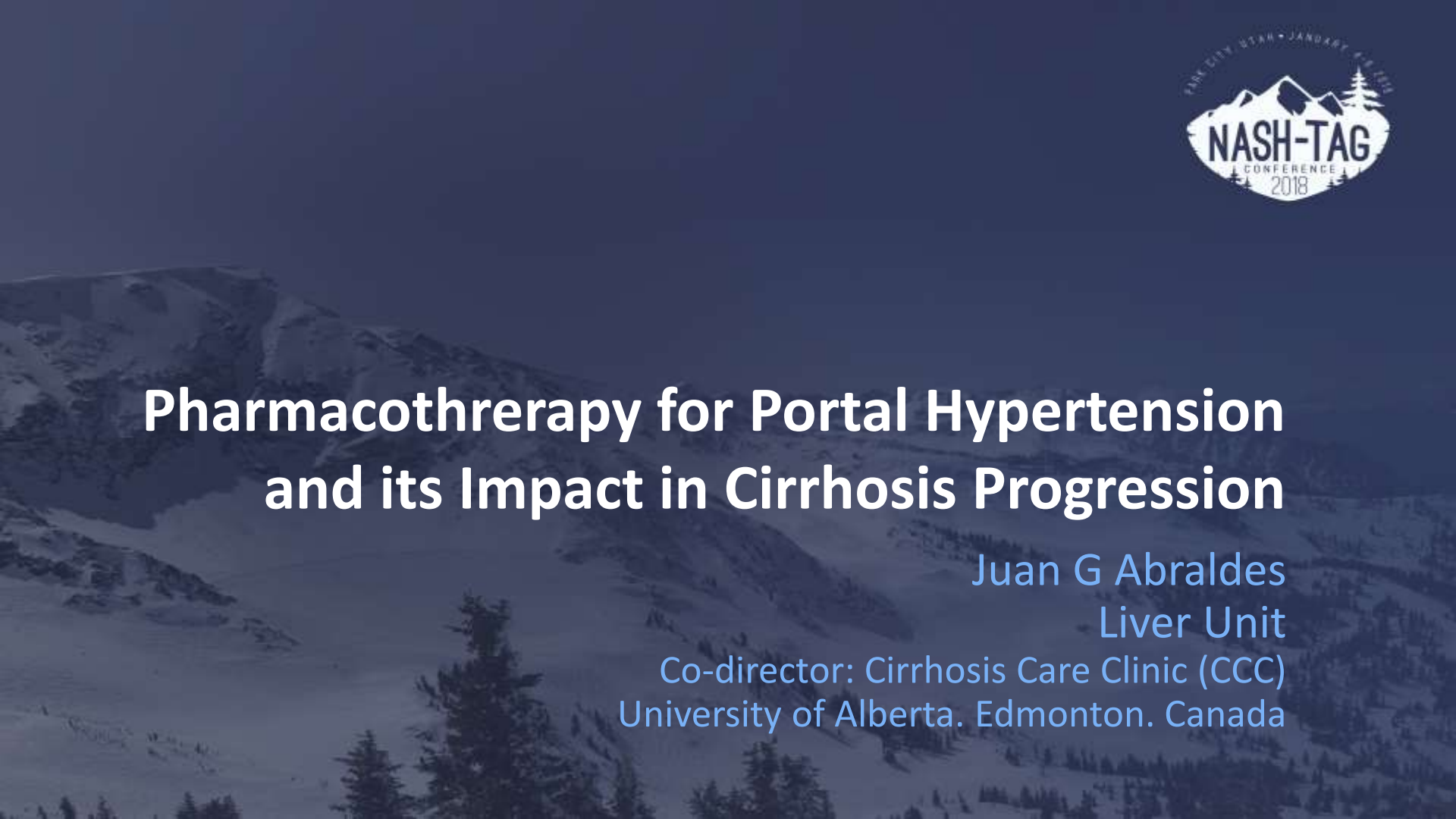

Pharmacothrerapy for Portal Hypertension and its Impact in Cirrhosis Progression

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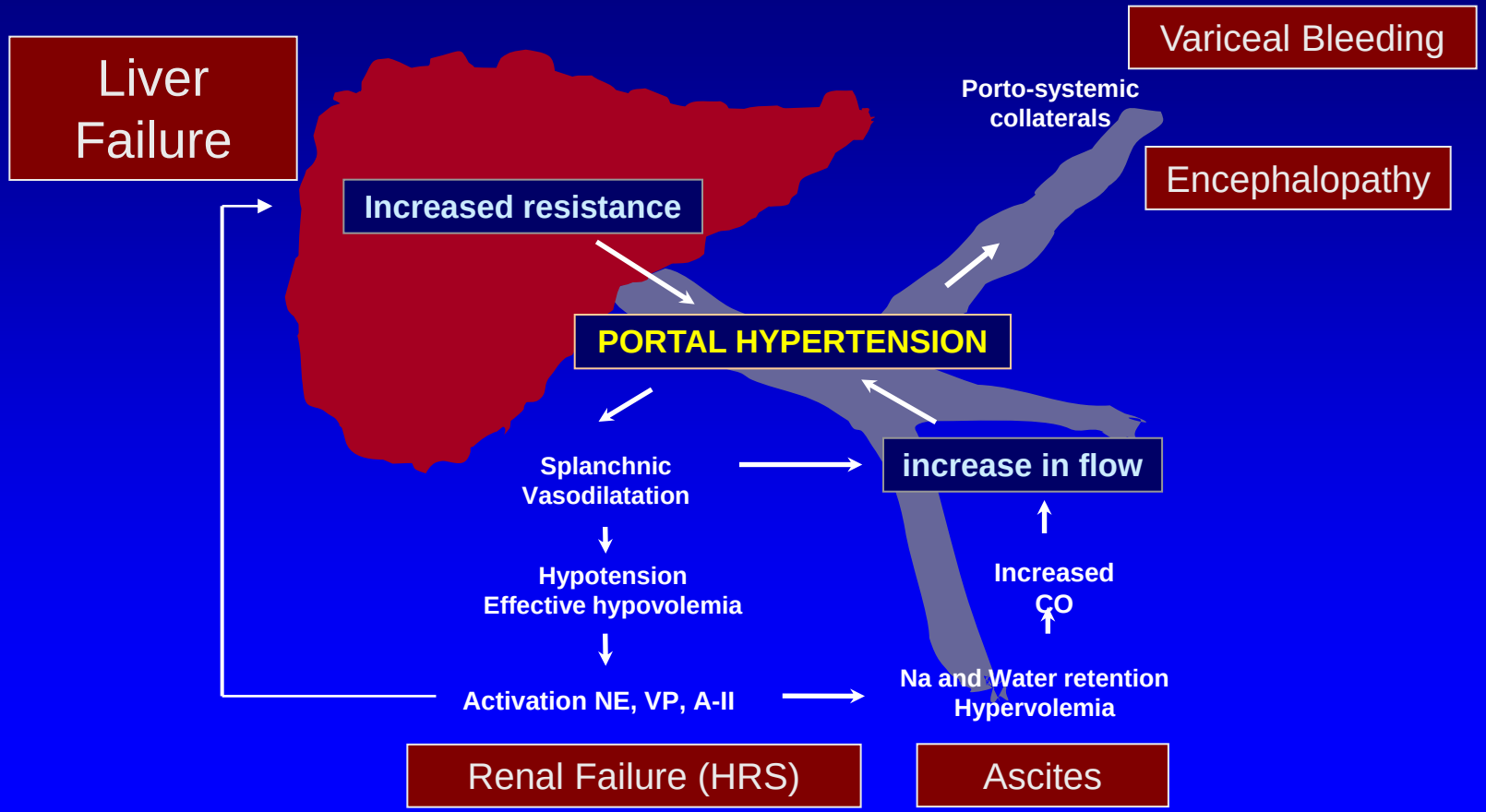
Conflicts

- Consulting
  - Theravance
- Lecture fees
  - Lupin Pharma
- Research support
  - Gilead

Outline

- Rationale for treating portal hypertension
- Key questions in a drug development program for portal hypertension
- How we can decrease portal pressure
- Current standard pharmacotherapy

Pathophysiology of Portal Hypertension in Cirrhosis



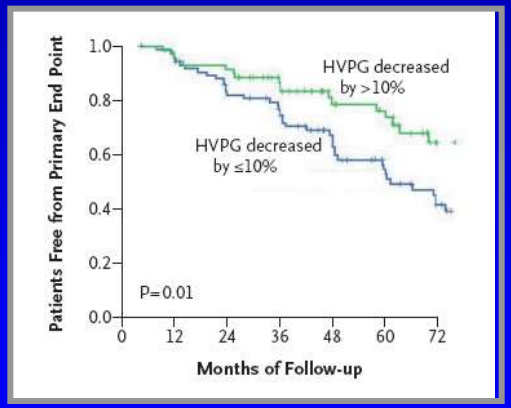
Why Do We Need Treatments for PH

- Need for specific treatments for portal hypertension
  - When the etiological factor cannot be eliminated and the patient already has significant portal hypertension (i.e. HVPG >=10 mmHg)
  - When, after the elimination of the etiological factor, significant portal hypertension persists

Rationale for the Pharmacological Treatment of PH

- Assumption → patient disease phenotype can be modified by decreasing portal pressure

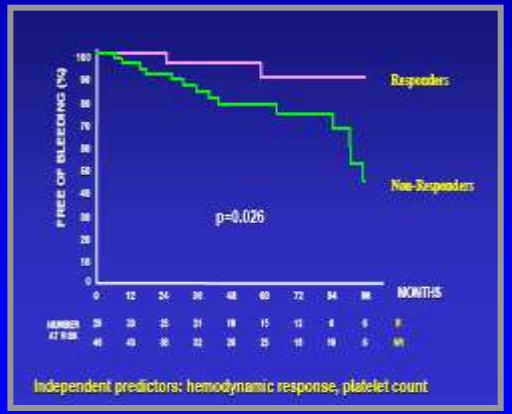
Prevention of Varices



Groszmann et al. N. Eng J Med 2005

>10% from baseline

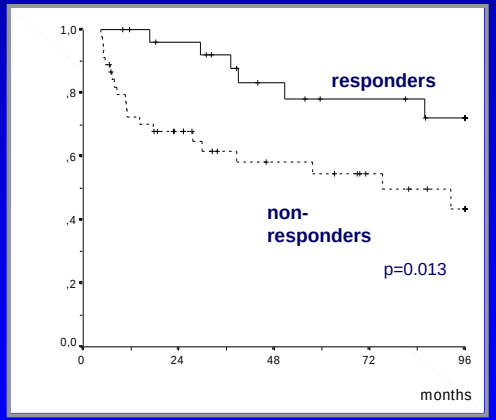
Prevention First Bleeding



Turnes et al Am J Gastro 2006

>20%/>10% or to <12 mmHg

Prevention Rebleeding



Abraldes et al. Hepatology 2003

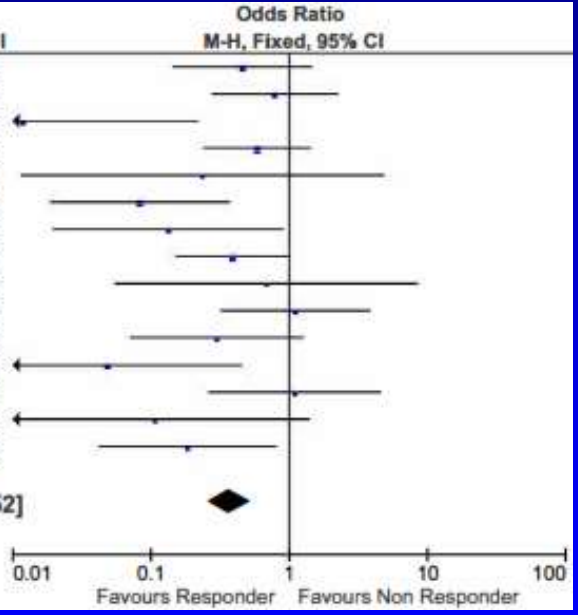
>20% or to <12 mmHg

In compensated patients with varices, development of decompensation* is significantly lower in HVPG responders (50%) than in non-responders

Study or Subgroup	Responder Events	Responder Total	Non Responder Events	Non Responder Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Abraldes 2003 Hepatol	8	19	19	31	7.8%	0.46 [0.14, 1.47]
Augustin, 2012 Hepatology	16	32	14	25	7.3%	0.79 [0.27, 2.25]
Bureau, 2002 Hepatology	1	13	7	8	7.4%	0.01 [0.00, 0.22]
Garcia-Pagan, 2009 Gut	10	36	23	58	11.8%	0.59 [0.24, 1.44]
Groszmann, 1990 Gastroenterology	0	15	3	28	2.2%	0.24 [0.01, 4.86]
Hernandez-Gea, 2012 Am J Gastr	8	20	24	27	11.4%	0.08 [0.02, 0.37]
Merkel, 2000 Hepatology	2	17	5	10	5.2%	0.13 [0.02, 0.92]
Reiberger, 2013 Gut	18	68	12	25	12.0%	0.39 [0.15, 1.01]
Sharma, 2009 APT	1	12	2	17	1.4%	0.68 [0.05, 8.50]
Turnes, 2009 Am J Gastro	10	16	18	30	4.4%	1.11 [0.32, 3.87]
Villanueva, 1996 NEJM	4	14	12	21	6.4%	0.30 [0.07, 1.27]
Villanueva, 2001 NEJM	1	13	12	19	8.4%	0.05 [0.01, 0.46]
Villanueva, 2004 J Hepatology	6	18	5	16	3.3%	1.10 [0.26, 4.65]
Villanueva, 2009 APT	3	10	4	5	3.5%	0.11 [0.01, 1.41]
Villanueva, 2009 Gastroenterology	7	26	8	12	7.4%	0.18 [0.04, 0.81]
Tota l (95% CI)		**329**		**332**	**100.0%**	**0.37 [0.26, 0.52]**
Total events	**95**		**168**			

Heterogeneity: Chi² = 23.79, df = 14 (P = 0.05); I² = 41%
Test for overall effect: Z = 5.69 (P < 0.00001)

N= 661



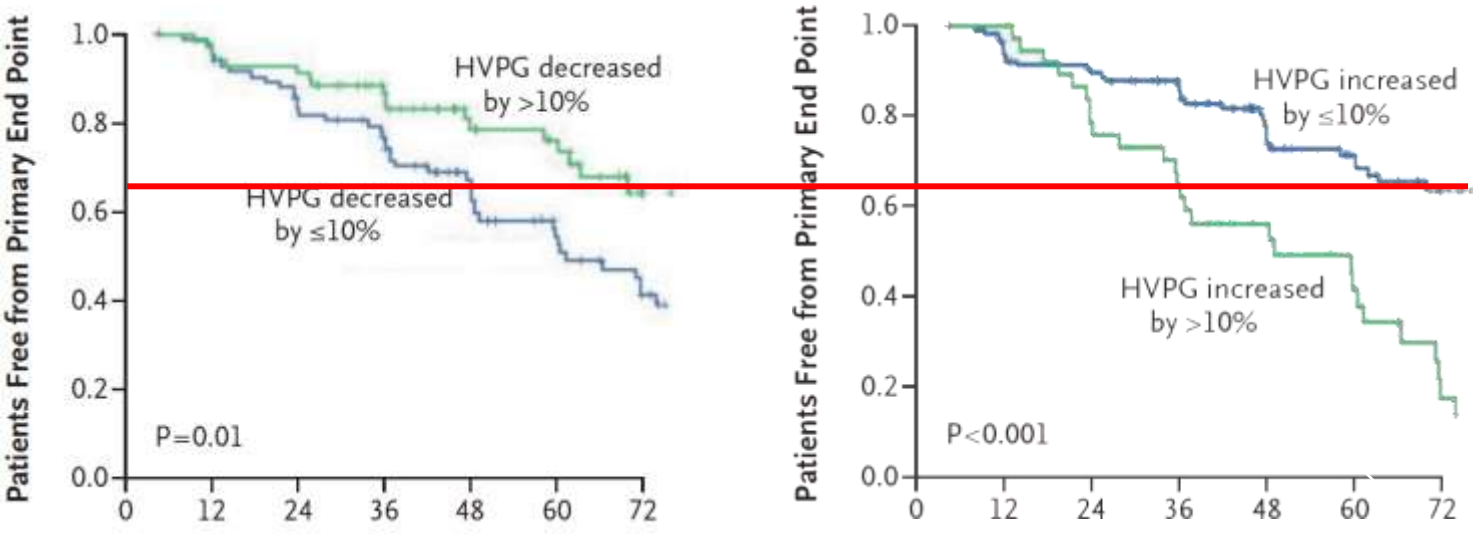
*Clinical events: ascites, variceal hemorrhage, or encephalopathy

Turco et al. EASL 2017.

Stratified meta-analysis of 1ary or 2ary prophylaxis trials for VH

Rationale for the Pharmacological Treatment of PH

- Definitions of a “good hemodynamic response” are still unclear

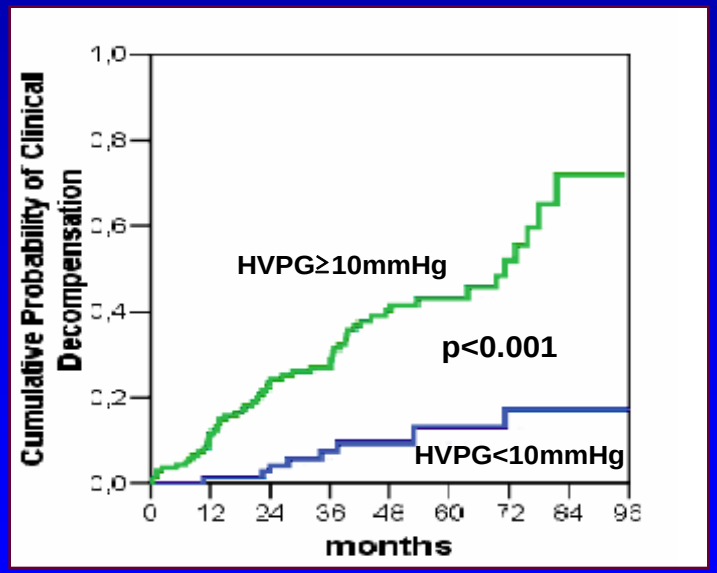


Groszmann et al NEJM 2005

Questions in drug development

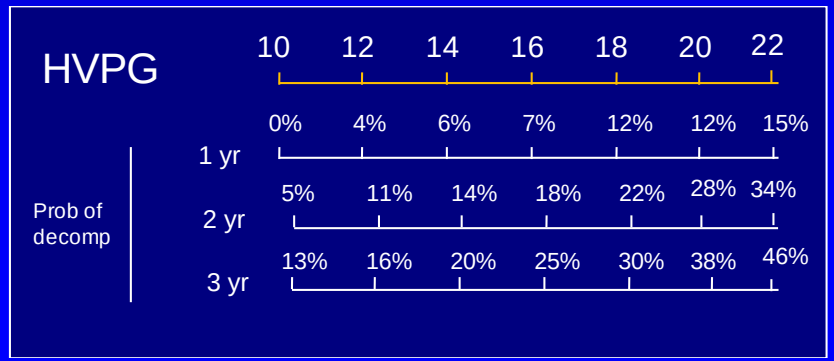
How Much do we Need to Decrease PP to Have a Clinical Benefit

- The effect of PP on prognosis is a continuum (above a threshold of HVPG 10 mmHg)



Ripoll et al Gastroenterology 2007

- Every 1 mmHg increase in baseline HVPG was associated with a 11% increase (adjusted by other predictors) in the relative risk of decompensation



Questions in drug development

How Much do we Need to Decrease PP to Have a Clinical Benefit

- If PP → risk is a continuum, PP decrease → improved prognosis is likely also a continuum
- The greater the ↓ PP (if achieved without AE, especially on systemic circulation) will likely be associated with a greater protective effect, but…
- There is no biological rationale or clinical evidence to suggest a minimal threshold of PP decrease to get a clinical benefit
- In drug development for PH, there is no good reason for dichotomizing PP response (responders / non-responders) according to a defined threshold (10% or 20%)

Questions in drug development

How Much do we Need to Decrease PP to Have a Clinical Benefit

- HVPG decrease is our main readout for efficacy in Phase II trials for new drugs for the treatment of portal hypertension

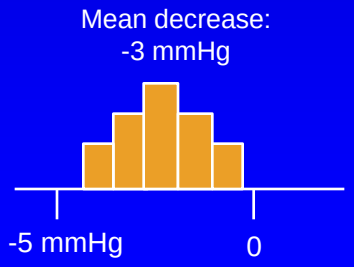
- What should be the threshold of HVPG response to go to Phase III?

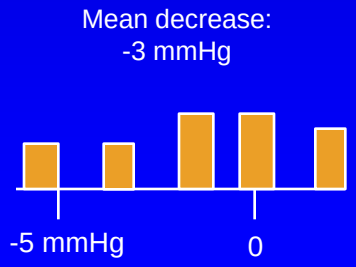
Questions in drug development

How Much do we Need to Decrease PP to Have a Clinical Benefit

- Criteria for "go / no go" to Phase III in a program for developing a drug for portal hypertension

Magnitude of response	Pattern of Response	Additional Readouts of Efficacy	Others



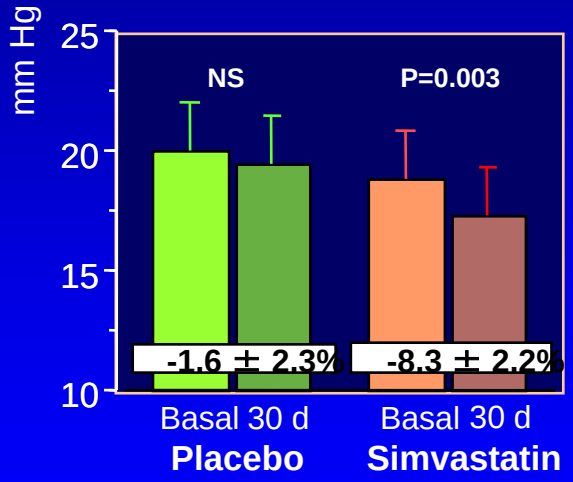


Systemic Hemodynamics
Liver flow
Collateral flow / PSS
Methacetin breath tests
Liver ICG clearance
Hepaquant

Safety
Tolerance
Usability
Costs

Simvastatin *vs* Placebo in Portal Hypertension: A Proof of Concept Randomized Controlled Trial

HVPG

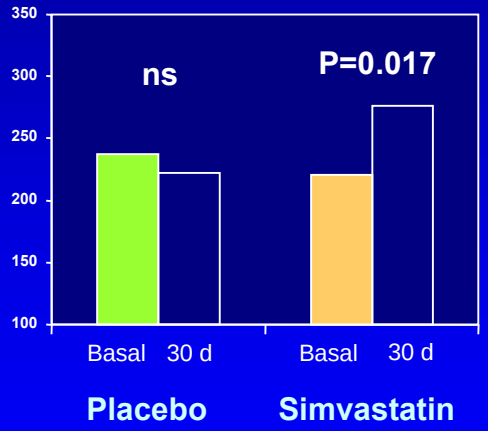


HBF			*p*
Placebo	939 ± 458	830 ± 339	0.109
Simvastatin	1124 ± 548	1216 ± 676	0.440

Estimated HVR			*p*
Placebo	2.07 ± 0.93	2.17 ± 0.97	0.463
Simvastatin	1.60 ± 0.79	1.35 ± 0.58	0.044

No changes in MAP

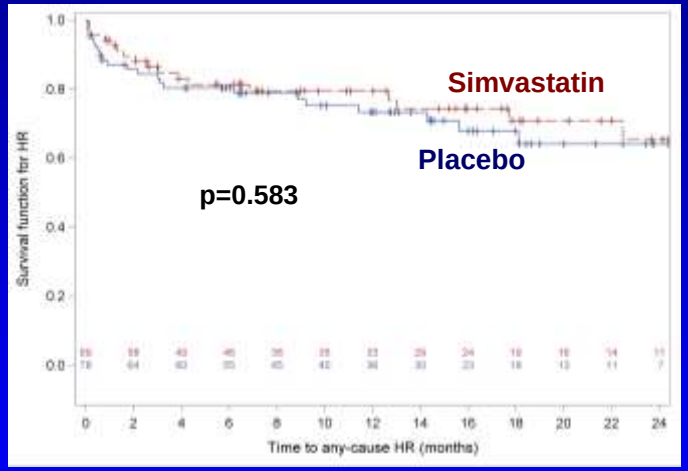
ICG clearance



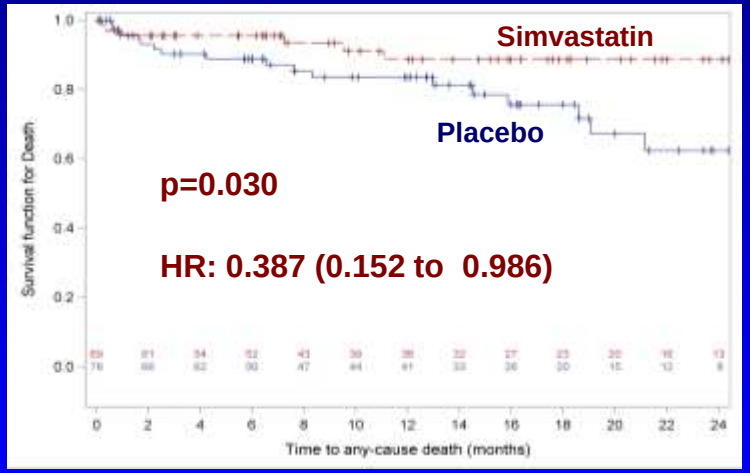
Abraldes, Albillos et al. Gastroenterology 2009

Addition of Simvastatin to Standard Therapy after a Variceal Hemorrhage (A multicenter Phase III study)

Rebleeding



Survival



Addition of simvastatin to standard therapy did not improve rebleeding but there was a marked survival benefit with simvastatin

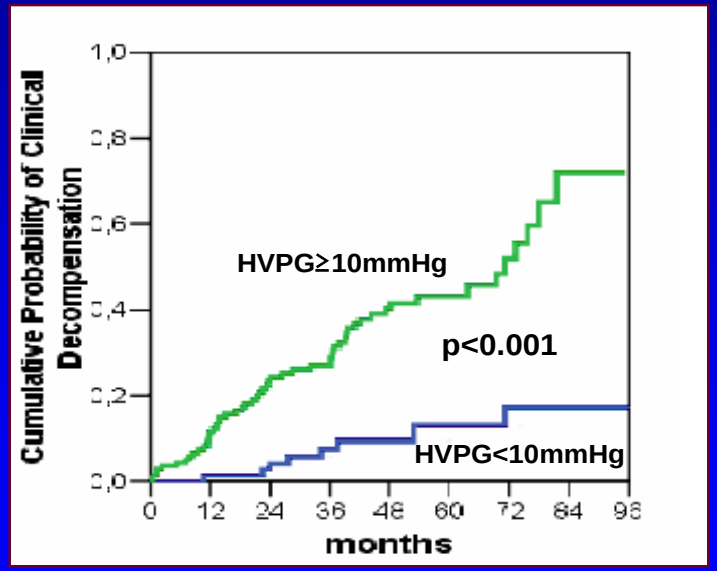
Abraldes, Villanueva et al Gastroenterology 2016

Questions in drug development

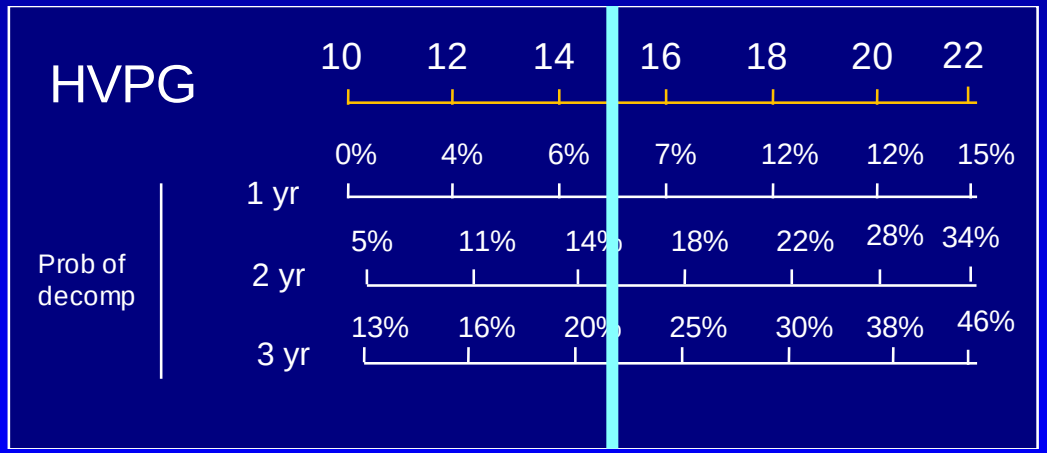
What should be the main endpoint in a Phase III in compensated cirrhosis

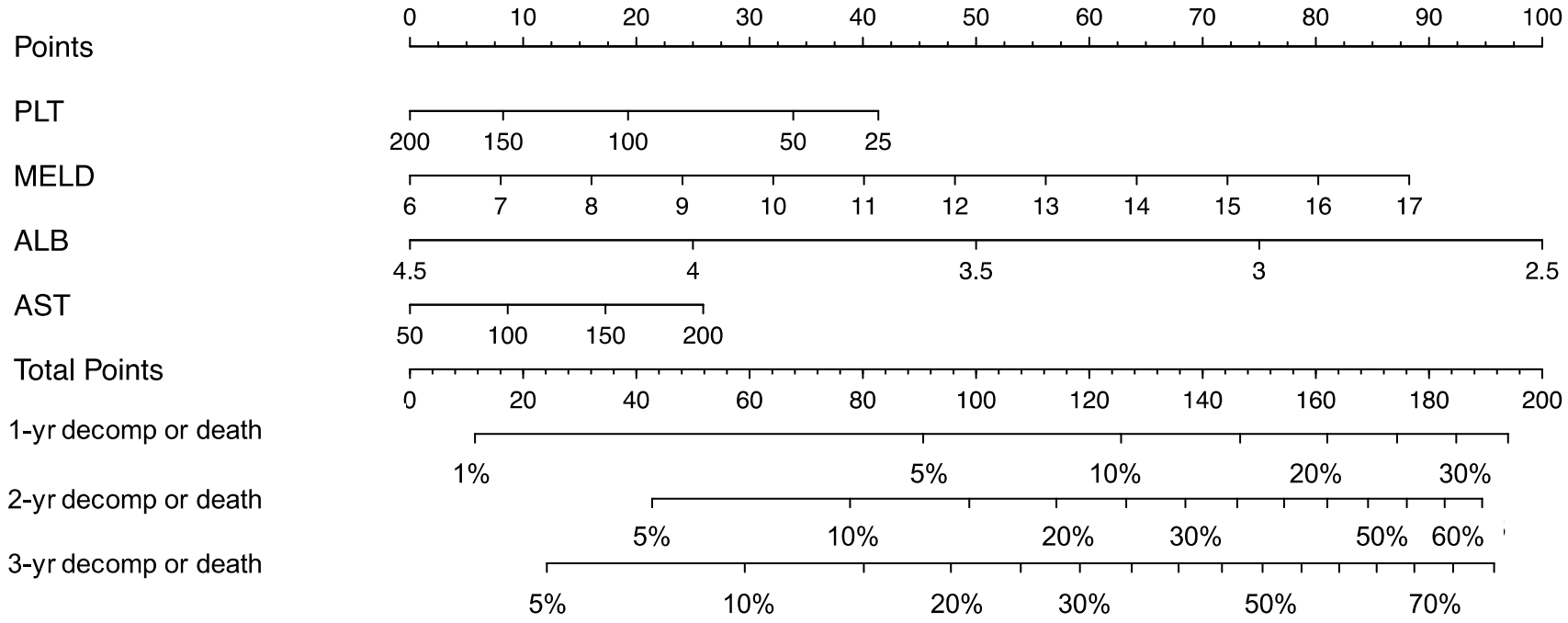
- In compensated cirrhosis the main goal is to prevent decompensation and this should be the primary endpoint
- The development of varices is a sign of progression, but…
  - Difficult to define small varices vs no varices
  - The increase in risk from no varices to varices is small (1 yr mortality 1% vs 2%)
- Use of HVPG response as a surrogate for accelerated approval?

The Myth of the Unfeasible Trial with Clinical Endpoints for Prevention of Decompensation



Ripoll et al Gastroenterology 2007

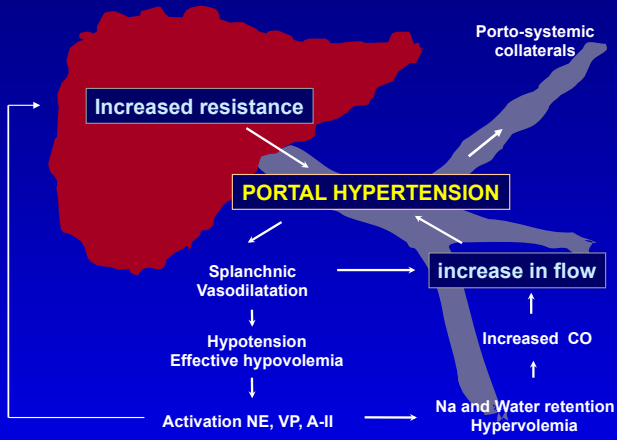


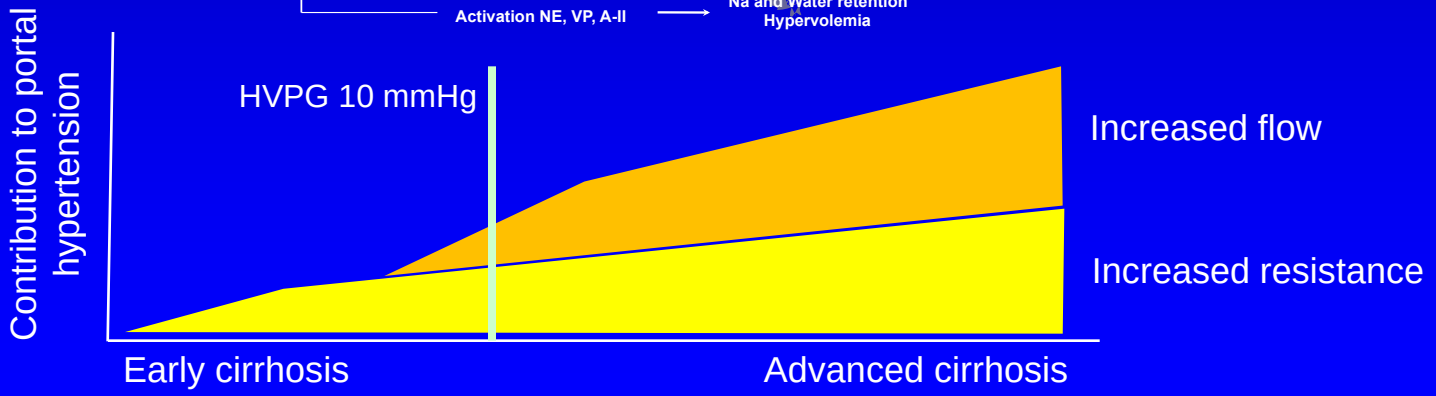


Constructed with data from Ripoll et al Gastroenterology 2007

How we can decrease portal pressure

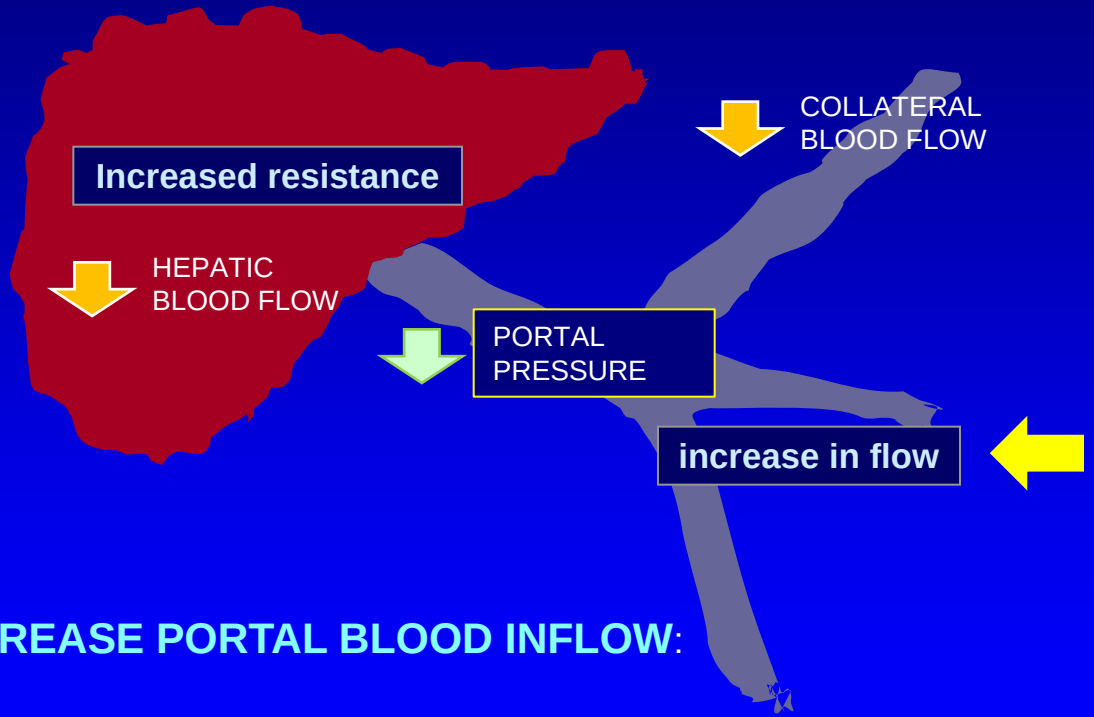
Pharmacological Approaches to Decrease Portal Pressure





Groszmann J Clin Gastro 2005

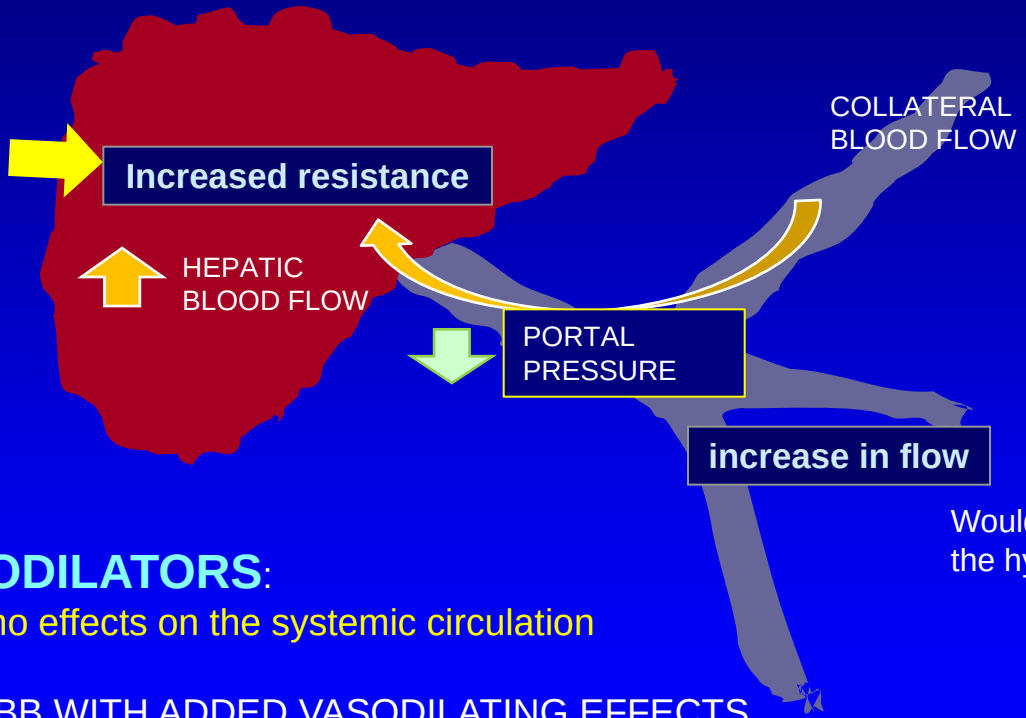
Pharmacological Approaches to Decrease Portal Pressure



DRUGS THAT DECREASE PORTAL BLOOD INFLOW:

- NSBBS
- OCTREOTIDE / SOMATOSTATIN
- TERLIPRESSIN

Pharmacological Approaches to Decrease Portal Pressure



Would eventually deactivate the hyperdynamic circulation

HEPATIC VASODILATORS:

Key characteristic: no effects on the systemic circulation

- CARVEDILOL: NSBB WITH ADDED VASODILATING EFFECTS.
- STATINS: SELECTIVE HEPATIC VASODILATORS. NOT YET STANDARD THERAPY

The Ideal Drug

- Should act by decreasing intrahepatic vascular resistance, decreasing portal pressure while maintaining or enhancing hepatic blood flow
- The vasodilatory effect should be limited to the hepatic circulation to prevent further splanchnic / systemic vasodilatation
- Improve liver function and decrease hepatic fibrosis
- Improve clinical endpoints

Bosch, Abraldes & Groszmann. J Hepatol 2003

Current Guidelines (AASLD 2016, Baveno 2015)

- Prevention of first variceal hemorrhage in patients with medium / large esophageal varices
  - NSBBs
- Acute variceal bleeding
  - Octreotide, somatostatin, terlipressin (used in combination with variceal ligation)
- Prevention of recurrent hemorrhage from esophageal varices
  - NSBBs (used in combination with variceal ligation)

Take Home Messages

- The degree of portal hypertension is associated with the probability of cirrhosis complications
- Treatment of the underlying disease might not be enough to decrease PP to safe levels
- Decreasing portal hypertension improves prognosis
- A major unmet need is a drug to prevent cirrhosis decompensation
- Trials with clinical endpoints in this setting are feasible selecting patients above a certain risk threshold for decompensation