



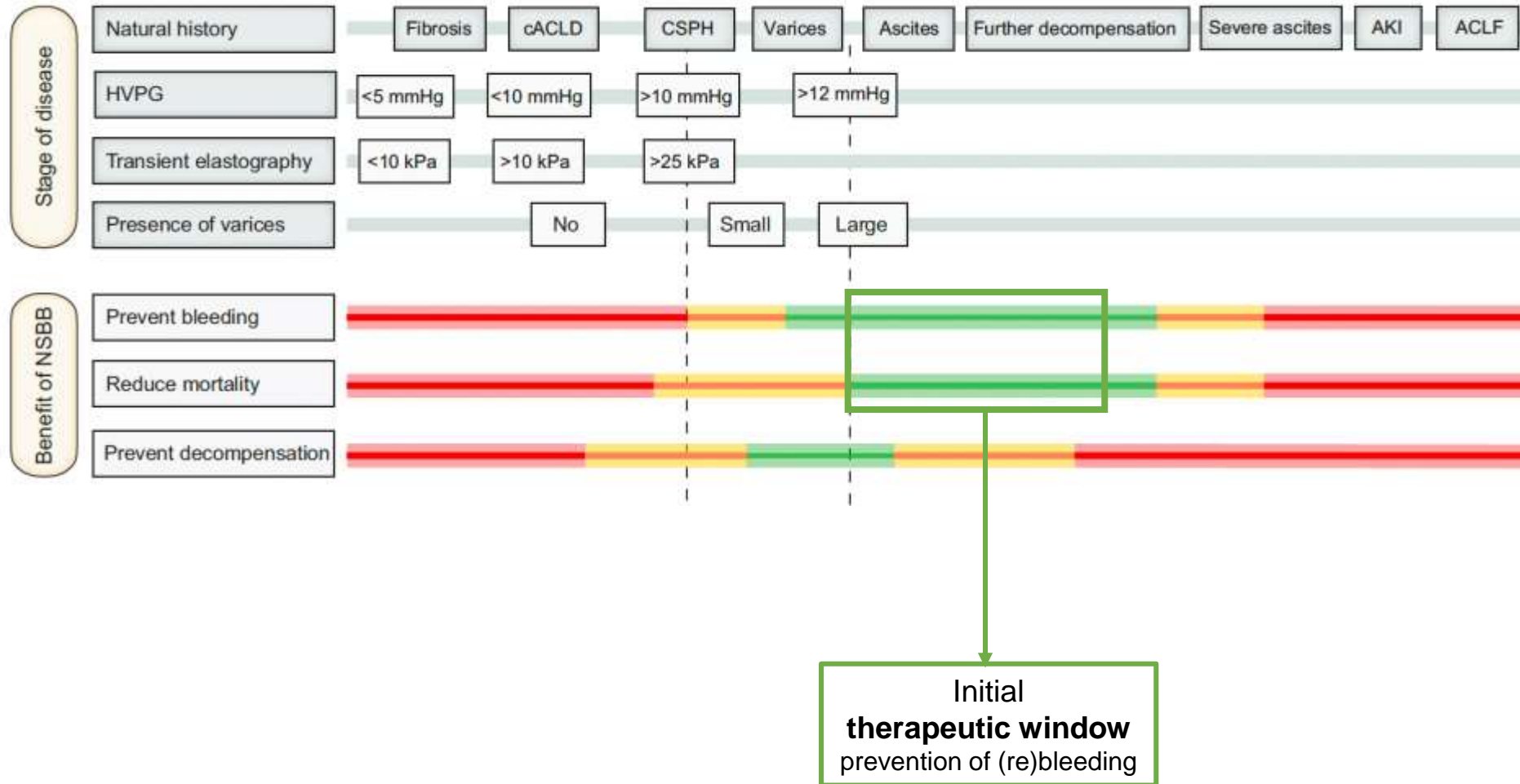
## “Uso de beta-bloqueantes en el paciente con cirrosis ¿Ha llegado la medicina de precisión?”

**Agustín Albillos Martínez**

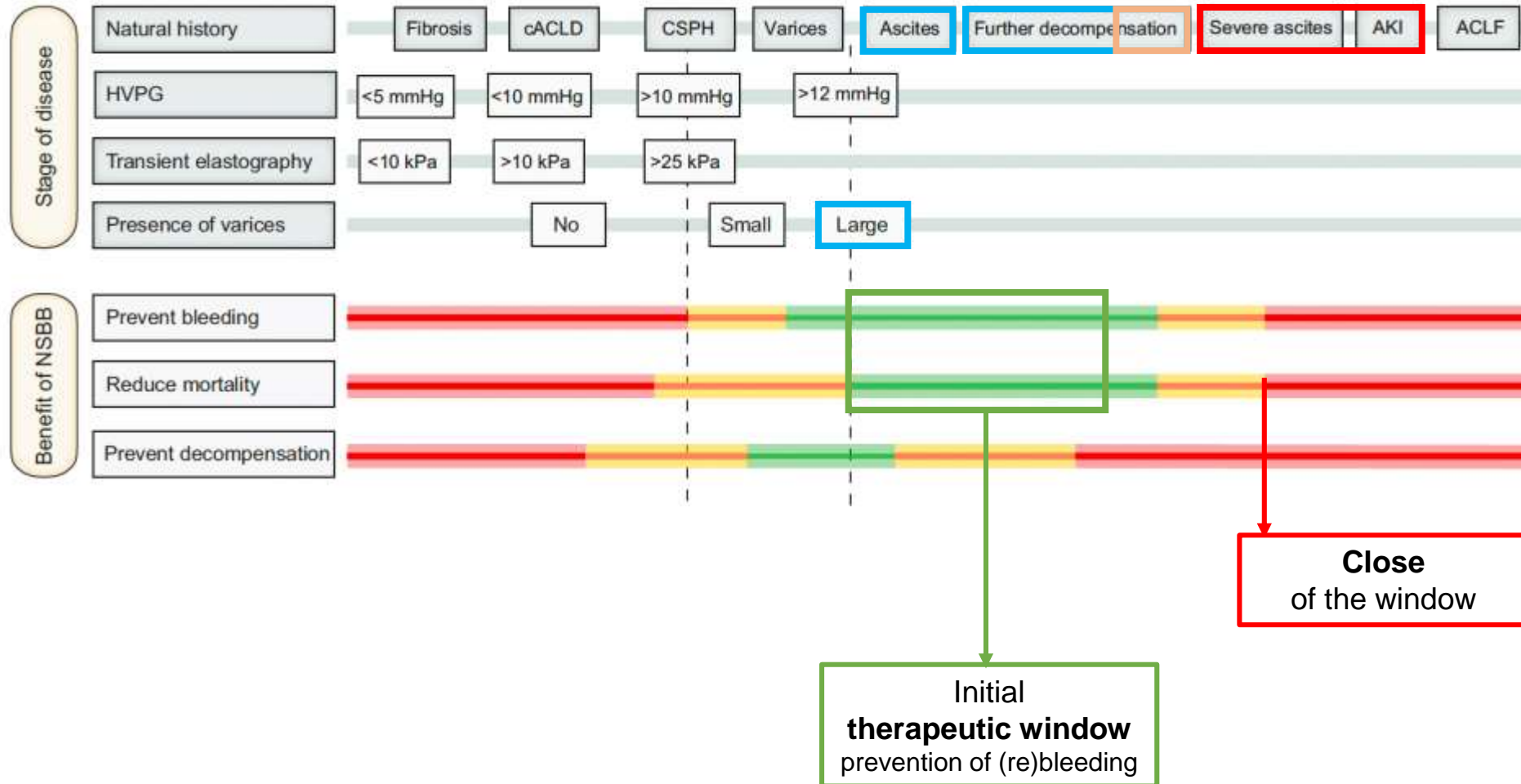
Hospital Universitario Ramón y Cajal  
Universidad de Alcalá  
Madrid



## Revisiting the therapeutic window of beta-blockers in cirrhosis

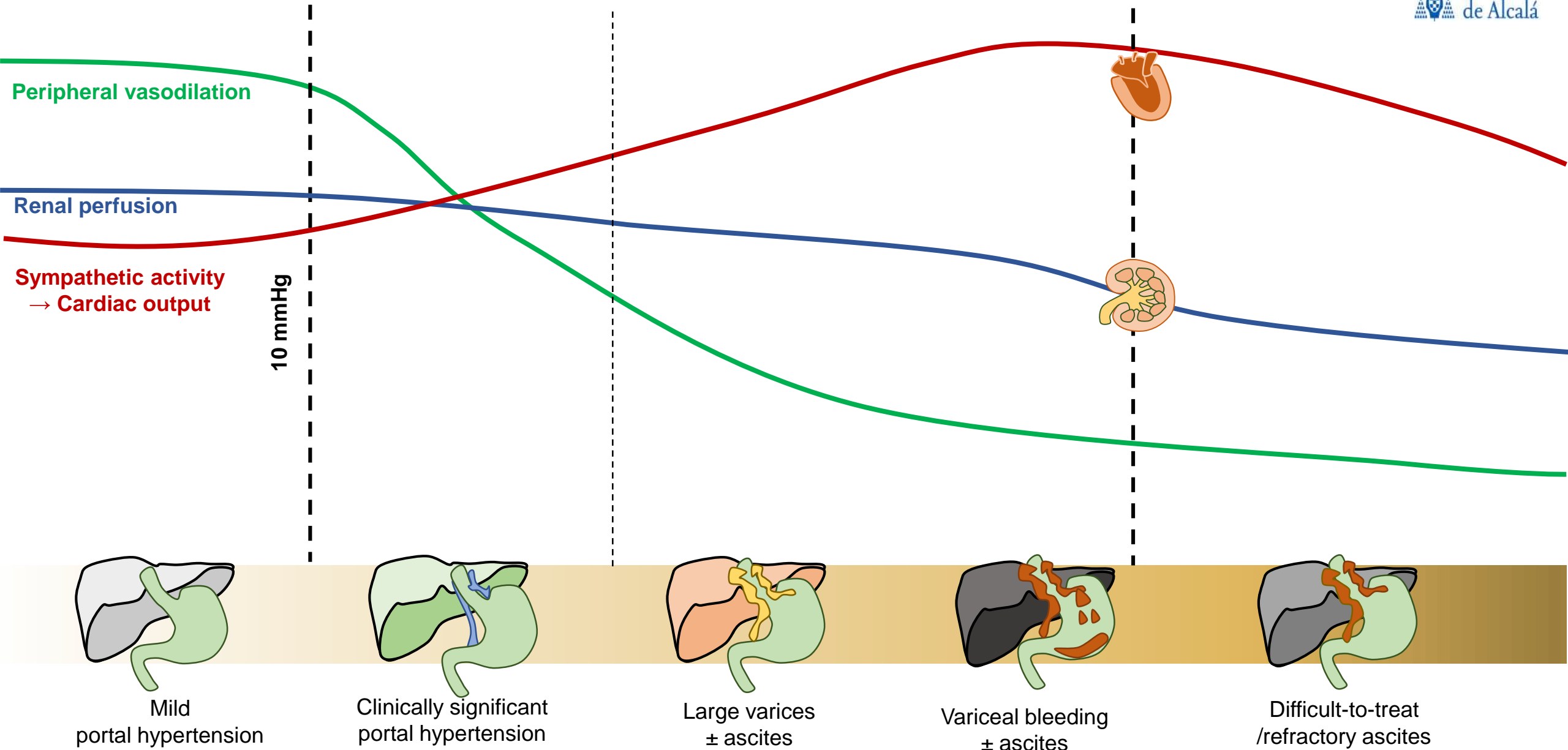


## Revisiting the therapeutic window of beta-blockers in cirrhosis



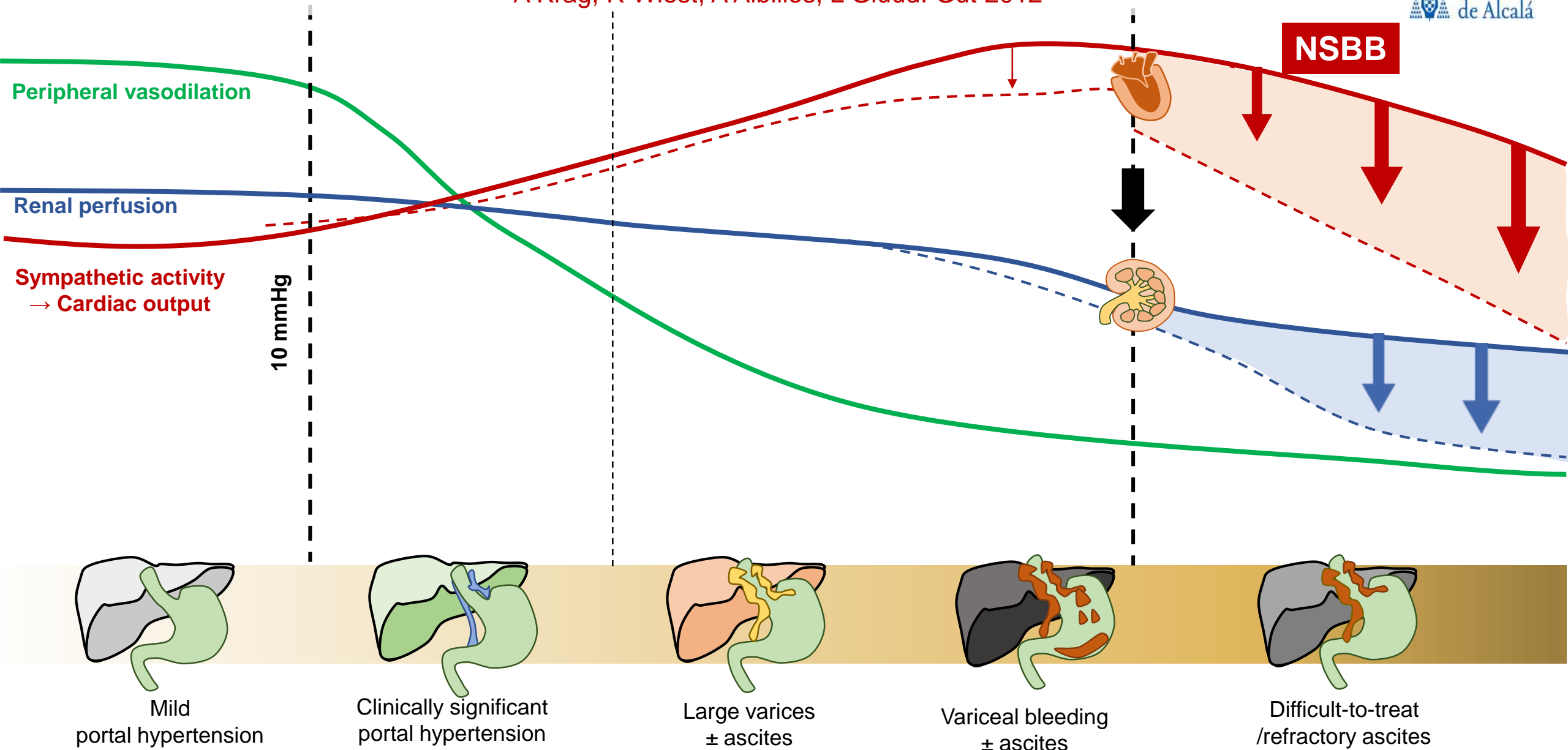
# The hypothesis of the therapeutic window of NSBB in cirrhosis

A Krag, R Wiest, A Albillos, L Gluud. Gut 2012



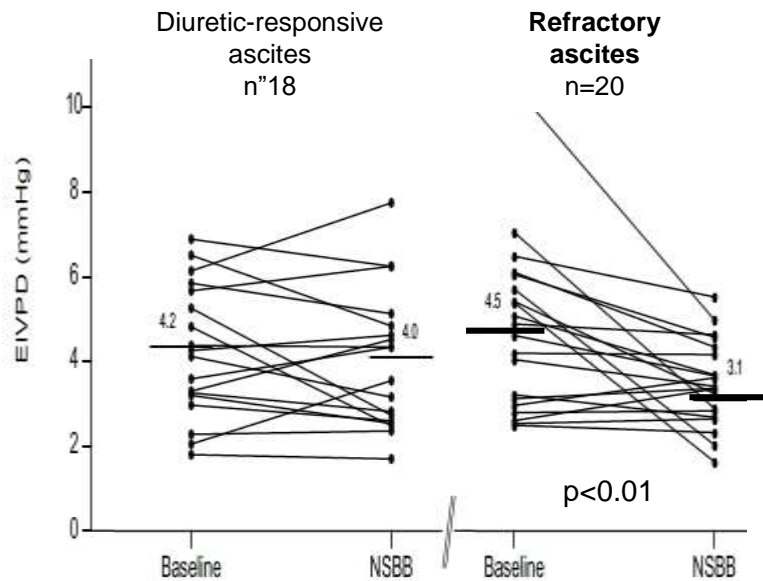
# The hypothesis of the therapeutic window of NSBB in cirrhosis

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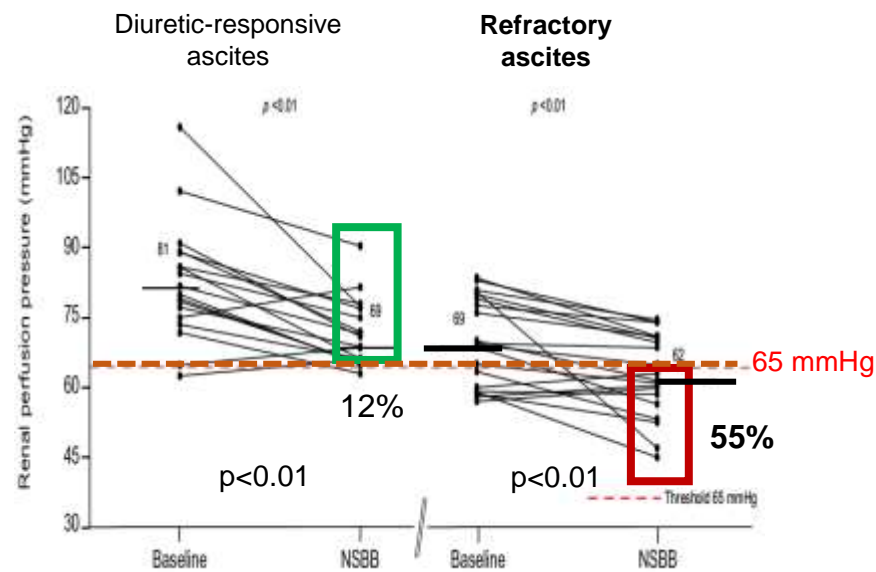


# NSBB impair global circulatory homeostasis and renal function in patients with refractory ascites

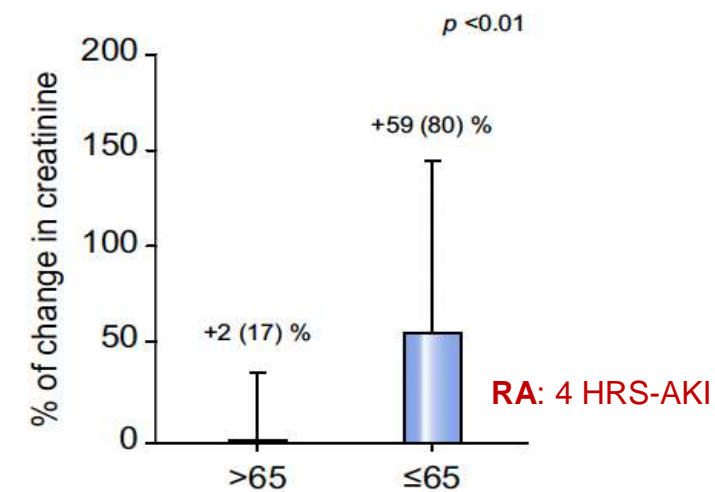
## Systolic function of left ventricle



## Renal perfusion pressure (mean arterial pressure - renal venous pressure)



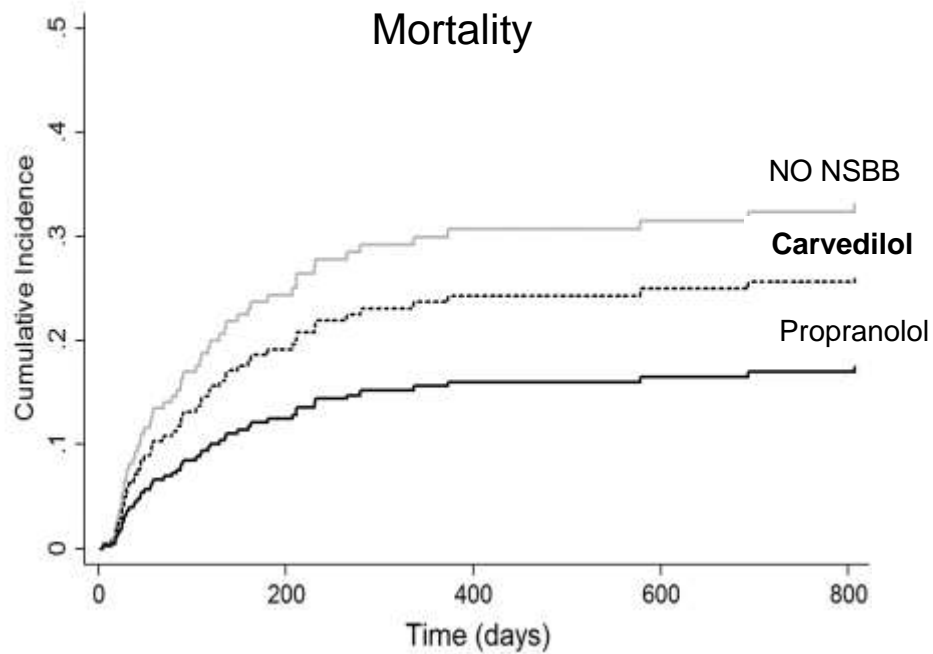
## Changes in creatinine and renal perfusion pressure



Systolic arterial Pr	median, mmHg
Baseline	113 104
After NSBB	107 90

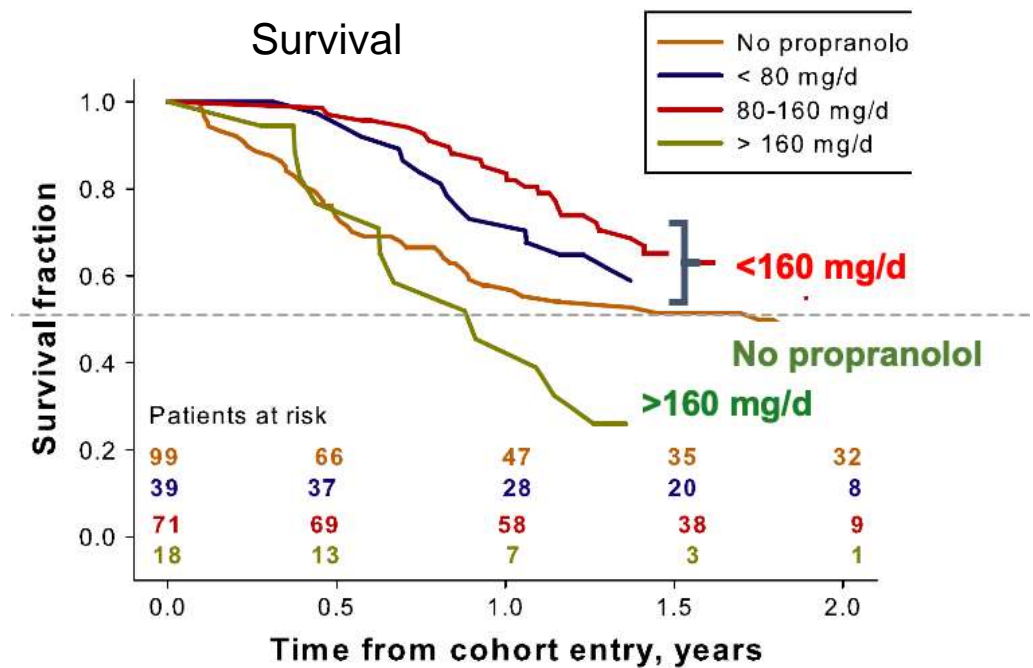
## Lower benefit of NSBBs in patients with difficult-to-treat ascites on carvedilol or high-dose of propranolol

Patients with ascites in the transplantation WL



J Leithead et al. Gut 2014

Difficult-to-treat ascites  
>4 paracentesis



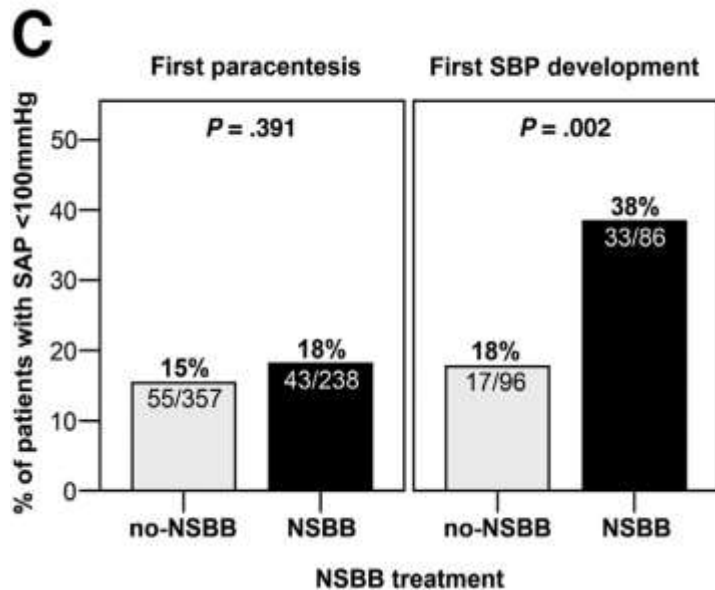
F Bang et al. Liv Int 2016



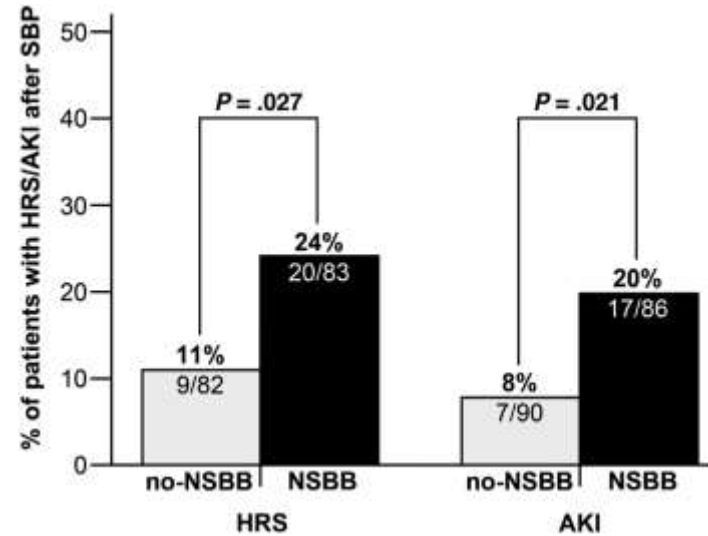
# Increased risk of low arterial pressure, HRS and death in patients with cirrhosis and SBP on NSBBs

Retrospective analysis, 607 patients with cirrhosis  
First paracentesis, 2006-2011

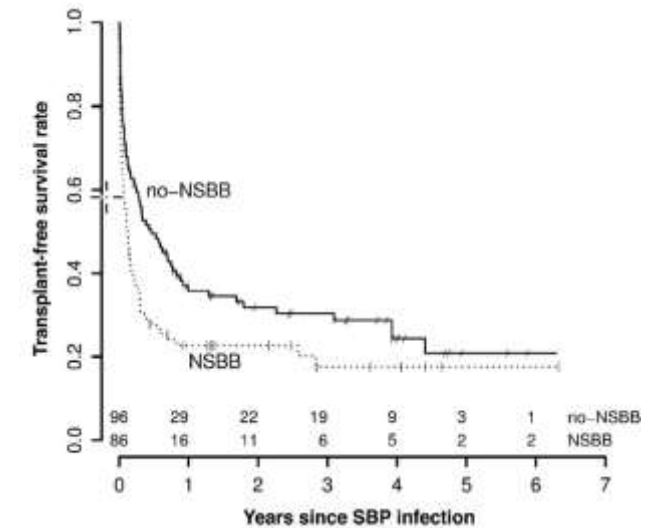
Effect of NSBB on SAP <100 mmHg



Influence of NSBB on HRS and AKI within 90 days after the first SBP



Influence of NSBB on survival within 90 days after the first SBP





## Practical tips

### Titration

#### All patients

- Maximum tolerated dose to reduce HR to 55-60 bpm provided SAP >90 mmHg
- Carvedilol, titration 6.25 → 12.5 mg/d

#### Patients with moderate-severe ascites

- Better propranolol than carvedilol
- Propranolol up to 160 mg/d

#### Patients with refractory ascites

- Avoid NSBB

### Limits

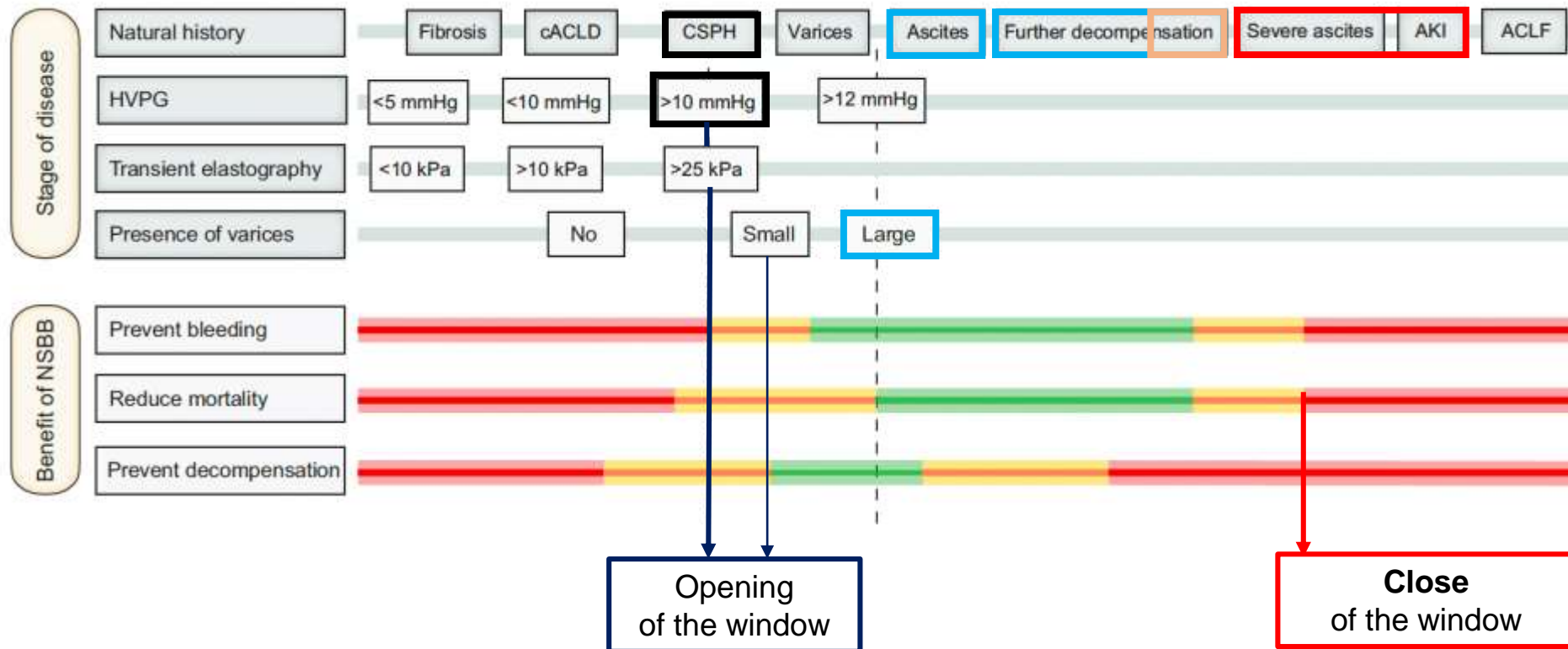
#### Withdrawal/dose reduction of NSBB

- Systolic arterial pressure <90 mmHg
- Acute kidney injury (AKI)

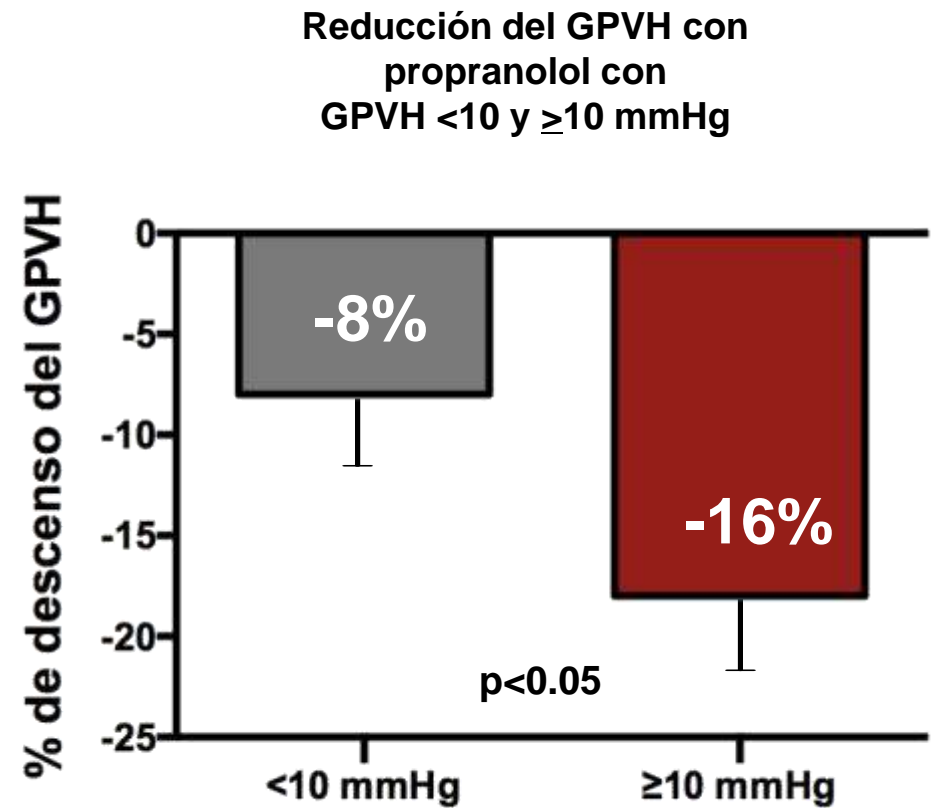
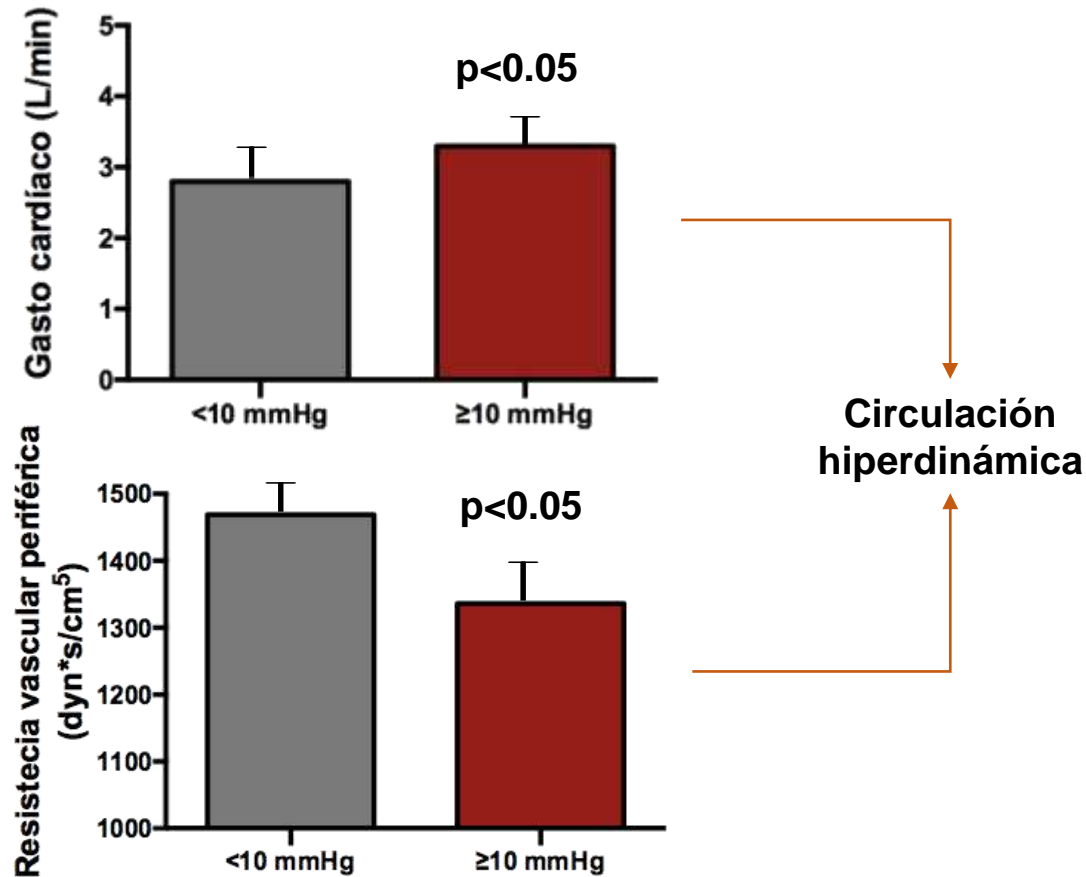
#### Once arterial pressure normalizes and/or AKI resolves

- Re-initiate and -titrate NSBB starting at lower doses

## Revisiting the therapeutic window of beta-blockers in cirrhosis

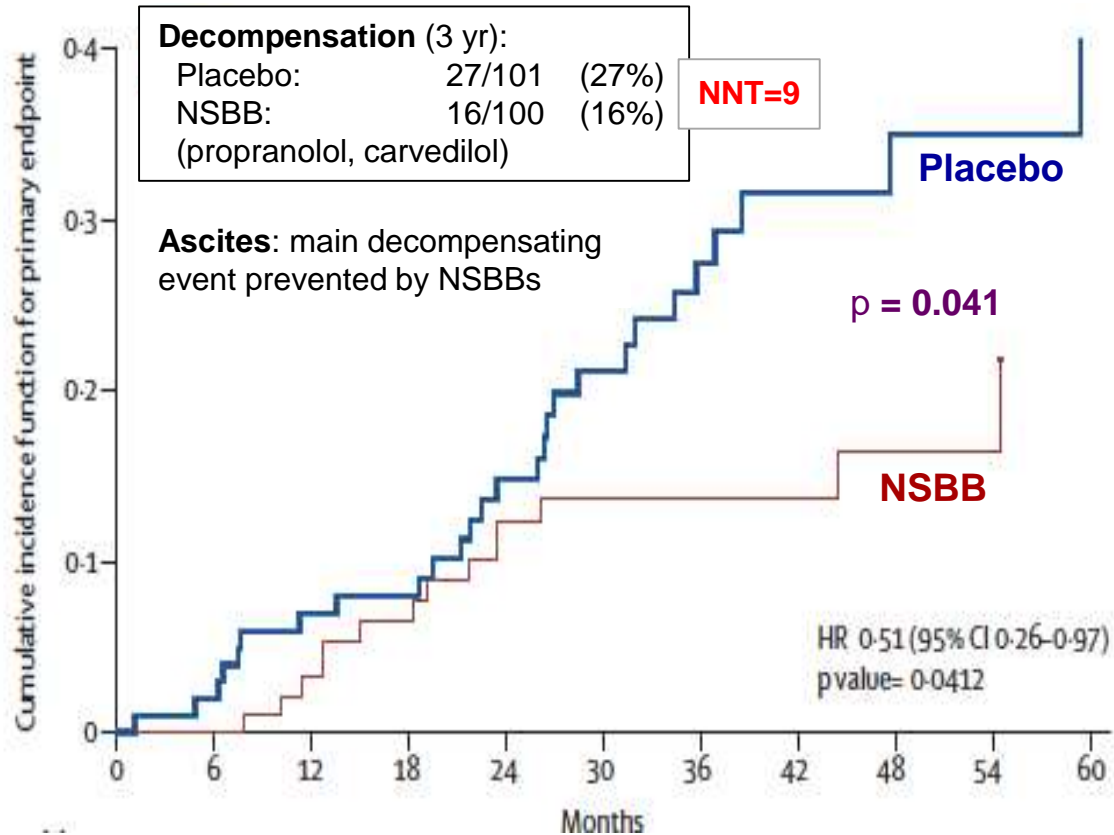


**Clinically significant portal hypertension (HVPG  $\geq 10$  mmHg) is needed for cardiac output and splanchnic blood flow to increase and contribute to portal hypertension**



# NSBB prevent first decompensation in patients with ascites and CSPH (HVPG $\geq 10$ mmHg) The PREDESCI trial

## Decompensation and/or death



## Subgroup analysis

B	$\beta$ -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 $\geq 6$	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 $\geq 16$				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%,  $p < 0.05$

## 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**

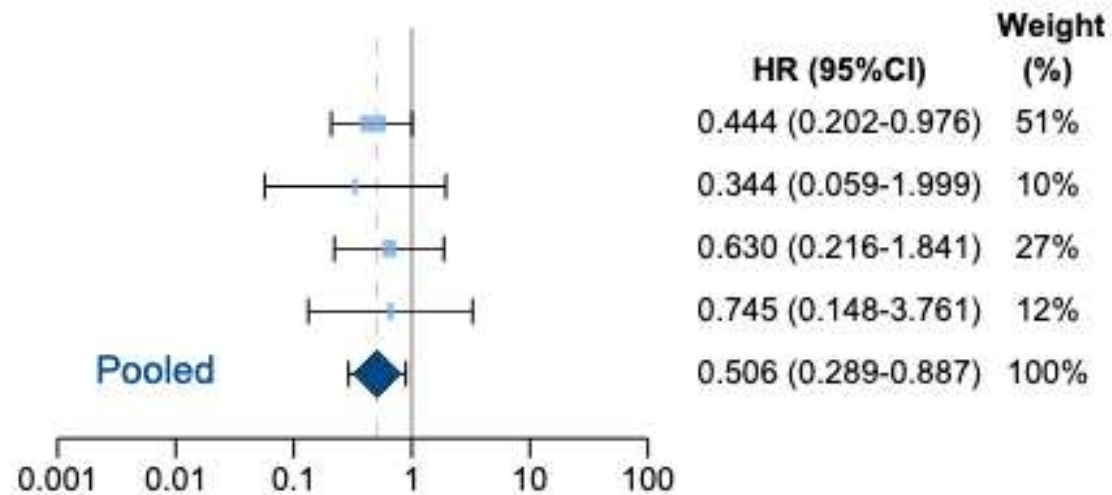
- no treatment effect in no varices

*Needs validation*

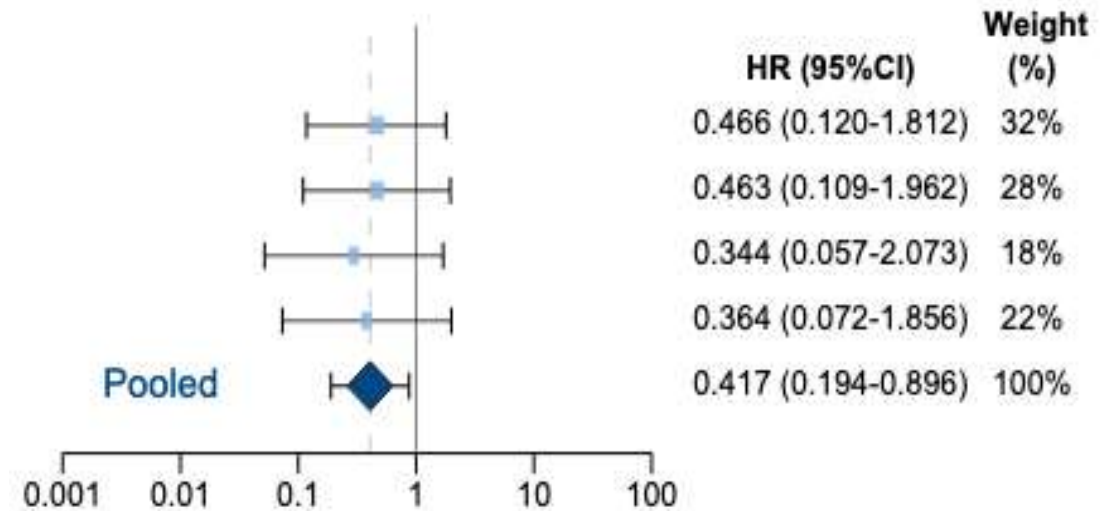
## Carvedilol reduces the risk of decompensation and mortality in compensated cirrhosis (CSPH?)

4 studies that provided IPD  
 352 patients with compensated cirrhosis  
 181 on carvedilol and 171 controls (79 EVL, 92 placebo)  
**Esophageal varices 92%**

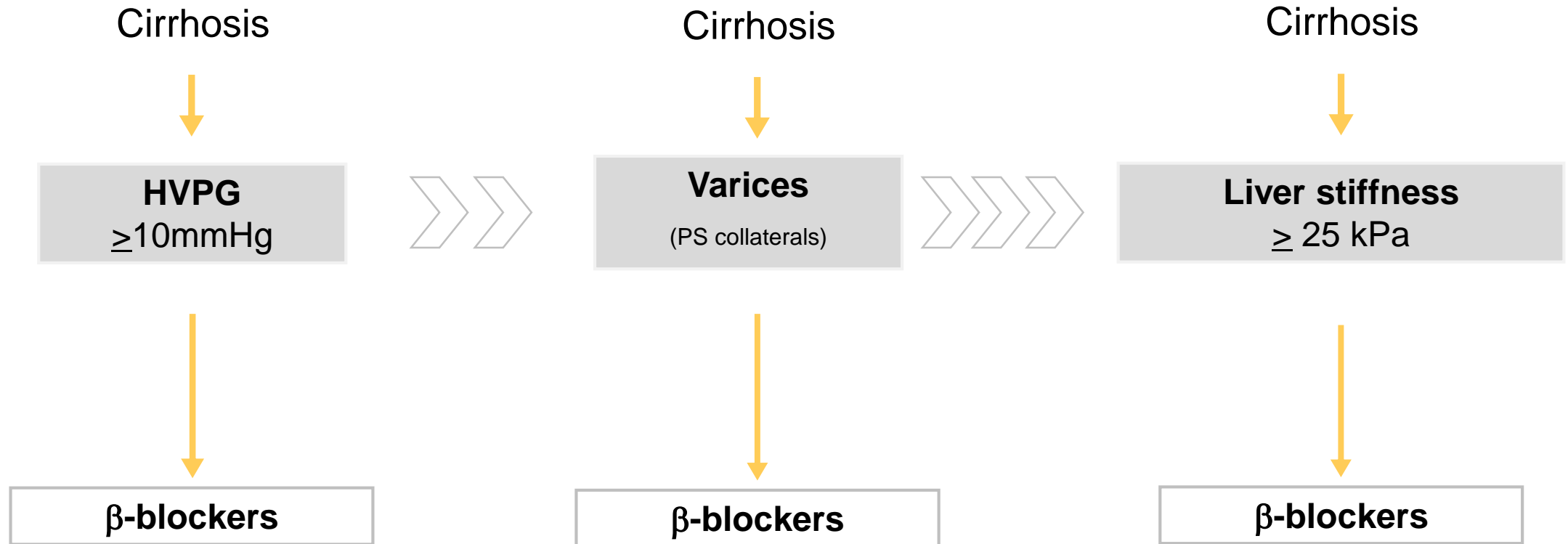
Carvedilol significantly decrease the risk of developing decompensation  
 (competing events death & liver transplant)



Carvedilol significantly improve survival  
 (liver transplant, competing event)



## Prevention of first decompensation



### Baveno VII

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



# Liver stiffness to predict cACLD and CSPH

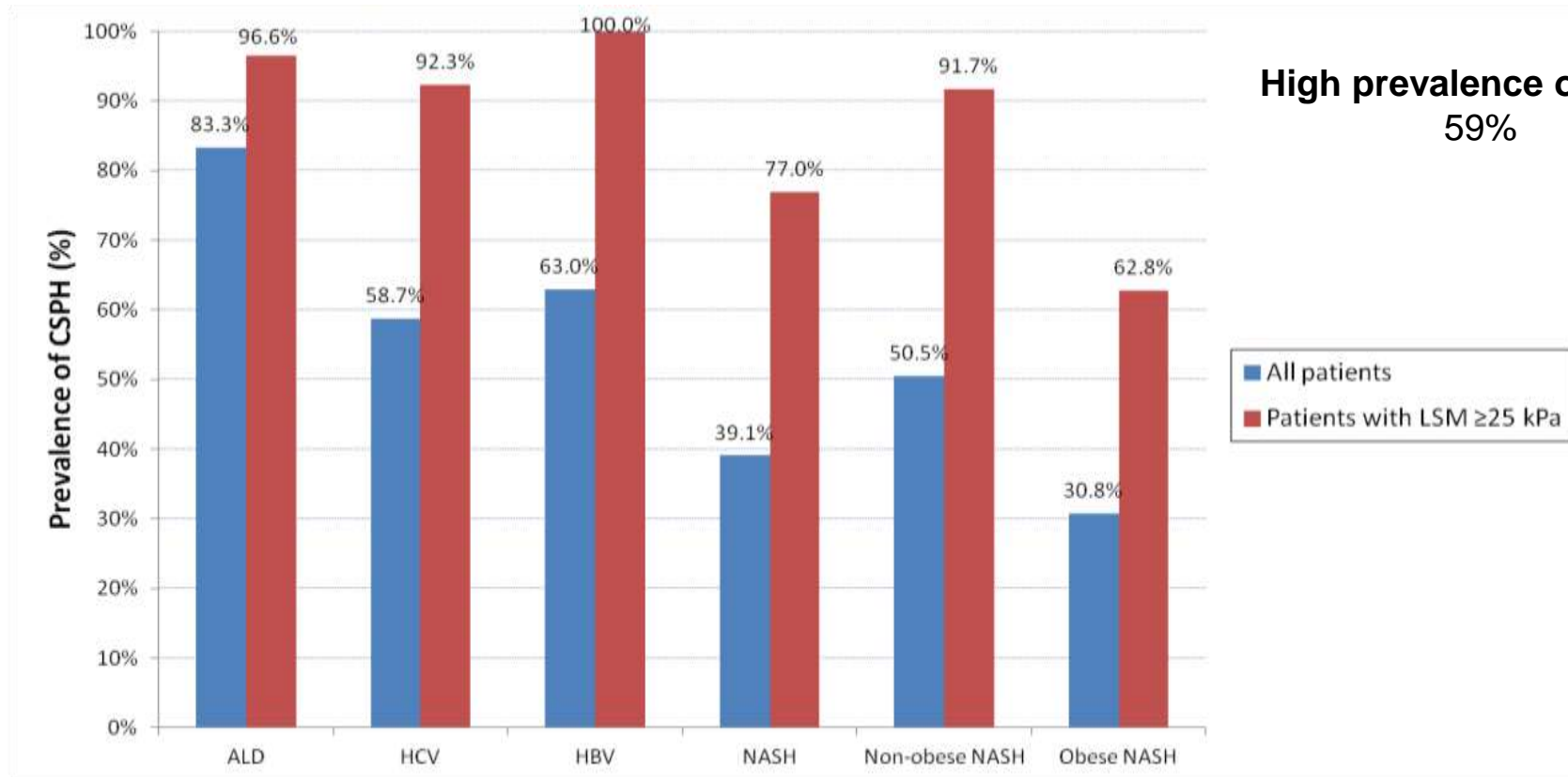
## The rule of 5

		compensated <b>Chronic Advanced Liver Disease</b> (cACLD)					
		cACLD excluded	CSPH dudosa	CSPH excluded	CSPH dudosa	CSPH identified	
<b>Liver stiffness (kPa)</b>		<(8-)10**	10-15	<15	15-20	20-15	≥25 *
<b>Platelets</b>				>150k	<110k	<150k	N/D

\* HBV, HCV, alcohol,  
NASH non-obese  
\*\* NASH obese

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

**LSM  $\geq$  25 kPa to rule-in CSPH**  
( $>90\%$  PPV,  $>90\%$  Sp)



## Practical tips

### cACLD patient

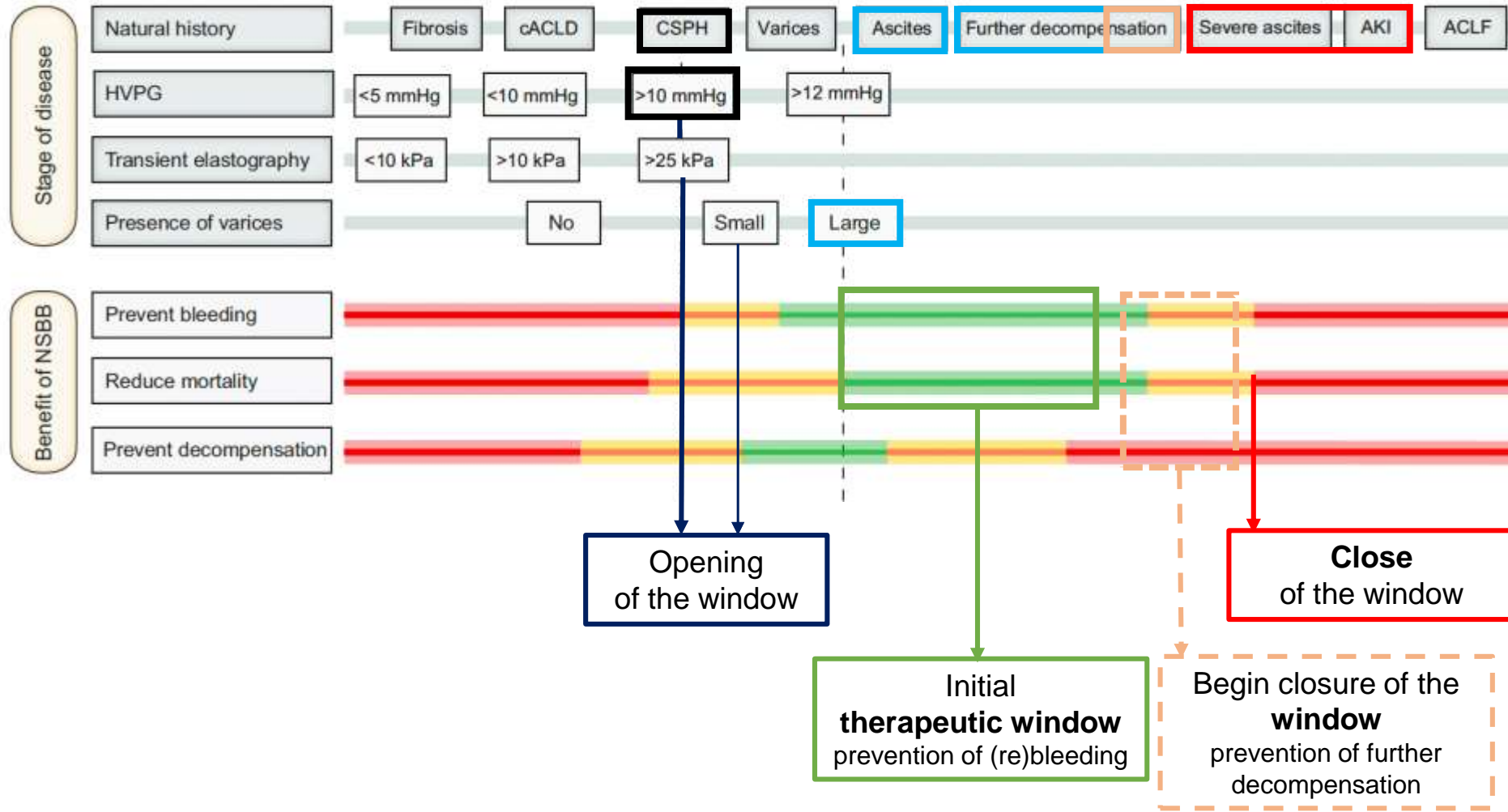
#### Small varices/abdominal collaterals

- Carvedilol as the NSBB of choice

#### LSM $\geq 25$ kPa

- Presence of small varices *reasserts* NSBB treatment
- Decision on individual basis if varices absent or no endoscopy (15% adverse effects)

## Revisiting the therapeutic window of beta-blockers in cirrhosis



Modified from A Albillos, A Krag. JHEP 2022

Unlikely to benefit  
Benefit uncertain or small  
Strong data support benefit

**Prevention of rebleeding** →  
Prevention of further decompensation

Variceal bleeding



**NSBB+EVL**

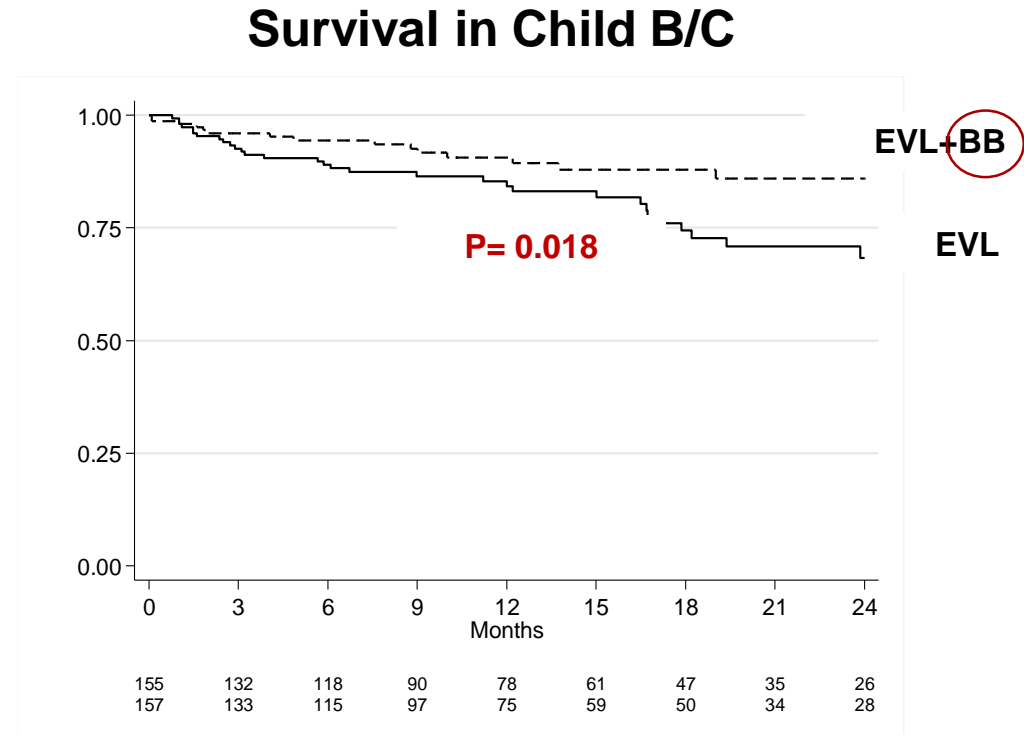
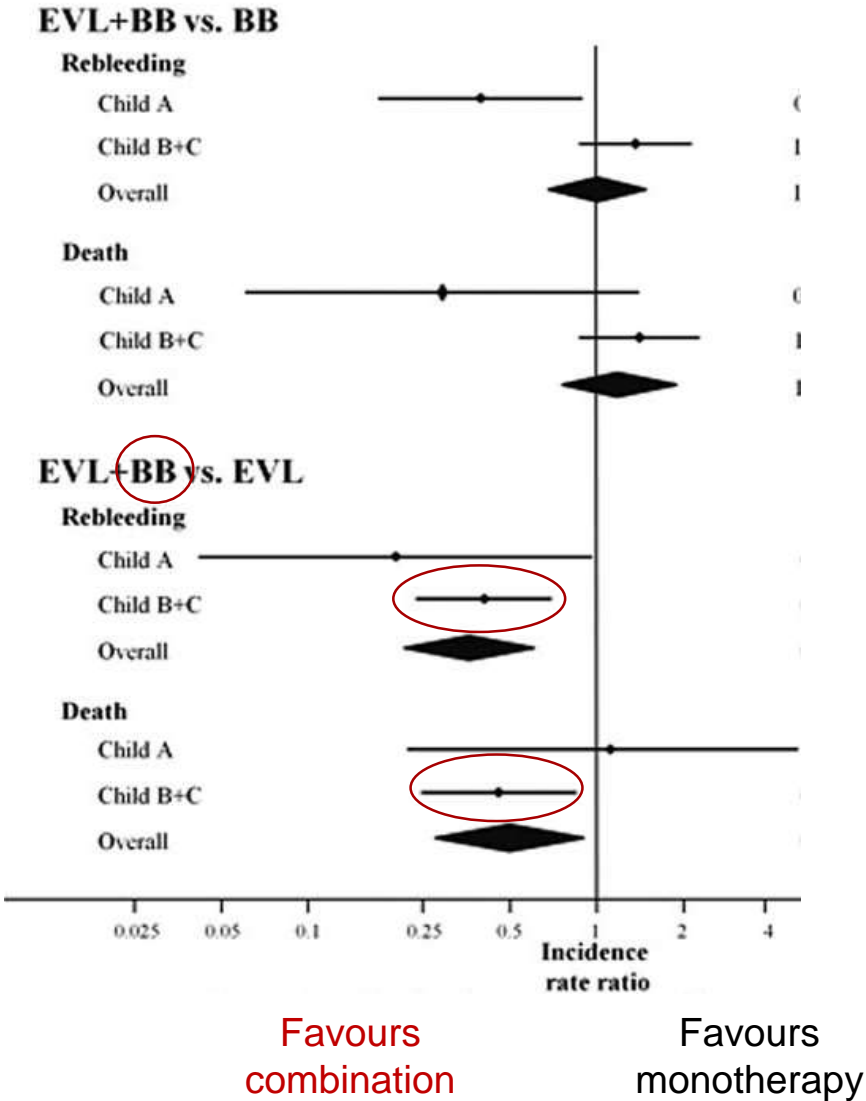


**TIPS**

End-point: variceal bleeding

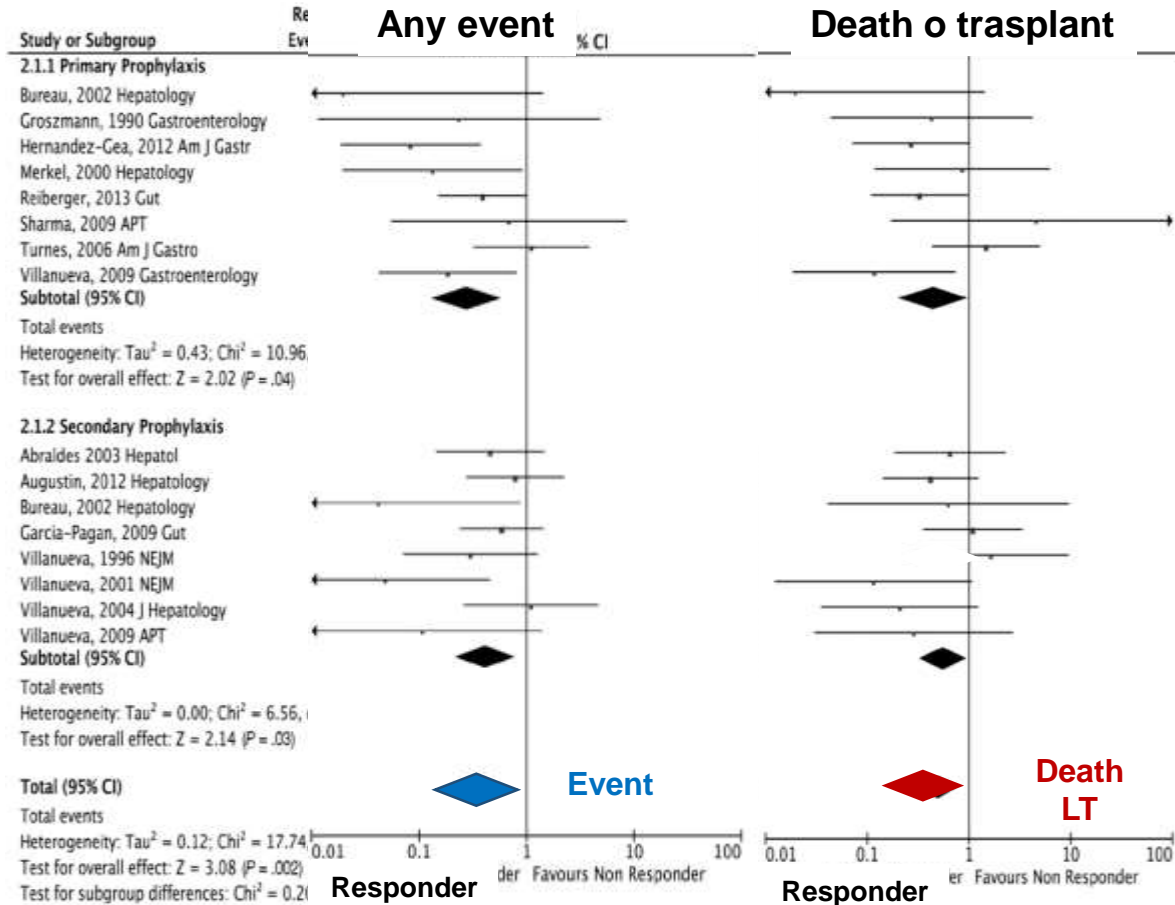
# Reduction of rebleeding and mortality in trials of rebleeding prevention

Individual patient data meta-analysis  
805 patients, 7 studies

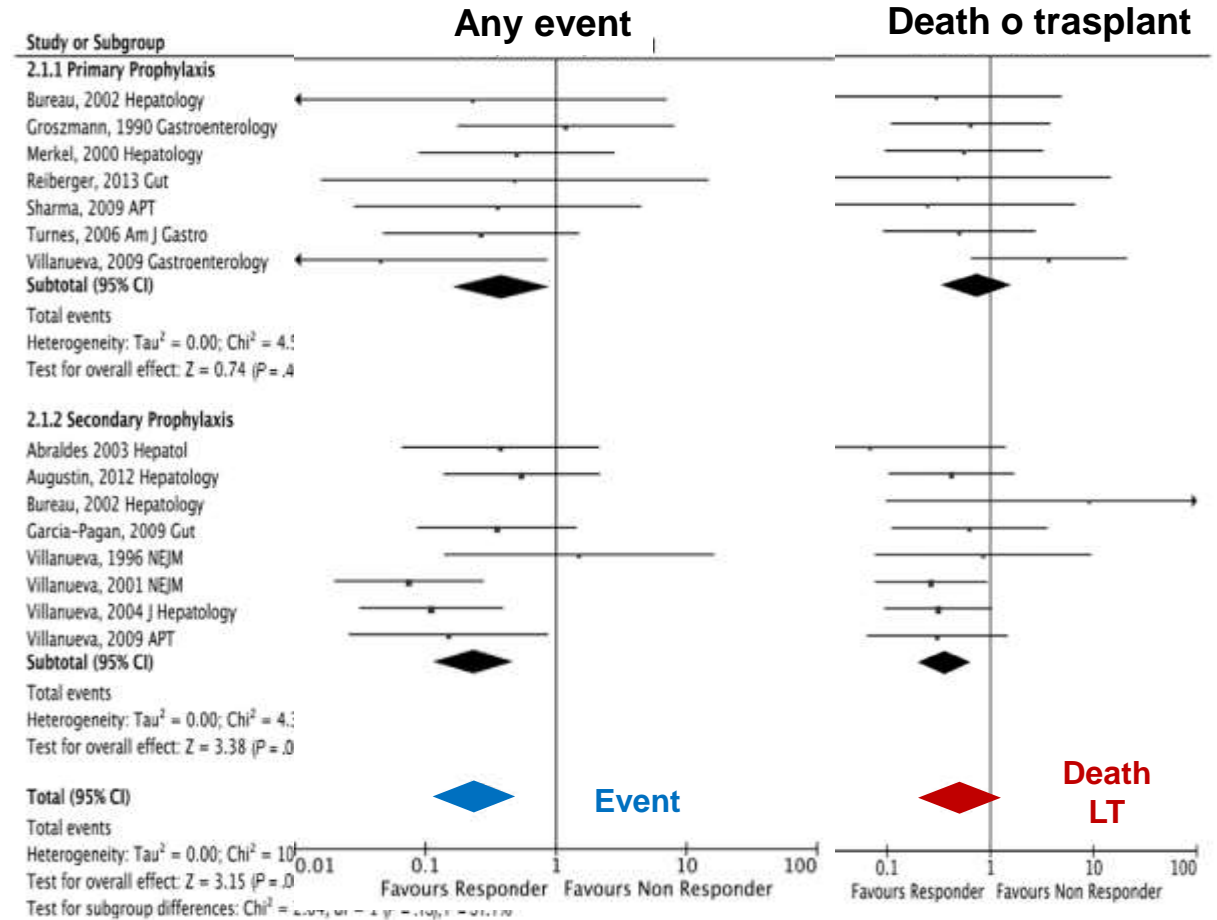


# Portal pressure reduction ( $\downarrow$ HVPG $>10-20\%$ , $<12$ mmHg) by NSBB decreases any event and increases survival (primary and secondary prophylaxis of variceal bleeding)

## Without ascites



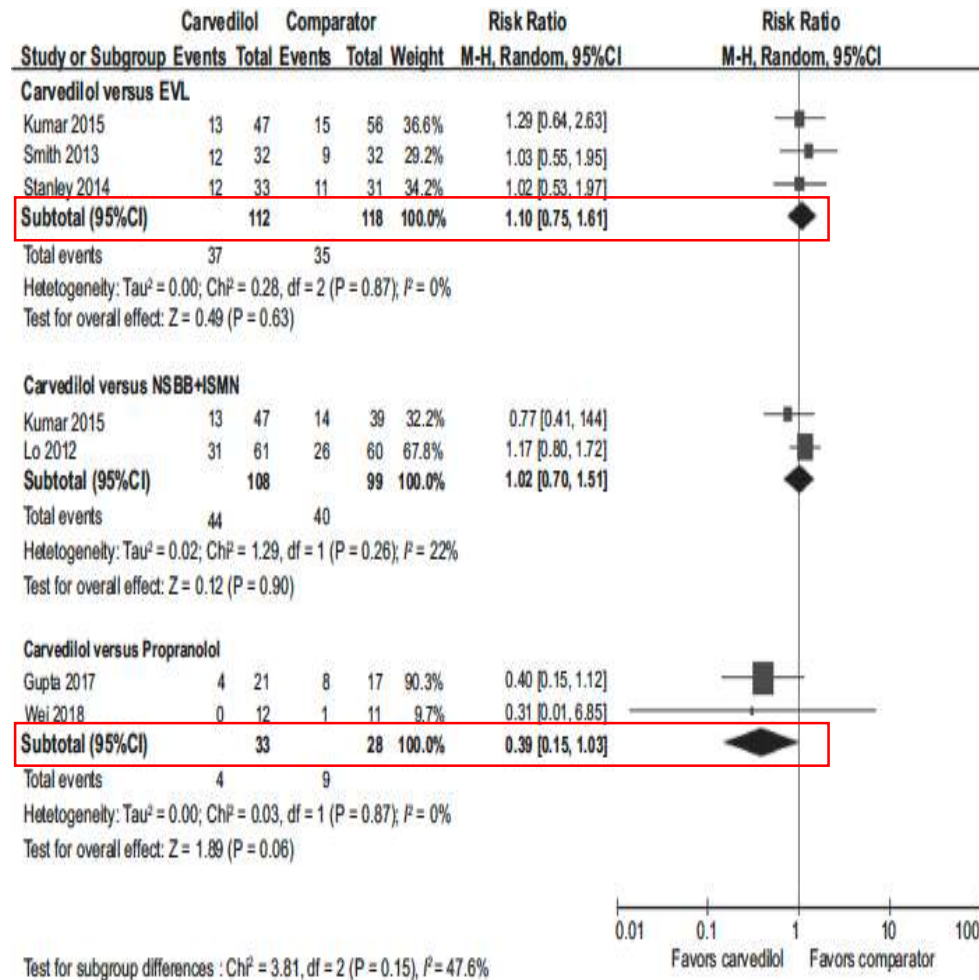
## With ascites



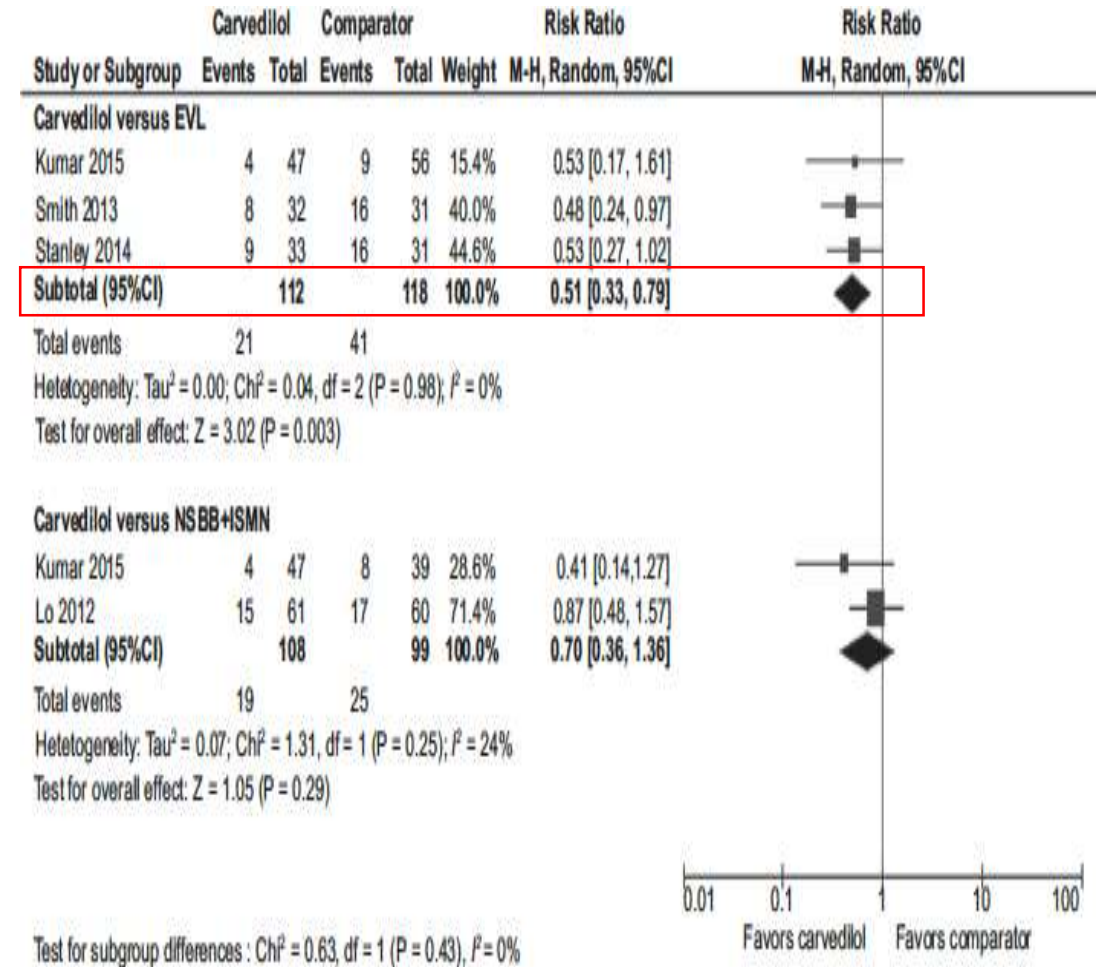


# Carvedilol in rebleeding prevention

## Variceal rebleeding

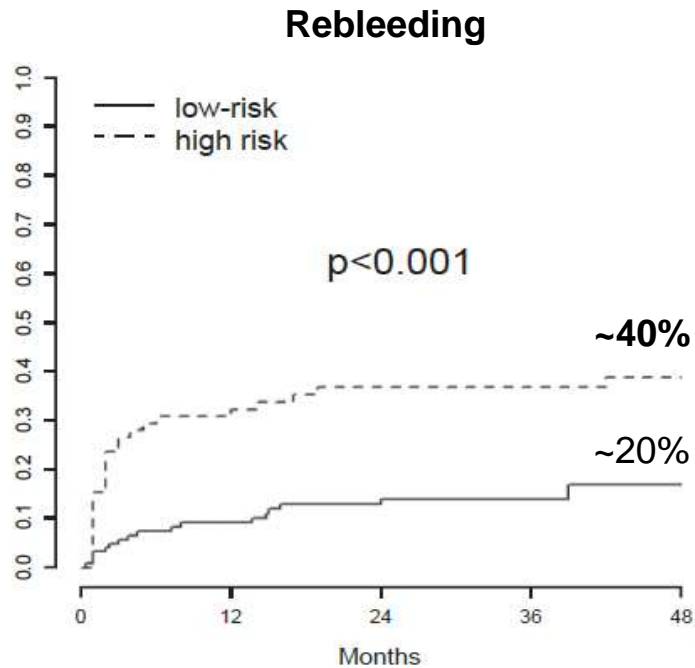


## Mortality



# Risk stratification after variceal bleeding

193 patients with AVB ± ascites or HE  
**NSBB+EVL**  
F-up 48 months

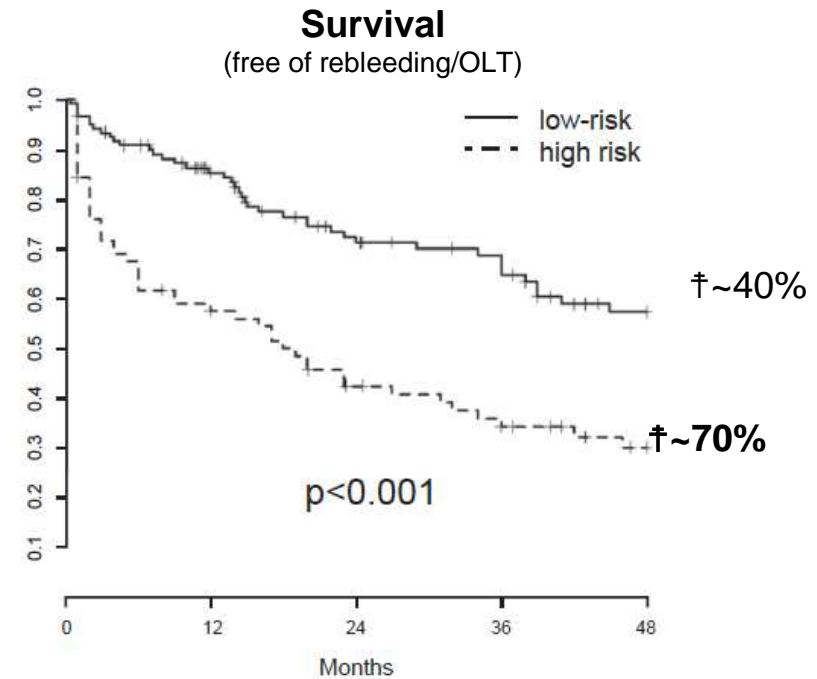


#### High-risk group

- HVPG non-response to NSBB
- Basal HVPG >16 mmHg

#### Low-risk group

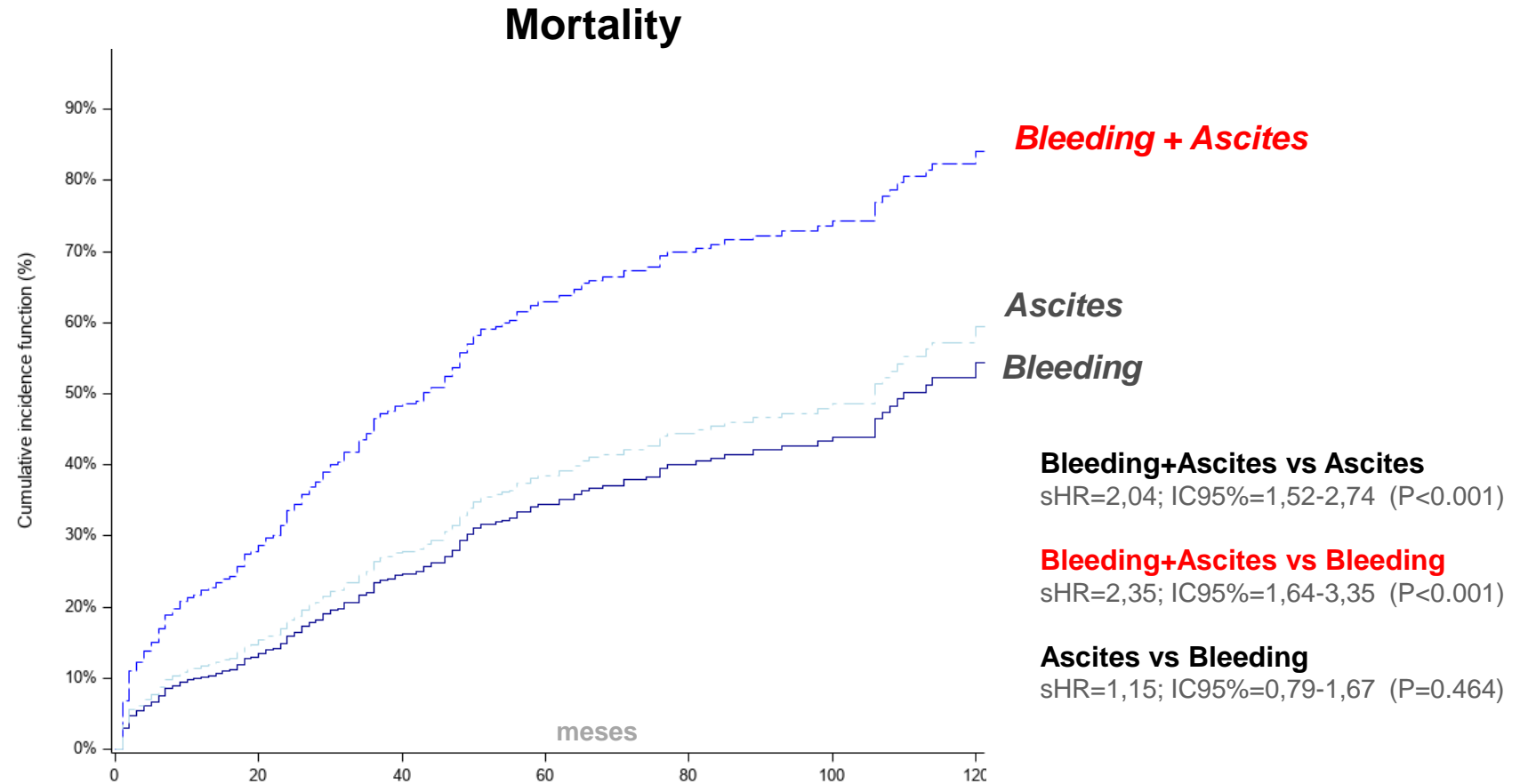
- Absence of ascites or HE
- Ascites or HE and basal HVPG <16 mmHg



#### Ascites or HE

- (bleeding as 2<sup>nd</sup> decompensation)
- Rebleeding **21%** at 4-yr
  - Death **52%** at 4-yr

## Greater mortality in the long-term of patients with variceal bleeding as 2nd decompensation



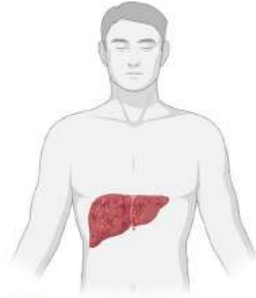
# TIPS prevents further decompensation and increases survival in patients with cirrhosis

## Background

### ○ Further decompensation

Second / recurrent liver decompensation

- Ascites
- Variceal Bleeding
- Hepatic encephalopathy
- Jaundice, HRS-AKI, SBP



### ○ Indication of TIPS



- Refractory ascites
- Pre-emptive TIPS
- Prevention of rebleeding

## Aims

To assess (i) the incidence of further decompensation and (ii) survival after TIPS vs. standard of care (SOC)

## Methods

### IPD meta-analysis

12 controlled studies:

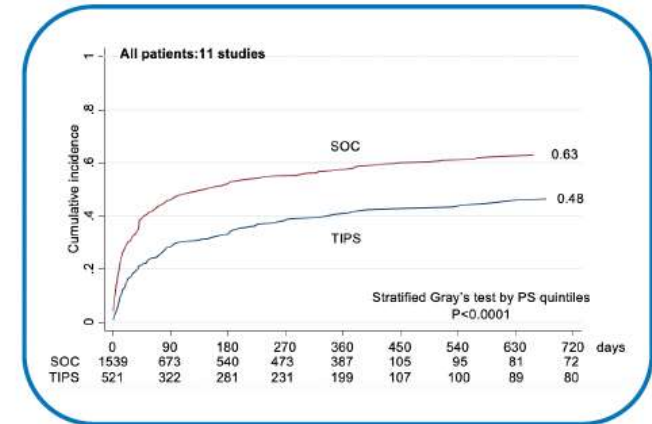
n=3949 comparing TIPS vs SOC. SOC n=3097, TIPS n=852

Adjusted by PS-matching: 2338 patients with similar characteristics

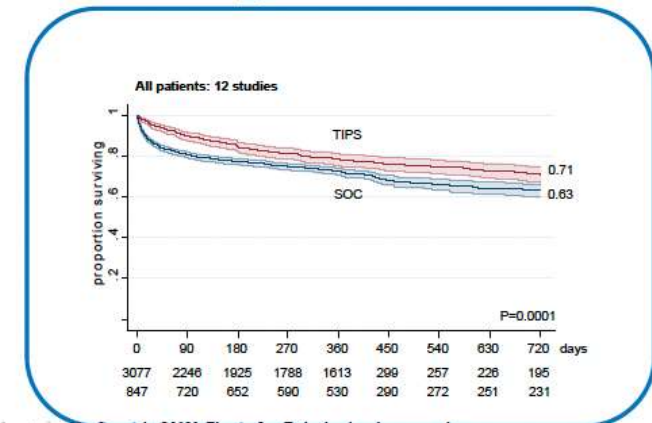
### Outcomes

- I: Incidence of further decompensation
- II: Overall survival

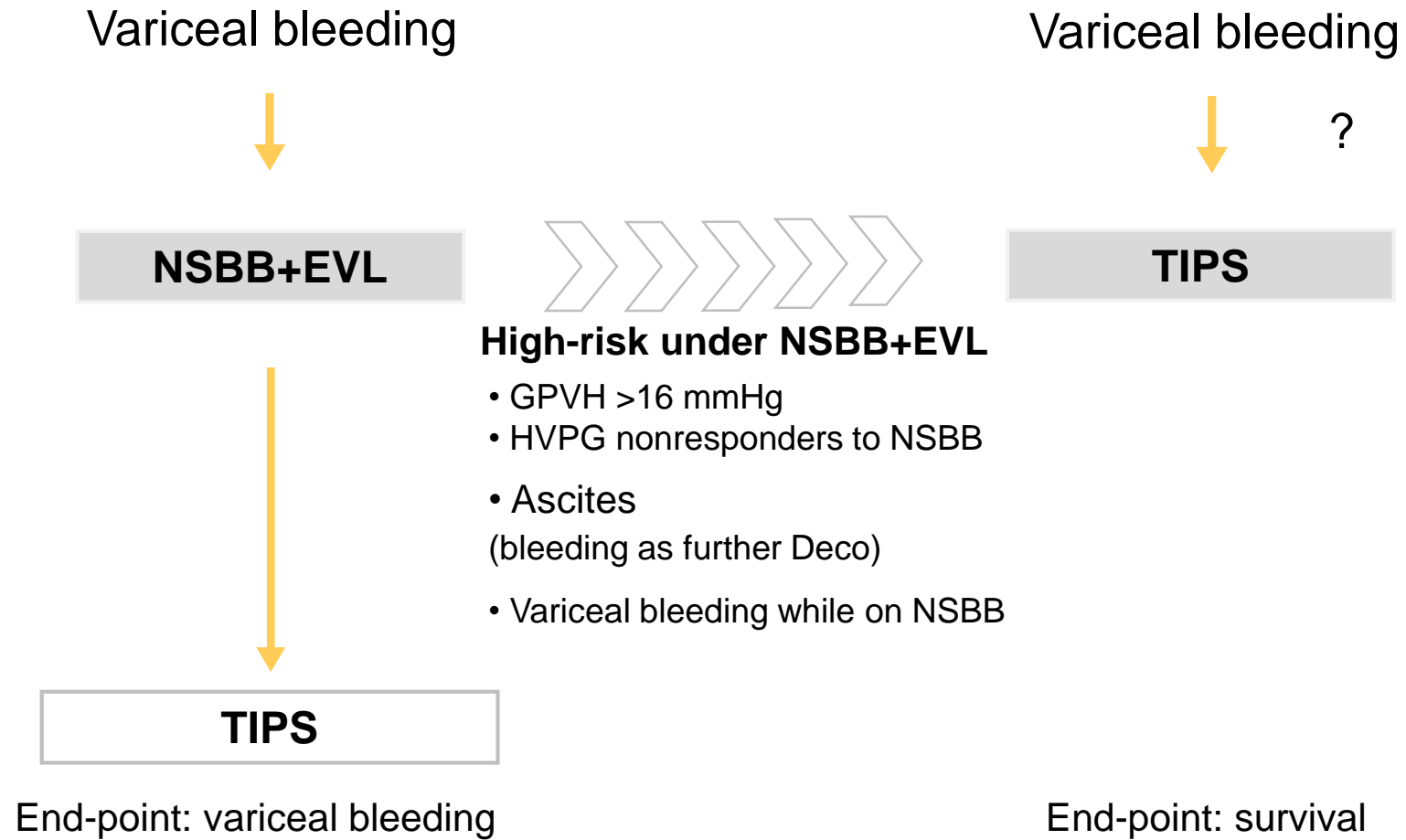
↓ Further decompensation



↑ Survival



## Prevention of rebleeding → Prevention of further decompensation



## Practical tips

### Prevention of rebleeding

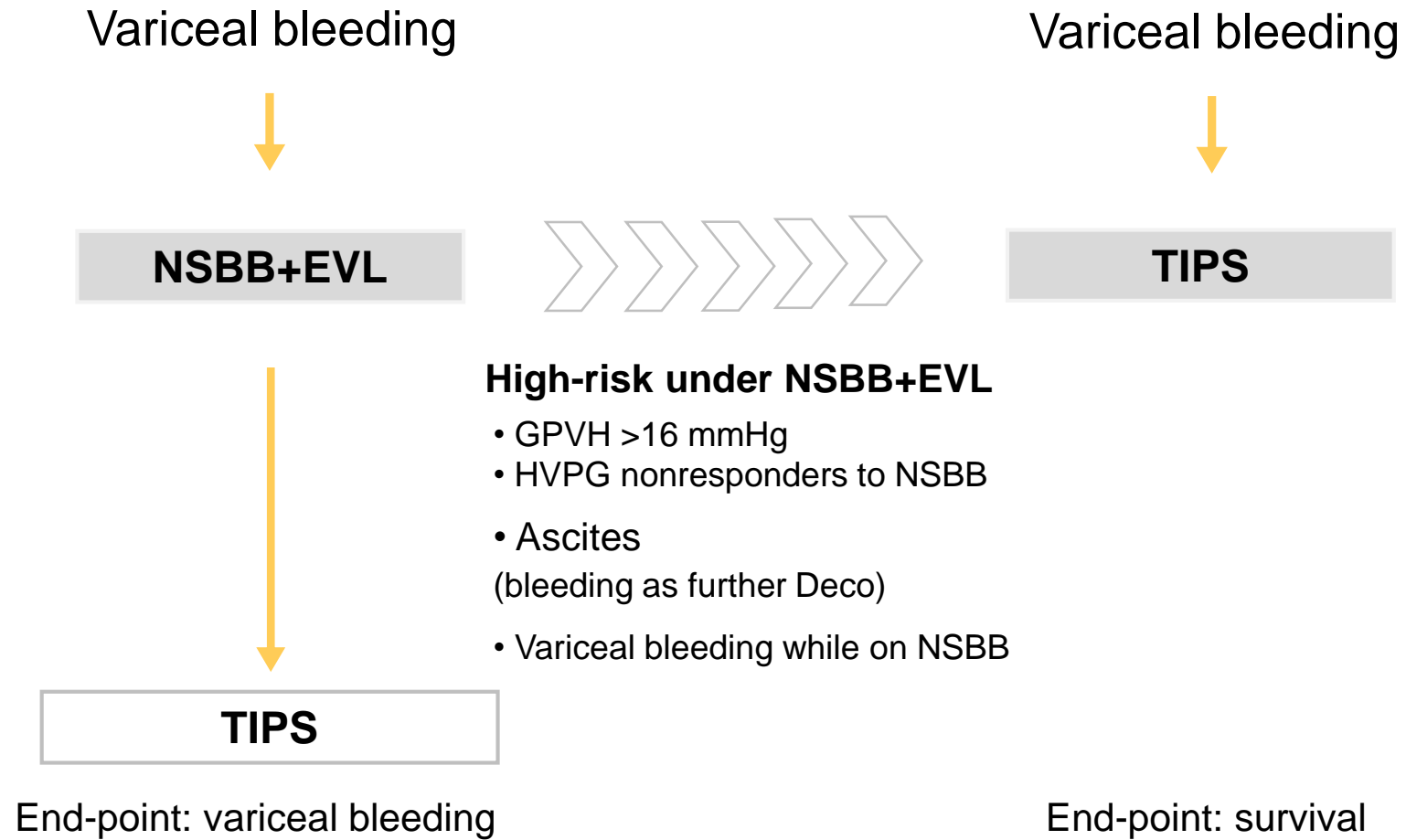
#### Standard of care

- NSBB + EVL
- NSBB as the main component
- Carvedilol of choice if no/diuretic-responsive ascites

#### TIPS

- Rescue therapy of SOC
- Consider as first option in bleeding as 2<sup>nd</sup> decompensation?

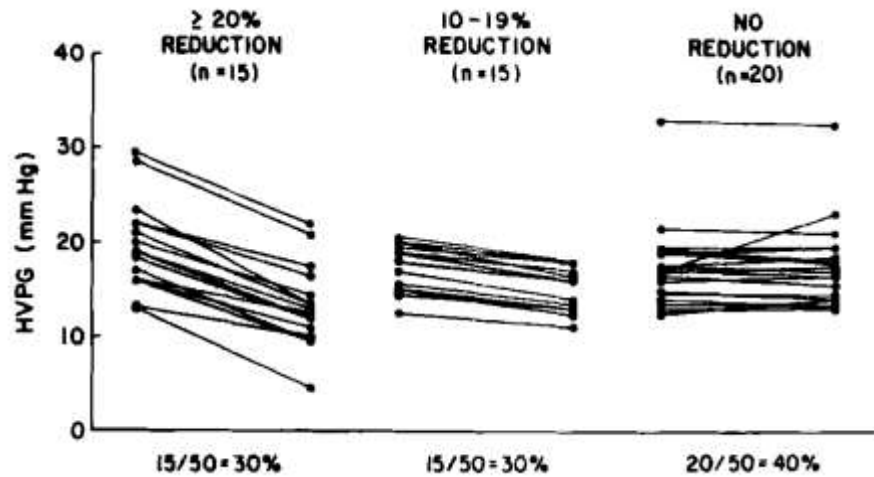
## Prevention of further decompensation





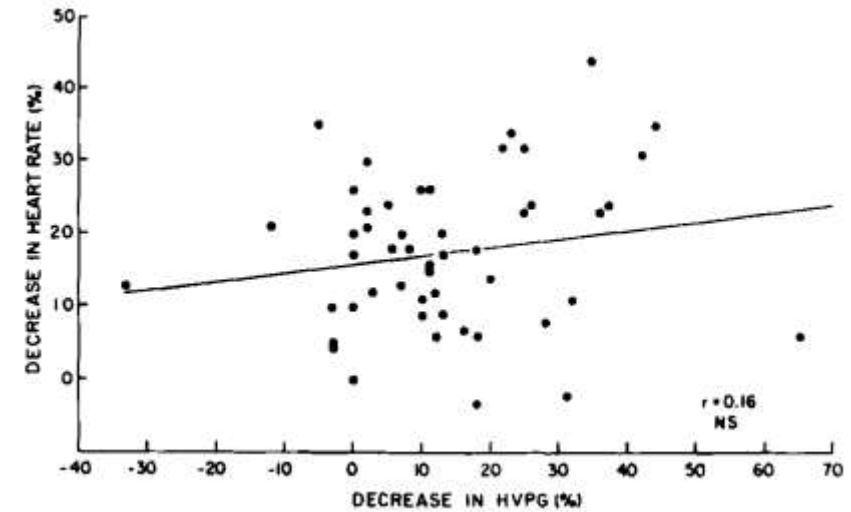
## Individual variability in the HVPG response to propranolol

Change in HVPG  
2 h after 40 mg propranolol



Non-response in 40%

Correlation between HVPG and  
decrease in heart rate



## Non-invasive assessment of HVPG response to NSBB

### Non-invasive hemodynamics

- US-Doppler: changes in portal blood flow
- Liver elastography (VCTE<sup>TM</sup>, MR): changes in liver-stiffness
- Spleen elastography (VCTE<sup>TM</sup>): changes in spleen-stiffness

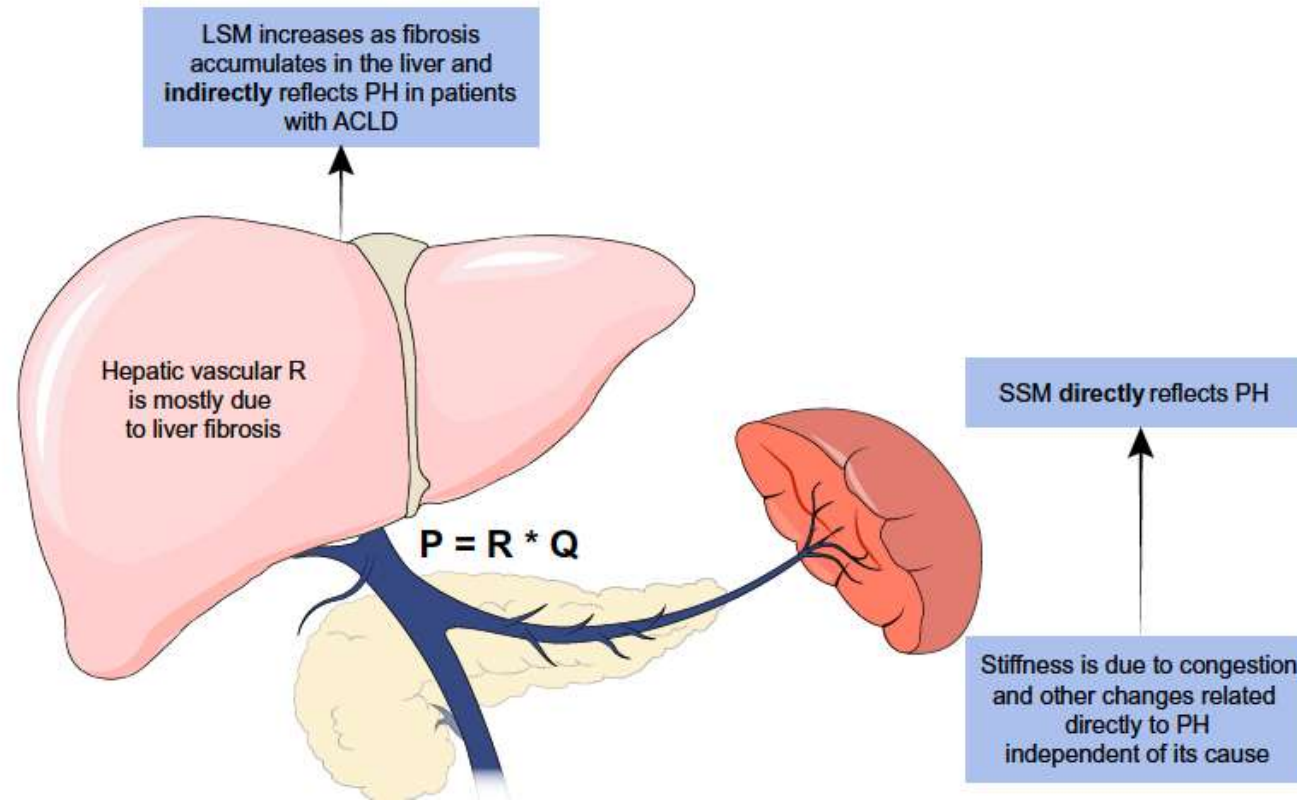
### Biomarkers

- Expression of  $\beta$ Arr2 and RhoA/ROCK2 in antrum mucosa
- miRNA signature in peripheral blood

### Genetics

- Polymorphisms in beta-2 adrenoreceptor and CYP2D6

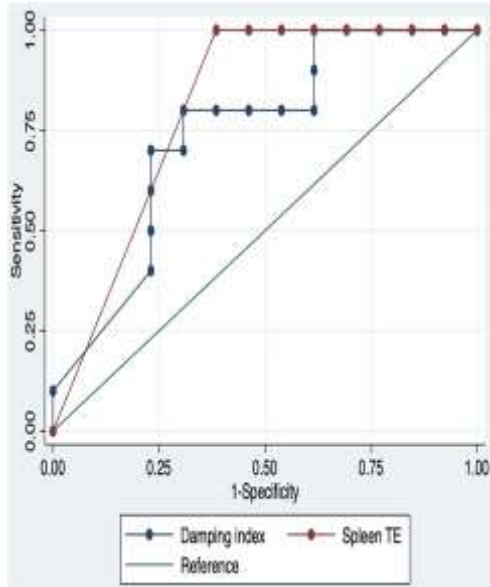
## Changes in spleen stiffness to assess the HVPG response to NSBB



# Changes in spleen stiffness to assess the HVPG response to NSBB

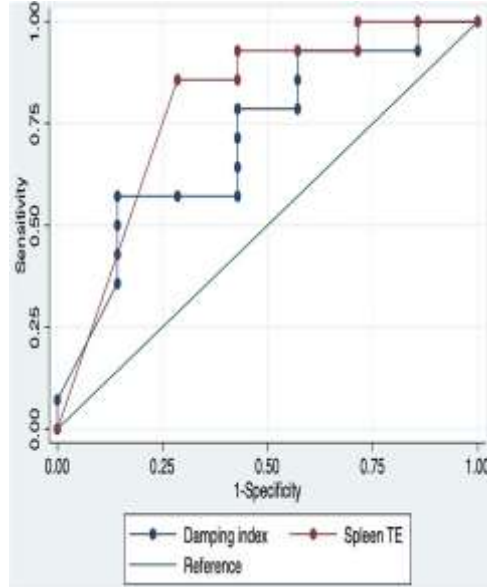
## Spleen stiffness by TE and ARFI

Acute response to propranolol



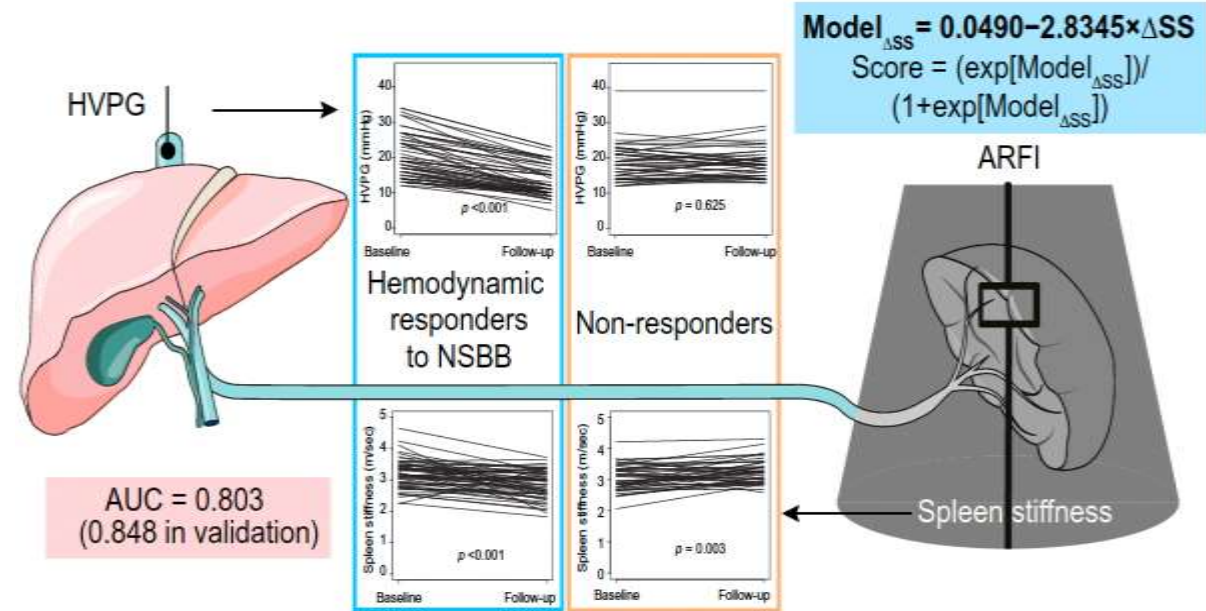
AUC = 0.8 for SSM

Chronic response to propranolol



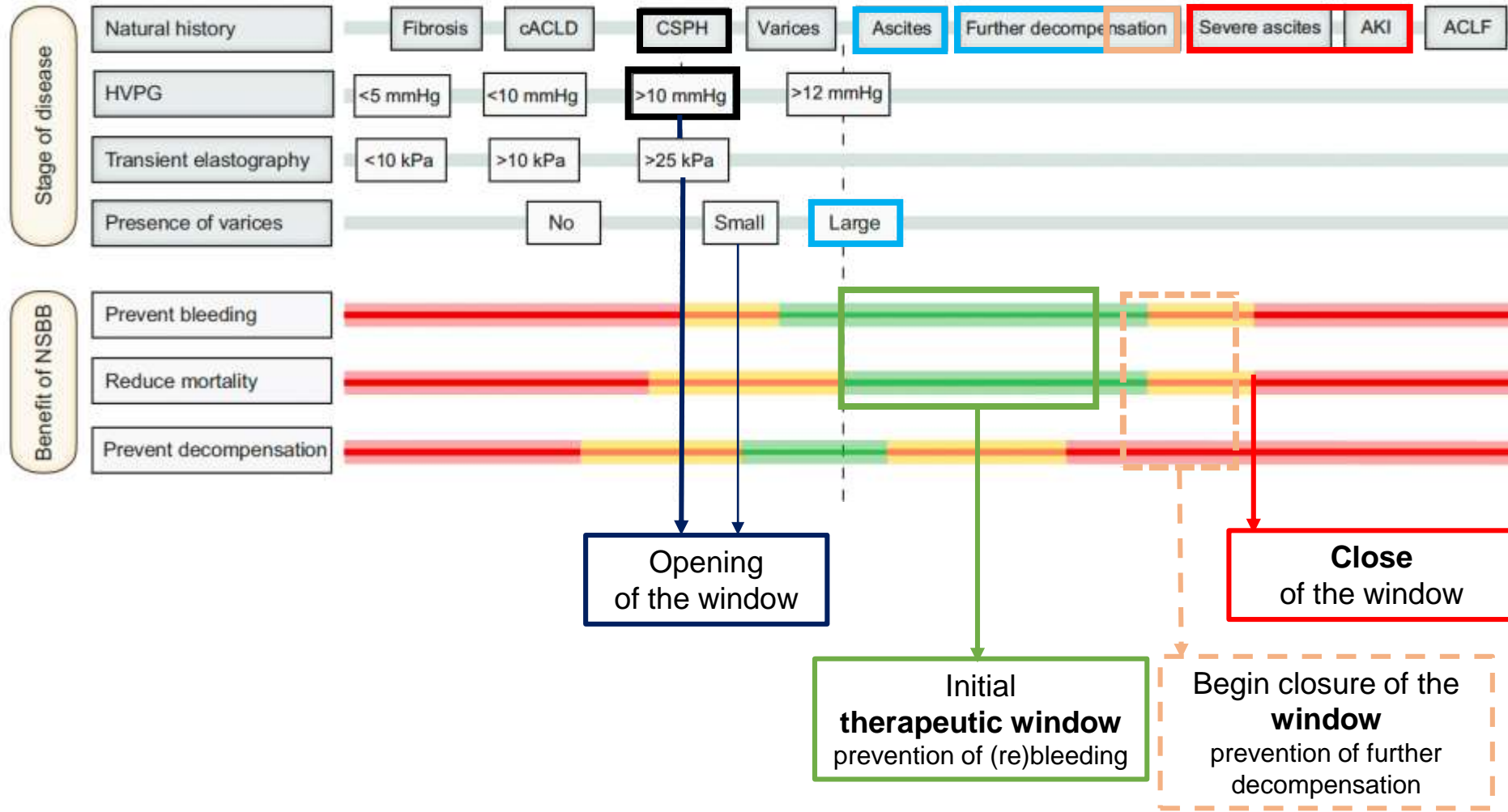
AUC = 0.8 for SSM

## Spleen stiffness by ARFI



- ARFI-measured DSS predicted hemodynamic response to prophylactic carvedilol.

## Revisiting the therapeutic window of beta-blockers in cirrhosis



Modified from A Albillos, A Krag. JHEP 2022

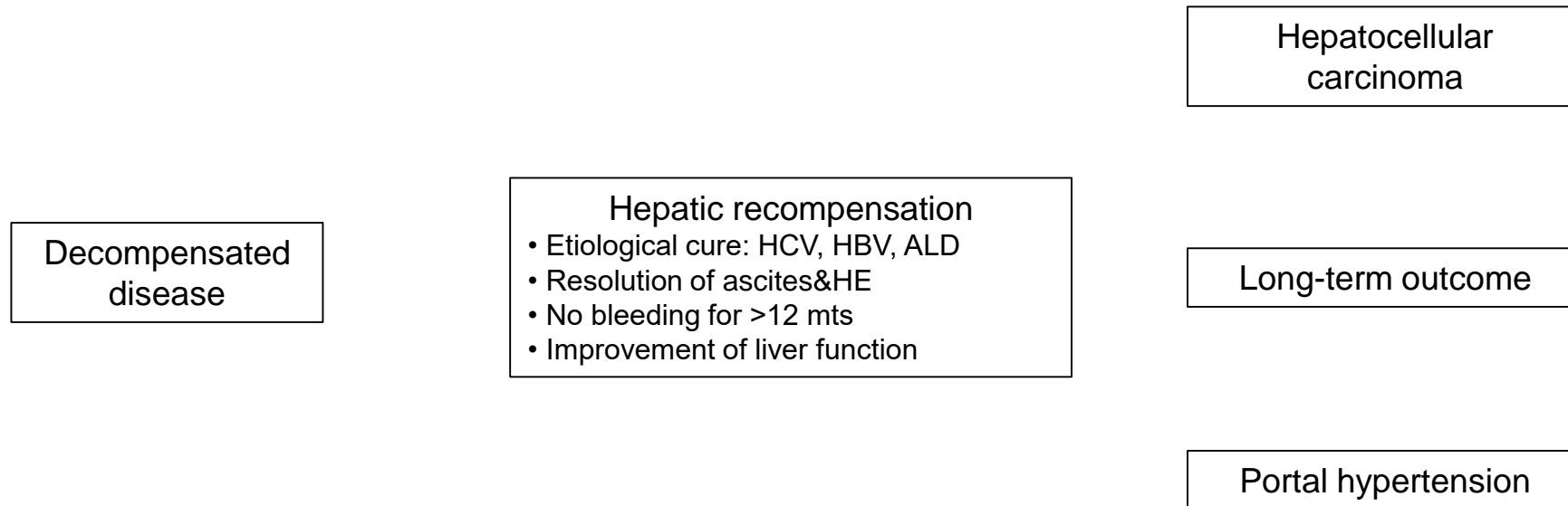
Unlikely to benefit  
Benefit uncertain or small  
Strong data support benefit



## Take-home messages

- NSBB from prevention of (re)-bleeding to prevention of decompensation, but *limited* efficacy to prevent further decompensation
- NSBB titration limited by arterial pressure/AKI.  
Carvedilol of choice in patients with no or mild ascites
- Changes in spleen stiffness to assess the HVPG response to NSBB under study

## The concept of recompensation according to Beveno VII





# Non-invasive tests for clinically significant portal hypertension after HCV cure

## Pooled analysis



418 patients with paired HVPG-measurements +/- NIT before and after HCV-cure

! Etiological cure modifies relationship between NIT and HVPG !

✓ Increased correlation LSM/HVPG

$r=0.45 \rightarrow r=0.60$

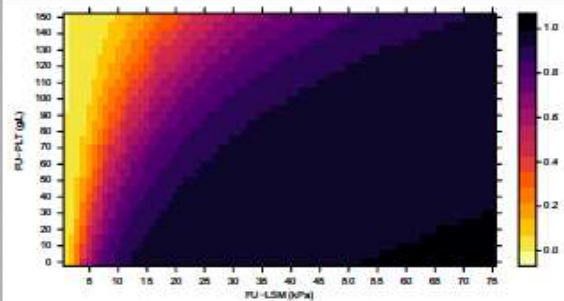
✓ Numerically higher accuracy for diagnosing CSPH

Decreased prevalence of CSPH after HCV cure  
80%  $\rightarrow$  54%,  $\downarrow$  18%

## Clinical decision rules

LSM <12 kPa & PLT >150 G/L  
 $\rightarrow$  CSPH excluded

## Estimated probability of CSPH



LSM  $\geq$ 25 kPa  
 $\rightarrow$  CSPH ruled-in

## Validation vs. Direct endpoints

755 cACLD patients followed for a median of 38 months

LSM <12 kPa & PLT >150 G/L

Prevalence

LSM >25 kPa

42.5%

40.7%

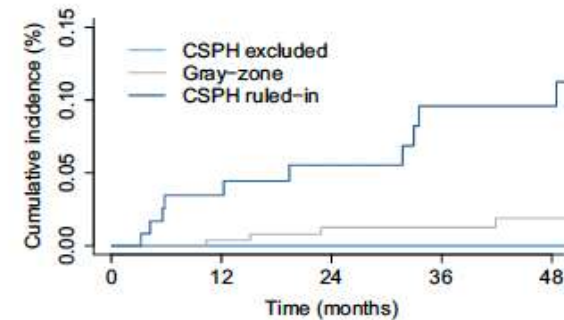
16.8%

Cumulative incidence of hepatic decompensation at 3 years

0%

1.3%

9.6%



## Practical tips

### NSBB discontinuation

#### **Conditions**

- Etiological cure
- Ascites and HE resolution, no bleeding >12 months
- Stable liver function tests

#### **Plus**

- LSM <25 kPa & no varices in confirmatory endoscopy, if no previous bleeding
- LSM <12 & Ptl >150k & no varices in confirmatory endoscopy, if previous bleeding