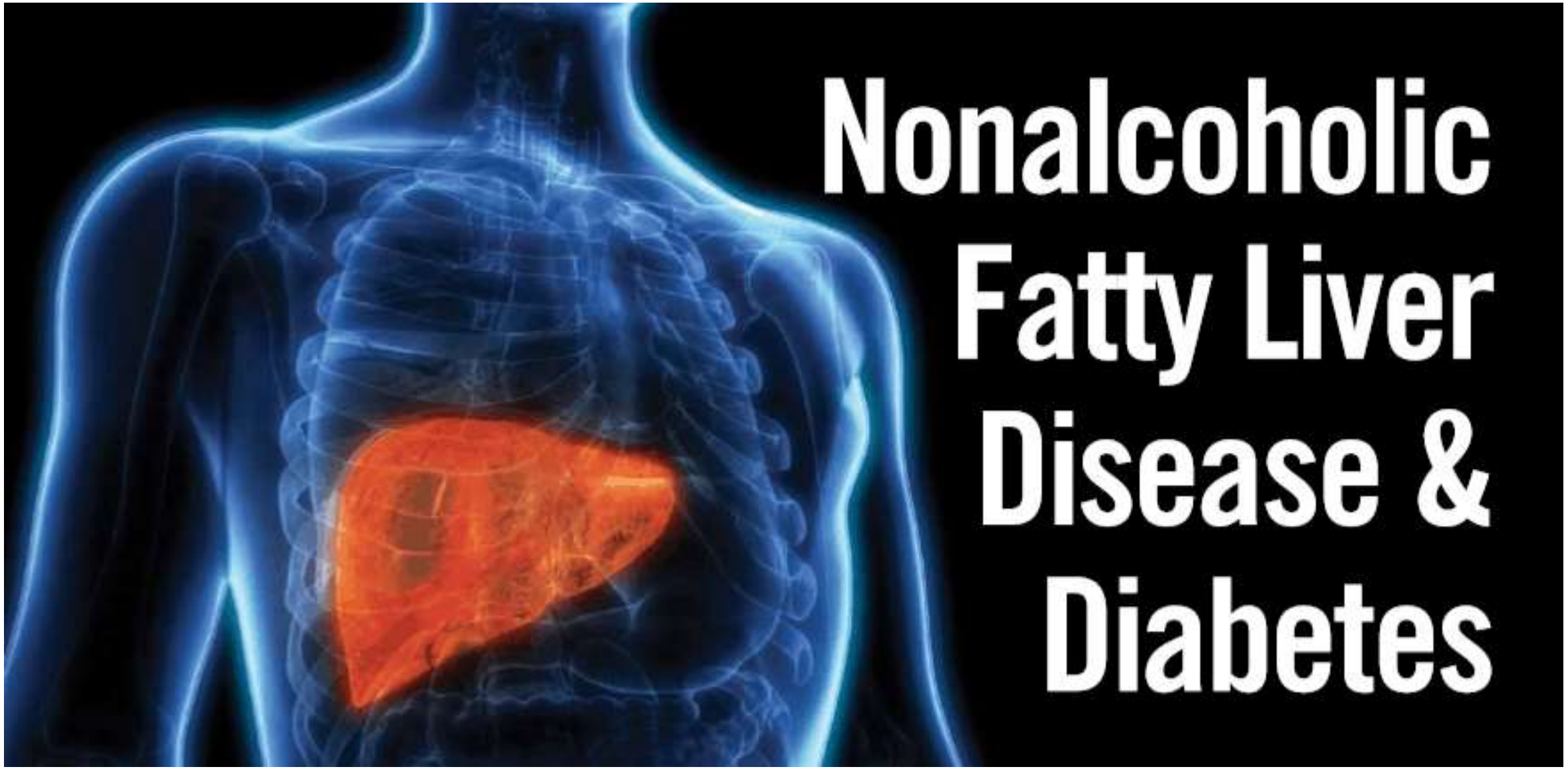
Hidden faces of diabetes and MAFLD

Prof. Elsayed Abdel Fattah Eid

Head of Medical department and Endocrinology ,

Faculty of Medicine

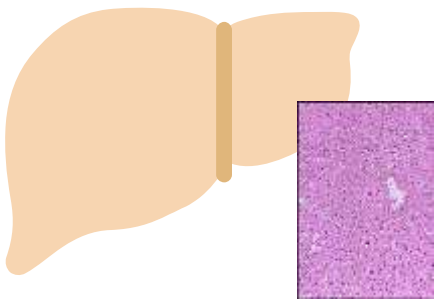
Delta university


Nonalcoholic
Fatty Liver
Disease &
Diabetes

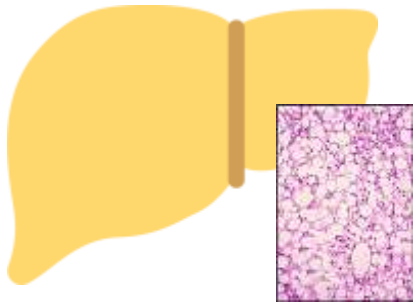
The MAFLD Continuum

MAFLD

Normal Liver

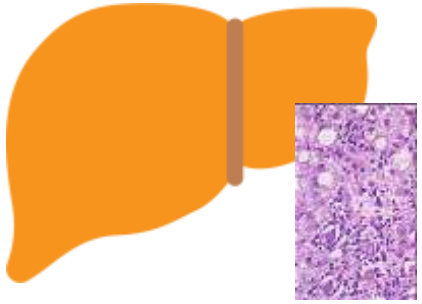


Steatosis "NAFL"



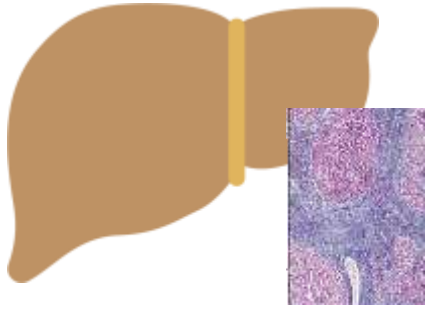
Fat infiltration ≥ 5% without ballooning, with or without inflammation

Steatohepatitis "NASH"



Fat infiltration ≥ 5% with necroinflammation and hepatocellular injury (ballooning, hepatocyte degeneration, Mallory bodies, or megamitochondria)

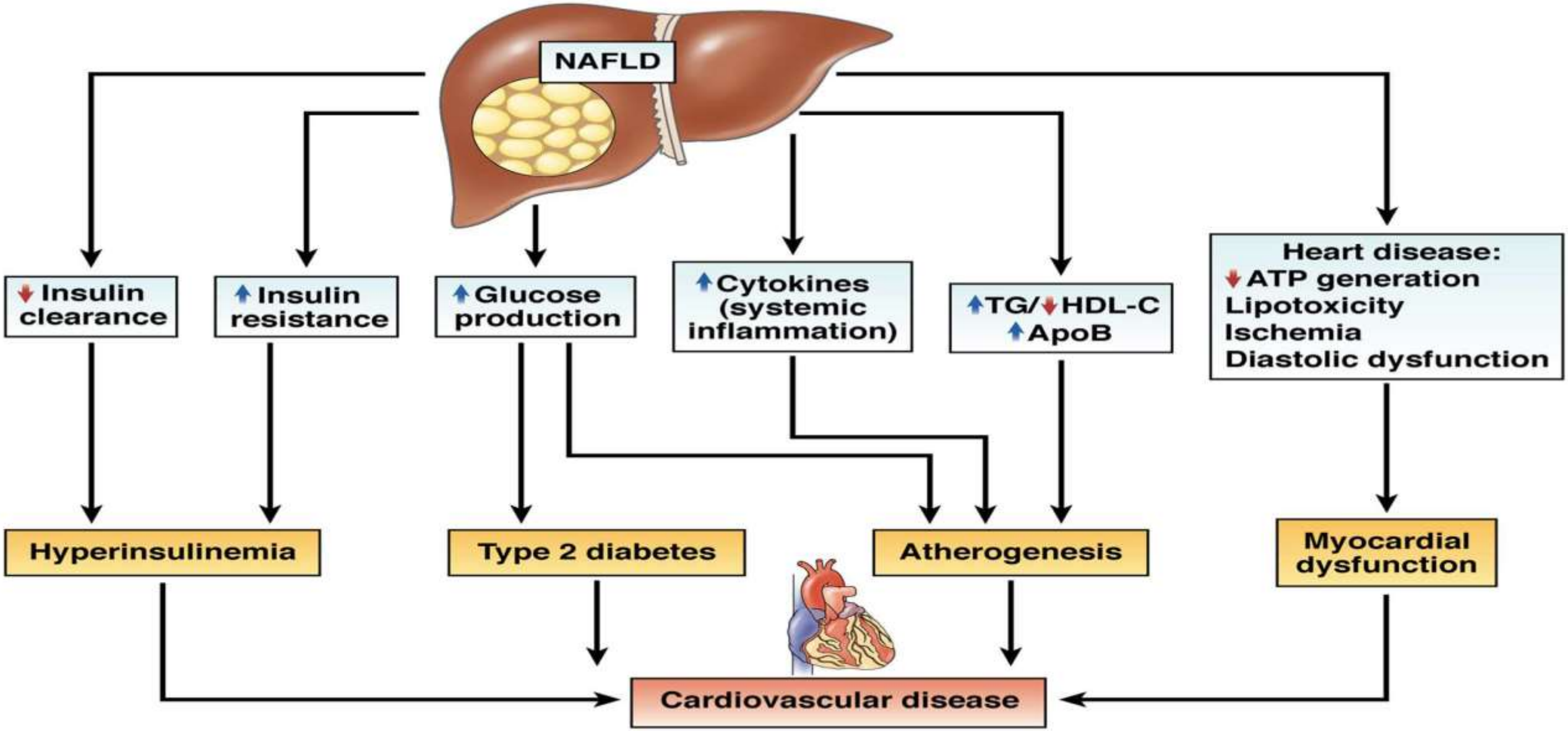
Cirrhosis



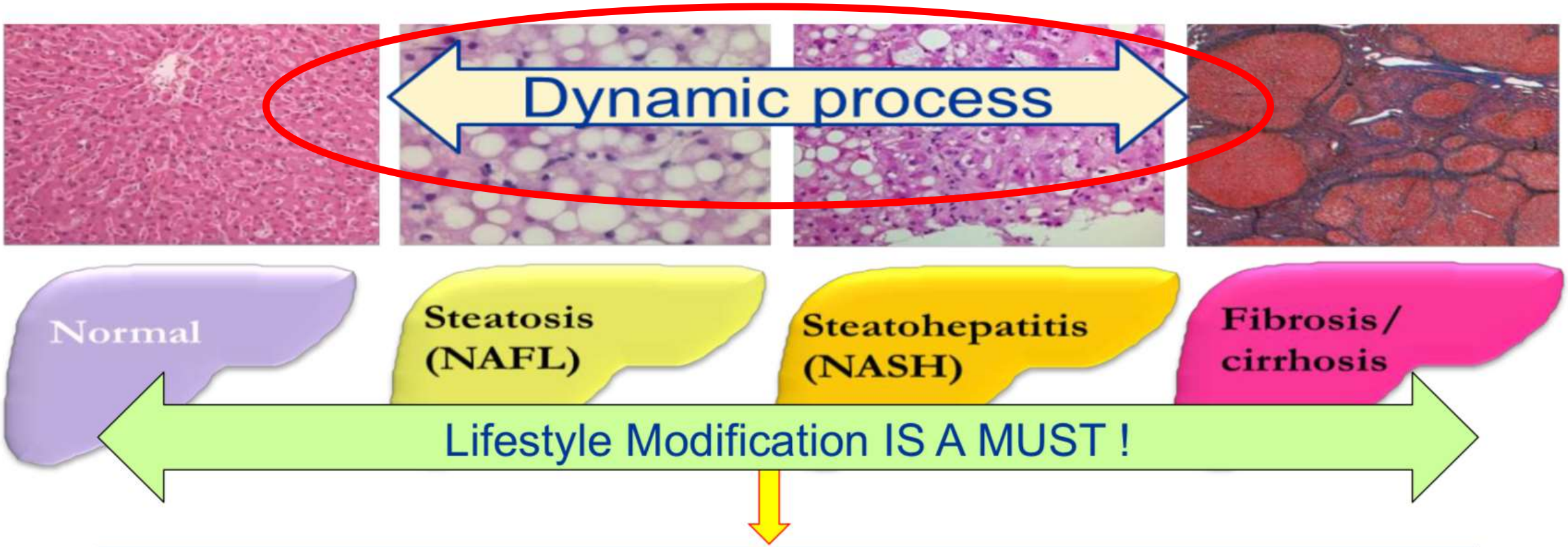
Increasing fibrosis, leading to cirrhosis

HCC

Chalasani. Hepatology. 2018;67:328.


NAFLD
↓Insulin clearance
↑Insulin resistance
↑Glucose production
↑Cytokines (systemic inflammation)
↑TG/↓HDL-C
↑ApoB
Heart disease:
↓ATP generation
Lipotoxicity
Ischemia
Diastolic dysfunction
Hyperinsulinemia
Type 2 diabetes
Atherogenesis
Myocardial dysfunction
Cardiovascular disease

Current Treatment of NAFLD

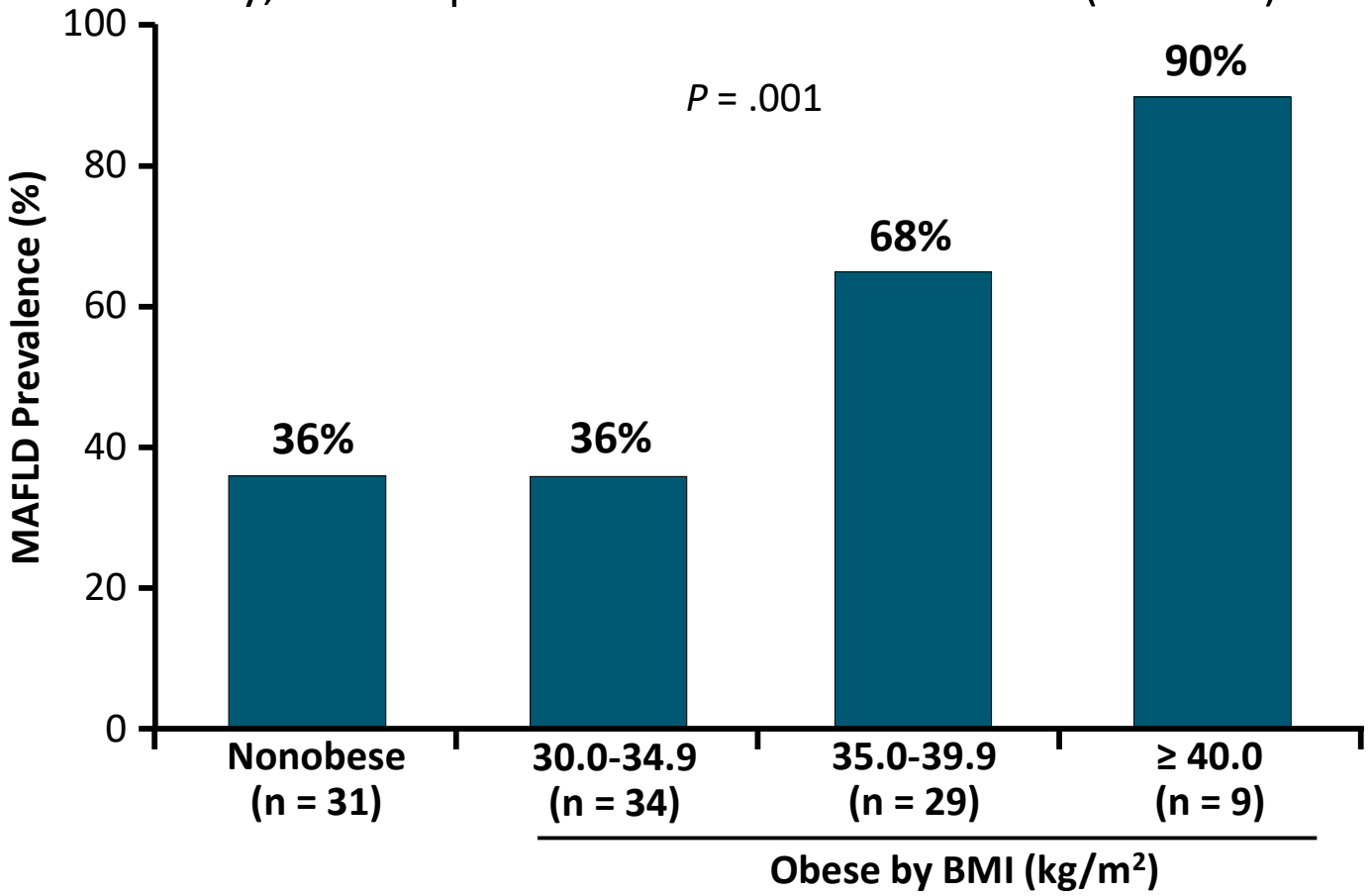


Targeted Pharmacotherapy for FDA approved indications
Targeting co-morbidities of NAFLD/NASH
(metformin, vitamin E, pioglitazone, GLP-1 Ras, SGLT2 inhibitors, statins)

Medical treatment unsuccessful: Consider bariatric endoscopy or surgery or referral for clinical trials

Prevalence of MAFLD and NASH in Patients With T2DM and Normal Plasma AST or ALT

- Patients with T2DM and normal AST or ALT evaluated for liver triglyceride content by H-MRS, insulin sensitivity, and adipose tissue insulin resistance (N = 103)

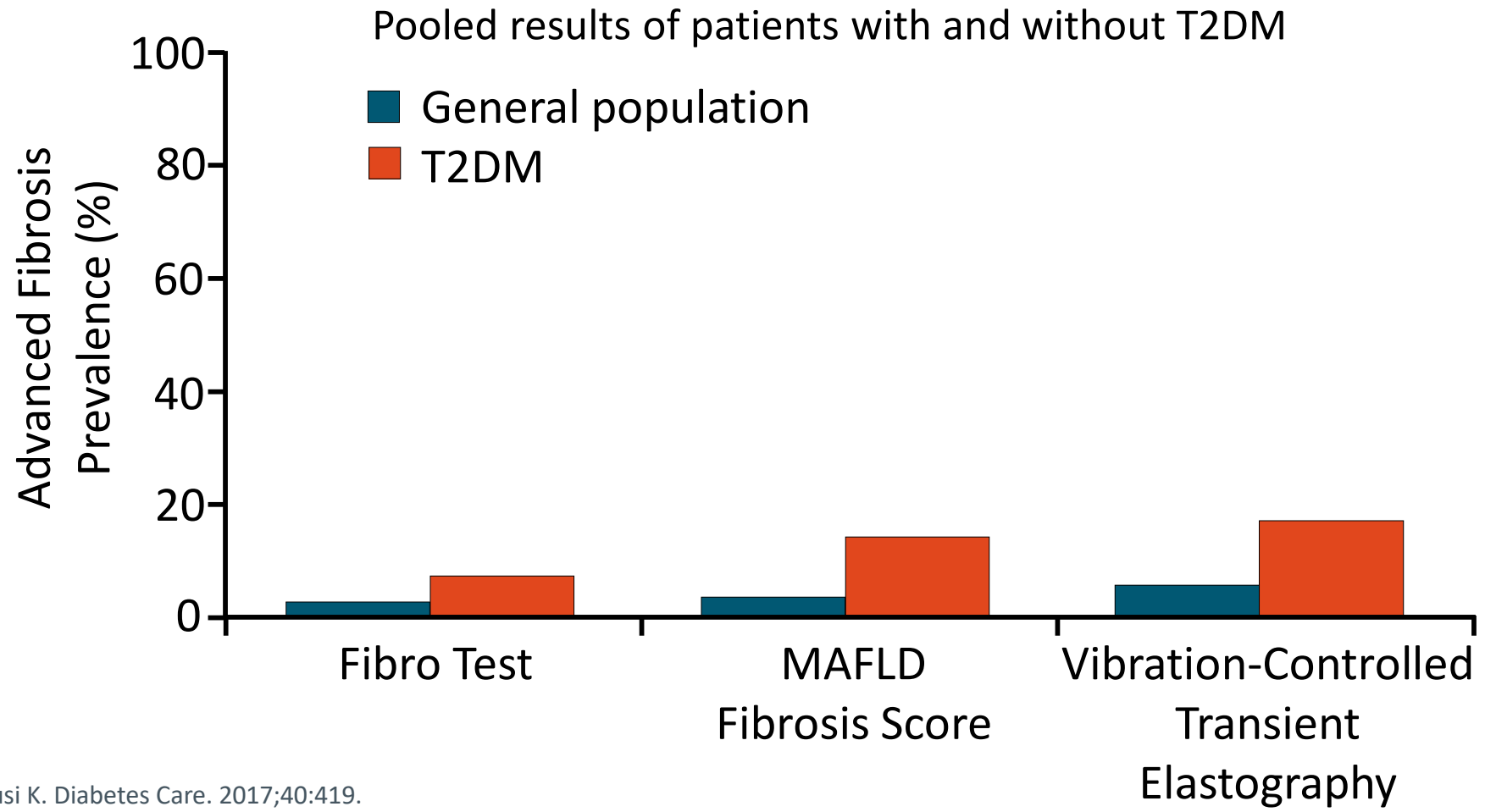


- Prevalence of MAFLD in overall cohort: 50%
  - Among these patients, prevalence of NASH: 56%

Portillo-Sanchez. J Clin Endocrinol Metab. 2015;100:2231. Stål. World J Gastroenterol. 2015;21:11077.

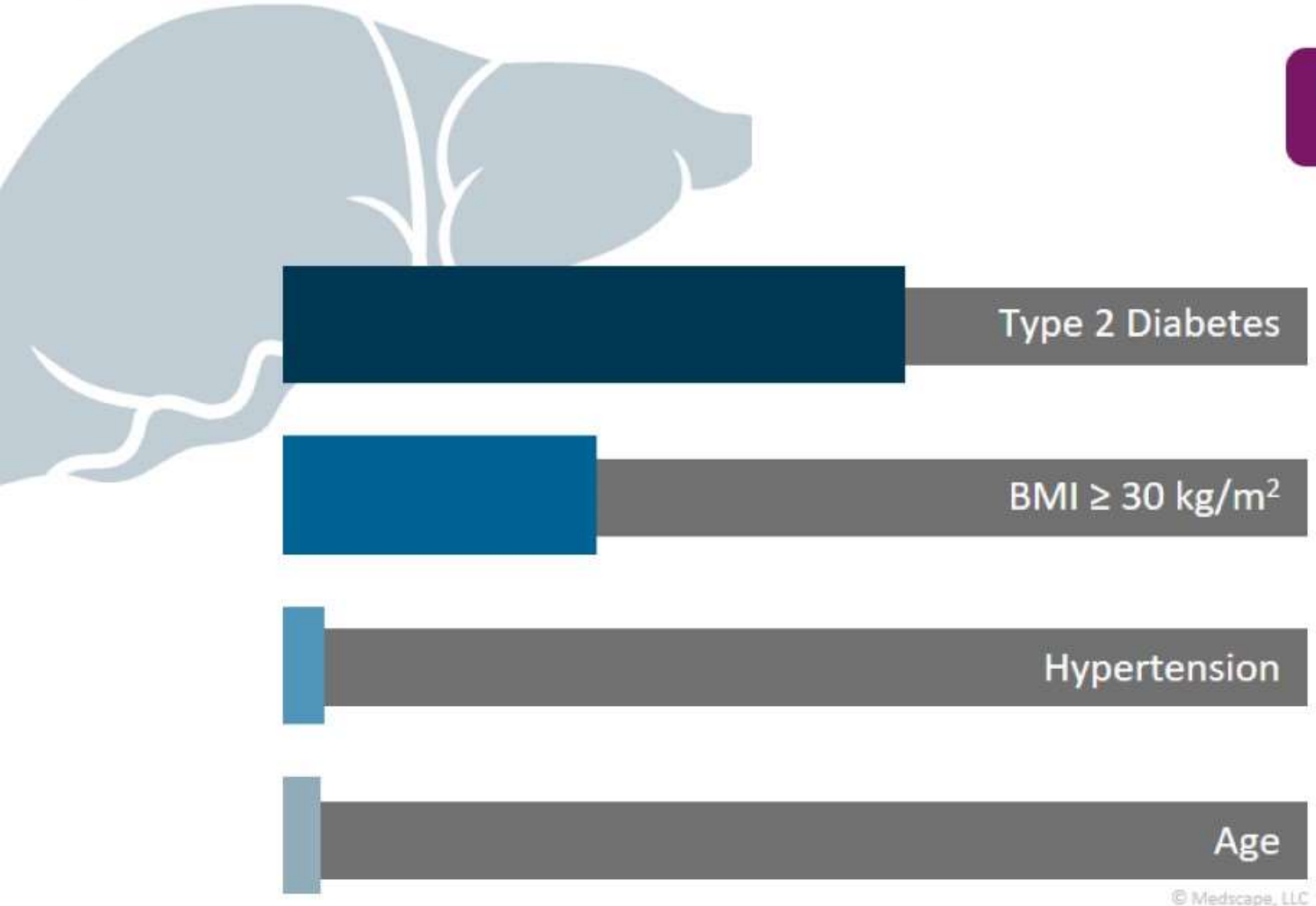
Advanced Fibrosis in Patients With vs Without T2DM By Diagnostic Approach

- Meta-analysis (N = 3229)



Bril F, Cusi K. Diabetes Care. 2017;40:419.

Diabetes is the Strongest Predictor of Advanced Fibrosis in NAFLD



	NHANES data (NFS)[a]	German tertiary care (histology, exc. cirrhosis)[b]
	OR for advanced fibrosis (95%CI) *P* value	
Type 2 Diabetes	**18.20** (4.7-70.1) *P*< .001	**4.12** (1.97-8.61) P< .001
BMI ≥ 30 kg/m²	**9.10** (2.37-35.0) *P*= .001	
Hypertension	**1.20** (0.36-4.2) *P*= .752	**2.70** (1.15-6.37) P< .05
Age	**1.08** (1.03-1.13) *P*= .001	

a. Wong RJ, et al. *Alimentary pharmacology & therapeutics*. 2017;46:974-80;
b. Labenz C, et al. *Alimentary pharmacology & therapeutics*. 2018;48:1109-16.

Goals of NASH Treatment

- Prevent liver-related morbidity and mortality
- Prevent cardiovascular morbidity and mortality

No need to diagnose NASH

if there are no treatments . . .

HEPATOLOGY

AASLD

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 1, 2018

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases

Naga Chalasani,[1] Zobair Younossi,[2] Joel E. Lavine,[3] Michael Charlton,[4] Kenneth Cusi,[5] Mary Rinella,[6] Stephen A. Harrison,[7] Elizabeth M. Brunt,[8] and Arun J. Sanyal[9]

WHOM TO TREAT

The management of NAFLD should consist of treating liver disease as well as the associated metabolic comorbidities such as obesity, hyperlipidemia, IR, and T2DM. Given that patients with NAFLD without SH or any fibrosis have excellent prognosis from a liver standpoint, pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis.

Approaches for Currently Available Treatments

No FDA-approved therapies for NASH (Off label)
Currently available therapeutics with proven efficacy

Weight loss[1-3]
- Lifestyle (diet, physical activity)
- Weight loss medications
- Bariatric surgery

In patients with advanced liver disease, choose or dose drugs appropriately.

Treat T2D and CV risk factors[4,5]
- Hyperglycemia (GLP-1 RA and/or SGLT-2i)
- Hypertension
- Dyslipidemia*

*MAFLD does not increase statin risk of drug-induced liver injury.[8]

Liver-directed treatment
- Vitamin E (except in diabetes)[6]
- Pioglitazone[6,7]

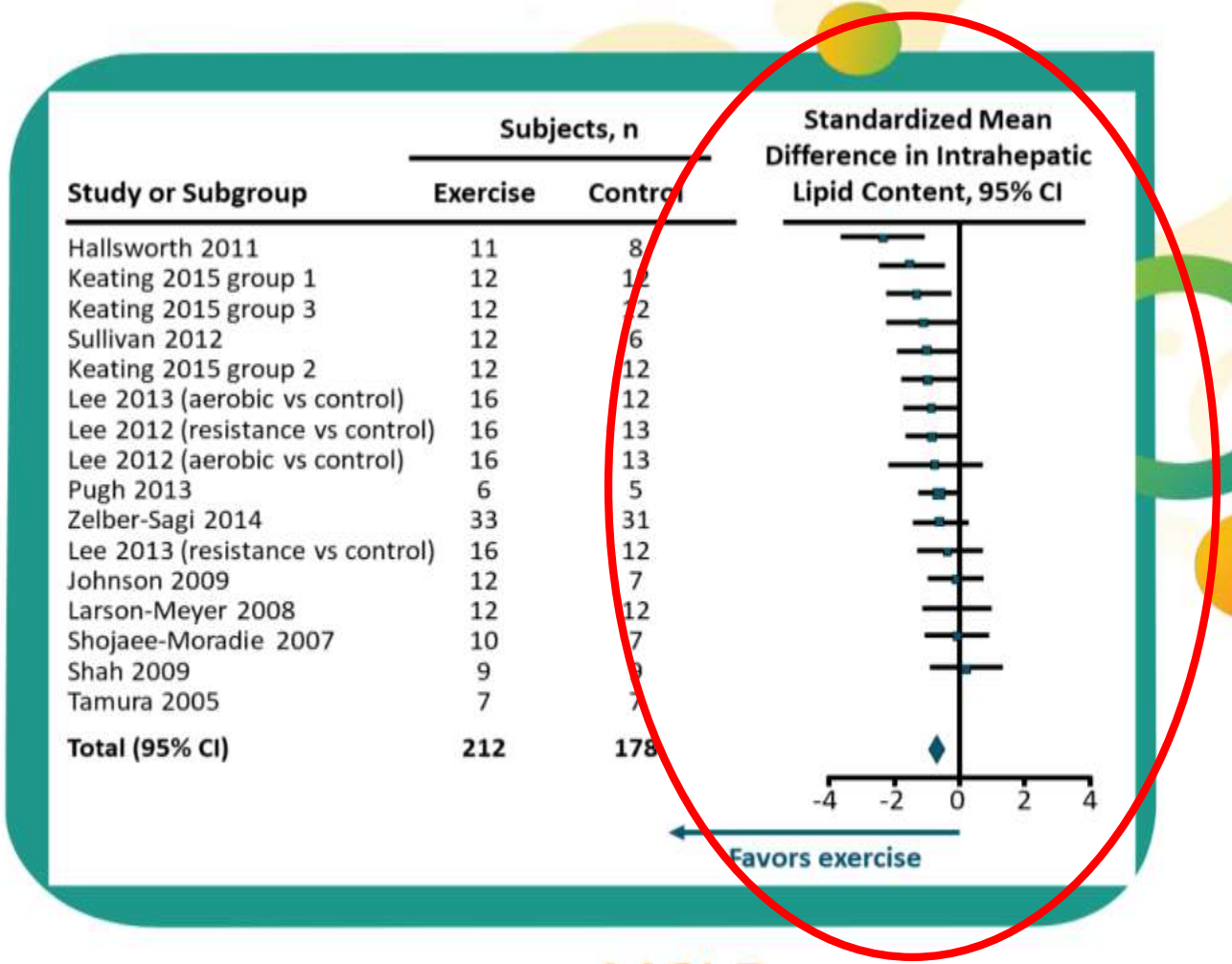
1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Sanyal. NEJM. 2010;362:1675. 7. Cusi. Ann Intern Med. 2016;165:305. 8. Bril. J Clin Endocrinol Metab. 2017;102:2950.

Lifestyle Guidelines in NAFLD/NASH

	AASLD 2018[1]	EASL 2016[2]	APASL 2020[3]
Program	Lifestyle modification including **dietary change**, **weight loss**, and structured **exercise** intervention		
Diet	500-1000 kcal energy deficit to induce a weight loss of 500-1000 g/wk ▪ Prospective trials comparing macronutrient diets in NAFLD are limited	▪ Exclusion of NAFLD-promoting components (processed food, added fructose) ▪ Mediterranean diet suggested	
Weight Loss	7% to %10% weight loss is the target of lifestyle interventions to improve NASH and fibrosis		
Exercise	▪ Exercise alone may prevent/ reduce hepatic steatosis – Effect on other aspects of liver histology unknown	▪ Both aerobic exercise and resistance training reduce liver fat – Tailor to patient preferences	
Bariatric Surgery	▪ Reduces liver fat, improves histologic lesions of NASH, including fibrosis ▪ Individualize decision in cirrhosis		

Exercise in NAFLD: Effect on Liver Fat and ALT

- 28 randomized trials of exercise-based interventions in patients with NAFLD and underlying metabolic disorders (N = 1644)
- Reduction in **intrahepatic lipid content**
  - Standardized mean difference: -0.69 (95% CI: -0.90 to -0.48)
- Reduction in **ALT**
  - Weighted mean difference: -3.30 IU/L (95% CI: 5.57 to -1.04)



AASLD The Liver Meeting®

Exercise and Weight Loss Decrease Portal Pressure

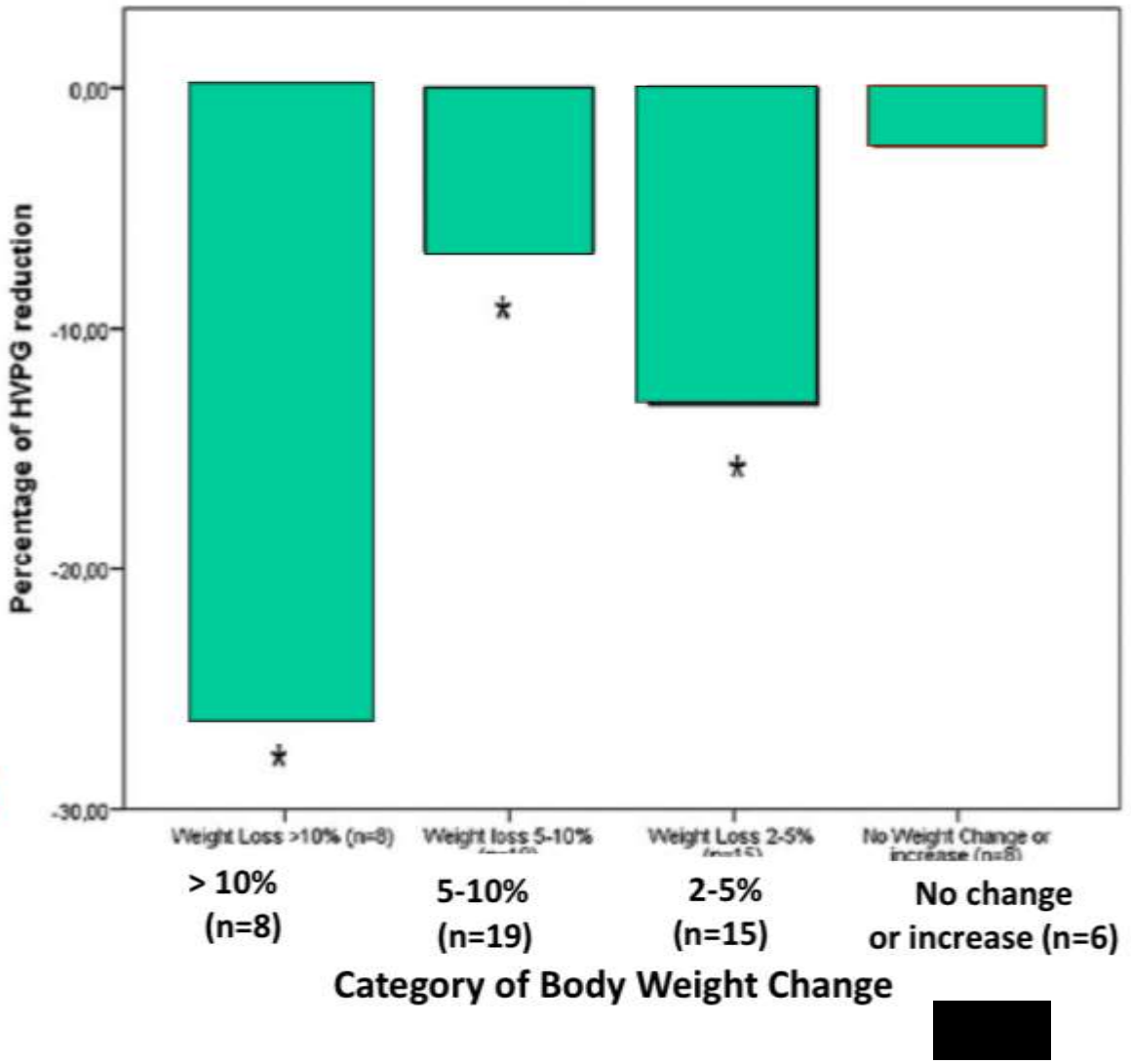
- 50 pts compensated cirrhosis (92% Childs A)
- HVPG ≥ 6 mmHg (72% HVPG ≥ 10 mmHg
- BMI ≥ 26 kg/m^2
- 16 week intensive life-style intervention

Average Δ BW = 5 Kg (-5.2%) (p<0.001)

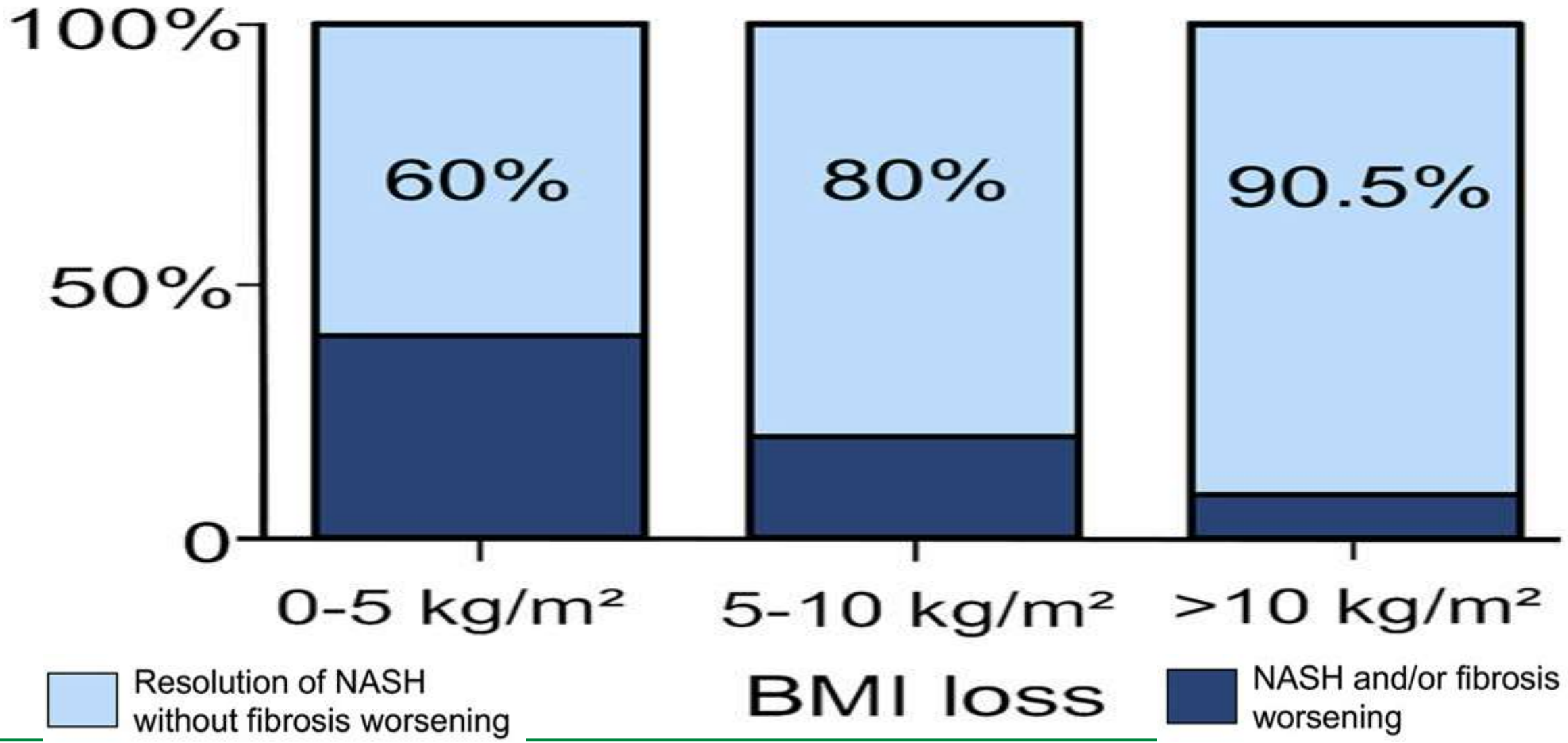
- Increase BW= 8%
- No change BW = 8%
- 2-5% BW decrease =32%
- 5-10% BW decrease = 36%
- ≥ 10% BW decrease = 16%

Average Δ HVPG = -1.7 mmHg; -10.7 % (p<0.001)

Berzigotti et al. Hepatology 2017.



Resolution of NASH according to weight loss



Percentage of Weight Loss Associated With Histologic Improvement in MAFLD

Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr[1]
≥ 10%[1]	Fibrosis regression (45% of patients)[1]	< 10%
≥ 7%[1]	NASH resolution (64% to 90% of patients)*	18%
≥ 5%[1-3]	Ballooning/inflammation improvement (41% to 100% of patients)*	30%
≥ 3%[1-4]	Steatosis improvement (35% to 100% of patients*)	Not reported

*Depending on degree of weight loss.

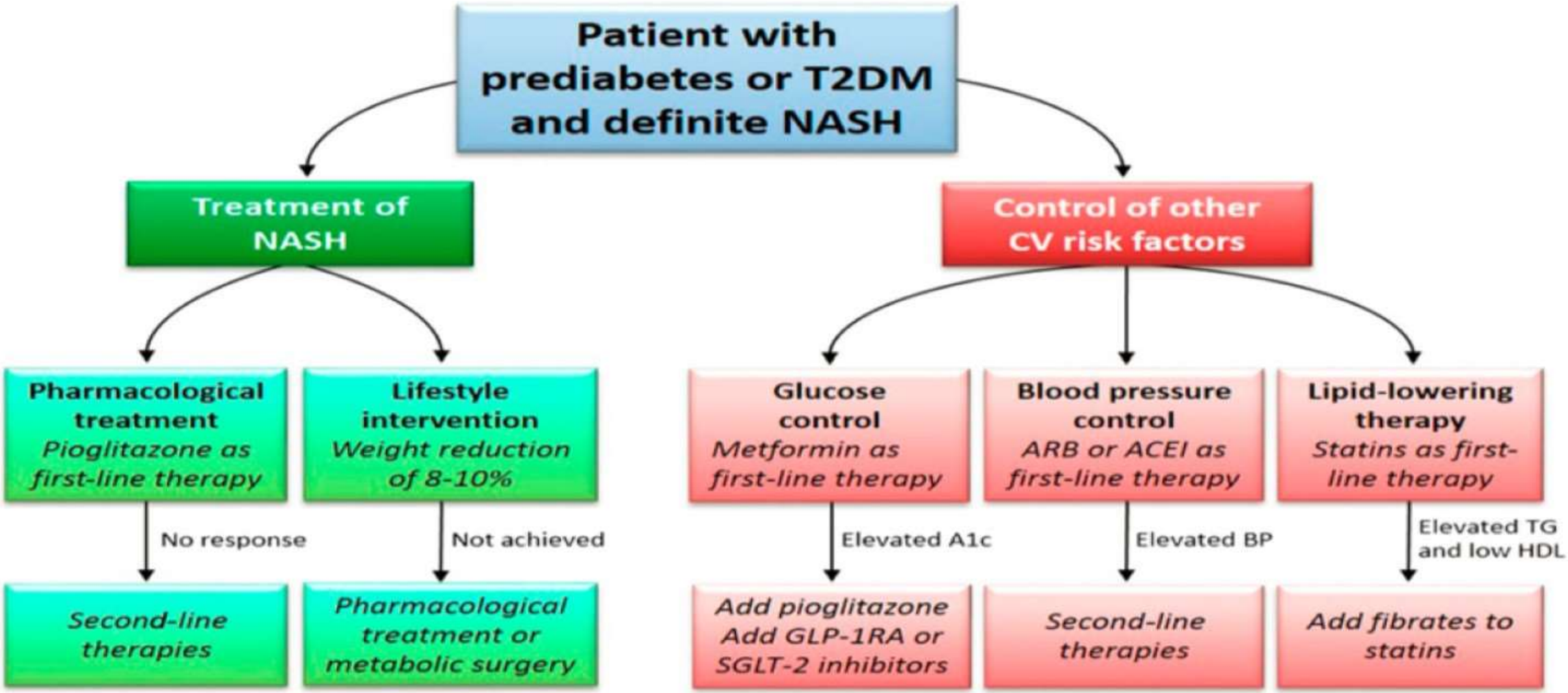
1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.
3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

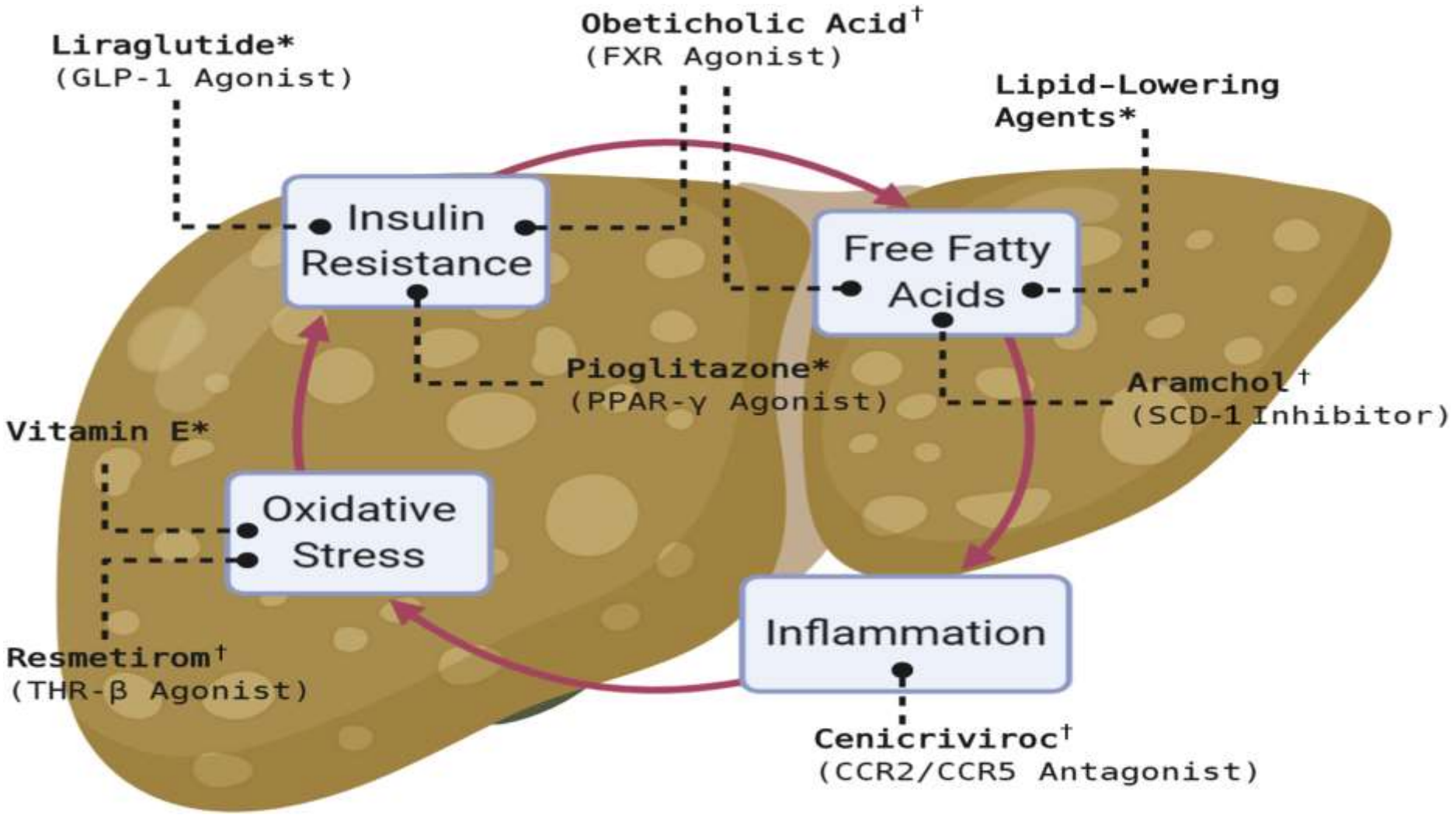
Table 3 | Principal lifestyle intervention studies for treatment of non-alcoholic fatty liver disease (NAFLD)

Author, year	Type of study; No of patients	Treatment and duration	Study target and outcome measures	Results
Lazo et al, 2010[112]	RCT; 96 T2DM	Intensive LS intervention (ILI, n=46) *v* diabetes support and education (DSE, n=50); 12 months	7-10% WL. Biochemistry; intra-abdominal fat (steatosis ≤5.5% IHTG at MRS)	Data collected as part of LookAhead study. At 1 year, ILI participants lost more weight (WL −8.0% *v* −0.5%) and had larger decline in IHTG content (−50.8% *v* −22.8%) *v* participants in DSE
Promrat et al, 2010[113]	RCT; 31 biopsy proven NASH	Intensive LS intervention (ILI, n=21) *v* standard care (SC, n=10); 48 weeks	WL ≥7%, improved biochemistry; reduced NAS (≥3 points) or post-treatment NAS ≤2; NASH remission at histology	WL 9.3% (SD 7.5) in ILI *v* 0.2% (6.1) in SC; NAS target reached in 72% *v* 30% (SC). In patients who achieved ≥7% WL, liver fat, ballooning, and lobular inflammation were improved, irrespective of treatment arm. Percent WL correlated with reduced ALT, steatosis, and activity
Sun et al, 2012[114]	RCT; 1087 NAFLD (ultrasonography)	LS treated (LS, n=724) *v* basic education (SC, n=363); 12 months	WL and liver enzymes; energy intake ≤25-30 kcal/kg BW; PA ≥23 METs/h/week + 4 METs of exercise. Visceral fat area by CT	WL larger in LS (−11.6% *v* 0.4% in SC); liver enzymes, IR, and parameters of MetS showed a larger improvement in LS *v* SC at 6 and 12 months. VFA was reduced in LS at 12 months
Wong et al, 2013[115]	RCT; 154 NAFLD (IHTG ≥5% and high ALT)	Intensive LS intervention (ILI, n=77) *v* standard care (SC, n=77); 12 months	NAFLD remission (IHTG content <5%), WL, changes in ALT, improvement in fibrosis (transient elastography)	ILI was associated with NAFLD remission (64% *v* 20% SC; difference 44%, 95% CI 30% to 58%), normal ALT (53%), and reduced fibrosis. 39% of ILI patients and no patient in SC had WL ≥10% (difference 39%, 28% to 50%). 97% of cases who achieved 10% WL target had NAFLD remission
Vilar-Gomez et al, 2015[116]	Cohort study; 293 biopsy proven NASH	All treated by intensive LS intervention (ILI); 261 cases had follow-up biopsies; 52 weeks	NASH resolution without fibrosis worsening; NAS improvement (≥2 points); improved histological lesions (≥1 point)	WL was ≥5% in 30% of cases. NASH remission was observed in 25%, NAS reduction in 47%, and fibrosis regression in 19%. Amount of WL was independently associated with improvement in all histological parameters (ORs 1.1-2.0). WL ≥10% was associated with NASH remission (90% of cases) and fibrosis regression (45%)
Khoo et al, 2017[117 118]	Pilot RCT; 24 obese MRI diagnosed NAFLD	Liraglutide (3 mg/day, n=12) *v* LS (diet and exercise, n=12); 26 weeks + 26 weeks of weight loss maintenance	WL, biochemistry, MRS elastography	Similar reduction in BW (−3.5 kg in both arms), liver enzymes, and liver stiffness (LS −0.21 kPa; liraglutide −0.26); liraglutide as effective as structured LS modification. at 52 weeks; liraglutide group significantly regained weight (+1.8 (SD 2.1) kg) and IHTG content (4.0% (5.3)), which were unchanged in LS group
Mazzotti, 2018[119]	Observational, cohort study; 716 ultrasonography assessed NAFLD	Web based LS program (WEB, n=278) *v* group based intervention (GROUP, n=438); follow-up, 2 years	WL ≥10%, changes in liver enzymes, surrogate markers of steatosis and fibrosis (FLI, NFS, Fib-4)	Attrition rate was higher in WEB (OR 1.87, 95% CI 1.20 to 2.90, at 6 months and 2.95, 2.04 to 4.26, at 2 years). 10% WL target was reached in 20% (WEB) *v* 15% (GROUP). 10% WL after 2 years was associated only with baseline BMI (OR 1.43, 1.13 to 1.81, per BMI/5). After adjustment for confounders and attrition, probability of reaching long term 10% WL was not reduced in WEB (OR 0.70, 0.38 to 1.27) *v* GROUP care

ALT=alanine aminotransferase; BMI=body mass index; BW=body weight; CT=computed tomography; Fib-4=Fibrosis-4 index; FLI=Fatty Liver Index; IHTG=intra-hepatic triglyceride; IR=insulin resistance; LS=lifestyle; MetS=metabolic syndrome; MRS=magnetic resonance spectroscopy; MRI=magnetic resonance imaging; NAS=NAFLD activity score; NFS=NAFLD fibrosis score; NS=not significant; OR=odds ratio; PA=physical activity; RCT=randomized controlled trial; SC=standard care; T2DM=type 2 diabetes mellitus; VFA=visceral fat area; WL=weight loss.

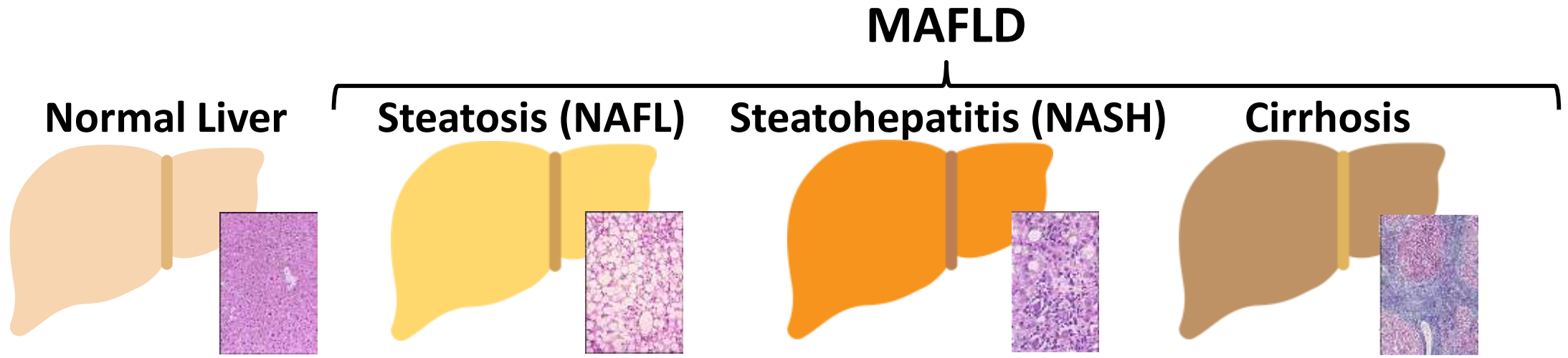
Management of CV Risk in Patients With NASH





Therapies used to control risk factors associated with development of nonalcoholic steatohepatitis.
†Investigational agents currently in Phase III clinical trials. CCR = C–C motif chemokine receptor; FXR = farnesoid X nuclear receptor; GLP-1 = glucagon-like peptide-1; PPAR = peroxisome proliferator–activated receptor; SCD-1 = stearoyl-CoA desaturase-1; THR-β = thyroid hormone receptor-β.

Targeting Pathophysiologic Processes



Targets related to insulin resistance and/or lipid metabolism

PPARγ: Pioglitazone
GLP-1: Liraglutide, Semaglutide
ACC: GS-0976
SCD1: Aramchol
FGF21: BMS-986036
THR-β: MGL-3196, VK 2807

Targets related to lipotoxicity and oxidative stress

PPARα/∂: Elafibranor
FXR: OCA, GS-9674, Tropifexor
FGF19: NGM282
Vitamin E

Targets related to inflammation and immune activation

CCR2/5: Cenicriviroc
TLR4: JKB-121

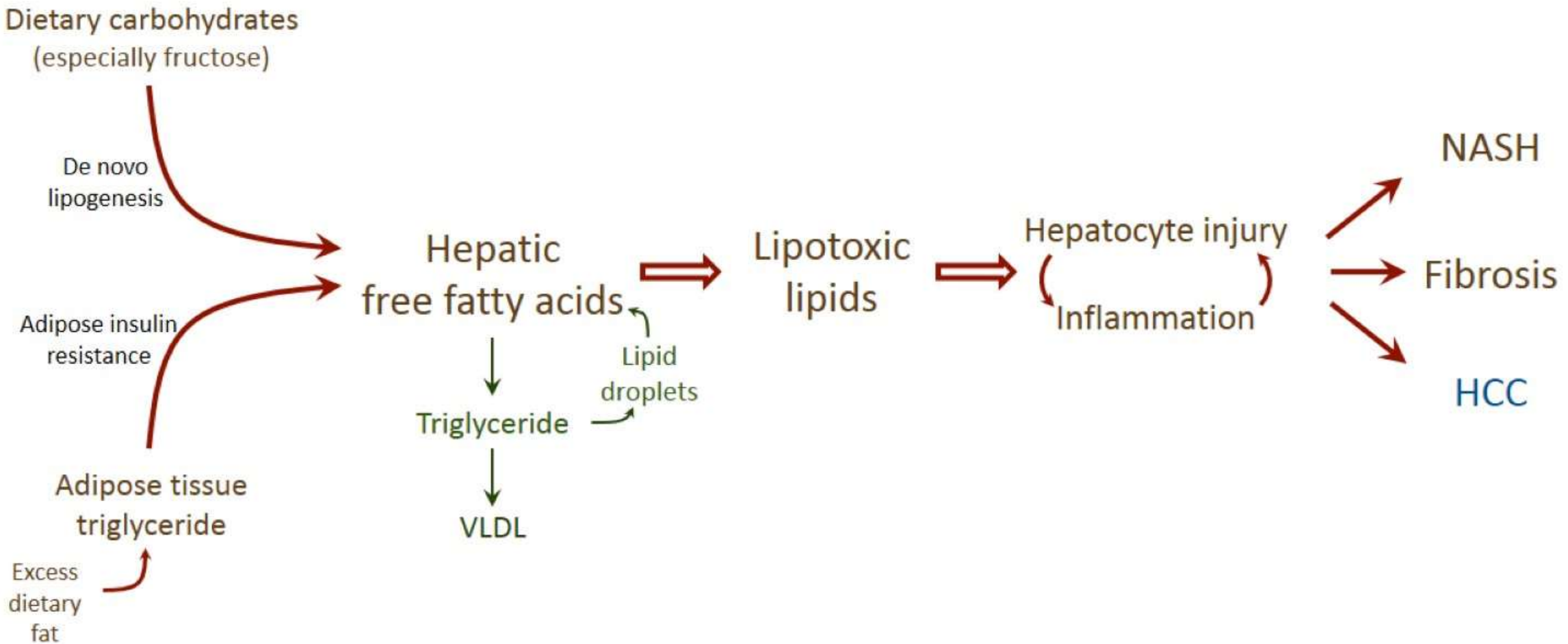
Targets related to cell death (apoptosis and necrosis)

ASK1: Selonsertib

Targets related to fibrogenesis and collagen turnover

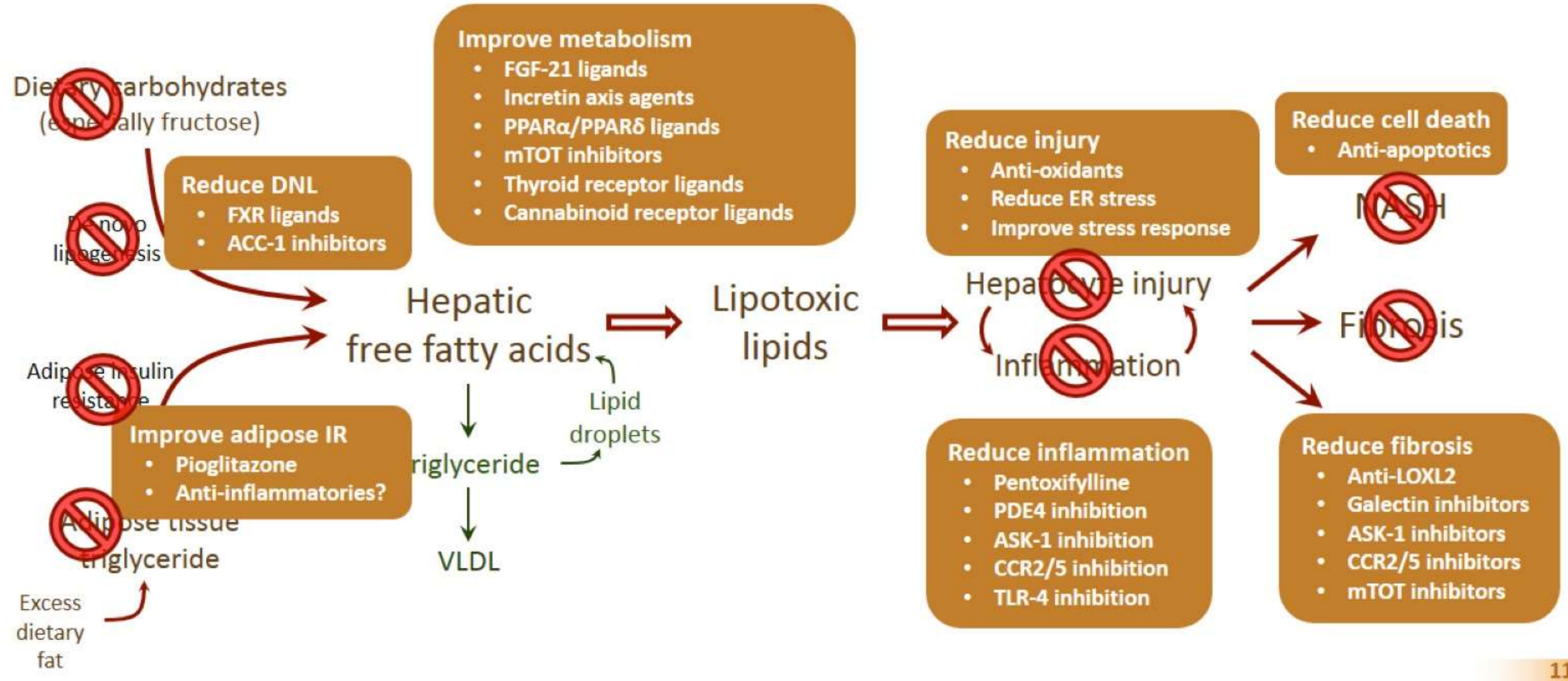
Galectin: GR-MD-02

Targets of Therapy and Ongoing Clinical Trials



Neuschwander-Tetri B. *BMC Medicine*. 2017;15:45.

Targets of Therapy and Ongoing Clinical Trials (cont)



Neuschwander-Tetri B. *BMC Medicine*. 2017;15:45.

Pharmacotherapy in NAFLD and NASH (Off Label)

	AASLD[1]	EASL-EASD-EASO[2]	APASL[3]
Metformin	Not recommended		
Vitamin E	**Recommended** in non-diabetic patients with biopsy-proven NASH (800 IU/day)	**Recommended** (800 IU/day)	Insufficient evidence. No firm recommendation
Pioglitazone	**Recommended** in patients with and without T2DM and biopsy-proven NASH	**Recommended** in patients with T2DM and biopsy-proven NASH	
Statins	Use to treat hyperlipidemia/dyslipidemia and decrease CV risk, not NASH		
UDCA	Not recommended		Not mentioned
Omega-3-Fatty Acids	Consider to treat hypertriglycidemia, not NASH		Not mentioned
Obeticholic acid	Further data needed		
GLP-1 Receptor Agonists	Further data needed		Improve fibrosis, weight
SGLT2 Inhibitors	Not mentioned		Further data needed

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. Eslam. Hepatol Intern. 2020:14:889.

Approach to Current Treatment for NAFLD/NASH

Weight Loss

Lifestyle Modification

FDA Approved
Anti-Obesity / Insulin Sensitizing
Pharmacotherapy

Bariatric Endoscopy
or Surgery

Treat Diabetes and Cardiovascular Risk Factors

Insulin Resistance
Metformin
HCC risk reduction

Dyslipidemia
Statins
Decrease HCC
Decrease Portal HTN

Hyperglycemia
Overweight / Obesity
GLP-1 RA /SGLT2

Other CV Risks
Smoking cessation
Sleep apnea

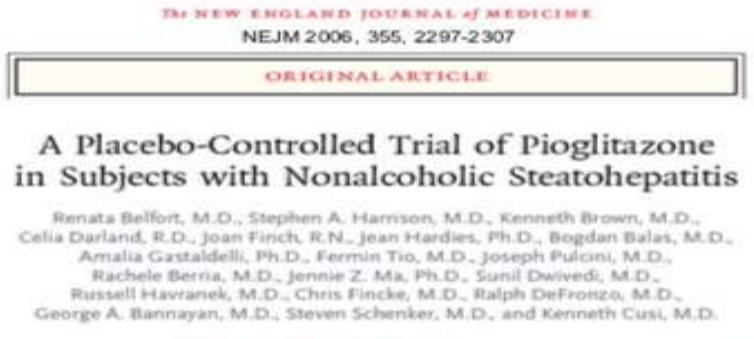
Liver Directed Pharmacotherapy (NASH with ≥F2)

Vitamin E in non-diabetic pre-cirrhotic adults with NASH*

Pioglitazone in diabetics pre-cirrhotic adults with NASH*

* Consider individualized risk-benefit ratio

TZDs



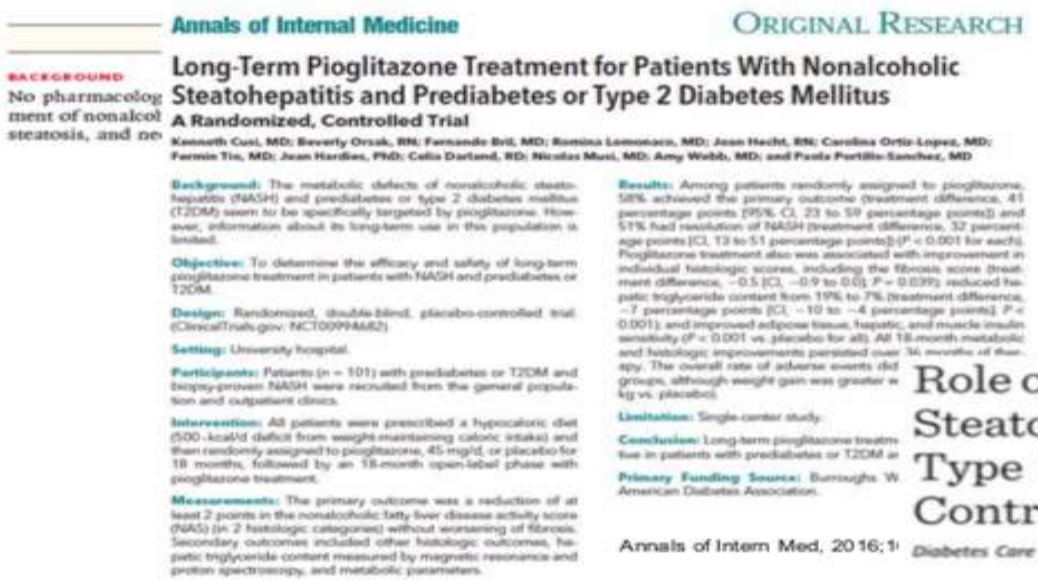
The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2006, 355, 2297-2307

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

Renata Belfort, M.D., Stephen A. Harrison, M.D., Kenneth Brown, M.D., Celia Darland, R.D., Joan Finch, R.N., Jean Hardies, Ph.D., Bogdan Balas, M.D., Amalia Gastaldelli, Ph.D., Fermin Tio, M.D., Joseph Pulconi, M.D., Rachele Berria, M.D., Jennie Z. Ma, Ph.D., Sunil Dwivedi, M.D., Russell Havranek, M.D., Chris Fincke, M.D., Ralph DeFronzo, M.D., George A. Bannayan, M.D., Steven Schenker, M.D., and Kenneth Cusi, M.D.



Annals of Internal Medicine

ORIGINAL RESEARCH

BACKGROUND

No pharmacolog ment of nonalcol steatosis, and ne

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized, Controlled Trial

Kenneth Cusi, MD; Beverly Orsak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fermin Tio, MD; Joan Hardies, PhD; Celia Darland, RD; Nicolas Musi, MD; Amy Webb, MD; and Paola Portillo-Sanchez, MD

Background: The metabolic defects of nonalcoholic steatohepatitis (NASH) and prediabetes or type 2 diabetes mellitus (T2DM) seem to be specifically targeted by pioglitazone. However, information about its long-term use in this population is limited.

Objective: To determine the efficacy and safety of long-term pioglitazone treatment in patients with NASH and prediabetes or T2DM.

Design: Randomized, double-blind, placebo-controlled trial. (ClinicalTrials.gov: NCT00994682)

Setting: University hospital.

Participants: Patients (n = 101) with prediabetes or T2DM and biopsy-proven NASH were recruited from the general population and outpatient clinics.

Intervention: All patients were prescribed a hypocaloric diet (500-kcal/d deficit from weight-maintaining caloric intake) and then randomly assigned to pioglitazone, 45 mg/d, or placebo for 18 months, followed by an 18-month open-label phase with pioglitazone treatment.

Measurements: The primary outcome was a reduction of at least 2 points in the nonalcoholic fatty liver disease activity score (NAS) (in 2 histologic categories) without worsening of fibrosis. Secondary outcomes included other histologic outcomes, hepatic triglyceride content measured by magnetic resonance and proton spectroscopy, and metabolic parameters.

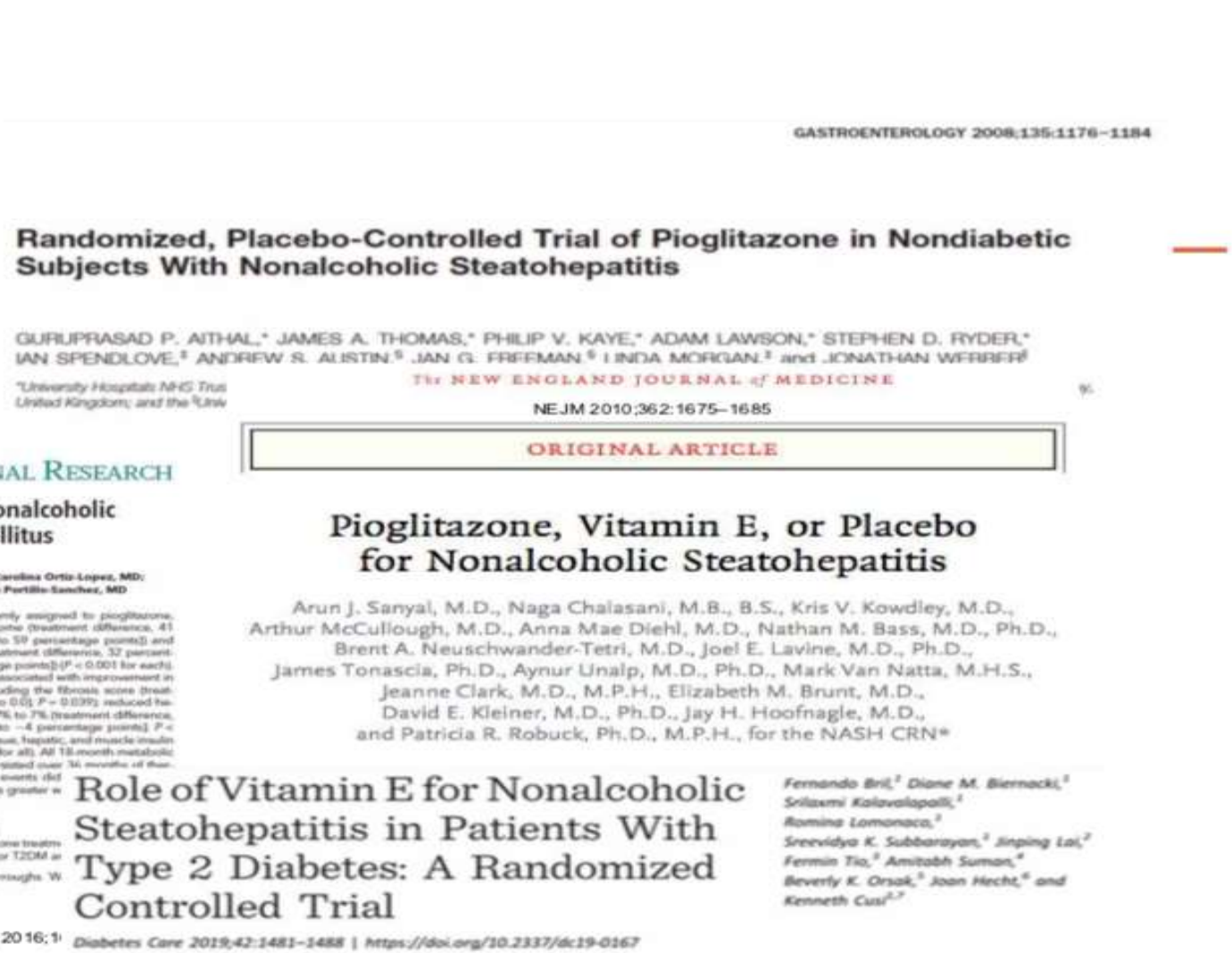
Results: Among patients randomly assigned to pioglitazone, 58% achieved the primary outcome (treatment difference, 41 percentage points [95% CI, 23 to 59 percentage points]) and 51% had resolution of NASH (treatment difference, 32 percentage points [CI, 13 to 51 percentage points]) ($P < 0.001$ for each). Pioglitazone treatment also was associated with improvement in individual histologic scores, including the fibrosis score (treatment difference, −0.5 [CI, −0.9 to 0.0]; $P = 0.039$); reduced hepatic triglyceride content from 19% to 7% (treatment difference, −7 percentage points [CI, −10 to −4 percentage points]; $P < 0.001$); and improved adipose tissue, hepatic, and muscle insulin sensitivity ($P < 0.001$ vs. placebo for all). All 18-month metabolic and histologic improvements persisted over 36 months of therapy. The overall rate of adverse events did not differ between groups, although weight gain was greater with pioglitazone (4 kg vs. placebo).

Limitation: Single-center study.

Conclusion: Long-term pioglitazone treatment is effective in patients with prediabetes or T2DM and

Primary Funding Source: Burroughs Wellcome Fund, American Diabetes Association.

Annals of Intern Med. 2016;1



GASTROENTEROLOGY 2008;135:1176–1184

Randomized, Placebo-Controlled Trial of Pioglitazone in Nondiabetic Subjects With Nonalcoholic Steatohepatitis

GURUPRASAD P. AITHAL,* JAMES A. THOMAS,* PHILIP V. KAYE,* ADAM LAWSON,* STEPHEN D. RYDER,* IAN SPENDLOVE,‡ ANDREW S. AUSTIN,§ JAN G. FREEMAN,§ LINDA MORGAN,‖ and JONATHAN WEBBER*

*University Hospitals NHS Trus United Kingdom; and the §Univ

The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2010;362:1675–1685

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial

Fernando Bril,[1] Dione M. Biernacki,[1] Srilaxmi Kalavalapalli,[1] Romina Lomonaco,[1] Sreevidya K. Subbarayan,[1] Jinping Lai,[1] Fermin Tio,[1] Amitabh Suman,[1] Beverly K. Orsak,[1] Joan Hecht,[1] and Kenneth Cusi[1,2]

Diabetes Care 2019;42:1481–1488 | https://doi.org/10.2337/dc19-0167

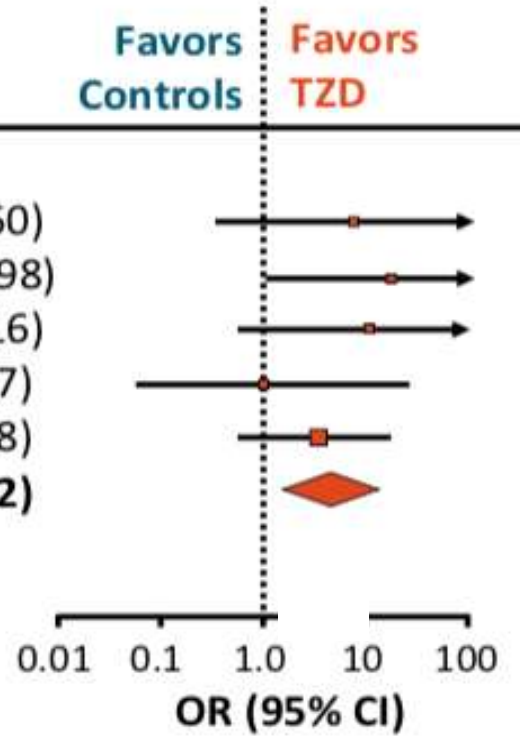
Pioglitazone is not approved for treatment of NAFLD or NASH.

UF UNIVERSITY of FLORIDA College of Medicine

Pioglitazone in NASH Without Diabetes

- Subset of n = 8 TZD studies in systemic review and meta-analysis of randomized trials examining outcomes in NAFLD/NASH (N = 516 patients)
- In biopsy-proven NASH, pioglitazone associated with **improvement in advanced fibrosis**

Source	TZD No. of Events	TZD No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)
Pioglitazone					
Aithal 2008	3	31	0	30	7.49 (0.37-151.50)
Belfort 2006	7	26	0	21	16.54 (0.89-308.98)
Cusi 2016	4	50	0	51	9.97 (0.52-190.16)
Sanyal 2004	1	10	1	10	1.00 (0.05-18.57)
Sanyal 2010	6	80	2	83	3.28 (0.64-16.78)
Total (95% CI)	**21**	**197**	**3**	**195**	**4.53 (1.52-13.52)**

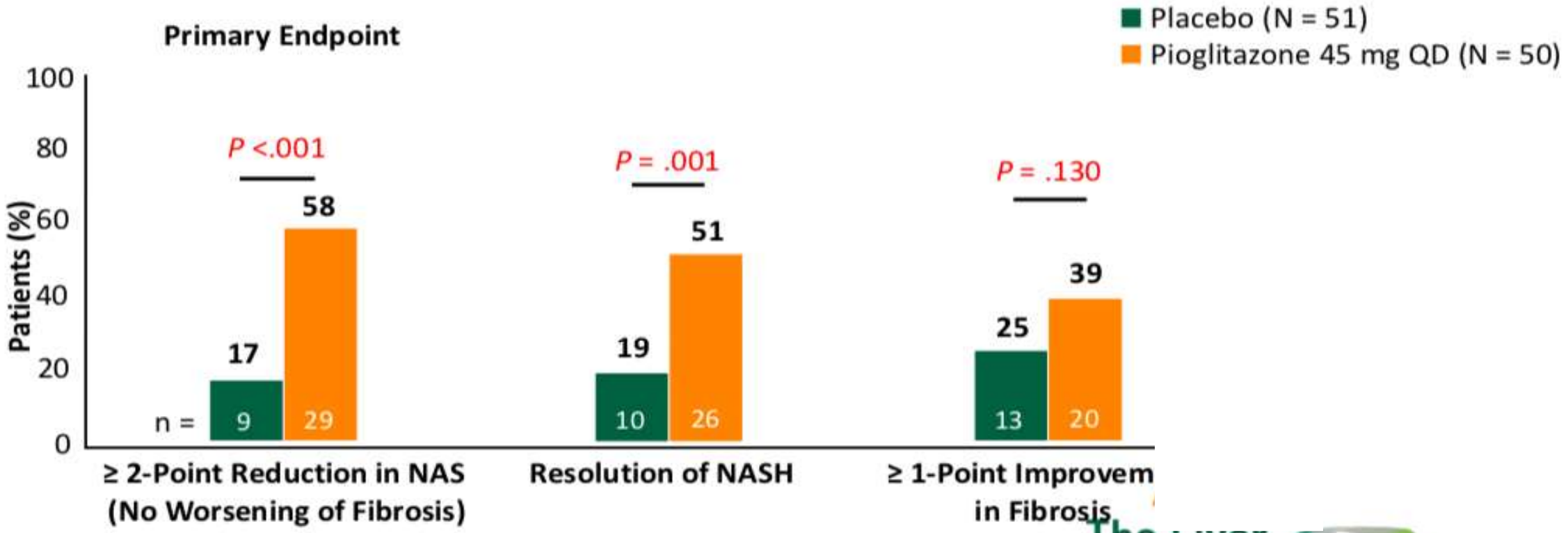


Heterogeneity: $T^2 = 0$; $x^{2/2} = 2.39$; $P = .66$; $I^2 = 0\%$
Overall effect: $z = 2.71$; $P = .007$

Musso. JAMA Intern Med. 2017;177:633.

Pioglitazone in NASH With Prediabetes/T2D

- Randomized, placebo-controlled, double-blind phase study of patients with NASH and prediabetes or T2D (N = 101)

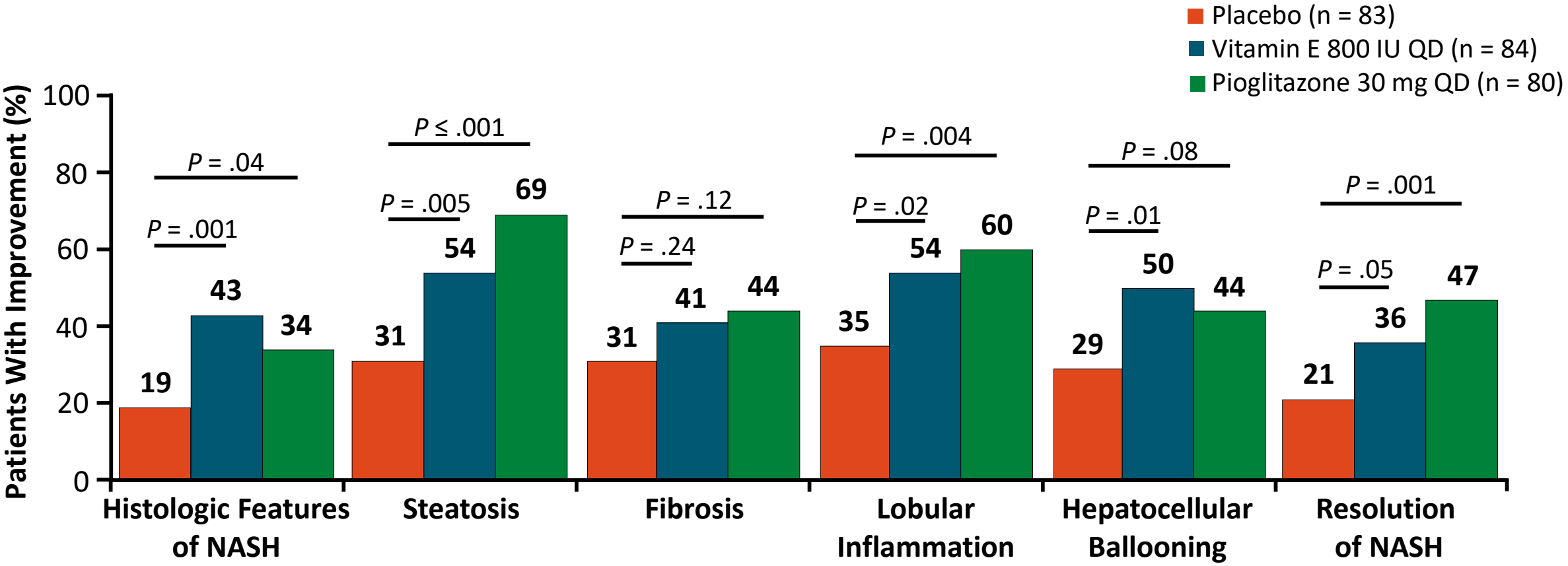


Cusi. Ann Intern Med. 2016;165:305.

The Liver Meeting®

PIVENS: 96-Wk Results of Pioglitazone and Vitamin E in Patients With NASH

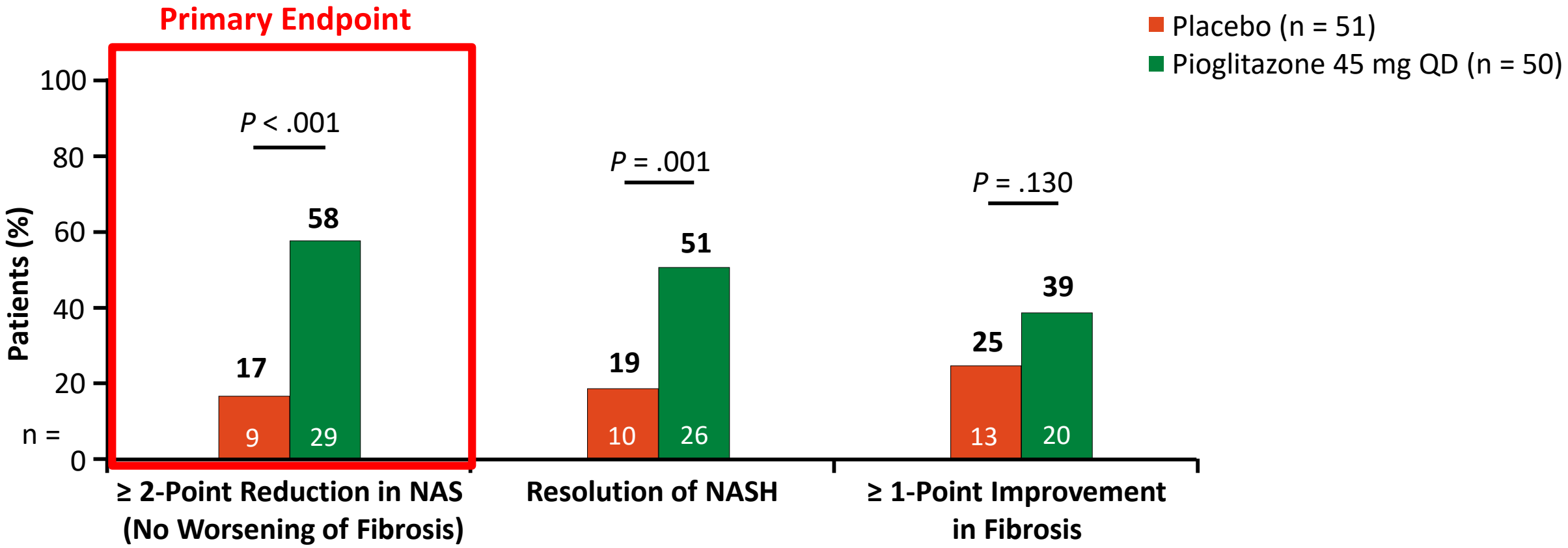
- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



Sanyal. NEJM. 2010;362:1675.

Pioglitazone in NASH and Prediabetes or Type 2 Diabetes: 18-Mo Outcomes

- Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or type 2 diabetes mellitus (N = 101)[1]



Cusi. Ann Intern Med. 2016;165:305.

Safety and Tolerability of Recommended Therapies (Off Label)

Vitamin E (800 IU/day)

- Possible all-cause mortality risk at > 800 IU/day[1]
- Increased hemorrhagic stroke risk[2]
  - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = .008)[3]

Pioglitazone

- Edema, weight gain (~ 2-3 kg over 2-4 yrs)[4]
- Risk of osteoporosis in women[5]
- Equivocal bladder cancer risk
  - Increased in some studies[6]
  - No association in most studies[7,8]

Use of these agents should be personalized for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio

1. Miller. Ann Intern Med. 2005;142:37. 2. Schurks. BMJ. 2010;341:c5702. 3. Klein. JAMA. 2011;306:1549.
4. Bril. Diabetes Care. 2017;40:419. 5. Yau. Curr Diab Rep. 2013;13:329. 6. Tuccori. BMJ. 2016;352:i1541.
7. Lewis. JAMA. 2015;314:265. 8. Davidson. Diabetes Complications. 2016;30:981.

Statins in Patients with NAFLD

MAFLD patients at high risk for CVD morbidity & mortality.
Aggressive modification of CVD risk factors is considered in all patients with MAFLD
Caution in patients with decompensated cirrhosis

Open label pilot study of patients with biopsy proven NASH (n=20)
Rosuvastatin 10 mg /day x 52 weeks improved liver enzymes (p<0.001) and resolved NASH in 19 of 20 (95%) [1]

Meta-analysis of Studies of Use of Statins in Patients with NAFLD (n=12 publications)[2]

Statins are indicated for CVD risk reduction in all patients[3]

Statins can improve LDL cholesterol and liver function

Statins are safe in patients with NAFLD

Consistent histologic data to support use of statins for the indication of NAFLD/NASH are still pending

AASLD The Liver Meeting

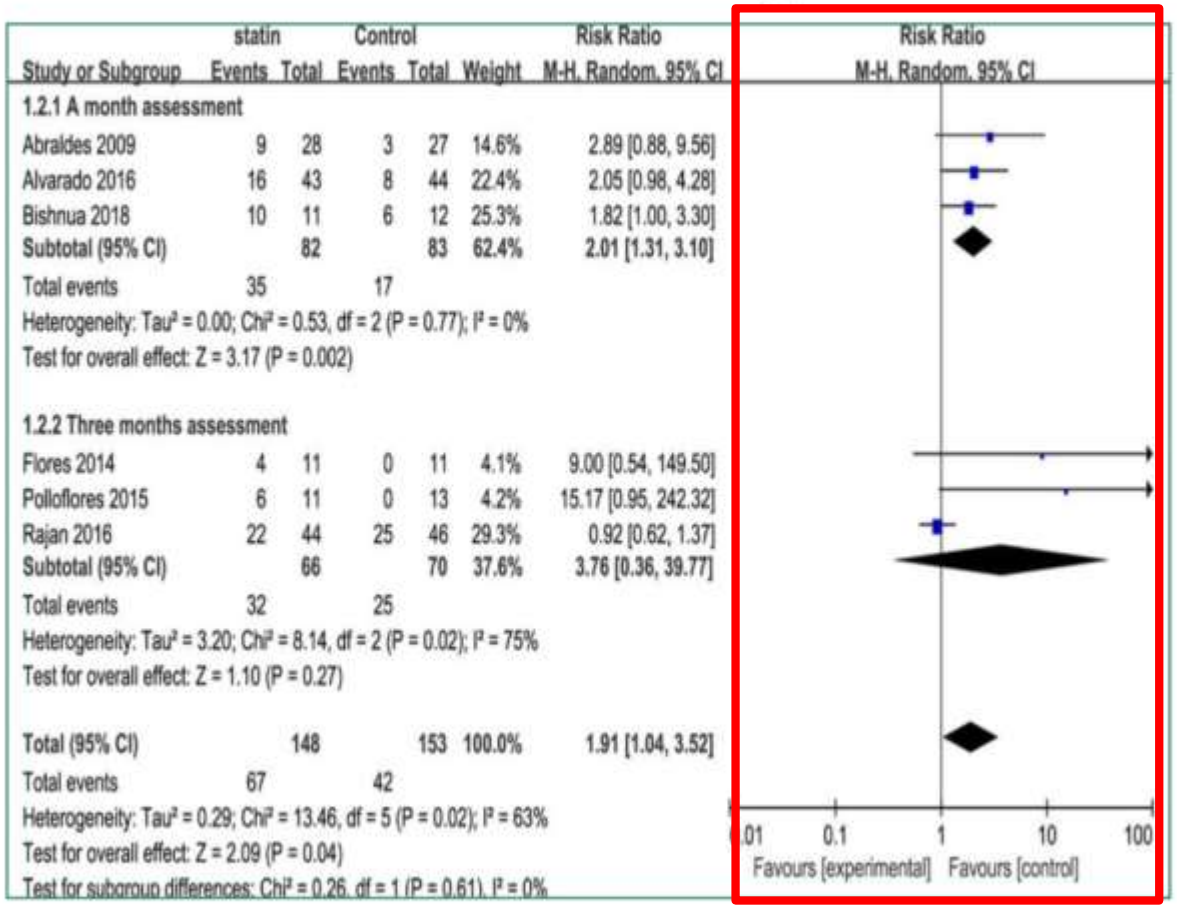
Statins are not approved for the treatment of NAFLD

CVD, cardiovascular disease; LDL, low-density lipoprotein;

1. Kargiotios et al. *World J Gastroenterol* 2015;21:7860–8; 2. Sigler et al. *Clin Med Insights Gastroenterol* 2018;11:1–9; 3. Chalasani et al. *Hepatology* 2018;67:328–57

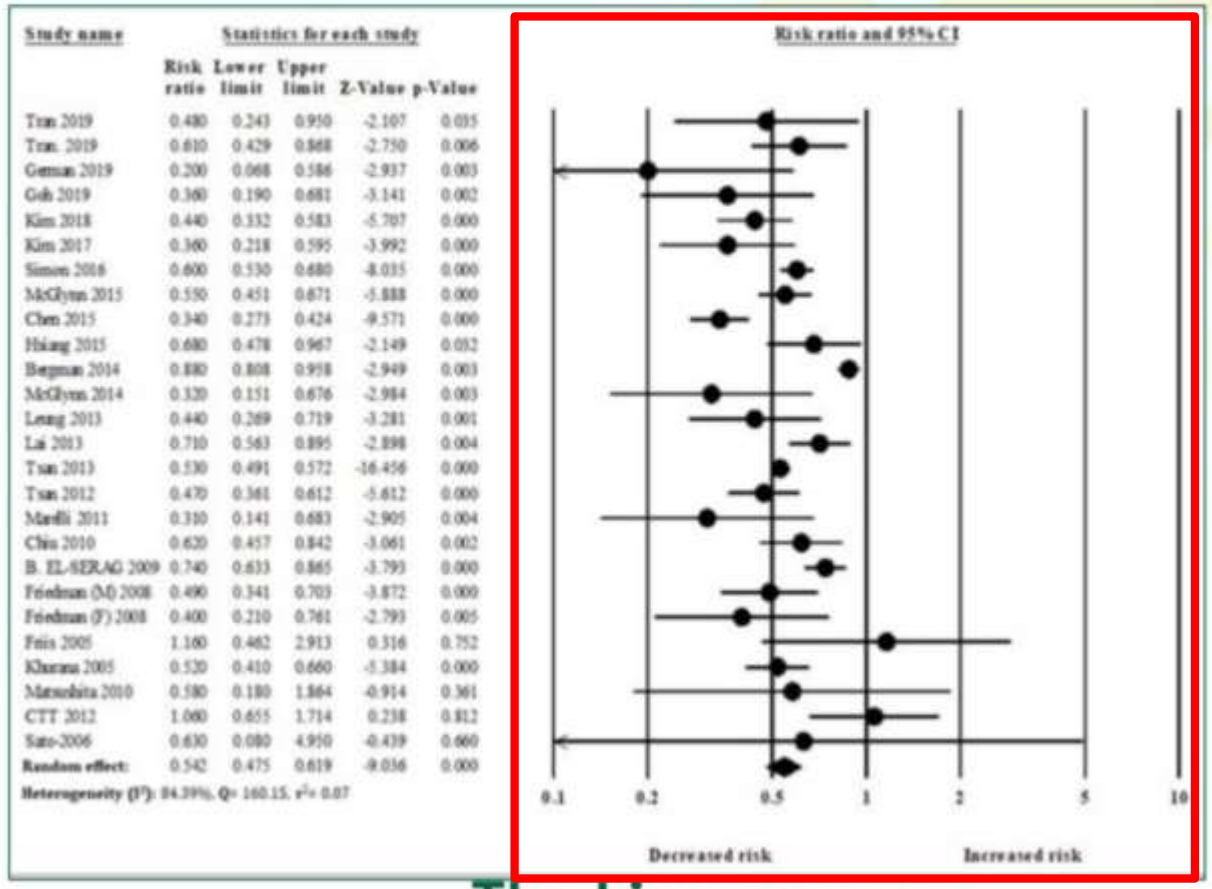
Statins Lower Portal HTN and HCC Risk

Decreased Risk of Portal Hypertension [1]



Study or Subgroup	statin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 A month assessment						
Abraldes 2009	9	28	3	27	14.6%	2.89 [0.88, 9.56]
Alvarado 2016	16	43	8	44	22.4%	2.05 [0.98, 4.28]
Bishnua 2018	10	11	6	12	25.3%	1.82 [1.00, 3.30]
Subtotal (95% CI)		82		83	62.4%	2.01 [1.31, 3.10]
Total events	35		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 3.17 (P = 0.002)						
1.2.2 Three months assessment						
Flores 2014	4	11	0	11	4.1%	9.00 [0.54, 149.50]
Polloflores 2015	6	11	0	13	4.2%	15.17 [0.95, 242.32]
Rajan 2016	22	44	25	46	29.3%	0.92 [0.62, 1.37]
Subtotal (95% CI)		66		70	37.6%	3.76 [0.36, 39.77]
Total events	32		25			
Heterogeneity: Tau² = 3.20; Chi² = 8.14, df = 2 (P = 0.02); I² = 75%						
Test for overall effect: Z = 1.10 (P = 0.27)						
Total (95% CI)		148		153	100.0%	1.91 [1.04, 3.52]
Total events	67		42			
Heterogeneity: Tau² = 0.29; Chi² = 13.46, df = 5 (P = 0.02); I² = 63%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						

Decreased Risk for HCC [2]



Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Tran 2019	0.480	0.243	0.950	-2.107	0.035
Tran. 2019	0.610	0.429	0.868	-2.750	0.006
German 2019	0.200	0.068	0.586	-2.937	0.003
Goh 2019	0.360	0.190	0.681	-3.141	0.002
Kim 2018	0.440	0.332	0.583	-5.707	0.000
Kim 2017	0.360	0.218	0.595	-3.992	0.000
Simon 2018	0.600	0.530	0.680	-8.035	0.000
McGlynn 2015	0.550	0.451	0.671	-5.888	0.000
Chen 2015	0.340	0.273	0.424	-9.571	0.000
Hsiang 2015	0.680	0.478	0.967	-2.149	0.032
Bergman 2014	0.880	0.808	0.958	-2.949	0.003
McGlynn 2014	0.320	0.151	0.676	-2.984	0.003
Leung 2013	0.440	0.269	0.719	-3.281	0.001
Lai 2013	0.710	0.563	0.895	-2.898	0.004
Tsan 2013	0.530	0.491	0.572	-16.456	0.000
Tsan 2012	0.470	0.361	0.612	-5.612	0.000
Marelli 2011	0.310	0.141	0.683	-2.905	0.004
Chiu 2010	0.620	0.457	0.842	-3.061	0.002
B. EL-SERAG 2009	0.740	0.633	0.865	-3.793	0.000
Friedman (M) 2008	0.490	0.341	0.703	-3.872	0.000
Friedman (F) 2008	0.400	0.210	0.761	-2.793	0.005
Fries 2005	1.160	0.462	2.913	0.316	0.752
Khurana 2005	0.520	0.410	0.660	-5.384	0.000
Matsubita 2010	0.580	0.180	1.864	-0.914	0.361
CTT 2012	1.060	0.655	1.714	0.238	0.812
Sato-2006	0.630	0.080	4.950	-0.439	0.660
Random effect:	0.542	0.475	0.619	-9.036	0.000
Heterogeneity (I^2): 84.39%, Q= 160.15, τ^2= 0.07					

[1] Wan et al. BMJ Open. 2019.
[2] Islam et al. Cancers. 2020.

The Liver Meeting®

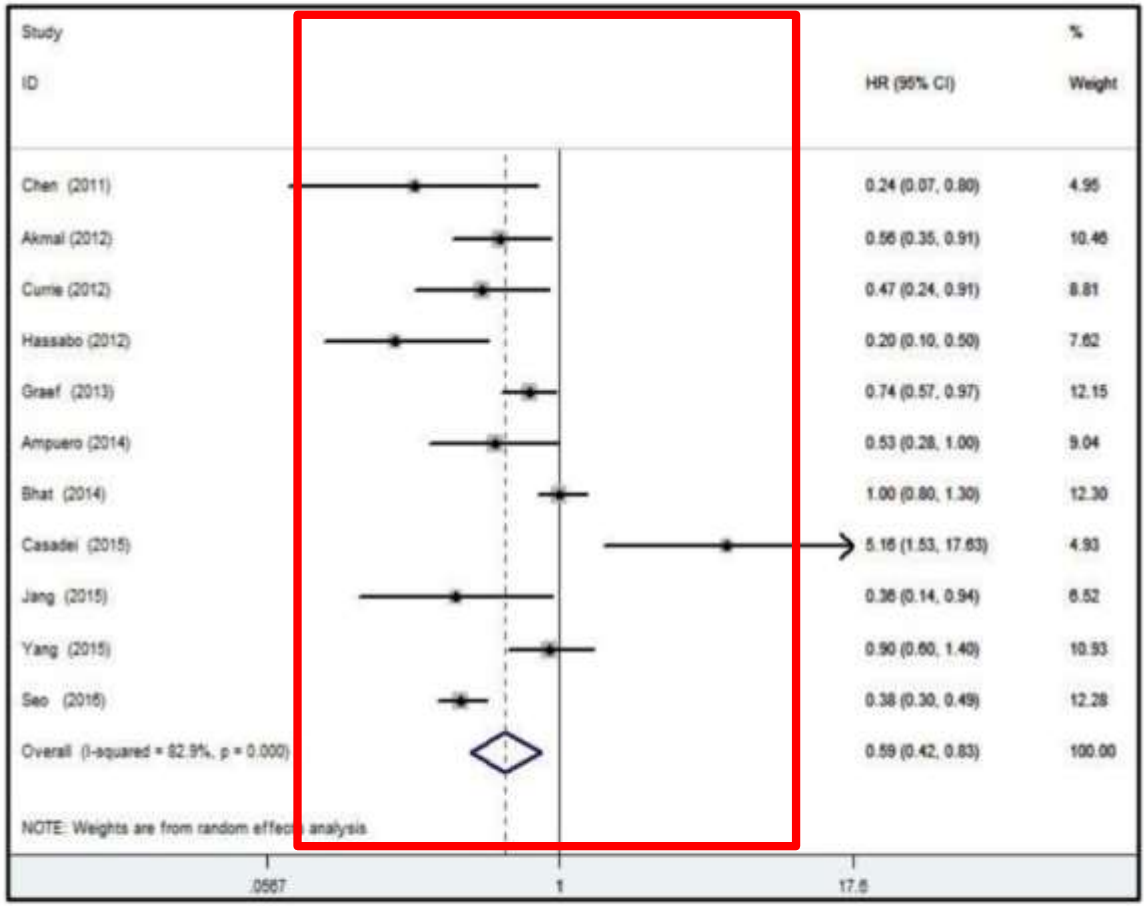
Metformin

Small, open-label, or non-randomized published trials in both diabetic and non-diabetic patients with biopsy-proven MAFLD

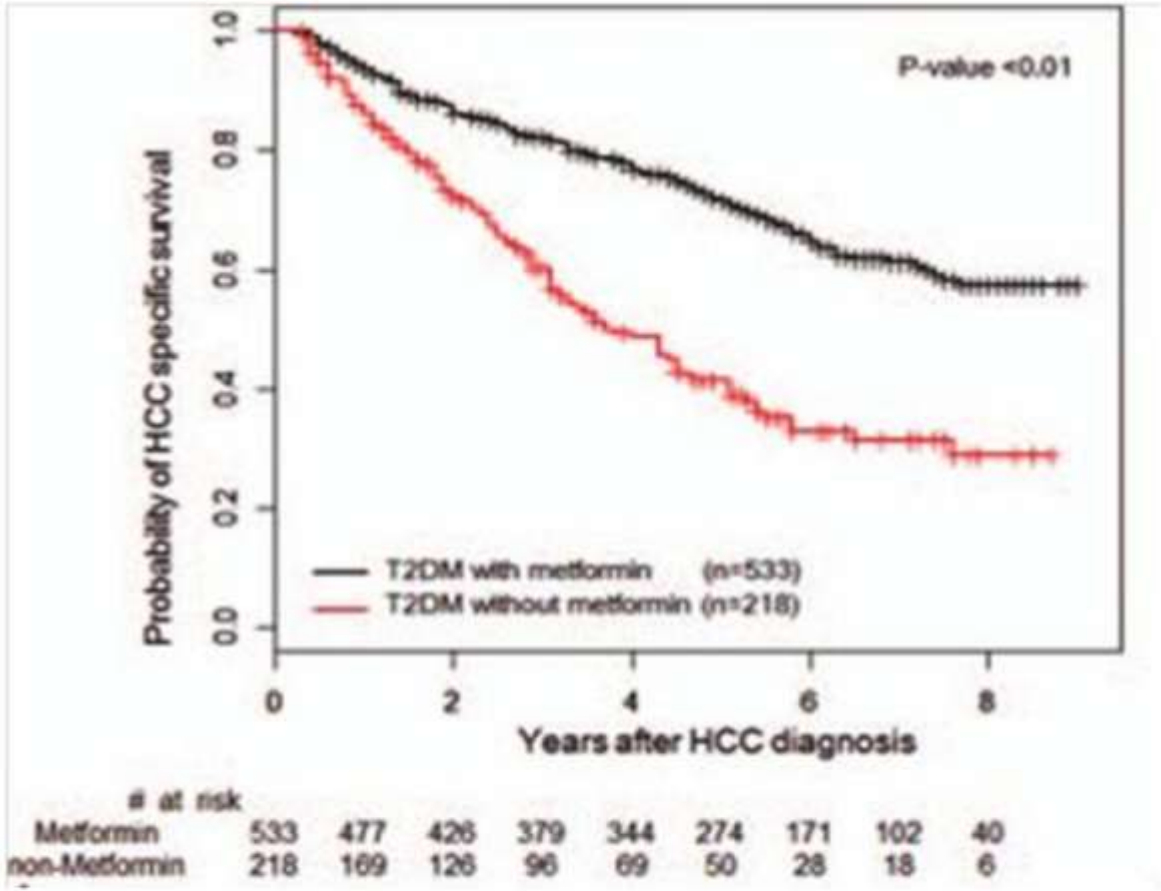
- Metformin is associated with improvement in insulin resistance, aminotransferase levels, and no effect on liver histology

Metformin Decreases Risk of HCC in Diabetes

Metformin Decreases Risk for HCC



Metformin Improves HCC Survival



Shu-Juan M et al. Oncotarget. 2016.
Young-Seok S et al. Medicine. 2016.

[redacted]

α-glucosidase inhibitors

In a small pilot study of diabetic patients with biopsy-confirmed NASH

- Miglitol reduce aminotransferase levels, hepatic steatosis, and histological inflammation after 12 months of therapy.

A randomized, placebo-controlled trial

- Acarbose has been shown to reduce serum ammonia level as well as to improve intellectual function and mild hepatic encephalopathy.

Sulfonylureas and glinides

Meta-analyses several case-control studies

revealed 3 folds increase in HCC development amongst patients with T2DM treated with sulfonylureas, possibly as a result of hyperinsulinemia.

Expert opinions advise that insulin secretagogues be avoided or used with extreme caution in patients with CLD/ESLD.

DPP-4 inhibitors

two open-label trials of **sitagliptin**

- **Reduction in intrahepatic lipid content** in diabetic patients with clinical MAFLD.
- Improvements in hepatic steatosis and ballooning in patients with biopsy-proven NASH irrespective of DM status.

Insulin

Observational studies

suggest an association between insulin therapy and HCC development amongst patients with T2DM

Expert opinions advise to reserve insulin therapy in patients with CLD to those who are unable to receive or inadequately managed by other antihyperglycemic medications

Pharmacotherapy Targeting Weight Loss and Insulin Resistance (Off Label)

Mechanism of Action	Compound	Weight Loss	Trial in NAFLD/NASH	Outcome
GLP-1 RA	Exenatide [1]	+	Phase 2b	Improvement of hepatic steatosis by ultrasound
	Liraglutide	+ Approved for obesity	L Trial	Resolution of NASH without worsening fibrosis
	Semaglutide	+++ Approved for obesity and diabetes	Phase 2b	Resolution of ANSH without worsening fibrosis
SGLT2	Canagliflozen	++	Multiple studies	Improvement in liver triglyceride by 1H-MRS; improvement in steatosis biomarkers
	Empagliflozin	+	Multiple studies	Improvement in liver fat by MRI-PDFF Improvement in CAP and liver stiffness by TE

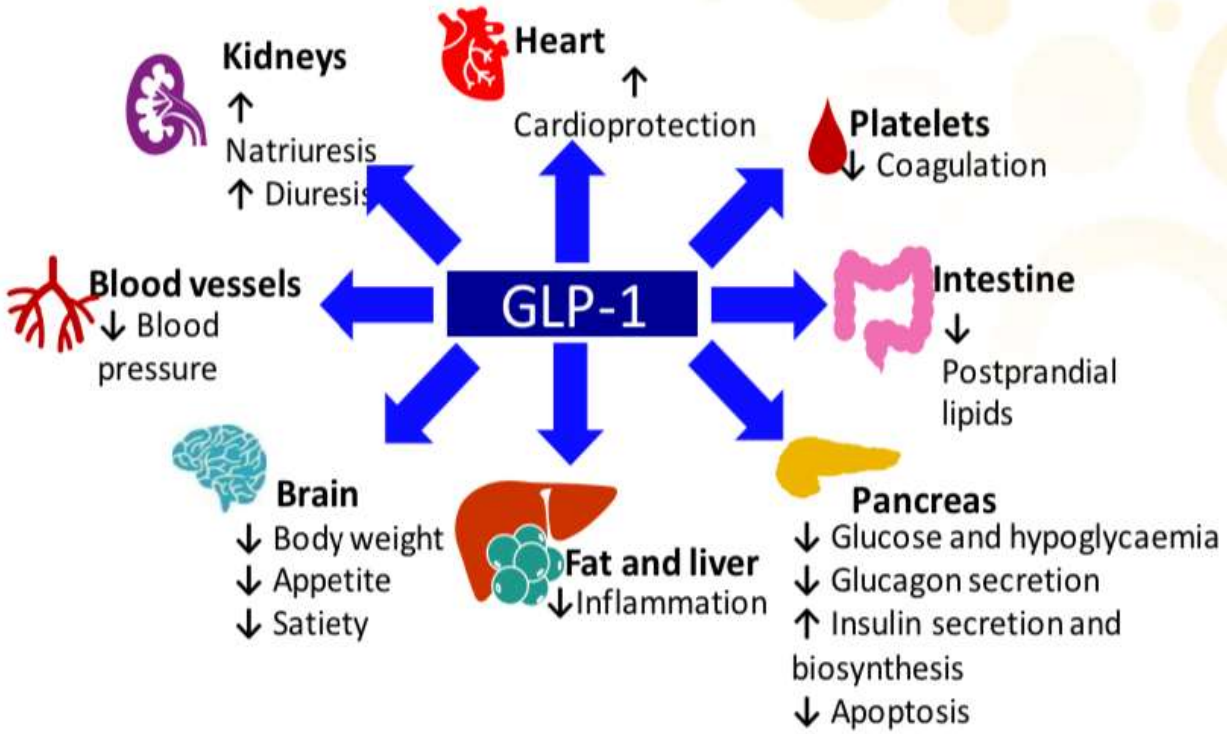
CAP= Capture attenuation parameter; TE = transient elastography

Shao. Diabetes/Metabolism Research Reviews. 2014;30:521. 2. Armstrong. Lancet. 2016;387:679-690. 3. Newsome. NEJM. 2021;384:1113. 4. Cusi. Diabetes Obes Metab. 2019;21:812.
5. Kuchay. Diabetes Care. 2018;41:1801. 6. Taheri. Advanc Ther. 2020;37:4697.

Gut-signals to brain to regulate appetite provide druggable therapeutic targets

Gut hormone	Cell source	receptor	Effect on food intake
CCK	L cells	CCK_A	↓
Ghrelin	stomach	GHS	↑
Pancreatic polypeptide	Pancreas /colon	Y4R	↓
PYY	L cells	Y2R	↓
Oxynto-modulin	L cells	?GLP-1	↓
GLP-1	L cells	GLP-1	↓

Perry and Wang, Nutrition and Diabetes (2012) 2, e26; doi:10.1038/nutd.2011.21



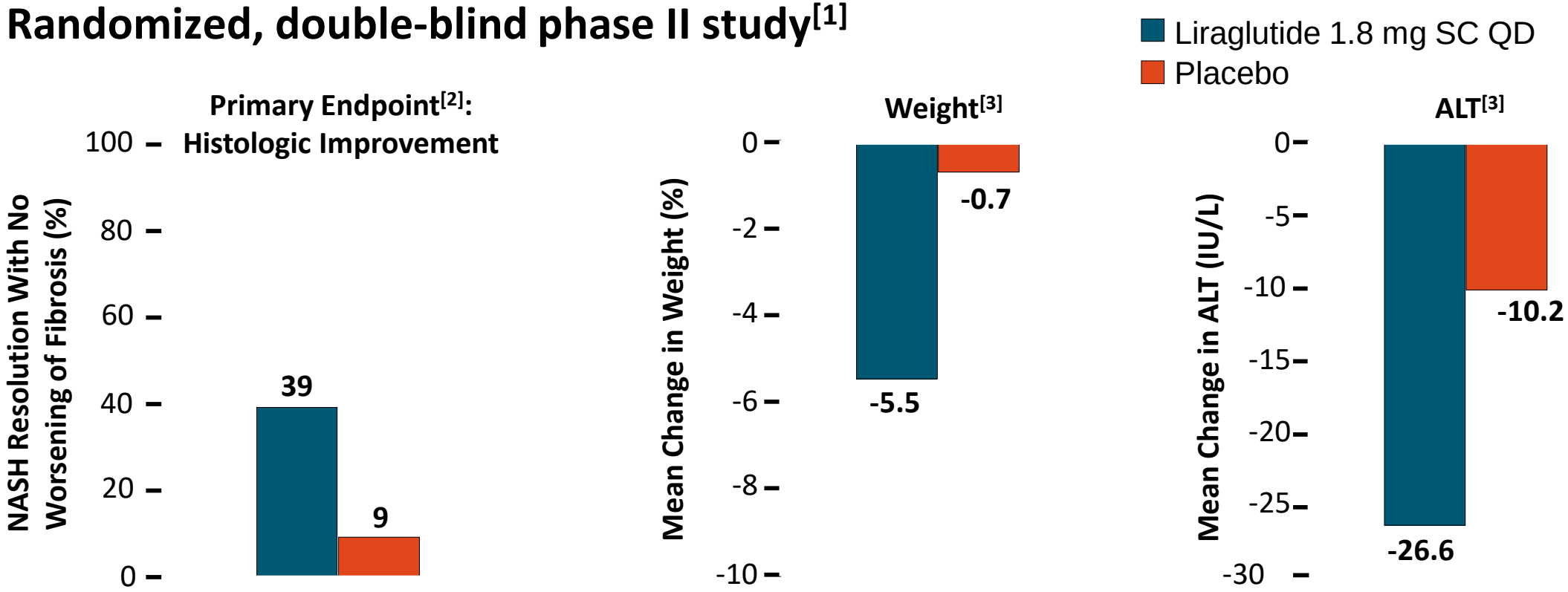
FA, fatty acid; FFA, free fatty acid; GLP-1, glucagon-like peptide-1; TG, triglyceride.
Wang XC et al. *World J Gastroenterol* 2014;20:14821–14830; Lee J et al. *Diabetes Metab J* 2012;36:262–267; Sharma S et al. *PLoS One* 2011;6:e25269.

AASLD The Liver Meeting®

LEAN: 48-Wk Results of Liraglutide vs Placebo in 52 Overweight Patients With NASH

It is premature to consider GLP-1 agonists to treat patients with MAFLD or NASH. (AASLD 2018)

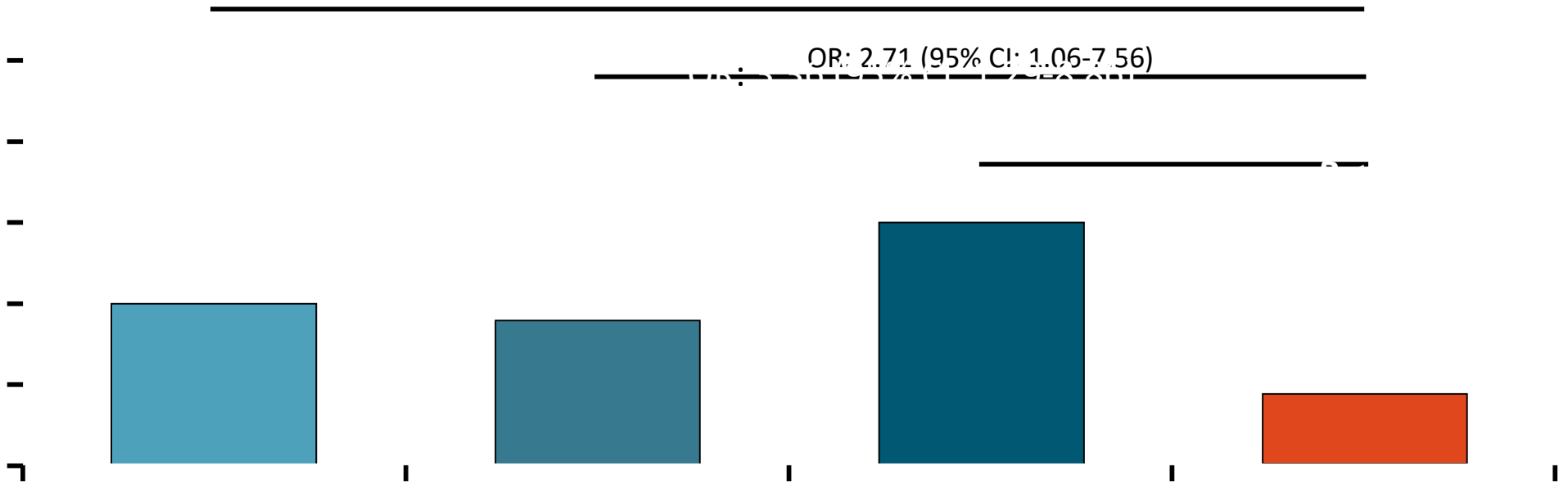
Randomized, double-blind phase II study[1]



1. Armstrong. BMJ Open. 2013;3:e003995. 2.Armstrong. Lancet. 2016;387:679. 3. Armstrong. EASL 2015. Abstr G01.

Semaglutide (GLP-1 agonists) in NASH: Primary Endpoint at 72 Wk

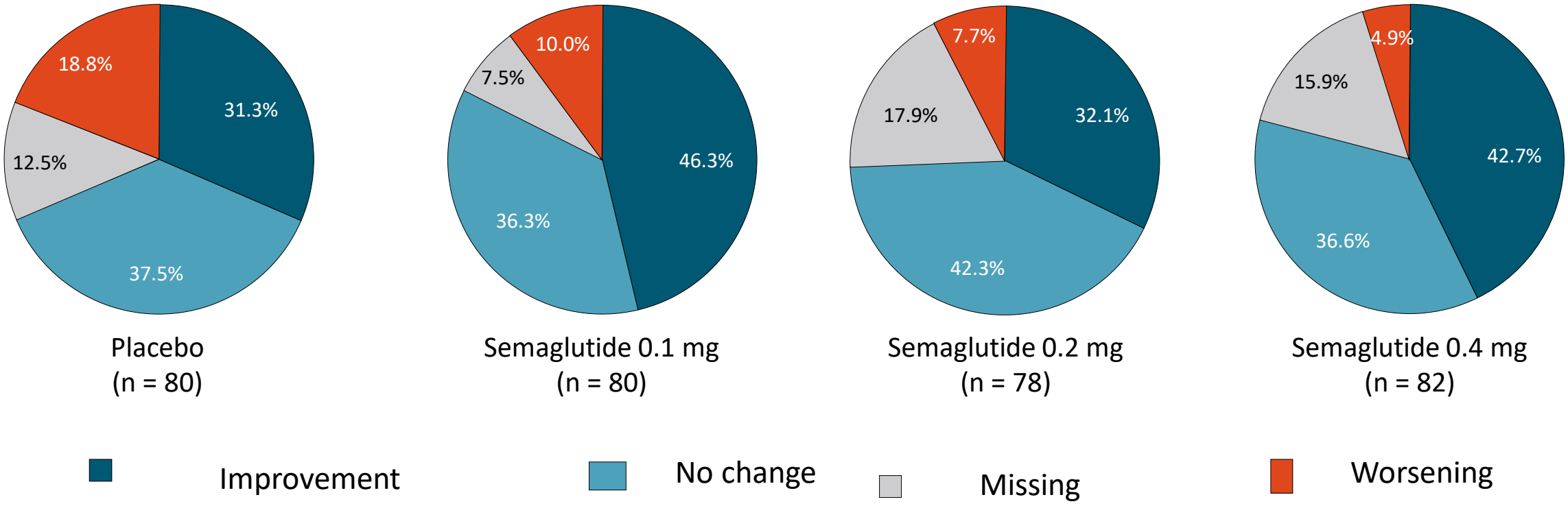
Randomized, double-blind, multicenter phase II trial in 320 adults with BMI >25 kg/m^2 and biopsy-proven NASH or fibrosis (F1, F2, F3)



Newsome. NEJM. 2021;384:1113.

Prevention of Fibrosis Progression

- **Secondary endpoint of phase II study of semaglutide in NASH**



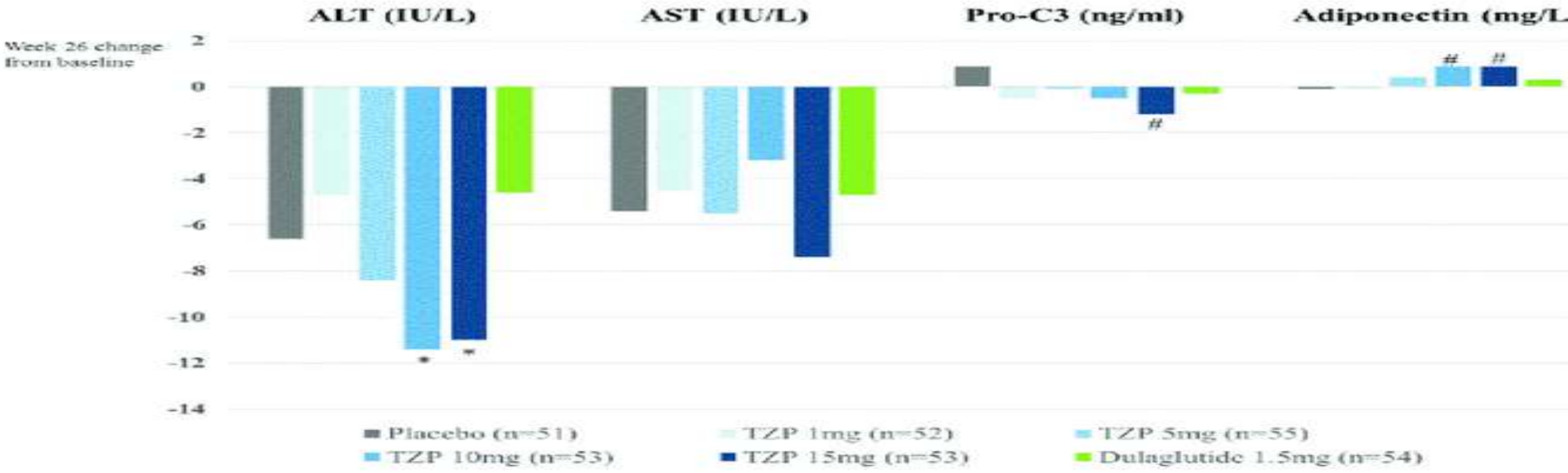
Tirzepatide

Check for updates

Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes

Mark L. Hartman,[1] Arun J. Sanyal,[2] Rohit Loomba,[3,4] Jonathan M. Wilson,[1] Amir Nikooienejad,[1] Ross Bray,[1] Chrisanthi A. Karanikas,[1] Kevin L. Duffin,[1] Deborah A. Robins,[1] and Axel Haupt[1]

Diabetes Care 2020;43:1352–1355 | https://doi.org/10.2337/dc19-1892



Tirzepatide significantly decreased NASH-related biomarkers and increased adiponectin in patients with T2DM.

Randomized Controlled Trial > Lancet Diabetes Endocrinol. 2022 Jun;10(6):393-406.
doi: 10.1016/S2213-8587(22)00070-5. Epub 2022 Apr 22.

Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

Amalia Gastaldelli [1], Kenneth Cusi [2], Laura Fernández Landó [3], Ross Bray [3], Bram Brouwers [3], Ángel Rodríguez [4]

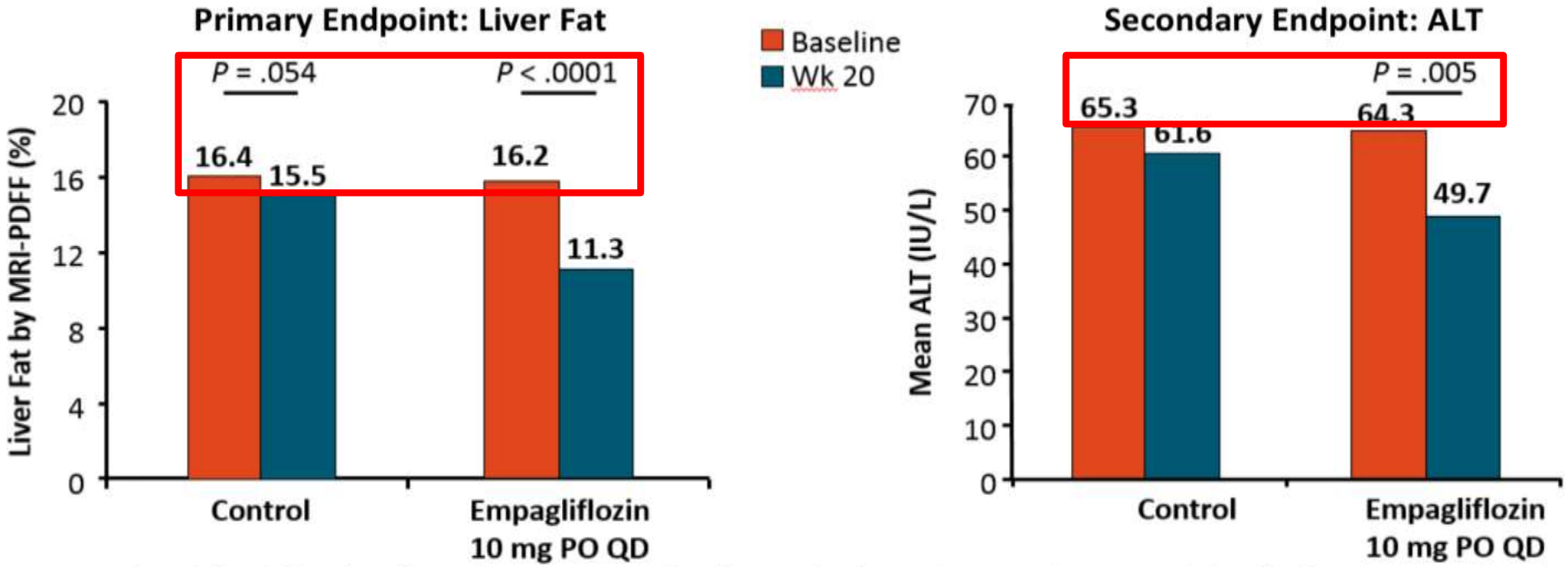
Affiliations + expand

PMID: 35468325 DOI: 10.1016/S2213-8587(22)00070-5

- Tirzepatide 10 mg and 15 mg were found to **reduce liver fat content** by **more than half** (by 8.09%, from a baseline of 15.71%) after **1 year of treatment**. The active comparator, insulin degludec, reduced fat levels by 3.38%.
- These results position tirzepatide as a promising future treatment for MAFLD.

SGLT2 Inhibitors in NAFLD: Effect on Liver Fat and ALT

- E-LIFT: randomized, open-label study of **empagliflozin** vs standard diabetes treatment in 42 patients with diabetes and NAFLD[1]



- In a separate double-blind, placebo-controlled study (n = 37 patients with diabetes and NAFLD), **canagliflozin 300 mg PO QD** associated with lower hepatic triglycerides, which correlated with weight loss[2]

1. Kuchay. Diabetes Care. 2018;41:1801. 2. Cusi. Diabetes Obes Metab. 2018;1-10.

SGLT2 Inhibitors in NAFLD

7 systematic reviews of SGLT2 inhibitors (including between 67 and 498 patients)

- 4 evaluated effects on **liver enzymes**
- 4 reported changes in **liver fat**
- 2 reported changes in **fibrosis biomarkers**

Results

- ✗ None rated as high quality, only 1 as moderate quality
- ✓ 5 systematic reviews indicated that SGLT2 inhibitors could **decrease liver fat and liver enzymes**
- ✓ 1 small, single-arm histologic study showed **improvement in steatosis**
- ✗ No evidence of **liver fibrosis** improvement

Shao. BMJ Open Diab Res Care. 2020.

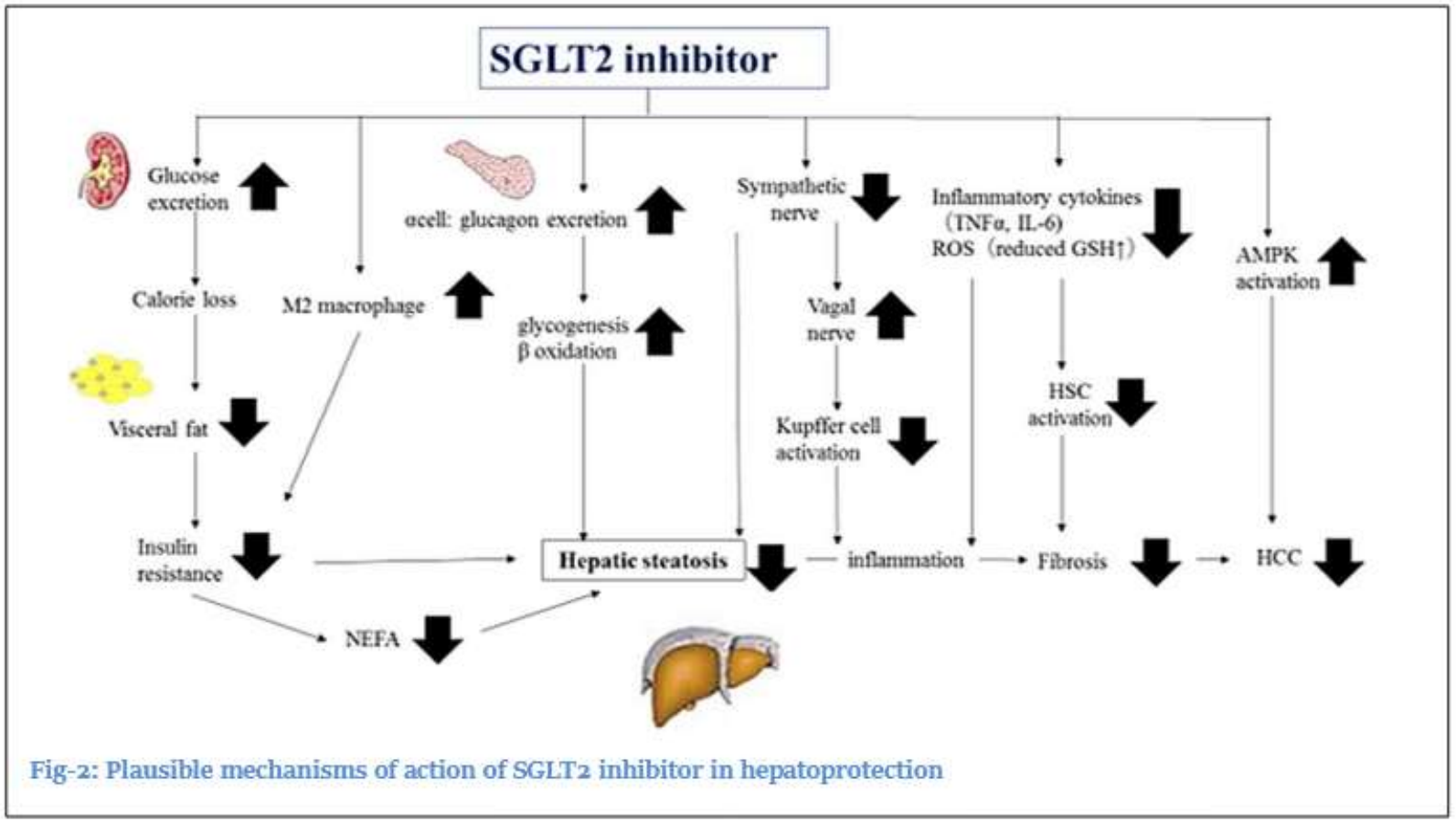


Fig-2: Plausible mechanisms of action of SGLT2 inhibitor in hepatoprotection

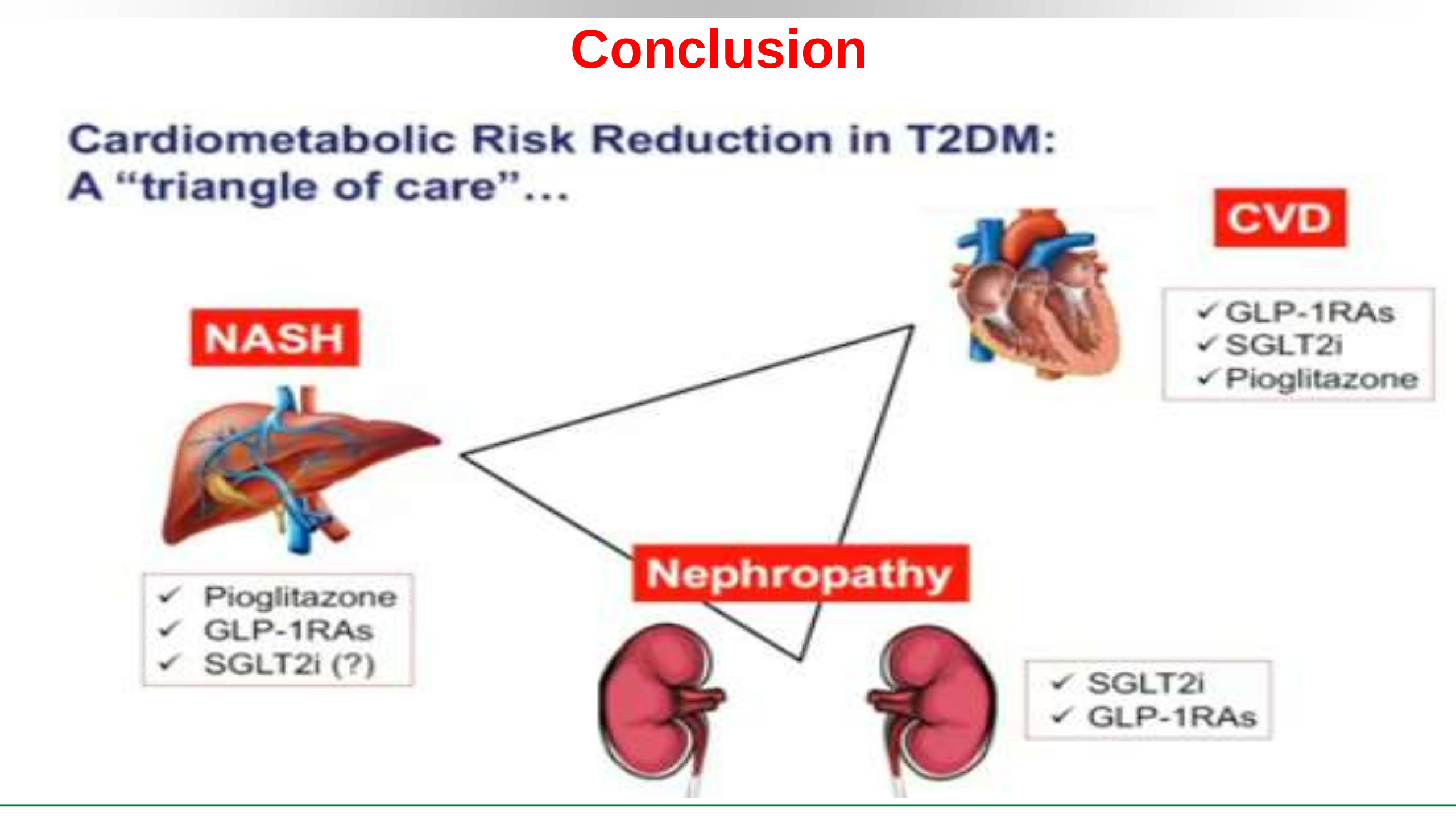
SGLT-2i treatment contributes to alleviation of MAFLD :
-by reduction of hyperglycaemia, improvement of systematic insulin resistance, elevation of caloric loss and reduction of body weight mostly due to glycosuria.
- A hepatoprotective effect through reduction of hepatic de novo lipogenesis, hepatic inflammation, apoptosis, ER-stress, oxidative stress, and increase of hepatic beta-oxidation. Reduced activation of hepatic satellite cells and p53/p21 pathways by SGLT-2i leads to amelioration of hepatic fibrosis and HCC development.
GNG: Gluconeogenesis; HSC: Hepatic stellate cells; ROS: Reactive oxygen species; ER-stress: Endoplasmic reticulum stress.

Recent randomized controlled trials of biopsy-proven MAFLD including anti-diabetic agents in recruitment

Name	Design	Estimated enrollment	Start date	Completion date
DEAN	Dapagliflozin 10 mg/d versus placebo	100 patients	March 20, 2019	June, 2022
SYNERGY-NASH	**Tirzepatide** 5, 10, 15 mg/week versus placebo	196 patients	November 19, 2019	**June, 2022**
REALIST	**Dulaglutide** 1.5 mg/week + dietversus dietary monitoring only	93 patients	September 1, 2019	March 30, 2024
COMBAT_T2_NASH	Empagliflozin 10 mg/d + semaglutide 1 mg/week versus empagliflozin versus placebo	192 patients	March 26, 2021	December 2023
AIM 2	Pioglitazone 15 mg/d versus placebo	138 patients	December 15, 2020	February 29, 2024

Conclusion

Cardiometabolic Risk Reduction in T2DM: A "triangle of care"…



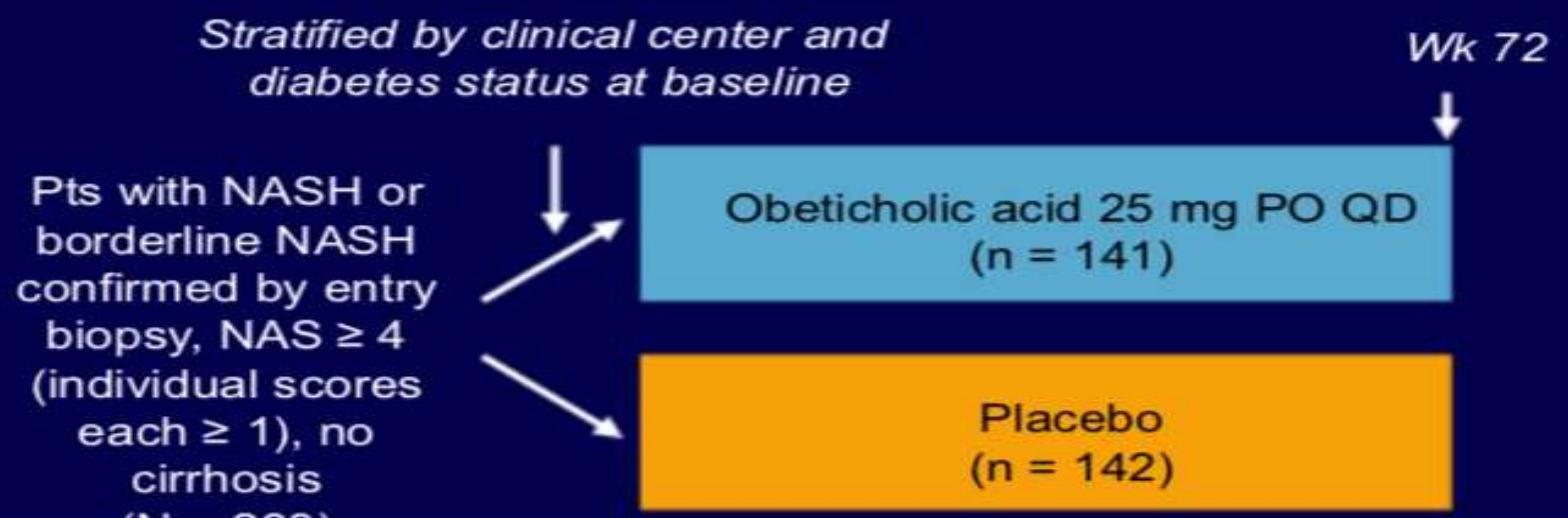
Obeticholic acid

- Farnesoid X Receptor (FXR) agonists
- OCA (Ocaliva): modified bile acid derived from CDCA, (natural ligand for FXR
- 100-fold more potent than CDCA
- ↓ Hepatic lipid synthesis and content.
- ↓ Lipogenesis
- ↓ Gluconeogenesis
- ↑ Insulin sensitivity
- ↑ Hepatic glycogen storage
- Direct inhibitory effects on pro-inflammatory gene expression.

Neuschwander-Tetri BA, et al. Lancet 2015

FLINT: Obeticholic Acid in Noncirrhotic Pts With NASH

- Double-blind, placebo-controlled, randomized, multicenter phase IIb trial



Primary Endpoint: Wk 72 Improvement in NAS ≥ 2 Points With No Worsening of Fibrosis	Wk 72 Improvement in Fibrosis
45% (50/110)	35% (36/102)
21% (23/109)	19% (19/98)
P = .0002	*P* = .004

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

REGENERATE: Study Design

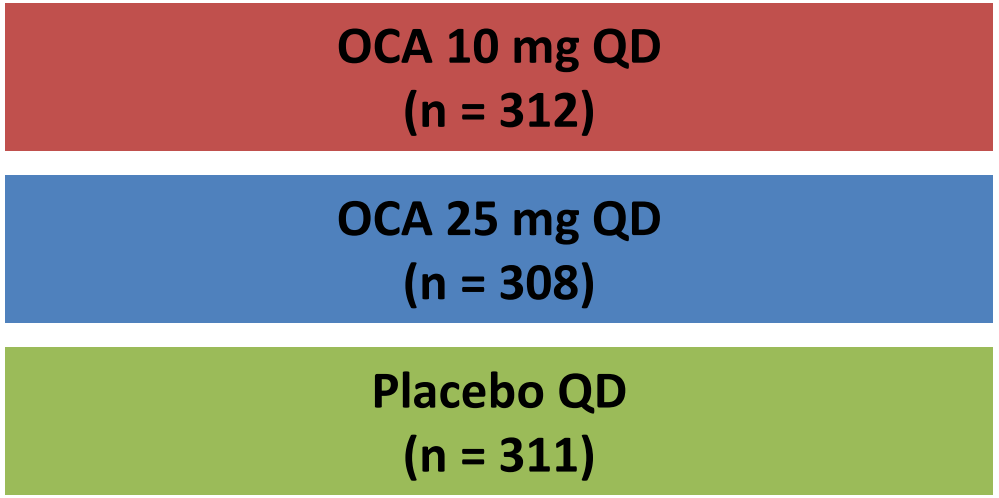
International, randomized, double-blind phase III study of FXR agonist obeticholic acid

Stratified by T2DM, treatment with thiazolidinediones or vitamin E

Patients with biopsy-confirmed NASH, fibrosis stage 2/3, MAFLD activity score ≥ 4 (target N ~ 2400)

Mo 18

Interim Analysis (Histology)



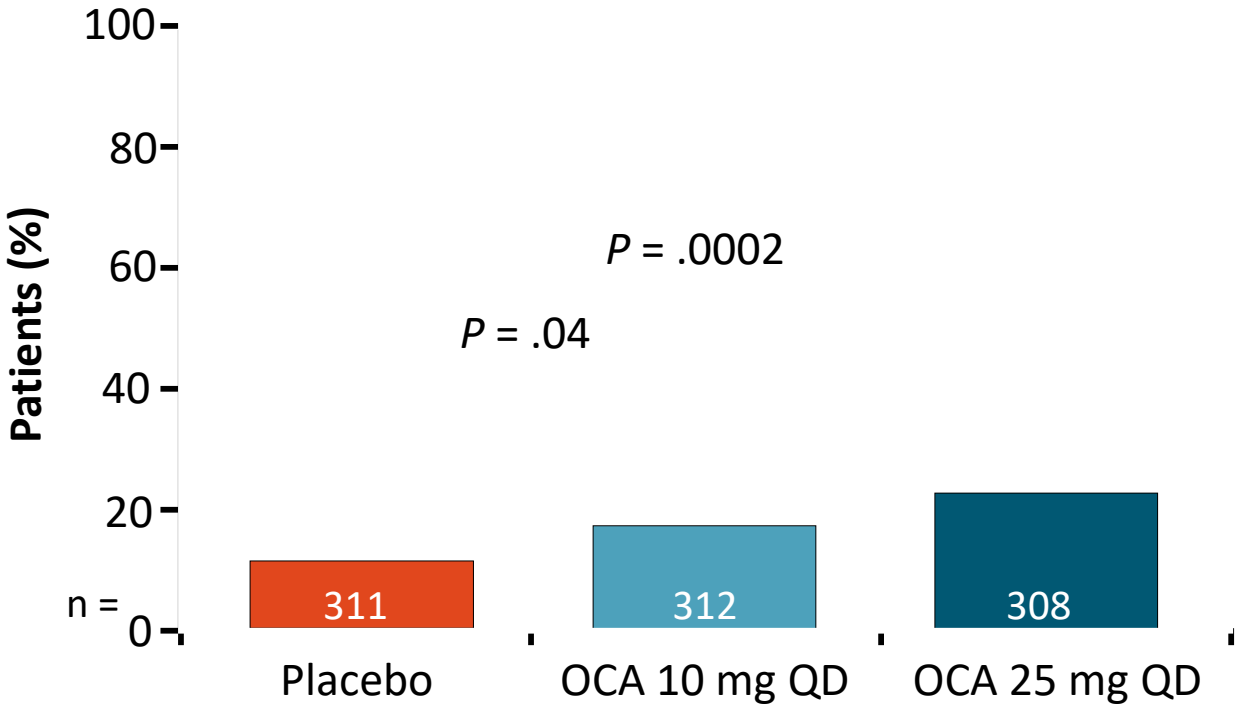
Primary endpoint at interim analysis by paired biopsy: either fibrosis improvement by ≥ 1 stage without NASH worsening or NASH resolution without fibrosis worsening

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

REGENERATE Primary Endpoint: Fibrosis Improvement

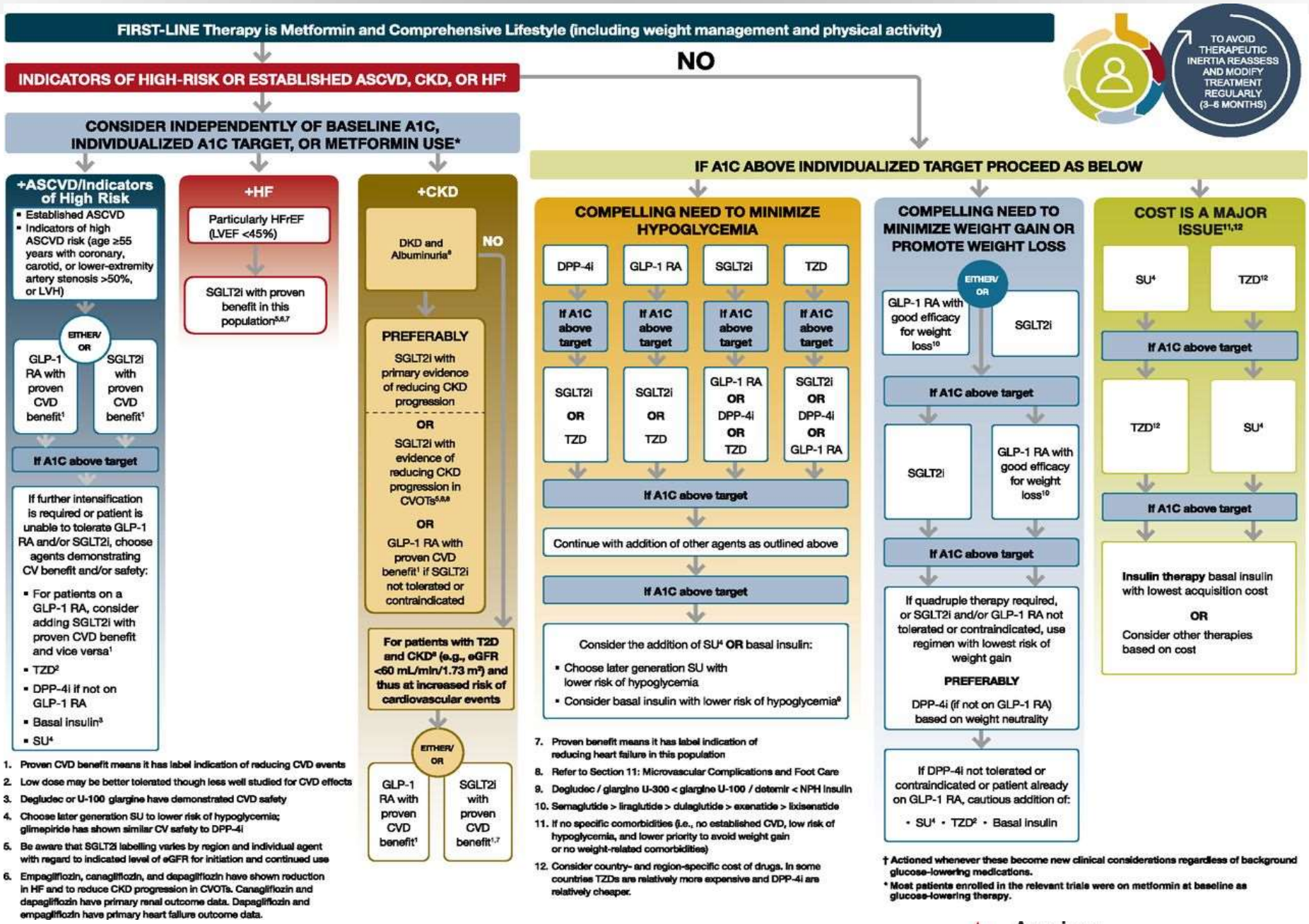
- Study met fibrosis primary endpoint at 18 mos (ITT)

Fibrosis Improvement by ≥ 1 Stage With No NASH Worsening



Younossi. EASL 2019. Abstr GS-06.

So, MAFLD may be the upcoming concern in management of type 2 DM

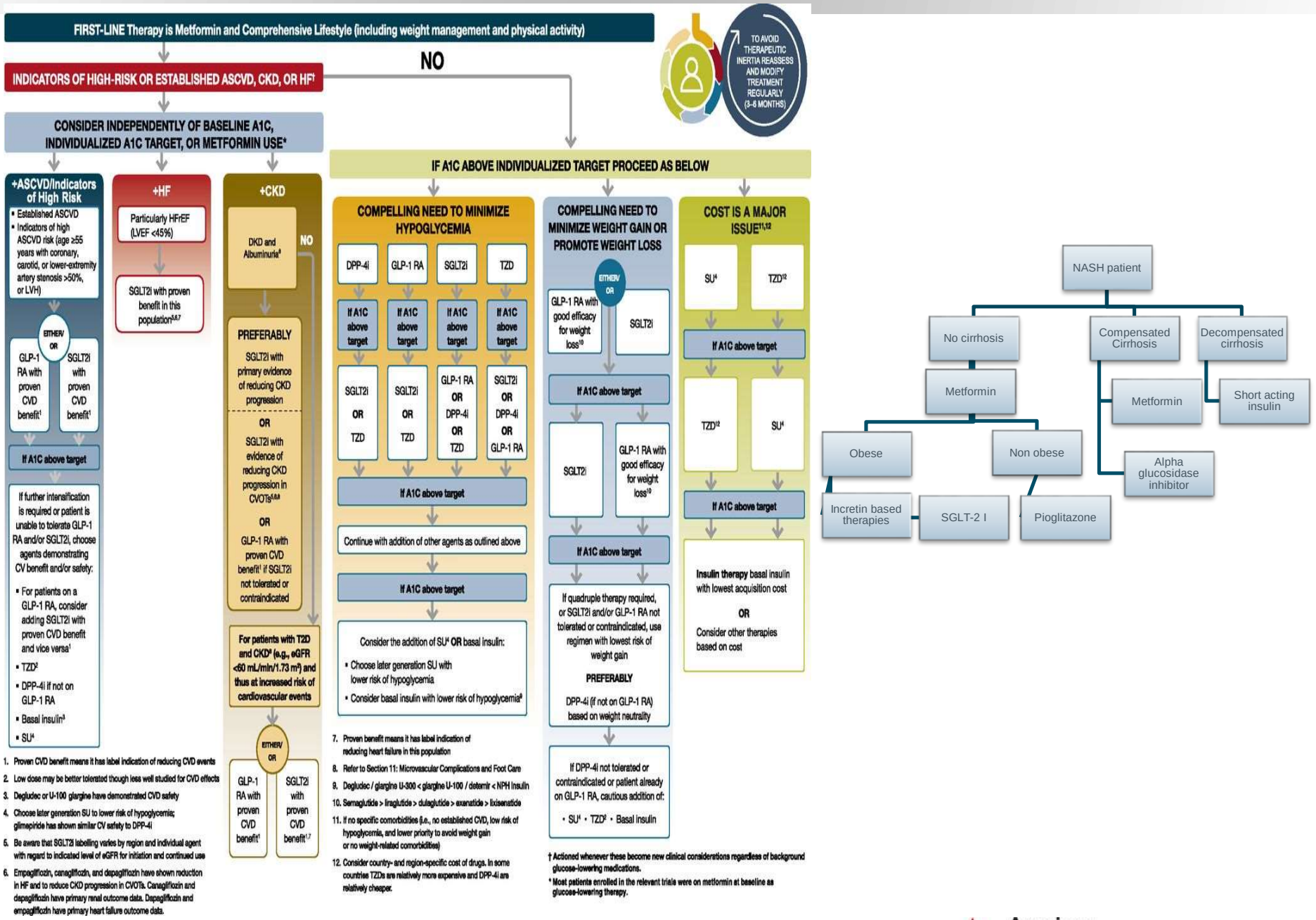


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

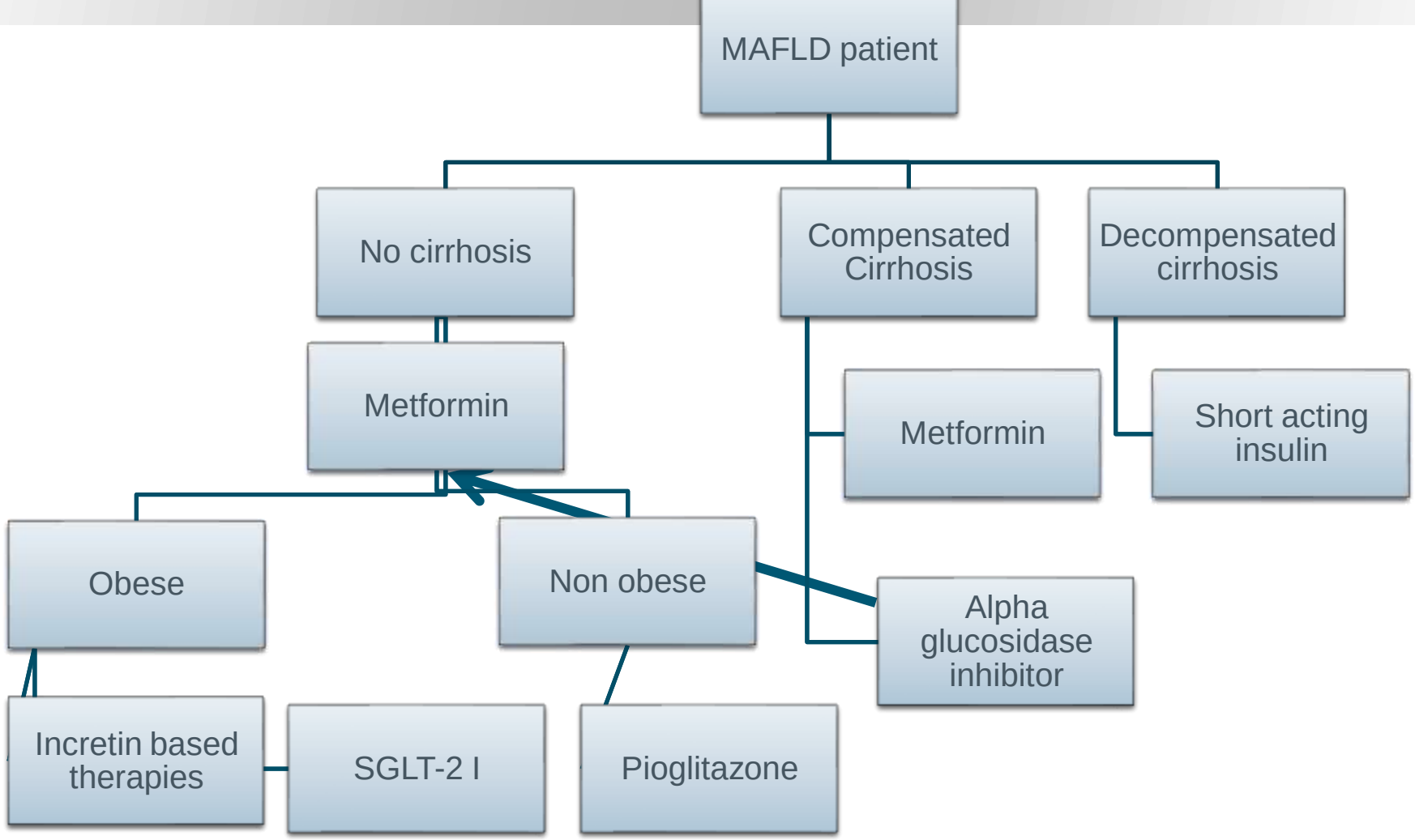
† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

American Diabetes Association.



American Diabetes Association.



- SU and glinides can be used with caution if no cirrhosis and should be stopped if there is cirrhosis
- Insulin is reserved only with failure of non-insulin therapy

Approaches for Currently Available Treatments

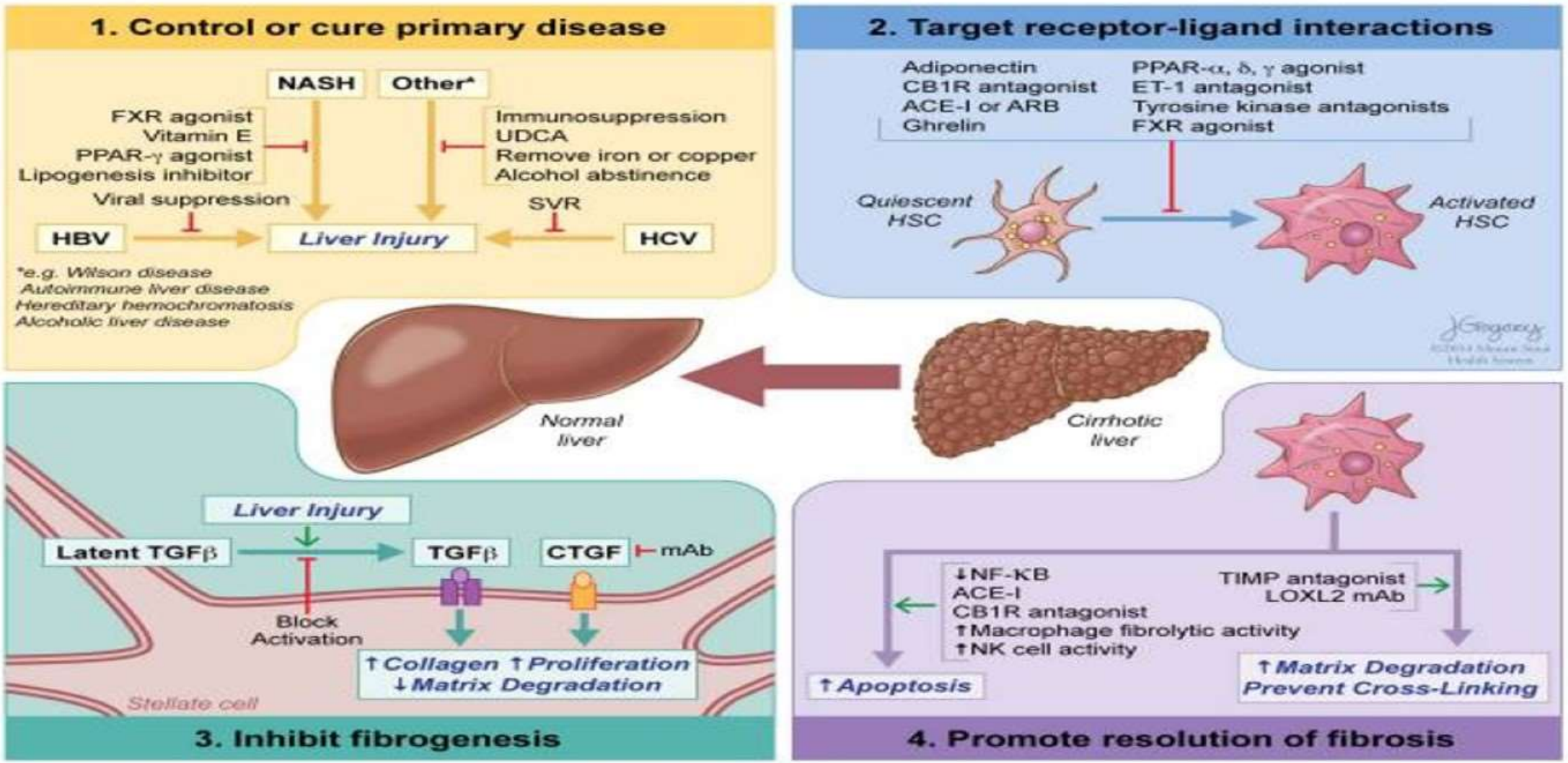
- Case: 45-yr-old patient with type 2 diabetes and NASH and F3 fibrosis asks to discuss therapeutic options

*MAFLD does not increase statin risk of drug-induced liver injury.[6]

1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Bril. J Clin Endocrinol Metab. 2017;102:2950. 7. Zhang. Scand J Gastroenterol. 2013;48:78. 8. Chen. Medicine (Baltimore). 2015;94:e1013. 9. Sanyal. NEJM. 2010;362:1675. 10. Cusi. Ann Intern Med. 2016;165:305. 11. Armstrong. Lancet. 2016;387:679.

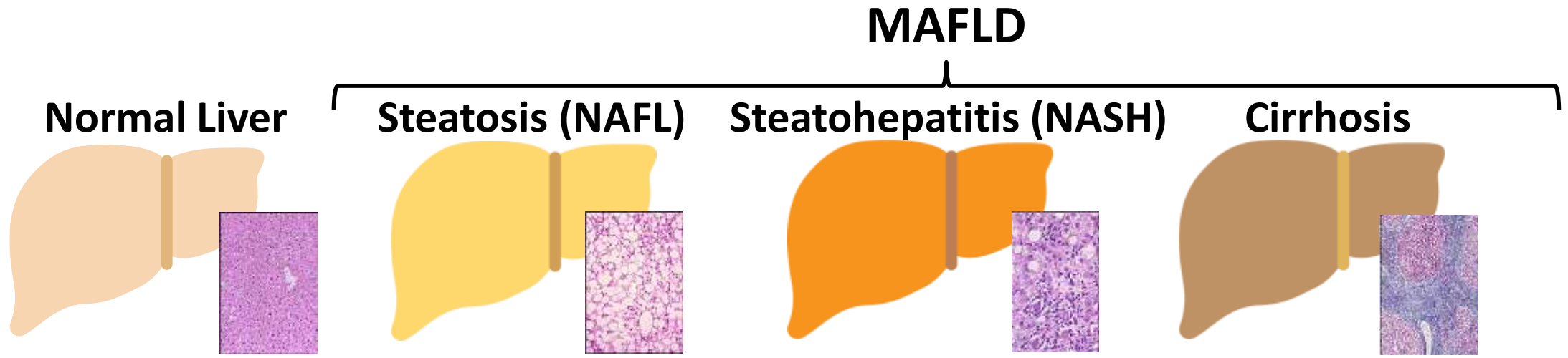
Emerging Treatment Options for NASH

Emerging Therapies for NASH



Reproduced from Lee YA, et al., *Gut*, 2015;64:830-841. With permission from BMJ Publishing Group Ltd.

Targeting Pathophysiologic Processes



Targets related to insulin resistance and/or lipid metabolism › **Targets related to lipotoxicity and oxidative stress** › **Targets related to inflammation and immune activation** › **Targets related to cell death (apoptosis and necrosis)** › **Targets related to fibrogenesis and collagen turnover**

PPARγ: Pioglitazone
GLP-1: Liraglutide, Semaglutide
ACC: GS-0976
SCD1: Aramchol
FGF21: BMS-986036
THR-β: MGL-3196, VK 2807

PPARα/∂: Elafibranor
FXR: OCA, GS-9674, Tropifexor
FGF19: NGM282
Vitamin E

CCR2/5: Cenicriviroc
TLR4: JKB-121

ASK1: Selonsertib

Galectin: GR-MD-02

Bold: Phase III

FDA: Liver Histologic Improvement Endpoints Likely to Predict Clinical Benefit

NASH Resolution

- Resolution of steatohepatitis on overall histopathologic reading

and

- No worsening of liver fibrosis

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage

and

- No worsening of steatohepatitis

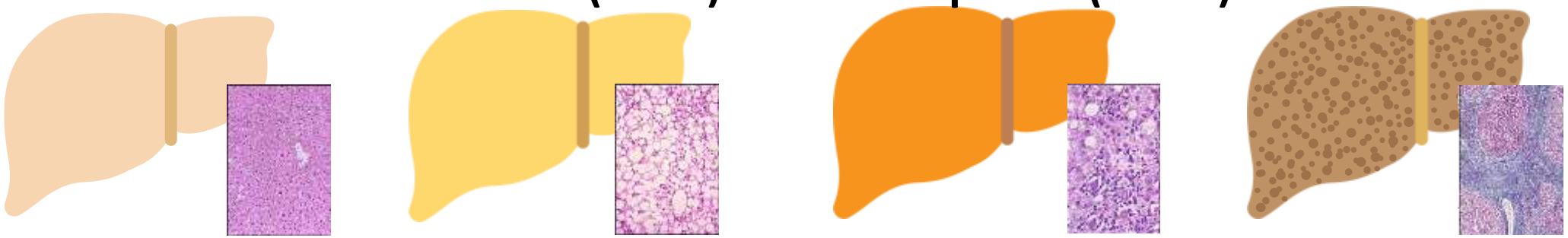
1. US FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

NASH Treatments in Phase III Investigations

Examples of NASH Treatments in Phase II or III Investigations

MAFLD

Normal Liver | **Steatosis (NAFL)** | **Steatohepatitis (NASH)** | **Cirrhosis**



Targets related to insulin resistance and/or lipid metabolism › **Targets related to lipotoxicity and oxidative stress** › **Targets related to inflammation and immune activation** › **Targets related to cell death (apoptosis and necrosis)** › **Targets related to fibrogenesis and collagen turnover**

PPARγ:	Pioglitazone
GLP-1:	Liraglutide, semaglutide
ACC:	GS-0976,PF-05221304
SCD1:	Aramchol
FGF21:	BMS-986036
THR-β:	MGL-3196, VK2809

PPARα/∂:	**Elafibranor**
PPARα/∂/γ:	Lanifibranor
FXR:	**OCA,** GS-9674, tropifexor
FGF19:	NGM282
MPC:	MSDC-0602K

CCR2/5: Cenicriviroc (inflammatory target but affects fibrosis)

P2X7R: SGM-1019

ASK1: Selonsertib (cell death target but affects fibrosis)

Caspase: Emricasan

Galectin: GR-MD-02

Bold = phase III

Some agents have multiple targets

NASH Treatments Currently in Phase III Investigations

Agent	MoA	Trial	N	Primary Endpoint(s)	Time Point
Cenicriviroc	CCR2/5 antagonist	AURORA[1]	2000	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Elafibranor	PPARα/σ agonist	RESOLVE-IT[2]	2000	Resolution of NASH with no fibrosis worsening	72 wks
Obeticholic acid	FXR agonist	REGENERATE[3]	2370	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	18 mos
		REVERSE[4]	540	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Selonsertib	ASK1 inhibitor	STELLAR 3[5]	808	≥ 1 stage fibrosis improvement with no NASH worsening; event-free survival	48 wks
		STELLAR 4[6]	883	NASH with compensated cirrhosis	240 wks

Phase III/IV studies use adaptive design

- Histologic endpoints for Subpart H conditional approval
- Clinical endpoints for full approval

1. NCT03028740. 2. NCT02704403. 3. NCT02548351. 4. NCT03439254. 5. NCT03053050. 6. NCT03053063.

Table 4 | Therapies for non-alcoholic steatohepatitis (NASH) in phase III development

Drug	Trial code; name (company)	No of patients	Study population	Route of delivery	Time to surrogate endpoint (biopsy)	Primary endpoint	Long term clinical outcome*
Anti-inflammatory, anti-fibrotic							
Obeticholic acid[142] (FXR agonist)	NCT02548351; REGENERATE (Intercept)	2480	NASH with fibrosis F2/F3, NAS ≥4; fibrosis F1 and diabetes, obesity, or inflammation	Oral	72 weeks	≥1 stage improvement of fibrosis without worsening of NASH or NASH resolution without worsening of fibrosis	Time to first event
Cenicriviroc[143] (dual CCR2/CCR5 antagonist)	NCT03028740; AURORA (Allergan)	2000	NASH with fibrosis F2/F3, NAS ≥4	Oral	52 weeks	≥1 stage improvement of fibrosis without worsening of NASH	Time to first event (up to EOS, about 5 years)
Metabolism modulators							
Elafibranor [144] (dual PPAR-α/δ agonist)†	NCT02704403; RESOLVE-IT (Genfit)	2000	NAS ≥4; fibrosis F1/F2/F3 (F1, limited number); BMI ≤45	Oral	72 weeks	NASH resolution (no ballooning, inflammation 0-1, no progression of fibrosis) without worsening of steatohepatitis	Time to first event (up to EOS, about 4 years)
Resmetirom (THRβ agonist)	NCT03900429; MAESTRO-NASH (Madrigal)	2000	NASH with fibrosis F2/F3, high risk F1	Oral	52 weeks	NASH resolution, no worsening of fibrosis. Composite clinical outcome	% patients with ›1 event (up to 54 months)
Aramchol (SCD-1 modulator)	NCT04104321; ARMOR (Galmed)	2000	NASH with fibrosis F2/F3, NAS ≥4; overweight/obese; pre-diabetes/T2DM	Oral	52 weeks	NASH resolution, no worsening of fibrosis or ≥1 stage improvement of fibrosis, no worsening of NASH	% patients with ›1 event (up to 5 years)

BMI=body mass index; CCR2-CCR5=chemokine receptor 2-5; EOS=end of study; FXR=farnesoid-X receptor; NAS=NAFLD activity score (sum of steatosis (0-3), lobular inflammation (0-3), hepatocellular ballooning (0-2); PPAR=peroxisome proliferator activated receptor; SDC-1=stearoyl-CoA desaturase modulator; T2DM=type 2 diabetes mellitus; THRβ=thyroid hormone receptor β.
*Long term outcomes include all cause mortality, transplant, and hospital admission due to hepatic decompensation.
†Recent early termination after interim analysis.

Effect of New Antidiabetics on Steatosis in Different Organs of Obese Rats and Nerve Conduction Velocity

Abdelaziz M. Hussein[1], Elsayed A. Eid[2], Ahmed Abdulatif Mosa[2], Omar A. Ammar[3], Nehal H. M. Abdel-Halim[1], Yomna M. Yehia[1], Hossam Arafa Ghazi[4], Sherif Arafa[5], Mohamed Elbasiony[4,6]

[1]Department of Medical Physiology, Mansoura Faculty of Medicine, Mansoura, Egypt

[2]Department of Internal Medicine, Faculty of Medicine, Delta University for Science and Technology, Gamasa, Egypt

[3]Basic Science Department, Delta University for Science and Technology, Gamasa, Egypt

[4]Department of Internal Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt

[5]Department of Cardiology, Faculty of Medicine, Mansoura University, Mansoura, Egypt

[6]Egyptian liver research institute, Sherben, Egypt

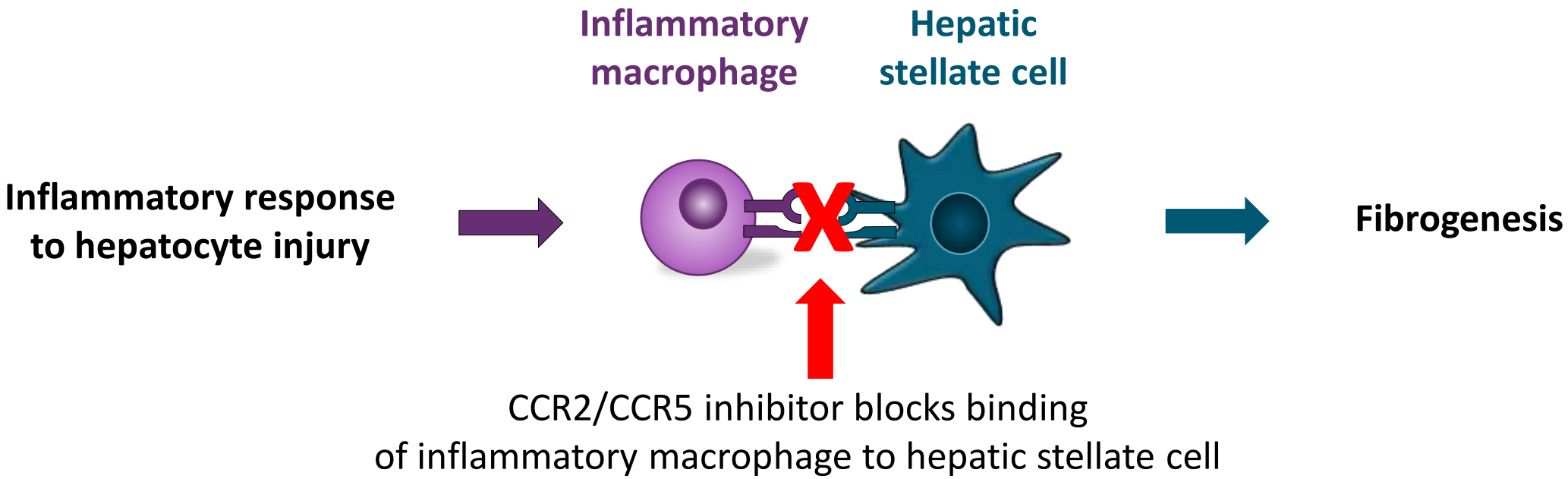
Key Take-Away Slide

- **MAFLD is a global epidemic & more frequent among diabetics & the commonest liver disease worldwide.**
- **Life style modification is corner stone in management of MAFLD.**
- **Strive for weight loss in patient tailor and individualized approach.**
- **In absence of FDA approved therapies for NASH, utilize available therapies for primary and secondary benefits.**
- **Aggressively treat /optimize all metabolic risk factors**
- **Reduction of cardiovascular risk is essential in patients with MAFLD (dyslipidemia, hypertension, DM, smoking)**
- **Treatment will probably be based on a combination of therapies in addition to lifestyle modification.**


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
merci
شكراً
obrigado
bedankt
dziękuję
go raibh maith agat
sukriya
kop khun krap
terima kasih
arigatô
dakujem
grazie
tapadh leat
mochchakkeram
спасибо
рахмат
Баярлалаа
faafetai lava
kiitos
dankie
dhanyavad
mauruuru
hvala
köszönöm
gràcie
bayarlalaa
nanni
nandri
enkosi
sobodi
děkuji
mèsi
didi madloba
sagolun
najis tuke
kam sah hamnida
তোমাকে ধন্যবাদ
rahmat
감사합니다
ありがとう
chnorakaloutioun
gratias ago
gràcies
sulpáy
taiku
tanemirt
rahmet
xièxie
ευχαριστώ
diolch
dhanyavadagalu
shukriya
mercé
мерси
trugarez
takk
mahalo
paldies
grazzi
matondo
misaotra
dank je
blagodaram
спасибі
vinaka
kia ora
barka
welalin
tack
spas
mersi
akun
dankon
ačiū
djiere dieuf
tau
дякую
mamnun
obrigada
asante
manana
хвала
murakoze
chokrane
tenki

Cenicriviroc

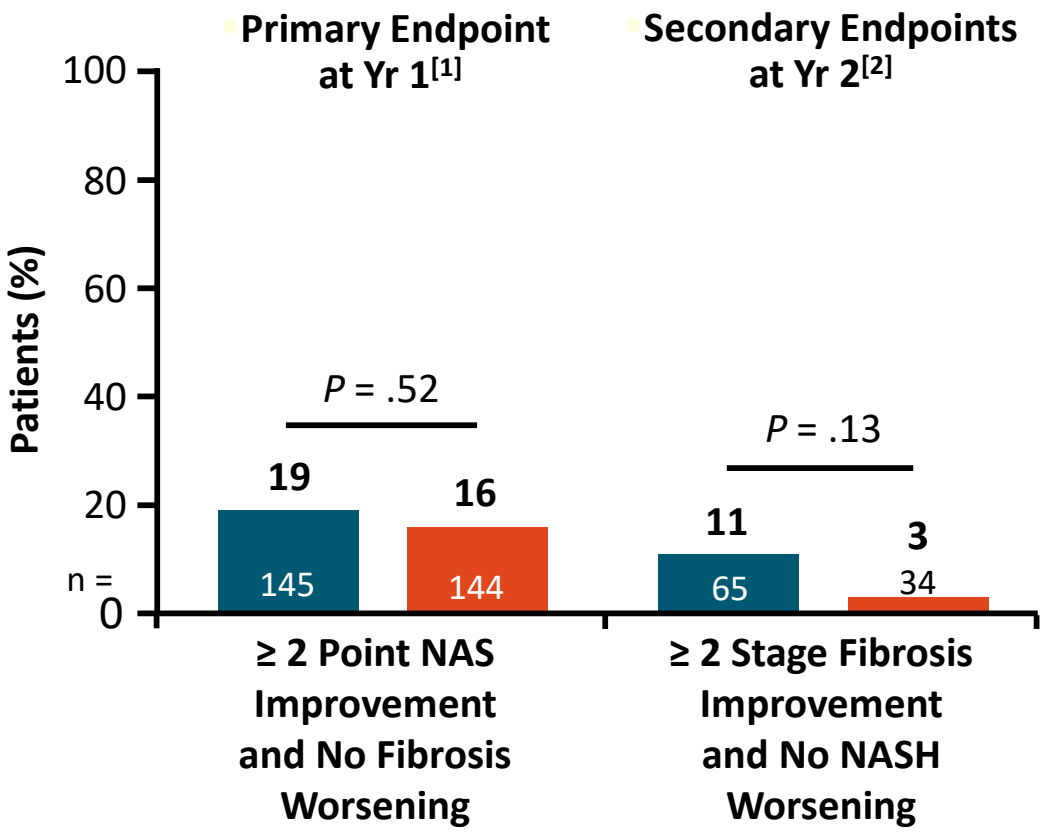
Cenicriviroc: CCR2/CCR5 Inhibitor

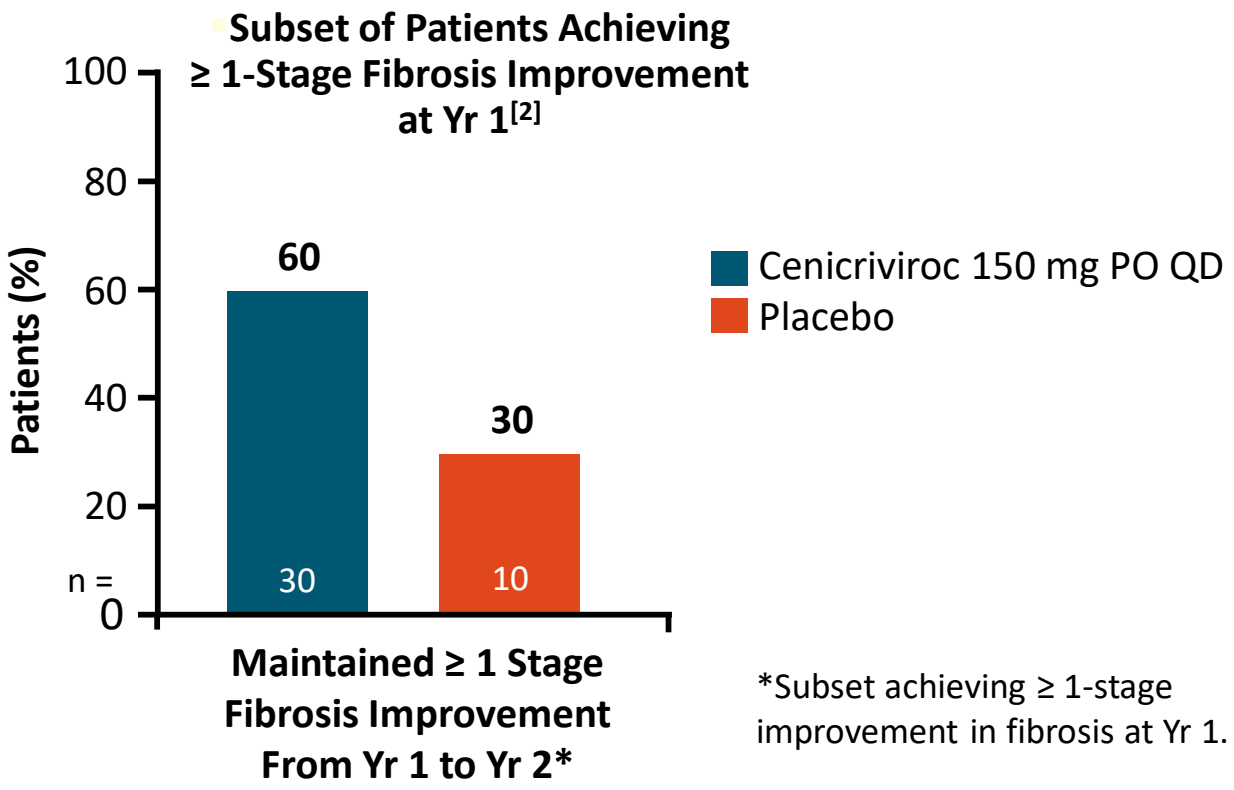


Friedman. Hepatology. 2018;67:1754.

CENTAUR: Cenicriviroc vs Placebo in Patients With NASH at Yr 1 and 2

- International, randomized, double-blind, phase IIb study in pts with NASH, NAS ≥ 4 and F1-F3 fibrosis (N = 289)[1]





*Subset achieving ≥ 1-stage improvement in fibrosis at Yr 1.

1. Friedman. Hepatology. 2018;67:1754. 2. Ratziu. EASL 2018. Abstr GS-002.

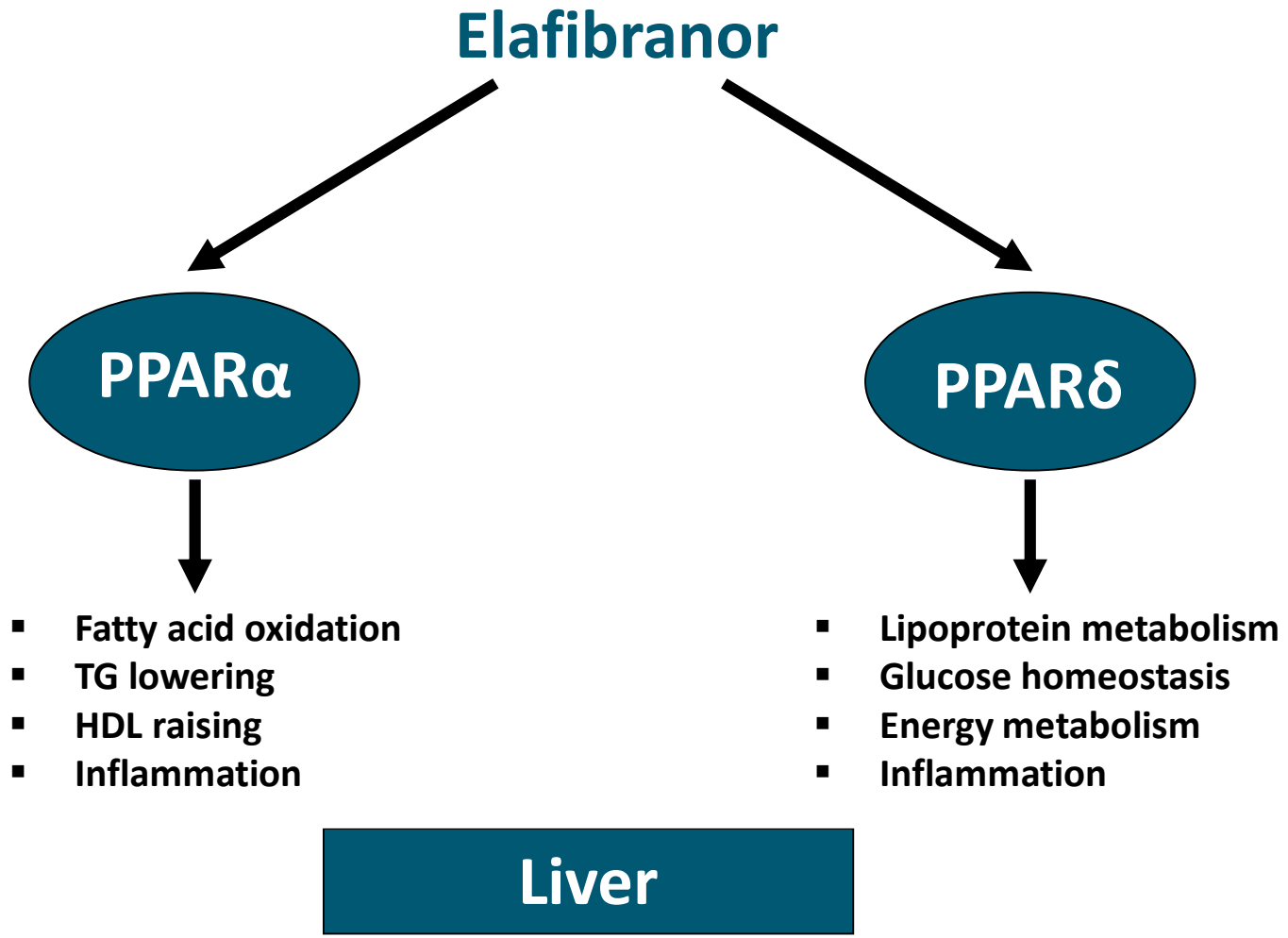
CENTAUR: Cenicriviroc Safety at Yr 2

- No clinically meaningful difference in overall incidence of AEs vs placebo
- Most AEs mild to moderate
- No deaths or study drug related, treatment-emergent serious AEs
- Drug-related AEs of grade ≥ 2 in ≥ 2% of patients occurred in 8.3% and 5.0% in cenicriviroc and placebo arms, respectively
- Serious AEs or ALT elevation no higher in cenicriviroc vs placebo arm

Ratziu. EASL 2018. Abstr GS-002.

Elafibranor

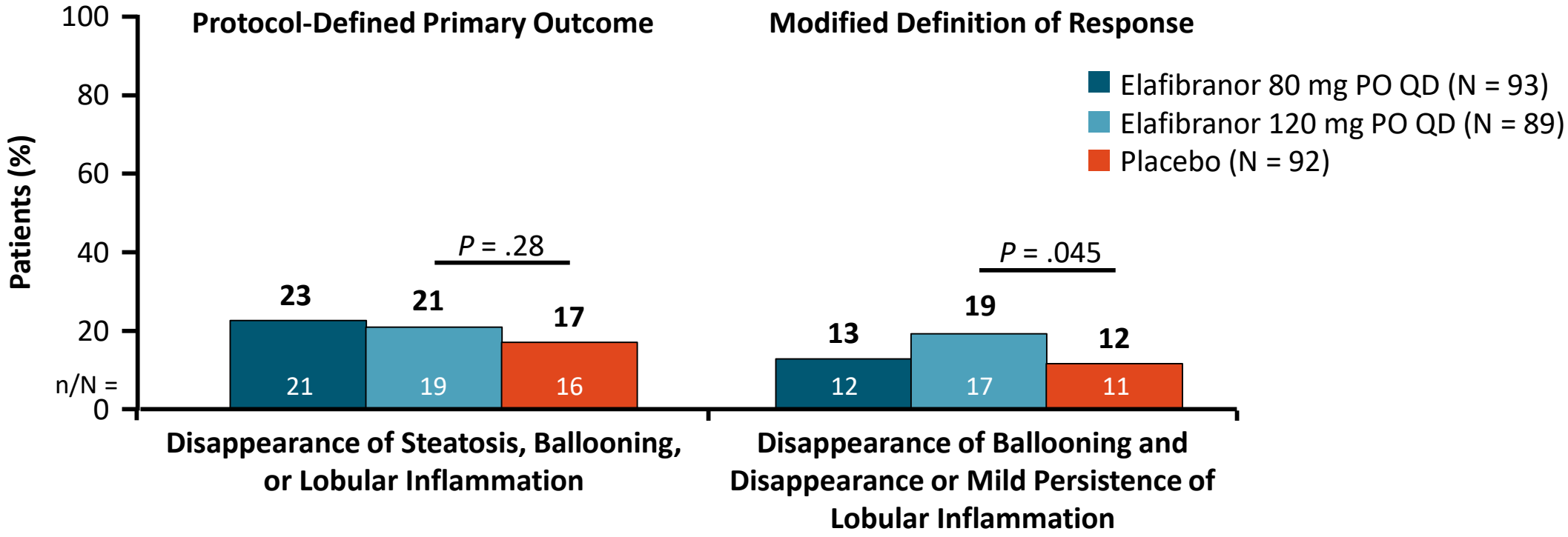
Elafibranor: PPARα/δ Agonist



Slide courtesy of Bart Staels, MD

GOLDEN-505: Elafibranor vs Placebo in Patients With NASH at Wk 52

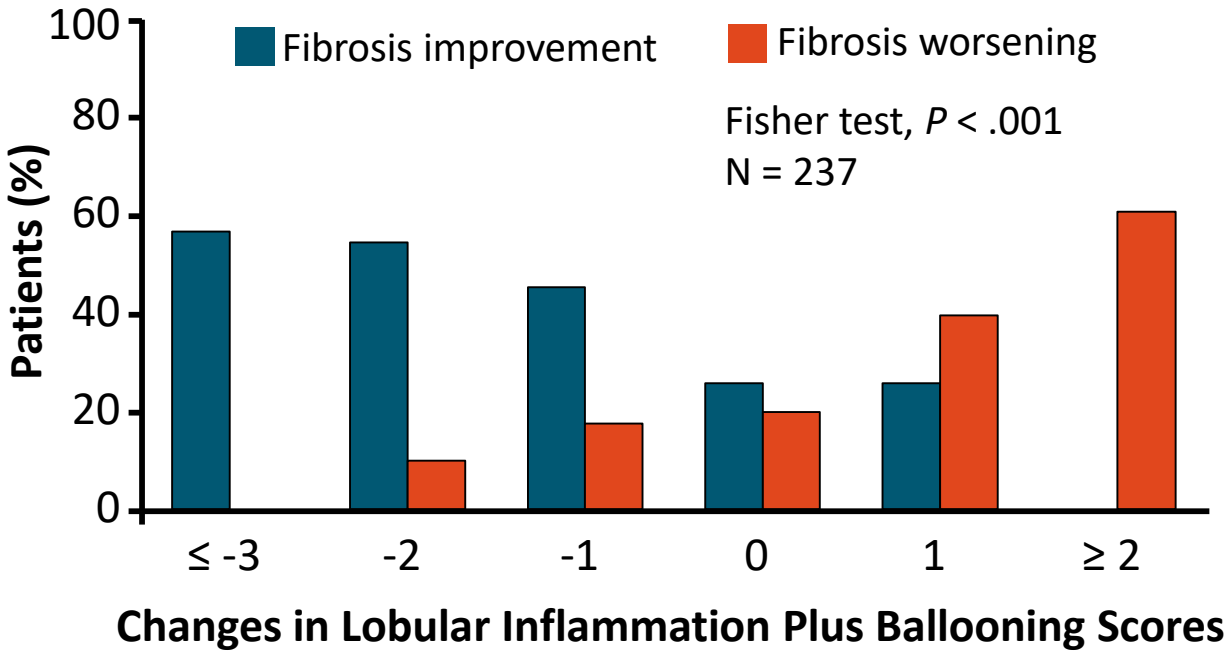
- Double-blind, placebo-controlled, randomized, international phase IIb study in patients with noncirrhotic NASH (N = 276)
  - Primary endpoint: resolution of NASH without fibrosis worsening at Wk 52



Ratziu. Gastroenterology. 2016;150:1147.

GOLDEN-505: Correlation Between NASH Histology and Fibrosis at Wk 52, Tolerability

- Changes in hepatocyte ballooning and lobular inflammation correlated with changes in fibrosis stage ($P = .04$ and $P < .001$, respectively)[1]
  - Changes in steatosis did not correlate with changes in fibrosis stage



- Liver enzymes, lipids, glucose profiles, and markers of systemic inflammation significantly lower in elafibranor 120-mg group vs the placebo group[2]
- Elafibranor well tolerated; no weight gain or cardiac events[2]
- Mild, reversible increase in serum creatinine (effect size vs placebo: increase of 4.31 ± 1.19 mmol/L; $P < .001$)[2]

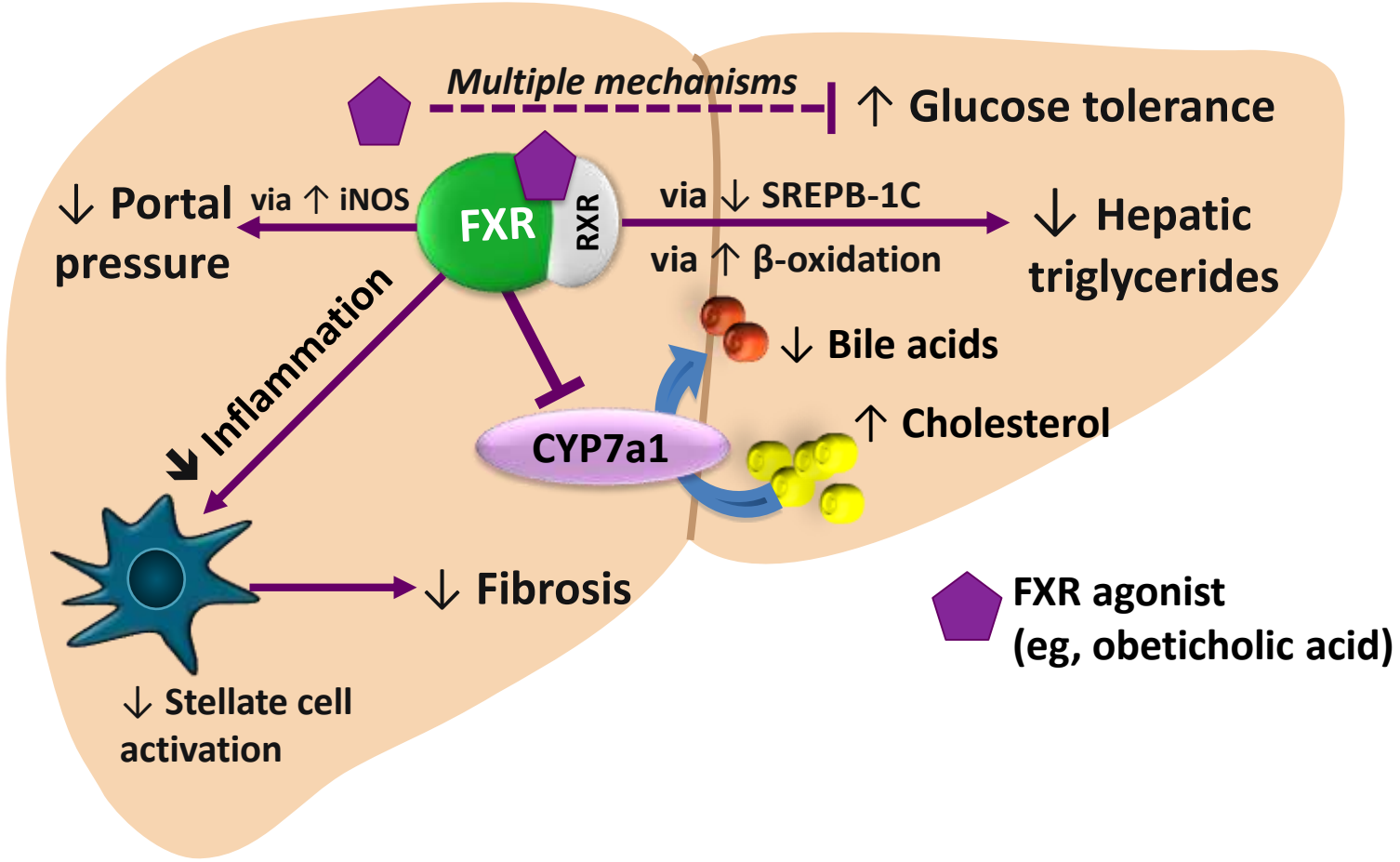
1. Ratziu. AASLD 2016. Abstr LB-37. 2. Ratziu. Gastroenterology. 2016;150:1147.

Farnesoid X receptor agonists

Obeticholic Acid

Obeticholic Acid: FXR Agonist

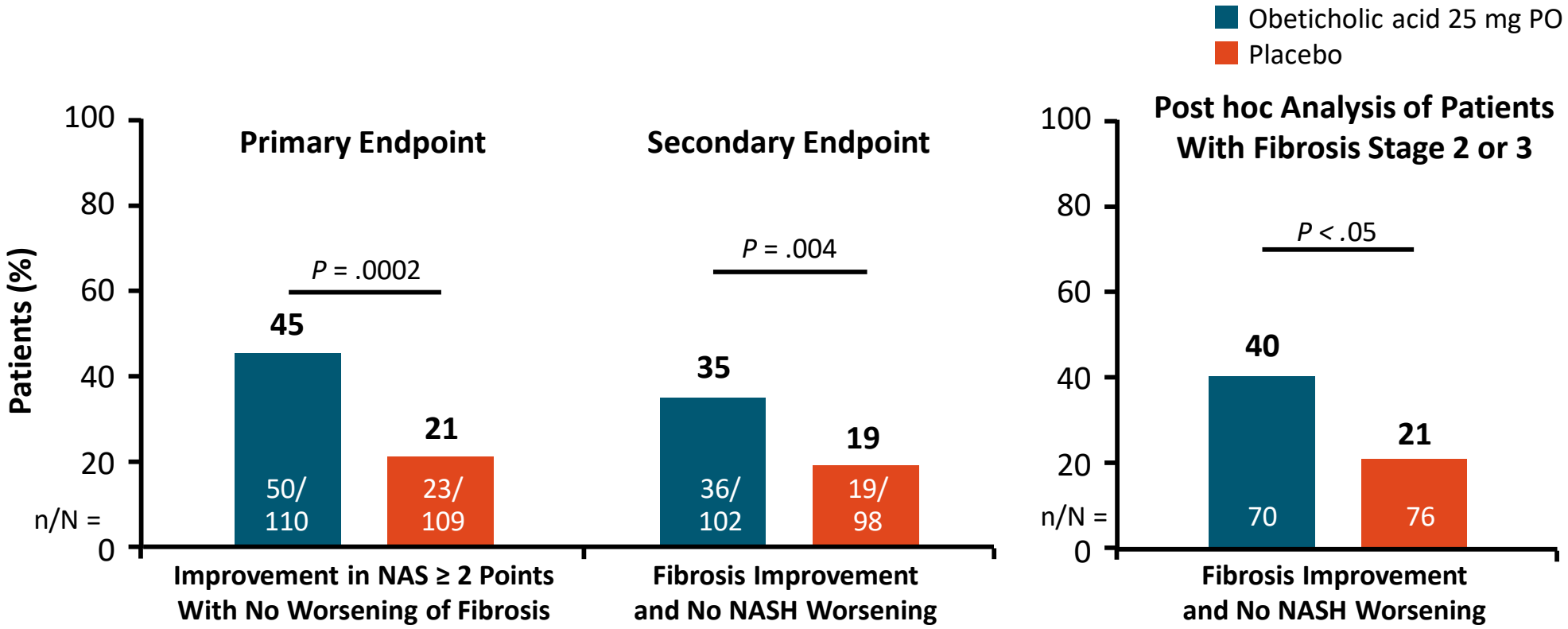
- FXR central to multiple key pathways in animal models



1. Cariou. Diabetes Metab. 2008;34:685. 2. Calkin. Nat Rev Mol Cell Biol. 2012;13:213. 3. Verbeke. Hepatology. 2014;59:2286.

FLINT: Obeticholic Acid vs Placebo in Noncirrhotic Patients With NASH at Wk 72

- Double-blind, placebo-controlled, randomized, international phase IIb study in patients with NASH or borderline NASH confirmed by entry biopsy, NAS ≥ 4 (individual scores each ≥ 1), no cirrhosis (N = 283)



Neuschwander-Tetri. Lancet. 2015;385:956.

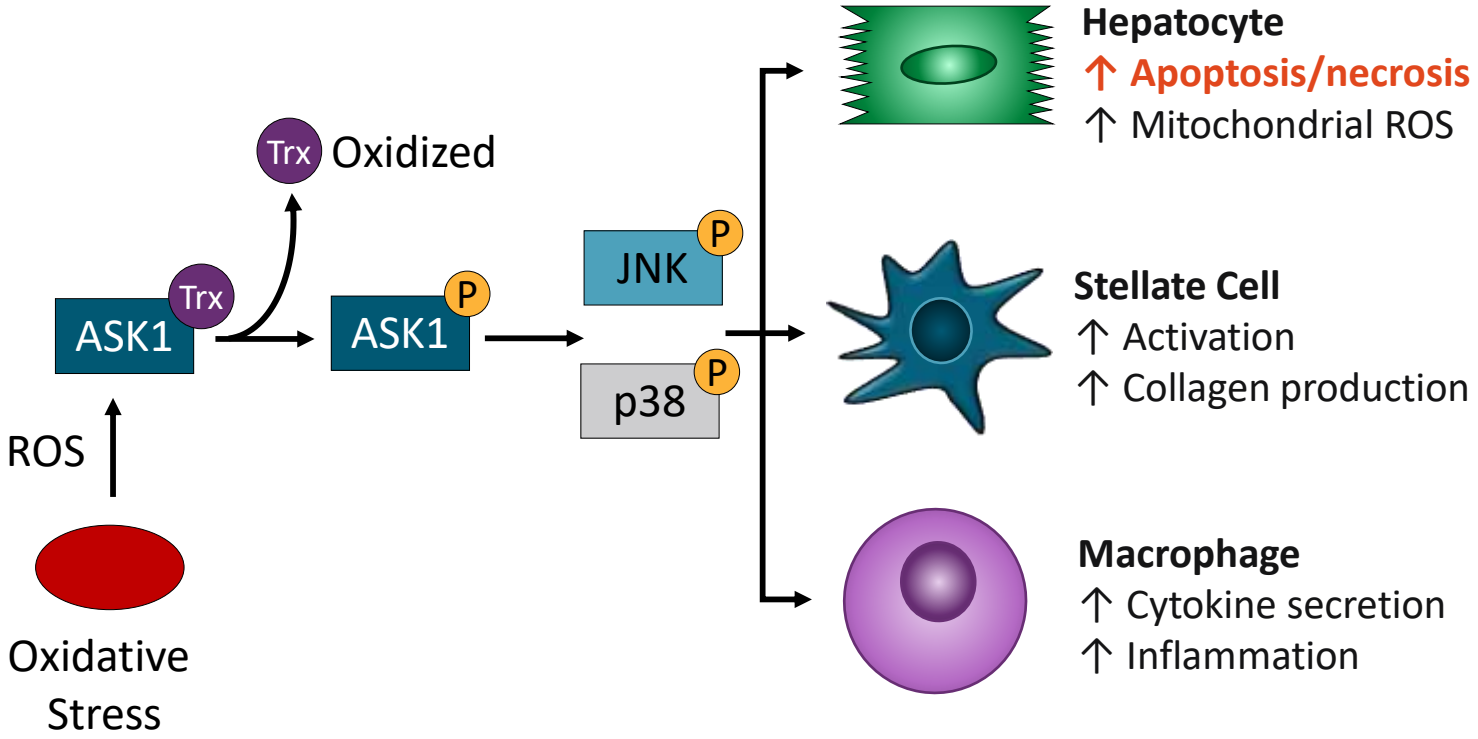
FLINT: Safety/Tolerability of Obeticholic Acid at Wk 72

- Clinical AEs generally mild to moderate, similar in the 2 groups for all symptoms except pruritus
- 33/141 (23%) of patients in obeticholic acid arm developed pruritus vs 9/142 (6%) in placebo arm ($P < .0001$)
  - Pruritus more severe in the obeticholic acid group
  - Led to the use of antipruritic medications ± short periods of withholding treatment in some patients
  - Treatment discontinuation in n = 1 patient in obeticholic acid group
- Liver enzymes, body weight, systolic blood pressure improved significantly with obeticholic acid vs placebo
- Higher TC, higher LDL-C, lower HDL-C with obeticholic acid vs placebo
  - Reversed after treatment discontinuation

Neuschwander-Tetri. Lancet. 2015;385:956.

Selonsertib

Selonsertib: ASK1 Inhibitor



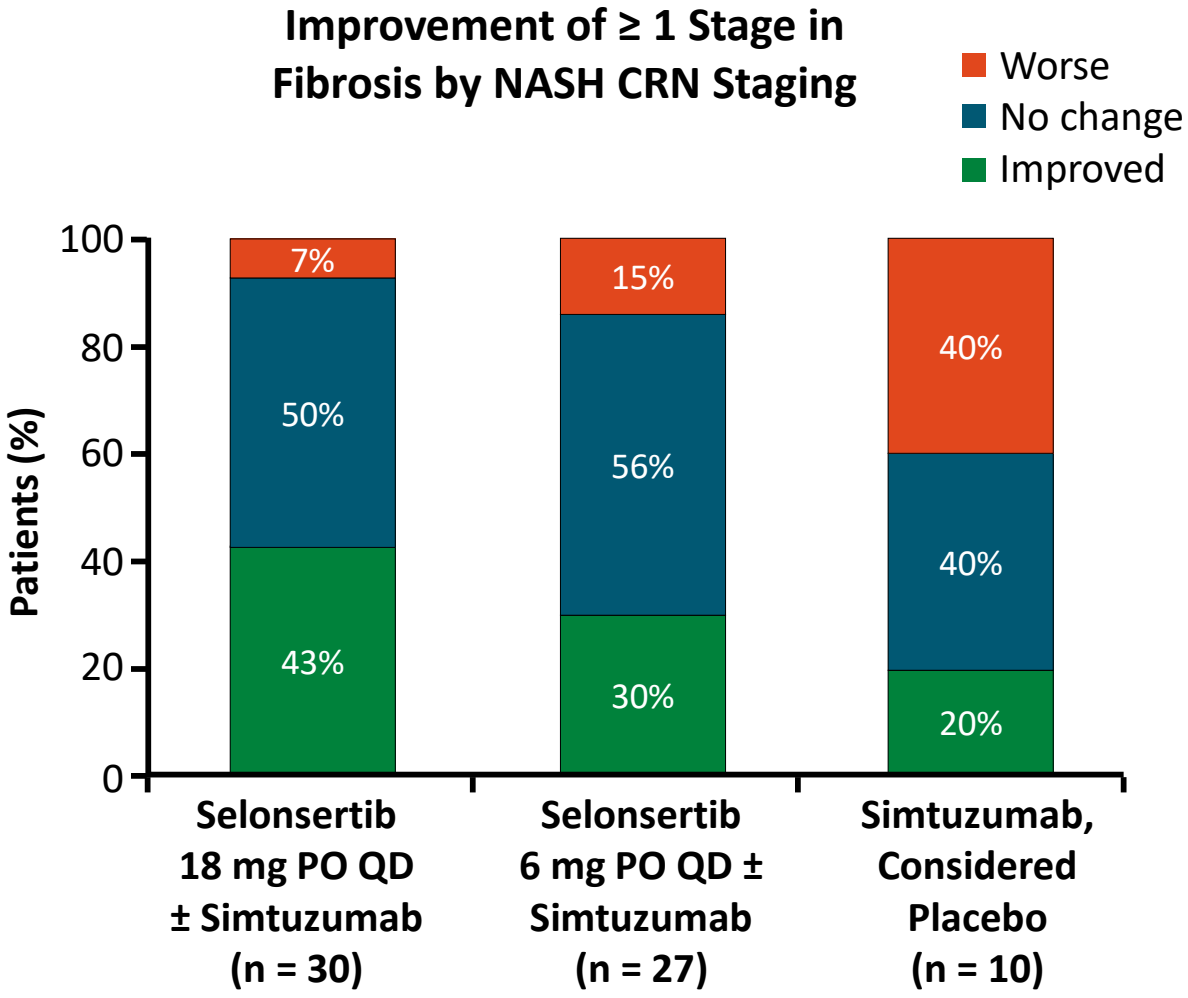
ASK1: Apoptosis Signal-Regulating Kinase

- Activated by oxidative stress
- **Promotes cell death,** fibrosis, and inflammation via JNK and p38 MAPK
- $ASK1^{-/-}$ mice are normal, protected in models of liver injury and fibrosis

Loomba. Hepatology. 2018;67:549.

Selonsertib: ASK1 Inhibitor in Patients With NASH at Wk 24

- Open-label phase II study in patients with biopsy-proven NASH, NAS ≥ 5, F2-F3 fibrosis (N = 72)
- Improvement in fibrosis associated with:
  - Reduction in liver stiffness by MRE
  - Reduction in collagen content and lobular inflammation on liver biopsy
  - Improvements in serum biomarkers of apoptosis and necrosis



Loomba. Hepatology. 2018;67:549.

Selonsertib: Safety and Tolerability at Wk 24

- Most AEs mild to moderate
  - 3 led to discontinuation in both selonsertib arms (worsening schizophrenia, numbness of face/upper extremities, elevated liver enzymes)
- 5 patients with serious AEs, all in selonsertib arms

Most Common AEs			
AE, n (%)	Selonsertib 18 mg ± Simtuzumab (n = 32)	Selonsertib 6 mg ± Simtuzumab (n = 30)	Simtuzumab (n = 10)
Headache	9 (28)	4 (13)	0
Nausea	6 (19)	4 (13)	0
Sinusitis	4 (13)	3 (10)	1 (10)
Nasopharyngitis	3 (9)	4 (13)	0
Upper abdominal pain	5 (16)	1 (3)	0
Fatigue	5 (16)	1 (3)	0

Investigational NASH Treatments in Phase II Trials

NASH Trial Endpoints

FDA: Liver Histologic Improvement Endpoints Likely to Predict Clinical Benefit

NASH Resolution

- **Resolution of steatohepatitis on overall histopathologic reading**

and

- **No worsening of liver fibrosis**

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage

and

- **No worsening of steatohepatitis**

1. US FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

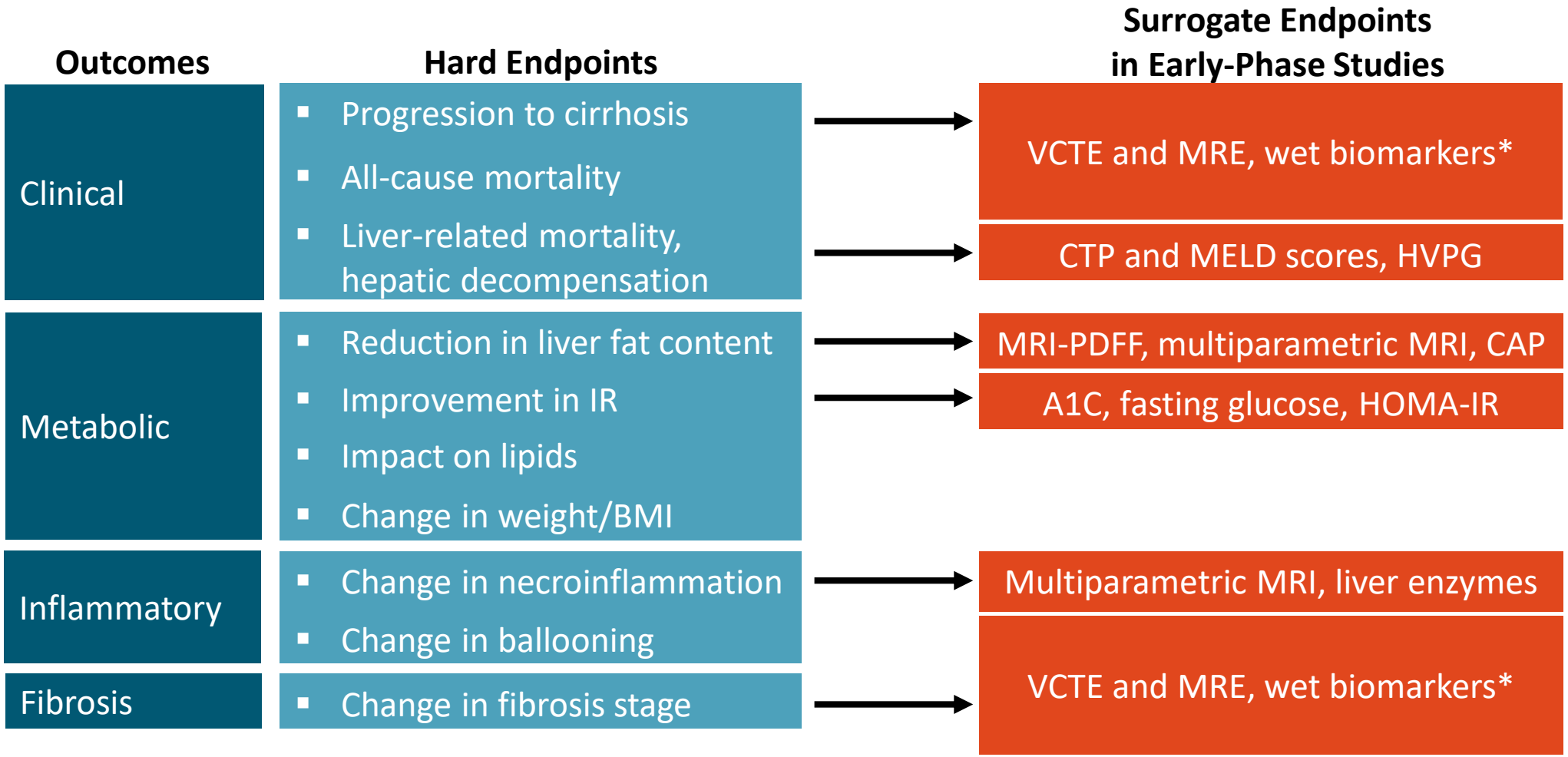
Endpoints for Outcome Measures in NASH

Outcomes	Hard Endpoints
Clinical	▪ Progression to cirrhosis ▪ All-cause mortality ▪ Liver-related mortality, hepatic decompensation
Metabolic	▪ Reduction in liver fat content ▪ Improvement in IR ▪ Impact on lipids ▪ Change in weight/BMI
Inflammatory	▪ Change in necroinflammation ▪ Change in ballooning
Fibrosis	▪ Change in fibrosis stage

- **Hard endpoints and clinical endpoints** may be challenging to measure owing to:
  - Slow disease progression
  - Liver biopsy limitations
- **Surrogate endpoints** used for conditional approval

Konerman. J Hepatol. 2018;68:362.

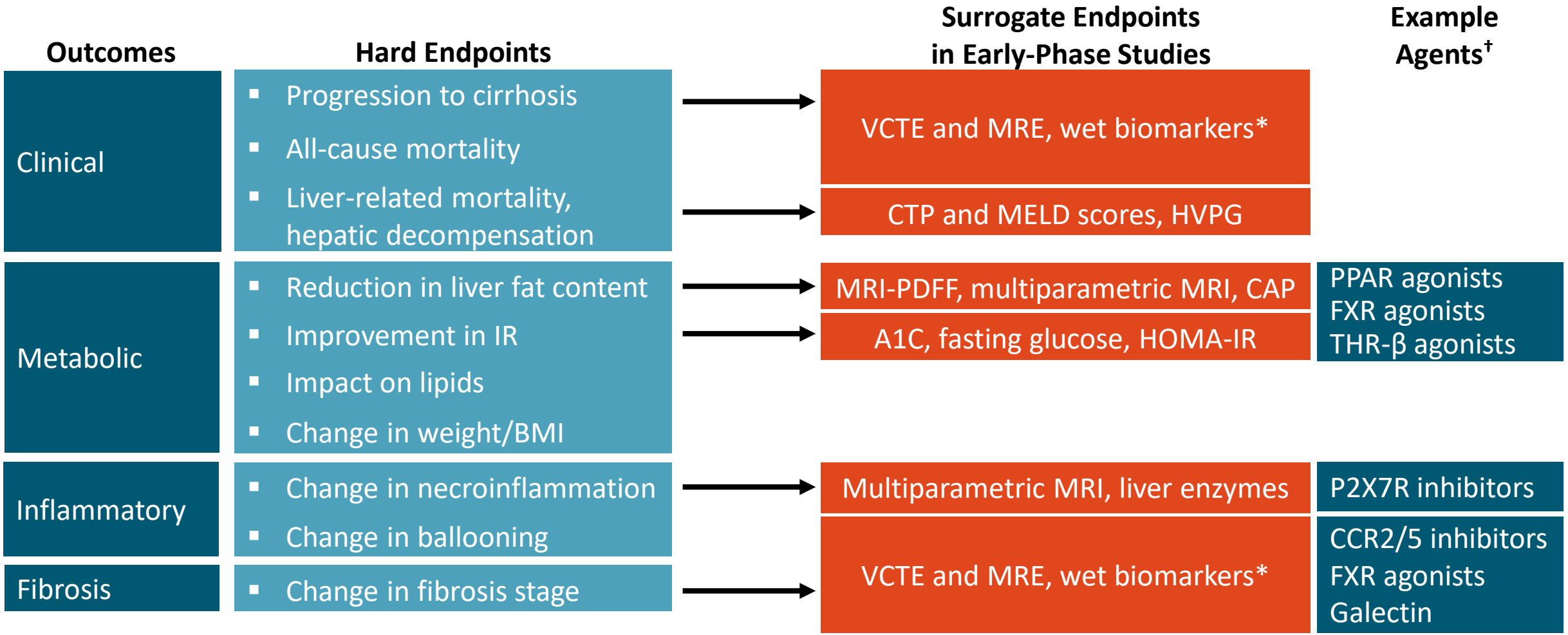
Endpoints for Outcome Measures in NASH



*eg, pro-C3, FIB-4, NFS, ELF.

Konerman. J Hepatol. 2018;68:362.

Endpoints for Outcome Measures in NASH Depend on Agent's Target(s)



*eg, pro-C3, FIB-4, NFS, ELF. †Some agents have multiple targets.

Konerman. J Hepatol. 2018;68:362.

NASH Clinical Trial Endpoints in Early Phase II Development

ALT

- 10 U/L reduction in ALT associated with histologic improvement or resolution of NASH[1]
- ≥ 17 U/L reduction predicted histologic response[2]

Liver Fat Fraction (MRI-PDFF)

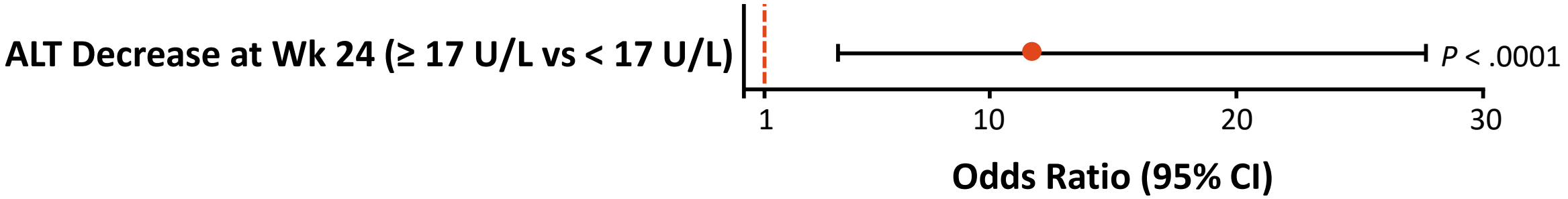
- ≥ 5% absolute reduction associated with improvement in steatosis[3]
- ≥ 30% relative reduction associated with improvement in MAFLD activity score without fibrosis worsening[4]

1. Vuppalanchi. Clin Gastroenterol Hepatol. 2014;12:2121. 2. Loomba. Gastroenterology. 2019;156:88.
3. Middleton. Gastroenterology. 2017;153:753. 4. Patel. Therap Adv Gastro 2016;9:692.

ALT: Correlation With Histologic Response

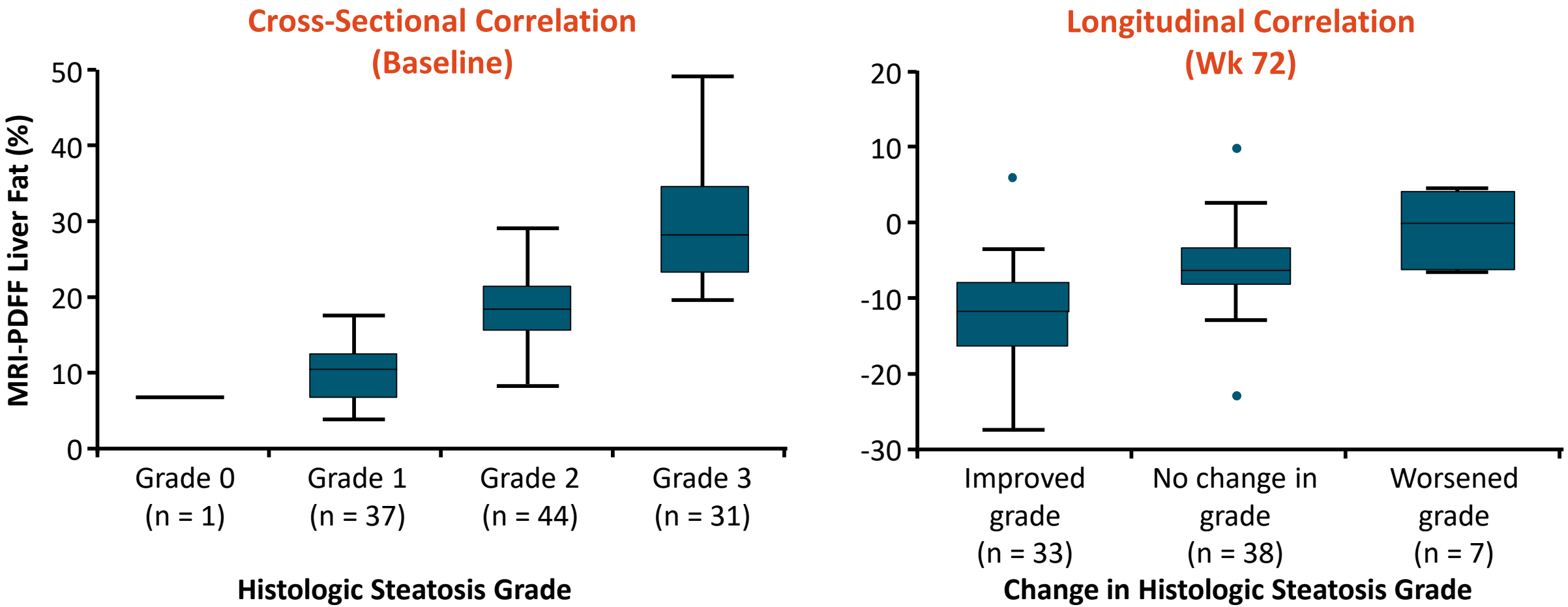
- Logistic regression model of factors associated with histologic response in a 72-wk study of obeticholic acid in adults with NASH (N = 283)
  - Histologic response: decrease in NAS by ≥ 2 points with no fibrosis worsening

ALT Decrease ≥ 17 U/L as Predictor of Histologic Response



Loomba. Gastroenterology. 2019;156:88.

Liver Fat by MRI-PDFF: Correlation With Steatosis Grade at Baseline and After Treatment



Median values given with IQRs, dots are outliers.

Middleton. Gastroenterology. 2017;153:753.

Table 5 | Therapies for non-alcoholic steatohepatitis (NASH) in late phase II development

Drug	Trial code; name (company)	No of patients	Study population	Route of delivery	Surrogate endpoint; time to endpoint	Primary endpoint
Metabolism modulators						
Aldafermin[145] (NGM282) (FGF19)	NCT03912532; ALPINE 2/3 (NGM)	152	NASH, fibrosis F2/F3	Subcutaneous	Biopsy; 24 weeks	% patients achieving histological treatment; safety and tolerability
BFKB8488A (bi-specific FGF21/ KLB ab)	NCT04171765; BANFF (Genentech)	260	NASH, fibrosis F2/F3; liver fat ≥8%	Subcutaneous	Biopsy; 52 weeks	NASH resolution without worsening of fibrosis
Icosabutate (structurally enhanced w-3 FA)	NCT04052516; ICONA (NorthSea)	264	NASH, fibrosis F1-F3, NAS ≥4; liver fat ≥10%	Oral	Biopsy; 52 weeks	NASH resolution without worsening of fibrosis
Lanifibranor [146] (pan-PPAR agonist)	NCT03008070; NATIVE (Inventiva)	247	NASH	Oral	Biopsy; 24 weeks	≥2 points reduction of SAF score without fibrosis progression
Licogliflozin (SGLT-1/2)	NCT03205150 (Novartis)	110	NASH, fibrosis F1-F3, elevated ALT or BMI ≥27 (Asian, ≥23); A_{1c} 6.5-10%	Oral	MRI; 12 weeks	Change in ALT
MSDC-0602K[147] (mTOT modulator, Insulin sensitizer)	NCT03970031; MMONARCh (Cirius)	402	NASH, fibrosis+T2D	Oral	Biopsy; 52 weeks	Change in HbA_{1c}; NASH resolution without worsening of fibrosis
Norursodeoxycholic acid [148] (homolog of ursodeoxycholic)	EudraCT2018-003443-31 (Dr Falk)	363	NASH, fibrosis	Oral	Biopsy; 72 weeks	NASH resolution without worsening of fibrosis
Pegbelfermin[149] (PEG-FGF21)	NCT03486899; FALCON 1 (BMS)	160	NASH, fibrosis F3; NAS score ≥1 for each NAS component	Subcutaneous (weekly)	Biopsy; 24 weeks	≥1 stage improvement of fibrosis; no worsening of NASH or NASH resolution; no worsening of liver fibrosis
Efruxifermin[150] (Fc-FGF21 fusion protein)	NCT03976401; BALANCED (Akero Ther.)	80	NASH, fibrosis F1-F3; ≥10% liver fat (MRI-PDFF); NAS score ≥4 (≥1 for each component)	Subcutaneous (weekly)	MRI; 12 weeks. Biopsy; 16 weeks	Change from baseline in hepatic fat fraction assessed by MRI-PDFF
Semaglutide[151] (GLP-1 receptor agonist)	NCT02970942 (Novo Nordisk)	320	NASH, fibrosis F2/F3; NAS ≥4	Subcutaneous	Biopsy; 72 weeks	NASH resolution without worsening of fibrosis
Tirzepatide[152] (dual GLP-1/GIP agonist)	NCT04166773; SYNERGY-NASH (Eli Lilly)	196	NASH, fibrosis F2/F3; BMI ≥27	Subcutaneous	Biopsy; 52 weeks	NASH resolution without worsening of fibrosis
VK2809[153] (THRβ agonist)	NCT04173065; VOYAGE (Viking)	337	NASH, fibrosis F1/F2/F3 NAS ≥4; liver fat ≥8%	Oral	Biopsy; 52 weeks	Change in liver fat
Anti-inflammatory, anti-fibrotic						
CC-90001 (JNK-1 inhibitor)	NCT04048876 (Celgene)	300	NASH, fibrosis <F4; NAS ≥4; BMI 35-45kg/$^{m}2$	Oral	Biopsy; 52 weeks	≥1 stage improvement of fibrosis
Tropifexor (FXR agonist)	NCT02855164; FLIGHT-FXR(Novartis)	351	NASH, elevated ALT; liver fat ≥10%	Oral	MRI; 12 weeks	Safety and change in ALT and AST

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; FA=fatty acid; Fc=fragment crystallizable region of IgG; FGF=fibroblast growth factor; FXR=farnesoid-X receptor; GIP=gastric inhibitory polypeptide; GLP-1=glucagon-like peptide-1; HbA_{1c}=glycated hemoglobin; JNK=c-Jun N-terminal kinases; KLB=βKlotho; MRI=magnetic resonance imaging; MRI-PDFF=magnetic resonance imaging derived proton density fat fraction; mTOT=mitochondrial target of thiazolidinediones; PEG=pegylated; PPAR=peroxisome proliferator activated receptor; SAF=Steatosis, Activity, Fibrosis; SDC-1=stearoyl-CoA desaturase modulator; SGLT=sodium-glucose cotransporter; T2D=type 2 diabetes; THRβ=thyroid hormone receptor β.

Phase II NASH Therapies With Biopsy Data

Agent	MoA	N	Primary Endpoint	Time Point
Aramchol [1,2]	SCD1 inhibitor	247	Percent change in the liver triglycerides concentration	52 wks
GR-MD-02[3]	Galectin-3 inhibitor	162	Reduction of hepatic venous pressure gradient (HVPG)	1 yr
MGL-3196[4]	THR-β agonist	125	Change in hepatic fat fraction assessed by MRI-PDFF	12 wks
NGM282[5,6]	FGF19 analogue	250	Change in hepatic fat fraction assessed by MRI-PDFF	12 wks

1. Ratziu. AASLD 2018. Abstr LB-5. 2. NCT02279524. 3. NCT02462967. 4.NCT02912260. 5. NCT02443116. 6. Harrison. Lancet. 2018;391:1174.

Example 1 of Liver Fat Endpoint: Aramchol

Wk 52 Outcome, % (n/N)	Placebo	Aramchol		
		400 mg	600 mg	*P* Value (600 mg vs Placebo)
≥ 5% absolute reduction in liver fat content by MR spectroscopy	24.4 (10/41)	36.7 (33/90)	47.0 (39/93)	.0279
Resolution of NASH without worsening fibrosis	5.0 (2/40)	7.5 (6/80)	16.7 (13/78)	.051
≥ 1 stage fibrosis improvement without worsening NASH	17.5 (7/40)	21.3 (17/80)	29.5 (23/78)	.211

Ratziu. AASLD 2018. Abstr LB-5.

Example 2 of Liver Fat Endpoint: MGL-3196

Change in Liver Fat Content by MRI-PDFF, %	Placebo (n = 38)		MGL-3196*			
			All Patients (n = 78)		High Exposure (n = 44)	
	Wk 12	Wk 36	Wk 12	Wk 36	Wk 12	Wk 36
Relative	-10	-8	-36	-37	-42	-49
Absolute	-1.6	-2.3	-7.6	-8.5	-8.8	-9.4
≥ 30% relative reduction	18	30	60	68	75	77

*P < .0001 vs placebo.

Change in Fibrosis or NASH by Biopsy, %	Placebo	MGL-3196	P Value
Reduction in fibrosis score ≥ 1 point			
▪ Second harmonic generation score	12	32	.03
▪ Pathology score	23	29	NS
Resolution of NASH	6	27	.02

Histology endpoints validate liver fat endpoints

Harrison. AASLD 2018. Abstr 14.

Phase II NASH Therapies With Biopsy Data

Agent	MoA	N	Primary Endpoint	Time Point
GR-MD-02[1]	Galectin-3 inhibitor	162	Reduction of hepatic venous pressure gradient (HVPG)	52 wks
Aramchol[2,3]	SCD1 inhibitor	247	Change in liver triglycerides by MR spectroscopy	52 wks
MGL-3196[4]	THR-β agonist	125	Change in hepatic fat fraction by MRI-PDFF	12 wks
NGM282[5,6]	FGF19 analogue	250	Change in hepatic fat fraction by MRI-PDFF	12 wks

- Potentially entering phase III in 2019

1. NCT02462967. 2. Ratziu. AASLD 2018. Abstr LB-5. 3. NCT02279524. 4. NCT02912260. 5. NCT02443116. 6. Harrison. Lancet. 2018;391:1174.

Drugs With Promise of Potential Benefit in Humans With NAFLD

Class	Drug
Incretin-based therapy	Liraglutide; exenatide; sitagliptin
SGLT2 inhibitor	Canagliflozin, ipragliflozin
PPAR agonists	Pioglitazone (PPARγ agonist); elafibranor (dual PPARα/δ agonist); saroglitazar (dual PPARα/γ agonist); MSDC-0602 (PPARγ sparing TZD)
FXR-bile acid axis	OCA (synthetic bile acid); GS-9674 (selective Farnesoid X receptor agonist); volixibat (ASBT inhibitor)

Townsend S, et al. *Aliment Pharmacol Ther*. 2017;46:494-507.

Drugs With Promise of Potential Benefit in Humans With NAFLD (cont)

Class	Drug
DNL/lipid	Aramchol (arachidic and cholic acid conjugate); NDI-010796 (acetyl Co-A carboxylase inhibitor); MGL-3196 (thyroid hormone receptor beta [THR-β] agonist)
Antioxidant	Vitamin E; cysteamine (aminothiol)
Targeting apoptosis	Emricasan (caspase inhibitor); selonsertib (ASK-1 inhibitor)
Anti-inflammatory	Cenicriviroc (C-C chemokine receptor types 2/5 antagonist)
Antifibrotic	Simtuzumab (LOXL2 antibody); GR-MD-02 (galectin inhibitor)
Dual therapies	Vitamin E + vitamin C; vitamin E + UDCA; selonsertib + simtuzumab; selonsertib + GS-9674

Townsend SA, et al. *Aliment Pharmacol Ther*. 2017;46:494-507.

Table 6 | Therapies for non-alcoholic steatohepatitis (NASH)-cirrhosis in late stage development

Drug	Trial code; name (company)	No of patients	Study population	Route of delivery	Surrogate endpoint; time to endpoint	Primary outcome
Aldafermin (NGM282) (FGF19)	NCT04210245; ALPINE 4 (NGM)	150	NASH, fibrosis F4 (compensated cirrhosis); liver fat ≥8% (MRI)	Subcutaneous	Biopsy; 48 weeks	≥1 stage improvement in fibrosis, no worsening of NASH; adverse events
Belapectin (galectin-3)	NCT04365868; NASH-CX (Galectin)	162	NASH, fibrosis F4; HVPG ≥6 mm Hg	Intravenous	HVPG; 52 weeks	Change in HVPG
Obeticholic acid (FXR agonist)	NCT03439254; REVERSE (Intercept)	919	NASH, fibrosis F4	Oral	Biopsy; 78 weeks	≥1 stage improvement of fibrosis, no worsening of NASH; or NASH resolution, no worsening of fibrosis
Pegbelfermin (PEG-FGF21)	NCT03486912; FALCON 2 (BMS)	152	NASH, fibrosis F4	Subcutaneous	Biopsy; 48 weeks	≥1 stage improvement of fibrosis, no worsening of NASH
Semaglutide SC (GLP-1 receptor agonist)	NCT03987451 (Novo Nordisk)	69	NASH, fibrosis F4; NAS ≥3; BMI ≥27; stiffness >14 kPa (MRE)	Subcutaneous	Biopsy; 48 weeks	≥1 stage improvement of fibrosis, no worsening of NASH

BMI=body mass index; FGF=fibroblast growth factor; FXR=farnesoid-X receptor; GLP-1=glucagon-like peptide-1; HVPG=hepatic vein pressure gradient; MRE=magnetic resonance elastography; MRI=magnetic resonance imaging; NAS=NAFLD activity score (sum of steatosis (0-3), lobular inflammation (0-3), hepatocellular ballooning (0-2); PEG=pegylated.

Table 1 | Comparative analysis of different guidelines on non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)

Recommendation	EASL-EASD-EASO[5]	AASLD[4]	NICE[73]	Asian-Pacific[74 75]
Diagnosis (after excluding alcohol and secondary causes)	Steatosis by imaging or histology or unexpectedly high liver enzymes	Steatosis by imaging or histology	Any evidence of excessive liver fat, regardless of liver enzymes. Use Fatty Liver Index if testing adults for NAFLD	Steatosis by ultrasonography or transient elastography as first step (where available)
Community screening	Not cost effective	Not considered	Non-effective	Cost effectiveness unknown
Screening in high risk patients	All patients with one or more features of metabolic syndrome	Not mentioned	Not mentioned. Consider that NAFLD is common in type 2 diabetes and metabolic syndrome	Consider in patients with type 2 diabetes and obesity
Screening by non-invasive tests	NFS or FIB-4, followed by elastography	NFS, FIB-4, and elastography	ELF test	Biomarkers and imaging effective (no specific test)
Genetic screening	Not cost effective	Not mentioned	Not mentioned	Cost effectiveness unknown
Screening for complications	Define cardiovascular and diabetes risk	Define cardiovascular and diabetes risk	Define cardiovascular and diabetes risk	Define presence of all features of metabolic syndrome
Follow-up	Not at risk of progression, every 2 years; at risk, every 6 months	Not defined	Every 3 years in patients not at risk of progression; if at risk, use NICE guidelines for cirrhosis	Not mentioned
Liver biopsy	Mandatory in drug trials	Consider in patients at risk for NASH or advanced fibrosis and/or to exclude other coexisting liver disease	Gold standard, but not feasible also in patients at risk	When the diagnosis is unclear or when fibrosis assessment by non-invasive tests is inconclusive
Treatment: diet and weight loss	Dietary restriction (deficit 500-1000 kcal/day). Prefer Mediterranean diet	Dietary restriction (deficit 500-1000 kcal/day). No specific diet	Consider NICE guidelines for obesity and weight gain prevention. No specific diet	Consider multidisciplinary approach. Dietary restriction (deficit 500-1000 kcal/day)
Treatment: physical activity	Aerobic or exercise training (150-300 min/week), 3-5 sessions	Aerobic or exercise training (>150 min/week)	Consider NICE guidelines for obesity and weight gain prevention	Aerobic or resistance exercise (moderate intensity ≥150 min/week or vigorous intensity ≥75)
Treatment: drugs	Pioglitazone (off-label in absence of diabetes). Vitamin E not indicated. Other drugs not indicated	Pioglitazone and vitamin E in patients with/without diabetes, respectively. Other drugs not indicated	Consider pioglitazone in diabetic and vitamin E in non-diabetic cases with advanced fibrosis (only in secondary or tertiary care settings)	Consider pioglitazone for short term use in diabetes or prediabetes. Consider vitamin E in non-cirrhotic, non-diabetic NASH. Other drugs not indicated

AASLD=American Association for the Study of Liver Diseases; EASL=European Association for the Study of the Liver/European Association for the Study of Diabetes/European Association for the Study of Obesity; ELF=Enhanced Liver Fibrosis; FIB-4=Fibrosis-4 index; NFS=NAFLD Fibrosis Score; NICE=National Institute for Health and Care Excellence.

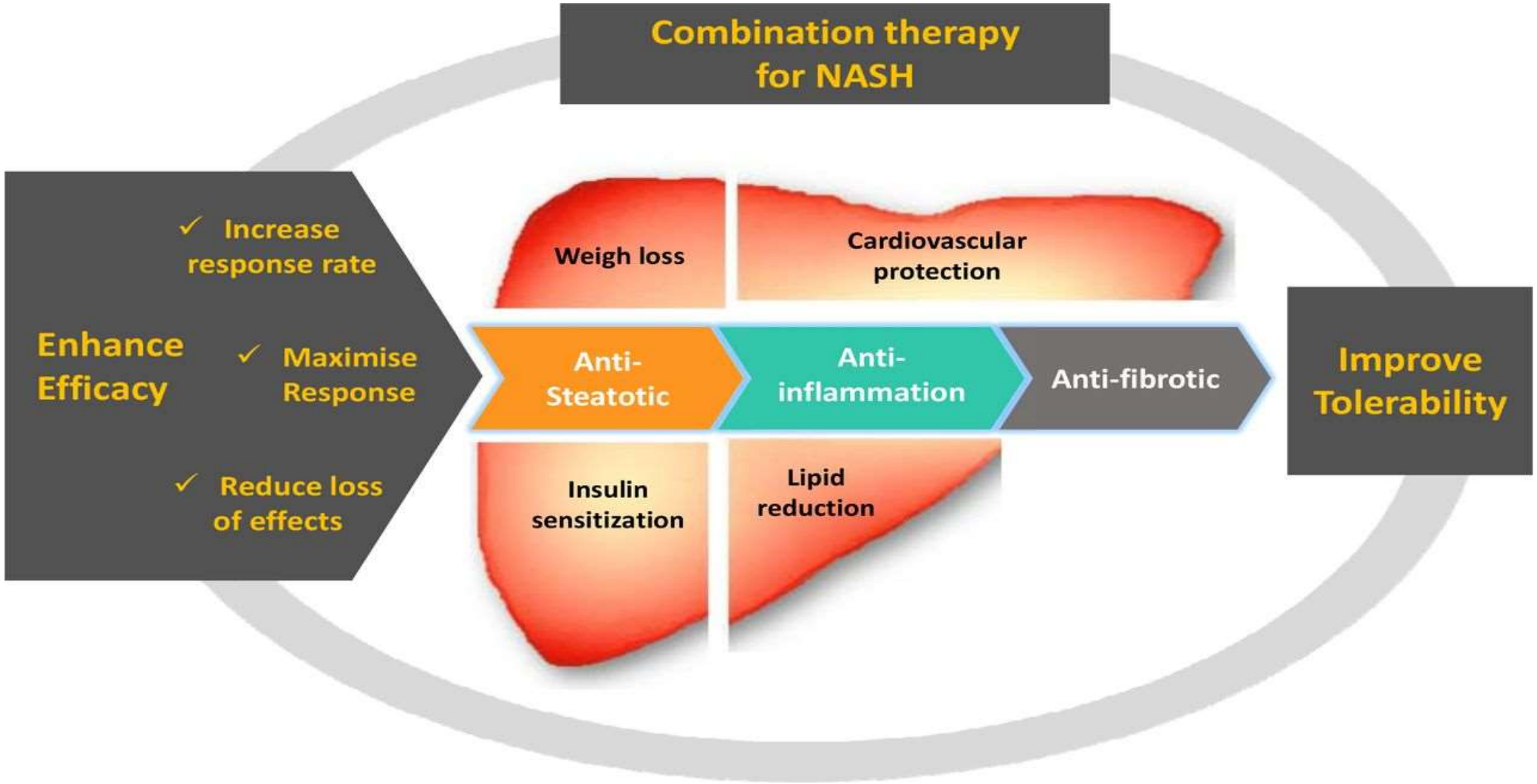
EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease

- Structured programmes aimed at lifestyle changes towards healthy diet and habitual physical activity are advisable in NAFLD (**C2**)
- Patients without NASH or fibrosis should only receive counselling for healthy diet and physical activity and no pharmacotherapy for their liver condition (**B2**)
- In overweight/obese NAFLD, a 7–10% weight loss is the target of most lifestyle interventions, and results in improvement of liver enzymes and histology (**B1**)
- Dietary recommendations should consider energy restriction and exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose. The macronutrient composition should be adjusted according to the Mediterranean diet (**B1**)
- Both aerobic exercise and resistance training effectively reduce liver fat. The choice of training should be tailored based on patients' preferences to be maintained in the long-term (**B2**)

- Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression (i.e. with diabetes, MetS, persistently increased ALT, high necroinflammation) could also be candidates to prevent disease progression (**B1**)
- While no firm recommendations can be made, pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short-term) or their combination could be used for NASH (**B2**)
- The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy; in patients with normal ALT at baseline, no recommendations can be made (**C2**)
- Statins may be confidently used to reduce LDL-cholesterol and prevent cardiovascular risk, with no benefits or harm on liver disease. Similarly *n*-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH (**B1**)

Journal of Hepatology **Volume 64 Issue 6 Pages 1388-1402 (June 2016)**

Rationale for combination therapy to treat non-alcoholic steatohepatitis (NASH).



Jean-François Dufour et al. Gut 2020;69:1877-1884

Summary

- Multiple pharmacologic targets in development for NASH
- 2 FDA approvable histologic endpoints for **phase III** trials
  - **Resolution of NASH** without worsening of fibrosis
  - **Improvement of fibrosis** without worsening of NASH
- Depending on MoA, various noninvasive surrogate markers in early-phase development
- Appropriately powered, dose-ranging phase II studies with paired liver biopsies required prior to phase III
- Adaptive trial design provides opportunity to speed drug development

Management of non-alcoholic fatty liver disease

Maria Letizia Petroni,[1] Lucia Brodosi,[1] Elisabetta Bugianesi,[2*] Giulio Marchesini[1*]

[1]Department of Medical and Surgical Sciences, "Alma Mater" University, IRCCS Policlinico Sant'Orsola, Bologna, Italy
[2]Division of Gastro-Hepatology, University of Turin, Turin, Italy
*Contributed equally
Correspondence to:
G Marchesini
giulio.marchesini@unibo.it

Cite this as: *BMJ* 2021;372:m4747
http://dx.doi.org/10.1136/bmj.m4747

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors.

Additional material is published online only. To view please visit the journal online.

ABSTRACT

Non-alcoholic fatty liver disease is a very common medical condition, driven by a combination of genetic and lifestyle factors, ultimately producing a severe chronic liver disease and increased cardiovascular risk. Most people are asymptomatic for a long time, and their daily life is unaffected, leading to difficulty in identifying and managing people who slowly progress to non-alcoholic steatohepatitis (NASH), NASH-cirrhosis, and eventually hepatocellular carcinoma. Despite advances in the understanding of pathogenic mechanisms and the identification of liver fibrosis as the strongest factor in predicting disease progression, no specific treatments have been approved by regulatory agencies. Outside controlled trials, treatment is generally limited to lifestyle intervention aimed at weight loss. Pioglitazone remains the drug of choice to reduce progression of fibrosis in people with diabetes, although it is often used off-label in the absence of diabetes. Vitamin E is mainly used in children and may be considered in adults without diabetes. Several drugs are under investigation according to the agreed targets of reduced NASH activity without worsening of fibrosis or improving fibrosis without worsening of NASH. Anti-inflammatory, anti-fibrotic agents and metabolism modulators have been tested in either phase III or phase IIb randomized controlled trials; a few failed, and others have produced marginally positive results, but only a few are being tested in extension studies. The development of non-invasive, easily repeatable surrogate biomarkers and/or imaging tools is crucial to facilitate clinical studies and limit liver biopsy.

Effective Lifestyle Modifications for PCOS and Fatty Liver