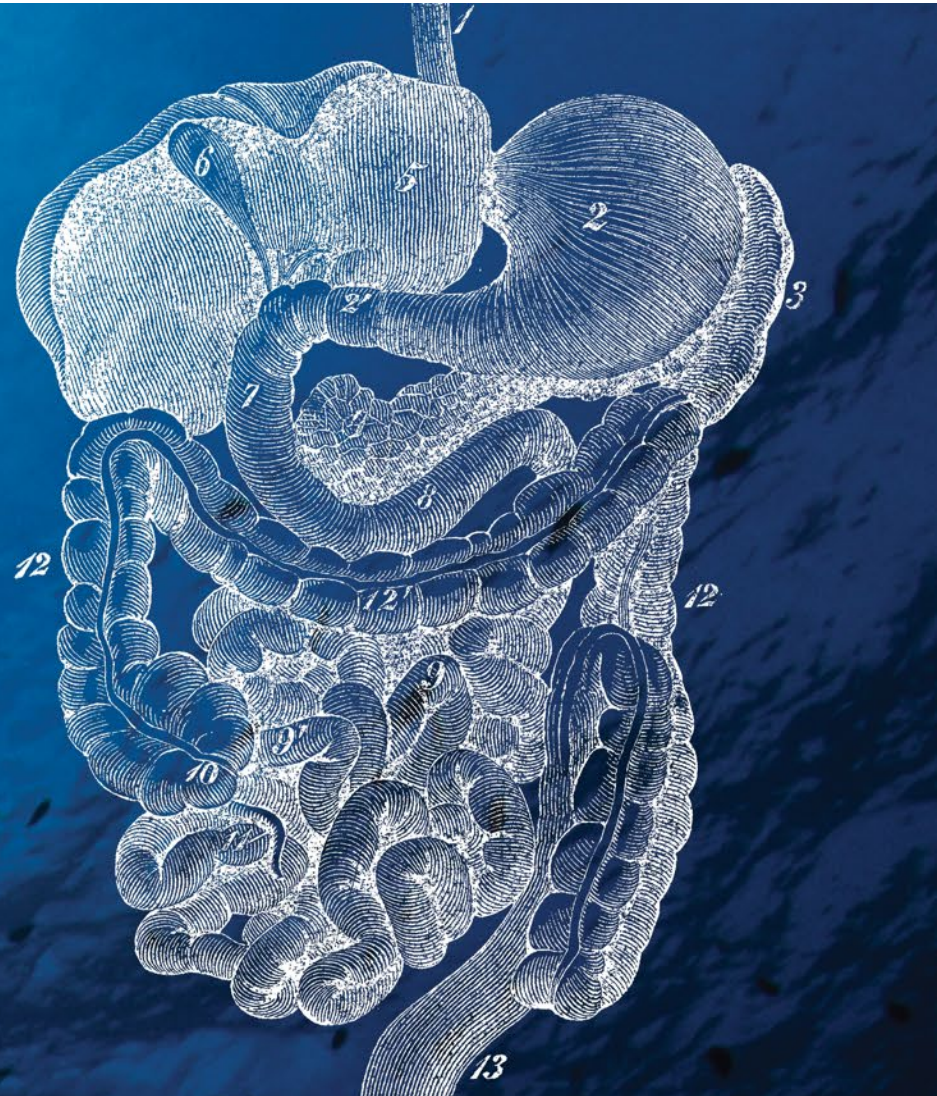
GUILD

Gastroenterology Updates
IBD • Liver Disease

GUILD Conference 2020
February 16-19
Wailea Beach Marriott • Maui, Hawaii

NASH: State of the Art 2020

Kris V. Kowdley MD, AGAF, FACG, FACP, FAASLD
Clinical Professor of Medicine
Washington State University
Director, Liver Institute Northwest
Seattle, WA



Disclosures

- Research:
  - Enanta, GSK, Gilead, HighTide, Genfit, Allergan, Novartis, Intercept, La Jolla, Conatus, Galectin, CymaBay, NGM Bio, Galectin,
- Consultant;
  - Genfit, HighTide, Gilead, Intercept, Enanta, Protagonist, La Jolla, Merck, Abbvie, Prometic, Corcept, Assembly BioSciences, Boeringer Ingelheim, IQVIA, Perspectum, WebMD, Callidtas
- Honoraria:
  - Gilead, Abbvie, Intercept,
- Royalties:
  - UpToDate

Real-World Analysis of Mortality Risk (2007-2015): NAFLD/NASH Patients

- Retrospective, observational, cohort study of Medicare data (n=10,826,260)
  - Adults with NAFLD/NASH (ICD-9-CM claims/diagnosis codes): 2.4%
    - Excluded: other causes of liver disease
- Primary outcomes
  - Baseline demographics and comorbidities
  - All-cause mortality (or time to event)
- NAFLD/NASH patients with (versus without) advanced liver disease ($P<0.05$)
  - Significantly higher rates of comorbidities, including CVD, diabetes mellitus, and renal impairment

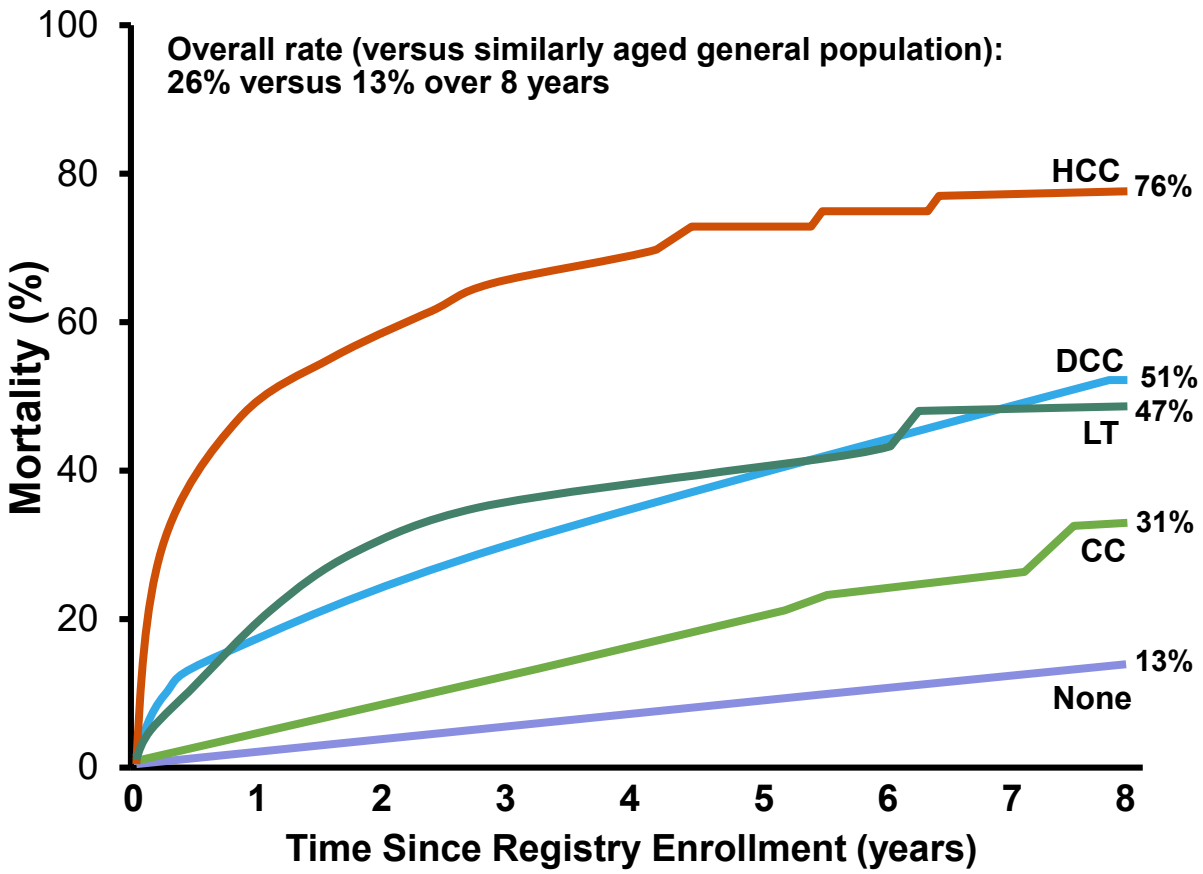
Baseline Characteristics of NAFLD/NASH Patients by Presence of Advanced Liver Disease

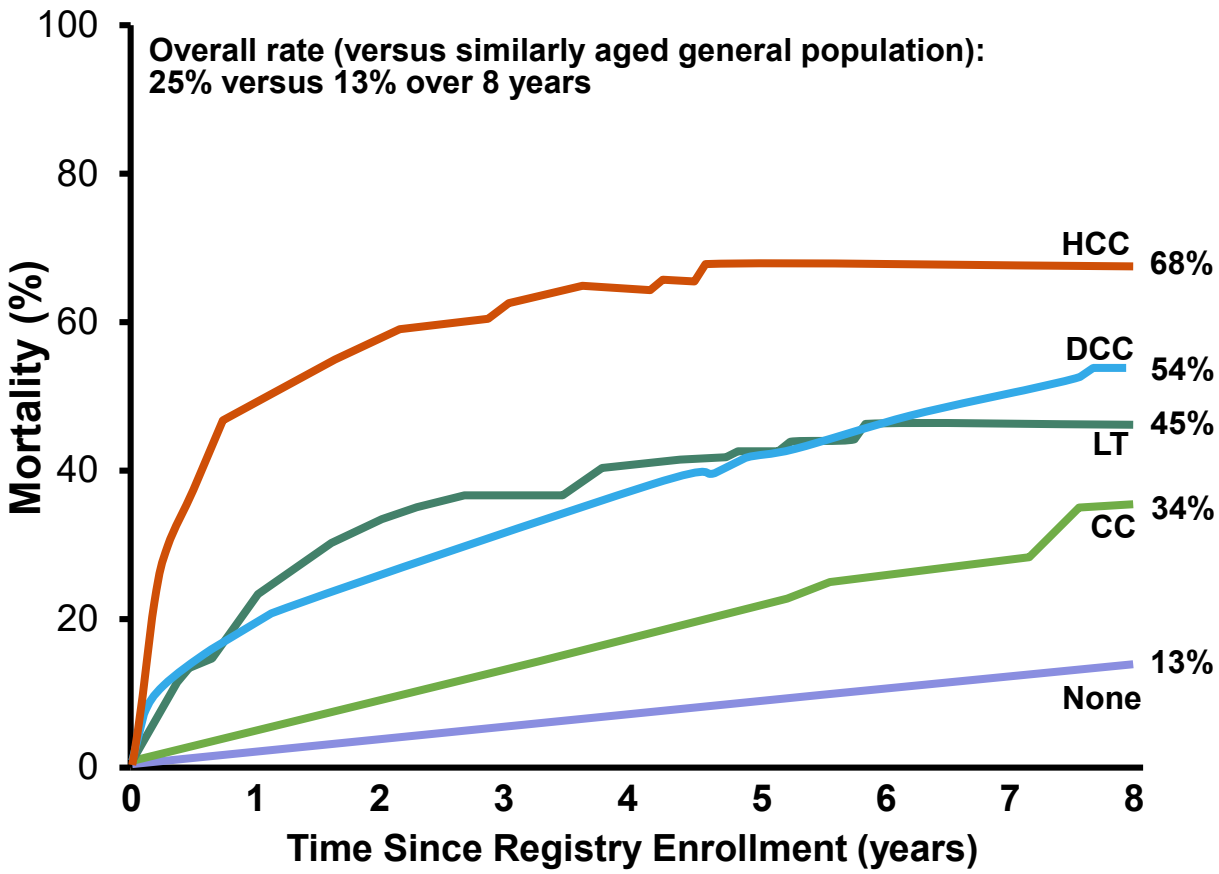
	None (n=185,407)	CC (n=3592)	DCC (n=71,912)	HCC (n=581)	LT (n=575)
Female (%)	60	63	60	54	50
Mean age (years)	67	67	71	73	67
White (%)	84	87	86	82	86
Comorbidities (%)					
Cardiovascular disease	65	74	88	84	83
Diabetes mellitus	54	70	64	66	71
Hyperlipidemia	84	87	88	87	86
Hypertension	84	89	93	91	91
Renal impairment	21	29	47	45	50
Smoking	25	31	40	37	45
Diabetes/hypertension/ hyperlipidemia	46	62	58	59	62

CC: compensated cirrhosis.
DCC: decompensated cirrhosis.
HCC: hepatocellular carcinoma.
LT: liver transplant.

Loomba R, et al. *Hepatology*. 2018;68(suppl S1):1294A. Abstract 2286.

All-Cause Mortality in NAFLD/NASH by Presence of Advanced Liver Disease





CC: compensated cirrhosis; DCC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplant.

Loomba R, et al. *Hepatology*. 2018;68(suppl S1):1294A. Abstract 2286.
Loomba R, et al. *Diabetes*. 2019;68(suppl 1). Abstract 1450-P.

Impact of Fibrosis Severity on Mortality and Liver-Related Outcomes in NAFLD/NASH

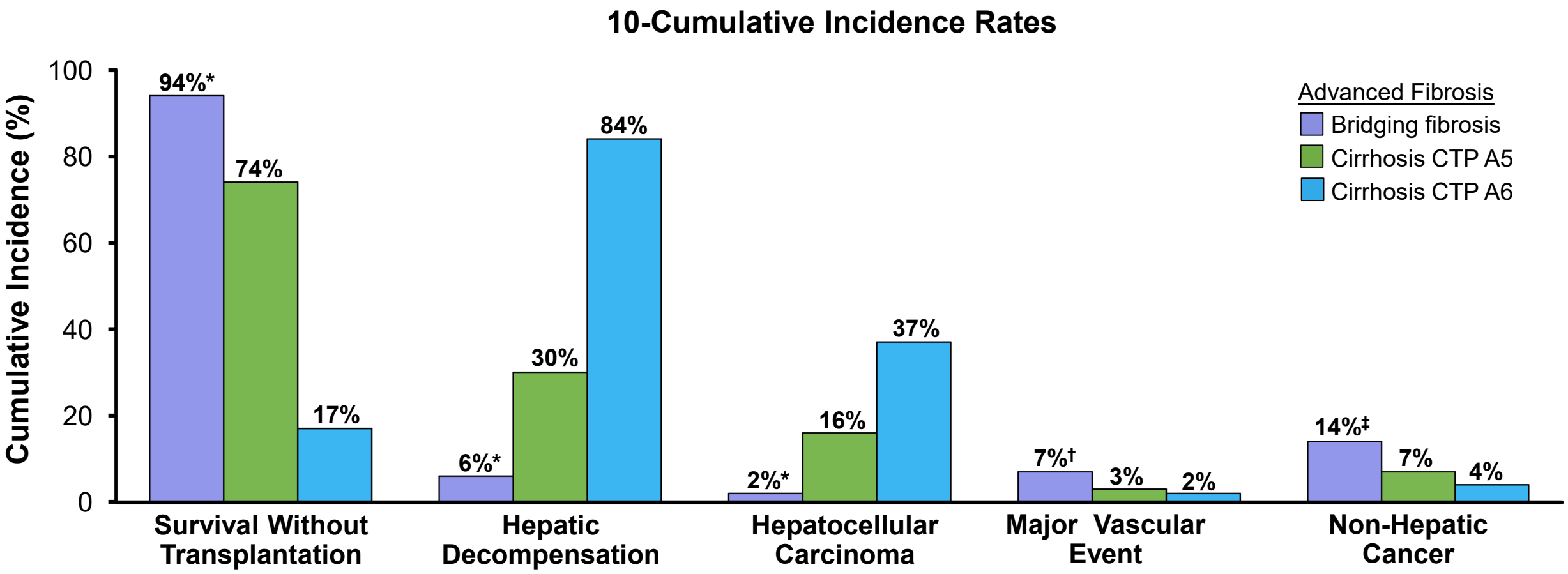
- International, prospective cohort registry study (1995-2013; n=458)
  - Biopsy-proven NAFLD/NASH with advanced fibrosis
    - Biopsy length (18.9 mm), portal tracts (9.7)
  - No bariatric surgery, significant body weight reduction via lifestyle changes, decompensated cirrhosis, HCC
- Comorbidities
  - Type 2 diabetes (67%), hypertension (61%), vascular disease (9%)
  - Vitamin E (1%), statins (24%)
- Clinical outcomes during follow-up (mean 5.5 years)
  - Deaths (n=37), liver transplantation (n=37), decompensation (n=90), HCC (n=41), major vascular events (n=14)

Baseline Characteristics

	Bridging Fibrosis (n=159)	Cirrhosis CTP A5 (n=222)	Cirrhosis CTP A6 (n=77)
Age (years)	54	57	57
Male (%)	50	46	52
White/Hispanic/Asian (%)	28/48/24	22/55/21	23/74/3
BMI (kg/m^2)	35	32	32
MELD score	7	8	11
NAS score ≥5 (%)	49	48	21
Steatosis <33% (%)	26	39	69
Lobular inflammation (%) 0 or <2 foci/200x field	52	52	77
Ballooning (%) 0 or few cells	75	63	83

Vilar-Gomez E, et al. *Gastroenterology.* 2018;155:443-457.

Impact of Fibrosis Severity on Mortality and Liver-Related Outcomes in NAFLD/NASH



*P<0.01 for bridging fibrosis versus cirrhosis CTP-A5 and A-6.
†P<0.01 for bridging fibrosis versus cirrhosis combined.
‡P=0.1 for bridging fibrosis versus cirrhosis combined.

Vilar-Gomez E, et al. *Gastroenterology.* 2018;155:443-457.

Risk Factors Associated With NAFLD

Common Comorbidities With Established Association

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

Other Conditions Associated With NAFLD

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

*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.

Risk Factors for NASH Among NAFL Patients

Main Factors

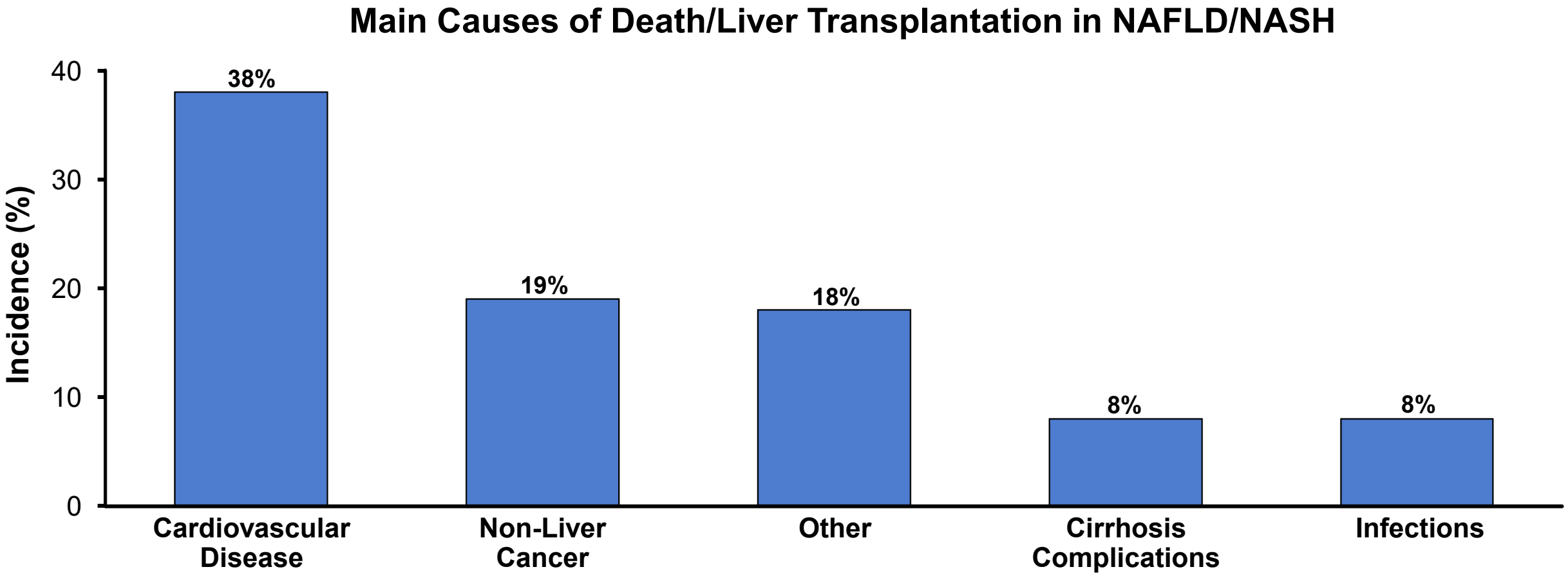
- Obesity
- Older age
- Female sex
- Non-African American race/ethnicity
- Diabetes mellitus
- Hypertension

Other Factors

- High AST/ALT
- Low platelet count
- Elevated C-peptide level
- Ultrasound steatosis score

Sanyal AJ. *Nat Rev Gastroenterol Hepatol*. 2019;16:377-386..
Chalasani N, et al. *Hepatology.* 2018;67:328-357.
Stefan N, et al. *Lancet Diabetes Endocrinol*. 2019;7:313-324.
Friedman SL, et al. *Nat Med*. 2018;24:908-922.

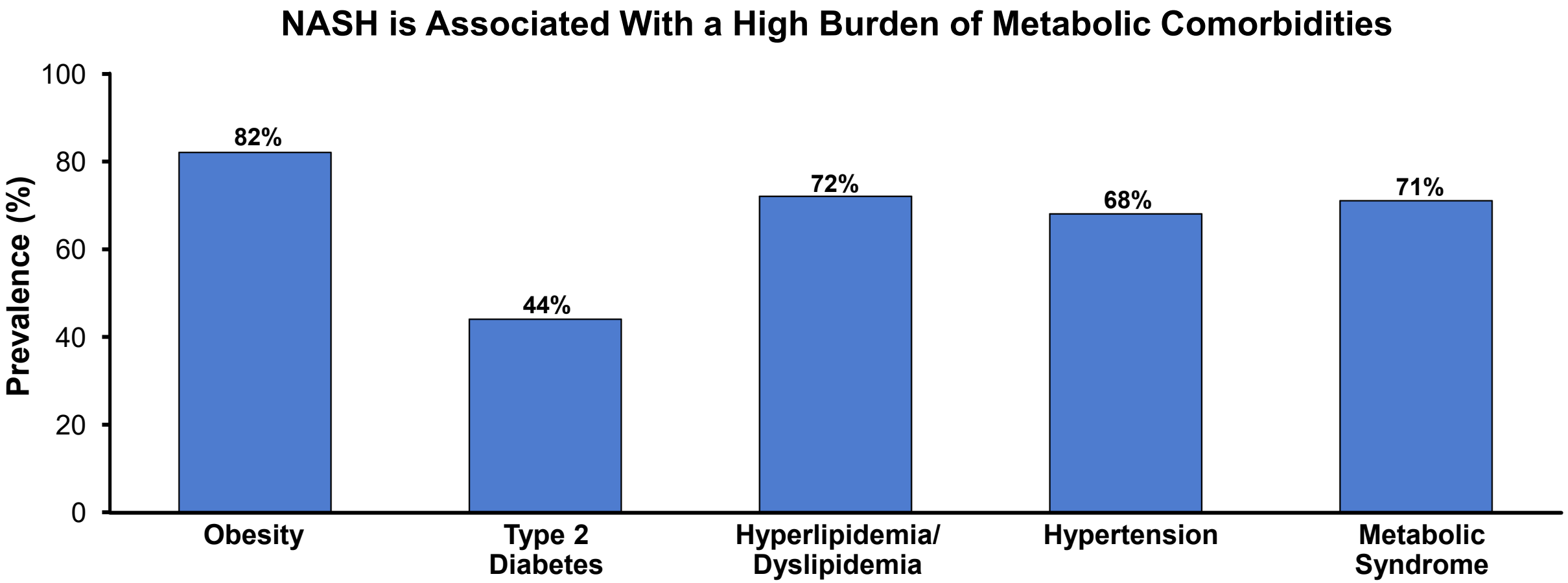
PRELHIN Study: Cardiovascular Disease Is the Most Common Cause of Death/Liver Transplantation in NAFLD/NASH



PRELHIN: Prognostic Relevance of Liver Histology In NAFLD (retrospective, longitudinal NAFLD/NASH cohort (n=619; 1975-2005) in the US, Europe, and Thailand. Overall mortality/liver transplantation (193/619).

Angulo P, et al. *Gastroenterology*. 2015;149:389-397.

Comorbidities Associated With NASH: Global Prevalence Among NAFLD Patients



Meta-analysis: data from studies that diagnosed NAFLD by imaging (US, CT, MRI/SPECT) and NASH by histology in NAFLD patients.
Number of studies reporting for NASH: obesity (n=4); type 2 diabetes (n=9); hyperlipidemia/dyslipidemia (n=4); hypertension (n=4); metabolic syndrome (n=2).

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

Pathophysiology

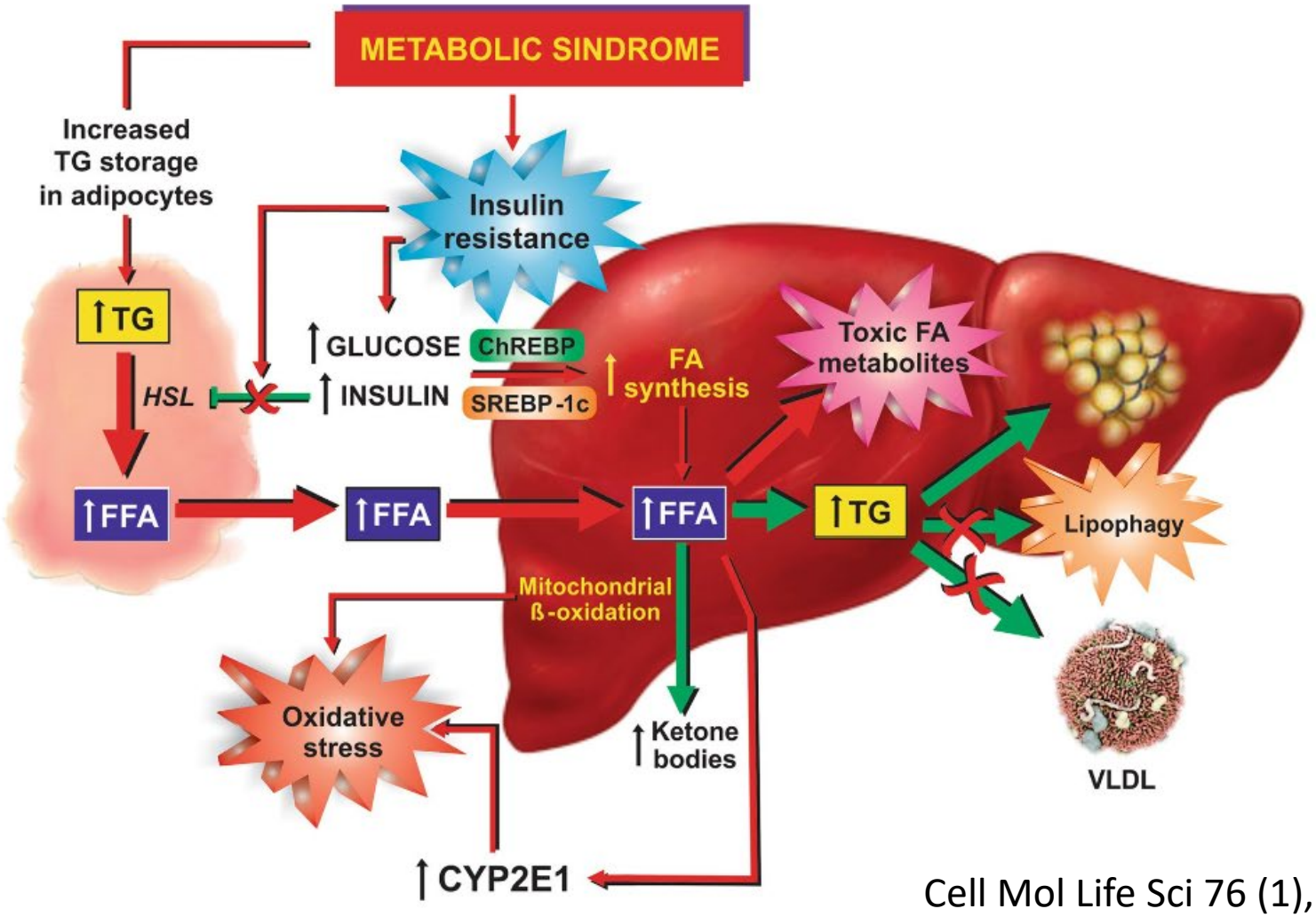
Pathogenesis of NAFLD

- NAFLD as a complex disease trait with genetic and environmental factors
- Obesity and insulin resistance are key pathogenic drivers
- Factors leading to hepatocellular injury
  - Oxidative stress, lipotoxicity, mitochondrial dysfunction, inflammatory activation and production of cytokines and adipokines, gut dysbiosis, ER stress
  - Stellate cell activation drives fibrosis
  - Dynamic interplay between pro and anti-steatotic mechanisms

Genetic factors are known to be important

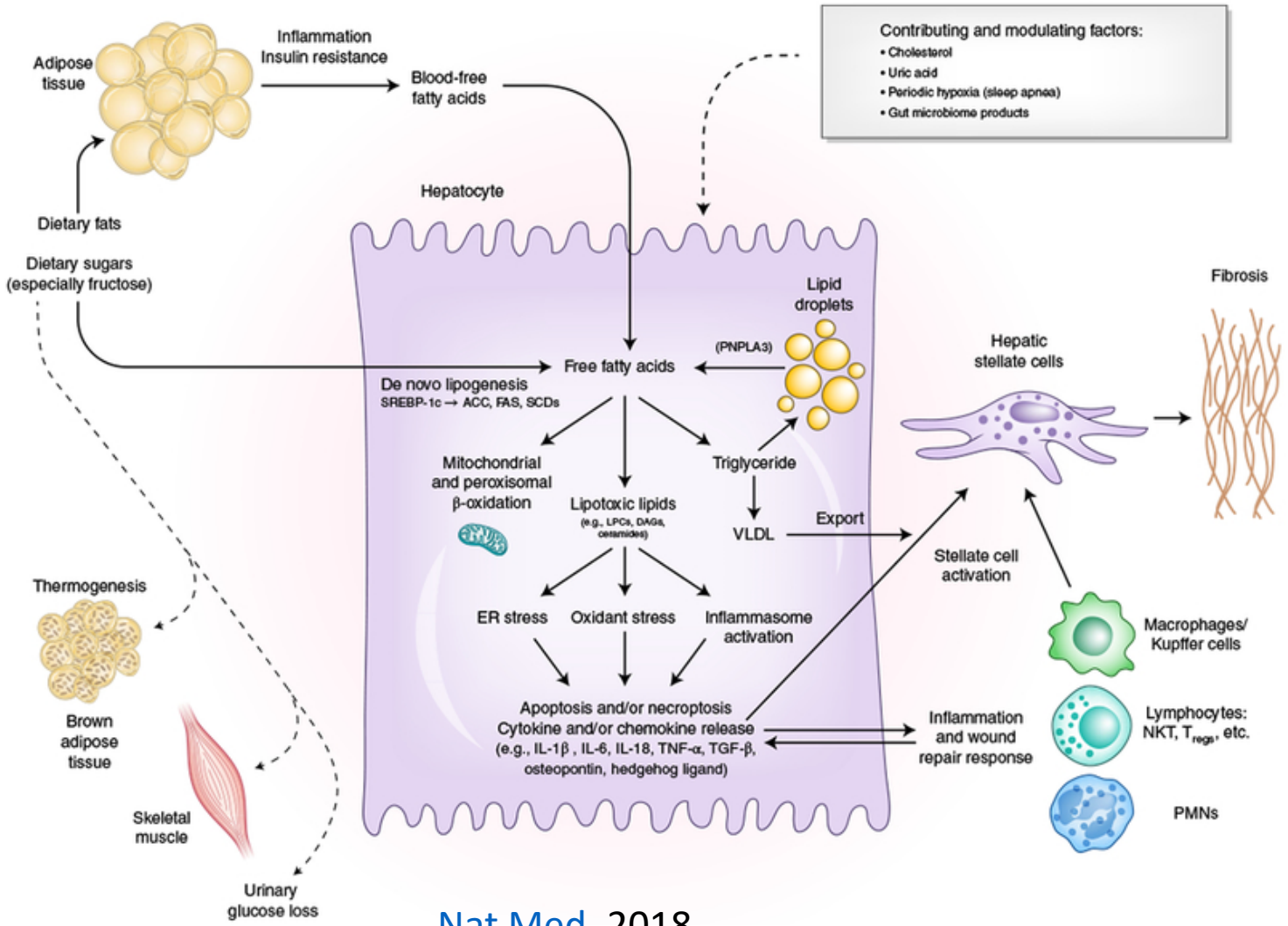
Alcohol is a modifier

Metabolic Basis of NASH Pathogenesis



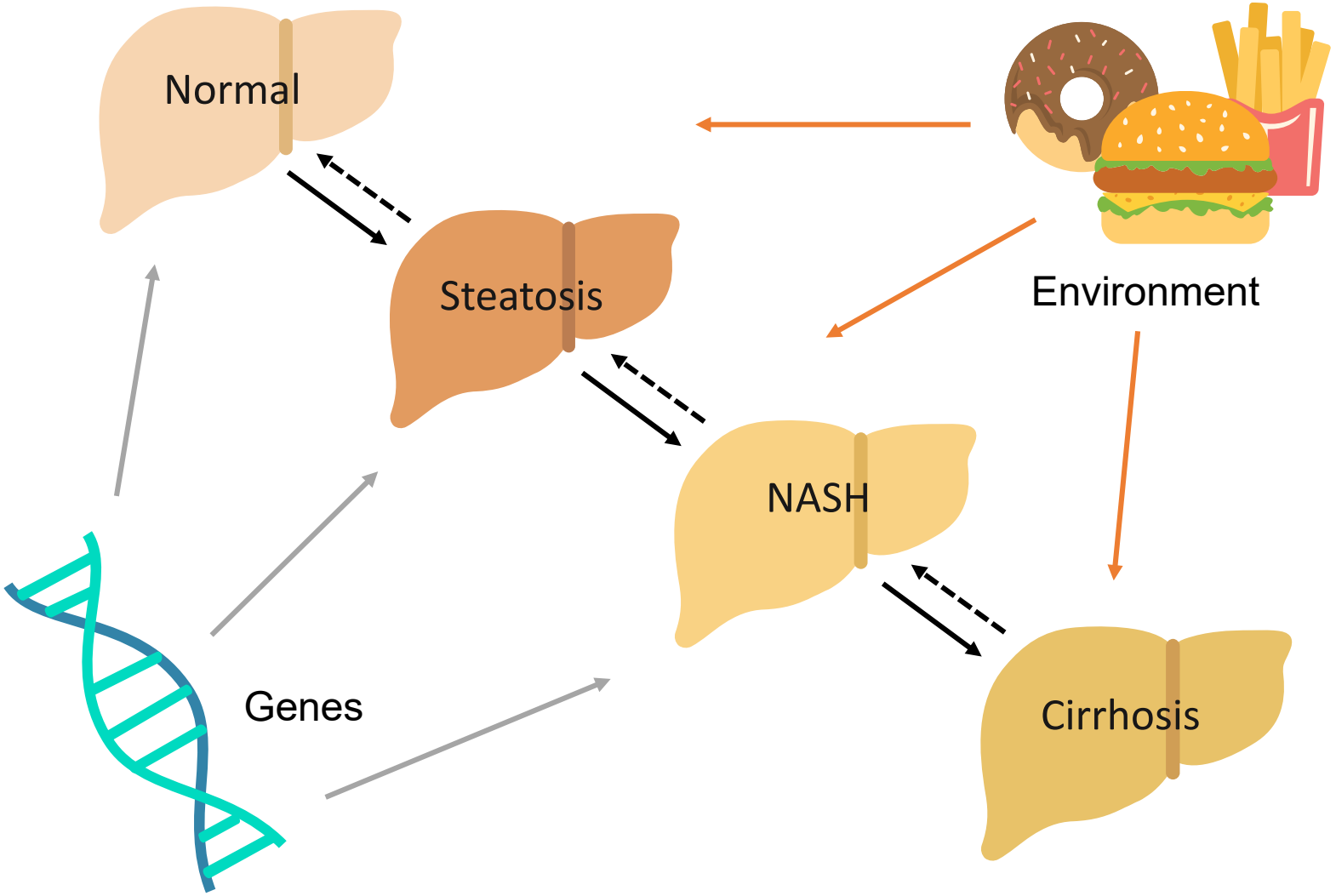
Cell Mol Life Sci 76 (1), 99-128. Jan 2019

Pathophysiology of NASH



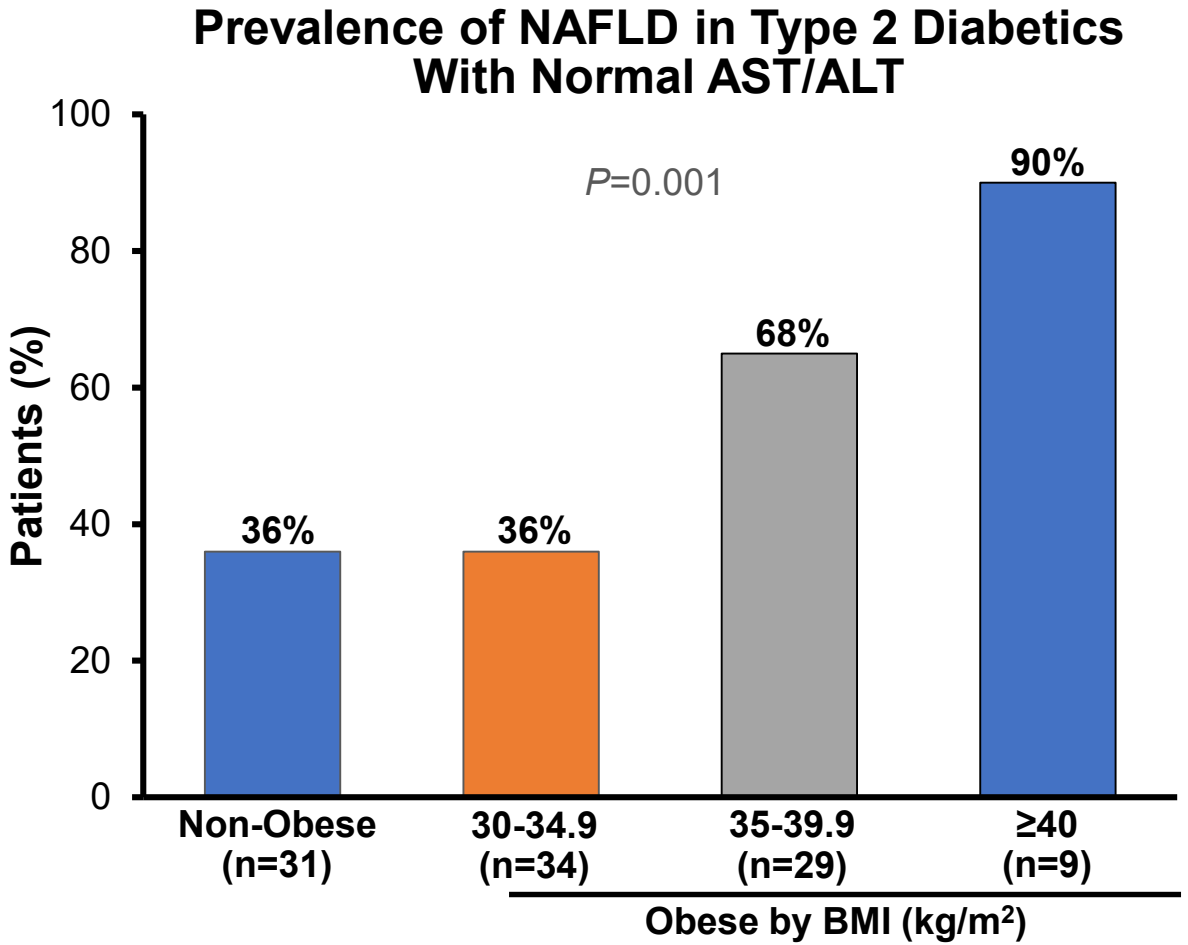
Nat Med. 2018

NAFLD as a Complex Disease Trait: Genetic and Environmental Modifiers



High Prevalence of NAFLD in Type 2 Diabetics With Normal AST/ALT Levels

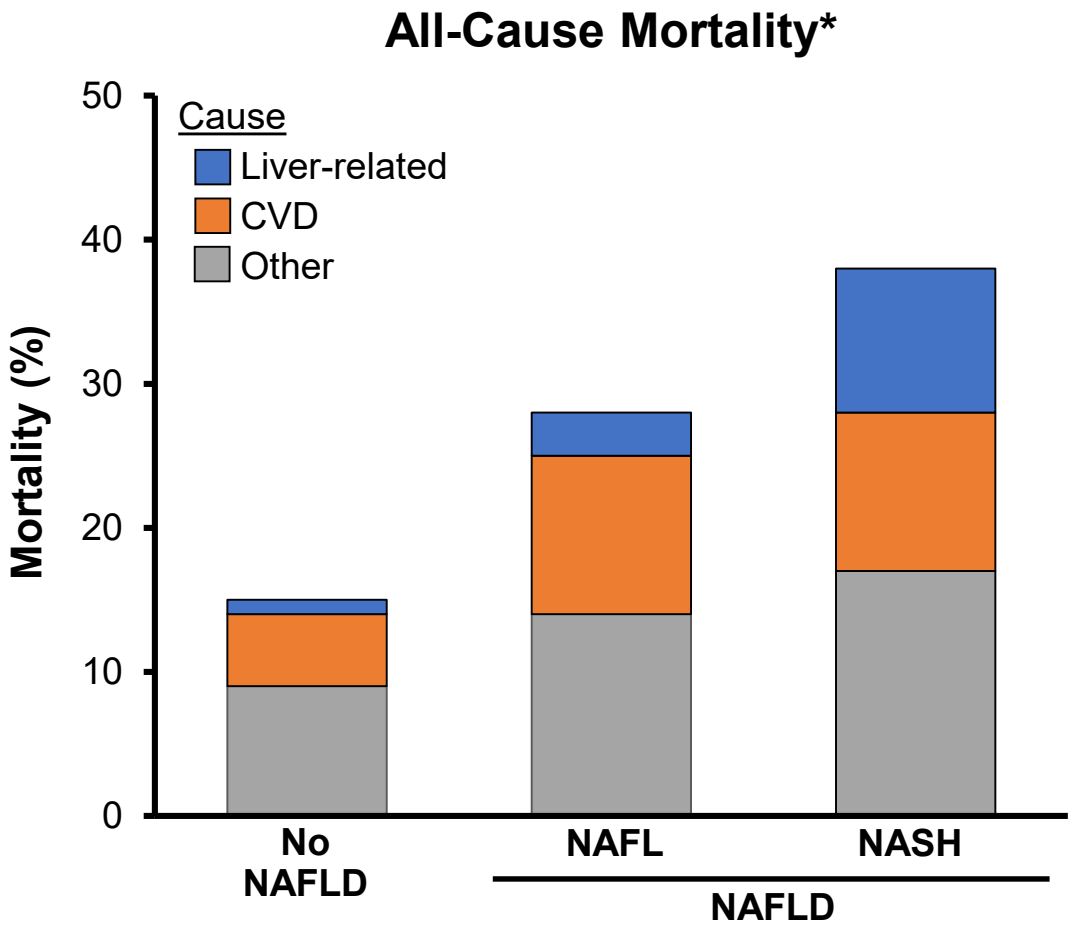
- Cohort of type 2 diabetics with normal AST/ALT levels (n=103)
  - No prior diagnosis of NAFLD, other causes of liver disease excluded
  - Male (80%), obese (70%)
  - Liver triglyceride content by ^{1}H-MRS
- Overall prevalence of NAFLD: 50%
  - Prevalence increased with increasing BMI (*P*<0.001)
  - NASH prevalence: 56%
- Confirmation of results from larger studies is needed
  - Potential implications for need of early screening for liver disease in type 2 diabetics



Portillo-Sanchez P, et al. *J Clin Endocrinol Metab*. 2015;100:2231-2238.

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

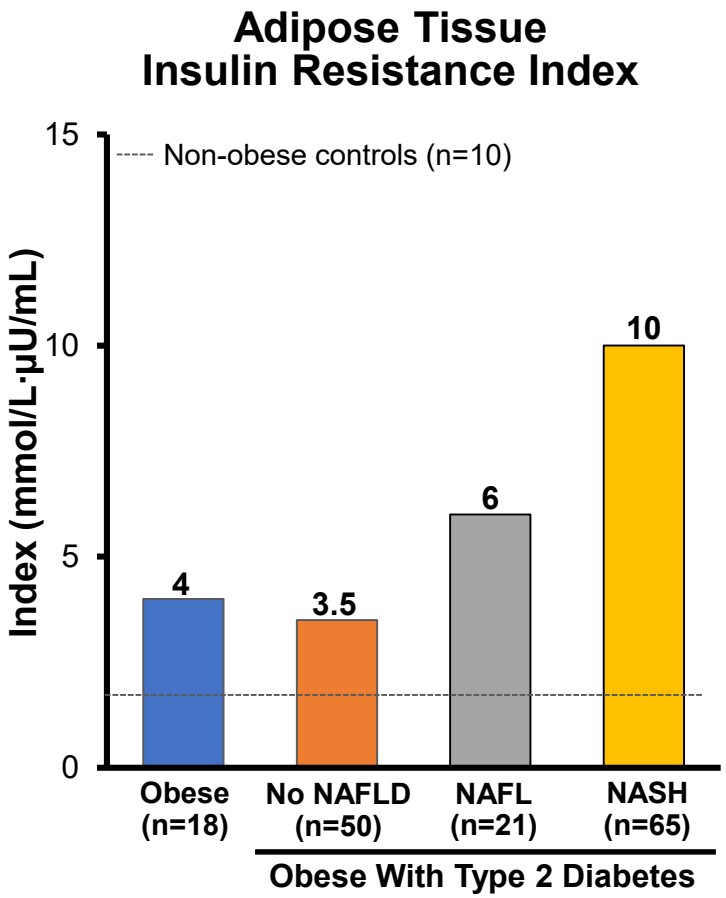
- NAFLD/NASH prevalence: ≥2-fold higher versus non-diabetics
- Faster progression to NASH and advanced fibrosis
  - NASH is associated with increased overall and liver-related mortality (type 2 diabetes increases the risk of both)
- Established link between type 2 diabetes, cirrhosis, and HCC
  - Type 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

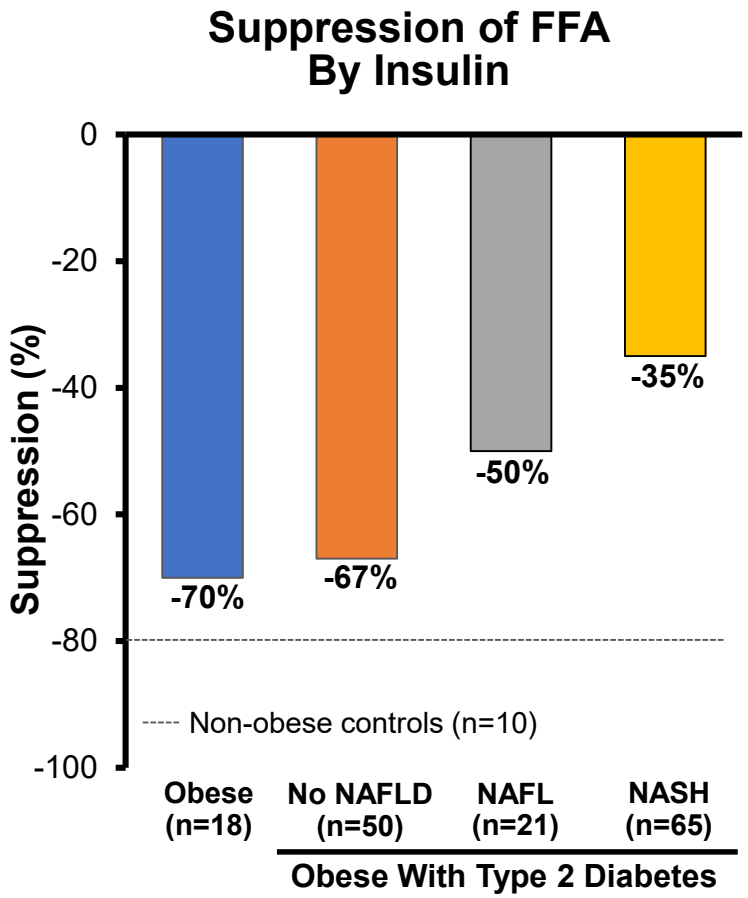


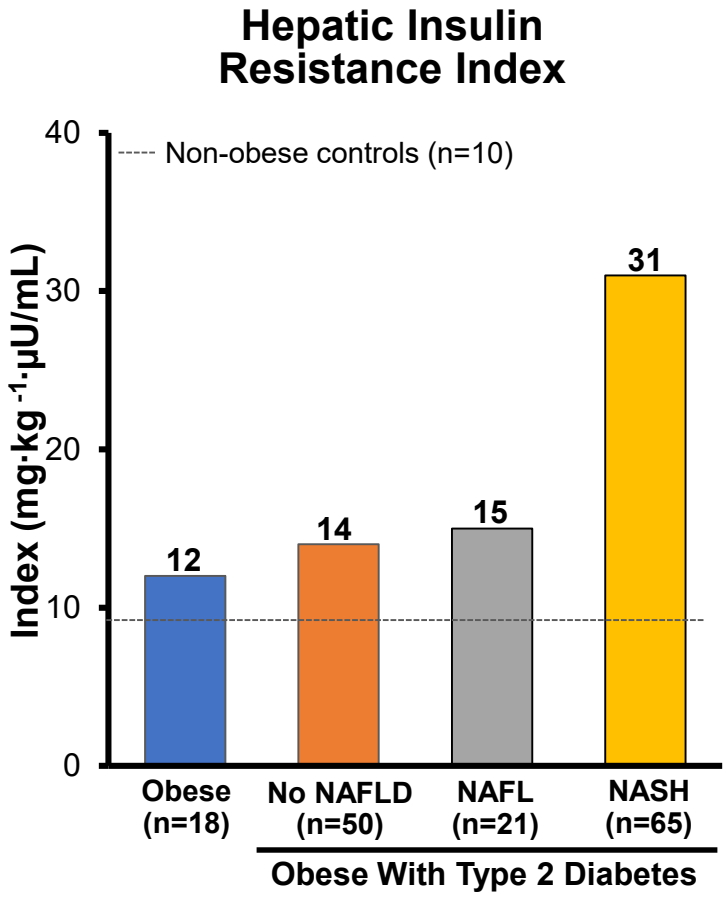
*Weighted mean follow-up: 13-14.5 years.

Chalasani N, et al. *Hepatology*. 2018;67:328-357.
Bril F, et al. *Endocrinol Metab Clin N Am.* 2016;45:765-781.
Cusi K. *Diabetologia.* 2016;59:1112-1120.

Metabolic Impact of NASH in Obese Type 2 Diabetics



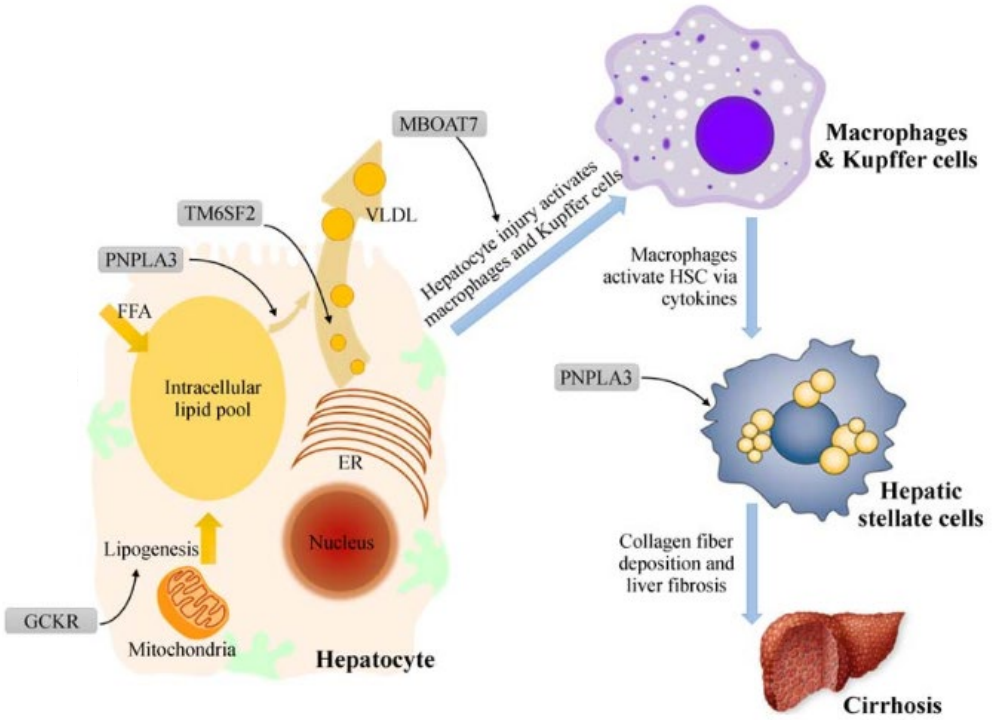




Cohort study (n=154). No significant differences in important baseline clinical characteristics such as sex, BMI, and total body fat among the groups.
Metabolic parameters worsened progressively with the presence of type 2 diabetes and the development of hepatic steatosis, with worse hyperinsulinemia, insulin resistance, and dyslipidemia (hypertriglyceridemia and low HDL cholesterol) in those with NASH (P<0.001).

Lomonaco R, et al. *Diabetes Care.* 2016;39:632-638.

Genetic Variants Associated With NAFLD and Progression to NASH

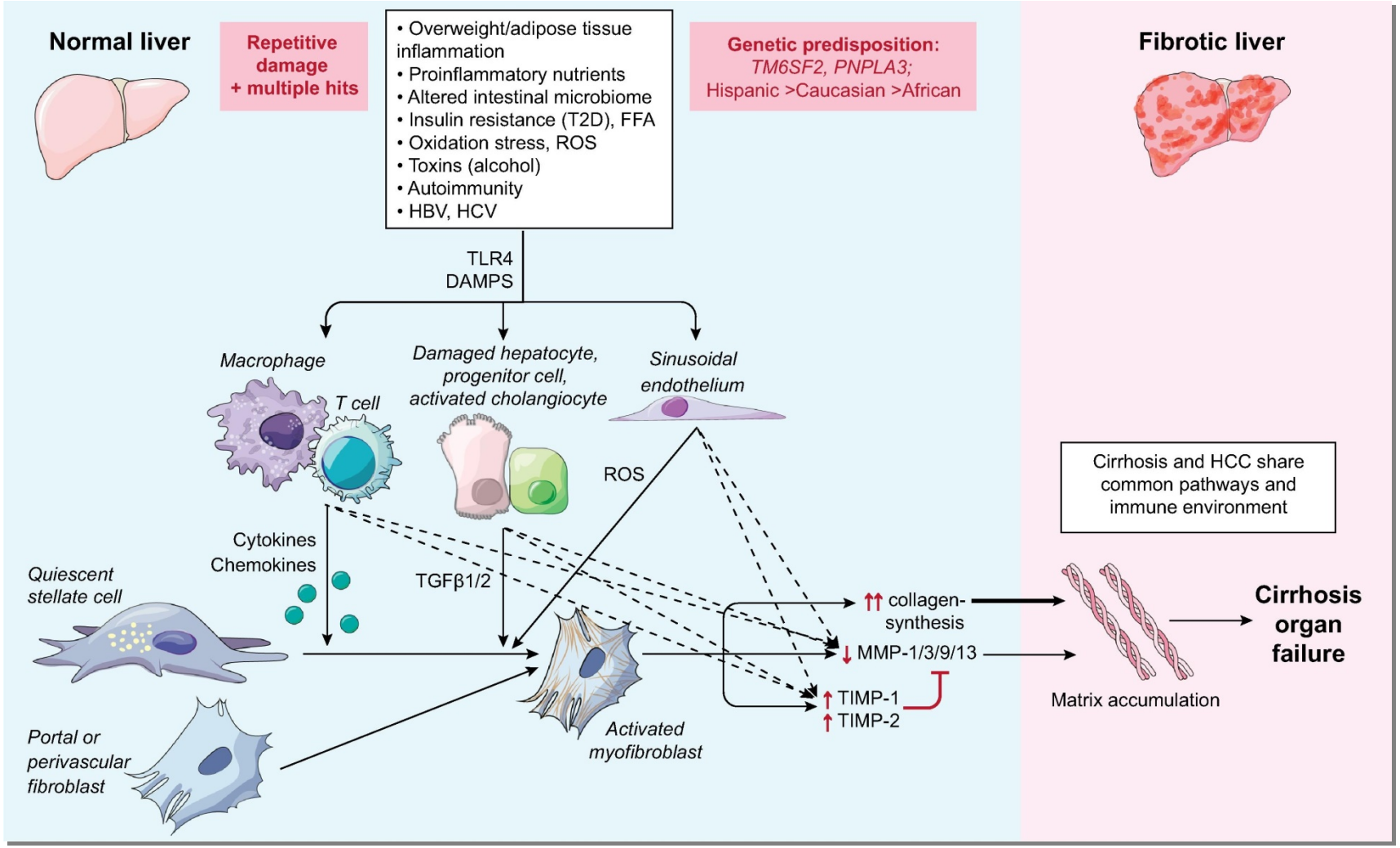


	Variant	Function	Variant Effect	Phenotype
PNPLA3	rs738409	Lipid droplet remodeling	Impaired mobilization of Fas from lipid droplets	↑NAFLD, NASH, fibrosis, and HCC
TM6SF2	rs585542926	VLDL secretion	Decreased VLDL secretion, hepatic triglyceride accumulation	↑NAFLD, NASH, and fibrosis
GCKR	rs1260326	Regulation of de novo lipogenesis	Increased de novo lipogenesis	↑NAFLD, NASH, and fibrosis
MBOAT7	rs641738	Remodeling of phosphatidylinositol	Increased hepatic inflammation	↑NAFLD, NASH, fibrosis, and HCC
HSD17B13	rs72613567	Unknown, localizes to hepatocyte lipid droplets	Decreased HSD17B13 and PNPLA3 production	↓NASH and fibrosis

PNPLA3: patatin-like phospholipase domain-containing protein 3.
TM6SF2: transmembrane 6 superfamily member 2.
GCKR: glucokinase regulatory protein.
MBOAT7: membrane-bound O-acyltransferase domain containing 7.

Danford CJ, et al. *J Biomed Res.* 2018;32:389-400.
Eslam M, et al. *J Hepatol.* 2018;68:268-279.
Kovalic AJ, et al. *J Clin Exp Hepatol*. 2018;8:390-402.
Abul-Husn NS, et al. *N Engl J Med*. 2018;378:1096-1106.
Barbara M, et al. *Hepatobiliary Surg Nutr*. 2018;7:372-381.

Factors Associated With Fibrosis Progression



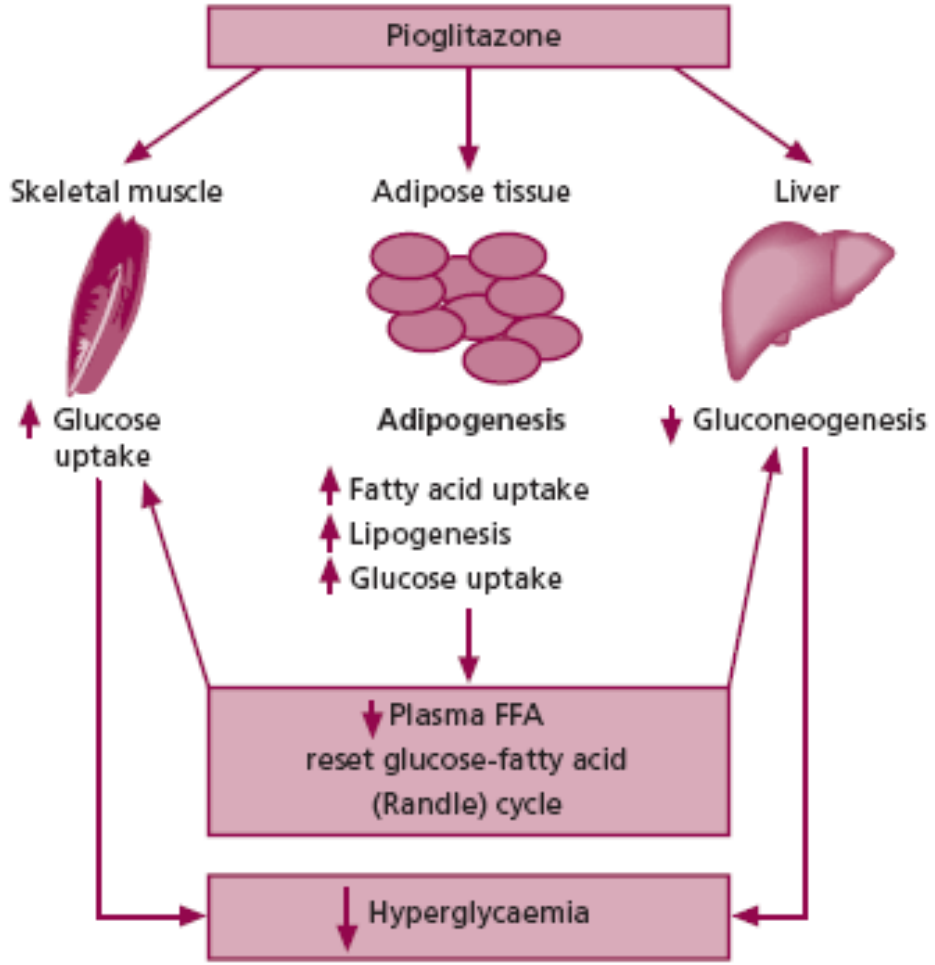
Schuppan D, et al. *J Hepatol.* 2018;68:238-250.

Medications Being Developed to Treat Patients With NASH Who Have Significant Fibrosis

- Major targets of medications for NASH (based on mechanism)
  - Gut-liver axis and bile acid enterohepatic circulation
  - Lipids and metabolism
  - Liver injury including hepatocyte death, inflammation, and fibrosis

Thiazolidinediones

- Improve insulin resistance through different pathways
  - Promote the differentiation of insulin-resistant large pre-adipocytes into small and insulin-sensitive adipocytes
  - Reduce inappropriate fat storage in muscle and adipocyte tissue with subsequent improvement in insulin sensitivity despite the expansion in fat mass
  - Upregulate production of adiponectin, an insulin-sensitizing and anti-steatogenic adipokine that increases fatty acid beta-oxidation in liver and muscle



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

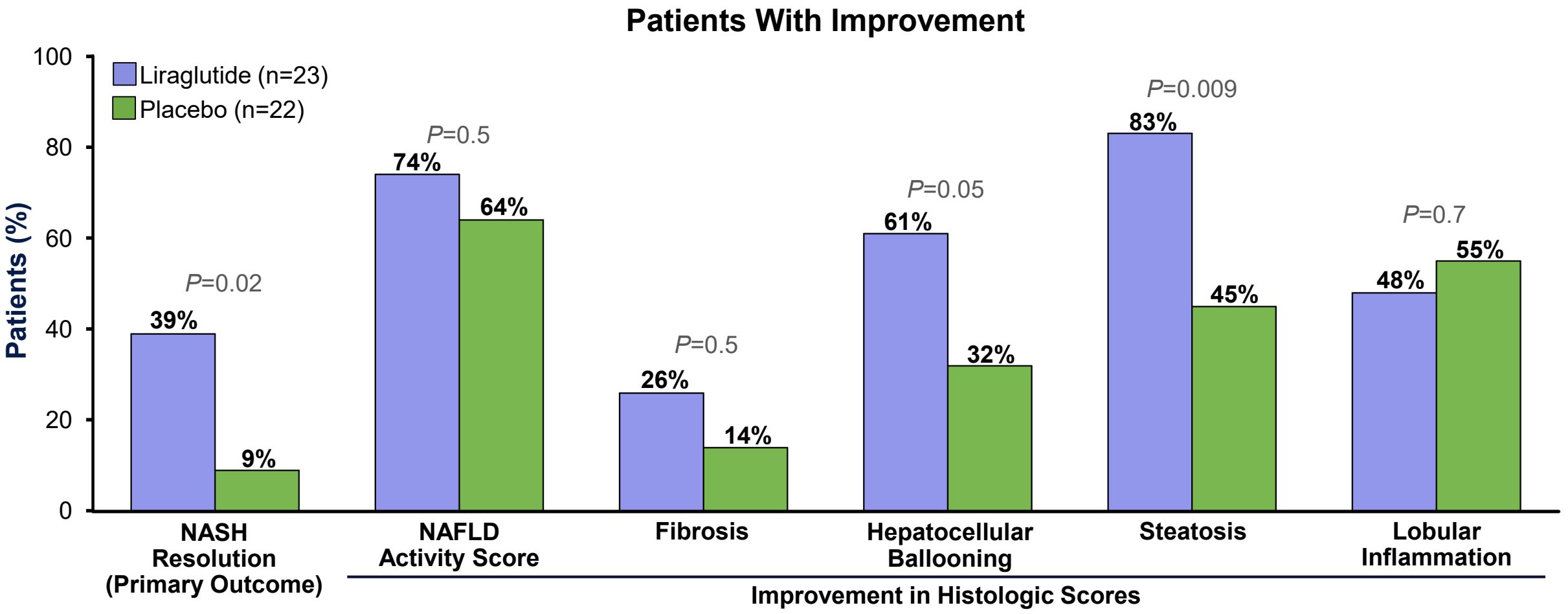
Baseline Characteristics

	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.

Vitamin E

2018 AASLD Practice Guidance

- 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

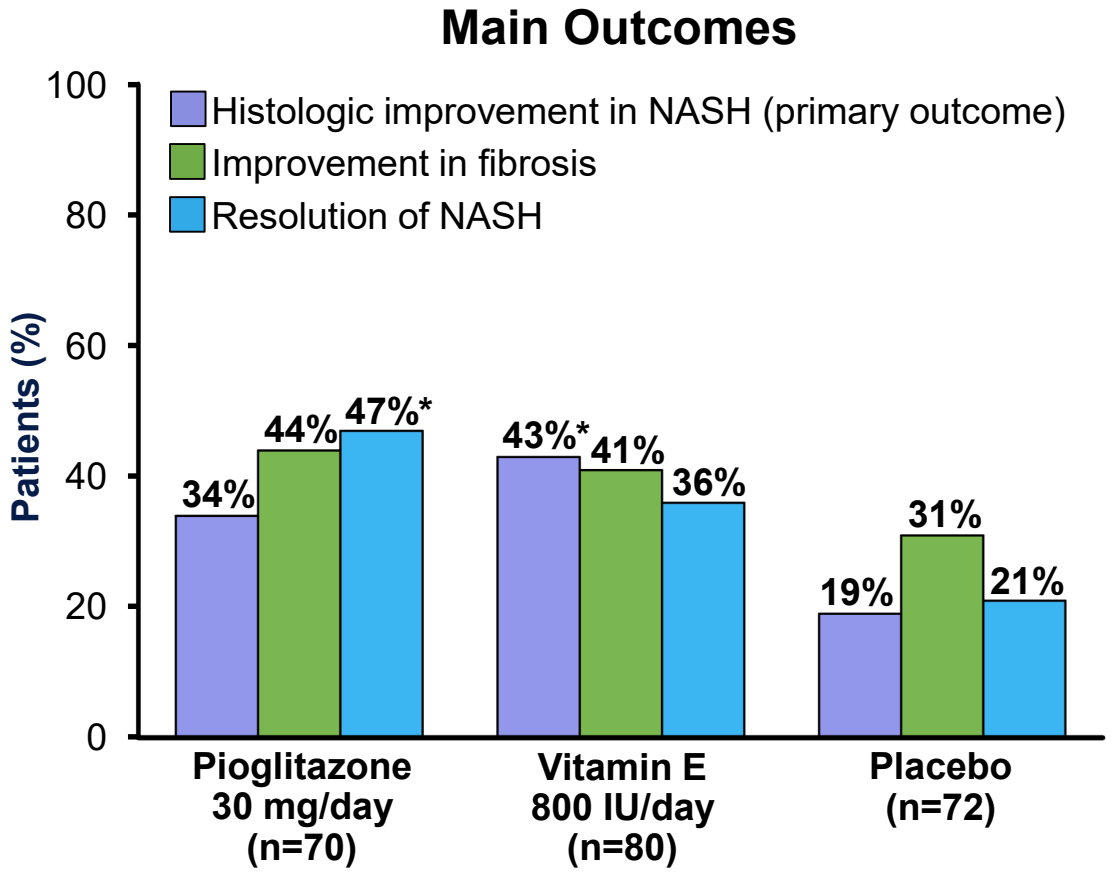
2019 Research Update

- Retrospective analysis of biopsy-confirmed NASH and advanced fibrosis (2004-2016)
  - Vitamin E (n=90) versus matched controls (n=90)
- Vitamin E users versus controls (median follow-up of 5.6 years)
  - Higher transplant-free survival (78% versus 49%; aHR 0.30 [*P*<0.01])
  - Lower hepatic decompensation rates (37% versus 62%; aHR 0.52 [*P*<0.01])
  - Benefits similar regardless of diabetes status

Chalasani N, et al. *Hepatology.* 2018;67:328-357.
Vilar-Gomez E, et al. *Hepatology.* 2018;Dec 1. [Epub ahead of print].

NASH CRN PIVENS Trial: Pioglitazone Versus Vitamin E in 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)



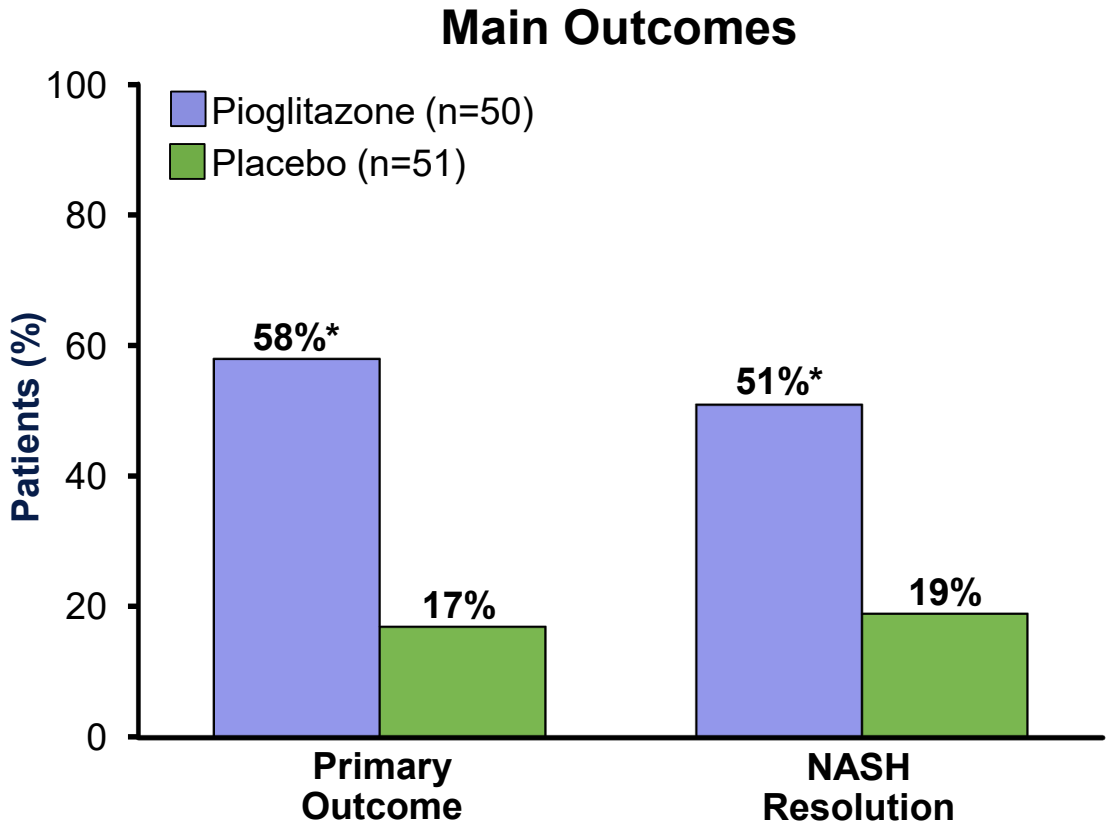
*P=0.001 versus placebo

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 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.

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

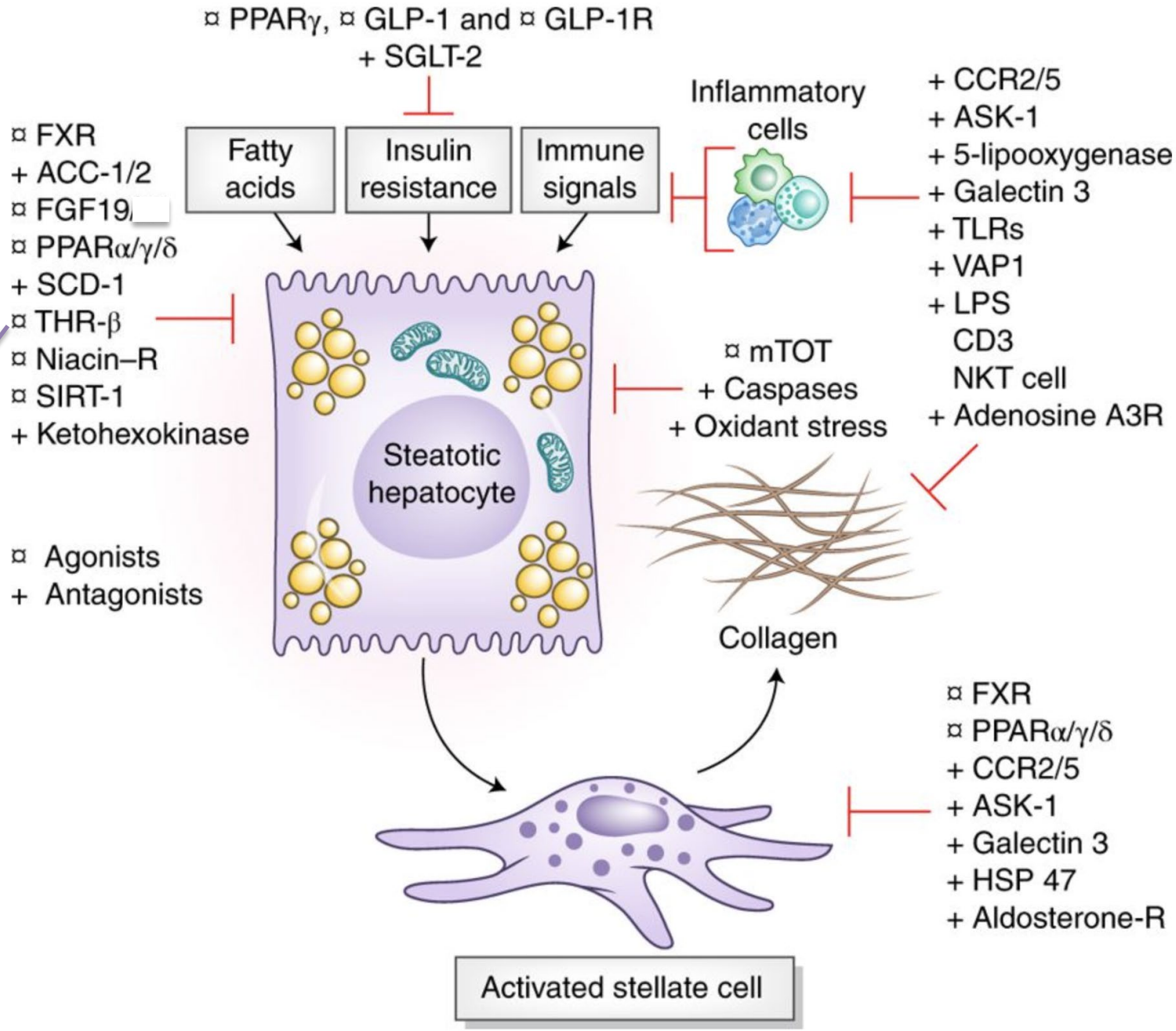
- Galectin-3 protein inhibitor

GS-9674
Tropifexor

NGM-282

Aramchol

MGL3196
VK2809



Courtesy of Mary Rinella

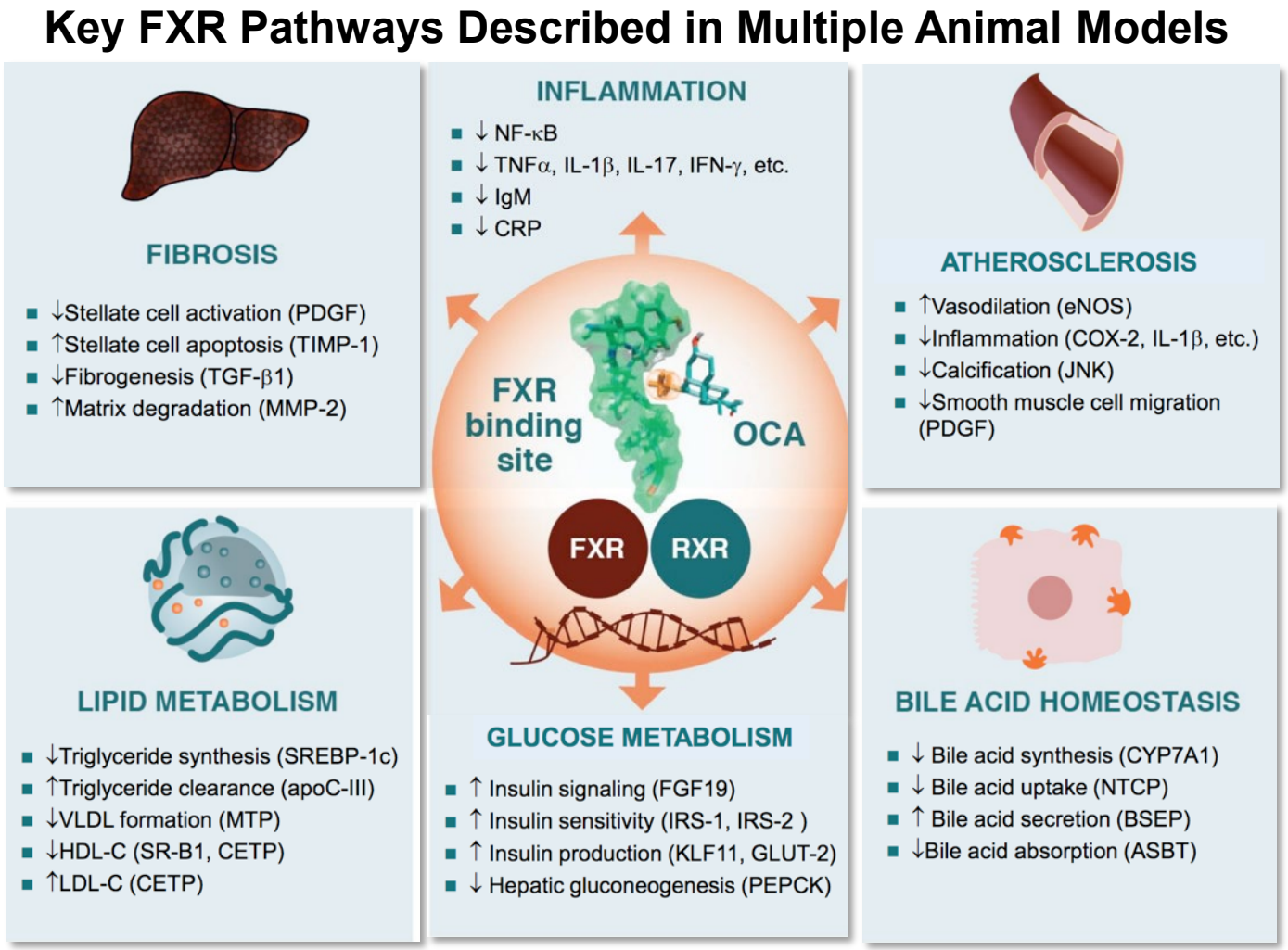
Friedman, Tetri, Rinella, Sanyal,
Nature Medicine 2018

Agents in Registrational Trials

- Currently in phase 3 trials
  - Obeticholic acid
  - Elafibranor
  - Selonsertib
  - Cenicriviroc
- AASLD Practice Guidance
  - Until further safety and efficacy data become available in patients with NASH, obeticholic acid should not be used off-label to treat NASH

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

FXR Agonist:Obeticholic Acid

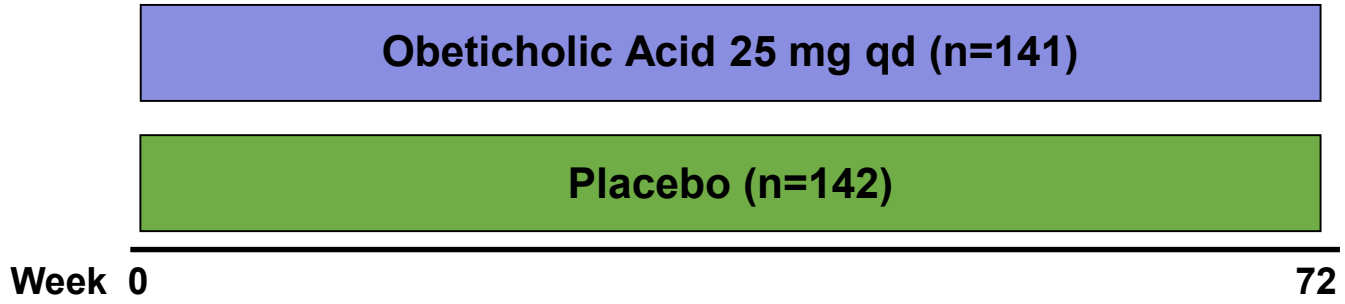


Sumida Y, et al. *J Gastroenterol.* 2018;53:362-376.
Gawrieh S, et al. *Clin Liver Dis.* 2018;22:189-199.

FLINT Study:
Obeticholic Acid in NASH Patients Without Cirrhosis

Phase 2b (n=141)
(US)

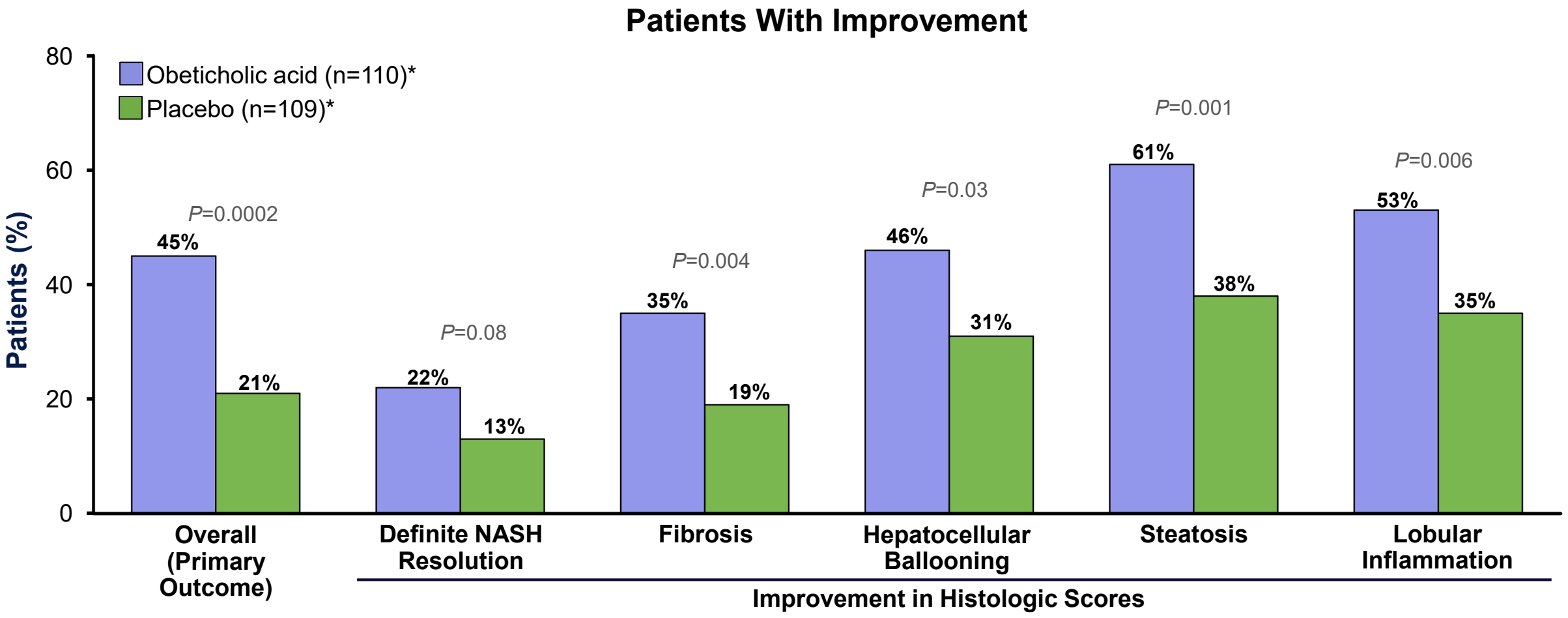
Placebo-controlled
Histologic evidence of definitive or borderline NASH
(liver biopsy within 90 days of entry)
NAFLD activity score ≥4
(individual scores each ≥1)
No cirrhosis



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.

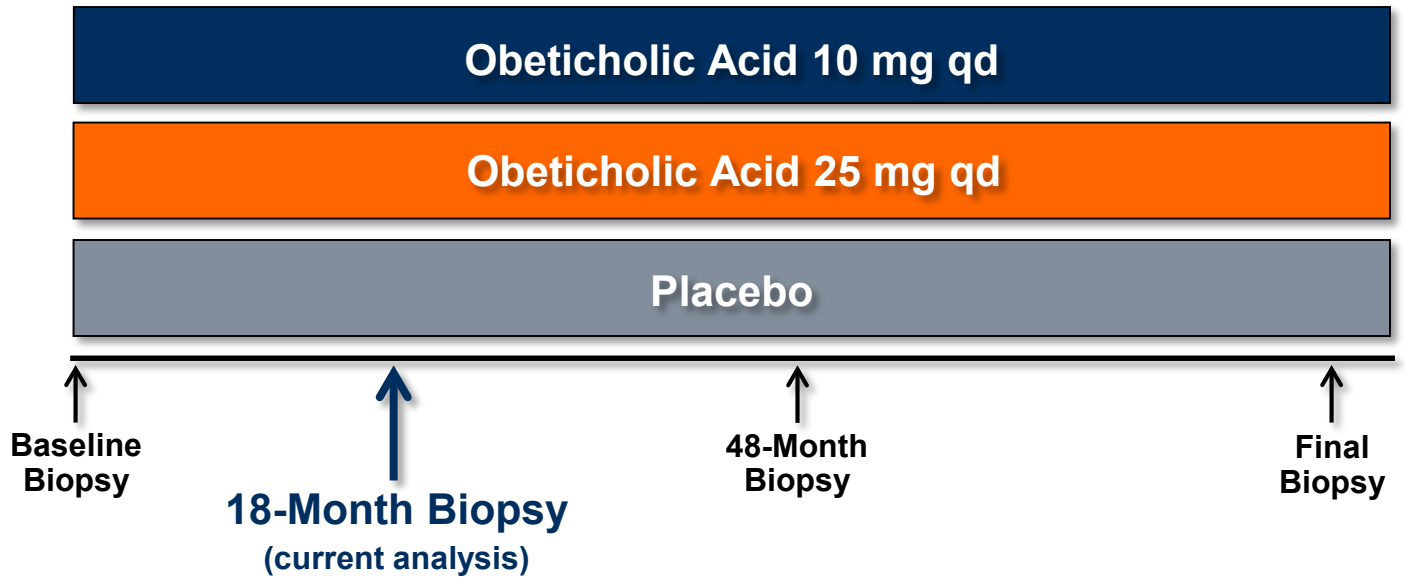
REGENERATE Study: Obeticholic Acid in NASH Patients Without Cirrhosis

FXR agonist

Phase 3 (n=2480)

Placebo-controlled
Biopsy confirmed NASH
(≤6 months to study entry)
Fibrosis stage 2 or 3 (NASH CRN)
NAFLD activity score ≥4
Planned interim analyses:
Month 18 and 28

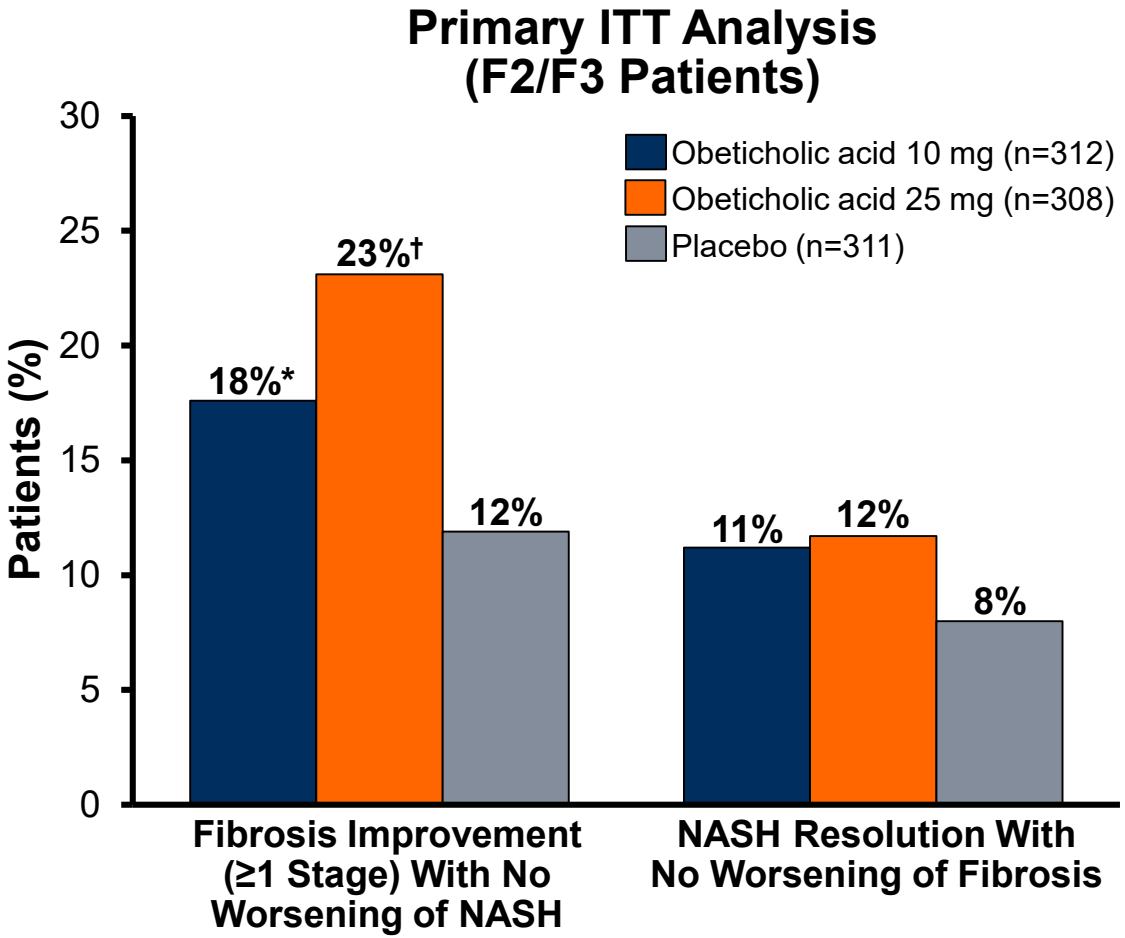
Total Study Duration Driven by the Time Required to Accrue 264 Outcome Events (~6 years)



REGENERATE: RandomizEd Global Phase 3 Study to Evaluate the Impact on NASH with FibRosis of Obeticholic Acid TreatmEnt.
Co-primary liver histology endpoints at 18 months:
Improvement in fibrosis by ≥1 stage with no worsening of NASH.
Resolution of NASH with no worsening in fibrosis stage.
Additional outcomes (time to first occurrence of any of the following adjudicated events):
Histological progression to cirrhosis; uncontrolled ascites; hospitalization for: variceal bleed, hepatic encephalopathy or spontaneous bacterial peritonitis; HCC; liver transplant or eligibility for liver transplant; and death.

Sanyal AJ, et al. *Hepatology*. 2019;70(suppl):23A-24A. Abstract 34.

REGENERATE Study: 18-Month Interim Efficacy Analysis

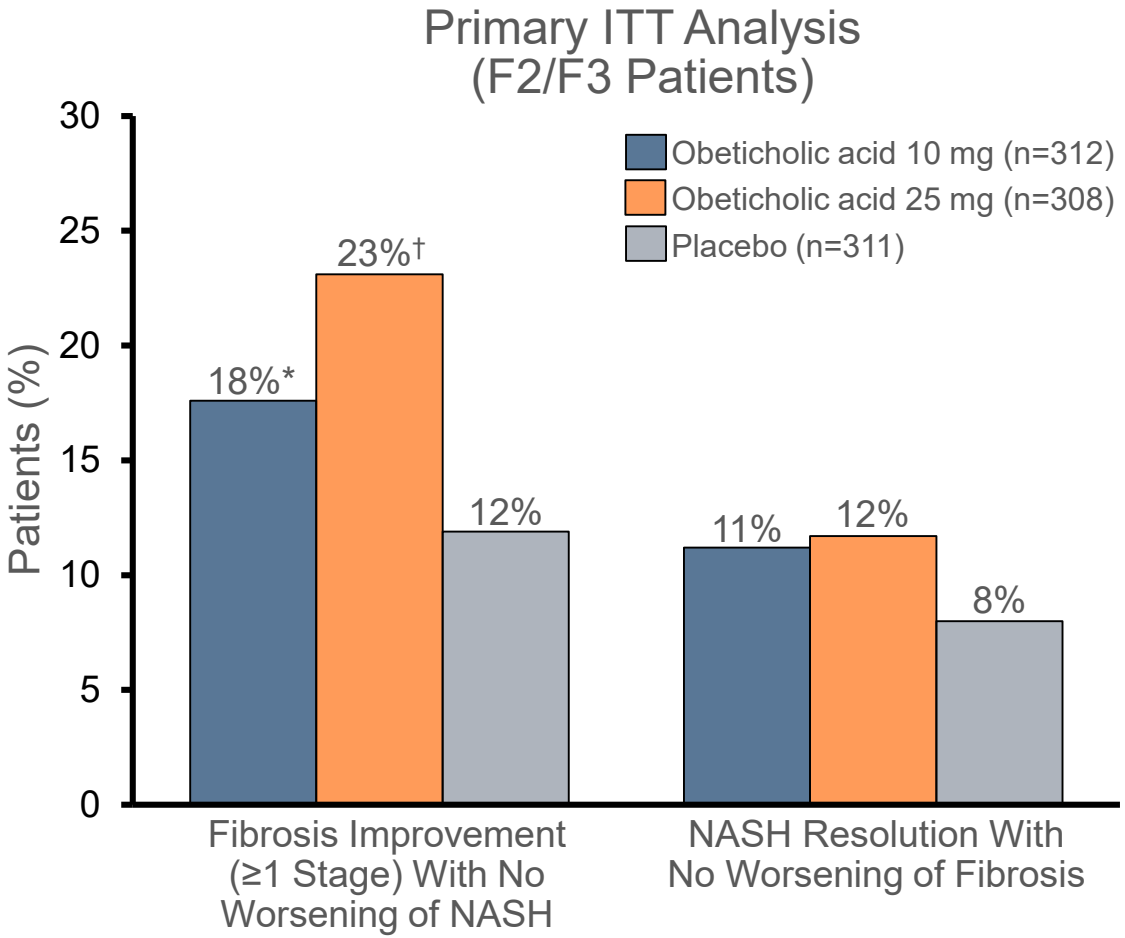


*P=0.04 and †P=0.0002 versus placebo.

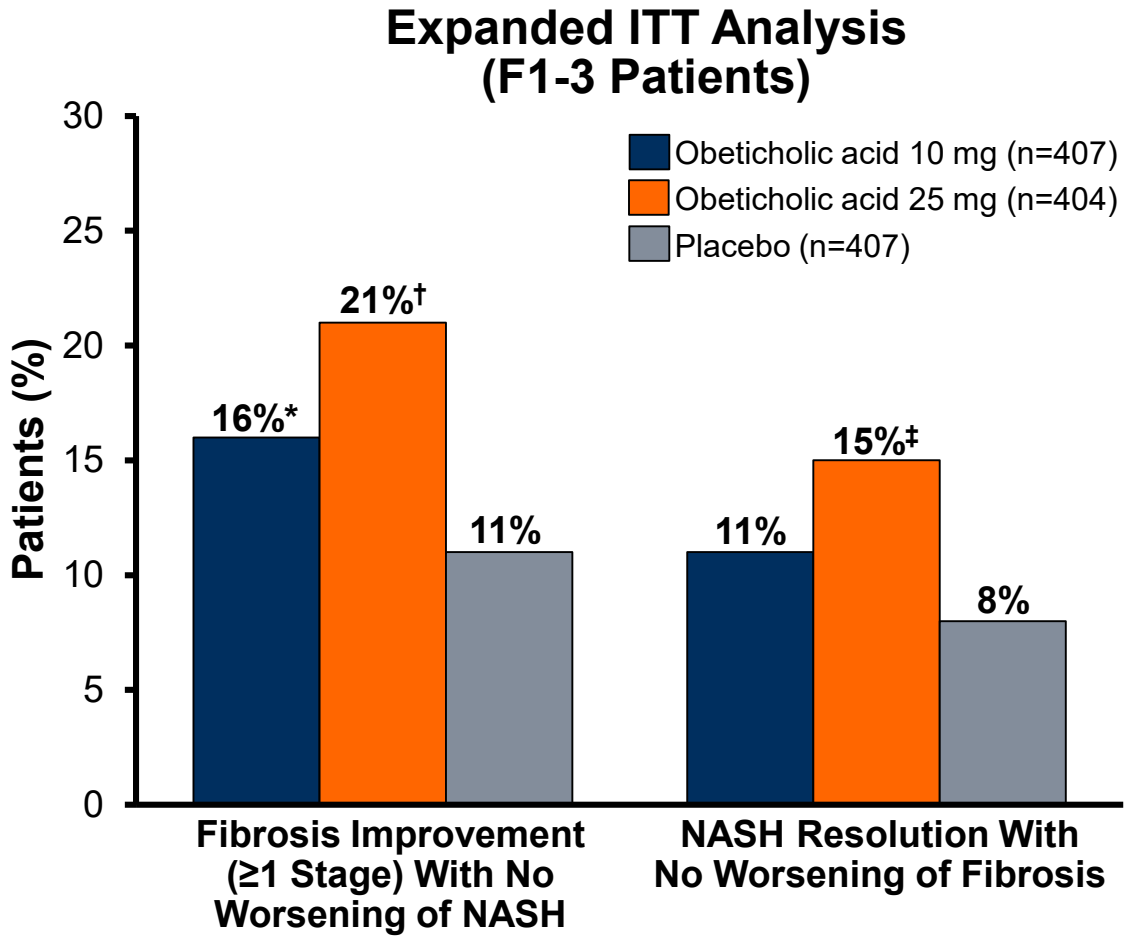
Worsening of NASH: no worsening of hepatocellular ballooning, lobular inflammation, and steatosis.
NASH resolution: overall histopathologic interpretation of (i) no fatty liver disease or (ii) fatty liver disease (simple or isolated steatosis) without steatohepatitis AND a NAFLD activity score of 0 for ballooning and 0-1 for inflammation.

Younossi Z, et al. *J Hepatol.* 2019;70(suppl):e5. Abstract GS-06.

REGENERATE Study: 18-Month Interim Efficacy Analysis



*P=0.04 and †P=0.0002 versus placebo.



*P=0.03, †P<0.0001, and ‡P=0.001 versus placebo.

Worsening of NASH: no worsening of hepatocellular ballooning, lobular inflammation, and steatosis.
NASH resolution: overall histopathologic interpretation of (i) no fatty liver disease or (ii) fatty liver disease (simple or isolated steatosis) without steatohepatitis AND a NAFLD activity score of 0 for ballooning and 0-1 for inflammation.

Sanyal AJ, et al. *Hepatology*. 2019;70(suppl):23A-24A. Abstract 34.

REGENERATE: Select AEs in Safety Population

Events, n (%)	Obeticholic Acid 10 mg (n = 653)	Obeticholic Acid 25 mg (n = 658)	Placebo (n = 657)
≥ 1 TEAE	579 (89)	601 (91)	548 (83)
▪ Leading to d/c	39 (6)	83 (13)	41 (6)
Serious AEs	72 (11)	93 (14)	75 (11)
AEs in ≥ 5% in either OCA group			
▪ Pruritis	183 (28)	336 (51)	123 (19)
▪ Nausea	72 (11)	83 (13)	77 (12)
▪ Abdominal pain	66 (10)	67 (10)	62 (9)
▪ Diarrhea	44 (7)	49 (7)	79 (12)
▪ Vomiting	34 (5)	44 (7)	33 (5)
▪ Urinary tract infection	54 (8)	62 (9)	49 (7)
▪ Upper respiratory tract infection	47 (7)	54 (8)	44 (7)
▪ Elevated LDL	109 (17)	115 (17)	47 (7)
▪ Arthralgia/Back pain	50 (8)/56 (9)	50 (8)/40 (6)	55 (8)/50 (8)
▪ Fatigue	78 (12)	71 (11)	88 (13)
▪ Headache/Dizziness	42 (6)/32 (5)	34 (5)/25 (4)	51 (8)/28 (4)

Younossi. Lancet. 2019;394:2184.

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

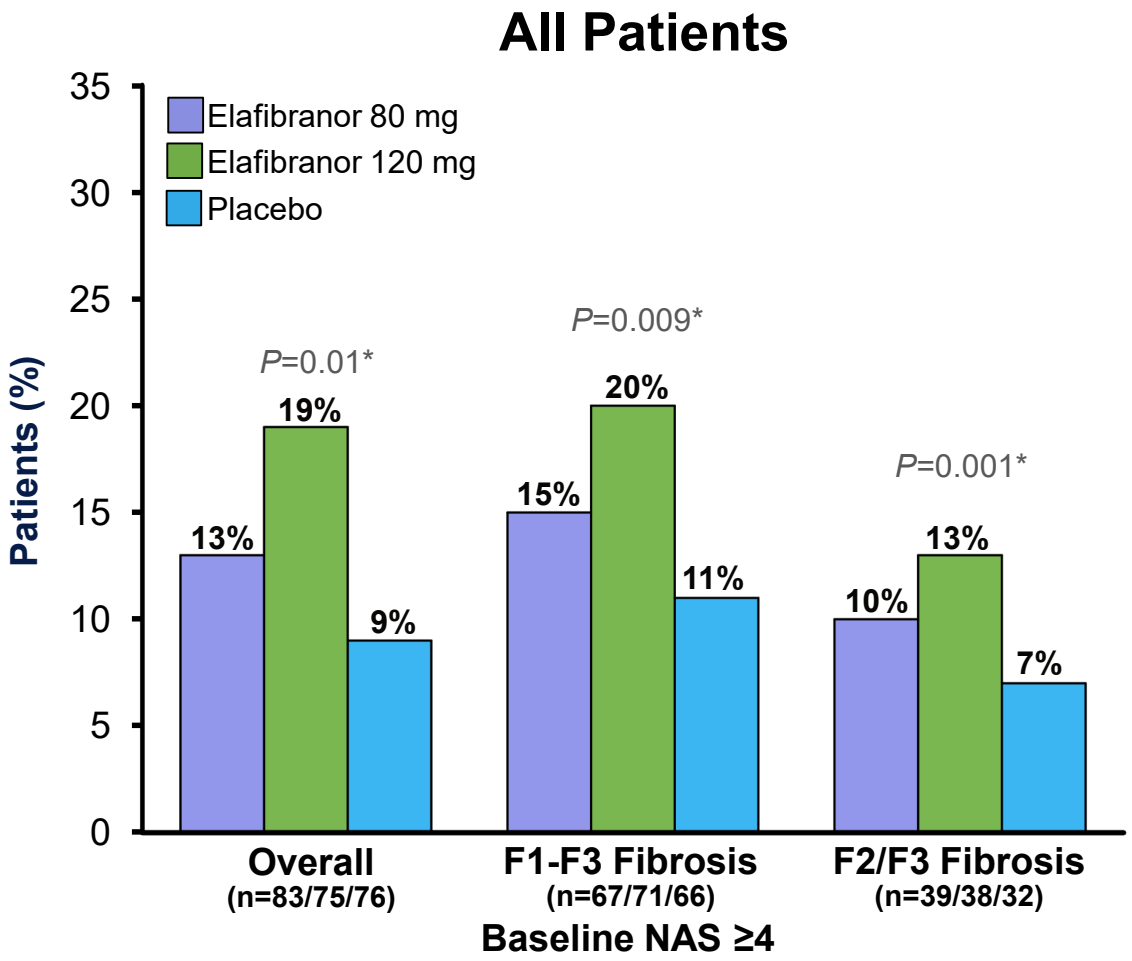
PPARδ Activation

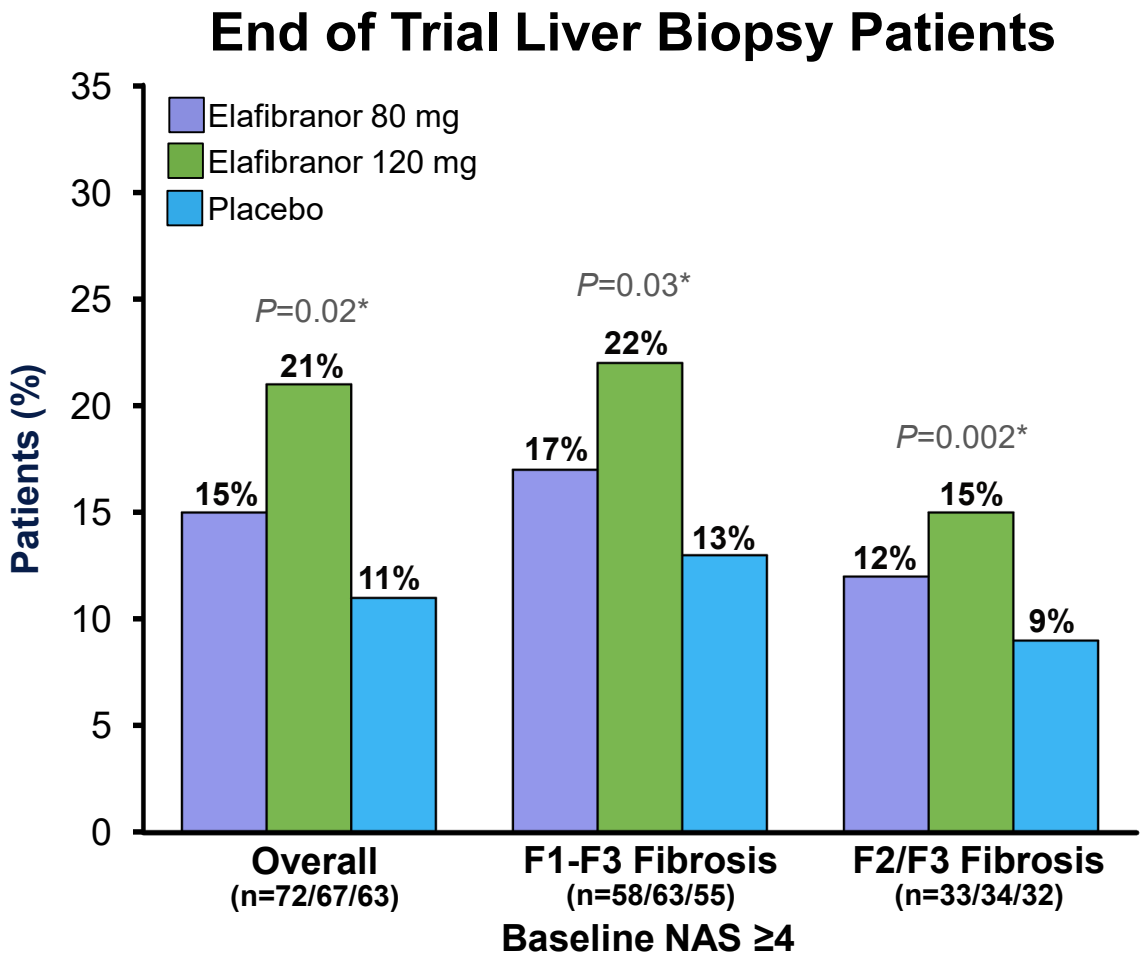
- Improves glucose homeostasis
- Inhibits hepatic lipogenesis
- Anti-inflammatory activity in macrophages and Kupffer cells

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



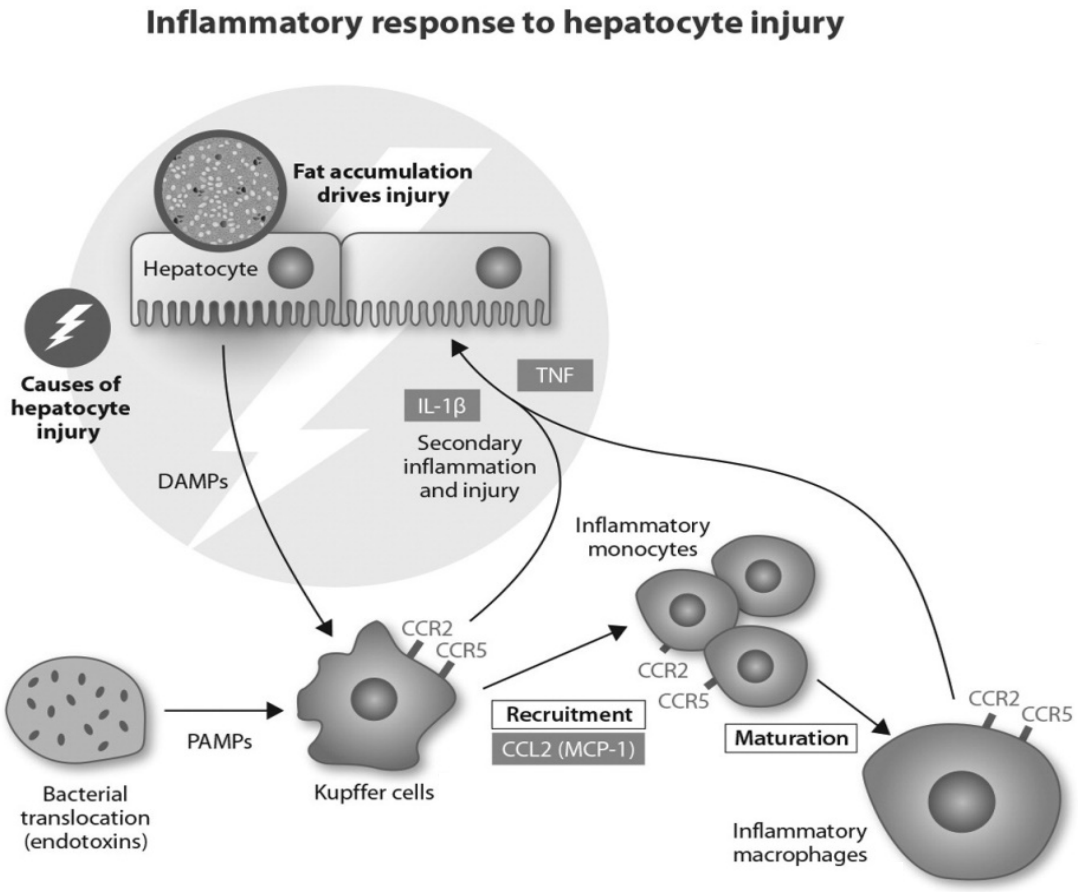


*Elafibranor 120 mg versus placebo.
Protocol-defined response results.

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

CCR Type 2/5 Antagonist: Cenicriviroc

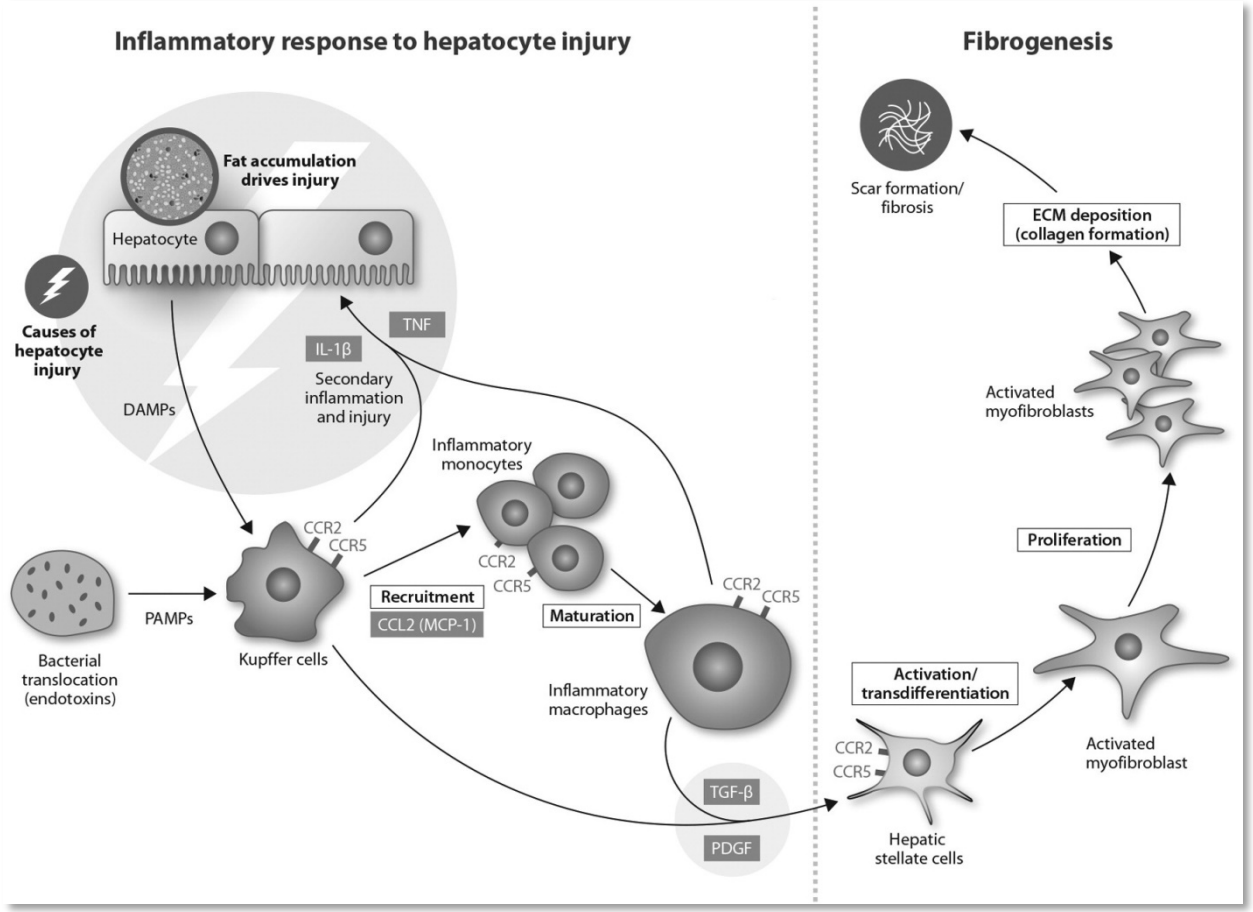
- Activation of CCR type 2/5 receptors
  - Promotes recruitment and migration of monocytes to the liver
    - Maturate into pro-inflammatory macrophages



Gawrieh S, et al. Clin Liver Dis. 2018;22:189-199.
Perazzo H, et al. *Liver Int.* 2017;37:634-647.
Friedman S, et al. *Contemp Clin Trials.* 2016;47:356-365.

CCR Type 2/5 Antagonist:Cenicriviroc

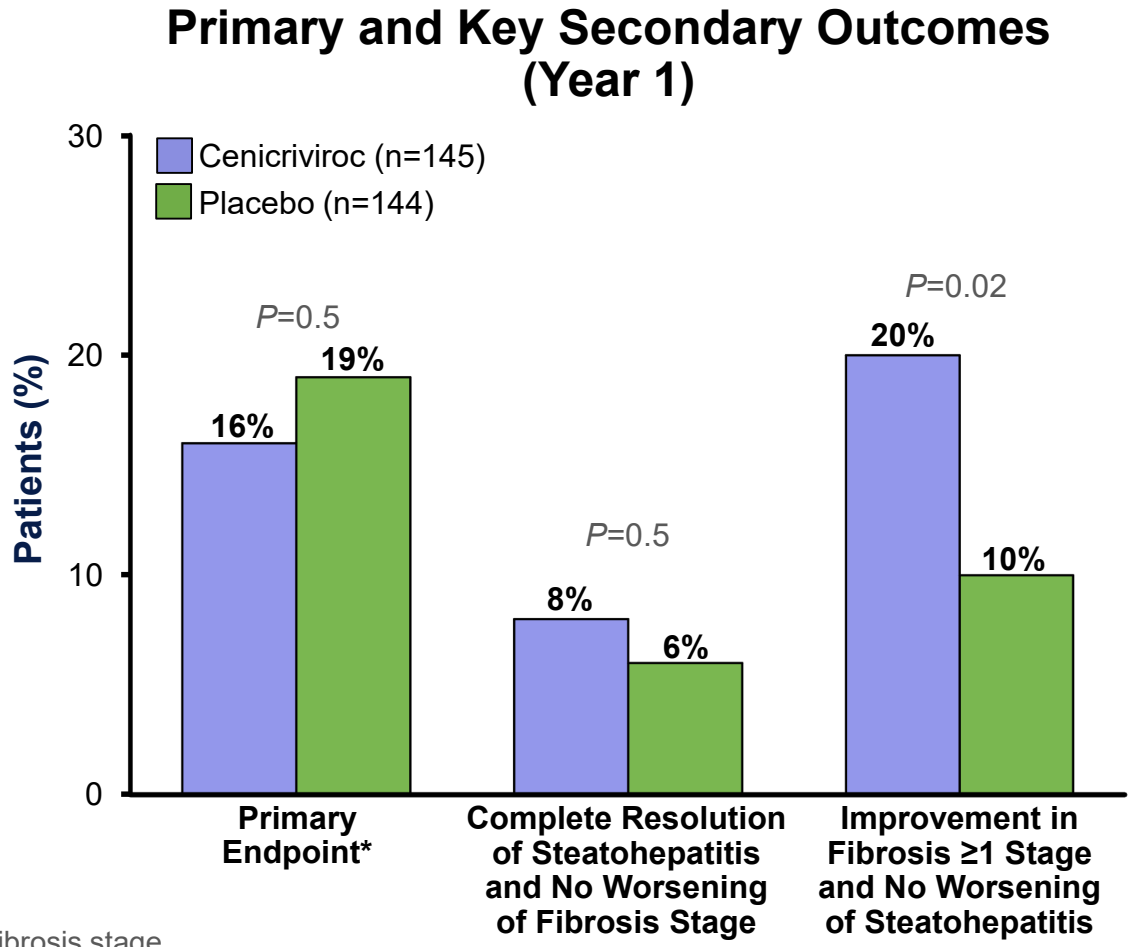
- Activation of CCR type 2/5 receptors
  - Promotes recruitment and migration of monocytes to the liver
    - Maturate into pro-inflammatory macrophages
- Leads to activation of
  - Kupffer cells
  - Hepatic stellate cells
  - Collagen production
  - Fibrogenesis



Gawrieh S, et al. Clin Liver Dis. 2018;22:189-199.
Perazzo H, et al. *Liver Int.* 2017;37:634-647.
Friedman S, et al. *Contemp Clin Trials.* 2016;47:356-365.

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

- Primary endpoint
  - No significant difference between cenicriviroc and placebo (16% versus 19%)
- Key secondary endpoints
  - Complete resolution of steatohepatitis and no worsening of fibrosis stage
    - No significant difference between cenicriviroc and placebo (8% versus 6%)
  - ≥1 stage improvement in fibrosis (NASH-CRN) and no worsening of steatohepatitis
    - Achieved by significantly more cenicriviroc patients versus placebo (20% versus 10%; *P*=0.02)



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

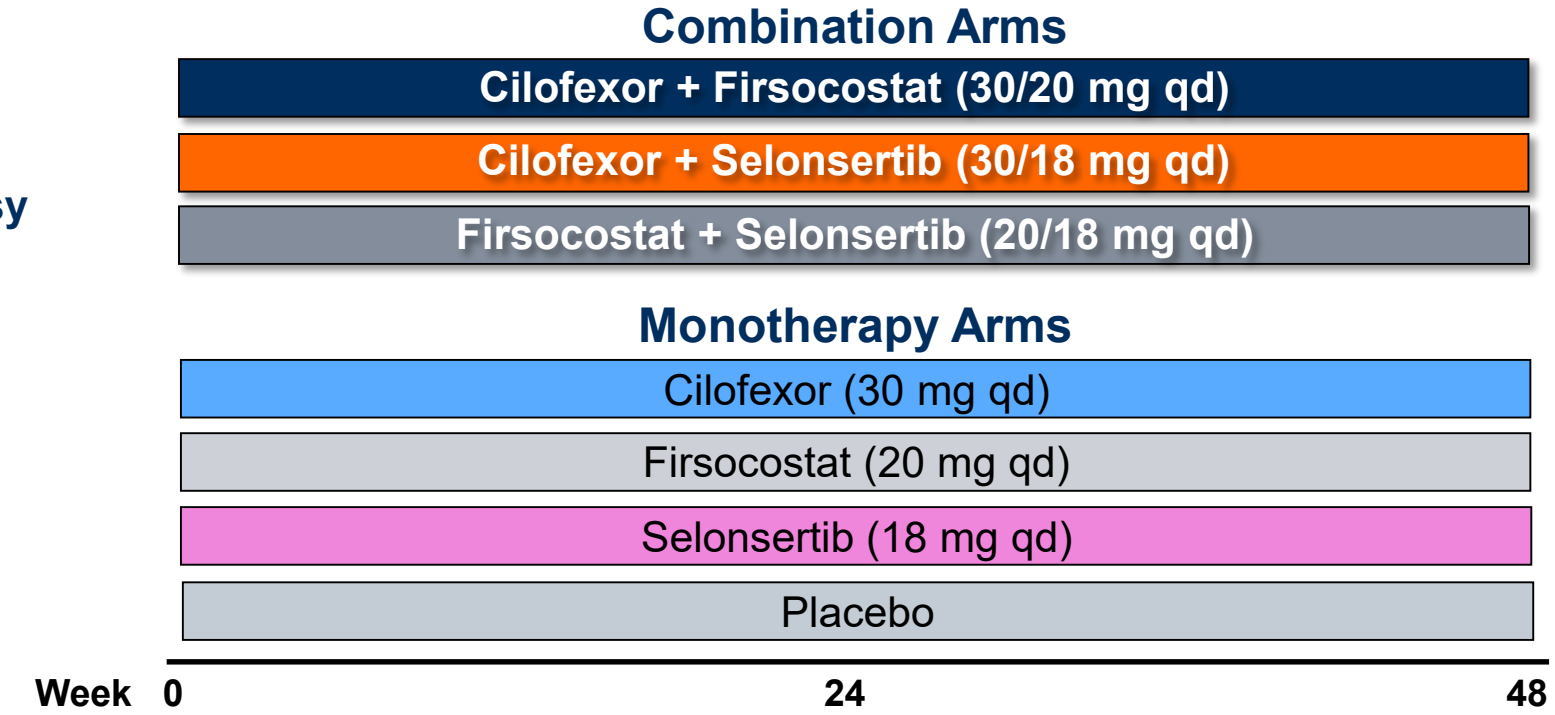
Ratziu V, et al. *J Hepatol.* 2018;68(suppl S1):S1-S2. Abstract GS-002.
Friedman SL, et al. *Hepatology*. 2018;67:1754-1767.

ATLAS Study:
Cilofexor ± Firsocostat ± Selonsertib in Patients With NASH

FXR agonist + ACC inhibitor + ASK1 inhibitor

Phase 2b (n=395 planned)

- Double-blind
- Biopsy-proven NASH
- Fibrosis stage 3 or 4 (NASH CRN)
- Non-invasive tests for those without biopsy
  - FibroScan
  - Enhanced liver fibrosis (ELF) score



Patients previously never had a liver biopsy, liver stiffness by FibroScan and enhanced liver fibrosis (ELF) test score.
Primary endpoints:
Safety and tolerability.
Fibrosis improvement in ≥1 stage without NASH worsening (week 48).

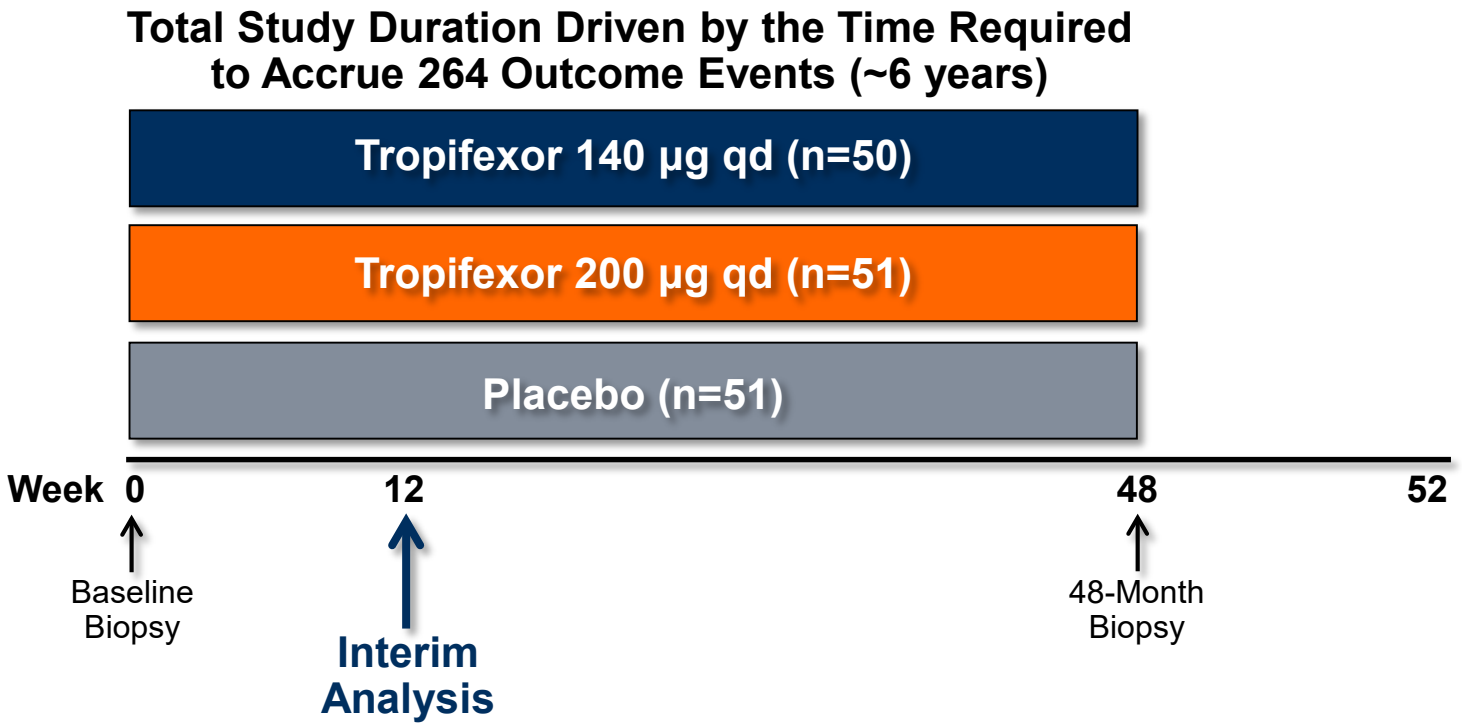
ClinicalTrials.gov. NCT03449446.

FLIGHT-FXR (Part C): Tropifexor in Patients With Fibrotic NASH

FXR agonist

Phase 2

Double-blind, placebo-controlled
Hepatic fat fraction ≥10%
Biopsy confirmed NASH (≤6 months to study entry)
Fibrosis stage 2 or 3 (NASH CRN)
NAFLD activity score ≥4



Primary endpoints (week 12):
- Change in ALT.
- Hepatic fat fraction (MRI-PDDF).

Additional outcomes:
- Change in body weight (week 12).
- Dose-response relationship: C4, GGT (week 12).
- Proportion of patients with ≥1 point improvement in fibrosis without worsening of NASH (week 48).
- Proportion of patients with resolution of NASH without worsening of fibrosis (week 48).

Lucas KJ, et al. *Hepatology.* 2019;70(suppl 1). Abstract L04.

FLIGHT-FXR (Part C): Interim Results With Tropifexor in Patients With Fibrotic NASH

- At 12 weeks, tropifexor treatment versus placebo resulted greater decreases in
  - ALT and GGT
  - Hepatic fat fraction and proportion of patients achieving ≥30% reduction in hepatic fat fraction
  - Body weight
- Safety of tropifexor at week 12
  - Overall comparable safety profile with placebo
  - Discontinuations due to adverse events
    - Highest with 200 µg (10%) compared with 140 µg (4%) and placebo (2%)
  - Tropifexor 200 µg was associated with pruritus (which rarely led to discontinuation)
  - No evidence of hepatoxicity

Interim Results (week 12)

	Tropifexor 140 µg qd (n=50)	Tropifexor 200 µg qd (n=51)	Placebo (n=51)
Change in ALT (U/L)	-20	-24*	-9
Change in GGT (U/L)	-39*	-41*	-3
Hepatic fat fraction			
Relative change (%)	-17	-34†	-10
≥30% reduction (%)	32	64	20
Weight loss (kg)	-3*	-3*	-1

*P<0.05 and †P<0.001 versus placebo.

Lucas KJ, et al. *Hepatology.* 2019;70(suppl 1). Abstract L04.

PPAR-Alpha/Gamma Agonist

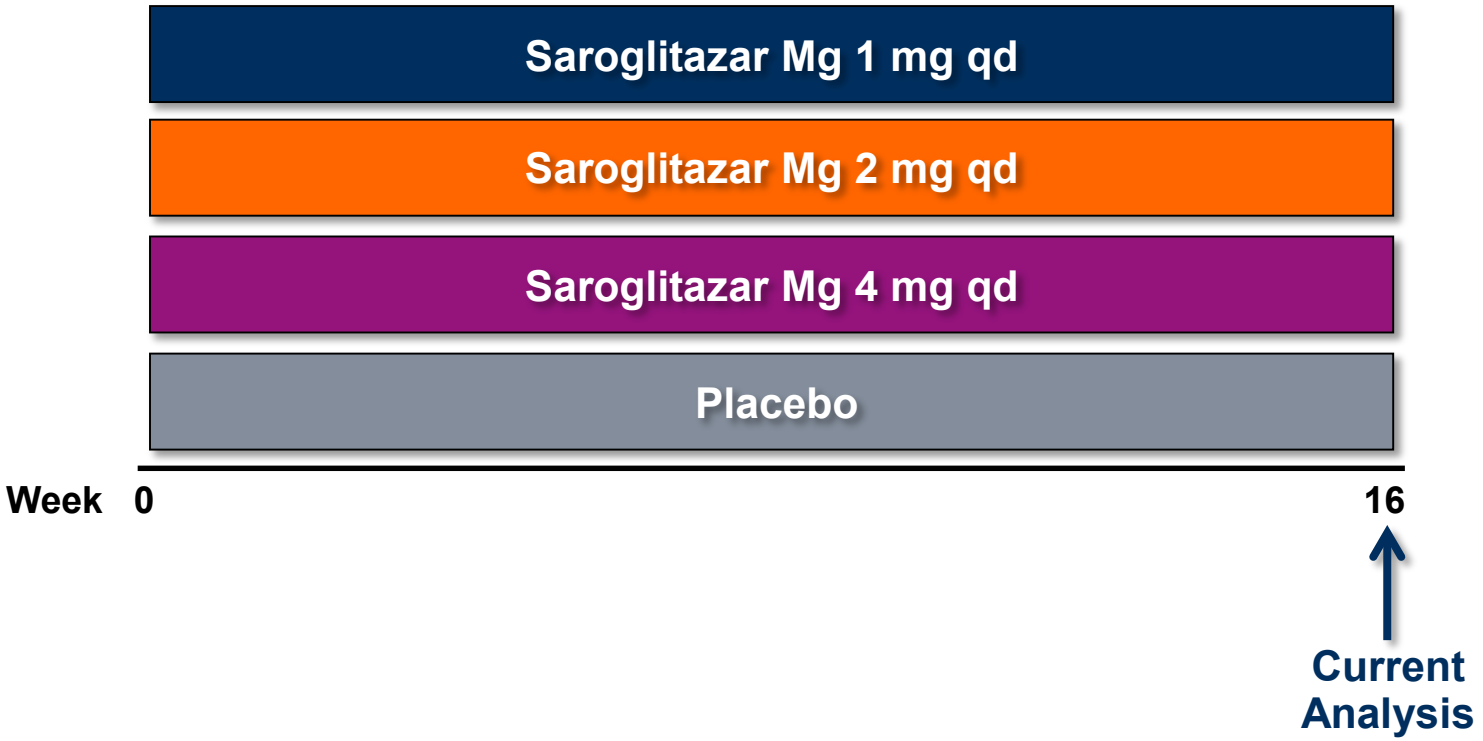
- Targets lipogenesis (eg, saroglitazar)
- PPAR-alpha
  - Target for fibrate drugs and when activated can decrease serum triglyceride levels
- PPAR-gamma
  - Target for thiazolidinediones with known effects on improving insulin sensitivity

EVIDENCES IV Study: Saroglitazar Mg in NAFLD/NASH Without Cirrhosis

PPAR-alpha/gamma agonist

Phase 2 (n=72)

Double-blind
NAFLD (imaging) or NASH (biopsy)
ALT ≥50 U/L
BMI ≥25 kg/m^2
No vitamin E doses >100 IU/day (3 months prior)
No cirrhosis



NASH patients (n=106).
Primary endpoint (week 16):
Change in ALT.
Secondary endpoint:
Change in hepatic fat content (MRI-PDFF).

Gawrieh S, et al. *Hepatology.* 2019;70(suppl 1). Abstract L10.

EVIDENCES IV Study: Outcomes With Saroglitazar Mg in NAFLD/NASH Without Cirrhosis

- Outcomes that were significantly improved with saroglitazar at week 16
  - ALT levels
  - Hepatic fat content
  - Insulin resistance
  - Dyslipidemia
- Safety at week 16 with saroglitazar
  - Overall, well tolerated
  - No serious adverse events related to drug
  - Few discontinuations due to adverse events (n=3, 1 probably related [mild rash])

Outcomes at Week 16

	Saroglitazar Mg (mg qd)			
	1 (n=26)	**2 (n=23)**	**4 (n=27)**	**Placebo (n=28)**
Change in ALT (U/L)	-27*	-33†	-44†	4
Hepatic fat fraction				
Relative change (%)	0.5	-0.4	-4‡	-0.3
≥30% reduction (%)	11	5	40‡	8
Weight change (%)	0.3	0.5	1.0	0.3

*P=0.0002, †P<0.0001, ‡P<0.01 versus placebo.

Gawrieh S, et al. *Hepatology.* 2019;70(suppl 1). Abstract L10.

Outcomes With Cotadutide in Overweight and Obese Subjects With Type 2 Diabetes

- Maximum reduction in HbA1c was reached by week 14 in all groups except placebo
  - Reductions maintained through week 26
- Significant reductions in body weight for all doses of cotadutide
- Greater reductions on ALT with cotadutide 200 and 300 µg versus liraglutide and placebo
- Improvements in NAFLD fibrosis score and FIB-4 with cotadutide versus placebo
- Safety with cotadutide at week 26
  - Discontinuations due to adverse events was higher (16%) versus liraglutide (2%) and placebo (4%)
  - Most common adverse events: nausea (35%), vomiting (17%), and diarrhea (14%)

Outcomes at Week 26

	Cotadutide (µg qd)				
	100 (n=100)	200 (n=256)	300 (n=256)	Liraglutide (n=110)	Placebo (n=112)
Weight change (%)	-3.4*	-4.2†	-5.4†‡	-4.2†	-1.2
LS mean change (%)					
ALT	-13	-18*‡	-19*‡	-10	-5
AST	-5	-9†	-10*‡	+0.3	+0.2
LS mean change					
NAFLD fibrosis score	-0.15*	-0.12*	-0.11*	-0.07	+0.07
FIB-4	-0.07*	-0.06*	-0.08*	+0.01	+0.03

*P<0.05 and †P<0.001 versus placebo.
‡P<0.05 versus liraglutide.

Nahra R, et al. *Hepatology.* 2019;70(suppl 1):24A-25A. Abstract 35.

Summary

- NASH is a complex trait disease
- Genetic Factors
- Environmental Factors
- Obesity, metabolic syndrome
- Type 2 Diabetes
- Interaction between visceral adipose tissue and liver
- Weight loss critical
- Insulin Resistance universal