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Advances in Hepatology

Topics

- NAFLD/NASH
- Coagulation in Cirrhosis
- Hepatocellular Carcinoma
- Miscellaneous

Definitions of NAFLD, NAFL and NASH

Nonalcoholic fatty liver disease (NAFLD)

a. Evidence of hepatic steatosis by imaging or histology

b. Lack of secondary causes of hepatic fat accumulation

Nonalcoholic fatty liver (NAFL)

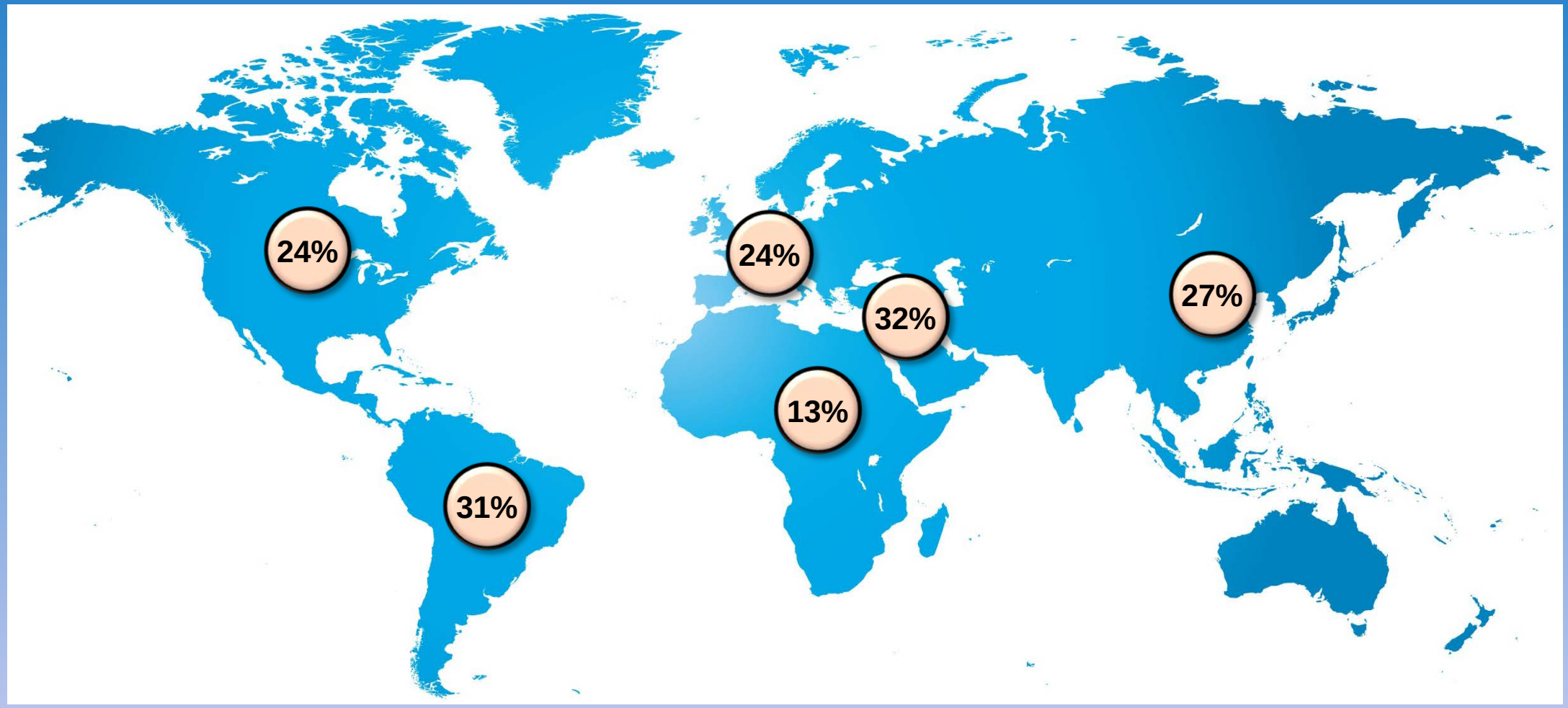
≥5% hepatic steatosis without evidence of hepatocellular injury in the form of hepatocyte ballooning

Non-alcoholic steato-hepatitis (NASH)

≥5% hepatic steatosis and inflammation with hepatocyte injury (eg, ballooning), with or without any fibrosis

Chalasani N, et al. Hepatology. 2017. doi:10.1002/hep.29367

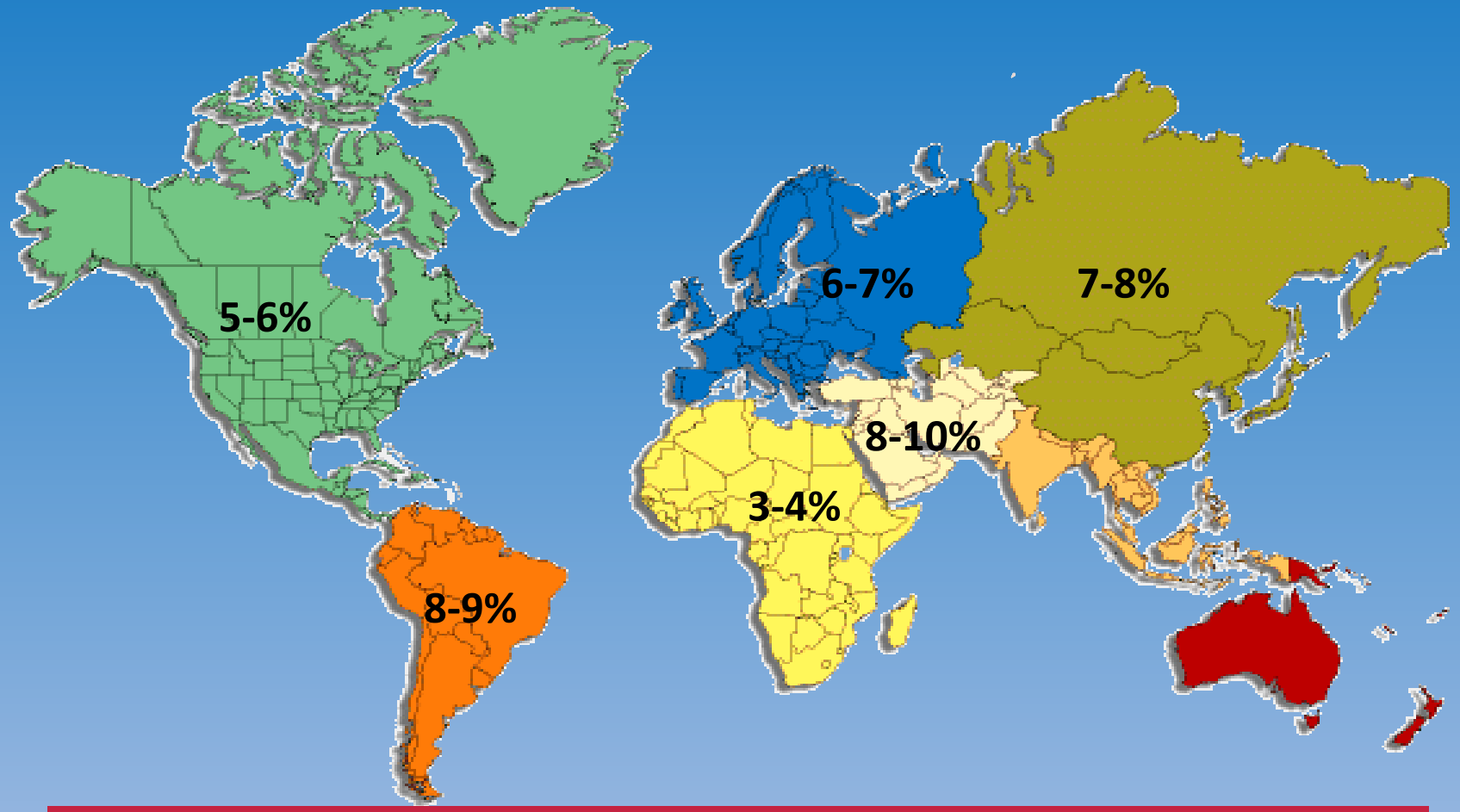
Estimated Global Prevalence of NAFLD: 25%



Meta-analysis: NAFLD diagnosed by imaging (US, CT, MRI/SPECT; n=45 studies).

Younossi ZM, et al. *Hepatology.* 2016;64:73-84.

Estimated Global NASH Prevalence



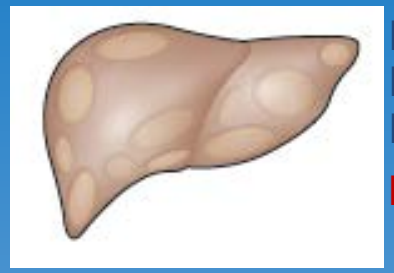
NASH is Prevalent Globally

*25-30% of NAFLD prevalence assumed to be NASH in the above map.

Younossi ZM, et al. *Hepatology* 2016;64:73-84; Williams CD, et al. *Gasteoenterology* 2011;140:124-131.

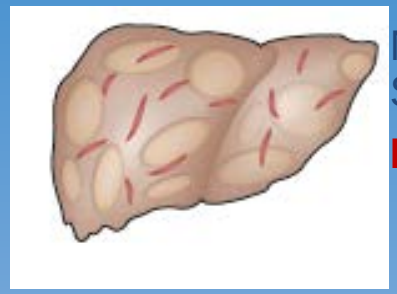
Estimated NASH Prevalence in the U.S.

Disease Spectrum



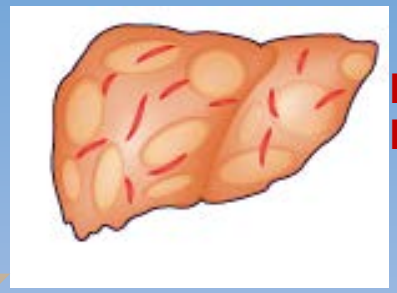
Non-Alcoholic Fatty Liver Disease

NAFLD



Non-Alcoholic Steatohepatitis

NASH



NASH with F3/F4 Fibrosis

~30% of U.S. adult population estimated to have NAFLD

83.1 Million

16.5 Million

3.3 Million

F3 = 2 M; F4 = 1.3 M

Unmet Need

Estes, et al. Hepatology. 2017. doi:10.1002/hep.29466.

Risk Factors Associated With NAFLD

Common Comorbidities With Established Association

- **Metabolic syndrome***
- Obesity
- Type 2 diabetes
- Dyslipidemia
- Polycystic ovary syndrome

Other Conditions Associated With NAFLD

- Hypothyroidism
- Obstructive sleep apnea
- Hypopituitarism
- Hypogonadism
- Pancreatoduodenal resection
- Psoriasis

National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)

*ATP III definition (requires the presence of ≥3 of the following features):
(1) waist circumference >102 cm in men or >88 cm in women; (2) triglyceride level ≥150 mg/dL; (3) HDL cholesterol level <40 mg/dL in men and <50 mg/dL in women; (4) SBP ≥130 mm Hg or DBP ≥85 mm Hg; and (5) fasting plasma glucose level ≥110 mg/dL.

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

Initial Evaluation of NAFLD Severity

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

- **Liver enzymes, Signs or Symptoms of Liver Disease, and co-morbidities**
- **Clinico-Laboratory Testing:** Identify higher likelihood of Advanced Fibrosis (F3) or Cirrhosis (F4).
  - ***NAFLD Fibrosis Score*** (NFS) (Age, BMI, Diabetes, AST, ALT, Platelets, Albumin)
    - < -1.455: predictor of absence of significant fibrosis (F0-F2 fibrosis)
    - > 0.675: predictor of presence of significant fibrosis (F3-F4 fibrosis)
  - ***Fibrosis-4 Index*** (FIB-4) (Age, ALT, AST, Platelet count)
    - Index > 2.67 indicates F3-F4 with an AUROC of 0.88;
    - Index < 1.3 indicates absence of advanced fibrosis (stage F2 or lower).
- **Radiologic Testing:** Identify Advanced Fibrosis (F3) or Cirrhosis (F4)
  - ***Vibration Controlled Transient Elastography*** (**VCTE** or FibroScan) or
  - ***MR Elastography*** (**MRE)**.

Impact of pre-screening with Fibrosis-4 index on a referral pathway for patients with suspected NAFLD

Aim:

To assess the potential impact of implementing a *FIB-4 first* strategy to triage patients using a clinical referral pathway for suspected non-alcoholic fatty liver disease (NAFLD) (abnormal ALT or steatosis on ultrasound)

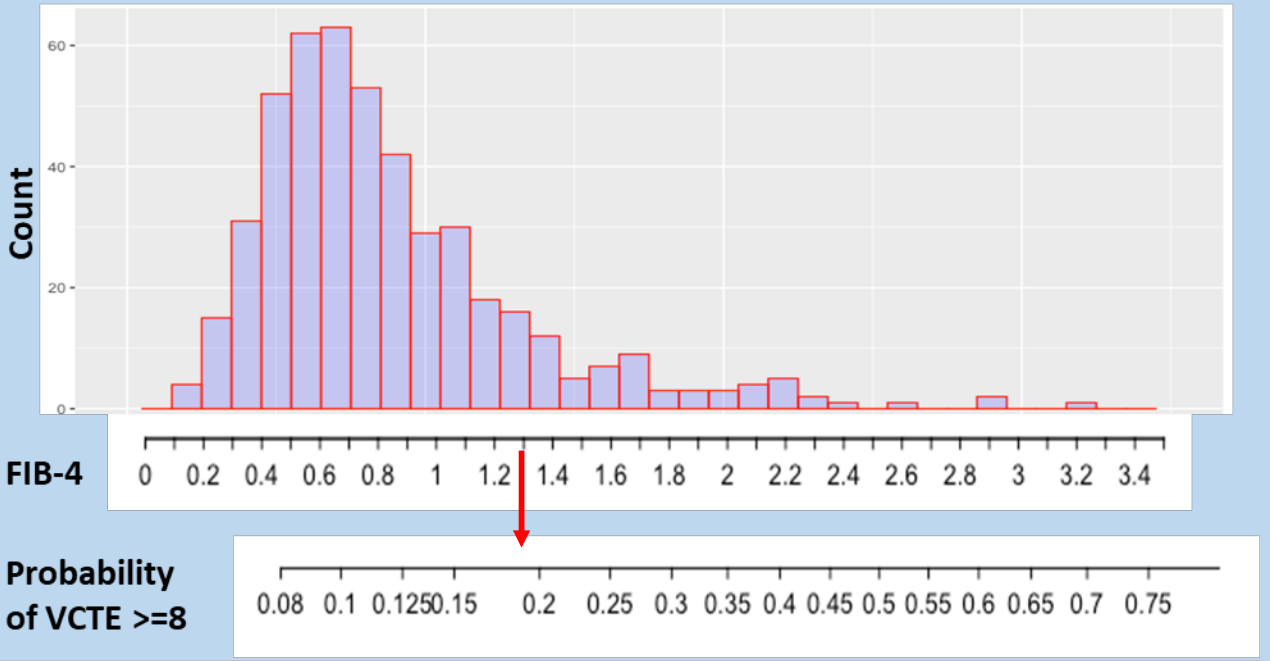
Methods:

All referred patients were risk stratified using FIB-4 and VCTE. The risk of finding a VCTE ≥8 kPa according to FIB-4 values was modelled with logistic regression.

Conclusions:

As compared with a referral pathway in which all patients with suspected NAFLD undergo VCTE for risk stratification, a *FIB-4 first* strategy with a threshold of 1.3 would save 85% of VCTE assessments.

Distribution of FIB-4 values in 481 patients using the referral pathway and predicted risk of VCTE ≥8 kPa

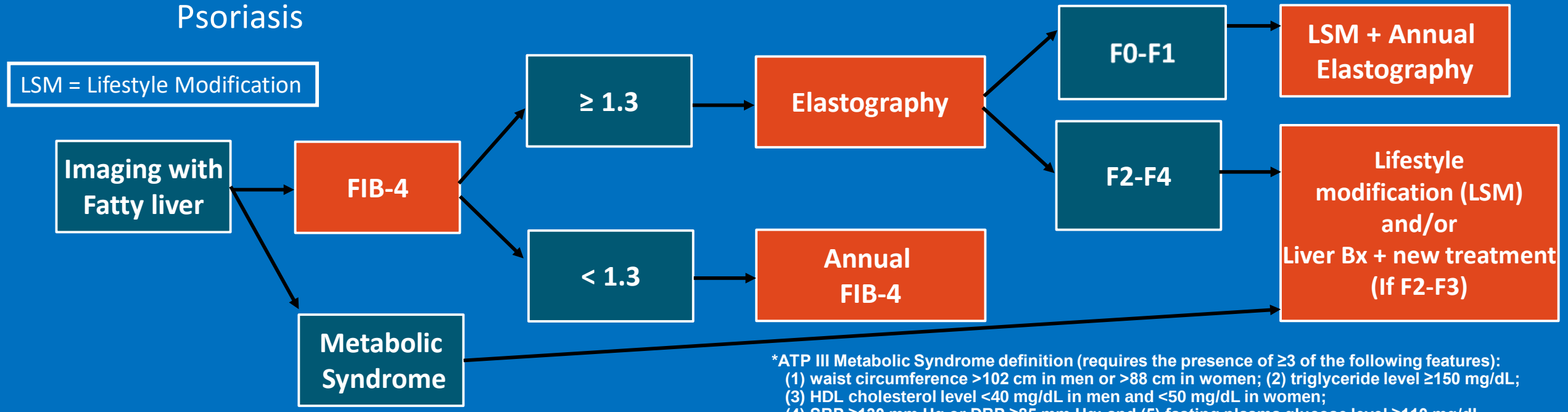


Davyduke TM, et al., Abstract 69

FIB-4 of >/= 1.3 identifies 82% of VCTE >/= 8 kPa (that means >/= F2) and decreases need of VCTE by 85%

Evaluation for NAFLD in Patients with Fatty Liver in Imaging

- Metabolic Syndrome* (ATP III)
- Elevated liver enzymes, or Signs or Symptoms of Liver Disease.
- Normal Liver enzymes and absent Sings/Symptoms of liver disease, but presence of:
  - Obesity, Diabetes Mellitus, Dyslipidemia, or PCOS
  - OSA, Hypothyroidism, Hypopituitarism, Hypogonadism, Pancreato-duodenal resection, or Psoriasis



*ATP III Metabolic Syndrome definition (requires the presence of ≥3 of the following features):
(1) waist circumference >102 cm in men or >88 cm in women; (2) triglyceride level ≥150 mg/dL;
(3) HDL cholesterol level <40 mg/dL in men and <50 mg/dL in women;
(4) SBP ≥130 mm Hg or DBP ≥85 mm Hg; and (5) fasting plasma glucose level ≥110 mg/dL.

AASLD Practice Guidance: Evaluation of Patients With NAFLD

Noninvasive Assessment of Advanced Fibrosis

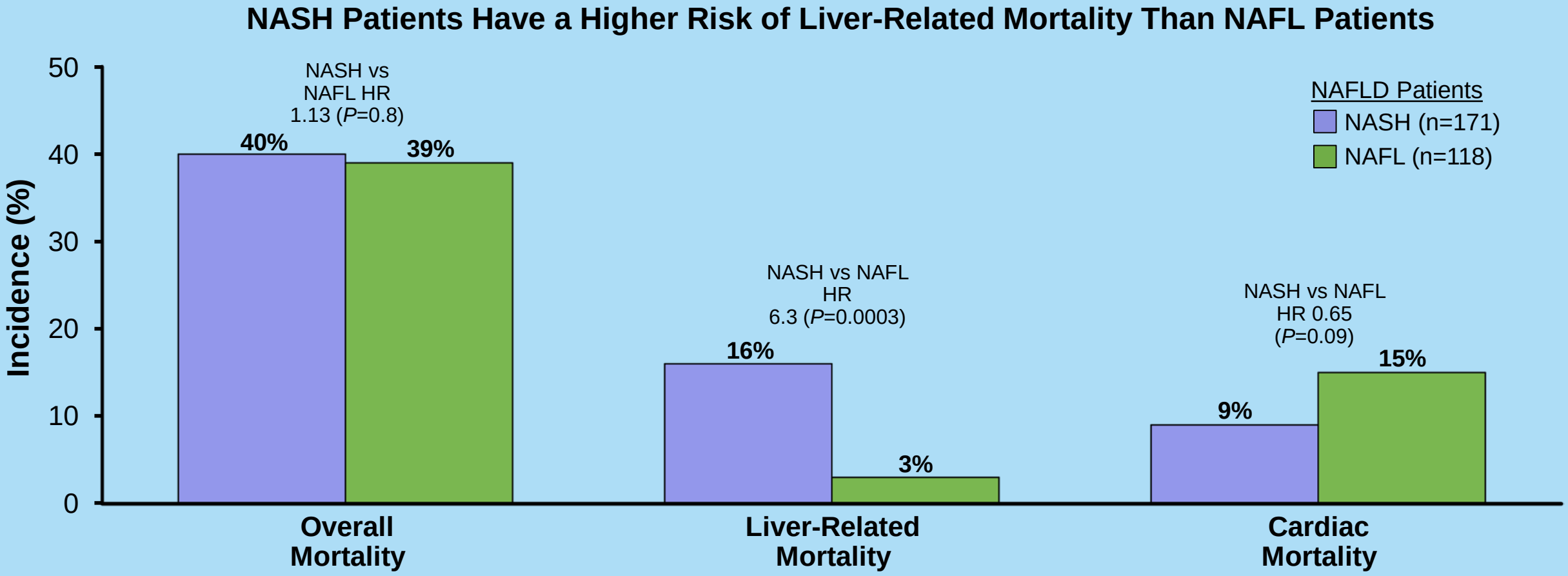
- **Metabolic syndrome**
  - Strong predictor for the presence of steatohepatitis in NAFLD patients
  - Its presence can be used to target NAFLD patients for a liver biopsy
- **NAFLD score** (> 0.675) **or FIB-4 index** (> 2.67)
  - Clinically useful to identify those with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4)
- **Vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE) Score** (if FIB-4 >/= 1.3)
  - Clinically useful to identify advanced fibrosis

When to Obtain a Liver Biopsy

- **Consider liver biopsy**
  - **Before Pharmacologic Therapy**
  - Presence of **Metabolic Syndrome**, “High” NAFLD score or FIB-4, or liver stiffness measured by VCTE or MRE
  - NAFLD patients at **increased risk** of having steatohepatitis and/or **advanced fibrosis**
  - Suspected NAFLD patients **with competing etiologies** for hepatic steatosis
  - Patients in whom the **presence and/or severity of coexisting chronic liver diseases** cannot be excluded without a liver biopsy

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

Predictors of All-Cause and Liver-Related Mortality in Biopsy-Proven NAFL/NASH (10-year Follow-up)

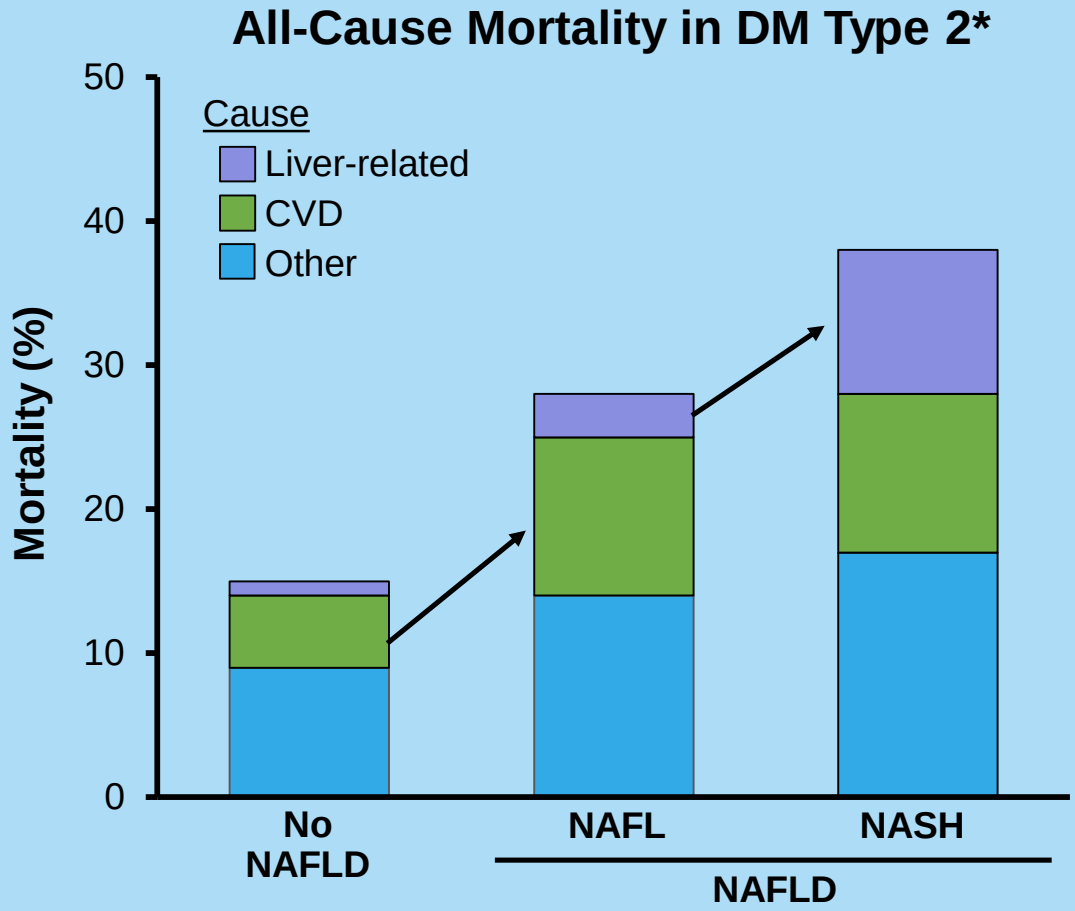


Two historic databases of biopsy-proven NAFLD patients (NAFL [n=118]; NASH [n=171]) with a minimum of 10 years mortality follow-up from date of liver biopsy. Median time between baseline biopsy and death for NAFL/NASH: 144/150 months.

Stepanova M, et al. *Dig Dis Sci.* 2013;58:3017-3023.

NAFLD/NASH: Why It's Important for Patients With **Type 2 Diabetes**

- NAFLD/NASH **prevalence: ≥2-fold higher** versus non-diabetics
- **Faster progression to NASH** and advanced fibrosis
  - NASH is associated with increased overall and liver-related mortality (type 2 diabetes increases the risk of both)
- Established **link** between type 2 diabetes, **cirrhosis, and HCC**
  - Type 2 diabetics: 2- to 4-fold higher prevalence rates of cirrhosis and HCC
- Presence of NAFLD in type 2 diabetics
  - Significantly **increases the risk of cardiovascular disease**
  - Promotes dyslipidemia, hyperinsulinemia
  - Subclinical inflammation



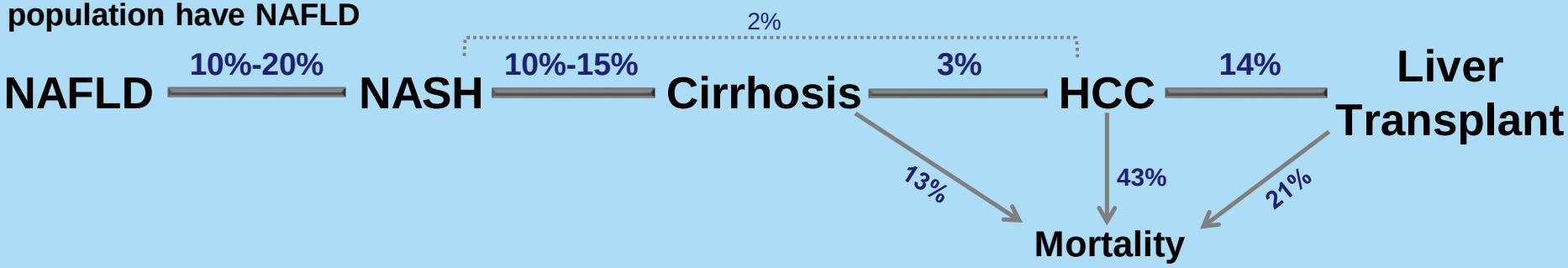
*Weighted mean follow-up: 13-14.5 years.

Bril F, et al. *Endocrinol Metab Clin N Am.* 2016;45:765-781.
Cusi K. *Diabetologia.* 2016;59:1112-1120.

Estimated Transition Rates in NAFLD: Non-Diabetic and Diabetic Patients

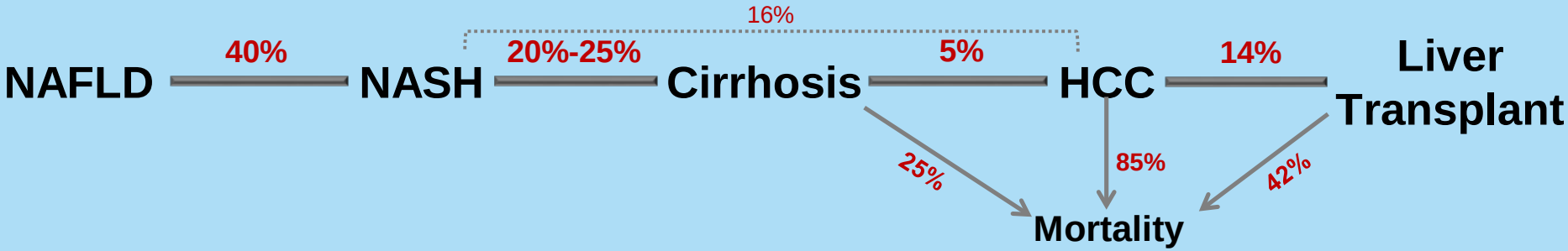
Non-Diabetic

~25% of US population have NAFLD



Diabetic

~38% of NAFLD patients have diabetes
33% to 66% of diabetics have NAFLD

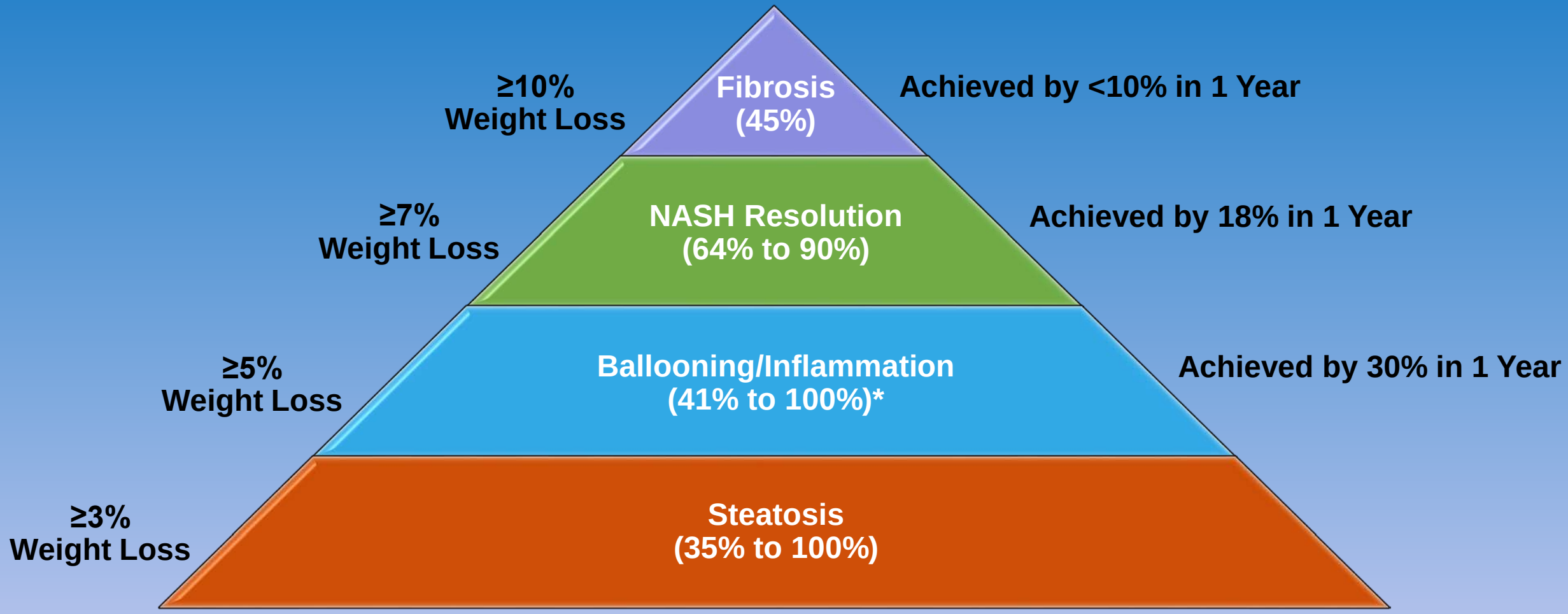


The exact circumstances under which patients with NASH can progress or regress is not well defined.
In general, the progressive course of NASH has been closely linked to the increasing number of metabolic comorbidities, especially type 2 diabetes.

Younossi ZM, et al. *Clin Liver Dis.* 2018;22:1-10.
Chalasani N, et al. *Hepatology.* 2018;67:328-357.

NASH Therapy
Lifestyle Modification

Weight Loss Pyramid



*Depending on degree of weight loss.

Vilar-Gomez E, et al. *Gastroenterology.* 2015;149:367-378; Promrat K, et al. *Hepatology.* 2010;51:121-129; Harrison SA, et al. *Hepatology.* 2009;49:80-86; Wong VW, et al. *J Hepatol.* 2013;59:536-542.

Physical Activity and Risk of Mortality in Non-Alcoholic Fatty Liver Disease: A Population Based Study of United States Adults (AASLD 2018: 67)

- **AIM:** Investigate the association between physical activity (PA) and mortality-risk related to: All-causes, Cardiovascular disease and Diabetes among US Adults with NAFLD.
- **Methods:**
  - Analyzed mortality-linked data (23 years following recruitment) for 2701 adults with NAFLD age 20 to 74 years who participated in NHANES III.
  - NAFLD was defined as mild, moderate, or severe hepatic steatosis on ultrasound in the absence of hepatitis B, hepatitis C, iron overload, or excessive alcohol drinking.
  - Leisure time PA was categorized into three groups inactive, recommended active and insufficiently active based on the Center of Disease Control and the American College of Sports Medicine recommendations.
- **Results:** Overall mortality was significantly higher amongst adults with NAFLD versus those without (20.02% vs 16.01%; *P*-value 0.002).
- **Conclusion:**
  - Recommended PA levels are significantly lower among NAFLD adults.
  - NAFLD patients with recommended levels of PA had significantly lower risks of mortality from all-causes, cardiovascular disease and diabetes.

Prevalence and association between physical activity and risk of mortality amongst U.S. adults with non-alcoholic fatty liver disease (NAFLD), the Third National Health and Nutrition Examination Survey (NHANES III)

Physical Activity Status [a]	Prevalence (n=2701)		All Cause	Cardiovascular Disease	Diabetes
	% (95% CI)	N (100,000)	aHR [b] (95% CI)	aHR [b] (95% CI)	aHR [b] (95% CI)
Inactive	15.51 (13.09 – 17.93)	45.10	Reference Group	Reference Group	Reference Group
Insufficiently Active	36.57 (32.98 – 40.15)	106.34	0.75 (0.56 – 1.01)	**0.53 (0.30 – 0.95)**	0.54 (0.26 – 1.11)
Recommended Active	47.92 (43.84 – 52.01)	139.37	**0.64 (0.48 – 0.86)**	**0.46 (0.25 – 0.84)**	**0.40 (0.23 – 0.72)**

aHR, adjusted hazard ratio; N, projected number of U.S. adults per physical activity status.
[a] Recommended Active: Adults with recommended levels of physical activity; Inactive: No reported leisure-time physical activity; Insufficiently Active: Adults who were not inactive nor met the recommended physical activity levels.
[b] Adjusted for age, gender, education, poverty index, marital status, access to health insurance, smoking, BMI, healthy eating index, race, alcohol intake, high-density lipoprotein, systolic blood pressure, waist circumference, triglycerides, and fasting blood glucose.

Recommended PA: 150 minutes of moderate, or 75 minutes of vigorous, aerobic physical activity per week

Treatment of NASH Currently Available Drug Therapy

AASLD Practice Guidance: Vitamin E

- **Vitamin E (rrr α-tocopherol) 800 IU/day**
  - May be considered for nondiabetic adults with biopsy-proven NASH (counsel patients on risks and benefits)
    - **Improves liver histology, but not fibrosis**
    - Long-term safety issues concerns linger (eg, impact on long-term mortality, prostate cancer)
- Vitamin E is **not** recommended to treat NASH in: diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
  - More data on safety and efficacy are needed
    - Increases risk of **prostate cancer** (absolute increase of **1.6 per 1,000 person-years**).
    - May increase all-cause mortality (evidence not found in large meta-analysis).

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

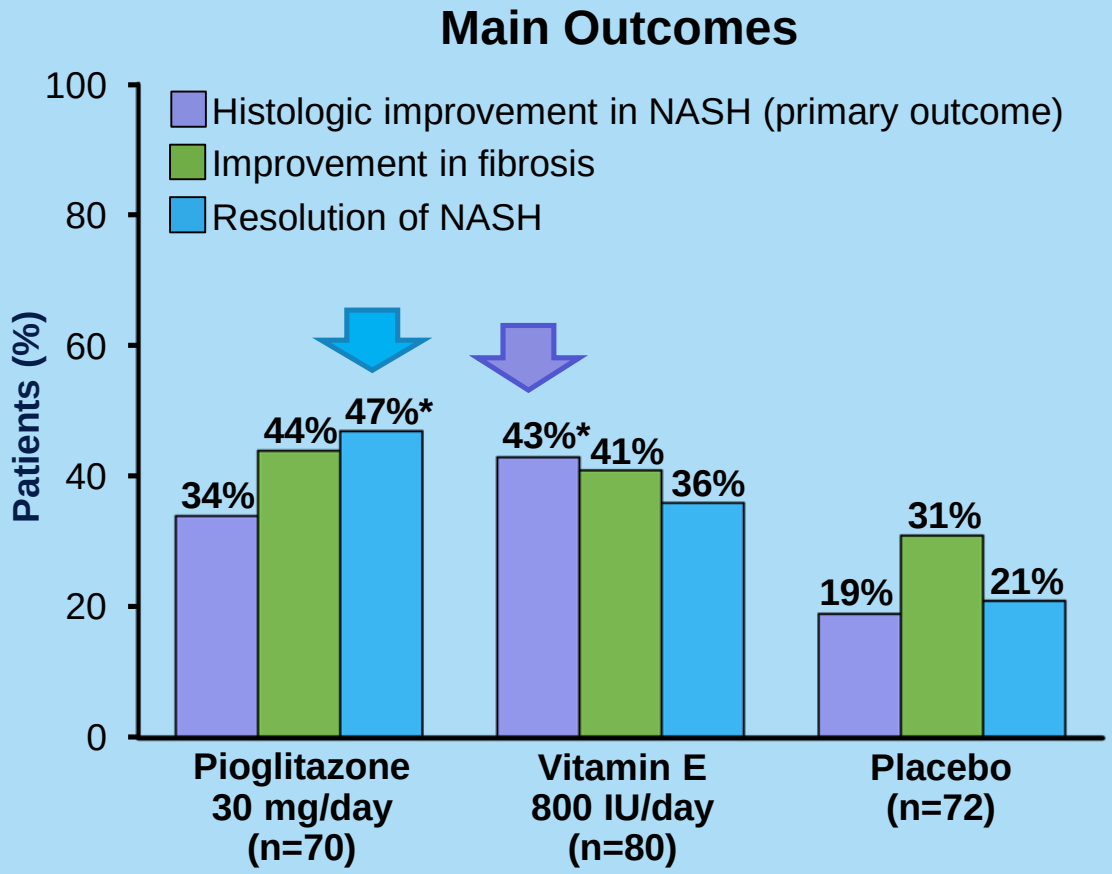
AASLD Practice Guidance: Use of Insulin Sensitizers to Treat NAFLD/NASH

- Metformin is not recommended for treating NASH in adult patients
  - Improves serum aminotransferases and IR, but does not significantly improve liver histology
- **Thiazolidinediones**
  - **Pioglitazone improves liver histology and NASH resolution** in patients with and without type 2 diabetes with biopsy-proven NASH
    - It may be used to treat these patients (counsel patients on risks and benefits)
  - Pioglitazone should not be used to treat NAFLD without biopsy-proven NASH
    - **Can lead to weight gain and can cause or exacerbate CHF**
    - More data on safety and efficacy are needed
- **Glucagon-like peptide-1 analogues**
  - It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH

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

NASH CRN PIVENS Trial: Pioglitazone Versus Vitamin E in Non-Diabetic Biopsy-Proven NASH

- Phase 3 study in biopsy-proven NASH (n=247)
  - No diabetes or cirrhosis
- Pioglitazone, vitamin E, or placebo for 96 weeks
- Key outcomes versus placebo
  - Vitamin E significantly improved histologic features of NASH (primary outcome); no benefit with pioglitazone
  - Vitamin E and pioglitazone
    - No difference in fibrosis improvement
    - Significantly reduced ALT, AST, and hepatic steatosis (*P*<0.001)



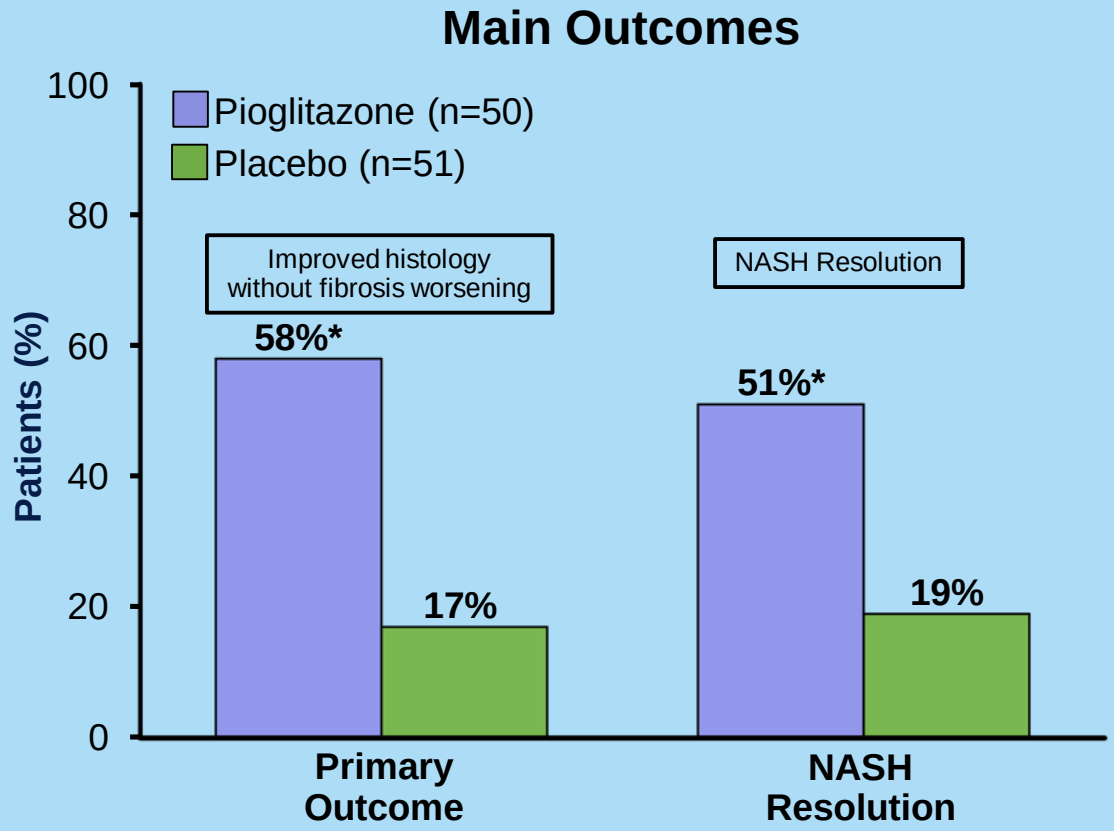
*P=0.001 versus placebo

PIVENS: Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis.

Sanyal AJ, et al. *N Engl J Med*. 2010;362:1675-1685.

Impact of Pioglitazone in Biopsy-Proven NASH in Patients With Prediabetes or Diabetes

- Double-blind, placebo-controlled, single-center study in biopsy-proven NASH (n=101)
  - Prediabetes or type 2 diabetes mellitus
- Pioglitazone 45 mg/day or placebo for 18 months, then open-label pioglitazone for another 18 months
- **Primary outcome** at 18 months
  - **Reduction of at least 2 points in 2 histologic categories of the NASH without worsening of fibrosis**
- Key outcomes versus placebo
  - Pioglitazone significantly improved histologic features of NASH (primary outcome) and greater percentage of patients achieving NASH resolution versus placebo
  - Improvement was maintained during open-label extension

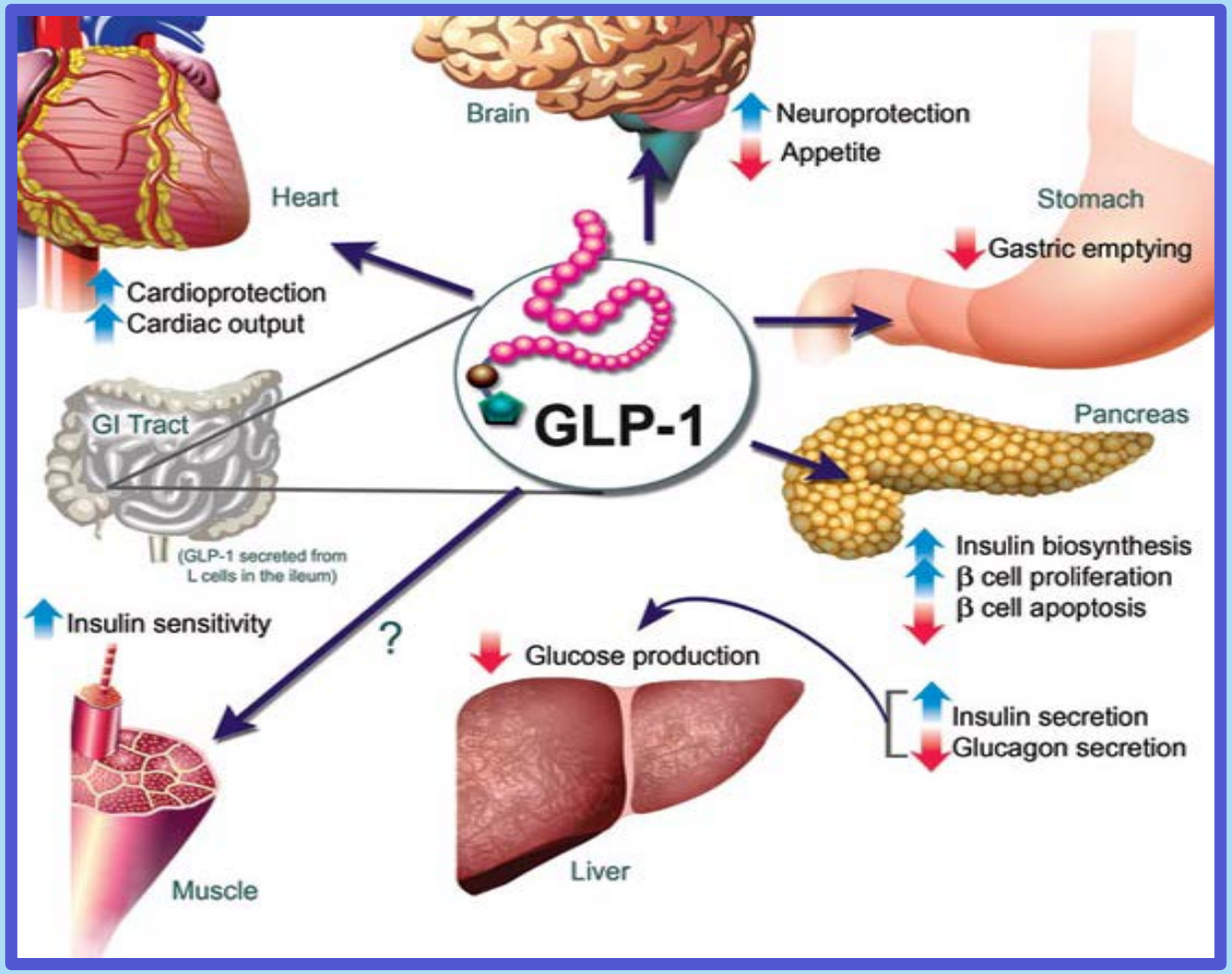


**P*=0.001 versus placebo

Cusi K, et al. *Ann Intern Med*. 2016;165:305-315.

Glucagon-Like Peptide-1 Analogue: Liraglutide

- GLP-1
  - Controls serum glucose
    - Induces insulin secretion
    - Reduces glucagon secretion
  - **Induces weight loss**, suppression of appetite and delayed gastric emptying



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

LEAN Study: Liraglutide in Overweight NASH Patients Without Cirrhosis

- Double-blind, placebo-controlled phase 2 study (n=52)
  - **Histologic evidence of definite NASH***
  - Patients **stratified by diabetes status**
  - Liver biopsy within 6 months of entry
  - **No Child-Pugh B/C cirrhosis**
- Liraglutide or placebo for 48 weeks
- **Primary endpoint** (week 72, ITT)
  - **Improvement in liver histology without worsening of fibrosis**
  - Improvement: disappearance of hepatocellular ballooning
  - Worsening of fibrosis: any increase in Kleiner fibrosis stage

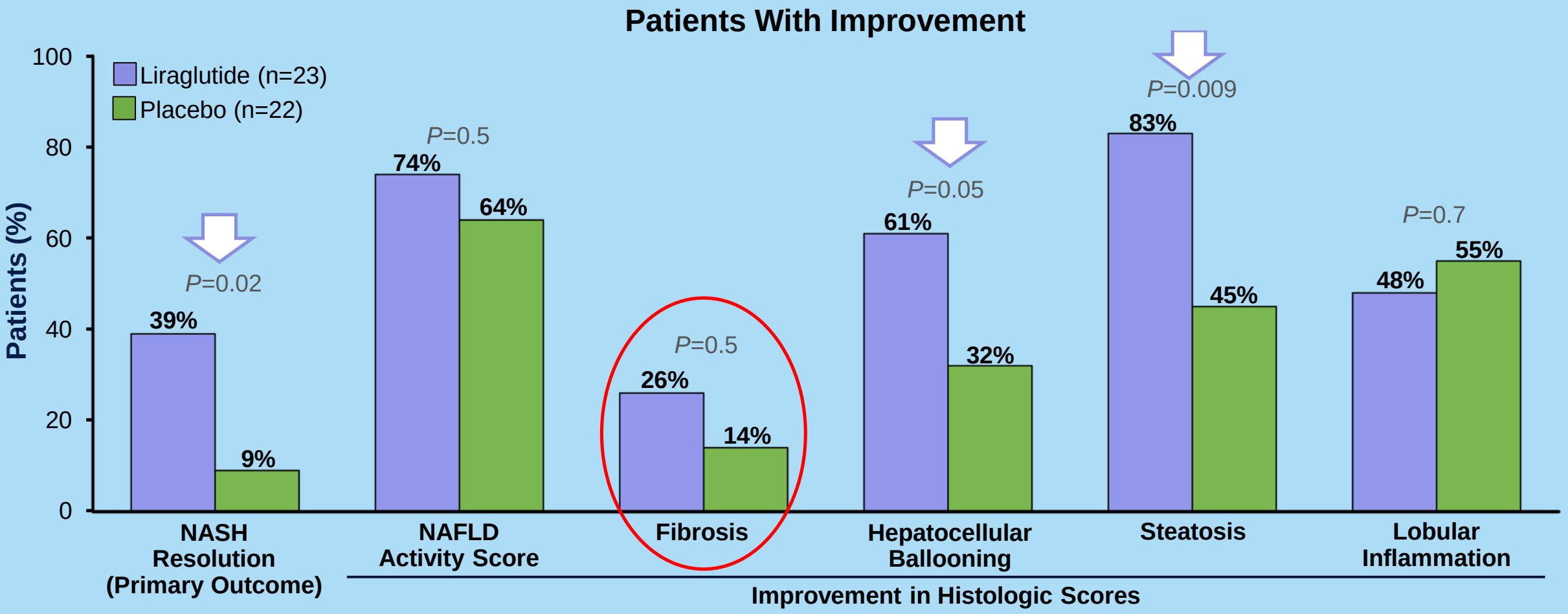
Baseline Characteristics

	Liraglutide (n=26)	Placebo (n=26)
Age (years)	50	52
Comorbidities		
Diabetes	35	31
Hypertension	58	54
Hyperlipidemia	35	27
Cardiovascular disease	0	15
HOMA-IR	6.7	9.6
Liver histology		
Mean NAFLD score (0-8)	4.9	4.8
Hepatocyte ballooning score (0-2)	1.5	1.5
Steatosis score (0-3)	2.1	1.9
Lobular inflammation score (0-3)	1.4	1.4
Fibrosis stage (%)		
F0-F2	54	42
F3-F4	46	58

LEAN: Liraglutide Efficacy and Action in NASH.
*Steatosis >5%, hepatocyte ballooning, lobular inflammation.

Armstrong MJ, et al. *Lancet.* 2016;387:679-690.

LEAN Study: Changes in Histologic Features at Week 48



LEAN: Liraglutide Efficacy and Action in NASH.

Armstrong MJ, et al. *Lancet.* 2016;387:679-690.

Investigational Agents for NASH

Metabolic Homeostasis

- Insulin sensitizer
- Farnesoid X receptor (FXR) agonist
- Peroxisome proliferator-activated receptor (PPAR) agonist
- Fibroblast growth factor (FGF) analogue
- Glucagon-like peptide-1 analogue
- Acetyl-CoA carboxylase (ACC) inhibitor
- Stearoyl coenzyme A desaturase 1 (SCD) inhibitor
- Growth hormone-releasing hormone
- Thyroid hormone receptor beta (THR-β) activation
- Apical sodium dependent bile acid transporter inhibitor

Oxidative Stress

- Antioxidant: Vitamin E
- Apoptosis signal-regulating kinase 1 (ASK1) inhibitor
- Vascular adhesion protein 1 (VAP-1 inhibitor)
- Phosphodiesterase (PDE5) inhibitor

Inflammation

- C-C chemokine receptor (CCR) antagonist

Apoptosis

- Caspase inhibitor

Fibrosis

- Galectin-3 protein inhibitor

Anti-Fibrosis Agents

Farnesoid X Receptor (FXR) Agonists

FXR Agonist: Obeticholic Acid

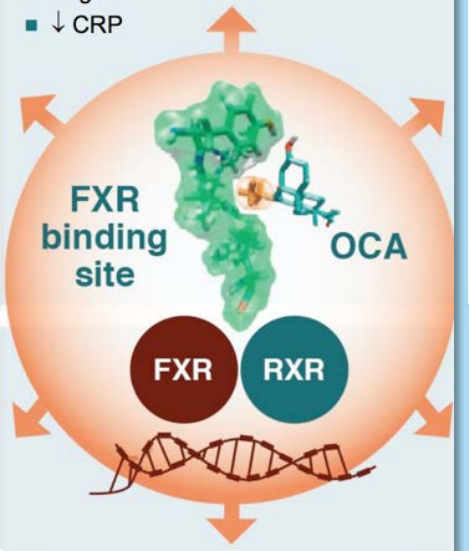
Key FXR Pathways Described in Multiple Animal Models

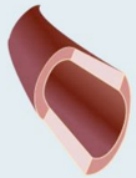
FIBROSIS

- ↓Stellate cell activation (PDGF)
- ↑Stellate cell apoptosis (TIMP-1)
- ↓Fibrogenesis (TGF-β1)
- ↑Matrix degradation (MMP-2)

INFLAMMATION

- ↓ NF-κB
- ↓ TNFα, IL-1β, IL-17, IFN-γ, etc.
- ↓ IgM
- ↓ CRP





ATHEROSCLEROSIS

- ↑Vasodilation (eNOS)
- ↓Inflammation (COX-2, IL-1β, etc.)
- ↓Calcification (JNK)
- ↓Smooth muscle cell migration (PDGF)

LIPID METABOLISM

- ↓Triglyceride synthesis (SREBP-1c)
- ↑Triglyceride clearance (apoC-III)
- ↓VLDL formation (MTP)
- ↓HDL-C (SR-B1, CETP)
- ↑LDL-C (CETP)

GLUCOSE METABOLISM

- ↑ Insulin signaling (FGF19)
- ↑ Insulin sensitivity (IRS-1, IRS-2)
- ↑ Insulin production (KLF11, GLUT-2)
- ↓ Hepatic gluconeogenesis (PEPCK)

BILE ACID HOMEOSTASIS

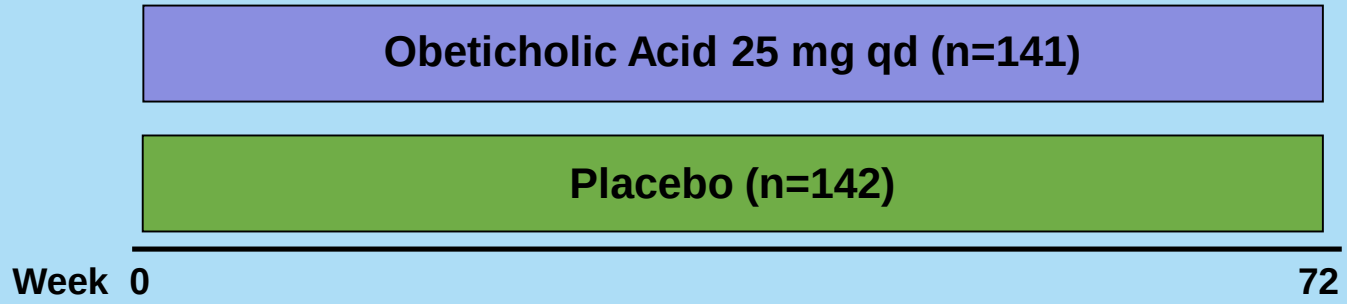
- ↓ Bile acid synthesis (CYP7A1)
- ↓ Bile acid uptake (NTCP)
- ↑ Bile acid secretion (BSEP)
- ↓Bile acid absorption (ASBT)

Sumida Y, et al. *J Gastroenterol.* 2018;53:362-376.
Gawrieh S, et al. *Clin Liver Dis.* 2018;22:189-199.

FLINT Study: Obeticholic Acid in NASH Patients Without Cirrhosis

Phase 2b (n=141)
(US)

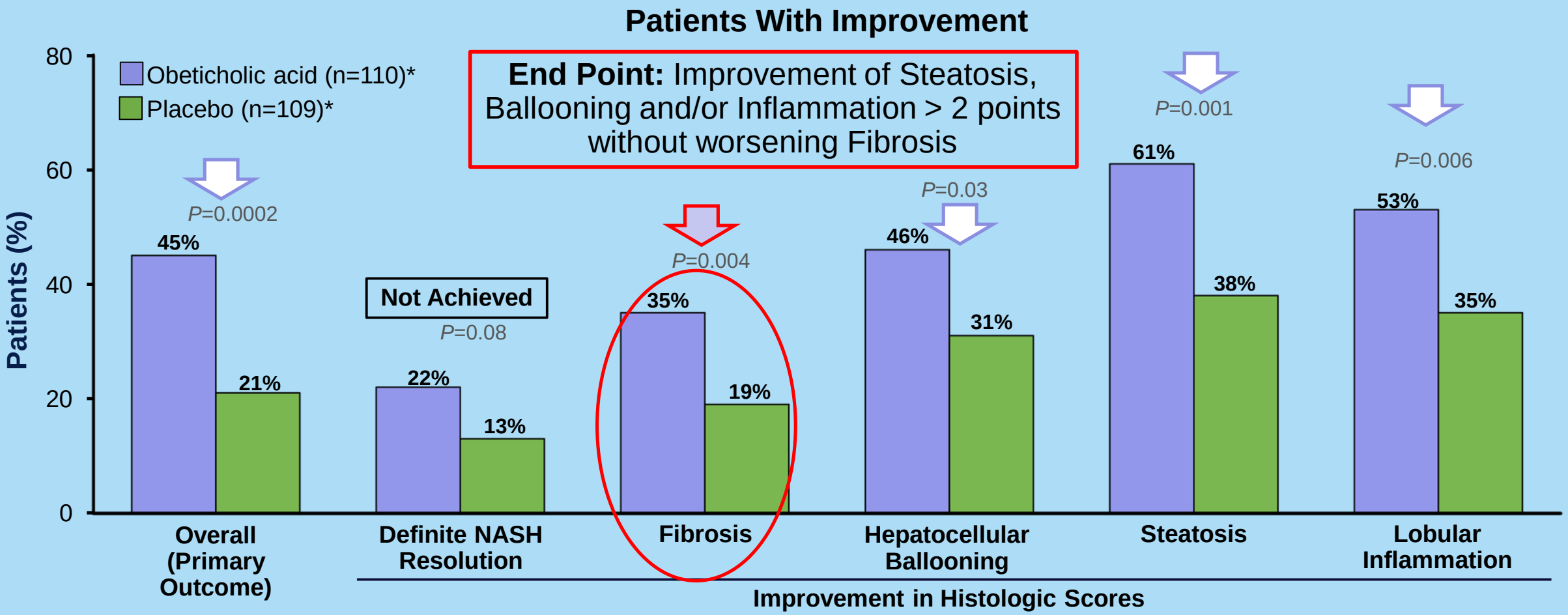
Placebo-controlled
Histologic evidence of definitive or borderline NASH
(liver biopsy within 90 days of entry)
NAFLD activity score ≥4
(individual scores each ≥1)
No cirrhosis



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

Neuschwander-Tetri BA, et al. *Lancet.* 2015;385:956-965.

FLINT Study:
Changes in Histologic Features at Week 72

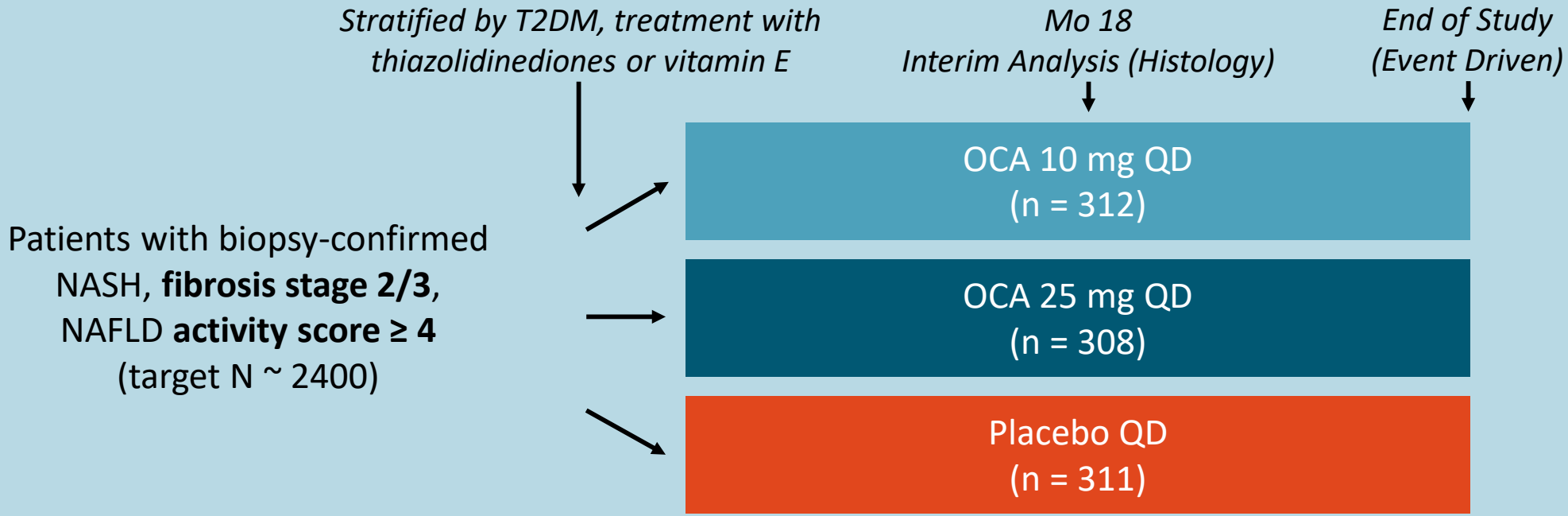


*Number of patients for changes in histologic features: obeticholic acid (n=102), placebo (n=98).

Neuschwander-Tetri BA, et al. *Lancet.* 2015;385:956-965.

REGENERATE: Study Design

- International, randomized, double-blind phase III study of FXR agonist obeticholic acid



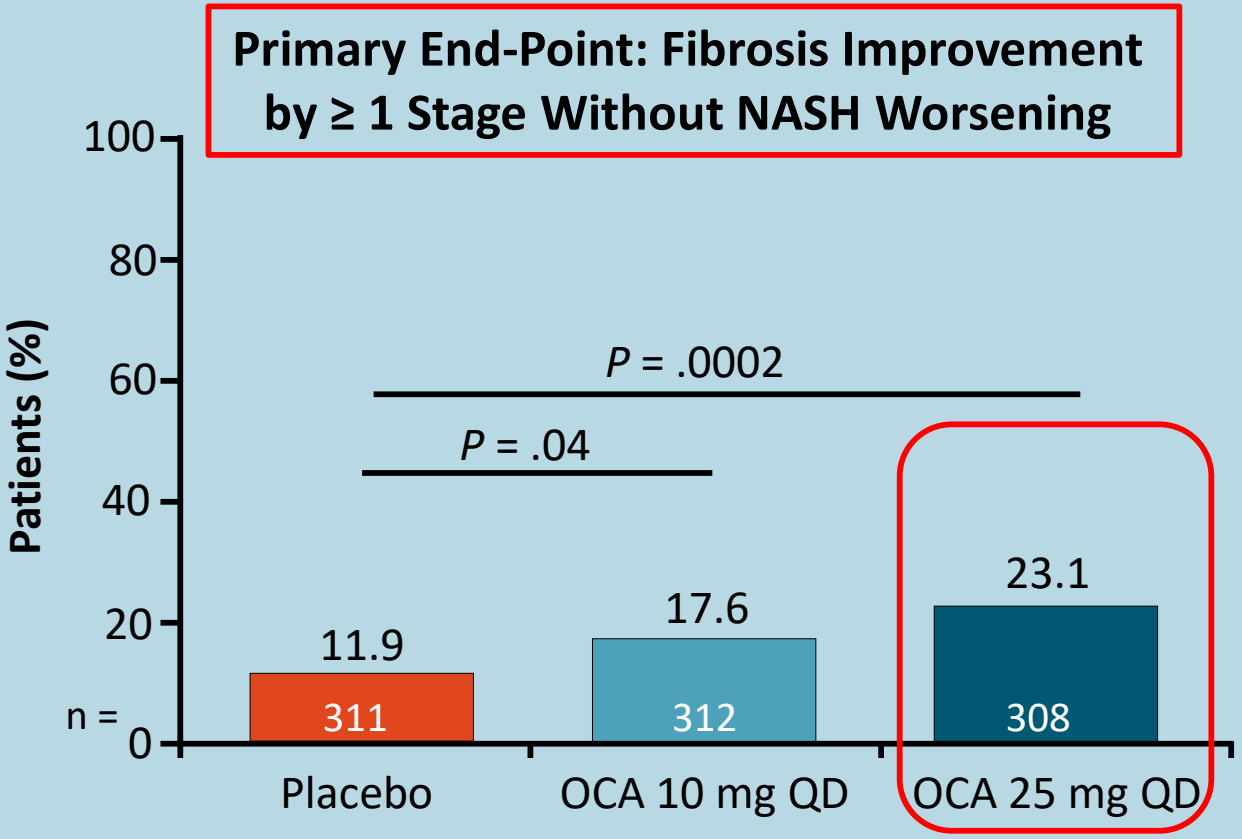
- Primary endpoint at interim analysis by paired biopsy: either fibrosis improvement by ≥ 1 stage without NASH worsening or NASH resolution without fibrosis worsening

Younossi. EASL 2019. Abstr GS-06. Ratziu. EASL 2016. Abstr THU-488.

Slide credit: clinicaloptions.com

REGENERATE Primary Endpoint: Fibrosis Improvement

- Study met fibrosis primary endpoint at 18 mos (ITT)



- **In PP analysis,** OCA 25 mg QD also associated with fibrosis improvement across subgroups defined by fibrosis stage, NAS, T2DM status

Younossi. EASL 2019. Abstr GS-06.

Slide credit: clinicaloptions.com

REGENERATE: Safety

- **Pruritus** incidence peaked within first 3 mos before declining
- In OCA 25 mg arm, 9% discontinued due to pruritus, mostly protocol driven
  - Rates comparable between arms
- **Cardiovascular AE rates** ≤ 2% in all arms
- **LDL increased** and **HDL decreased** early with OCA; recovered with clinical management
- **Hepatic TEAE** rates similar across arms
  - Hepatic serious AEs in < 1%, numerically more cases in OCA 25 mg arm
  - Low rates of cholelithiasis, cholecystitis AEs

TEAEs Occurring in ≥ 10% of Patients in Any Arm, n (%)	OCA 10 mg (n = 653)	OCA 25 mg (n = 658)	Placebo (n = 657)
Pruritus	183 (28)	336 (51)	123 (19)
LDL increased	109 (17)	115 (17)	47 (7)
Nausea	72 (11)	83 (13)	77 (12)
Fatigue	78 (12)	71 (11)	88 (13)
Constipation	65 (10)	70 (11)	36 (5)
Abdominal pain	65 (10)	67 (10)	62 (9)
Diarrhea	44 (7)	49 (7)	79 (12)

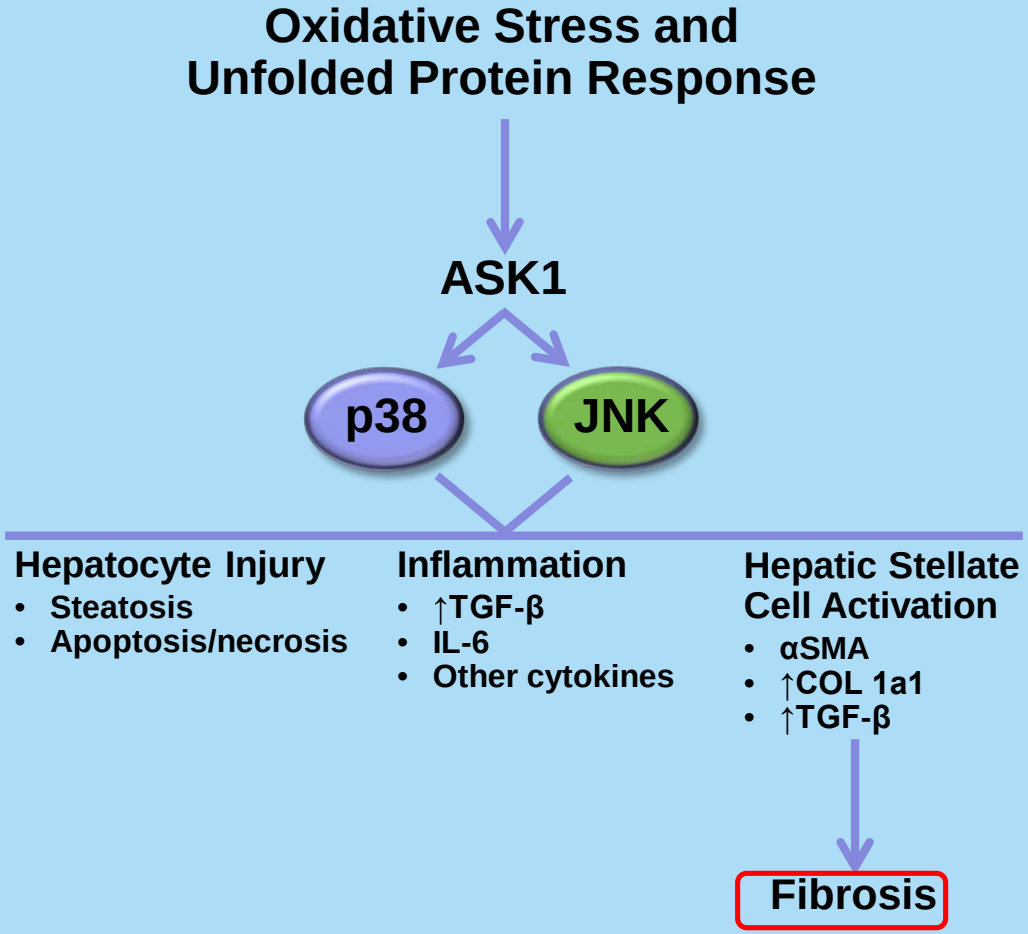
Younossi. EASL 2019. Abstr GS-06.

Slide credit: clinicaloptions.com

Apoptosis signal-regulating kinase 1 (ASK1) Inhibitors

Apoptosis Signal-Regulating Kinase 1 Inhibitor: Selonsertib

- ASK1
  - Mitogen-activated protein kinase
  - Transduction of apoptotic signals under oxidative stress conditions
- ASK1 pathway activated in NASH and correlates with fibrosis stage
  - **Inhibition of ASK1 improves steatosis, inflammation, and fibrosis in rodent models**
- Selonsertib
  - ASK1 EC_{50}: 10.8 nM

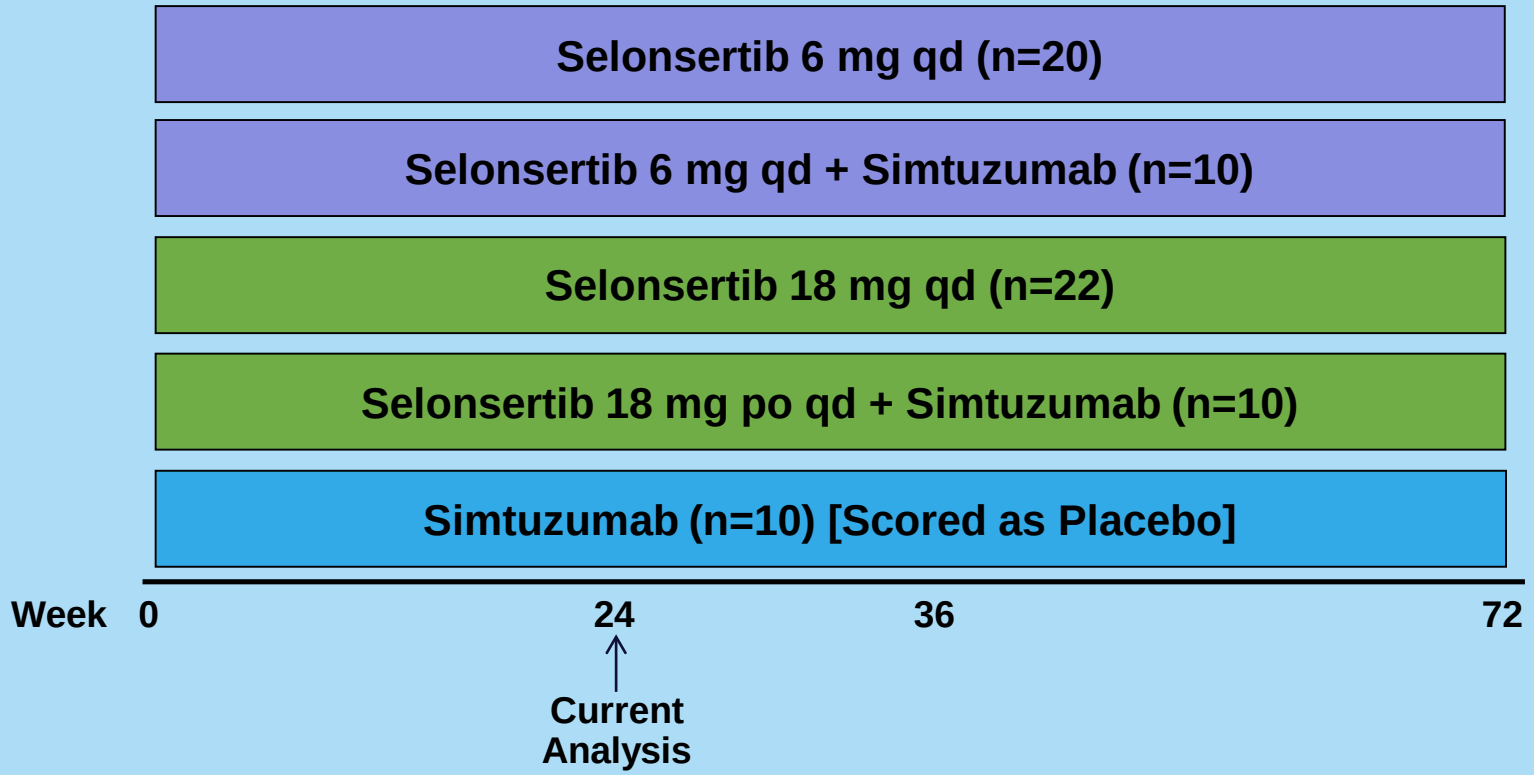


Perazzo H, et al. *Liver Int.* 2017;37:634-647.
Ikenaga N, et al. *Hepatology.* 2015;62(suppl S1):881A. Abstract 1367.
Xiang M, et al. *J Hepatol.* 2016;64:1365-1377.
Budas G, et al. *Hepatology.* 2016;64(suppl S1):788A. Abstract 1588.

Study 1497:
Selonsertib ± Simtuzumab in NASH Patients Without Cirrhosis

Phase 2 (n=72)
(US)

Open-label
Biopsy proven NASH
NAS ≥5
(individual scores each ≥1)
F2-F3 fibrosis
No cirrhosis

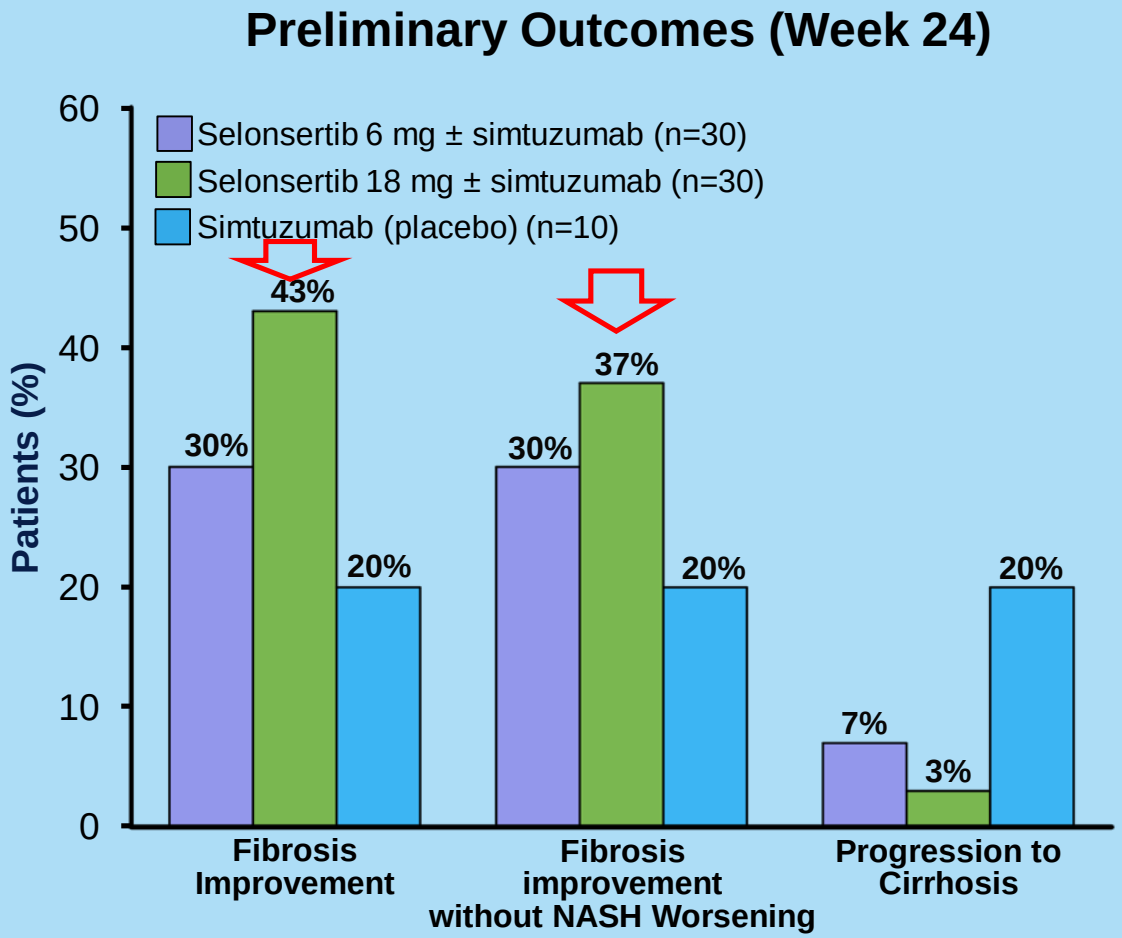


Patients stratified by diabetes status.
Simtuzumab 125 mg sq once weekly.
Endpoints:
- Fibrosis improvement in ≥1 stage.
- Fibrosis improvement without NASH worsening.
- Progression to cirrhosis.

Loomba R, et al. *Hepatology.* 2017;Sep 11. [Epub ahead of print].

Study 1497: Preliminary Results

- Selonsertib ± simtuzumab had beneficial effects (by biopsy) on
  - **Primary End-Point: Fibrosis improvement (≥1 fibrosis stage)** and reduced progression
- Generally well tolerated
  - No deaths
  - Discontinuations due to adverse events (18 versus 6 mg): 6% versus 3%
  - Serious adverse events (18 versus 6 mg): 3% versus 0%
  - Most common adverse events
    - Headache, nausea, sinusitis, nasopharyngitis, abdominal pain, fatigue
- Overall progression to cirrhosis: 7%



Data for patients with liver biopsies evaluable for fibrosis at baseline and week 24.

Loomba R, et al. *Hepatology.* 2017;Sep 11. [Epub ahead of print].

Anti-Steatosis Agents

Peroxisome proliferator-activated receptor (PPAR) agonists

PPARα/δ Agonist: Elafibranor

- PPARα/δ regulate lipid metabolism in liver and glucose homeostasis

PPARα Activation

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

PPARδ Activation

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

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

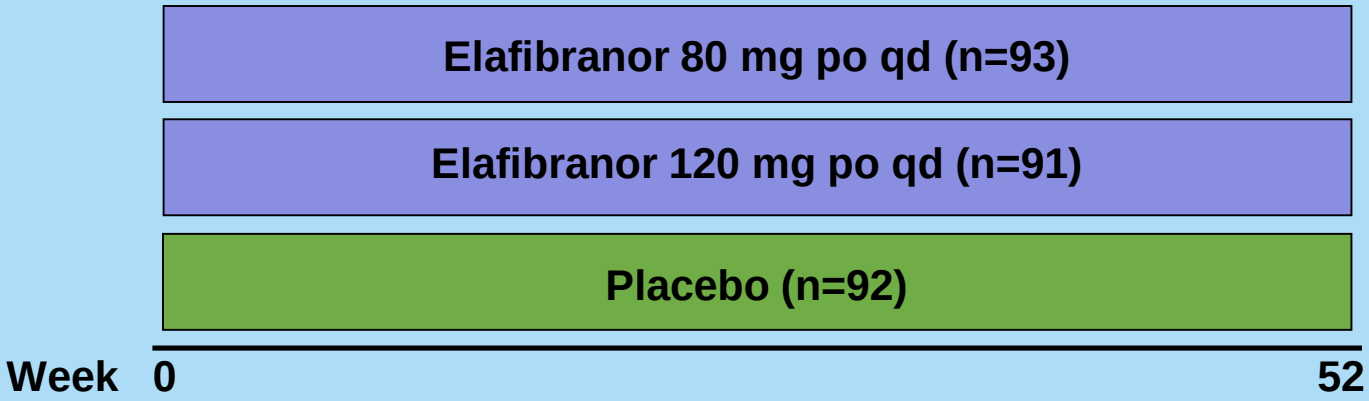
Perazzo H, et al. *Liver Int.* 2017;37:634-647.
Gawrieh S, et al. *Clin Liver Dis.* 2018;22:189-199.

GOLDEN-505 Study: Elafibranor in NASH Patients Without Cirrhosis

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

Placebo-controlled
NASH (biopsy diagnosis)
- **Steatosis >5% hepatocytes**
- **Hepatocyte ballooning**
- **Lobular inflammation**

NAS score 3-8
F0-F3
No cirrhosis



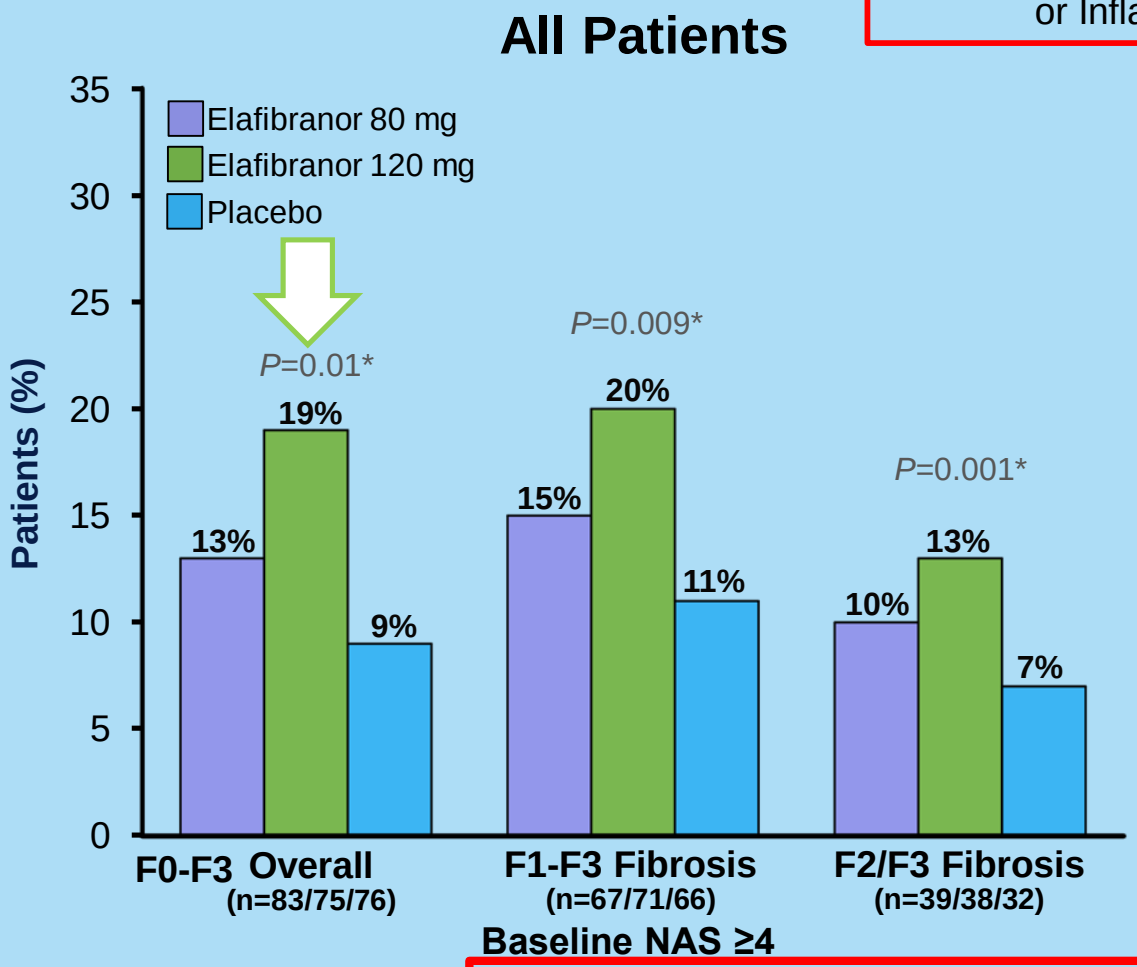
Patients stratified by diabetes status.
Primary endpoint (week 52, ITT):
- Reversal of NASH without worsening of fibrosis.
  - Reversal: absence (score of 0) of at least 1 of the 3 components of NASH (steatosis, ballooning, and inflammation).
  - Worsening of fibrosis: progression to bridging fibrosis or cirrhosis in patients without bridging fibrosis at baseline or to cirrhosis in patients with bridging fibrosis at baseline.

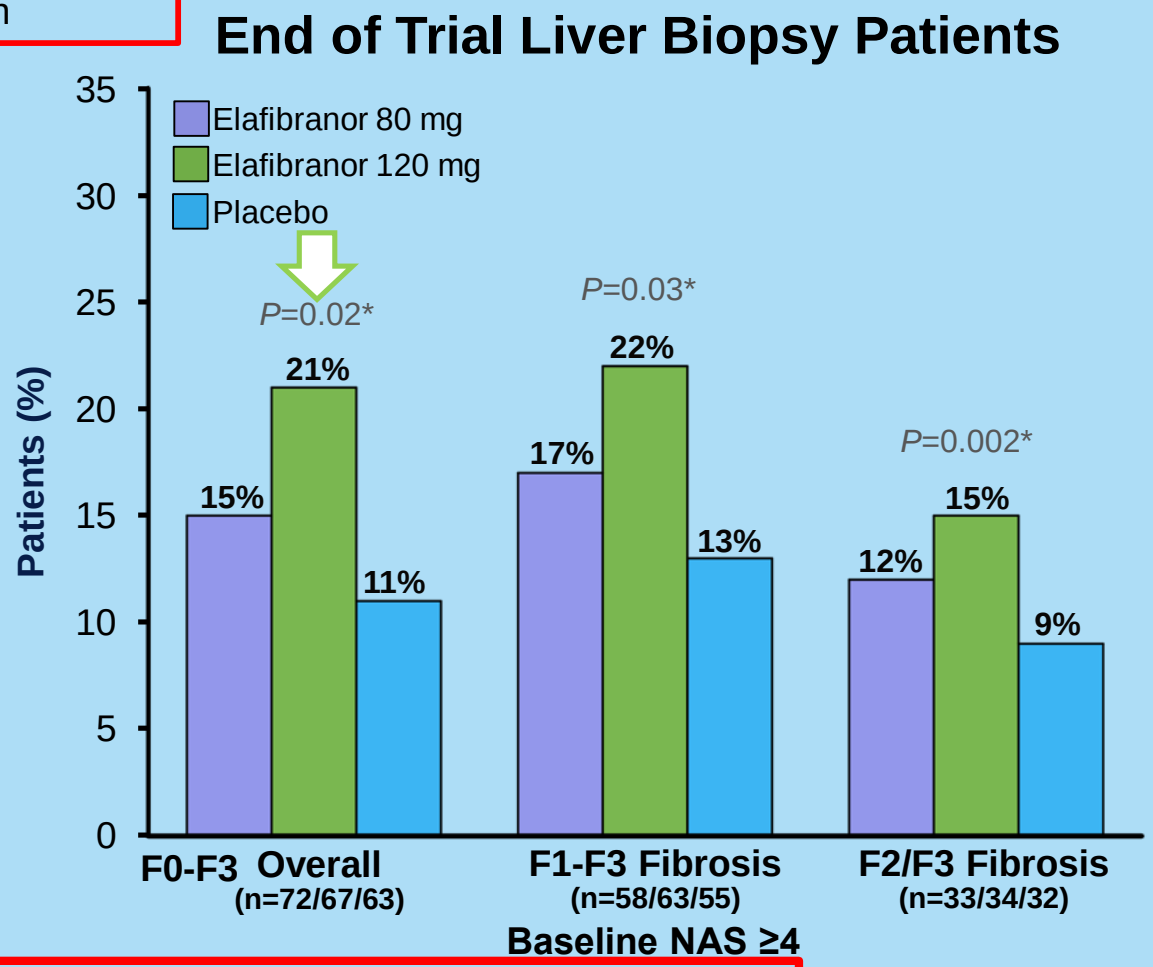
Post-hoc analysis of a modified definition of response:
- Resolution of NASH: disappearance of ballooning (score 0), together with either disappearance of lobular inflammation or the persistence of mild lobular inflammation only (score 0 or 1), and resulting in an overall pathologic diagnosis of either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

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

GOLDEN-505 (Elafibranor in NASH Patients Without Cirrhosis): Response in More Severe NASH (NAS ≥4 at Baseline)

Reversal of Steatosis, Ballooning or Inflammation





*Elafibranor 120 mg versus placebo. Protocol-defined response results.

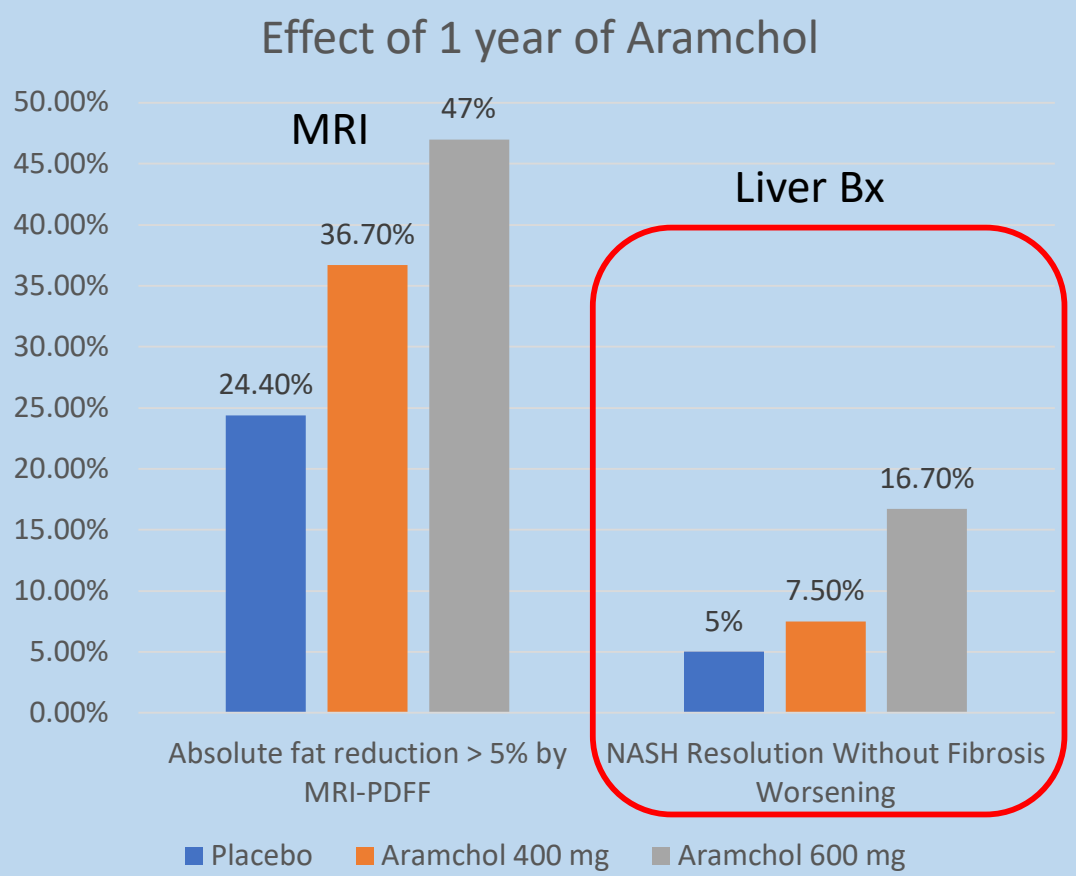
NASH Resolution without worsening of Fibrosis with 120 mg dose (**19%** vs 12%; odds ratio = 2.31; p=0.045)

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

Stearoyl coenzyme A desaturase 1 (SCD) Inhibitors

One-Year Results of the Global Phase 2b Randomized Placebo-Controlled Arrest Trial of Aramchol, a Stearoyl CoA type 1 Desaturase (SCD) Inhibitor, in Patients with NASH (AASLD 2018; LB-5)

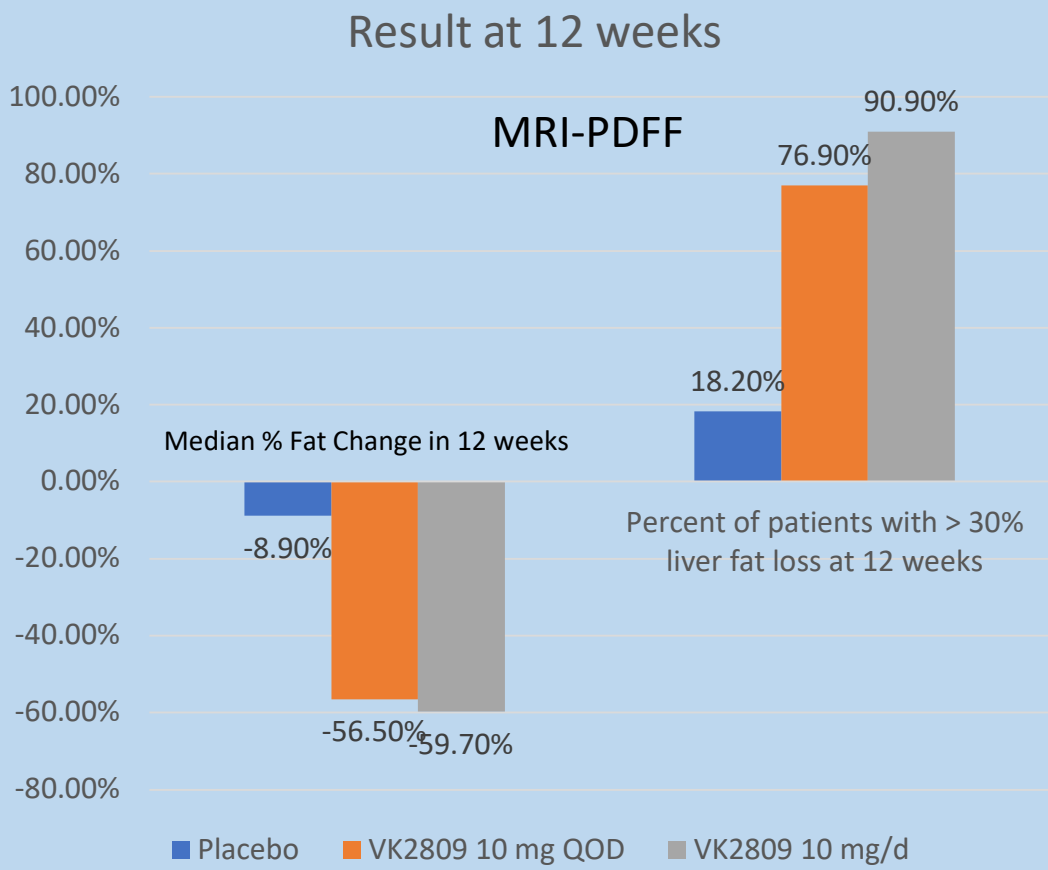
- AIM: Evaluate the effect of **Aramchol** in reducing liver fat (MRI-PDFF) and in **Reducing NASH activity without worsening fibrosis**
- **Methods:**
  - **247 overweight/obese** pts with pre-diabetes or diabetes and **biopsy-proven NASH** (with NAS ≥4; F<4).
  - **Liver biopsy** and liver fat measurement by **MR spectroscopy** (LF-MRS) were performed at baseline and week 52.
  - The primary endpoint was the absolute change from baseline in LF-MRS (**400 mg vs 600 mg vs placebo**).
  - Key secondary endpoints included: NASH resolution without fibrosis worsening, ≥1 stage fibrosis reduction without NASH worsening and ALT reduction.
- **Conclusion:** Aramchol significantly reduced liver fat, improved histology, hepatic biochemistry and glycemic control with excellent safety and tolerability. A phase 3 trial will be done.



Thyroid hormone receptor beta (THR-β) activation

VK2809, a liver-directed Thyroid Receptor Beta Agonist (THRBA), significantly reduces liver fat in patients with NAFLD: Phase 2 Randomized Placebo-Controlled Trial (AASLD 2018; LB-4)

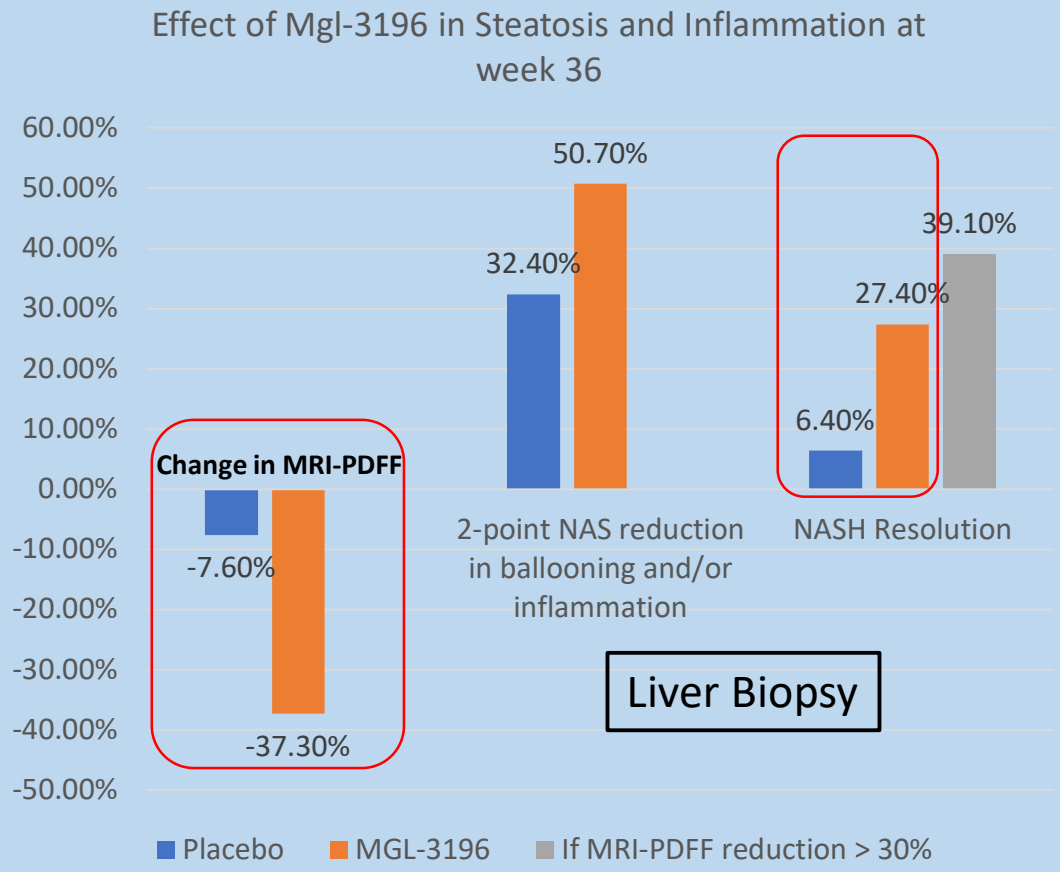
- **AIM:** Safety and efficacy of oral **VK2809** vs Placebo in **reduction of MRI Proton Density Fat Fraction (MRI-PDFF) over 12 weeks**, in NAFLD with Hypercholesterolemia (elevated LDL-C)
- **Methods:** Multicenter, double-blind, placebo controlled. **35 NAFLD patients** with liver fat > 8% by MRI-PDFF, and with LDL-C >/= 110 mg/dL and Triglycerides >/= 120 mg/dL. Divided in **Placebo vs VK2809 10 mg QOD vs VK2809 10 mg QD**
- **Results:** VK2809 patients reduced LDL-C by 20% or more as well as liver fat by MRI-PDFF
- **Conclusion:** VK2809 produced significant reductions in LDL-C and Liver fat content in NAFLD patients.



Background: MRI Proton Density Fat Fraction > 15.7% is associated with higher risk of fibrosis progression in NAFLD
Gastroenterology 2018 Aug;155(2):307-310

In a Placebo-Controlled 36-Week Phase 2 Trial, Treatment with **Mgl-3196** Compared to Placebo Results in Significant Reductions in Hepatic Fat (MRI-PDFF), Liver Enzymes, Fibrosis Biomarkers, Atherogenic Lipids, and Improvement in Nash on Serial Liver Biopsy (AASLD 2018; Abstract 14)

- **AIM:** assess efficacy of **Mgl-3196** (THR-Beta Agonist) in the 12-week interim analysis of the 36-week Phase 2 NASH study of MGL-3196.
- **Methods:**
  - 36-week multicenter, randomized, double-blind, pbo-controlled study of **107 adults with biopsy-confirmed NASH (NAS ≥4, F1-F3)** and hepatic fat fraction ≥10%, assessed by MRI-PDFF.
  - Serial MRI-PDFF, and paired liver biopsy study.
  - **Randomized 2:1**; patients received **daily oral MGL-3196 80 mg (73 pts) or pbo (34 pts)**, for 36 weeks.
- **Conclusion:**
  - At Week 36, MGL-3196 treatment compared with pbo resulted in significant and sustained reductions in hepatic fat on MRI-PDFF, liver enzymes, fibrosis biomarkers, atherogenic lipids and improvement in NASH on liver biopsy.
  - In MGL-3196 treated patients, ≥30% fat reduction (MRI-PDFF) at Week 12 predicted an improved NASH histologic response at Week 36.



Coagulation in Cirrhosis A Precarious Re-Balance

Clinical Practice Update

The State of Coagulation in Cirrhosis

O'Leary JG et al. Gastroenterology 2019 Jul;157(1):34-43

Re-balanced Systems (precarious state)

- Platelet deficit and dysfunction is **counterbalanced by** increased endothelial derived vWF and increased circulating activated platelets.
- Decreased liver-derived pro-coagulant factors V, VII, X are **counterbalanced with** low Protein C

Increased Bleeding Risk:

- **Portal Pressure** driven (not related to coagulation/fibrinolysis).
  - Worsen by excessive transfusion.
- Mucosal or Puncture site bleeding: due to
  - **Thrombocytopenia** due to sequestration (1/3), decreased survival, and low thrombopoietin (TPO)
  - **Premature clot dissolution** due to **"Accelerated Intravascular Coagulation and Fibrinolysis"** (AICF)
    - In DIC Factor VIII is low; in **AICF Factor VIII is high**.

Increased Thrombosis Risk:

- Due to elevated Endothelial-derived Factor VIII + low Protein C + venous stasis +/- endothelial injury.
  - Risk of Portal vein and Mesenteric vein thrombosis
  - Risk of Peripheral limb DVT

Hemostasis Tests in Cirrhosis

O'Leary JG et al. Gastroenterology 2019 Jul;157(1):34-43
Intagliata NM et al. Thromb Haemost 2018;118:1491–1506

Platelet Count:

- **Testing recommended** before **"High Risk"** procedures
- Traditionally **50,000 to 56,000** needed to promote thrombin generation
  - Low count, but **increased platelet effectiveness** due to **increased circulating activated platelets and elevated endothelial-derived vWF**.

Fibrinogen Level:

- **Testing recommended** before **"High Risk"** procedures
- **Level needed is > 120 mg/dL.**
- **Better at predicting bleeding risk than INR.**
- Fibrinogen Levels decreased because:
  - Most (98%) is generated in the liver.
  - Its half life is shortened in cirrhosis (normal is 4 days).

INR (International Normalization Ratio):

- **Testing NOT recommended.**
- **Does NOT predict risk of bleeding.**
  - Measures pro-coagulant factors I, II, V, VII and X.
  - Does not measure the effect of the deficit of Protein C.
  - Depends in which thromboplastin is used to run the test (different INR in different hospitals).
- **Attempts to correct it with FFP increases portal pressure.**

Complications of Blood Product Transfusion

Rahimi RS et al, HEPATOLOGY, Vol. 63, No. 2, 2016; 368-370

Timing	Complication
Short Term	Cost per Unit: Platelets = $ 500; FFP = $ 1600-2400 Transfusion reactions Cross-match errors Exacerbation of portal hypertension Transfusion-related acute lung injury (TRALI) Prolonged ventilator time Increased mortality Infection transmission Potential hypercoagulable complications, eg, portal vein thrombosis
Intermediate Term	Increased intensive care unit stay Increased hospital length of stay Systemic inflammatory response syndrome (SIRS) Transfusion-related acute lung injury (TRALI) Increased mortality
Long Term	HLA antibody formation Disease transmission Increased mortality

Procedure Related Bleeding Risk in Cirrhosis

Intagliata NM et al. Thromb Haemost 2018;118:1491–1506.

- Correction of Coagulation is NOT recommended before Low nor Intermediate Risk Procedures
- **Individualization is often necessary**

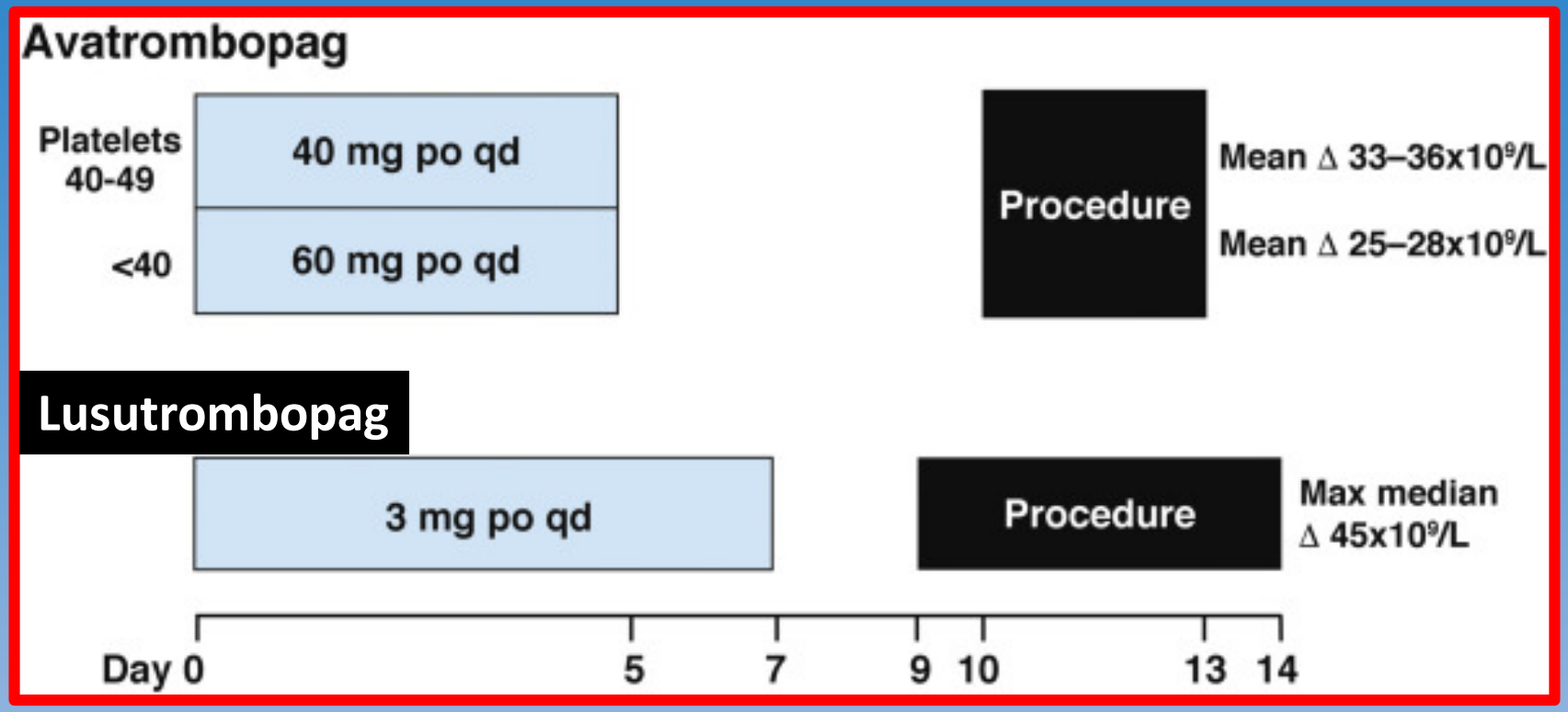
Higher risk procedures	Intermediate risk procedures	Lower risk procedures
Brain or spinal surgery	Lumbar puncture	Paracentesis
All major surgery (cardiac, intra-abdominal and orthopedic)	Percutaneous or transjugular liver biopsy	Thoracentesis
Intra-cranial pressure catheter insertion	Transjugular intrahepatic portosystemic shunt	Dental extraction
Endoscopy (large polypectomy with endoscopic mucosal or sub-mucosal resection, NOTES)	Endoscopy (e.g. percutaneous gastrostomy placement, cystgastrostomy, biliary sphincterotomy)	Endoscopy (e.g. diagnostic, variceal band ligation, uncomplicated polypectomy)
	Percutaneous biopsy of extra-hepatic organ or lesions	Cardiac catheterization
	Trans-arterial or percutaneous HCC therapies	Central line placement

Correction of Coagulation Parameters in Cirrhosis Before High Bleeding Risk Procedures

- In high risk procedures, correction of **Platelet count < 50,000** is reasonable
  - One-unit single donor platelets increases plat count by 5-10,000
  - In **elective procedures** can be corrected with oral **Avatrombopag** 40-60 mg/day x 5 days, or **Lusutrombopag** 3 mg a day x 7 days
- In high risk procedures, correction of **Fibrinogen < 120 mg/dL** is reasonable.
  - One unit of cryoprecipitate (10-20 mL each unit) per 10 kg of weight, increase fibrinogen by 50 mg/dL
- In bleeding after procedure consider **Antifibrinolytic agents**:
  - Likely related to **"Accelerated Intravascular Coagulation and Fibrinolysis"** (High Factor VIII)
  - Suspect in delayed or diffuse mucosal or puncture site bleeding
  - Aminocaproic acid 3 grams oral QID, or Intravenous 5 grams in 250 mL NS over 1 hour + 1 gm in 50 mL NS per hour until bleeding stops
  - Tranexamic acid 1 gm IV every 6 hours, until bleeding stops.

- O'Leary JG et al. Coagulation in Cirrhosis. Gastroenterology 2019

Oral Agent to Treat Thrombocytopenia



65 to 69% pf patients reach Platelet count >/= 50,000

Hepatocellular Carcinoma

Update

Groups with Surveillance Benefit for HCC

Population group	Threshold for Surveillance Efficacy	HCC Incidence
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
PBC Stage 4 (cirrhosis)	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown

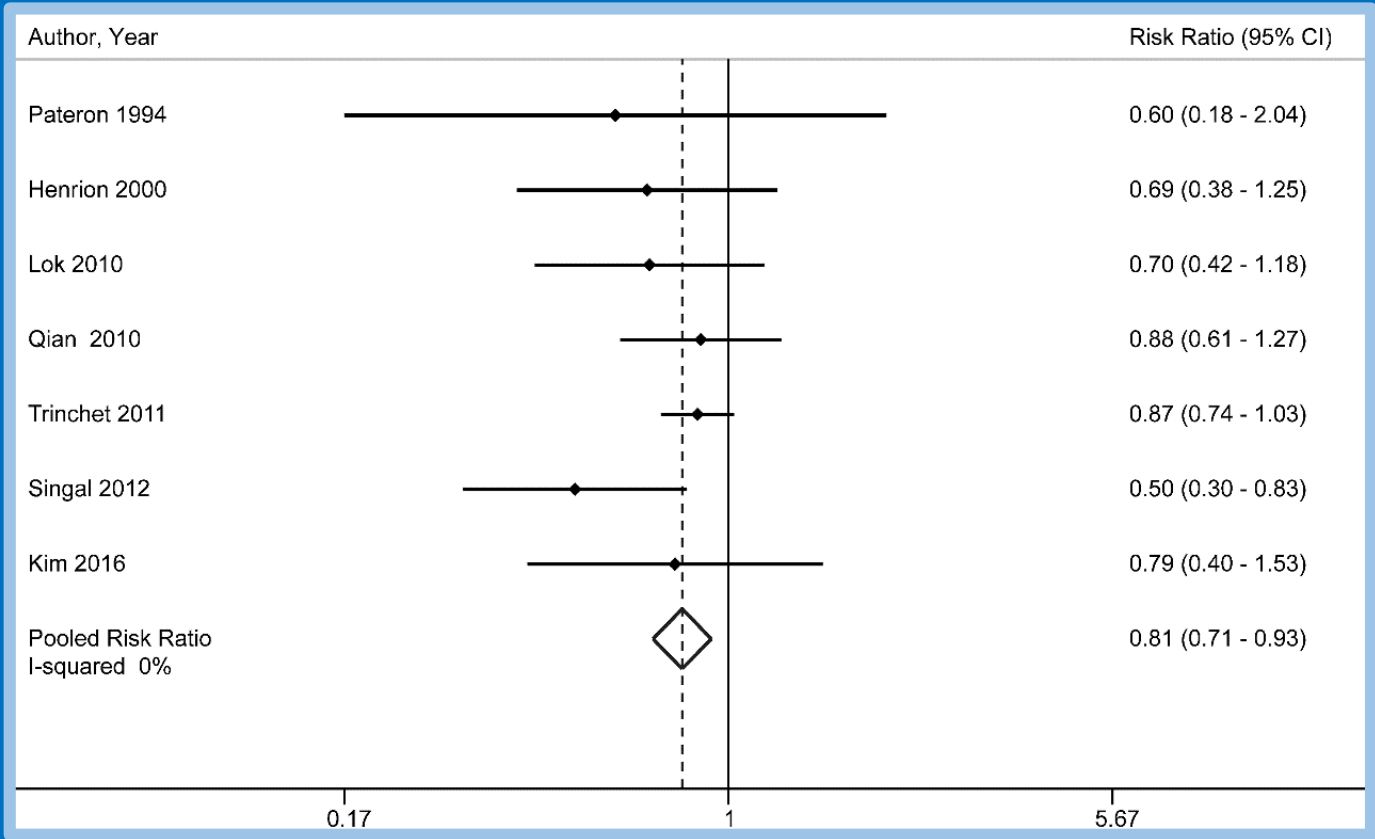
Groups with Uncertain Surveillance Benefit for HCC

Population group	Threshold for Surveillance Efficacy	HCC Incidence
Hepatitis B carriers younger than 40 (males) or 50 (females), without family history of HCC	0.2	< 0.2% per year
Hepatitis C with stage 3 fibrosis	1.5	< 1.5% per year
NAFLD without cirrhosis	1.5	< 1.5% per year

Surveillance Testing Method
AASLD 2018

- **Ultrasound +/- <u>Alpha-Fetoprotein</u> every 6 months**
  - Surveillance NOT recommended for patients with cirrhosis with Child's class C unless they are on the transplant waiting list, given the low anticipated survival for patients with Child's C cirrhosis.
  - Multiphase CT and MRI are not recommended as the primary modality for the surveillance.
    <u>May be utilized for surveillance in</u>:
    - Select patients with a high likelihood of having an inadequate Ultrasound
    - If Ultrasound is attempted but inadequate.
- **<u>RECALL</u>:**
  - US lesion >/= **1 cm** or AFP **> 20 ng/mL** (or raise > 5 ng/mL/month)
  - Performed with Multi-phase CT Scan or Four-phase MRI, "liver mass" protocol.
  - Lesions < 1 cm in cirrhosis are followed with repeat US +/- AFP in 3-6 months (AASLD 2018), or with Four-Phase MRI or Multiphase CT in 3-6 months (**J AM COLL RADIOL** 2017;14:1429–1437).

Sensitivity of Ultrasound +/- AFP for Early HCC



Benefit of AFP consistent across subgroups

-Prospective studies:

RR 0.78 (0.66 – 0.92)

-Studies in United States:

RR 0.59 (0.41 – 0.85)

-Cirrhosis-only studies:

RR 0.76 (0.60 – 0.95)

-Studies after 2000:

RR 0.79 (0.66 – 0.95)

Diagnostic odds ratio

-Ultrasound: 7 (3-15)

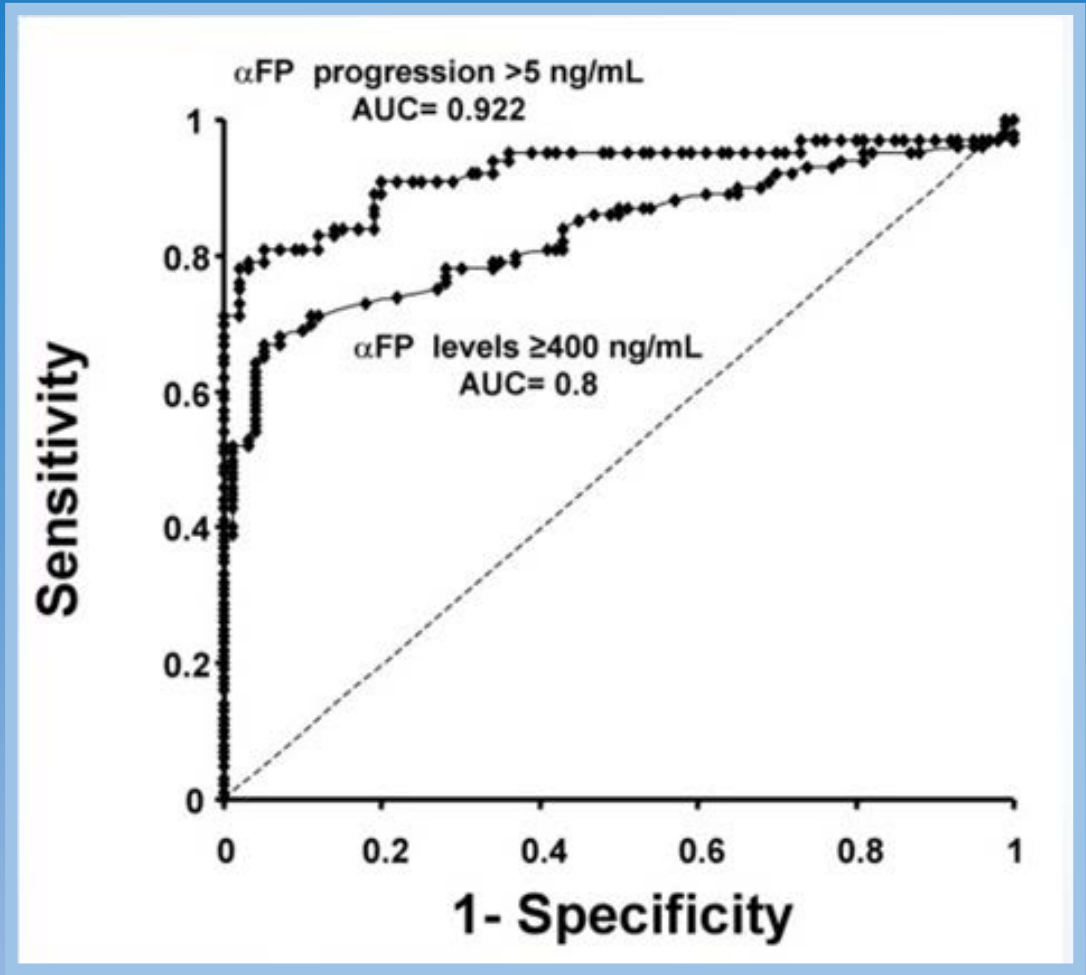
-US+AFP: 8 (3-23)

Sensitivity: Ultrasound 45% (30-62%) vs. US+AFP: 63% (48-75%)

Specificity: Ultrasound: 92% (85-96%) vs. US+AFP: 84% (77-89%)

Singal et al, ILCA 2018

Progressive Rise of AFP over Time

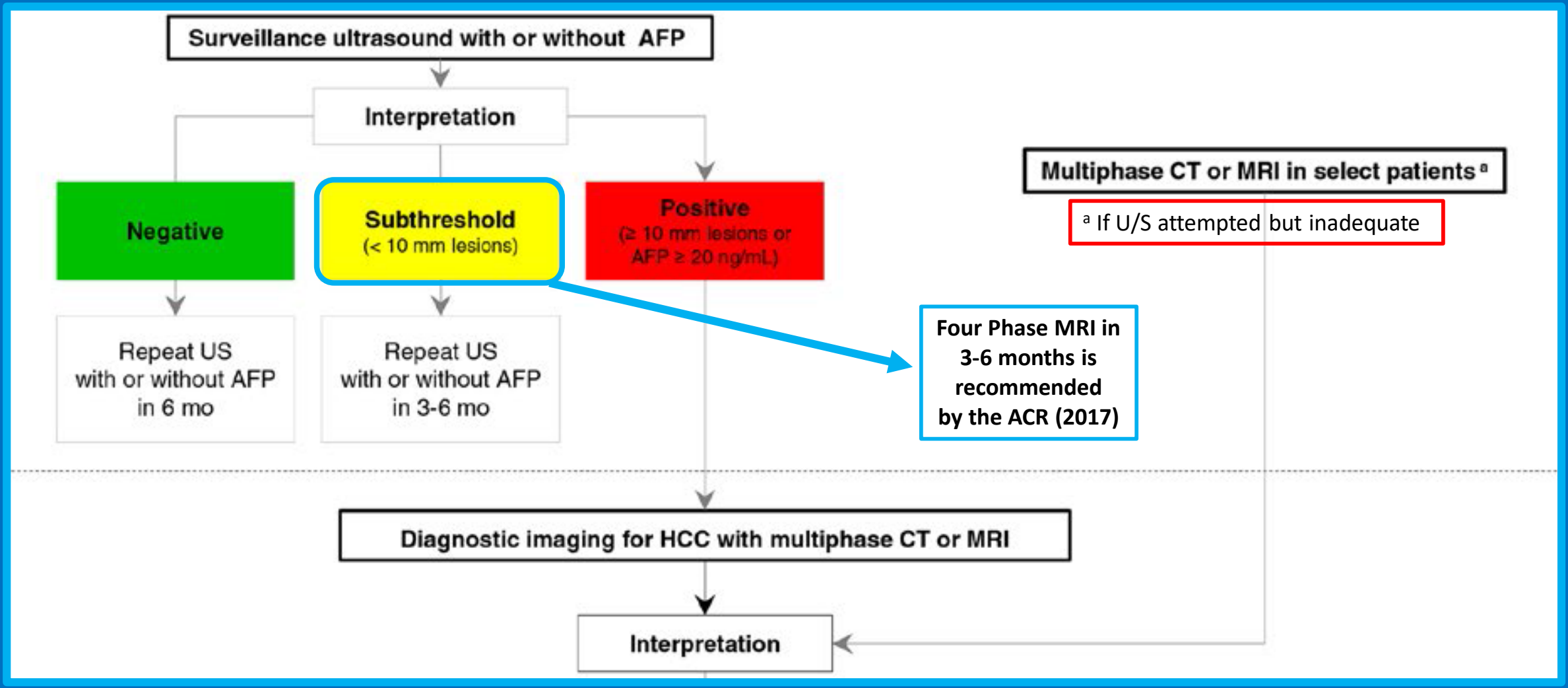


αFP	HCC Prevalence (%)	PPV (%)	NPV (%)
≥200 ng/ml	10	97.58	93.4
	5	95.03	96.7
≥400 ng/ml	10	95.7	91.86
	5	91.4	95.97
Elevation ≥7 ng/ml/month	10	98.7	96.92
	5	97.4	98.52

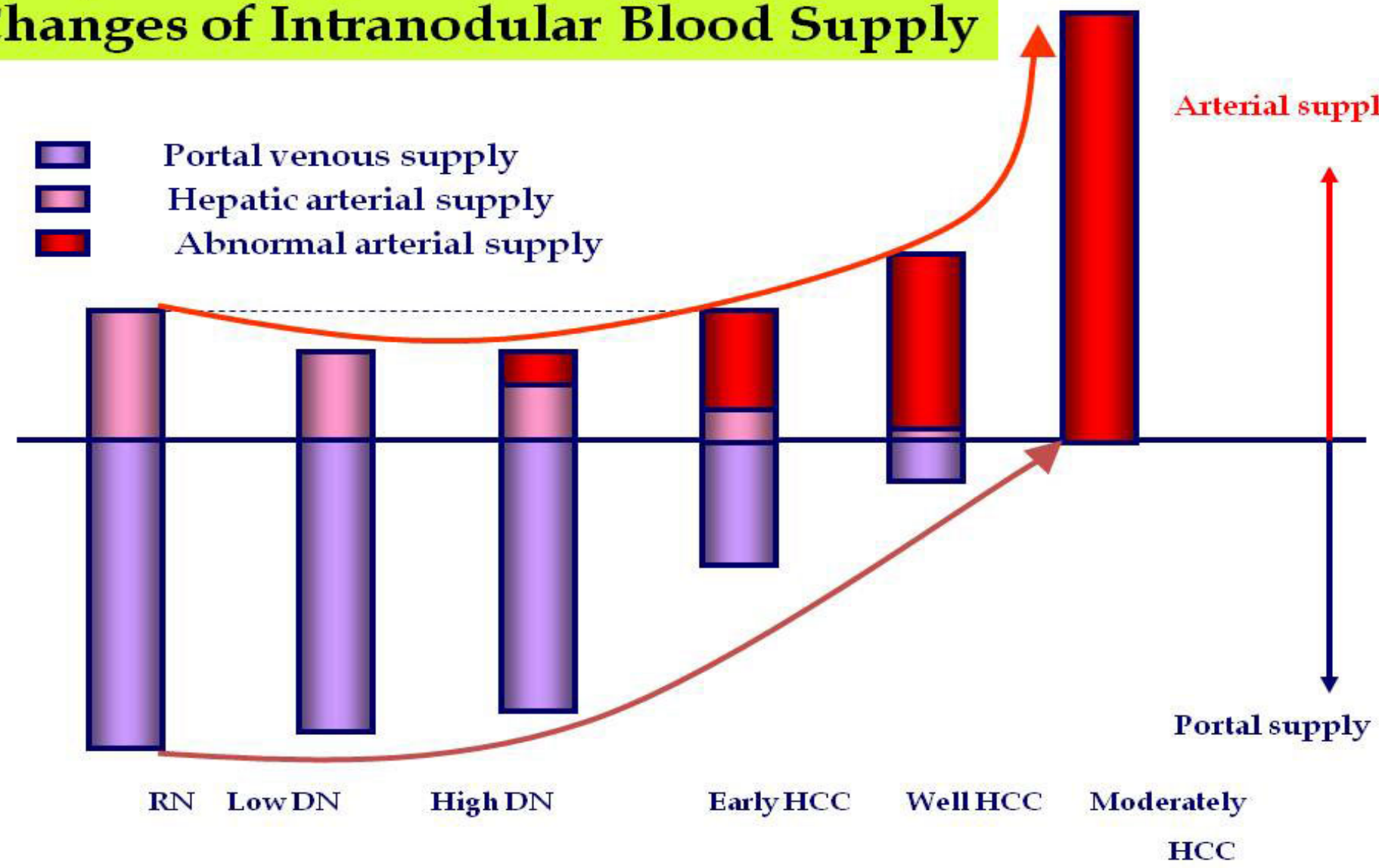
Arrieta et al, BMC Cancer 2007, Lee et al, Clin Gastro Hep 2013

HCC Surveillance every 6 months

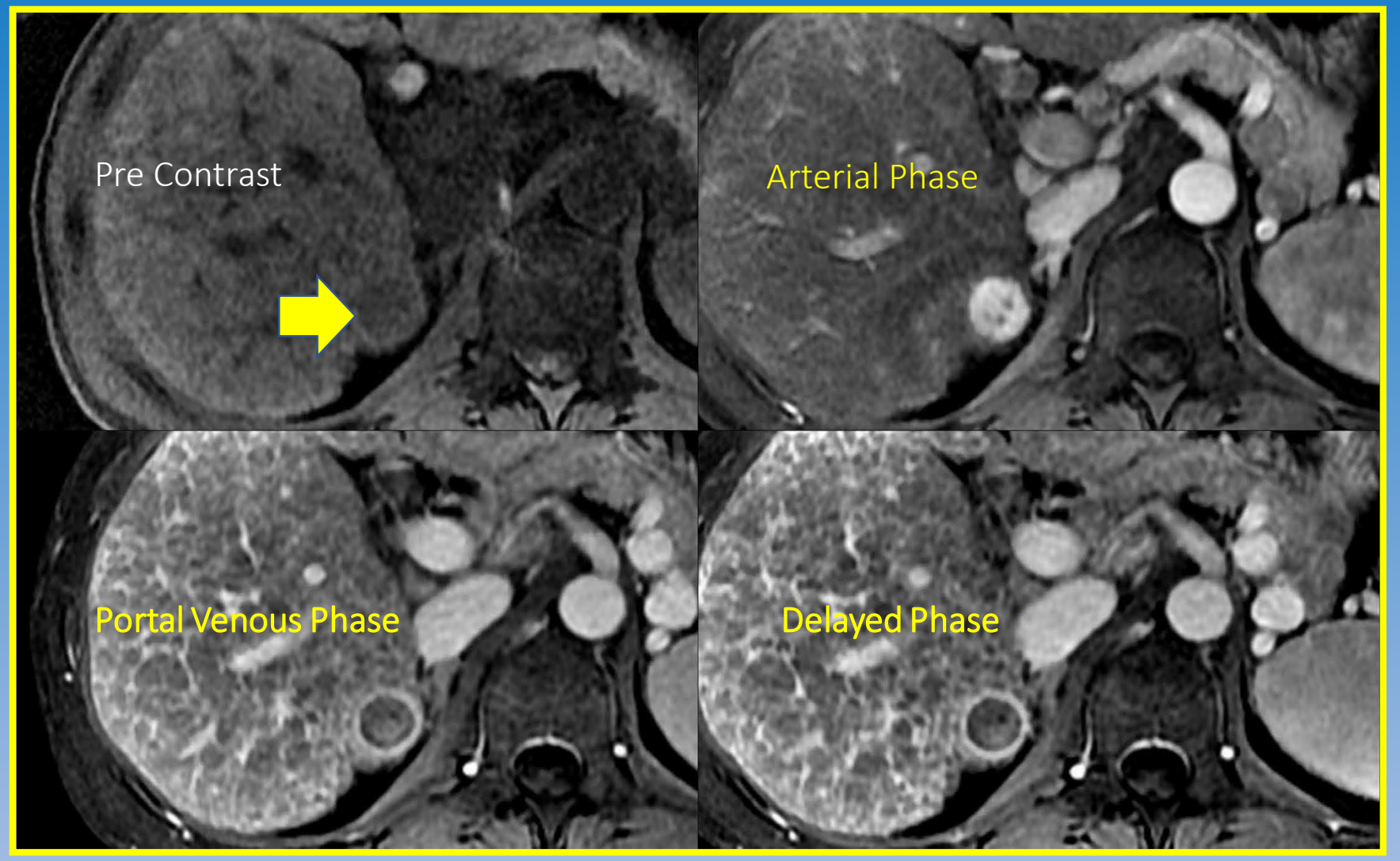
AASLD 2018



Stepwise Hepatocarcinogenesis and Changes of Intranodular Blood Supply



Four Phase Imaging of Hepatocellular Carcinoma



Li-RADS Criteria for HCC Diagnosis 2018

CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5

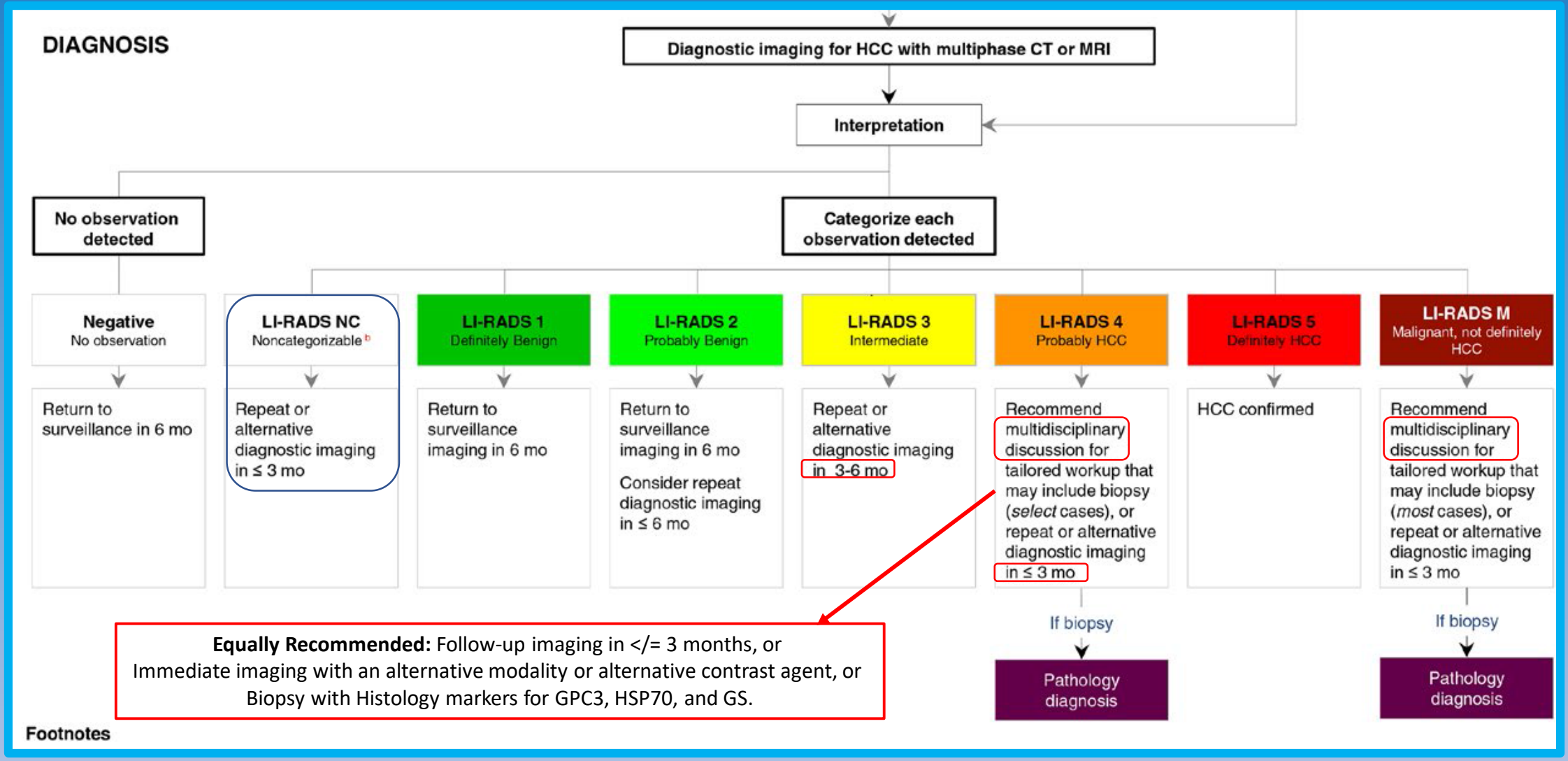
Observations in this cell are categorized based on one additional major feature:

- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

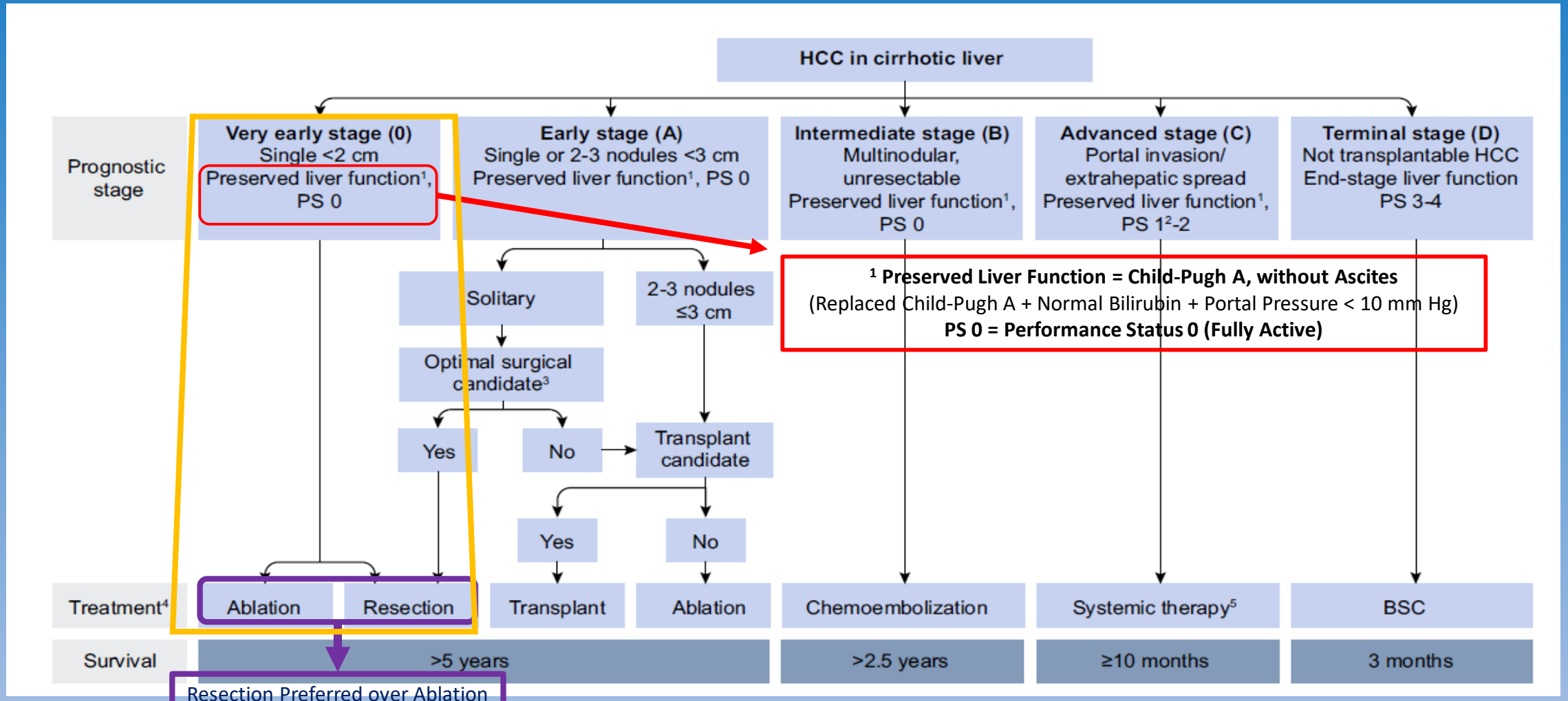
If unsure about the presence of any major feature: characterize that feature as absent

No Radiologic Dx of HCC if lesion < 10 mm, or if without Arterial Phase Hyper Enhancement

Evaluation of Cirrhosis with Liver Nodule >/= 1 cm or AFP > 20 ng/mL
AASLD 2018

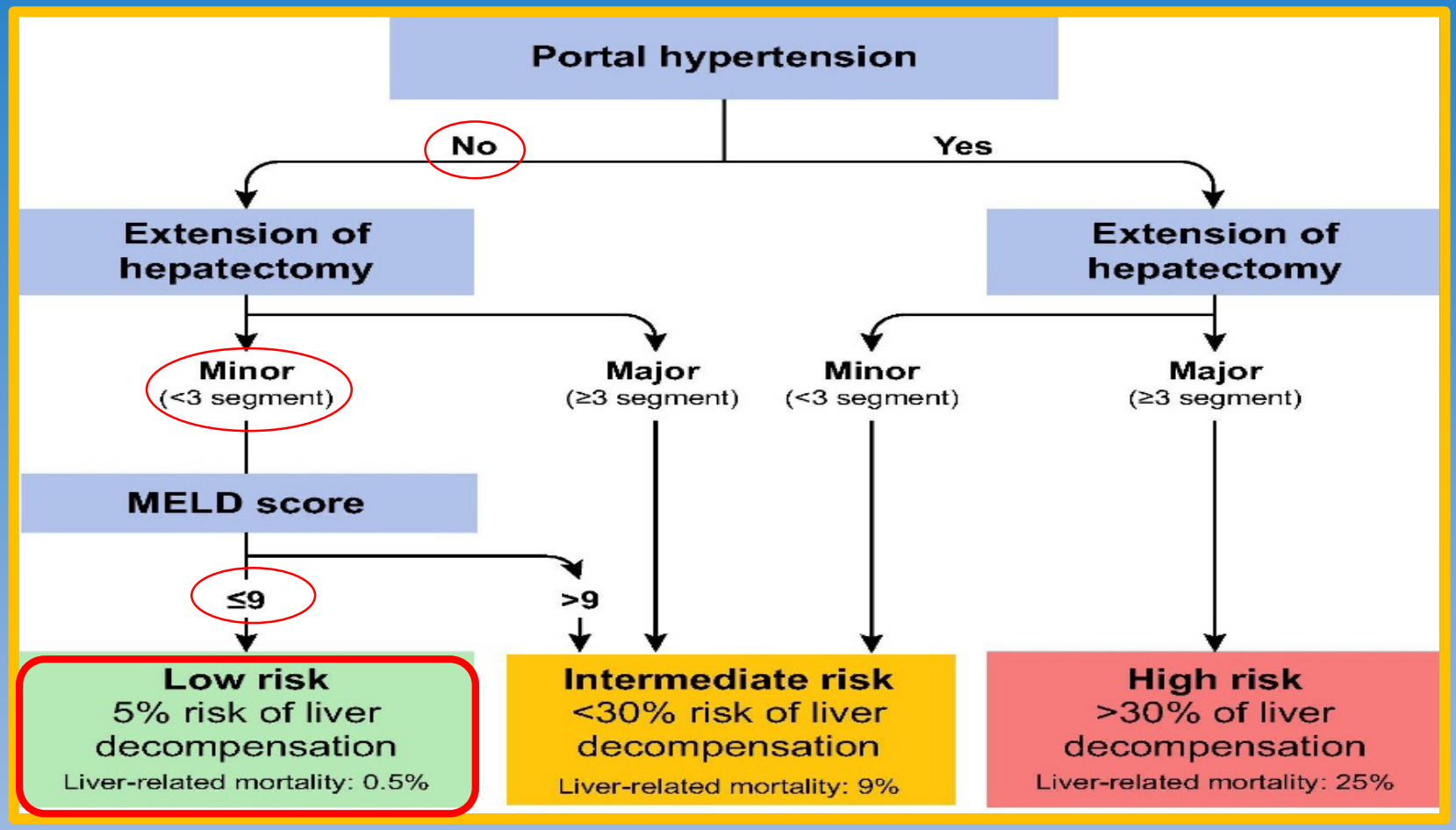


Staging and Treatment of HCC – AASLD Guidelines based on BCLC proposal



EASL Clinical Practice Guidelines, 2018 and AASLD Practice Guidelines, 2018

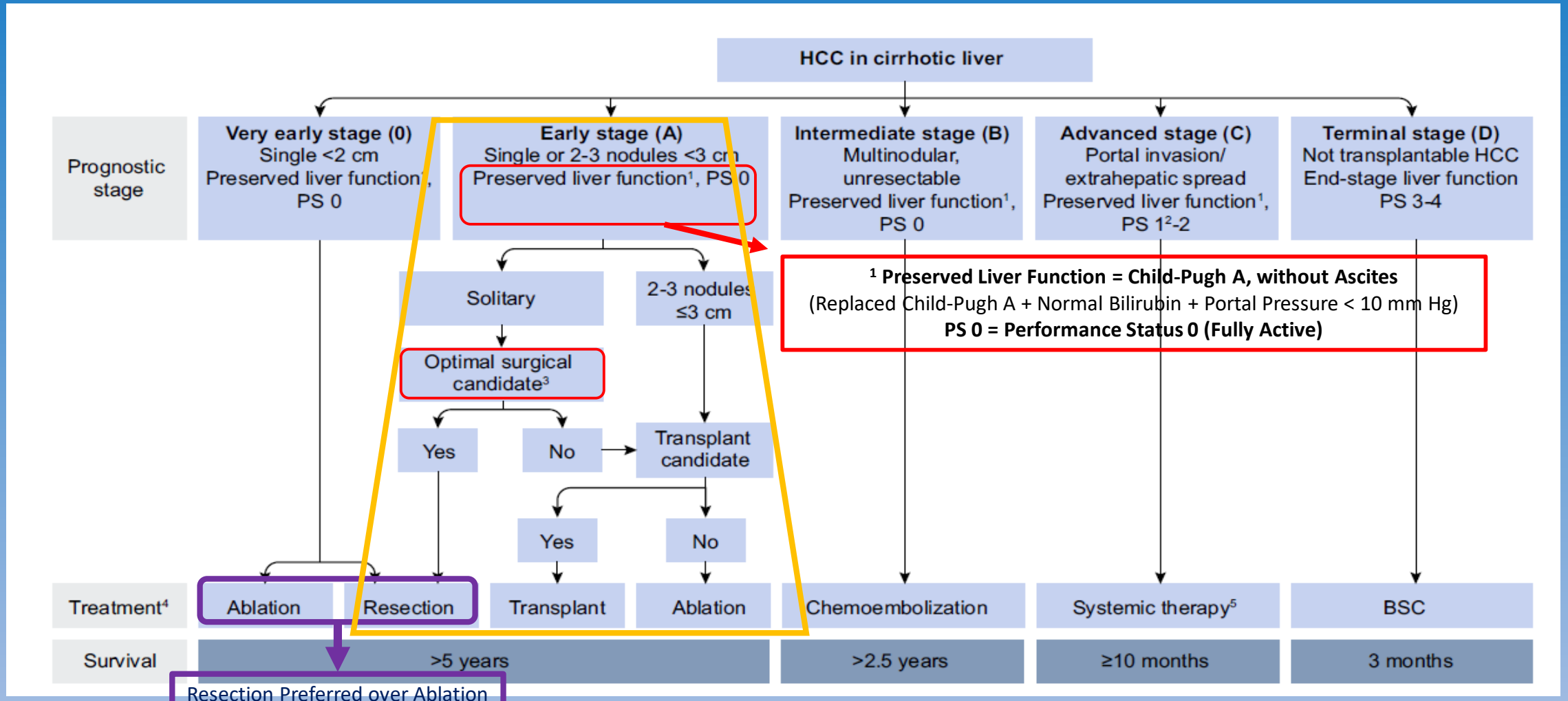
BCLC Definition of "Optimal Surgical Candidate"



Portal Hypertension = HVPG > 10 mm Hg

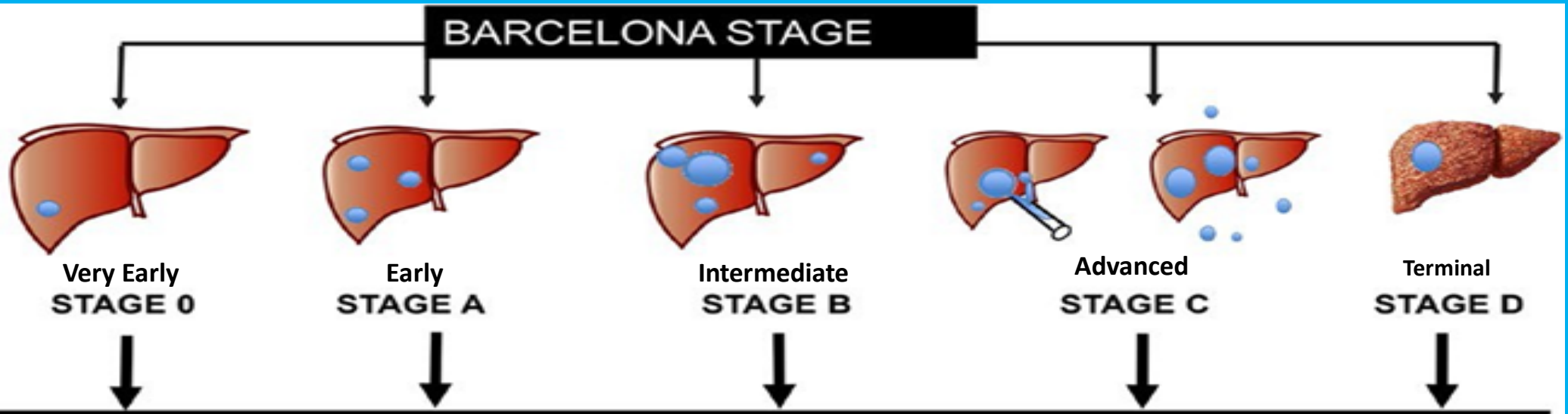
EASL Clinical Practice Guidelines 2018

Staging and Treatment of HCC – AASLD Guidelines based on BCLC proposal



EASL Clinical Practice Guidelines, 2018 and AASLD Practice Guidelines, 2018

HCC Therapy 2019



Level of Evidence	Very Early STAGE 0	Early STAGE A	Intermediate STAGE B	Advanced STAGE C	Terminal STAGE D
1	Resection		TACE	Sorafenib (1L) Lenvatinib (1L) Regorafenib (2L) Cabozantinib (2L)	
2	RFA MWA	Resection OLT RFA MWA TARE TACE SBRT	TARE Downsize OLT	Nivolumab (2L) Pembrolizumab (2L)	OLT BSC
3				TARE	

Resection if: "Optimal Surgical Candidate" and "Preserved Liver Function"

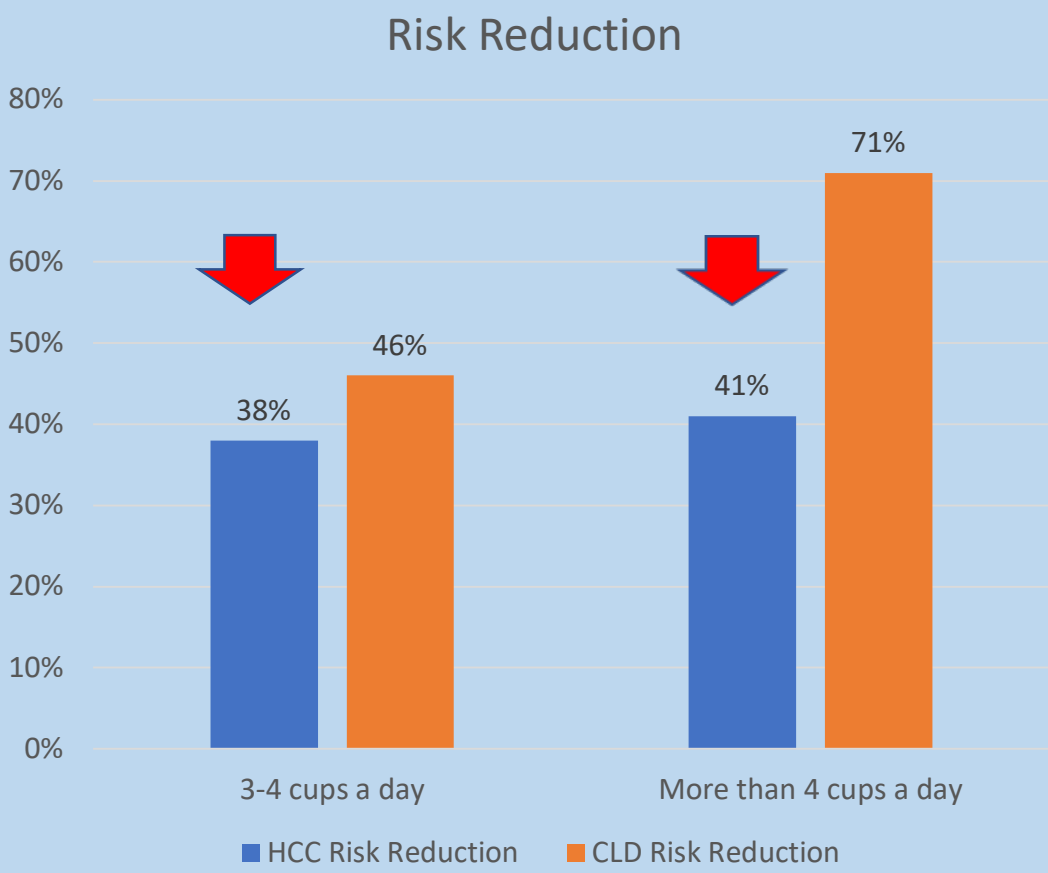
Landscape of Systemic Therapy 2019

Agent	Class	Line of Treatment	Status	Result
SYSTEMIC MEDICAL THERAPY				
Sorafenib	TKI	**First line**	SOC	Median OS 10.7 mos
Lenvatinib	TKI	**First line**	Approved 2018	Median OS 13.6 mos
Regorafenib	TKI	Second line	FDA Approved 2017	Median OS 10.6 mos
Cabozantinib	TKI, Anti-MET	Second line	Approved 2019	Median OS 10.2 mos
Ramucirumab	Anti-VEGFR2	Second line for AFP >400	Phase III	Median OS 8.5 mos
IMMUNOTHERAPY				
Nivolumab	Anti-PD-1	Second line	FDA Conditionally Approved 2017	Median OS 13.2 mos phase 1/2
Pembrolizumab	Anti-PD-1	Second line	FDA Approved 2018	Median OS> 12 mos

Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort

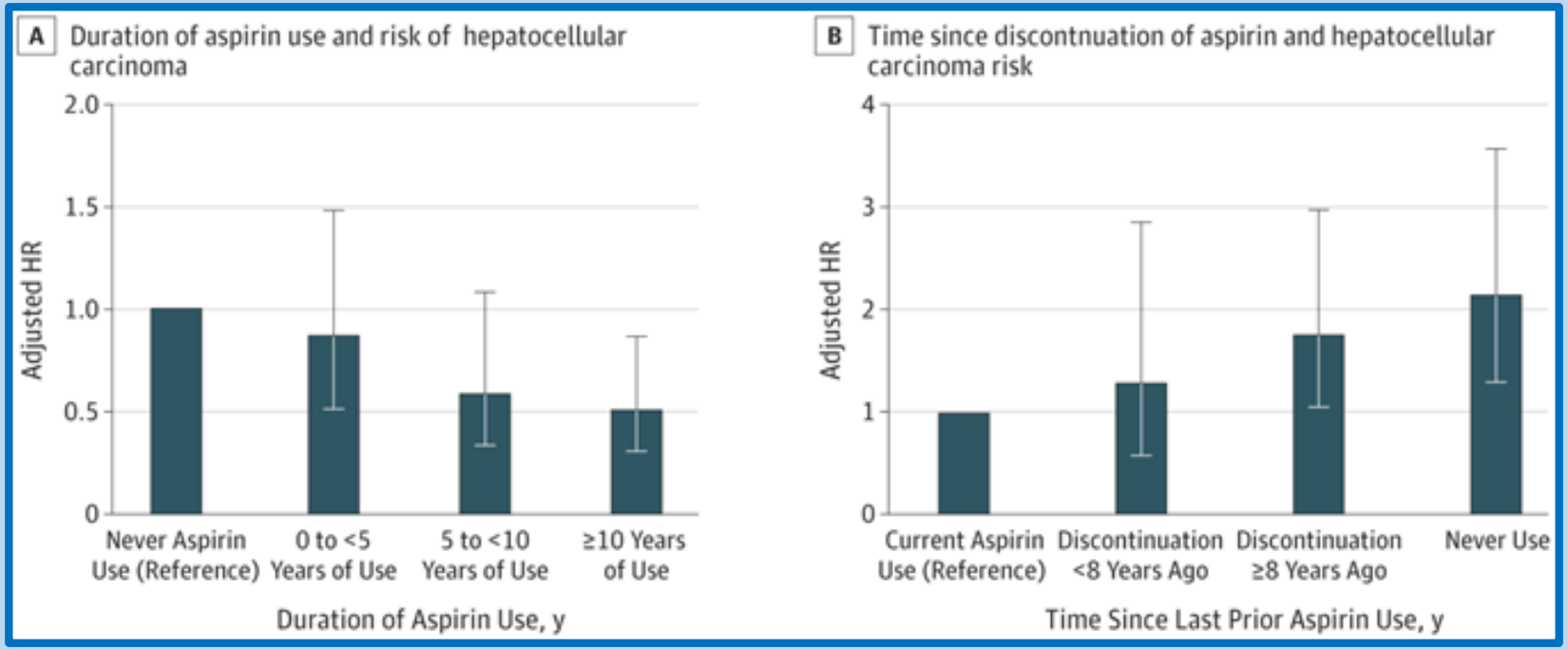
Setiawan VW et al. Gastroenterology. 2015 Jan;148(1):118-25

- Large Prospective study: Multi-ethnic Cohort (MEC): **>215,000 participants**
  - Designed to assess diet, lifestyle and genetic risks for cancer and chronic disease.
  - CA and Hawaii: established 1993-1996
- Looked at CLD, HCC and coffee consumption
- Equal for **decaf and caffeinated**
- Equal among all ethnic groups and gender
- Results were also independent of BMI, smoking status, alcohol intake and Diabetes status.



Aspirin Use May Also Decrease Risk of HCC

- Pooled analysis done of 2 prospective US cohort studies, including 133,371 participants, more than 26 years of follow up, and over 4 million person-years.
- Regular aspirin use was associated with reduced risk of HCC (adjusted HR 0.51; 95% CI 0.34-0.77)



Simon et al, JAMA Oncology 2018

Lipophilic statins and risk of hepatocellular carcinoma (HCC) and mortality in chronic viral hepatitis

Lipophilic Statins: atorvastatin, simvastatin, fluvastatin and lovastatin

Aim:

To examine the associations between lipophilic and hydrophilic statin use and risk for incident HCC and death, in a prospective, nationwide population with confirmed chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection

Methods:

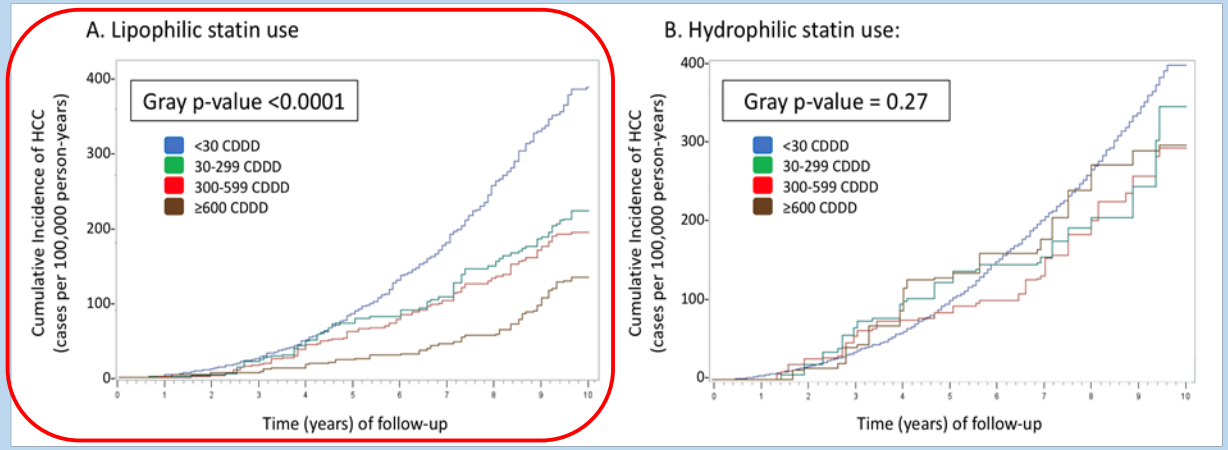
- Using validated Swedish nationwide registers, we conducted a prospective, nationwide cohort study, using a 1:1 propensity score-matched, new-user design.
- Using Cox proportional hazards modeling that accounted for competing risks, we estimated the subdistribution hazard ratios and 95% confidence intervals for incident HCC and death.

Conclusions:

Lipophilic but not hydrophilic statin use is associated with dose-dependent reductions in risk for incident HCC and death.

Simon TG, et al., Abstract 93

Cumulative incidence of HCC with lipophilic statins (A) or hydrophilic statins (B)



Cumulative defined daily dose (cDDD) of lipophilic statins and risk for HCC:

	Non-use	30-299 cDDD	300-599 cDDD	≥ 600 cDDD	*P*-trend
No. Cases / Person-Years	341/88,695	63/22,250	46/21,094	76/33,822	--
Crude	1 (Reference)	0.81 (0.49-1.14)	0.59 (0.48-0.82)	0.43 (0.29-0.67)	<0.001
Adjusted*	1 (Reference)	0.85 (0.51-1.22)	0.57 (0.47-0.79)	0.46 (0.31-0.72)	<0.001

* Model adjusted for age (years), sex, duration of HBV/HCV (years), cirrhosis (yes vs no), ever-use of antiviral therapy, type 2 diabetes (yes vs no), obesity (yes vs no), use of aspirin (yes vs no), use of metformin (yes vs no).

ALT levels and HCC risk in Caucasian CHB patients under long-term therapy with ETV or TDF

Hypothesis/Aim/Objective:

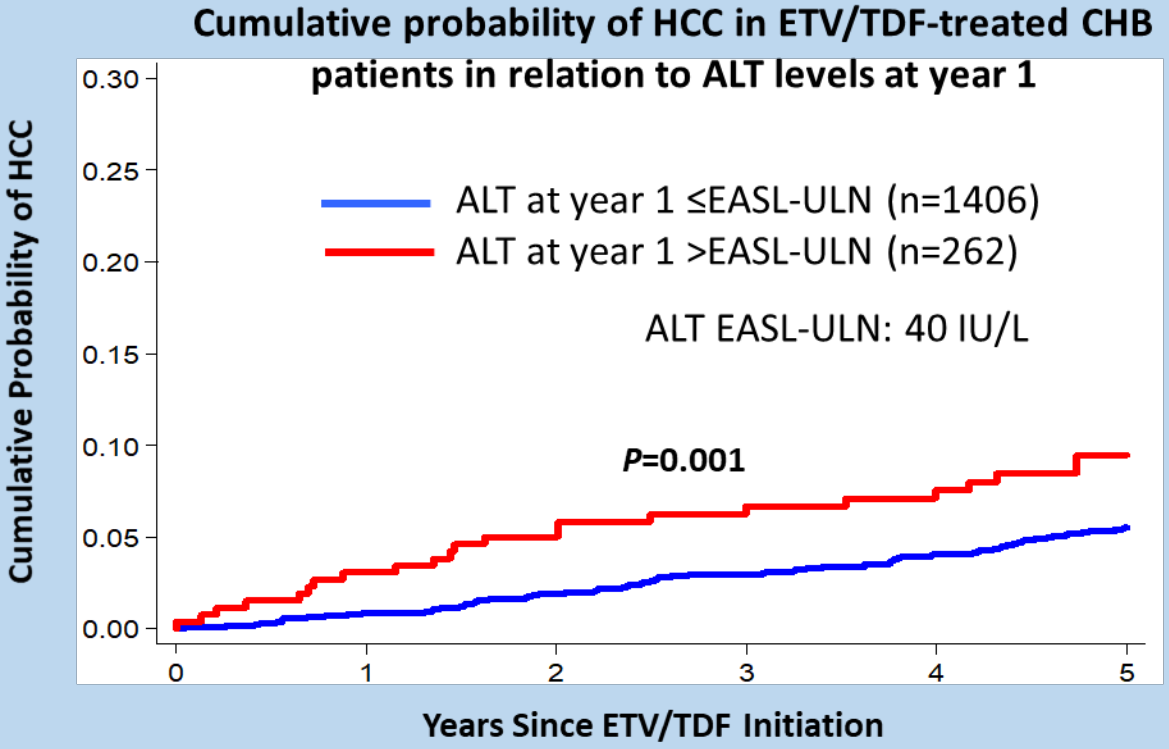
To assess whether ALT levels affect the incidence of HCC in CHB patients treated with long-term ETV/TDF therapy

Methods:

- PAGE-B cohort: 1951 adult Caucasians with CHB ± compensated cirrhosis
- Age: 53 ± 14 years, males: 71%, HBeAg-positive: 18%, compensated cirrhosis: 27%
- Mean follow-up: 6.9 ± 2.8 (median: 7.3) years from ETV/TDF onset

Conclusions:

In ETV/TDF-treated Caucasian CHB patients, elevated ALT (>EASL-ULN=40 IU/L) at 1 year of therapy increases the HCC risk, particularly in patients with cirrhosis at baseline.



ALT >EASL-ULN at year 1 was independently associated with development of HCC in patients with baseline cirrhosis (adjusted HR: 2.9, 95% CI: 1.3-3.9; *P*=0.003)

Papatheodoridis GV, et al., Abstract 265

Prediction and need for HCC surveillance after first 5 years of ETV/TDF therapy in Caucasian CHB patients of PAGE-B cohort

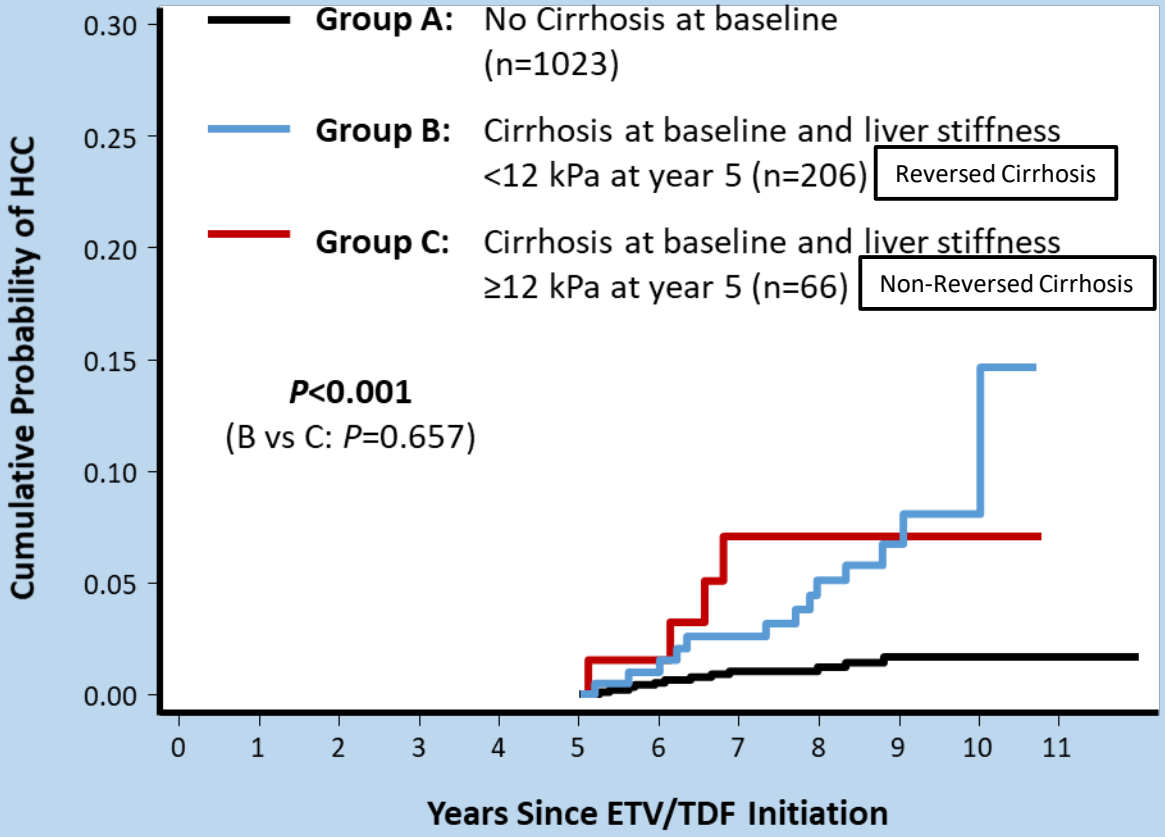
Hypothesis/Aim/Objective:
To assess predictors and need for HCC surveillance beyond year 5 of ETV/TDF in CHB patients

Methods:

- Patient population: 1427 (73%) of the 1951 adult Caucasians with CHB ± compensated cirrhosis included in the PAGE-B cohort who have completed follow-up >5 years without HCC until year 5
- Age at year 5: 57 ± 13 years, males: 70%, baseline cirrhosis: 26%
- Mean follow-up: 8.1 ± 1.6 (median: 8.3) years from ETV/TDF onset

Conclusions:
HCC after the first 5 years of ETV/TDF therapy seems to develop exclusively in patients older than 50 years, while elastographic reversion of cirrhosis at year 5 does not appear to decrease the HCC risk.

Cumulative probability of HCC beyond year 5 of ETV/TDF therapy in CHB patients without HCC within the first 5 years



Papatheodoridis GV, et al., Abstract 17

HCC Risk With TDF vs ETV in Patients With CHB

- Study of patients from **Clinical Data Analysis and Reporting System**, large database covering **public hospitals and clinics in Hong Kong**
  - Eligibility: Chinese adults with CHB receiving TDF or ETV, as primary therapy, between January 2008 and June 2018
  - Exclusion criteria: **HCV, HDV, or HIV coinfection**; cancer or liver transplantation before or < 6 mos from starting HBV treatment; HBV treatment duration < 6 mos; **prior pegIFN or other NAs (eg, 3TC, adefovir, telbivudine)**
- Analyses: multiple imputation, **propensity score** (weighting and matching), competing risk, negative control outcome
- **N = 29,350 included**; n = 1309 TDF vs n = 28,041 ETV (HCC cases: 8 vs 1386, respectively)
  - Overall: 64% male, 31% HBeAg positive, 13% cirrhosis
  - Baseline characteristics well balanced after propensity score weighting

Yip. EASL 2019. Abstr LB-03.

Slide credit: clinicaloptions.com

HCC Risk With TDF vs ETV in Patients With CHB: Results

- **CONCLUSION: Among patients with CHB in Hong Kong, the risk of HCC was lower with primary use of TDF vs ETV**

5-Yr Cumulative HCC, % (95% CI)	TDF	ETV
Univariate*	1.1 (0.5-2.3)	7.0 (6.6-7.3)
PS weighting	1.2 (0.5-2.4)	3.1 (1.9-4.8)
PS matching	1.2 (0.6-2.5)	2.3 (1.4-4.0)

*$P < .001$

Analysis	HCC Risk With TDF vs ETV	
	SHR (95% CI)	*P* Value
Multivariate	0.32 (0.16-0.65)	.002
PS weighting	0.36 (0.16-0.80)	.013
PS weighting†	0.35 (0.12-0.98)	.045
PS matching	0.42 (0.17-1.04)	.060

†**Adjusted for HBV DNA suppression, ALT normalization** (< 35 U/L for men, < 25 U/L for women) at Yr 1.

- No associations observed between HBV treatment and negative control outcomes (ie, lung cancer, acute MI)

Yip. EASL 2019. Abstr LB-03.

Slide credit: clinicaloptions.com

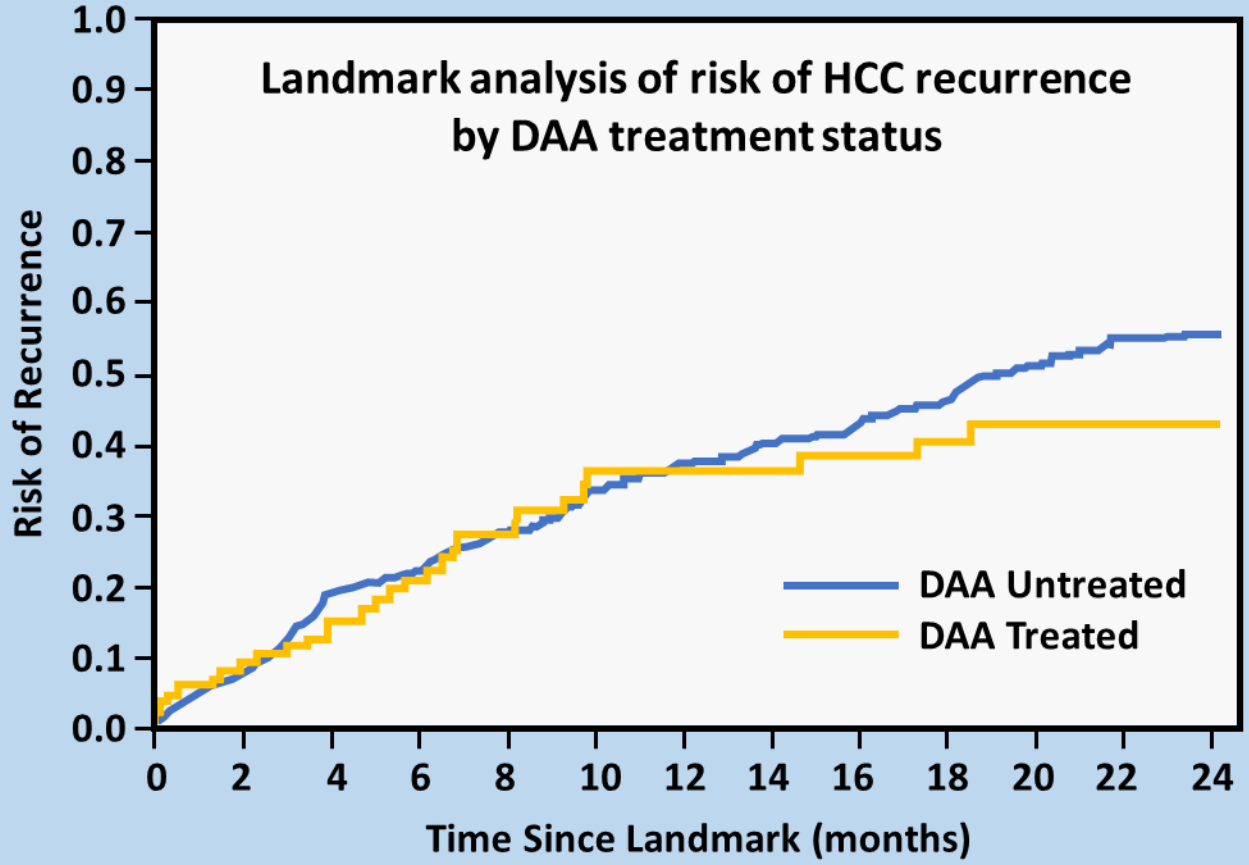
Direct-acting antiviral therapy is not associated with HCC recurrence: A multicenter North American cohort study

Aim: To compare risk of hepatocellular carcinoma (HCC) recurrence between direct-acting antiviral (DAA)-treated and -untreated hepatitis C-infected patients who achieved complete response to HCC treatment

Methods: Multicenter retrospective cohort study examining the association between DAA therapy and HCC recurrence among 795 patients with hepatitis C-related HCC who achieved complete response to HCC treatment from 1/2013 to 12/2017

Main findings: DAA therapy was not associated with HCC recurrence (adjusted HR 0.90, 95% CI 0.70 – 1.16) or early HCC recurrence (adjusted HR 0.96, 95% CI 0.69 – 1.33).

Conclusions: In a large cohort of North American patients with hepatitis C-related HCC, DAA therapy was not associated with increased risk of overall or early recurrence. HCC recurrence patterns, including response to treatment, were similar in DAA-treated and -untreated patients.



Singal AG, et al., Abstract 92

Patients were treated **AFTER Complete Response of HCC**
(there is evidence that patients with HCC have lower SVR rates)

Miscellaneous

Serum bilirubin within normal range is associated with increasing mortality in PBC patients regardless of UDCA treatment

Objective:

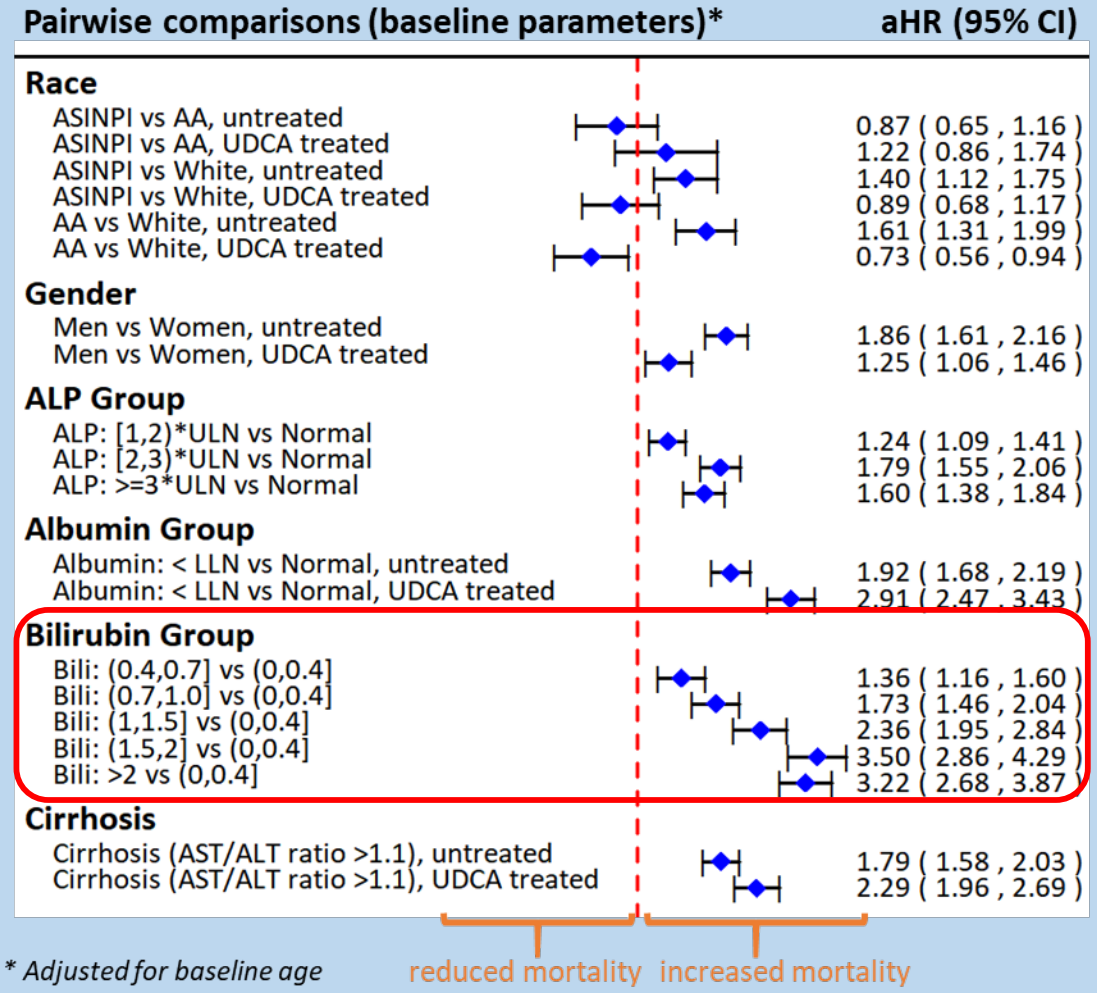
Study the effect of total bilirubin, race, gender, and ursodeoxycholic acid (UDCA) treatment on all-cause mortality in PBC patients

Methods:

- Racially/geographically diverse cohort of 4238 PBC patients under routine care at 11 U.S. healthcare systems (2006–present)
- Cox regression time-to-event model, evaluating baseline parameters including variable-by-UDCA interactions, and propensity score adjustment for treatment selection bias

Conclusions:

- Baseline total bilirubin – in high-normal as well as mid-normal ranges – is independently associated with increased mortality.
- Mortality risk among black versus white patients diverges based on UDCA treatment status.



Gordon SC, et al., Abstract 47

** Adjusted for baseline age*

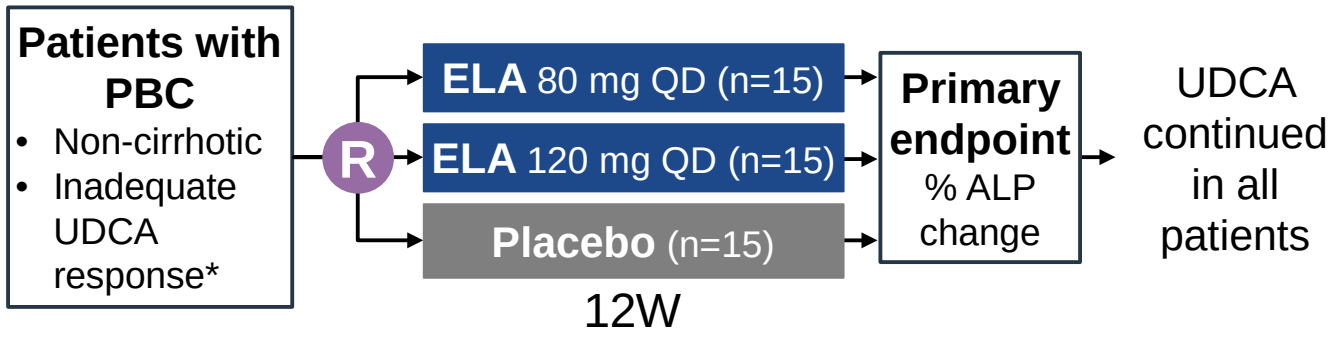
In PBC we knew that mortality started to go up with Bili >/= 2; this shows that starts going up with Bili > 0.4 mg/dL

Elafibranor demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to UDCA

BACKGROUND & AIMS

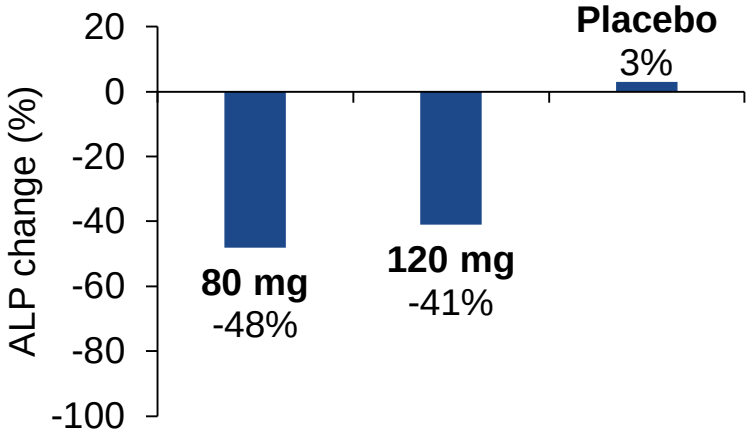
- Up to 40% of UDCA-treated patients have suboptimal response and are at high risk of disease progression
- **Aim:** This phase 2a, double-blind, placebo-controlled study investigated elafibranor (ELA), a dual **PPARα/δ agonist**, as a new anti-cholestatic treatment for PBC

METHODS



RESULTS

- **Primary endpoint:** ELA demonstrated significant decreases in mean ALP at Week 12



- Highly significant treatment effect vs. placebo (both p<0.001)
  - 80 mg: -52% (95% CI -62.5, -41.5)
  - 120 mg: -44% (95% CI -55.7, -32.1)

*Defined as ALP >1.67x ULN.

Jörn S, et al. ILC 2019; LB-02

EASL™ The Home of Hepatology

Elafibranor demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to UDCA

RESULTS (Cont.)

- Composite endpoint of **ALP <1.67x ULN + ALP decrease >15% + total bilirubin <ULN**
  - **80 mg: 67%** patients (p=0.002); **120 mg: 79%** patients (p<0.001) vs. **placebo: 6.7%**
- GGT also highly significant vs. placebo
  - 80 mg: -39% (p=0.001); 120 mg -40% (p=0.002)
- ELA-treated patients showed **improvement in lipid markers,* reduction of inflammatory markers**,† and a decrease in C4 (an intermediate of bile acid synthesis)
- By self-reported **VAS**, patients with BL **pruritus** (10/group) showed **improvement at Week 12**
  - **80 mg: -24%**; **120 mg: -49%**; **placebo: -7%**
- Both doses of ELA were well tolerated

CONCLUSIONS ELA demonstrated a substantial anticholestatic effect in patients with PBC and inadequate response to UDCA. This was associated with anti-inflammatory and potential antipruritic effects, which make it a promising novel treatment candidate

*Including total cholesterol, low-density lipoprotein, and triglycerides; †IgM, CRP, haptoglobin, and fibrinogen.

Jörn S, et al. ILC 2019; LB-02

Efficacy and safety of seladelpar in PBC: 52-week analysis from a randomized phase 2 study

Objective:
To assess the safety and efficacy of daily seladelpar treatment for up to 52 weeks from an ongoing open-label phase 2 study in primary biliary cholangitis (PBC)

Methods:
Randomized, open-label, dose ranging, phase 2 study assessing the efficacy and safety of seladelpar in patients with PBC with either an inadequate response to ursodeoxycholic acid (UDCA) or an intolerance to UDCA and an alkaline phosphatase (AP) ≥1.67 x upper limit of normal (ULN)

Conclusions:
Seladelpar maintained a potent anti-cholestatic effect over 52 weeks, was generally safe, well tolerated, and not associated with pruritus.

Primary and secondary outcomes

Seladelpar	5/10 mg (n=17)	10 mg (n=17)
Baseline Mean/Median AP	351/301 U/L	279/248 U/L
Responders* (n)	59% (10)	71% (12)
AP Mean Change	-47%	-46%
AP Normalized (n)	24% (4)	29% (5)

*AP <1.67 x ULN, ≥15% decrease in AP, and total bilirubin ≤ ULN.

- Median ALT decreases: -31% and -33% in the 5/10 mg and 10 mg groups, respectively

Bowlus C, et al., Abstract LB-3

Seladelpar is a Selective Peroxisome Proliferator-Activated (**PPAR**) Receptor **Delta agonist**

Efficacy of induced hematopoietic stem cell therapy in decompensated cirrhosis: An open-label RCT

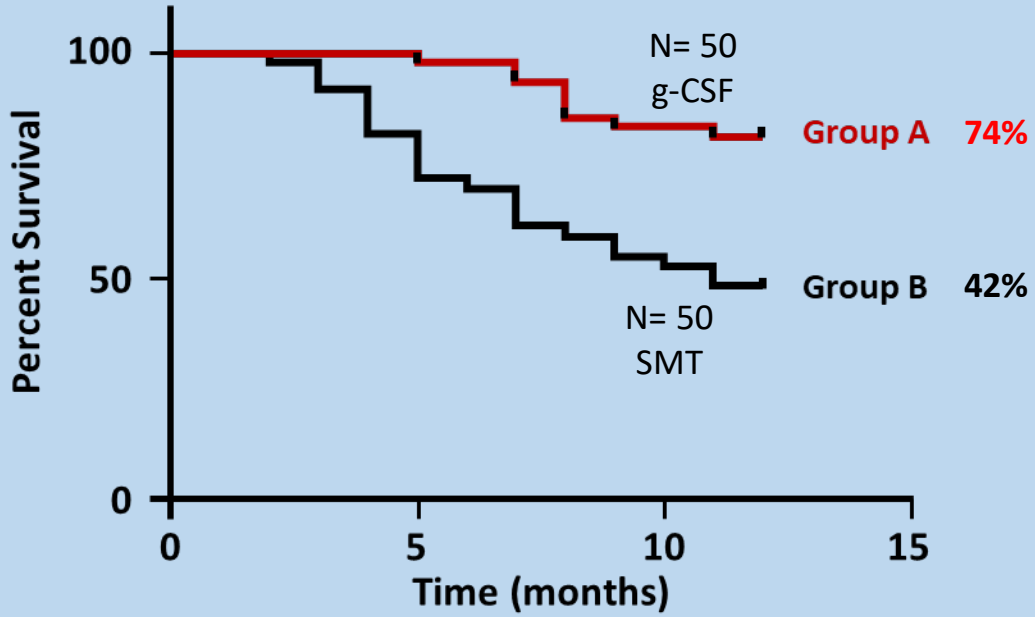
Objective:
To study safety and efficacy of multiple cycles of granulocyte colony stimulating factor (G-CSF) and 1-year transplant-free survival (TFS) in patients with decompensated cirrhosis (DC)

Methods:
One hundred DC patients were openly randomized to receive either four cycles of five days of G-CSF (5µg/kg subcutaneously every 12 hours for five consecutive days) at three monthly intervals with standard medical therapy (SMT) (Group A, n=50) or SMT alone (Group B, n=50).

Conclusions:
Multiple cycles of G-CSF improved 12-month TFS, mobilized CD34+ cells, improved disease severity scores, fibrosis, quality of life (QOL) scores, control of ascites and reduced infections, hospitalisations, and need for LT in DC.

Singh V, et al., Abstract 110

Kaplan Meier curve showing transplant-free survival



Transplant-Free Survival - 12 Months		
Group A	Group B	*P*-value
74%	42%	<0.001

High SVR in PWID with HCV Despite Imperfect Medication Adherence: Data from the Anchor Study (AASLD 2018; 18)

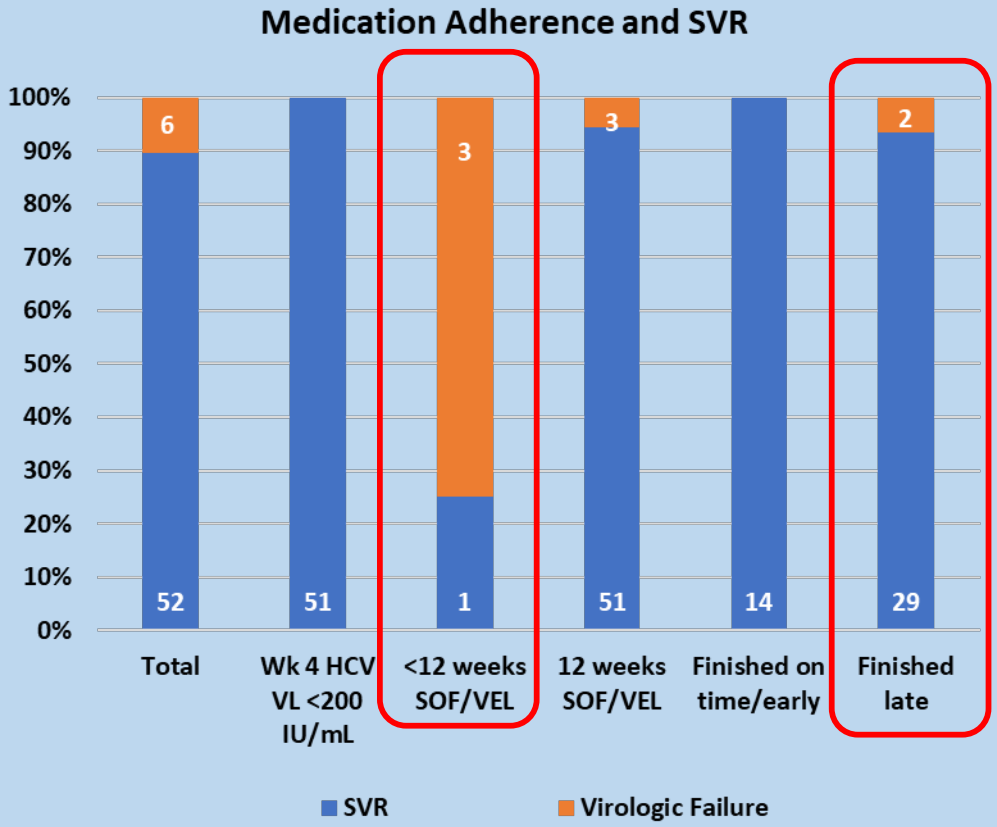
Objective: To understand if people who inject drugs (PWID) with HCV and active injection drug use (IDU) can adhere to DAAs and achieve SVR

Methods: Single-center study of PWID with chronic HCV, opioid use disorder, and active IDU of heroin within 3 months, treated with SOF/VEL x12 weeks

Main findings:

- Of the patients who have reached the SVR time point and have attended the week 24 visit, 52 (90%) patients achieved SVR.
- SVR was significantly associated with HCV VL <200 IU/mL at week 4 (p=0.004) and taking all 84 pills of SOF/VEL (p=0.003).
- Completing treatment after 12 weeks did not impact SVR, even in patients finishing more than 14 days late.

Conclusions: PWID with HCV and ongoing IDU have high rates of adherence, treatment completion, and SVR. Even with imperfect adherence, patients are able to achieve high rates of SVR with completion of treatment.



93% took 12 weeks therapy;
SVR was 94% even **with total interruptions up to 14 days,** if 12 weeks of therapy were taken

Thank you for your attention