# Diagnostiek en behandeling van NAFLD

Prof. Dr. S. Francque

Dienst Gastroenterologie Hepatologie, Universitair Ziekenhuis Antwerpen

Laboratory of Experimental Medicine and Paediatrics, Faculteit Geneeskunde en Gezondheidswetenschappen, Universiteit Antwerpen

# Vraag 1

Ik screen niet voor NASH want ik kan er toch niets aan doen, er is geen behandeling voor.

# Vraag 2

Als ik een medicamenteuse behandeling zou starten voor NASH, dan kan dat na de diagnose te hebben gesteld op basis van een combinatie van klinische, biologische en beeldvormingsparameters.

- Wat te diagnosticeren? Wie te behandelen?
- Hoe te diagnosticeren? Case finding en screening?
- Niet-pharmacologische behandeling
- Pharmacologische behandeling

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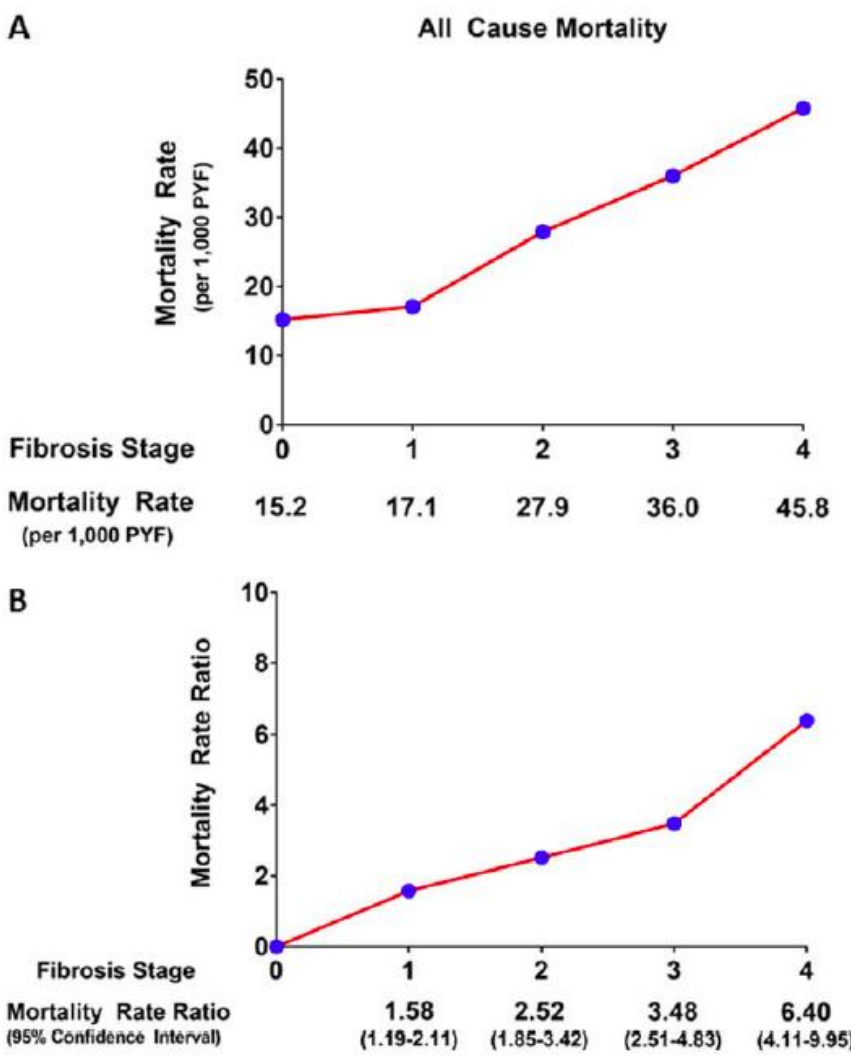
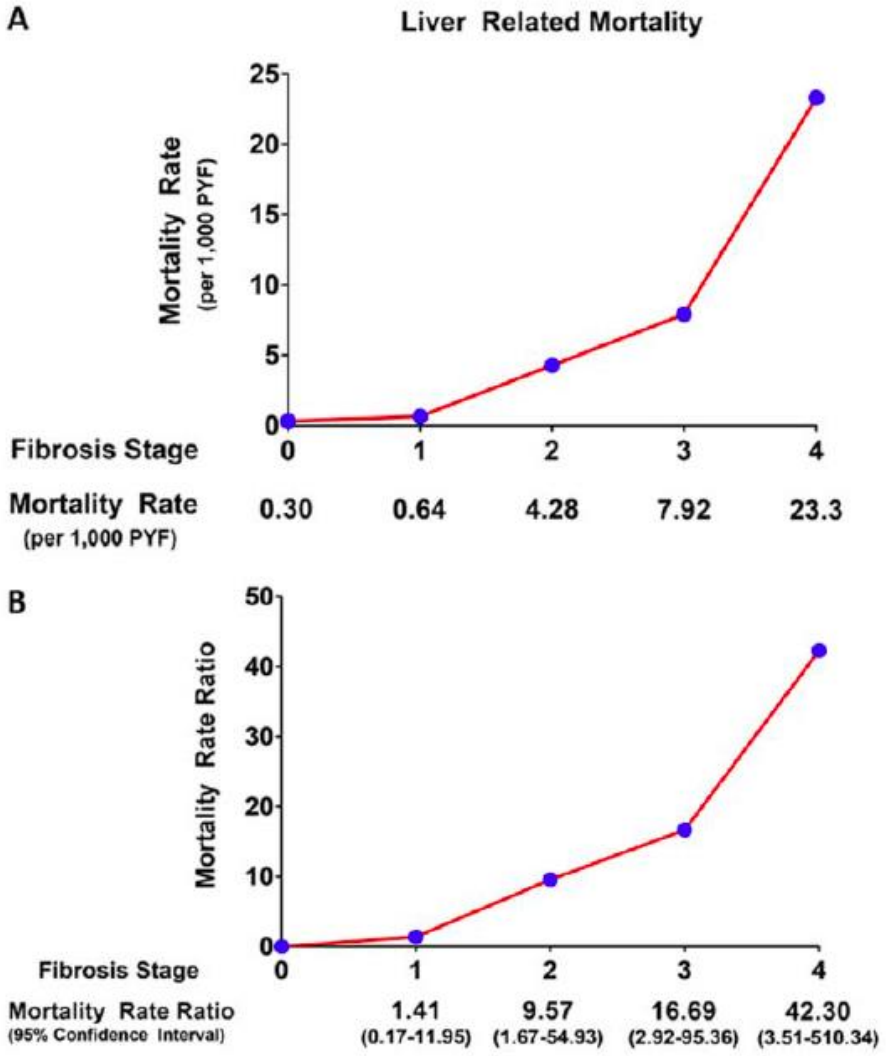

A
All Cause Mortality
Mortality Rate
(per 1,000 PYF)
50
40
30
20
10
0
Fibrosis Stage
0 1 2 3 4
Mortality Rate
(per 1,000 PYF)
15.2 17.1 27.9 36.0 45.8
B
Mortality Rate Ratio
10
8
6
4
2
0
Fibrosis Stage
0 1 2 3 4
Mortality Rate Ratio
(95% Confidence Interval)
1.58 (1.19-2.11)
2.52 (1.85-3.42)
3.48 (2.51-4.83)
6.40 (4.11-9.95)


A
Liver Related Mortality
Mortality Rate
(per 1,000 PYF)
25
20
15
10
5
0
Fibrosis Stage
0 1 2 3 4
Mortality Rate
(per 1,000 PYF)
0.30 0.64 4.28 7.92 23.3
B
Mortality Rate Ratio
50
40
30
20
10
0
Fibrosis Stage
0 1 2 3 4
Mortality Rate Ratio
(95% Confidence Interval)
1.41 (0.17-11.95)
9.57 (1.67-54.93)
16.69 (2.92-95.36)
42.30 (3.51-510.34)

| | | Final fibrosis stage | | | | | Total stages of fibrosis progressed | Person-years of follow-up evaluation | FPR (95% CI) | Time taken to progress by 1 stage (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| NAFLD (11 studies) | | | | | | | | | | |
| | | 0 | 1 | 2 | 3 | 4 | | | | |
| Baseline fibrosis stage | 0 (131) | 79 | 28 | 13 | 7 | 4 | +91 | 968 | 0.13 (0.07–0.18) | 7.7 (5.5–14.8) |
| | 1 (119) | 26 | 44 | 32 | 15 | 2 | +43 | 628.4 | 0.10 (0.04–0.16) | 10.0 (6.2–25.0) |
| | 2 (61) | 9 | 17 | 14 | 13 | 8 | −6 | 331.8 | NA | - |
| | 3 (34) | 2 | 5 | 10 | 7 | 10 | −16 | 153.4 | NA | - |
| | 4 (21) | 0 | 0 | 1 | 6 | 14 | −8 | 63.8 | NA | - |
| | Overall (366) | | | | | | +104 | 2145.4 | NA | - |
| | Stage 0 plus stage 1 fibrosis (250) | | | | | | +134 | 1596.4 | 0.12 (0.07–0.16) | 8.3 (6.2–14.3) |
| NAFL (6 studies) | | | | | | | | | | |
| | | 0 | 1 | 2 | 3 | 4 | | | | |
| Baseline fibrosis stage | 0 (81) | 52 | 16 | 8 | 4 | 1 | +48 | 751.3 | 0.07 (0.02–0.11) | 14.3 (9.1–50.0) |
| | 1 (39) | 6 | 13 | 14 | 6 | 0 | +20 | 112.6 | 0.15 (-0.09 to 40) | NA |
| | 2 (13) | 2 | 3 | 5 | 2 | 1 | −3 | 40.7 | NA | - |
| | 3 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NA | - |
| | 4 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | NA | - |
| | Overall (133) | | | | | | +75 | 904.6 | NA | - |
| | Stage 0 plus stage 1 fibrosis (120) | | | | | | +68 | 863.9 | 0.09 (0.04–0.14) | 11.1 (7.1–25.0) |
| NASH (7 studies) | | | | | | | | | | |
| | | 0 | 1 | 2 | 3 | 4 | | | | |
| Baseline fibrosis stage | 0 (21) | 10 | 7 | 2 | 1 | 1 | +18 | 115.5 | 0.14 (0.07–0.21) | 7.1 (4.8–14.3) |
| | 1 (49) | 9 | 25 | 9 | 5 | 1 | +13 | 396.6 | 0.08 (-0.01 to 0.17) | NA |
| | 2 (25) | 3 | 10 | 4 | 4 | 4 | −4 | 222.3 | NA | |
| | 3 (16) | 0 | 4 | 4 | 2 | 6 | −6 | 95.8 | NA | |
| | 4 (5) | 0 | 0 | 0 | 1 | 4 | −1 | 12.6 | NA | |
| | Overall (116) | | | | | | +20 | 842.8 | NA | |
| | Stage 0 plus stage 1 fibrosis (70) | | | | | | +31 | 512.1 | 0.10 (0.03–0.17) | 10.0 (5.9–33.3) |

# Who to treat?

- Fibrosis is most important predictor of prognosis
  - Marker of longstanding active disease
- NASH driver of disease
  - Liver-related outcomes
  - CV and diabetes

➔ NASH with some degree of activity and with some degree of fibrosis is the target

# Treatment Indication

Biopsy proven

NASH

+

Some degree of activity

NAS ≥ 4

+

Some degree of fibrosis

F ≥ 2

Or

F1 + risk factors (NAS ≥ 5, DM2, obesity,…)

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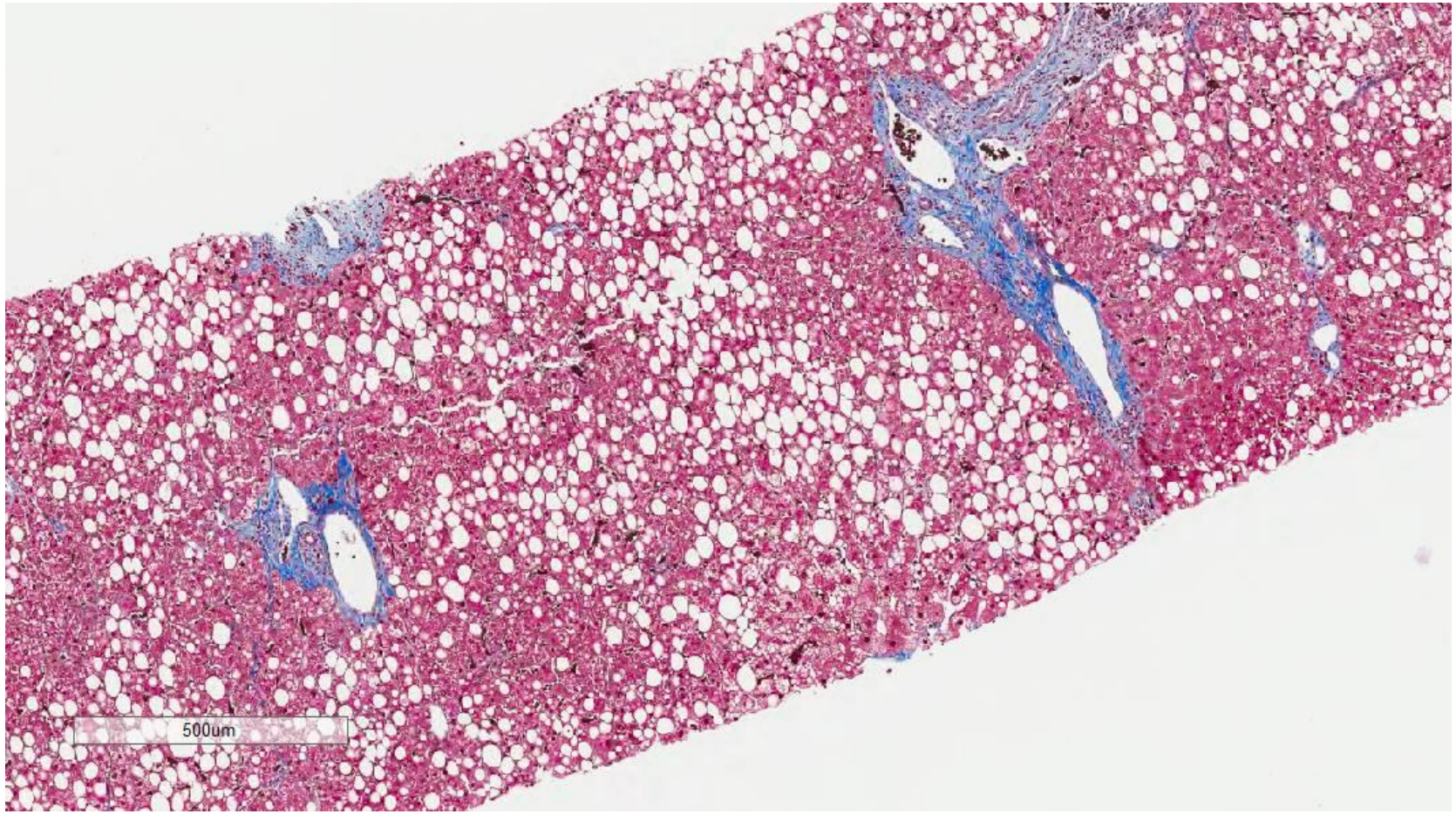
# The issue is tissue



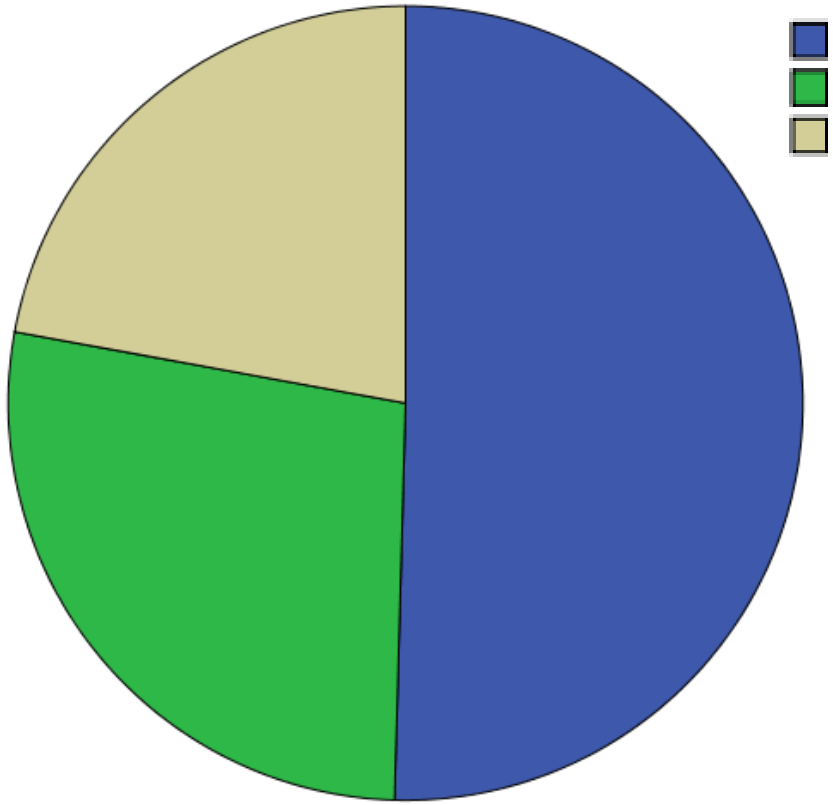

Courtesy P. Bedosssa

# Case

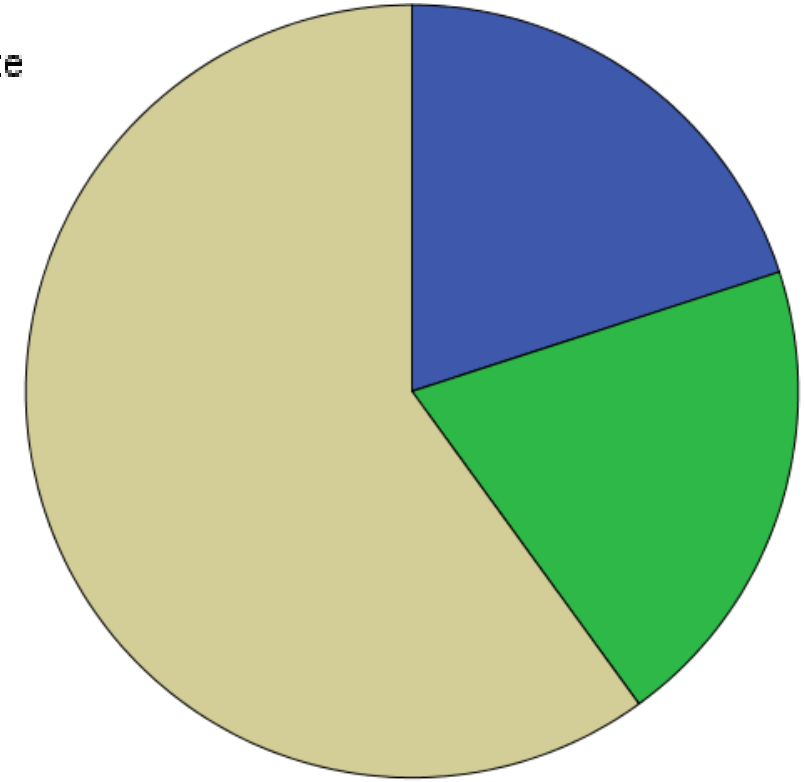
- Male, 48y
- L 1m68, G 85 kg, Waist 109 cm
- No medical history, does not smoke nor drink
- check-up 1y ago
  - Diagnosis T2DM -> metformin 500 mg/d
  - Diagnosis AHT -> amlodipin 5 mg/d
- Status praesens
  - AST 36 U/L, ALT 39 U/L, GGT 45 U/L, TRC 161x10e9/L, albumin 4.1 g/dL
  - US: grade 1 steatosis

➡ How do you interpret the transaminases (AST 37 U/L, ALT 39 U/L)?

ALT ≤ 40 U/L




ALT > 40 U/L



p<0.001

# ALT cut-off values

- Male:
  - ALT 29-33 U/L
- Female
  - ALT 19-25 U/L

ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACG, FAASLD[1], Stanley M. Cohen, MD, FACG, FAASLD[2] and Joseph K. Lim, MD, FACG, FAASLD[3]

Am J Gastroenterology 2016

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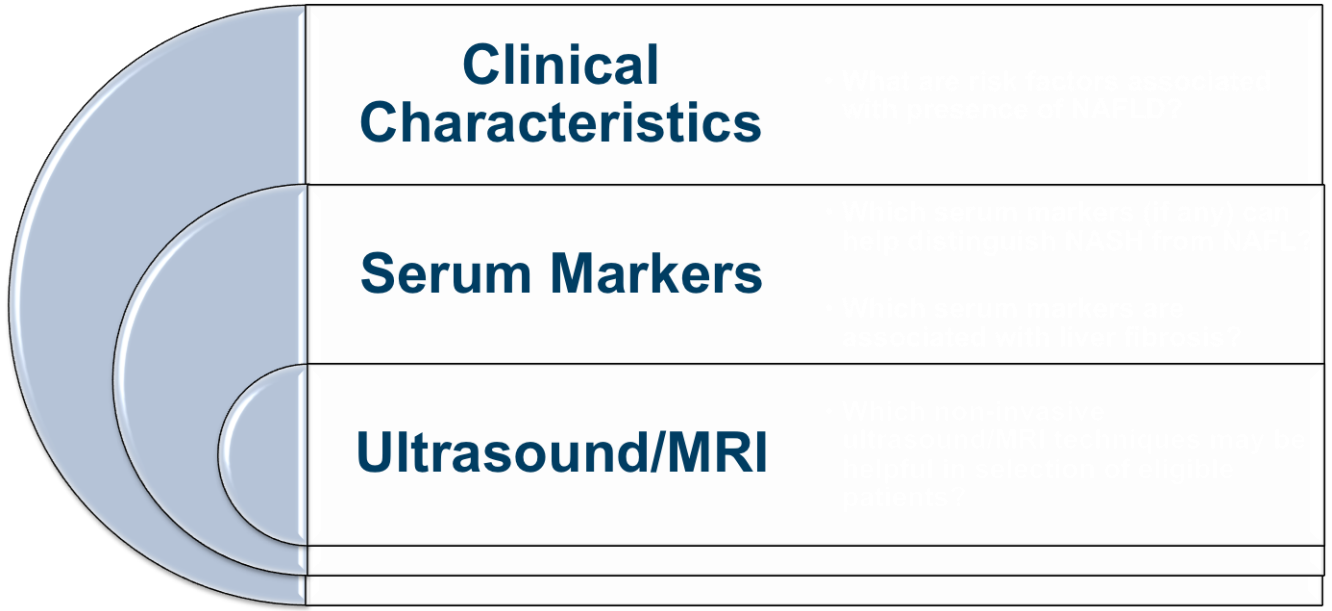
  - US: grade 1 steatosis

➡ Would you consider this patient for further hepatological referral/biopsy?

# How to select patients at high risk of meeting the criteria?



# Clinical Risk Factors Associated with Fatty Liver Disease

- Presence of multiple features of the metabolic syndrome
  - Abdominal obesity: a waist circumference ≥102 cm (40 in) in men and ≥ 88 cm (35 inches) in women.
    For Asian Americans, the cutoff values are ≥90 cm (35 in) in men or ≥80 cm (32 in) in women.
  - Serum triglycerides ≥ 150 mg/dl
  - HDL cholesterol ≤40mg/dl in men and ≤50mg/dl in women
  - Blood pressure of ≥ 130/85
  - Fasting blood glucose of ≥ 100 mg/dl
- Presence of type 2 diabetes mellitus (T2DM)
- Persistently elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels
- Increasing age
- Increasing BMI

# Non-invasive scoring systems

- Fatty Liver Index
  - BMI, age, AST,ALT
- NAFLD Fibrosis Score
  - Age, BMI, IFG/2DM, AST/ALT, platelets, albumin
- Fib-4
  - Age, AST, platelet count, ALT

- Low PPV but **high NPV**

Bedogni G. et al, *BMC Gastroneterol* 2006;6:33
Angulo P. et al, *Gastronetrology* 2007;45:846–54
McPherson S. et al, *Gastroenterology* 2010;25:652–58

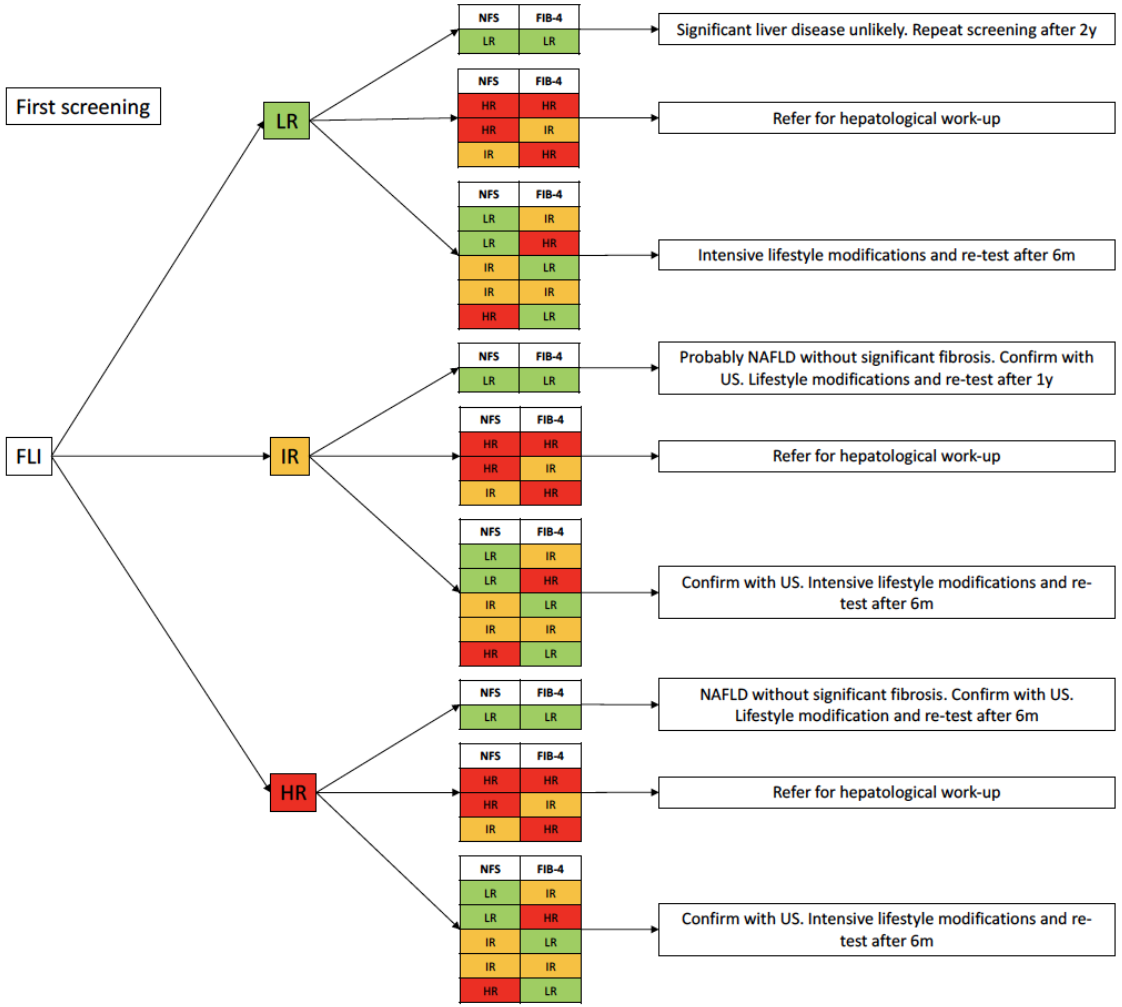
# Non-invasive assessments of clinically significant fatty liver disease such as NASH and liver fibrosis

**Serum markers**

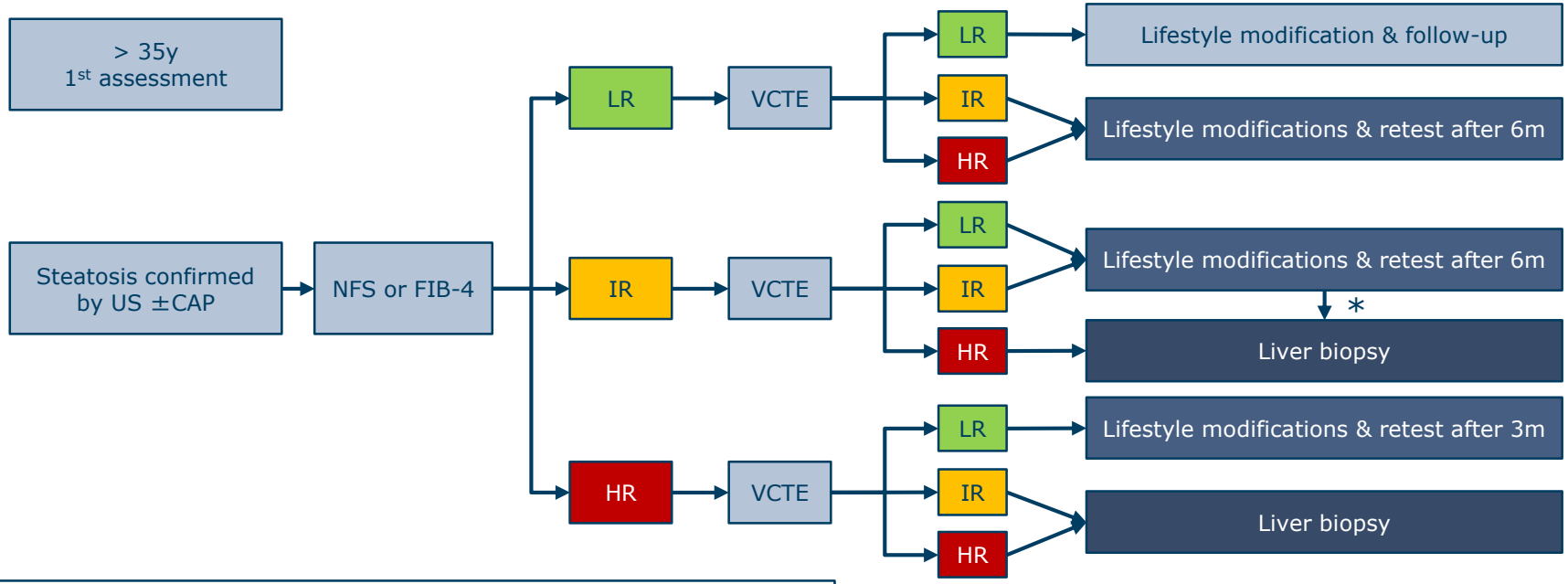
- APRI, FIB-4, AST/ALT ratio
- Enhanced liver fibrosis score (ELF)
- NAFLD fibrosis score (NFS)
- FibroTest® (FibroSure®)
- CK-18
- HepaScore®

**Liver ultrasound elastography and imaging methods**

- Ultrasound Vibration Controlled Transient Elastography (VCTE)/ Controlled Attenuation Parameter (CAP®)
- Magnetic Resonance (MR) Elastography (MRE)
- Acoustic radiation ARFI
- MR spectroscopy for Proton Density Fat Fraction (PDFF)



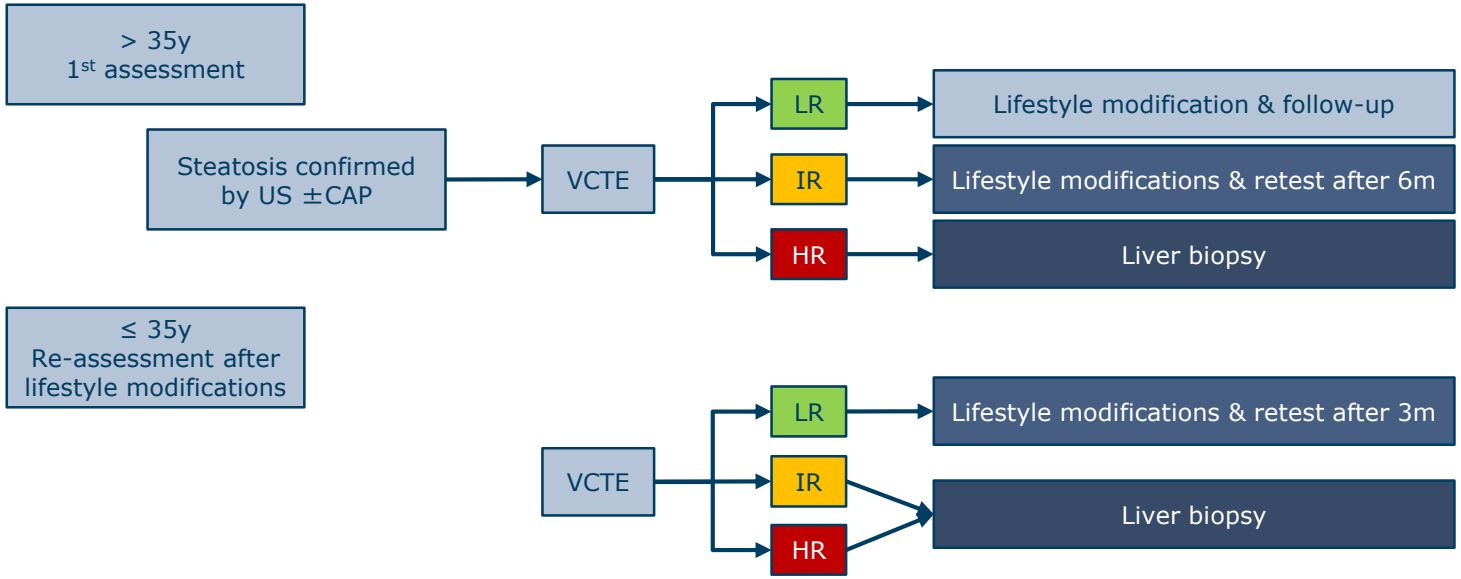

Francque *et al*. Acta Gastroenterol Belg 2018




**Cut-off values:**

- Age ≤ 35 yrs: the NFS and FIB-4 are unreliable and an alternative method (e.g. elastometry) should be used to screen for fibrosis
- Age 35-65 yrs: NFS, LR < -1.455 < IR < 0.676 < HR
  FIB-4, LR < 1.30 < IR < 2.67 < HR
- Age ≥ 65 yrs: NFS, LR < 0.120 < IR < 0.676 < HR
  FIB-4, LR < 2.00 < IR 2.67 < HR
- All ages: FLI, LR < 30 < IR < 60 HR

Francque *et al*. Acta Gastroenterol Belg 2018

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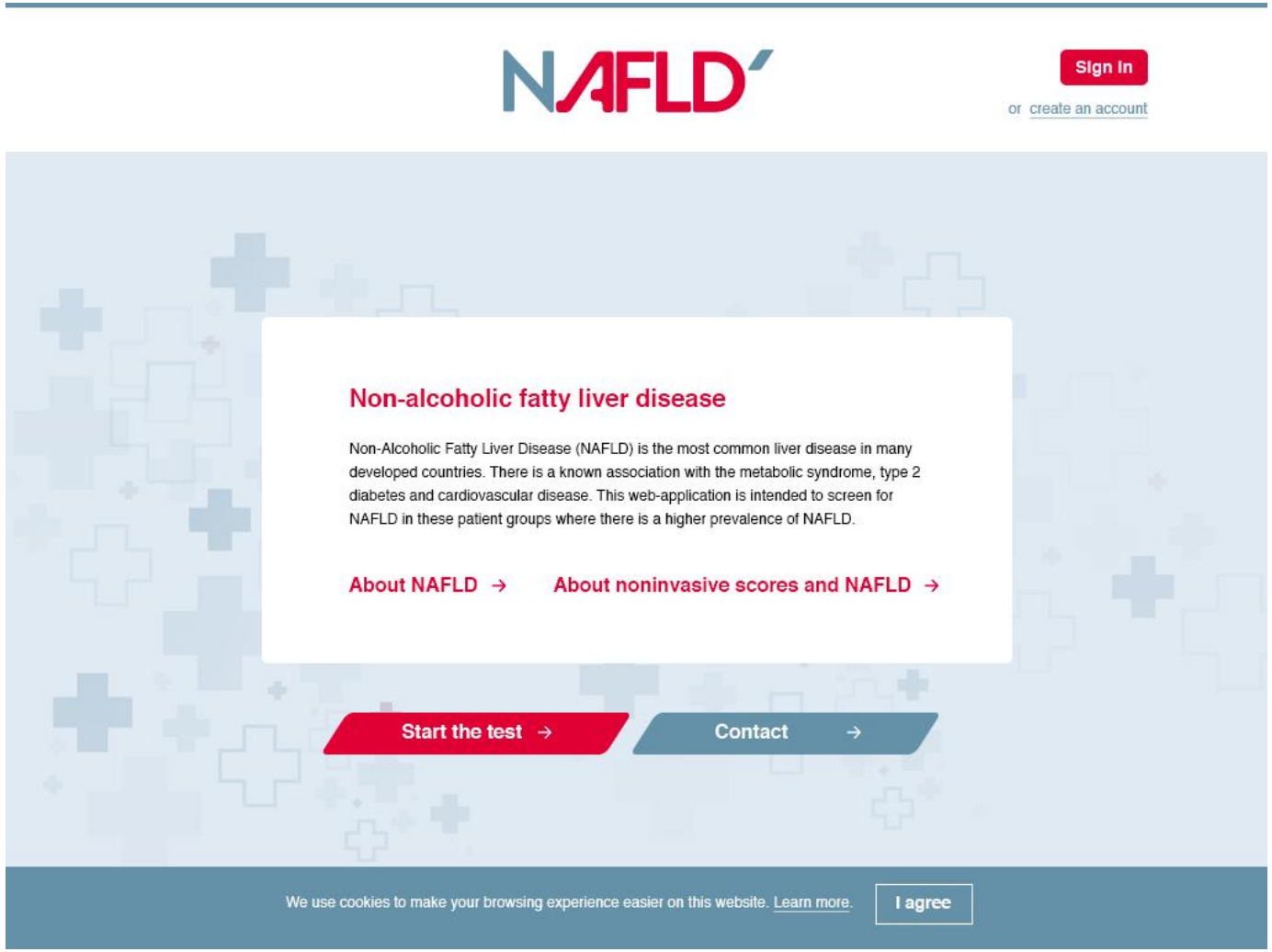
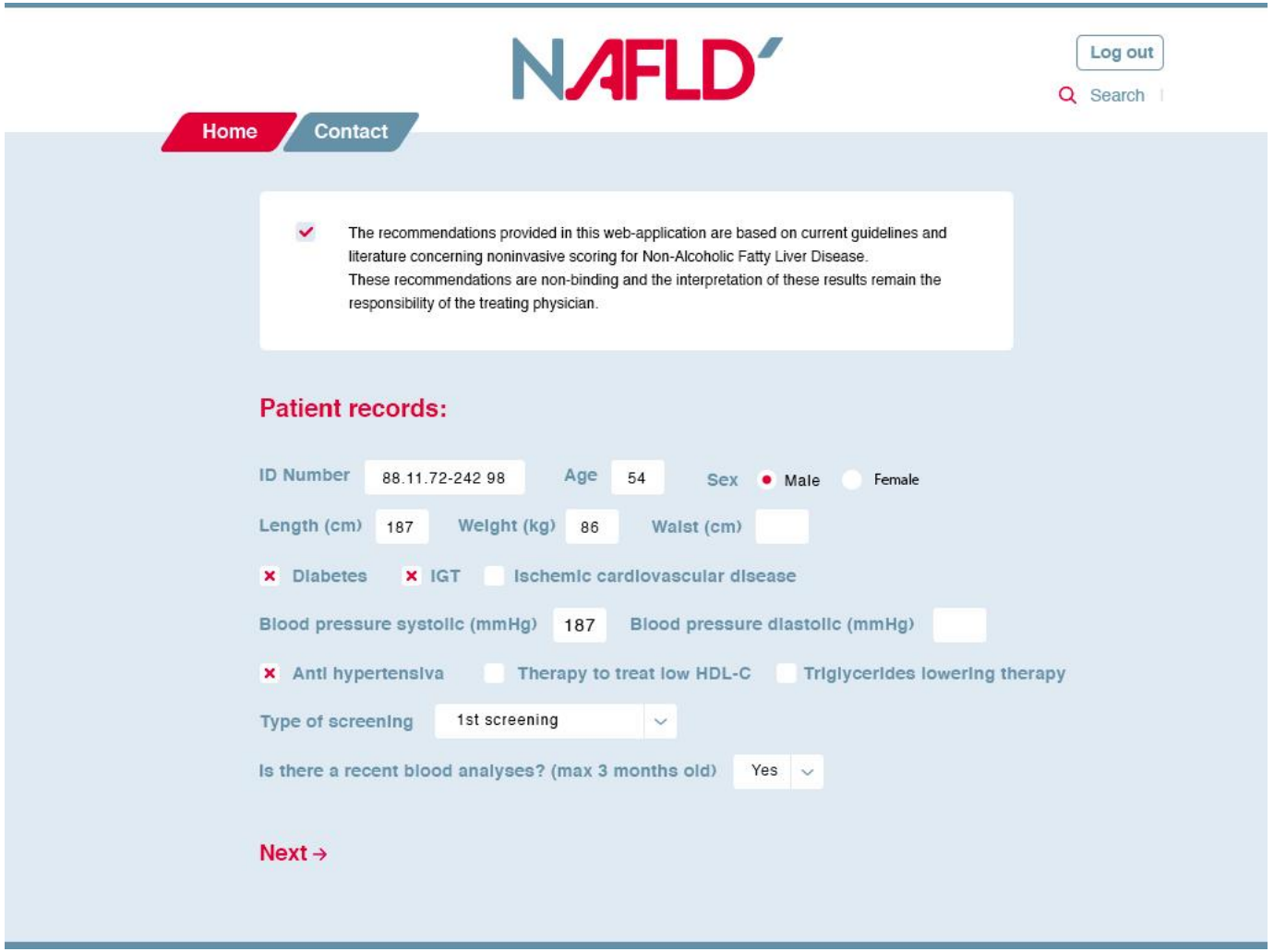
  FIB-4, LR < 2.00 < IR 2.67 < HR
- Fibroscan: M-probe, LR < 7.9 kPa < IR < 9.6 kPa < HR
  XL-probe, LR < 7.2 kPa < IR 9.3 kPa < HR

Francque *et al*. Acta Gastroenterol Belg 2018

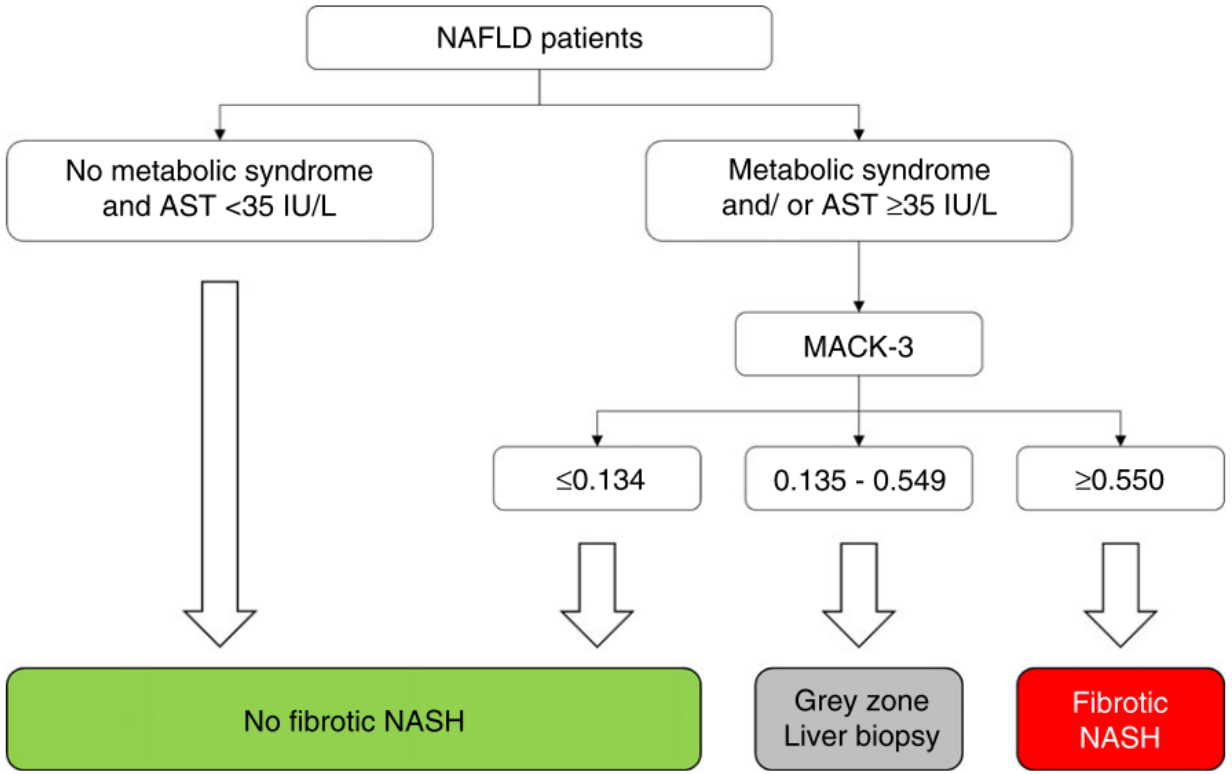



www.antwerpnafldguide.com




www.antwerpnafldguide.com

# Non-invasive diagnosis of fibrotic NASH




**Diagnosis of fibrotic NASH**

- MACK-3
  **AST + HOMA + CK-18**
  **AUROC = 0.85**

- Algorithm
  **93.2% well classification**

Boursier J, Francque *et al*. Aliment Pharmacol Ther 2018;47:1387–1396

## ALGORITHM TO IDENTIFY PATIENTS WITH A SAF ACTIVITY SCORE > 2 IN TYPE 2 DIABETIC PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) - DEVELOPMENT IN A LARGE PROSPECTIVE MULTICENTER UK STUDY

P.J. EDDOWES[1], M. ALLISON[2], E. TSOCHATZIS[3], Q.M. ANSTEE[4], D. SHERIDAN[5], I.N. GUHA[6], J.F. COBBOLD[7], V. PARADIS[8], P. BEDOSSA[8], P.N. NEWSOME[1]


Parameters calculated

- SFR: 1-PPV
  [Proportion of "improperly" screened/biopsied patients
- MCR: 1-Se
  [Proportion of initial target patient who wouldn't have been biopsied]
- SIR: $(N-N_{total})/N_{total} * 100$
  [Proportion of "saved" LB in comparison if all patients would have underwent LB]

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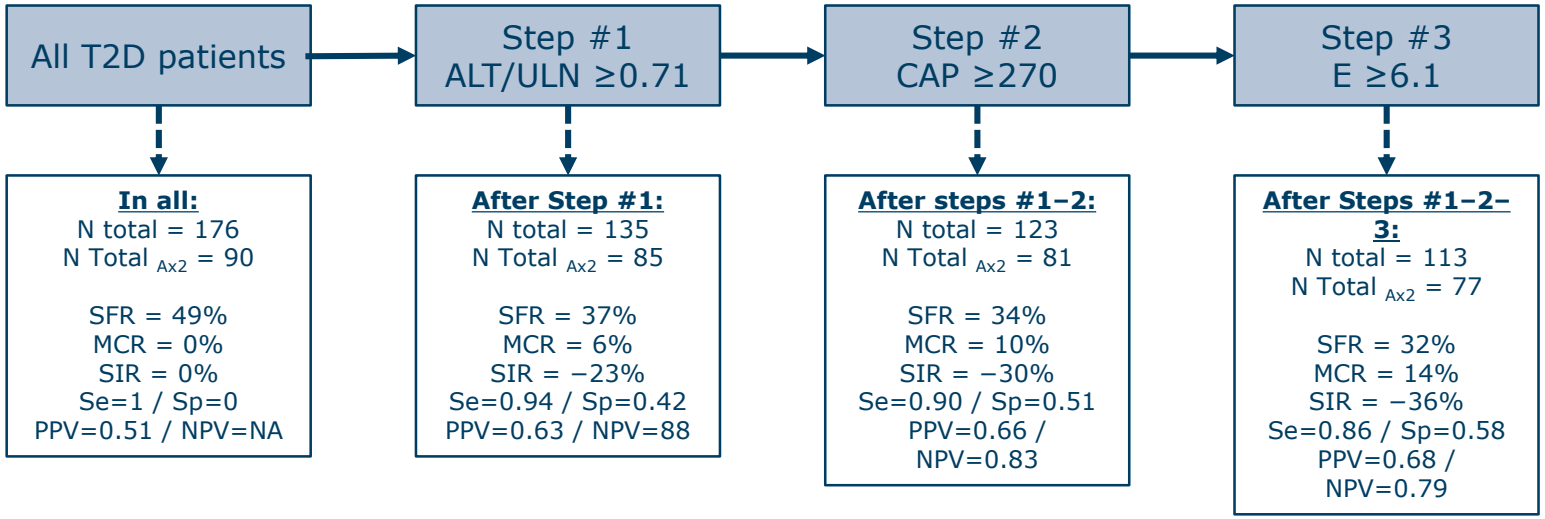
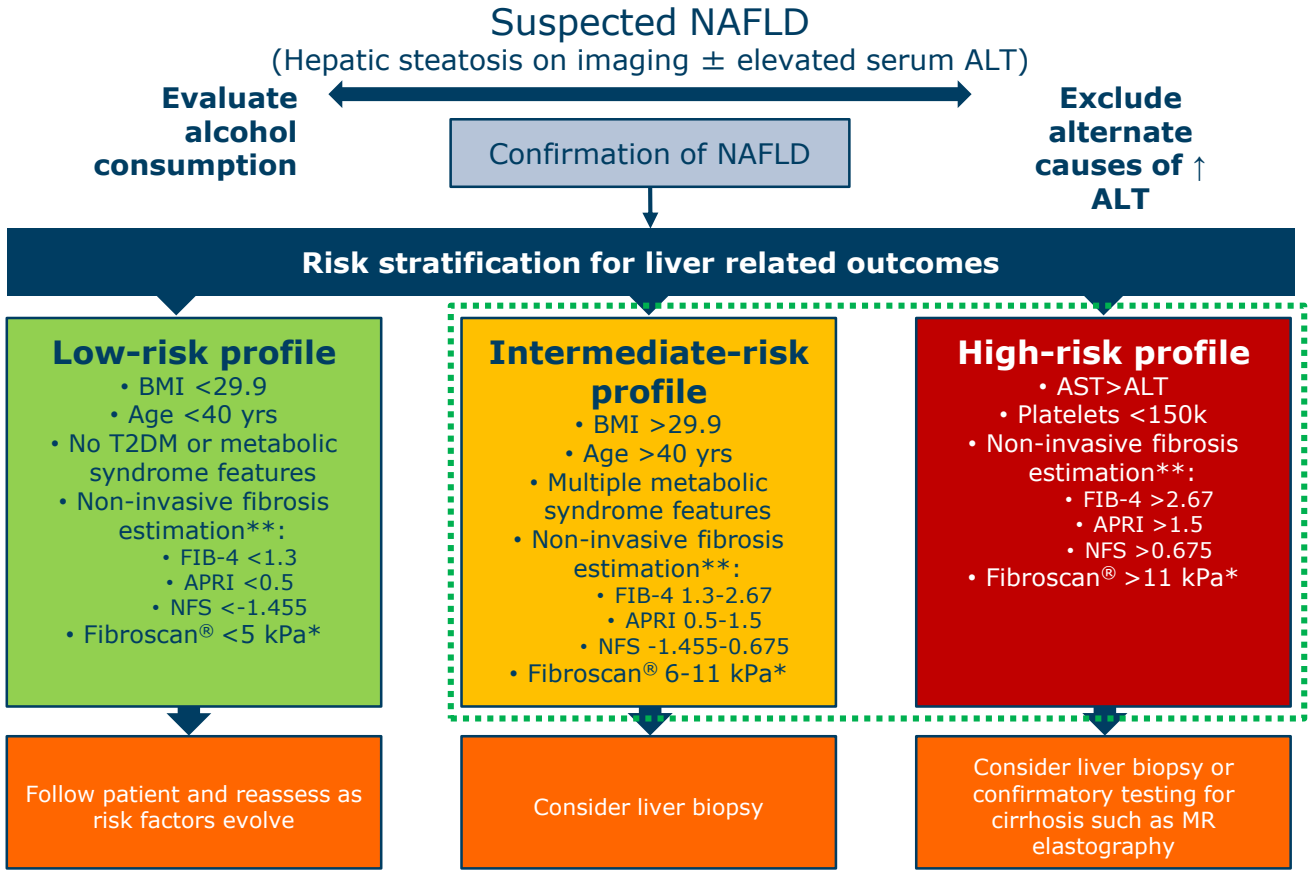
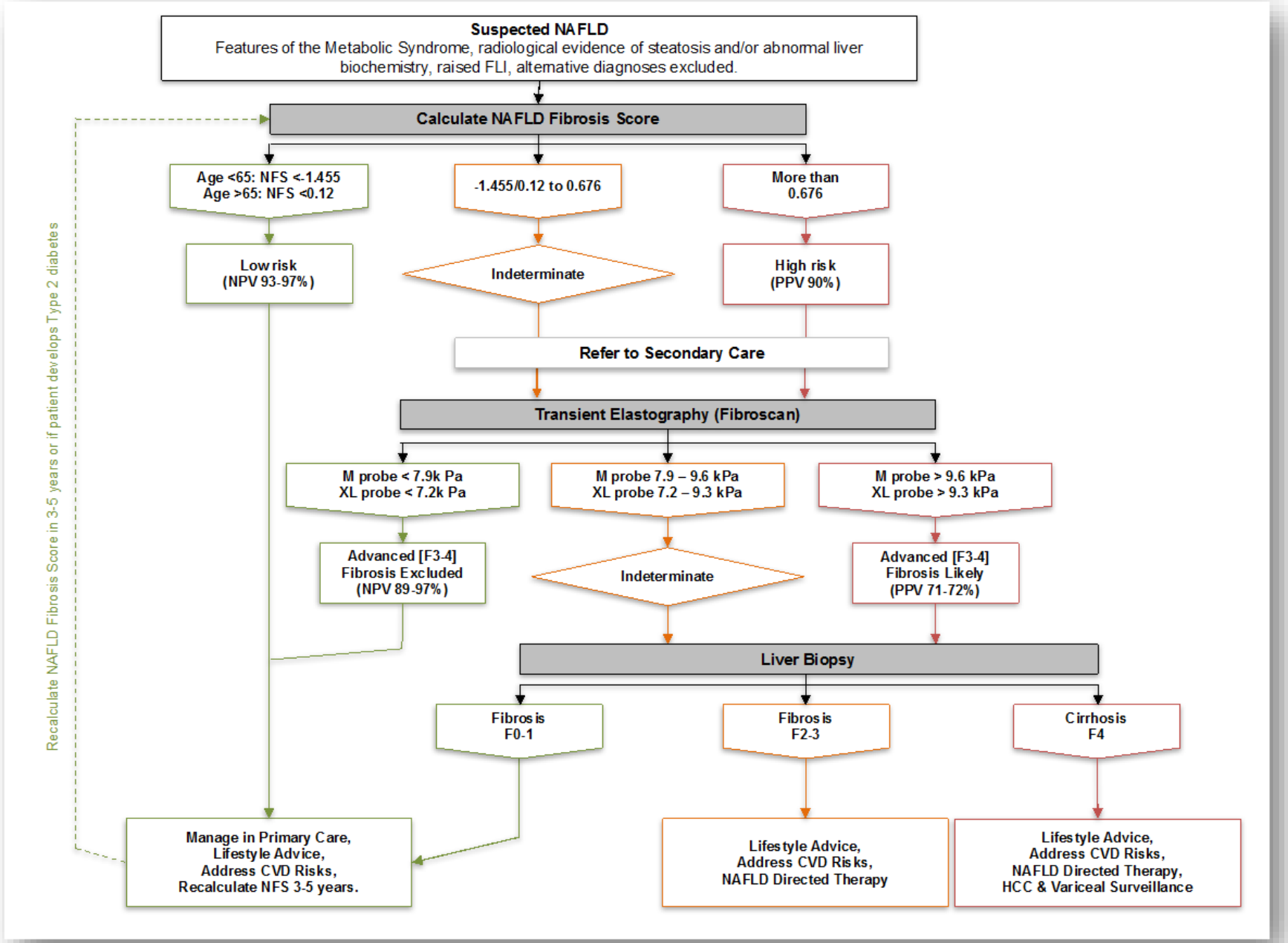





Rinella M and Sanyal A, *Nature Reviews Gastroenterology and Hepatology* 2016; 13:196–205




Courtesy of Q. Anstee

- NAFLD Liver Fibrosis Score
  - Age, BMI, IFG/DM, AST/ALT, platelets, albumin
  - 0.269 -> indeterminate score
  - Cut-offs: -1.455 and 0.675
  - Adjust for age
  - High NPV

- Fibroscan 8.4 kPa

- Biopsy NASH with S2A3F3

# Screening

## WHO?

- Elevated liver enzymes
- Obesity/metabolic syndrome
- Diabetes
- Cardiovascular event

## HOW?

- Liver enzymes
- Scores
  - Routine parameters
  - ELF, Fibotest,…
- Fibroscan

Clinical Practice Guidelines

CrossMark

EASL JOURNAL OF HEPATOLOGY

**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)

- All individuals with steatosis should be screened for features of MetS, independent of liver enzymes. All individuals with persistently abnormal liver enzymes should be screened for NAFLD, because NAFLD is the main reason for unexpectedly elevated liver enzymes (**A1**)
- In subjects with obesity or MetS, screening for NAFLD by liver enzymes and/or ultrasound should be part of routine work-up. In high risk individuals (age >50 years, T2DM, MetS) case finding of advanced disease (i.e. NASH with fibrosis) is advisable (**A2**)

**The Belgian Association for Study of the Liver Guidance Document on the Management of Adult and Paediatric Non-Alcoholic Fatty Liver Disease**

Sven Francque[1,2], Nicolas Lanthier[3], Len Verbeke[4], Hendrik Reynaert[5], Christophe van Steenkiste[6,7], Luisa Vonghia[1,2], Wilhelmus Kwanten[1,2], Jonas Weyler[1,2], Eric Trépo[8], David Cassiman[5], Françoise Smets[9], Mina Komuta[10], Ann Driessen[11], Eveline Dirinck[2,12], Etienne Danse[13], Bart Op de Beeck[14], Emeline van Creanenbroeck[15], Yves Van Nieuwenhove[16], Guy Hubens[17], Ania Geerts[4*] and Christophe Moreno[8*]

Francque *et al*. *Acta Gastroenterol Belg* 2018

- Wat te diagnosticeren? Wie te behandelen?
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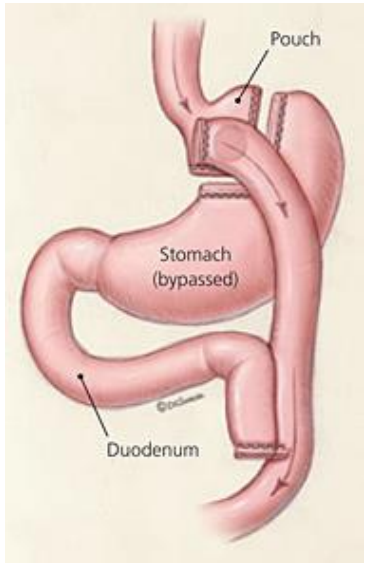
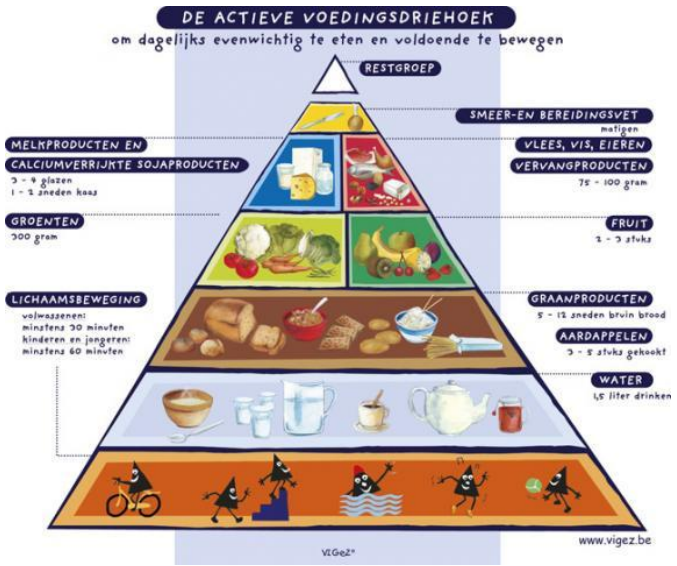
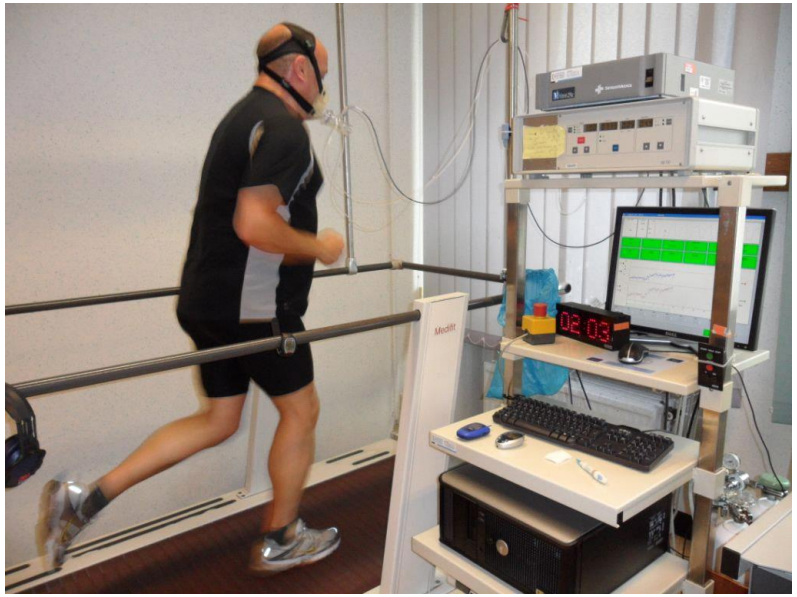
# Life style modification and weight loss

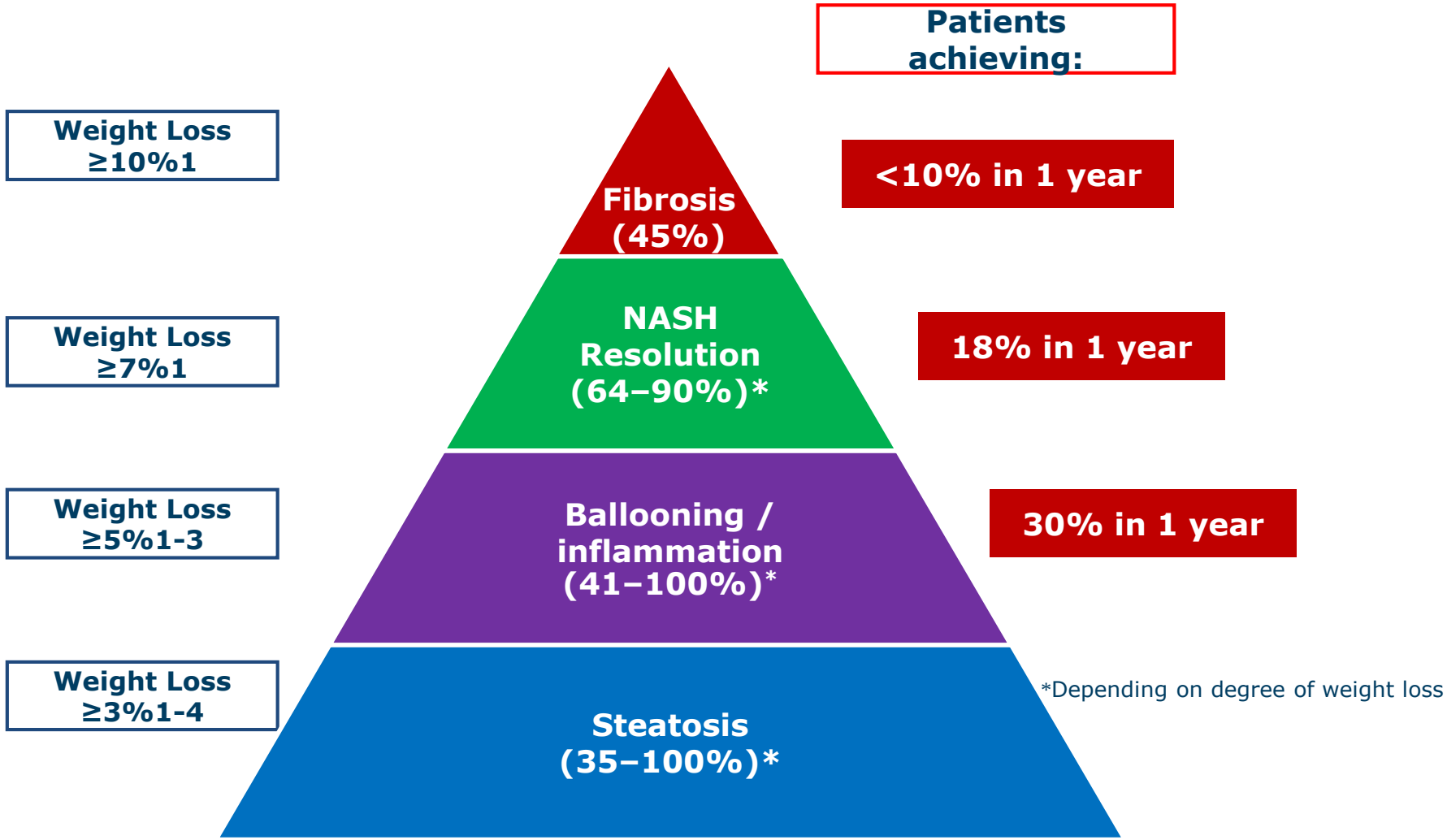
- Weight reduction
  - Diet
  - Physical activity
  - Bariatric surgery ?



# Weight loss pyramid




*Depending on degree of weight loss

Vilar-Gomez E, et al. Gastroenterology. 2015;149:367-78

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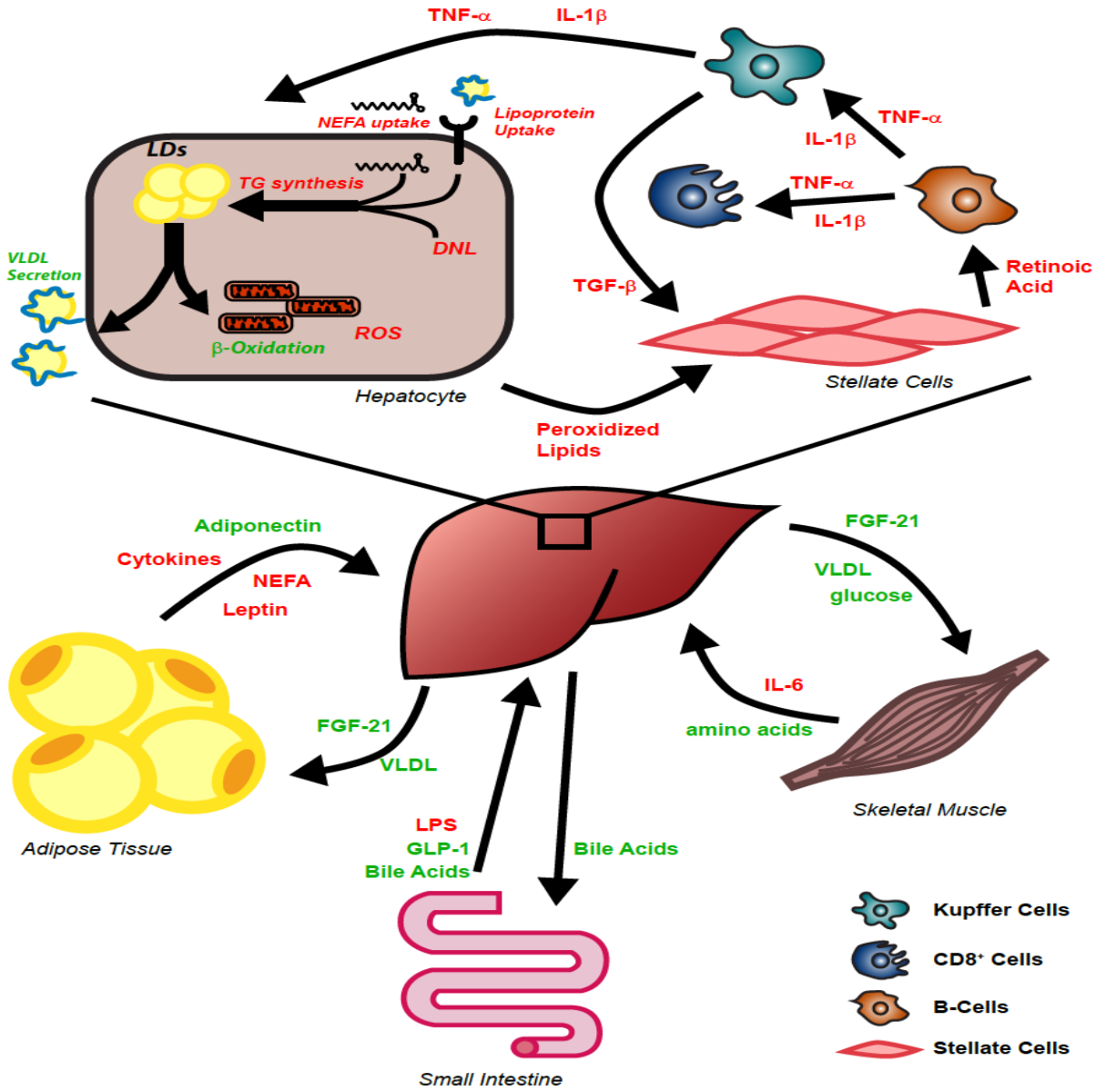


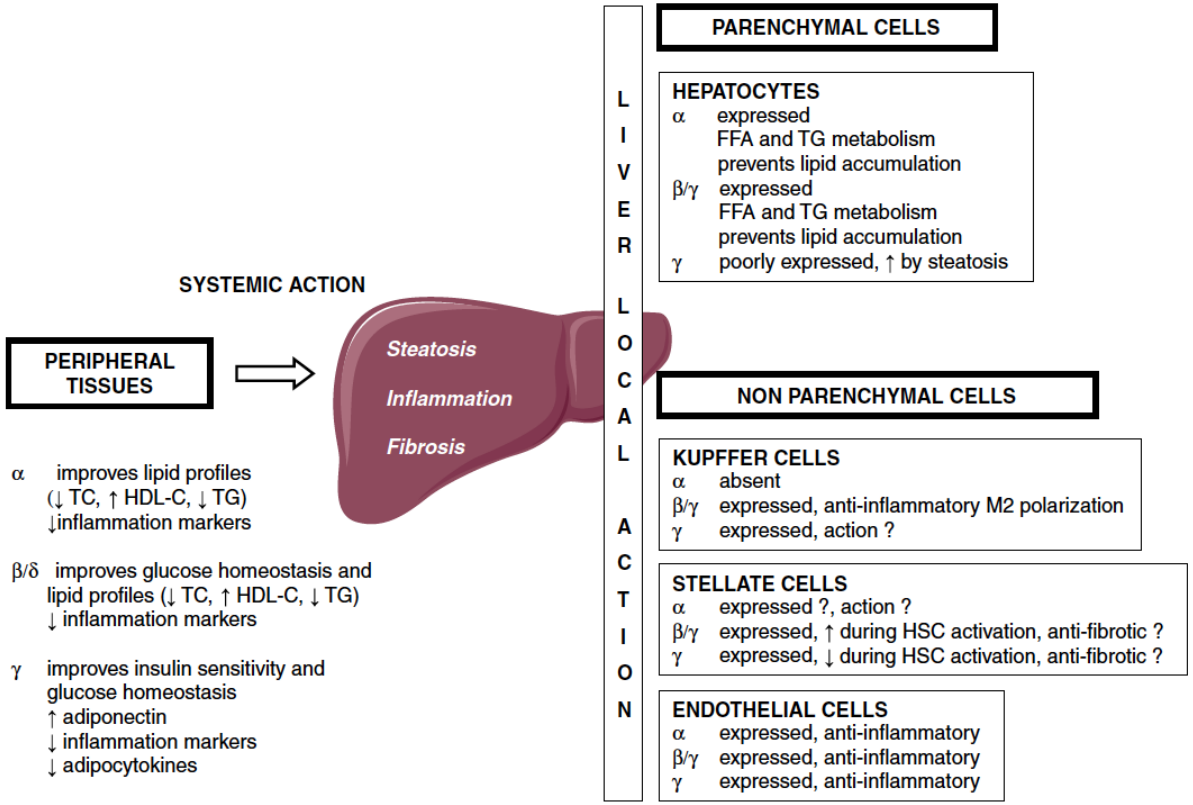

Haas, Francque & Staels. Ann Rev Physiol 2016

# Currently available drugs

- Not licensed for NASH
- Tested specifically for NASH in RCT with histological end-points

- TZD: Pioglitazone
- Vit E
- GLP-1: liraglutide

# PPARs




Tailleux *et al*. BBA 2012

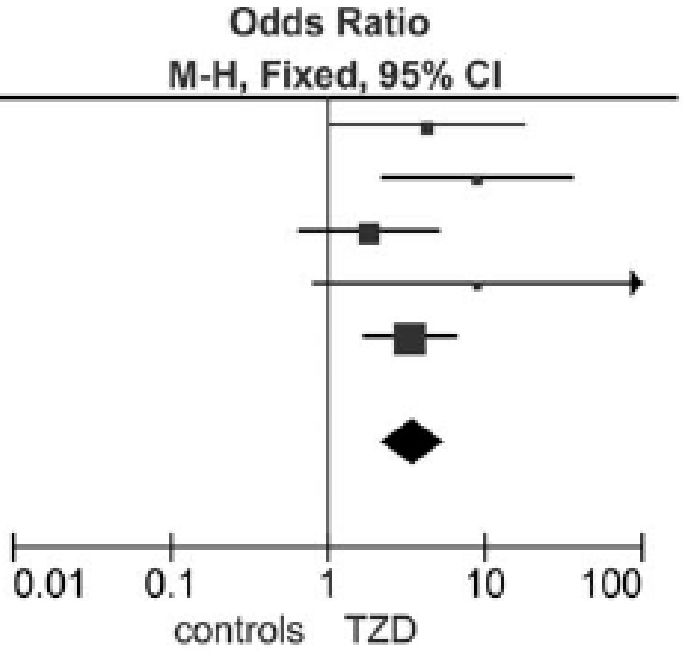
# Thiazolidinediones

| Study or Subgroup | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|
| Aithal 2009 | 10.8% | 4.29 [1.05, 17.56] |
| Belfort 2006 | 7.1% | 8.94 [2.24, 35.61] |
| Ratziu 2008 | 29.3% | 1.82 [0.66, 5.00] |
| Sanyal 2004 | 2.6% | 9.00 [0.81, 100.14] |
| Sanyal 2009 | 50.1% | 3.31 [1.70, 6.45] |
| **Total (95% CI)** | **100.0%** | **3.53 [2.21, 5.64]** |

Total events

Heterogeneity: Chi² = 4.08, df = 4 (P = 0.40); I² = 2%

Test for overall effect: Z = 5.28 (P < 0.00001)




Musso *et al*. Hepatology 2010

# Thiazolidinediones

- Confirmed in recent reports
  - Long term treatment
    - 18m + 18 m open label
    - Improvement confirmed and sustained
  - With and without T2DM
    - Greater effect in T2DM compared to prediabetes

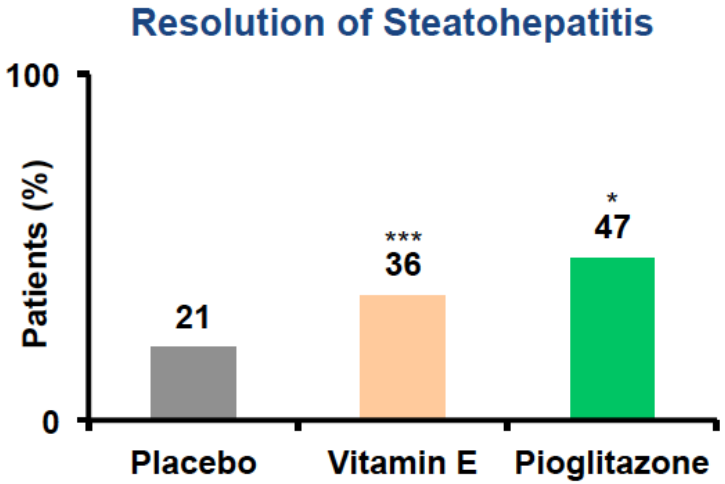
Cusi *et al*. Annals Int Med 2016
Bril *et al*. Clin Gastroenterol Hepatol 2018

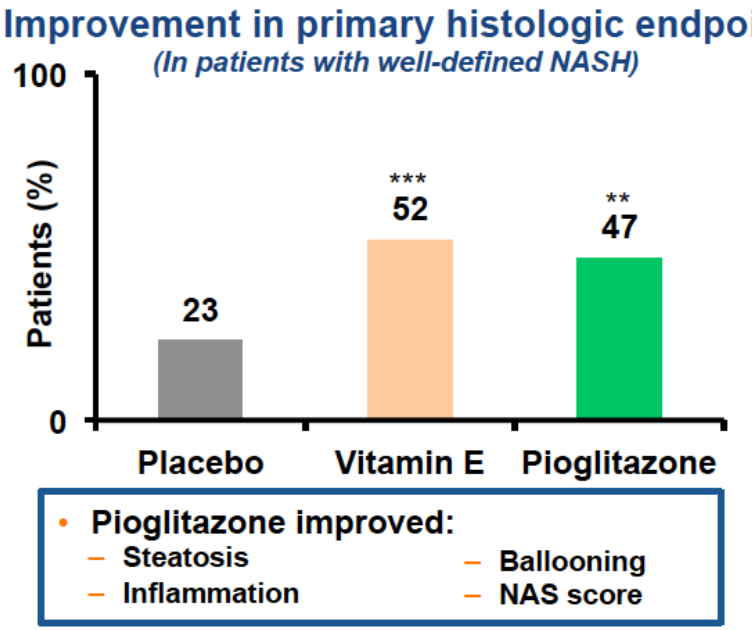
# TZD

- Pioglitazone improves liver histology in pts ± T2DM with biopsy-proven NASH.
  - ⇢ can be used to treat these patients
  - Not in label (only T2DM)
  - Risks
    - Weight gain (adipose tissue expansion + fluid retention)
    - Bone fracture
    - Cardiovascular?
      - Improves CV outcomes
      - Heart failure?
        - » Only if pre-existing reduced myocardial function
    - Carcinogenesis? Bladder cancer?
  - Until further data: not use to treat NAFLD without biopsy-proven NASH.
- Rosiglitazone
  - Inferior to pio
    - No PPAR alpha-effect
  - Less favorable safety profile

Kernan *et al*. NEJM 2016
Liao *et al*. BMJ 2017
Paneni, Lüscher. Am J Med 2017

# 2 yr PIVENS trial pioglitazone or vit E in non-diabetic NASH




*p=0·05; **p<0·01; ***p<0·001 vs placebo

*Sanyal AJ, et al. N Engl J Med. 2010;362:1675-85*

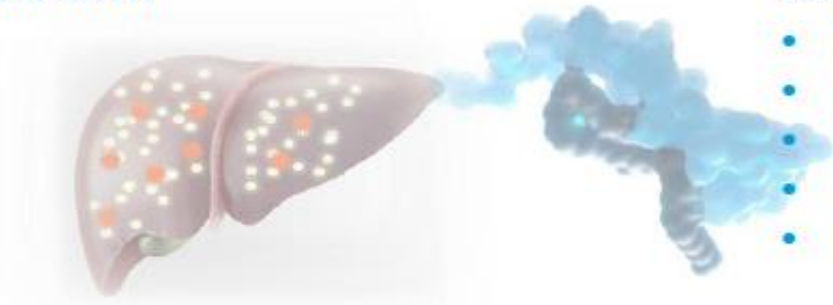
# Vit E

- Vit E (rrr α-tocopherol) 800 IU/day
  - Improves liver histology in non-diabetic adults with biopsy-proven NASH
- Safety concerns
  - CVA?
  - Prostate cancer?
- Not recommended because no data in RCT
  - NASH in diabetic patients
  - NAFLD without liver biopsy
  - NASH cirrhosis or cryptogenic cirrhosis.

# GLP-1

**NASH is associated with**

- Obesity
- Insulin resistance
- Inflammation



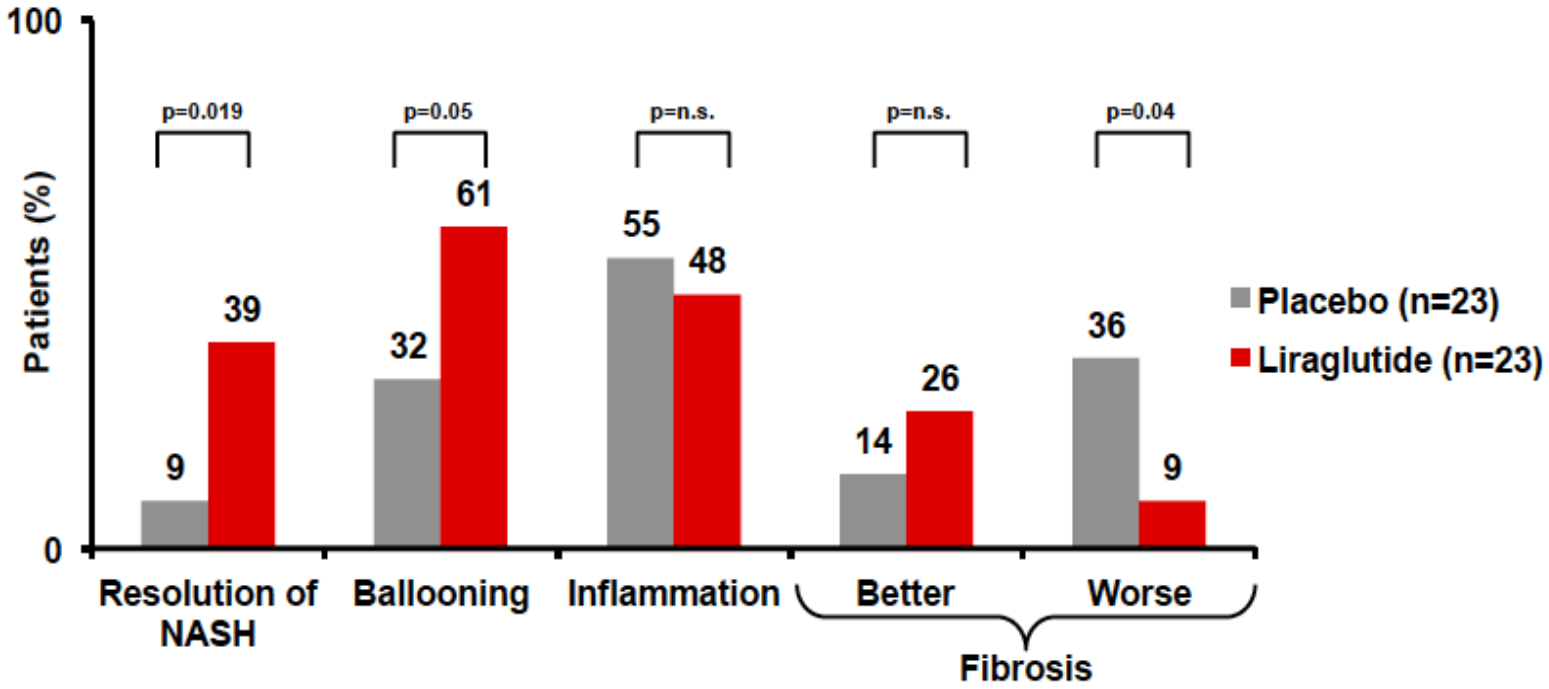
**Potential benefits of GLP-1 receptor agonists**

- Weight loss
- Improved glucose metabolism
- Improved lipid metabolism
- Reduced inflammation
- Resolution of NASH (LEAN study)[1]

- Approved for treatment of T2DM and obesity
- RCT of liraglutide in NASH
- Larger phase 2 semaglutide currently enrolling

[1] Armstrong *et al*. Lancet 2016

# The LEAN 1 year trial of liraglutide: Histological improvement




*Armstrong MJ, et al. Lancet. 2016;387:679-90*

- No effect
  - UDCA, metformin, fibrates, ezetimibe, SGLT2,…
- Interesting properties but not formally tested
  - Statins
  - Asprine
  - Sartans

# What to expect in the near future?

- Compounds in phase 3
  - Based on Phase 2 with positive results on histological endpoints

  - Elafibranor: PPAR alpha-delta dual agonist
  - Obeticholic acid (OCA): steroid FXR agonist
  - Selonsertib: ASK-1 inhibitor
  - Cenicriviroc: dual CCR2-CCR5 antagonist

# Drug pipeline

- PPAR agonists
  - PanPPAR Lanifibranor
- FXR
  - Bile acid (norUDCA) and non-bile acid FXR agonists
- FGF21
- FGF19
- TGR5
- THR beta agonist
- SCD1
- …

- Combination therapies
  - CVC + Tropifexor
  - …

Treatment opportunities for patients with persistent NASH despite optimisation of cardiometabolic co-morbid conditions

Tailored treatments in the future

# Vraag 1

Ik screen niet voor NASH want ik kan er toch niets aan doen, er is geen behandeling voor.

# Vraag 2

Als ik een medicamenteuse behandeling zou starten voor NASH, dan kan dat na de diagnose te hebben gesteld op basis van een combinatie van klinische, biologische en beeldvormingsparameters.