UPDATES ON NON-ALCOHOLIC FATTY LIVER DISEASE

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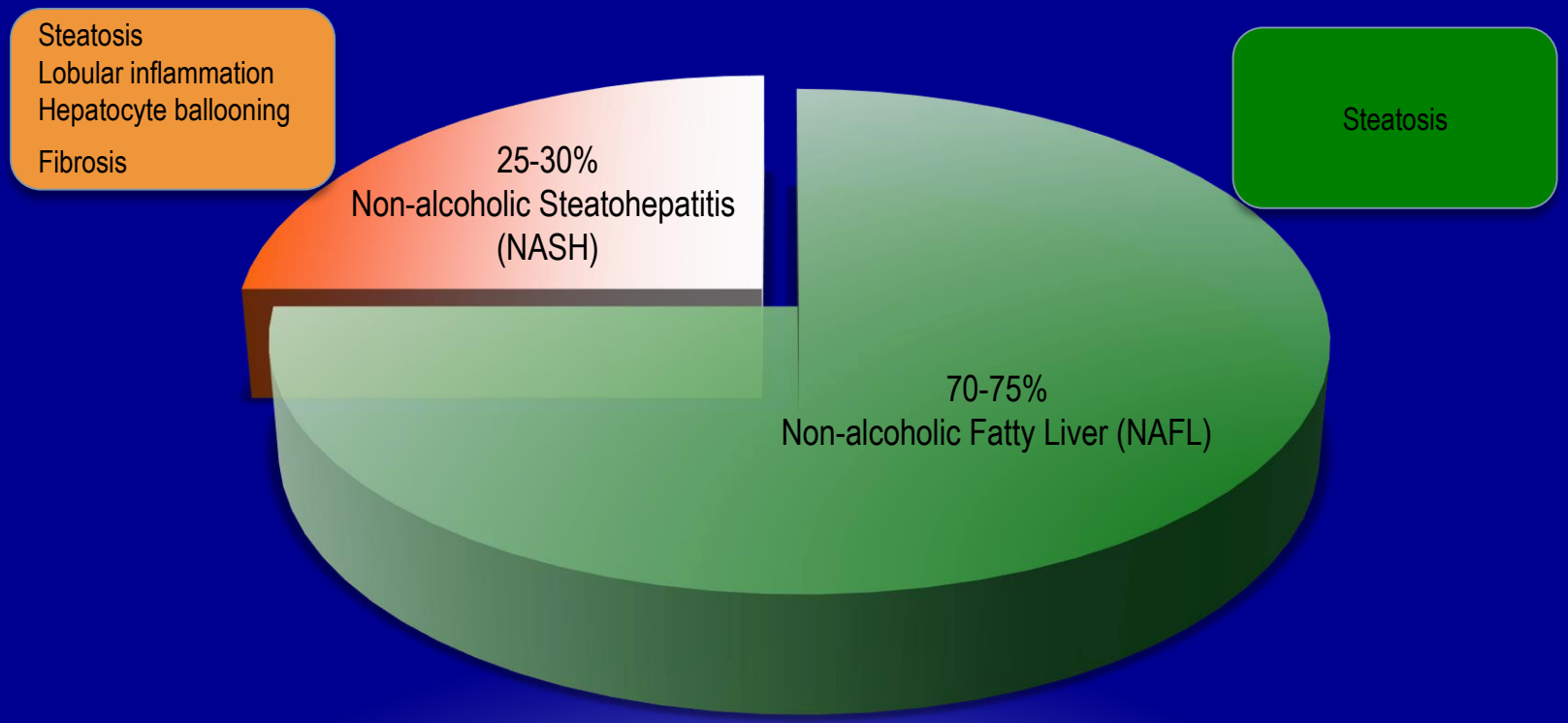
DISCLOSURE

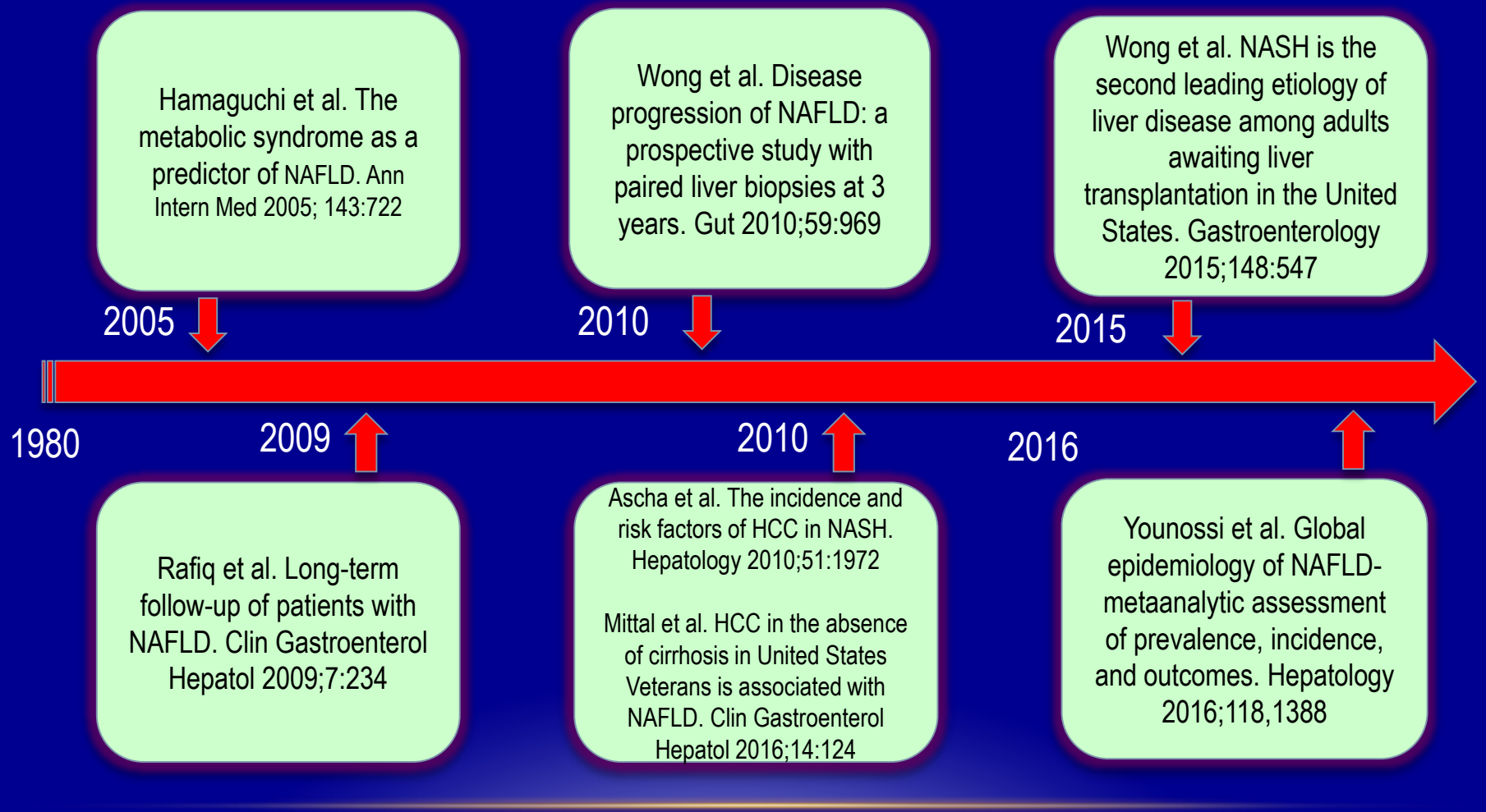
- None

Non-alcoholic Fatty Liver Disease (NAFLD)



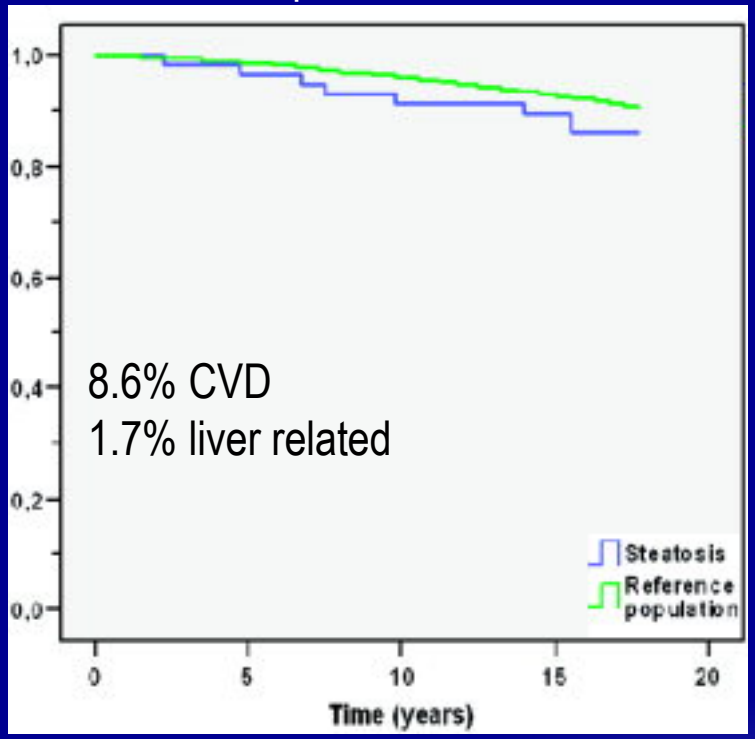
Rinella ME, et al.JAMA 2015;313:2263-73

EVOLVING KNOWLEDGE ON NAFLD

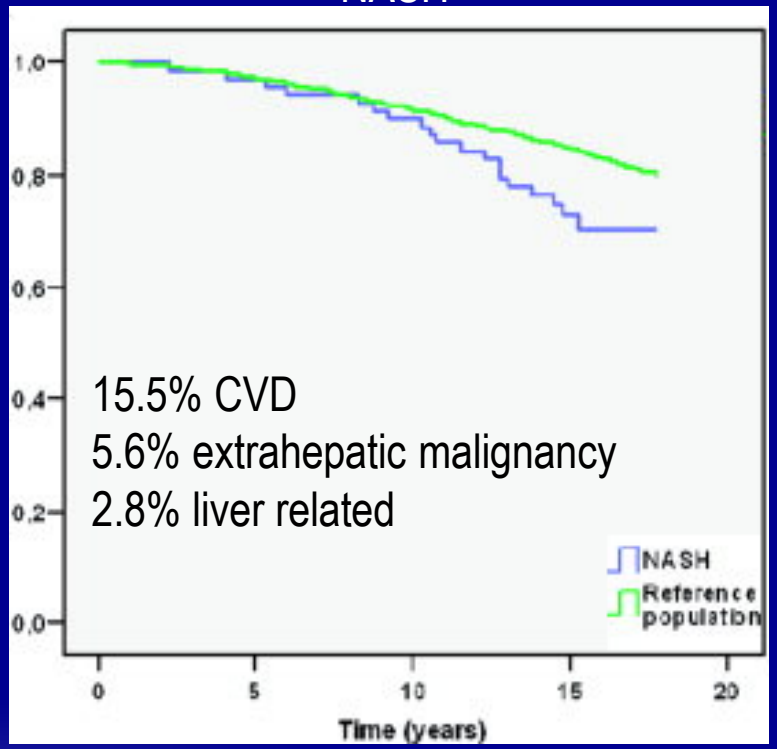


MORTALITY RISK RELATED TO **NASH**

Isolated hepatic steatosis

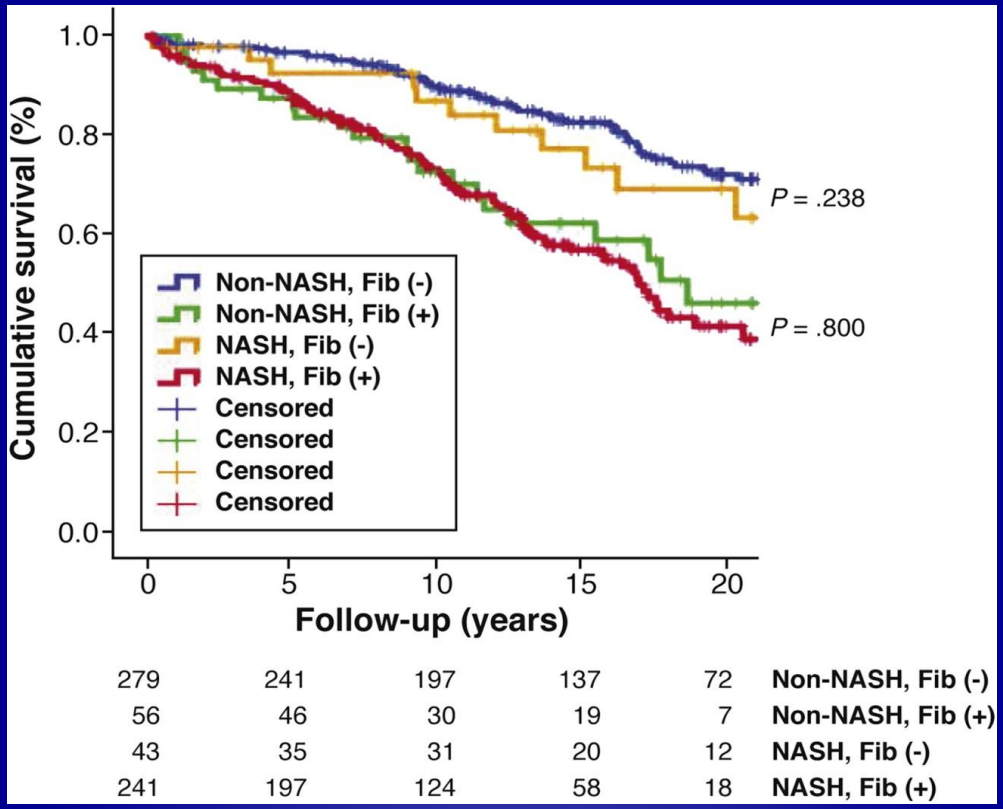


NASH



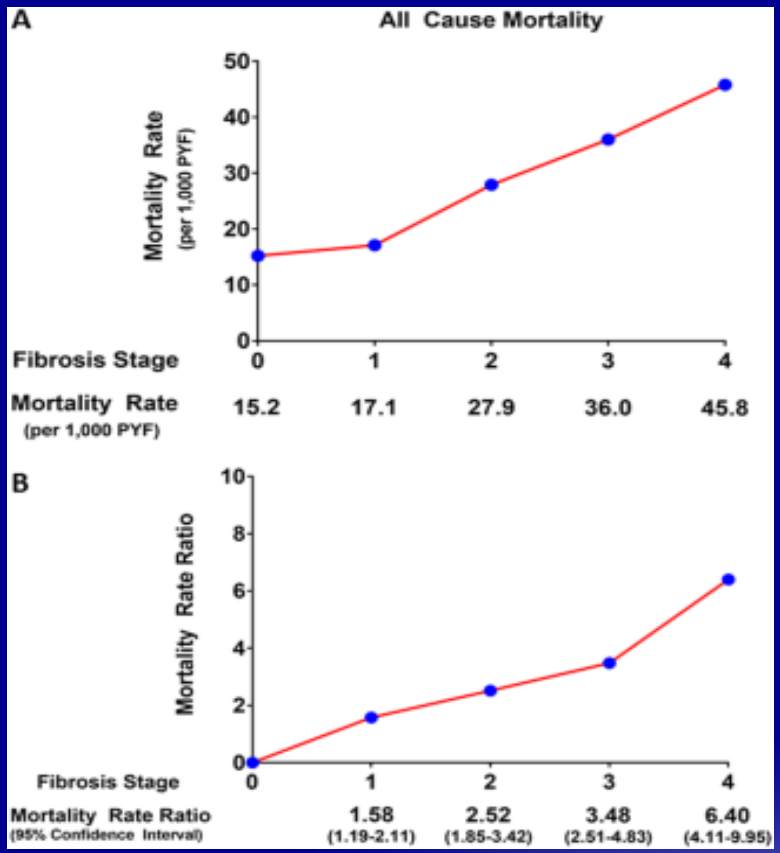
Ekstedt M, etl al. Hepatology 2006;44:865-873

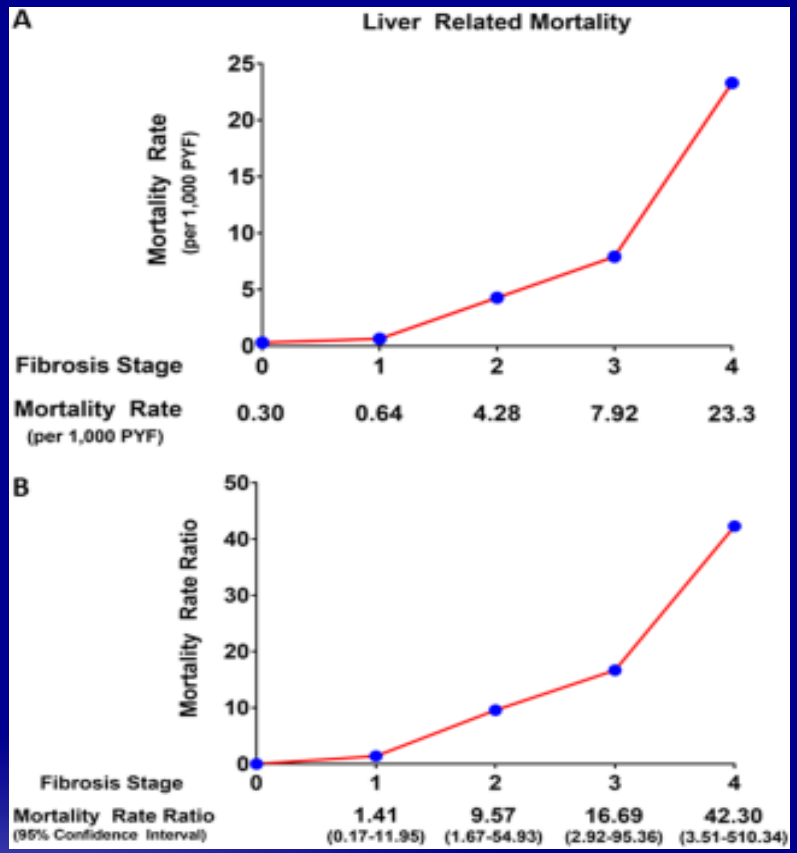
FIBROSIS IS THE ONLY HISTOLOGICAL FEATURE ASSOCIATES WITH LONG TERM OUTCOMES



Angulo P, et al. Gastroenterology 2015;149:389

FIBROSIS STAGE CORRELATES WITH ALL-CAUSE MORTALITY



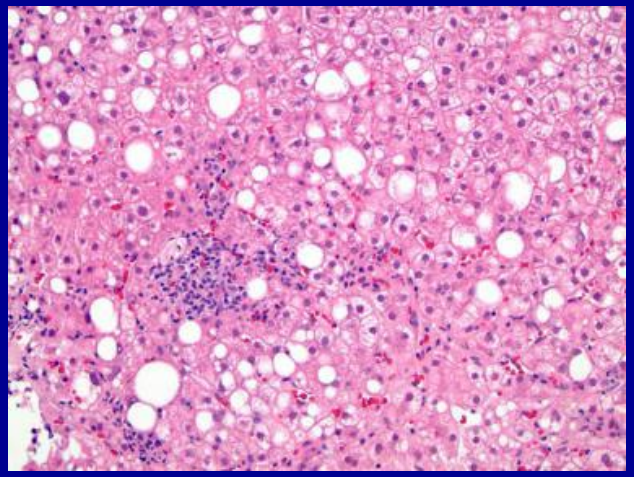


Dulai PS, et al. Hepatology 2017;65:1557-1565

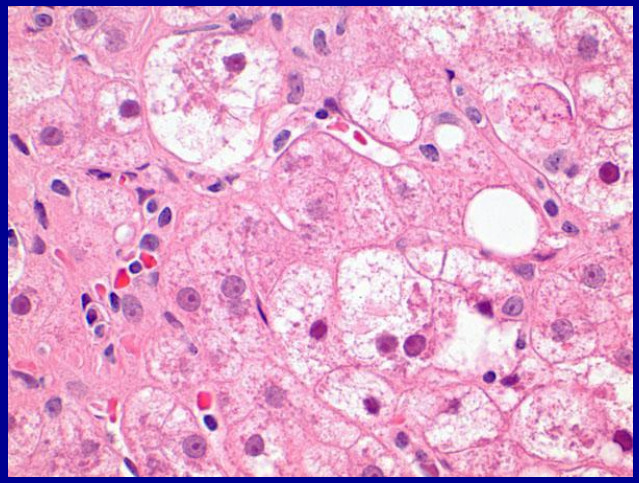
NAFLD

- Whether the patient have NAFLD?
- Whether the patient have NASH?
- Whether the patient have any fibrosis or advanced fibrosis?

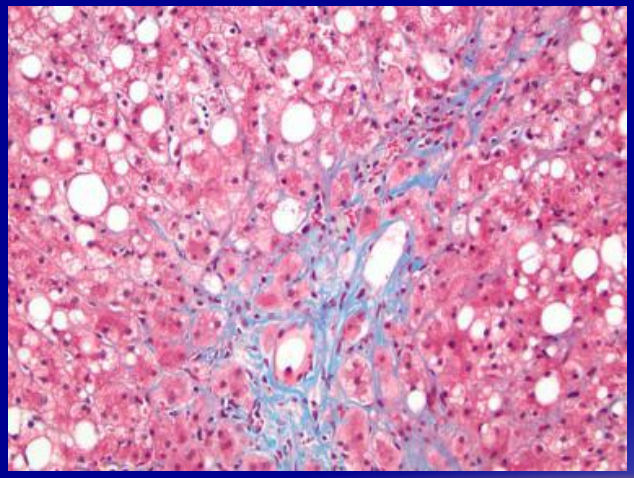
LIVER BIOPSY



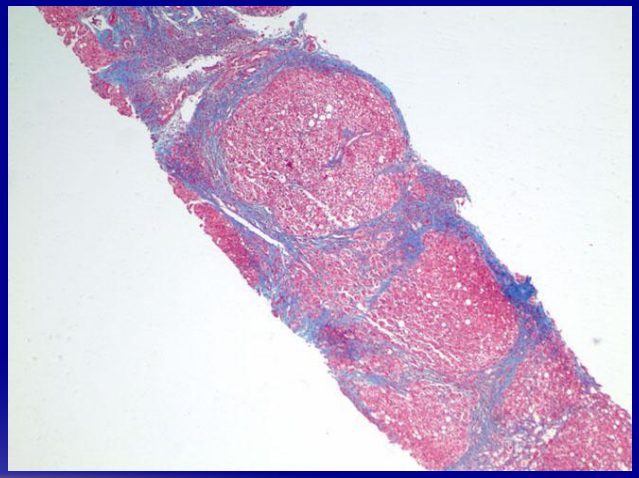
Macrovesicular steatosis
Lobular inflammation



Hepatocyte ballooning
Mallory-Denk body



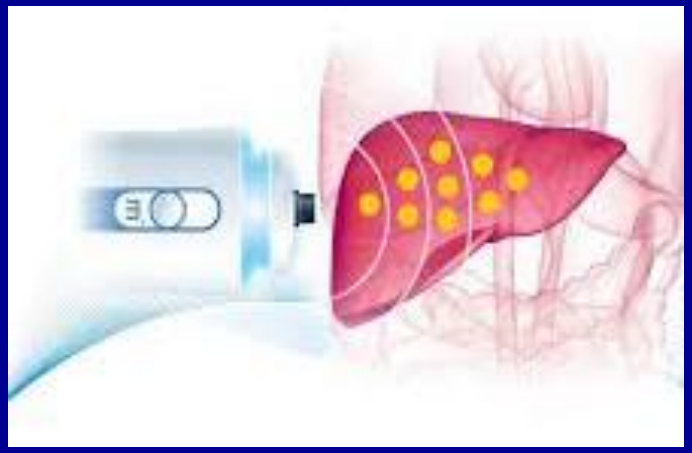
Perivenular/pericellular
(chicken wire) fibrosis



cirrhosis

Yeh MM. http://emedicine.medscape.com/article/2038493-overview

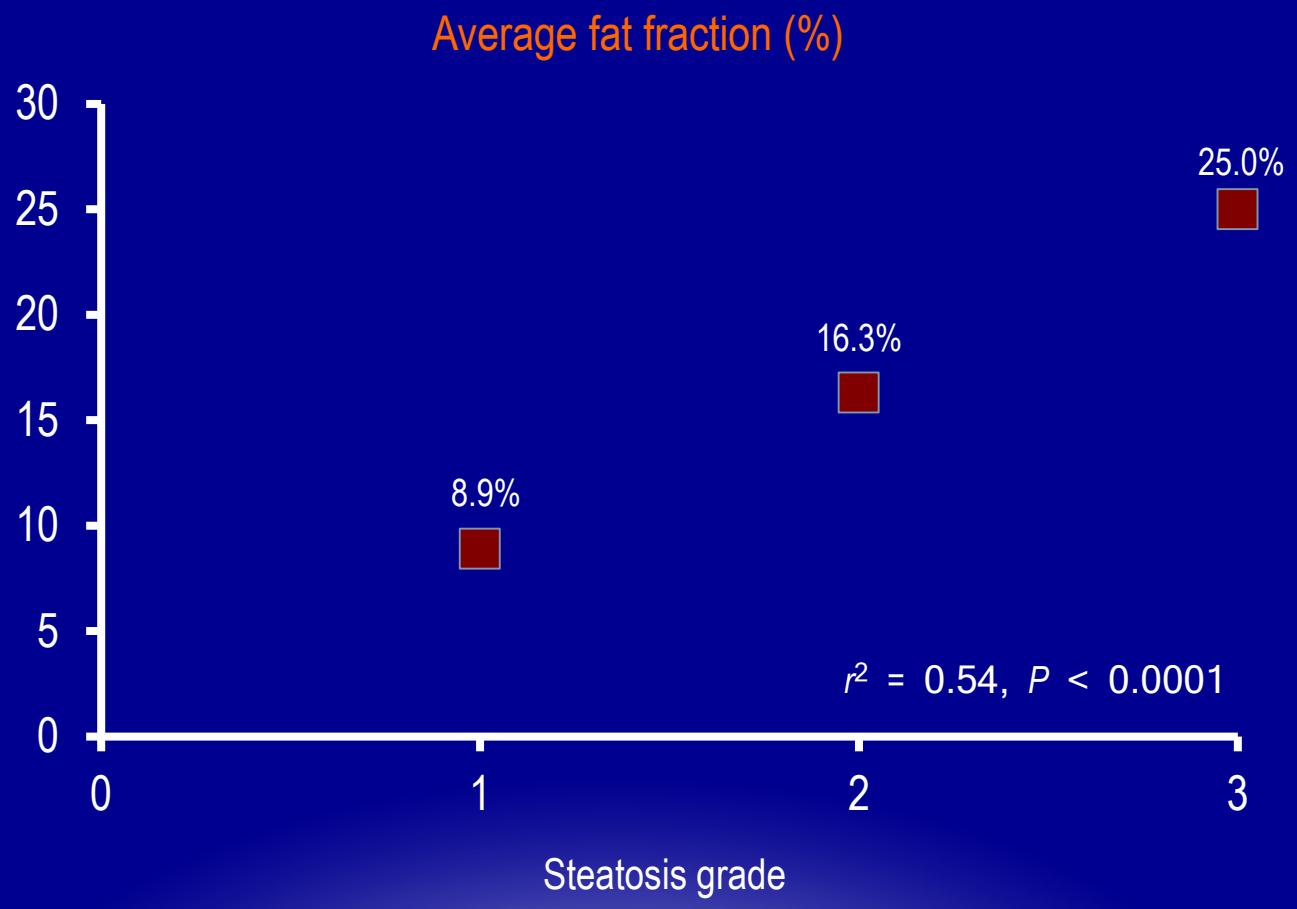
DIAGNOSIS OF NAFLD
- Controlled Attenuation Parameter (CAP)



CAP	Cut-off 222 dB/m	Cut-off 290 dB/m
Sensitivity (%)	94.2	72.5
Specificity (%)	51.5	89.7
PPV (%)	**85.5**	**95.5**
NPV (%)	74.5	51.7

Wong V, et al J Hepatol 2017;67:577

MRI-Proton Density Fat Fraction (MRI-PDFF)



Permutt Z, et al. Aliment Pharmacol Ther 2012;36:22.

Comparison between commonly used modalities for liver fat quantification

Modality	Cost	Accuracy	Point of care	Quantitative	Caveats
CUS	+	++	Yes	No	May fail in obesity and in iron overload and cirrhosis
CT	++	++	No	Semi-quantitative	Ionising radiation
CAP	+	++	Yes	Yes, but not linear in higher liver fat content	Affected by type of probe and fibrosis
MRI-PDFF	++	++	No	Yes	Not suitable for screening

Loomba R. J Hepatol 2018;68:296

DIAGNOSIS OF NASH

- Normal values ALT: men 29-33, women 19-25
- ALT < 250 usually
- ALT > AST
- ALT falls as fibrosis progresses to cirrhosis
- ALT value does not correlate with histological findings
- 40-60% patients normal range ALT

Mofrad P, et al. Hepatology 2003;37:1286-92
Rinella ME.JAMA 2015;313:2263-73

10 THE RED SECTION

nature publishing group

Nonalcoholic Fatty Liver Disease is Underrecognized in the Primary Care Setting

Pierre Blais, MD[1], Nisreen Husain, MD[1,2], Jennifer R. Kramer, MPH, PhD[3,4], Marc Kowalkowski[3,4], Hashem El-Serag, MD, MPH[1–3] and Fasiha Kanwal, MD, MSHS[1–3]

Am J Gastroenterol 2015;110:10-14

DIAGNOSIS OF FIBROSIS

- Thrombocytopenia
- AST > ALT
- NAFLD fibrosis score, Fibrosis-4 (FIB-4), APRI
- Fibrosure/FibroTest/FibroSpect

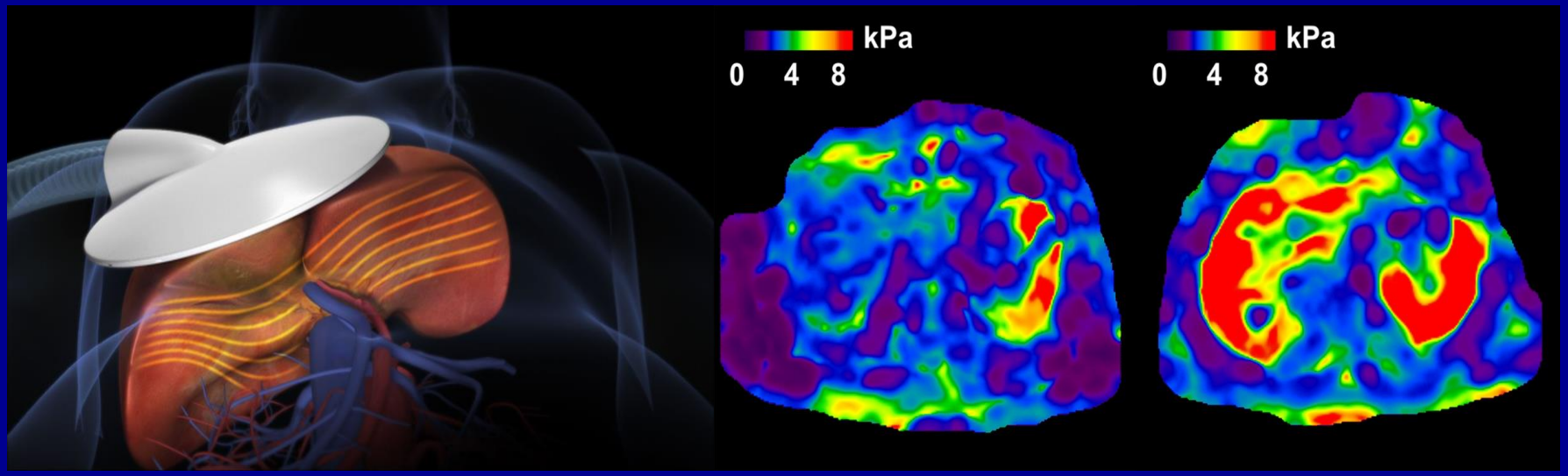
Mofrad P, et al. Hepatology 2003;37:1286-92
Rinella ME.JAMA 2015;313:2263-73

Vibration Controlled Transient Elastography (VCTE) – FibroScan®

VCTE Cutoff	NPV	PPV	Sensitivity	Specificity
7.6kPa	**92.5%**	43.2%	84.2%	63.8%
14.6kPa	**96.8%**	64.3%	81.8%	92.4%

Chen J, et al. Radiology 2017;283:418

MR Elastography (MRE)



MRE cutoff	NPV	PPV	Sensitivity	Specificity
3.60kPa	**94.1%**	61.5%	84.2%	82.8%
4.52kPa	**96.8%**	60.0%	81.8%	90.9%

Chen J, et al. Radiology 2017;283:418

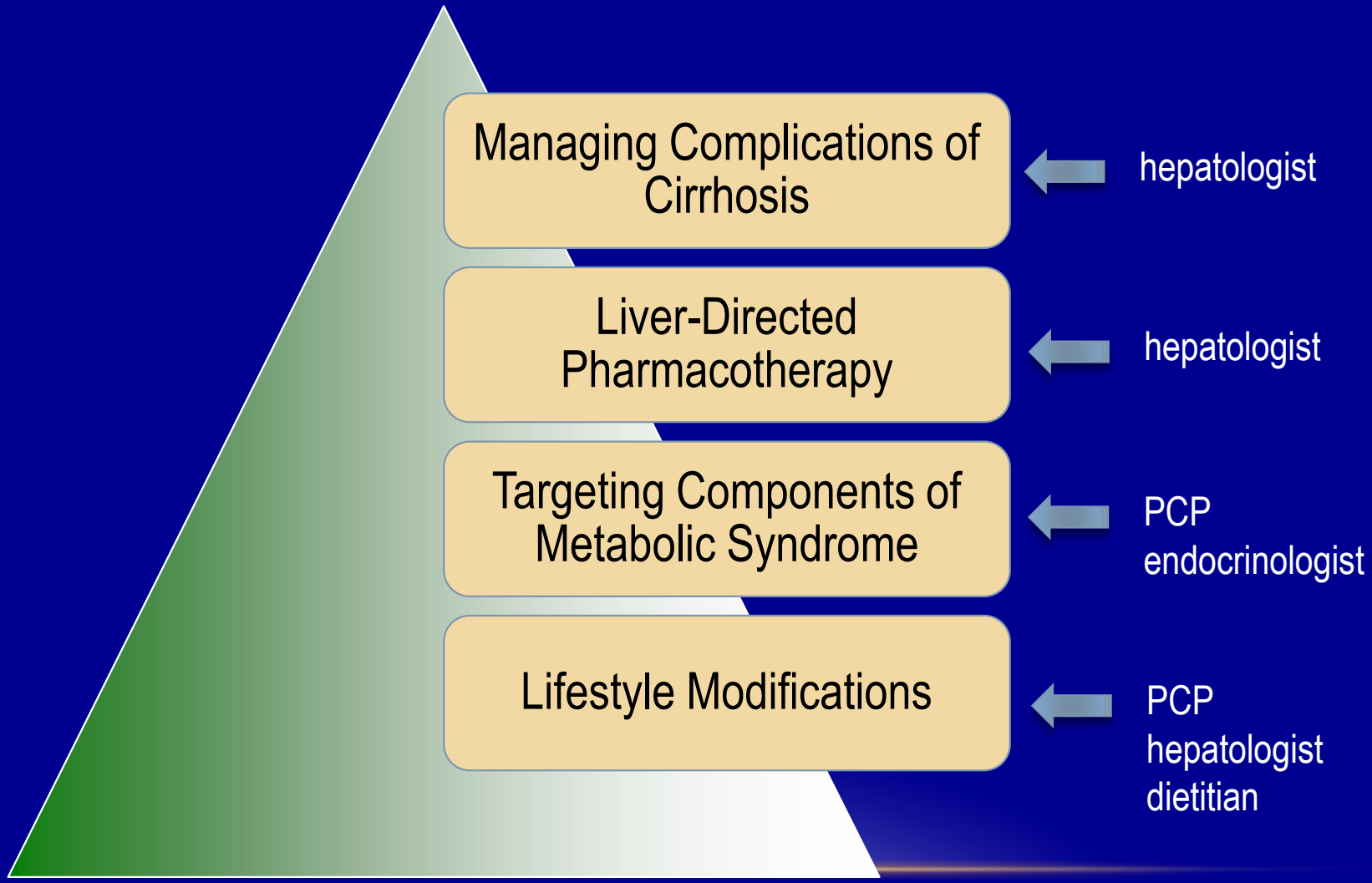
Comparison between commonly used modalities for fibrosis

Modality	Cost	Accuracy	Point of care	Quality criteria	Caveats
VCTE	+	++	Yes	standardized	Increased variability in morbid obesity and cirrhosis
ARFI/SWE	+	++	Can be	Not yet	Increased variability in morbid obesity and cirrhosis
MRE	++	+++	No	Not yet	Excellent accuracy in obesity and cirrhosis May fail in the setting of iron overload

Loomba R. J Hepatol 2018;68:296

UPDATES ON TREATMENT FOR NASH

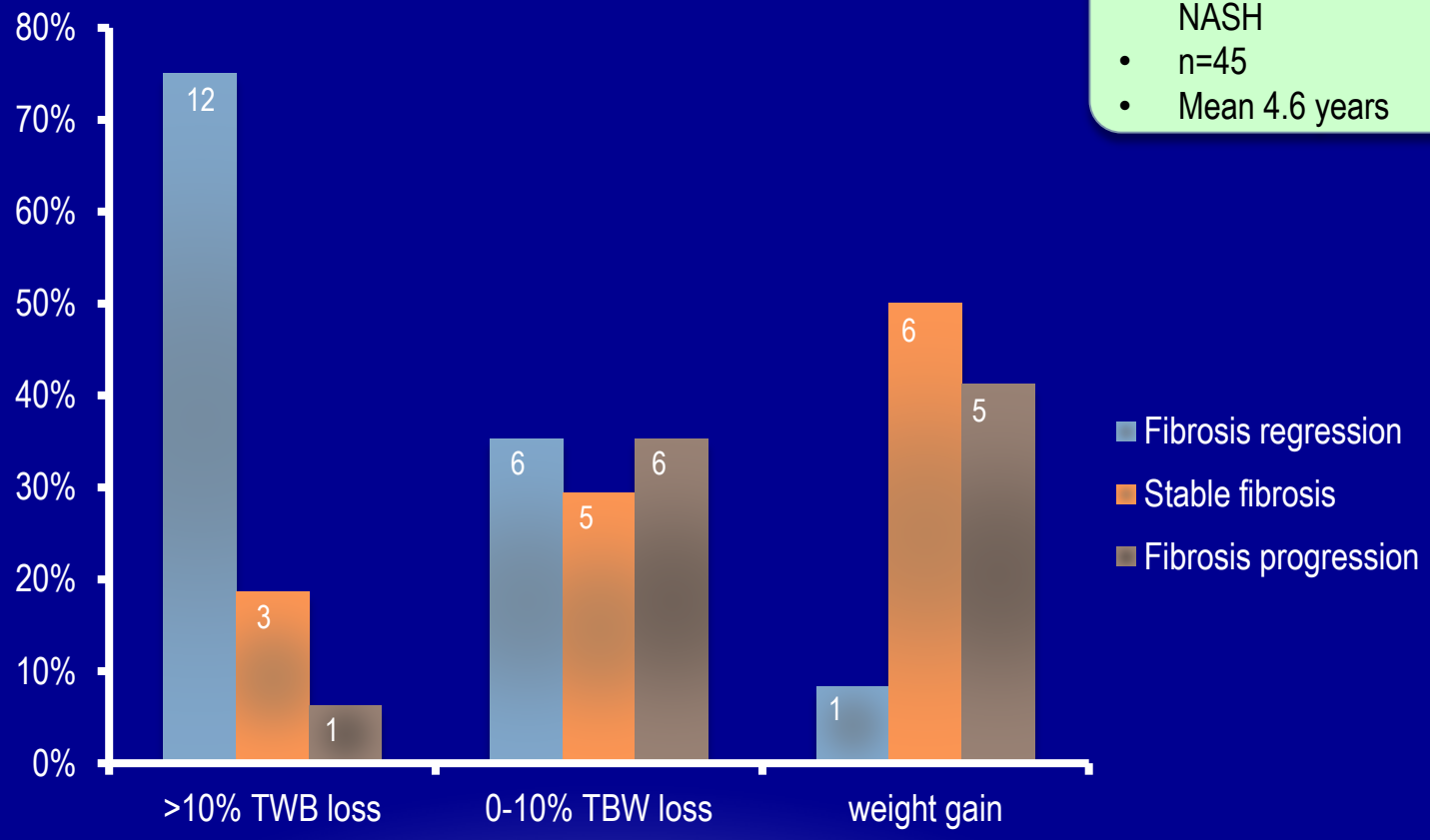
MANAGEMENT OF NAFLD



Dyson JK, et al. Frontline Gastroenterol 2014;5:277-86

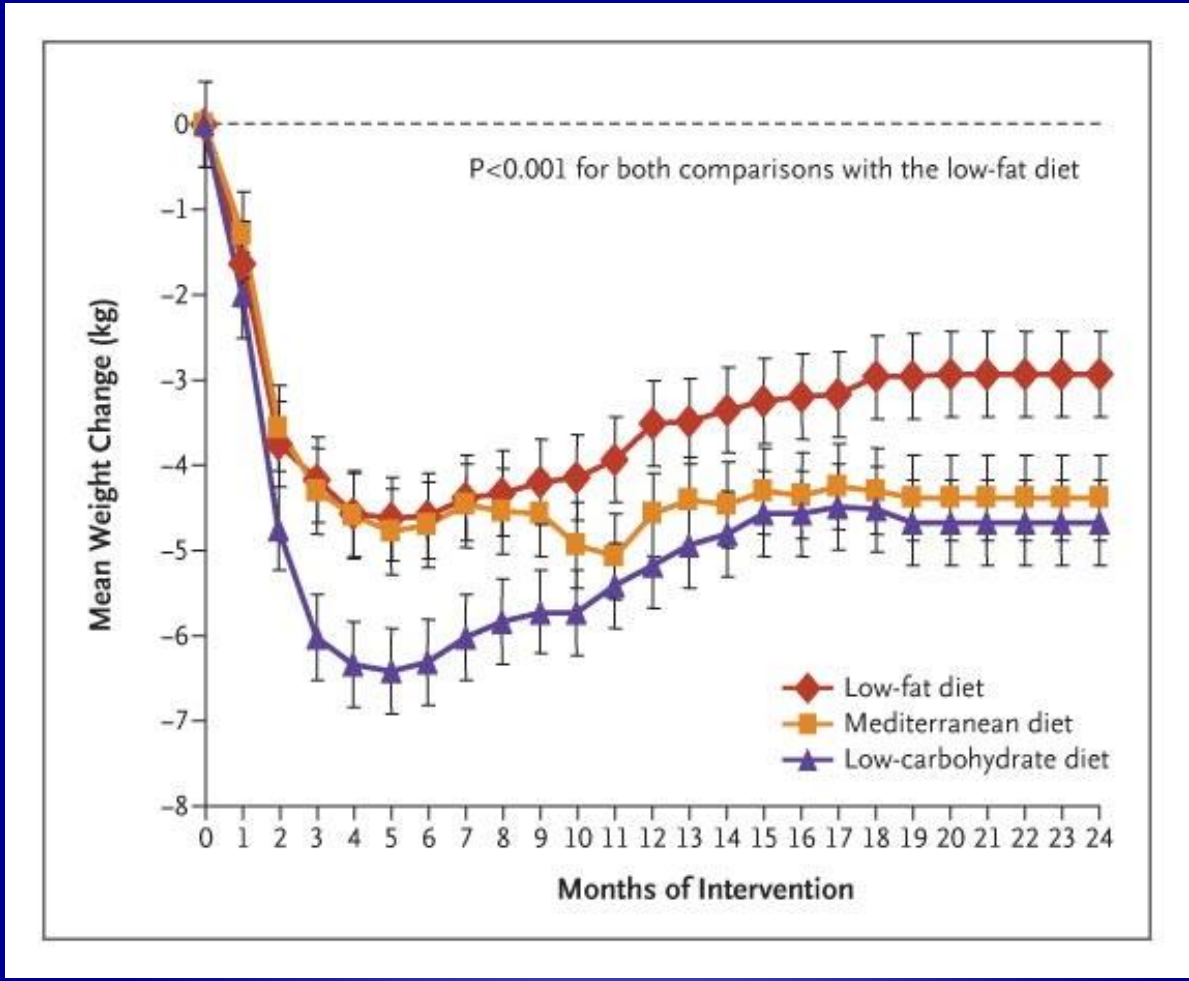
Weight Loss Improves NASH

- Biopsy proven NASH
- n=45
- Mean 4.6 years



Glass L, et al. Dig Dis Sci 2015;60:1024

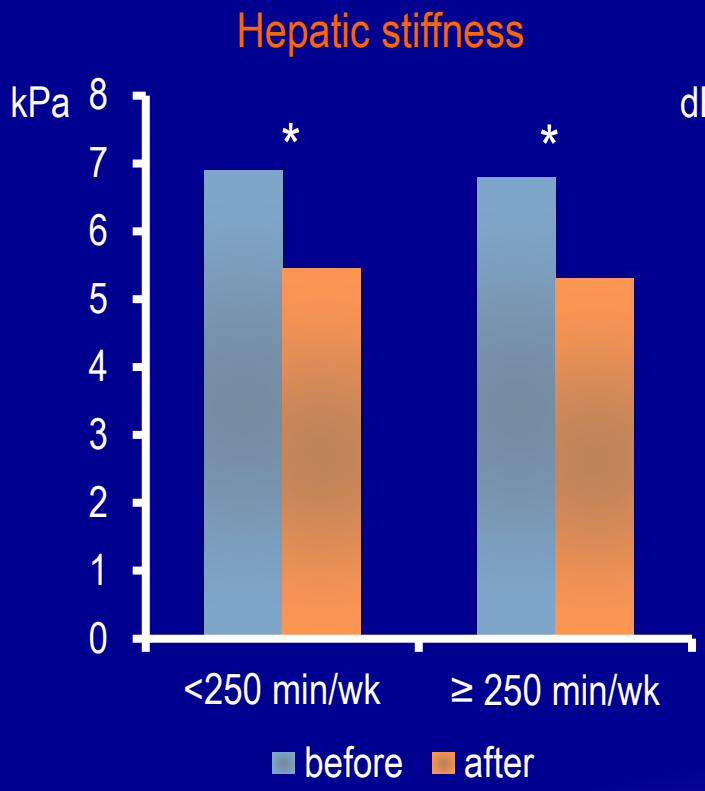
Weigh Loss With A Low-carbohydrate, Mediterranean, Or Low-fat Diet

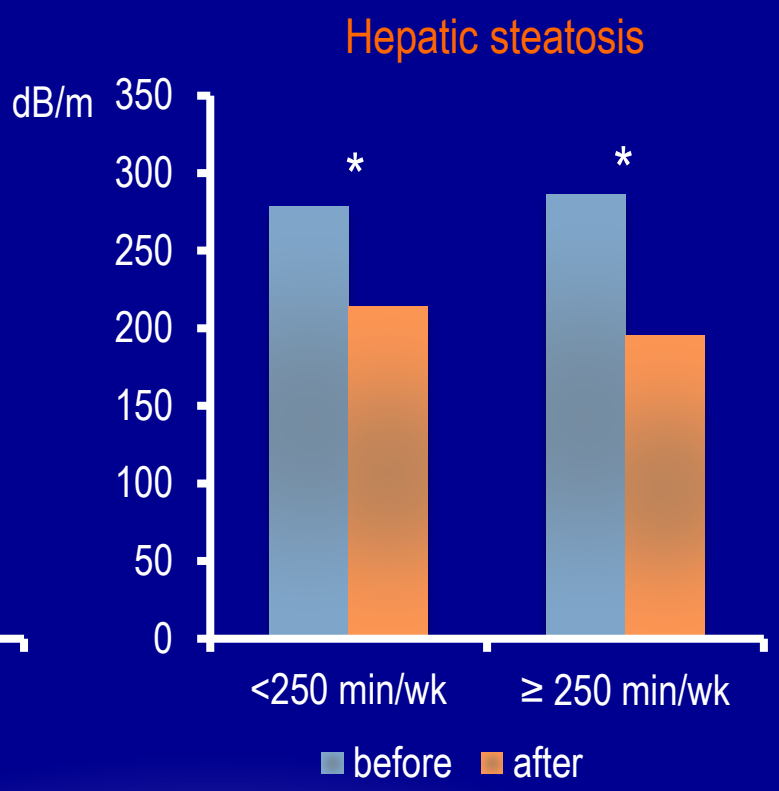


- n=322
- 86% male
- obese

Shai I, et al. NEJM 2008;359:229-241

Role Of Exercise In NASH



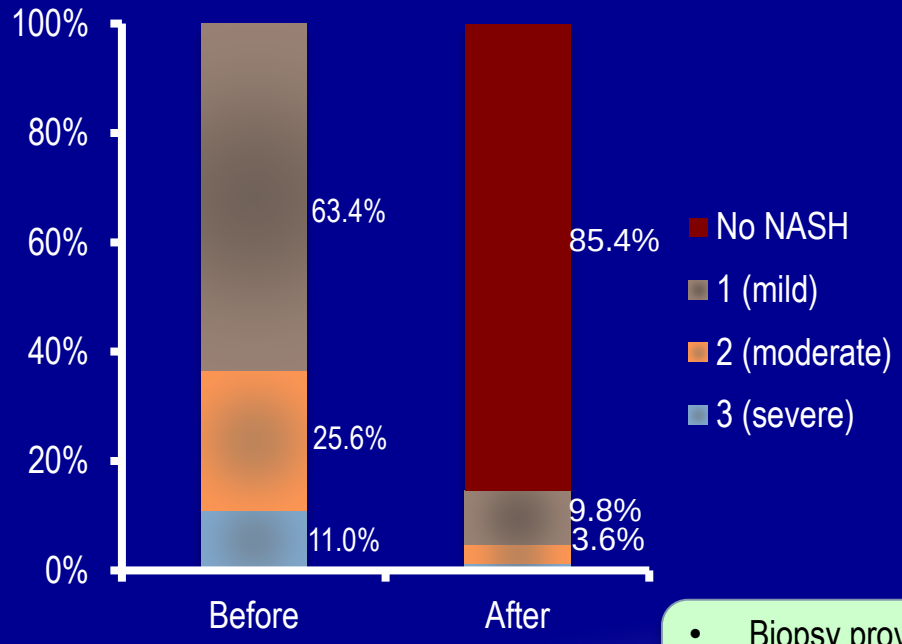


- n=169
- Obese men
- 12 weeks weight reduction with dietary + aerobic exercise

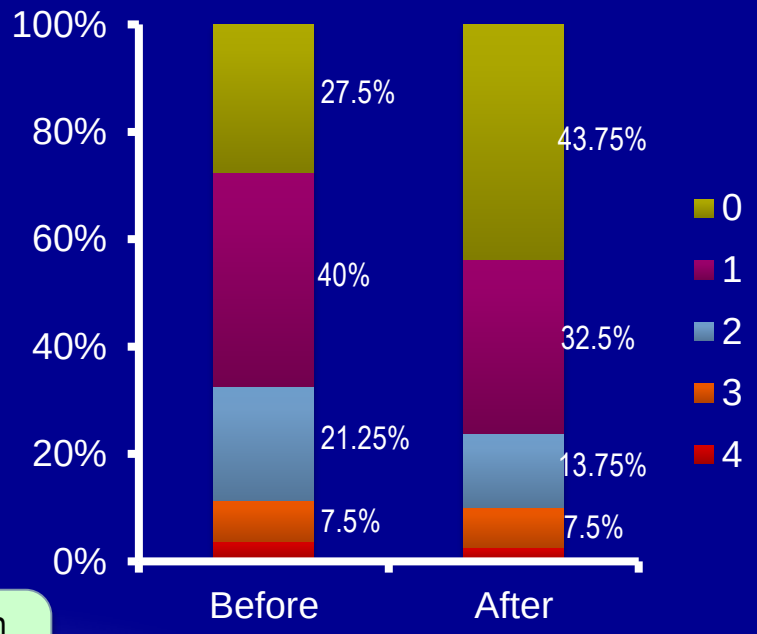
Oh S, et al. Hepatology 2014;61:1205

Role Of Surgery In Subjects With NASH And Obesity

Distribution of NASH inflammatory activity grade before and 1 year after surgery



Distribution of fibrosis stage before and 1 year after surgery



- Biopsy proven NASH
- n=109

Lassailly G, et al. Gastroenterology 2015;149:379

Liver Directed Pharmacotherapy

- Metformin
- Pioglitazone
- Vitamin E
- Pentoxifyline
- Ursodeoxycholic acid
- Omega-3 fatty acids
- Statins
- Ezetimibe
- Aramchol
- Liraglutide
- Sitagliptin

NO medications are currently FDA-approved for NASH!

PIOGLITAZONE

PIVENS trial (NEJM 2010;362:1675-1685)

- Non-DM, biopsy-proven NASH, 30mg/d, 96 weeks, n=247, 3 groups (pio, vit E, placebo)
- Significance in reduction of AST, ALT
- NS in NASH histology (34% vs. 19%) and fibrosis
- Comparable adverse events except weight gain (4.7kg vs. placebo)

Pioglitazone trial (Ann Intern Med 2016;165:305-315)

- Pre-DM or T2DM, biopsy-proven NASH, hypocaloric (500kcal/d deficit) 45mg/d,18mon, 2 groups (pio, placebo)
- Significance in NASH histology (51% vs. 19%) including fibrosis
- Comparable adverse events except weight gain (2.5kg vs. placebo)

Side effects: Weight gain, fracture, CHF, bladder cancer

VITAMIN E

PIVENS trial (NEJM 2010;362:1675-1685)

- Non-DM, biopsy-proven NASH, 800IU, 96 weeks, n=247, 3 groups (pio,vit E, placebo)
- Significance in NASH histology (43% vs. 19%)
- Significance in reduction of AST, ALT
- NS in fibrosis

TONIC Trial (Hepatology 2012;55:1292-1295)

- Age 8-17years, non-DM, Biopsy-proven NASH, 800IU, 96 weeks, n=173, 3 groups (vit E, metformin, placebo)
- NS in reduction in ALT (26% vs. 17%)
- Significance in resolution of NASH (58% vs. 28%)
- NS in fibrosis

Side effects: ? prostate cancer, ? All cause mortality, hemorrhagic stroke

STATIN

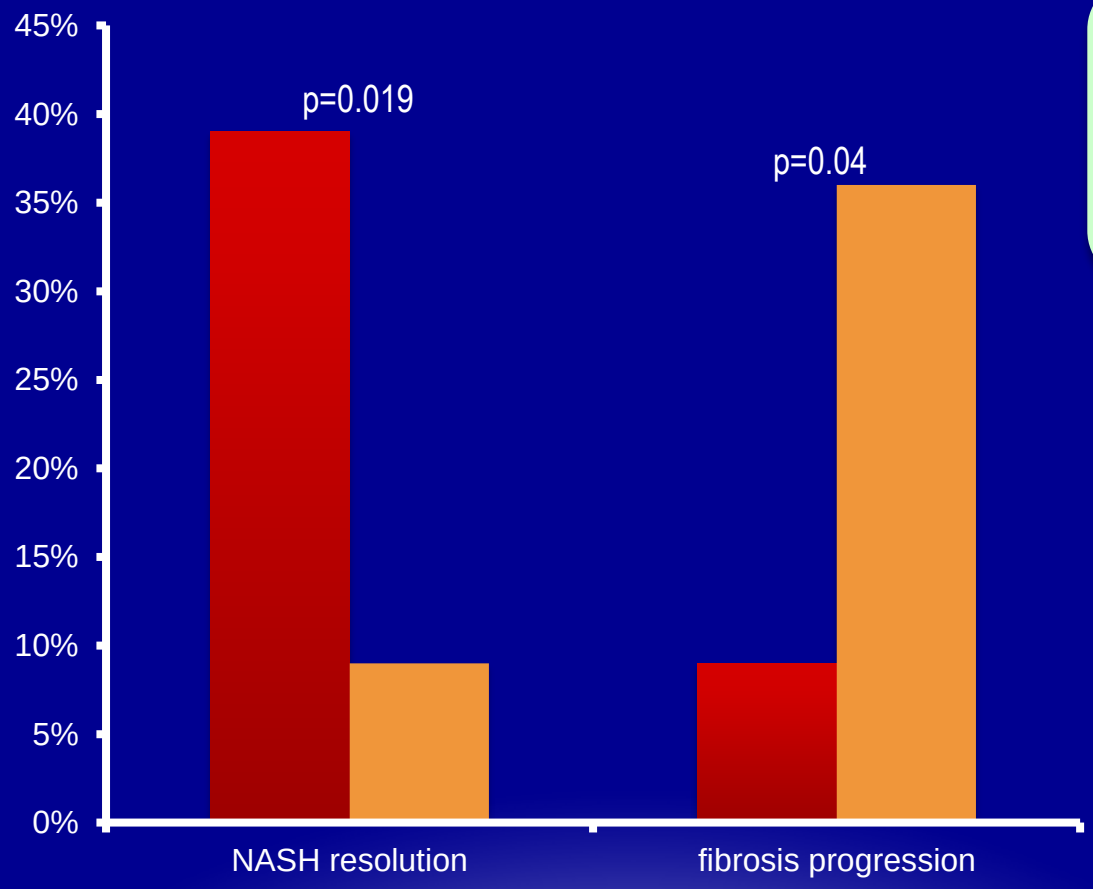
GREACE study (Lancet 2010;376:1916-22)

- Prospective ITT study
- n=437 with elevated ALT/AST, statin use n=227
- Significance in reduction of CV events (10% vs. 30%)
- Significance in reduction of ALT, AST
- <1% discontinued statin due to liver-related adverse effect

Statin in NASH (J Hepatol 2015;63:705-712)

- Biopsy proven NASH, a cohort of 1201 European, n=100 with 1:1 matching
- Significant protection from steatosis (OR 0.09), steatohepatitis (OR 0.25), fibrosis F2-4 (OR 0.42) in a dose dependent manner

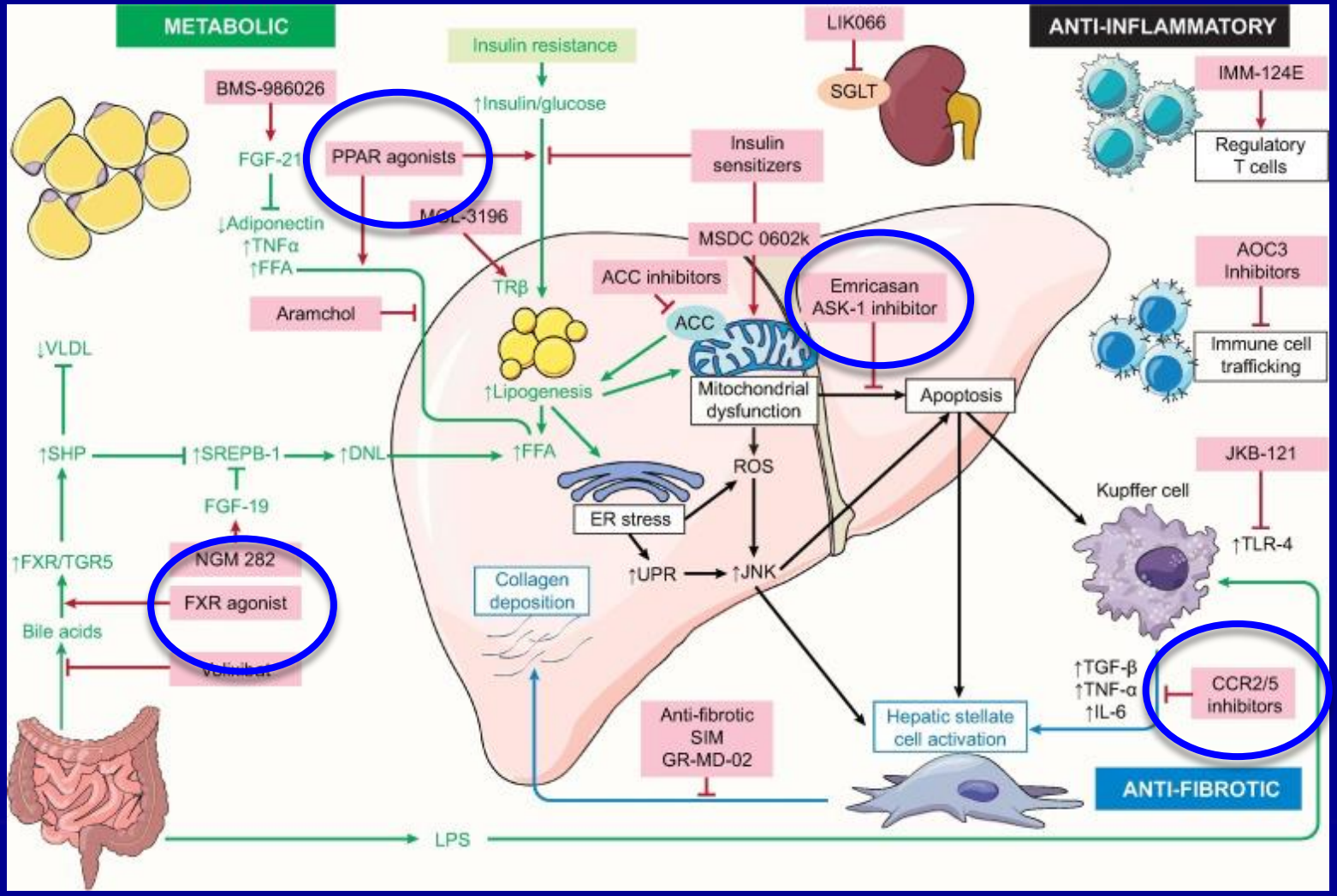
LEAN Trial- Phase II Study Of Liraglutide In NASH



- Non-cirrhotic NASH
- 1:1 randomization
- 18mg sq daily
- 48 weeks
- n = 52
- AD: GI disorders

Armstrong MJ, et al. Lancet 2016;387:679

Mechanism of action of pharmacologic treatments for NAFLD and NASH

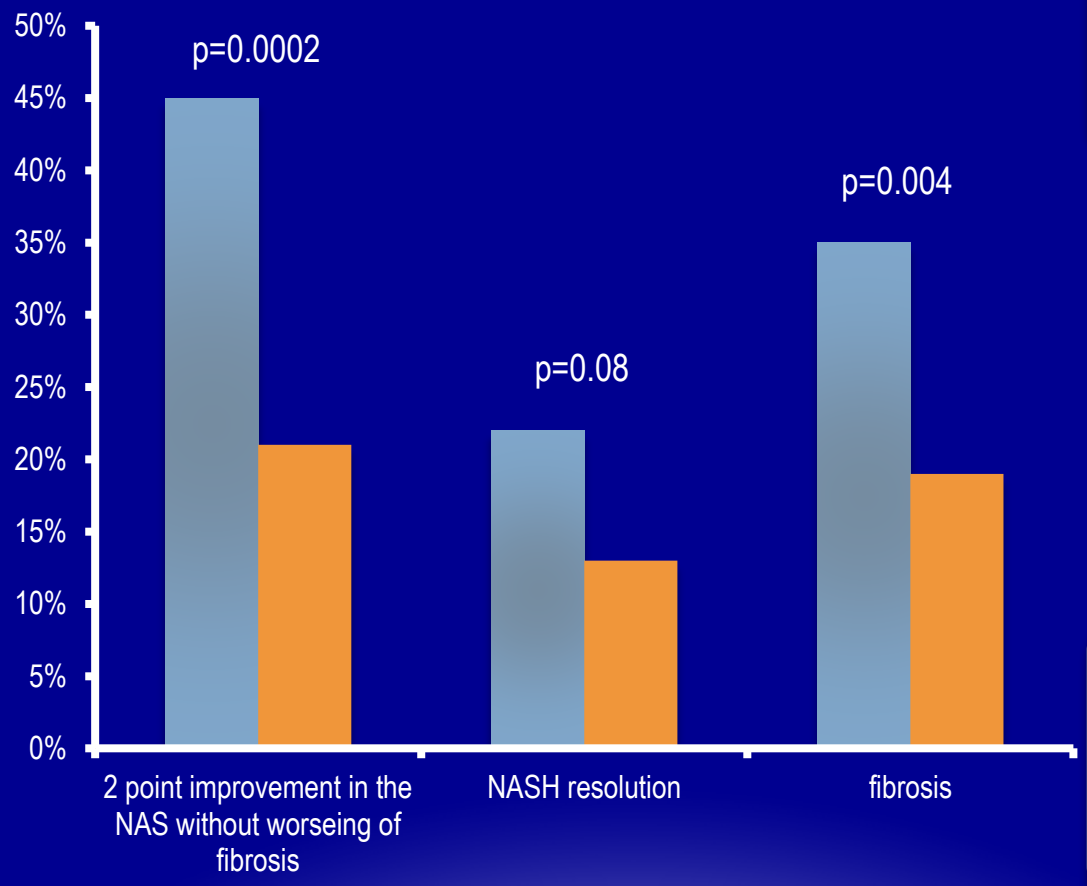


Konerman MA, et al. 2018;68:362

Obeticholic Acid

- Semi-synthetic derivative of chenodeoxycholic acid
- Farnesoid X receptor (FXR) agonist
- Down regulates hepatic glucose and lipid metabolism

FLINT trial- phase II study of OCA in NASH



- Non-cirrhotic NASH
- 1:1 randomization
- 72 weeks
- n = 283
- AD: pruritus, lipids

Phase III trial

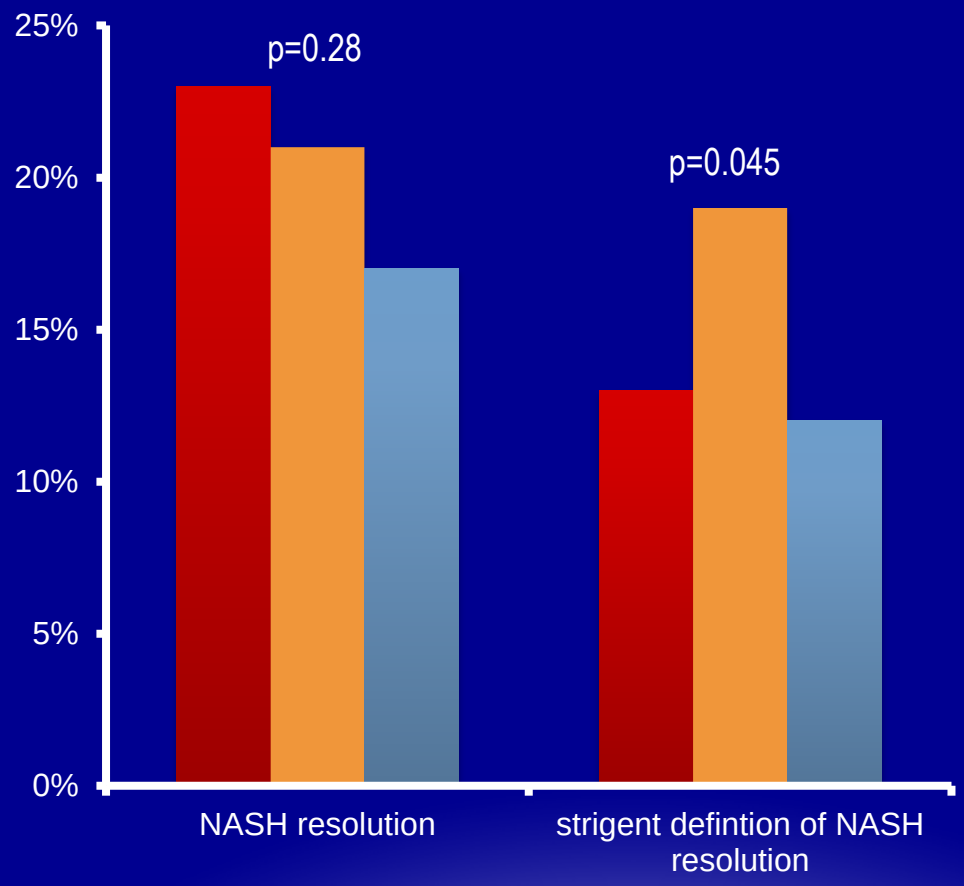
- REGENERATE & REVERSE
- F1-3 & F4
- 72 weeks

Neuschwander-tetri Ba, Et Al. Lancet 2015;385:956

Elafibranor

- Dual peroxisome proliferator-activated receptor (PPAR)-α/δ agonist
- PPAR-α: Regulator of fatty acid transport and inducer of β-oxidation of fatty acids
- PPAR-δ: reduces fatty acid uptake in the liver and decreases it in the adipocytes, increase insulin sensitivity

GOLDEN-505 Trial- Phase II Study Of Elafibranor In NASH



- Non-cirrhotic NASH
- 1:1:1 randomization
- 52 weeks
- n = 276

Phase III trial

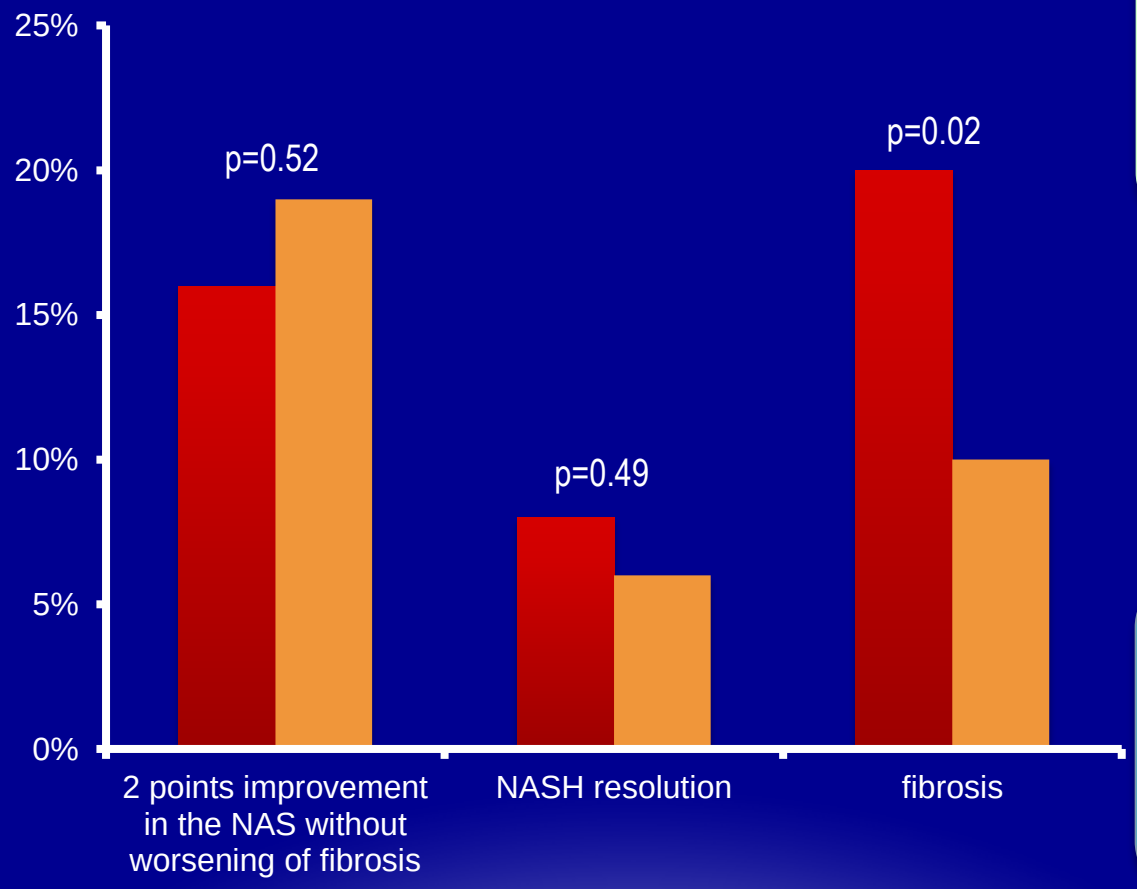
- RESOLVE-IT
- F1-3
- 72 weeks

Ratziu V, Et Al. Gastroenterology 2016;150:1147

Cenicriviroc

- Dual CCR2/CCR5 chemokine receptor antagonist
- Inhibit initiation of an inflammatory response and fibrosis

CENTAUR Trial- Phase II Study Of Cenicriviroc In NASH



- Non-cirrhotic NASH
- 1:1:1 randomization
- CVC 150mg vs. placebo->CVC vs. placebo
- 2 year
- n = 289

Phase III trial

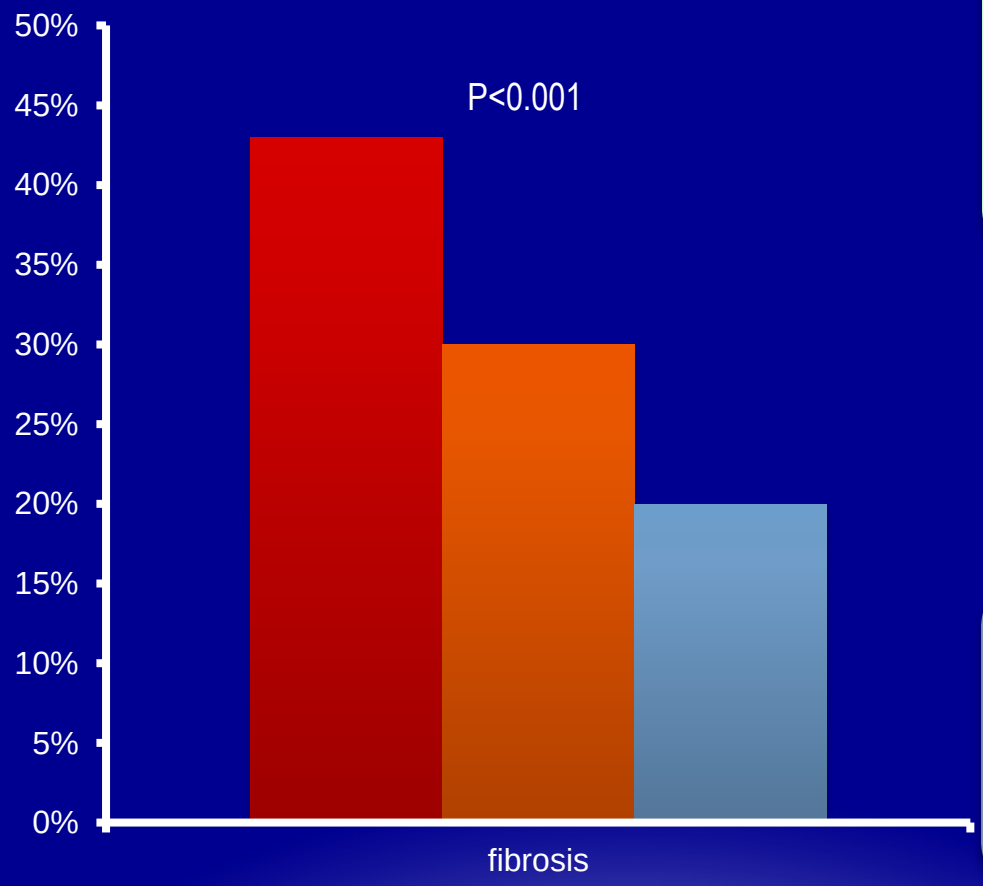
- AURORA
- F2-3
- ≥1 year

Friedman SI, Et Al. Hepatology 2018,67:1754

Selonsertib

- Apoptosis signal-regulating kinase 1 (ASK1) inhibitor
- Reduce oxidative stress-related cell death, fibrosis, and inflammation

Phase II Study Of Selonsertib In NASH



- Non-cirrhotic NASH
- 2:2:1:1:1 randomization
- SEL vs. SIM sq
- 24 weeks
- n = 72
- Simtuzumab (SIM) as placebo

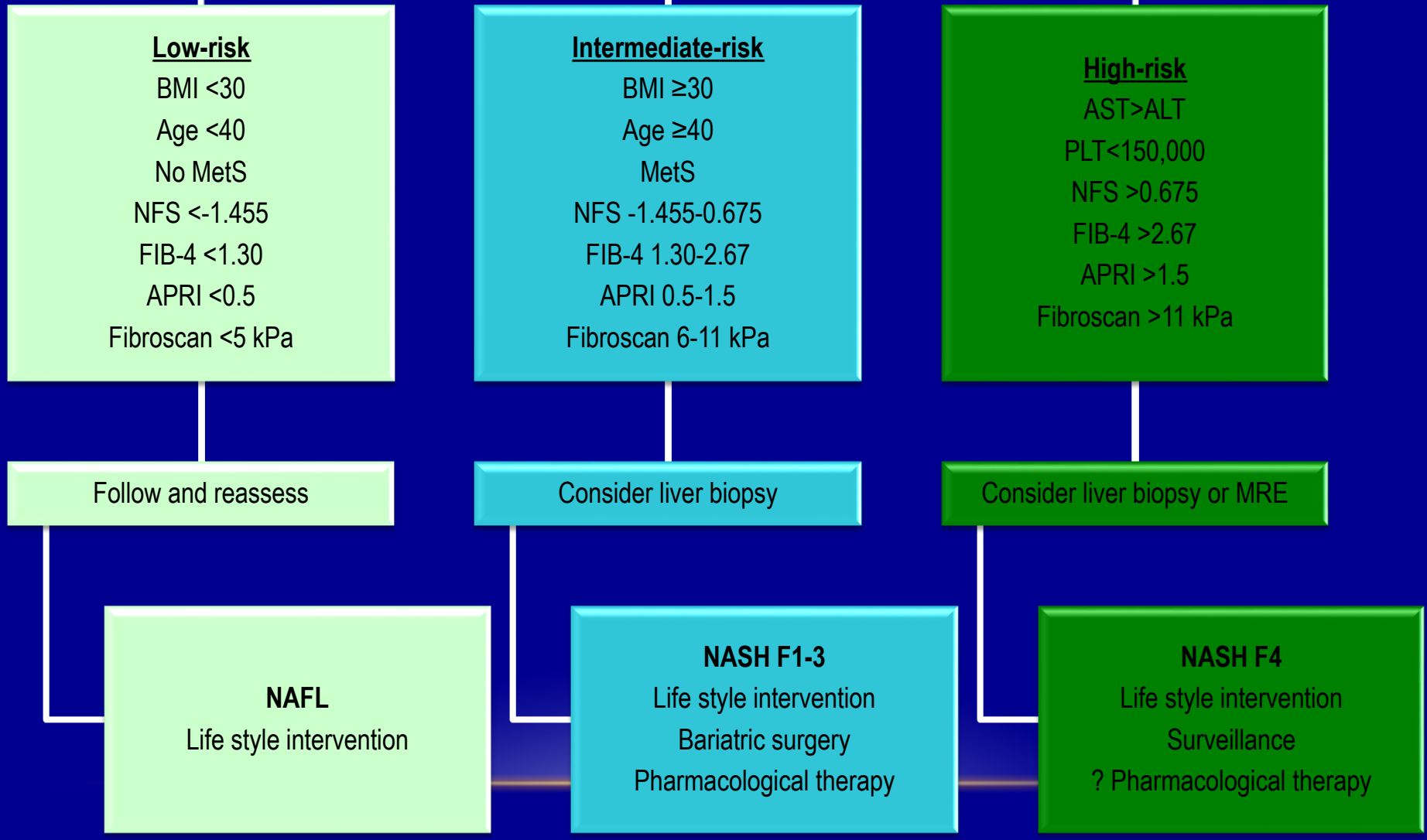
SEL 18mg ± SIM
SEL 6mg ± SIM
SIM

Phase III trial

- STELLAR-3 & -4
- F2-3 & F4
- 48 weeks

Loomba et al. Hepatology 2018;67:549

Risk stratification of NAFLD



Rinella ME, et al. Nat Rev Gastroentrol Hepatol. 2016:13:196-205

SUMMARY

- NASH and fibrosis stage correlate with higher mortality
- Fibrosis assessment is the most important diagnostic step
- Elastography-based method can be used as the initial workup
- VCTE is preferred for patients BMI <35 kg/m^2; consider MRE in patients with morbid obesity
- Weight loss (>10%) with diet/exercise or bariatric surgery improves NASH and fibrosis
- No FDA approved pharmacological therapy for NASH
- Active and rapid-growing Phase II & III clinical trials for NASH

New Horizon ……