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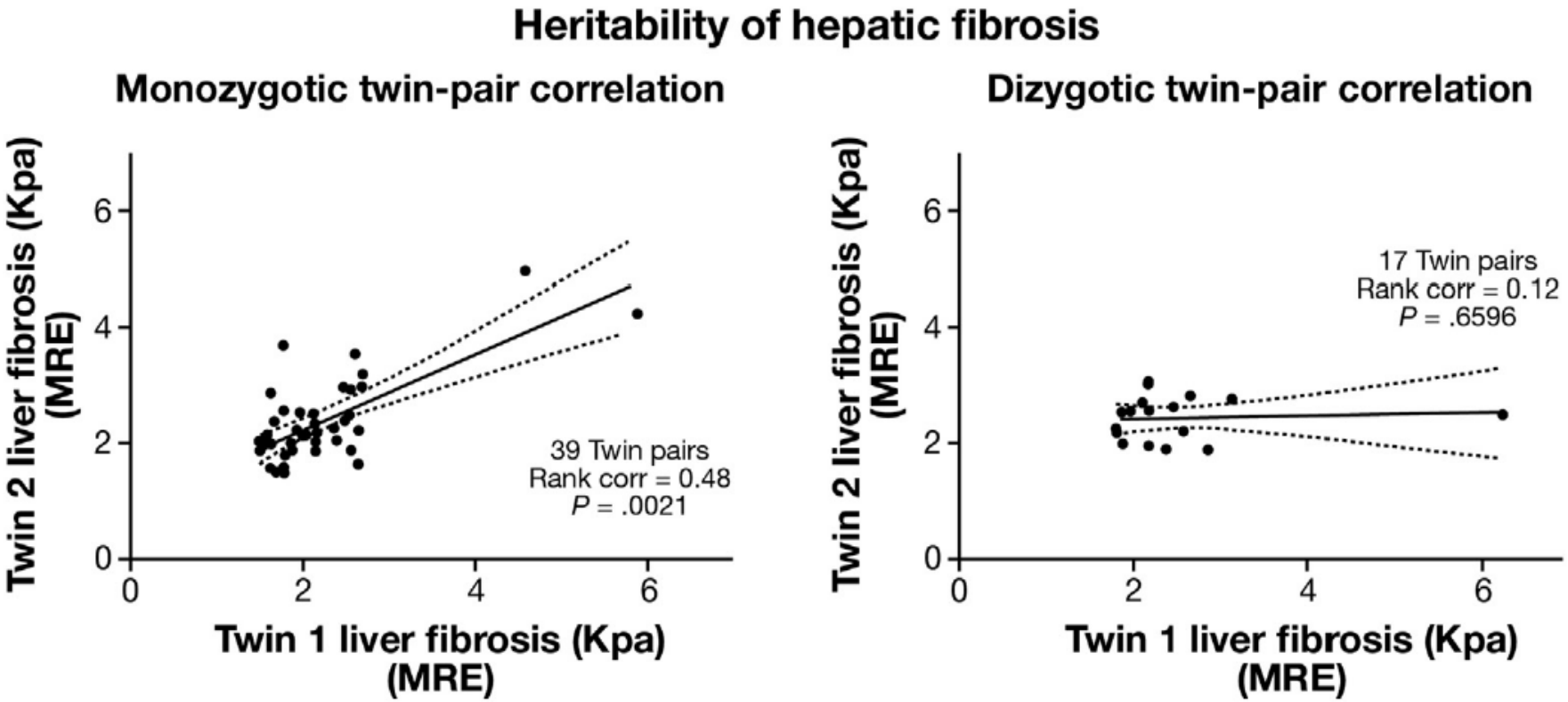
Nonalcoholic Fatty Liver Disease and NASH –

AASLD Update

Michael Charlton, MD, FRCP
Director, Transplant Institute,
Director, Center for Liver Diseases
University of Chicago

Heritability of hepatic fibrosis content Twin Study



Heritability estimate of hepatic fibrosis (as assessed by MRE) was 0.5 (95% confidence interval (CI): 0.31–0.73, $P < 1.1 \times 10^{-11}$)

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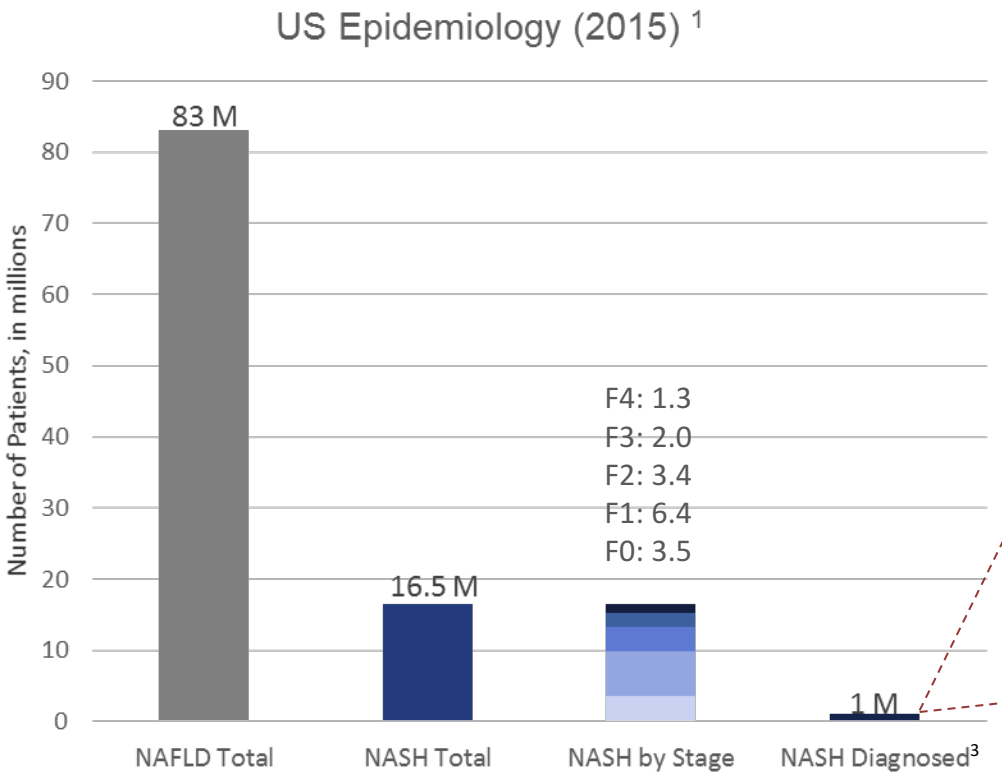
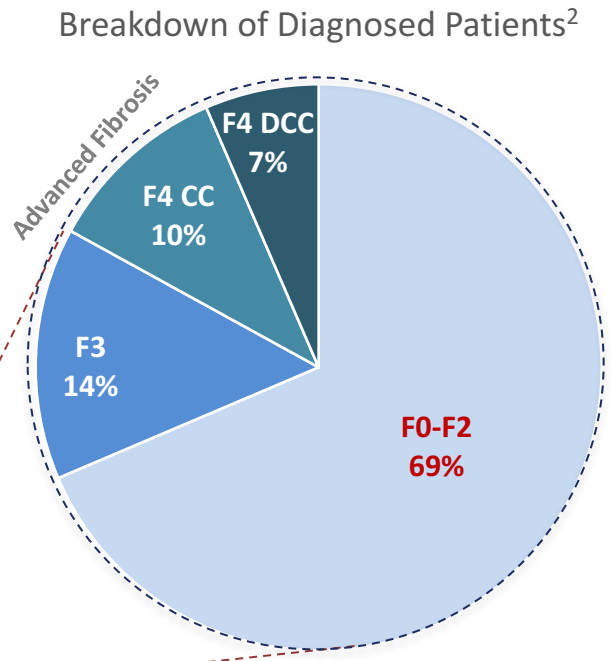
Loomba et al. Gastroenterology 2015

What is the prevalence of NASH with advanced fibrosis?

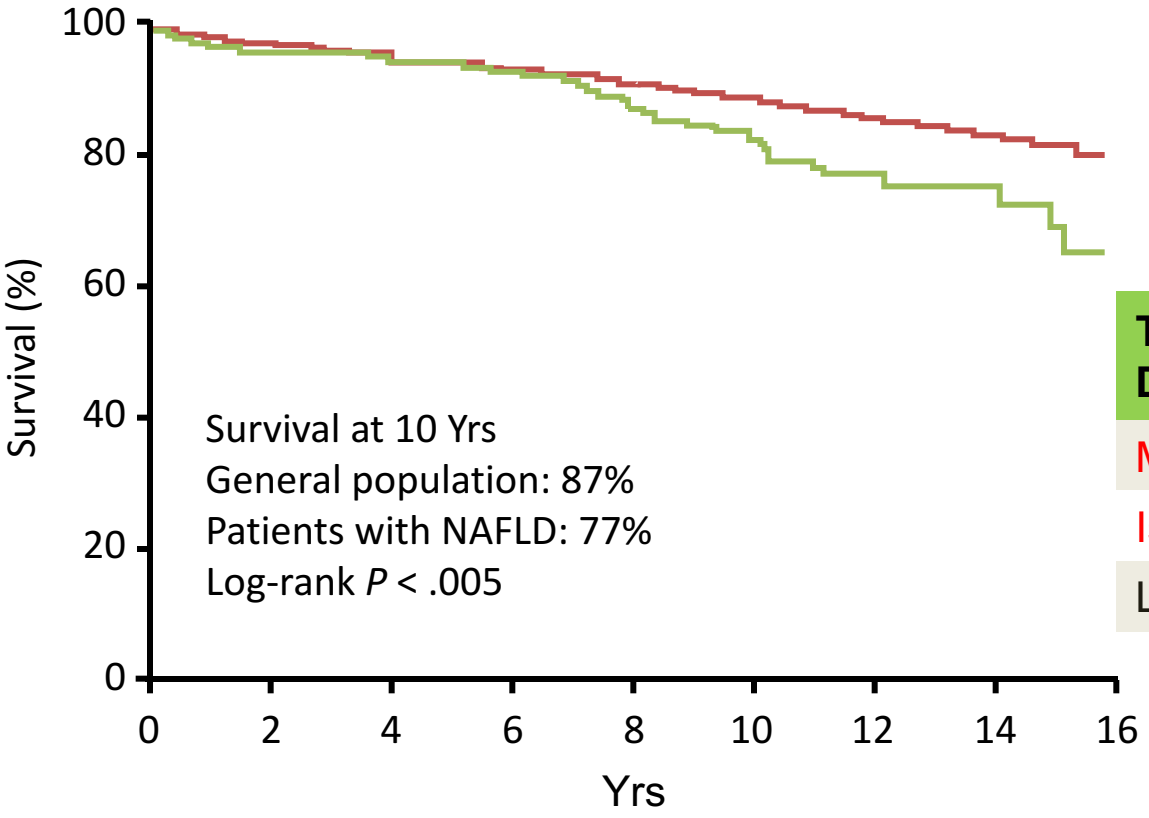




Source: 1. Estes, et al. Hepatology. 2017. doi:10.1002/hep.29466. 2. Average fibrosis distributions from 9 published studies (N=699). 3. Global NASH Epidemiology Study 2016 Total diagnosed NASH population (US claims and electronic medical records analyses (Humedica, Pharmetrics and SHA)

Mortality in NAFLD

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



Top 3 Causes of Death in NAFLD, %	Patients (n = 53)
Malignancy	28
Ischemic heart disease	25
Liver disease	13

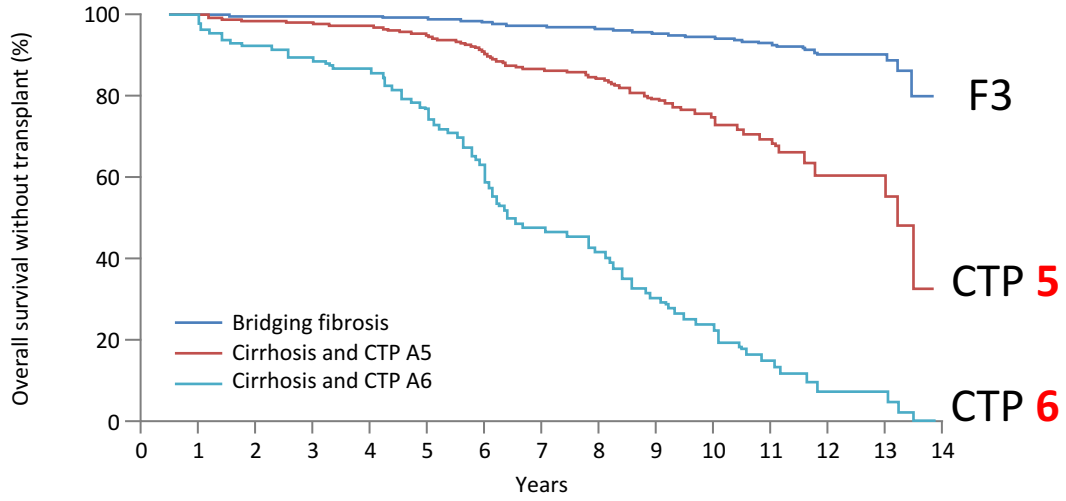
Adams LA, et al. Gastroenterology. 2005;129:113-121.

The long-term clinical course of histologically advanced NAFLD: Impact of fibrosis severity on major clinical outcomes

- Prospective cohort study of 458 NAFLD patients with biopsy-proven bridging fibrosis (F3=159) or compensated cirrhosis (Child-Turcotte-Pugh [CTP] A5=222 and A6=77)
- Most deaths were liver related (35/41; 85%)

Transplant-free survival

Stratified by fibrosis and CTP classes



Adj. Log-rank p<0.01 for difference among groups

Overall mortality or transplant (n=84)

Variable	HR (95% CI)
Cirrhosis, yes	4.66 (1.79–12.1)†
Age, years	1.02 (1.01–1.05)*
Gender, male	1.87 (1.12–3.13)†
Smoking	1.72 (1.03–2.89)*
T2DM	3.79 (1.75–8.21)†
CTP	
Class A5	4.98 (1.75–14.15)†
Class A6	25.72 (9.16–72.4)†
NFS	1.62 (1.39–1.90)†
Steatosis <33%	2.29 (1.25–4.16)†

*p<0.05; †p<0.01

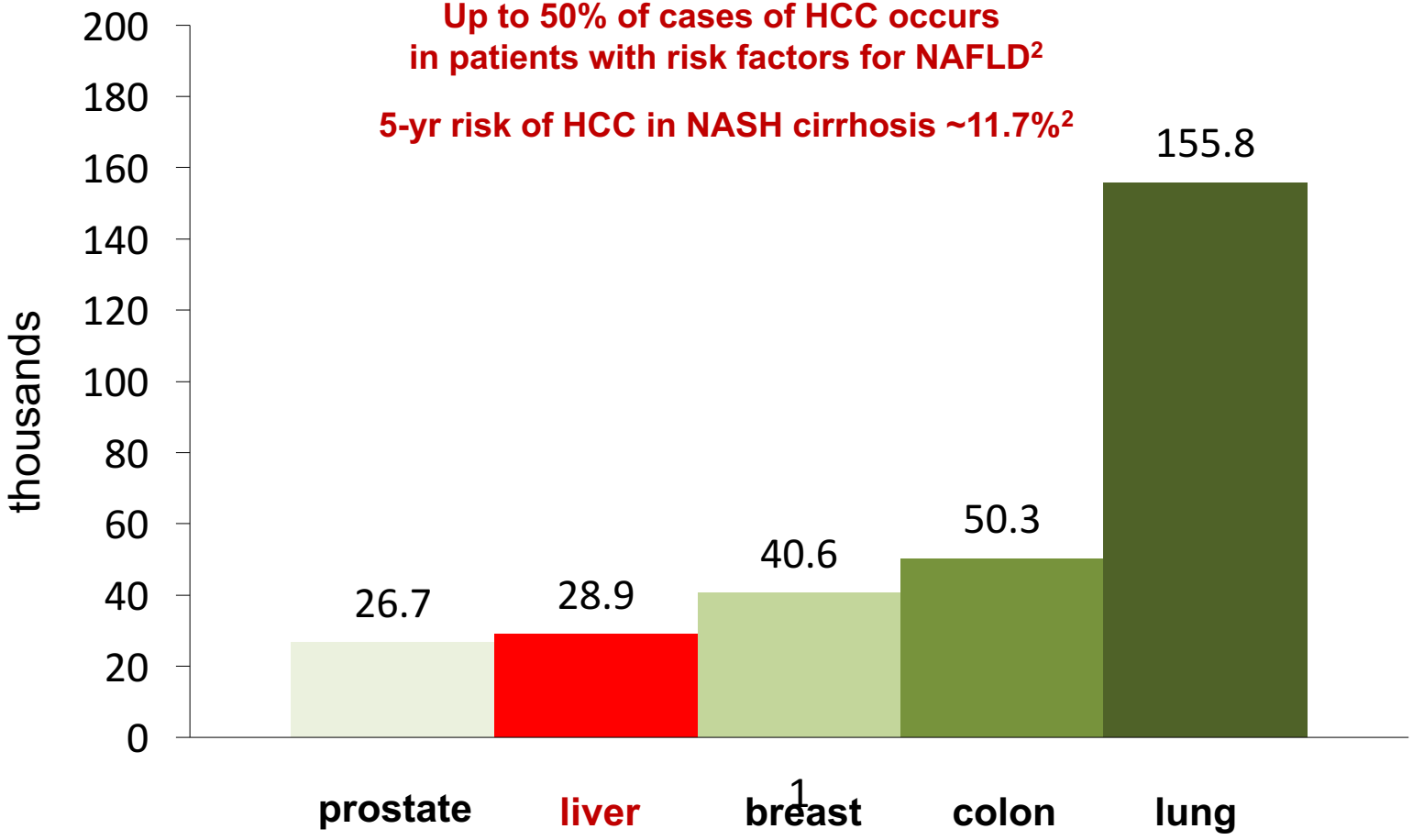
Vilar-Gomez E, et al. AASLD 2017, Washington DC. #60

Cancer Deaths in the United States

4th most common cause of cancer deaths[1]

Up to 50% of cases of HCC occurs in patients with risk factors for NAFLD[2]

5-yr risk of HCC in NASH cirrhosis ~11.7%[2]



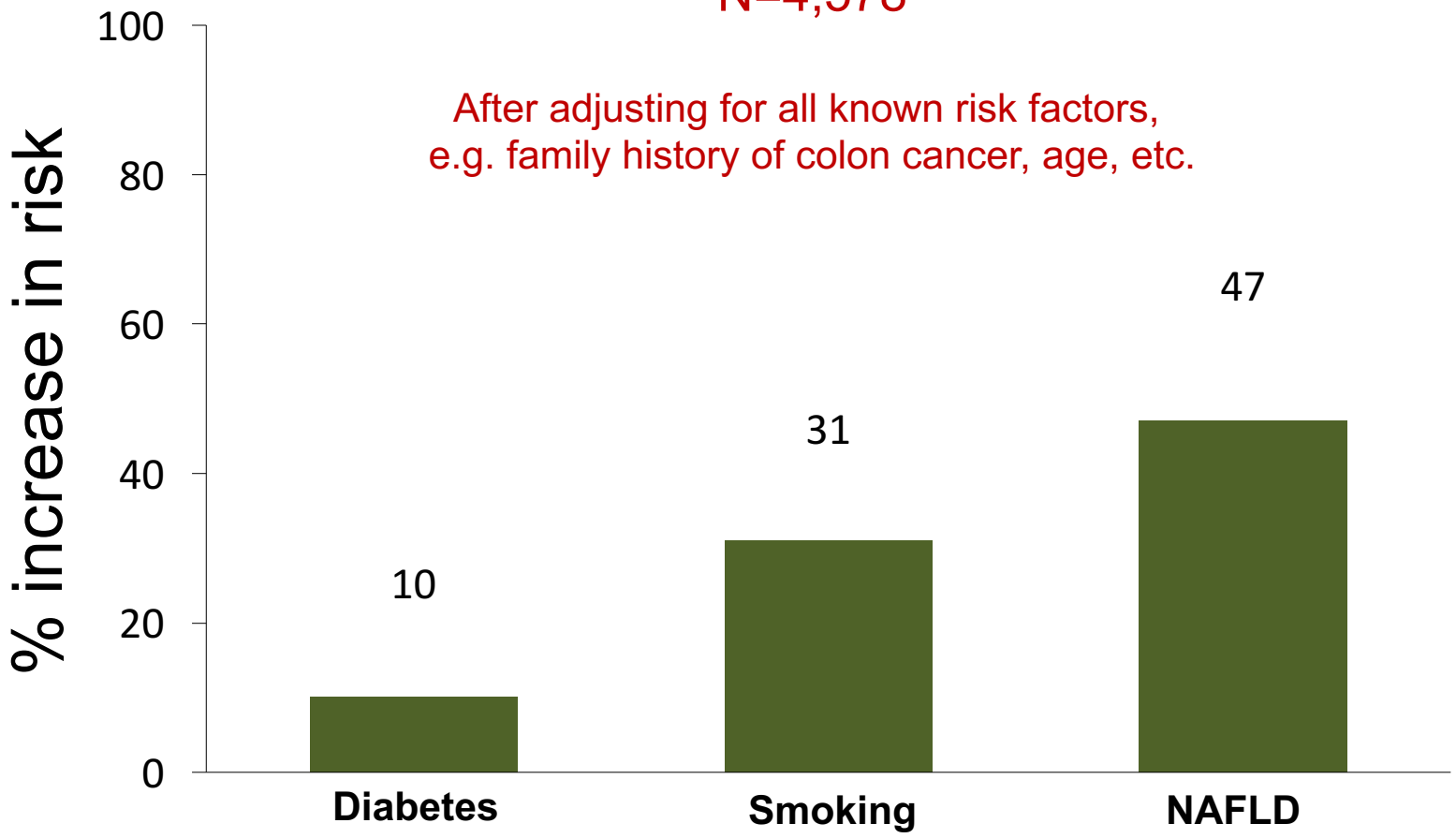
[1]https://seer.cancer.gov/statfacts/html/livibd.html.

[2]*Hepatology* 2010;51:1820–1832.

NAFLD as a Risk Factor for Colon Cancer on Follow-Up Colonoscopy

N=4,578

After adjusting for all known risk factors,
e.g. family history of colon cancer, age, etc.



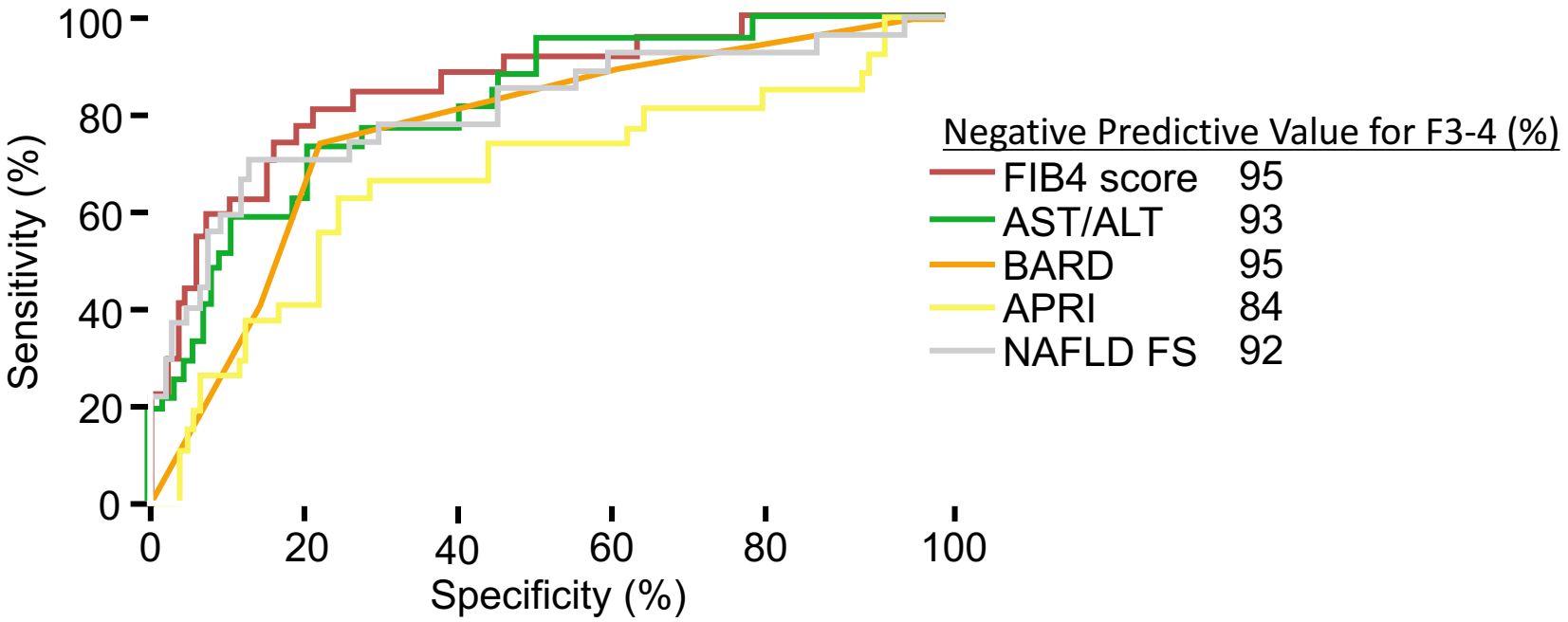
Yang et al., *PLoS One*. 2017; 12(8).

Illustrative Case

- 51 yr old woman
- H/O BRCA positive breast cancer, 1999
  - On tamoxifen subsequently
- BMI 29.8, healthy diet, exercises 5x/wk
- Dyslipidemia, on simvastatin
- AST 59, ALT 51, all other tests normal
  - Viral, autoimmune, metabolic markers negative
- Exam normal other than BMI and scars
- U/S shows "echogenic liver"

WET BIOMARKERS

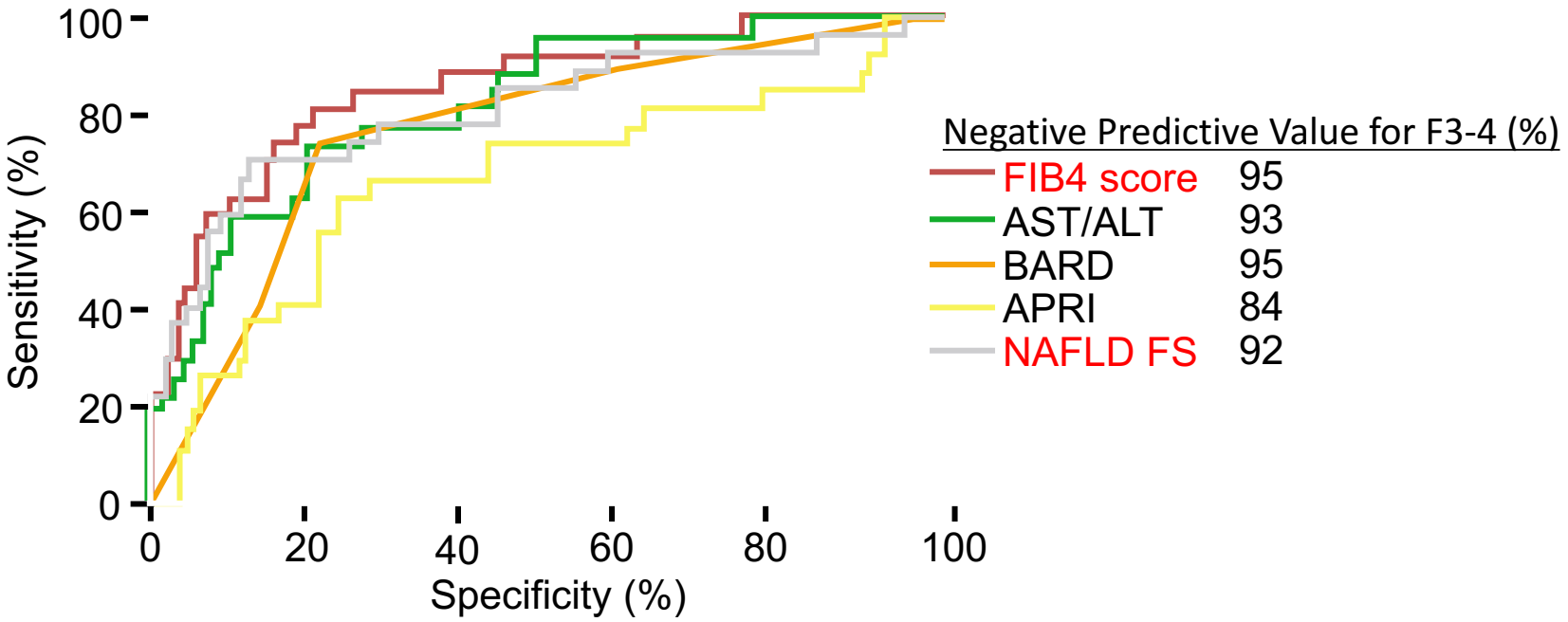
Can serologic biomarkers distinguish NASH Stages 0-2 vs 3-4?



- Strength of noninvasive fibrosis predictive tests is in their ability to **exclude** advanced disease (F3-F4)
- Least accurate in identifying middle ranges of fibrosis

McPherson S, et al. Gut. 2010;59:1265-1269.
McPherson S, et al. Am J Gastroenterol. 2016.

Can serologic biomarkers distinguish NASH Stages 0-2 vs 3-4?



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McPherson S, et al. Am J Gastroenterol. 2016.

Pro-C3 "FIB-C3 score" for detection and staging of advanced NAFLD

- Discovery Cohort (N=322)

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

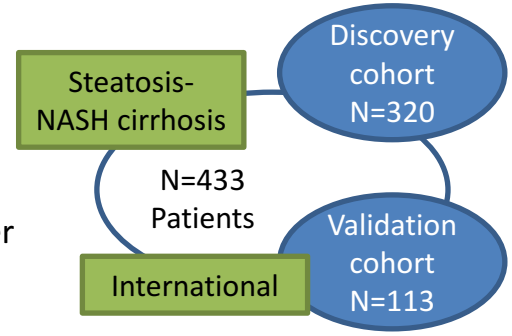
- Best simple test to differentiate early (F0–2) from advanced (F3–F4) fibrotic NASH[1,2]

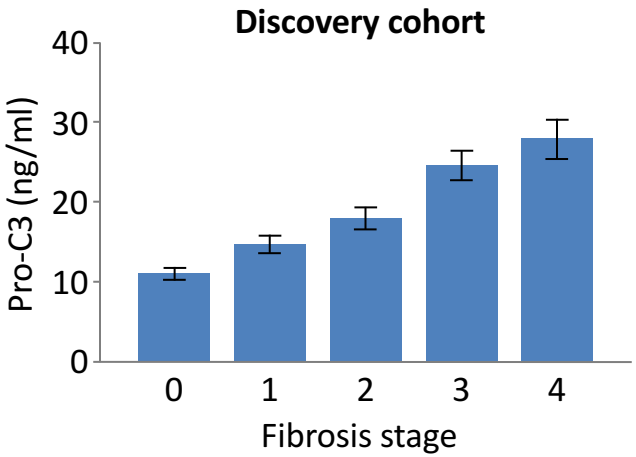
Pro-C3: well defined peptide epitope generated by cleavage of the N-propeptide of procollagen III during fibril formation

- Best current single test for fibrogenesis[3,4]

Diagnosis of NAFLD

- EPoS follow-up cohort
- Liver biopsy steatosis >10% hepatocytes
- Appropriate exclusion of other chronic liver diseases





Plasma Pro-C3:

- Stepwise correlation with fibrosis stage
- (r_s=0.46, p<0.0001)

[1]Sterling RK et al, Hepatology 2006; [2]Shah AG et al, Clin Gasteroenterol Hepatol 2011; [3]Nielsen MJ et al, Liver Int 2015; [4]Karsdal MA et al, Am J Physiol 2016

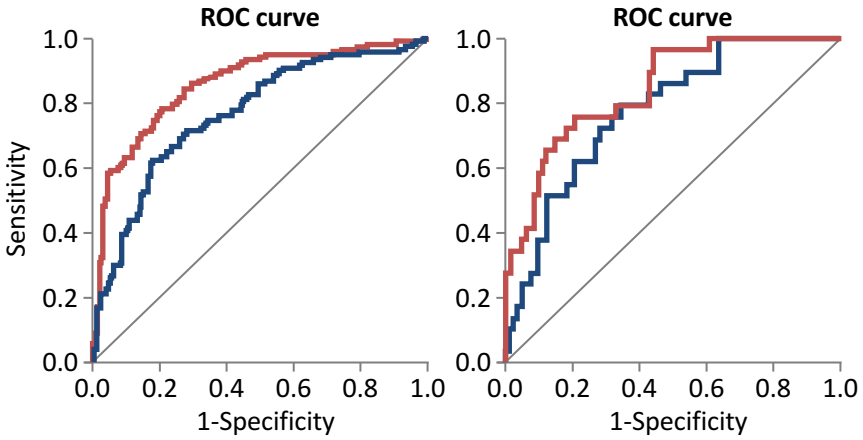
Boyle MP, et al. AASLD 2017, Washington DC. #93

Pro-C3 “FIB-C3 score” for detection and staging of advanced NAFLD

Predictive value of scoring system obtained from discovery and validation groups

Discovery Cohort (N= 320)
FIB- 4 AUROC 0.77
FIB-C3 AUROC 0.86
CI 0.817, 0.903, *p<0.0001*

Validation Cohort (N= 113)
FIB- 4 AUROC 0.78
FIB-C3 AUROC 0.847
CI 0.769, 0.924, *p<0.0001*



Test	Cohort	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95%CI)	Likelihood ratio (+)
FIB4 (≥2.67)	Discovery (N=320)	25.2 (17.9–33.7)	91.1 (86.3–94.7)	64.0 (51.0–75.2)	66.1 (63.6–68.5)	2.78
FIB-C3 (≥-0.29)		77.0 (68.7–84.0)	80.4 (74.1–85.8)	**71.8** (65.4–77.5)	**84.3** (79.5–88.2)	3.93
FIB4 (≥2.67)	Validation (N=113)	29.0 (14.2–48.0)	86.8 (78.1–93.0)	42.9 (25.9–61.6)	78.2 (73.9–82.0)	2.2
FIB-C3 (≥-0.29)		76.7 (57.7–90.1)	75.9 (65.3–84.6)	**53.5** (42.8–63.9)	**90.0** (82.3–94.6)	3.18

- FIB-4 is a simple serum biomarker score with predictive power to separate NASH patients with F0-2 from those with F3-F4
- Pro-C3 is a novel serum marker of fibrogenesis
- The combination of FIB-4 with Pro-C3 (FIB-C3 score) improves the predictive power from that of an acceptable (AUROC 0.78) to a good (AUROC 0.85) diagnostic test

Boyle MP, et al. AASLD 2017, Washington DC. #93

Biomarkers for NASH

- No biomarker currently can diagnose NASH
- Serological markers/calculations good at excluding advanced fibrosis
- Need for biomarkers that correlate with current and future treatment response

IMAGING

Imaging to Assess NASH Fibrosis: Elastography

- Vibration controlled transient elastography (*Fibroscan*)
  - Accurate in detecting advanced fibrosis
  - Predicts risk of decompensation and complications
  - Correlates well with portal pressure
  - Most reliable in ruling out advanced disease
  - Most widely used
- Shear wave elastography (SWE)
  - Uses acoustic radiation force impulse (ARFI) technology
  - Point quantification SWE or 2-D Supersonic shear imaging (SSI) SWE
- MR Elastography
  - Most accurate of the imaging modalities
  - Costly, no point of care access

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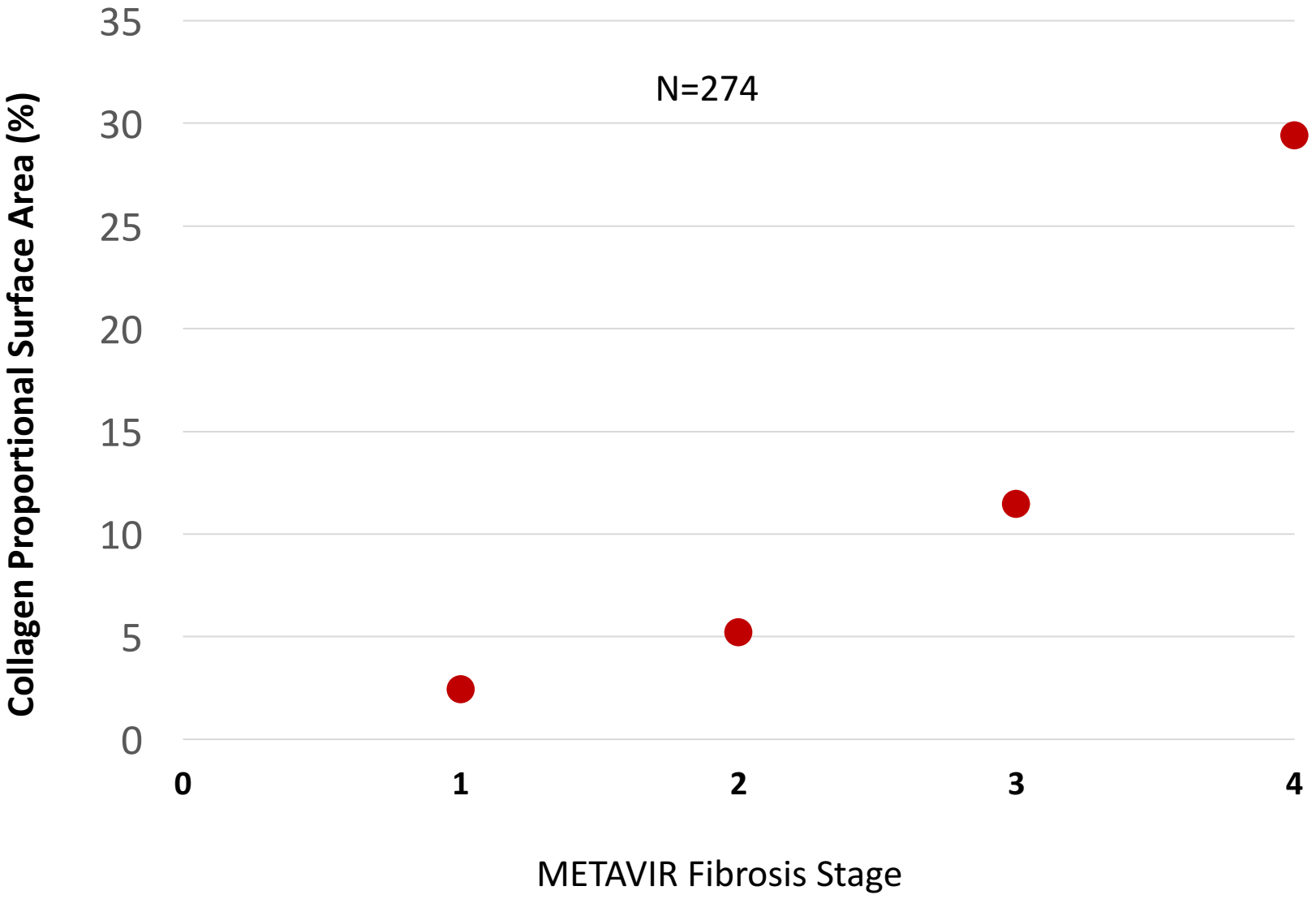
Liver Collagen Burden is not Linear Across Fibrosis Stages



Chen et al., *Medicine* 2016 Aug; 95(35): e4736

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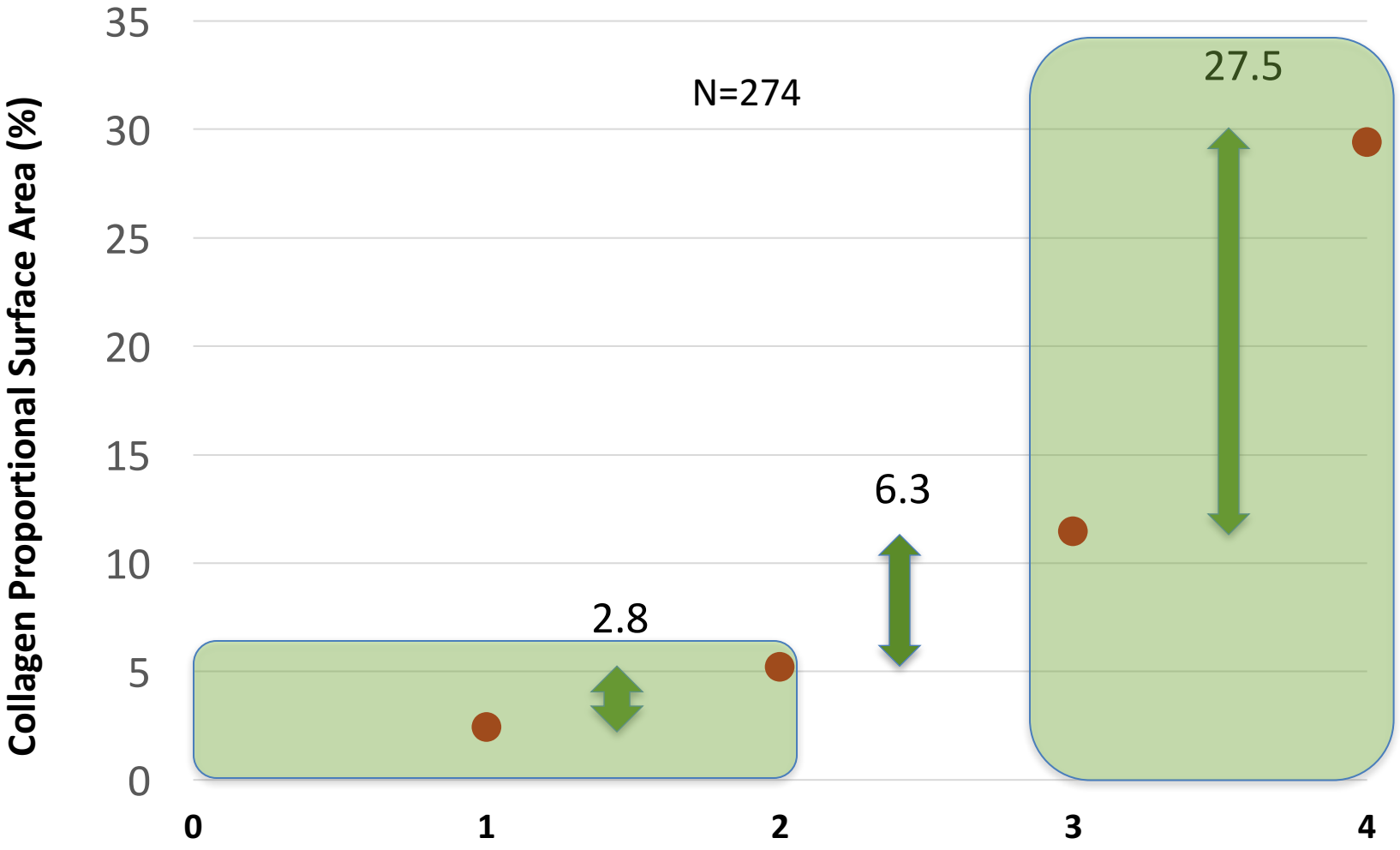

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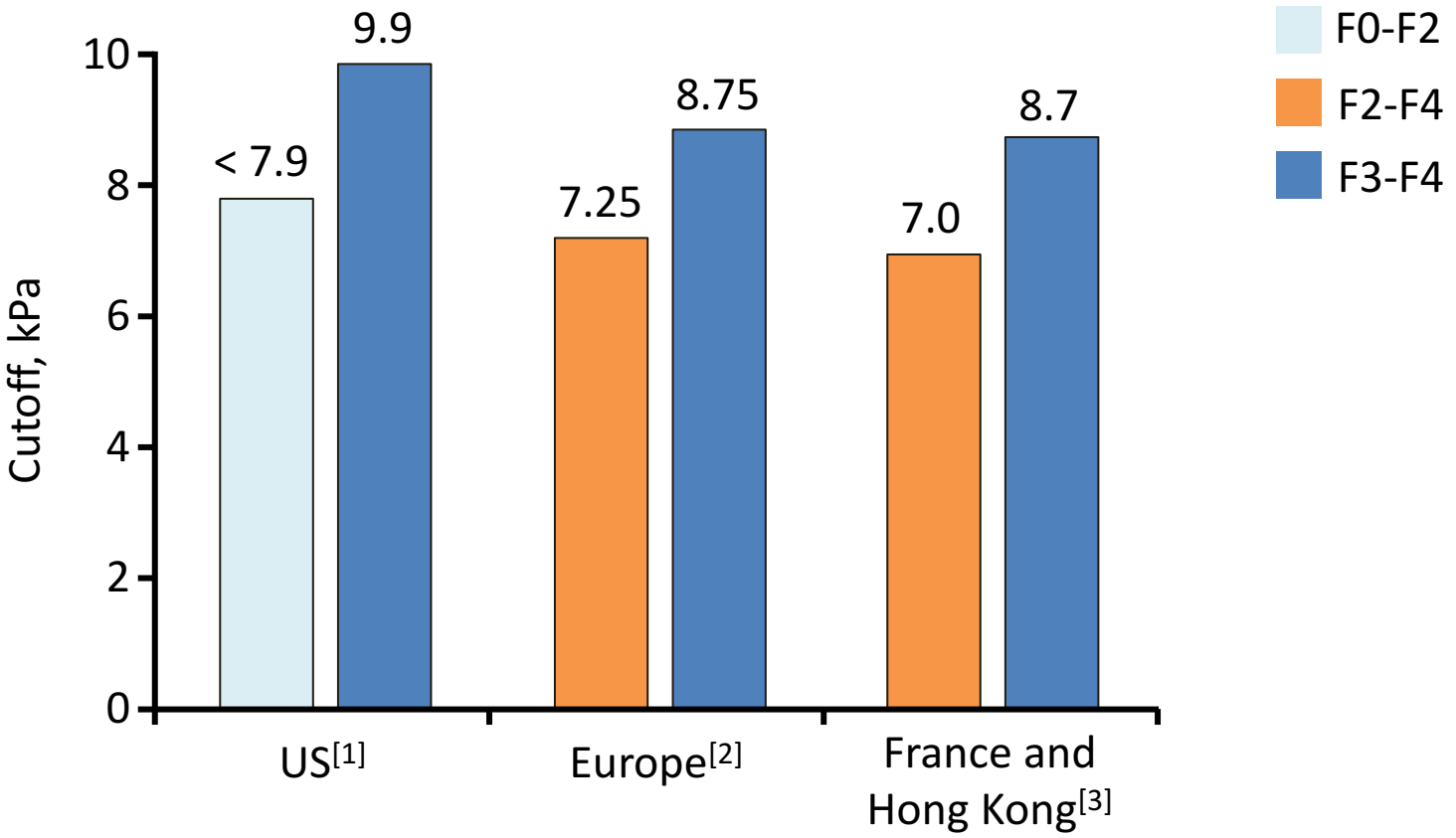
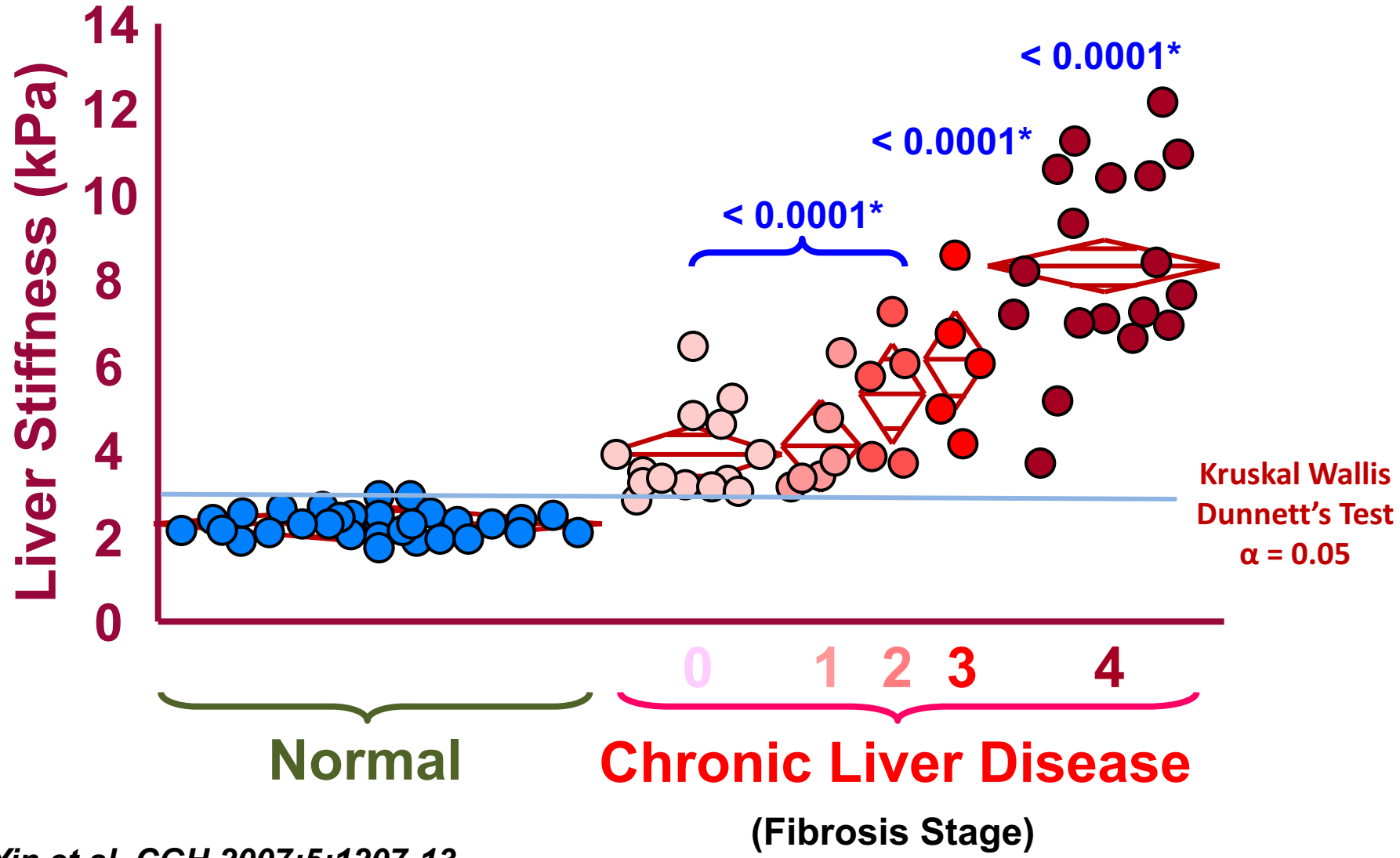
Vibration-Controlled Transient Elastography: Cutoffs for Fibrosis



1. Tapper EB, et al. Am J Gastroenterol. 2016;111:677-684.
2. Petta S, et al. Aliment Pharmacol Ther. 2011;33:1350-1360.
3. Wong VW, et al. Hepatology. 2010;51:454-462.

Liver Stiffness Correlates with Fibrosis Stage



Yin et al. CGH 2007;5:1207-13

2006

24 exams

2006

25 exams

2007

85 exams

2007

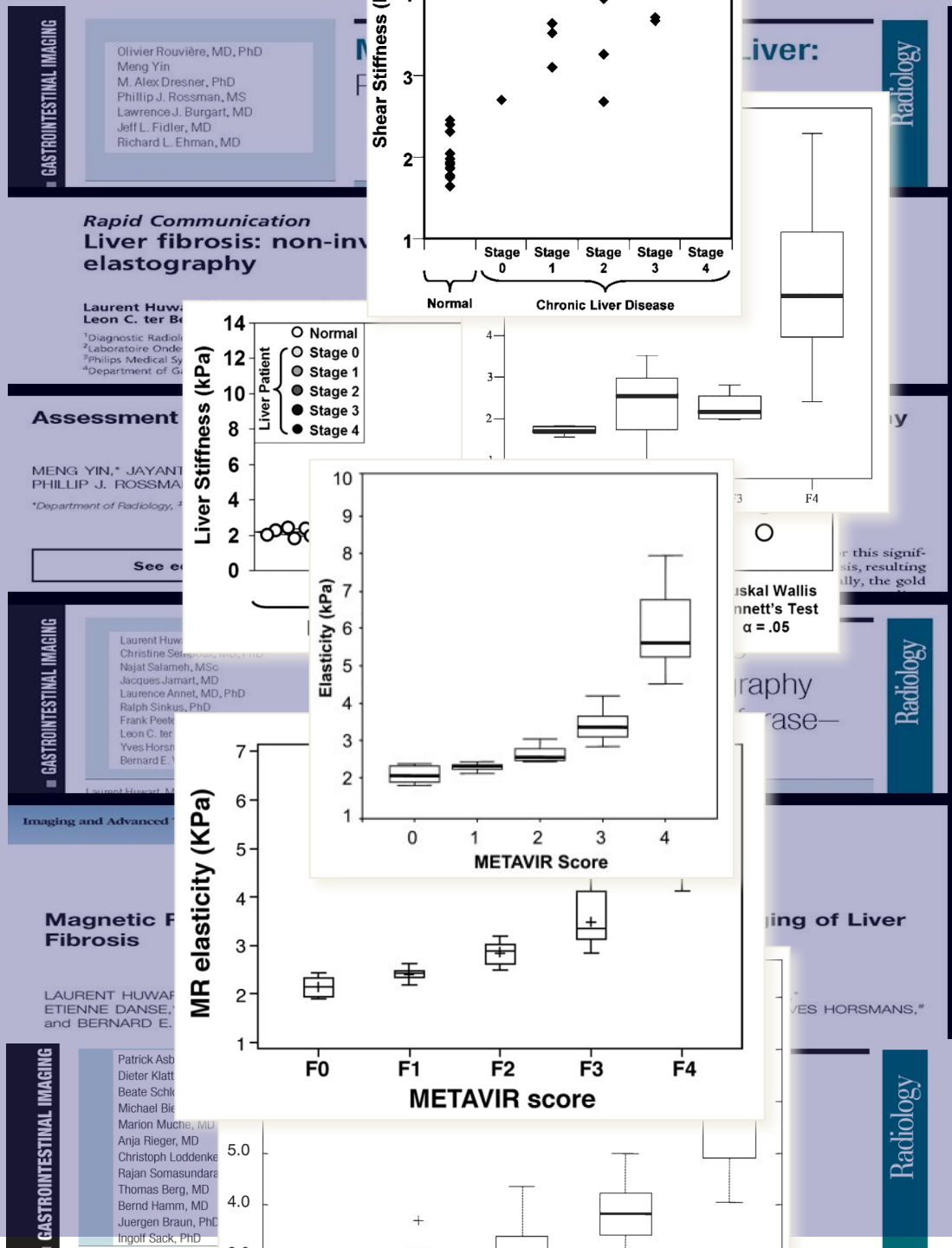
88 exams

2008

141 exams

2010

88 exams



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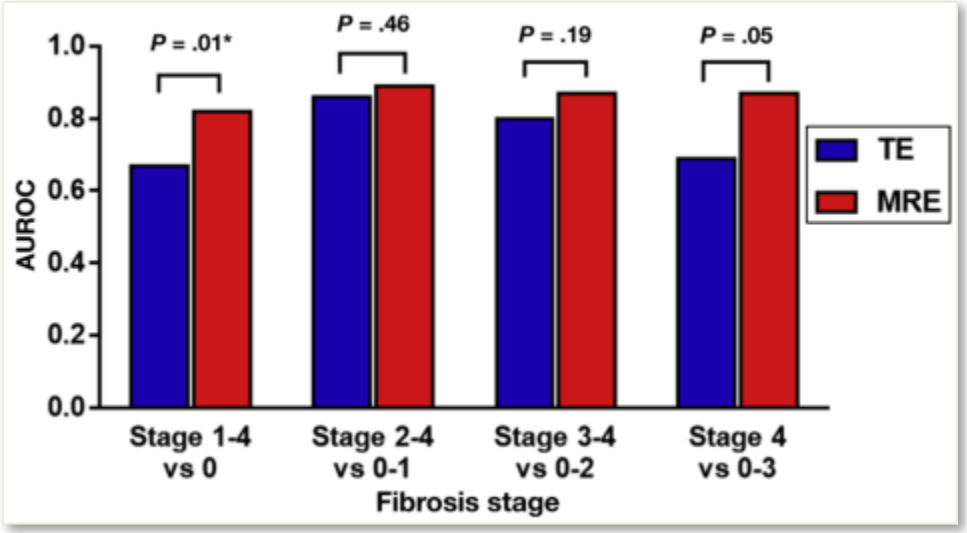
Gastroenterology

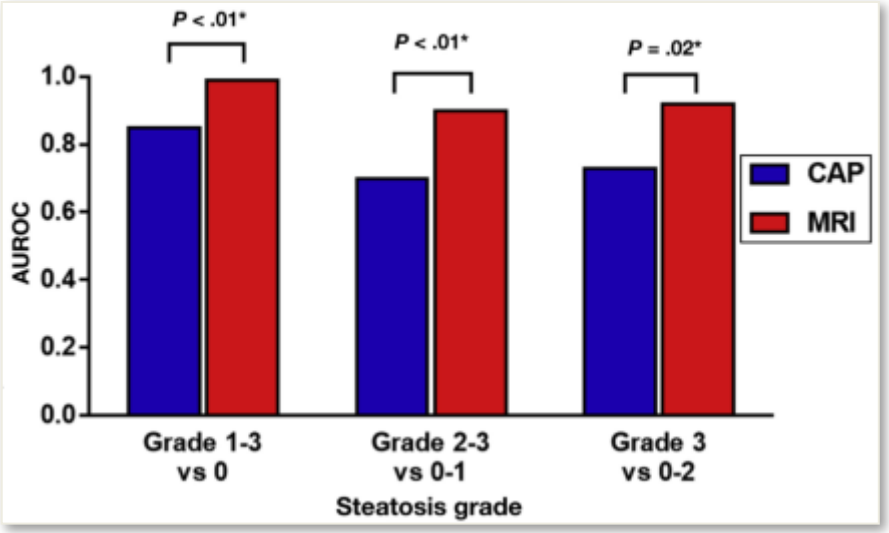
ARTICLE IN PRESS

Gastroenterology 2016;■:1–10

Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients With Biopsy-Proven Nonalcoholic Fatty Liver Disease

Charlie C. Park,[1] Phirum Nguyen,[1] Carolyn Hernandez,[1] Ricki Bettencourt,[1] Kimberly Ramirez,[1] Lynda Fortney,[1] Jonathan Hooker,[2] Ethan Sy,[2] Michael T. Savides,[1] Mosab H. Alquiraish,[1] Mark A. Valasek,[3] Emily Rizo,[1] Lisa Richards,[1] David Brenner,[1,4] Claude B. Sirlin,[2] and Rohit Loomba[1,4,5]





EMERGING IMAGING TECHNOLOGIES

The American Journal of GASTROENTEROLOGY VOLUME 111 | JULY 2016 www.amjgastro.com

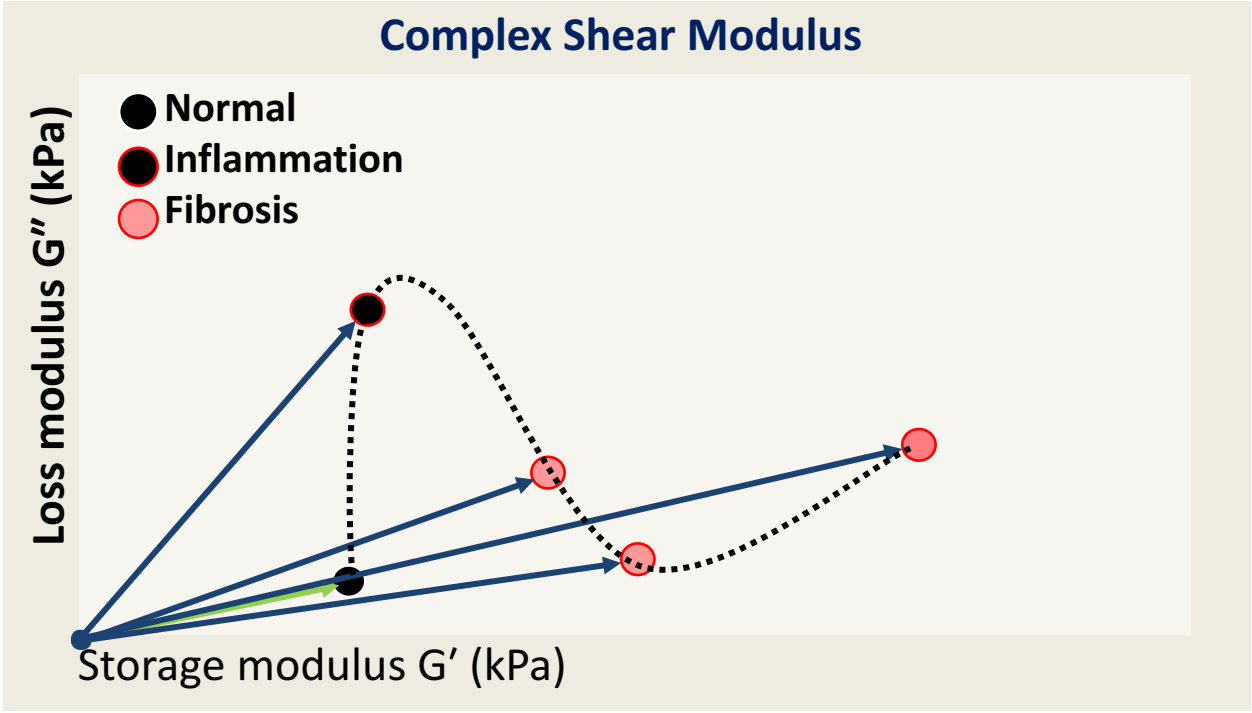
Novel 3D Magnetic Resonance Elastography for the Noninvasive Diagnosis of Advanced Fibrosis in NAFLD: A Prospective Study

Table 3. AUROC and diagnostic cutoffs of 3D- and 2D-MRE for the detection of different stages of fibrosis

	Primary outcome		Secondary outcomes					
	Stage 3–4 vs. stage 0–2	Cutoff (kPa)	Stage 1–4 vs. stage 0	Cutoff (kPa)	Stage 2–4 vs. stage 0–1	Cutoff (kPa)	Stage 4 vs. stage 0–3	Cutoff (kPa)
2D-MRE (60 Hz)	0.921	3.80	0.854	3.13	0.878	3.65	0.981	5.68
3D-MRE (60 Hz)	0.927	3.40	0.855	2.53	0.840	2.89	0.983	4.08
3D-MRE (40 Hz)	0.981	2.43	0.848	1.77	0.856	2.38	0.993	3.21

CONCLUSIONS: **Utilizing a prospective study design, we demonstrate that 3D MRE at 40 Hz has the highest diagnostic accuracy in diagnosing NAFLD advanced fibrosis. Both 2D- and 3D-MRE at 60 Hz, the standard shear-wave frequency, are also highly accurate in diagnosing NAFLD advanced fibrosis.**

Am J Gastroenterol 2016; 111:986–994; doi:10.1038/ajg.2016.65; published online 22 March 2016



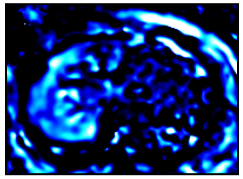
	Hepatic Inflammation	Hepatic Fibrosis	Venous Congestion	Portal Hypertension
Shear Stiffness & Storage Modulus	↑	↑	↑	↑
Damping Ratio & Loss Modulus	↑	–	↓	↑
Volumetric Strain & Compressibility	–	–	↓	↓

↑↓ Significant +/- relationship

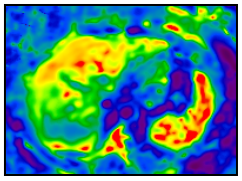
– No significant findings

MR Hepatogram

Multifrequency MRE



Damping ratio



Shear stiffness

Inflammation and ballooning

MRI proton density fat fraction (PDFF)

Fat fraction

Steatosis

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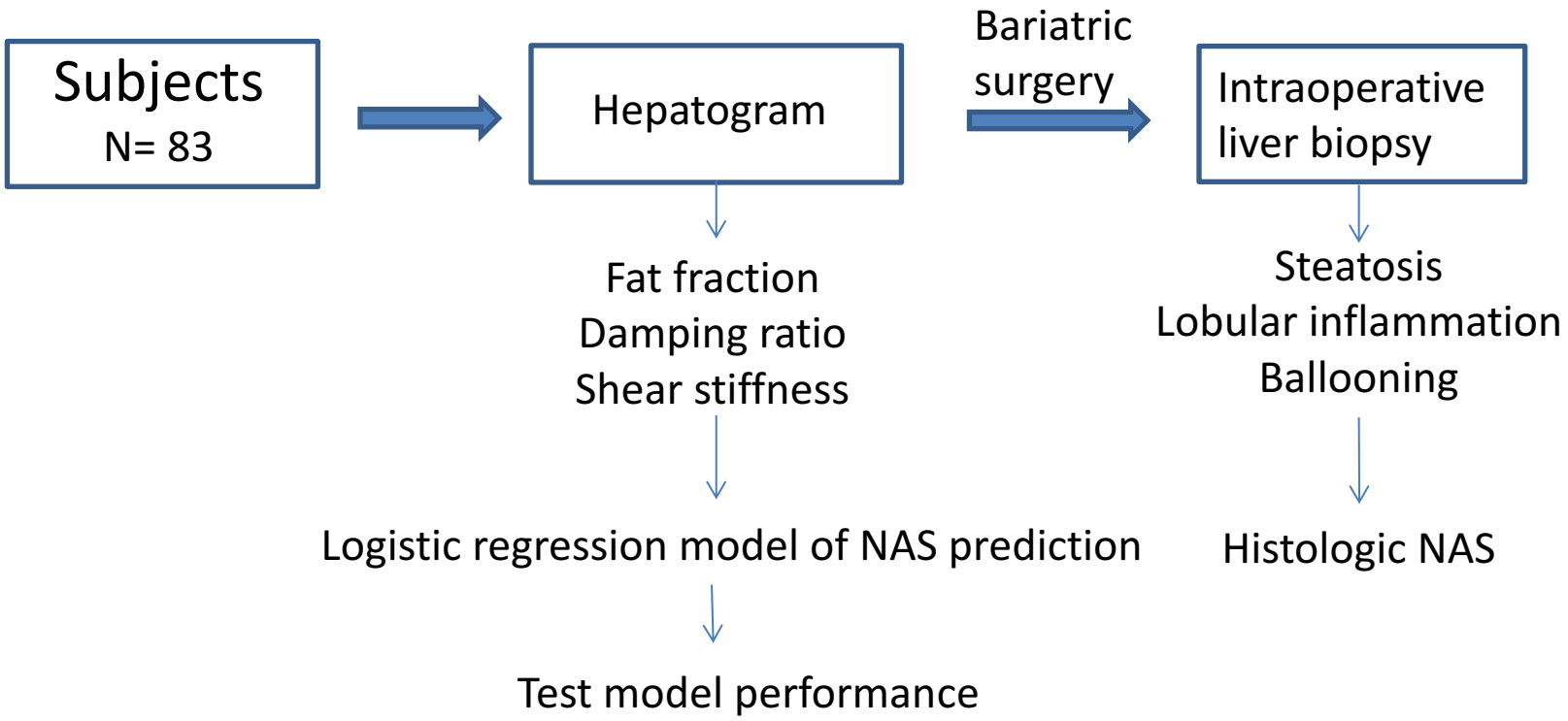
Allen et al., AASLD, Washington DC, October 2017.

Study protocol and methods



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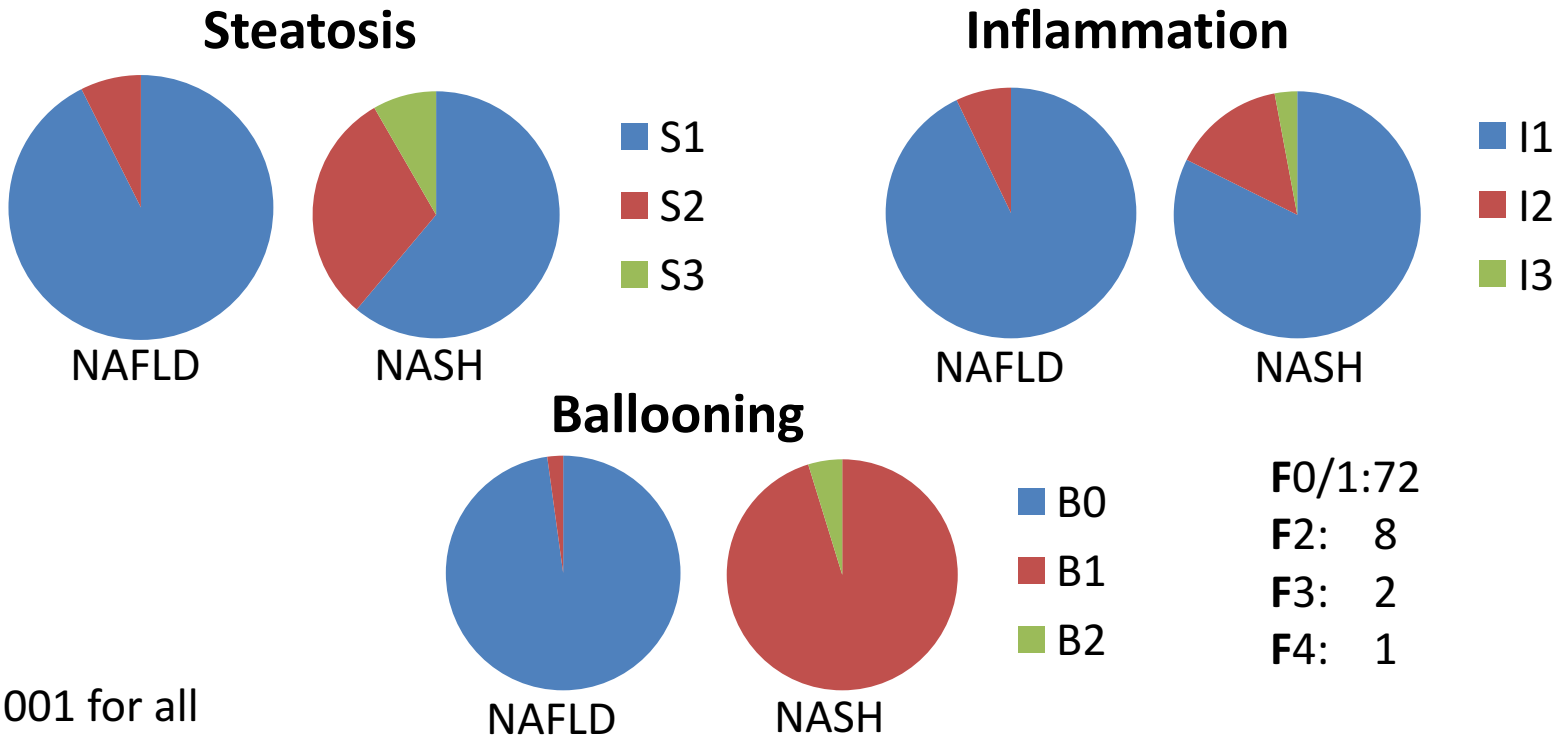
Allen et al., AASLD, Washington DC, October 2017.

Histologic parameters



F0/1:72
F2: 8
F3: 2
F4: 1

P<0.001 for all

Allen et al., AASLD, Washington DC, October 2017.

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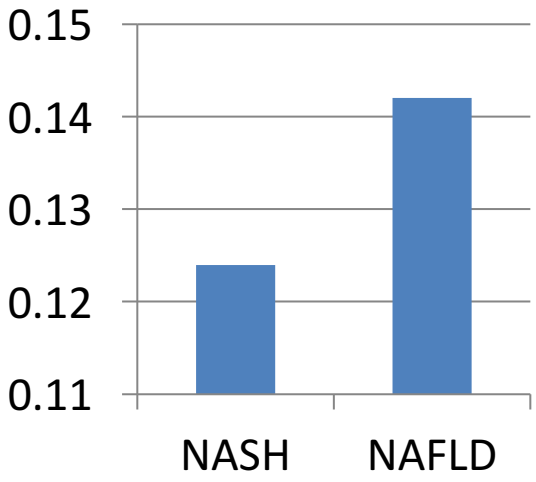
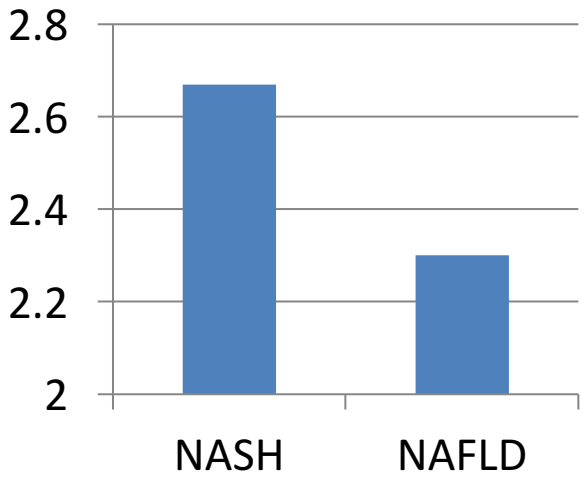
Imaging parameters

Damping ratio



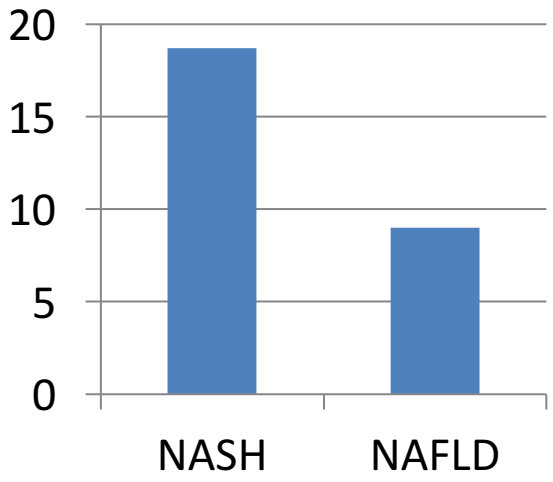
p=0.006

Shear stiffness (kPa)



p=0.005

Fat fraction (%)



p<0.001

Allen et al., AASLD, Washington DC, October 2017.

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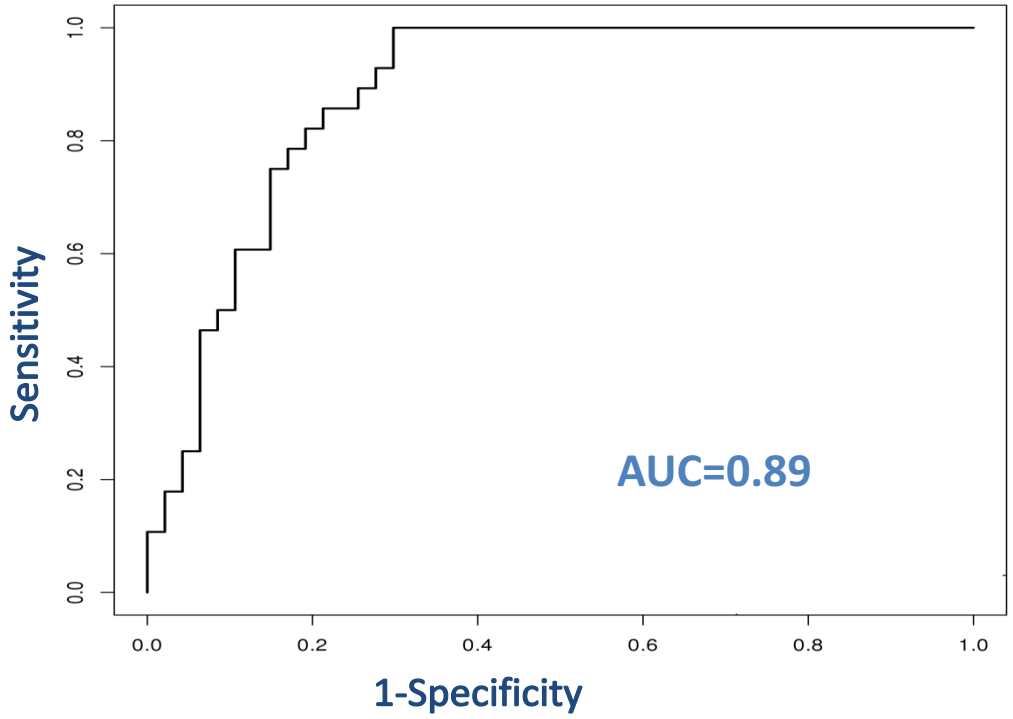
MR Hepatogram predicts NASH with high performance



Sensitivity= 0.68
Specificity= 0.85
PPV= 0.73
NPV= 0.82

Allen et al., AASLD, Washington DC, October 2017.

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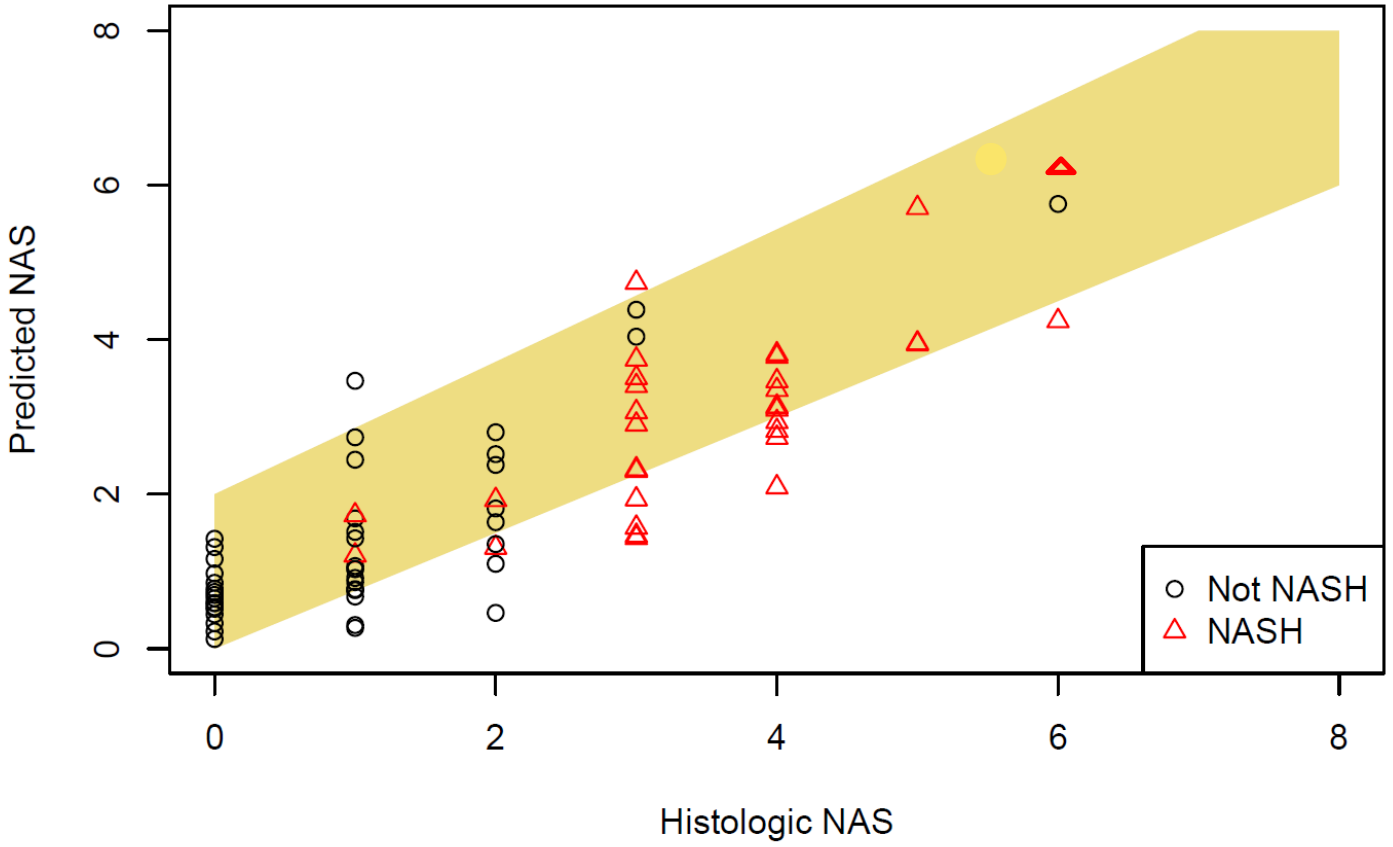
MR Hepatogram predicts disease activity



Allen et al., AASLD, Washington DC, October 2017.

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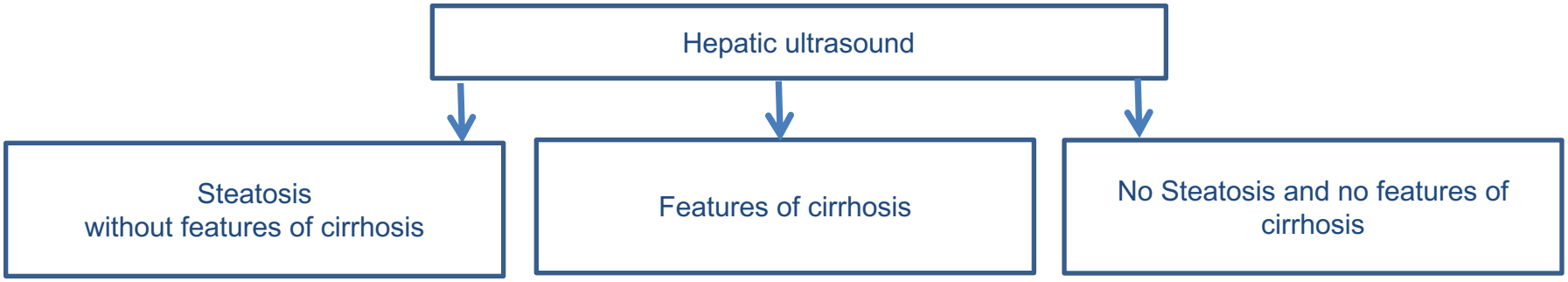
Evaluation of Patients in High Risk Groups for NASH



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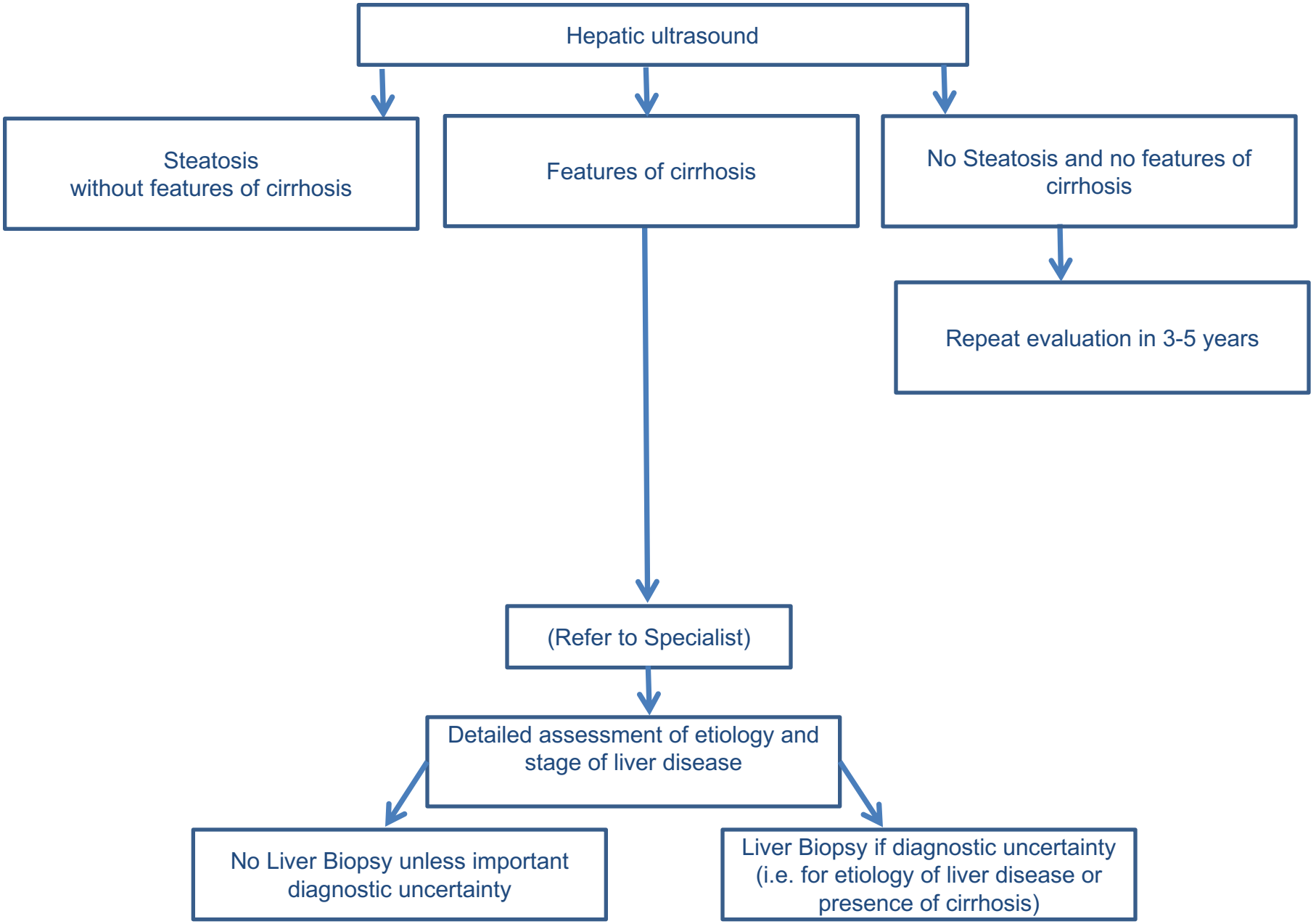

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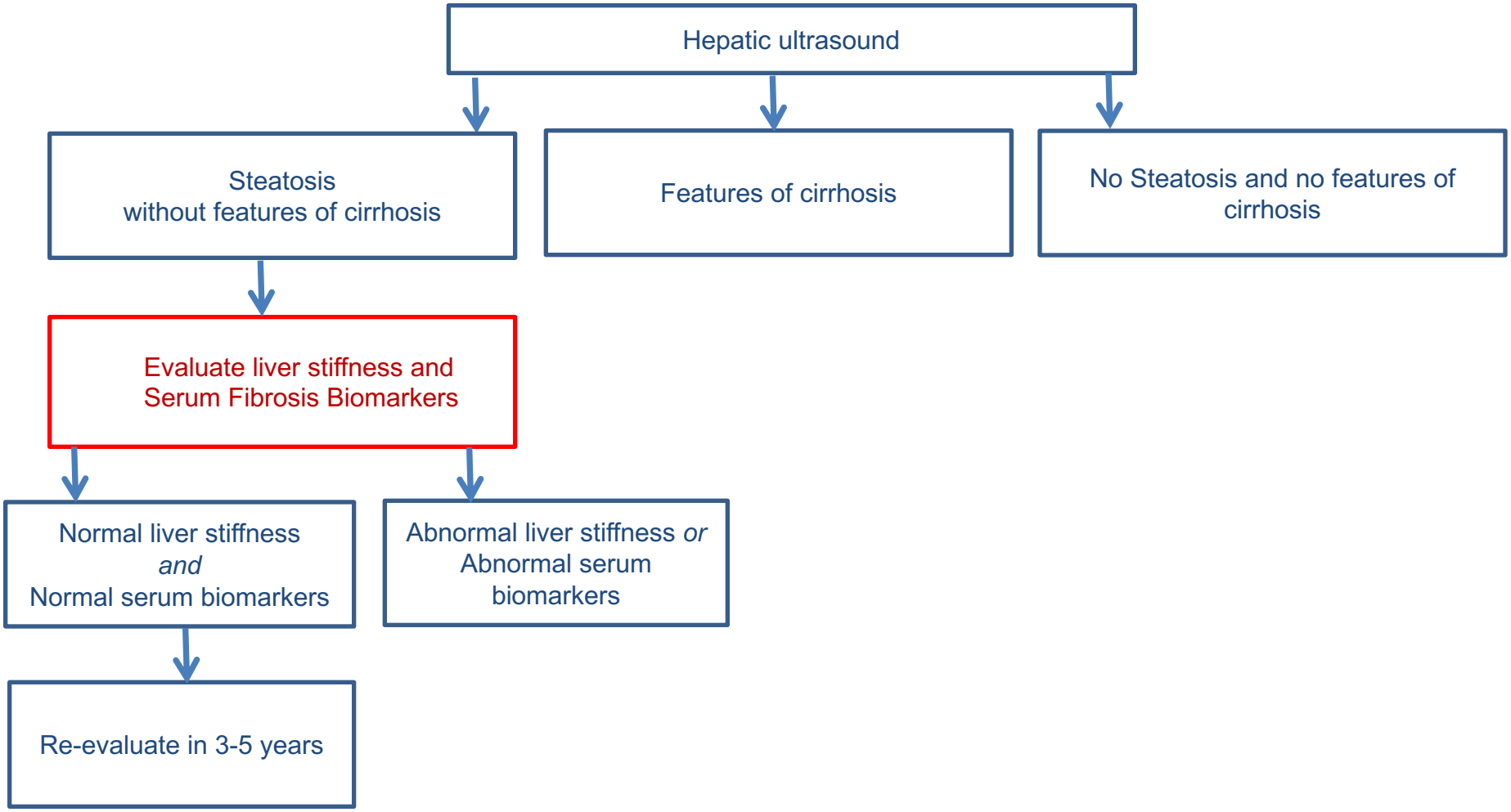

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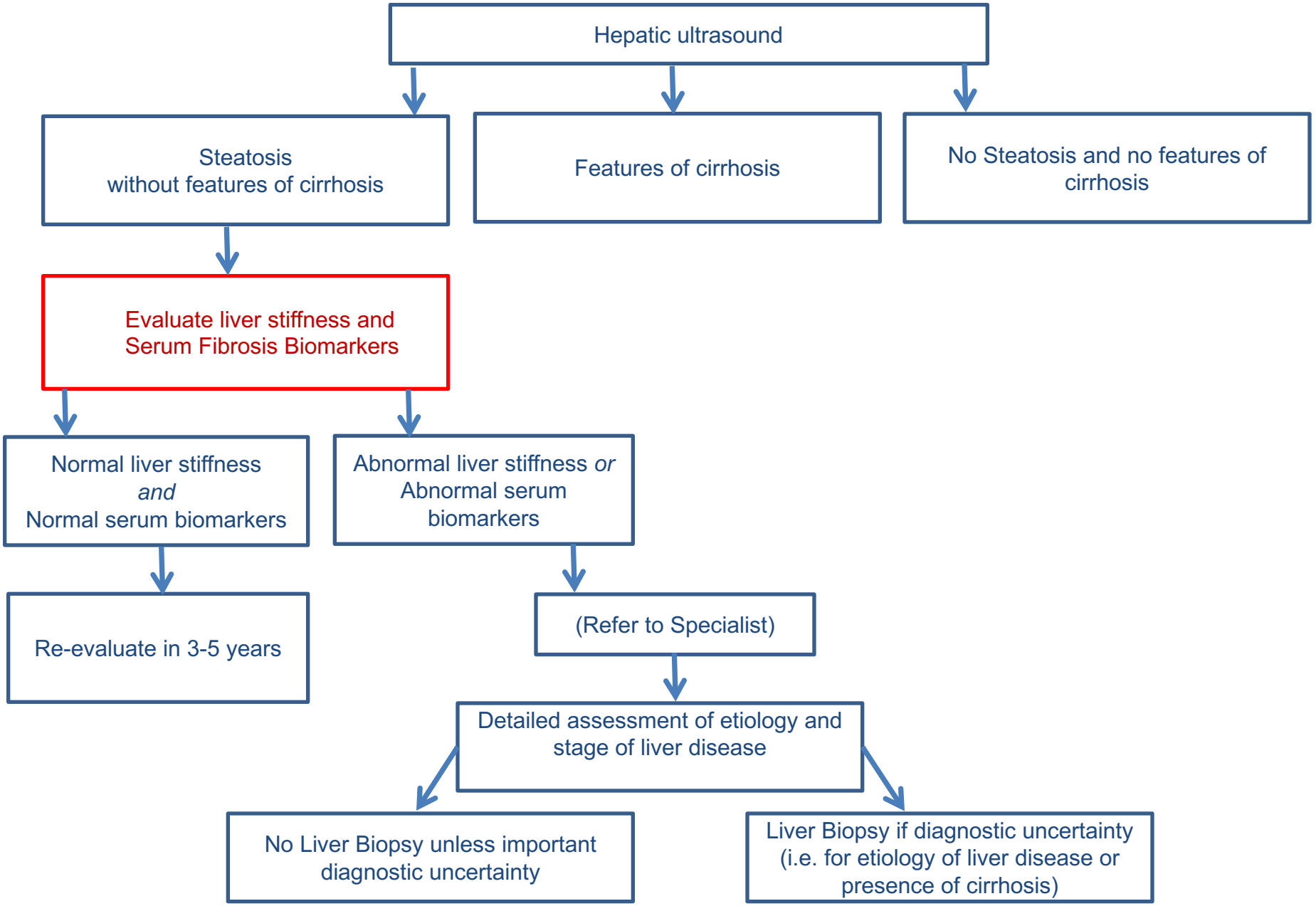
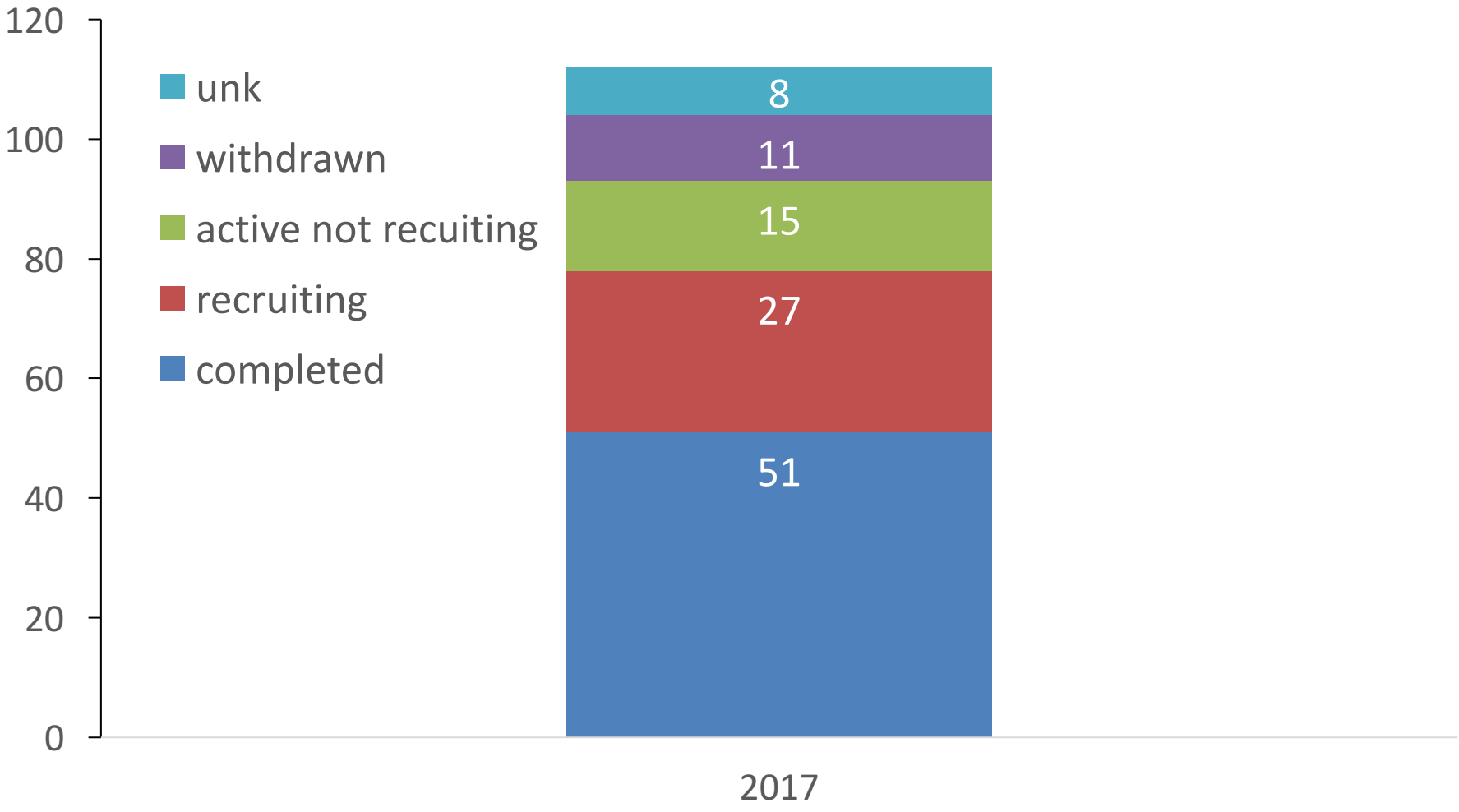


Developments in Therapeutics

Clinical Studies for NAFLD/NASH – Clintrials.gov



Source Clintrials.gov accessed 11/12/2017
Search terms: NASH, nonalcoholic steatohepatitis
Phases 1-4

NASH Pipeline in 2018 - Front Runners

Phase 1	Phase 2 a/b	Phase 3	2017	2018	2019	2020	2021	2022+

- Gilead GS-426-3897 (ACC1 inhib) / Gilead Selonsertib (ASK-1 inhib) — Phase 2 open label data reported → 2022+ Launch
- Gilead GS-402-1852 (FXR agonist) / Intercept OCA (FXR) *PO* — Phase 2b data *published* → 2020 + Launch
- Taiwan JJKB-121 (TLR-4 antag) / Immuron IMM-124E (Immune Mod)_ / Genfit GFT-505 (PPARα/δ) — Phase 2b data *published* → 2020 + Launch
- NuSirt NS-0200 (Met-Leu-sildenafil) / BMS BMS-986036 (FGF-21) / Conatus Emricasan (Caspase PI)_
- Shire SHP-626 (ASBT inhib) / NGM NGM-282 (FGF-19) / Tobira CVC (CCR2/5) — Phase 2b interim data reported, Phase 3 planned → 2022+ Launch
- BirdRock namacizumab (CNR1 mab) / Merck Solithromycin (Antibiotic)_ / Galmed Aramchol (SCD1) — Phase 2b data in 2018 → 2022+ Launch
- Pharmaxis PXS-S1 (LOX-2 sm mol) / Novo Victoza (GLP-1) — Phase 2b data published, approved for Diabetes → approved for T2DM
- **Gilead Simtuzumab (LOXL2)** — *abandoned*
- **Galectin GR-MD-02 (Galectin-3)_** — Phase 2b data in 4Q17 *(accelerated review)* → 2021 Launch

- cirrhosis
- non-cirrhotic
- FDA noted liver tox signal

Represents earliest and most aggressive approval timelines.

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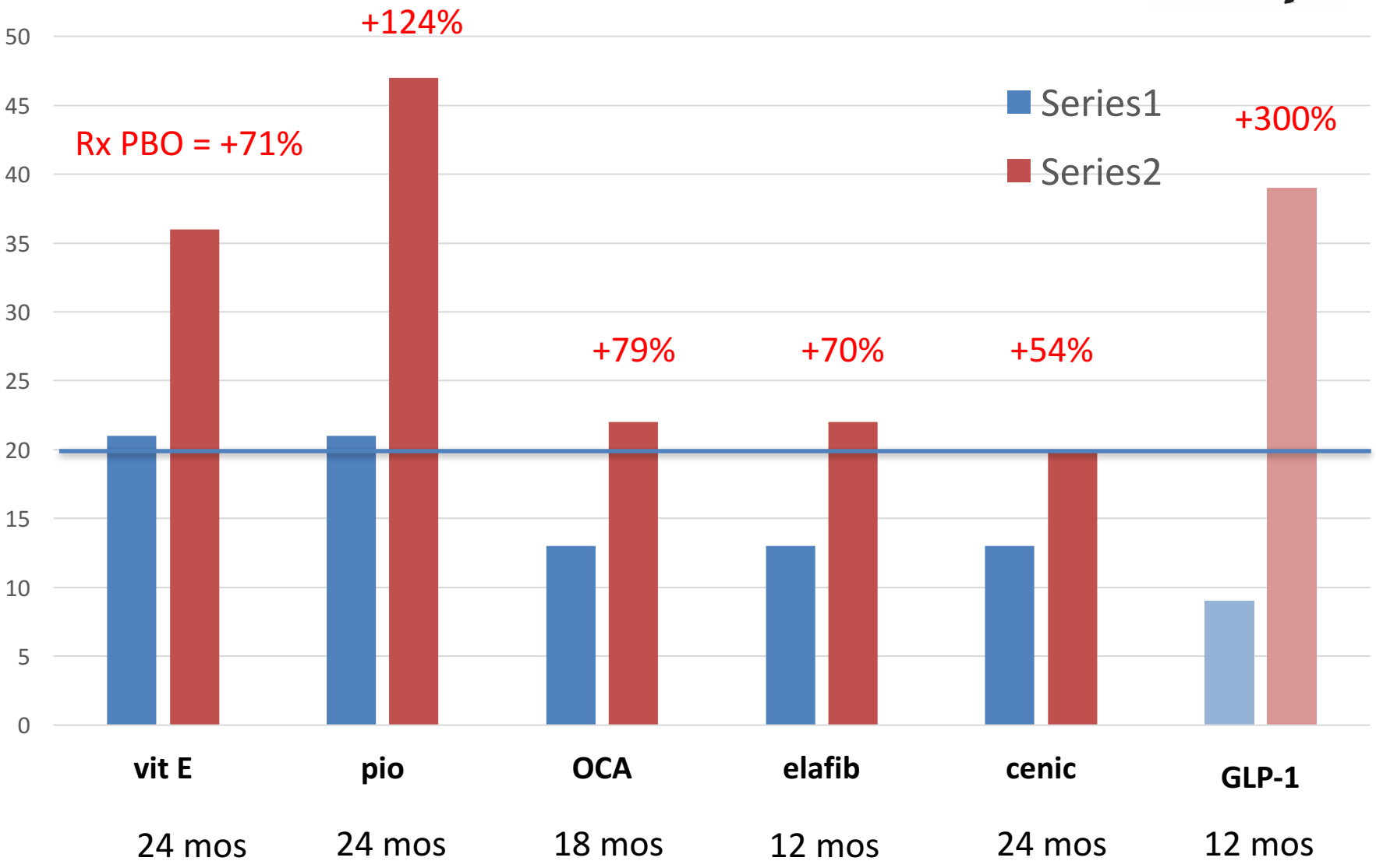
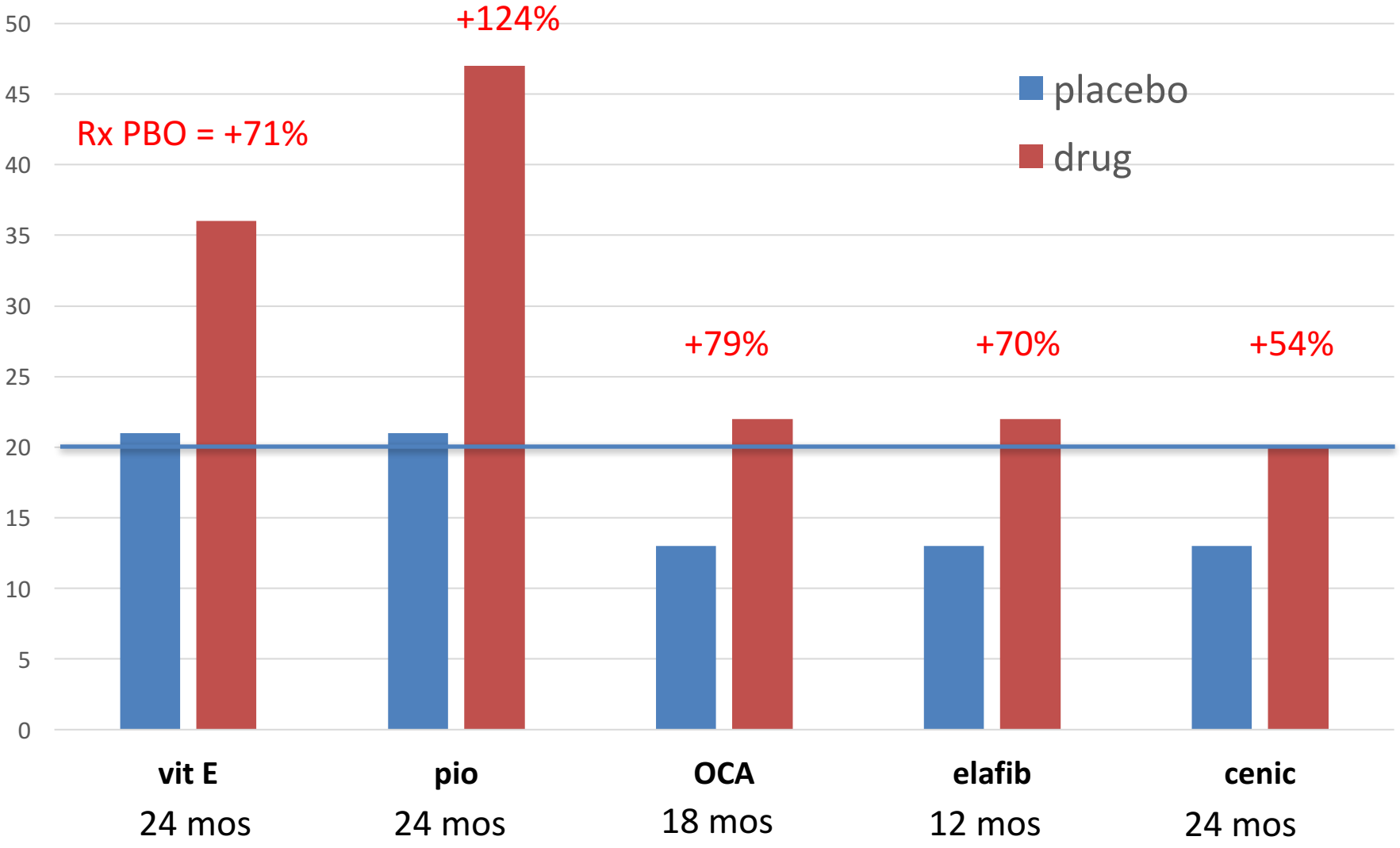
Phase 2 Results – NAS Resolution vs. Placebo



Phase 2b Results – NAS Resolution vs. Placebo



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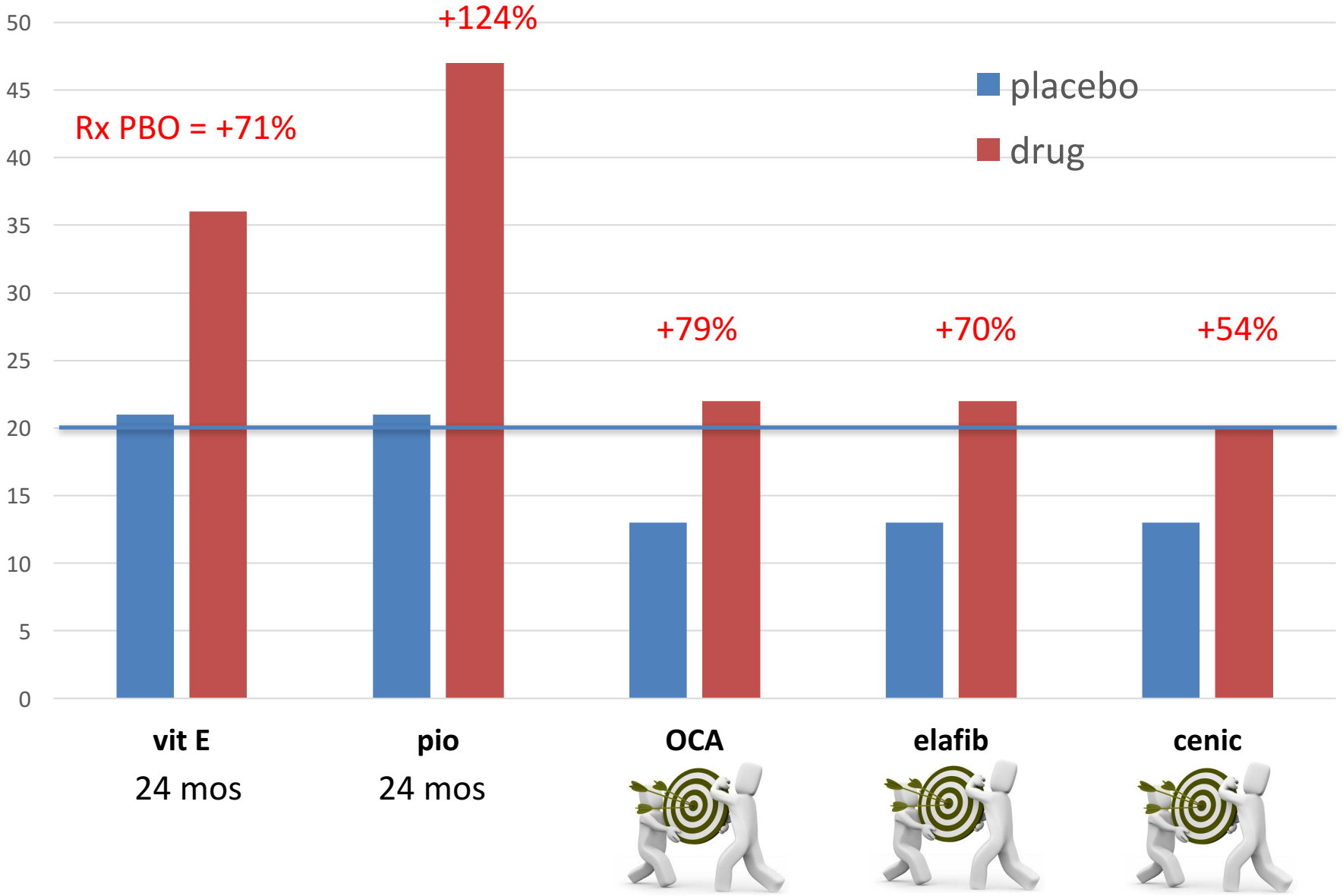
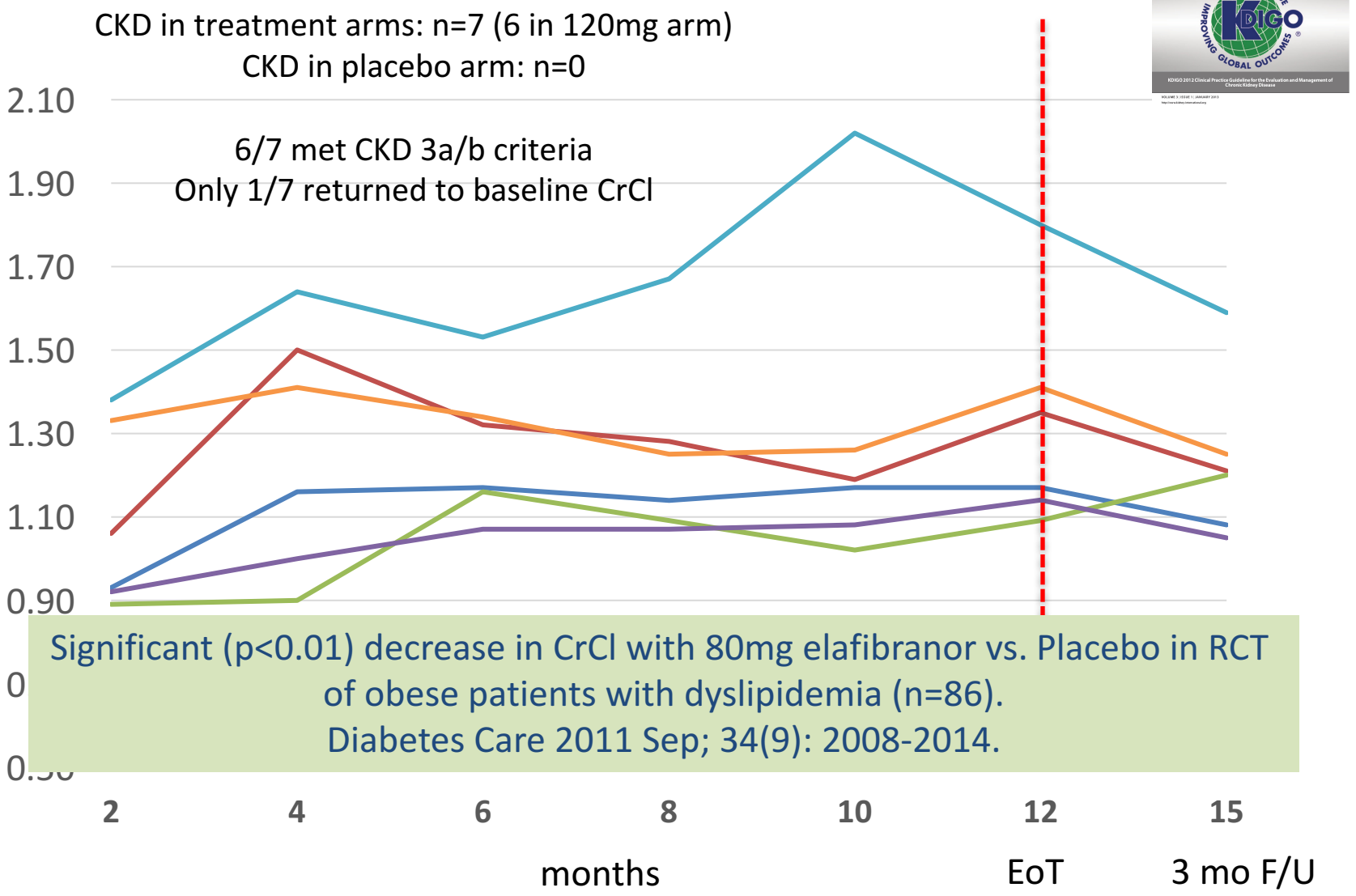


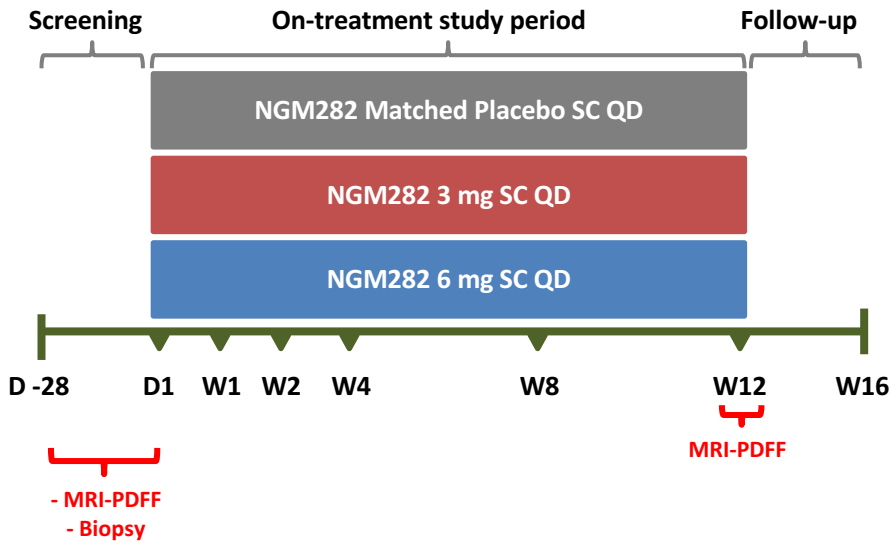
Elafibranor and Chronic Kidney Disease (CKD)



Significant ($p<0.01$) decrease in CrCl with 80mg elafibranor vs. Placebo in RCT of obese patients with dyslipidemia (n=86).
Diabetes Care 2011 Sep; 34(9): 2008-2014.

Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013. 3:1-150

NGM282 significantly reduces hepatic steatosis and key biomarkers of NASH: Results of a Phase 2 Study



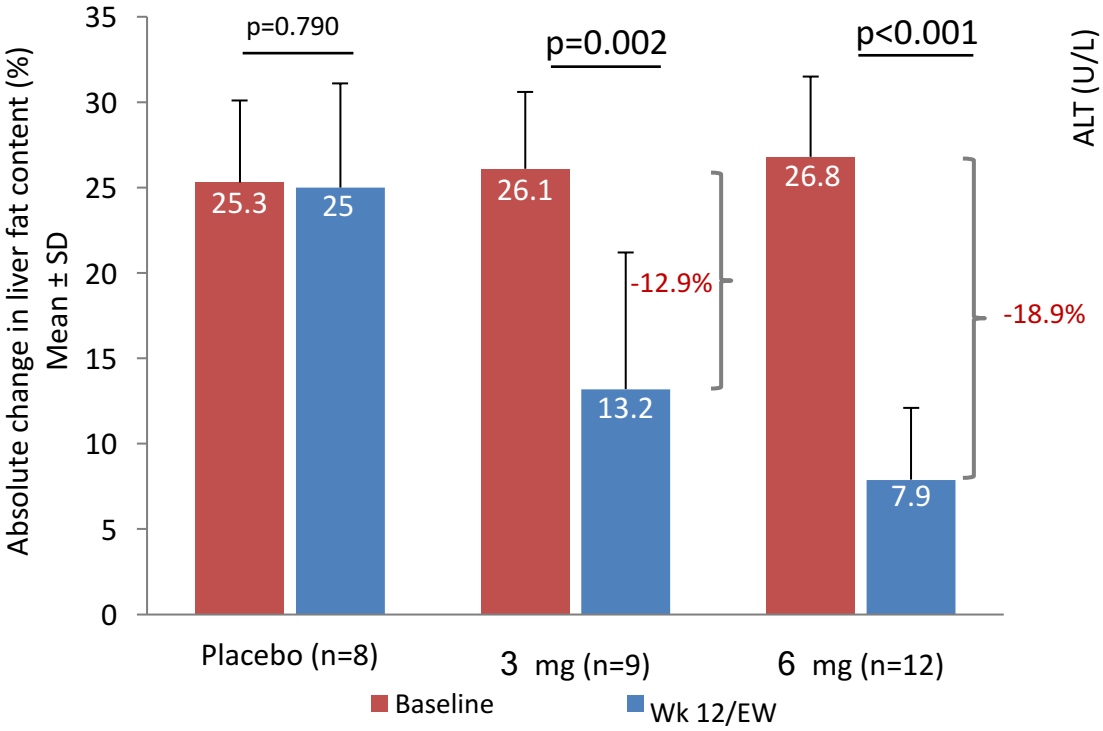
- NGM282: a novel non-tumorigenic, engineered variant of human FGF19
- >150 variants screened to identify molecules retaining the metabolic activity of FGF19 while eliminating the tumorigenic effects
- Specific amino acid substitutions remove the IL6/STAT3 activation associated with FGF19 tumorigenicity

- Randomized, double-blinded, placebo controlled
- 82 subjects enrolled at 18 sites
- Biopsy confirmed NASH with a minimum NAS ≥4
- Stage 1–3 fibrosis
- Minimum 8% absolute liver fat content by MRI-PDFF
- ALT >19 IU/L in females; >30 IU/L in males
- Primary endpoint: decrease in absolute liver fat content >5%

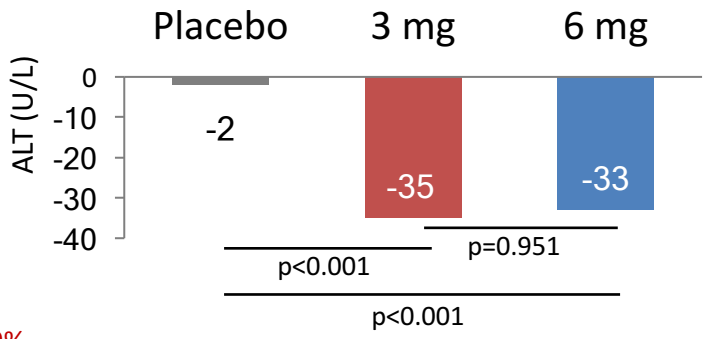
Harrison S, et al. EASL 2017, Amsterdam. #LBO-07

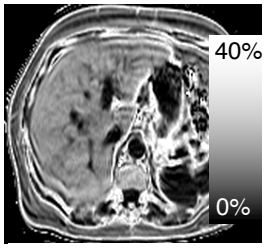
NGM282 significantly reduces hepatic steatosis and key biomarkers of NASH: Results of a Phase 2 Study

Greatest magnitude of effect in subjects with most active disease: baseline MRI-PDFF >20%

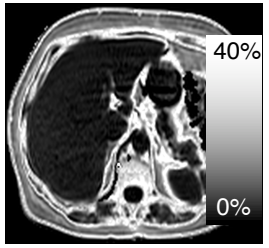


ALT: absolute change





Baseline MRI-PDFF = 24.1%



Week 12 MRI-PDFF = 3.6%

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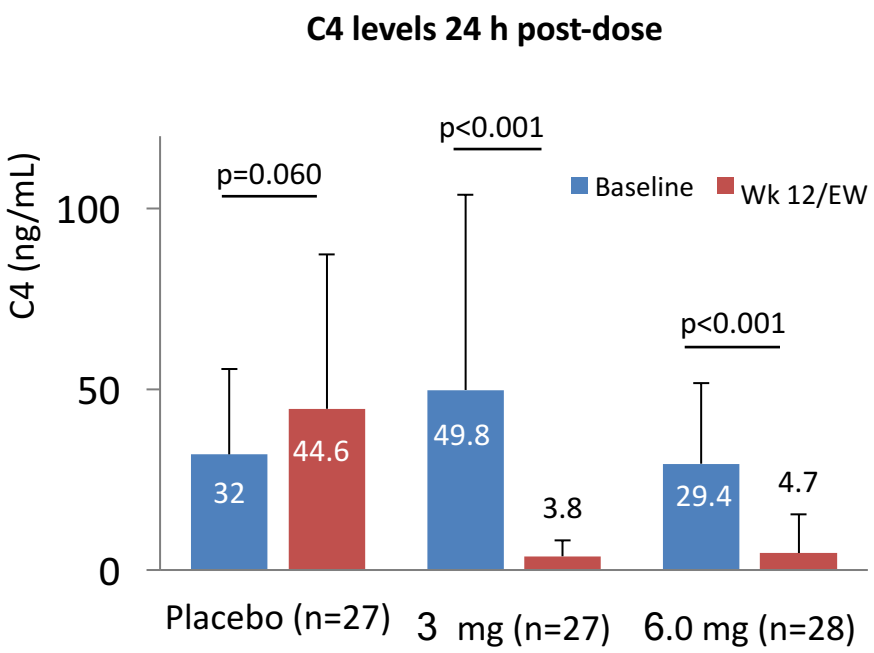
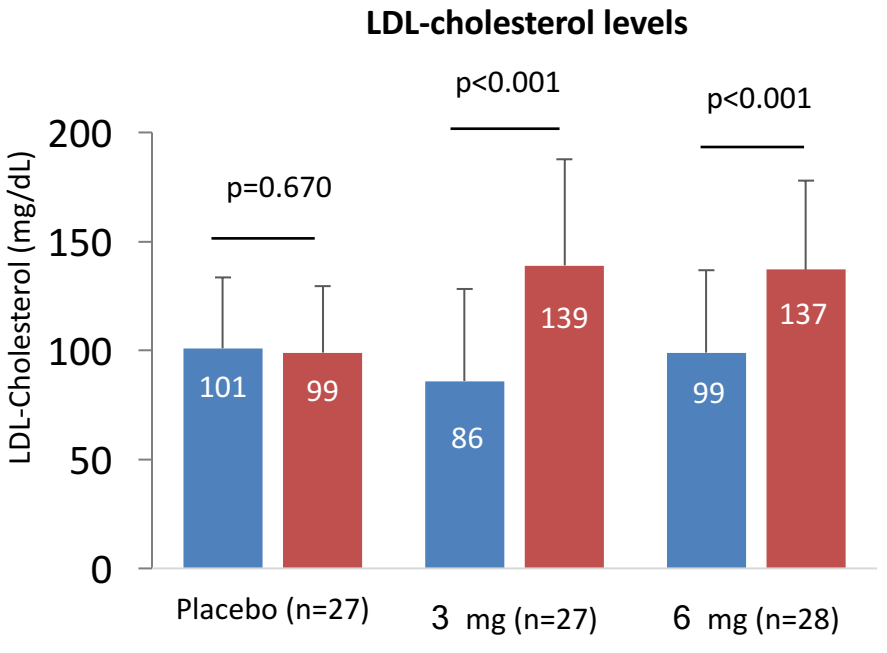
Harrison S, et al. EASL 2017, Amsterdam. #LBO-07

Bile Salt and Lipid Metabolism

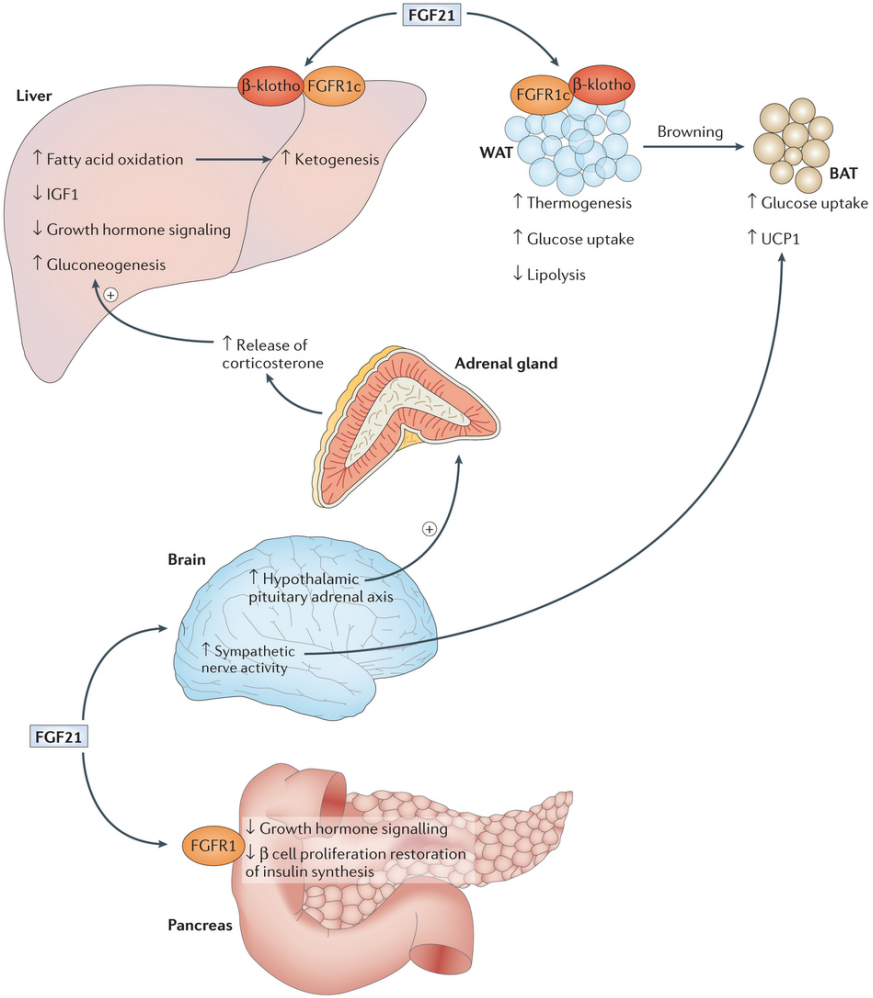




Assay of 7 -hydroxy- 4-cholesten-3-one (C4), an intermediate in bile acid synthesis, strong correlation to the enzymatic activity of hepatic C7 OH, both at steady-state conditions (*r* 0.929)

Harrison S, et al. EASL 2017, Amsterdam. #LBO-07

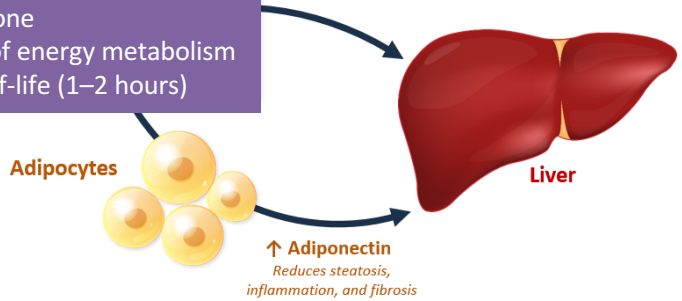
FGF 21 Mimetics



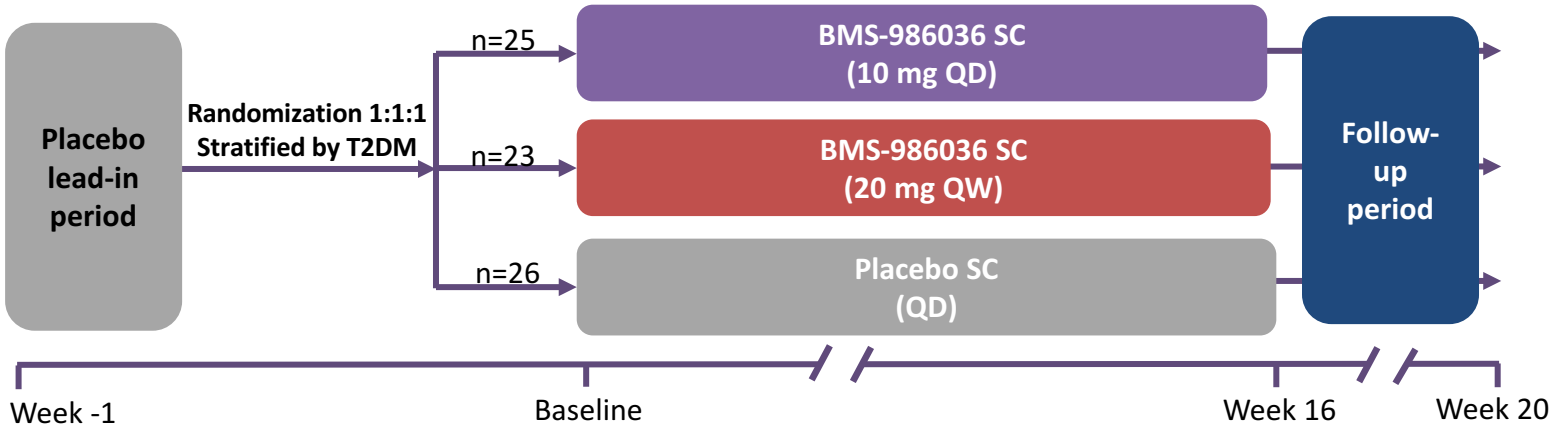
Nature Reviews | Drug Discovery

BMS-986036 (pegylated FGF21) in patients with NASH: A Phase 2 study

FGF21
- Non-mitogenic hormone
- Important regulator of energy metabolism
- FGF21 has a short half-life (1–2 hours)



- **Key eligibility criteria:** Biopsy-proven NASH with fibrosis Stage 1–3 (within 1 year of screening); BMI ≥25 kg/m^2; hepatic fat fraction MRI-PDFF ≥10%
- **Primary efficacy endpoint:** Change in hepatic fat fraction (%) from baseline to Week 16



Sanyal AJ, et al. AASLD 2017, Washington DC. #182

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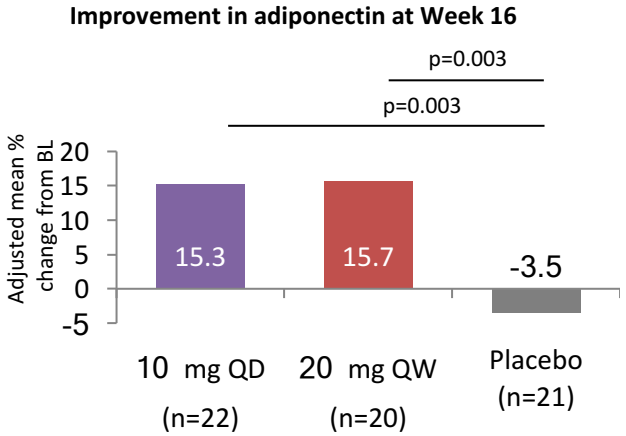
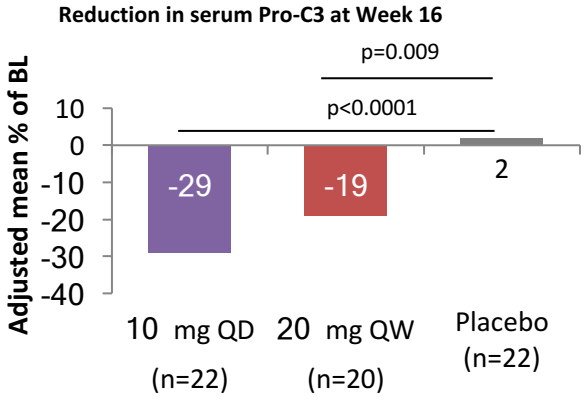
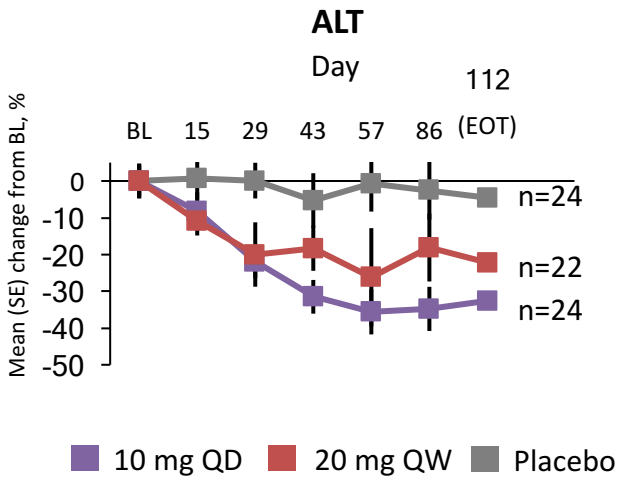
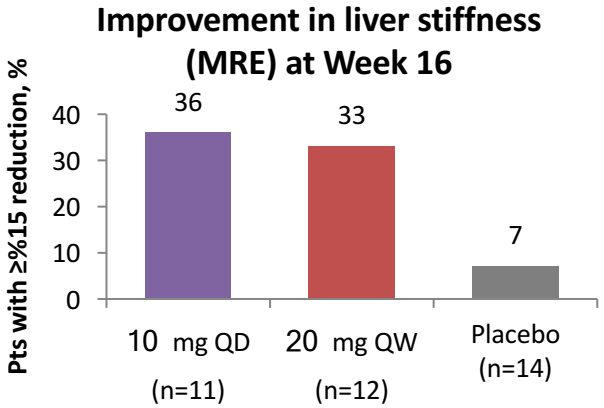






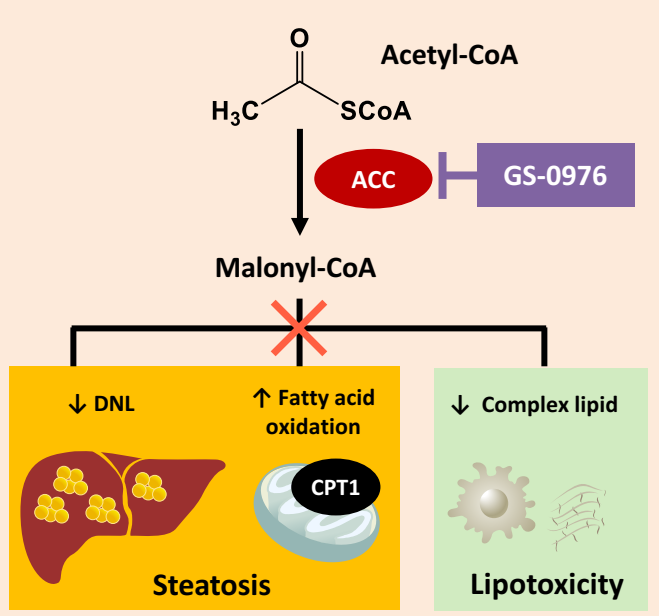


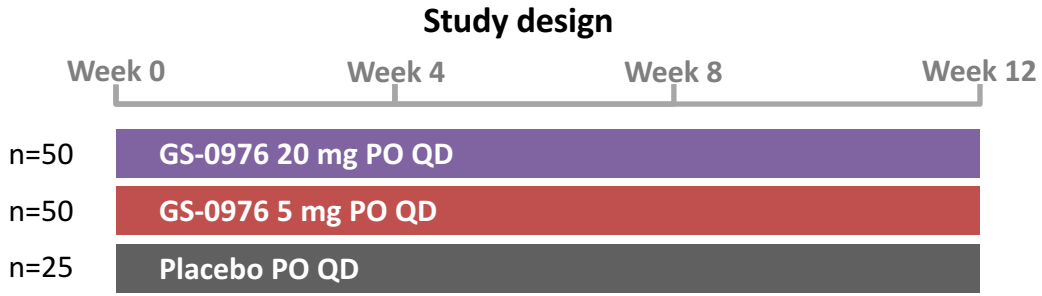
- BMS-986036 10 mg QD and 20 mg QW for 16 weeks significantly decreased hepatic fat fraction in NASH (F1–F3) vs placebo
- BMS-986036 QD and QW associated with improvements in biomarkers of fibrosis (MRE and pro-C3), metabolic parameters (adiponectin and lipids), and markers of hepatic injury (ALT and AST) vs placebo
- Further assessment of efficacy in improving histologic endpoints is

Sanyal AJ, et al. AASLD 2017, Washington DC. #182

ACC inhibitor GS-0976: Phase 2, randomized, placebo-controlled trial of patients with NASH

- GS-0976, a liver-directed inhibitor of ACC, reduced DNL and liver fat in a proof-of-concept study of NASH patients





- 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.

Loomba R, et al. AASLD 2017, Washington DC. #LB-9

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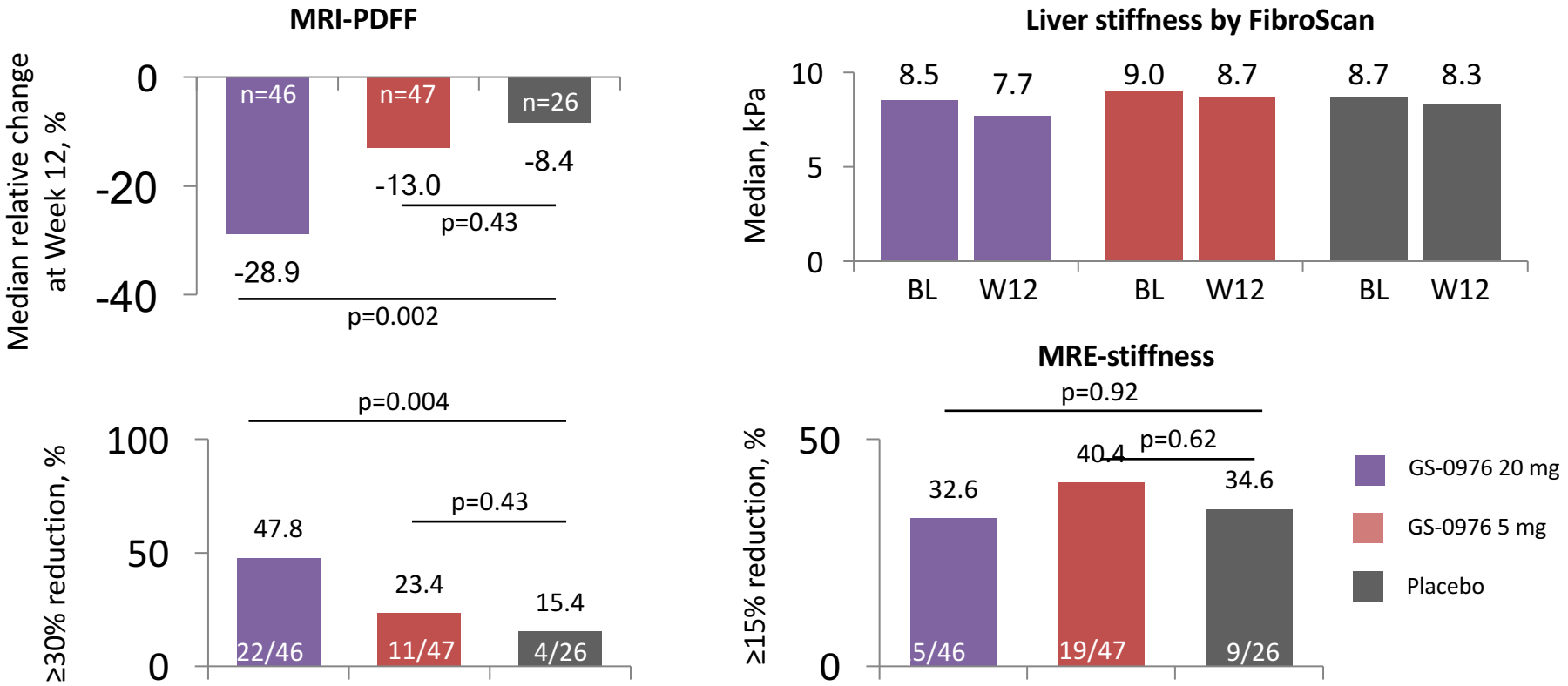

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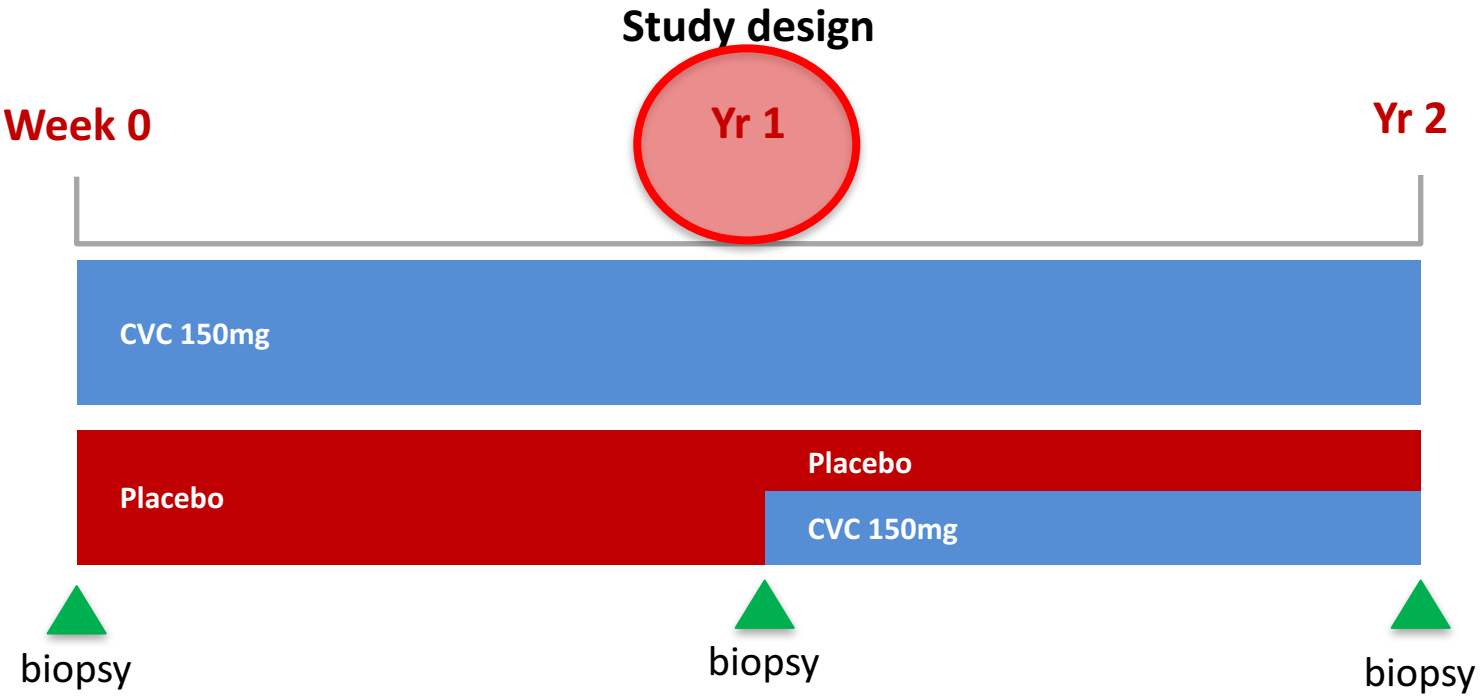
Cenicriviroc (CCR5/2 inhibitor) Phase 2b Study



Biopsy showing NAS of >= 4 with at least 1 in each component of NAS

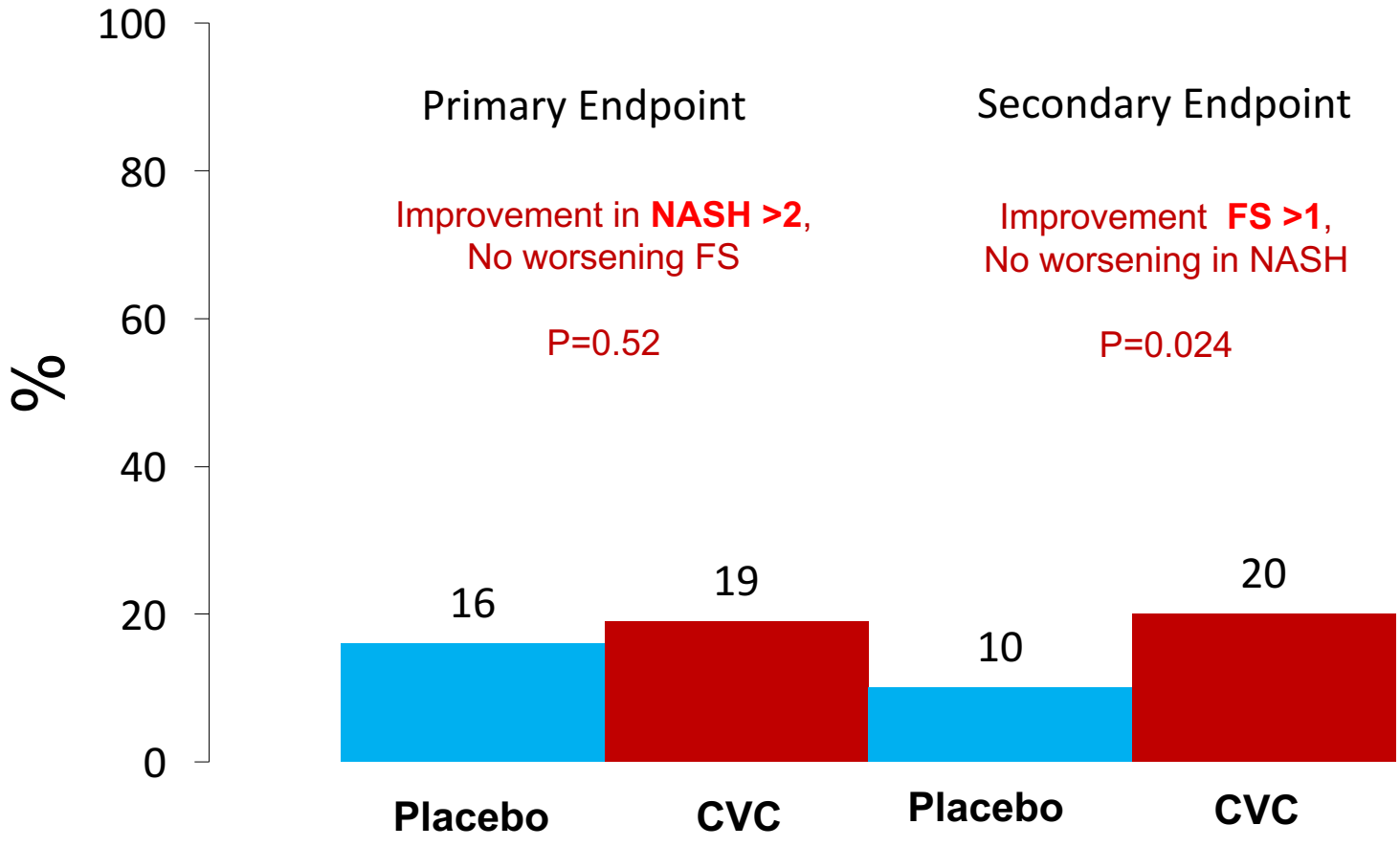
Fibrosis Stage 1 to 3

One of:

- type 2 diabetes mellitus
- BMI > 25 kg/m2, with at least one feature of metabolic syndomre:
- Bridging fibrosis (NASH CRN Stage 3) and/or definite NASH (NAS ≥ 5)

Cenicriviroc Phase 2b Study

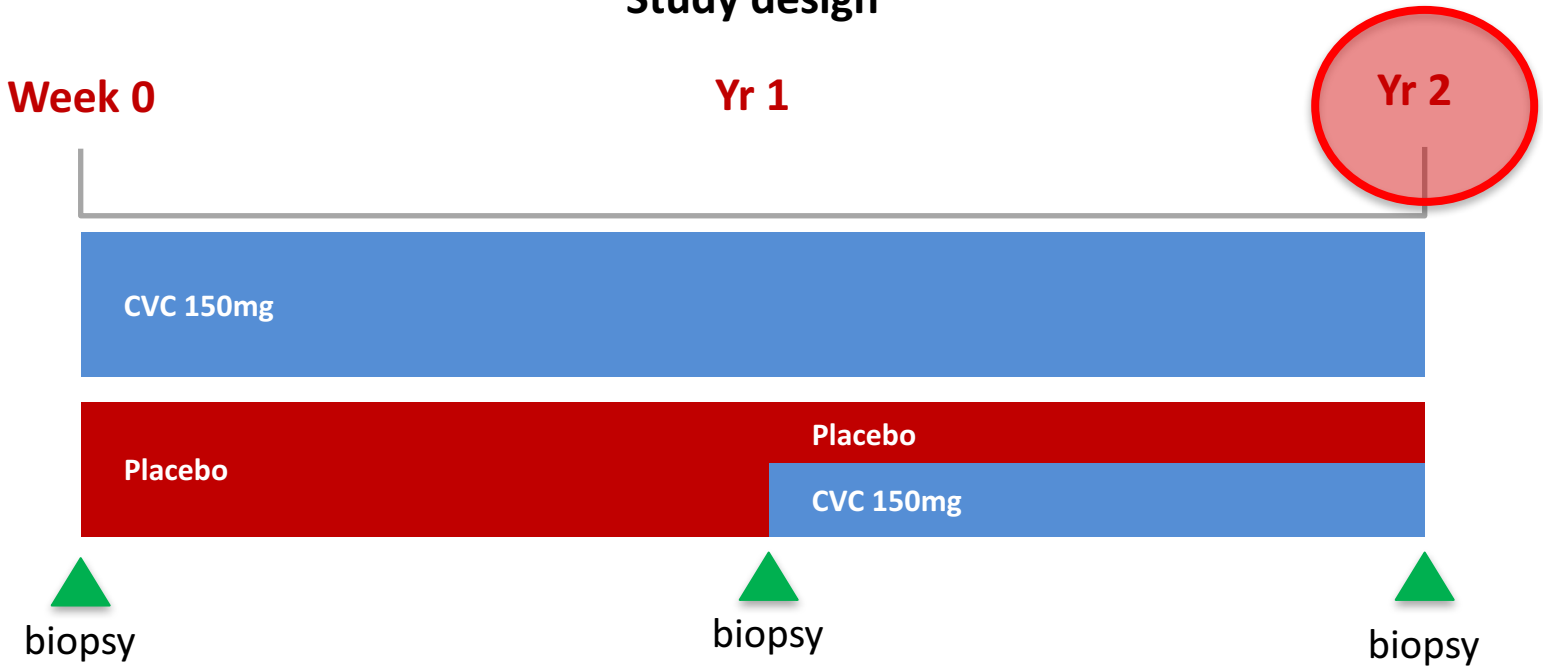
ITT population = 289



Sanyal et al., *AASLD* 2016.

Cenicriviroc (CCR5/2 inhibitor) Phase 2b Study

Study design



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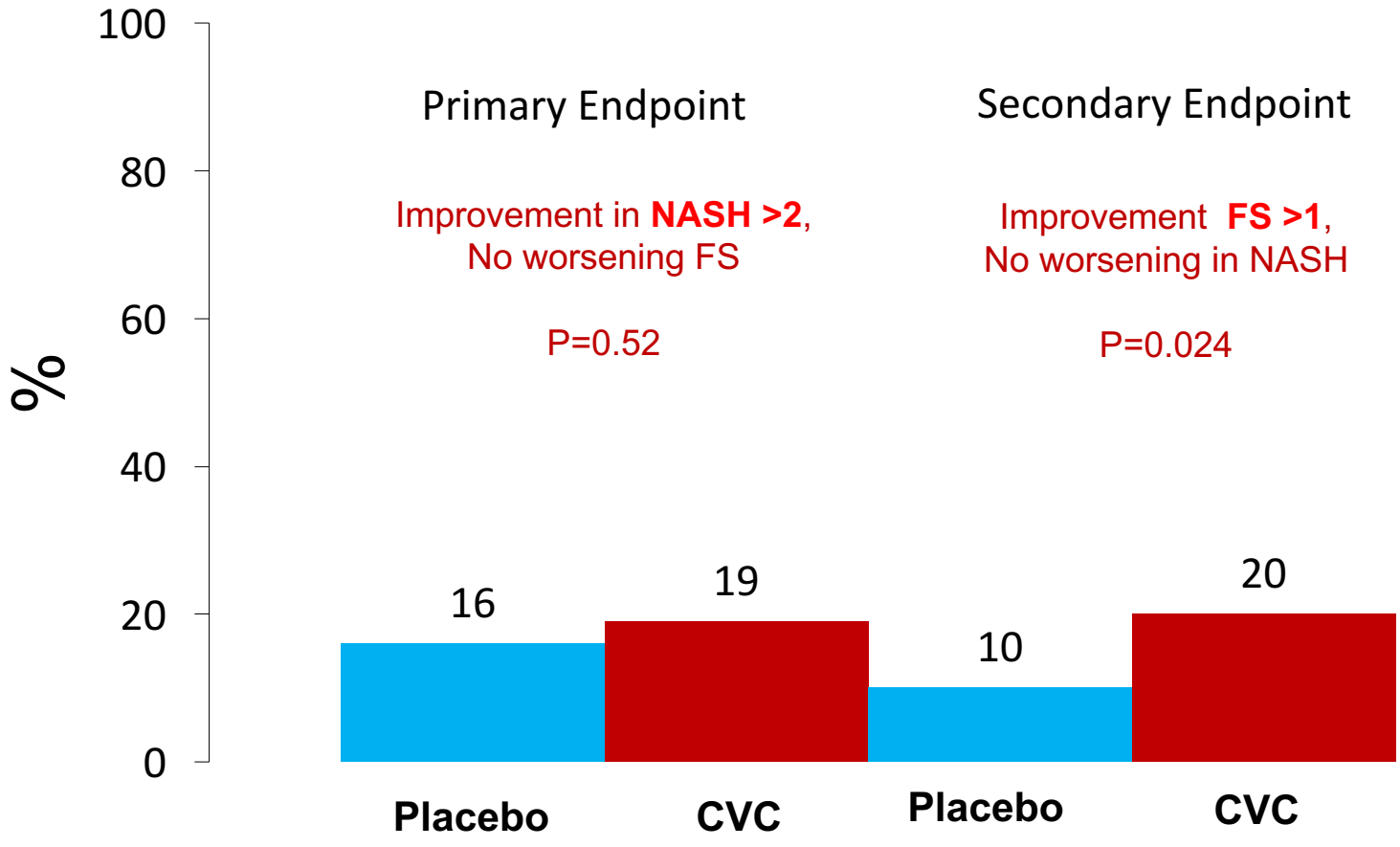

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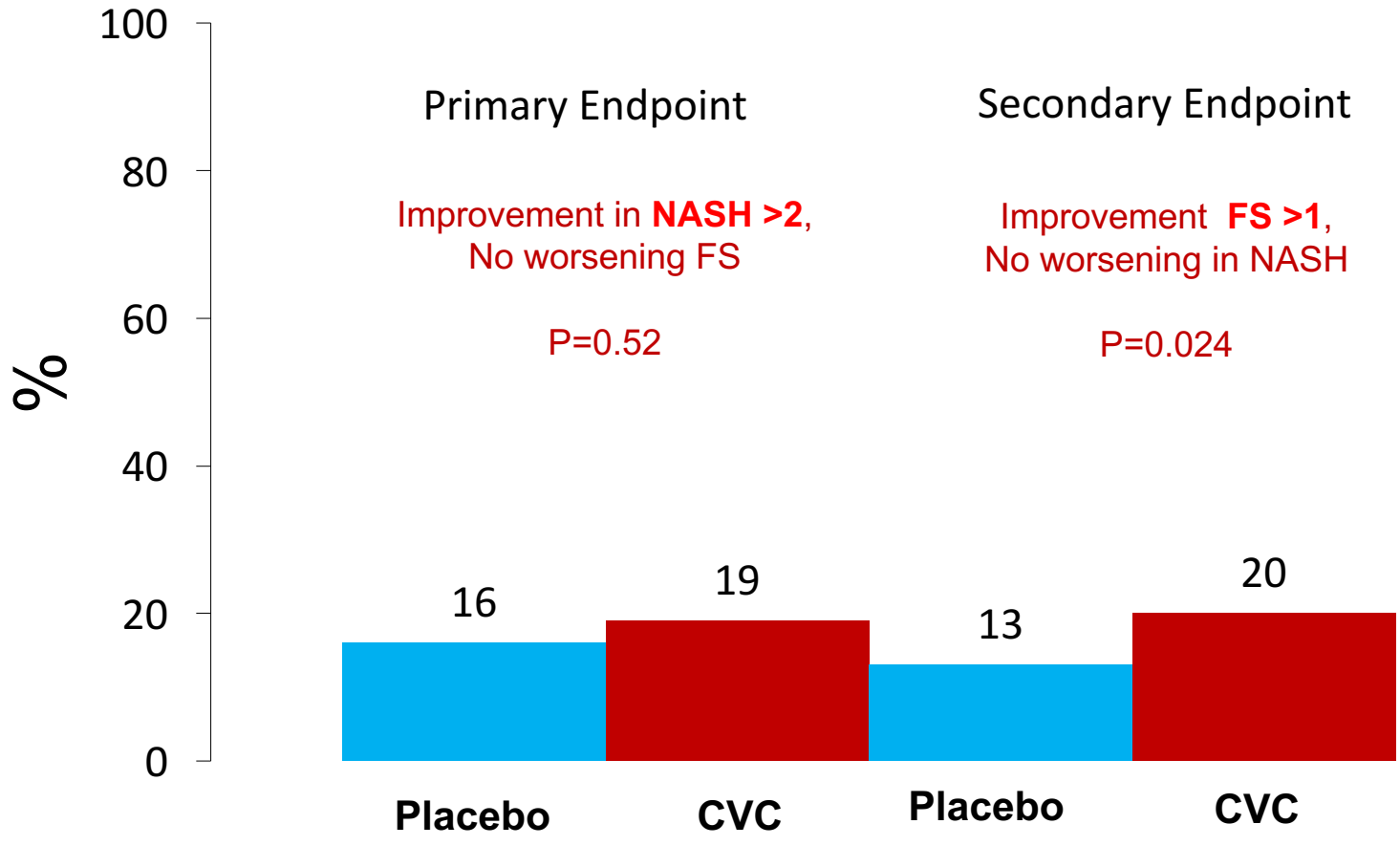
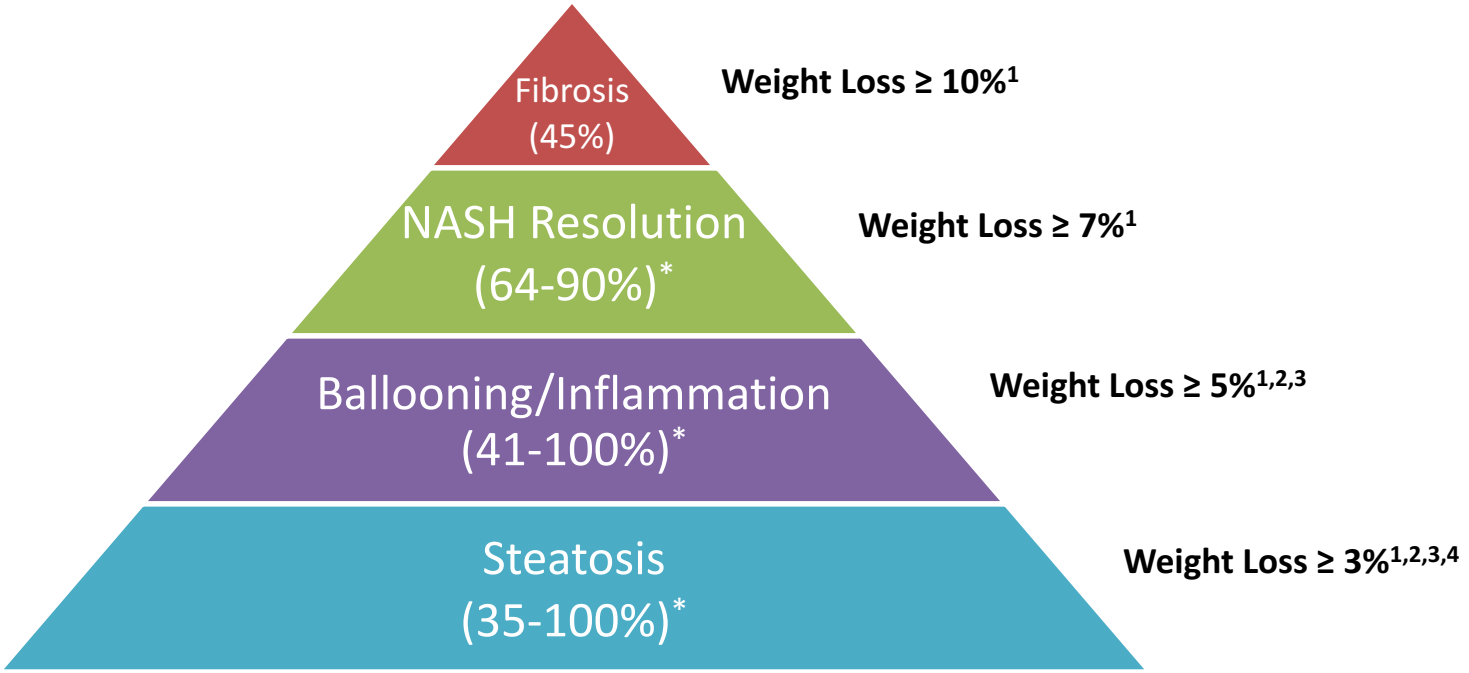


Sanyal et al., *AASLD* 2016.

So, what can I recommend now?

Weight Loss Pyramid



1 Vilar-Gomez. Gastroenterology 2015; 2 Promrat. Hepatology 2010; 3 Harrison. Hepatology 2009; 4 Wong. J Hepatol 2013, 5. Harrison. Hepatology 2015

*Depending on degree of weight loss

Weight Reduction in Fatty Liver Disease – It Doesn't Really Happen

- Seven trials, total of 373 patients

1 month to 1 year duration

No conclusive evidence of benefit

15% "success", most of these regain weight

Cochrane Database Syst Rev. 2011 Jun 15;(6):CD003619.

J Hepatol. 2012 Jan;56(1):255-66

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Non-Pharmacological

From: Coffee, Cirrhosis, and Transaminase Enzymes

Arch Intern Med. 2006;166(11):1190-1195.

Table 2. Adjusted* Relative Risk of Cirrhosis According to Whether an Individual Drinks Coffee or Tea

Coffee or Tea, Cups per Day	Subjects With Cirrhosis	
	Alcoholic	Nonalcoholic
Coffee		
Never or seldom	1.0	1.0
<1	0.7 (0.4-1.1)	1.2 (0.6-2.2)
1-3	0.6 (0.4-0.8)†	1.5 (1.0-2.1)
≥4	0.2 (0.1-0.4)†	0.7 (0.4-1.3)
Per cup of coffee per day‡	0.8 (0.7-0.9)†	0.9 (0.8-1.0)
Tea		
Never or seldom	1.0	1.0
<1	0.6 (0.4-1.0)§	1.0 (0.7-1.6)
≥1‖	1.0 (0.7-1.5)	1.1 (0.7-1.7)
Per cup of tea per day‡	0.9 (0.8-1.1)	1.0 (0.9-1.2)

*By Cox proportional hazards models adjusted for sex, race or ethnicity, smoking, alcohol use, education, and body mass index. Values in parentheses are 95% confidence intervals.

†$P<.001$.

‡Continuous with following values assigned: never or seldom = 0, less than 1 cup per day = 0.5, 1 to 3 cups per day = 2, 4 to 6 cups per day = 5, and more than 6 cups per day = 7.

§$P<.05$.

‖Number of subjects reporting drinking 1 or more cups of tea per day, 23 735.

N=125,580
F/U 22 yrs

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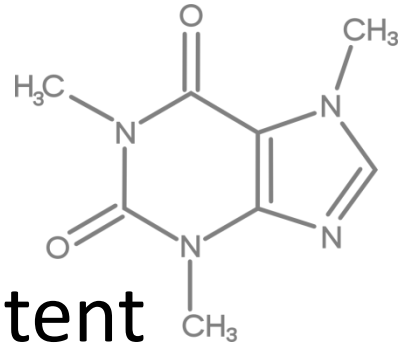
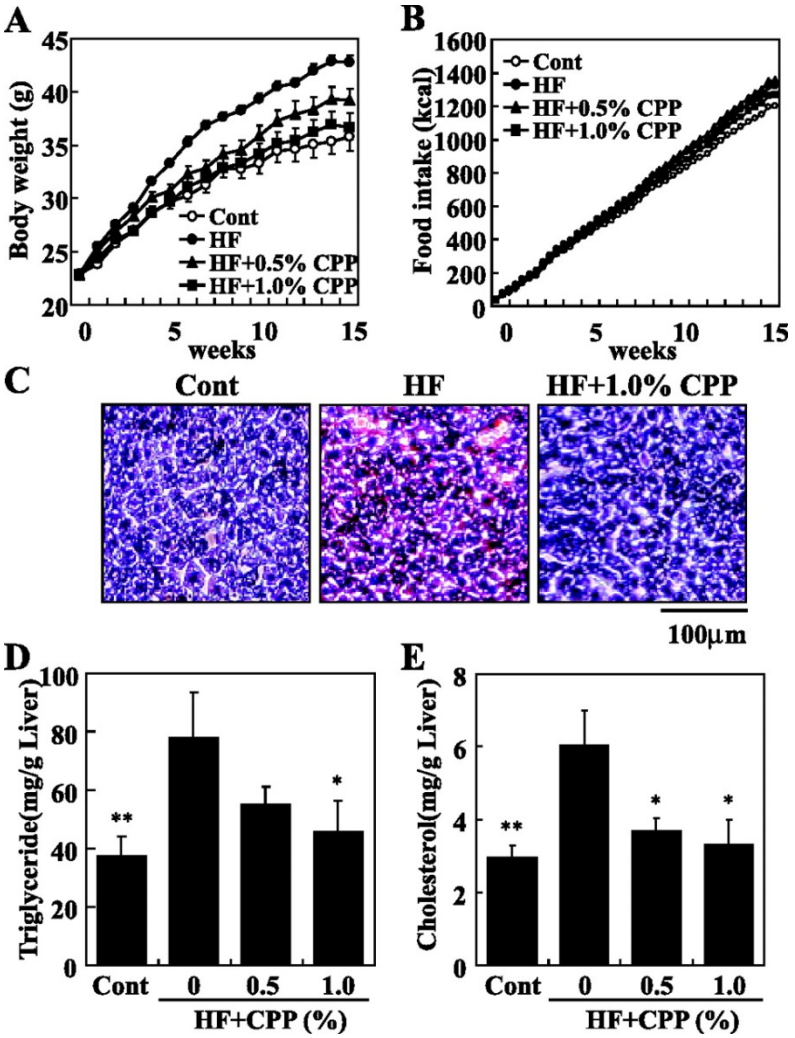
The 411 on Coffee



- Caffeine is ubiquitous and bean content highly variable.
  - Robusta = more, Arabica = less
  - Caffeine tastes bitter, deters insects
- Caffeine is toxic in all species (plant, insect and animal) other than humans.
- No other life form seeks it.

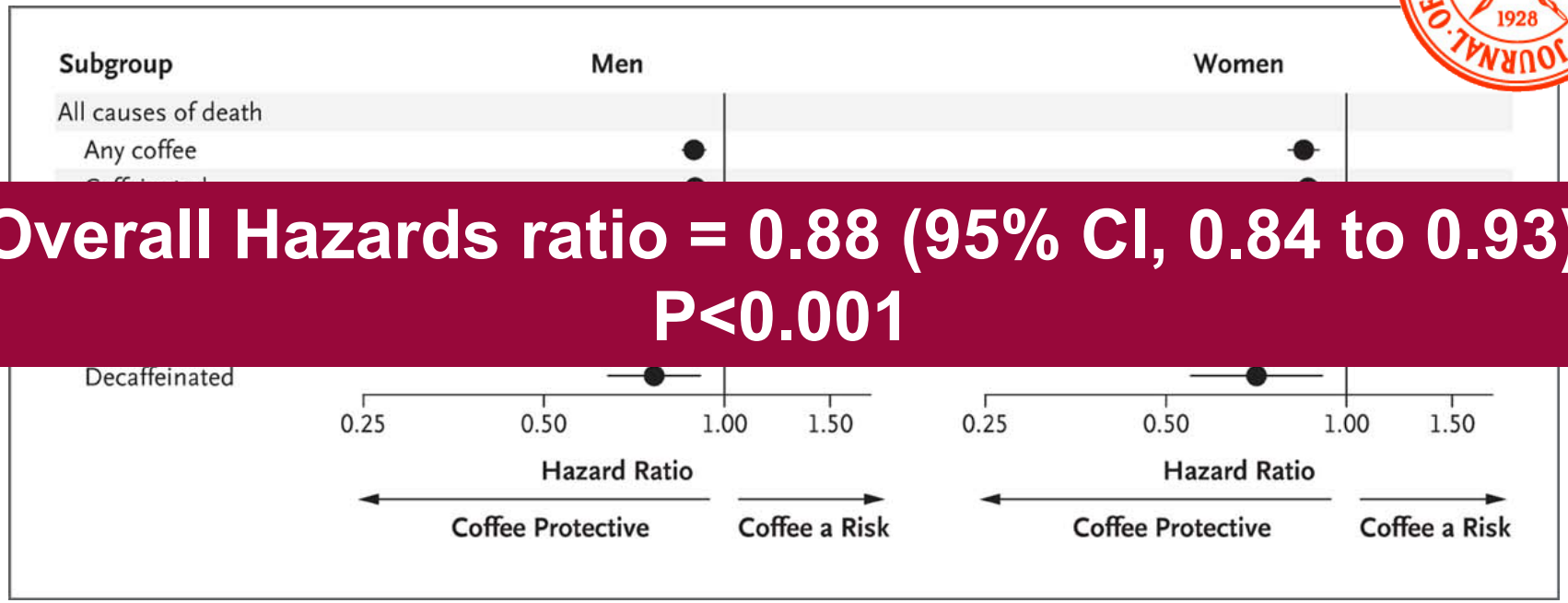
Effect of coffee polyphenols (CPP) on body fat accumulation.



Murase T et al. Am J Physiol Endocrinol Metab 2011;300:E122-E133

AMERICAN JOURNAL OF PHYSIOLOGY
Endocrinology and Metabolism

Associations between the Consumption of 4 or More Cups of Coffee per Day and Mortality



Overall Hazards ratio = 0.88 (95% CI, 0.84 to 0.93)
P<0.001

N=617,000 follow up 5,148,000 person years

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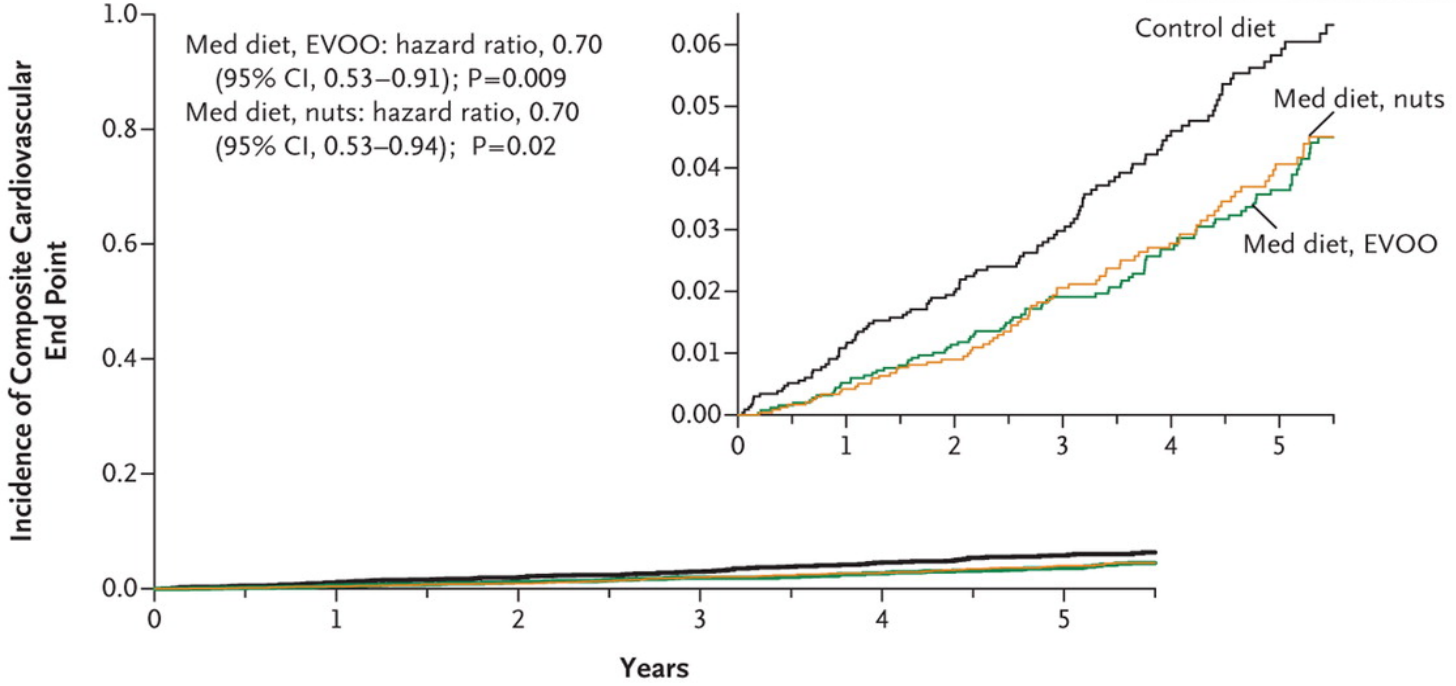
Impact of Olive Oil on Mortality, Stroke and MI

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

Estruch R et al. N Engl J Med 2013;368:1279-1290.

Olive Oil

Anti-inflammatory and immunomodulatory effects
- ***Oleic acid***

Anti-oxidants:
- ***Oleic acid***

Decrease lipid peroxidation
- ***Hydroxytyrosol, oleuropein, caffeic acid, vanillic acid, and 3,4- 3,4-DHPEA***

Decrease oxidative DNA damage
- ***Oleic acid***

Decreases arachidonic acid
- ***Protocatecuic acid***

Inhibits lipooxygenase
- ***Hydroxytyrosol***

Inhibits HMG-CoA reductase
- ***Squalene***

Decreases RAS activation
- ***Squalene***

Regulation of gene expression in liver regeneration:
- ***Oleic acid***

Olive Oil for NASH

A randomised controlled trial of a Mediterranean Dietary Intervention for Adults with Non Alcoholic Fatty Liver Disease (MEDINA)

94 patients with type 2 DM and NASH will be randomized into either a Mediterranean or low fat diet group for a 3 month intervention period.

Management of Fatty Liver Disease

- Lifestyle
  - Mediterranean diet –
    - Foods without labels
    - 60mls of extra virgin olive per day + nuts
    - Avoid animal fats, red meats
  - Exercise – 4,000 to 10,000 steps per day (give away pedometers)
  - Coffee >/=3 cups caffeinated, filtered

Management of Fatty Liver Disease

- Meds
  - Vitamin E ($\alpha\alpha\alpha$–tocopherol) 800 IU/day for 12 mos if fibrosing NASH
  - Metformin, glitazones, GLP-1 agonists only if otherwise indicated
  - If fibrosing NASH, consider referral to center participating in clinical trials
  - Don't stop statins or ACE inhibitors
  - Consider ASA
  - Council against herbal supplements

Management of Fatty Liver Disease

- Follow up
  - Weight Watchers
  - Nutritionist
  - Q6 monthly CBC and chemistry group
  - Consider re-imaging in 3 years
  - BMI consistently >40kg/m2 with metabolic syndrome, consider referral to bariatric surgery, sleeve better than roux-en-y?

Thank you!