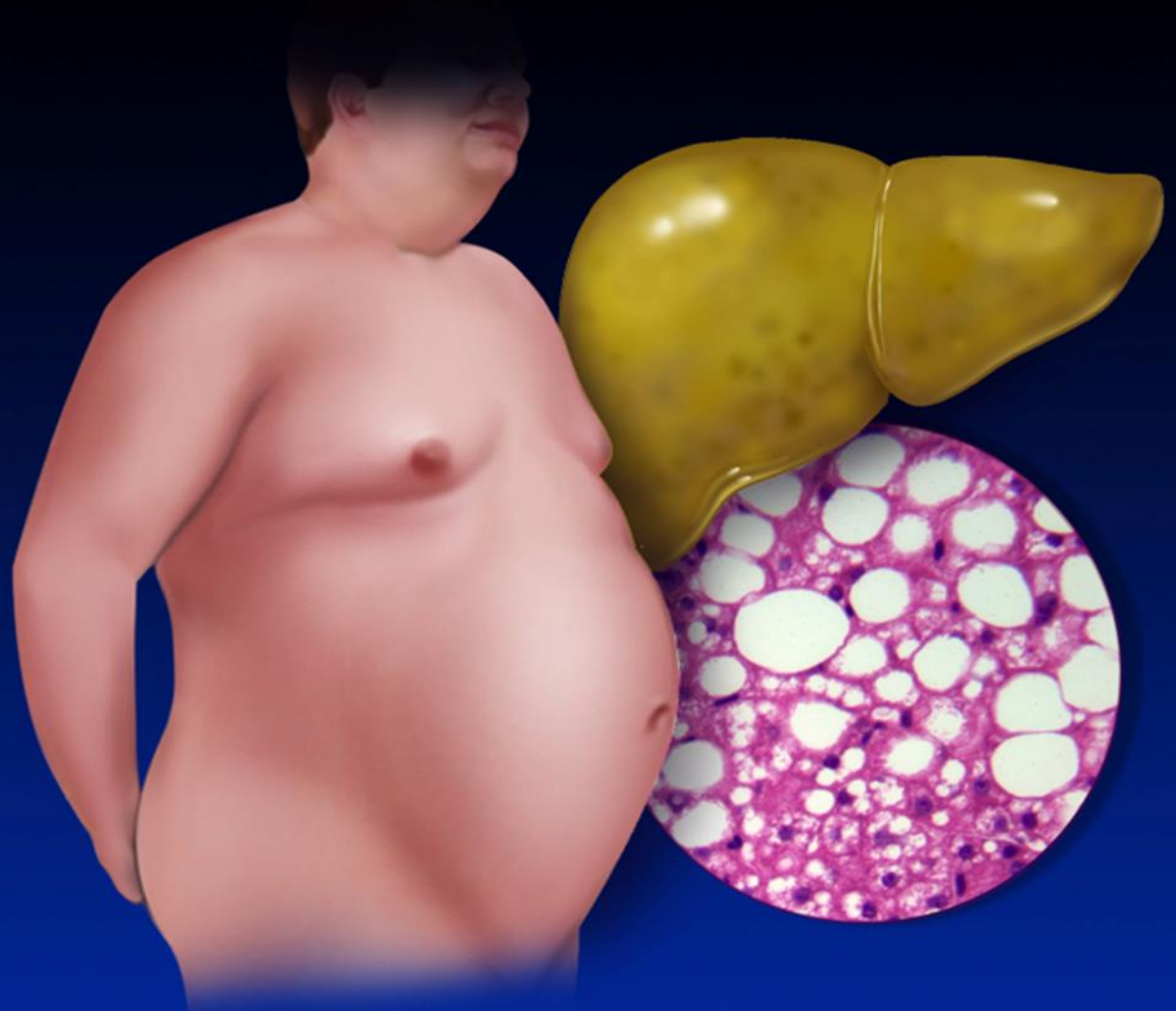

Insights for the diagnosis and management of Non-alcoholic liver disease

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PONCE SCHOOL OF MEDICINE
19 PUERTO RICO 77

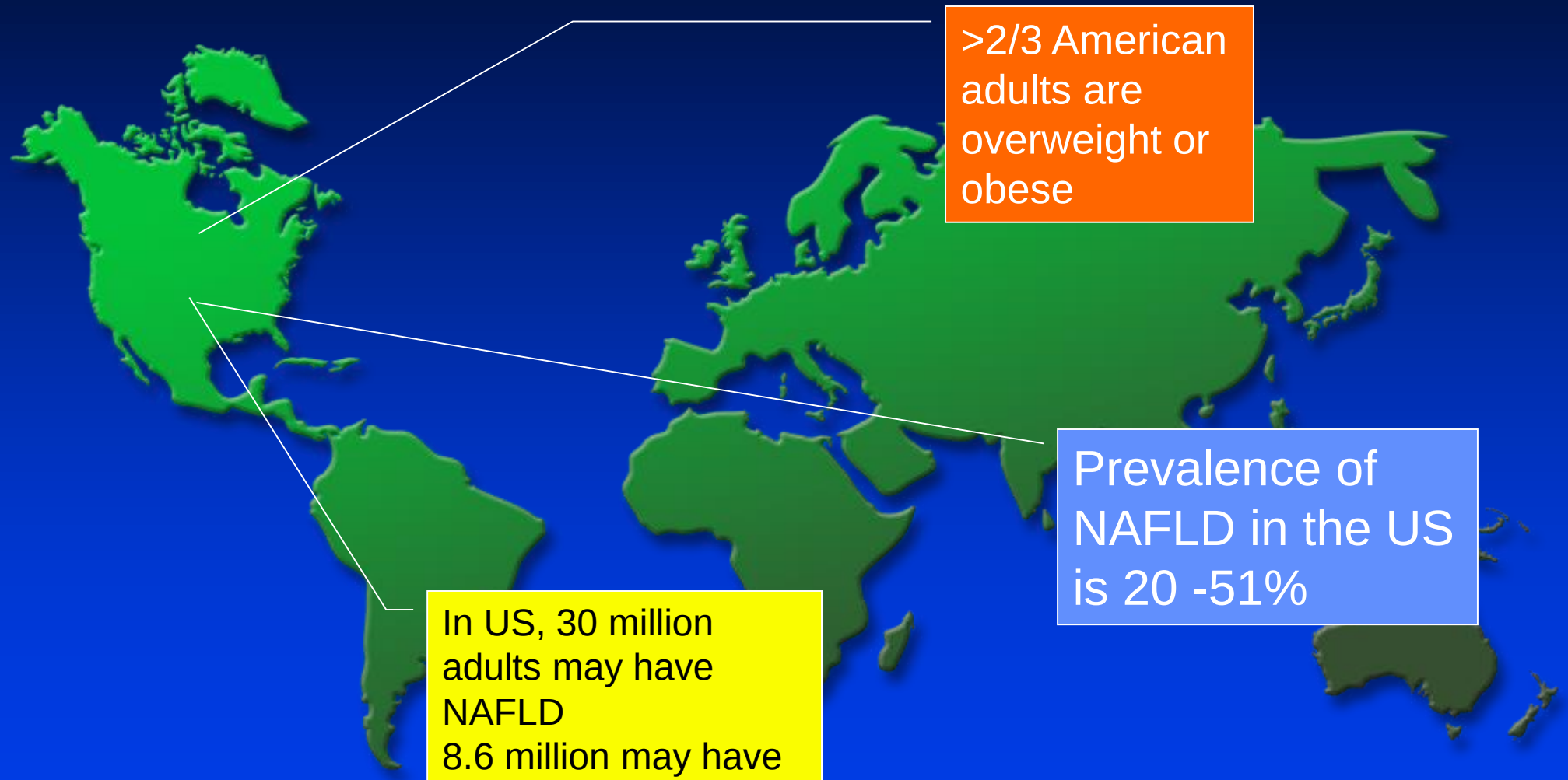
Disclosures

Abbvie Speaker
Gilead Speaker

Objectives

- Understand the epidemiology and natural history of NAFLD
- Recognize the clinical presentation of NAFLD
- Understand the strategies for the diagnosis and treatment of NAFLD

NAFLD: A Global Challenge



>2/3 American adults are overweight or obese

Prevalence of NAFLD in the US is 20 -51%

In US, 30 million adults may have NAFLD
8.6 million may have NASH !!

Non-Alcoholic Fatty Liver Disease (NAFLD)

- What is it?
- Why care?
- Whom to treat?

NAFLD

- Evidence of hepatic steatosis either by imaging or histology
- No other causes for secondary hepatic fat accumulation
  - Significant alcohol consumption
    - > 3 drinks on any day (> 30gm/day) or > 21 drinks per week in men
    - > 2 drinks on any day (>20gm/day) or > 14 drinks per week in women
  - Use of steatogenic medications
  - Hereditary disorders

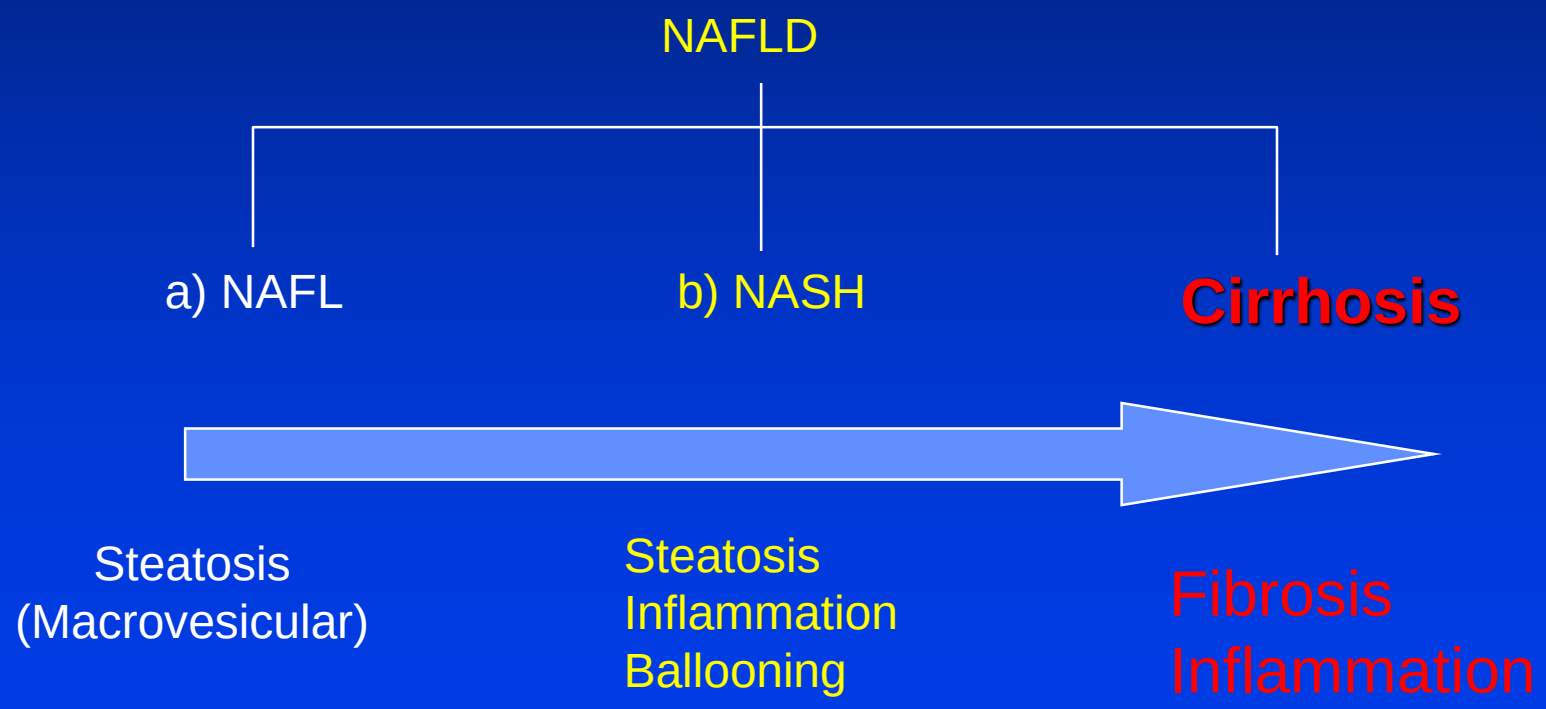
NAFLD

- NAFL (nonalcoholic fatty liver)
  - Steatosis – imaging or histology (>5%)
  - No other cause of steatosis
- NASH (nonalcoholic steatohepatitis)
  - Histological diagnosis
  - Fat (>5%) + inflammation + ballooning
  - With or without fibrosis
- NASH cirrhosis
  - Cirrhosis with current or previous histological evidence of fat or steatohepatitis

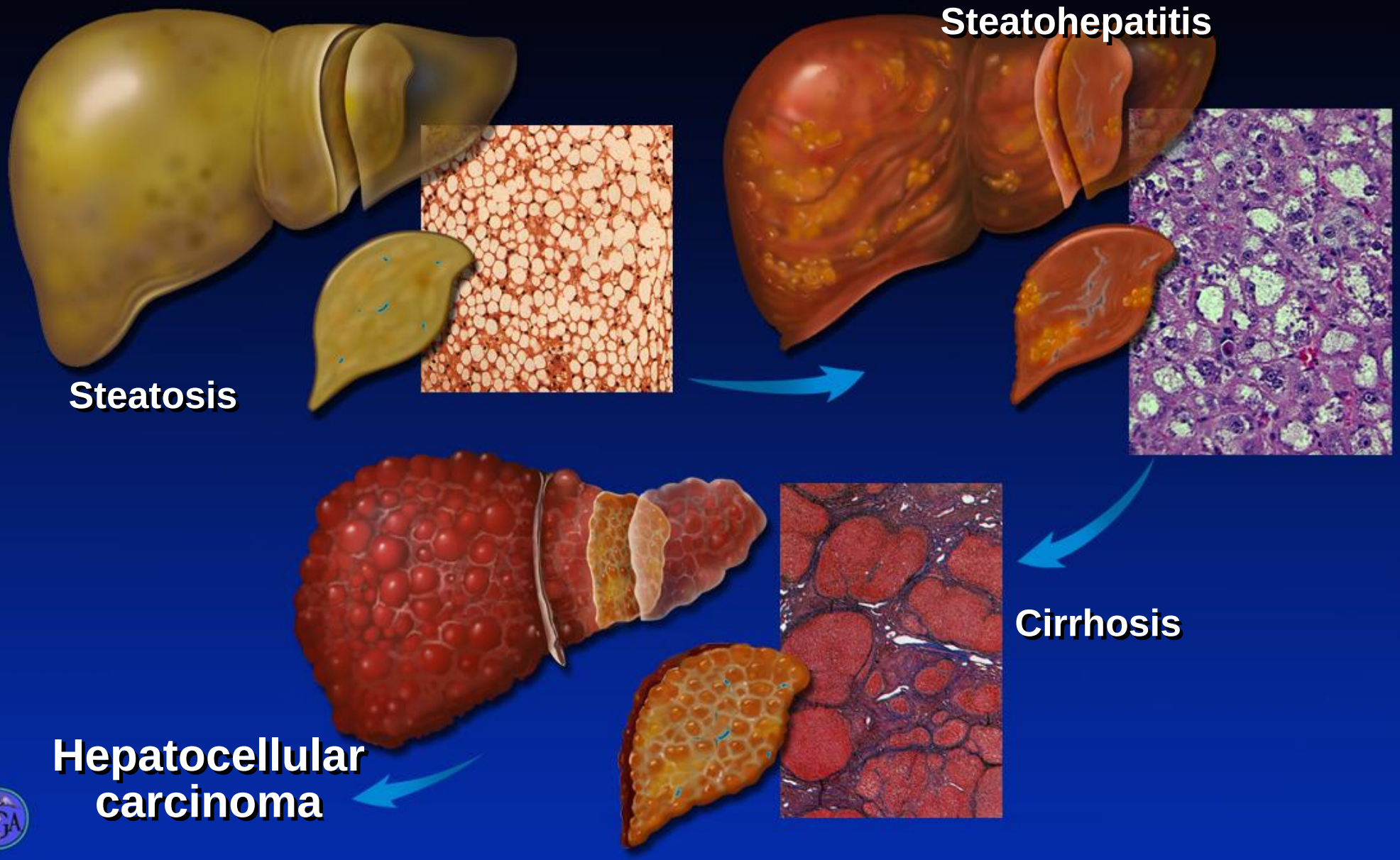
Chalasani N, et al. Hepatology 2018;67:328-357

NAFLD: Disease Spectrum

NAFLD: Nonalcoholic fatty liver disease
NAFL: nonalcoholic fatty liver
NASH: nonalcoholic steatohepatitis



NAFLD
Spectrum of Hepatic Pathology



NAFLD: Natural History

25% of patients with NASH progress to cirrhosis with and increased incidence of HCC
12.1% die of liver-related causes

NAFL NASH Cirrhosis

Liver Failure

HCC

Non-Alcoholic Fatty Liver Disease (NAFLD)

- What is it?
- Why care?
- Whom to treat?

Clinical Implications of NAFLD

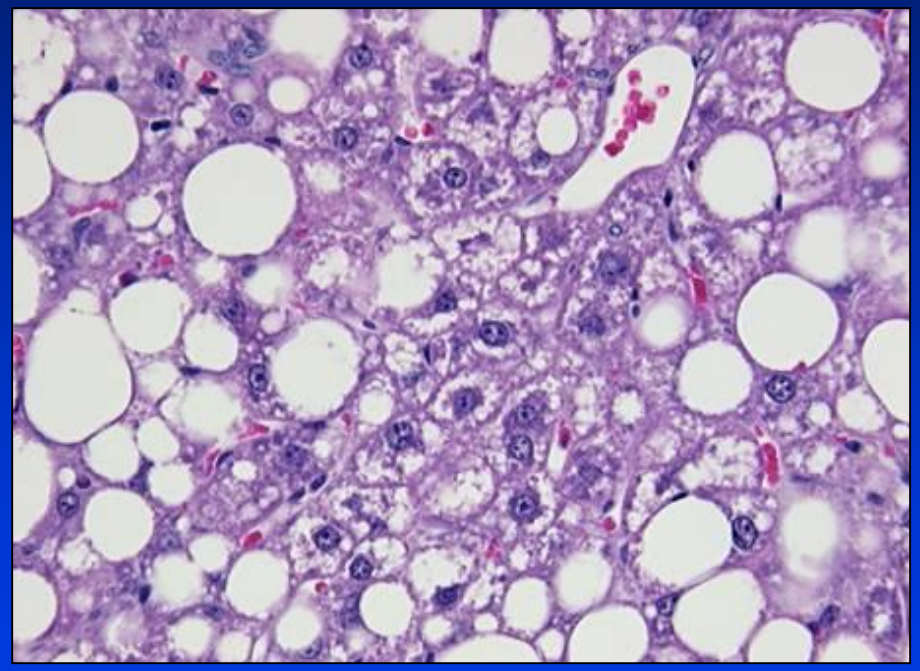
NAFLD increases the risk of death

- Increased cardiovascular mortality
- Increased liver-related mortality
- Increased cancer-related mortality

NASH HAS GREATER IMPACT ON MORTALITY THAN FATTY LIVER

Non-Alcoholic Fatty Liver Disease
Clinical Implications

Steatosis

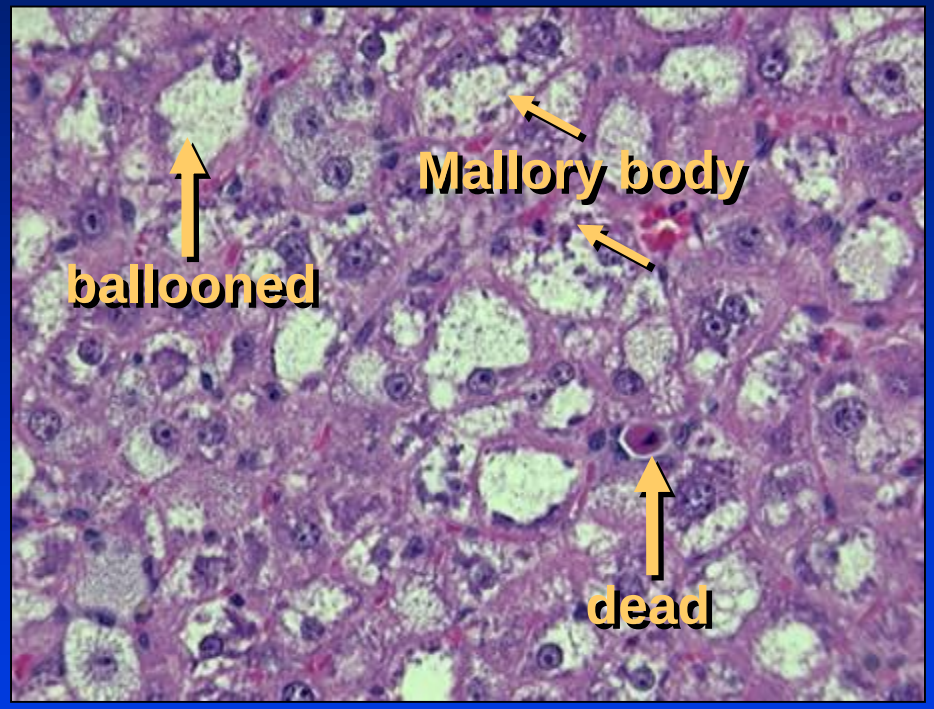


- **Benign course?**
  - **<10% go to cirrhosis**
  - **1.7% liver related mortality**
  - **cardiovascular disease is most common cause of death**

Lomonaco 2012

Non-Alcoholic Fatty Liver Disease
Clinical Implications

Steatohepatitis

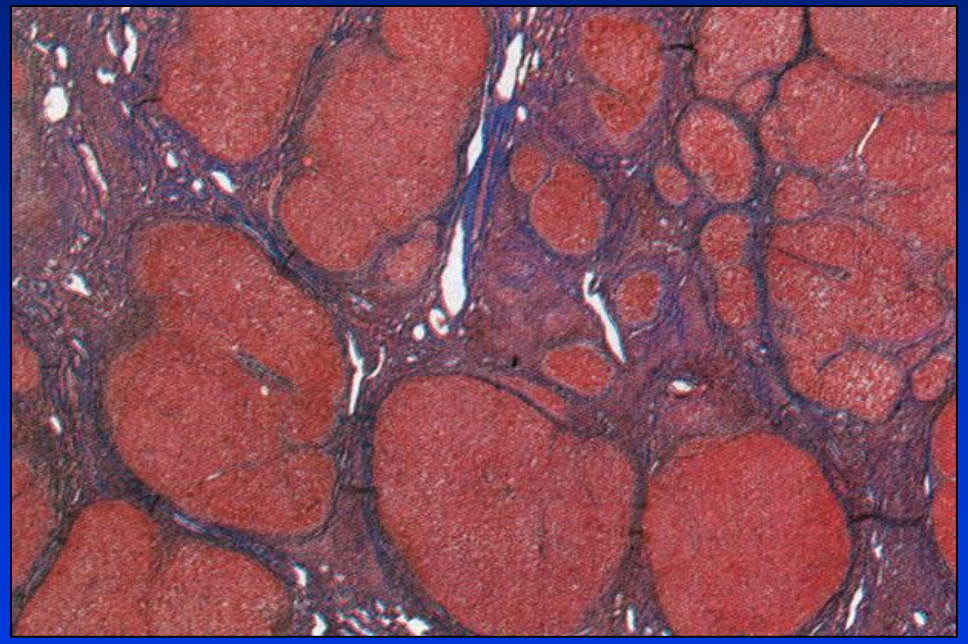


- More severe metabolic syndrome
- ~ 30% advanced fibrosis
- May promote HCC
- 8.6% liver related mortality

Lomonaco 2012

Non-Alcoholic Fatty Liver Disease
Clinical Implications

Cirrhosis (F4)



- Morbidity / mortality
  - significant
  - liver-related
  - co-morbidities
- HCC risk high
- 12.1% liver related mortality

Lomonaco 2012

NAFLD

- NAFLD is the most common cause of CLD in US
- It is strongly associated with metabolic risk factors: obesity, HBP, diabetes mellitus, and dyslipidemia
- Prevalence is higher in men and in hispanics (PNPLA-3 gene)

Risk of Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease

- Meta analysis 3497 patients
- Strongly associated with carotid artery thickness and atherosclerotic plaques compared with controls
- Histological severity correlates with cardiovascular disease

N Eng J Med 2010: 363; 1341-1350

Long-term Outcomes

- Patients with NAFLD have increase overall mortality
- Most common cause of death in patients with NAFLD (NAFL and NASH) is cardiovascular disease
- Patients with NASH (not NAFL) have an increased risk of liver-related mortality including HCC and cancer related mortality (stomach, pancreas, lung)

Clinical Features and Risk Factors

Clinical Features: NAFLD

- Most are asymptomatic (77%)
- Diagnosed on “routine” laboratory testing or abdominal imaging
- Symptoms: fatigue, malaise, vague RUQ abdominal pain
- Hepatomegaly (up to 75%), splenomegaly (up to 25%)
- 53-80% are overweight
- > 1/3 have the metabolic syndrome

Bacon B., et al. Gastroenterology. 1994
Powell EE., et al.Hepatology. 1990
Okolo PI., et al. Sleisenger and Fortran’s, 6th Ed. 1998

Who might have NASH?

The Metabolic Syndrome

Metabolic syndrome
(Syndrome X)

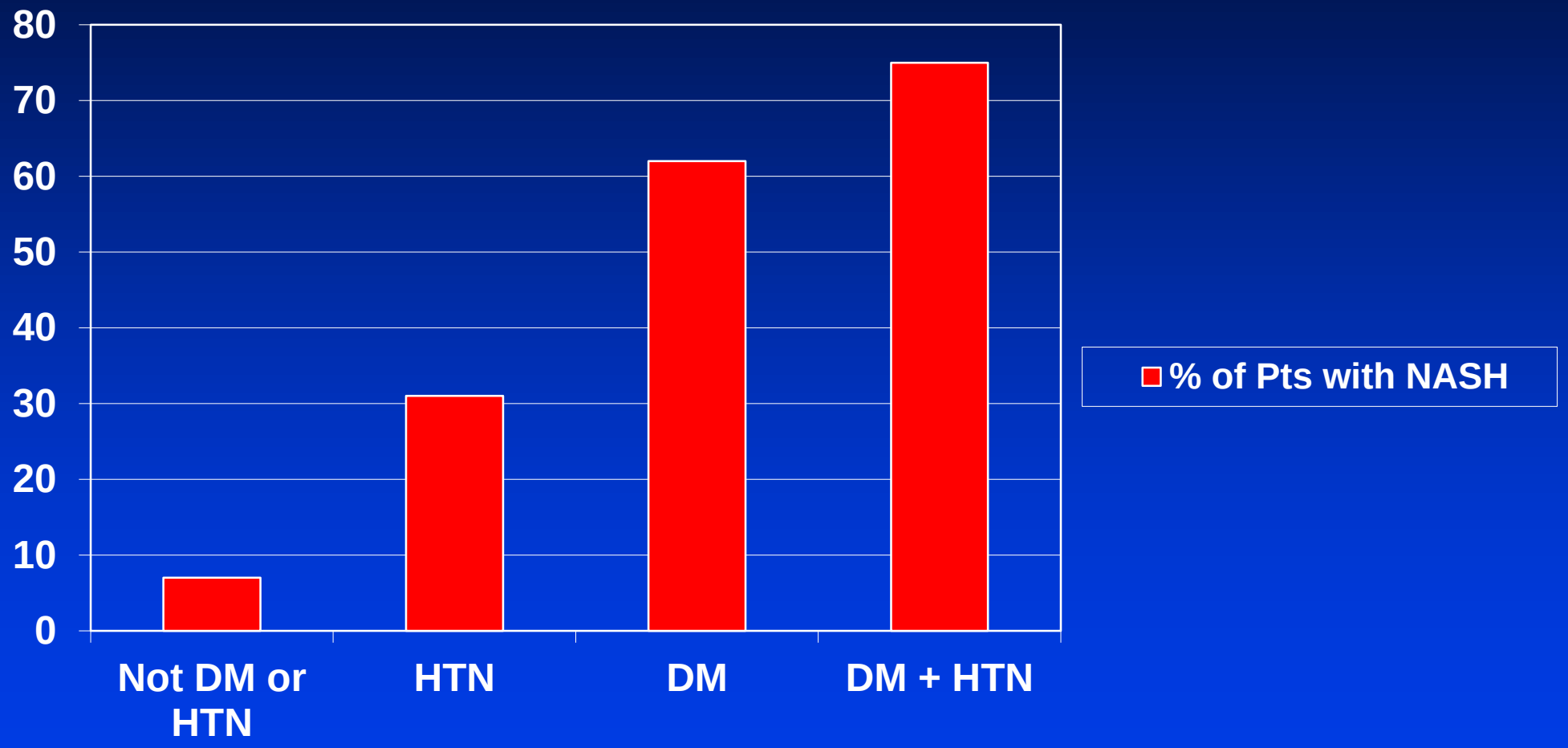
- Central obesity
  WC >102 cm M and 88cm W
- High blood pressure
  >130/85mmhg
- High triglycerides
  >150mg/dl
- Low HDL-cholesterol
  <40 M and <50 W
- Insulin resistance

Fasting plasma glucose level
>110mg/dl

- **Strong predictor for NASH**

**** MAY IDENTIFY PATIENTS WITH ABNORMAL LIVER TESTS WHO WILL BENEFIT FROM A LIVER BIOPSY****

Risk of NASH



Dixon JB, Gastro 2001

Fatty Liver Risk Increases with Daily Intake of Sugary Drinks

- 5908 participants
- Adults who drink more than one sugar sweetened drink per day had 55% more chance of having Fatty Liver disease
- Sucrose and high fructose corn syrup

Journal of Hepatology 2015 vol 63; 462-469

Diagnosis

Initial Evaluation

- Negative viral / autoimmune / genetic markers

- Patients with NAFLD can present with mild elevation of ferritin.
  - Patients with persistent increased ferritin level and increase iron saturation in the context of homozygous or heterozygous C282Y HFE mutations → liver biopsy
  -

- 21% of patients with NAFLD can present with mild elevations of autoantibodies level (ANA 1:160; ASMA 1:40)
  - High serum titers of autoantibodies with other features of autoimmune liver disease → complete workup

Table 2. Common causes of secondary hepatic steatosis

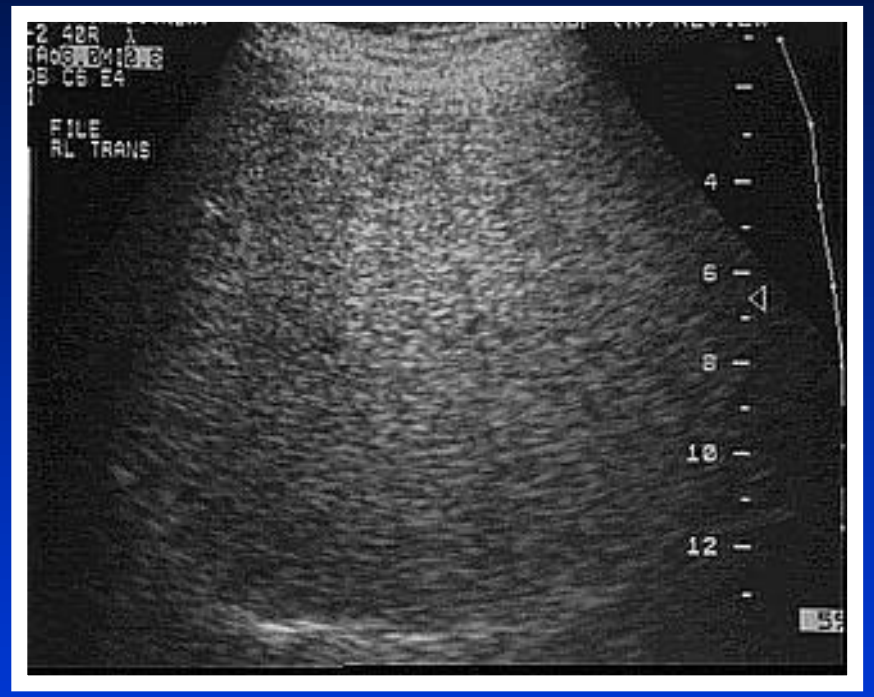
Macrovesicularsteatosis
Excessive alcohol consumption
Hepatitis C (genotype 3)
Wilson's disease
Lipodystrophy
Starvation
Parenteral nutrition
Abetalipoproteinemia
Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)
Microvesicularsteatosis
Reye's syndrome
Medications (valproate, antiretroviral medicines)
Acute fatty liver of pregnancy
HELLP syndrome
Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)

NAFLD Practice guidelines:Hepatology, Vol. 55, No. 6, 2012

Diagnostic evaluation: Liver Profile

- ALT and/or AST are only mildly-moderately elevated
- Normal liver biochemistry results do not exclude advance fibrosis
- +/- Increase in alkaline phosphatase and GGT

Imaging Techniques



- Abdominal ultrasound is your first choice for suspected NAFLD
- Can suggest the presence of cirrhosis when manifestations of portal hypertension are evident

Cannot distinguish simple steatosis from steatohepatitis

Imaging studies for NAFLD- Non-invasive assessment of fibrosis

If fibrosis is suspected:

Transient Elastography (Fibroscan) or MR Elastography (MRE) should be performed

MRE is very accurated for diagnosing fibrosis in NASH but the accuracy is offset by the expense and availability

Non-Invasive Markers of Fibrosis

- NAFLD Fibrosis Score (http://nafldscore.com)
  - Age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio
    - < -1.455 had 90% sensitivity and 60% specificity to exclude advanced fibrosis
    - > 0.676 had 67% sensitivity and 97% specificity to identify the presence of advanced fibrosis

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

Age (years)

BMI (kg/m^2)

IGF/diabetes

AST

ALT

Platelets ($x10^9/l$)

Albumin (g/l)

calculate score

BMI: body mass index
IGF: impaired fasting glucose

© 2009 nafldscore.com

concept: Dr Matthew Armstrong
site construction and design: Dr Jeremy Jones

FORMULA

NAFLD Score = -1.675 + (0.037*age [years]) + (0.094*BMI [kg/m^2]) + (1.13*IFG/diabetes [yes = 1, no = 0]) + (0.99*AST/ALT ratio) – (0.013*platelet count [×10^9/L]) – (0.66*albumin [g/dl])

FACTS & FIGURES

NAFLD Score	Correlated Fibrosis Severity
< -1.455	F0-F2
-1.455 – 0.675	Indeterminant score
> 0.675	F3-F4

Fibrosis Severity Scale

- F0 = no fibrosis
- F1 = mild fibrosis
- F2 = moderate fibrosis
- F3 = severe fibrosis
- F4 = cirrhosis

Non Invasive Markers of Fibrosis

FIB-4 Index

- Algorithm based on platelet count, age, AST, ALT
- Using the Fibrosis-4 score(<1.45 low risk, >3.25 high risk)

  - Srivastava et al, Abstract PS -121 April 22, 2017 International Liver Congress

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

Favorite ★

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

Age		years
AST Aspartate aminotransferase	Norm: 0 - 40	U/L
Platelet count	Norm: 150 - 350	$\times 10^3/\mu L$ ⇋
ALT Alanine aminotransferase	Norm: 0 - 35	U/L

Result:

Please fill out required fields.

When to obtain a liver biopsy in patients with NAFLD?

Predictors of Advanced Fibrosis: Risk for Disease Progression

- Age ≥ 45-50
- Obesity (BMI ≥ 28-30 Kg/m^2)
- AST/ALT >1
- Type 2 Diabetes Mellitus
- Triglycerides > 160
- ALT > 2X normal

Angulo et al: Hepatology (1999)
Ratzui et al. Gastroenterology (2000)

2018 AASLD guidelines:

- The presence of the metabolic syndrome, elevated score by NFS, FIB-4 and/or Fibroscan may be used to identify patients with advanced fibrosis and possible NASH
- In patients with NAFLD in whom coexistent liver disease can not be excluded w/o a liver biopsy

Treatment of NAFLD

Lifestyle Intervention – Diet

- Weight loss results in histological improvement
  - ≥5% of body weight lost = improves HS
  - ≥7% of body weight lost = improves inflammation
  - ≥10% of body weight lost = improvement in all features of NASH, including fibrosis
- Weight loss more important than diet composition
  - Decrease caloric intake by 30% or about 750-1,000 kcal/day

Musso G, et al. Diabetologia 2012;55:885-904

Dietary and Physical Activity Intervention

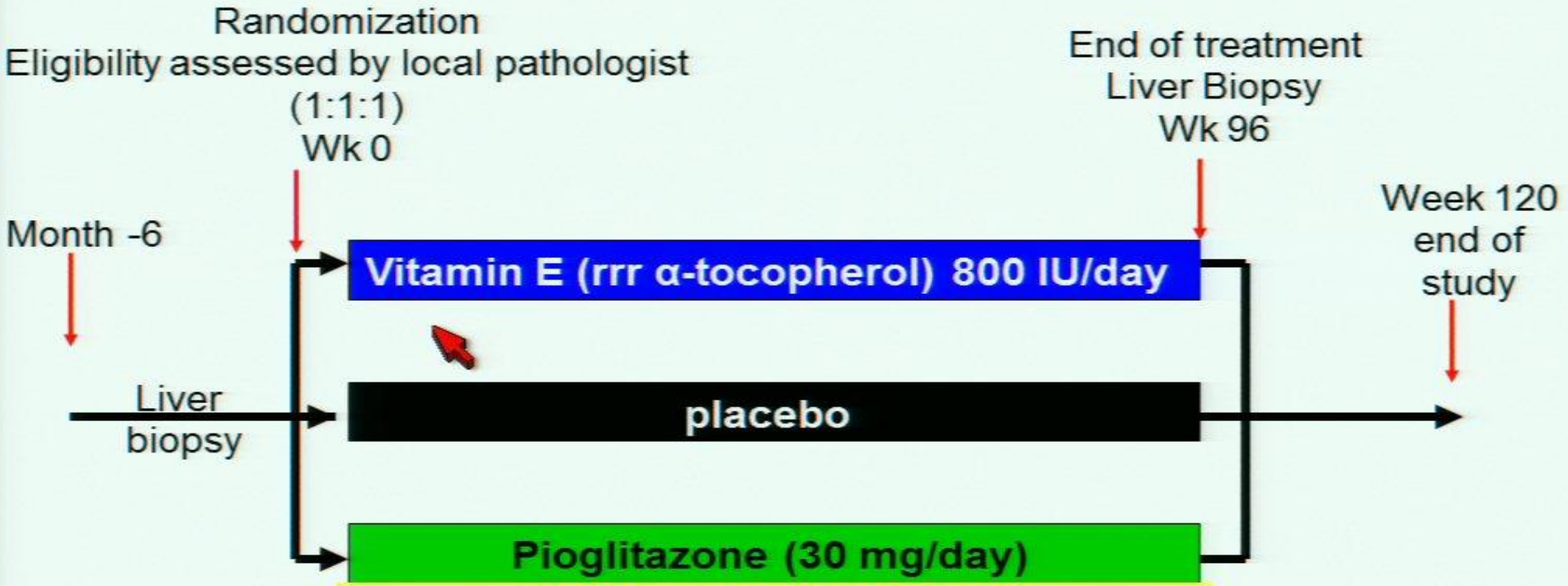
- 5-10% weight loss is achievable with a moderately hypocaloric diet
- More than 150 min/week or increase in activity level by 60 min/week
- Aerobic and resistance exercise are both effective

  - BMJ 2017

Treatment

- Avoid alcohol intake
- Evaluate medication profile
- Immunization against HAV and HBV in patients with cirrhosis
- Antioxidants: Vitamin E 800 IU/d
- Thiazolidinediones: Pioglitazone (30-45 mg/d)

PIVENS Study Design

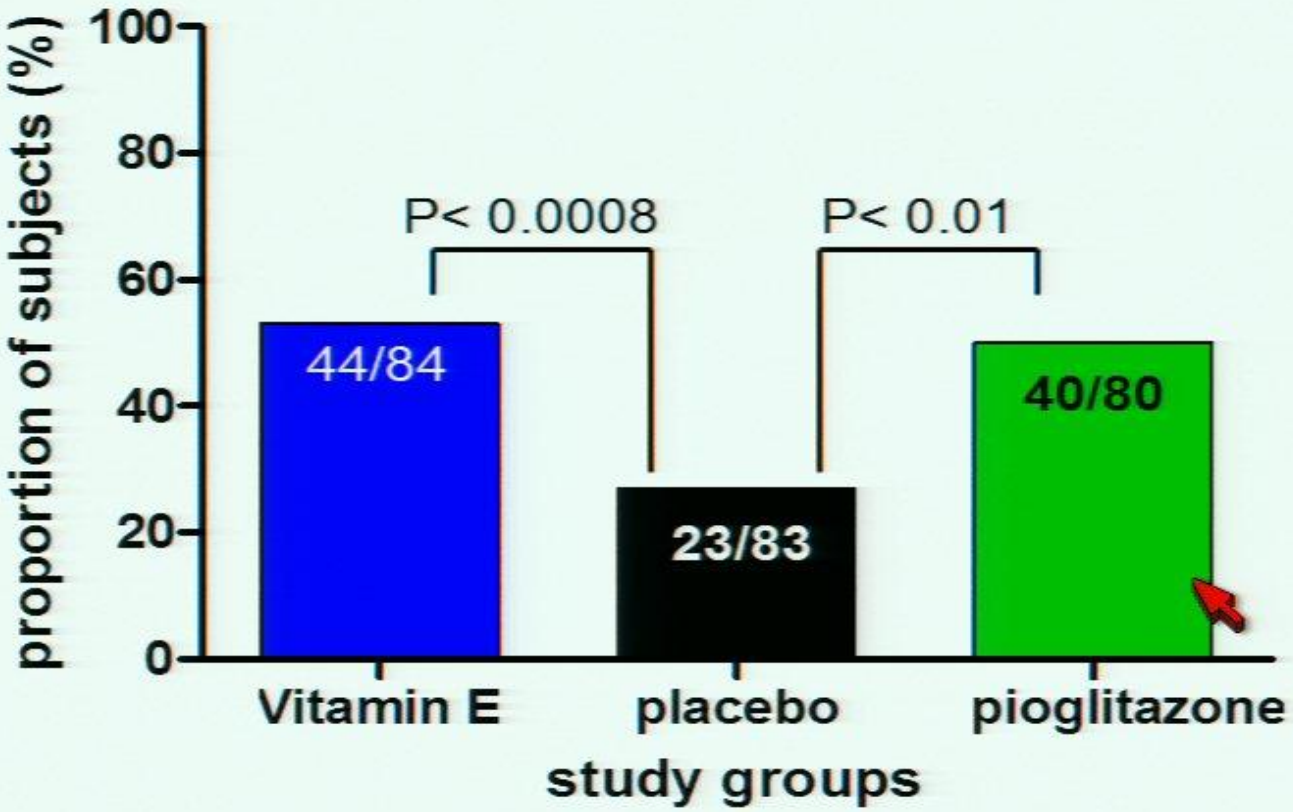


Primary endpoint

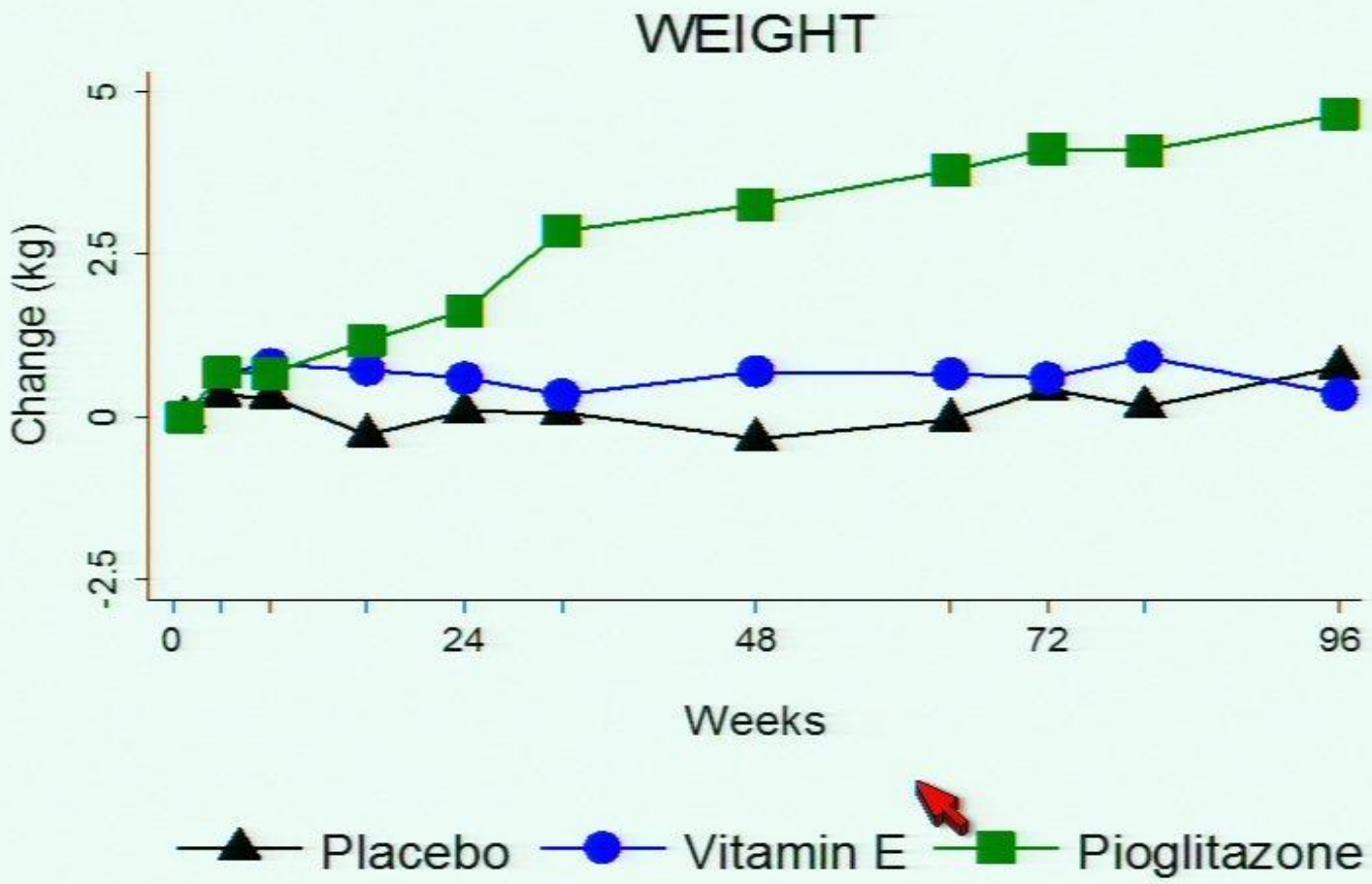
Decrease in NAS by 2 or more points, with at least a 1 point drop in ballooning, and no worsening of fibrosis

Sanyal et al, NEJM, April 28, 2010

Both vitamin E and pioglitazone increased the proportion of subjects with resolution of NASH



Change in body weight



Vitamin E

- Summary of studies in NASH
  - Vitamin E decreases serum aminotransferases
  - Improves steatosis, inflammation and ballooning and achieves resolution of NASH in a subset of nondiabetic patients
  - No effects on hepatic fibrosis

Chalasani N, et al. Hepatology 2018;67:328-357

Vitamin E

Vitamin E - Concerns

- Questionable association with long-term all-cause mortality with doses >800IU/d
- One study found an association with increased risk of prostate cancer

Abner EL, et al. Curr Aging Sci 2011;4:158-170
Klein EA, et al. JAMA 2011;306:1549-1556

Vitamin E – AASLD Guidance

- Vitamin E (*rrr* α-tocopherol) 800 IU/day improves liver histology in nondiabetic with biopsy proven NASH
- Risk and benefits should be discussed with each patient
- Vitamin E is not recommended to treat NAFLD without biopsy proven NASH

Chalasani N, et al. Hepatology 2018;67:328-357

Vitamin E for NASH in T2DM

- Double-blind, placebo controlled trial from 2010-2016
- T2DM with biopsy proven NASH (105) randomized to Vitamin E 400 IU bid plus pioglitazone 45 mg/day, Vitamin E alone vs placebo for 18 months
- Primary endpoint: two point reduction in NAS without worsening of fibrosis
  - 54% on the combination therapy achieved primary endpoint versus 19% placebo group, P=0.003 but not with Vitamin E alone (31%, P=0.26)
  - No improvement in fibrosis was observed in any group

Bril F, et al. Diabetes Care. 2019

Pioglitazone

- 55 patients w NASH and prediabetes and T2DM treated with pioglitazone (45 mg/day) versus placebo
  - Improved insulin sensitivity, aminotransferases, steatosis, inflammation, and ballooning
  - NAS improved with pioglitazone in 73% compared to 24% of placebo treated patients ($p<0.001$)

    Belfort et al. NEJM 2006

Pioglitazone

- 101 patients with prediabetes (49) and T2DM (52) with a hypocaloric diet and pioglitazone (45 mg/day) or placebo for 18 months followed by an 18 month open label phase with pioglitazone
- Primary outcome was a reduction of at least 2 points in the NAS without worsening of fibrosis
  - 58% of pioglitazone treated patients achieved primary outcome and 51% had resolution of NASH
    - Cusi et al. Ann Intern Med 2016

Glucagon-like Peptide-1 agonist

- Randomized, placebo-controlled trial of 52 patients with biopsy proven NASH with liraglutide 1.8 mg administered once daily(26) for 48 weeks vs placebo (26)
  - Associated with greater resolution of steatohepatitis (39%)
  - Less progression of fibrosis
    - Armstrong MJ et al. Lancet 2016
- Guidance: It is premature to consider GLP-1 agonists to treat liver disease in patients with NASH

Anti-hyperglycemic drugs in patients with NAFLD

- Systematic review of 29 RCTs (2, 617 patients, 45% had T2DM)
- Metformin (n=6 studies), glitazones (n=8 studies), glucagon-like peptide-1 agonists (n= 6 studies), dipeptidyl peptidase- 4 inhibitors (n=4 studies) or sodium-glucose cotransporter-2 inhibitor (n= 7 studies)
- Only pioglitazone and liraglutide showed an improvement of histological features of NAFLD, with mild beneficial effect on liver fibrosis for pioglitazone only.
- Mantovani A, et al. Diabetes Metab 2020

Pioglitazone-AASLD Guidance

- Pioglitazone improves liver histology in patients with and without T2DM with biopsy proven NASH
- Risks and benefits should be discussed
- Pioglitazone should not be used to treat NAFLD without biopsy proven NASH

Bariatric Surgery – AASLD Guidance

- **Bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH**
- **Bariatric surgery is not yet an established option to specifically treat NASH**
- **Type, safety and efficacy of bariatric surgery in otherwise eligible patients with cirrhosis is not established**

Chalasani N, et al. Hepatology 2018;67:328-357

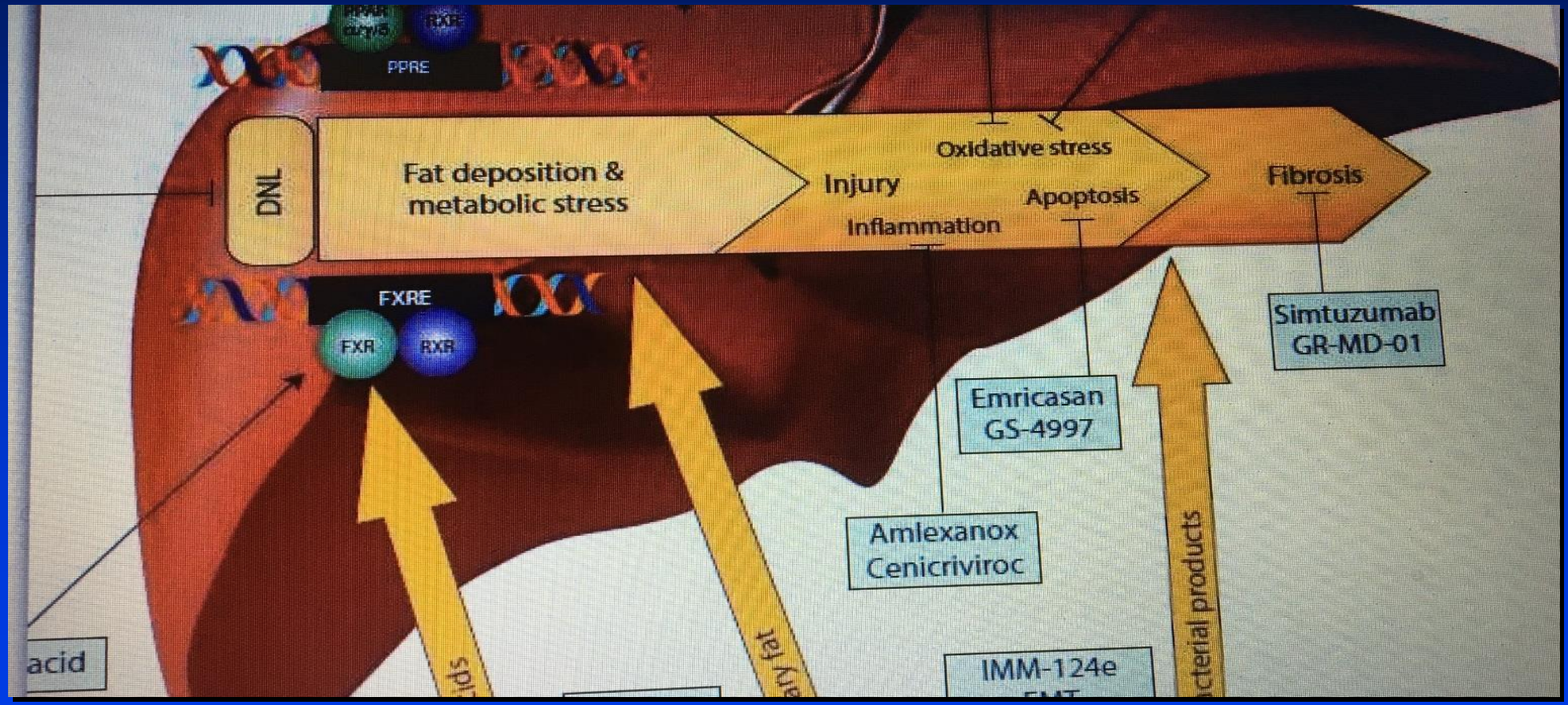
Cardiovascular disease in NAFLD

- **Cardiovascular disease is the leading cause of death**
- **Patients with NAFLD should be risk stratified for Cardiovascular disease and managed accordingly**
- ***Statins can be used safely to treat dyslipidemia since there is no evidence that patients with NAFLD and NASH are at higher risk for serious liver injury than those w/o liver disease (2018 AASLD guidelines)***

No Role in NAFLD

- Metformin
- Ursodeoxycholic acid
- Omega-3 fatty acids

The Future in Therapy for NAFLD



Rapidly Changing Landscape for NAFLD therapeutics

- 2013: 8 active clinical trials
- Nov 2015: 265 active clinical trials
- April 2016: 394 active clinical trials
- Multi-targeted therapy as seen in Hep C is the future

Regimens in Phase 3 Clinical Trials

- Obeticholic acid (Farnesoid X receptor agonist-FXR) met fibrosis endpoint in phase 3 REGENERATE
- Elafibranor (PPAR) met NASH endpoint in phase 3 Golden-505, Phase 3 RESOLVE-IT is ongoing

Regenerate trial: 18-month interim efficacy analysis

- 2730 pts with NASH (F1-3):
  - Obeticholic acid 10 mg, 25 mg or placebo
  - Fibrosis improvement (>1 stage with no worsening of NASH): 18% for 10 mg, 23% for 25 mg, 12% for placebo)
  - No statistical difference for NASH resolution

Summary and Conclusions

- NAFLD is a common disorder, its more severe form (NASH) has a potential to progress to cirrhosis
- Most common cause of death in patients with NAFLD is cardiovascular disease and statins can be used safely to treat dyslipidemia
- Patients with NASH have an increased risk of liver-related mortality including HCC

Summary and Conclusions

- **The metabolic syndrome is a strong predictor of NASH and advanced fibrosis**
- **Liver biopsy is the gold standard for histologic stratification but non-invasive tests can provide insight of presence of fibrosis**
- **Pharmacological therapy research is very active**
- ***The mainstay of treatment is to control the predisposing conditions***


WARNING
This is not
good for your
LIVER


Fatty Liver: The Silent Threat

THANK YOU!


STOP
TM


JUST SAY
NO
TO A FATTY LIVER