
Northern California Society
for Clinical Gastroenterology
1ST ANNUAL
NCSCG
POST-AASLD
SYMPOSIUM
UNIVERSITY OF
Cincinnati
Jointly provided by the University Of Cincinnati College Of Medicine
and the Northern California Society for Clinical Gastroenterology.

Northern California Society for Clinical Gastroenterology

New Treatment Guidelines for the Management of NAFLD/NASH

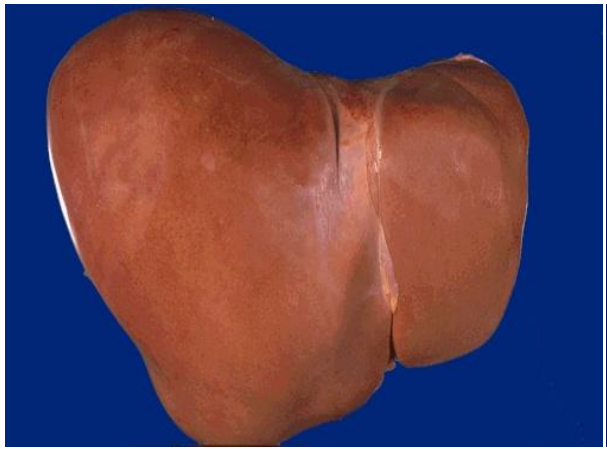
Raphael B. Merriman, MD, FRCPI, FACP,
Director, Metabolic Liver Disease Research,
Medical Director, Liver Transplantation,
California Pacific Medical Center and Research Institute,
San Francisco, CA

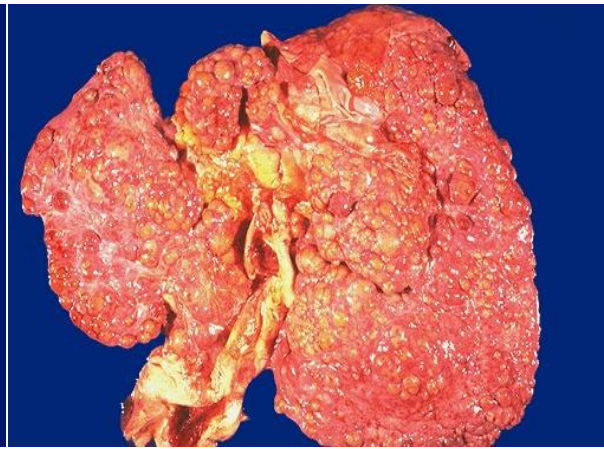
merrimr@sutterhealth.org

Disclosures

- I have no business / pharmaceutical relationships to disclose
- I do not engage in commercial speaker training and have no information or data obtained from speaker training
- I will be discussing the off-label, non-FDA approved use of pharmaceutical agents

(Idiopathic) NAFLD - The Liver And The Waistline: 30 Years A Growing



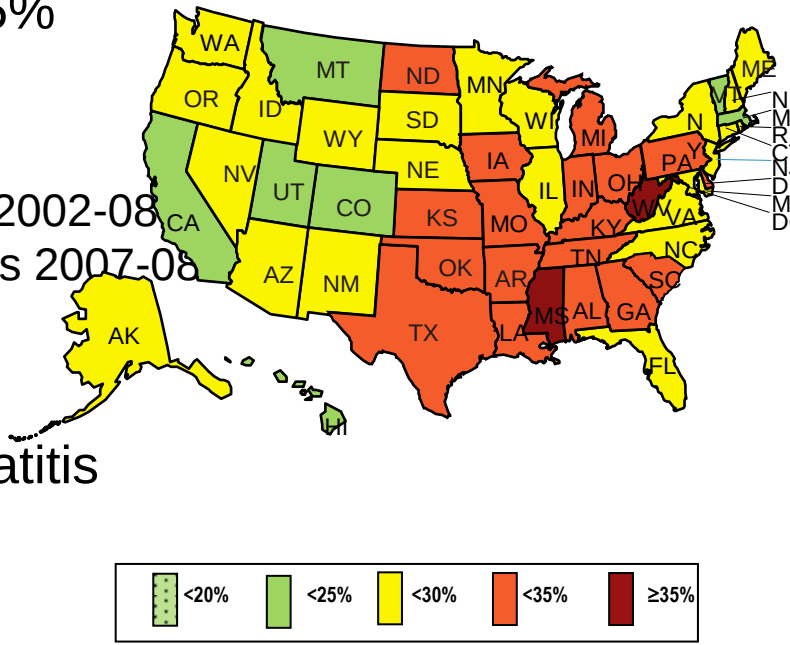


Ludwig J.
Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease.
Mayo Clin Proc 1980;55:434–438

‘The Times They Are A Changin’……’

Obesity and NAFLD Overview

- Bad News:
  - Prevalence of obesity in US adults ~ 35%
- Good News:
  - Rates appear to be leveling off…
    - Adults - 2009-10 rates were the same as 2002-08
    - Children - 2009-10 rates were the same as 2007-08
- No Longer News….
  - 2/3 obese patients have steatosis
  - Of these, ~ 20% progress to steatohepatitis
  - Of these, ~ 15% progress to cirrhosis
    (3-5 million persons)



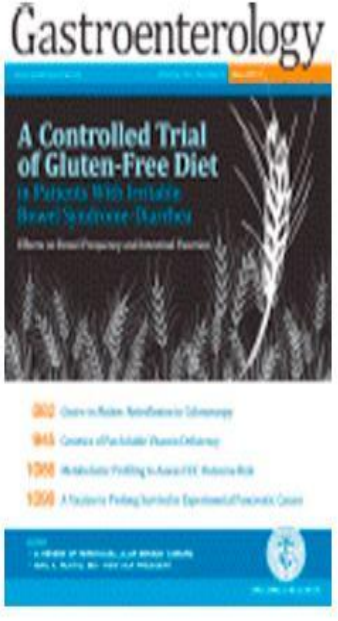
Flegal JAMA 2012, Ogden JAMA 2012, Janssen Can J Diab 2013, Angulo NEJM 2002

Indications for Liver Transplantation

Accepted Manuscript

Nonalcoholic Steatohepatitis is the Second Leading Etiology of Liver Disease Among Adults Awaiting Liver Transplantation in the U.S.

Robert J. Wong , Maria Aguilar , Ramsey Cheung , Ryan B. Perumpail , Stephen A. Harrison , Zobair M. Younossi , Aijaz Ahmed



NASH HCC is the # 2 HCC Indication for LT

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Nonalcoholic Steatohepatitis Is the Most Rapidly Growing Indication for Liver Transplantation in Patients With Hepatocellular Carcinoma in the U.S.

Robert J. Wong,[1,2] Ramsey Cheung,[1,2] and Aijaz Ahmed[1]

Wong Hepatol 2014

Therapeutic Management of NASH, *circa* 2010

AASLD NAFLD PRACTICE GUIDELINES

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

AASLD PRACTICE GUIDELINE

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Naga Chalasani, MD, FACG,[1] Zobair Younossi, MD, FACG,[2] Joel E. Lavine, MD, PhD,[3] Anna Mae Diehl, MD,[4] Elizabeth M. Brunt, MD,[5] Kenneth Cusi, MD,[6] Michael Charlton, MD,[7] and Arun J. Sanyal, MD[8]

- Intended to be flexible and adjustable for individual patients
- Specific recommendations are evidence-based wherever possible
- When such evidence is not available/inconsistent, recommendations are made based on the consensus opinion of the authors

Chalasani Hepatol 2012

AASLD NAFLD PRACTICE GUIDELINES

- # 1 Ongoing or recent alcohol consumption > 21 drinks on average per week in men and > 14 drinks on average per week in women is a reasonable definition for significant alcohol consumption when evaluating patients with suspected NAFLD in clinical practice

- #3 In patients with unsuspected hepatic steatosis detected on imaging who are asymptomatic and have normal liver biochemistries, a liver biopsy cannot be recommended

- #7 When evaluating a patient with suspected NAFLD, it is essential to exclude competing etiologies for steatosis and co-existing common chronic liver disease

AASLD NAFLD PRACTICE GUIDELINES

- #10 As the metabolic syndrome predicts the presence of steatohepatitis in patients with NAFLD, its presence can be used to target patients for a liver biopsy

- #13 Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis

- #14 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

AASLD NAFLD PRACTICE GUIDELINES

- #17 Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation

- #19 Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH

- #20 Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH –
  - majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long term safety and efficacy of pioglitazone in patients with NASH is not established

PIVENS - Summary

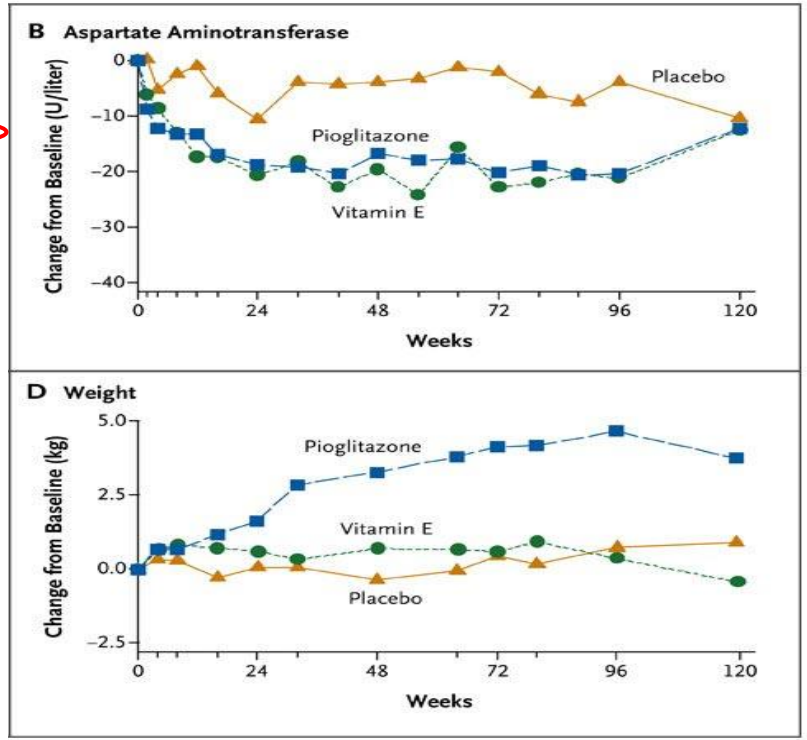
Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

Variable	Placebo	Vitamin E	Pioglitazone	P Value*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04
Changes from baseline in histologic features					
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70		
Steatosis					
Subjects with improvement (%)	31	54	69	0.005	<0.001
Mean change in score	−0.1	−0.7	−0.8	<0.001	<0.001
Lobular inflammation					
Subjects with improvement (%)	35	54	60	0.02	0.004
Mean change in score	−0.2	−0.6	−0.7	0.008	<0.001
Hepatocellular ballooning					
Subjects with improvement (%)	29	50	44	0.01	0.08
Mean change in score	−0.2	−0.5	−0.4	0.03	0.01
Total NAFLD activity score (mean change)	−0.5	−1.9	−1.9	<0.001	<0.001
Fibrosis‡					
Subjects with improvement (%)	31	41	44	0.24	0.12
Mean change in score	−0.1	−0.3	−0.4	0.19	0.10
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001

* P values were calculated with the use of the Mantel–Haenszel chi-square test, stratified according to clinic, for the primary outcome; Fisher's exact test for the binary secondary outcomes; and analysis-of-covariance models, regressing change from baseline to 96 weeks on treatment group and baseline value of the outcome, for secondary outcome scores.

† The primary outcome was an improvement in histologic findings, which required improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the activity score for nonalcoholic fatty liver disease to a score of 3 points or less or a decrease in the activity score of at least 2 points, with at least a 1-point decrease in either the lobular inflammation or steatosis score. A total of 11 subjects in the placebo group, 4 in the vitamin E group, and 10 in the pioglitazone group had missing histologic data at week 96, and the results for these subjects were imputed as a lack of improvement. The NAFLD activity score was assessed on a scale of 0 to 8, with higher scores indicating more severe disease; the components of this measure include steatosis (assessed on a scale of 0 to 3), lobular inflammation (assessed on a scale of 0 to 3), and hepatocellular ballooning (assessed on a scale of 0 to 2).

‡ Fibrosis was assessed on a scale of 0 to 4, with higher scores indicating more severe fibrosis.

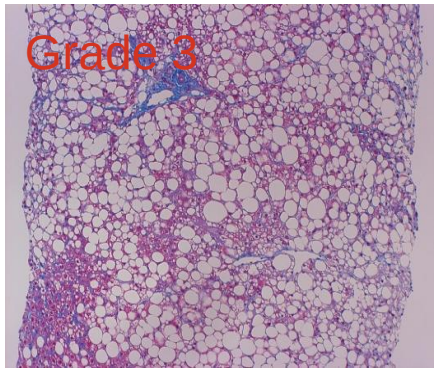


Sanyal NEJM 2010

NAFLD Activity Score (NAS)

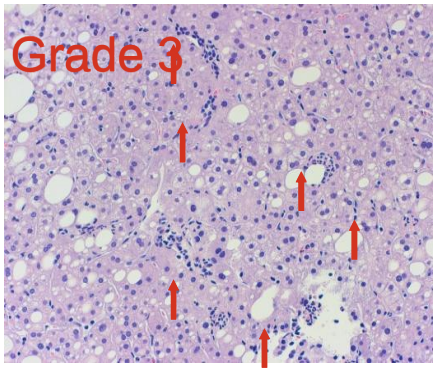
Steatosis:

- 0 < 5% (normal)
- 1 5% - 33%
- 2 > 33% - 66%
- 3 > 66%



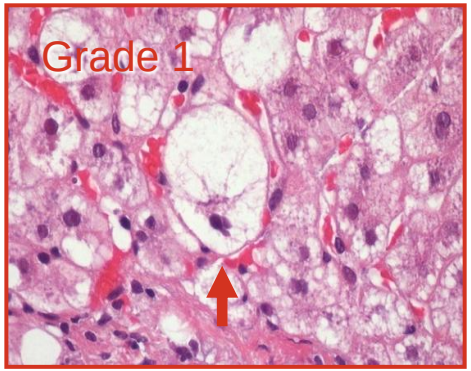
Lobular inflammation:
(Inflamm. foci per 20x)

- 0 None
- 1 < 2 per 20x
- 2 2 - 4 per 20x
- 3 > 4 per 20x



Ballooning:

- 0 None
- 1 Few, small
- 2 Many



Kleiner Hepatol 2005

NAFLD Activity Score (NAS)

"**Activity Score**" was defined for use in clinical trials to objectively measure histologic improvement

NAS Score (0-8)=Steatosis (0-3) + Lob. Inf. (0-3) + Ballooning (0-2)

- NAS ≤ 2 = Not diagnostic of steatohepatitis
- NAS 3-4 = Suspicious/borderline
- NAS ≥5 = Definitely steatohepatitis

(NASH Clinical Trial minimal criteria)

Kleiner Hepatol 2005

PIVENS -Conclusions

- Vitamin E was superior to placebo (43% vs. 19%) for the treatment of NASH in adults without diabetes

- There was no benefit of pioglitazone over placebo for the primary outcome; however, significant benefits of pioglitazone were observed for some of the secondary outcomes

Sanyal NEJM 2010

AASLD NAFLD PRACTICE GUIDELINES

- #21 Vitamin E administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population
- #22 Until further data, ..vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

- #28 Patients with NAFLD should not consume heavy amounts of alcohol
- #29 No recommendation can be made with regards to non-heavy consumption of alcohol by individuals with NAFLD
  - (No other medical therapeutics recommended)

#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]

[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

Objectives

- To assess US physicians' level of awareness of NASH clinical guidelines, and their current practices in diagnosing and treating NASH

Methods

- An invitation to complete an online 35-item survey regarding NASH was sent to 9514 physicians from specialties typically involved in NASH management: gastroenterologists, hepatologists, endocrinologists, and internists/primary-care providers (PCPs)
- Responding physicians were required to meet the following criteria:
  - Currently manage NASH patients
  - Spend ≥25% of time treating patients (vs research, teaching, etc)
  - Not employed by or directly affiliated with pharmaceutical company

#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]
[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

Survey Respondents

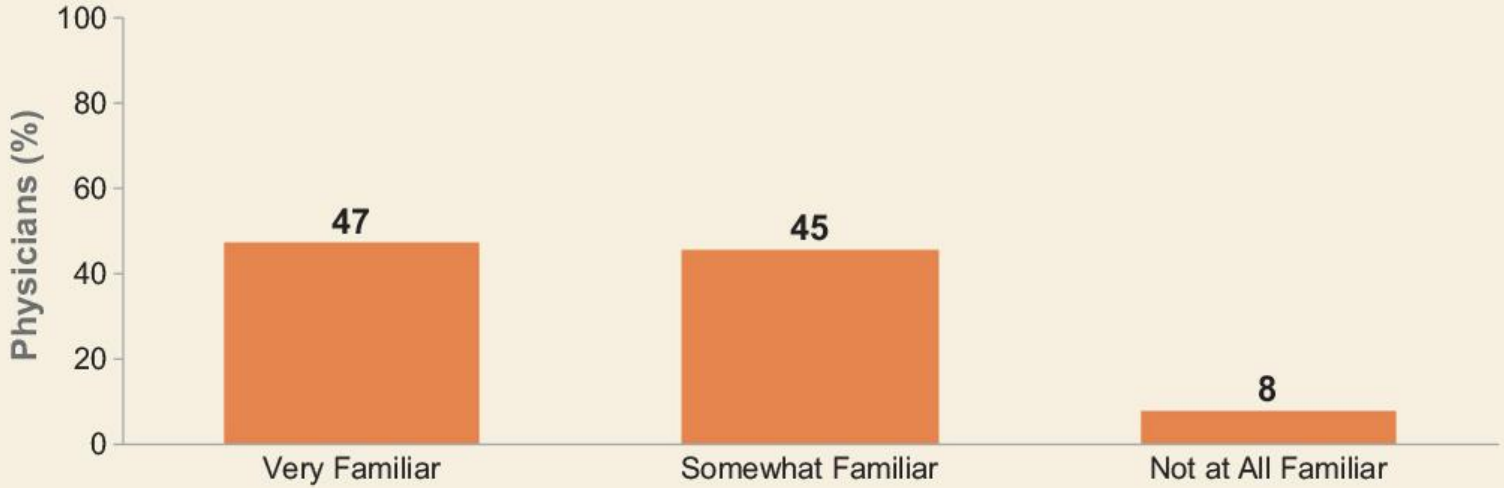
		Gastroenterologists n=75	Hepatologists n=75	Endocrinologists n=64	Internists/PCPs n=75	Total N=289
Mean years in practice		14	12	17	19	15
Years in practice, n	2–10 y	30	42	16	10	98
	11–20 y	28	19	26	39	112
	21–30 y	17	14	22	26	79
Practice setting, n	Hospital: university affiliated	46	66	28	26	166
	Hospital: nonuniversity	7	4	6	5	22
	Public health clinic	0	0	1	2	3
	Private health clinic	5	1	8	8	22
	Private office	17	4	21	34	76
Practice location, % respondents	Northeast	32	19	39	39	32
	Midwest	20	23	16	25	21
	South	24	33	24	26	27
	West	24	25	22	9	20
Mean patients seen/mo, n	Any disease	283	204	302	371	289
	NASH	25	35	18	24	26

#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]
[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

92% of Physicians Were Very or Somewhat Familiar With NAFLD Practice Guidelines (N=289)



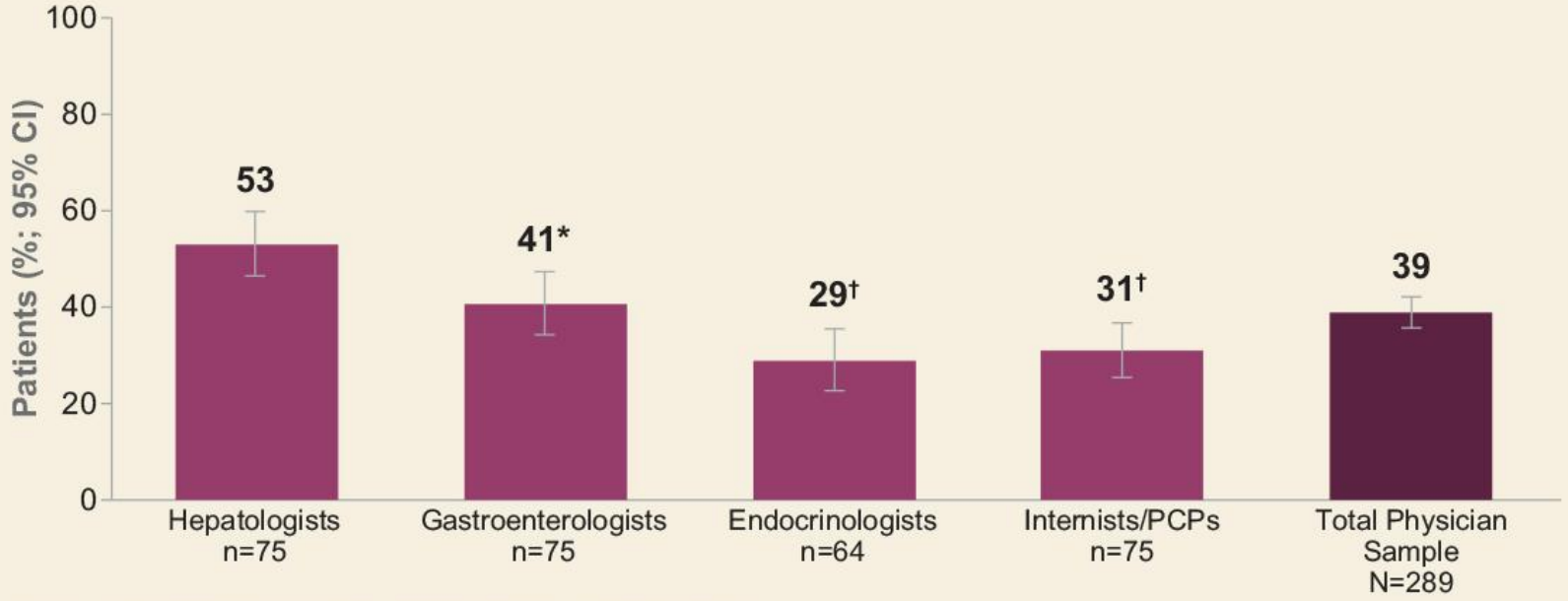
#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]

[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

A Minority of Patients Had a Liver Biopsy to Confirm NASH Diagnosis; Hepatologists Performed the Greatest % of Biopsies



*p=0.03; †p<0.001 vs hepatologists by Tukey's honest significant difference. CI, confidence interval.

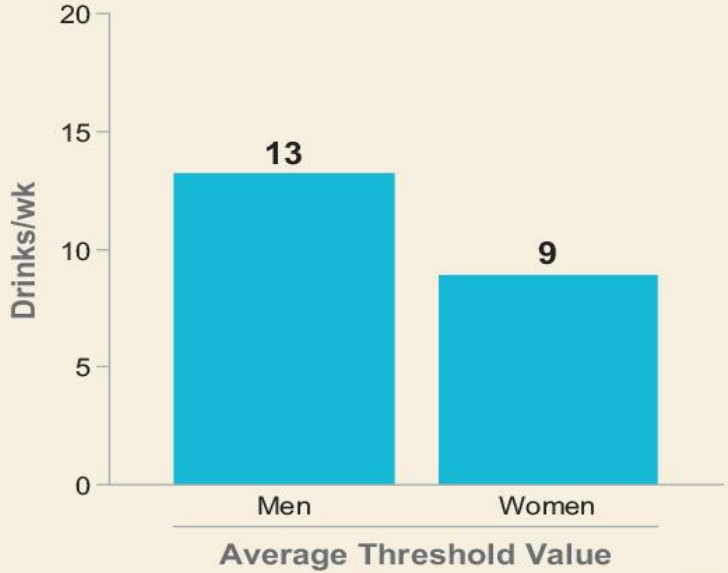
#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

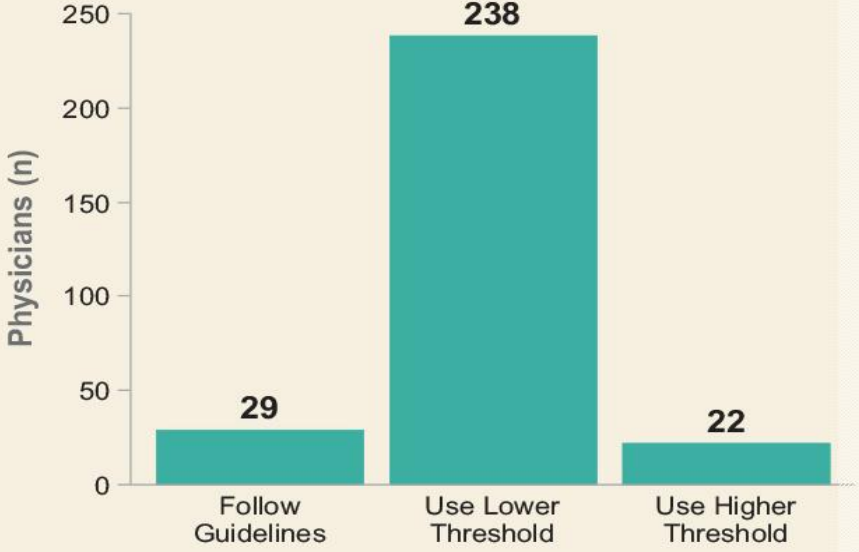
Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]
[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

Alcohol Thresholds to Exclude NASH Were Lower Than Expected

Reported Definition of "Significant Alcohol Consumption"*



Physicians Following Guideline Definition



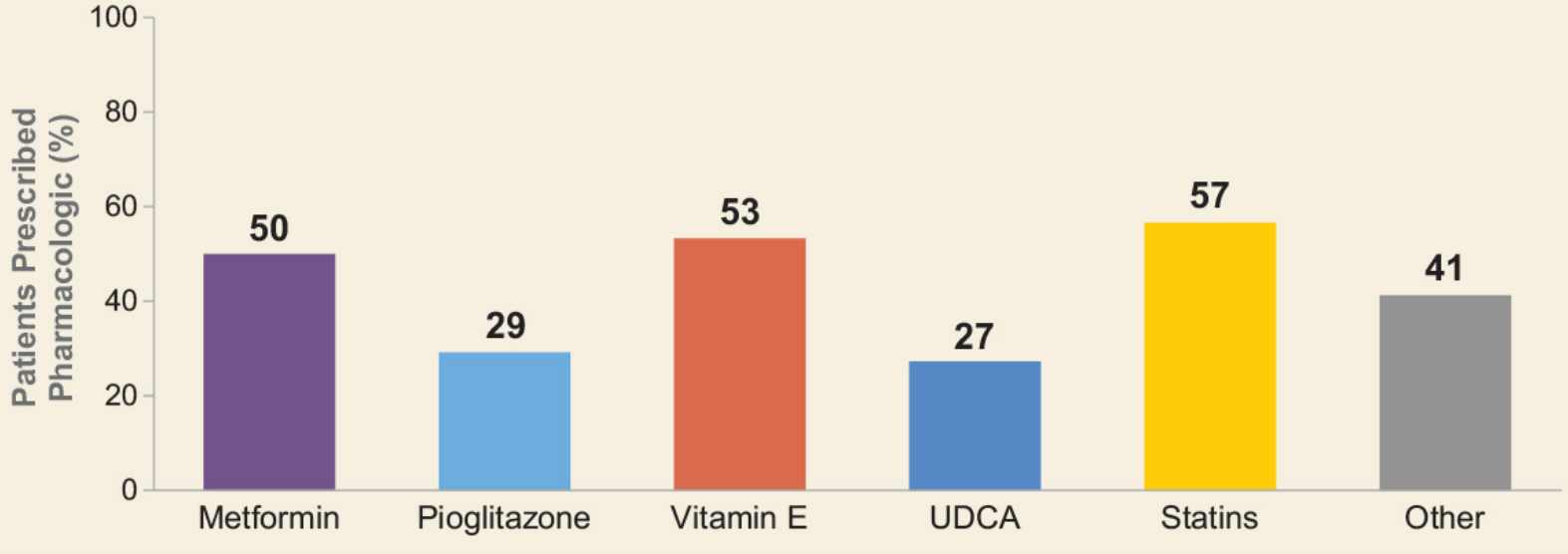
*p <0.001 for men and women vs guidelines definition of >21 drinks/wk for men and >14 for women using t test.

#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]
[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

The Majority of NASH Patients Were Prescribed a Pharmacologic Intervention



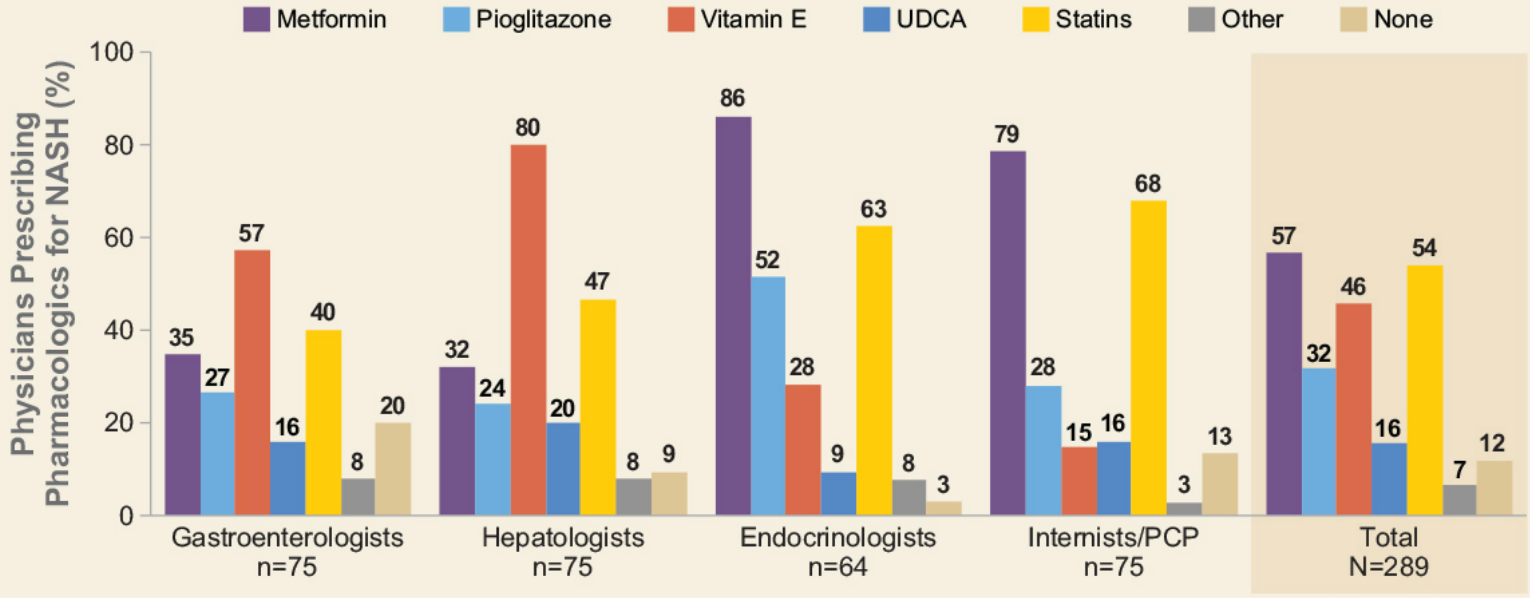
#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]

[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

Pharmacologic Intervention Usage Varied Across Specialties



#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]

[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

Physician Practices Differed From the Guidelines in 3 Areas

	NAFLD Guidelines	Survey Results on Physician Practices
Liver biopsy to confirm NASH diagnosis	Required	Mean 39% of patients considered to have NASH diagnosis received liver biopsy
Definition of "significant alcohol consumption" supporting evaluation of NAFLD/NASH	Men: >21 drinks/wk Women: >14 drinks/wk	Men: mean 13 drinks/wk Women: mean 9 drinks/wk
Use of pharmacologic interventions for treatment of liver disease in NASH patients	Metformin: not recommended (Strength – 1)	% of physicians (N=289) who prescribed following pharmacologic interventions for treatment of NASH: Metformin: 57% Pioglitazone: 32% Vitamin E: 46% UDCA: 16% Statins: 54%
	Pioglitazone: can be used in biopsy-proven NASH; long term safety/efficacy in NASH not established (Strength – 1)	
	Vitamin E: consider for nondiabetic, biopsy-proven NASH (Strength – 1); not recommended for diabetic NASH or NASH cirrhosis (Strength – 1)	
	UDCA: not recommended for NASH (Strength – 1)	
	Statins: not recommended to specifically treat NASH (Strength – 1)	

UDCA, ursodeoxycholic acid.

#890

US Physician Survey of Current Practices in the Diagnosis and Treatment of Nonalcoholic Steatohepatitis (NASH)

Stephen A. Harrison,[1] Min Wang,[2] Arun Sanyal[3] Other Contributors: Sheldon Y. Okada,[2] Cathy A. Su,[2] Jeff D. Bornstein,[2] Matthew S. Paulson[2]
[1]Brooke Army Medical Center, Fort Sam Houston, TX; [2]Gilead Sciences, Inc., Foster City, CA; [3]Virginia Commonwealth University School of Medicine, Richmond, VA

Conclusions

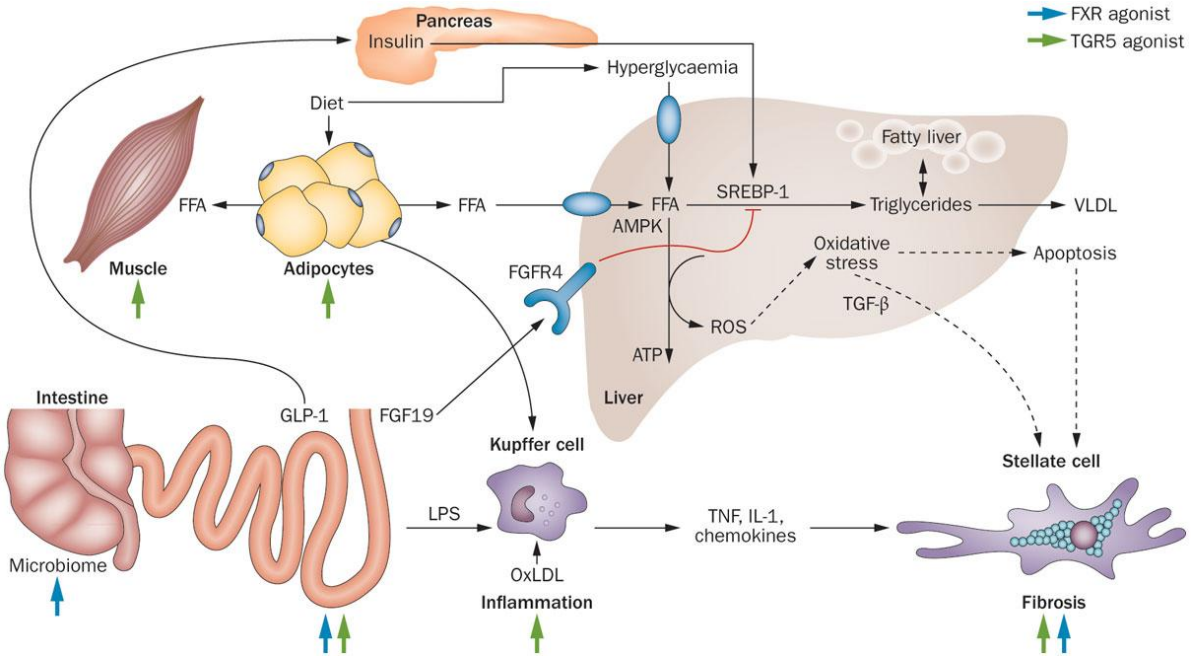
- The results of this survey highlight the following:
  - A potential knowledge gap concerning implementation of the NAFLD practice guidelines
  - Without an effective pharmacologic treatment for NASH, there were inconsistencies between physicians and the guidelines with regard to current utilization of pharmacologic interventions
  - Physicians appeared to be hesitant to perform liver biopsies to diagnose NASH, highlighting the need to develop noninvasive tests that are highly sensitive and specific

Guidelines…

- ‘Datapenia’
- Lack of effective therapeutics,
- Lack of practical diagnostic tools

- Practices will and do vary widely …in spite of Guidelines
- Better therapeutic and diagnostics needed…

Bile Acid Signalling – Targets of FXR in NASH



- Farnesoid X receptor (FXR)

- Intracellular nuclear receptors
- Respond to bile acids by activating multiple transcriptional networks and/or signaling cascades

- Cascade activation affects the expression of a great number of target genes
  - bile acid
  - cholesterol
  - lipid and carbohydrate metabolism
  - inflammation
  - fibrosis
  - carcinogenesis

Schaap Nat Rev Gastroenterol Hepatol 2013

Bile Acids - Mechanisms Of Action

- Established roles in dietary lipid absorption and cholesterol homeostasis

- Metabolically active signaling molecules with downstream targets
  - Control of hepatic de novo lipogenesis, very-low-density lipoprotein-TG export and plasma TG turnover.
  - Regulation of hepatic gluconeogenesis, glycogen synthesis and insulin sensitivity
  - Stimulate glucagon-like peptide-1 secretion in the small intestine and energy expenditure in brown adipose tissue and skeletal muscle
- Effectors, integrators and effectors of metabolism (‘steroids on steroids’)

Karpen, Gastroenterol 2013

Obeticholic Acid In NASH

GASTROENTEROLOGY 2013;145:574–582

CLINICAL—LIVER

Efficacy and Safety of the Farnesoid X Receptor Agonist Obeticholic Acid in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease

SUNDER MUDALIAR,[1] ROBERT R. HENRY,[1] ARUN J. SANYAL,[2] LINDA MORROW,[3] HANNS–ULRICH MARSCHALL,[4] MARK KIPNES,[5] LUCIANO ADORINI,[6] CATHI I. SCIACCA,[7] PAUL CLOPTON,[1] ERIN CASTELLOE,[7] PAUL DILLON,[8] MARK PRUZANSKI,[6] and DAVID SHAPIRO[7]

Phase 1 study, proof-of-concept, improved insulin sensitivity, biochemistry, markers

#?

THE LANCET

Published Online November 7, 2014

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

*Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network**

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NATIONAL CANCER INSTITUTE

Partial funding for the trial, obeticholic acid, and placebo were provided by Intercept Pharmaceuticals under a Collaborative Research and Development Agreement with the NIDDK.

Selected slides courtesy of Dr. Brent Tetri, adapted

The FLINT Trial

- Obeticholic acid (OCA), 25 mg orally daily *vs.* placebo
- Inclusion: adults with NASH on biopsy, NAS ≥ 4 (at least one point for each component), biopsy within 90 days
- Exclusion: cirrhosis, alcohol > 20g/d F, > 30 gm/d M
- N = 283 patients randomized at 8 clinical centers, 72 weeks of treatment
- Biopsy ≤ 3 months before treatment and after 72 weeks
- Primary endpoint
  - Improvement in NAFLD Activity Score (NAS) ≥ 2 pts with no worsening of fibrosis

Neuschwander-Tetri Lancet 2014

FLINT Key Baseline Characteristics

	Obeticholic acid (n = 141)	Placebo (n = 142)
Age (years)	52 ± 11*	51 ± 12
% Female	69%	63%
% Hispanic	16%	15%
BMI (kg/m^2)	35 ± 7	34 ± 6
Diabetes	53%	52%
Hypertension	62%	60%
Hyperlipidemia	62%	61%
Vitamin E use	21%	23%
ALT (IU/L)	83 ± 49	82 ± 51
NAFLD Activity Score (NAS)	5.3 ± 1.3	5.1 ± 1.3
Fibrosis stage	1.9 ± 1.1	1.8 ± 1.0

(*± SD)

Neuschwander-Tetri Lancet 2014

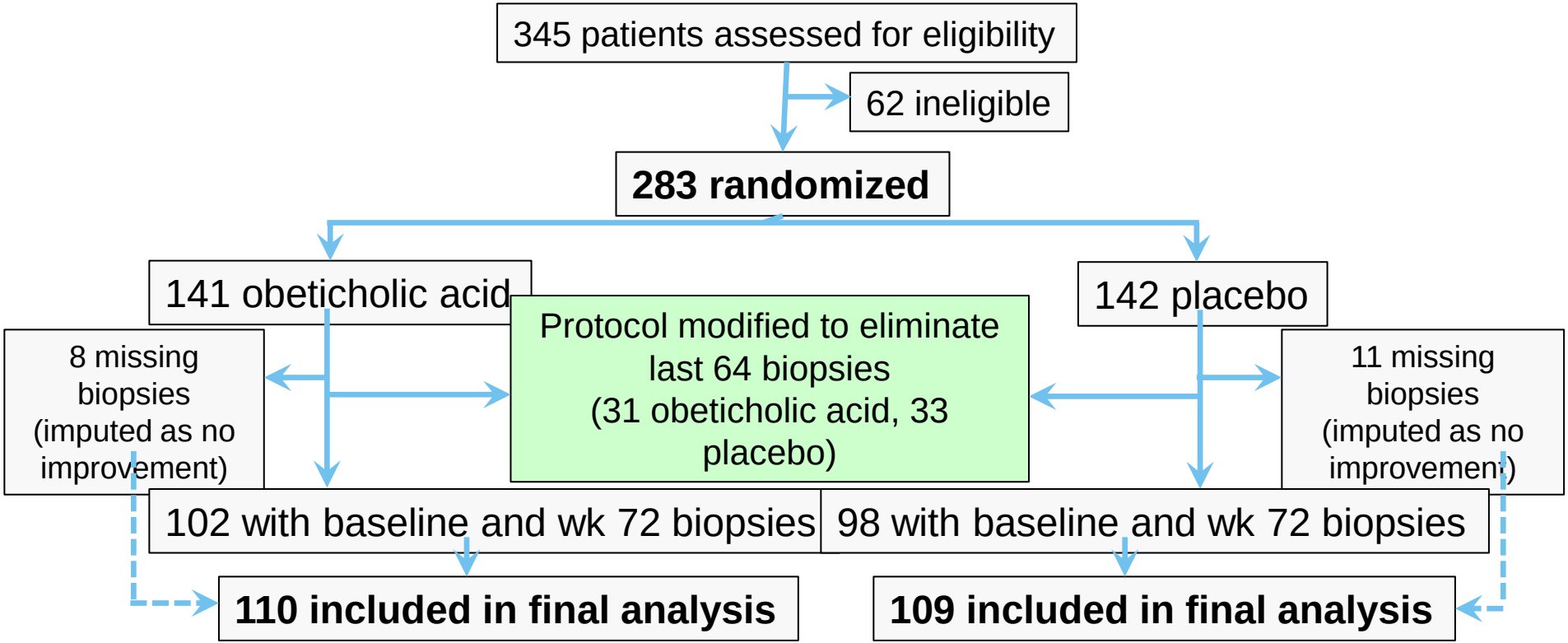
The FLINT Trial

- Cholesterol concentrations increased with OCA –
  - DSMB-mandated lipid control
- Central Pathology Review
  - 80% definite NASH , 22% Stage 3 fibrosis

- Planned interim DSMB analysis to avoid unnecessary biopsies when > 50% follow up biopsies completed:
  - Criteria for superiority for primary outcome for OCA met (p=0.0031) and final 64 biopsies not completed and excluded in ITT analysis

Neuschwander-Tetri Lancet 2014

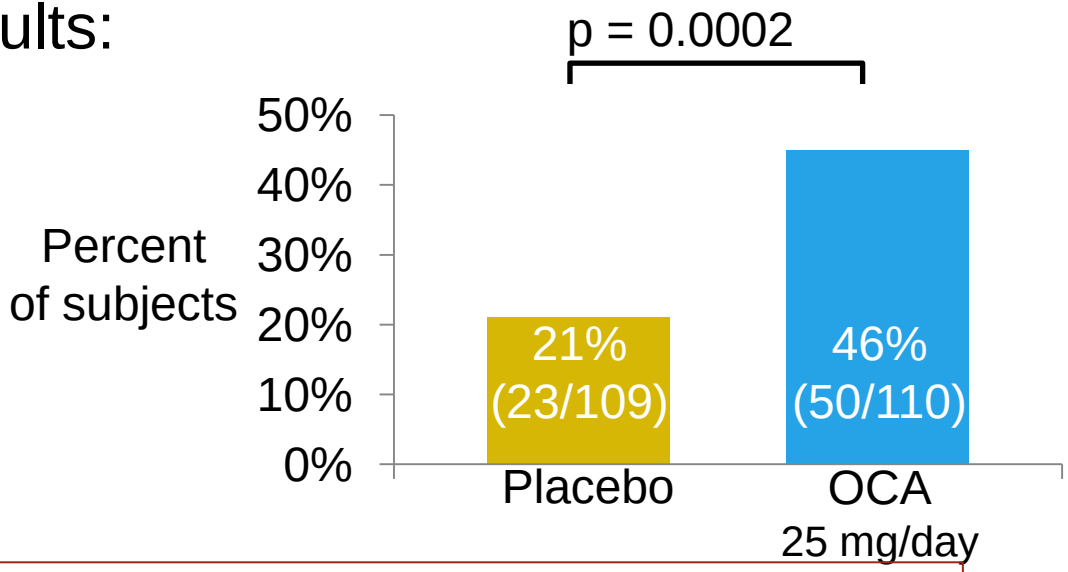
FLINT Study Design



Neuschwander-Tetri Lancet 2014

FLINT Primary Endpoint

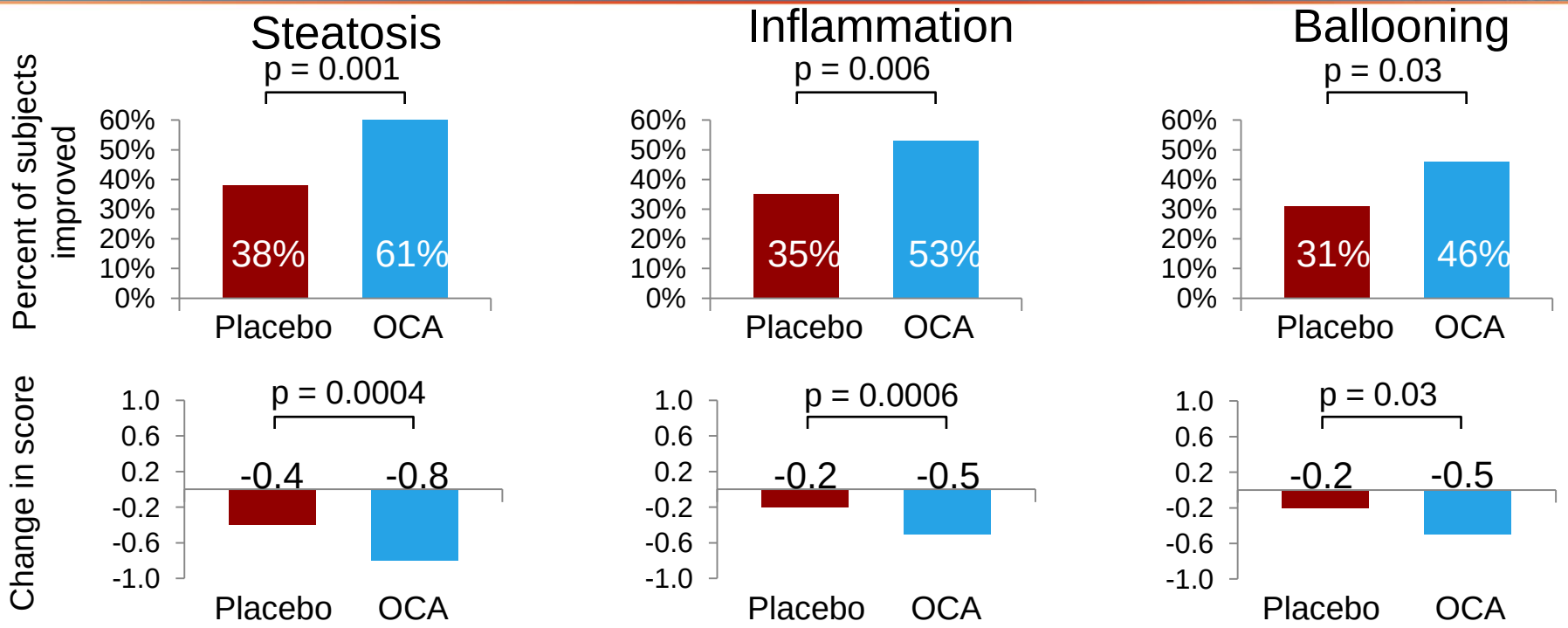
- Improvement in NAFLD activity score* (NAS) ≥ 2 pts
  - * NAS = steatosis grade (0-3) + inflammation grade (0-3) + ballooning grade (0-2)
- No worsening of fibrosis
- Results:



Mean reduction in NAS: 0.7 *vs.* 1.7

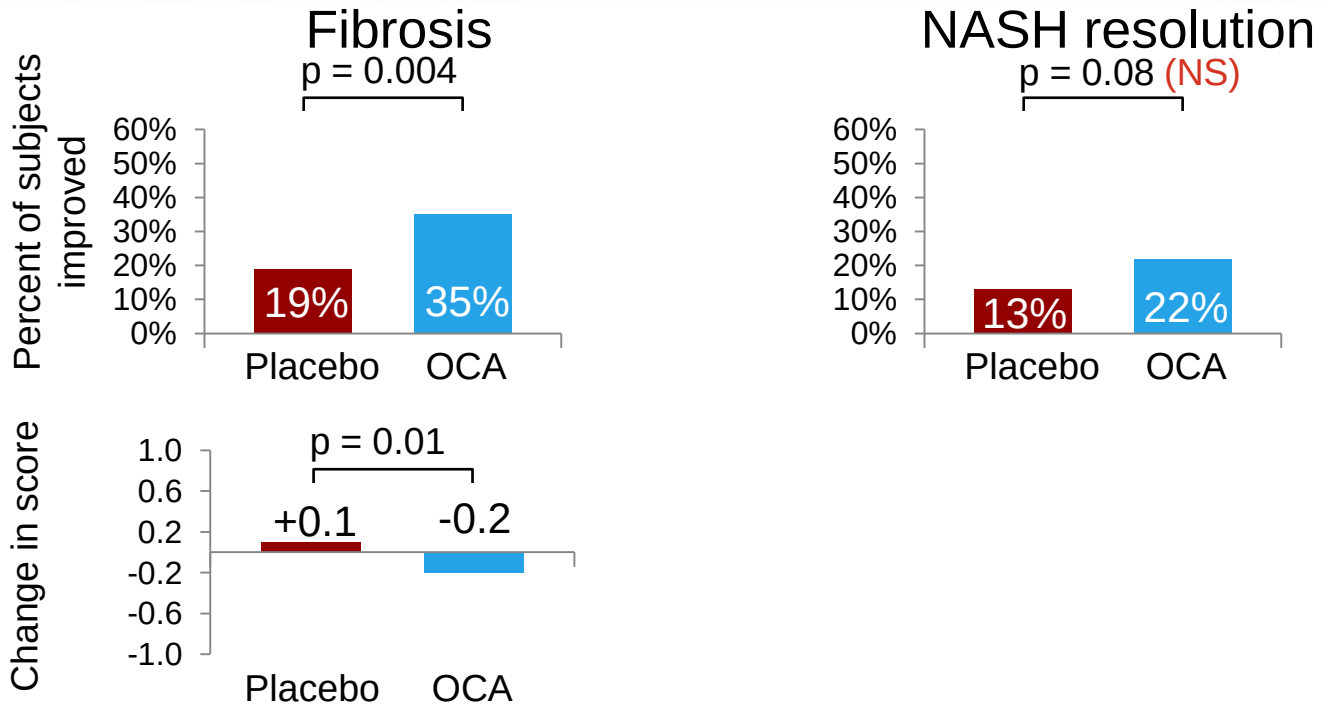
Neuschwander-Tetri Lancet 2014

Improvement in NAS Components



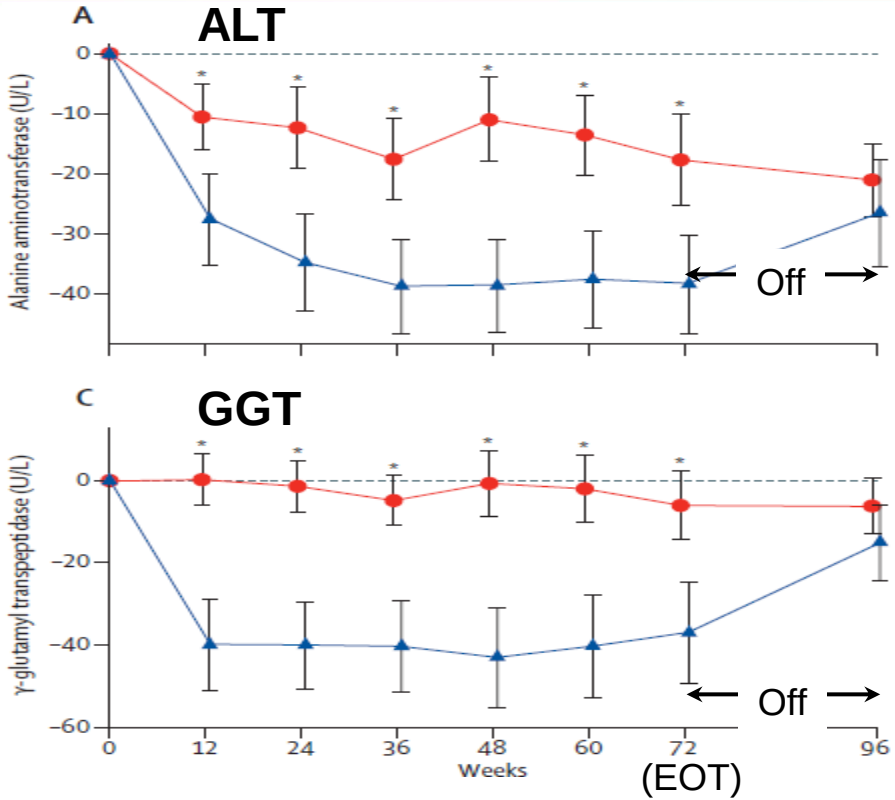
Neuschwander-Tetri Lancet 2014

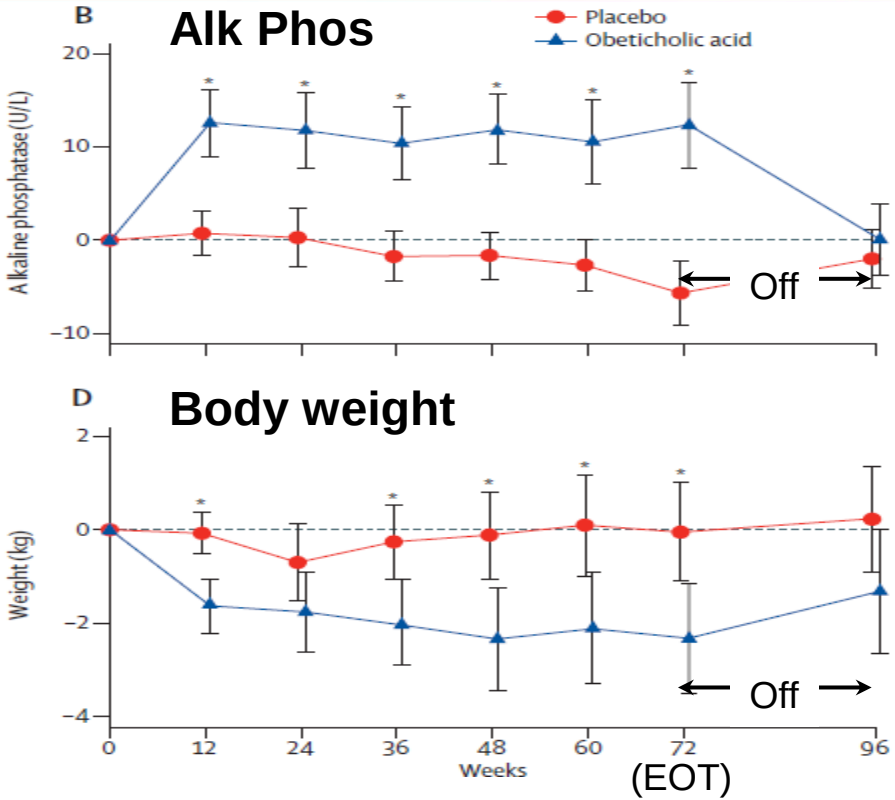
Improvement in Fibrosis and NASH Resolution



Neuschwander-Tetri Lancet 2014

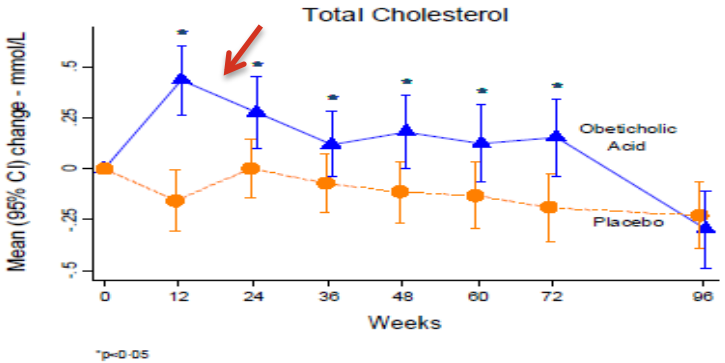
Changes In Enzymes and Body Weight

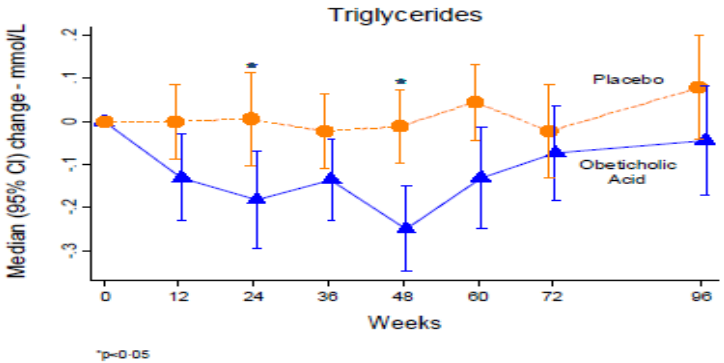


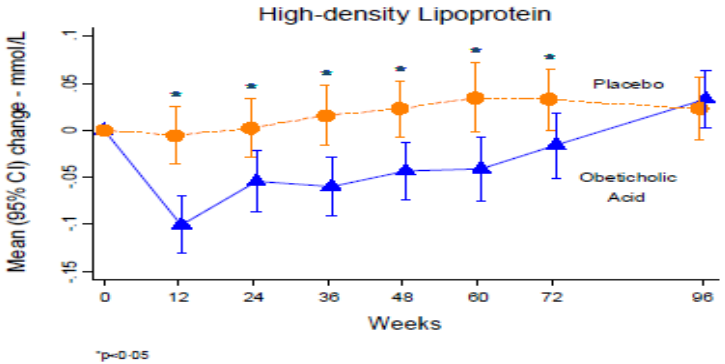


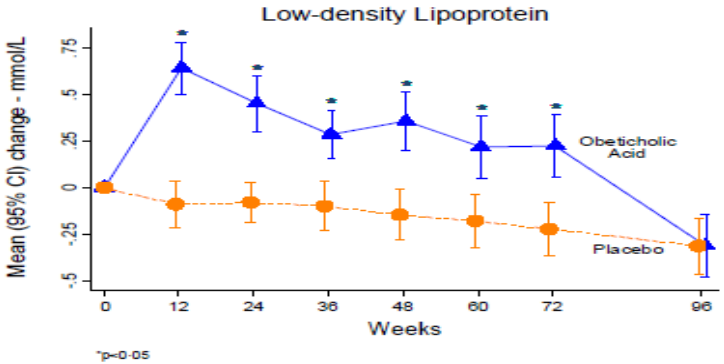
Neuschwander-Tetri Lancet 2014

Changes in Serum Lipids







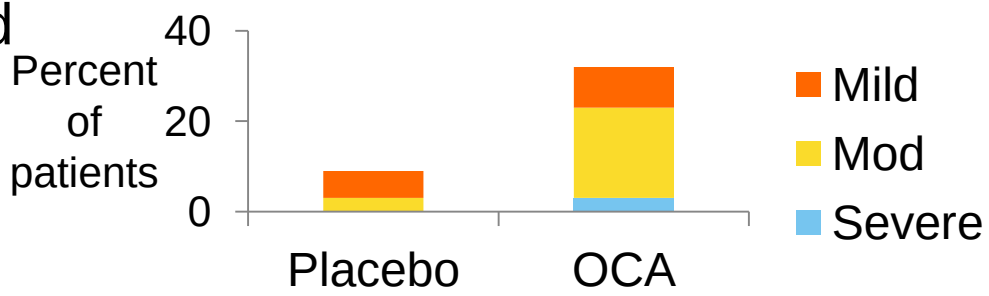


Neuschwander-Tetri Lancet 2014

Adverse Events

- 6 severe adverse events in obeticholic acid group
  - 4 severe pruritus (1 stopped treatment)
  - 1 hypoglycemia
  - 1 possible cerebral ischemia (dysarthria and dizziness)
- Moderate or severe pruritus
  - 23% in obeticholic acid
  - 6% in placebo

P < 0.0001



Neuschwander-Tetri Lancet 2014

FLINT Summary

- Obeticholic acid improved histological features of NASH including fibrosis
- Obeticholic acid treatment was associated with pruritus that was severe in 3%
- Elevated total and LDL cholesterol and decreased HDL cholesterol warrant further scrutiny in future trials

NASH CRN

Neuschwander-Tetri Lancet 2014

FLINT Throws A Spark…

- Clear indication of efficacy in NASH…but

- Lack of detailed data about cholesterol interventions
- Not powered to assess fibrosis change
- NAS does not predict liver-related mortality
- No difference in resolution of NASH
- Twenty percent did not have definite NASH
- Truncated trails tend to overestimate the treatment benefits
- Substantial proportion of non-responders
- Atherogenic lipoprotein subfractions altered?

#58

Northern California Society for Clinical Gastroenterology

Novel MRI and MRE assessment of ezetimibe versus placebo for the treatment of nonalcoholic steatohepatitis: A randomized-controlled trial MOZART Trial

Rohit Loomba , Claude Sirlin, Brandon Ang, Ricki Bettencourt, Rashmi Jain, Joanie Salotti, Linda Soaft, Jonathan Hooker, Yuko Kono, Archana Bhatt, Laura Hernandez, Phirum Nguyen, Mazen Noureddin, William Haufe, Catherine Hooker, Meng Yin, Richard Ehman, Grace Lin, Mark Valasek, David Brenner, Lisa Richards for **the San Diego Integrated Research Consortium (SINC)**

NAFLD Translational Research Unit, Division of Gastroenterology, Department of Medicine,
Division of Epidemiology, Department of Family and Preventive Medicine,
Liver Imaging Group, Department of Radiology, University of California at San Diego, La Jolla, CA
Department of Radiology, Mayo Clinic, Rochester, MN
Department of Pathology,
University of California at San Diego, La Jolla, CA

Selected slides courtesy of Dr. Rohit Loomba, adapted

Introduction

- Ezetimibe inhibits intestinal lunem cholesterol absorption and lowers low-density-lipoprotein (LDL) cholesterol by binding to the Niemann-Pick C1-like1 sterol transporter in the enterocyte brush border

- Several in-vivo studies have shown that ezetimibe improves liver histology in animal models of NASH

- Uncontrolled studies have suggested that it reduces liver fat as estimated by ultrasound in nonalcoholic steatohepatitis (NASH)

Aim

- To examine the efficacy of ezetimibe versus placebo in reducing liver fat by **magnetic-resonance-imaging** derived **proton-density-fat-fraction (MRI-PDFF)** in patients with biopsy-proven NASH

Hypothesis

- Ezetimibe would be better than placebo in reducing liver fat by MRI-PDFF in patients with biopsy-proven NASH

Methods

- **Design:** Randomized, double-blind, allocation-concealed, placebo-controlled, clinical trial
- **Duration of enrollment:** Between January, 2013 and December, 2013
- **Setting:** San Diego Integrated NAFLD Research Consortium
- **Patient population:** 50 patients with biopsy-proven NASH
- **Duration of study:** 24 weeks
- **Sample size estimation:** Based upon our prior studies, we expected that we would need 22 subjects in each arm to find an absolute difference in MRI-PDFF between the treatment and placebo arm of 5% (net reduction) assuming baseline MRI-PDFF to be 17% and this would yield a power of 90% with a two-tailed alpha of 0.05

Inclusion and Exclusion Criteria

Inclusion Criteria:

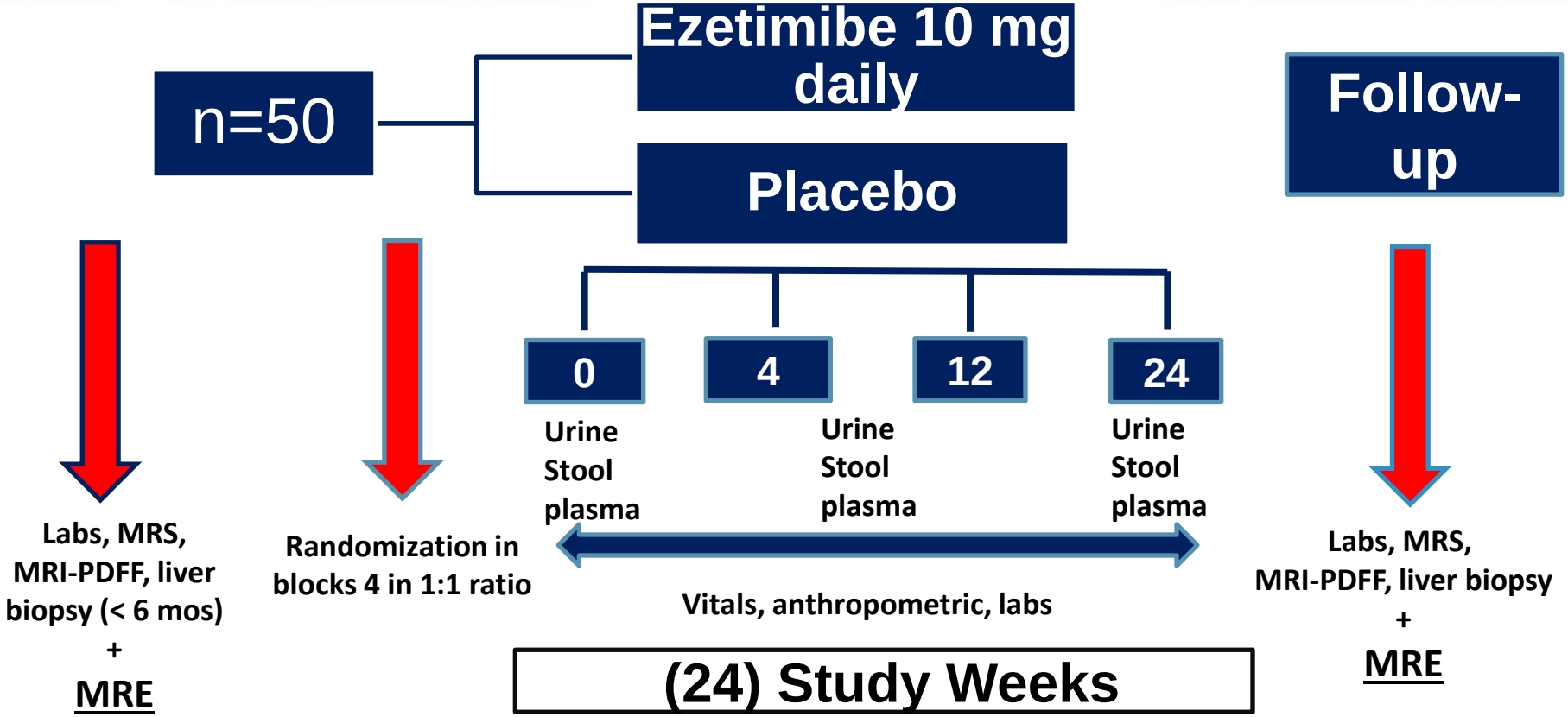
- Age 18 years or older,
- Elevated ALT
- Biopsy-proven NASH
- Presence of hepatic steatosis as defined by ≥ 5% MRI-PDFF on MRI-PDFF

Exclusion Criteria:

- Evidence of other forms of liver disease …
- Alcohol intake of more than 30 grams per day in the previous 10 years or greater than 10 grams per day in the previous year
- Decompensated cirrhosis with Child-Pugh score >7, active substance abuse, significant systemic illnesses, renal insufficiency, positive HIV test, pregnancy, evidence of hepatocellular carcinoma,
- Ingestion of drugs known to cause hepatic steatosis, ingestion of drugs known to improve NASH such as vitamin E or pioglitazone, contraindications to liver biopsy or inability to undergo magnetic resonance imaging.

MOZART Trial Design: Ezetimibe vs Placebo

First trial to assess 2D and 3D MRE in NASH

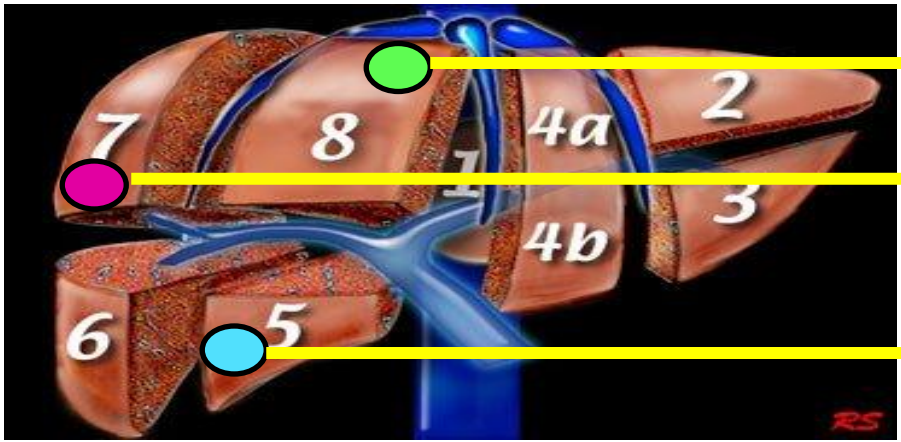


Outcomes

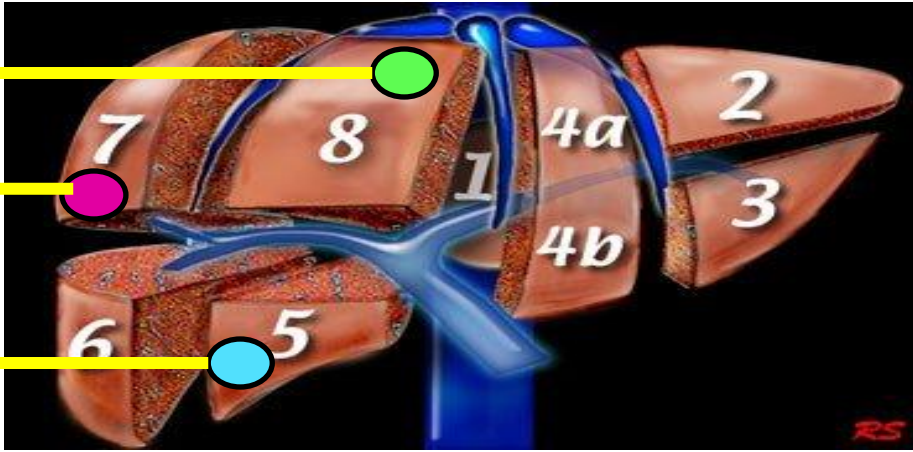
- **Primary outcome:**
  - Change in liver fat as measured by MRI-PDFF in co-localized regions of interest within each of the nine liver segments
- **Secondary outcome:**
  - Histology-determined two-point reduction in NAFLD Activity Score without worsening fibrosis
  - LDL reduction
  - Cross-validate MRI-PDFF with MR**S**-PDFF
- **Exploratory outcome:**
  - 2D and 3D MR **elastography** (MR**E**)-derived reduction in liver stiffness in co-localized regions of interest

Co-Localized MRI-PDFF
(and Cross-Validated With MRS)

BASELINE



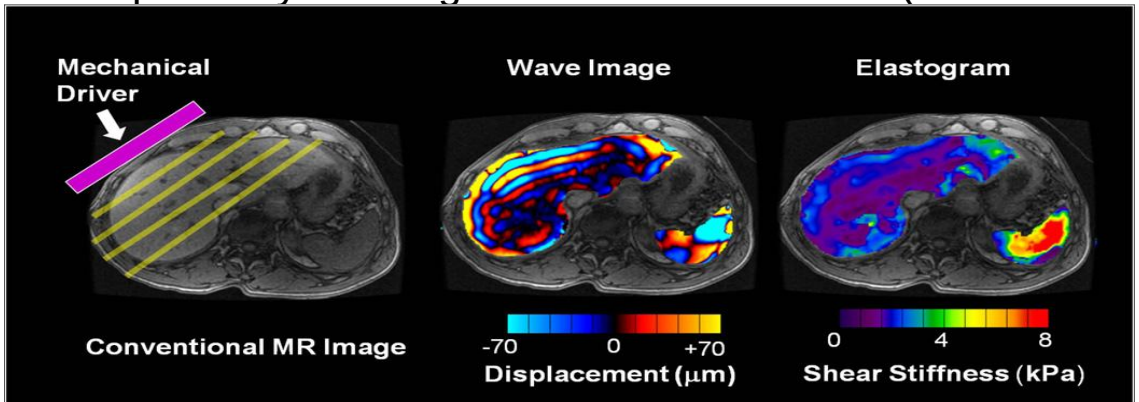
POST-TREATMENT



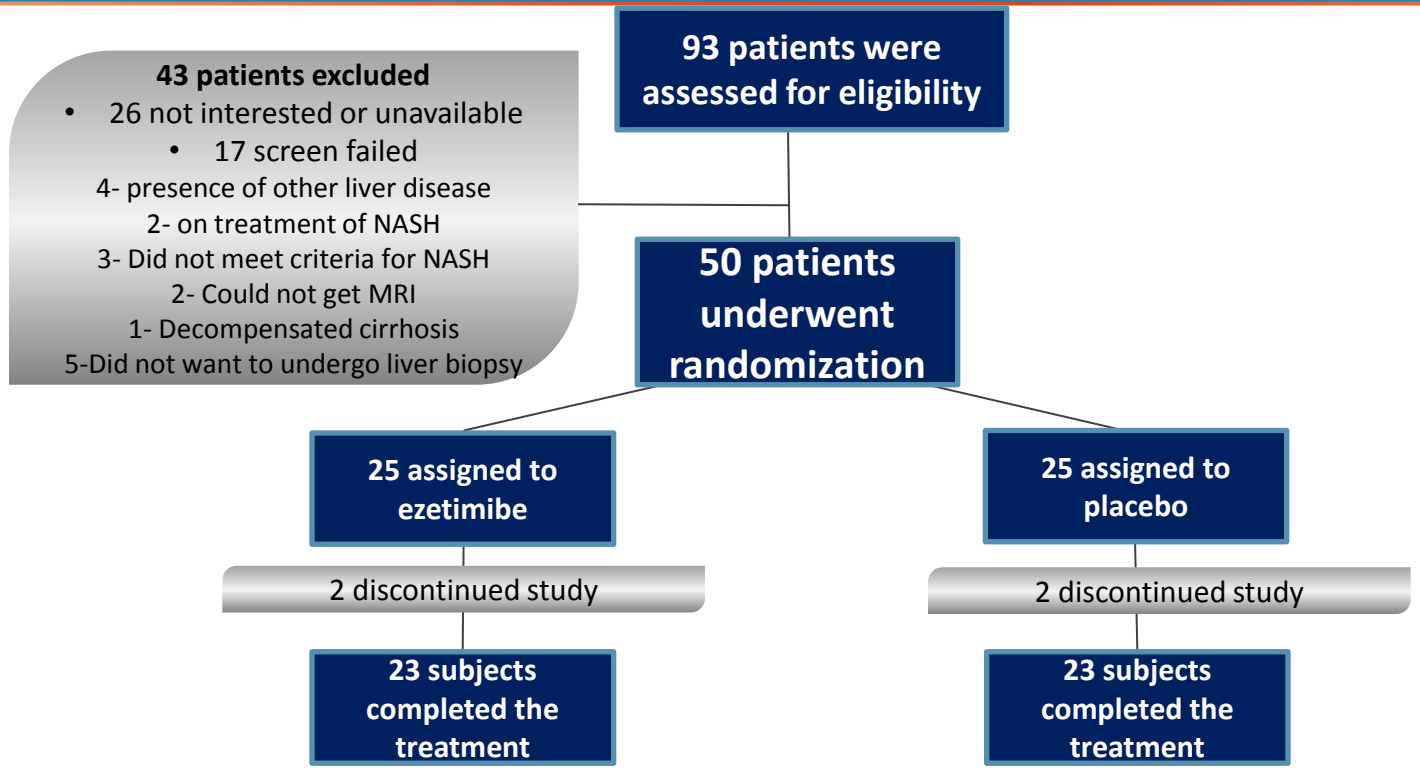
- PDFF is an objective, interpreted quantitatively and non-invasive imaging biomarker of liver fat content; the measurement is independent of scanner manufacturer, scanner platform, field strength, and other confounders (MRS is the reference standard – but cumbersome and platform dependent)
- - PDFF recorded in regions of interests (ROI)s ~300-400mm^2
- - Same ROIs in each of the 9 liver segments measured at baseline and post-Rx
- - Each segment fat fraction = 1 ROIs, total liver fat fraction = average 9 ROIs

MR Elastography

- MRE performed in three steps
  - Vibration source placed on body generates mechanical waves in the liver
  - Special MRE pulse sequence with synchronized motion encoding gradients is used to image the displacements caused by the propagating waves (wavelength of the shear waves is longer in stiffer tissues..)
  - Wave images are then automatically processed with an “inversion algorithm” to create quantitative images depicting the liver stiffness
  - Used as an exploratory radiologic biomarker of fibrosis (2D and 3D at 40/60MHz)



Derivation of MOZART Trial



Results - Baseline Characteristics

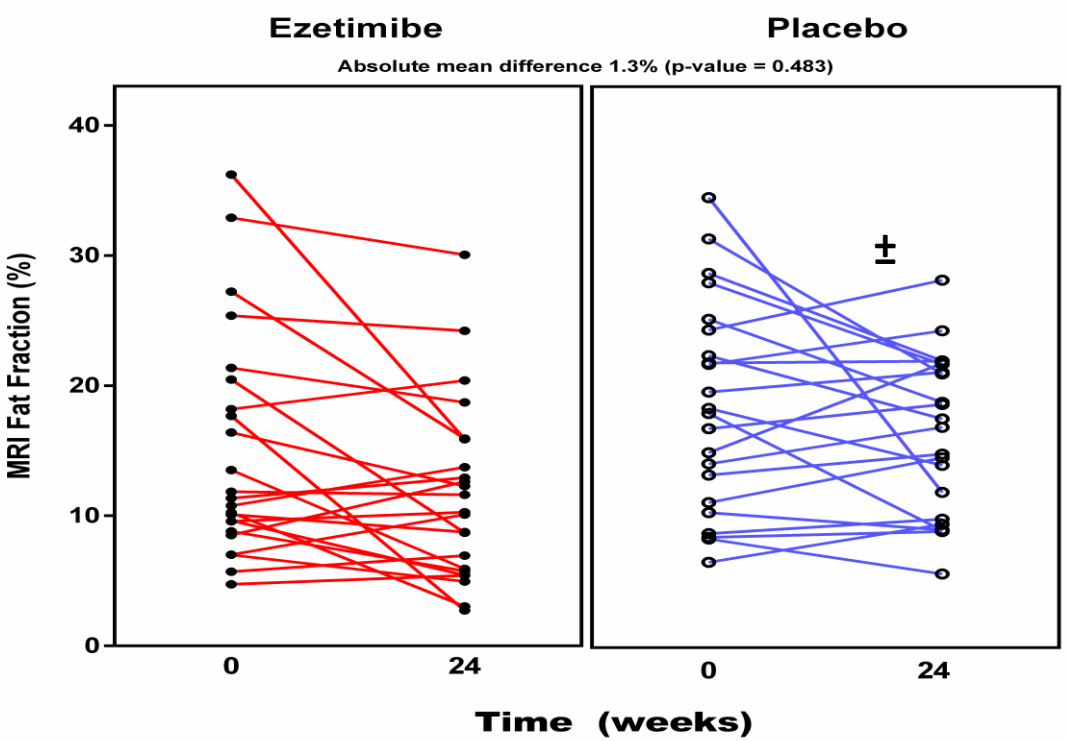
	Ezetimibe (n=25)	Placebo (n=25)	P-Value
Demographics			
Age (years)	49.0 ± 14.9	49.5 ± 13.7	.91
Female patients	14 (56%)	17 (68%)	.38
Weight (kg)	94.1 ± 18.1	91.8 ± 18.9	.67
Height (m)	1.7 ± 0.1	1.7 ± 0.1	.98
BMI (kg/m^2)	33.8 ± 5.2	32.9 ± 5.1	.54
White (vs. non-White)	19 (76%)	21 (84%)	.48
Hispanic (vs. non)	8 (32.0%)	9 (36%)	.77
Diabetes	7 (28%)	7 (28%)	1.000
Biochemical profile			
ALT (IU/L)	51.0 (29.0)	47.0 (26.0)	.96
AST (IU/L)	33.0 (23.0)	32.0 (28.0)	.66
Alk Phos (U/L)	72.0 (29.0)	72.0 (37.0)	.46
GGT (U/L)	49.0 (32.0)	32.5 (42.0)	.41
Total bilirubin (mg/dL)	0.5 (0.4)	0.4 (0.2)	.72
Glucose (mg/dL)	104.0 (25.0)	106.0 (41.0)	.65
Insulin (µU/mL)	23.0 (15.5)	26.5 (18.0)	.23
Hgb A1C (%)	5.9 (0.7)	6.1 (1.0)	.70
FFA (mmol/L)	0.5 (0.3)	0.7 (0.3)	.21
HOMA-IR	6.4 (5.1)	6.5 (5.7)	.22
Triglycerides (mg/dL)	152.0 (58.0)	149.0 (104.0)	.56
Total cholesterol (mg/dL)	182.0 (25.0)	170.0 (54.0)	.50
LDL (mg/dL)	100.0 (32.0)	90.0 (50.5)	.38
Histology			
Steatosis	2.0 (2.0)	3.0 (1.0)	.14
Lobular inflammation	1.0 (1.0)	2.0 (1.0)	.17
Ballooning	1.0 (1.0)	1.0 (1.0)	.70
Fibrosis	1.0 (1.0)	1.0 (3.0)	.69
NAS	5.0 (2.0)	5.0 (2.0)	.18

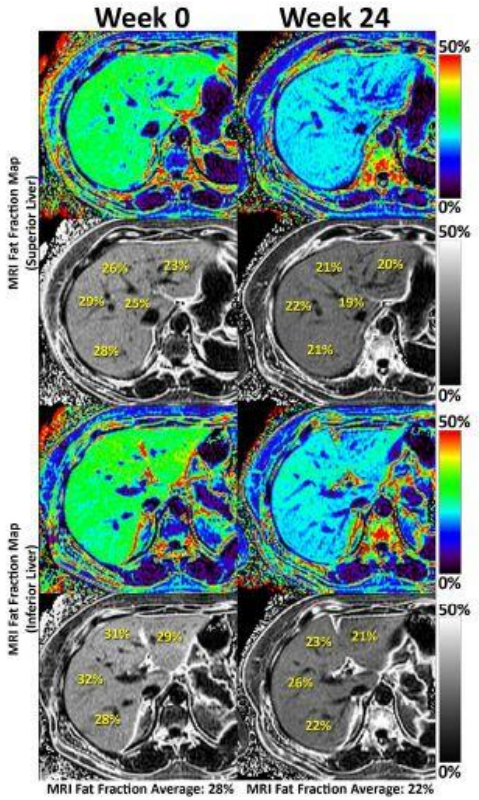
No differences..

MRI-PDFF In All Nine Liver Segments By Treatment Group – Detailed Topographic Analysis

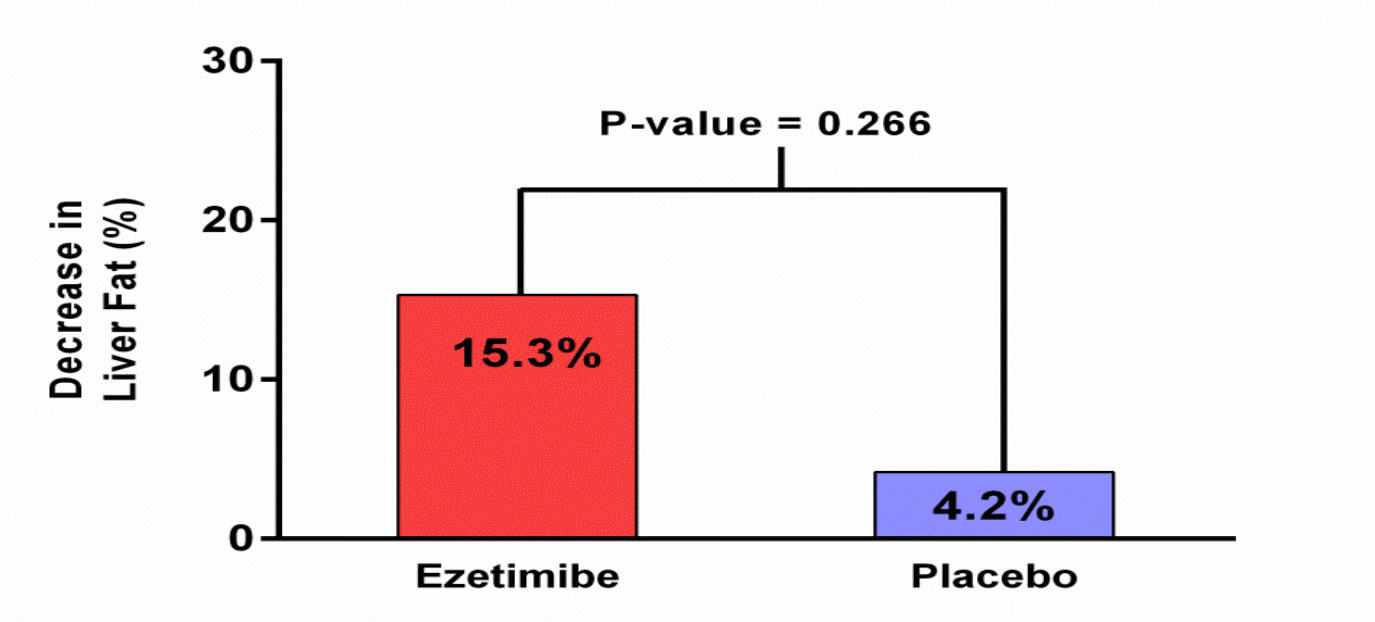
Table	Ezetimibe (n=23)			Placebo (n=22)			Difference (P-value)
Liver segments	Baseline	Post-Tx	P-value	Baseline	Post-Tx	P-value	
1	15.1 (8.6)	11.9 (6.8)	**.0249**	18.1 (7.5)	16.5 (5.9)	.2298	-1.5 (.4341)
2	13.9 (8.3)	10.8 (6.5)	**.0336**	17.3 (7.9)	15.7 (5.9)	.2458	-1.3 (.4913)
3	14.8 (9.1)	11.9 (7.8)	.0585	18.2 (7.7)	16.5 (6.1)	.2803	-1.2 (.5832)
4a	15.6 (8.8)	11.9 (6.9)	**.0044**	18.6 (7.8)	16.7 (5.8)	.1677	-1.8 (.3028)
4b	15.1 (8.9)	12.0 (7.3)	**.0326**	18.6 (7.7)	16.3 (6.6)	.0712	-0.8 (.6646)
5	15.0 (9.7)	11.3 (7.5)	**.0148**	18.9 (9.3)	16.5 (7.1)	.1119	-1.3 (.5149)
6	14.8 (8.9)	11.2 (7.1)	**.0170**	18.3 (8.6)	15.9 (6.3)	.1232	-1.2 (.5462)
7	15.2 (8.6)	11.5 (6.6)	**.0067**	19.1 (8.8)	16.7 (6.5)	.1526	-1.4 (.4951)
8	15.4 (8.6)	11.7 (6.8)	**.0098**	19.2 (8.6)	17.0 (6.5)	.1562	-1.5 (.4547)
MRI PDFF	15.0	11.6	**.0158**	18.5 (8.0)	16.4	.1512	-1.3 (.4839)

MRI Assessed Treatment Response Showing Individual Patient Data



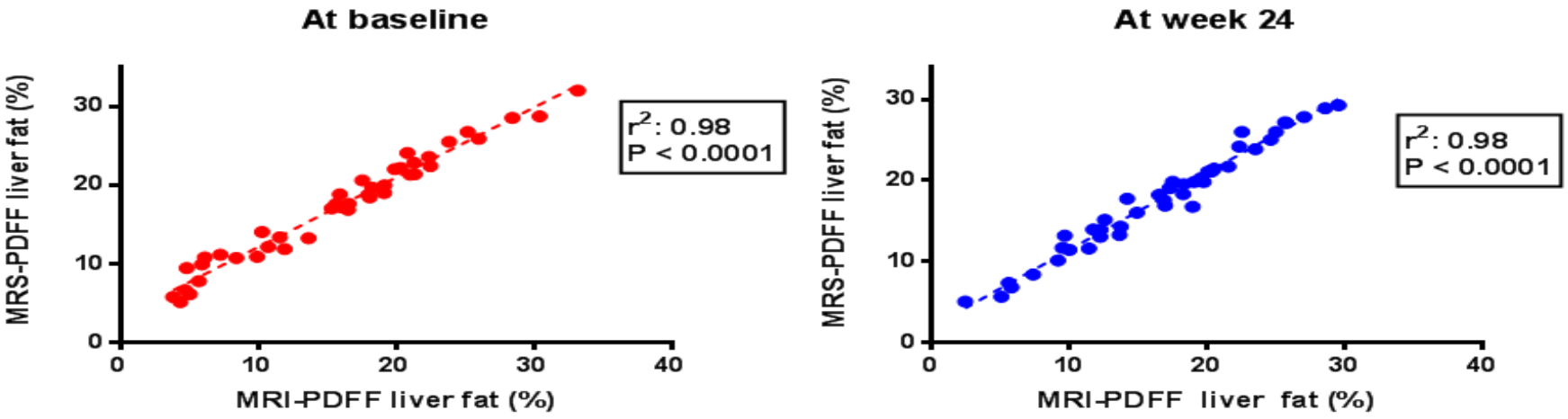


Percent Decrease Relative To Baseline In Liver Fat Arms



Ezetimibe lowered liver fat by a small but clinically unimportant amount

Correlation Between MRI-PDFF And MRS At Baseline And At Week 24



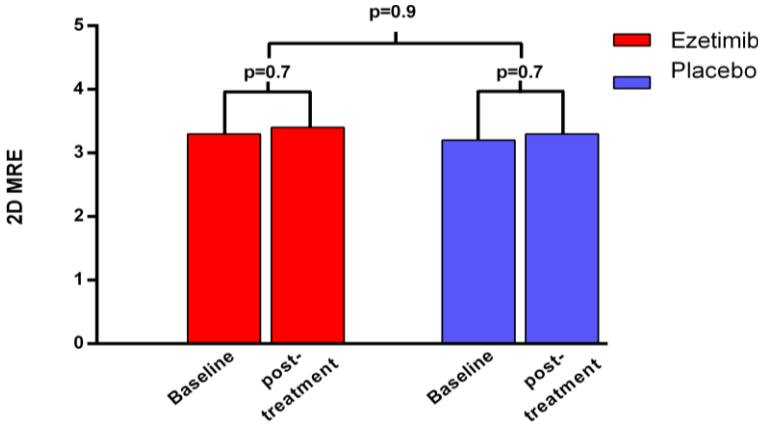
Internal cross-validation of the MRI-PDFF by MRS-PDFF correlated robustly for measurements of fat fraction with the very high r^2

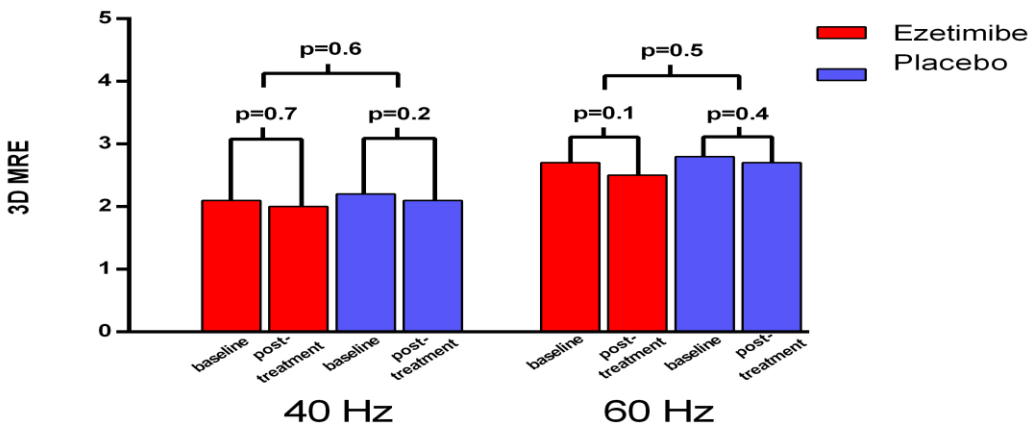
Results

	Ezetimibe (n=23)			Placebo (n=22)			Difference
	Baseline	**Post-treatment**	**P-Value**	**Baseline**	**Pos-ttreatment**	**P-Value**	**(P-Value)**
BMI (kg/m2)	33.6 ± 5.2	33.2 ± 5.5	.2225	33.6 ± 5.1	33.4 ± 5.0	.2969	-0.3 (.4839)
ALT (IU/L)	47.0 (29.0)	48.0 (43.0)	.7682	45.5 (32.0)	42.0 (14.0)	.5110	2.0 (.6702)
AST (IU/L)	33.0 (23.0)	33.0 (36.0)	.9332	31.0 (34.0)	32.0 (33.0)	.2124	1.0 (.6004)
AST/ALT	0.8 (0.6)	0.8 (0.4)	.4065	0.8 (0.4)	0.7 (0.4)	.4584	0.0 (.9304)
Glucose (mg/dl)	104.0 (25.0)	99.0 (24.0)	.9500	108.5 (40.0)	106.5 (24.0)	.6598	-5.0 (.8101)
Insulin (µU/mL)	22.5 (13.0)	26.5 (15.0)	.3787	24.5 (18.5)	33.0 (19.0)	.0889	-3.0 (.5177)
Hgb A1C (%)	5.9 (0.6)	5.9 (0.9)	.1699	6.1 (1.0)	6.0 (0.8)	.5538	0.2 (.1663)
Triglycerides (mg/dl)	152.0 (63.0)	125.0 (59.0)	.2139	144.5 (110.0)	142.0 (107.0)	.3883	-8.5 (.0977)
Total Cholesterol (mg/dl)	182.0 (26.0)	152.0 (46.0)	**.0003**	169.0 (56.0)	175.0 (37.0)	.3344	**-24.0 (.0024)**
LDL (mg/dl)	99.0 (37.0)	76.0 (30.0)	**<.0001**	89.0 (53.0)	90.5 (39.0)	.8048	**-20.0 (.0019)**
GGT (IU/L)	44.0 (36.0)	41.5 (38.0)	.5286	33.0 (38.0)	36.5 (31.0)	.5523	3.0 (.5069)
Total Bilibrubin (mg/dl)	0.4 (0.4)	0.4 (0.3)	.1088	0.4 (0.3)	0.4 (0.2)	.8865	0.1 (.1993)
HOMA-IR	6.4 (4.5)	6.4 (6.2)	.6502	6.5 (5.4)	9.1 (5.2)	.6215	0.7 (.8257)

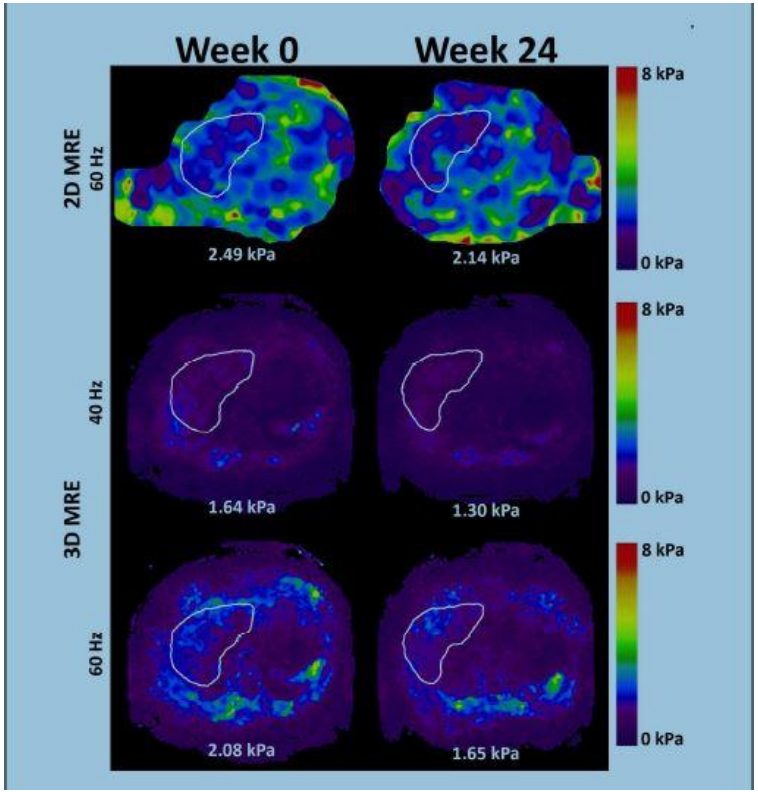
Secondary And Exploratory Outcomes

- **Ezetimibe-** well-tolerated, no differences in adverse events between groups
- **Histology -** No difference in histologic response between the ezetimibe and the placebo-groups
  - 5 patients in both groups had histologic response
- **MRE -** No difference fibrosis in 2D and 3D MRE between the ezetimibe and the placebo-groups





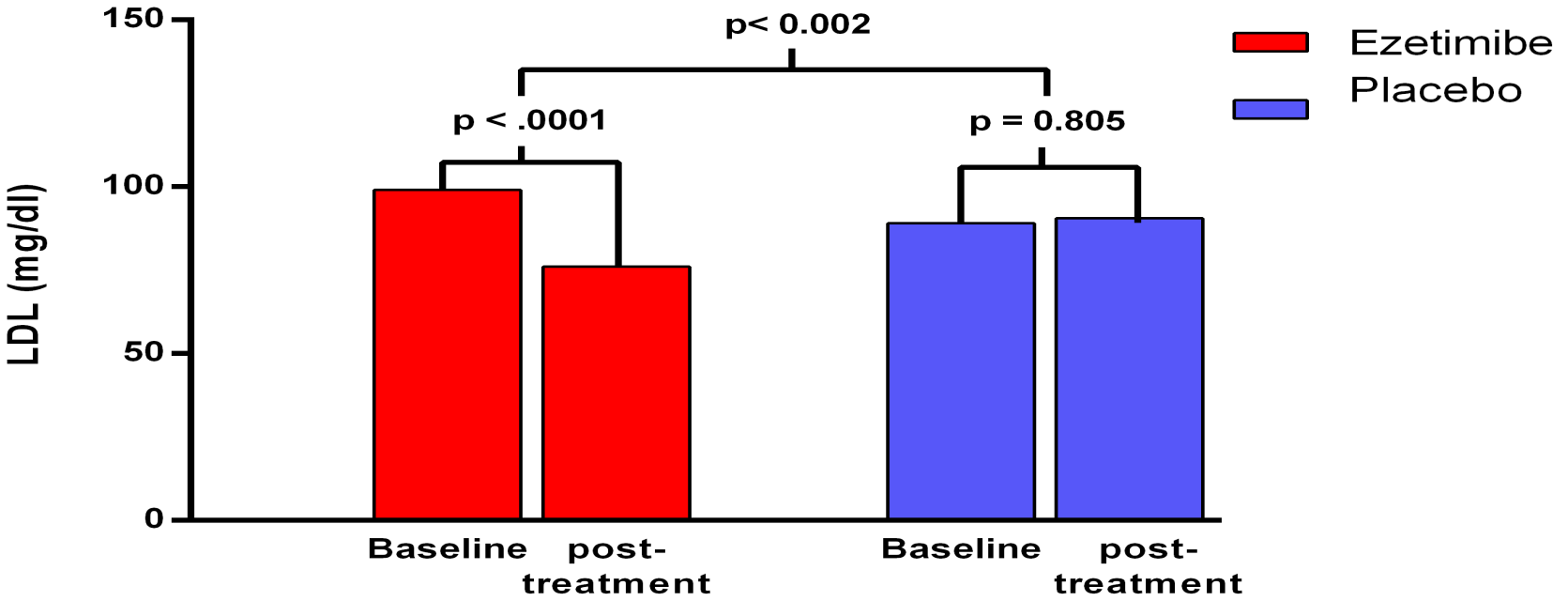
MRE Before And After Ezetimibe



MRI-PDFF Detected Significant Fat Decline

- Compared to histologic non-responders (25/35), histologic responders (10/35) had a significantly greater reduction in in MRI-PDFF
  - -4.35%, $p < 0.02$

Ezetimibe Was Better Than Placebo In Reducing LDL Cholesterol…



Summary

- Ezetimibe is not better than placebo in reducing liver fat in patients with biopsy-proven NASH

- The study provides a prototype for co-localized assessment of treatment response by advanced MR-based methods
  - Demonstrates proof-of-concept feasibility of 2D and 3D MRE and co-localization in NASH and anti-fibrotic trials

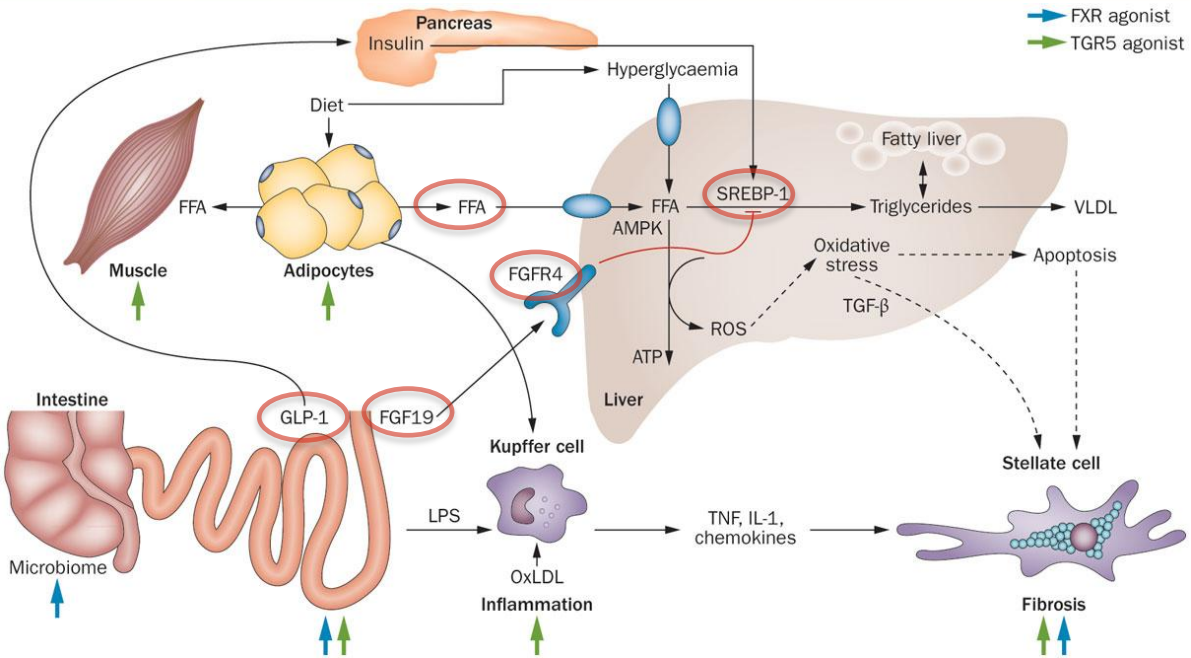
  - MRI-PDFF is a robust biomarker for assessing longitudinal changes in liver fat in the setting of NASH trials

Strengths

- Rigorous assessment of the efficacy of ezetimibe in the treatment of biopsy-proven NASH
- Utilized a novel, accurate and precise non-invasive imaging biomarker - the MRI-PDFF, for assessment of treatment response in liver fat
- Explored the role of advanced MR methods (2D and 3D MRE) in the setting of a clinical trial as an exploratory end-point and described a protocol that may be used for assessment of longitudinal changes after treatment in MRE-derived liver stiffness in clinical trials – adjunct or complementary to conventional methods of fibrosis assessment in NASH

- More informative if intervention had a larger effect effect…

Bile Acid Signaling – Multiple New Targets in NASH

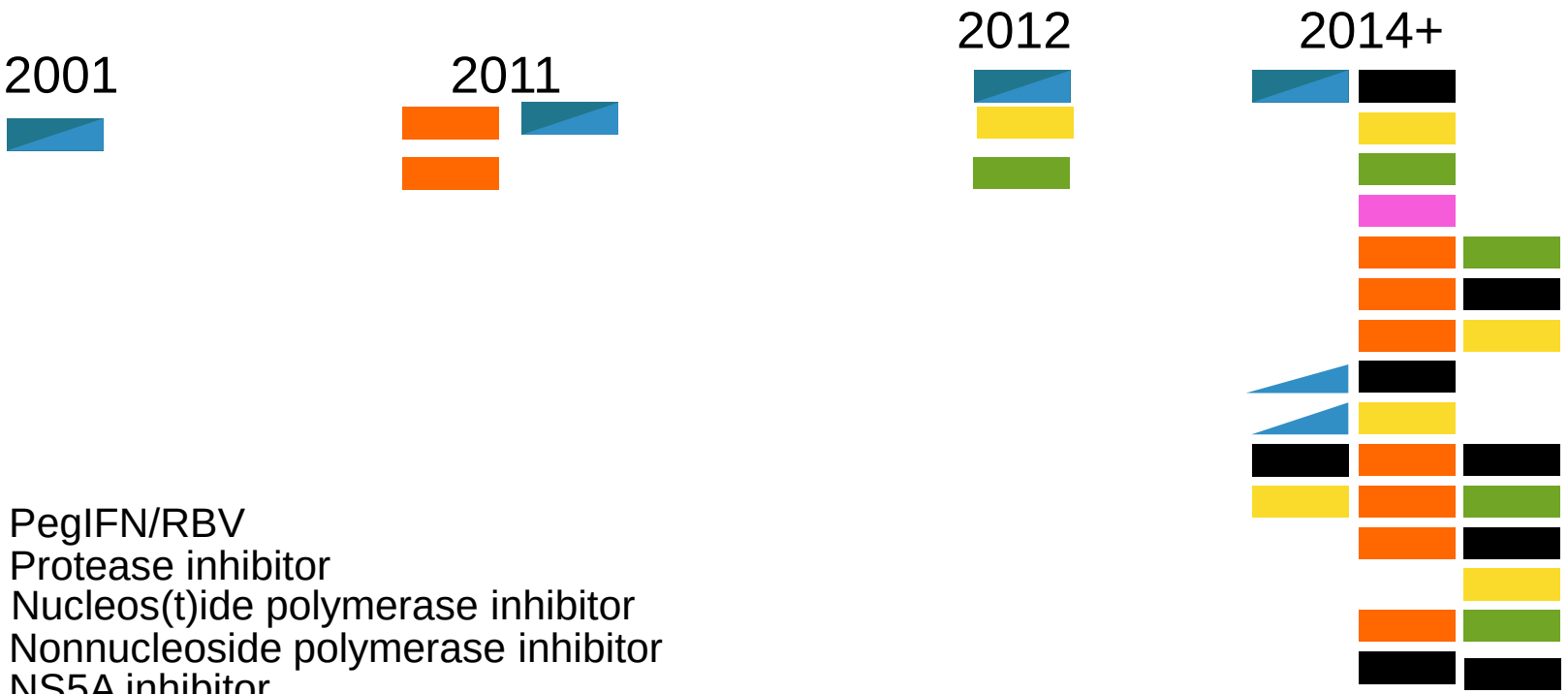


- Bile acids and targeting their receptor/signaling pathways represents a promising approach to treat NASH

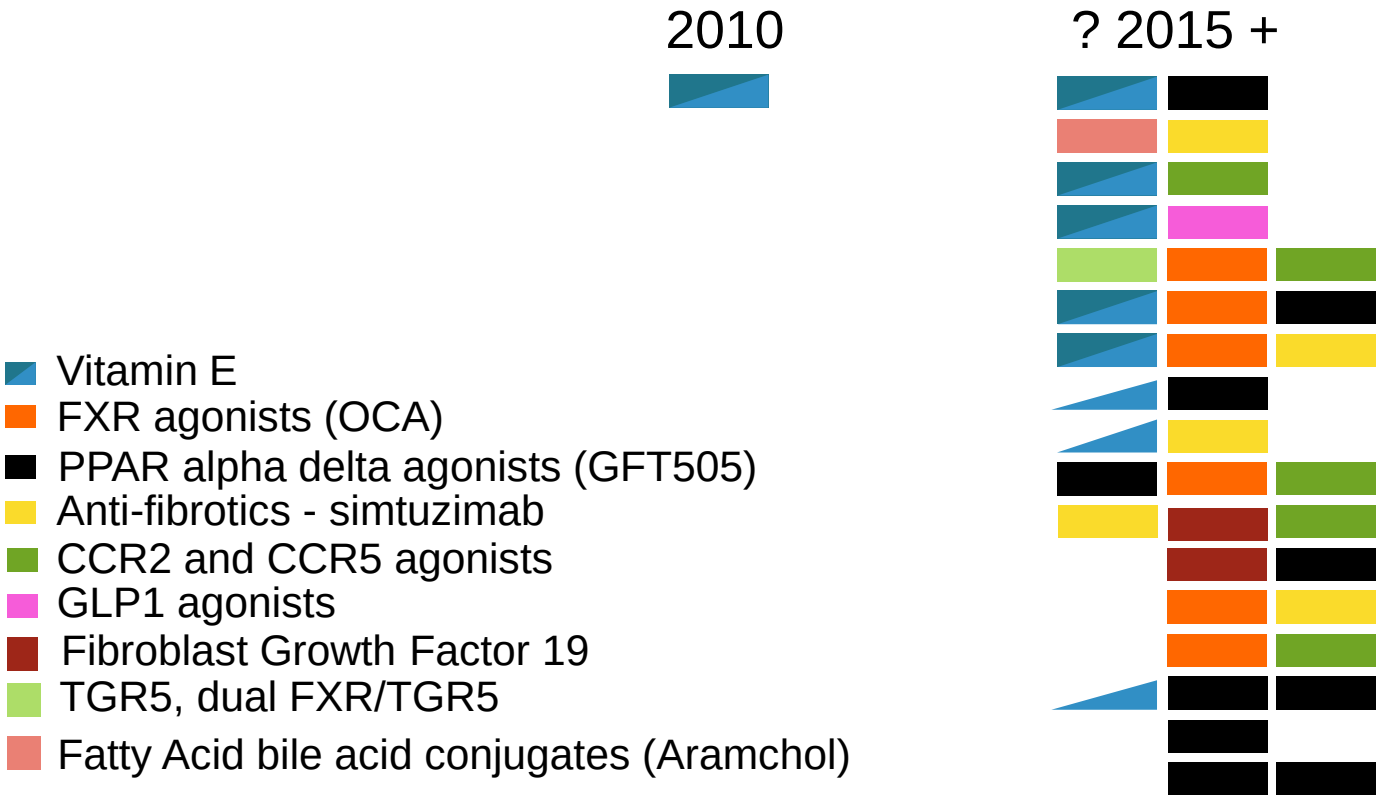
… and closely linked disorders such as obesity, diabetes, dyslipidemia and arteriosclerosis

Schaap Nat Rev Gastroenterol Hepatol 2013

Evolution Of HCV Therapy



? Evolution Of NASH Therapy



AASLD And NASH – Take Home

- New Guidelines…will need updating..
- New therapeutics and robust pipeline…
- Emerging non-invasive ways of assessing therapeutic efficacy…