

Treatment of NAFLD: Current management and future therapies

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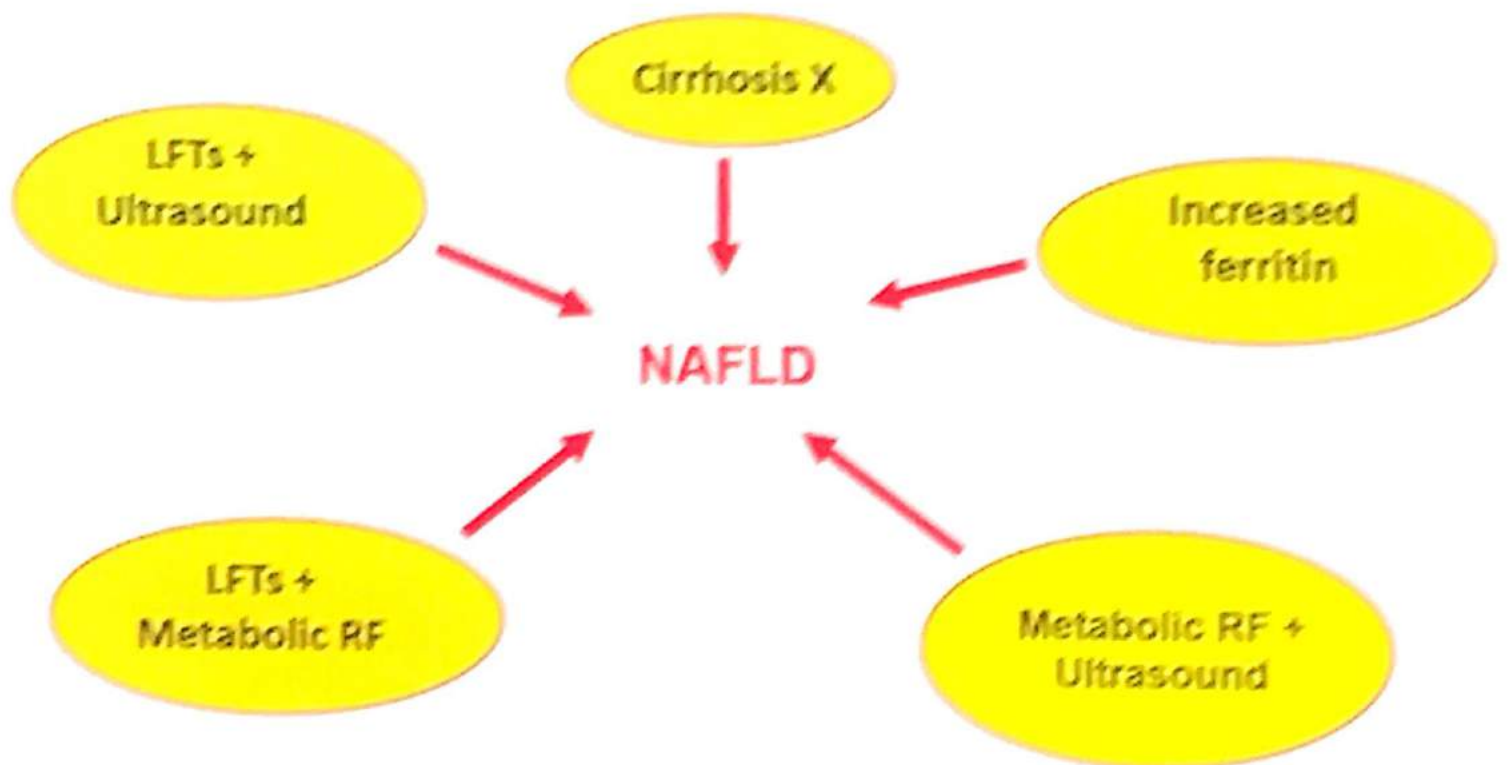
Hôpital Saint-Antoine, Paris



Managing NAFLD in 3 simple steps



When to suspect NAFLD is present



NAFLD is under recognized in the primary care setting

251 patients identified with NAFLD in VA database
(ALT>2N, HBV/HCV neg, no alcohol)

Medical record review



Recognition of abnormal ALT :39.4%

Mention of NAFLD as possible diagnosis: 21.5%

Recommendation for diet or exercise : 14.7%

Referral to a specialist: 10.4% (3% with high fibrosis)

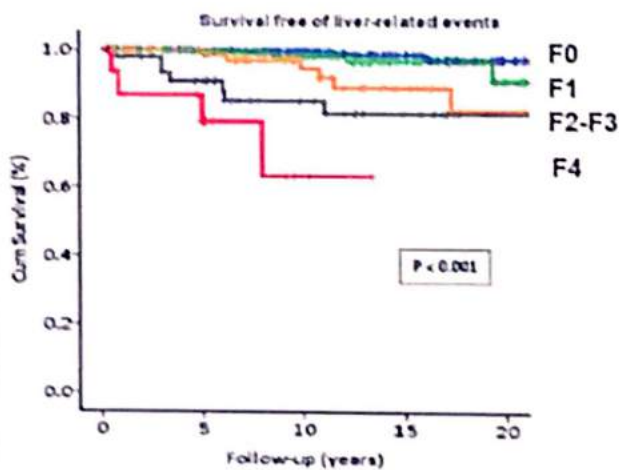
Magnitude of ALT elevation was the only factor associated with receiving specified NAFLD care

Managing NAFLD in 3 simple steps

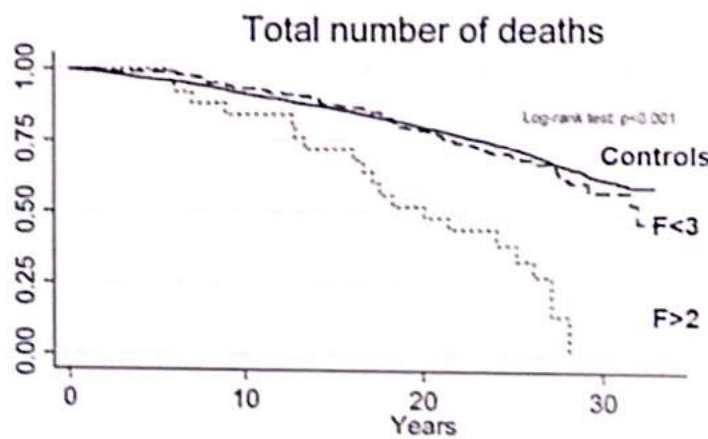


Fibrosis stage is predictive of survival

619 biopsy-proven NAFLD, FU 12.6 yrs



229 biopsy-proven NAFLD, FU 26 yrs



Cause of death: cardiovascular 38-43%, cancer 19%, cirrhosis 4-8% HCC 1-5%

Independent predictors: fibrosis, diabetes, tobacco, statin use

Angulo P et al. *Gastroenterology* 2015

Ekstedt M et al. *Hepatology* 2015

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Non-invasive assessment of liver fibrosis

Blood tests

Generation	Characteristics	Virus	NAFLD
1 st	Indirect markers Low cost Easy to calculate	APRI FIB4	FIB4 NAFLD Fibrosis Score
2 nd	Indirect and/or direct markers Higher cost Computing calculation	Fibrotest Hepascore FibroMeter ^{Virus}	ELF FibroMeter ^{NAFLD}

Elastography



Fibroscan



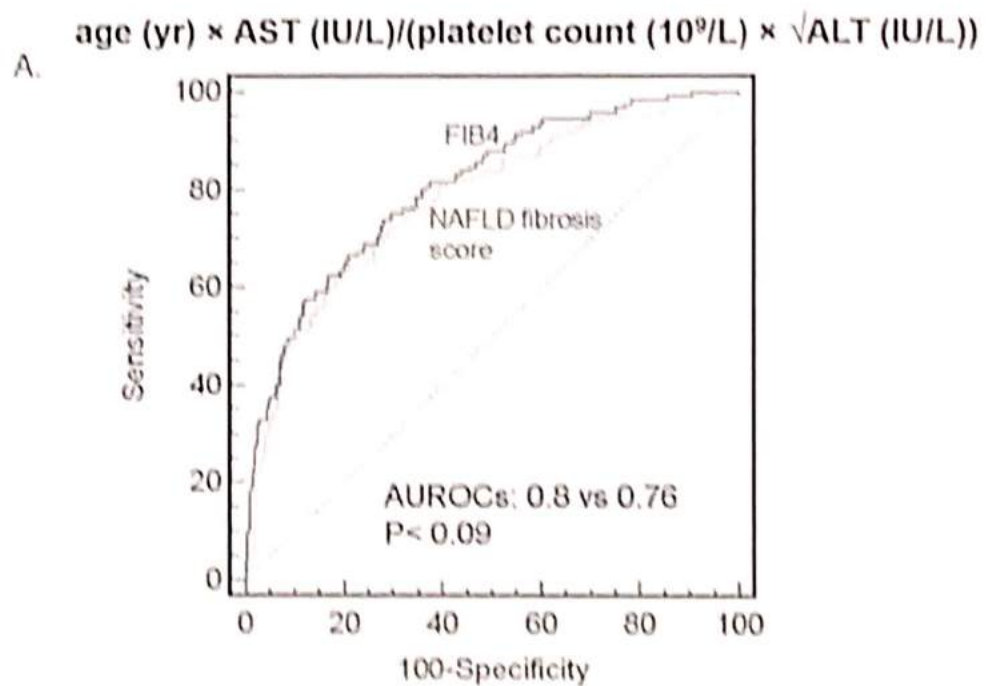
ARFI



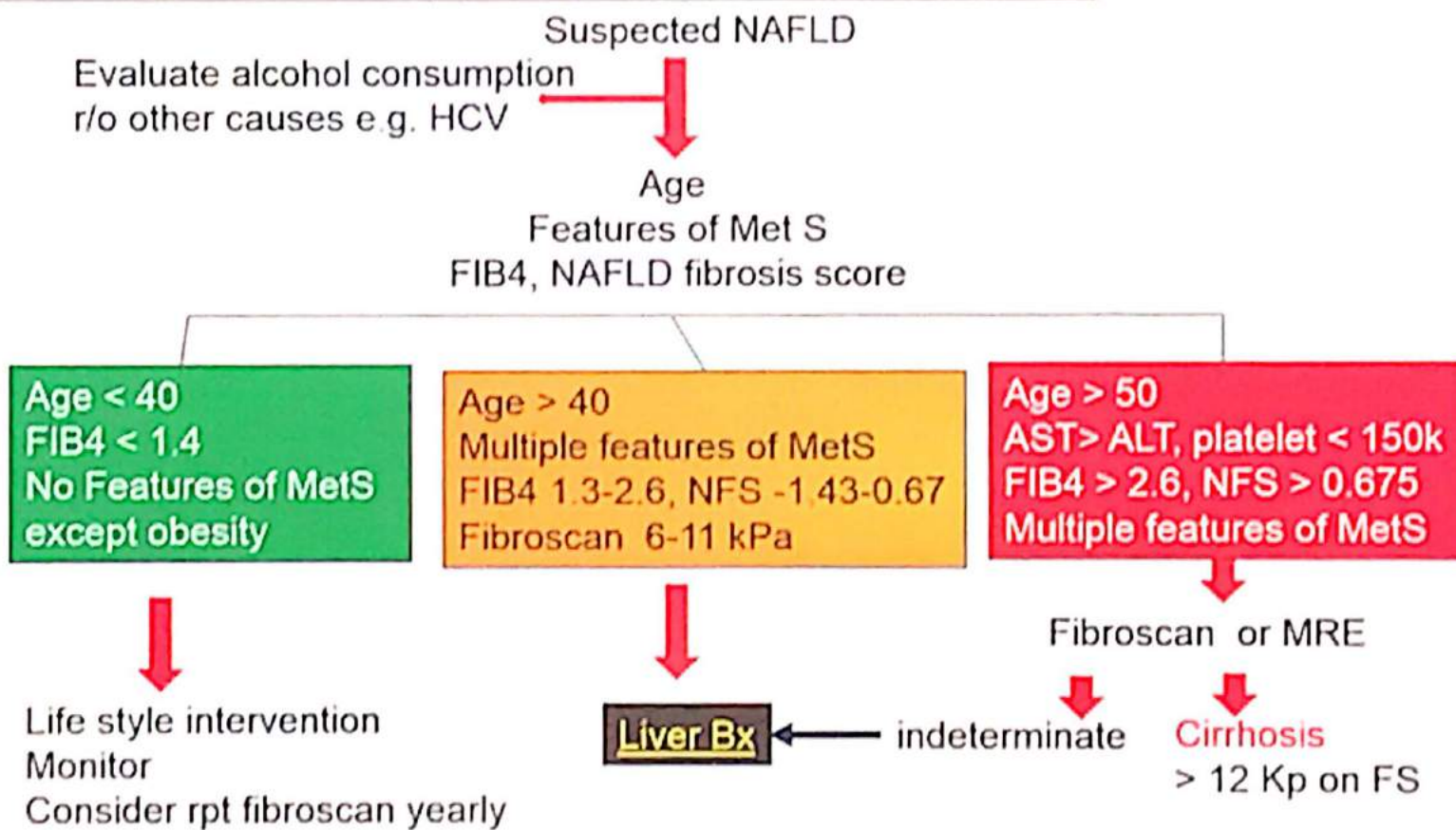
SSI



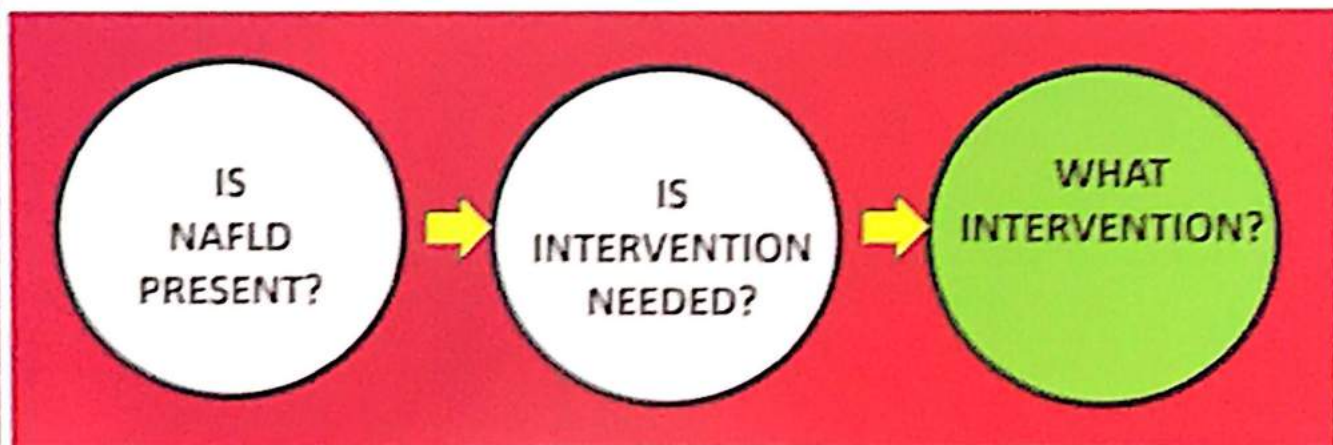
FIB4: a non-invasive way to detect advanced fibrosis



Risk stratification and who to biopsy



Managing NAFLD in 3 simple steps



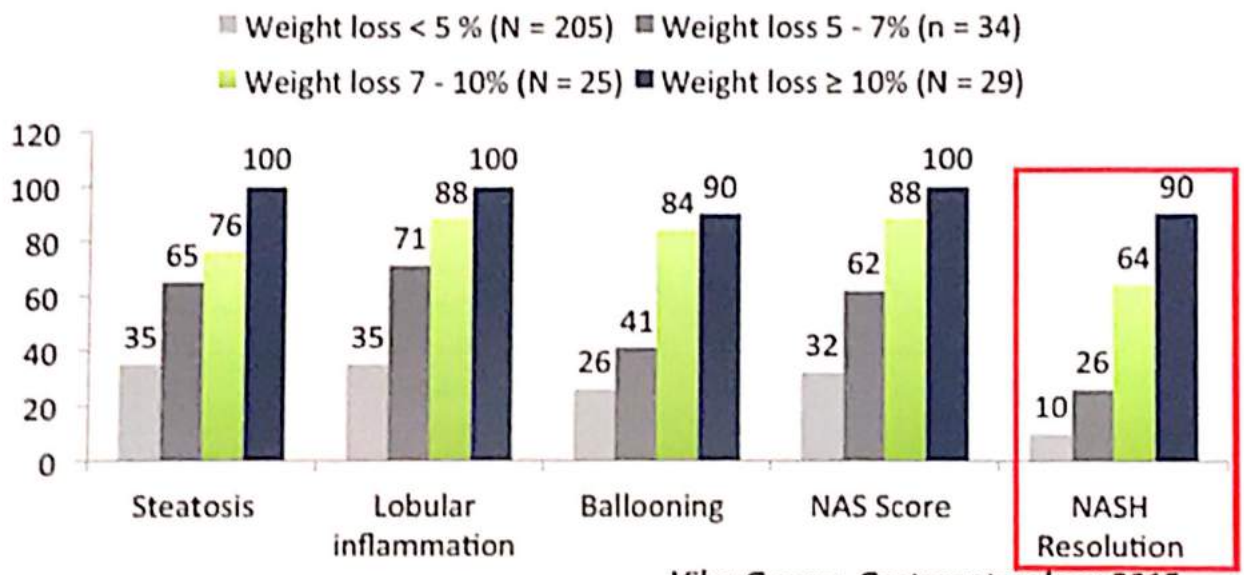
Do we need a drug ?

Life style changes and histological improvement

293 patients; 89% with paired liver biopsy

F/u: 52 weeks

Low-fat hypocaloric diet (- 750 kcal)

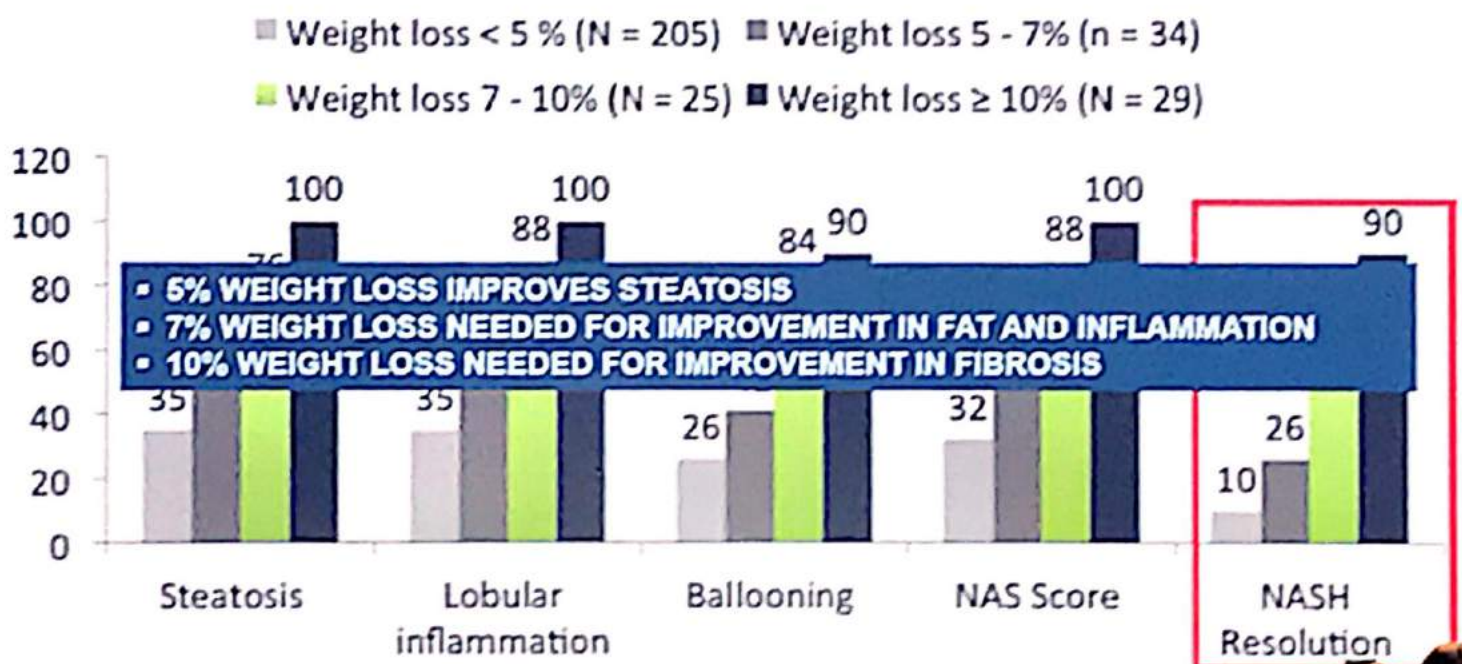


Vilar Gomez, Gastroenterology 2015

Do we need a drug ?

Life style changes and histological improvement

293 patients; 89% with paired liver biopsy
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Low-fat hypocaloric diet (- 750 kcal)



Vilar Gomez, Gastroenterology 2014

Life style recommendations

Lifestyle recommendations	Specifically incorporate	Specifically avoid
General		
<ul style="list-style-type: none"> • Weight loss $\geq 5-10\%$ of initial body weight • Identify psychological barriers to lifestyle change • Identify physical barriers to lifestyle change • Get sufficient sleep • Maintain weight loss 	<ul style="list-style-type: none"> • Water and zero calorie beverages in place of sugary beverages • More active lifestyle • Portion control • Limit alcohol • Coffee* • Use stairs when possible • Wear pedometer 	<ul style="list-style-type: none"> • Late-night eating • Sugary beverages and deserts
Diet		
Restriction of calorie intake by 500-1000kcal daily	Count calories daily: ~1200-1500 kcal daily for individuals <115kg ~1500-1800 kcal daily for individuals >115kg	<ul style="list-style-type: none"> • High-calorie foods • High-sugar beverages
Low carbohydrate diet (<40-45%)	<ul style="list-style-type: none"> • Vegetables (3-5 servings daily) • Fruits (2-4 servings daily) 	Simple carbohydrates and high-fructose corn syrup
Replace calories with PUFA, MUFA	<ul style="list-style-type: none"> • Extra virgin olive oil (60 ml daily) • Nuts, avocado, olives • Oily fish (salmon, tuna, mackerel, sardines) 	Herbal supplements and nonprescribed vitamins
Avoid trans fats, limit saturated fats (7-10%)	Olive oil, olives	Fast food, fried foods
Exercise		
Increase physical activity as tolerated based on medical conditions	<ul style="list-style-type: none"> • Cardiovascular training 5 times per week • Resistance training ≥ 2 times per week • 150-300 min weekly at moderate intensity or 75-150 min weekly at vigorous intensity 	Sedentary lifestyle

Failure of current treatments

- Insulin sensitizing molecules
 - ~~Metformin~~
 - ~~PPAR γ agonist (glitazones)~~
 - ~~CB1 inhibitor~~

- Hepatoprotective/antioxidant treatment
 - ~~Ursodeoxycholic acid~~
 - Vitamine E, betaine, pentoxiphylline
 - Silimarin, fibrates, statins
 - ~~Phlebotomy~~

Histological improvement in Vit E RCTs

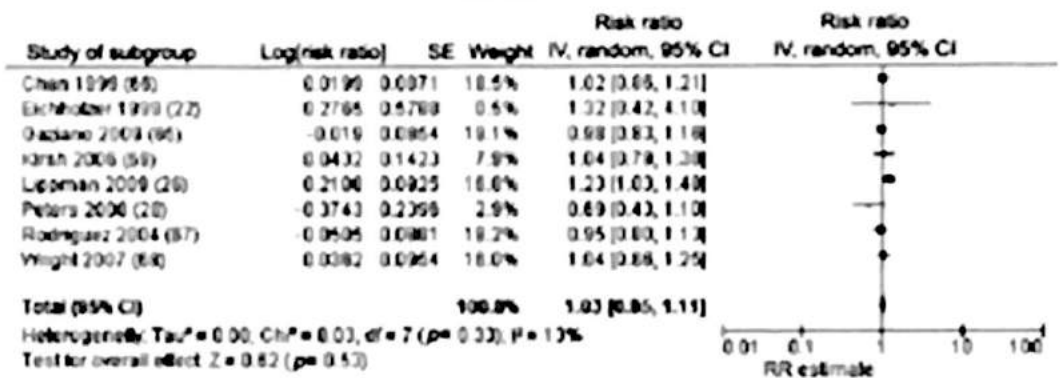
Steatosis Inflammation Ballooning NASH resolution Fibrosis

Harrison/1yr	-	-	-	-	-
PIVENS/2yrs	+	+	+	+	-
Nobili/2yrs	-	-	-	-	-
TONIC/2yrs	-	-	+	+	-

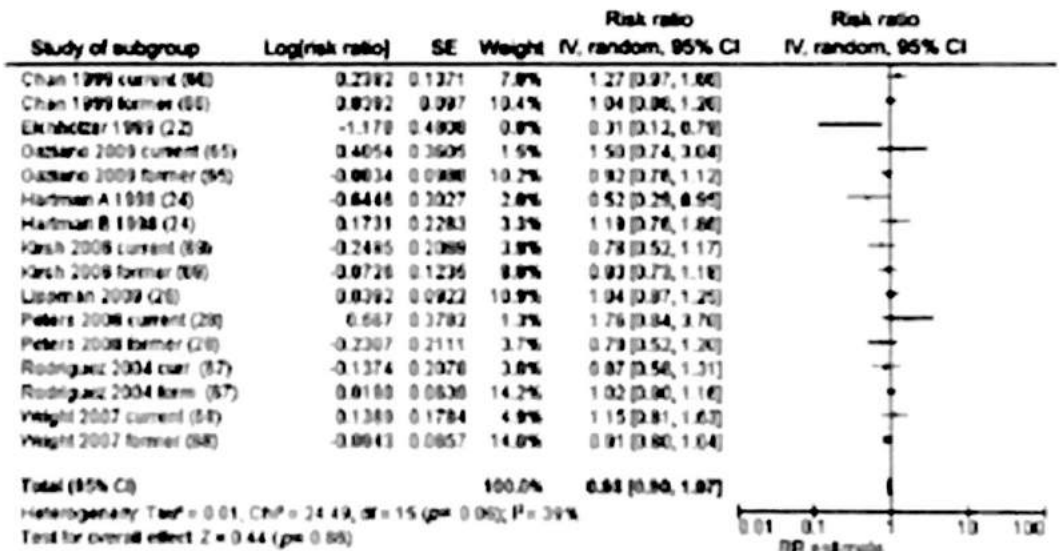
*+ denotes improvement;
vs. placebo*

Vitamin E and prostate cancer: where is the proof?

Never smokers



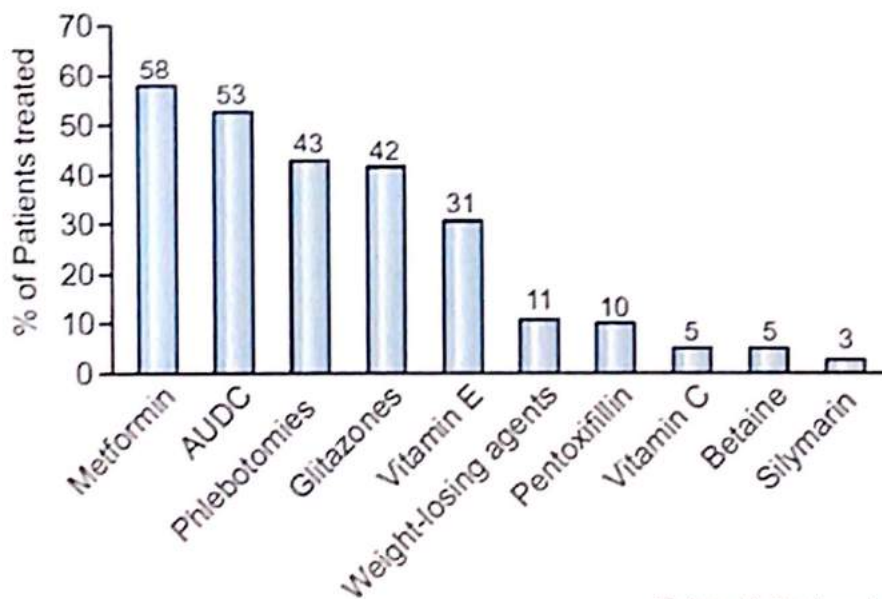
Ever smokers



Practice survey of NAFLD 352 French gastroenterologists in 2011

Diet and life style changes: 72%

Pharmacological agents: 28%



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Ratziu V, Cadranet JF, Serfaty L et al. J Hepatol 2012

Future therapies

Targets for NASH treatment

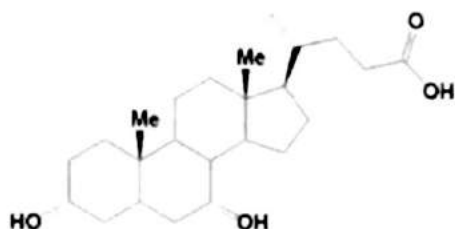


Obeticholic Acid - 6 α -Ethyl Chenodeoxycholic Acid - INT-747

Semi-Synthetic Derivative of Chenodeoxycholic Acid

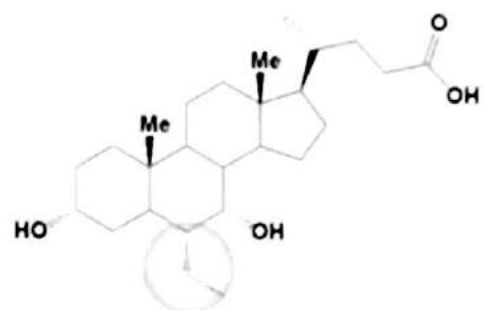
CDCA

chenodeoxycholic acid



INT-747

6 α -ethyl chenodeoxycholic acid

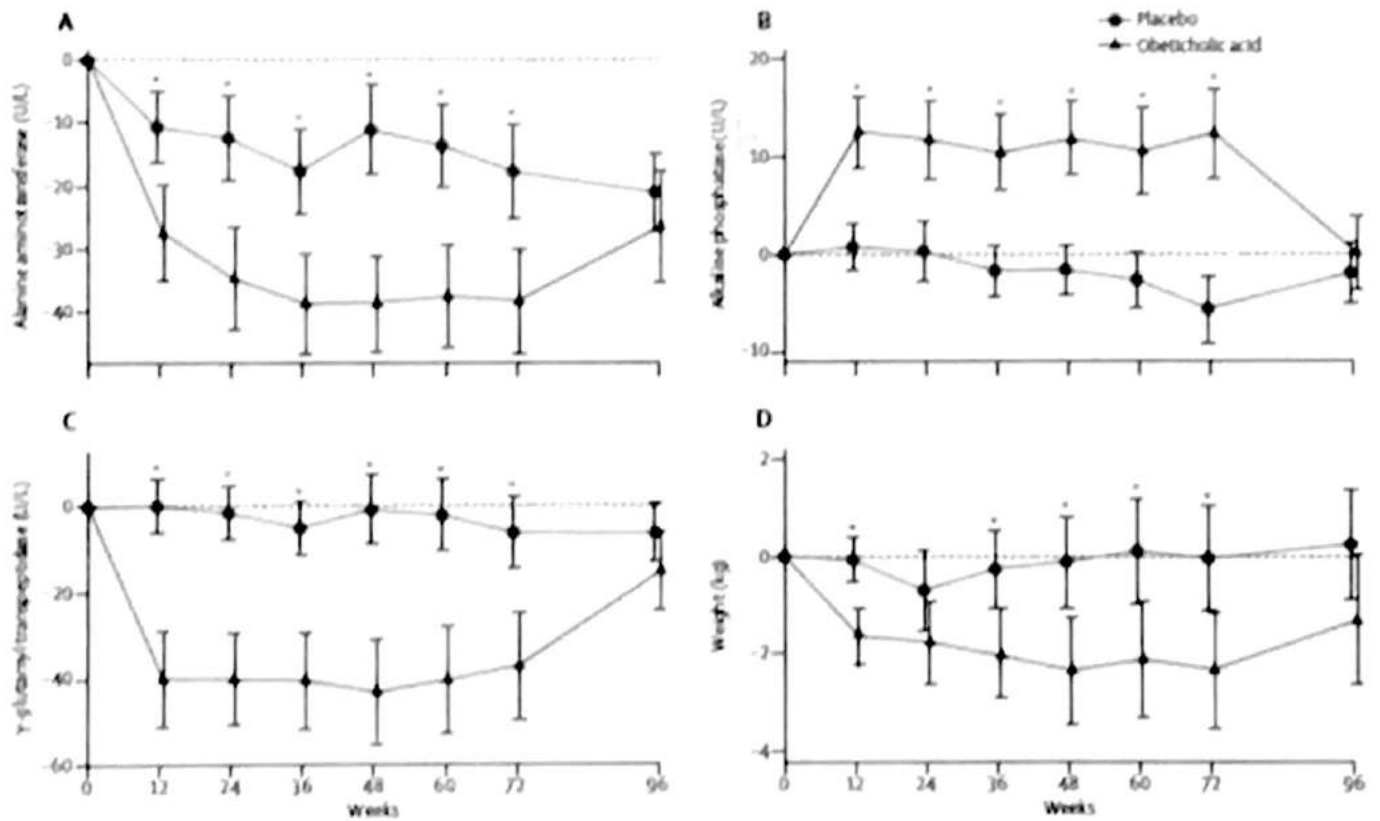


FXR EC₅₀
(agonism) 8.66 μ M

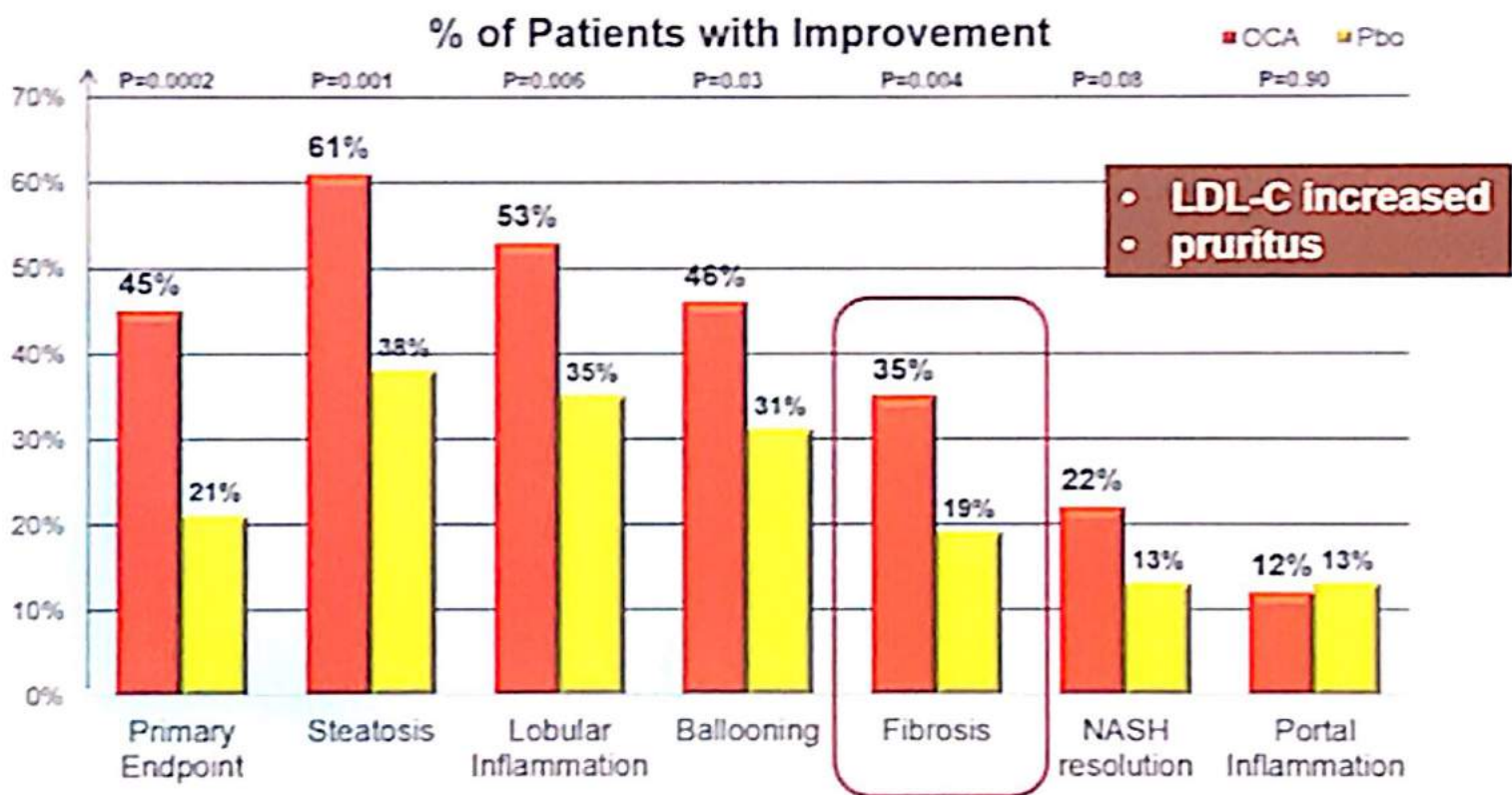


0.099 μ M

FLINT: liver tests and weight outcome



FLINT: Primary and Secondary Histological Endpoints



Elafibranor (GFT505): mechanism of action

- Dual PPAR alpha/delta agonist¹

	PPAR- α	PPAR- δ
Expression	Hepatocytes	Ubiquitous
Action	Lipid and lipoprotein metabolism	Mitochondrial function, fatty acid oxidation, and insulin sensitivity
	Anti-inflammatory	Anti-inflammatory

- Improves lipid and glucose metabolism in prediabetic patients²
- Improves hepatic and peripheral insulin sensitivity in obese patients³
- Improves steatohepatitis and fibrosis in mouse NASH models¹
- Antifibrotic and anti-inflammatory effect¹

Abbreviations: NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor.

1. Staets B, et al. *Hepatology*. 2013;58:1941-1952. 2. Canou B, et al. *Diabetes Care*. 2011;34:2008-2014. 3. Cariou B, et al. *Diabetes Care*. 2013;36:2923-2930.

One year elafibranor vs placebo in NASH

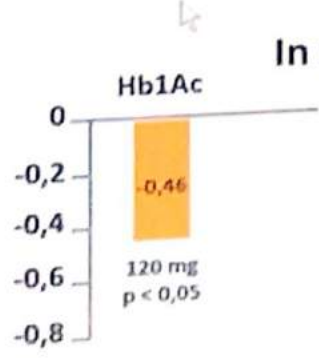
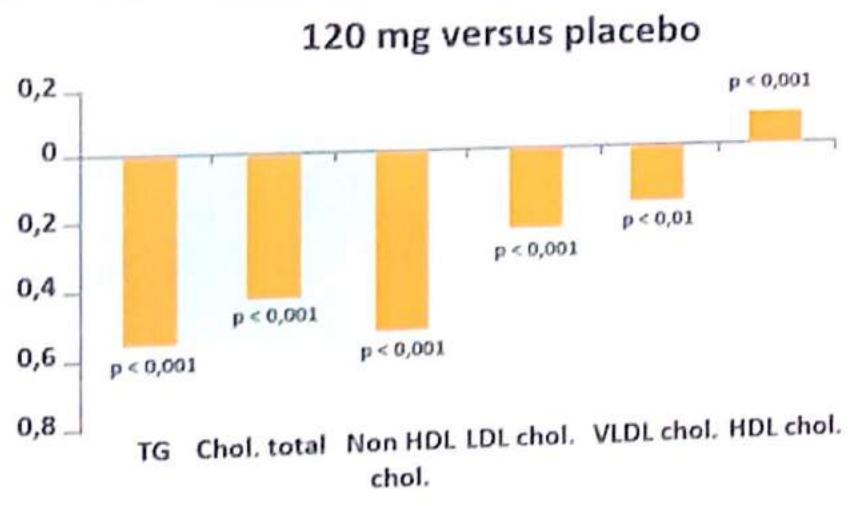
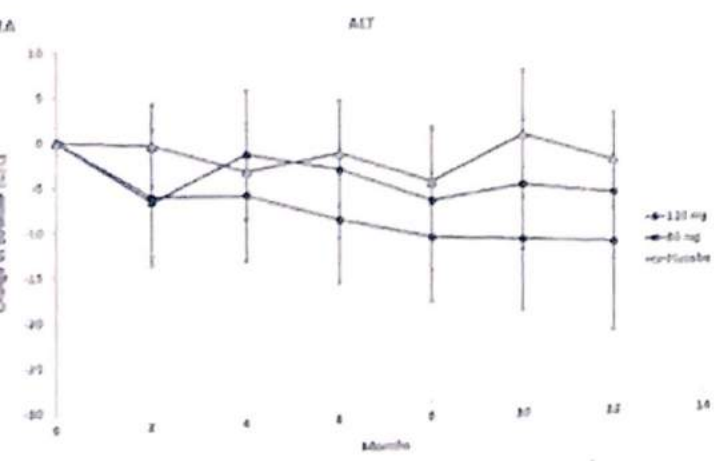
ITT analysis

	Placebo (n = 92)	Elafibranor 80 mg (n = 93)	Elafibranor 120 mg (n = 89)	p (120 mg vs placebo)
Primary endpoint*	17 %	23 %	21 %	0,28

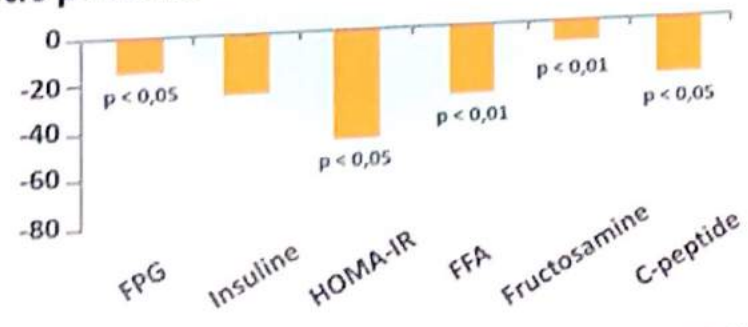
Post hoc analysis in NAS ≥ 4

	Placebo (n = 76)	Elafibranor 80 mg (n = 83)	Elafibranor 120 mg (n = 75)	p (120 mg vs placebo)
Primary endpoint*	11 %	20 %	20 %	0,018

Metabolic and biochemical outcomes

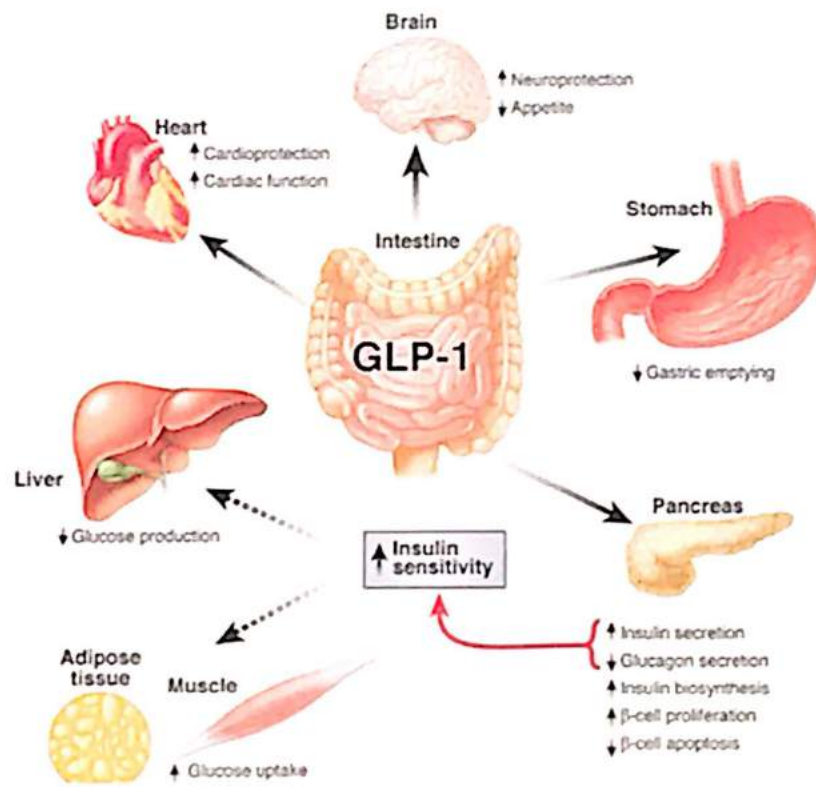


In diabetic patients

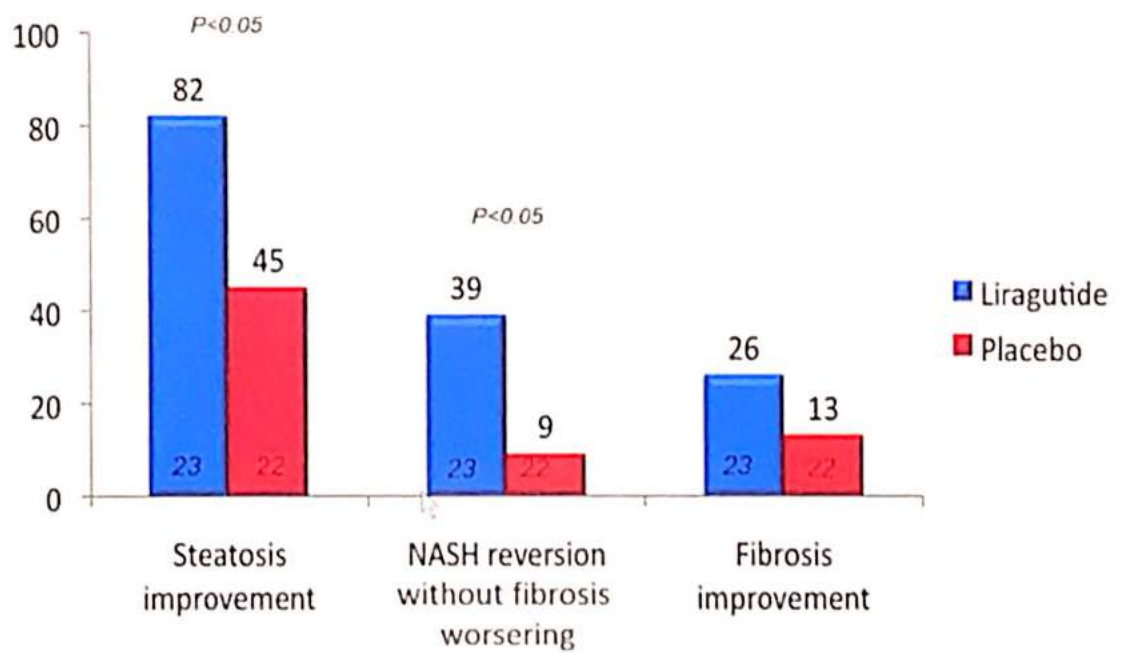


et al. Gastroenterology 2016

GLP-1: incretin with multi-systemic action

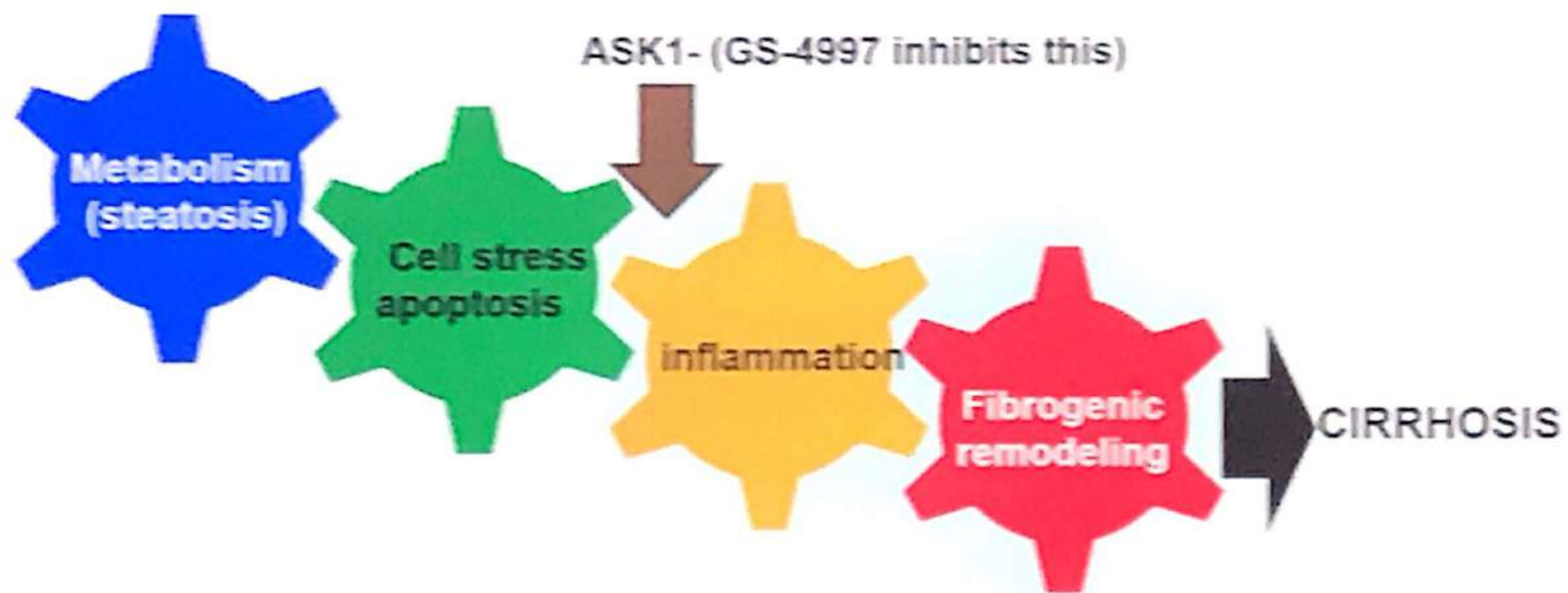


LEAN: Liver pathology outcomes



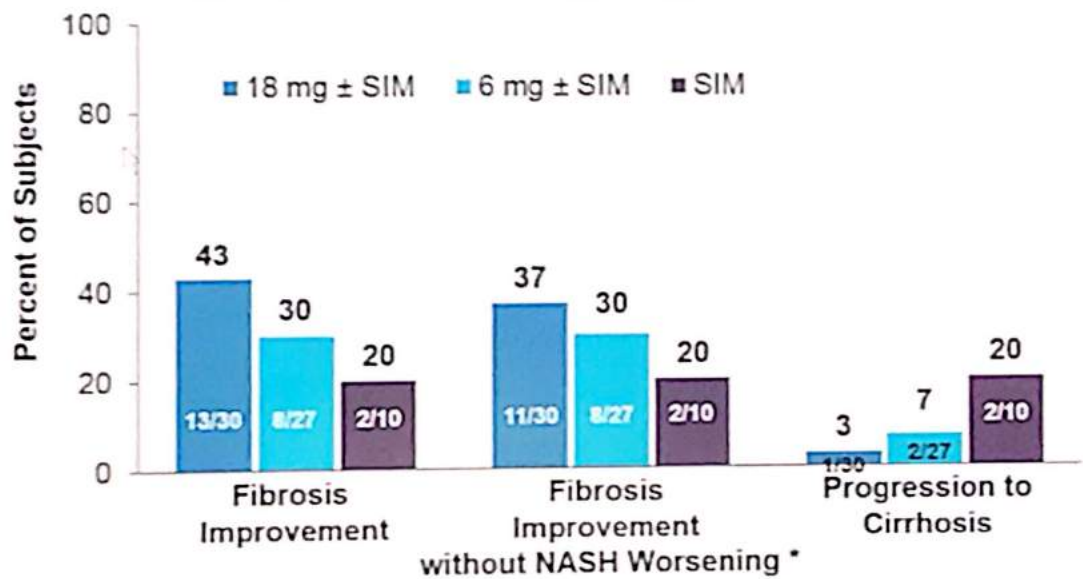
LEAN: Metabolic and biochemical outcomes

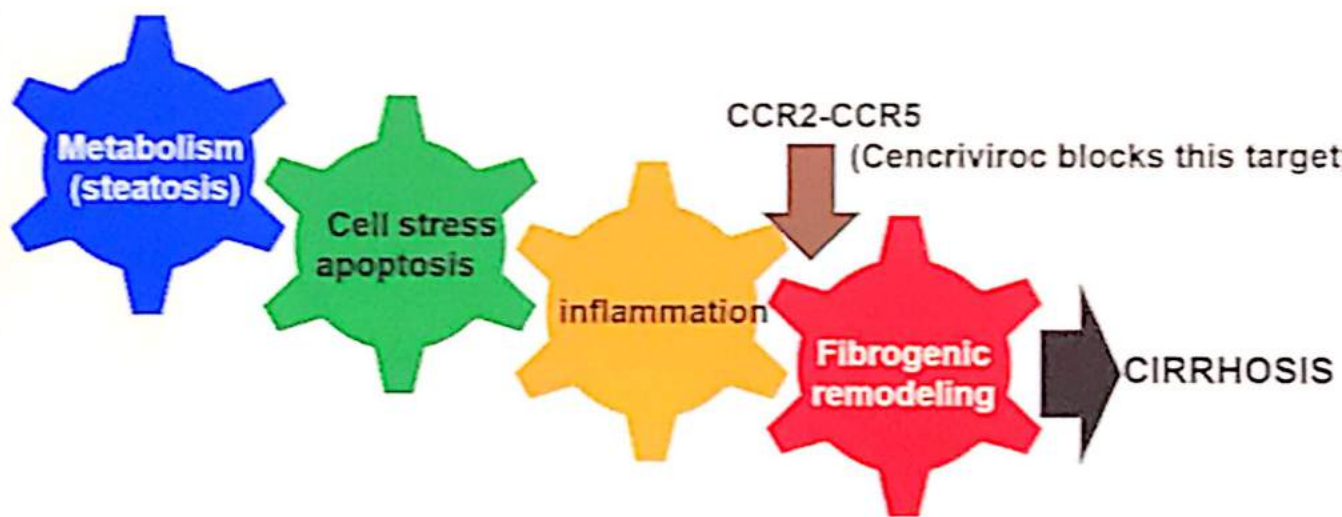
	Liraglutide (n = 26)	Placebo (n = 26)	p
Metabolic			
BMI (kg/m²)	-1.84	-0.27	0.005
Weight (kg)	-5.25	-0.58	0.003
Systolic (mmHg)	-5.0	-3.0	ns
HbA1c (%)	-0.49	0.04	0.074
Glucose (mmol/l)	-1.04	0.73	0.006
HDL cholesterol (mmol/l)	0.07	-0.04	0.014
Liver tests			
ALT (IU/ml)	-26.6	-10.2	ns
AST (IU/ml)	-15.8	-8.6	ns
GGT (IU/ml)	-33.7	-7.2	0.013
Cytokeratine 18 (IU/ml)	-185	-92	0.097
ELF test	-0.25	0.09	0.052



GS-4997, an inhibitor of apoptosis signal-regulating kinase (ASK1), alone or in combination with Simtuzumab

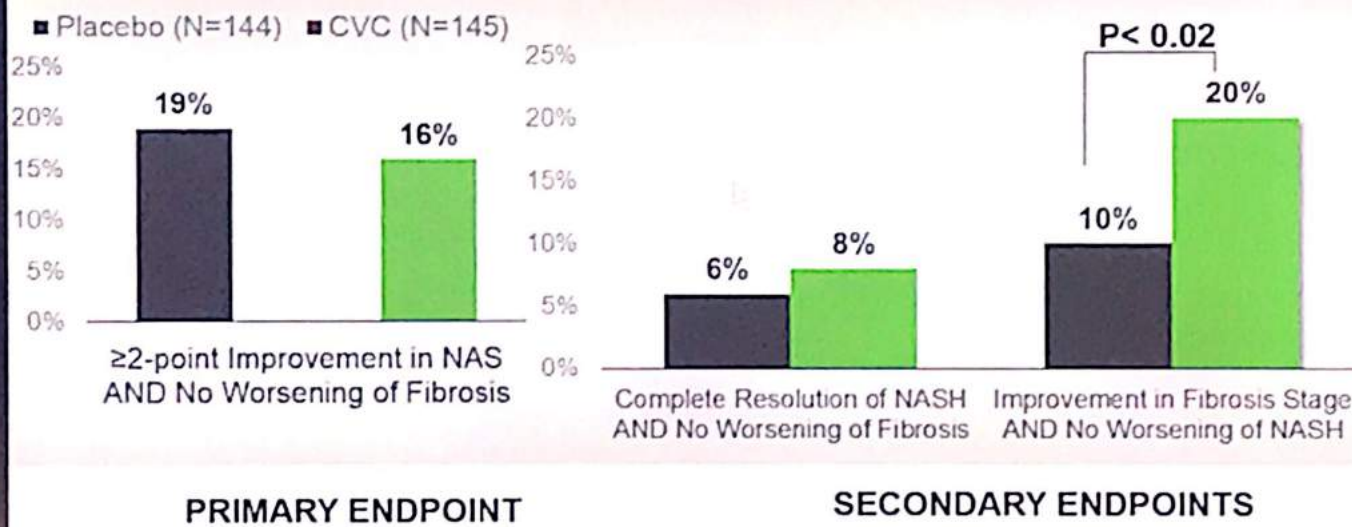
- GS4997 (2 doses) + Sim vs Sim alone
- 2:2:1:1 randomization, Stratified by diabetes
- NASH, NAS \geq 5, F2-3



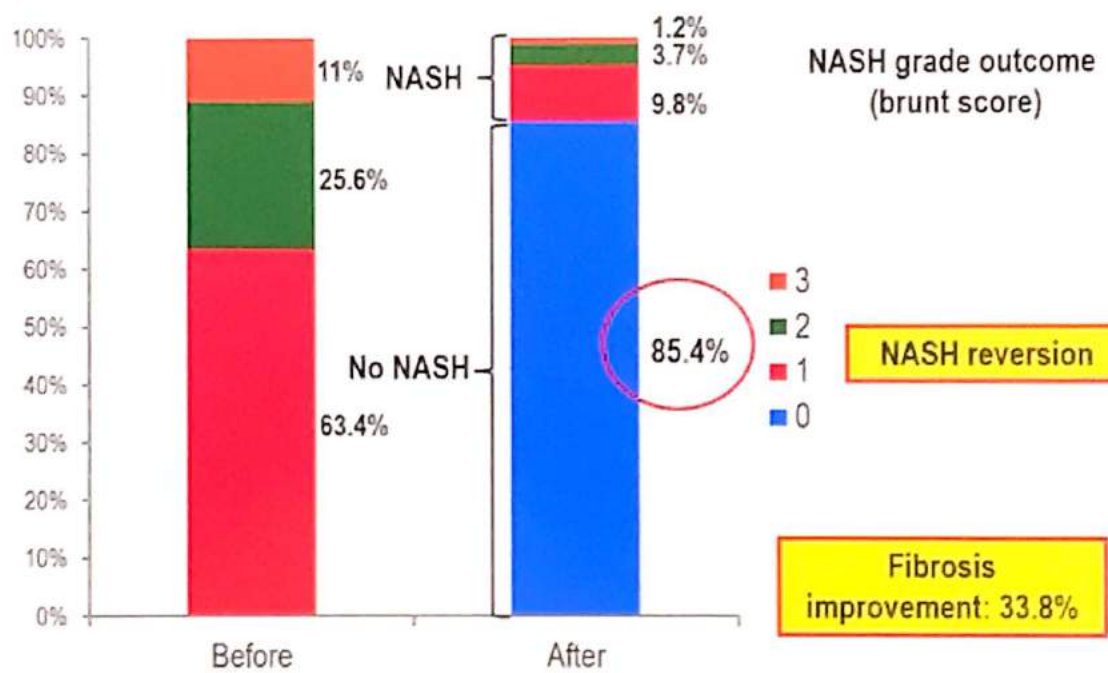


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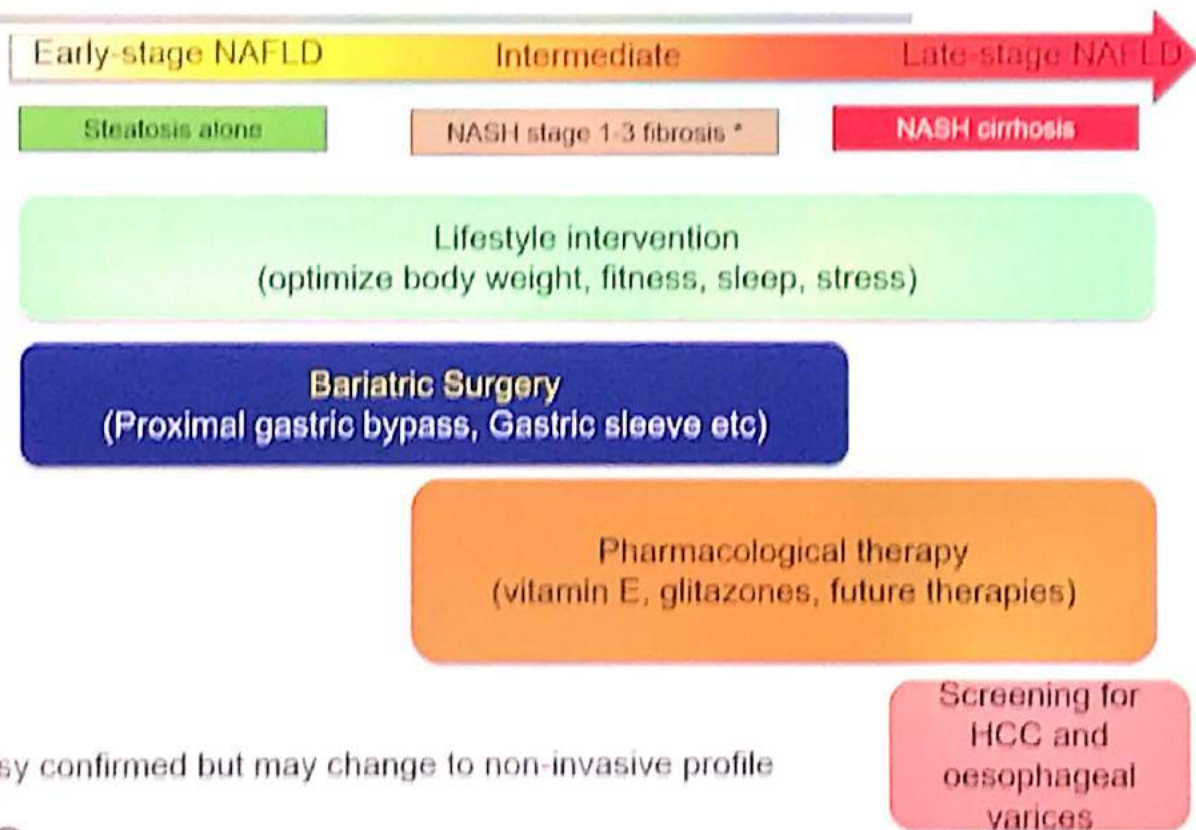
CENTAUR: primary endpoint not met but key secondary endpoint on fibrosis improvement met



Bariatric surgery



Stage-based approach to the treatment of NAFLD



* Biopsy confirmed but may change to non-invasive profile

Conclusions

- The majority of NASH patients are likely unrecognized with a low rate of referral to specialist.
- Screening of populations at risk (diabetes, obese, unexplained cytolysis) with simple non invasive markers of fibrosis is a valuable strategy to assess risk profile of NAFLD patients.
- Lifestyle modifications is associated with liver improvement but achieved in a small proportion of patients.
- Pharmacological intervention is indicated in patients with fibrosis .
- In the absence of approved drug, vitamine E (800U/d or 500mg/d) is the first choice with a good safety profile.

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