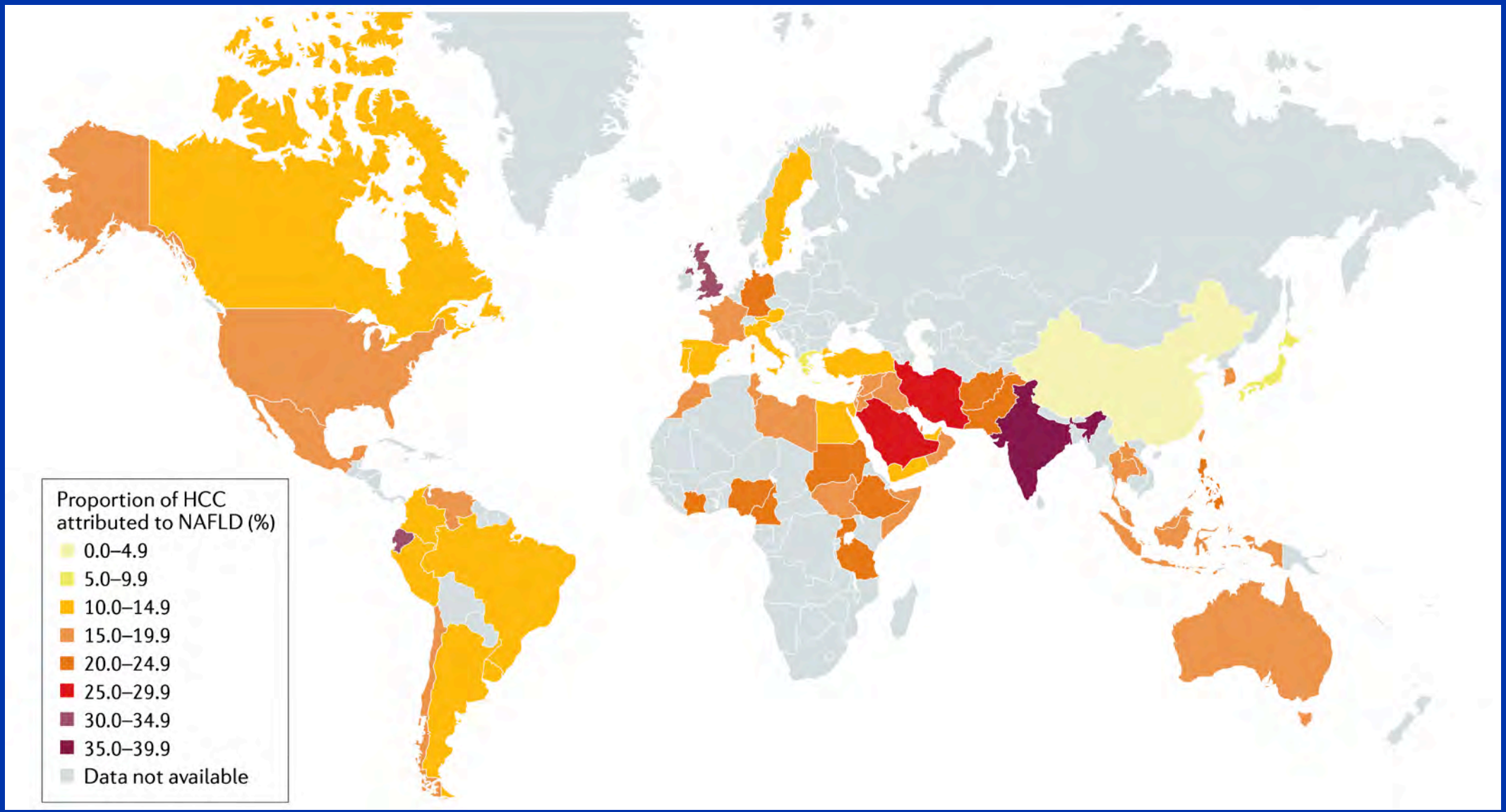
Journal of Hepatology VOLUME 65, ISSUE 3, P589-600, SEPTEMBER 01, 2016

Accelerated Renal Disease

- Meta-analysis - 13 studies with 1,222,032 individuals, 28.1% with NAFLD and 33,840 with incident CKD stage ≥3
- CKD defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2
- Median follow-up of 9.7 years.
- Patients with NAFLD had a higher risk of CKD, hazard ratio HR = 1.43, 95%CI 1.33-1.54.
- Risk independent of age, sex, obesity, hypertension, diabetes and other conventional CKD risk factors.

Alessandro Mantovani MD et al, https://eprints.soton.ac.uk/445427/1/NAFLD_CKD_risk_meta analysis_accepted.pdf

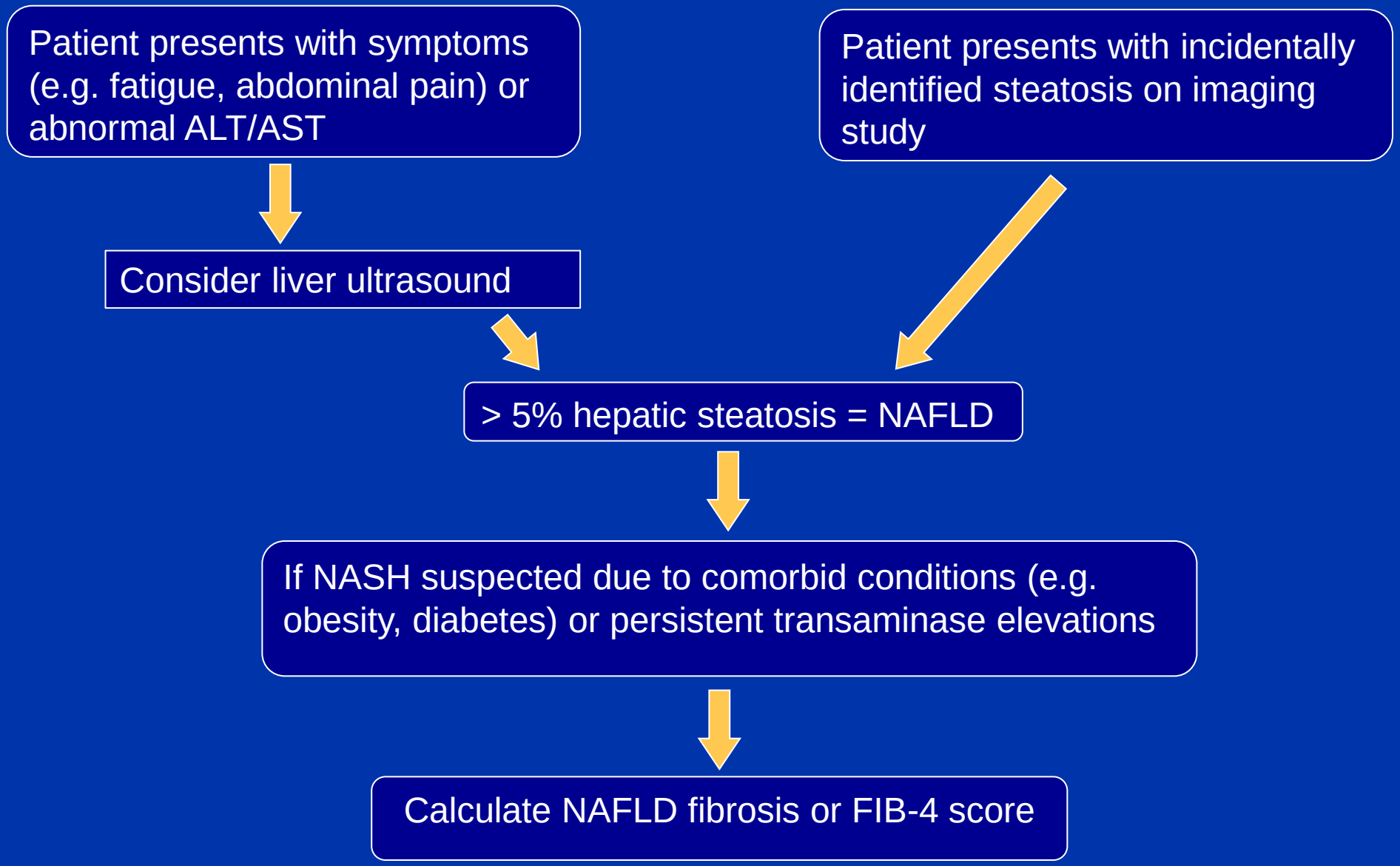
Proportion of Liver Cancer Attributable to NAFLD



Nat Rev Gastroenterol Hepatol **18**, 223–238 (2021)

Making the Diagnosis!

Suspected NALFD: Typical Diagnostic Algorithm



Scoring Formulae for Fibrosis

$$\text{FIB4 Index} = \frac{\text{Age x ALT}}{\text{Platelet count x } \sqrt{\text{AST}}}$$

$$\text{NAFLD Fibrosis Score} = -1.65 + .037 \text{ x age} + 0.94 \text{ x BMI} + 1.13 \text{ x IFG or T2DM (yes} = 1, \text{no} = 0) + 0.99 \text{ x AST/ALT ratio} - .013 \text{ x platelet count} - 0.66 \text{ x albumin}$$

Interpretation

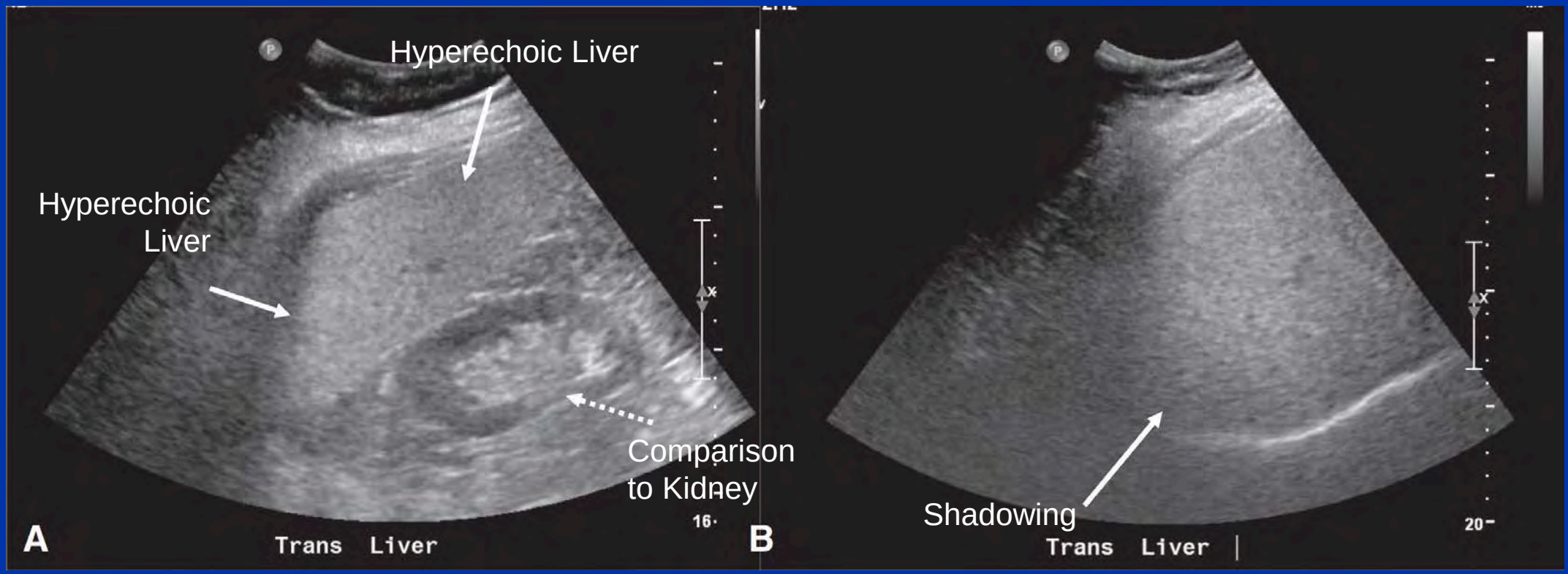
A value of FIB-4 below 1.30 is considered as low risk for advanced fibrosis; a value of FIB-4 over 2.67 is considered as high risk for advanced fibrosis; and FIB-4 values between 1.30 and 2.67 are considered as intermediate risk of advanced fibrosis.

NAFLD fibrosis score	**Interpretation**
Less than -1.455	Low probability of fibrosis
From -1.455 to 0.676	Intermediate score
More than 0.676	High probability of fibrosis

Consider ordering a liver ultrasound

Abdominal Ultrasound Focused on Liver

Fatty liver is hyperechoic compared with kidney and attenuates deeper ultrasound signal

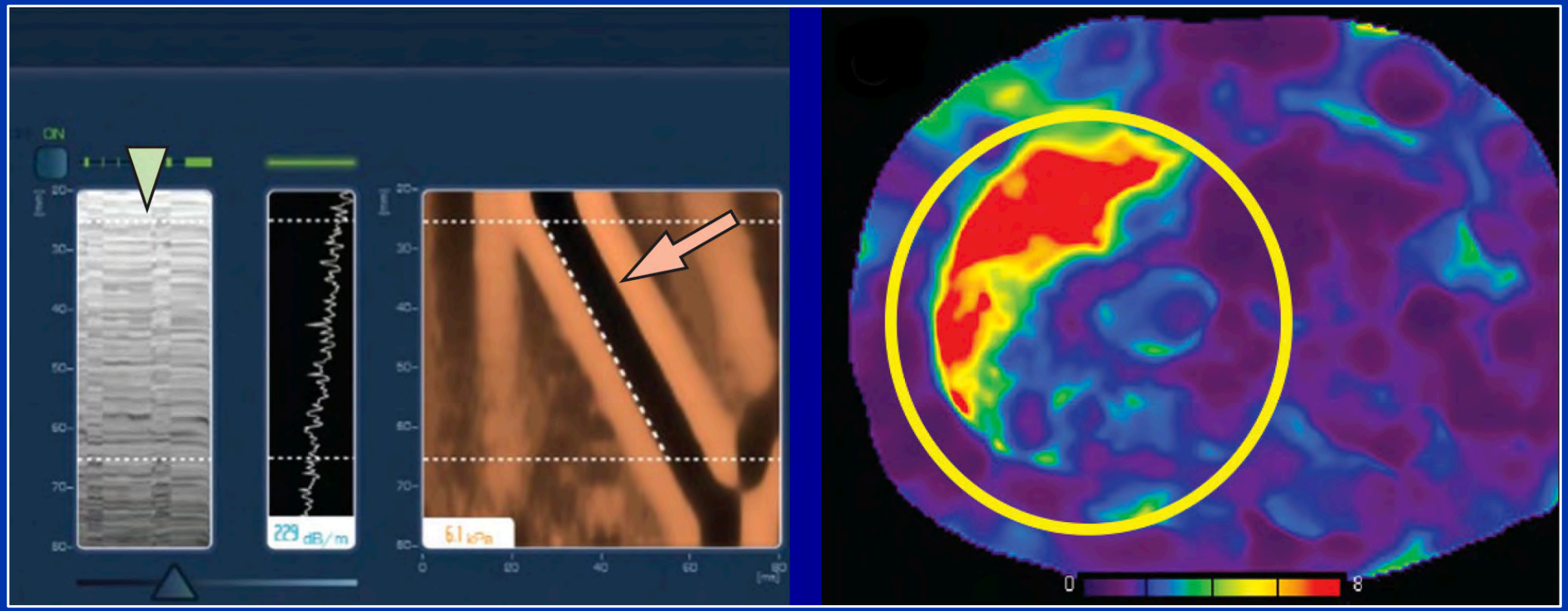


Clinical Liver Disease, vol 16, no 2, August 2020

Advanced Imaging to Assess Liver Stiffness

Ultrasound elastography

MRI elastography



Adapted from Lancet 2021; 397: 2212–24

Treatment

Approved Drug Therapy for NAFLD/NASH

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Treatment: Lifestyle Modifications

- Target 7-10% reduction in body weight.
- Limit consumption of drinks sweetened with high-fructose corn syrup
- Limit consumption of alcohol to 1 ≤ drink/day (women) and ≤ 2 drinks/day (men)
- Encourage ≥ 2 cups of coffee per day. Caffeine effect.
- Mediterranean diet and aerobic exercise?

Adapted from N Engl J Med 2017;377:2063-72.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

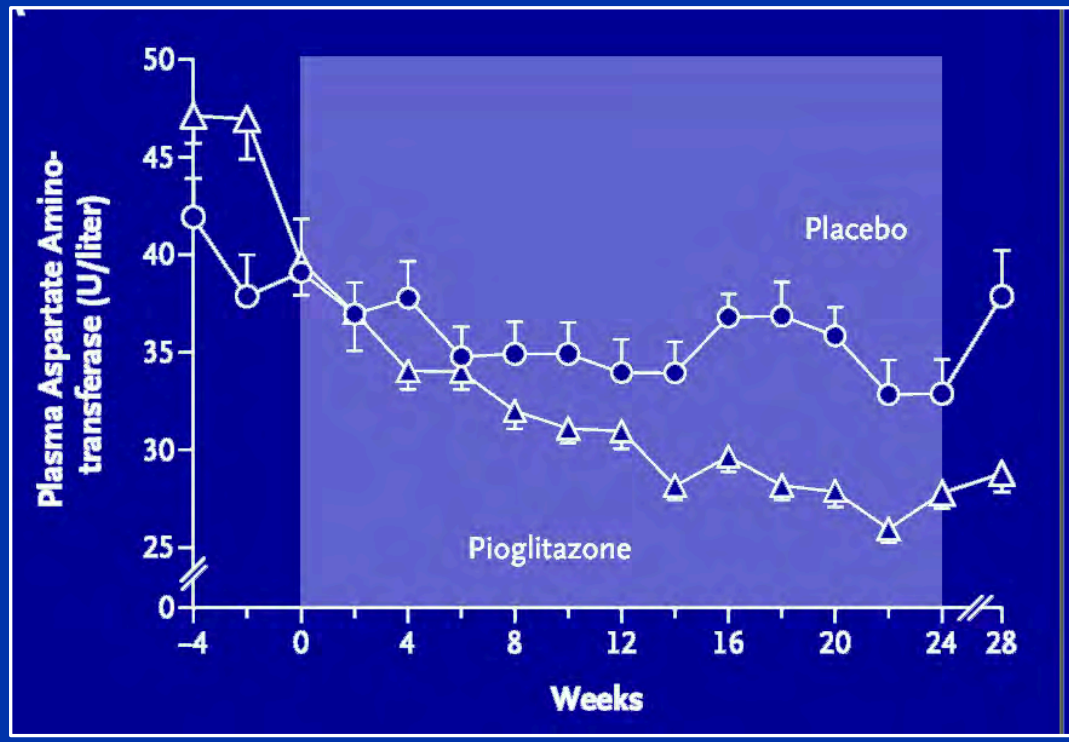
Renata Belfort, M.D., Stephen A. Harrison, M.D., Kenneth Brown, M.D., Celia Darland, R.D., Joan Finch, R.N., Jean Hardies, Ph.D., Bogdan Balas, M.D., Amalia Gastaldelli, Ph.D., Fermin Tio, M.D., Joseph Pulcini, M.D., Rachele Berria, M.D., Jennie Z. Ma, Ph.D., Sunil Dwivedi, M.D., Russell Havranek, M.D., Chris Fincke, M.D., Ralph DeFronzo, M.D., George A. Bannayan, M.D., Steven Schenker, M.D., and Kenneth Cusi, M.D.

ABSTRACT

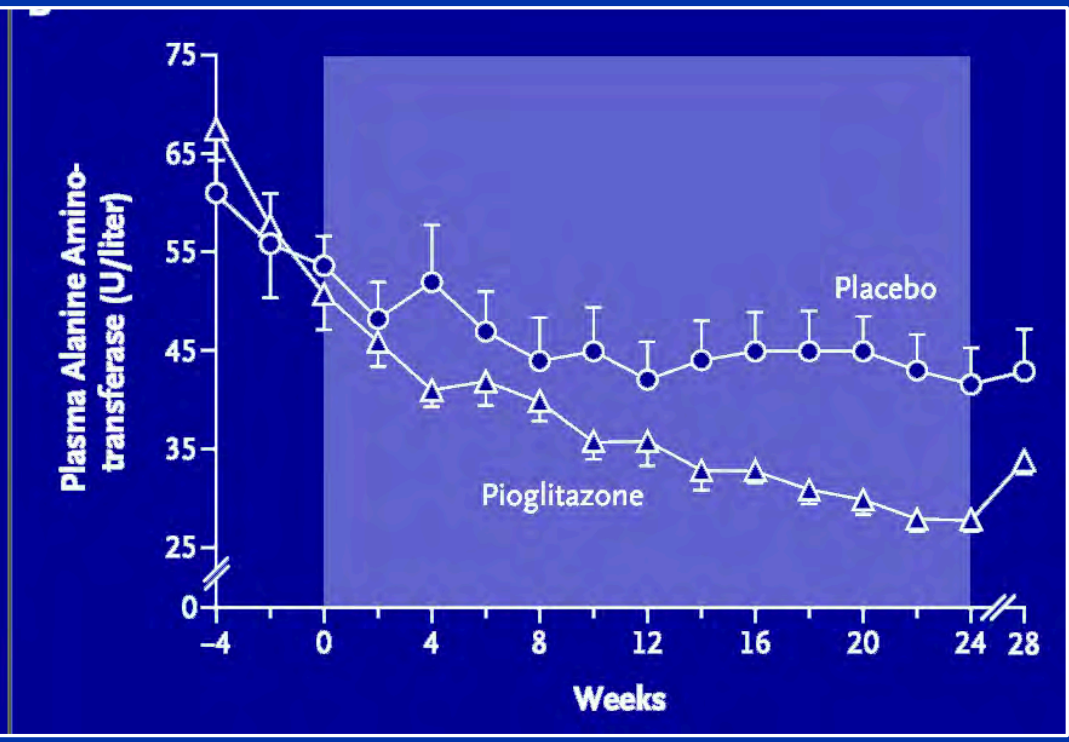
BACKGROUND

Effect of Pioglitazone on AST and ALT

AST over Time

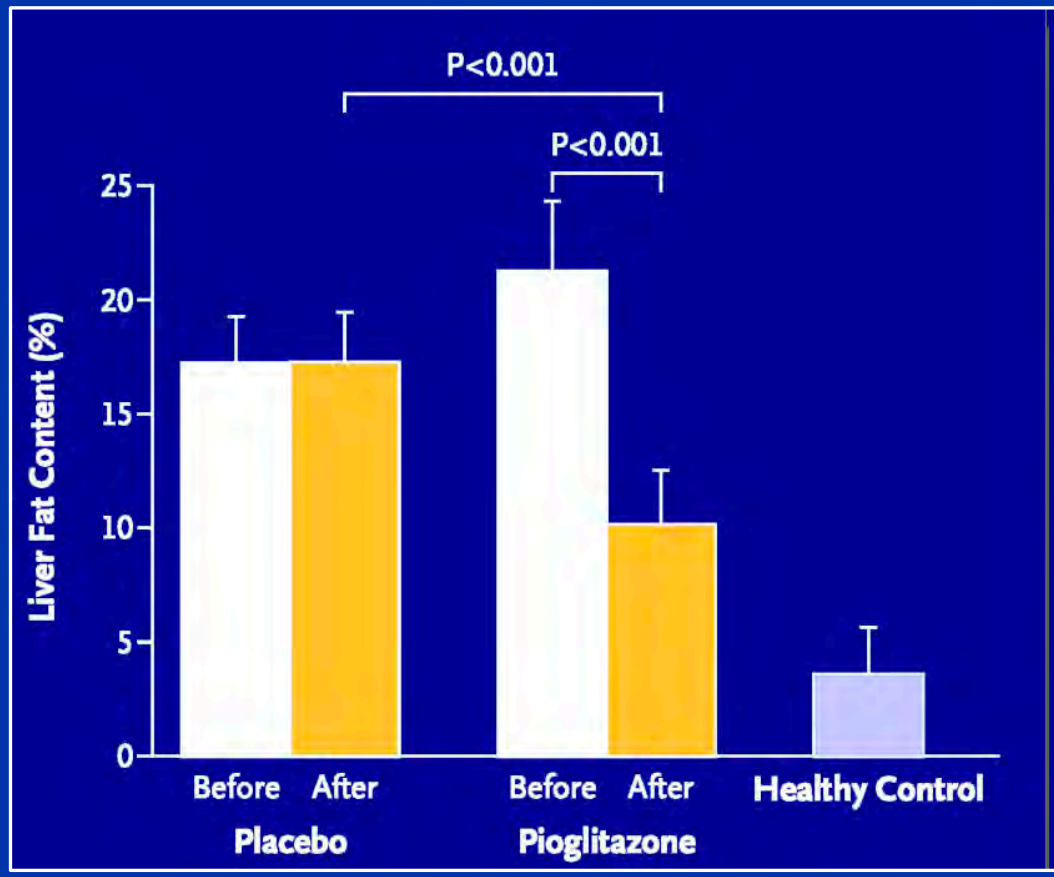


ALT over Time

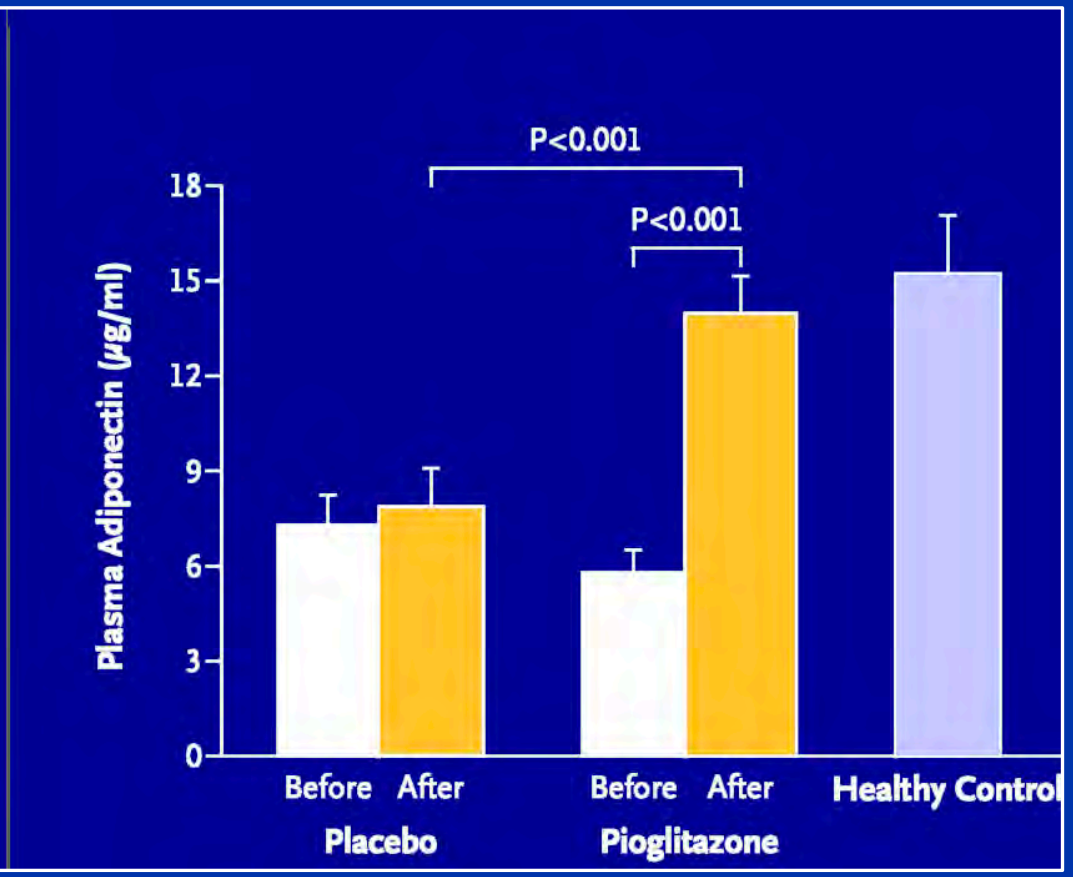


Pioglitazone Effect on Liver Fat and Adiponectin

Liver Fat

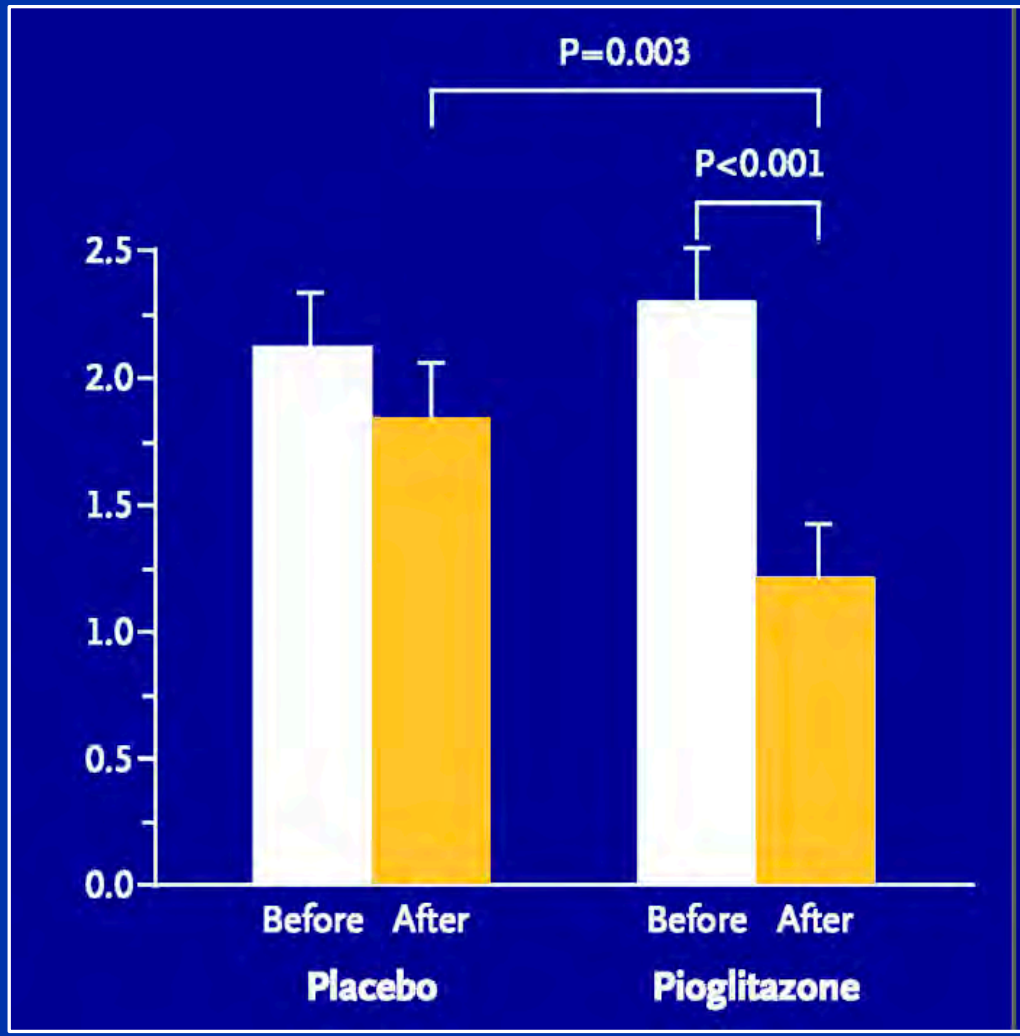


Adiponectin

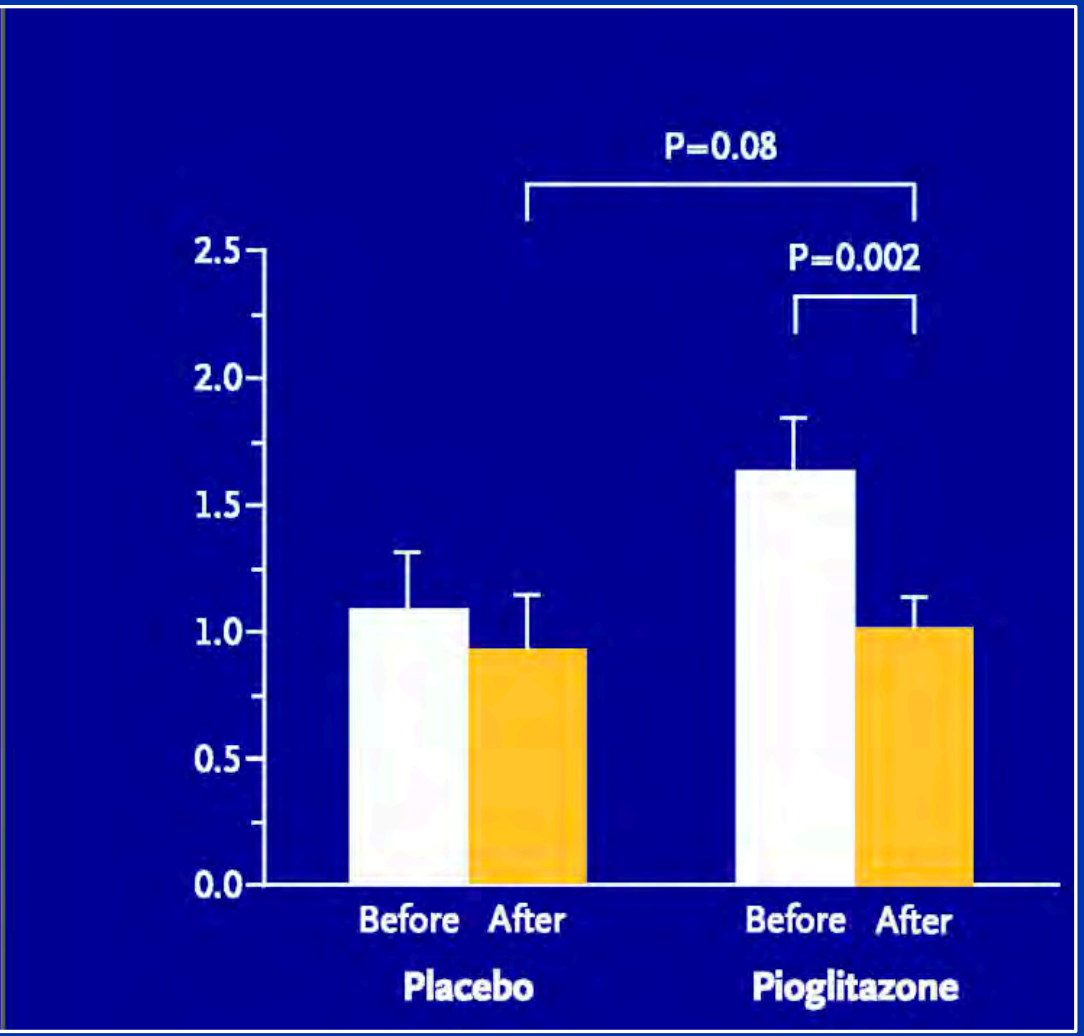


Pioglitazone Effect on Steatosis and Fibrosis

Steatosis

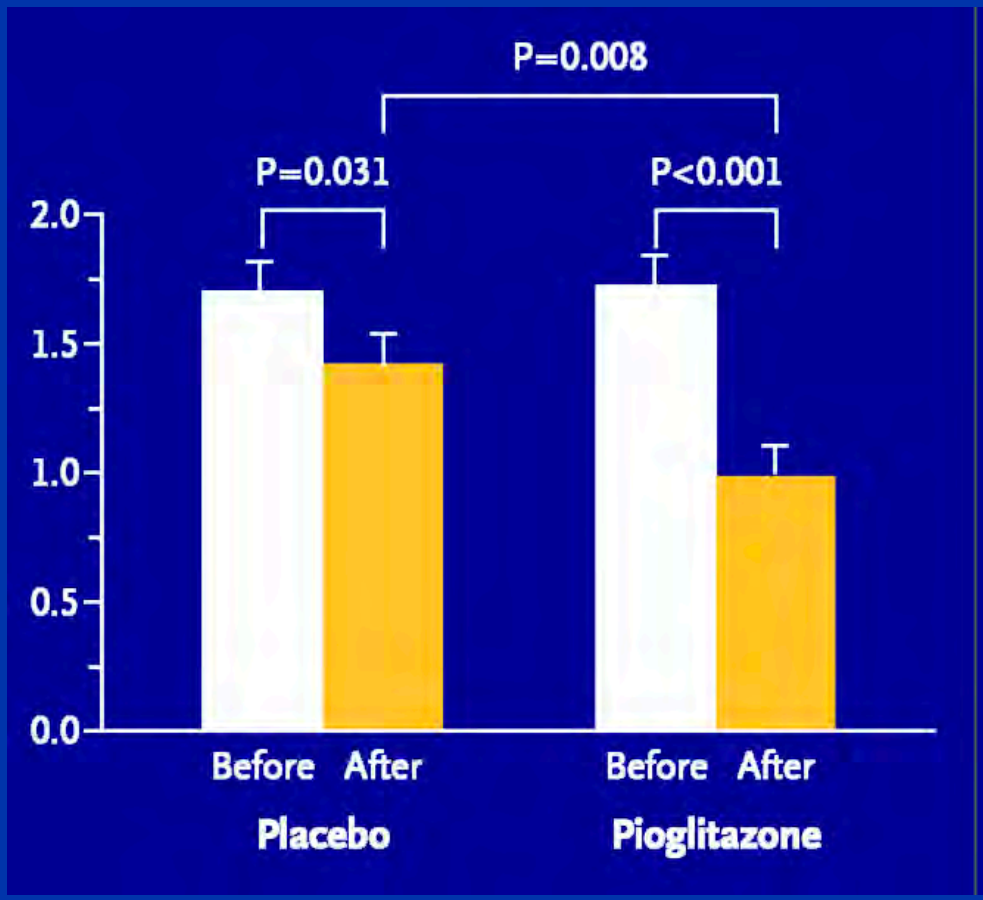


Fibrosis

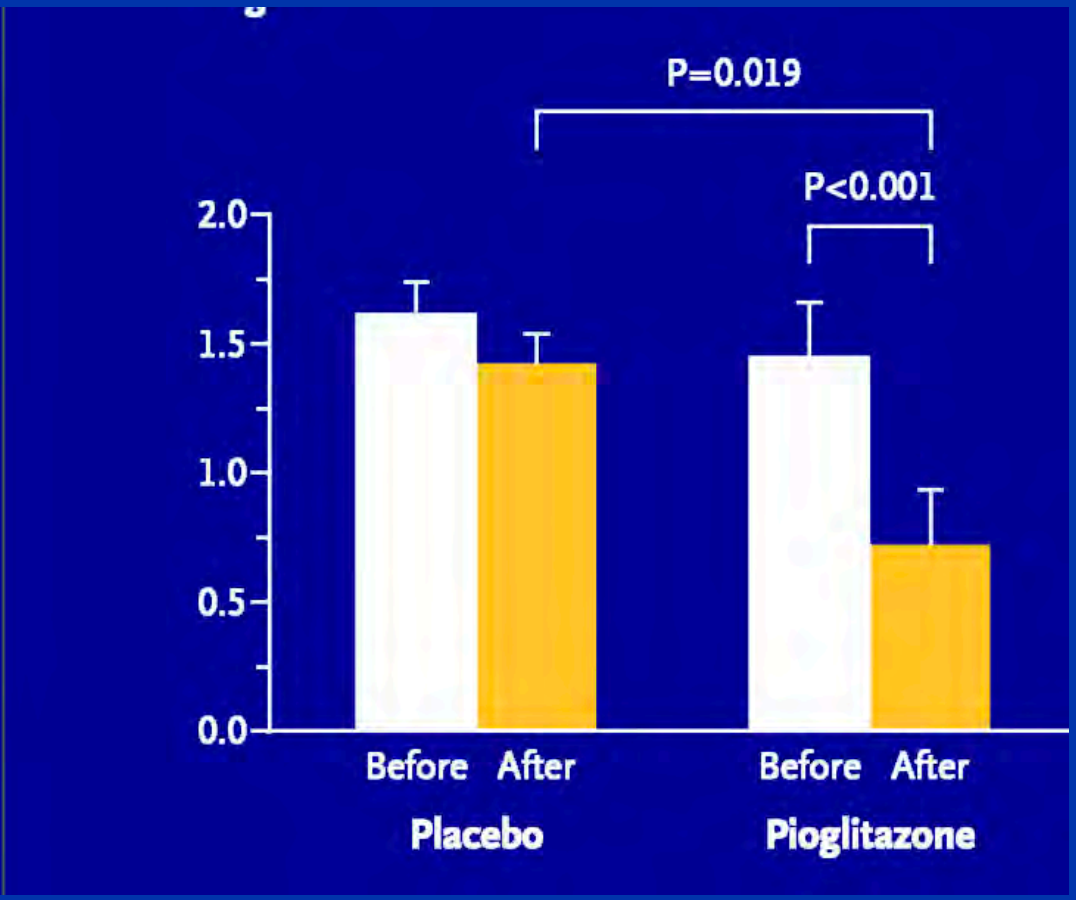


Effect on Inflammation and Ballooning Necrosis

Inflammation



Ballooning Necrosis



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

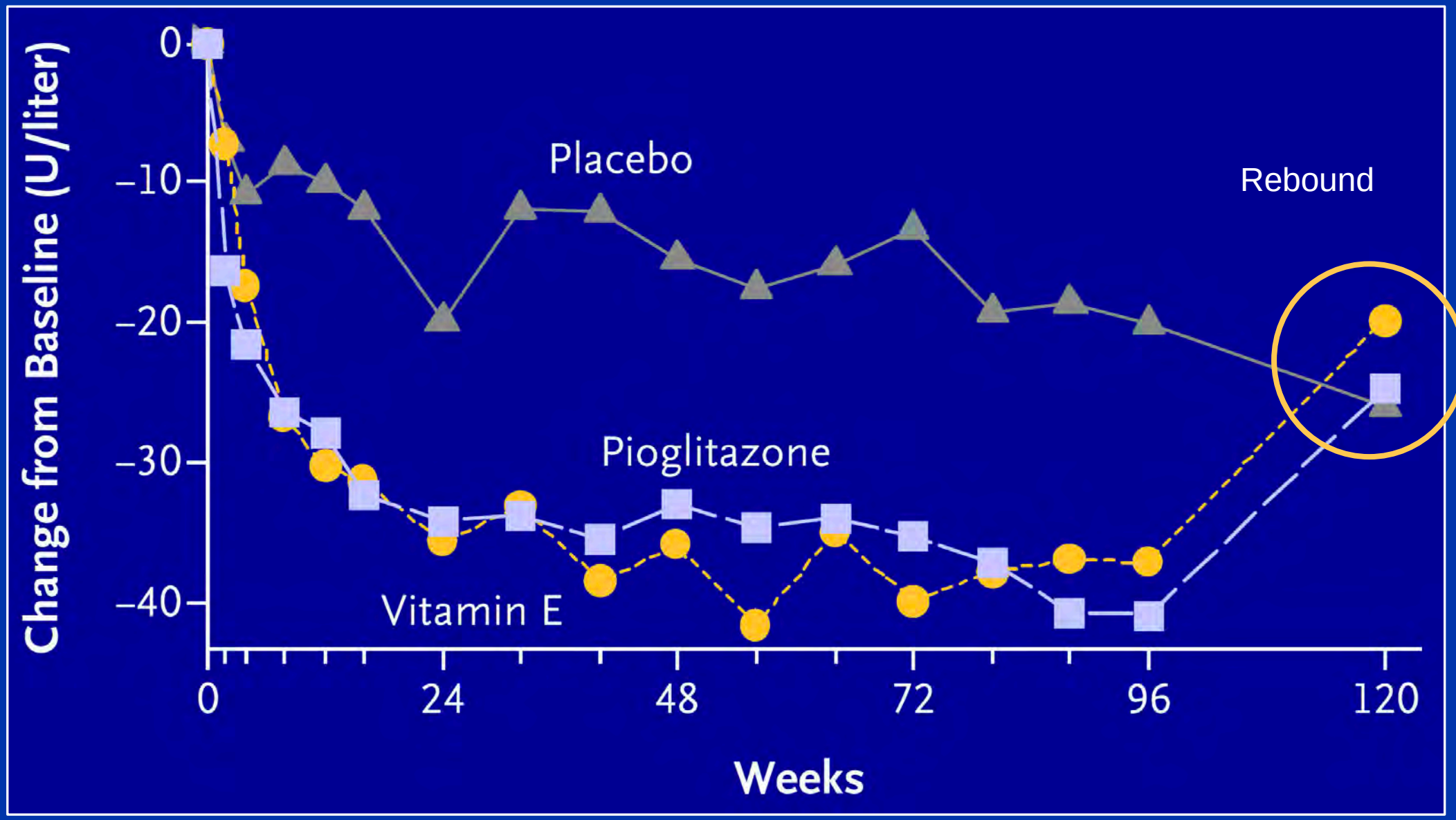
Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

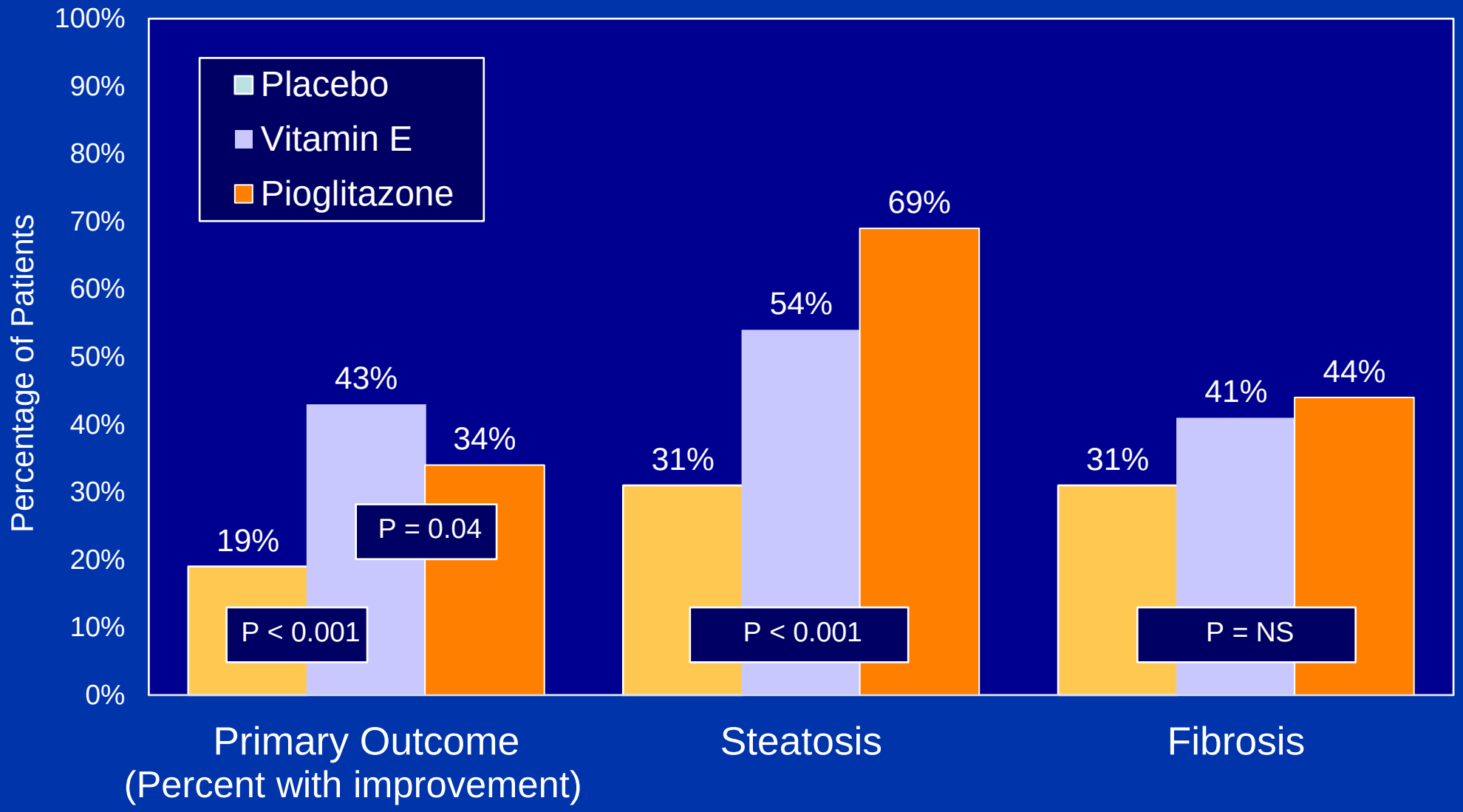
Study Design

- Trial started between 2005 and 2007 sponsored by NIDDK
- 247 adults with biopsy confirmed NASH, but without diabetes
- Randomized to pioglitazone 30 mg daily or vitamin E, 800 IU daily, or placebo (83 subjects), for 96 weeks.
- The primary outcome was an improvement in histologic features of NASH:
  - Assessed with from composite of scores for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis.

Changes in ALT over Time by Treatment Group

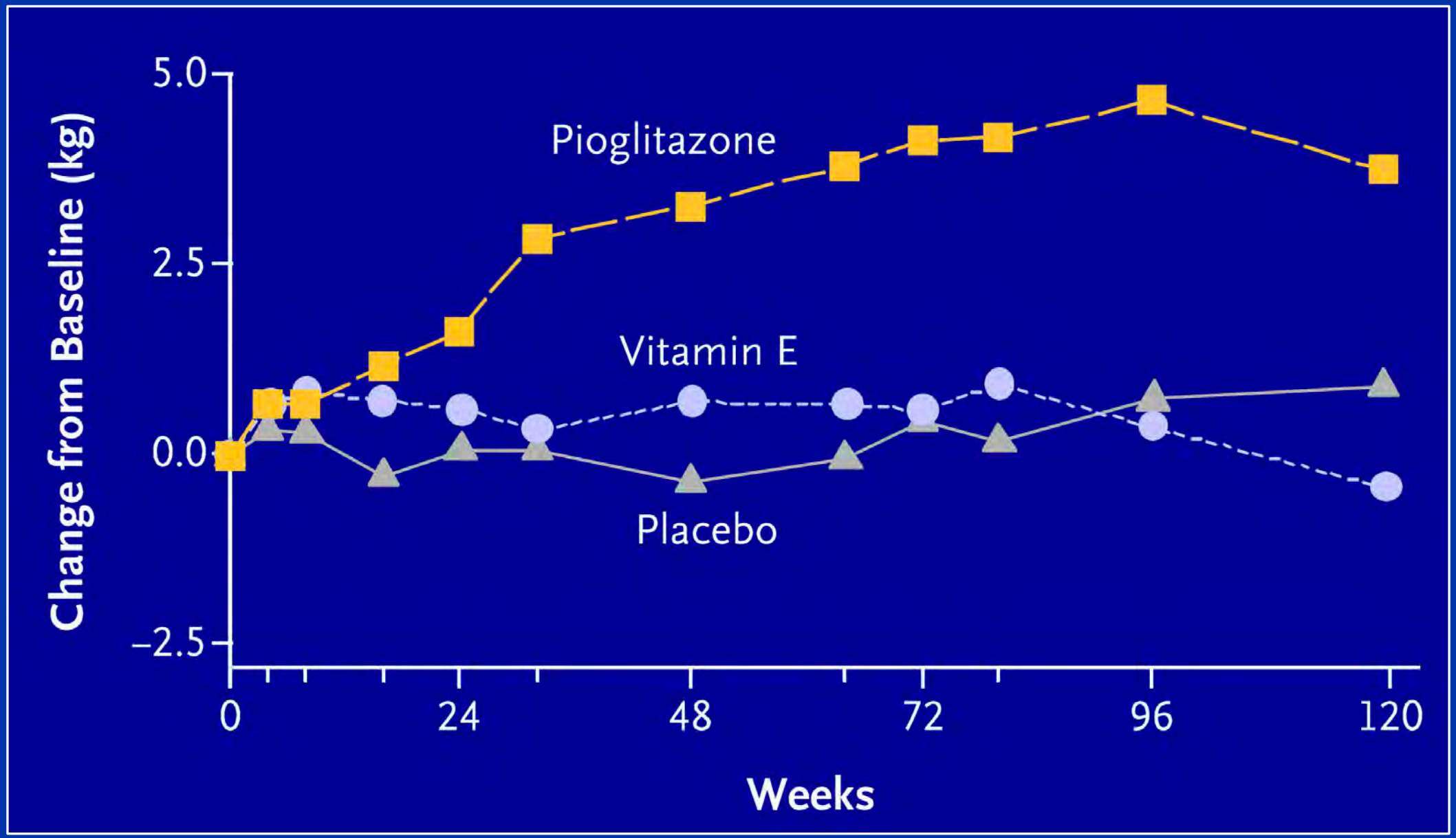


Primary Outcome and Change in Steatosis/Fibrosis



Adapted from N Engl J Med 2010;362:1675-85.

Change in Body Weight by Treatment Group



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

ABSTRACT

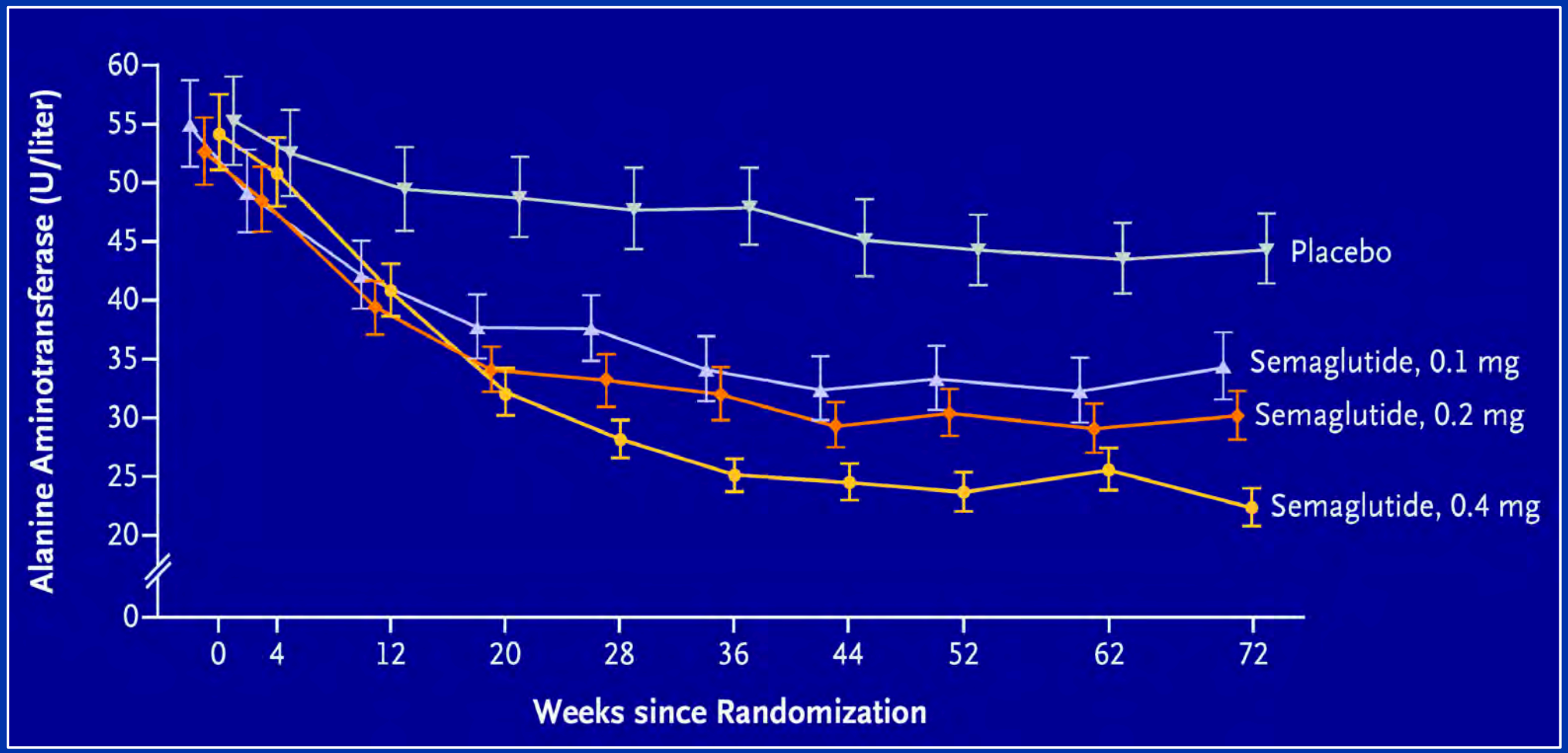
BACKGROUND

Nonalcoholic steatohepatitis (NASH) is a common disease that is associated with

Study Design

- 320 adults with biopsy confirmed NASH, 50% with diabetes
- Randomized to semaglutide 0.1 mg, 0.2 mg, 0.4 mg or placebo for 72 weeks.
- The primary outcome was an improvement in histologic features of NASH with no worsening of fibrosis
- The secondary was improvement fibrosis with no worsening of NASH

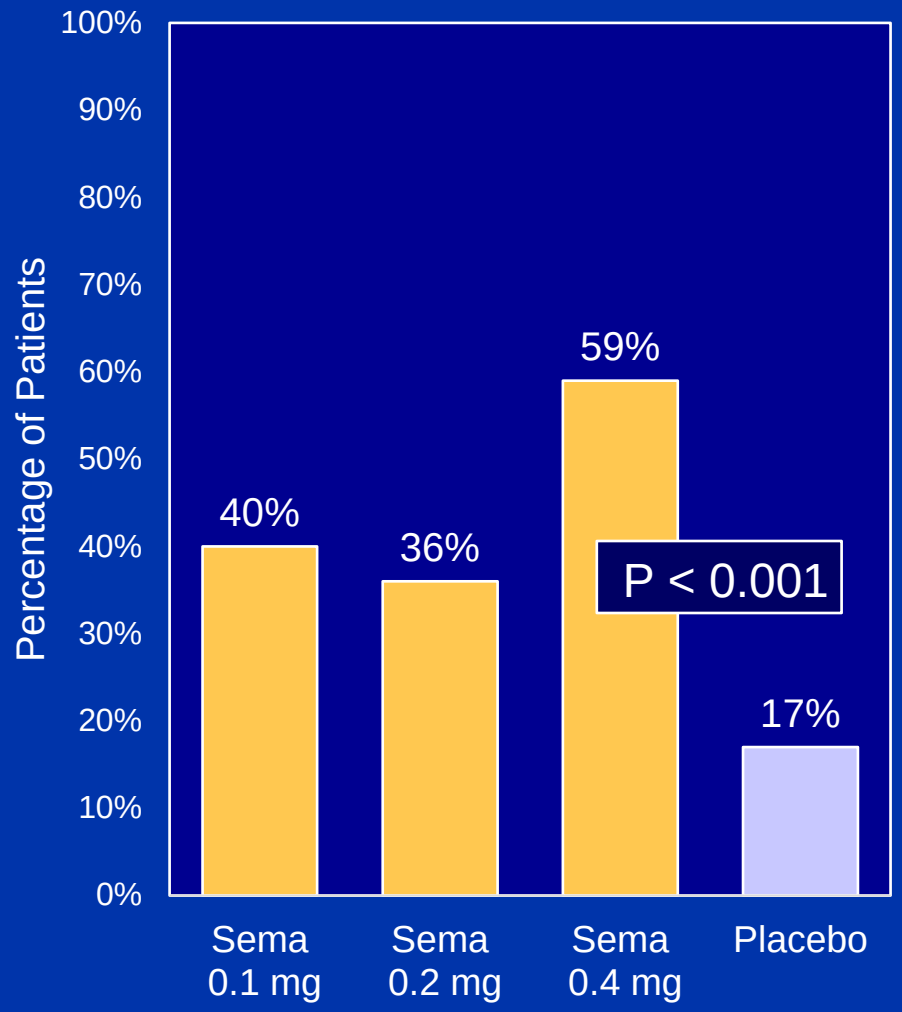
Changes in ALT over Time by Treatment Group



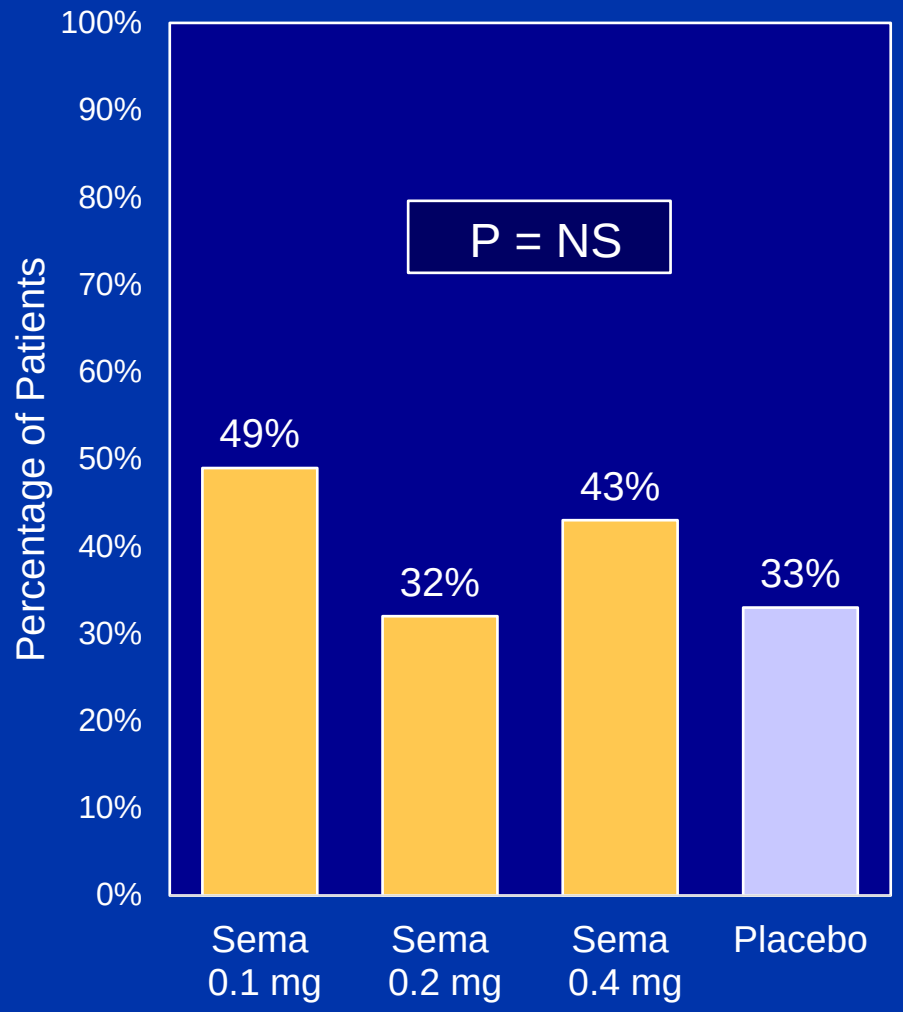
N Engl J Med 2021;384:1113-24.

Primary and Secondary Outcomes by Treatment

NASH resolution without worsening of fibrosis



Improvement in fibrosis stage without worsening of NASH



N Engl J Med 2021;384:1113-24.

Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial

Zobair M Younossi, Vlad Ratziu*, Rohit Loomba, Mary Rinella, Quentin M Anstee, Zachary Goodman, Pierre Bedossa, Andreas Geier, Susanne Beckebaum, Philip N Newsome, David Sheridan, Muhammad Y Sheikh, James Trotter, Whitfield Knapple, Eric Lawitz, Manal F Abdelmalek, Kris V Kowdley, Aldo J Montano-Loza, Jerome Boursier, Philippe Mathurin, Elisabetta Bugianesi, Giuseppe Mazzella, Antonio Olveira, Helena Cortez-Pinto, Isabel Graupera, David Orr, Lise Lotte Gluud, Jean-Francois Dufour, David Shapiro, Jason Campagna, Luna Zaru, Leigh MacConell, Reshma Shringarpure, Stephen Harrison†, Arun J Sanyal†, on behalf of the REGENERATE Study Investigators*

Summary

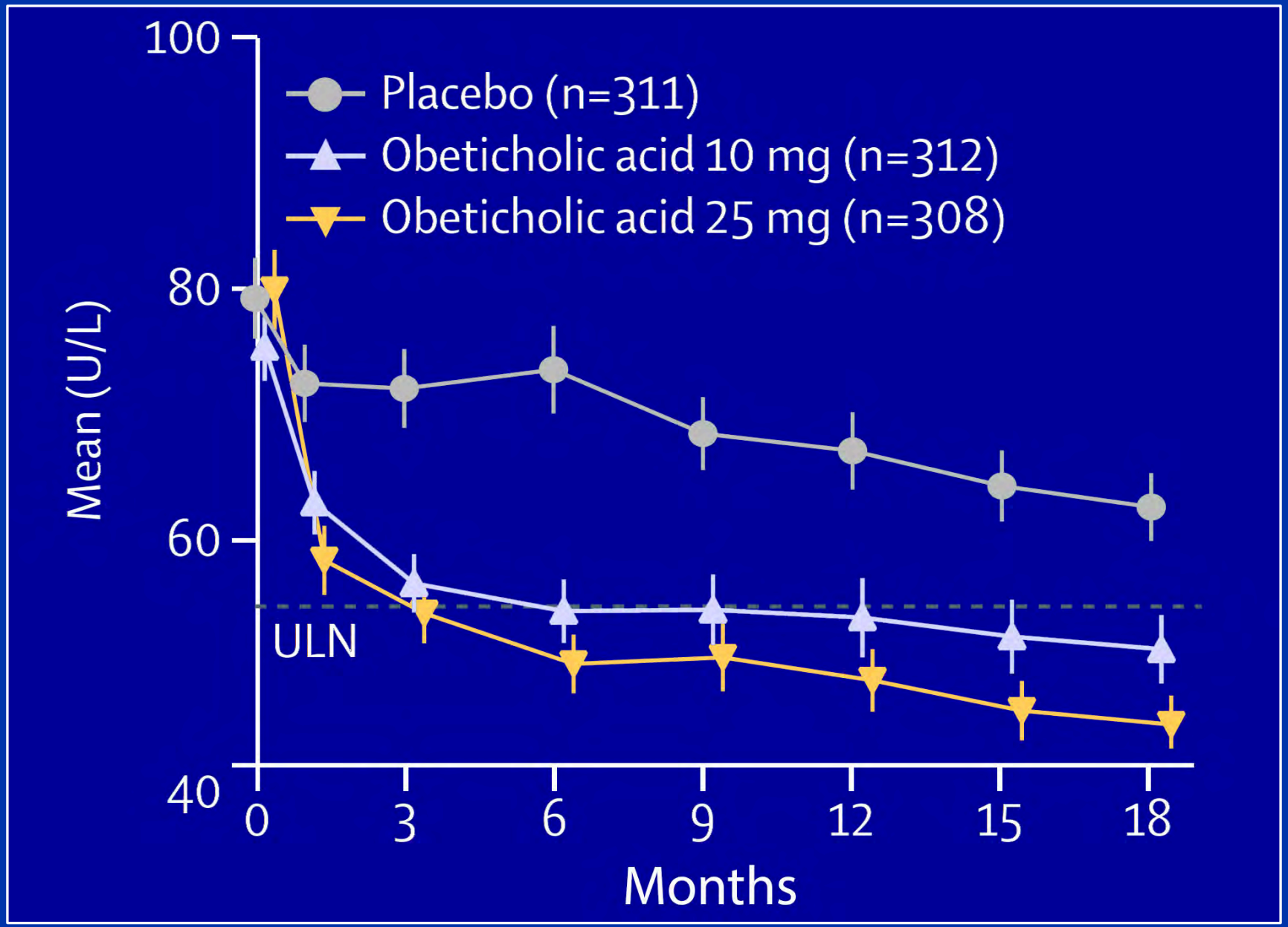
Background Non-alcoholic steatohepatitis (NASH) is a common type of chronic liver disease that can lead to cirrhosis. Obeticholic acid, a farnesoid X receptor agonist, has been shown to improve the histological features of NASH. Here we report results from a planned interim analysis of an ongoing, phase 3 study of obeticholic acid for NASH.

Methods In this multicentre, randomised, double-blind, placebo-controlled study, adult patients with definite NASH, non-alcoholic fatty liver disease (NAFLD) activity score of at least 4, and fibrosis stages F2–F3, or F1 with at least one accompanying comorbidity, were randomly assigned using an interactive web response system in a 1:1:1 ratio to receive oral placebo, obeticholic acid 10 mg, or obeticholic acid 25 mg daily. Patients were excluded if cirrhosis, other chronic liver disease, elevated alcohol consumption, or confounding conditions were present. The primary endpoints for the month-18 interim analysis were fibrosis improvement (≥1 stage) with no worsening of NASH, or NASH resolution with no worsening of fibrosis, with the study considered successful if either primary endpoint was met. Primary analyses were done by intention to treat, in patients with fibrosis stage F2–F3 who received at least one dose of treatment and reached, or would have reached, the month 18 visit by the prespecified interim analysis cutoff date.

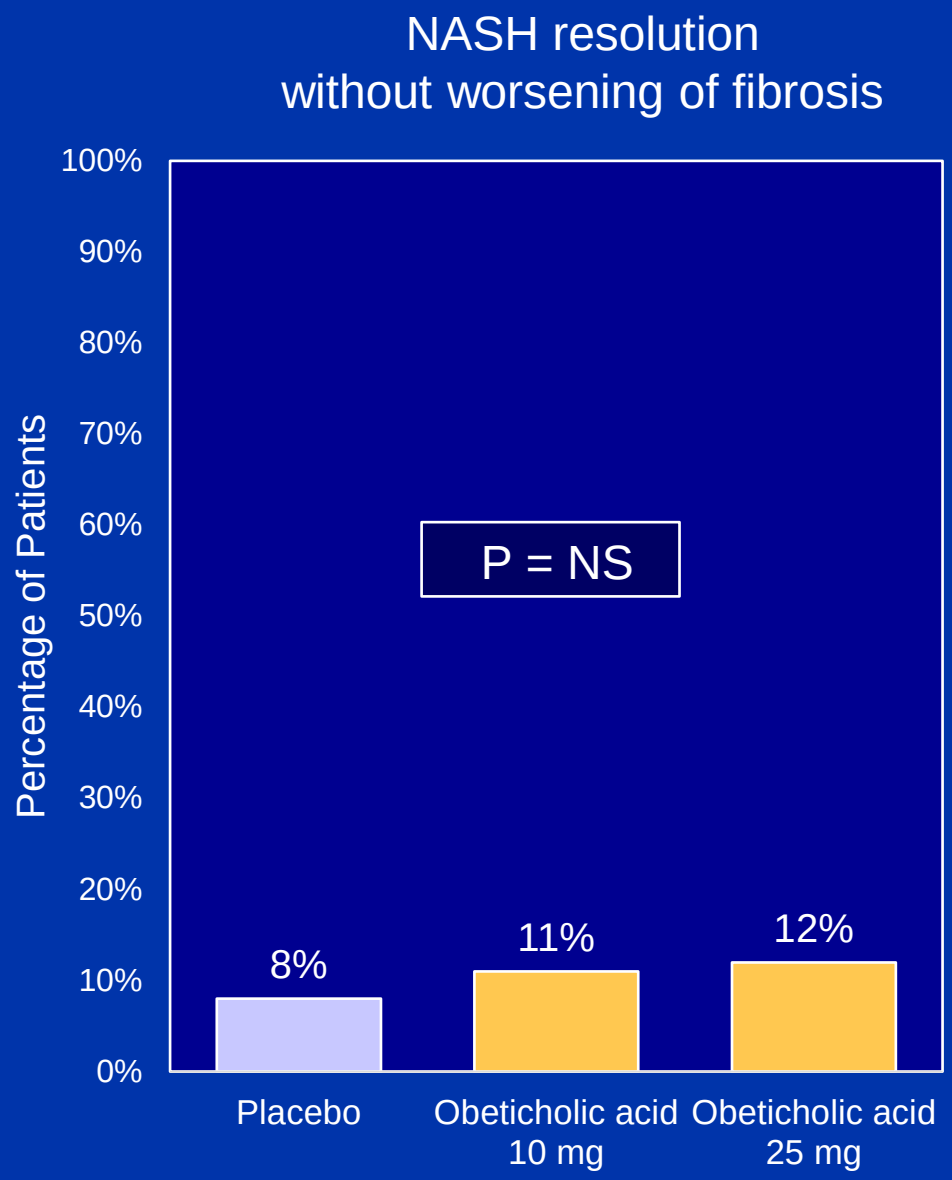
Study Design

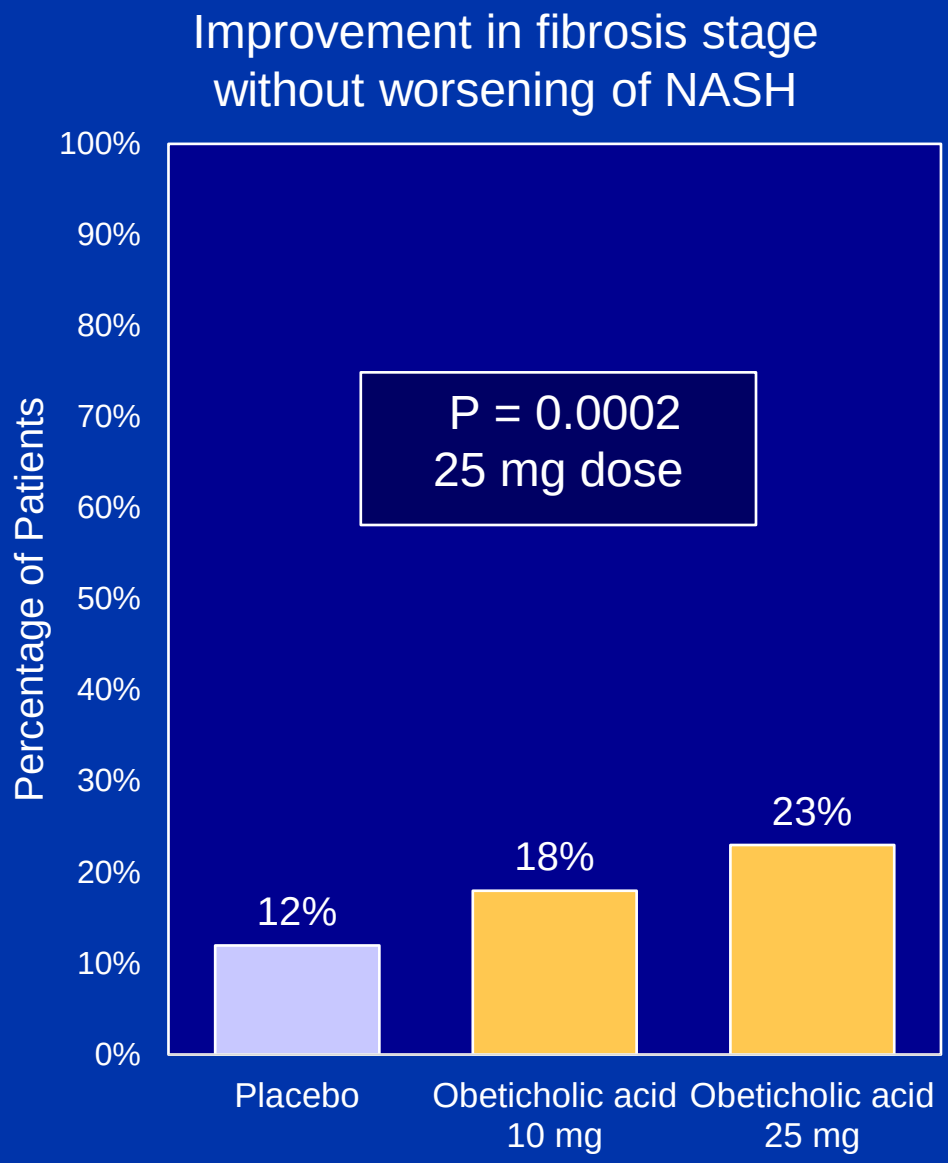
- 1968 adults with biopsy confirmed NASH, 56% with diabetes
- Randomized to FXR agonist obeticholic acid 10 mg, 20 mg, or placebo for 18 months.
- For this interim analysis co-primary outcome was
  - Either improvement in histologic features of NASH with no worsening of fibrosis or improvement in fibrosis with no worsening of NASH

Changes in ALT over Time by Treatment Group



Co-Primary Outcomes by Treatment Group





Adapted from Lancet 2019; 394: 2184–96

Obeticholic Acid Status

- Approved in 2016 for primary biliary cirrhosis (PBC)
- FDA added warning in 2017 for use in advanced PBC due to increased risk of liver injury and death when improperly dosed
- In 2021, FDA restricted use in PBC patients with advanced cirrhosis, but stated that benefits exceed risks in patient who do not have advanced cirrhosis
- FDA rejected application for approval for treatment of NASH, requesting more evidence of benefit.

Healio NEWS
Gastroenterology

May 19, 2023

‘Unfavorable benefit-risk’: FDA panel votes against obeticholic acid approval for NASH

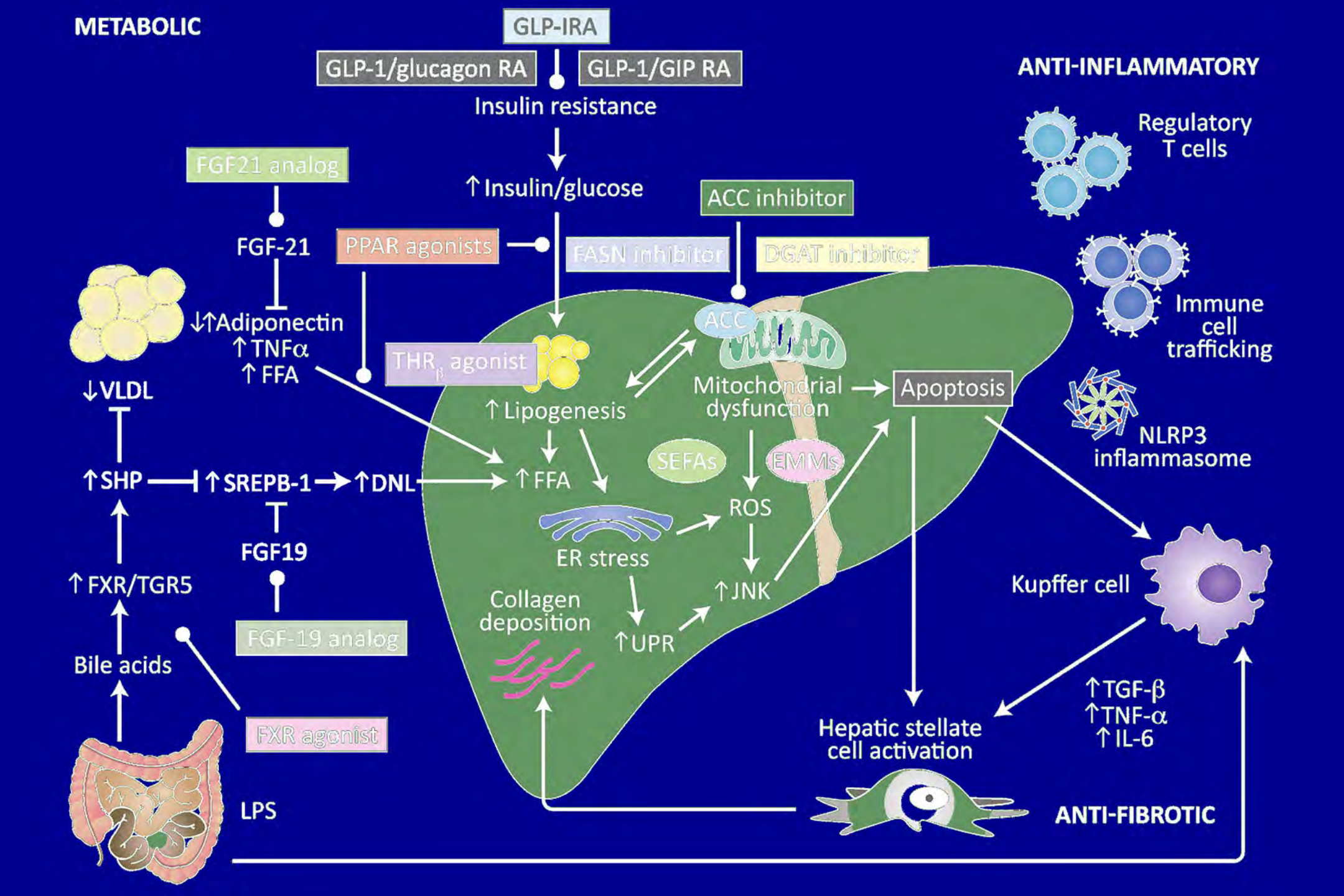
Key takeaways:

•FDA panel voted 12-2 against approval for obeticholic acid for pre-cirrhotic patients with liver fibrosis due to nonalcoholic steatohepatitis.

•Advisors reported a “concerning” benefit-risk profile for obeticholic acid.

An FDA advisory committee voted against approval for obeticholic acid in pre-cirrhotic patients with liver fibrosis due to nonalcoholic steatohepatitis, citing a “concerning” benefit-risk profile.

The Gastrointestinal Drug Advisory Committee voted 12 to 2 with 2 abstentions that the benefits of 25 mg obeticholic acid (Ocaliva, Intercept Pharmaceuticals) do not outweigh its risks among patients with NASH and stage 2 or 3 fibrosis, most notably drug-induced liver injury and quality of life.


METABOLIC
GLP-IRA
GLP-1/glucagon RA
GLP-1/GIP RA
Insulin resistance
ANTI-INFLAMMATORY
Regulatory T cells
FGF21 analog
↑Insulin/glucose
ACC inhibitor
FGF-21
PPAR agonists
FASN inhibitor
DGAT inhibitor
Immune cell trafficking
↓↑Adiponectin
↑TNFα
↑FFA
ACC
THRβ agonist
↓VLDL
↑Lipogenesis
Mitochondrial dysfunction
Apoptosis
NLRP3 inflammasome
↑SHP
↑SREPB-1
↑DNL
↑FFA
SEFAs
EMVs
ROS
FGF19
ER stress
↑FXR/TGR5
Collagen deposition
↑UPR
↑JNK
Kupffer cell
FGF-19 analog
Bile acids
↑TGF-β
↑TNF-α
↑IL-6
FXR agonist
Hepatic stellate cell activation
LPS
ANTI-FIBROTIC

Is a NASH treatment on the horizon?

First indicated drug possible in early 2020

Drug Name	Developer	Development Notes	Future Activity
obeticholic acid	Intercept	Goal: fibrosis improvement and NASH resolution.[a] New drug application filed September 2019.[b]	FDA approval possible Q2 2020.[b]
elafibranor	Genfit	Goal: NASH resolution.[a] Phase 3 trial results expected Q1 2020.[c]	Filing with the FDA expected by the end of 2020.[c]
cenicriviroc	Allergan	Goal: fibrosis improvement.[a] Phase 3 results expected August 2020.[d]	Possible release in Q4 2021.[d]
selonsertib	Gilead	Goal: fibrosis improvement without worsening of NASH.[a] Phase 3 results in April 2019 showed inferior to placebo.[e]	Phase 2 trial for 3-drug combination including selonsertib in-progress.[e]

All these drugs failed to meet FDA specified favorable outcomes

AMERICAN LIVER FOUNDATION™

NASH Treatment

1. Lose weight

This is one of the best treatments for NAFLD and NASH, because it moderates the conditions that contribute to fatty liver disease. Losing just 3 to 5 percent of your body weight can reduce fat in your liver; losing 7 percent can decrease inflammation as well. If you are overweight or obese, doctors typically recommend you gradually lose 7 to 10 percent of your body weight over the course of one year. Rapid weight loss through fasting is not recommended, as it can make NAFLD worse.

Effect of Weight Loss Through Bariatric Surgery

JAMA | Original Investigation

Association of Bariatric Surgery With Major Adverse Liver and Cardiovascular Outcomes in Patients With Biopsy-Proven Nonalcoholic Steatohepatitis

Ali Aminian, MD; Abbas Al-Kurd, MD; Rickesha Wilson, MD; James Bena, MS; Hana Fayazzadeh, MD; Tavankit Singh, MD; Vance L. Albaugh, MD, PhD; Faiz U. Shariff, MD; Noe A. Rodriguez, MD; Jian Jin, MS; Stacy A. Brethauer, MD, MBA; Srinivasan Dasarathy, MD; Naim Alkhouri, MD; Philip R. Schauer, MD; Arthur J. McCullough, MD; Steven E. Nissen, MD

IMPORTANCE No therapy has been shown to reduce the risk of serious adverse outcomes in patients with nonalcoholic steatohepatitis (NASH).

OBJECTIVE To investigate the long-term relationship between bariatric surgery and incident major adverse liver outcomes and major adverse cardiovascular events (MACE) in patients with obesity and biopsy-proven fibrotic NASH without cirrhosis.

DESIGN, SETTING, AND PARTICIPANTS In the SPLENDOR (Surgical Procedures and Long-term Effectiveness in NASH Disease and Obesity Risk) study, of 25 828 liver biopsies performed at a US health system between 2004 and 2016, 1158 adult patients with obesity were identified who fulfilled enrollment criteria, including confirmed histological diagnosis of NASH and presence of liver fibrosis (histological stages 1-3). Baseline clinical characteristics, histological disease activity, and fibrosis stage of patients who underwent simultaneous liver biopsy at the time of bariatric surgery were balanced with a nonsurgical control group using overlap weighting methods. Follow-up ended in March 2021.

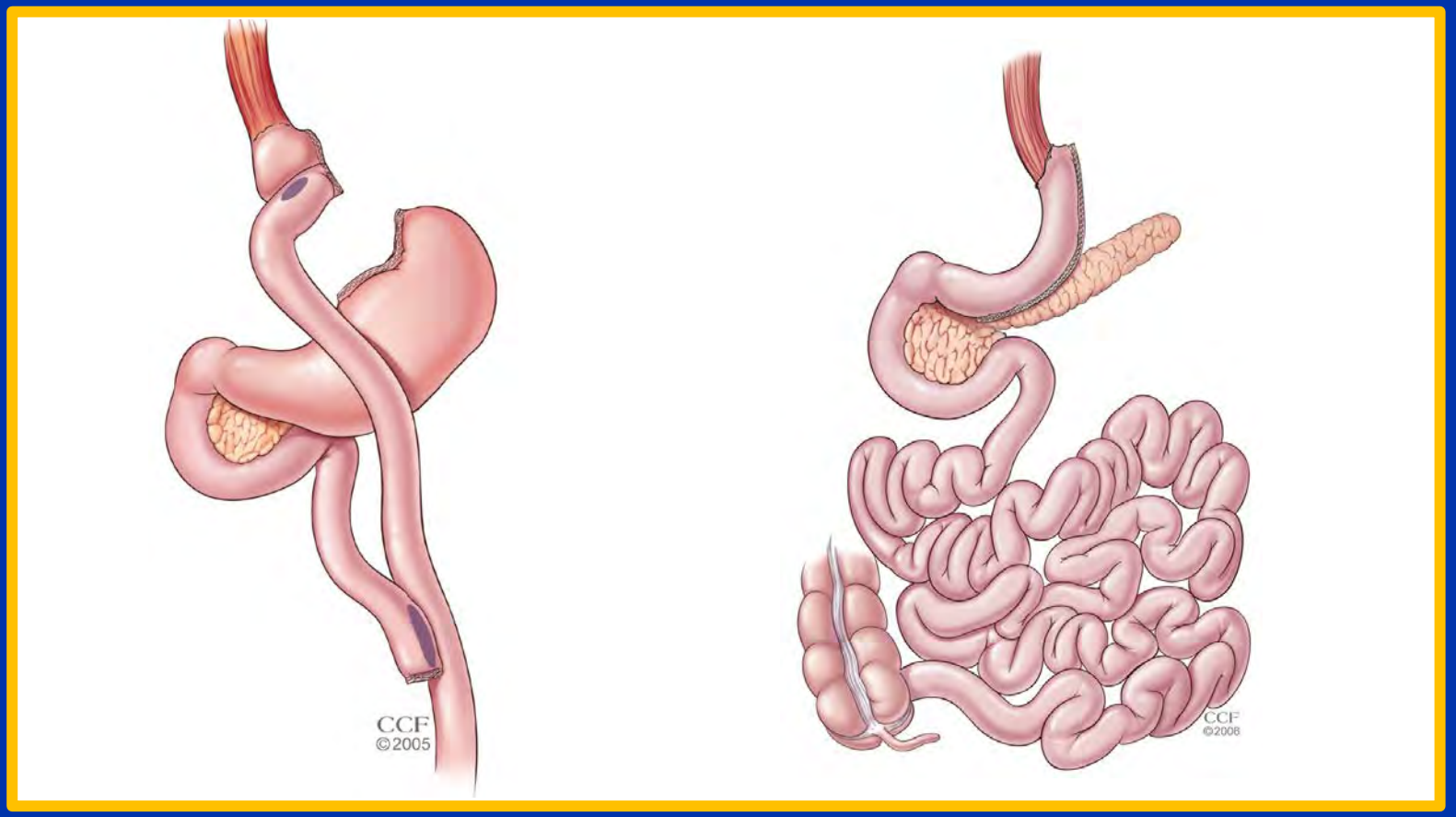
EXPOSURES Bariatric surgery (Roux-en-Y gastric bypass, sleeve gastrectomy) vs nonsurgical care

Editorial

Supplemental content

CME Quiz at jamacmelookup.com

Metabolic Surgical Procedures (N=650)

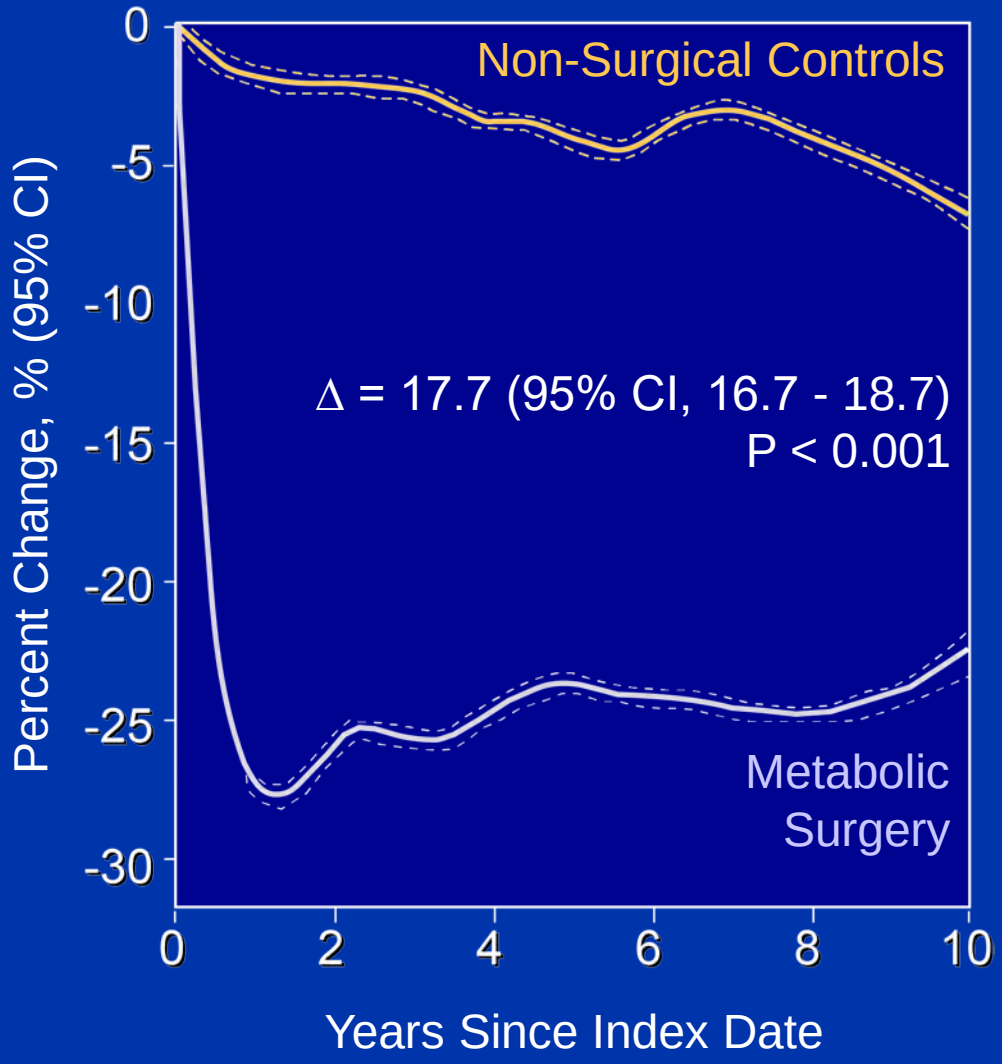


Gastric Bypass
N=537 (83%)

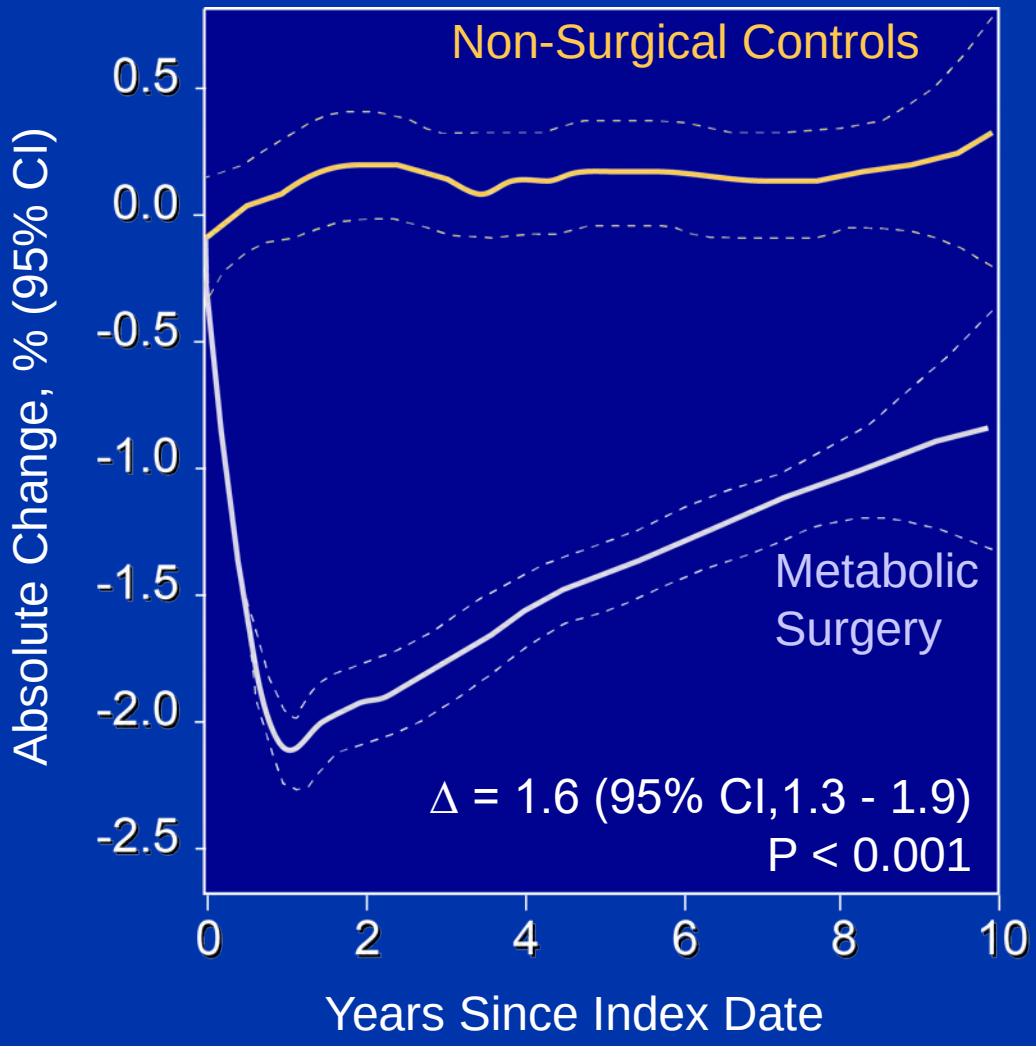
Sleeve Gastrectomy
N=113 (17%)

Metabolic Surgery: Effect on Weight and HbA1c

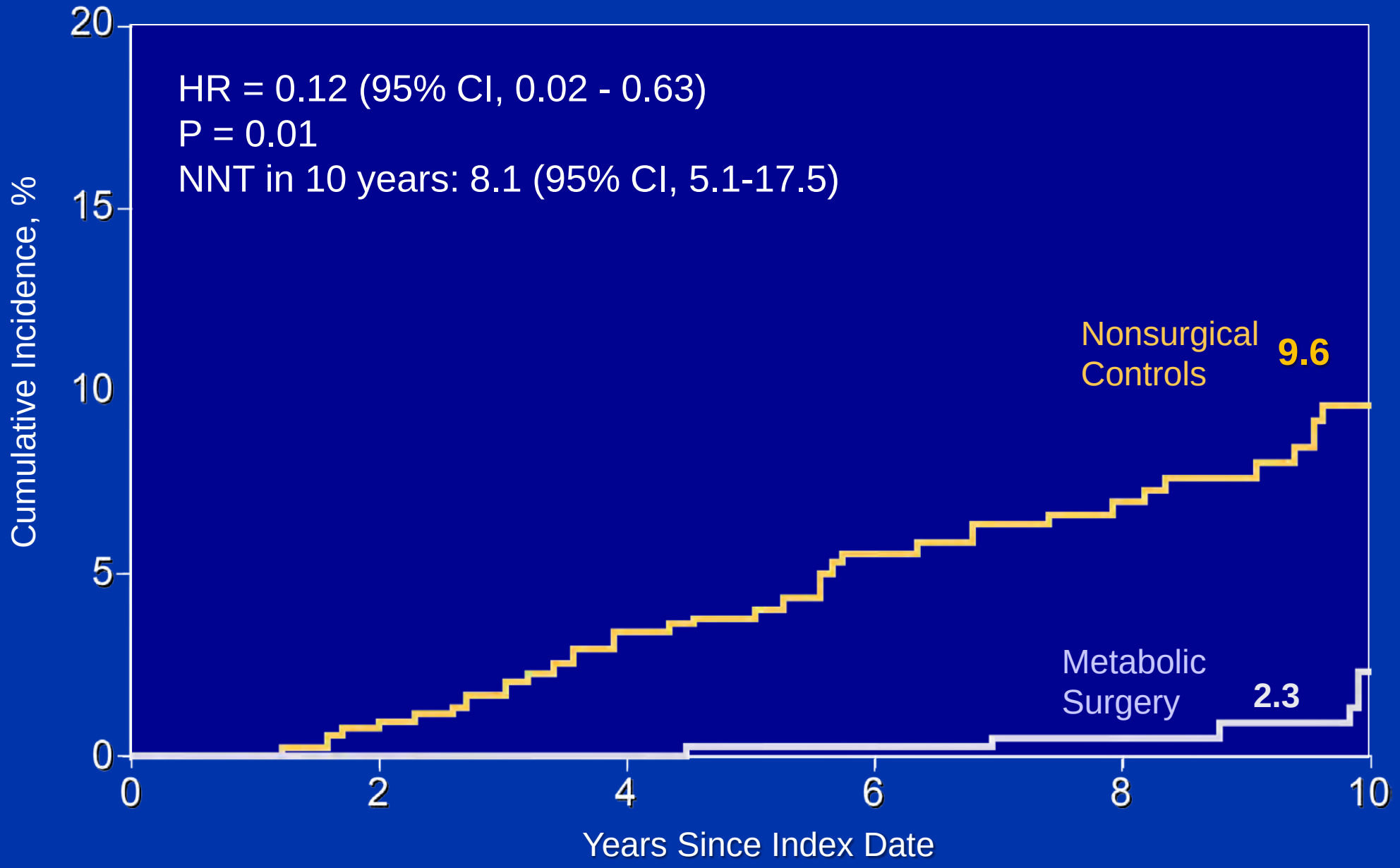
Total Weight Loss (%)



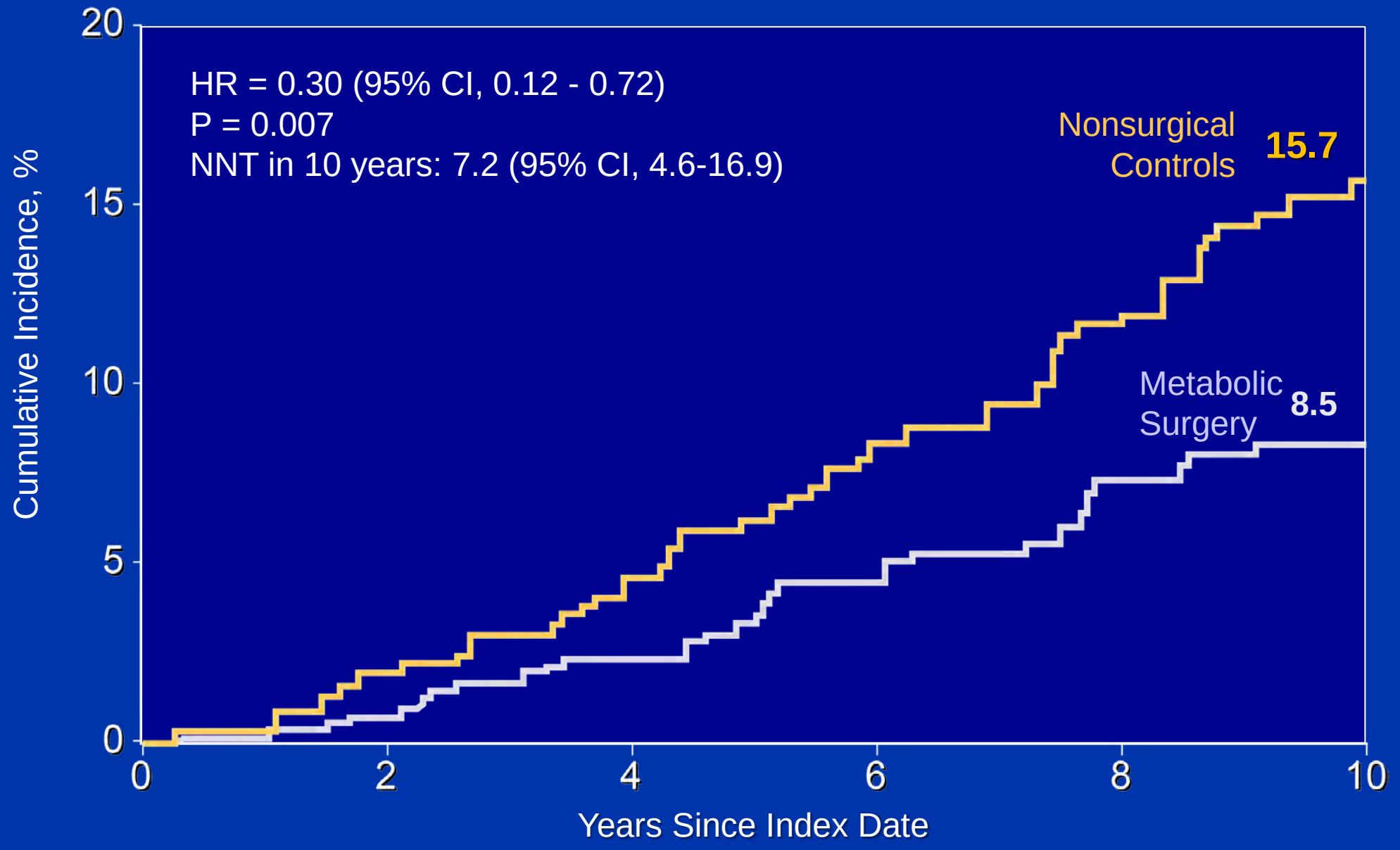
HbA1c Change (%)



Major Adverse Liver Outcomes (MALO)

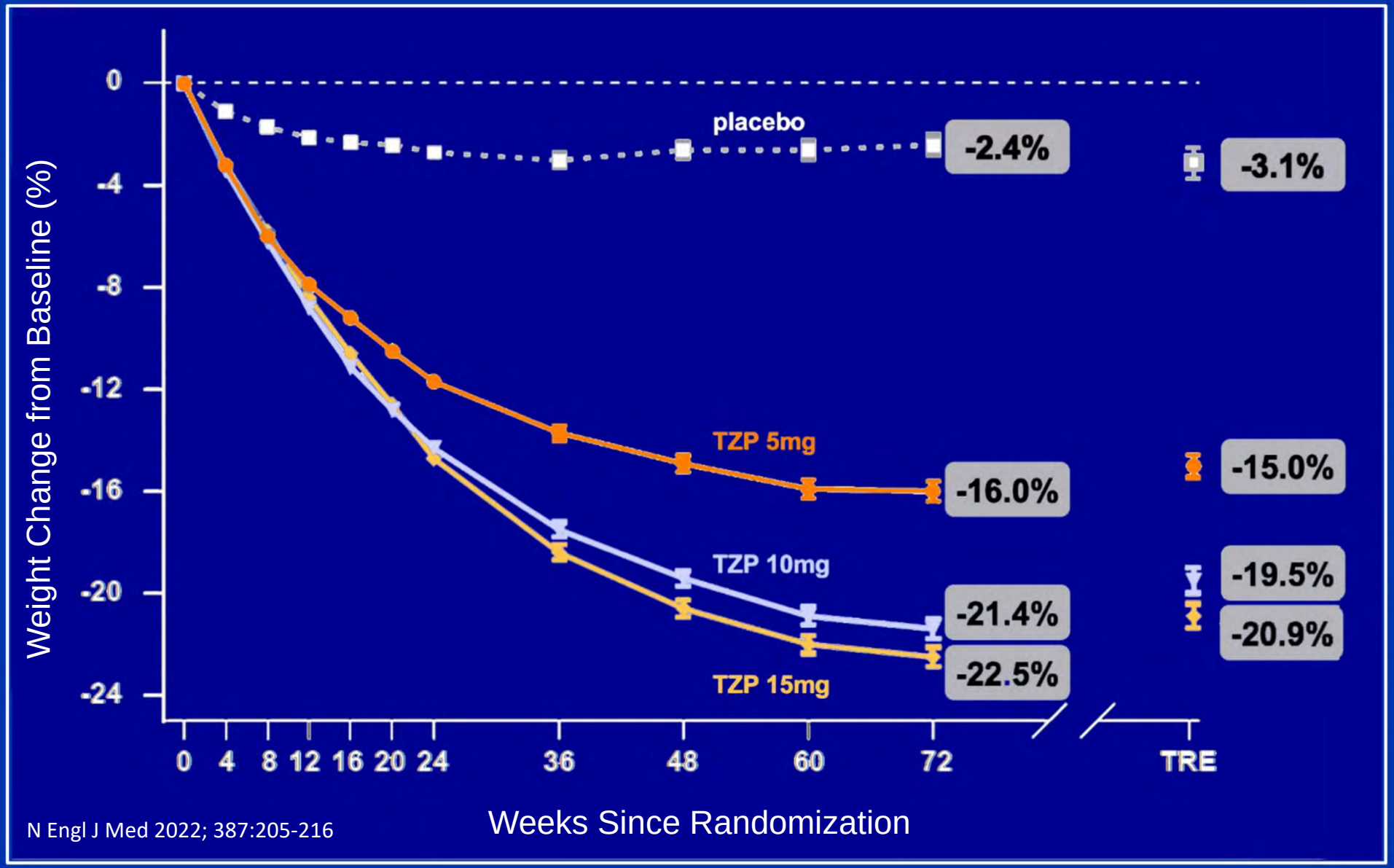


Major Adverse Cardiovascular Events (MACE)



Can newer pharmacological therapies achieve the weight loss offered by bariatric surgery?

Change in Body Weight by Dose (72 Weeks)



N Engl J Med 2022; 387:205-216

Summary

- NAFLD is very common, associated with obesity and diabetes, and a leading cause of cirrhosis, potentially leading to cancer.
- Detection often starts with abnormal liver enzyme on routine lab panel and liver ultrasound is the easiest next step.
- Some scoring systems can predict progression of NAFLD to NASH and cirrhosis.
- Lifestyle management very important, particularly weight loss
- No drugs approved yet. Weight loss through bariatric surgery appears to greatly reduce likelihood of disease progression

Prespecified Composite Endpoints

- First occurrence of major adverse cardiovascular events (MACE):
  - Coronary artery events, cerebrovascular events, heart failure, or cardiovascular mortality.
- First occurrence of Major Liver Events (MALO):
  - Progression to clinical or histologic (F4 on repeat liver biopsy) cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver-related mortality.

Statistical Analysis

- 650 surgical patients (with simultaneous liver biopsy) & 508 nonsurgical control patients were followed through March 2021.
- Doubly robust estimation combining the overlap weighting and outcome regression.
  - 6 *a priori*–identified potential confounders were used for overlap weighting.
  - Firth's penalized method in fully-adjusted Cox proportional hazard framework was utilized by adjusting models for 17 variables.