25ο ΕΤΗΣΙΟ ΣΕΜΙΝΑΡΙΟ ΣΥΝΕΧΙΖΟΜΕΝΗΣ ΙΑΤΡΙΚΗΣ ΕΚΠΑΙΔΕΥΣΗΣ

Γ. Ν. Α. "Ο Ευαγγελισμός" 17-21 Φεβρουαρίου 2020

Κλινική σημασία - Διάγνωση και Θεραπεία της μη-αλκοολικής λιπώδους νόσου του ήπατος

Δρ. Βασίλειος Α. Σεβαστιανός

Δ' Παθολογική Κλινική

Γ.Ν.Α «Ο Ευαγγελισμός»

ΕΝΩΣΗ ΕΠΙΣΤΗΜΟΝΙΚΟΥ ΠΡΟΣΩΠΙΚΟΥ
Γ.Ν.Α. «Ο ΕΥΑΓΓΕΛΙΣΜΟΣ» (Ε.Ε.Π.Ν.Ε.)

25ο Ετήσιο Σεμινάριο Συνεχιζόμενης Ιατρικής Εκπαίδευσης Γ.Ν.Α. «Ο Ευαγγελισμός»

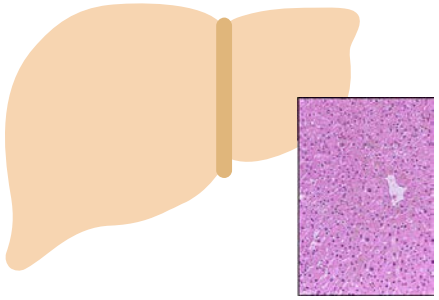
Δεν υπάρχει σύγκρουση συμφερόντων με τις Χορηγούς Εταιρείες:

NOVARTIS
Roche
astellas
WinMedica Serving Health for Life
GILEAD Advancing Therapeutics. Improving Lives.
MEDIWAY
Pfizer Oncology
SANDOZ A Novartis Division
Bristol-Myers Squibb
abbvie
Abbott
AMGEN
cardio innovation
GENESIS pharma
Janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson
Pfizer Hospital
Boehringer Ingelheim
Lilly ΦΑΡΜΑΣΕΡΒ
SERVIER
Baxter
DEMO ABEE ΒΙΟΜΗΧΑΝΙΑ ΦΑΡΜΑΚΩΝ
emergy products
AENORASIS Intuition in Healthcare
Rontis Driven by innovation
Specifar A Teva Company

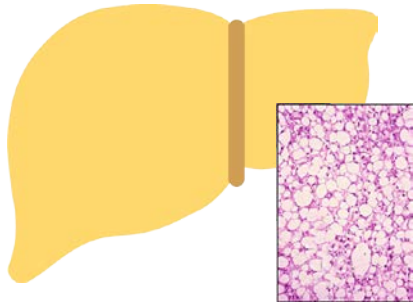
Μη αλκοολική λιπώδης νόσος του ήπατος (ΜΑΛΝΗ)

NAFLD

Normal Liver

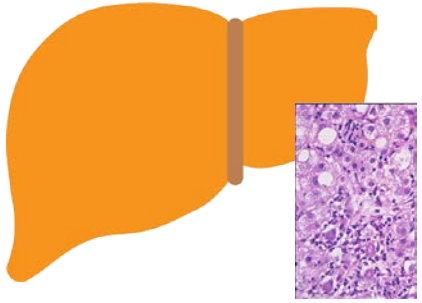


Steatosis "NAFL"

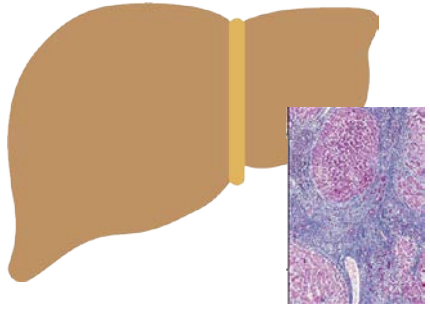


Fat infiltration ≥ 5% without ballooning, with or without inflammation

Steatohepatitis "NASH"



Cirrhosis



Risk factor for NASH include metabolic syndrome
(Obesity, Hypetension, Dyslipidemia & T2DM/insulin resistance**)**

- For NAFLD, alcohol consumption <20/30gr/d
- Other causes for liver dysfunction/hepatotoxins excluded

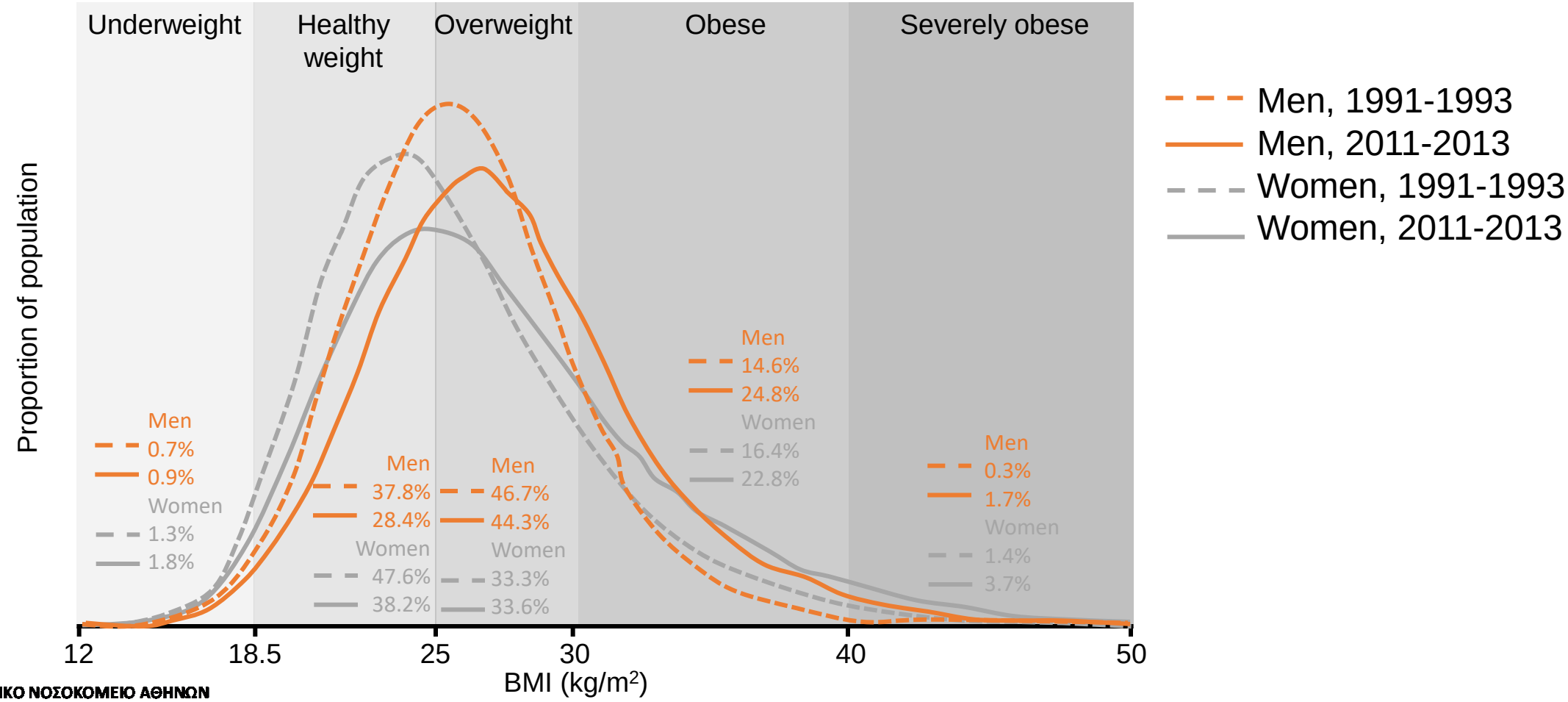
Increasing fibrosis, leading to cirrhosis

HCC

Chalasani N, et al. Hepatology. 2018;67(1):328-357

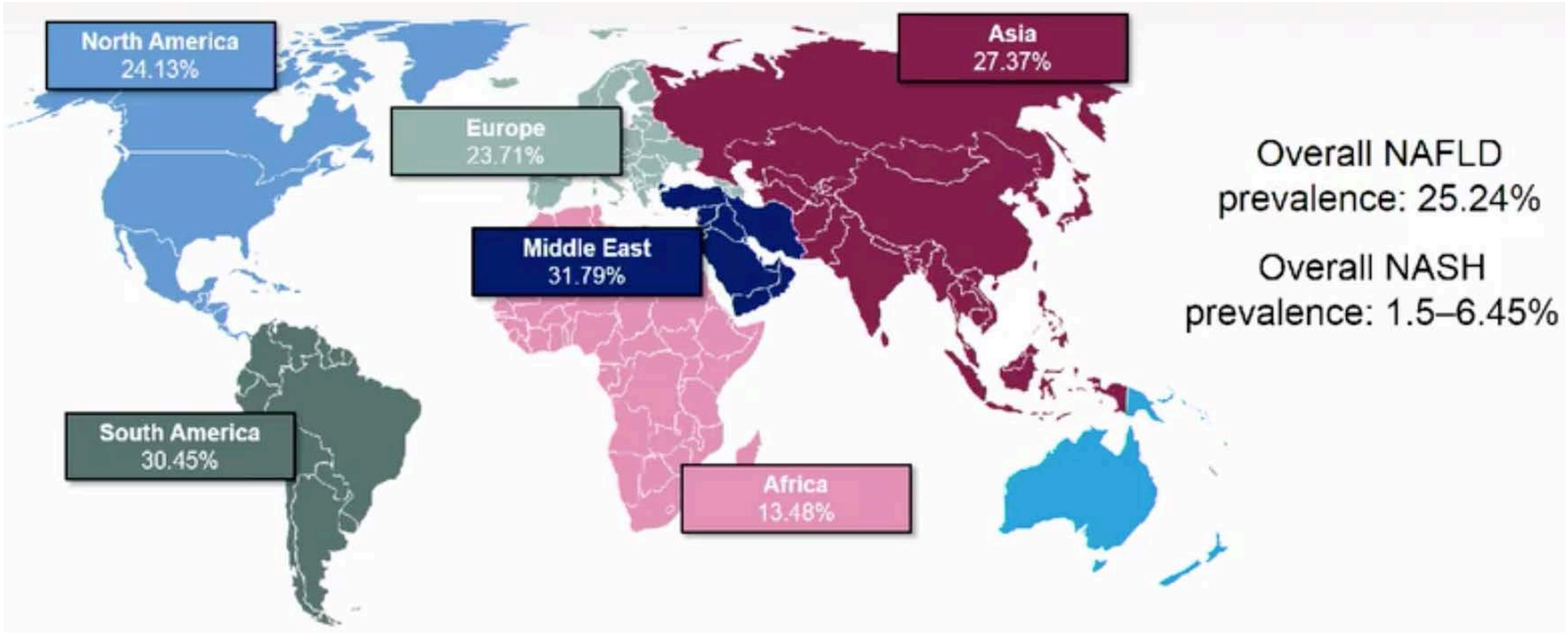
A “Right-Shift” in Population Body Weight

UK Distribution of BMI in Adults Aged ≥ 18 Yrs (Population Weighted)



Public Health England. Patterns and trends in adult obesity. April 2016.

Prevalence and Burden of NAFLD



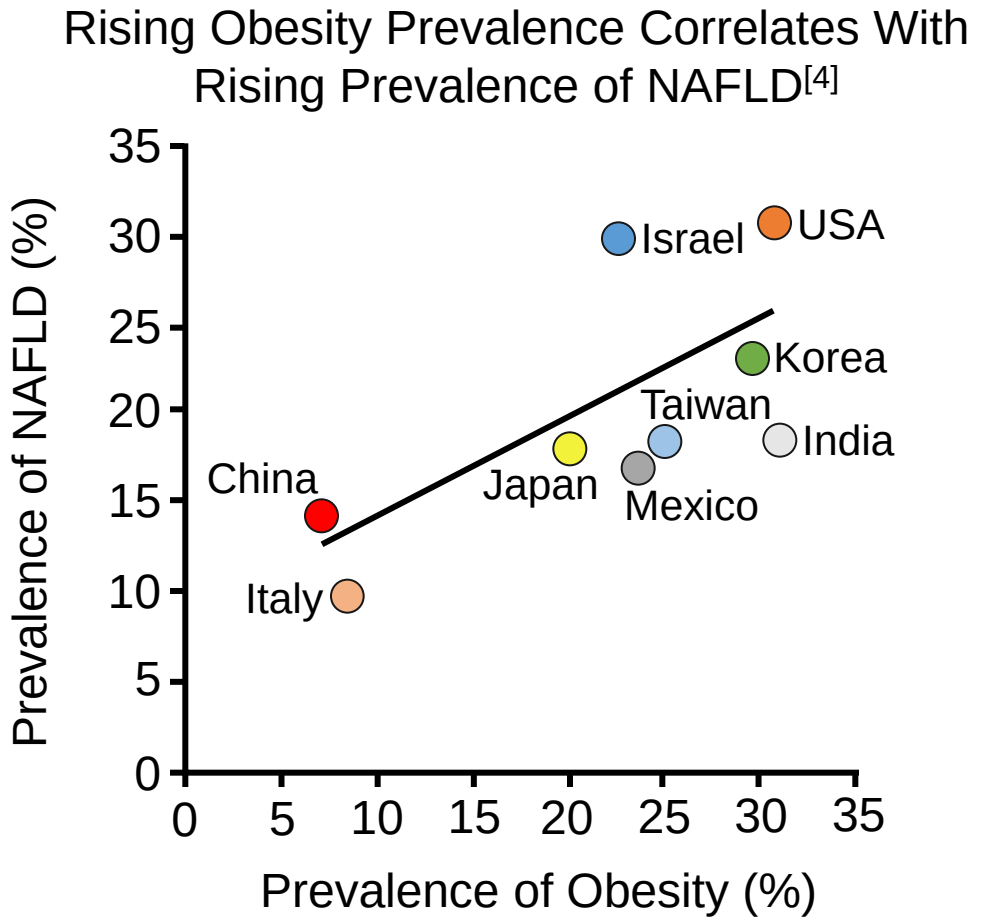
Younossi ZM, et al. Hepatology. 2016;64(1):73-84

Prevalence of NAFLD in the General Population

In a US population sample (n = 328)[1]:
- NAFLD by ultrasound 46%
- NASH 12.2% (29.9% of those with NAFLD)

In the Dionysos study, NAFLD present in[2]:
- Obese pts (BMI > 30), 94%
- Overweight pts (BMI > 25), 67%
- Normal weight pts, 25%

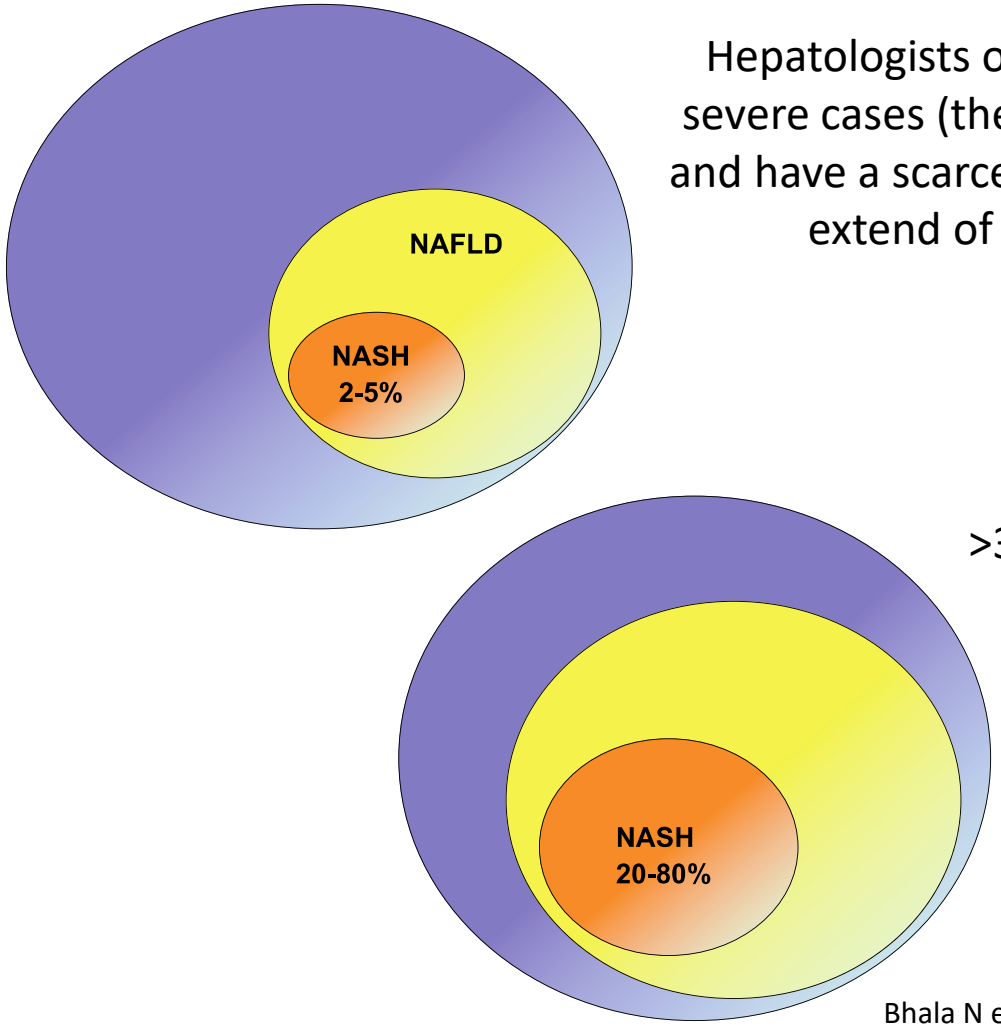
In apparently healthy living liver donors, histological NASH in[3]:
- Europe, 3% to 16%
- USA, 6% to 15%



1. Williams CD, et al. Gastro. 2011;140:124-31. 2. Bellentani S, et al. E J Gastro Hep. 2004; 1087-1093. 3. Anstee et al. Nat Rev Gastroenterol Hepatol. 2013;10:330-344. 4. Loomba R, et al. Nat Rev Gastroenterol Hepatol. 2013;10:686-690.

NAFLD: The dimension of the problem

Obesity
1 billion people overweight or obese around the world

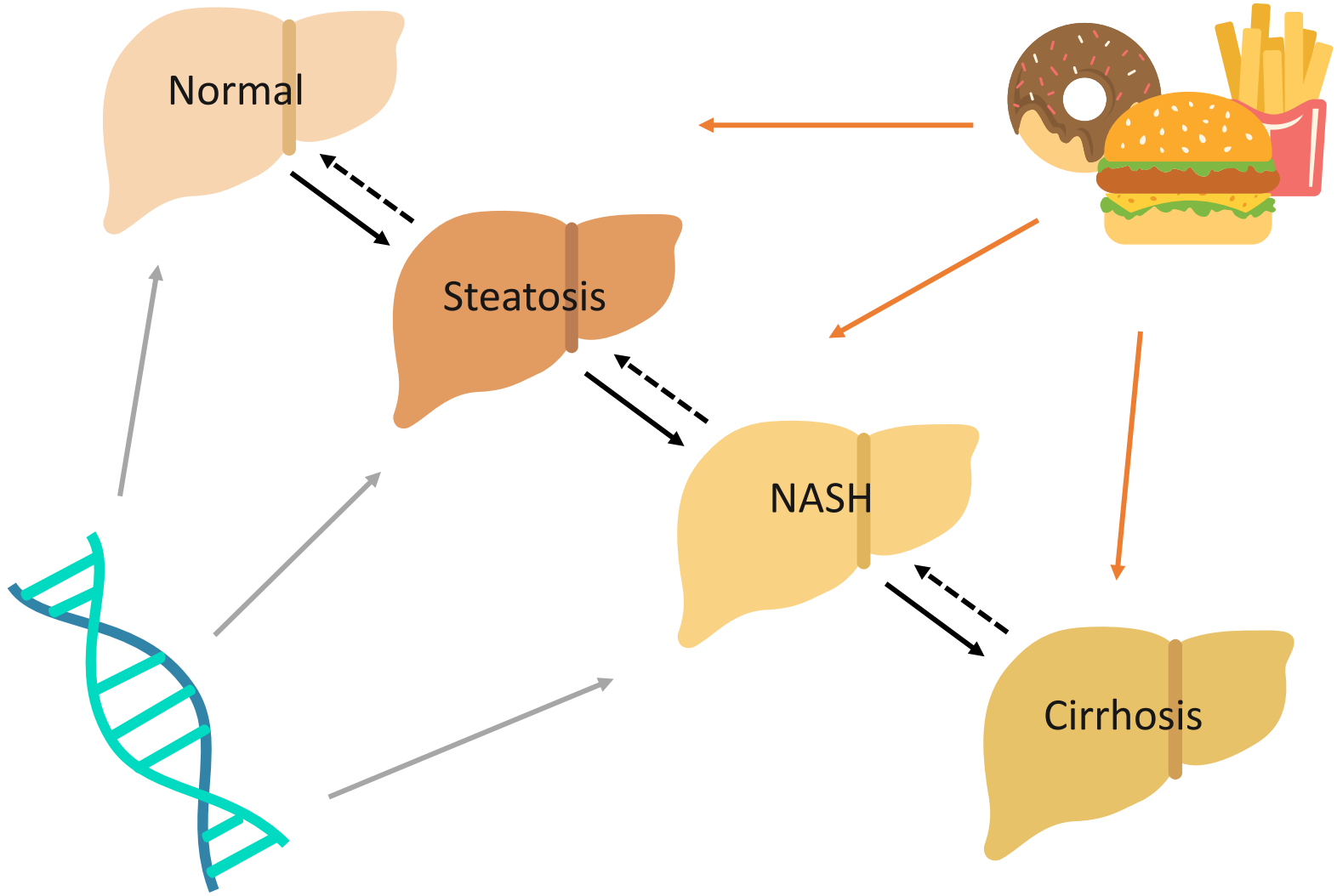


Hepatologists only see the most severe cases (the tip of th iceberg) and have a scarce idea of the global extend of the disease

Diabetes
>380 million cases
(550 in 2030)

Bhala N et al. Curr Pharm Des. 2013;19(29):5169-76

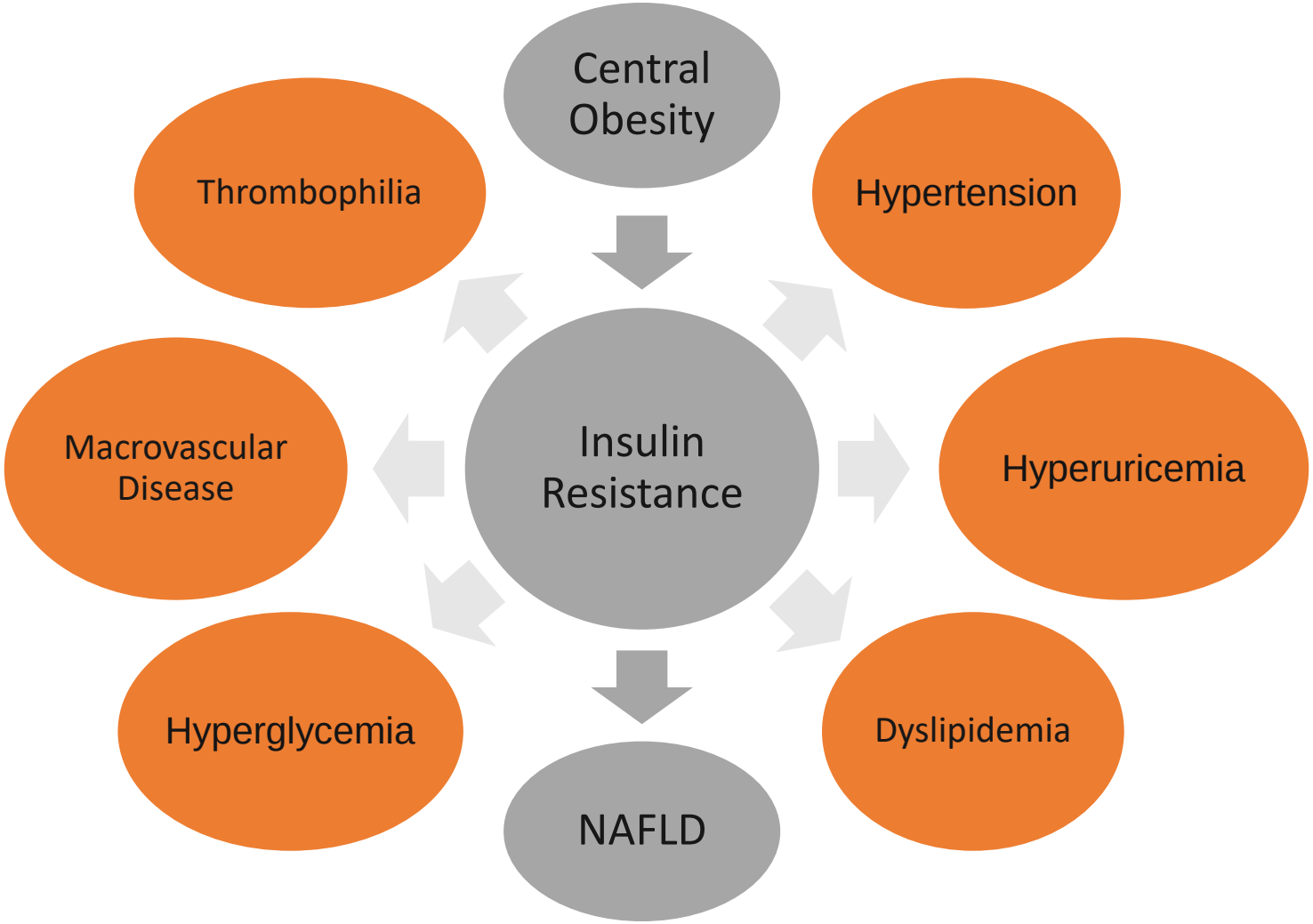
NAFLD as a Complex Disease Trait



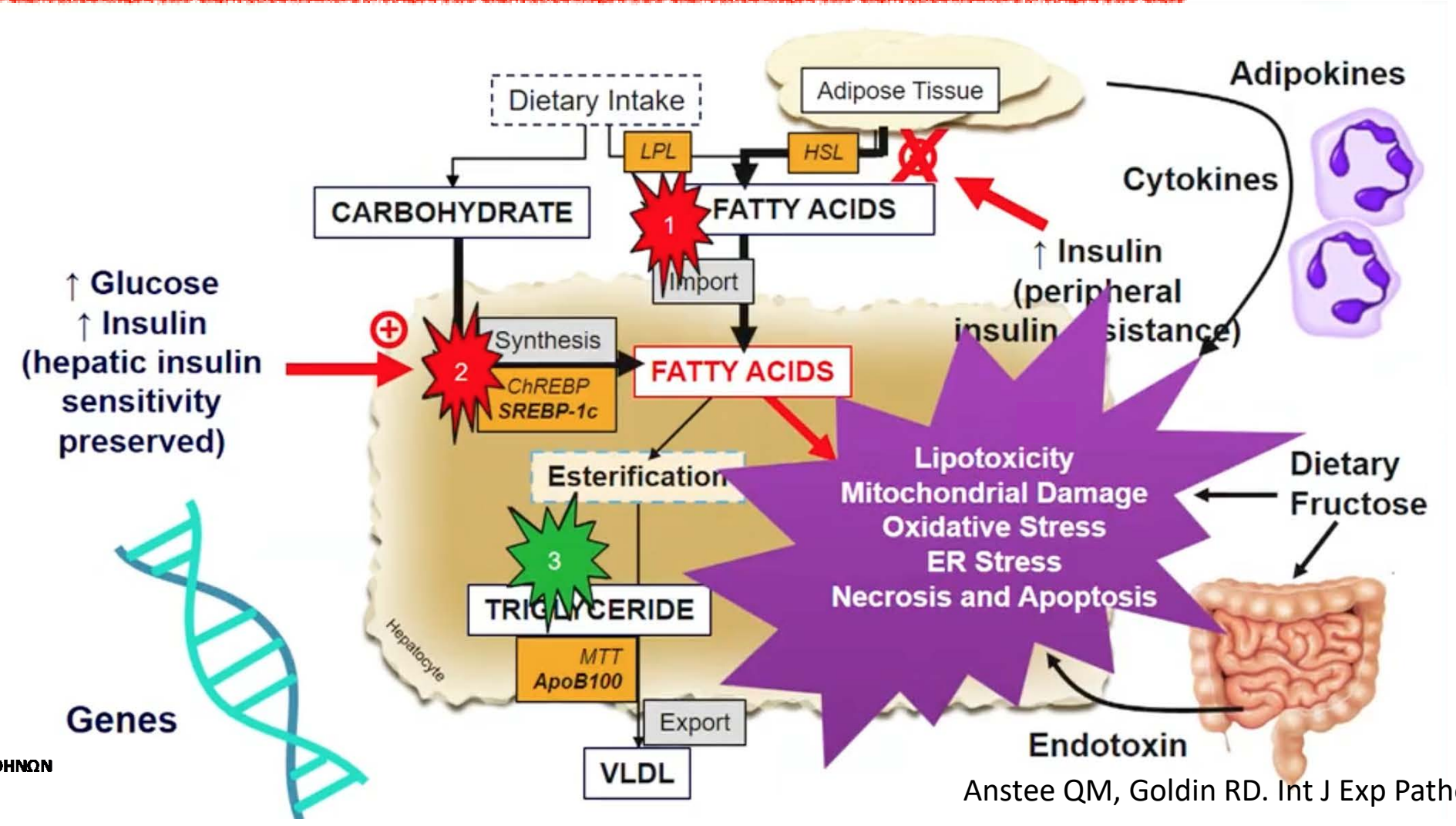
Environment
Sedentary lifestyle
Snacking, fast food
Saturated fats
Trans fats
Processed red meat

Genes
PNPLA3
TM6SF2
GCKR
SOD2
MBOAT7

Obesity and Insulin Resistance as Pathogenic Drivers

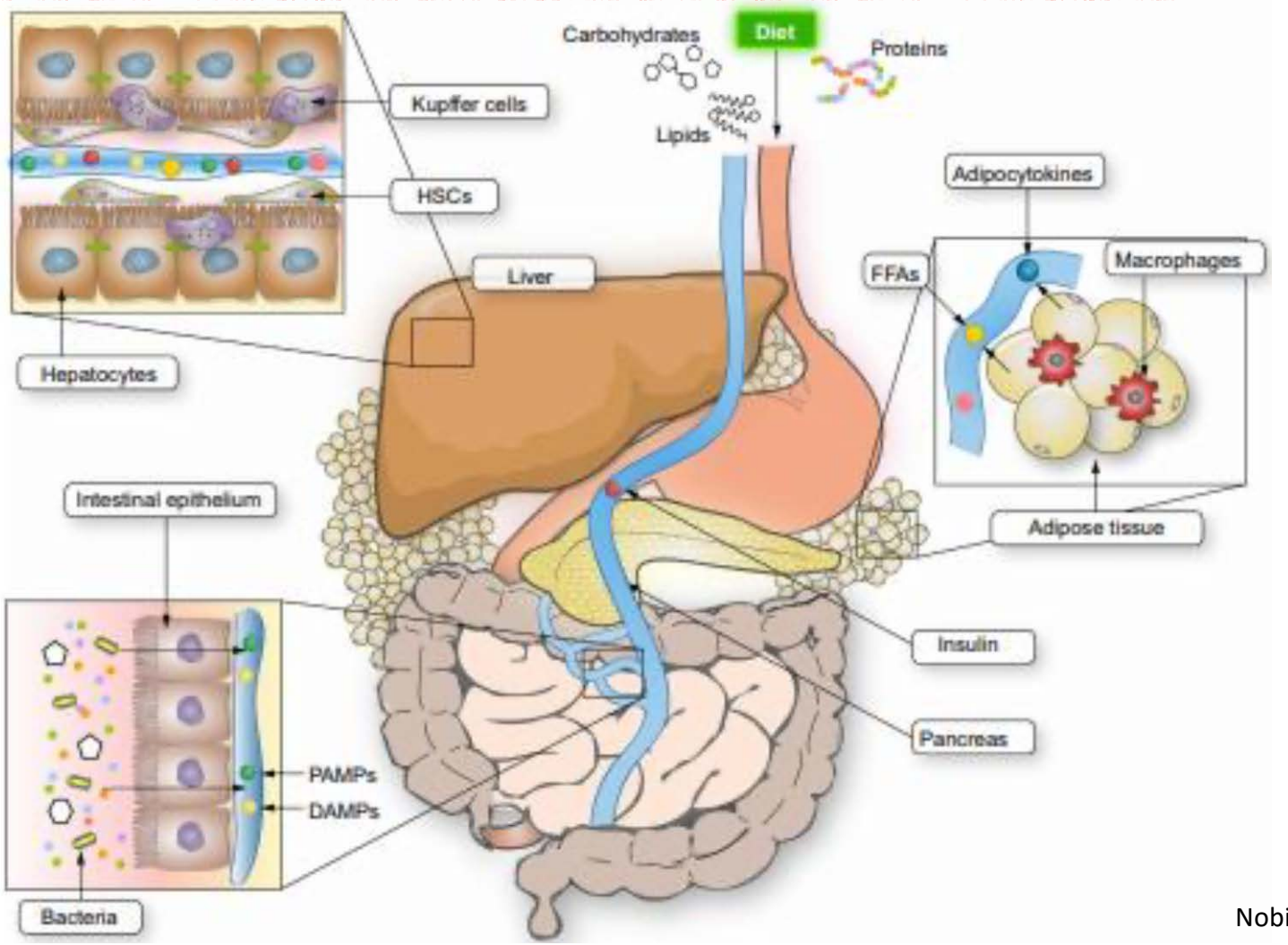


Multiple parallel ”hits” drive NASH pathogenesis



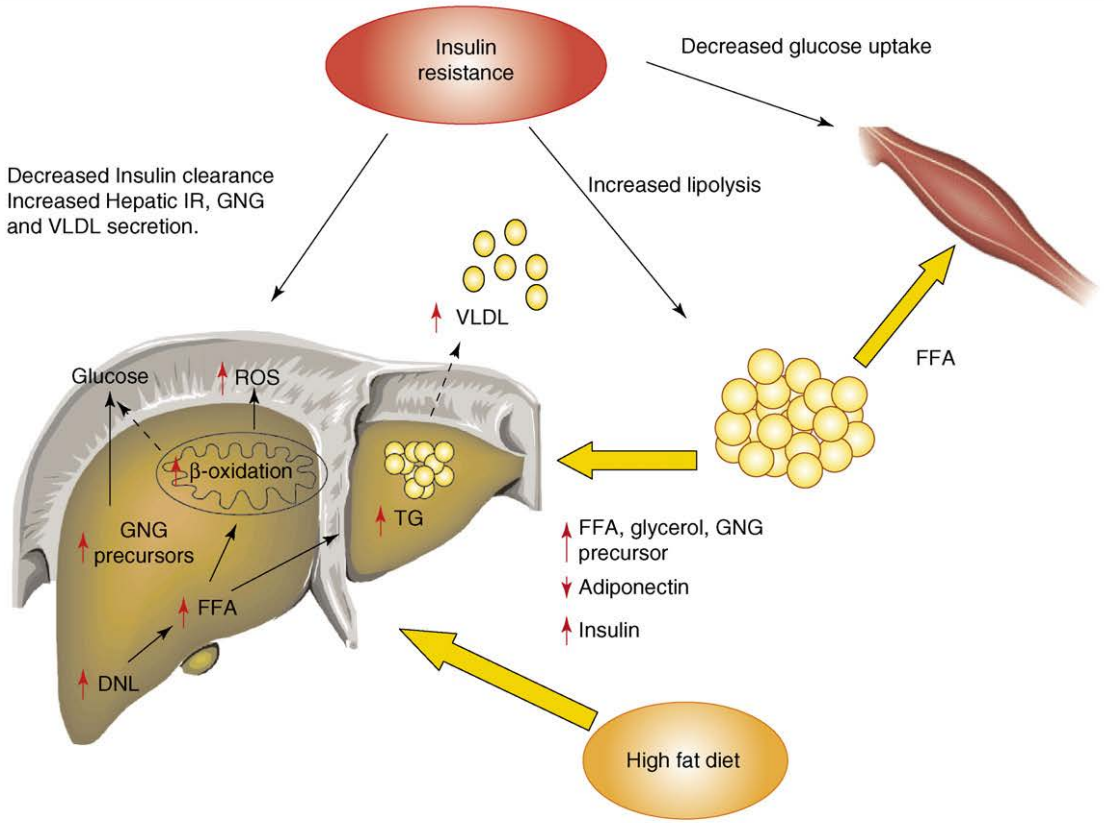
Anstee QM, Goldin RD. Int J Exp Pathol. 2006;87:1-16.

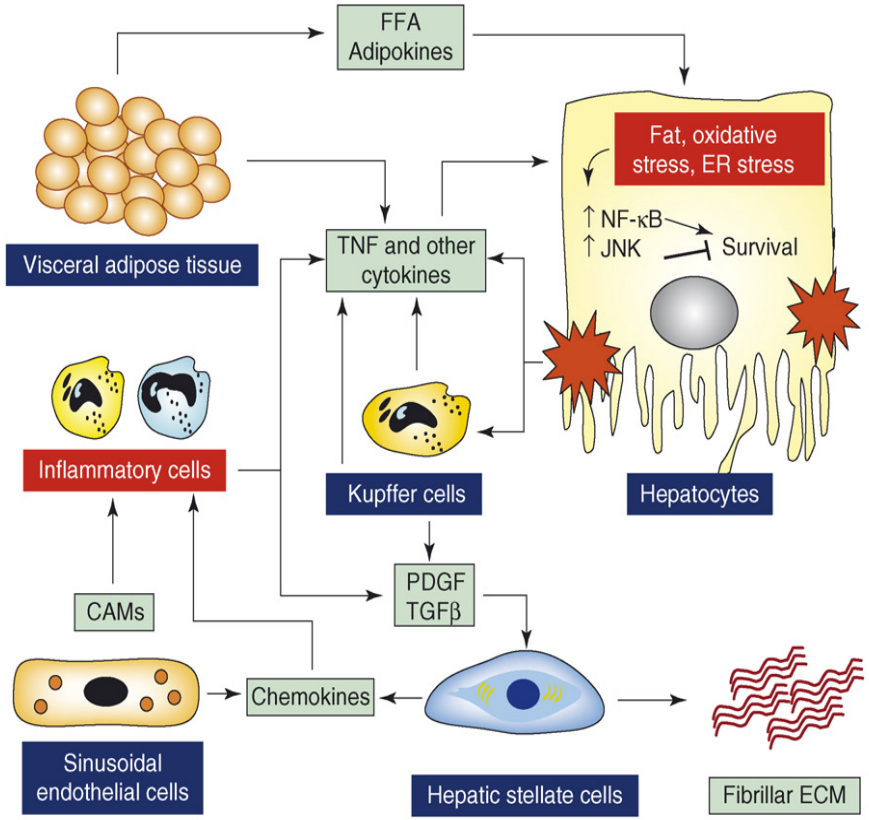
Pathogenesis of NAFLD probably involves inter-organ crosstalk



Nobili, V et al. J Hepatol 2013;58:1218-29

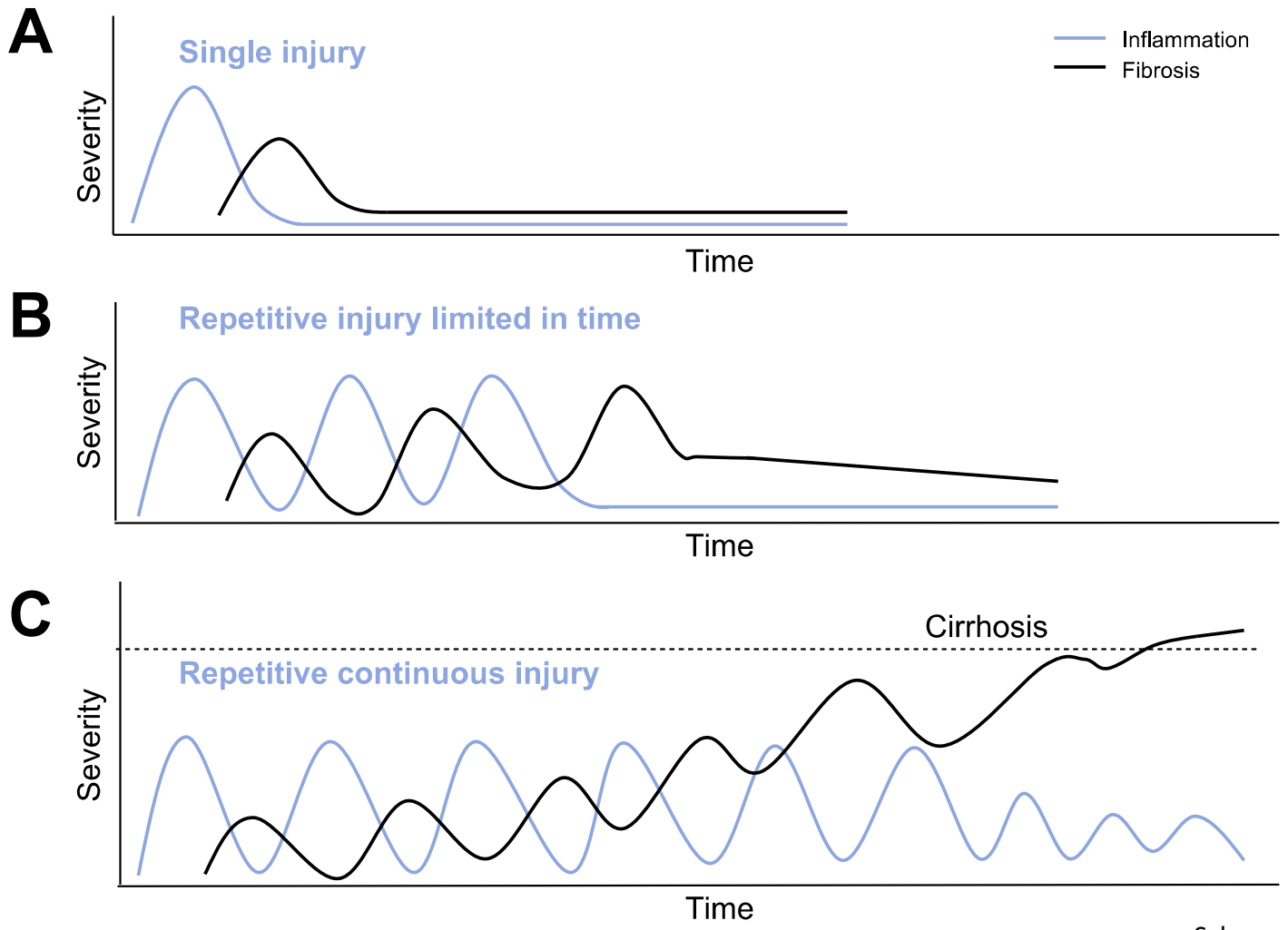
Pathogenesis of fibrosis in NAFLD





Marra F, et al. Trends Mol Med 2008;14:72–81

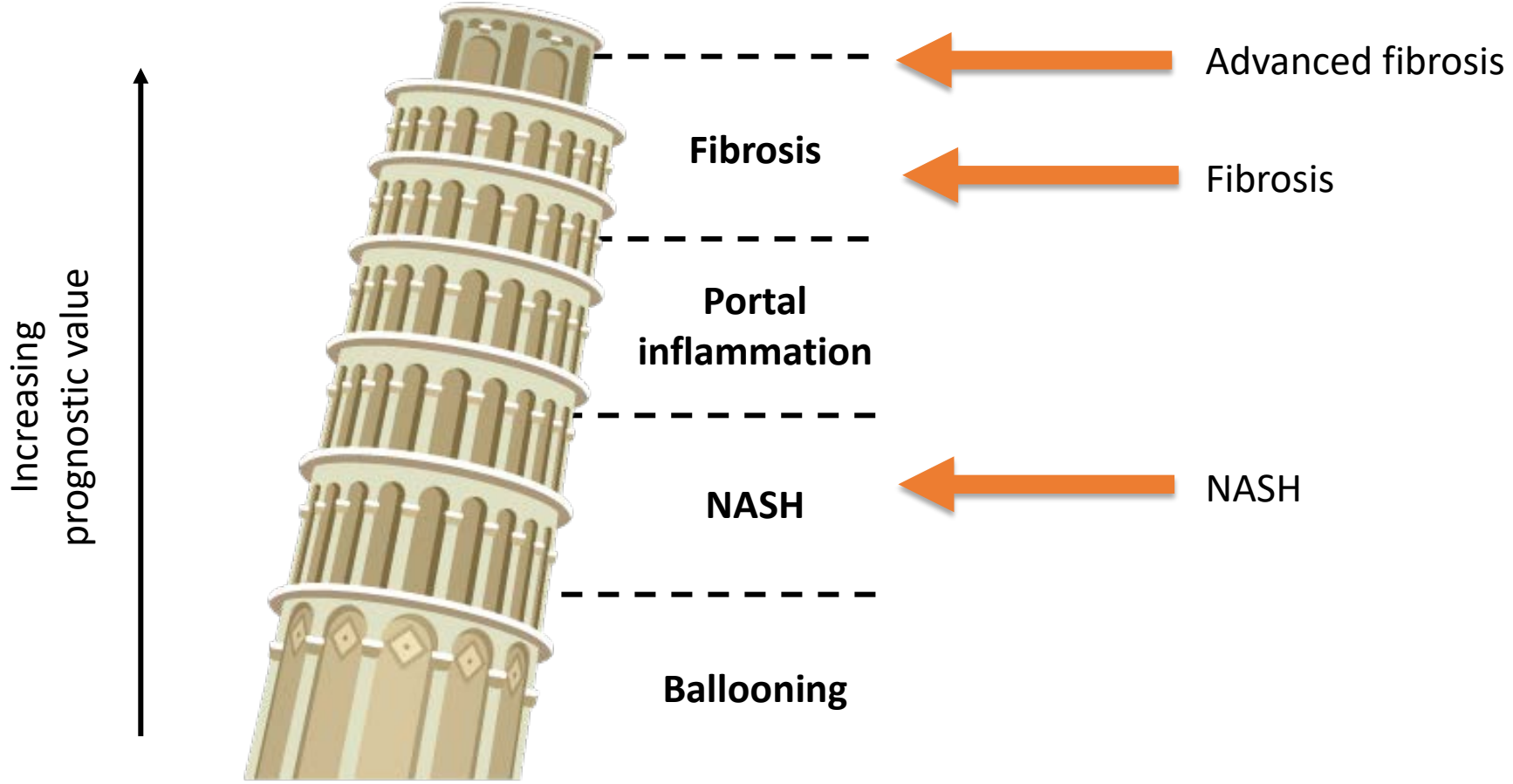
A new view of fibrosis progression in NASH



Schuppan D, et al. J Hepatol. 2018;68(2):238-250

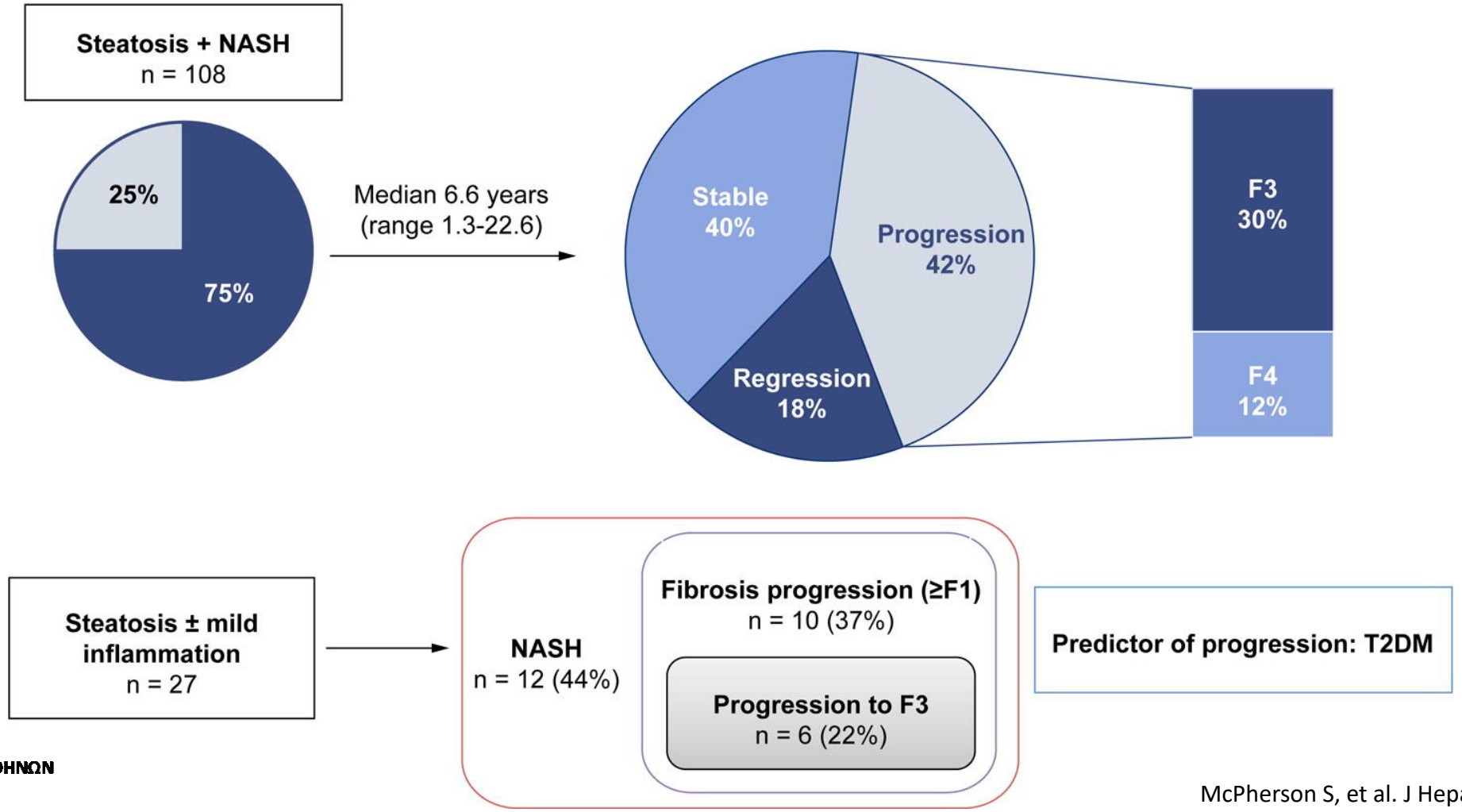
Key Histologic Predictors of Mortality in NAFLD

Fibrosis is the single most important predictor of mortality in NASH



Angulo P, et al. Gastroenterology. 2015;149:389-397. Loomba R, et al. Gastroenterology. 2015;149:278-281.

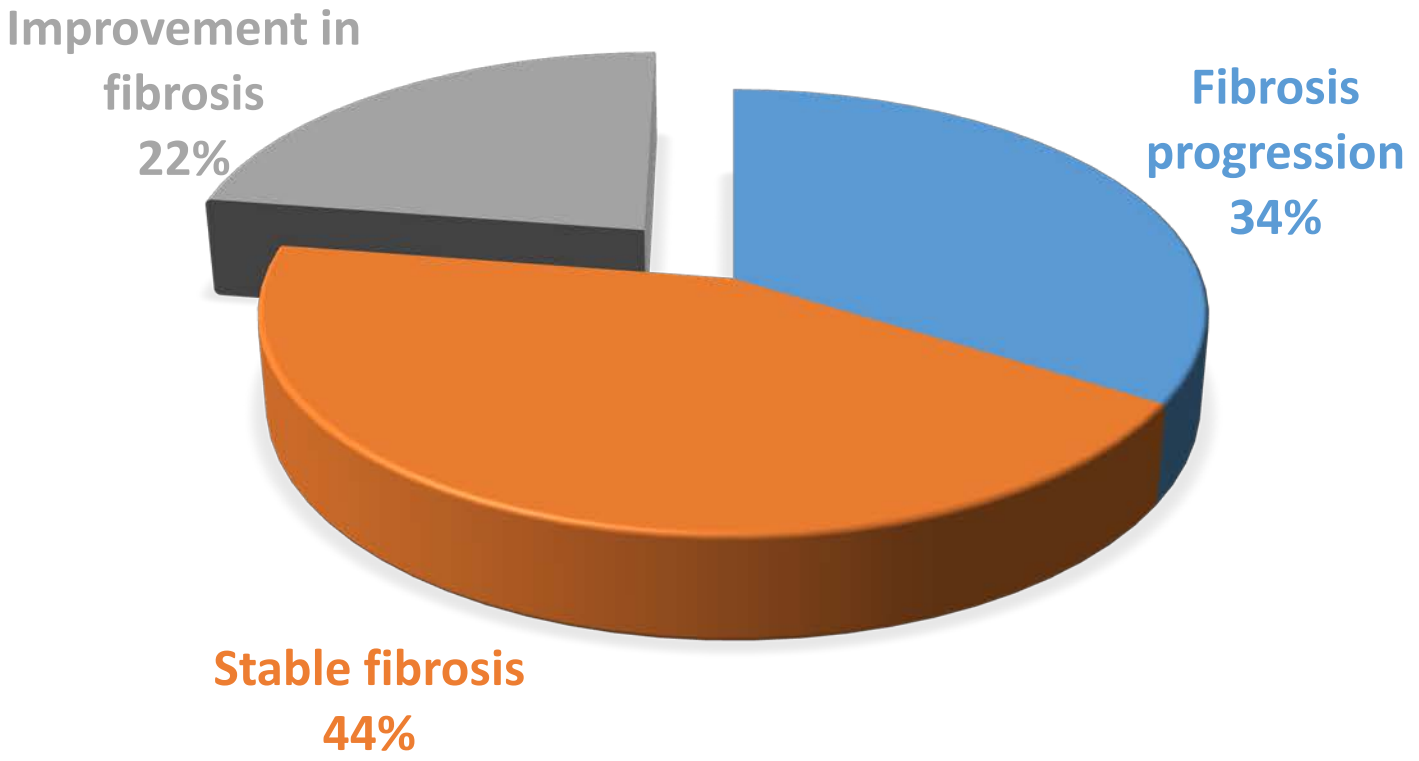
Ιστολογική εξέλιξη της ΜΑΛΝΗ σε συνδυασμένες βιοψίες



McPherson S, et al. J Hepatol. 2015;62(5):1148-55

Progression of Fibrosis in Pts With NAFLD

- Meta-analysis of 11 paired-biopsy studies (N = 411) with 2145.5 person-years of follow-up

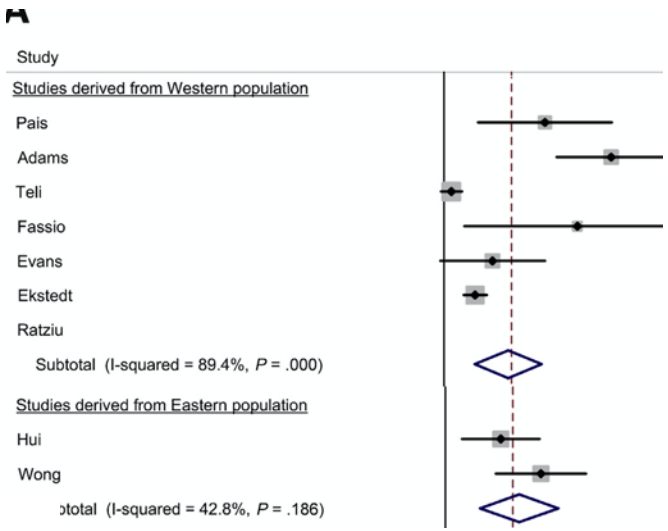


Singh S, et al. Clin Gastroenterol Hepatol. 2015;13:643-654.

Εξέλιξη της ίνωσης στη ΜΑΛΝΗ

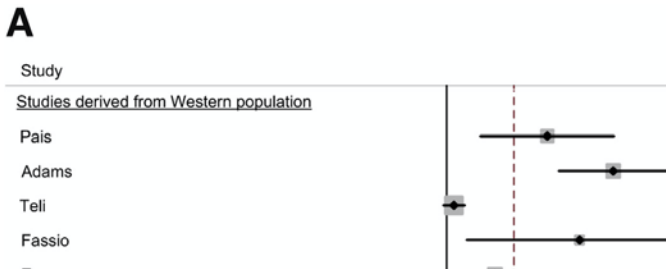
Meta-analysis 11 cohort studies [411 pts (150 steatosis, 261 NASH] 2145 person yrs

Steatosis



39% progressed,
0.07 stages/yr (95% CI 0.02-0.11)
One stage in 14.3 (95% CI 9.1-50.0) yrs

NASH



35% progressed,
0.14 stages/yr (95% CI 0.07-0.21)
One stage in 7.1 (95% CI 4.8-14.3) yrs

Singh S, et al. Clin Gastroenterol Hepatol. 2015;13(4):643-54

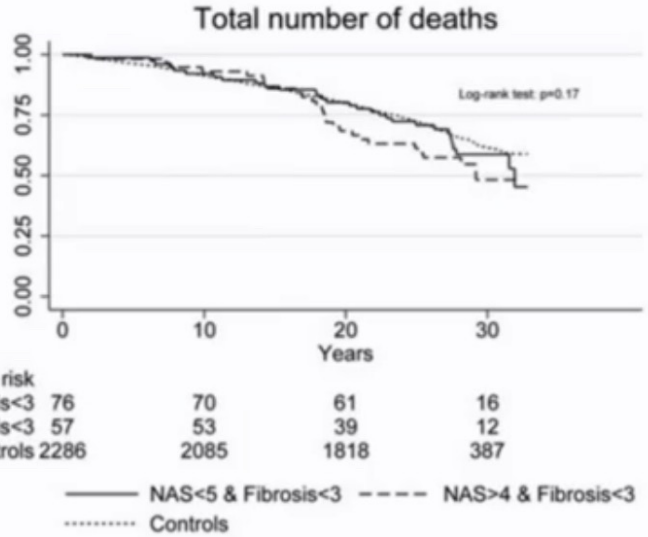
Η ΜΑΛΝΗ οδηγεί στην εμφάνιση κλινικών συμβάντων

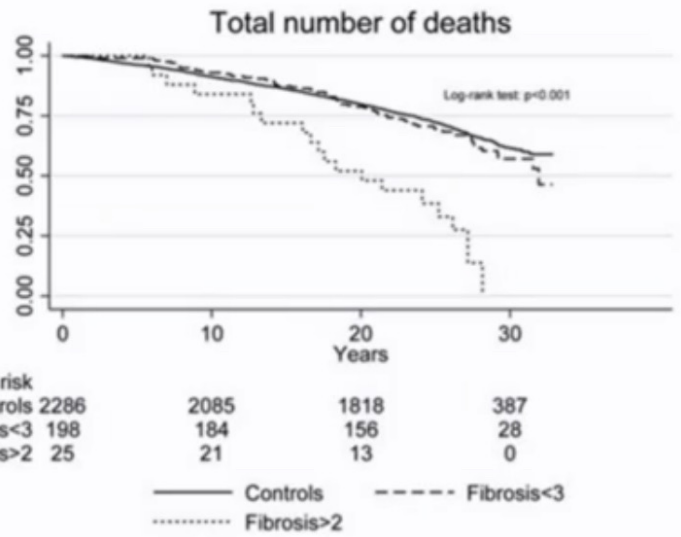
229 patients with histologically characterized NAFLD (mean follow-up 26.4±5.6 years [range 6-33 years])

96 deaths

	N	
CVD	41	(43%)
HCC	5	(5%)
Liver-Death	4	(4%)

Caution:
Very small number of liver-related events!





Cause of Death	Entire Cohort (n = 229)	P	NAS 0-4, F0-2 (n = 76)	P	NAS 5-8, F0-2 (n = 57)	P	NAS 0-8, F3-4 (n = 16)	P
Overall mortality	1.29 (1.04-1.59)	0.020	1.13 (0.79-1.60)	0.511	1.41 (0.97-2.06)	0.072	3.28 (2.27-4.76)	<0.001
Cardiovascular disease	1.55 (1.11-2.15)	0.01	1.19 (0.65-2.20)	0.557	1.38 (0.72-2.65)	0.335	4.36 (2.29-8.29)	<0.001
Hepatocellular carcinoma	6.55 (2.14-20.0)	0.001	No outcome	–	15.7 (4.1-59.9)	<0.001	16.9 (1.95-146)	0.01
Cirrhosis	3.2 (1.05-9.81)	0.041	4.86 (1.08-22.0)	0.04	No outcome	–	10.8 (1.38-83.9)	0.023

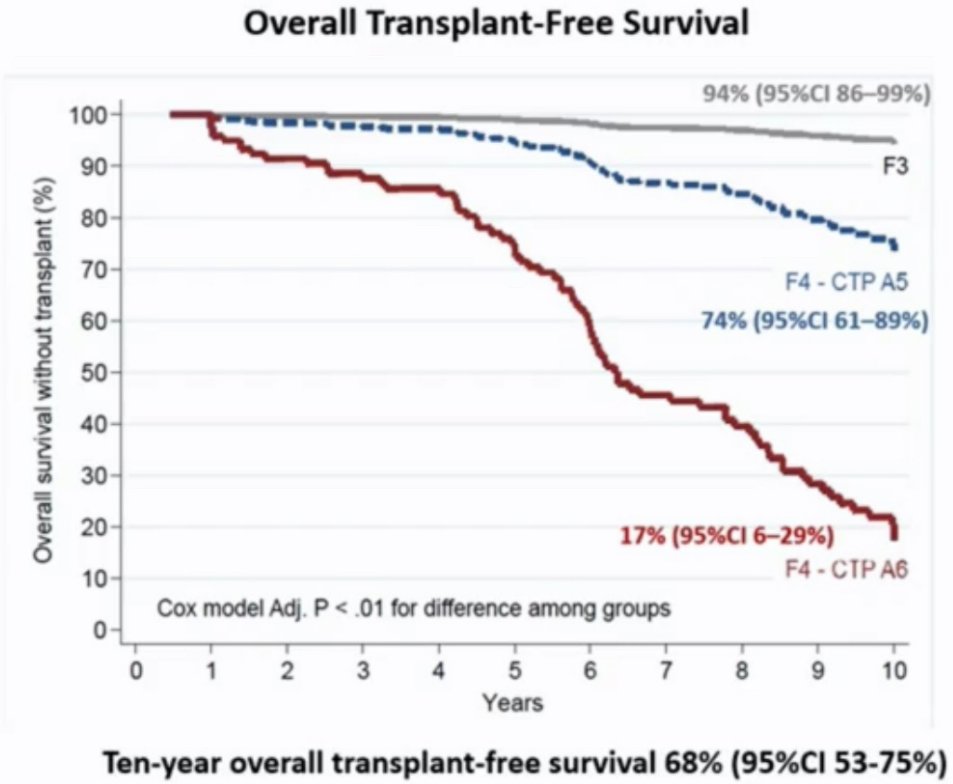
Ekstedt M, et al. Hepatology. 2015;61(5):1547-54

Η κλινική πορεία ποικίλει ανάλογα με το στάδιο της νόσου

Longitudinal study: n=458 biopsy proven NAFLD (F3: n=159; F4: n=299)

Mean follow-up time of 5.5 years (range 2.7–8.2 years)

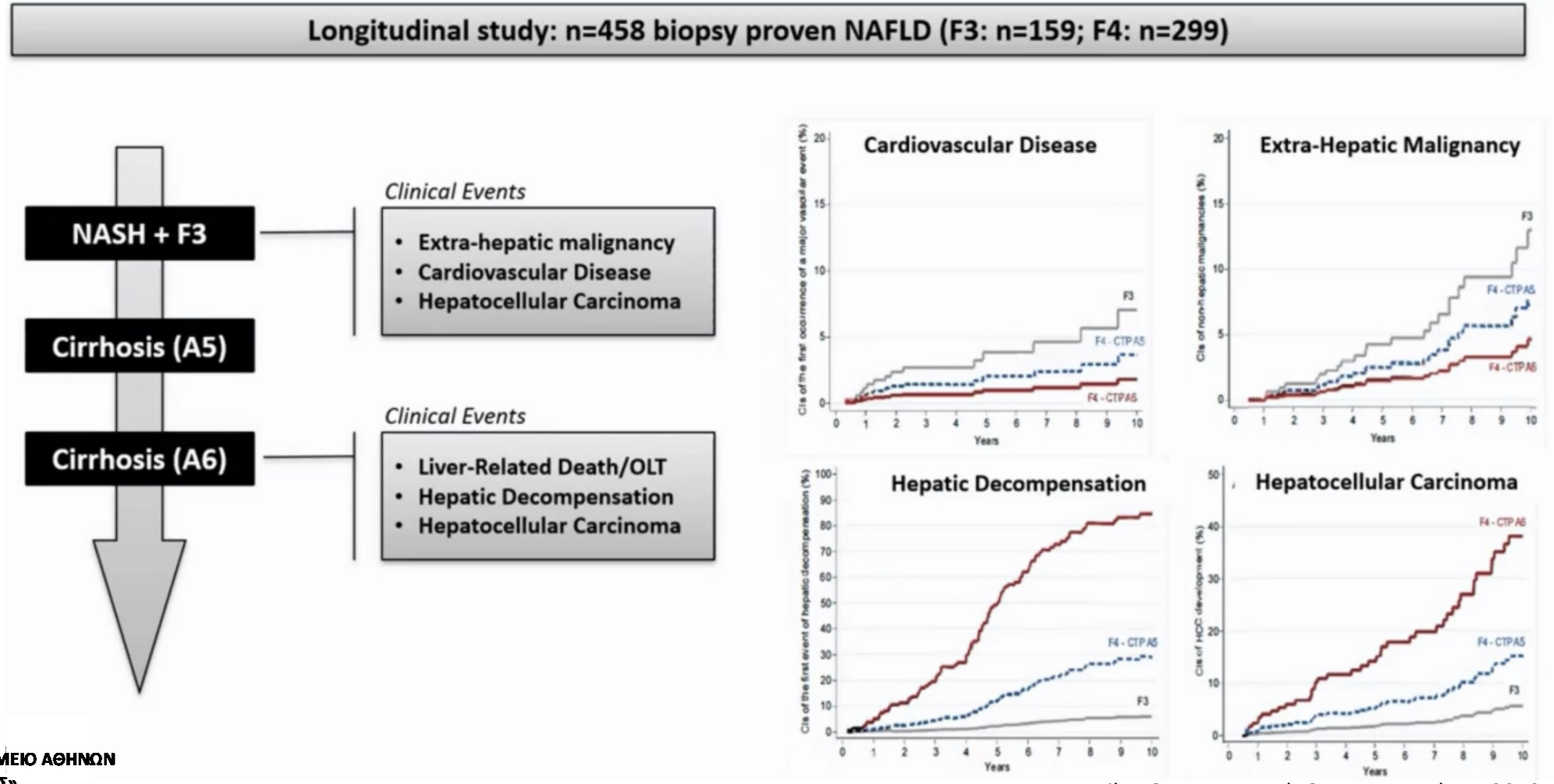
Events	N	Annualised Incidence Rates by Fibrosis Stage		
		F3	F4 (CTP-A5)	F4 (CTP-A6)
CVD	14	**0.9** (0.5-1.8)	**0.4** (0.2-1.0)	**0.2** (0.03-0.6)
HCC	41	**0.2** (0.02-0.9)	**1.8** (1.1-2.7)	**4.7** (3.0-7.5)
Decompensation	88	**0.6** (0.2-1.4)	**3.3** (2.4-4.6)	**15.6** (11.7-20.9)
Death/OLT	74	**0.5** (0.2-1.2)	**2.1** (1.4-3.1)	**11.1** (8.3-14.8)



Ten-year overall transplant-free survival 68% (95%CI 53-75%)

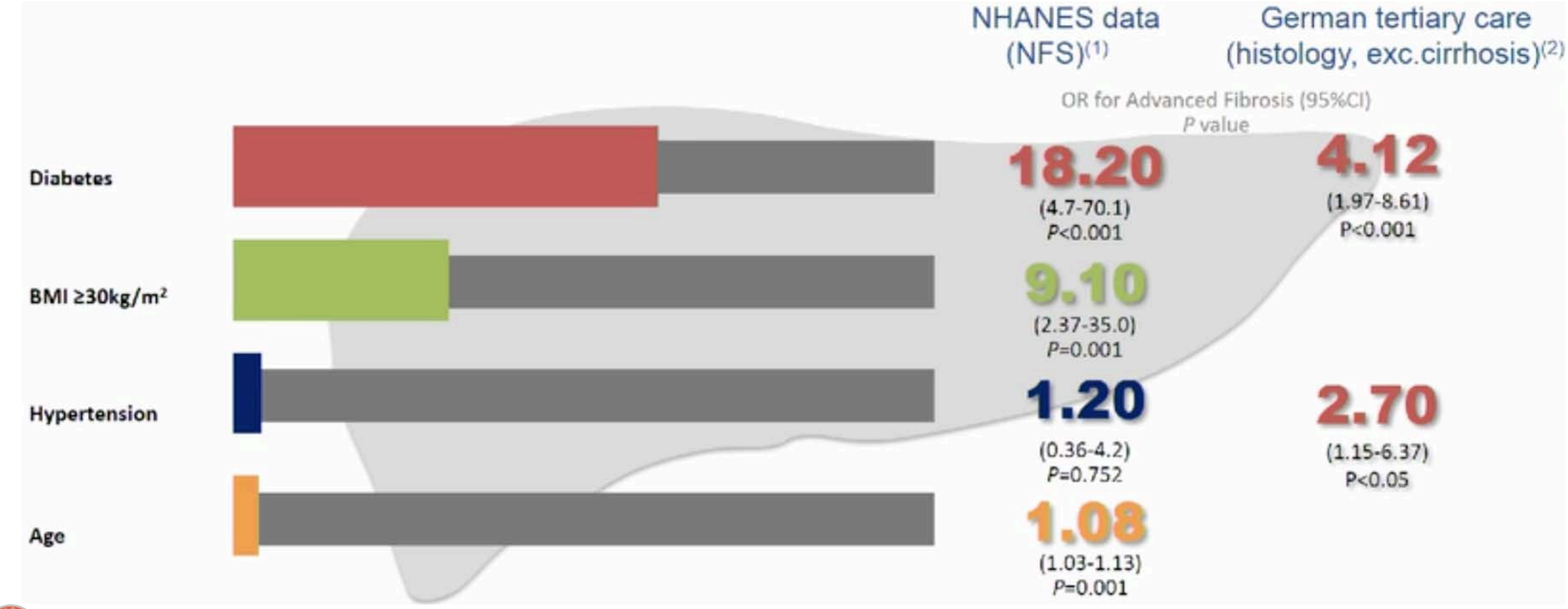
Vilar-Gomez E, et al. Gastroenterology. 2018;155(2):443-457.e17

Τα κλινικά συμβάματα ποικίλουν ανάλογα με το στάδιο της νόσου



Vilar-Gomez E, et al. Gastroenterology. 2018;155(2):443-457.e17

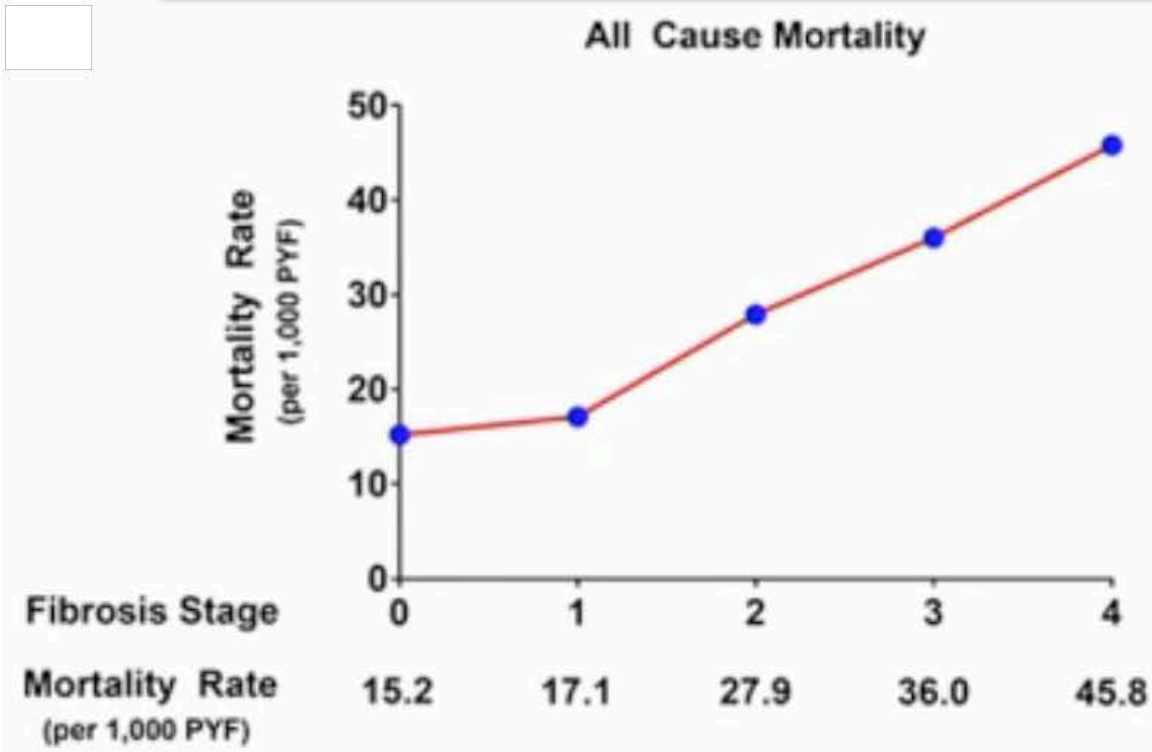
Diabetes is the strongest predictor of advanced fibrosis

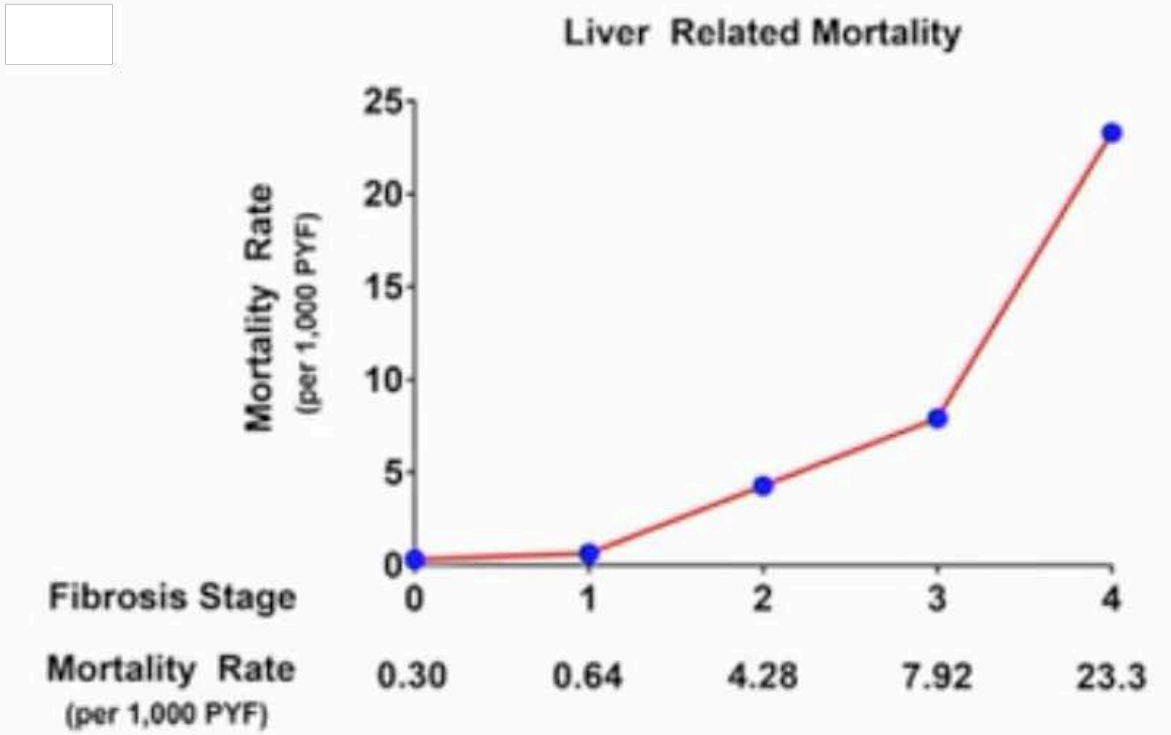


1. Wong RJ, et al. Aliment Pharmacol Ther. 2017;46(10):974-980, 2. Labenz C et al. Aliment Pharmacol Ther. 2018;48(10):1109-1116

Mortality in pts with NAFLD is multicasual

Systematic review and meta-analysis of 5 studies 1495 NAFLD pts with 17.452 pt/yrs follow-up



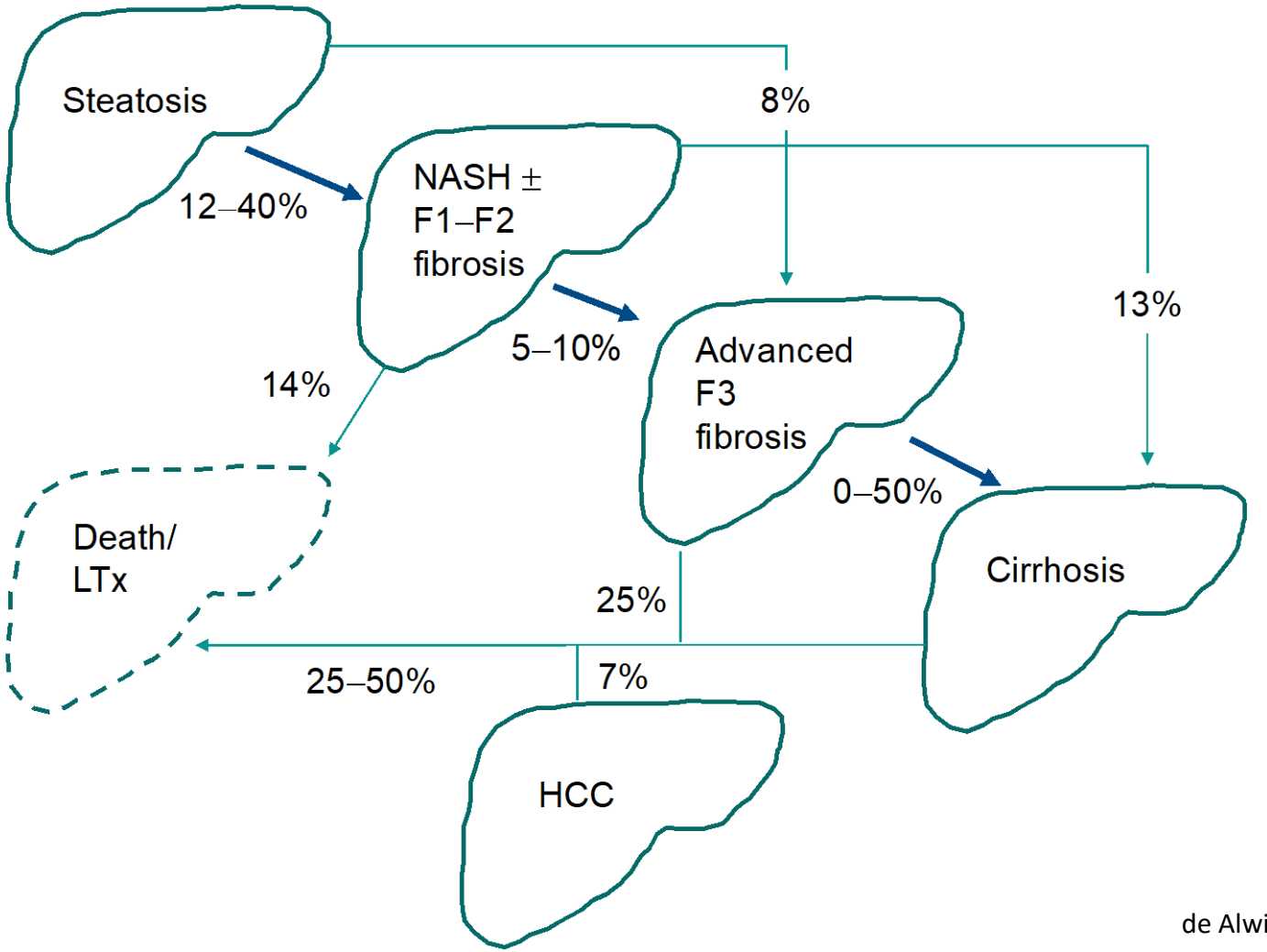


Causes of death:

1. Cardiovascular disease
2. Non-hepatic cancer
3. Liver-related causes

Dulai PS, et al. Hepatology. 2017;65(5):1557-1565

Natural history of NAFLD over 8-13 yrs



de Alwis NMW, Day CP. J Hepatol 2008;48:S104–12

NAFLD Presentation

Symptoms

- Usually asymptomatic; majority discovered by chance
- Fatigue frequently present

Often an "incidental finding"

- Incidental abnormal LFTs
- Incidental "bright liver" on imaging
- Incidental hepatomegaly

Common scenarios

- Statin monitoring
- "Annual reviews" in T2D/lipid/ hypertension clinics
- Medical insurance/occupational health checks

De Alwis NM. et al. Dig DIS 2016;34:19-26

Pragmatic First Steps in Suspected NAFLD

1. Risk Identification

- Metabolic syndrome or other high prevalence group

2. History

- Alcohol intake (< 14/21 units/wk)
- No known preexisting liver disease

3. Investigations

- Liver biochemistry (ALT, AST, etc)
- Exclude/identify other liver diseases:
  - Negative HBV & HCV serology
  - Negative autoantibodies (ANA, AMA, SMA, LKM1, ANCA)
  - Negative coeliac serology
  - Normal immunoglobulins, ferritin, A1AT, Cu2+, etc
- Liver ultrasound: increased echogenicity (steatosis)

Chalasani N, et al. Hepatology. 2018;67(1):328-357

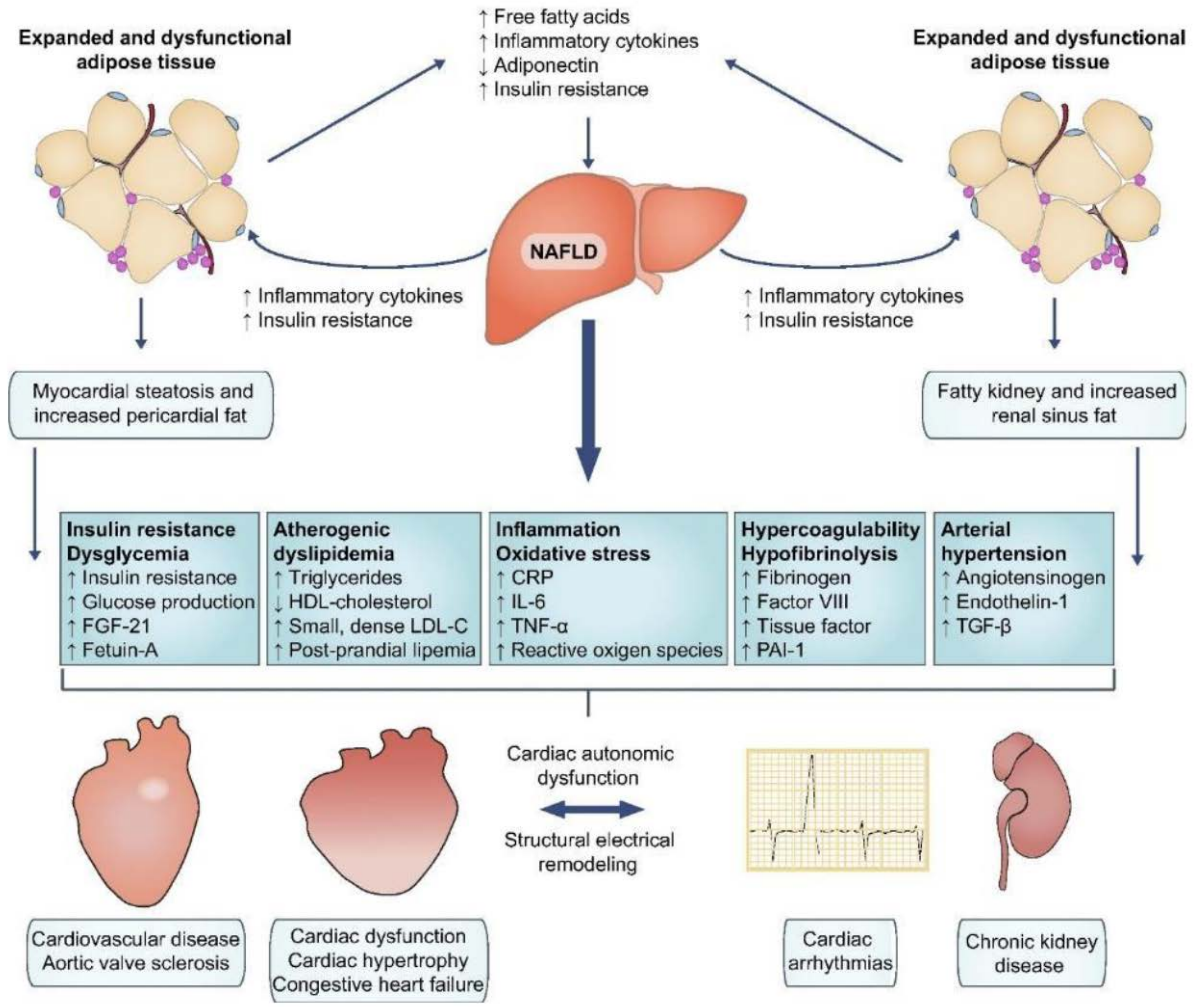
Spectrum of NAFLD and concurrent disease

Sub-classification of NAFLD*	Most common concurrent diseases
NAFL • Pure steatosis • Steatosis and mild lobular inflammation	**AFLD†** **Drug-induced fatty liver disease†** **HCV-associated fatty liver disease (GT 3)†** **Others†** • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism – Wolman disease (lysosomal acid lipase deficiency)
NASH • Early NASH (no or mild fibrosis) • Fibrotic NASH (significant/advanced fibrosis) • NASH cirrhosis	
HCC‡	

*Also called primary NAFLD and associated with metabolic risk factors/components of MetS †Also called secondary NAFLD.

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Putative connection between NAFLD, CVD and CKD



Byrne CD, Targher G. J Hepatol 2015;62:S47–64

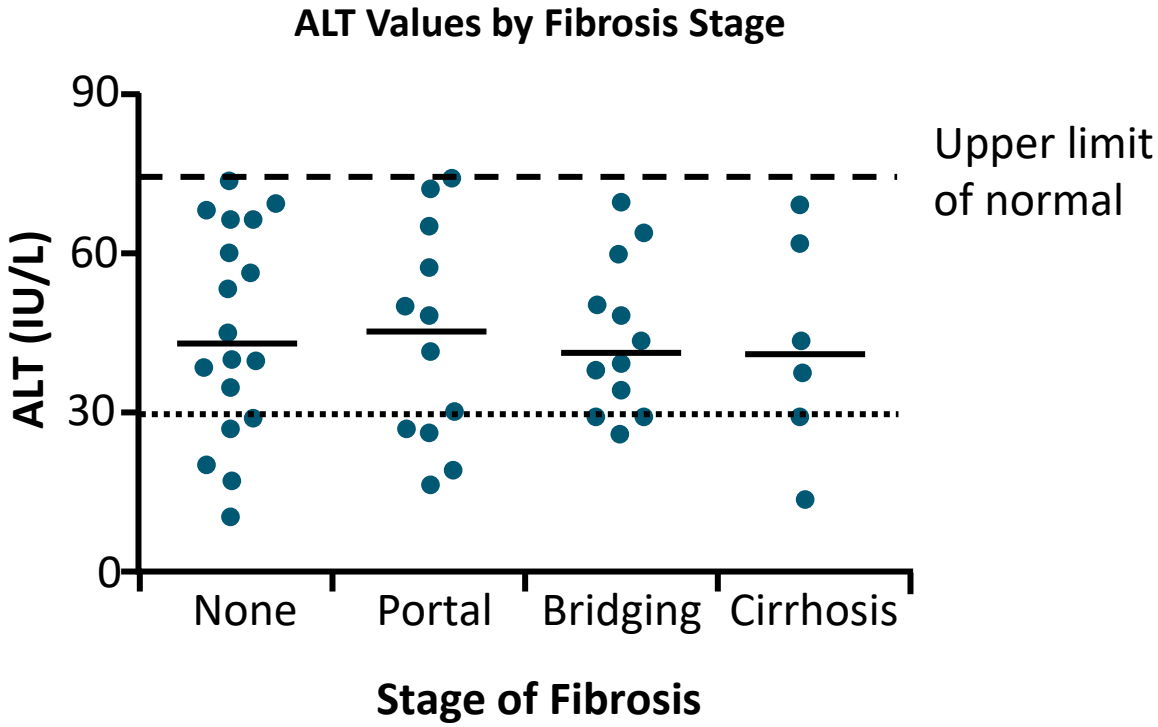
Liver Enzymes: Inadequate in Assessing NAFLD/NASH

- ALT can be normal in > 50% of individuals with NASH, 80% of individuals with NAFLD[1,2]
- ALT can be elevated in > 50% of individuals with NAFLD but without NASH
- In NAFLD, ALT is neither indicative nor predictive of NASH or fibrosis stage[3]:
  - Normal ALT does not preclude NASH/progressive disease
  - Elevated ALT cannot predict NASH or fibrosis
  - **ALT and AST not sensitive for NAFLD/NASH**

1. Browning JD, et al. Hepatology. 2004 Dec;40(6):1387-95, 2. Dyson JK, et al. Frontline Gastroenterol. 2014 Jul;5(3):211-218,
3. Mofrad P, et al. Hepatology. 2003 Jun;37(6):1286-92

NAFLD Grade and Stage Similar With Normal vs Abnormal LFTs

Pattern	Normal ALT (n = 51)	Abnormal ALT (n = 50)	*P* Value
Fat alone, n	8	10	NS
Fat + scattered inflammation, n	8	10	NS
Fat + ballooning ± inflammation, n	13	11	NS
Fat + ballooning ± Mallory hyaline ± pericellular fibrosis, n	22	19	NS



Mofrad P, et al. Hepatology. 2003 Jun;37(6):1286-92

Non invasive assessment to fibrosis

Blood

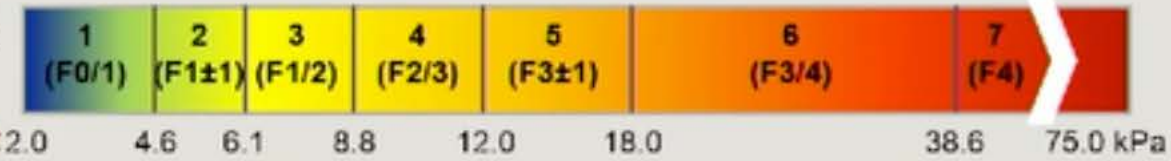
- AST/ALT ratio
- AST to platelet ratio index
- BARD
- FIB-4
- NAFLD fibrosis score

ELF score	Severity of liver fibrosis
<7.7	None-to-mild
7.7–9.8	Moderate
>9.8	Severe

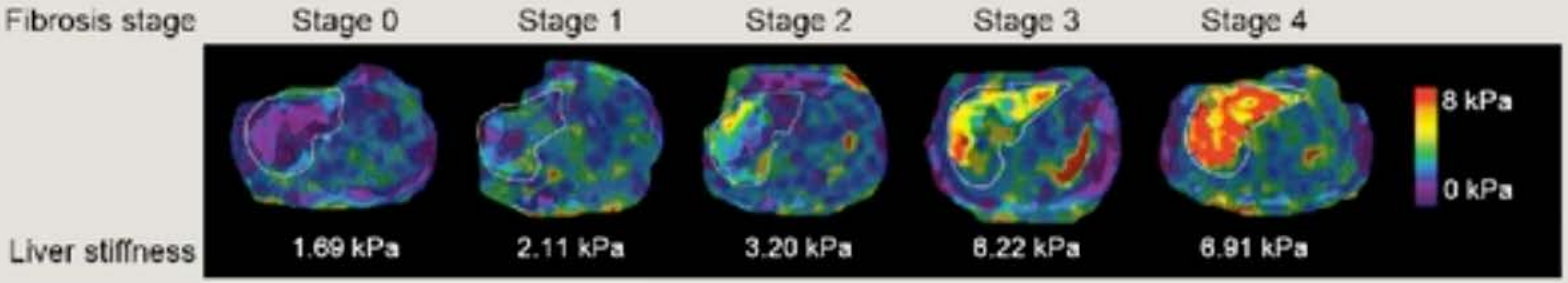
Imaging

ARFI

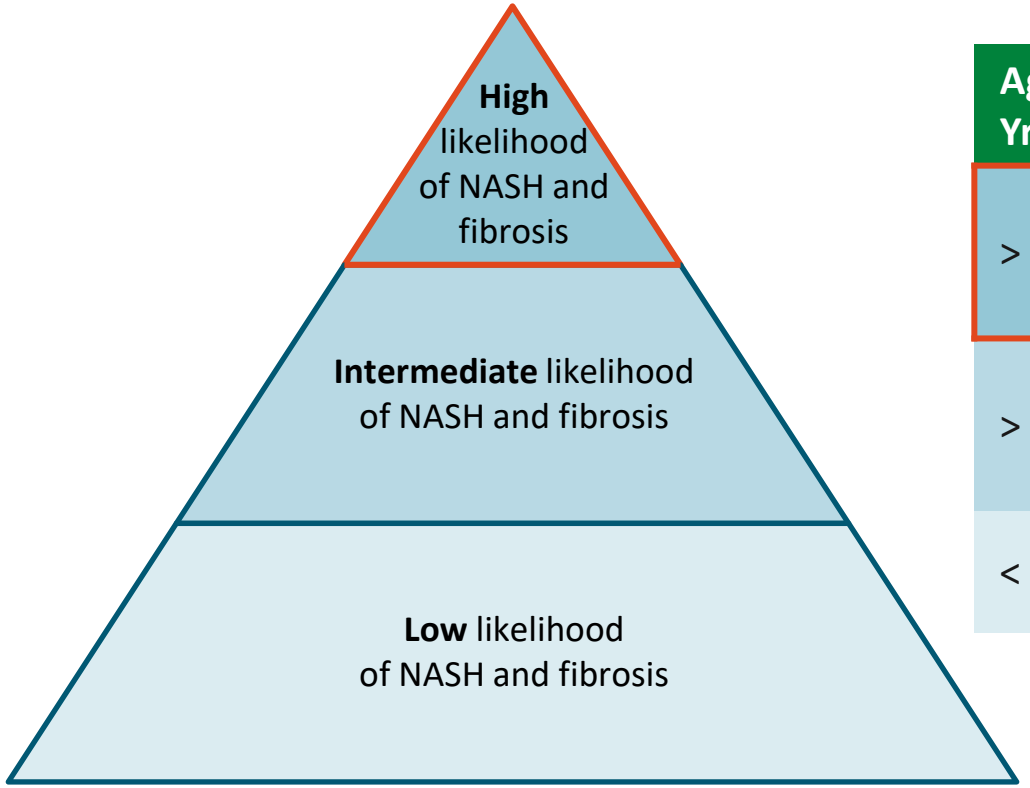
Fibrosis Classification: (equivalence in fibrosis stage)



MRE



Determining High-Risk Features for NASH



Prescreening Criteria for NASH Clinical Trials

Age, Yrs	Comorbidities	VCTE, kPA	AST, IU/L	NFS	FIB-4	Other
> 50	DM, obesity, HTN	> 8.5	> 40	> .676	> 2.67	Hispanic, AST:ALT ratio ≥ 1
> 40	Well-controlled DM, obesity, HTN	> 7.0	> 20			
< 40	No DM, no obesity	< 7.0	< 20	< -1.455	< 1.30	

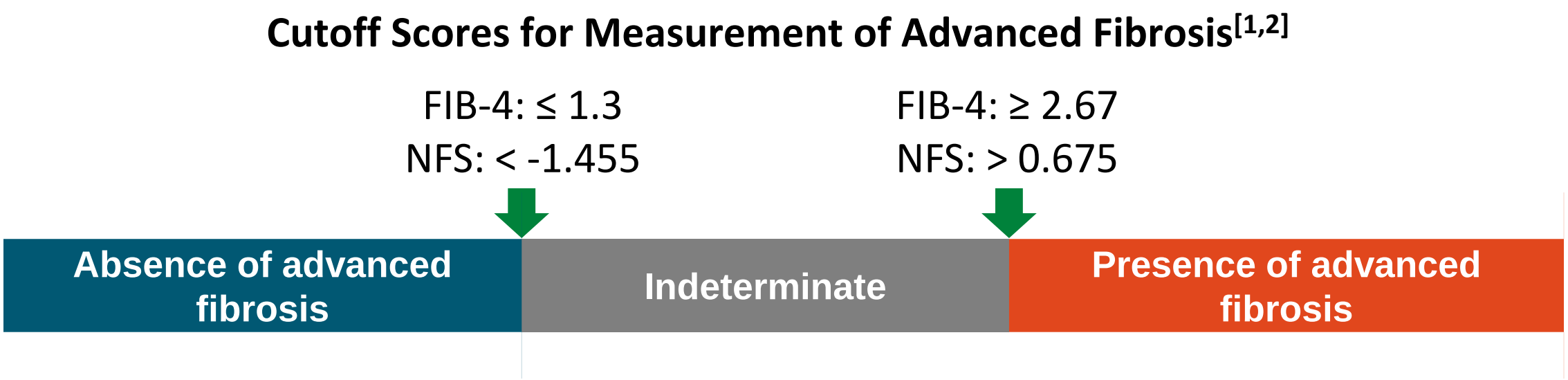
VCTE: Imaging

NFS, FIB-4: Scores based on labs

Konerman MA, et al. J Hepatol. 2018;68(2):362-375

NAFLD Fibrosis Score and FIB-4

Cutoff Scores for Measurement of Advanced Fibrosis[1,2]

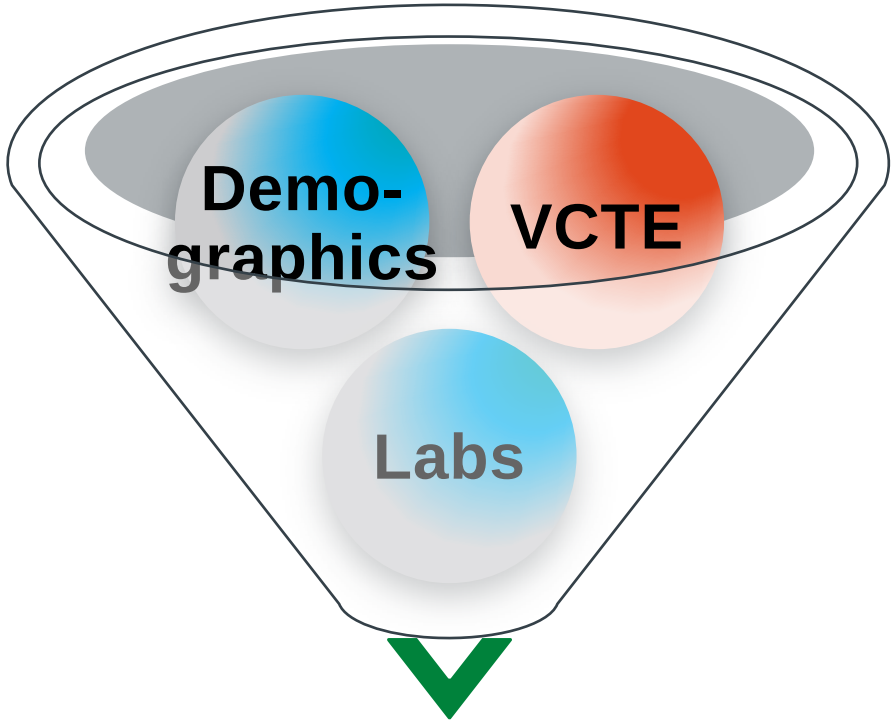


Both FIB-4 and NFS lack sufficient PPV to be used alone to predict NASH and fibrosis

1. Alkhouri N, et al. Gastroenterol Hepatol (N Y). 2012;8(10):661-8, 2. Shah AG, et al. Clin Gastroenterol Hepatol. 2009 Oct;7(10):1104-12

Noninvasive Tests

- Proper use of noninvasive tests—**including imaging**—can aid risk stratification



Enrich for NASH and F2/3 Fibrosis

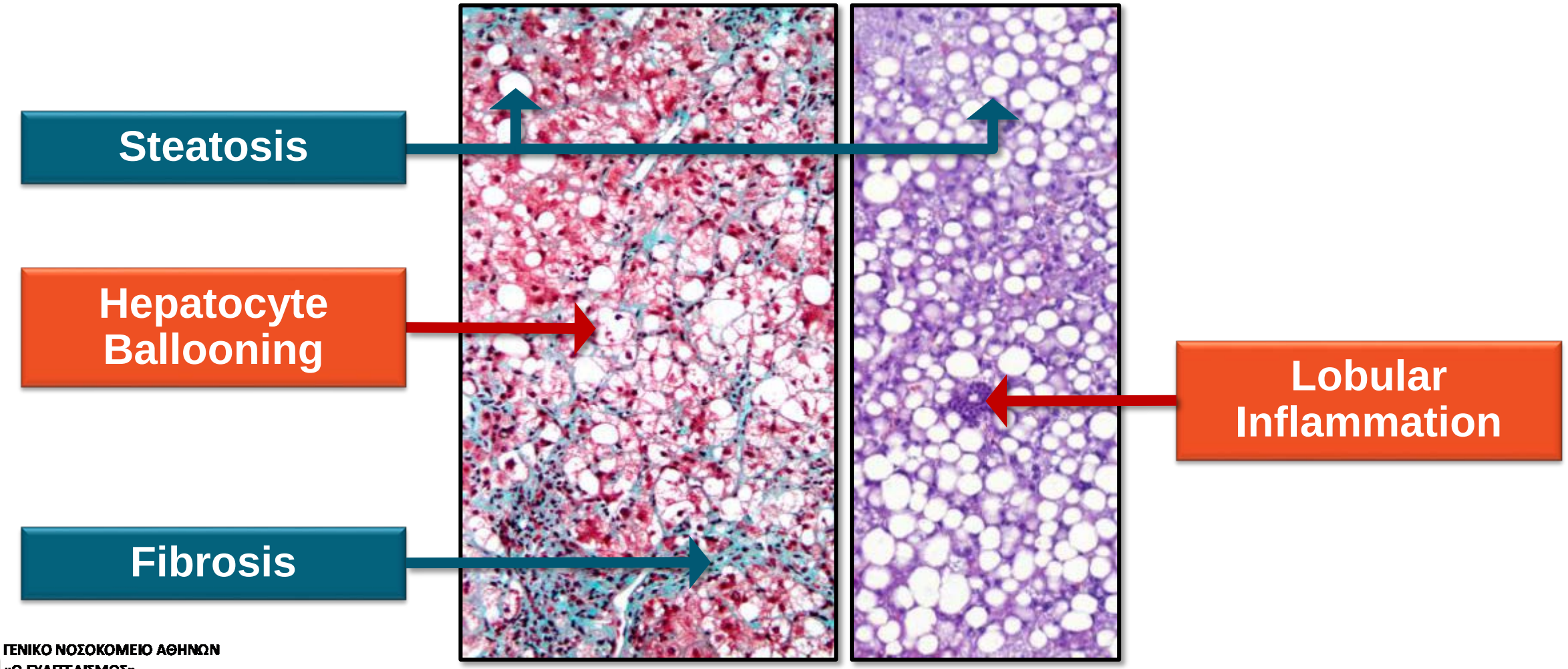
Chalasani N, et al. Hepatology. 2018;67(1):328-357

Is a Liver Biopsy Always Necessary in NAFLD?

- Not always required but remains necessary and useful in many cases
  - Confirm diagnosis and exclude alternative/secondary pathology
  - Stage disease
  - Stratify progression risk
- Use of biopsy should be tailored to the individual patient
  - Marked biochemical abnormalities on LFTs
  - Diagnostic doubt
  - Noninvasive scores that are high or indeterminate risk
  - Patient choice

Chalasani N, et al. Hepatology. 2018;67(1):328-357, Nalbantoglu IL et al. World J Gastroenterol. 2014;20(27):9026-37

Histological Features of NAFLD and NASH



Components of a life style approach to NAFLD

Energy restriction

- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake

- Avoid fructose-containing food and drink

Coffee consumption

- No liver-related limitations

Comprehensive lifestyle approach

Daily alcohol intake

- Strictly below 30 g men and 20 g women

Macronutrient composition

- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity

- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Weight loss in NAFLD

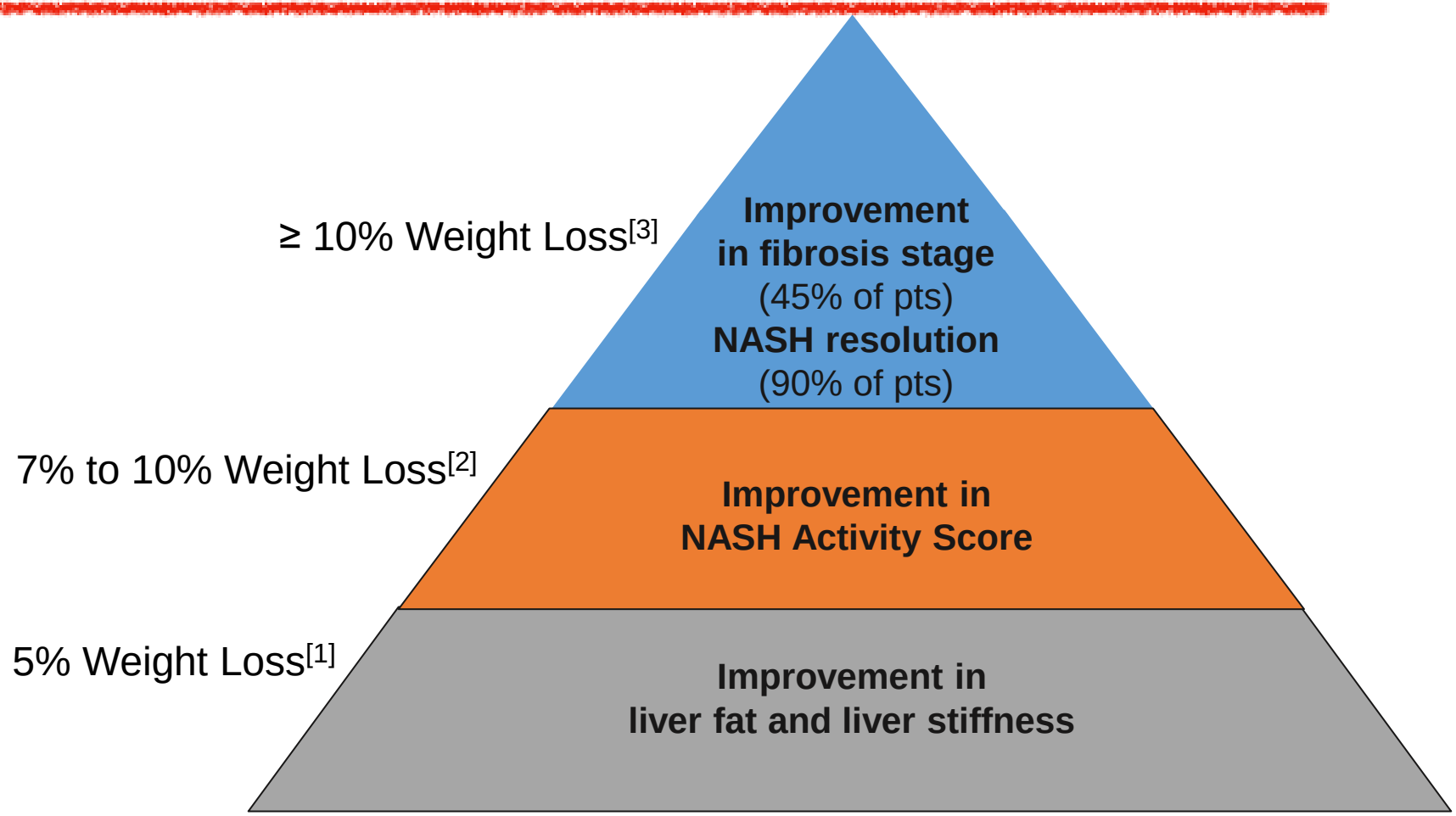
- Counsel all patients on healthy lifestyle with **diet, exercise, lifestyle**
- To achieve and maintain weight loss, consider adjunctive **pharmacologic approaches in all overweight individuals (BMI > 27)** and **surgical** approaches *in otherwise eligible obese individuals*

Diet, Exercise, Lifestyle	Pharmacologic Approaches	Bariatric Surgery
~ 5% to 8% weight loss[1]	~ 8% to 10% weight loss[1]	~ 10% to 30% weight loss[2]

1/3 to 2/3 of dieters regain more weight than they lost on their diets despite bias toward showing successful weight loss maintenance[3].

1. Garvey WT, et al. Endocr Pract. 2016;22(7):842-84, 2. Maciejewski ML, et al. JAMA Surg. 2016;151(11):1046-1055,
3. Mann T, et al. Am Psychol. 2007 Apr;62(3):220-33

How Much Weight Loss Is Needed for Improvement in NASH?



1. Patel NS, et al. Clin Gastroenterol Hepatol. 2017;15:463-464. 2. Promrat K, et al. Hepatology. 2010;51:121-129. 3. Vilar-Gomez E, et al. Gastronterol. 2015;149:367-378.

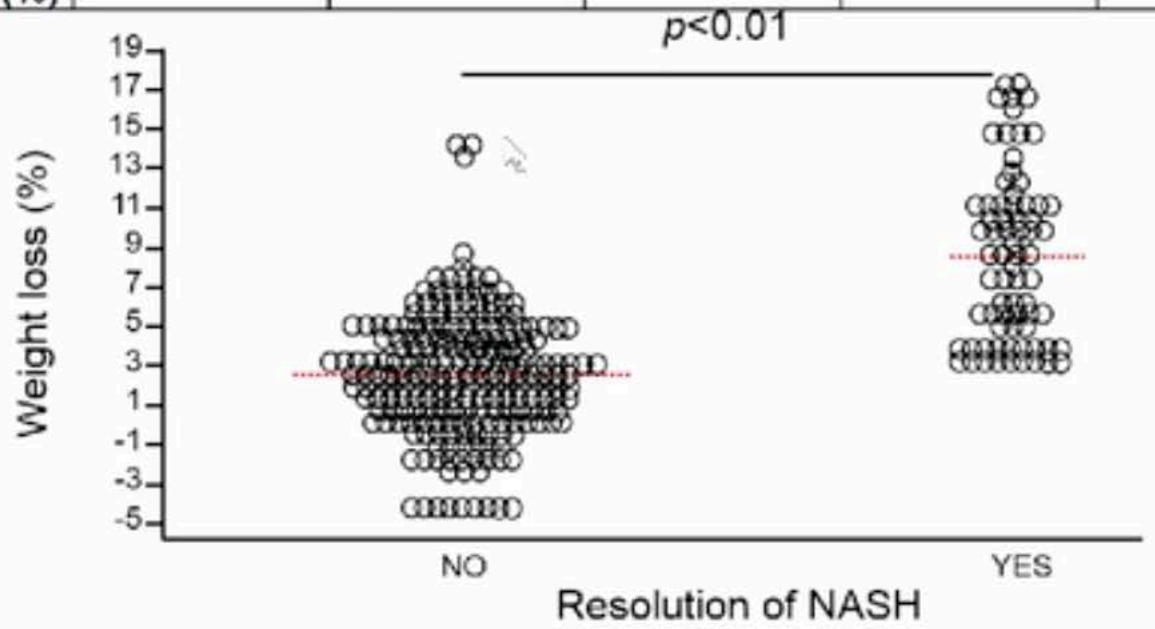
Effects of weight loss on NAFLD/NASH

Prospective study with biopsy-proven NASH

Lifestyle changes over 52 weeks:

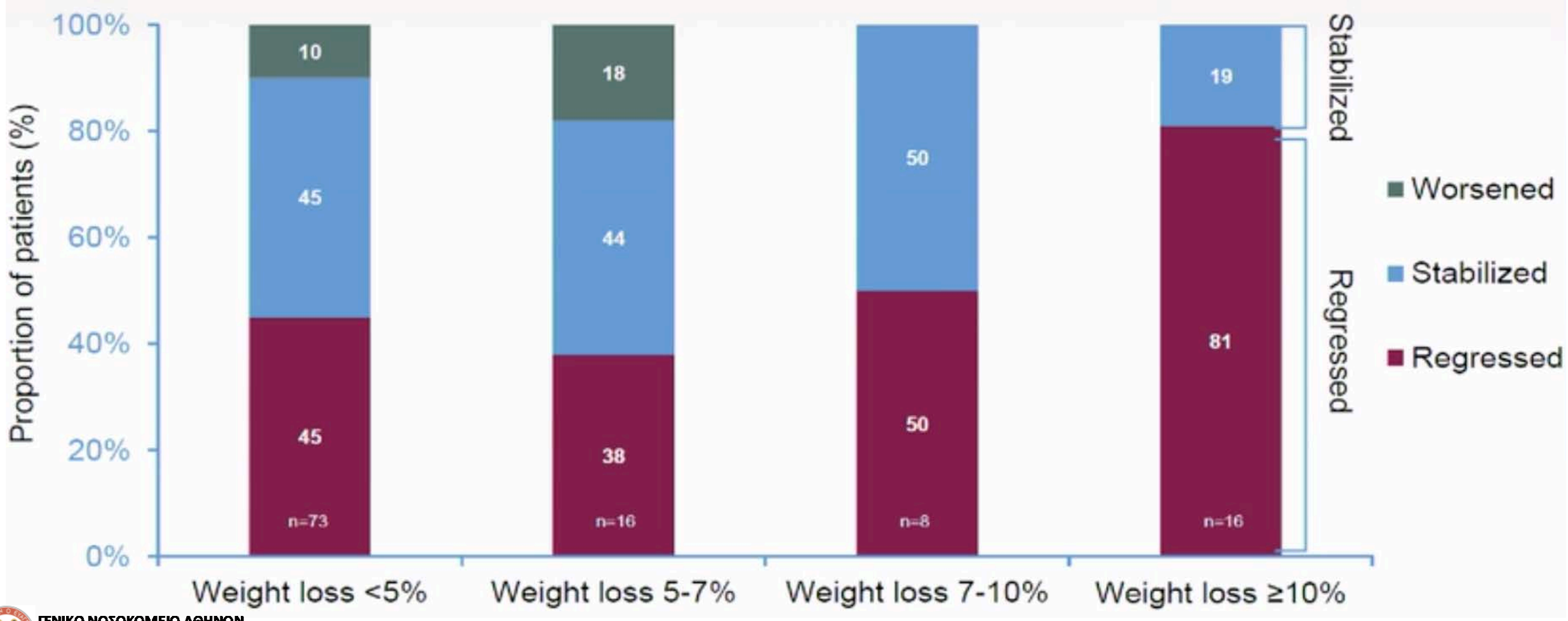
1. ↓750 kcal/day
2. Walk 200 min/week
3. Behavioural session (every 8 weeks)

Variables	Overall (n=293)	WL <5 (n=205)	WL = 5–6.99 (n=34)	WL = 7–9.99 (n=25)	WL ≥10 (n=29)
Weight loss, %	3.8 ± 2.7	1.78 ± 0.16	5.86 ± 0.09	8.16 ± 0.22	13.04 ± 6.6
Resolution of Steatohepatitis, n (%)	72 (25)	21 (10)	9 (26)	16 (64)	26 (90)



Vilar-Gomez E, et al. Gastroenterology. 2015 Aug;149(2):367-78.e5

Weight loss through life style modifications improves fibrosis



Vilar-Gomez E, et al. Gastroenterology. 2015 Aug;149(2):367-78.e5

Treatment of NAFLD/NASH

>20 *preclinical programs*

29 *compounds in phase I development*

45 *Phase II trials*

4 *Phase III trials*

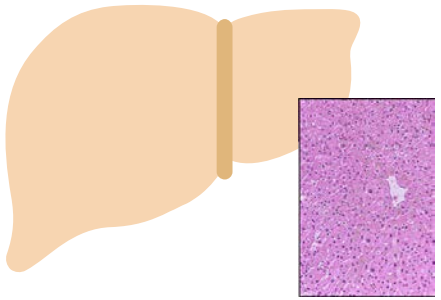
There is no treatments currently licensed for the treatment of NASH

Konerman MA, et al. J Hepatol. 2018;68(2):362-375

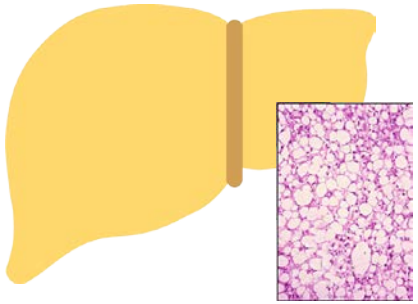
Examples of NASH Treatments in Phase II or III Investigations

NAFLD

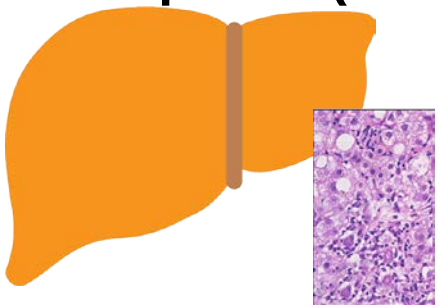
Normal Liver



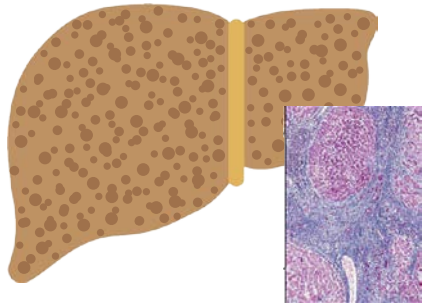
Steatosis (NAFL)



Steatohepatitis (NASH)



Cirrhosis



Insulin resistance and/or lipid metabolism → **Lipotoxicity and oxidative stress** → **Inflammation and immune activation** → **Cell death (apoptosis and necrosis)** → **Fibrogenesis and collagen turnover**

PPARγ:	Pioglitazone
GLP-1:	Liraglutide, semaglutide
SGLT:	Empagliflozin, licogliflozin, canagliflozin
DPP-4	Sitagliptin
ACC:	GS-0976, PF-05221304
SCD1:	Aramchol
ASBT:	Volixibat

PPARα/∂:	Elafibranor
PPARα/γ:	Saroglitazar
Pan-PPAR:	Lanifibranor
FGF19:	NGM282
FGF21:	Pegbelferim
FXR:	OCA, cilofexor, tropifexor, nidufexor
MPC:	MSDC-0602K
TGR-5:	INT-767/777
THR-β:	MGL-3196, VK2809

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

AOC3:	BI-1467335
P2X7R:	SGM-1019
TLR-4:	JKB-121/122

ASK1: Selonsertib (cell death target but affects fibrosis)

Caspase:	Emricasan

Galectin:	GR-MD-02
LOXL2:	Simtuzumab

Phase III

Some agents have multiple targets

Currently Available Pharmacologic Agents (Off Label)

Targeting Insulin Resistance

Compound	Mechanism of Action	Trial	Primary Endpoint(s)	AASLD Recommendation as NASH Treatment
Metformin	Multiple	Multiple studies	Various	Not recommended for NASH per se
Pioglitazone	PPARγ agonist	PIVENS Multiple studies	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in patients with biopsy-proven NASH
Liraglutide	GLP-1 receptor agonist	LEAN*	Resolution of NASH without fibrosis worsening	Premature to consider GLP-1 receptor agonists

Targeting Oxidative Stress

Compound	Mechanism of Action	Trial Name	Primary Endpoint(s)	AASLD Recommendation as NASH Treatment
Vitamin E	Antioxidant	PIVENS TONIC	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in **nondiabetic** adults with biopsy-proven NASH

Chalasani N, et al. Hepatology. 2018;67(1):328-357

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]

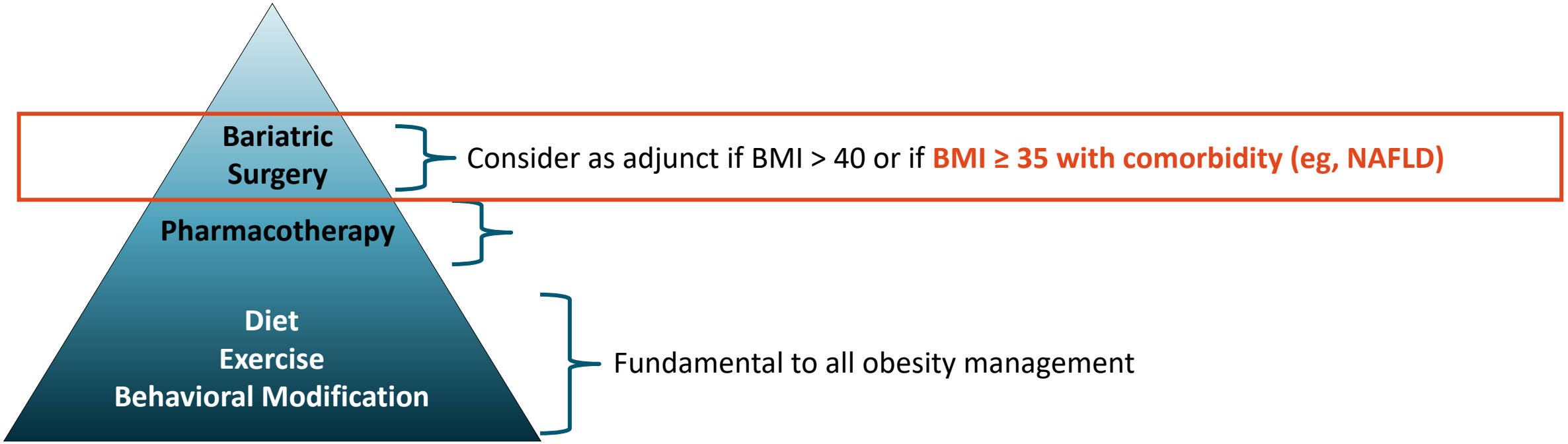
Pioglitazone

- 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.

Bariatric surgery



" . . . we suggest the use of approved weight loss medication (over no pharmacologic therapy)"

Apovian CM, et al. J Clin Endocrinol Metab. 2015;100(2):342-62

Bariatric Surgery Improves Liver Histology in Obese Patients

- Prospective study in morbidly obese patients with **biopsy-validated NASH,** ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)[1]

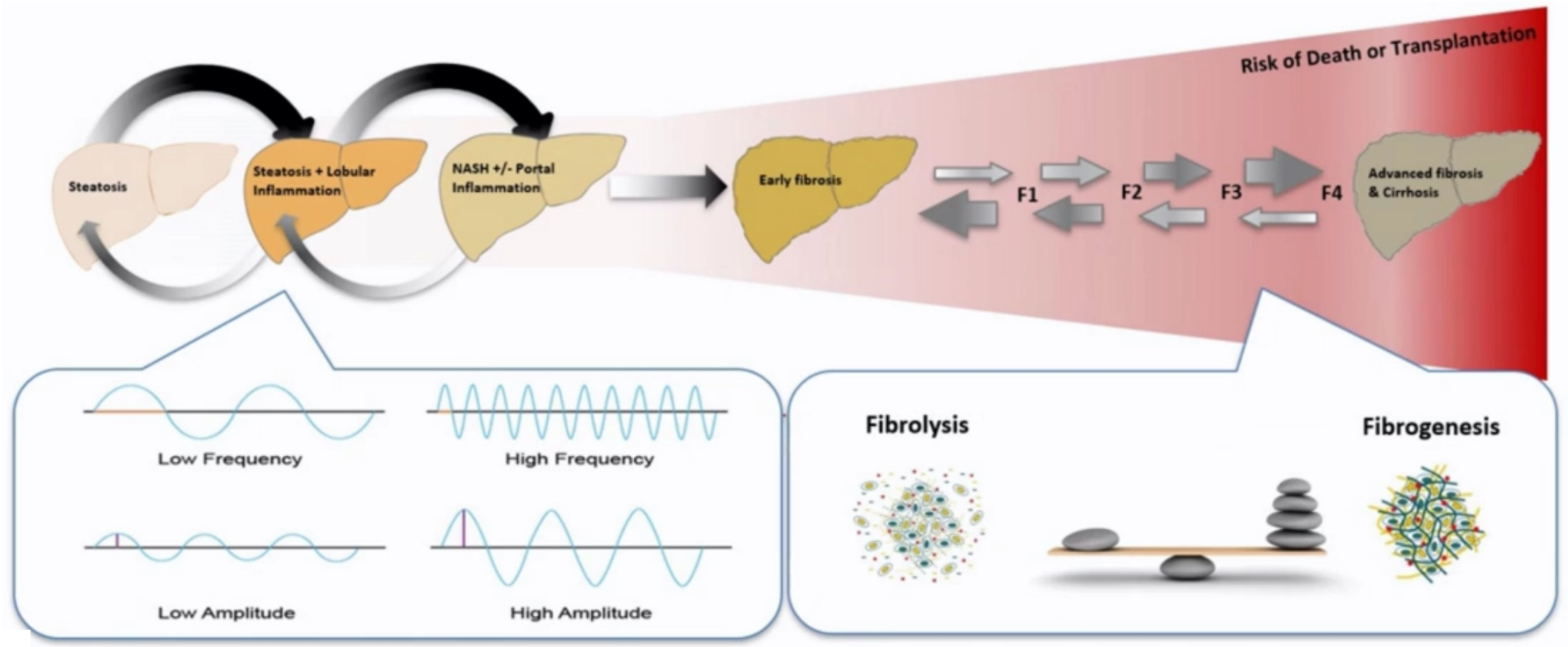
Outcome	Baseline	After 1 Yr
Mean BMI ± SD	49.3 ± 8.2	37.4 ± 7.0
Patients with NASH resolution, %	NA	85.0
Patients with fibrosis reduction, %	NA	33.8

- Meta-analysis of 32 cohort studies of bariatric surgery in obese patients (n = 3093 biopsies)[2]

Characteristic	Outcome
Mean reduction in NAS, points	2.39
Patients with resolution of NAFLD components, %	
▪ Steatosis	66
▪ Inflammation	50
▪ Ballooning	76
▪ Fibrosis	40
Patients with new or worsening histologic NAFLD components, %	12

1. Lassailly G, et al. Gastroenterology. 2015;149(2):379-88, 2. Lee Y, et al. Clin Gastroenterol Hepatol. 2019;17(6):1040-1060.e11

Conclusions



Ερωτήσεις – συζήτηση