

# MÁSTER EN HEPATOLOGÍA



**UAM**  
Universidad Autónoma  
de Madrid

 Universidad  
de Alcalá

## Esteatosis hepática metabólica / NAFLD / MAFLD y diabetes mellitus II

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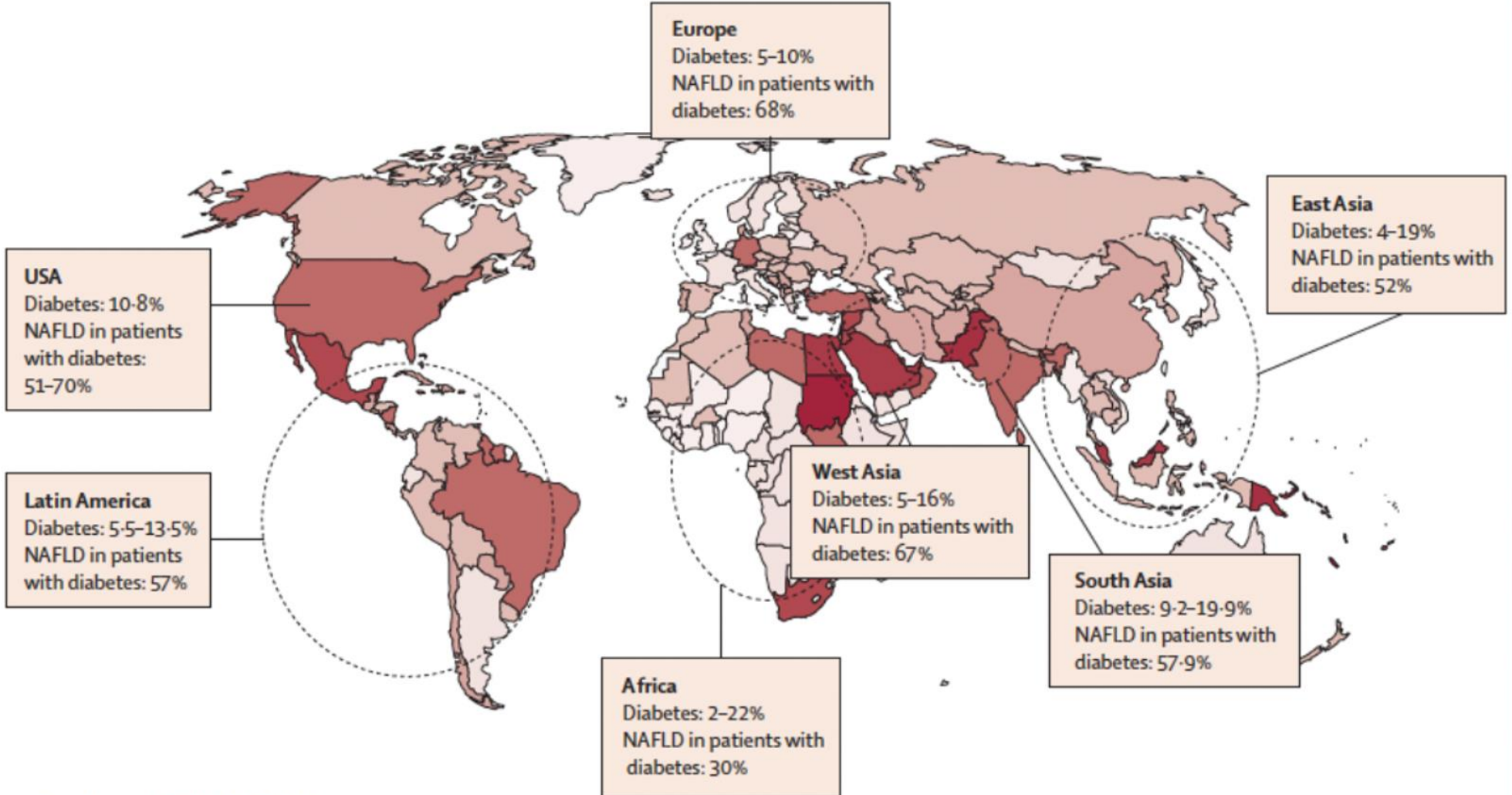
 **Valdecilla**  
Instituto de  
Investigación  
Sanitaria **IDIVAL**

 **Valdecilla**  
Hospital Universitario Marqués de Valdecilla

Global prevalence of NAFLD in patients with diabetes: 55-70%

Global prevalence of non-alcoholic steatohepatitis in patients with diabetes: 30-40%

Global prevalence of fibrosis (F2-F4) in patients with diabetes: 12-20%

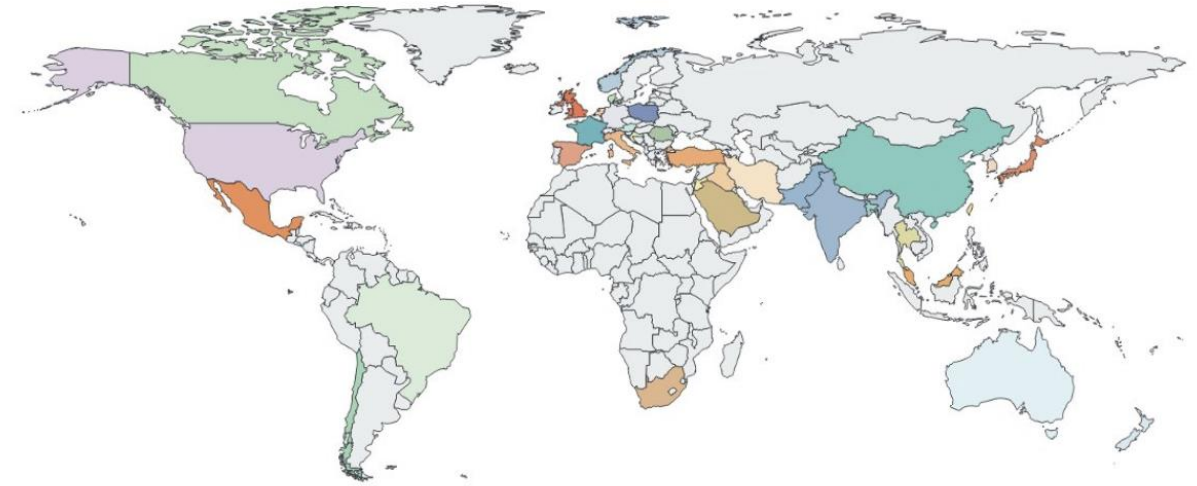
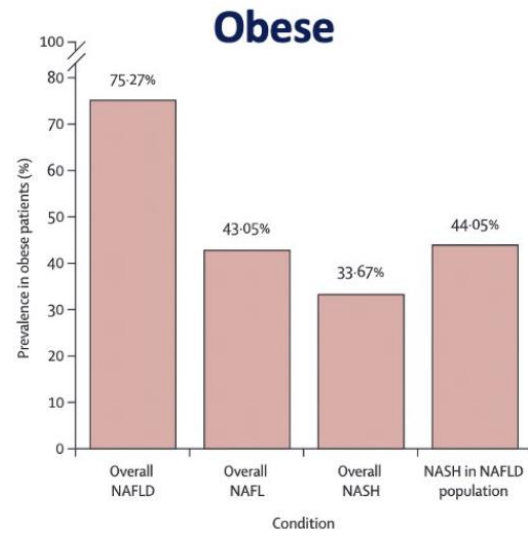
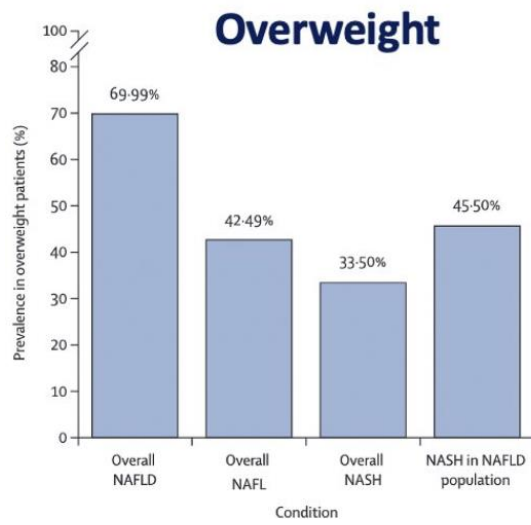


Prevalence of diabetes in 2019



# Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis

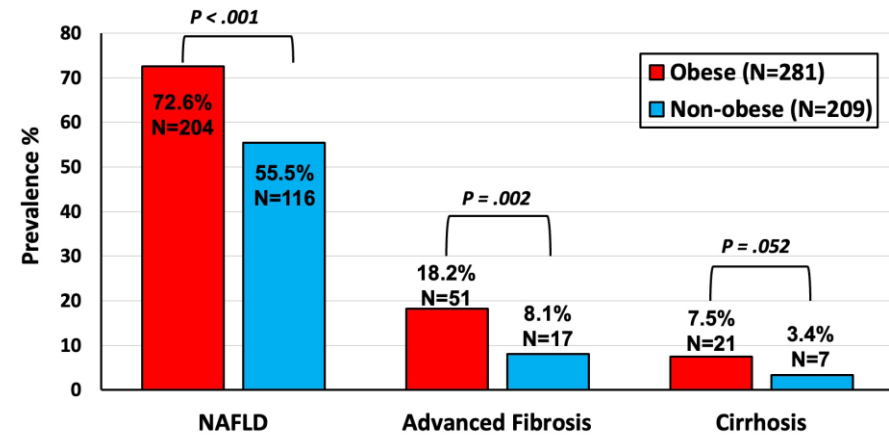
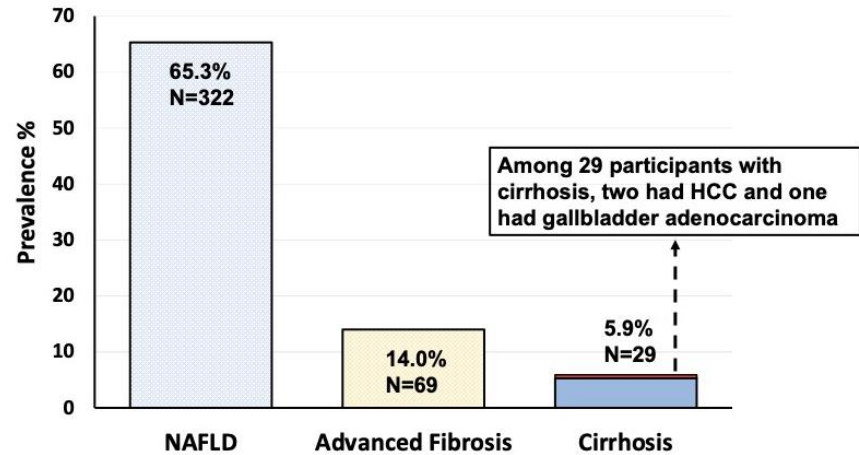
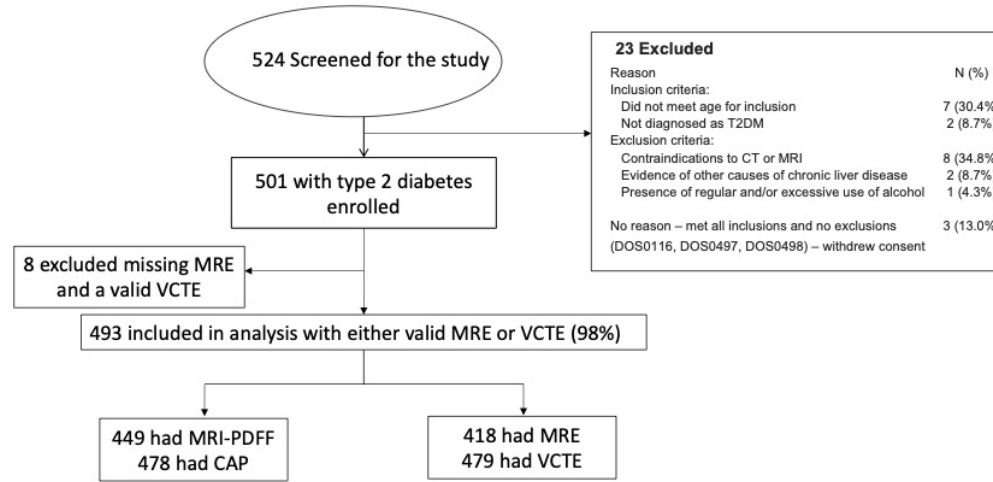
Jingxuan Quek\*, Kai En Chan\*, Zhen Yu Wong\*, Caitlyn Tan, Bryan Tan, Wen Hui Lim, Darren Jun Hao Tan, Ansel Shao Pin Tang, Phoebe Tay, Jieling Xiao, Jie Ning Yong, Rebecca Wenling Zeng, Nicholas W S Chew, Benjamin Nah, Anand Kulkarni, Mohammad Shadab Siddiqui, Yock Young Dan, Vincent Wai-Sun Wong, Arun J Sanyal, Mazen Nouredin, Mark Muthiah†, Cheng Han Ng†



**Prevalence of NAFLD in overweight population**

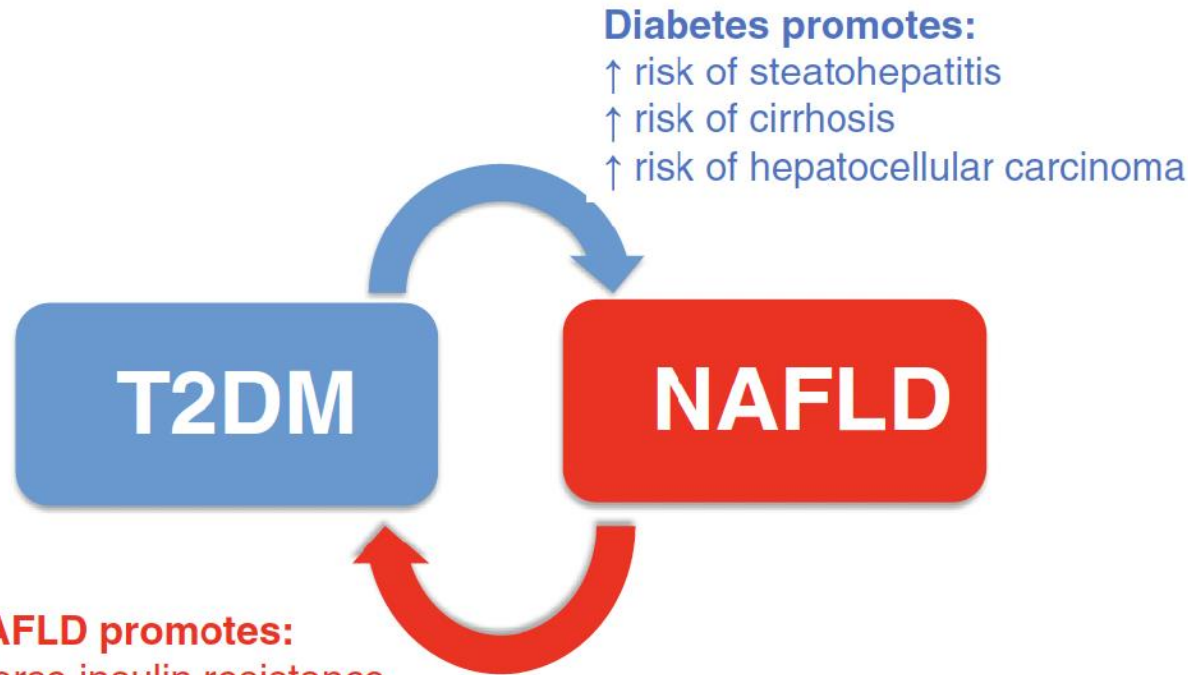
Australia (70.27%)	Croatia (68.06%)	Iraq (68.00%)	New Zealand (88.46%)	South Korea (47.69%)
Austria (84.00%)	Denmark (48.48%)	Italy (82.36%)	Norway (74.91%)	Spain (88.55%)
Bangladesh (30.39%)	France (83.18%)	Japan (63.38%)	Pakistan (71.98%)	Taiwan (53.60%)
Brazil (79.43%)	Germany (69.38%)	Jordan (83.45%)	Poland (57.25%)	Thailand (61.75%)
Canada (76.26%)	Hong Kong (40.69%)	Malaysia (56.60%)	Romania (32.17%)	Türkiye (88.66%)
Chile (62.99%)	India (72.41%)	Mexico (63.48%)	Saudi Arabia (75.66%)	USA (73.24%)
China (60.33%)	Iran (57.85%)	Netherlands (31.04%)	South Africa (47.64%)	UK (30.64%)

# Prevalencia NAFLD en DMII





# Consecuencias clínicas interacción DMII / NAFLD



**NAFLD promotes:**  
Worse insulin resistance  
↑ risk of atherogenic dyslipidemia  
↑ risk of T2DM, ↑ difficulty to manage  
↑ risk of cardiovascular disease

American Diabetes Association recommendation for NAFLD:

**Recommendation**

**4.14** Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**



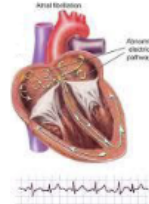
**¡¡TODOS!!**

# DMIII-MAFLD una dupla de alto riesgo vascular

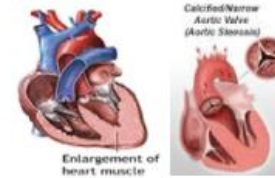
Riesgo eventos CV (fatales y no fatales)



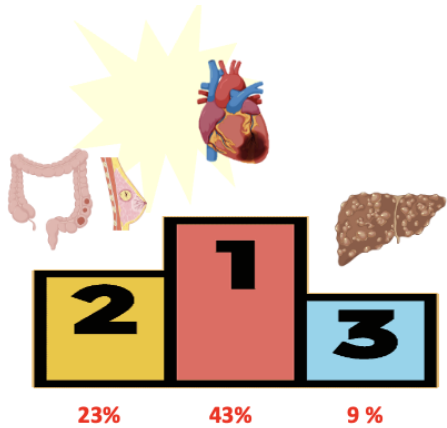
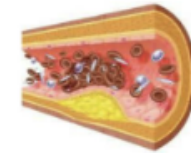
- AC x FA
- Tostornos ritmo



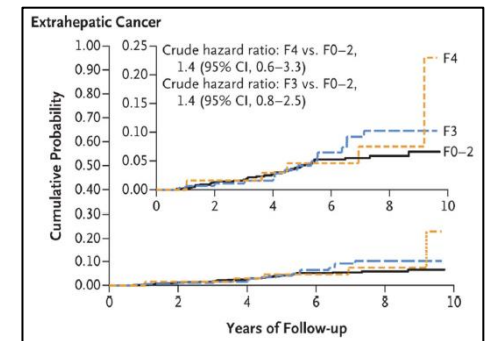
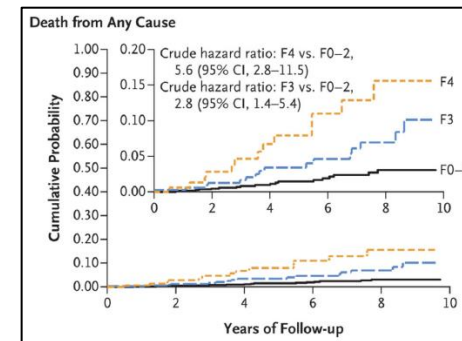
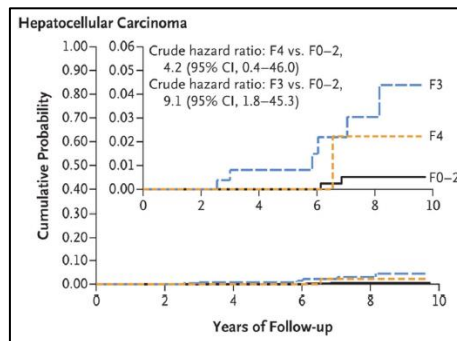
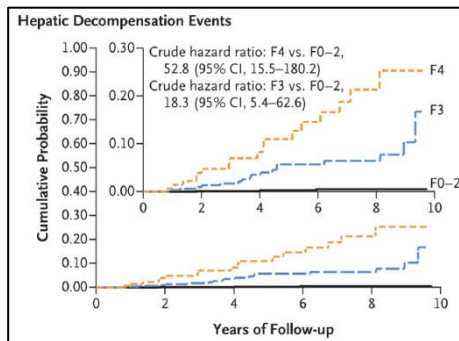
- Disfunción diastólica
- Esclerosis Ao



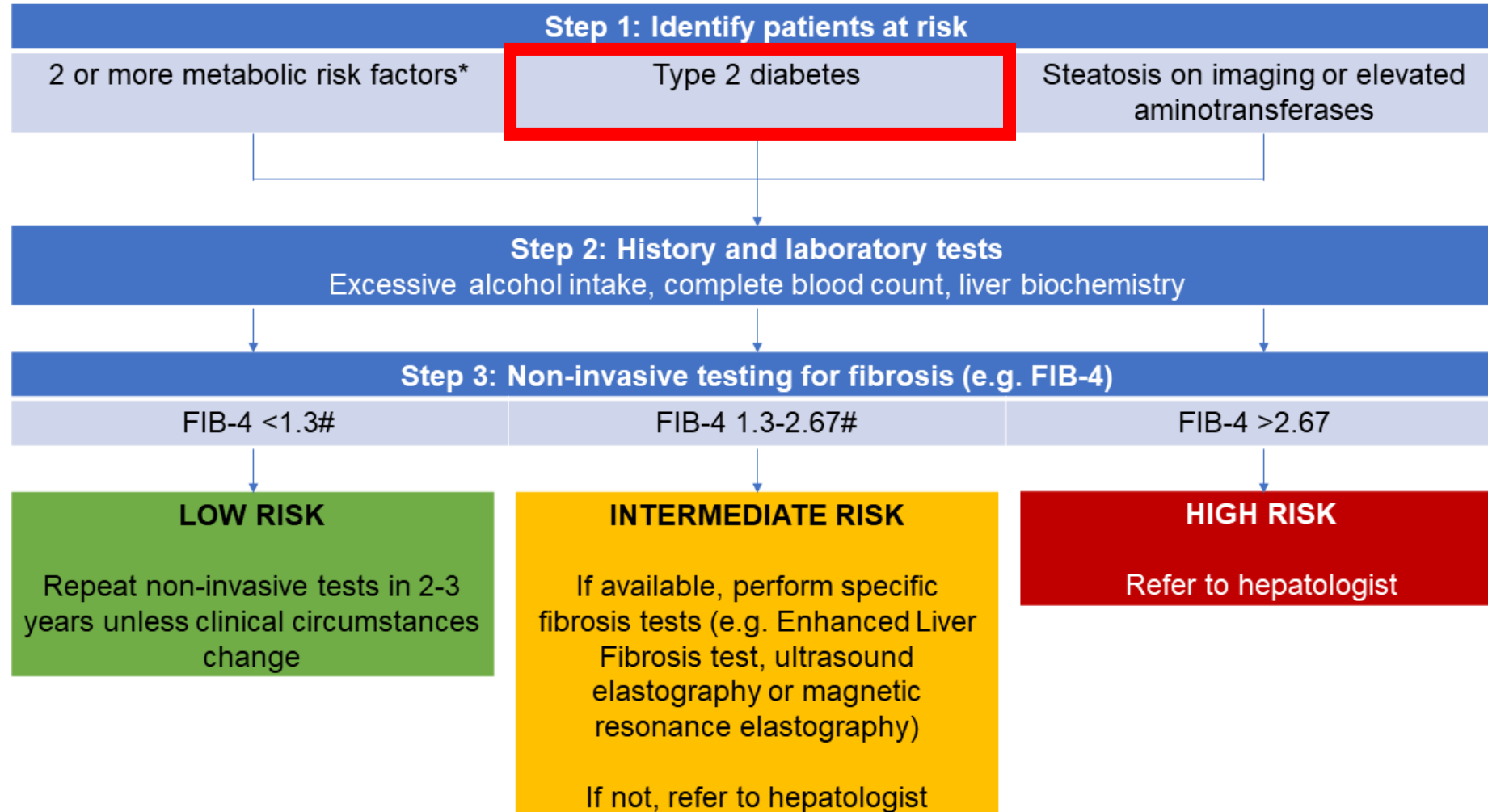
- Calcificación coronaria
- Rigidez arterial
- Íntima-media carótida
- Disfunción endotelial



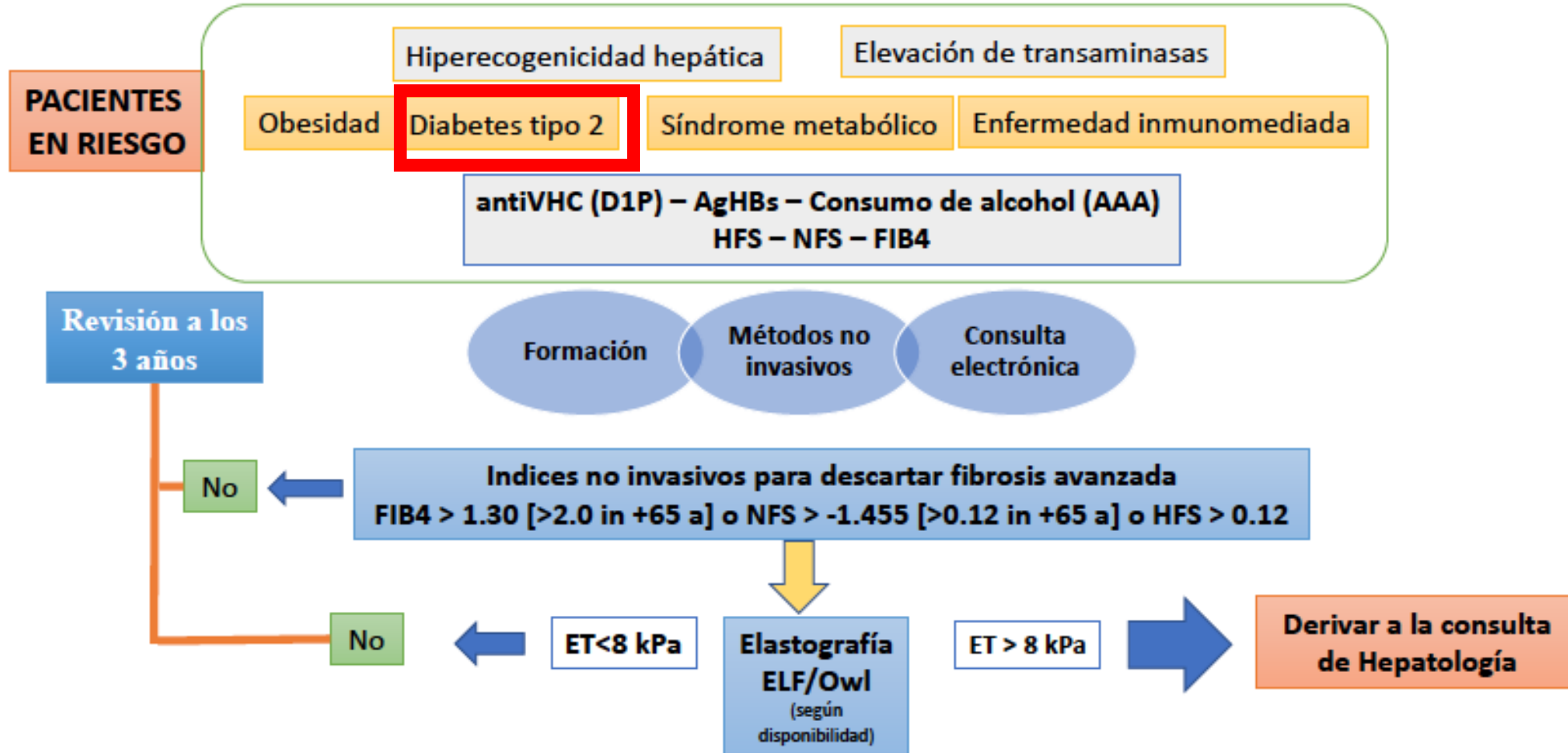
**MORTALIDAD**



# Diagnóstico / cribado NAFLD en DMII

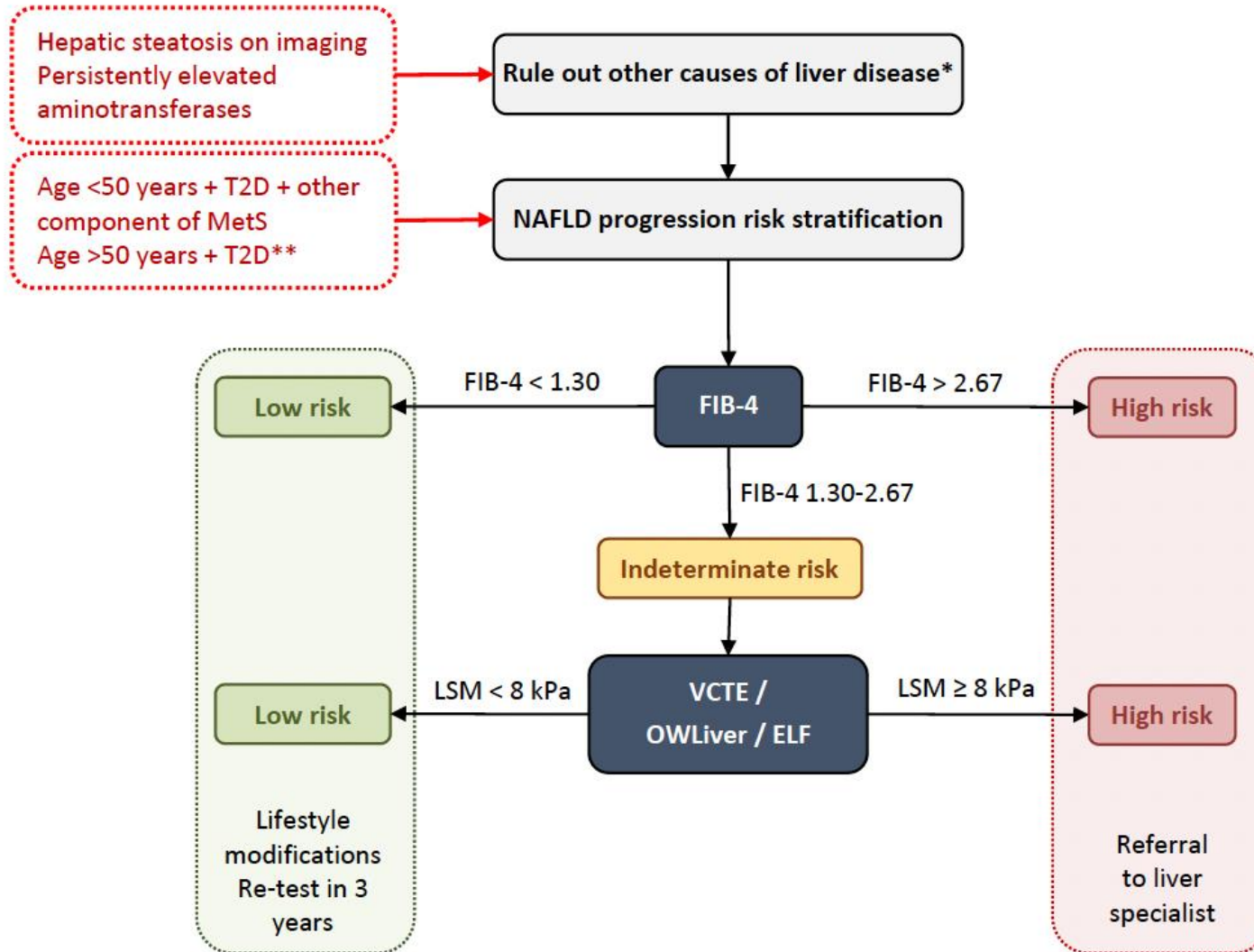


# Diagnóstico / cribado NAFLD en DMII





# Diagnóstico / cribado NAFLD en DMII



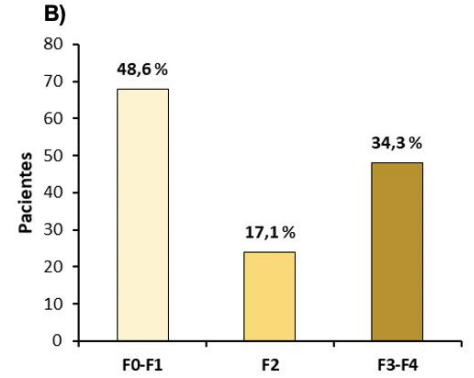
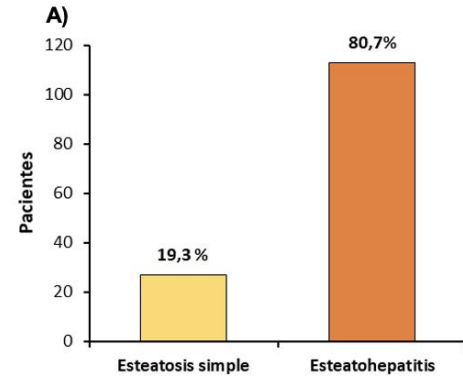
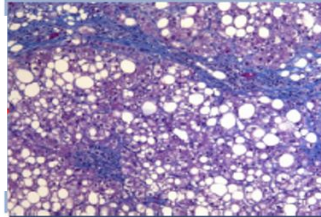
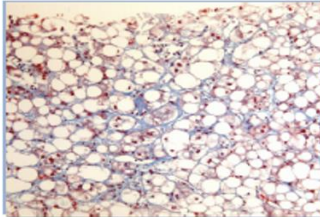
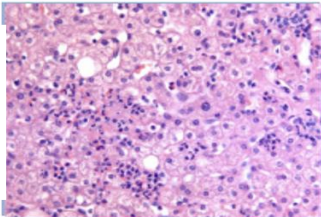
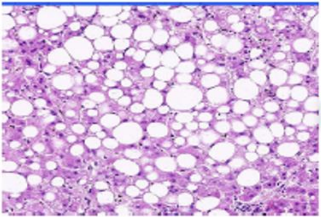
# Diagnóstico / cribado NAFLD en DMII

Analítica completa, fibroscan + FIB-4  
(biopsia y analítica < 1 año)  
N = 124

NAFL  
N = 23 (18,6%)

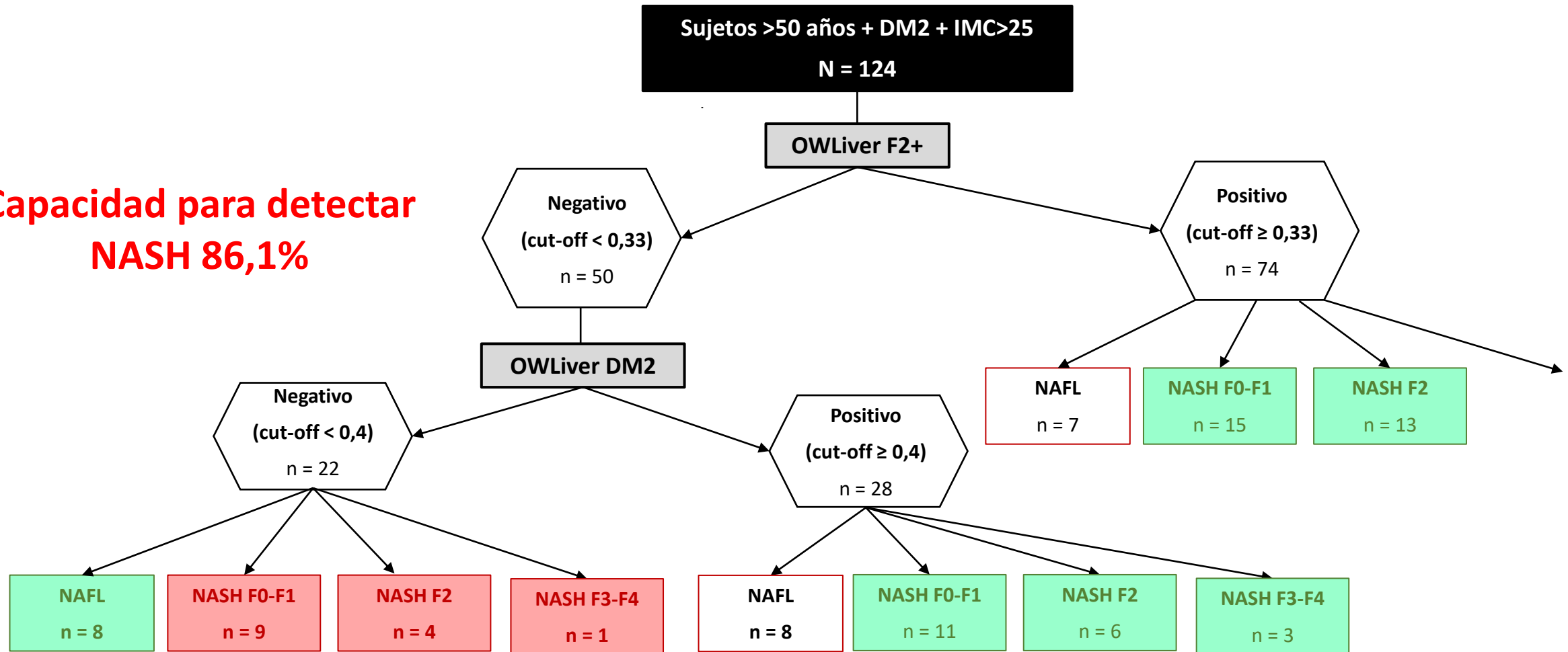
NASH (F0-F1)  
N = 35 (28,2%)

NASH (F2-F4)  
N = 66 (53,2%)



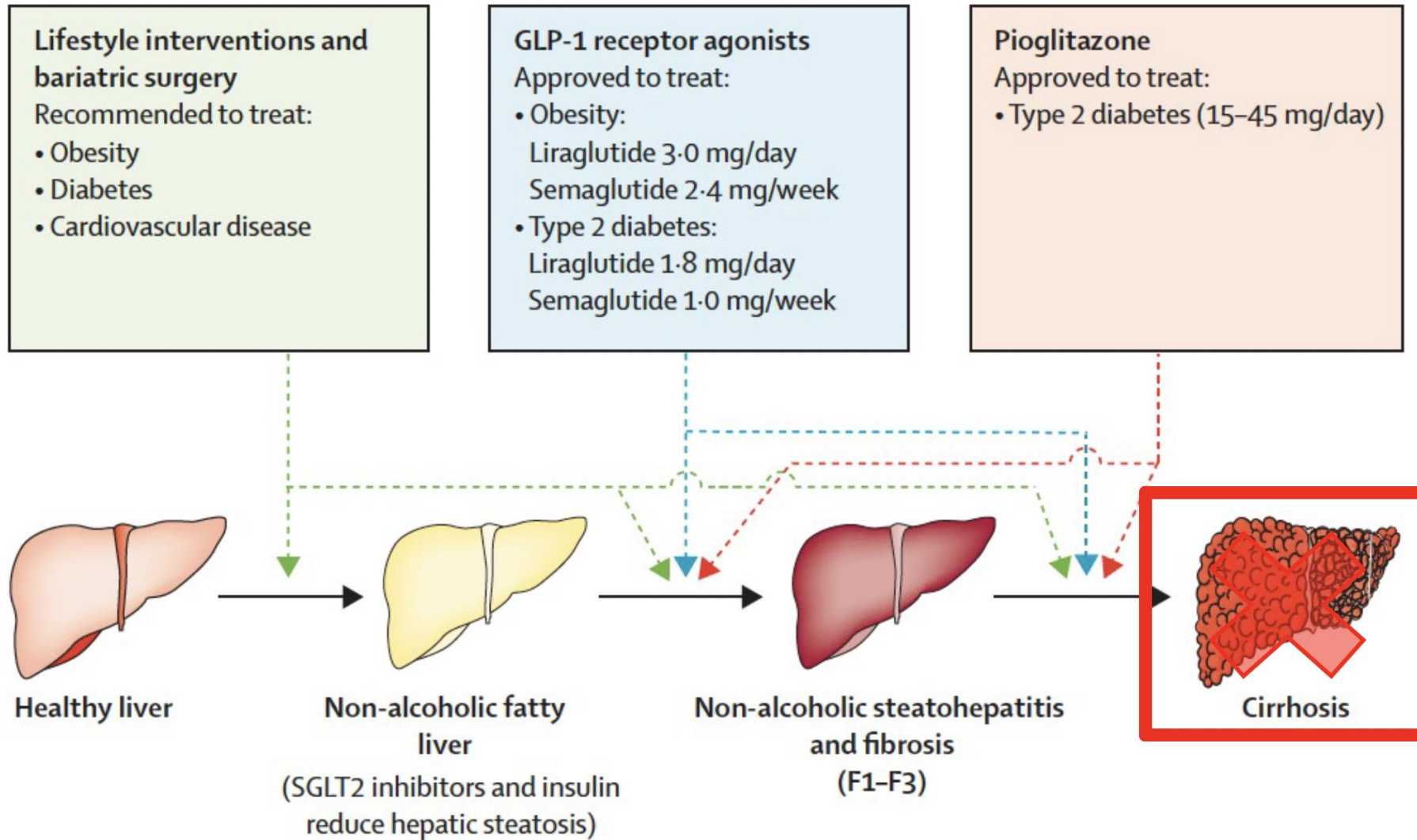
# Diagnóstico / cribado NAFLD en DMII

Capacidad para detectar  
NASH 86,1%



Test	n	Accuracy	Sensitivity	Specificity	PPV	NPV
OWLiver F2+ & OWLiver DM2	124	76.6%	<b>86.1%</b>	34.8%	85.3%	36.4%

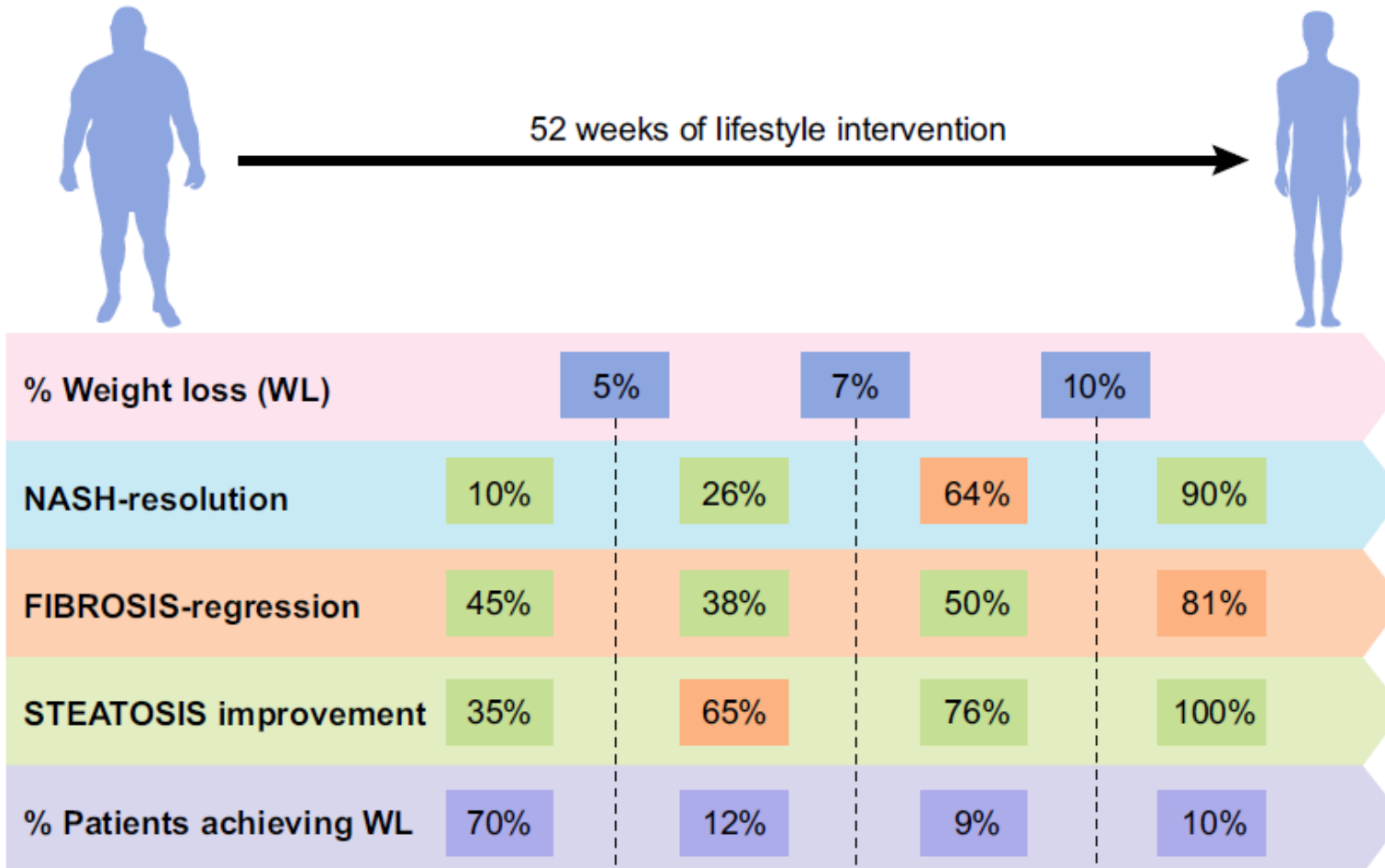
## Potencial aproximación terapéutica





## Potencial aproximación terapéutica. Obesidad.

Una pérdida de peso de  $\geq 10\%$  pueden inducir una resolución casi universal de la esteatohepatitis y una mejora de la fibrosis en al menos un estadio.



# Potencial aproximación terapéutica. Obesidad.

## Overweight/obesity NAFLD

### Weight reduction

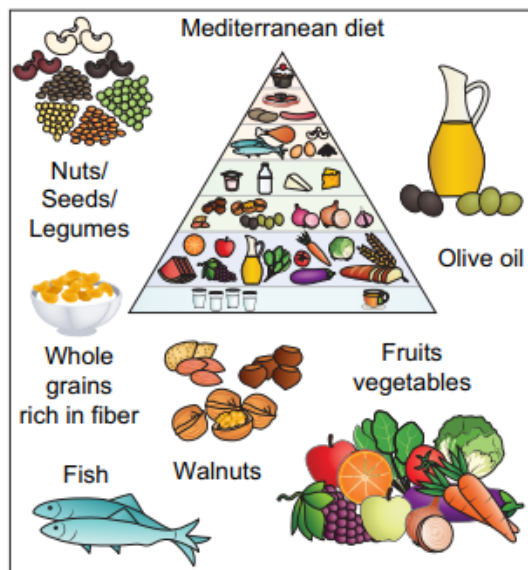
- The more severe the liver disease is, the higher the goals are in terms of weight loss
- Healthy diet with caloric restriction tailored for your preferences

## Non-obesity NAFLD

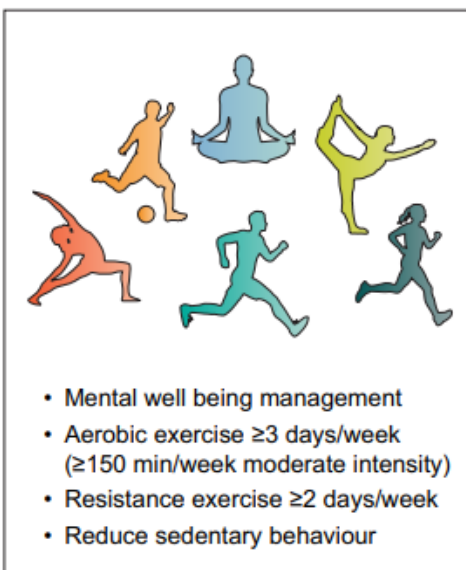
- 3-5% reduction of weight even within the normal BMI range (especially if recent weight gain occurred or if abdominal obesity is present)

## Lifestyle advice for ALL patients with NAFLD

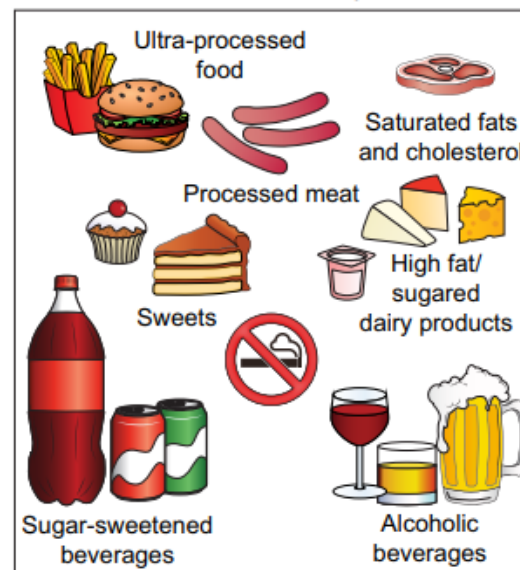
### Recommended foods



### Recommended activity



### Non-recommended foods/ Minimize consumption



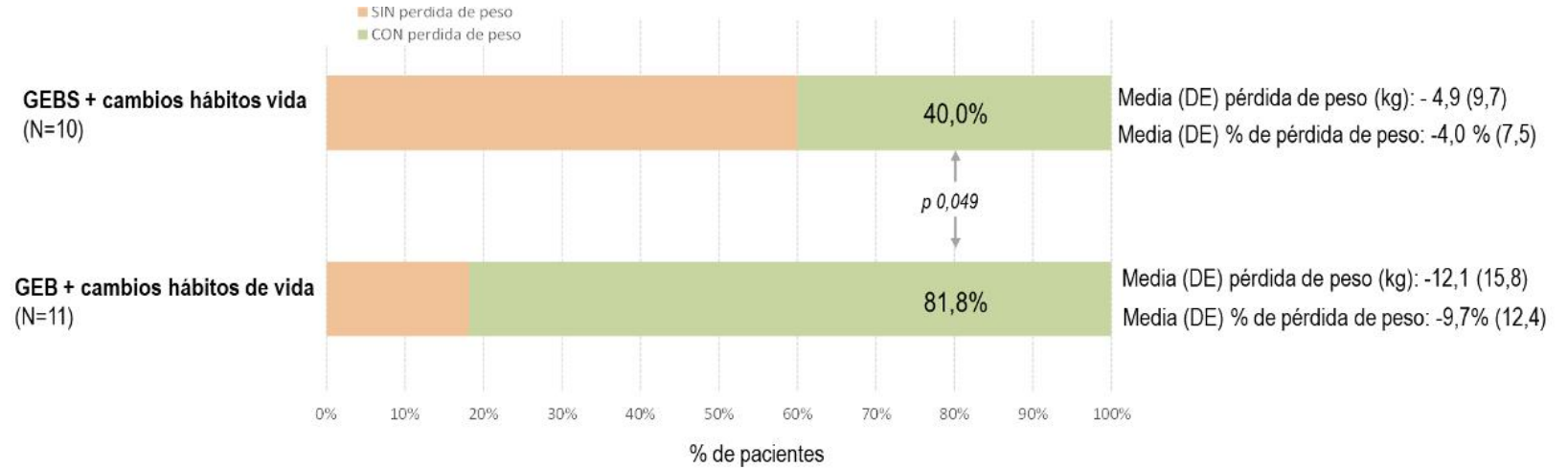
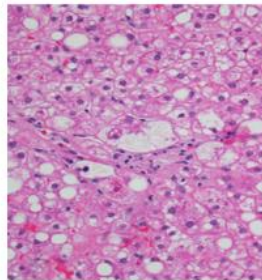
- Reduce added sugar (e.g. by reducing sweets, processed foods, sugared dairy products, etc.)
- Avoid sugar-sweetened beverages
- Reduce saturated fat and cholesterol (e.g. by eating low fat meat and low fat dairy products)

- 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

## Potencial aproximación terapéutica. Obesidad.

### LA REDUCCIÓN DE PESO MEDIANTE GASTROPLASTIA ENDOSCÓPICA BARIÁTRICA SE ASOCIA A MEJORÍA HISTOLÓGICA EN PACIENTES CON ESTEATOHEPATITIS.

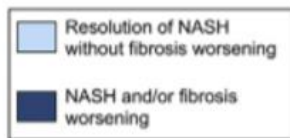
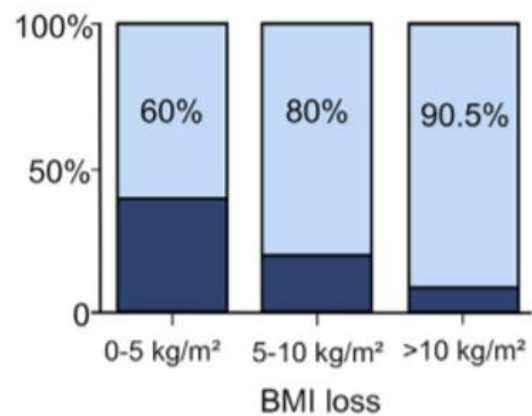
Análisis intermedio de un estudio aleatorizado multicéntrico doble ciego con biopsias pareadas (Estudio APOLLO-NASH)



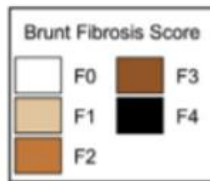
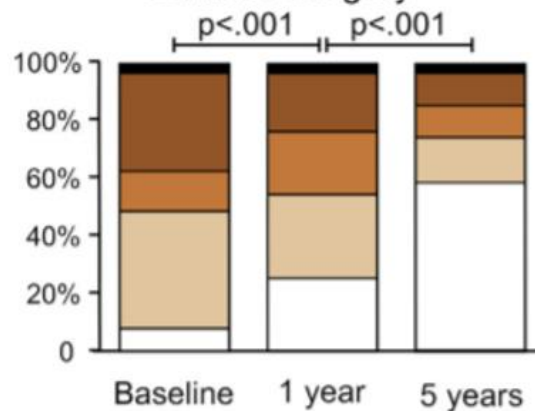
	No pierde peso (N=8)	Si pierde peso (N=13)	<i>p</i>
NAS score	0.00 (1.07)	-3.00 (1.96)	0.001
Esteatosis	-0.13 (0.64)	-1.38 (0.77)	0.001
Inflamación Lobulillar	0.13 (0.83)	-0.54 (0.78)	0.080
Ballooning	0.00 (0.53)	-1.08 (0.86)	0.005
	Pérdida<10% (N=14)	Pérdida>10% (N=7)	<i>p</i>
NAS score	-0.57 (1.45)	-4.43 (0.53)	<0.001
Esteatosis	-0.43 (0.65)	-1.86 (0.69)	<0.001
Inflamación Lobulillar	0.07(0.83)	-1.00 (0.00)	0.003
Ballooning	-0.21(0.70)	-1.57 (0.53)	<0.001

## Bariatric Surgery Provides Long-term Resolution of NASH and Regression of Fibrosis

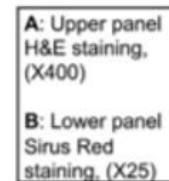
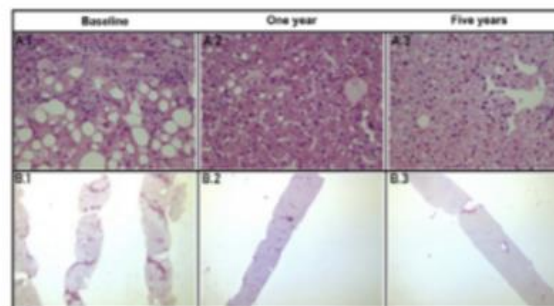
Resolution of NASH according to weight loss



Evolution of Fibrosis after Bariatric Surgery



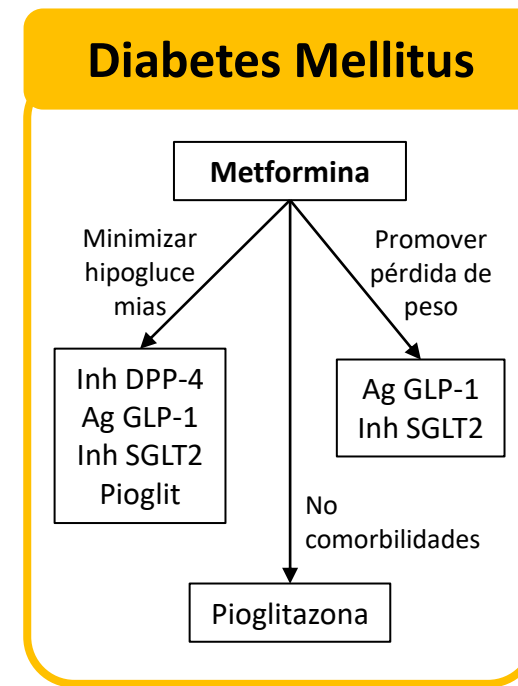
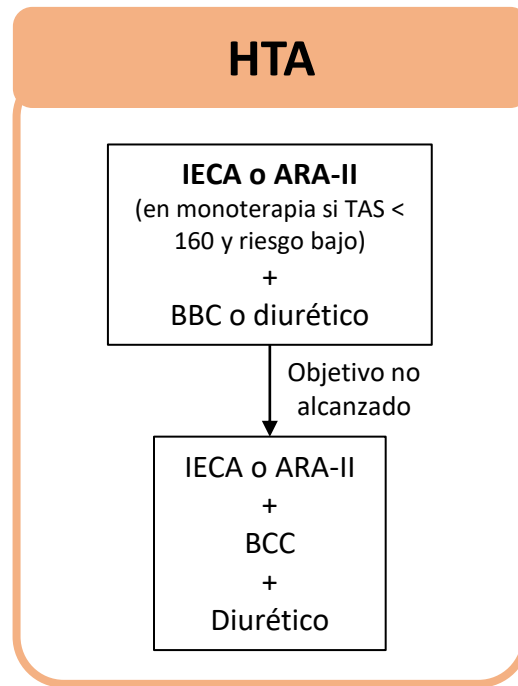
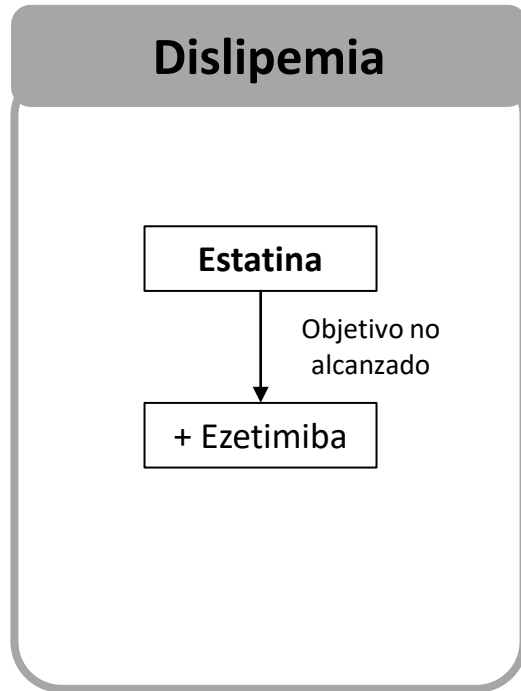
Histological Evolution of NASH and Fibrosis after Bariatric Surgery



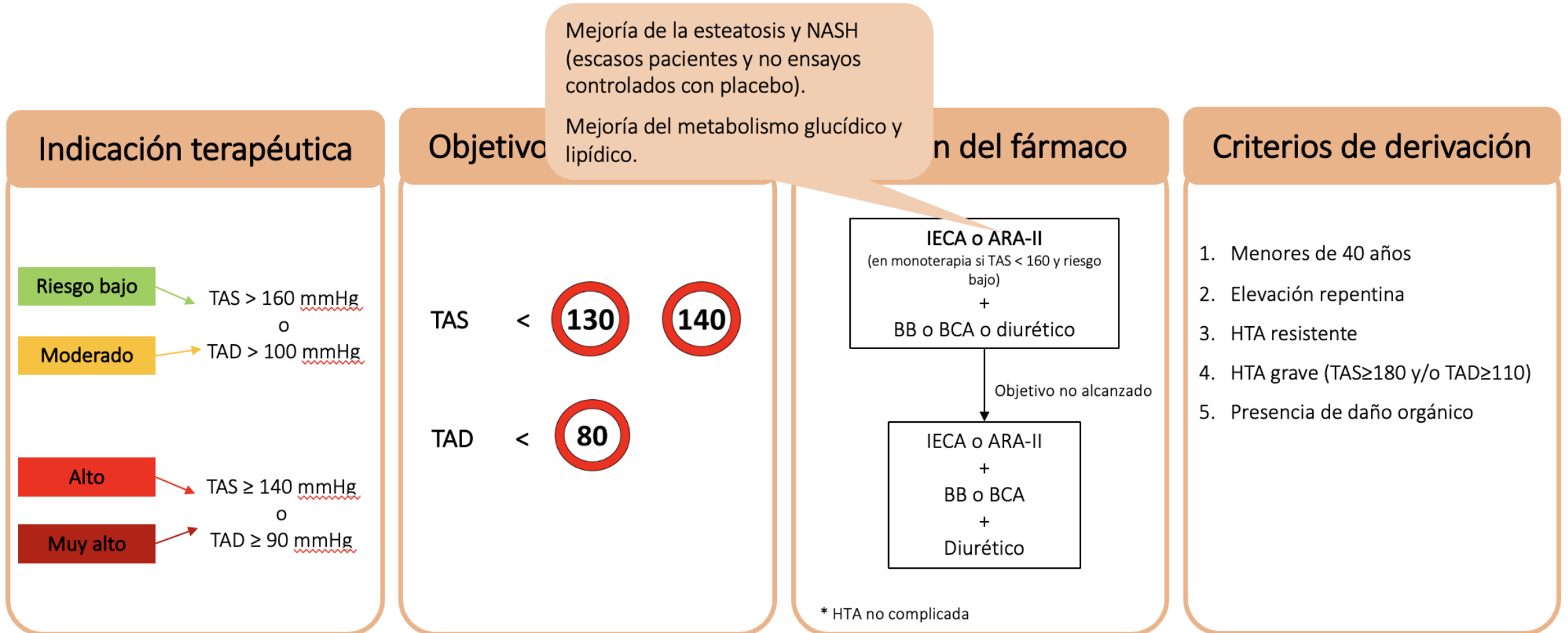
Gastroenterology



# Potencial aproximación terapéutica. Elección farmacológica.



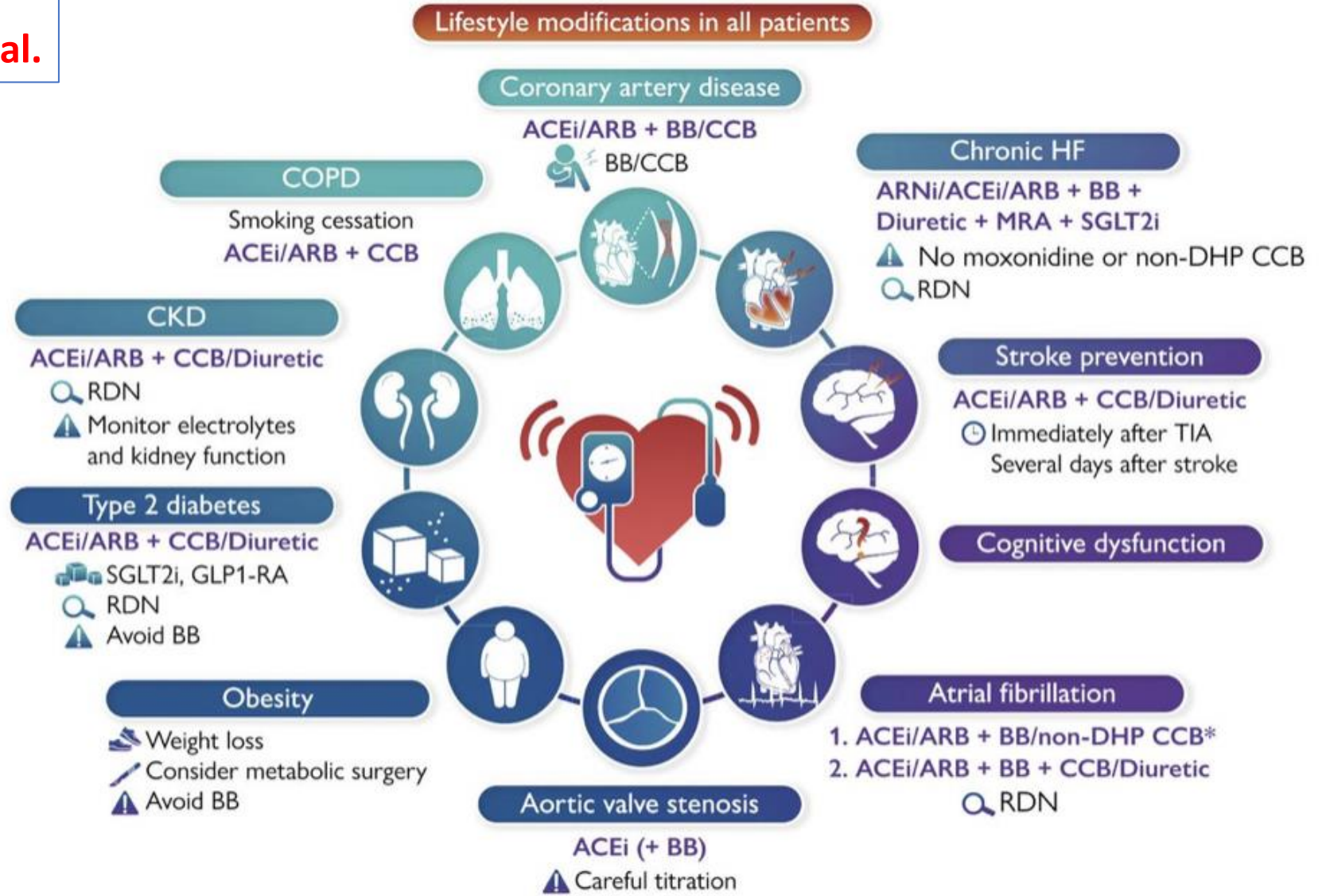
# Potencial aproximación terapéutica. Elección farmacológica. Hipertensión arterial.



BB = Beta bloqueante  
BCA = Bloqueante de los canales de calcio

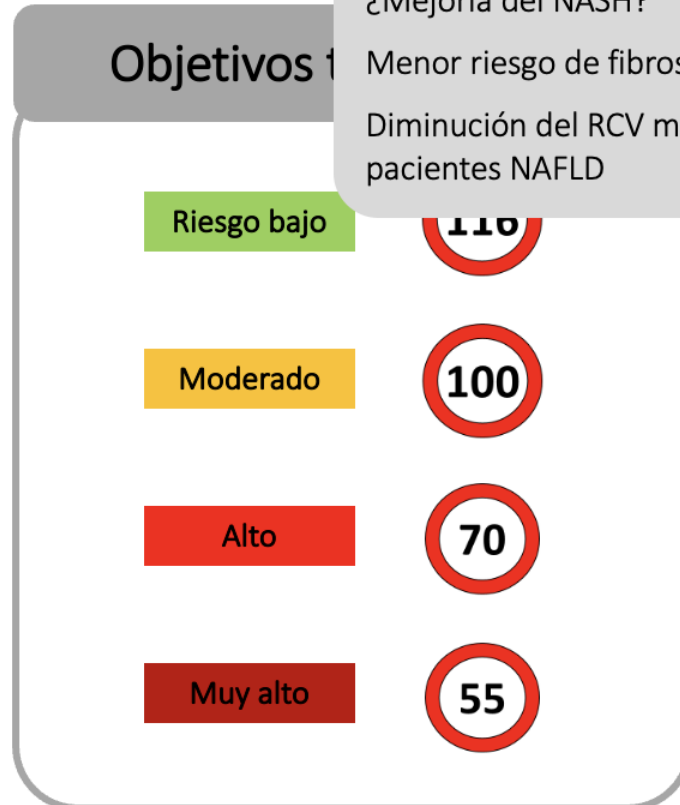
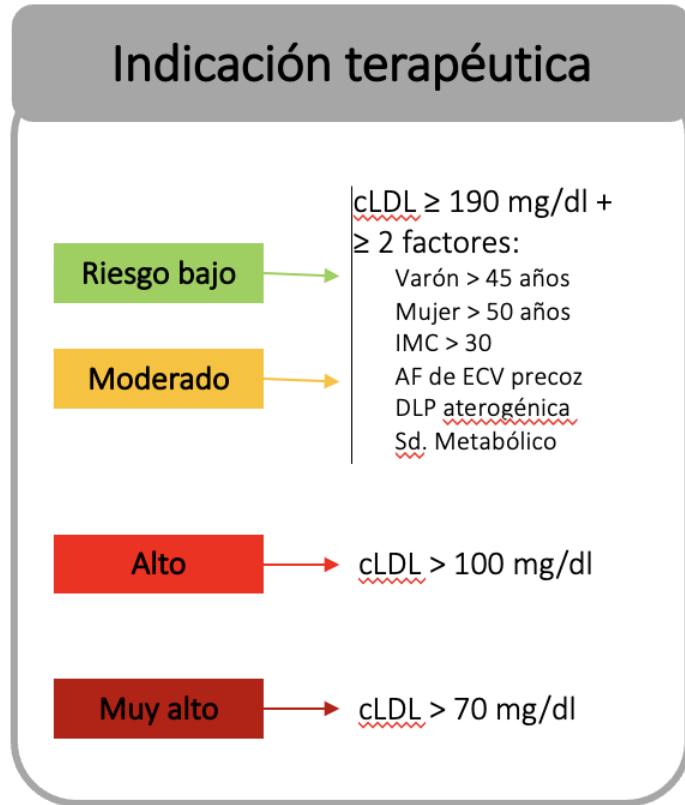
**Potencial aproximación terapéutica. Hipertensión arterial.**

-EVITAR uso de beta-bloqueantes como anti-HTA en pacientes con pre-diabetes, DM y obesidad (< sensibilidad a la insulina, > peso y > dislipidemia).

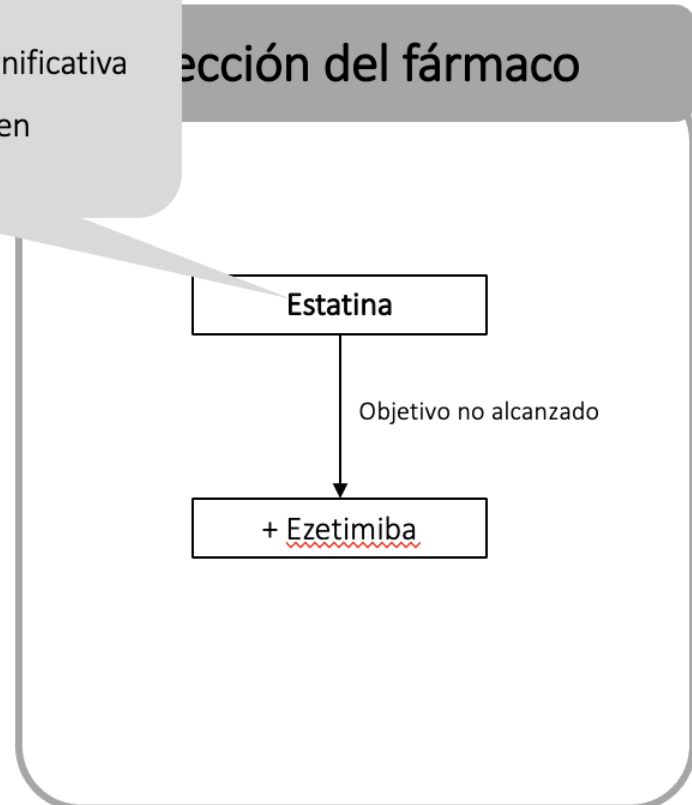


🔍 Under investigation    🏠 Antidiabetic therapy    🏃 Physical exercise    🧑 Coronary artery disease  
⚠ Noteworthy    🕒 Timing    🔪 Surgery

# Potencial aproximación terapéutica. Elección farmacológica. Dislipemia.



¿Mejoría del NASH?  
Menor riesgo de fibrosis significativa  
Diminución del RCV mayor en  
pacientes NAFLD



► **Hipertrigliceridemia:** Misma actitud que para cLDL. Si persiste TGC > 200 mg/dl, añadir **fenofibrato** o **ác. grasos omega-3**



# Potencial aproximación terapéutica. Elección farmacológica. Diabetes.

## Indicación terapéutica

### Diabetes Mellitus tipo 2

- Gluc  $\geq$  126 mg/dl, o
- Gluc 2h tras SOG de 75 g  $\geq$  200 mg/dl, o
- HbA1c  $\geq$  6,5%

### Prediabetes

- Gluc 110-125 mg/dl, y
- HbA1c  $\geq$  6,1%, y
- IMC  $>$  35

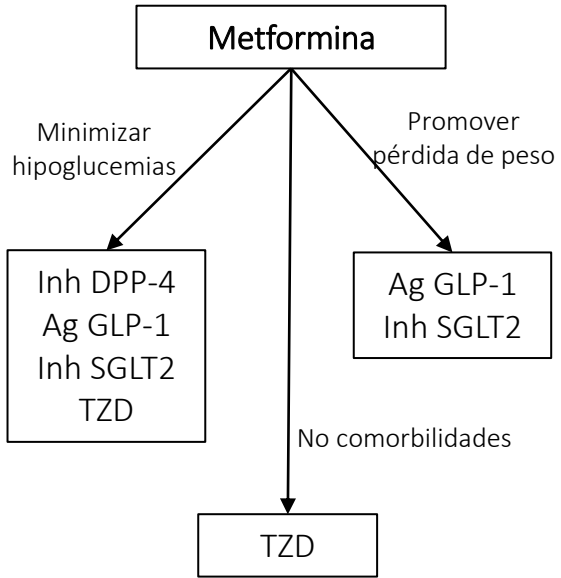
## Objetivos terapéuticos

HbA1c  $\leq$  7 %

HbA1c 7 - 8 %

- Mayor riesgo de hipoglucemia
- Edad avanzada o corta expectativa de vida
- Larga evolución de la DM2
- Comorbilidades importantes y/o antecedentes de ECV
- Poca capacidad de autocuidado y/o limitado apoyo familiar.

## Elección del fármaco



## Criterios de derivación

1. Fracaso 1ª línea + ECV o ERC
2. Fracaso 2ª línea
3. Hiperglucemia sintomática
4. Presencia de daño orgánico

**Agonistas GLP-1:** Dulaglutida (Trulicity), semaglutida (Ozempic), liraglutida (Victoza)  
**Inhibidores DPP-4:** Sitagliptina, linagliptina (Trajenta), saxagliptina  
**Inhibidores SGLT2:** Dapagliflozina, canagliflozina, empagliflozina  
**Tiazolidinedionas:** Pioglitazona, rosiglitazona

## Potencial aproximación terapéutica. Elección farmacológica. Diabetes.

Hypoglycemic drugs	Metabolic effects	Hepatic effects	Cardiovascular effects
<i>Metformin</i>	↓↓ glycemia ↓↓ IR = / ↓ AD = / ↓ weight	↓ steatosis = inflammation = fibrosis ↓ HCC	? ASCVD = heart failure
<i>Pioglitazone</i>	↓↓ glycemia ↓↓↓ IR ↓↓ AD ↑ weight	↓↓↓ steatosis ↓↓ inflammation ↓ fibrosis	↓ ASCVD ↑ heart failure (in pre-existing heart disease)
<i>GLP-1 receptor agonists</i>	↓↓ glycemia ↓↓ IR ↓ AD ↓↓ weight	↓↓ steatosis ↓ inflammation = fibrosis	↓ ASCVD = heart failure
<i>DPP-4 inhibitors</i>	↓ glycemia = / ↓ IR = AD = weight	= steatosis ? inflammation ? fibrosis	= ASCVD ↑ heart failure (saxagliptin)
<i>SGLT-2 inhibitors</i>	↓↓ glycemia ↓ IR = AD ↓ weight	↓ steatosis ? inflammation ? fibrosis	↓ ASCVD ↓ heart failure

**Table 1.** Effects of noninsulin glucose-lowering agents.

AD, atherogenic dyslipidaemia; ASCDV, atherosclerotic cardiovascular disease; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-; HCC, hepatocellular carcinoma; IR, insulin resistance; SGLT-2: sodium-glucose linked transporter 2.

Idoia Genua, Paula Iruzubieta, Juan Carlos Rodríguez-Duque, Antonio Pérez, Javier Crespo. NAFLD and type 2 diabetes: A practical guide for the joint management. G y H 2022. In press.

# Potencial aproximación terapéutica. Elección farmacológica. Diabetes.

## Indicación terapéutica

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## Objetivos terapéuticos

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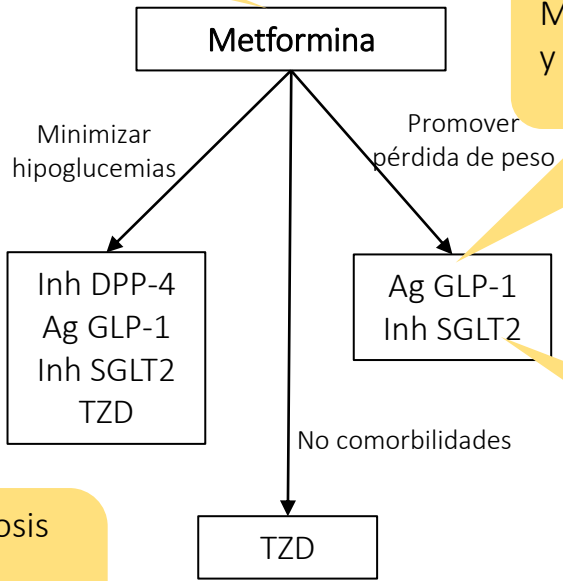
- Mayor riesgo de hipoglucemia
- Edad avanzada o corta expectativa de vida
- Larga evolución de la DM2
- Comorbilidades importantes y/o antecedentes de ECV
- Poca capacidad de adaptación o limitado apoyo

Mejoría del NASH y fibrosis avanzada

Aumento de peso y riesgo de fracturas

No mejoría del NASH  
Disminución del riesgo de cánceres, entre ellos el HCC

## Selección del fármaco



## Criterios de derivación

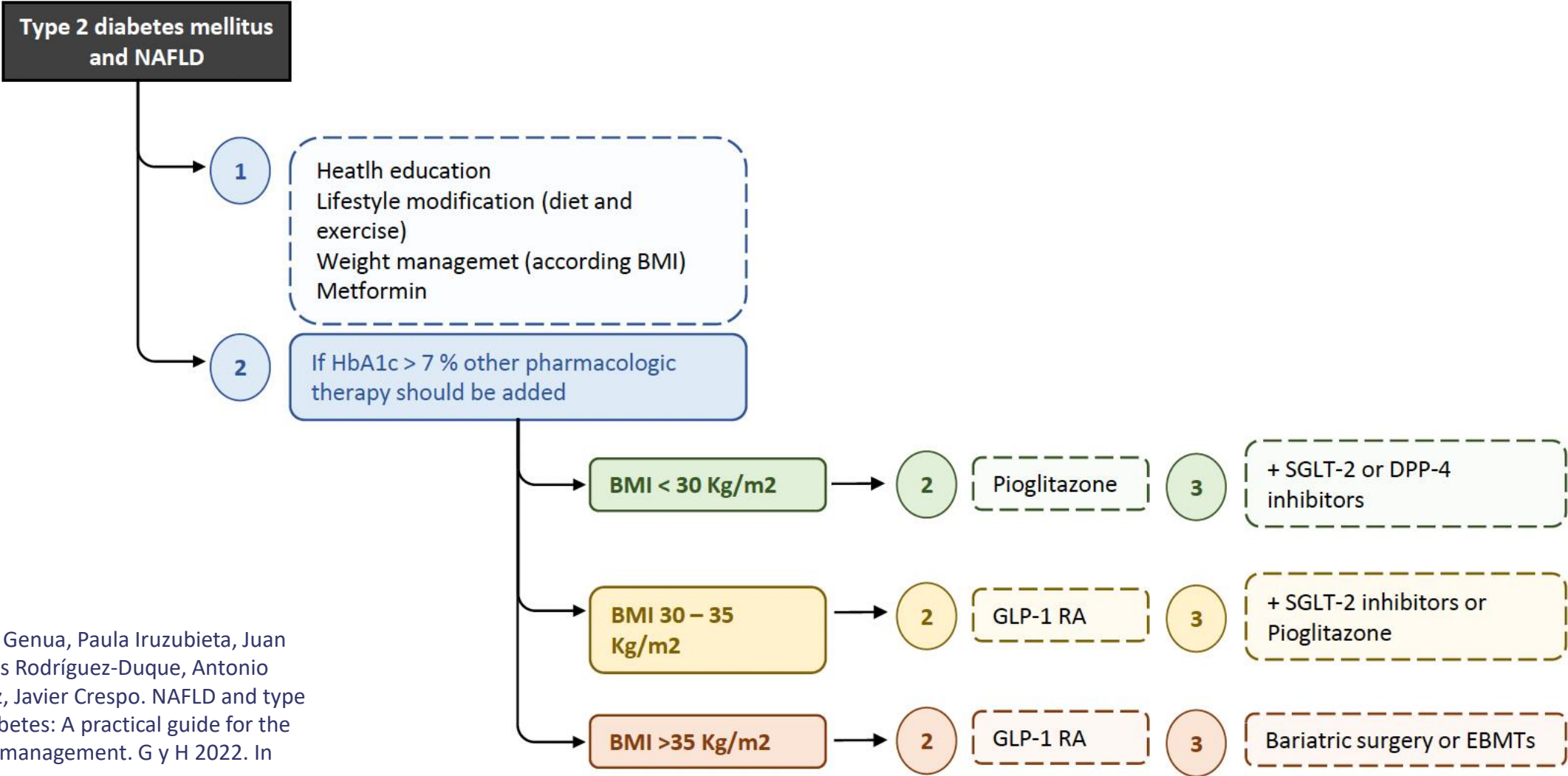
Mejoría del NASH (liraglutida y semaglutida)

3. Hiperglucemia sintomática
4. Presencia de daño orgánico

Reducción de la grasa y fibrosis (empaglifozina)

- Agonistas GLP-1:** Dulaglutida (Trulicity), semaglutida (Ozempic), liraglutida (Victoza)
- Inhibidores DPP-4:** Sitagliptina, linagliptina (Trajenta), saxagliptina
- Inhibidores SGLT2:** Empaglifozina, canaglifozina, empaglifozina
- Tiazolidinedionas:** Pioglitazona, rosiglitazona

# Potencial aproximación terapéutica. Elección farmacológica. Diabetes.



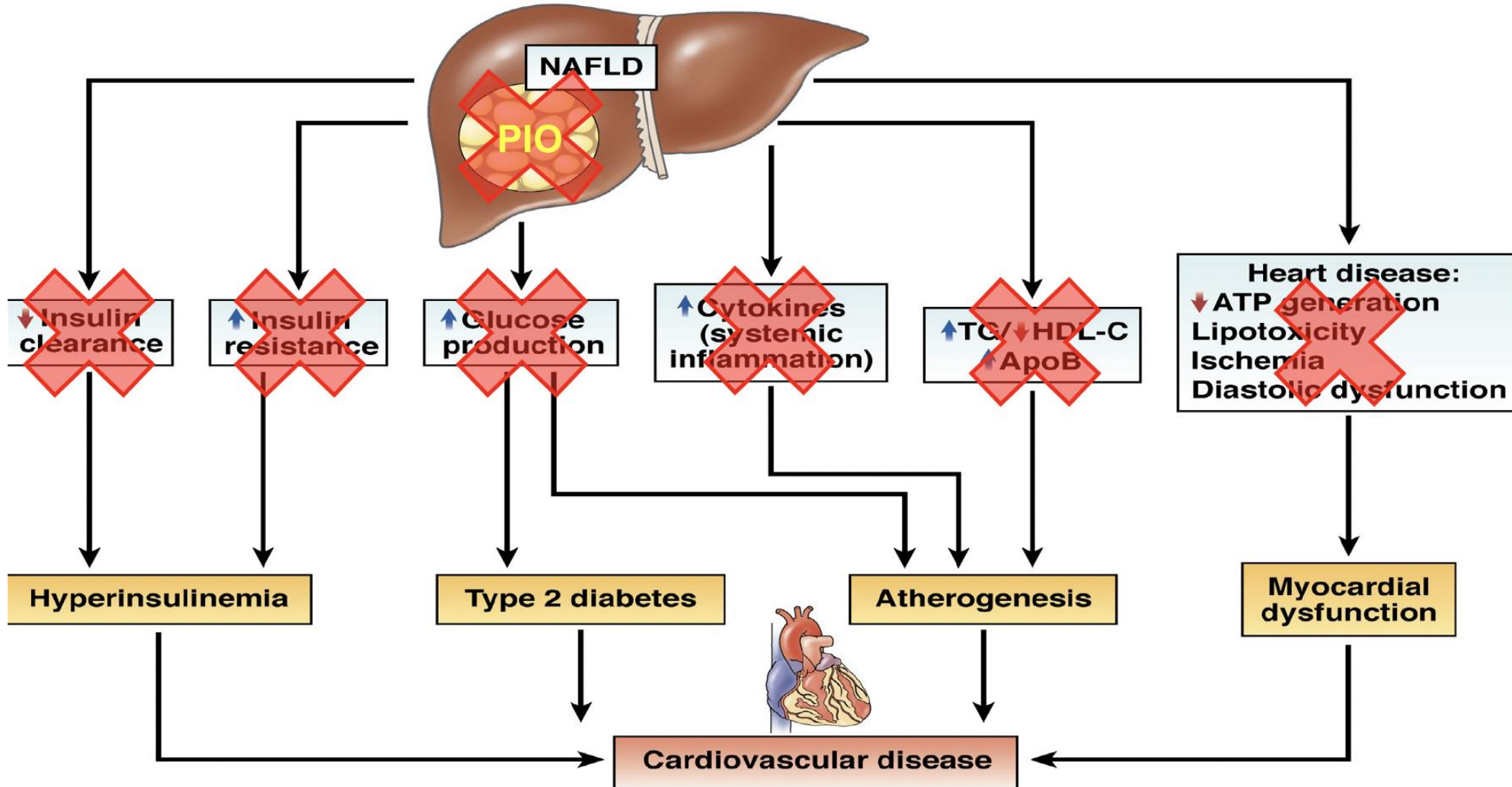
Idoia Genua, Paula Iruzubieta, Juan Carlos Rodríguez-Duque, Antonio Pérez, Javier Crespo. NAFLD and type 2 diabetes: A practical guide for the joint management. G y H 2022. In press.

Cusi K, et al. Endocrine Practice 2022



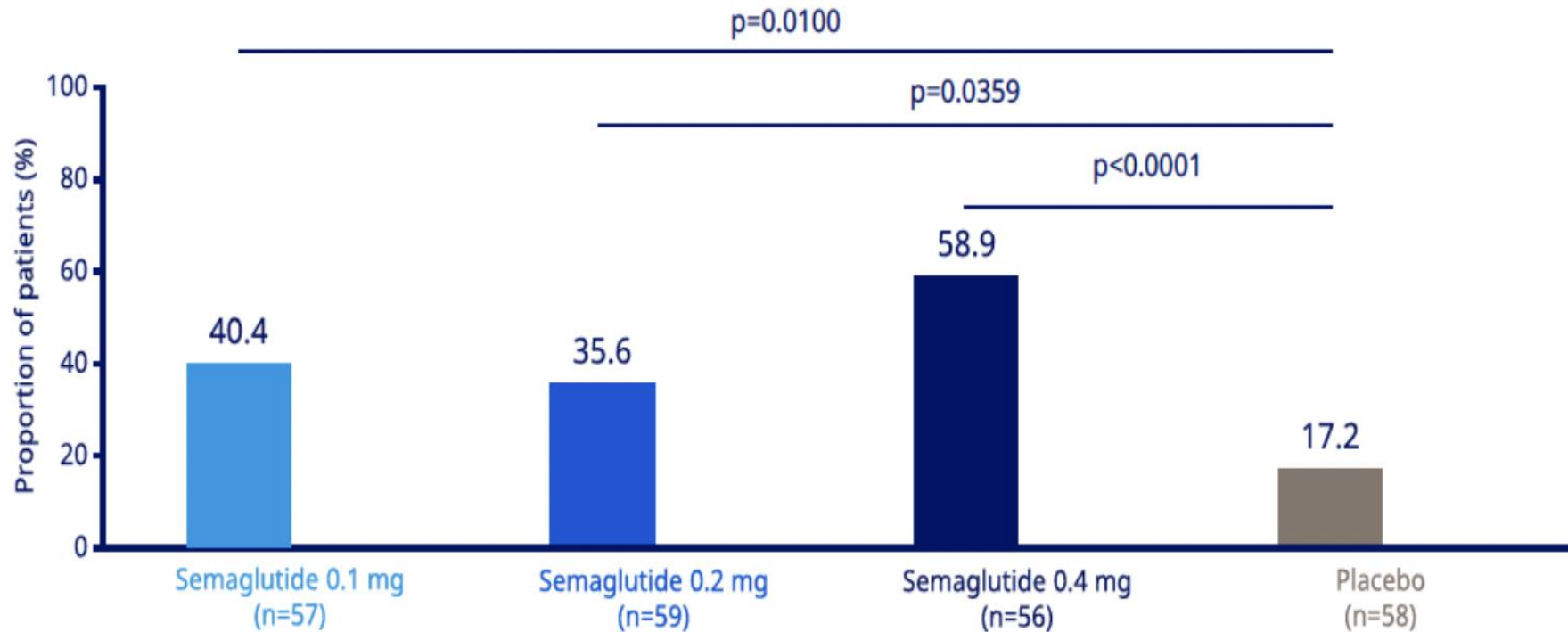
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## Pioglitazona



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**Semaglutide**

**Resolution of steatohepatitis and no worsening in liver fibrosis**  
(Patients with fibrosis stage 2 or 3 at baseline)



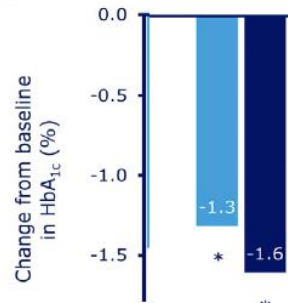
Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Patients with missing data handled as non-responders. p<0.05 signifies statistical significance.

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## Sema + Pioglitazona

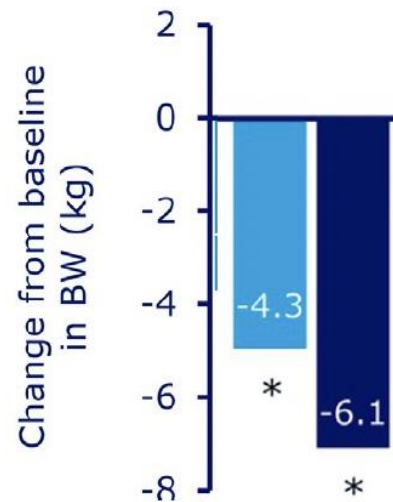
### HbA1c

Treatment duration:  
HbA<sub>1c</sub> at baseline:

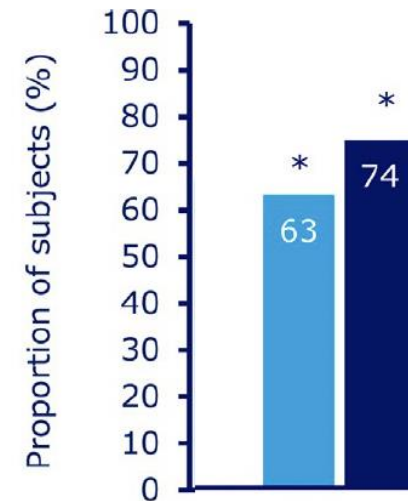


Background: (MET, TZD,  
MET/TZD)  
Treatment duration: 56 weeks

### Weight loss (kg) with semaglutide added to pioglitazone



### Patients achieving HbA<sub>1c</sub> <7.0% with no weight gain and no hypoglycemia

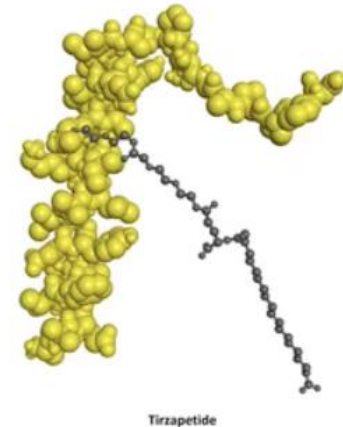


■ Semaglutide 0.5 mg    ■ Semaglutide 1.0 mg

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## Tirzepatide: Dual GIP/GLP-1 receptor agonist

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIP and GLP-1 receptors
- 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Mean half-life of ~5 days (116.7 h), enabling once-weekly dosing
- *In vitro*, it has similar affinity as native GIP at the GIPR and is less potent than native GLP-1 at the GLP-1R (“imbalanced”)



**Single agent possessing activity at 2 pharmacologic targets**

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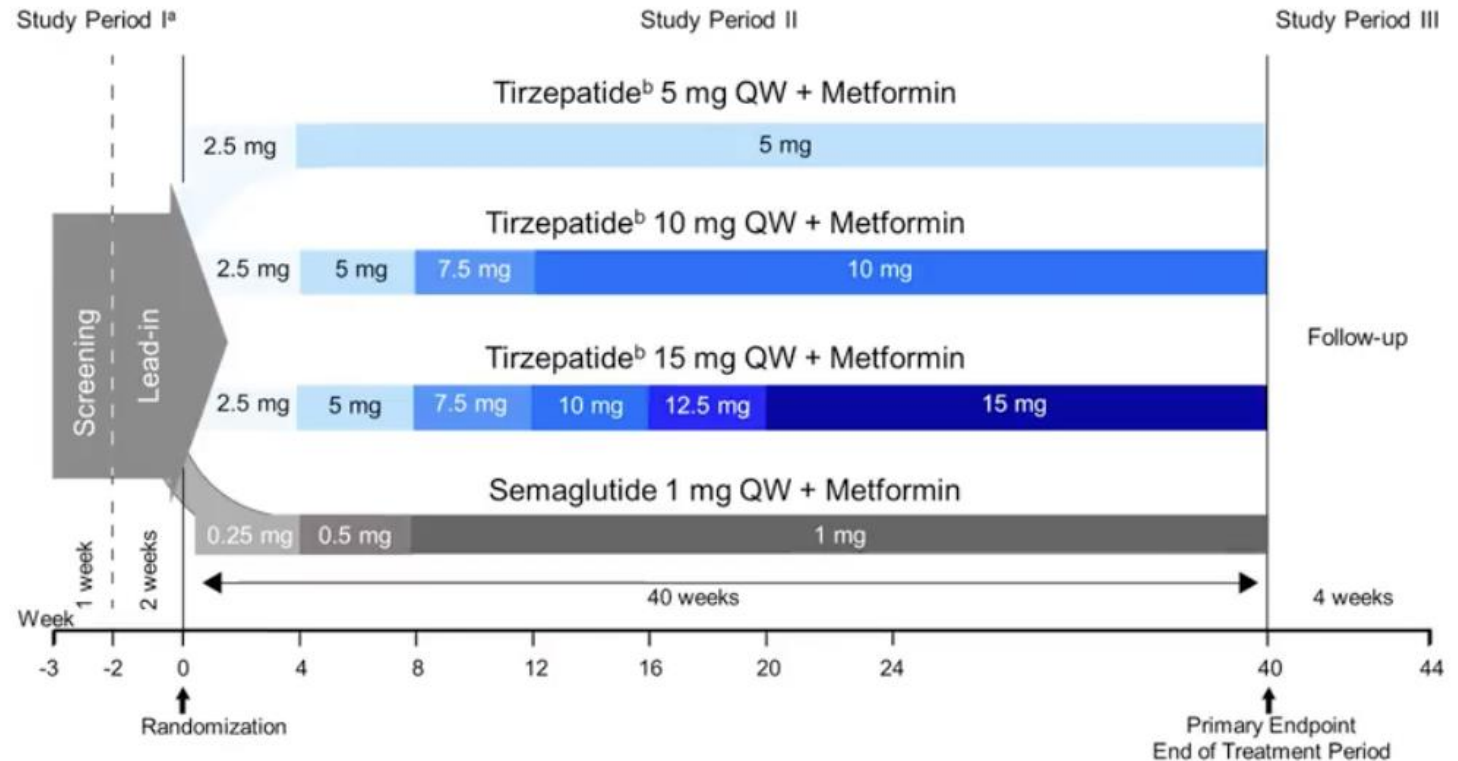
**TIRZEPATIDE.** Randomizado, abierto multicéntrico, multinacional, controlado con semaglutide, grupos paralelos.

### Key Inclusion Criteria

- T2D
- HbA1c  $\geq 7.0\%$  to  $\leq 10.5\%$  at screening
- BMI  $\geq 25$  kg/m<sup>2</sup> with stable weight
- Have been on stable T2D treatment with metformin  $\geq 1500$  mg/day in the 3 months prior to screening and between screening and randomization

### Key Exclusion Criteria

- T1D
- History of acute pancreatitis
- eGFR  $< 45$  mL/min/1.73 m<sup>2</sup>
- Use of any antihyperglycemic treatment other than metformin in the 3 months prior to screening

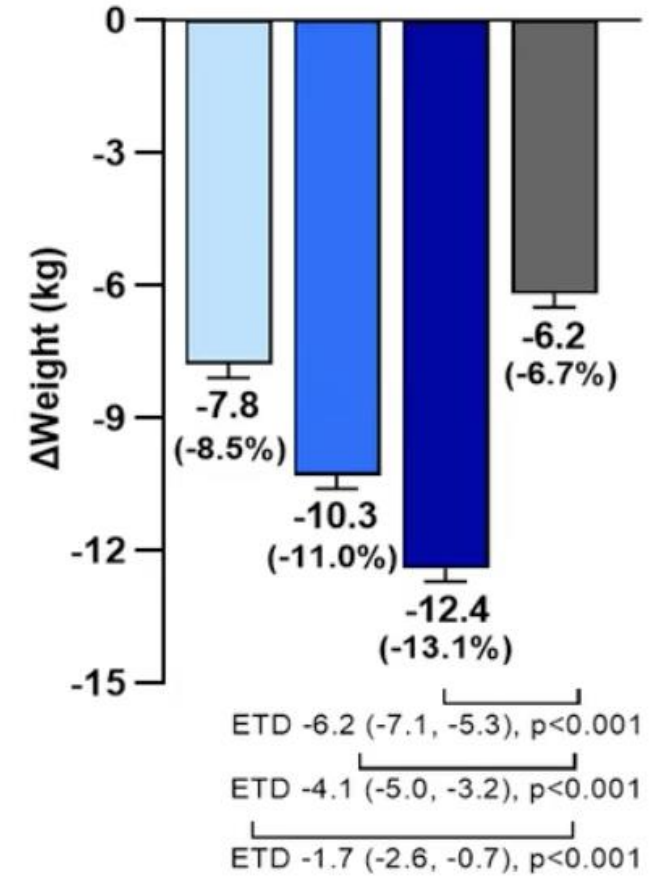
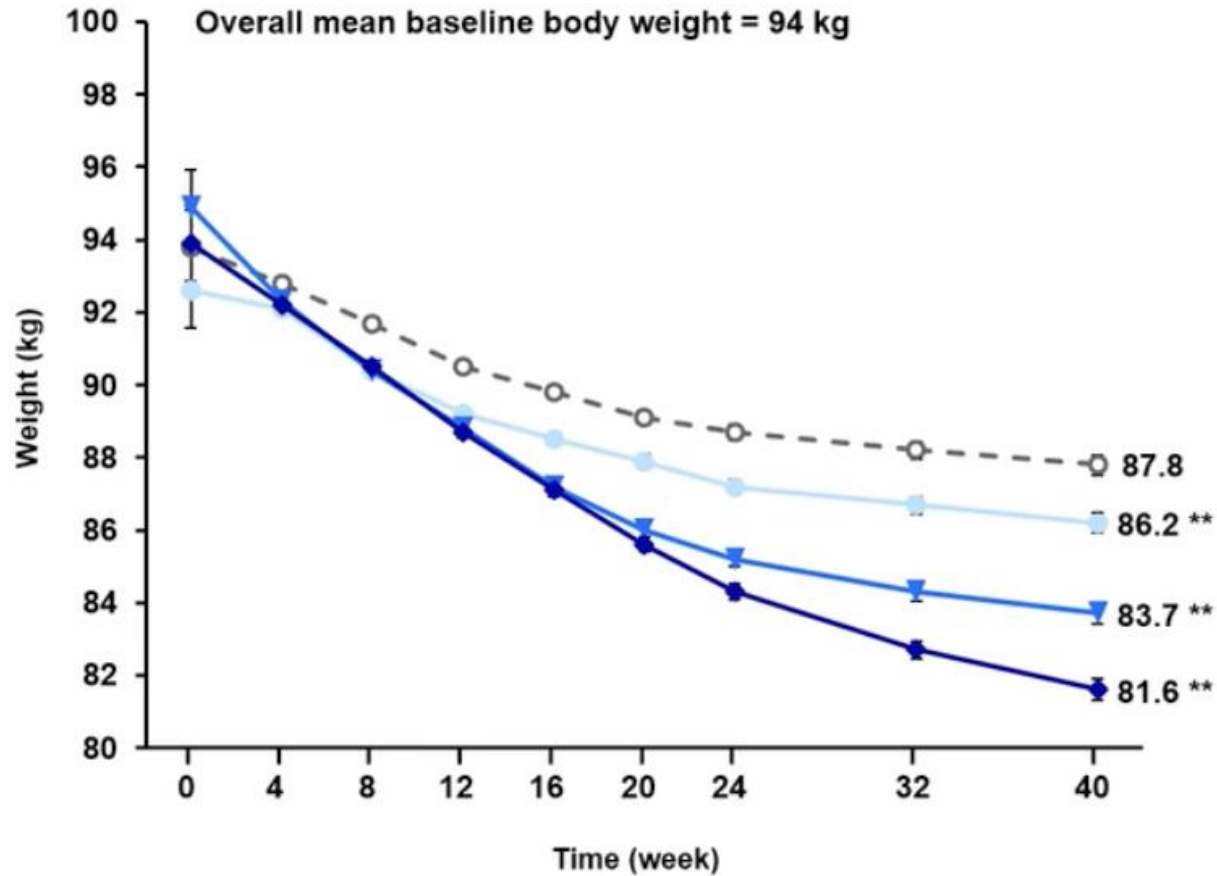


Participating Countries: US, Argentina, Australia, Brazil, Canada, Israel, Mexico and UK.

<sup>a</sup>Stable doses of metformin  $\geq 1500$  mg/day for at least 3 months prior to Visit 1 and during the screening/lead-in period. <sup>b</sup>All tirzepatide doses were double-blinded.

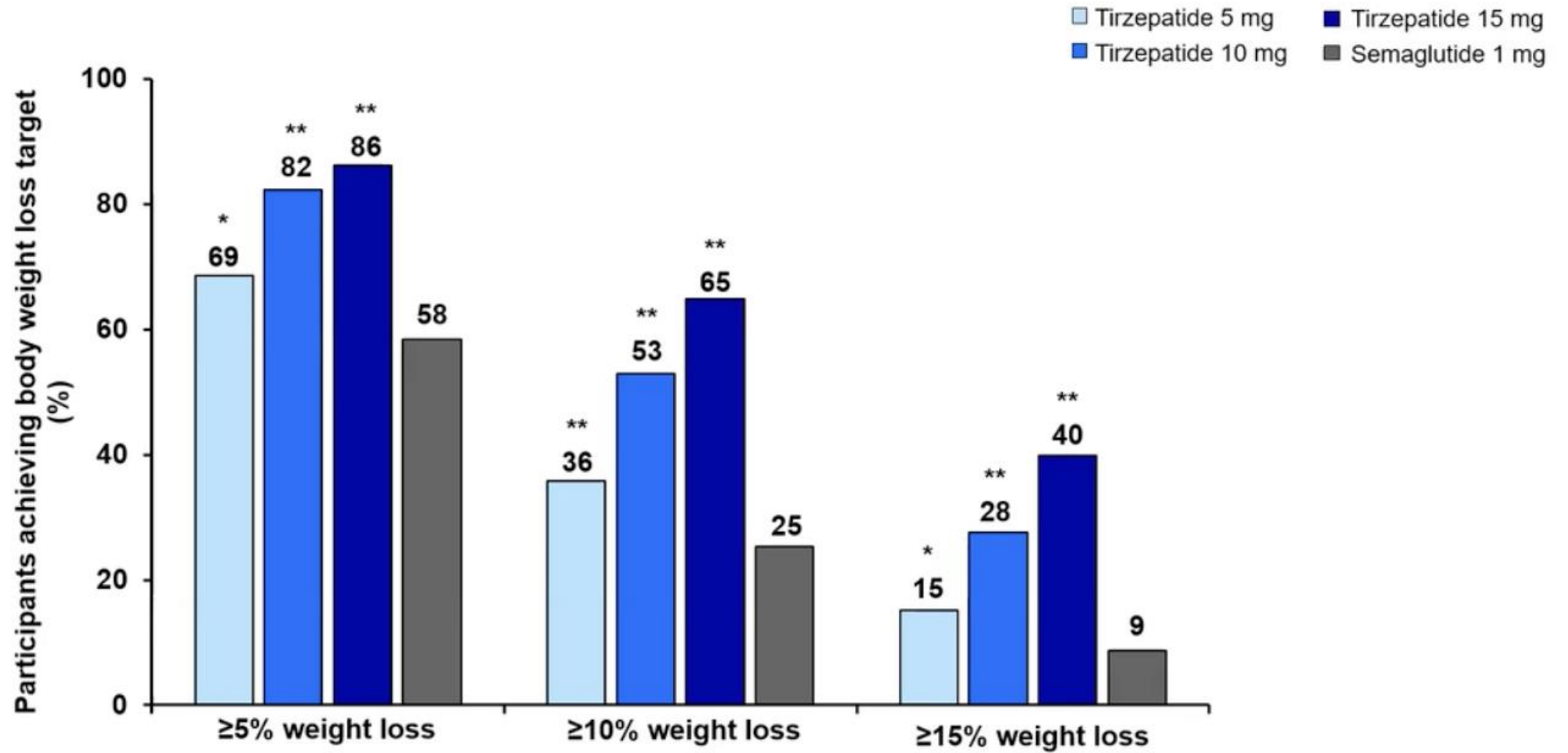


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Data are LSM (SE). Estimated treatment differences at 40 weeks are LSM (95%CI); mITT (efficacy estimand) ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved. \*\*p<0.001 vs. semaglutide 1 mg

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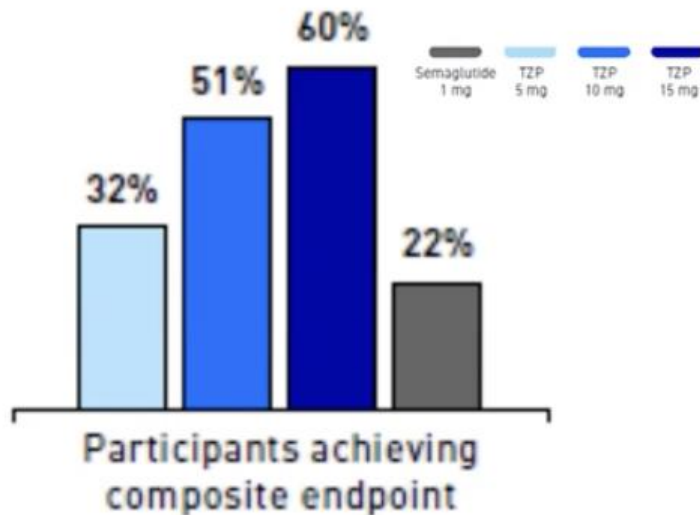


Data are estimates; mITT (efficacy estimand). Logistic regression. \*p<0.05 and \*\*p<0.001 vs. semaglutide 1 mg

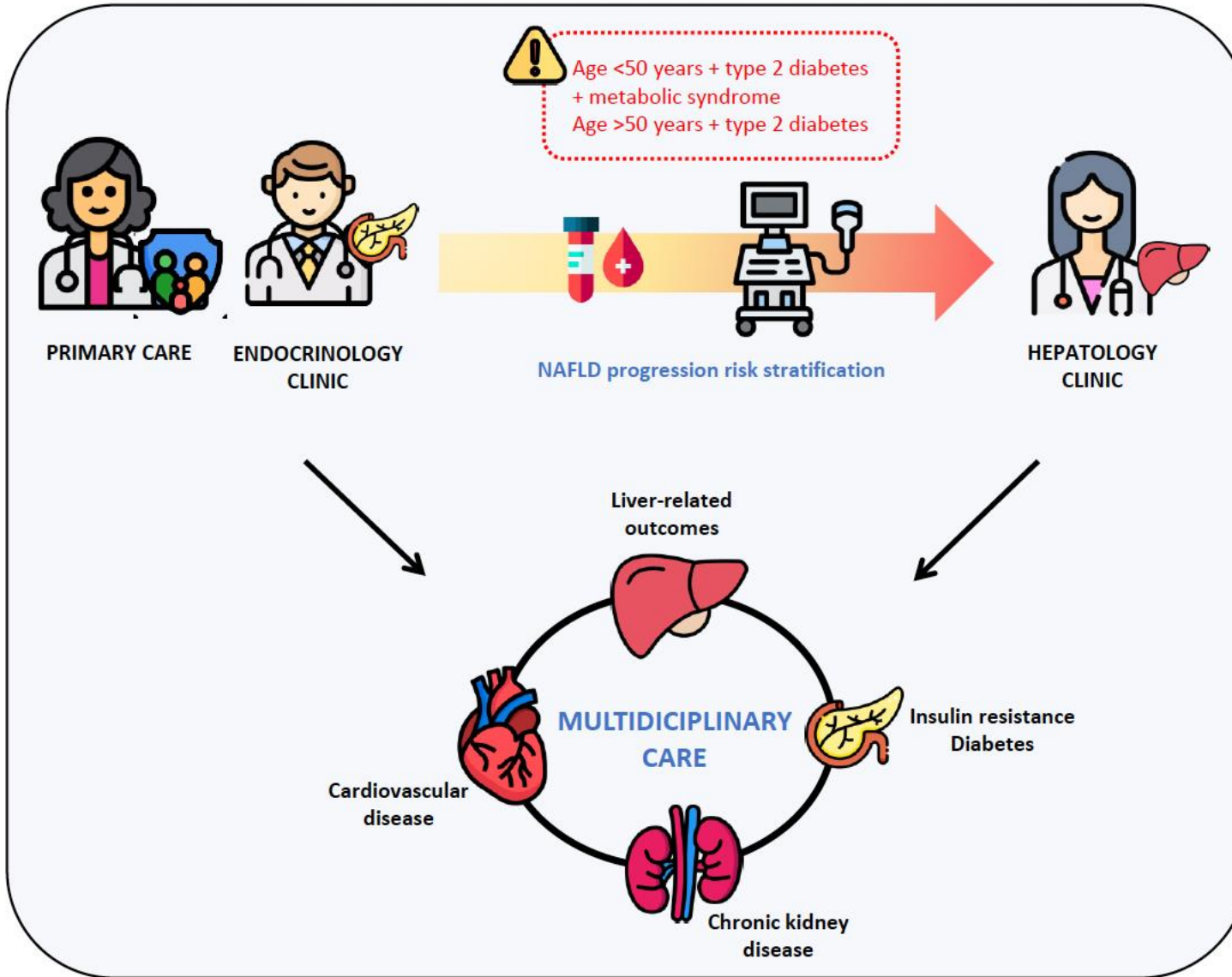
Potencial aproximación terapéutica. **Elección farmacológica. Diabetes.**

**Prespecified composite endpoint:**

- HbA<sub>1c</sub> ≤6.5%, and
- Weight loss ≥10%, and
- No Level 2 (<54 mg/dL [3.0 mmol]) or Level 3 (severe) hypoglycemia



**Up to 60% of participants on tirzepatide achieved composite endpoint compared to 22% on once-weekly semaglutide 1 mg**



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NAFLD and type 2 diabetes: A practical guide for the joint management. G y H 2022. In press.



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# Gracias

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