Con il Patrocinio di

Sharing
experience
in Diabetologia
ed Endocrinologia

Incontro con gli esperti
sul paziente polipatologico

Corso di
aggiornamento ECM RES

TORINO
18 settembre 2023

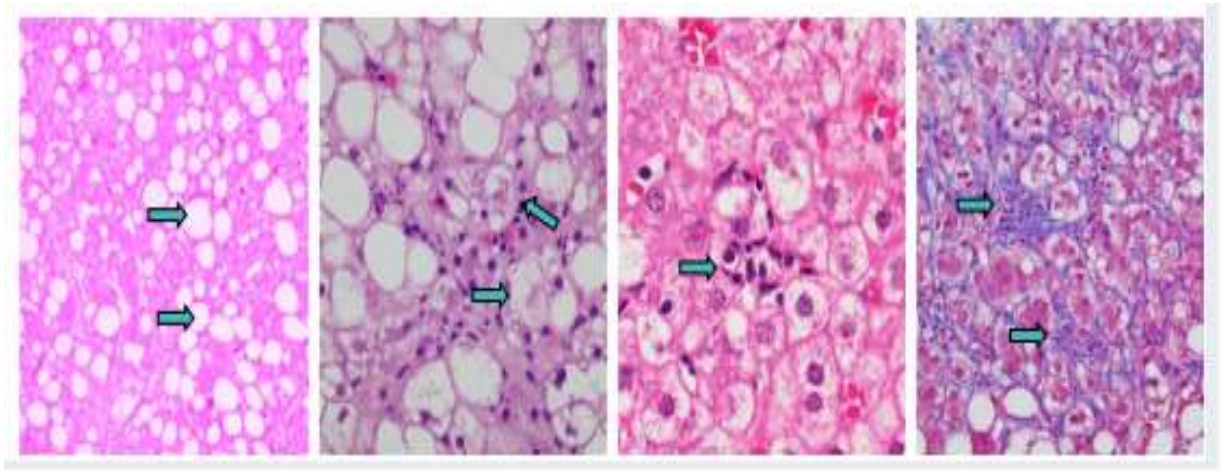
GLP1 – RAs & SGLT2 inhibitors in NAFLD

Floriano Rosina
Hepato-Metabolic Unit
Medical Team - Torino

Nessun Conflitto di Interesse

Spectrum of NAFLD

NASH: histopatological evidence of lobular inflammation and balooning

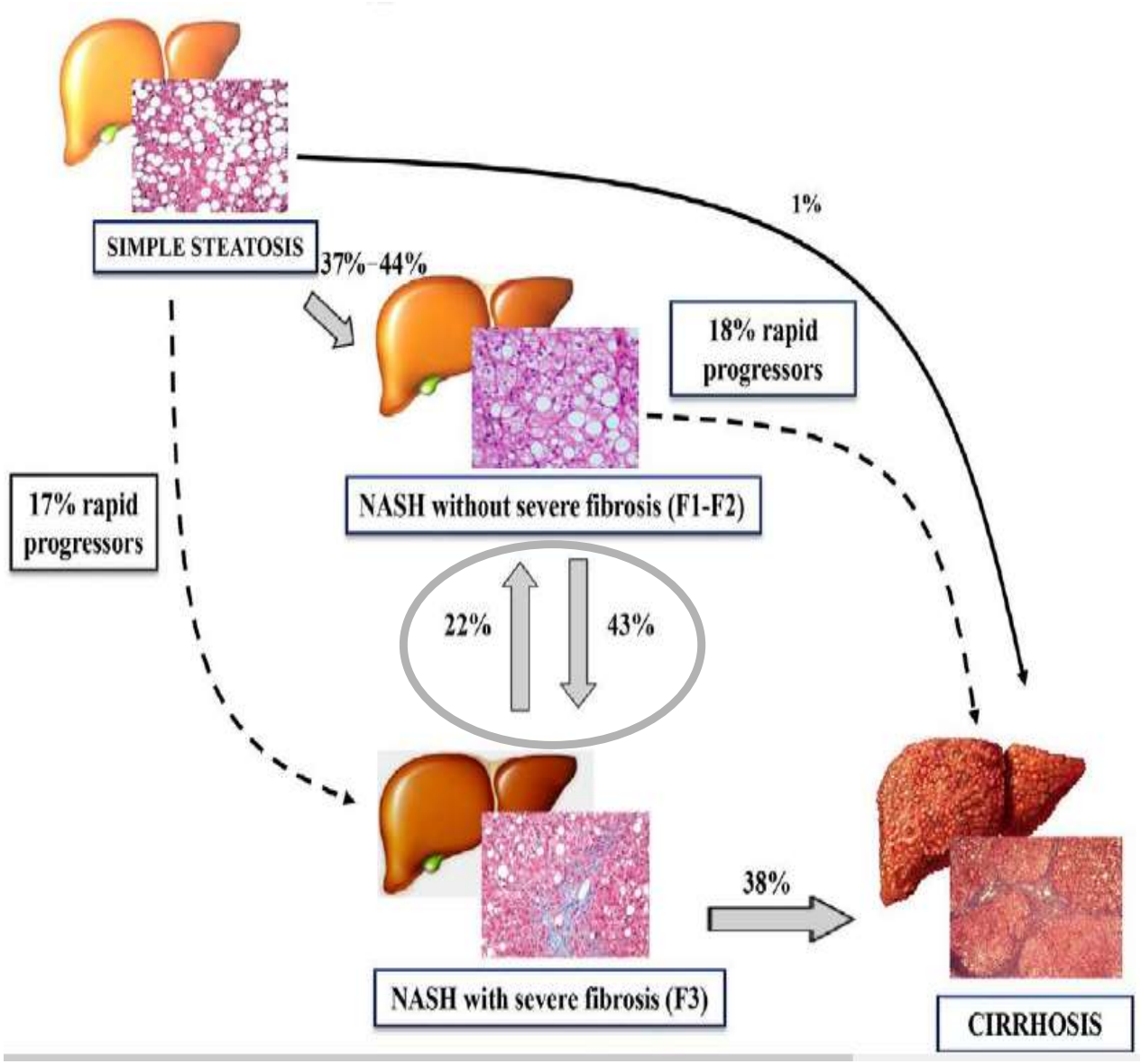


NAFL: simple steatosis >5% in absence of significant alcohol consumption (2-3 U/die)

Fibrosing NASH: highest impact on prognosis

Friedman SL et al, Nat Med 2018

Natural history of NAFLD

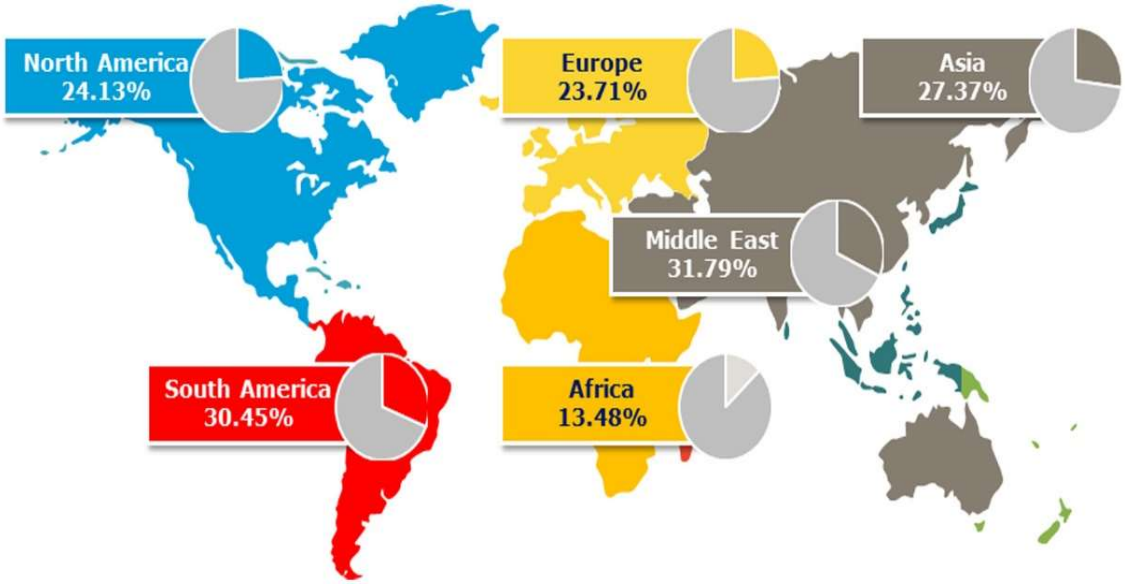


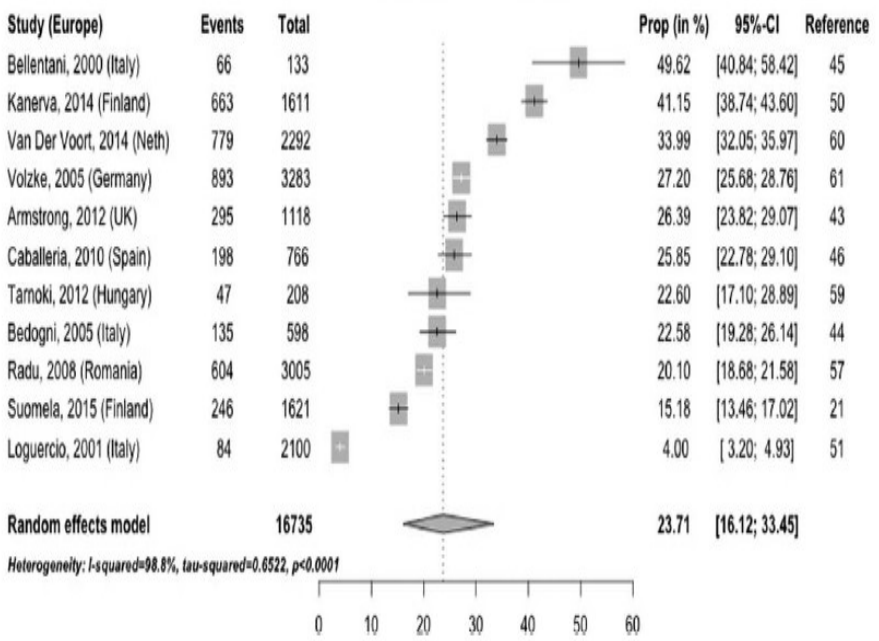
Marengo A et al, Clin Liver Dis 2016

A totally histological diagnosis

Global epidemiology

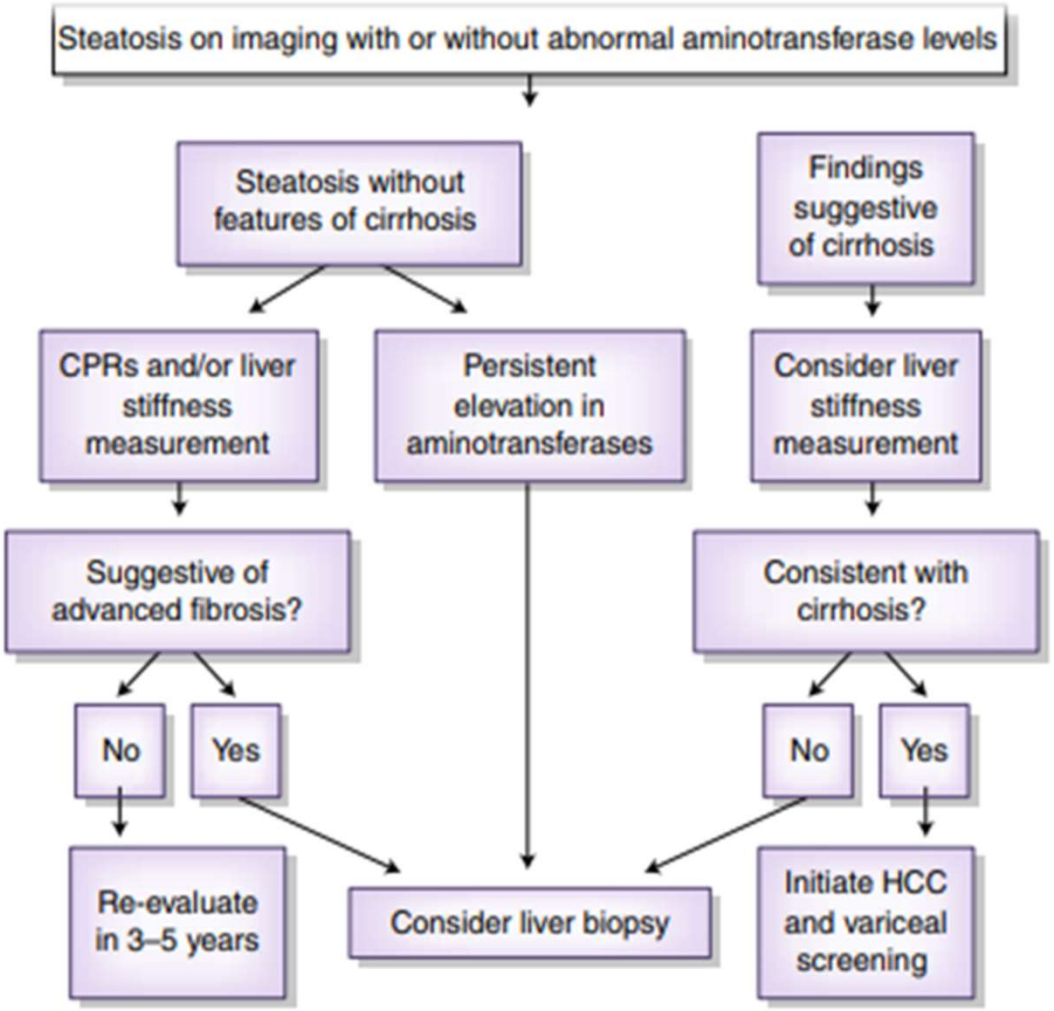
Data from a worldwide meta-analysis including 8.515.431 NAFLD patients





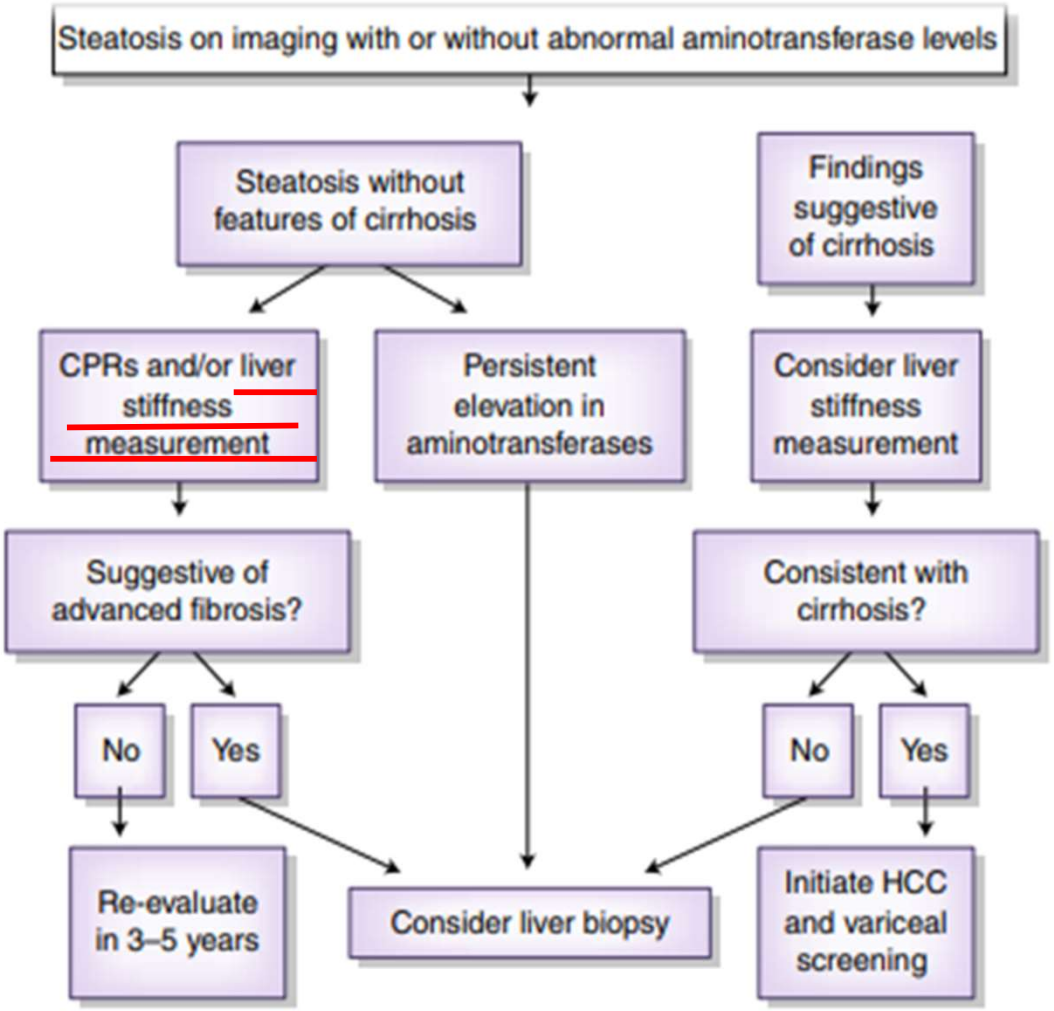
Younossi ZM et al, Hepatology 2016

Diagnostic work-up



Friedman SL et al, Nat Med 2018

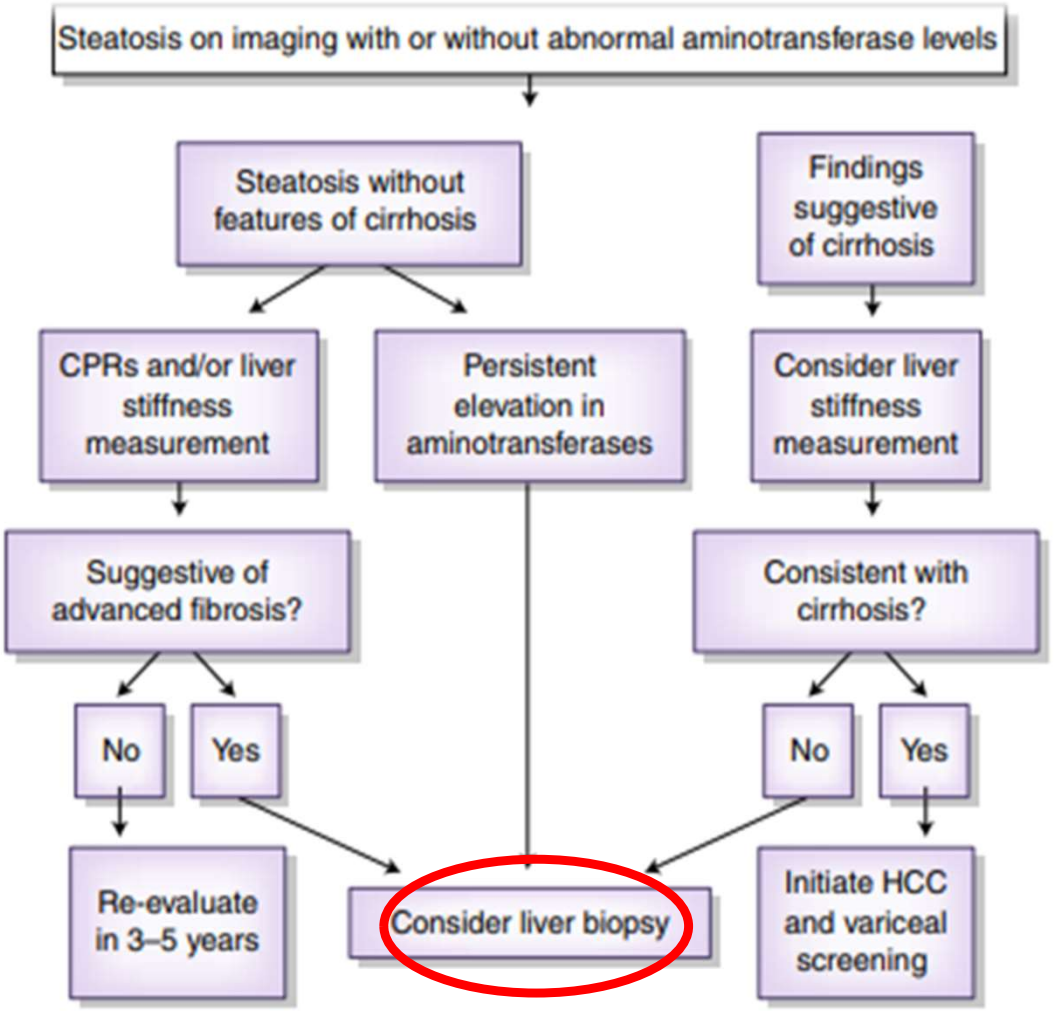
Diagnostic work-up



Friedman SL et al, Nat Med 2018

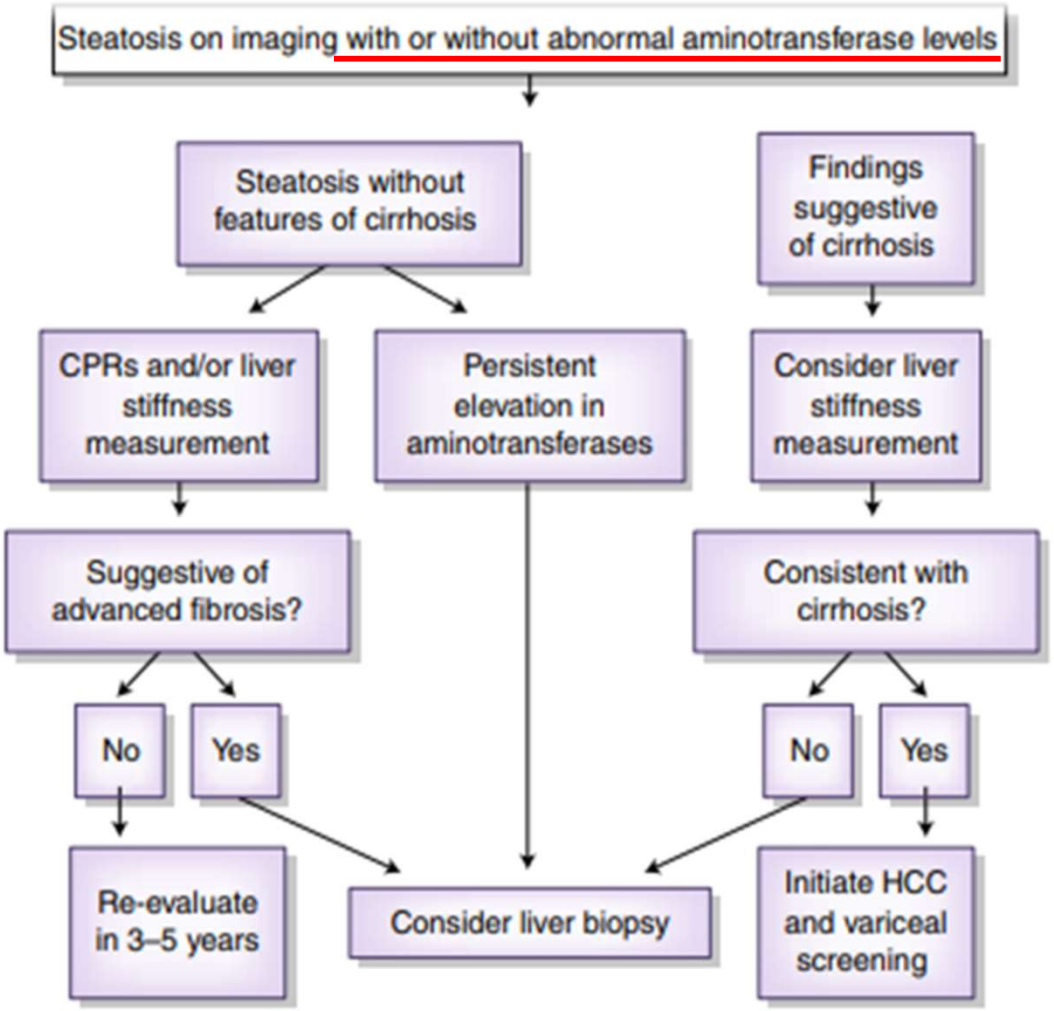
Fibroscan – CAP

Diagnostic work-up



Friedman SL et al, Nat Med 2018

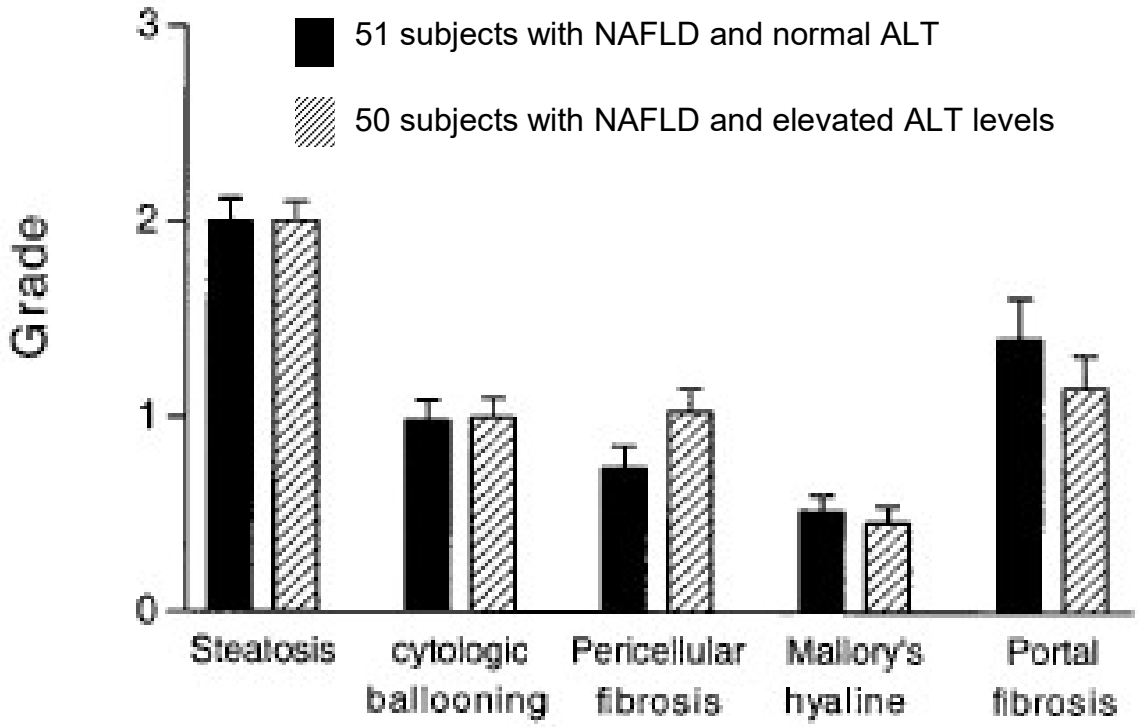
Diagnostic work-up



Friedman SL et al, Nat Med 2018

NAFLD vs ALT

A Paradigma in need to be changed



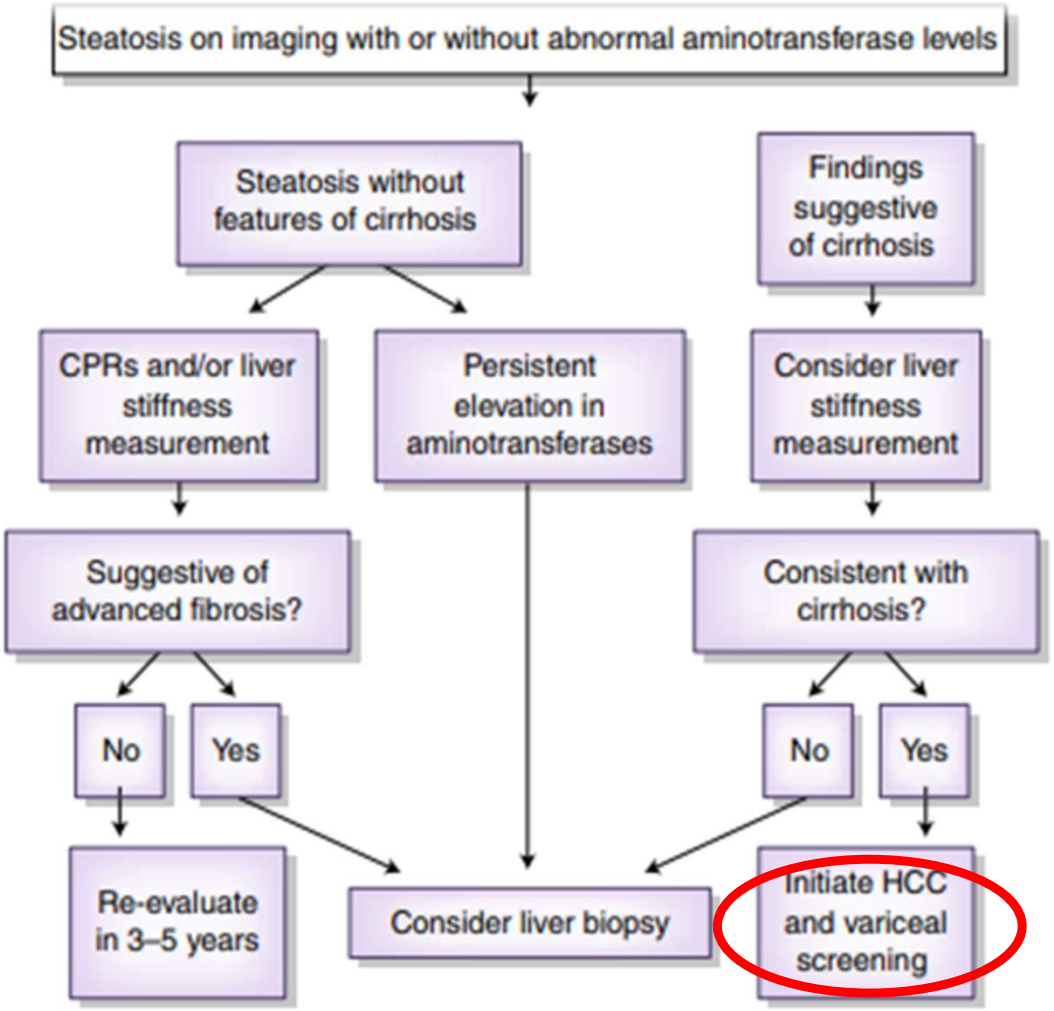
The histologic spectrum of NAFLD in those with normal ALT is comparable with those with elevated ALT

5/15 with normal ALT levels (< 30 IU/L) had advanced fibrosis compared with 13/36 individuals with high ALT levels (31-75 IU/L)

Mofrad P et Al. Hepatology 2003

Gawrieh S et al, Am J Gastroenterol 2019

Diagnostic work-up

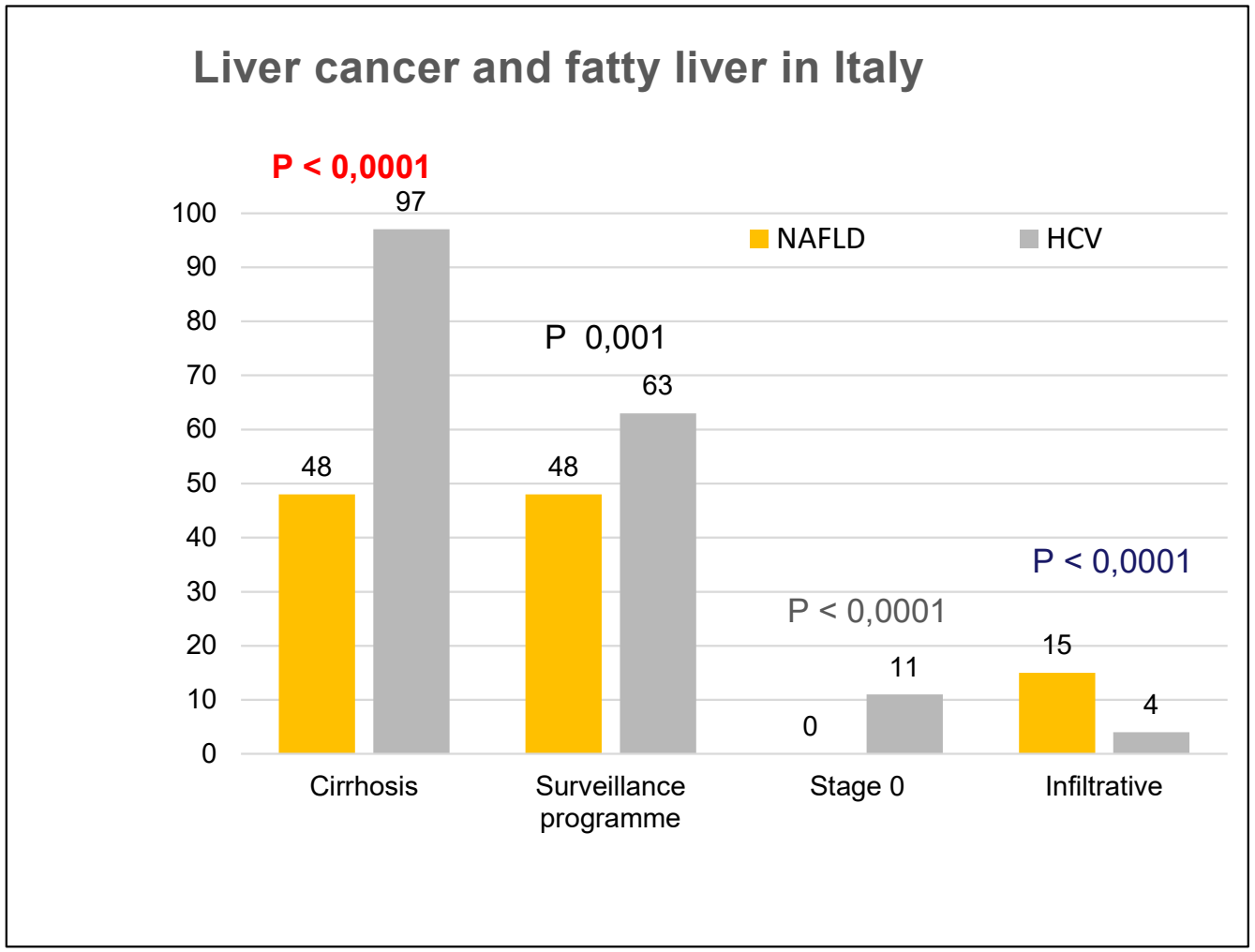


HCC onset in pre-cirrhotic liver!

Friedman SL et al, Nat Med 2018

NAFLD vs HCC

The second Paradigma in need to be changed

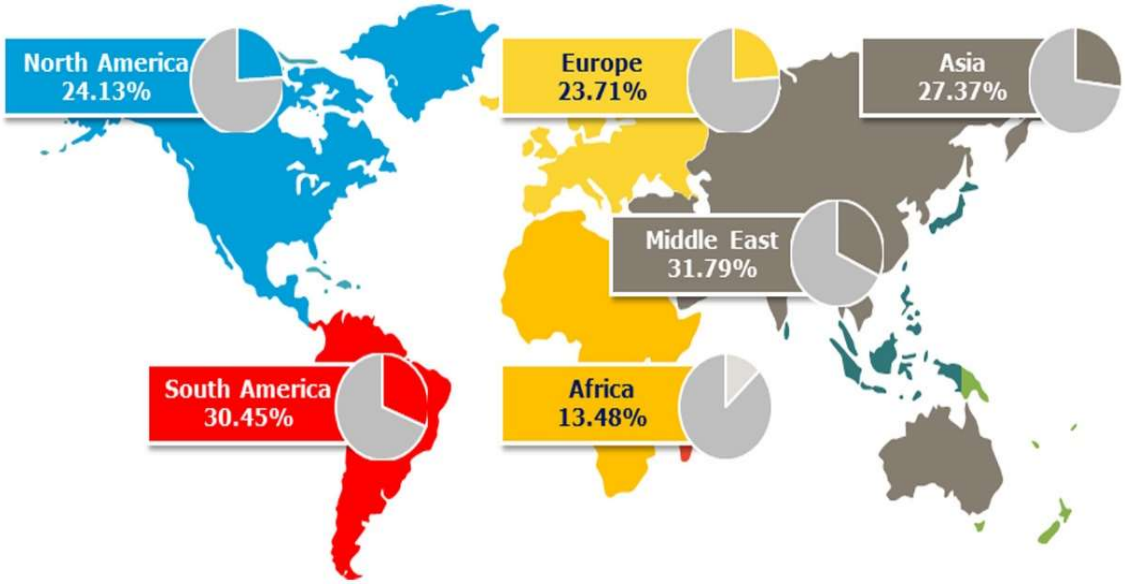


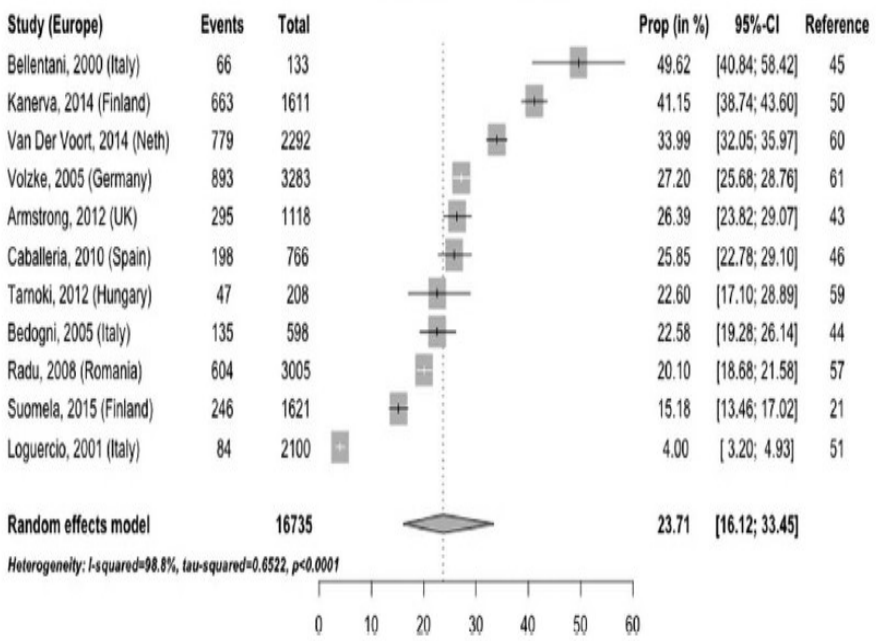
52 %** of NAFLD-related **HCC** are diagnosed in patients **without cirrhosis

Piscaglia F et al, Hepatology 2016

Global epidemiology

Data from a worldwide meta-analysis including 8.515.431 NAFLD patients





Younossi ZM et al, Hepatology 2016

Prevalence of obesity, T2DM and MetS in NAFLD

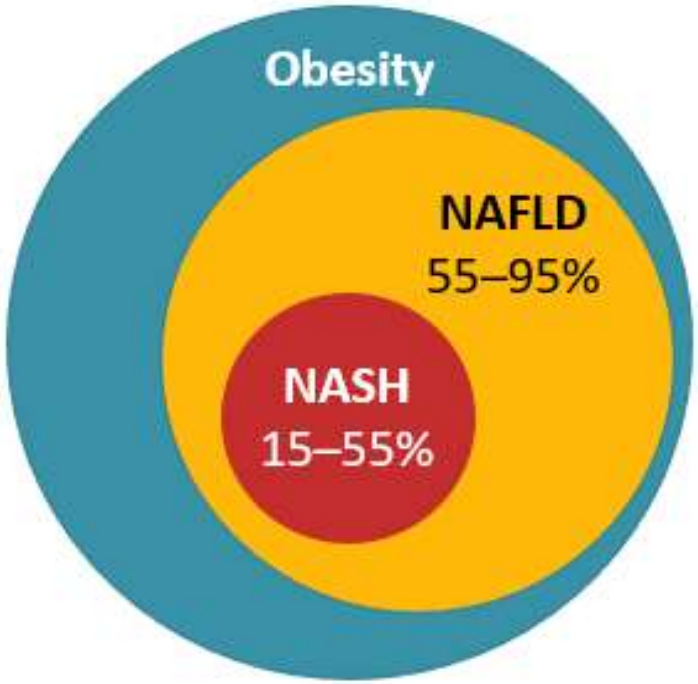
Comorbidity	Region & Diagnosis Technique	N	Prevalence (%)	95% CI (%)	I2 (%)
Obesity	Asia, Imaging	5	63.96	(48.54 - 76.96)	96.071
	Europe, Imaging	8	36.76	(19.58 - 58.13)	97.077
	North America, Self report	1	60.38	(46.77 - 72.54)	NA
	North America, Imaging	5	57.02	(47.82 - 65.76)	95.541
	North America, Blood Test	1	39.66	(36.36 - 43.06)	NA
	Overall	22	50.81	(41.29 - 60.27)	99.344
Diabetes	Africa, Imaging	1	76.92	(47.85 - 92.37)	NA
	Asia, Imaging	8	8.66	(2.60 - 25.22)	98.656
	Europe, Imaging	5	29.85	(21.37 - 39.99)	82.549
	North America, Self report	1	35.85	(24.17 - 49.49)	NA
	North America, Imaging	12	25.28	(19.06 - 32.70)	98.370
	North America, Blood Test	2	13.74	(11.07 - 16.92)	69.405
	Overall	38	22.04	(17.85 - 26.89)	99.544
Metabolic Syndrome	Asia, Imaging	5	12.61	(0.84 - 71.09)	99.311
	Europe, Blood Test	1	69.93	(66.04 - 73.55)	NA
	Europe, Mixture	1	38.27	(31.11 - 45.98)	NA
	Europe, Imaging	2	44.25	(16.79 - 75.74)	96.911
	Middle East, Imaging	1	30.71	(23.31 - 39.25)	NA
	North America, Self report	1	30.19	(19.39 - 43.74)	NA
	North America, Imaging	6	66.59	(51.05 - 79.21)	98.985
	North America, Blood Test	2	48.88	(38.43 - 59.43)	95.201
	North America, ICD Code	1	28.70	(28.21 - 29.20)	NA
	South America, Imaging	2	43.32	(32.26 - 55.08)	38.724
	Overall	22	45.05	(34.67 - 55.88)	99.418

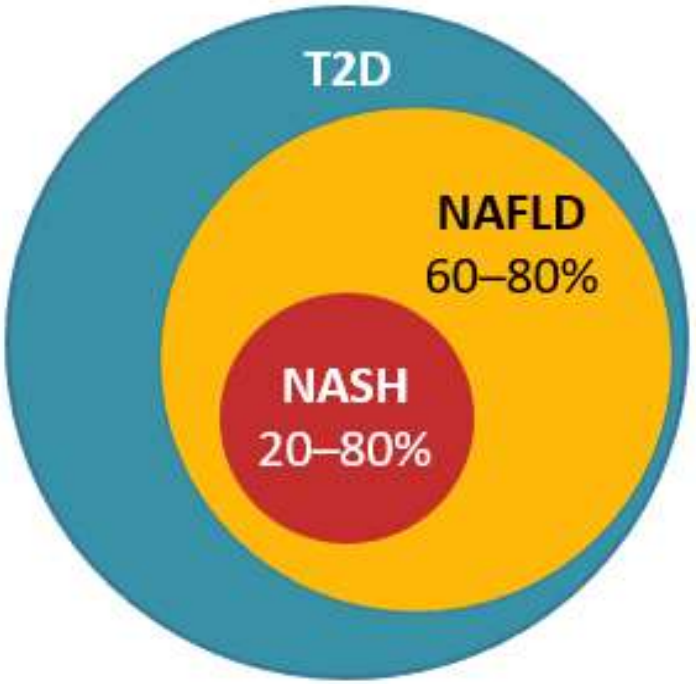
Conditions	Cutoff points
Hypertension (mm Hg) or drug treatment for hypertension control	≥130/85
Tryglicerides (mg/dL)	≥ 150
High density lipoprotein cholesterol (mg/dL)	
Men	< 40
Women	< 50
Waist Circumference (cm)	
Men	≥ 90
Women	≥ 80
Glucose (mg/dl) or drug treatment for glucose control	≥ 100

Adapted from Alberti KGMM. *et al.*
(Three or more conditions).

Younossi ZM et al, Hepatology 2016

Prevalence of NAFLD and NASH in high risk groups





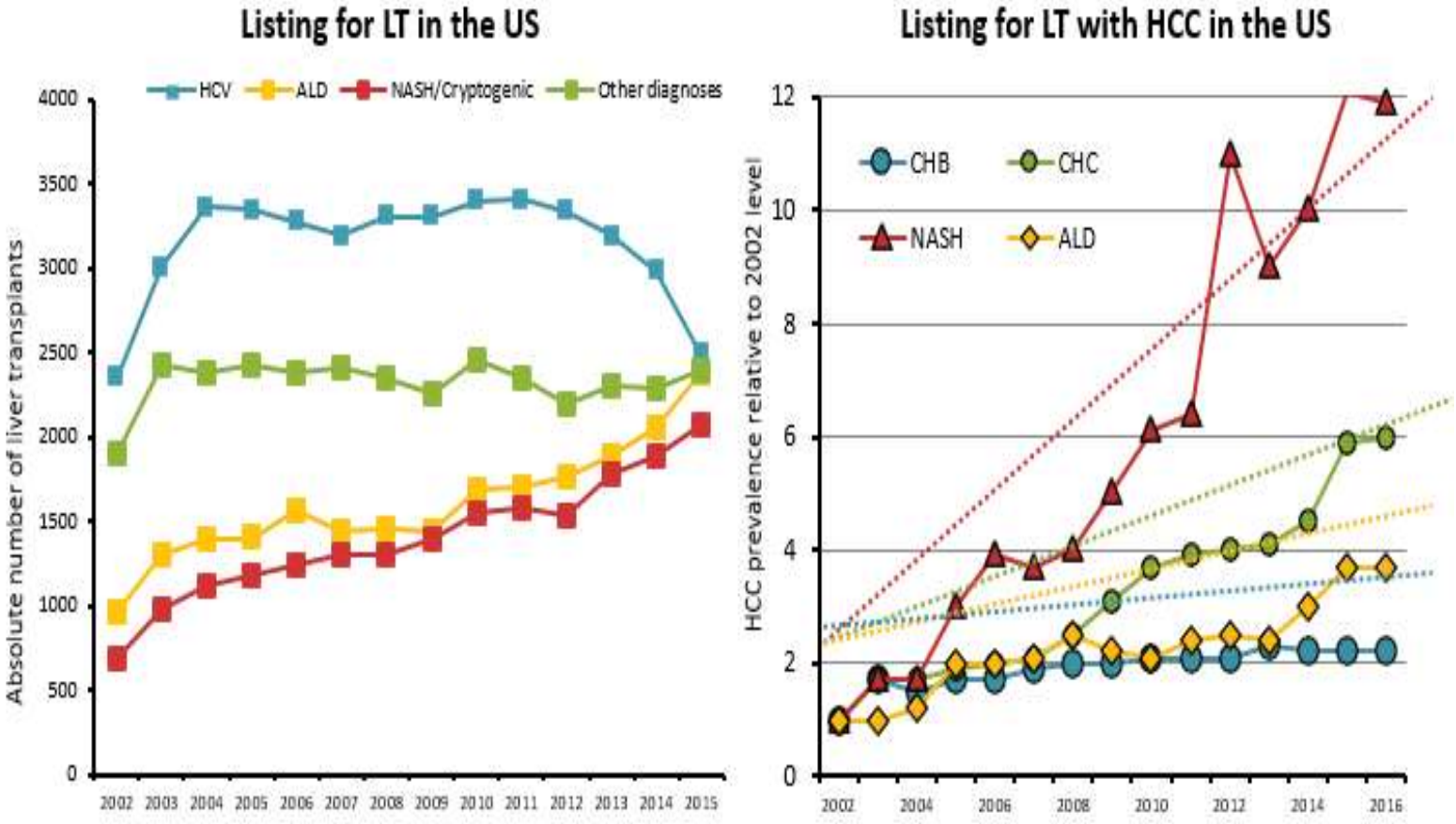
Bhala N et al, Curr Pharma Des 2013

Mortality in NAFLD and NASH

Population	Outcome	Incidence Rate Per 1,000 Person-Years*	Number of Studies	95% CI	I^2 (%)	Follow-up (Years)
NAFLD	CVD-specific mortality	4.79	6	(3.43-6.7)	91.17	12.96
NAFLD	HCC	0.44	3	(0.29-0.66)	0.00	5.82
NAFLD	Liver-specific mortality	0.77	7	(0.33-1.77)	91.84	13.17
NAFLD	Overall mortality	15.44	7	(11.73-20.34)	97.17	13.17
NASH	Advanced fibrosis	67.95	3	(46.84-98.56)	9.80	4.05
NASH	HCC	5.29	1	(0.75-37.56)	NA	4.50
NASH	Liver-specific mortality	11.77	3	(7.1-19.53)	0.00	8.08
NASH	Overall mortality	25.56	2	(6.29-103.8)	73.85	6.17
		IRR*				
NAFLD	Liver-specific mortality	1.94	5	(1.28-2.92)	26.78	13.38
NAFLD	Overall mortality	1.05	5	(0.7-1.56)	97.99	13.38
NASH	Liver-specific mortality	64.6	3	(35.43-117.8)	0.00	8.08
NASH	Overall mortality	2.56	2	(0.63-10.39)	73.76	6.17
		AHR Ratio*				
NAFLD	Liver-specific mortality	2.6	5	(0.91-7.42)	76.66	13.23
NAFLD	Overall mortality	1.04	5	(1.03-1.04)	0.08	13.23
		Fibrosis Progression				
NASH	Percent fibrosis progression†	40.76	4	(34.69-47.13)	5.70	4.91
NASH	Mean fibrosis annual progression rate†	0.09	2	(0.06-0.12)	0.00	4.01

Younossi ZM et al, Hepatology 2016

Evidence supporting progressiveness of NASH



Goldberg D et al, Gastroenterology 2017

NASH TREATMENT

- *Preludio*
- *The Gold Standard*
- *What Drugs Today*
- *What Drugs in the next future*

NASH TREATMENT

- *Preludio*
- *The Gold Standard*
- *What Drugs Today*
- *What Drugs in the next future*

NASH Treatment …. Preludio

Preludio

….NO FDA and EMA approved therapies for NASH

NASH TREATMENT

- *Preludio*
- *The Gold Standard*
- *What Drugs Today*
- *What Drugs in the next future*

EASL – EASD – EASO
Clinical Practice Guidelines

- 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**)

Journal of Hepatology 2016 vol. 64 - 1388-1402

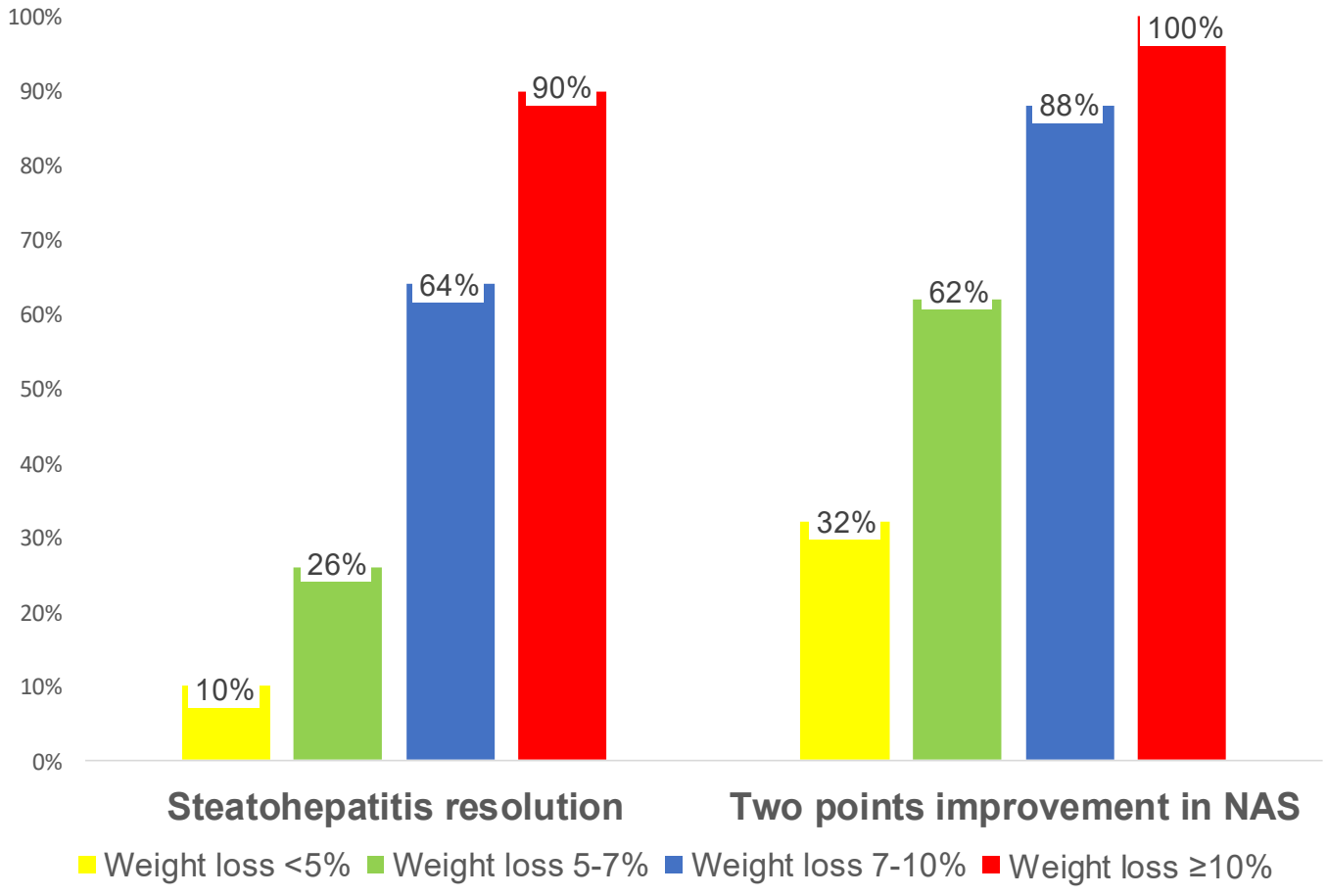
EASL – EASD – EASO
Clinical Practice Guidelines

Area	Suggested intervention
Energy restriction	• 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week
	• 7-10% total weight loss target
	• Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment

Journal of Hepatology 2016 vol. 64 - 1388-1402

NAFLD / NASH Treatment

NASH resolution & NAS Improvement according to weight loss



45% of pts with > 10 % weight loss had FIBROSIS REGRESSION

293 pts from Cuba

Low-fat hypocaloric diet 750 kcal/d less than daily energy need

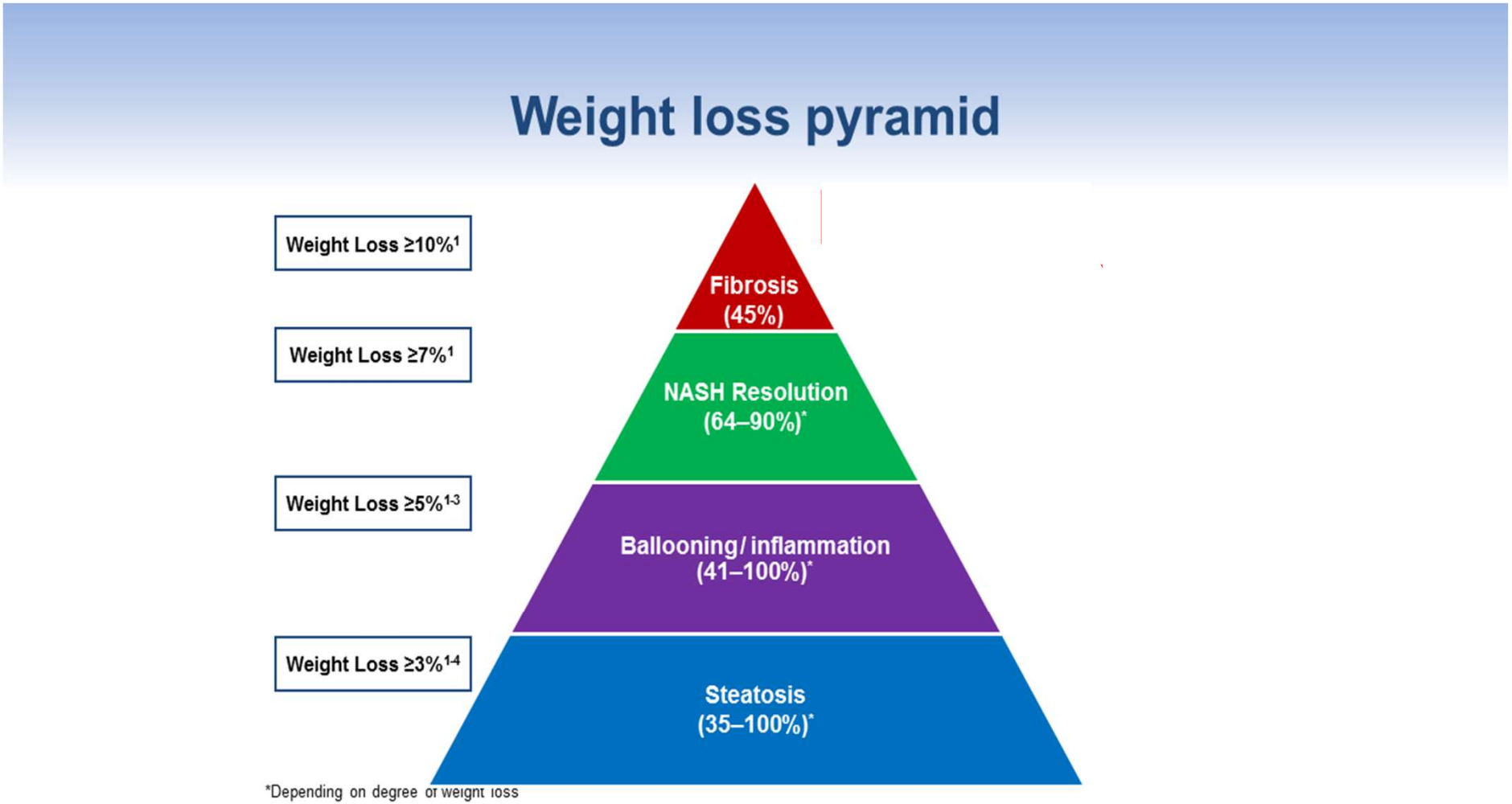
- *carbohydrates 64%;*
- *fat 22% (<10% of saturated fatty acids)*
- *protein 14%.*
- *200 minutes walk/week*
- *Behavioral individual sessions / 8 weeks*

Liver Biopsy
- *Baseline*
- *At 52 weeks*
- *Paired liver biopsies: 261*

Villar-Gomez E et al. Gastroenterology 2015

NAFLD / NASH Treatment

NASH resolution & NAS Improvement according to weight loss

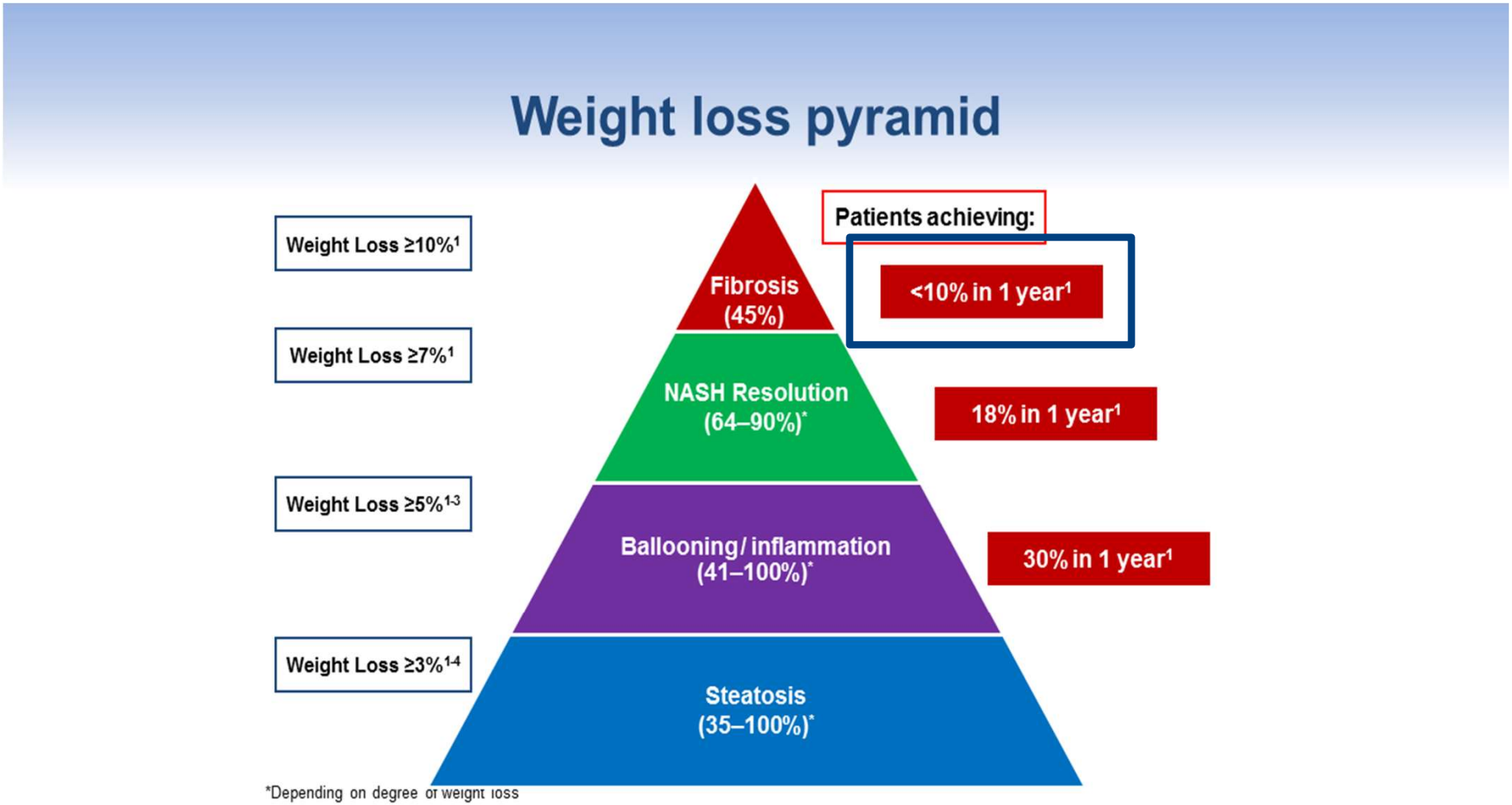


1 Vilar-Gomez E, et al. Gastroenterology. 2015;149:367-78. 2 Promrat K, et al. Hepatology. 2010;51:121-9
3 Harrison SA, et al. Hepatology. 2009;49:80-6. 4 Wong VW, et al. J Hepatol. 2013;59:536-42

Slide courtesy of S. Harrison

NAFLD / NASH Treatment

NASH resolution & NAS Improvement according to weight loss

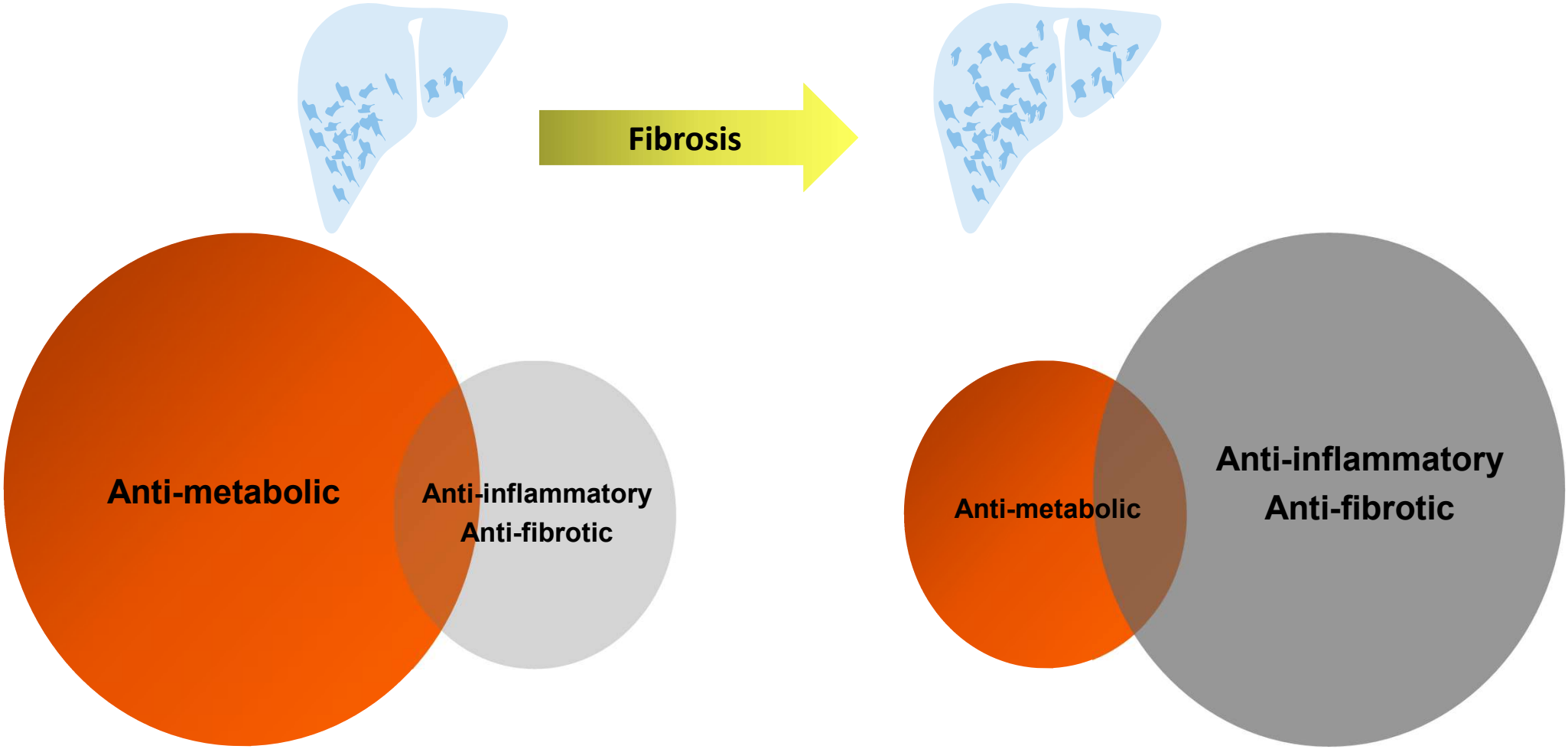


1 Vilar-Gomez E, et al. Gastroenterology. 2015;149:367-78. 2 Promrat K, et al. Hepatology. 2010;51:121-9
3 Harrison SA, et al. Hepatology. 2009;49:80-6. 4 Wong VW, et al. J Hepatol. 2013;59:536-42

Slide courtesy of S. Harrison

- *Drugs targeting Metabolism*
- *Drugs targeting inflammatory pathways and fibrosis*

The Future of Combination Therapy



GLP1 – RAs and NAFLD

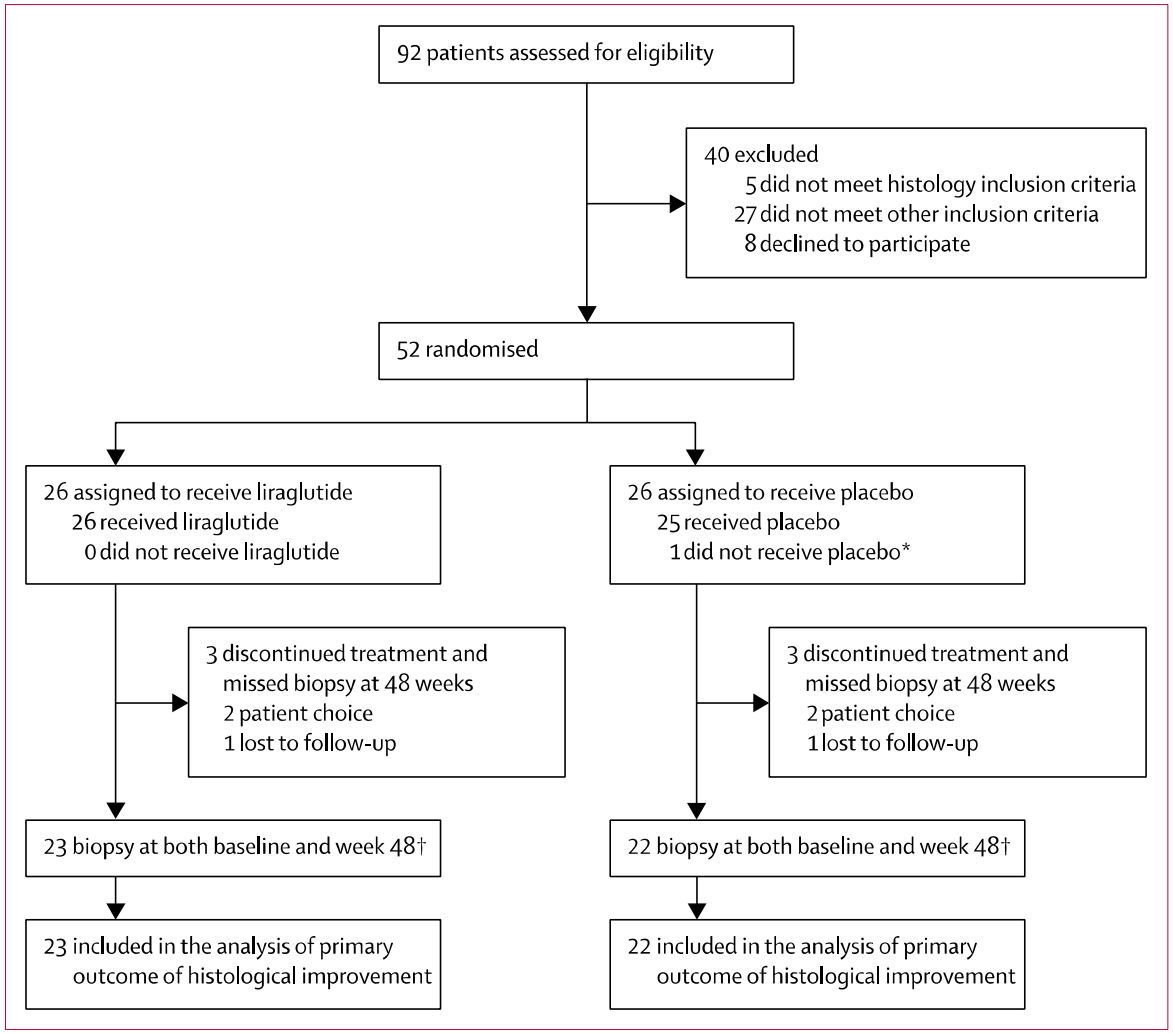
Metabolic Effects of GLP-1 Receptor Agonists

GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Campbell, Drucker. Cell Metab 2013;17:819–37; 2. Baggio, Drucker. J Clin Invest 2014;124:4223–6; 3. Flint et al. J Clin Invest 1998;101:515–20; 4. Blundell et al. Diabetes Obes Metab 2017;19:1242–51; 5. Tong, D'Alessio. Diabetes 2014;63:407–9; 6. Armstrong et al. J Hepatol 2016;64:399–408; 7. Armstrong et al. Lancet 2016;387:679–90; 8. MacDonald et al. Diabetes 2002;51(Suppl 3):S434–42; 9. Drucker. Cell Metab 2016;24:15–30.

NAFLD / NASH Treatment

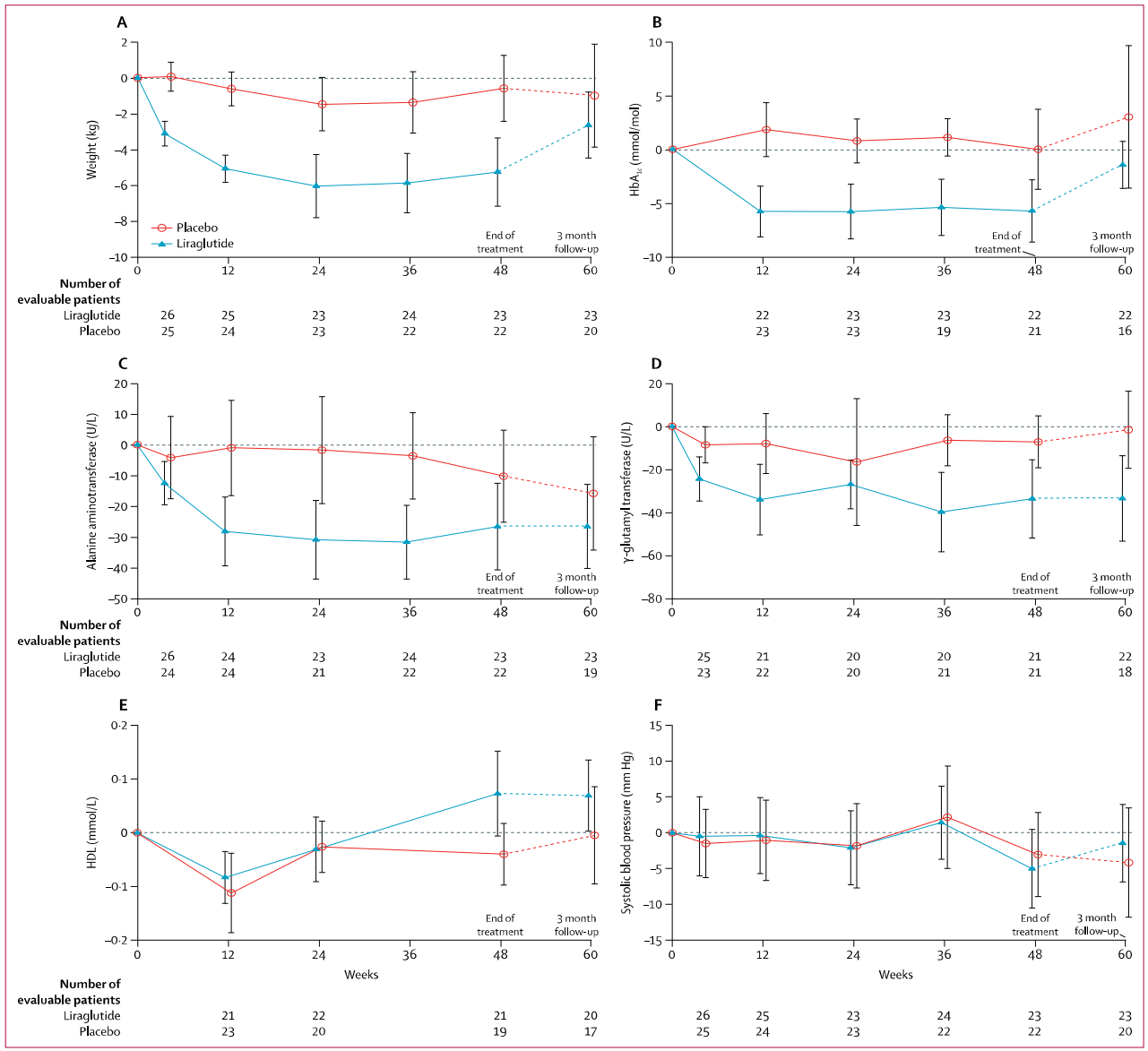
GLP-1 Agonist: LIRAGLUTIDE



Armstrong MJ et al , Lancet 2016

NAFLD / NASH Treatment

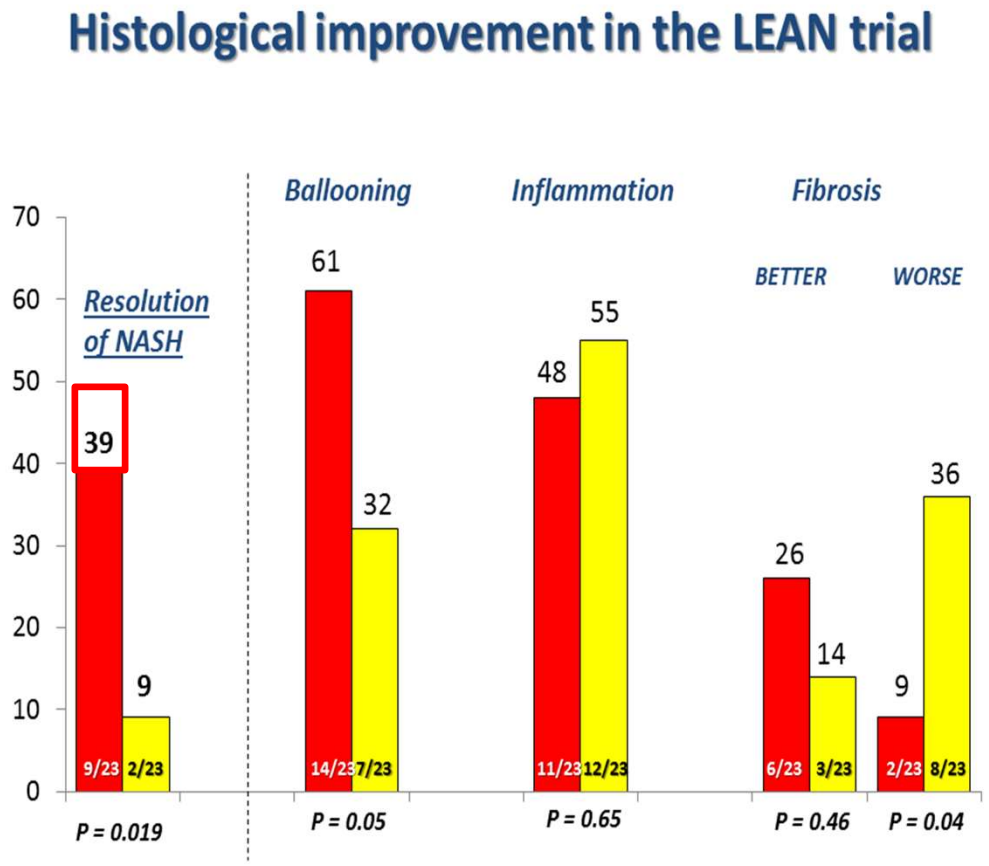
GLP-1 Agonist: LIRAGLUTIDE



Armstrong MJ et al , Lancet 2016

NAFLD / NASH Treatment

GLP-1 Agonist: LIRAGLUTIDE

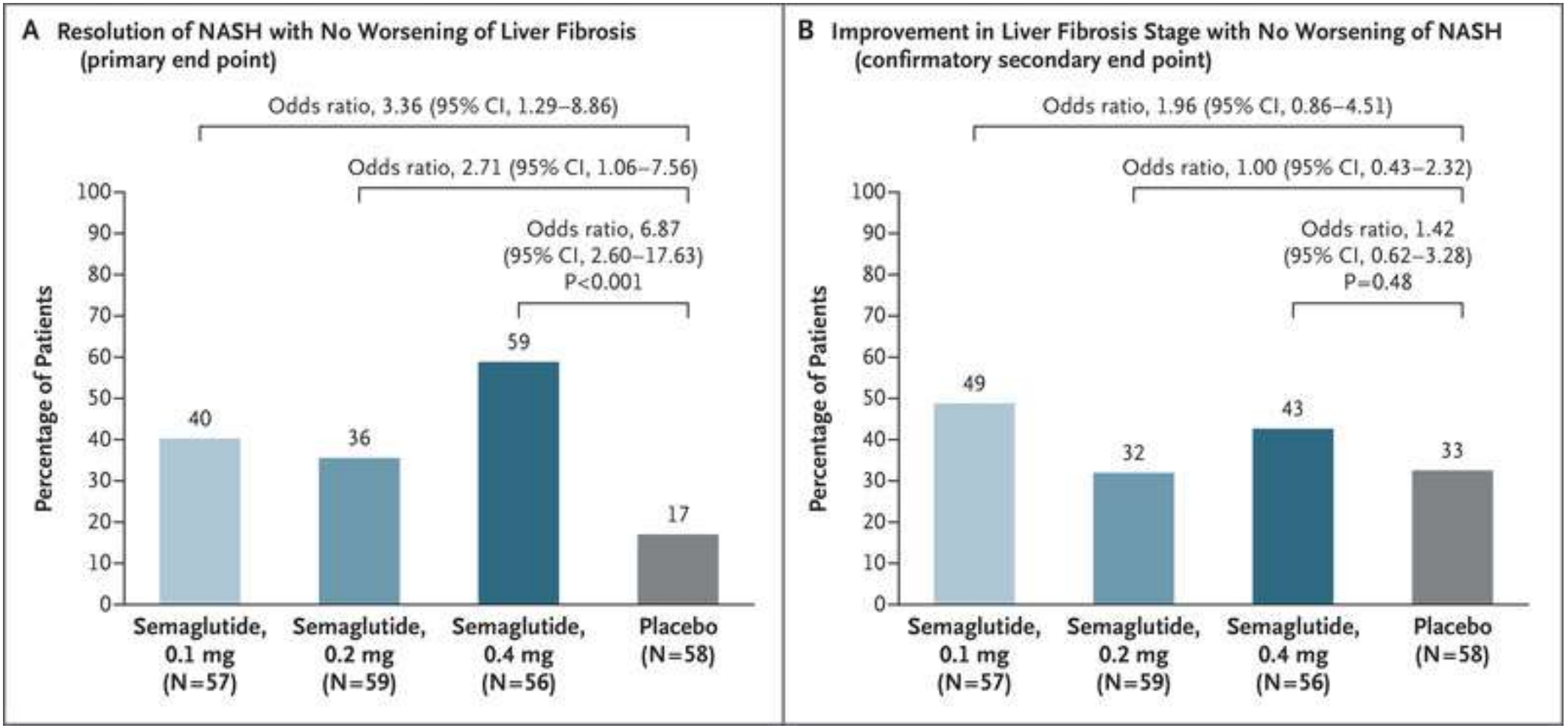


Liraglutide
(GLP-1 agonist)
↑ *Insulin secretion*
↓ *appetite*
↑ *weight loss*

Armstrong MJ et al , Lancet 2016

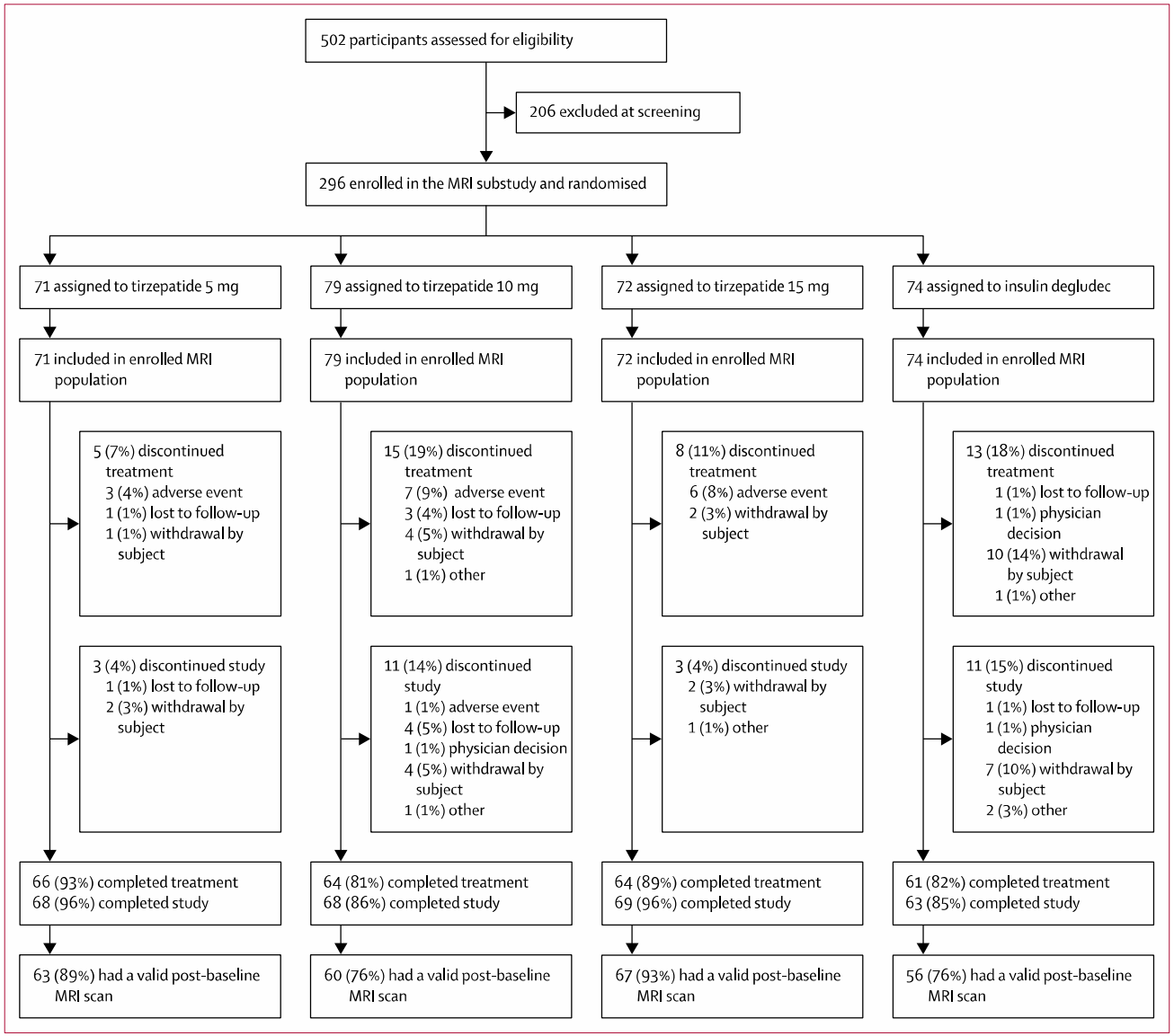
Semaglutide in NASH Phase 2 Trial

- A 72-week, Phase 2 study of 320 participants with NASH, fibrosis stage 1, 2, or 3
- **Interventions**: Placebo vs semaglutide 0.1 , 0.2 or 0.4 mg once-daily subcutaneous
- **Primary outcome: Resolution of NASH and no worsening in liver fibrosis**
- The safety of GLP1-RA in NASH was consistent with the observed profile in other trials and disease areas
- The most common adverse events with semaglutide were gastrointestinal (nausea, constipation and vomiting)



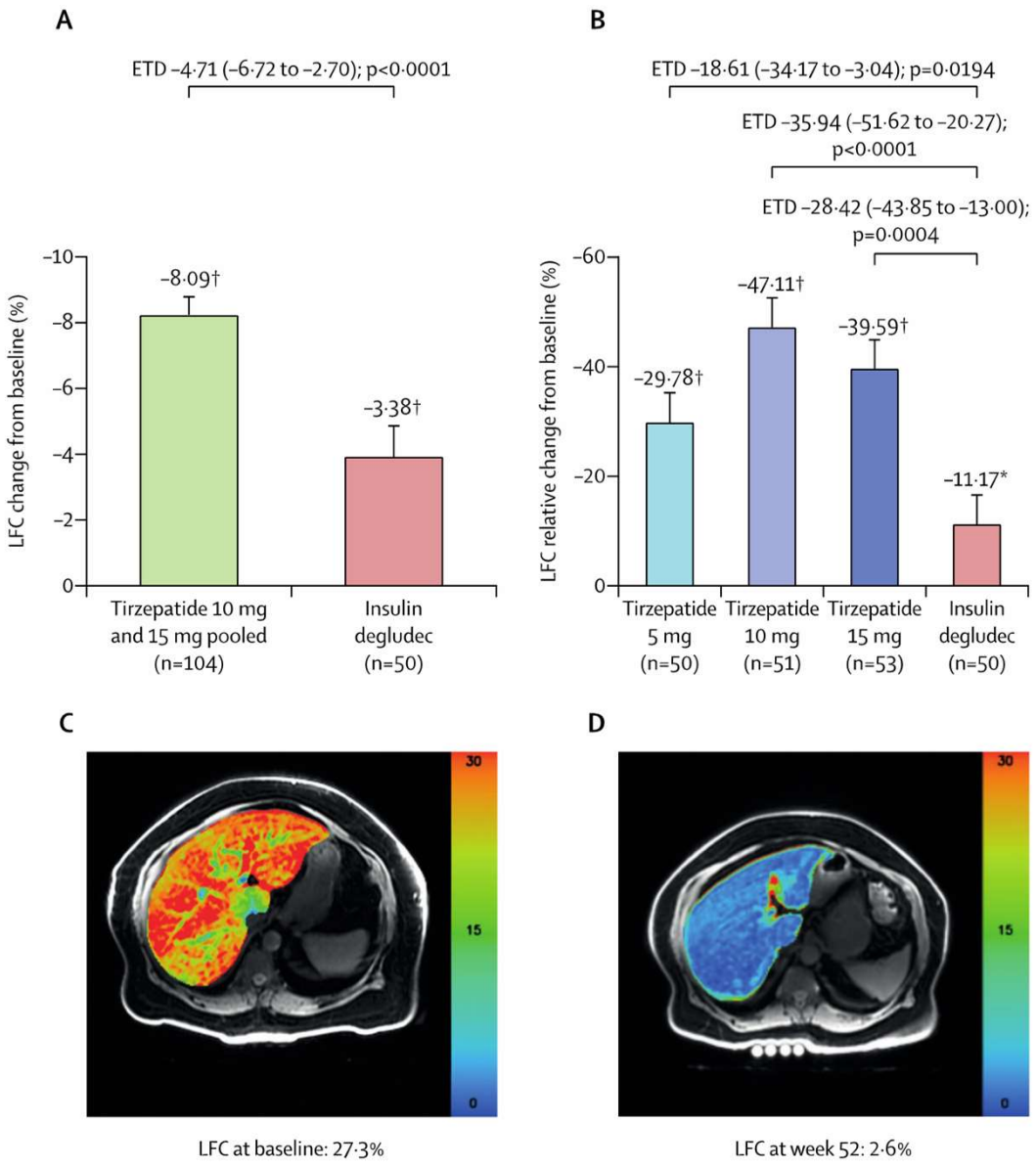
Newsome PN, Harrison SA, et al. N Engl J Med. 2021;384:1113–24.

Tirzepatide in NAFLD reduces liver fat content and abdominal adipose tissue (SURPASS-3 MRI)



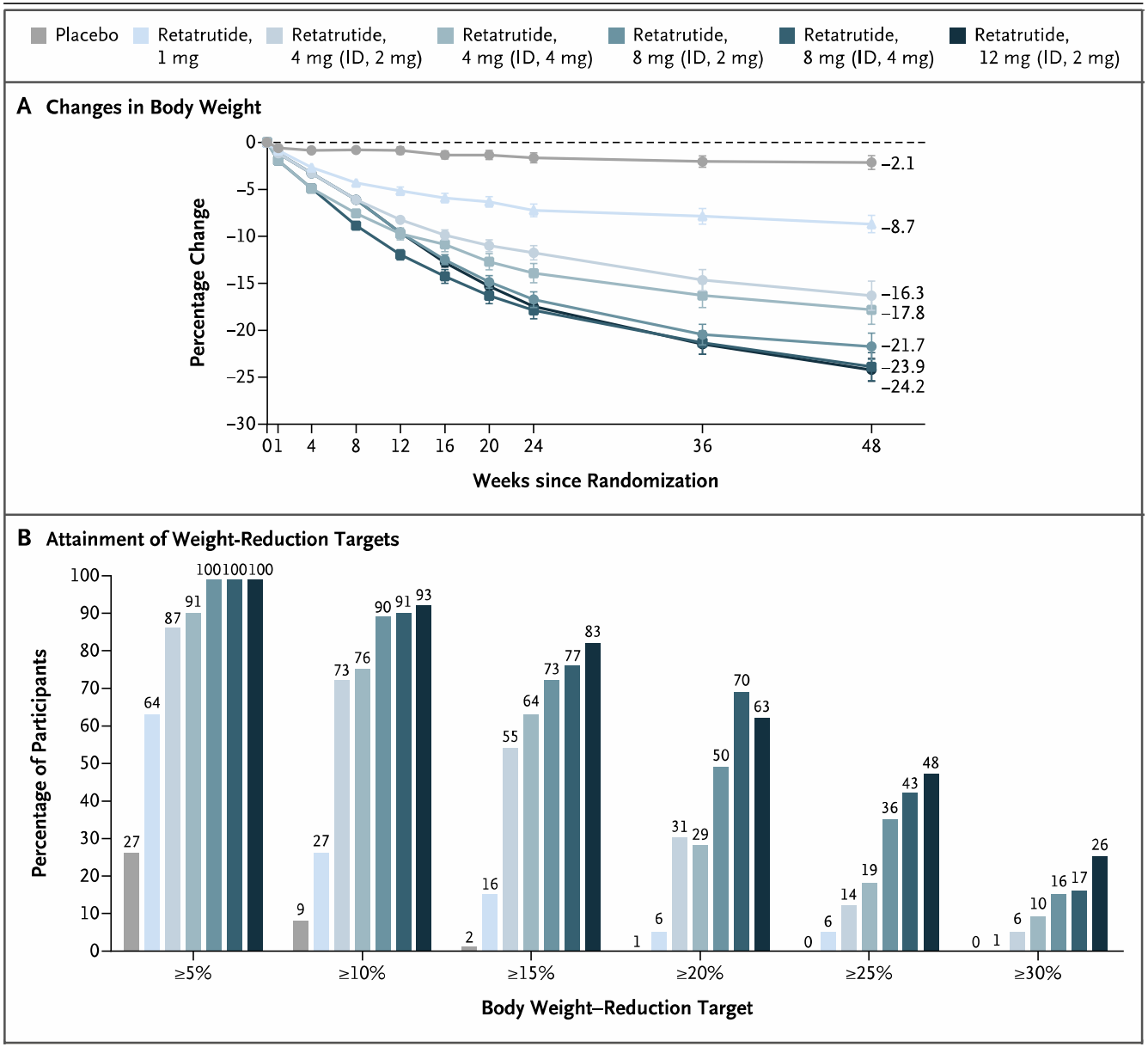
Gastaldelli A, et al. Lancet Diabetes Endocrinol 20221

Tirzepatide in NAFLD reduces liver fat content and abdominal adipose tissue (SURPASS-3 MRI)



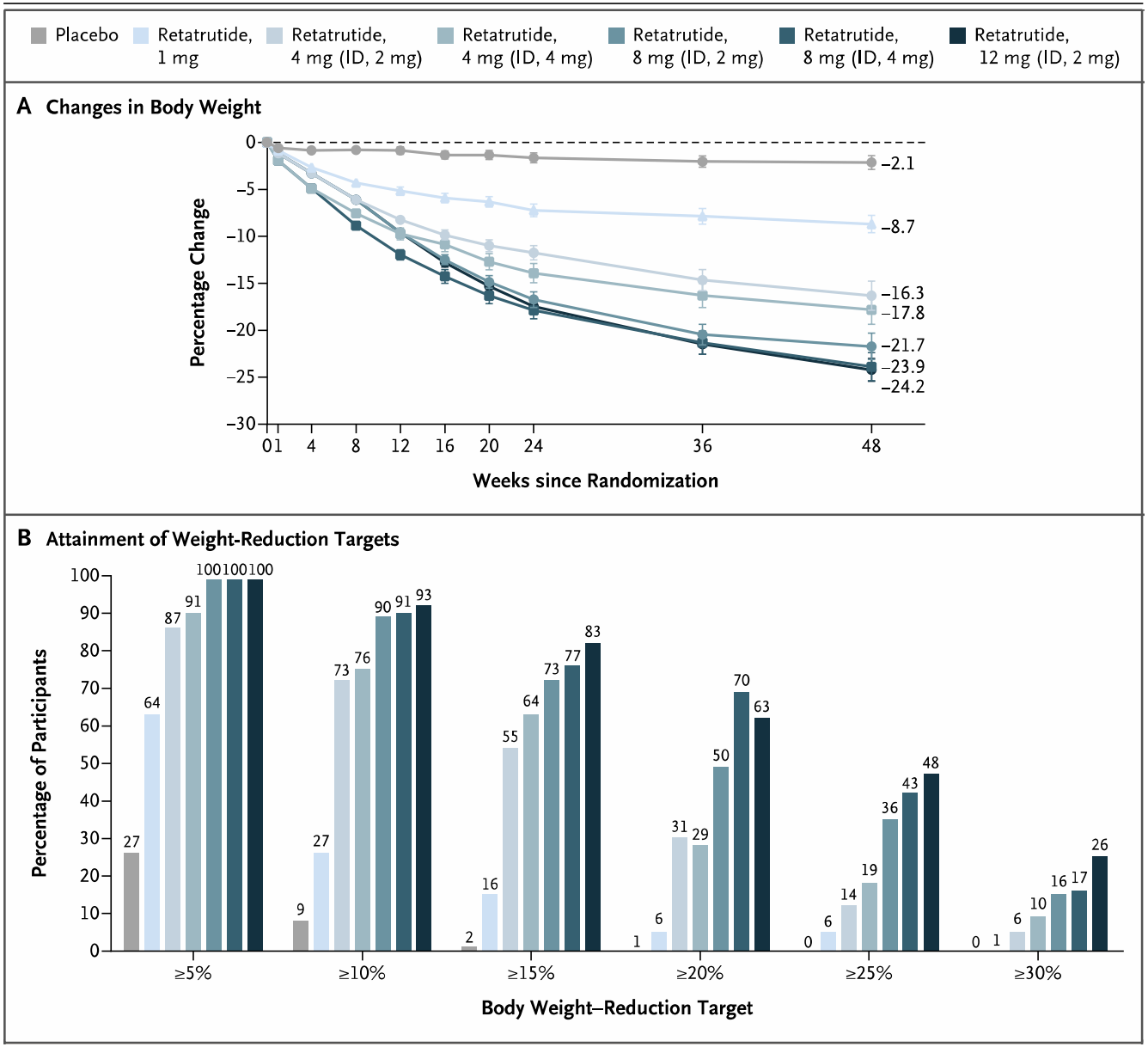
Gastaldelli A, et al. Lancet Diabetes Endocrinol 20221

Triple-Hormone-Receptor Agonist Retatrutide for Obesity



Jastreboff AM, et al. N Engl J Med 2023

Triple-Hormone-Receptor Agonist Retatrutide for Obesity



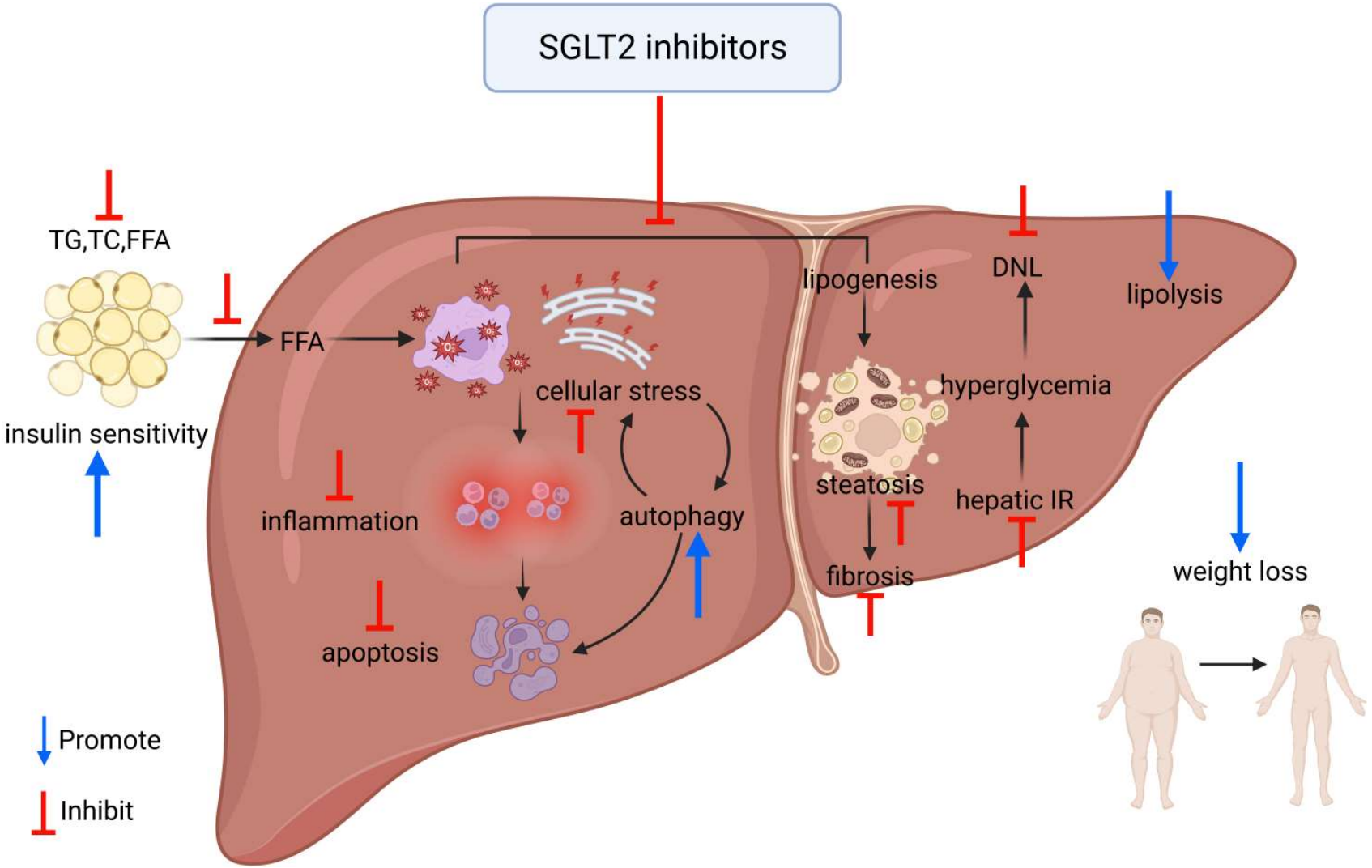
98 person in the trial with NAFLD

Normalized Liver Fat Content in 90% of pts treated with Retatrutide at the higher dose (12 mg)

Sanyal AJ, et al. 83rd Scientific Session of the American Diabetes Association, S Diego CA, June 26, 2023

SGLT2 Inhibitors and NAFLD

SGLT2 Inhibitors mechanism of Improvement in NAFLD



Xu R et al. Front Biosci 2023

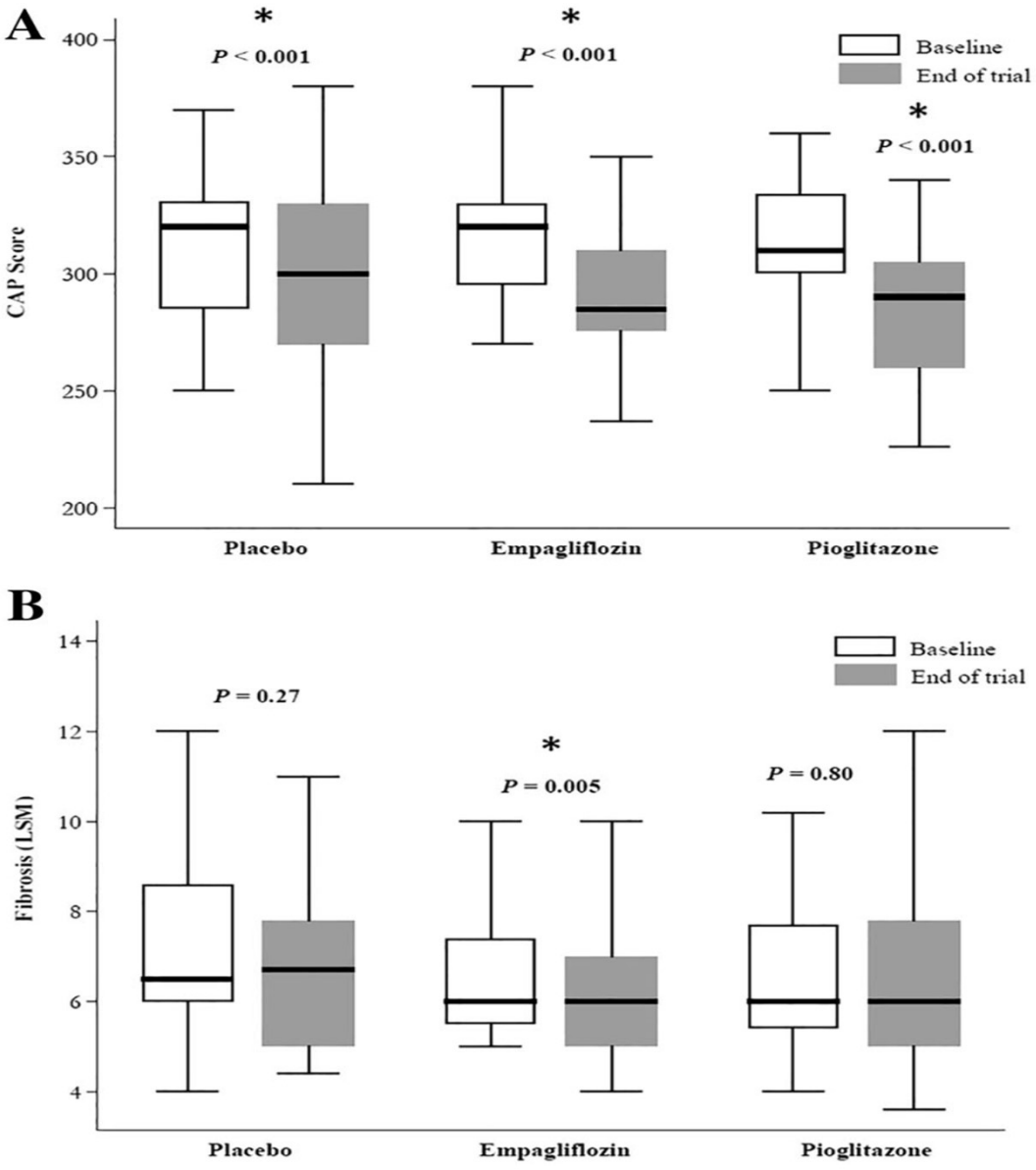
Clinical Studies of SGLT2 Inhibitors in NAFLD

Table 3. Clinical studies of SGLT-2 inhibitors in the treatment of NAFLD.

Types of drugs	Study population	Duration (weeks)	Hepatic benefits	Diabetic benefits	Refs
Canagliflozin	T2DM, NAFLD	48	↓ HFF, ↓ ALT, AST and GGT	↓ HbA1c, ↓ BMI and FM	[91]
	T2DM, NAFLD	24	↓ steatosis	↓ HbA1c, ↓ weight, ↓ HOMA-IR	[92]
	T2DM, NASH	12	↓ fibrosis, ↓ AST, GGT	↓ HbA1c, ↓ BMI	[93]
Dapagliflozin	T2DM, NAFLD	24	↓ ALT, GGT	↓ HbA1c, ↓ weight, ↓ HOMA-IR, ↓ VAT	[94]
	T2DM, NAFLD	12	↓ ALT, AST and GGT	↓ HbA1c, ↓ weight, ↓ HOMA-IR, ↓ VAT	[95]
	T2DM, NAFLD	12	↓ lipid contents, ↓ ALT	↓ HbA1c, ↓ weight, ↓ body fat	[96]
	NAFLD	12	↓ ALT and AST	↓ HbA1c, ↓ weight, ↓ BMI	[97]
Empagliflozin	T2DM, NAFLD	20	↓ liver fat, ↓ ALT	↔	[29]
	NAFLD	24	↓ steatosis, ↓ ALT and AST, ↓ LSM	↓ fasting insulin	[98]
	T2DM, NAFLD	24	↓ steatosis and fibrosis, ↓ AST, ↓ LSM	↓ HbA1c	[99]
	T2DM, NASH	24	↓ steatosis, fibrosis and ballooning, ↓ GGT	↓ BMI, ↓ FBG, ↓ TC	[100]

Xu R et al. Front Biosci 2023

Empaglifozin in NAFLD



106 pts T2DM + NALFD
- 35 pts Empaglifozin 10 mg
- 34 pts Pioglitazone 30 mg
- 37 pts Placebo

24 week vs Baseline

Evaluated by
- Fibroscan-CAP

Chehrehgosha et al. Diabetes Ther 2021

Tofoglifozin vs Glimepiride in NAFLD with T2DM

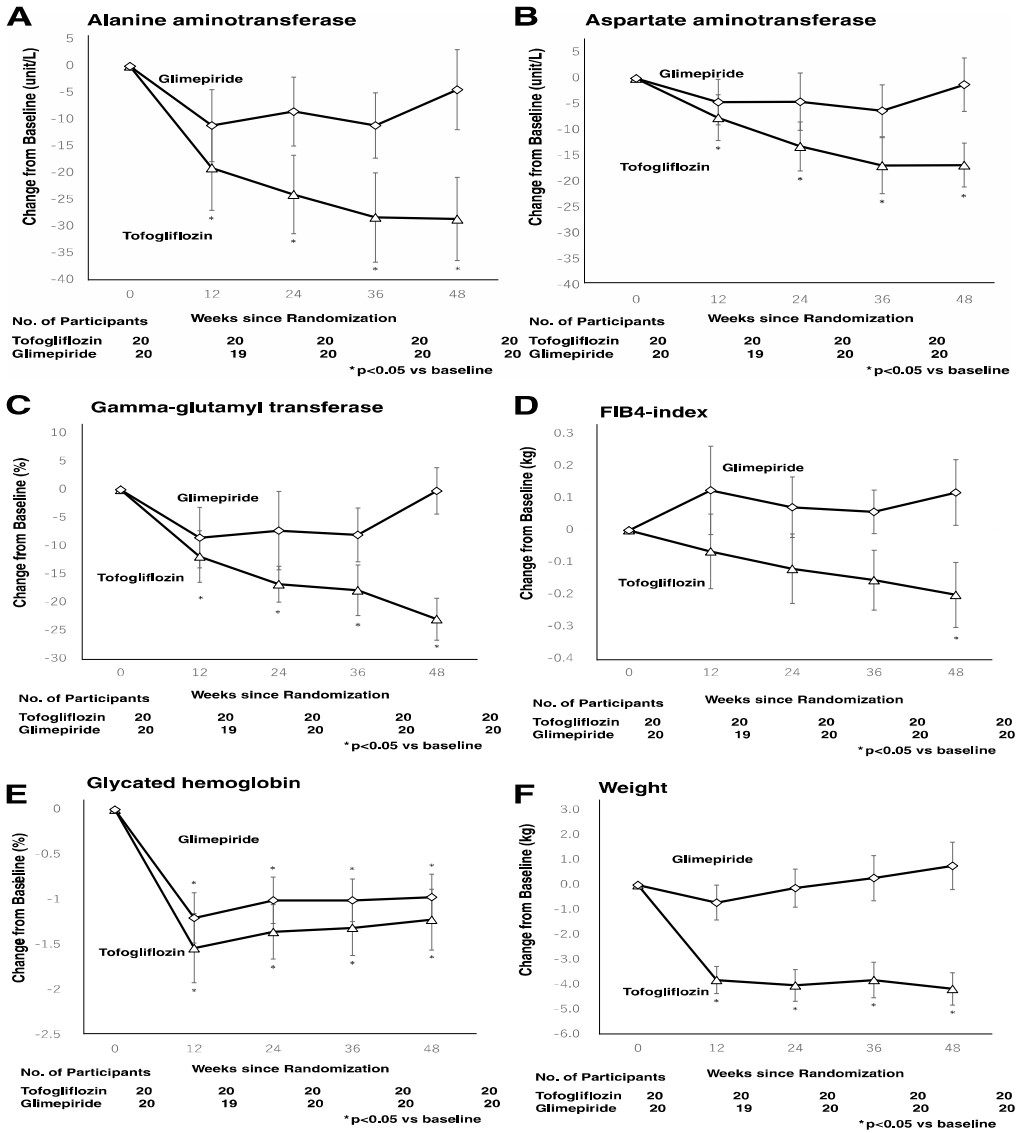


Figure 1—Changes from baseline in liver-related parameters, HbA_{1c}, and weight, according to the study group. Mean values are shown for changes from baseline (the value at follow-up minus the baseline value) for ALT levels (*A*), AST levels (*B*), γ-glutamyl transferase (*C*), FIB-4 index (*D*), HbA_{1c} (*E*), and weight (*F*) among the 20 subjects in the tofogliflozin group and the 20 subjects in the glimepiride group.

Takeshita Y et al. Diabetes Care 2022

Tofoglifozin vs Glimepiride in NAFLD with T2DM

Table 2—Hepatic histological scores

Histologic features	Tofogliflozin (*n* = 20) Before	Tofogliflozin (*n* = 20) After	Tofogliflozin *P* value†	Glimepiride (*n* = 20) Before	Glimepiride (*n* = 20) After	Glimepiride *P* value†	*P* value (tofogliflozin vs. glimepiride)‡
Steatosis							
Score, *n* subjects							
0 (<5%)	0	5		0	0		
1 (5–33%)	8	11		6	11		
2 (33–66%)	8	3		9	5		
3 (>66%)	4	1		5	4		
Improvement, %		65	0.001		30	0.058	0.141
Hepatocellular ballooning							
Score, *n* subjects							
0 (None)	3	10		1	5		
1 (few balloon cells)	10	9		14	11		
2 (many balloon cells)	7	1		5	4		
Improvement, %		55	0.002		25	0.025	0.098
Lobular inflammation							
Score, *n* subjects							
0 (0 focus)	1	4		0	0		
1 (<2 foci per 200*field)	11	16		13	14		
2 (2–4 foci per 200*field)	7	0		7	6		
3 (>4 foci per 200*field)	1	0		0	0		
Improvement, %		50	0.003		15	0.655	0.064
Fibrosis							
Score, *n* subjects							
0 (none)	3	10		2	6		
1 (perisinusoidal or periportal)	7	7		11	7		
2 (perisinusoidal and portal or periportal)	8	1		3	3		
3 (bridging fibrosis)	2	2		3	4		
4 (cirrhosis)	0	0		1	0		
Improvement, %		60	0.001		35	0.096	0.172

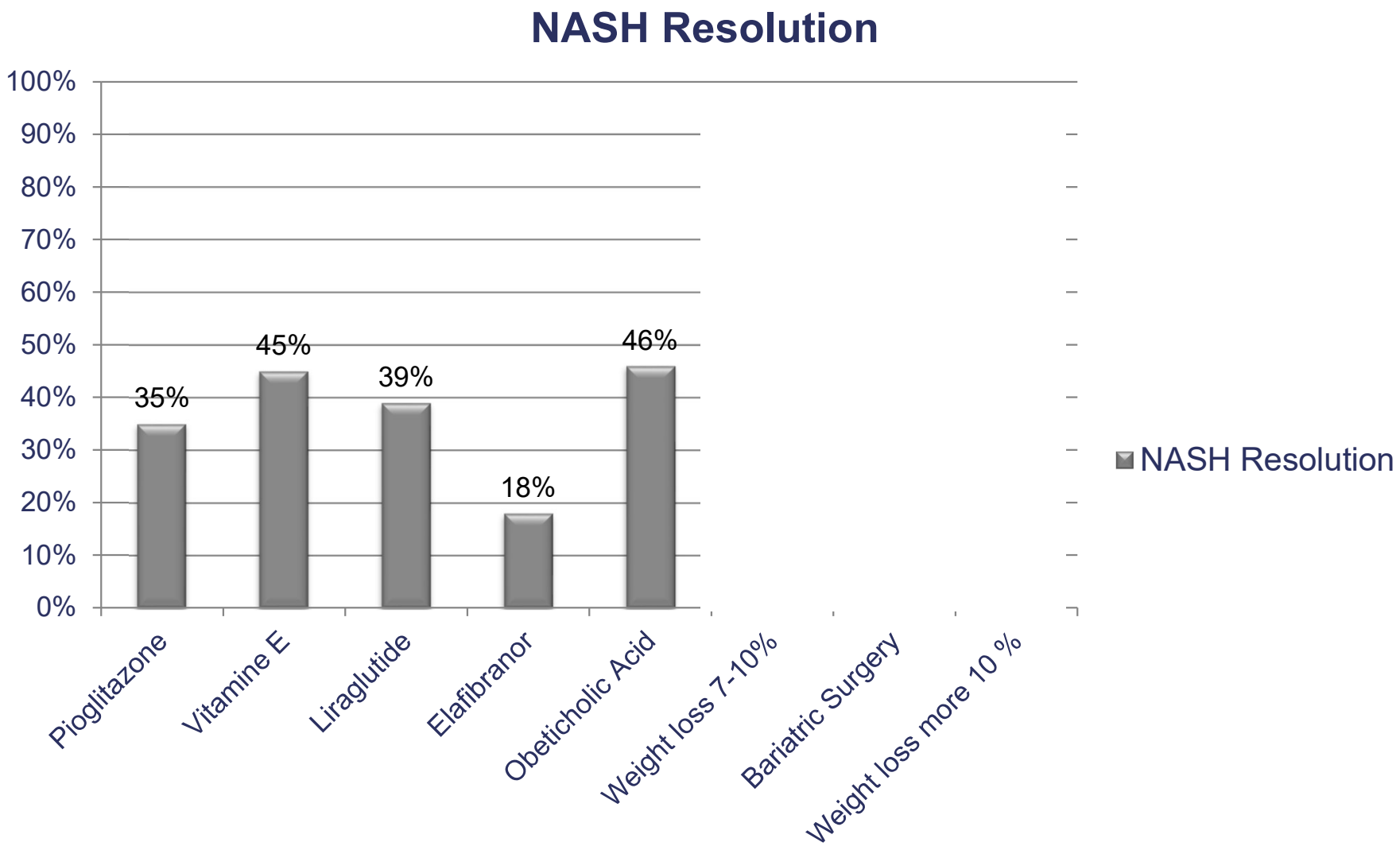
†The *P* values were calculated with the Wilcoxon signed rank test. ‡The between-group comparison for the effect of treatment (change from baseline) was performed with the χ^2 test.

Takeshita Y et al. Diabetes Care 2022

Summary

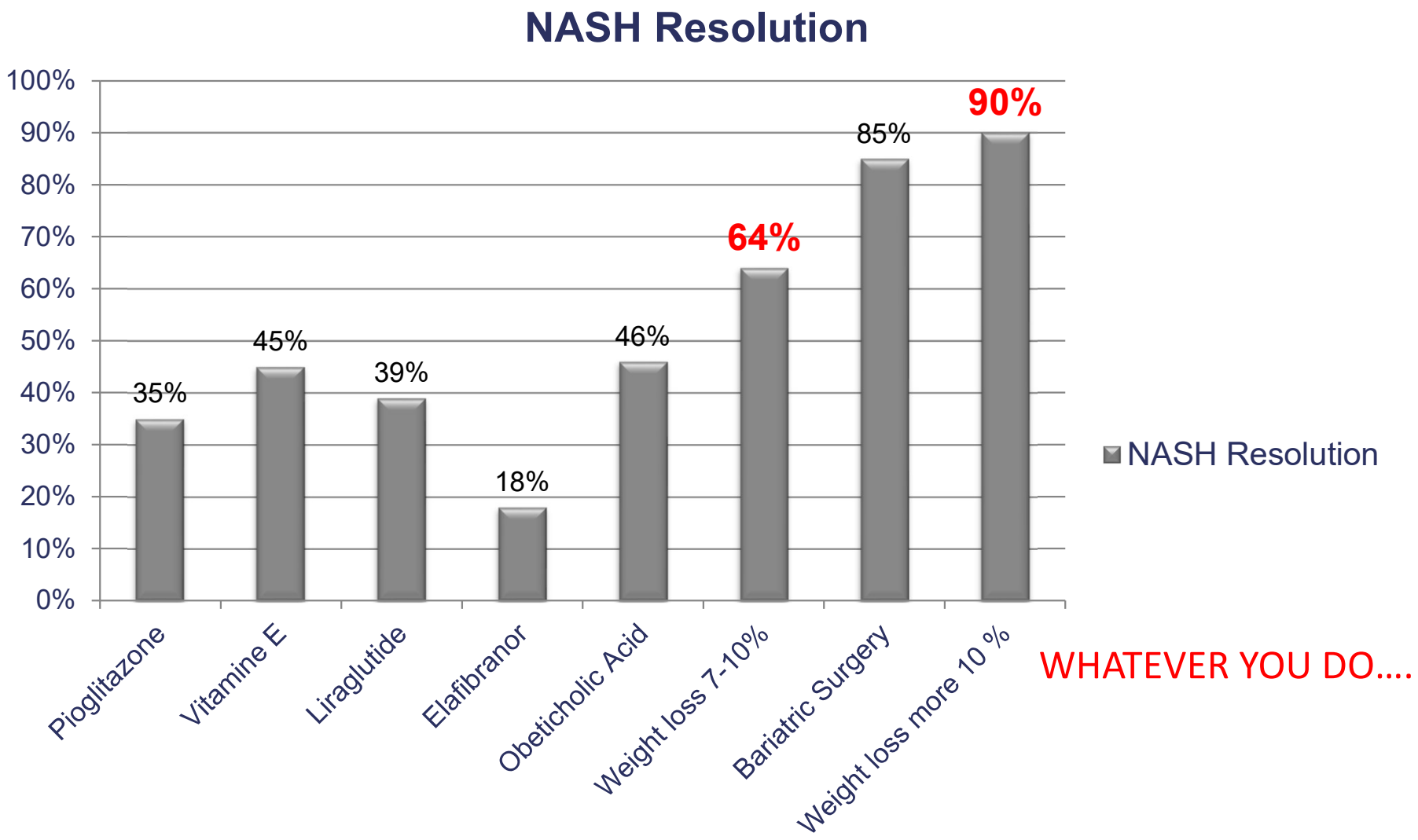
NAFLD / NASH Treatment

Summary



NAFLD / NASH Treatment

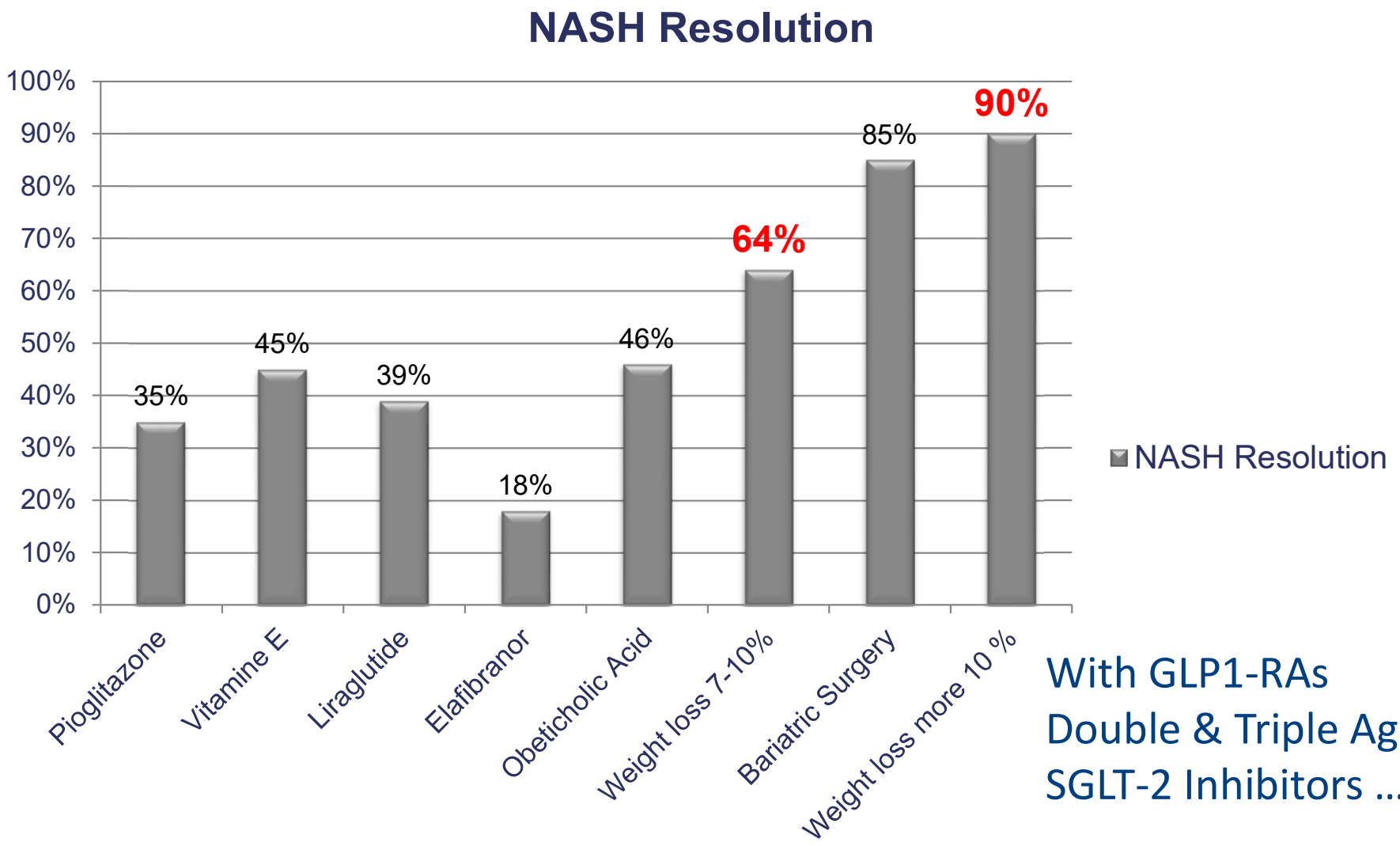
Summary



WHATEVER YOU DO….

NAFLD / NASH Treatment

Summary

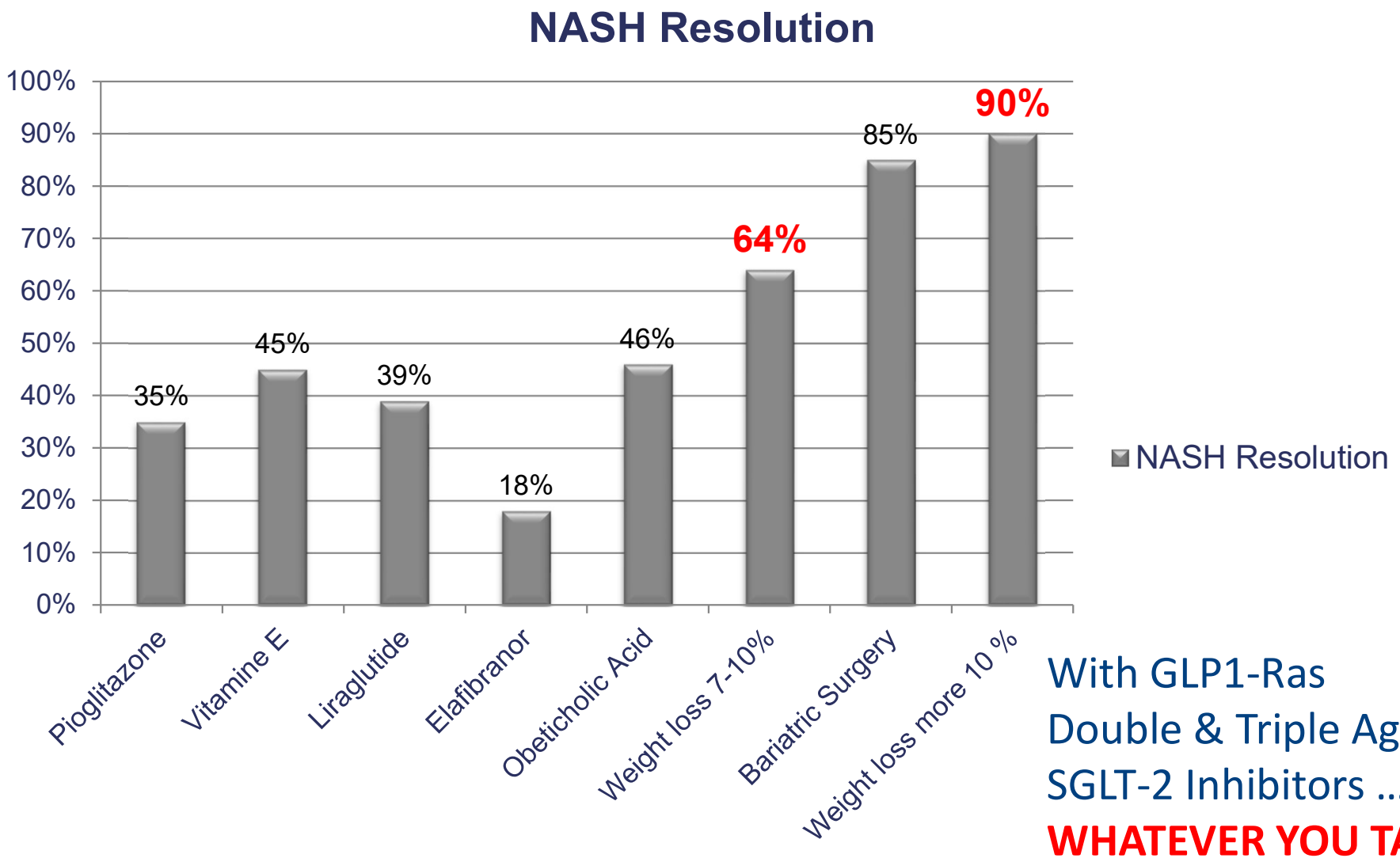


With GLP1-RAs
Double & Triple Agonists
SGLT-2 Inhibitors ….

medical team

NAFLD / NASH Treatment

Summary



With GLP1-Ras
Double & Triple Agonists
SGLT-2 Inhibitors ….
WHATEVER YOU TAKE

medical team