



What's New in Portal Hypertension ?



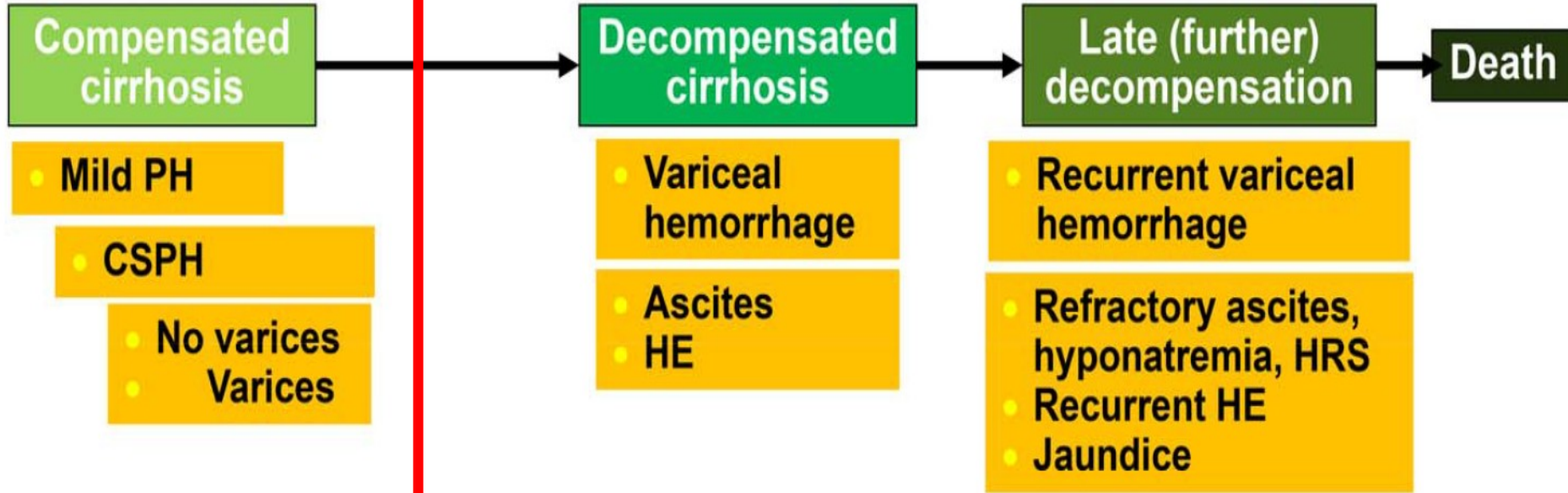
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Disclosures

I have no disclosures related to this topic

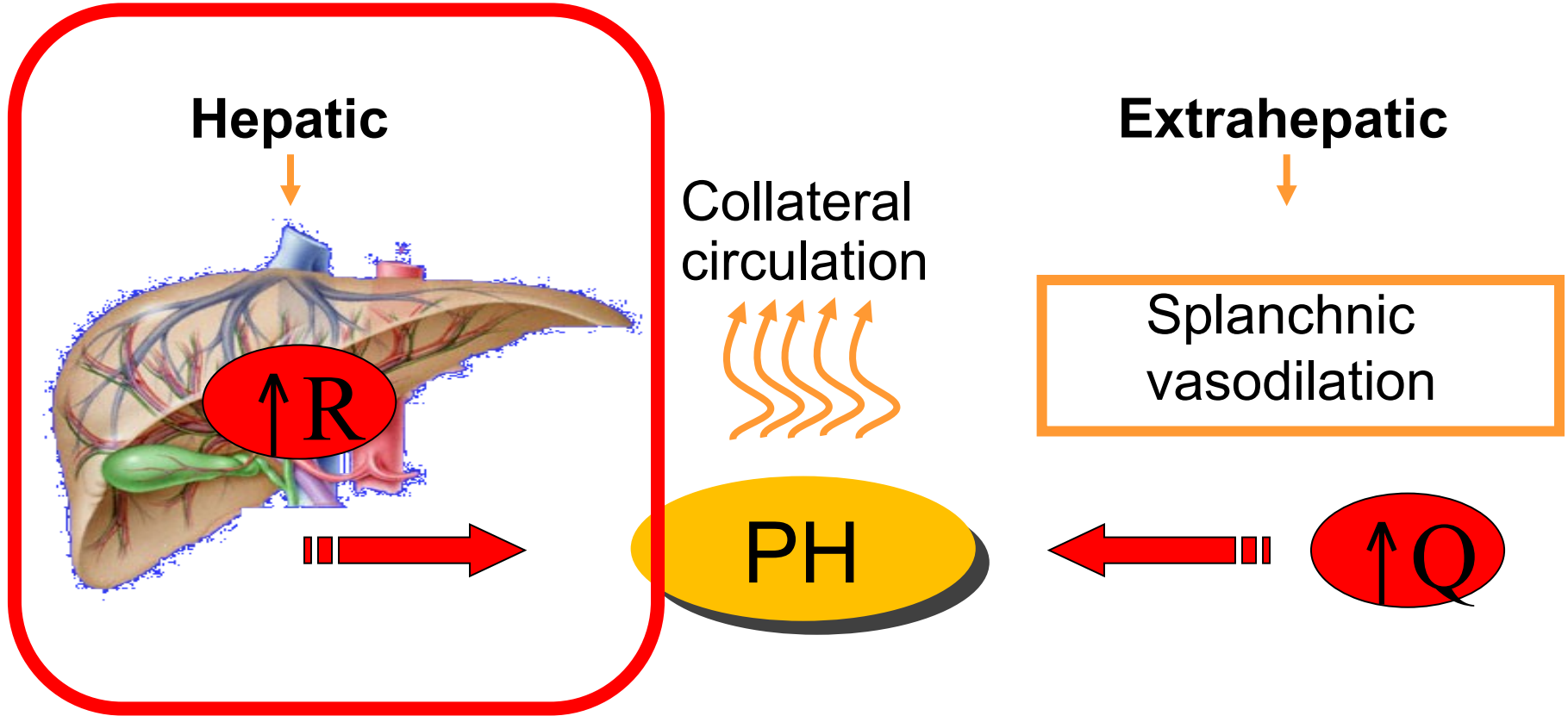
Natural History of Cirrhosis

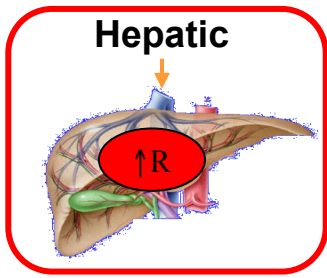


→ Risk stratification and individualizing care for PH

What's New in the Pathogenesis of Portal Hypertension ?

PH: Pathophysiology





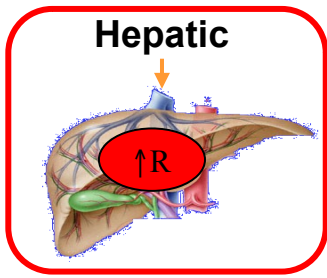
Cirrhosis



↑ Resistance to portal flow



Sub-clinic Portal Hypertension: $\geq 6 < 10$ mmHg



Cirrhosis



↑ Resistance to portal flow



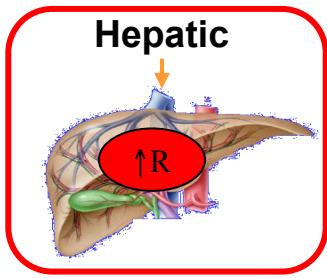
Sub-clinic Portal Hypertension: $\geq 6 < 10$ mmHg



Aim



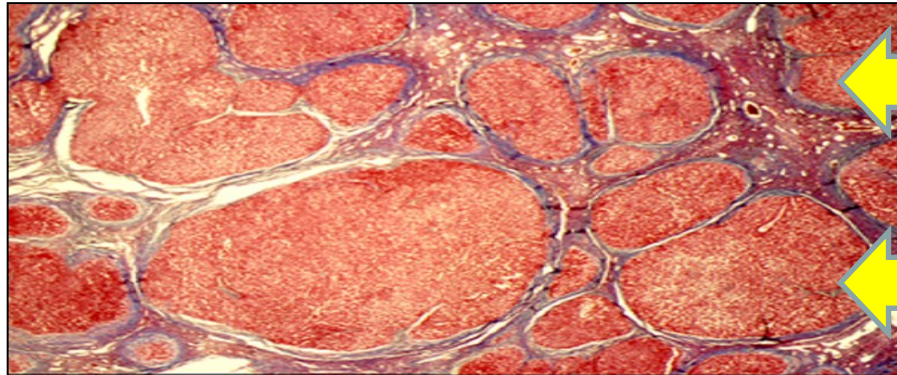
To prevent the outcome to Clinically Significant Portal Hypertension (CSPH)



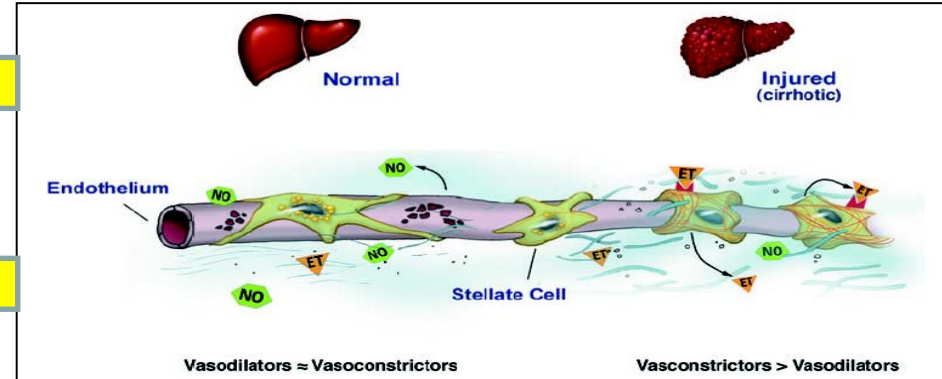
Cirrhosis

↓
↑ Resistance to portal flow
↓

Sub-clinic Portal Hypertension: $\geq 6 < 10$ mmHg



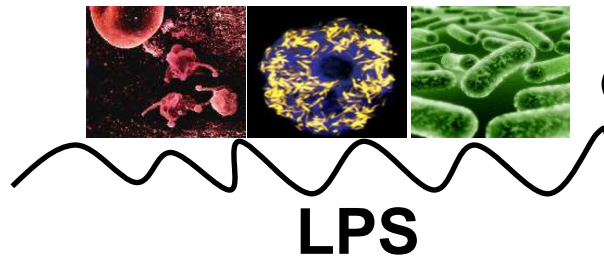
Structural component



Functional component

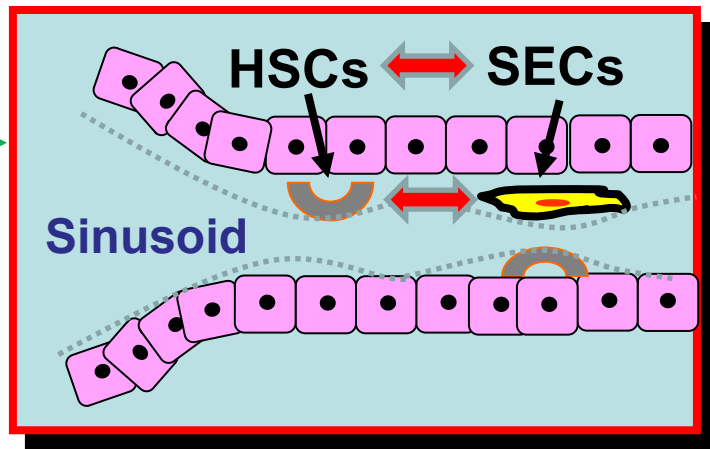


Inflammation



GUT MICROBIOTA

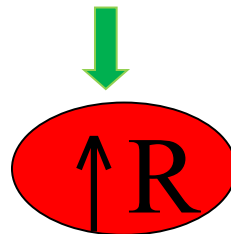
LPS

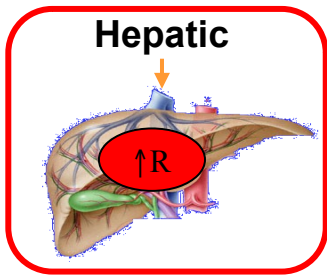


**Prothombotic
condition**

**Fibrosis
Angiogenesis
Capillarization
Microthrombi**

**HSCs: Hepatic Stellate Cells. * SECs: Sinusoidal Endothelial Cells*





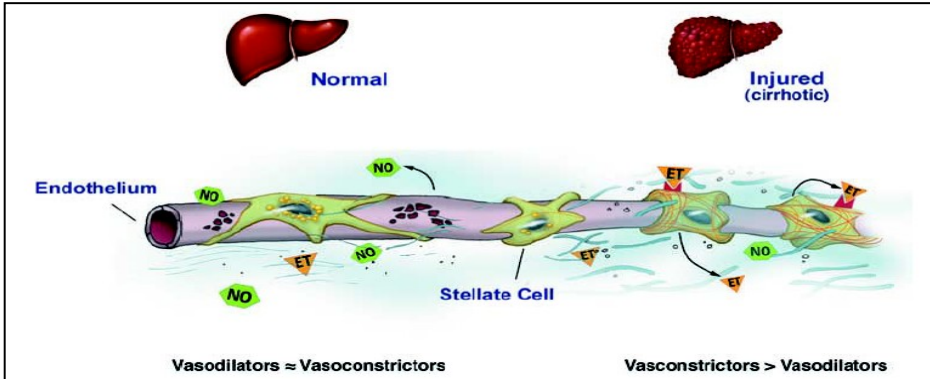
Cirrhosis

↓
↑ Resistance to portal flow
↓

Sub-clinic Portal Hypertension: $\geq 6 < 10$ mmHg

- etiology
- antifibrotic agents
- anticoagulants
- intestinal bacteria...

Structural component



Functional component

What's New in the Diagnosis of Portal Hypertension ?

What's New in the Diagnosis of Portal Hypertension ?

- Invasive Tests:
 - Endoscopy
 - Portal pressure measurement (HVPG)
- Noninvasive Tests:
 - Liver Doppler ultrasound
 - Liver stiffness measurement → Elastography
 - Spleen stiffness measurement → Elastography

What's New in the Diagnosis of Portal Hypertension ?

Liver Stiffness Measurement (LSM) by Transient Elastography:

- Ability to identify the presence of CSPH

LSM \geq 21 kPa **rules in CSPH**

- Ability to rule out the presence of high-risk varices

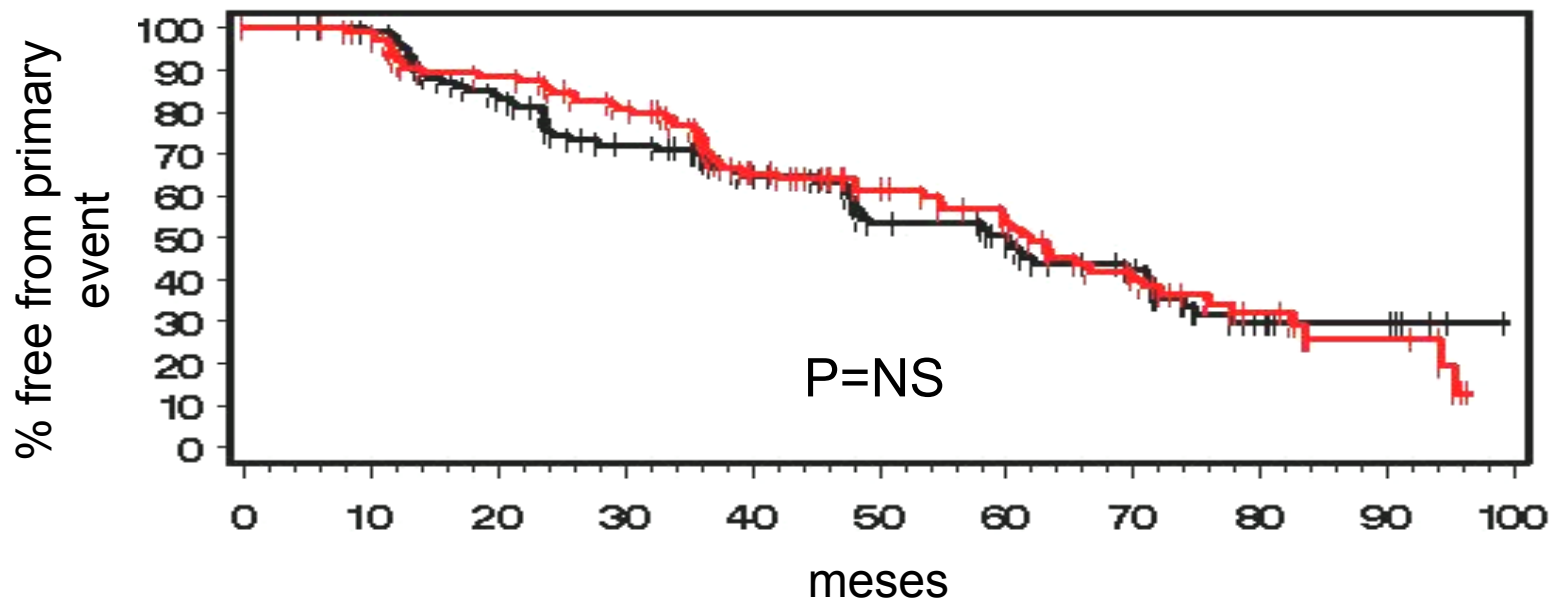
LSM < 20 kPa and a platelet count > 150.000/mm³ **very unlikely to have high risk varices** → 21 % EGDs could be avoided...

What's New in the Treatment of Portal Hypertension ?

Prevention of the First Bleeding Episode

- There is **no indication** for beta blockers to prevent the formation of varices in patients without varices or with small varices.

Probability of remaining free of varices in patients with cirrhosis with HVPG 6 mmHg



+++++ Placebo
(n.105)

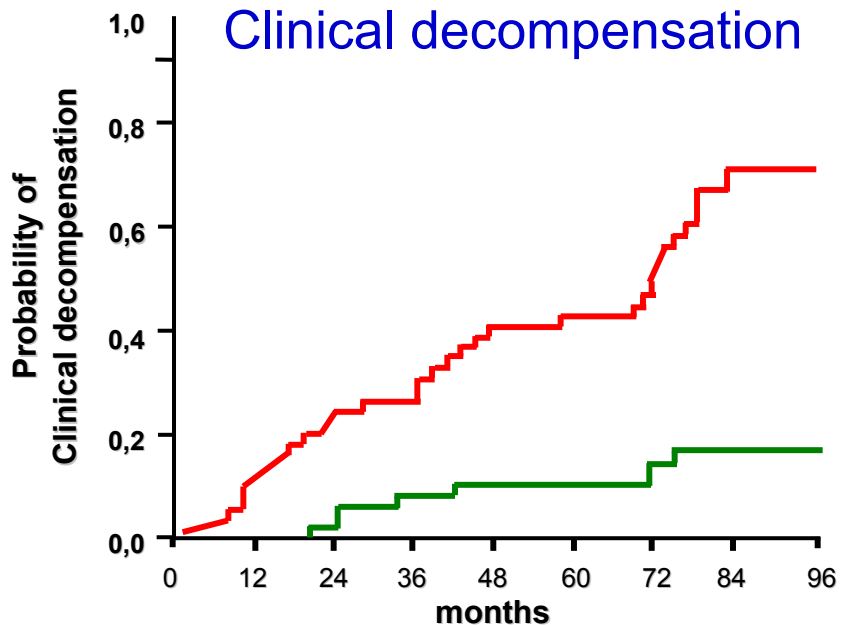
+++++ Timolol
(n.108)

More severe side effects (18% vs. 6%)

Prevention of the First Bleeding Episode

- There is **no indication** for beta blockers to prevent the formation of varices in patients without varices or with small varices.
- Primary prophylaxis of VH is indicated **in patients at a high risk of bleeding**:
 - (1) patients with medium/large varices
 - (2) patients with small varices with red wale signs
 - (3) decompensated patients with small varices
- In patients with medium/large varices, either **NSBBs (propranolol, nadolol), carvedilol, or band ligation can be used to prevent first VH.**

Clinical decompensation: relationship with PH



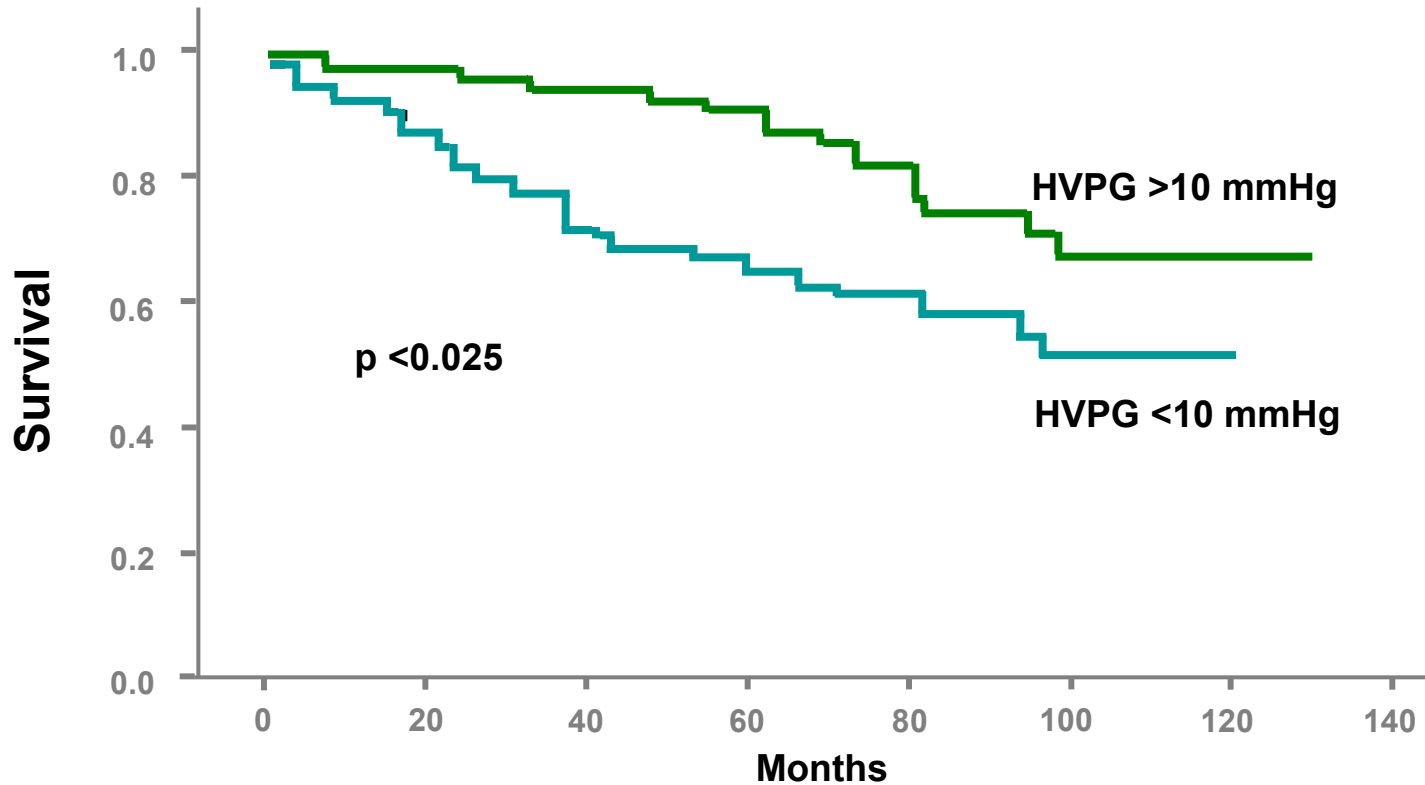
HVPG <10 mmHg

At risk	79	72	66	55	44	32	14
Events	0	0	2	4	6	6	8

HVPG ≥10 mmHg

At risk	134	112	86	73	49	34	3
Events	0	15	29	33	44	47	54

Compensated cirrhosis: HVPG and survival



New attempt at early therapy: The PREDESCI Study

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

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*†

New attempt at early therapy: The PREDESCI Study

PREventing the DEcompensation of Cirrhosis with non-selective beta-blockers

- Cooperative, multicenter, placebo-controlled, randomized clinical trial
- Population studied: compensated cirrhotics with HVPG ≥ 10 mmHg (CSPH), **without high risk varices or previous decompensation** (n=201)

Acute HVPG response to iv Propranolol*:



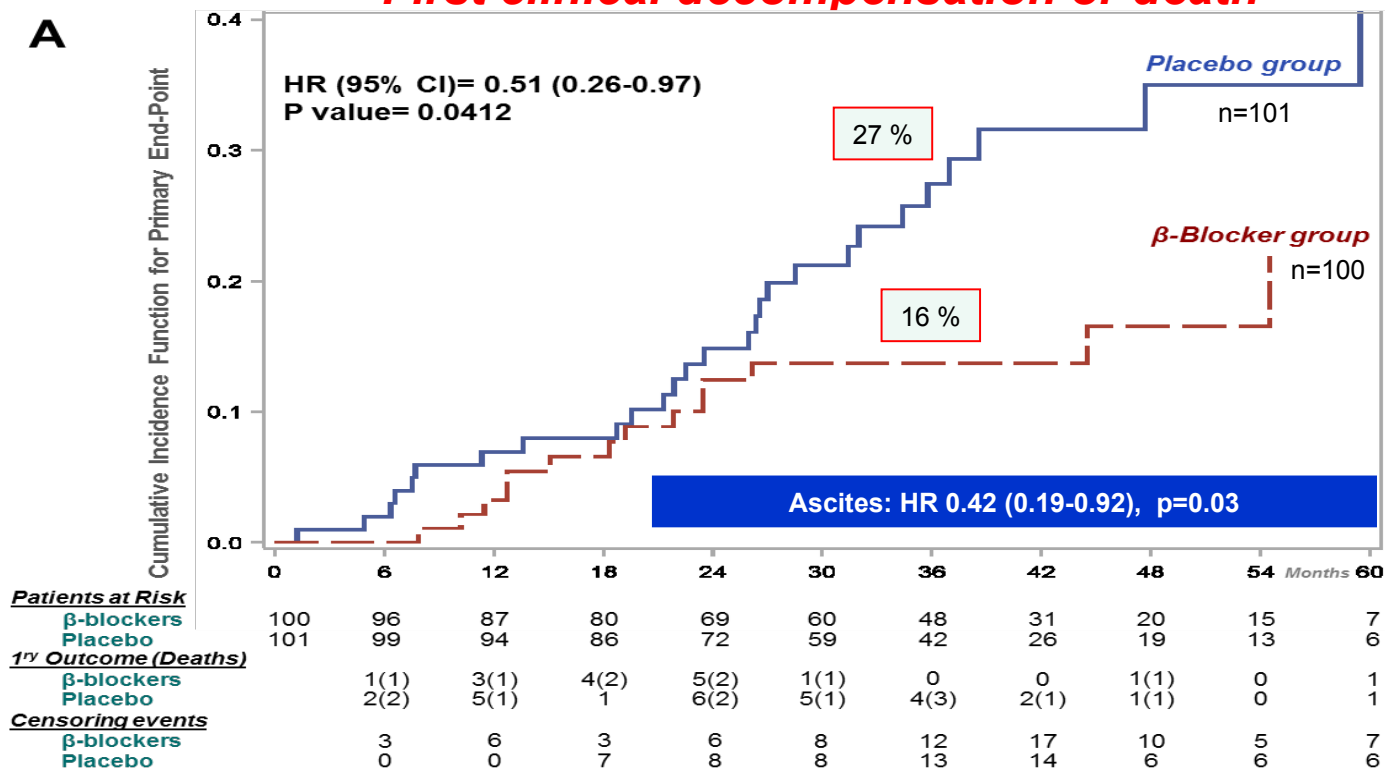
- Primary endpoint: Decompensation (ascites, bleeding or encephalopathy) or death.

* 0.15 mg/Kg IV; Acute Responders: HVPG $\geq 10\%$ of baseline

Propranolol/Carvedilol (according to HVPG response) prevents decompensation of cirrhosis: The PREDESCI Study

First clinical decompensation or death

A



New attempt at early therapy: The PREDESCI Study

- The PREDESCI trial is the first study showing that long-term treatment with NSBBs decreases almost by half the risk of decompensation (mostly ascitis) or liver-related death.
- This finding might result in a new indication for NSBBs in patients with compensated cirrhosis.
- Although HVPG measurement constitutes a limitation, noninvasive tools such as elastography might be helpful to select patients in the near future...

What's New in the Treatment
of Portal Hypertension ?

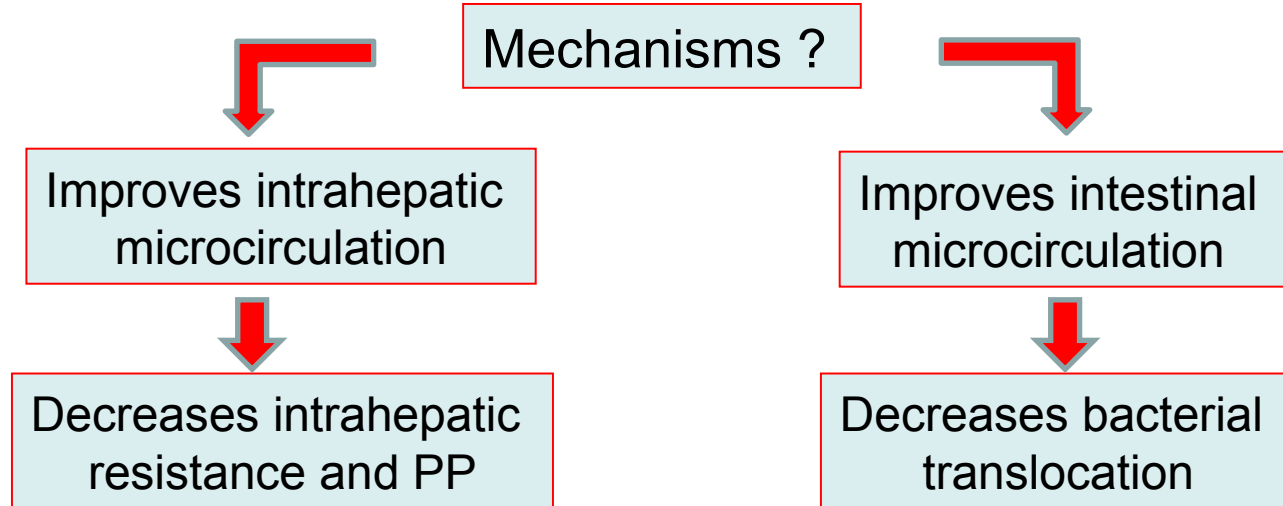


What about anticoagulation ?

Anticoagulation in Portal Hypertension ?

In an RCT a 12-month of enoxaparin (4000 IU/d, subcutaneously) versus no treatment **delayed the occurrence of decompensation** (38.2% vs 83%; $P < .0001$) and **improved survival** (23 % vs 26 %; $P < .02$), in patients with cirrhosis.

Villa et al, Gastroenterology 2012



**Cirroxxaban (NCT02643212, Spain): Rivaroxaban 10 mg/d vs placebo.
Primary outcome: survival and liver disease progression at 24 months**

Treatment of Acute Variceal Bleeding

1. ICU or closely monitored setting
2. ABC's – careful volume repletion
3. Intubation (selected cases)
4. Stratify patients
5. Antibiotics
6. I.V. vasoactive therapy
7. Adequate blood transfusion (Hb 7-9 g/dL)
8. No recommendation regarding coagulopathy
9. Prompt endoscopic therapy (EBL)
10. Ultrasound
11. Possibility of tamponade
12. Possibility of TIPS / Early TIPS



*Baveno VI, J Hepatol 2015
AASLD Guidance, Hepatology 2017
EASL Guidelines 2018*

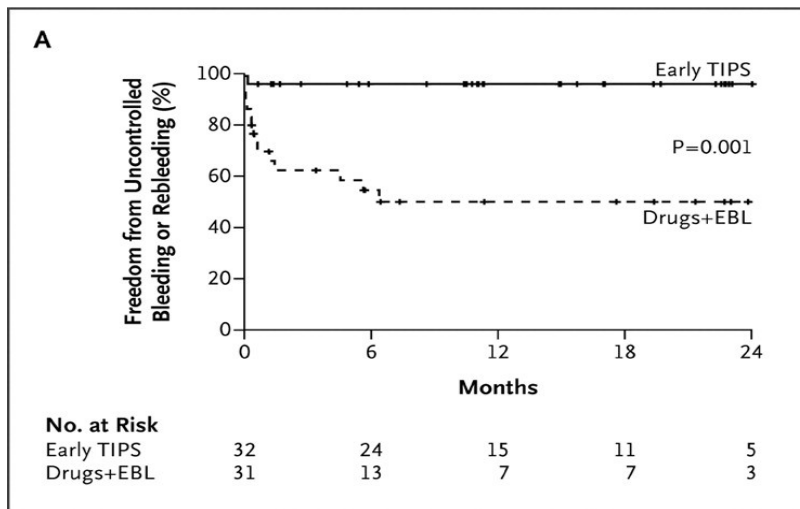
Rescue TIPS in Treatment Failures

Author	Patients	Child A/B/C	Control of bleeding	Mortality
Mc Cormick	20	1/7/12	100%	55%
Jalan	19	3/3/13	100%	42%
Sanyal	30	1/7/22	100%	40%
Chau	112	5/27/80	98%	37%
Gerbes	11	1/3/7	100%	27%
Banares	56	11/22/23	96%	28%
Azoulay	58	3/8/47	93%	30%
Bouzbib	106	6/32/68	80%	38% (d42)

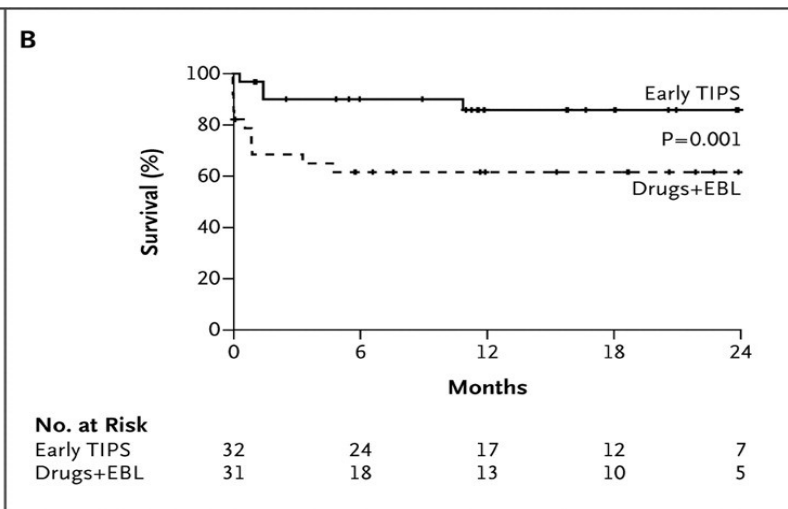
Should TIPS be placed **earlier** in high risk patients ?

Multicenter RCT of Early TIPS (1st 72 hrs) vs SMT in Patients with Acute Variceal Bleeding
(Child B with active bleeding and Child C \leq 13)

Primary end-point



Survival



An early TIPS with PTFE-covered TIPS within 72 hours (ideally ≤ 24 hours) must be considered in patients bleeding from EV, GOV1 and GOV2 at high-risk of treatment failure (e.g. Child-Pugh class C <14 points or Child class B with active bleeding) after initial pharmacological and endoscopic therapy (1b;A).

Criteria for high-risk patients should be refined...



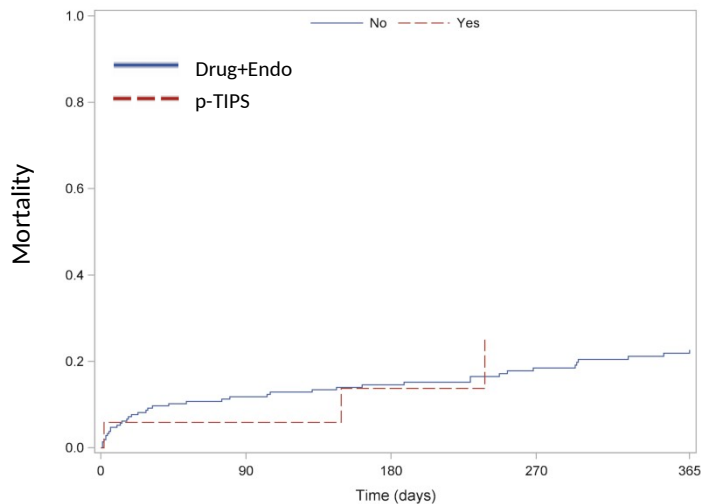
Preemptive-TIPS improves outcome in high-risk variceal bleeding

(Propensity score matched analysis)

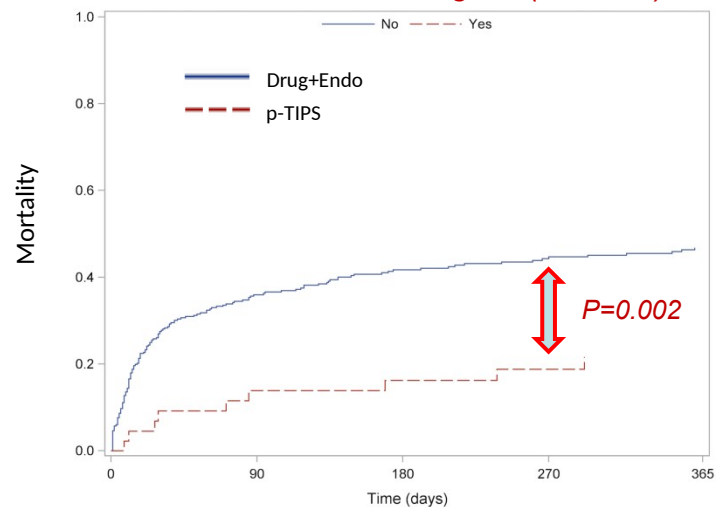
Multicenter, international study in 34 centers

66 Early TIPS vs 605 Drugs and EBL

Child-Pugh B + Active Bleeding



Child-Pugh C (10 to 13)



What's New in the Treatment
of Portal Hypertension ?



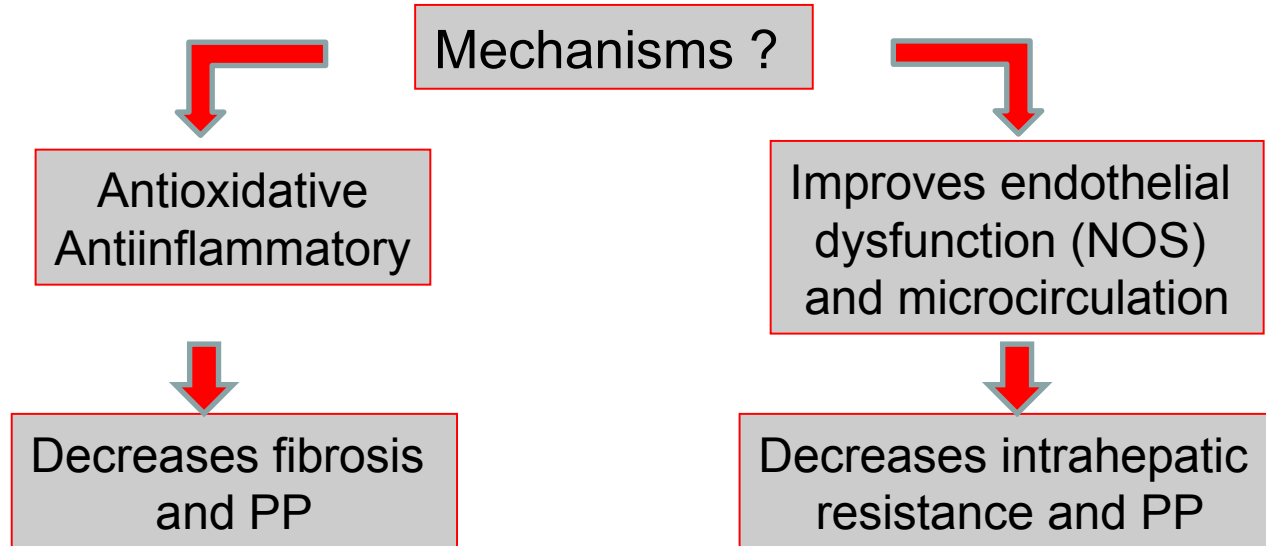
What about statins ?

Statins in Portal Hypertension ?

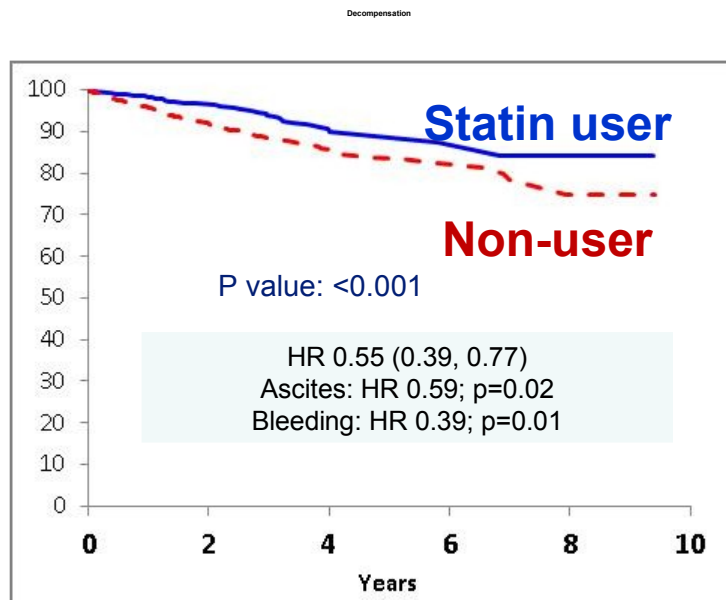
Simvastatin protects the cirrhotic liver during **acute bleeding** (Meireles et al, Shock 2016)

Simvastatin prevents **ACLF** in cirrhotic rats (Tripathi et al, Gastroenterology 2018)

Simvastatin prevents microthrombosis **after exposure to LPS** (LaMura et al, AASLD 2019)

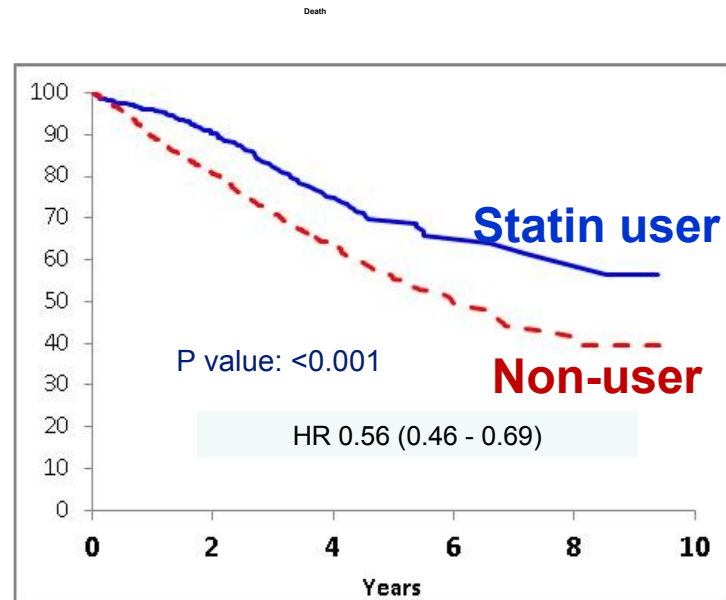


Statins are associated with a decreased risk of decompensation and death in compensated HCV cirrhosis*



No. at risk

User	685	386	154	48	13
Nonuser	2062	924	333	92	22



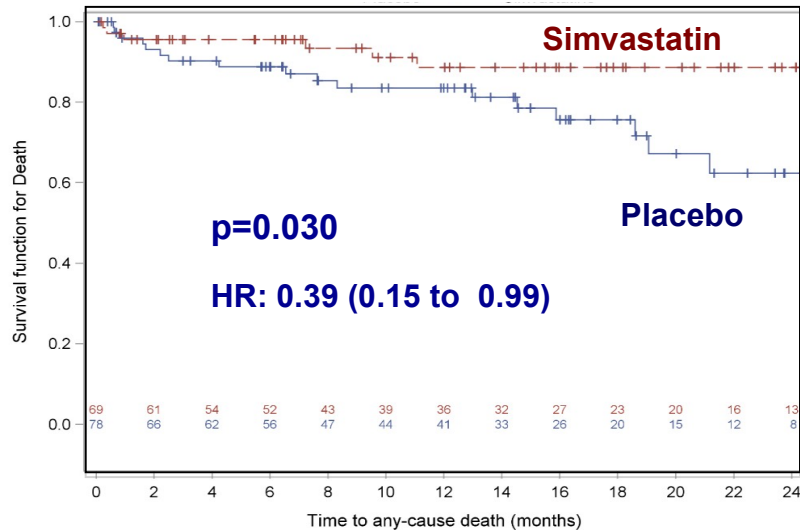
No. at risk

User	685	399	165	53	17
Nonuser	2062	991	370	107	27

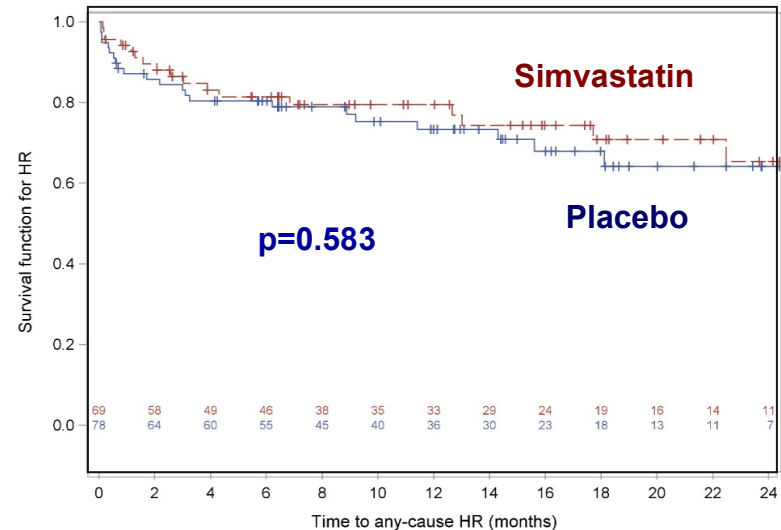
*Propensity score matched study

Simvastatin on top of standard of care (NSBB + EBL) improves prognosis after variceal bleeding (**BLEPS Study**)

Death*



Rebleeding n=158



* less deaths due to bleeding and infections

Abraldes et al. Gastroenterology 2016

Formal recommendation ? ➡ Waiting forward to Baveno VII

Take home messages

- Cirrhosis should be described and managed in two distinct clinical stages, compensated and decompensated, defined by the presence or absence of overt clinical complications (ascites, VH, and HE).
- The identification of patients with cirrhosis and clinically significant portal hypertension (CSPH) is extremely important. Non invasive tests will probably be of great help as diagnostic tools.
- In patients with cirrhosis and CSPH but without varices, the objective of treatment should be to prevent clinical decompensation. New recommendations concerning therapy related to this issue will probably show up in the near future...

Take home messages

After an episode of acute variceal bleeding in patients at high risk of failure or rebleeding, an “early” (pre-emptive) TIPS within 72 hours from EGD/EBL may benefit selected patients (Child C...).

Anticoagulation may improve intrahepatic microcirculation from a theoretical point of view but its clinical impact still needs to be demonstrated.

Statins have shown to lower the incidence of decompensation and mortality in different populations of patients with cirrhosis. Therefore, they might become an additional tool in the management of these patients.



Jean-Pierre Benhamou



Didier Lebrec



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Thank you !!!!



