Emerging Therapies for NASH: What Can We Look Forward to and When?

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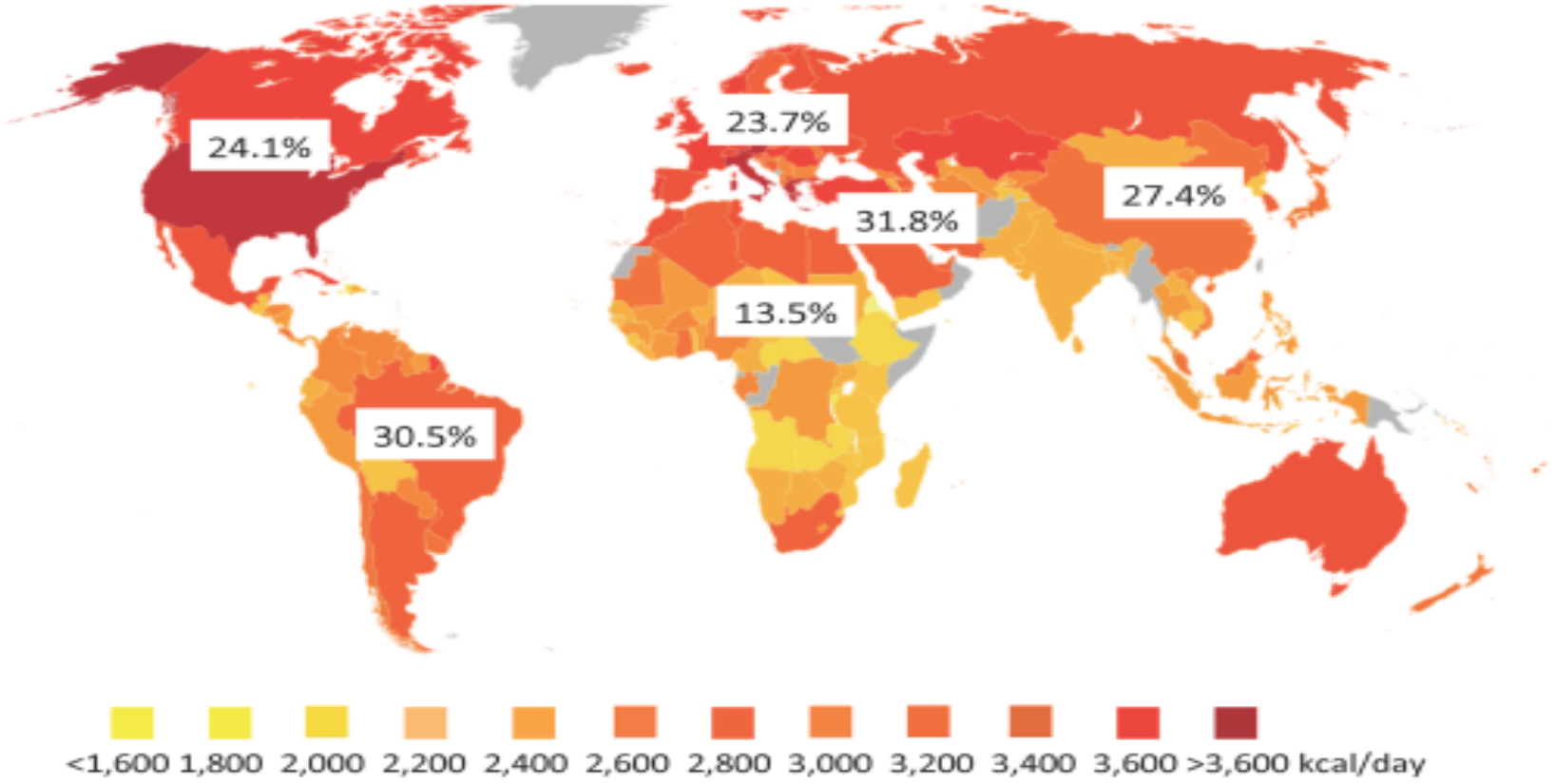
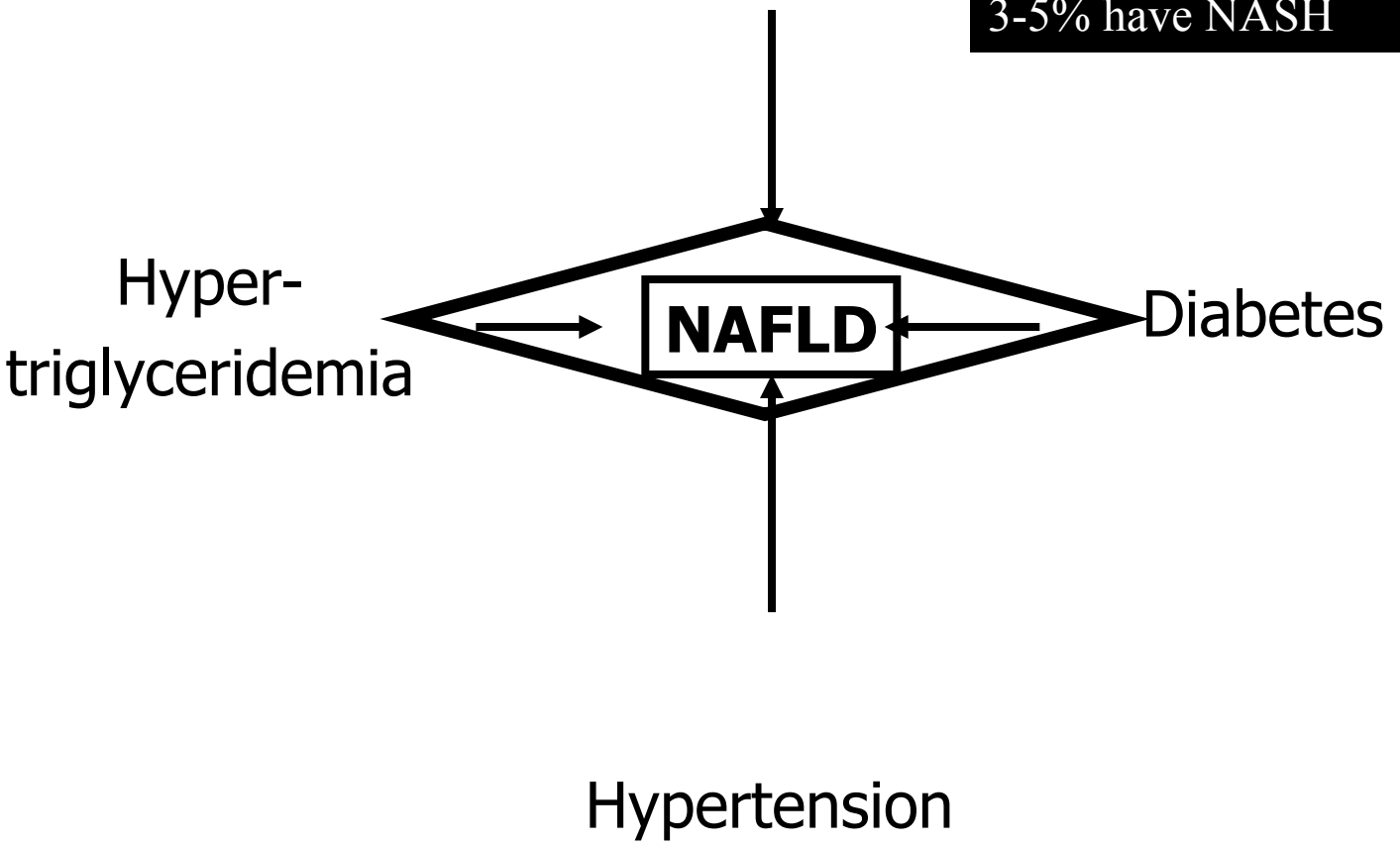
NAFLD seen Globally



NAFLD: the hepatic manifestation of the metabolic syndrome

120 million have metabolic syndrome
~80% have NAFLD
30% of US population has a fatty liver
3-5% have NASH

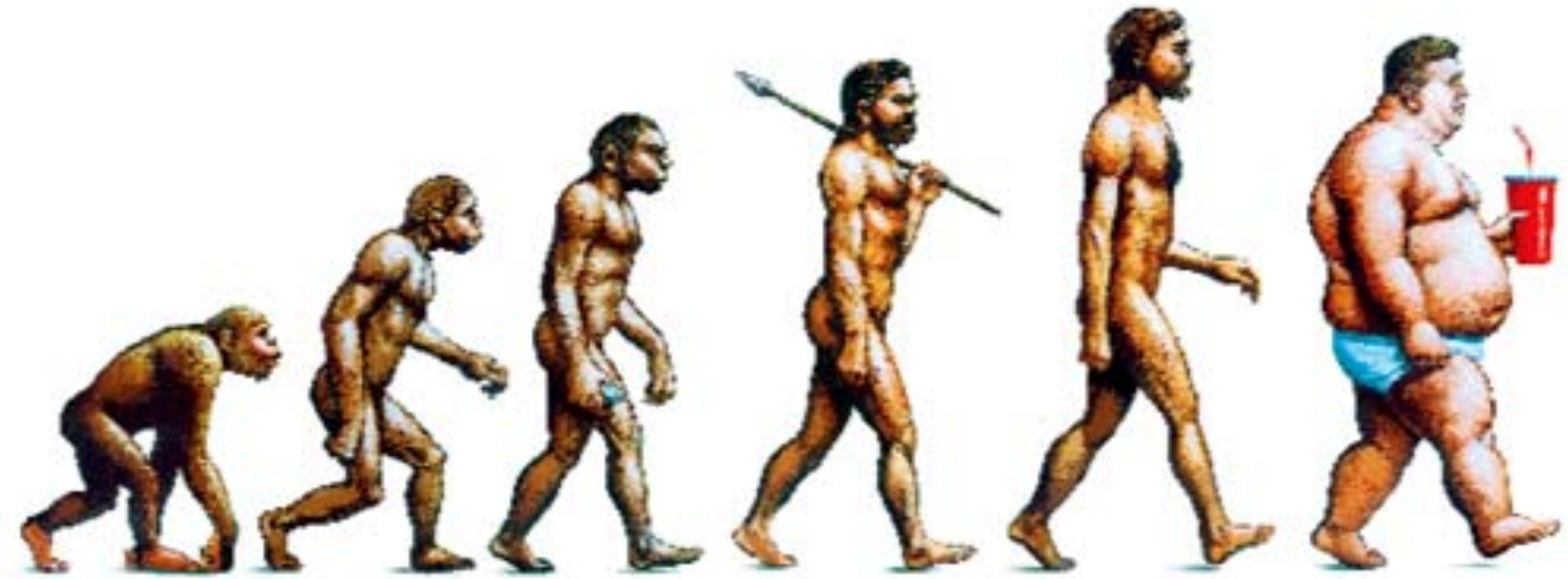


Outcomes in NAFL-D

	Surrogates	# Studies	OR [95% CI]
Overall Mortality	•NAFLD vs. General Population	8 studies	1.57 [1.18-2.10]
Incident CVD	•ALT as a surrogate •GGT as a surrogate •Imaging as a surrogate	6 studies 10 studies 7 studies	1.10 [0.85-1.41] 1.57 [1.42-1.74] 2.05 [1.81-2.31]
Incident type2 DM	•ALT as a surrogate •GGT as a surrogate •Imaging as a surrogate	17 studies 12 studies 3 studies	1.97 [1.77-2.20] 2.74 [2.39 – 3.14] 3.51 [2.28-5.41]

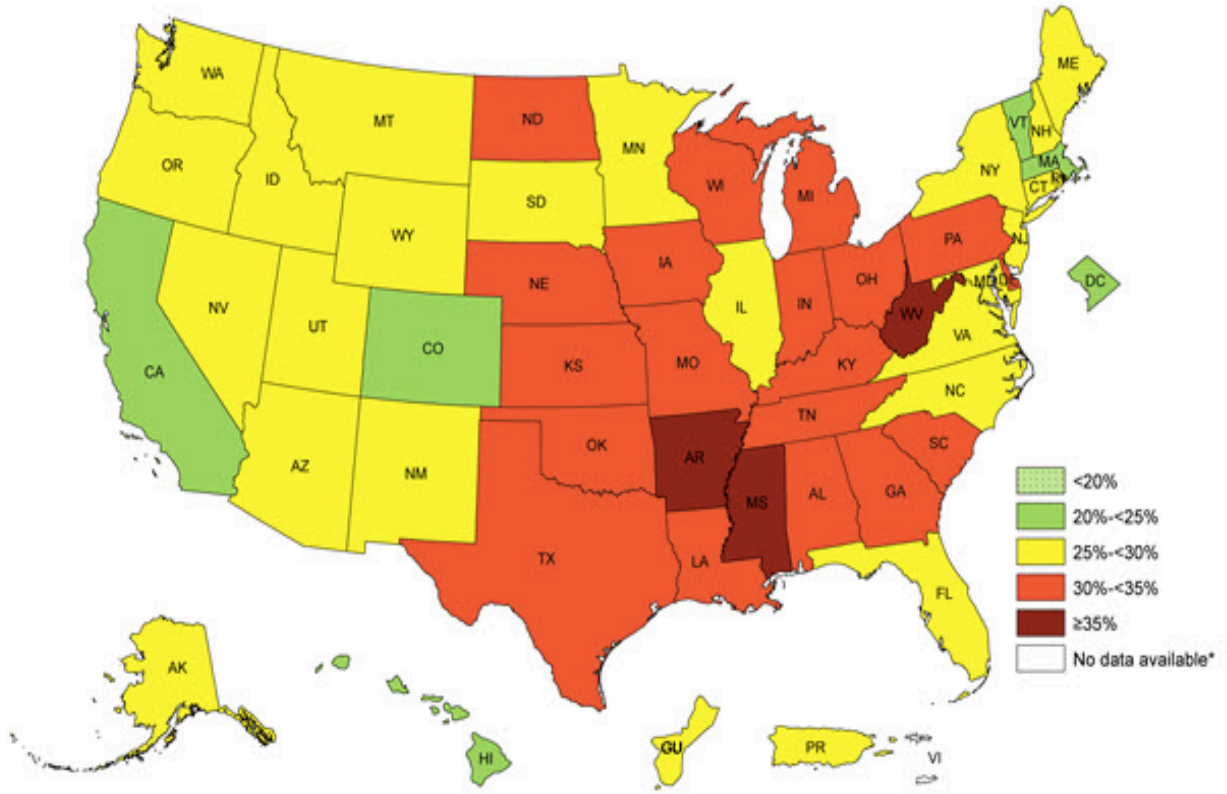
Williams Annals of Internal Medicine 2011

A Disturbing Evolutionary Development



Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014

¶Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



Source: Behavorial Risk Factor Surveillance System, CDC.

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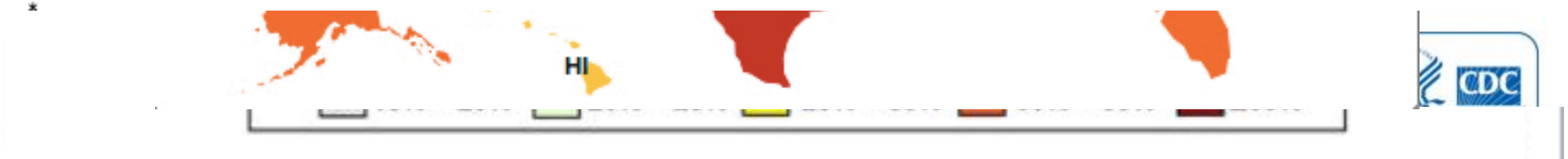
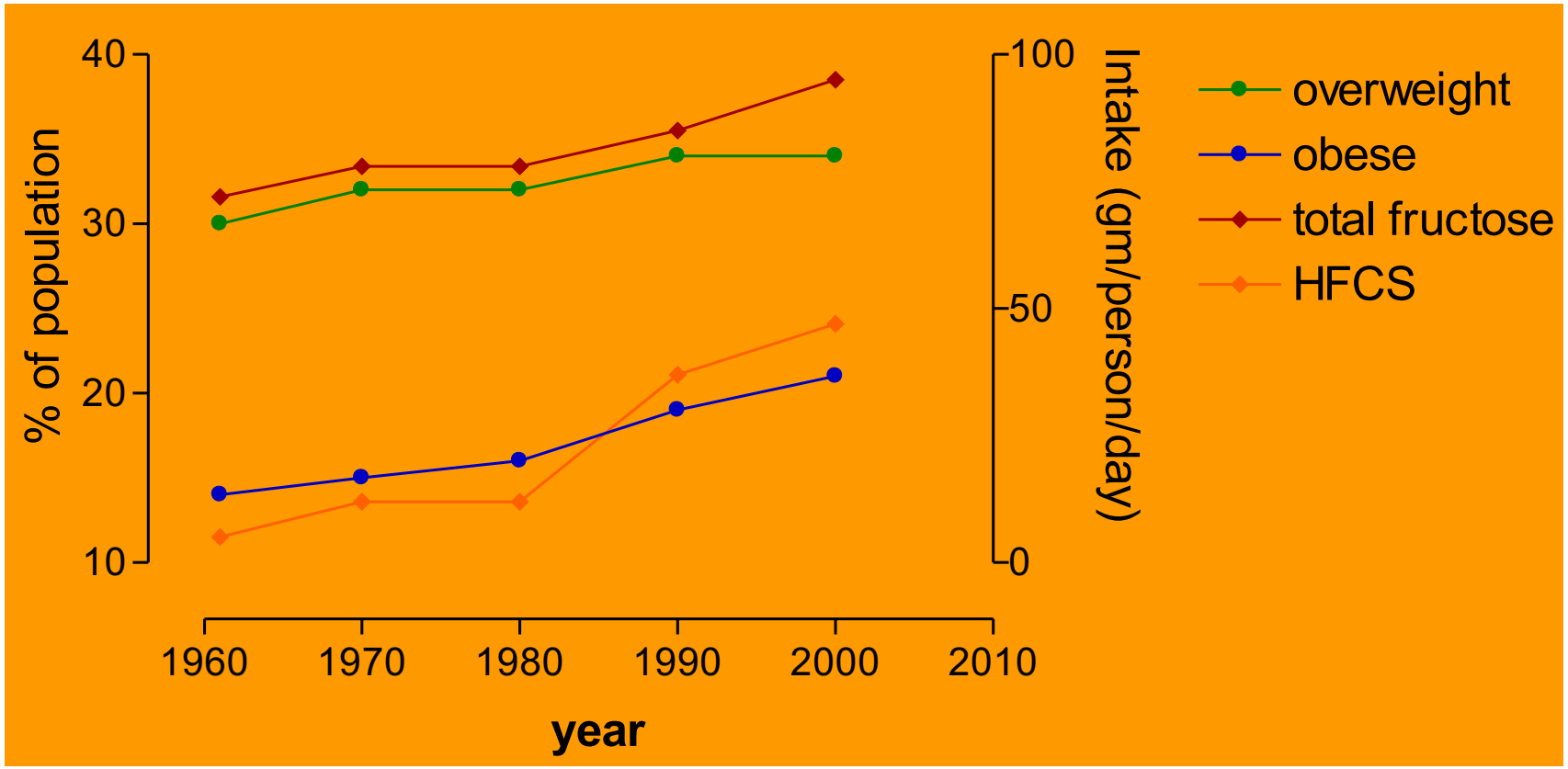


Risk Factors for NAFLD

Major Co-morbidities	**Emerging Associations**
Type 2 Diabetes	Hypothyroidism
Dyslipidemia	Sleep Apnea
Obesity	Hypopituitarism
Metabolic Syndrome	Polycystic Ovary Syndrome

Estimated fructose intake and weight trends in the U.S.



Bray et al, Am J Clin Nutr, 2004, 79:537-43

Fructose

- Dietary Carbohydrates can be converted to fat in the liver
- Fructose (alone or as part of sucrose) drives lipogenesis and promotes NAFLD
- Epidemiologic studies, clinical trials, and animal studies show that excess carbohydrate consumption contributes to NAFLD
- High fructose consumption depletes hepatic ATP and impairs recovery from ATP depletion

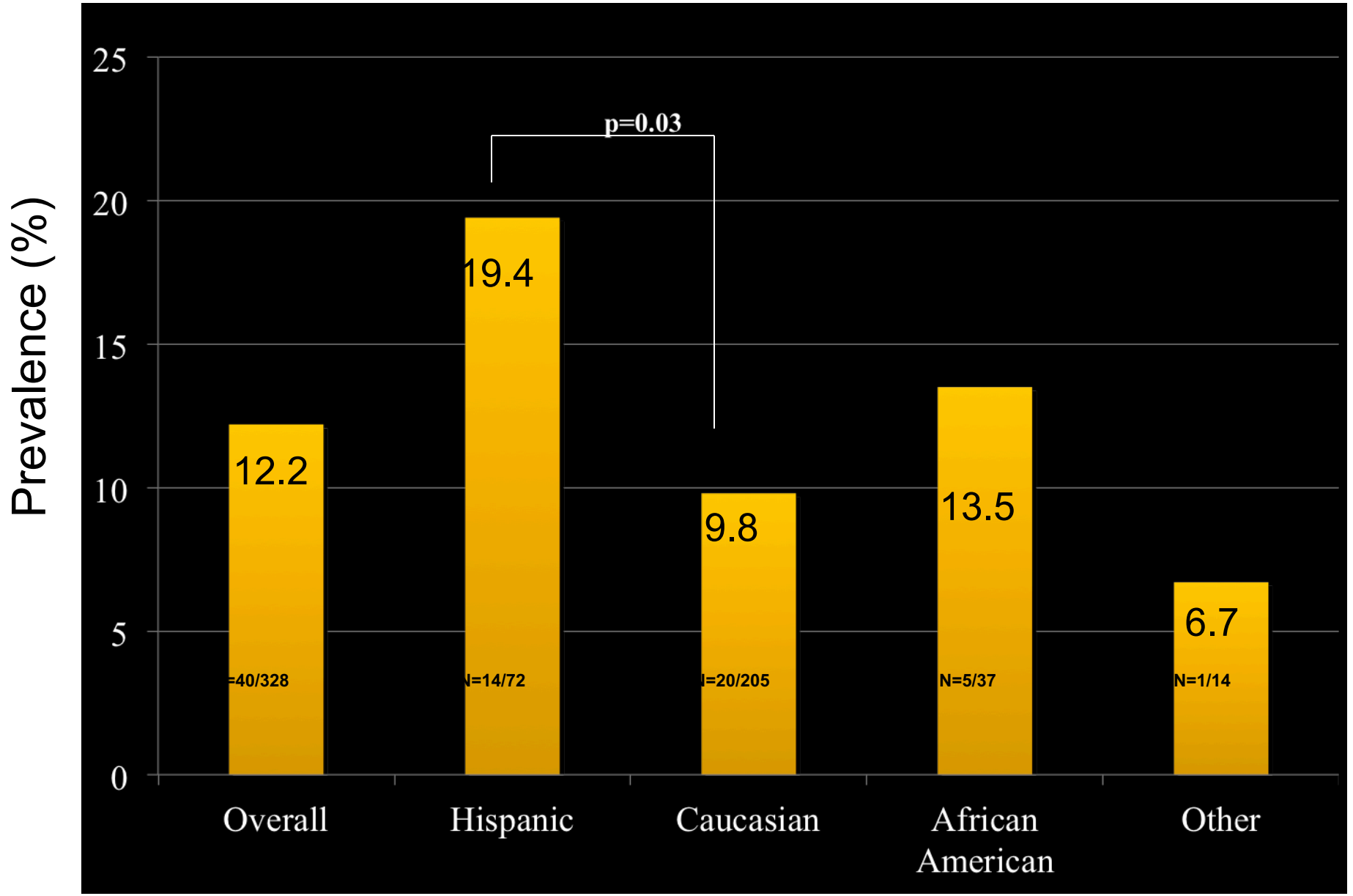
NAFLD and Ethnicity

- Hepatic TG content by MRS* in 2,287 subjects
- 32.1% White, 48.3% Black, 17.5% Hispanic
- One-third had hepatic steatosis
- 45% Hispanics, 33% Whites, 24% Blacks
- Most (79%) had normal serum ALT
- Steatosis related to IR, obesity in Hispanics
- Not related to these risk factors in Blacks
- Steatosis > Men:Women except in Blacks

*proton magnetic resonance spectroscopy

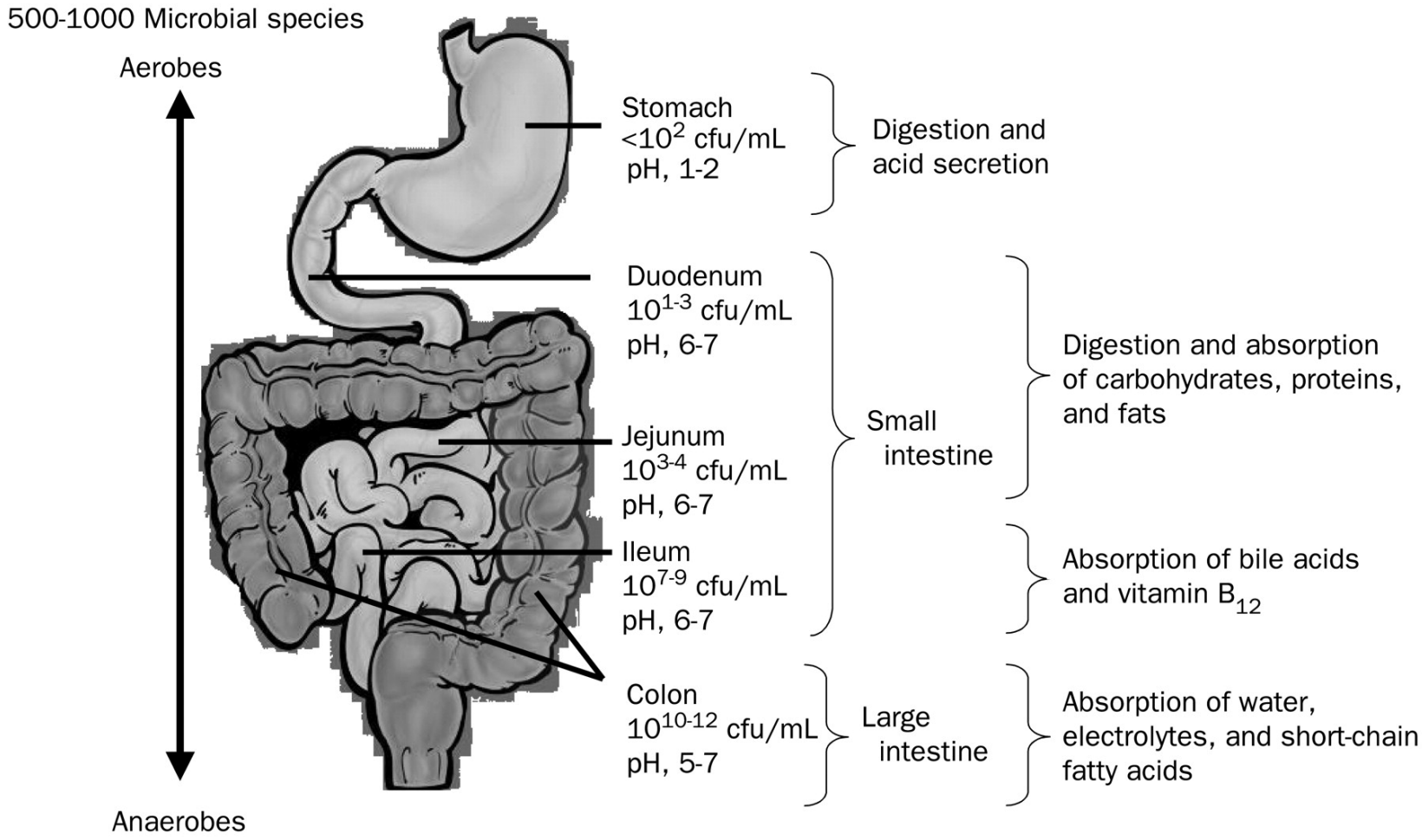
Browning et al. Hepatology. 2004 ;40:1387-95

NASH Prevalence Among Ethnic Groups



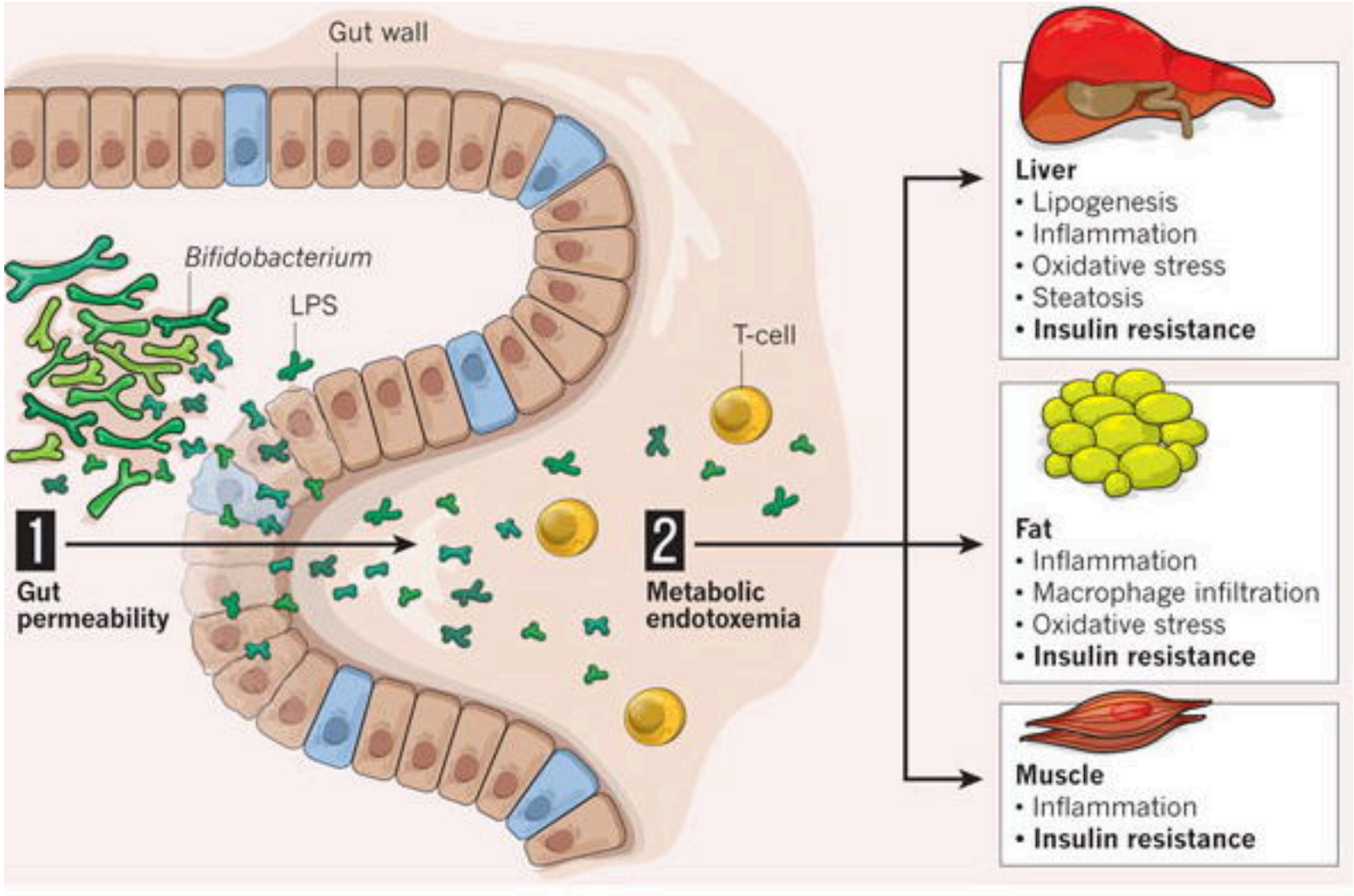
Williams, Gastroenterology 2011

Key physiologic and microbiological features of the gut

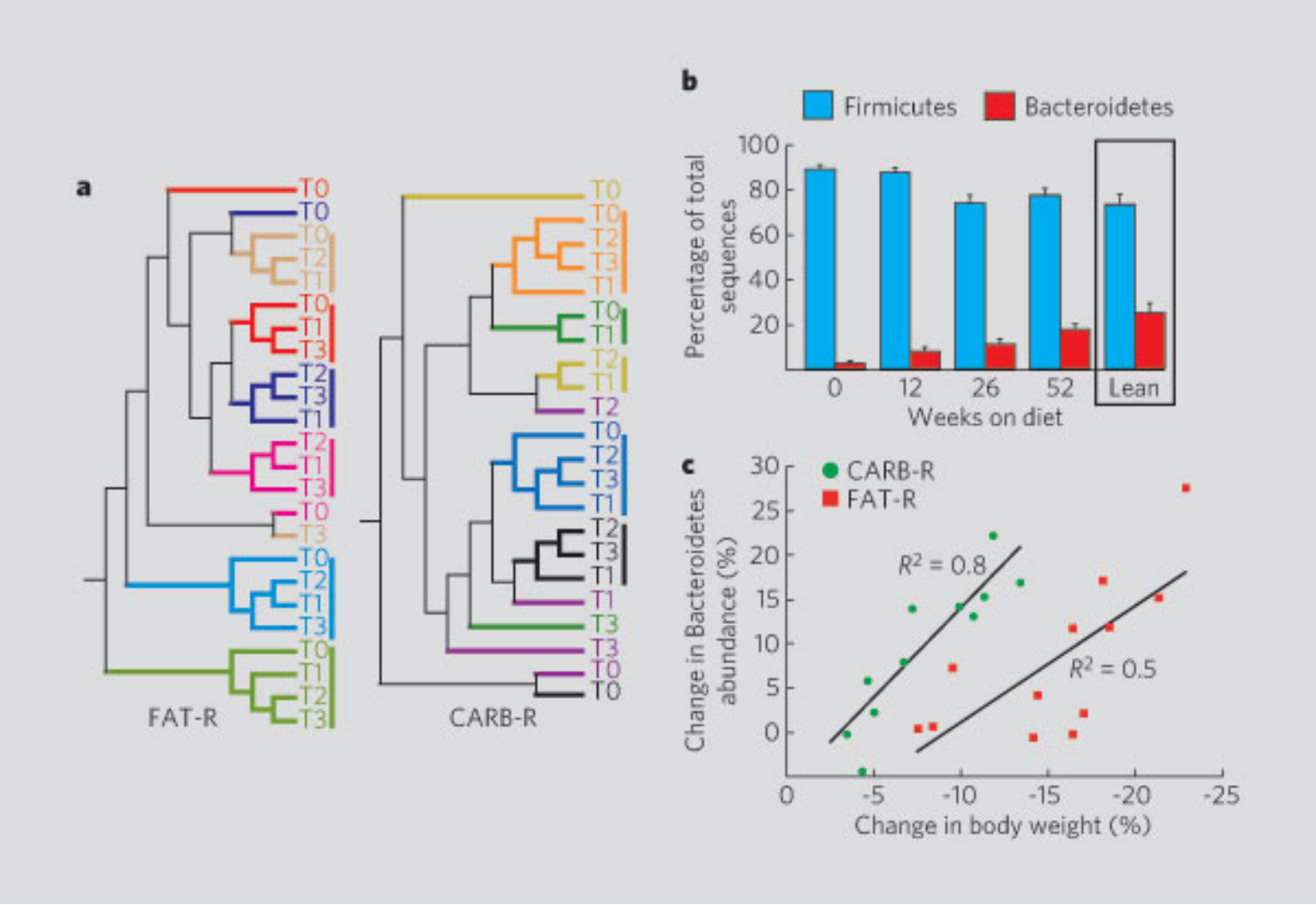


DiBaise J K et al. Mayo Clin Proc. 2008;83:460-469

The intestinal microbiome modulates insulin resistance and metabolism



Before diet therapy, obese people had fewer Bacteroidetes (P<0.001) and more Firmicutes (P=0.002) than did lean controls

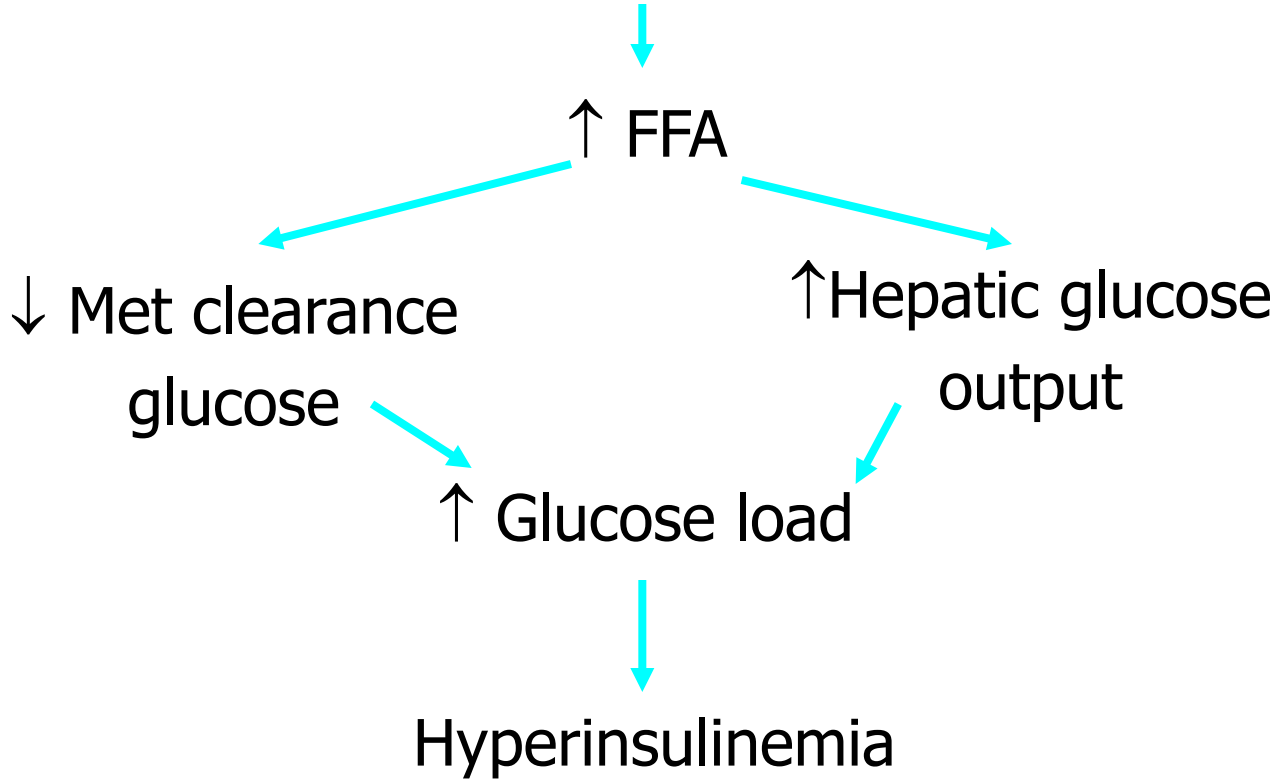


Nature **444**, 1022-1023(21 December 2006)

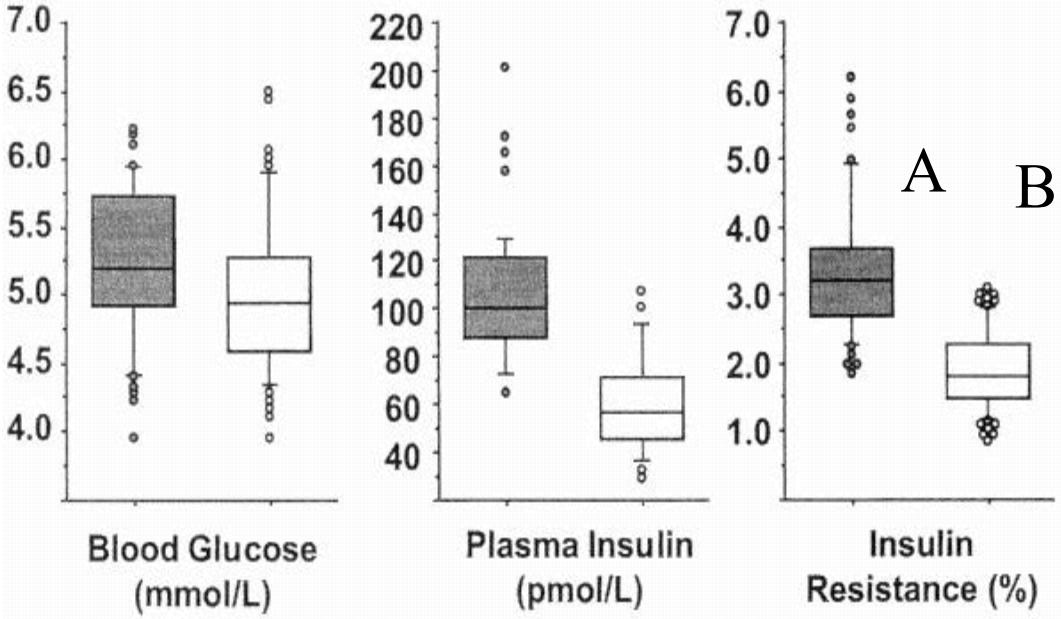
Risk Factors for NAFL-Dis of NAFLD

Obesity, Genetics, Environment (bacteria), Diet, Activity

(Insulin sensitivity vs resistance)



Insulin Resistance in NASH



A=NASH
B=Control

Marchesini et al., Am J Med 1999;107:450-5

Stages of fatty disorders of liver those with fatty liver rarely progress to steatohepatitis

- **Fatty liver**

Mortality: ~ 3%

Risk factors: age, diabetes, BMI

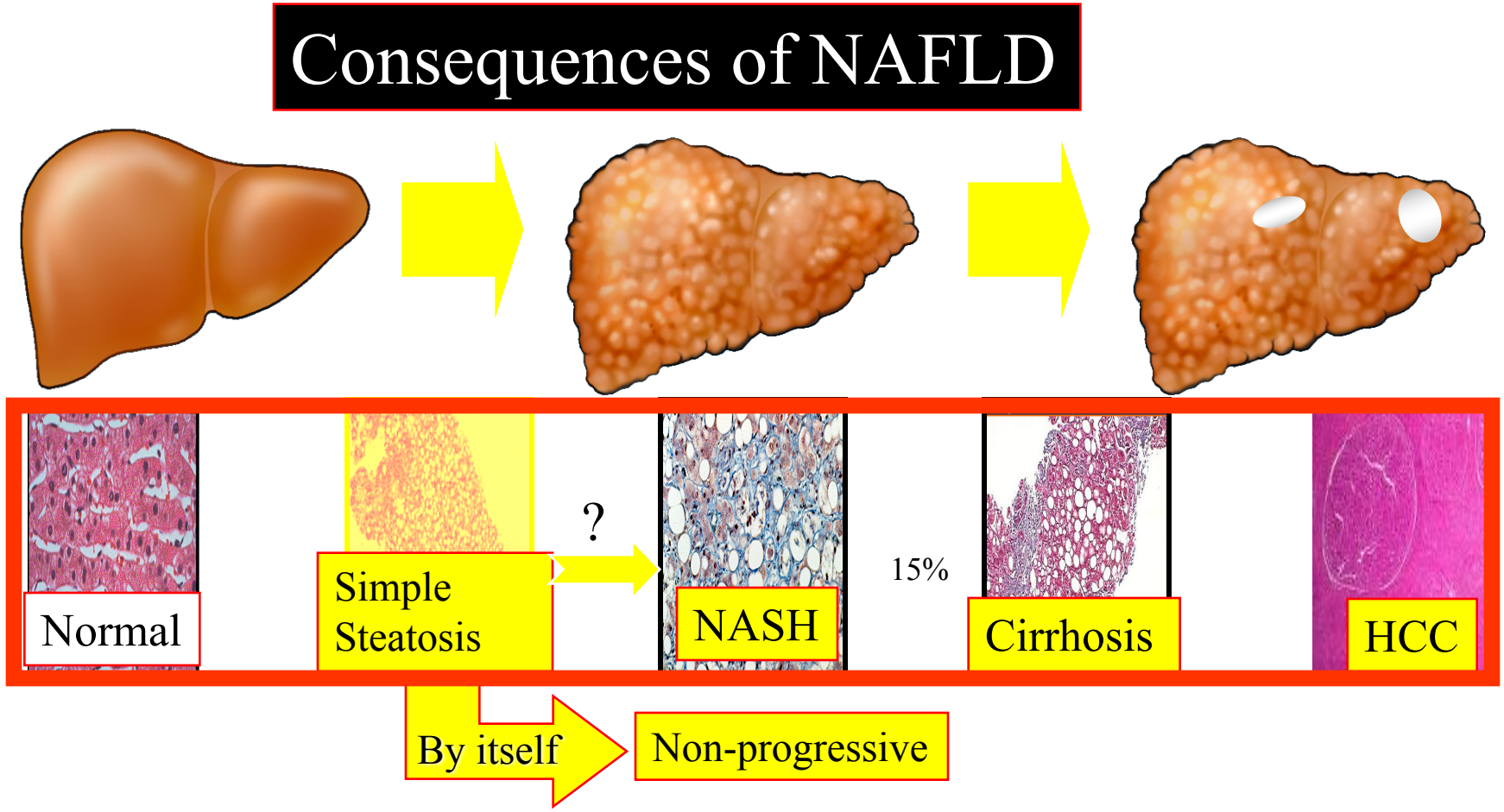
- **steatohepatitis**

- **Steatohepatitis + fibrosis**

- **Steatohepatitis + cirrhosis**

Hepatocellular cancer

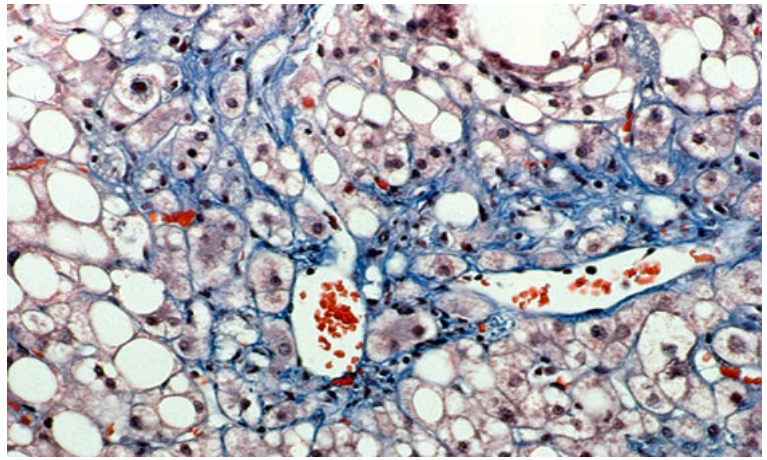
IS NAFLD Progressive?



Ludwig 1980 , Diehl 1988, Lee 1989, Powell 1990, Bacon 1994, Matteoni 1999, Angulo 1999, Caldwell 1999, Ponawala 2000, Contos 2001, Ong 2001,, Bugianesi 2002, Ratziu 2002, Harrisson 2003, Marchesini 2003, Younossi 2004, Fassio 2004Sanyal 2004, Ong 2005, Adams 2005, Ong 2006, Rafiq 2008

Types of Fatty Liver Disease

NASH

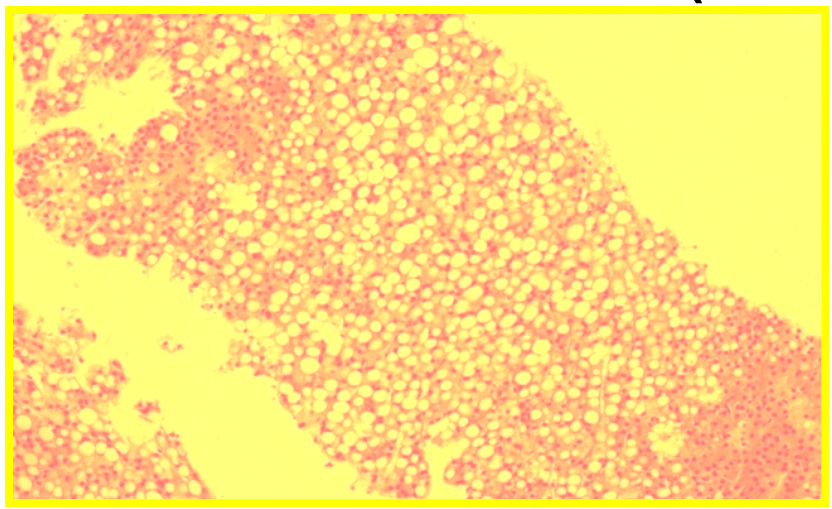


Over 10 years

10%-20%

Cirrhosis

Steatosis alone (NAFL)



By itself

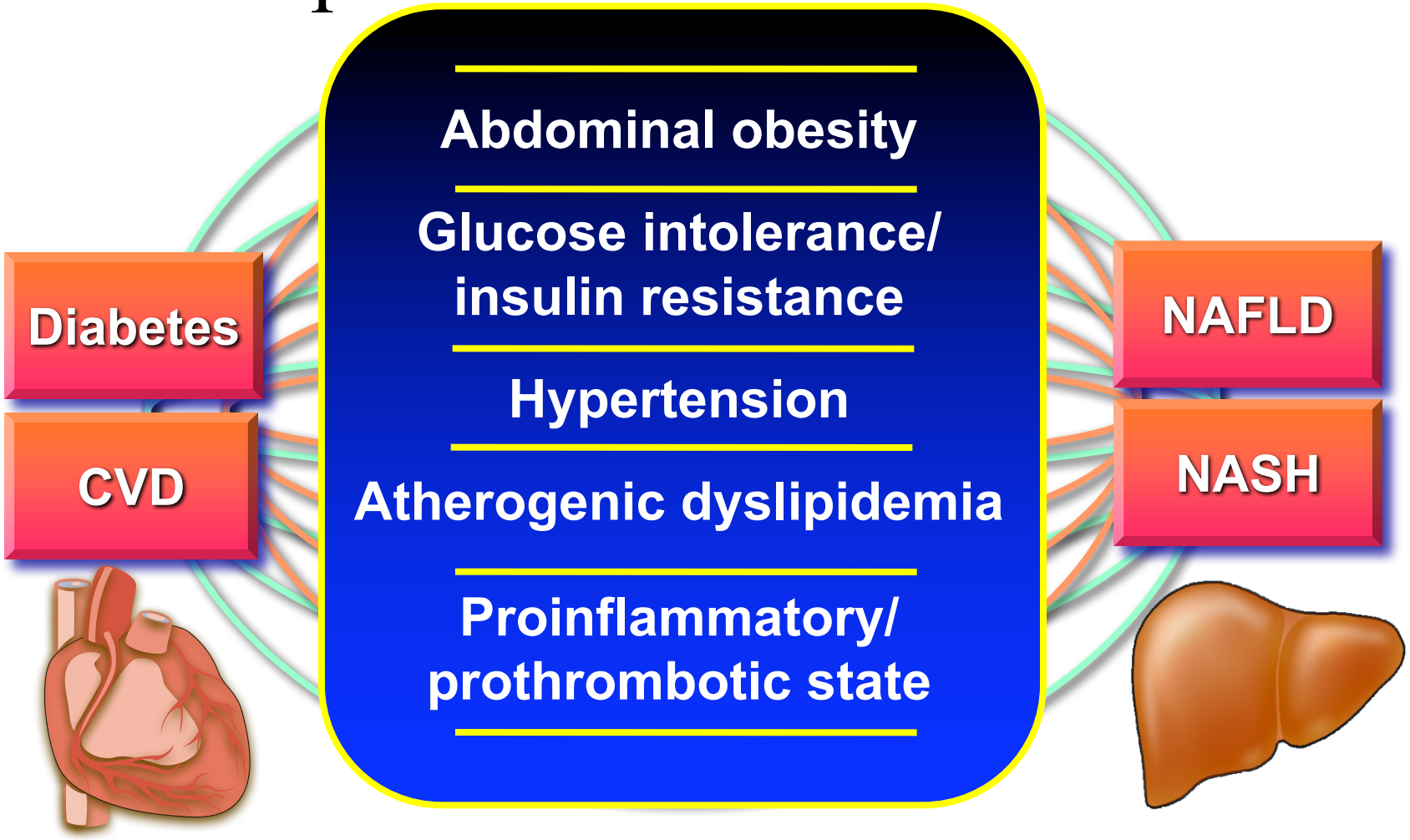
Benign

Liver-Related and Overall Mortality in Patients with NAFLD

	Author	n	Follow-up (mean, yrs)	Liver-related mortality	Overall mortality	Increased Mortality¶
Simple Steatosis	Matteoni et al (1999)	49	9	2.0%	33.0%	No
	Ekstedt et al (2006)	58	14	0.0%	12.1%	No
	Rafiq et al (2009)	74	19*	2.7%	56.8%	No
	Soderberg et al (2010)	67	21	3.0%	34.3%	No
	Dam-Larsen et al (2009)	170	21	0.6%	28.2%	No
	Total/mean	**418**	**17**	**1.7%**	**32.9%**	
NASH	Matteoni et al (1999)	29	8	10.0%	30.0%	Yes
	Ekstedt et al (2006)	71	14	2.8%	26.8%	Yes
	Rafiq et al (2009)	57	19*	17.5%	63.2%	Yes
	Soderberg et al (2010)	51	21	5.9%	47.1%	Yes
	Evans et al (2002)	26	9	-	15.0%	Yes
	Adams et al (2005)	49	8	8.1%	35.0%	Yes
	Younossi et al (2011)	131	10*	15.7%	21.3%	NR
	Total/mean	**349**	**11**	**8.6%**	**34.1%**	
NAFLD-related cirrhosis	Hui et al (2003)	23	7	21.0%	26.0%	NR
	Sanyal et al (2006)	152	10	14.5%	19.1%	NR
	Yatsuji et al (2009)	68	5	7.3%	27.9%	NR
	Bhala et al (2011)	247	7	5.7%	13.4%	Yes
	Total/mean	**490**	**7**	**12.1%**	**24.3%**	

Lomonaco & Cusi, 2012

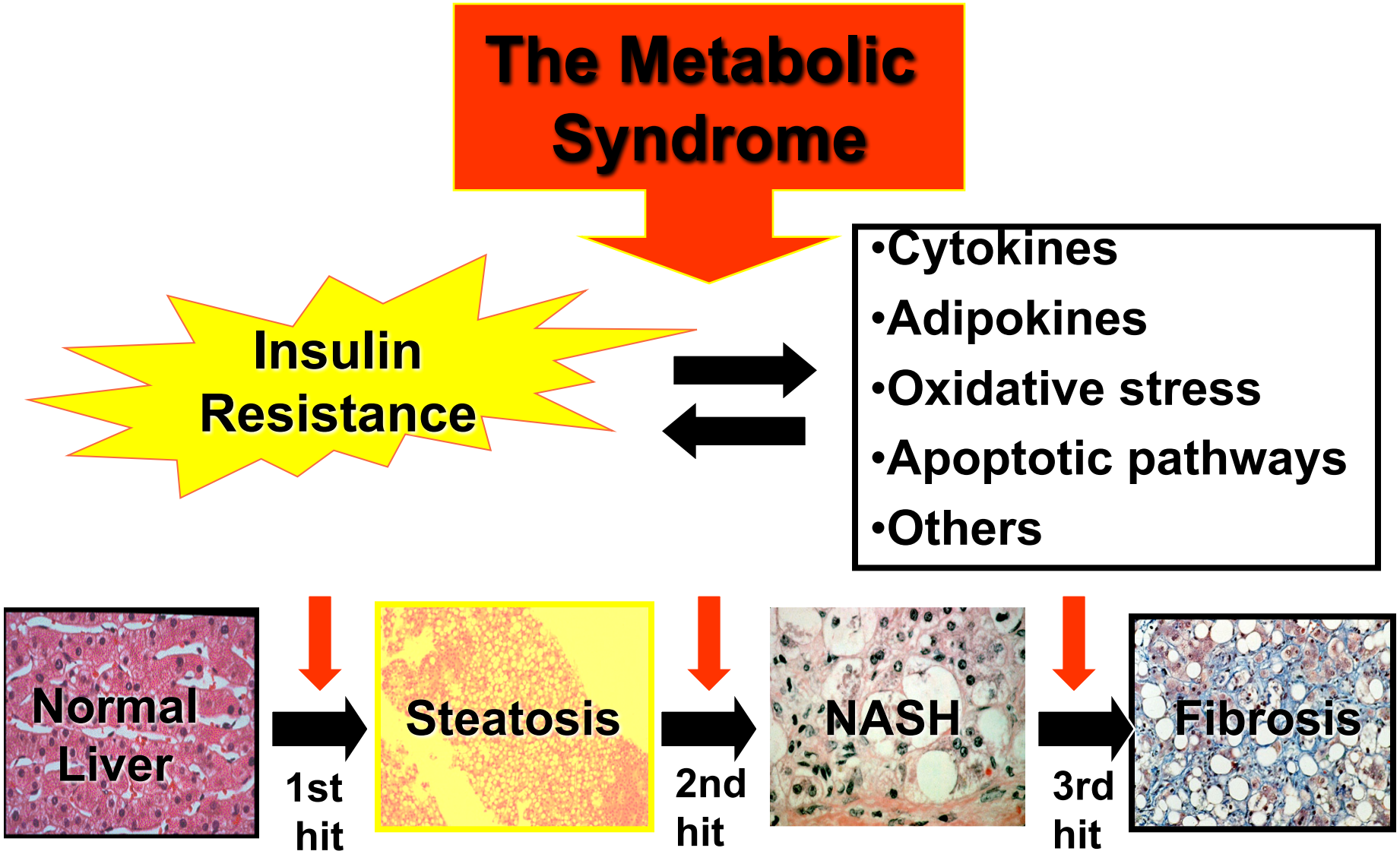
Metabolic Syndrome and Its Hepatic Manifestation



National Cholesterol Educational Program (NCEP), Adult Treatment Panel (ATP) III; 2001.

Pathogenesis of NASH

The Multi-hit Hypothesis



Clinical Features of NAFL/NASH

Symptoms:

Variable
Vague (fatigue, malaise, RUQ discomfort)
Mostly absent

Signs:

Hepatomegaly common
Splenomegaly in some
Portal hypertension unusual

Labs:

Increased AST, ALT typical
± increased Alk. Phos., GGT
Increased cholesterol, triglycerides common
Increased glucose common
Viral markers (-)
Autoantibodies (-)
Iron studies abnormal sometimes

Imaging:

Fatty liver

Work up of patients with NAFLD

- Imaging to establish the presence of steatosis
- Meticulous alcohol and medication history
- Exclusion of co-existing or competing etiologies
- Auto-antibodies and hyperferritenemia are common
- Fasting lipid profile and measures of insulin resistance
- Liver biopsy to establish the presence of NASH

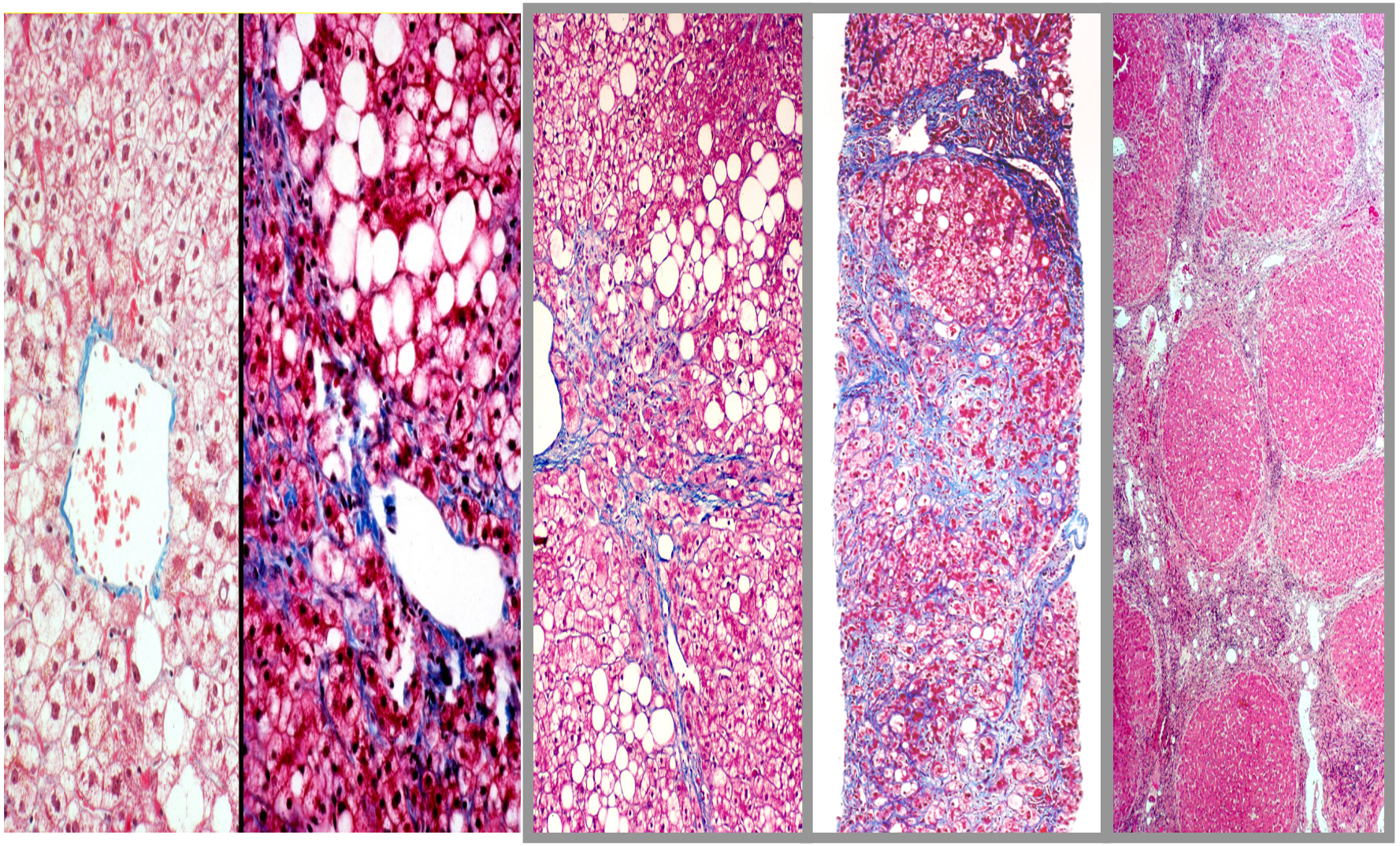
Imaging Techniques for Evaluating Hepatic Steatosis

- Ultrasound with elastography
- Computed tomography
- Magnetic resonance imaging
  - Percent fat calculations
  - Estimated protein-density fat-fraction
  - Magnetic resonance elastography
- Controlled attenuation parameter
  - FibroScan

How to establish diagnosis of NAFLD and identify patients with NASH ?

- Patients with NAFLD or NASH are generally asymptomatic
- Clinical presentations cannot distinguish NASH
- Current radiologic modalities are unable to distinguish NASH or accurately detect fibrosis
- Non-invasive biomarkers are not established (getting closer)
- Therefore, in 2017, liver biopsy remains “the imperfect gold standard” to diagnosis and stage NASH

Histologic Progression of NASH



Stage 0 **Stage 1** **Stage 2** **Stage 3** **Stage 4**

Courtesy of Goodman, Z

How to decide when to do a liver Bx

NASH Practice Guidelines

↑ ALT

Rule out other causes of liver disease

Causes found

No causes found

Metabolic syndrome present

YES

NO

BX

Will Bx change Rx

Yes

No

Discuss risks/benefits

Make patient aware of risks

Of not doing Bx

Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis. (Strength – 1, Evidence - B)

The presence of metabolic syndrome and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis. (Strength – 1, Evidence - B)

Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy. (Strength – 1, Evidence - B)

Surrogate Markers for NASH± Advanced Fibrosis

Predict NASH

- Metabolic Syndrome
- CK-18 fragments
- CK-18 + sFas
- Oxidized Fatty acids
- NASH test
- NASH Predictive Index
- Obesity NAFLD score
- NASH Clinical Score
- NAFIC (ferritin, insulin, collagen)

Predict advanced fibrosis

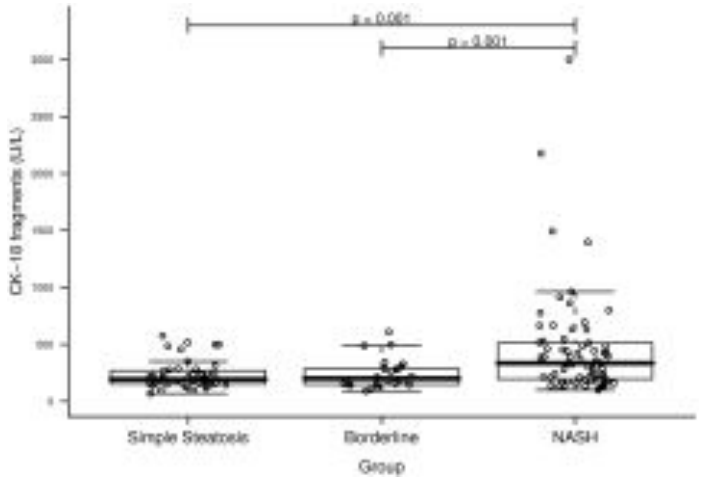
- Fibrotest
- NAFLD Fibrosis Score
- BARD score
- ELF
- Fibrometer
- OWL Genomics
- IU panel
- Transient elastography
- MR elastography

Clinical Factors that are different between Isolated Fatty Liver and NASH

Clinical Variable	Not NASH (n=89)	NASH (n=40)	P Value
BMI	31.7 (5.3)	34.4 (5.4)	0.01
Fasting Insulin	14 (8.4)	23.2 (13)	<0.0005
ALT (U/L)	36.2 (15.7)	50.9 (19.6)	<0.0005
AST (U/L)	25.6 (7.4)	36.3 (13.1)	<0.0005
HDL (mg/dL)	49.2 (15.7)	44.3 (9)	0.03
Adiponectin (ng/mL)	11028 (13078)	7815 (4811)	0.02
hsCRP (ng/mL)	5355 (5537)	7351 (6397)	0.04
CK-18 (U/L)	210.3 (118)	307.1 (233.1)	0.02

Williams CD, Gastroenterology 2011

CK-18 Fragments

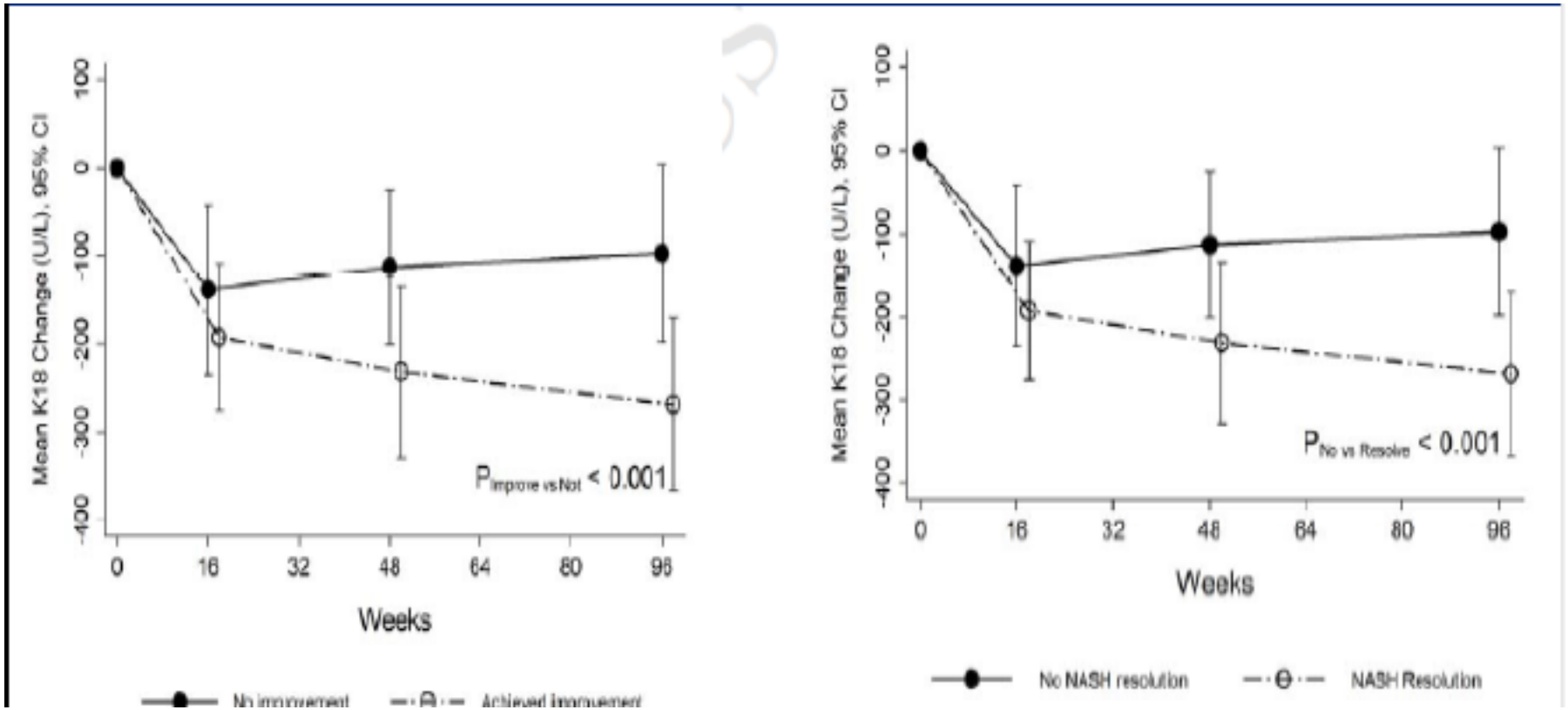


For every 50 U/L increase in plasma CK-18, the likelihood of having NASH increased 30%

K-18 level (U/L)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
246	75 (64-83)	81 (61-93)
279	71 (60-80)	85 (65-96)
281	67 (57-77)	89 (70-98)
287	65 (54-75)	92 (75-99)

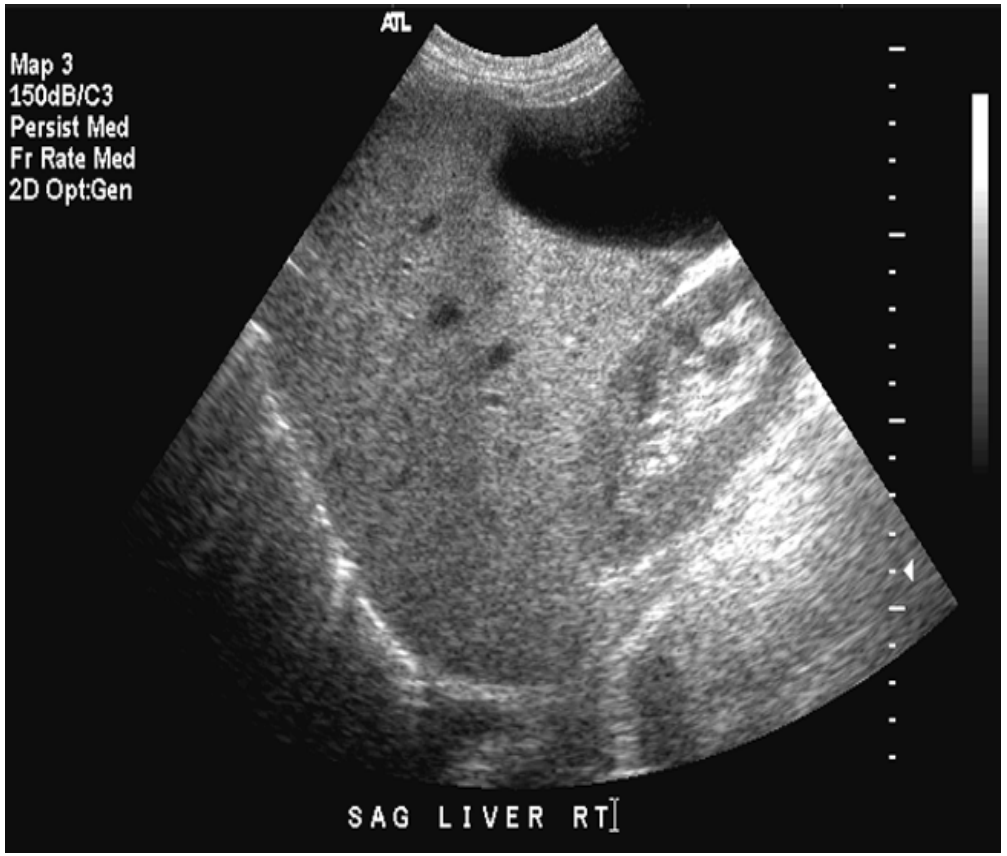
Feldstein AE, Hepatology 2009;50:1072-1078.

Changes in K-18 levels in PIVENS Trial



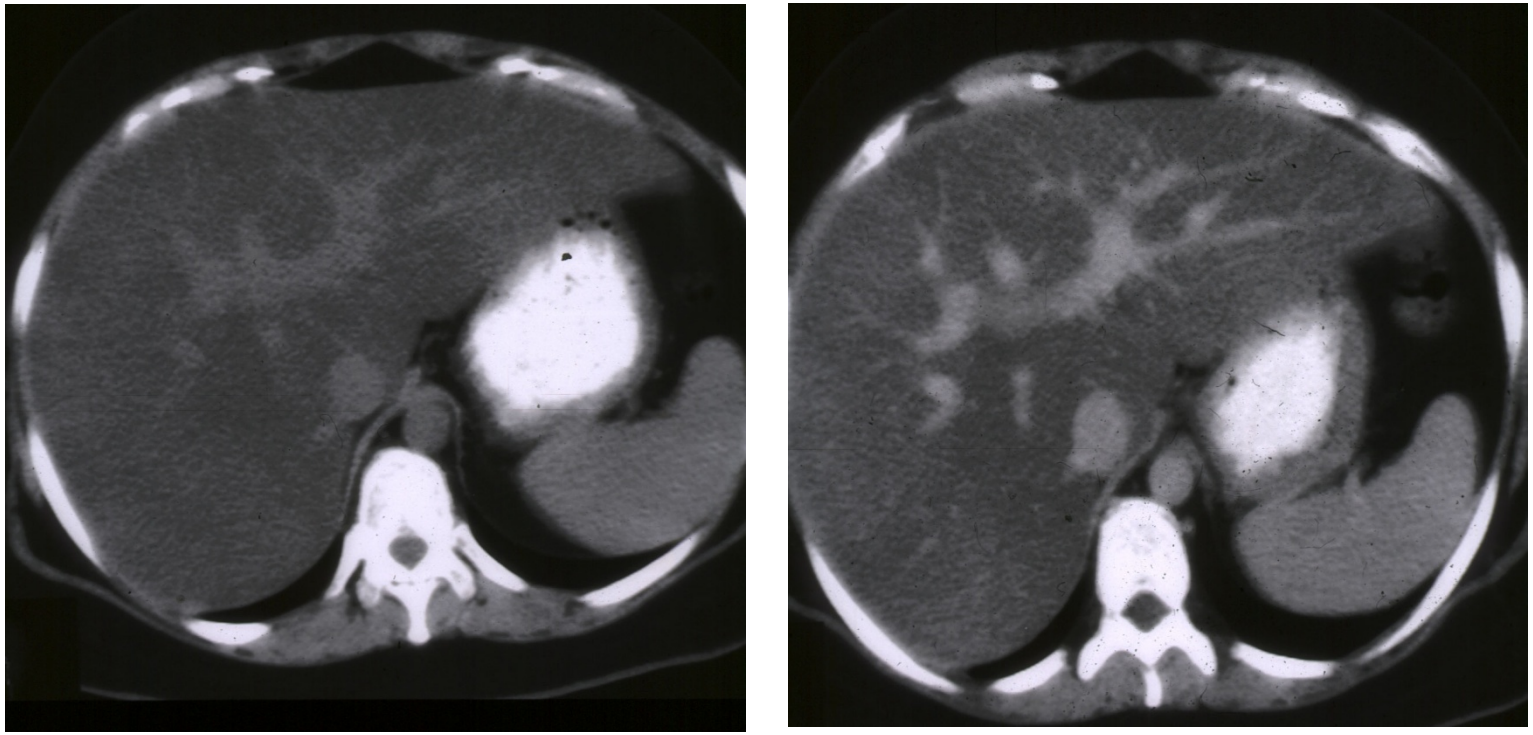
Vuppalanchi CGH 2014

NAFLD: sonographic evidence

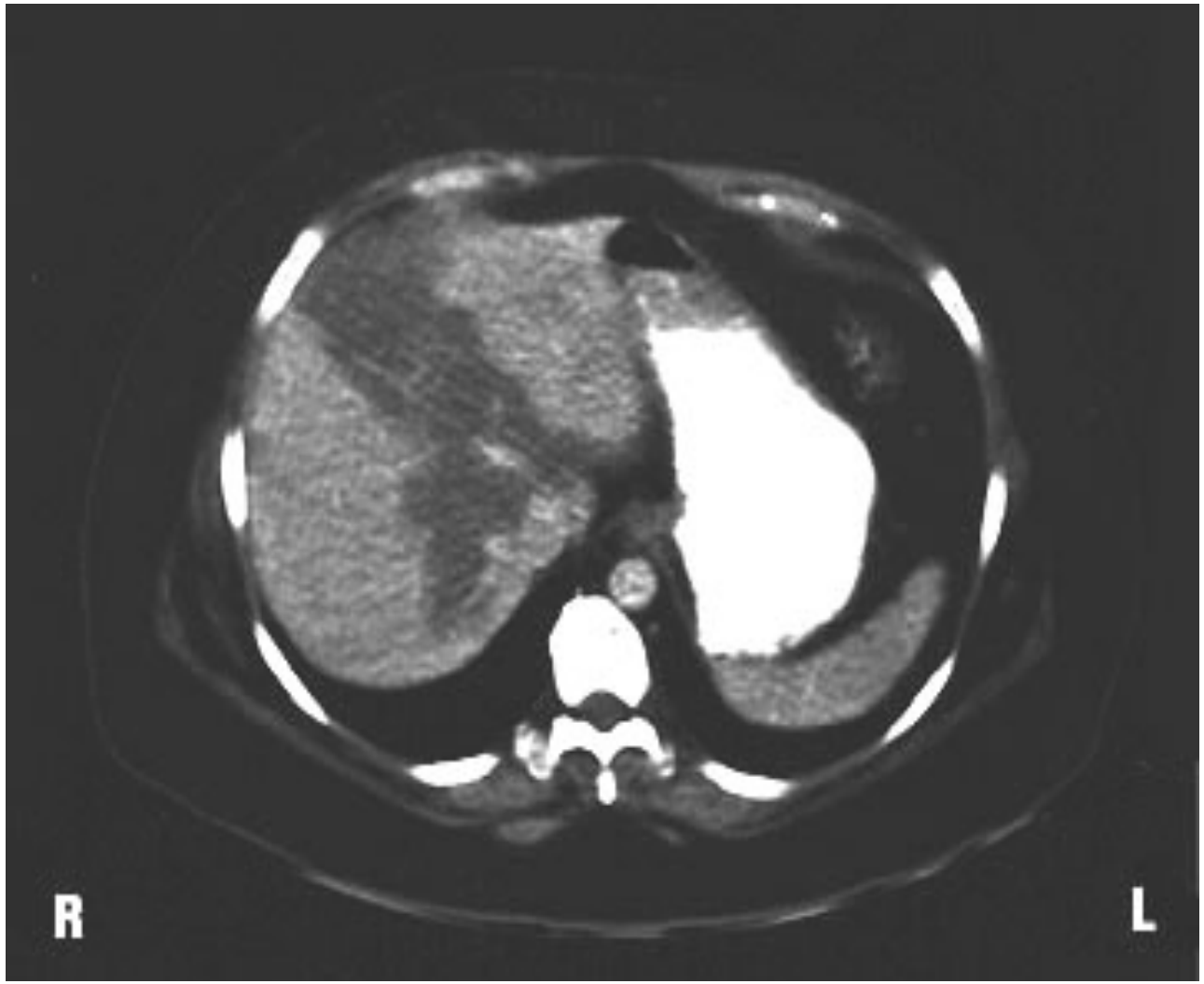


- Bright liver
- echotexture increased compared to kidney
- vascular blurring

CT scan: fatty liver

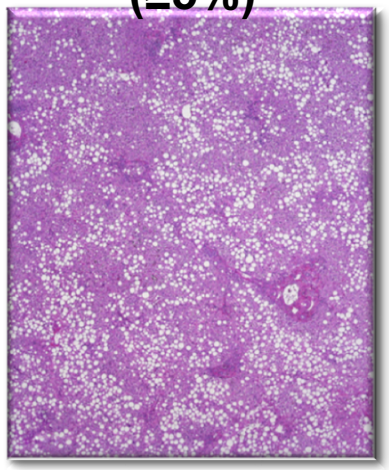


Fat in the liver may be focal



Histopathology of NASH: Necessary Components for a Diagnosis

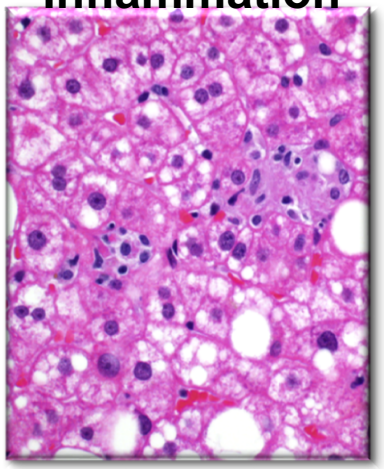
Steatosis (≥5%)



Macro>Micro
Accentuated in zone 3
Periportal areas usually spared in early disease

+

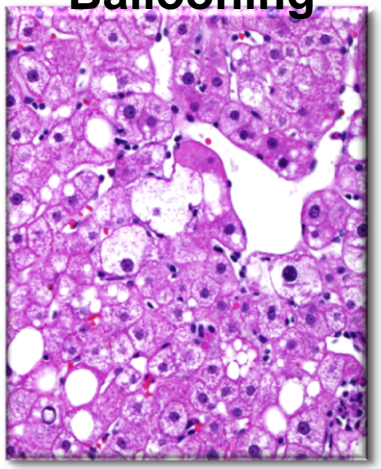
Lobular Inflammation



Any degree (mixed, mild)
Scattered polymorphonuclear leukocytes as well as mononuclear cells

+

Hepatocellular Ballooning

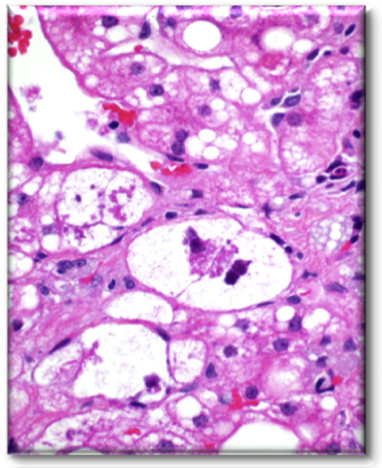


Most apparent near steatotic liver cells
Typically zone 3

Chalasani N, et al. *Hepatology*. 2012;55:2005-2023.
Takahashi Y, et al. *World J Gastroenterol.* 2014;20:15539-15548.
Kleiner DE, et al. *Clin Liver Dis.* 2016;20:293-312.

Histopathology of NASH: Helpful Features, But Not Required for Diagnosis

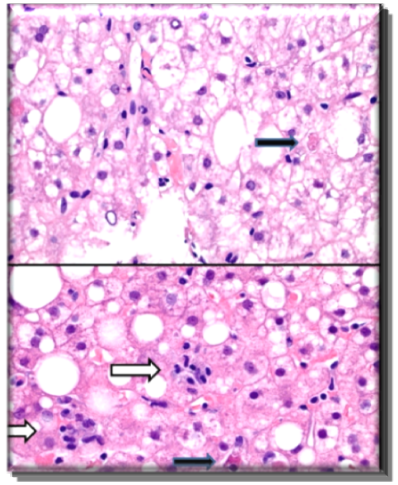
Mallory-Denk Bodies



Large cytoplasmic inclusions seen in ballooned hepatocytes

Protein aggregates comprising misfolded keratins

Apoptotic Bodies (dark arrows)

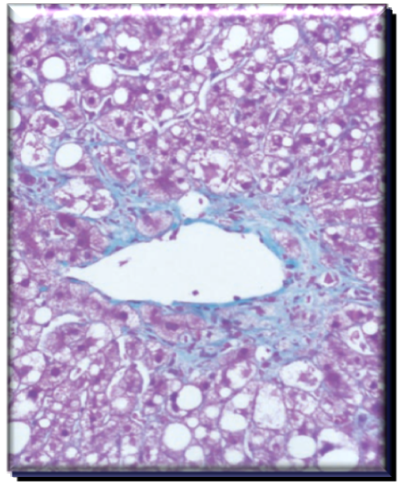


Also known as acidophil bodies

Correlate with disease activity

Commonly present with ballooned hepatocytes and lobular infiltrates (white arrows)

Perisinusoidal Fibrosis

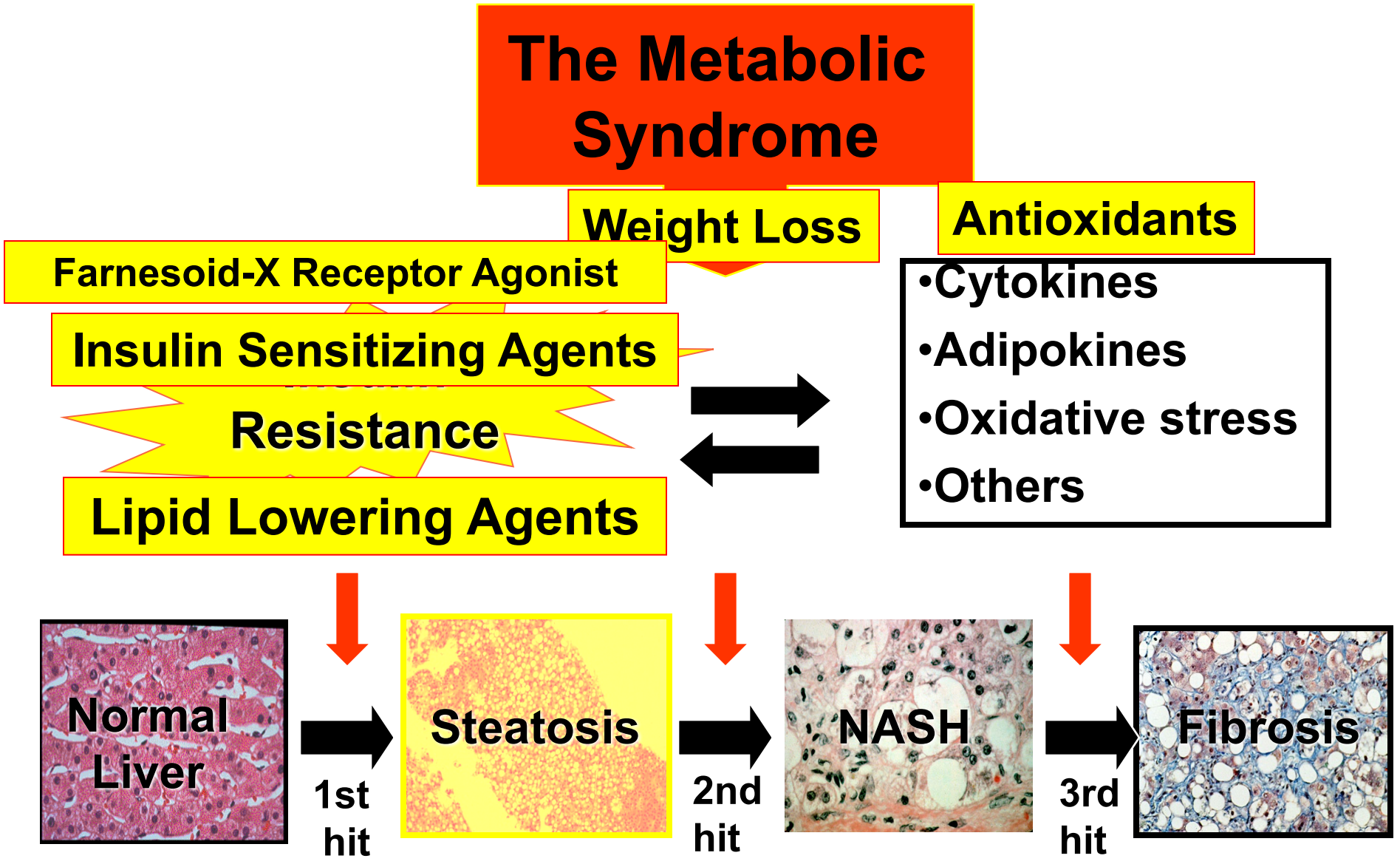


Typically zone 3

Delicate collagen strands between ballooned hepatocytes

Yeh MM, et al. *Hum Pathol.* 2016;52:28-37.
Kleiner DE, et al. *Clin Liver Dis.* 2016;20:293-312.

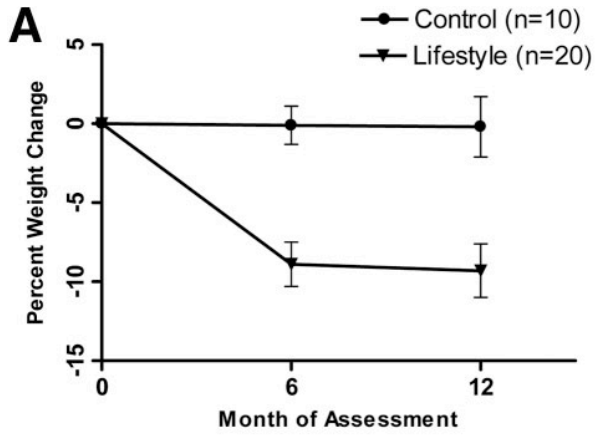
Treatment of NASH

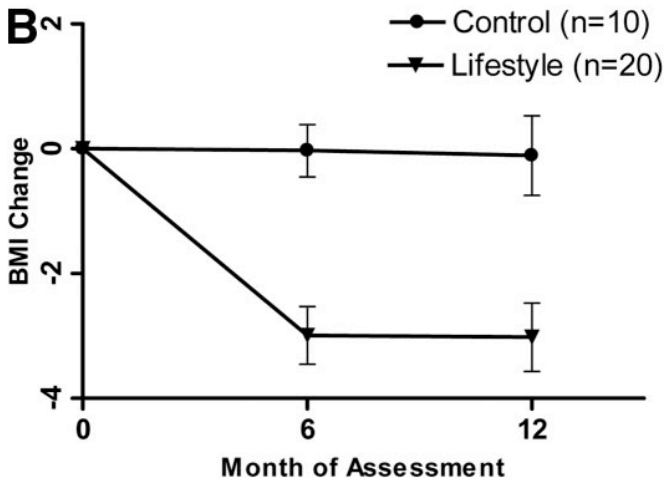


Treatment: Weight Loss

Study	N	Intervention	Duration (months)	Design	ALT	Histology
Hickman	31	Diet	15	Open label	+	N/A
Huang	16	Diet	12	Open label	-	+
Palmer	39	Diet	2-111	Case series	+	N/A
Andersen	41	Diet	4-23	Open label	+	+/-*
Kugelmas	8	Diet/Ex	3	Open label	+	N/A
Ueno	15	Diet/Ex	3	Open label	+	+
Zhu	34	Diet/Ex	12	Open label	+	N/A
Suzuki	348	Diet/Ex	12-24	Open label	+	N/A
Harrison	10	Orlistat		Open label	+	+
Sabuncu	13/12	Sibutramine/ Orlistat	6	Open label		N/A
Luyckx	69	Surgery	27	Case series	+	+/-*
Silverman	91	Surgery	2-61	Case series	+	+
Kral	104	Surgery	41	Case series	+	+
Dixon	36	Surgery	26	Case series	+	+

Weight Loss Works

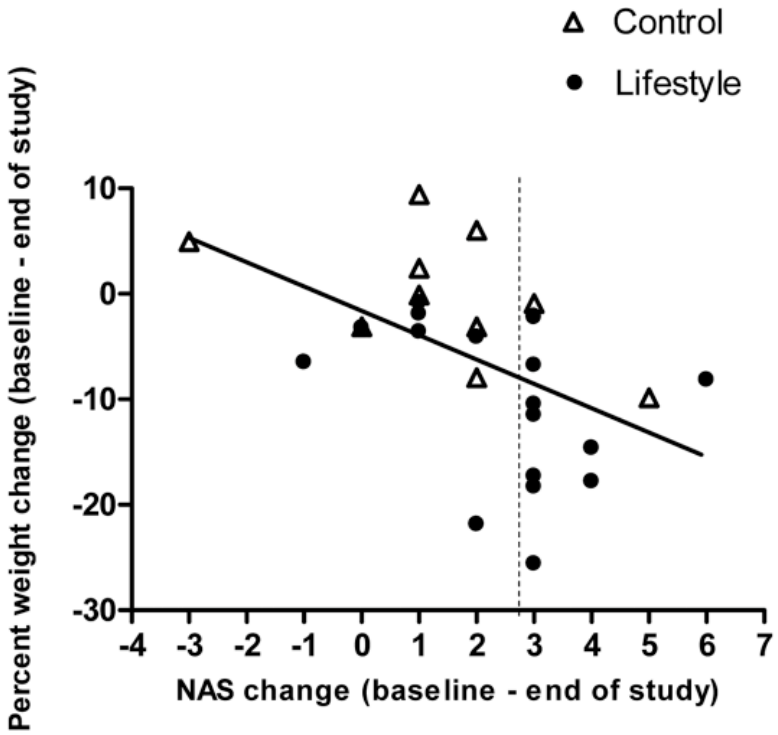




31 Patients Randomized, controlled trial

40% in intervention group lost 10% body weight vs 0% in control group

72% vs 30% achieved study endpoint



Weight loss of ≥ 7% associated with improvement in all parameters of NASH except fibrosis (need 10% for fibrosis)

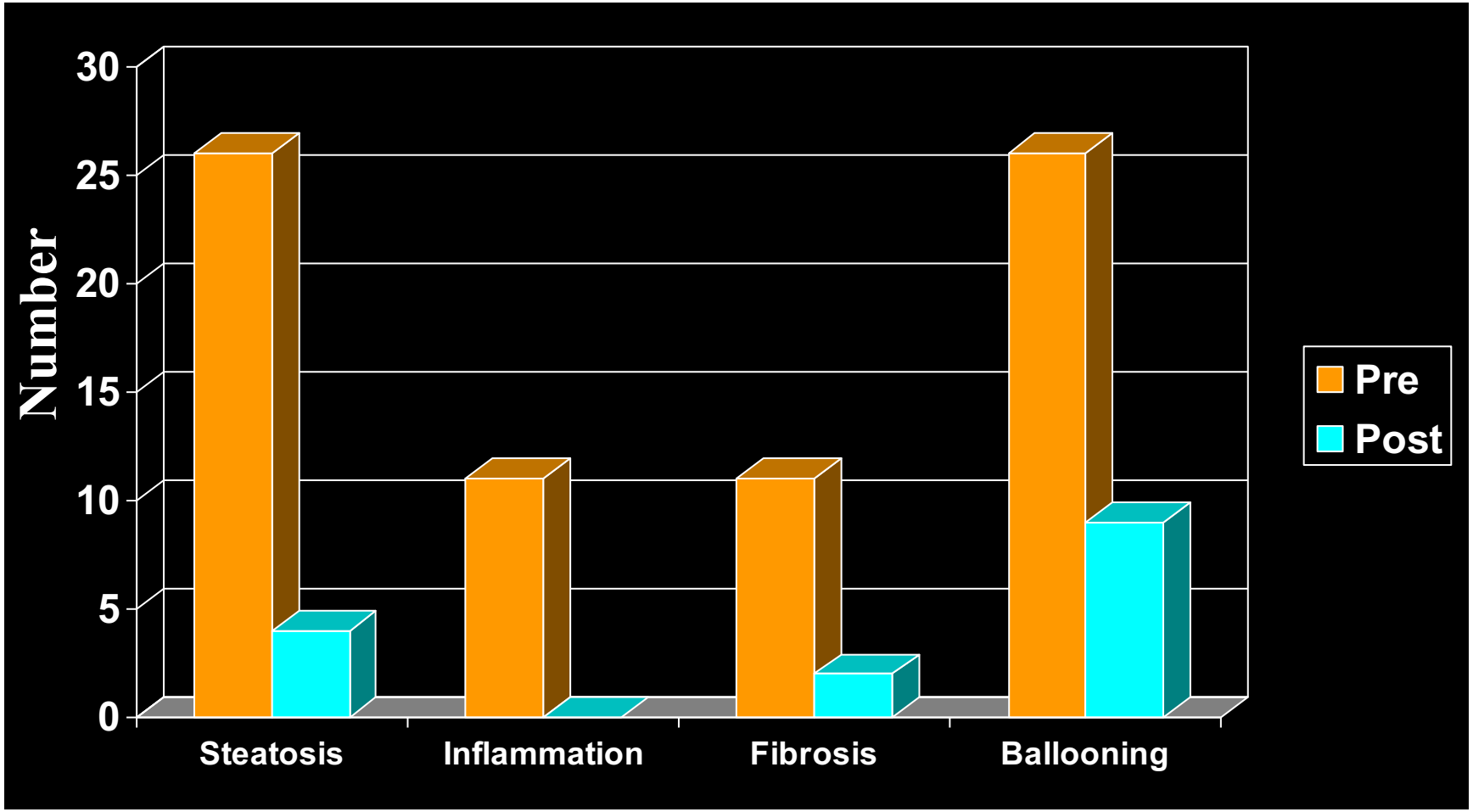
Promrat K, Hepatology 2010;51:121-129

Non-alcoholic fatty liver disease
Weight loss works

- 36 patients with obesity underwent paired liver biopsies at time of laparoscopic gastric banding and 24 months later
- Mean weight loss 34 kg
- Histologic improvements in steatosis, inflammation, and fibrosis
  - Only 4 fulfilled criteria for NASH at second biopsy (24 at entry)
  - 18 had improvement in fibrosis by 2 stages

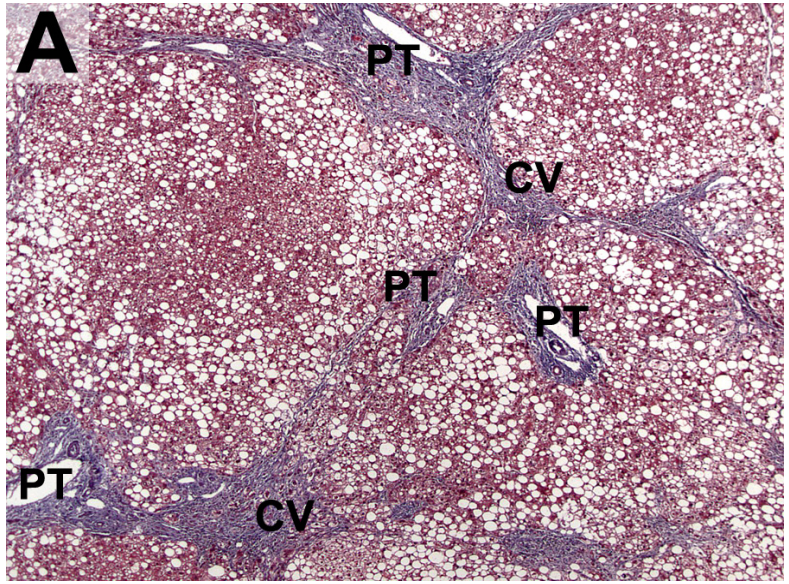
Dixon et al. Hepatology.2004:39(6):1647

Liver Histology After Gastric Bypass

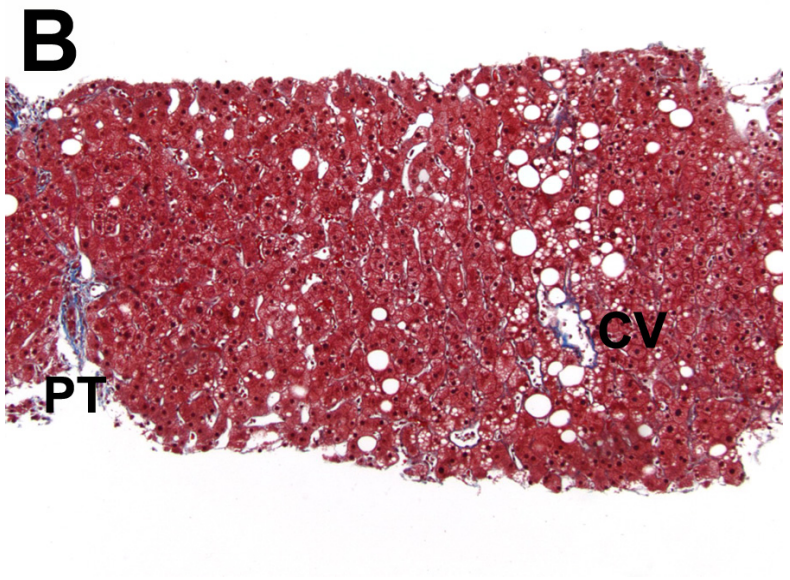


Hepatology 2004;39:1647-54

Significant Improvement in histology following bariatric surgery



1st biopsy



2nd biopsy at 8.5 months

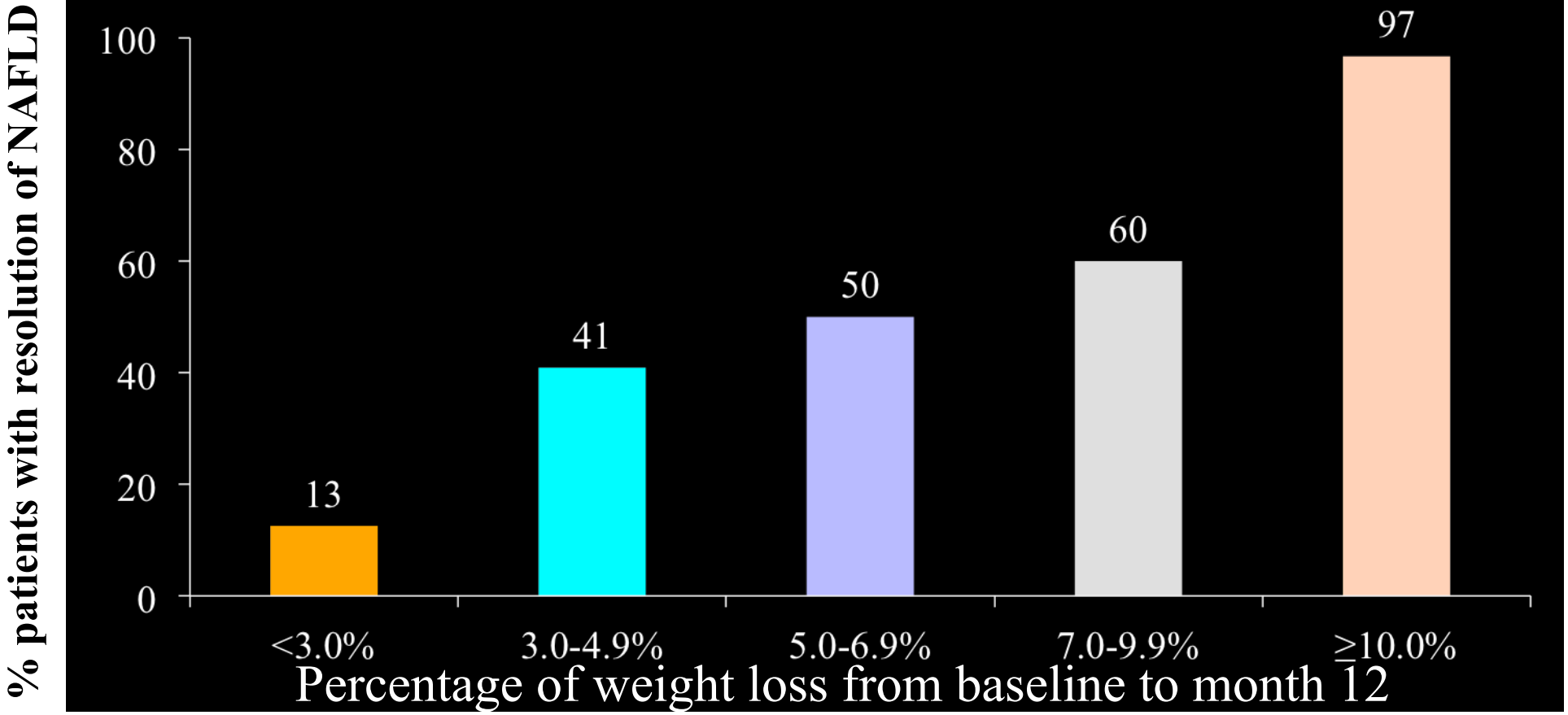
Mattar SG et al. Annals of Surgery 2005; 242: 610-620

Lifestyle Modification Program

- Assessed benefits of dietician led lifestyle modification for 12 months
  - Weekly meetings x 4 month, then monthly x 8
  - Moderate carbohydrate, low fat, low glycemic index
    - Emphasis on fruits and vegetables
  - Exercise: moderate intensity for 30 minutes 3-5 days/week
    - Increased to daily
- 154 Patients Enrolled
- Primary Endpoint
  - Remission of NAFLD: IHTG of < 5% by MRS
- 64% in intervention group resolved NAFLD
- 20% in control group resolved NAFLD

Wong VW, J Hepatol 2013

Degree of weight loss and resolution of NAFLD by hepatic TG content



n =	72	22	10	20	30

Wong VW, J Hepatol 2013

Low Glycemic Index Foods

- Beans
- Almonds
- Peanuts
- Walnuts
- Chickpea
- Small seeds
  - Sunflower
  - Flax
  - Pumpkin
- Whole intact grains
- Most vegetables
- Most sweet fruits (peaches, strawberries, mangos)

Exercise

- A recent large, cross-sectional study assessed the relationship between meeting/exceeding US national guidelines for physical activity and NAFLD severity
  - Self-reported
  - 813 patients
  - Divided into 3 exercise categories based on time spent in activity and metabolic equivalents (METS):
    - Inactive (54%)
    - Moderate (20%):>150 min/week; Activities with MET values 3-5.9
    - Vigorous (26%):>75 min/week: Activities with MET values >6

Kistler KD, Am J Gastroenterol 2011;106:460-468

Exercise

- Vigorous exercise associated with decreased adjusted odds of having NASH
  - OR: 0.65 (0.43-0.98)
- Doubling recommended time spent in vigorous exercise (>150 min/week), associated with decreased adjusted odds of advanced fibrosis
  - OR:0.53 (0.29-0.97)

Younger age, higher education, higher income, lower BMI and no diabetes

Kistler KD, Am J Gastroenterol 2011;106:460-468

Exercise

- Optimal Intensity
  - Goal is to maintain a lifestyle change
  - Moderate exercise, burning ~400 kcal/session
    - 3 times/week
    - Improves insulin resistance
    - Overall energy expenditure achieved per work-out more important than intensity
      - » Training at 60% VO2max as effective as 80% VO2max
  - Weight loss
    - Need to work out for longer period of time

Ryan AS, Aging Health, 2010

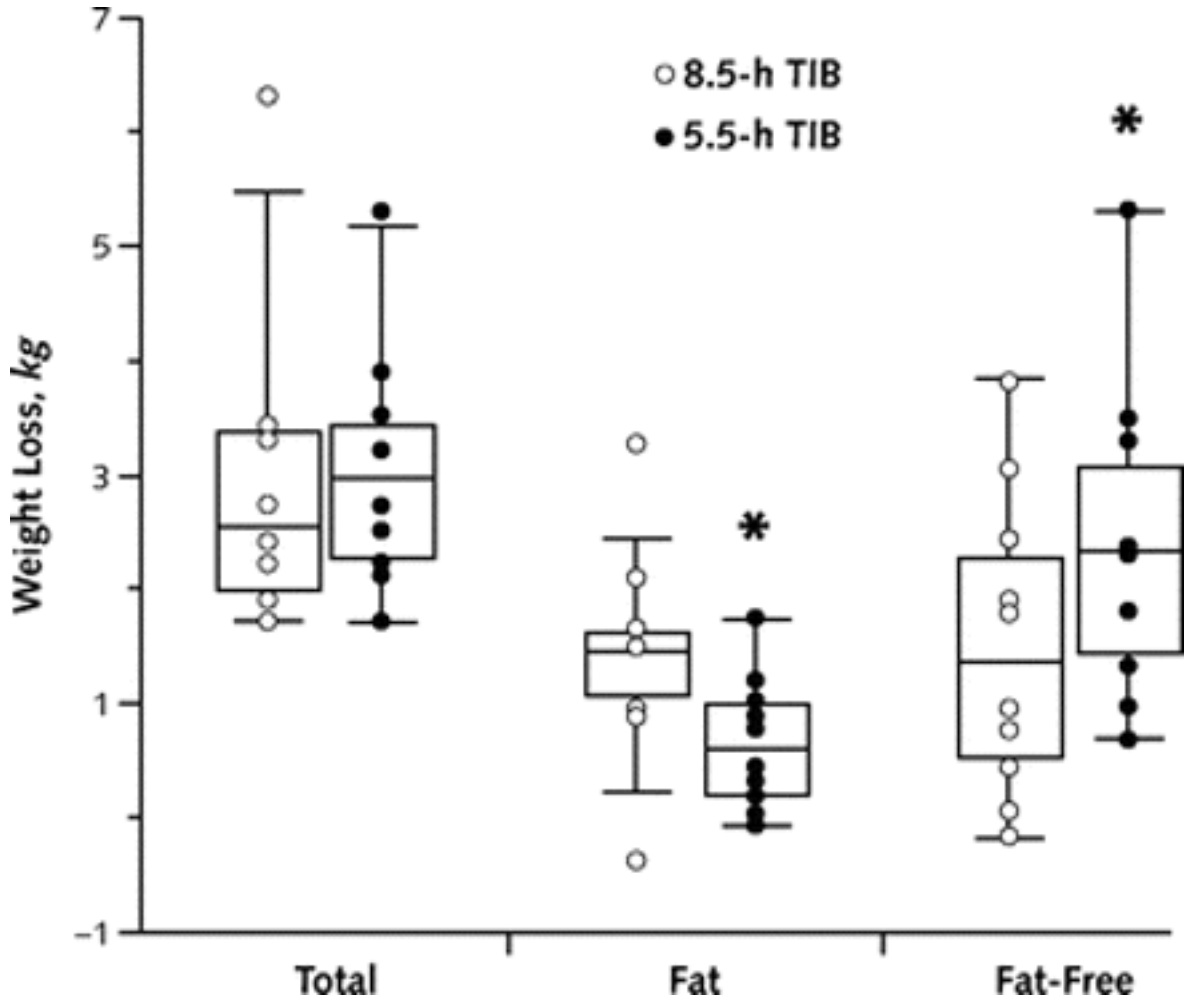
Sleep

10 overweight adults assigned to sleep 8.5 vs 5.5 hours each night for 14 days

Moderate caloric restriction

Lost same amount of weight (~6.6 pounds)

Sleep curtailment decreased proportion of weight lost as fat by 55% and increased loss of fat-free mass by 60%



Nedeltcheva AV, Ann Intern Med 2010

Treatment: Lipid Lowering Agents

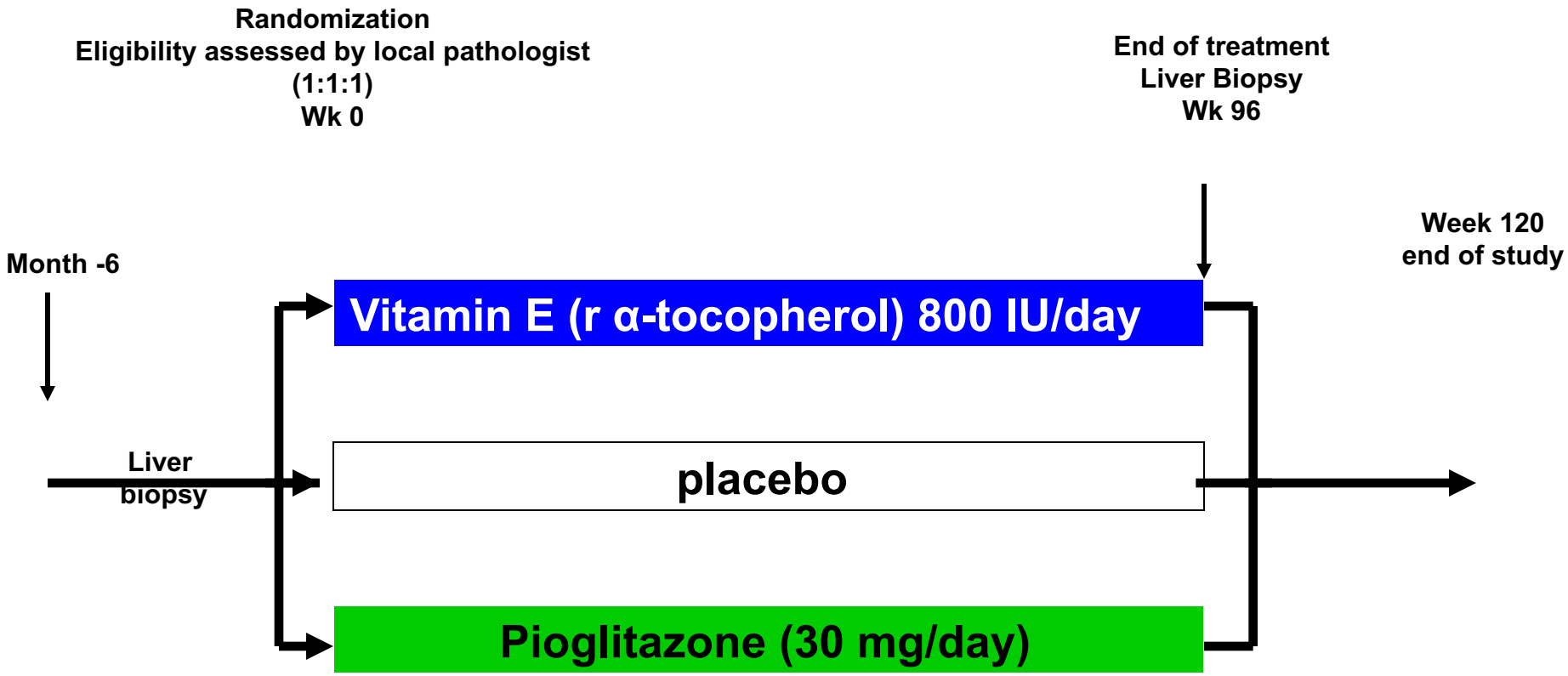
Study	Design (mts)	Meds	N	ALT	Hist
Laurin	Open label (12)	Clofibrate	16	-	-
Basaranoglu	RCT (1)	Gemfibrozil	46	+	NA
Horlander	Open label (12)	Atrovastatin	7	+	+
Kiyici	Open label (6)	Atrovastatin	27	+	NA
Hatzitolios	Open label (6)	Atrovastatin		+	NA
Gomez-Dominguez	Open label (12)	Atrovastatin	25	+	NA
Rallidis	Open label (7)	Pravastatin	5	+	+/-
Merat	RCT (6)	Probucol	30	+	NA

Statins are safe, improve ALT, not histology

Treatment: Insulin Sensitizing Agents

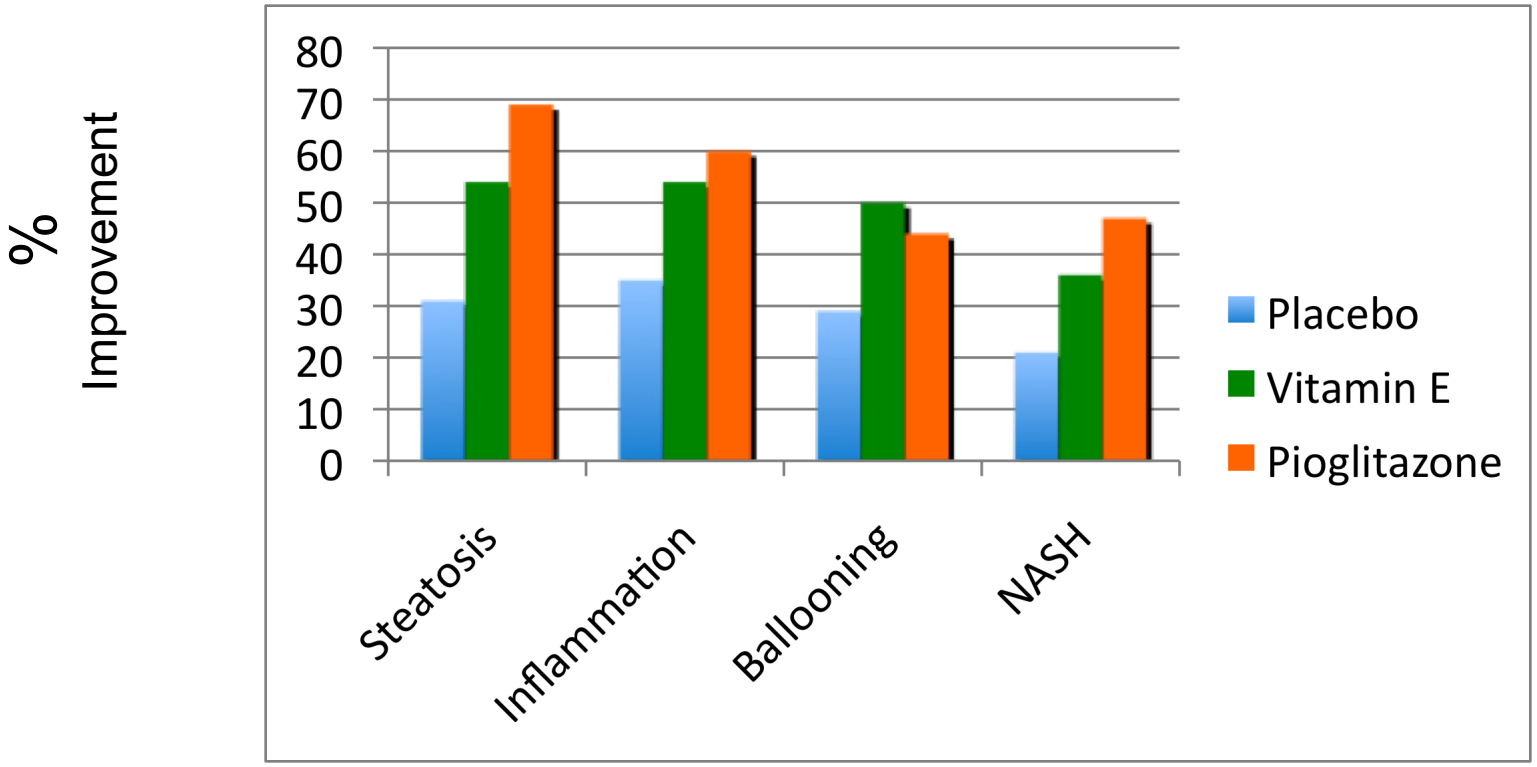
Study	N	Drug	Duration (months)	Design	ALT	Histology
Caldwell	10	Troglitazone	3-6	Open label	+	+
Acosta	8	Pioglitazone	2-12	Open label	+	N/A
Shadid	5	Pioglitazone	4.5	Open label	+	N/A
Sanyal	21	Pioglitazone + Vit E	6	RCT	+	+
Promrat	18	Pioglitazone	12	Open label	+	+
Tetri	30	Rosiglitazone	12	Open label	+	+
Belfort	55	Pioglitazone ± Diet	6	RCT	+	+
Marchesini	14	Metformin	4	Open label	+	N/A
Nair	15	Metformin	12	Open label	+	N/A
Bugianesi	55	Metformin	6	RCT	+	+
Uygun	17	Metformin	6	RCT	+	-
Duseja	7	Metformin	6	Open label	+	N/A
Schwimmer	10	Metformin	6	Open label	+	N/A

PIVENS Study Design



Sanyal et al., *NEJM* 2010

Pioglitazone and Vitamin E
PIVENS Trial



Sanyal AJ, New Engl J Med 2010

Summary of PIVENS findings

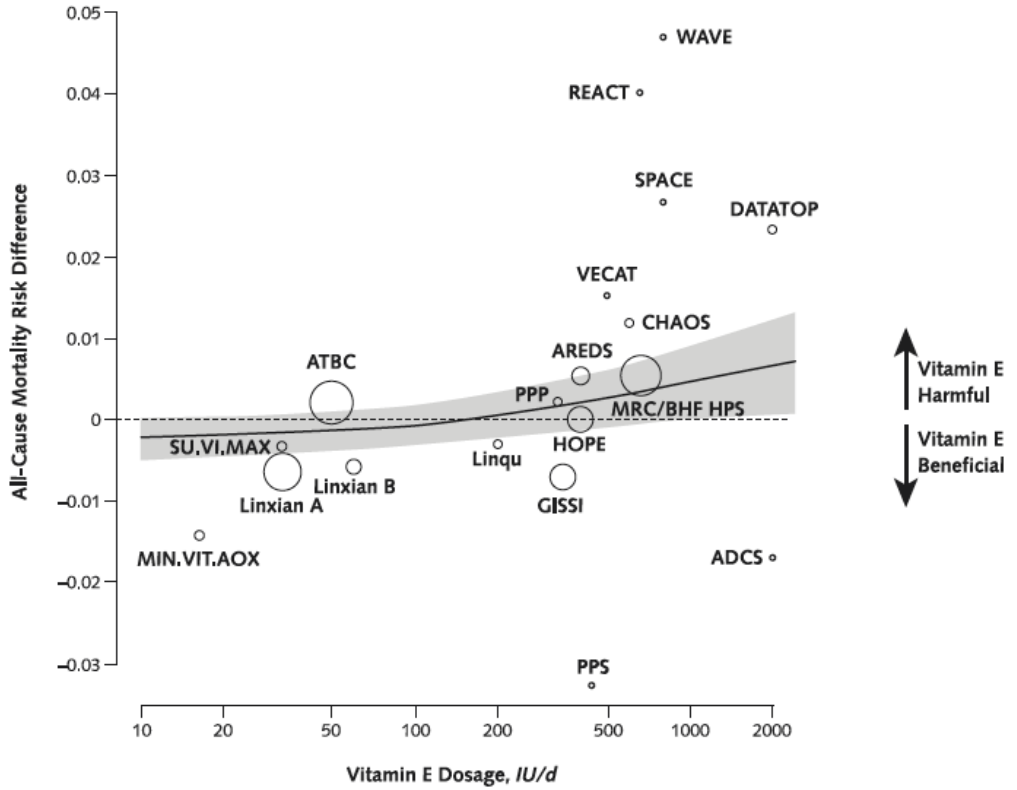
- Vitamin E effective over placebo for NASH
- Pioglitazone improved, IR, ALT, steatosis and inflammation, but not 1° outcome
- Only 34% (Pio) and 43% (Vit E) had histological response, neither improved fibrosis
- Cannot generalize to diabetics or cirrhotics

Why not empirically treat suspected NAFLD with vitamin E ?

- 70-75% have NAFLD, most isolated steatosis
- 50% of patients don't respond to Vitamin E
  - liver enzymes are not reliable to assess quiescence or progression
- The long-term safety remains unknown
- Prostate cancer risk? (absolute increase 1.6 per 1000 person yrs)

Metanalysis of Vitamin E – increased mortality?

- Different forms of Vitamin E
- Confounders not controlled for:
  - High dose Zn supplementation
  - Use of concomitant vitamin A
  - Smoking
- Trials not uniformly using Vit E as a treatment
- RCTs with no death excluded



***Annals of Int Med*, 2005**

Pioglitazone for NASH

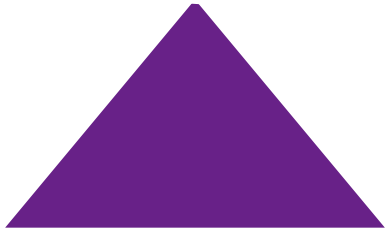
- Weight gain **(2–4.7 kg)**
- Cardiac toxicity[1]
- Fracture risk[2]
- ? Bladder cancer[3]

Cons

Improve[2]

- Insulin sensitivity
- ALT
- Steatosis
- Inflammation
- ? Ballooning

Pros



Meta-analysis of 19 trials (16,390 patients) with T2DM, pioglitazone[1]

- Death, MI, or CVA: 4.4% of pioglitazone vs 5.7% of control (*P* = 0.005)
- More CHF in pioglitazone (2.3%) vs control (1.8%) (*P* = .002), no effect on mortality

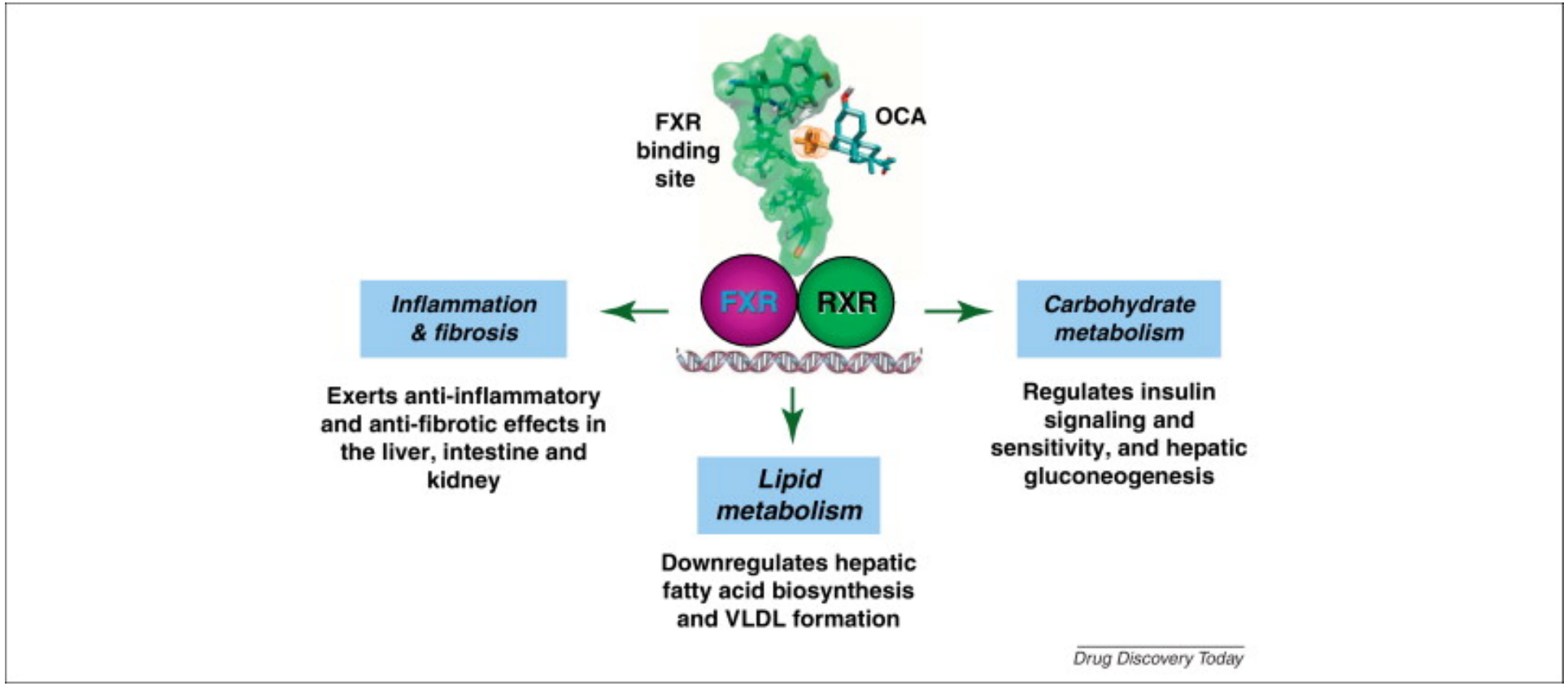
Abbreviations: ALT, alanine aminotransferase; CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

1. Lincoff AM, et al. *JAMA.* 2007;298:1180-1188. 2. Ratziu V. *Nat Rev Gastroenterol Hepatol*. 2013;10;646-685.
3. Lewis JD, et al. *Diabetes Care.* 2011;34:916-922.

Courtesy of Mary Rinella, MD.

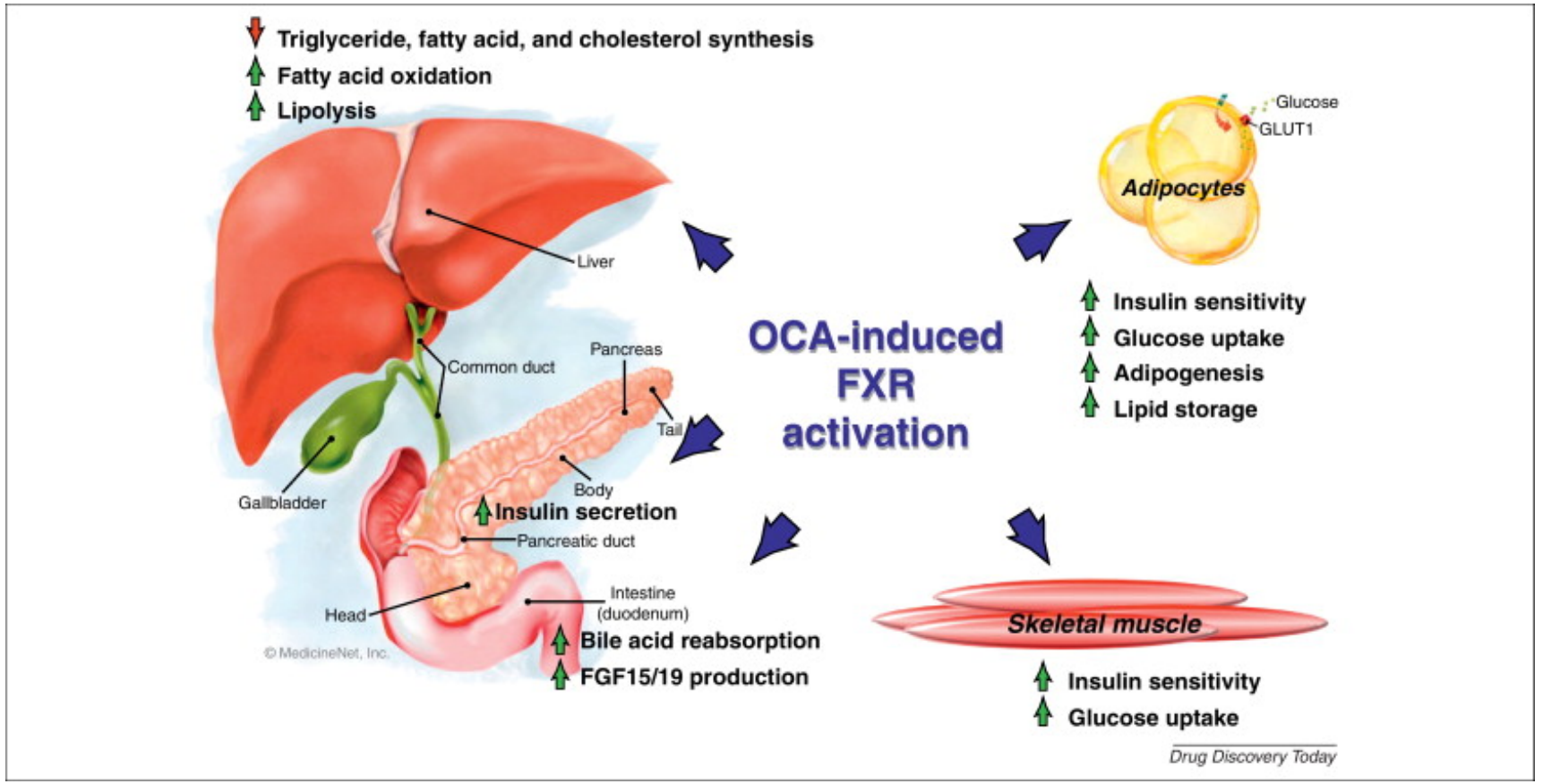
Obeticholic acid

- Semi-synthetic bile acid derivative
- Farnesoid-X Receptor (FXR) agonist



Adorini L, Drug Dis Today 2012;17:988-997

Obetacholic Acid



FLINT Study: Obeticholic Acid in NASH Patients Without Cirrhosis

Phase 2b (n=283)
(US)

Placebo-controlled
Histologic evidence of definitive or borderline NASH
(liver biopsy within 90 days of entry)
NAFLD activity score ≥4
(individual scores each ≥1)
No cirrhosis

Obeticholic Acid 25 mg qd (n=141)

Placebo (n=142)

Primary endpoint: Improved histology
- **NAS decrease of ≥2**
- **No increase in fibrosis**

	OCA 25 mg	Placebo
Patients meeting primary endpoint (%)	46%	21%

FLINT: Farnesoid X receptor ligand obeticholic acid in NASH Treatment.
Patients stratified by diabetes status.
Primary endpoint (week 72, ITT):
Improvement in liver histology without worsening of fibrosis.
Improvement: decrease in NAFLD score ≥2 points.
Worsening of fibrosis: any increase in fibrosis stage.

PPARα/δ Agonist:Elafibranor

PPARα Activation

- Control of lipid influx
  - Improves fatty acid oxidation
  - Lowers triglyceride level
  - Raises HDL-C levels
- Induce inflammatory genes and increase necro-inflammatory activity

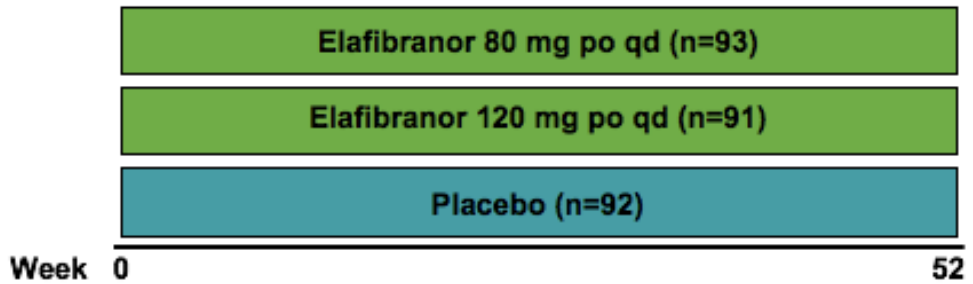
PPARδ Activation

- Improves glucose homeostasis
- Inhibits hepatic lipogenesis
- Anti-inflammatory activity in macrophages and Kupffer cells

- Activation of both PPAR α/δ leads to improvement of different pathways to regulate liver metabolism involved in NASH pathogenesis

Proof-of-Concept, Phase 2 (n=276)
(US, EU)

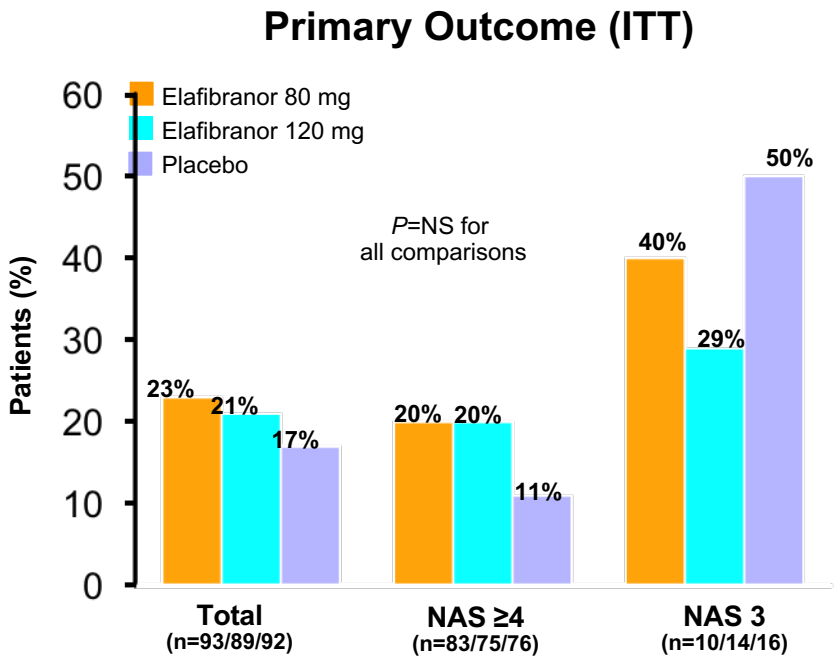
Placebo-controlled
NASH (biopsy diagnosis)
Steatosis >5% hepatocytes
Hepatocyte ballooning
Lobular inflammation
NAS score 3-8
F0-F3
No cirrhosis

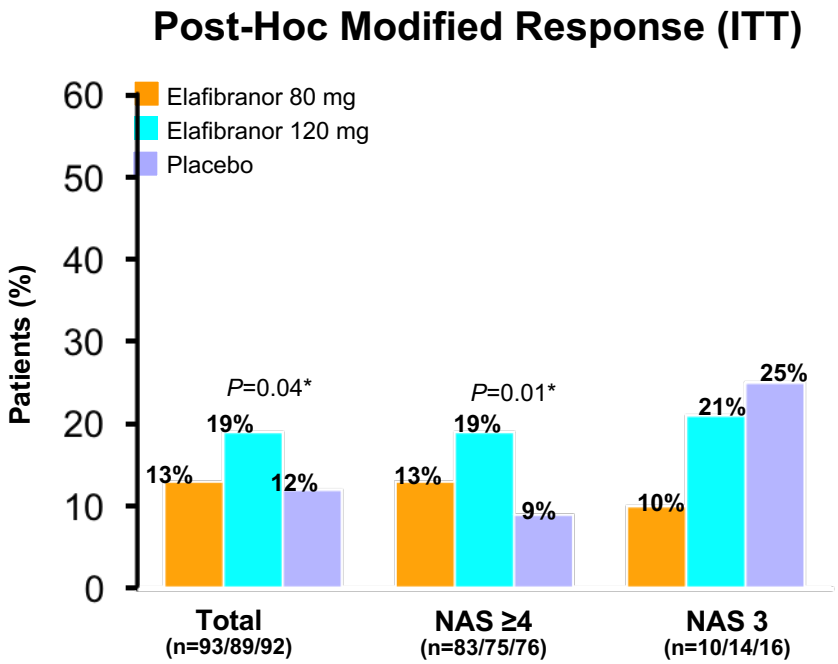


PPARα/δ regulate lipid metabolism in liver and glucose homeostasis

Perazzo H, et al. *Liver Int.* 2017;37:634-647.

GOLDEN-505 (Elafibranor in NASH Patients Without Cirrhosis): Response Rates



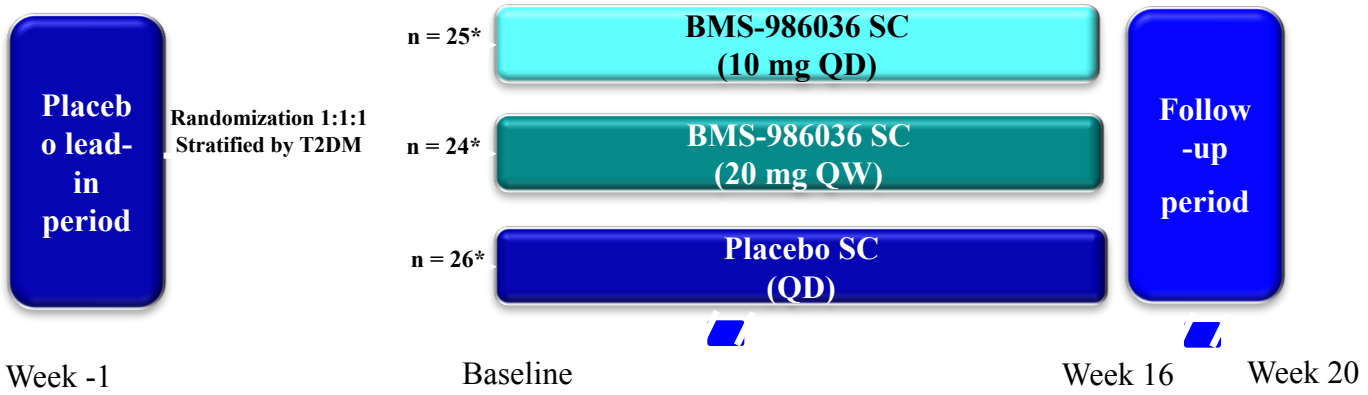


Ratziu V, et al. *Gastroenterology*. 2016;150:1147-1159.

*Elafibranor 120 mg versus placebo.
Post-hoc analysis of a modified definition of response:
Resolution of NASH: disappearance of ballooning (score 0), together with either disappearance of lobular inflammation or the persistence of mild lobular inflammation only (score 0 or 1),
and resulting in an overall pathologic diagnosis of either steatosis alone or steatosis with mild inflammation.
Worsening of fibrosis: any stage increase in fibrosis.

Fibroblast Growth Factor 21 (FGF21)
Phase 2 Double-Blind, Placebo-Controlled Study

FGF2:Associated with increased insulin sensitivity, decreased lipogenesis, improvement in lipids, and antifibrotic effects

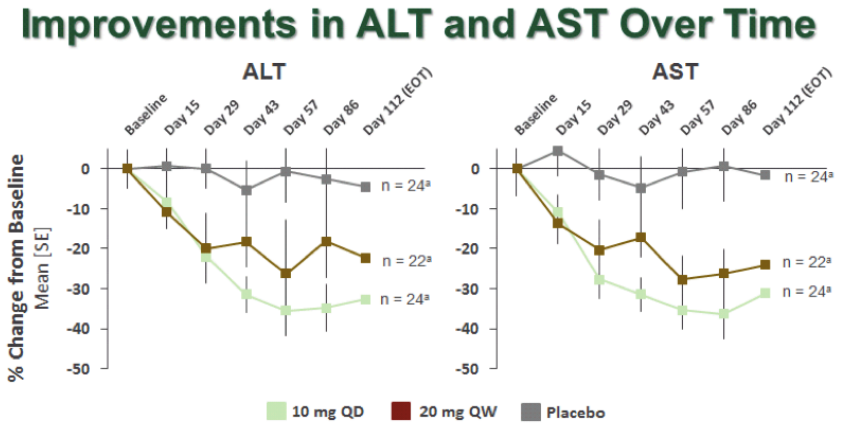


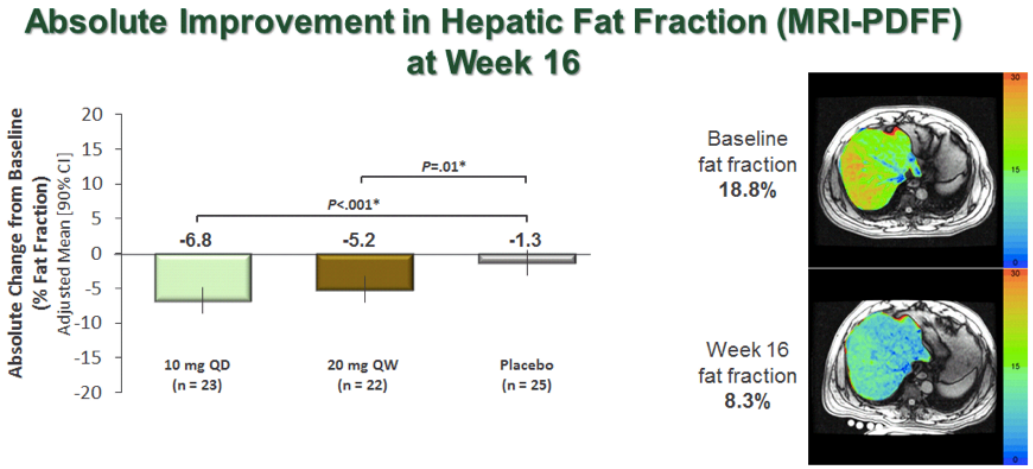
- **Key Eligibility Criteria:** biopsy-proven NASH with fibrosis stage 1-3 (within 1 year of screening), BMI ≥25 kg/m^2, hepatic fat fraction ≥ 10% (MRI-PDFF)
- **Primary Efficacy Endpoint:** change in hepatic fat fraction (%) from baseline to Week 16
- **Key Exploratory Endpoints**: adiponectin, lipids, ALT, AST, MRE, and serum Pro-C3
- **Safety Assessments:** AEs, laboratory parameters, and vital signs

*Planned sample size was 30 per group; enrollment ended early due to the significant effect of BMS-986036 on the primary endpoint seen during preplanned interim analysis at treatment Week 8.

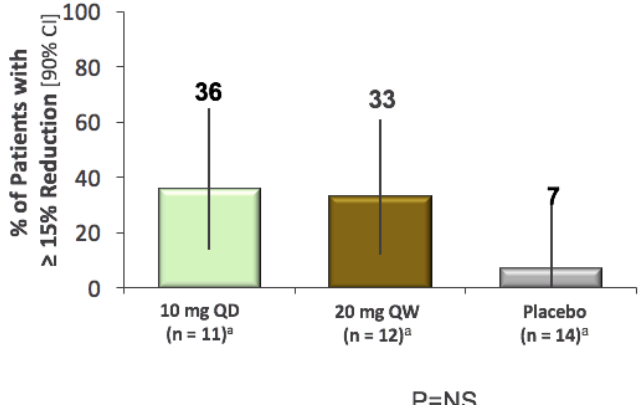
Sanyal et al. BMS. Abstract 182

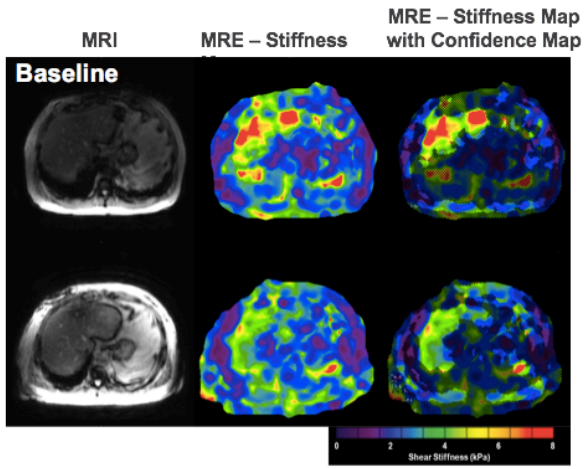
Improvement in ALT, Fat, And Stiffness





Liver Stiffness (MRE) at Week 16

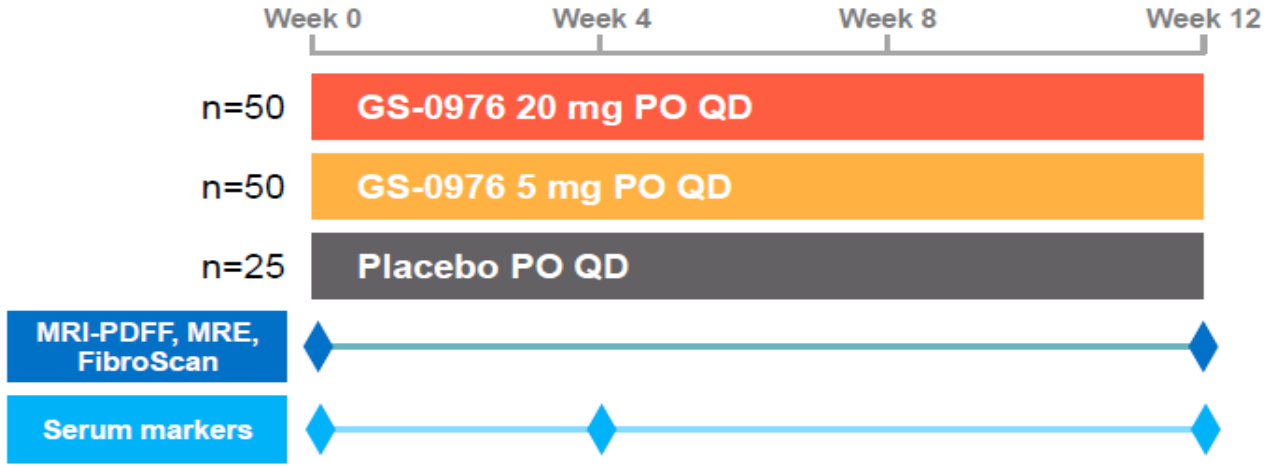




Acetyl-CoA Carboxylase Inhibitor GS-0976

- Increased de novo lipogenesis is pathogenic in NASH
- Acetyl-CoA carboxylase (ACC) catalyzes the rate limiting step in de novo lipogenesis
- In preclinical models, ACC inhibition improves steatosis, inflammation, and fibrosis

Study Design:
Randomized, Placebo-Controlled Trial at 41 U.S. Sites

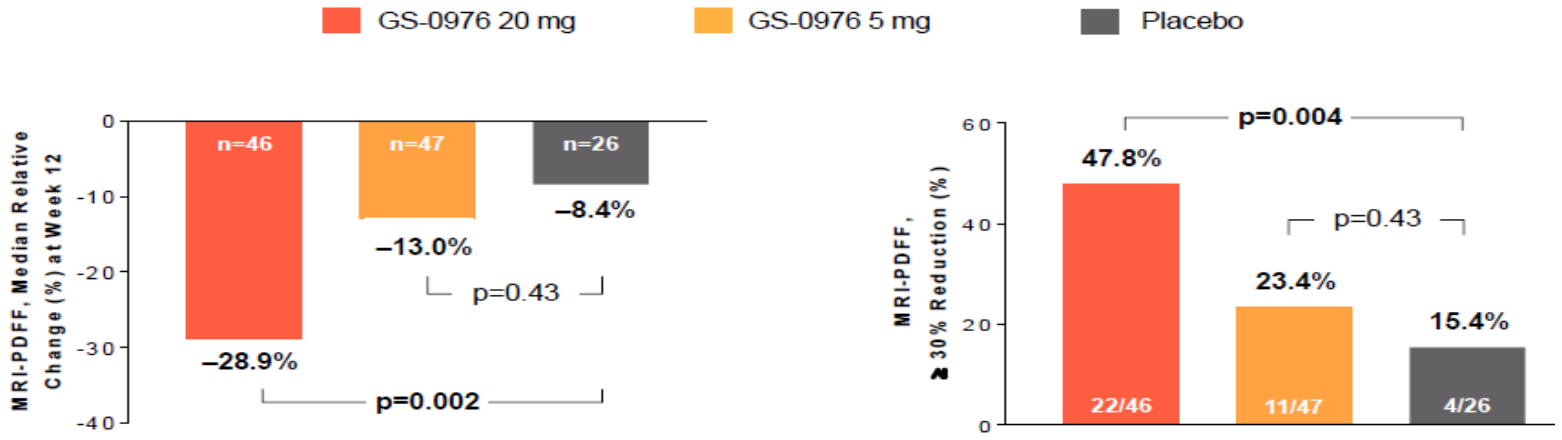


- Key inclusion criteria
  - Clinical diagnosis of NAFLD
  - MRI-PDFF ≥8% and MRE ≥2.5 kPa, or biopsy consistent with NASH and F1-F3
  - Noncirrhotic (FibroTest < 0.75, historical imaging and liver biopsy)
- Stratified by presence or absence of diabetes

Loomba R et al. Gilead. abstract LB9 AASLD 2017

Acetyl-CoA Carboxylase Inhibitor GS-0976

Results: Significant Reduction in MRI-PDFF



- GS-0976 20 mg resulted in a clinically significant reduction in MRI-PDFF[1,2]

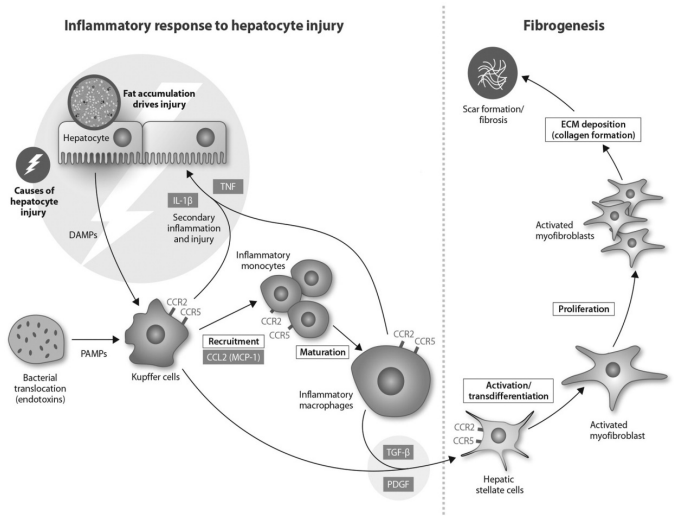
GS-0976 20 mg resulted in reductions in ALT, TIMP-1, and PIII-NP at Week 12

– ELF did not change

- Fibroscan and MRE NS change

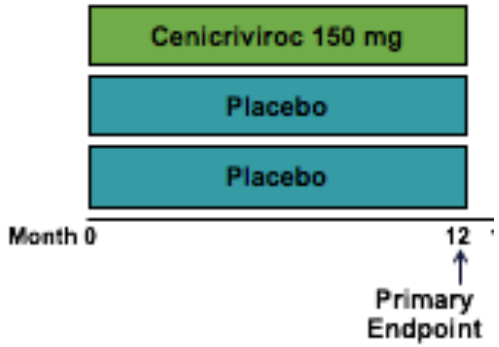
CCR Type 2/5 Antagonist: Cenicriviroc

- Activation of CCR type 2/5 receptors
  - Promotes recruitment and migration of monocytes to the liver
    - Maturate into pro-inflammatory macrophages
- Leads to activation of
  - Kupffer cells
  - Hepatic stellates cells
  - Collagenous production
  - Fibrogenesis



Phase 2b (n=289)
(US, EU, Australia, Hong Kong)

Double-blind
Placebo-controlled
NASH (biopsy diagnosis)
  Biopsy diagnosis, NAS ≥4, fibrosis stage 1-3 (NASH-CRN)
Stratified by NAS (4 or ≥5) and fibrosis stage (≤2 or >2)



Perazzo H, et al. *Liver Int.* 2017;37:634-647.
Friedman S, et al. *Contemp Clin Trials.* 2016;47:356-365.

CENTAUR Study (Year-1 Primary Analysis): Primary and Key Secondary Endpoint Results

Primary endpoint

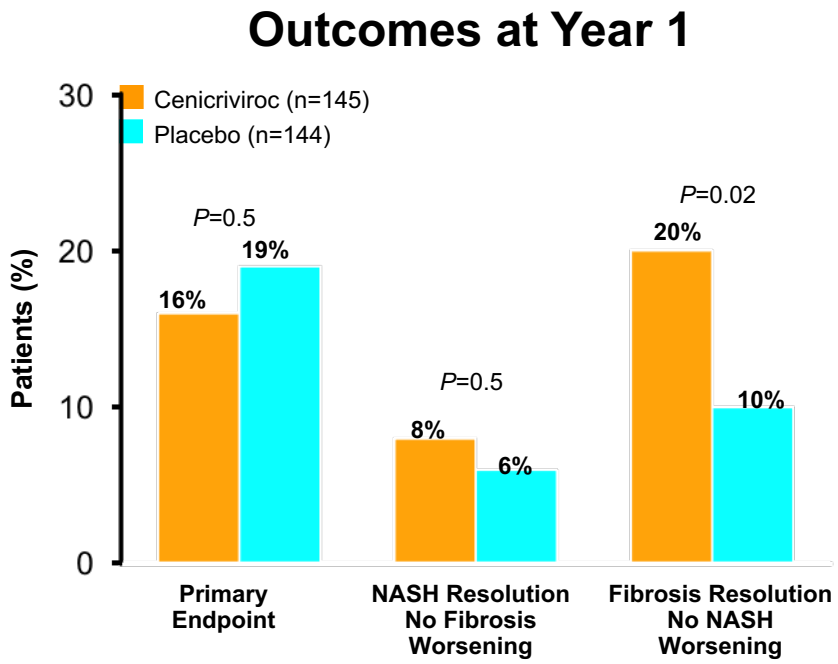
No significant difference between cenicriviroc and placebo (16% versus 19%)

Key secondary endpoints

Complete NASH resolution and no fibrosis worsening

No significant difference between cenicriviroc and placebo (6% versus 8%)

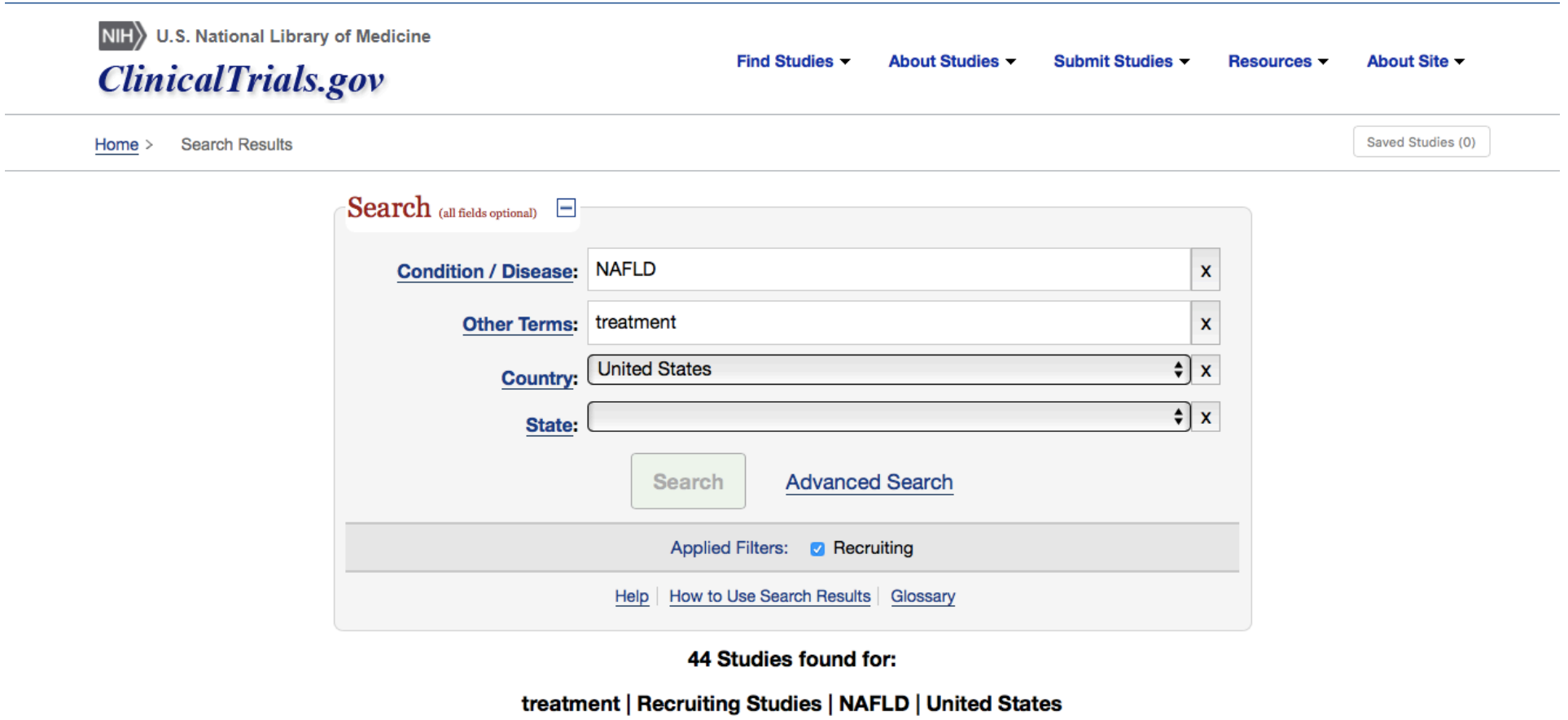
≥1 stage improvement in fibrosis (NASH-CRN) and no worsening of NASH achieved by significantly more cenicriviroc patients versus placebo (20% versus 10%; *P*=0.02)



Primary endpoint:
≥2 point NAS improvement.
≥1-point reduction in either lobular inflammation or hepatocellular ballooning and no worsening of fibrosis stage.

Sanyal AJ, et al. *Hepatology*. 2016;64(suppl S1):1118A. Abstract LB-1.

Lots of Trials for NAFLD Actively Enrolling



Summary

- NAFLD is part of a systemic process and other diseases (cardiovascular) are associated
- More prevalent than previously estimated
  - Hispanics and diabetics at particular risk
- Biopsy is required, steatosis benign from hepatic point of view, NASH can progress to cirrhosis
- Smoking and excess alcohol are bad, but coffee and sleep likely good

Summary

- Weight loss goal of 10% is best for histopathology improvement
- Moderate exercise may not be enough to effect change in NASH. Vigorous exercise for >150 min/week ideal
- Vitamin E may be considered for patients with biopsy proven NASH with caveats (non-diabetic NASH)
- Pioglitazone can be used in NASH (non-diabetic NASH)
- Omega 3 fatty acids should also be considered. Not due to good data in NASH necessarily, but for cardiovascular benefit
- Statins are safe
- Bariatric surgery is a solution

- Refer for clinical trial of choice (we have multiple enrolling)
- pkwo@stanford.edu