

# **Nonalcoholic Fatty Liver Disease Management & Treatment Options**

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**No Disclosures**

# Objectives

- 1. Definition and Epidemiology of NAFLD**
- 2. Clinical Features and Diagnosis of NAFLD**
- 3. Non-pharmacologic and Pharmacologic Management of NAFLD**

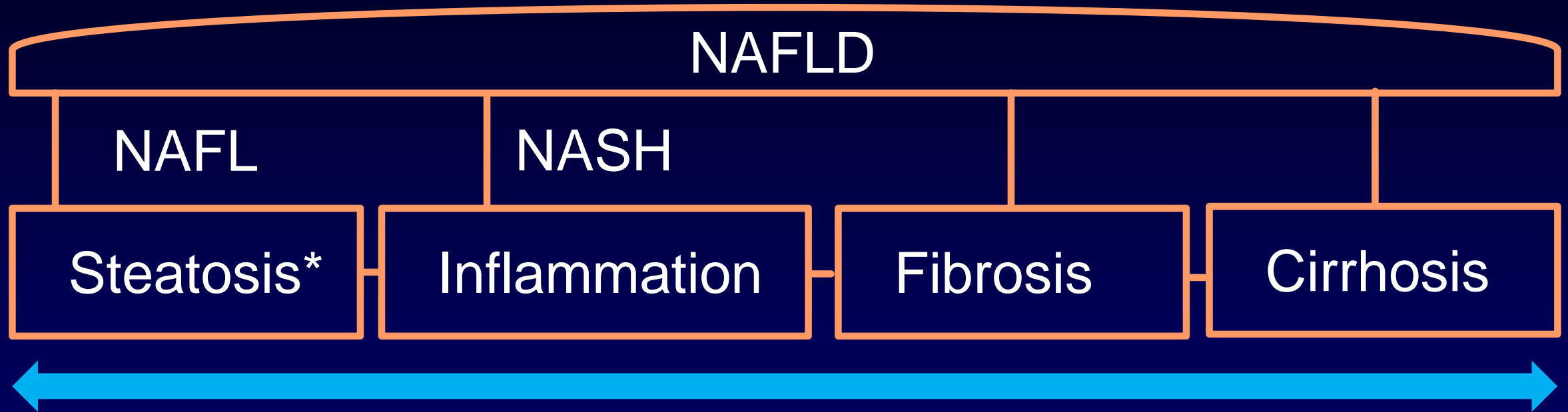
# Non-Alcoholic Fatty Liver Disease (NAFLD)

- Alcohol-like liver disease in individuals who do not consume significant amount of alcohol
  - ( ♂ : >21 drinks/week) ~2 year time, ≥3 drinks/d
  - ( ♀ : >14 drinks/week) ~2 year time, ≥2 drinks/d

# Definition of NALFD

- Evidence of hepatic steatosis (imaging/histology)
- Lack of secondary causes of hepatic fat accumulation:
  - significant alcohol consumption
  - long term use of a steatogenic medication
  - monogenic hereditary disorders

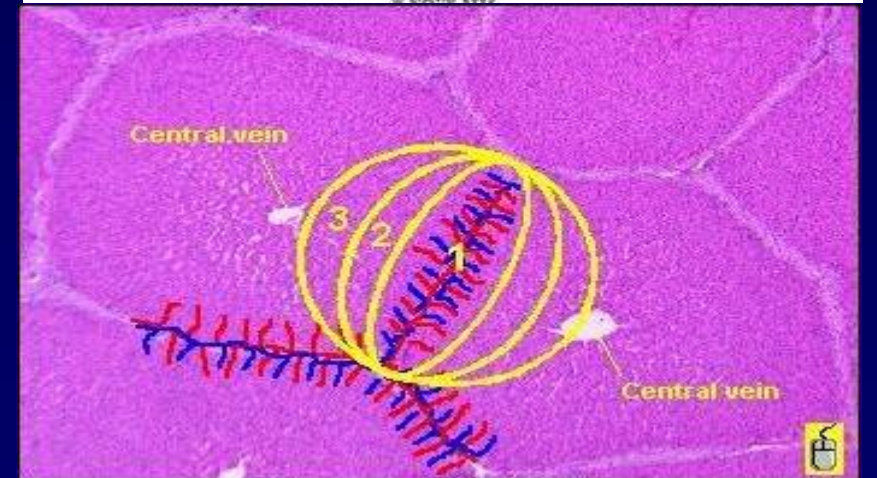
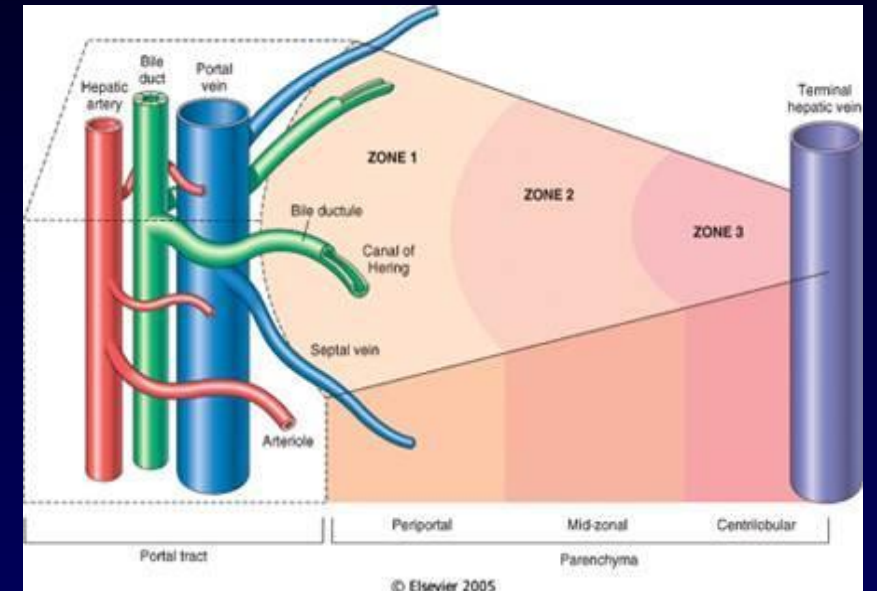
# NAFLD is a spectrum of liver disease



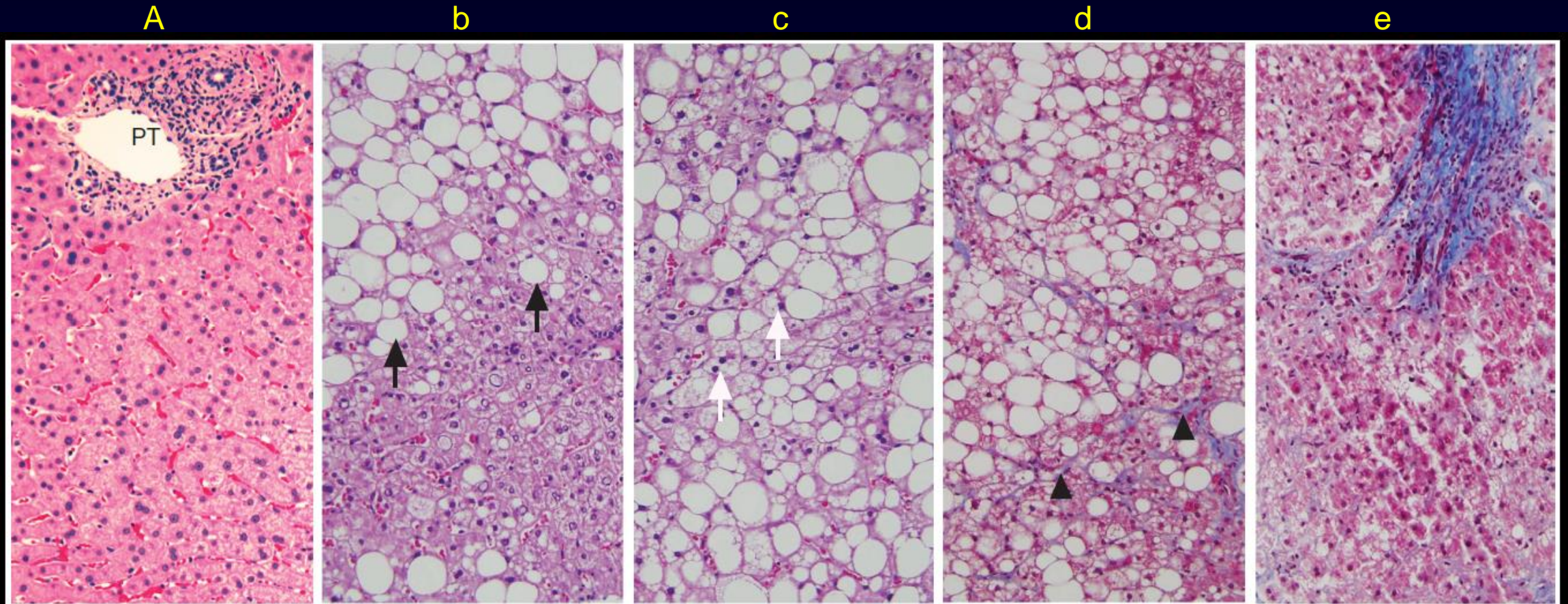
\*  $\geq 5\%$  of hepatocytes

# Steatohepatitis (NASH)

- **Histologic spectrum of liver damage**
  - Steatosis +
  - Lobular inflammation +
  - Cellular injury (ballooning) predominantly centrilobular (zone 3) +
  - Mallory-Dink bodies



# Histologic Spectrum of NAFLD



Normal liver

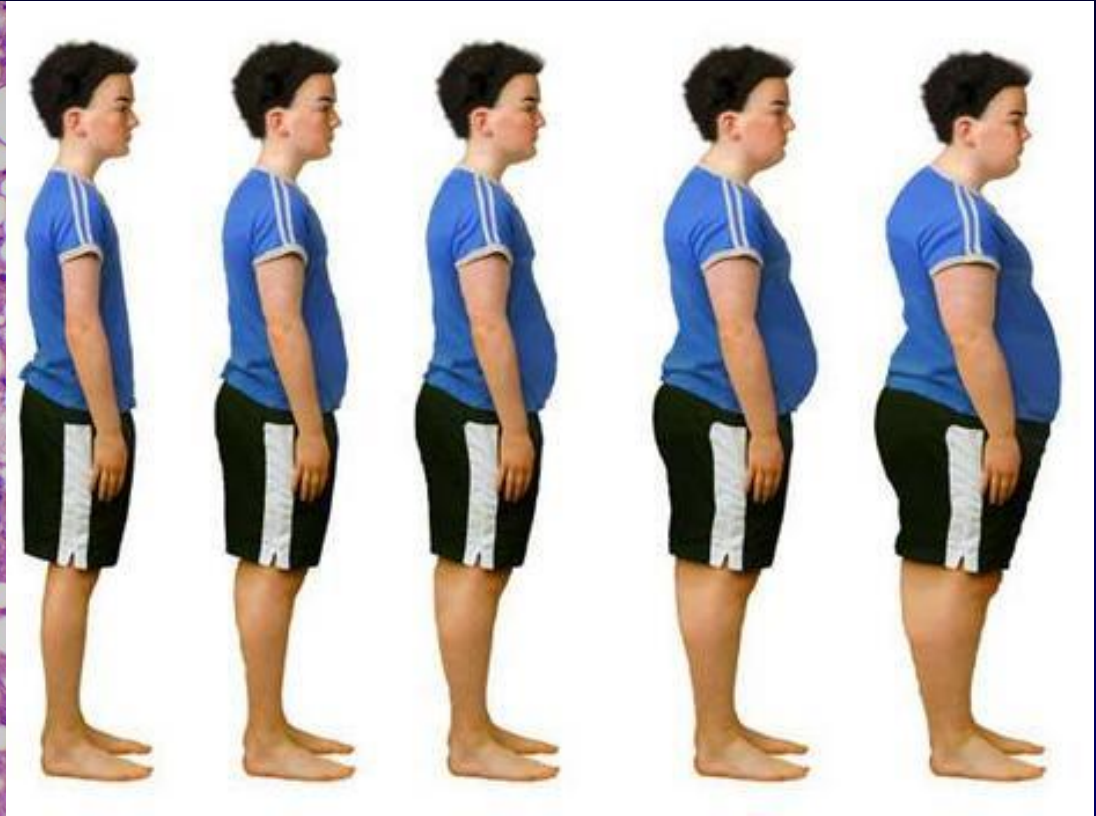
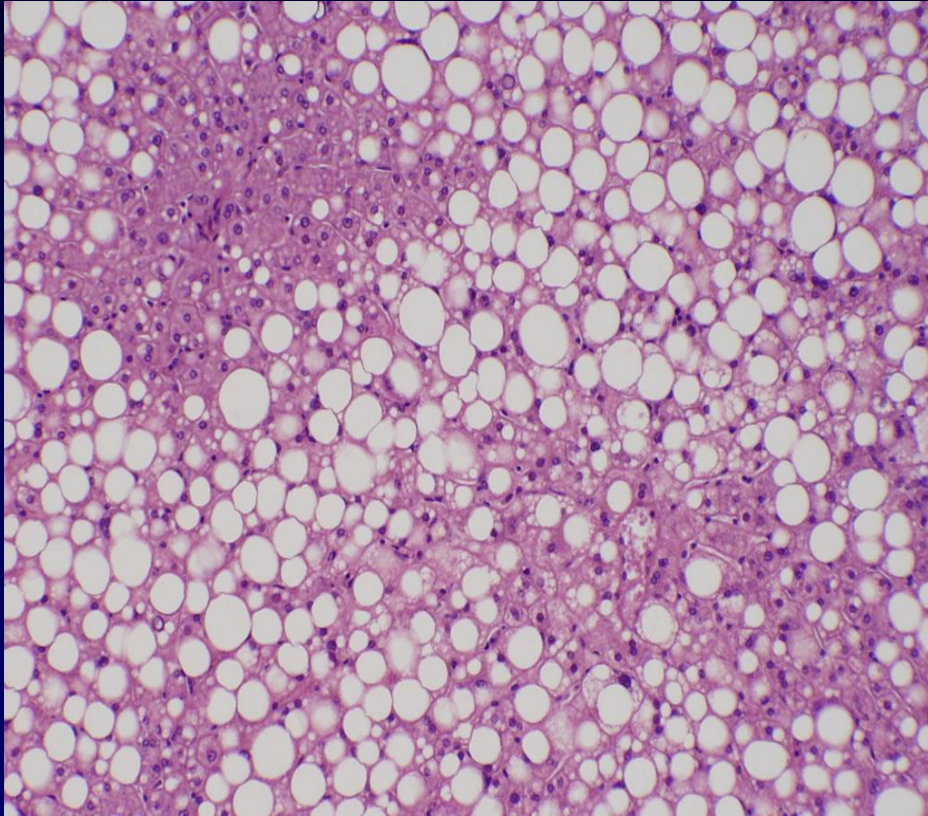
Macrovesicular Steatosis

Steatohepatitis

Pericellular fibrosis

Cirrhosis

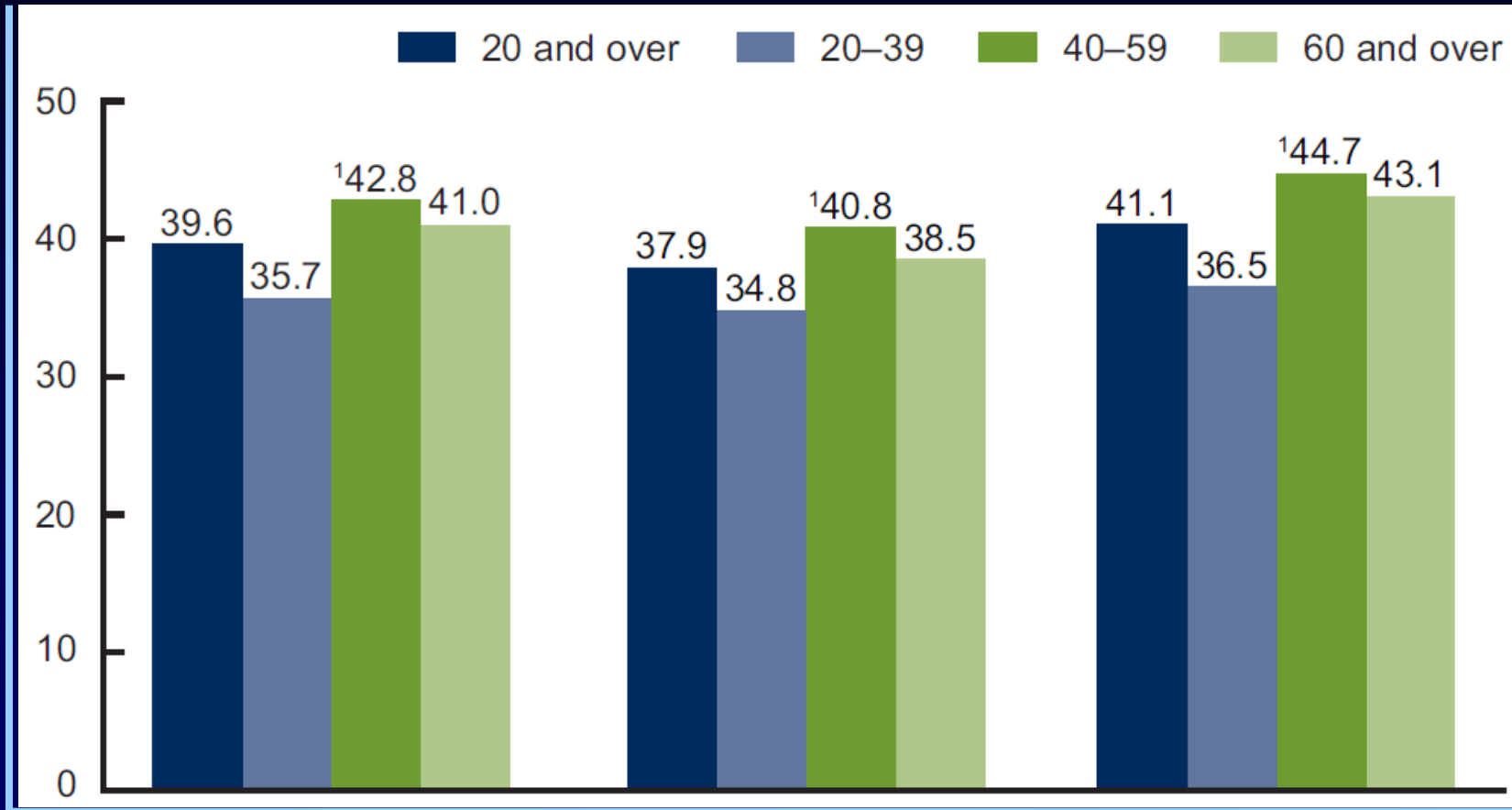
# NAFLD is linked to obesity





# Prevalence of Obesity in The US 2015-2016

Prevalence of Obesity (%)



# How Common NAFLD in US?

- **~40% of US population (~100 million)**
  - **Simple steatosis (NAFL): 14-34%**
  - **NASH: 1.5-6%**
- **Most common cause of ↑ALT in general population**
  - **Obesity: 80%, Dyslipidemia: 44%, DM: 44%**

# Prevalence of NAFLD in High-Risk Populations

- **Type 2 Diabetes**
  - NAFL: 12%
  - NASH: 87%
  - Advanced fibrosis: 20%
- **Morbidly Obese Gastric Bypass Patients**
  - NAFL: 30-90%
  - NASH: 33-42%
  - Advanced fibrosis (F3-F4): 14%

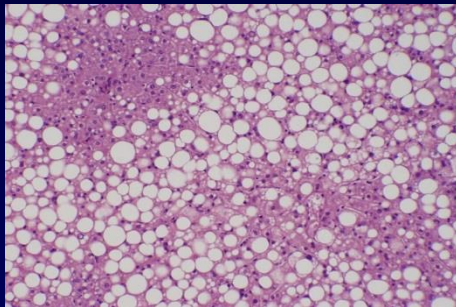
*Frantzides et al. J Gastrointest Surg 2004;8:849-855.*

*Gupter et al. J Gastro Hepatol 2004;19:854-859.*

*Tolman et al. Ann Intern Med 2004; 141:946-956.*

# Prognostic Implications of NASH + Fibrosis

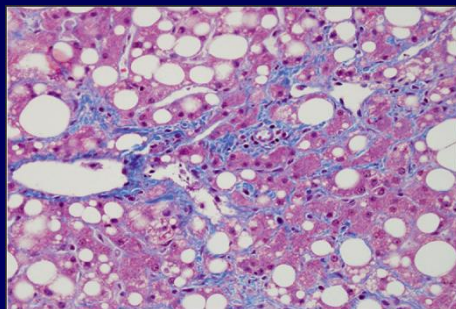
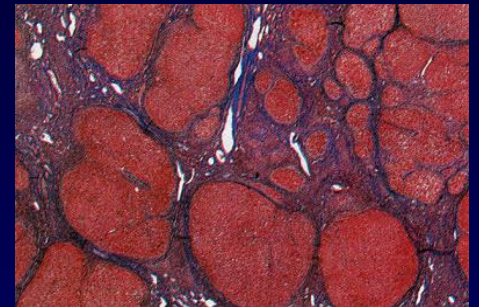
- More consistent and rapid progression to cirrhosis than just steatosis



**Steatosis  
(NAFL)**



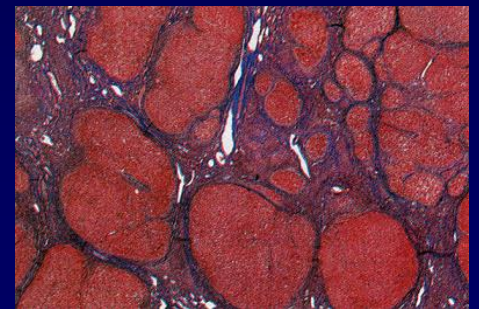
**Cirrhosis  
3%**



**NASH +  
Fibrosis**

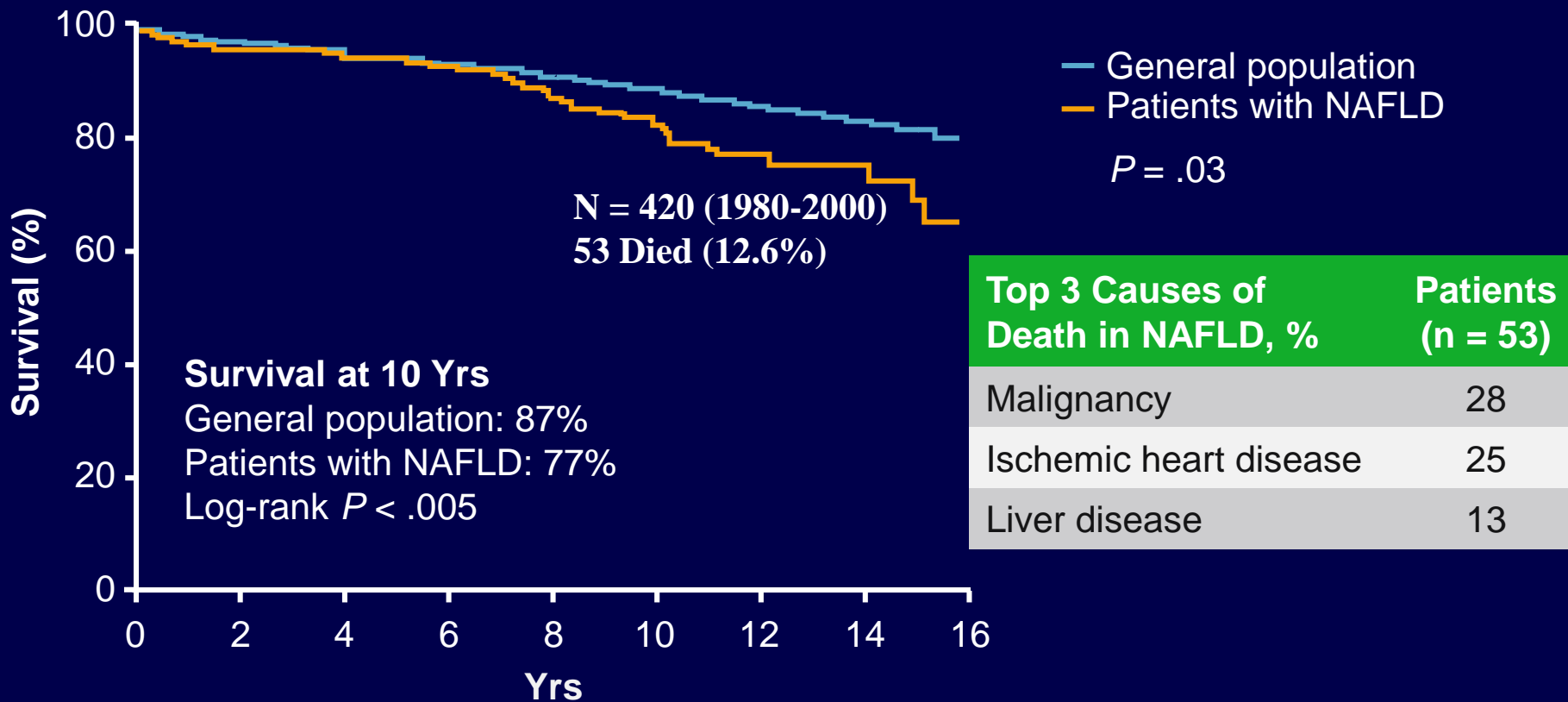


**Cirrhosis  
30%**



# Mortality in Patients With NAFLD

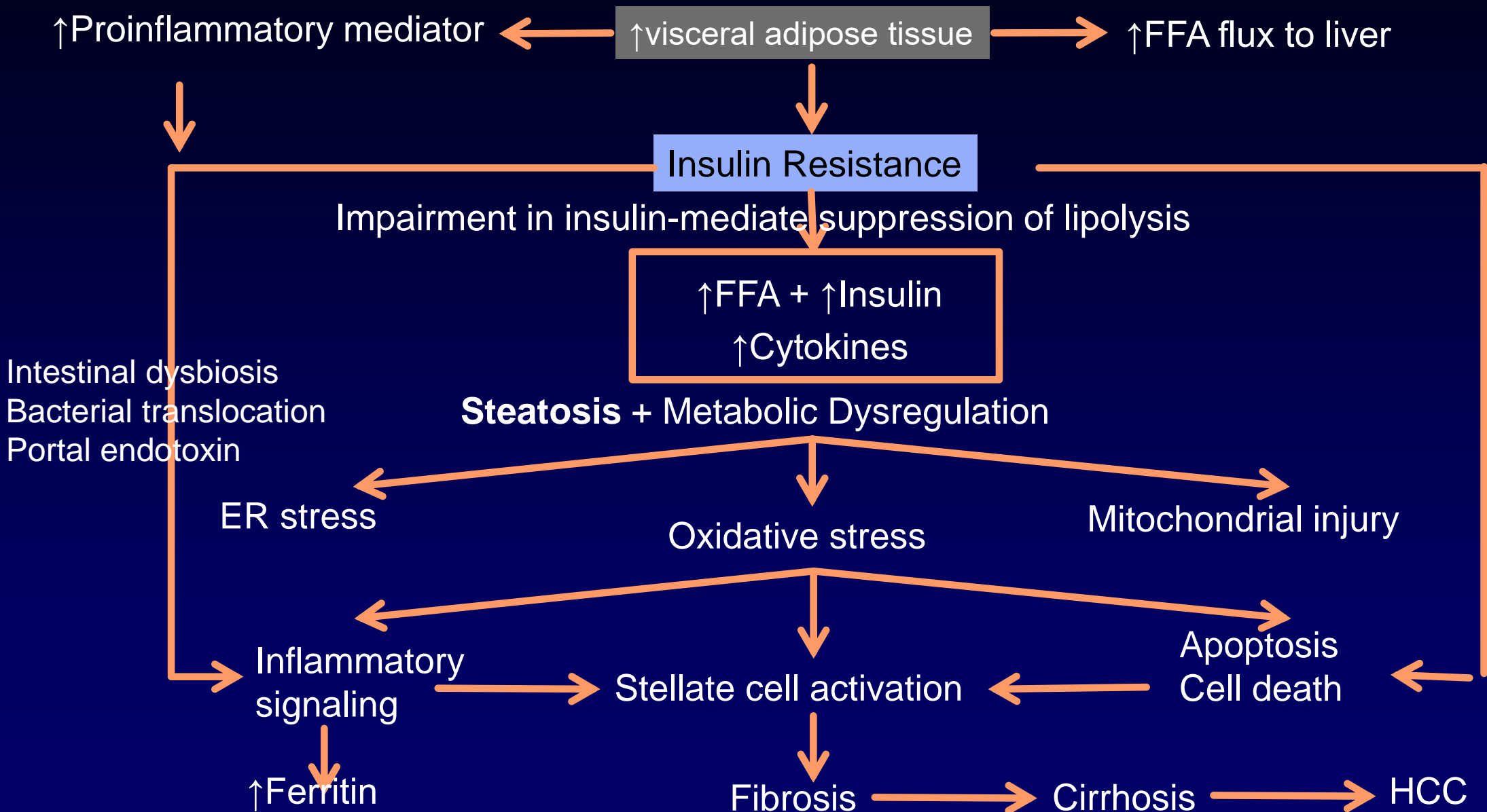
- Patients with NAFLD (N = 420) matched by age and sex to general population in Minnesota, followed for 7.6 ± 4.0 yrs



# Conditions Associated with NAFLD

- **Insulin resistance**
  - DM, HTN, dyslipidemia, obesity
- **Dietary abnormalities**
  - CHO excess, starvation, TPN
- **Drugs**
  - Tamoxifen, steroids, amiodarone, estrogen, CCB, zidovudine, valproate, tetracycline
- **Toxins**
  - Amanita phalloides, volatile hydrocarbons
- **Altered small bowel anatomy**
  - Short gut, SB diverticula
- **Metabolic diseases**
  - Wilson disease, hemochromatosis, Abetalipoproteinemia, Weber-Christian syndrome, hypothyroidism
- **Infections**
  - HCV-3, AIDS, bacterial overgrowth, bacillus cereus

# Pathogenesis of NASH



# Clinical Features & Diagnosis

NAFLD



# Clinical Features of NAFLD

- **Symptoms**
  - Fatigue
  - Fullness in the RUQ
- **Signs**
  - **Abdominal obesity (50%-90%)**
  - **Hepatomegaly**
  - ↑Dorsocervical fat (28%)
  - **Acanthosis nigricans**
  - Features of metabolic syndrome (66%)
  - Stigmata of chronic liver disease



# Clinical Conditions Commonly Encountered in Patients with NAFLD

- **Cardiovascular morbidity and mortality 25-43%**
- **Malignancy 19-28%:** Esophageal, adenoma, CRC, HCC
- **Infection 5-11%**
- **Sleep abnormalities:** ↑risk of OSA, abnormal sleep pattern
- **Psychiatric disorders:** ↑depression and anxiety disorders
- **Chronic fatigue and pain syndrome:** ↑fatigue, malaise, lethargy, narcotic intake
- **Coagulopathy:** ↑prothrombotic state (↑TF, VII)
- **Metabolic:** Hypothyroidism, hypopituitarism, hypogonadism, PCOS, hyperuricemia, hyperferritinemia, vit D deficiency, osteoporosis

# What to do when suspect NASH?

## Other conditions that cause fatty liver

- Excessive alcohol consumption
- Malnutrition
- Medications
- Parenteral nutrition

## Other liver diseases

- Hepatitis B or C (HBsAg, HBcAb, anti-HCV)
- $\alpha$ 1-Antitrypsin deficiency ( $\alpha$ 1-antitrypsin level)
- Wilson disease (ceruloplasmin)
- Autoimmune (ANA, ASMA, LKM)
- Lysosomal acid lipase deficiency
- Hemochromatosis (ferritin/TIBC/iron)

# Noninvasive Diagnosis of Fibrosis

## Serologic Markers

### ■ Simple

- AST/ALT ratio
- APRI
- FIB-4 index
- NAFLD fibrosis score

### ■ Complex

- NASH  
*FibroSURE*
- ELF
- HA

## Imaging

### ■ Elastography

- VCTE
- MR  
Elastography
- ARFI

*NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ALT, alanine transaminase; AST, aspartate aminotransferase.*

*APRI, AST-to-platelet ratio index; ARFI, acoustic radiation force impulse; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 score; HA, hyaluronic acid; MR, magnetic resonance; VCTE, vibration-controlled transient elastography.*

# 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).

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = 3.53$$

## Interpretation:

Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

# NAFLD Fibrosis Score

AUROC of 0.85

## NAFLD fibrosis score Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**  
*A noninvasive system that identifies liver fibrosis in patients with NAFLD*  
Hepatology 2007;45(4):846-854 [doi:10.1002/hep.21496](https://doi.org/10.1002/hep.21496)

Age (years)

BMI (kg/m<sup>2</sup>)

IGF/diabetes

AST

ALT

Platelets (x10<sup>9</sup>/l)

Albumin (g/l)

BMI: body mass index  
IGF: impaired fasting glucose

Age (years)

BMI (kg/m<sup>2</sup>)

IGF/diabetes

AST

ALT

Platelets (x10<sup>9</sup>/l)

Albumin (g/l)

**Score**

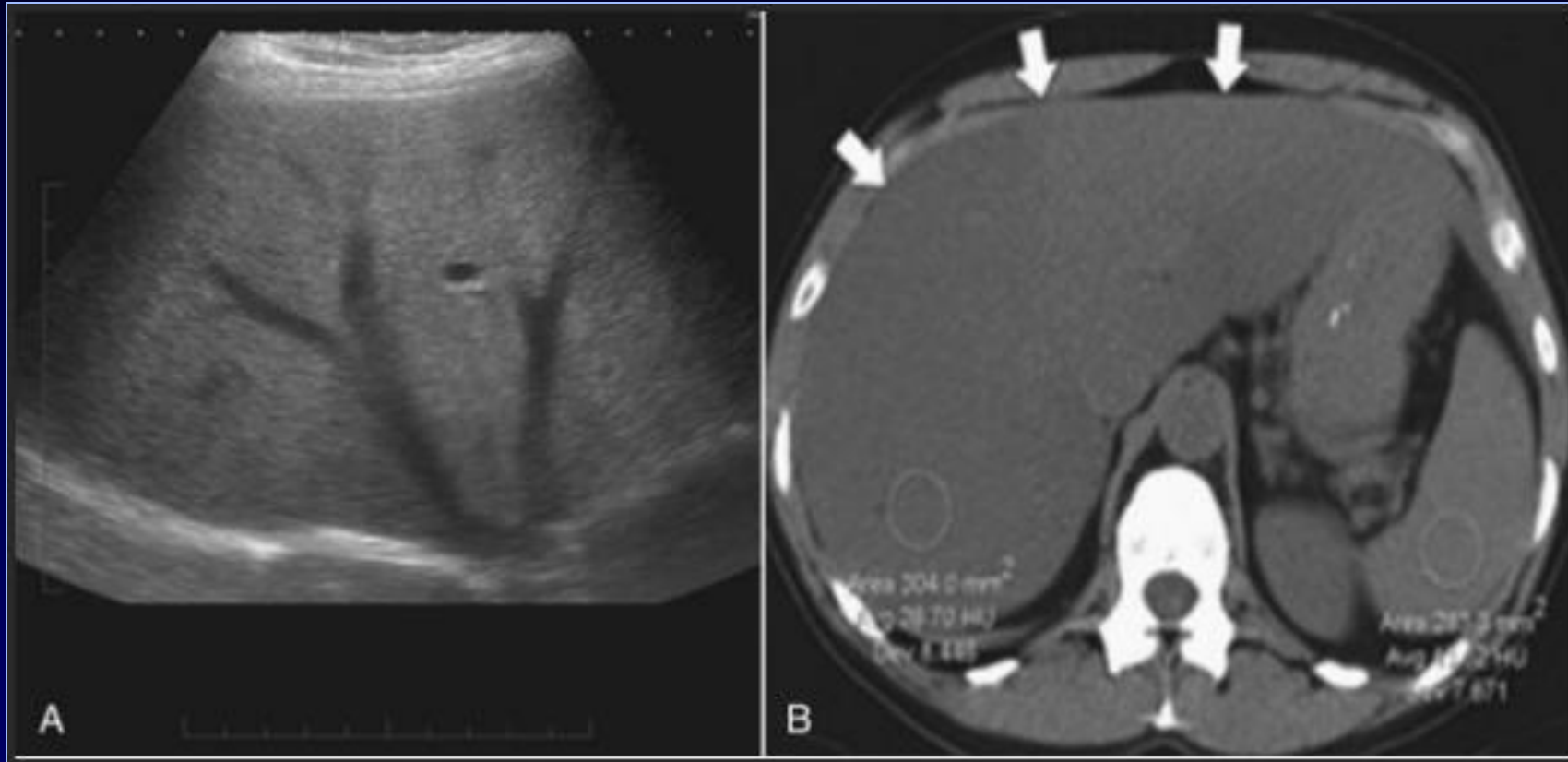
< -1.455: predictor of **absence** of significant fibrosis (F0-F2 fibrosis)  
≤ -1.455 to ≤ 0.675: indeterminate score  
> 0.675: predictor of **presence** of significant fibrosis (F3-F4 fibrosis)

# FibroScan-Hepatic Elastography

- Vibration-controlled transient elastography-liver shear wave speed and equivalent stiffness through pulse-echo ultrasonic acquisition
- Rapid, noninvasive, and can be performed easily at the bedside
- Can serve as a surrogate for degree of fibrosis
- Provide estimate of degree of steatosis (CAP)



# Imaging



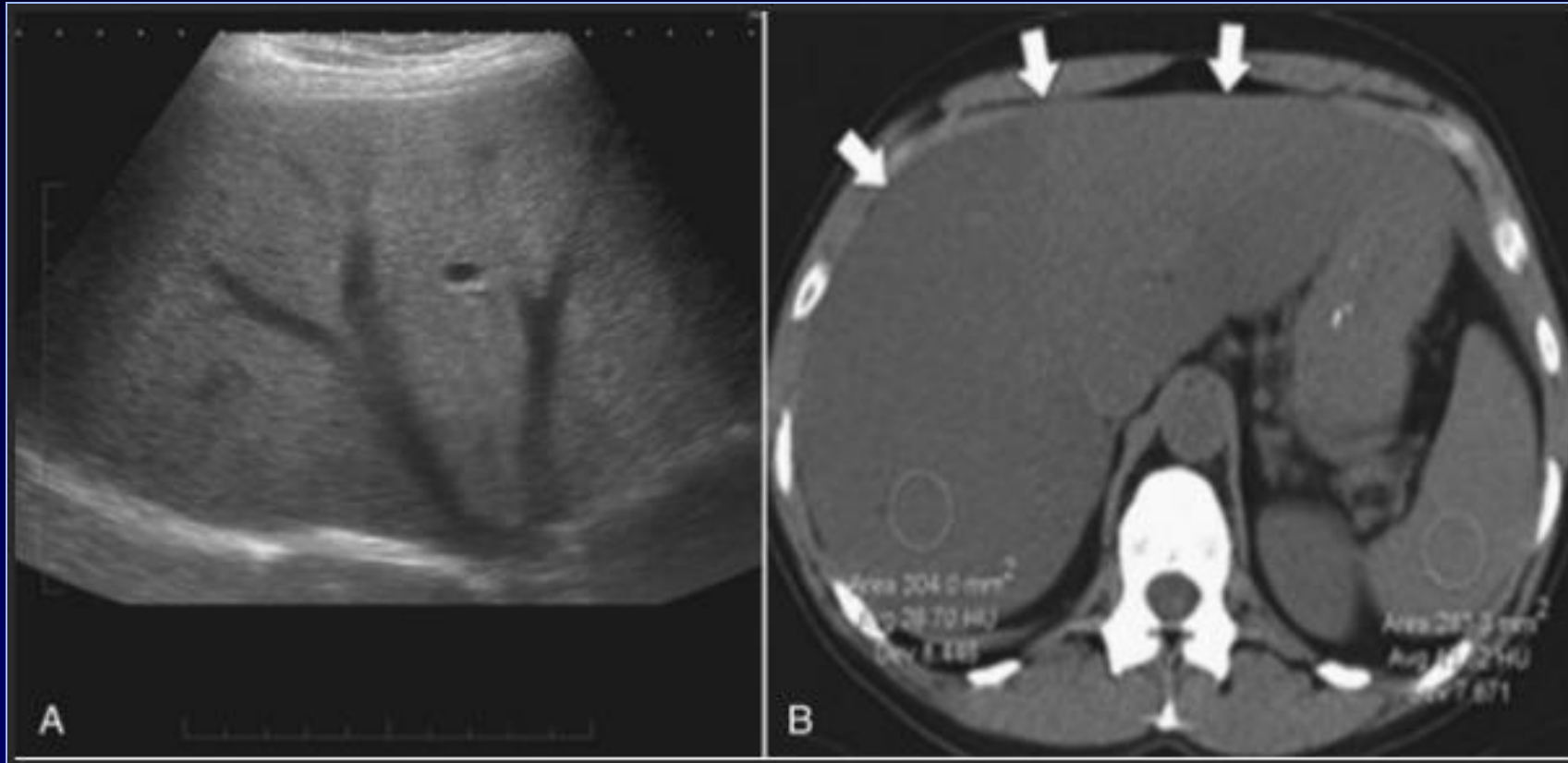
Hyperechoic liver parenchyma  
Vascular blurring

↓ Hepatic attenuation  
Liver is dark in comparison to spleen



# Imaging

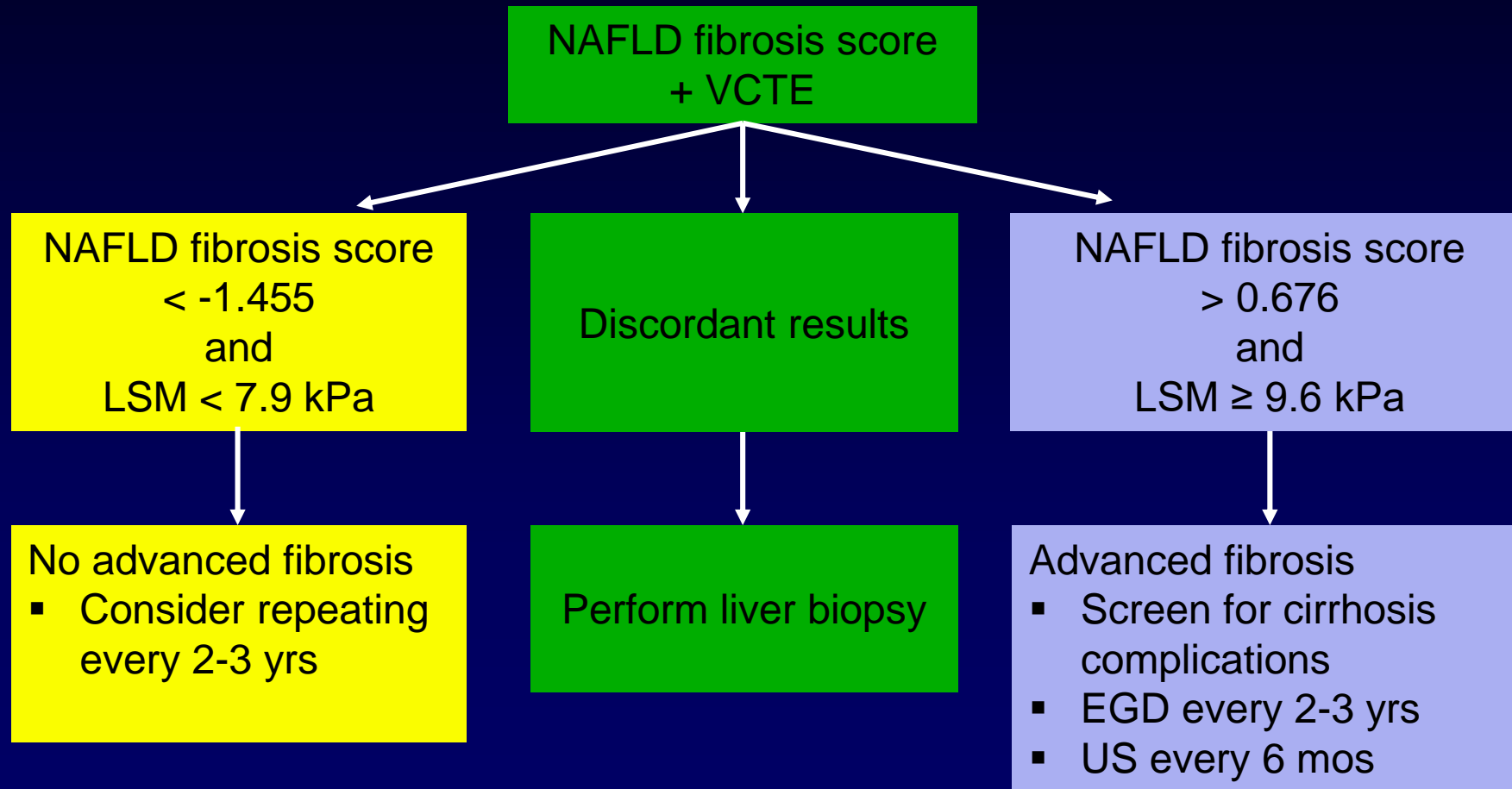
## Don't differentiate NAFL from NASH



Sensitivity 85%-95%  
PPV 62%

Sensitivity  
PPV 76%

# Potential Approach to Evaluating Fibrosis in Adult Patients With NAFLD



# Predictors of Fibrosis on Liver Biopsy in Patients With NAFLD

- Age > 50 years
- Obesity
- Diabetes
- AST/ALT > 1

*Angulo et al. Hepatology 1999;30.*

*Ratziu et al. Gastroenterology 2000;118:1117-1123.*

# **Non-pharmacologic & pharmacologic Management**

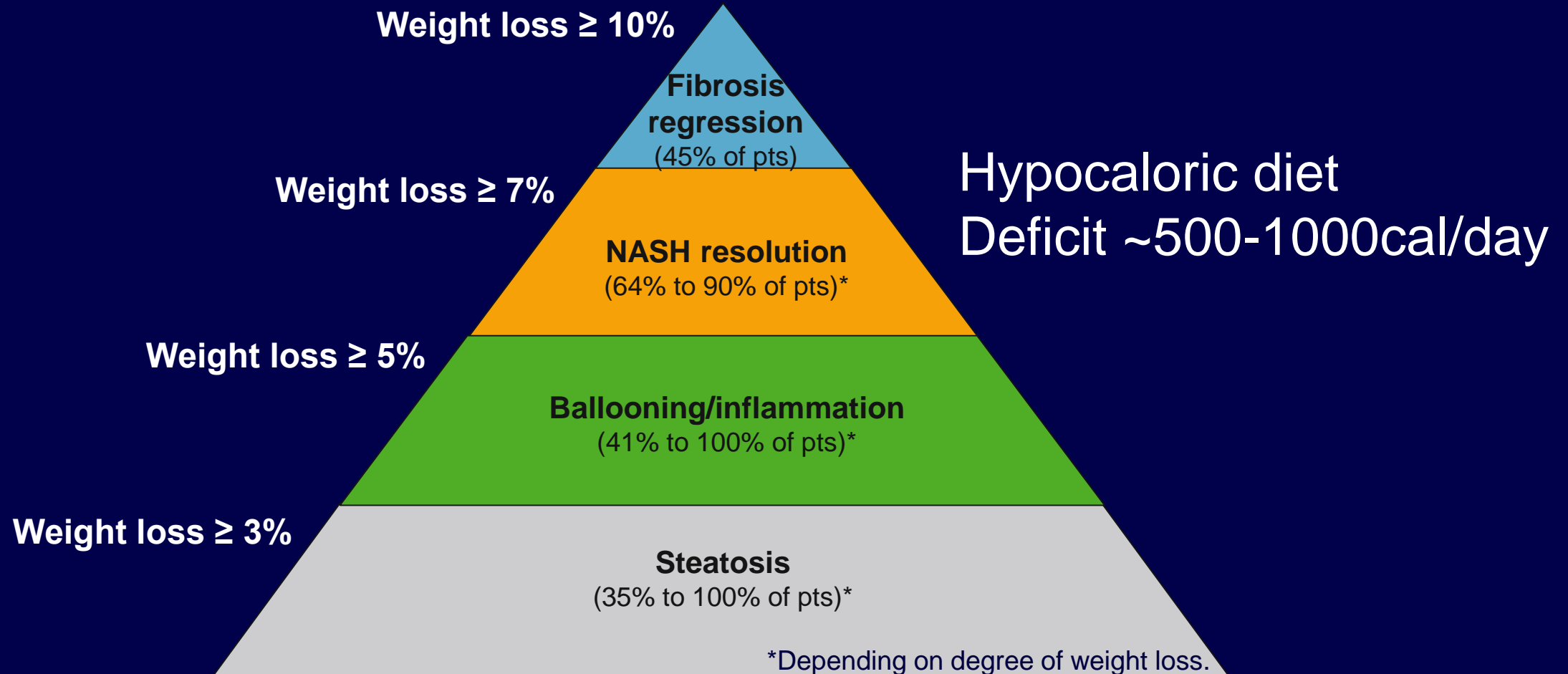
**NAFLD**

# **Non-pharmacologic and Pharmacologic Management of NAFLD**

- **Lifestyle intervention**
- **Medication**
- **Surgery**

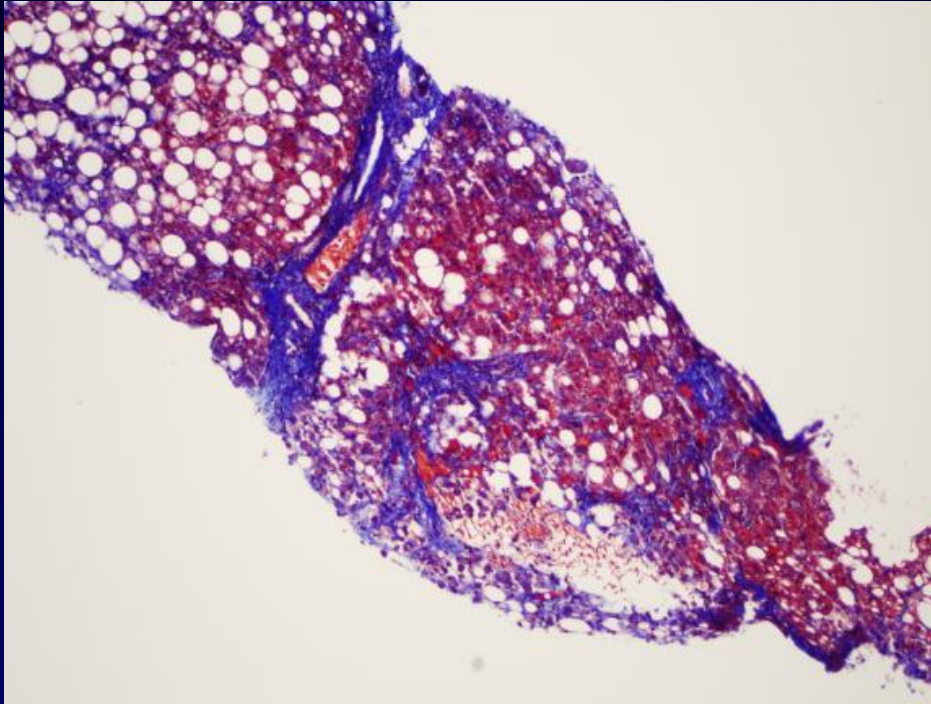
# Percentage of Weight Loss Associated With Histological Improvement in NAFLD

- Analysis of data from 4 randomized studies



# 10% Reduction in Body Weight ~6 months

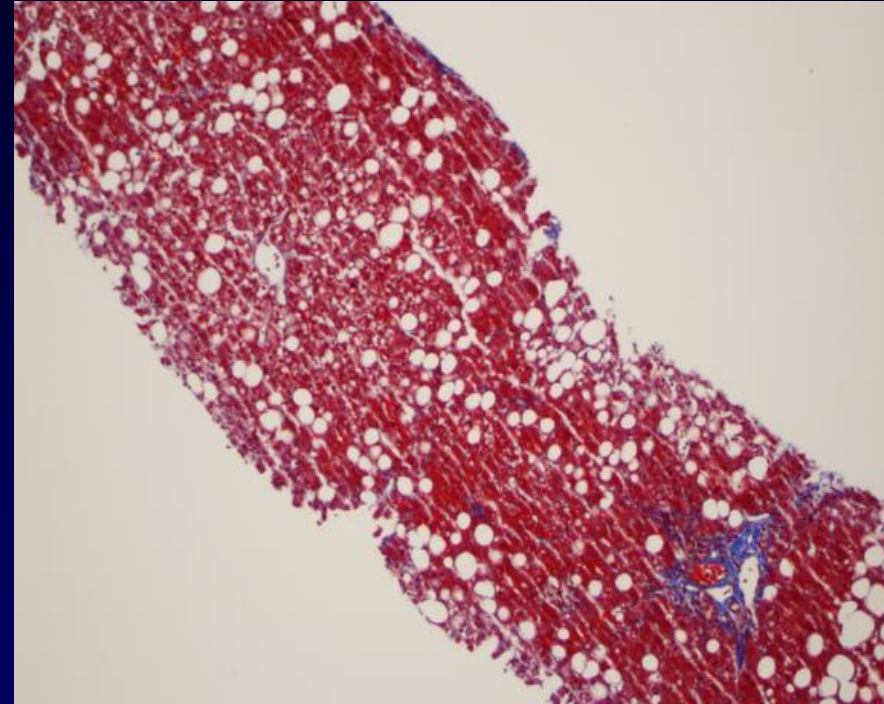
PRE



## TRICHROME STAINING

- Bridging fibrosis (stage 3)

POST



## TRICHROME STAINING

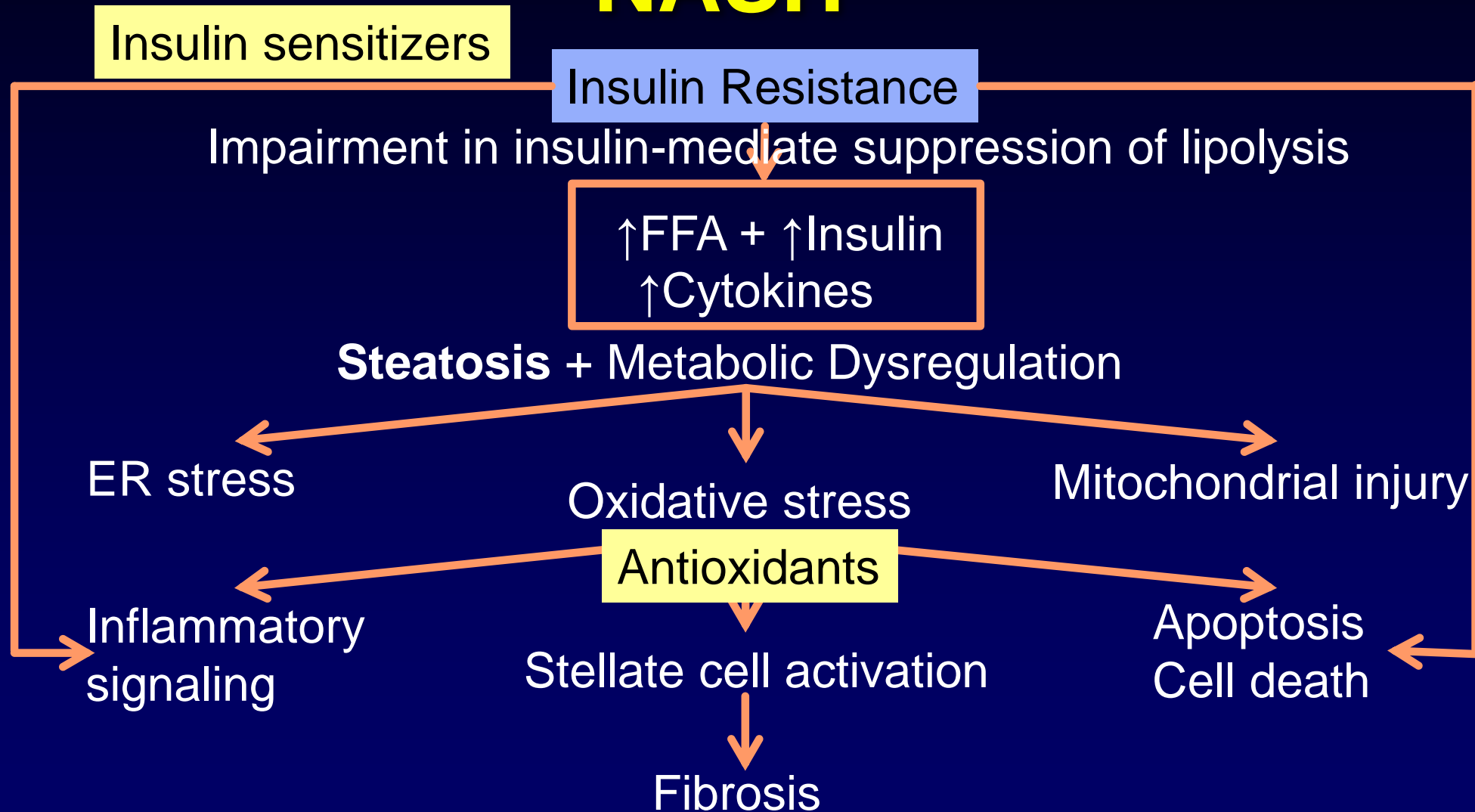
- Zone 3 perivenular perisinusoidal/pericellular fibrosis, focal (stage 1a)

# Exercise and Weight Loss in Treatment of NAFLD/NASH

- Hypocaloric diet (-ve 500-1,000 kcal/d) and moderate-intensity exercise is likely to provide sustaining weight loss over time.
- Weight loss  $\geq 3\%$ -5% of body weight improve steatosis, 7%-10% is needed to improve the majority of the histopathological features of NASH, including fibrosis.
- Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown.



# Rationale for the Therapeutics for NASH

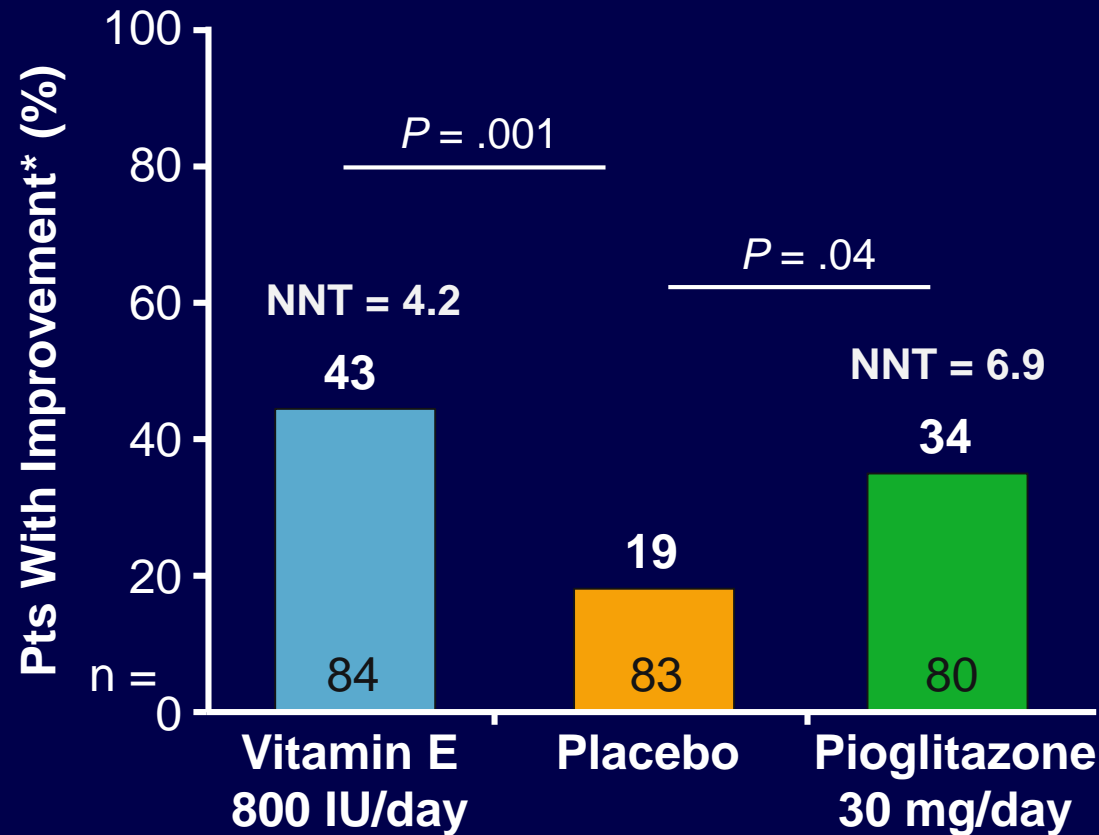


# Pharmacologic Approach to the Management of NASH

- **Metformin**: is not recommended for treating NASH in adult patients.
- **Rosiglitazone**: is no longer available in most countries, and its prescribing remains severely restricted in the US because of controversial findings of an increase in coronary events
- **UCDA**: is not recommended for the treatment of NAFLD or NASH.
- **Omega-3 fatty acids**: should not be used as a specific treatment of NAFLD or NASH, but may be considered to treat hypertriglyceridemia in patients with NAFLD.

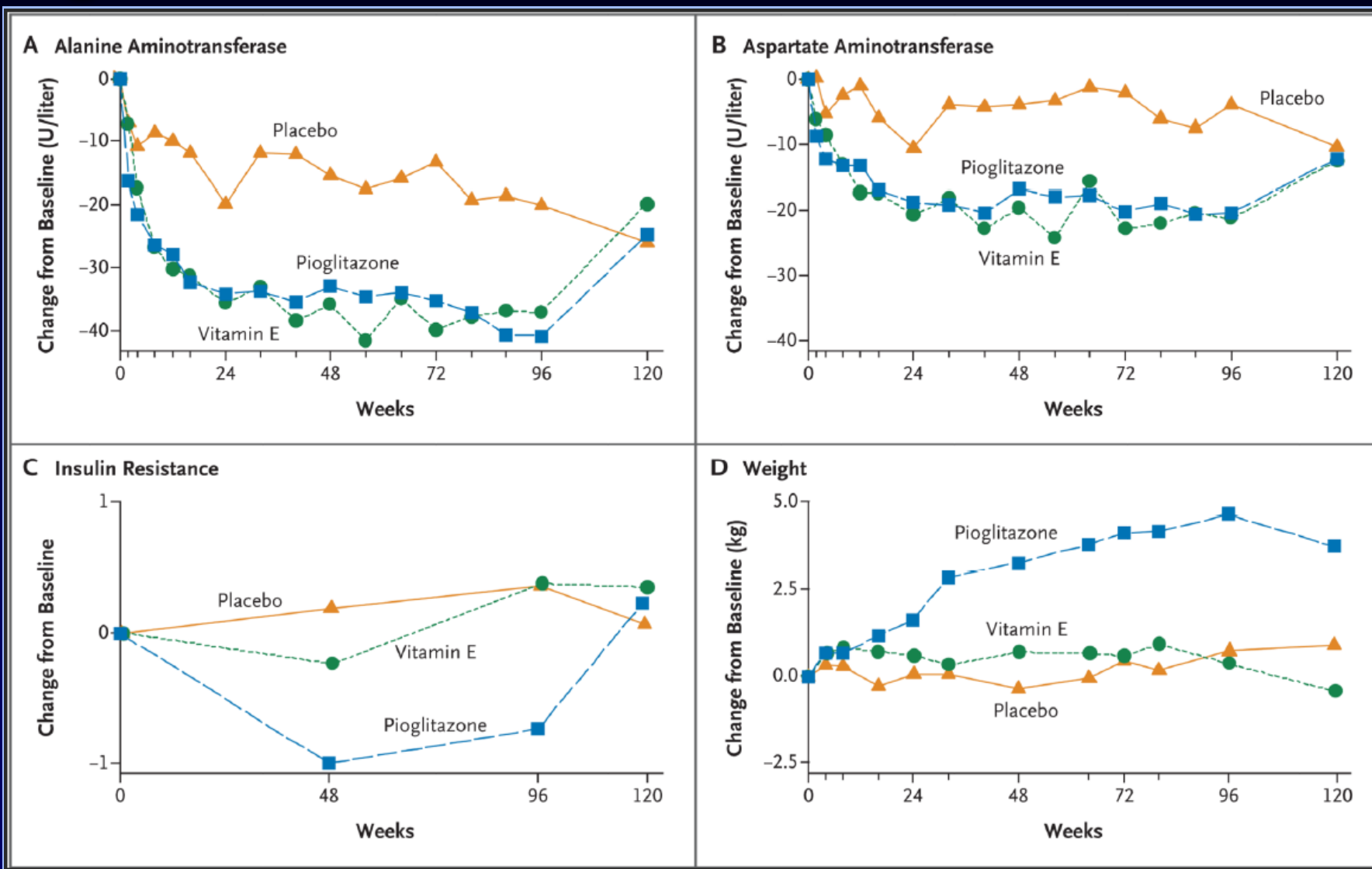
**What about Vitamin E?**

# PIVENS: Histologic Improvement at Wk 96 With Vitamin E vs Pioglitazone

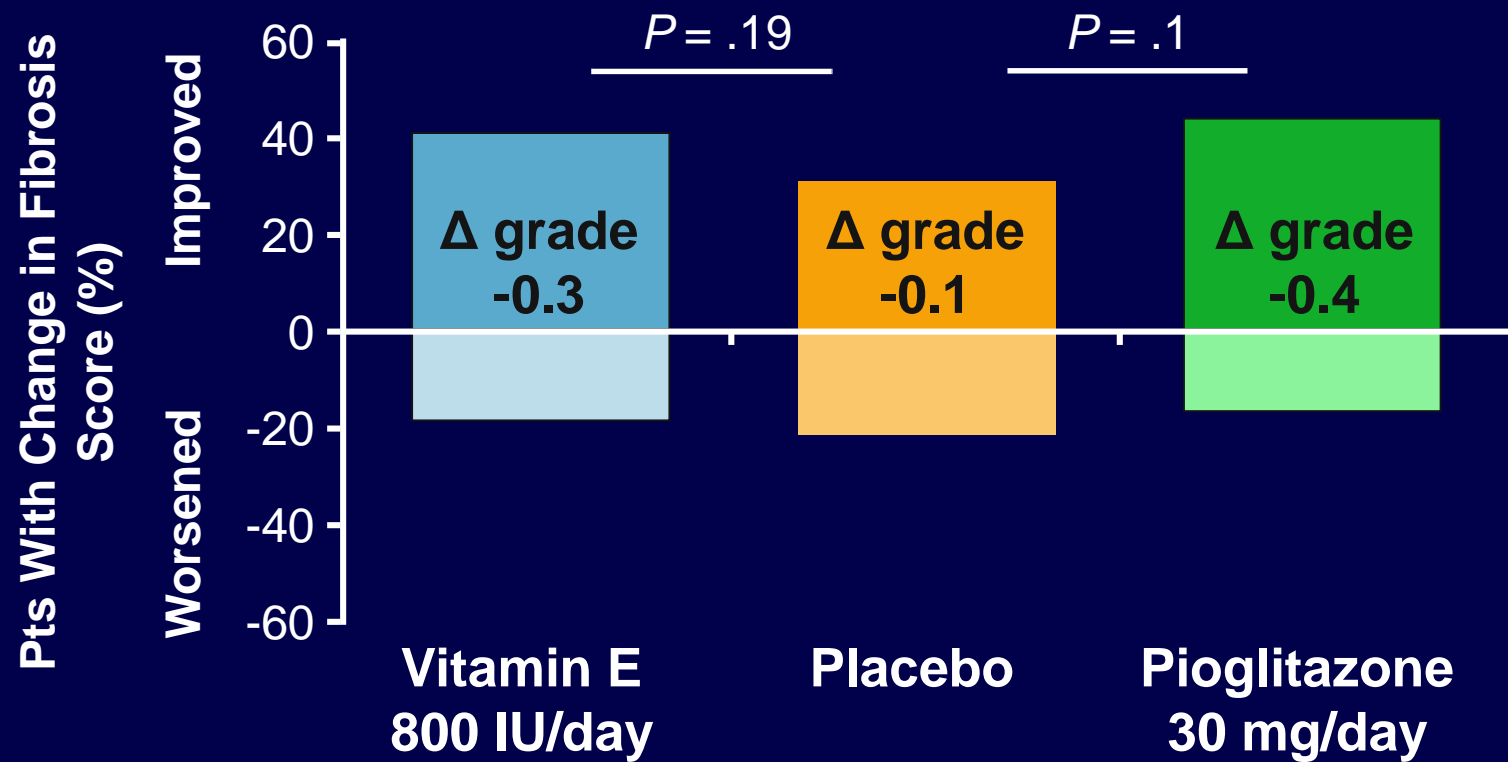


\*Histologic improvement:  $\geq 1$ -point improvement in hepatocellular ballooning score, no increase in fibrosis score, and either a decrease in NAS to  $\leq 3$  or a  $\leq 2$ -point decrease in NAS plus  $\geq 1$ -point decrease in either the lobular inflammation or steatosis score.

# Pioglitazone or Vitamin E vs Placebo for NASH



# PIVENS: No Significant Improvement in Fibrosis at Wk 96 for Vitamin E or Pioglitazone

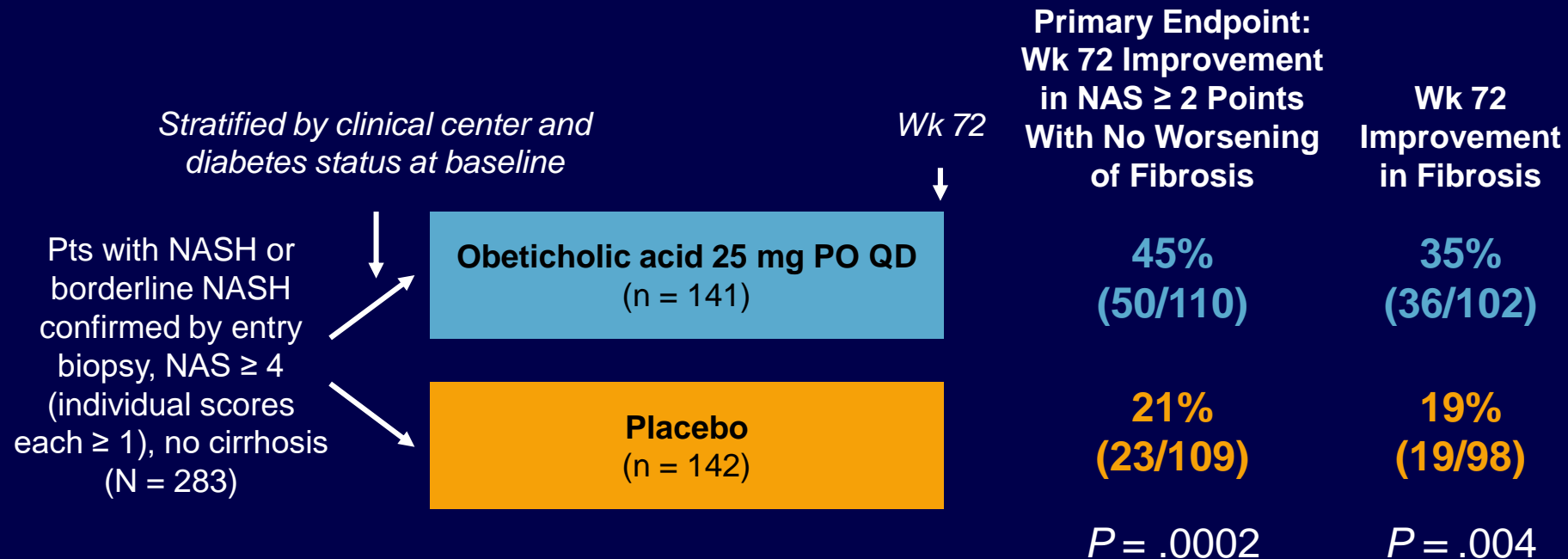


# Vitamin E and Pioglitazone: AASLD guidelines 2018

- **Vitamin E:** 800U/day improves liver histology in non-diabetic adults with biopsy-proven NASH, however it is not recommended in NASH diabetic patients, NAFLD without liver biopsy, NASH cirrhosis or cryptogenic cirrhosis
- **Pioglitazone:** improves liver histology in patients with and without T2DM with biopsy-proven NASH. Risks and benefits should be discussed with each patient before starting therapy.

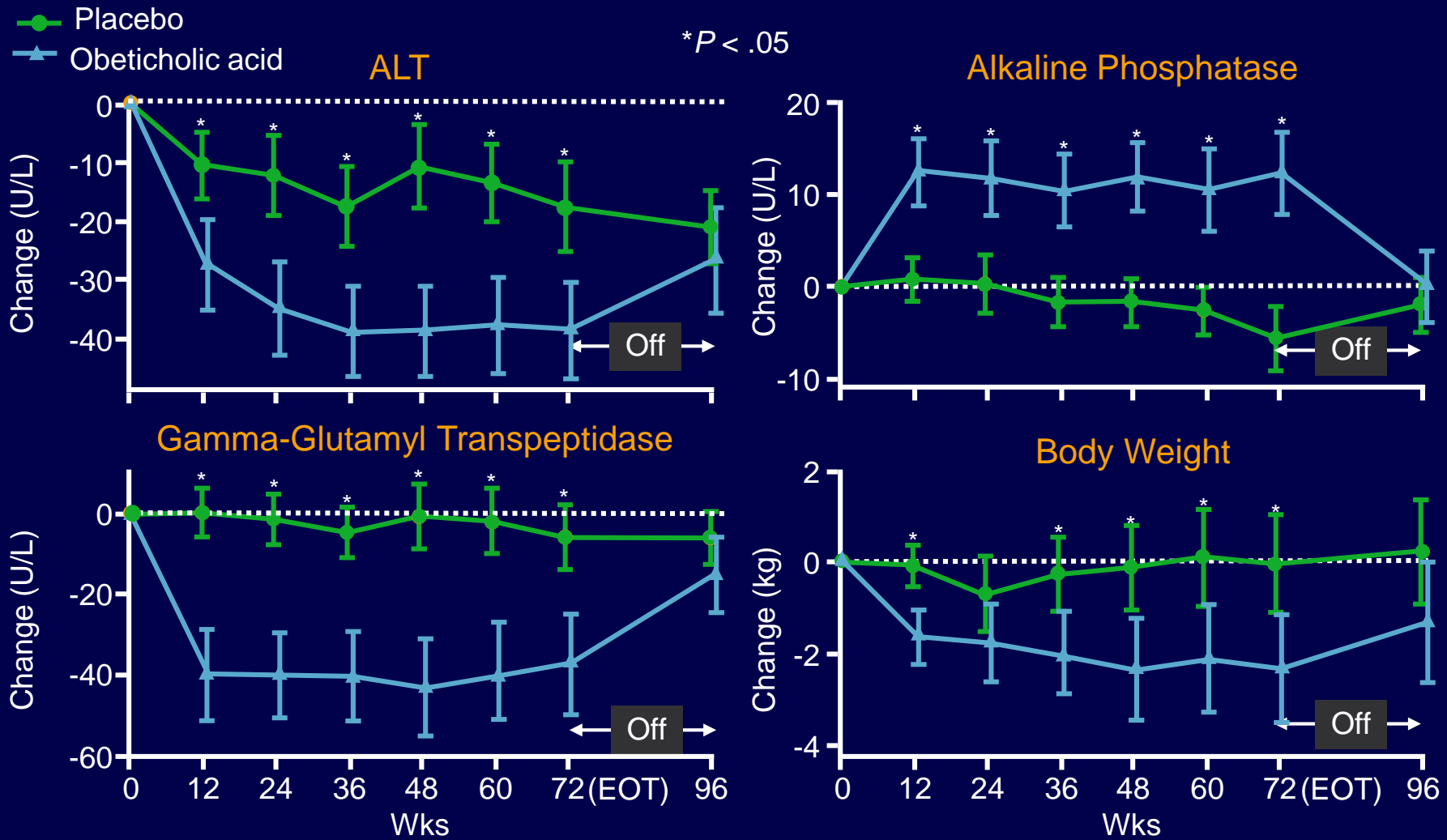
# FLINT: Obeticholic Acid in Noncirrhotic Patients With NASH

- Double-blind, placebo-controlled, randomized, multicenter phase IIb trial





# Changes in Enzymes and Body Weight



- **Obeticholic acid:** Not recommended till further safety and efficacy data become available in patients with NASH
- **Elafibranor:** (a dual PPAR $\alpha$ / $\delta$  agonist) 120 mg/day, in phase 2 study showed improvement in NASH without fibrosis worsening over a 12-month study period. there was a mild, reversible increase in serum creatinine.

**Ratziu V et al. Elafibranor, Gastroenterology 2016;150:1147-1159**

# Bariatric Surgery in NASH

- 12 studies between 2004 – 2007 evaluating liver histology following bariatric surgery
  - 431 patients with NASH
- All studies report improvements in
  - Steatosis
  - Ballooning
  - Inflammation
- Mixed results of improvement in fibrosis
- Resolution of NASH in 75-100% of patients

# Bariatric Surgery and NASH

- Foregut bariatric surgery is not contraindicated in eligible obese patients with NAFLD or NASH without cirrhosis but it is premature to consider it as an established option to treat NASH (AASLD guidelines 2018)

# Summary

- **NAFLD is the hepatic manifestation of the metabolic syndrome**
- **NAFLD is the most common cause of persistent abnormal liver transaminases in North America**
- **The prevalence varies among different risk groups (2.8-46%)**
- **NAFLD consist of a spectrum of NAFL, NASH, NASH+fibrosis, NASH+cirrhosis**
- **Oxidative stress is a key mechanism in the genesis of NASH**
- **Exercise & Weight loss affords the greatest impact on NAFLD**
- **Vitamin E, Pioglitazone, Liraglutide and Obeticholic acid have shown some promises in treatment of patients with NASH**
- **Surgical interventions are significantly more effective than lifestyle / pharmacological therapy in promoting weight loss, improvement in NASH in selected population**

**Thank you**