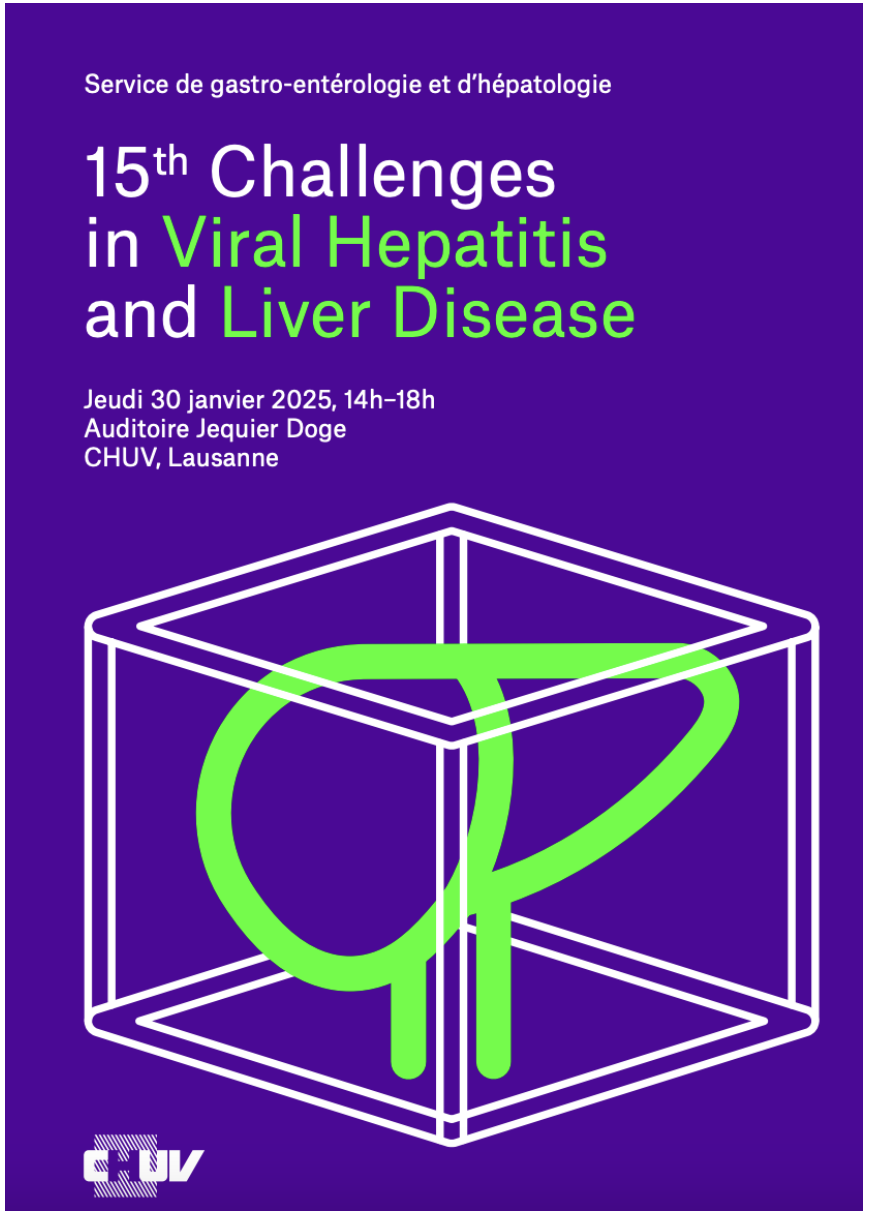


ADVANCES AND CURRENT CHALLENGES IN PORTAL HYPERTENSION

Juan G Abraldes

University of Alberta

Disclosures

- **Consulting (last 24 months)**
  - Boehringer Ingelheim — Current
  - Novo Nordisk — Current
  - Astra Zeneca — Current
  - 89Bio — Current
  - Boston Pharmaceuticals — Current
  - Terumo — Current
  - Agomab — Current
- **Grant support (paid to the University of Alberta)**
  - Gilead — Current
  - Cook — Finished
- **Trials (paid to the Alberta Health services)**
  - Salix — Current

Outline

1. Conceptual framework: PH in cirrhosis with Clinical-Pathophysiological correlates → Rational basis for the treatment of portal hypertension
2. Non-invasive diagnosis of clinically significant portal hypertension
3. Are there responders and non responders to beta-blockers

Cirrhosis: Disease Trajectory

F3

Compensated

Decompensated

First decompensation

Ascites
Bleeding
HE

Disease Activity
Fibrosis progression
Portal Hypertension

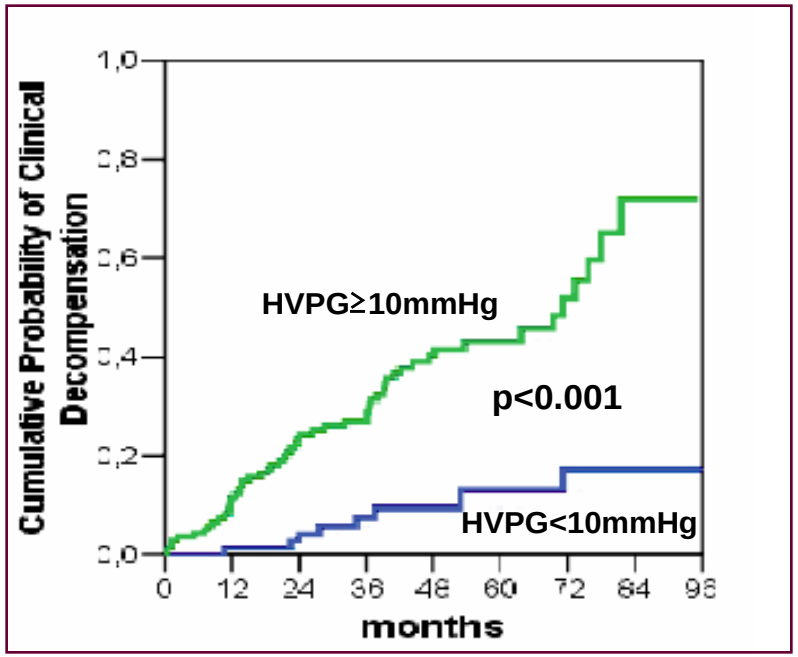
D'Amico, Alim Pharm Ther 2014

Systemic Inflammation
Systemic circulatory dysfunction

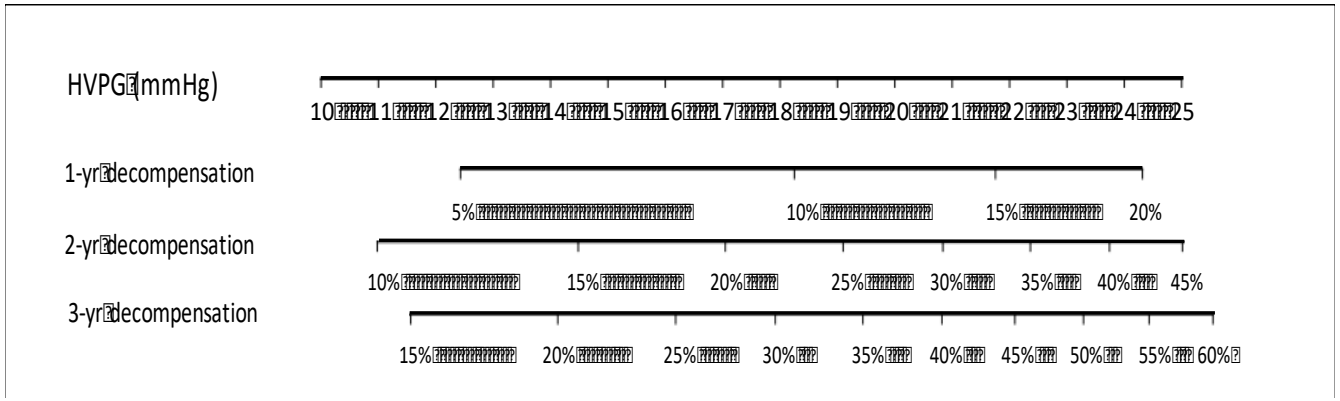
Portal Hypertension as a Driver of Decompensation

The concept of Clinically Significant Portal Hypertension (CSPH)

Probability of Decompensation



Ripoll et al Gastroenterology 2007



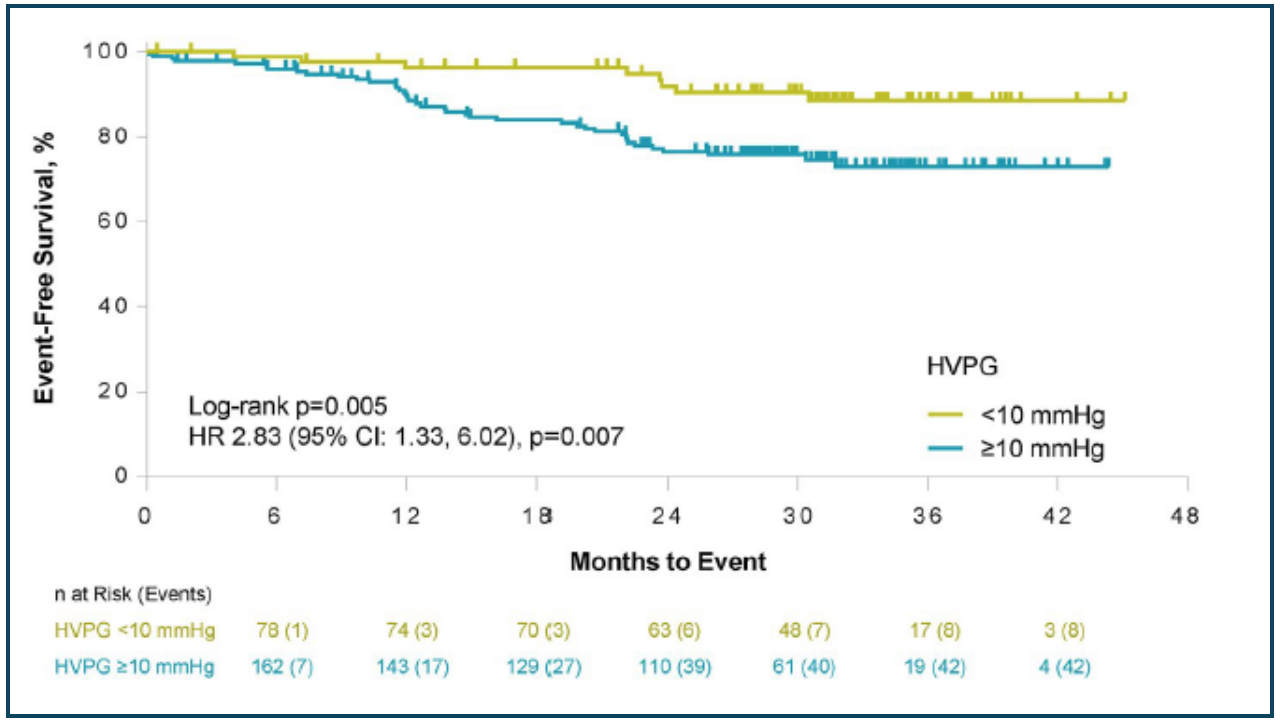
Abraldes et al Hepatology 2019 (with data from Ripoll et al).

adjusted **HR (p**er 1 mmHg increase in HVPG): **1.11**

Based on Timolol trial cohort (mostly Hep C and ETOH)

Natural History of **MASLD** Cirrhosis and Portal Hypertension

Probability of “Liver Events” *

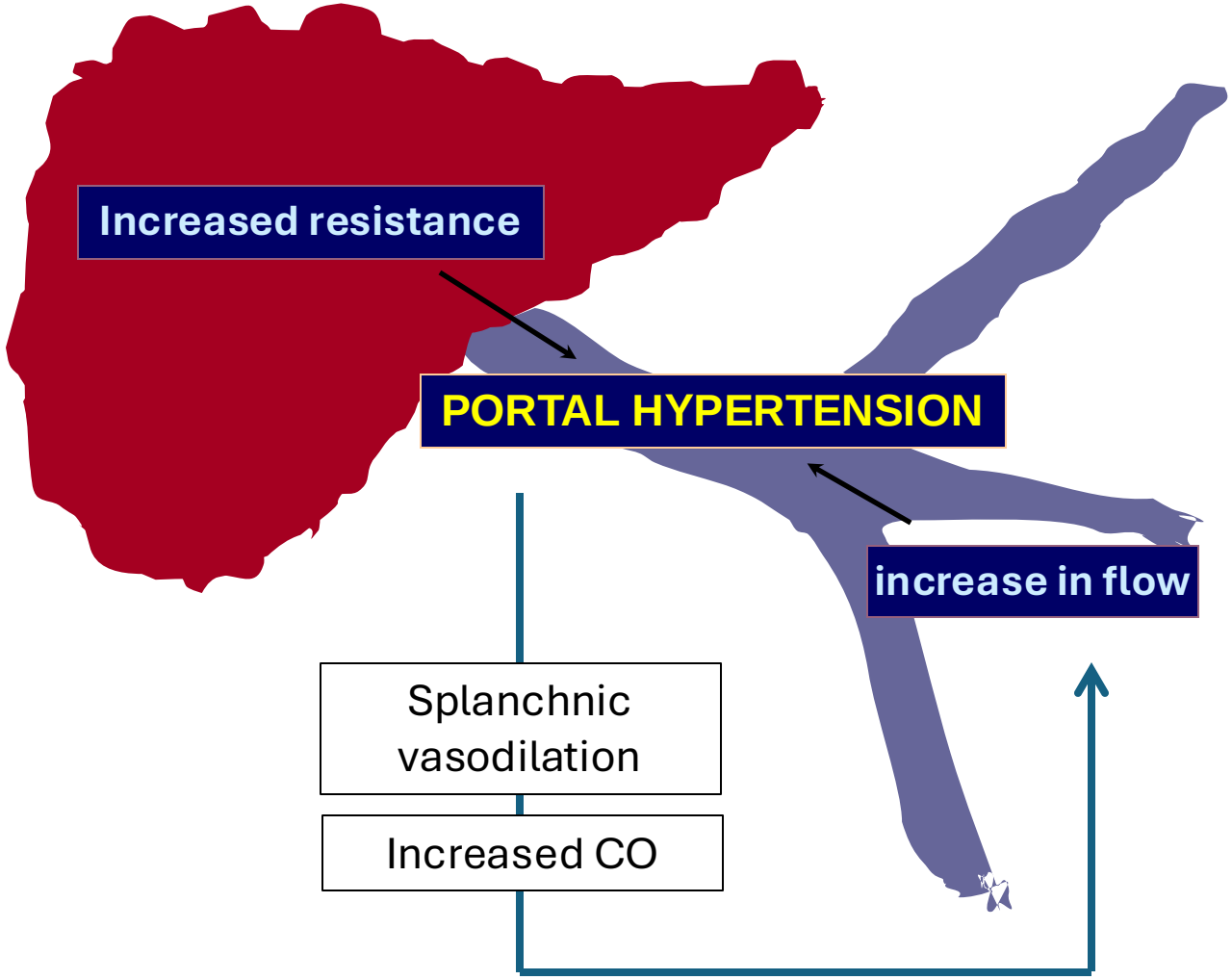


* Includes decompensation, new varices, ≥2-point increase in CP score and/or MELD ≥15

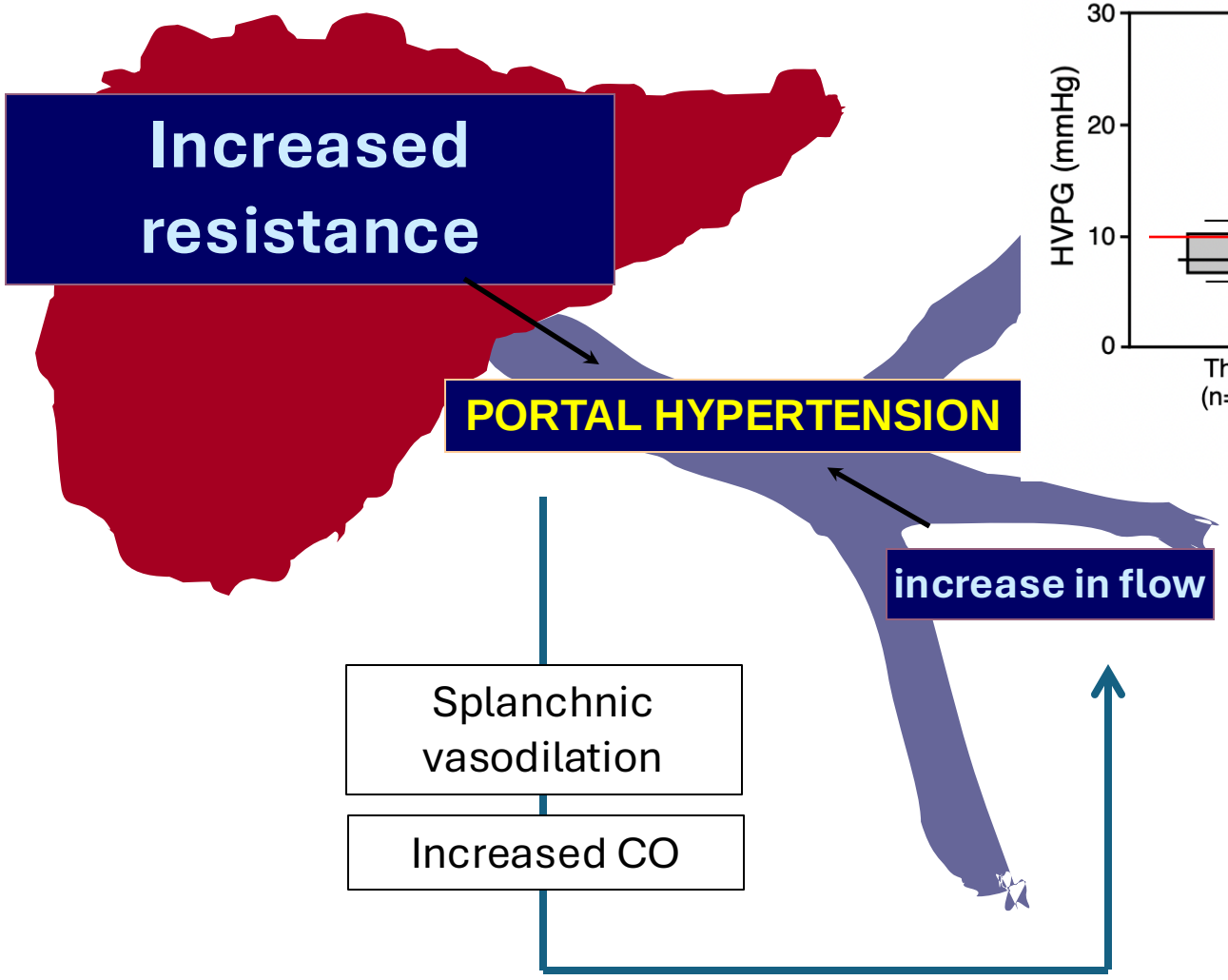
Sanyal et al Hepatology 2019 (data from Sintuzumab trial)

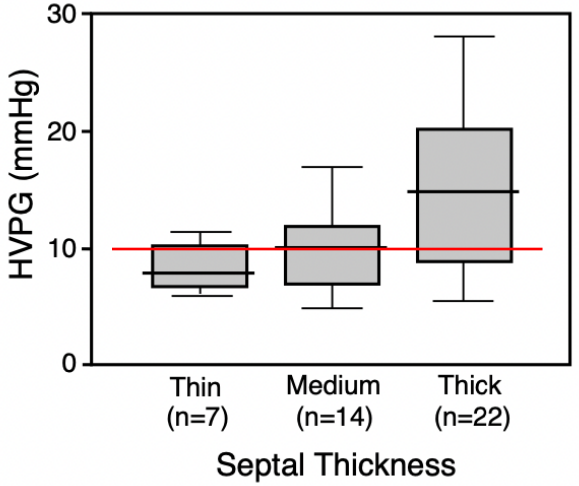
	HR (95% CI)	p-value
HVPG	**1.11 (1.05-1.18)**	**<0.001**
Albumin	0.20 (0.10-0.41)	<0.001

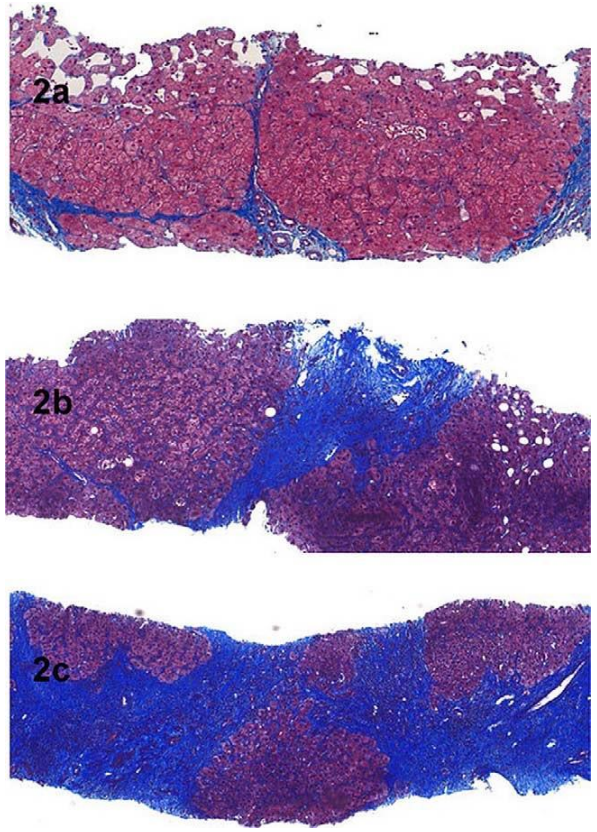
More on Pathophysiology Correlates: Resistance and Flow



More on Pathophysiology Correlates: Resistance and Flow

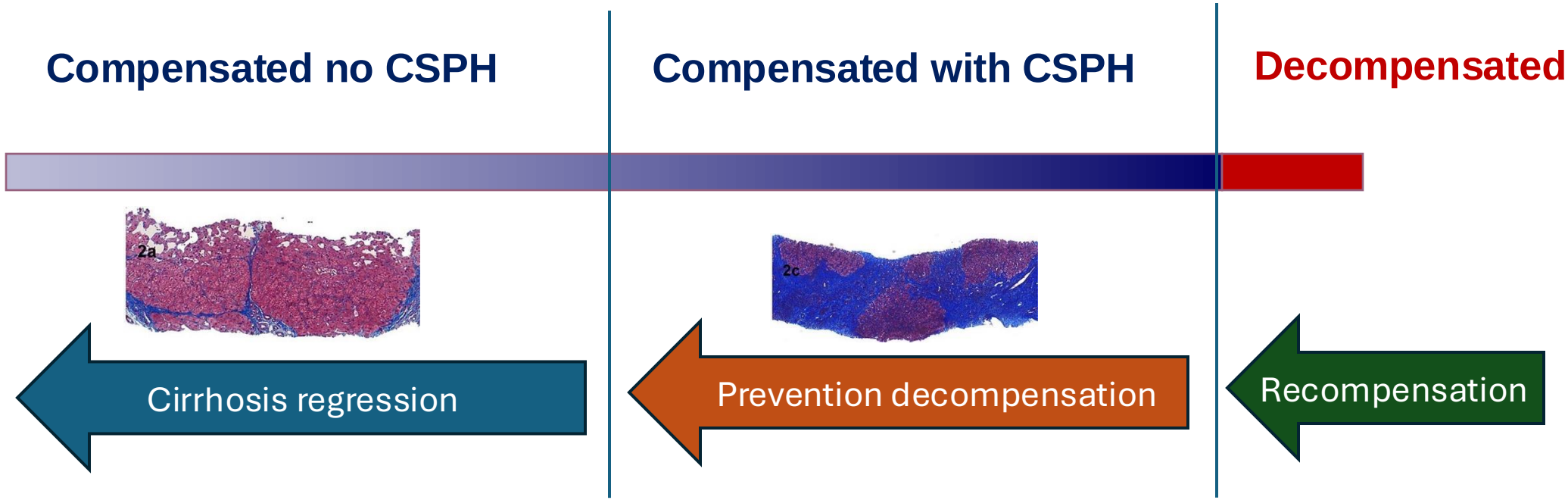




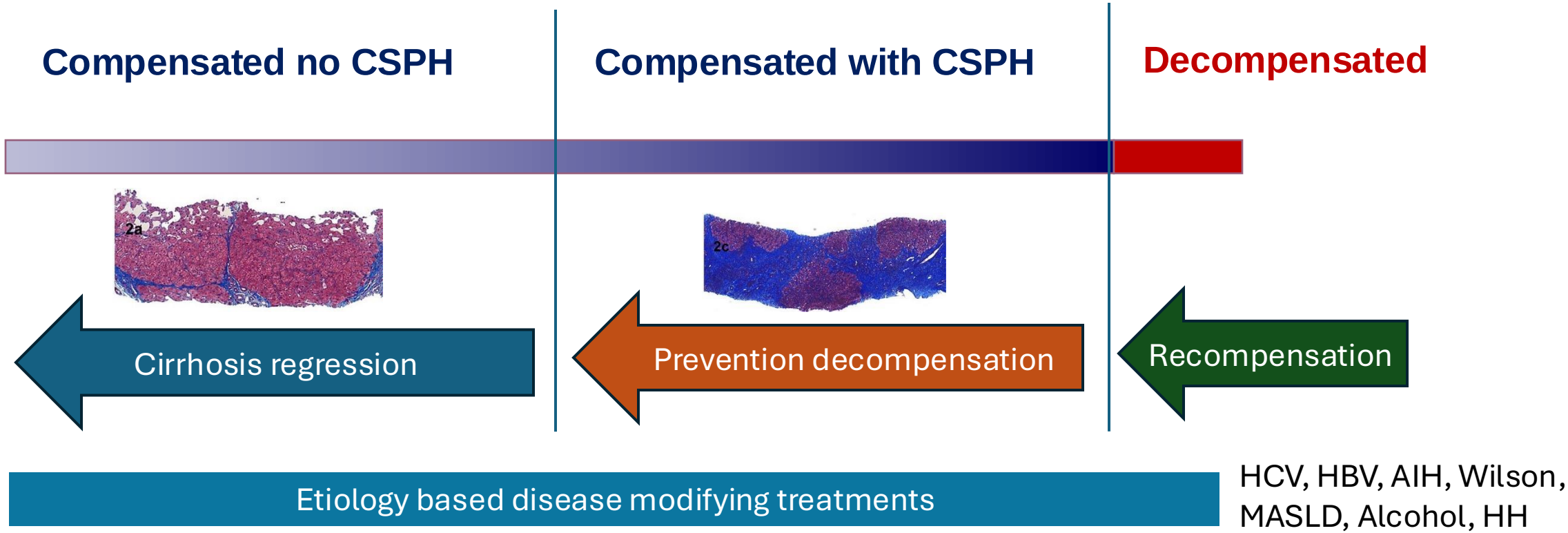


Nagula et al J Hep 2006

General Approach to the Management of Cirrhosis

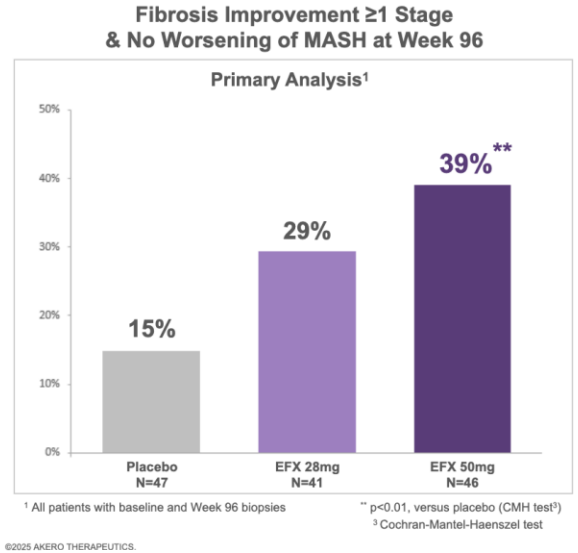


General Approach to the Management of Cirrhosis



Compensated no CSPH

Reversal of Cirrhosis with FGF-21 agonist Efruxifermin



ITT Analysis²

Placebo (N=61)	EFX 28mg (N=57)	EFX 50mg (N=63)
12%	21%	29%*

² Missing biopsy = failure
* p<0.05, versus placebo (CMH test)

Akero Press release Jan 24 2025

Compensated with CSPH

ORIGINAL ARTICLES: VIRAL HEPATITIS

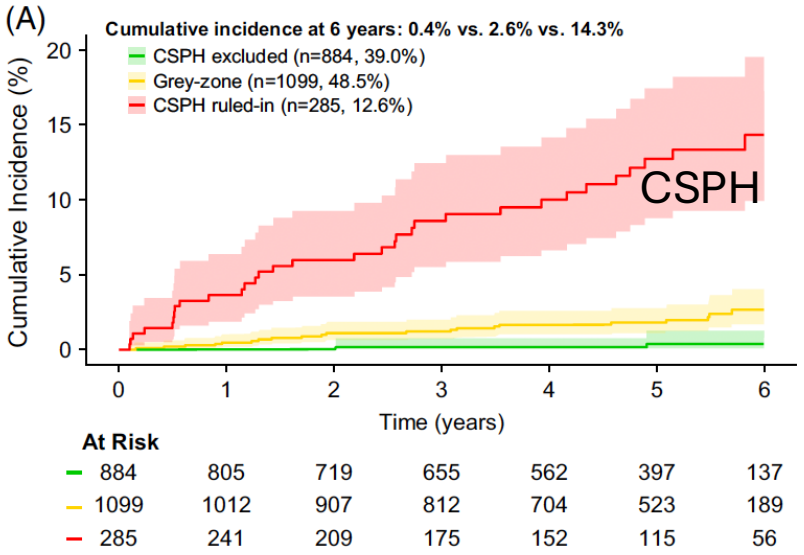
Long-term outcome and risk stratification in compensated advanced chronic liver disease after HCV-cure

Semmler, Georg[1,2]; Alonso López, Sonia[3,4,5]; Pons, Monica[6]; Lens, Sabela[7,8]; Dajti, Elton[9,10]; Griemsmann, Marie[11]; Zanetto, Alberto[12]; Burghart, Lukas[1,13]; Hametner-Schreil, Stefanie[14]; Hartl, Lukas[1,2]; Manzano, Marisa[15]; Rodriguez-Tajes, Sergio[7,8]; Zanaga, Paola[12]; Schwarz, Michael[1,2,13]; Gutierrez, María L.[16]; Jachs, Mathias[1,2]; Pocurull, Anna[7,8]; Polo, Benjamín[17]; Ecker, Dominik[14]; Mateos, Beatriz[18]; Izquierdo, Sonia[19]; Real, Yolanda[20]; Balcar, Lorenz[1,2]; Carbonell-Asins, Juan A.[21]; Gschwantler, Michael[13]; Russo, Francesco P.[12]; Azzaroli, Francesco[9,10]; Maasoumy, Benjamin[11]; Reiberger, Thomas[1,2]; Forns, Xavier[7,8]; Genesca, Joan[6,8]; Bañares, Rafael[3,4,5]; Mandorfer, Mattias[1,2]

Collaborators

Author Information

Hepatology 81(2):p 609-624, February 2025. | *DOI:* 10.1097/HEP.0000000000001005



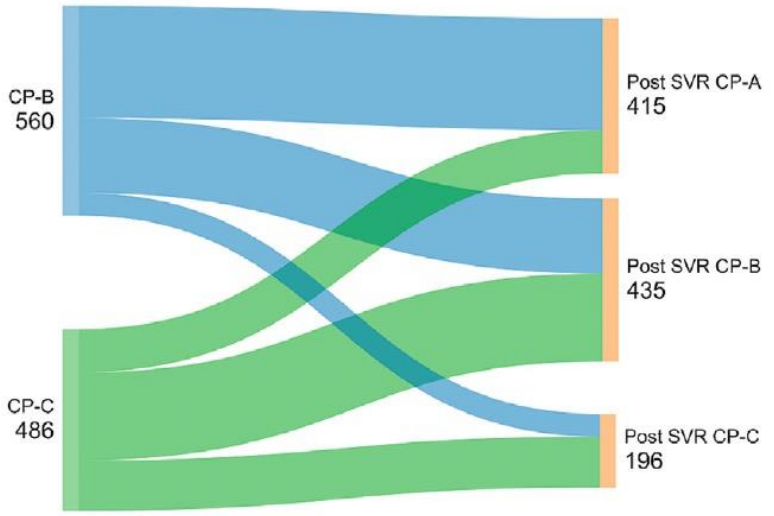
Decompensated

Gastroenterology
Volume 167, Issue 7, December 2024, Pages 1429-1445

Original Research
Full Report: Hepatobiliary

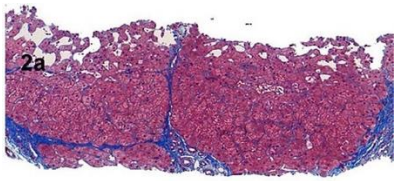
Recompensation of Chronic Hepatitis C–Related Decompensated Cirrhosis Following Direct-Acting Antiviral Therapy: Prospective Cohort Study From a Hepatitis C Virus Elimination Program

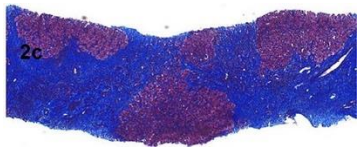
Madhumita Premkumar [1], Radha K. Dhiman [2 3], Ajay Duseja [1], Rohit Mehtani [4], Sunil Taneja [1], Ekta Gupta [5], Pankaj Gupta [6], Anchal Sandhu [1], Prerna Sharma [1], Sahaj Rathi [1], Nipun Verma [1], Anand V. Kulkarni [7], Harish Bhujade [6], Sreedhara B. Chaluvashetty [6], Naveen Kalra [6], Gagandeep S. Grover [8], Jasvinder Nain [1], K. Rajender Reddy [9]



General Approach to the Management of Cirrhosis

Compensated no CSPH | **Compensated with CSPH** | **Decompensated**





Cirrhosis regression

Prevention decompensation

Recompensation

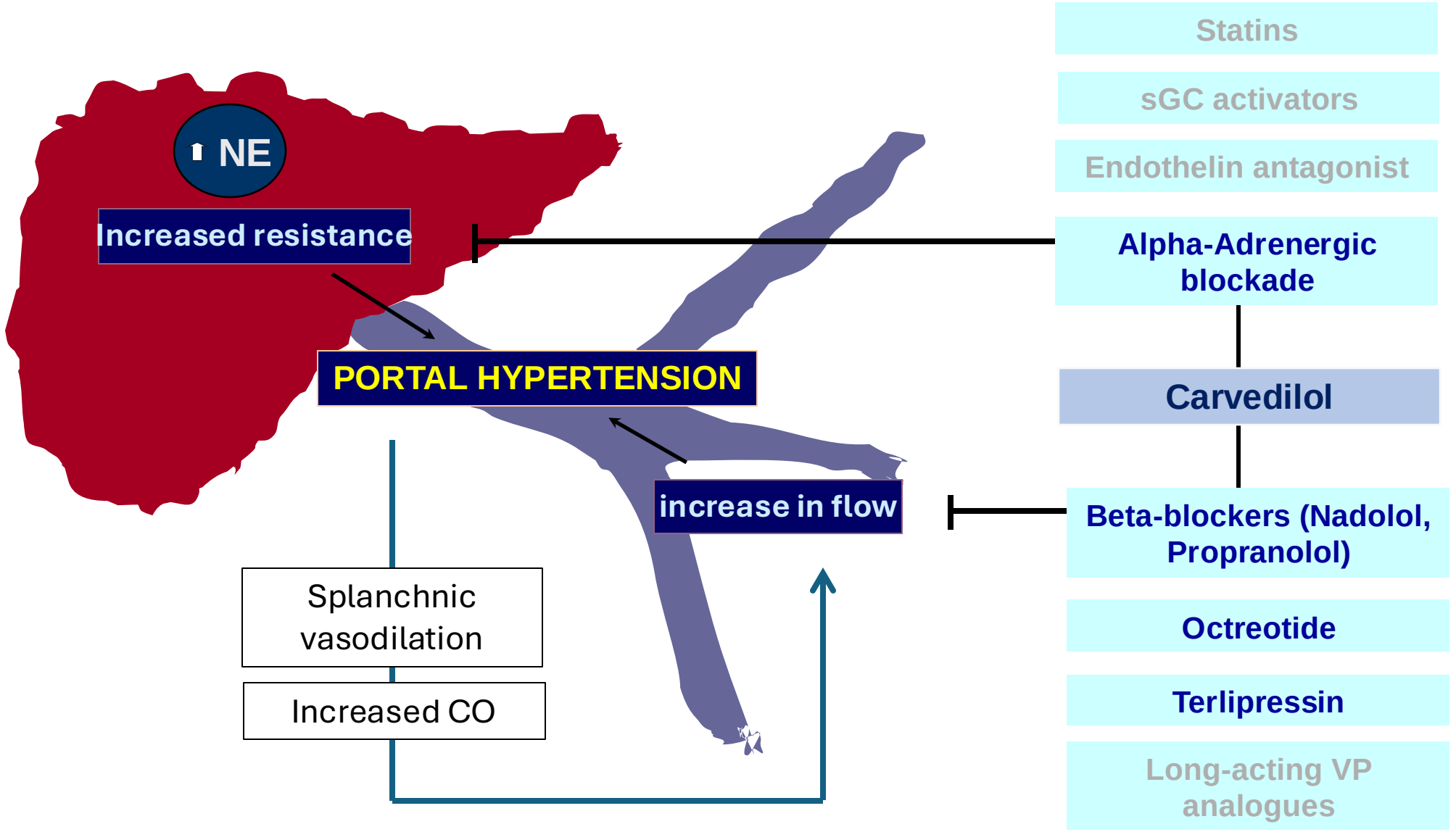
Etiology based disease modifying treatments

HCV, HBV, AIH, Wilson, MASLD, Alcohol, HH

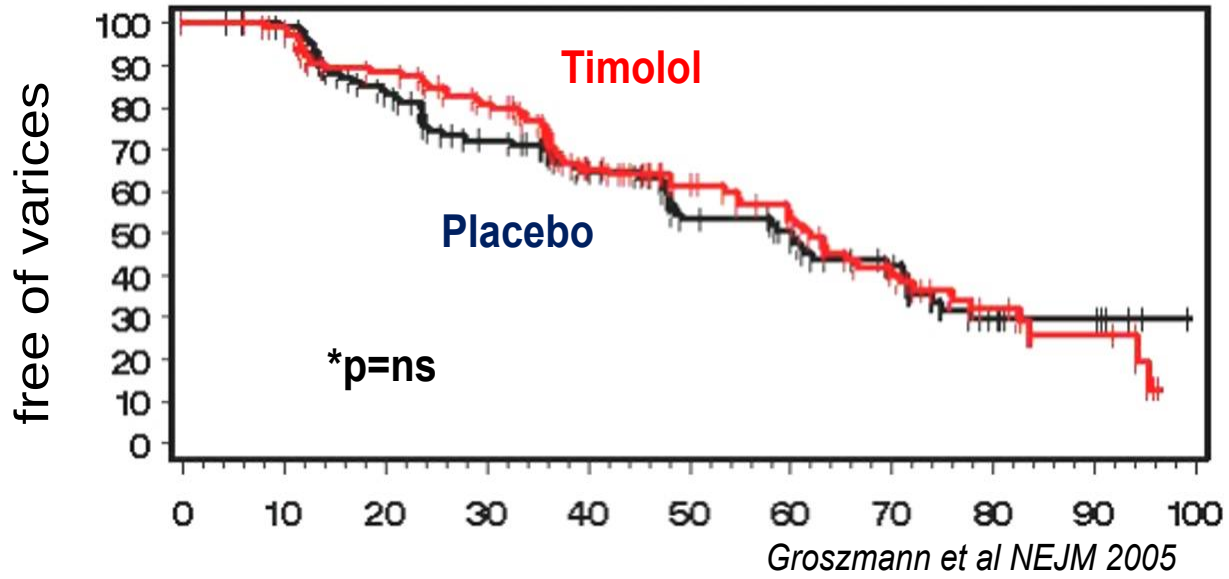
Antifibrotic treatments

Vasoactive Treatment of Portal Hypertension (BB)

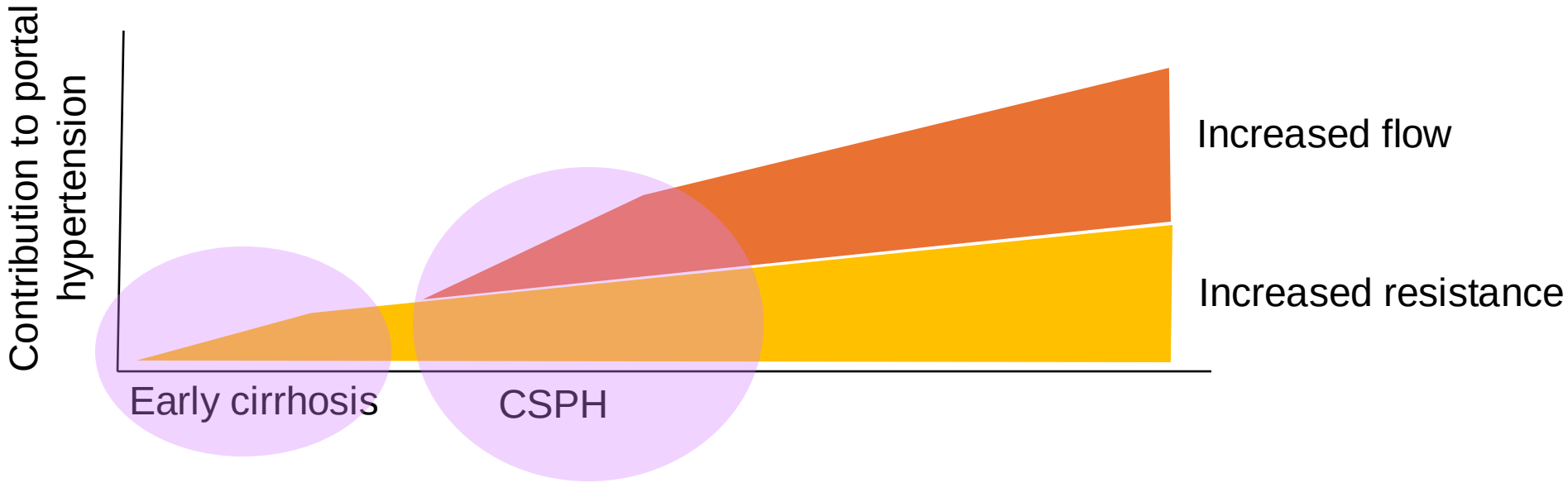
Vasoactive Treatment of Portal Hypertension



No varices



Groszmann et al NEJM 2005

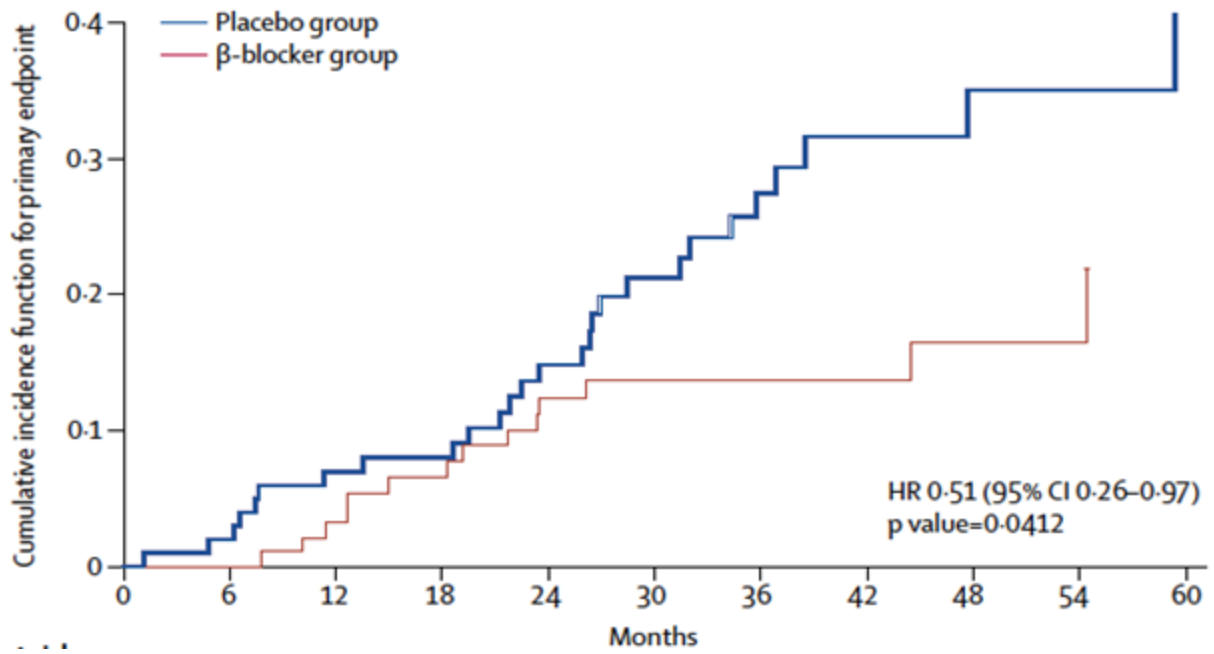


β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial

(HVPG >= 10 mmHg)

Càndid Villanueva*, Agustín Albillos, Joan Genescà, Joan C Garcia-Pagan, José L Calleja, Carles Aracil, Rafael Bañares, Rosa M Morillas, María Poca, Beatriz Peñas, Salvador Augustin, Juan G Abraldes, Edilmar Alvarado, Ferran Torres, Jaume Bosch*†

The Lancet 2019



Current Guidelines (Baveno VII, AASLD 2024)

Compensated cirrhosis
Clinically Significant Portal Hypertension

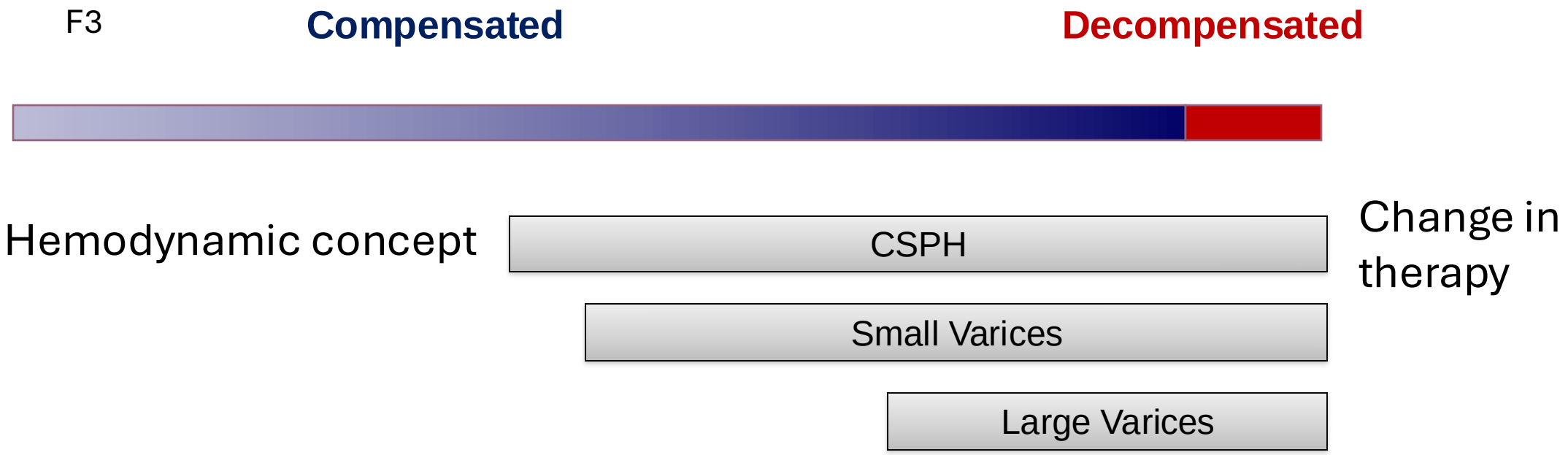
Carvedilol

Summary #1

- Portal Hypertension is a downstream consequence of disease progression, but once clinically significant PH is established, it contributes *on its own* to decompensation
- This concept has been demonstrated in RCTs: vasoactive drugs that do not have a liver disease modifying effect (i.e. beta-blockers) improve prognosis
- Even after the control of etiology, patients with CSPH are still at risk of decompensation and might need treatment to reduce portal pressure

Non-invasive diagnosis of Clinically Significant Portal Hypertension

Clinical Landmarks in cACLD



Non-invasive prediction

HEPATOLOGY

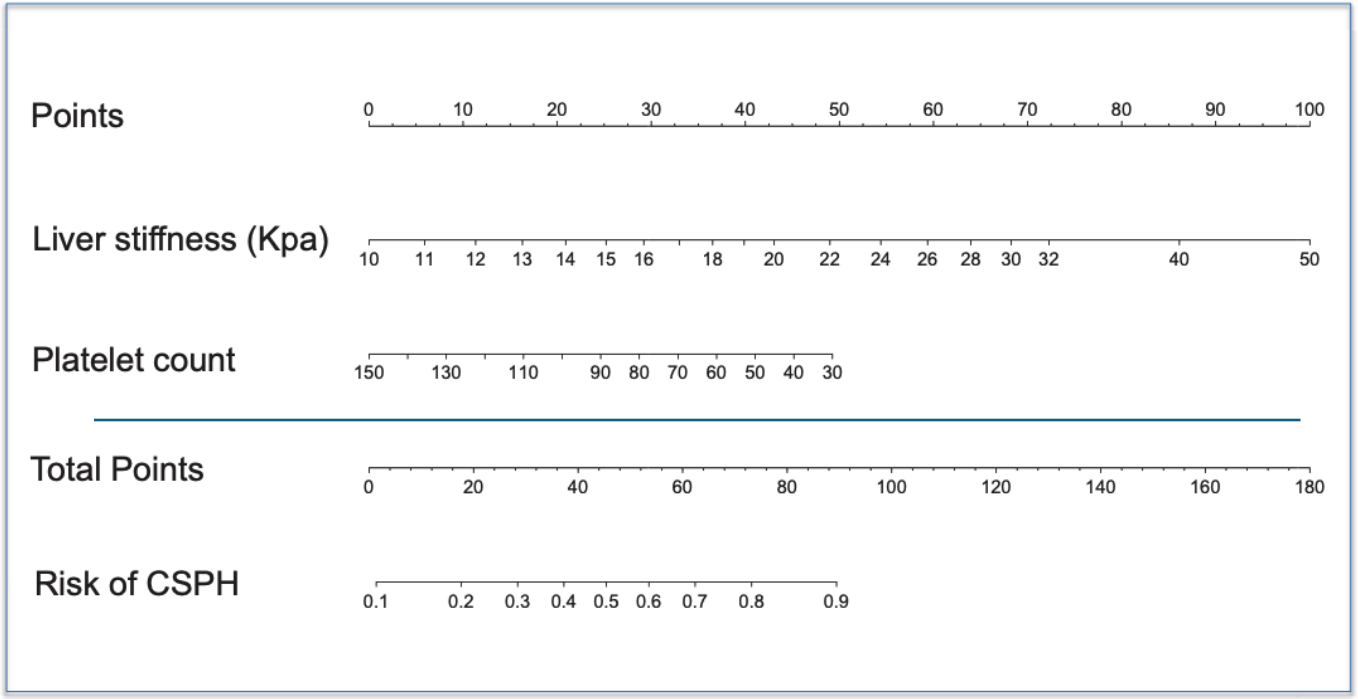
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY, VOL. 64, NO. 6, 2016

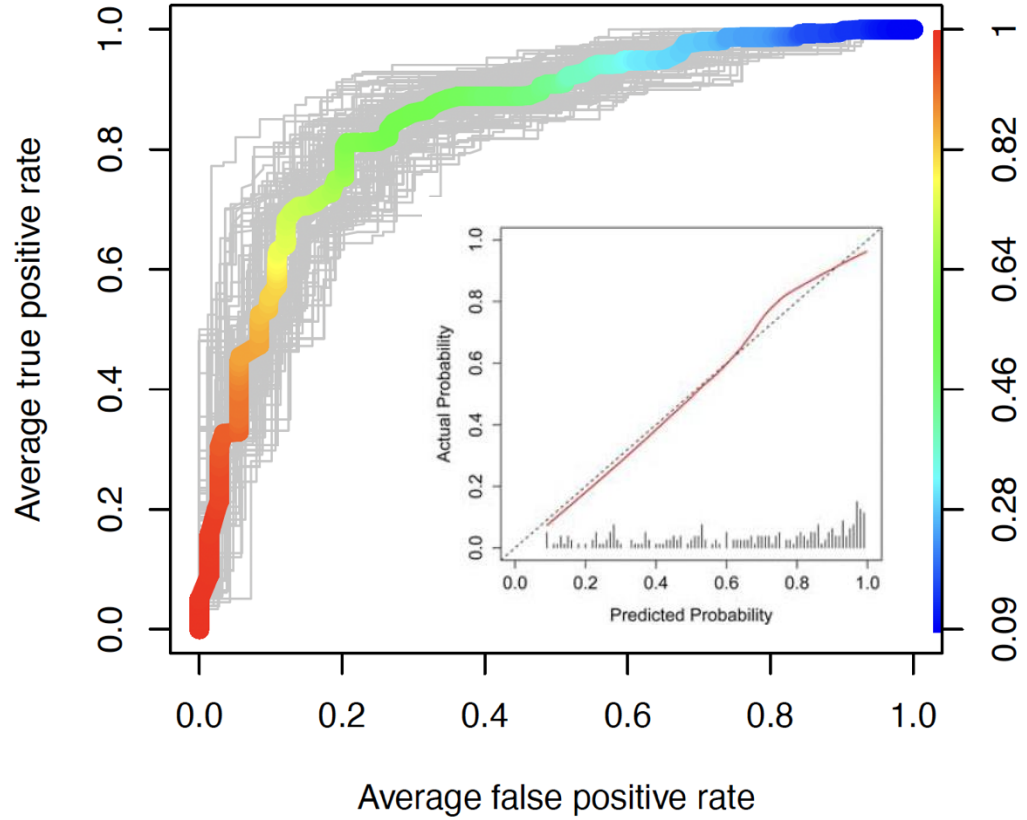
Noninvasive Tools and Risk of Clinically Significant Portal Hypertension and Varices in Compensated Cirrhosis: The "Anticipate" Study

Juan G. Abraldes,[1] Christophe Bureau,[2] Horia Stefanescu,[3] Salvador Augustin,[4] Michael Ney,[1] Hélène Blasco,[2] Bogdan Procopet,[3,5] Jaime Bosch,[5,6] Joan Genesca,[4] and Annalisa Berzigotti,[5,6] for the Anticipate Investigators

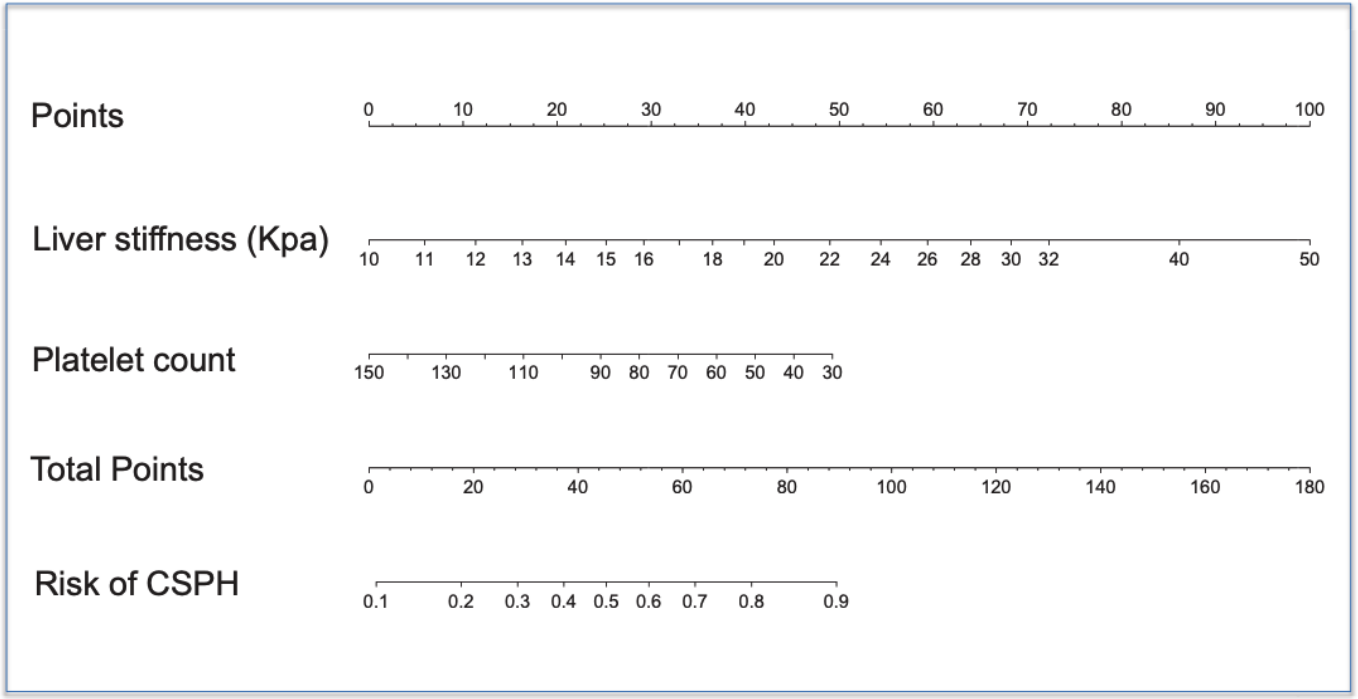
ANTICIPATE-CSPH model



Abraldes et al, Hepatology 2016, Pons et al AJG 2021

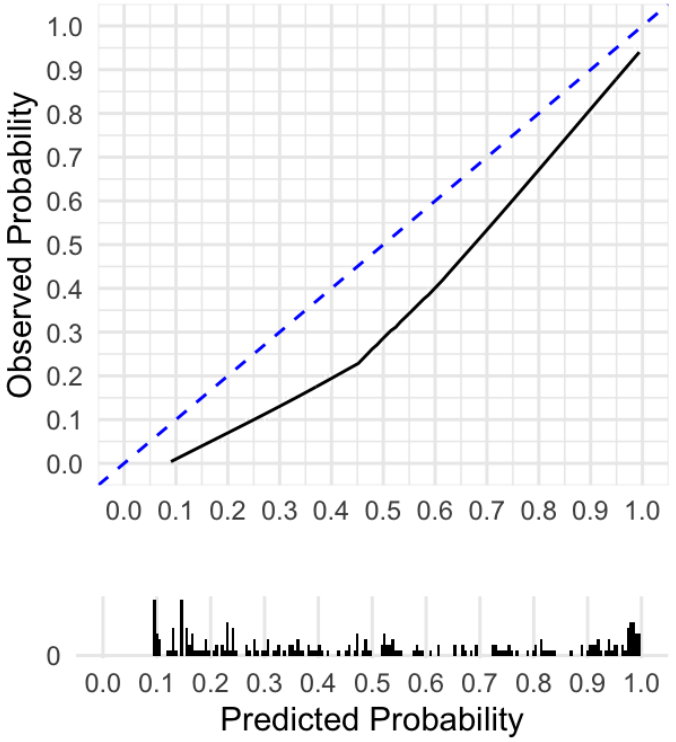


ANTICIPATE-CSPH model



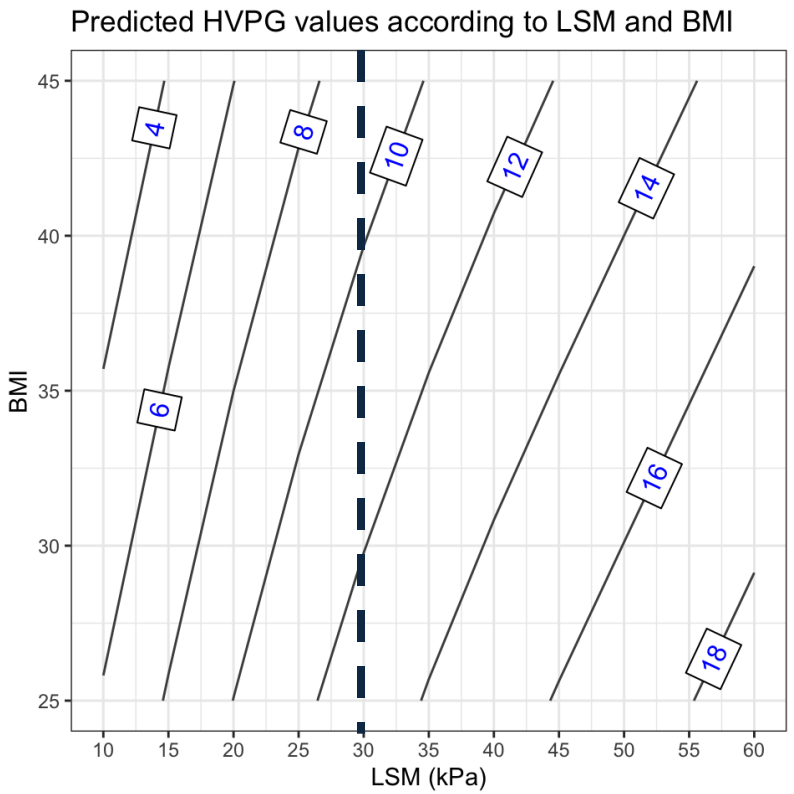
AUC in MASH patients: 0.90

ANTICIPATE-CSPH overestimates risk of CSPH in NASH

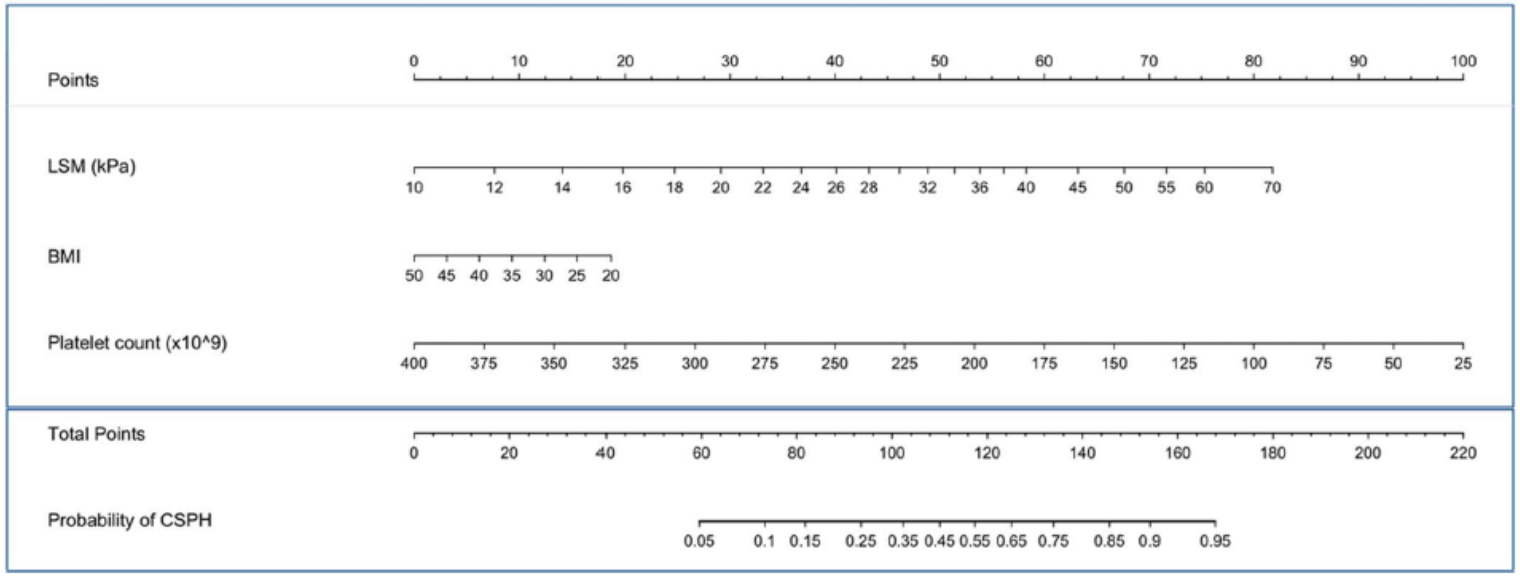


Pons et al. AJG 2021

Prediction of CSPH in MASH



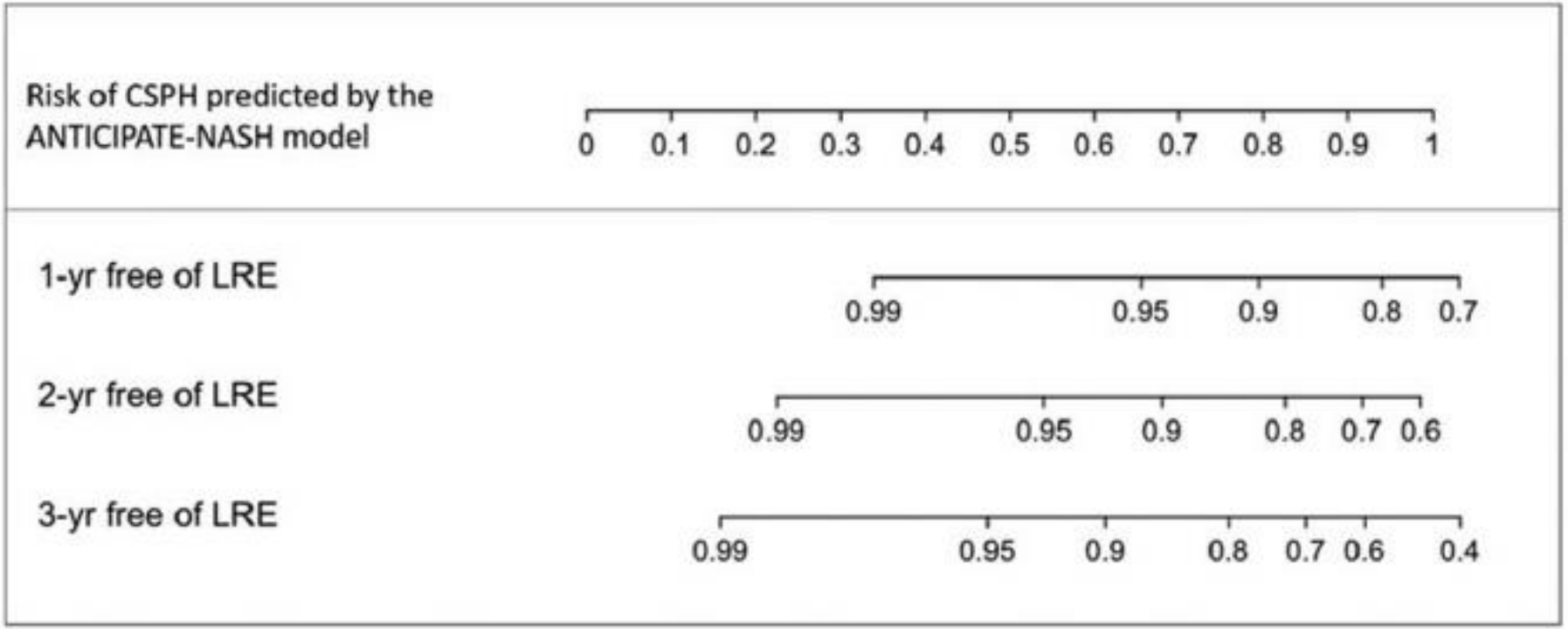
ANTICIPATE-NASH model



Pons et al. AJG 2021

ANTICIPATE-NASH model (which predicts CSPH) captures the risk of Liver-Related Events in people with MASLD

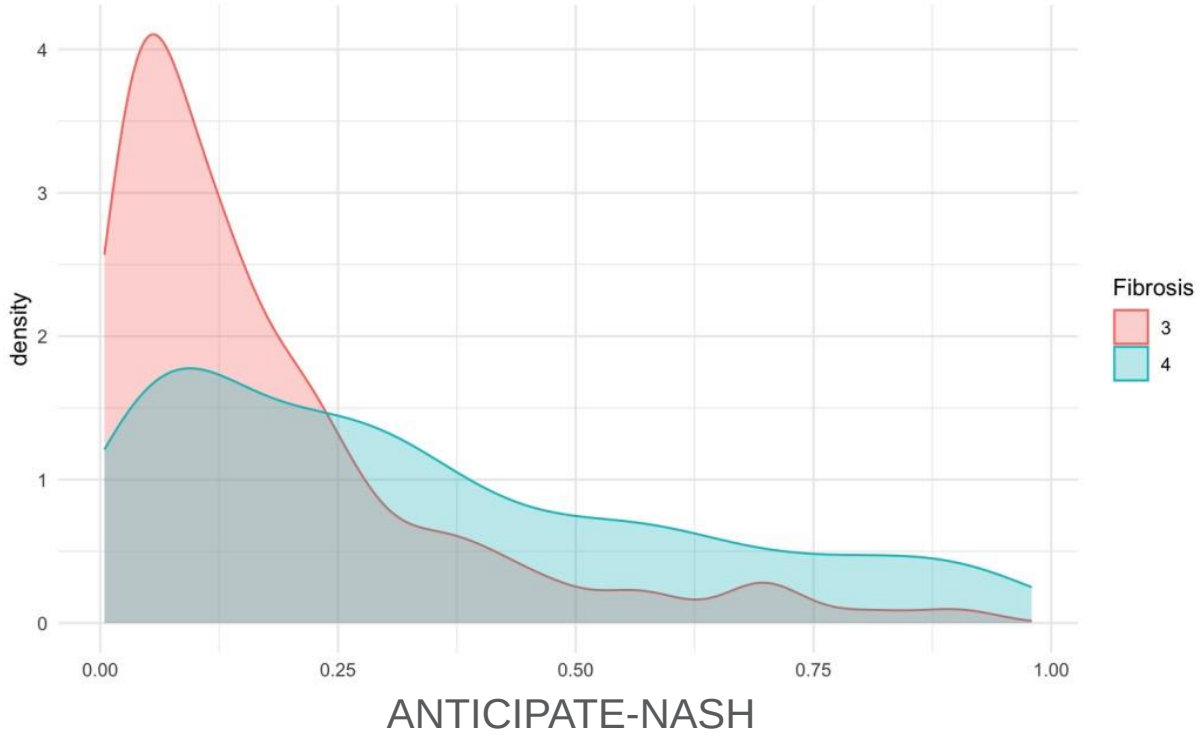
Multicenter cohort Spain/Canada/France/Hong Kong (n=2638)



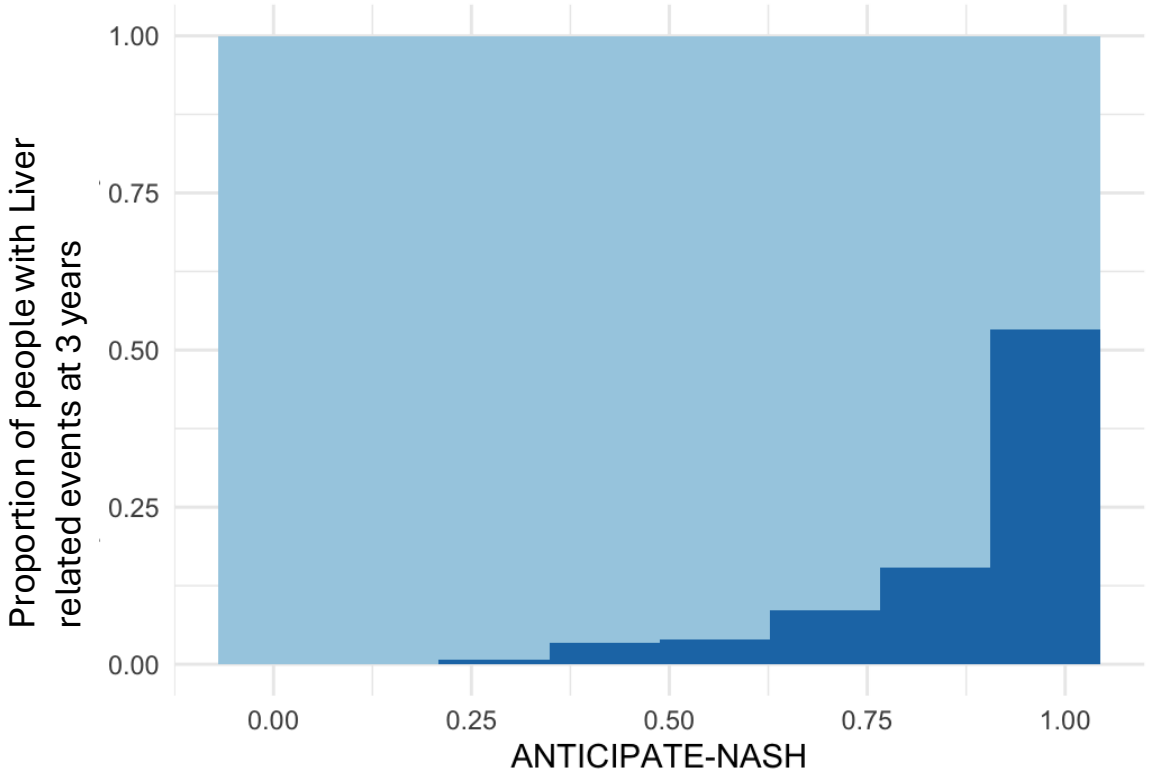
Pons et al 2024 CGH

NITs (ANTICIPATE-NASH) vs Liver Biopsy in predicting LREs

700 patients: half F3 / half F4



Predictions of events were not different in F3 and F4



Aceituno et al, presented at EASL meeting June 2024

Summary #2

- Models based on transient elastography such as ANTICIPATE and ANTICIPATE-NASH can predict the probability of CSPH and liver related events
- A simplified version of these models is recommended by current guidelines to start beta-blockers
  - VCTE>25
  - VCTE 20-25 + PLT <150
  - VCTE 15-20 + PLT <110

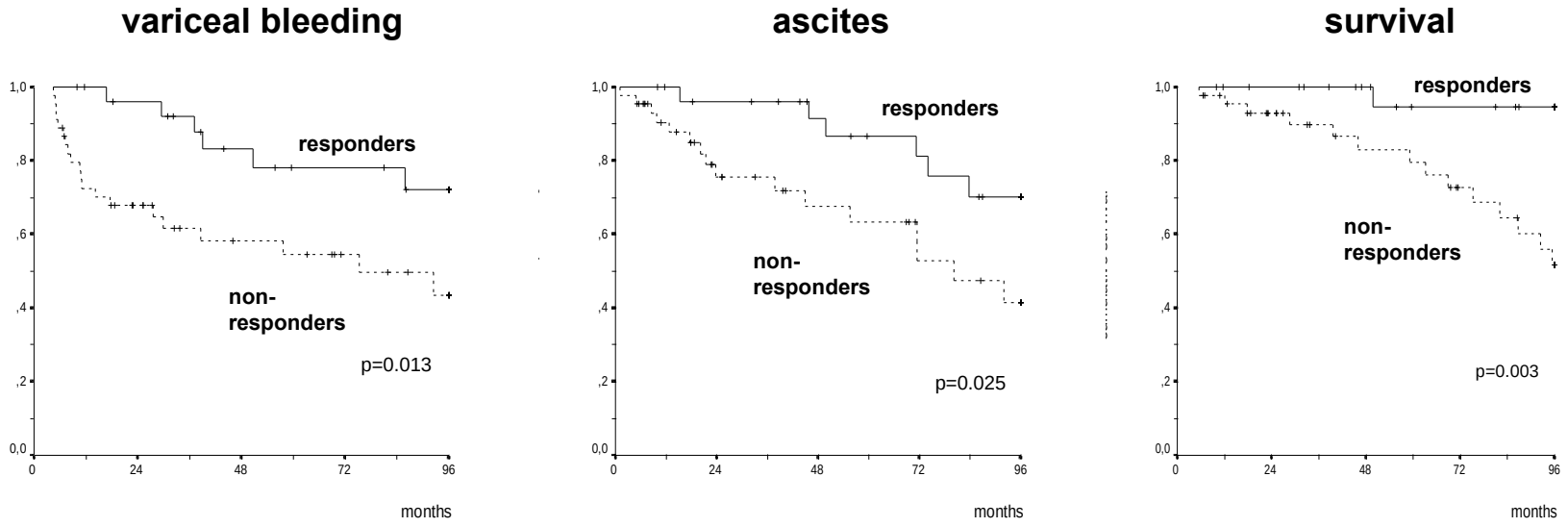
Are there responders and non-responders to Beta-Blockers?
…And is it worth to measure response

Motivation

An unintended and unforeseen consequence of a research study

Abraldes et al, Hepatology 2003

- Research question: does decreasing portal pressure improve prognosis?



"In conclusion, in patients receiving BB for prevention of variceal rebleeding, a decrease in **HVPG >20% or to <12 mm Hg** is associated with a marked reduction in the long-term risk of developing complications of portal hypertension and with improved survival. ~40% of the patients achieve these hemodynamic targets"

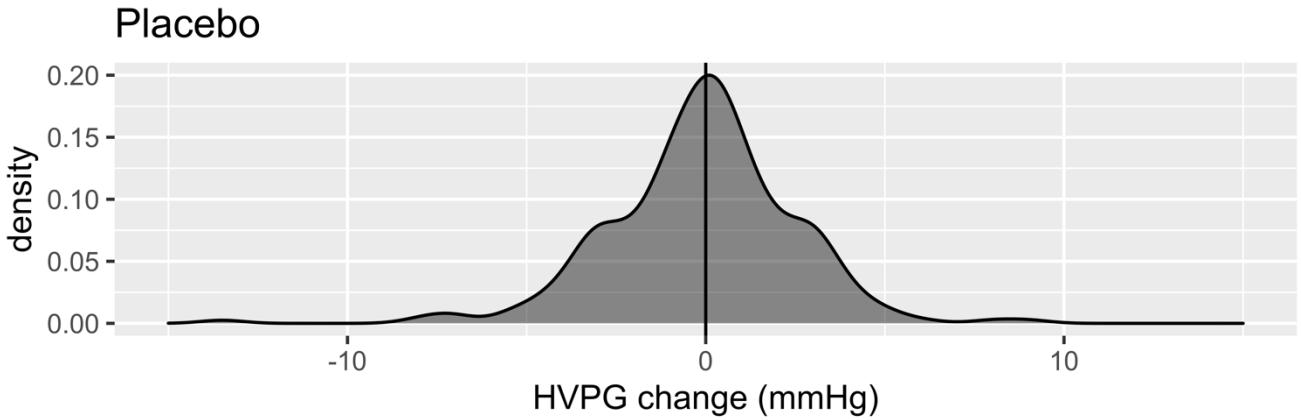
Impact of the paper

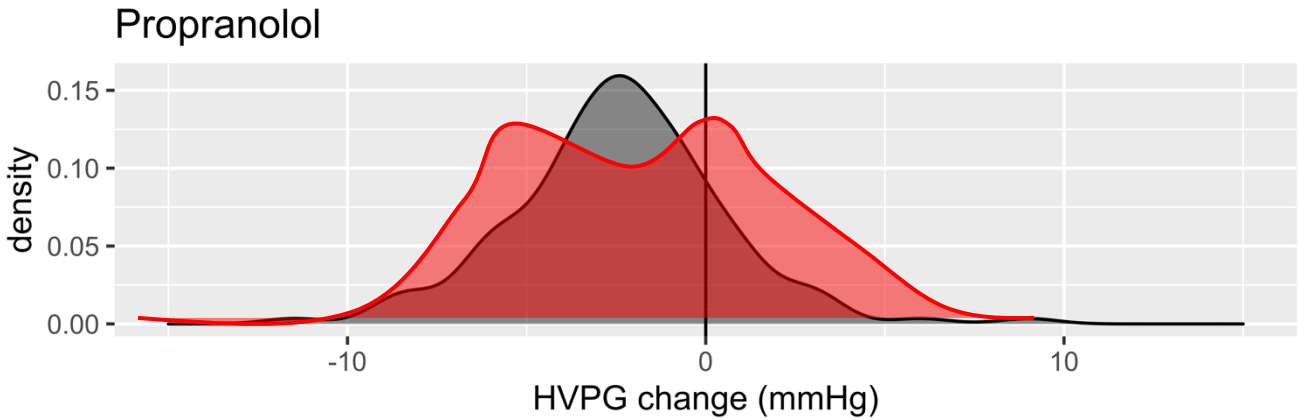
- Intended
  - Demonstrate the concept that decreasing PP → improve in prognosis
  - Guide for drug development in portal hypertension

- Many additional unintended readings
  - “only 30-40% of the patients treated with beta-blockers benefit from them”
  - “I do not use beta-blockers: I cannot measure portal pressure, and thus I cannot tell if they are working. I use endoscopic treatments since I know it is working”
  - “You cannot give beta-blockers in the dark, without knowing if the patient responds”
  - Several studies trying to non-invasively identify non-responders → failed

- Almost the totality of evidence showing that NSBBs improve outcomes in cirrhosis have not used PP measurements to guide therapy

Individual responses to NSBBs





Test–Retest Reliability and Consistency of HVPG and Impact on Trial Design: A Study in 289 Patients from 20 Randomized Controlled Trials

Wayne Bai,[1] Mustafa Al-Karaghouli,[1] Jesse Stach,[1,2] Shuen Sung ,[1] Granville J. Matheson,[3,4*] and Juan G. Abraldes[1*]

HEPATOLOGY 2021

Cohort of 144 patients treated with NSBBs

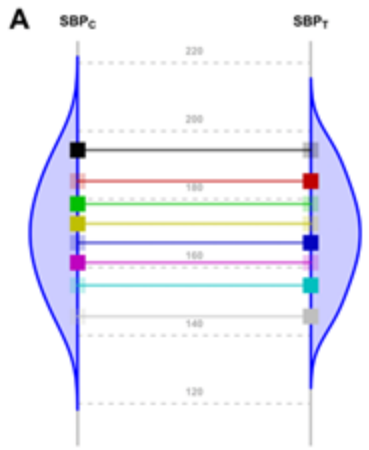
"Responder" does not mean "was caused to improve", but "was observed to improve"

Between patient variability of response in RCTs:

The Variability Ratio Approach

Heterogeneous response

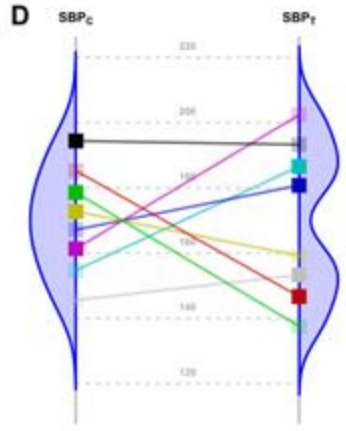
Placebo



Variability ratio > 1

Variance in Treatment >> Variance in placebo

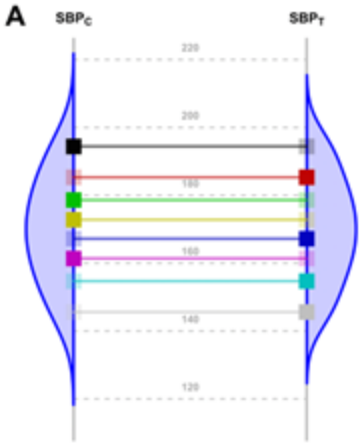
BB



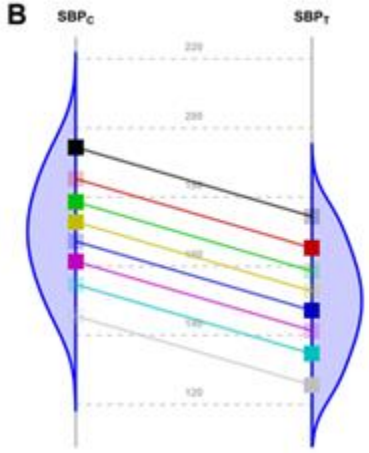
Non-responders

Responders

Homogeneous response



Variance in Treatment = Variance in placebo

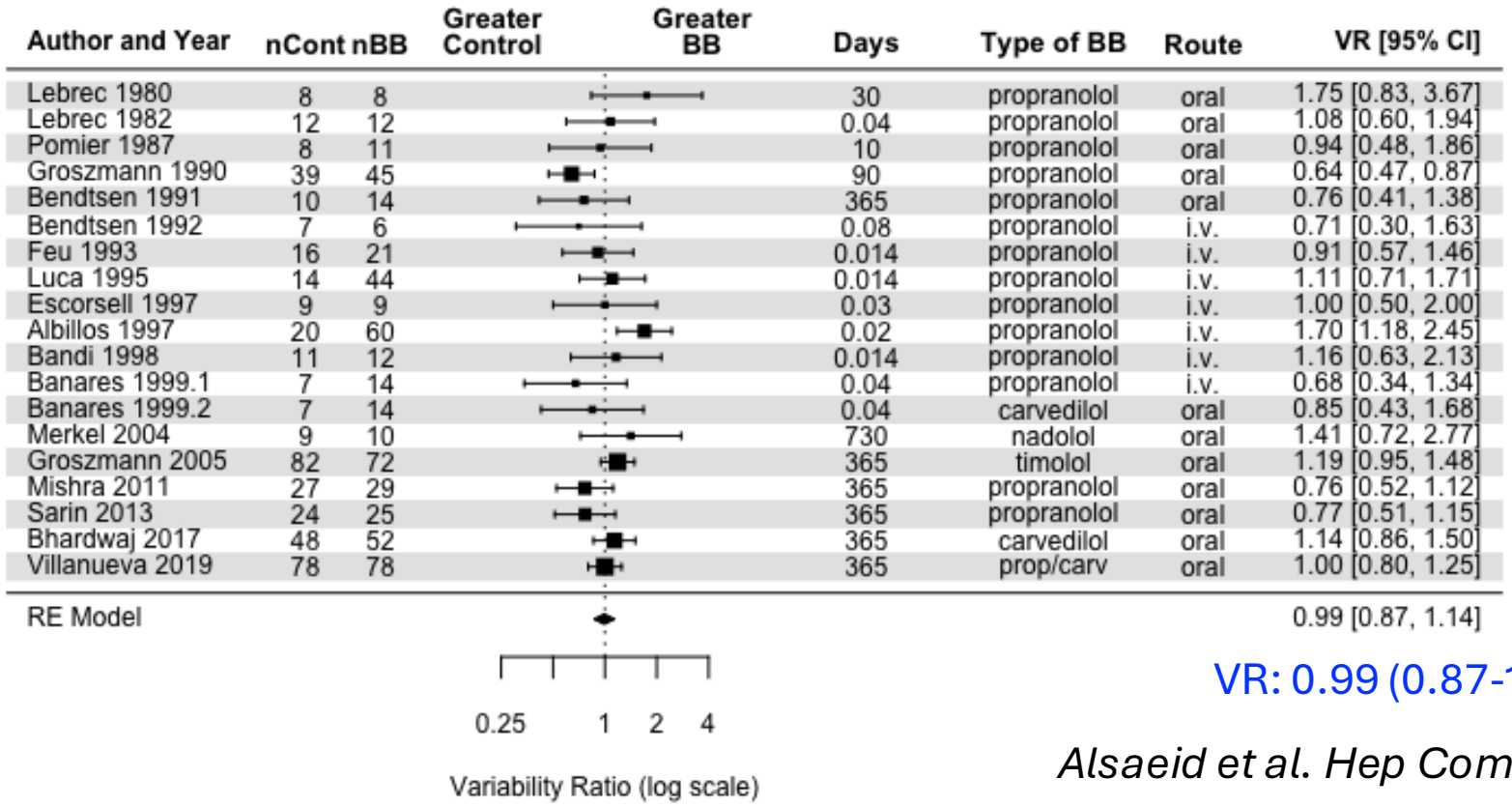


Variability ratio ~ 1

Cortes et al, F1000 2018

Systematic review

19 RCTs comparing the effects of NSBB vs Placebo on portal pressure (965 patients)

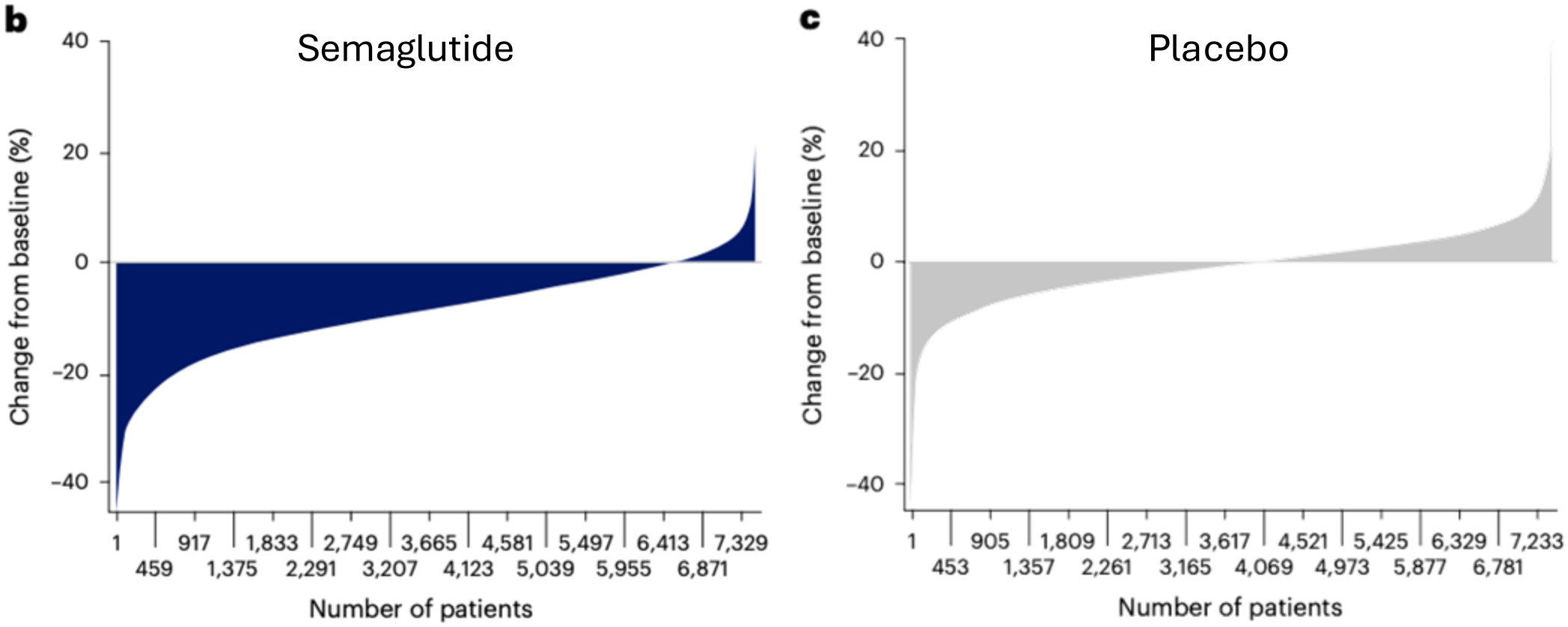


VR: 0.99 (0.87-1.14)

Alsaeid et al. Hep Comm 2024

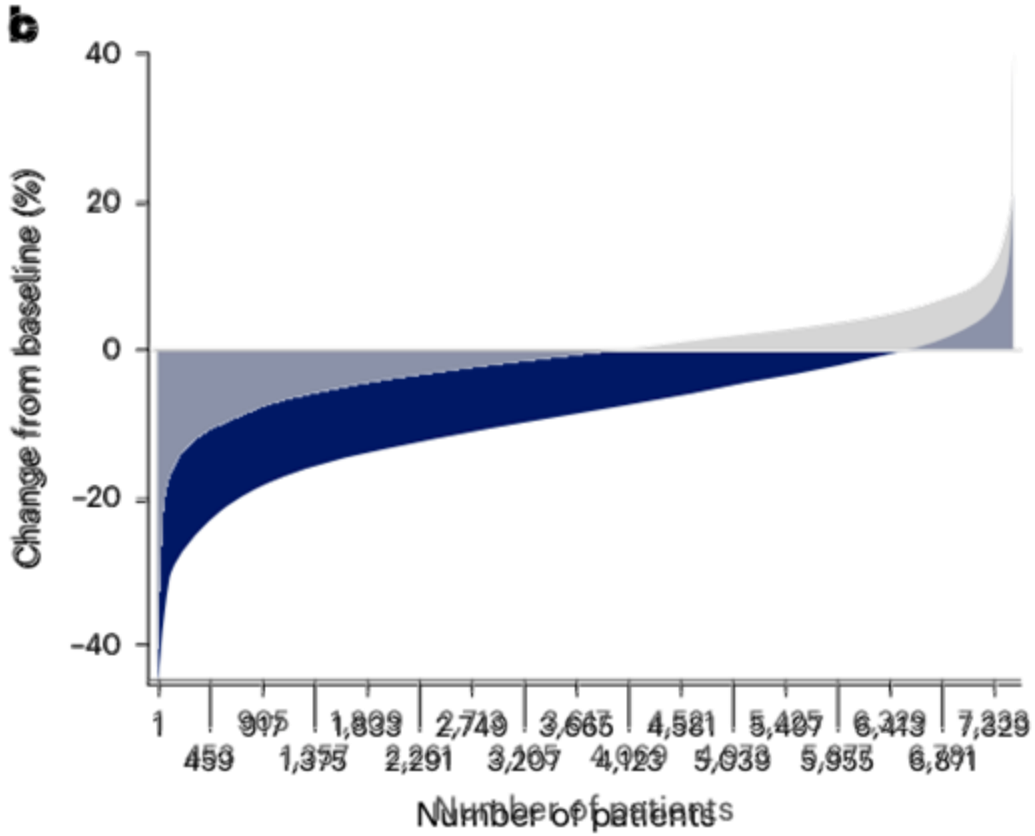
These results do not suggest heterogeneity in patient-to-patient response to beta-blockers. Hence, when treating a patient, it is reasonable to expect that the average decrease in portal pressure described in RCTs applies to individual patients

Weight Decrease with Semaglutide



Select trial, NEJM 2023

Weight Decrease with Semaglutide



Select trial, NEJM 2023

Summary #3

- Probably most patients with cirrhosis that take beta-blockers benefit from them, and the concept that less than half of the patients are responders is a misinterpretation of the available data
- Thus, there is no indication to assess for hemodynamic response to beta-blockers