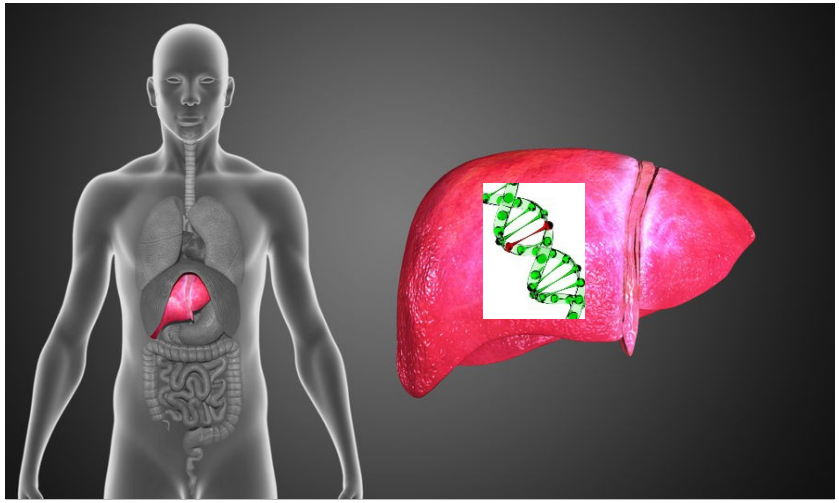
Future therapeutics for NASH



Arun J. Sanyal M.B.B.S., M.D.

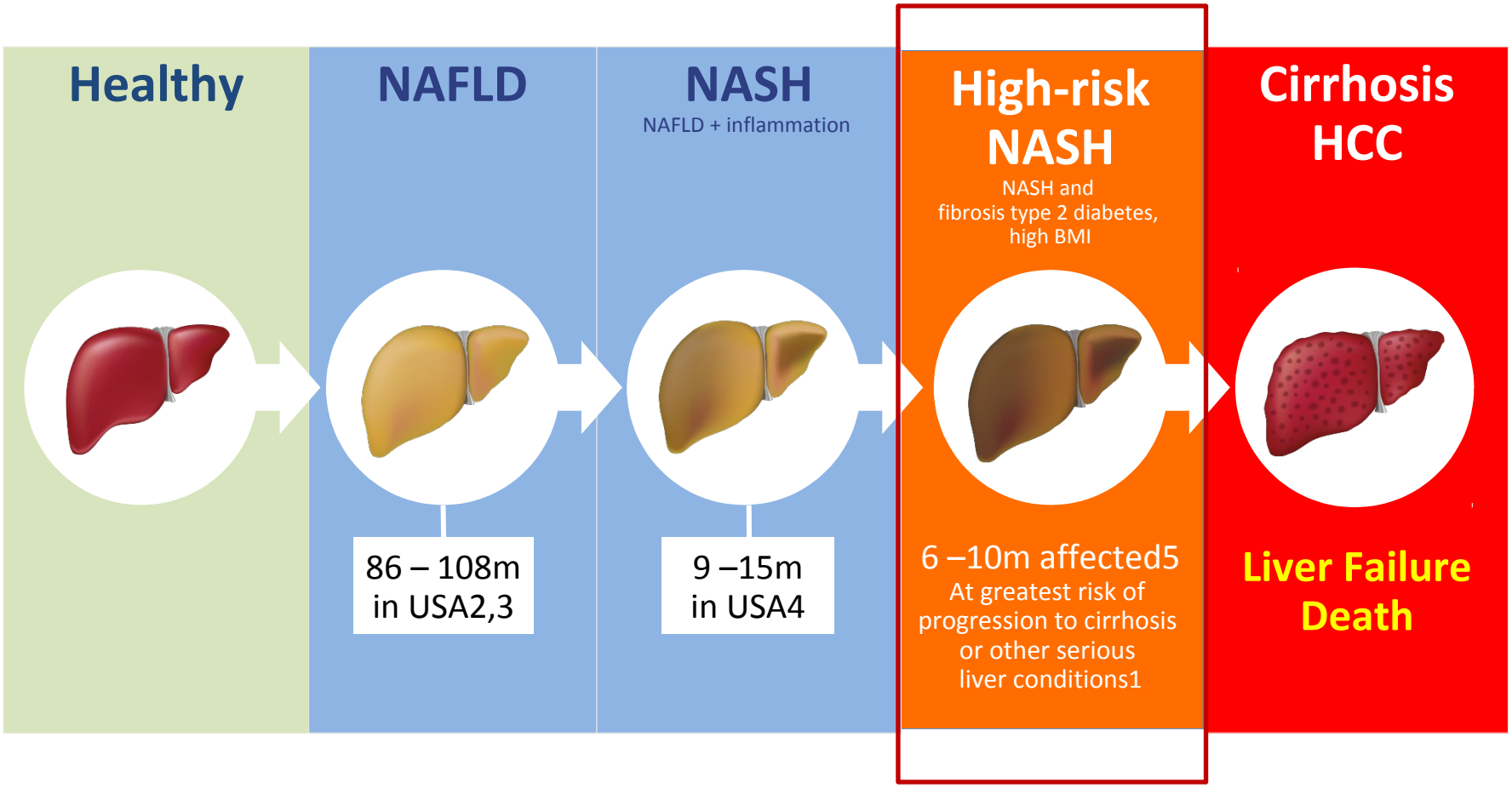
Z. Reno Vlahcevic Professor of Medicine, Physiology and Molecular Pathology

Virginia Commonwealth University School of Medicine

Conflicts of Interest

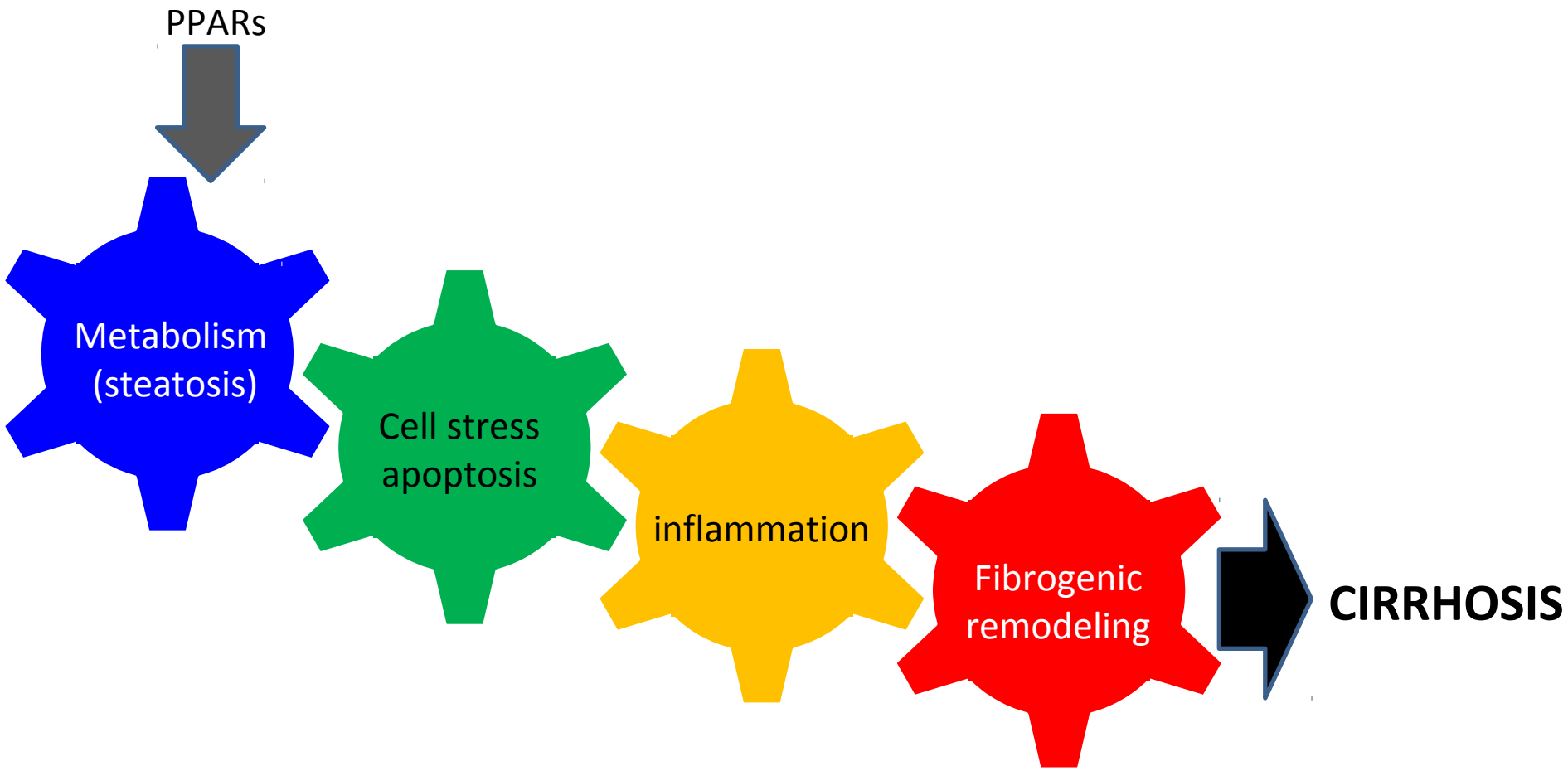
- President, Sanyal Biotechnologies
- Stock options: Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, Hemoshear
- Advisor with compensation: Lilly, Pfizer, Novartis, Ardelyx, Salix, Hemoshear
- Advisor without compensation: Galectin, Intercept, Merck, Bristol Myers, Immuron, Gilead, Chemomab, Affimmune, Protalix, Nitto Denko, Novo Nordisk, Cirius, Boehringer Ingelhiem
- Grants to institution: Gilead, Tobira, Allergan, Merck, Bristol Myers, Astra Zeneca, Immuron, Intercept, Novo Nordisk, Shire, Boehringer Ingelhiem, Cirius

NASH: who to treat?

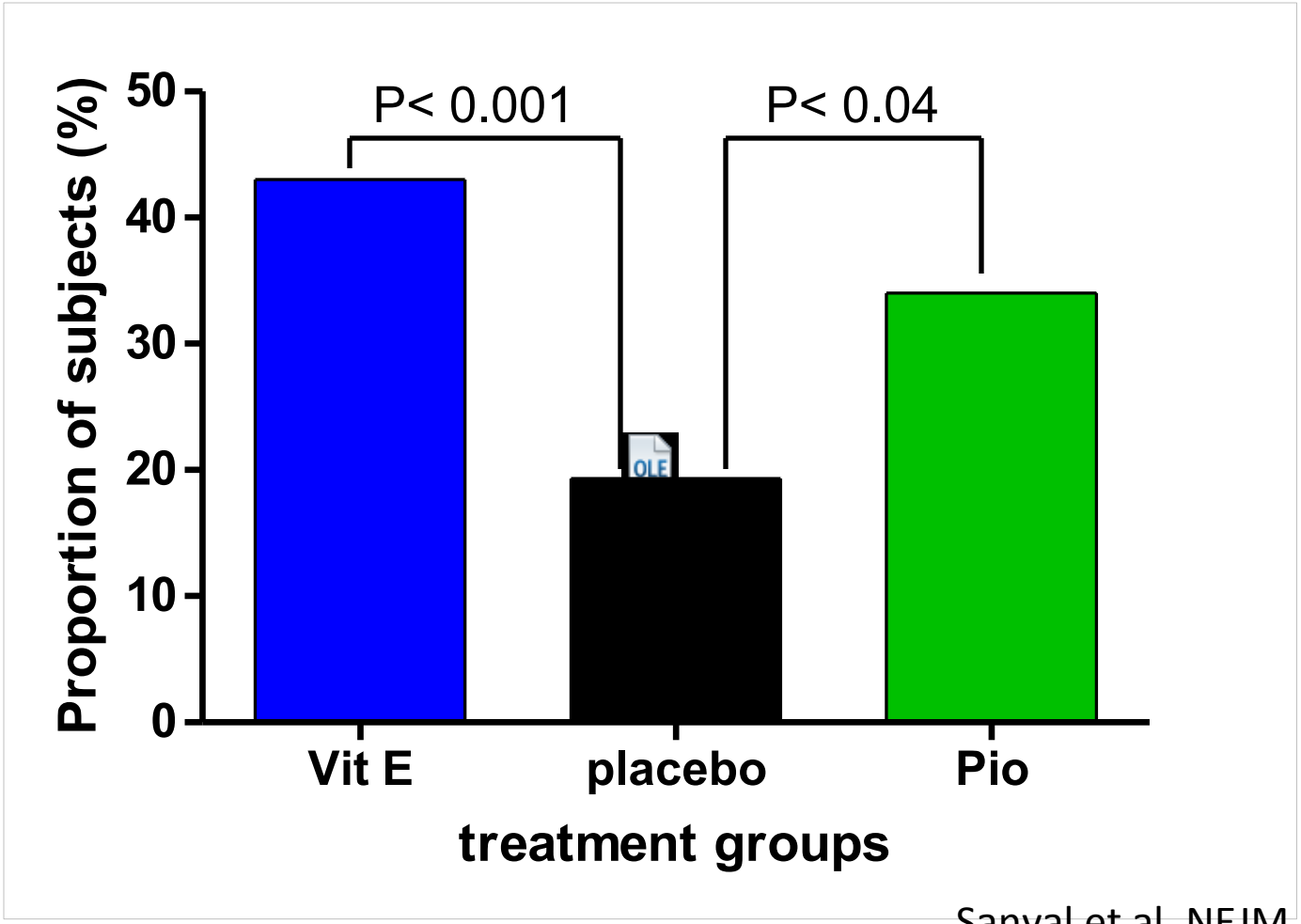


Goals of therapy

- Improve all cause mortality, quality of life and functional outcomes:
  - cardiovascular outcomes
  - liver related outcomes
  - cancer related outcomes

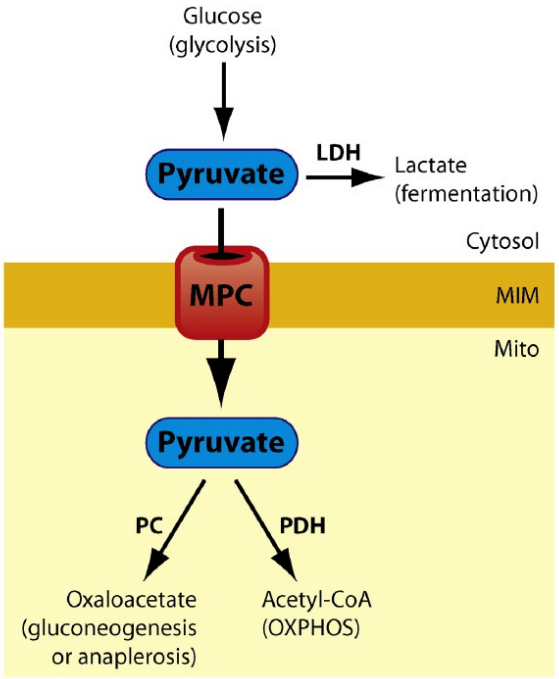

PPARs
Metabolism (steatosis)
Cell stress apoptosis
inflammation
Fibrogenic remodeling
CIRRHOSIS

Thiazolidinediones for NASH



Sanyal et al, NEJM 2010

Mitochondrial target of thiazolidinediones (mTOT)



Effects on pathways that impact NASH and Diabetes

Liver (direct and indirect effects on multiple cell types)

Hepatocytes
- Reduced lipid storage, increased fat oxidation
- Improved insulin sensitivity
- Decreased glucose production

Stellate cells
- Reduced inflammation
- Reduced stimuli for scarring

Macrophages
- Reduced inflammation

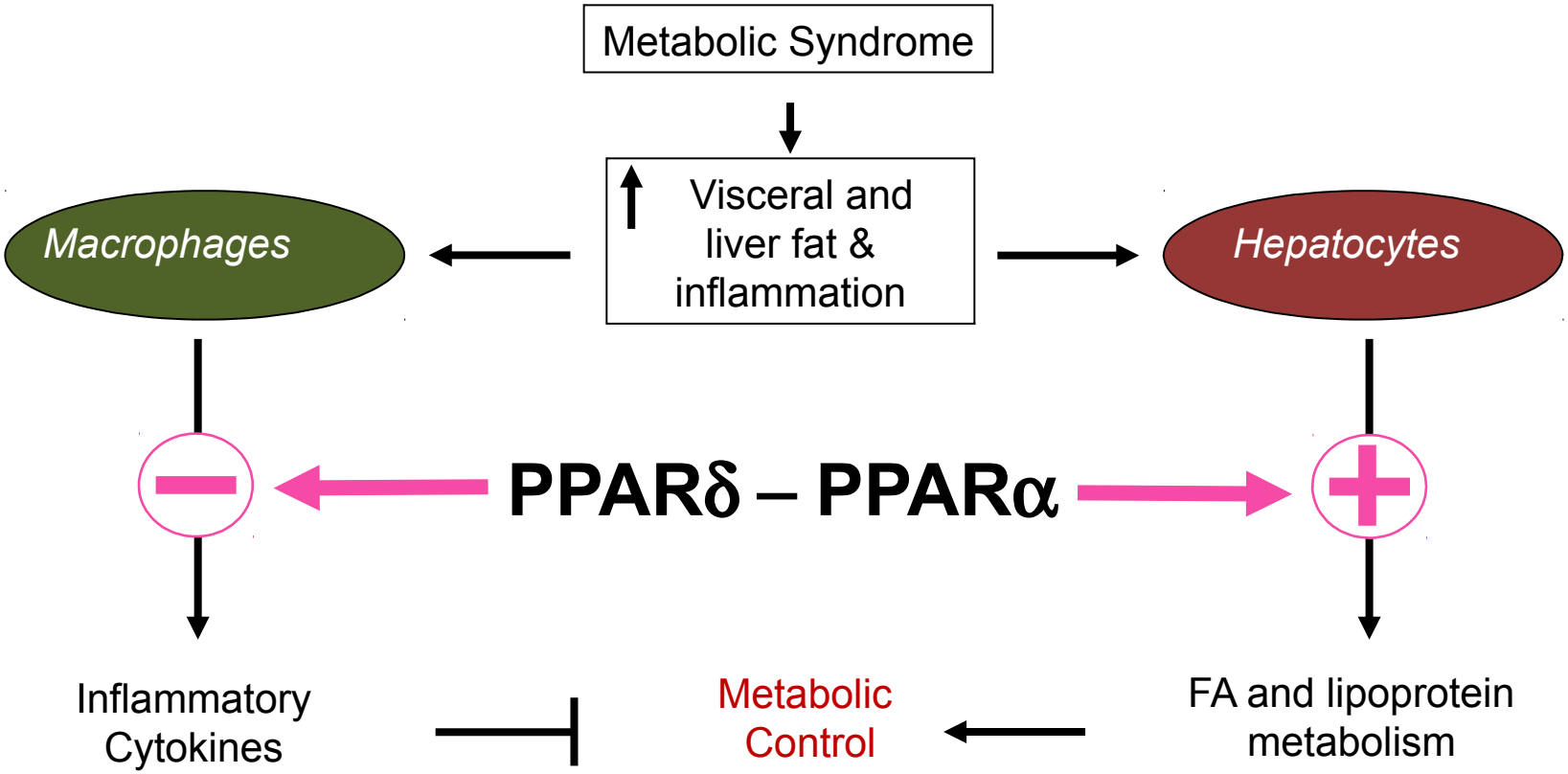
Muscle
- Decreased fat content
- Increased insulin sensitivity

Fat
- Decreased inflammation, increased adiponectin
- Increased insulin sensitivity

Pancreas
- Preservation of b-cell phenotype

Chen et al, J Biol Chem. 2012 287(28):23537-48.

Improvement of NASH by PPARα/δ activation



Tailleux, Wouters & Staels BBA 2012 ;1821:809-18

Primary outcome (based on FDA definition)

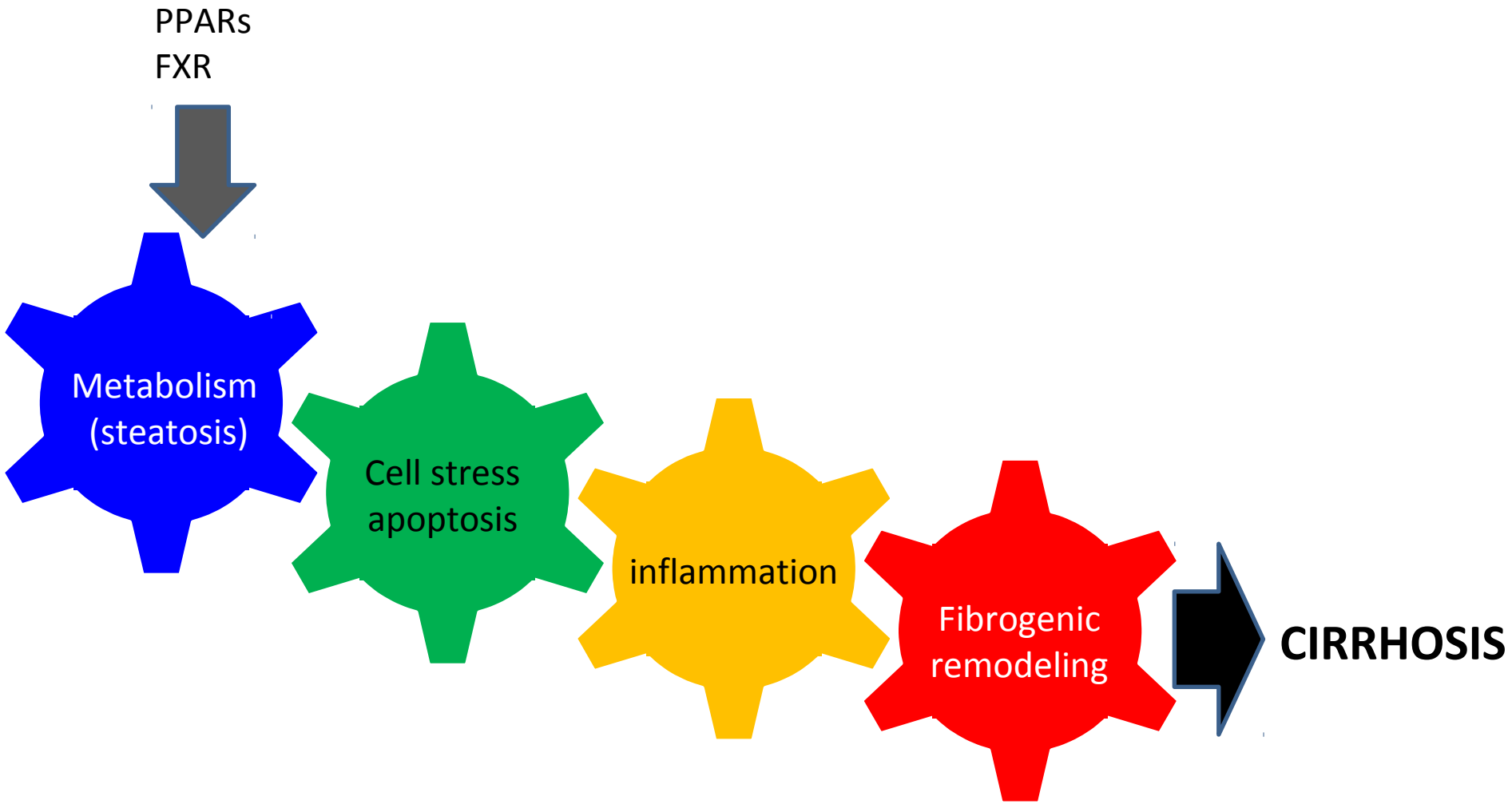
Efficacy on NAS≥4 at various stage of fibrosis

		Placebo	Elafibranor 80mg	Elafibranor 120mg	OR* [CI 95%]	p-value*
All NAS≥4 (F0-F1-F2-F3)	FAS, N=234	9%	13%	19%	3·52 [1·32,9·40]	0·013
	EES, N=202	11%	15%	21%	3·26 [1·17, 9·02]	0·024
NAS≥4 (F1-F2-F3)	FAS, N=204	11%	15%	20%	3·75 [1·39,10·12]	0·009
	EES, N=176	13%	17%	22%	3·22 [1·15, 8·99]	0·026
NAS≥4 (F2, F3)	FAS, N=118	7%	10%	13%	18·46 [4·80,70·96]	0·0001
	EES, N=99	9%	12%	15%	10·59 [2·52,44·50]	0·002

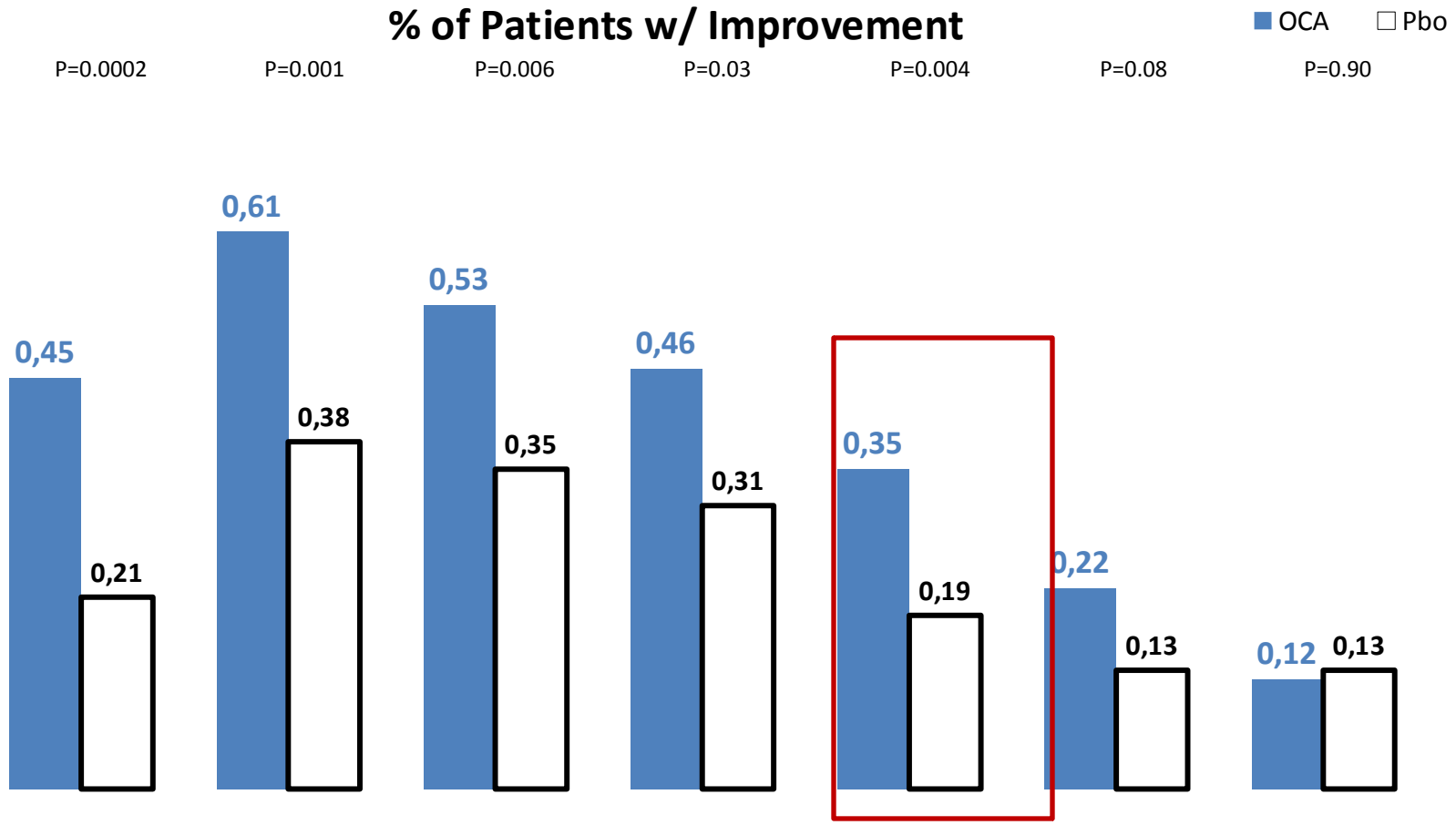
* comparison Elafibranor-120 mg vs Placebo

The 120 mg dose was effective in subpopulations of patients with any fibrosis (F1-F3), as well as in those with moderate or advanced fibrosis (F2-F3)

Ratziu et al, Gastroenterology 2016


PPARs
FXR
Metabolism
(steatosis)
Cell stress
apoptosis
inflammation
Fibrogenic
remodeling
CIRRHOSIS

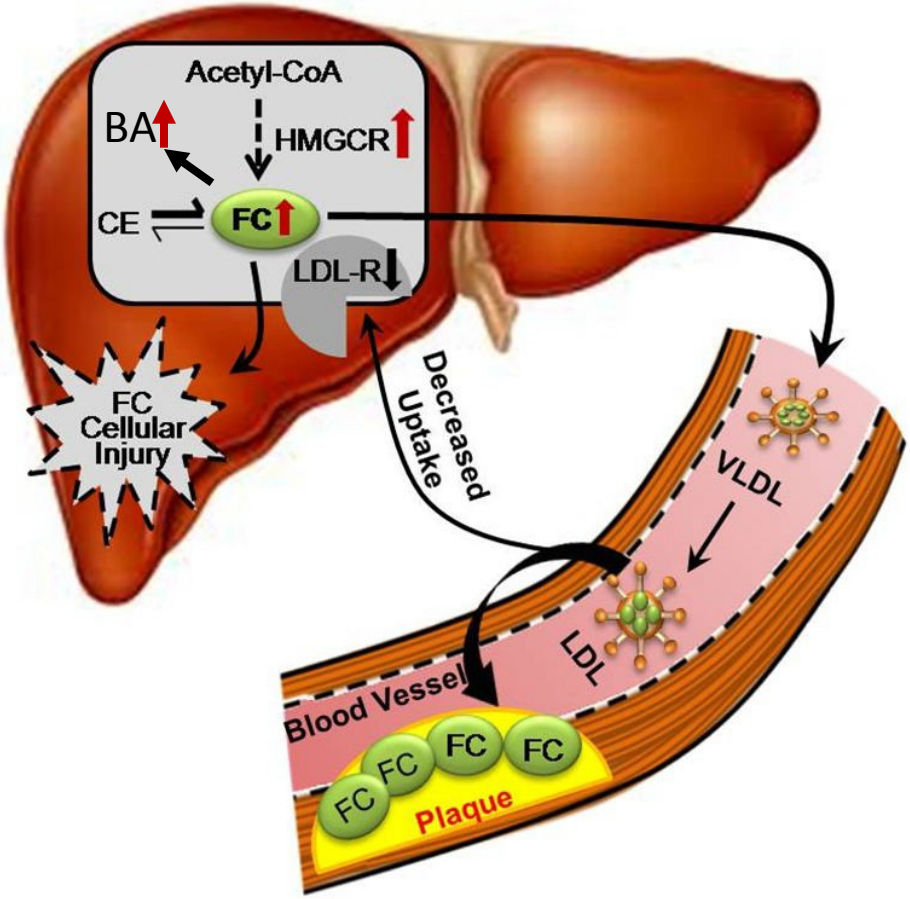
Effect of OCA on steatohepatitis



1: Data from Tetri et al. *The Lancet*. Published online November 7, 2014.

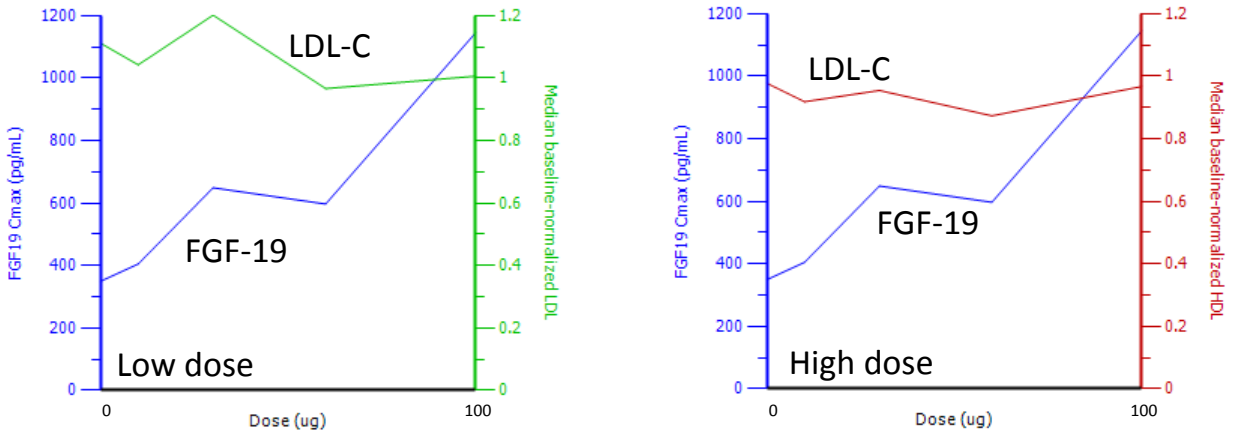
2: All p-values compared to placebo. P-value calculated with the Cochran-Mantel-Haenszel test, stratified by clinic and diabetes status.

A model for how NASH may affect LDL-C mediated atherogenesis



Min et al, Cell Metabolism, 2012

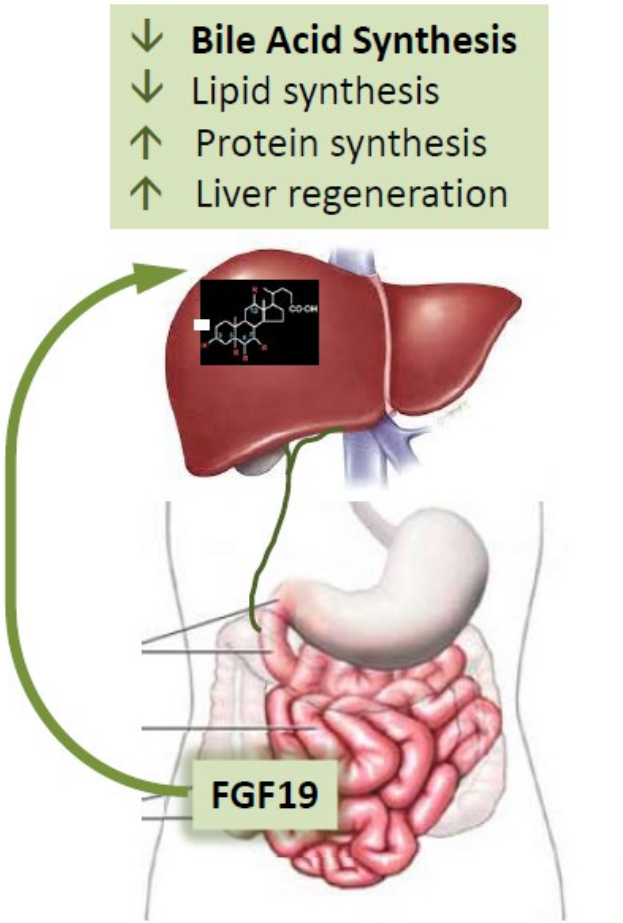
LJN 452: first human experience

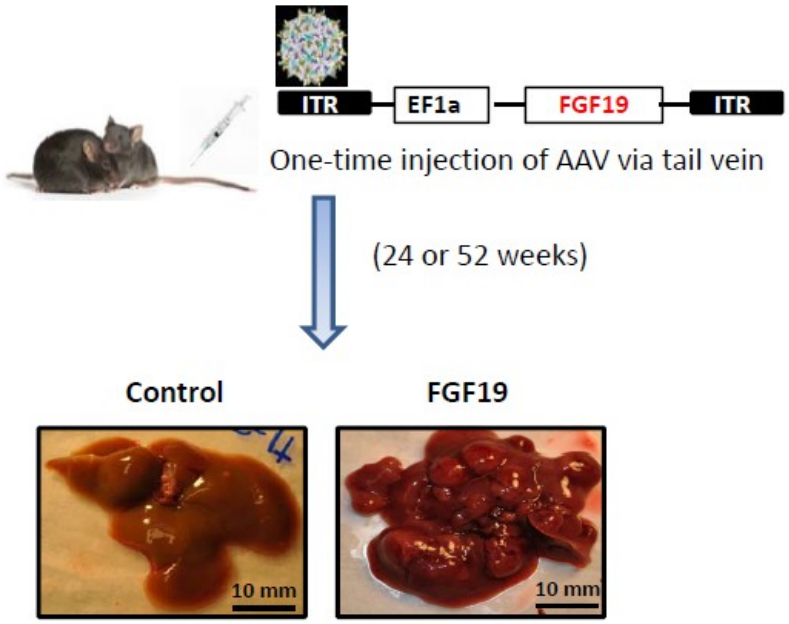


- Rationale: to de-risk the FXR pathway
- Single ascending dose and Multiple ascending dose
- Safe, well tolerated and transient dose-dependent increase in FGF-19, a marker of intestinal FXR engagement noted without LDL-C rise

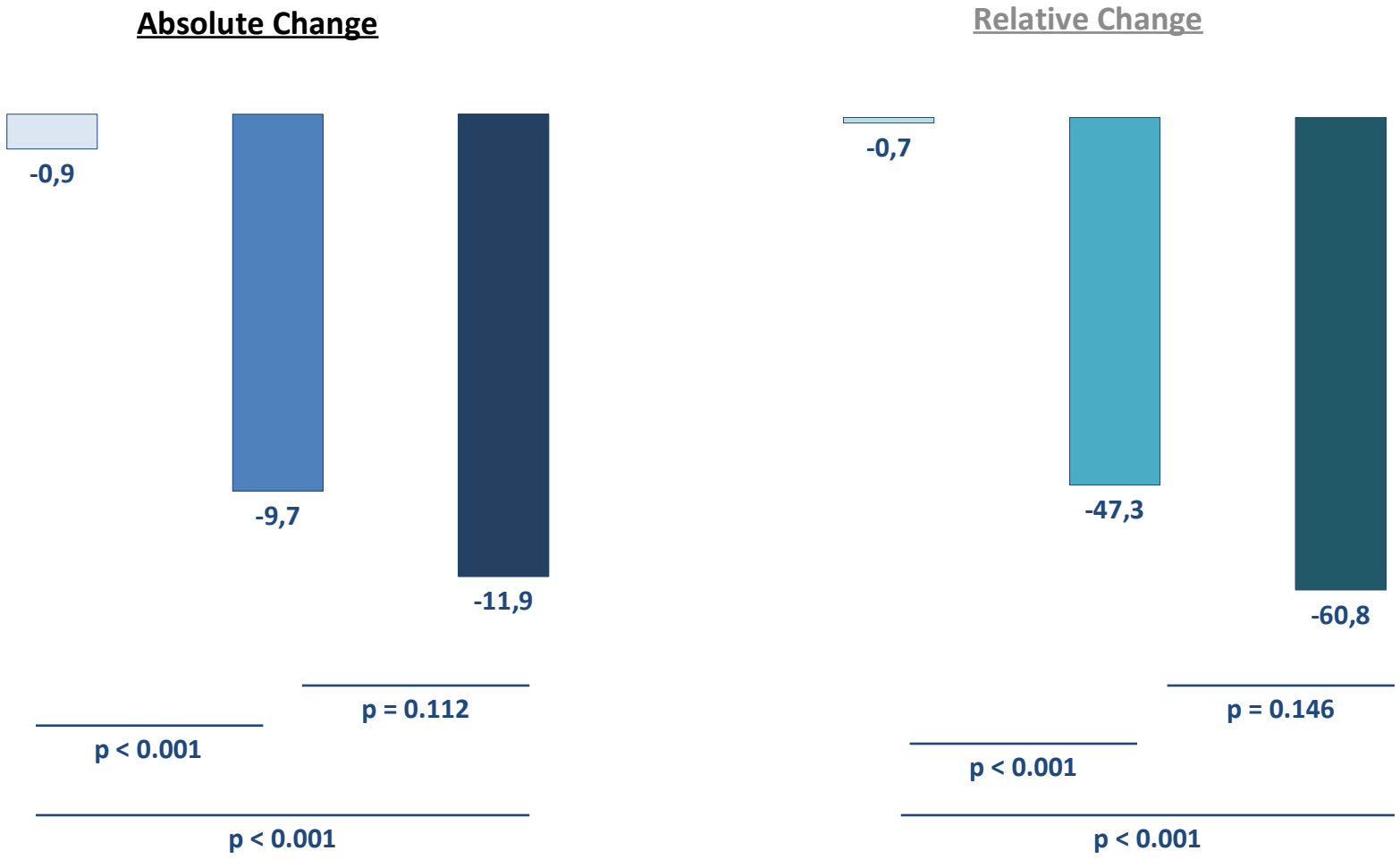
Abstract # 32: Badman et al, Novartis Institutes for Biomedical Research, AASLD

FGF19 is a Key Component of the Gut-Liver Axis in Regulating Metabolism



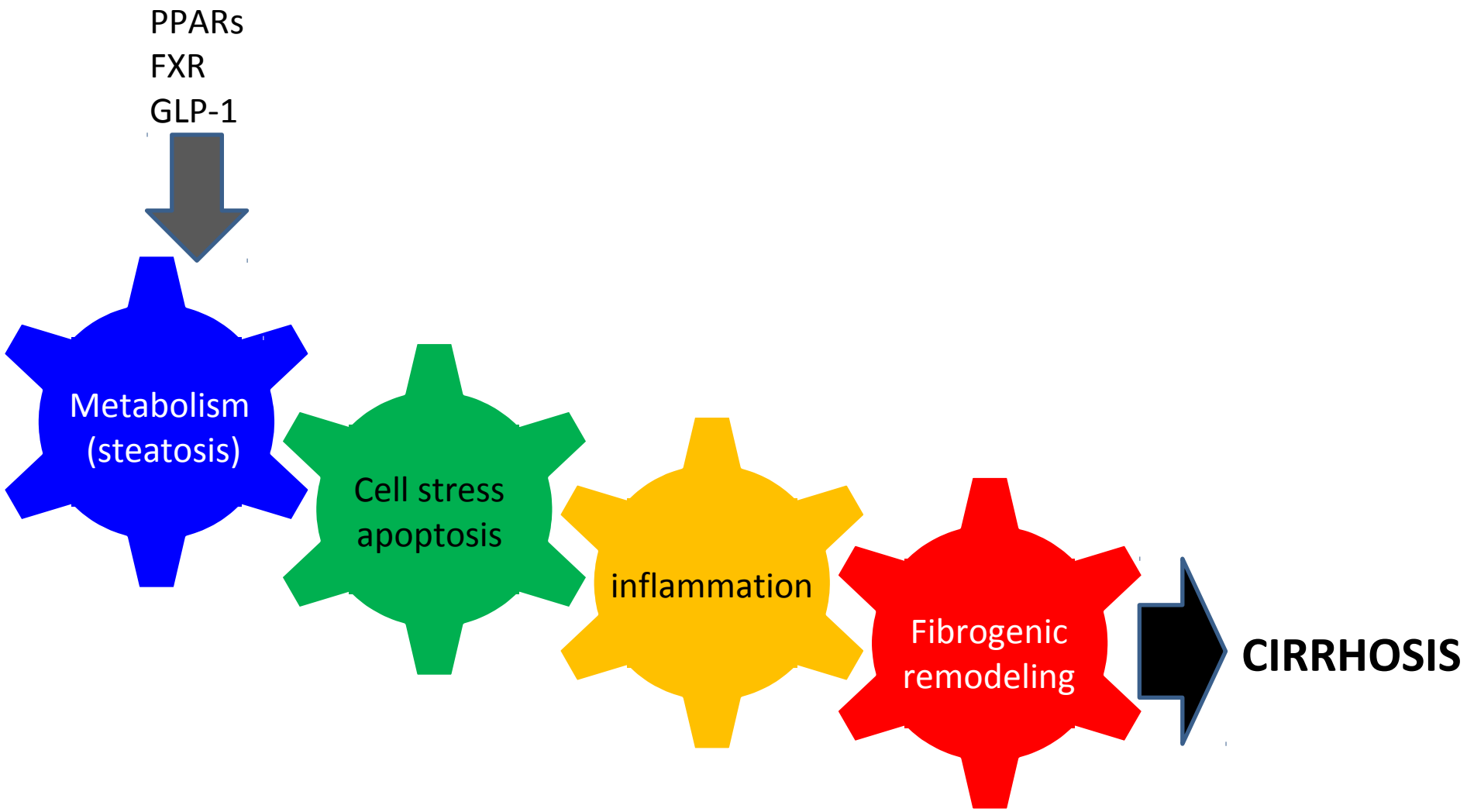


Primary Endpoint Met with Clinically Meaningful Changes in Liver Fat Content



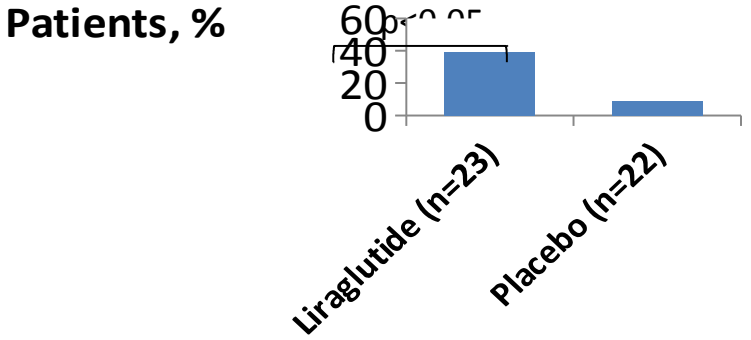
Decreases in liver fat strongly correlate with a reduction in ALT, AST and C4

Harrison et al, EASL 2017


PPARs
FXR
GLP-1
Metabolism (steatosis)
Cell stress apoptosis
inflammation
Fibrogenic remodeling
CIRRHOSIS

Liraglutide improved NASH in a multicenter, double-blinded, randomised, placebo-controlled phase II trial

Primary endpoint: NASH resolution with no worsening of fibrosis



Secondary endpoints

	Liraglutide (n=23)	Placebo (n=22)
Kleiner fibrosis	-0.2 (0.8)	0.2 (1.0)
Improvement, n (%)	6 (26.1)	3 (13.6)
Worsening, n (%)	2 (8.7)*	8 (36.4)

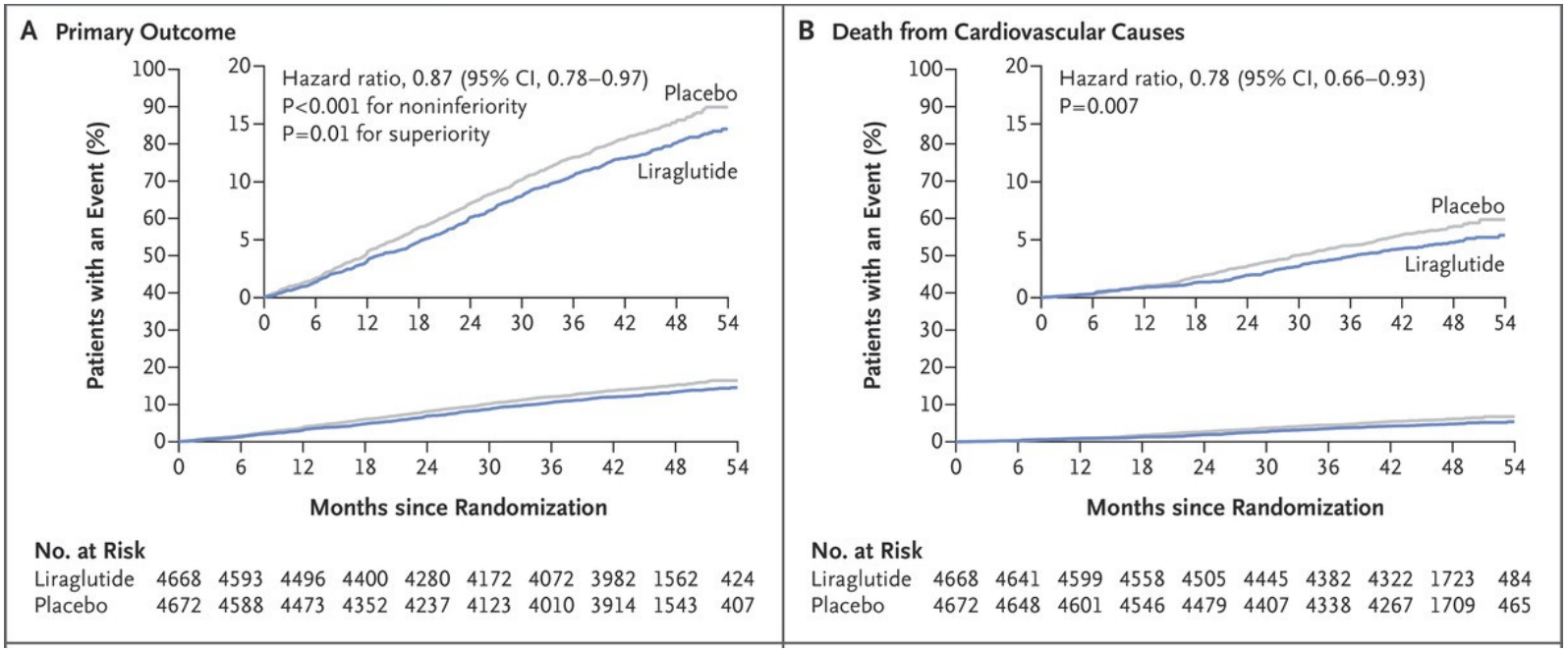
*p<0.05 vs placebo

- Liraglutide, a long-acting GLP-1 agonist dosed once daily SC, with overall benefits in T2DM

More diarrhea with liraglutide

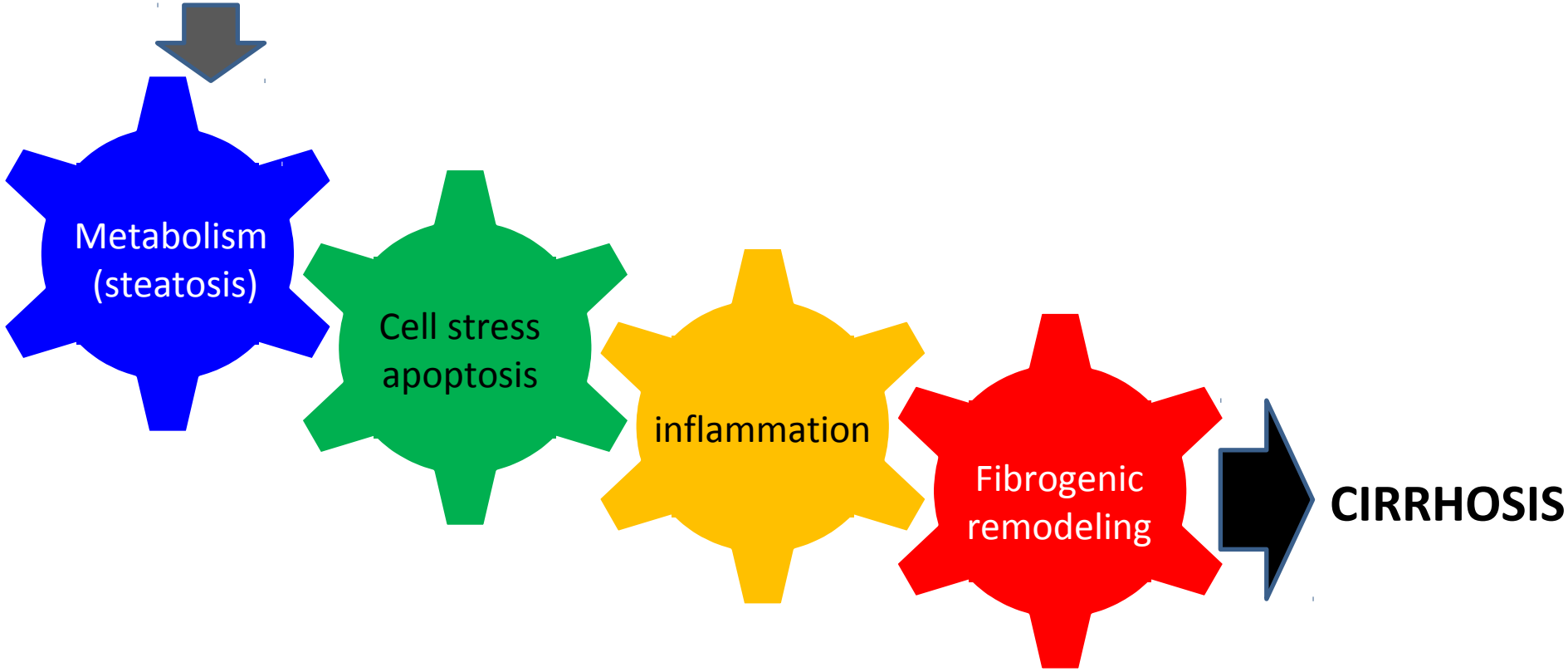
Armstrong MJ, et al. EASL 2015, Vienna. #G01

Liraglutide improves MACE



Marso et al, N Engl J Med. 2016 Jul 28;375(4):311-22

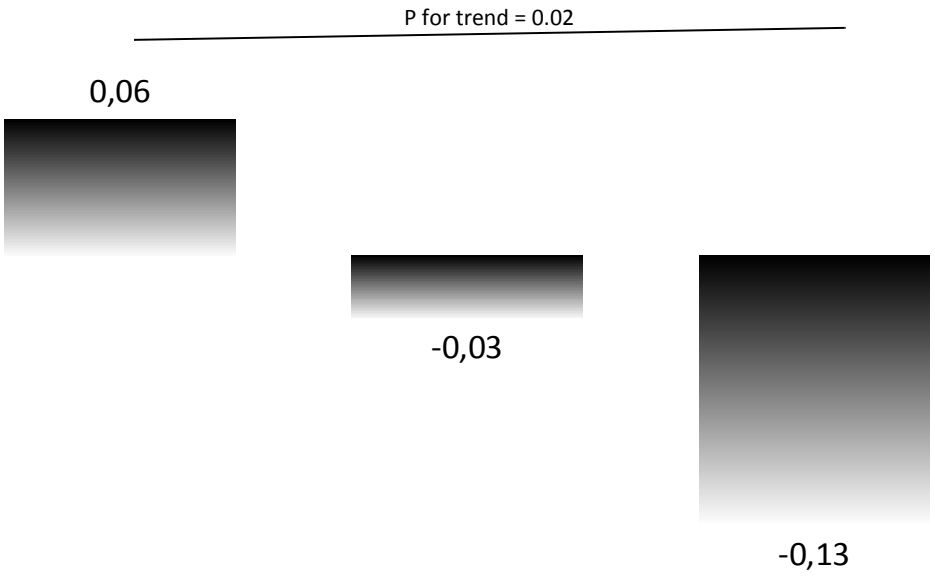
PPARs
FXR
GLP-1
FABAC
FGF21
Thyroxine beta receptor agonist



Fatty acid-bile acid conjugate (Aramchol) Phase IIa Trial

Mechanism of action: SCD1 inhibition

- Results: Liver fat change by NMRS *

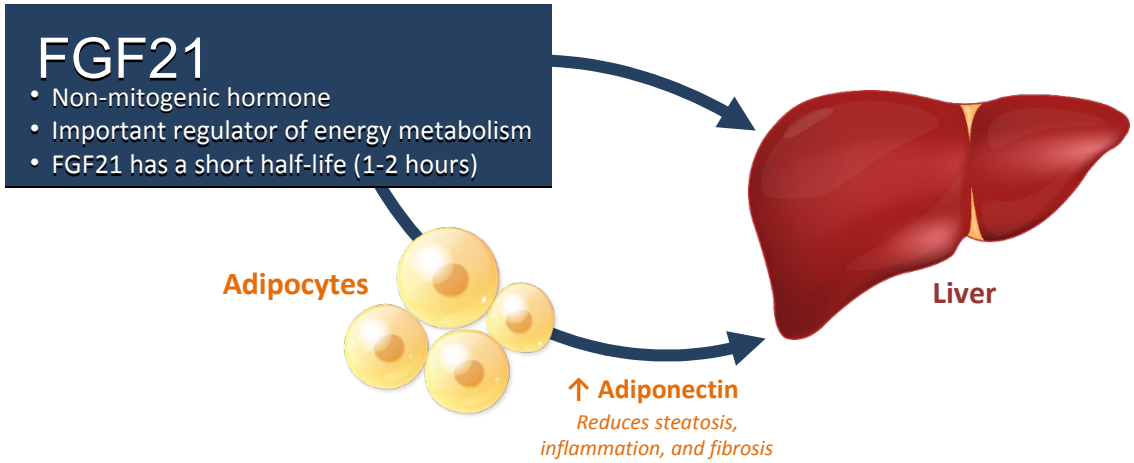


* Magnetic resonance spectroscopy (MRS) is generally considered the clinical gold-standard noninvasive technique for in vivo fat and metabolite quantification. It is routinely used for measuring liver fat. (Houchun H. et al. ***Obesity 2010***;18(4):841–7.)

11.Safadi R. et al. Clinical Gastroenterology and Hepatology 2014; 12(12):2085-91

Galmed Pharmaceuticals

Fibroblast Growth Factor 21 (FGF21)



Beneficial metabolic effects

↑ Insulin sensitivity

↓ Lipogenesis & improvement in lipids

Anti-fibrotic effects

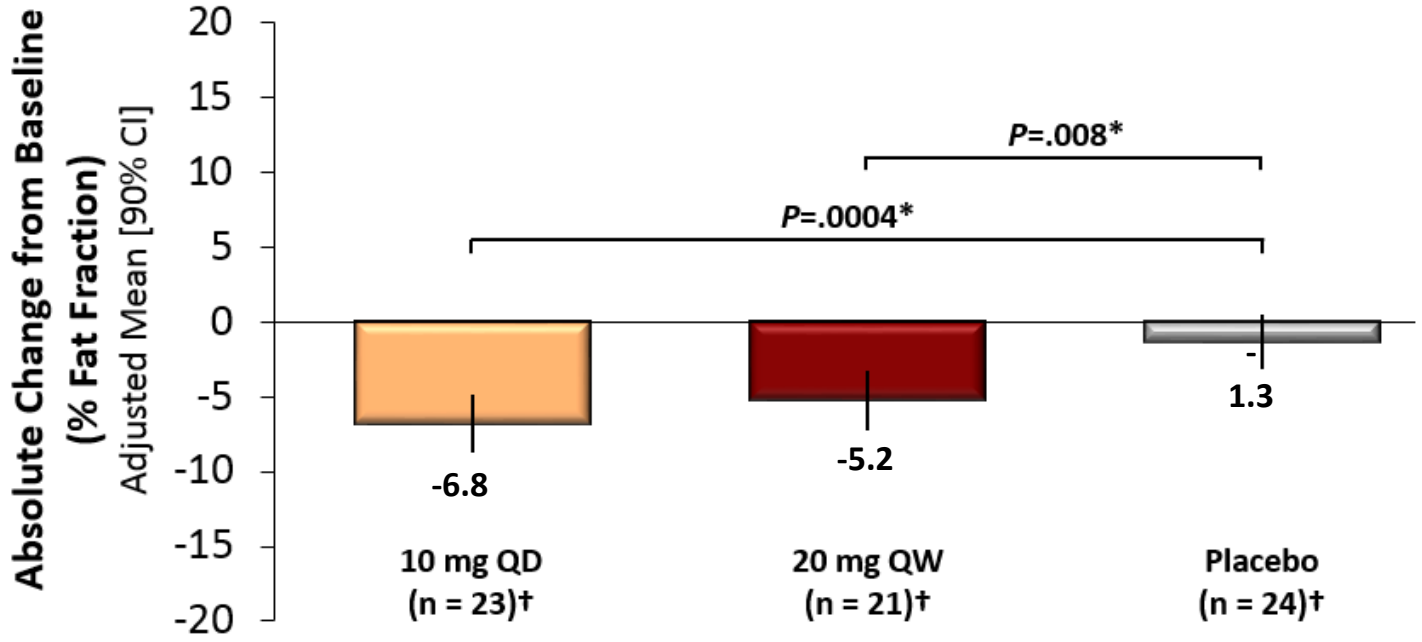
↓ Pro-C3 (biomarker of fibrosis)

FGF21 may have direct and indirect beneficial effects on non-alcoholic steatohepatitis (NASH) and NASH-related hepatic fibrosis

FGF, fibroblast growth factor; HDL, high density lipoprotein; LDL, low density lipoprotein.

Owen BM, *et al. Trends Endocrinol Metab.* 2015; **26**(1):22-29;
Gimeno RE, Moller DE. *Trends Endocrinol Metab.* 2014; **25**(6):303-11;
Polyzos SA. Et al. *Diabetes Obes Metab*. 2010**;12**(5): 365-83;
Kharitonenkov A and Larsen P, *Trends Endocrinol Metab.* 2011;**22**(3):81-86;
Charles E. et al. *Hepatology* 2016;**64**(Suppl):17A.

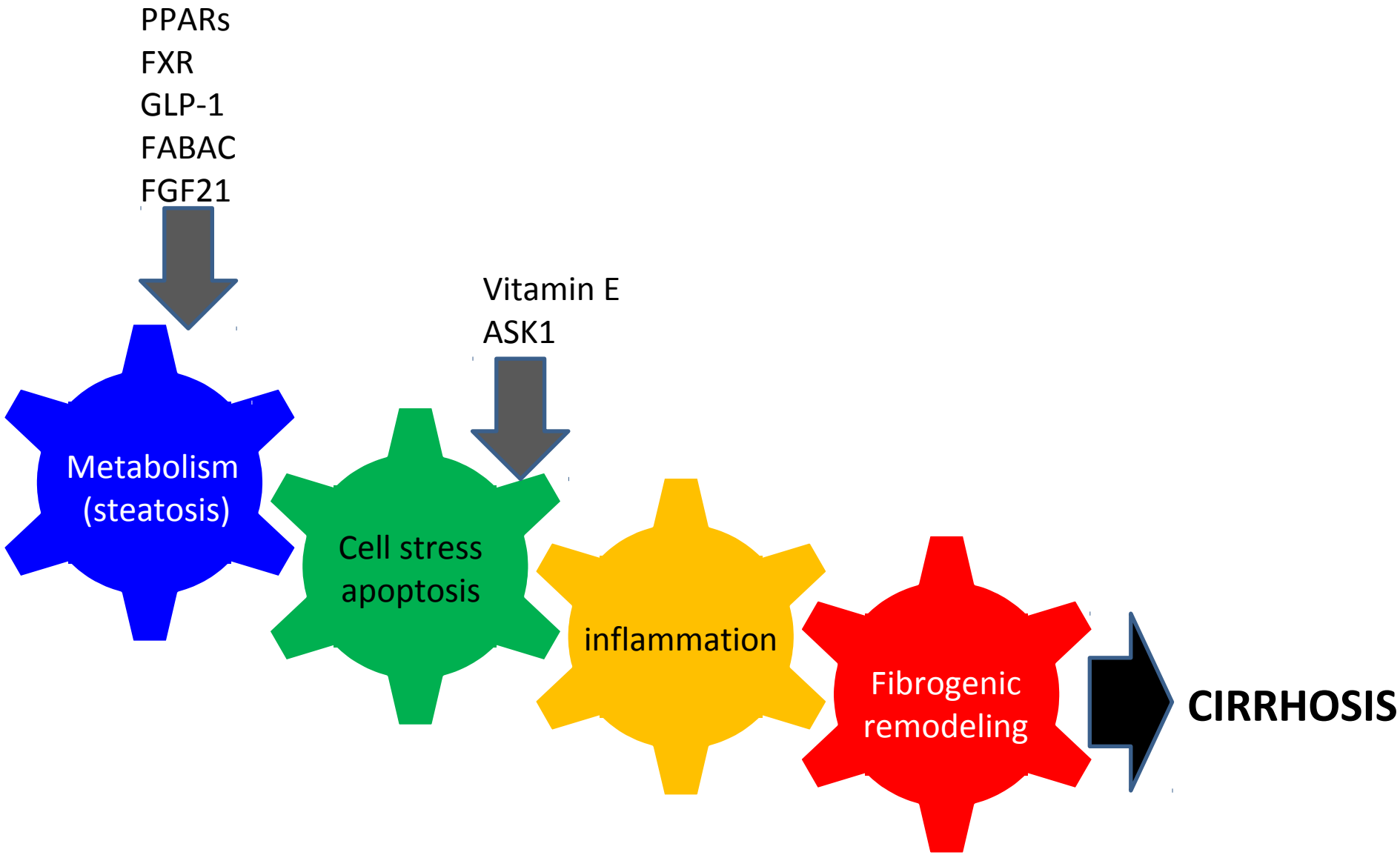
Absolute Improvement in Hepatic Fat Fraction (MRI-PDFF) at Week 16



BMS-986036 QD and QW treatment compared with placebo significantly reduced hepatic fat fraction

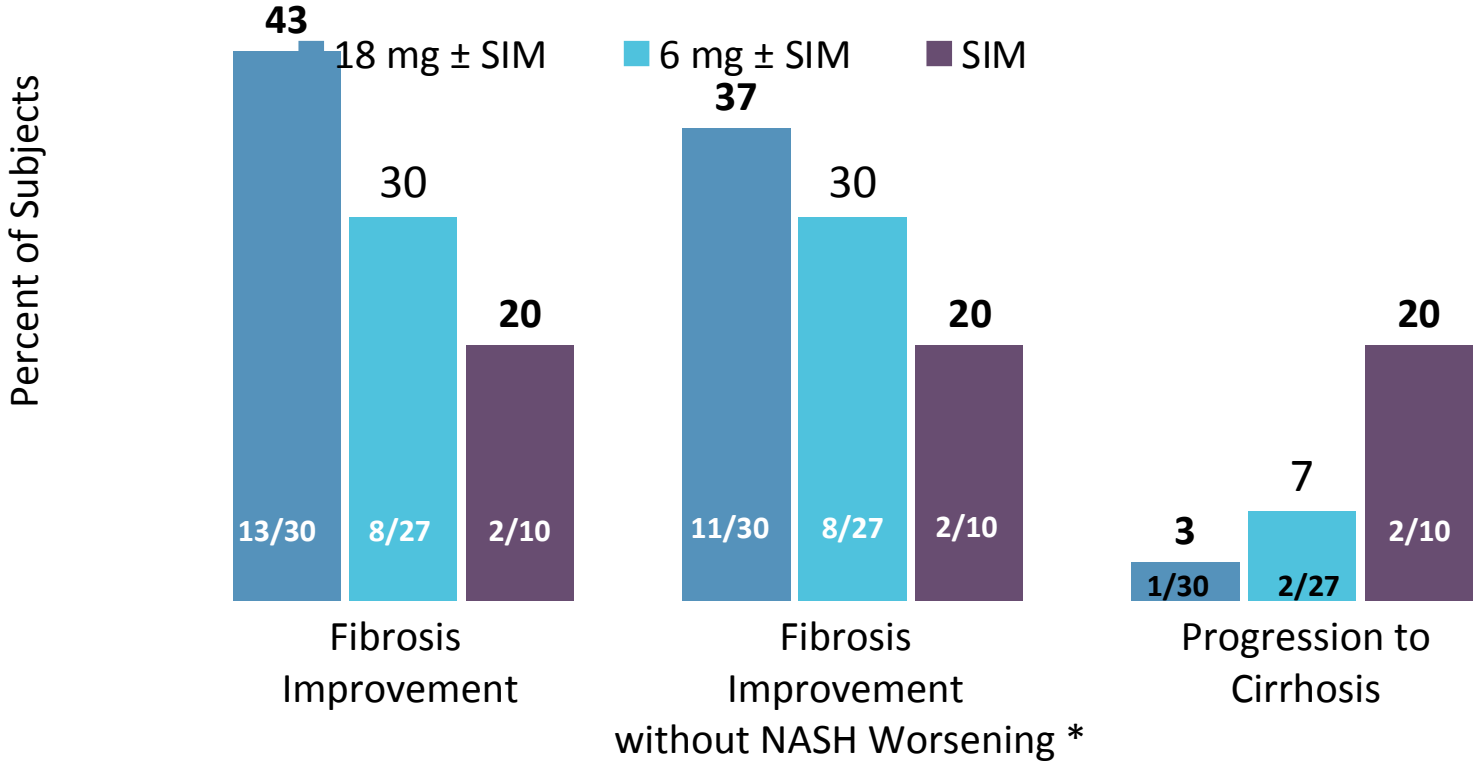
*Inferential statistical analyses were conducted using a MMRM and not adjusted for multiple comparisons;
†1 patient in each group completed treatment but did not have adequate MRI-PDFF scans at baseline and Week 16.

CI, confidence interval; MRI-PDFF, magnetic resonance imaging-proton density fat-fraction; MMRM, mixed effects model for repeated measures; QD, once daily; QW, once weekly.

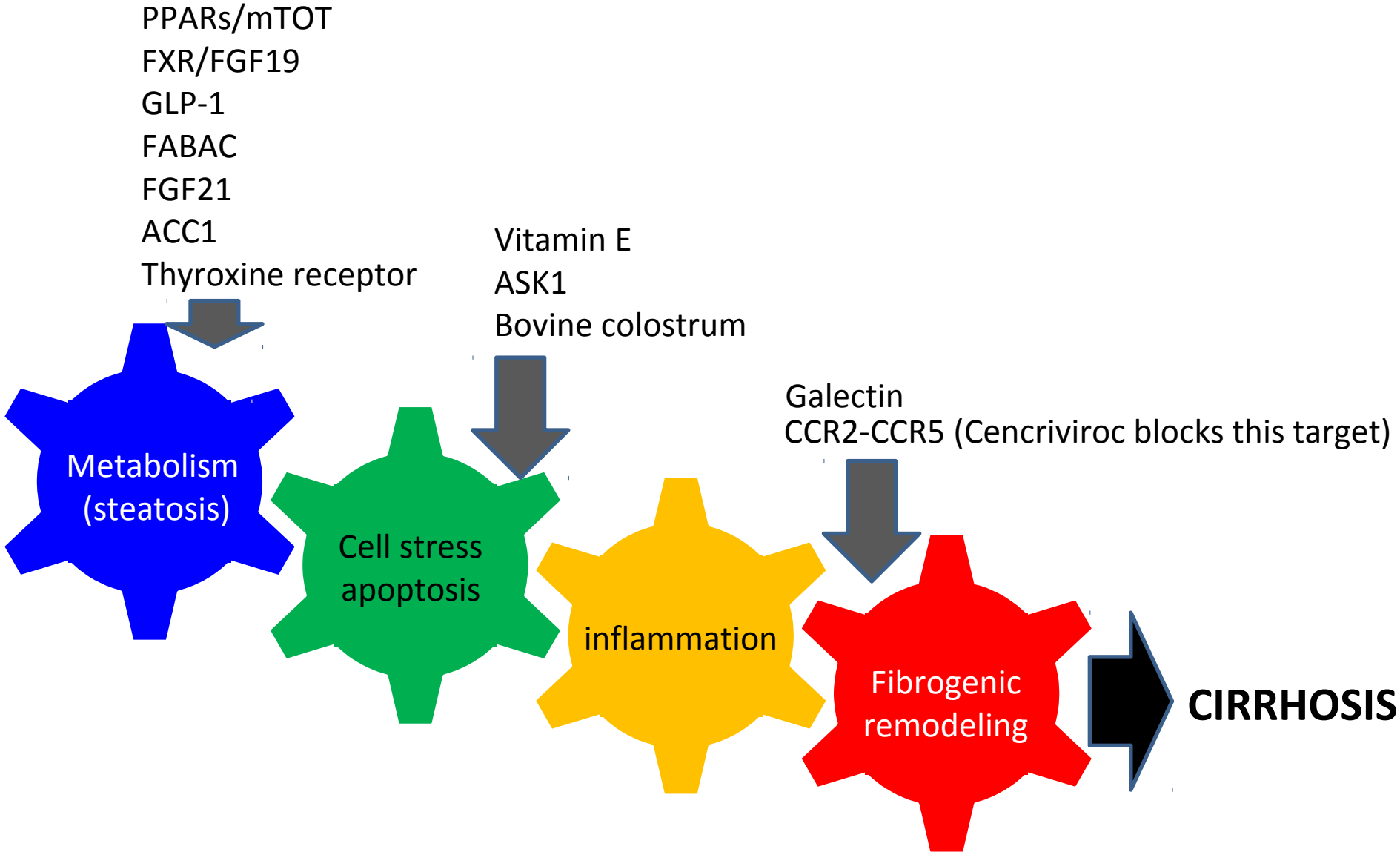

PPARs
FXR
GLP-1
FABAC
FGF21
Vitamin E
ASK1
Metabolism (steatosis)
Cell stress apoptosis
inflammation
Fibrogenic remodeling
CIRRHOSIS

GS-4997, an Inhibitor of Apoptosis Signal-Regulating Kinase (ASK1), Alone or in Combination with Simtuzumab for the Treatment of Nonalcoholic Steatohepatitis (NASH): A Randomized, Phase 2 Trial

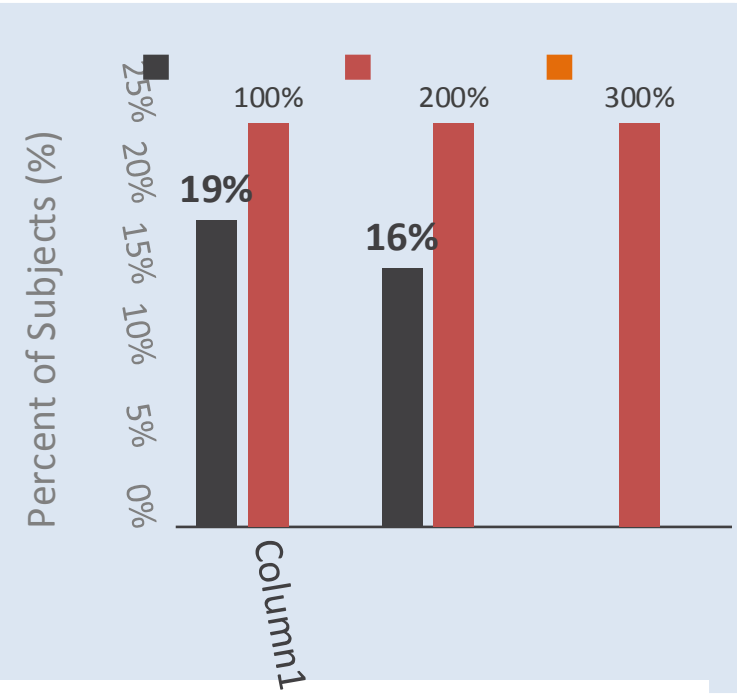
- GS4997 (2 doses) + Sim vs Sim alone
- 2:2:1:1:1 randomization, Stratified by diabetes
- NASH, NAS ≥ 5, F2-3



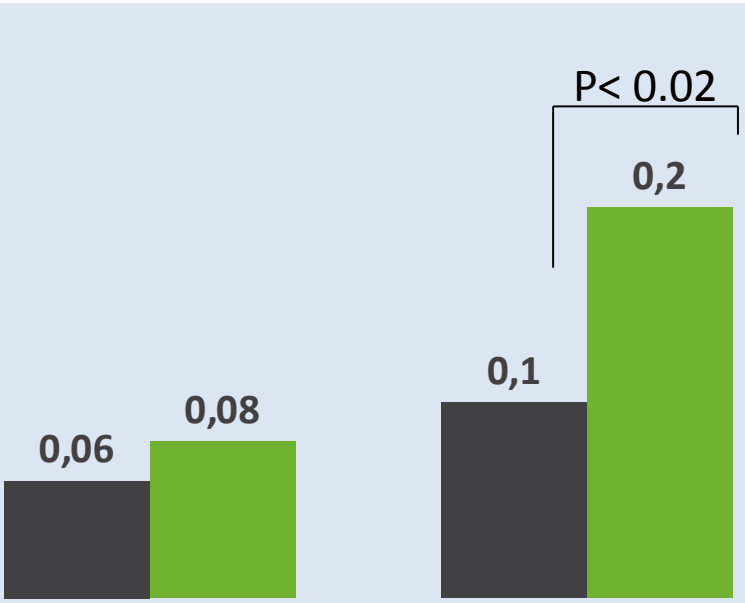
Loomba et al, Hepatology 2017


PPARs/mTOT
FXR/FGF19
GLP-1
FABAC
FGF21
ACC1
Thyroxine receptor
Vitamin E
ASK1
Bovine colostrum
Galectin
CCR2-CCR5 (Cencriviroc blocks this target)
Metabolism (steatosis)
Cell stress apoptosis
inflammation
Fibrogenic remodeling
CIRRHOSIS

Cenicrivaroc for NASH

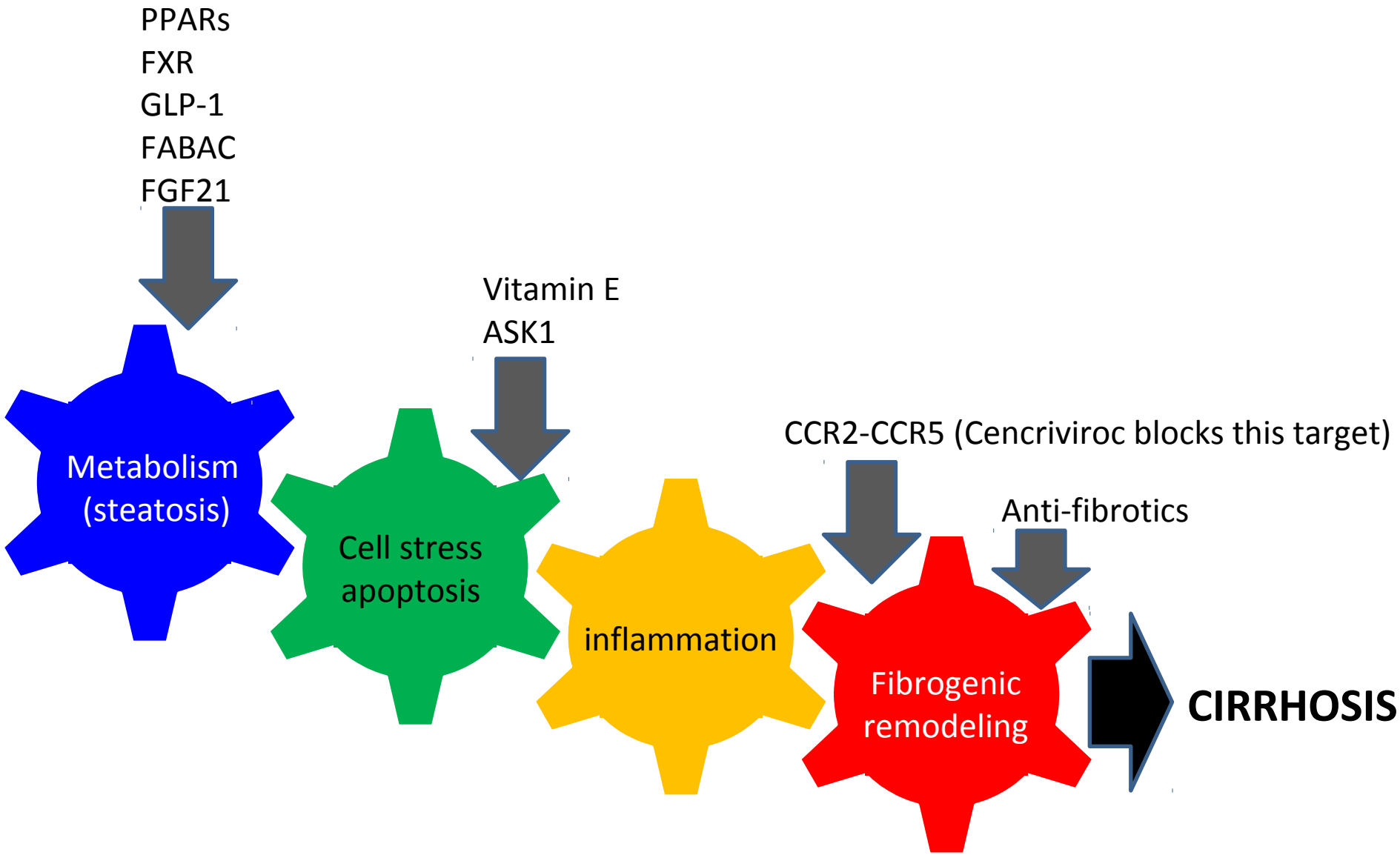


PRIMARY ENDPOINT

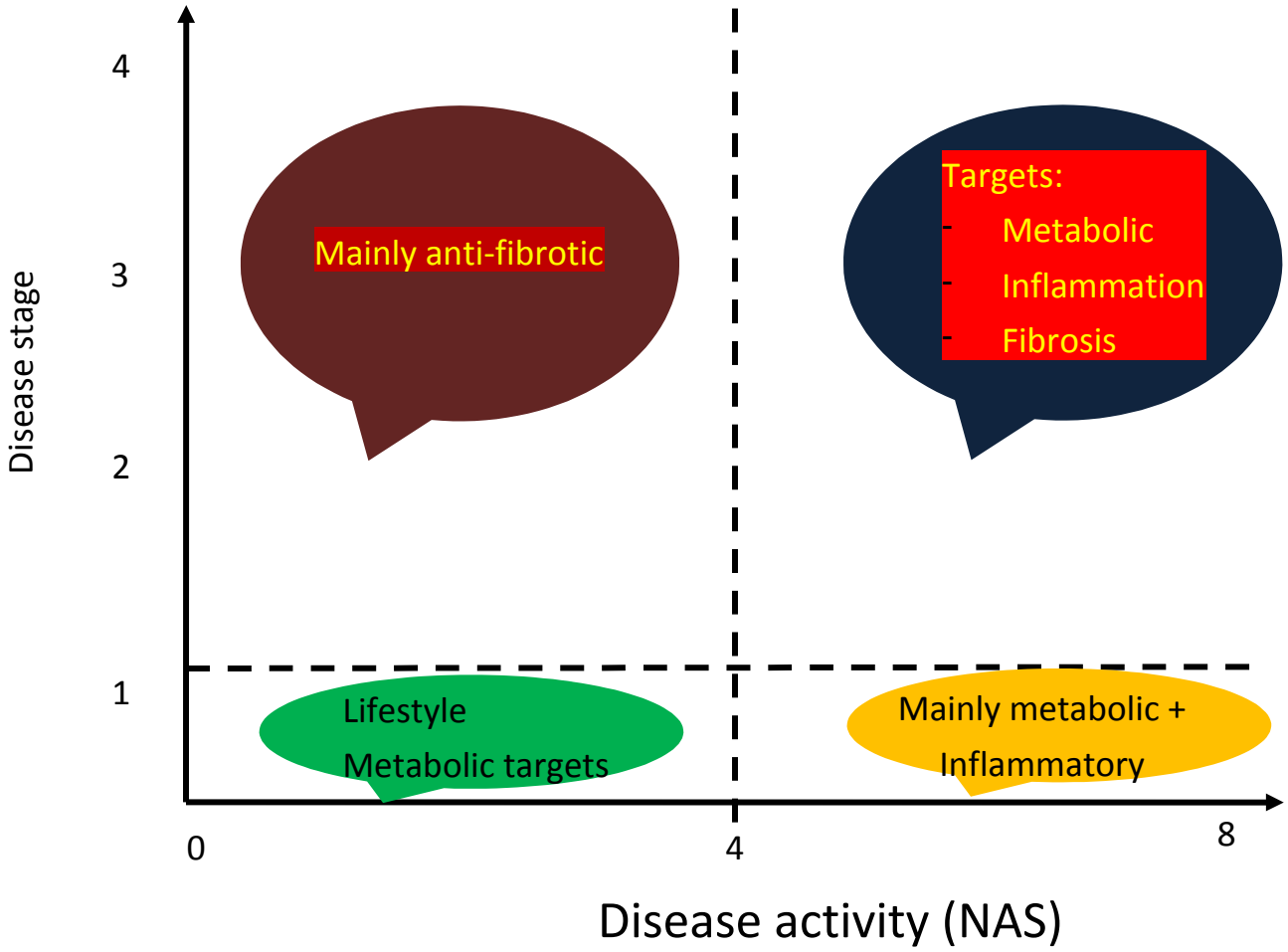


SECONDARY ENDPOINTS

Sanyal et al, AASLD 2016


PPARs
FXR
GLP-1
FABAC
FGF21
Vitamin E
ASK1
CCR2-CCR5 (Cencriviroc blocks this target)
Anti-fibrotics
Metabolism (steatosis)
Cell stress apoptosis
inflammation
Fibrogenic remodeling
CIRRHOSIS

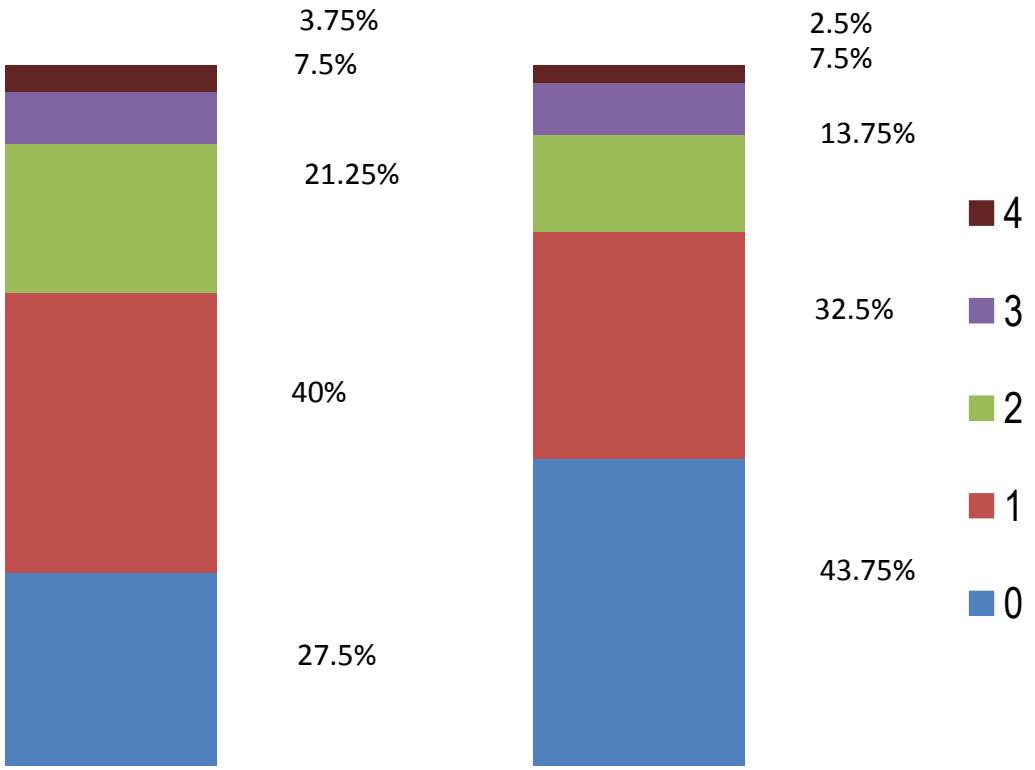
Rational approach to therapeutics for NASH



Results: Evolution of Fibrosis after surgery

Lassailly et al, Gastroenterology. 2015 Aug;149(2):379-88

Fibrosis improves after bariatric surgery



Metavir scale.

p<0.003

Histologic feature	Improvement	p Value
Fibrosis (Kleiner score)	33.8%	p<0.003

Effect of endoscopic duodenal mucosal resurfacing on glycemic control

Van Baar et al, MS submitted

Steatosis alone

NASH stage 1-3 fibrosis *

NASH cirrhosis

Lifestyle intervention
(optimize body weight, fitness, sleep, stress)

Bariatric Surgery
(Proximal gastric bypass, Gastric sleeve etc)

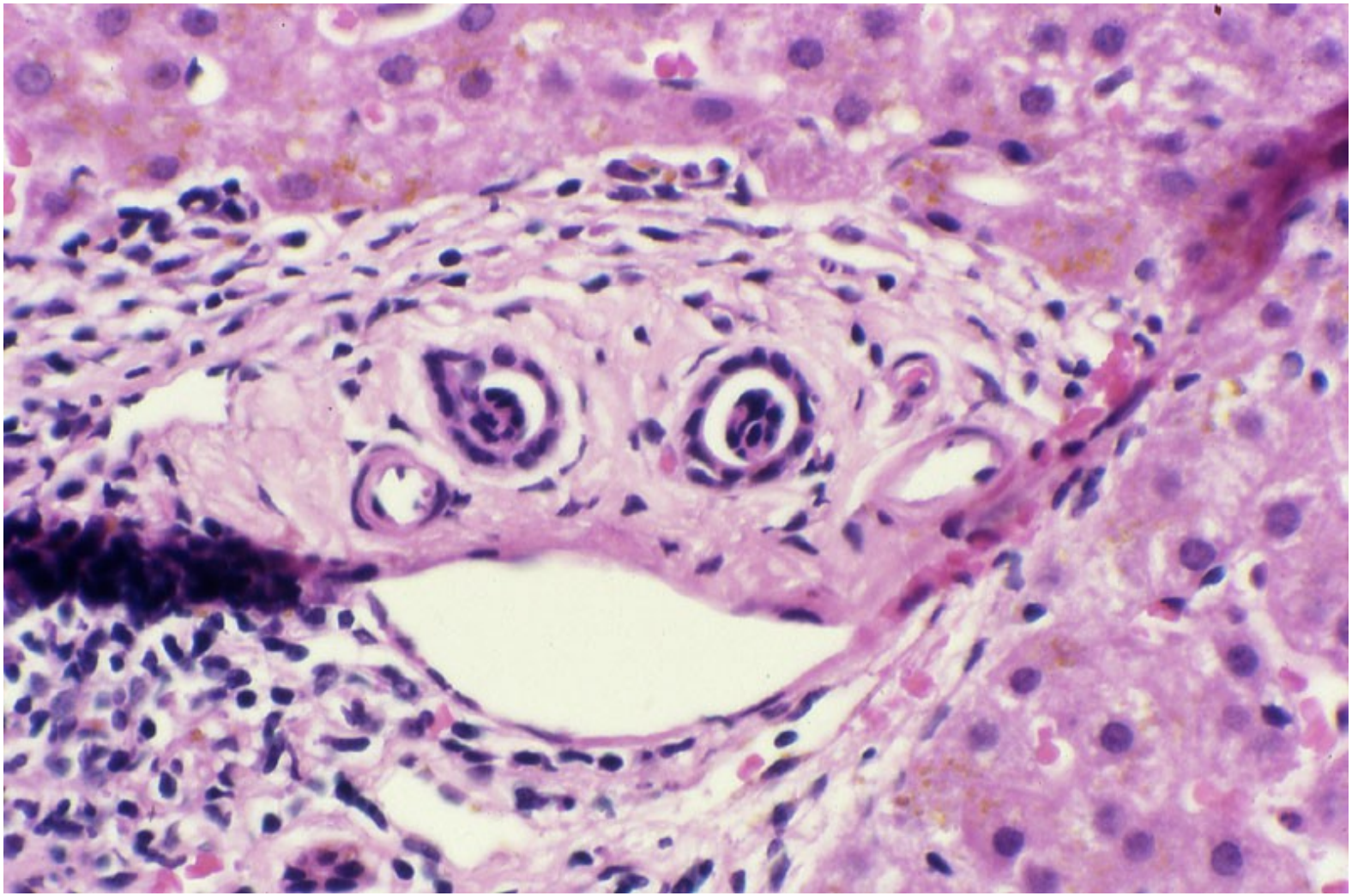
Pharmacological therapy
(vitamin E, glitazones, future therapies)

Screening for HCC and oesophageal varices

* Biopsy confirmed but may change to non-invasive profile

Rinella and Sanyal, Nature Reviews March 2016

Thank You



Courtesy- Dr. David Kleiner