

# FETGE GRAS METABÒLIC: COMORBIDITATS I TRACTAMENT

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# COMORBIDITATS HEPÀTIQUES

## FACTORS DE RISC

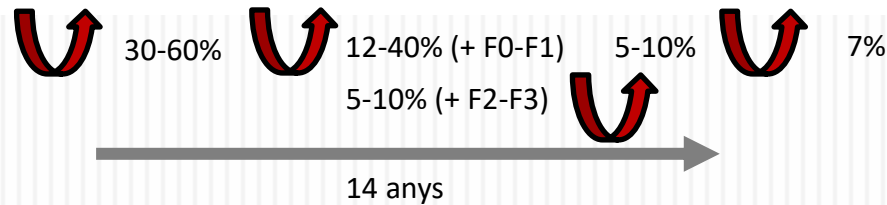
Obesitat  
Diabetis  
Dislipèmia  
Hipertensió arterial  
Síndrome metabòlica  
Resistència a la insulina  
Sexe masculí  
Edat

## MECANISMES

Estrès oxidatiu  
Peroxidació lipídica  
Citoquines proinflamatòries  
Disfunció mitocondrial  
Apoptosi  
Necro-inflamació

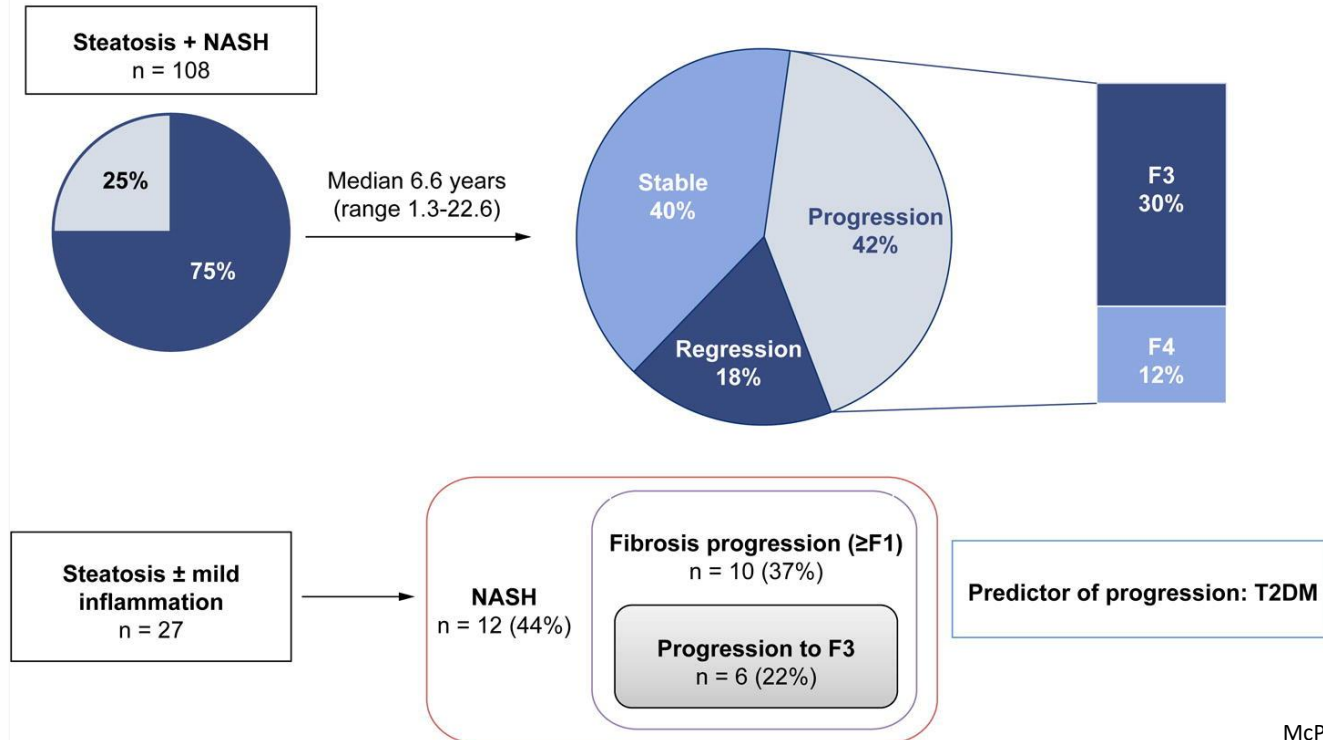


Imatge adaptada per Martínez-Escudé, A.

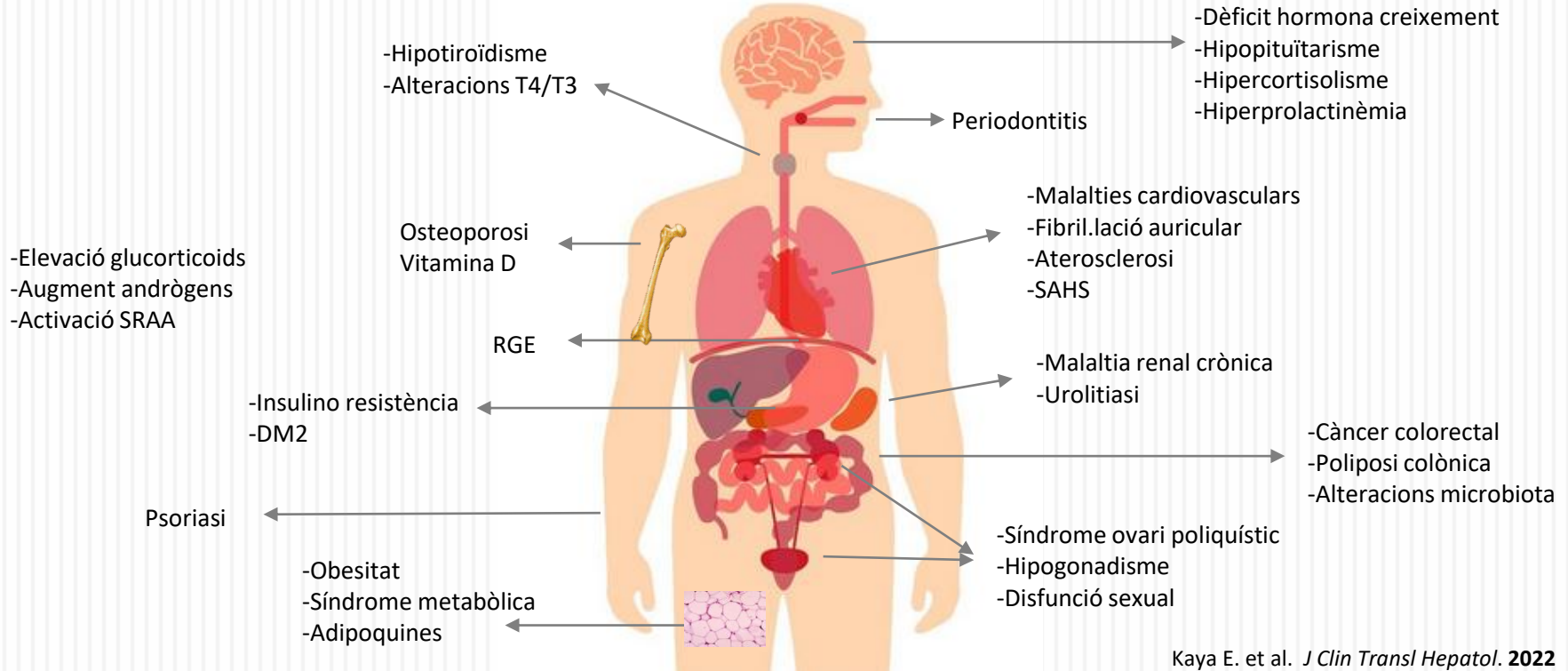


# PROGRESSIÓ DEL FGNA

## Histological progression of NAFLD in paired biopsies



# COMORBIDITATS EXTRAHEPÀTIQUES



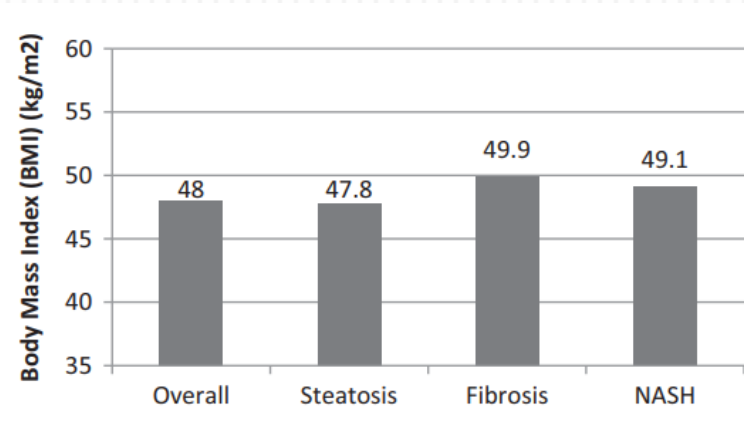
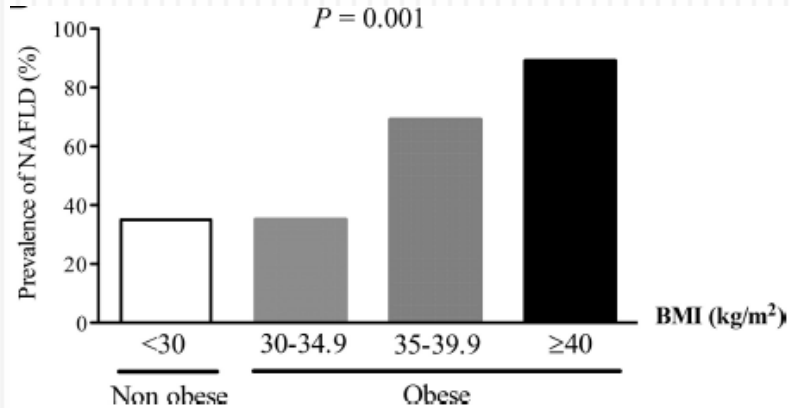
Imatge adaptada per Martínez-Escudé, A.

Kaya E. et al. *J Clin Transl Hepatol.* **2022**

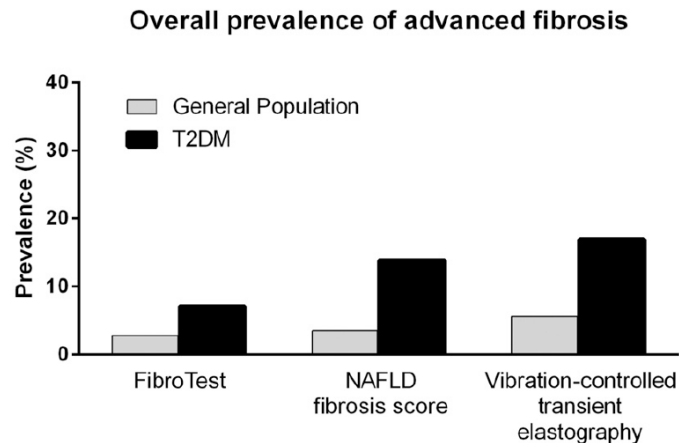
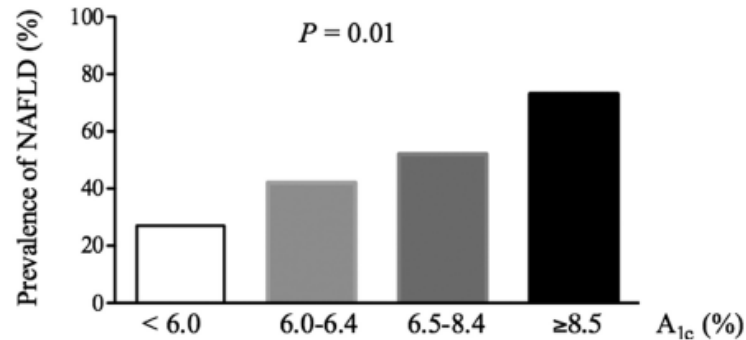
Rosato V. et al. *Int J Environ Res Public Health.* **2019**

Marino L et al. *World J Gastroenterol.* **2015**

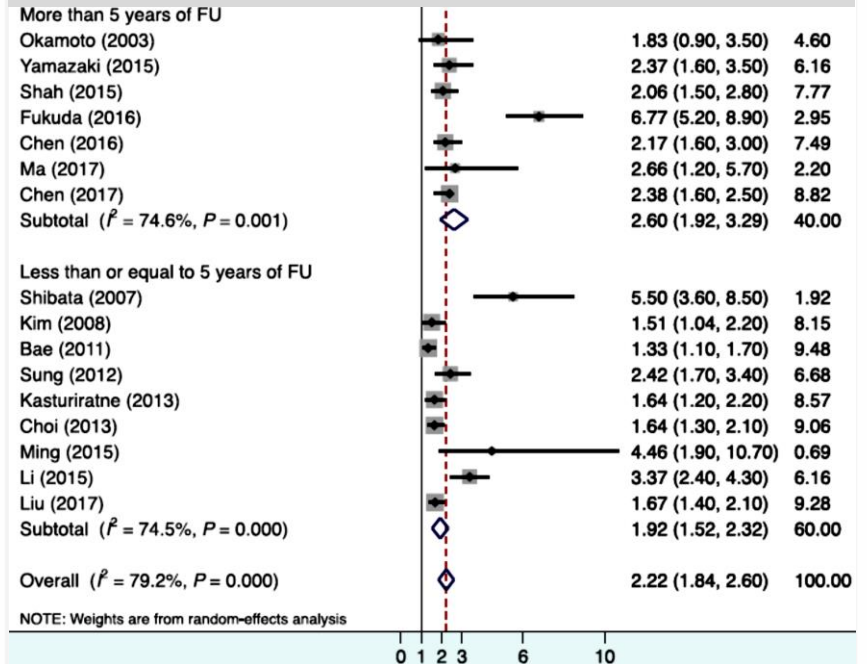
# COMORBIDITATS: OBESITAT



# COMORBIDITATS: DIABETIS



## Risc de DM2 incident en pacients amb FGNA



Mantovani A. et al. *Diabetes Care*. 2018

Bril F. et al. *Diabetes Care*. 2017

Portillo-Sanchez P. et al. *J Clin Endocrinol Metab*. 2015

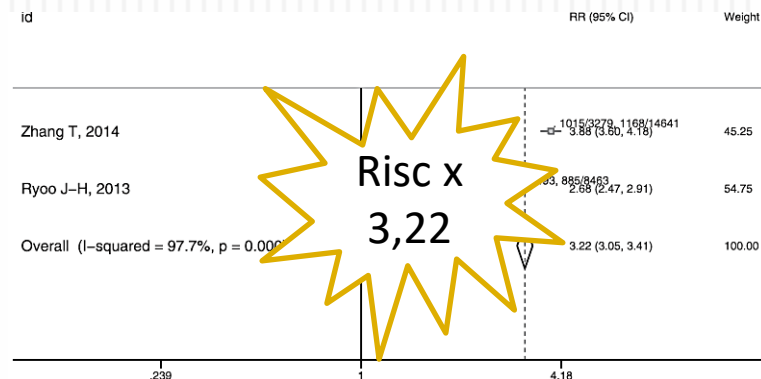
# COMORBIDITAT: SÍNDROME METABÒLICA

Els components de la SM són un factor de risc pel FGNA (1) i/o la fibrosi hepàtica (2)

|  | OR   | p      |
|--|------|--------|
| 1  |      |        |
| Obesidad central (perímetro abdominal $\geq 102$ cm varón, 88cm mujer)                 | 1,95 | 0,001  |
| Hipertensión (presión sistólica $\geq 130$ mmHg y/o presión diastólica $\geq 85$ mmHg) | 1,47 | 0,041  |
| Hiperglucemia (glucemia $\geq 110$ mg/dl)  | 1,69 | 0,019  |
| Colesterol HDL bajo (< 40 mg/dl varón, < 50 mg/dl mujer)                               | 1,06 | 0,814  |
| Triglicéridos elevados ( $\geq 150$ mg/dl)   | 1,75 | 0,013  |
| Resistencia a la insulina (HOMA $\geq 3,8$ )   | 3,32 | <0,001 |

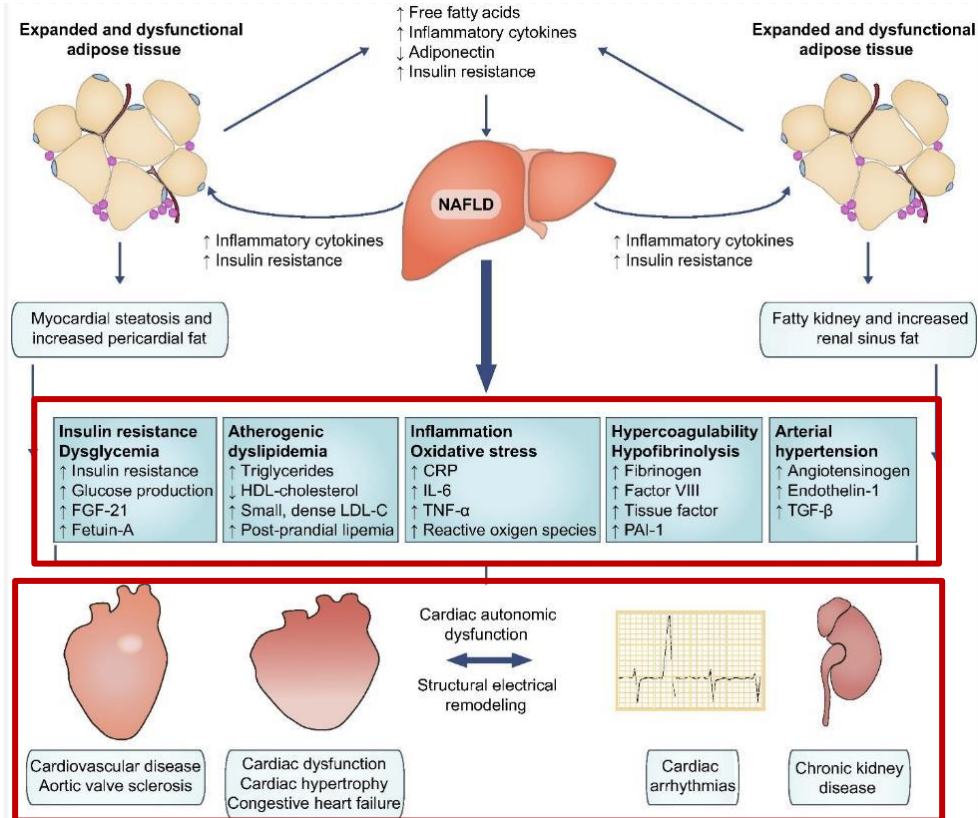
|                                     | 8.0 kPa |           |         |  |
|-------------------------------------|---------|-----------|---------|--|
|                                     | OR      | 95% CI    | P value |  |
| 2                                   |         |           |         |  |
| Male sex                            | 2.71    | 1.90 3.87 | .000    |  |
| AST and/or ALT > ULN <sup>a</sup>   | 1.95    | 1.26 3.03 | .003    |  |
| Abdominal obesity <sup>b</sup>      | 4.28    | 2.78 6.59 | .000    |  |
| Glucose level $\geq 100$ mg/dL      | 2.06    | 1.38 3.07 | .000    |  |
| Low HDL <sup>c</sup>                | 1.68    | 1.16 2.44 | .006    |  |
| Triglyceride level $\geq 150$ mg/dL | 1.73    | 1.21 2.47 | .003    |  |
| Type 2 diabetes                     | 2.00    | 1.33 3.01 | .001    |  |

Els pacients amb FGNA tenen major risc de SM



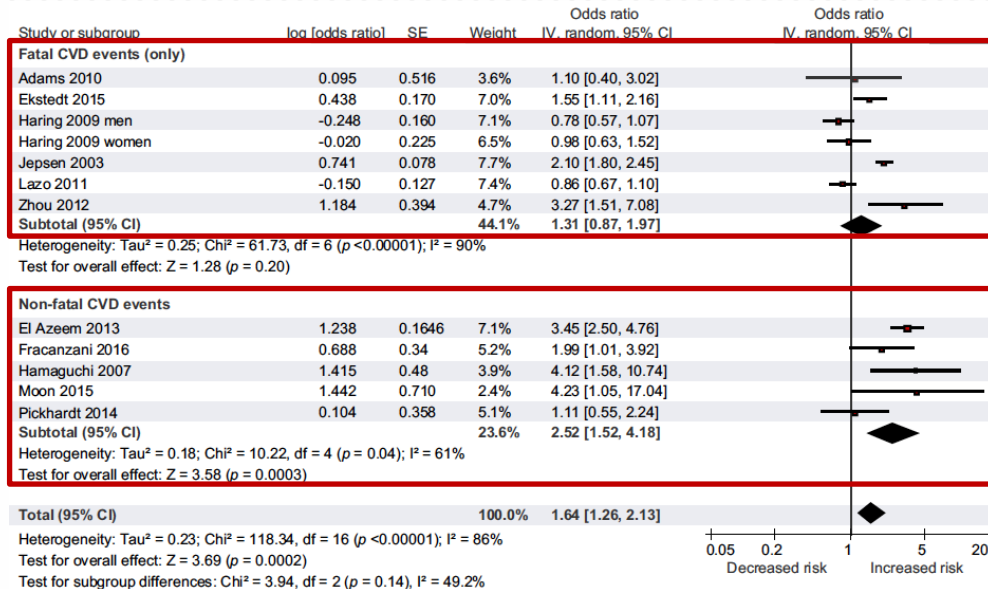
- ✓ Meta-anàlisi de 81.411 individus
- ✓ Seguiment 4,5 anys

# COMORBIDITATS: CARDIO-RENAL

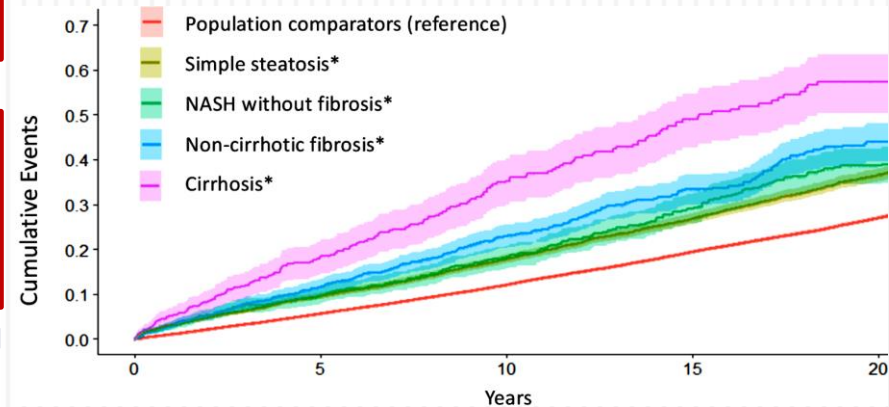




# COMORBIDITATS: MALALTIA CARDIOVASCULAR



✓ A major severitat de la malaltia per FGNA, major risc d'events CV.

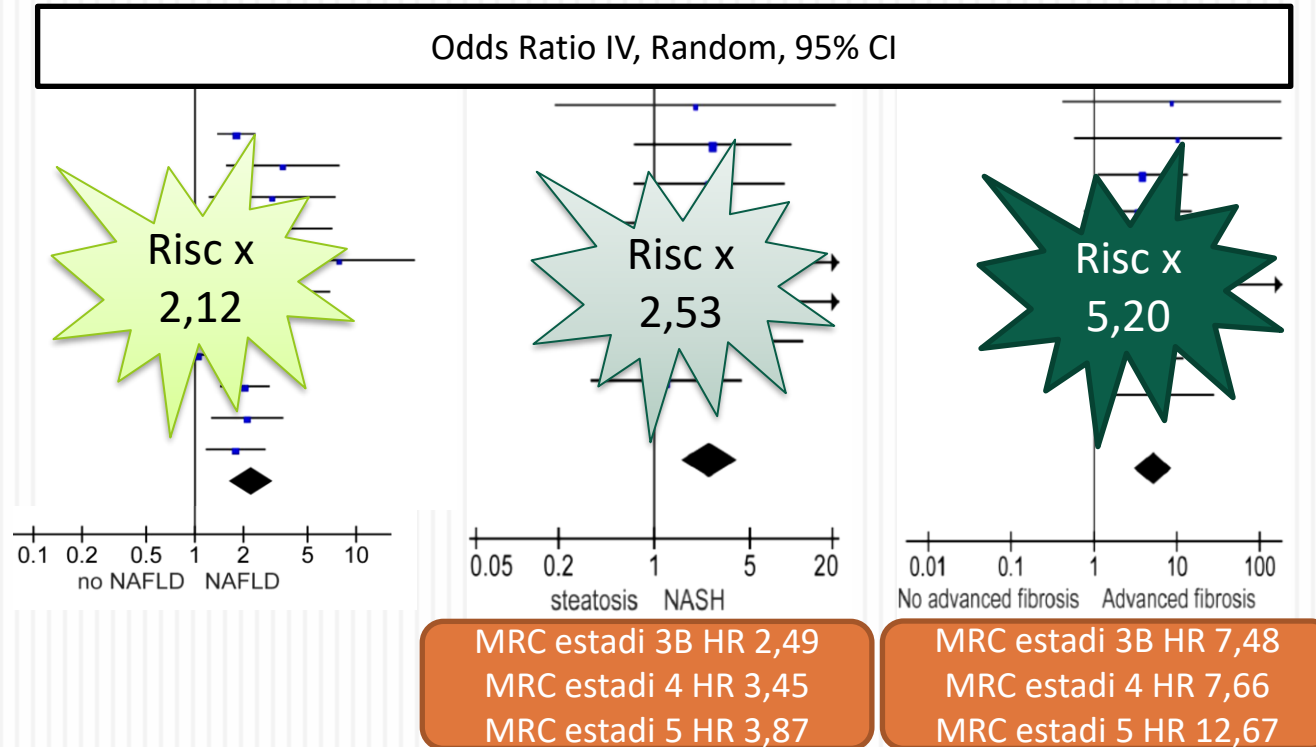


✓ Globalment, en pacients amb FGNA hi ha un 64% més de risc de patir un event CV.

# COMORBIDITATS: MALALTIA RENAL CRÒNICA

## Risc de presentar MRC en pacients amb FGNA (no cirròtics)

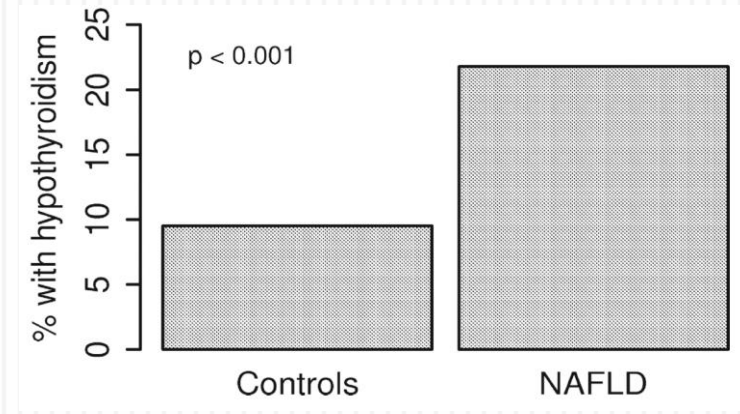
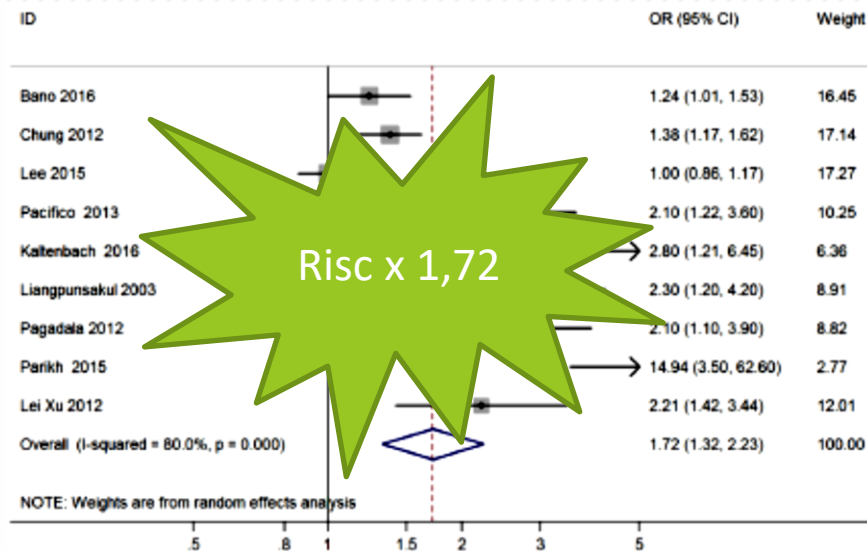
Musso G et. al. M. *PLoS Med.* 2014



# COMORBIDITATS: HIPOTIROIDISME

- ✓ Meta-anàlisi de 13 estudis observacionals
- ✓ N=37.194 individus
- ✓ L'hipotiroïdisme (subclínic i clínic) s'associa de forma independent a major risc de FGNA.

- ✓ Els pacients amb FGNA i/o fibrosi hepàtica tenen xifres significativament més elevades de TSH.
- ✓ Major prevalença d'hipotiroïdisme en FGNA



# TRACTAMENT: GUIES DE PRÀCTICA CLÍNICA

Clinical Practice Guidelines



 **EASL** | JOURNAL OF HEPATOLOGY

**EASL–EASD–EASO Clinical Practice Guideline for the management of non-alcoholic liver disease**\*

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

2016

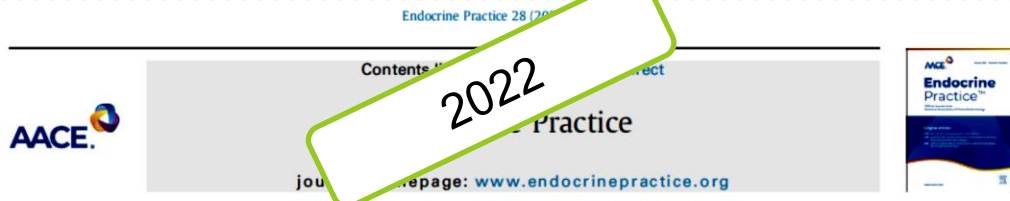
**HEPATOLOGY**



PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 1, 2018

**The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guideline from the American Association for the Study of Liver Diseases**

2018



Endocrine Practice 28 (2022)

Contents

AACE

Endocrine Practice

www.endocrinepractice.org

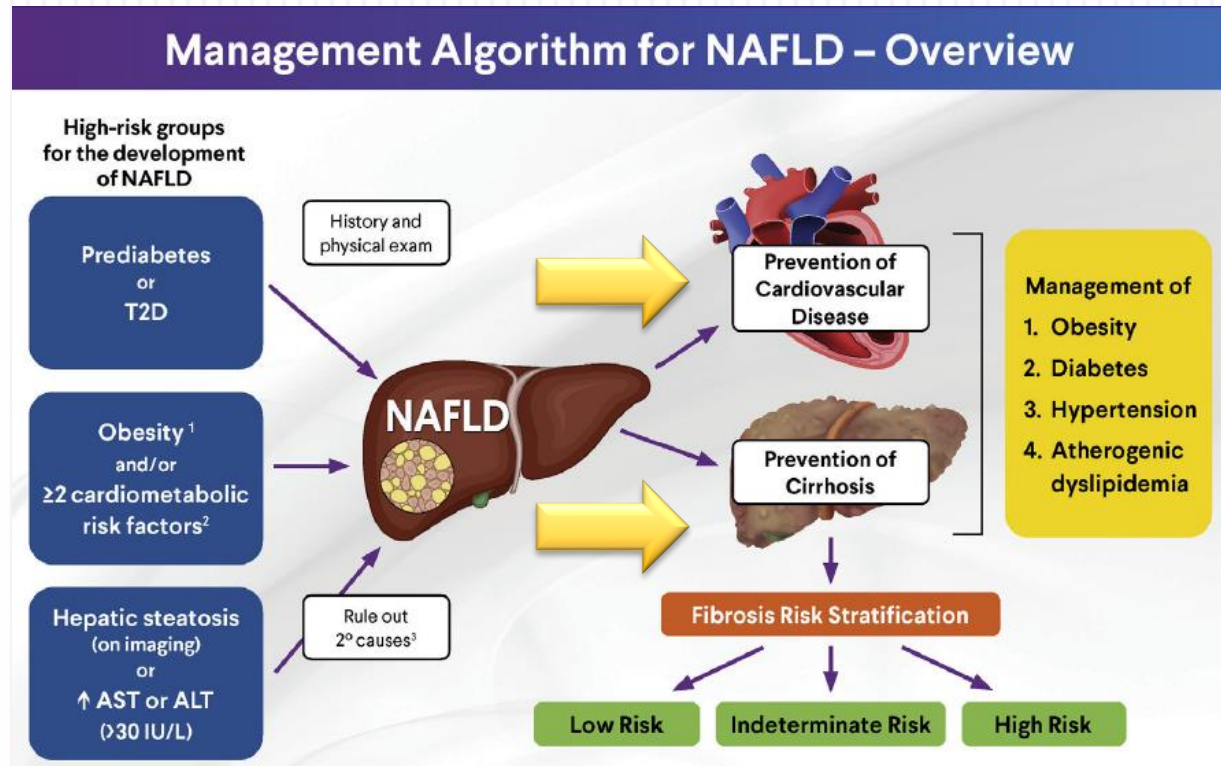
2022

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)



# TRACTAMENT: OBJECTIUS





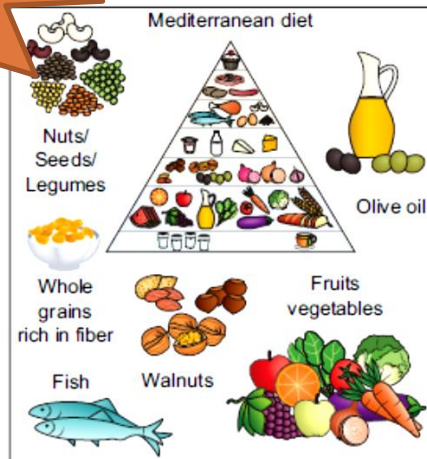
# TRACTAMENT: PILAR PRINCIPAL (I)

Dieta

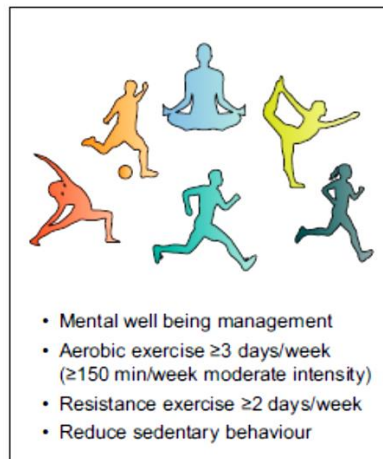
Lifestyle advice for ALL patients with NAFLD

Exercici

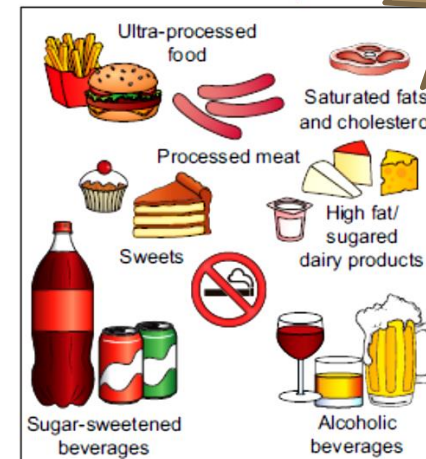
## Recommended foods



## Recommended activity



## 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

# TRACTAMENT: PILAR PRINCIPAL (II)

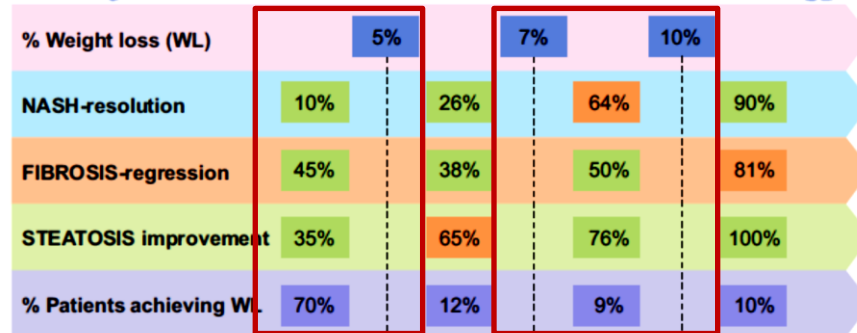
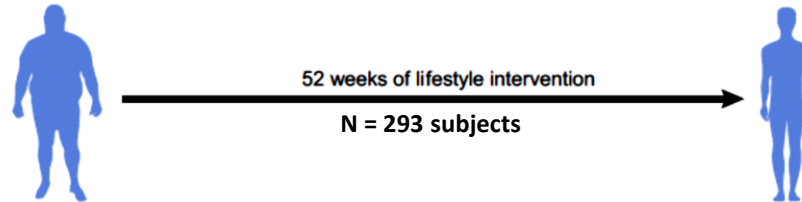
**Pèrdua de pes**

## Overweight/obesity NAFLD

- 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

## Non-obesity NAFLD

- 3-5% reduction of weight even within the normal BMI range (especially if recent weight gain occurred or if abdominal obesity is present)



## Dieta, exercici i pèrdua de pes:

- Millora FGNA / EHNA
- Descens de transaminases
- Millora la sensibilitat a la insulina

# TRACTAMENT: CIRURGIA BARIÀTRICA

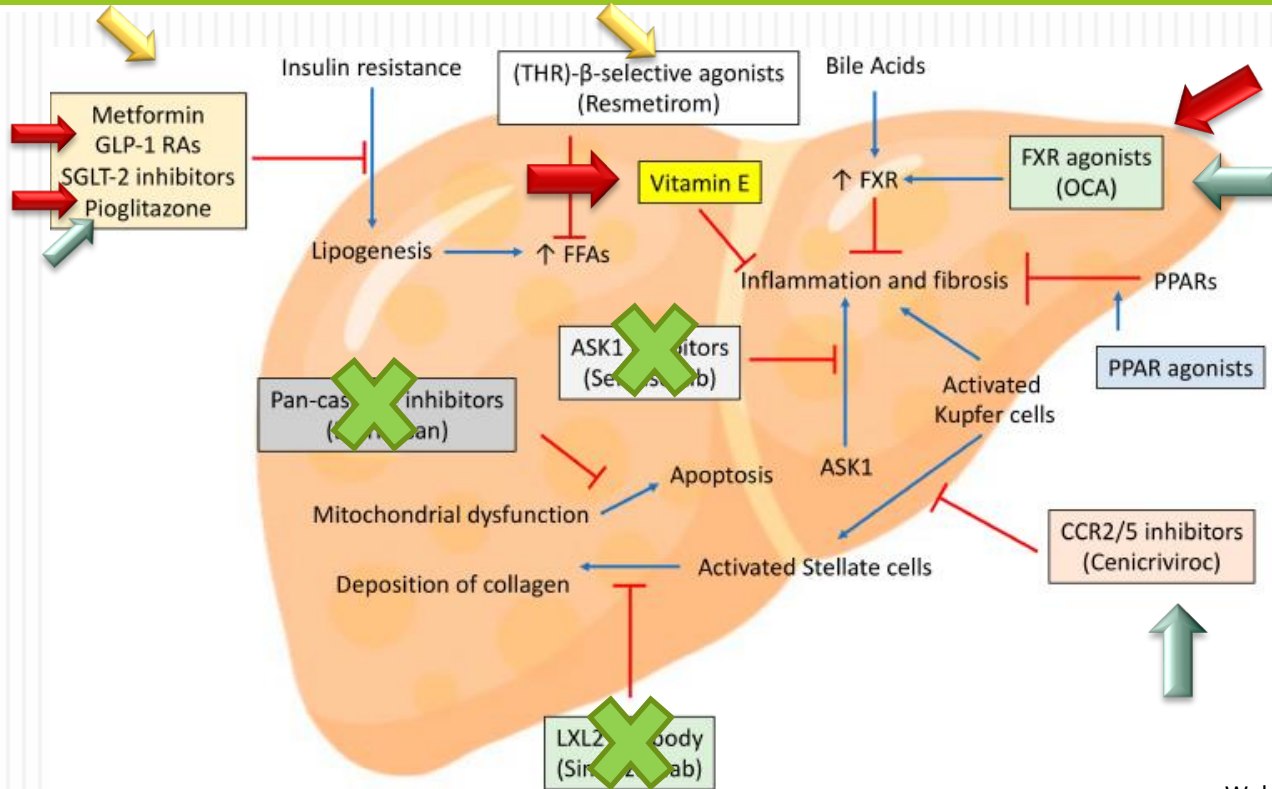
- ✓ Eficaç per perdre pes i mantenir el pes en pacients amb obesitat. Eficaç per eliminar el greix intrahepàtic, millorar la EHNA i la fibrosi.
- ✓ El criteris pel tractament quirúrgic de l'obesitat i els trastorns metabòlics ( $IMC \geq 40$  o  $\geq 35$  amb trastorns complicats sense resolució després del tractament mèdic) també són aplicables al FGNA.

*Recommendation 3.5.1.* Clinicians should consider bariatric surgery as an option to treat NAFLD (**Grade B; Intermediate Strength of Evidence; BEL 2**) and improve cardiometabolic health (**Grade A; High/Intermediate Strength of Evidence; BEL 2; upgraded based on the cardiometabolic and all-cause mortality benefits in all persons with or without NAFLD**) in persons with NAFLD and a BMI of  $\geq 35$  kg/m<sup>2</sup> ( $\geq 32.5$  kg/m<sup>2</sup> in Asian populations), particularly if T2D is present. It should also be considered an option in those with a BMI of  $\geq 30$  to  $34.9$  kg/m<sup>2</sup> ( $\geq 27.5$  to  $32.4$  kg/m<sup>2</sup> in Asian populations) (**Grade B; Intermediate/Weak Strength of Evidence; BEL 2**).

*Recommendation 3.5.2.* For persons with NASH and compensated cirrhosis, clinicians should exercise caution in recommending bariatric surgery, which should be highly individualized if prescribed and performed at experienced centers (**Grade B; Intermediate/Weak Strength of Evidence; BEL 2**). In persons with decompensated cirrhosis, bariatric surgery should not be recommended due to limited evidence and potential for harm (**Grade B; Intermediate/Weak Strength of Evidence; BEL 2**).



# TRACTAMENT: FARMACOLÒGIC



## PIOGLITAZONA

- ✓ Agonista del PPAR- $\gamma$
- ✓ Múltiples estudis
- ✓ Millora l'esteatosi, la sensibilitat a la insulina, la EHNA i la fibrosi hepàtica
- ✓ Dosis de 30-45mg/dia
  
- ✓ Augment de pes (2-4% del pes basal)
- ✓ Retenció hídrica, risc ICC
- ✓ Risc de càncer de bufeta
- ✓ Risc fractures òssies

### Guidance Statements: AASLD Guidelines 2018

*24. Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH. Therefore, it may be used to treat these patients. Risks and benefits should be discussed with each patient before starting therapy.*

## ANÀLEGS GLP-1

- ✓ Liraglutide and semaglutide
- ✓ Millora l'esteatosi, la EHNA i a dosis altes sembla que hi ha menys progressió a fibrosi, tot i que no s'ha demostrat que millori la fibrosi
- ✓ Importants beneficis cardiorrenals en pacients amb DM2
  
- ✓ Pèrdua de gana, nàusees, restrenyiment, diarrea

### Guidance Statement: AASLD Guidelines 2018

*26. It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH.*

## RESMETIROM

- ✓ Agonista del THR- $\beta$
- ✓ *Assaig clínic en fase 3*
- ✓ Millora l'esteatosi, la EHNA, disminueix LDL, TG i transaminases (assaig clínic fase 2). Podria millorar la fibrosi (disminueix PRO-C3)
- ✓ Dosis 80mg/dia

✓ Diarrea, nàusees

✓ No hi ha recomacions al respecte, dades preliminars

## ÀCID OBETICÒLIC

- ✓ Agonista del receptor X farnesoide
- ✓ *Assaig clínic en fase 3*
- ✓ Millora la EHNA i la fibrosi hepàtica (assaig clínic en fase 2). Millora la sensibilitat a la insulina i regula metabolisme glicèmic i lipídic
- ✓ Dosis de 25mg/dia
- ✓ Aprovat pel tractament de la CBP




✓ Pruija cutània, augment LDL

*Guidance Statement:* **AASLD Guidelines 2018**




*38. Until further safety and efficacy data become available in patients with NASH, we recommend that OCA should not be used off-label to treat NASH.*

# TRACTAMENT: DELS FACTORS METABÒLICS ASSOCIATS (I)

## Fibrosis Risk Stratification

|          |  | FGNA  |   |  |
|----------|--|---|---|--|
|          |  |  <p><b>Low Risk</b><br/>FIB-4: &lt;1.3<br/>LSM &lt;8 kPa<br/>ELF &lt;7.7</p> |  <p><b>Indeterminate Risk</b><br/>FIB-4: 1.3 - 2.67<br/>LSM 8 - 12 kPa<br/>ELF 7.7 - 9.8</p> |  <p><b>High Risk</b><br/>FIB-4: &gt;2.67<br/>LSM &gt;12 kPa<br/>ELF &gt;9.8</p> |
| Obesitat | 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. <sup>3,4</sup>   | GLP-1 RA preferred for NASH. <sup>3,4</sup>  |
|          | 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.  |
| DM2      | 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 <sup>3</sup> . No evidence that SGLT2i improve steatohepatitis.                                    | Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA <sup>3</sup> . No efficacy data in cirrhosis.   |
|          | Metformin, sulfonyleurea, 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       |

# TRACTAMENT: DELS FACTORS METABÒLICS ASSOCIATS (II)

|  |  | Fibrosis Risk Stratification  |  |   |
|--|--|---|--|---|
| FGNA                                       |  |  <p><b>Low Risk</b></p> <p>FIB-4: &lt;1.3<br/>LSM &lt;8 kPa<br/>ELF &lt;7.7</p>      |  <p><b>Indeterminate Risk</b></p> <p>FIB-4: 1.3 - 2.67<br/>LSM 8 - 12 kPa<br/>ELF 7.7 - 9.8</p> |  <p><b>High Risk</b></p> <p>FIB-4: &gt;2.67<br/>LSM &gt;12 kPa<br/>ELF &gt;9.8</p> |
| <p><b>HTA</b></p> <p><b>Dislipèmia</b></p> | Pharmacotherapy for hypertension <sup>9</sup>  | First-line therapy: ACEIs and ARBs.   | First-line therapy: ACEIs and ARBs.  | Same but avoid ACEI or ARB if decompensated cirrhosis.  |
|  | Intensification of therapy   | Second agent: CCB, BB <sup>6</sup> or thiazide diuretic (as additional agents as needed).   |  | Same but individualize if decompensated cirrhosis. Use diuretics with caution (risk of excessive diuresis).   |
|  | First line pharmacotherapy: Statins  | Use a moderate-to-high intensity statin <sup>2</sup> , unless contraindicated. Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C). |  |   |
|  | If LDL-C not at goal <sup>3</sup> : Intensify statin therapy                                 | Use higher dose or higher potency statin.   |  |   |
|  | If LDL-C not at goal (or statin intolerant) <sup>4</sup> : add 2nd agent, then add 3rd agent | Ezetemibe, PCSK9 inhibitor, bempedoic acid, colesvelam, inclisiran.   |  |   |
|  | If triglycerides > 500 mg/dL   | Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone). <sup>5</sup>                                       |  |   |
|  | If TG 135-499 mg/dL on max statin dose   | Emphasize diet (as above).  | Add icosapent ethyl. <sup>6</sup>  | Add icosapent ethyl. <sup>6</sup>   |

# TRACTAMENT: ALTRES RECOMANACIONS

## VACUNES

### Immunizations for Persons With Chronic Liver Disease<sup>227,228</sup>

- Hepatitis A vaccine
- Hepatitis B vaccine
- Pneumococcal polysaccharide vaccine (PPSV23)
- Additional vaccines:
  - Influenza vaccine
  - Tdap vaccine
  - Zoster vaccine
  - HPV vaccine
  - MMR vaccine
  - Varicella vaccine
  - COVID-19 vaccine

Abbreviations: HPV = human papilloma virus; MMR = measles, mumps, and rubella; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; Tdap = tetanus, diphtheria, and pertussis.



## TÒXICS



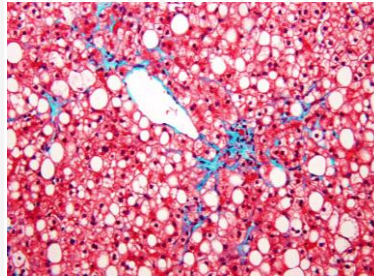
- ✓ S'aconsella no fumar
- ✓ S'ha d'evitar qualsevol consum d'OH en persones amb cirrosi hepàtica.
- ✓ S'ha d'evitar el consum de OH de risc (> 21/14 UBE/setm homes/dones).
- ✓ En pacients amb FGNA no s'aconsella el consum lleu d'OH (no hi ha consens entre guies).

*Guidance Statements:* **AASLD Guidelines 2018**

*34. Patients with NAFLD should not consume heavy amounts of alcohol.*

*35. There are insufficient data to make recommendations with regard to nonheavy consumption of alcohol by individuals with NAFLD.*

# Moltes gràcies



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