EASL
The Home of Hepatology

FIRST NAFLD SUMMIT

Random thoughts

Rome, Nov 9th 2017

Vlad Ratziu, Université Pierre et Marie Curie, Hôpital Pitié Salpêtrière, Paris, France

ICAN
Institute of Cardiometabolism And Nutrition

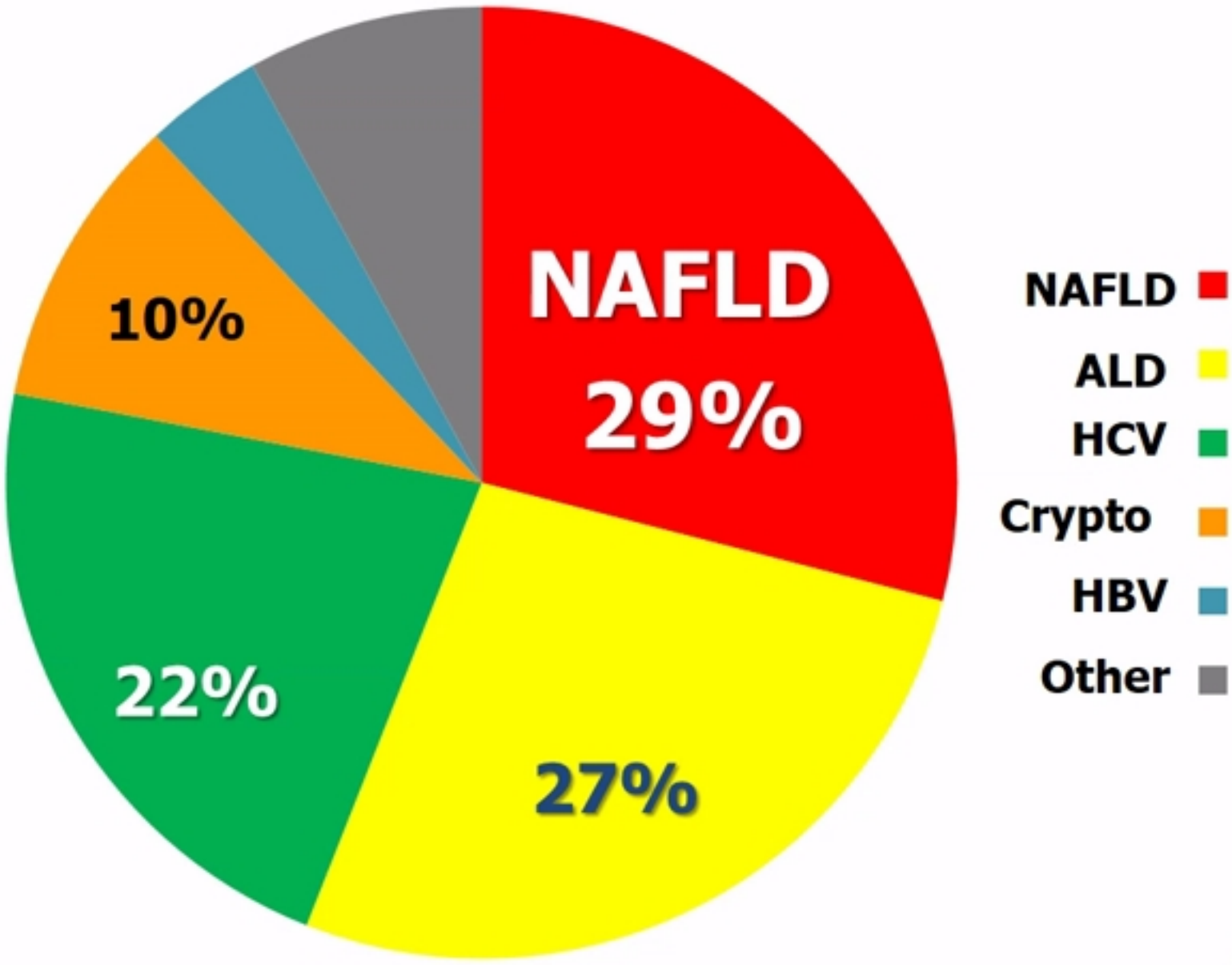
faculté de médecine
Pierre et Marie CURIE

Disclosures

- Consultancy (past 2 years)
  - Allergan, Boehringer-Ingelheim, Enanta, Enyo, Galmed, Genfit, Intercept, Madrigal, Novartis, Pfizer, Sanofi-Aventis, Verlyx
- Grants
  - Gilead, Intercept

Causes of Cirrhosis (US)

Multiethnic Cohort, Medical Claims, Medicare claims 1999-2012



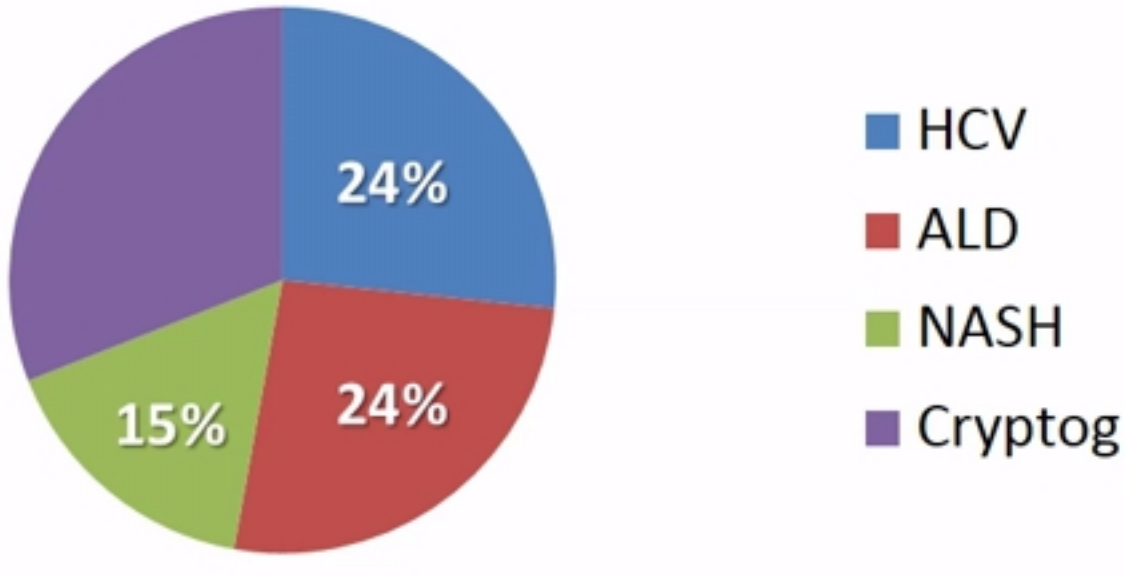
Setiawan, Hepatology 2016

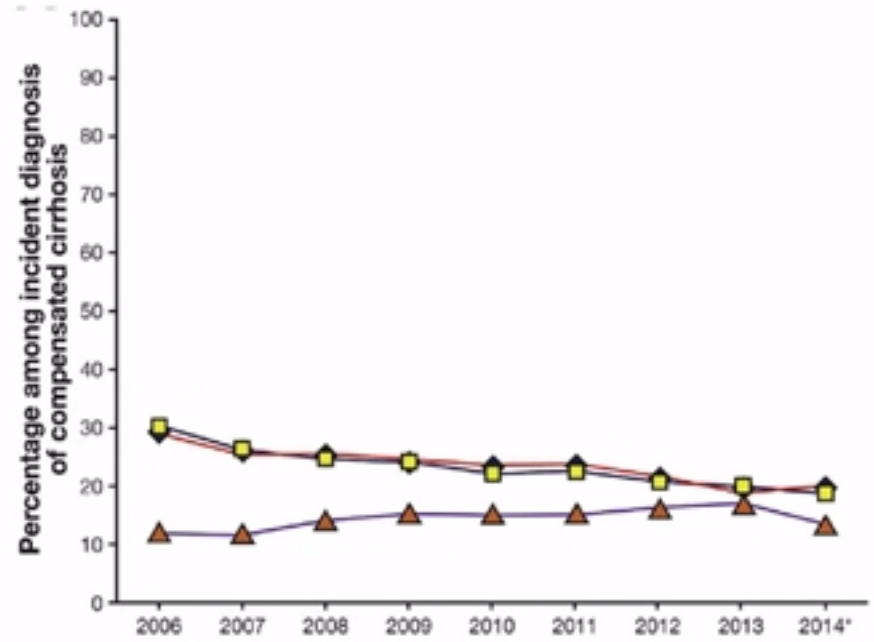
HealthCore integrated research database on cirrhosis and ESLD

UNOS database

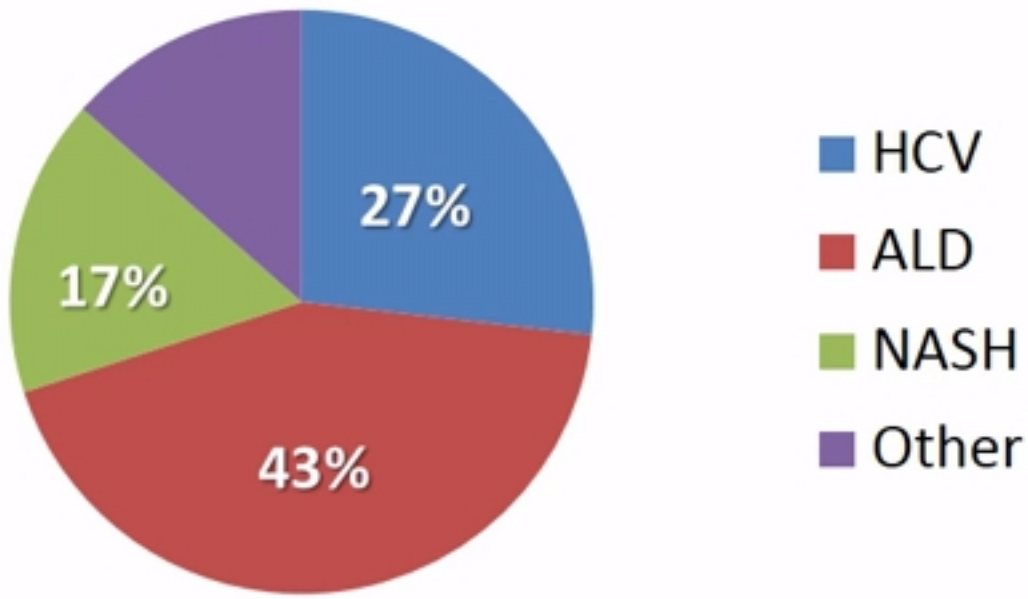
Goldberg, Gastroenterology 2017

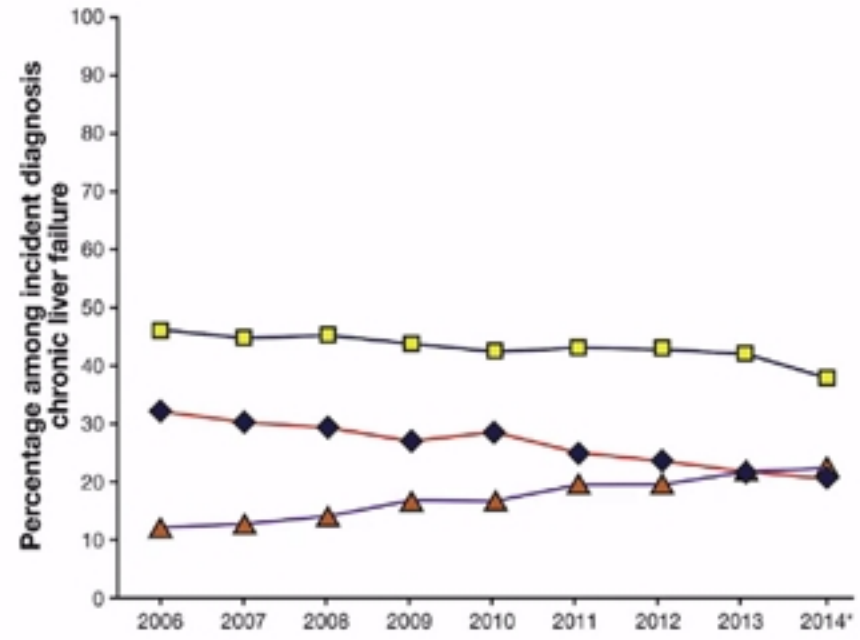
COMPENSATED CIRRHOSIS (N=24,258)c





DECOMPENSATED CIRRHOSIS (N=14,971)



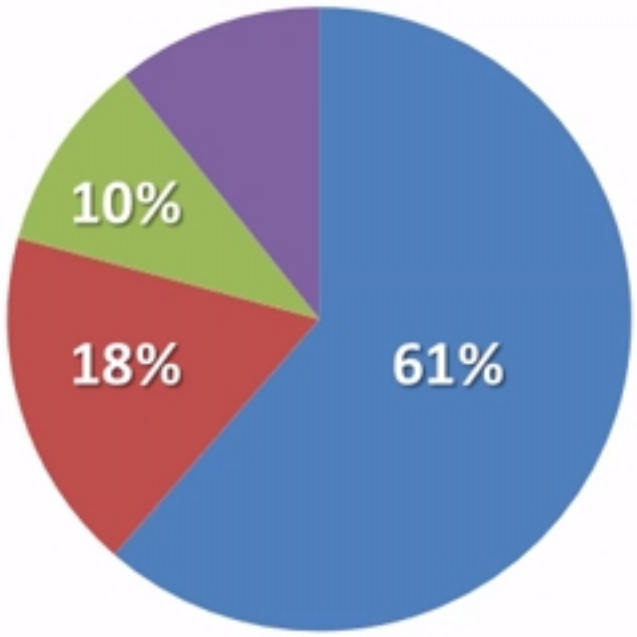


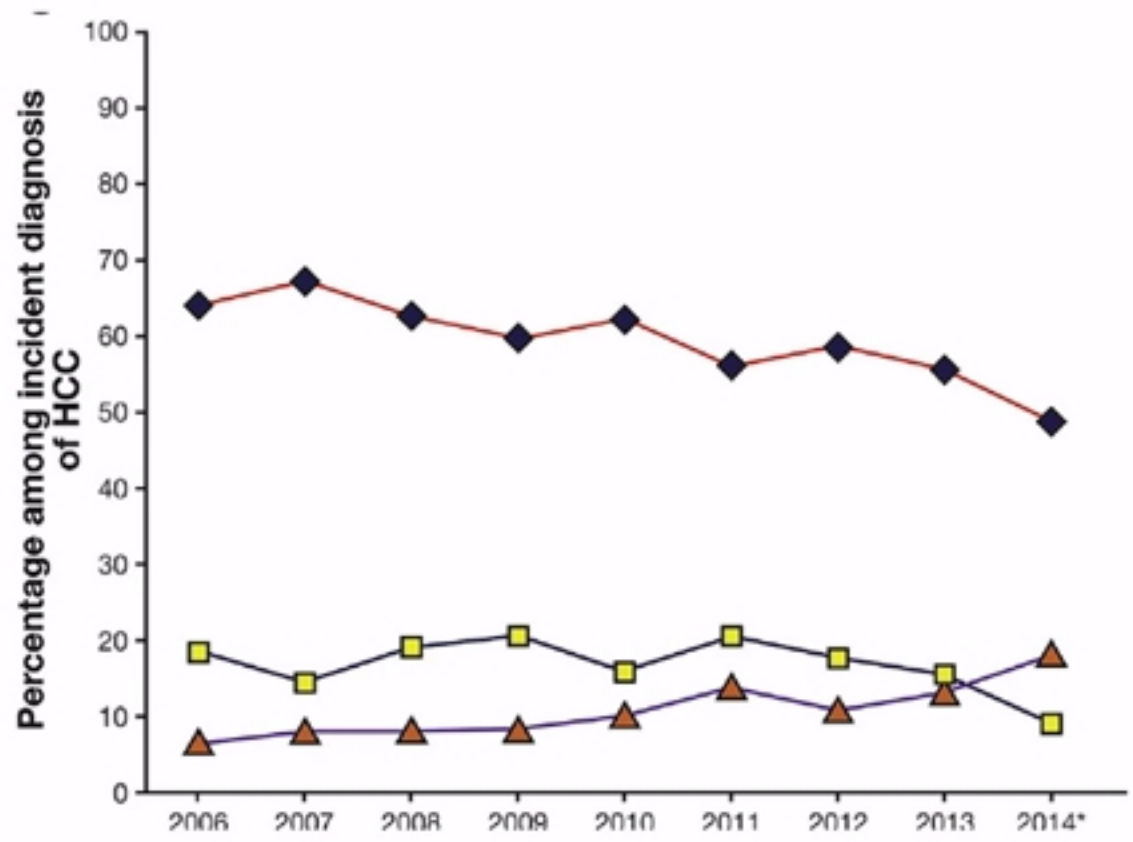
HealthCore integrated research database on cirrhosis and ESLD

UNOS database

Goldberg, Gastroenterology 2017

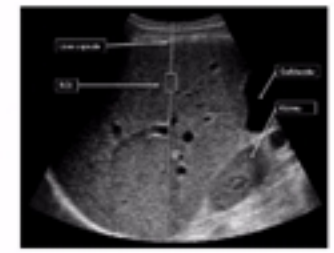
CIRRHOTIC HCC (N=1853)





Prevalence of NAFLD and NAFLD fibrosis in the general population (>45 yrs)

N= 3041 indiv, general pop, >45 yrs



35.5 %

NAFLD

27 %

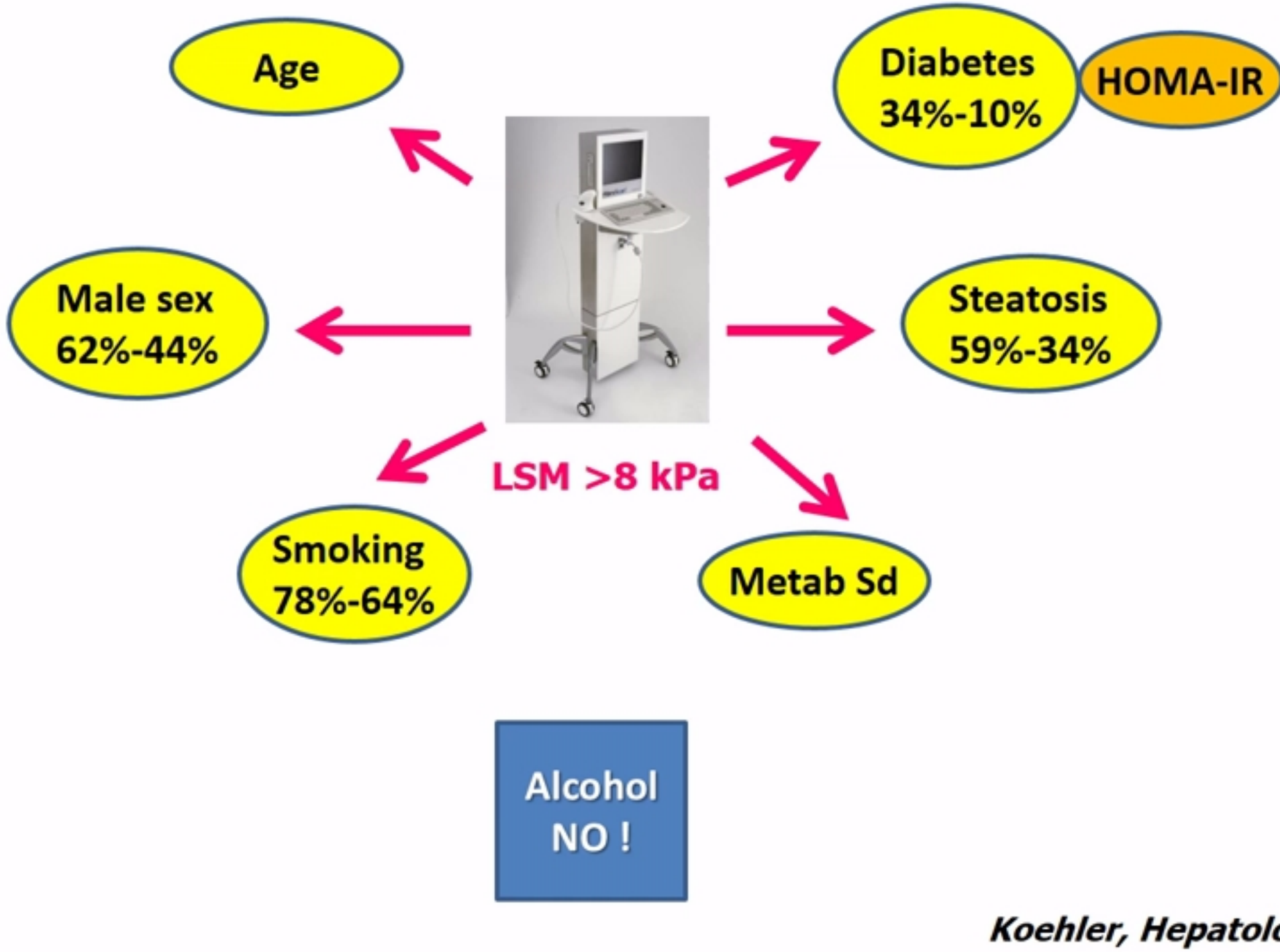
Alcohol, drugs, viruses…

2.3 %

NAFLD fibrosis

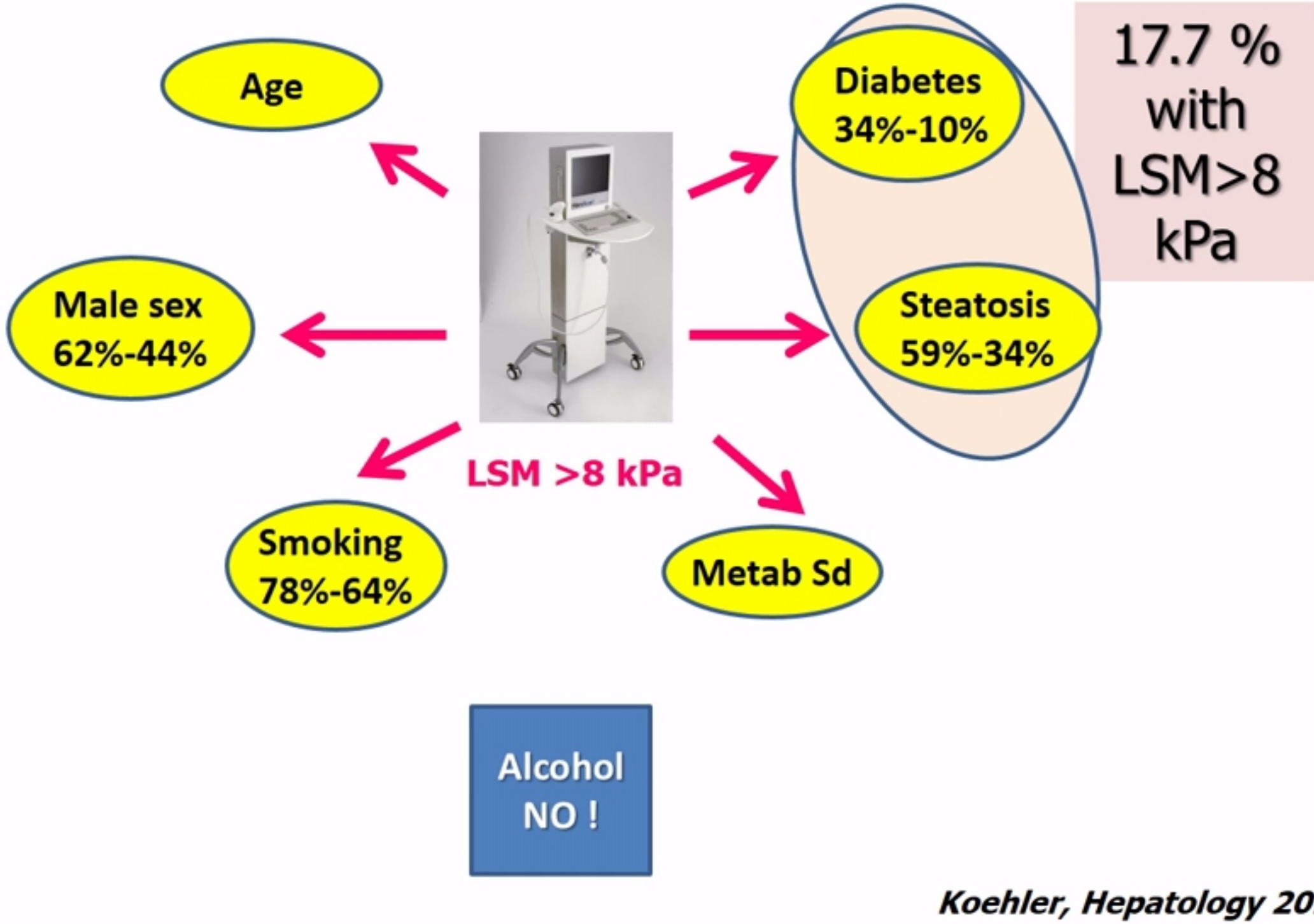
Koehler, Hepatology 2016

Factors associated with Fibrosis in the general population older than 45 yrs



Koehler, Hepatology 2016

Factors associated with Fibrosis in the general population older than 45 yrs



Koehler, Hepatology 2016

Screening for fibrosis in the general population

7463 healthy subjects

FibroTest

Fibrosis (≥2)	2.8 %
Cirrhosis	0.3%

Poynard et al. BMC Gastroenterol 2010

1190 healthy subjects

FibroScan

Fibrosis (≥2)	7.5 %
Cirrhosis	0.7%

Roulot et al. Gut 2011

Prevalence estimates

TERTIARY CENTERS

100 % NAFLD

33-50 % NASH

20-25% advanced fibrosis/cirrhosis

10-15% cirrhosis

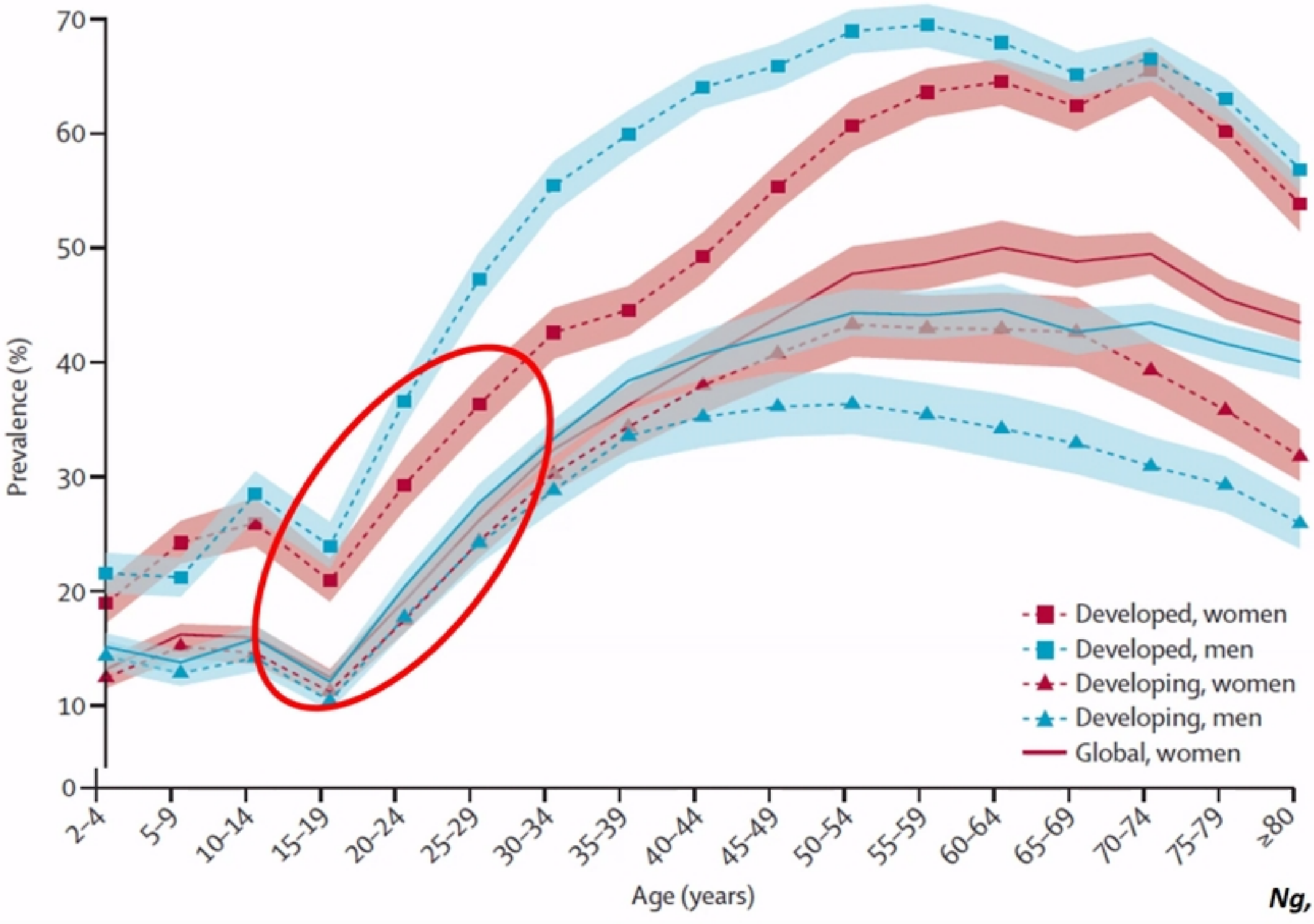
GENERAL POPULATION

25 % NAFLD

10 % NASH (2.5 %)

10-15 % advanced fibrosis/ cirrhosis (0.25-0.4 % total)

Prevalence of obesity and overweight by age and sex, 2013



Ng, Lancet, 2014

Long-term hepatic consequences of childhood/adolescence overweight

Research Article

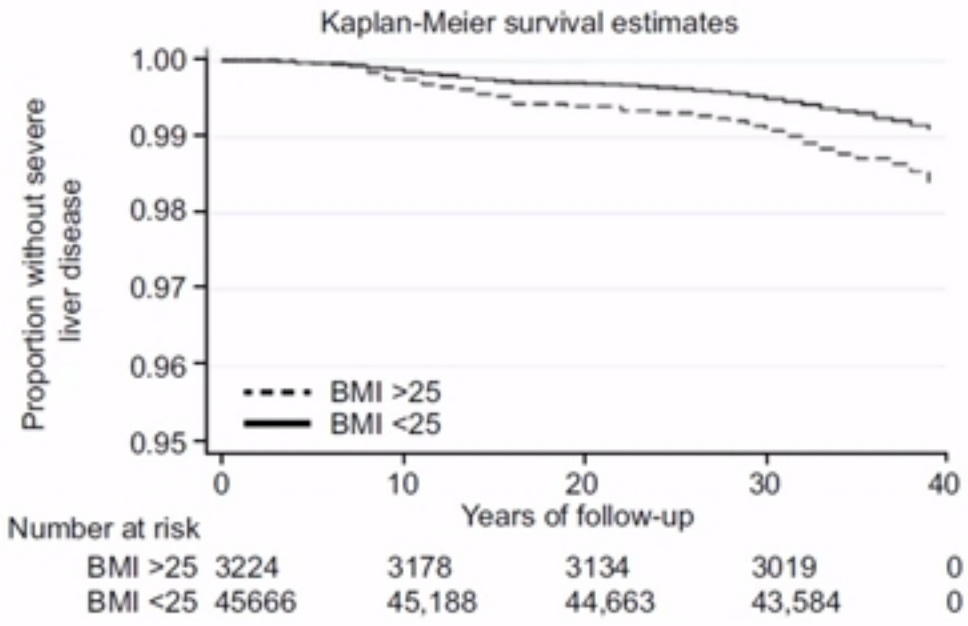
EASL | JOURNAL OF HEPATOLOGY

Overweight in late adolescence predicts development of severe liver disease later in life: A 39 years follow-up study

Hannes Hagström[1,2,*], Per Stål[1,2], Rolf Hultcrantz[1,2], Tomas Hemmingsson[3,4], Anna Andreasson[5,6]

[1]Centre for Digestive Diseases, Division of Hepatology, Karolinska University Hospital, Stockholm, Sweden; [2]Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden; [3]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [4]Centre for Social Research on Alcohol and Drugs, Stockholm University, Stockholm, Sweden; [5]Stress Research Institute, Stockholm University, Stockholm, Sweden; [6]Division of Family Medicine, Department of Neurobiology, Care sciences and Society, Karolinska Institutet, Huddinge, Sweden

See Editorial, pages 249–251



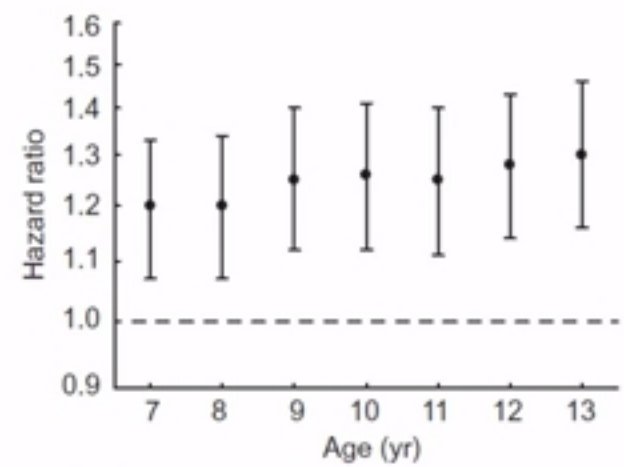
Research Article

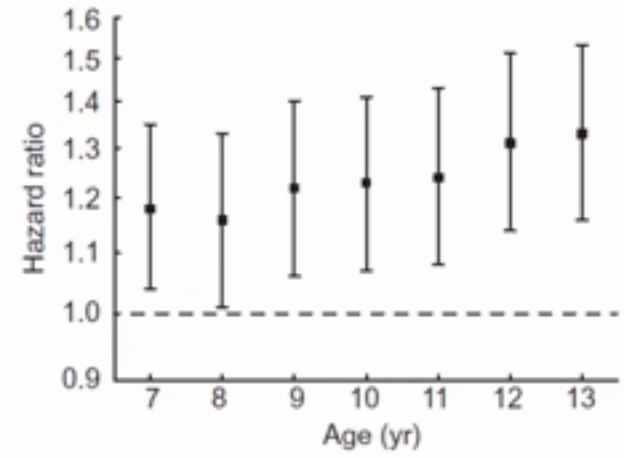
EASL | JOURNAL OF HEPATOLOGY

Body mass index in childhood and adult risk of primary liver cancer

Tina Landsvig Berentzen[1], Michael Gamborg[1], Claus Holst[1], Thorkild I.A. Sørensen[1,2], Jennifer L. Baker[1,2,*]

[1]Institute of Preventive Medicine, Bispebjerg and Frederiksberg Hospitals, The Capital Region, Copenhagen, Denmark; [2]The Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, Faculty of Health Sciences, University of Copenhagen, Denmark



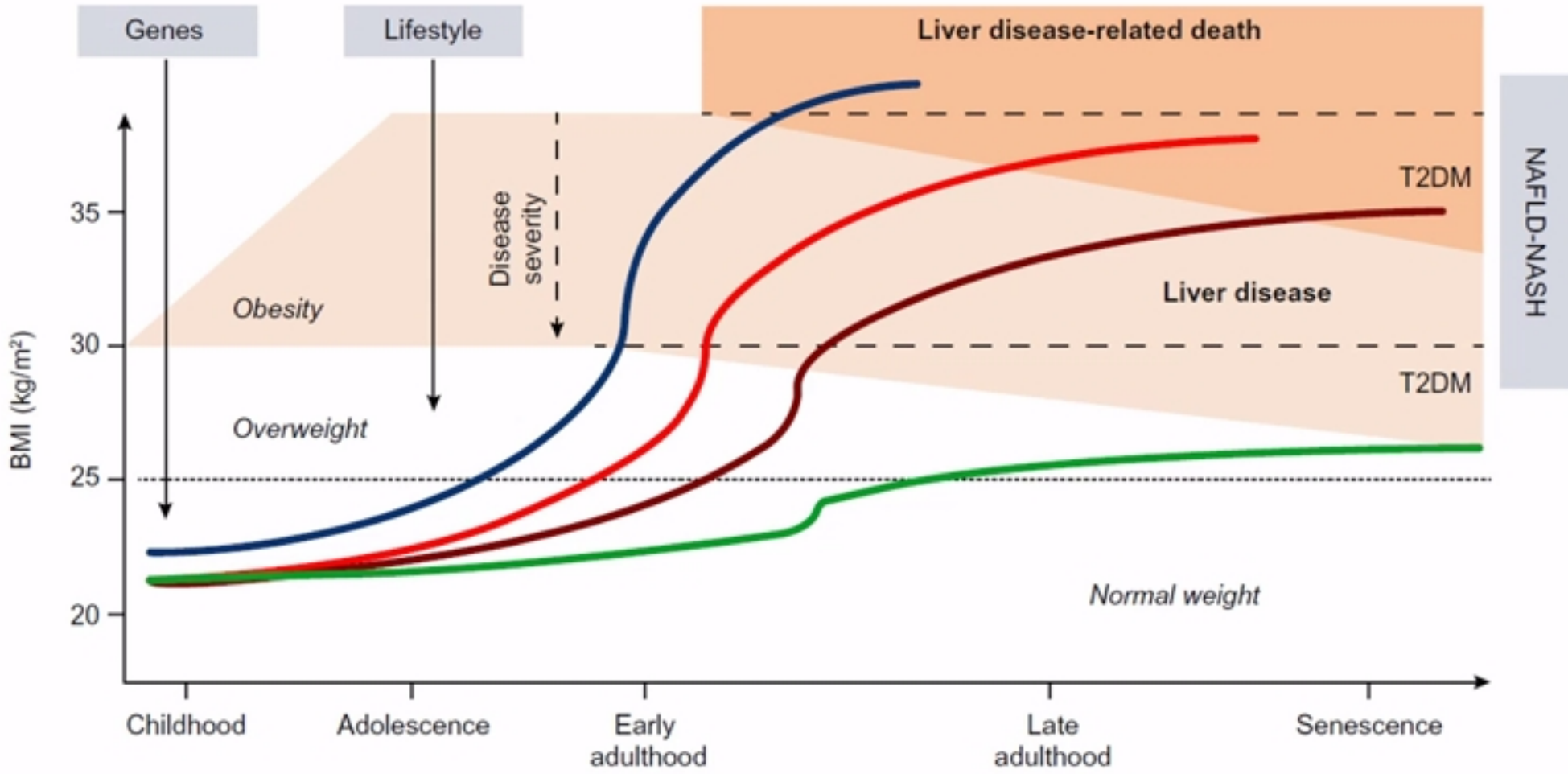


J Hepatol 2016; J Hepatol 2014

When the journey form obesity to cirrhosis takes an early start

Vlad Ratziu[1], Giulio Marchesini[2,*]

[1]*Hôpital Pitié-Salpêtrière, Institute of Cardiometabolism and Nutrition, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France;* [2]*Unit of Metabolic Diseases and Clinical Dietetics, "Alma Mater" University, Bologna, Italy*



NASH : when to think about it ?

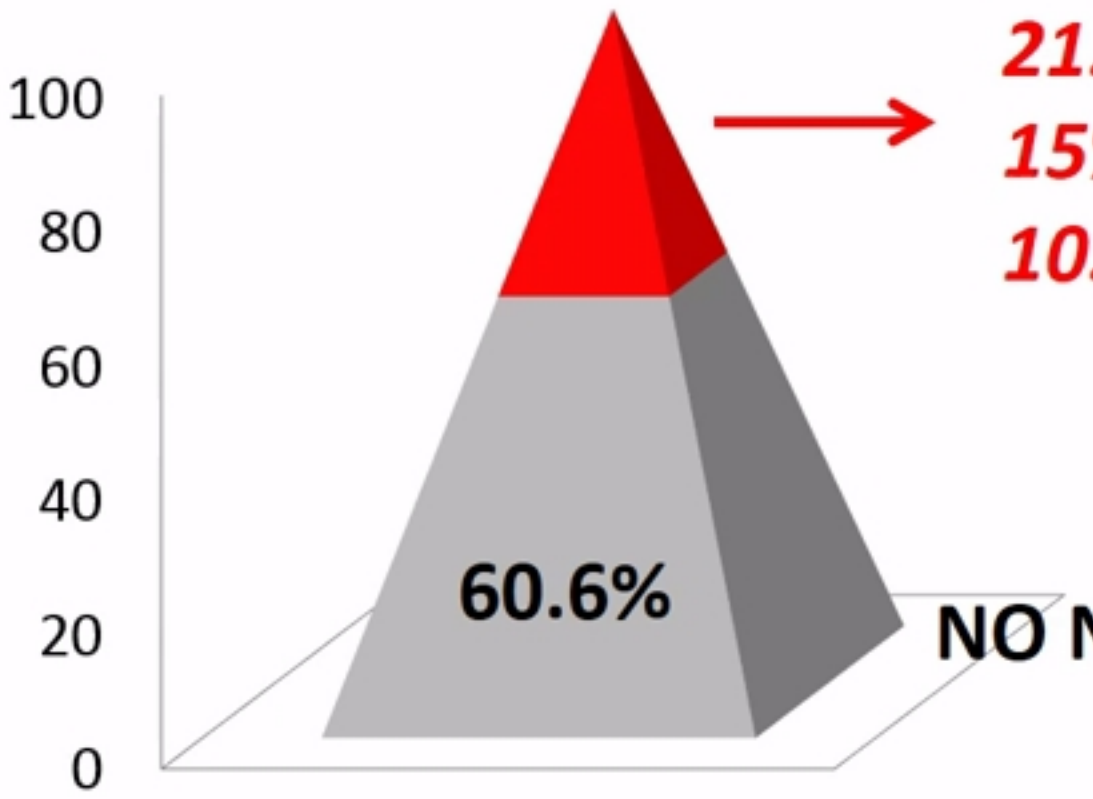
Metabolic risk factors

(diabetes, dyslipidemia, CAD)

Altered LFTs

Steatosis (ultrasound)

NAFLD : an underrecognized disease



39.4% ***recognition of ALT increase***
21.5% ***diagnosis of NAFLD/NASH***
15% ***lifestyle modifications***
10.5% ***referral specialist evaluation***

Only the magnitude and proportion of ALT elevation were predictive of receiving NAFLD care

Blais, Am J Gastroenterol 2014

First records of CLDs in Scotland by diabetes status

Retrospective population-based cohort
Scottish Diabetes Register & National hospital cancer and death records
2004-2013; 40-89 years; 26 M Pt/years of F/u
97% mono diagnosis of CLD

	Type 2 diabetes		No diabetes		
Type of liver disease	Deaths	Hospital admissions	Deaths	Hospital admissions	
Alcoholic liver disease	213	1773 #2	2532	13345	#1
Autoimmune liver disease	19	218	129	1925	
Hemochromatosis	11	410	42	1966	
Hepatocellular carcinoma	52	844	116	1932	
Non-alcoholic fatty liver disease	327 #1	2942	1435	8283	#2
Viral liver disease	26	220	242	2515	

Wild, J Hepatol 2016

Sex-specific rate ratios in diabetes for CLDs

Type of liver disease	Men	Women
	Age and SES quintile adjusted	Age and SES quintile adjusted
Alcoholic liver disease*	1.38 (1.15-1.65)	1.57 (1.28-1.93)
Autoimmune liver disease	1.50 (1.12-2.01)	1.25 (1.04-1.49)
Hemochromatosis	1.67 (1.43-1.94)	1.60 (1.23-1.97)
Hepatocellular carcinoma	3.36 (2.97-3.81)	3.55 (3.02-4.17)
Non-alcoholic fatty liver disease*	3.03 (2.68-3.43)	5.11 (4.45-5.87)
Viral liver disease	1.28 (0.86-1.92)	2.20 (1.52-3.18)

Wild, J Hepatol 2016

A position statement on NAFLD/NASH based on the EASL 2009 special conference☆

J Hepatol 2009

Vlad Ratziu[a], Stefano Bellentani[b,*], Helena Cortez-Pinto[c], Chris Day[d], Giulio Marchesini[e]

1. No screening general population
2. Case finding of advanced NASH in pts with IR or the metabolic syndrome
3. If other CLD: screen for metabolic risk factors, insulin resistance, steatosis
4. Liver biopsy perioperatively when bariatric surgery or cholecystectomy

J Hepatol 2016

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

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

- In persons with NAFLD, screening for diabetes is mandatory, by fasting or random blood glucose or HbA1c (**A1**) and if available by the standardized 75 g OGTT in high-risk groups (**B1**)
- In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since T2DM patients are at high risk of disease progression (**A2**)

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 C. [illegible] Stephen A. Harrison,[7] Elizabeth M. Brunt,[8] and Arun J. Sanyal[9]

Guidance Statements:

4. Routine Screening for NAFLD in [illegible] groups attending primary care, di[illegible] ics is not advised at th[illegible] surroundin[illegible] along wit[illegible] fits and cos[illegible]

5. There[illegible] NAFLD an[illegible] Clinical decis[illegible] (FIB-4) or vibration controlled transient elastography (VCTE) can be used to identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis).

Not routine screening, but vigilance for chronic liver disease in patients with type 2 diabetes

Vincent Wai-Sun Wong[1,*], Naga Chalasani[2,*]

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong Shatin, N.T., Hong Kong; [2]Indiana University School of Medicine, Indianapolis, IN, USA

Hepatology 2017 in press

MRF present[1]

Ultrasound
(steatosis biomarkers[2])/
LIVER FUNCTION TESTS[3]

STEATOSIS PRESENT

STEATOSIS ABSENT

LFTs
Normal

Serum fibrosis markers[5]

Low risk[6]

Medium/high risk[6]

Follow-up/2 years

LFTs, fibrosis
biomarkers

LFTs
Abnormal[4]

Specialist referral

Identify other CLDs
In-depth assessement of disease severity
Decision to perform liver biopsy
Initiate monitoring/therapy

LFTs
Normal

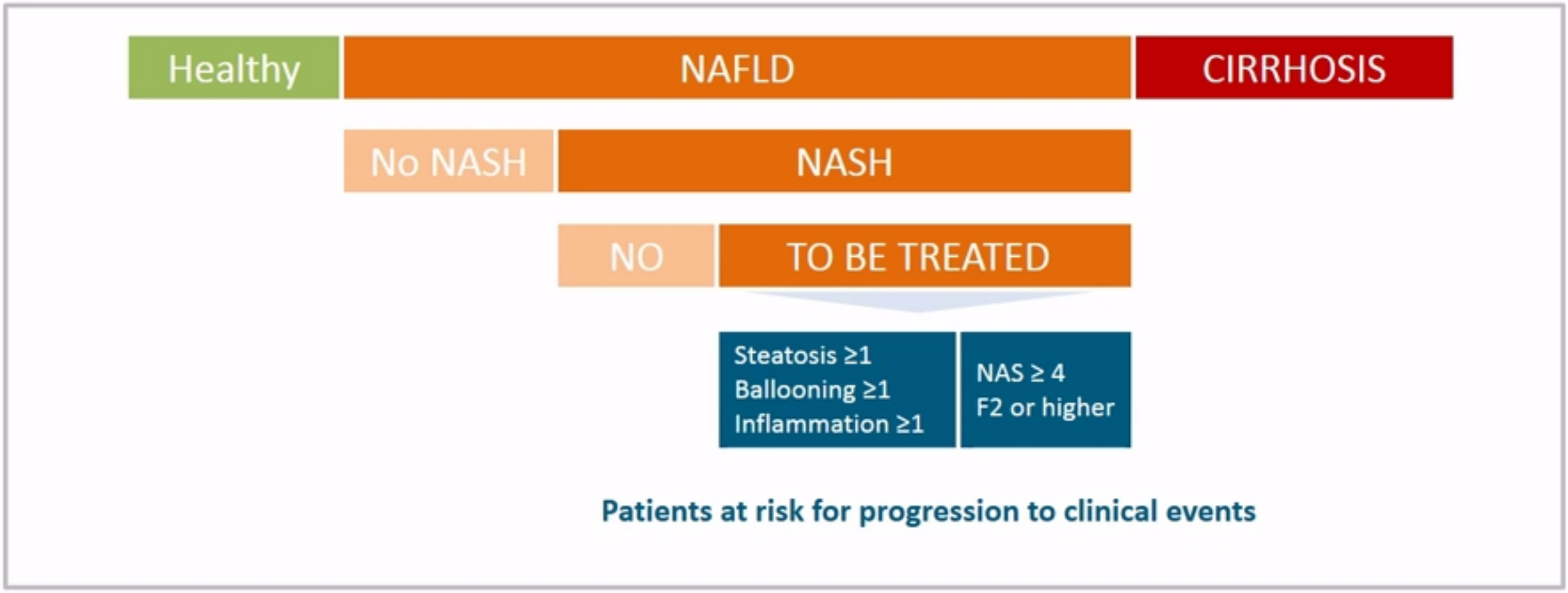
Follow-up/3-5 years

Ultrasound/
LFTs

NASH CPG EASL 2016

Two conceptual approcahes to screening

- **Favor the exclusion of patients at very low risk of advanced disease**
- **Favor the identification of some of the patients in need for therapy**

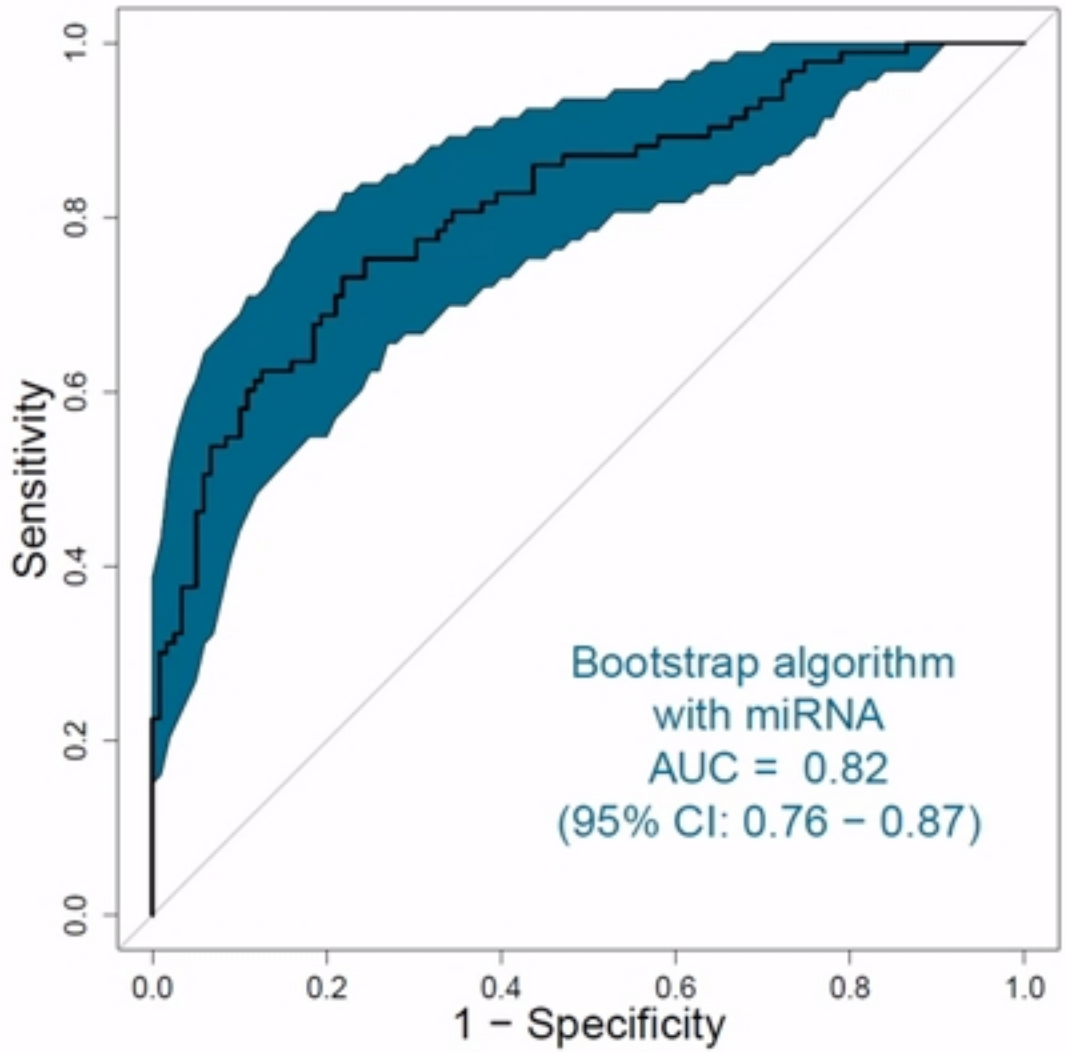


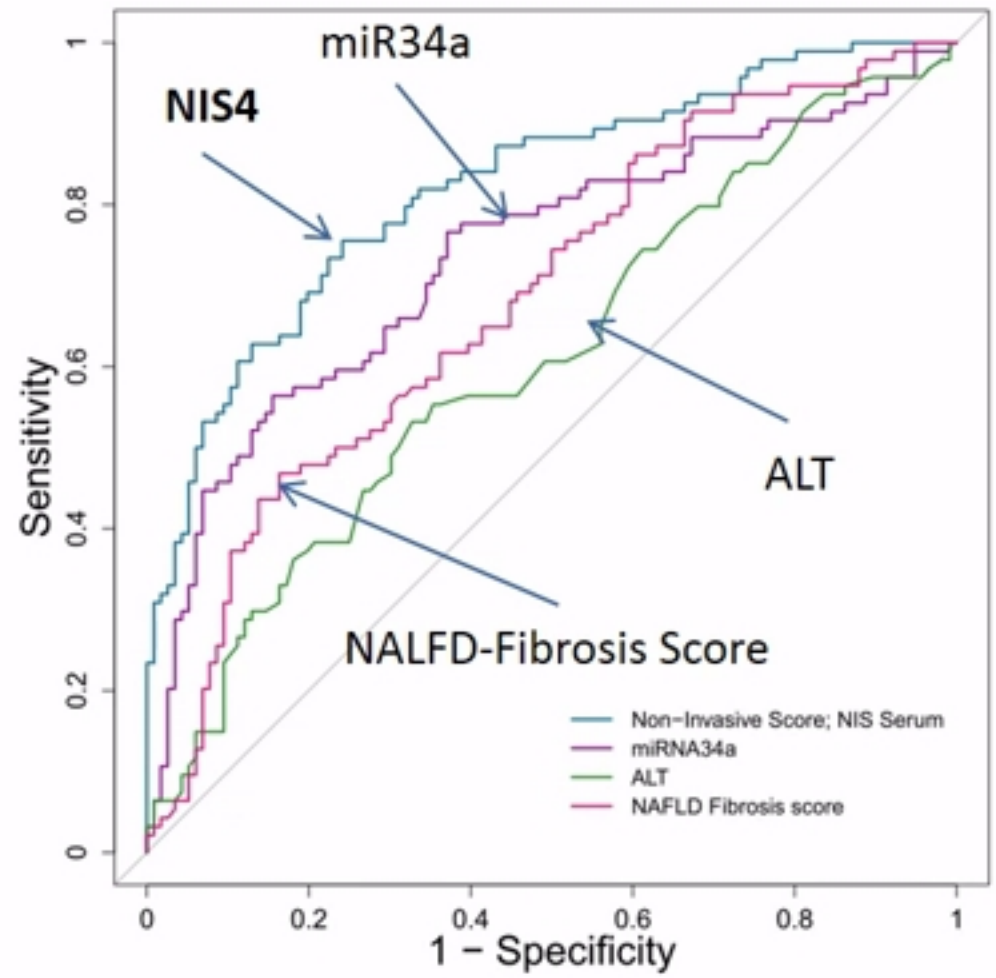
Courtesy R Hanf, Genfit

Biomarker signature for patients “to be treated”

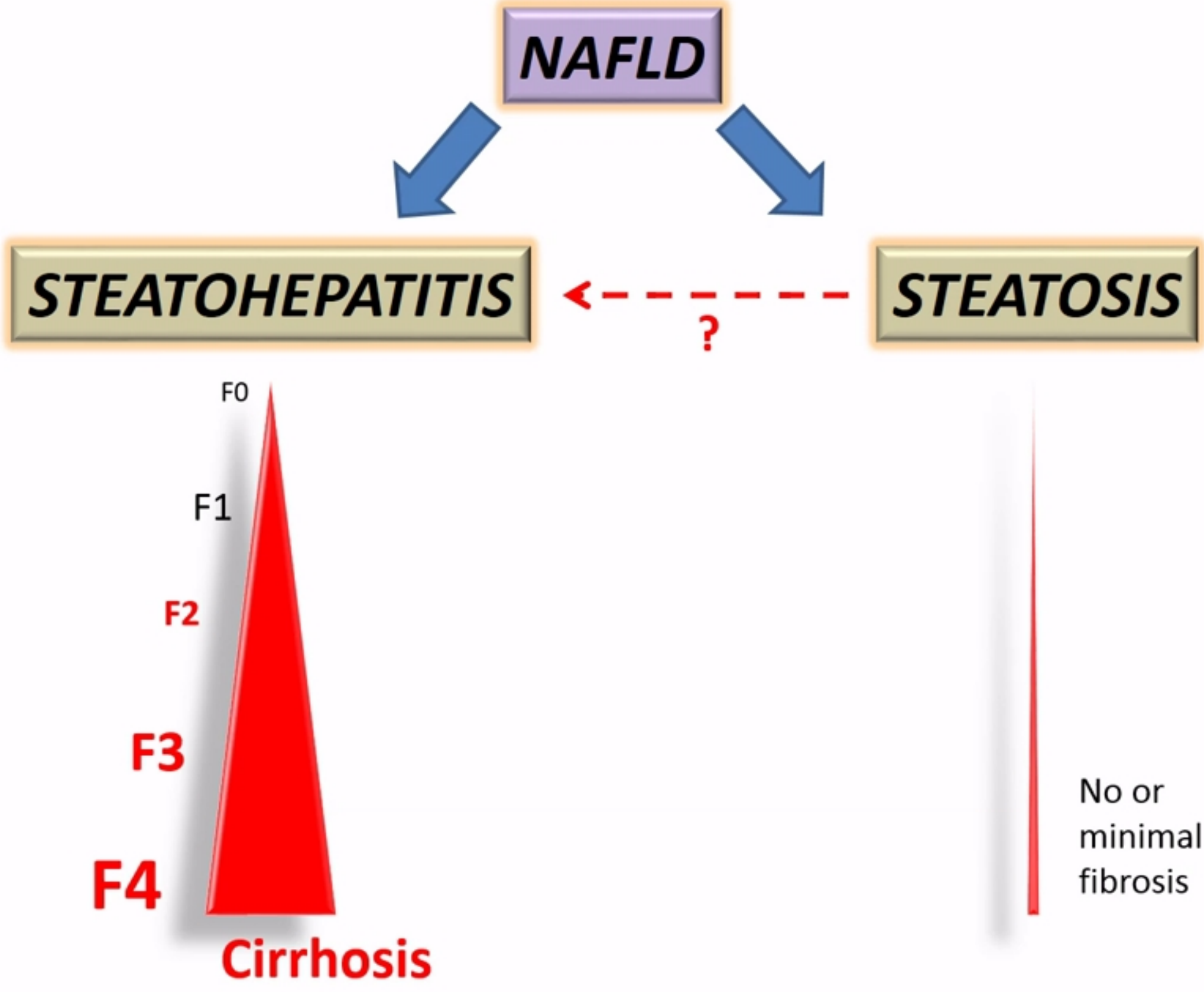
To-be-Treated (NAS≥4, F≥2) vs. Not-To-Be –Treated (NAS<4, F<2)

NIS4 includes: miR34a, Alpha2-macroglobulin, CH3L1 (YKL40) and HbA1C

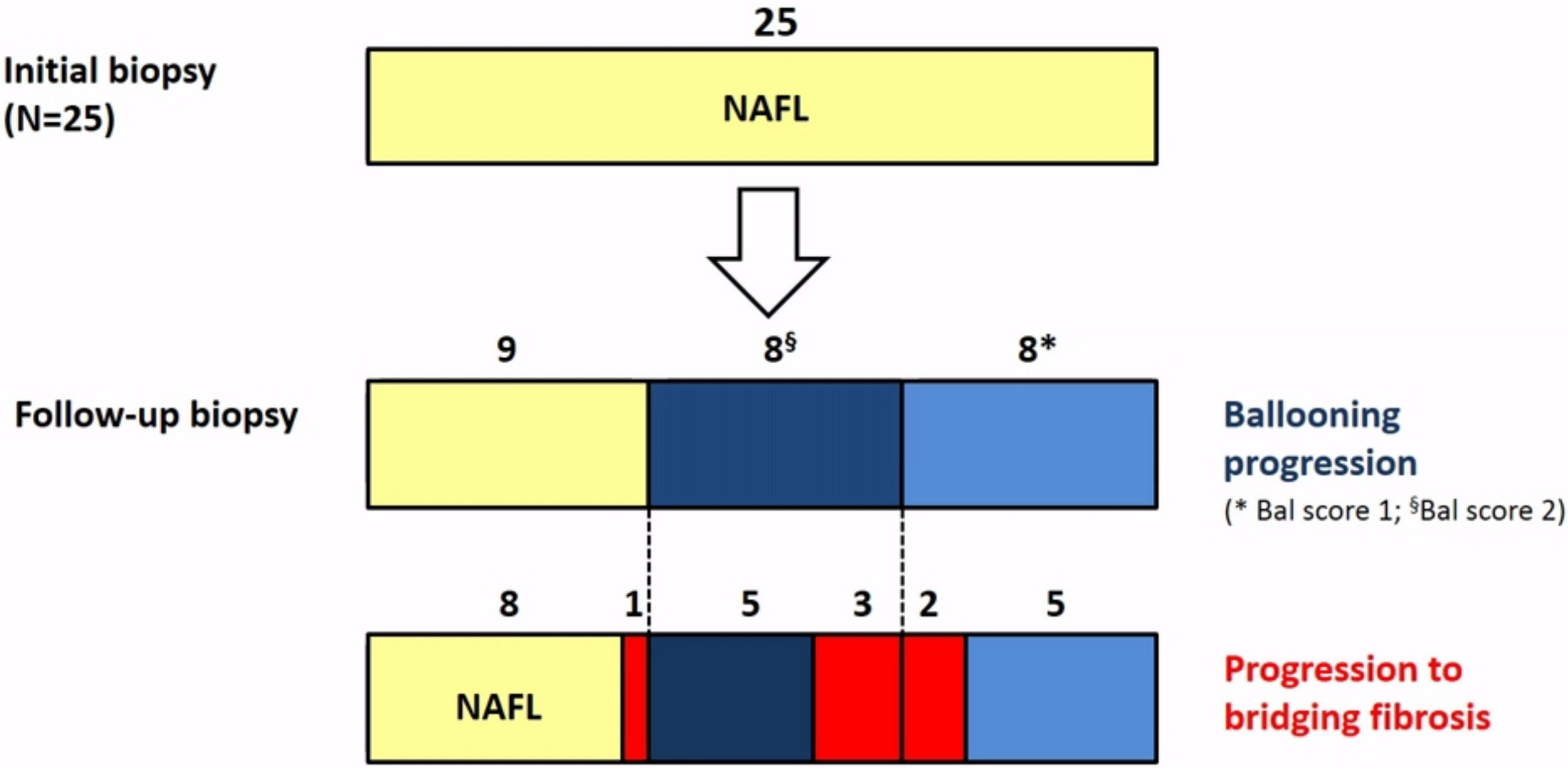




Courtesy R Hanf, Genfit


NAFLD
STEATOHEPATITIS
?
STEATOSIS
F0
F1
F2
F3
F4
Cirrhosis
No or
minimal
fibrosis

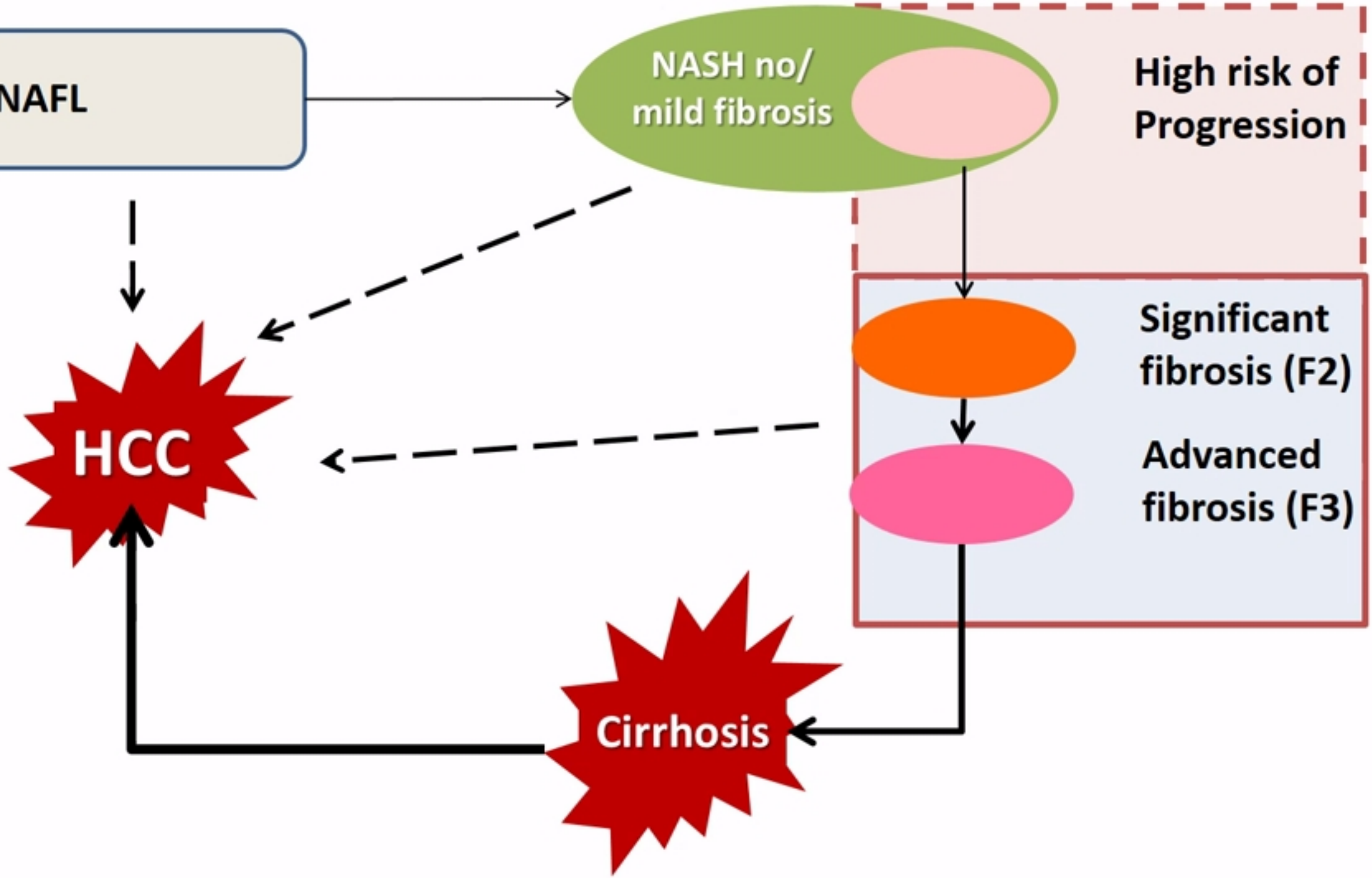
Impact of ballooning on fibrosis progression



Similar results in McPherson, J Hepatol 2015

Pais, J Hepatol 2013

Current view of the natural history of NAFLD



Progression to bridging fibrosis in NAFLD

270 NAFLD pts without bridging fibrosis

Repeat liver biopsy 4.4 yrs (1-17.3) apart

16 % progressed to bridging fibrosis

Crude HRs for fibrosis progression

Diabetes	***HR 3.61***
Metab Syd	***HR 6.16***
ALT (log)	***HR 3.12***
HOMA	***HR 2.27***

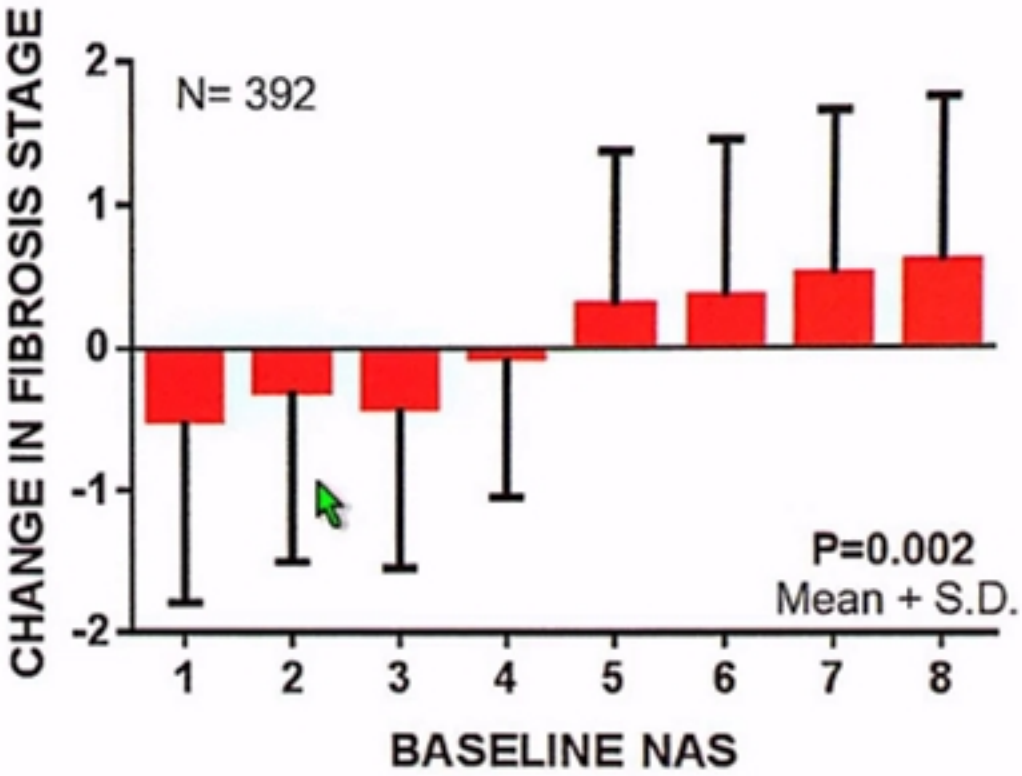
Brunt, NASH CRN AASLD 2013

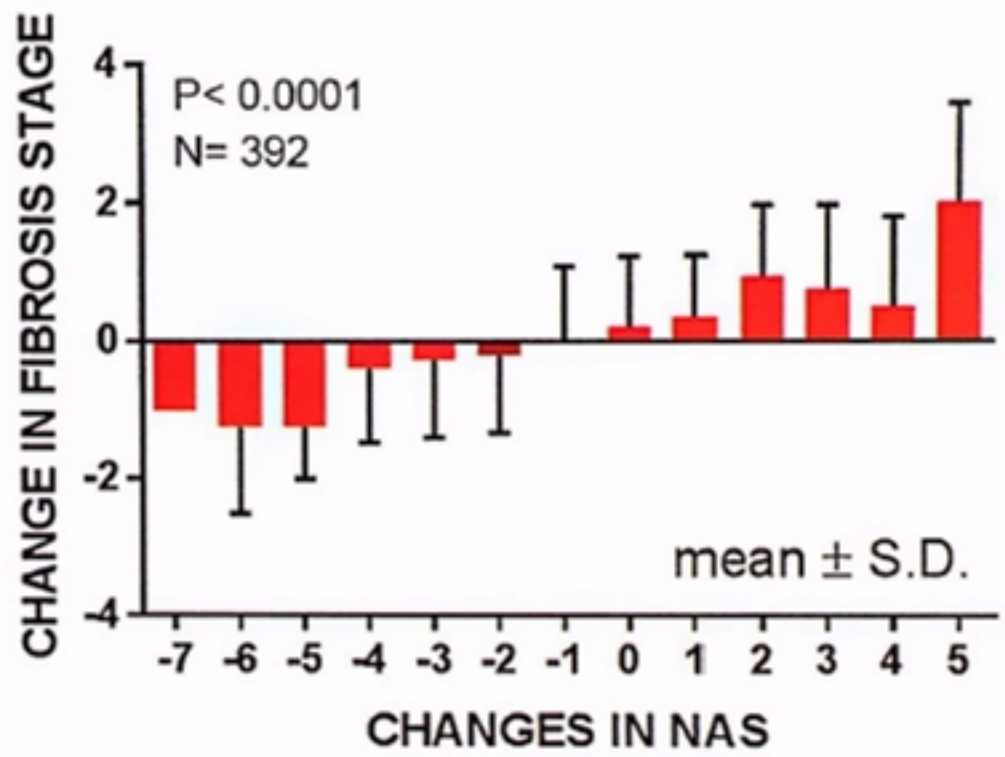
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

DIAGNOSTIC PATTERN AND DISEASE ACTIVITY ARE RELATED TO DISEASE PROGRESSION AND REGRESSION IN NONALCOHOLIC FATTY LIVER DISEASE

David Kleiner M.D., Elizabeth M. Brunt M.D., Patricia H. Belt, Laura A. Wilson, Cynthia D. Guy M.D., Matthew M. Yeh M.D., Ryan Gill M.D., Kris V. Kowdley M.D., Brent A. Neuschwander-Tetri M.D., and **Arun J. Sanyal** M.D. for the NIDDK NASH CRN.

NIDDK | NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES



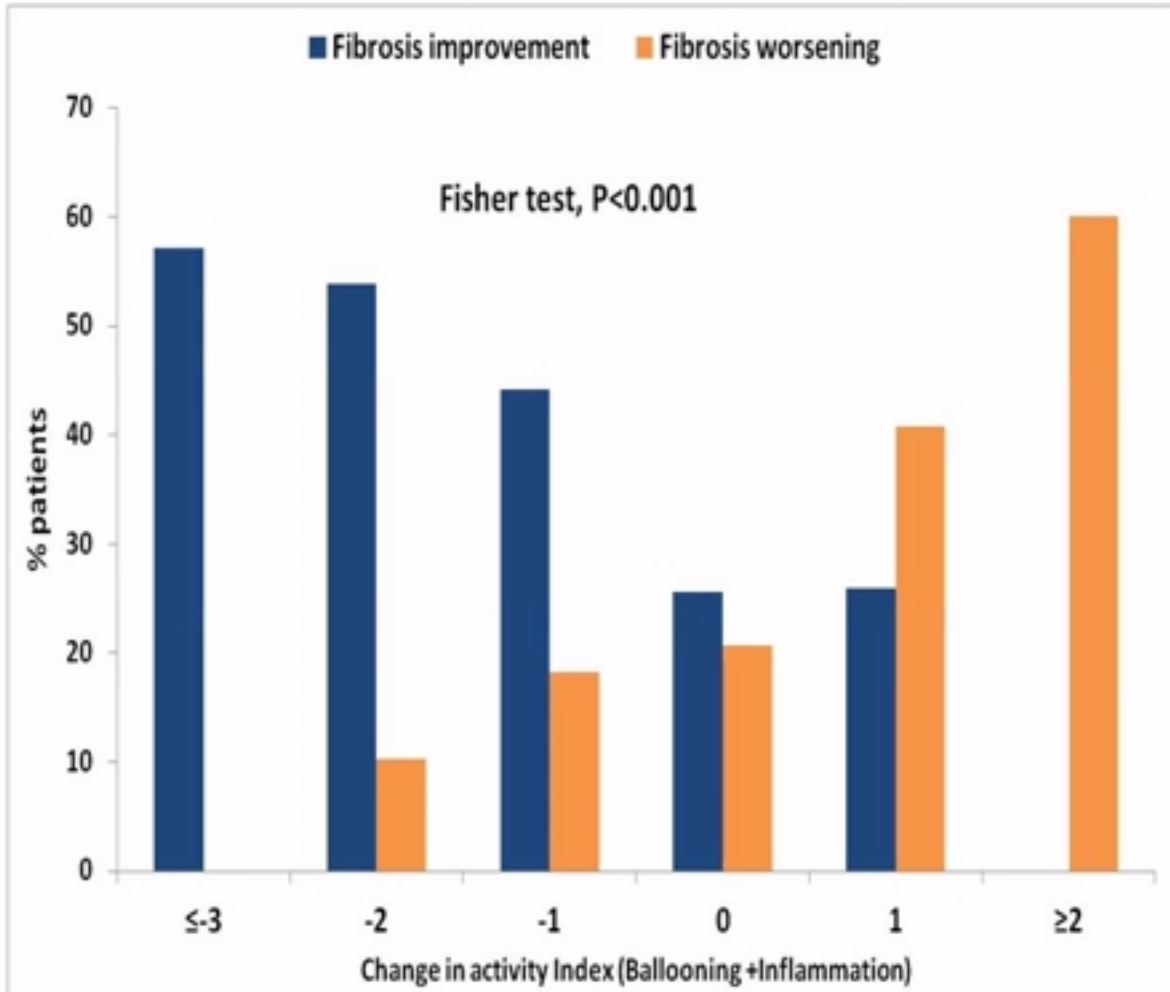


Changes in NASH activity index and fibrosis evolution

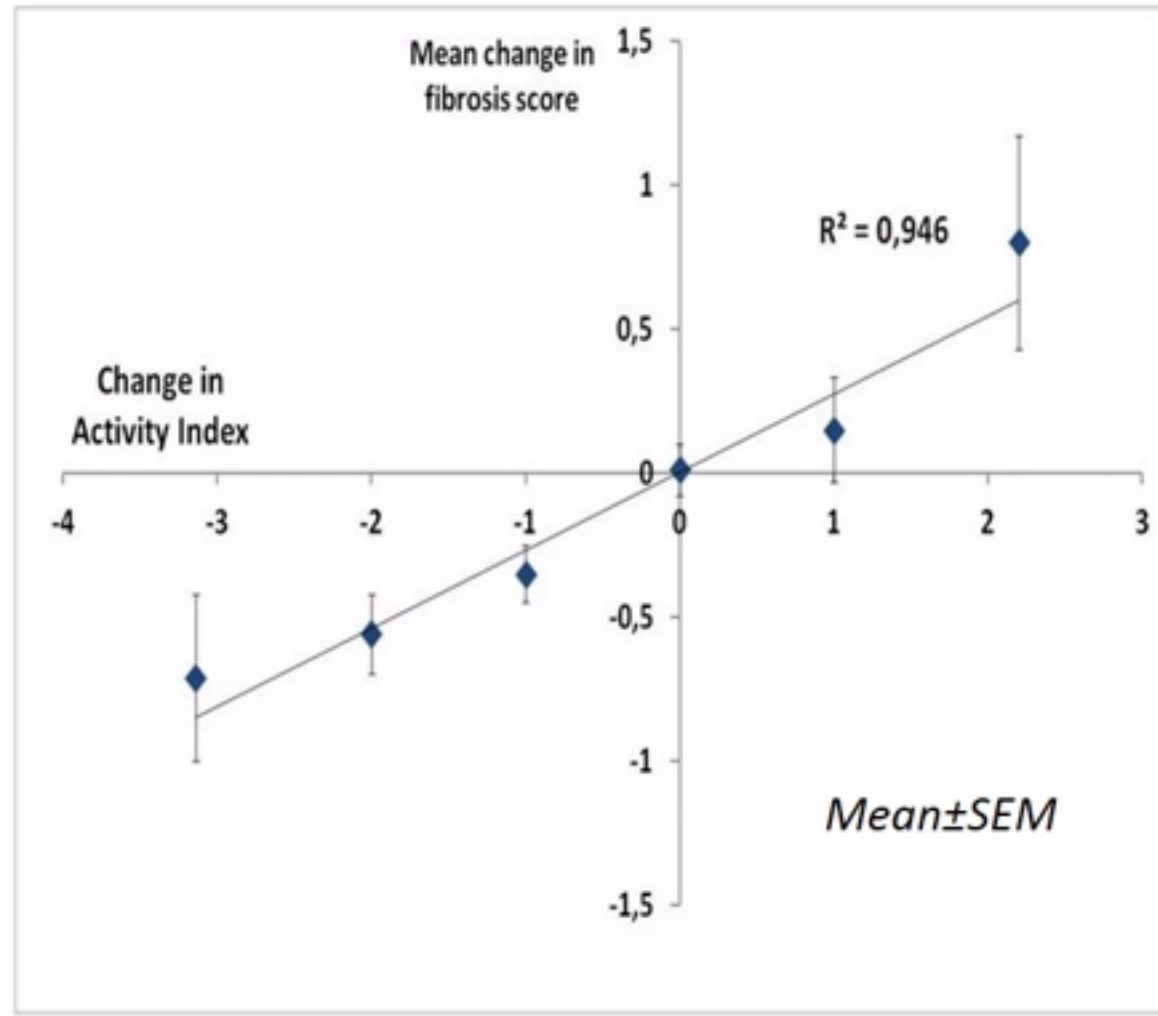
Activity Index : sum of scores for ballooning and inflammation

N=234

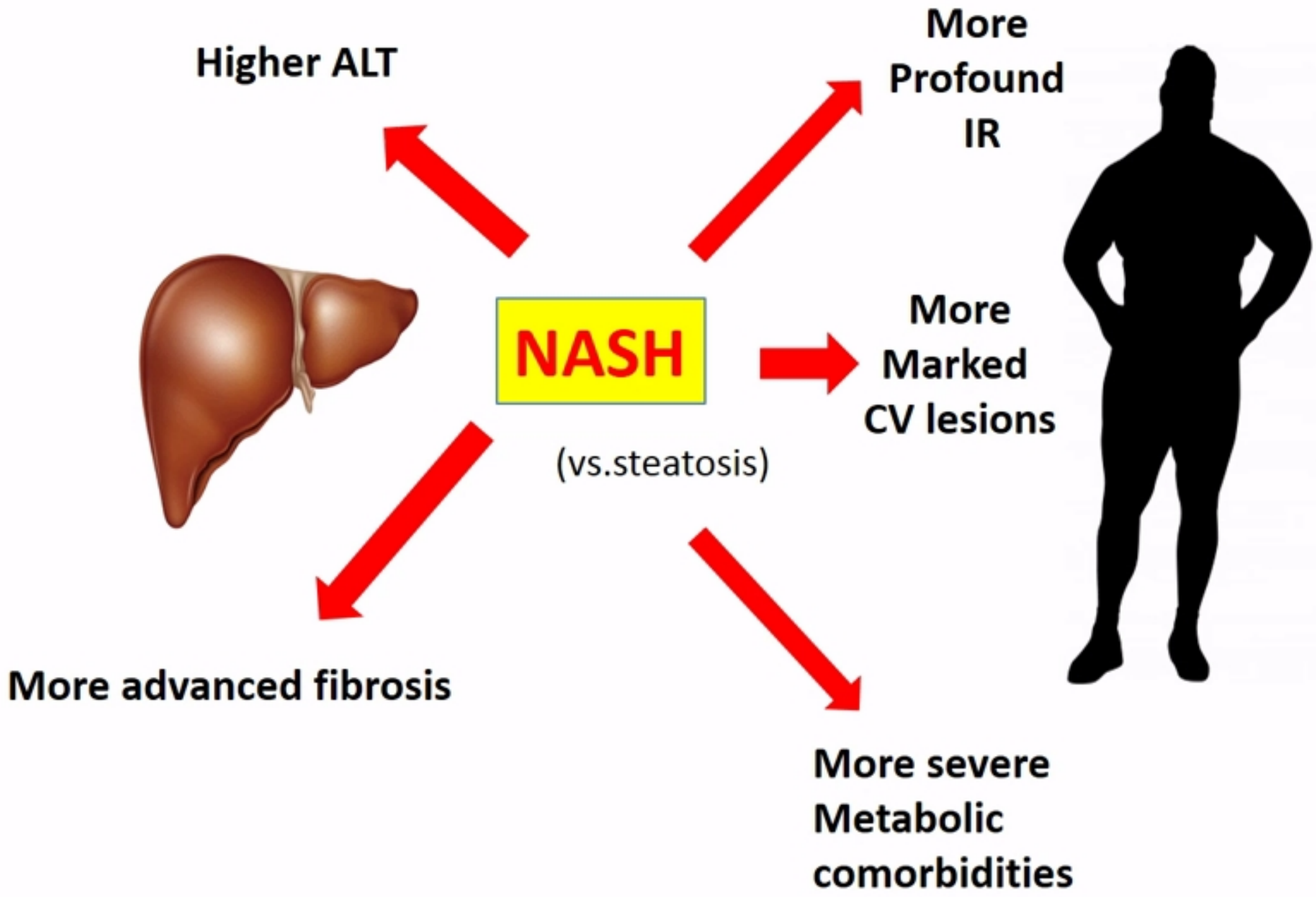
% of Pts with fibrosis change



Mean change in scores

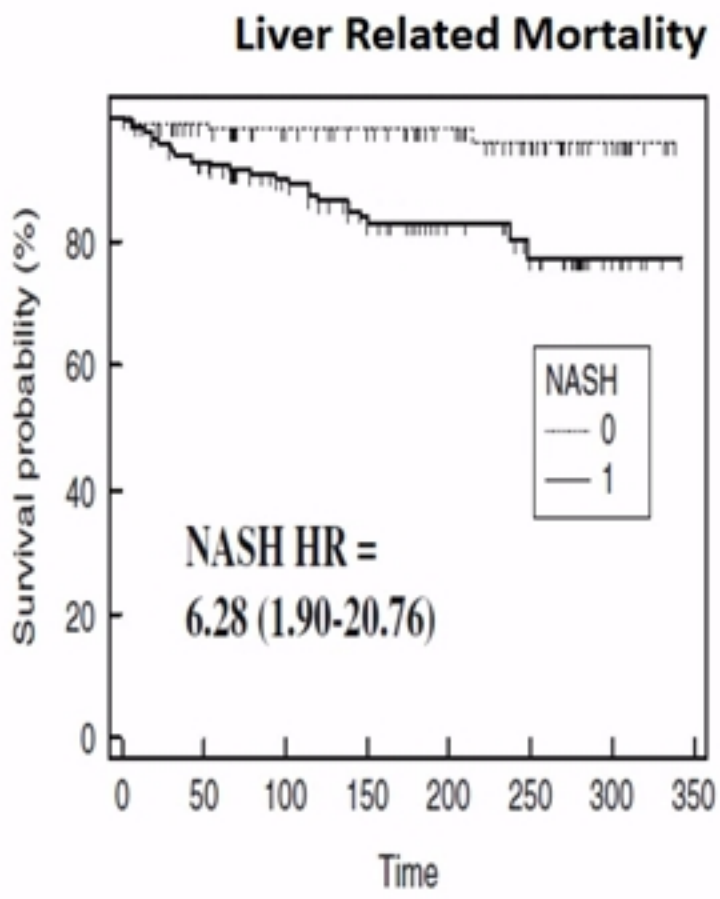


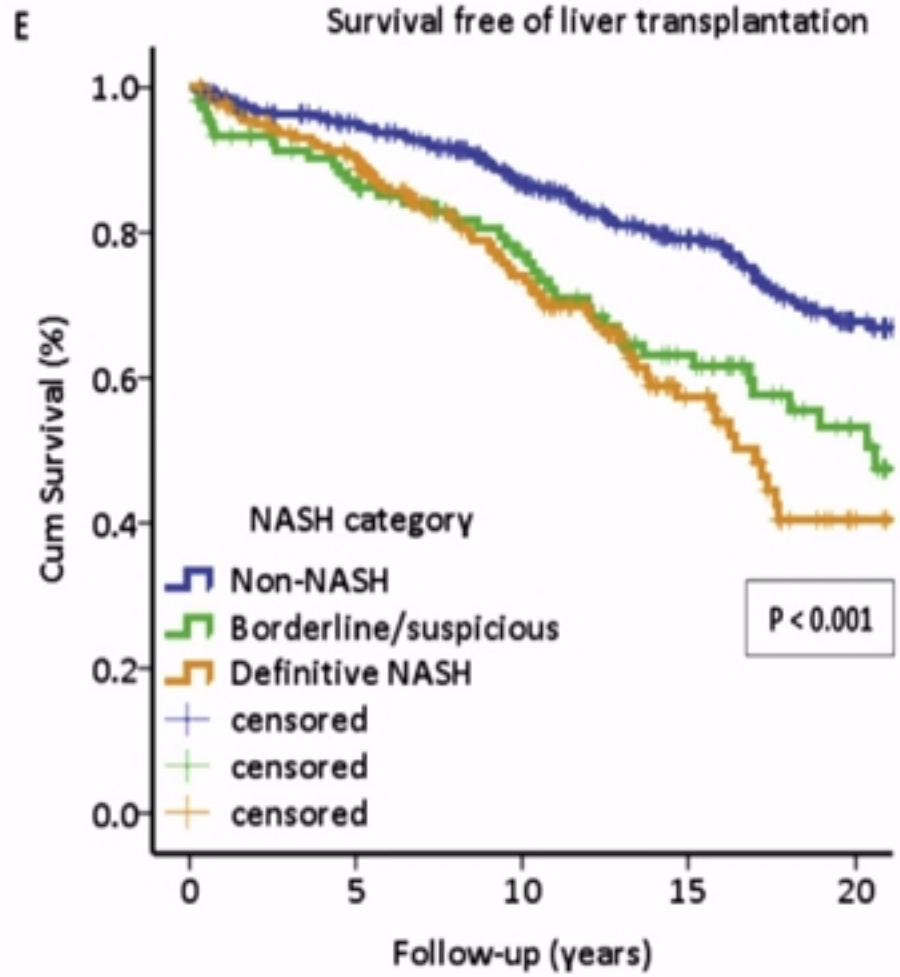
NASH is associated with more severe hepatic and systemic disease



NASH increases liver-related mortality

Cumulative LRM according to **PRESENCE OF NASH** on index liver biopsy





Non-NASH	335	287	227	156	79
Bord/susp	105	84	65	42	19
Def. NASH	179	148	90	36	11

- NASH patients have higher risk of mortality than non NASH

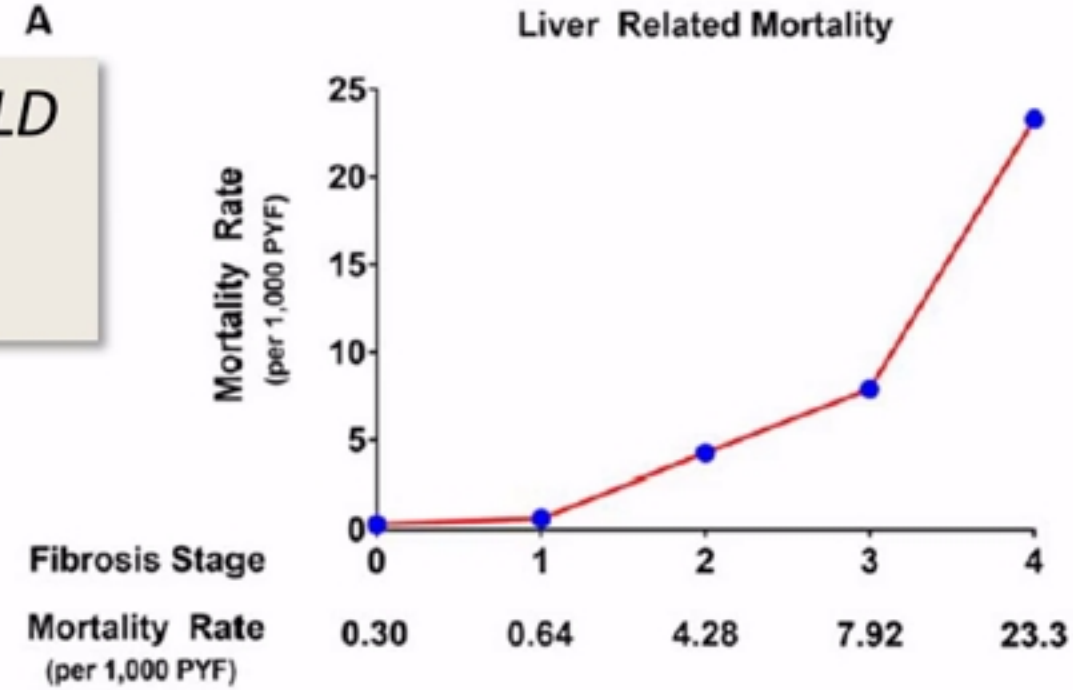
Matteoni CA, Younossi ZM, Gramlich T, Gastroenterology. 1999
Ekstedt M, Hagström H, Nasr P, et al. Hepatology 2014

Younossi ZM, Stepanova M, Rafiq N, et al.. Hepatology 2011
Stepanova M, Rafiq N, Makhlouf H et al. Dig Dis Sci 2013

Fibrosis stage-specific liver-related mortality

5 studies with histologically documented NAFLD
1495 pts ; 17,452 yrs. of f/up
Stages 0/1/2/3/4: 38%/29/14/12/7.4%

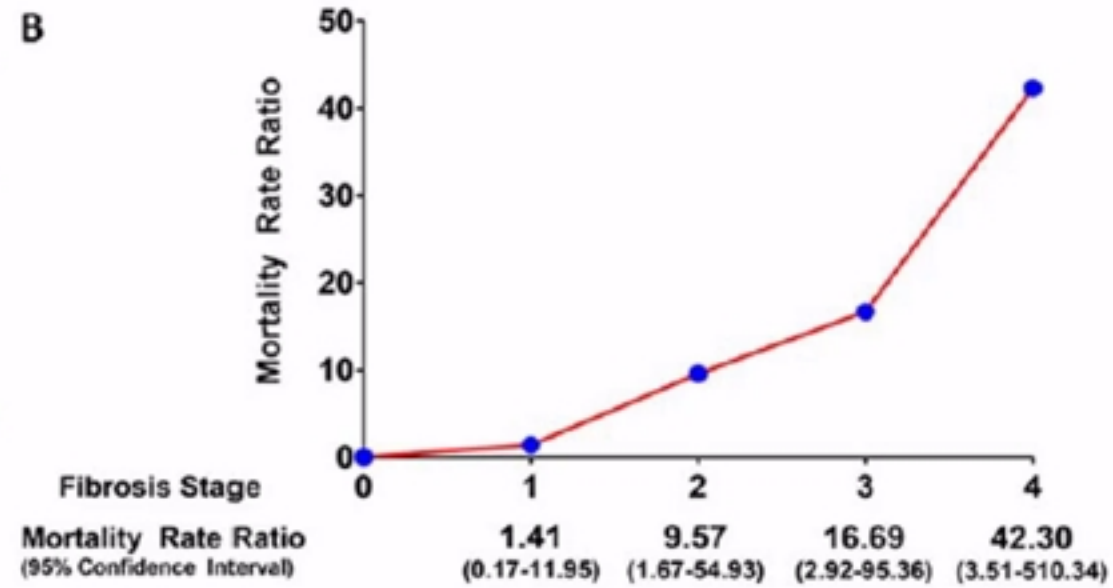
A



Liver-Related Mortality

	Mortality rate (per 1,000 PYF)	MRR (95% CI)
Stage 0	0.30	Reference
Stage 1	0.64	1.41 (0.17-11.95)
Stage 2	4.28	**9.57 (1.67-54.93)**
Stage 3	7.92	**16.69 (2.92-95.36)**
Stage 4	23.3	**42.30 (3.51-510.34)**

B



Dulai, Hepatology 2017

How does steatohepatitis drive disease progression in NAFLD ?

- NASH is associated with more profound IR, more severe metabolic disease, higher ALT and hepatic fibrosis
- NAS[illegible]ver
- Ste[illegible]
- NAS[illegible]
- Pro[illegible]s through NASH
- The concept of disease activity in NAFLD
  - Non-drug induced changes in NAS score correlate with fibrosis progression
  - Drug-induced resolution of steatohepatitis and improvement in necro-inflammation correlates with fibrosis regression

Editorial

EASL | JOURNAL OF HEPATOLOGY

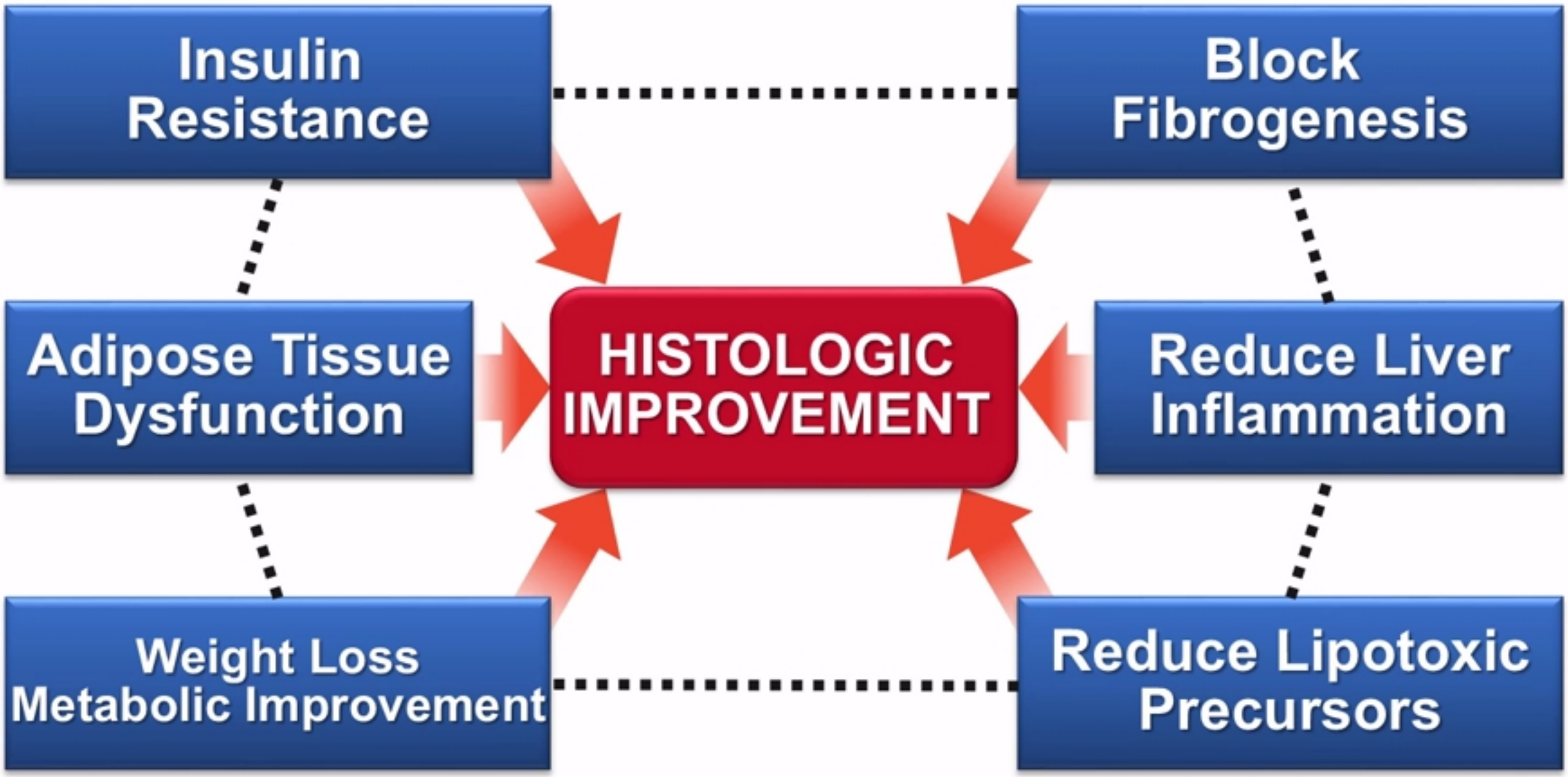
Back to Byzance: *Querelles byzantines* over NASH and fibrosis

Vlad Ratziu*

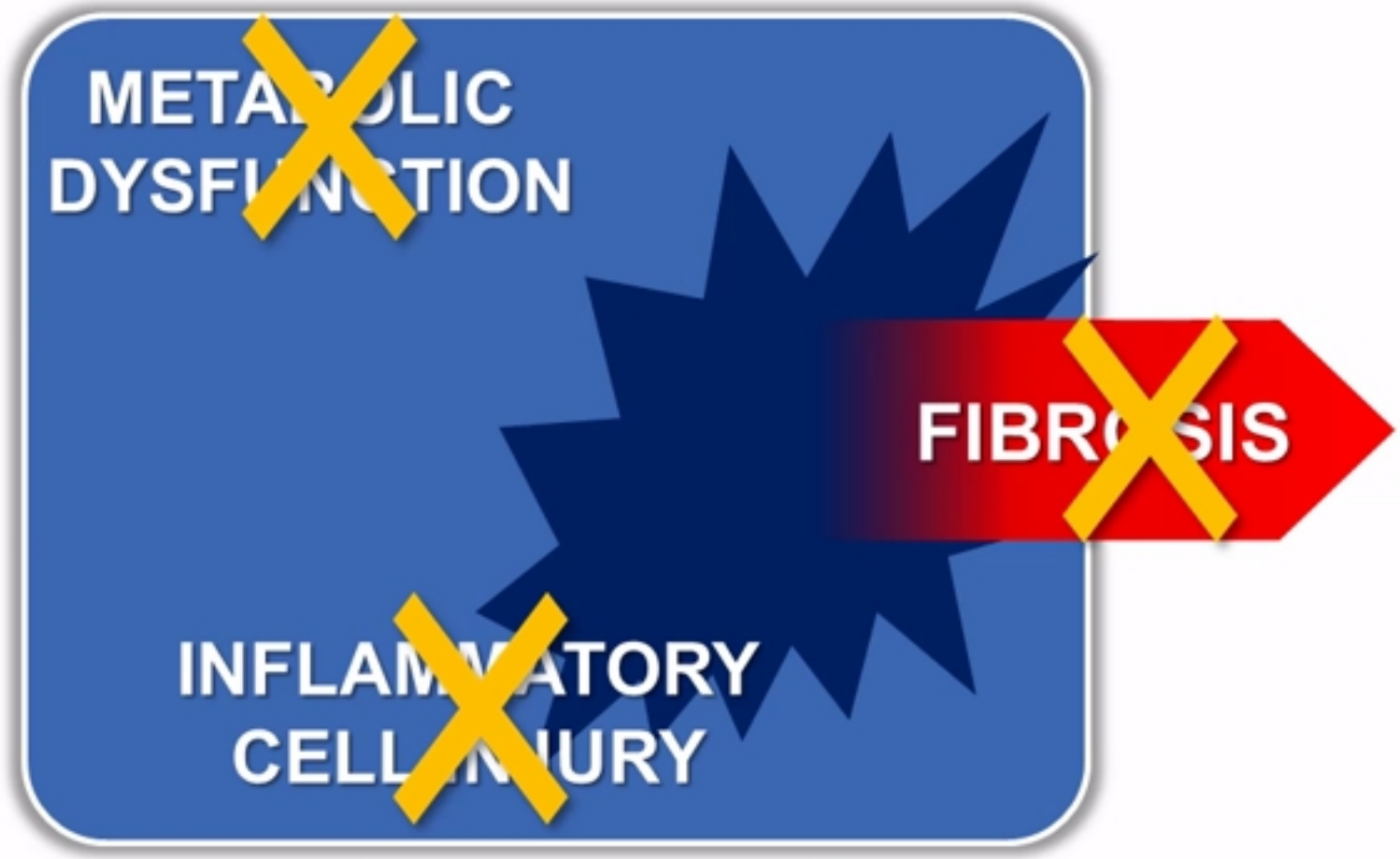
Hospital Pitié-Salpêtrière, Institute of Cardiometabolism and Nutrition, Sorbonne Universités, Paris, France

See Article, pages xxx-xxx

Controlling Disease Progression

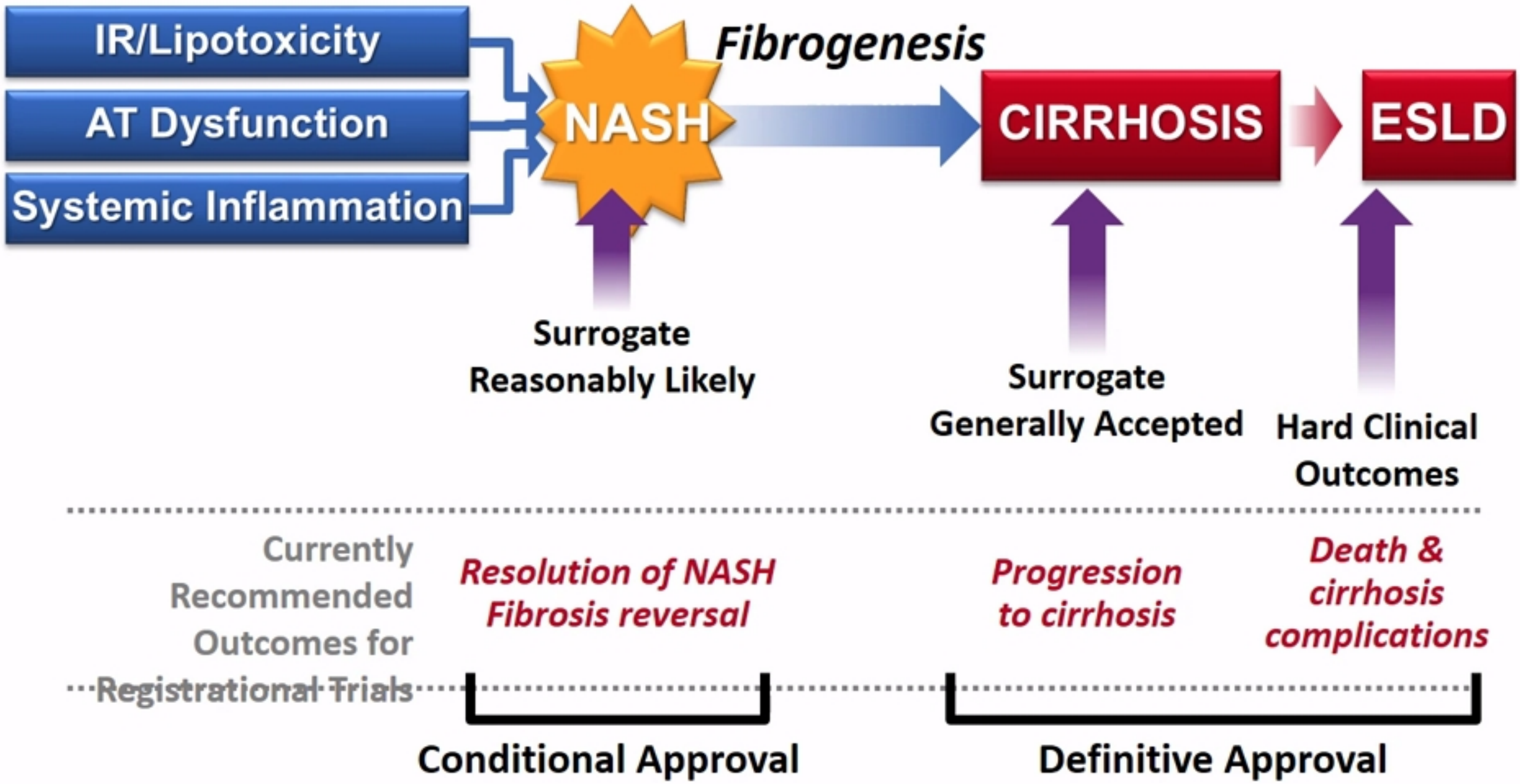


Disease Progression and Targets for Therapy

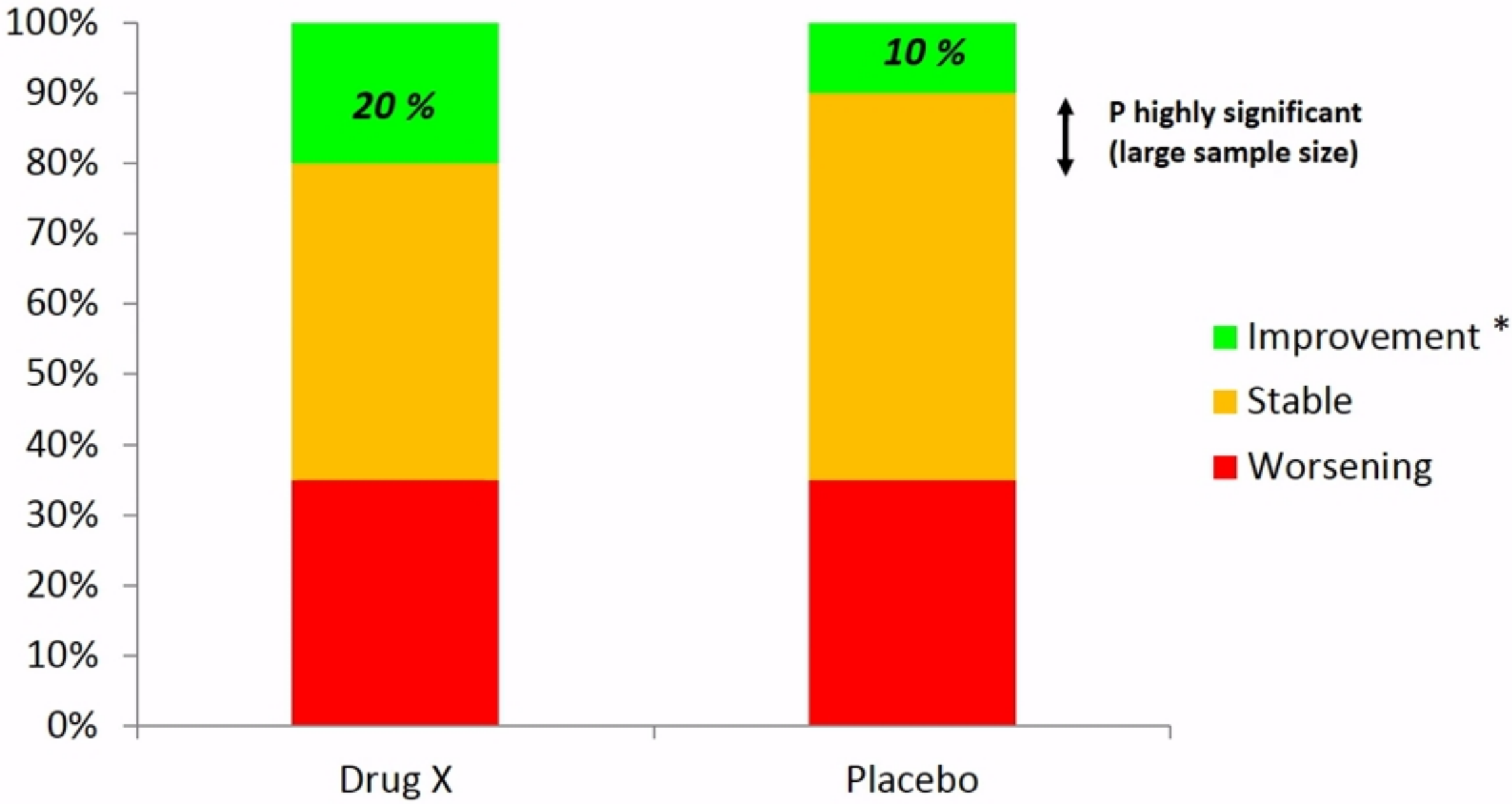


IR, insulin resistance; AT, adipose tissue; ESLD, end stage liver disease.

Regulatory Pathway for Late Stage RCTs in NASH

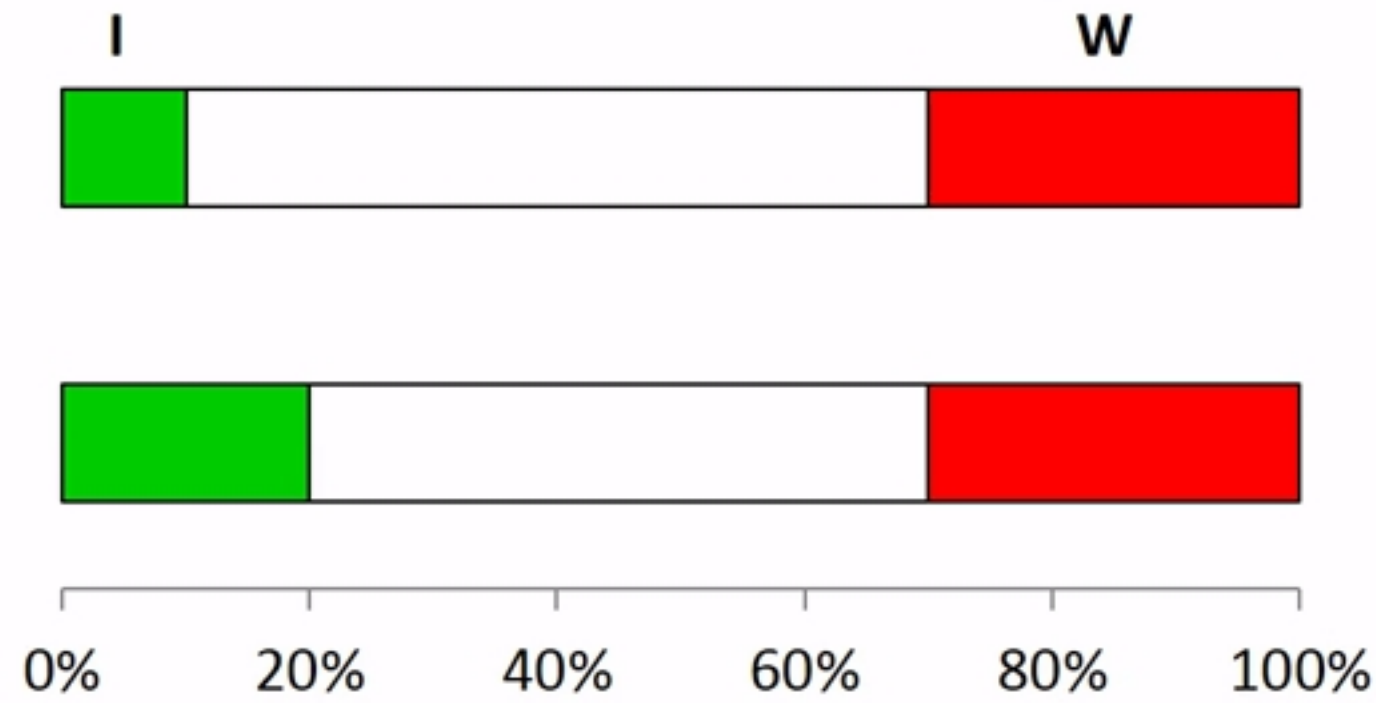


Hypothetical drug : effect on fibrosis



* ≥1 stage

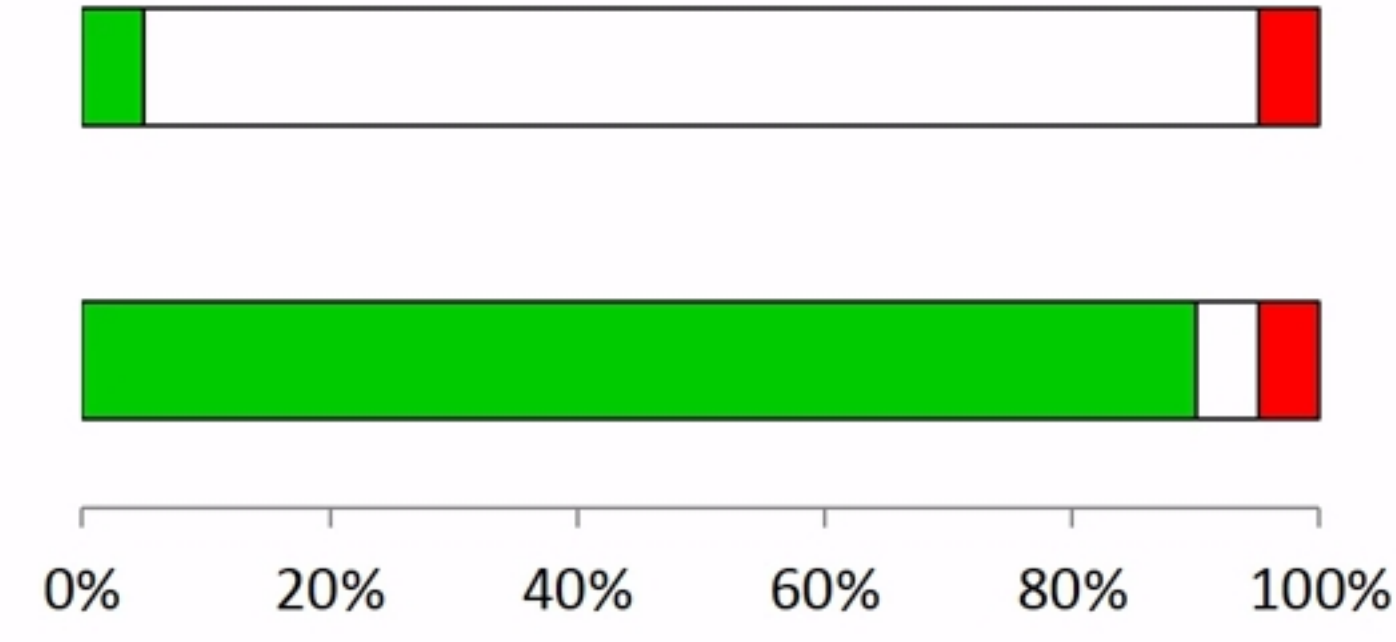
Scenario 1.



Improvement index : $\frac{\text{I-W}}{\text{I}}$

Should be closest to 1…

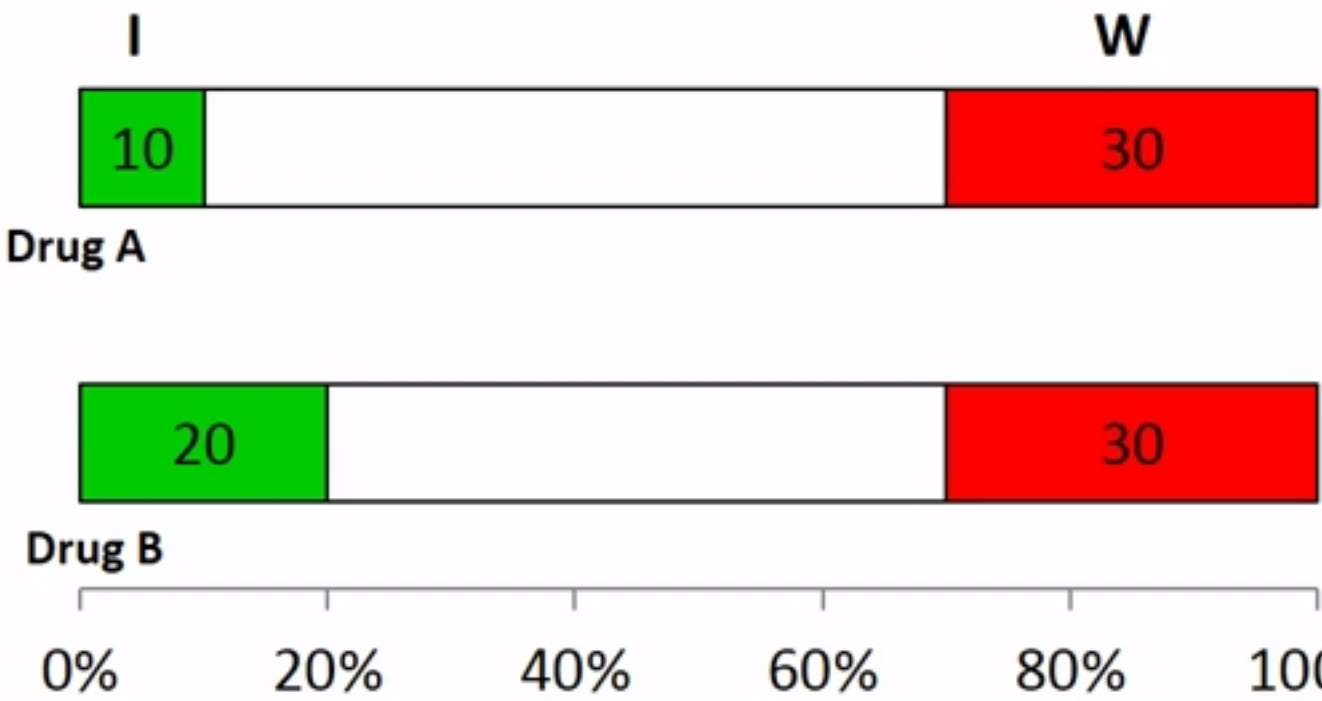
Scenario 2.



Progression index : $\frac{\text{W-I}}{\text{W}}$

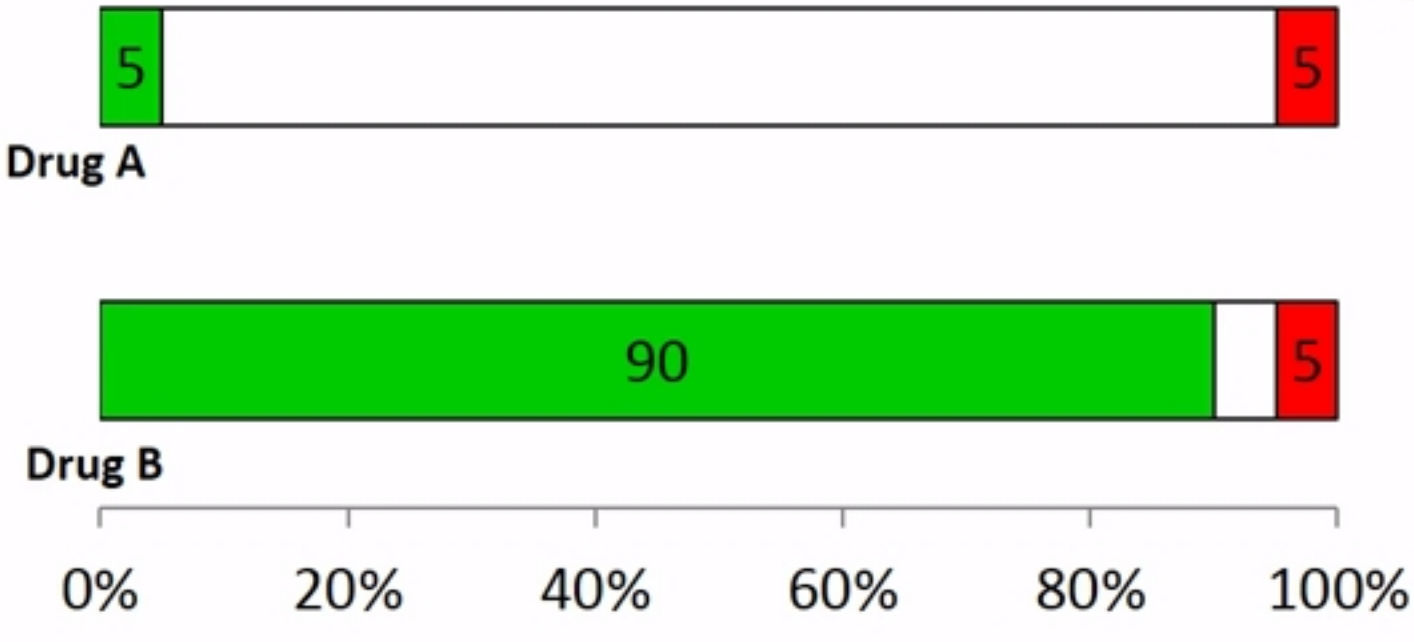
Should be as low as possible (negative)

Scenario 1.



STandardized Improvement of Fibrosis (STIF) Index

Scenario 2.



Improvement index :

$$\frac{5-5}{5} = 0$$

$$\frac{90-5}{90} = 0.94$$

Progression index :

$$\frac{5-5}{5} = 0$$

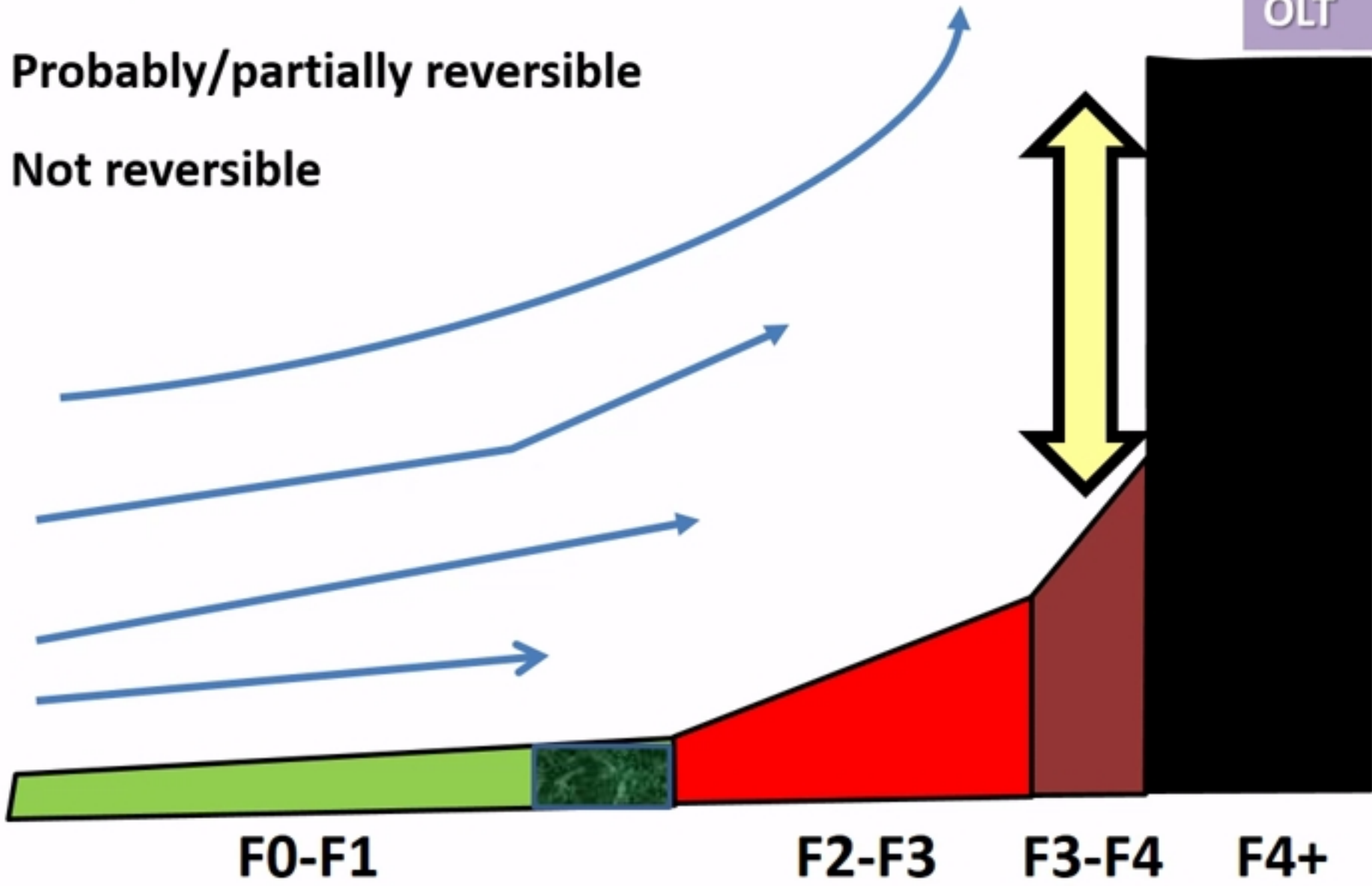
$$\frac{5-90}{5} = -17$$

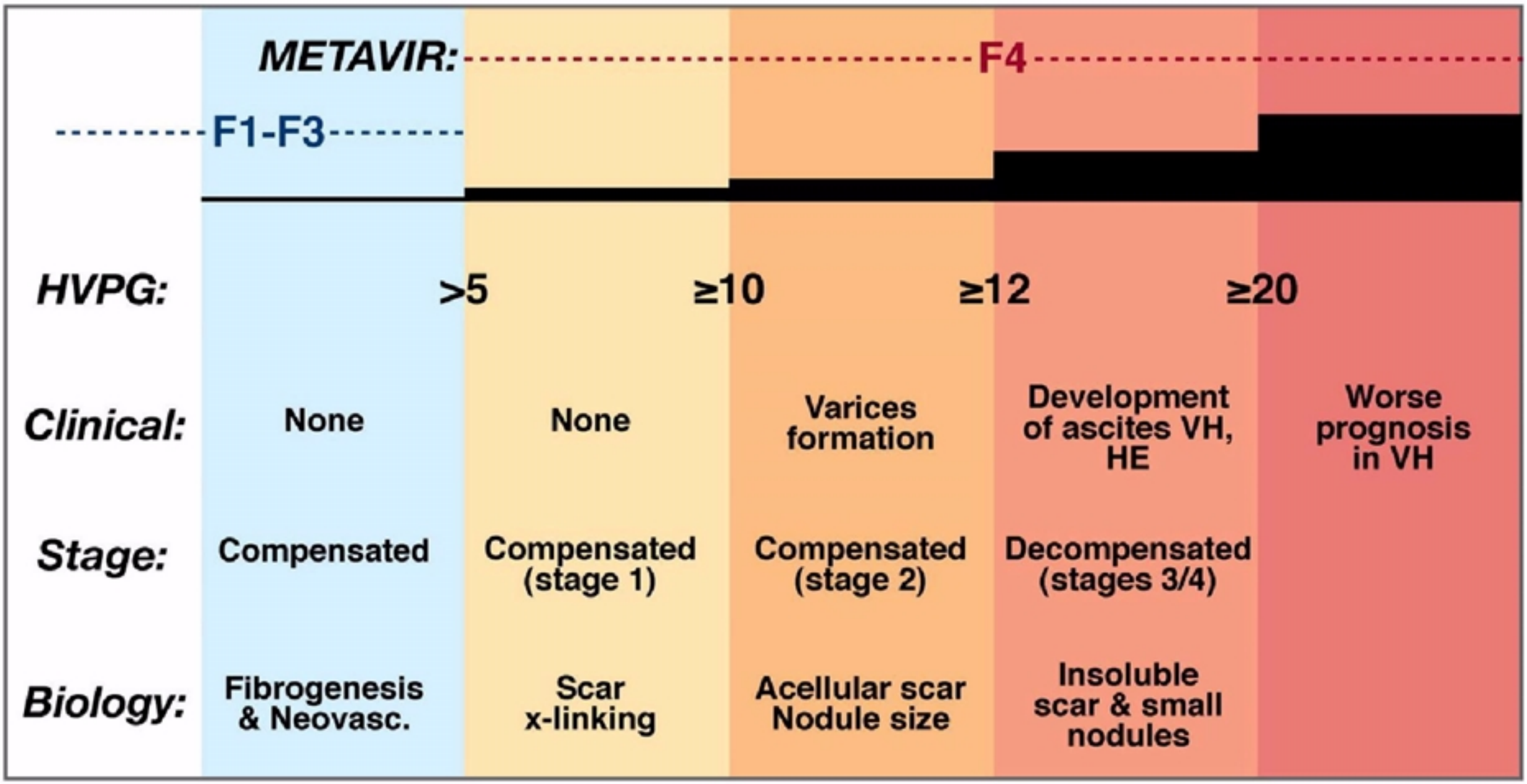
Reversible

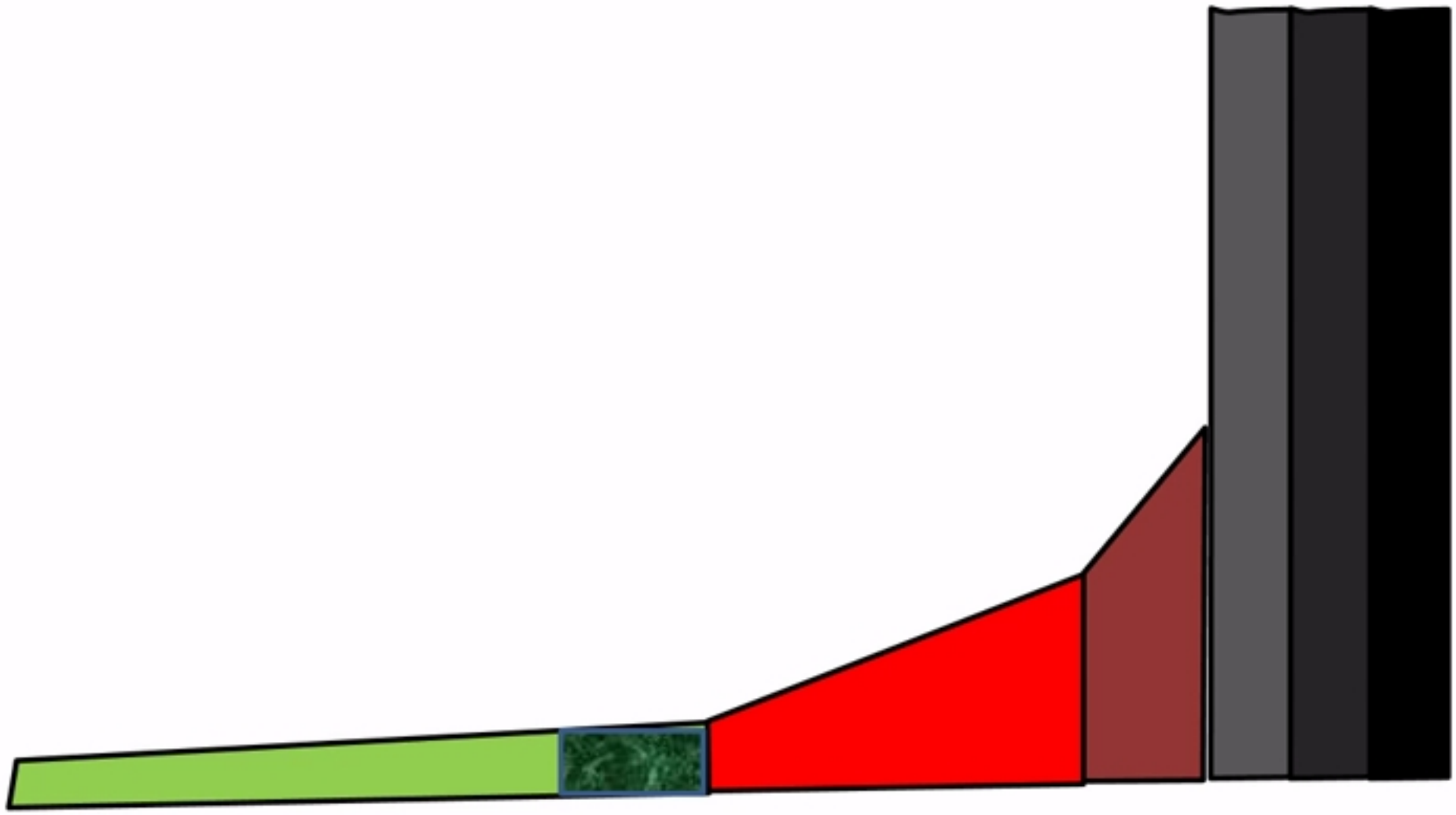
Reversible

Probably/partially reversible

Not reversible




METAVIR:
F4
F1-F3
HVPG:
>5
≥10
≥12
≥20
Clinical:
None
None
Varices formation
Development of ascites VH, HE
Worse prognosis in VH
Stage:
Compensated
Compensated (stage 1)
Compensated (stage 2)
Decompensated (stages 3/4)
Biology:
Fibrogenesis & Neovasc.
Scar x-linking
Acellular scar Nodule size
Insoluble scar & small nodules



Prevention of progression

Reversal

Prevention of complications

Bridge to OLT

NASH

Lipo toxicity

Inflam mation

Cell death

FIBROSIS

Challenges for treating cirrhotic patients with NASH drugs

Insulin resistance multifactorial

Steatohepatitis absent

CIRRHOSIS

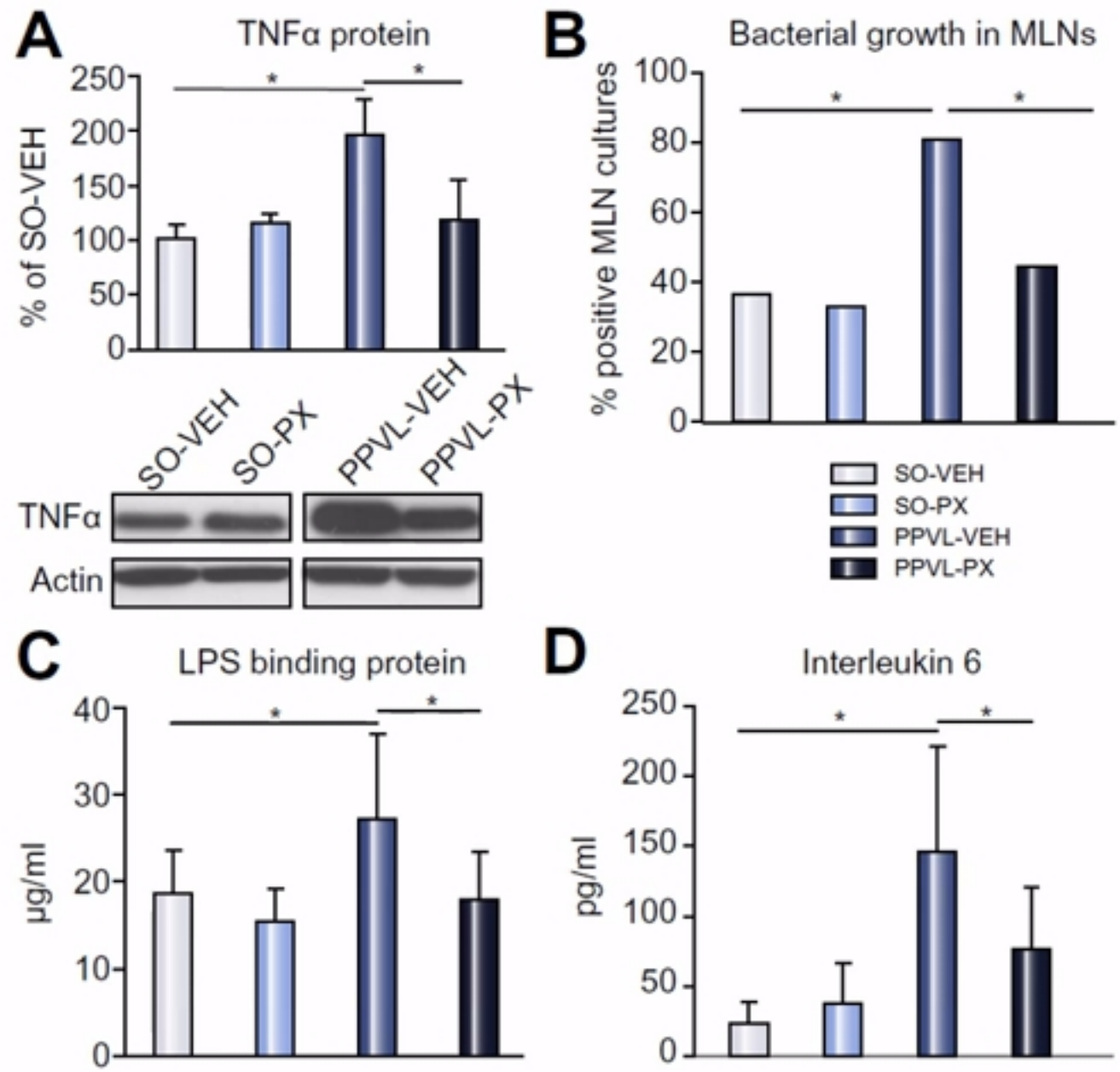
Fibrosis & architectural changes beyond reversibility

Other mechanisms trigger decompensation
- *portal HTN*
- *bacterial translocation*
- *circulatory dysfunction*

FXR agonists reduce intestinal inflammation and bacterial translocation

- ***REDUCTION IN PORTAL PRESSURE***
- Reduced fibrogenesis
- Sinusoidal vasodilation (increased e-NOS, reduces ET-1)
- Improvment in endothelial dysfunction
- Improvement in sinusoidal remodeling

- ***REDUCTION IN BACTERIAL TRANSLOCATION***



Schwabl, J Hepatol 2017

Random thoughts

- Burden of severe NASH
- Real prevalence estimates
- Disease awareness – screening issues
- How to screen ?
- Transition steatosis advanced NASH
- Patients at risk of progression
- Endpoints for trials
- Issues with treating cirrhotics