Management of Non-Alcoholic Fatty Liver Disease in Belgium

S. Francque, MD, PhD

Senior Full Professor of Medecine

Antwerp University

Chairman, Department of Gastroenterology Hepatology

University Hospital Antwerp

Dolce La Hulpe 2022

European Reference Network

for rare or low prevalence complex diseases

Network Hepatological Diseases (ERN RARE-LIVER)

Disclosures

consultancy and/or speaker for Gilead, MSD, BMS, Roche, Bayer, Aktelion, Janssen, Intercept, Genfit, Inventiva, GSK, Boehringer Ingelheim, Galmed, Genentech, Galapagos, Aligos, Enyo, Novartis, Novo Nordisk, Astra Zeneca, Promethera, Echosens, Madrigal, NGMBio, Coherus, Julius Clinical.

Patient guideline

JHEP|Reports

Non-alcoholic fatty liver disease: A patient guideline

Sven M. Francque,[1,2,3,4,*] Giulio Marchesini,[5,6] Achim Kautz,[7] Martine Walmsley,[8] Rebecca Dorner,[7] Jeffrey V. Lazarus,[9] Shira Zelber-Sagi,[10,11] Kate Hallsworth,[12,13] Luca Busetto,[14,17] Gema Frühbeck,[15,17] Dror Dicker,[16,17] Euan Woodward,[17] Marko Korenjak,[18] José Willemse,[19] Gerardus H. Koek,[20,21] Shlomo Vinker,[22,23,24,25,26] Mehmet Ungan,[23] Juan M. Mendive,[27,28] Christos Lionis[28,29]

Clinical Practice Guidelines

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)

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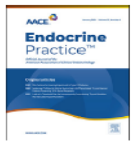


Clinical Practice Guidelines

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

Kenneth Cusi, MD, FACE, FACP, Co-Chair [1,*], Scott Isaacs, MD, FACE, FACP, Co-Chair [2], Diana Barb, MD, ECNU [3], Rita Basu, MD [4], Sonia Caprio, MD [5], W. Timothy Garvey, MD, MACE [6], Sangeeta Kashyap, MD [7], Jeffrey I. Mechanick, MD, ECNU, MACE, FACP, FACN [8], Marialena Mouzaki, MD, MSc [9], Karl Nadolsky, DO, FACE, DABOM [10], Mary E. Rinella, MD, AASLD Representative [11], Miriam B. Vos, MD, MSPH [12], Zobair Younossi, MD, AASLD Representative [13]

POSITION STATEMENT 55

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

S. Francque[1,2], N. Lanthier[3], L. Verbeke[4], H. Reynaert[5], C. Van Steenkiste[6,7], L. Vonghia[1,2], W. J. Kwanten[1,2], J. Weyler[1,2], E. Trépo[8], D. Cassiman[5], F. Smets[9], M. Komuta[10], A. Driessen[11], E. Dirinck[2,12], E. Danse[13], B. Op de Beeck[14], E. van Craenenbroeck[15], Y. Van Nieuwenhove[16], G. Hubens[17], A. Geerts[4*], C. Moreno[8*]

Management

- Diagnosis
- Monitoring
  - Follow-up
- Treatment
  - Assessment of treatment response

Diagnosis

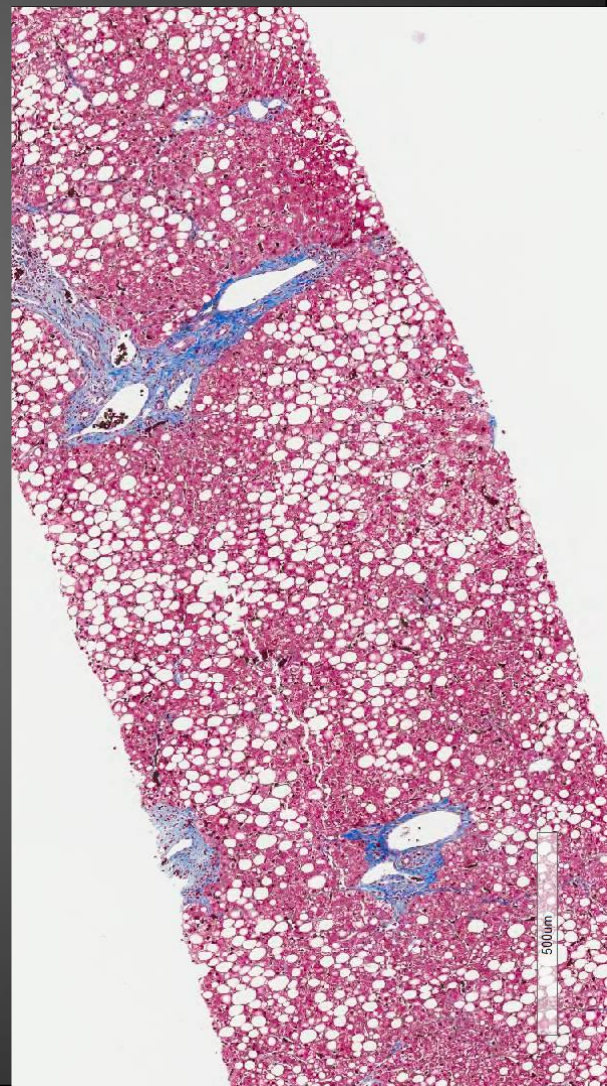
Diagnosis of what?

- Steatosis?
  - Severity?
- NASH
  - Presence or absence
  - Severity/activity?
- Fibrosis
  - Precise stage?
  - Significant (F2 or more)?
  - Advanced (F3 or more)?
  - Cirrhosis

- NASH is the driver of disease progression
- Fibrosis is the consequence of active disease
- Fibrosis is the most important predictor of prognosis
- Changes in NASH activity correlate with evolution of fibrosis over time
- Improvement in fibrosis correlates with improved clinical outcomes

Diagnosis
NITs

- Steatosis
  - Different modalities:
    - US, CAP, MRI (MRS, MR PDFF)
- NASH
  - No good biomarkers
  - cT1?
- Fibrosis
  - Serumbiomarkers
    - NFS, FIB4, ELF, Pro-C3, FibroTest…
  - Liver stiffness
    - VCTE, shear wave elastometry…
    - MRE



Variability of NITs

Elastometry

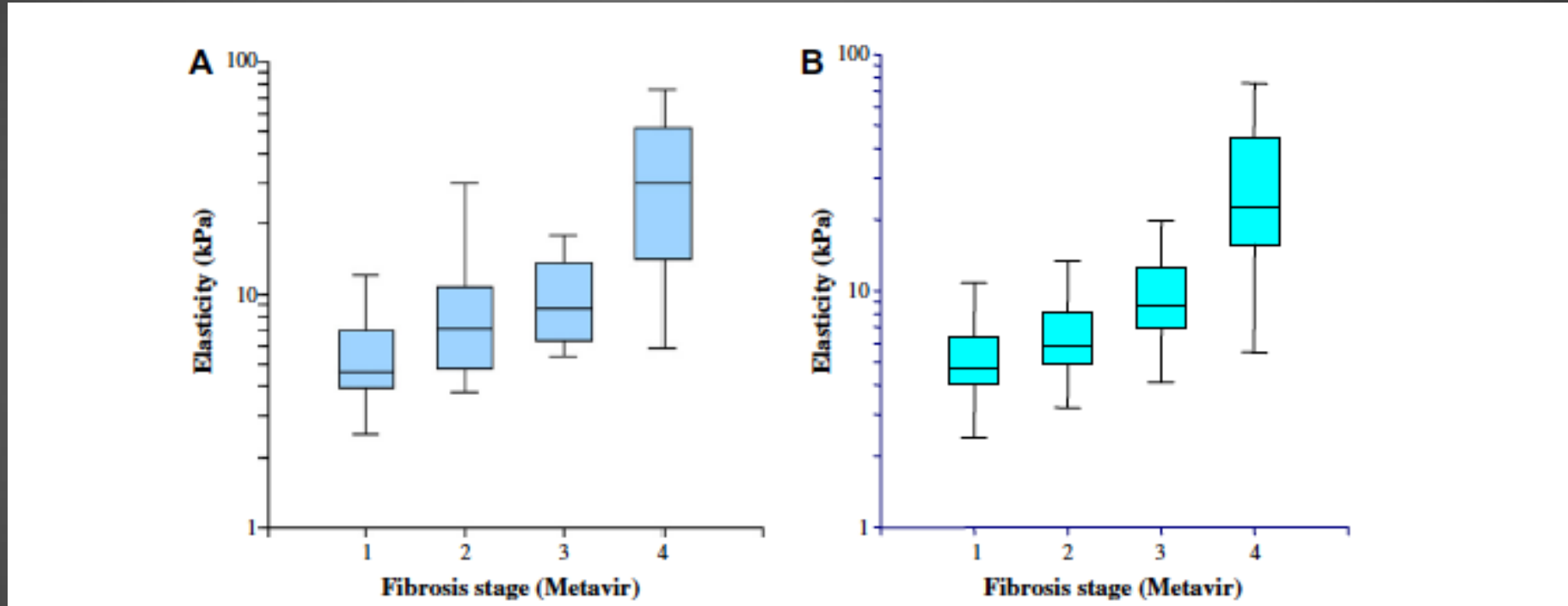
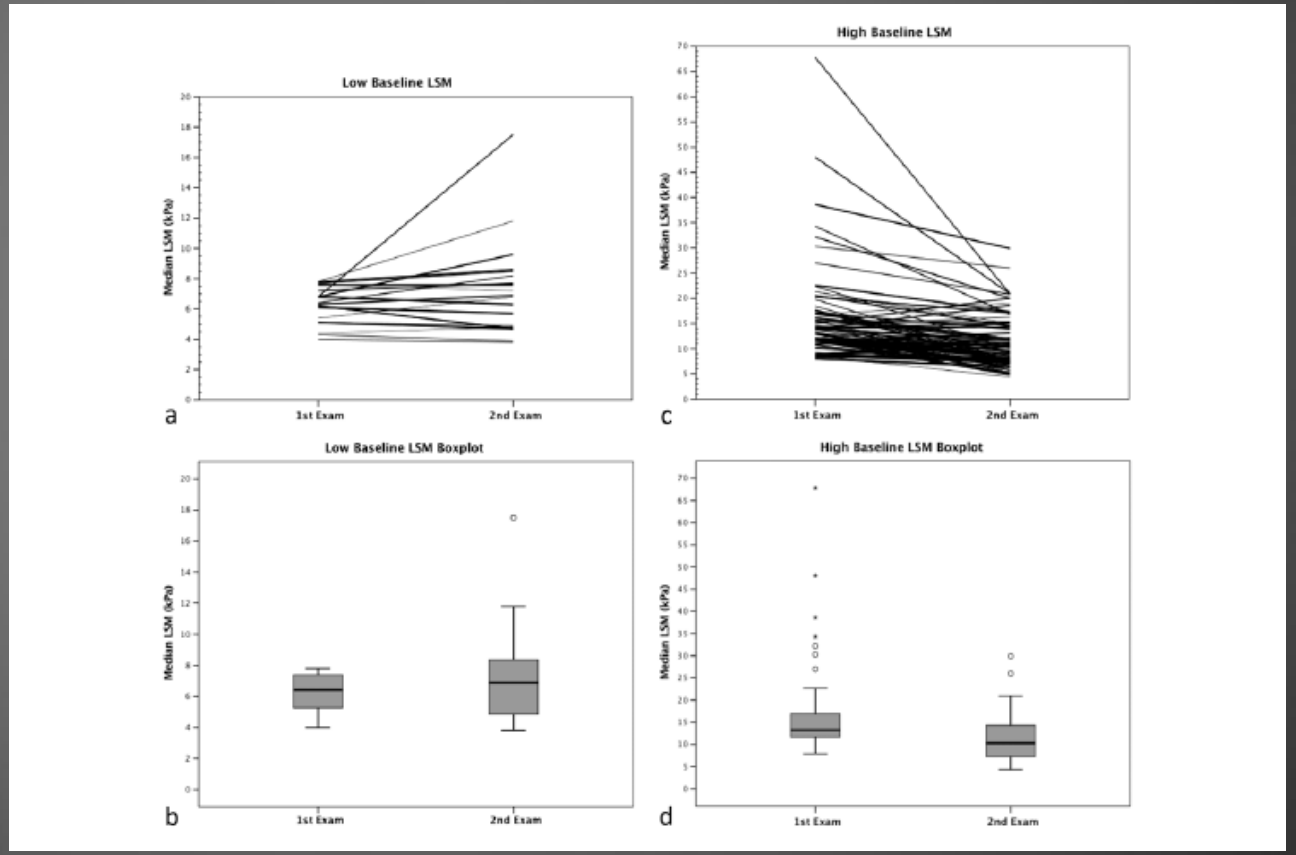


Fig. 3. Box-plots of liver stiffness values for each fibrosis stage (Metavir). Because of the wide range of FS values for *F4*, the vertical axis is in logarithmic scale. Adapted from (A) Ziol et al. [18] and (B) Castera et al. [17].

Castera *et al*. J Hep 2008

VCTE repeated measurements

- 1/3 of elevated values not confirmed upon repeat exam



Chow *et al*. JCGH 2019

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Within subjects variation of ALT

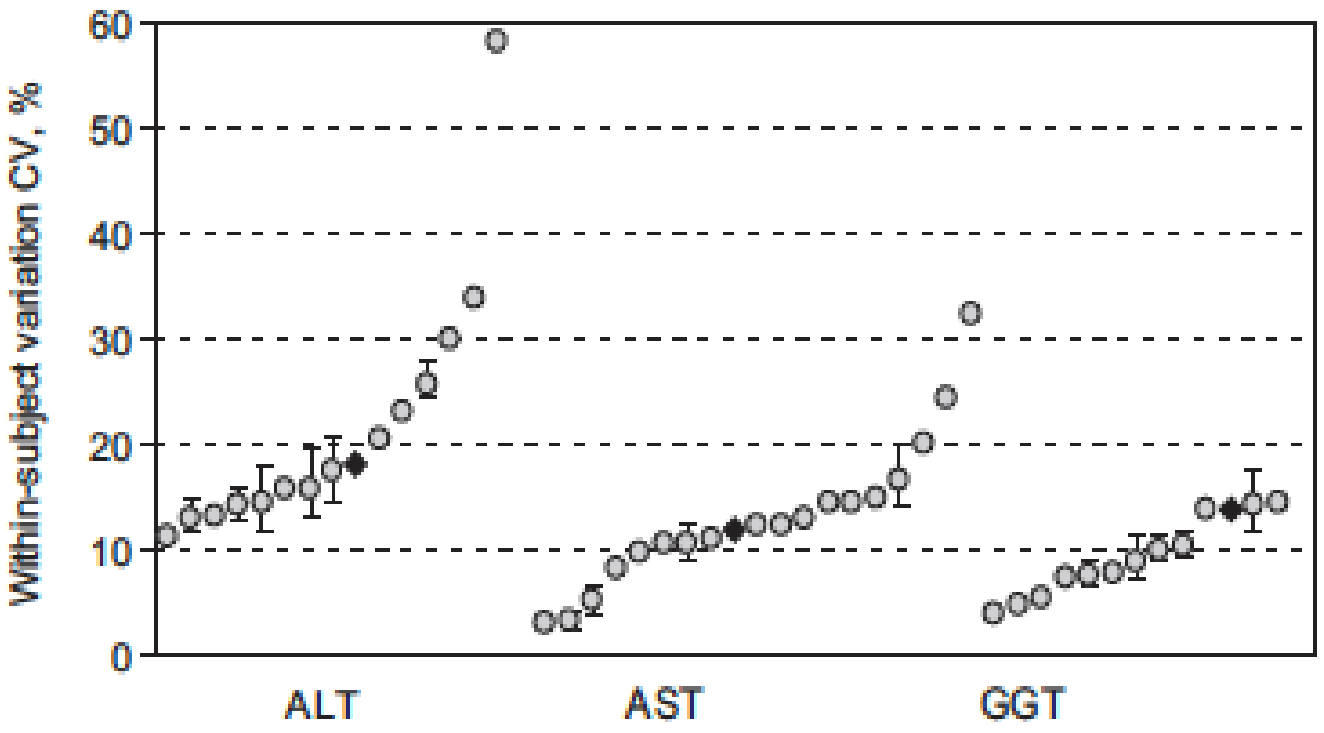
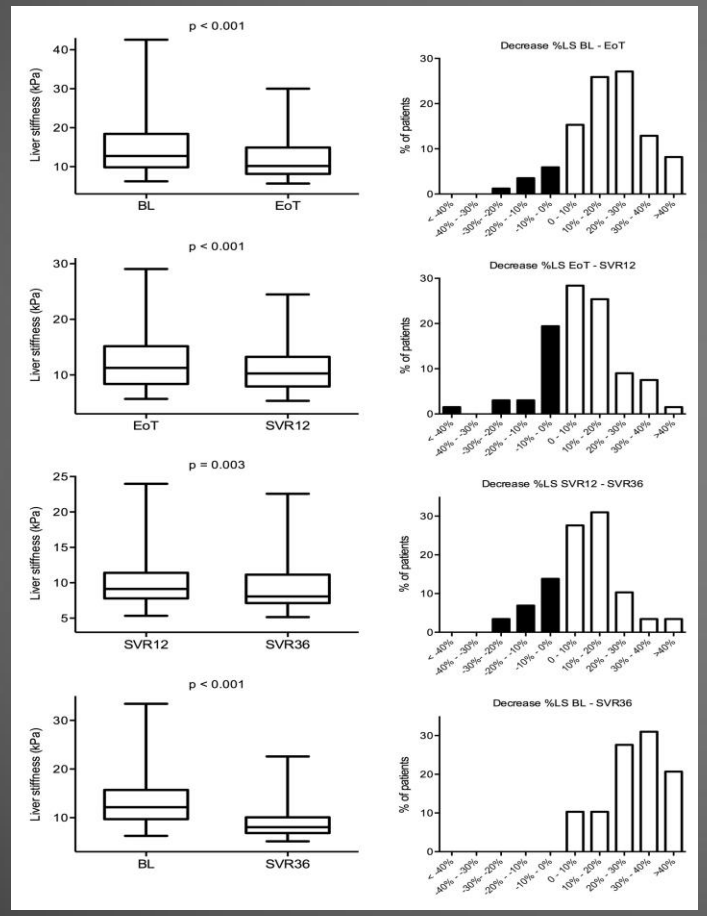


Figure 1 CV, % within-subject from the papers found ± CI (where available).

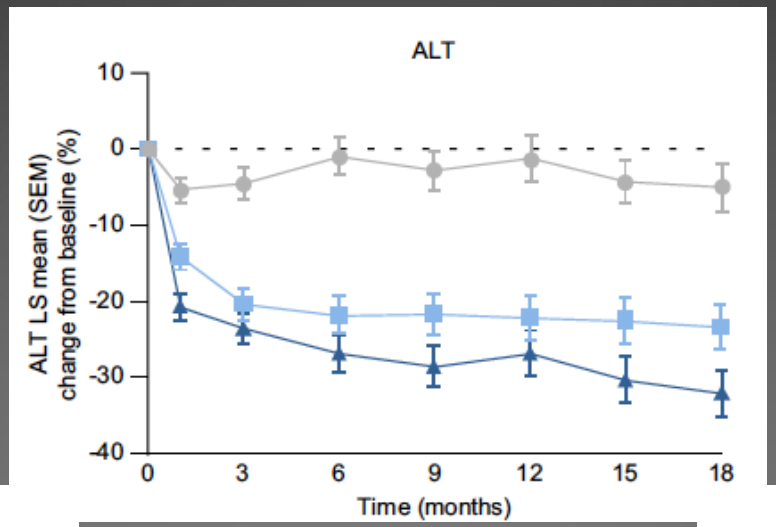
Carbone *et al*. Clin Chem Lab Med 2013

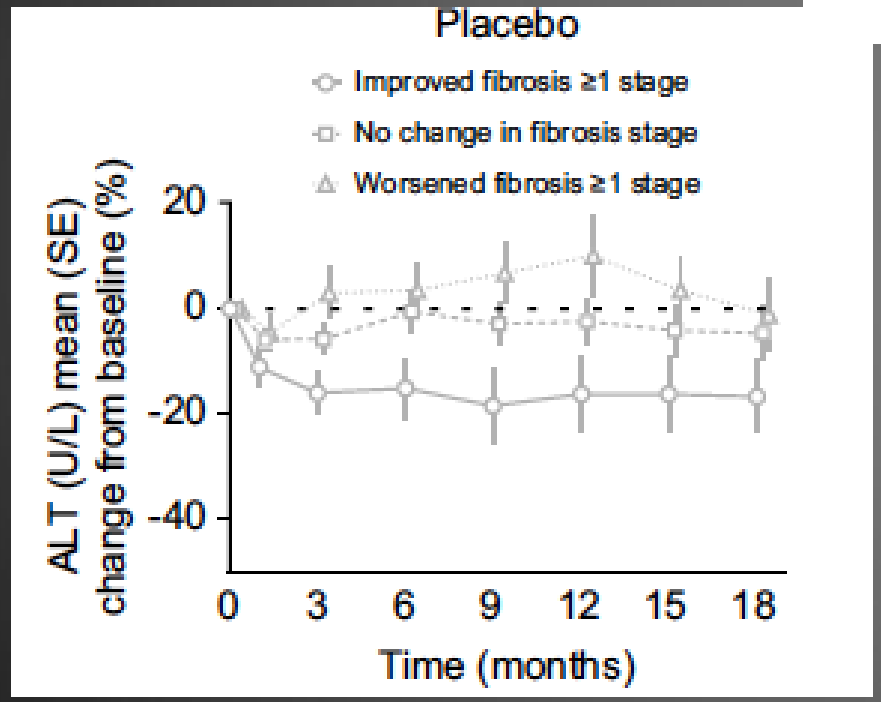
Changes in NITs over time

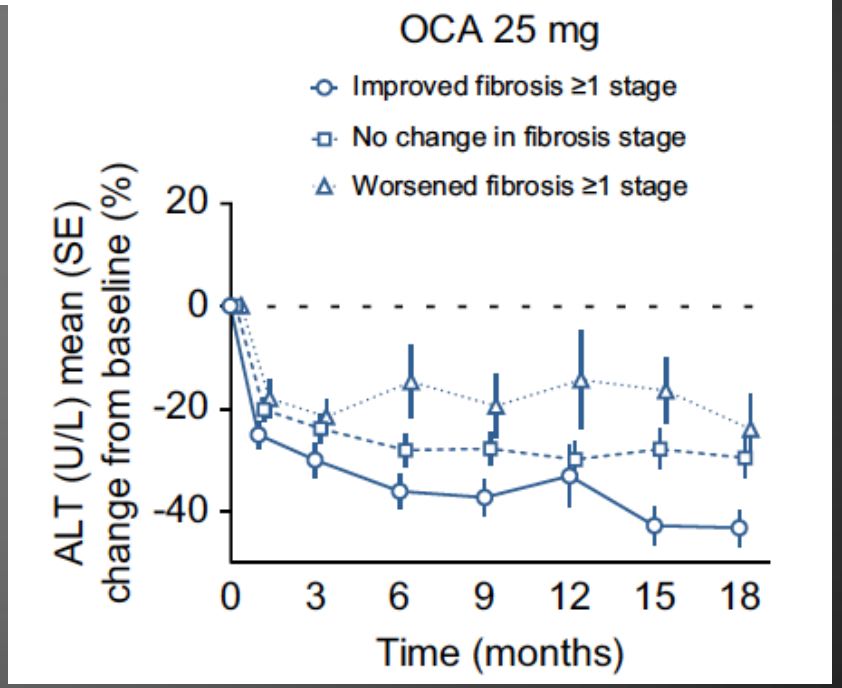
Liver stiffness and antiviral treatment



Verlinden, Francque *et al*. Hepatology 2016

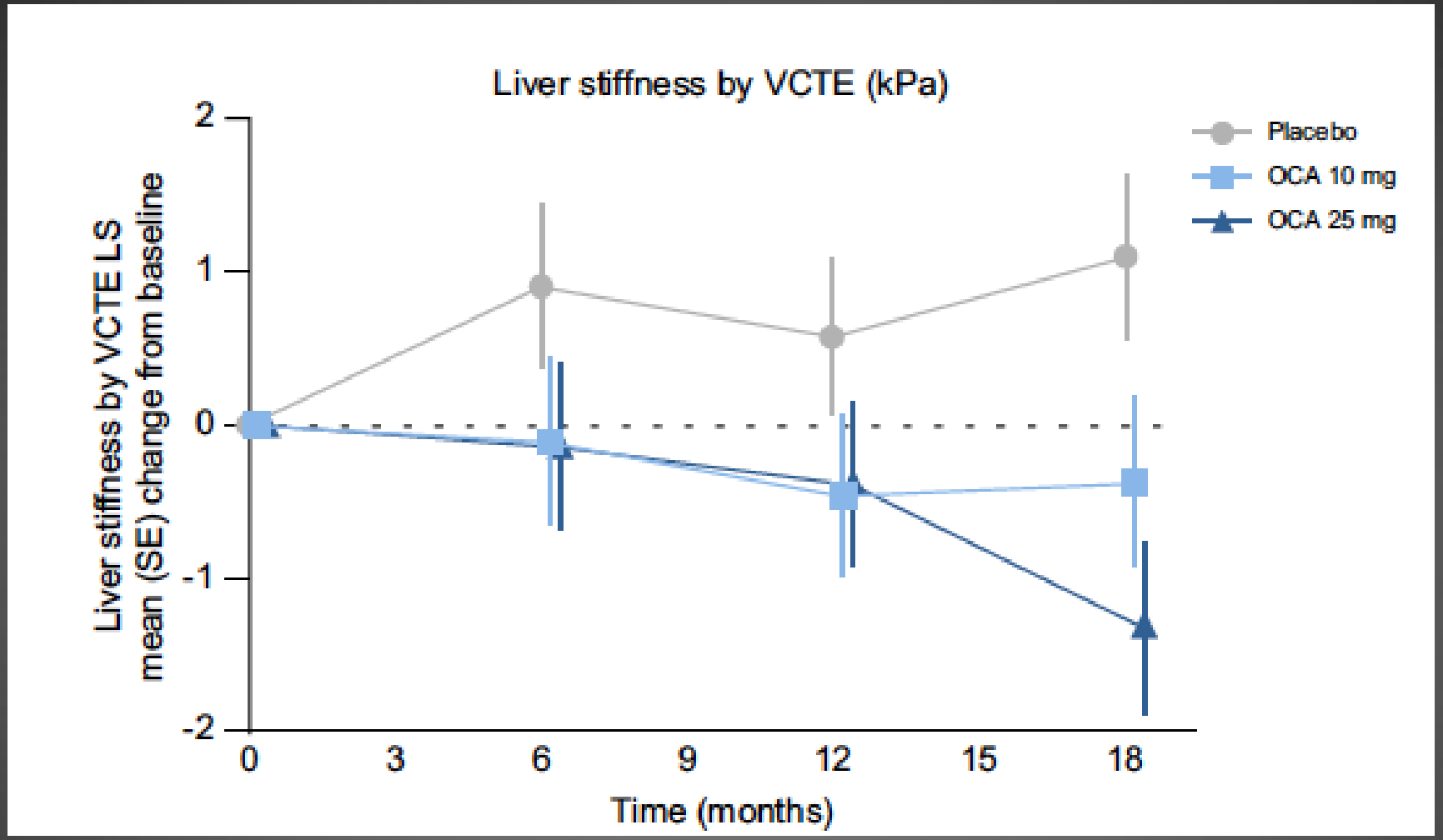




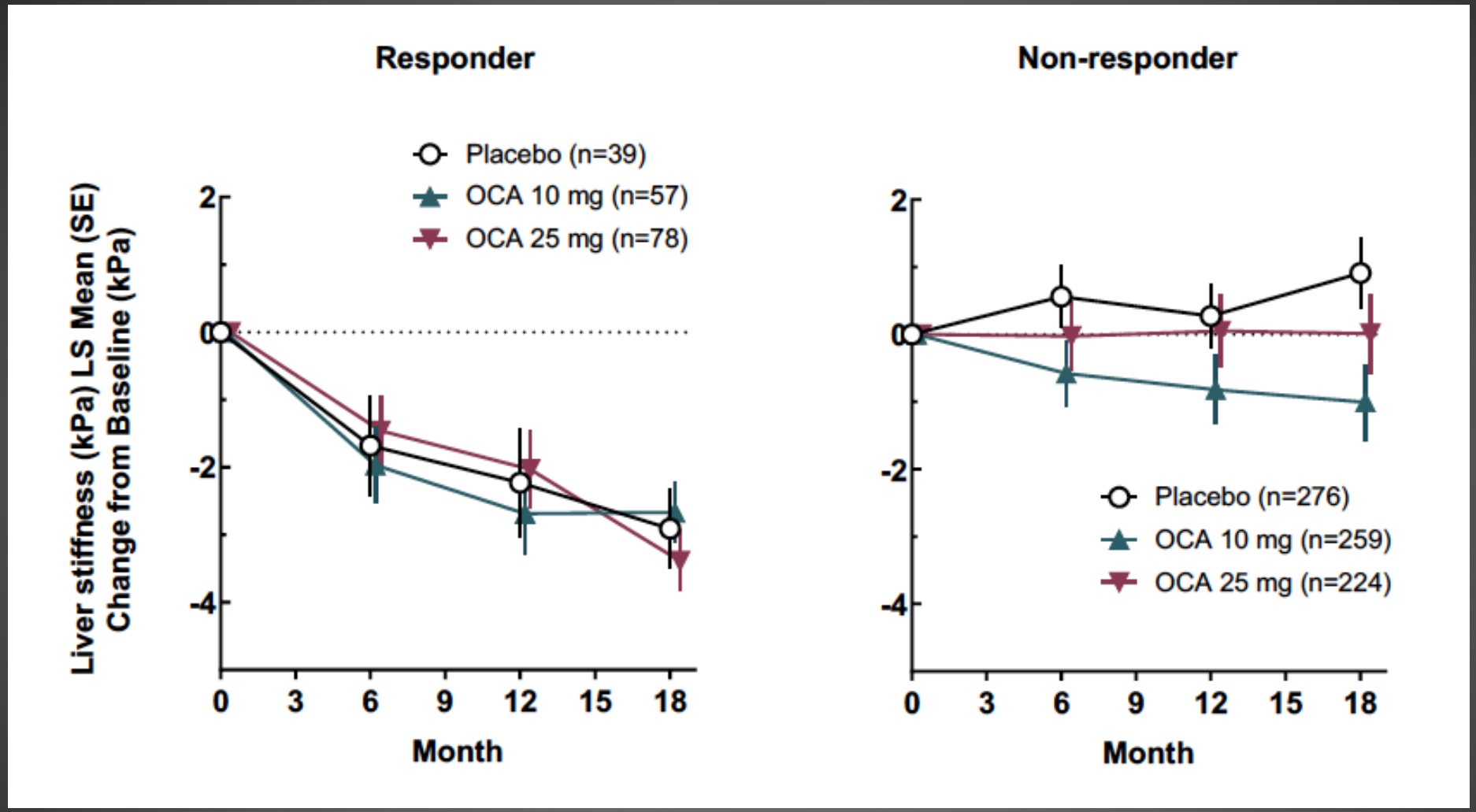


Rinella *et al*. J Hep 2022

Dolce La Hulpe 2022



Rinella *et al*. J Hep 2022



Anstee, Francque *et al.* AASLD 2019

Concept

- You need a combination of tests to indicate that fatty liver is associated with damage and inflammation and hence risk of progressive disease
  - Can include histology
- You need a change in a combined set of tests pointing towards the same direction to conclude on improvement
  - Can include histology
  - Exact criteria/endpoints still to be defined

NITs and prognosis

- Data on prognostic value of NITs
  - Liver stiffness, Shili-Masmoudi *et al*. Liv Int 2020
  - ELF, Trembling *et al*. BMC Gastroenterol 2020
  - …
- NIT predicts prognosis = NIT improvement means improved prognosis

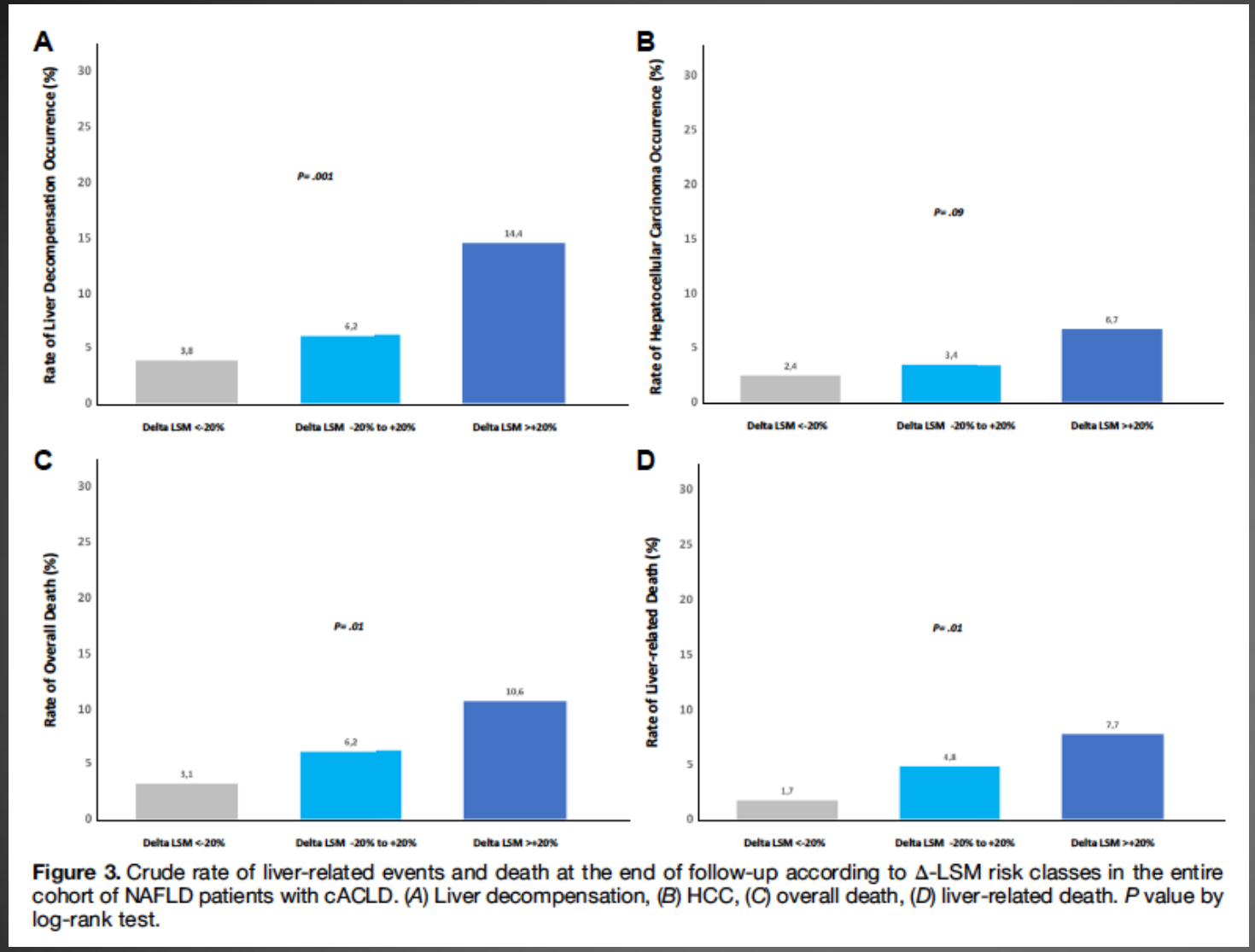


Figure 3. Crude rate of liver-related events and death at the end of follow-up according to Δ-LSM risk classes in the entire cohort of NAFLD patients with cACLD. (*A*) Liver decompensation, (*B*) HCC, (*C*) overall death, (*D*) liver-related death. *P* value by log-rank test.

Petta *et al*. CGH 2020

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- 50% of patients with liver events had persistently low FIB-4
- 1/3 of the population had intermediate or high FIB-4 at one of the tests

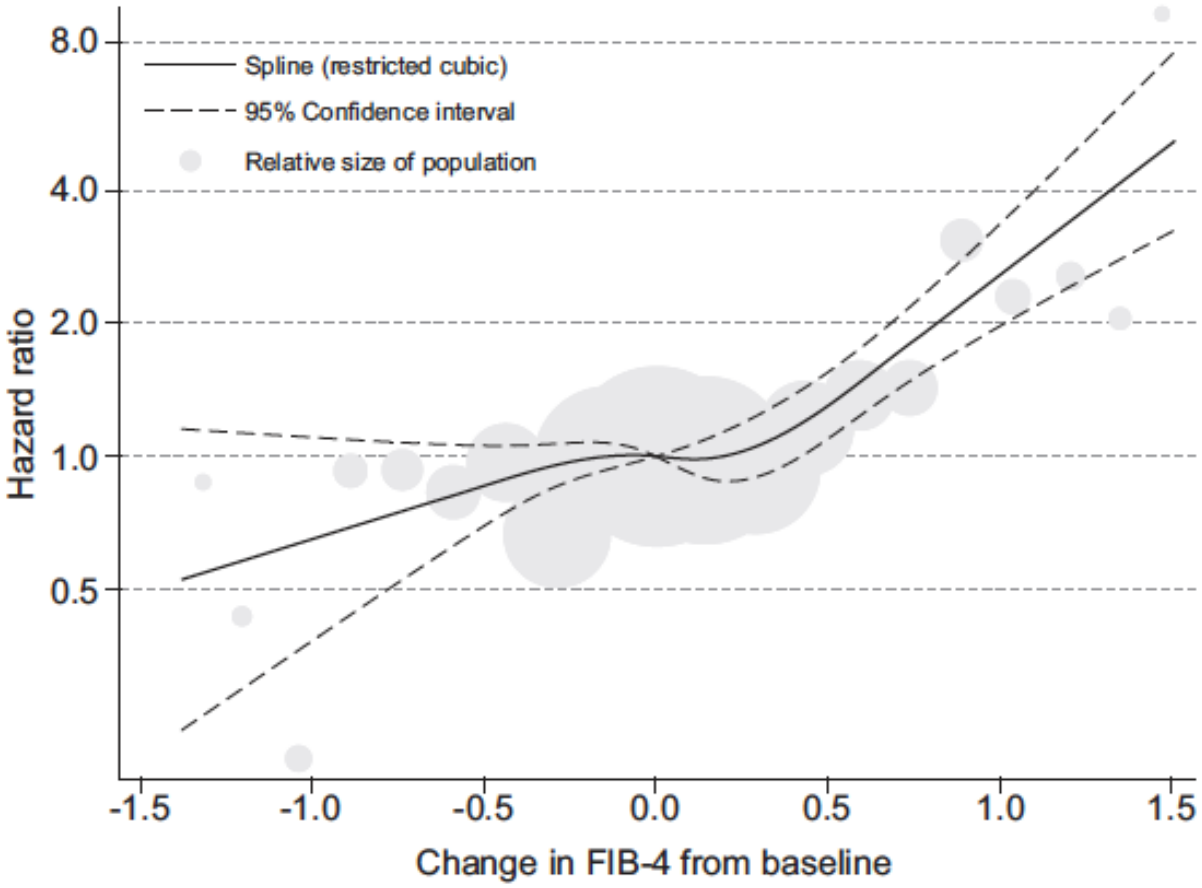
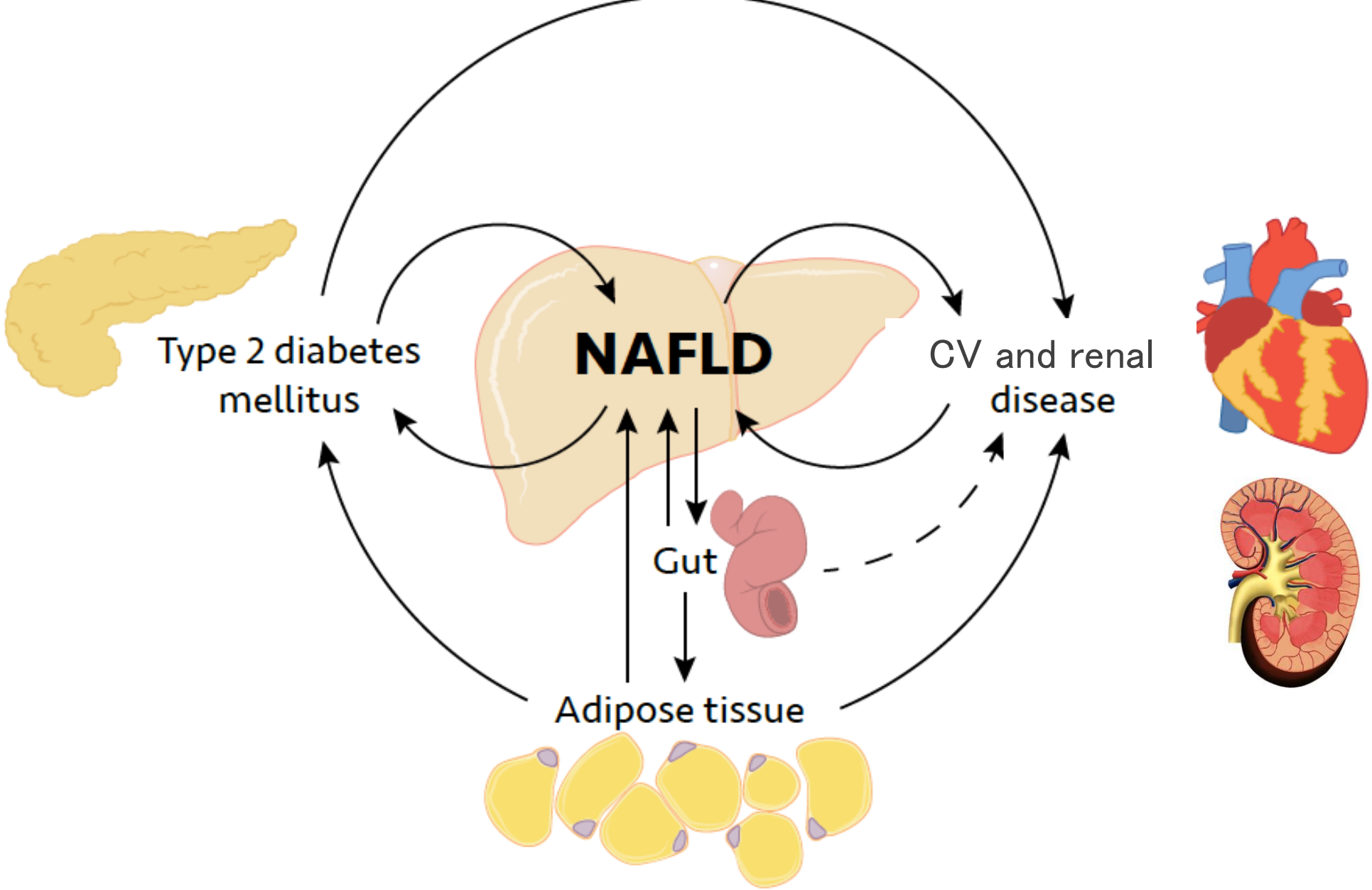


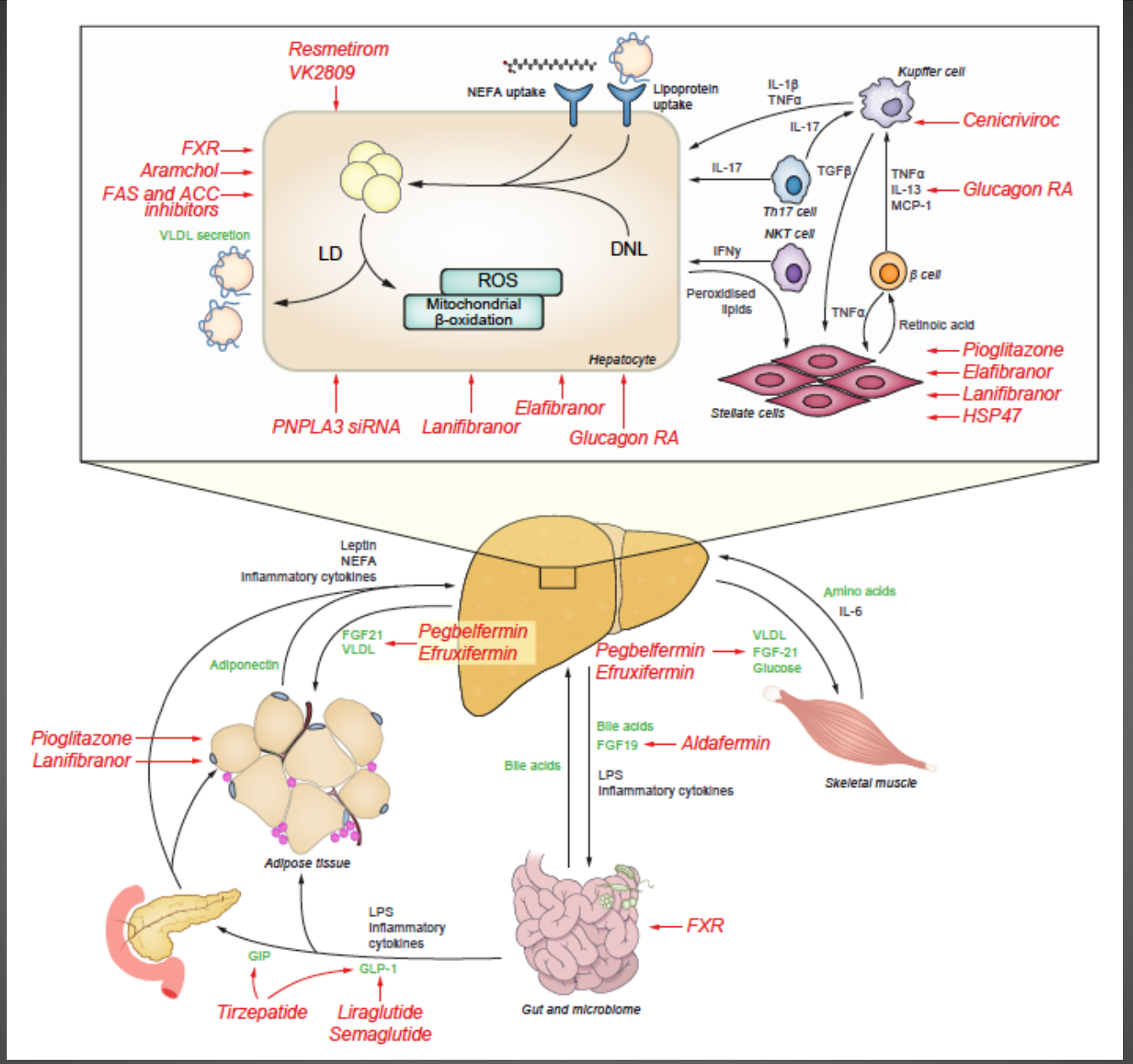
Fig. 2. Restricted cubic spline reflecting the risk of severe liver disease and change in the FIB-4 between 2 time points. FIB-4, fibrosis-4 index.

Hagström *et al*. J hep 2020

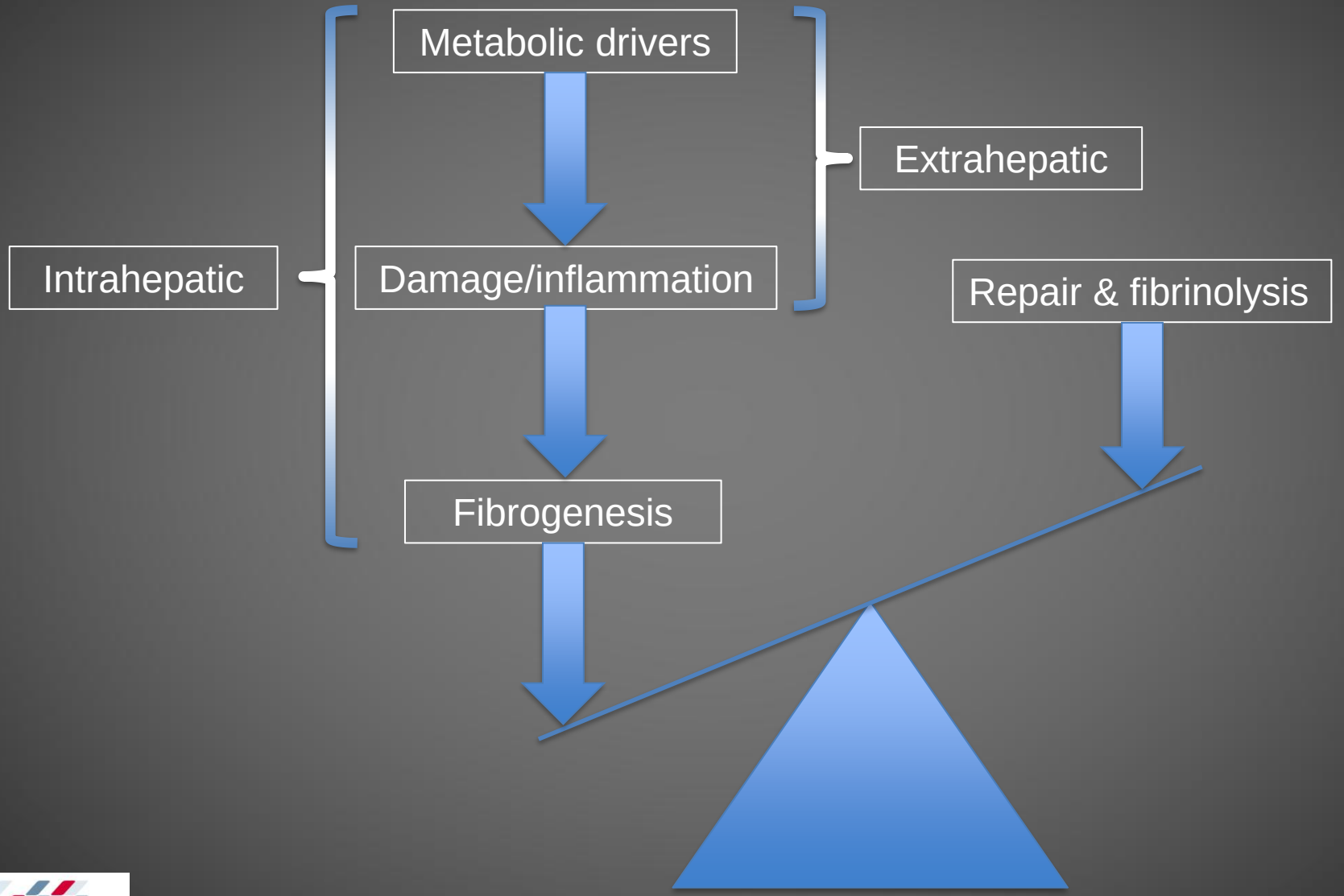
Treatment of NAFLD
General concepts



Adapted from Francque *et al.* J Hep 2016



Haas, Francque & Staels. Ann Rev Physiol 2016
Francque & Vonghia. Advances in Therapy 2019
Ratziu, Francque, Sanyal. J Hep 2022



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Francque *et al*. J Hep Rep 2021

Management of NAFLD
Current treatment options

Co-morbidities

- Patients with NAFLD should be checked for cardiometabolic co-morbidities
- If identified: should be appropriately treated according to corresponding guidelines
- Some drugs (statins, aspirin) also have beneficial effects on liver

NASH specific treatment

- Indication
  - NASH + NAS 4 + F2
- Biopsy?

- Goals
  - Resultion of NASH
  - Regression of fibrosis
  - Combination of both

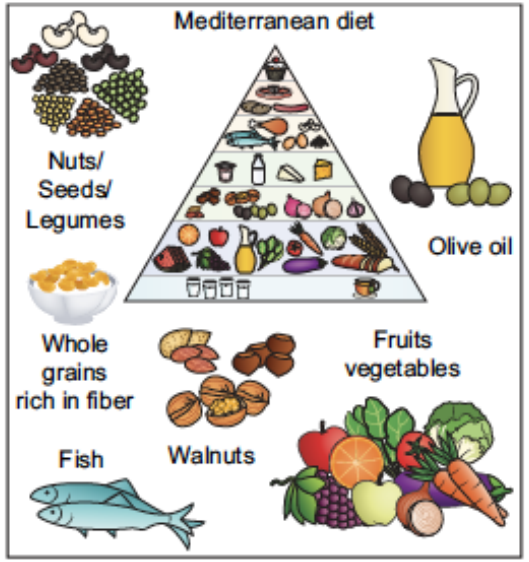
NASH specific treatment

- With proven benefit
  - Life style modification and weight loss
    - Including bariatric surgery and endoscopic procedures
  - Vit E
  - Pioglitazone
  - GLP-1 RA: liraglutide, semaglutide
  - Pipeline of drugs in development

	Overweight/obesity NAFLD	Non-obesity NAFLD
Weight reduction	• The more severe the liver disease is, the higher the goals are in terms of weight loss • Healthy diet with caloric restriction tailored for your preferences	• 3-5% reduction of weight even within the normal BMI range (especially if recent weight gain occurred or if abdominal obesity is present)

Lifestyle advice for ALL patients with NAFLD

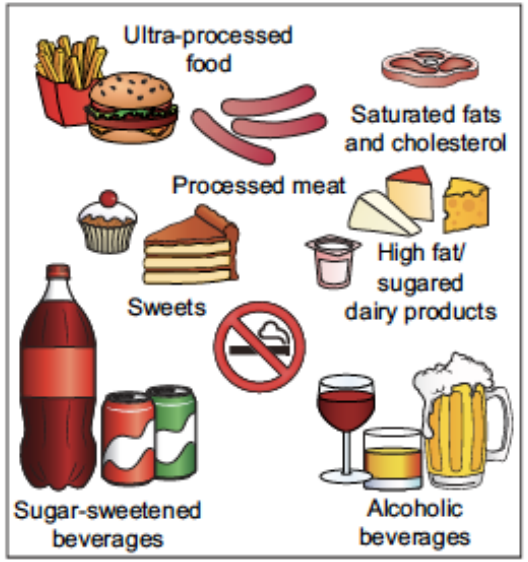
Recommended foods



Recommended activity

- Mental well being management
- Aerobic exercise ≥3 days/week (≥150 min/week moderate intensity)
- Resistance exercise ≥2 days/week
- Reduce sedentary behaviour

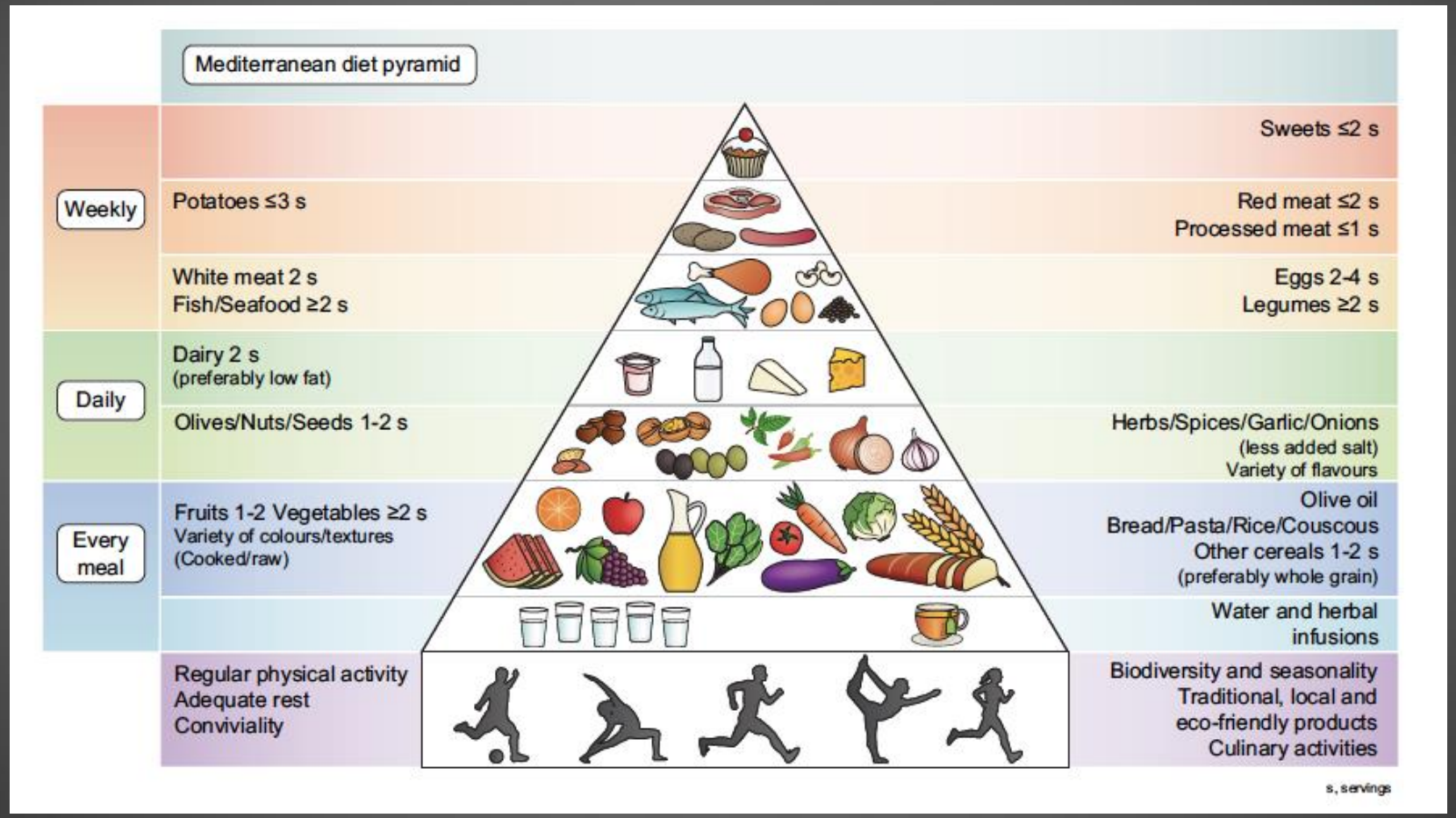
Non-recommended foods/ Minimize consumption



- Reduce added sugar (*e.g.* by reducing sweets, processed foods, sugared dairy products, *etc.*)
- Avoid sugar-sweetened beverages
- Reduce saturated fat and cholesterol (*e.g.* by eating low fat meat and low fat dairy products)
- Increase n-3 fatty acids found in fish, and walnuts; utilize olive oil over other oils more often
- Minimize "fast food" and ultra-processed food
- Home-cooked meals are preferable
- Try to follow the Mediterranean dietary pattern

Francque *et al*. J Hep Rep 2021

Life style modification and weight loss



Francque *et al*. J Hep Rep 2021

Guidance statement : There is no safe limit for alcohol consumption. Abstinence or a limit of max. 14 units/week is recommendable, and patients should be instructed on the impact of alcohol on caloric consumption and efficacy of physical training.

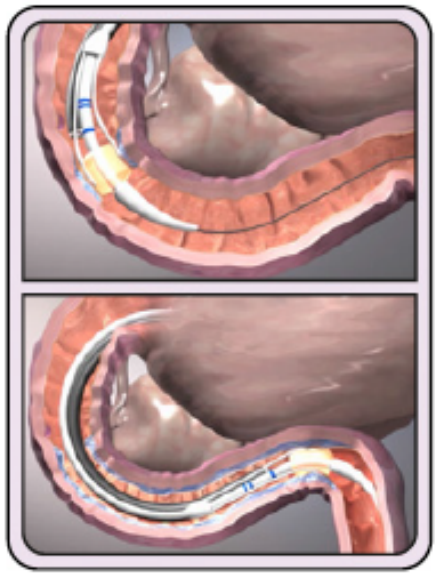
Francque *et al*. Acta Gastroenterol Belg 2018

Bariatric surgery

- GABY, sleeve, gastric balloon
  - Improve liver histology
  - If advanced fibrosis at baseline
    - 50% remain in the advanced fibrosis state
    - Despite NASH resolution
- Weight loss and beyond
- Take NAFLD into consideration when discussing indication for bariatric surgery
- Bariatric surgery in NASH cirrhosis
  - Refer to specialised centres

Lasaille *et al*. Gastroenterology 2015
Pais *et al*. AASLD 2019

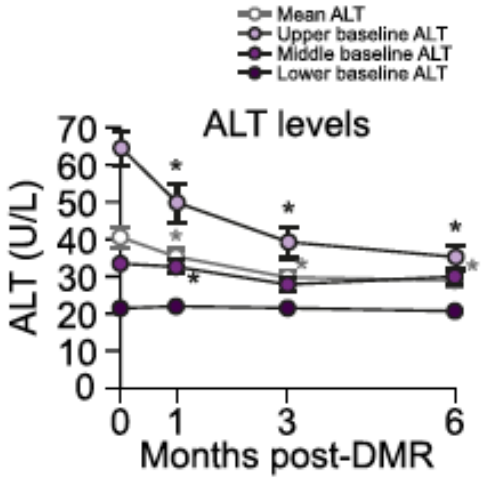
Endoscopic duodenal mucosal resurfacing (DMR)



Hydrothermal ablation of the duodenum by DMR elicits a metabolic benefit in patients with T2DM, manifesting as improvements in both glycaemic and hepatic indices

Reduced glycaemia
- ↓ HbA1c
- ↓ Fasting plasma glucose
- ↑ 1,5-AG

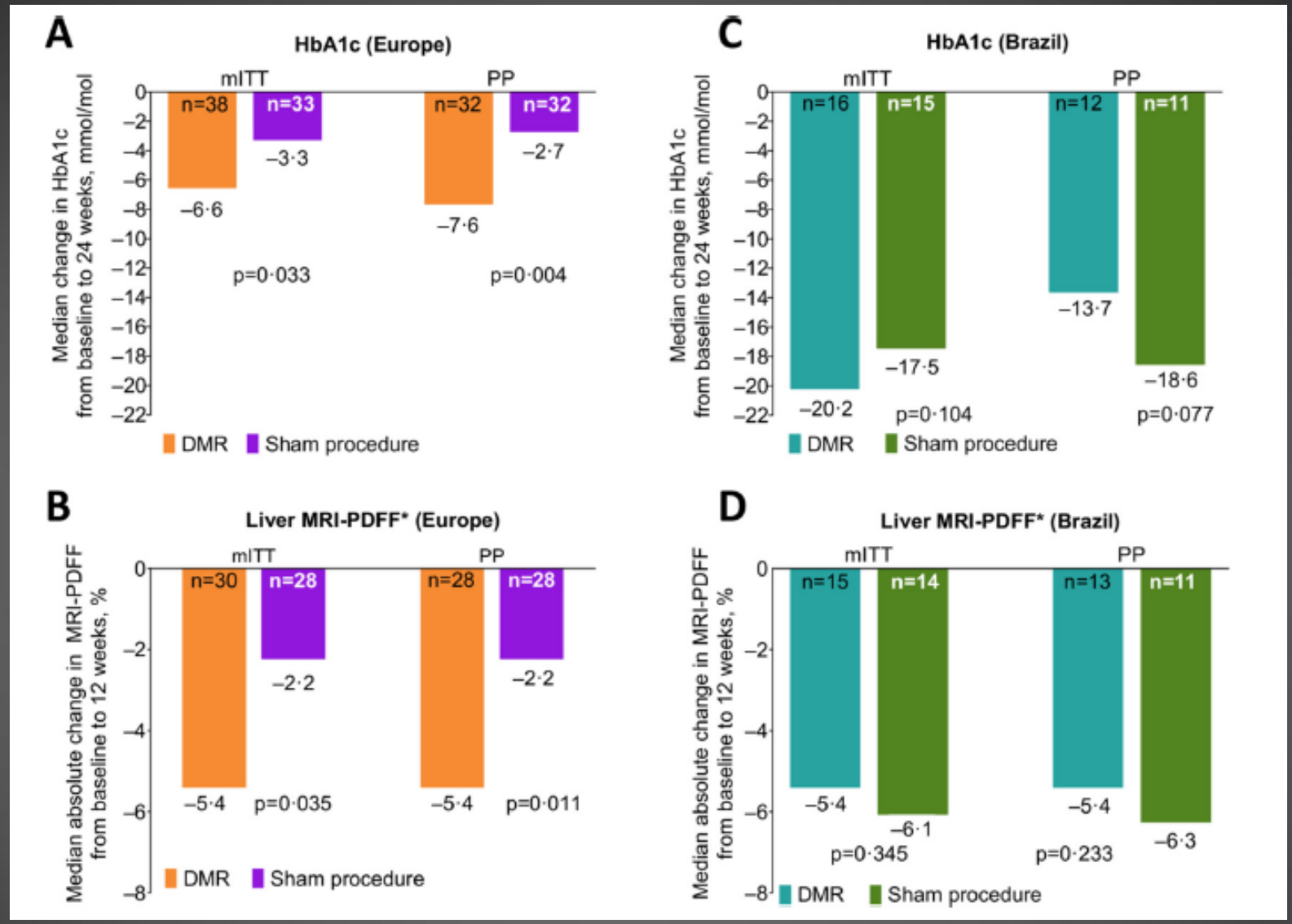
Improved hepatic indices
- ↓ ALT
- ↓ AST
- ↓ FIB-4



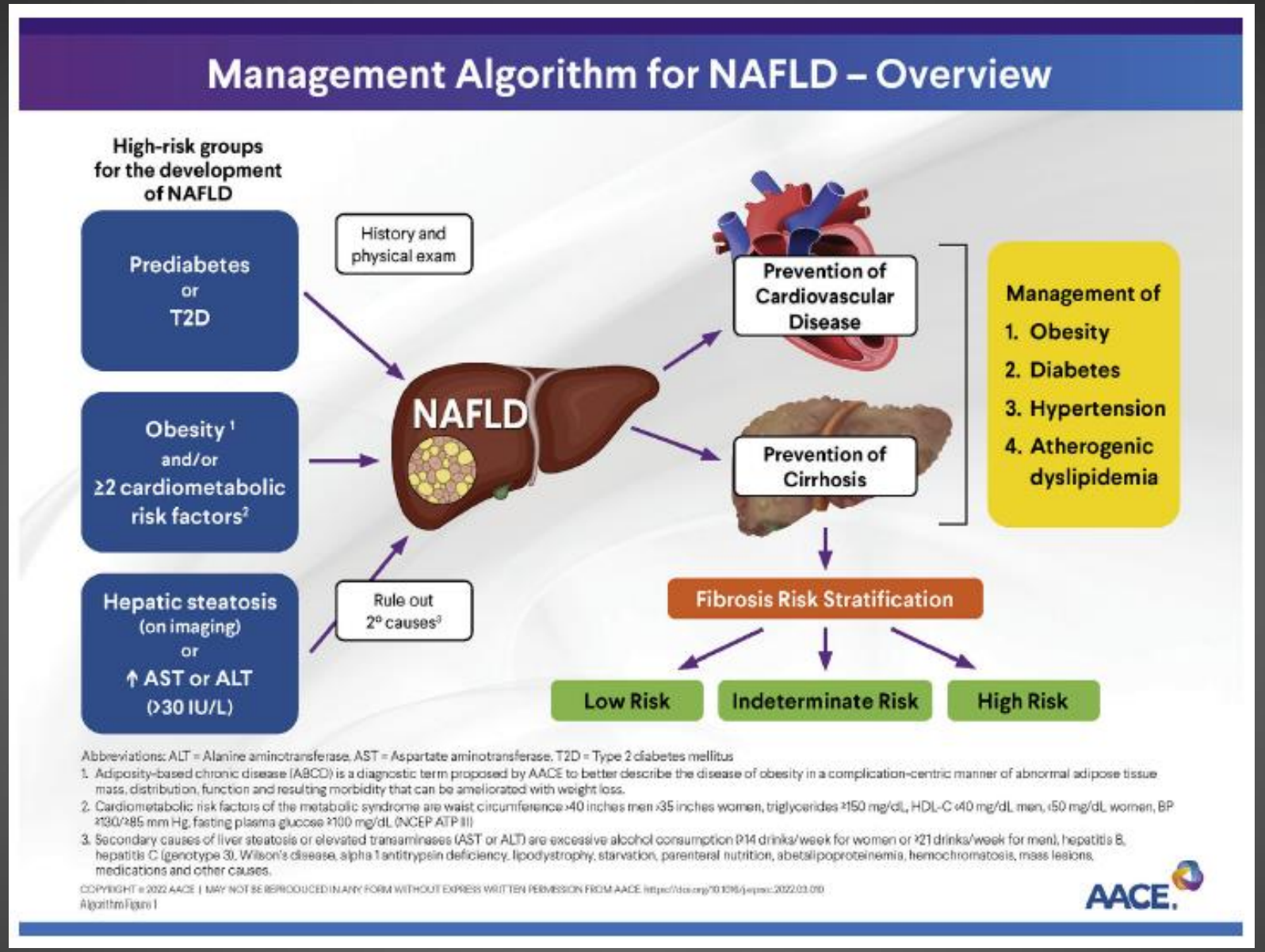
Insulin sensitizing
- ↓ HOMA-IR
- ↓ Lactate:Pyruvate ratio
- ↓ 2-Hydroxybutyrate

Improved metabolic parameters
- ↓ Lipids (TAGs, DAGs, FFAs)
- ↑ Anti-inflammatory (↓ leukotriene B4 & 5-HETE)
- ↑ Antioxidant capacity (↑ cysteine, glycine, glutathione)

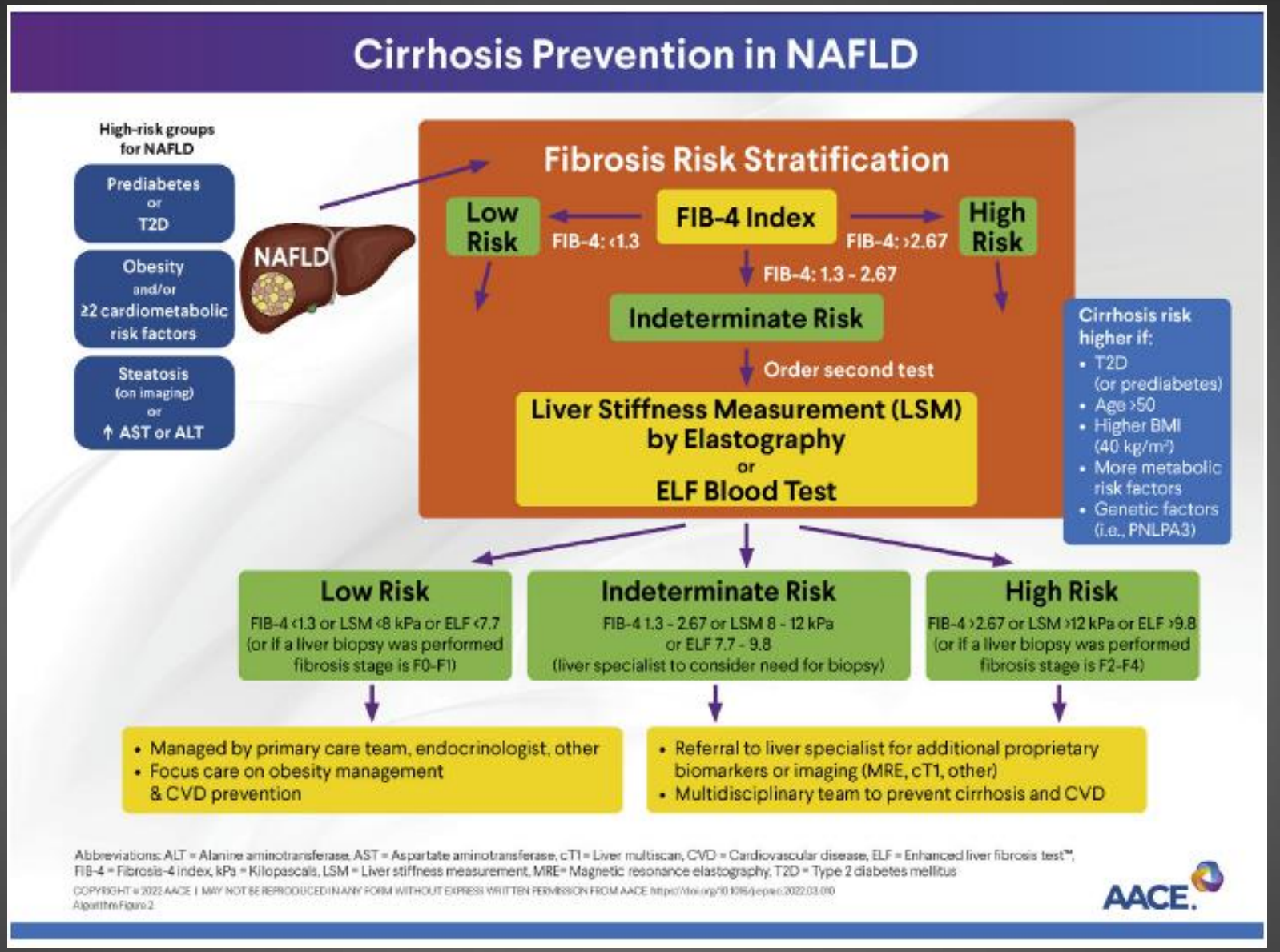
Van Baar *et al*. J Hep Rep 2019



Migrone *et al*. Gut 2021



Cusi *et al*. Endocrine Practice 2022



Cusi *et al*. Endocrine Practice 2022

Diabetes Management in NAFLD

Fibrosis Risk Stratification

	Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	High Risk[1] FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize glycemic control using preferred agents that reverse steatohepatitis, whenever possible. Prefer GLP-1 RA and SGLT2i in CVD. Prefer SGLT2i in CKD and HF.		
Dietary recommendations	Glycemic load reduction via emphasis on whole food carbohydrates (vegetables, legumes, fruit) versus sugar/processed carbohydrates.		
Individualize A1c target	≤6.5% for persons without concurrent serious illness and at low hypoglycemic risk (>6.5% otherwise).		In advanced cirrhosis[1], caution with risk of hypoglycemia and avoid oral agents[2]
Preferred diabetes pharmacotherapy	Consider agents that reduce liver fat (pioglitazone, GLP-1 RA, SGLT2i).	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No evidence that SGLT2i improve steatohepatitis.	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No efficacy data in cirrhosis.
Metformin, sulfonylurea, DPP-4i, acarbose and insulin	May continue but limited benefit on liver histology in NAFLD.	May continue but limited benefit on liver histology in NAFLD.	May continue (F2-F3) but avoid oral agents if advanced cirrhosis present. Cannot avoid insulin in patients with advanced liver cirrhosis – often only option

Abbreviations: CKD = Chronic kidney disease, CVD = Cardiovascular disease, DPP-4i = Dipeptidyl peptidase 4, GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HF = Heart failure, NASH = Nonalcoholic steatohepatitis, SGLT2i = Sodium-glucose cotransporter-2 inhibitors.

1. Advanced cirrhosis is defined as persons with cirrhosis based on biopsy and Child class B or C with clinical evidence of comorbidities (varices, portal hypertension, ascites, etc.).
2. Limited data on oral diabetes medications and GLP-1 RA in persons with cirrhosis. Avoid metformin, GLP-1 RA appear safe, insulin preferred. Avoid oral agents in advanced cirrhosis.
3. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

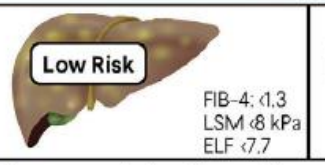
Algorithm Figure 4

AACE.

Cusi *et al*. Endocrine Practice 2022

Weight Management in NAFLD

Fibrosis Risk Stratification



FIB-4: <1.3
LSM <8 kPa
ELF <7.7

FIB-4: 1.3 - 2.67
LSM 8 - 12 kPa
ELF 7.7 - 9.8

FIB-4: >2.67
LSM >12 kPa
ELF >9.8

General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[2]	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liraglutide 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH.[3,4]	GLP-1 RA preferred for NASH.[3,4]
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.

Abbreviations: GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HCC = Hepatocellular carcinoma, NASH = Nonalcoholic steatohepatitis

1. Persons with confirmed cirrhosis based on biopsy or high likelihood based on LSM >13.6kPa from vibration controlled transient elastography (FibroScan®), ELF ≥9.8 or >5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM >20 kPa or platelet count of <150,000/mm^3.
2. These goals should only be taken as a broad guidance. NAFLD/NASH may also improve by changes in macronutrient content, exercise and other factors beyond magnitude of weight loss. All high-quality studies available limited to a maximum of 12 month duration.
3. No high-quality evidence for pharmacotherapy in persons with NASH cirrhosis. Treatment should be individualized and used with caution only by liver specialists.
4. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

 https://doi.org/10.1016/j.eprac.2022.03.010
Algorithm Figure 3

AACE.

Cusi *et al*. Endocrine Practice 2022

Liver transplantation

- Increasing indication
- Patients
  - Older
  - Co-morbidities
    - Cardiovascular!!!
- Late but rapid deterioration
- Early thorough cardiovascular assessment
- Timely referral

How to monitor patients over time?

- Non-invasive tests
  - Steatosis
    - US, CAP, MRI (MRS, MR PDFF)
  - NASH
    - No accurate NITs
    - cT1?
  - Fibrosis

How to monitor patients over time?

- Non-invasive tests
  - Fibrosis
    - Serumbiomarkers
      - NFS, FIB4, ELF, Pro-C3, FibroTest…
    - Liver stiffness
      - VCTE, shear wave elastometry…
      - MRE
    - Variability!!!
      - Be careful with interpretation of changes in individual patient
- Cirrhosis (and F3?)
  - Every 6 months
  - Quality of US?

Conclusions

- Treatment of cardiometabolic co-morbidities should be optimised
  - Several drugs have interesting properties for NASH
- Life style modification & weight loss
  - Including bariatric/metabolic surgery and other interventions with impact on metabolism
- Pharmacological ttm for NAFLD
  - Currently only in biopsy proven NASH and some degree of fibrosis
  - Pioglitazone,Vit E, liraglutide, semaglutide
  - Large pipeline of drugs
- NITs
  - Combination needed for diagnosis and follow-up