“Hipertensión portal clínicamente significativa: historia natural y manejo”

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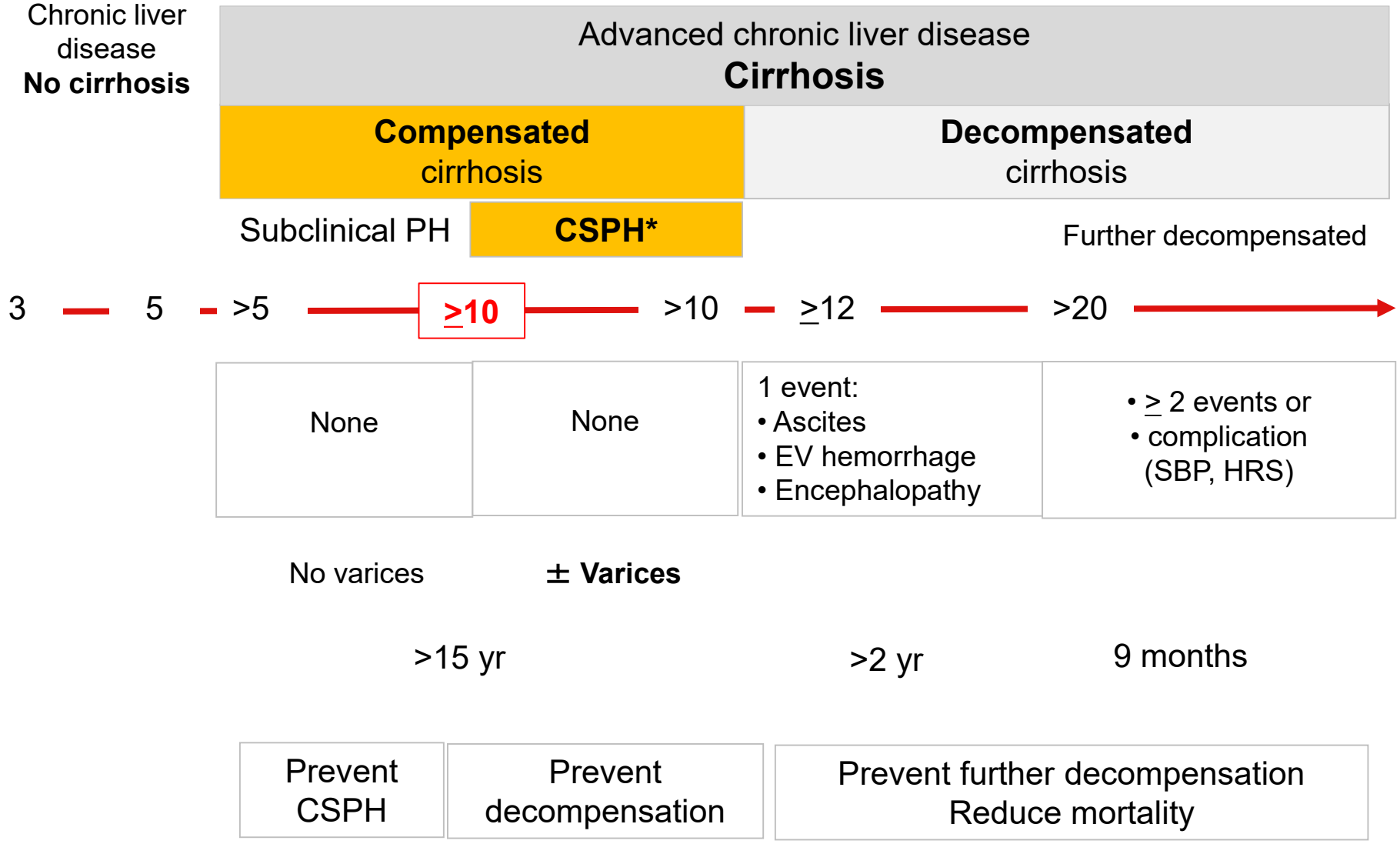
Nuevos paradigmas en cirrosis compensada: De Baveno VI a VII

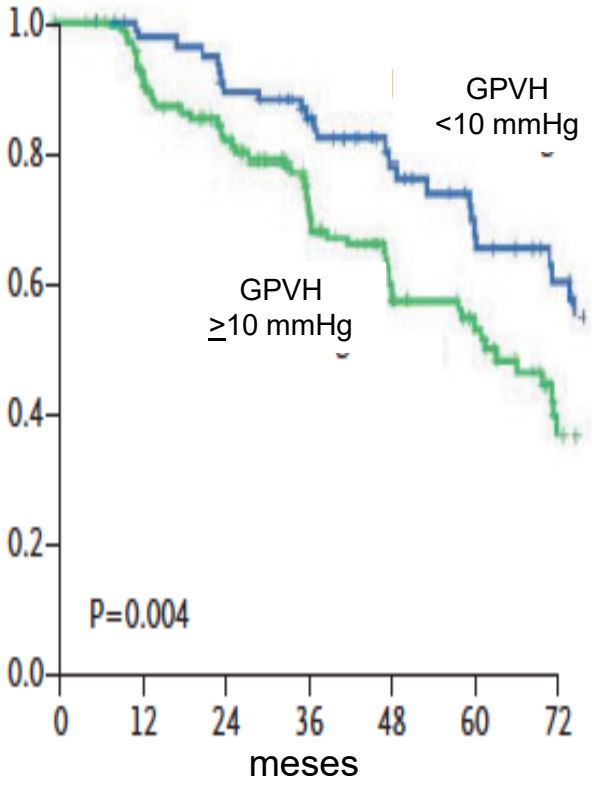
- Enfermedad hepática crónica avanzada (cACLD) ➔ cirrosis
- Hipertensión portal clínicamente significativa (“CSPH”) ➔ estratificar el riesgo en cirrosis compensada (“cACLD”)
- Diagnóstico de CSPH ➔ tests no invasivos
- Beta-bloqueantes ➔ reducir el riesgo de descompensación en CSPH

Stages of cirrhosis



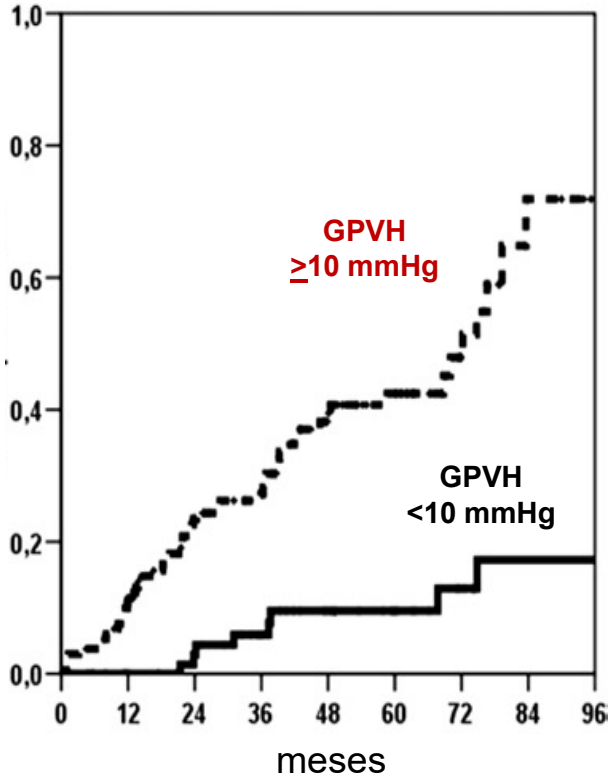
Hipertensión portal clínicamente significativa (GPVH ≥10 mmHg):
Riesgo de desarrollar varices y descompensación clínica en cirrosis

Probabilidad de desarrollo de varices



RJ Groszmann et al.
NEJM 2005

Probabilidad de descompensación clínica

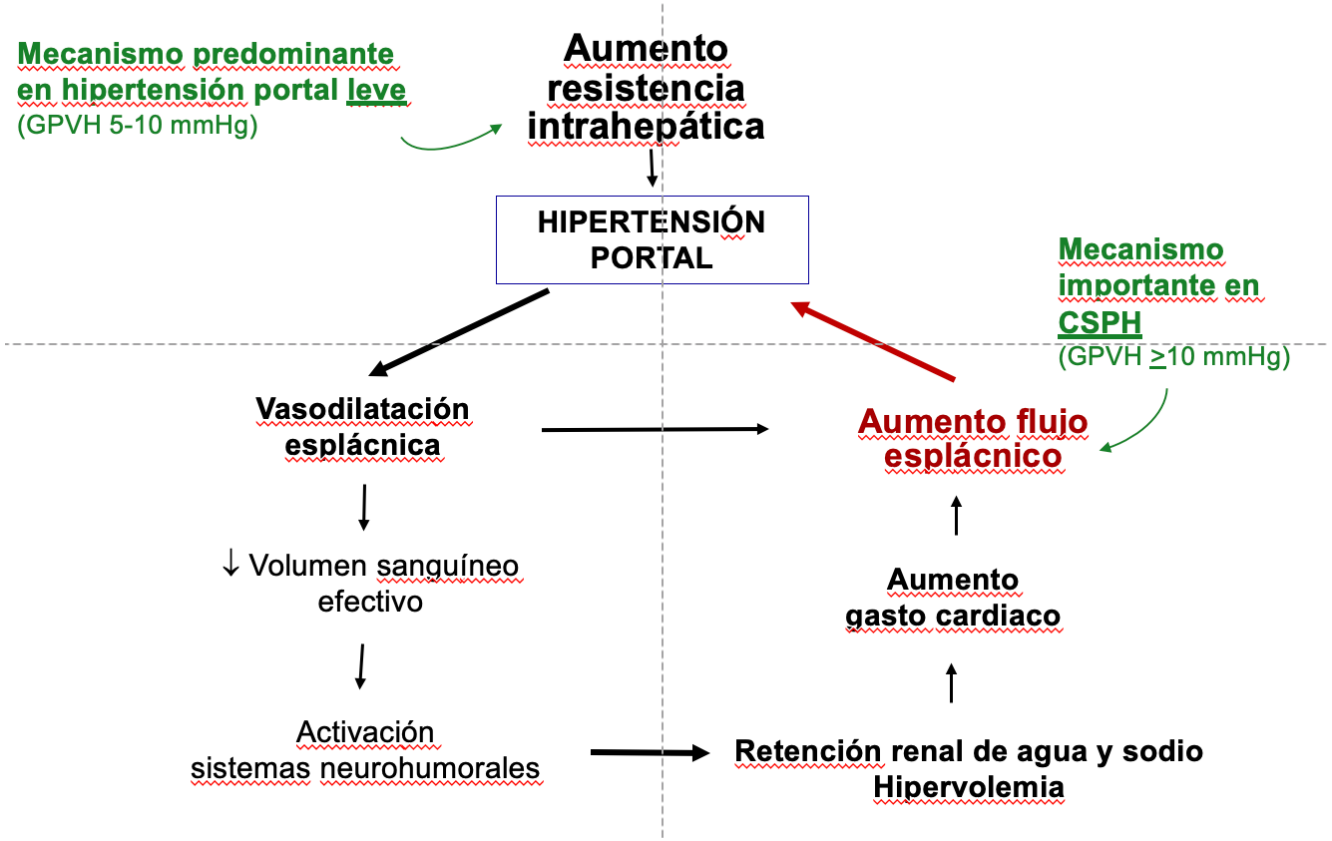


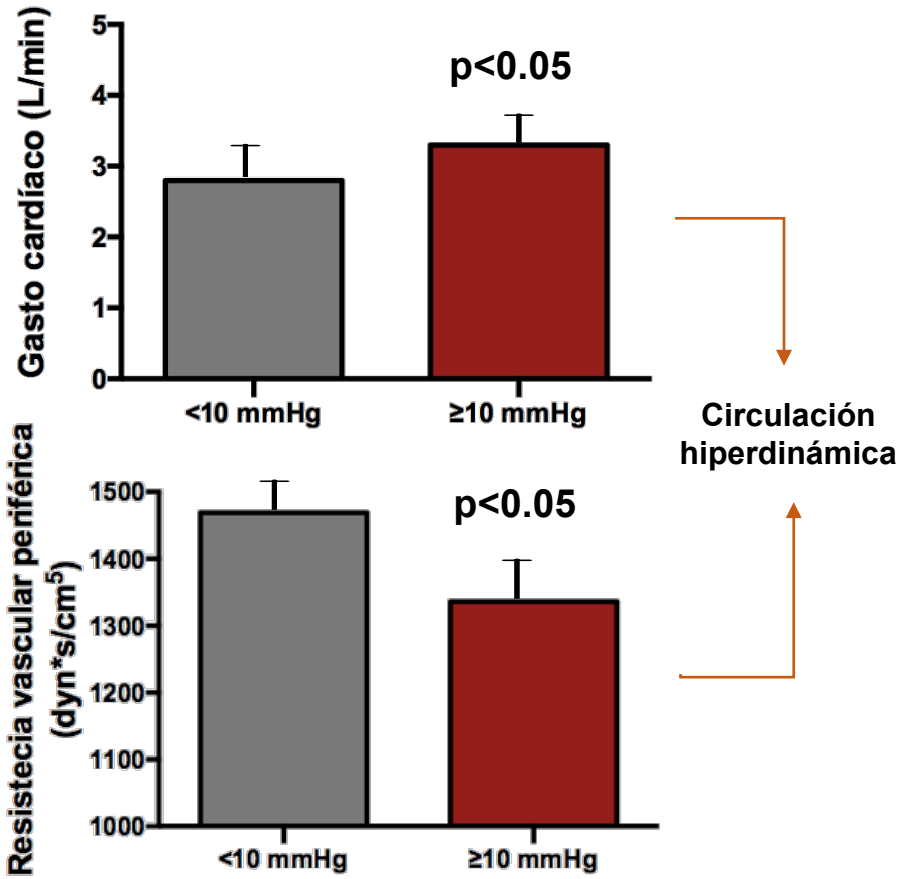
213 pacientes cirrosis compensada:
29% descompensación
- 21% ascitis
- 3% hemorragia
- 5% encefalopatía

Valor predictivo negativo 90% para ***NO*** desarrollo de descompensaciónx

C Ripoll et al.
Gastroenterology 2007

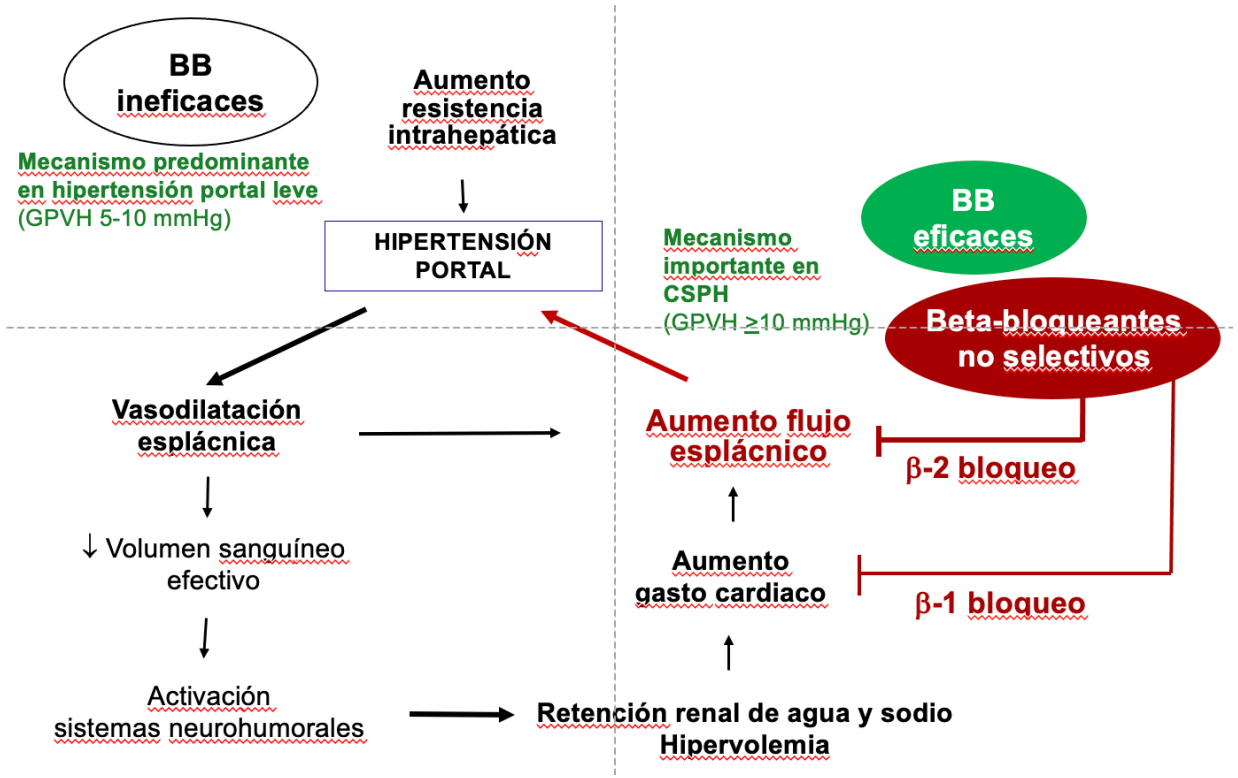
Hipertensión portal clínicamente significativa (GPVH ≥10 mmHg): Contribución del aumento del flujo esplácnico a la hipertensión portal



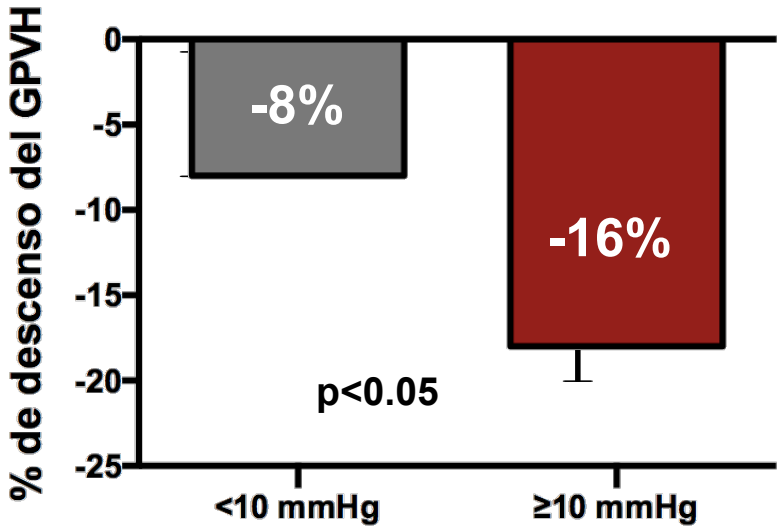


C Villanueva et al. Hepatology 2015

Hipertensión portal clínicamente significativa (GPVH ≥10 mmHg):
Mayor reducción de la presión portal con beta-bloqueantes



Reducción del GPVH con propranolol en pacientes con cirrosis compensada GPVH <10 o ≥10 mmHg



C Villanueva et al. Hepatology 2015

Hipertensión portal clínicamente significativa (GPVH ≥10 mmHg): Riesgo de primera descompensación clínica en cirrosis

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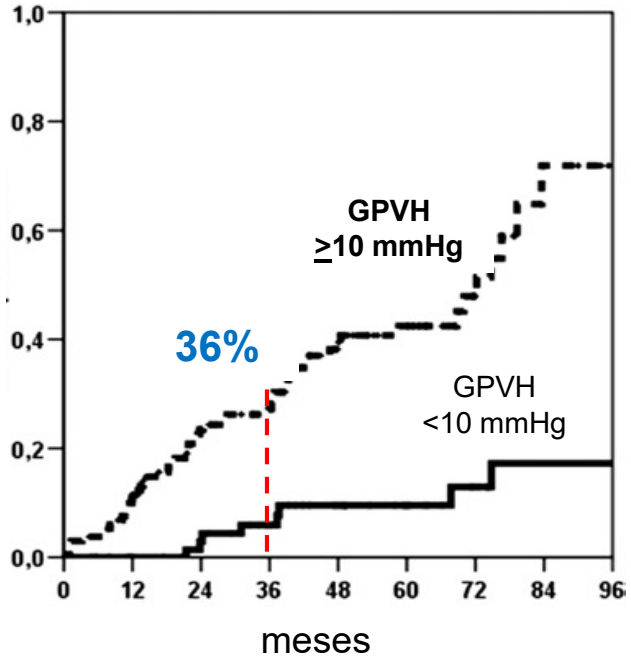
Probabilidad de descompensación clínica

213 cirrosis compensada con GPVH < o ≥10mmHg

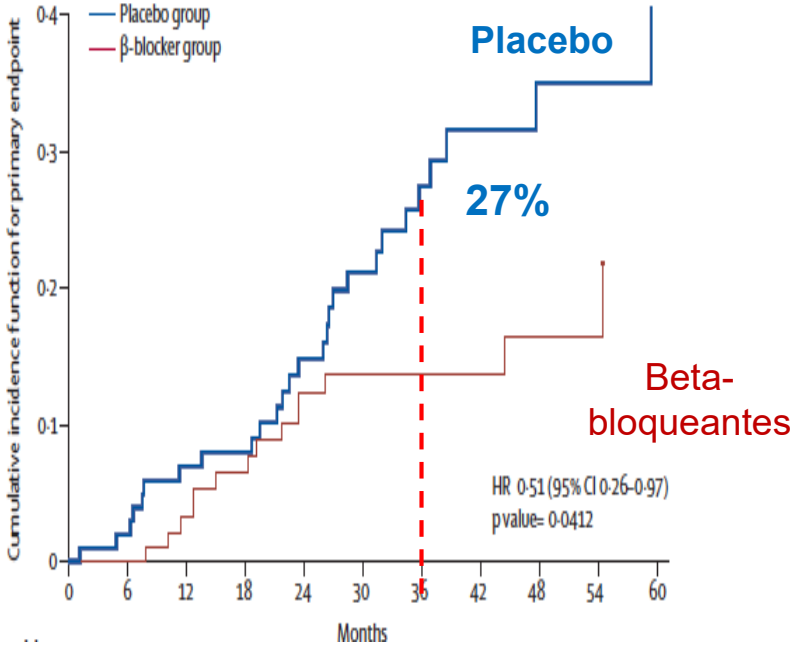


213 pacientes cirrosis compensada:
24% alcohol
62% VHC

C Ripoll et al. Gastroenterology 2007

Probabilidad de descompensación clínica

201 cirrosis compensada con GPVH ≥10mmHg tratados con Placebo o Beta-bloqueantes



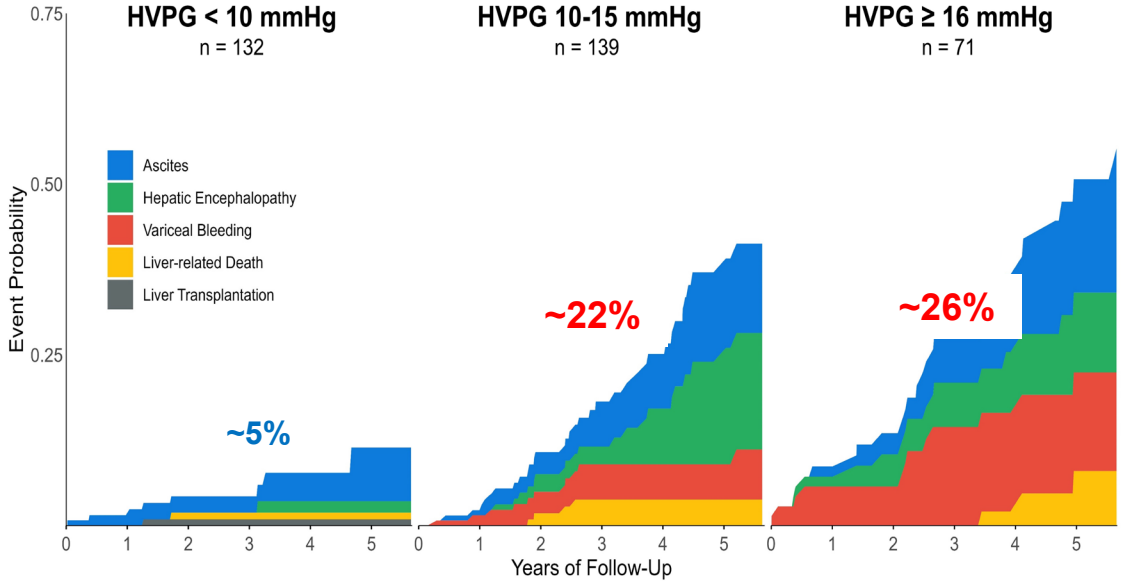
201 pacientes cirrosis compensada:
23% alcohol
56% VHC

C Villanueva et al. Lancet 2019

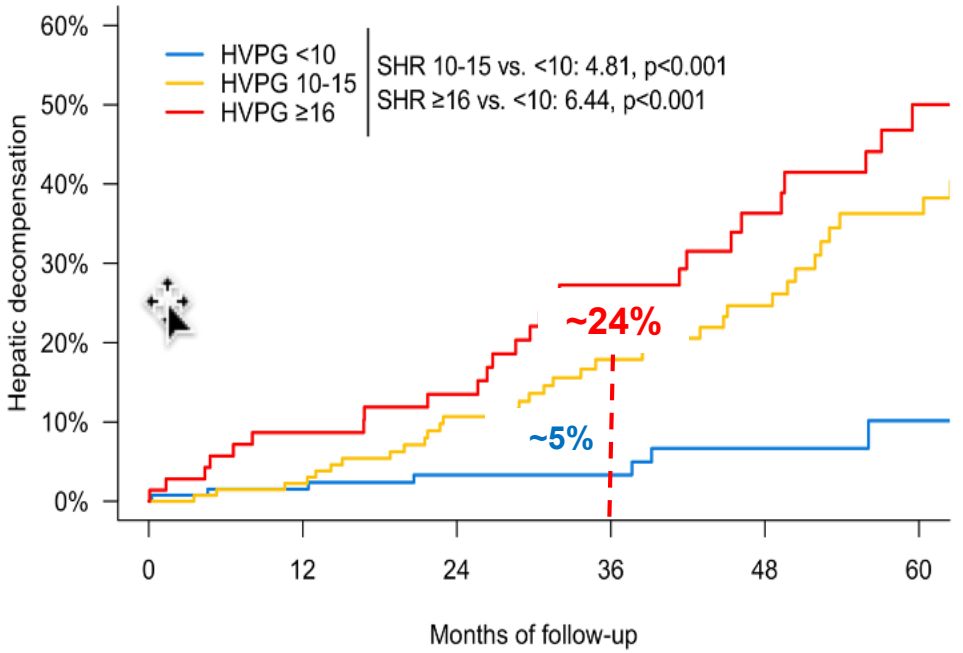
Accuracy of HVPG to predict the risk of decompensation in compensated cirrhosis by MASLD

European cohort, 342 patients
Compensated cirrhosis (cACLD) due to **MASLD**
F-up 41.5 m

Incidence of first liver-related events according to severity of portal hypertension



Incidence of hepatic decompensation according to the absence/presence of CSPH

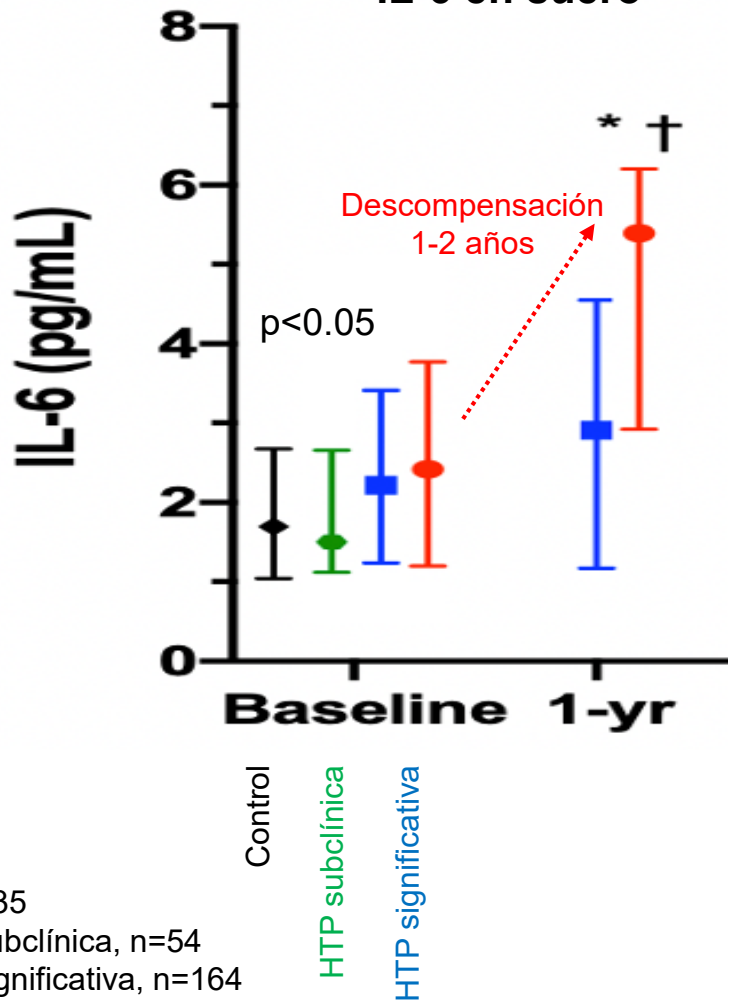


R Paternostro et al. EASL 2023

Hipertensión portal clínicamente significativa

Inflamación sistémica de bajo grado que aumenta precediendo a descompensación

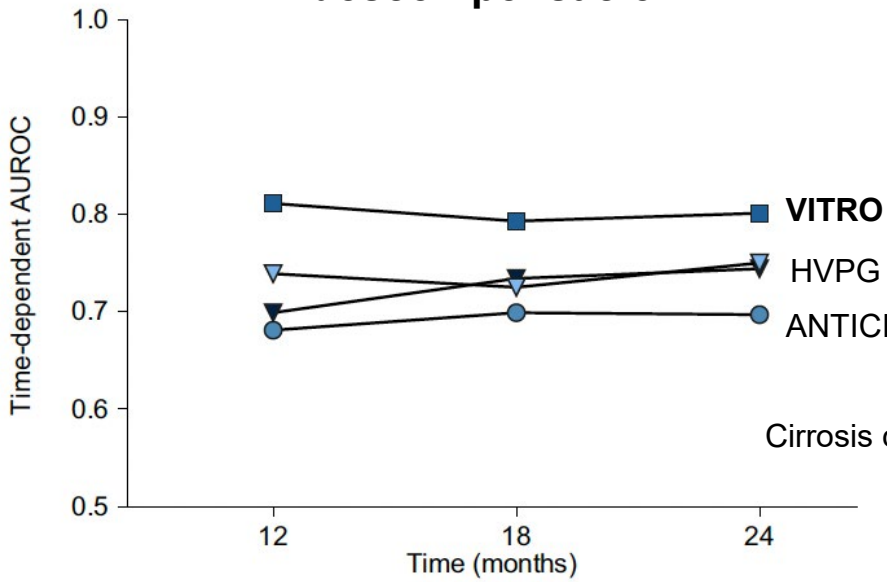
IL-6 en suero



Controles, n=35
Cirrosis HP subclínica, n=54
Cirrosis HP significativa, n=164

R Sánchez et al. En revisión

AUROC para primera descompensación



Cirrosis compensada, n=420

N° at risk			
HVPG	0.739	0.725	0.750
VITRO	0.811	0.793	0.801
ANTICIPATE	0.683	0.702	0.699
LSM/PLT ratio	0.699	0.734	0.744

→ All identify patients at substantial risk
→ VITRO greater diagnostic accuracy

M Jachs et al. JHEP 2024

Diagnosis of clinically significant portal hypertension

Definition: HVPG ≥10 mmHg

Meaning:
- at risk of clinical decompensation
- ↑ splanchnic blood flow contributes to portal hypertension

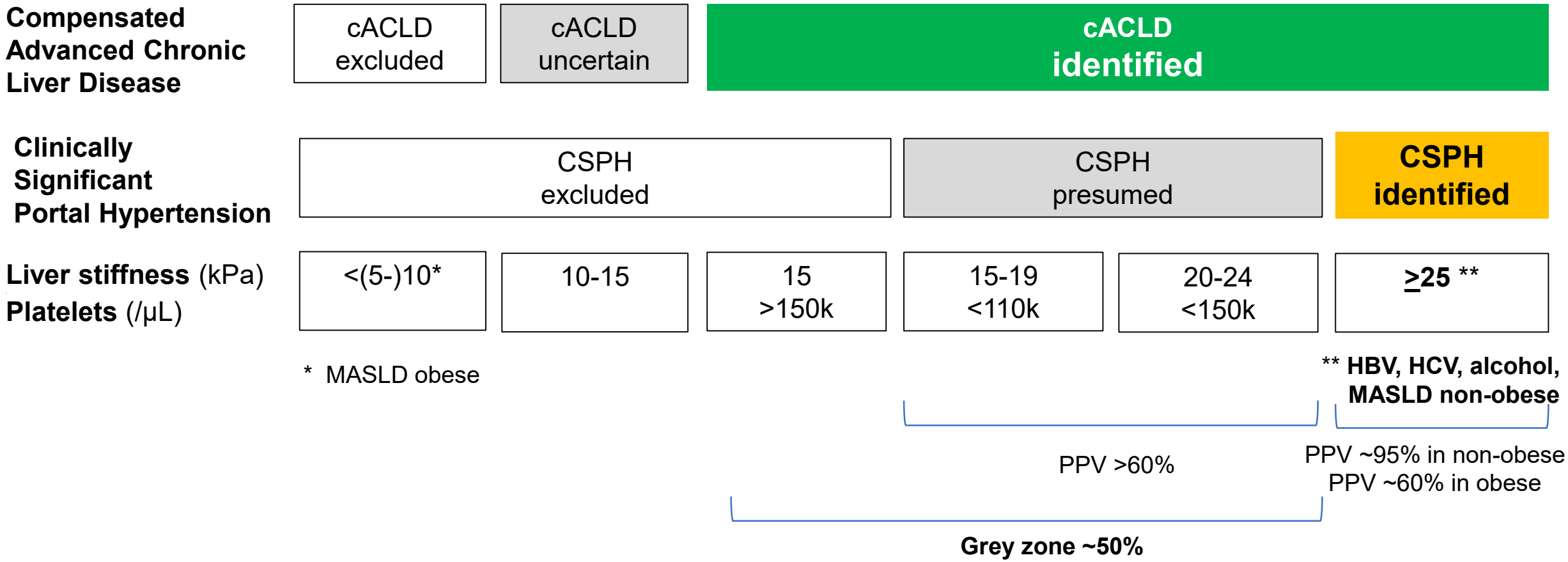
Diagnosis:

- Gastro/esophageal varices (endoscopy, CT)
- Portosystemic collateral vessels (US, CT)
- **Rule of 5:** transient elastography and platelets

R De Franchis et al. Baveno VII. JHEP 2022

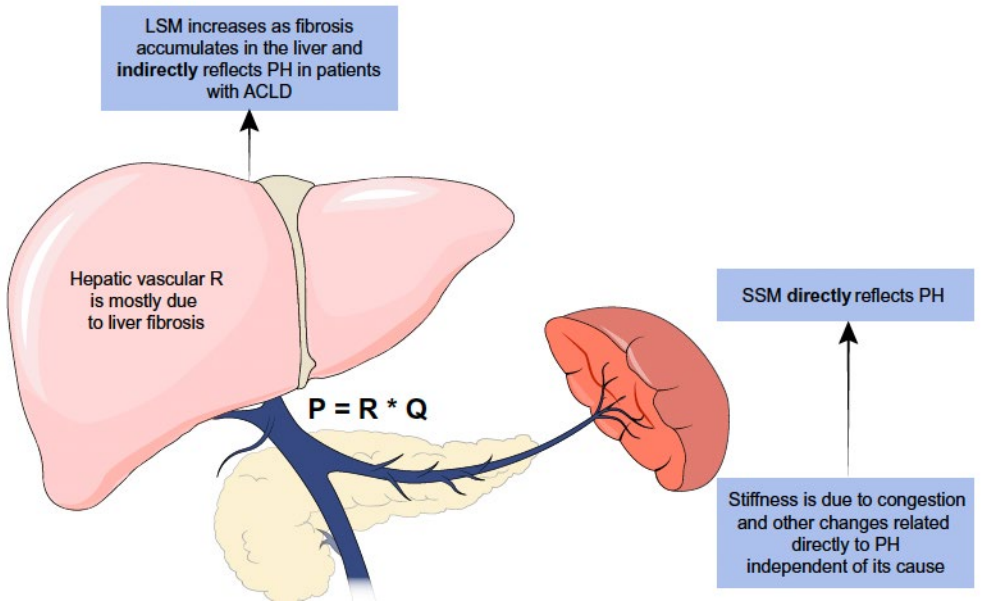
Liver stiffness by transient elastography (VCTE™) to predict cirrhosis (cACLD) and CSPH

The rule of 5

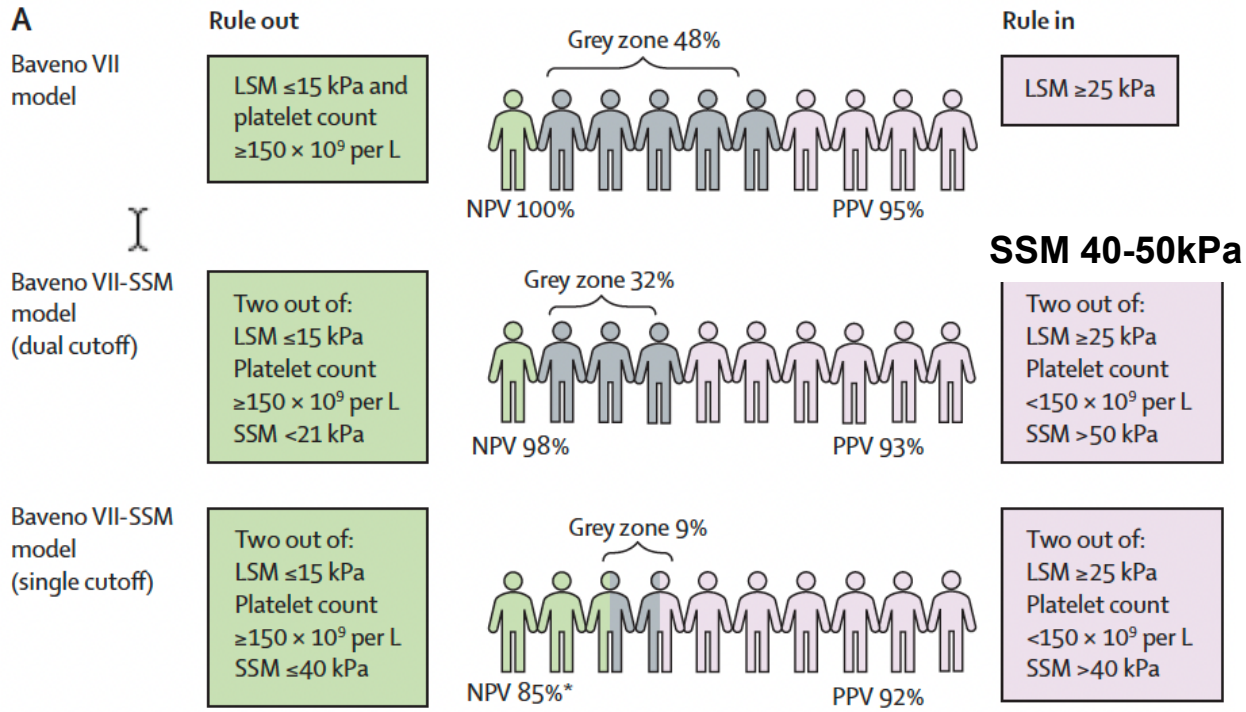


Adapted from M Mendizabal… A Albillos. Ann Hepatol 2023
R De Franchis et al. Baveno VII. JHEP 2022

Spleen stiffness by transient elastography (VCTE™) to predict cirrhosis (cACLD) and CSPH



IPD meta-analysis
17 studies, 1245 patients

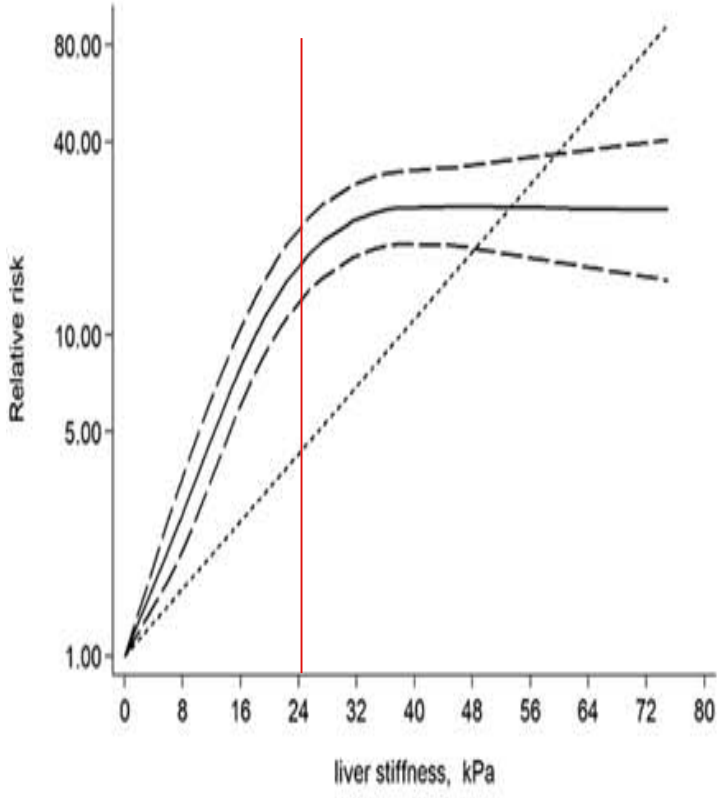


E Dajti et al. Lancet 2023

Relationship between liver stiffness by TE and liver-related events and mortality in cirrhosis

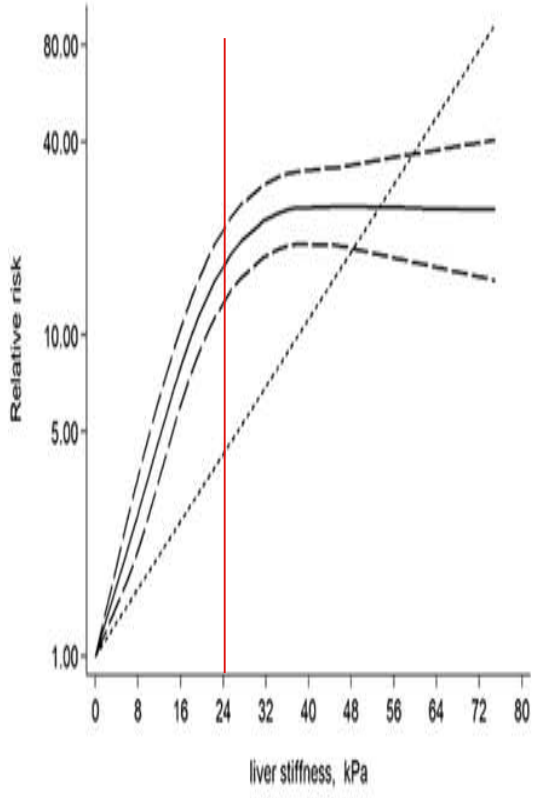
Hepatic decompensation

Meta-analysis, 62 studies, 43.817 patients



Y Shen et al.
Hepatology Int 2019

Relative risk of mortality



J Wang et al.
Hepatol Comm 2018

Prevention of first variceal bleeding

Cirrhosis

↓

"High risk" varices

↓

β-blockers

Endoscopic band ligation
If contratindication/intolerance to NSBB

End-point: ↓ variceal bleeding

"High risk" varices

- Median/large esophageal varices: F2-F3, ≥II-IV/IV
- Any size esophageal varices with red signs
- Any size esophageal varices in decompensated cirrhosis

Low probability of "High risk" varices, avoid endoscopy!

- LSM <20 kPa + platelets >150k

Baveno VI criteria

NIEC et al. NEJM 1998
C Merkel AJG 2000

Beta-blockers prevent first decompensation in compensated cirrhosis with CSPH (HVPG ≥10 mmHg)

The PREDESCI trial

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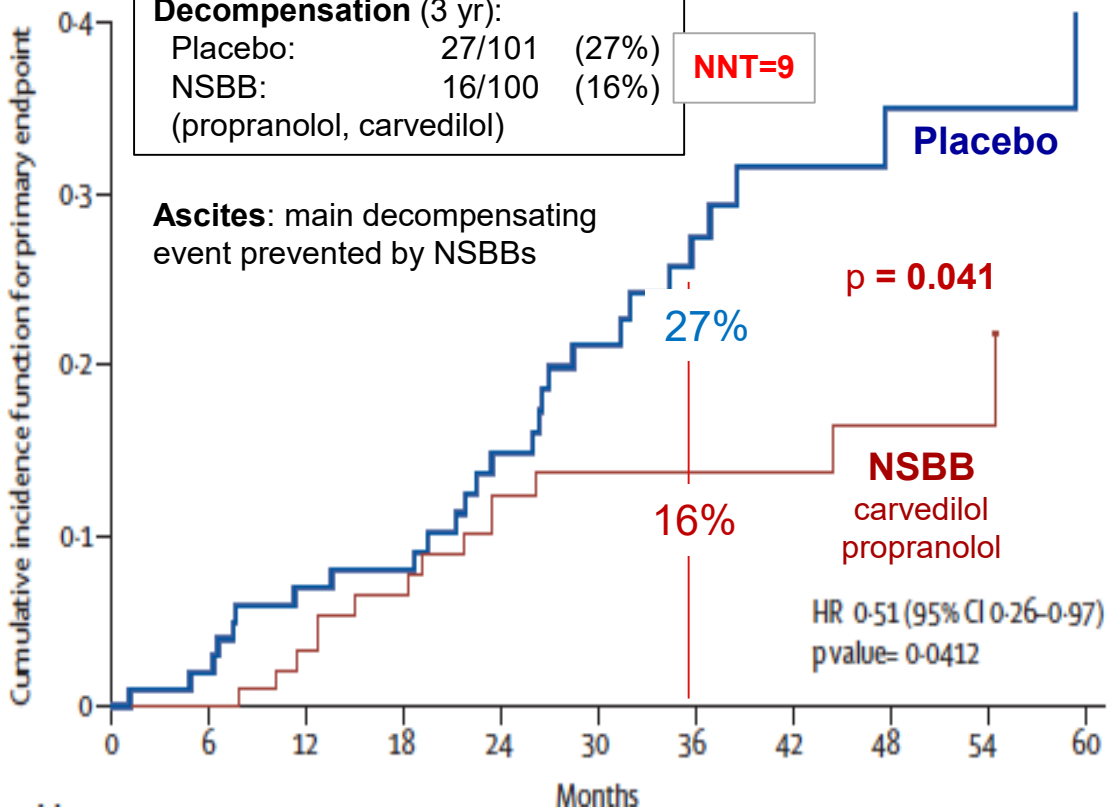
Decompensation and/or death

201 patients with compensated cirrhosis and CSPH

Decompensation (3 yr):
Placebo: 27/101 (27%)
NSBB: 16/100 (16%)
(propranolol, carvedilol)

NNT=9

Ascites: main decompensating event prevented by NSBBs



Subgroup analysis

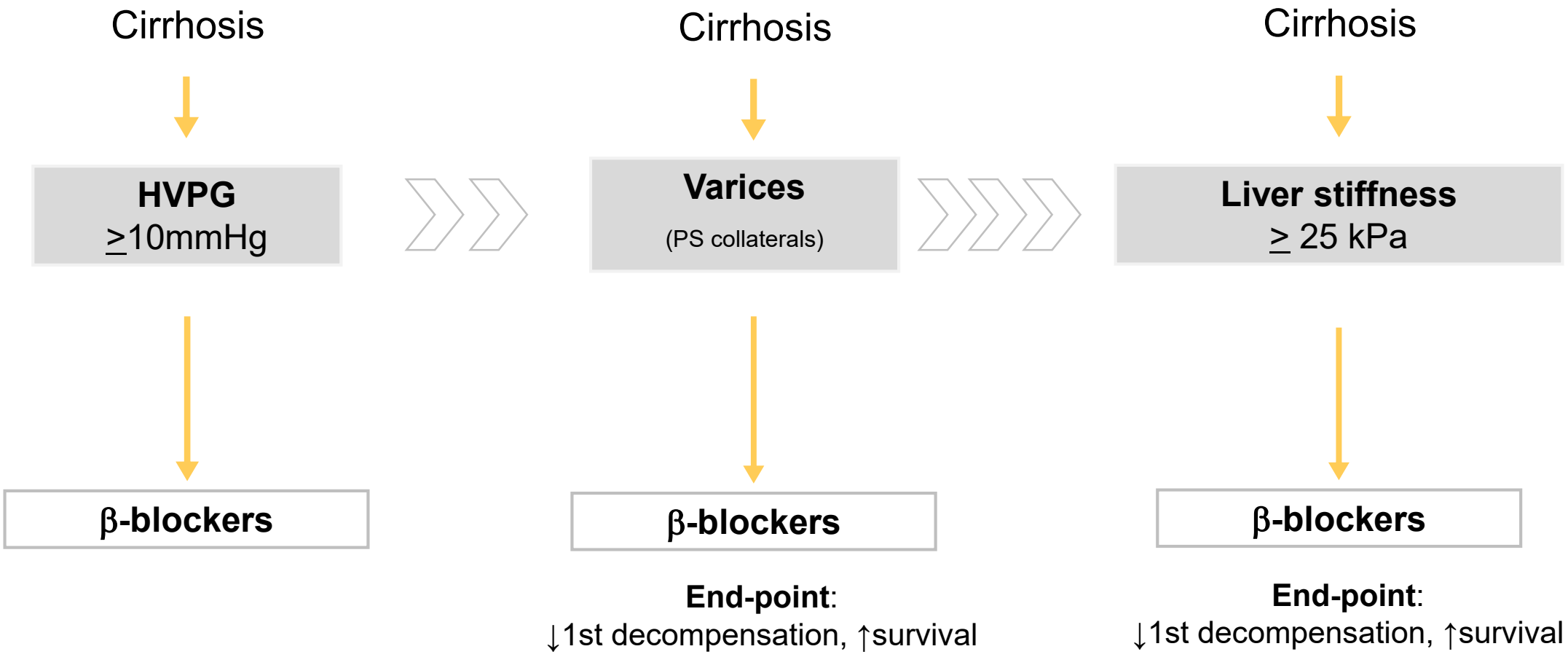
B

	β-blocker group n/N (%)	Placebo group n/N (%)	Hazard ratio (95% CI)	p value for interaction
Child-Pugh				0·175
Score <6	4/56 (7%)	8/49 (16%)	0·44 (0·13–1·46)	
Score ≥6	12/44 (27%)	19/52 (37%)	0·76 (0·37–1·56)	
Varices				0·219
No varices	6/44 (14%)	7/43 (16%)	0·84 (0·29–2·44)	NNT=5
Small varices*	8/56 (14%)	20/58 (34%)	0·45 (0·20–0·98)	
HVPG ≥16				0·409
No	7/73 (10%)	14/72 (19%)	0·49 (0·20–1·21)	
Yes	9/27 (33%)	13/29 (45%)	0·84 (0·36–1·20)	
Cause				0·221
Alcoholic†	7/28 (25%)	5/22 (23%)	1·01 (0·33–3·13)	
Non-alcoholic	9/72 (13%)	22/79 (28%)	0·43 (0·20–0·94)	
Overall	**16/100 (16%)**	**27/101 (27%)**	**0·51 (0·26–0·97)**	

Greater reduction in HVPG at 1 yr with **carvedilol vs. propranolol**
-16% vs. -10%, p<0.05

C Villanueva et al. Lancet 2019

Prevention of first decompensation according to Baveno VII



Baveno VII
Treatment with NSBBs (propranolol, nadolol or carvedilol) should be considered for the prevention of decompensation in patients with CSPH (B1). **New**

R De Franchis et al. JHEP 2021

Caution to extend the findings of the PREDESCI trial to all patients with compensated cirrhosis and CSPH

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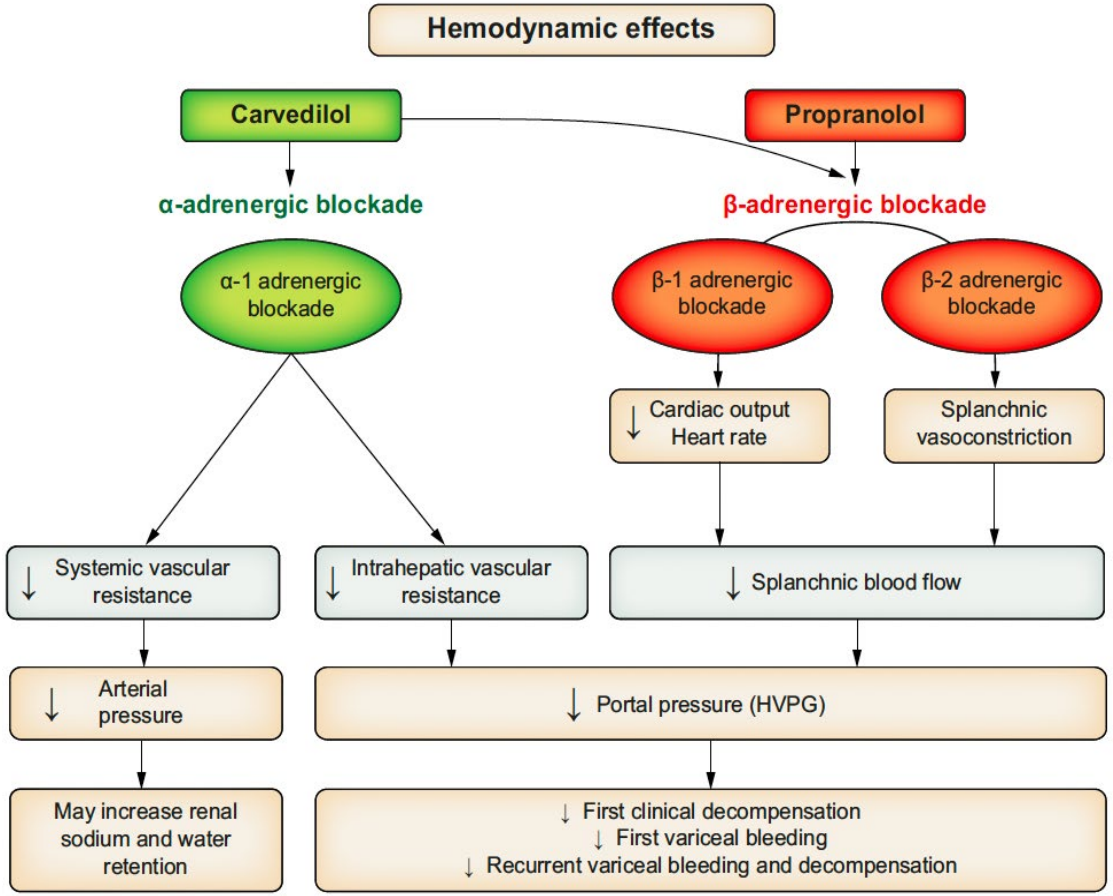
Critical appraisal of the PREDESCI trial

- **Etiology**
  - most (>50%) patients HCV, 2010-13, pre-DAA
  - <20% alcohol use disorder
- **Small effect size**
  - smallest stat significance
  - NNT of 9 at 37 months
  - no change in Child-Pugh
  - f-up extended from 3 to 5 months
- **Effect restriction**
  - no treatment effect in no varices

Needs validation?

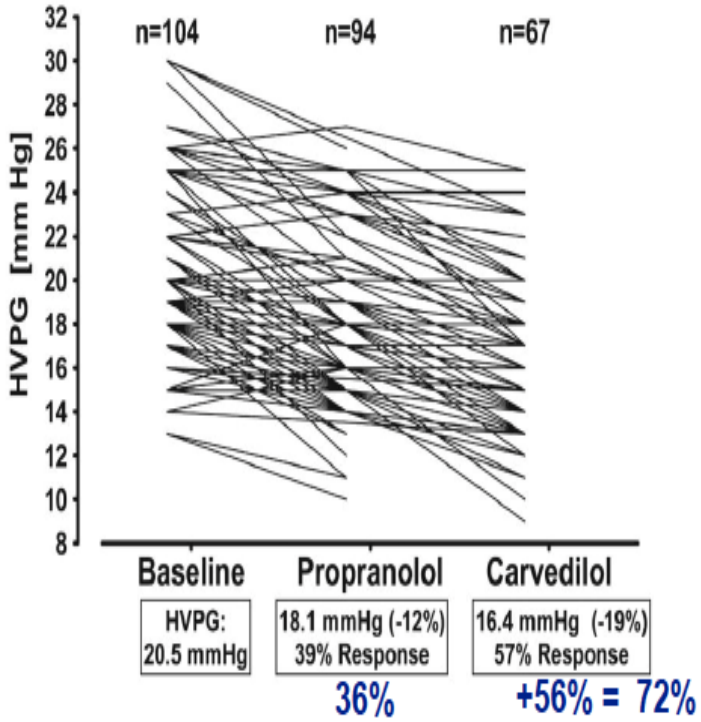
A Albillos, A Krag. JHEP 2022

Carvedilol as the beta-blocker of choice in cirrhosis with portal hypertension



A Albillos, A Krag. JHEP 2022

HVPG after propranolol and carvedilol



T Reiberger et al. Gut 2013

Is there need to measure portal pressure
(or alternative non-invasive measures)
to guide therapy with beta-blockers?

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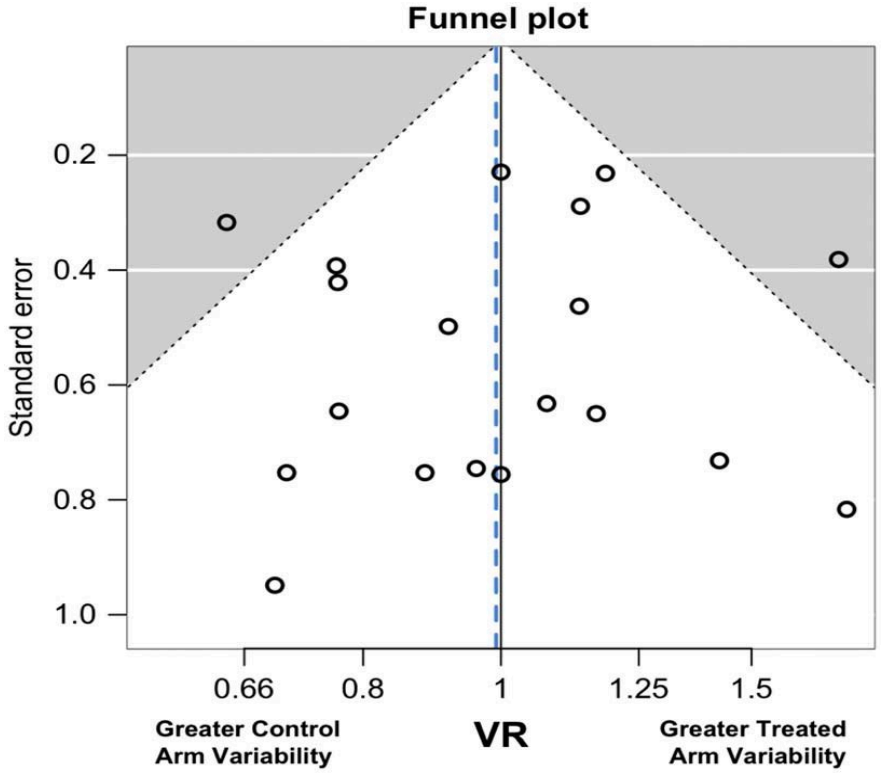
Reasons for NO NEED

- Benefit of NSBB beyond the HVPG response (non- and -hemodynamic mechanisms)
- Few (~25%) non-responders with current SOC, carvedilol
- Limited therapeutic alternatives in non-responders
- Unsensitivity of HVPG to detect minor changes in long-term
- Homogeneous hemodynamic response to NSBB at the individual patient level

Variability Ratio at outcome between treatment and control arms
19 comparisons (965 patients) at the individual patient level



M Alsaeid … J Abraldes et al. Hep Comm 2024

Manejo del paciente con cirrosis compensada e hipertensión portal significativa

Varices/colaterales abdominales

- Carvedilol como beta-bloqueante de elección

Rigidez hepática (LSM) **≥25 kPa**

- Individualizar la decisión, si no varices o endoscopia no realizada.

  Confirmar el valor de rigidez hepática

  Presencia de varices *reafirma* el tratamiento (15% efectos adversos)

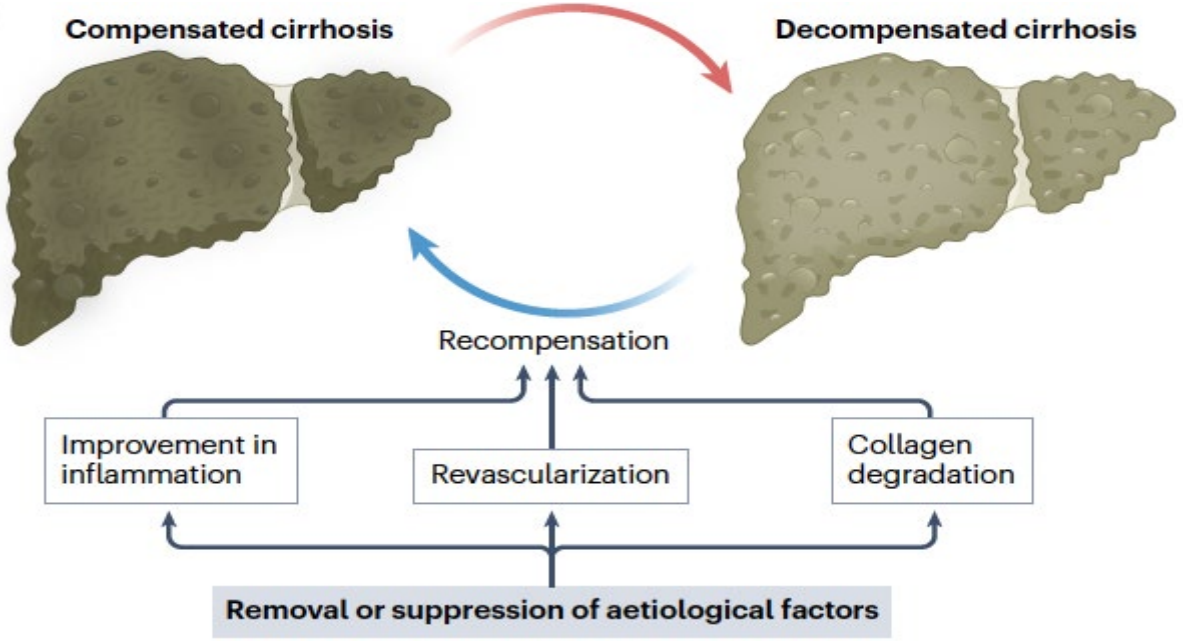
- Realizar endoscopia, si contraindicación o intolerancia a beta-bloqueantes

Regresión de la fibrosis y recompensación hepática de acuerdo con Baveno VII

Posibles mecanismos implicados

Regresión de la fibrosis y de la hipertensión portal

- **Cura del factor etiológico** (curación VHC, abstinencia…)
- Desaparición de las varices
- Rigidez hepática <12 kPa plaq & >150kPa



Recompensación

- **Cura del factor etiológico**
- Resolución de ascitis y EH
- No hemorragia por >12 m
- Mejoría de la función hepática

Pronóstico a largo plazo

↓ descompensaciones

Hipertensión portal

↓ descompensaciones

Carcinoma hepatocelular

Riesgo ↓, pero persiste

R De Franchis et al. Baveno VII. JHEP 2022
G Feng et al. NRGH 2023

Utilidad pronóstica de la medida de la rigidez hepática después de la curación del VHC

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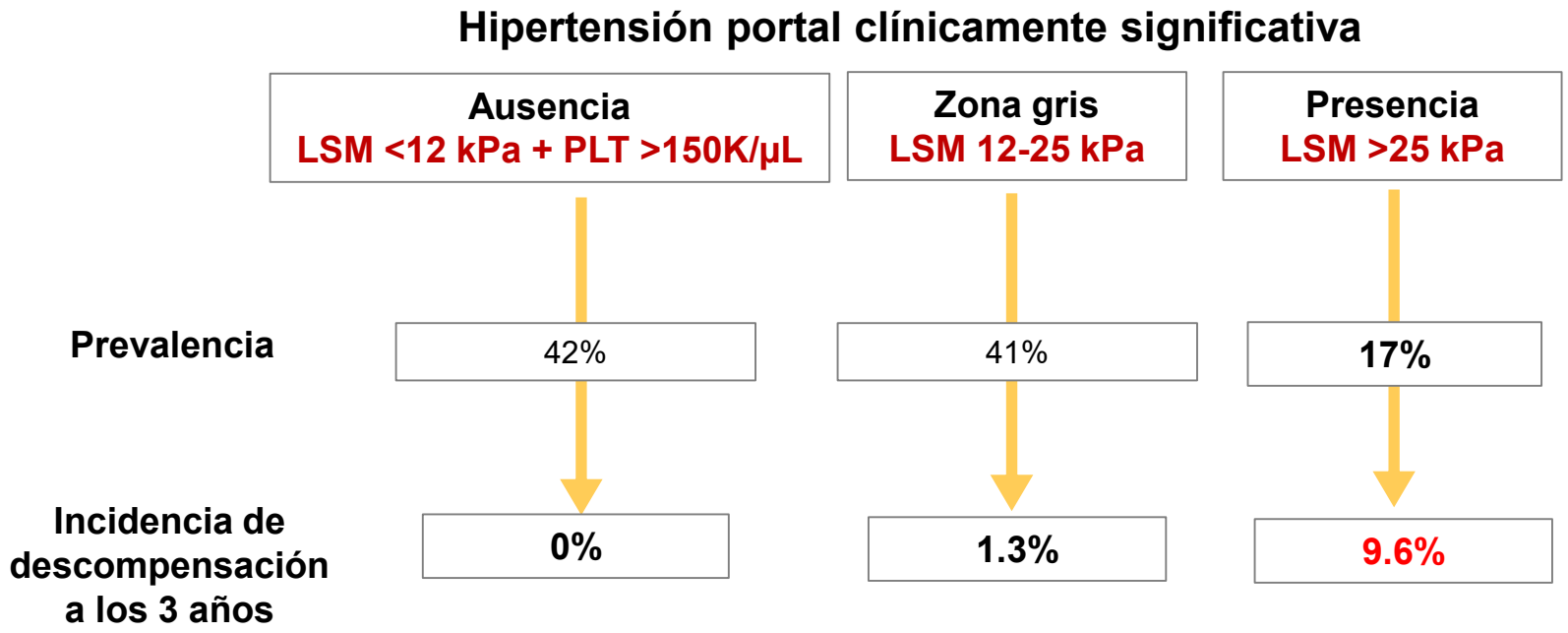
755 pacientes con cirrosis compensada

GPVH y rigidez hepática antes y después de curación VHC con AAD

Descenso de la presión portal:

- ↓ en ~80%, ↓ media -18%
- Ningún paciente desarrolla CSPH



Segundo estudio, 2335 pacientes, 15 centros europeos

- **LSM ≥20 kPa** → descompensación 7% a 3 años
- Descenso del LSM → sin significado pronóstico

G Semmler et al. JHEP 2024

G Semmler et al. JHEP 2022

Manejo del paciente con cirrosis compensada tras curación del VHC en ausencia de otra causa de enfermedad hepática **(3 años)**

Rigidez hepática

- **<10 kPa** → retirar beta-bloqueantes, no seguimiento ends
- **<10-20 kPa** → no varices en endoscopia de confirmación, retirar beta-bloqueantes, no seguimiento ends
- **>20-25 kPa** → continuar/añadir carvedilol (7-9% riesgo de descompensación a 3 años)

Conclusiones

- Hipertensión portal clínicamente significativa ("CSPH"):

- estratifica el riesgo en cirrosis compensada
- riesgo de descompensación ~20(-25%) en 2-3 años
- aumento del flujo esplácnico contribuye a hipertensión portal
- inflamación sistémica de bajo grado

- Diagnóstico no invasivo CSPH:

- Regla del 5 combinando rigidez hepática y plaquetas
- Rigidez >25kPa con VPP 95% de CSPH

- Tratamiento de CSPH

- Carvedilol como beta-bloqueante de elección
- Necesidad no cubierta: mjeorar estratificación del riesgo de descompensación

- Curación del VHC

- Rigidez residual ≥20-25kPa: riesgo de descompensación

Manejo del paciente con cirrosis compensada e CSPH

Small varices/abdominal collaterals

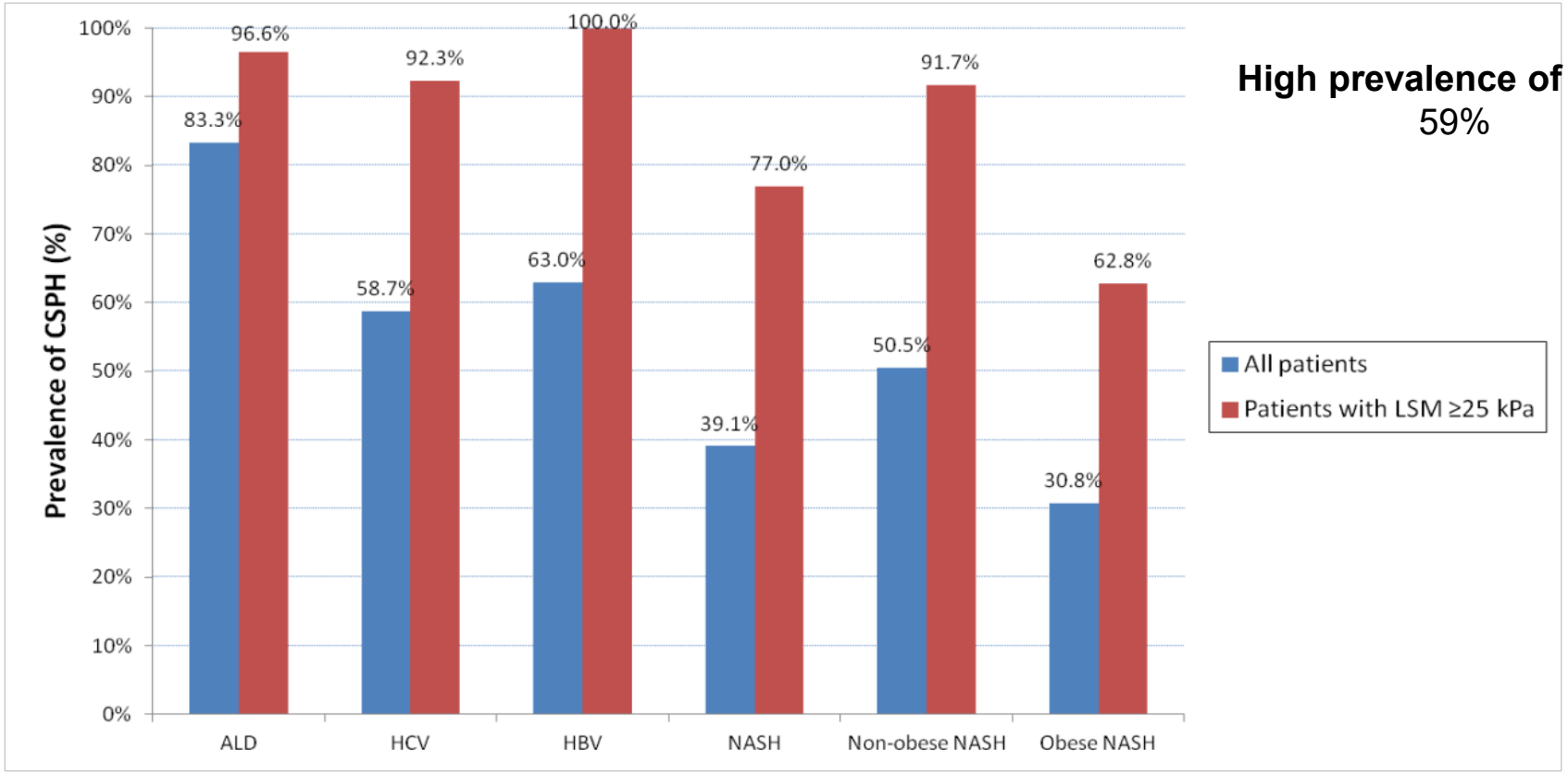
- Carvedilol as the NSBB of choice

LSM ≥25 kPa

- Presence of small varices *reasserts* NSBB treatment
- Decision on individual basis if varices absent or no endoscopy (15% adverse effects). Co
- Endoscopy if NSBB contraindicated or not tolerated

Diagnosis of clinically significant portal hypertension (CSPH) with transient elastography

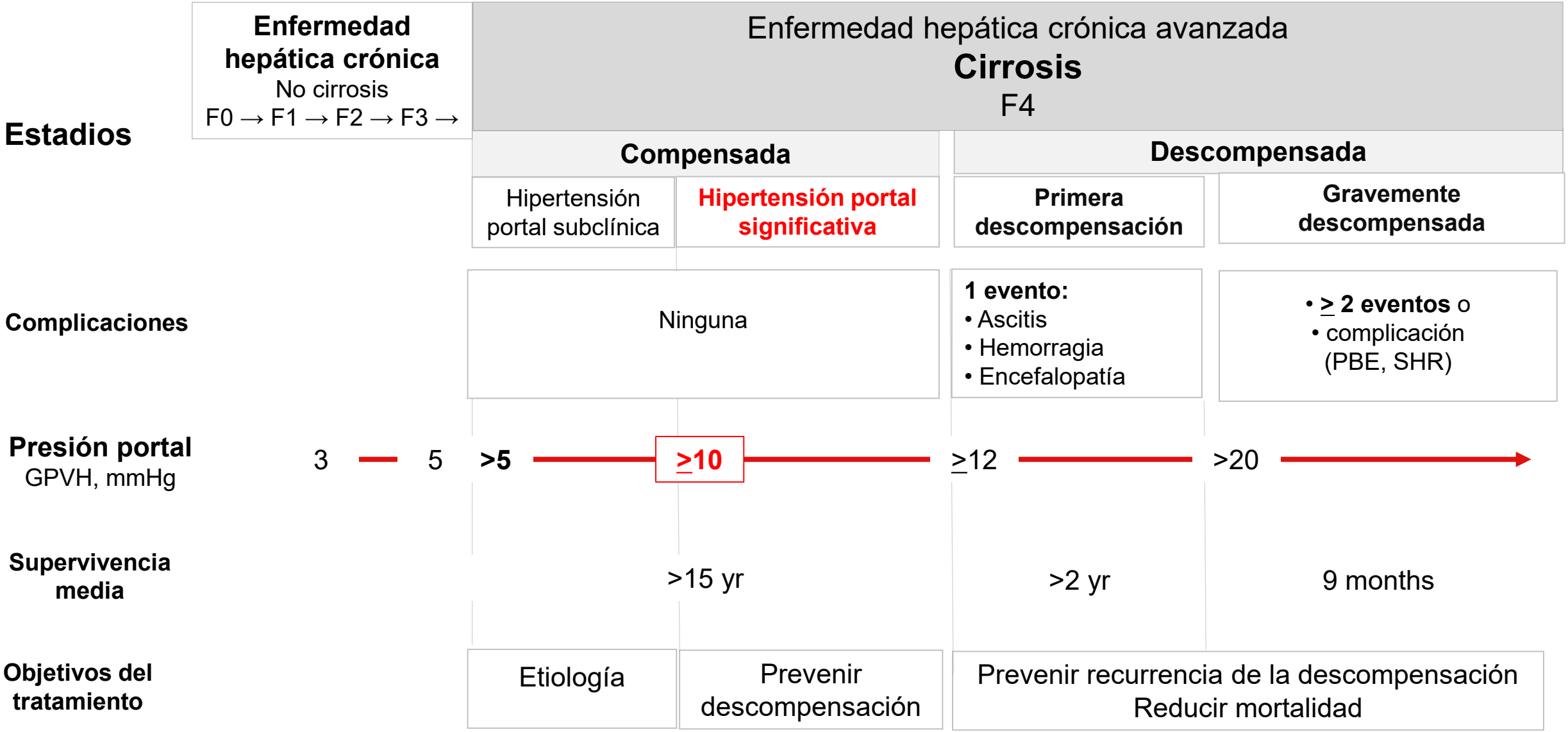
LSM≥25 kPa to rule-in CSPH
(>90% PPV, >90% Sp)



High prevalence of CSPH
59%

M Pons, et al. AJG 2021

Estadios y subestadios de la cirrosis



More than 70% of patients with CSPH do not decompensate at 3 years despite not receiving NSBB

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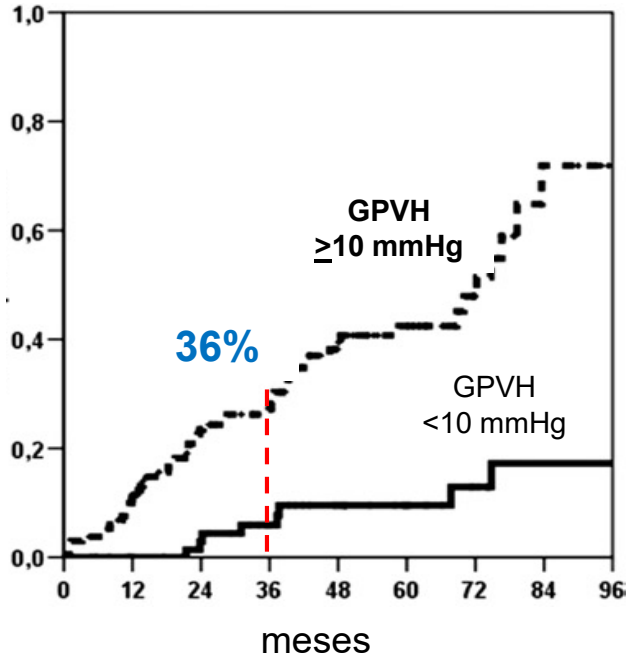
Probabilidad de descompensación clínica

213 cirrosis compensada con GPVH < o ≥10mmHg



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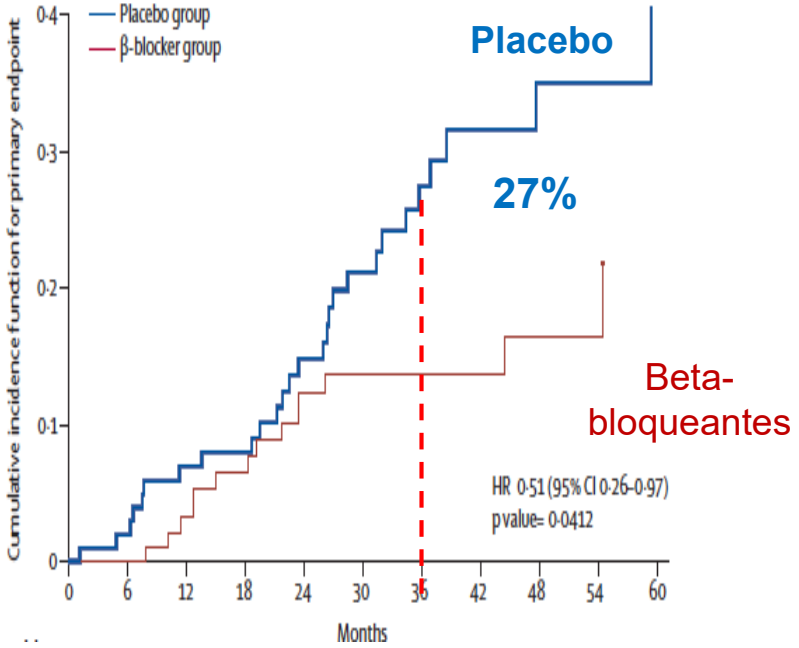

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